CHAPTER 6

BIOLOGICAL EFFECTS OF RADIATION

LEARNING OBJECTIVES

After the completion of this chapter, you should be able to,

- *Explain the possible effects of X-rays on human body*
- *Describe the process of DNA damage by direct and indirect effects*
- *Outline the various cellular effects caused by the radiation*
- *Provide a note on cellular sensitivity to radiation*
- *Explain the acute radiation syndrome*
- *Discuss the genetic, somatic and in-utero effects caused by chronic doses of radiation.*

1. INTRODUCTION

X-rays were first discovered by Professor Wilhelm Conrad Roentgen in the year 1895. This was immediately followed by the discovery of natural radioactivity by Henri Becquerel. However, the scientific community were unaware of the possible dangerous effects now associated with X-rays and other radiations. Due to this notion, practice of unshielded X-rays and unshielded operators was the general norm. Since these X-ray tubes were not built to offer any protection to the operator, not only the patients but even the roentgenologists were exposed to the X-rays. Several clinical and experimental procedures using radiations resulted in the development of somatic effects in the patients and workers who complained of hair loss, erythema, skin burns etc. These somatic effects were not considered serious as these radiations were not associated with any possible dangerous effects and moreover these effects appeared several weeks after the exposure to X-rays.

Eventually, researchers began to understand that exposure to X-rays and other radiations was the main cause of emergence of several biological effects. Researchers complained of eye irritation, burn-like dermatitis upon working unshielded with X-rays and other fluorescent substances. Experiments were also conducted to determine the relationship between X-rays and injury. Once it was ascertained that radiations are capable of inducing biological effects, X-ray exposure guidelines were developed which suggested the limiting dose (≅ 10 rem/day) to which whole body exposure would be considered to be safe as this would reduce the risk of injury. Subsequently, it came to the notice of researchers that radiation dose of even 50-100 rem/year was capable of precipitating long term effects. This fact was concluded by studies that compared the life-spans of non-radiologists and radiologists who were not shielded from radiations or radioactive materials. It was found that the latter had comparatively shorter life-spans and were even highly susceptible to cancers. Biological effects which later manifest as clinical symptoms occur when the human body is exposed to radiations from external sources due to internal consumption of radioactive substances. Rate and extent of absorption of radiations determine the nature, severity and time of appearance of the clinical symptoms. These symptoms arise because the atoms of biomolecules are ionized by the ionizing radiation which induces chemical changes in them, thereby either altering their function or entirely eliminating them. Hence such ionization is responsible for modifying the behaviour of the amino groups of the proteins, deactivation of enzymes, peroxidation of lipids, dissociation of carbohydrates, and structural modifications of nucleic acid chains. The most serious effect is generated when the DNA is targeted by the radiation as it holds necessary information relating to the functioning and replication of cells, in the form of genes or chromosomes. Biological effects of radiation can be direct, wherein energy from the radiation is directly transmitted to the biomolecules, which are subsequently ionized, or may be indirect wherein water molecules in the cell are ionized by the radiation to generate free radicals which in turn result in cellular destruction. This factor has been discussed in detail in the upcoming section.

One of the features that distinguishes nuclear radiation from other types of radiations such as light, heat etc., is the transfer of energy while its passage through the matter which results in the production of ion pairs. Thus X-rays, high energy β-rays, and γ-rays have very high penetrating ability and have long ranges. In contrast, particulate radiation such as α-particles, neutrons etc., have low penetrating ability and short range. Thus *linear energy transfer* (LET) of a radiation is related to range, and is defined as the amount of energy deposited by the radiation per unit of path length. Low LET values are characteristic of X-rays, γ-rays etc., which have a long range, while particulate radiation exhibit high LET values as they have a short range. Interaction of ionizing radiation with a cell is followed by cellular deposition of the ionizing energy. Thus, biological effect produced by a radiation is dependent upon its LET.

2. PROCESSES OF CELLULAR DAMAGE

It is the general notion that biological damage caused by the ionizing radiation is due to its interaction with the biological cells, however, the actual process involved is that the ionizing radiation interacts with the atoms that form the cell. This ionizing radiation removes tightly bound electrons from the atomic orbits due to which the atom is rendered ionized or charged, and the process involved is known as *ionization*. The charged atom so formed interacts with the neighbouring atoms and form newer chemical bonds. Basically, two mechanisms have been proposed by which the ionizing radiation results in ultimate damage to the biological cells. These include indirect and direct effects.

1. **Indirect Effect**

This effect which is more common, involves the generation of free radicals due to the absorption of radiation energy. Since a free radical is deficient in an electron in its outermost shell, it has high chemical reactivity. Since the cells are abundant in water and oxygen, their ionization (due to the deposition of radiation energy in the cell) results in the formation of free radicals.

$$H_2O \rightleftharpoons H^+ + OH^-$$

$$O_2 \rightleftharpoons O^- + O^+$$

Ionization of water is more predominant, thereby resulting in the formation of hydroxyl (OH^-) ion, which is the major oxidizing agent. However, in under 10^{-5} seconds both the above reactions proceed in the reverse direction to again form water and oxygen, thereby precluding any biological effects. However, it may so happen that these free radicals may combine to produce toxic substances such as hydrogen peroxide (H_2O_2) which is a very strong oxidizing agent. These free radicals and the oxidizing agents may then attack the DNA, which is their primary target thereby resulting in the destruction of the cell.

2. **Direct Effect**

Direct effect involves the direct interaction of the radiation with the atoms of either DNA or any other component, that is vital for cell survival. Thus, the atoms of the target (DNA, chromosomes, genes etc.,) may be ionized or charged which initiates a cascade of events eventually resulting in biological changes. Direct action is associated with genetic effects, which may even appear in succeeding generations. Radiations such as α-particles, protons and neutrons, which have high LET exhibit direct effect.

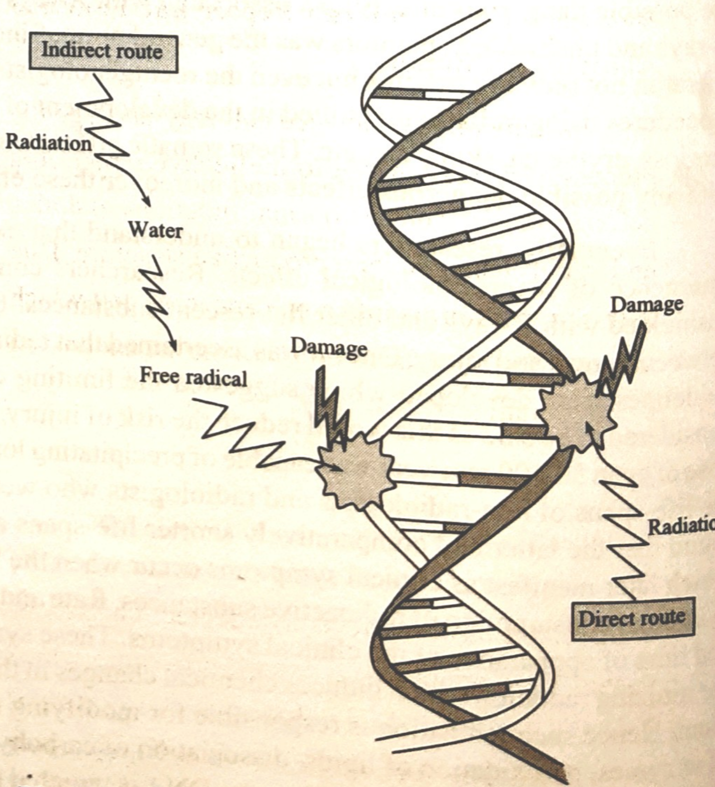

Figure: DNA Damage Through Direct and Indirect Routes

3. POSSIBLE CELLULAR EFFECTS

Following are the possible cellular effects that may be caused by the radiation.

1. **Cells Remain Undamaged**

   It may so happen that although the body may be struck by the radiation but some cells may not be hit and remain undamaged. It may also happen that certain chemically active substances may be produced due to the interaction of ionizing radiation, which may induce any structural alterations in the cell. If such alterations are those that also occur even under normal physiological conditions, then the cells remain undamaged.

2. **Damaged Cells Undergo Normal Repair**

   Interaction with the radiation may result in the formation of abnormal compounds which adversely affects the cell structure. In case of limited damage, the cell undergoes the process of repair thereby avoiding the chances of permanent damage. Even damaged chromosomes are also repaired. This process is generally evident when the individuals have been exposed to low doses of LET radiation.

3. **Damaged Cells Undergo Repair but Function Abnormally (Mutate)**

   Very infrequently, a damaged cell may undergo the process of repair but due to ineffective repair, it is not able to carry out its normal functions and also undergo a change in its reproductive structure. Due to this, it transforms into a precancerous cell which may eventually (in the future) become the underlying cause of malignant tumours.

4. **Cell Death**

   Cell death is pertinent when it has been extensively damaged by the radiation and also when its ability to reproduce has been severely affected. This can be compared to apoptosis, a normal procedure which involves the death of cells that are no longer useful to the body. The debris of the dead cell is removed by the blood and a new cell (regenerated via normal biological processes) takes its place.

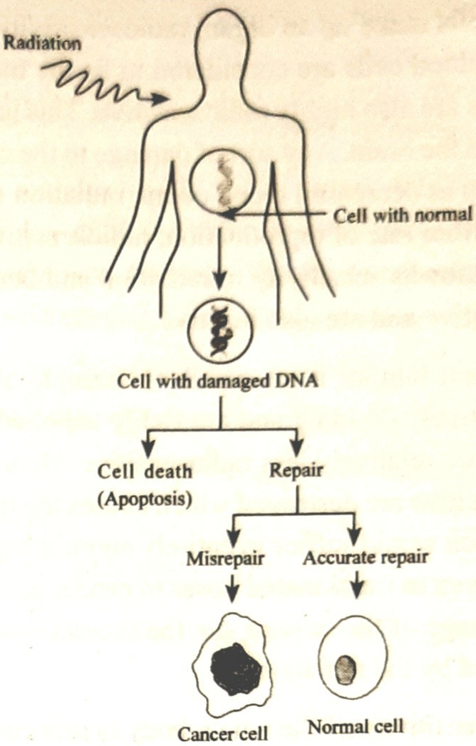

Figure: Cellular Effects of Radiation

4. CELLULAR SENSITIVITY TO RADIATION

All the living cells of the body do not respond similarly to radiation. It has been found that cells which are actively producing and are undifferentiated are relatively more sensitive to radiation than other cells. This fact has been explained by the *Law of Bergonie and Tribondeau* according to which radiosensitivity of cells is directly proportional to growth rate and indirectly proportional to the degree of specialization. Hence in simple terms, cells that are more sensitive towards radiation are those that are actively dividing and are undifferentiated (but would undergo specialization in the near future). The reason behind this is thought to be that, actively dividing cells are heavily dependent upon correct DNA information which is essential for the growth and survival of the cell as well as its daughter cells. When a radiation interacts directly with the DNA of a rapidly dividing cell, it would lead to either mutation or death of the targeted cells. However in contrast, such pronounced, adverse effects are not seen upon direct interaction of a radiation with the DNA of a dormant cell. Living cells can be classified based on their rate of reproduction. Since radiosensitivity is directly proportional to the rate of reproduction, cells which differ in their rate of reproduction also differ in their radiosensitivities. Lymphocytes, immature blood cells and intestinal crypt cells are rapidly dividing cells that are most radiosensitive. These are followed by reproductive and gastrointestinal cells whose turnover is comparatively less and hence they are less sensitive. Least radiosensitive cells are muscles and nerve cells because they exhibit very slow rate of regeneration.

Since cells make up an organ, radiosensitivity of an organ system is dependent upon the type of cells it is made up of. Immature blood cells are considered to be the most radiosensitive due to their high rate of reproduction, hence blood forming organs are also highly radiosensitive. This is followed by reproductive and GI organs, followed by skin and finally by muscles and the brain. Any sort of damage to the cells of an organ system by radiation is exhibited in the form of clinical symptoms such as decreased blood count, radiation sickness, birth defects etc. Another long term effect is the high risk of cancer. Apart from rate of reproduction, radiosensitivity of a cell is also influenced by oxygen supply. Presence of oxygen in a cell increases its sensitivity to radiation and hence anoxic cells (cells with insufficient oxygen) are considered to be less radiosensitive and are also inactive.

Malignant tumour is an excellent example of a radiosensitive cell system. Cells that make up the outer layer of tumour are actively dividing and are richly supplied with blood and oxygen (meaning more radiosensitive), while inner layer of cells are relatively less radiosensitive. Hence when the tumour is exposed to radiation, outer layer of cells being most radiosensitive are destroyed which causes the tumour to shrink in size and expose the inner cells. Although a massive dose of radiation would suffice in entirely eliminating the tumour, but it would also jeopardize the life of the patient. Hence, radiation is given in fractionated doses to cancer patients which would serve two purposes. First would be to enable in the gradual shrinkage of the tumour and the second would be to provide a chance to the healthy tissues to recover from any damage caused by the radiation.

Radiosensitivity of the whole body is influenced by the most radiosensitive organs, which in turn is influenced by the most radiosensitive cells. Several factors govern the biological effects that would be manifested due to exposure to radiation. Some of these include total dose, type of cell affected, type of radiation, age of the individual, part of the body exposed to radiation, general health status of the individual, tissue volume exposed etc.

5. ACUTE AND CHRONIC EFFECTS OF RADIATION

Biological effects of radiation becomes more severe when it is accompanied with another type of trauma. This is known as *combined injury*. It has been found that when two injuries (that are generally less lethal or sublethal alone) occur together, they increase the risk of mortality.

For example, exposure of rats to 250 rads gamma radiation is not mortal while 33% burns is associated with 50% mortality. However, when both these injuries occurred together in rats, then the rate of mortality was observed to be 100%. When combined injuries occur, the normal defence mechanisms of the host is severely compromised. This induces changes in the properties of epithelial surfaces of the host thereby leading to lethal consequences.

Biological effects caused by radiation can be categorised into two, acute and chronic. Acute effects refer to exposure to high doses of radiation over short time period while chronic effects refer to exposure to low doses of radiation for prolonged time period. Exposure to high doses of radiation adversely affects numerous cells resulting in their death, due to which tissues and organ systems are also affected. This eventually results in the development of whole body response which is also known as *Acute Radiation Syndrome* (ARS). This syndrome is manifested by local effects such as burns, hair loss, blisters, desquamation, blood vessel damage while whole body symptoms include nausea, radiation sickness, reduction in blood cell count etc. Chronic effects involve the exposure to low doses of radiation that extend over prolonged time period. Hence effects caused due to such exposure are not immediate and may result in anaemias, cataracts, cancers etc., in the near future. Moreover, damage caused to individual cells by radiation induces certain effects in the human body which can be classified as somatic and hereditary (genetic).

1. Somatic effects are observed only in individuals exposed to radiation and arise due to the damage to the somatic cells.
2. Genetic or hereditary effects arise to due damage incurred upon reproductive cells by the radiation, which can be passed on to future generations.

5.1 ACUTE DOSES OF RADIATION

Acute radiation syndrome (ARS) basically refers to clearly identifiable symptoms that are caused by acute doses of radiation. An acute radiation dose may be defined as the dose of radiation exceeding 10 rads to which the entire body has been exposed to for a short period of time. When the radiation dose exceeds 200 rads, it results in significant damage to the radiosensitive cells and is manifested by symptoms of radiation sickness that may appear in few days or weeks. Some of these include nausea, vomiting, fatigue, hair loss, diarrhoea, blood changes, dizziness, haemorrhage, nervous disorders and even death. Acute whole body exposure to doses greater than 400 rads is associated with $LD_{50/60}$ meaning that without medical care it is statistically expected that, 50% of the individuals exposed may die within 60 days. When the whole body exposure dose is greater than 700 rads, then it is associated with LD_{100} meaning that inspite of being provided with medical care, it is statistically expected that none of the exposed individuals would survive.

The above mentioned somatic effects are the initial signs and symptoms of ARS seen due to exposures to doses of 200 rads. When the whole body exposure dose exceeds this value, then one of the following three syndromes begin to appear, depending upon the dose of exposure.

1. **Haematopoietic Syndrome**

Since haematopoietic stem cells found in spleen, bone marrow and lymphatic tissue, represent the most radiosensitive cells, exposure to radiation doses exceeding 200 rads impairs their functioning thereby adversely affecting the normal haematopoietic processes. Precursor stem cells that are mitotically active are most affected due to which the production of mature RBCs, WBCs and platelets is severely reduced. Due to reduced supply of new mature cells which cannot replace the old circulating blood cells, it results in the development of symptoms characteristic to haemotapoietic syndrome such as anaemia, internal bleeding, fatigue, lowered immunity, fever, high risk of infections etc. When an individual is exposed to doses exceeding 500 rads, he develops pancytopaenia (decrease in the count of all blood cells) after 3-4 weeks. Other manifestations include purpura, petechiae, uncontrolled bleeding resulting in anaemia, fever due to bacterial and mycotic infections (in turn caused due to decreased production of antibodies and granulocytes). Recovery from haematopoietic syndrome is possible when at least 10% of stem cells have retained their function or else death ensures within a month.

2. **Gastrointestinal System Syndrome**

Gastrointestinal tract comprises cells that are less actively dividing and hence are relatively less radiosensitive. Among these, cells of the small intestine are most susceptible than those of stomach, colon and rectum. Exposure to radiation dose exceeding 700 rads prevents the lining of the digestive system in renewing itself, thus resulting in its breakdown. Breakdown of gastrointestinal mucosal lining enables the bacteria to access the vasculature unharmed due to reduced production of granulocytes. Symptoms of this syndrome are cramping, nausea, vomiting, diarrhoea, inability to digest, bleeding ulcers etc. Ulcerated intestinal mucosa is responsible for leakage of essential electrolytes thereby leading to dehydration, electrolyte imbalance, shock and finally death (within 4-10 days of exposure).

3. **Central Nervous System Syndrome**

This syndrome manifest upon exposure to radiation dose exceeding 5000 rads. It involves the destruction of least radiosensitive cells i.e., the nerve cells. It is manifested by nausea and vomiting seen within minutes of exposure, nervousness, confusion, loss of consciousness, disorientation, breathing problems, seizures, coma etc. Exposed individual dies within few days before the appearance of haematopoietic and GI symptoms due to increased cranial pressure.

Table: Brief Account of Acute Radiation Syndrome (ARS)

Dose	Syndrome causes	Signs and symptoms	Final outcome	Comments
1. <100 rads	Prodromal syndrome	Nausea, vomiting, diarrhoea.	Individual may recover completely	May also experience late effects
2. 100-1000 rads	Haemotopoietic syndrome	- Decreased number of erythrocytes, leucocytes and platelets. - Decreased formed elements	- Maximum recovery possible below $LD_{50/60}$ - Chances of 50% mortality at 350 rads - No survivors at 1000 rads	All survivors experience late effects
3. 1000-5000 rads	Gastrointestinal syndrome	Diarrhoea, blood in stools, removal of mucosal layer.	Death	–
4. > 5000 rads	CNS syndrome	Loss of vission, nervousness, confusion, seizures, loss of consciousness, coma etc.	Death	–

Delayed Somatic Effects

Individuals that have recovered from the biological effects due to acute whole body exposures may experience the following delayed somatic effects.

1. Exposure to a single dose of 600-800 rad results in erythema (reddening of the skin) which resembles a mild sunburn.
2. Acute doses of about 500 rad results in epilation (hair loss) due to damage to hair follicles.
3. Acute neutron doses of about 200 rads are known to cause cataracts.
4. 50% of women exposed to acute doses of 125-200 rad experience prolonged or permanent cessation of menses.
5. Exposure of ovaries or testes to 600 rad results in permanent sterilization.

5.2 CHRONIC DOSES OF RADIATION

Chronic or low doses of radiation refers to exposure to low doses of radiation over a prolonged time period which eventually gives rise to chronic or long term effects. A chronic dose of radiation is basically a small dose of radiation to which an individual has been exposed to over a prolonged time period. Such exposure is an example of occupational exposure, generally found in workers that are closely associated with radiation sources. However, human body is relatively more tolerant towards a chronic dose when compared to an acute dose of radiation. Reason behind this is that, at any given time only a small fraction of cells are damaged by the radiation and the body has enough time to carry out the process of repair as well as to replace dead cells with new ones. Exposure to low or chronic doses of radiation may produce certain long term effects which may be categorized as genetic, somatic and *in-utero*.

1. Genetic Effects

Genetic effects refer to the mutation of reproductive cells (egg or sperm) of an individual caused due to exposure to radiation. Damage to the reproductive cells may appear as genetic mutations, birth defects or any other conditions in the offsprings and future generations of the exposed individuals. Radiation can be categorised as the physical agent of mutation. Mutations caused by radiation cannot be distinguished from those caused by other agents such as chemical, viruses etc. Studies have revealed that low-dose exposure to radiation has not resulted in adverse genetic effects which may be attributed to the fact that mutation of the reproductive cells ultimately give rise to a zygote that is non-viable and hence is either resorbed or aborted in the early stages itself. Although harmful or even lethal genetic effects are not generally seen, but it has been observed that the rate of mutation may be increased by the ionizing radiation and thus cannot be considered insignificant. Hence, according to USNRC Regulation (10 CFR Part 20) exposure to radiation should be absolutely minimum or As Low As Reasonably Achievable (ALARA).

2. **Somatic Effects**

As the name suggests, somatic effects occur due to damage caused by the radiation to somatic cells of the individual exposed. Such effects are suffered by the individual himself and are also called as carcinogenic effects because the primary result of such effects is cancer. Somatic or carcinogenic effects generally occur due to occupational exposure and typically results in cancer or leukaemia in the exposed individual. Although genetic effects of radiation are not well documented, studies have shown the direct link between radiation and cancer. For example, uranium miners have greater risk of lung cancer, radiologists are susceptible to skin cancers and leukaemia has been reported in therapy patients, radiologists and bomb survivors.

3. ***In-utero* Effects**

In-utero effect is mistakenly considered to be a genetic effect of radiation exposure because it becomes pronounced in the embryo or foetus and becomes evident after birth. However, *in-utero* effect is basically a special category of somatic effect because here exposed individual is the embryo or the foetus. Since the foetal or embryonal cells are rapidly dividing and are also rich in oxygen and blood supply, these are highly radiosensitive with radiosensitivity being comparable to a tumour. However the consequences of exposure to radiation with embryo differ markedly from those seen with a tumour. Some of the potential effects seen with prenatal radiation doses include low birth weight, microcephaly, mental ratardation and increased susceptibility to leukaemia and solid tumours in the near future. Studies have shown that when compared to an adult or a child, an unborn child is more sensitive to ionizing effects of radiation and such sensitivity is time dependent. First trimester i.e., 2-8 weeks of pregnancy is the period during which the embryonal foetus is most radiosensitive, as this period witnesses organogenesis i.e., development of various organs from rapidly differentiating cells. Childhood cancer has been reported in children, who as foetus, were exposed to low levels of radiation (10 rads). Hence, Federal Agency advices to implement a Pregnancy Surveillance Program at the workplace which would ensure that the foetus and his pregnant worker mother would not be exposed to doses that exceed 10% of a radiation worker's whole body exposure limit i.e., about 500 mrem. It is presumed that such low levels of exposure to radiation would not pose any major risk to the foetus.