

Biological effects of ionizing radiation

Previous chapter: 5.2.7 *Ionizing radiation protection*

A dose of ionizing radiation absorbed in a biological environment will initiate a complex process of various events. The physical events start with **energy transfer** from the ionizing particles to the atoms and molecules of surrounding tissues. This process takes about 10^{-13} seconds. Following this, physicochemical processes take place, such as intramolecular energy transfers, excitation and ionization of atoms. The time length of this is about 10^{-10} s. Then the chemical processes start. At this point primary damage to biological structures begins at the time length of about 10^{-6} seconds. Following the chemical processes, biological processes starts to occur. In this phase the damaged biological structures can be either *repaired* or *irreversibly damaged*. Biological damage can lead to **cellular death**, which can occur over time periods from *seconds* and up to *years*. All these processes lead to the final radiobiological effect of the radiation on the human body. Ionizing radiation can, apart from causing damage, also lead to activation of **adaptive** and **protective mechanisms**.

The pathogenesis of ionizing radiation damage starts at with the **physicochemical processes**. These processes give origin to reactive compounds that act on molecular level and cause **radiation cellular changes**. This causes cells to losing their specific properties. At the subcellular level there are irregularities happening to the biochemical processes:

1. The activity of *enzymes* changes
2. *phosphorylation mechanisms* are disrupted
3. the synthesis of *nucleic acid*
4. specific *proteins* do no longer work.

The cellular level of damage first manifests itself with a decrease in the number of **proliferating cellular populations**. The loss of specialized cells causes the biochemical changes to intensify. The changes starts to interfere with the functions of vitally important organs such as *hematopoietic tissues*, *intestinal epithelium* etc. The resulting organ and systemic changes to the whole organism initiates the development of **radiation sickness**. There are also latent *somatic* and *genetic damages*, which can be seen on a population level.

Biological effects of the same doses of ionizing radiation can differ greatly. These effects depend on the *linear energy transfer* and on the *spatial distribution* of a given dose. **DNA molecules** are the most critical cellular structures that can be affected by ionizing radiation. Ionizing radiation can induce a number of changes in the *size*, *structure* and *shape* of these molecules.

Understanding of how the ionizing radiation affects the cell is an essential prerequisite to understand the pathogenic mechanisms that causes somatic and genetic damage to human tissues.

One of the most important properties of cells is the ability to *divide* and *create identical daughter cells*. The cell cycle consists of 4 phases:

- The first (*post-mitotic*) **G1 phase** starts immediately after the cell division and is characterized by the synthesis of *RNA*, *proteins* and *DNA precursors*. G1 lasts up to tens of hours. In this phase it is decided whether the cell is going to continue in the cell cycle, differentiate, die or enter the resting G0 phase. In G0, the cells stop dividing. At the end of the G1 phase the cell is the most radiosensitive, and is about to enter the S phase, which lasts 5-10 hours.
- **S phase**. This phase is characterized by the *lowest radio sensitivity*. The DNA in the nucleus is duplicated, and a number of specific proteins are synthesized. Following the S-phase, the cell enters the G2 phase.
- **G2 phase** is rather short; it lasts approximately 1-3 hours. This phase shows gradual increase radio sensitivity. The G2 phase ends with the beginning of mitosis.
- The **M phase**, *mitotic phase*, is the shortest one of all, lasting only 0,5-1 hours. The M-phase is divided into 4 separate phases, called prophase, metaphase, anaphase, and telophase. The high level of chromosomal activity causes the M-phase to represent the time when the cell reaches its second highest radio sensitivity. During mitosis, the chromosomal DNA is divided between two newly created nuclei. Both of these nuclei contain identical copies of the cell's genetic material. Immediately after the mitosis the whole cell itself is divided, giving origin to two identical daughter cells.

Cells of certain tissues, for example *bone marrow*, go through the cell cycle many times during their life. Highly specialized cells, such as *neurons*, do normally not divide at all, and spend their whole life "trapped" in the G0 phase.

There are two different types of damaging **biological effects** due to ionizing radiation on the cellular level. Exposure can cause either *cell death*, or it can change its genetic information through *mutations*, leaving the cell able to reproduce itself. In an irradiated population, both of these processes generally work simultaneously, i.e. part of the cells dies and another part is a subject to mutations or malignant transformation. The origin of malignancies lies in changes of the functional parts of chromosomes, the genes. These mutations can originate spontaneously, but the effects of ionizing radiation can significantly increase the number of mutations. Even under normal circumstances, there are about 10^{10} spontaneous genome changes during the human lifetime.

The **final result of the exposure** to ionizing radiation is defined by the **extent of reparation processes**. These processes are able to repair a part of the radiation damage, but the ability to correct mistakes depends on the time factor. Molecular level or reparation includes *enzymatic activity* which repairs the damaged DNA structures. In order to restore the organ functions, the most important aspect is the restoration via *proliferation of new cells*, which originates from the remaining fraction of healthy stem cells.

The basic mechanism of the biological effects of the ionizing radiation

When the ionizing electromagnetic radiation passes through a biological environment, they induce *ionization* and *excitation* of the atoms and molecules located near their trajectory. Each ionizing reaction causes 2 to 4 excitations. As it is described above, the particles with electric charge are able of direct ionization. The electromagnetic radiation and neutrons cause indirect ionization. The ions, excited atoms, and molecules give origin to chemically reactive compounds, which are mainly free radicals.

The effect of ionizing radiation can be either **direct** or **indirect**:

- The **direct effect** of ionizing radiation and the radiant energy is immediately absorbed inside the cellular nucleus. This is not very probable for radiation with low linear energy transfer. The following changes in chemical bonds cause *inactivation*, or even *disintegration* of the irradiated molecule. Direct effects are typical for cells with low water content.
- The **indirect effect** induces *radiolysis of water*, which produces very aggressive free radicals responsible for radiation damage of important molecules. The absorption of radiation in biological environment depends on high water content. Up to 50% of the ionizing radiation energy can be absorbed in free water. During radiolysis of water, production of free radicals such as H. and OH occurs. The resultant radicals can interact with DNA molecules and cause single- or double-strand DNA breaks. This may have lethal consequences. Other products of this reaction are so called molecular products of radiolysis (H₂, O₂, H₂O₂). The lifetime of these products is about 10⁻⁶ s. They undergo fast recombination or energy migration and transform into different reactive products. The resulting products can cause various redox reactions.

In all of the chemical reactions following radiolysis, the major role is played by the **presence of oxygen**. Oxygen is one of the main factors influencing the radio sensitivity of cells because the oxygen can act as a **radiation sensitizer**. This means that tissues with lower oxygen content, for example hypoxic areas inside solid tumours can be more radio resistant. The influence of oxygen presence is most significant in the case of radiation with low linear energy transfer (X-rays, gamma radiation, electrons). Due to the significance of the oxygen presence, a new term is established, the **oxygen ratio**. Oxygen ratio is defined as the ratio between doses causing the same effect in *hypoxic cells* and in cells that are sufficiently *saturated with oxygen*. The presence of oxygen increases the production of free radicals and interferes with the reparation processes within the cell. Cells that are sufficiently saturated with oxygen are also 2-3 times more sensitive to radiation. The number of cells with insufficient oxygen saturation within tumours is generally between 10-15%. In the final phase of radiotherapy, these cells decide the long-term positive effect of the radiation therapy

The ionizing radiation's ability to ionize atoms and molecules, including biologically important macromolecules, is the main factor of biological effects to the exposed organism. The resulting products are chemically highly reactive compounds, called **free radicals**. The primary physical and physicochemical processes are followed by other reactions, which leads to the damage of the whole irradiated organism. This damage gradually manifests itself by morphological and functional changes, and can be proved on molecular, cellular, organ and systemic level (i.e. the damage affects all of the levels of internal organisation of the organism). The amount of ions generated along the trajectory of ionizing particles per unit of track is called **ion density**. The higher the ion density, the higher the probability of hitting some of the important molecules and thus achieving greater biological effect.

The **final effects of ionizing radiation** depend mainly on the *radiation dose*, the *dose rate*, *way of exposure*, the *spatial distribution*, and *type of radiation*. Metabolic condition of the organism at the time of exposure also influences the effects on an organism.

Types of radiation damage

Stochastic effects of ionizing radiation (Fig. 5.11a) are defined as a *non-threshold function of the dose*. This means that even minimum dose of radiation is able to cause pathological changes in the affected organism. The effects can be divided into two groups, **somatic** and **hereditary**. **Somatic effects** affect the *exposed individual*, and **hereditary effects** affect the descendants of the exposed individual. A very important somatic risk accompanying radiation exposure, even at low doses, is the origin of *malignancies*. Generally it can be said that even minimum radiation dose can lead to the origin and development on malignant tumors. The probability of developing a malignant tumour increases with increasing radiation dose.

Deterministic (non-stochastic) effects (Fig. 5.11b) of ionizing radiation are represented by **acute radiation sickness**. This usually develops as a result of a massive, external radiation exposure. Chronic radiation sickness originates as a result of *repeated irradiation* by small doses, or as a result of overcoming acute form of the disease.

Radiation sickness is a complex of pathological changes in the organism, caused by the effect of large doses of ionizing radiation. The character of the disease depends on the *penetrability of the radiation*, *ionising density*, *type of exposure*, *time factor*, etc. Damage to different organ systems depends on the dose and radio sensitivity of the

cells/tissue. Generally the radio sensitivity is very high in cells with low level of differentiation and with very high levels of mitotic activity.

Acute radiation sickness is characterised by a typical clinical course, which can be divided into 4 individual phases:

- The *period of initial symptoms* is called the **prodromal phase**. This phase of the disease is very short. Immediately or within in a couple of hours of exposure, the patients show signs of *general nausea, weakness, thirst and headaches*. They also feel the *urge to vomit* and complain of *dry mouth*. Body temperature starts to gradually increase, and in the case of large doses of radiation there can be *gastrointestinal disorders* and *diarrhoea* present. Some patients display signs of *shock* and other experience *consciousness* and *sleep disorders*. The experience from Chernobyl-patients shows that the vomiting symptom is an important sign of future prognosis. The sooner the vomiting starts, the worse the prognosis of further development.
- The *period without apparent clinical symptoms* is called the **latent phase**. This phase varies in length. Usually the length increases with decreasing absorbed radiation dose. Following the short period of initial symptoms, there is a period without any apparent symptoms. The affected individuals show no signs of problems once the initial symptoms start to subside. The temperature decreases to normal values; headaches and consciousness disorders disappear, and vomiting stops. The **reason for the temporary improvement** is the *maximum activity of all available protective mechanisms*. However development of the disease covertly continues.
- The *period of full sickness development* is called the **clinical phase**. This third period is initiated following the latent phase and it is characterized by a complex of accompanied by **fevers** lasting up to *several weeks*, disorders. The length is dependent on the size of absorbed radiation dose. The instigation of fever is accompanied by *haemorrhagic symptoms*. Another clinical signs include *inflammatory changes* to the oral mucosa and signs of *damage to gastrointestinal tract*. At this point the fever is caused by an onset of infection induced by the failure of the body's protective mechanisms. There are very significant **cardiovascular malfunctions**, such as *tachycardia, extra systole, and failure of circulation*. The intestinal wall stops acting as a barrier against bacterial invasion, leading to intensified vomiting and diarrhoea, and later presents with traces of blood. The combined effect of diarrhoea and vomiting leads to severe *dehydration* and the renal functions are in danger. The patients start to lose weight due to low food intake. There is damage to the liver and reproductive organs. The production of blood cells is severely limited. This period lasts 2-3 weeks and death can be caused by any of the previously mentioned changes, for example severe *anaemia, infection and sepsis, circulation and kidney failure* or combination of all these. A number of patients die from *pneumonia or bronchopneumonia*. For doses of about 4,5 Gy (LD50) the damage is mainly localized to hematopoietic tissue and immune system. With the increasing doses there is increased incidence of the „intestinal“ form of the disease. Damages to the intestines leads to intestinal micro flora penetrating the intestinal wall, reaching the bloodstream, and finally causes sepsis. Death can also result from disruptions to the acid-base homeostasis and the water/mineral metabolism. Exposure to doses higher than the absolute lethal dose, about 10 Gy, leads to very fast death due to failure of the central nervous system. (ALD = LD100).
- The **period of convalescence**: Patients who have not been exposed to lethal dose of radiation can gradually recuperate and reach *partial recovery*. In the case of exposure to very small doses of radiation, *complete recovery* is possible. The experienced state of the exposed individual slowly improves, and objective symptoms start to subside. The temperature decreases; the appetite returns; and normal sleeping patterns are established. The production of new blood cells gradually adjusts to normal values.

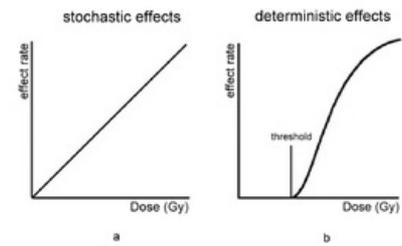


Fig. 5.11. Stochastic (a) and deterministic/non-stochastic (b) effects of radiation exposure

Patients who have survived acute radiation sickness show higher incidence of *leukaemia* and *other malignancies*. Most the women become *infertile*, while pregnant women display higher probability of miscarriages. There is also a higher incidence of giving birth to physically or mentally disabled children.

After radionuclides enter the organism via *ingestion* of contaminated food, *inhalation*, or *through injured skin*, there is **internal contamination** by radioactive elements. The water-soluble compounds are relatively quickly dissolved and enter the blood. Blood then transports them into vital organs, where they are absorbed. Monovalent cations in the organism are distributed quite evenly, while the bivalent ones have high affinity to bone tissue. Trivalent and multivalent are distributed among bones, lymphatic tissue, liver and bone marrow.

The effects of internal contamination can be visible early or late. The gastrointestinal tract, and the thyroid gland are easily damaged by radionuclides of iodine and happen early. However, most of the effects are of the late category. They usually manifest themselves a couple of year after exposure in the form of neoplastic blood disorders, leukaemia and malignant tumors in various locations.

The goal of radiation protection is to completely prevent from the development of non-stochastic effects and to keep the probability of stochastic effects to the minimum.

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