THE PHYSICAL AND BIOLOGICAL BASIS OF RADIATION ONCOLOGY

Ever since the discovery of x-ray by Rontgen, a German physicist in 1985, x-ray has been used in various types of medical procedures. The very first medical use of x-rays was reported in January of 1896 which indicated that the x-rays were used to locate a piece of a knife in the backbone of a drunken sailor who was paralyzed until the fragment was removed following its localization. At that time this new technology very rapidly spread through Europe and the United States and the field of diagnostic radiology was born. Not too long after that the radiation was used to treat shallow tumors of the skin by doctors.

RADIOBIOLOGY

Radiobiology is the study of the action of ionizing radiation on living things. This certainly involves a fair amount of radiation physics and a good understanding of various types of ionizing radiation as well as a description of the physics and chemistry of the processes by which radiation is absorbed.

- X-ray was discovered in December 1895 by a German Physicist “Wilhelm Conrad Rontgen”.
- First medical use of X-ray is reported as early as January 1896. After this time, the field of Radiology was born.
- Reports indicate the first therapeutic use of X-ray was in 1897 to treat skin melanoma.
- Radioactivity was discovered by “Antonio Henri Becquerel” in 1898.
- Radium was isolated by “Pierre & Marie Curie” also in 1898.

- First recorded radiobiology experiment was performed by Becquerel, when he inadvertently left a Radium container in his pocket, resulting in skin erythema that came about 2 weeks later.

- The ulcer took several weeks to heel.

- In 1901 Pierre Curie repeated this experiment on his forearm and produced an ulceration and he charted its healing.

- Field of Radiobiology began in 1901

- Definition of Radiobiology: Study of the action of ionizing Radiation on Living Tissue.

TYPES OF IONIZING RADIATION

- When energy from radiation is absorbed in biological matter it may lead to either excitation or ionization.

- Excitation is the raising of an electron in an atom or a molecule to a higher energy level without actual ejection of an electron.

- Ionization happens when the radiation has enough energy to eject one or more orbital electrons from the atom or molecule.

- A good number to remember is that the energy dissipated per ionization event is about 34 electron volts (eV) which is more than enough to break a strong chemical bond.

- Most of the experiments with biological systems have involved x-rays or gamma-rays, which are two different forms of electromagnetic radiation.

- The x-rays and gamma-rays are essentially the same except from their point of origin, i.e., where they originate from.

- **X-rays** are produced from the outside of the nucleus or by the interaction of orbital electrons; while **gamma-rays** are produced from within the nucleus of the atom.

- Whether x-rays or gamma-rays, these electromagnetic waves move with a velocity which has a value of $(3x10)^{10}$ cm/sec^2 in a vacuum.

- The relationship between wave length and speed is given by the formula:
  $C = \nu\lambda$.
  Here C=speed of light, $\nu=1/f$ = frequency, λ=wavelength.

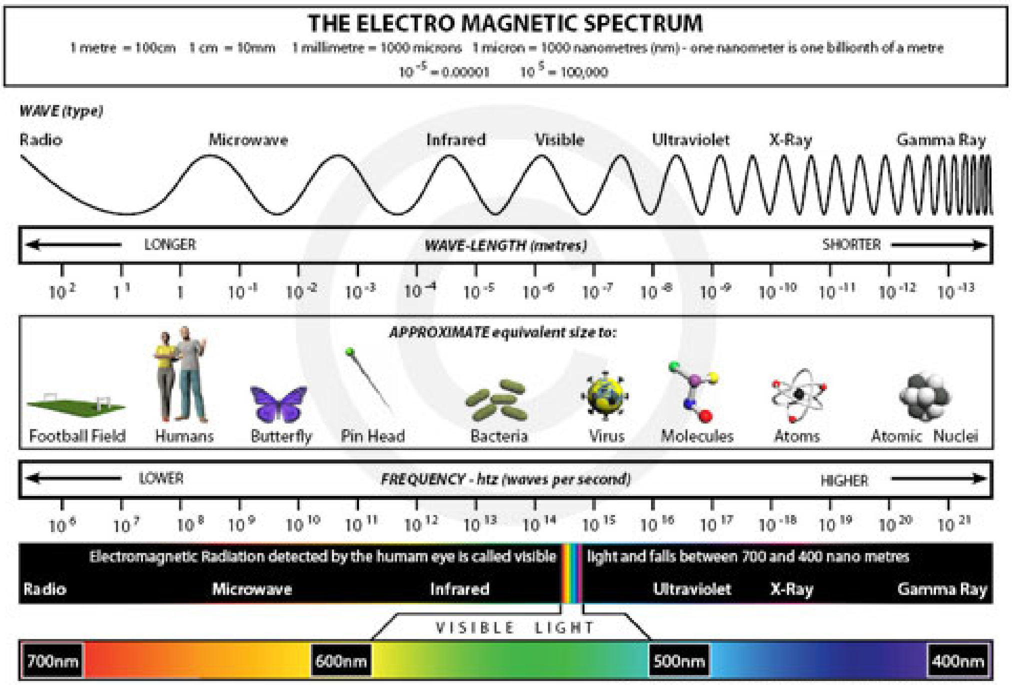
- The relationship between energy and frequency is given by the equation:
  $E=h\nu$
- From these two relationships, we can calculate for the frequency ν, to get:
  $\nu=c/\lambda$
- and the photon energy then, may be written as: **$E=hc/\lambda$**

- If energy of the photon is in KeV and the wavelength λ in angstroms, the relationship $E=12.4/\lambda$ is true.

  - e.g. Calculate the energy of a γ ray with a wavelength of 0.01 A^o.

$$E=hc/\lambda$$
$$= (6.62x10^{-34}\text{ j-sec})(3x10^{-8}\text{m/sec})/[\ \lambda(A^o)(10^{-10}\text{m/A})(1.6x10^{-16}\text{ J/keV})$$
$$= 12.4/\lambda(A^o) \Rightarrow E = 1240\text{ keV}.$$

Recall the electromagnetic spectrum.



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- The photons in the energy range of 10^{-10} and below, up to 10^{-4} are of the AM/FM and TV range frequencies.

- Photons in the energy range 10^{-4}, to 10^{2} electron volts (eV) are of the Radar, infra-red, visible and ultra-violet kind.

- Photons or particles in the energy range from a few KV to hundreds of MeV are of ionizing radiation type.

PARTICULATE RADIATIONS

_Other types of radiation that occur in nature and also are used experimentally are electrons, protons, α-particles, neutrons, negative п-mesons, and heavy charged ions.

_Some of these particles are used in radiation therapy and have a potential in diagnostic radiology not yet explored.

Electrons: are small, negatively charged particles that can be accelerated to high energy to a speed close to that of light by means of an electrical device, such as a betatron or linear accelerator.

_They are widely used for cancer therapy.

Protons: are positively charged particles and are relatively massive, having a mass almost 2,000 times greater than that of an electron.

_Because of their mass, they require more complex and more expensive equipment, such as a cyclotron, to accelerate them lo useful energies, and they are used for cancer treatment in quite a few facilities around the country, 4 within 100 miles of Toledo.

_In nature, the earth is showered with protons from the sun, which represent part of the natural background radiation. We are protected on earth to a large extent by the earth's atmosphere and the magnetic field held around the earth, which deflect charged particles.

_Protons are a major hazard to astronauts on long-range space missions.

α –Particles: are nuclei of helium atoms and consist of two protons and two neutrons in close association.

_They have a net positive charge and therefore can be accelerated in large electrical devices similar to those used for protons.

_α-Particles also are emitted during the decay of heavy naturally occurring radionuclides such as uranium and radium.

_α-Particles are the major source of natural background radiation to the general public.

_Radon gas seeps out of the soil and builds up inside houses, where, together with its decay products, if it is breathed in will irradiates the lining of the lung causing lung cancer.

_It is estimated that 10,000 to 20,000 cases of lung cancer are caused each year by this means in the United States, mostly in smokers.

Neutrons: are particles with a mass similar to that of protons, but they carry no electrical charge.

_Because they are electrically neutral, they cannot be accelerated in an electrical device. They are produced if a charged particle, such as a deuteron, is accelerated lo high energy and then made to impinge on a suitable target material.

_A **deuteron** is the nucleus of deuterium and consists of a proton and a neutron in close association.

_Neutrons are also emitted as a by-product of heavy radioactive atoms when they undergo fission, i.e., split to form two smaller atoms.

_Consequently, neutrons are present in large quantities in nuclear reactors and are emitted by some artificial heavy radionuclides.

_They are also an important component of space radiation and contribute significantly to the exposure of passengers and crews of high-flying jetliners.

Heavy charged particles are nuclei of elements such as carbon, neon, argon, or even iron that are positively charged because some or all of the planetary electrons have been stripped from them.

_To be useful for radiation therapy, they must be accelerated to energies of thousands of millions of volts and therefore can be produced in only a few specialized facilities.

_There is no longer any such facility operational in the United States, but heavy-ion therapy is used increasingly in Europe and in Japan.

_Charged particles of enormous energy are encountered in space and represent a major hazard to astronauts on long missions, such as the proposed trip to Mars.

_During the lunar missions of the 1970’s, astronauts "saw" light flashes while their eyes were closed in complete darkness, which turned out to be caused by high-energy iron ions crossing the retina.

_Similar experience is reported with radiation therapy patients who undergo photon treatments where it might be attributed to photon interaction with heavy metals in the head of the accelerator…

Units and Measurements:

Units of radiation are expressed in Rontgen, Rad, or Gray.

_The Rontgen (R) is the unit of exposure and is related to the ability of x-rays to ionize air. 1R = $2.58\text{x}10^{-4}$ C/kg or 1 C/kg = 3876 R.

_The rad is the unit of absorbed dose and corresponds to an energy absorption of 100 erg/gr. In the case of x- and y-rays, an exposure of 1 R results in an absorbed dose in water or soft tissue roughly equal to 1 rad.

_ICRU has recommended for many years now, that the rad be replaced as a unit by the gray (Gy), which corresponds to an energy absorption of 1 J/kg. Consequently, 1 Gy = 100 rad..

BASIC BIOLOGIC INTERACTIONS OF RADIATION

Points to keep in mind:

1. The interaction of radiation in cells is a probability function or a matter of chance.
   i.e., it may or may not interact and if interaction occurs, damage may or may not be produced.

2. The initial deposition of energy occurs very rapidly in a period of ~ 10^{-17} seconds.

3. Radiation interaction in a cell is non-selective.
   i.e.,
   _The energy from ionization radiation is deposited randomly in the cell –
   _No areas of the cell are “preferred” or “chosen” by the radiation.

4. The visible changes in the cells, tissues and organs resulting from radiation are not unique;
   i.e., They cannot be distinguished from damage produced by other types of trauma.

5. The biologic changes from radiation occur only after a period of time (latent period) which depends on:
   _The initial dose and varies from minutes to weeks, or even years.

BASIC INTERACTIONS OF RADIATION

When ionizing radiation interacts with a cell, possibility of either ionization or excitation exists in Macromolecules (e.g., DNA) or in the medium, based on the site of these interactions, the action of radiation on cell can be classified as 1) DIRECT, or 2) INDIRECT actions.

Direct Action:

Occurs when an ionizing particle interacts with and is absorbed by a biologic Macromolecule such as:

DNA = Deoxyribonucleic Acid
RNA = Ribonucleic Acid,
Protein, or Enzyme in the cell

These ionized Macromolecules are now abnormal structures. Therefore, damage is produced by direct absorption of energy and the subsequent ionization of a biologic macromolecule in the cell.

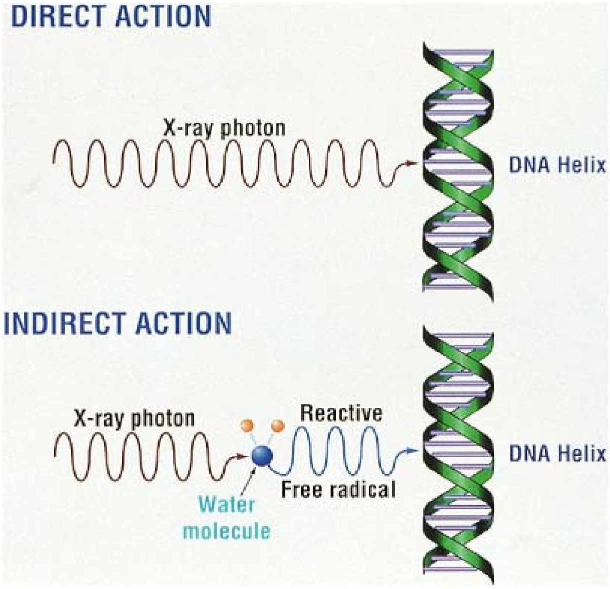


FIG. 6-3. The action of radiation on the cell can be direct or indirect. It is direct when ionizing particles interact with a vital biologic macromolecule such as DNA. The action is indirect when ionizing particles interact with a water molecule resulting in the creation of ions and reactive free radicals that eventually produce toxic substances that can create biologic damage. (From *Mosby's radiographic instructional series: radiobiology and radiation protection,* St Louis, 1999, Mosby.)

Indirect Action:

Refers to absorption of ionizing radiation in the medium when the molecules are suspended primarily in water (HOH). Absorption of radiation by water molecule results in production of ion pairs (HOH^+, HOH^-)

$$HOH \xrightarrow{\text{Radiation}} HOH^+ + e^-$$

The free e- is then gets captured by a second water molecule forming the second ion. Then:

$$HOH + e^- \text{ ---------------> } HOH^-$$

The two ions produced by the above reactions are unstable and rapidly dissociate (providing that the normal water molecules are present) forming another ion and a free radical as following:

$$HOH^+ \text{ -------------------------> } H^+ + OH^{\bullet}$$

$$HOH^- \text{ -------------------------> } OH^- + H^{\bullet}$$

_The ultimate result of the interaction of radiation with water is the formation of an ion pair (H^+, OH^-) and free radicals ($H\cdot$, $OH\cdot$).

_The consequences of these products to the cell are many and varied.

_The ion pair may react in one of two ways:

1. The ions can recombine and form a normal water molecule-the net effect in this case will be no damage to the cell

   $H^+ + OH^- = HOH$
2. The ion pair can chemically react and damage cellular macromolecules.

_Generally, because the H+ and OH- ions do not contain an excessive amount of energy, the probability that they will recombine, not causing damage in the cell, is great provided they are in the vicinity of each other.

_The free radicals produced are extremely reactive due to their chemical and physical properties and can undergo a number of reactions, a few of which are:

1. Recombine with each other producing no damage, e.g., $H\cdot + OH\cdot \text{ ==> } H20$.

2. Join with other free radicals, possibly forming a new molecule that may be damaging to the cell, e.g., $OH\cdot + OH\cdot \text{ ---> } H_2O_2$ (hydrogen peroxide, an agent toxic to the cell).

3. React with normal molecules and biologic macromolecules in the cell forming new or damaged structures, e.g., $H\cdot + O_2 ==> HO_2$
   - free radical combined with oxygen forming a new free radical;

   $RH + H\cdot ==> R\cdot + H_2$

   _here, free radical reacts with a biologic molecule (RH) removing H and forming a biologic free radical.

_The effects of free radicals in the cell are compounded by their ability to initiate chemical reactions, and therefore cause damage at distant sites in the cell.

_Although many other reactions occur and many other products are formed by the interaction of radiation with water, free radicals are believed to be a major factor in the production of damage in the cell.

_Free radicals symbolized by a dot, e.g., $OH^{\bullet}$ and $H^{\bullet}$, contain a single unpaired orbital e- that renders them highly reactive because of the tendency of the unpaired e- to pair with another e-.

IN SUMMARY:

_Direct action produces damage by direct ionization of a biologic macromolecule

_ Indirect action produces damage through chemical reactions initiated by the ionization of water

_ In both cases, the primary interaction (ionization) is the same. The definition of direct and indirect action depends on the site of ionization and energy absorption in the cell.

_An important point to keep in mind is, because there exists more water in the cell than any structural component, the probability of radiation damage occurring through indirect action is >> than the probability of damage occurring through direct action.

_In addition, indirect action occurs primarily but not exclusively from free radicals resulting from ionization of water.

_The ionization of other cellular constituents, particularly fat, also can result in free radicals formation.

_See figure below for comparison of direct and indirect action in the cell.

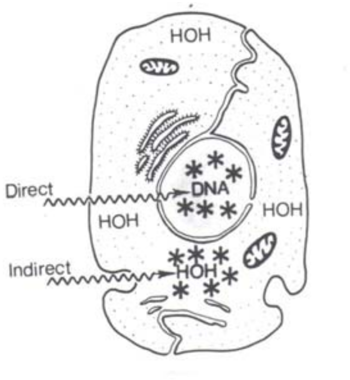
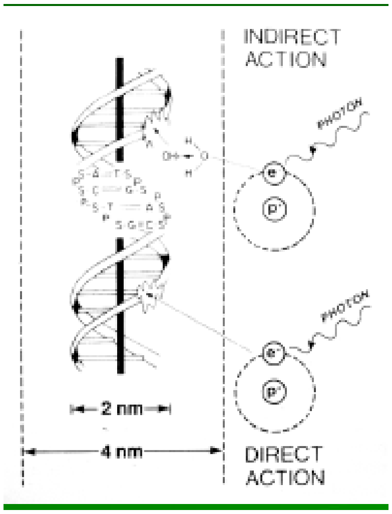
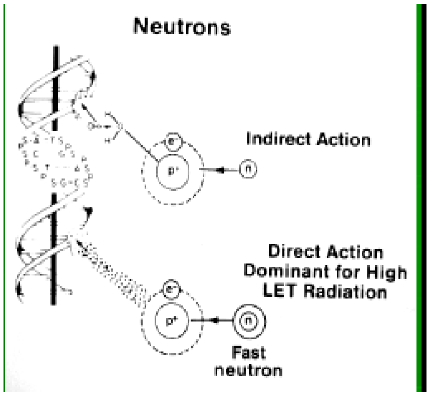


Illustration of direct and indirect action of radiation in the cell. Interactions are shown in biologic macromolecules (e.g., DNA) or intracellular water (HOH)

Radiation Absorption:

- Direct Action
    - Absorbed radiation can interact directly
    - High LET radiation
- Indirect Action
    - Interact with other atoms or molecules to produce free radicals.
    - 80% of cell is composed of water
    - 2/3 of x-ray damage due to hydroxyl radical
- Heavy particles have higher LET
    - They are more damaging to DNA





Early Effects of Radiation:

- Hematologic Syndrome
- G.I. Syndrome
- CNS Syndrome
- Tissue Damage-erythema, Desquamation
- Hematologic Damage
- Cytogenic Damage

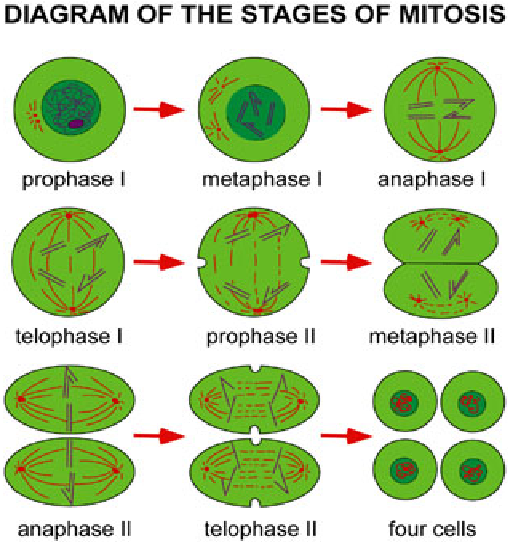
Late Effects of Radiation:

- **Leukemia**
- **Bone Cancer**
- **Breast Cancer**
- **Thyroid Cancer**
- **Local Tissue Damage**
- **Lifespan Shortening**
- **Genetic Damage**
- **Cytogenic Damage**

Fetal Radiation Effect:

- **Prenatal Death**
- **Neonatal Death**
- **Congenital Malformation**
- **Childhood Malignancy**
- **Diminished Growth and Development**

Stages of Mitosis:



Cell Response to Radiation:

LYNPHOCYTES	Radiosensitive
SPERMATOGONIA	“
OSTEOBLASTS	
SPERMATIDS	
MUSCLE CELL	
NERVE CELL	Radioresistant

LAW OF BERGOINE AND TRIBONDEAU

In 1906 Bergonie and Tribondeau realized that:

- Cells are least sensitive when in the S phase, then the G1 phase, then G2 phase and the most sensitive in the M phase of the cell cycle.
- X-rays are more effective on cells which have a greater reproductive activity

Also they formulated that cells were most sensitive to radiation when they are:

- Rapidly Dividing
- Undifferentiated
- Have a long Mitotic Future

LET and RBE:

Linear Energy Transfer (LET) is a term describing a physical property of a particular type of radiation – the rate at which energy is deposited as a charge particle travels through matter.

_LET expressed in keV/µ or energy deposited per unit distance of path traveled by the particle, is a function of the physical properties of the radiation, i.e., mass and charge.

_Electromagnetic radiation (X- and γ- rays), although having no mass of charge, produces fast electron particles with negligible mass and a charge of -1.

_Because of these physical properties, the probability of an electron interacting with an atom is relatively small; therefore, the interactions of this primary agent of damage are sparse and the ionization produced are distant from each other.

_For this reason, X-rays and γ-rays are termed low LET radiation.

_In contrast to electromagnetic radiations, highly ionizing, particulate radiations (e.g., α-particles, neutrons), having appreciable mass and/or charge, have a greater probability of interacting with matter.

_These types of radiations lose energy rapidly, producing many ionizations in a very short distance.

_Alpha particles and neutrons are high LET radiations. Some average LET values for different types of radiation are given in Table below.

LET Values – Basic Biologic Interaction of Radiation

Type of Radiation	LET (keV/μ
Co-60	0.3
3 MeV X-ray	0.3
250 keV X-ray	3.0
5 MeV Alpha particle	100
Neutron: 19.0 MeV 2.5 MeV	7.0 20
Electrons: 1.0 MeV 1.0 keV	0.25 12.3

_Because of these differences in rate of energy loss, different LET radiations will produce different degrees of the same biologic response, i.e., equal doses of radiations of different LET's do not produce the same biologic response.

_A term relating the ability of radiations with different LET ranges to produce a specific biologic response is *relative biologic effectiveness (*RBE).

RBE is defined as the comparison of a dose of test radiation to a dose of 250 keV X-ray which produce the same biologic response. This is expressed in the following formula:

$$RBE = \frac{(\text{Dose in rads from 250 keV X} - \text{ray})}{\text{Dose in rads from another radiation delivered under the same conditions}}$$

_250 keV x-ray is the *standard* for determining RBE because of its widespread use at the time the concept of RBE was adopted. Today, although this energy and even cobalt-60 is no longer used, still the 250 keV x-ray remains the standard radiation for determining RBE.

_Notice the biologic response is the constant, *not* the dose of radiation; what is actually measured is the biologic effectiveness of radiations of different LET's.

_Although the relationship between LET and RBE has been discussed in simple terms, it is much more complex.

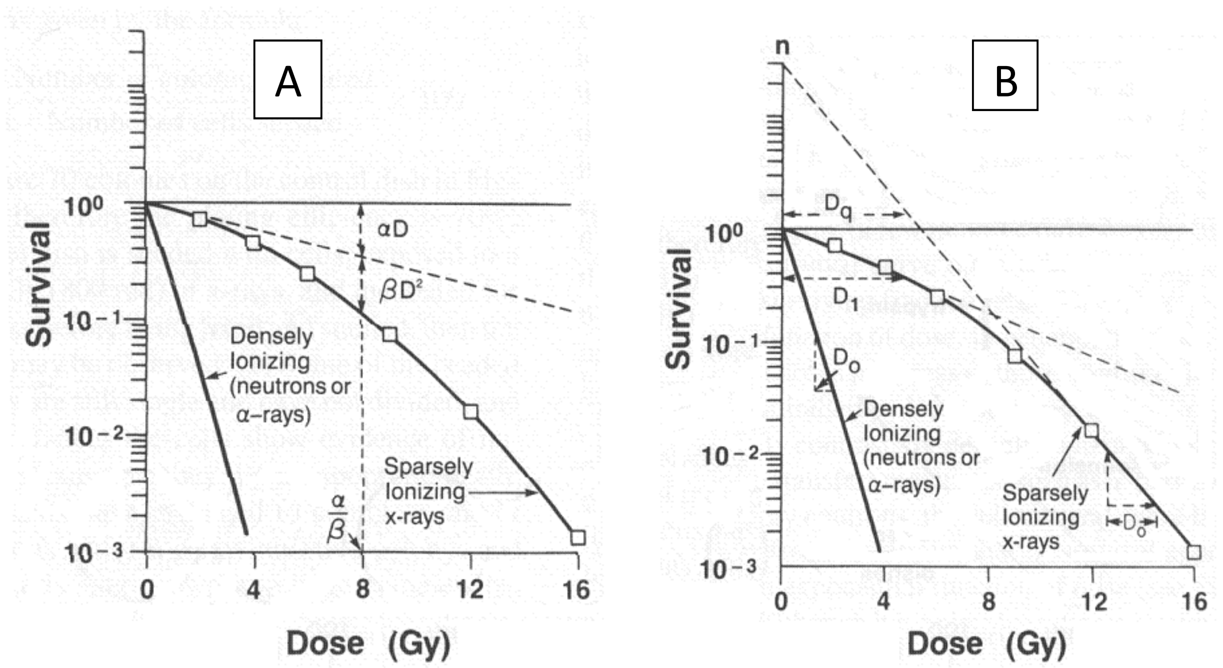
_RBE does provide useful information concerning the biologic effectiveness of different types of radiation, but it must be carefully used. RBE is a meaningful value if both the test system used and the biologic endpoint measured are identical.

_One of the major problems encountered in RBE determinations is that as radiation travels through matter, losing energy, the LET increases after each interaction until the ionizing particle finally stops; therefore, RBE also changes.

_For this reason, systems and endpoints must be carefully chosen. In addition, other factors such as the chemical environment of the cell will have an effect on the relationship of LET and RBE.

_Another important point to keep in mind is that the RBE will change depending on the biologic response studied.

SURVIVAL CURVES:



Shape of survival curve for mammalian cells exposed to radiation.

_The fraction of cells surviving is plotted on a logarithmic scale against dose on a linear scale.

_For α-particles or low energy neutrons (said to be densely ionizing) the dose-response curve is a straight line from the origin (i.e., survival is an exponential function of dose).

_The survival curve can be described by just one parameter, the slope.

_For x or y-rays (said to be sparsely ionizing), the dose-response curve has an initial linear slope, followed by a shoulder. At higher doses the curve tends to become straight again.

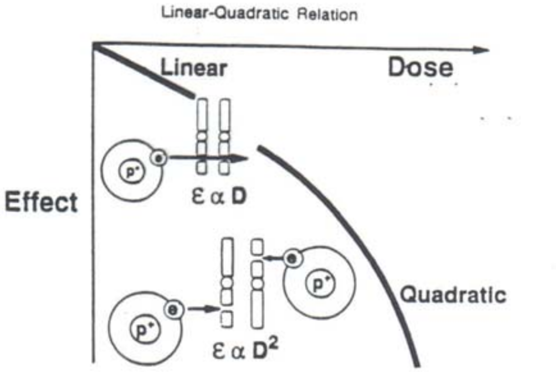
(A) The experimental data are fitted to a linear-quadratic function. There are two components of cell killing: one is proportional to dose (αD), while the other is proportional to the square of the dose (βD^2).

_The dose at which the linear and quadratic components are equal is the ratio α/β.

_The linear-quadratic curve bends continuously but is a good fit to experimental data for the first few decades of survival.

(B) The curve is described by· the initial slope (D_1), the final slope (D_0), and a parameter that represents the width of the shoulder, either *n* or D_Q.

Relationship between chromosome aberrations and cell survival.



_Cells that suffer exchange-type chromosome aberrations (such as a dicentric) are unable to survive and continue to divide indefinitely.

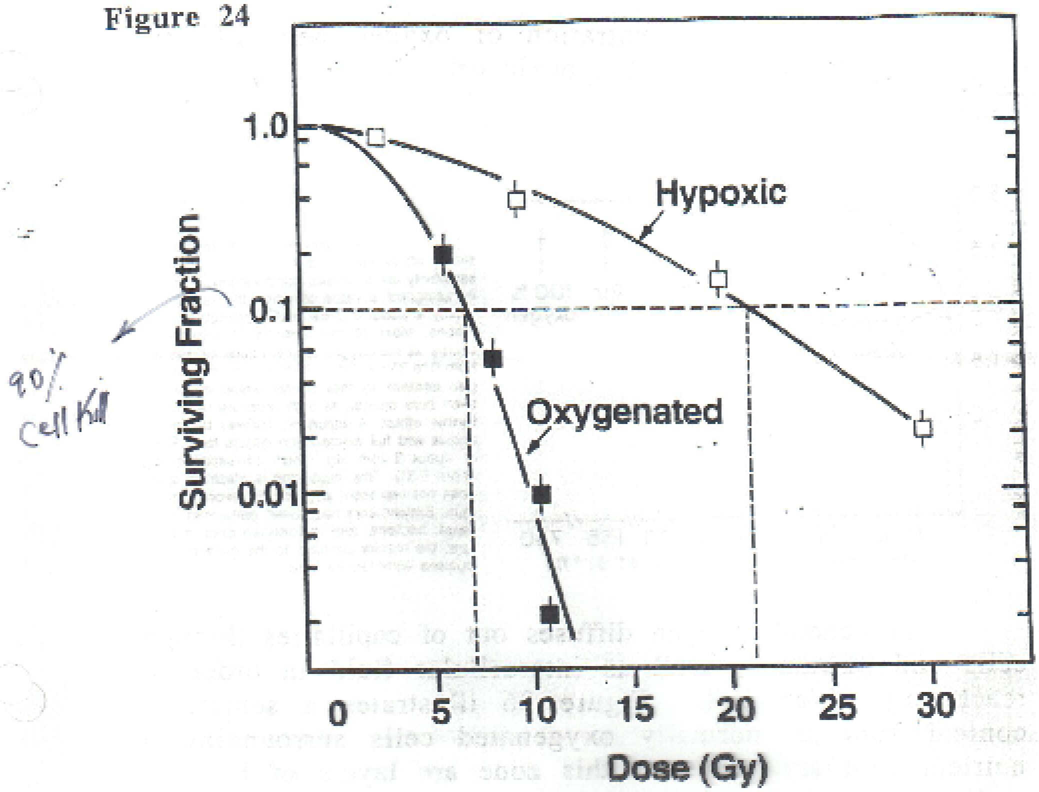
_At low doses, the two chromosome breaks are the consequence of a single electron set in motion by the absorption of x- or y-rays.

_The probability of an interaction between the breaks is proportional to dose: this is the linear portion of the survival curve.

_At higher doses. The two chromosome breaks may result also from two separate electrons. The probability of an interaction is then proportional to $(\text{dose})^2$.

_The survival curve bends when the quadratic component dominates.

Figure 24



a function of radiation dose under hypoxic and oxygenated conditions. The hypoxic cells demonstrate marked radioresistance as compared to the oxygenated cells. Note that in this example in order to achieve 90% cell kill (surviving fraction = 0.1) a dose of only 7 Gy is required for **oxygenated** cells whereas a dose of 21 Gy is required to achieve the same level of cell kill under **hypoxic** conditions. The ratio between these two radiation doses necessary to achieve the same level of cellular lethality (hypoxic/oxic) is called the **OXYGEN ENHANCEMENT RATIO (OER)**. In this example OER = 21/7 = 3.0. For sparsely ionizing (**low LET**) radiations such as X- & gamma-rays, the OER at high doses typically lies between **2.5** and **3.0**. The OER for densely ionizing (**high LET**) radiations such as alpha-particles is **1.0** (there is no significant oxygen effect). The OER for fast neutrons has an intermediate value.

The Concept of Oxygen Enhancement Ratio

The actual concentration of oxygen necessary to improve radiosensitization of hypoxic cells is really quite low (Figure 25).

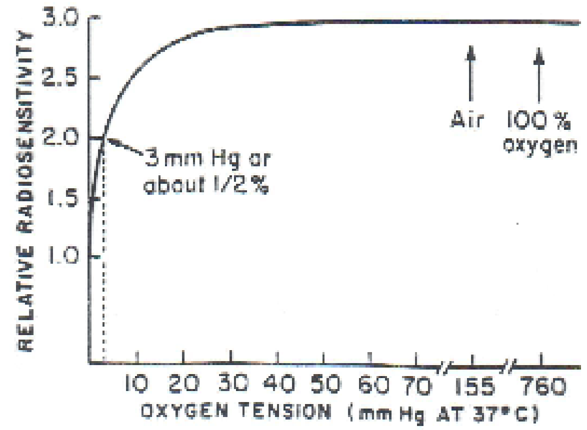


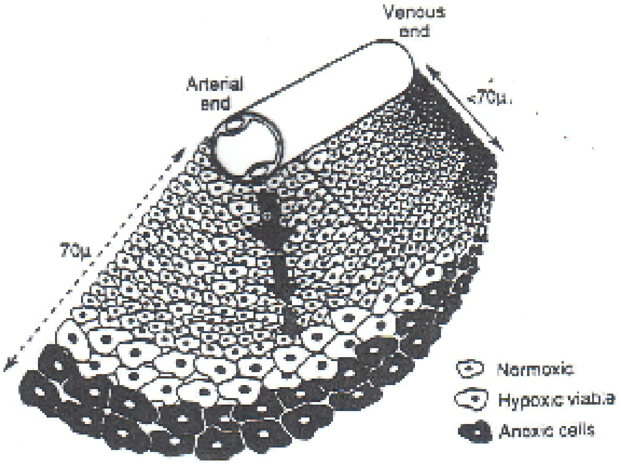
Figure 25

The dependence of radiosensitivity on oxygen concentration. If the radiosensitivity under anoxic conditions is arbitrarily assigned a value of unity, the radiosensitivity is about 3 under well-oxygenated conditions. Most of this change of sensitivity occurs as the oxygen concentration increases from 0 to 30 mm Hg. A further increase of oxygen content to that characteristic of air or even pure oxygen at high pressure has little further effect. A sensitivity halfway between anoxia and full oxygenation occurs for a PO_2 of about 3 mm Hg, which corresponds to about 0.5%. This illustration is idealized and does not represent any specific experimental data. Experiments have been performed with yeast, bacteria, and mammalian cells in culture; the results conform to the general conclusions summarized here.

In general, oxygen diffuses out of capillaries through cells and stroma as well as intercellular fluid in order to reach any given cell. Figure 26 illustrates a somewhat conical zone of normally oxygenated cells surrounding a nutrient capillary. Beyond this zone are layers of hypoxic and anoxic cells that, by virtue of their **inherent radioresistance**, are belived to negatively impact radiocurability in certain clinical situations.

Figure 26

The diffusion of oxygen from a capillary through tumor tissue. The distance to which oxygen can diffuse is limited largely by the rapid rate at which it is metabolized by respiring tumor cells. For some distance from a capillary, cells are well oxygenated (*white*). At greater distances oxygen is depleted, and tumor cells become necrotic (*black*). Hypoxic tumor cells form a layer, perhaps one or two cells thick, in between (*gray*). In this region the oxygen concentration is high enough for the cells to be viable but low enough for them to be relatively protected from the effects of x-rays. These cells may limit the radiocurability of the tumor. The distance to which oxygen can diffuse is about 70 μm at the arterial end of a capillary and less at the venous end.



approaches 100% asymptotically. In this example the normal tissue complication curve lies to the right of the tumor control curve, but both curves have the same general shape. Analyzing the figure, it is apparent that if one wishes to avoid complications altogether, one must not administer a dose greater than A. At this dose the tumor control rate is seen to be only 15%-20%. If one is willing to risk a 10% complication rate (dose B), however, a tumor control rate of 50%-55% may be obtained. On the other hand, if one wishes to achieve a 95% tumor control rate (dose C), one must be prepared to accept an 80%-85% normal tissue complication rate. These types of considerations are encountered many times daily in the Radiation Therapy Clinic.

Figure 29