Radiobiology Overview

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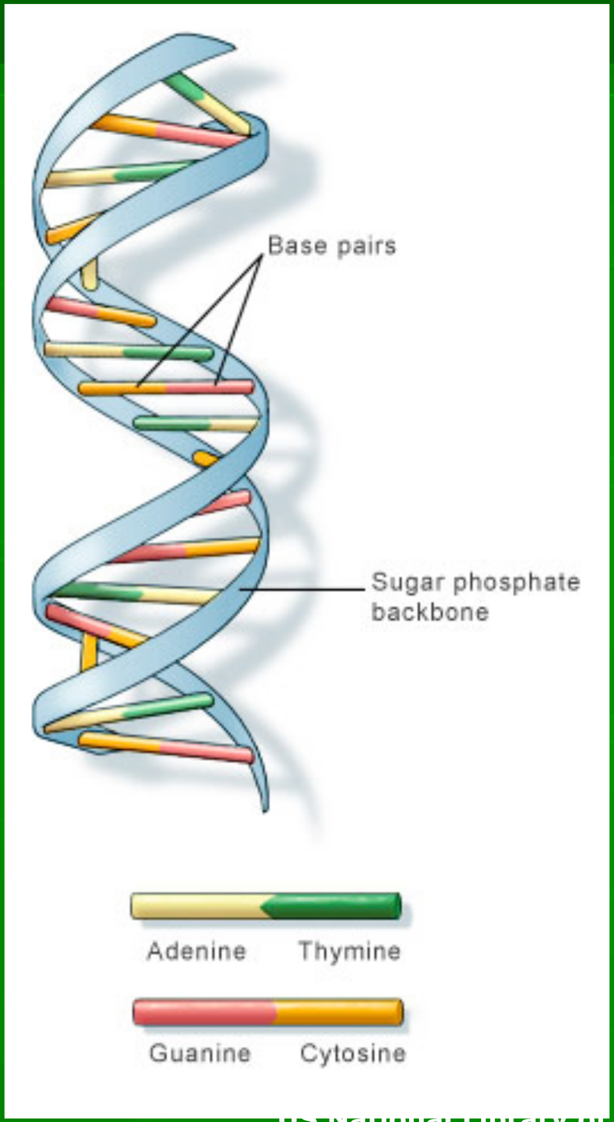
Objectives

- DNA Structure & Strand Breaks
- Ionizing Radiation & Cell Killing
- LET & RBE; Radiation Absorption
- Cell Survival
- Stochastic & Deterministic Effects
- Radiation Carcinogenesis & Latency
- 4 R's of Radiobiology
- Fractionation

DNA Structure

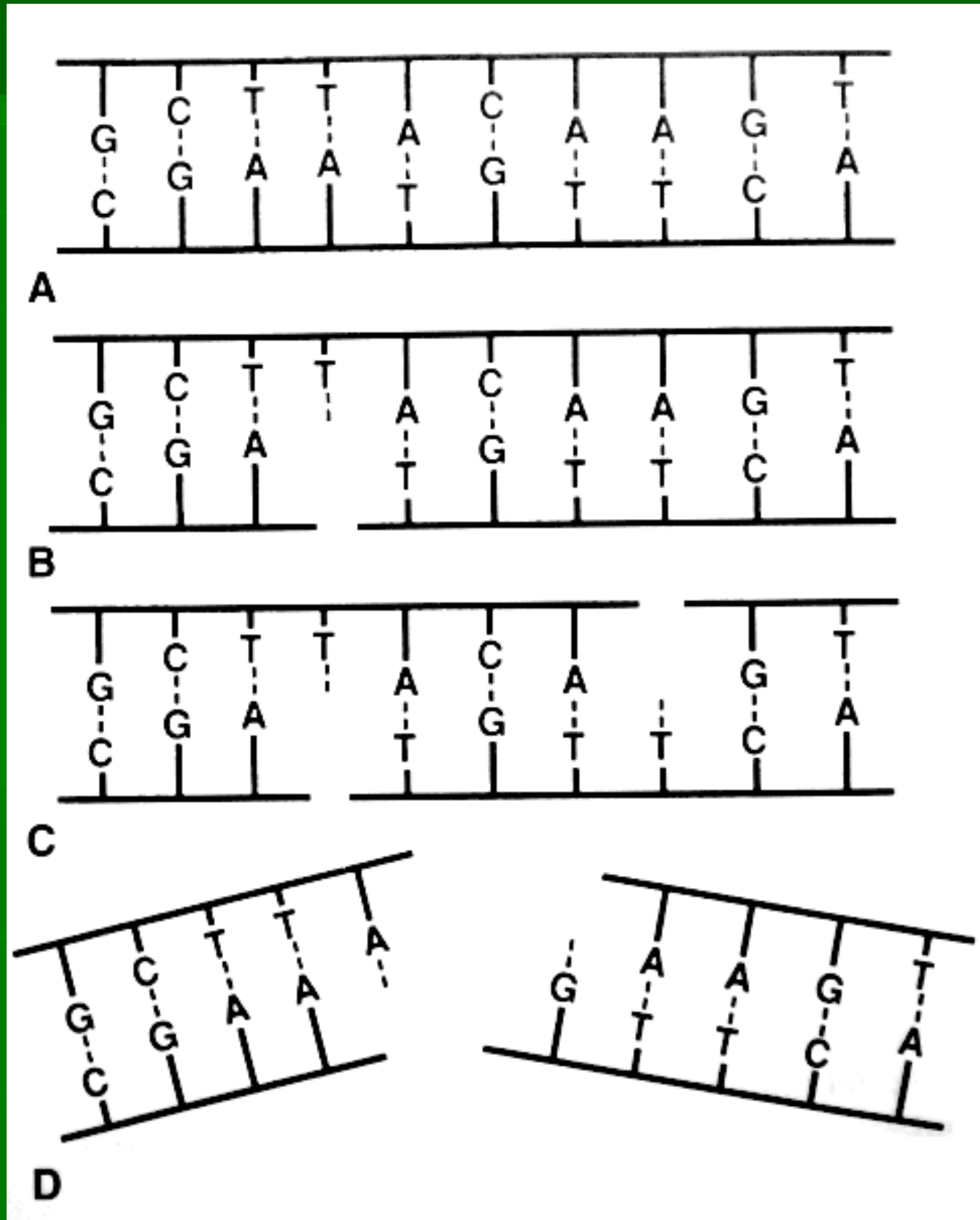
- DNA is a large molecule with a double-helix structure
  - Sugar phosphate backbone with nitrogenous bases (ACTG)
    - Adenine – Thymine
    - Cytosine – Guanine



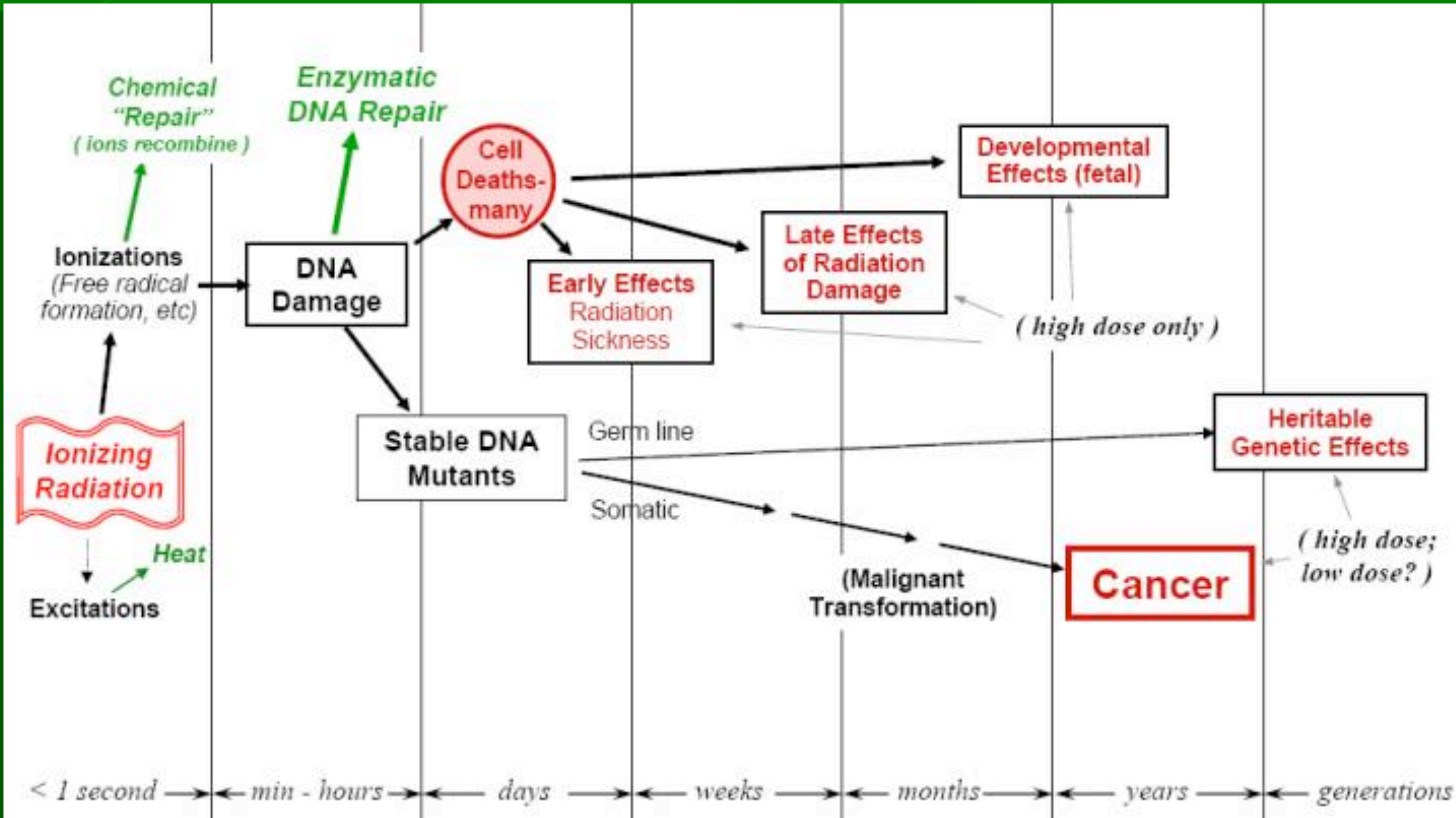
US National Library of Medicine

DNA Strand Breaks

- A Normal
- B SSB
  - readily repaired
- C SSB
  - readily repaired (if well separated)
- D DSB
  - 0.04x SSBs



Classic Radiation Injury Paradigm



Ionizing Radiation – Targeting DNA

- Directly Ionizing
  - Disrupt the atomic structure, producing chemical and biologic changes
    - α particles, protons
    - electrons, β^-, β^+
- Indirectly Ionizing
  - Give up energy to charged particles, which are able to produce damage.
    - Neutrons
    - EM Radiation

Cell Killing

- Cell death defined for:
  - Differentiated cells that do not proliferate (nerve, muscle or secretory)
    - Loss of a specific function
  - Proliferating cells (stem cells in hematopoietic system)
    - Loss of reproductive integrity
- Dose needed to destroy cell function:
  - Differentiated: 100 Gy
  - Proliferating: < 2 Gy

LET & RBE

- Linear Energy Transfer (LET)
  - Describes the expected value o f local energy deposition per unit path length
- Relative Biological Effect (RBE)
  - Relates the dose required to cause a specific effect from a particula r type of radiation, to that of a reference dose.

Linear Energy Transfer (LET)

- Different ionizing particles have different rates of energy deposition.
- Why do we care about the rate?
- Biological effect is hard to measure and quantify either by experiment or by simulations.
- But energy is easy to measure and quantify.
- Can we come up with a relation between energy and biology effect?

Linear Energy Transfer (LET)

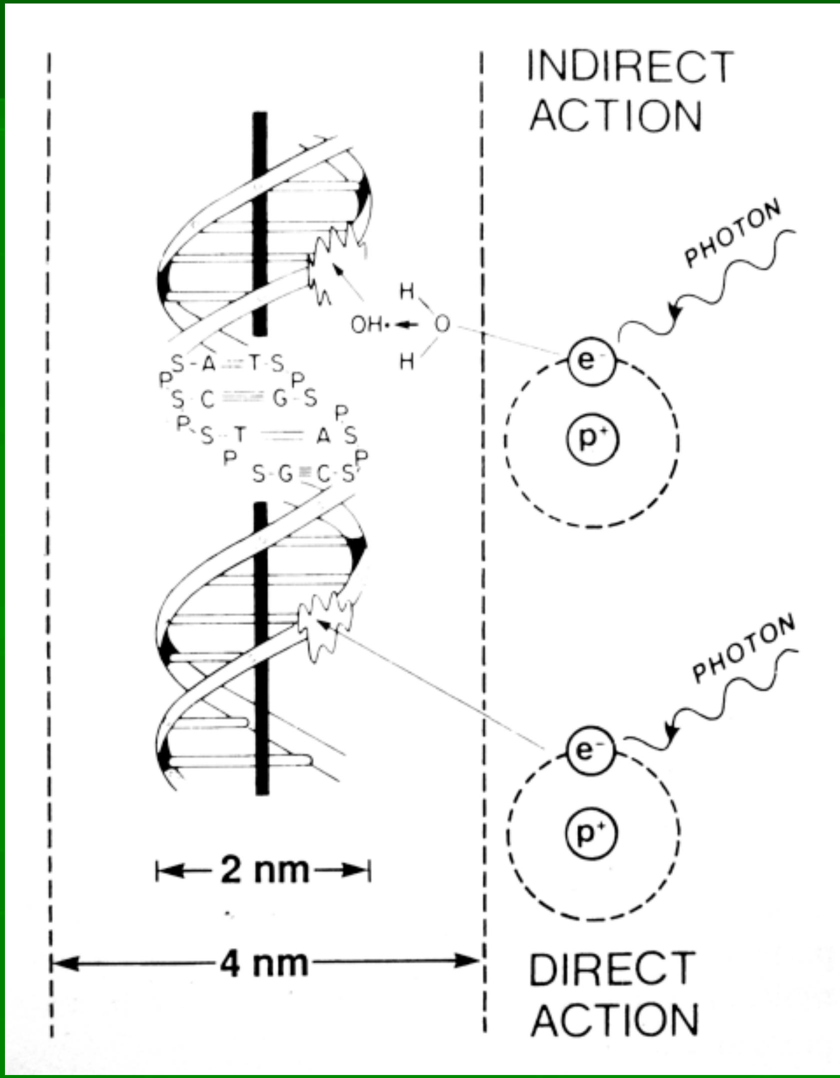
- The rate at which energy is deposited as a charged particle travels through matter
- What would be a good unit for LET?
  - keV / micron
- Lower LET radiation
  - X-rays and γ-rays
- High LET radiation
  - α particles and neutrons

Relative Biological Effect (RBE)

- Equal doses of different types of radiation do not produce equal biologic effects.
- The key to the difference lies in the pattern of energy deposition.
  - X-rays vs neutrons
- Relative to what?
  - To a dose of 250 keV x-rays which produce the same biological response

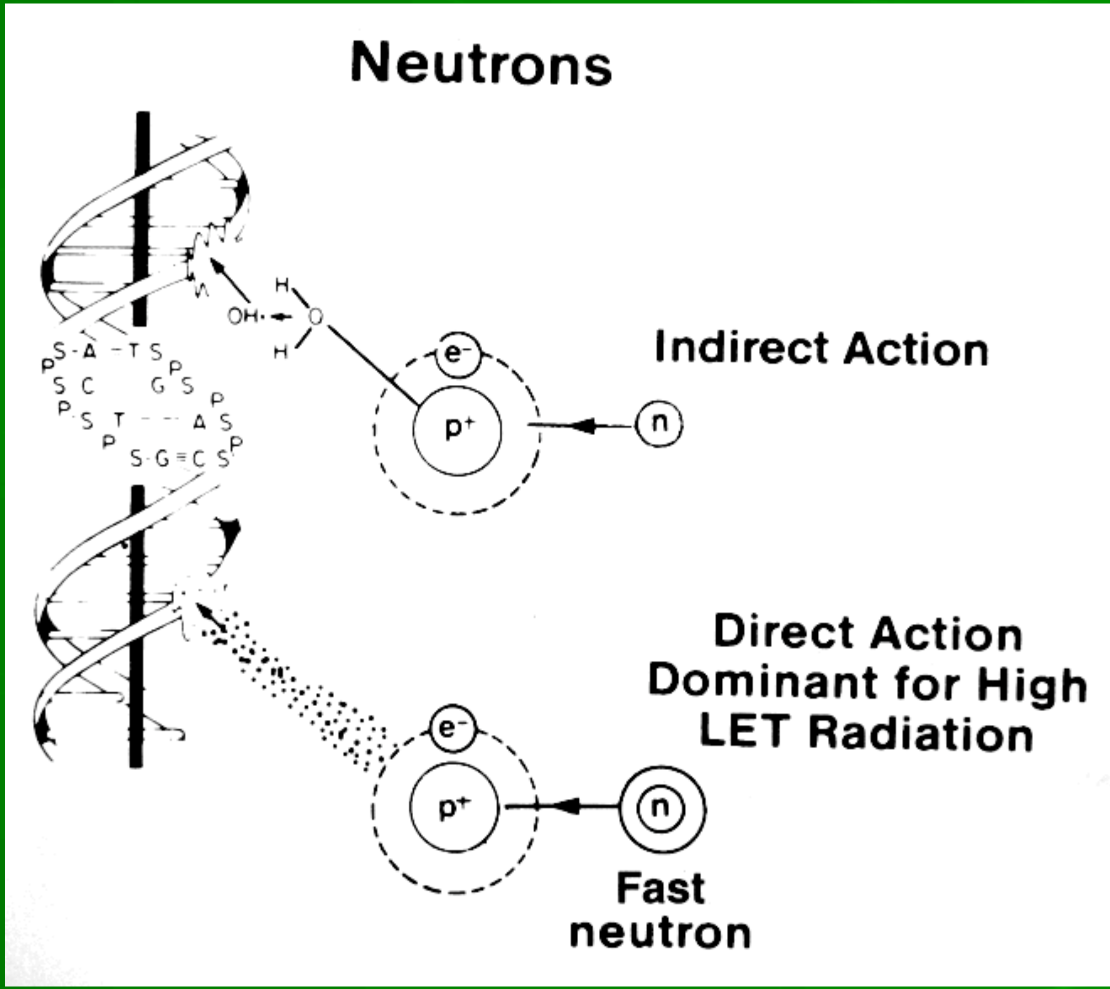
Radiation Absorption

- Direct Action
  - Absorbed radiation can interact directly
  - High LET radiation
- Indirect Action
  - Interact with other atoms or molecules to produce free radicals.
  - 80% of cell is composed of water
  - 2/3 of x-ray damage due to hydroxyl radical

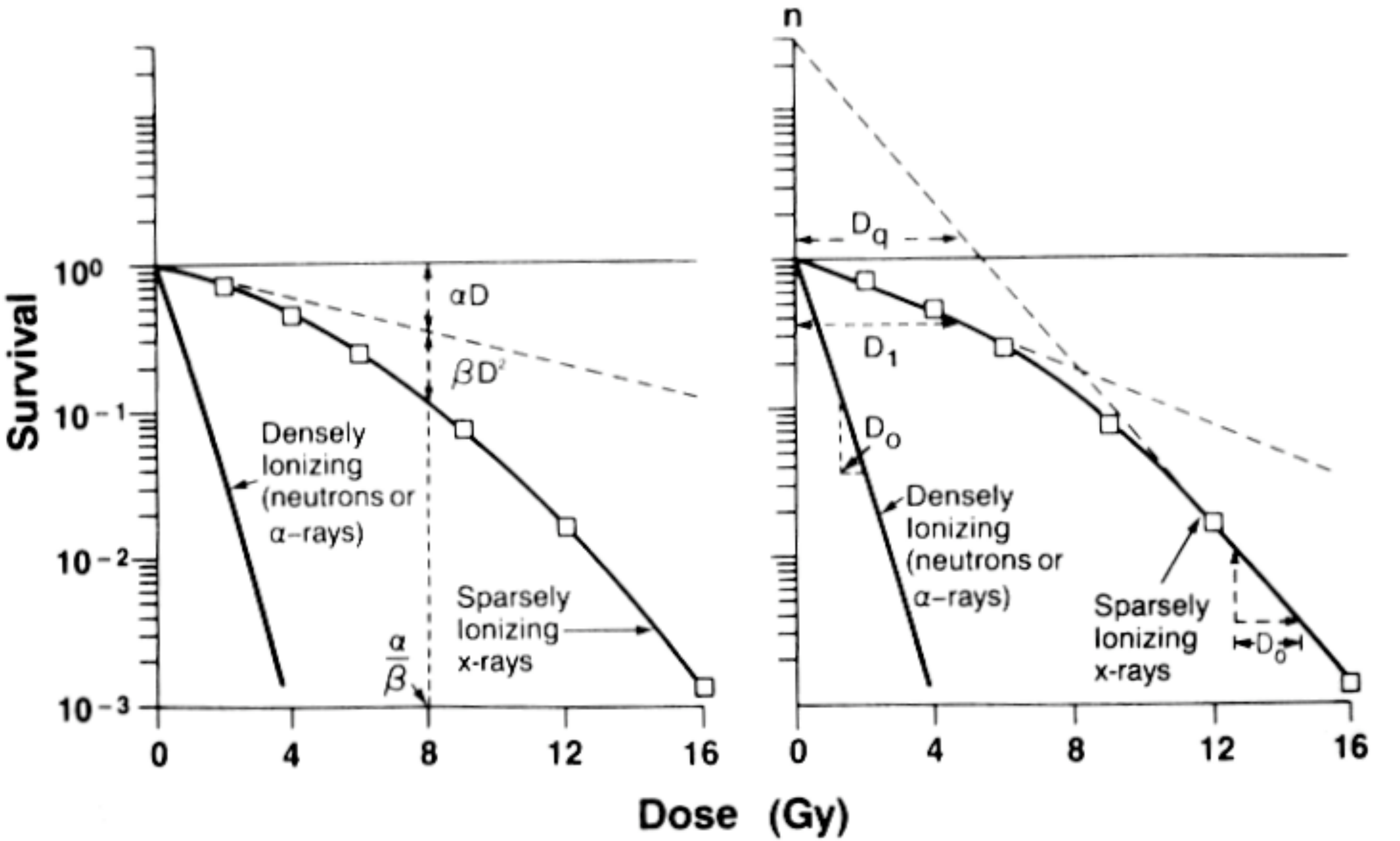


Why do heavy particles have higher energy transfer rates?

- Which one is more damaging?
  - Bows & arrows
  - Cannons & bombs

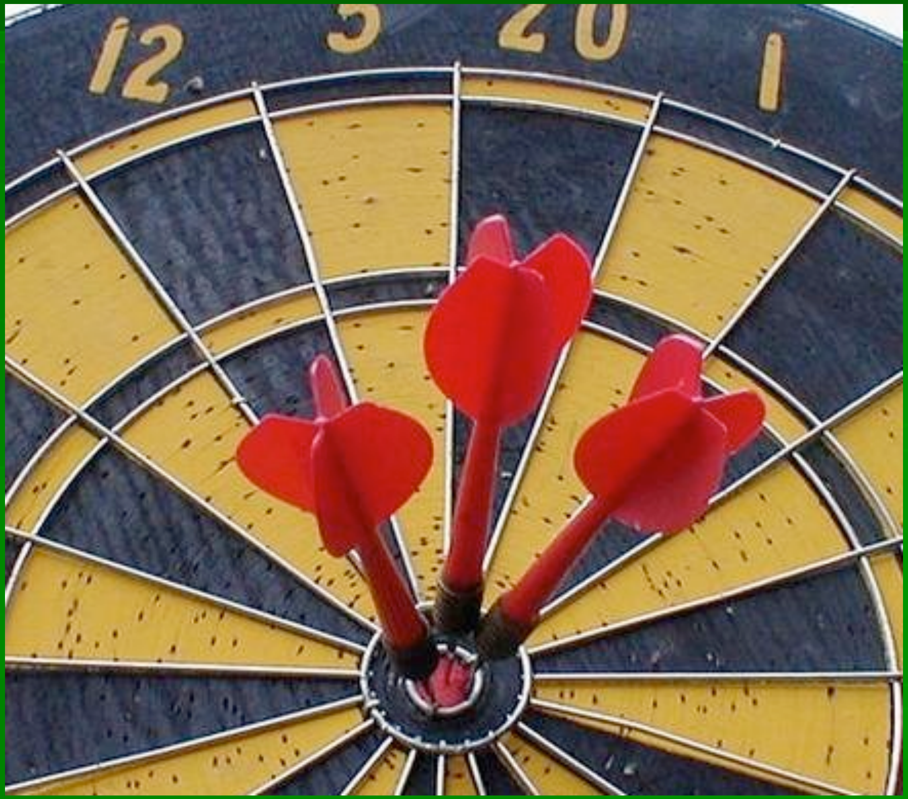


Cell Survival



Stochastic & Deterministic Effects

- Stochastic
  - Probability increases, not severity



- Deterministic (Non-Stochastic)
  - Severity increases, not probability
  - Sunburn (with a threshold)

Radiation Carcinogenesis

- Radiation is a “universal carcinogen”
  - Most tissues, any species, any age
- Relatively weak
  - Viruses and chemicals are more effective
- Risk estimates
  - Based on animal and human data
- ~1% of induced cancers

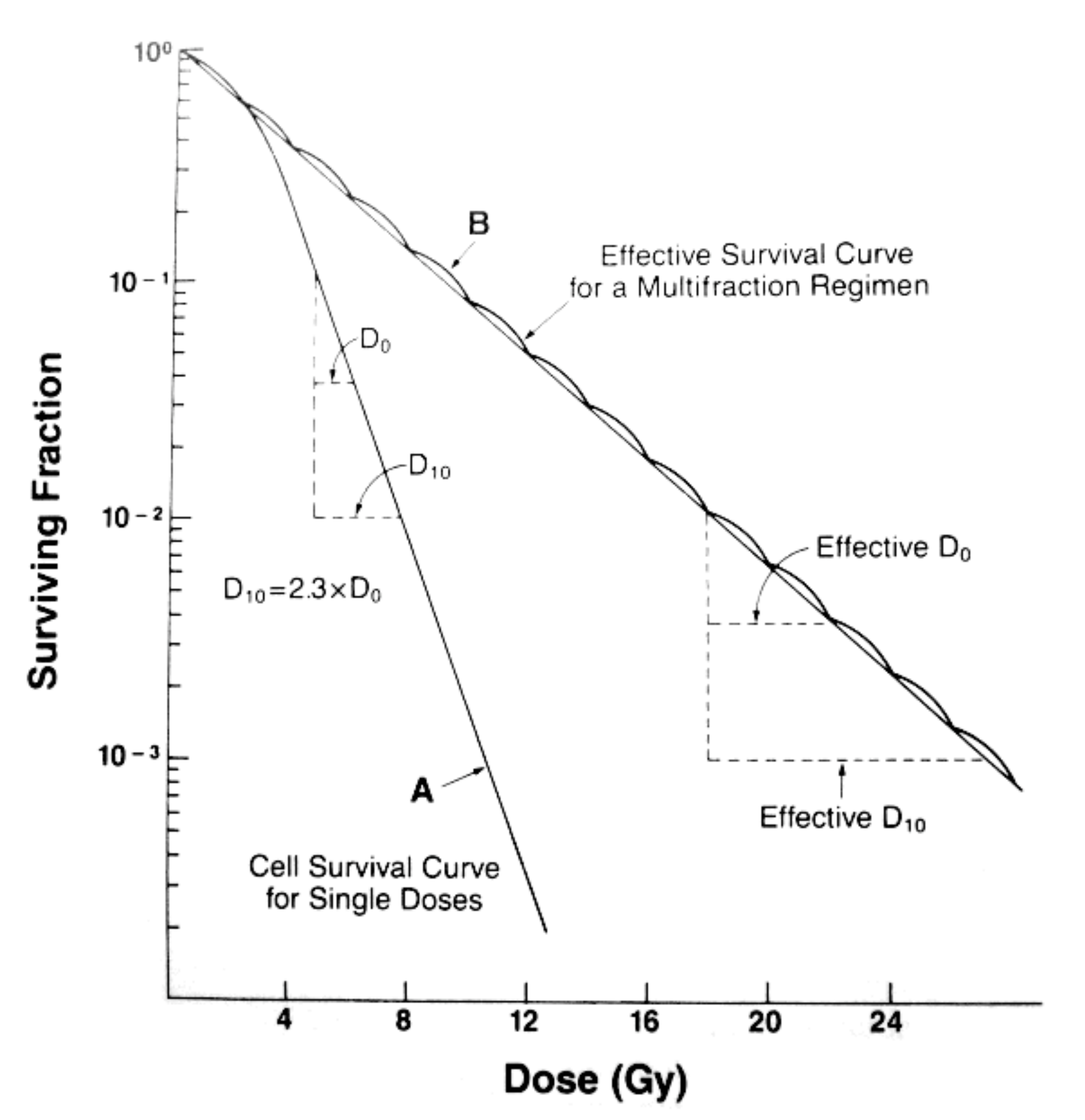
Latency

- Time interval between irradiation and the appearance of the malignancy
  - Leukemia, 5-7 years
  - Solid tumors, 45+ years
- Radiation-induced malignancies tend to appear at the same age as spontaneous malignancies of the same type
- Lifelong elevation of the natural age-specific cancer risk.

Dose Fractionation

- What is dose fractionation?
  - Divide a prescribed high dose into daily fractions over a period of time

Dose Fractionation



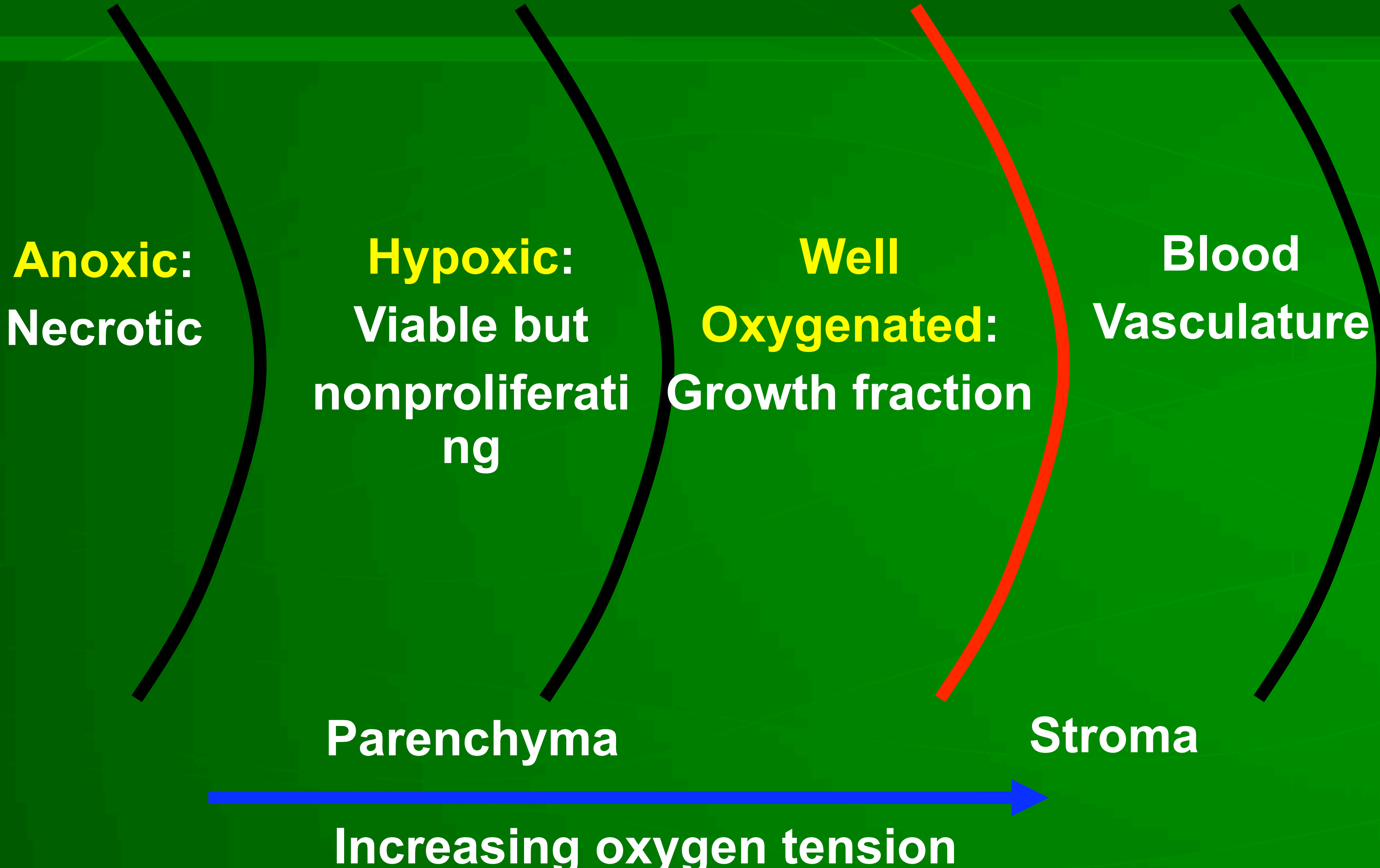
Dose Fractionation

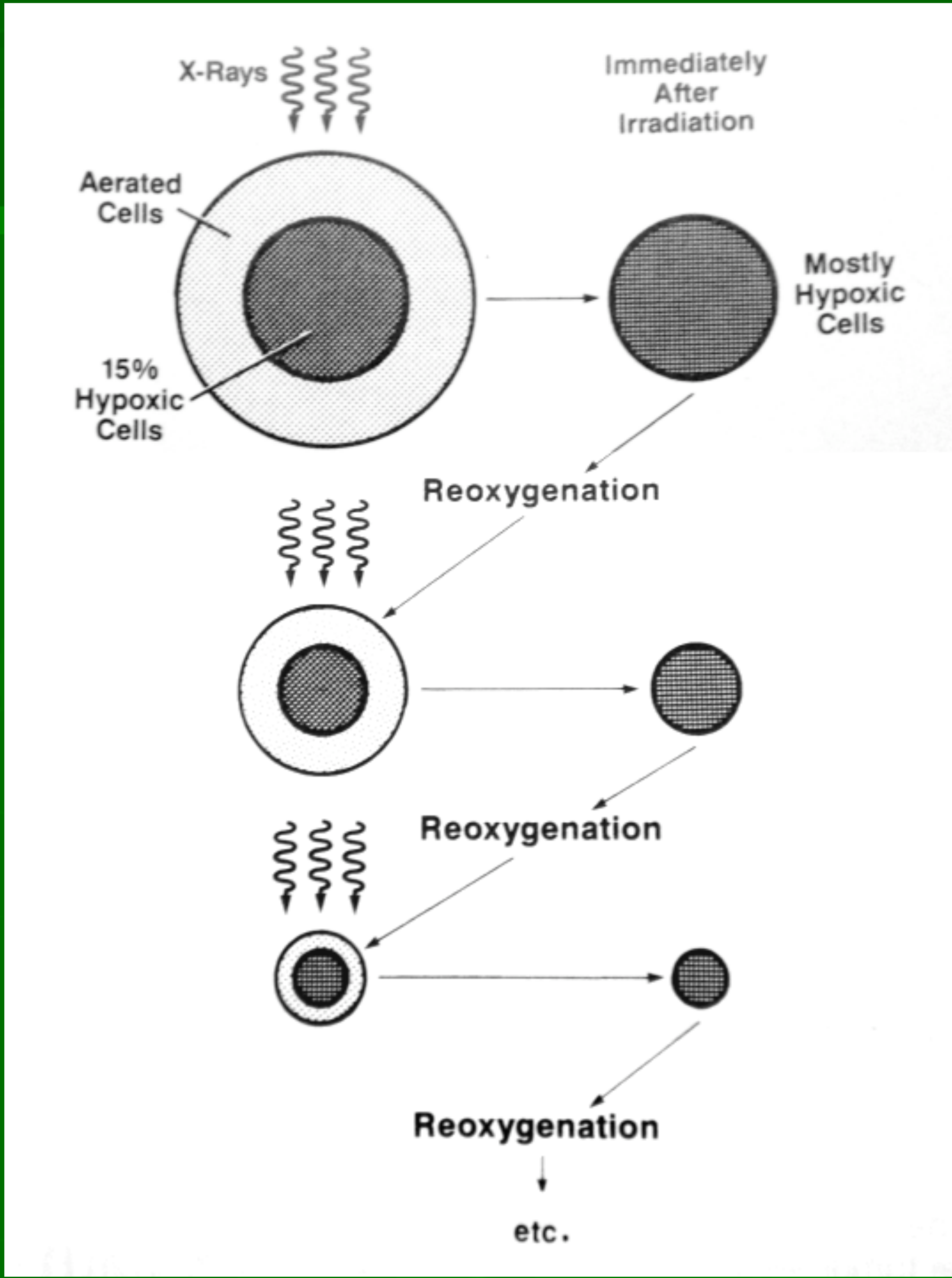
- Factors affecting dose fraction
  - Repair of sub-lethal damage
  - Reassortment of cells within the cell cycle
  - Repopulation
  - Reoxygenation
- Why fractionation?
  - Repair of sub-lethal damage and repopulation of the non-cancerous cells
  - Reoxygenation and reassortment of tumor cells into radiosensitive phases

Role of Oxygen in Tumor Growth

- Typical tumor architecture:
  - a central region of necrosis surrounded by a rim of viable cells
- The gradient of oxygen tension within the tumor
- Hypoxic pose the biggest concern

Oxygen Tension




X-Rays
Immediately
After
Irradiation
Aerated
Cells
15%
Hypoxic
Cells
Mostly
Hypoxic
Cells
Reoxygenation
Reoxygenation
Reoxygenation
etc.

Repair

- Repair of intracellular sub-lethal damage occurs within a few hours post-irradiation.
- What factors affects repair?
  - Well oxygenated cells are capable of repair
  - Normal cells are well oxygenated
  - Tumor cells vary

Reassortment

- Cellular response to radiation
  - Inter-phase death
  - Division delay
  - Reproductive failure
- Radiation causes a delay in the progression of cells through the cell cycles, subsequently producing reassortment and synchronous progression of cells in their life cycles.

Reassortment

- Why is reassortment important?
  - Radio-sensitivity is a function of the position of the cells in cell cycles
- Question
  - Is it possible to administer succeeding fractions when tumor cells are in the most sensitive phase while normal cells are in the most resistent phase?

Repopulation

- During a multi-fraction treatment, cells in both the tumor and the normal tissue divide and repopulate
- Why is repopulation important?
  - Tumor repopulation risks treatment failure, i.e. tumor recurrence.
  - Normal cell repopulation is desirable and necessary in preventing treatment complication.

Reoxygenation

- Tumor exhibits a gradient of oxygen tension
  - Normal → Hypoxic → Anoxic
- Hypoxic tumor cells have a sufficient amount of available oxygen to repair sub-lethal damage, but has a tension low enough to confer a certain degree of radio-resistance may be the determining factor of treatment success.