DEPARTMENT

OF

ORAL MEDICINE AND RADIOLOGY

NOTES ON

"RADIATION BIOLOGY"

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READER

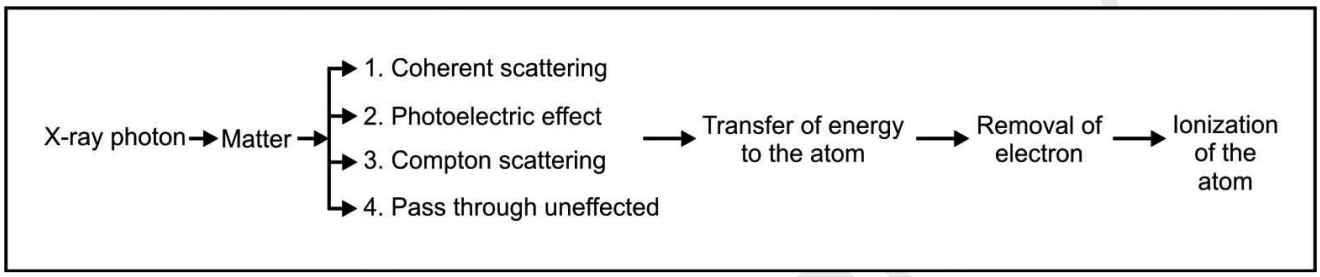
CONTENTS

RADIATION BIOLOGY

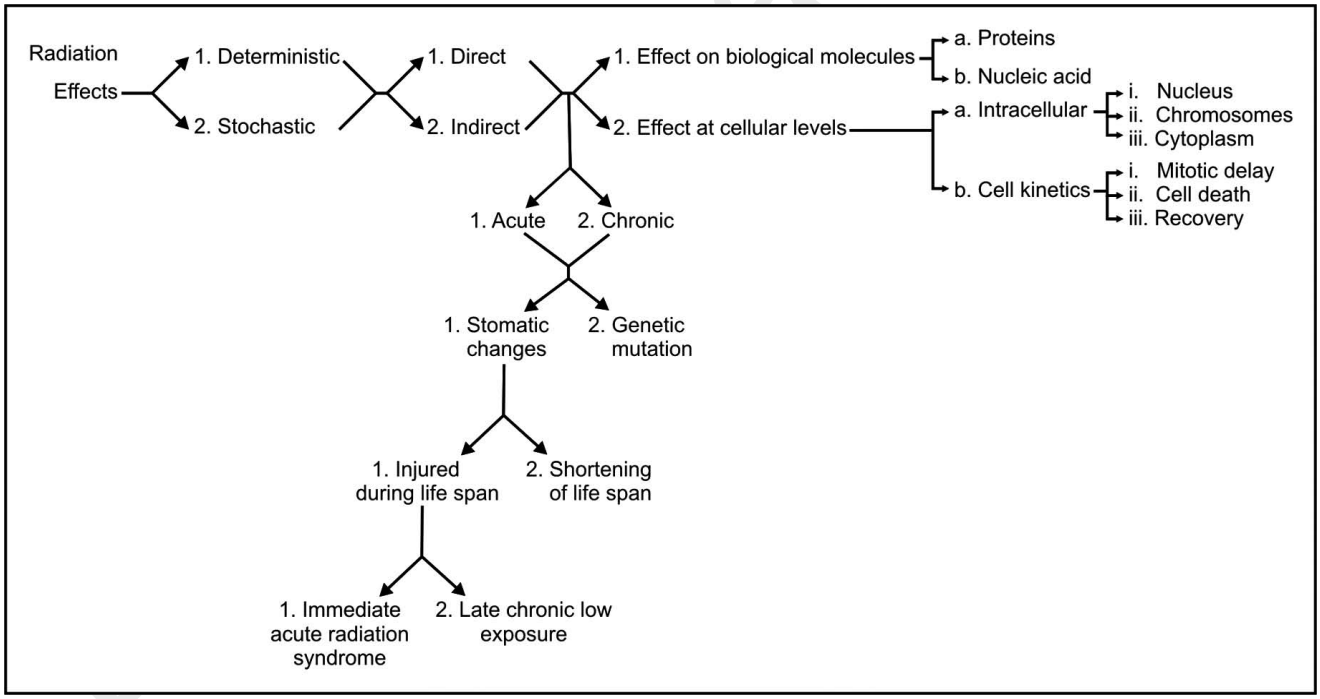
Radiation Biology is defined as the study of the effects of ionizing radiation on living systems. The initial interaction between radiation and matter occurs at the level of the electron. These initial changes are the basis for subsequent modification of biological molecules.

In turn these molecular changes may result in alteration in the cells and organism. These changes may persist for hours, decades or possibly for generations, or the changes may be so drastic that they may result in the death of the cell or organism.

Sequence of Events which Occur when an X-ray Photon Strikes Matter



Effect of Radiation on the Biological Tissues



Deterministic effect: Is an effect in which the severity of the response is proportional to the dose. These effects have a dose threshold below which the response is not seen. For example oral changes after radiation therapy. This effects usually in cell killing, and may occur in all people when the dose is large enough.

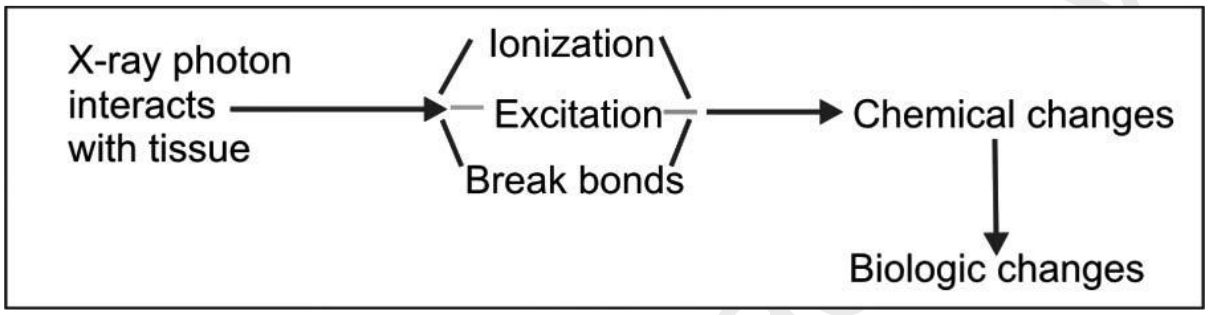
Stochastic effect: It is that effect for which the probability of the occurrence of a change, rather than its severity is dose dependent. These effects do not have a dose threshold. For example radiation induced cancer, because the greater exposure of a person or population to radiation increases the probability of the cancer but not its severity.

Direct or Target Action Theory

Director or Target Action Theory is that effect which occurs when the energy of a photon or secondary electron ionizes biological macromolecules.

This states that the changes occur due to:
• Absorption of energy by biological molecules.
• Transfer of energy between unstable intermediate molecules.
• Formation of stable damaged molecules by disassociation or cross-linking.

The resultant molecules differ structurally from the original molecule hence the consequence is a biological change in the irradiated organism.



Specific targets within the cell, probably the DNA or RNA in the nucleus take a direct hit from an incoming X-ray photon, or an ejected high energy electron, which breaks the relatively weak bonds between the nucleic acids. The subsequent effect includes:
• Inability to pass on information.
• Abnormal replication.
• Cell death.
• Only temporary changes- the DNA being repaired successfully before further cell division.

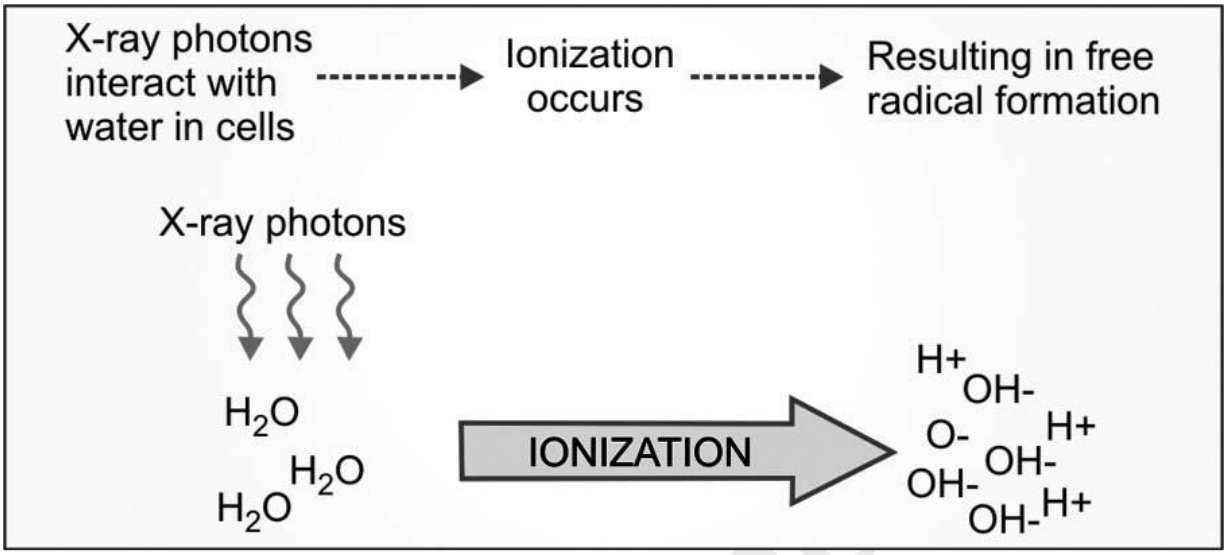
If the radiation hits some somatic cells, the effects on the DNA could result in radiation induced malignancy.

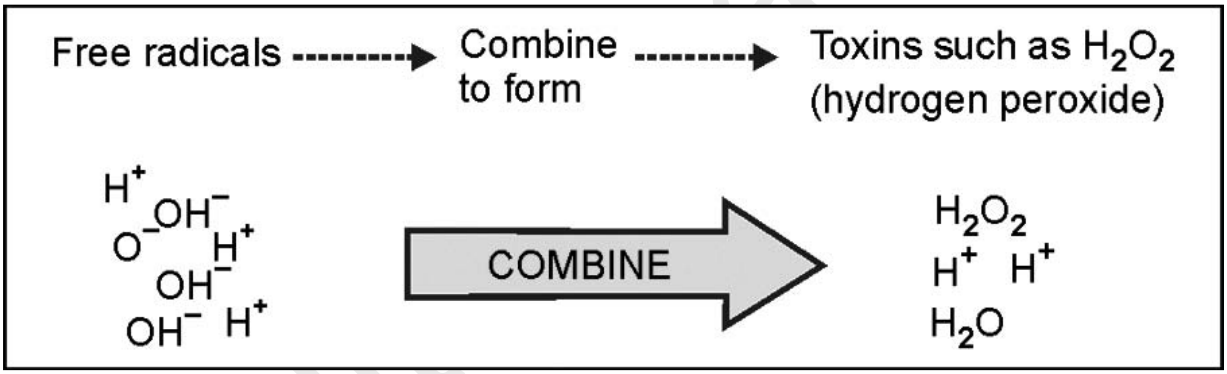
If the damage is to reproductive stem cells, the result would be radiation-induced congenital abnormalities.

What actually happens depends on several factors, such as:
• The type and number of nucleic acid bonds those are broken.
• The intensity and type of radiation.
• The time between exposures.
• The ability of the cell to repair the damage.

Indirect Action or Poison Chemical Theory

Water is a predominant molecule of the biological system. When the photon is absorbed by the water molecule, it is ionized and releases free radicals which further interact and produce changes in the biologic molecule, this effect is termed 'indirect'.





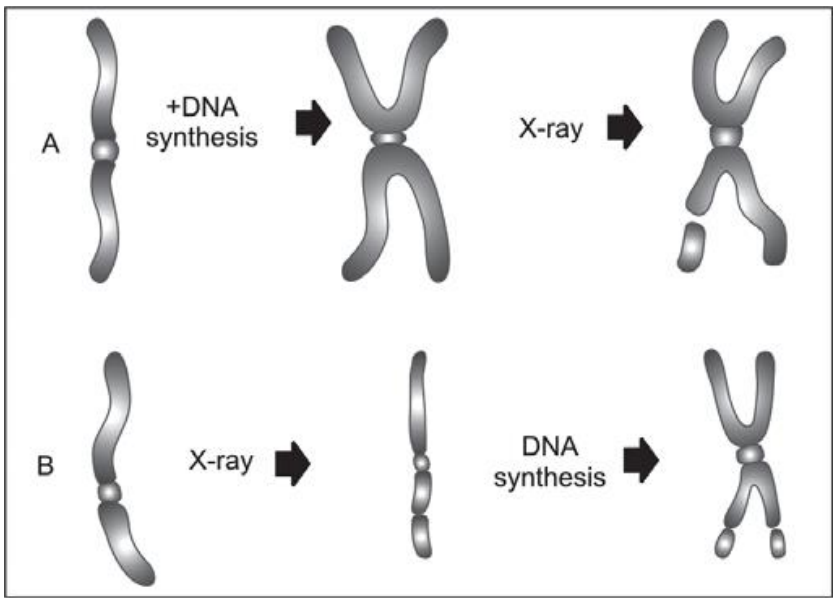
Effect on Biological Molecules

• Proteins
  – Denaturation.
  – Inter- and intramolecular cross-linking.
  – Enzymes get inactivated leading to failure or conversion of substrate to product.
• Nucleic acids
  – Change or loss of base.
  – Disruption of hydrogen bonds between DNA strands.
  – Breakage of DNA strands.
  – Cross-linking of DNA strands.

Effects at Cellular Levels

Intracellular

• Nucleus: inhibition of cell division.
• Chromosomes: single or double armed chromosomal aberrations.
• Cell cytoplasm:
  – Increased permeability of plasma membrane to sodium and potassium ions.
  – Swelling and disorganization of mitochondria.
  – Focal cytoplasmic necrosis.



Effect on Cell Kinetics

This basically effects cell division and cell maturation process and depends upon:

• Dose of radiation

a. High

b. Low

• Period of radiation

a. Acute

b. Chronic

• Nature of dose of radiation

a. Fractionalized

b. At one time

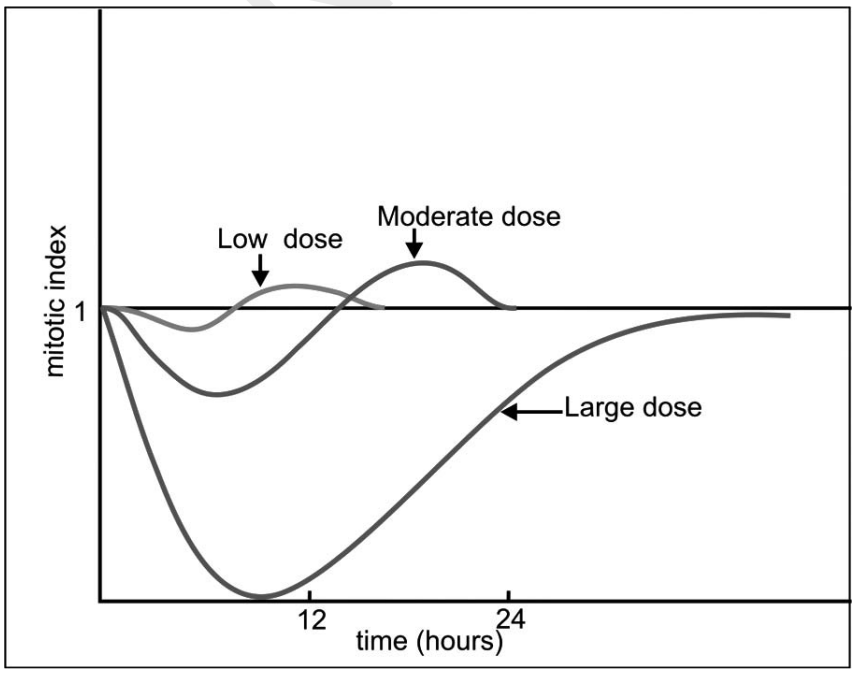
• Interval period between doses

The effects seen are:

• Mitotic delay: Inhibition of progression of cell through the cell cycle.

• Cell death: If damage is total there can be no recovery.

• Recovery: The capacity to recover depends on the above given factors.



Acute Exposure

This occurs when a large dose of radiation is absorbed in a short period of time, e.g. nuclear accident.

The radiation damage caused by acute radiation is much more than that caused by chronic exposure to radiation.

This type of exposure is not seen when using Dental Diagnostic Radiations.

Chronic Exposure

This occurs when small amounts of radiations are absorbed repeatedly over a long period of time.

Somatic Damage

This damage occurs in the living cell/organism and is not carried forward once the cell/organism dies.

This can be observed as:

- Injuries during the life span
  - –The most important are the radiation induced cancers. It is believed that radiation causes cancer by modifying the DNA, still the exact mechanism of induction of cancer by ionizing radiation is not well understood. The most commonly found cancers are:
    a. Thyroid cancer.
    b. Esophageal cancer.
    c. Brain and nervous system cancers.
    d. Salivary gland cancers: The incidence is increased in patients treated for diseases of the head and neck. It was believed that the risk of salivary gland tumors may be highest in patients receiving full mouth examinations before the age of 20 years but it has been seen that this may be true only in individuals who have received a cumulative parotid dose of 500 mGy or more.
    e. Cancer of other organs, like skin, paranasal sinuses and bone marrow also show excess neoplasia after exposure.
    f. Leukemia.
  - –Other Late Somatic Changes:
    a. Growth and development is retarded subject to the age and amount of radiation the individual was exposed to.
    b. Mental retardation: as estimated 4 percent chance of mental retardation per 100 mSv exists at 8 to 15 weeks of gestation age.
    The exposure to the embryo from a full set of dental radiographs, using lead apron, is less than 3 mSv.
    c. Cataracts: the threshold for induction of cataracts is from 2 Gy to more than 5 Gy.
- Shortening the life span.

Genetic damage

Genetic cells are the germ cells found in the reproductive organs. These contain chromosomes which have genes which are made up of DNA.

Any damage will lead to loss or rearrangement of the genetic material, which results in genetic mutations.

These changes are more commonly seen in the next and subsequent generations.

Doubling dose:

It is the amount of radiation a population requires to produce in the next generation as many additional mutations as arise spontaneously.

In humans the genetic doubling dose for mutations resulting in death is approximately 2 Sv.

Short-term Effects
These effects of radiation on a tissue are determined primarily by the sensitivity of its parenchymal cells.
If continuously proliferating cells are irradiated (bone marrow, oral mucous membrane), the effect of irradiation becomes apparent relatively quickly, (highly radio sensitive).
Tissues composed of cells that rarely or never divide (muscle) demonstrate little or no radiation induced hypoplasia (low radiosensitivity) over a short-term.

Long-term Effects
The long-term deterministic effects of radiation on tissues and organs depend primarily on the extent of damage to the fine vasculature. The relative radiosensitivity of capillaries and connective tissue is intermediate. Irradiation of capillaries causes swelling, degeneration and necrosis, which increase capillary permeability and initiate progressive fibrosis around the vessels, leading to deposition of fibrous scar tissue and premature narrowing of vascular lumens. This impairs transport of oxygen, nutrients and waste products resulting in cell death, leading to progressive fibroatrophy of the irradiated tissue, and loss of cell function with a reduced resistance of the irradiated tissue to infection and trauma.
In India, around 40 percent of all cancers are detected as oral cancers. In addition for patients with cancer of the nose, nasopharynx, paranasal sinuses and oropharynx, radiotherapy is one of the modality of treatment used.
Radiotherapy is frequently used as an adjuvant form of treatment in the management of head and neck cancer. This radiotherapy may produce an oral sequelae that causes considerable misery to the patient.

***Radiocurability*:**
is defined as the ability of radiations to reduce the number of malignant cells below a critical level such that no further clinical manifestation of their presence will occur during the remaining life time of the host.
Radiocurability of a tumor is related to its radiosensitivity regardless of its radioresponsiveness.

***Radiosensitivity*:**
is defined as the ability of radiations to biologically change, (i.e. cell killing or a destruction of reproduction integrity) cells comprising a tumor or other tissue.
These changes manifest clinically as an alteration in the structure or function.

***Radioresponsiveness*:**
This refers to the time required for any changes to occur and can be measured in terms of the rate at which the clinical manifestations of radiation induced biologic change take place.
A tumor that shrinks rapidly following administration of any amount of radiation would be called radioresponsive.
Different cells of the same individual may respond differently to the same irradiation. Casarett has divided mammalian cells into five categories of radiosensitivity on the basis of histologic observations of early cell death.

1. ***Vegetative intermitotic cells*:**
   These are most radiosensitive. These cells divide regularly, have long mitotic futures and do not undergo differentiation between mitosis, have a short life span, e.g. early precursor stem cells such as those in spermatogenic or erythroblastic series, basal cells of the oral mucous membrane.
2. ***Differentiating intermitotic cells*:**
   These are less radiosensitive. They divide regularly but less often and undergo some differentiation between divisions, e.g. Intermediate dividing and replicating cells of

the inner enamel epithelium of developing teeth, cells of hematopoietic series that are in the intermediate stages of differentiation, spermatocytes and oocytes.

3. ***Multipotential connective tissue cells*:**
   These have intermediate radiosensitivity. They divide regularly with limited differentiation, e.g. vascular endothelial cells, fibroblasts and mesenchymal cells.
4. ***Reverting postmitotic cells*:**
   These are radioresistant. They divide infrequently, have a long life span and die without dividing. These divide only under special conditions and are specialized in function, e.g. acinar and ductal cells of salivary glands and pancreas, and parenchymal cells of the liver, kidney and thyroid.
5. ***Fixed postmitotic cells*:**
   These are most radioresistant. These do not divide even in functional demand, e.g. neurons, striated muscle cells and squamous epithelial cells that have differentiated and are close to the surface of the oral mucous membrane.

The relative radiosensitivity of various organs is as follows:

***High sensitivity*:**
Lymphoid organs, bone marrow, testes, intestines, mucous membrane.

***Intermediate sensitivity*:**
Fine vasculature, growing cartilage, growing bone, salivary glands, lungs, kidneys, liver.

***Low sensitivity*:**
Optic lens, mature erythrocytes, muscle cells, neurons.

Factors Effecting Biologic Tissues

1. Nature of tissue irradiated.
   i. Radioresponsive.
   ii. Radioresistant.
2. Area irradiated: For the same dose, if a smaller area is irradiated, the effect of radiation is less.
3. Rate of dose: Smaller the dose, distributed over a large period of time results in a smaller or lesser effect of the radiation.
4. Fractionization: Division of the dose, with sufficient gaps, helps in tissue recovery resulting in lesser effect of the radiation.
5. Latent period: This is the period between the time of irradiation and the appearance of the effect.
6. Age of the patient: Younger the patient greater the chances of recovery.
7. Recovery power of the tissue: Undifferentiated cells have a greater power of recovery.
8. Type of cell: The effect of radiation is seen in the same generation if a somatic cell is effected, and in case of the genetic cell the effect of radiation will be seen in the next generation.
9. Type of irradiation: There are different types of irradiations—low energy, high energy or linear energy transfer.
10. Oxygenation: Greater oxygenation of the tissue, chances of recovery are greater, e.g. hyperbaric oxygen is used to treat radiation necrosis but it is important to note that the radioresistance of many biologic systems increases by a factor of 2 or 3 when irradiation is conducted with reduced oxygen (hypoxia).
11. Chemical protectors: Amino compounds or disulphides and amino groups, these act as free radical scavengers and prevent the damaging effects of organic free radicals.
12. Stage of development of the tissue: The effect of irradiation depends on the stage of development of the tissue, e.g. primitive and undifferentiated and still undergoing mitosis when irradiated the damage caused is greater.

13. Tissue threshold: Greater the tissue threshold, lesser the damage seen. This depends on the amount of radiation absorbed. Somatic changes do not occur until a minimum of tissue threshold is exceeded. Genetic changes occur with any given dose.
14. Part of the body exposed: The hazard of radiation is increased when a larger part of the body is exposed. Local or isolated part of the body may receive larger doses without risk, but the same dose given to the whole body may prove lethal.
15. Species and individuals: Different species respond differently. The median lethal dose varies in different species. Similarly in individuals of the same species the response may be variable. This variation of the Maximum Permissible Dose is approximately 50 percent.

In dental radiography the critical organs receiving scattered radiation include:

Bone marrow –

13 mR for full mouth intraoral periapical radiographs.

A maximum dose of 200 R is required for any damage to the marrow or blood forming organs. Hence, the risk of bone marrow damage from dental X-rays is small. The primary somatic risk from dental radiography is leukemia induction, especially in young individuals. This is because at birth all bones contain only red bone marrow, (one of the blood forming organs of the body), but with age some marrow changes to yellow (fatty) bone marrow, thus younger individuals are at a greater risk of developing leukemia.

Thyroid –

40 mR for full mouth intraoral periapical radiographs.

A dose of 10 R will produce thyroid cancer. All dental radiography gives scattered radiation to the thyroid, except cephalometry and curved surface tomography, where the thyroid is in the direction of the primary beam.

Gonadal –

A single intraoral radiograph gives 100 to 900 mR to the face. From this;

Male gonads receive 0.3 mR.

Female gonads receive 0.03 to 0.001 mR, as these are placed internally.

A person on an average receives 0.3 mR by way of exposure from the sun and other radioactive materials. Thus, gonadal exposure is minimal with dental radiography.

The radiation to the gonads is principally via scattered radiation.

Eye –

A series of full mouth intraoral periapical radiographs, will give only a few mR.

Cataract of the lens is produced after 500 R of exposure.

General Effects of Radiation

Skin: The reaction of the skin to radiation may be categorized as:

i. Early or acute signs:
- Increased susceptibility to chapping.
- Intolerance to surgical scrub.
- Blunting and leveling of finger ridges.
- Brittleness and ridging of finger nails.

ii. Late or chronic signs:
- Loosening of hair and epilation.
- Dryness and atrophy of skin, due to destruction of the sweat glands.
- Progressive pigmentation, telangiectasis and keratosis.
- Indolent type of ulcerations.
- Possibility of malignant changes in tissue.

All these changes in the skin are due to radiation trauma to:
- The blood vessels.
- Connective tissue.
- Epithelium.

Early erythema may appear from a single dose of about 450 rads.
With lower doses no erythema occurs.

2. Hematopoietic injury:

The usual picture of blood reaction to radiation is leukopenia, which in some cases may progress to leukemia, anemia, lymphopenia, and loss of specific immune response.

3. Eyes:

- Epilation of eyelashes.
- Inflammation, fibrosis and decreased flexibility of the eyelid.
- Damage to the lacrimal glands, leading to dryness.
- Ulceration of the cornea.
- Initiation of cataract formation from the periphery towards the center.

4. Ears:

- Columnar epithelium of the middle ear may be desquamated.
- Edema of the mucosa and collection of sterile fluid in the middle ear, which leads to obstruction of the eustachian tube – Radiation Otitis Media.
- Deafness due to rupture of the ear drums.

5. Testicles:

- Suppression of germinal activity.
- Alteration in fertility.
- Functional changes in the offspring may be seen.

6. Ovary:

- The various cells respond differently to irradiation.
- Increase in frequency of hemangioma in children receiving dose of radiation *in utero*.

7. Oral mucous membrane:

- Shows reddening and inflammation (mucositis).
- The next step is the breakdown, with the formation of white to yellow pseudomembrane.
- Sloughing of the mucosa.
- Secondary infection is very common.
- After termination of the therapy, the healing may be complete after about two months, but the mucous membrane tends to become atrophic, thin and relatively avascular, due to the obliteration of fine vasculature and fibrosis of the underlying connective tissue.
- Patient is usually prone to oral ulcerations and is unable to tolerate dentures.

8. Taste buds:

These are sensitive to radiation and patient realizes a loss of taste in the second or third week of radiation therapy:

- Posterior two-third of the tongue when irradiated effects the bitter and acid flavors.
- Anterior third of the tongue when irradiated effects sweet and salty flavors.

These changes in the taste perception may also be attributed to the salivary changes that occur due to radiation.

9. Salivary glands:

The parenchymal component of the gland is sensitive to radiation. The gland demonstrates progressive fibrosis, adiposis, loss of fine vasculature and simultaneous parenchymal degeneration.

- There is marked decrease in the salivary flow.
- The composition of saliva is affected.
- There is increased concentration of sodium, chloride, calcium, magnesium ions and proteins.
- The saliva loses its lubricating properties.
- The mouth becomes dry and tender due to xerostomia.

- The pH of saliva is decreased which may initiate decalcification of enamel.
- A compensatory hypertrophy of the salivary gland may take place and the xerostomia may subside after six to twelve months after therapy. The xerostomia that persists beyond a year is less likely to show return to normal.

10. Teeth:

Adult teeth are resistant to the effects of radiation. When teeth are exposed to radiation in their developing stage, their development may be retarded.

- Prior to calcification, the tooth buds get destroyed.
- After initiation of calcification, there may be inhibition of cellular differentiation causing malformation or arrest of growth.
- The pulp shows decreased vascularity, reduced cellularity and the tooth becomes more prone to pulpitis.

Radiation caries:

This is a rampant form of caries. These lesions occur secondary to changes in the salivary glands and saliva, due to the:

- Decreased salivary flow.
- Decreased pH of saliva.
- Increased viscosity of saliva.
- Decreased lubricating properties of saliva.

All of the following leads to the decalcification of the enamel and increased accumulation of the food debris.

Clinically three types of radiation caries are seen:

i. Primarily involving cementum and dentin in the cervical areas. This lesion progresses around the tooth circumference and ultimately results in the amputation of the crown.
ii. Generalized superficial lesions attacking the buccal, occlusal, incisal and palatal surfaces of the teeth.
iii. Dark pigmentation of the crown.

11. Bone:

- The primary damage to the mature bone is because of the damage to the fine vasculature which is already sparse in a dense bone such as the mandible.
- Due to the loss of vasculature and hematopoietic elements, the marrow is replaced by fatty marrow and fibrous connective tissue.
- The endosteum becomes atrophic, and shows lack of osteoblasts and osteoblastic activity.
- The complication following irradiation is called osteoradionecrosis:
  - In this, the bone becomes hypovascular, hypocellular and hypomineralized, with decreased blood supply.
  - It is more often seen in the mandible than the maxilla, this is commonly attributed to the fact that the mandible has a single blood supply.
  - On the radiograph, osteoradionecrosis does not show any periosteal reaction as that seen in the case of osteomyelitis.
  - Osteoradionecrosis of the bone usually occurs due to infection or necrosis of the bone following tooth extraction or a chronic denture sore.

12. Whole body irradiation:

When the whole body is exposed to low or moderate doses of radiation there are characteristic changes seen, called Acute Radiation Syndrome; which may be followed by death within one month. Individuals surviving ARS may show late somatic effects which may be seen as:

- Prodromal syndrome (1-2 Gy): Shortly after exposure the patient may develop nausea, vomiting, diarrhea and anorexia.

- Latent period: This is a period of apparent well being, the extent of which is dose related. Symptoms follow the latent period when the individuals are exposed in the lethal range (appx 2 to 5 Gy) or the supralethal range (more than 5 Gy).
- Bone marrow (hemopoietic) syndrome (2 to 7 Gy): Here severe damage may be caused to the circulatory system. The bone marrow being radiosensitive, results in fall in the number of granulocytes, platelets and erythrocytes. Clinically this is manifested as lymphopenia, granulocytopenia and hemorrhage due to thrombocytopenia and anemia due to depletion of the erythrocytes.
- Gastrointestinal syndrome (7 to 15 Gy): This causes extensive damage to the gastrointestinal tract, leading to anorexia, nausea, vomiting, severe diarrhea and malaise.

  Injury to the basal cell epithelial cells of the intestines causes denuded mucosal surfaces, leading to loss of plasma and electrolytes, hemorrhage and ulcerations leading to diarrhea, dehydration and loss of weight. Finally leading to septicemia.
- Cardiovascular and central nervous system syndrome (more than 50 Gy): This produces death within one or two days. Individuals show intermittent stupor, incordination, disorientation and convulsions suggestive of extensive damage to the nervous system.

13. Shortening of the life span:

The life span is diminished following brief whole body radiation exposure, or a small amount of radiation given over a long period of time. There is an acceleration of the aging process resulting in a shortened life span.

14. Radiation effect on embryos and fetuses:

Embryos and fetuses are considerably more radiosensitive than adults because most embryonic cells are relatively undifferentiated and rapidly mitotic. The fetus of a patient exposed to dental radiography receives less than 0.25 mGy from a full mouth examination when a leaded apron is used.

The most sensitive period for inducing developmental abnormalities is during the period of organogenesis, between 18 and 45 days of gestation. These effects are deterministic in nature.

Irradiation during the fetal period (more than 50 days after conception) does not cause gross malformations. However, general retardation of growth may persist through life. There is also an increased risk for childhood cancer, (leukemia and solid tumors), after irradiation *in utero*.

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