Types of Cellular Damage due to Radiation

Faculty of Applied Science- Department of Radiology

Course Name: Radiobiology Course Code: MTR 211

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Outlines

- How Radiation Interacts with Cells.
- Direct vs Indirect Action and Free Radical Formation.
- Types of DNA Damage.
- Repair Pathways.
- Misrepair and Mutagenesis.
- Chromosomal Damage Overview.
- Structural and Numerical Chromosomal Aberrations.
- Dicentric, Ascentric, and Ring Chromosomes.
- Cellular Outcomes of Damage.
- Sublethal, Potentially Lethal, and Lethal Damage.
- Tissue-Level Effects and Reactions.
- Stochastic and Genetic Effects of Radiation.

Learning Outcomes

By the end of the lecture, students should be able to:

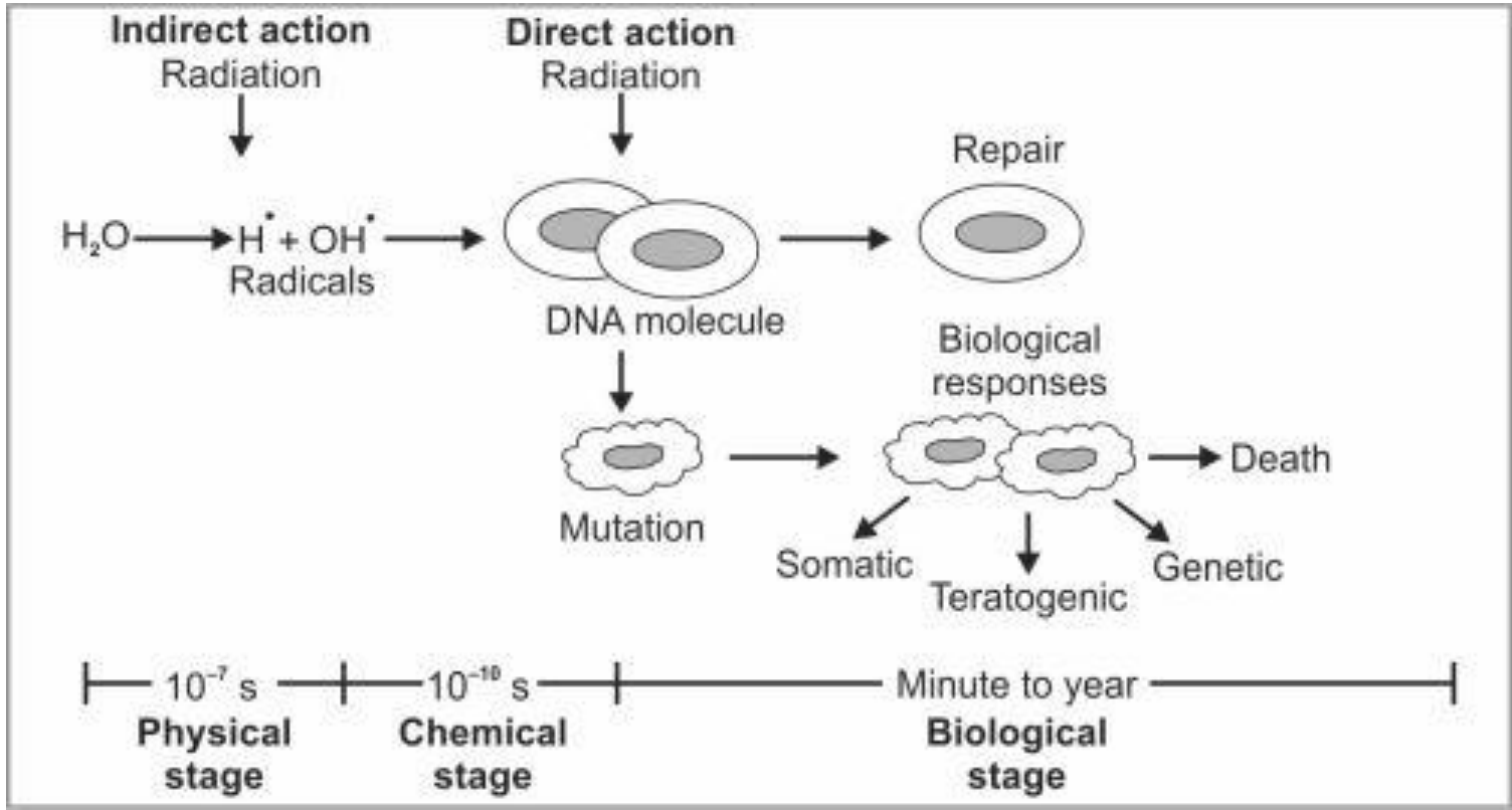
- Describe how radiation interacts with cells.
- Distinguish direct vs indirect DNA damage.
- Explain types of DNA lesions.
- Understand chromosomal and cellular outcomes.
- Identify deterministic vs stochastic effects.

How Radiation Interacts With Cells

- **Radiation** ⟶ Ionizing vs non-ionizing.
- Ionizing radiation has the energy to **remove electrons.**

Examples: X-rays, gamma rays, alpha, beta.

1. **Energy deposition** in tissues.
2. Ionization **of biomolecules**.
3. Generation of **reactive species**.
4. **DNA** is the main target.



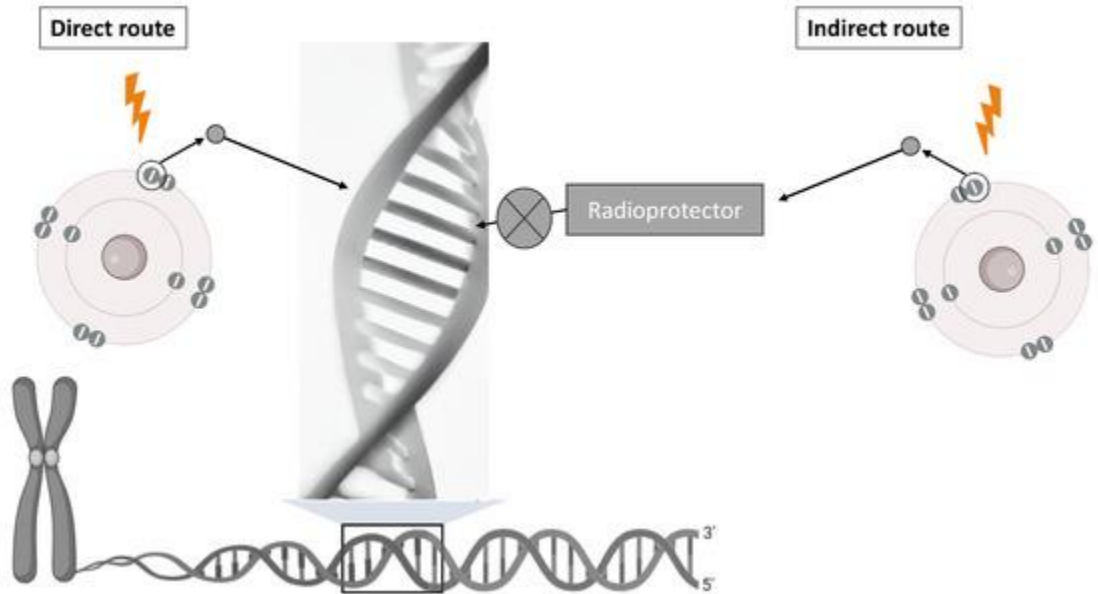
Direct vs Indirect Action and Free Radical Formation

Direct: radiation hits DNA directly

Indirect: radiation ionizes water → free radicals → damage DNA

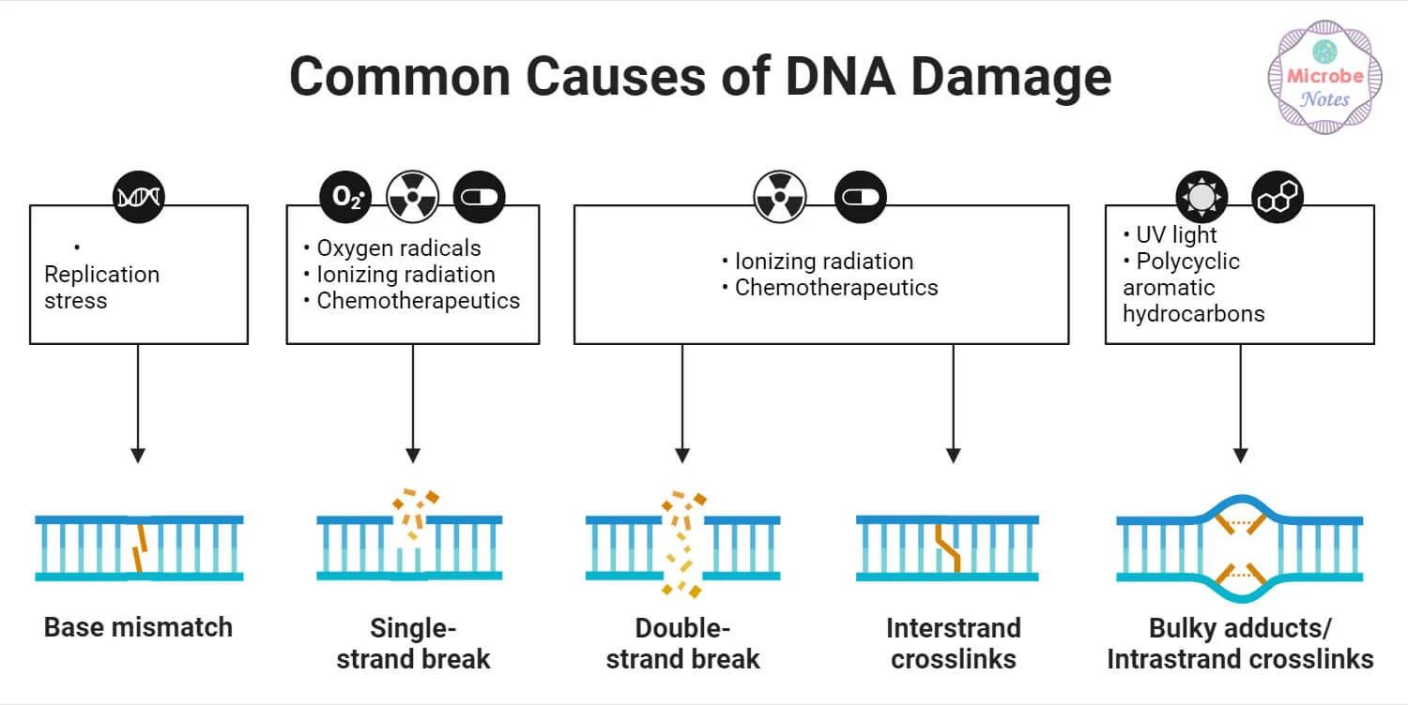
Indirect is more common (~70%)

1. Ionization of water → **OH·, H·**
2. Highly reactive.
3. Cause **strand breaks**, **base alterations**.
4. Radicals persist for microseconds but cause major damage.



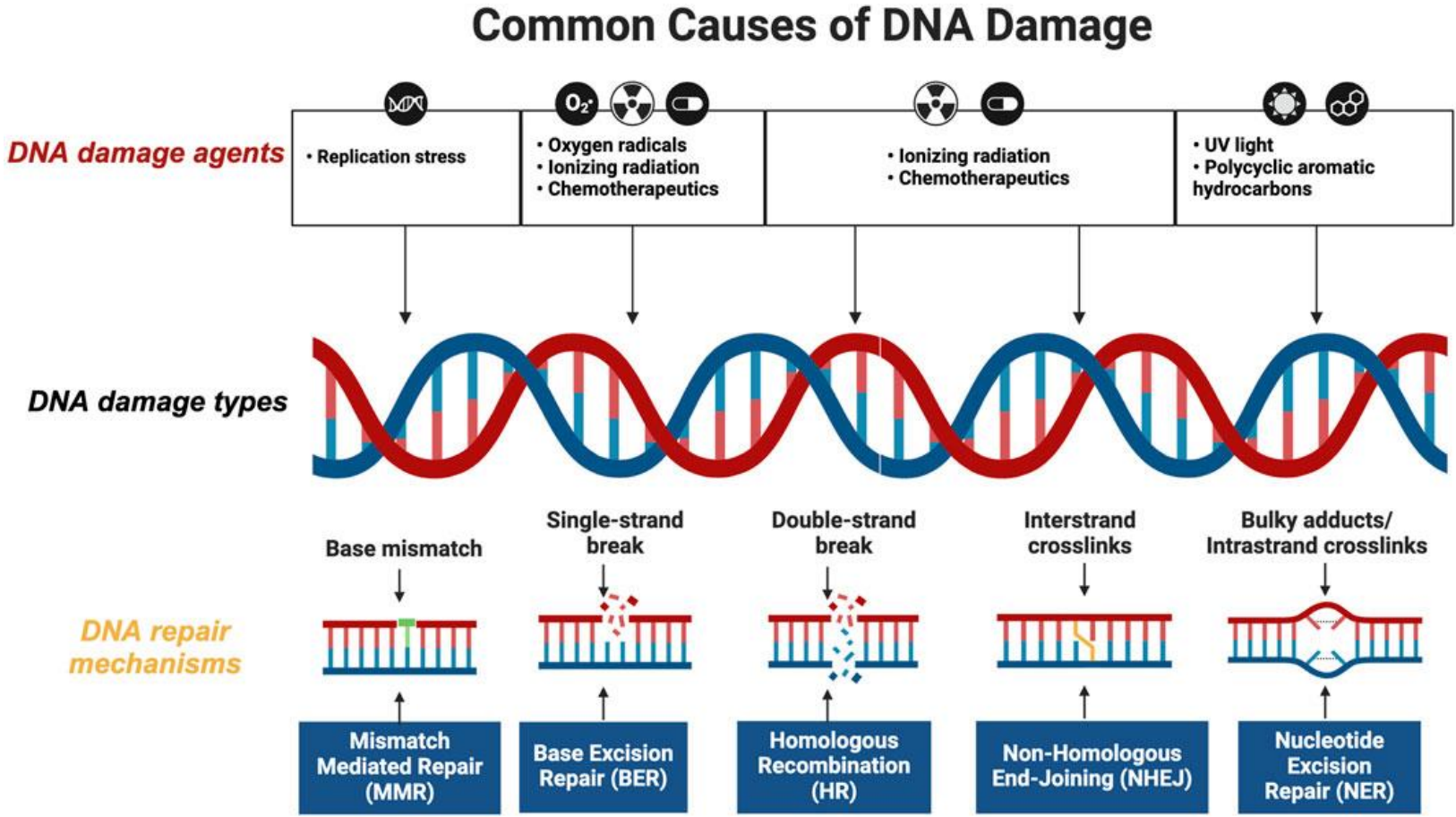
Types of DNA Damage

- **Base Damage:** Small chemical changes to DNA bases that may cause mutations.
- **Single-Strand Breaks (SSBs):** A break in one DNA strand that is usually repairable.
- **Double-Strand Breaks (DSBs):** Breaks in both DNA strands, often leading to cell death if not repaired.
- **DNA–DNA or DNA–Protein Crosslinks:** Abnormal bonds that block DNA replication and transcription.
- **Clustered Lesions:** Several nearby DNA damages occur together, making repair difficult.



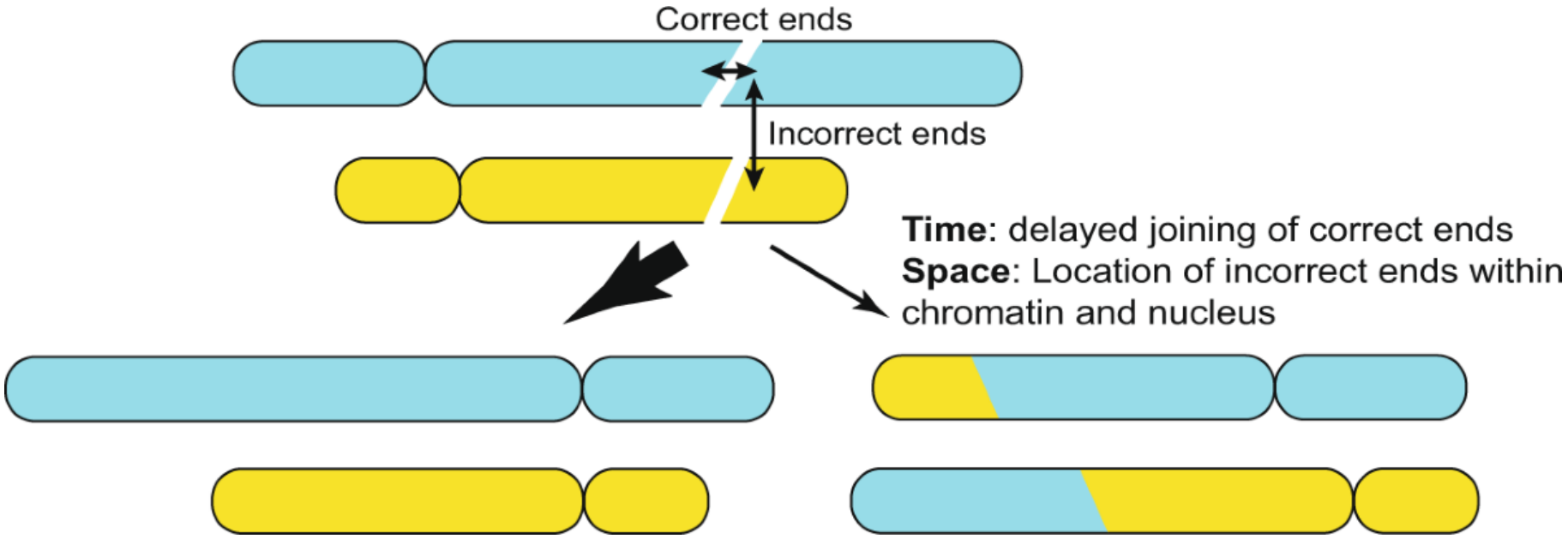
Repair Pathways

- Base excision repair (**BER**)
- Nucleotide excision repair (**NER**)
- Non-homologous end joining (**NHEJ**)
- Homologous recombination (**HR**)



Misrepair and Mutagenesis

- **Incorrect rejoining of DNA ends:** When the cell repairs double-strand breaks incorrectly, DNA fragments join in the wrong order.
- **Results in chromosomal mutations:** Misrepair can create deletions, translocations, dicentrics, or other chromosomal abnormalities.
- **Can initiate carcinogenesis:** These permanent genetic changes may activate oncogenes or disable tumor-suppressor genes, increasing cancer risk.



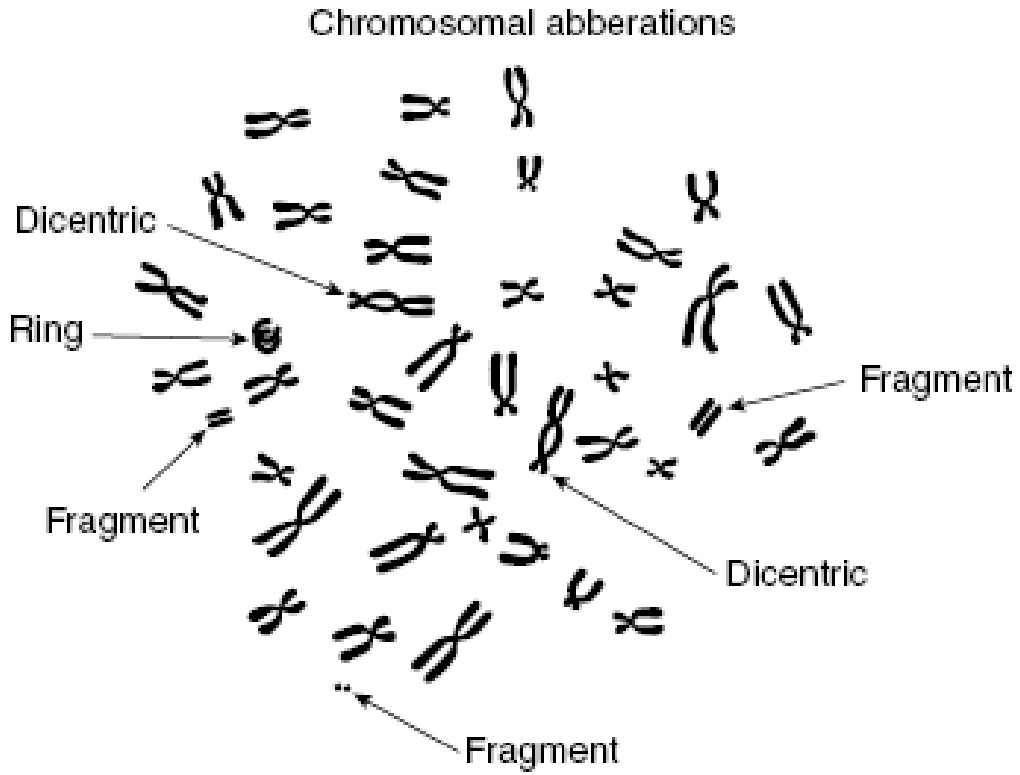
Chromosomal Damage Overview

- Radiation causes DNA breaks that alter whole chromosomes, leading to **visible abnormalities during cell division**.

Two main types of chromosomal damage:

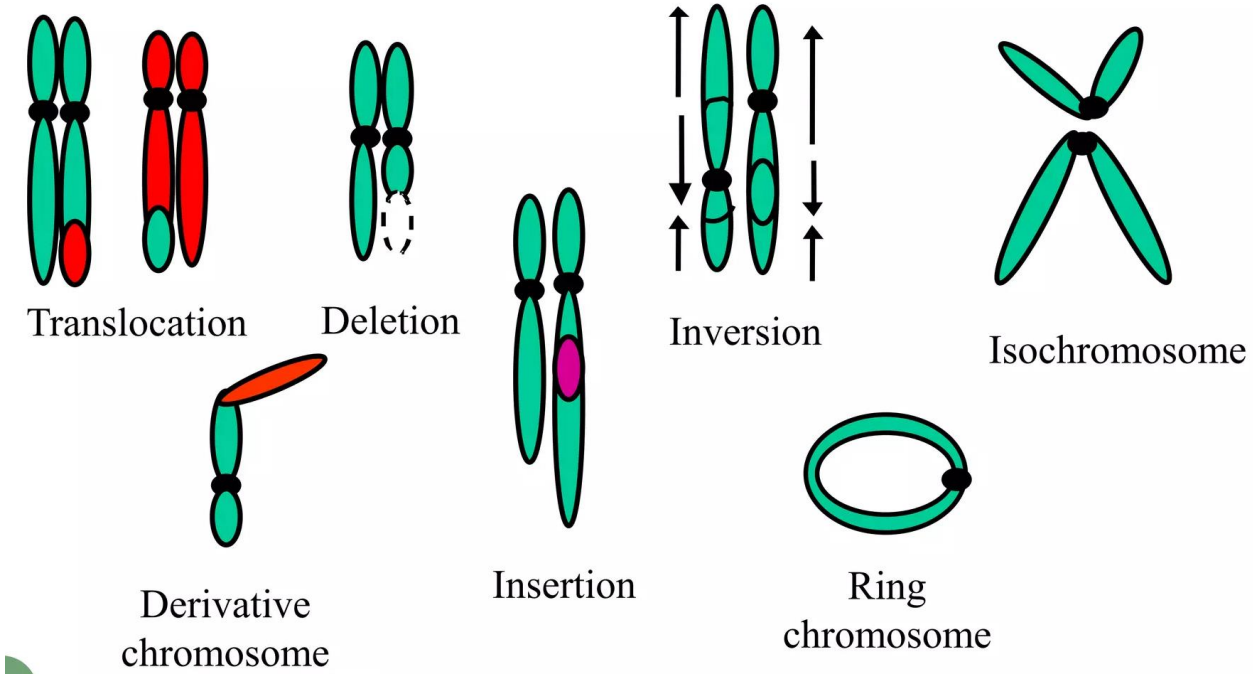
1. **Structural changes:** breakage and incorrect rejoining (e.g., deletions, translocations).
2. **Numerical changes:** loss or gain of entire chromosomes.

- These abnormalities **disrupt normal cell function**, causing **cell death**, **impaired division**, or **long-term genetic consequences**.



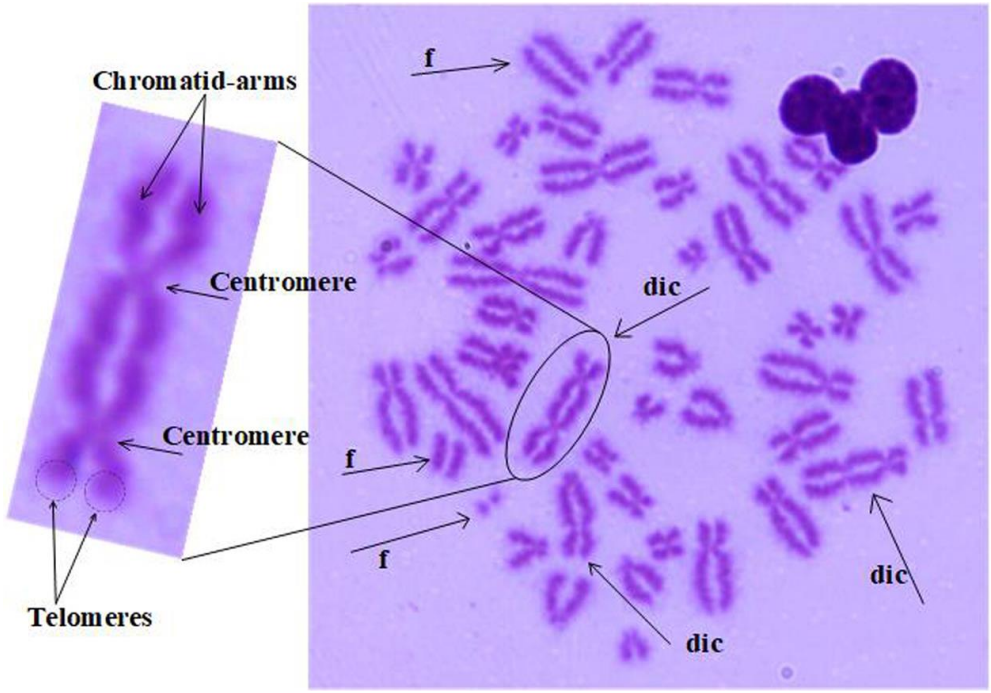
Structural Chromosomal Aberrations

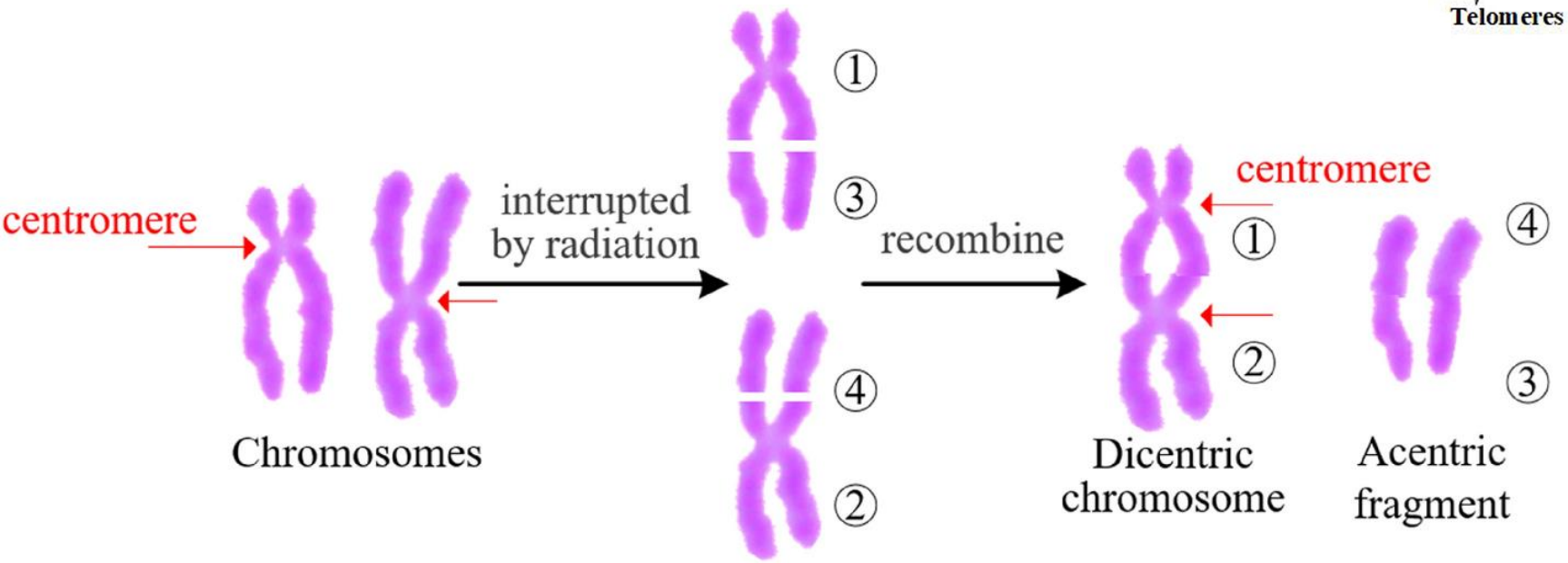
1. **Deletions:** A chromosome segment **is lost** due to unrepaired breaks, resulting in the loss of genetic material.
2. **Duplications:** A section of a chromosome is **copied twice**, resulting in extra genetic material.
3. **Inversions:** A chromosome fragment **breaks and reattaches in the reverse orientation**, disrupting gene order.
4. **Translocations:** DNA fragments from different chromosomes are **incorrectly exchanged or joined**, creating abnormal gene arrangements.



Dicentric Chromosomes

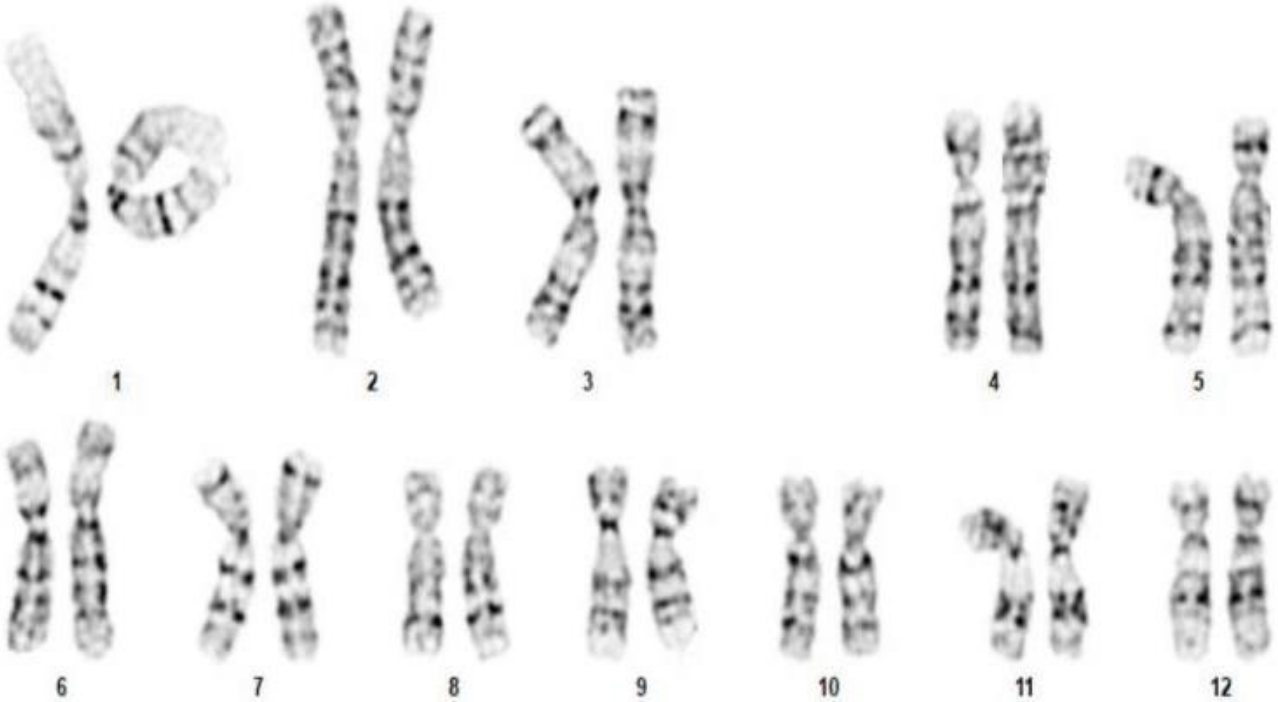
- Formed when **two chromosome fragments with centromeres join incorrectly**, creating a chromosome with **two centromeres**.
- A **hallmark of radiation exposure**, commonly seen after **double-strand break misrepair**.
- Unstable during cell division, **often pulled to opposite poles, leading to breakage and cell death**.

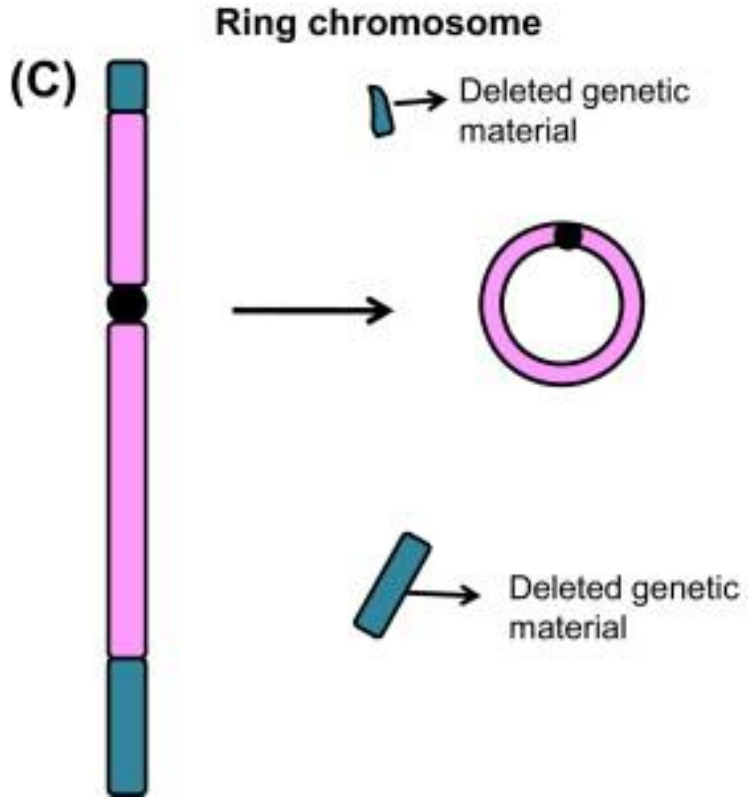




Ring Chromosomes

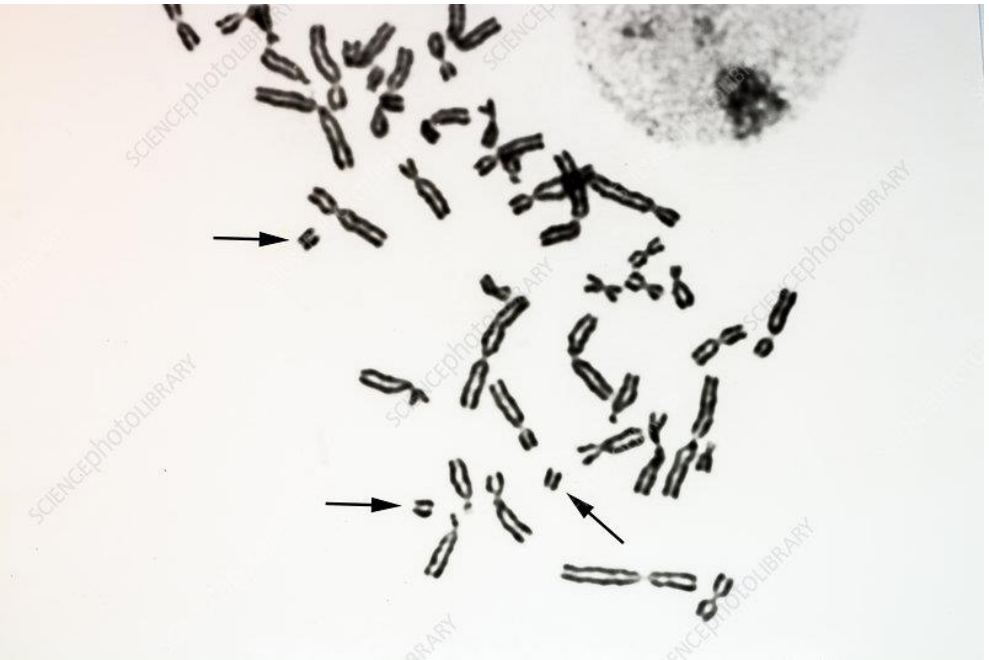
- Formed when **both ends of a chromosome break and rejoin in a circular shape**, losing the terminal fragments.
- Often produced after **high doses of radiation**, due to multiple breaks on the same chromosome.
- Unstable during mitosis, leading to **mis-segregation**, **breakage**, and a **high chance of cell death**.

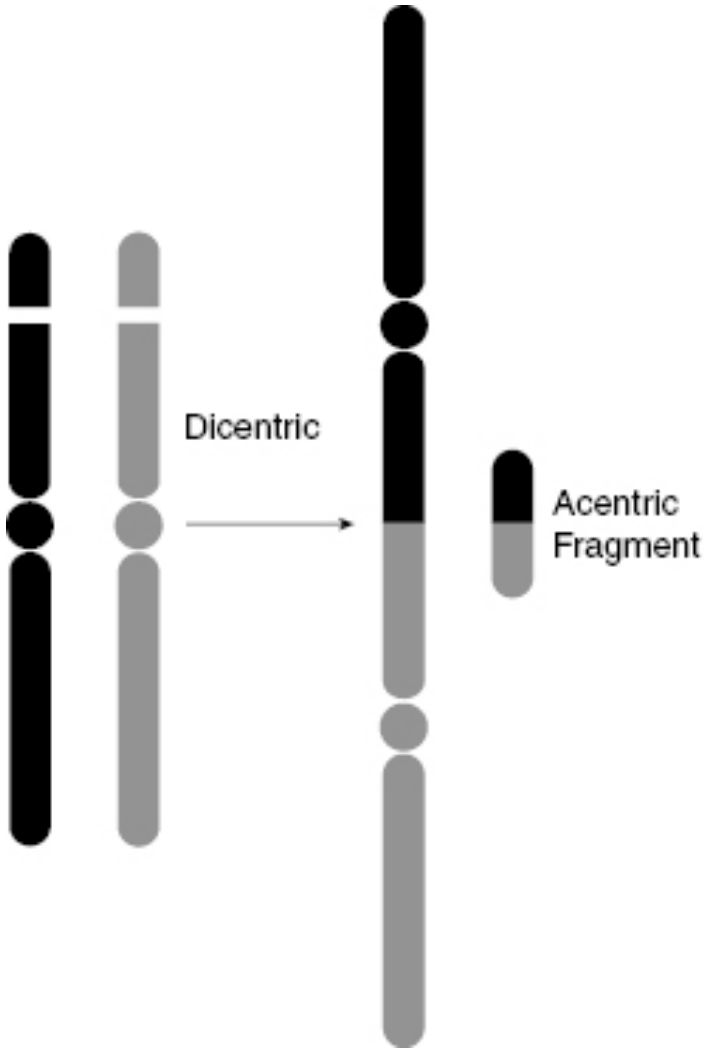




Acentric Fragments

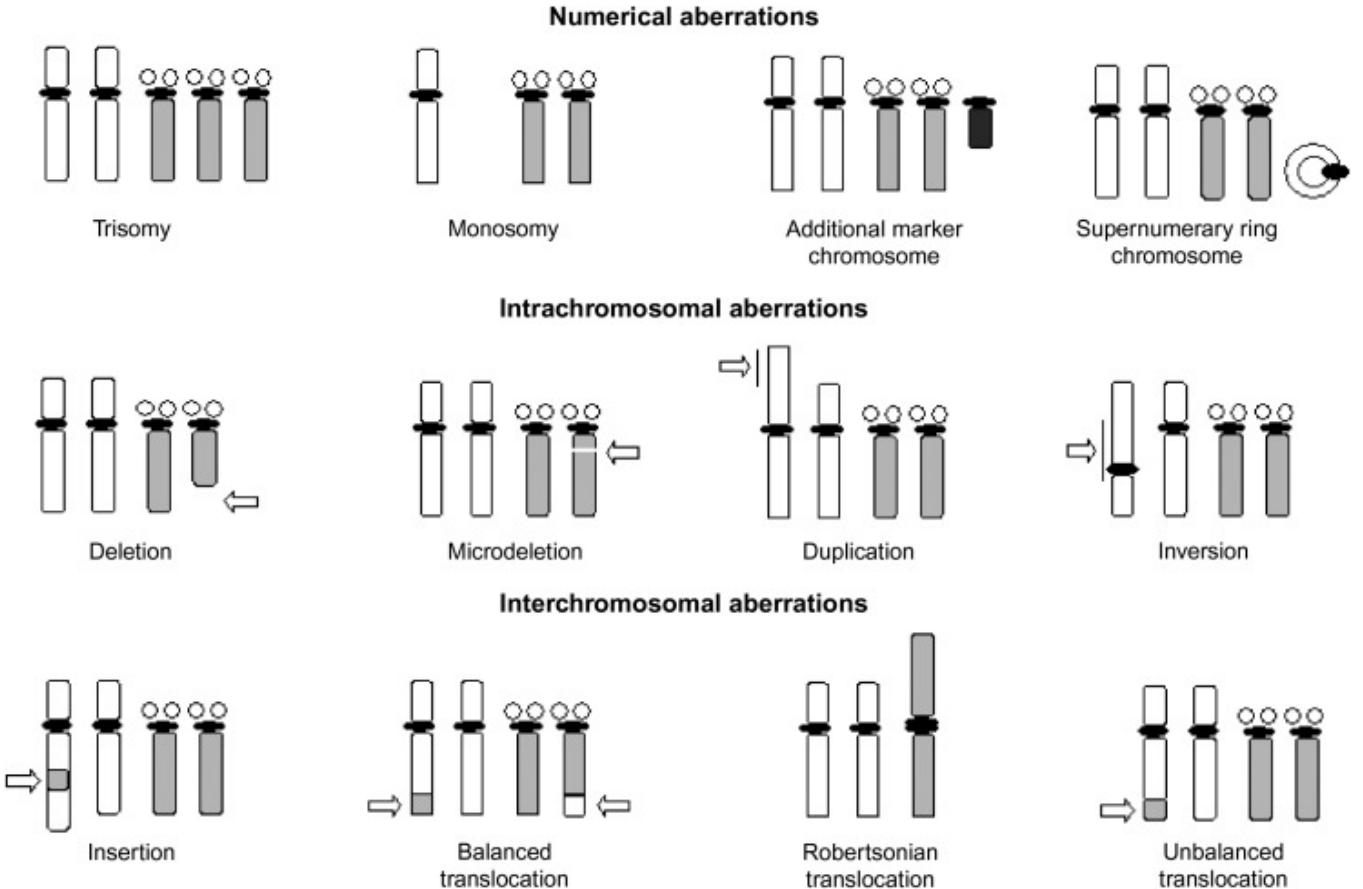
- Chromosome pieces that **lack a centromere**, usually formed after radiation-induced breaks.
- **Cannot attach to the mitotic spindle**, so they fail to move properly during cell division.
- Frequently lost during mitosis, leading to loss of genetic material and contributing to cell death.





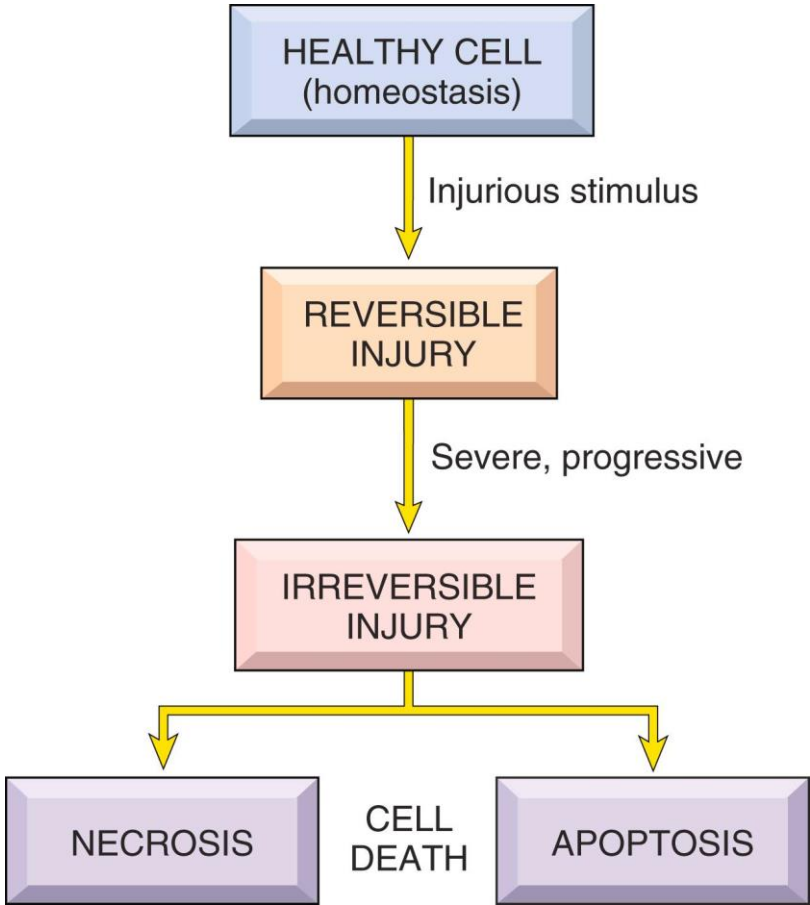
Numerical Aberrations

- **Changes in the number of whole chromosomes** caused by radiation disrupt mitosis.
- **Aneuploidy:** loss or gain of one or more chromosomes.
- It can lead to **developmental abnormalities or impaired cell function**, depending on the genes affected.



Cellular Outcomes of Damage

1. **Sublethal damage:** Can be repaired if conditions are favorable.
2. **Potentially lethal damage:** May be repaired, but success depends on the cell environment.
3. **Lethal damage:** Irreversible damage leading to cell death.
4. **Mutation or transformation:** Misrepair may cause permanent genetic changes.
5. **Reproductive death:** Cells survive but lose the ability to divide.



Sublethal, Potentially Lethal and Lethal Damage

Sublethal Damage

- Damage that cells can repair **if given time and favorable conditions**.
- Not immediately fatal, but **repeated or additional hits** can accumulate and become lethal.
- Basis for **fractionated radiotherapy**, where doses are split to allow normal cells to repair.

Potentially Lethal Damage

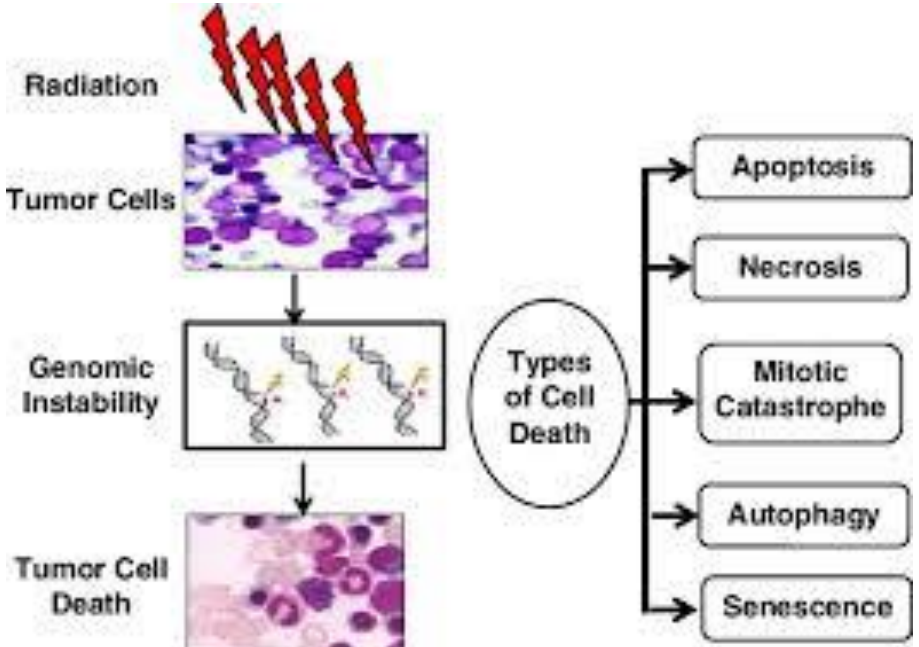
- Damage that **may be repaired** depending on the cell's environment (e.g., nutrient availability, oxygen levels).
- Repair is **less efficient under stressful conditions**, increasing the likelihood of cell death.
- Highlights the importance of cellular context in radiation response

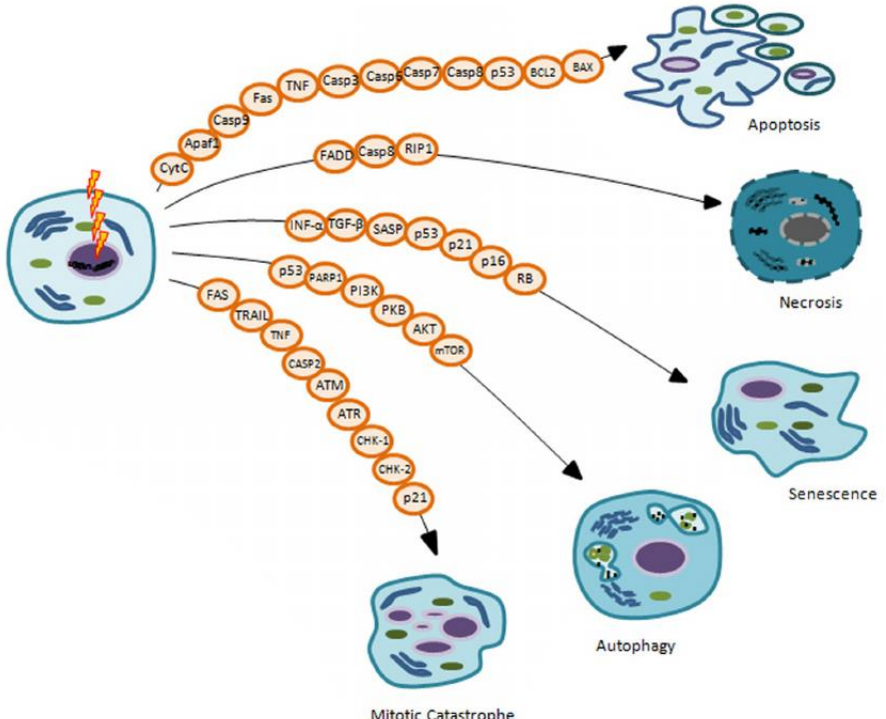
Lethal Damage

- Irreversible damage that **cannot be repaired by the cell**.
- **Always leads to cell death**, either immediately or after attempted division.
- Results from severe DNA or chromosomal damage, overwhelming cellular repair mechanisms.

Types of Cell Death After Radiation

1. **Apoptosis:** Programmed cell death triggered by DNA damage.
2. **Necrosis:** Uncontrolled cell death, usually after very high radiation doses.
3. **Mitotic (Reproductive) Death:** Cells survive but cannot divide due to chromosomal damage.
4. **Senescence:** Permanent growth arrest; cells remain metabolically active but do not divide.





Tissue-Level Effects and Reactions

- **Rapidly dividing tissues** are **most sensitive** to radiation, e.g., bone marrow, gastrointestinal tract, and gonads.
- **Slow-dividing or non-dividing tissues** are **more resistant**, e.g., muscle and nerve cells.
- The extent of tissue damage depends on **cell turnover rate and repair capacity**.

Deterministic Effects (Tissue Reactions)

- Have a **threshold dose** below which effects do not occur.
- Severity increases with higher radiation doses.
- **Examples:** skin burns, cataracts, bone marrow suppression.
- Result from significant cell death in a tissue.

Stochastic Effects

- No threshold dose; **even small doses carry some risk**.
- Probability of effect increases with **dose**, but **severity does not**.
- **Examples:** cancer and genetic mutations.
- Result from misrepaired DNA or mutations in surviving cells.

Radiation Carcinogenesis

- Misrepaired DNA can activate **oncogenes or inactivate tumor-suppressor genes**.
- Leads to **permanent genetic changes** that may trigger **cancer development**.
- The latency period can be **years before cancer appears**.
- **Examples:** leukemia, thyroid cancer, and other solid tumors.

Genetic (Heritable) Effects

- Radiation **can damage germline cells** (sperm or eggs).
- Mutations may be **passed to offspring**, affecting future generations.
- Risk increases with **higher doses or exposure** during sensitive developmental stages.
- Important consideration for reproductive protection and radiological safety.

Factors Affecting Radiation Damage

1. **Dose:** Higher doses cause more severe damage.
2. **Dose rate:** Slower delivery allows more repair; faster rates increase damage.
3. **LET (Linear Energy Transfer):** High LET radiation (alpha, neutrons) causes more dense DNA damage than low LET (X-rays, gamma).
4. **Oxygenation:** Oxygen enhances DNA damage (oxygen effect).
5. **Cell cycle phase:** Cells are most sensitive in G2/M, less in S phase.

Questions? Comments?

Thank you!