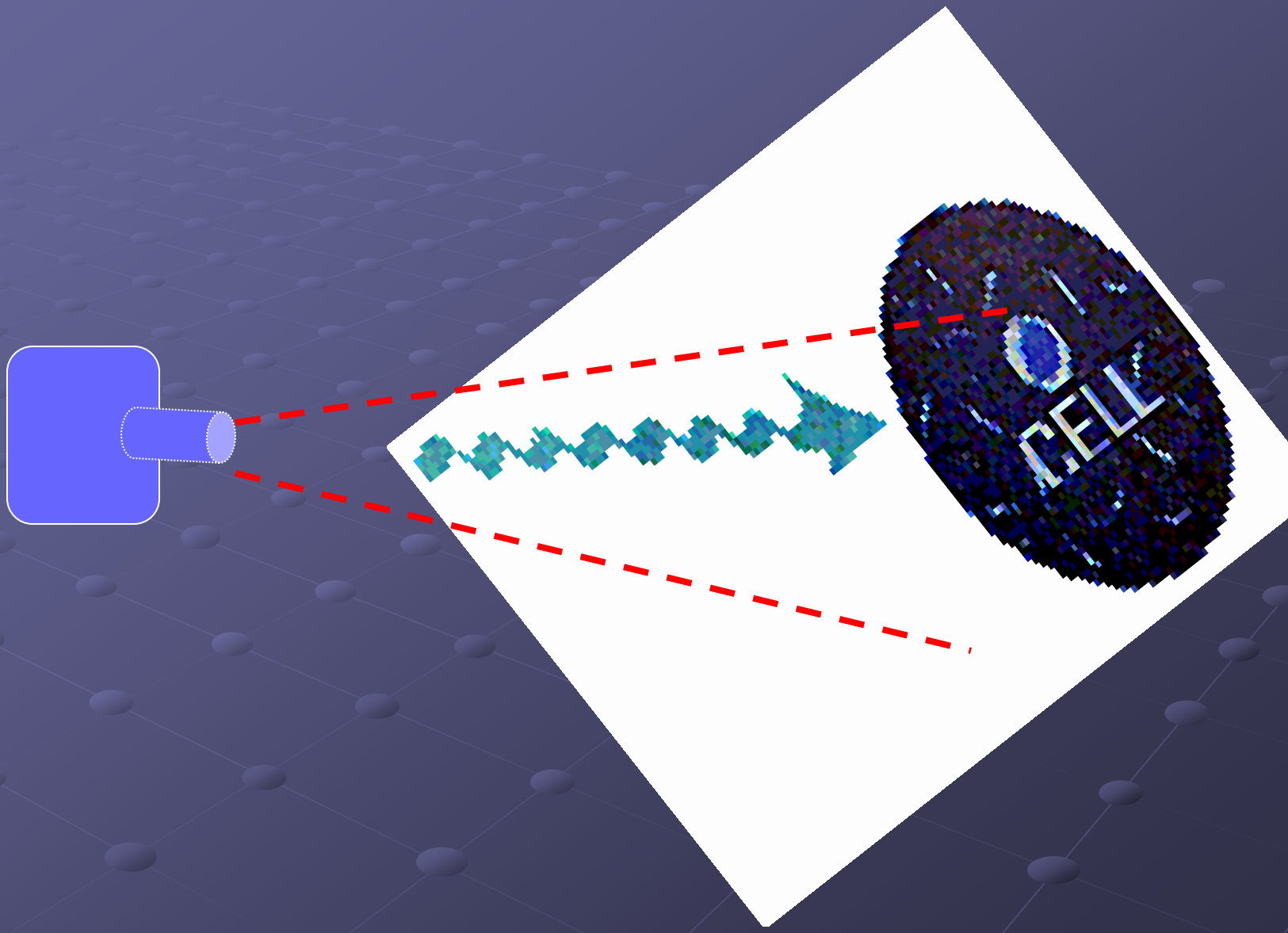
RADIATION BIOLOGY


CELL

INTRODUCTION

- *RADIATION BIOLOGY* IS THE STUDY OF THE EFFECTS OF IONIZING RADIATION ON LIVING SYSTEMS.
- This discipline requires studying many level of organisations within biologic systems spanning broad ranges in size and temporal scale.

INTRODUCTION

- The initial interaction between ionizing radiation and matter occurs within first 10^{-13} seconds after exposure.
- Subsequent modification of biologic molecules within the following seconds to hours.
- Later these molecular changes may result in alterations in cells and organisms that may perists for hours,decades and possibly for generations.

INTRODUCTION

- Biologic effects of ionizing radiation may be divided into two broad categories:
- Deterministic effects
- Stochastic effects

DETERMINISTIC EFFECTS

- Deterministic effects are those effects in which the severity of response is proportional to the dose.
- Deterministic effects have a dose threshold below which the response is not seen.
- Examples: oral changes after radiation therapy, and radiation sickness after whole body irradiation.

Stochastic effects

- **Stochastic effects are those for which the probability of occurrence of the change, rather than its severity ,is dose dependent.**
- **They are *all or none effects*.**
- **They do not have dose thresholds.**
- **Example: Radiation induced cancer is stochastic effects because of greater exposure of a person.**

RADIATION CHEMISTRY

Action of radiation
On
Living system

Direct effects

Indirect effects

Direct effects and indirect effects

- When the energy of a photon or secondary electron is transferred directly to biologic macromolecules , the effect is termed as "*direct*".
- When the photon is absorbed by the water, the water molecules are ionized and form free radicals that in turn interact with and produce changes in biologic molecules , the effect is called as "*indirect*"

Direct effects

- Direct effects involves three steps:
- *Absorption of energy by the biologic molecules.*
- *Transfer of energy between unstable intermediate molecules*
- *Formation of stable , damaged molecules.*

Direct effects

- The resultant molecules then either undergo dissociation or undergo cross linking.
- RH + X-RADIATION → $R^+ + H^+ + e^-$
- FREE RADICAL FATES:
- Dissociation: $R^{\cdot} \rightarrow X + Y$
- Cross linking: $R^{\cdot} + S^{\cdot} \rightarrow RS$

RADIOLYSIS OF WATER

- **Complex series of chemical changes occur in water after exposure to ionizing radiation, and these reactions are known as *radiolysis of water.***
- **First step in this process is the ionization of water that may result from absorption or a photoelectron or Compton electron.**

RADIOLYSIS OF WATER

- The absorbed energy displaces an electron from the water molecule resulting in an electron pair, a positively charged water molecule.(H_2O^+)
- Photon + H_2O ⟹ e^- + H_2O^+

RADIOLYSIS OF WATER

- Then the electron would be absorbed by +vely charged ion to reform a stable water molecule or it may be captured by an unionized water molecule. The result in another -vely charged water molecule.
- $e^- + H_2O \rightarrow H_2O^-$
- $H_2O^+ \rightarrow H^+ + OH^-$
- $H_2O^- \rightarrow OH^- + H^-$

RADIOLYSIS OF WATER

The +vely charged water molecule will dissociate to form hydrogen ion and hydroxyl free radical , the –vely charged water molecule will dissociate to form a hydroxyl ion and a hydrogen free radical.

RADIOLYSIS OF WATER

- When dissolved molecular oxygen is present in irradiated water , then hydroperoxyl free radical is formed which may later form hydrogen peroxide.
- Both these are oxidizing agents and alter biologic molecules and thus cause cell destruction.

INDIRECT EFFECTS

- Indirect effects of radiation are those changes in biologic molecules that are mediated through the hydrogen and hydroxyl free radicals from ionized water molecules.
- They react with organic molecules may result in formation of organic free radicals.

INDIRECT EFFECTS

- $RH + OH\cdot \rightarrow R\cdot + H_20$
- $RH + H\cdot \rightarrow R\cdot + H_2$

- These organic molecules are unstable and may transform into new molecules by undergoing condensation or rearrangement reactions.

Radiation effects at cellular level

- EFFECTS ON INTRACELLULAR STRUCTURES:
- A: NUCLEUS
- B:CHROMOSOME ABERRATIONS
- C: CYTOPLASM
- EFFECTS ON CELL KINETICS:
- A: MITOTIC DELAY
- B: CELL DEATH
- C: RECOVERY

EFFECTS ON INTRACELLULAR STRUCTURES

- The initial molecular changes are produced within a fraction of a second after exposure, cellular changes require a minimum of hours to become apparent.
- These changes are manifest initially as structural and functional changes in cellular organelles.
- Later cell death may occur.

Effects on intracellular structures

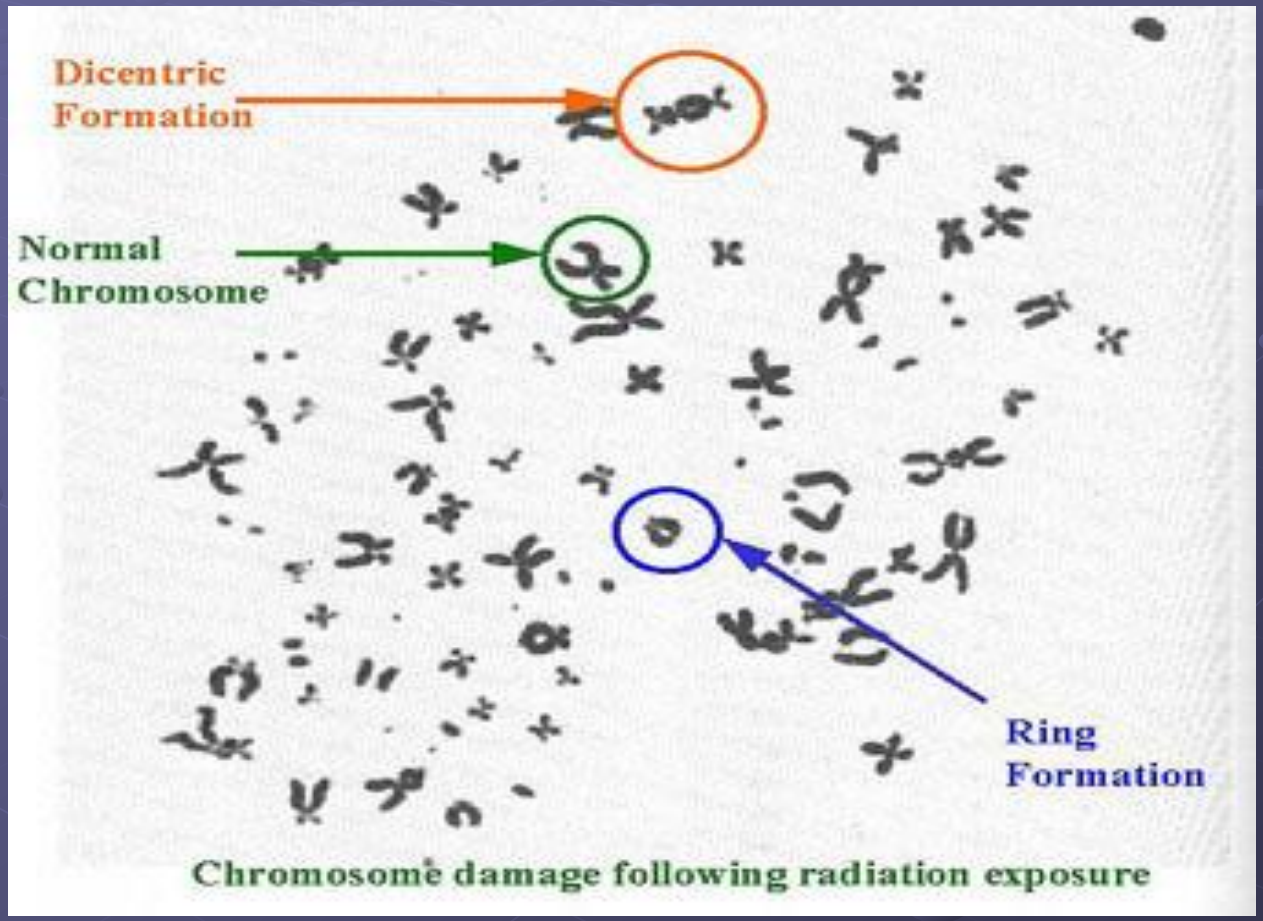
- **Nucleus: The nucleus is more radiosensitive than cytoplasm , especially in dividing cell.**
- ***The sensitive site in the nucleus is the DNA within the chromosomes.***

NUCLEIC ACIDS

- It is clear that damage to DNA molecule is primarily responsible for cell death after radiation exposure.
- Following alternations occurs in the DNA:
- Change or loss of a base
- Disruption of hydrogen bonds between DNA strands.
- Breakage of one or both DNA strands
- Cross linking of DNA strands within the helix, to the other strands or to proteins.

Effects on intracellular structures

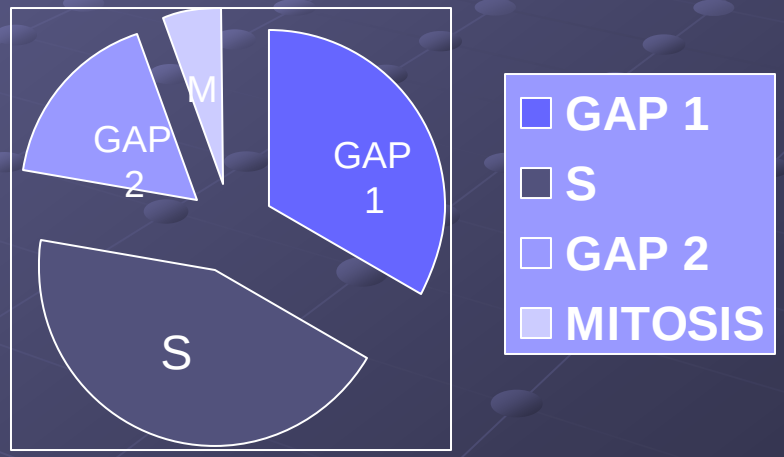
- **Chromosome aberrations: Chromosomes serve as a useful marker for radiation injury.**
- **Chromosome aberrations are observed in irradiated cells at the time of mitosis when the DNA condenses to form chromosomes.**
- **The type of damage that may be observed depends on the stage of the cell in the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



Chromosome damage following radiation exposure

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..



Chromosome aberrations

- If radiation exposure occurs after the DNA synthesis (in G_2 or mid and late S)

  only one arm of chromosome is broken.

  If the radiation induced break occurs before DNA replication (G_1 or early S) damage occurs at both the arms of chromosomes.

Radiation Induced Genetic Damage

- The 7 million mice, "*Megamouse"* project revealed the following conclusions (Lam 1992):
- Different mutations differ significantly in the rate at which they are produced by a given dose.
- There is a substantial dose rate effect with no threshold for mutation production.
- The male was more radiosensitive than the female. The males carried most of the radiation induced genetic burden.
- The genetic consequences of a radiation dose can be greatly reduced by extending the time interval between irradiation and conception. Six months to a year is recommended.
- The amount of radiation required to double the natural and spontaneous mutation rate is between 20 to 200 rads

Radiation Induced Genetic Damage

- Radiation apparently does not cause unique types of mutations, but simply increases the mutations rate above their natural rate of occurrence

Effects on the intracellular structures

- Cytoplasm: Large doses of radiation(30 to 50 Gy) , mitochondria demonstrate increased permeability , swelling and disorganisation of the internal cristae.

Changes in biologic molecules

- Proteins: Irradiation of proteins in solution causes disruption of secondary and tertiary structure through disruption of side chains or the breakage of hydrogen or disulfide bonds.
- Primary structure is not altered.

Effects on cell kinetics

- Mitotic delay: Mitotic delay occurs after irradiation of a population of dividing cells.
- Low dose causes mild mitotic delay in G_2 cells.
- A moderate dose results in longer mitotic delay (G_2 block) and some cell death.
- Larger doses causes profound mitotic delay with incomplete recovery.

Effects on cell kinetics

- Cell death:Mitosis linked death in a cell population is loss of the capacity for mitotic division.
- Cell death results due to damage to the nucleus
- This damage causes the cell to die, usually while attempting to complete the first few mitosis after irradiation.

Cell death

- Reproductive death occurs in a dividing cell population after exposure to a moderate dose of irradiation.
- For non dividing cells longer time and larger doses are required to cause cell death.

Recovery

- Cell recovery involves enzymatic repair of single strand breaks of DNA.
- Because of this repair a higher total dose is required to achieve a given degree of cell killing when multiple fractions are used.
- Damage to both strands of DNA at the same site is usually lethal to the cell.

Radiosensitivity and cell type

- **Different cells of different organs in the same individual responds differently to radiation , this was recognised by Bergonie and Tribondeau.**
- **They observed that most radiosensitive cells are those that:**
- ***1:have high mitotic rate***
- ***2:undergo many future mitosis***
- ***3:are most primitive in differentiation.***

RADIOSENSTIVITY AND CELL TYPE

- Mammalian cells can be divided into five categories of radiosensitivity on the basis of histologic observations of early cell death.
- *Vegetative intermitotic cells*
- *Differentiating intermitotic cells*
- *Multipotential connective tissue cells*
- *Reverting post mitotic cells*
- *Fixed post mitotic cells*

Examples

- Vegetative intermitotic cells: erythroblastic series, spermatogenic series, basal cell layer of oral mucous membrane.
- Differentiating intermitotic cells: intermediate dividing cells of inner enamel epithelium of developing cells,cells of hematopoietic cells,spermatocytes and oocytes.

Examples

- Multipotential connective tissue cells:vascular endothelial cells ,fibroblasts,and mesenchymal cells.
- Reverting postmitotic cells:acinar and ductal cells of salivary glands and pancreas
- Fixed post mitotic cells: neurons,striated muscle cells,squamous epithelial cells.

Increasing Sensitivity to Radiation

- Lymphocytes
- Erythrocytes, Granulocytes
- Epithelial Cells
- Endothelial Cells
- Connective Tissue Cells
- Bone Cells
- Nerve Cells
- Brain Cells
- Muscle Cells

Radiation effects at tissue and organ level

- There are basically two effects:
- Short term effects
- Long term effects

Radiation effects at tissue and organ level

- Short term effects: The short term effects of radiation on a tissue are determined primarily by:
- Sensitivity of its parenchymal cells.
- A: Rapidly proliferating cells
- B: Rarely dividing cells.
- Long term effects: It primarily depends on the extent of damage to the fine vasculature.

Long term effects of radiation

1:Radiation → capillaries → swelling ,degeneration

2: necrosis → increase permeability → fibrosis

3: fibrous scar → premature narrowing of lumen

4: obliteration of vascular lumen → impair transport

5: lack of oxygen , nutrients → fibroatrophy

Modifying factors

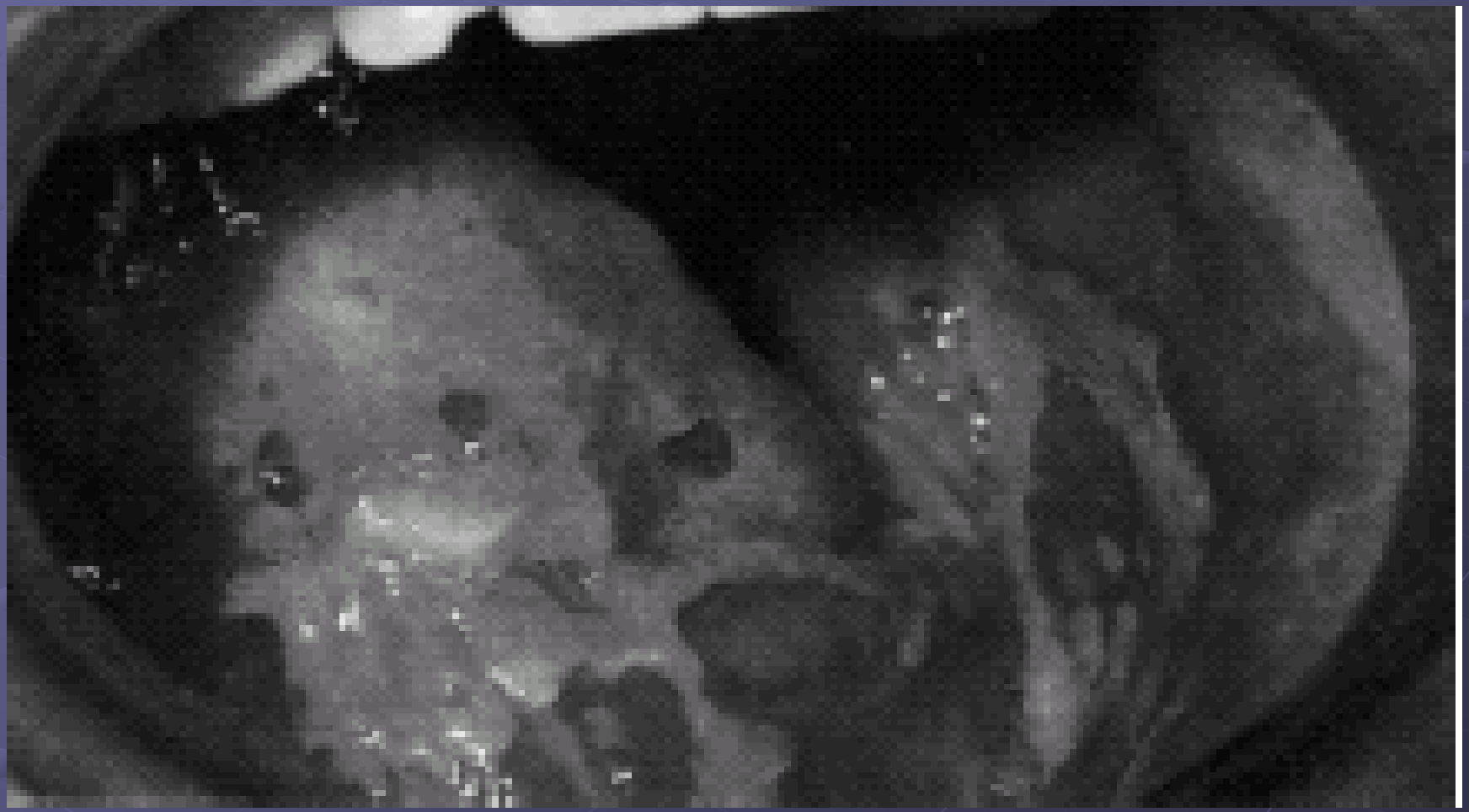
- 1: Dose
- 2: Dose rate
- 3:Oxygen
- 4: Linear energy transfer

RADIATION EFFECTS OF ORAL CAVITY

- **ORAL MUCOUS MEMBRANE:**
- **1: At the end of second week of therapy , mucous membrane shows areas of redness , and inflammation(mucositis).**
- **2: Further irradiation formation of white to yellow pseudomembrane**
- **3:Candidial infection a complication**
- ***Treatment:***
- **1:good oral hygiene**
- **2: topical anesthetics**
- **3: heals in about 2 months may be atropic**

TABLE 8-4 Management of Mucositis

Diluting agents	
	Saline, bicarbonate rinses, frequent water rinses, dilute hydrogen peroxide rinses
Coating agents	
	Kaolin-pectin, aluminum chloride, aluminum hydroxide, magnesium hydroxide, hydroxypropyl cellulose, sucralfate
Lip Lubricants	
	Water-based lubricants, lanolin
Topical anesthetics	
	Dyclonine HCl, xylocaine HCl, benzocaine HCl, diphenhydramine HCl
Analgesic agents	
	Benzydamine HCl



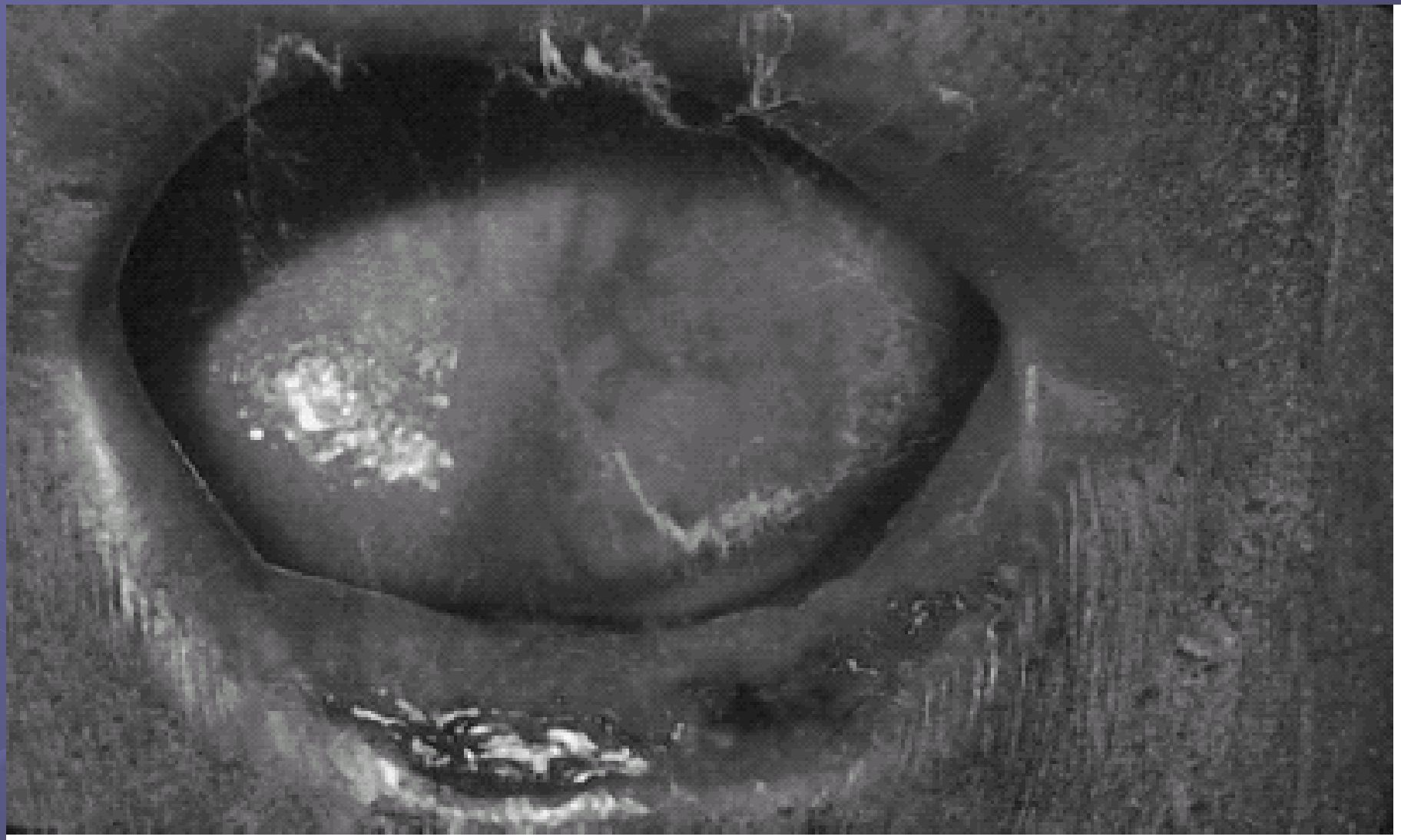


FIGURE 8-37 Radiation mucositis complicated by candidiasis, resulting in increased severity of mucositis and angular cheilitis.

Taste buds

- 1: Degeneration of taste buds
- 2: Loss of taste sensations
- 3: Taste acuity decreases

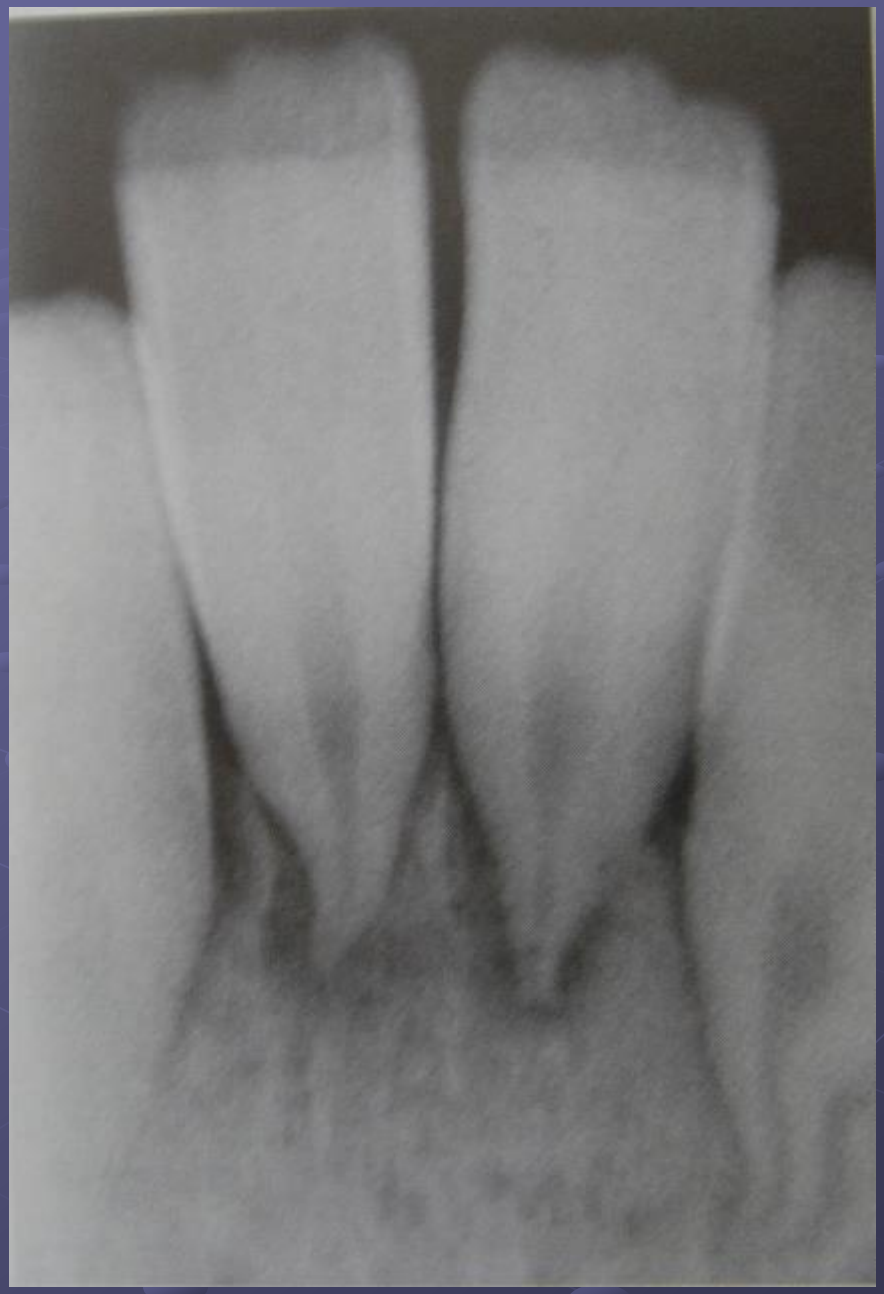
RECOVERY TO NEAR NORMAL LEVELS SOME 60 TO 120 DAYS AFTER IRRADIATION.

SALIVARY GLANDS

- 1: Progressive loss of salivary secretions
- 2: Salivary flow reduced to zero at 60 Gy
- 3:Mouth is dry tender, swallowing difficult and painful.
- 4:Viscous saliva
- 5: Radiation caries

Teeth

- 1: If precedes calcification, it may destroy the tooth bud.
- 2: After calcification , may inhibit cellular differentiation, causing malformations, and arresting general growth.
- 3: Children receiving radiation may have retarded root development, dwarfed teeth,or failure to form teeth.
- 4: Teeth irradiated during development may cause premature eruption of teeth.
- 5: Pulpal tissue may show fibroatrophy.



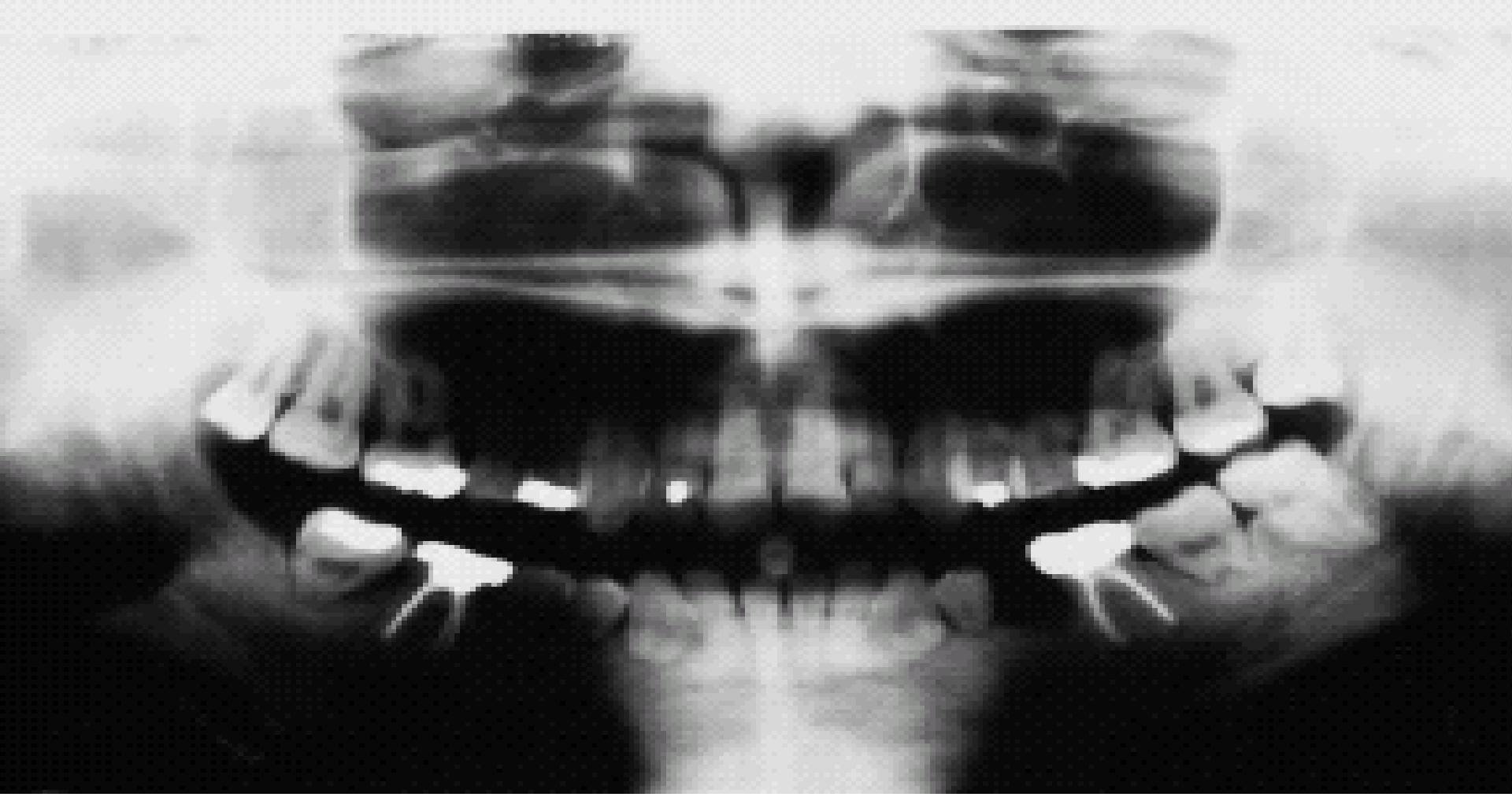


FIGURE 8-46 Radiograph showing the effects of radiation on th
development of the dentition. Agenesis, shortened root forms, lack of ro
development, and premature closure of apical foramina are seen in teet
that were in the primary radiation field and that were in the process
development during radiation therapy.

RADIATION CARIES

Rampant form of caries occuring after radiation exposure especially of the salivary glands.

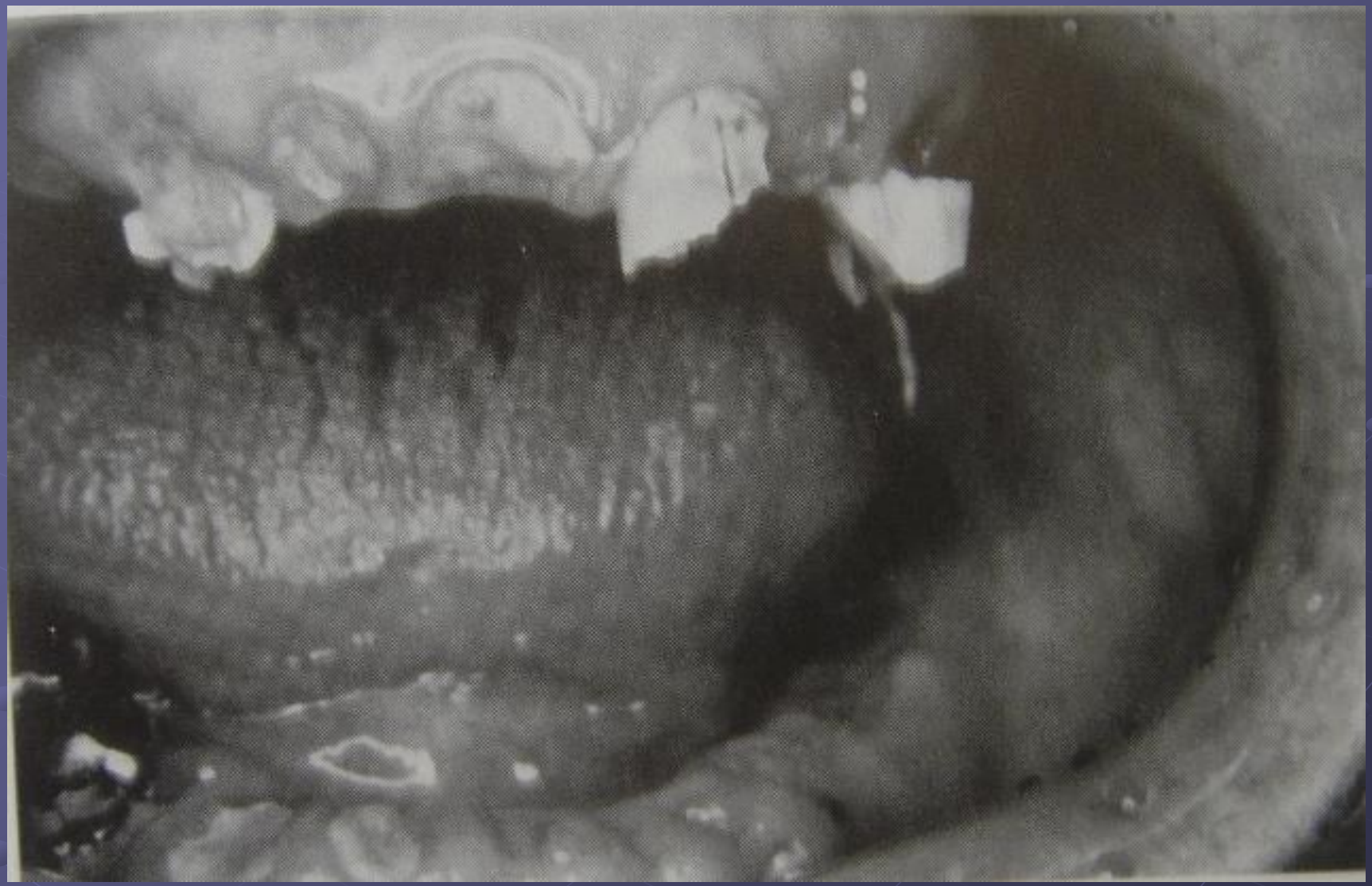
Causes: Changes in saliva and salivary glands

reduced flow of saliva

Decreased pH

Reduced buffering capacity of saliva

Increased viscosity



RADIATION CARIES

- Clinically three types are present.
- 1: Superficial lesions affecting buccal,occlusal, incisal and palatal surfaces
- 2: Affecting cemetum and dentin in cervical region
- 3:Dark pigmentation of the entire crown

RADIATION CARIES

- Treatment:
- 1: Daily application of topical neutral sodium fluoride for five minutes
- 2:Avoidance of dietary sucrose
- 3:Restorative dental procedures
- 4:Excellent oral hygiene
- 5: Grossly decayed teeth extracted before irradiation.

BONE

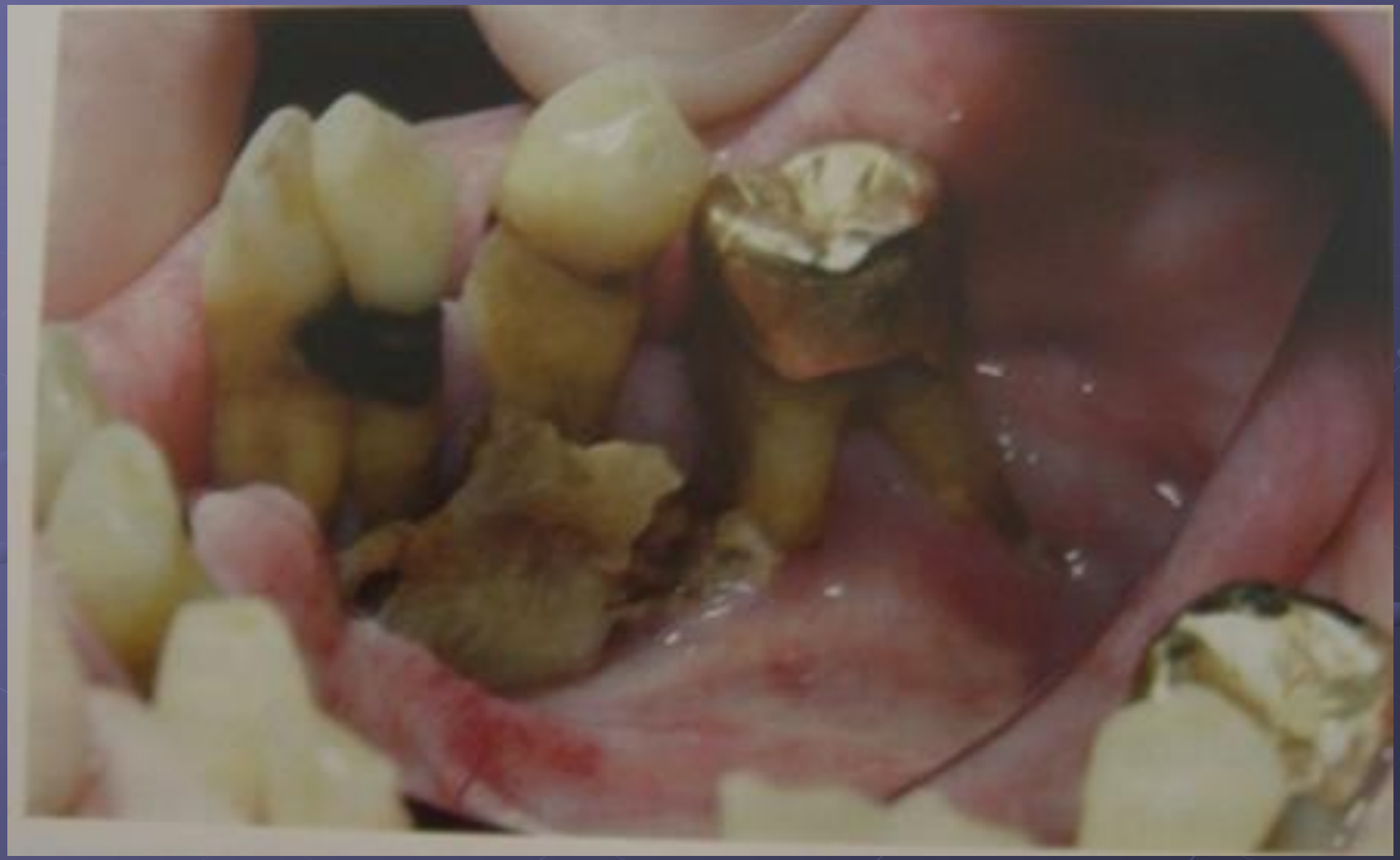
- The primary damage to the mature bone results from radiation induced damage to the vasculature of the periosteum and cortical bone .
- Radiation acts by destroying osteoblasts and to lesser extend osteoclasts.

Osteoradionecrosis

- Radiation causes marrow tissue to become hypoxic,hypovascular,and hypocellular.
- Endosteum is atropic shows lack of osteoblasts
- Degree of mineralisation is reduced leading to brittleness .
- Finally bone death results and leads to osteoradionecrosis.

Osteoradionecrosis

- Mandible is more commonly affected than maxilla because of the
- 1: richer vascular supply of the maxilla
- 2:mandible is more frequently irradiated.



Radiological features

- Radiographic feature similar to chronic osteomyelitis.
- Periphery is ill defined . If the lesion reaches the inferior border of mandible irregular resorption of the cortex is seen.
- Internal structure shows features of either bone formation or bone resorption.
- Balance heavily loaded toward bone formation.
- Scattered area of radiolucency with or without central sequestra.

Differential diagnosis.

- 1: malignant neoplasm
- 2: chronic osteomyelitis.

STAGE	DESCRIPTION	TREATMENT
1	Resolved healed	Prevention of recurrence
1a	No patho.fract	
1b	Past patho fract	
2	Chronic non progressive	Local wound care HBO if needed
2a	No patho fract	
2b	Patho fract	
3	Active progessive	Local wound care , HBO and surgery
3a	No patho fract	
3b	Patho fract	

Osteoradionecrosis

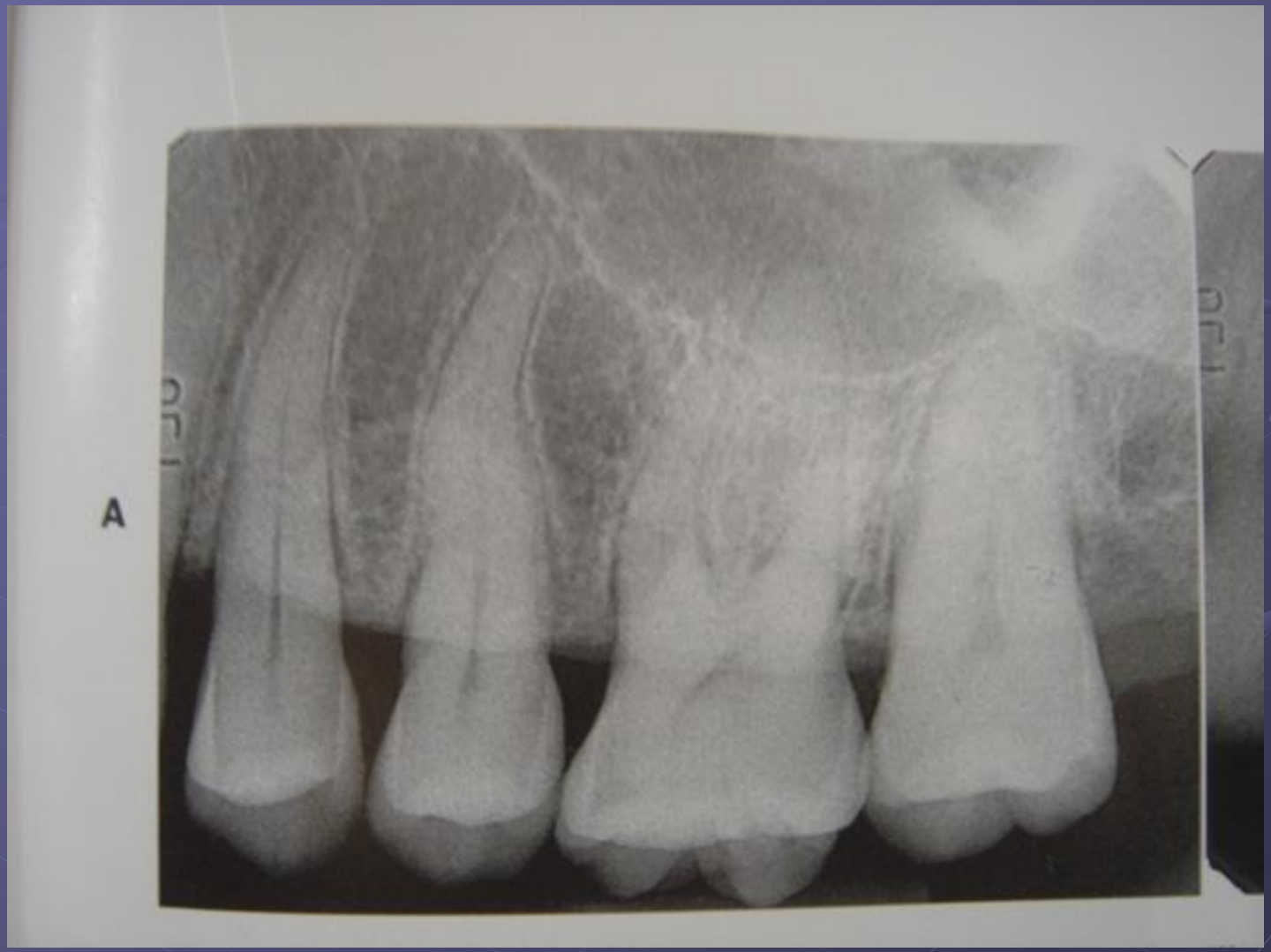
- **Prevention:** Dental care should be done before radiation therapy.
- 1: Restoring all carious lesions
- 2: Initiating good oral hygiene measures.
- 3: Extraction of hopeless teeth
- 4:Allow sufficient time to heal of wound before initiating the therapy
- 5:Adjustment of dentures to avoid denture sore
- 6:After irradiation , if teeth are to extracted do it under antibiotic cover and atraumatic surgical procedures should be followed.

Hyperbaric oxygen

- Mechanism of action:
- 1: It increases the oxygen tension
- 2: It increases the leukocyte bactericial activity.
- 3: It increases the fibroblastic activity.
- 20 T0 30 DIVES AT 100% OXYGEN AND 2 TO 2.5 ATMOSPHERE OF PRESSURE.
- IT IS GIVEN 5 DAYS A WEEK.

HYPERBARIC OXYGEN

- Prophylactic HBO is given when:
- 1: When surgery is required after radiation therapy.
- 2: When patient is felt to be at extreme risk due to high dose radiation to the bone with a high biologic effect.
- When extensive surgery is required.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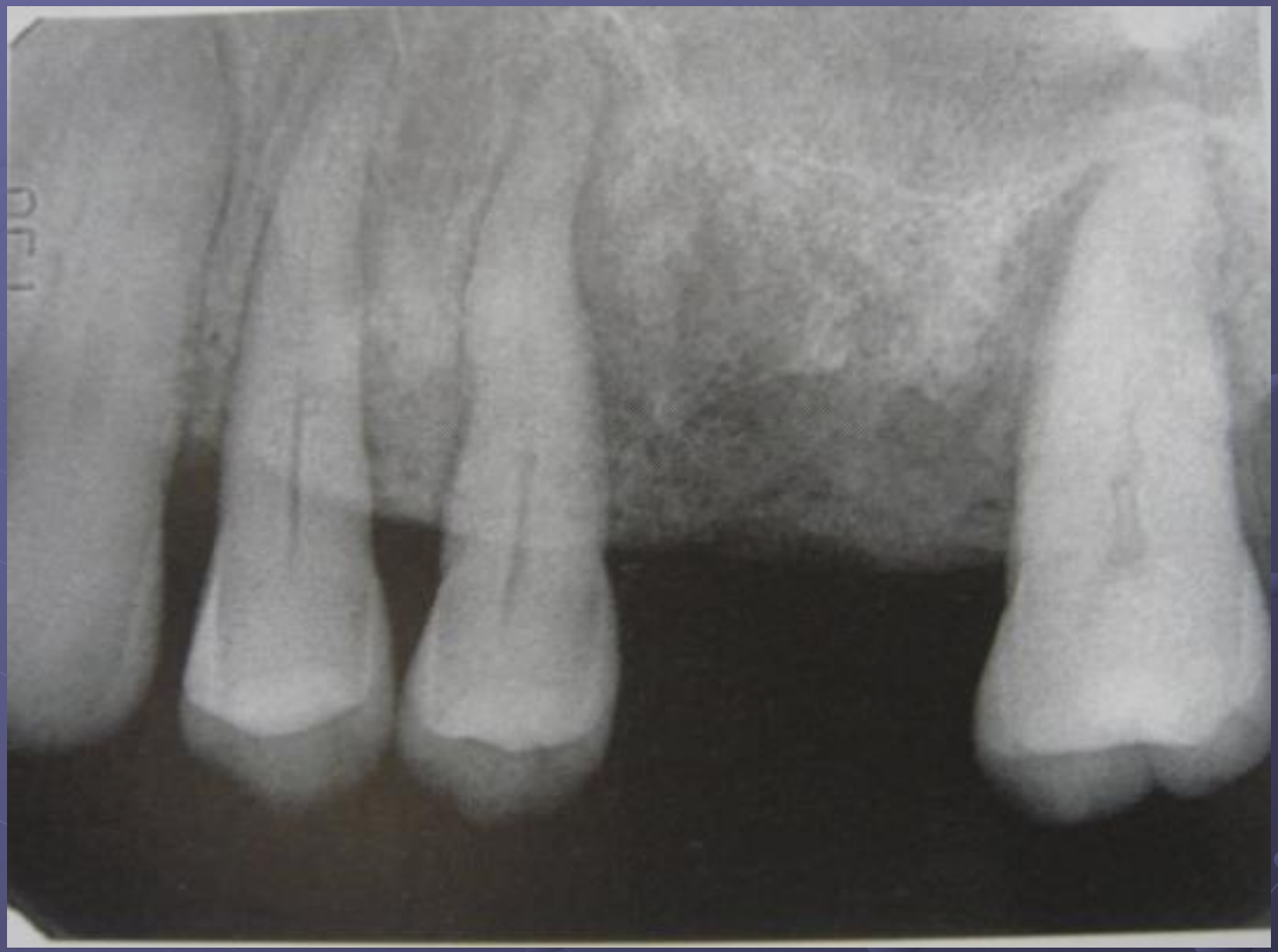


Acute radiation syndrome

Syndrome	Symptoms	Dose(rad)
Radiation sickness	Nausea, vomiting	> 100 rad
Hemopoietic	Significant disruption of ability to produce blood products	➢250 rad
LD50/60d	Death in half the population	➢> 250 - 450 rad
GI	Failure of GI tract lining, loss of fluids, infections	➢> 500rad
CNS	Brain death	➢> 2,000 rad

Radiation Effect	Threshold to Produce (rad)	Amount of Fluoroscopy to produce @ 5R/min	Amount of Cine to produce @ 30 R/min	Time to effect
Transient Erythema	200	0.7 hours	0.1 hours	24 hours
Epilation	300	1 hours	0.2 hours	3 weeks
Main Erythema	600	2 hours	0.3 hours	10 days
Pericarditis	800	2.7 hours	0.4 hours	>10 weeks
Dermal Necrosis	1800	6 hours	1 hours	>10 weeks
Skin Cancer	None Known	NA	NA	>5 years

Radiation Induced Premature Aging

- In animal populations, radiation was correlated with premature aging

In-utero Radiation Health Effects

- Once conception has occurred (mother is pregnant), the unborn child (fetus) can be harmed by radiation. Certainly, the unborn child can have the same health problems that an adult might have such as cancer and genetic defects. The Law of Bergonie and Tribondeau predicts that a fetus would be exquisitely sensitive to radiation since they are
- 1. Rapidly dividing;
- 2. Undifferentiated; and
- 3. Have a long mitotic future.

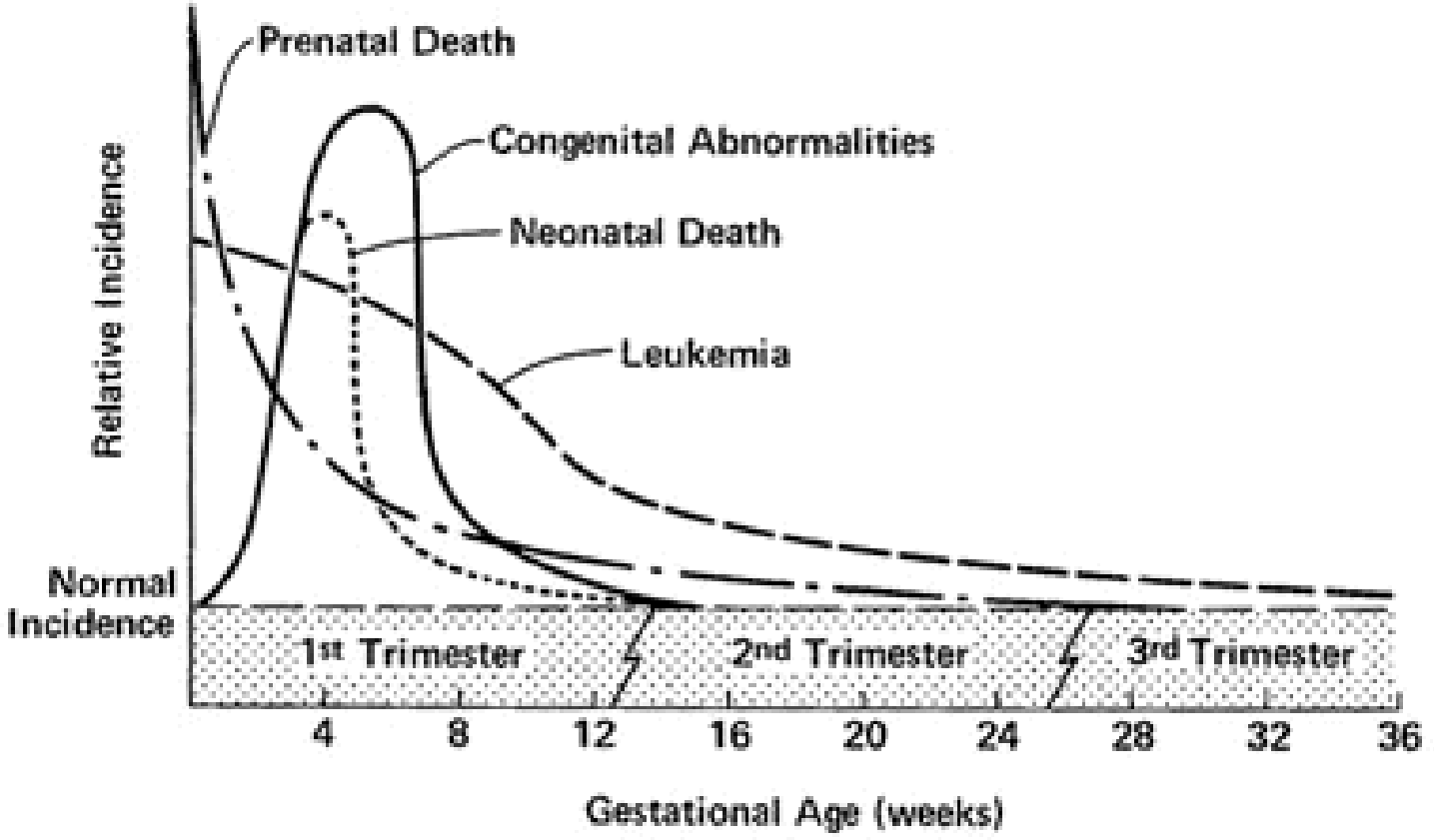
In-utero Radiation Health Effects

- In addition to the health effects which are a concern for an adult, there is also a serious concern about the possibility of developmental errors (teratogenesis) which can occur. There are three general prenatal effects which have been observed:
- Lethality;
- Congenital abnormalities at birth; and
- Delayed effects, not visible at birth, but manifested later in life.

In-utero Radiation Health Effects

- A human embryo exposed to greater than 250 rads before 2 to 3 weeks of gestation will likely result in prenatal death (miscarriage). Fortunately, those infants, who survive to term at these extreme doses generally do not exhibit congenital abnormalities.

  Irradiation of the human fetus between 4 to 11 weeks of gestation may cause multiple severe abnormalities of many organs.
- Irradiation during the 11th to 15th week of gestation may result in mental retardation and microcephaly.
- After the 20th week, the human fetus is more radioresistant, however, functional defects may be observed.
- In addition, a low incidence (one in 2000) of leukemia has been observed in individuals who received prenatal radiation.

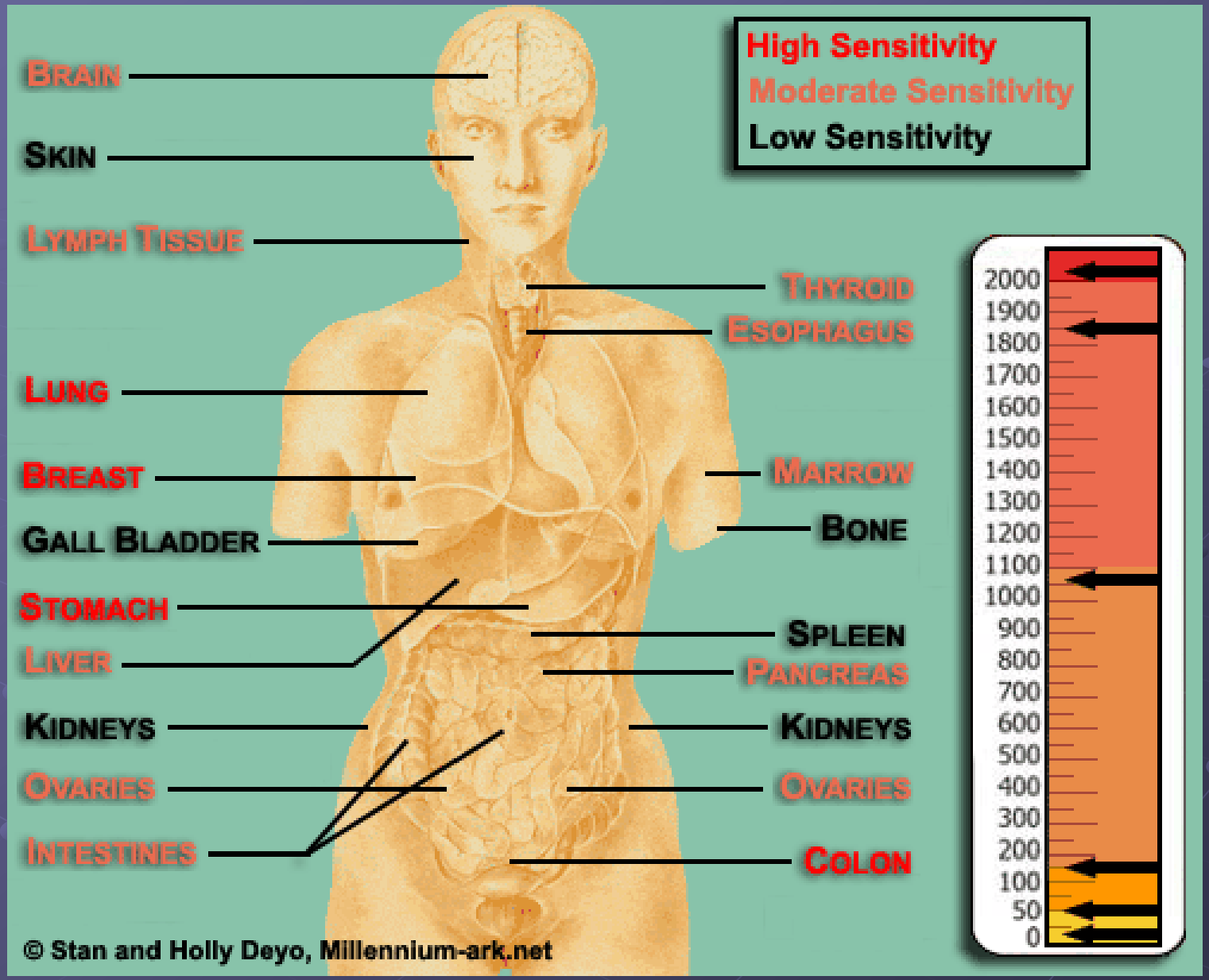

Prenatal Death
Congenital Abnormalities
Neonatal Death
Leukemia
Relative Incidence
Normal Incidence
1st Trimester
2nd Trimester
3rd Trimester
4
8
12
16
20
24
28
32
36
Gestational Age (weeks)

Late somatic effects

- Somatic effects are those seen in the irradiated individual .
- The most important are radiation induced cancers.
- Such lesions are stochastic effect of radiation in that the probability of an individual getting cancer depends upon the amount of radiation exposure.

Radiation a human carcinogen?

- Is not well understood.
- Radiation acts as a initiator ,it produces change in the cell so that it no longer undergoes terminal differentiation.
- Evidence are also there that radiation acts a promoter stimulating cells to multiply
- It may convert premalignant cells to malignant.


High Sensitivity
Moderate Sensitivity
Low Sensitivity
Brain
Skin
Lymph Tissue
Lung
Breast
Gall Bladder
Stomach
Liver
Kidneys
Ovaries
Intestines
Thyroid
Esophagus
Marrow
Bone
Spleen
Pancreas
Kidneys
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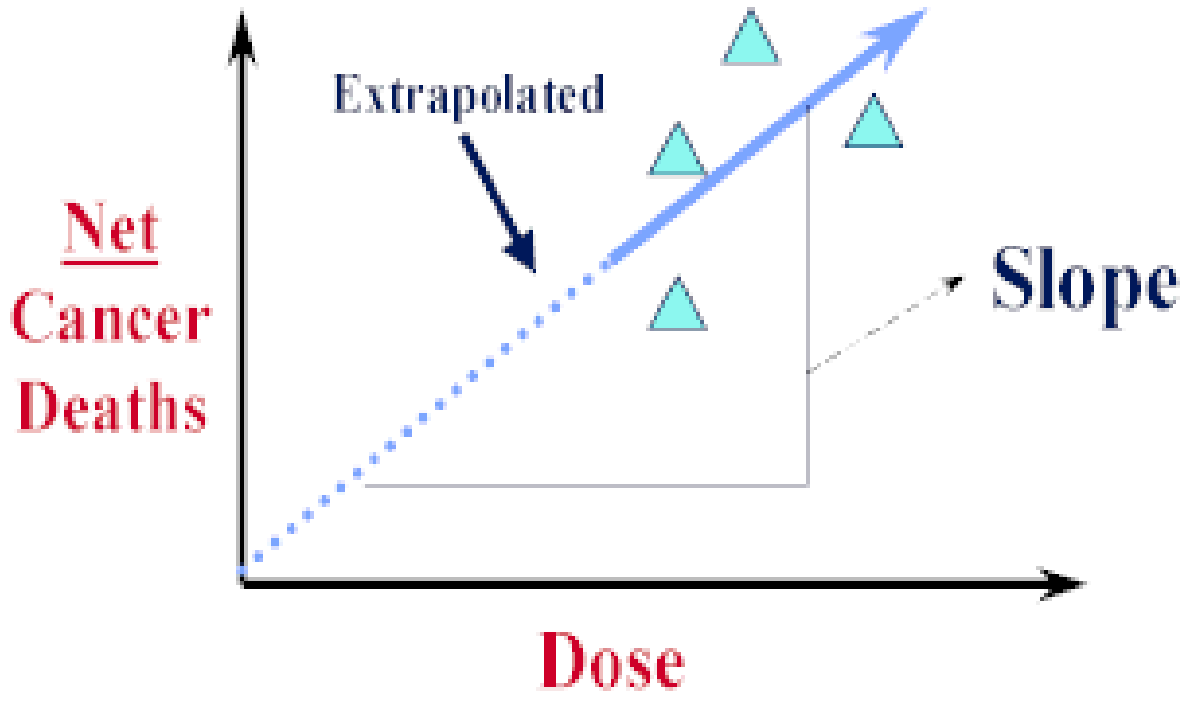
Stochastic Effects

Population

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