The Basic Biological Effects of Ionizing Radiation on the Cell and its Genetic Material

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OBJECTIVES

The attendee will understand:

- **That the cells in tissues are the primary element for radiation exposure leading to physiological harm**

- **That damage to the DNA in the cells can lead to cell death and physiological harm, mutation, and/or cancer**

- **That the initial events after the physical deposition of energy is the generation of free radicals**

- **That damage to the DNA is either direct, or through the indirect action of free radicals**

OBJECTIVES (Cont.)

- That cell killing, mutation, or cancer are all dose dependent, whether the source of radiation is internal or external

- That cell killing has a measurable threshold, and and the extent of cell killing increases with increasing dose (deterministic effect)

- That it is the risk of inherited mutation or cancer that increases with dose, and these all or none events will occur to some (but not everyone) in the exposed population as the dose to the population increases

Overview of Radiobiology

Time Frame

Physical Interactions
10^{-19} – 10^{-12} sec

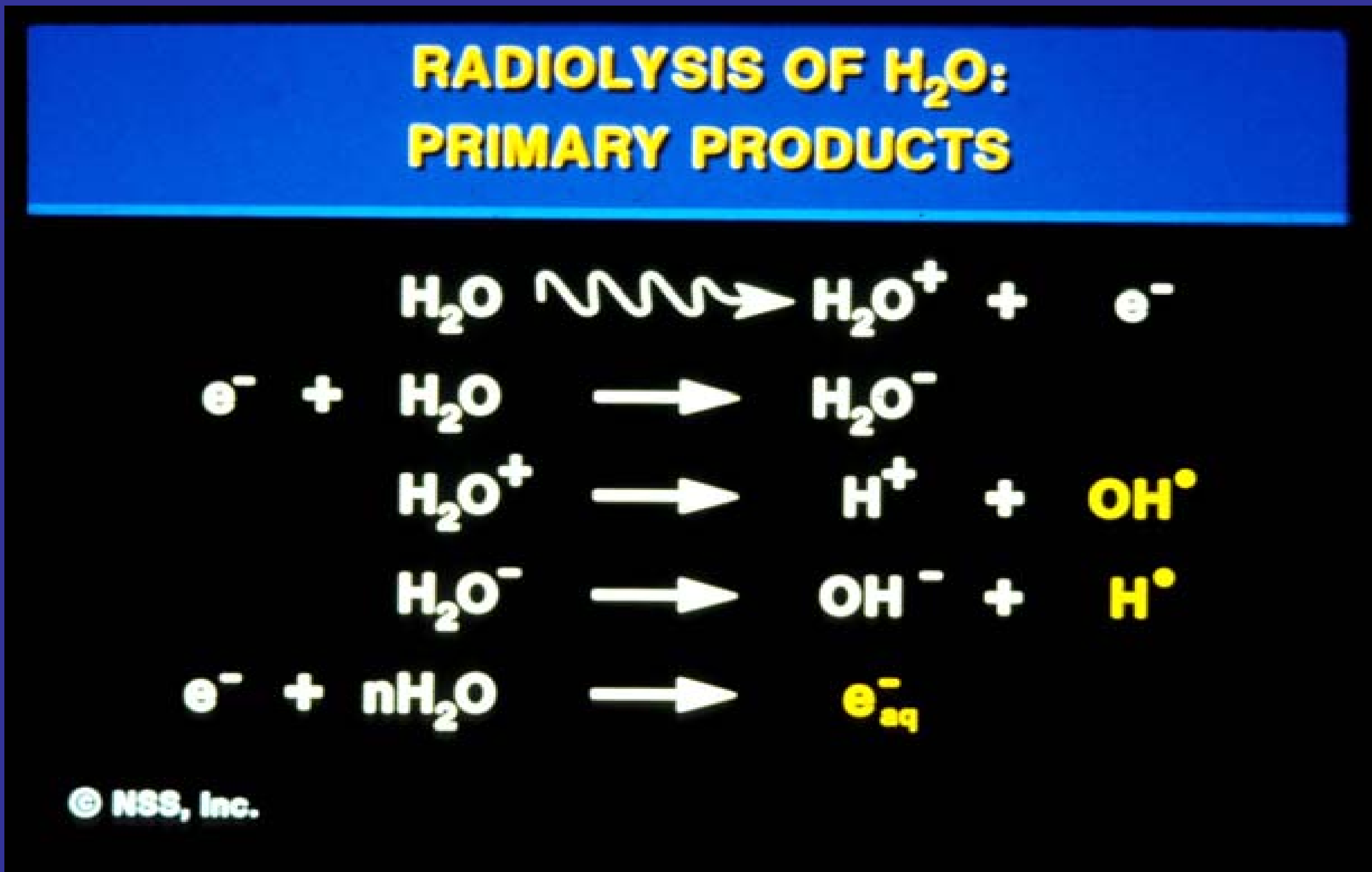
↓

Chemical Interactions
Free radical lifetimes and Interactions
Out to 10^{-5} sec

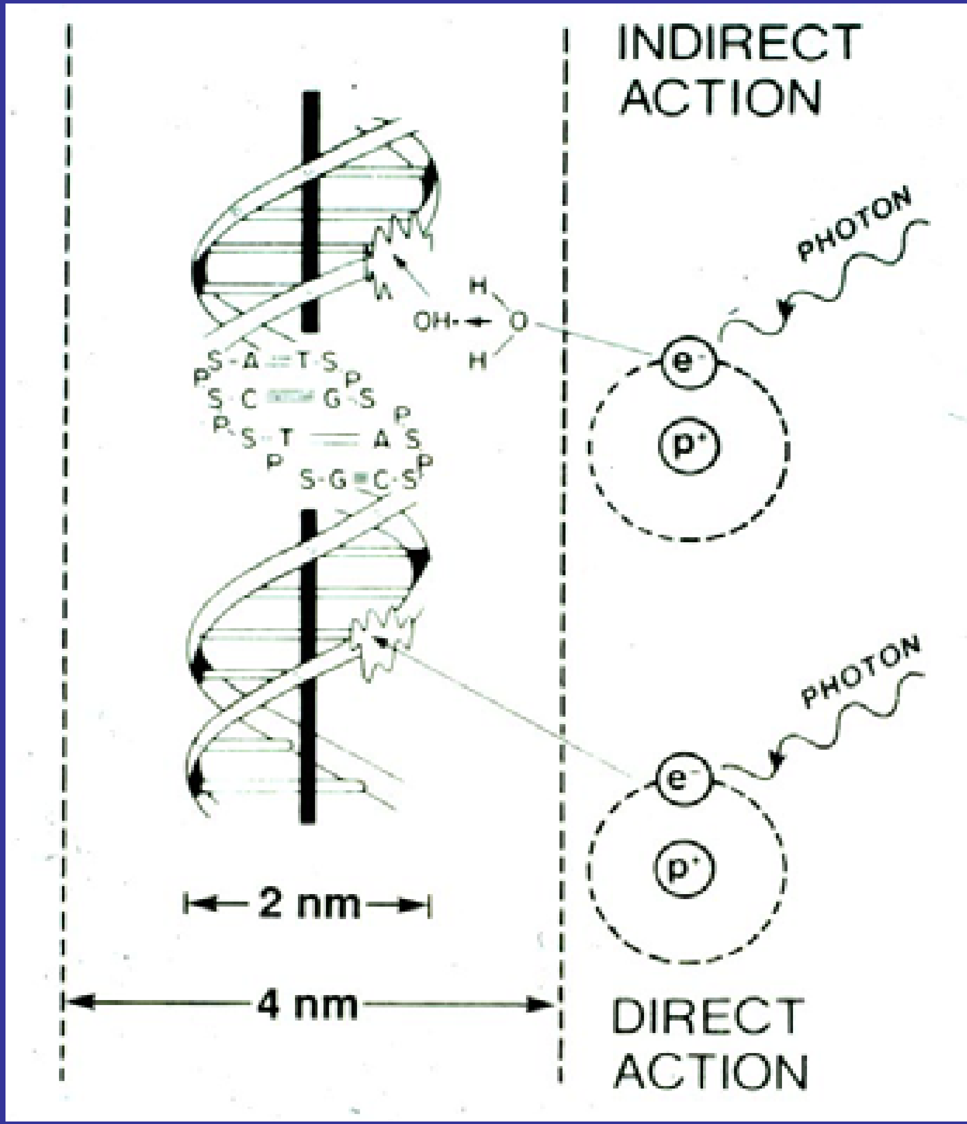
↓

Observable Biological Responses
Secs, mins, hrs, days, weeks, months, years
[Depending on the Biological Endpoint]

RADIATION INDUCED FREE RADICALS IN WATER



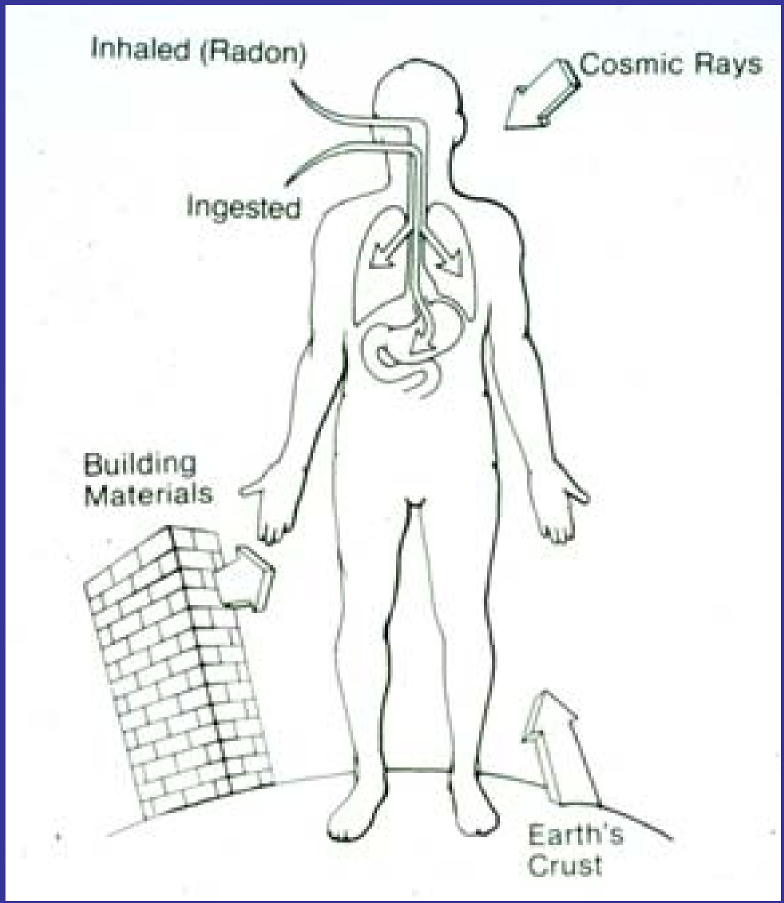
DIRECT VS INDIRECT EFFECT



Levels of Biological Organization and Background Radiation Sources

Man/Woman

- **Body Parts**
- **Organs-Structural and Functional**
- **Comprised of Tissue-again structural (e.g. bone and cartilage) and/or functional**



THE RELATIVE RADIOSENSITIVITY OF THE CELLS IN THE BODY

- Fully differentiated, functional and non-dividing cells (e.g, nerve cells, muscle cells) are <u>RADIORESISTANT</u>

- Partially differentiated cells that can be called upon to divide again (e.g., liver cells, glandular cells) are <u>somewhat less radioresistant</u>

- Cells which can divide but lend support to the other cells in a tissue (e.g. endothelial cells lining the blood vessels, fibroblasts of the connective tissue) are <u>intermediate in radiosensitivity</u>

RELATIVE CELL RADIOSENSTIVITY

•Dividing cells which start to differentiate (e.g., myelocytes, spermatocytes) are <u>fairly radiosensitive</u>

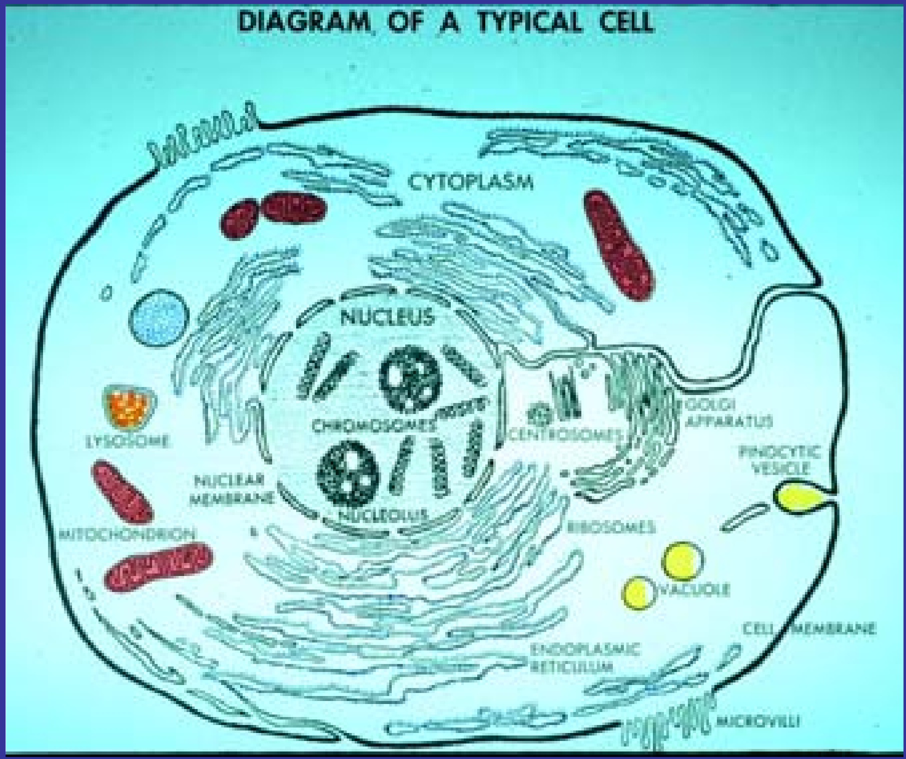
•Continuously dividing stem cells (such as found in the bone marrow, the intestine, the skin, and the testes) are <u>very radiosensitive</u>. If not killed, these stem cells can rapidly allow the tissue and organ to recover.

•Two cell types not in the last category, but which are very radiosensitive, are the oocyte and the small lymphocyte (whose death will have immediate negative impact on the immune system)

The Mammalian (Human or Animal) Cell

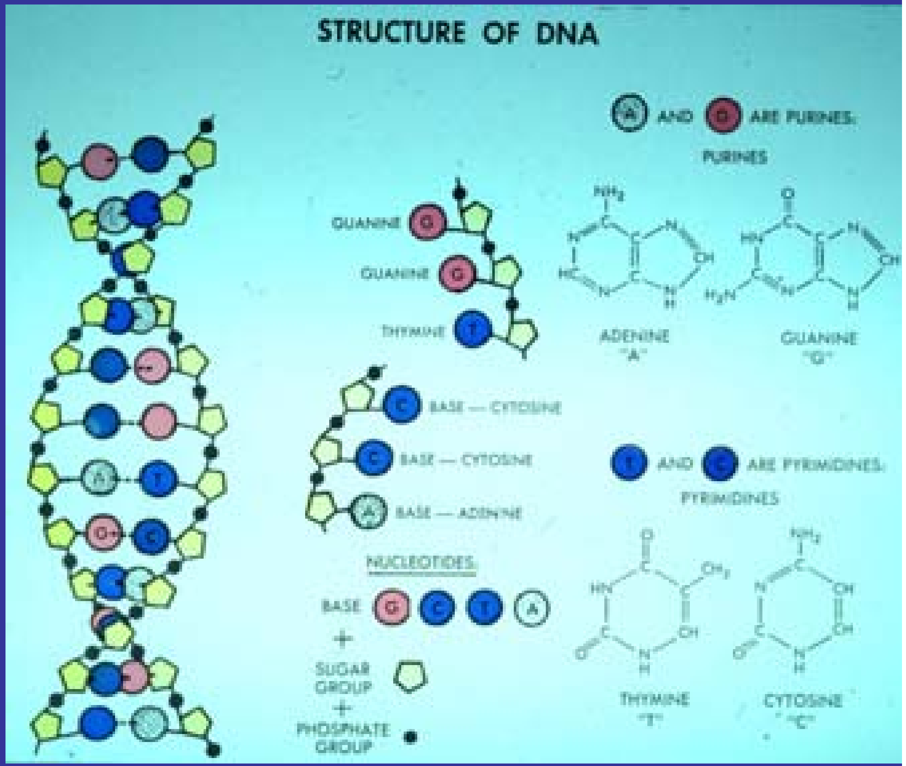
<u>Components</u>

- **<u>NUCLEUS</u>**
  - **Nucleoplasm**
  - **Nucleolus**
  - **DNA (the genetic material)**
  - **Nuclear membrane**
- **<u>CYTOPLASM</u>**
  - **Mitochondria**
  - **Golgi apparatus**
  - **Endoplasmic reticulum**
  - **Vacuoles (e.g., lysosomes)**
  - **Biomolecules much smaller than DNA (e.g. RNA, protein, lipids,,etc.)**
  - **Cytoplasmic membrane**



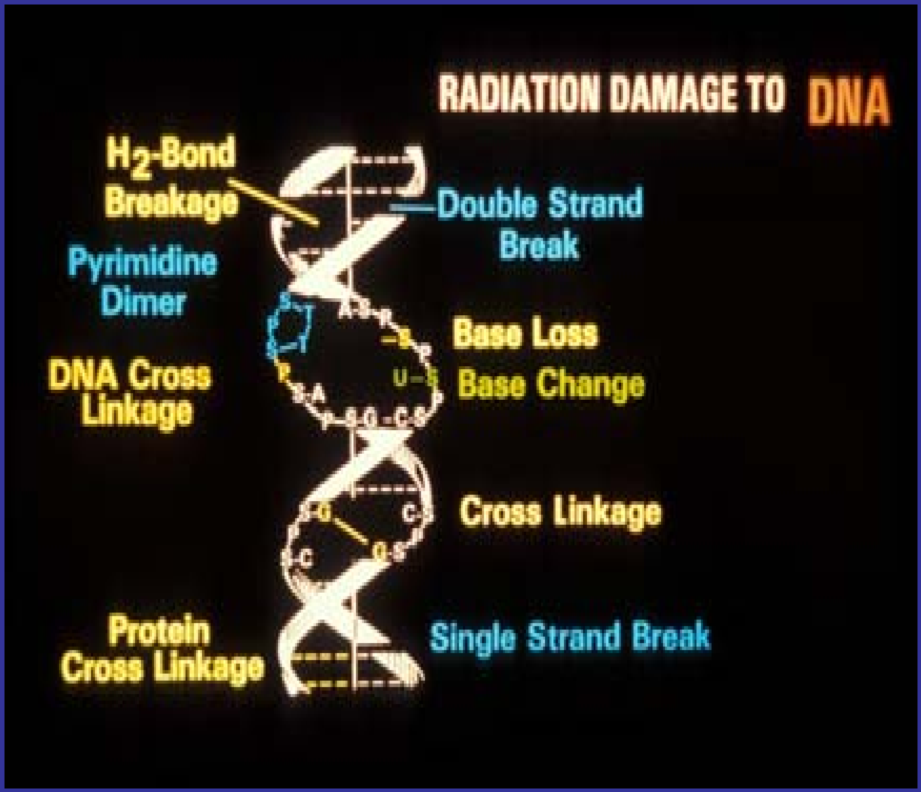
With all of these cellular components present, the main and most important molecule in the cell, with respect to ionizing radiation damage through either a direct interaction ("hit") or the indirect effect of free radical generation, are the DNA MOLECULES in the nucleus

- The DNA is a very large molecule, with a backbone of two intertwined single strands of DNA
- Each strand is made up of repeating sugar molecules and phosphate groups
- Extending in the center of the strands are the four bases, which by their sequence, carry the genetic information of the cell



THE TYPES OF DAMAGE TO THE DNA INCLUDE:

- DNA Single Strand Breaks
- DNA Double Strand Breaks
- Sugar Damage
- Base Damage
- Local Denaturation (Separation of the 2 strands)
- DNA-DNA Cross-links
- DNA-Protein Cross-links



THESE DAMAGES CAN LEAD TO:

- Slowdown in the cell synthesizing copies of its DNA, so that there is a delay in one cell dividing into two cells
- Delays (to allow repair) as the cell progresses towards its next cell division (delay in cell cycle progression)
- Decrease in the overall rate of cell proliferation (increase in cell number) of a population of cells
- Death of the cell
- Mutation of the cell
- Changes in the cell which will make it cancer-like (called cell transformation)

DIFFERENT TYPES OF CELL DEATH

General Description

INTREPHASE DEATH: Death before the next cell division, or death of a cell that does not divide

REPRODUCTIVE DEATH: Death of the cell (and its daughter cells) after one or more cell divisions

Specific Description

NECROSIS: Death of a contiguous (touching) field of cells

Does not require energy; the contents of the cells leak into the surrounding tissue and blood supply

CELL LYSIS: The cell simply bursts open, releasing its contents

APOPTOSIS (or Programmed Cell Death): This type of death is under genetic control (specific genes must be present and active or inactive). It requires energy, and when the cells die, DNA fragments of specific sizes, and the contents of the cells, are encapsulated in membranes as small vesicles.

Sequence of Events in Radiobiology

Physical interactions

↓

Chemical interactions

↓

After the DNA is damaged, DNA Repair

[Error Prone or Error Free]

[Although other biochemical and biological responses can be occurring]

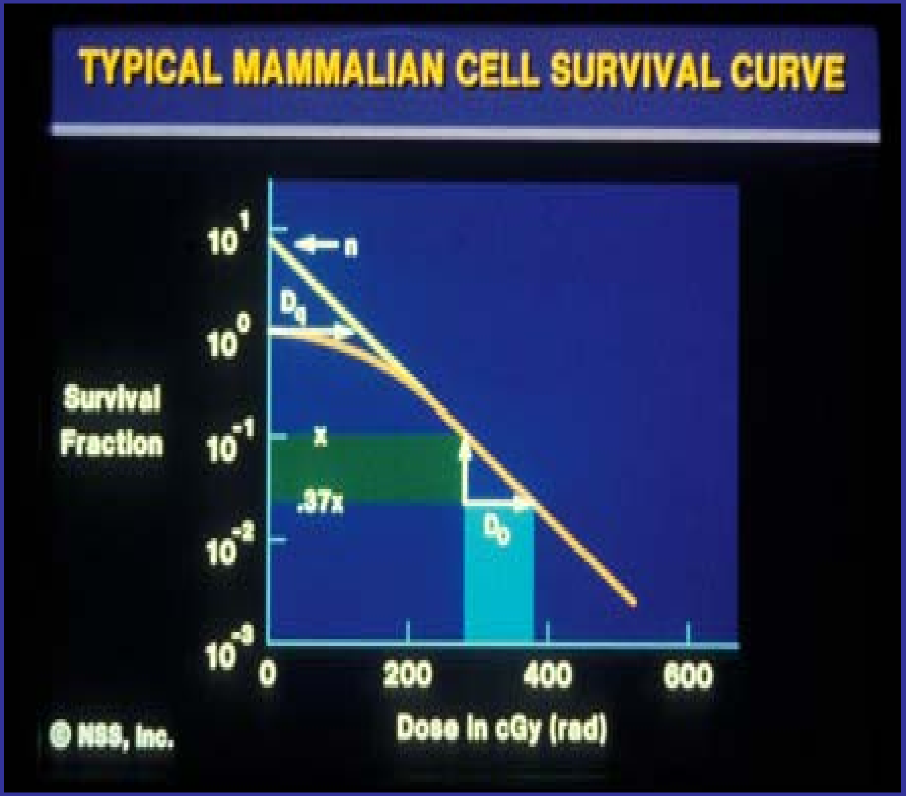
High Dose
Cell Killing, Tissue Damage, Organ Toxicity

Effects on the Embryo/ Fetus

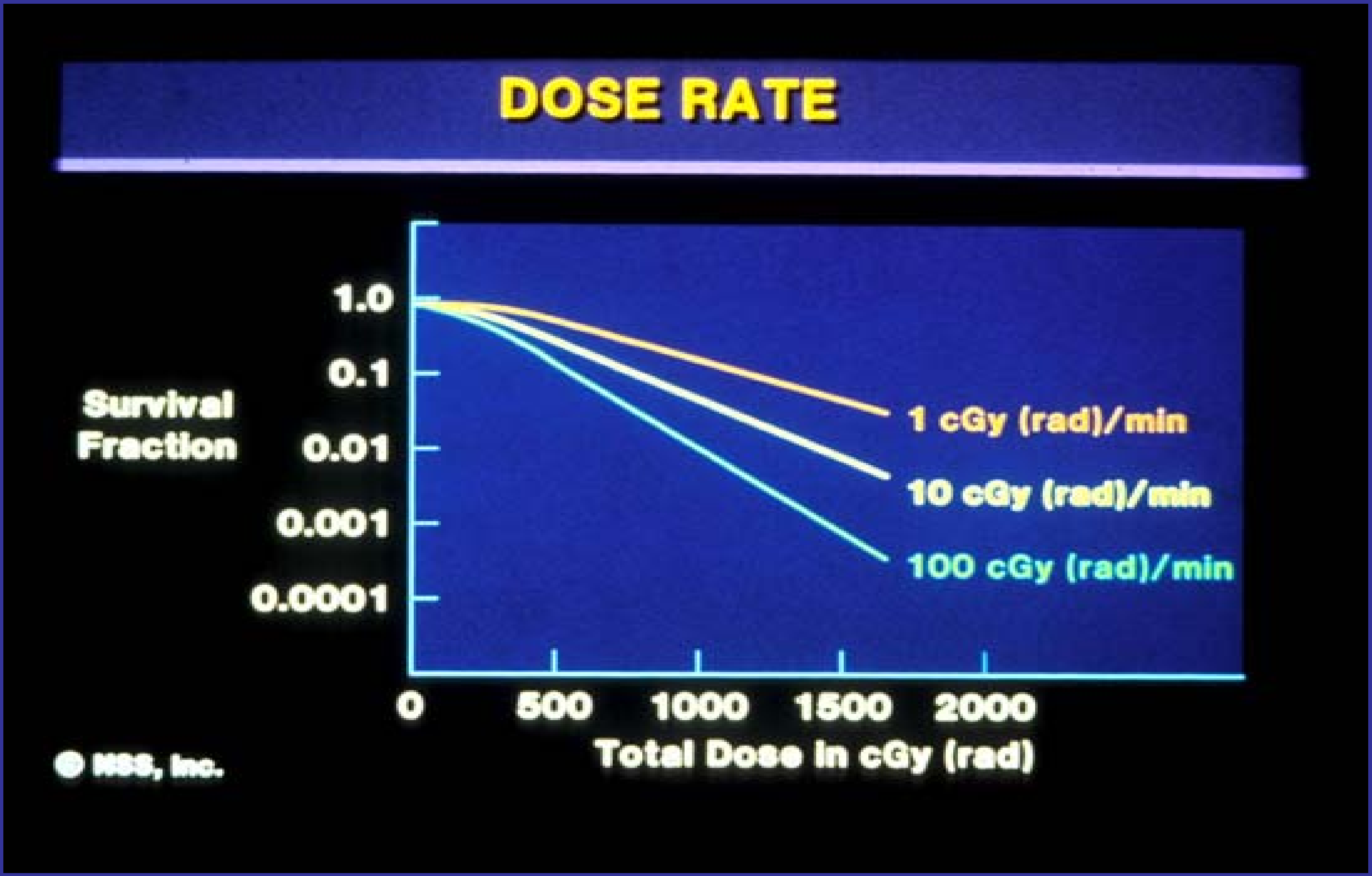
Low Dose
Inherited Mutations Cancer

MAMMALIAN CELL SURVIVAL CURVE: Survival vs. Dose

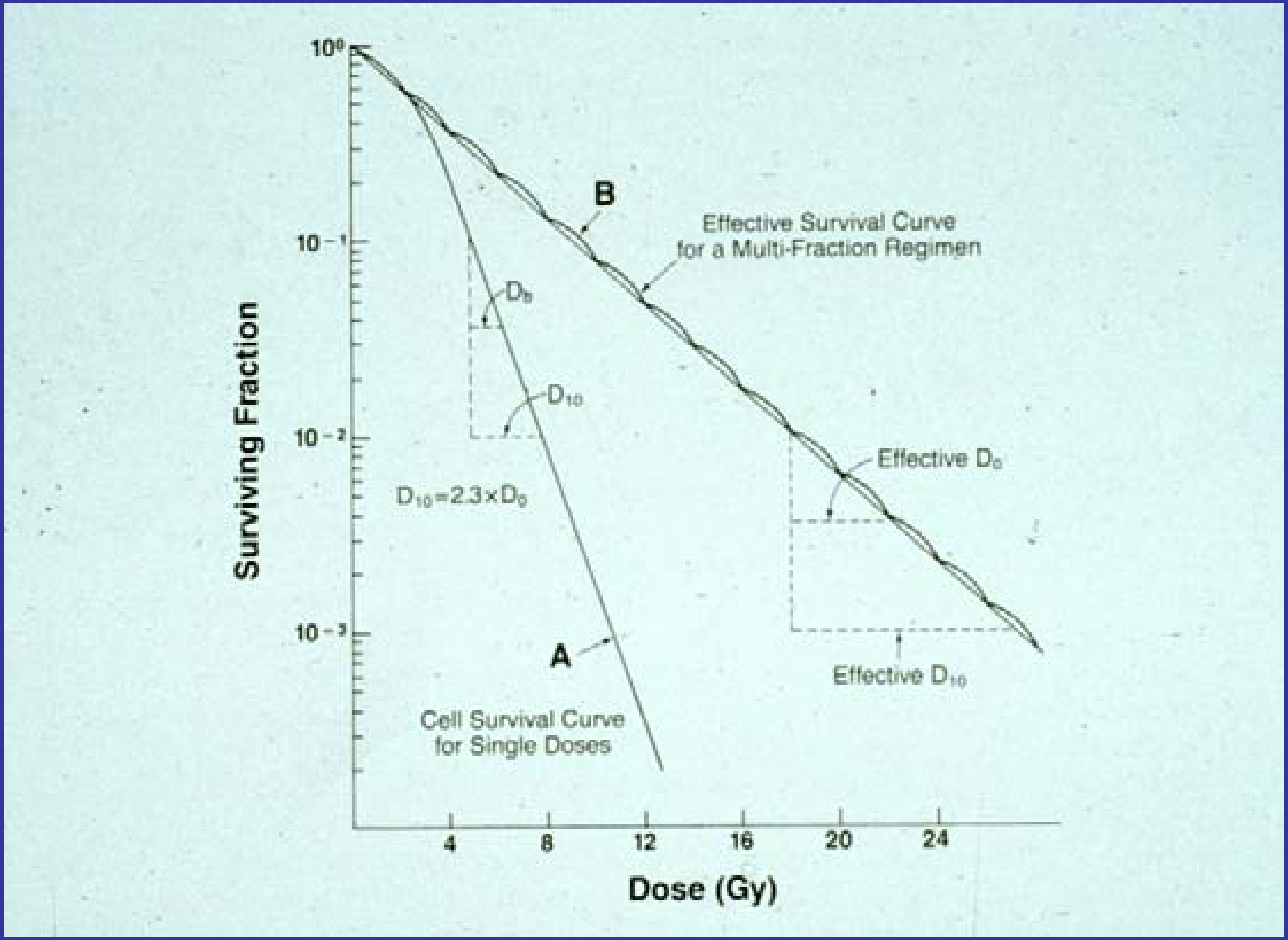
- Shoulder Region
  - Shows accumulation of SUB-LETHAL DAMAGE
  - The larger the shoulder region, the more dose will initially be needed to kill the same proportion of cells
- Beyond the Shoulder Region
  - The Do Dose, or the inverse of the slope of the curve, indicates the relative radiosensitivity. The smaller the Do dose, the greater the radiosensitivity



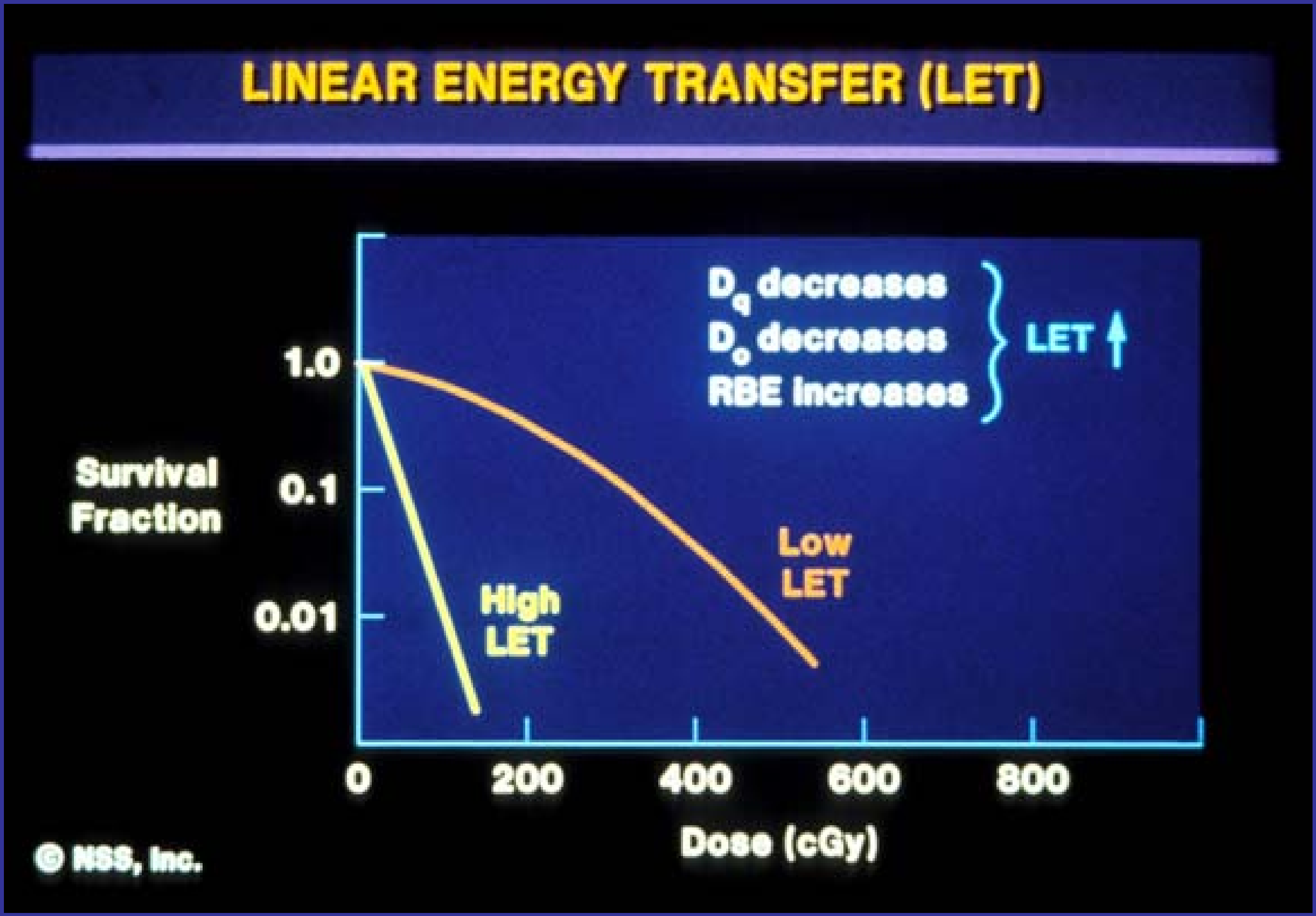
MAMMALIAN CELL SURVIVAL CURVE:
The Effect of Lowering the Dose Rate



MAMMALIAN CELL SURVIVAL CURVE: The Effect of Fractionating the Dose



MAMMALIAN CELL SURVIVAL CURVE:
The Effect of Radiations of Different Type and Linear Energy Transfer



CHROMOSOME ABERRATIONS
Types, Dose and Dose Rate Dependence

- Ionizing radiation exposure results in many different types of aberrations, with the type depending on where the cell is in relation to its next division (position in its cell cycle).
- The most commonly measured types of aberrations are ring and dicentric aberrations, which can be used for biological dosimetry after an acute whole-body exposure above 10 – 25 cGy (within a defined period after the exposure)
- There are many other types of aberrations that can occur, and if they (like the ring and dicentric aberrations) are obvious upon microscopic observation, the cell with those aberrations would likely have died.
- Certain kinds of chromosome aberrations, as well as genetic mutations of the DNA in the chromosomes, can be associated with causing cancer.

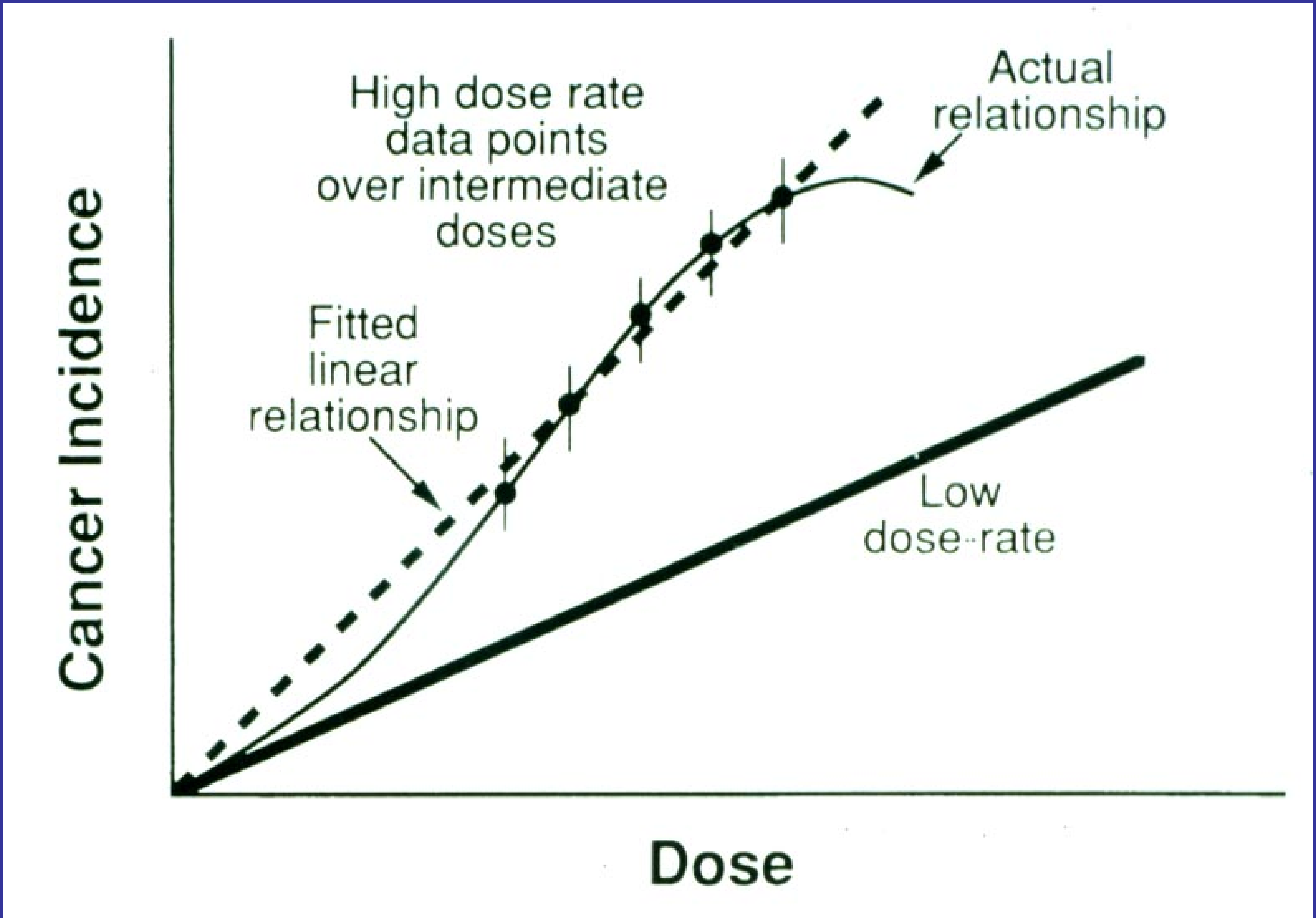
MUTATIONS
Types, Dose, and Dose Rate Dependence

- Inherited mutations resulting from exposure of the sperm or oocytes is a "stochastic" or probability phenomena (as is cancer)
- The outcome is either yes or no, and there is no threshold of dose below which ionizing radiation cannot induce mutations
- The types of inherited mutations due to exposure of a large number of persons to ionizing radiation will be the same as naturally occur in the population.
- At low doses and dose rates, the risk of mutation is very low-It is lower for low dose rates at all doses.
- The relationship may be either linear or linear-quadratic, depending on the type of radiation (e.g. gamma rays result in a linear quadratic increase-at low doses the relationship is linear with increasing dose, while at higher doses, the relationship is dependent on the dose-squared)

RADIATION AND CANCER

- Cancer resulting from exposure of cells to ionizing radiation is a “stochastic” or probability phenomena
- The outcome is either yes or no, and there is no threshold of dose below which ionizing radiation cannot induce cancer
- The types of cancers due to exposure of a large number of persons to ionizing radiation include both blood cancers and solid tumors
- The relationship may be either linear or linear-quadratic, depending on the type of cancer (e.g., for blood cancers, the incidence increases in a linear quadratic manner with dose, while for solid tumors, the increase is linear with dose, and fractionation does not decrease the risk

Increase in Cancer Incidence with Dose



SUMMARY

- Exposure of cells to high doses of ionizing radiation can be expected to be harmful to the cells, and therefore to the body, either immediately or at later times after the exposure. Some protection is afforded by low dose rates
- Exposure of cells to low doses, and especially at low dose rates, is unlikely to result in obvious cell harm. However, continued exposure at even low dose rates to large numbers of people will increase the risk of such stochastic hazardous events as cancer and inherited mutation.

IMAGE SOURCES

- American Cancer Society
  - Slide 13
  - Slide 14
- "Radiobiology for the Radiologist," E. Hall, Ed. 5th Edition
  - Slide 9
  - Slide 10
  - Slide 21
  - Slide 26
- NSS, Inc.
  - Slide 8
  - Slide 19
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