# Sri Aurobindo College of Dentistry

## Indore, Madhya Pradesh

## INDIA

# MODULE PLAN

- TOPIC : RADIATION BIOLOGY
- SUBJECT:OMDR
- TARGET GROUP: UNDERGRADUATE DENTISTRY
- MODE: POWERPOINT – WEBINAR
- PLATFORM: INSTITUTIONAL LMS
- PRESENTER:DR.NAVDEEP JOHAR

# INTRODUCTION

- Radiation biology is the study of the effects of ionizing radiation on living systems.
- The initial interaction between ionizing radiation and matter occurs at the level of the electron within the first $10^{-13}$ second after exposure.
- These changes result in modification of biologic molecules within the ensuing seconds to hours.

- In turn, the molecular changes may lead to alterations in cells and organisms that persist for hours, decades, and possibly even generations.
- If enough cells are killed in an individual, it may cause injury or death.
- If cells are modified, such changes may lead to cancer or disorders in the descendents of the exposed individual.

# TYPES OF RADIATION EFFECTS

- Biologic effects of ionizing radiation may be divided into two broad categories: deterministic effects and stochastic effects.

1. Deterministic effects: These are those effects in which the severity of response is proportional to the dose.

- These effects, usually cell killing, occur in all people when the dose is large enough.

- Deterministic effects have a dose threshold below which the response is not seen.
- Examples of deterministic effects include oral changes after radiation therapy.

2. Stochastic effects: These effects are those for which the probability of the occurrence of a change, rather than its severity, is dose-dependent.

- Stochastic effects are all-or-none: a person either has or does not have the condition.

- For example, radiation induced cancer is a stochastic effect because greater exposure of a person or population to radiation increases the probability of cancer but not its severity.

- Stochastic effects are believed not to have dose thresholds.
- It is therefore assumed that every exposure to ionizing radiation carries with it the possibility of inducing a stochastic effect.

# Other radiation effects

1. Somatic effects

- Somatic cells are all the cells in the body except the reproductive cells.
- Radiation effects produced in the somatic cells are called as somatic effects.
- These effects are seen in the person irradiated and produce poor health of the irradiated person.
- These changes are not transmitted to future generations.
- For example: Induction of cancer, leukemia and cataract.

## 2. Genetic effects

- The reproductive cells are called as genetic cells and radiation effects produced in these cells are called as genetic effects.
- They donot affect the health of the irradiated person.
- These effects are not seen in the person irradiated but are passed on to the future generation.
- For example: Genetic mutations

## 3. Short-term effects

- Following the latent period, effects that are seen within minutes, days, or weeks are termed short-term effects.
- Short-term effects are associated with large amounts of radiation absorbed in a short period of time.
- For example:
  - Exposure to a nuclear accident or the atomic bomb.
  - Acute radiation syndrome.
- Short-term effects are not applicable to dentistry.

## 4. Long term effects

- Effects that appear after years, decades or generations are termed long-term effects.
- They are associated with small amounts of radiation absorbed repeatedly over a long period of time.
- Examples: Induction of cancer, birth anomalies, genetic defects.
- Long-term effects are applicable to dentistry.

## 5. Direct effects

- Cell damage resulted when ionizing radiation directly hits critical areas or targets within the cell.

- For example, if x-ray photons directly strike the DNA of a cell, critical damage occurs causing injury to the irradiated organism.

- Mostly, direct effects from radiation occur infrequently, because most of the x-rays pass through the cell and cause little or no damage.

## 6. Indirect effects

- This theory suggests that x-ray photons are absorbed within the cell and cause the formation of toxins, which in turn damage the cell.
- For example, when x-ray photons are absorbed by water within a cell, free radical formation occur which combine to form toxins like hydrogen peroxide and hydroperoxyl radicals and cause cellular damage and dysfunction.

# RADIATION CHEMISTRY

## Direct effects

- Accounts for app. 1/3$^{rd}$ of biologic effects.
- Direct alteration of biologic molecules (RH, where R is the molecule and H is a hydrogen atom) by ionizing radiation begins with absorption of energy by the biologic molecule and formation of unstable free radicals (atoms or molecules having an unpaired electron in the valence shell).
- The generation of free radicals occurs in less than $10^{-10}$ second after the passage of a photon.

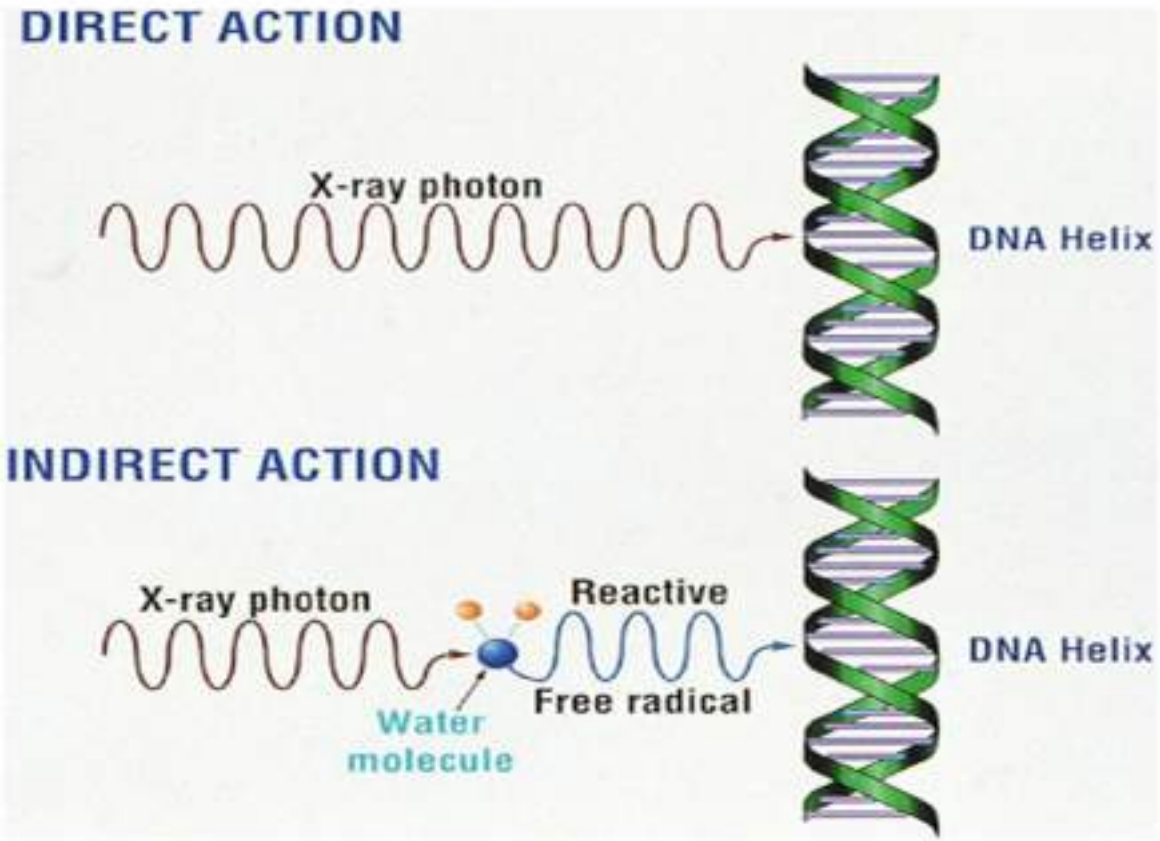



**FIG. 6-3.** The action of radiation on the cell can be direct or indirect. It is direct when ionizing particles interact with a vital biologic macromolecule such as DNA. The action is indirect when ionizing particles interact with a water molecule resulting in the creation of ions and reactive free radicals that eventually produce toxic substances that can create biologic damage. (From *Mosby's radiographic instructional series: radiobiology and radiation protection,* St Louis, 1999, Mosby.)

- They are extremely reactive and have very short lives, quickly reforming 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.

Free radical production:

$RH + \text{x-radiation} \rightarrow R^{O} + H^{+} + e^{-}$

Free radical fates:

- Dissociation:

  $R^0 \rightarrow X + Y^0$

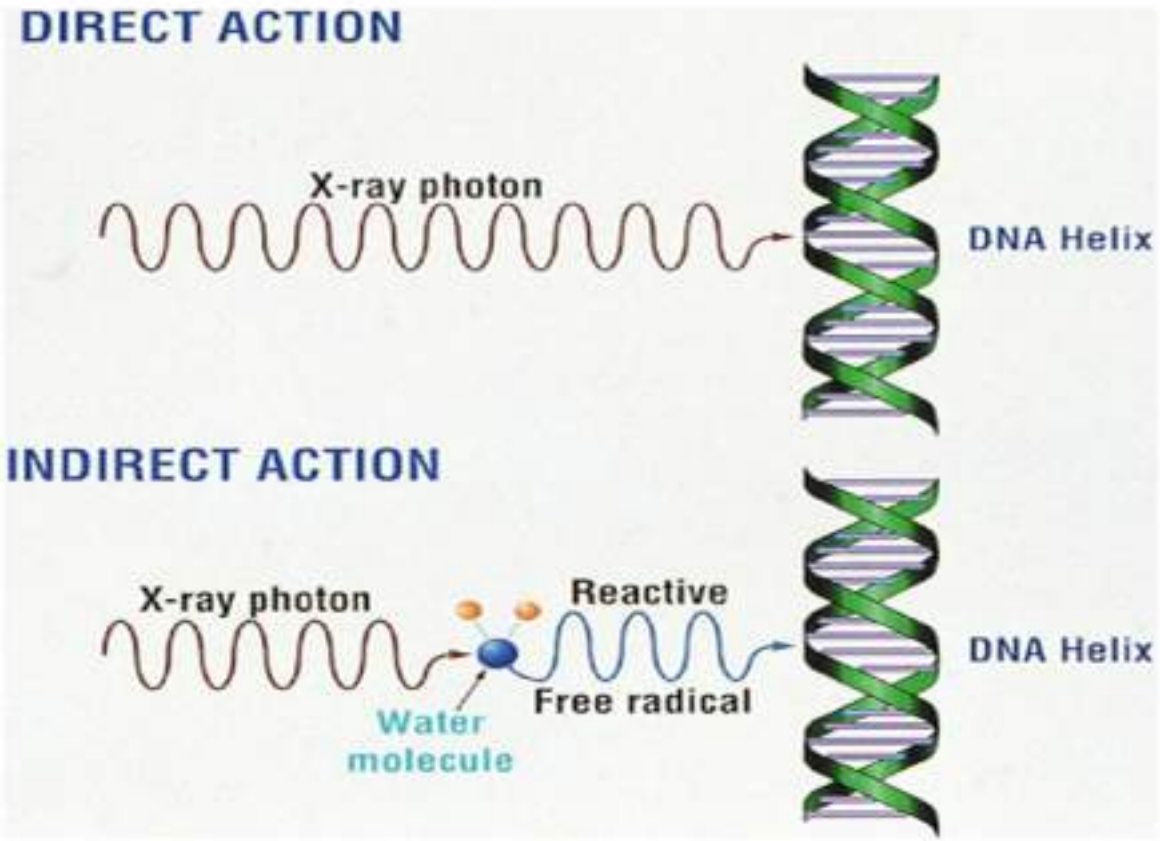
- Cross-linking:

  $R^0 + S^0 \rightarrow RS$

- Because the altered molecules differ structurally and functionally from the original molecules, the consequence is a biologic change in the irradiated organism.

# INDirect effects

- Accounts for 2/3$^{rd}$ of the biologic effects.
- When DNA is acted on by free radicals or toxic products of free radicals, it is called an indirect action.
- This is because the deposition of x-ray photon was not the immediate cause of damage to the biologically active molecule.

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- It involves 4 steps:

1. Absorption of photon in biologic system.
2. Interaction of photon with water molecules.
3. Formation of free radicals (like peroxyl) and hydrogen peroxide which are oxidizing agents.
4. Interaction of free radicals with the biologic molecules and cause formation of altered biologic molecules causing a biologic change in irradiated molecule.

# RADIOLYSIS OF WATER

- Indirect effects include an important chemical reactions known as radiolysis of water.
- Because water is the predominant molecule in biologic system (about 70% by weight), it frequently participates in the interactions between x-ray photons and the biologic molecules of an organism.
- A complex series of chemical changes occurs in water after exposure to ionizing radiation.
- Collectively these reactions result in the radiolysis of water.

- The first step is ionization of water resulting from the absorption of a photon or interaction with a photoelectron or Compton electron.

- Displacement of an electron from the water molecule results in an ion pair, a positively charged water molecule ($H_2O^+$) and the displaced electron:

  Photon + $H_2O$ → e- + $H_2O^+$

  Photoelectron e- + $H_2O$ → 2e- + $H_2O^+$

- The displaced electron is usually captured by a water molecule to form a negatively charged water molecule ($H_2O^-$):

  e- + $H_2O$ → $H^2O^-$

- These molecules are not stable and dissociate rapidly to form a hydroxyl ion and hydrogen free radical:

  $H_2O^- \rightarrow OH^- + H^O$

- The positively charged water molecule reacts with another water molecule to form a hydroxyl free radical:

  $H_2O^+ + H_2O \rightarrow H_2O^+ + OH^O + H^+$

- Water may also be excited and dissociate directly into hydrogen and hydroxyl free radicals:

  $Photon + H_2O \rightarrow H_2O^* \rightarrow OH^O + H^O$

- When dissolved molecular oxygen ($0_2$) is present in irradiated water, hydroperoxyl free radicals may also be formed:

$$H^{O} + O_2 \rightarrow H0_2{}^{O}$$

- Hydroperoxyl free radicals also may contribute to the formation of hydrogen peroxide in tissues:

$$HO_2{}^{O} + H^{O} \rightarrow H_2O_2$$

$$HO_2{}^{O} + HO_2{}^{O} \rightarrow O_2 + H_2O_2$$

- Both peroxyl radicals and hydrogen peroxide are oxidizing agents that can significantly alter biologic molecules and cause cell destruction.

- They are considered to be major toxins produced in the tissues by ionizing radiation.

# DETERMINANTS OF RADIATION INJURY

- There are many factors that determine the severity of tissue damage after exposure to radiation.

- They can be categorised as:
  - Radiation factors
  - Host factors

# RADIATION FACTORS

1. Type of radiation: (Linear energy transfer)

Sparsely ionizing radiations, such as x-rays and gamma rays, deposit their energy in widely separated energy depositing events or uniformly when compared with the densely ionizing radiation which deposit all their energy in a very short distance.

So the potential biologic effect of x-rays is less than that associated with alpha particles.

# LET-LINEAR ENERGY TRANSFER

- The rate of loss of energy from a particle as it moves along its track through matter (tissue) is its *linear energy transfer (LET) .*
- The average energy deposited per unit length of track - kev/ μm
- A particle loses kinetic energy each time it ionizes adjacent matter; the greater its physical size and charge and the lower its velocity, the greater is its LET.

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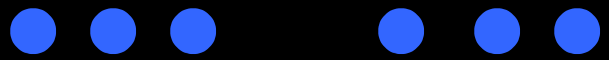

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LOW LET

- Gamma rays
- Beta rays
- X-rays

HIGH LET

- Alpha particles
- Ions of heavy nuclei
- Charged particles
- Low energy neutrons

# LOW-LET RADIATION DAMAGE TO BIOLOGIC TISSUE:

## INDIRECT ACTION

# HIGH-LET RADIATION DAMAGE TO BIOLOGIC TISSUE:

## DIRECT ACTION

- Higher LET radiation (alpha particles) are more efficient in damaging biologic system because their high ionization density is more likely to cause double-strand breakage in DNA, as compared to lower-LET radiations such as x-rays & gamma rays as they deposit their energy uniformly in the absorber and thus are more likely to cause single-strand breakage & hence, less biologic damage.

- When the biologic response to different types of radiation is compared, it is common to use the term relative biologic effectiveness (RBE), where x rays are used as a reference.

- For instance, if the dose of x rays required to kill 50% of the cells in a culture was 5 Gy and the dose of neutrons required to achieve the same end point was 2 Gy, then the RBE of neutrons would be 2.5 (5Gy + 2Gy).

## 2. Total Dose & Dose Rate

Total dose: The larger the amount of energy deposited in tissue (total dose), more severe the radio-biologic effect.

Very often a clinical threshold dose exists below with no adverse effects seen.

Dose Rate: It indicates the rate of exposure.

Exposure of biologic systems to a given dose at a high dose rate causes more damage than exposure to the same total dose but given at a lower dose rate.

Because a greater opportunity exists for repair of damage with lower dose rate, thereby resulting in less net damage.

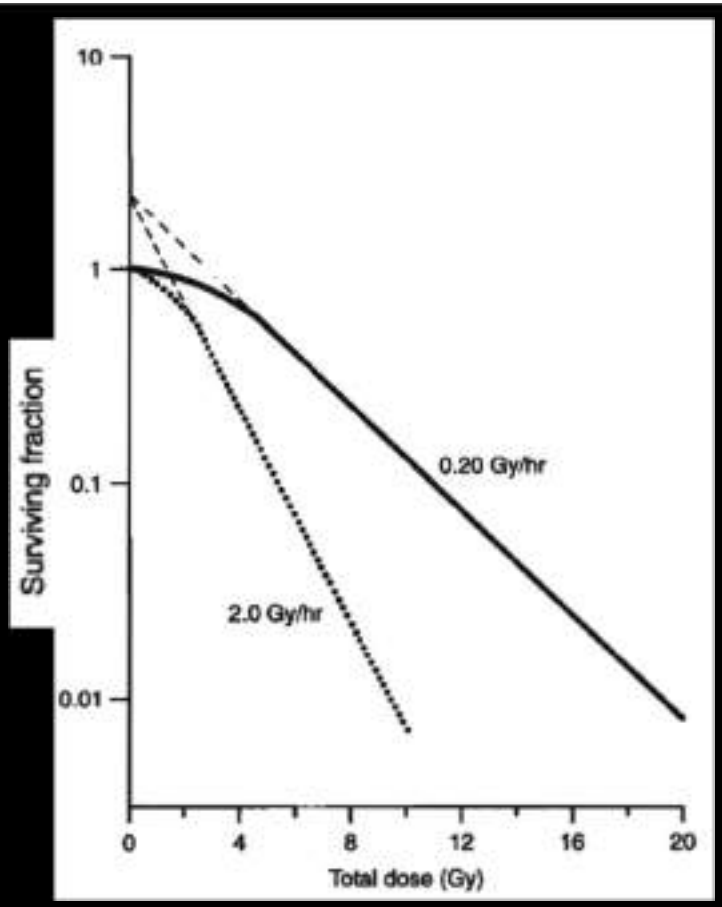



FIG. 2-6 Survival curve for mammalian cells grown in Culture after irradiation at low and high dose rates. Exposure at a high dose rate kills more cells per unit dose because less time exists for repair of sublethal damage.

3. Quality of beam: (Penetrating ability of Radiation)

- The more penetrating the beam is, the more severe biologic damage occurs.

- Lower energy radiations tend to be absorbed by the superficial layers of tissue and therefore, the potential harm to the deeper tissues is reduced.

## 4. Acute versus chronic exposure

Acute exposure to an ionizing radiation occurs when all the energy is given in a very short period.

Chronic exposure occurs when a small amount of radiation is given over a prolonged period.

For chronic exposure, the radio-biologic effect is less because body/tissue has an oppurtunity to repair the damage between successive exposures.

S

## 5. Local versus whole body exposure

- Exposure of the whole body produces more severe systemic effects than exposure to a small area.
- Dental radiographic units expose a small, well-defined area of the head & neck, thus, dental radiographic procedures are not considered to result in significant exposure to the whole body.
- In dentistry, the circular beam of radiation is limited to only the area of interest and this circular area (2.75 inches in diameter) may further be reduced by the use of rectangular collimator.

# HOST FACTORS

1. Intrinsic resistance of the organism/species of animal
2. Type & sensitivity of the tissue
3. Oxygen concentration

## 1. Intrinsic resistance of the organism/species of animal

- Mammals are relatively sensitive to radiation effects when compared to reptiles, insects & bacteria.

- Individuals who might be more or less sensitive to radiation effects, but this cannot be identified by any physical characteristic or feature.

## 2. Type & sensitivity of the tissue:

Different tissues of the body have differing sensitivities to developing radiation effects.

Three types of tissue: Experiments clearly demonstrate that some of the cells & tissues of the human body

- Radiosensitive
- Radio-resistant
- Intermediate

- The radiosensitivity of tissues depend upon:
  1. Rate of cell division
  2. Phase of cell cycle

## Rate of cell division:

- Cells that divide rapidly during their normal life tend to be more sensitive to radiation damage than cells that donot divide at all.
- For example, malignant tumor cells divide rapidly and can be destroyed by radiation whereas enamel doesnot divide & is radio-resistant.

# LAW OF BERGOINE AND TRIBONDEAU

- This variation was recognised as early as 1906 by French radiobiologists Bergonie & Tribondeau
- They observed that the most radiosensitive cells are those that:
  1. Have high mitotic rate
  2. Undergo many future mitosis.
  3. The most primitive in differentiation
- These findings are still true except for lymphocytes & oocytes, which are radiosensitive even though they are highly differentiated & non-dividing.

- Phase of cell cycle:

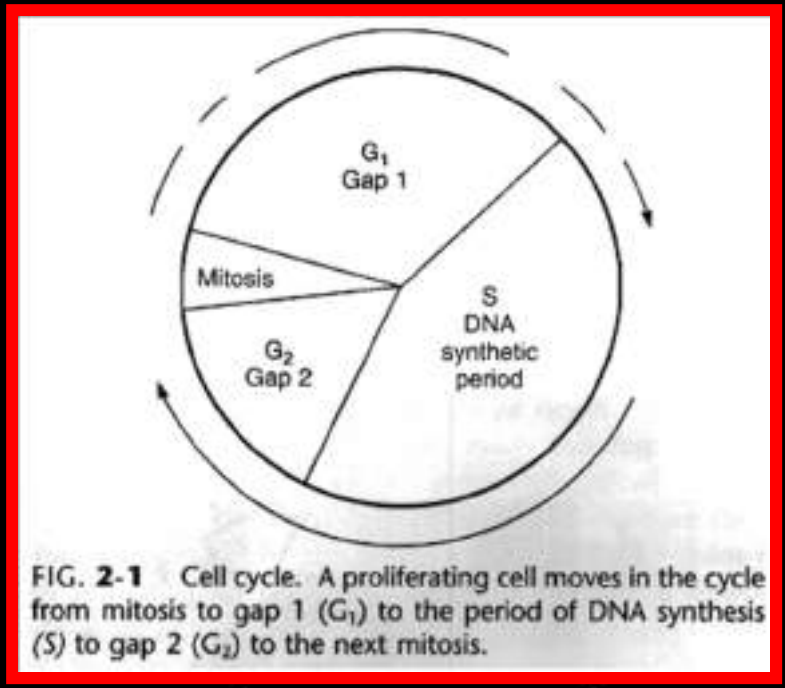



FIG. **2-1** Cell cycle. A proliferating cell moves in the cycle from mitosis to gap 1 ($G_1$) to the period of DNA synthesis *(S)* to gap 2 ($G_2$) to the next mitosis.

# RADIOSENSITIVITY AND CELL TYPE

- Mammalian cells may be divided into five categories of radiosensitivity on the basis of histologic observations of early cell death:

1. Vegetative intermitotic cells are the most radiosensitive.
- They divide regularly, have long mitotic futures, and do not undergo differentiation between mitoses.

- These are stem cells that retain their primitive properties and whose function is to replace themselves.

- Examples include early precursor cells, such as those in the spermatogenic or erythroblastic series, and basal cells of the oral mucous membrane.

2. Differentiating intermitotic cells are somewhat less radiosensitive than vegetative intermitotic cells because they divide less often.

- They divide regularly, although they undergo some differentiation between divisions.
- Examples of this class include intermediate dividing and replicating cells of the inner enamel epithelium of developing teeth, cells of the hematopoietic series that are in the intermediate stages of differentiation, spermatocytes, and oocytes.

3. Multipotential connective tissue cells have intermediate radiosensitivity.

- They divide irregularly, usually in response to a demand for more cells, and are also capable of limited differentiation.
- Examples are vascular endothelial cells, fibroblasts, and mesenchymal cells.

4. Reverting postmitotic cells are generally radioresistant because they divide infrequently.

- They also are generally specialized in function.
- Examples include the acinar and ductal cells of the salivary glands and pancreas as well as parenchymal cells of the liver, kidney, and thyroid.

5.Fixed postmitotic cells are most resistant to the direct action of radiation.

- They are the most highly differentiated cells and, once mature, are incapable of division.
- Examples of these cells include neurons, striated muscle cells, squamous epithelial cells that have differentiated and are close to the surface of oral mucous membrane, and erythrocytes.

# HOST FACTORS

1. Intrinsic resistance of the organism/species of animal
2. Type & sensitivity of the tissue
3. Oxygen concentration

## 3. Oxygen

- The radioresistance of many biologic systems increases by a factor of 2 or 3 when irradiation is conducted with reduced oxygen (hypoxia).
- The greater cell damage sustained in the presence of oxygen is related to the increased amounts of hydrogen peroxide and hydroperoxyl free radicals formed.

- The oxygen enhancement ratio measures the extent of this damage.
- It is the dose required to achieve a given endpoint (e.g.50% survival of a cell population) under anoxic conditions divided by the dose required to produce the same endpoint under fully oxygenated conditions.
- This is important clinically because hyperbaric oxygen therapy may be used during radiation therapy of tumors having hypoxic cells.

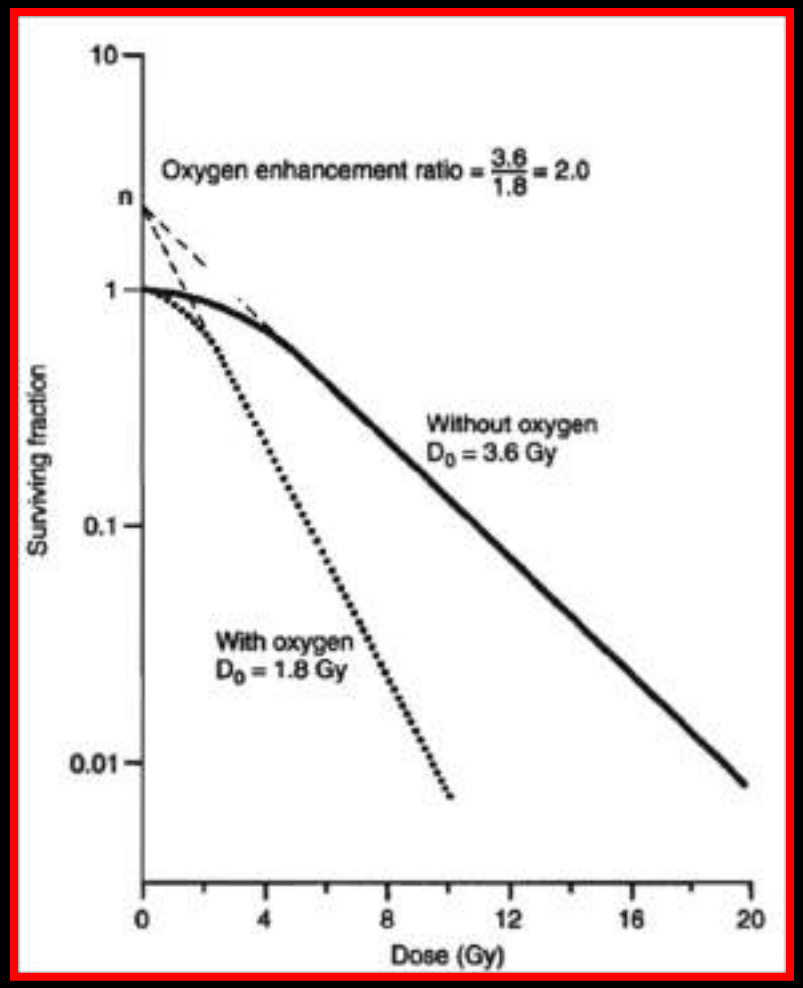



FIG. Survival curve for mammalian cells grown in culture after irradiation with and without oxygen. The presence of oxygen increases the cells' sensitivity to radiation. In this example the Do value is reduced from 3.6 Gy when irradiated without oxygen to 1.8 Gy in the presence of oxygen. The oxygen enhancement ratio measures the influence of oxygen.

# CHANGES IN BIOLOGIC MOLECULES

1. Nucleic Acids

- The last few decades have seen a growing appreciation for the crucial role of nucleic acids in determining cellular functions.

- It is clear that damage to the deoxyribonucleic acid (DNA) molecule is the primary mechanism for radiation-induced cell death, mutation, and carcinogenesis.

Radiation produces a number of different types of alterations in DNA, including the following:

- Breakage of one or both DNA strands
- Cross-linking of DNA strands within the helix, to other DNA strands, or to proteins
- Change or loss of a base
- Disruption of hydrogen bonds between DNA strands

## 2. Proteins

- Irradiation of proteins in solution usually leads to changes in their secondary and tertiary structures through disruption of side chains or the breakage of hydrogen or disulfide bonds.
- Such changes lead to denaturation.
- The primary structure of the protein is usually not significantly altered.
- Irradiation may also induce intermolecular and intramolecular crosslinking.

# Radiation Effects at the Cellular Level

## 1. Effects on intracellular Structures

- The effects of radiation on intracellular structures result from radiation-induced changes in their macromolecules.
- Although the initial molecular changes are produced within a fraction of a second after exposure, cellular changes resulting from moderate exposures usually require a minimum of hours to become apparent.
- These changes are manifested initially as structural and functional changes in cellular organelles. Later, cell death may occur.

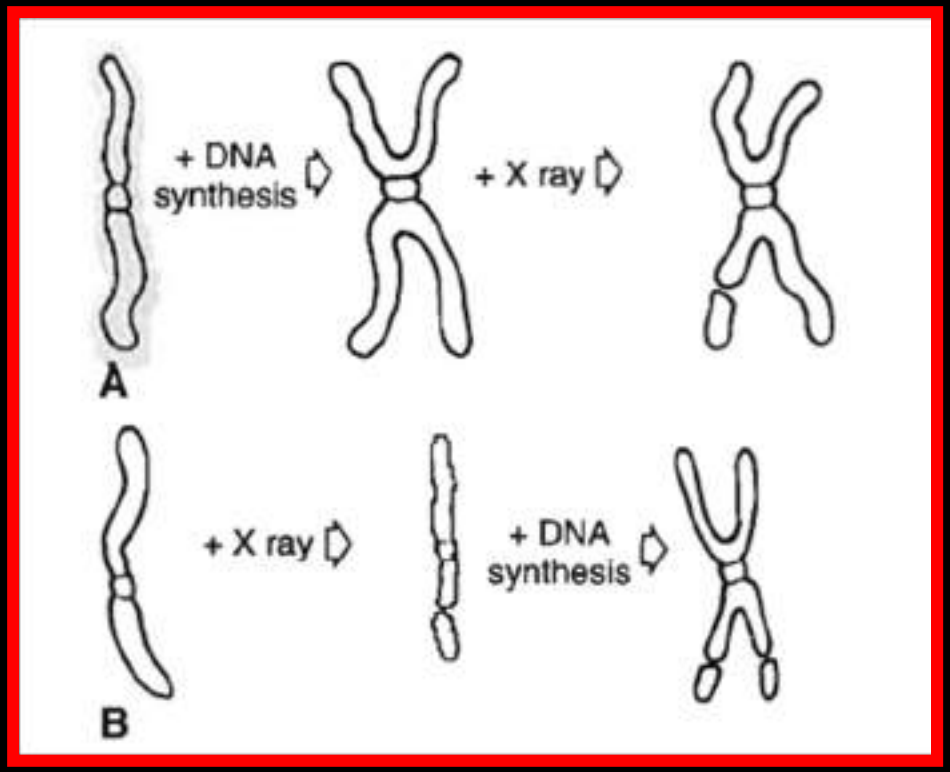
## 2. Nucleus

- A wide variety of radiobiologic data indicate that the nucleus is more radiosensitive (in terms of lethality) than the cytoplasm, especially in dividing cells.

- The sensitive site in the nucleus is the DNA within chromosome.

## Chromosome Aberrations

- Chromosomes serve as useful markers for radiation injury.
- Chromosome aberrations are observed in irradiated cells at the time of mitosis when the DNA condenses to form chromosomes.
- The type of damage that may be observed depends on the stage of the cell in the cell cycle at the time of irradiation.




A, Irradiation of the cell after DNA synthesis results in a single-arm (chromatid) aberration.

B, Irradiation before DNA synthesis results in a double-arm (chromosome) aberration.

## 3. Cytoplasm

- After relatively large doses of radiation (30 to 50Gy), mitochondria demonstrate increased permeability, swelling, and disorganization of the internal cristae.

- Such permeability and structural changes probably play only a minor role in the cellular changes seen in rapidly dividing cells after exposure to moderate doses of radiation (2 to 4Gy).

# Radiation Effects on the Oral Cavity

## 1. Oral Mucous Membrane

- The oral mucous membrane contains a basal layer composed of radiosensitive vegetative and differentiating intermitotic cells.
- Near the end of the second week of radiotherapy, as some of these cells die, the mucous membranes begin to show areas of redness and inflammation (mucositis).
- As the therapy continues, the irradiated mucous membrane begins to break down, with the formation of a white to yellow pseudomembrane (the desquamated epithelial layer).

- At the end of therapy the mucositis is usually most severe, discomfort is at a maximum, and food intake is difficult.
- Good oral hygiene minimizes infection.
- Topical anesthetics may be required at meal times.
- Secondary yeast infection by Candida albicans is a common complication and may require treatment.

- After irradiation is completed, the mucosa begins to heal rapidly.
- Healing is usually complete by about 2 months.
- At later intervals (months to years) the mucous membrane tends to become atrophic, thin, and relatively avascular.
- This long-term atrophy results from progressive obliteration of the fine vasculature and fibrosis of the underlying connective tissue.
- These atrophic changes complicate denture wearing because they may cause oral ulcerations of the compromised tissue.

- Ulcers can result from a denture sore, radiation necrosis, or tumor recurrence.
- A biopsy may be required to make the differentiation.

## 2. Taste Buds

- Taste buds are sensitive to radiation.
- Doses in the therapeutic range cause extensive degeneration of the normal histologic architecture of taste buds.
- Patients often notice a loss of taste acuity during the second or third week of radiotherapy.
- Bitter and acid flavors are more severely affected when the posterior two thirds of the tongue is irradiated, and salt and sweet when the anterior third of the tongue is irradiated.

- Taste acuity usually decreases by a factor of 1,000 to 10,000 during the course of radiotherapy.

- Alterations in the saliva may account partly for this reduction, which may proceed to a state of virtual insensitivity, with recovery to near normal levels some 60 to 120 days after irradiation.

## 3. Salivary Glands

- The major salivary glands are at times unavoidably exposed to 20 to 30 Gy during radiotherapy for cancer in the oral cavity or oropharynx.

- The parenchymal component of the salivary glands is rather radiosensitive (parotid glands more so than submandibular or sublingual glands).

- A marked and progressive loss of salivary secretion is usually seen in the first few weeks after initiation of radiotherapy,
- The extent of reduced flow is dose-dependent and reaches essentially zero at 60 Gy
- The mouth becomes dry (xerostomia) and tender, and swallowing is difficult and painful because the residual saliva also loses its normal lubricating properties.

- The small volume of viscous saliva that is secreted usually has a pH value 1 unit below normal (i.e., an average of 5.5 in irradiated patients compared with 6.5 in unexposed individuals).

- This pH is low enough to initiate decalcification of normal enamel. In addition, the buffering capacity of saliva falls as much as 44% during radiation therapy.

- If some portions of the major salivary glands have been spared, dryness of the mouth usually subsides in 6 to 12 months because of compensatory hypertrophy of residual salivary gland tissue.

- Reduced salivary flow that persists beyond a year is unlikely to show significant recovery.

- Salivary changes have a profound influence on the oral microflora and secondarily on the dentition, often leading to radiation caries.
- After radiotherapy that includes the major salivary glands, the microflora undergo a pronounced change, rendering them acidogenic in the saliva and plaque.
- Patients receiving radiation therapy to oral structures have increases in Streptococcus mutans, Lactobacillus and Candida.
- Because of their small volume of thick, viscous, acidic saliva, such patients are quite prone to radiation caries.

## 4. Teeth

- Irradiation of teeth with therapeutic doses during their development severely retards their growth.

- Such irradiation may be for local disease (e.g., eosinophilic granuloma) or a generalized condition (leukemia being treated with whole-body irradiation followed by bone marrow transplantation).

- If it precedes calcification, irradiation may destroy the tooth bud.

- Irradiation after calcification has begun may inhibit cellular differentiation, causing malformations and arresting general growth.

- Children receiving radiation therapy to the jaws may show defects in the permanent dentition such as retarded root development, dwarfed teeth, or failure to form one or more teeth.

- Teeth irradiated during development may complete calcification and erupt prematurely.
- In general, the severity of the damage is dose-dependent.
- Irradiation of teeth may retard or abort root formation, but the eruptive mechanism of teeth is relatively radiation-resistant.
- Irradiated teeth with altered root formation still erupt.

- Adult teeth are very resistant to the direct effects of radiation exposure.

- Pulpal tissue, which consists primarily of reverting and fixed postmitotic cells, demonstrates long-term fibroatrophy after irradiation.

- Radiation has no discernible effect on the crystalline structure of enamel, dentin, or cementum, and radiation does not increase their solubility.

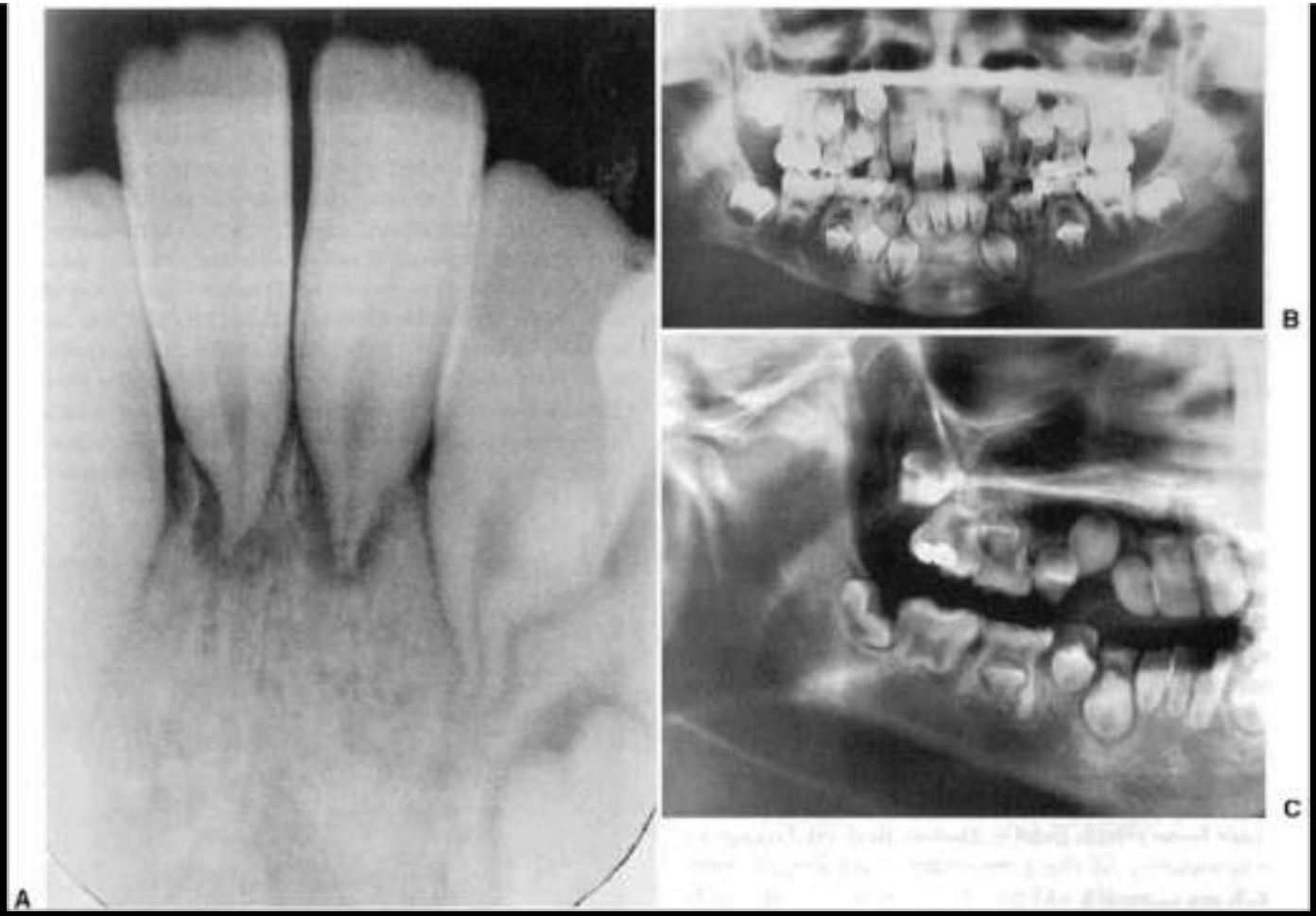



Fig: Dental abnormalities after radiotherapy in two patients. The first, a 9-year-old girl who received 35 Gy at the age of 4 years because of Hodgkin's disease, had severe stunting of the incisor roots with premature closure of the apices at 8 years (A) and retarded development of the mandibular second premolar crowns with stunting of the mandibular incisor, canine, and premolar roots at 9 years (B). The other patient (C) a 10-year-old boy who received 41 Gy to the jaws at age 4 years, had severely stunted root deveropment of all permanent teeth with a normal

## 5. Radiation Caries

- Radiation caries is a rampant form of dental decay that may occur in individuals who receive a course of radiotherapy that includes exposure of the salivary glands.

- The carious lesions result from changes in the salivary glands and saliva, including reduced flow, decreased pH, reduced buffering capacity, and increased Viscosity.

- Because of the reduced or absent cleansing action of normal saliva, debris accumulates quickly.

- Irradiation of the teeth by itself does not influence the course of radiation caries.

- Clinically, three types of radiation caries exist.
- The most common is widespread superficial lesions attacking buccal, occlusal, incisal, and palatal surfaces.
- Another type involves primarily the cementum and dentin in the cervical region.
- These lesions may progress around the teeth circumferentially and result in loss of the crown.

- A final type appears as a dark pigmentation of the entire crown.
- The incisal edges may be markedly worn.
- Some patients develop combinations of all these lesions.
- The histologic features of the lesions are similar to those of typical carious lesions.
- It is the rapid course and widespread attack that distinguish radiation caries.

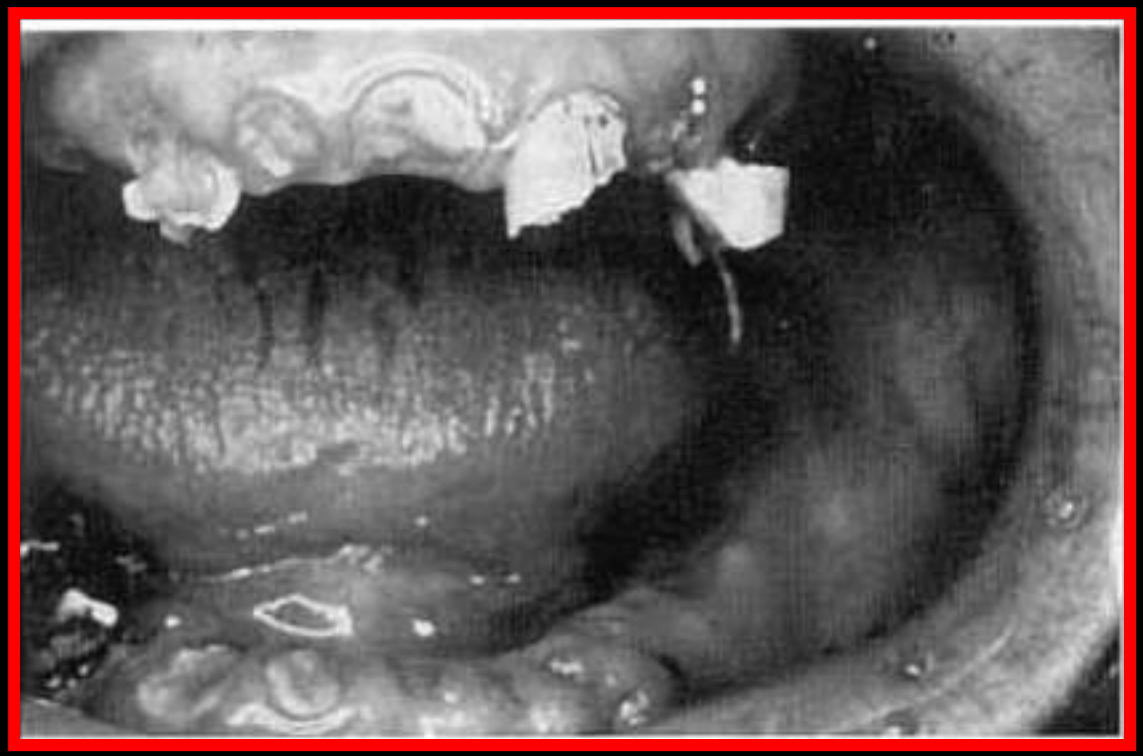


Fig: Radiation caries. Note the extensive loss of tooth structure in both jaws resulting from radiation-induced xerostomia.

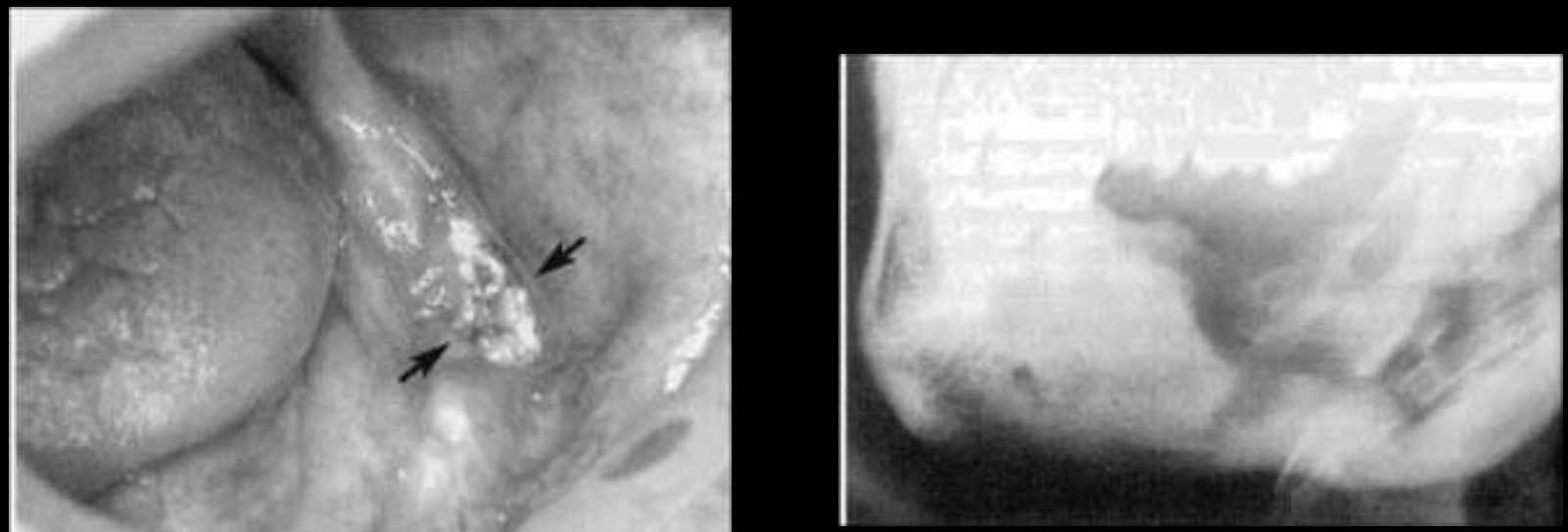
## 6. Bone

- Treatment of cancers in the oral region often includes irradiation of the mandible.
- The primary damage to mature bone results from radiation-induced damage to the vasculature of the periosteum and cortical bone, which are normally already sparse.
- Radiation also acts by destroying osteoblasts and, to a lesser extent, osteoclasts.

- Subsequent to irradiation, normal marrow may be replaced with fatty marrow and fibrous connective tissue.
- The marrow tissue becomes hypovascular, hypoxic, and hypocellular.
- In addition, the endosteum becomes atrophic, showing a lack of osteoblastic and osteoclastic activity, and some lacunae of the compact bone are empty, an indication of necrosis.
- The degree of mineralization may be reduced, leading to brittleness, or little altered from normal bone.
- When these changes are so severe that bone death results, the condition is termed osteoradionecrosis.

- Osteoradionecrosis is the most serious clinical complication that occurs in bone after irradiation.
- The decreased vascularity of the mandible renders it easily infected by microorganisms from the oral cavity.
- This bone infection may result from radiation-induced breakdown of the oral mucous membrane, by mechanical damage to the weakened oral mucous membrane such as from a denture sore or tooth extraction, through a periodontal lesion, or from radiation caries.

- This infection may cause a non-healing wound in irradiated bone that is difficult to treat.
- It is more common in the mandible than in the maxilla, probably because of the richer vascular supply to the maxilla and the fact that the mandible is more frequently irradiated.
- The higher the radiation dose absorbed by the bone, the greater the risk for osteoradionecrosis.



- FIG. 2-11 Osteoradionecrosis. A, Area of exposed mandible after radiotherapy. Note the loss of oral mucosa. B, Destruction of irradiated bone resulting from the spread of infection.

# Effects of Whole-Body Irradiation

- When the whole body is exposed to low or moderate doses of radiation, characteristic changes (called the acute radiation syndrome) develop.

- The clinical picture after whole-body exposure is quite different from that seen when a relatively small volume of tissue is exposed.

- The acute radiation syndrome is a collection of signs and symptoms experienced by persons after acute whole-body exposure to radiation.

| DOSE (Gy) | MANIFESTATION |
|---|---|
| 1 to 2 | Prodromal symptoms |
| 2 to 4 | Mild hematopoietic symptoms |
| 4 to 7 | Severe hematopoietic symptoms |
| 7 to 15 | Gastrointestinal sypmtoms |
| 50 | Cardiovascular & central nervous smptoms |

## Prodromal Period

- Within the first minutes to hours after exposure to whole-body irradiation of about 1.5 Gy, symptoms characteristic of gastrointestinal tract disturbances may occur.
- The individual may develop anorexia, nausea, vomiting, diarrhoea, weakness, and fatigue.
- These early symptoms constitute the prodromal period of the acute radiation syndrome. their cause is not clear but probably involves the autonomic nervous system.

## Latent Period

- After this prodromal reaction comes a latent period of apparent well-being, during which no signs or symptoms of radiation sickness occur.
- The extent of the latent period is also dose-related.
- It extends from hours or days at supralethal exposures (greater than approximately 5 Gy) to a few weeks at sublethal exposures (less than 2 Gy).

## Hematopoietic Syndrome

- Whole-body exposures of 2 to 7 Gy cause injury to the hematopoietic stem cells of the bone marrow and spleen.
- The high mitotic activity of these cells and the presence of many differentiating cells make the bone marrow a highly radiosensitive tissue.
- As a consequence, doses in this range cause a rapid and profound fall in the numbers of circulating granulocytes, platelets, and finally erythrocytes

- The clinical consequences of the depression of these cellular elements become evident as the circulating levels decline.
- Hence, in the weeks after radiation injury, infection appears first, followed later by anemia.
- The clinical signs of the hematopoietic syndrome include infection (in part from the lymphopenia and granulocytopenia), hemorrhage (from the thrombocytopenia), and anemia (from the erythrocyte depletion).

- Individuals may survive exposure in this range if the bone marrow and spleen recover before the patient dies of one or more clinical complications.
- The probability of death is low after exposures at the low end of this range but much higher at the high end.
- When death results from the hematopoietic syndrome, it usually occurs 10 to 30 days after irradiation.

- Because periodontitis results in a likely source of entry for microorganisms into the bloodstream, the role of the dentist is important in preventing infection in hematopoietic syndrome.
- After moderate injury, about 7 to 10 days pass before clinically significant leukopenia develops.
- During this time the dentist should remove all sites of infection from the mouth.
- The removal of sources of infection, the vigorous administration of antibiotics, and in some cases the transplantation of bone marrow have saved individuals suffering from the acute radiation syndrome.

## Gastrointestinal Syndrome

- Whole-body exposures in the range of 7 to 15 Gy cause extensive damage to the gastrointestinal system.
- This damage, in addition to the hematopoietic damage described previously, causes signs and symptoms called the gastrointestinal syndrome.
- It causes loss of the epithelial layer of the intestinal mucosa, denuded mucosal surface leads to loss of plasma and electrolytes and reduced intestinal absorption occurs.

- All these changes cause:
  - Diarrhoea
  - Dehydration
  - Loss of weight
  - Endogenous intestinal bacteria invade the denuded surface, producing septicemia

## Cardiovascular and Central Nervous System Syndrome

- Exposures in excess of 50 Gy usually cause death in 1 to 2 days.
- The few human beings who have been exposed at this level showed collapse of the circulatory system with a precipitous fall in blood pressure in the hours preceding death.
- Autopsy revealed necrosis of cardiac muscle. Victims also may show intermittent stupor, incoordination, disorientation, and convulsions suggestive of extensive damage to the nervous system.

- Although the precise mechanism is not fully understood, these latter symptoms most likely result from radiation induced damage to the neurons and fine vasculature of the brain.
- The syndrome is irreversible, and the clinical course may run from only a few minutes to about 48 hours before death occurs.
- The cardiovascular and central nervous system syndromes have such a rapid course that the irradiated individual dies before the effects of damage to the bone marrow and gastrointestinal system can develop.

# RADIATION EFFECTS ON EMBRYOS AND FETUSES

- Embryos and fetuses are considerably more radiosensitive than adults because most embryonic cells are relatively undifferentiated and rapidly mitotic.

- Prenatal irradiation may lead to death or specific developmental abnormalities depending on the stage of development at the time of irradiation.

- The fetus of a patient exposed to dental radiography receives less than 0.25 µGy 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.

# CARCINOGENESIS

- Radiation causes cancer by modifying the DNA.
- Although most such damage is repaired, imperfect repair may be transmitted to daughter cells and result in cancer.
- Data on radiation-induced cancers come primarily from populations of people that have been exposed to high levels of radiation; however, even low doses of radiation may initiate cancer formation in a single cell.

- The mechanism of induction of cancer by ionizing radiation is not well understood.
- Most likely the basis is radiation-induced gene mutation.
- Most investigators believe that radiation acts as an initiator, that is, it induces a change in the cell so that it no longer undergoes terminal differentiation.
- Evidence also exists that radiation acts as a promoter, stimulating cells to multiply.
- Finally, it may also convert premalignant cells into malignant ones.

# Susceptibility of different tissues to Radiation induced cancer

| HIGH | MODERATE | LOW |
|---|---|---|
| Colon | Breast | Bladder |
| Stomach | Esophagus | Liver |
| Lung | | Thyroid |
| Bone Marrow | | Skin |
| | | Bone Surface |
| | | Brain |
| | | Salivary Glands |

# Radiation Genetics

## Genetic mutations

- In general, radiation causes increased frequency of spontaneous mutations rather than inducing new mutations.
- Furthermore, the frequency of mutations increases in direct proportion to the dose, even at very low doses, with no evidence of a threshold.
- The vast majority of mutations are deleterious to the organism.
- Dose rate is important in that at low dose rates the frequency of induced mutations is greatly reduced.

- Males are much more radiosensitive than females.
- The rate of mutations is reduced as the time between exposure and conception increases.

## Doubling Dose

- One way to measure the risk from genetic exposure is by determining the doubling dose.
- This is the amount of radiation a population requires to produce in the next generation as many additional mutations as arise spontaneously.
- In human beings the genetic doubling dose for mutations resulting in death is approximately 2 Sv.
- Because the average person receives far less gonadal radiation, radiation contributes relatively little to genetic damage in populations.

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YOU

- For comparison, the gonadal dose to males from a full-mouth radiographic examination is very low, about 1 μSv or less.
- This exposure is contributed largely by the maxillary views, which are angled caudally.
- The dose to the ovaries is about 50 times less, in the range of 0.02 μSv.

- The mature circulating granulocytes, platelets, and erythrocytes themselves are very radioresistant, however, because they are non-replicating cells. their paucity in the peripheral blood after irradiation reflects the radiosensitivity of their precursors.
- The differential changes in the blood count do not all appear at the same time.
- Rather, the rate of fall in the circulating levels of a cell depends on the life span of that cell in the peripheral blood.
- Granulocytes, with short lives in circulation, fall off in a matter of days, whereas red blood cells, with their long lives in circulation, falloff only slowly.