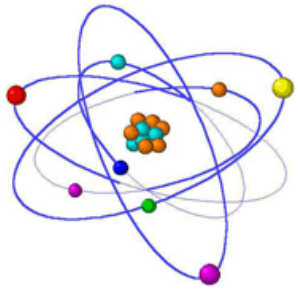
# Radioisotope and Radiation Applications (FS2013)



## Biological Effects of Radiation (Week 2b)

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24.09. 2013

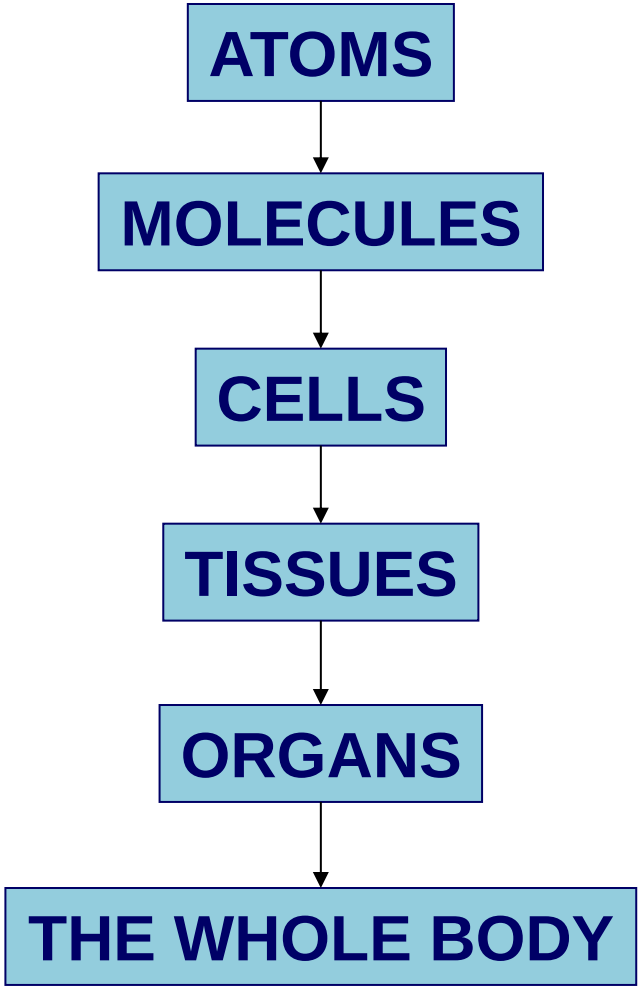
# Biological Effects of Radiation: Outline

- Introduction: Radiobiology
- Basic Biological Concepts
  - Cells, types of cells
  - Cell cycle and cell death
- Classification of Radiation (Supplement)
  - Linear Energy Transfer (LET)
  - Relative Biological Effectiveness (RBE)
- Irradiation of Cells
  - Processes of radiation damage
  - Types of radiation damage, radiation effects
  - Repair of radiation damage
  - Cellular, tissue and organ sensitivity to radiation
- Measures of Biological Effects of Radiation
  - Cell survival curves
  - Dose response curves
  - Measurement of radiation damage in tissue
- Therapeutic Ratio, Dose Rate and Fractionation, Oxygen Effect, Radioprotectors and Radiosensitizers

# Introduction: Radiobiology (in German: “Strahlenbiologie”)

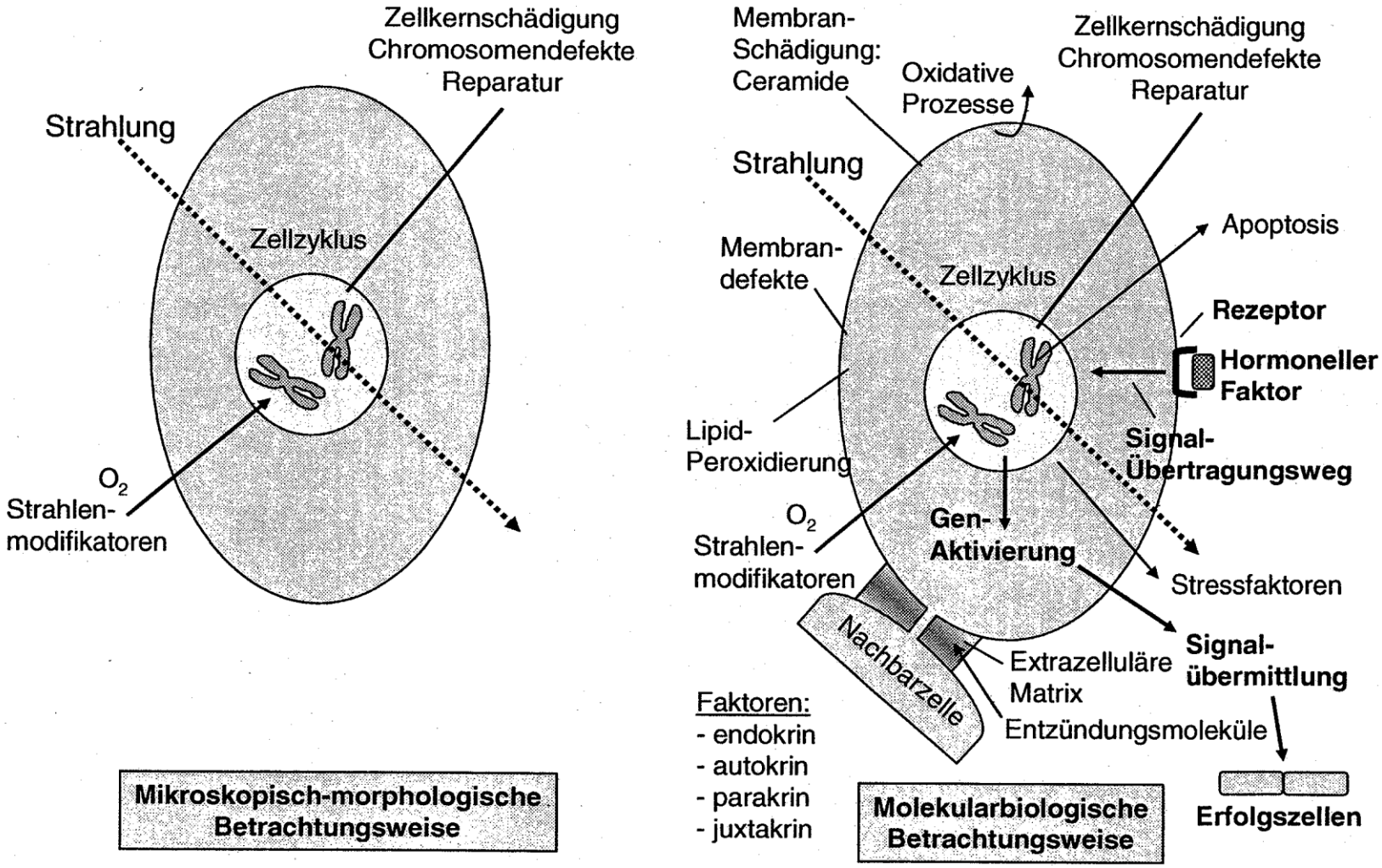
- **Radiobiology** is a branch of science **concerned with the action of ionizing radiation on biological tissue and living organisms.**
- It is a combination of two (or even three) disciplines:
  - Radiation physics
  - (Radiation chemistry)
  - Biology
- Radiation effects on humans proceed from the lowest to the highest levels.

**Radiation causes ionizations of**



# Radiobiology: Warning! There is much more to say…

- The **classical radiobiology model** of 1980 (left) is compared with the more complex model of 2000+ based on a **biomolecular view** (right).



# Research in the area of Radiobiology is very important!

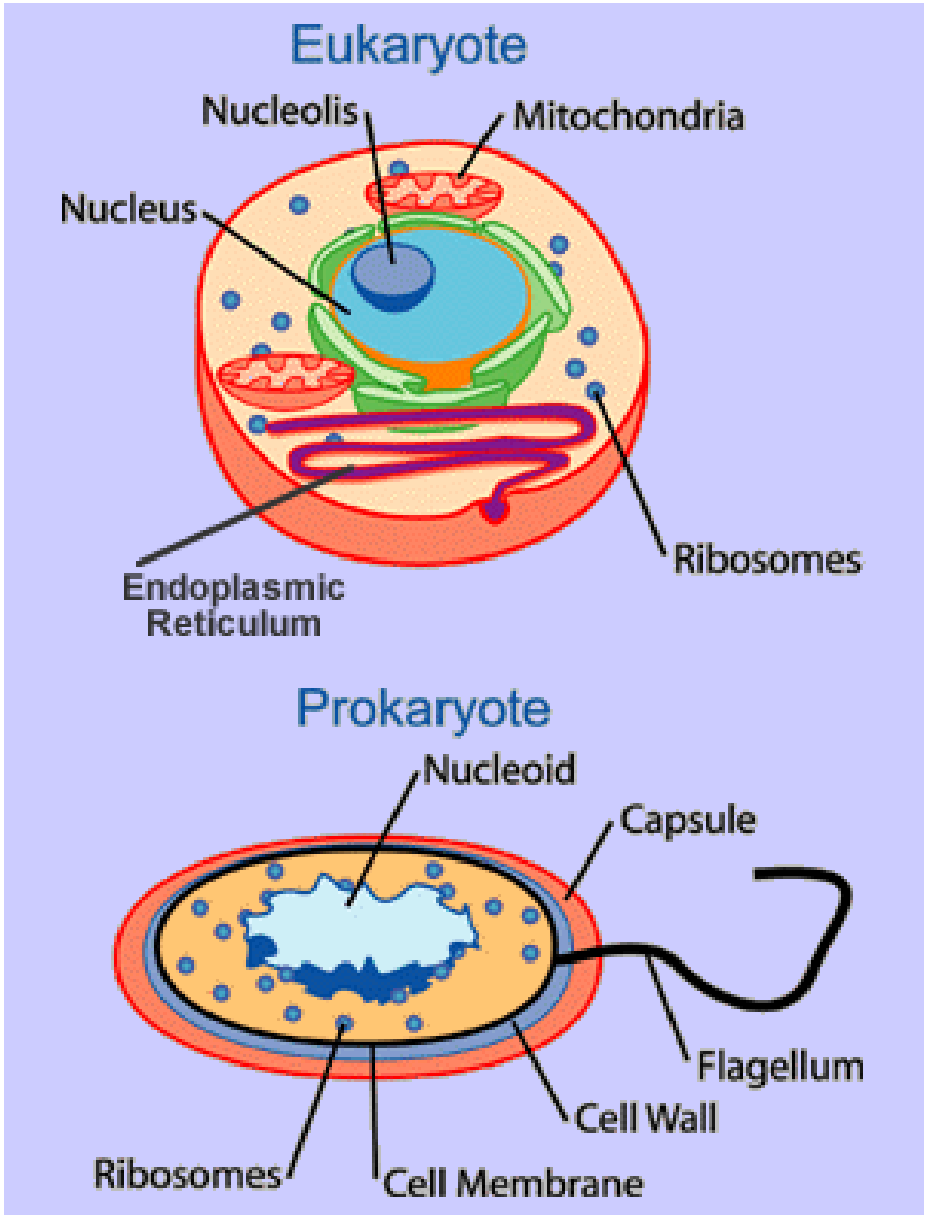
Greek bust of Janus,
Vatican Museums.

- Following the International Commission on Radiological Protection (ICRP) [ICRP-Publication 60 (1990): Recommendations of the International Commission on Radiological Protection, 60]:

  "Biological effects of ionizing radiation must be studied in order to protect human beings and other species from its harmful effects and to maximize the benefits of its use."

# Basic Biological Concepts: Cells

- All living things are composed of one or more **cells**.
  - A group of cells that perform one or more functions form a **tissue**.
  - Tissues organize in **organs**.
  - A system of organs is referred to as **organism**.
- Each human being has an estimated ~$10^{14}$ cells. A typical cell size is 10µm. A typical cell mass is 1 nanogram.
- The main constituents of a cell are:
  - The **cytoplasm**, which supports all metabolic functions.
  - The **nucleus**, which contains the genetic information (**chromosomes**, i.e., organized structures of **DNA** and protein).



# Basic Biological Concepts: Types of Cells

## Somatic cells:

- The most common cells in the human body.
- They reproduce through **mitosis**: one cell gives birth to **two** cells with the same number of chromosomes as the parent.
- Somatic cells are classified as:
  - **Stem cells** can differentiate into specialized cells: epidermis, lining of intestine, bone marrow.
  - **Transit cells** are cells in the process of differentiation: reticulocyte.
  - **Mature cells** are fully differentiated and do not exhibit mitotic activity: muscle cells and nervous tissue.

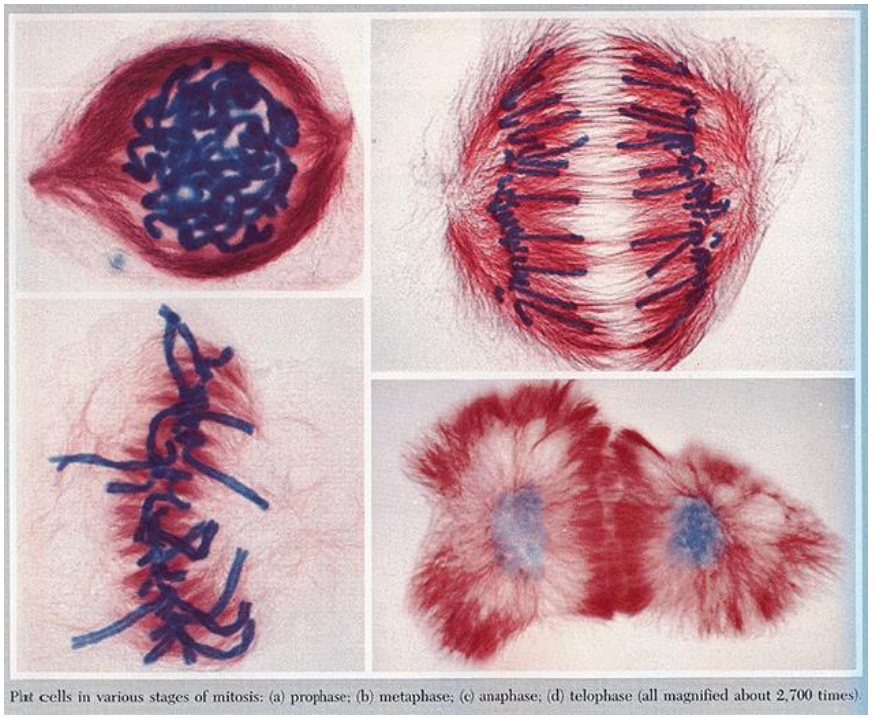
## Germ cells:

- Cells used in the reproduction of the organism: spermatozoa, ova.
- They divide by **meiosis**: the two cells have half the number of chromosomes.

# Basic Biological Concepts: Cell Cycle and Death

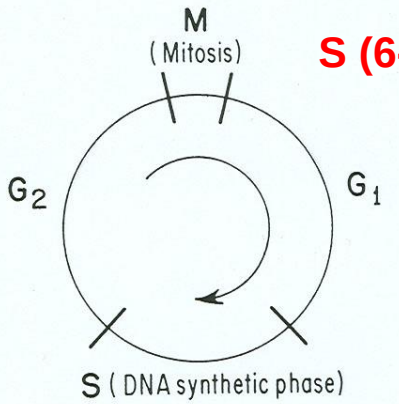
- Tissues grow and are maintained through cell replication (regeneration). The time between successive divisions (mitoses) is called the cell cycle time.
- Some cells never divide once adulthood is reached.
- There is a specific set of steps involved in the cell proliferation cycle.

| | | |
|---|---|---|
| • G1 (G0) | Gap 1 | Functional cell |
| • S | Synthesis | DNA synthesis |
| • **G2** | Gap 2 | Other metabolic proc. |
| • **M** | Mitosis | Cell division |



Plat cells in various stages of mitosis: (a) prophase; (b) metaphase; (c) anaphase; (d) telophase (all magnified about 2,700 times).

- Cell death is defined as, for :
  - non-proliferating cells: loss of function.
  - proliferating cells: loss of reproductive integrity.

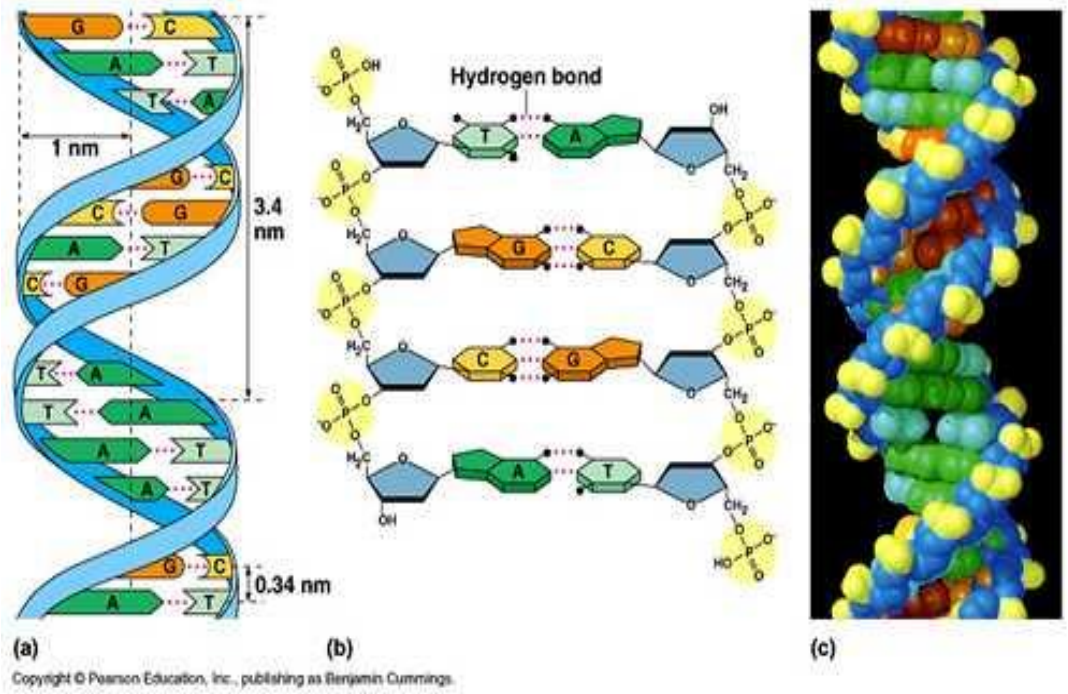



**S (6-8h), M (<1h), G2 (2-4h), G1 (1-8h)**

The stages of the mitotic cycle for actively growing mammalian cells. M, mitosis; S, DNA synthetic phase; $G_1$ and $G_2$, "gaps" or periods of apparent inactivity between the major discernible events in the cycle.

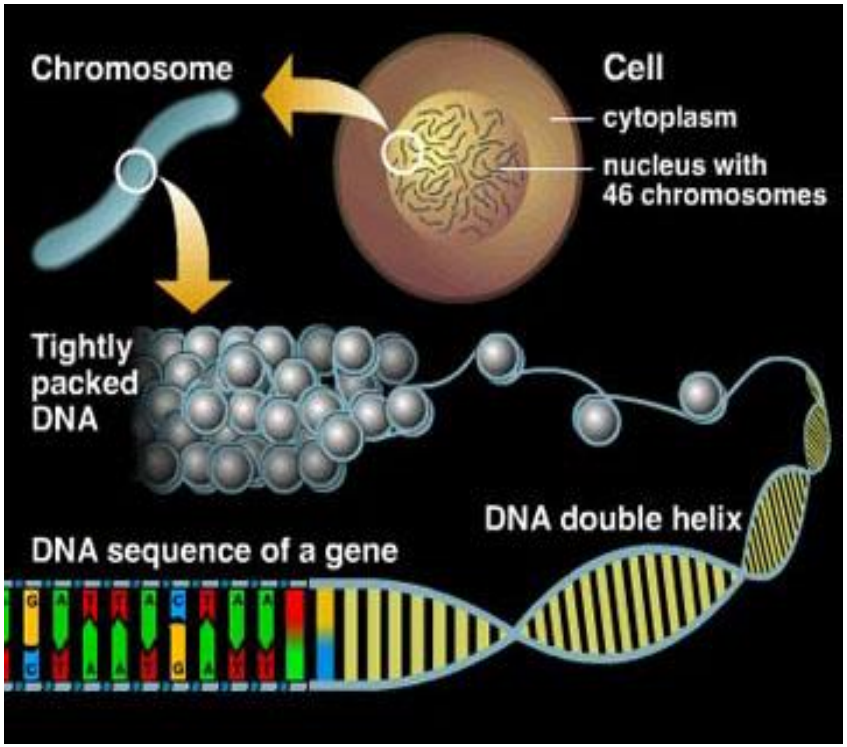
# Basic Biological Concepts: The DNA Molecule

- DNA (deoxyribonucleic acid) is a very large molecule. There are about 3 x $10^9$ base pairs in the human genome, it contains 23 chromosomes, and an estimated 20,000-25,000 distinct genes.
- The 3-D configuration (shape) of the molecule changes constantly and is important to function.
- DNA is replicated at cell division.
- Double-stranded helix pattern:
  - Side rails of ladder composed of sugar molecules bound together by a phosphate.
  - Rungs are composed of the nitrogenous bases Adenine, Thymine, Guanine and Cytosine.
  - Adenine and Thymine combine to make up one type of rung and Guanine and Cytosine combine to make up another type.



# Basic Biological Concepts: The Genome

- The DNA makes up the chromosomes of the cell and carries all of the functional encoding information of the cell or organism.
- All of the chromosomes together make up the genome.
- The genome is composed of many genes.
- The individual genes are composed of sequences of nitrogenous bases attached to the molecular backbone. These sequences encode for protein functions etc., which control all cell functions.



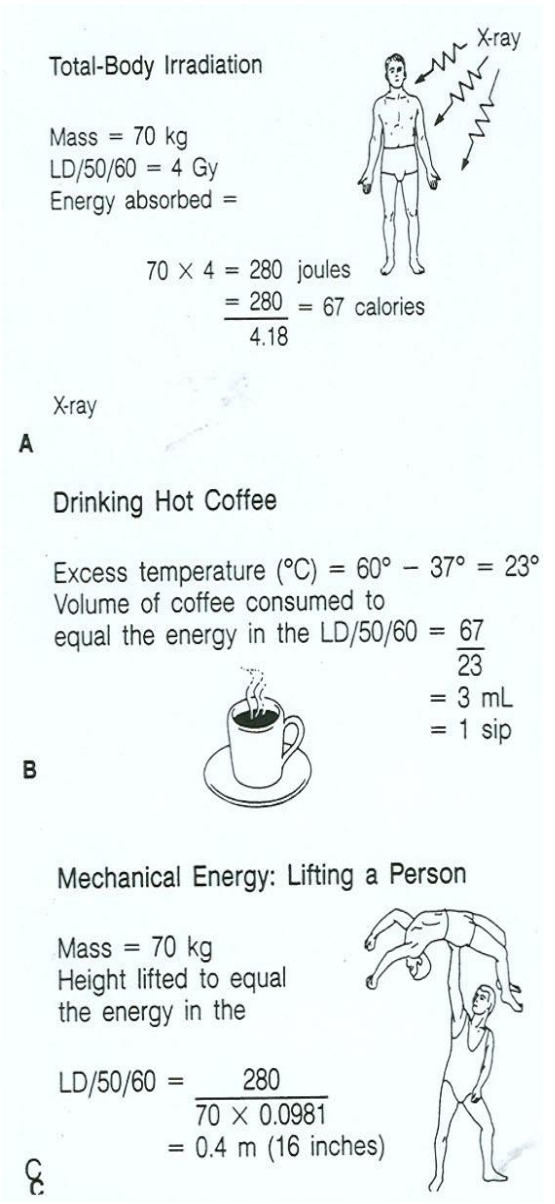

# Classification of Radiation (Supplement)

- The physical quantity useful for defining the quality of ionizing radiation is the **Linear Energy Transfer**, **LET = $-(dE/dx)_{col}$**.
  - LET is generally given in units of keV/μm (stopping power in MeV/cm).
  - It is measured by dividing the track of particles in equal energy increments and taking the average of their lengths.

*Typical Linear Energy Transfer Values*

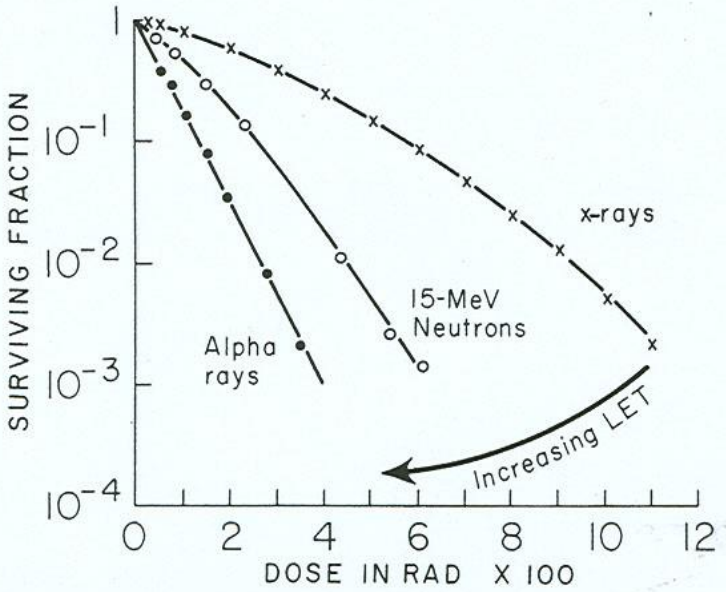
| Radiation | Linear Energy Transfer, KeV/μm | |
|---|---|---|
| Cobalt-60 γ-rays | 0.2 | |
| 250-kV x-rays | 2.0 | |
| 10-MeV protons | 4.7 | |
| 150-MeV protons | 0.5 | |
| | Track Avg. | Energy Avg. |
| 14-MeV neutrons | 12 | 100 |
| 2.5-MeV α-particles | 166 | |
| 2-GeV Fe ions | 1,000 | |

- **The biological effect of radiation is not determined by how much total energy is absorbed, but by the photon or packet size of the energy (and how it is absorbed and where).**



# Relative Biological Effectiveness (RBE)

- As LET of radiation increases, the ability of radiation to produce biological damage also increases.
- RBE compares the dose of standard radiation with the dose of the test radiation.
- The standard radiation has been taken as 250kV X-Rays.
- RBE depends on:
  - Radiation quality (LET)
  - Radiation dose
  - Number of dose fractions.
  - Dose rate.
  - Biological system or endpoint.




Survival curves for cultured cells of human origin exposed to 250-kVp x-rays, 15-MeV neutrons, and 4-MeV α-particles. As the linear energy transfer of the radiation increases, the slope of the survival curves gets steeper and the size of the initial shoulder gets smaller. (Adapted from Broerse JJ, Barensen GW, van Kersen GR: Int J Radiat Biol 13:559–572, 1967; and Barendsen GW: Curr Top Radiat Res Q 4: 293-356, 1968, with permission.

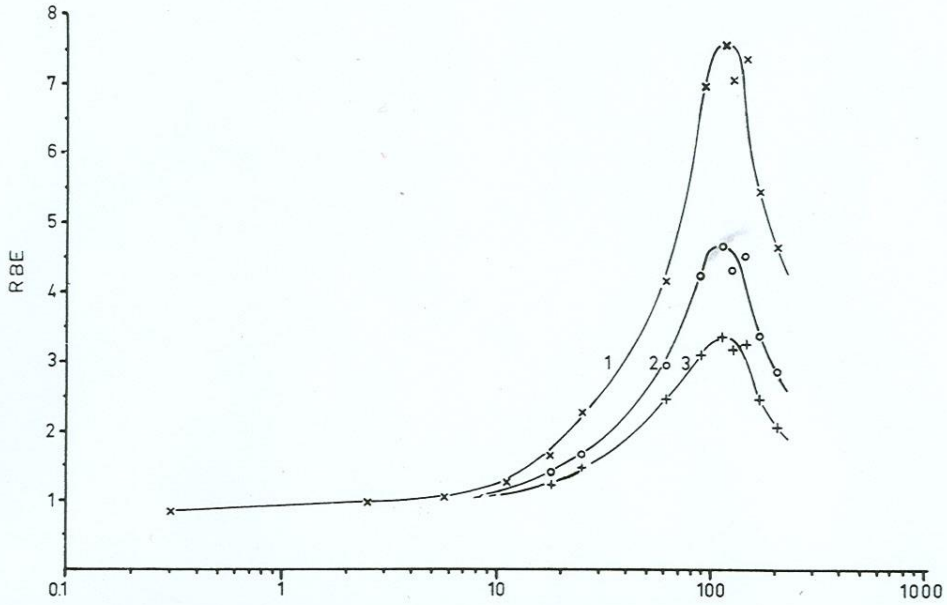
***Source Hall (2000)***

$$\text{RBE} = \frac{\text{Dose from Standard Radiation to produce a given biological Effect}}{\text{Dose from Test Radiation to produce a given biological Effect}}$$

# RBE as a function of LET

## Over-kill effect

## RBE peaks at a LET-value of ≈100 keV/μm




Variation of relative biologic effectiveness (RBE) with linear energy transfer (LET) for survival of mammalian cells of human origin. The RBE rises to a maximum at an LET of about 100 keV/μm and subsequently falls for higher values of LET. Curves 1, 2, and 3 refer to cell-survival levels of 0.8, 0.1, and 0.01, respectively, illustrating that the absolute value of the RBE is not unique but depends on the level of biologic damage and, therefore, on the dose level. (From Barendsen GW: Curr Top Radiat Res Q 4:293–356, 1968, with permission.)

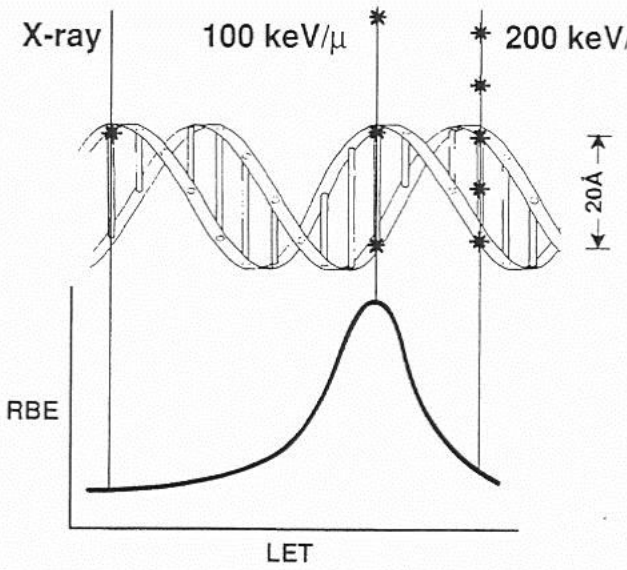



Diagram illustrating why radiation with a linear energy transfer of 100 keV/μm has the greatest relative biologic effectiveness for cell killing, mutagenesis, or oncogenic transformation. For this transfer, the average separation between ionizing events coincides with the diameter of the DNA double helix (*i.e.*, about 20 Å or 2 nm). Radiation of this quality is most likely to produce a double-strand break from one track for a given absorbed dose.

***Source Hall (2000)***

# Irradiation of Cells: Processes/Timescale of Damage

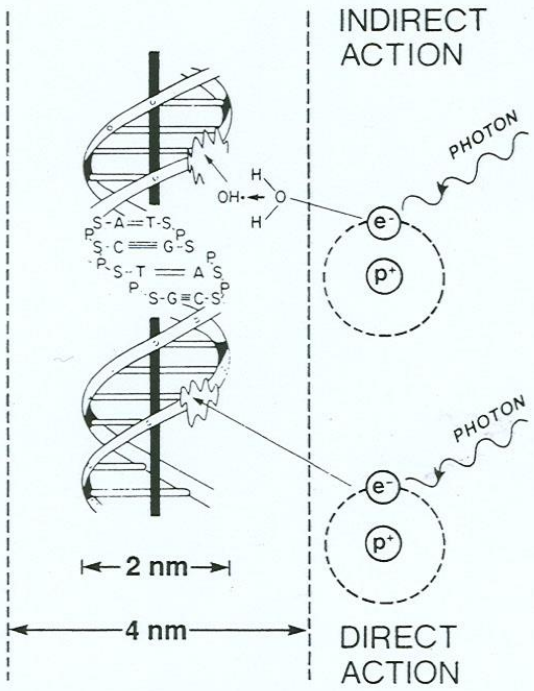
- **Biological effects** are usually thought of **as effects on cells**.
- Ionizing radiation interacts with atoms by ionization.

| Stage | Process | Duration |
|---|---|---|
| **Physical** | Energy absorption, ionization. | $10^{-18}$ to $10^{-12}$ s |
| **Physico-Chemical** | Interaction of ions with molecules, formation of free radicals. | $10^{-14}$ to $10^{-6}$ s |
| **Chemical** | Interaction of free radicals with molecules, cells and DNA. | $10^{-12}$ to seconds |
| **Biochemical / Biological** | Cell death, change in genetic data in cell, mutations, cancer. | $10^{-3}$ seconds to tens of years |

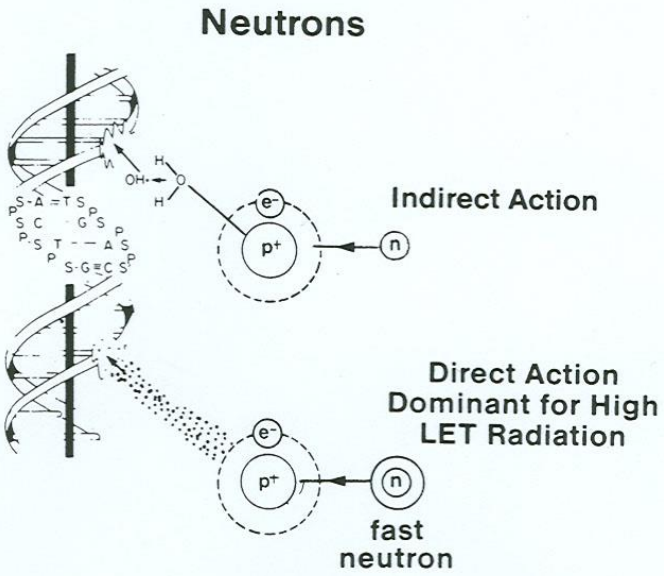
# Irradiation of Cells: The two Ways of Damage

- **The biological effects of radiation result mainly from damage to the DNA, which is the most critical target within the cell.**
- Direct Action Damage:
  - The radiation interacts **directly** with the critical target in the cell.
  - The atoms of the target are ionized or excited through Coulomb interactions.
  - The interactions lead to the chain of physico-chemical events that will produce the biological damage.
  - This is the dominant process for high LET radiation.
- Indirect Action Damage:
  - The radiation interacts **indirectly** with other molecules: 80% water.
  - **Production of free radicals**.
  - The free radicals produce chemical damage in the critical target molecule.
  - This is the dominant process for low LET radiation (2/3 of damage).

# Indirect and Direct Action Damage




Direct and indirect actions of radiation. The structure of DNA is shown schematically. In direct action a secondary electron resulting from absorption of an x-ray photon interacts with the DNA to produce an effect. In indirect action the secondary electron interacts with, for example, a water molecule to produce a hydroxyl radical (OH·), which in turn produces the damage to the DNA. The DNA helix has a diameter of about 20 Å (2 nm). It is estimated that free radicals produced in a cylinder with a diameter double that of the DNA helix can affect the DNA. Indirect action is dominant for sparsely ionizing radiation, such as x-rays. *S*, sugar; *P*, phosphorus; *A*, adenine; *T*, thymine; *G*, guanine; *C*, cytosine.




Direct action dominates for more densely ionizing radiations, such as neutrons, because the secondary charged particles produced (protons, α-particles, and heavier nuclear fragments) result in a dense column of ionizations more likely to interact with the DNA. The local density of DNA radicals produced by direct ionization of DNA is so high that the additional contribution of DNA radicals produced by HO· radical attack does not add substantially to the severity of the lesion.

***Source Hall (2000)***

# Indirect Action Cell Damage Mechanisms

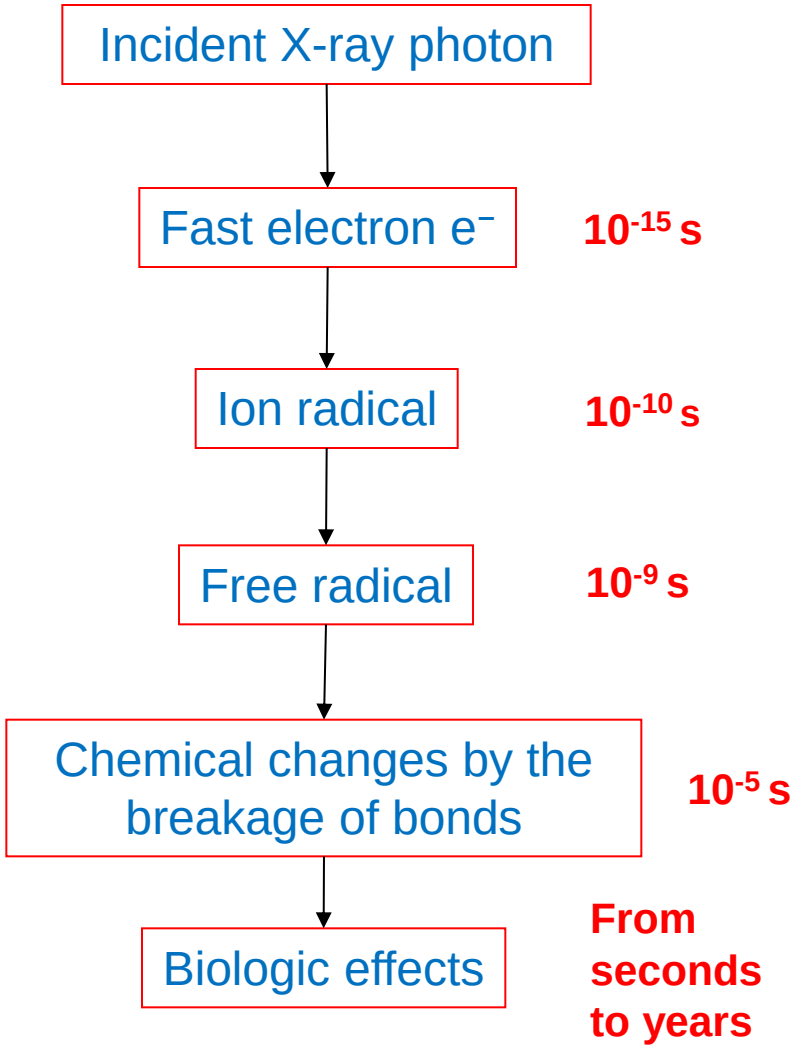
- Radiation interacts with a water molecule (80% cell is water).
- Ionization of the water molecule:

$$H_2O \rightarrow H_2O^+ + e^-$$

- Ion radical forms free radical:

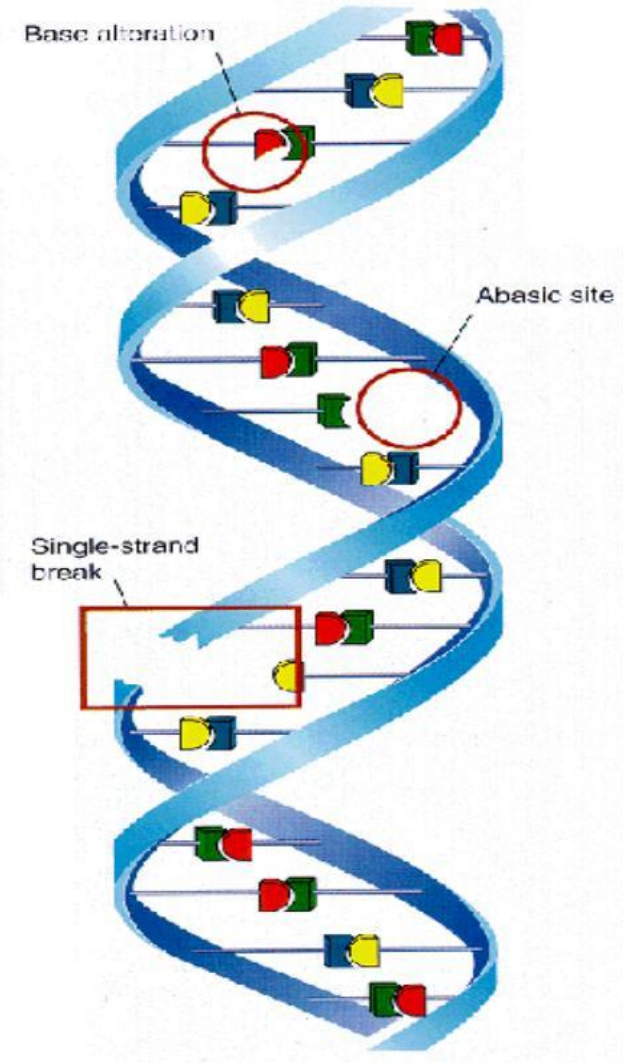
$$H_2O^+ + H_2O \rightarrow H_3O^+ + OH^\bullet$$

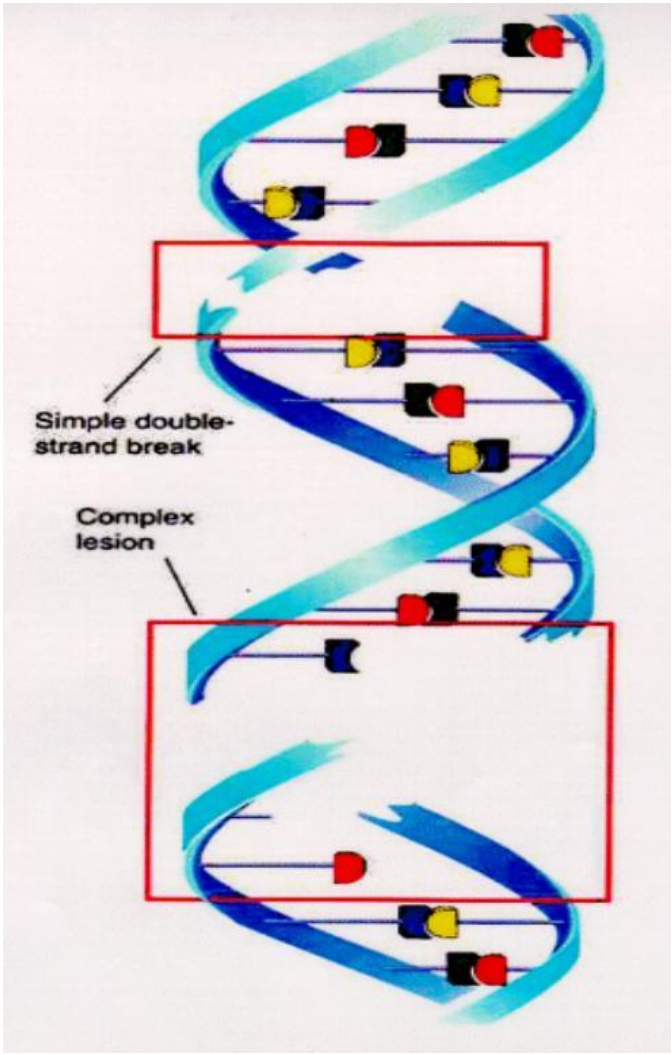
- Hydroxyl radical $OH^\bullet$ diffuses and attacks the DNA molecule.



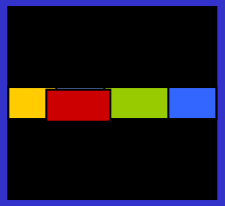
# Radiation Injury to DNA

- Base pair deletion
- Cross-linking injuries
- Single strand break
- Double strand break
- Multiple (complex) lesions



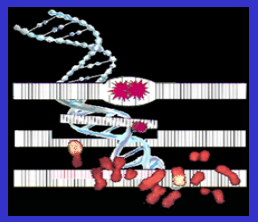



# Effects of DNA Damage



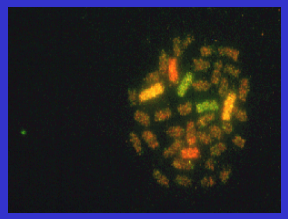
**Gene Expression**

A gene may respond to the radiation by changing its signal to produce protein. This may be protective or damaging.



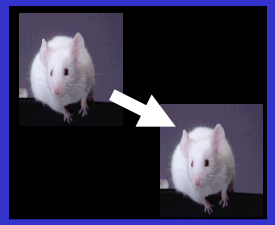
**Gene Mutation**

Sometimes a specific gene is changed so that it is unable to make its corresponding protein properly.



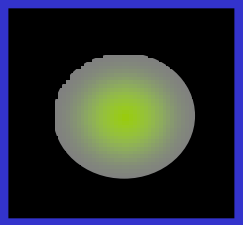
**Chromosome Aberrations**

Sometimes the damage effects the entire chromosome, causing it to break or recombine in an abnormal way. Sometimes parts of two different chromosomes may be combined.



**Genomic Instability**

Sometimes DNA damage produces later changes which may contribute to cancer.



**Cell Killing**

Damaged DNA may trigger apoptosis, or programmed cell death. If only a few cells are affected, this prevents reproduction of damaged DNA and protects the tissue.

**Studies have shown that most radiation-induced DNA damage is normally repaired by the body.**

# Fate of Irradiated Cells

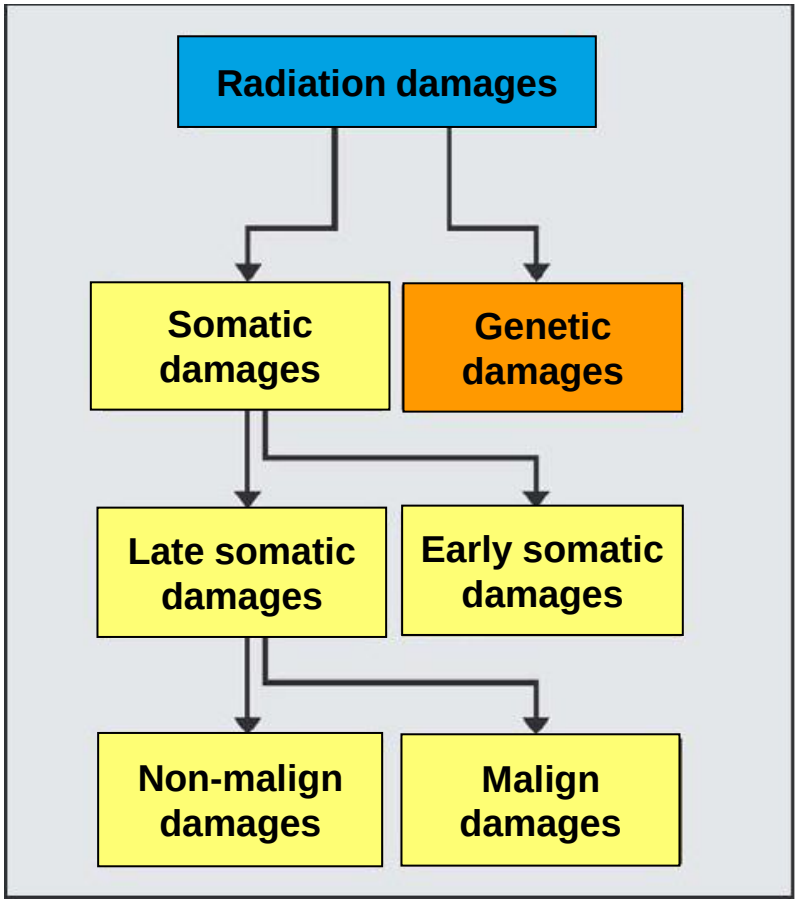
- **No effect**.
- **Division delay**.
- **Apoptosis**: cell death before it can divide.
- **Reproductive failure**: cell death when attempting **mitosis**.
- **Genomic instability**: delayed reproductive failure.
- **Mutation**: cells survives, but contains mutation in genome.
- **Transformation**: mutation leads to carcinogenesis.
- **Bystander effects**: damaged cell induces damage in surrounding ones.
- **Adaptive response**: increased resistance to radiation.

# Types of Radiation Damage, Radiation Effects (1)

- Radiation damage to mammalian cells can be classified into three categories:
  - **Lethal damage (LD),** which is irreversible, irreparable and leads to cell death.
  - **Sublethal damage (SLD),** which can be repaired in hours unless additional sublethal damage is added that eventually leads to LD.
  - **Potentially lethal damage (PLD),** which can be manipulated by repair when cells are allowed to remain in a non-dividing state.

- Effects of radiation may be divided into:
  - **Genetic or hereditary effects**, that are radiation induced mutations to the genes and DNA and can contribute to the birth of defective descendants.
  - **Somatic effects** that harm the exposed individuals during their lifetime such as radiation induced cancers, sterility, opacification of the eye lens. Induced cancers may be **malign or non-malign**.

- Furthermore, based on the timescale between irradiation and biologic effect, one may oppose:
  - Early (deterministic) effects after cell kill.
  - Late effects like induction of cancer.



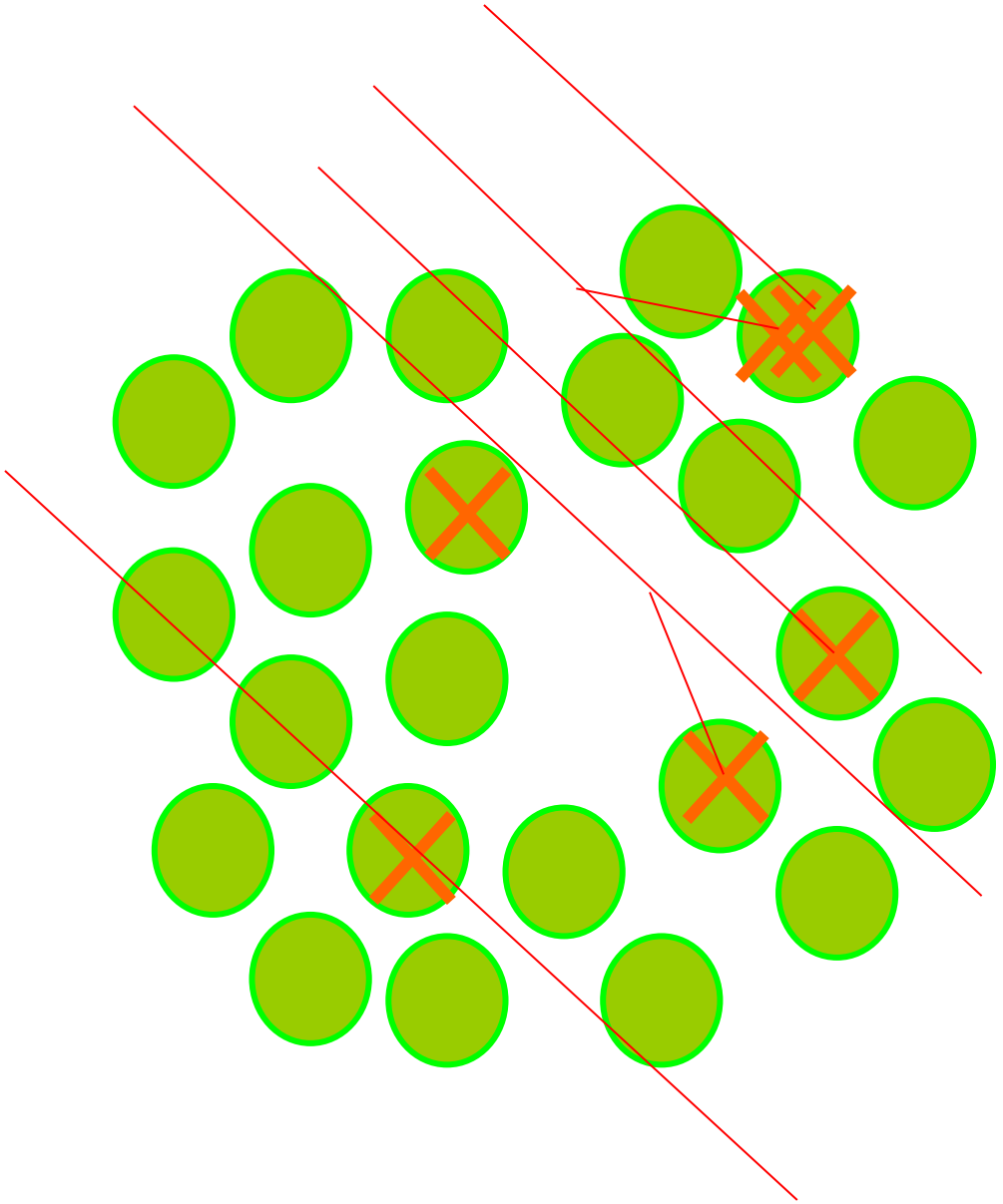
# Types of Radiation Damage, Radiation Effects (2)

- The harmful effects of radiation may be classified into:
  - ***Stochastic***: the probability of the effect increases with dose. There is no threshold, but it may be assumed that there is always a small probability the event occurring even at small doses.
  - ***Deterministic***: there is a threshold for the effect, above which the severity increases with dose.

- Related to the response of an organ or tissue to radiation:
  - ***Acute*** (after high doses): cells are killed in large quantities. Tissues and organs are damaged. Rapid body response.
  - ***Late*** (after low doses): cells are damaged or changed. Slow body response.

# Stochastic Effects (1)

- Due to cell changes (DNA) and proliferation towards a malignant disease.
- Severity (*i.e.* cancer) independent of the dose.
- No dose threshold (they are presumed to occur at any dose however small).
- Probability of effect increases with dose.
- At low doses, damage to a cell is a random effect - either there is energy deposition or not.



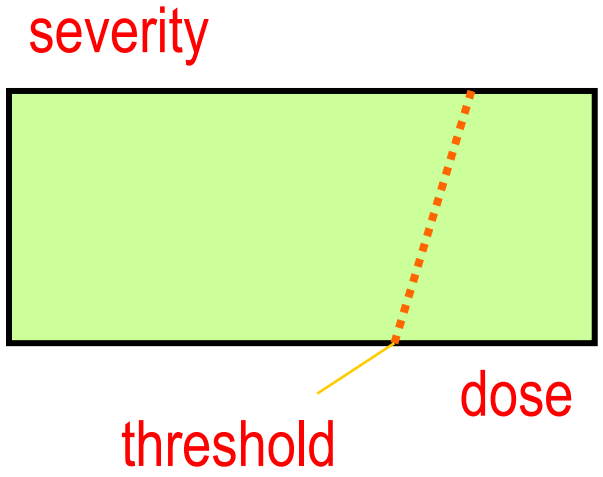
# Stochastic Effects (2)

- Orders of magnitude:
  - 1cm$^3$ of tissue = $10^9$ cells.
  - 1 mGy --> 1 in 1000 or $10^6$ cells hit.
  - 999 of 1000 lesions are repaired - leaving $10^3$ cells damaged.
  - 999 of 1000 damaged cells die (not a major problem as millions of cells die every day in every person).
  - 1 cell may live with damage (could be mutated).
- Cancer induction:
  - The most important stochastic effect for radiation safety considerations
  - Is a multistage process - typically several steps: each of them requires an event…
  - Is a complicated process involving cells, communication between cells and the immune system...

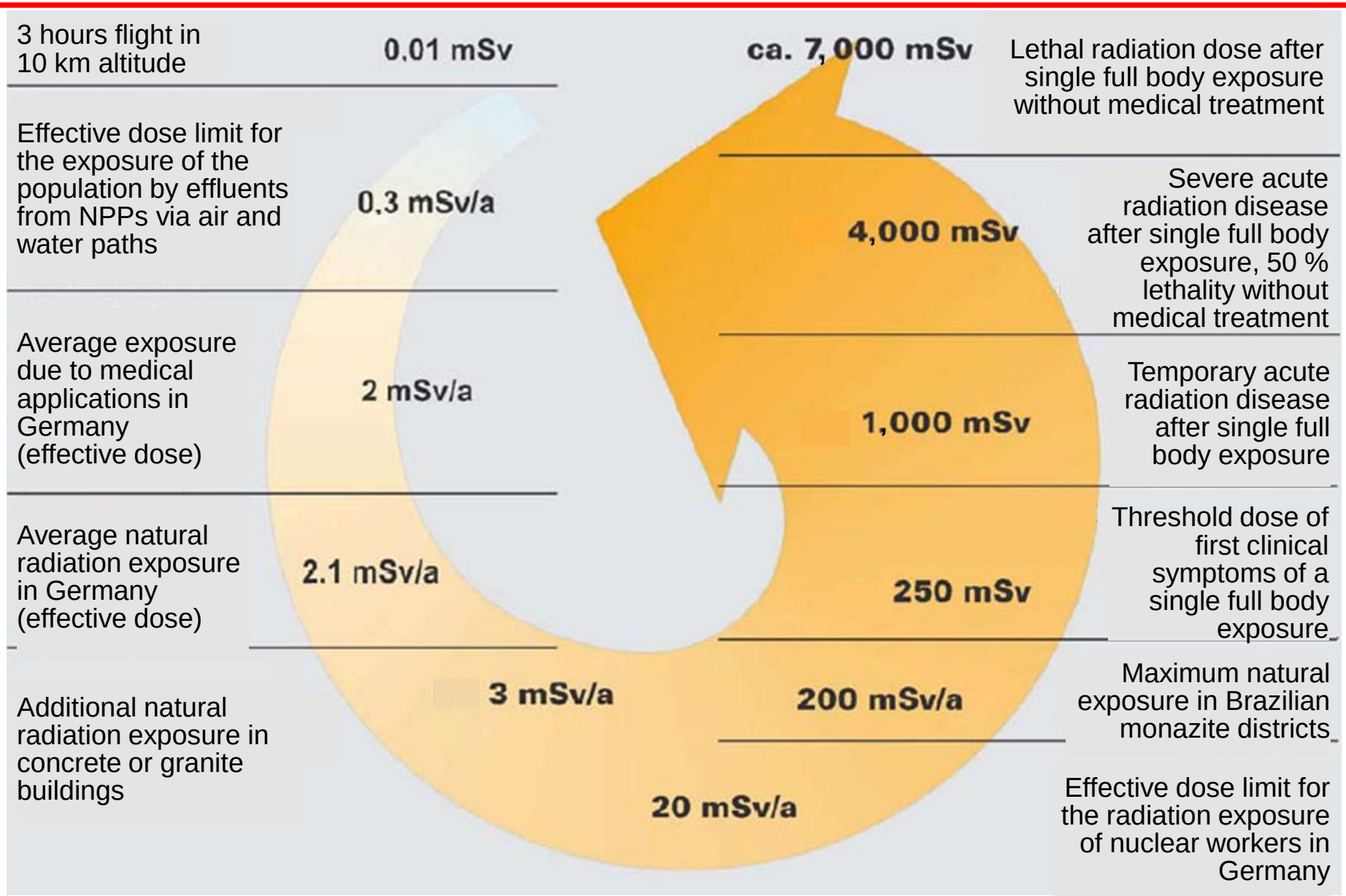
# Deterministic Effects

- Due to cell killing.
- Have a dose threshold.
- Specific to particular tissues.
- Severity of harm is dose dependent.
- Examples:
  - Skin breakdown
  - Cataract of the lens of the eye
  - Sterility
  - Kidney failure
  - Acute radiation syndrome (whole body)

- Thresholds for deterministic effects:
  - Cataracts of eye lens: 2-10 Gy
  - Permanent sterility
    - males 3.5-6 Gy
    - females 2.5-6 Gy
  - Temporary sterility
    - males 0.15 Gy
    - females 0.6 Gy



# Radiation effects: Dose Ranges



# Repair of Radiation Damage (1)

- Cellular mechanisms are in place which can repair most if not all types of radiation injury to the DNA.
- Repair is a time sensitive process:
  - Repair of DNA injury of all types is essentially completed 6 hours post irradiation.
  - External factors affecting cellular metabolic rate may delay or accelerate it.
  - Foundation of modern radiotherapy.
- Repair is a cell cycle dependent process:
  - Different phases have different repair capabilities (in increasing order):
    - Mitosis has the least repair capability.
    - $G_2$ .
    - $G_1/G_0$.
    - S phase has the most repair capability.
- Repair is **dose rate** dependent, **dose** dependent **and radiation type dependent**.

# Repair of Radiation Damage (2): Principal Steps

Altered base

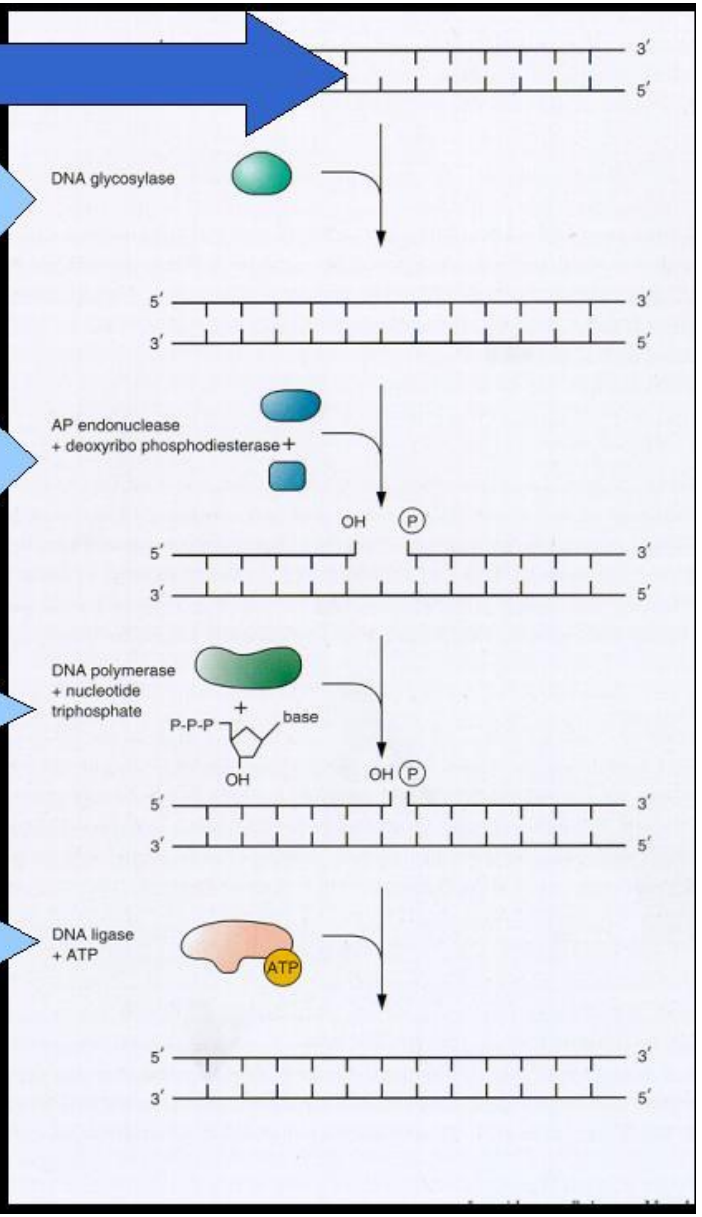
Enzyme *Glycosylases* recognizes lesion and releases damaged base

*AP-endunuclease* makes incision and releases remaining sugar

*DNA-polymerase* fills resulting gap but nick remains

*DNA ligase* seals the nick
Repair completed

DNA has been repaired with no loss of genetic information

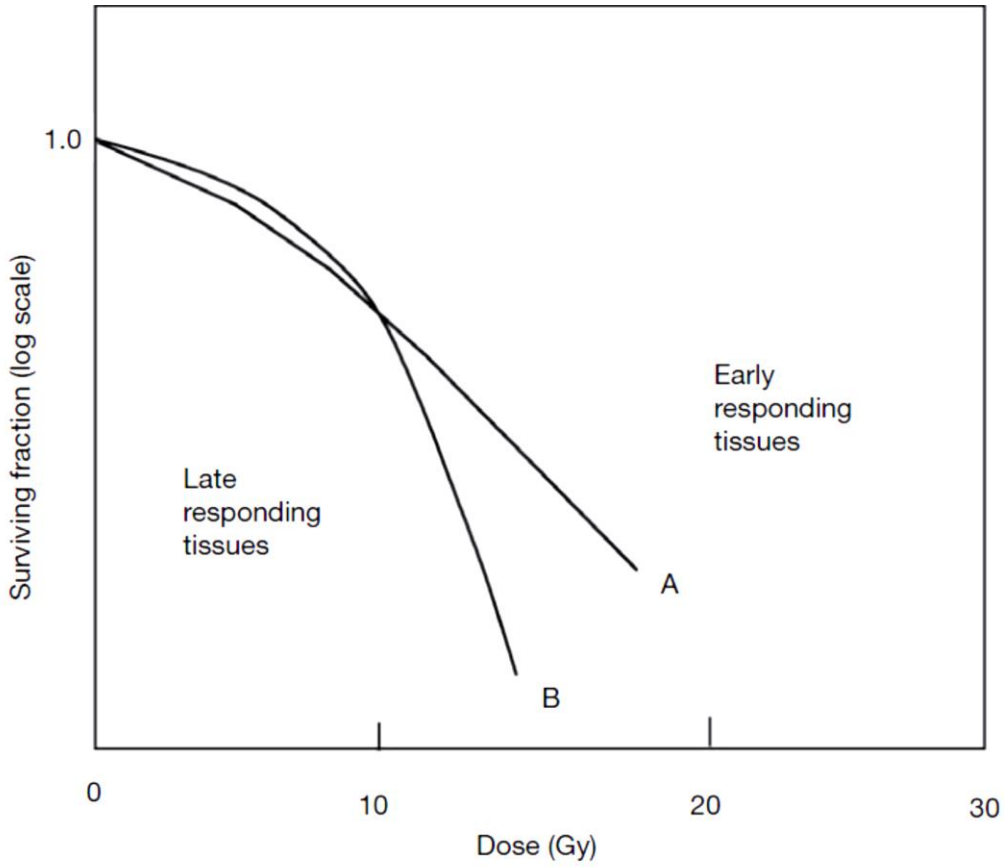


# Cellular Sensitivity to Radiation

- Not all cells are equally sensitive to radiation.
- Those cells actively reproducing are more sensitive:
  - DNA is exposed to damage when the cell is dividing.
  - Non reproducing cells are more resistant to radiation.
- Classify cells according to their rate of reproduction:
  - Constantly reproducing: e.g. Lymphocytes.
  - Moderate regeneration: e.g. Gastrointestinal lining cells.
  - Slowest to regenerate: e.g. Muscle and Nerve cells.
- Fast reproducing cells well oxygenated are the most susceptible:
  - Tumour at the periphery. Irradiation causes rapid shrinkage. Fractional irradiation.
  - Foetus: the sensitivity of the developing embryo is very large.

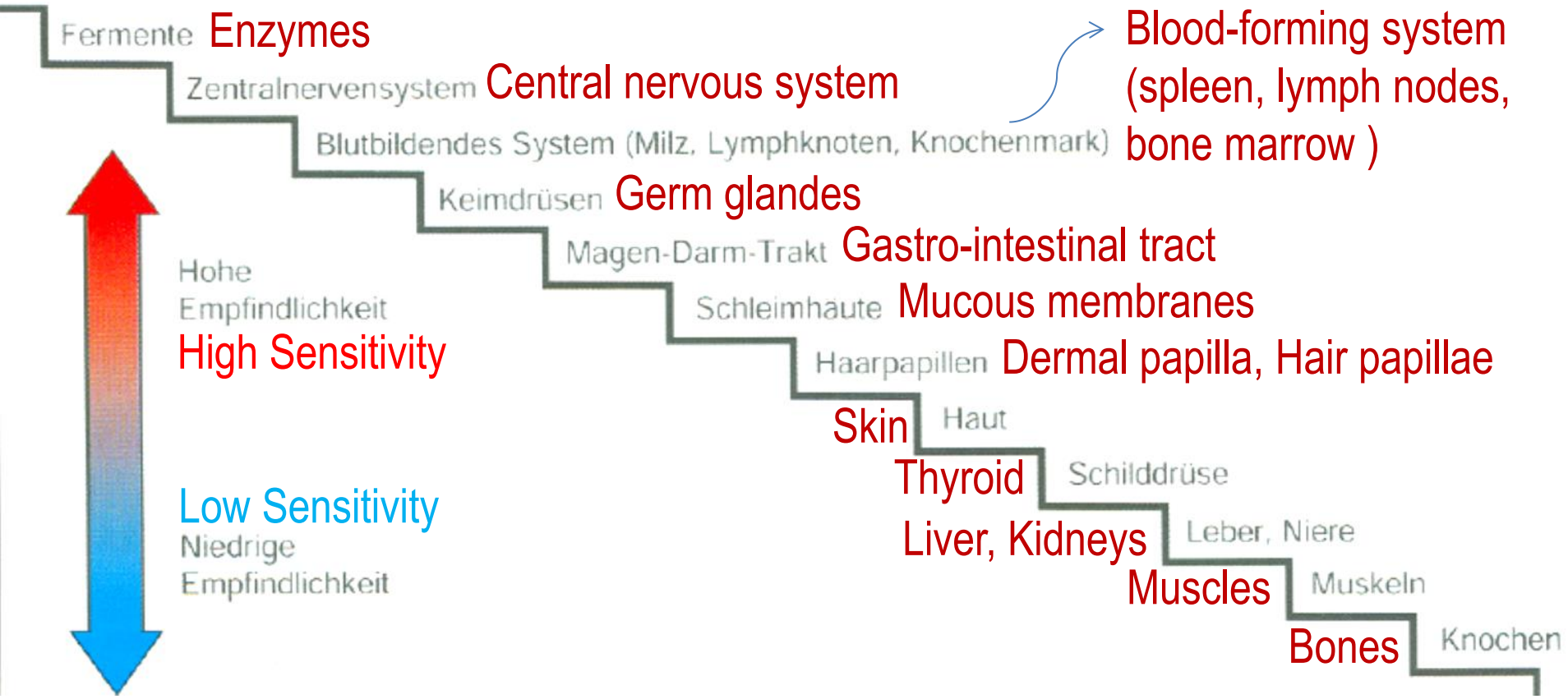
# Tissue and Organ Sensitivity to Radiation (1)

- Not all tissues and organs respond in the same manner to radiation.
- Two main factors:
  - Inherent sensitivity of the individual cells.
  - Kinetics of the cell population.
- Sensitivity:
  - Early responsive: skin, mucosa, intestinal epithelium.
  - Late responsive: spinal cord.




*Hypothetical target cell survival curves for (curve A) early responding tissues and (curve B) late responding tissues.*

# Tissue and Organ Sensitivity to Radiation (2)

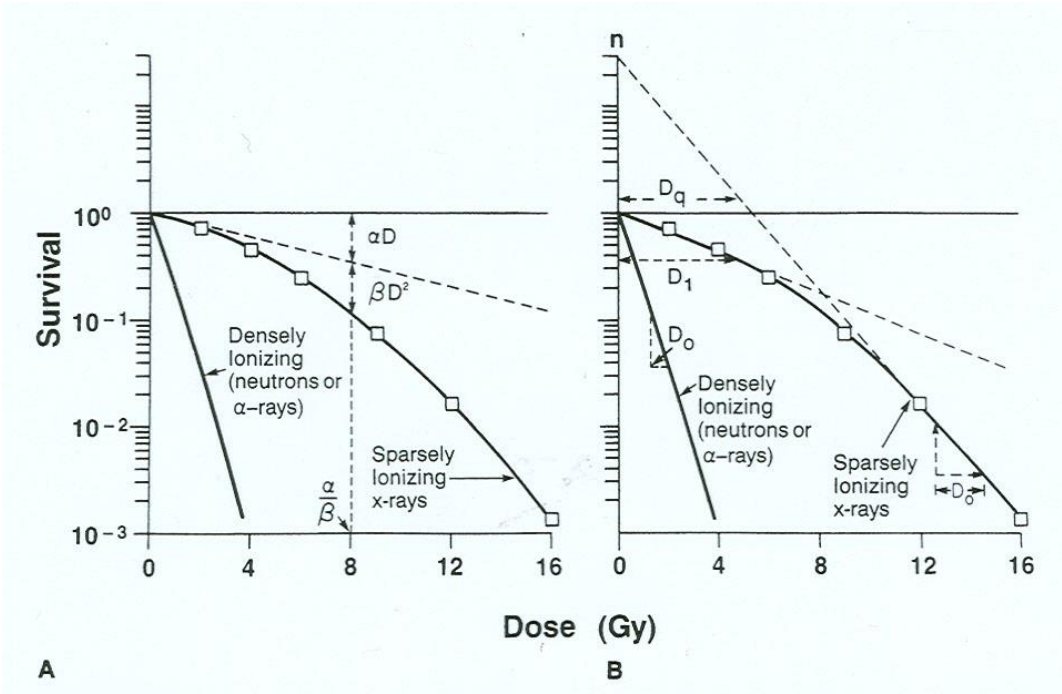


# Measures of Biological Effects of Radiation: Cell Survival Curves

- Describe the relationship between the surviving fraction of cells and the absorbed dose.
- The surviving fraction is determined in vitro or in vivo.
- The shape is influenced by the type of radiation:
  - High LET: exponential function.
  - Low LET: two slopes separated by a "shoulder".
- Mathematical models are based on the random nature of energy deposition by radiation:
  - (A) Linear Quadratic Model:

$$S(D) = e^{-\alpha D - \beta D^2}$$

  - (B) Initial and final slope plus shoulder.

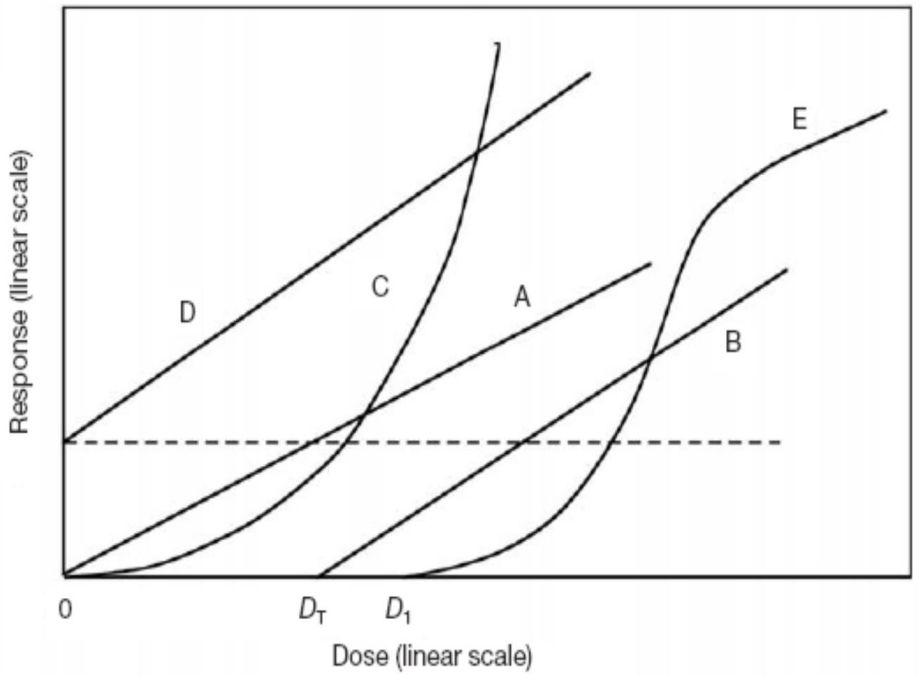



Shape of survival curve for mammalian cells exposed to radiation. The fraction of cells surviving is plotted on a logarithmic scale against dose on a linear scale. For α-particles or low-energy neutrons (said to be densely ionizing) the dose–response curve is a straight line from the origin (*i.e.*, survival is an exponential function of dose). The survival curve can be described by just one parameter, the slope. For x- or γ-rays (said to be sparsely ionizing), the dose–response curve has an initial linear slope, followed by a shoulder; at higher doses the curve tends to become straight again. **A:** The experimental data are fitted to a linear-quadratic function. There are two components of cell killing: one is proportional to dose (αD), the other is proportional to the square of the dose ($\beta D_2$). The dose at which the linear and quadratic components are equal is the ratio α/β. The linear-quadratic curve bends continuously but is a good fit to experimental data for the first few decades of survival. **B:** The curve is described by the initial slope ($D_1$), the final slope ($D_0$), and a parameter that represents the width of the shoulder, either n or $D_q$.

***Source Hall (2000)***

# Measures of Biological Effects of Radiation: Dose Response Curves

- They are a plot of a specific **biological effect** against the dose given.
- Three types are known:
  - Linear.
  - Linear quadratic.
  - Sigmoid.
  - They may or may not have a threshold.
- **Threshold**: largest dose for a particular effect below which no effect will be observed.



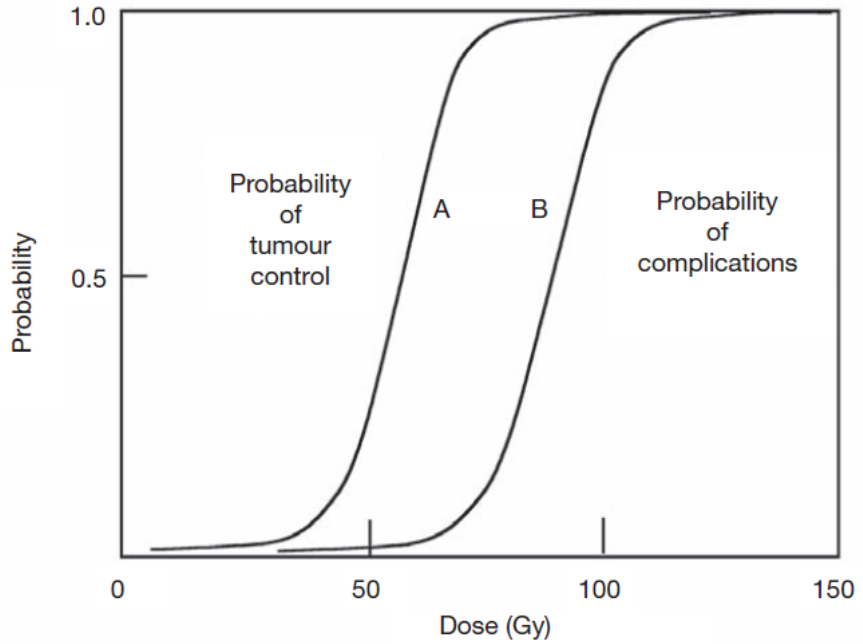

*Typical dose response curves for cancer induction (curves A, B, C and D) and for tissue response (curve E). Curve A represents a linear relationship with no threshold; curve B represents a linear relationship with threshold $D_T$; curve C represents a linear quadratic relationship with no threshold (assumed for stochastic effects, for example carcinogenesis); curve D represents a linear relationship with no threshold (the area below the dashed line represents the natural incidence of the effect, for example carcinogenesis); and curve E represents a sigmoid relationship with threshold $D_1$, as is common for deterministic effects in tissues, for example tumour control or treatment morbidity. The curves are diagrammatic only and are separated for clarity (in practice the dashed line would be lower).*

# Measurement of Radiation Damage in Tissue

- The effects of radiation on tissue as a function of dose are measured with assays and the results are given in the form of cell survival curves or dose response curves. Three categories of tissue assay are used:
  - **Clonogenic assays** measure the reproductive integrity of the clonogenic stem cells in tissue and result in cell survival curves.
  - **Functional assays** measure functional end points of various tissues and produce dose response curves with a graded reaction scale.
  - **Lethality assays** quantify the number of animal deaths after irradiation of the whole animal or a specific organ. The experiments usually result in deduced values of the parameter LD50.

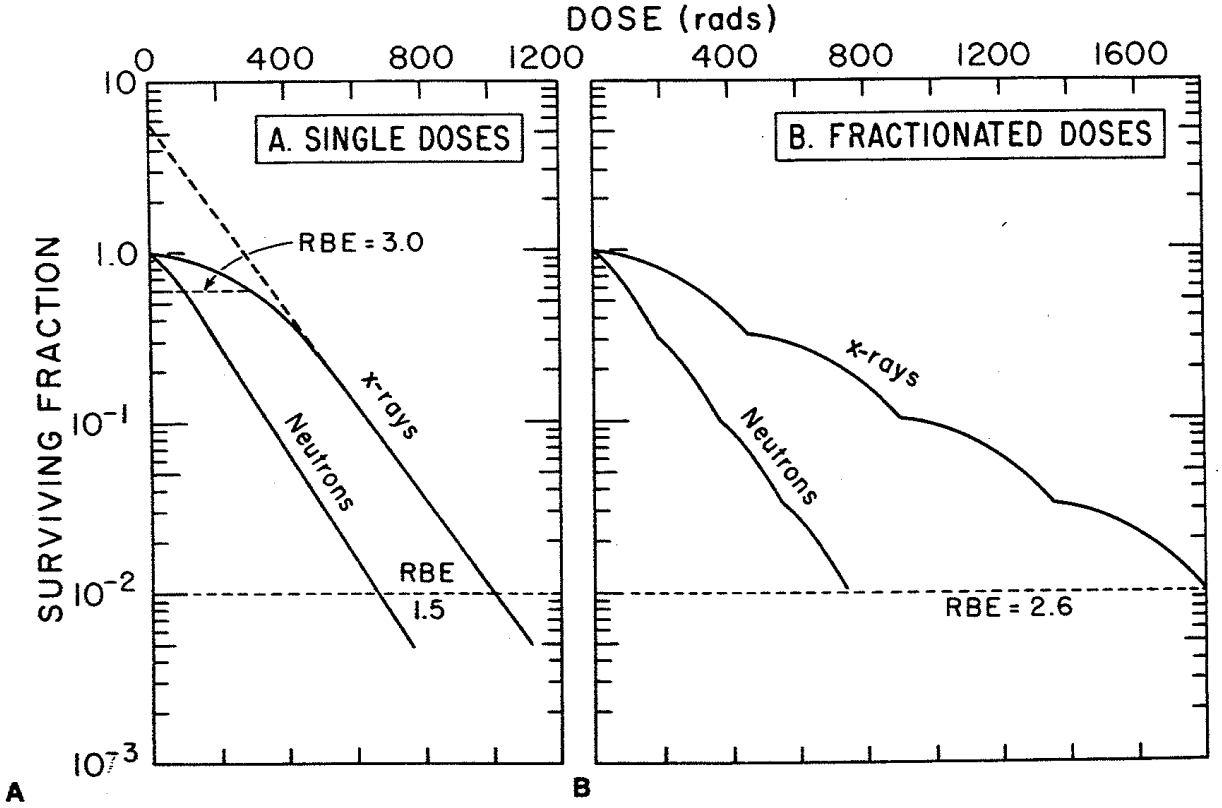
# Therapeutic Ratio

- The aim of radiotherapy is to deliver enough radiation to the tumour to destroy it without irradiating normal tissue to a dose that will lead to serious complications.
- Two sigmoid curves , one for the tumour control probability (TCP) and the other for the normal tissue complication probability (NTCP) can be plotted.
- The optimum choice of radiation dose delivery technique in the treatment of a given tumour is such that it maximizes the TCP (>0.5) and simultaneously minimizes the NTCP (≤0.05).
- The therapeutic ratio generally refers to the ratio of the TCP and NTCP at a specified level of response (typically 0.05) for normal tissue.




*The principle of therapeutic ratio. Curve A represents the TCP, curve B the probability of complications. The total clinical dose is usually delivered in 2 Gy fractions.*

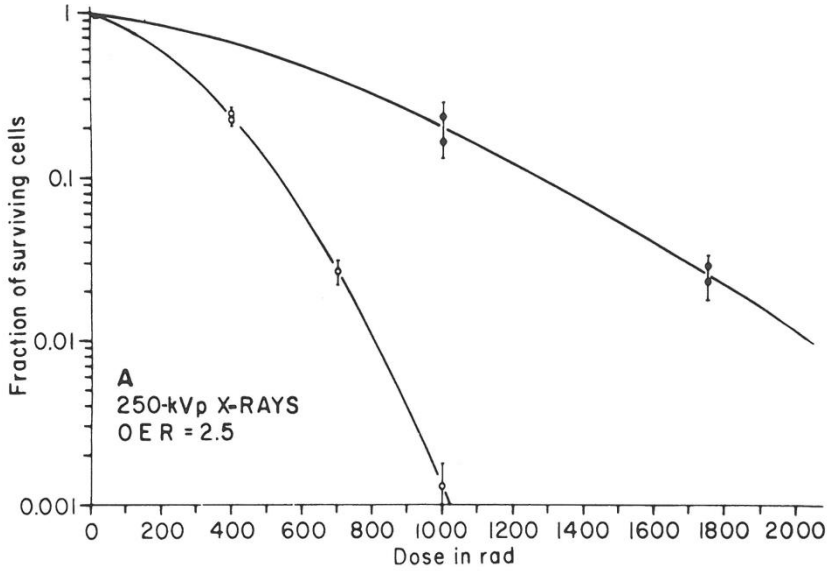
# Dose Rate and Fractionation



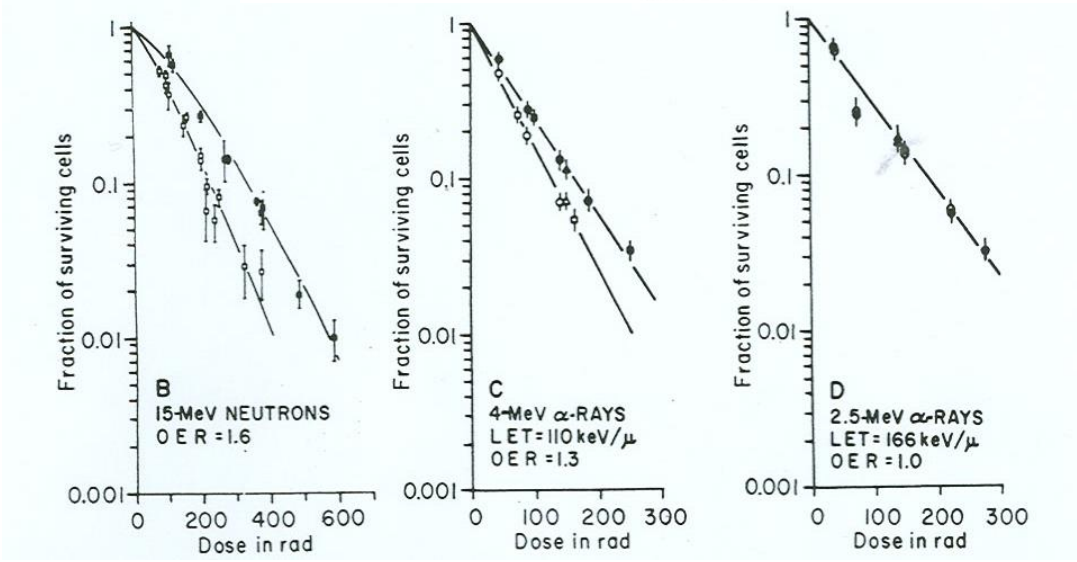

Typical survival curves for mammalian cells exposed to x-rays and fast neutrons. **A:** Single doses. The survival curve for x-rays has a large initial shoulder; for fast neutrons the initial shoulder is smaller and the final slope steeper. Because the survival curves have different shapes, the relative biologic effectiveness (RBE) does not have a unique value but varies with dose, getting larger as the size of the dose is reduced. **B:** Fractionated doses. The effect of giving doses of x-rays or fast neutrons in four equal fractions to produce the same level of survival as in **A**. The shoulder of the survival curves is reexpressed after each dose fraction; the fact that the shoulder is larger for x-rays than for neutrons results in an enlarged RBE for fractionated treatments.

# The Oxygen Effect (1)

- The presence or absence of molecular oxygen influences the biological effect of ionizing radiation:
  - The larger the content of $O_2$ above anoxia, the larger the biological effect of radiation.
  - Important for low LET radiation.
  - Effect decreases as LET increases.
  - The effect reaches saturation.
- Oxygen Enhancement Ratio (OER):
  - Important in Radiotherapy



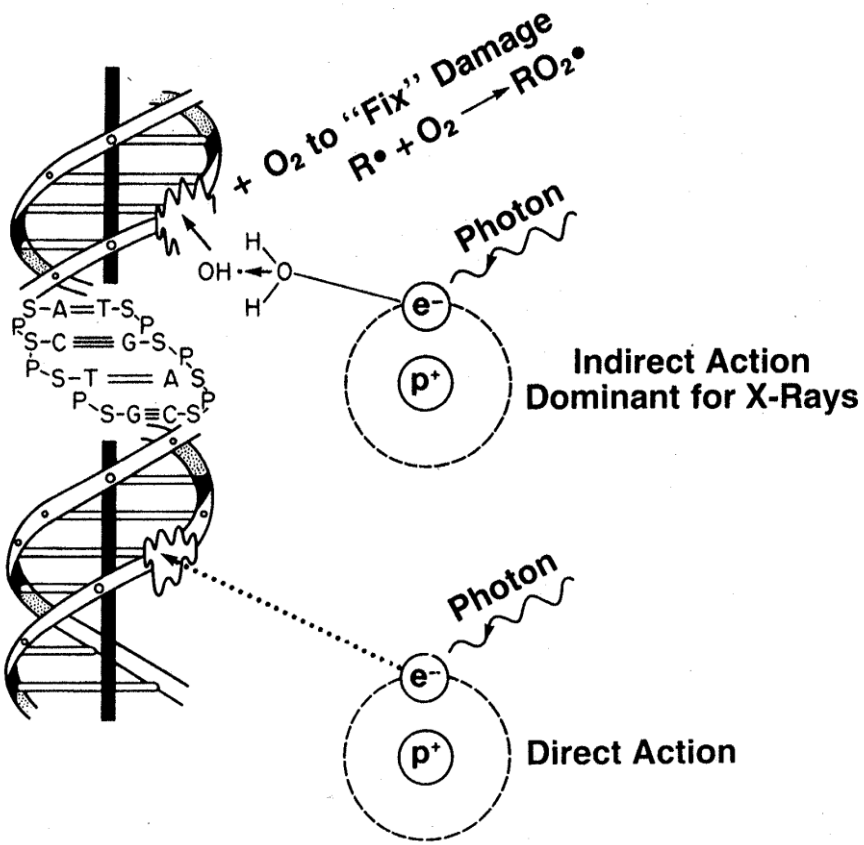

*Source Hall (2000)*



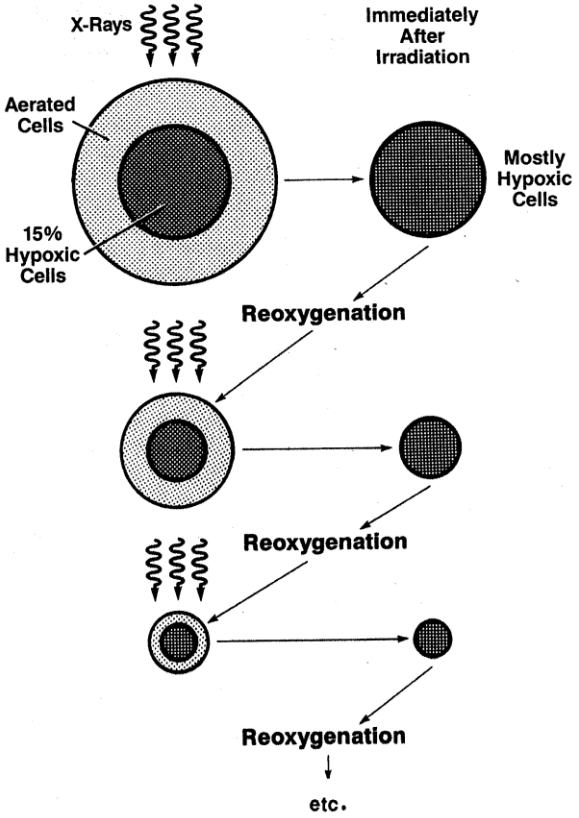

Survival curves for cultured cells of human origin determined for four different types of radiation. *Open circles* refer to aerated and *closed circles* to hypoxic conditions. **A:** For 250-kVp x-rays, oxygen enhancement ratio (OER) = 2.5. **B:** For 15-MeV $d^+$ ? T neutrons, OER = 1.6. **C:** For 4-MeV α-particles, linear energy transfer = 110 keV/μm, OER = 1.3. **D:** For 2.5-MeV α-particles, linear energy transfer = 166 keV/μm, OER = 1. (Adapted from Broerse JJ, Barendsen GW: Int J Radiat Biol 13:559, 1967; and Barendsen GW, Koot CJ, van Kersen GR, Bewley DK, Field SB, Parnell CJ: Int J Radiat Biol 10:317–327, 1966, with permission.)

$$\text{OER} = \frac{\text{Dose to produce a given effect without oxygen}}{\text{Dose to produce a given effect with oxygen}}$$

# The Oxygen Effect (2)




The oxygen fixation hypothesis. About two thirds of the biologic damage produced by x-rays is by indirect action, mediated by free radicals. The damage produced by free radicals in DNA can be repaired under hypoxia but may be "fixed" (made permanent and irreparable) if molecular oxygen is available.



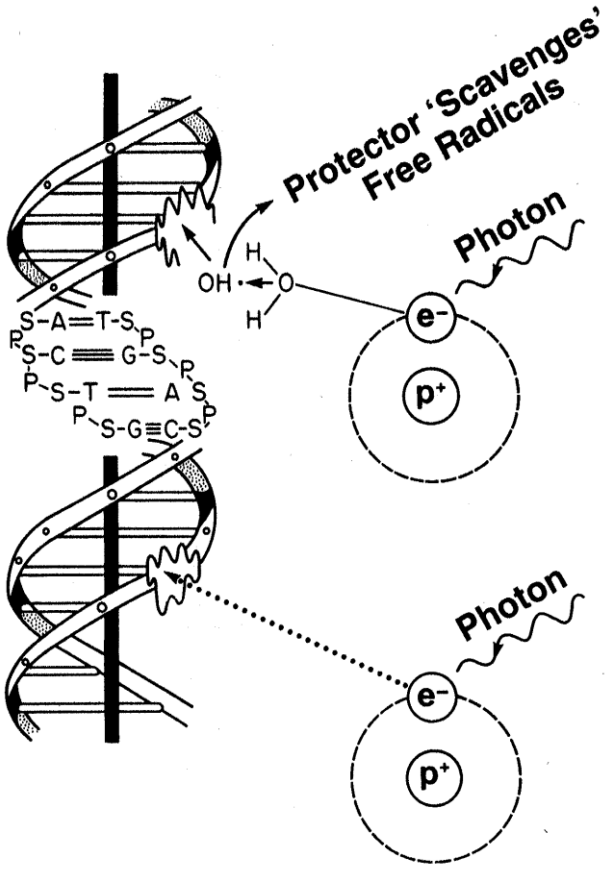

The process of reoxygenation. Tumors contain a mixture of aerated and hypoxic cells. A dose of x-rays kills a greater proportion of aerated than hypoxic cells, because they are more radiosensitive. Immediately after irradiation, most cells in the tumor are hypoxic. But the preirradiation pattern tends to return because of reoxygenation. If the radiation is given in a series of fractions separated in time sufficiently for reoxygenation to occur, the presence of hypoxic cells does not greatly influence the response of the tumor.

# Radioprotectors and Radiosensitizers

- Chemical agents that may alter the cell response to ionizing radiation either enhancing or reducing the cell response.
- Radioprotectors reduce cell response:
  - Influence the indirect effects of radiation by scavenging the production of free radicals.

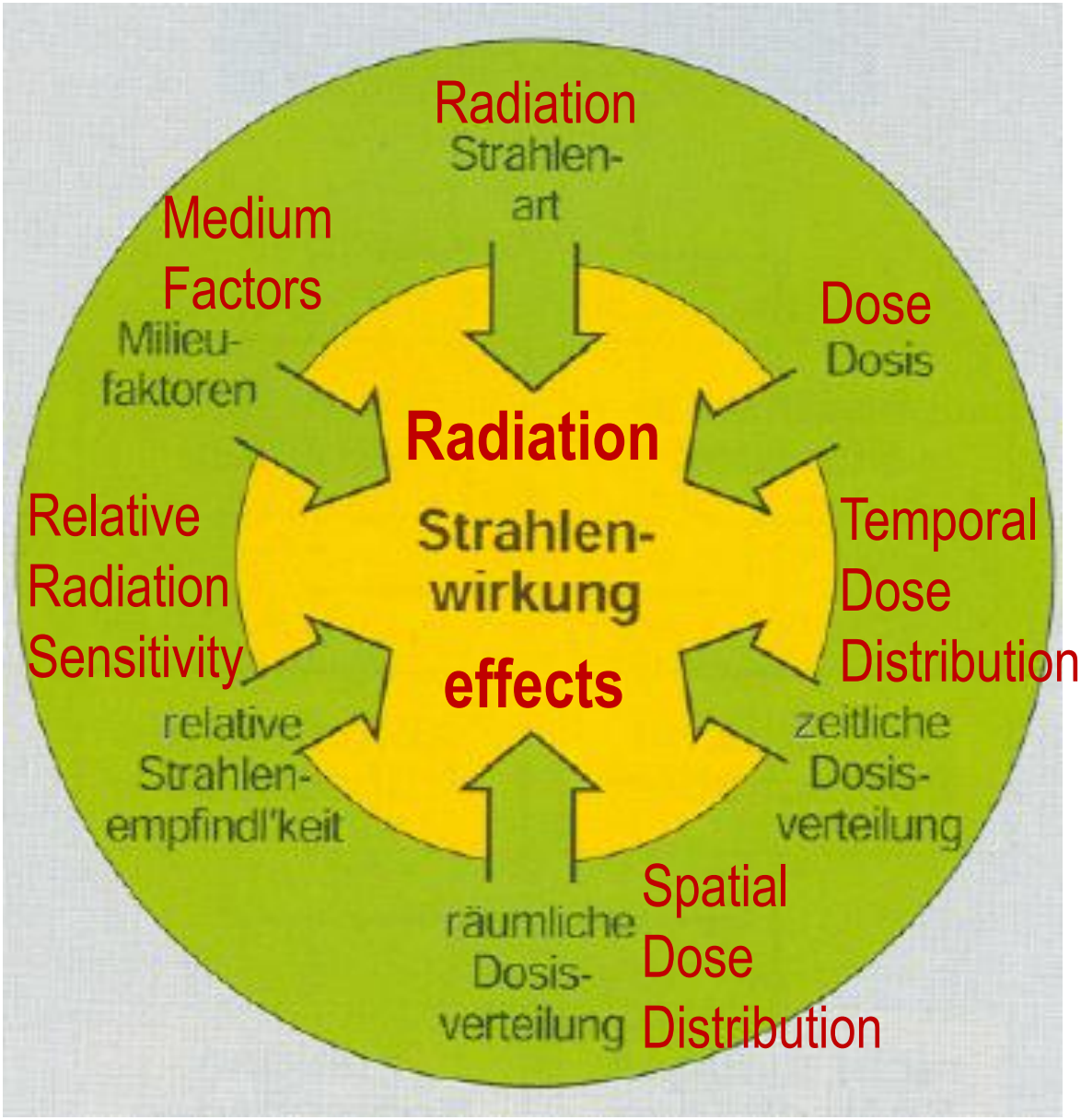
$$\text{Dose Modifying Factor (DMF)} = \frac{\text{Dose to Produce an effect with Radioprotector}}{\text{Dose to Produce an effect without Radioprotector}}$$

- Radiosensitizers enhance the cell response:
  - Promote direct and indirect effects.
  - Inhibit DNA repair or act like oxygen.
  - Boron Neutron Capture Therapy ($\alpha$-particles).




Radioprotectors containing a sulfhydryl group exert their effect by scavenging free radicals and by reducing free-radical damage to DNA. They are most effective for low linear energy transfer radiations, becoming progressively less effective with increasing linear energy transfer because the amount of local damage is so great.

# The biological effects of radiation depend on many factors



# Literature / WWW-references


- E.J. Hall and A.J. Giaccia, "Radiobiology for the Radiologist", Lippincott Williams & Wilkins (6th edition, 2006).
- A.H.W. Nias, "An Introduction to Radiobiology", John Wiley & Sons (Edition 1990).
- N. Suntharalingam et *al.*, "Basic Radiobiology", http://www-naweb.iaea.org/nahu/dmrp/pdf_files/Chapter14.pdf
- International Commission on Radiological Protection (ICRP): http://www.icrp.org/
- International Commission on Radiation Units & Measurements (ICRU): http://www.icru.org/