

RADIATION BIOLOGY

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Lecture Learning Outcomes

- Describe the biological effects of radiation on living cells
- Enumerate the effects of radiation from molecular to macromolecular level of living cells
- Describe the the oral and maxillofacial effects of of x-radiation

Introduction

- Radiation Biology is Study of effects of Ionizing Radiation on living system

How does radiation interact with cells?

Past Theory

Hit Theory

Radiation causes Free Radicals to damage Only the cell that is “Hit” by Direct Ionization

Current Theories

By-stander Effects

Radiation causes Free Radicals to Trigger Cell-cell communication and Cell-matrix communication to cells Other than those which are “hit” by the direct ionization

Terminology

- Deterministic Effect

Are “Definitive” damaging effects to the body when exposed to specific high dose radiation, depending upon the radiation dose

Eg: Radiation mucositis

- Stochastic Effect

Are effects that “May” develop when exposed to radiation, donot depend on the amount of radiation dose Eg: Radiation induced cancer

Radiation Chemistry

- Initial interaction between Ionizing Radiation and tissues takes place within 10^{-13} seconds
- Effects of Ionizing radiation on cells may persist for hours, decades, or generations

Mechanism of Radiation Caused Damage

- Direct Effect: Energy of photon or secondary electron Ionizes biologic molecule
- Indirect Effect: Energy of photon or Secondary electron Ionizes water and forms Free Radicals and free radicals in-turn cause damage to biologic molecules

Direct Effect

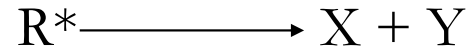
- Organic Molecule and hydrogen atom [RH]
- $\text{RH} + \text{X-Radiation} \longrightarrow \text{R}^* + \text{H} + \text{e}$
- R^* is a Free Radical
- The Generation of free radicals takes place in less than 10^{-10} secs
- Free radicals are extremely reactive and have very short life

Sequalae of Free Radical Formed by Direct Hit

- They quickly become stable molecules by either

1. Dissociation or
2. Cross-linking

- Dissociation

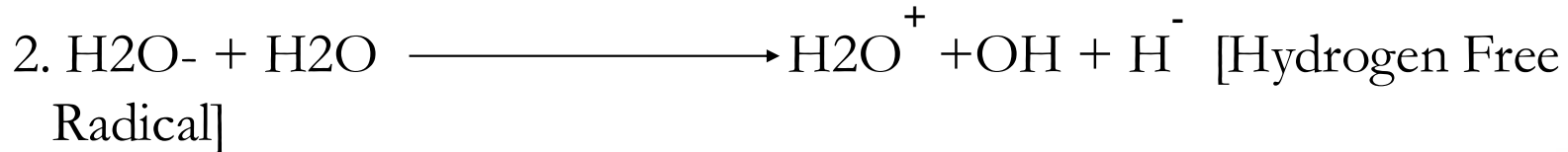
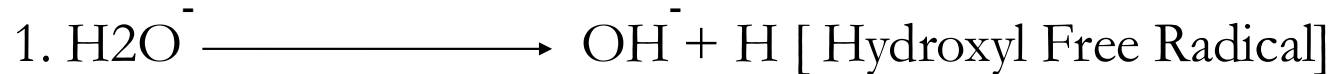


- Cross-linking $R^* + S^* \longrightarrow RS$

- Only 1/3 of effects are by Direct Interaction

Indirect Effect

- “Hydrogen” [H] and “Hydroxyl” [OH] Free Radicals are formed by Radiolysis of water



- 2/3 of harmful effects are caused by Indirect effect

Indirect Effect Cont...

- Interaction of Hydrogen and Hydroxyl Free Radicals with organic molecules results in formation of “Organic free radicals”
- Hydroxyl radical is more important in causing tissue damage
- $\text{RH} + \text{H}^\cdot \longrightarrow \text{R}^\cdot + \text{H}_2$
- $\text{RH} + \text{OH}^\cdot \longrightarrow \text{R}^\cdot + \text{HO}_2$

Factors Affecting Radiosensitivity of Cells

- Depends on

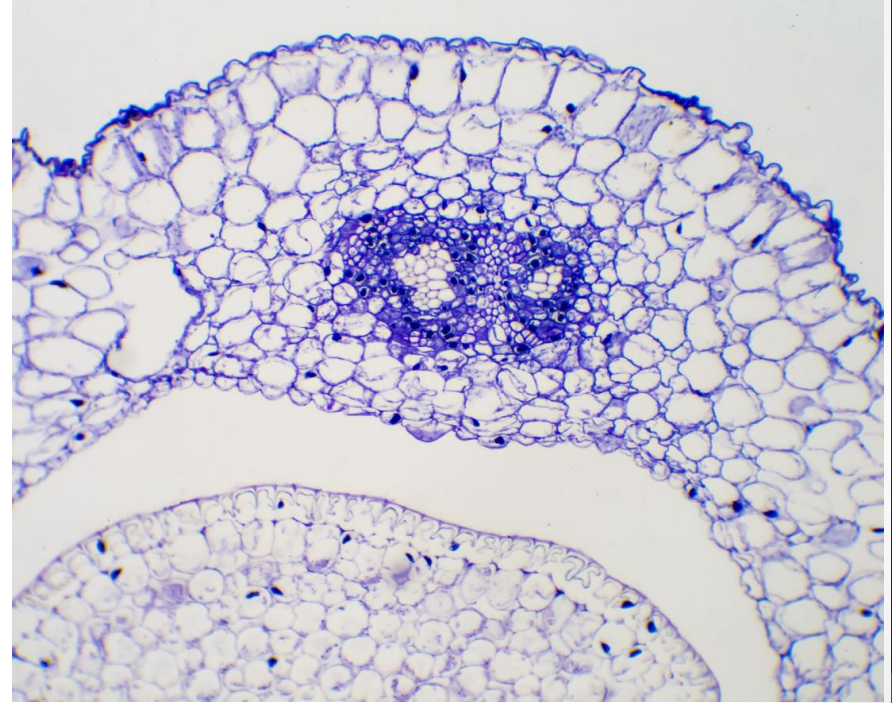
1. Mitotic Rate

2. Cells with potential to under-go mitosis in future

3. Primitive cells

Radiosensitivity Cells Based on Histology of Cells

- Vegetative Intermitotic Cells
- Differentiating Intermitotic Cells
- Multipotential Connective tissue Cells
- Reverting Post-mitotic cells
- Fixed Post-mitotic Cells



Radiosensitivity Cells Based on Histology of Cells

■ Vegetative Intermitotic Cells

- Divide regularly and have long mitotic future
- Most radiosensitive cells
- These are precursor cells that function to replace worn-out cells
- Eg: Spermatogenic Cells, Erythroblastic series and Basal cells of Oral Mucous Membrane

■ Differentiating Intermitotic Cells

- Less radiosensitive
- They divide less often they also undergo some amount of differentiation between divisions
Eg: Spermatocytes, Oocytes

Radiosensitivity Cells Based on Histology of Cells

Cont...

■ Multipotential Connective Tissue Cells

- Intermediate radiosensitive cells
- Divide less regularly and usually in response to a demand for more cells Eg: Vascular endothelial cells, Fibroblast, Mesenchymal cells

■ Reverting Post-mitotic cells

- Radioresistant cells because they divide Infrequently
- These cells are specialized cells in function
- Eg: Acinar and ductal cells of Salivary glands, paranchyma of Pancreas, Liver, kidney and Thyroid

Radiosensitivity Cells Based on Histology of Cells

Cont...

- Fixed Post-mitotic Cells
 - Most resistant, highly differentiated cells, once mature, are incapable of division
 - Eg: Neurons, Striated muscle, Squamous epithelial cells and Erythrocytes

High	Intermediate	Low
1.Lymphoid Organ	1.Fine Vasculature	1.Optic Lens
2.Bone Marrow	2.Growing Cartilage	2.Mature Erythrocytes
3.Testes	3.Growing Bone	3.Muscle Cells
4.Intestine	4.Salivary Glands	4.Nerves
5.Mucous Membrane	5.Lungs, Kidney, Liver	

Effects of Radiation

I. On Biological [Biochemical] molecules

I.1.Nucleic acids

I.2.Proteins

II. Effects at cellular level:

II.1.Nucleus

II.2.Chromosomal Aberration

II.3.Cytoplasmic changes

III. Effects on Cell Kinetics

III.1.Mitotic delay

III.2.Cell death

I. Changes In Biologic [Biochemical] Molecules

1. Nucleic Acids

2. Proteins

I.1. Nucleic Acid

- Change or loss of Base-pairs
- Disruption of Hydrogen bonds between DNA strands
- Damaged to DNA by radiation leads to Mutation, Carcinogenesis and Cell Death

I.2. Proteins

- Radiation damage leads to changes in the secondary and Tertiary structures
- Disruption of side chains or breakage of Hydrogen and Disulfide Bonds
- Amplify or Retard Enzyme System, alters the biologic effects of enzyme system

II. Radiation Effects At Cellular Level

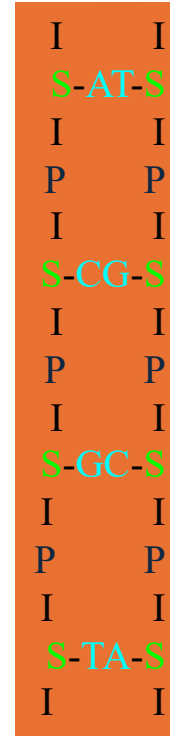
II.1. Nucleus

II.2. Chromosomes

II.3. Cytoplasm

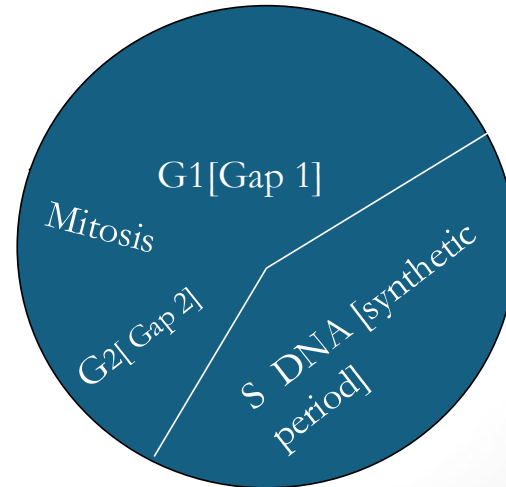
II.1. Nucleus

- Takes a few hours for changes to take place at cellular
- Nucleus is more radiosensitive in terms of damage
- The most sensitive site is the DNA can lead to,
 1. Breakage of one or both strands of DNA
 2. Cross-linking within DNA strands
 3. Cross-linking within the Helix



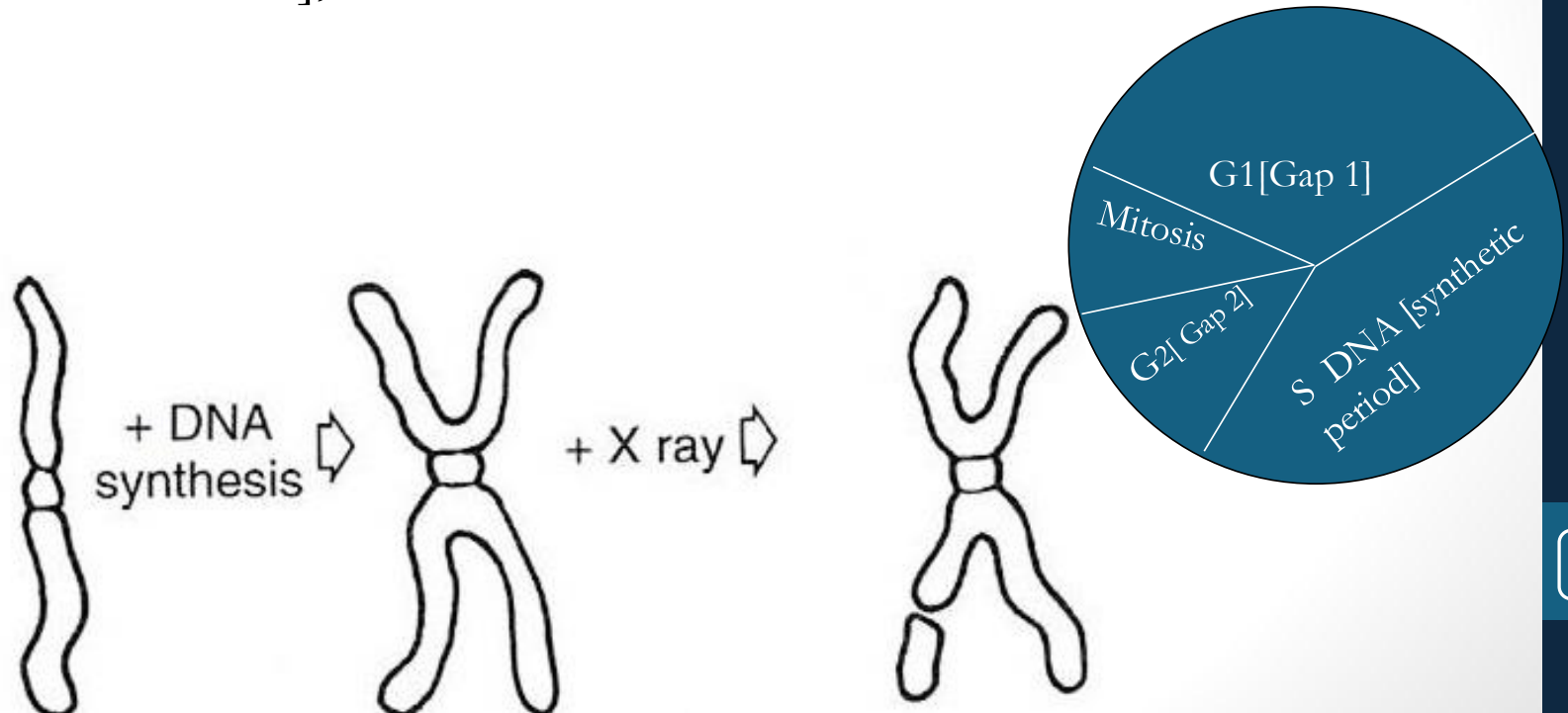
II.2. Chromosomes

- Chromosome aberration in cell is found at time of cell division
- Type of damage depends on the stage of Cell Cycle
- Stages of Cell Cycle



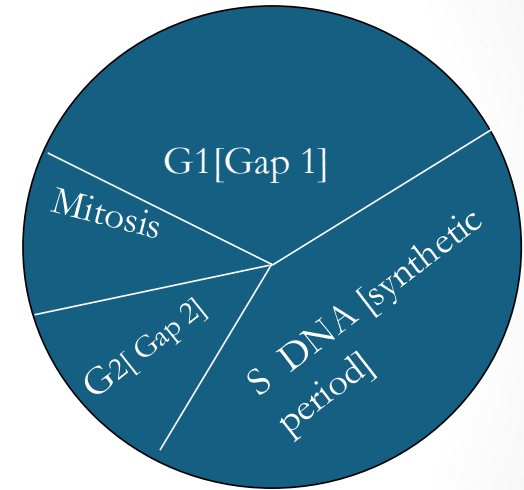
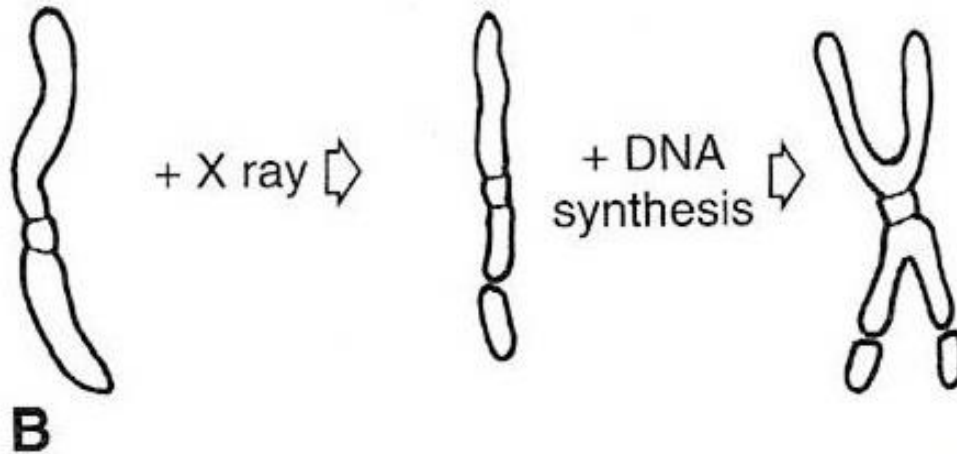
II.2. Chromosomes Cont...

- Chromatid Aberration: Radiation exposure occurs after DNA synthesis [G₂ or mid and late S], one arm of the chromosome is affected



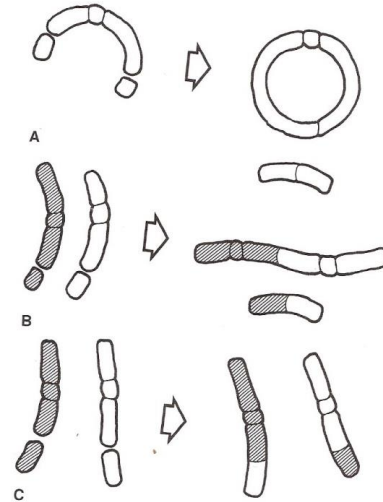
II.2. Chromosomes Cont...

- Chromosome Aberration: radiation exposure occurs before the DNA has replicated [G_1 or early S], both the arms of affected chromosome are affected



II.2. Chromosomes Cont...

- Chromatid Aberration: Are repaired by biologic process and go unrecognized
- Chromosome Aberration: Are not repaired or improperly repaired, leading to Mutation



Thank You

II.3. Cytoplasm

- Higher doses are required to cause radiation damage to other cellular organelle[30-50Gy]
- Increased permeability of Mitochondria leading to swelling and disorganization of internal Cristae

III. Radiation Effects at Tissue And Organ Level

- Short term Effects
- Long Term Effects

Early Effects of Radiation on Humans

- Very high dose of radiation delivered in a short time
e.g: Cancer Radiotherapy [Deterministic effect]
- Hematologic syndrome
- G.I. syndrome
- CNS syndrome
- Tissue damage-erythema, desquamation
- Hematologic damage
- Cytogenic damage

Late Effects

Low dose radiation for long time, e.g: Diagnostic radiation
[Stochastic effect]

- Leukemia
- Bone cancer
- Breast cancer
- Thyroid cancer
- Local tissue damage
- Lifespan shortening
- Genetic damage
- Cytogenic damage

Short Term Effect

- Determined by sensitivity of cells
- Continuously proliferating cells are irradiated they are lost by Mitosis linked cell death

Long Term Effects

- Depend primarily on the extent of damage to the Fine Vasculature

Radiation

Capillary Swelling, Degeneration and Necrosis

Increase in capillary permeability and progressive
Fibrosis around Blood Vessels

Impairs nutrition, oxygen and removal of waste

Cell Death

Radiation Effects On Oral Cavity

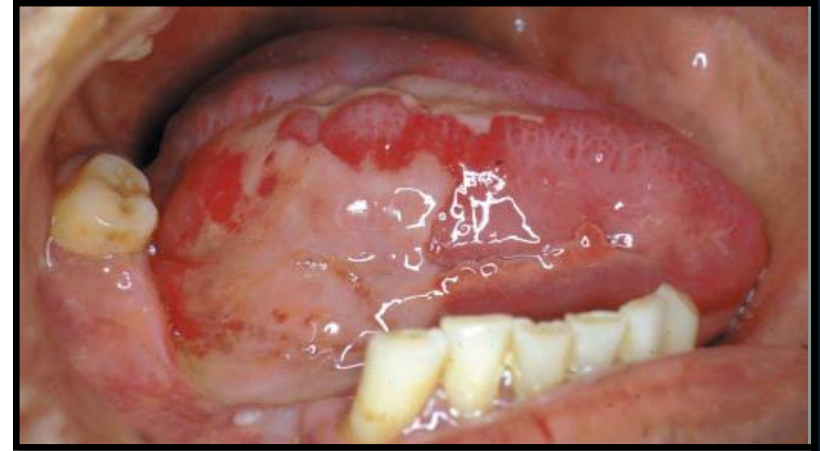
- Acute reactions/Complications: Direct tissue toxicity and possibly secondary bacterial infections
- Chronic complications: Due to change in the vascular supply, fibrosis in connective tissue and muscle, and change in the cellularity of tissues

Radiation Effects On Oral Cavity

- Oral Mucous Membrane
- Taste Buds
- Salivary Glands
- Teeth
- Bone
- Mandibular Dysfunction

Oral Mucous Membrane

- Basal cell layer are radiosensitive Vegetative and Differentiating Intermittent Cells
- At the end of second week cells in the basal layer die
- Mucous membrane begins to break down and forms white to yellow pseudomembrane



Oral Mucous Membrane Cont...

- Sequelae of Mucositis: severe pain, increased risk for Local and Systemic Infection, compromised Oral and Pharyngeal function, and Oral Bleeding
- Healing completes by 2 months
- Mucosa continues to be thin, atrophic and avascular for months or years

Treatment

- Good Oral Hygiene
- Topical Ansthetics: Benzocaine, Lidocaine, Benzydamine hydrochloride
- Antibiotic Mouth Rinse: Chlorhexidine Gluconate
- Coating Agents: Milk of Magnesia, Kaopectate

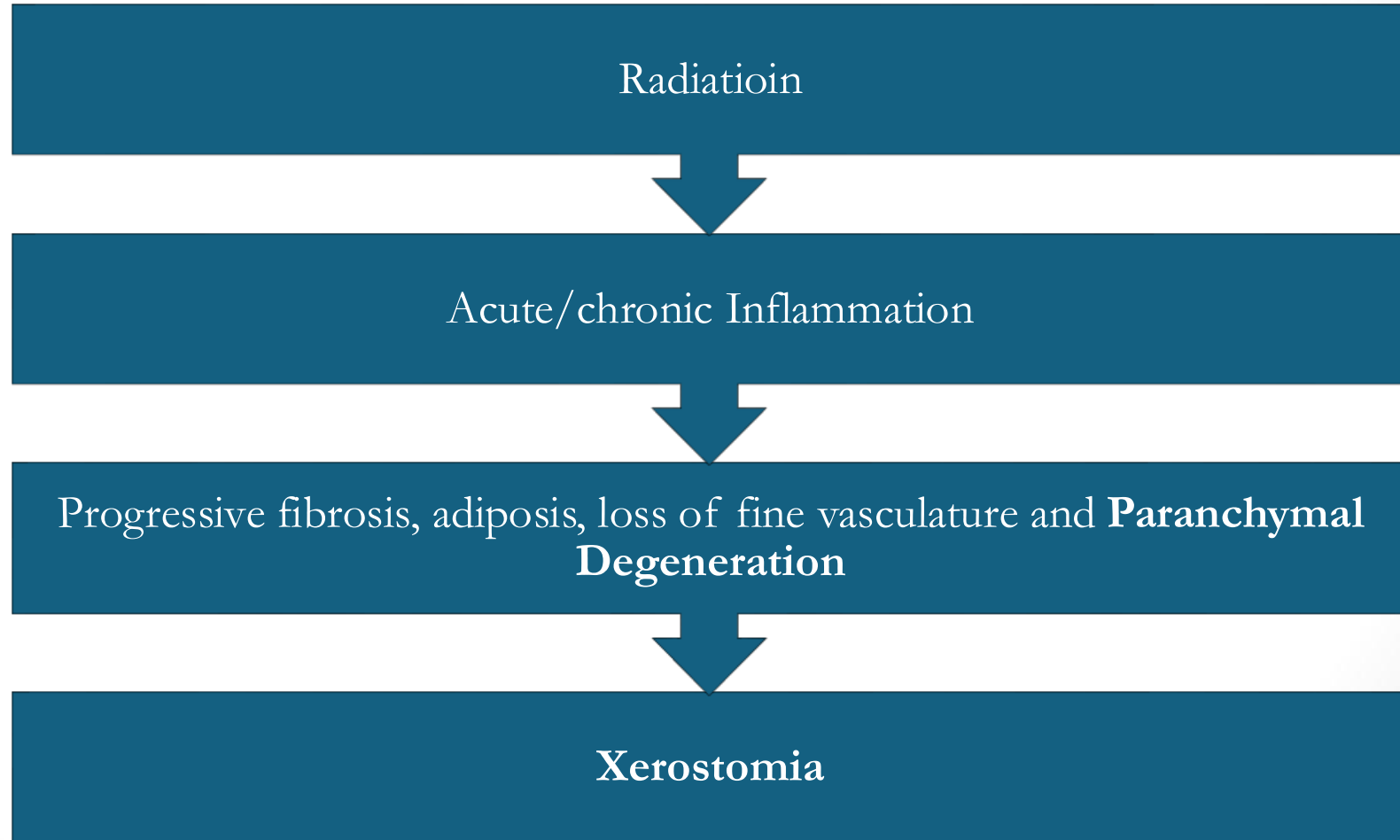
Taste Buds

- Second to third week of radiation therapy the Taste Buds are affected
- Taste may be affected directly by radiation damage to taste buds, or indirectly, due to hypo salivation and secondary infections
- Reverts to normal in 2-4 months
- Very high dose radiation can cause permanent damage to the taste buds
- Zinc supplementation [zinc sulfate, 220 mg twice daily] may be useful

Salivary Glands

- Serous Acini are more Radiosensitive than Mucus Acini
- Parotid gland is more sensitive than Sub-mandibular or Sub-lingual glands
- Paranchymal part is more sensitive than the ductal system
- The extent of damage is dose dependent

Salivary Glands Pathogenesis



Effects Of Radiation On Salivary Glands

- Reduced pH and Buffering capacity leads to decalcification of dental tissues
- Oral microbial flora becomes more Acido-genic
- Increased incidence of Candidiasis and viral infections
- Difficulty in speech, formation of bolus, deglutation

Treatment

- Good Oral Hygiene
- Topical Fluoride application
- Mouth-wetting agents/saliva substitutes: repeated sipping of water, artificial salivary substitutes
- Sialogouges: Pilocarpine 15 mg/d, Bethanechol 75-200 mg/day

Teeth

1. Radiation Precedes Tooth Development

- Pulpal tissue consist of Reverting Post-mitotic Cells, tooth bud is destroyed

2. Radiation after initiation of calcification:

- Tooth malformations, retarded root development, dwarfed teeth, failure to form teeth

Radiation Following tooth Development

Radiation Caries due to:

1. Hyposalivation and Increased viscosity
2. Increased pH
3. Loss of buffering capacity
4. Loss of remineralizing potential
5. Change in the bacterial flora

- Types of caries

1. Superficial buccal, occlusal, incisal, and palatal

2. Cementum and Dentine Caries at cervical region

3. Dark pigmentation of entire crown

Bone

- Radiation damages the vasculature of Periostium and Cortical Bone:
Hypovascular, Hypoxia
- Destroys Osteoblast and Osteoclast: Hypocellular
- Marrow is replaced by fatty and fibrous tissue

Bone Cont...

- Marrow tissue becomes Hypovascular, Hypoxic, and Hypocellular
- Reduced mineralization of bone
- Finally leading to “Osteoradionecrosis “



Prevention

- Removal of caries lesions before radiotherapy
- Extraction of mobile and periodontally tooth as atraumatic as possible
- Adjustment of dentures if necessary
- Desirable to postpone radiography for at least 6 mons post radiotherapy

Mandibular Dysfunction

- Musculoskeletal syndromes arise due to Fibrosis of Muscles



Treatment

- Occlusal stabilization appliances, Physiotherapy
- Exercises
- Trigger point injections
- Analgesics , Muscle relaxants, Tricyclic medications, and

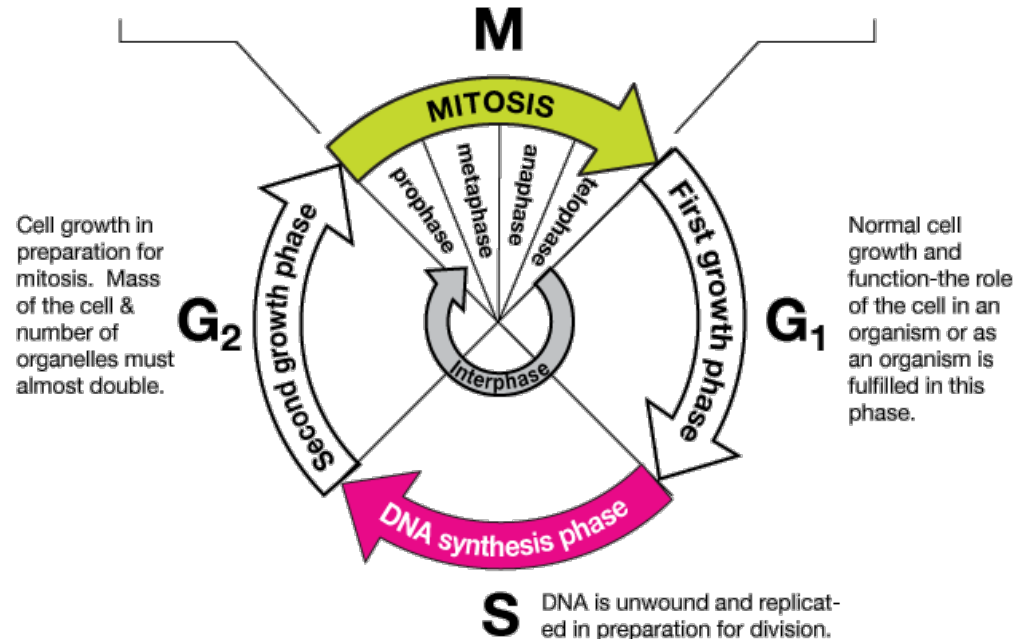
Dentofacial Abnormalities

- Agenesis of teeth, roots, abnormal root forms and abnormal calcification
- Growth of the facial skeleton in the radiated field can result in Micrognathia, Retro-gnathia, altered growth of the maxilla
- Growth and development may get affected if treatment affects the Pituitary Gland

Thank you

Cell Cycle

Prophase	Metaphase	Anaphase	Telophase
DNA coils into chromosomes, tightly-coiled DNA that is visible in a light microscope.	Microtubules bind to centromeres of chromosomes (point where sister chromatids attach).	Sister chromatids are pulled apart, each moving toward a new daughter cell.	Reverse of prophase, new nuclear membranes form, cytokinesis begins.



Length of Time in Phases of the Cell Cycle

Cells:

Phase of cell cycle	CHO cells (hours)	HeLa cells (hours)
Tc	11	24
Tm	1	1
Ts	6	8
TG2	3	4
TG1	1	11

Variation from one cell type to another is greatest for G1 phase.