❖ **Radiobiology:** The study of the effects of ionizing radiation on living systems.

In diagnostic radiography, not all x-rays passing through the patient and reach the dental x-ray film; some are absorbed by the patient's tissues, refers to the total transfer of energy from the x-ray photon to patient tissues. Energy Photons from a diagnostic or therapeutic x-ray beam interact with the patient's tissues, causing ionization of biologic molecules. These initial interactions occur almost instantaneously, within $\mathbf{10^{-13}}$ seconds after exposure.

Subsequent modification of biologic molecules follows within seconds to hours, and the damage from these modifications may manifest in hours, days, years, and even generations, or the changes may result in the death of the cell or organism, depending on the extent and type of damage.

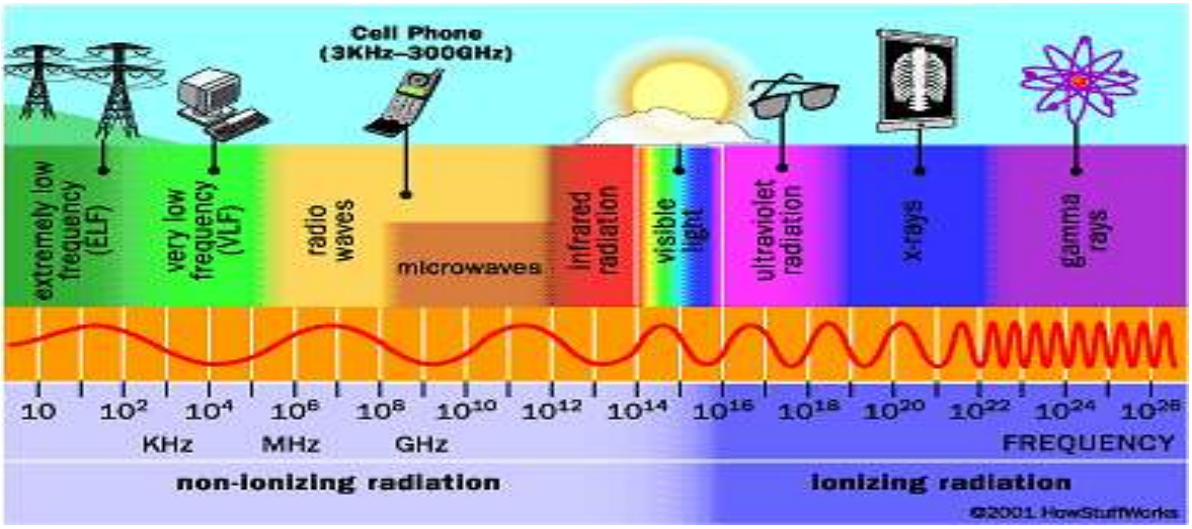


Fig 1: Types of radiation.

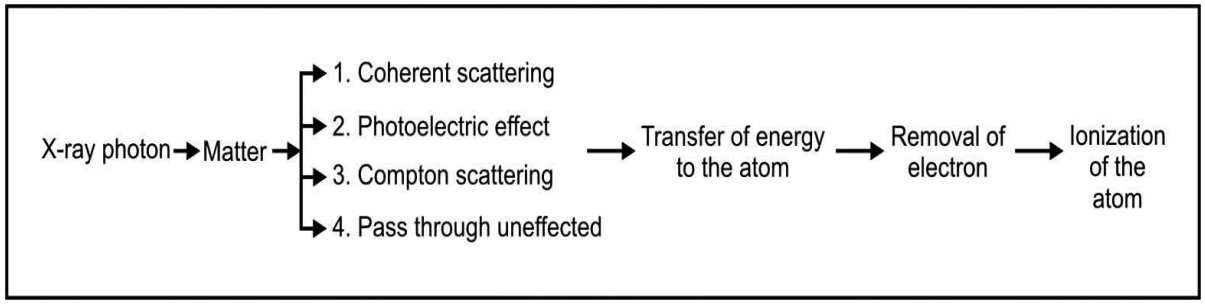


Fig2: Sequence of events occurred when an x-ray photon strikes matter.

❖ Types of radiation in general:

1- **Ionizing radiation:** the radiation that carried enough energy to liberate electron from atom or molecule by ionizing them, such as X- ray, gamma ray, beta and alpha particles.

2- **Non-ionizing radiation:** any type of electromagnetic radiation that does not carry enough energy to ionize atom or molecule, such as visible light, infrared, microwave, and radiowaves.

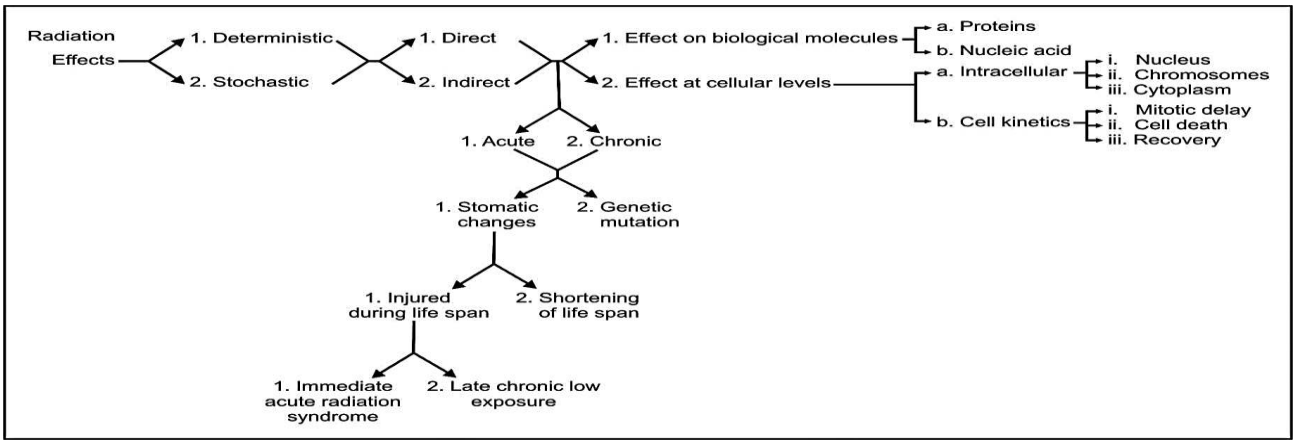


Fig3: Types of radiation.

Radiation Injury:

What happens when x-ray energy is absorbed by patient tissues? Chemical changes occur that result in biologic damage. Two specific mechanisms of radiation injury are possible: (1) ionization (2) free radical formation.

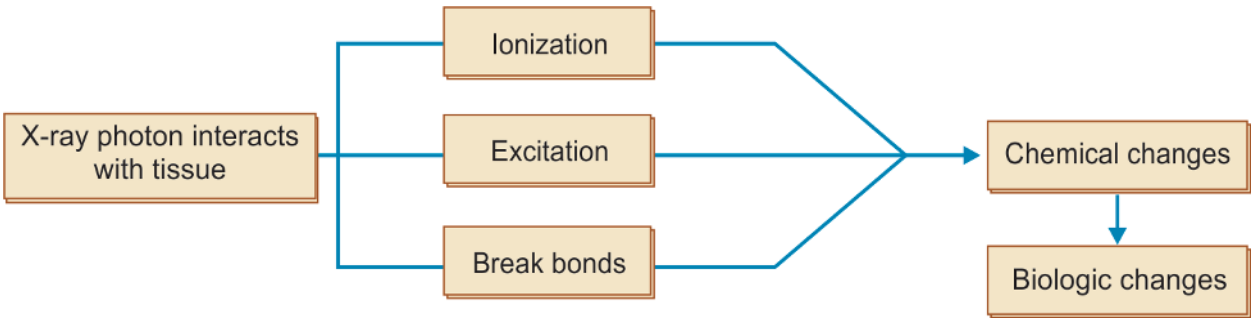


Fig4: Interaction of X-ray photon with tissue and produce biological changes.

Theories of radiation injury to the living systems:

Two theories are used to describe how radiation damages biologic tissues: (1) direct theory and (2) indirect theory.

In ***direct actions***, the photon directly interacts with and ionizes a biologic macromolecule. The free electrons produced by the ionization interaction (secondary electrons) may also interact directly with biologic macromolecules. In contrast, in ***indirect actions***, photons and secondary electrons interact with water and the products of water ionizations cause biologic damage.

Direct Effect: The direct theory of radiation injury suggests that cell damage results when ionizing radiation directly hits (DNA) of a cell. The biologic molecules (RH, where R is the molecule and H is a hydrogen atom) ionized by absorbing energy from X-ray photon or secondary electron and within $\mathbf{10^{-10}}$seconds form unstable free radicals. These free radicals quickly re-form into stable configurations by dissociation (breaking apart) or cross-linking (joining of two molecules). Free radicals play a dominant role in producing molecular changes in biologic molecules. Because the altered biologic molecules differ structurally and functionally from the original molecules, the consequence is a biologic change in the irradiated organism. Approximately one third of the biologic effects of x-ray exposure result from direct effects.

1. Free radical production: X-radiation + RH $\longrightarrow$ R• + H^+ + e^-

2. Free radicals are extremely reactive and have very short lives, quickly reforming into stable configurations by:

- ✓ dissociation (breaking apart): R• $\longrightarrow$ X + Y•
- ✓ or cross-linking (joining of two molecules): R• + S• $\longrightarrow$ RS

- **Indirect Effects:** In **indirect actions,** the initial interaction of a photon occurs with a water molecule—which constitutes approximately 70%. *Indirect actions are the predominant mode of x-radiation–induced biologic damage*. Ionizing radiation initiates a complex series of chemical changes in water, collectively referred to as **radiolysis of water**. The initial series of interactions of x-ray photon with water produce hydrogen (**H•**) and hydroxyl (**OH•**) free radicals that

interact with biologic macromolecules. *The hydroxyl radical is highly reactive and is estimated to cause two-thirds of the biologic damage to mammalian cells from x-rays*. The resulting organic free radicals are unstable and transform into stable, altered molecules, as described in the previous section on direct effects. These altered molecules have different chemical and biologic properties from the original molecules.

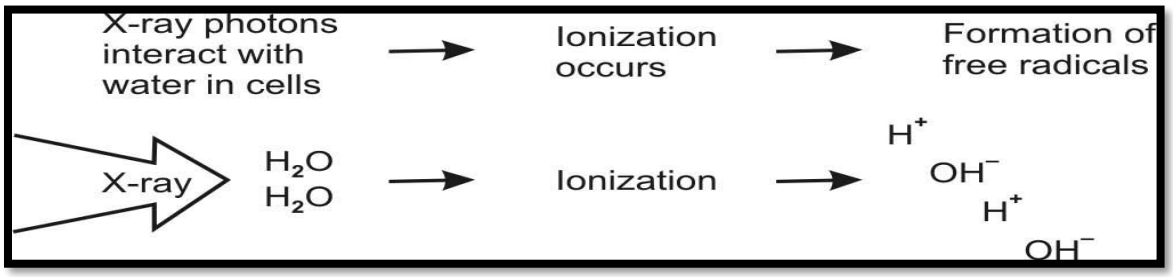


Fig 5: X-ray photon interaction with water in cells.

The free radicals are unstable and highly reactive. The lifetime of a free radical is about 10^{-10} seconds. The free radicals attain stability either by:

1. Recombining without causing any changes in the molecule.

2. Combining with other free radicals to cause changes.

3. Combining with ordinary molecules to form toxic substances, (e.g. hydrogen peroxide) [H2O2].

$$\text{X-radiation+H2O} \longrightarrow \text{H}\bullet + \text{OH}\bullet$$

Water is largely converted to hydrogen and hydroxyl free radicals [H• + OH•] that interact with

- ✓ **organic molecules** and results in the formation of organic free radicals R• by removing hydrogen atom from it.

$$\text{RH+ OH}\bullet \longrightarrow \text{R}\bullet + \text{H2O}$$

$$\text{RH+H}\bullet \longrightarrow \text{R}\bullet + \text{H2}$$

- ✓ When dissolved oxygen is present, as in normal tissues, hydroperoxyl free radicals may also be formed HO2•:

$$O2 + H\bullet \longrightarrow HO2\bullet$$

- ✓ Hydroperoxyl free radicals contribute to the formation of hydrogen peroxide [H2O2] in tissues:

$$HO2\bullet + H\bullet \longrightarrow H2O2$$

$$HO2\bullet + HO2\bullet \longrightarrow O2 + H2O2$$

Both hydroperoxyl radicals and hydrogen peroxide are **oxidizing agents** and are the primary **toxins** produced in the tissues by ionizing radiation. The reactions of these oxidizing agents with organic molecules are another form of indirect effects and can alter the chemical composition of hormones and enzymes and other body secretions make them partially or totally in effective and this effect depend on the amount of exposure to X-ray.

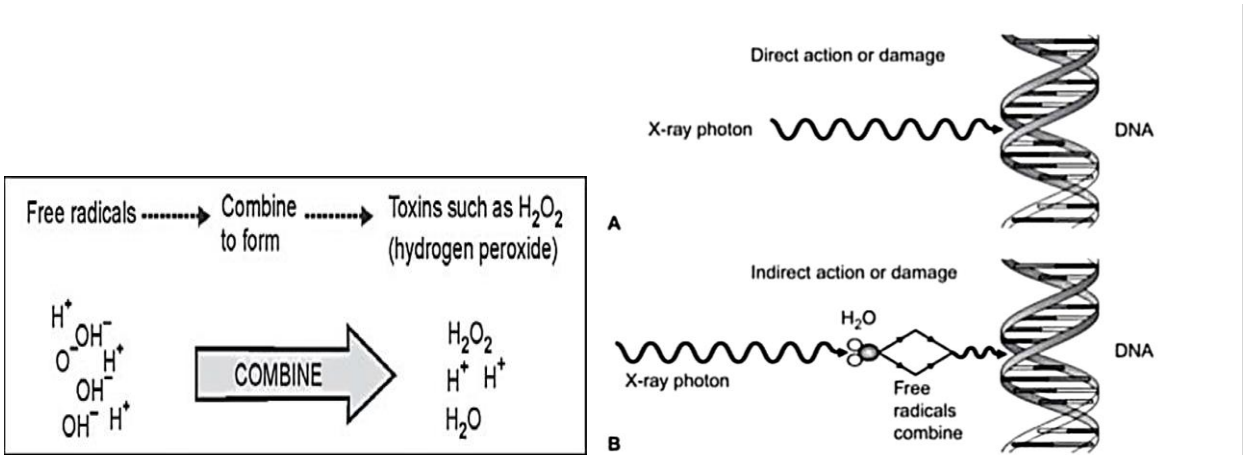


Fig6: Direct and indirect effects of radiation on DND.

Stochastic and Deterministic effects:

A. Stochastic effects (genetic effect): Response occur when the body is exposed to any dose of radiation. However, the severity of the damage ***is not related to the size of the inducing dose***. Their development is random and depends on the law of chance or probability.

Stochastic effects are considered to occur without a dose threshold.

• A single x-ray photon has the potential to cause a DNA mutation. Thus, even the smallest radiation dose could cause a heritable effect or cancer.

• As radiation dose increases, the number of radiations induced DNA damage sites in increased and the risk of subsequent disease-causing mutation is higher. Thus, *the probability of a stochastic effect increases with dose*.

The probability of a stochastic effect is increased with increasing doses, but the severity of the response is not proportional to the dose (e.g. two people may get the same dose of radiation, but the response will not be the same in both people).

- As radiation dose increases, the number of radiation-induced DNA damage sites is increased and the risk of subsequent disease-causing mutation is higher. Thus, *the probability of a stochastic effect increases with dose*.

B. Deterministic effect (somatic effect): Effects require larger radiation doses to cause serious damage so severity of response is proportional to the dose, i.e. greater the dose greater the effect.

- The deterministic effects have a threshold and that increase in severity with increasing absorbed dose.
- At doses below the threshold, the effect does not occur. Most individuals who receive doses higher than the threshold will develop the effect.
- The severity of this effect is proportional to the dose: the higher the dose, the more severe the effect.
- Diagnostic radiologic examinations are designed to keep the dose below the threshold dose, and thus deterministic effects are not encountered in diagnostic maxillofacial radiography. Examples of deterministic effects include erythema, loss of hair (threshold: 2–5 Gy), cataract formation (threshold: 5 Gy), and fetal abnormality (threshold: 0.1–0.5 Gy).

	Stochastic Effects	Deterministic Effects
Caused by	Sublethal DNA damage	Cell killing
Threshold dose	No	Yes
	There is no minimum threshold dose. Effect can be caused by any dose of radiation	Effect occurs only when the threshold dose is exceeded
Severity of clinical effects and dose	Severity of clinical effects is independent of dose; all-or-none response—an individual either manifests effect or does not	Severity of clinical effects is proportional to dose; the higher the dose, the more severe the effect
Relationship between dose and effect	Frequency of effect proportional to dose; the higher the dose, the higher the risk of manifesting the effect	Probability of effect independent of dose; most individuals manifest effect when threshold dose is exceeded
Caused by doses used in diagnostic radiology	Yes	No
Examples	Radiation-induced cancer	Osteoradionecrosis
	Heritable effects	Radiation-induced cataract formation
	Radiation-induced skin cancer	Radiation-induced skin burns

Long-Term and Short-Term Effects:

1. Long-term effect: Appear in years, decades, or generation after radiation exposure. The long-term effects are due to small amounts of radiation absorbed repeatedly over a long period of time. Repeated low levels of radiation exposure are linked to the induction of cancer, birth abnormalities, and genetic defects. The long-term deterministic effects are primarily caused by death of replicating cells, replacement with fibrous tissue, and damage to the fine vasculature.

2. Short-term effect: Refer to the damage occurring within minutes, days, or weeks. Short-term effects are due to large amounts of radiation absorbed in a short period of time as in nuclear accidents or atomic bomb explosions. Acute radiation syndrome (ARS) is a short-term effect characterized by: nausea, vomiting, diarrhea, hair loss, and hemorrhage. Short-term effects are not applicable to dentistry.

Radio sensitivity of tissues and organs:

- Radiosensitivity of tissues and organs measured by its response to radiation and produce biological changes.
- Cells are more sensitive to radiation when they are immature, undifferentiated, and rapidly dividing.
- If cells are more oxygenated, they are more susceptible to radiation damage which is known as oxygen enhancement ratio.
- Damage to the nucleus affects the chromosomes containing DNA and results in disruption of cell function or cell death.
- A cell that is sensitive to radiation is termed radiosensitive; and the cells that is resistant to radiation is termed radioresistant.
- Radiosensitive cells: include blood cells, immature reproductive cells, young bone cells, and small lymphocyte.
- Radioresistant cells: include cells of bone, muscle, and nerve.

❖ Modifying factors:

1. **Dose:** refers to the amount of radiation energy absorbed and produce tissue damage.
2. **Dose Rate:** Dose rate is the rate at which exposure to radiation occurs and absorption takes place (dose rate = dose/time). High dose rate results in more radiation damage as there is no sufficient time for the cellular damage to be repaired.
3. **Oxygen:** the greater cell damage occur in presence of oxygen is related to the increase the amount of hydrogen peroxide and hydroperoxyl free radicals (both are oxidizing agents that alter biological molecules and cause cell destruction and considered to be major toxins produced in tissues by ionizing radiation).
4. **Amount of tissue irradiated:** Areas of the body exposed to radiation. Total-body irradiation produces more adverse systemic effects than if small, localized areas of the body are exposed.
5. **Cell sensitivity:** More damage occurs in cells that are most sensitive to radiation, such as rapidly dividing cells and young cells.
6. **Age:** Children are more susceptible to radiation damage than are adults.

The response of a cell to radiation exposure is determined by the following:

1. Mitotic activity: Cells that divide frequently or undergo many divisions over time are more sensitive to radiation.

2. Cell differentiation: Cells that are immature or are not highly specialized are more sensitive to radiation.

3. Cell metabolism: Cells that have a higher metabolism are more sensitive to radiation.

The fallowing tissues and organs are listed in order to their susceptibility to X-ray:

1. **High radio sensitivity:** lymphoid organs, blood forming tissues (bone marrow), intestines, stem cells, lymphocytes and reproductive cells.
2. **Intermediate radio sensitivity:** young and growing bone, growing cartilage, glandular tissue, salivary glands, kidney, liver, lungs and epithelium of alimentary canal.
3. **Low radio sensitivity:** skin, muscle and optic lens.
4. **The least effect:** seen in nerve tissue and adult bone.

Critical organ:

Critical organs exposed during dental radiographic procedures in head and neck region include the following:

- Skin
- Thyroid gland
- Lens of the eye
- Bone marrow

Local tissue damage

- When only part of the body is exposed to radiation, higher dose is required to produce a response, compared to doses required for whole- body irradiation responses.
- The immediate response of the tissue or organ is dependent on the radiosensitivity of the tissue.
- The skin may demonstrate some early effects of radiation. A single dose may produce erythema within one or two days. Also, may demonstrate epilation (loss of hair).
- Loss of fertility in the reproductive cells are vary susceptible to radiation injury.

- Female (suppression of menstruation) may occur, and mature ovum are susceptible to radiation.
- Mature sperm are quite radioresistant, especially compared to the mature ovum.

Effects of radiotherapy on oral tissue: للأطلاع

— Dentists are likely to manage patients who are undergoing radiation therapy or have received such treatment for management of head and neck malignancies. Often, the radiotherapy approach is combined with surgery and chemotherapy.

1. Oral Mucosal lesions:

One of the first reactions appear is an erythema and edema of the oral mucosa, or radiation mucositis (areas of redness and inflammation). Ulceration and desquamation, follow after about 2 weeks of radiotherapy.

2. Taste Buds:

Taste buds are sensitive to radiation. Bitter and acid flavors are more severely affected when the posterior two-thirds of the tongue is irradiated, and salt and sweet flavors are affected more when the anterior third of the tongue is irradiated. Alterations in the saliva may partly account for this reduction. Taste loss is reversible, and recovery takes 2 to 4 months.

3. Salivary Glands:

Salivary glands are highly sensitive to radiation, this is likely due to radiation-induced apoptosis of salivary acinar cells. Within the first week of radiation therapy, patients experience an approximately 50% decrease in salivary flow, attributed to apoptosis of the acinar cells and Xerostomia is a significant result of irradiation of salivary gland tissue.

4. Radiation caries:

The radiation itself has no effect on erupted teeth, but xerostomia, accompanying loss of lubrication, buffering, and antibacterial capacities of saliva, and the shift in oral flora populations are causes of the caries. Xerostomic environment favors, streptococcus mutans and lactobacillus species, organisms that are highly implicated in caries production.

5. Teeth:

The effect on teeth depends on the stage of tooth development. If exposure occurs at early development, irradiation may destroy the tooth bud. In partially developed teeth irradiation may inhibit cellular differentiation, causing malformations and arresting general growth. Irradiated teeth with altered root formation typically erupt, even if rootless. Children receiving radiation therapy to the jaws may show defects in the permanent dentition, such as retarded root development, or failure to form one or more teeth.

6. Bone:

The primary damage to mature bone results from radiation-induced damage to the vasculature of the periosteum and cortical bone. Osteoradionecrosis (ORN) is a late complication of radiation therapy and occurs when an area of irradiated bone becomes devitalized. A widely-accepted model is that radiation induced microvascular changes create a state of hypoxia, hypovascularity, and hypocellularity, thereby disturbing normal bone homeostasis, and leading to a chronic, nonhealing wound.