1. Radiation Units

The biological effect of radiation can be understood in terms of the transfer of energy from the radiation (photons and particles) to the tissue. When the energy of radiation is deposited in the body, it can disrupt the chemical bonds and alter tissue. It is important to understand some of the details of this transfer. The radiation dose depends on the intensity, energy and type of the radiation, the exposure time, the area exposed and the depth of energy deposition. Various quantities such as the absorbed dose, the equivalent dose and the effective dose are used to specify the dose received and the biological effectiveness of that dose.

1.1 Absorbed Dose

The absorbed dose (D) is defined as the energy (E) imparted by ionizing radiation per unit mass of irradiated material (m):

$$D = E/m$$

Absorbed dose is defined for all types of ionizing radiation. The unit of radiation absorbed dose is gray (Gy). 1Gy is defined as the deposition of 1 joule of energy of ionizing radiation in one kilogram of matter (1 Gy = 1 $J.kg^{-1}$).

The biological effect of radiation is not directly proportional to the energy deposited by radiation in an organism. It depends, in addition, on the way in which the energy is deposited along the path of the radiation, and this in turn depends on the type of radiation and its energy. Thus the biological effect of the radiation increases with the linear energy transfer, LET [Kev/ μm]. The LET of radiation is defined as the mean energy loss per unit track length in the absorbing material. Thus for the same absorbed dose, the dense ionization tracks of high LET radiation (alpha particles, protons or neutrons) deposit their energy over a much shorter range and are much more damaging to cells than the spare ionization pattern associated with low LET radiation (X-ray, gamma, beta rays).

1.2 Equivalent Dose

The equivalent dose (H_T) is used to express the damage done in biological systems from different types of radiation. It is defined in terms of the absorbed dose multiplied by radiation weighting factor, which depends on the type and energy of radiation:

$$H_T = w_R \, . \, D_T$$

where D_T is the absorbed dose in tissue T and w_R is the radiation weighting factor.

The SI unit for equivalent dose is joule per kilogram with the special name of the sievert (Sv), where 1 Sv = 1 $J.kg^{-1}$. **The radiation weighting factor w_R** (see in Table 1) is a number that takes into account the nature of the radiation and the severity of the biological damages it causes.

Radiation used in diagnostic imaging (x-rays and gamma rays) as well as electrons of all energies have w_R =1, thus, the equivalent doses are numerically identical to the absorbed doses, though the two have different units. For heavy charged particles such as alpha particles, the LET is much higher, and thus, the biologic damage and the associated w_R are much greater. For example, 10 mGy from alpha radiation may have the same biological effectiveness as 200 mGy of x-rays.

Table 1: Radiation weighting factors (w_R)

Radiation	w_R
photons (gamma, X-ray)	1
electrons (all energies)	1
protons	5
α, fusion products	20

1.3 Effective Dose

Biological tissues vary in sensitivity to the effects of ionizing radiation. The thyroid, for example, is much less sensitive than bone marrow. Due to the fact that tissues have different sensitivitiies to radiation, the effective dose (E) is defiend as the sum of the equivalent dose to each tissue irradiated (H_T) and the corresponding tissue weighting factor (w_T, see Table 2):

$$E = \sum H_T \, . \, w_T$$

The effective dose is expressed in the same units as the equivalent dose - sievert (Sv).

Table 2: Tissue weighting factors (w_T)

Radiation	w_T
Bone-marrow (red), colon, lung, stomach, breast	0.12
Gonads	0.08
Bladder, oesophagus, liver, thyroid	0.04
Bone surface, brain, salivary glands, skin	0.01
Remaining tissues(*)	0.12

(*) Remaining tissues: Adrenals, extrathoracic region, gall bladder, heart, kidneys, lymphatic nodes, muscle, oral mucosa, pancreas, prostate, small intestine, spleen, thymus, uterus/cervix.

In terms of the levels of radiation exposure encountered in the working environment, the gray and the sievert are very large units. It is often convenient to use smaller units, and this is done by using the prefixes milli (one-thousandth), abbreviated to m, and micro (one-millionth), abbreviated to μ. Thus:

1 Gy = 1 000 mGy = 1 000 000 μGy

1 Sv = 1 000 mSv = 1 000 000 μSv

NOTE:

Living cell can be classified according to their rate of reproduction, which also indicates their relative sensitivity to radiation. This means that different cell systems have different sensitivities. Lymphocytes (white blood cells) and cells which produce blood are constantly regenerating, and are therefore, the most sensitive. Reproductive and gastrointestinal cells are not regenerating as quickly

and are less sensitive. The nerve and the muscle cells are the slowest to regenerate and are the least sensitive cells. The sensitivity of the various organ of the human body correlate with the relative sensitivity of the cells from which they are composed. For example, since the blood forming cells were one of the most sensitive cells due to their rapid regeneration rate, the blood forming organs are one of the most sensitive organs to radiation. Muscle and nerve cells were relatively insensitive to radiation, and therefore, so are the muscles and the brain.

2. Molecular effects of radiation

All biological damage effects begin with the consequence of radiation interactions with the atoms forming the cells. Ionizing radiation interacts with atoms by a process called **ionization**.

There are two mechanisms by which radiation ultimately affects cells. These two mechanism are commonly called **direct** and **indirect** effects.

2.1 Direct effect

If radiation interacts with the atoms of the DNA molecule or some other cellular component critical to the survival of the cell, it is referred to as a **direct effect**. If a cell is exposed to radiation, the probability of the radiation interacting with the DNA molecule is very small since these critical components make up such a small part of the cell. On the other hand, approximately 70% of the cell consists of water molecules. This gives rise to the second and more common mode of radiation-induced DNA damage, indirect effect.

2.2 Indirect effect

Indirect effect results from a chemical reaction between the DNA molecule and one of the products of the radiolysis of water – free radicals. When radiation interacts with water, it may break the bonds that hold the water molecule together, producing fragments such as hydrogen (H) and hydroxyls (OH). These fragments may recombine or may interact with other fragments or ions to form compounds, such as water, which would not harm the cell. However, they could combine to form toxic substances, such as hydrogen peroxide (H_2O_2), which can contribute to the destruction of the cell.

Indirect action is predominant with low LET radiation (X-rays, gamma rays, electrons) while direct action is predominant with high LET radiation (α particles, protons and neutrons).

NOTE:

A free radical is an atom or molecule that has no electrical charge but is highly reactive because it has an odd number of electrons with an unpaired electron in its outer shell. Free radicals tend to quickly recombine to form stable electron configurations. However, in high enough concentrations in the cell, they can create organic free radicals (R) and H_2O_2* (hydrogen peroxide), a toxic molecule. Organic free radicals in DNA lead to breakage of the strands and cross-linking. OH*, since it oxidizes (remove electrons), is more damaging than H*, which is a reducing agent (gives up its electron).*

2.3 DNA damage and repair

Radiation exposure produces a wide range of lesions in DNA such as single strand breaks (SSBs), double strand breaks (DSBs), base damage, protein–DNA cross-links and protein–protein cross-links. Repair of radiation damage occurs at molecular, cellular, and tissue levels. A complex series of enzymes and cofactors repair most radiation-induced DNA lesions within hours and, to the extent possible, damaged cells are often replaced within days following irradiation. As a result, not all radiation effects are irreversible. In many instances, the cells are able to completely repair any damage and function normally.

If the damage is severe enough, the affected cell dies. In some instances, the cell is damaged but is still able to reproduce. The daughter cell, however, may be lacking in some critical life-sustaining component, and they die.

The other possible result of radiation exposure is that the cell is affected in such a way that it does not die but is simply mutated. The mutated cell reproduces and thus perpetuates the mutation. This could be the beginning of a malignant tumor.

2.4 Chromosomal Aberrations

Direct evidence that ionizing radiation can damage DNA comes from well-documented information on chromosomal aberrations. When samples of human peripheral blood are cultured in such a way that the lymphocytes are stimulated into cell division and chromosome spreads are prepared during mitosis, a variety of abnormalities are observed if the blood has been irradiated. The induction of chromosomal changes in human lymphocytes by radiation has been studied at doses below 100 mGy.

3. Deterministic and Stochastic Effects

Biological effects of radiation exposure can be classified as either stochastic or deterministic.

3.1 Deterministic effects

3.1.1 Characteristics of deterministic effects

Deterministic (also called non-stochastic) effects:

- Show a well-defined dose threshold, below which, the effect does not occur. On the other hand above this threshold, radiation damage can be expected in all exposed individuals. The dose threshold is dependent on the deterministic effect studied. For instance, the dose threshold for skin erythema is 3-5 Gy while for skin necrosis about 50 Gy.
- The severity of the damage will increase non-linearly as the dose of exposure increases.
- The time between radiation exposure and the initiation of deterministic effects generally is measured in hours to days.

Deterministic effects can be caused by severe radiation accidents and can be observed in healthy tissue that is unavoidably irradiated during radiation therapy. However, with the exception of some

lengthy, fluoroscopically guided interventional procedures, they are unlikely to occur as a result of routine diagnostic imaging procedures.

For deterministic effect radiation protection principles are straightforward. All doses must be kept well below any threshold at which such effects might occur.

3.1.2 Acute Radiation Syndromes

When the whole body (or large portion of the body) is exposed to a high acute radiation dose (> 1 Gy), there are a series of characteristic clinical responses known collectively as the acute radiation syndrome (ARS). The ARS referes to a group of syndromes occurring in stages over a period of hours to weeks after the exposure as the injury to various tissues and organ systems is expressed. These syndromes result from the differing radiosensitivities of these organ system. In order of their occurrence with increasing radiation dose, the ARS is divided into the **hematopoietic**, **gastrointestinal** and **neurovascular** syndromes.

The ARS is characterised by four distinct phases:

- The **prodromal period** includes nonspecific clinical symptoms, such as nausea, vomiting and easy fatigability (hematological changes may also occur during this period). The greater the dose the shorter the duration of the prodromal stage, the more severe the symptoms.
- During the **latent period** the prodomal sypmtoms typically subside.
- **Manifest illness** is marked by symptoms related to the involved organ (see syndromes listed below).
- The **recovery phase** may extend from weeks to years if the radiation dose is not acutely lethal.

The overall duration of these stages is dependent on the dose the patient received.

Depending on dose, the following syndromes can be manifest:

- **Hematopoietic syndrome (or Bone marrow syndrome):** the full syndrome will usually occur with the dose between 0.5 and 10 Gy. The prodromal symptoms consist of nausea, vomiting, diarrhea, headache, fever. During the latent period of 2–3 weeks, the patient will feel relatively well, but the number of circulating red blood cells, white blood cells and platelets will be steadily decreasing. Following the latent phase, the manifest illness is characterized by infection and hemorrhage. In most cases, bone marrow cells will begin to repopulate the marrow. Healthy adults with proper medical care almost always recover from doses lower than 2 Gy, whereas doses greater than 8 Gy are almost always fatal unless advanced therapies such as bone marrow transplatation are successful. In the abscence of medical care, the human $LD_{50/60}$ (the dose that would be expected to kill 50% of an exposed population within 60 days) is approximately 3,5 – 4,5 Gy to the bone marrow. The $LD_{50/60}$ may extend to 5 to 6 Gy with supportive care such as the use of transfusions and antibiotics an may be as high as 6 to 8 Gy with effective use of hematopoietic growth factors in an intensive care setting.
- **Gastrointestinal (GI) syndrome:** the full syndrome will usually occur with a dose greater than approximately 10 Gy although some symptoms may occur as low as 6 Gy. Survival is extremely unlikely with this syndrome. Destructive and irreparable changes in the GI tract and bone marrow usually cause infection, dehydration, electrolyte imbalance and sepsis. Death usually occurs within 2 weeks.

- **Cardiovascular (CV)/ Central Nervous System (CNS) syndrome:** the full syndrome will usually occur with the dose greater than approximately 30-50 Gy. The patient will suffer nearly immediate nausea, vomiting, hypotension, ataxia, convulsions and loss of consciousness. There is an abbreviated latent period (4 to 6 hours), during which some improvement is noted, followed by a severe manifest illness stage. Death occurs within 3 days. Death likely is due to collapse of the circulatory system as well as increased pressure in the confining cranial vault as the result of increased fluid content caused by edema, vasculitis and meningitis.

3.1.3 Local Radiation Injury to the Skin

The reaction of skin to ionizing radiation often reffered to as the cutaneous radiation injury (CRI) is injury to the skin and underlying tissues from acute exposure to a large external dose of radiation. With CRI, the visible skin effects depend on the amount of the dose and the depth of penetration into the underlying tissues. Unlike the skin lesions caused by chemical or thermal damage, the lesions caused by radiation exposures do not appear for hours to days following exposure, and burns and other skin effects tend to appear in cycles. In most cases, healing occurs by regenerative means; however, large radiation doses to the skin can cause permanent hair loss, damaged sebaceous and sweat glands, atrophy, fibrosis, decreased or increased skin pigmentation and ulceration or necrosis of the exposed tissue.

A generalized erythema can occur within hours following an acute dose of 2 Gy or more of low-LET radiation (X-ray, gamma-ray) and will typically fade within a few hours or days. This inflammatory response, often referred to as **early transient erythema**, is largely caused by increase capillary dilatation and permeability secondary to the release of vasoactive amines (e.g. histamine). Higher doses produce earlier and more intense erythema. [3]

Two characteristic skin findings following radiation exposure at higher doses are dry and wet desquamation. **Dry desquamation** is a reddened, dry flaking, itchy skin due to partial damage of the basal layer. It occurs above a threshold of 8 – 12 Gy, typically 25 – 30 days following exposure.
Moist desquamation is characterized by blistering, redness, pain, and a weeping discharge resulting from the complete damage of the basal layer of the skin. Moist desquamation occurs beginning on 20–28 day at a threshold of 15–20 Gy [2].

For all end points, the higher the dose and dose rate the shorter the latency and more severe the effect. However, it is important to recognize that the dose ranges shown in text above are not to be interpreted as clear demarcations between various skin reactions and their associated dose. There are number of factors that may cause the individual patient to be more or less sensitive to radiation exposure. Biological factors, such as diabetes mellitus, systemic lupus erythematous have increased sensitivity and potential for severe skin reactions. Other physical and biological variables that can substantially modify the severity of radiation-induced skin damage include size of the exposure area, anatomical location, fractionation, patient health and medications. [3]

3.1.4 Radiation effects In Utero

Developing organisms are highly dynamic systems that are characterized by rapid cell proliferation, migration and differentiation. Thus, the developing embryo is extremely sensitive to ionizing radiation. Exposure to ionizing radiation can produce very severe effects on the embryo and foetus.

The effects of exposure can be teratogenic, carcinogenic, or mutagenic and vary depending on the gestation age, the dose, and also the dose rate.

The gestional period can be divided into three stages:

- *Preimplantation (0 - 2 weeks)*
- *Major organogenesis (3 weeks – 8 weeks)*
- *Fetal periods (9 weeks – 20 weeks)*

Each of these stages is characterized by different responses to radiation exposure, owing principally to the relative radiosensitivities of the tissues at the time of exposure.

The conceptus is very sensitive druing the **preimplantation stage** (blastogenesis) and susceptibility to the lethal effects of irradiation is a concern. Exposure to a radiation dose greater than 100 mGy (0,1 Gy) is associated with a risk of failure to implant, representing „all-or nothing“ response, in which, if the exposure is not lethal, the damaged cells are repaired or replaced and the conceptus will survive without significant abnormalities.

Irradiation during **organogenesis** (3 – 8 weeks) is the period of most concern. For this reason, it is often noted that radiation should be particularly limited during “the first trimester”. Embryos are sensitive to lethal, teratogenic and growth-retarding effects because of the criticality of cellular activities and the high proportion of radiosensitive cells. Intrauterine growth retardation, gross congenital malformations, microcephaly and mental retardation are the predominant effects for doses > 500 mGy. Radiation induced damage to the central nervous system in man is first observed at the end of organogenesis (approx. 8 weeks gestation) and extends well into the foetal period.

The foetal growth stage in humans begins after the end of major organogenesis (day 50) and continues until term. During this period the occurrence of radiation – induced prenatal death and congenital anomalies is, for the most part, negligible, unless the exposures are exceptional high and in the therapeutic range. Anomalies of the nervous system and sense organs are the primary radiation-induced abnormalities observed during early foetal period (8 – 15 weeks), which coincides with their relative growth and development. Studies of Japanese atomic bomb survivors have shown that a threshold dose of 300 mGy (0.3 Gy) at 8 weeks to 15 weeks after conception is associated with an increased risk of severe mental retardation. IQ data in this cohort fit a linear dose-response model, with an average IQ loss of approximately 25 to 31 points per 1 Gy beyond 0.1 Gy. After 16 weeks postconception, the threshold dose for non-cancer effects increases to approximately 0.70 Gy.

In utero exposure to ionizing radiation at any dose is associated with an increased risk of childhood malignancy, especially leukemia. Throughout most of pregnancy, the embryo/fetus is assumed to be at about the same risk for potential carcinogenic effects of radiation as are children.

Fetal doses from most diagnostic x-ray and nuclear medicine examinations are typically much lower than 50 mGy and have not been demonstrated to produce any significant impact on fetal growth and development. Neveretheless, every fertile female patient should be asked whether she might be pregnant before diagnostic examinations or therapeutic procedures using ionizing radiation are performed. Diagnostic radiological and nuclear medicine procedures should be prescribed to pregnant woman only when they are abolutely necessary (alternative procedures are inappropriate)

and only when the benefits outweigh the risks of radiation injury to the unborn. The first trimester is the most sensitive.

3.2 Stochastic effects

3.2.1 Characteristics of stochastic effects

Stochastic effects, of which carcinogenesis and mutagenesis are the most important, have these major characteristics:

- Stochastic effects are assumed to show no threshold, because damage to a few cells or even a single cell could theoretically result in production of the disease. There is no "safe" level of radiation so all doses to both staff and patients must be as low as reasonably achievable.
- If the dose is increased the frequency (risk) of stochastic effects will increase, but the severity of the response is independent of the dose (the severity of cancer is not associated with the amount of dose received. You are more likely to get cancer if you receive a higher dose, but the severity of the disease is not based on the dose).
- These effect generally manifest many years, even decades, after radiation exposure.
- We cannot definitively associate these effect with the radiation exposure. A radiation-induced cancer is indistinguishable from a „spontaneous" cancer.

In general, it is predominantly stochastic effects which need to be considered as potential side effects from diagnostic uses of radionuclides. For radionuclide therapy applications, the concerns relate to both stochastic and deterministic effects.

3.2.2 The risk of stochastic effects

The inciedence of certain cancers-such as leukemia, head, neck, pharyngeal, thyroid, breast and lung tumor – historically has been shown to be increased following radiation exposure (as observed in populations following radiation disasters such as the bombing of Hiroshima and Nagasaki). The risk factor to an individual whose exposure history is known can be estimated by multiplying the absorbed dose by the risk factor. The risk factor currently used for cancer induction for the adult working population exposed to low dose rate is 4×10^{-2} cases of cancer per sievert (1 in 25 per Sv). The risk factor for general population is somewhat higher at is 5×10^{-2} cases of cancer per sievert (or 5% per Sv or 1 in 20 per Sv). The rlsk factor for the working population (those aged 18 to 65 years) is lower because it does not contain children and young people who have more years at risk after exposure.

The risk of fatal cancer varies greatly with age and usually with sex. The younger the age at exposure, the greater the risk of developing cancer during lifetime. It can be explained by two reasons. The first reason is that the younger organism has more radiosensitivity due to higher rate of cell division, and the second, younger persons have a higher chance of overcoming (surviving) the latency period of cancer induction.

Fewer men get cancer from radiation exposure and die from that cancer compared to females of the same age at the same level of radiation exposure. The difference is not small: for every two men who get cancer, three women suffer this disease. The reasons are not yet fully understood, but the scientitsts suggest that one basis may be that the female body has a higher percentage of reproductive tissue than the male body.

3.2.3 Radiation risk models

The linear relationship was established based on observations made of comparatively high doses. The lack of reliable data has led to massive speculation with regards to what happens in the range of doses below 100 or 200 mSv. Reflecting the uncertainties, many alternative forms have been proposed for the shape of the curve relating cancer risk and radiation dose. These include:

- The linearity assumption.
- Greater risk at low doses than implied by linearity („supra-linearity“).
- A linear-quadratic curve in which the low-dose risk is depressed.
- A negative region at very low doses, corresponding to a beneficial effect (this is termed hormesis).
- A threshold, below which there is no appreciable cancer induction.

A linear relationship with no threshold clearly overestimates the risks posed by low doses if, in reality, this threshold did exist. Despite its limitations, the relationship has a useful regulatory role because it provides an easy and effective framework for radiation protection.

Linear quadratic dose-response curve demonstrates a reduced effectiveness for radiogenic cancer induction at lower dose and higher effectiveness at higher dose that eventually flattens out, reflecting doses associated with substantial cell killing. In addition, there is epidemiological evidence for a threshold for some cancers (include bone, soft tissue sarcoma, rectum, and nonmealnoma skin cancer). On the other hand, there are sites for which there is no evidence for a radiation-induced increase in cancer risk (e.g., prostate, pankreas, testes, cervix). However, even though there is evidence for a threshold dose for some types of radiation exposure in specific tissues below which no radiogenic cancer risk is evident, the evidence supporting this model is not sufficient to be accepted for general use in assessing cancer risk from radiation exposure.

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