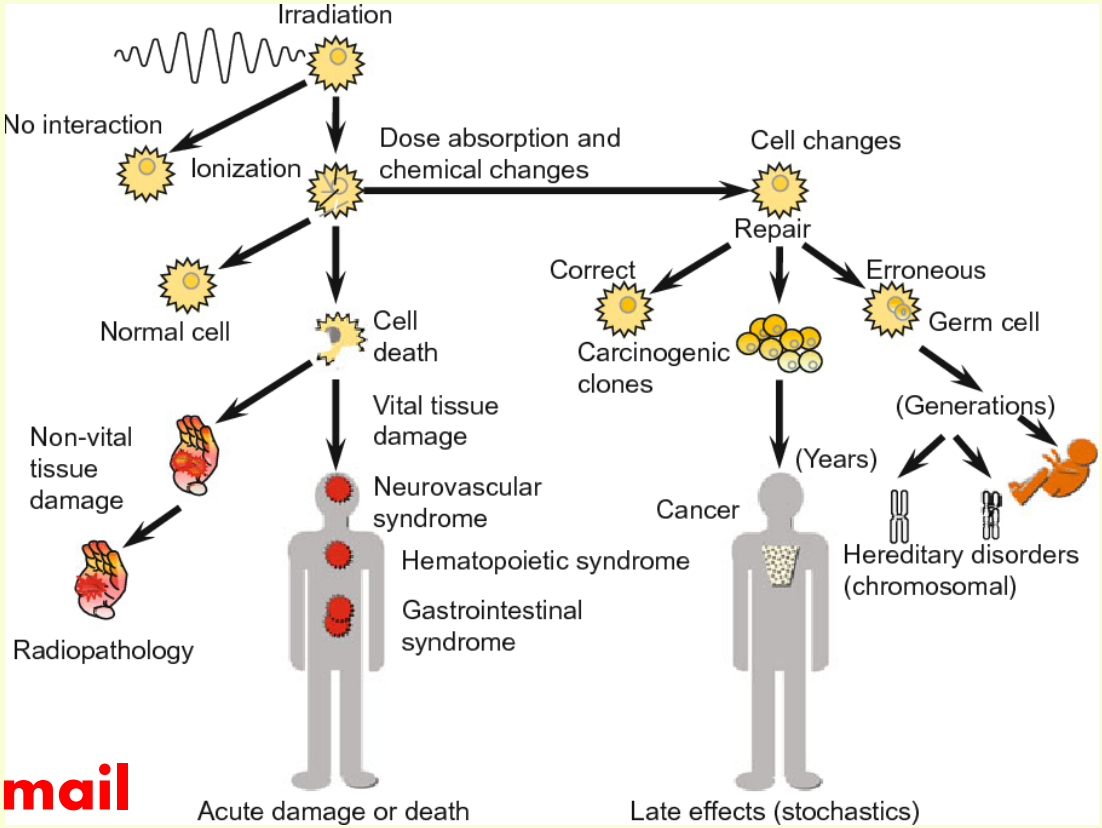
Chapter Four : Biological Effects of Radiation

(Biological Effects due to radiation interaction with tissue)



Prof. Dr. Asaad H. Ismail
PhD Medical Physics
Salahaddin University-Erbil
E-mail: asaad.ismail@su.edu.krd

Objectives

- **Understand interaction of ionizing radiation with matter on the molecular level.**
- **Understand how molecular-level effects lead to damage at the cell and tissue levels.**
- **Identify major effects of radiation on humans.**

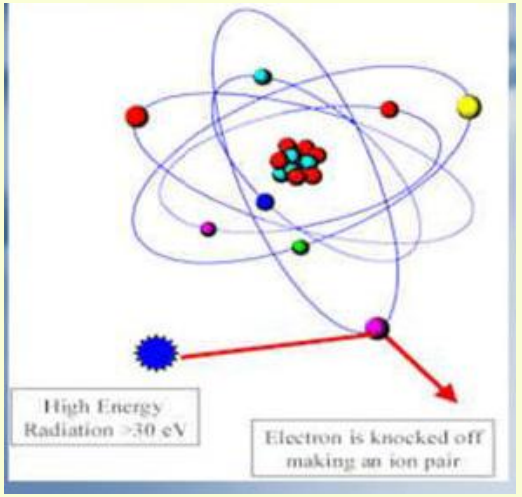
Introduction: This chapter is concerned with the deposition of energetic radiation into living tissues. Before discussing the biological effects of radiation, we will consider ionizing radiation interactions in tissue. This includes the processes through which radiation interacts with tissue and how these interactions affect biological systems. Finally, damage produced by different types of radiation will be explain .

There is no direct evidence of radiation-induced genetic effects in humans, even at high doses. Various analyses indicate that the rate of genetic disorders produced in humans is expected to be extremely low, on the order of a few disorders per million live born per rem of parental exposure.

The Biological Effects of Ionizing Radiation

How dose ionizing radiation damage occur?

Ionizing radiation can remove tightly bound electrons from their atomic orbits. This causes the atom to become charged or ionized. The atom can react with neighboring atoms , forming new chemical bonds



Interactions with cell materials

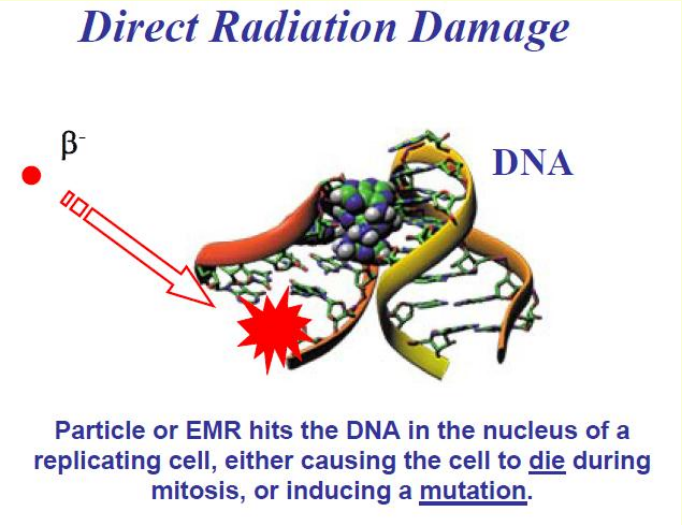
- Biological damage occurs due to chemical changes caused by ionization the cellular level
- Charged particles can ionize directly
- X-ray must first undergo interactions to produce free electrons , which can then ionize

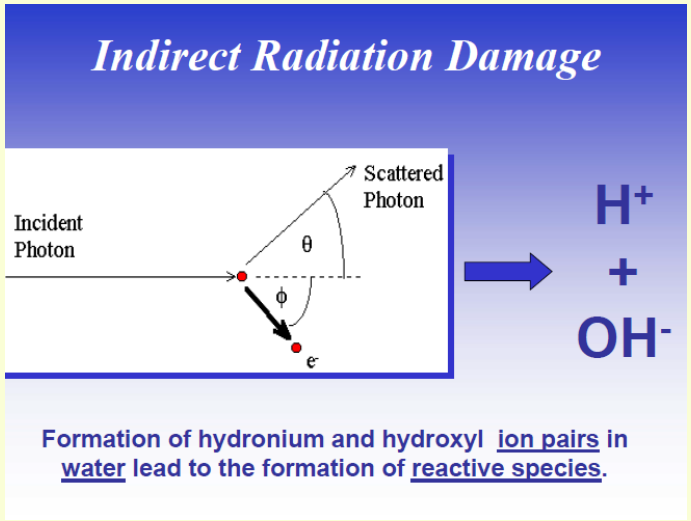
DNA is the primary target for biological damage

Radiation damage starts at the cellular level. Radiation which is absorbed in a cell has the potential to impact a variety of critical targets in the cell, the most important of which is the DNA. Evidence indicates that damage to the DNA is what causes cell death, mutation, and carcinogenesis. The mechanism by which the damage occurs can happen via one of two scenarios.

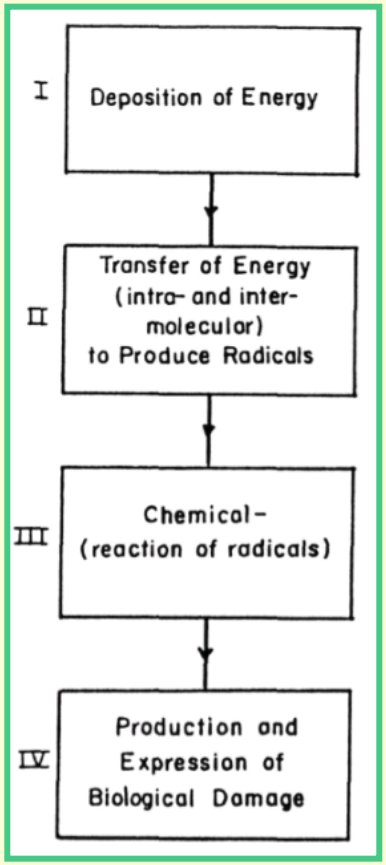
A.Direct Action In the first scenario, radiation may impact the DNA directly, causing ionization of the atoms in the DNA molecule. This can be visualized as a "direct hit" by the radiation on the DNA, and thus is a fairly uncommon occurrence due to the small size of the target; the diameter of the DNA helix is only about 2 nm. It is estimated that the radiation must produce ionization within a few nanometers of the DNA molecule in order for this action to occur.

B. Indirect Action In the second scenario, the radiation interacts with non-critical target atoms or molecules, usually water. This results in the production of free radicals, which are atoms or molecules that have an unpaired electron and thus are highly reactive. These free radicals can then attack critical targets such as the DNA (see the figure). Because they are able to diffuse some distance in the cell, the initial ionization event does not have to occur so close to the DNA in order to cause damage. Thus, damage from indirect action is much more common than damage from direct action, especially for radiation that has a low specific ionization.

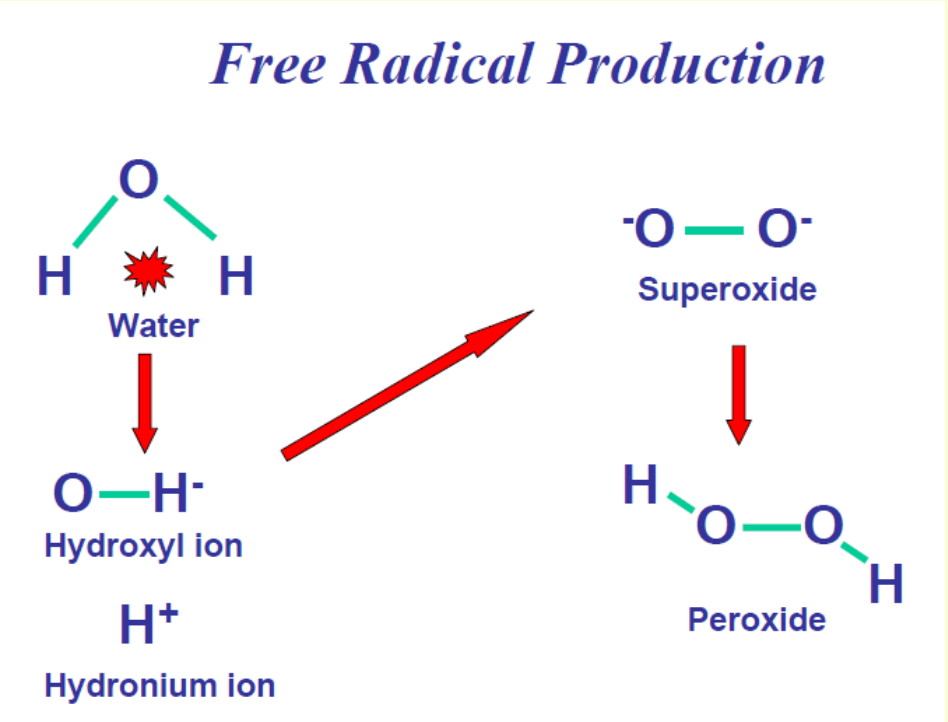




Formation of hydronium (H^+) and hydroxyl (OH^-) ion pairs in water lead to the formation of reactive species (a group of living organisms consisting of similar individuals capable of exchanging genes or interbreeding)



Free radicals are atoms, ions, or molecules that contain an unpaired electron. The unpaired electron makes them unstable and highly reactive. In a process called oxidation, free radicals steal electrons from other molecules—fats, proteins, cell membranes, and even DNA—altering the fundamental structure of the affected molecule. One unbalanced molecule may not sound like a major concern, but oxidation sets off a chain reaction by damaging a cell's DNA, structure, and ability to function. Over time, oxidative damage accumulates and contributes to aging .



Damage and Recovery

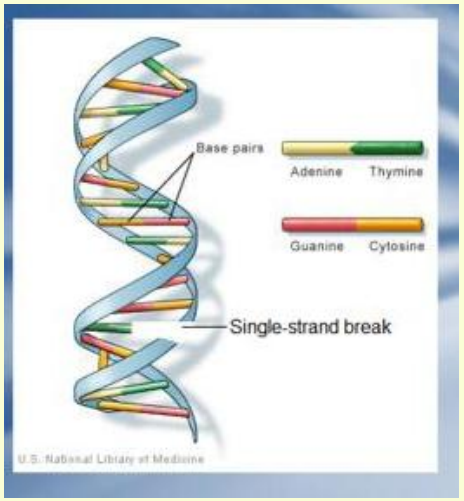
- Single –stand breaks

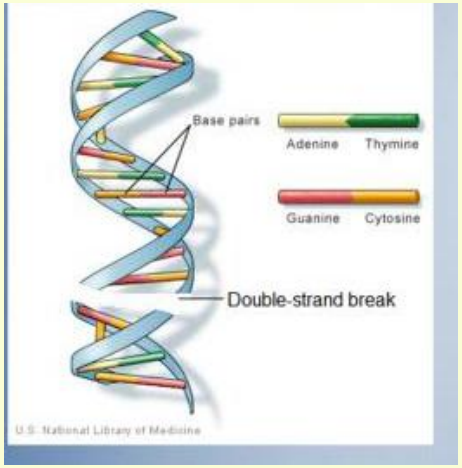
Most DNA damage is repaired , with no long-term effects

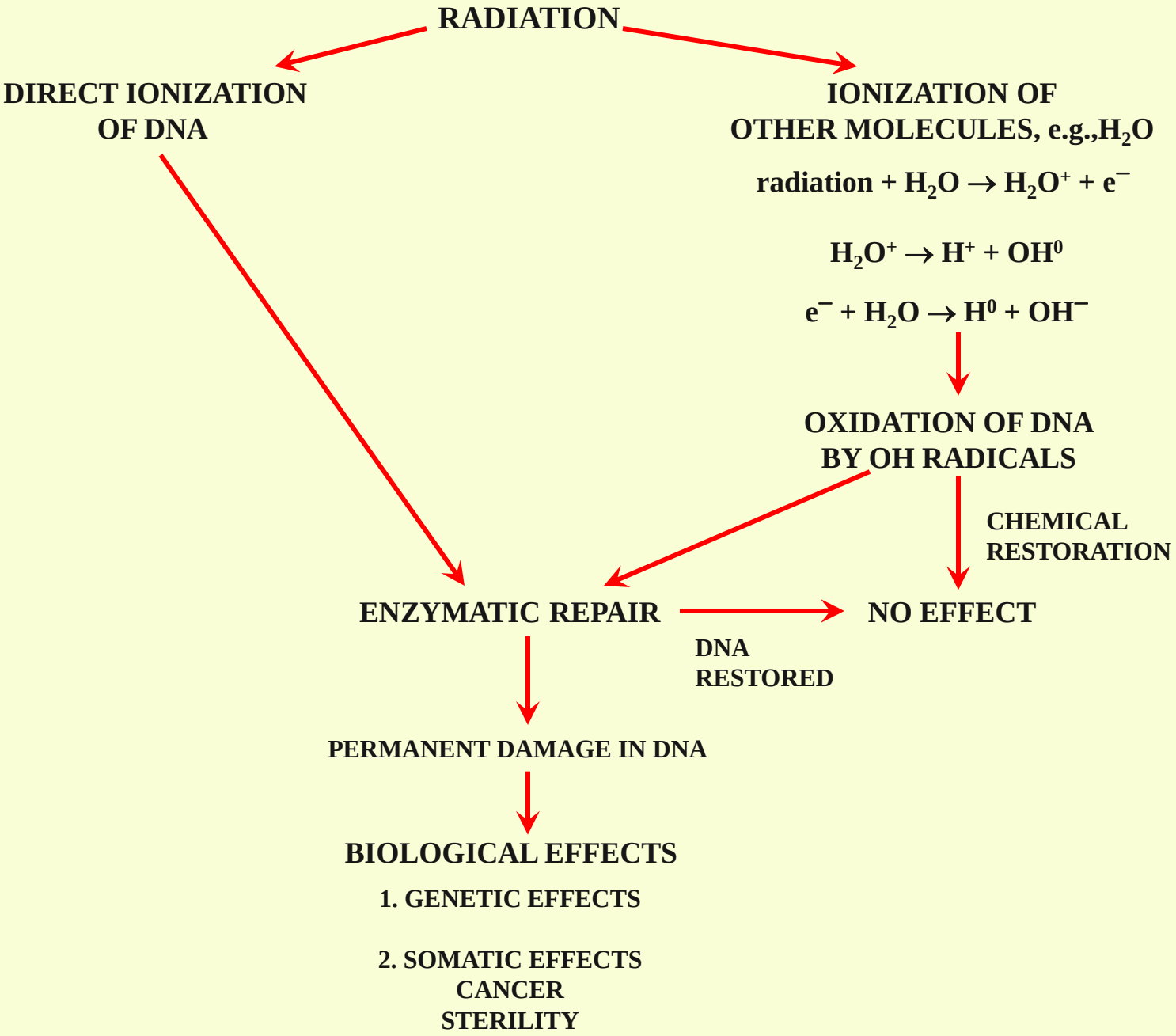
- Double-stand breaks

-No as easily repaired , more potential for long-term damage

- Comparatively rare






RADIATION
DIRECT IONIZATION OF DNA
IONIZATION OF OTHER MOLECULES, e.g.,H_2O
radiation + $H_2O \rightarrow H_2O^+ + e^-$
$H_2O^+ \rightarrow H^+ + OH^0$
$e^- + H_2O \rightarrow H^0 + OH^-$
OXIDATION OF DNA BY OH RADICALS
CHEMICAL RESTORATION
ENZYMATIC REPAIR
NO EFFECT
DNA RESTORED
PERMANENT DAMAGE IN DNA
BIOLOGICAL EFFECTS
1. GENETIC EFFECTS
2. SOMATIC EFFECTS
CANCER
STERILITY

Possible Effects to cells

Four things can happen when radiation enters a cell:

1. The radiation may pass through without any damage occurring;
2. The radiation may damage the cell, but the cell repairs the damage;
3. The radiation may damage the cell…the damage is not repaired…and the cell replicates itself in the damaged form;
4. The cell dies.

Damage from radiation exposure

There are two types of radiation health effect; acute disorder and late on-set disorder (Chronic). Acute disorder is a deterministic effect that the symptoms appear by exposure above a threshold. Tissues and cells that compose the human body have different radiation sensitivity respectively, and the symptoms appear in order, from highly radiosensitive tissues

Acute

- High dose in short time
- Local : Burns, hair loss , desquamation (Etching) , blistering , damage to blood vessels , sterility , cataracts
- Whole –body: reduction in blood cell counts , nausea , radiation sickness

OR

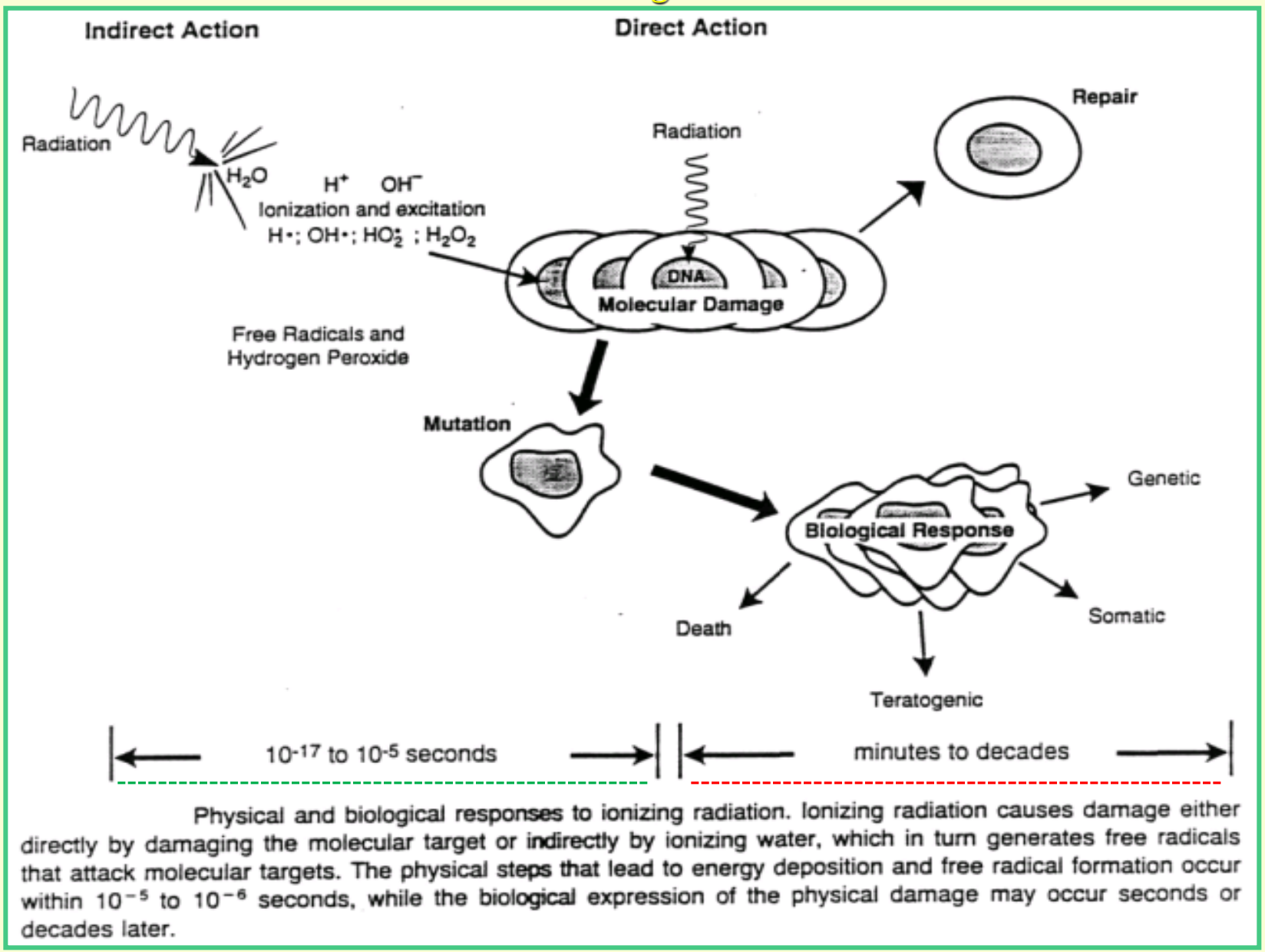
Chronic

- Low dose over long period of time
- Cancer , anemia , cataracts

Table 1: Acute Radiation Syndrome

Dose	**100-200 rad**	**200-400 rad**	**400-600 rad**	**600-1000 rad**	**> 1000 rad**
Latent Period	> 30 days	18-28 days	8-18 days	< 7 days	3-5 days
Symptoms	Fatigue, weakness	Fever, infections, bleeding, weakness, hair loss	High fever, infections, bleeding, hair loss	High fever, diarrhea, vomiting, dizziness, low blood pressure	Nausea, vomiting, prolonged diarrhea, lethargy
Lethality	0%	0-50%	20-70%	50-100%	100%

The time scales for the short and long term effects of radiation are symbolized in the figure



Physical and biological responses to ionizing radiation. Ionizing radiation causes damage either directly by damaging the molecular target or indirectly by ionizing water, which in turn generates free radicals that attack molecular targets. The physical steps that lead to energy deposition and free radical formation occur within 10^{-5} to 10^{-6} seconds, while the biological expression of the physical damage may occur seconds or decades later.

Time Frame for Effects of Ionizing Radiation

Times	Events
Physical stage $\leq 10^{-15}$ s	Formation of H_2O^+, H_2O^*, and subexcitation electrons, e^-, in local track regions (≤ 0.1 μm)
Prechemical stage $\sim 10^{-15}$ s to $\sim 10^{-12}$ s	Three initial species replaced by H_3O^+, OH, e^-_{aq}, H, and H_2
Chemical stage $\sim 10^{-12}$ s to $\sim 10^{-6}$ s	The four species H_3O^+, OH, e^-_{aq}, and H diffuse and either react with one another or become widely separated. Intratrack reactions essentially complete by $\sim 10^{-6}$ s
Biological stages	
$\leq 10^{-3}$ s	Radical reactions with biological molecules complete
≤ 1 s	Biochemical changes
Minutes	Cell division affected
Days	Gastrointestinal and central nervous system changes
Weeks	Lung fibrosis develops
Years	Cataracts and cancer may appear; genetic effects in offspring

Determinations of Biological Effects

- Rate of Absorption
- Area exposed
- Variations in species and individual sensitivity
- Variations in cell sensitivity

Rate of Absorption

The rate at which the radiation is administered or absorbed is most important in the determination of what effects will occur. Since a considerable degree of recovery occurs from the radiation damage, a given dose will produce less effect if divided than if it were given in a single exposure.

Area Exposed

The portion of the body irradiated is an important exposure parameter because the larger the area exposed, other factors being equal, the greater the overall damage to the organism. This is because more cells have been impacted and there is a greater probability of affecting large portions of tissues or organs. Even partial shielding of the highly radiosensitive blood-forming organs such as the spleen and bone marrow can mitigate the total effect considerably.

Variation in Species and Individual Sensitivity

There is a wide variation in the radiosensitivity of various species. Lethal doses for plants and microorganisms, for example, are usually hundreds of times larger than those for mammals. Even among different species of rodents, it is not unusual for one to demonstrate three or four times the sensitivity of another.

Within the same species, individuals vary in sensitivity. For this reason the lethal dose for each species is expressed in statistical terms, usually for animals as the LD50/30 for that species, or the dose required to kill 50 percent of the individuals in a large population in a thirty day period. For humans, the LD50/60 (the dose required to kill 50 percent of the population in 60 days) is used because of the longer latent period in humans (see section V). The LD50/60 for humans is estimated to be approximately 300-400 rad for whole body irradiation, assuming no treatment is given. It can be as high as 800 rad with adequate medical care. It is interesting to note that the guinea pig has a LD50 similar to humans.

Cell sensitivity

Most sensitive cells are

- **Hematopoietic cells :** Hematopoiesis is the process by which blood cells are produced. Hematopoietic stem cells (HSC) are generally found in the bone marrow, where they self-renew and begin their journey of differentiating into all the different blood cell types)
- **White blood cells (Lymphocytes)** :A lymphocyte is a type of white blood cell that is part of the immune system. There are two main types of lymphocytes: B cells and T cells. The B cells produce antibodies that are used to attack invading bacteria, viruses, and toxins. The T cells destroy the body's own cells that have themselves been taken over by viruses or become cancerous.
- **Red Blood Cells:** The blood cells that carry oxygen. Red cells contain hemoglobin and it is the hemoglobin which permits them to transport oxygen (and carbon dioxide). Hemoglobin, aside from being a transport molecule, is a pigment. It gives the cells their red color . Red blood cells are sometime simply called red cells. They are also called erythrocytes or, rarely today, red blood corpuscles.
- **Epithelial cells (intestinal tract, skin):** Epithelial cells are a type of cell that lines the surfaces of your body. They are found on your skin, blood vessels, urinary tract, and organs. An epithelial cells in urine test looks at urine under a microscope to see if the number of your epithelial cells is in the normal range. It's normal to have a small amount of epithelial cells in your urine. A large amount may indicate an infection, kidney disease, or other serious medical condition.
- **Muscle cells:** Muscle cells, commonly known as myocytes, are the cells that make up muscle tissue. There are 3 types of muscle cells in the human body; cardiac, skeletal, and smooth.

Least sensitive cells

- **Nerve cells :** Neurons are nerve cells, or cells found in the nervous system. These are specialized cells designed to stimulate other cells in the body in order to communicate. Neurons are **excitable**, which means they function by using electrical stimulation. Through this electrical message, known as an **action potential**, neurons are able to initiate action in the cells they target.

Variation in Cell Sensitivity

Within the same individual, a wide variation in susceptibility to radiation damage exists among different types of cells and tissues. In general, those cells which are rapidly dividing or have a potential for rapid division are more sensitive than those which do not divide. Further, cells which are non-differentiated (i.e., primitive, or non-specialized) are more sensitive than those which are highly specialized. Within the same cell families, then, the immature forms, which are generally primitive and rapidly dividing, are more radiosensitive than the older, mature cells which have specialized in function and have ceased to divide. This radiosensitivity is defined as the "Law of Bergoniè and Tribondeau". One exception to this law is mature lymphocytes, which are highly radiosensitive.

Cell sensitivity

The degree of cell sensitivity is directly related to the reproductive capacity of cells and tissues , thus stem cells (germ cells) are more radiosensitive than mature differentiated cells

Law of Bergonie and Tribondeau

Radiosensitivity is:

Directly proportional to growth rate

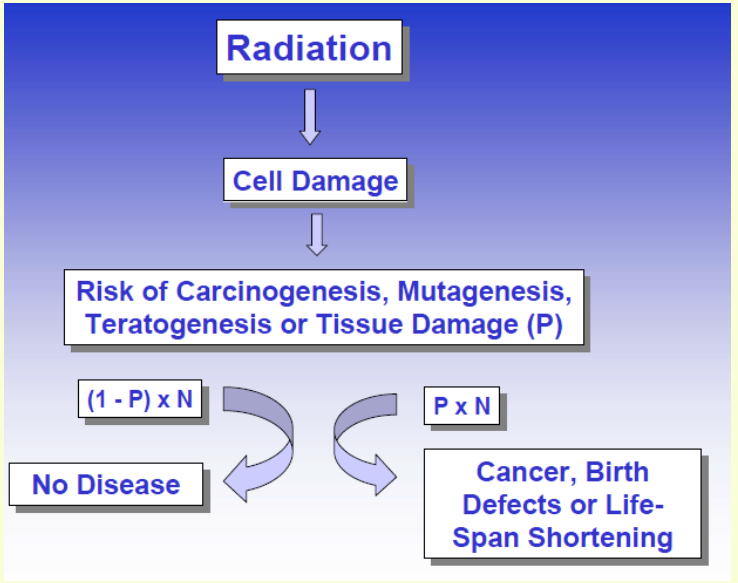
Indirectly proportional to degree of specialization

In general the law is

(A fundamental law of radiation biology that states that the radiosensitivity of a tissue is increased the greater the number of undifferentiated cells in the tissue, the greater the mitotic activity, and the greater the length of time that they are actively proliferating.)

Damage to the Organism

• Interactions of radiation with living material may result in damage at the molecular or cellular levels.
• May be a result of mutation or cell death.
• Translates into disease in the organism or its offspring



Factors Related to Risk of Disease ("P")

- • Magnitude of Radiation Dose
- • Type of Radiation ("Quality Factor")
- • Duration of Accumulation Period and Ability to Repair Damaged DNA
- • Sensitivity of Specific Tissues
- • Stochastic versus "Dose-Related" Effects

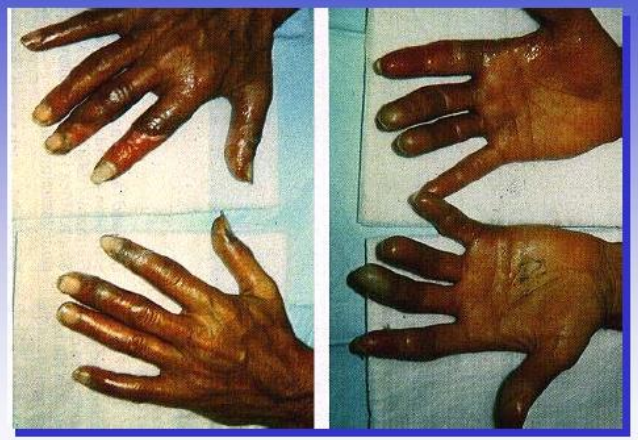
Deterministic versus Stochastic Effects

- Deterministic (Non-stochastic): Severity (intensity) is dose-related, and there is a threshold below which effect is not seen. Tend to occur at whole-body doses 100 rem.
- Stochastic: Probability of occurrence is dose-related. Type or severity of effect is not related to dose. No threshold is assumed for stochastic effects but are documented only at doses > 10 rem.

Examples of Deterministic and Stochastic Effects

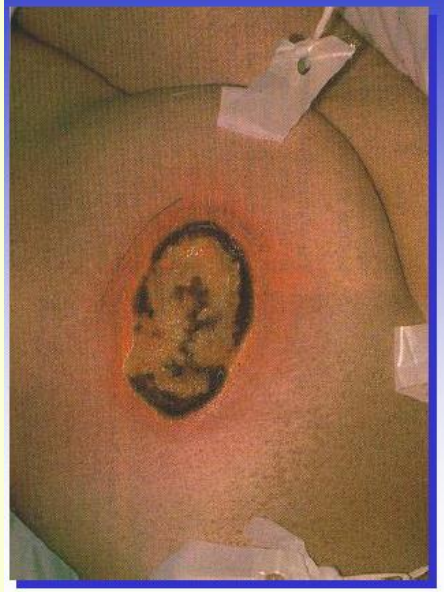
• Deterministic: erythema, cataracts, decreased sperm count, bone marrow depression, GI symptoms.
• Stochastic: life-shortening, cancer induction, mutagenesis.

Skin Injuries

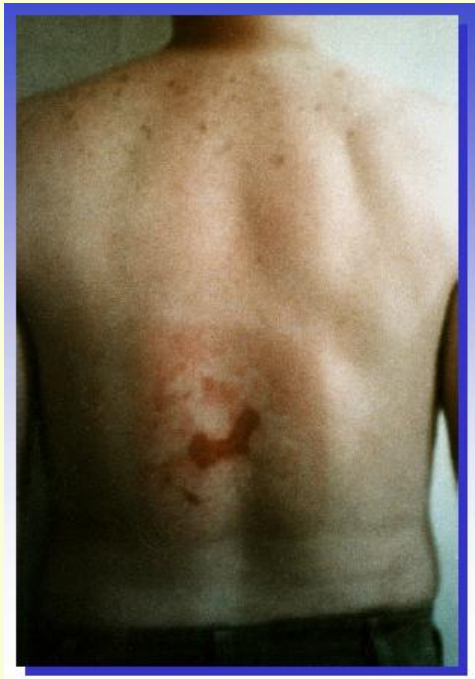


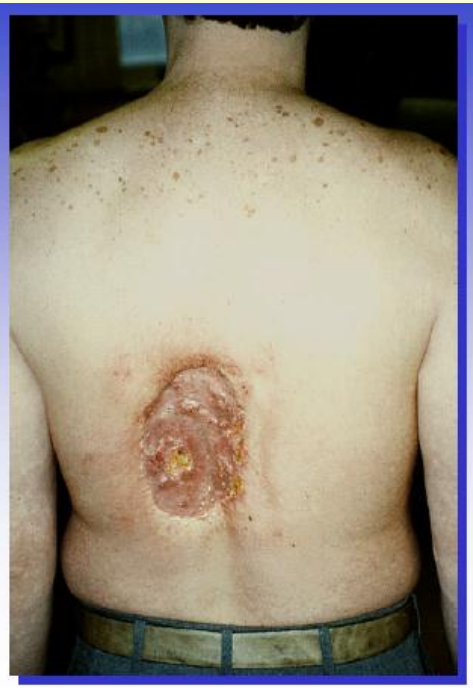
"Radiation burns" of hands secondary to inadvertent handling of an industrial radiography source.

Skin Injuries



Extensive necrosis of skin and underlying soft tissues in an individual who carried an iridium-192 industrial radiography source in his back pocket for several days.





THE DOSE-RESPONSE CURVE

For any biologically harmful agent, it is useful to correlate the dosage administered with the response or damage produced, in order to establish acceptable levels of exposure. "Amount of damage" in the case of radiation might be the frequency of a given abnormality in the cells of an irradiated animal, or the incidence of some chronic disease in an irradiated human population. In plotting these two variables, a dose-response curve is produced. With radiation, an important question has been the nature and shape of this curve. Two possibilities are illustrated in Figures 2a and 2b.

Figure 2a represents a typical "threshold" curve. The point at which the curve intersects the abscissa is the threshold dose, i.e., the dose below which there is no response. If an easily observable radiation effect, such as reddening of the skin, is taken as a "response," then this type of curve is applicable. The first evidence of the effect does not occur until a certain minimum dose is reached, although unobserved effects may exist.

Figure 2b represents a linear, non-threshold relationship, in which the curve intersects the abscissa at the origin. Here it is assumed that any dose, no matter how small, involves some degree of response. There is some evidence that the carcinogenic effects of radiation constitute a non-threshold phenomenon, so one of the underlying (and prudent) assumptions in the establishment of radiation protection guidelines has been the existence of a non-threshold effect. Thus, some degree of risk is assumed when large populations of people are exposed to even very small amounts of radiation. This assumption often makes the establishment of guidelines for acceptable radiation exposure a complex task, since the concept of "acceptable risk" comes into play, in which the benefit to be accrued from a given radiation exposure must be weighed against its hazard.

Figure 2(a)

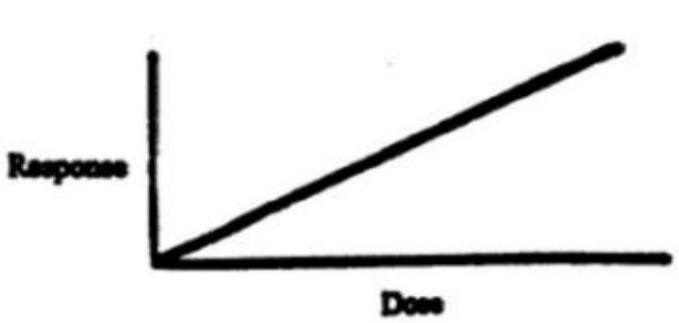


Figure 2(b)

Types of Radiation Interactions with tissue

Charged Particle Interactions

Charged particles interact with the tissue through electrostatic interactions. These interactions result in slowing of the charged particle and a loss of kinetic energy (KE). The lost energy is transferred to the surrounding tissue by excitation and ionization.

Ionization occurs when a charged particle removes an orbital electron from an atom. The result of ionization is a free electron and a positively charged ion. The negative electron and positive ionized atom are called an ion pair. For air and tissue, the average energy per ion pair is approximately 34 eV. Roughly, a third of this energy goes into removing the electron from the atom, and the rest goes into excitation and KE. Ionization in water and organic material is very important in radiation biology due to the formation of free radicals, which is an important cause of radiation damage.

The electrostatic interaction of a charged particle is proportional to the charge of the particle. Particles with multiple charges such as alpha particles (+2 charge) have stronger electrostatic interactions with the medium than singly charged particles such as electrons (−1 charge). As a result, alpha particles lose energy more rapidly in matter than do electrons.

Another mechanism of energy loss by charged particles is radiative emission. In this case, a charged particle interacts with the electromagnetic (EM) field of an atom and the resulting electrostatic force changes the direction of the charged particle. This abrupt change in direction results in the emission of EM energy. The emitted photons are referred to as “bremsstrahlung,” a German word for “braking radiation.” Bremsstrahlung emission is only of importance for light charged particles, namely electrons and positrons, which are readily deflected from a straight path.

EM Radiation Interactions

X-rays and gamma rays are high-energy EM radiations with zero mass and zero electrical charge. The basic unit or "packet" of EM radiation is the photon. High-energy photons have higher frequencies and shorter wavelengths, and they penetrate more deeply in tissue than low-energy photons.

Ionizing photons have three main interaction mechanisms—

(1) the photoelectric effect,

(2) Compton scattering, and

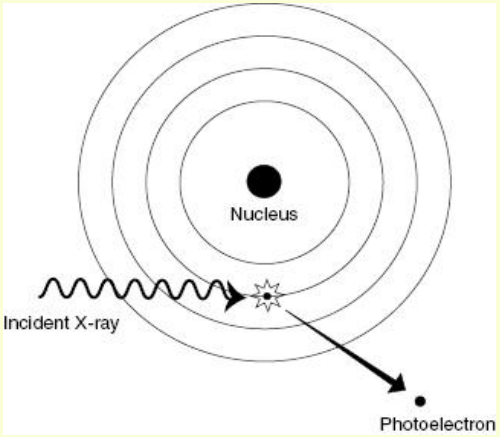
(3) pair production—each of which is prevalent over a different energy range.

The photoelectric interaction and Compton scattering are dominant for the lower energies used in diagnostic imaging. The total likelihood of a photon interacting with a medium *decreases* with increasing photon energy.

(1) The photoelectric effect is the dominant process at low photon energies (tens of electron volts up to 100 keV). In a photoelectric interaction, the incident photon is completely absorbed by the atom, and the photon energy is transferred to an orbital electron. For the photoelectric interaction to occur, the orbital electron must have a binding energy (BE) that is less than the energy of the photon. The atom is ionized when this electron, which gains enough energy from the photon to overcome its BE, is ejected from the atom. The ejected electron is called a photoelectron. Thus, the photoelectron's KE differs from the photon energy by its BE: $KE_e = E_{ph} - BE_e$.

The net result of the photoelectric effect is the complete absorption of the incident X-ray and the ejection of a photoelectron

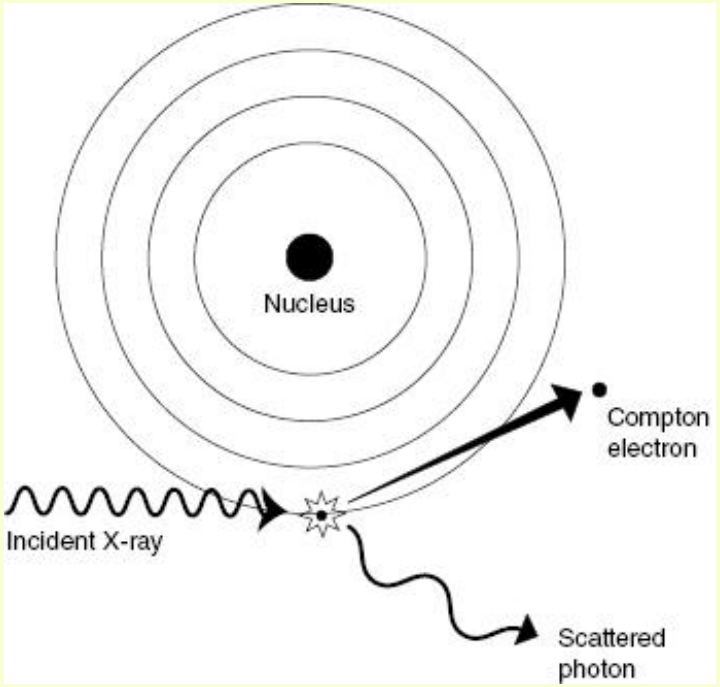
At energies encountered in diagnostic imaging, the photoelectron travels less than a few millimeters in tissue. If an inner shell electron is ejected, then an outer shell electron will fill the inner shell vacancy. The inner shell has a stronger BE, and the excess energy is usually released as a characteristic X-ray. Characteristic X-rays from tissue elements (i.e., carbon, nitrogen, and oxygen) have very low energies and do not exit the patient because of their low energies.



2)Compton Scattering

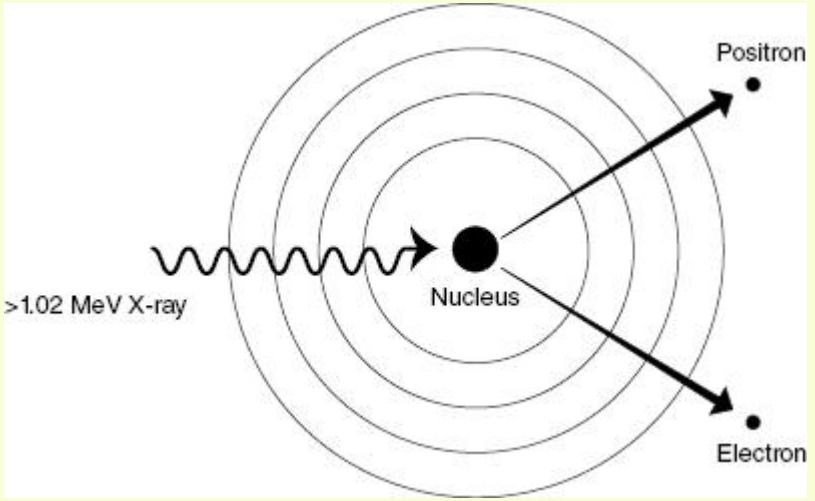
The Compton interaction typically involves an interaction between an incident photon and an outer shell electron, resulting in a scattered photon and a scattered electron. The incident photon loses a portion of its energy in the collision and changes direction (which causes blurring of diagnostic X-ray images). Outer shells of an atom are lightly bound, so removal of the electron from the atom does not require much energy. The incident photon energy is shared between the scattered photon and the scattered electron. Compton scattering is the dominant process at intermediate photon energies (100 keV to 10 MeV).

Unlike the photoelectric effect, Compton scattering results in a recoil electron and a scattered photon, both of which are capable of producing further ionization. Recall that the net result of the photoelectric interaction is complete absorption of the photon and emission of an energetic electron. The major contribution of the Compton interaction in medical imaging is an increase in patient dose and loss of contrast in the image.

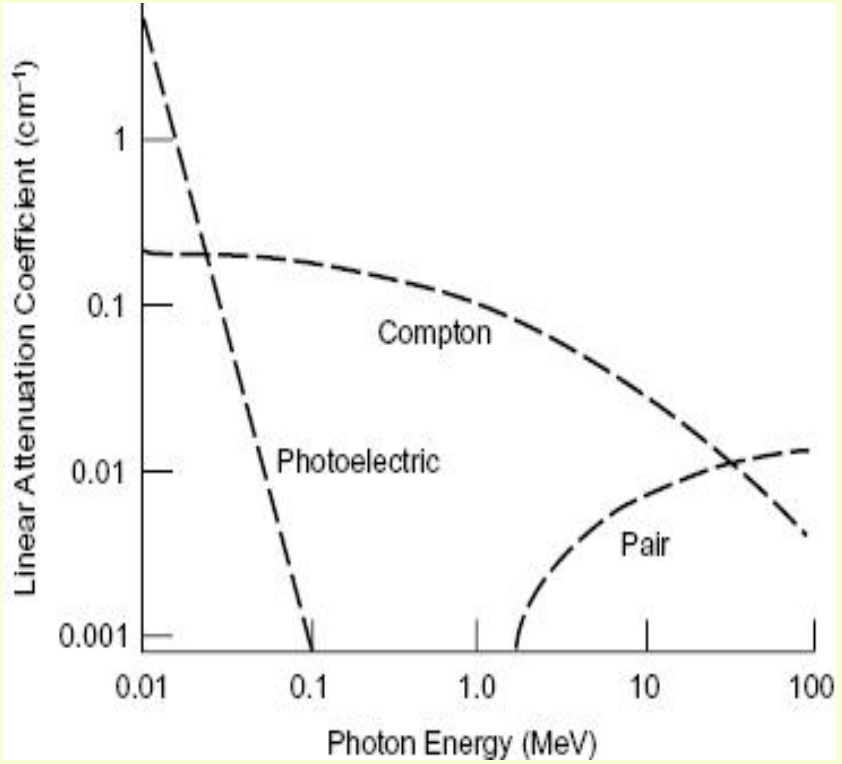


3)Pair Production

Pair production occurs when the incident photon interacts with a nearby nucleus, creating an electron–positron pair. A positron is the antiparticle of the electron. The positron has the same mass as an electron but opposite charge. From Einstein's equation for mass–energy equivalence ($E = mc^2$), the mass of an electron or positron is equivalent to an energy of 0.511 MeV. For pair production to occur, the incident photon must therefore have an energy of at least 1.022 MeV, because the mass of the electron–positron pair is formed from the incident photon energy. Any energy above the threshold is shared as KE between the electron–positron pair.



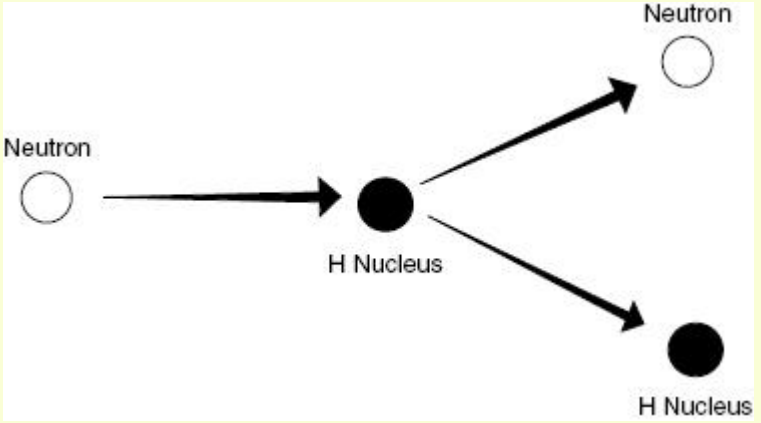
The photoelectric effect and Compton scattering are the most important modes of interaction for photons in the diagnostic energy range. As summarized in this figure below approximately 100 keV, the photoelectric effect is the most frequent mode of interaction between photons and tissue. Compton scattering is the dominant mode of interaction in the 100 keV to 10 MeV range. Above approximately 10 MeV, pair production becomes the most common mode of interaction for photons in tissue. It is important to keep in mind that in all three processes, energy is transferred from a photon to electrons.



Neutrons

Neutrons are indirectly ionizing particles that cannot interact by the Coulomb force due to their neutral charge. Instead, neutrons lose energy by collisions that transfer KE to the tissue.

Neutron interactions are complex and depend on the neutron KE. A discussion of all types of neutron interactions is beyond the scope of this book. The majority of the energy lost by neutrons in a hydrogen-containing medium (such as living tissue) is through collisions with hydrogen nuclei producing recoil protons. These energetic protons, like energetic electrons, then go on to damage biological systems via ionization of atoms/molecules along the particle path. The figure shows how an uncharged neutron can transfer energy through a collision with a charged nucleus producing subsequent ionizations.



Specific Ionization

For charged particles, we can define the specific ionization as the number of ion pairs formed per unit path length. Alpha particles can produce several thousand ion pairs per millimeter. For beta particles (electrons), the specific ionization is 50–100 ion pairs per millimeter. Energetic neutral particles, such as neutrons and photons, can liberate charged particles (e.g., protons, electrons) for which the specific ionization can then be defined. Specific ionization differs for different materials and tissues.

Linear Energy Transfer (LET)

LET is the energy transferred by radiation per unit path length in soft tissue. LET is the product of the average energy transferred per ion pair and the specific ionization (number of ion pairs per unit length). LET is usually expressed in units of keV/μm. The specific ionization (ion pairs per path length) is greatest for heavy charged particles such as the alphas. Alphas leave a densely (thickly) ionized particle track (high specific ionization) *and* deposit a relatively large amount of energy per unit length. Alphas and neutrons (which produce recoil protons) are considered high-LET radiations. On the other hand, betas and photons (which liberate electrons) leave a sparsely ionized particle track. The amount of energy deposited per unit path length is relatively low, so beta particles and X-rays/gamma rays are considered low-LET radiations.

Although photons do not carry charge, they set electrons in motion and thus produce ionization. Once a photon transfers energy to an electron, the LET is that of electrons. Likewise, neutrons do not carry charge, but they set protons in motion. The LET for neutrons is therefore similar to that of protons.

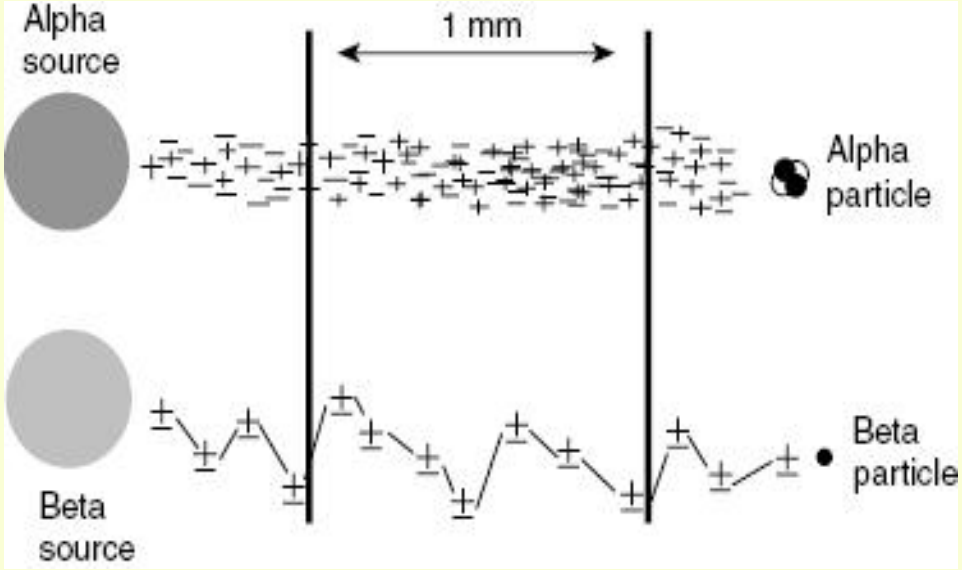
The LET depends on the type of radiation and its energy. Lower-energy particles interact more strongly and have a higher LET, compared with higher-energy particles of the same type.

The total deposited energy divided by the length of the "track" is the linear energy transfer of the radiation, or LET.

Path and Range of Charged Particles

Charged particles undergo electrostatic interactions, attractive or repulsive, that may deflect the particle from a straight path. Charged particles with low mass such as the electron are easily deflected. The *path* of an electron is therefore a series of random scatters that appears as a contorted (screw) path as shown in the following figure . Heavy charged particles, such as alphas, which are over 7000 times more massive than an electron and have twice the charge, are not as easily deflected. These particles tend to take relatively straight paths as they lose energy in matter. The path length of a particle is a measure of the actual distance that the particle has traveled, not the distance "as the crow flies."

As particles slow, the rate of energy transfer increases. Heavy ions therefore exhaust most of their KE at the end of the particle track



SRIM - The Stopping and Range of Ions in Matter (Software) (http://www.srim.org)

SRIM is a collection of software packages which calculate many features of the transport of ions in matter. Typical applications include:

· *Ion Stopping and Range in Targets:* Most aspects of the energy loss of ions in matter are calculated in *SRIM,* the *S*topping and *R*ange of *I*ons in *M*atter. SRIM includes quick calculations which produce tables of stopping powers, range and straggling distributions for any ion at any energy in any elemental target. More elaborate calculations include targets with complex multi-layer configurations.

· *Ion Implantation*: Ion beams are used to modify samples by injecting atoms to change the target chemical and electronic properties. The ion beam also causes damage to solid targets by atom displacement. Most of the kinetic effect s associated with the physics of this kind of interactions are found in the *SRIM* package.

· *Sputtering:* The ion beam may knock out target atoms, a process called *ion sputtering*. The calculation of sputtering, by any ion at any energy, is included in the *SRIM* package.

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Ion Transmission: Ion beams can be followed through mixed gas/solid target layers, such as occurs in ionization chambers or in energy degrader blocks used to reduce ion beam energies.

· Ion Beam Therapy: Ion beams are widely used in medical therapy, especially in radiation oncology. Typical applications are included.