L.11 **Radiation biology and radiation protection**

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Biological Effects of Ionizing Radiation at Cell Level:

Radiation exposure affects the center of life; the cell, then eventually the chromosomes: the critical target is DNA ionizing.

Chromosomes in cells are made up of many strands of DNA that are twisted, forming a double helix.
A single strand of DNA consists of 2 sugar-phosphate molecular backbones that are loosely bonded by complementary nitrogenous bases. There are 2 complementary nitrogenous base pairs: adenine, which bonds with thymine, and cytosine, which bonds with guanine. In all, there are about 3 billion base pairs and 35000 genes in the human genome.
Radiation energy is transferred to the irradiated tissues primarily by Photoelectric and Compton's processes which produce ionizations and excitations of essential cell molecules such as DNA, enzymes, ATP, coenzymes, etc.
The functions of these molecules are altered. The cells with damaged molecules cannot function normally. The severity of biological effect is related to the type of molecule absorbing radiation. Effect on DNA molecule is more harmful than on cytoplasmic organelles.
Mechanisms of radiation damage:
Two mechanisms of radiation damage, mostly on DNA:

I. Indirect damage.

Water molecule is ionized. The ions, H_2O^+ and H_2O^-, are very unstable and break up into OH free radicals. OH free radical contains an unpaired electron in the outer shell and is highly reactive: reacts with DNA.
Free radicals may also combine with each other to produce hydrogen peroxide

$$OH\bullet + OH\bullet \text{------->} H_2O_2$$

Hydrogen peroxide is a cell poison that may contribute to biological damage. 75% of radiation-caused DNA damage is due to OH free radical.

These free radicals lead to oxidation of DNA by OH radicals, if chemical restoration occurs so no effect, if not permanent damage in DNA lead to biological effects; genetic effects and somatic effects: cancer – sterility.

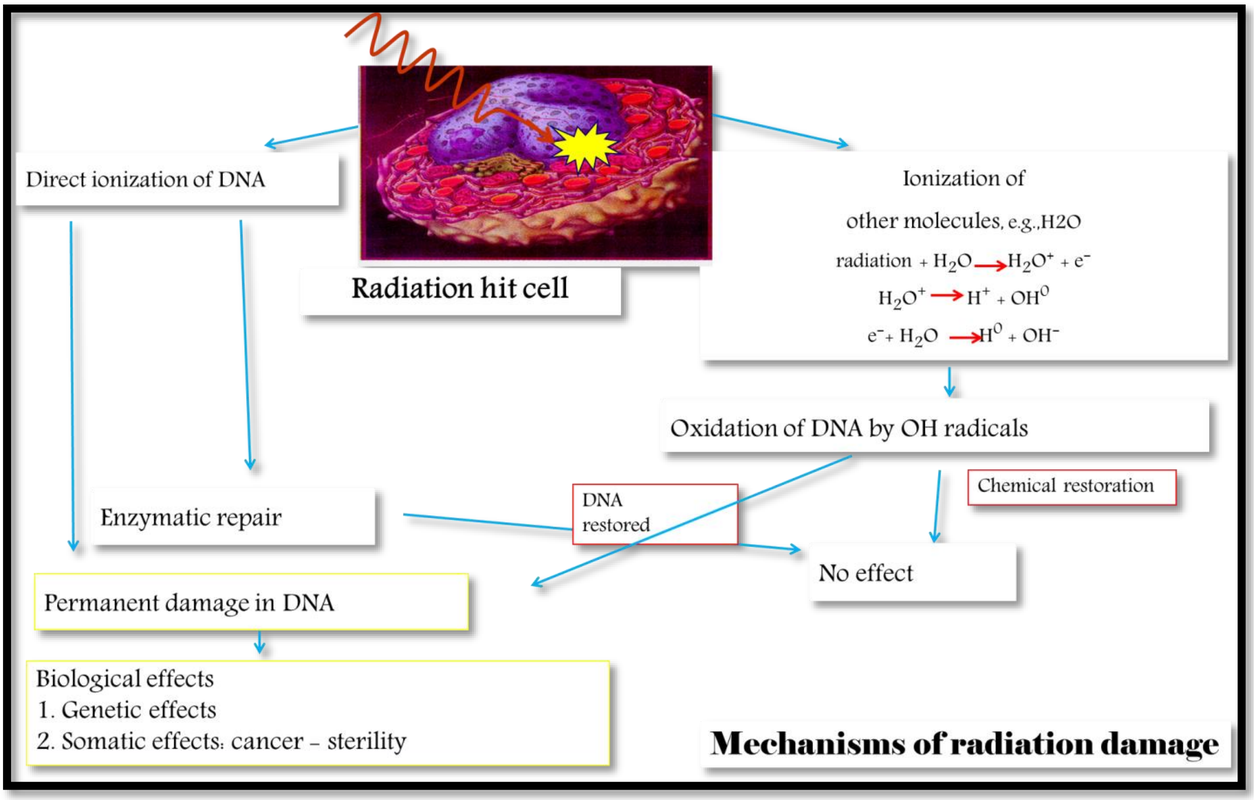
Radiation +H_2O..... $H_2O^+ + e^-$

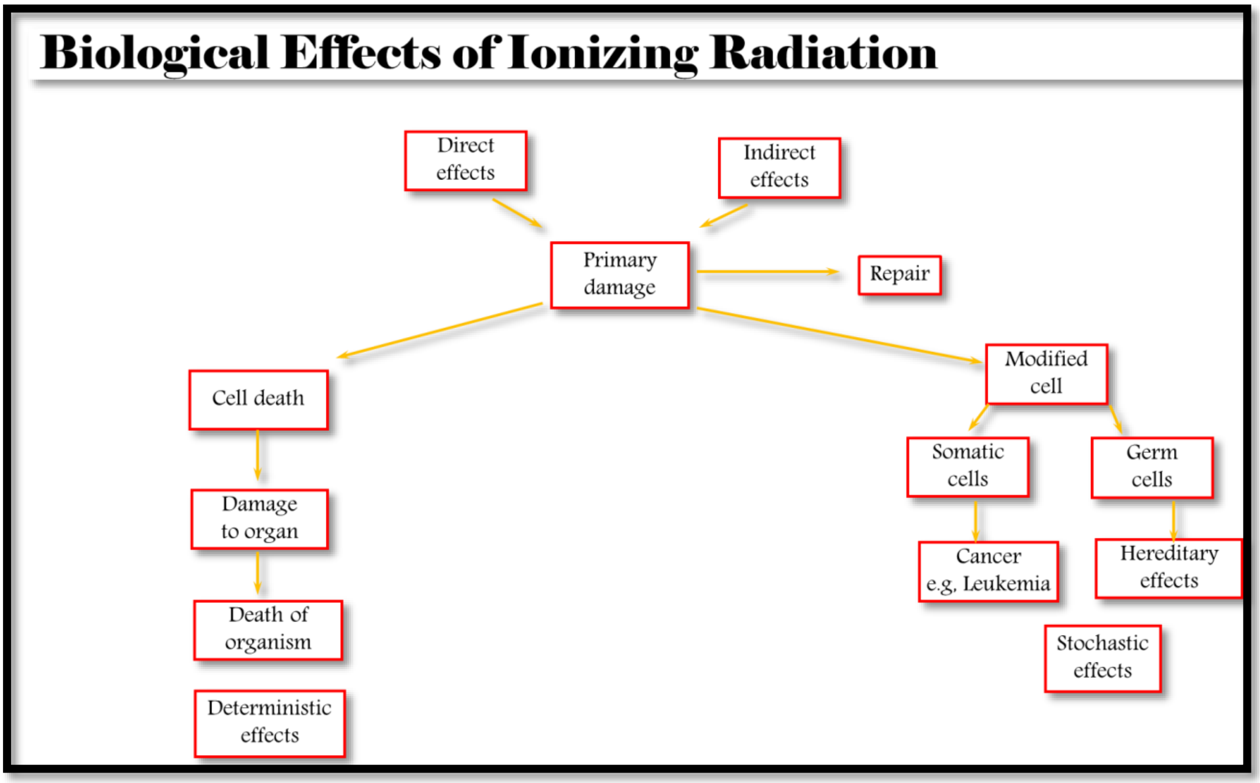
H_2O^+ .....> $H^+ + OH^0$

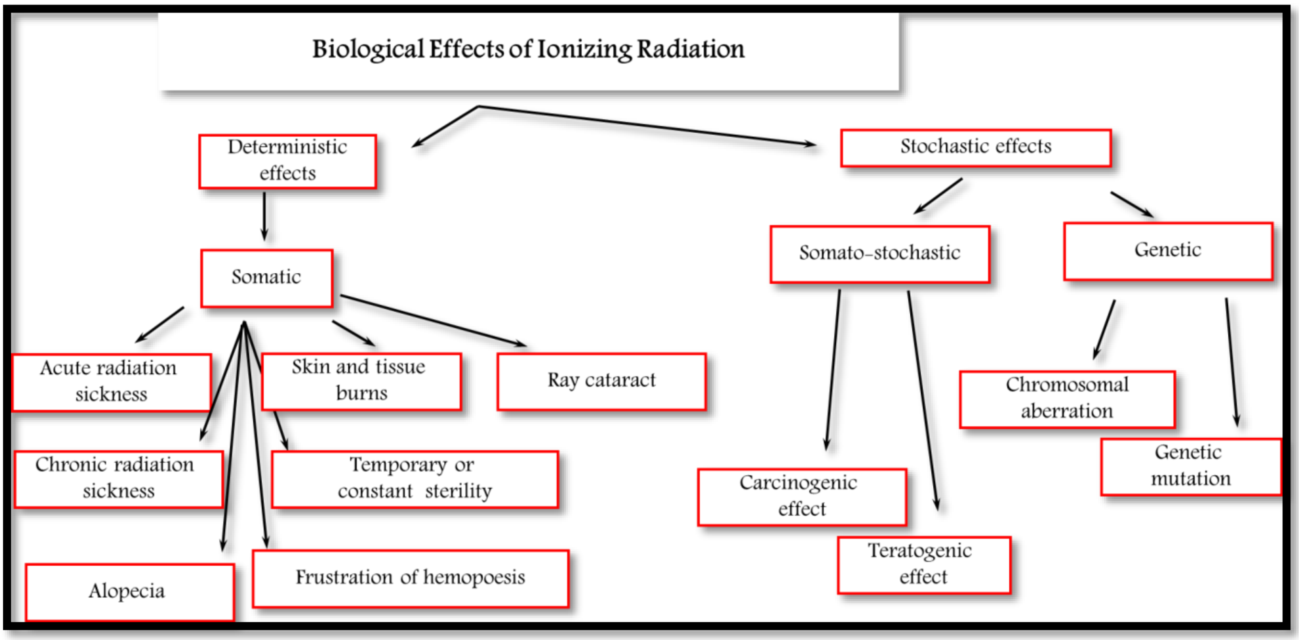
$e^- + H_2O$ .....> $H^0 + OH^-$

II. Direct damage

- DNA molecule is struck by radiation, ionized, resulting in damage. Radiation hit cell, lead to direct ionization of DNA; if enzymatic repair occurs there is no effect, and if not permanent damage in DNA lead to biological effects; genetic effects and somatic effects: cancer – sterility.

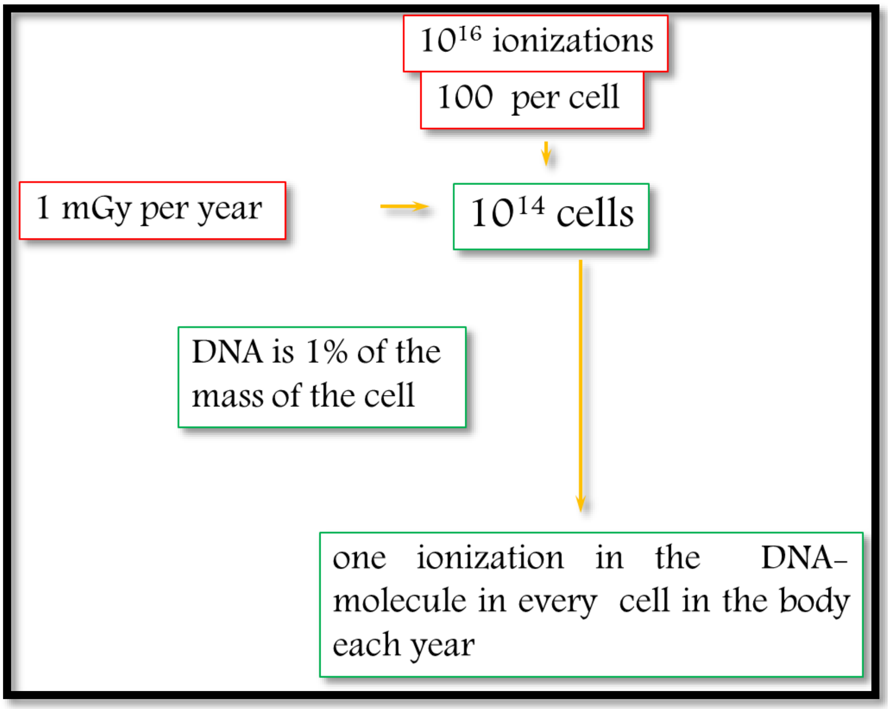






Natural Annual Ionization:

- The human body contains about 10^{14} cells.
- An absorbed dose of 1 mGy (milliGray) per year (natural sources) will produce about 10^{16} ionizations, which means 100 ionizations per cell in the body.
- If we assume that the mass of DNA is 1% of the mass of the cell, the result will be one ionization in the DNA-molecule in every cell in the body each year.



What Follows Chromosome Damage?

The cell might:

1. Repair mild damage.
2. Have some mild damage that sits inactive until another agent interacts with the same cell.
3. If it is a reproductive cell like sperm or egg cells having damage to the genetic code, that doesn't show up until future generations.
4. Have some damage, causing its multiplication to become a cancer.
5. Stop functioning.
6. Be killed.

Order of magnitudes:

- 999 of 1000 lesions are repaired.
- 999 of 1000 damaged cells die (not a major problem as millions of cells die every day in every person).
- Many cells may live with damage (could be mutated).

Deterministic Effects on Cells

1. Intracellular Structures
2. Chromosome Aberrations
3. Cell Replication
4. DNA Damage
5. Apoptosis

Chromosome Breaks

I. Point mutations:

- Effect of radiation on individual gene is referred to as point mutation.
- The effect can be loss or mutation in a gene or a set of genes.
- The implication of such a change is that the cell may now exhibit an abnormal pattern of behavior.

II. Chromosome alterations:

- Several kinds of alterations in the chromosomes have been described. Most of these are clearly visible under the microscope.
- The effect upon chromosomes can result in the breaking of one or more chromosomes. The broken ends of the chromosome seem to possess the ability to join together again after separation.
- Such damage may be repaired rapidly in an error-free fashion by cellular repair processes (restitution) using the intact second strand as a template.
- However, if the separation between broken fragments is great, the chromosome may lose part of its structure (deletion).
- If more than one break, the broken fragments may join in different combinations.
- Inversion of the middle segment followed by recombination

III. Double-strand breakage:

- When both strands of a DNA molecule are damaged. Sections of one broken chromosome may join sections of another broken chromosome.

- A large proportion of damage will result in disrepair that can result in the formation of gene and chromosomal mutations that may cause malignant development.

Chromosome alterations:

- Formation of a ring and fragments followed by replication of chromosomes.
- Interchange between two chromosomes forms a chromosome with two centromeres and fragment followed by replication.

Recovery

Cell recovery from DNA damage and the bystander effect involves enzymatic repair of single-strand breaks of DNA. Because of this repair, a higher total dose is required to achieve a given degree of cell killing when multiple fractions are used (e.g., in radiation therapy) than when the same total dose is given in a single brief exposure. Damage to both strands of DNA at the same site is usually lethal to the cell.

Arrested Mitosis

- Ionizing radiations also affect cell division, resulting in arrested mitosis and, consequently, in retardation of growth. This phenomenon is the basis of radiotherapy of neoplasms.
- The extent of arrested mitosis varies with the phase of the mitotic cycle that a cell is at the time of irradiation. Cells are most sensitive to radiation during the last part of interphase and the early part of prophase.

Radiation Effects at Tissue Level

Somatic effects:

- Somatic effects include responses of all irradiated body cells except the germ cells of the reproductive system.
- Somatic effects are deleterious to the person irradiated.
- Somatic effects may be stochastic or deterministic.
- Somatic tissues do not always react to doses of ionizing radiation so as to give immediate clinically observable effects.
- There may be a time-lapse before any effects are seen.

- Basically, somatic effects are classified in two categories:
  - Early (Acute or immediate) effects.
  - Late (Delayed or chronic) effects.

Early Somatic Effects

- Appear rather soon after exposure to a single massive dose of radiation or after several smaller doses of radiation delivered within a relatively short period of time.
- In general, effects that appear within 60 days of exposure to radiation are classified as early effects.

Late Somatic Effects

- Late effects may occur anywhere from two months to as late as 20 years or more after exposure to radiation.
- The time lapse between the exposure to radiation and the appearance of effects is referred to as the "latent period."
- In radiobiology, the term “latent period” is usually used only in relation to stochastic effects (malignancy).

Variables in Somatic Effects

The magnitude of somatic effects depend on the following variables:

1. Cellular and tissue variability.
2. Source of radiation (External and Internal).
3. Individual variability.
4. Extent of exposure (Full or Partial Body).
5. Total dose.
6. Dose rate.
7. Age at exposure.

Effects of Radiation Therapy on Oral Tissues:

Adult teeth:

- Very resistant to the direct effect of radiation exposure.
- No effect on the crystalline structure of enamel, dentin and cementum.

➢ Radiation caries:

- In individuals whose salivary glands have been damaged resulting in xerostomia. Secondary to changes in saliva; i.e., reduced flow, pH and buffering capacity and increased viscosity.

Developing teeth:

- <10 Gy has very little or no visible effect.

Effects to an infant may include:

1. Destruction of tooth bud.
2. Tooth malformation.
3. Delay in eruption.

Bone:

- The most serious complication; Jaw **osteoradionecrosis**. This is primarily due to damage to the blood vessels of the jaw and consequent decreased capacity of the bone to resist infection. Tooth extraction or other injury and possibility of bone infection and necrosis becomes very high. More common in the mandible than in maxilla.

Salivary glands: <u>Xerostomia:</u> Marked and progressive loss of salivary secretion. The mouth becomes dry (xerostomia) and tender. The pH of saliva falls below normal (5.5 as compared to 6.5 in normal saliva). The salivary changes influence oral microflora, and secondarily contribute to the formation of radiation caries. Whether xerostomia is temporary or permanent depends upon the volume of glands exposed.

Mucosa: <u>Mucositis:</u> At 3rd or 4th week of RT, oral mucosa becomes red and inflamed (mucositis).

As the RT continues, mucosa forms yellow pseudomembrane. Secondary infection by Candida albicans is a common complication. Mucositis is most severe at the end of the treatment period. Healing begins soon after treatment and is usually complete in about two months after therapy. The mucosa tends to become atrophic, thin, and relatively avascular permanently.

Taste buds:

- Taste acuity is reduced or lost in about 4 weeks into the radiation treatment. In general, bitter and sour flavors are more severely affected when posterior third of the tongue is irradiated, salt and sweet when anterior third is irradiated. Complete recovery of taste usually occurs in two to four months following treatment completion.

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