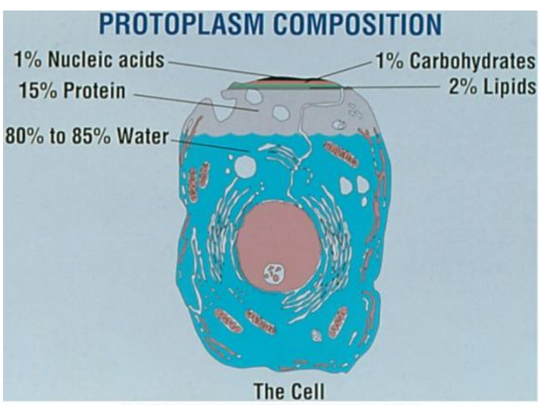
Radiation Biology

Physician Assistant Fluoroscopy

Bushong, Chapter 29

Cell Chemical Composition

- Protoplasm
- Cytoplasm
- Inorganic compounds
- Organic compounds



(From Radiobiology and radiation protection: Mosby's radiographic instructional series, *St Louis, 1999, Mosby.*)

Cell Membrane

- Semipermeable structure
- Plays primary role in cell's transport system
  - Passive transport
    - Substance moves through cell membrane by osmosis
  - Active transport
    - Cell must expend energy to pump substances into and out of it

Cytoplasm

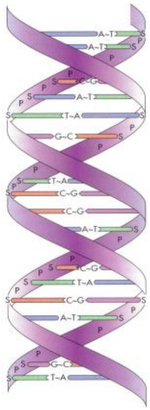
- Accepts unrefined materials for incorporation
- Breaks down materials to produce energy
- Packages substances for distribution
- Eliminates waste

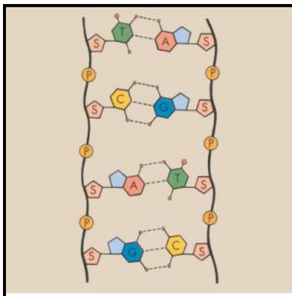
Nucleus

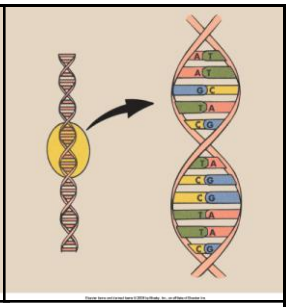
- Contained in the protoplasm
- Separated by a membrane (nuclear envelope)
- Contains DNA
- RNA is contained in the nucleolus
- Supervises and coordinates cytoplasmic activities

Organic Compounds

- Units of DNA:
  - Deoxyribose (sugar component)
  - Phosphate
- Adenine – Thymine
- Cytosine – Guanine
  - These form the "rungs" in DNA







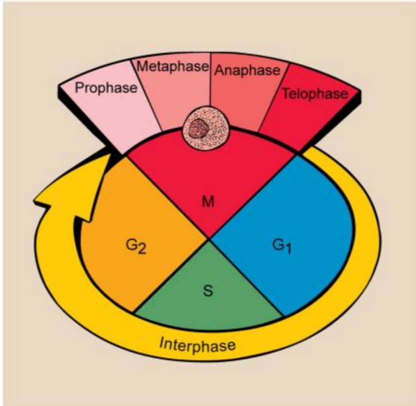
DNA is the radiation-sensitive target molecule

Chromosomes and Genes

Chromosomes

- Tiny rod-shaped bodies that under a microscope appear to be long threadlike structures that become visible <u>only in dividing cells</u>
- Composed of protein and DNA
- Normal human has 46 different chromosomes (23 pairs) in each somatic cell
- Reproductive cells (*germ cells*) have 23 chromosomes each

Mitosis



Interphase

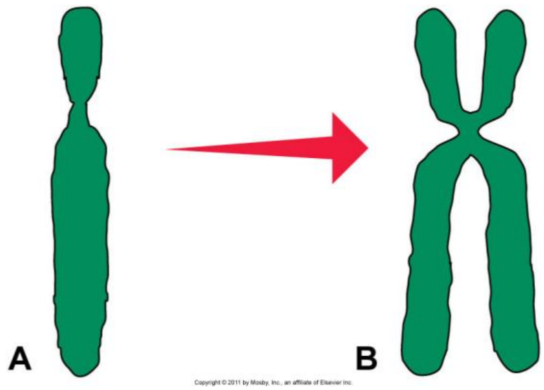
- Comprises about 90% of the cell cycle.
- Cellular growth:

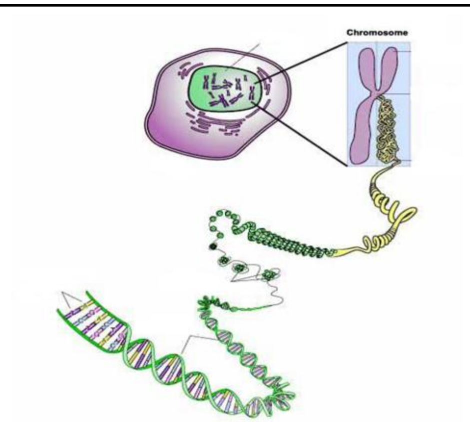
  Made up of three phases:

  1. G_1 phase
  2. S phase
  3. G_2 phase

Interphase (cont)

- G_1 (gap) phase:
  - protein synthesis and metabolic activities
- S phase:
  - DNA replication takes place
- G_2 (gap) phase:
  - Cellular growth and preparation for mitosis phase





Mitotic Phase

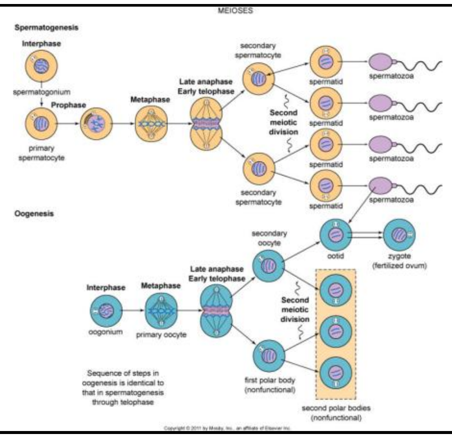
<u>Mitosis</u>:

- Final phase of the cell cycle
- Nuclear division of <u>genetic material</u>
- Four sub-phases
  - Prophase
  - Metaphase
  - Anaphase
  - Telophase

Meiosis

- Meiosis is similar to mitosis with some chromosomal differences
- There are two meiotic divisions compared a single mitotic division
- Because of the second meiotic division, the number of chromosomes are reduced in ½ (23 instead of 46)
- Another important event during meiosis is crossover, where sister chromatids swap genes to increase the genetic diversity of the species

http://www.youtube.com/watch?v=jdQeKjEsj0U&feature=related



Tissues and Organs

- Smallest unit
  - The cell
- Cells form tissues
- Tissues form organs
- Organs form systems

Tissues and Organs

- A system
  - May consist of one type of cell or many types of cells
  - Differing in size, shape and function
- **Radiosensitivity** is based on the most sensitive cell in the system

Cell Radiosensitivity

- High
  - Lymphocytes
  - Spermatogonia
  - Erythroblasts
  - Intestinal crypt cells
- Intermediate
  - Endothelial cells
  - Osteoblasts
  - Spermatids
  - Fibroblasts
- Low
  - Muscle cells
  - Nerve cells

Principles of Radiation Biology

Bushong, Chapter 30

Law of Bergonié & Tribondeau

- Two French scientists
- Theory developed in 1906
- Radiosensitivity is a function of the metabolic state of the cell receiving the exposure

Tissues / cells having the most pronounced effects:
- **immature / unspecialized cells**
- **cells with long mitotic phases**
- **high rate of reproduction**

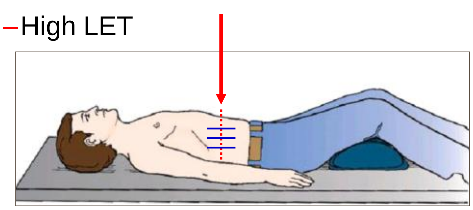
Radiation Energy Transfer Determinants

- Linear energy transfer (**LET**)
- Relative biologic effectiveness (**RBE**)
- Oxygen enhancement ratio (**OER**)

Characteristics of ionizing radiation such as charge, mass, and energy vary among the different types of radiation.

Linear Energy Transfer (LET)

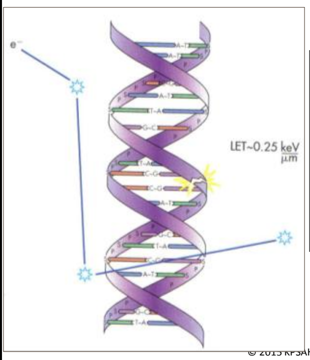
- Average energy deposited per unit length of track or path (keV/µm)
- Radiation is divided into two categories:
  - Low LET
  - High LET



Low-LET Radiation

- X-rays and gamma rays
- Sparsely ionizing
- Interacts randomly
- Damage mostly through indirect action
  - Free radicals
- May cause damage through direct action
  - Single-strand breaks in DNA

Low-LET Radiation

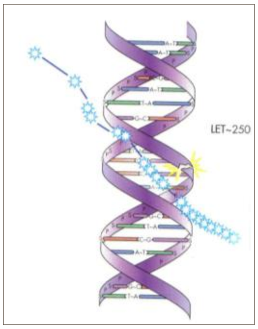


Most cell damage caused by indirect action, but damage can also occur through direct action.

High-LET Radiation

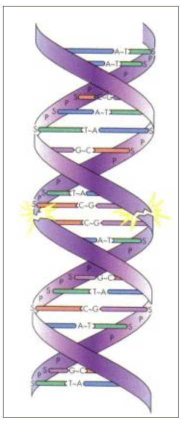
- Particles with substantial mass and charge
  - Alpha particles
- Dense ionization along their track
- Damage caused through direct action
  - Multiple-strand breaks in DNA
  - Complete chromosome breakage

High-LET Radiation



Considered to cause a single strand or multiple strand break

Effect of High-LET Radiation



Considered a complete chromosomal break

Relative Biologic Effectiveness (RBE)

- Describes the ability of radiations with different LETs to produce a particular biologic reaction

$$\text{RBE} = \frac{\text{dose (Gy) of standard radiation to produce a given effect (200 – 250 kVp x-ray)}}{\text{dose (Gy) of test radiation}}$$

Fractionation / Protraction

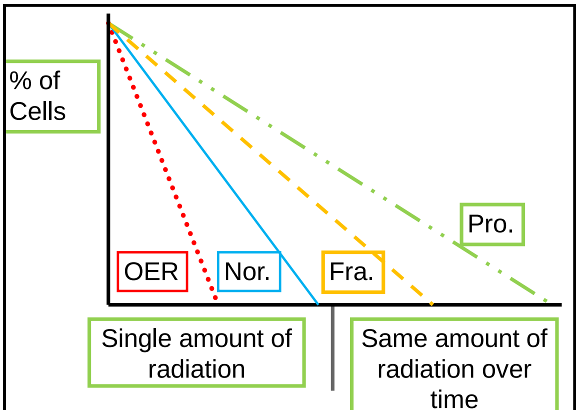
- Methods of delivering a radiation dose over time
- Fractionation is the delivery of a certain dose using smaller portions
- Protraction is delivering a small dose continuously
- In either case, cells have an opportunity to repair and recover over time

Oxygen Enhancement Ratio (OER)

- Also called the oxygen effect
- Cells are more radiosensitive in the presence of oxygen

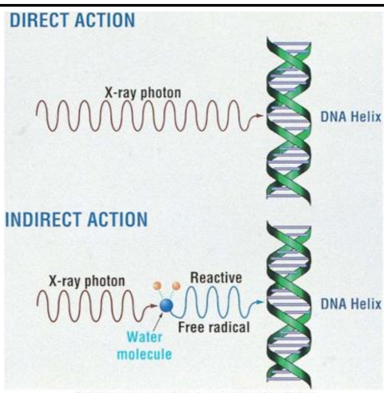
$$\textbf{OER} = \frac{\text{Radiation dose required to cause biologic response without } O_2}{\text{Radiation dose required to cause biologic response with } O_2}$$

OER is highest with low LET radiation



Direct vs. Indirect Actions (Effects)

- Direct Action (Effect)
  - The initial ionizing event occurs on the target molecule
- Indirect Action (Effect)
  - Initial ionization occurs on a distant molecule
  - Energy of ionization is <u>transferred</u> to target molecule



(From Radiobiology and radiation protection: Mosby's radiographic instructional series, St Louis, 1999, Mosby.)

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.

Other Factors Affecting Radiosensitivity

- Age
- Cell recovery
- Chemical agents

Age

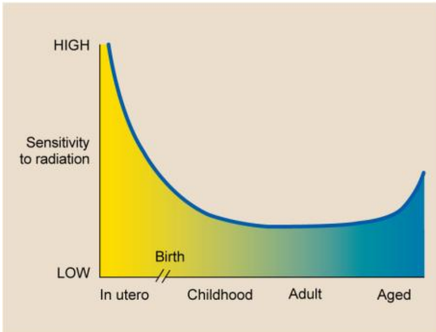


Fig. 30-3. Radiosensitivity varies with age. Experiments with animals have shown that very young and very old individuals are more sensitive to radiation.

Recovery

Intracellular Repair + Repopulation

Results from sublethal damage

If the radiation dose is high enough, the tissue/organs atrophy

Apoptosis: cellular interphase death
- **DNA is replicated during "S" phase**
- **If the cell dies before DNA replication, there is no recovery**

Chemical Agents

Radiosensitizers:
- Make the cell more sensitive to the effects of radiation

Radioprotectors:
- Protect cells against radiation damage
  - Lethal to human cells

Radiation Dose-Response Relationships

Threshold:

- Point at which a response or reaction to an increasing stimulation first occurs
- Means that at below a certain radiation level or dose, biologic effects are not observed

Radiation Dose-Response Relationships

Nonthreshold:

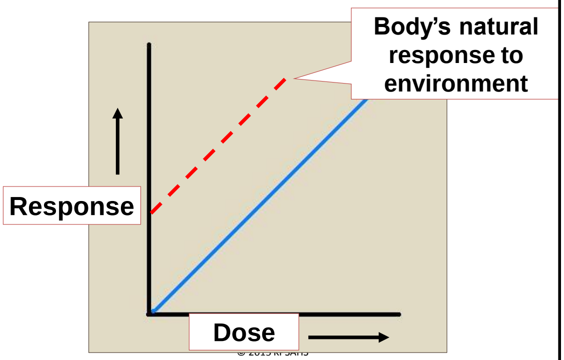
- Any radiation dose will produce a biologic effect
- No radiation dose is believed to be absolutely safe

Linear, Nonthreshold

- No level of radiation can be considered completely safe
- A response occurs at every dose
- Response is directly proportional to the amount of radiation received
- Most types of cancer fall into this category

ALARA is based on this model

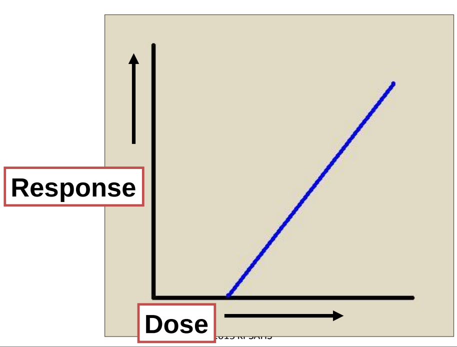
Linear, Nonthreshold



Linear, Threshold

- Lower doses of radiation result in no response
- When the threshold dose is exceeded, the response is proportional to the dose received

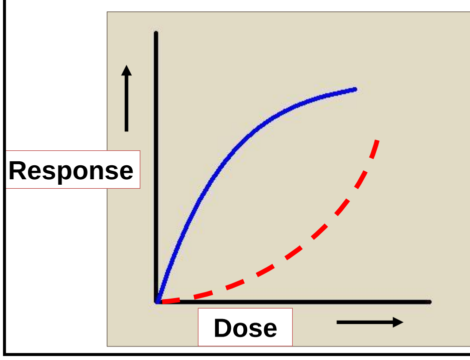
Linear, Threshold



Nonlinear, Nonthreshold

- No level of radiation is considered completely safe
- A response occurs at every dose
- The response is <u>not proportional</u> to the dose received
- The effect could be large even with a small increase in dose

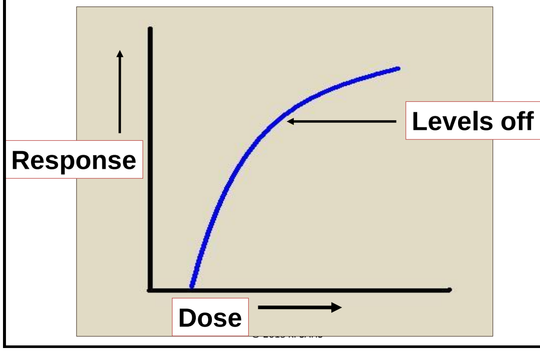
Nonlinear, Nonthreshold



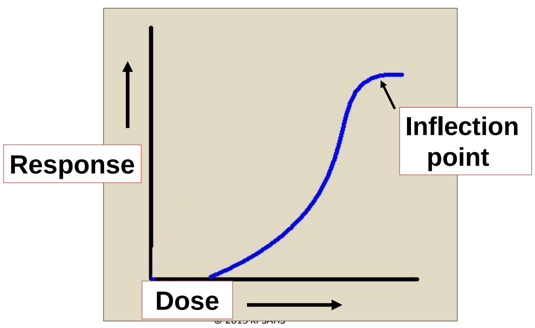
Nonlinear, Threshold

- No response at lower dose
- Once the threshold is exceeded, the response is not proportional to the dose received and is increasingly effective per unit dose

Nonlinear, Threshold



Sigmoid “S-shaped”, Threshold Curve



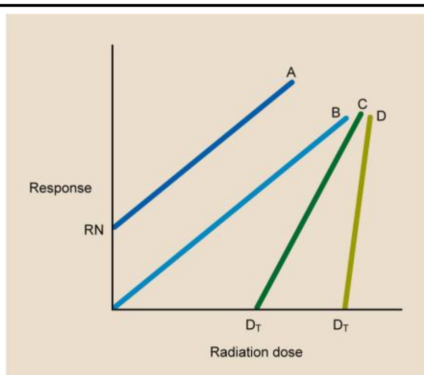


Fig. 30-4. Linear dose-response relationships *A* and *B* are nonthreshold types; *C* and *D* are threshold types. RN is the normal incidence or response with no radiation exposure.

Molecular / Cellular Radiobiology

Bushong, Chapters 31 & 32

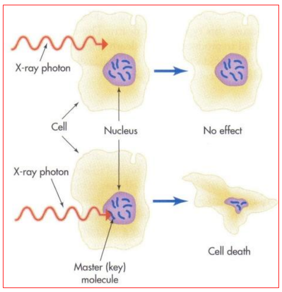
Terminology

Ion: an atom (or group of atoms) which has acquired an electrical charge through the gain (or loss) of an electron (or electrons)

Free Radical: an uncharged molecule that contains a single unpaired electron in the outer shell

Target Theory

- The cell will die after exposure to ionizing radiation **only** if the master (or key) molecule (DNA) is inactivated in the process

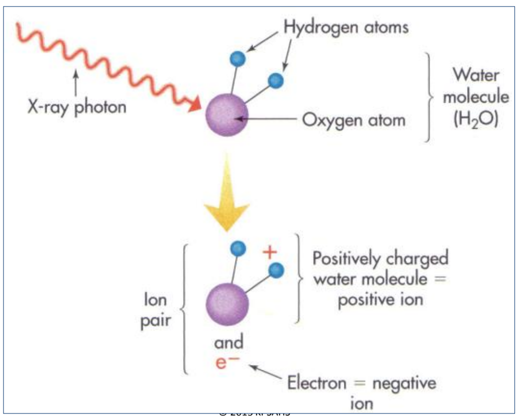


Indirect Interaction

Radiolysis:

- An x-ray photon interacts with a water molecule (ejecting an electron) creating an ion pair (electrically charged particles)

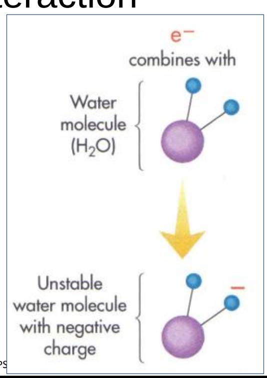
$HOH^{+} + e^{-}$

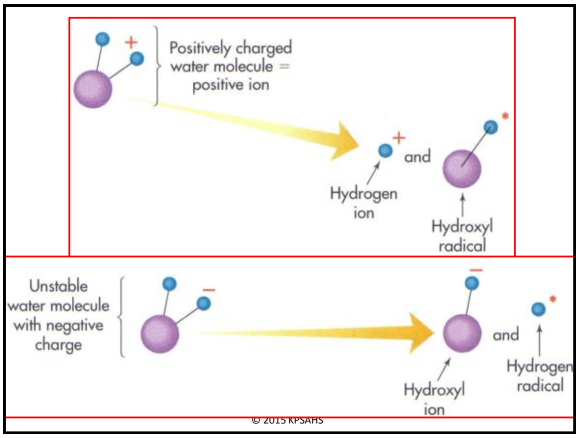


Indirect Interaction

- The electron may join with another water molecule, producing a negative water ion

$H_2O + e^{-} = HOH^{-}$



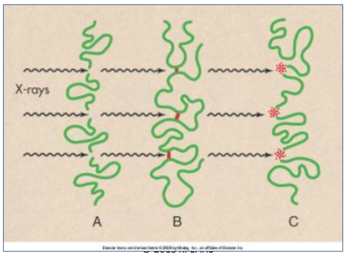


Indirect Interaction (cont)

- Hydrogen and hydroxyl free radicals can transfer their excess energy to other molecules causing the breakage of their chemical bonds, causing point lesions.
- Two hydroxyl radicals may bond creating hydrogen peroxide (H_2O_2)
- If a hydrogen free radical combines with molecular oxygen, a hydroperoxyl radical is formed.

Direct Interactions

DNA response to radiation: main-chain scission (A); cross-linking (B); and point lesions (C)



Main-Chain Lesions (scission)

Double strand break:

- One or more breaks in each of the sugar-phosphate chains (side rail severed)
- More difficult to repair
- If repair doesn't occur, there may be further separation of the DNA chain

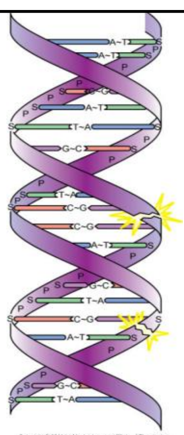
Main-Chain Lesions

Double strand break in same rung:

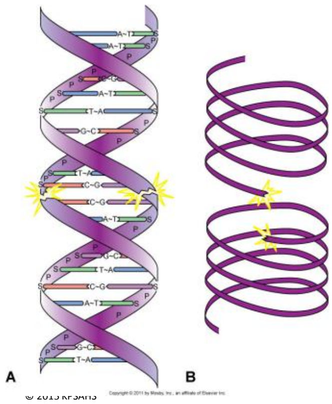
- Results in a broken chromosome
- The resulting daughter cells will have unequal amount of genetic material
- Results in cell death or impaired functioning

Double Strand Break

(Scission)



Main-chain scission on the same rung

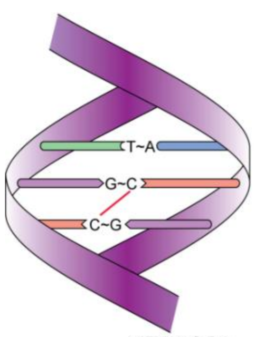


Covalent Cross-Links

Cross linking:

- Chemical unions created when atoms share one or more pairs of electrons
- Can occur between two places on the same DNA strand:
  - Intrastrand cross-link
- Can occur between two DNA molecules:
  - Interstrand cross-links

Covalent Cross-Links



Point Lesions (Mutations)

- Radiation interactions can result in a disruption of single chemical bonds (point lesions or point mutations)
- Not detectable but can cause minor modification of the molecule which can cause malfunction within the cell

Point Lesions

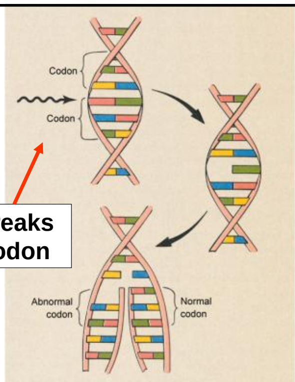


Fig. 31-7. A point mutation results in the change or loss of a base, which creates an abnormal gene. This is therefore a genetic mutation that is passed to one of the daughter cells.

Breaks codon

Now the gene is abnormal

The abnormal genetic material is passed on to the new cells

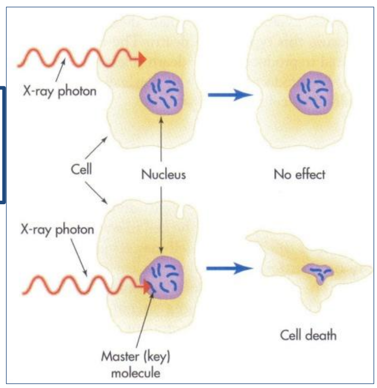
Point Lesions

- No shape change of molecule
- No cytoplasmic changes
- Generally repairable
- ***<u>At low radiation doses, point lesions are considered to be cellular radiation damage resulting in late radiation effects observed at the whole-body level</u>***

Mutation

- A change in the nitrogenous base will create an alteration in the genetic information that is passed on to future generations

Target Theory

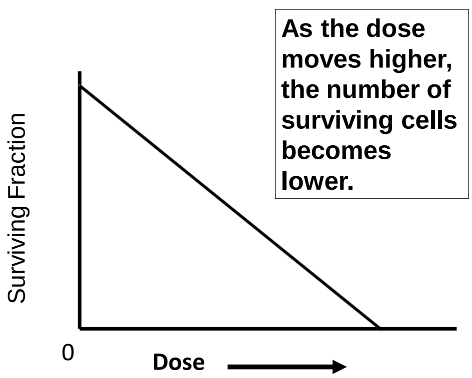


Cell Survival Curves

- The relationship between radiation exposure and proportion of cells that survive
- Cell kill is a random event
  - Some cells receive more than one hit
  - Some cells receive only one hit
  - Some cells will not be hit

Cell Survival Curves

- Cell death is exponential – *the same dose always kills the same proportion of cells* although absolute number of cell deaths varies
- Represents a logarithmic relationship between radiation dose and the proportion of cells that survive



Target Theories & Cell Survival Curves

- The target theory states there are *n* targets in a cell that all must be "hit" in order to kill the cell
- If even one target is missed, the cell can survive and repair the damage

Target Theories & Cell Survival Curves

- There are areas on the DNA chain that, if damaged, can have an impact on the survival rate of cells
- So as the dose increases all cells reach a *n-1* state where one more “hit” will kill the cell, this corresponds to the exponential portion (straight line) of the survival curve

Single Target / Single Hit Theory

- Some DNA sequences are so important to the cell that damage to any of these targets will kill the cell
- This type of cell is most sensitive to radiation
- Linear survival curve
- Applies to biologic targets, including simple cells

Example of Simple Survival Curve:

As the dose moves higher, the number of surviving cells becomes lower.

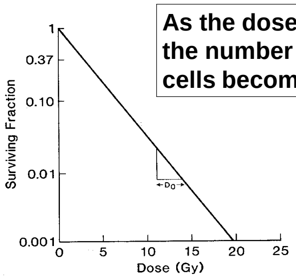


FIG 3–4.
Survival curve for bacteria *(Escherichia coli)*, showing that in this system survival is a simple exponential function of dose.

Single Hit / Multiple Target

- Few mammalian cells show linear relationships between dose and cell survival
- Human cells have two of each chromosome, so it is believed that both of them must be damaged in order for the damage to kill the cell

Single Hit / Multiple Target

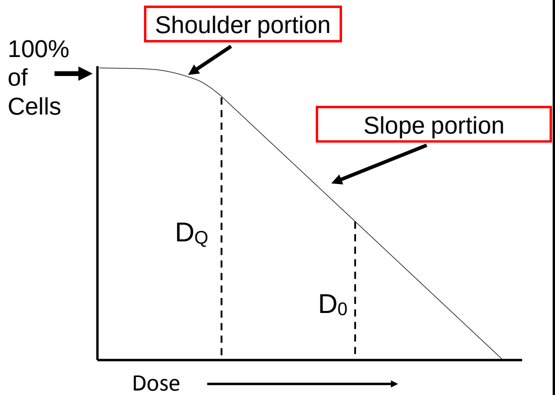
- Human cell survival curves have a “shoulder” at low doses which suggests single hit / multiple-target (two-chromosome) theory
- At higher doses, however, every chromosome would have hits, resulting in a linear curve

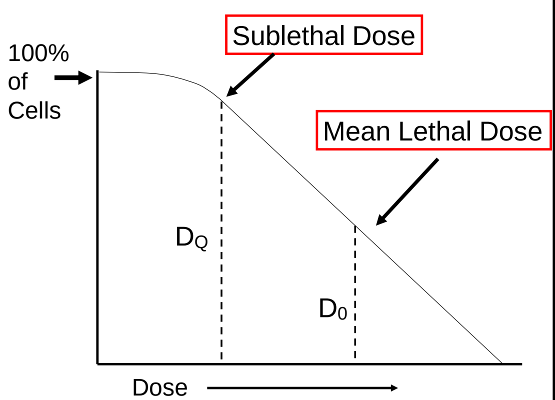
Cell Survival Curves

- Description of “shouldered” survival curves
- *N* - extrapolation number
  - Assumed to represent the number of targets in cell to cause cell death
  - Ranges from 2-10 for mammalian cells

Cell Survival Curves

- *D_Q* - (<u>threshold dose</u>)
  - Width of the shoulder
  - Surviving fraction
- *D_0* – (straight line portion of curve)
  - Defined as the dose that inactivates all but 37% of the population
  - Is an expression of radiosensitivity of a cell population





Cell Survival Curves

- Shallow curves are **less** sensitive
  - The longer the D_0, the shallower the survival curve; the less sensitive the cell is to the radiation
- Steep curves are **more** sensitive
  - The shorter the D_0, the steeper the survival curve; the more sensitive the cell is to radiation
- D_0 doses for mammalian cells vary between 1 – 2 Gy

Summary of Cell Response

- Some cells will receive no damage
- Some will accumulate enough damage to be lethal and will die in the next division
- Some cells will accumulate a degree of damage that is not lethal (sublethal) and which, given enough time, can be repaired (shoulder)

Survival Curves & Repair

- If more damage is received before repair occurs, the two (damages) may interact to become lethal
- Exposure to low LET radiation allows repair
- Sublethal Damage (SLD)
  - Allows repair to occur between two doses of radiation separated by time
  - Most sublethal damage repair occurs in the 2 hours after exposure

Survival Curves & Repair (cont)

- Sublethal damage accounts for shouldered curves
- Cells and tissues with a broad shoulder on the curve exhibit a large amount of sublethal damage repair (i.e. jejunum)
- Cells and tissues with a narrow shoulder on the curve exhibit little to no sublethal damage repair (i.e. bone marrow)