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Introduction to Radiation Oncology Pre-clinical

Ted Lawrence, MD, PhD

Department of Radiation Oncology

University of Michigan

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University of Michigan Medical School

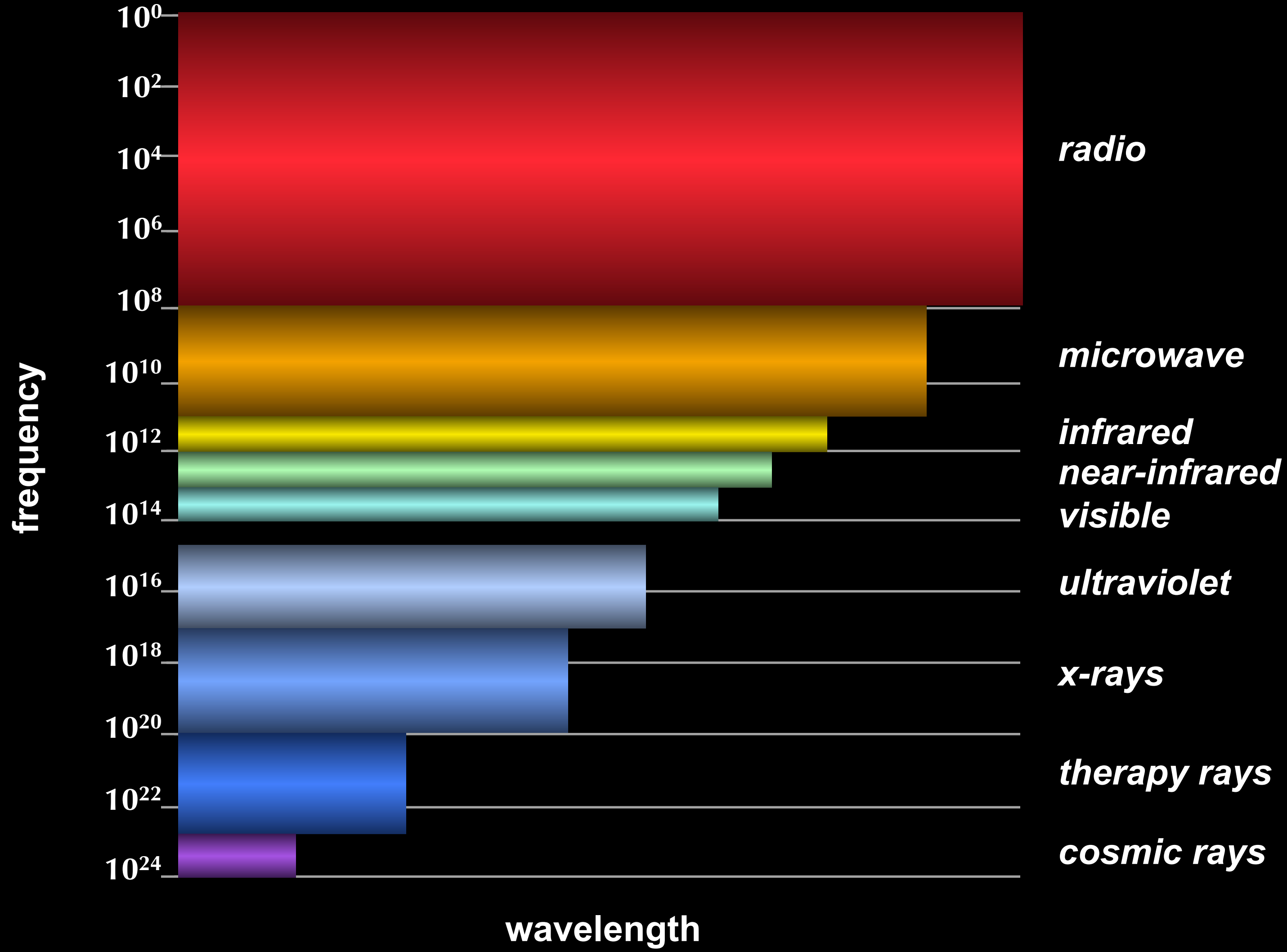
Overview

- Radiation Oncology depends on the fields of radiation physics, radiation biology and medicine
- The understanding and application of each is enhanced by a knowledge of the other
- In these lectures, we will review how radiation interacts with tissue physically and biologically, and then focus on how to apply these concepts to treat patients

What is a radiation oncologist?

- An oncologist
- A specialist and a generalist (all parts of the body)
- A person expert in applications of radiation
  - Uses radiation in a clinic and in an operating room
  - Directs therapists (who place patients on the machines), dosimetrists (who do dose calculations), and physicists
- A member of a multidisciplinary team
- A teacher

Electromagnetic Spectrum



Kinds of radiation - Photons

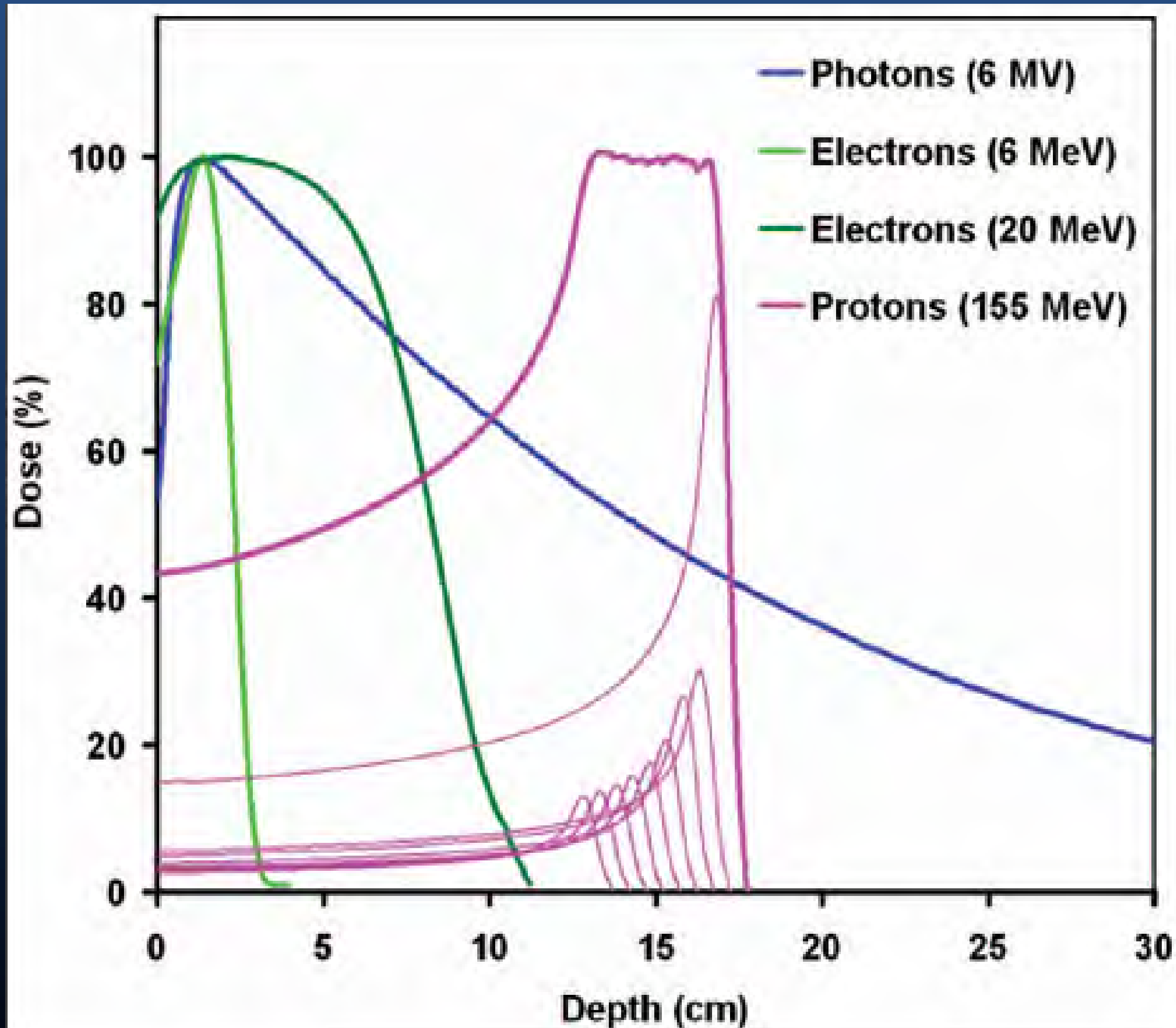
- Gamma rays and x-rays
- Penetrates deeply, so that the dose to the skin is less than the deep dose ("skin sparing")
- Depth of penetration moderately dependent on the energy of the beam.
- This is the main form of radiation used because it permits us to treat deep tumors without skin damage.

Kinds of radiation - Electrons

- Electrons interact directly with tissues, so that the dose to the skin tends to be high compared to deeper tissues
- Depth of penetration is strongly dependent on the energy of the beam
- This type of radiation is used to treat skin cancers, or other cancers that are relatively close to the surface of the body (< 6 cm)

Kinds of radiation - Charged particles

- Charged particles (protons and carbon nuclei) have better depth dose characteristics than photons and electrons
  - Depth of penetration is strongly dependent on the energy of the beam
    - Can go deeper than electrons with more skin sparing
- Carbon nuclei can kill hypoxic cells as effectively as well oxygenated cells
- However- MUCH (at least 20x) more expensive



Photons (6 MV)
Electrons (6 MeV)
Electrons (20 MeV)
Protons (155 MeV)
Dose (%)
100
80
60
40
20
0
0
5
10
15
20
25
30
Depth (cm)

How radiation is produced-teletherapy

- Teletherapy – radiation delivered by a machine
- Cobalt (rarely used in the modern era)
  - Radioactive material (activated in a cyclotron) and placed in the head of a machine
- Linear accelerator
  - Electrons are accelerated and made very energetic
    - Can be used directly
  - Can be directed at a metal target to produces high energy photons (x-rays)

Brachytherapy-basics

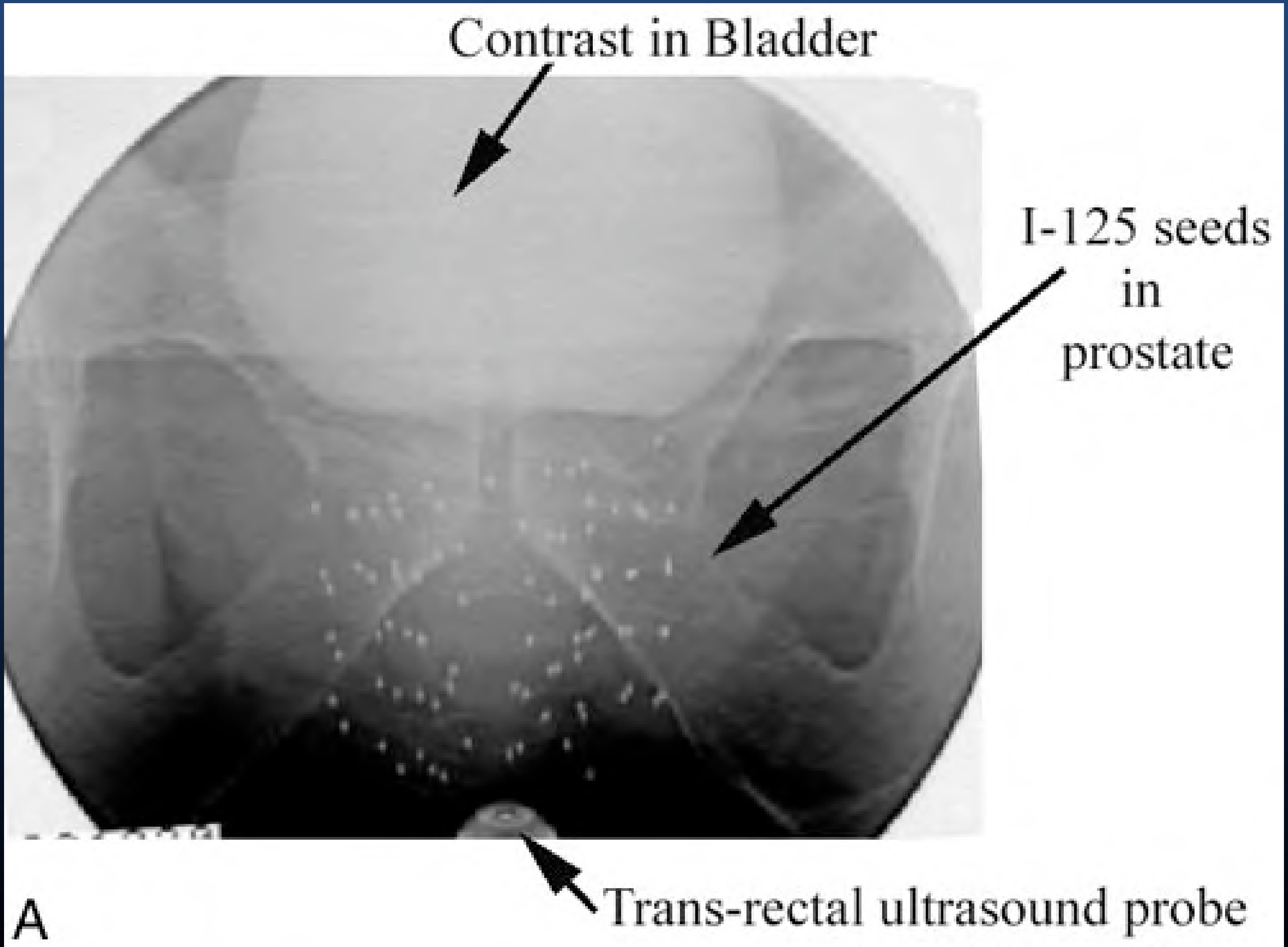
- The placement of radioactive sources into or next to the tumor
- Depends on the "inverse square" rule of radiation
- The intensity of the radiation depends on the square of the distance from the source (2x the distance, decrease the intensity by 4x)

Brachytherapy-concepts

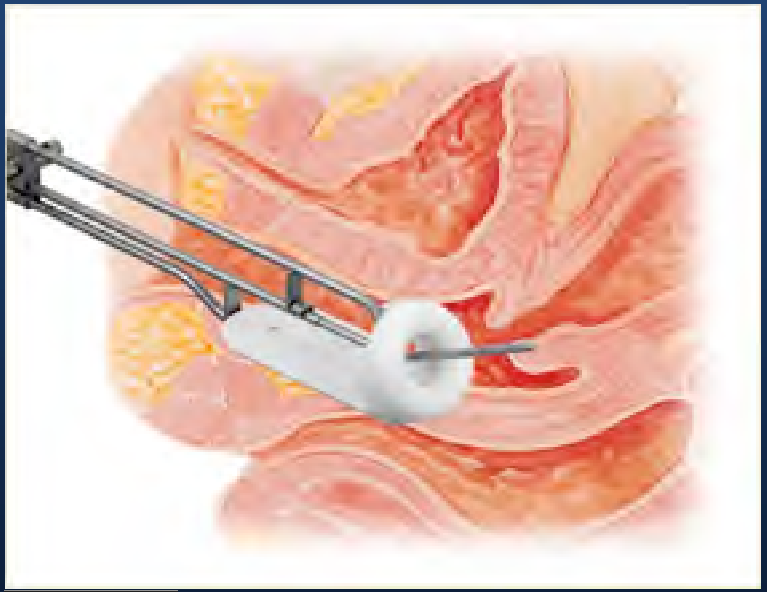
- Advantage: can permit much more radiation to be given to the tumor compared to the normal tissue
- Disadvantage: harder to make the dose uniform to the tumor
- Placement can be permanent or temporary (minutes to days)

Results of Treatment

Prostate brachytherapy



High dose rate brachy (HDR) Example – Ring and Tandem



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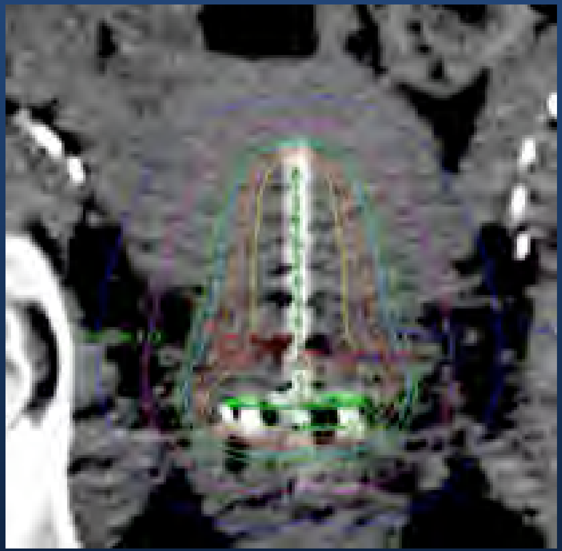

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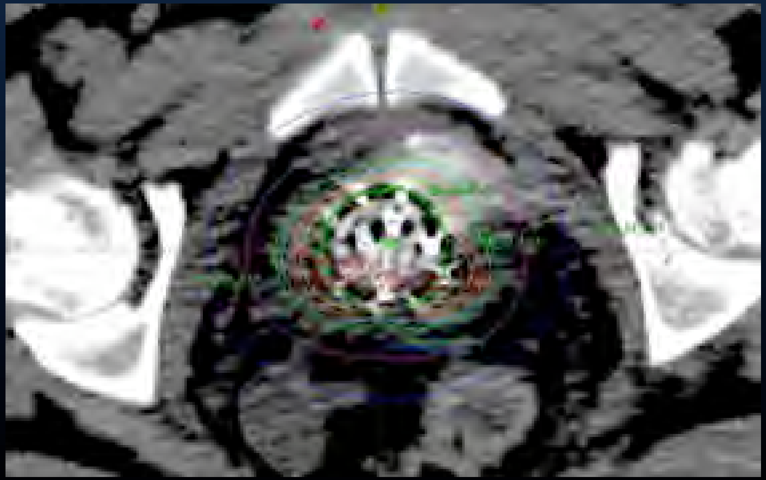

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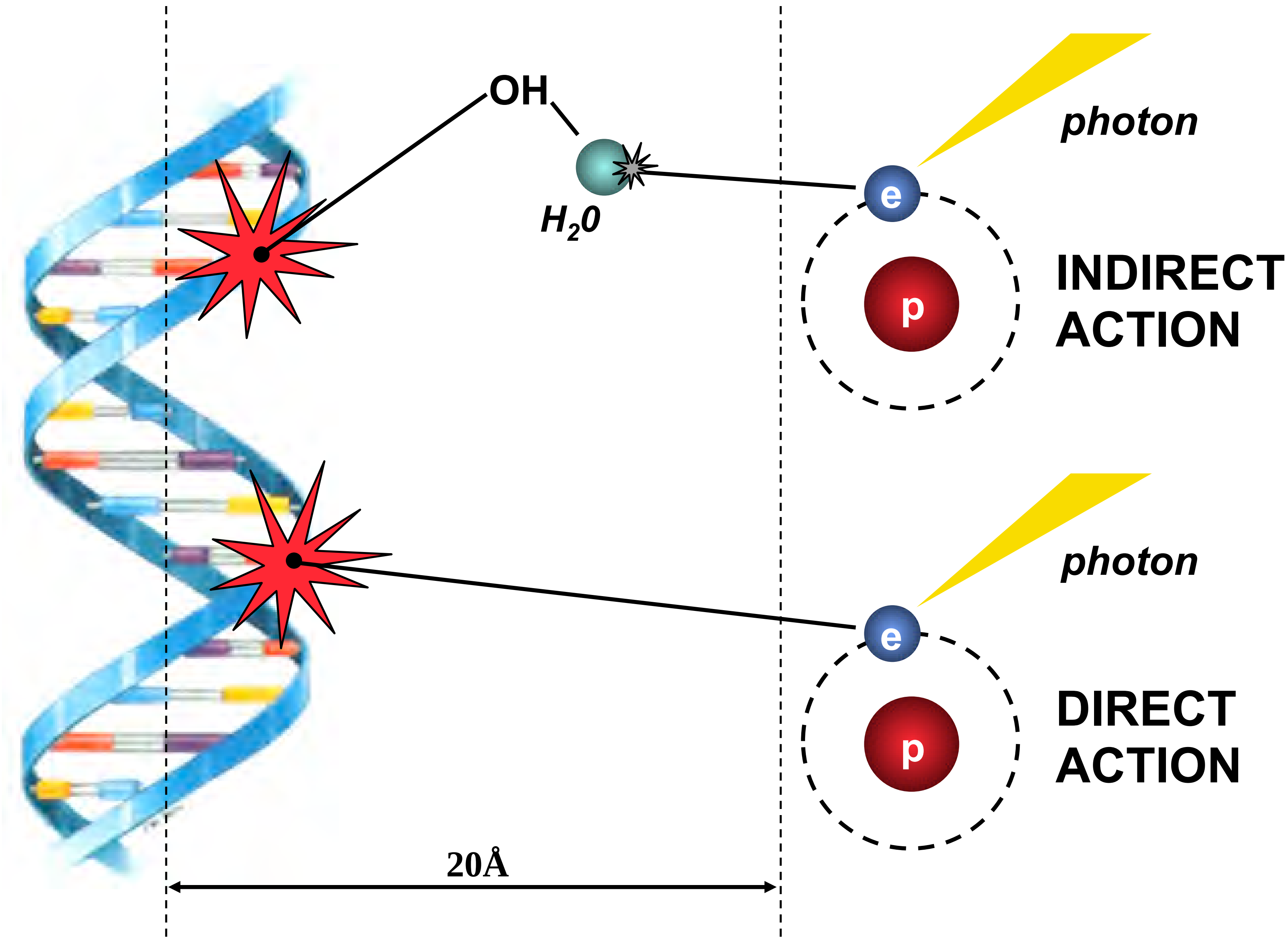
Used to treat cervical and endometrical cancer

Interaction of radiation with cells

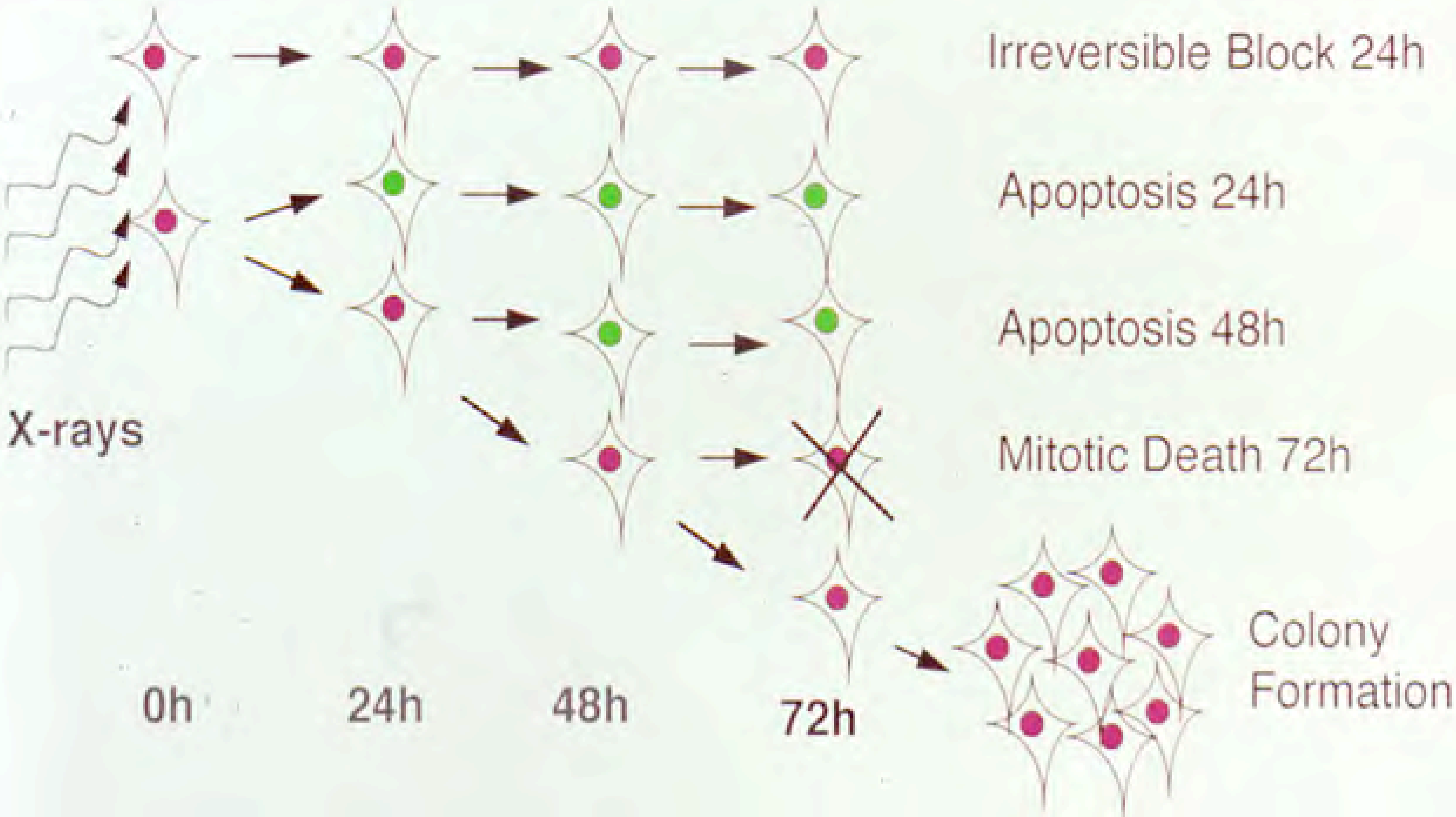
- Electrons can interact directly (direct effect)
- Electrons can produce free radicals (particularly OH•, O•, and H_20_2) which then interact

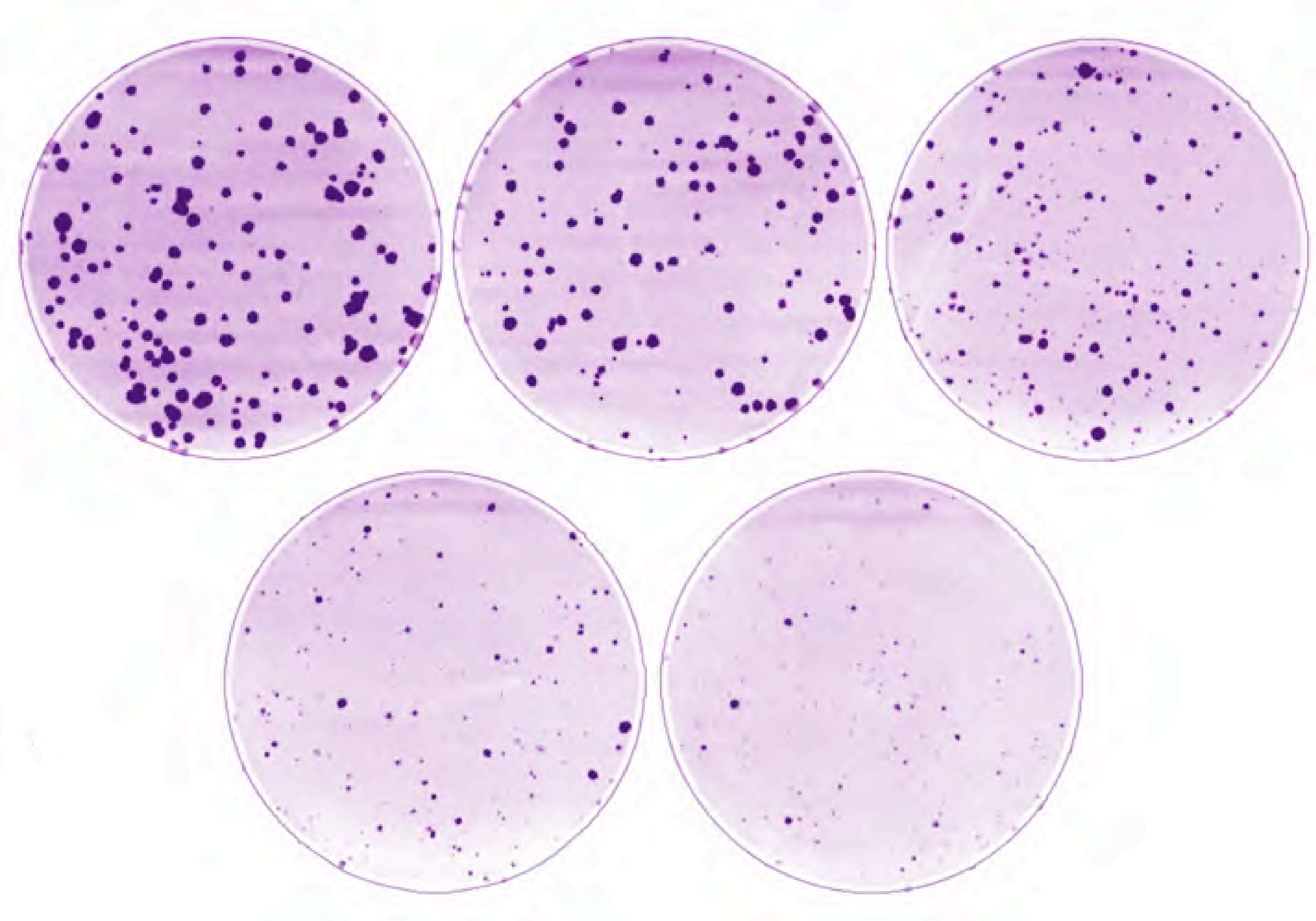

OH
H_2O
photon
e
p
INDIRECT ACTION
photon
e
p
DIRECT ACTION
20Å

Effects at the cellular level

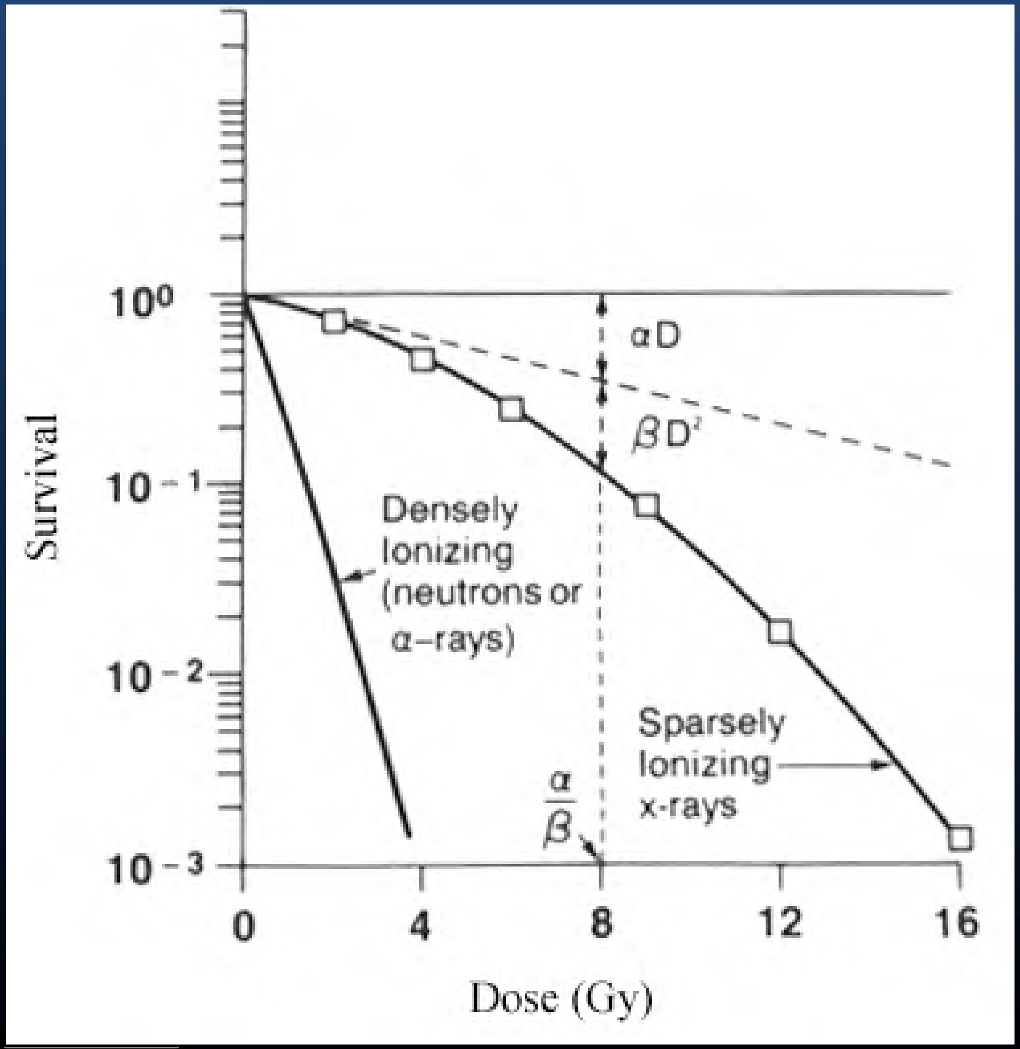
- Free radicals exist for microseconds to milliseconds after the radiation
- Biological effects occur over hours, days, and years
- Molecular and cellular targets of radiation
  - DNA
  - Cell membrane

Cellular Response
Genotoxic Stress





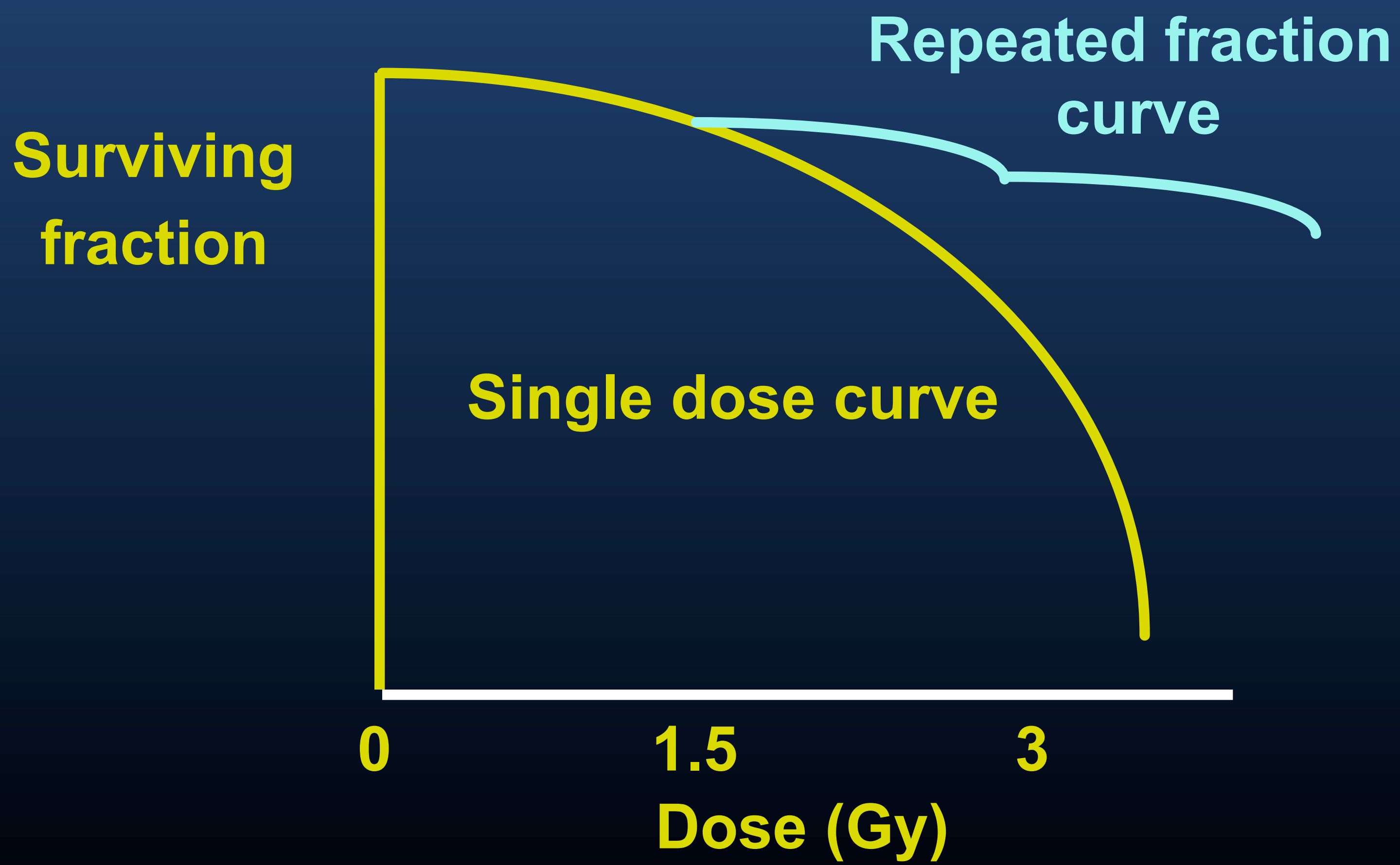
Cell survival curve



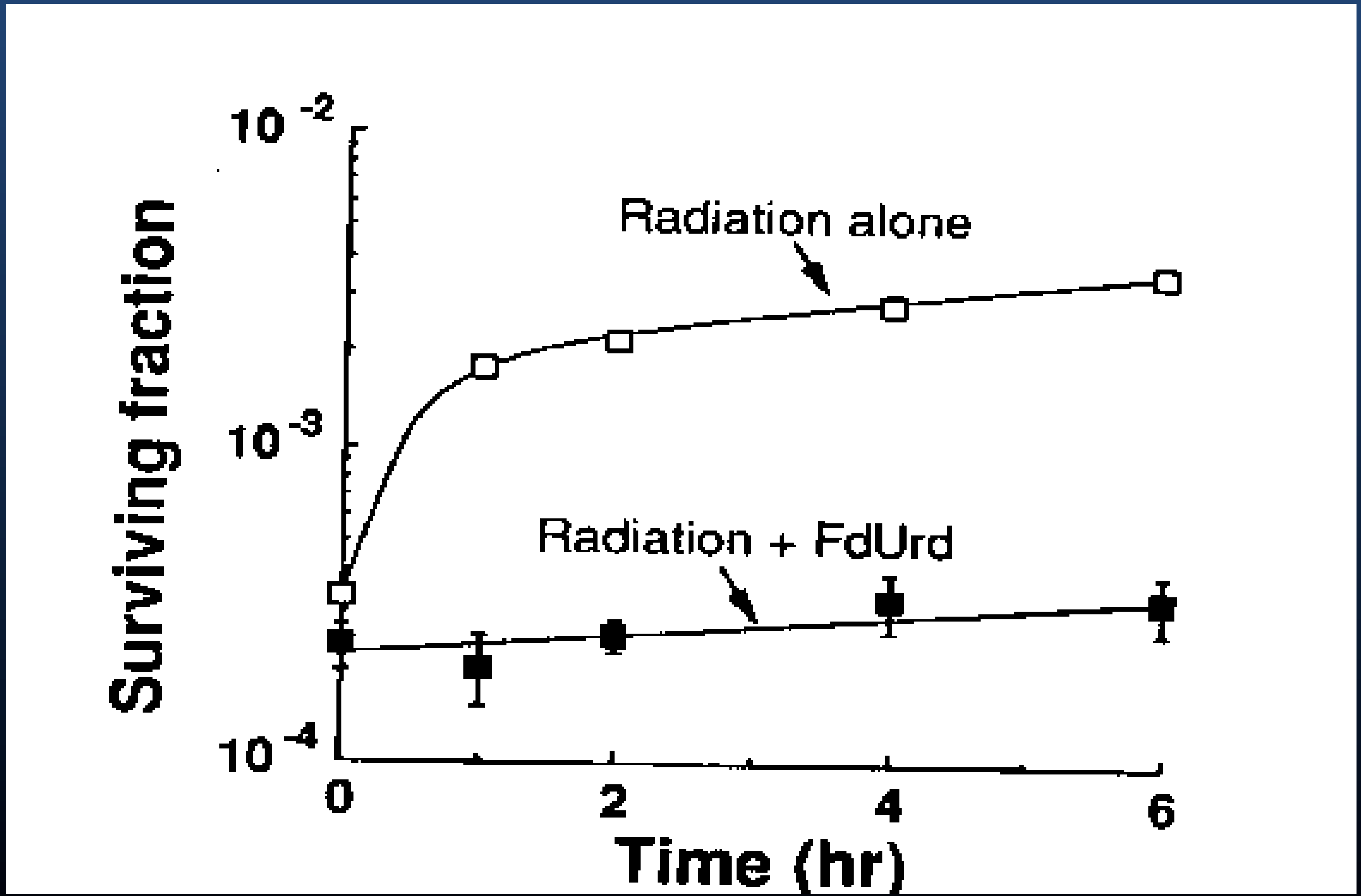
Effects of radiation on DNA

- Single and double strand breaks
- Single strand breaks are well repaired, because there is an intact (correct) template in the other strand
- Repair occurs during next 6 hours

Sublethal damage repair



Fluorodeoxyuridine inhibits SLDR



Results of DNA damage

- The double strand break appears to be the lethal lesion- cell must "guess" what to put back in place
- One double strand break can kill a cell
- Can lead to mutations and second cancers (≈ 1/1000 patients)

Mechanisms of cell death after DNA damage-mitosis

- During mitosis, chromosomes become condensed , align, and move to the two daughter cells
- Cells with chromosomal damage cannot perform mitosis properly and die in the attempt
- This explains why it can take months to years for tumors to shrink

Effect of Irradiation ± BrdUrd on Chromosomes 1 and 4

Mechanisms of cell death after DNA damage- Apoptosis

- Programmed cell death
- DNA damage can cause some cells to activate a death pathway
- Often happens during a phase of the cell cycle other than mitosis
- Mechanism for cell death of lymphocytes (lymphomas) and spermatocytes (seminoma)

Apoptosis

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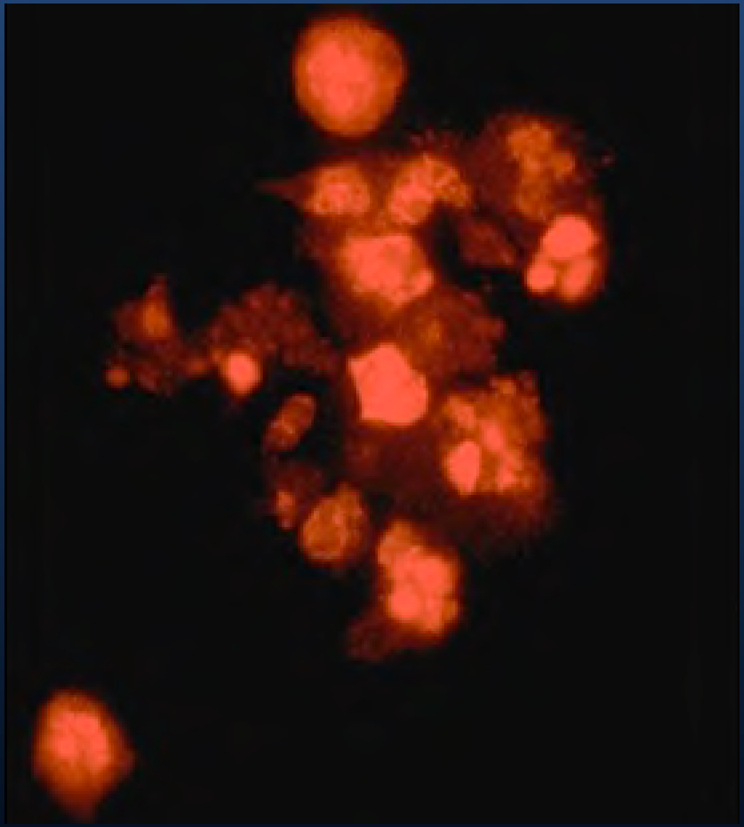
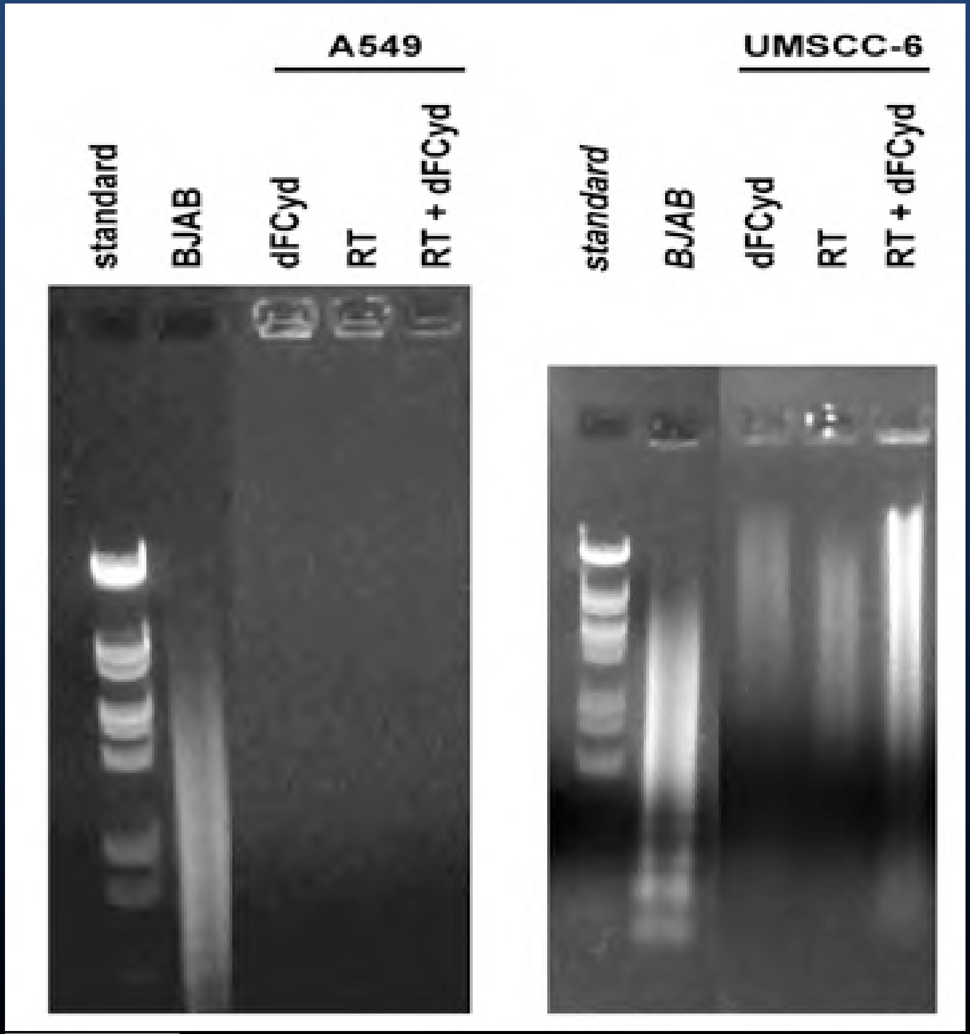
Control Cells



Apoptotic Cells

DNA fragmentation



Effects of radiation on the cell membrane

- The cell membrane is the origin of many "life" (growth factor receptor) and "death" (apoptotic) signals
- Radiation can activate or suppress the former and activate the latter

Effects of RT depend on biology

- Genetics
- Oxygen status
  - Hypoxic cells (in tumors) are resistant
- Cell cycle
  - S phase resistant, M is sensitive
- Chemical modifiers (protectors/sensitizers)

Effect of radiation depends on physics

- Kind of radiation (High LET vs Low LET)
- How fast radiation is given (1 Gy/min causes more effects than 1 Gy/hr)
- How many fractions
  - 30 Gy in 3 Gy fractions causes more effects than 30 Gy in 2 Gy fractions
- The total time
  - 60 Gy in 2 Gy fractions given 6 times a week causes more effects than 60 Gy in 2 Gy fractions given 5 times a week
- How much tissue is irradiated (normal tissue)

Effects at the tumor/organ level

- The 4 R's
- Fractionation
  - Hyperfractionation
  - Accelerated fractionation
- Radiation modifying drugs
- Parallel and serial organs
- Therapeutic index
- Why does radiation cure cancers?

4 “R’s” of Radiation Biology

- Repopulation - tumor cells can grow back during a course of radiation
  - Accelerated repopulation
- Reoxygenation- tumor O2 increases as cells die
- Redistribution - cell cycle distribution changes
- Repair - cells can repair damage between fractions

Hyperfractionation

- Standard: 1.8 to 2 Gy per day
- Hyperfractionation: two treatments per day
  - Each treatment is with less dose than standard (1.1-1.2 Gy)
  - Overall treatment time about the same as standard
- Rapidly proliferating cancers (head and neck)
  - Normal cells repair damage of many fractions better than tumor
- Clinical result: for same anti-tumor effect, less late toxicity

Accelerated fractionation

- Standard: 1.8 to 2 Gy per day
- Accelerated fractionation
  - Giving 2 treatments a day (same as hyperfractionation)
  - Each treatment is about the same dose as standard
    - This means more dose per day than standard
  - Overall treatment time is shorter than standard
- Goal: prevent tumor from growing during treatment (accelerated repopulation)

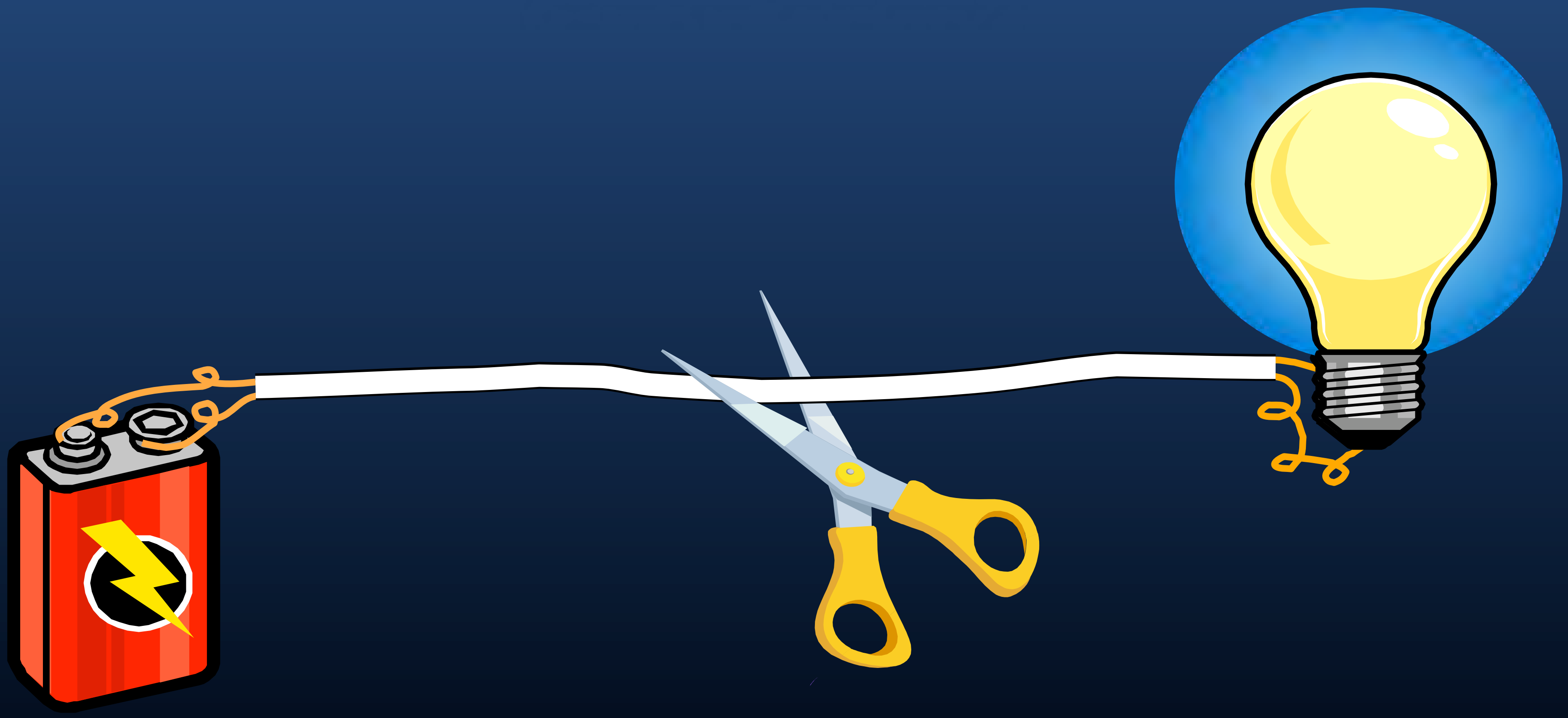
Chemical modifiers

- **Radiation sensitizers**
  - Hypoxic cell sensitizers
  - Chemotherapeutic agents
  - Molecularly targeted therapies
- Radiation protectors
  - Scavenge free radicals
  - Prevent cytokine induced damage (anti-inflammatory)

Normal Tissues: Parallel and Serial Organs

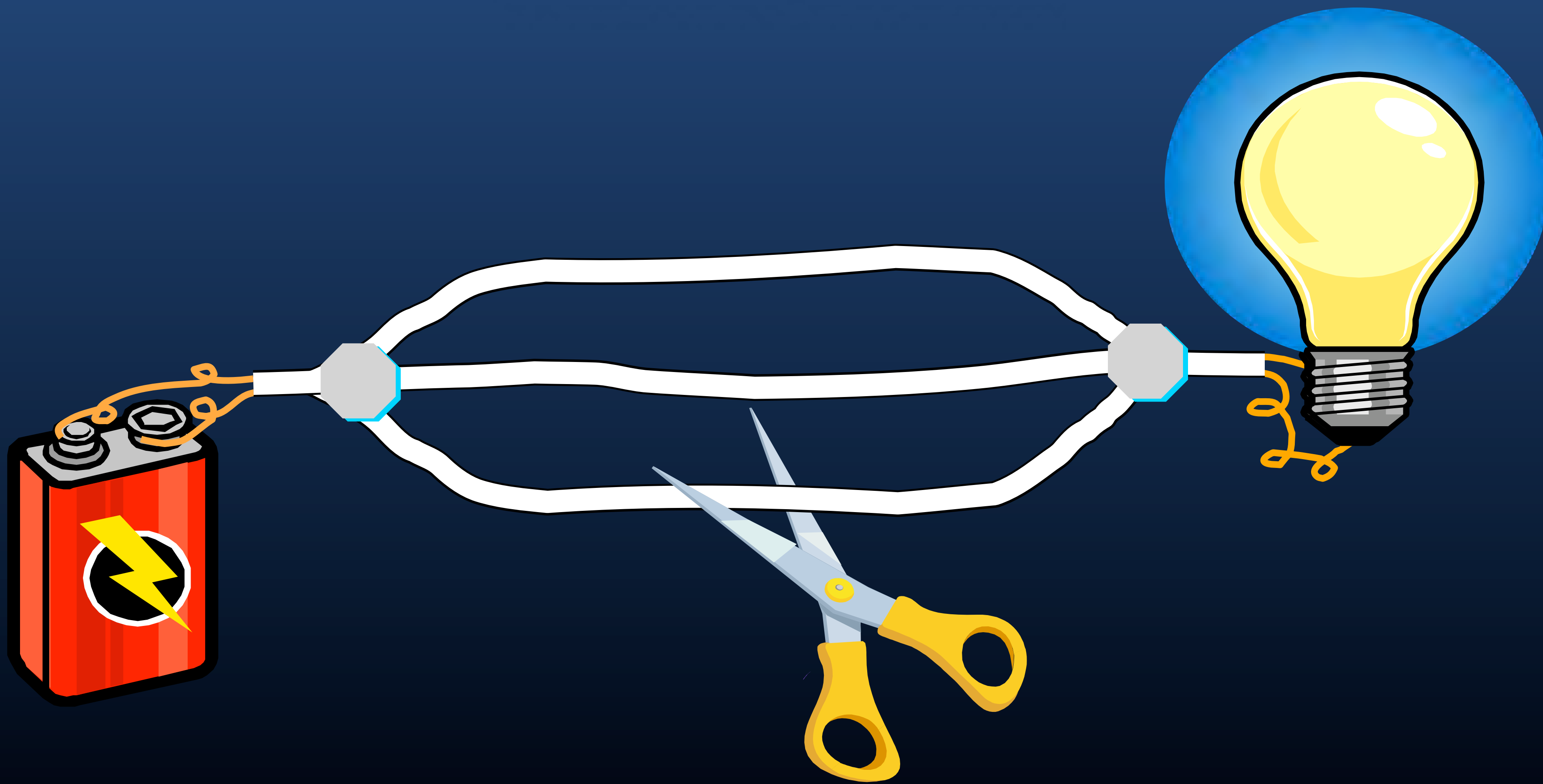
- **Parallel organ**
  - Damage to small fraction has no clinical toxicity
  - Clinical toxicity occurs when pass a threshold for fraction of the organ injured
  - Examples: lung and liver
- Serial organ
  - Damage to a small fraction produces toxicity
  - Examples: esophagus and spinal cord

Serial Circuit

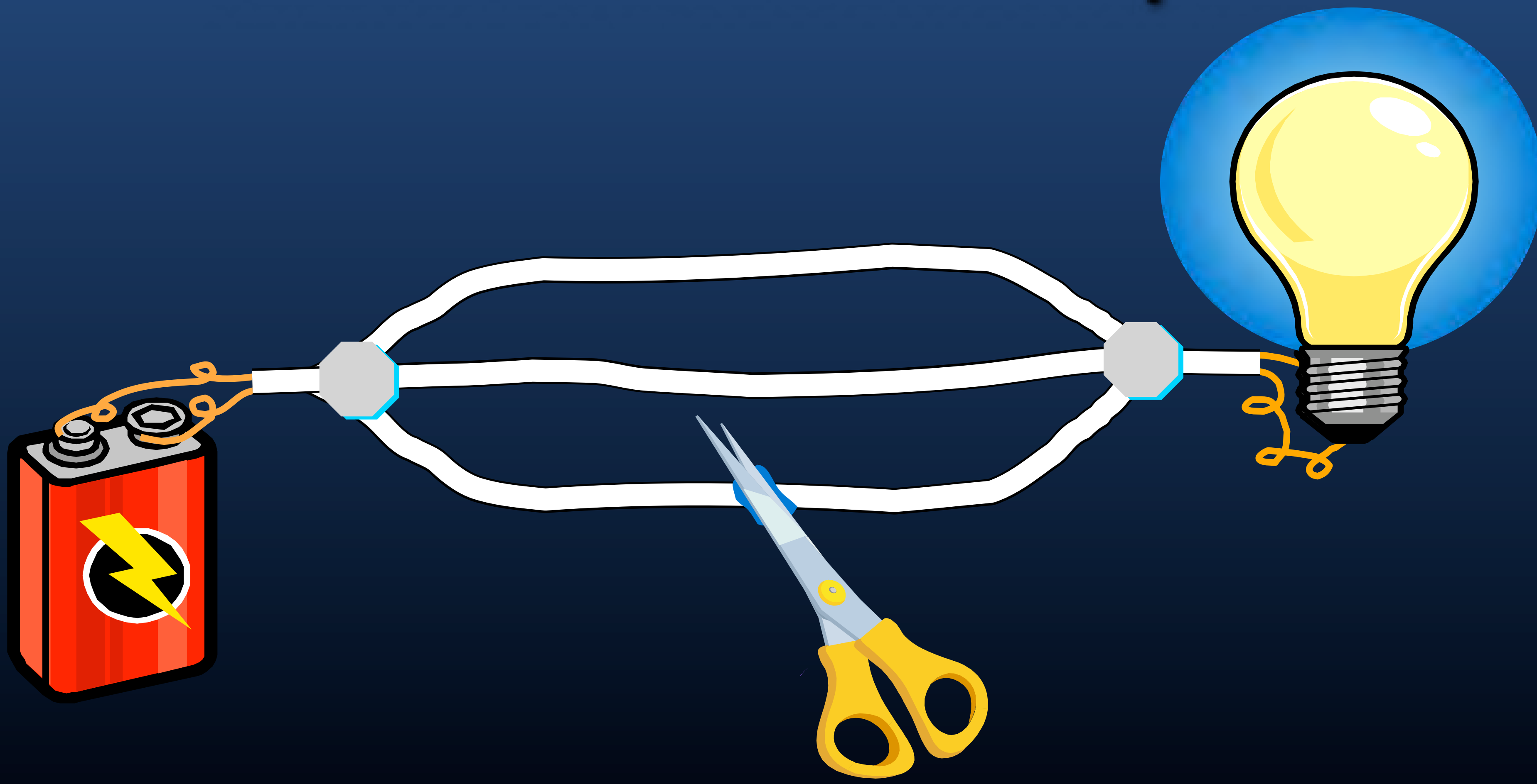


Serial Circuit: *Interruption*

Parallel Circuit



Parallel Circuit: *No Interruption*



Effect of radiation on normal organs

- Organs vary in radiation tolerance
  - Kidney - 20 Gy in daily 2 Gy fractions
  - Liver - 30 Gy
  - Spinal cord - 46 Gy
- Parenchyma of the organ
- Vasculature leading to the organ

Therapeutic index

- Definition: selectivity of radiation for killing the cancer compared to the normal cells
- The therapeutic index for a single radiation treatment is small
- How can we increase the therapeutic index?
  - Multiple fractions ($1.2^{30} = 36$)
  - Drugs that selectively sensitize tumor cells
  - Drugs that selectively protect normal cells

Fractionation versus single fraction

- Small tumors not abutting critical structures can be treated with a single fraction
  - Usually 10-20 Gy
  - Concept is ablation
    - Metastases to brain, lung, and liver
- Larger tumors or tumors that contain normal tissues
  - Concept is therapeutic index: treatment causes at least slightly more tumor kill than normal tissue damage
  - By giving 20-40 treatments of 1.8 to 2 Gy each, this effect is multiplied

Why does radiation fail?

- Tumor size
  - Can't give enough radiation to kill every tumor stem cell without intolerable damage to normal tissue [fractionation; tumor sensitization; normal tissue protection]
  - Genetic radiation resistance [tumor sensitization]
- Tumor physiology
  - Hypoxic cells are relatively resistant to radiation, and may reside in the center of tumors [fractionation; tumor sensitization]
  - Rapidity of tumor cell growth [accelerated fractionation; tumor sensitization]

Why does radiation cure cancers?

- Normal cells migrate back into irradiated field
- Cancer cells may not repair DNA damage correctly
  - Cancer cells often have disordered cell cycle checkpoints
  - May attempt to replicate DNA before it is properly repaired
- Greater dependence of tumor on new vasculature, which may be more sensitive to radiation
- Probably <u>not</u> due to initial damage from radiation
  - For same dose of radiation, cancer cells and normal cells have same number of DNA double strand breaks

Summary

- Radiation affects tissues through the generation of free radicals
- Cell death is caused chiefly by DNA double strand breaks
- The effects of radiation can be modified by
  - Physical factors (fraction size, total time, total dose, dose rate, and radiation type)
  - Volume of organ irradiated
  - Tumor genetics
  - Tumor physiology (the 4 R' s)
  - Chemical modifiers

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