Fundamental Principles of Radiobiology

In This Lecture

- Radiosensitivity
- Law of Bergonie & Tribondeau
- Physical factors effecting radiation response
- Biological factors effecting radiation response
- Dose-response relationships

Radiosensitivity

- Some types of tissue respond more quickly to lower does of radiation than others
- Dose response relationship
  - Mathematical function/graph relating radiation dose to observed response

Law of Bergonie & Tribondeau

- Radiosensitivty of living tissues varies with maturation & metabolism;
  1. Stem cells are radiosensitive. More mature cells are more resistant
  2. Younger tissues are more radiosensitive
  3. Tissues with high metabolic activity are highly radiosensitive
  4. High proliferation and growth rate, high radiosensitivty

Radiosensitivity

- Response of tissue determined by amount of energy deposited per unit mass (dose in Gy)
- Two identical doses may not produce identical responses due to other modifying factors

Physical Factors
- Linear energy transfer
- Relative biological effectiveness
- Fractionation & protraction

Biological Factors
- Oxygen Effect
- Age
- Recovery
- Chemical Agents
- Hormesis

Physical Factors Effecting Radiosensitivty

- Linear energy transfer
- Relative biological effectiveness
- Fractionation & protraction

Linear Energy Transfer

- Measure of the rate at which energy is transferred from ionizing radiation to tissue.
- Another way of expressing radiation quality & determining the value of the tissue weighting factor (W_T)
- W_T accounts for relative radiosensitivty of various tissues

Linear Energy Transfer

- Expressed in units of keV of energy transferred per micron of tracklength in soft tissue (keV/µm)
- Ability of radiation to produce biological response increases as LET of radiation increase
- LET of diagnostic X-rays ~3keV/µm

Relative Biological Effectiveness

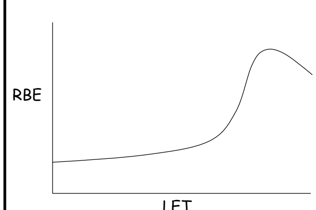
- Higher LET, higher ability to produce damage
- Quantitatively described by **relative biological effectiveness** (RBE)

Relative Biological Effectiveness

$$RBE = \frac{\text{Dose of standard radiation to produce a given effect}}{\text{Dose of test radiation to produce a given effect}}$$

- Standard radiation, by convention, is X-radiation in the 200- to 250-kVp range
- For diagnostic X-rays, RBE = 1

LET & RBE



Type of Radiation	LET	RBE
25-MV x-rays	0.2	0.8
^{60}Co X-rays	0.2	0.9
1-MeV electrons	0.3	0.9
Diagnostic X-rays	3.0	1.0
10-MeV protons	4.0	5.0
Fast Neutrons	50.0	10
5-MeV alpha particles	100.0	20

Example:

When rats are irradiated with 250 kV x-rays, 15 Gy is necessary to produce death. If similar rats are irradiated with heavy nuclei, only 0.5 Gy is needed.

What is the RBE of the heavy nuclei ?

Fractionation & Protraction

- A dose is delivered over a long period of time is less effective than that delivered quickly.
- If the time of irradiation is lengthened, higher dose is required to produce the same effect.
- Lengthening of time accomplished in two ways;

Fractionation

- Divide dose into series of small doses
- Example:
  If the 12 Gy dose is delivered at the same dose rate (4Gy/min), but in 12 equal fractions of 1 Gy each separated by 24 hours, the rat will survive. The dose is said to be **fractionated**
- Dose fractionation causes less effect due to intracellular repair & recovery between doses.
- Routinely used in oncology

Protraction

- Reduced Dose Rate
- If the dose is delivered continuously but at a lower dose rate, it is said to be protracted.
- Example:
  A total of 12 Gy is delivered in 3mins (4Gy/min) is lethal for a rat. However, when 12 Gy is delivered at a rate of 1 Gy/hour for a total of 12 hours the rat survives.

Biological Factors Effecting Radiosensitivty

- Oxygen Effect
- Age
- Recovery
- Chemical Agents
- Hormesis

Oxygen Effect

- Tissue is more sensitive when irradiated in oxygenated or aerobic state than in anoxic or hypoxic state
- Oxygen Enhancement Ratio (OER)

$$OER = \frac{\text{Dose under anoxic conditions to produce a given effect}}{\text{Dose under aerobic conditions to produce the same effect}}$$

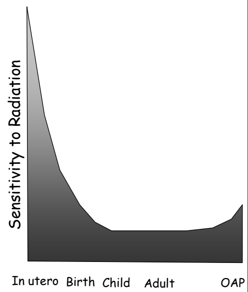
- Diagnostic x-rays are administered under conditions of full oxygenation

Example

- When mouse mammary carcinomas are clamped and irradiated under hypoxic conditions, the tumor control dose is 106 Gy. When not clamped the control dose is 40.5 Gy
- Calculate the OER

Age

- Age of biological structure affects radiosensitivity
- Humans are most sensitive at birth
- Sensitivity decreases until maturity
- In old age, radiosensitivity increases
- Many theories have been developed to explain this. – None universally accepted



Recovery

- Cells are capable of recovering from radiation damage
- At whole body level, recovery is assisted via repopulation by surviving cells

Recovery = Repair + Repopulation

Chemical Agents

- Radiosensitivty of cells, tissues, and organs can be modified by chemical agents
- Must be present during irradiation

Chemical Agents

<u>Radiosensitizers</u>

- Examples:
  - Halgenated pyrimidines
  - Methotrexate
  - Actinomycin D
  - Hydroxyurea
  - Vitamin K
- All have effectiveness of ~2
- If 90% of cell culture is killed by a 2 Gy dose, then in the presents of sensitising agent only 1 GY is required

Chemical Agents

<u>Radioprotectors</u>

- Examples:
  - Sulphydryl groups
  - Cysteine and Cysteamine
- Not found applications in humans
- To be effective, must be administer in toxic levels (can be worse than effects of radiation)

Hormesis

- Evidence that a small dose of radiation produces helpful effect
- Prevailing Explanation

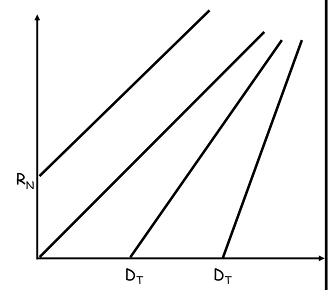
  Stimulation of hormonal and immune responses to other toxic environmental agents

Dose-Response Relationships

- Mathematical relationship between radiation dose & magnitude of observed response
- Two important implications
  1. Planning therapeutic treatment
  2. Provide information on low dose irradiation
- Two characteristics: Either linear or nonlinear

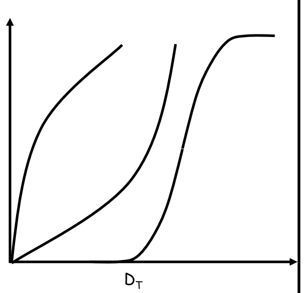
Linear Dose-Response

- Response directly proportional to dose
- Radiation-induced cancer & genetic effects follow a linear, non-threshold relationship



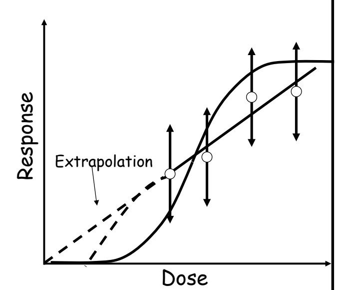
Nonlinear Dose-Response

- Radiation death and skin effects of high dose fluoroscopy follow sigmoid-type response



Constructing Dose-Response Relationships

- Nearly impossible to measure low dose, late effects
- Limited number of subjects
- Resort to irradiating small number of animals with high dose



Summary

- Radiosensitivity
- Law of Bergonie & Tribondeau
- Physical factors effecting radiation response
- Biological factors effecting radiation response
- Dose-response relationships