S. A. ZHADAN, F. I. VISMONT,
E. V. MELENCHUK

DAMAGING ACTION OF IONIZING RADIATION

Minsk BSMU 2016

МИНИСТЕРСТВО ЗДРАВООХРАНЕНИЯ РЕСПУБЛИКИ БЕЛАРУСЬ
БЕЛОРУССКИЙ ГОСУДАРСТВЕННЫЙ МЕДИЦИНСКИЙ УНИВЕРСИТЕТ
КАФЕДРА ПАТОЛОГИЧЕСКОЙ ФИЗИОЛОГИИ

С. А. Жадан, Ф. И. Висмонт, Е. В. Меленчук

ПОВРЕЖДАЮЩЕЕ ДЕЙСТВИЕ ИОНИЗИРУЮЩЕЙ РАДИАЦИИ

DAMAGING ACTION OF IONIZING RADIATION

Учебно-методическое пособие

Минск БГМУ 2016

УДК 616-001.28 (811.111)-054.6 (075.8)
ББК 53.6 (81.2 Англ-923)
Ж15

Рекомендовано Научно-методическим советом университета в качестве учебно-методического пособия 20.05.2015 г., протокол № 9

Р е ц е н з е н т ы: д-р мед. наук, чл.-кор. НАН Беларуси, проф. Л. М. Лобанок; д-р мед. наук, проф. М. К. Недзьведь

Жадан, С. А.

Ж15 Повреждающее действие ионизирующей радиации = Damaging action of ionizing radiation : учеб.-метод. пособие / С. А. Жадан, Ф. И. Висмонт, Е. В. Меленчук. – Минск : БГМУ, 2016. – 28 с.

ISBN 978-985-567-424-6.

Рассматриваются основные вопросы влияния ионизирующих излучений на организм человека, механизмы лучевых поражений, этиология и патогенез острой и хронической лучевых болезней, отдаленные последствия ионизирующей радиации.

Предназначено для студентов 2–3-го курсов медицинского факультета иностранных учащихся, обучающихся на английском языке.

УДК 616-001.28 (811.111)-054.6 (075.8)
ББК 53.6 (81.2 Англ-923)

ISBN 978-985-567-424-6

MOTIVATIONAL CHARACTERISTIC OF THE TOPIC

Methodical recommendations are developed for the purpose of optimization of educational process and are recommended for training of students for practical class in a topic «Damaging Action of Ionizing Radiation». This subject is considered in the section «General Nosology».

Lesson Purpose: to investigate the pathophysiological aspects of Ionizing Radiation influence on the human body, the mechanisms of radiation injury, the etiology and pathogenesis of acute and chronic radiation sickness and distant effects of ionizing exposure.

Lesson objectives. The student should:

1. Know:

– general characteristics of ionizing radiation;

– classification of ionizing exposure;

– general effects of radiation on different levels of biological organization of organism;

– pathogenesis of radiation damage;

– long-term consequences of radiation sickness.

2. Be able:

– to make a conclusion about the character of Radiation Sickness;

– to solve situational tasks relating to the topic of the lessons.

3. Be familiar with:

– clinical manifestations and main pathogenetic mechanisms of acute radiation syndromes and forms;

– clinical manifestations and main pathogenetic mechanisms of acute radiation sickness;

– clinical manifestations and main pathogenetic mechanisms of chronic radiation sickness;

– clinical manifestations and main pathogenetic mechanisms of radiation sickness caused internal exposure.

Requirements for the initial level of knowledge. For better mastering of the topic student must go over the next notions from:

– Radiation and ecological medicine: «dose of exposure», «ionizing radiation», «radioresistance», «radiosensitivity», «acute radiation syndrome», «acute and chronic radiation sickness».

– Biological chemistry: «free radicals», «antioxidants» and «lipid peroxidation».

The control questions of adjacent disciplines:

1. Types of ionizing radiation.
2. Basis of ionizing radiations action.
3. The radiosensitivity. Radiation injury of man.
4. Deterministic and stochastic effects of irradiation.
5. Medical and biological effects of radiation.
6. Levels of population exposure.

7. General understanding of cell metabolism.

8. Structure of mitochondrial membranes. Complexes of the respiratory chain, participate in the processes of biological oxidation.

9. The formation and the role of free radicals in the cell.

Control questions:

1. Ionizing radiation. The definition, general characteristic.
2. Peculiarities of ionizing radiation effect as a damaging factor.
3. Dose characteristics of ionizing radiations.
4. Radiosensitivity of cells and tissues. Master factors. The notion of critical organs.
5. Reversible and irreversible radiation induced injuries of cells; destruction of cells, its kinds.
6. Radiation injuries. Etiology. Classification. General characteristic.
7. Pathogenesis of radiation injuries.
8. Acute radiation sickness. Its forms, course, outcome.
9. The characteristic of the formation period of a typical bone marrow form of acute radiation sickness, basic clinical syndromes, therapeutic principles.
10. General characteristic of chronic radiation sickness; peculiarities of etiology and pathogenesis, clinical manifestations, basic clinical syndromes.
11. Radiation sickness due to internal irradiation, its peculiarities.
12. Local effect of ionizing radiations.
13. Distant consequences of small doses of ionizing radiation on the organism.

GENERAL CHARACTERISTIC OF IONIZING RADIATION

People are exposed to natural radiation on a daily basis. Natural radiation comes from many sources including more than 60 naturally-occurring radioactive materials found in soil, water and air. Radon, a naturally-occurring gas, emanates from rock and soil and is the main source of natural radiation. Every day, people inhale and ingest radionuclides from air, food and water.

People are also exposed to natural radiation from cosmic rays, particularly at high altitude. On average, 80% of the annual dose that a person receives from a background radiation is due to naturally occurring terrestrial and cosmic radiation sources. Background radiation levels vary due to geological differences. Exposure in certain areas can be more than 200 times higher than the global average.

Human exposure to radiation also comes from human-made sources ranging from nuclear power generation to medical uses of radiation diagnosis or treatment. Today, the most common human-made sources of ionizing radiation are X-ray machines and other medical devices.

Humanity, as well as all living world in total, previously has not experienced the effects of high doses of ionizing radiation, so in the course of evolution they have not formed specific receptor structures, and haven't adapted to its damaging effect and as a result, haven't acquired strong individual defense mechanisms.

Ionizing radiation has no color or smell, no taste; its impact in high doses is so significant that it can cause severe disturbances of vital activity.

CLASSIFICATION OF IONIZING RADIATION

Different kinds of ionizing radiation are classified according to several criteria:

1. According to the physical nature of ionizing radiation there are:

– ***high-energy electromagnetic waves*** (*X-rays and* γ*-rays* accompanying the radioactive decay). *X-rays and γ-rays* are electromagnetic radiation (i. e. photons) of very short wavelength can penetrate deep into tissue (many centimeters). While some photons deposit all their energy in the body, other photons of the same energy may only deposit a fraction of their energy and others may pass completely through the body without interacting.

– ***corpuscular*** — charged particles: α*-particles (helium nuclei),* β*-rays (electrons) and neutrons without an electrical charge*.

Alpha particles are energetic helium nuclei emitted by some radionuclides with high atomic numbers (e. g., plutonium, radium, uranium); they cannot penetrate skin beyond a shallow depth (< 0.1 mm).

Beta particles are high-energy electrons that are emitted from the nuclei of unstable atoms (e. g., cesium-137, iodine-131). These particles can penetrate more deeply into skin (1 to 2 cm) and cause both epithelial and subepithelial damage.

Neutrons are electrically neutral particles emitted by a few radionuclides (e. g., californium-252) and produced in nuclear fission reactions (e. g., in nuclear reactors); their penetration depth varies from a few millimeters to several tens of centimeters, depending on their energy. They collide with the nuclei of stable atoms, resulting in emission of energetic protons, alpha and beta particles, and gamma radiation.

Because of these characteristics, alpha and beta particles cause the most damage when the radioactive atoms that emit them are *within* the body (internal contamination) or, in the case of beta-emitters, directly *on* the body; only tissue in close proximity to the radionuclide is affected. Gamma rays and x-rays can cause damage distant from their source and are typically responsible for *acute radiation syndrome.*

Their damaging effect depends on their penetration path and ionization density in the tissues. The shorter the penetration path in the tissue, the greater the density of ionization and the more is the damaging effect.

Alpha-rays have the greatest ionizing ability with a mean free path in biotissues corresponding to a few tens of microns, while — γ-rays have the smallest ability. Penetration of ionizing radiation is so great that in case of the total radiation no single area of the body is left intact.

2. According to the exposure pathways. Radiation exposure may involve:

– radioactive contamination;

– irradiation.

Radioactive contamination is the unintended contact with and retention of radioactive material, usually as a dust or liquid. Contamination may be: *external and internal.*

External contamination is that on skin or clothing, from which some can fall or be rubbed off, contaminating other people and objects. Internal contamination is unintended radioactive material within the body, which it may enter by ingestion, inhalation, or through breaks in the skin. Once in the body, radioactive material may be transported to various sites (e. g., bone marrow), where it continues to emit radiation until it is removed or decays.

Internal contamination is more difficult to remove. Although internal contamination with any radionuclide is possible, historically, most cases in which contamination posed a significant risk to the patient involved a relatively small number of radionuclides, such as phosphorus-32, cobalt-60, strontium-90, cesium-137, iodine-131, iodine-125, radium-226, uranium-235, uranium-238, plutonium-238, plutonium-239, polonium-210, and americium-241.

Irradiation is exposure to radiation but not radioactive material (i. e., no contamination is involved). Radiation exposure can occur without the source of radiation (e. g., radioactive material, x-ray machine) being in contact with the person. When the source of the radiation is removed or turned off, exposure ends. Irradiation can involve the whole body, which, if the dose is high enough, can result in systemic symptoms and radiation syndromes (e. g., Acute Radiation Syndrome), or a small part of the body (e. g., from radiation therapy), which can result in local effects. People do not emit radiation (i. e., become radioactive) following irradiation.

3. By the duration of exposure:

– *single*;
– *fractional*;
– *prolonged*.

In case of fractional and prolonged exposure the damage caused to the body is greater than in case of a single exposure (more than the total absorbed doses).

HARMFUL EFFECTS OF IONIZING RADIATION

The effects of ionizing radiation are revealed at all levels of biological organization (table 1). It is fraught with *local* changes (radiation burns, necrosis, cataracts), *general* ones (Acute and Chronic Radiation Sickness) and *long-term effects*.

The degree of severity of the biological and clinical effects, the type of radiation reactions, their importance to the body and the development time (immediately after exposure, shortly after, or after a long-term period) are determined by: 1) *the kind of ionizing radiation*; 2) *its physical characteristics*; 3) *radiation dose (dose-effect)*; 4) *its power (dose-effect power)*; 5) *nature of exposure (external or internal, general or local, single or fractional)*; 6) *total reactivity of the organism*; 7) *radiosensitivity of the tissues, organs and systems essential for the survival of the organism.*

Table 1

Effects of radiation exposure on all levels of biological organization

Levels of biological organization	Radiation damage
Molecular	damage of enzymes, DNA, RNA, metabolism
Subcellular	damage of cell membranes, nuclei, chromosomes, mitochondria, lysosomes
Cellular	ceasing of cell division and cell death, transformation into malignant cells
Tissue, organ	damage of the central nervous system, bone marrow, gastrointestinal tract
Body	the reduction in the organism life or death
Population	genetic changes due to mutations

Radiosensitivity is the ability of the living organism to respond to the impact of ionizing radiation by a definite reaction.

Cells and tissues differ in their radiosensitivity. According to the Bergonie-Tribondeau Law (1906) *radiosensitivity is based on the metabolic state of the tissue being irradiated.* Low metabolic rate decreases radiosensitivity, however high metabolic rate increases it. Thus, the radiation sensitivity of tissue is directly proportional to their proliferative activity and inversely proportional to the degree of differentiation of its component cells.

Radiation injury occurs in various forms, with each type dependent on the ionizing radiation involved, its penetrating ability, the portion of the body exposed, the exposure duration, and the total dose. Radiation injury occurs most readily in tissues and organs consisting of rapidly proliferating cells, as, for example, skin, lining of the gastrointestinal tract, and a bone marrow, where progenitor cells multiply continuously to replace the mature cells that are constantly being lost through normal aging. The effects of radiation on these organs result primarily from the destruction of the progenitor cells and the consequent interference with the replacement of the mature cells, which is so vital to the maintenance of tissue structure and function.

According to sensitivity to ionizing radiation two types of cells and tissues can be distinguished:

a) *radiosensitive* (dividing cells and poorly differentiated tissue), i. e. the blood-forming cells of the bone marrow, the germ cells of the testes, intestinal and skin epithelium;

b) *radioresistant* (nondividing cells and differentiated tissues), i. e. brain, muscles, liver, kidney, cartilage, ligaments (except for *lymphocytes*, which in spite of their differentiation and inability to divide are highly sensitive to the ionizing radiation).

According to susceptibility to ionizing radiation tissues can be located in the following descending order of priority: 1) *lymphoid cells*; 2) *germ cells*; 3) *proliferating bone marrow cells*; 4) *intestinal epithelial cells*; 5) *epidermal stem cells*; 6) *hepatic cells*; 7) *epithelium of lung alveoli and biliary passages*; 8) *kidney epithelial cells*; 9) *endothelial cells (pleura and peritoneum)*; 10) *connective tissue cells*; 11) *bone cells*; 12) *muscle, brain, and spinal cord cells.*

Organs or systems with the highest radiosensitivity are called ***critical***. These include: *red bone marrow, gonads, lens, epithelium of mucous membranes and skin.*

It is discovered, that the more complex the living organism is, the more it is sensitive to radiation.

PATHOGENESIS OF RADIATION INJURY

The structural and metabolic theory by A. M. Kuzin, 1986 reveals pathogenesis of radiation damage most fully. According to this theory the effects after of radiation exposure occur at all levels of biological organization (molecular, cellular, organ, tissue, and organism) and are realized by the interaction of both the processes normally occurring in the body and processes developing after exposure.

In accordance to the theory in the development of radiobiological injury the following stages are usually distinguished:

1) the primary effect of ionizing radiation on the irradiated structure (direct and indirect) (*molecular level*);

2) the effects of ionizing radiation on cells *(cellular level)*;

3) the effects of radiation on the entire organism *(organism level).*

1. ***The primary effects of ionizing radiation*** consist of the following phases:

– *physical* — physical interaction, absorption of the radiation energy;

– *radiation and chemical processes* — formation of free radicals (due to radiolysis of water) and radiotoxins;

– *radiation damage of biochemical processes* (as a result of radicals and radiotoxins influence);

– *ultrastructural and visible damage*.

The primary effect of ionizing radiation can be *direct* (immediate) and *indirect* (mediated).

The *direct* effects of ionizing radiation include the changes resulting from the absorption of radiation energy by target molecules of the irradiated tissue (fig. 1). It is manifested by ionization, excitation of atoms and molecules of all the constituent elements of the body.

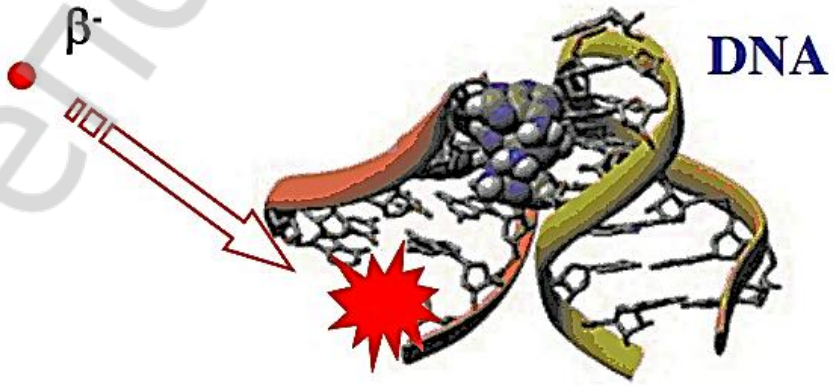


Fig. 1. Direct Radiation Damage

The most dangerous is water ionization (radiolysis-induced activity), resulting in the formation of free radicals (atomic hydrogen (H·), hydroxyl (OH·), hydroperoxyl (HO_2·), hydrogen peroxide (H_2O_2). Also a free electron (e-) combines with water and forms the negative water molecule called «heavy water», a precursor to the hydroxyl radical ($OH^{\cdot}$) (fig. 2).

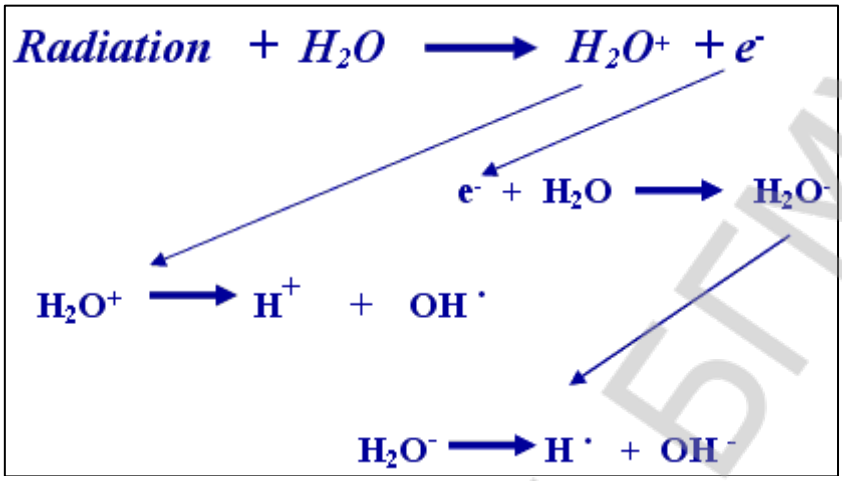


Fig. 2. Radiolysis of water

There are four potential outcomes for those chemical species formed by radiolysis (fig. 3).

1. **Two hydroxyl radical can combine to form hydrogen peroxide (H_2O_2) that is converted back to water by the organelle called the peroxisome:**

$$OH^{\cdot} + OH^{\cdot} \longrightarrow H_2O_2$$

2. **The hydrogen radical and the hydroxyl radical can combine to form water:**

$$H^{\cdot} + OH^{\cdot} \longrightarrow H_2O$$

3. **The hydrogen ion and hydroxyl ion can combine to form water:**

$$H^{+} + OH^{-} \longrightarrow H_2O$$

4. **The hydrogen free radical can combine with molecular oxygen to form a highly reactive hydroperoxyl radical which continues the chain of radical damage to biomolecules:**

$$H^{\cdot} + O_2 \longrightarrow HO_2^{\cdot}$$

Fig. 3. Potential outcomes of water radiolysis

Free radicals then react with enzyme systems containing SH-groups, converting them into inactive disulfide groups (S=S).

Direct interaction of free radicals with cell can cause injury of cellular macromolecules (proteins or DNA) and either kill the cell or cause the mutation of the DNA.

Many different types of direct hits can occur, and the type of damage that occurs determines whether or not the cell can repair itself. Generally, if a direct hit causes a complete break in the DNA or some other permanent damage, the cell dies immediately or will die eventually. However, humans have an abundance of cells and somatic cellular reproduction (mitosis) is always occurring to replace cells that die. Therefore, it is only when this system of replacing cells fails that radiation effects are seen. This occurs at higher doses of radiation. In M phase of mitosis (in which cells divide in two) the chromosomes are condensed and paired. So it is the most radiosensitive. More DNA is present in one area at this point in the cycle, which is why it is theorized that this is the most radiosensitive time.

Indirect (mediated) effects of ionizing radiation are associated with changes in the structure of DNA, enzymes, proteins, etc., induced water radiolysis or dissolved substances, causing an oxidation reaction, formation of lipid and quinone primary «radiotoxins» inhibiting the synthesis of nucleic acids. *Radiotoxins* are free radical oxidation products forming in irradiated tissues of the organisms. They suppress the activity of enzymes; increase the permeability of biological membranes changing the diffusion processes in a cell; cause metabolic disorders, structural and functional damage of cells, organs and body systems.

It occurs when radiation energy is deposited in the cell, and the radiation interacts with cellular water rather than with macromolecules within the cell.

The reaction that occurs is radiolysis of the water molecule, resulting in a hydrogen molecule and hydroxyl radical molecule. If the 2 hydroxyl molecules recombine, they form hydrogen peroxide, which is highly unstable in the cell. This will form a peroxide hydroxyl, which readily combines with some organic compound, which then combines in the cell to form an organic hydrogen peroxide molecule, which is stable.

In the pathogenesis of radiation damage lipid radiotoxins (lipid hydroperoxides, epoxides, aldehydes, ketones) are considered to be of the great significance. Being intermediate and final products of lipid peroxidation, they accumulate in the cell membranes impairing their barrier functions.

Antioxidants block hydroxyl radical recombination into hydrogen peroxide, preventing stable organic hydrogen peroxide compounds from occurring. This is one way in which the body can defend itself from indirect radiation interactions on a cellular level, and is one reason why antioxidants have received so much attention recently as radioprotectors and cancer prevention agents.

2. ***The effects of ionizing radiation on cells.*** Violation of organelles ultrastructure and associated with it changes in metabolism are the basis of the radiation damages *on cell level*.

Failure of cytoplasmic structures is manifested by violation of the energy supply of cells and cell membrane permeability, changing of metabolism, damage of lysosomes integrity leading to autolysis and finally to cell death.

Changes in the cell nucleus lead to inhibition of DNA synthesis. Single-strand and double strand breaks appear, leading to chromosomal aberrations and gene mutations. In case of single-strand breaks and other minor injuries reparative processes can develop. Nucleus damage leads to the synthesis of modified proteins that subsequently contribute to the formation of malignant tumors, secondary radiotoxins causing radiation sickness and premature aging. Cell genome and the chromosomal apparatus damages are the most dangerous as they lead to disruption of mitosis.

In high doses (tens and hundreds of Gy) lethal changes occur in cells, leading to their death prior to the entry into mitosis (interphase death).

Cell death is the basis of radiation damage of the body. *Interphase death* is preceded by changes in the permeability of the nuclear, mitochondrial and cytoplasmic membranes. Changes in the structure and permeability of the lysosomal membranes lead to the release and activation of DNase, RNase, cathepsins, phosphatases, glycosaminoglycan enzymes hydrolysis and others. There is also depression of cellular respiration and degradation of the deoxyribonucleic complex in the nucleus and various degenerative changes (pyknosis of nuclei, fragmentation of chromatin, etc.).

At lower doses, a *reproductive form of death* may occur, the main causes of reproductive cell death are structural DNA damages (chromosome aberration) caused by radiation. All dividing cells and significantly renewed tissues (hematopoietic, immune and intestinal mucosa, reproductive cells) die.

There are two mechanisms of ray cell death: *apoptosis and necrosis.*

At *apoptosis* death begins with changes in the nuclear. Morphologically, *apoptosis* is characterized by cellular shrinkage, chromatin condensation, nuclear fragmentation, and membrane blebbing (fig. 4). In response to radiation, apoptosis is predominantly observed in cells of the hematopoietic system, and it is critically regulated by the mitochondrial, intrinsic death pathway.

The cardinal events involve the permeabilization of the mitochondrial outer membrane (MOMP) and the release of various proteins from the mitochondrial intermembrane space into the cytosol, thus stimulating the formation of the apoptosome, activation of effector caspases and promote the final stages of apoptosis and the disintegration of the cell. In apoptosis development the crucial role play the hyperactivation of the DNA repair enzyme poly-ADP-ribose-polymerase (PARP) and the subsequent and substantial depletion of intracellular ATP levels.

Necrosis is characterized by violation of permeability of biological membranes and swelling of cell organelles and secondary changes in the nucleus. Of all cellular responses the most universal is temporary inhibition of cell division (mitosis blocking radiation) (fig. 4). Delay in time division depends on the radiation dose and rises with its increase, and the stage of the cell cycle in which cells are located in case of radiation: the longest time is in cases when the cells are irra-

diated at the stage of DNA synthesis or postsynthesis; and the shortest time is in case of radiation in mitosis. In contrast to the time of oppression, the complete suppression of mitosis occurs after exposure to high doses of ionizing radiation, when the cell continues to live for a long time, but irreversibly loses its ability to divide. As a result of an irreversible reaction to radiation giant cells abnormal forms containing multiple sets of chromosomes due to their replication within one and the same nondivided cell often develop.

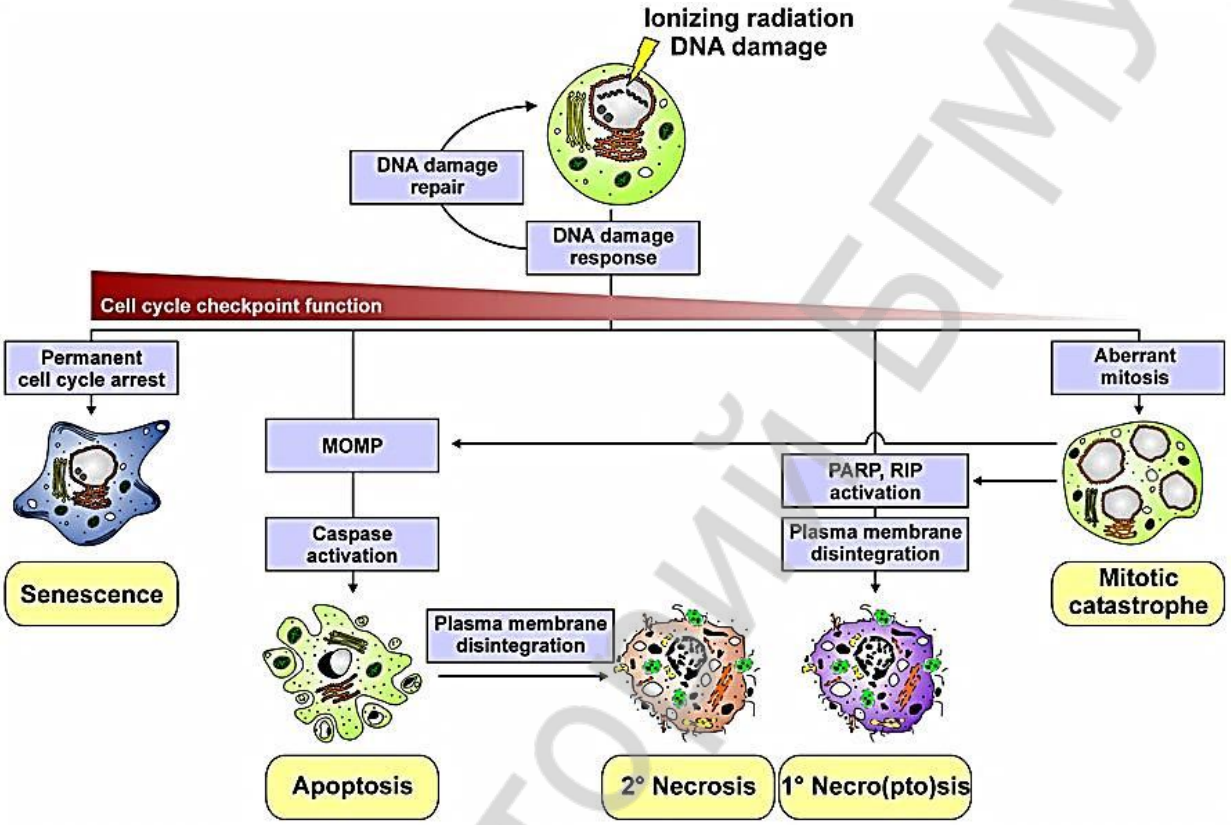


Fig. 4. Different cell death modalities induced by ionizing radiation
(figure mentioned in http://journal.frontiersin.org/article/10.3389/fonc.2012.00116/abstract)

In case of radiation there are other secondary mechanisms of death. For example, the collapse of cells or tissues may occur due to impaired circulation, hemorrhage and hypoxia.

3. ***The effects of radiation on the entire organism.*** The effects of ionizing radiation on the whole organism are revealed in the form *of Radiation Sickness.*

Human Radiation Sickness is a disease developing as a result of the radiation effects on the body in doses exceeding the permissible levels. Changes in the nervous and endocrine systems, violations in the activity of other body systems along with the cell-tissue lesions form the clinical manifestations of Radiation Sickness.

There are: *1. Acute Radiation Sickness. 2. Chronic Radiation Sickness. 3. Radiation Sickness Caused Internal Exposure.*

ACUTE RADIATION SICKNESS

Acute radiation sickness or **acute radiation syndrome** (ARS) is a term used to describe a constellation of signs and symptoms that occur after whole-body or significant partial-body irradiation of certain amount of radiation (> 1.0 Gy) delivered at high-dose rate. These signs and symptoms are the consequences of severe radiation damage of organism.

Acute Radiation Sickness occurs after *total single external uniform* irradiation in the dose of *more than 1.0 Gy.* In such a case all systems, organs, tissues and cells are exposed to radiation in the same dose. Acute Radiation Sickness is a kind of cell-tissue pathology due to direct radiation damage of the irradiated biosubstrates.

ACUTE RADIATION SYNDROMES

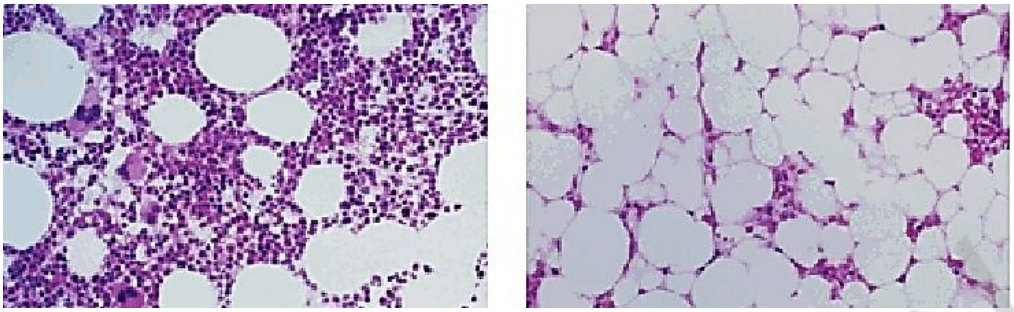
In development of Acute Radiation Sickness three major clinical syndromes are distinguished:

1. ***Bone marrow (hematologic) syndrome***. The full bone marrow syndrome usually will occur with a dose between 0.7 and 10 Gy (70–1,000 rads) though mild symptoms may occur as low as 0.3 Gy (30 rads).

Hematopoietic stem cell and progenitors cells of the bone marrow that are rapidly dividing cells (stem cell compartment and differentiating compartment) are highly sensitive to the effects of ionizing radiation. Animal studies indicate that hematopoietic stem cells have a D_0 of about 0.95 Gy. It means that a dose of 0.95 Gy reduces the population of stem cells to 37 %. For this reason, hematopoietic syndrome is seen with radiation exposures exceeding 1 Gy. At doses below 1 Gy, surviving proliferating cells (through accelerated proliferation) will be able to replenish mature functioning compartment and only an insignificant clinical decrease in blood cell counts can be seen. As the absorbed dose increases, more and more hematopoietic stem cell and precursors cells will be killed and only a few cells or no cells will enter in post-mitotic compartment. Mature circulating cells unaffected by radiation will die after their lifespan at their physiological rate. So, the *basic reason* of this syndrome development is the primary radiation damage of the progenitor cell elements, mainly stem cells, and mass death of dividing cells in the bone marrow, which lead to hypo- or aplastic anemia (fig. 5).

The onset of signs and symptoms will appear depending on the physiological cellular loss rate of circulating cells and the dose-dependent reduced supply of mature cells from the depleted proliferating compartments. The balance between these two phenomena results in different degree of *pancytopenia* with predisposition to *infection* due to leucopenia and *bleeding* due to thrombocytopenia.

The severity of signs and symptoms (hypoplasia or aplasia of the bone marrow) and the probability to recover will depend on the absorbed dose, the dose rate and the overall bone marrow volume irradiated. If no regeneration, death usually occurs due to infection and/or hemorrhage at doses of 4.5–6 Gy without supportive care.



a ***b***

Fig. 5. Bone marrow biopsy specimen from healthy patient (*a*), aplastic anemia patient (*b*). Complete absence of hemopoietic cells in bone marrow (*b*).
http://www.angelfire.com/apes2/bharaty/Diagnosis.htm

2. *Gastrointestinal (epithelial cell) syndrome*. The full gastrointestinal syndrome usually will occur with a dose between 10 and 100 Gy (1000–10 000 rads) though some symptoms may occur as low as 6 Gy or 600 rads.

Survival is extremely low with this syndrome. Clinical signs and symptoms are due to the lack of cells replacement in the surface of the villi because stem and proliferating cells located in the crypts are damaged by radiation and die in mitosis (fig. 6, 7, 8).

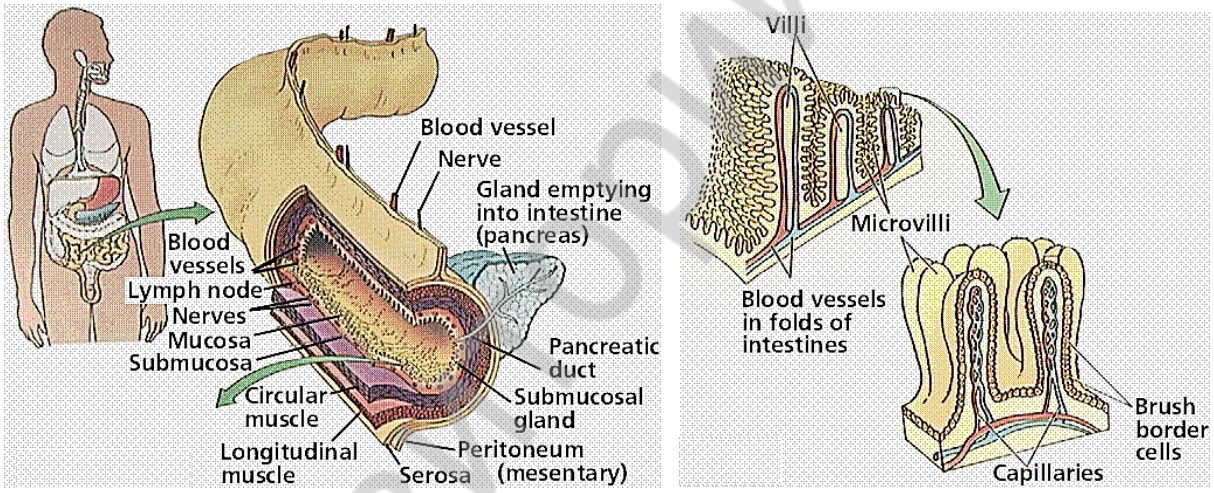


Fig. 6. Morphological structure of gastrointestinal tract

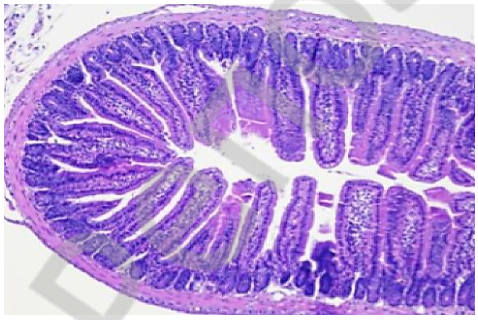


Fig. 7. Normal Jejunum

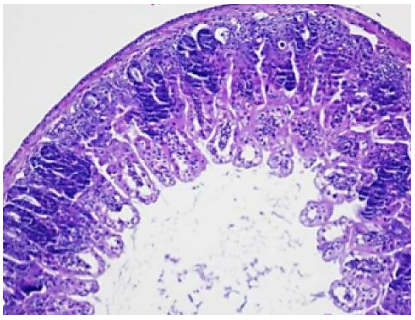


Fig. 8. Damaged Jejunum

Images above represent the epithelial architecture of the villi and crypts of normal jejunum (left) and damaged jejunum (right) 4 days after exposure to radiation.
http://www.biomodels.com/animal-models/radiation-countermeasures/gastrointestinai-acute-radiation-syndrome-gi-ars

Between 7 and 10 days after exposure, the denudation of intestinal mucosa produces watery *diarrhea, dehydratation and electrolyte loss, gastrointestinal bleeding and perforation.* The breakdown of the mucosal barrier facilitates the entry of bacterias into the bloodstream. Of course, the immunosuppression associated with the hematopoietic syndrome favors opportunistic infections and thrombocytopenia favors hemorrhage. Death from the gastrointestinal syndrome usually occurs within two weeks and is due to sepsis, bleeding, dehydratation and multisystem organ failure.

3. *Cerebral syndrome*. The full cerebral syndrome usually can occur with a dose greater than 50 Gy (5,000 rads) though some symptoms may occur as low as 20 Gy or 2,000 rads. Cerebral syndrome is characterized by the damage of the central nerve system, violation of the blood circulation and the flow of cerebrospinal fluid with the development of *brain edema and coma*. The cause of nerve cells death may be their direct or indirect damage (damage of other systems, such as blood vessels). Death occurs within three days.

FORMS OF ACUTE RADIATION SICKNESS

Depending on the ionizing radiation dose that causes Acute Radiation Sickness and the prevalence of this or that a syndrome there are several forms of Acute Radiation Sickness: 1) *Typical Medullary*; 2) *Intestinal*; 3) *Toxemic*; 4) *Cerebral* form.

I. Typical Medullary (*or bone marrow*) form of ARS develops during irradiation by the doses equal to 1–10 Gy and is characterized by a primary lesion of the bone marrow (*bone marrow syndrome*). Mortality rate is 50 %.

During this form of Acute Radiation Sickness three periods are distinguished:

– *the period of formation;*
– *the period of recovery;*
– *the period of outcomes and consequences.*

1. *The period of formation* takes place in four phases: a) *prodromal* — phase of primary acute reaction; b) *latent* — clinical phase of the imaginary well-being; c) *critical* — phase of the expressed clinical manifestations; d) *final* — early recovery phase.

a) *Prodromal phase or primary acute reaction* occurs at doses exceeding 1 Gy, develops during the first minutes, hours after exposure and lasts for 1–3 days. Such symptoms as nausea, vomiting, dry and bitter taste in the mouth, feeling of heaviness in the head, headache, weakness, drowsiness appear. In severe cases decrease of blood pressure, transient loss of consciousness, low-grade fever, asymmetry of tendon reflexes, cutaneous vasomotor reactions may also occur. As a result of radiation injury of cells *in the peripheral blood* the neutrophil leukocytosis with the leukocyte count shift to the left, alternated with leukopenia, absolute and relative lymphopenia may be observed. *In the bone marrow* the reduction of the mitotic index and the disappearance of young forms of cells are noted. The resulting activation of the pituitary-adrenal system leads to the increased secretion of adrenal hormones, which may have adaptive significance.

b) *Latent or clinical phase of the imaginary well-being* is characterized by switching on the protective mechanisms of the body. The state of patients' health becomes satisfactory and clinical signs of disease disappear. The duration of this phase is from 1–2 weeks to 1 month. However, at this phase the growing blood damage may be observed (lymphopenia which progresses against leukopenia, neutropenia, reduced content of reticulocytes and platelets). In the bone marrow depletion of all sprouts of blood circulation, hair removal, gonads atrophy, changes in the small intestine and skin may develop.

c) *Critical or phase of the expressed clinical manifestations*. The health of patients is sharply deteriorating. Increasing weakness recurrence of dyspeptic disorders, fever, increased erythrocyte sedimentation rate, progressive anemia and thrombocytopenia agranulocytosis, hemorrhagic syndrome (degree of severity varies widely, depending on the severity), additional injuries increase bleeding events are observed. Lymph nodes are increased at the expense of hemorrhagic impregnation. Profuse bleedings within the skin, mucous membranes, stomach, intestines, adrenal glands, lungs, brain and heart may be crucial in the outcome of the disease. The situation is aggravating by the emerging infectious complications including ulcerous-necrotic gingivitis, necrotic angina, pneumonia, inflammatory changes in the intestine. All this poses a threat to the life of the patient.

d) *Final or early recovery phase* is characterized by normalization of body temperature, general state, appetite and sleep, ceasing of bleeding, dyspepsia, gaining body weight, restored morphological and biochemical parameters of blood and urine. The duration of the recovery phase is 2–2.5 months, although some manifestations (alopecia, the ability to reproduce) are only resumed in 4–6 months.

The total duration of Acute Radiation Sickness formation period and its phases are determined by the dose and the individual radiosensitivity of the body. Fatal outcome is also possible.

2. *The period of recovery.* Recovery or death depends on the absorbed dose, dose rate and the heterogeneity of exposure. Most patients who do not recover will die within several months of exposure. The recovery process lasts from several weeks up to two years.

3. *The period of outcomes and consequences.* The outcomes and consequences with patients after Acute Radiation Sickness vary on the amount absorbed and the time frame of when the radiation is taken in to when the person seek medical attention. It may be asthenic syndrome, functional failure of the bone marrow of different degree, the tendency to leucopenia, etc.

Depending on the radiation dose there are four degrees of severity of ARS typical medullary form: *mild (1–2 Gy)*; *moderate (2–4 Gy)*; *severe (4–6 Gy)* and *very severe (more than 6 Gy).*

A good summary of signs and symptoms and their correlation with absorbed doses has been published by the International Atomic Energy Agency (IAEA) and is reproduced in table 2–4. The time course and severity of clinical signs and symptoms are summarized in table 5 (Appendix).

II. Intestinal form of Acute Radiation Sickness occurs in case of radiation exposure in the dose range of *10–20 Gy*. The main clinical manifestations associated with lesions of the gastrointestinal tract are as follows: nausea, vomiting, bloody diarrhea, flatulence, paralytic ileus. Leukopenia, lymphopenia and sepsis may also be noted. Death (often 100 %) occurs due to dehydration, accompanied by loss of electrolytes and protein, development of the irreversible shock, associated with the activity of microbial and tissue toxins, intoxication of the organism by the intestinal content due to impaired intestine barrier function.

III. Toxemic form of Acute Radiation Sickness occurs when the body is exposed to radiation at doses of *20–80 Gy*. It is revealed by the pronounced hemodynamic disturbances (mainly in the intestine, liver), vascular paresis, tachycardia, bleeding, severe autointoxication and meningeal symptoms (swelling of the brain). Oliguria and hyperasotemia are also observed as a result of kidney damage. Intoxication of the body by the products of food decay is developed. Death occurs in 4–7 days (*100 % mortality rate*).

IV. Cerebral form of Acute Radiation Sickness occurs when the body is exposed to radiation at doses of *80 Gy or higher*. Death occurs within 1–3 days immediately after or during the exposure («death under the beam»). It is characterized by the development convulsively paralytic syndrome, disorders of the blood and lymph circulation in the central nervous system, vascular tone and body temperature. Later disorders of the gastrointestinal tract appear resulting in a progressive decrease in blood pressure (*100 % mortality rate*). The cause of death is severe and irreversible central nerve system disorders characterized by significant structural changes, loss of cortical cells and hypothalamus nuclei neurons.

CHRONIC RADIATION SICKNESS

Chronic Radiation Sickness (CRS) is an independent form of radiation pathology, emerging from an extended single-and multiple-body irradiation by small doses and the intensity of 0.1–0.5 cGy/day and after a total dose of 0.7–1.0 Gy. It differs by the phase of development. Specific features of chronic radiation sickness depend on the nature of external exposure, diverse clinical syndromes, a combination of damage symptoms of critical organs and the adaptive nature of the reactions.

Chronic Radiation Sickness is never developed as the outcome of Acute Radiation Sickness. But clinical picture of CRS is largely similar to the one which stay for the whole life of patient after ARS (asthenic syndrome, different degrees of bone marrow failure, a tendency to leukopenia).This is due to the fact that at the basis of development of both Chronic Radiation Sickness and the residual effects after ARS are the same mechanisms of radiosensitive cell damage with the development of repair processes, resulting in save of more radioresistant stromal cells.

There are two variants of CRS:

1) with a *detailed clinical syndrome* caused by a common external exposure or intake of isotopes that is uniformly distributed in the organs and tissues;

2) with a *clinical syndrome of pre-emptive destruction of individual organs and systems* from internal or external exposure.

The general reactions of the organism with Chronic Radiation Sickness include: impairment of neurovisceral regulation, asthenia, organic central nerve system lesions (disseminated encephalomyelosis) changes of regional and general hemodynamics (vegetative dystonia, circulatory disorders in the brain, skin, extremities), the development of myocardial dystrophy, inhibition of secretory and enzyme activity of the digestive glands, motility disorders of the stomach and intestines, hypo-and an acidic gastritis, leukopenia and neutropenia with a shift to the left of white blood cells on degenerative type, thrombocytopenia; with a large dose of radiation — anemia. The risk of leukemia increases with long-term exposure.

There are three severity degrees of Chronic Radiation Sickness due to a common exposure: mild (1), moderate (2) and severe (3).

1. *Mild or first degree* is characterized by fatigue, headache, and sleep disorders, disorders of various organs, transient leukopenia, thrombocytopenia.

2. *Moderate or second degree* is characterized by hematology, hemorrhagic and asthenic syndrome.

3. *Severe or third degree* is characterized by irreversible changes (!): hypoplasia of hematopoietic tissue; gastrointestinal mucosa; infectious and toxic complications; circulatory disorders; necrotizing character inflammatory process

RADIATION SICKNESS CAUSED INTERNAL EXPOSURE

Radiation Sickness caused internal exposure is an independent nosological form that is predominantly *chronic disease*, with a selective damage of individual organs and systems. It differs significantly from Radiation Sickness due to an external radiation, and is caused by the penetration of radioactive substances in the body.

Internal exposure compared with the outside one is fraught with more serious consequences for the organism, as nowadays there are no enough effective methods of protection. At this form of pathology there is a contact exposure — prolonged exposure to the tissue; there is no absorption of α-particles by horny layer of the skin (in which radionuclides are concentrated), as a result organs and tissues are damaged.

Radioactive substances can come to the organism by different ways, singly or multiply. Depending on the dose, they lead to different effects: from minor impairments of the body (radiation reaction) to the actual Radiation Sickness.

Specific features of the Radiation Sickness development in case of an internal exposure are determined by the ways of radionuclides penetration and the type of their distribution in the body.

Distribution of radionuclides in the body depends on their properties and chemical nature and comes in three basic types: *skeletal, reticuloendothelial and diffuse*.

Radionuclides of alkaline-earth elements accumulating in the mineral part of the skeleton, — calcium, strontium, barium, radium are distributed mainly on the skeletal type. Reticuloendothelial type of a distribution is characteristic of rare earth element nuclides — zinc, thorium, americium, transuranic elements. Alkaline elements — potassium, sodium, cesium, rubidium, hydrogen and other nuclides are distributed on the diffuse type.

It is known «organotropic» radionuclides which are selectively accumulated in certain organs (e. g., isotopes of iodine accumulating in the thyroid gland).

The clinic of Radiation Sickness from an internal radiation consists of syndromes of a general and selective (local) damage in areas of predominant penetration of radioactive substances to the body, their removal and accumulation in tissues and organs.

LOCAL EFFECTS OF IONIZING RADIATION

Radiation burns (or radiation dermatitis) occur in the local impact of ionizing radiation. They may be the result of an overdose of radiation therapy, accidents at nuclear reactors, skin radioactive isotopes, etc.

Symptoms of radiation dermatitis include hair loss, dry or wet peeling skin (desquamation), decreased sweating, edema, ulcerations, bleeding, and skin cell death (fig. 9). The extent of the symptoms depends on the total radiation dose, the size of the irradiated area and the type of radiation.

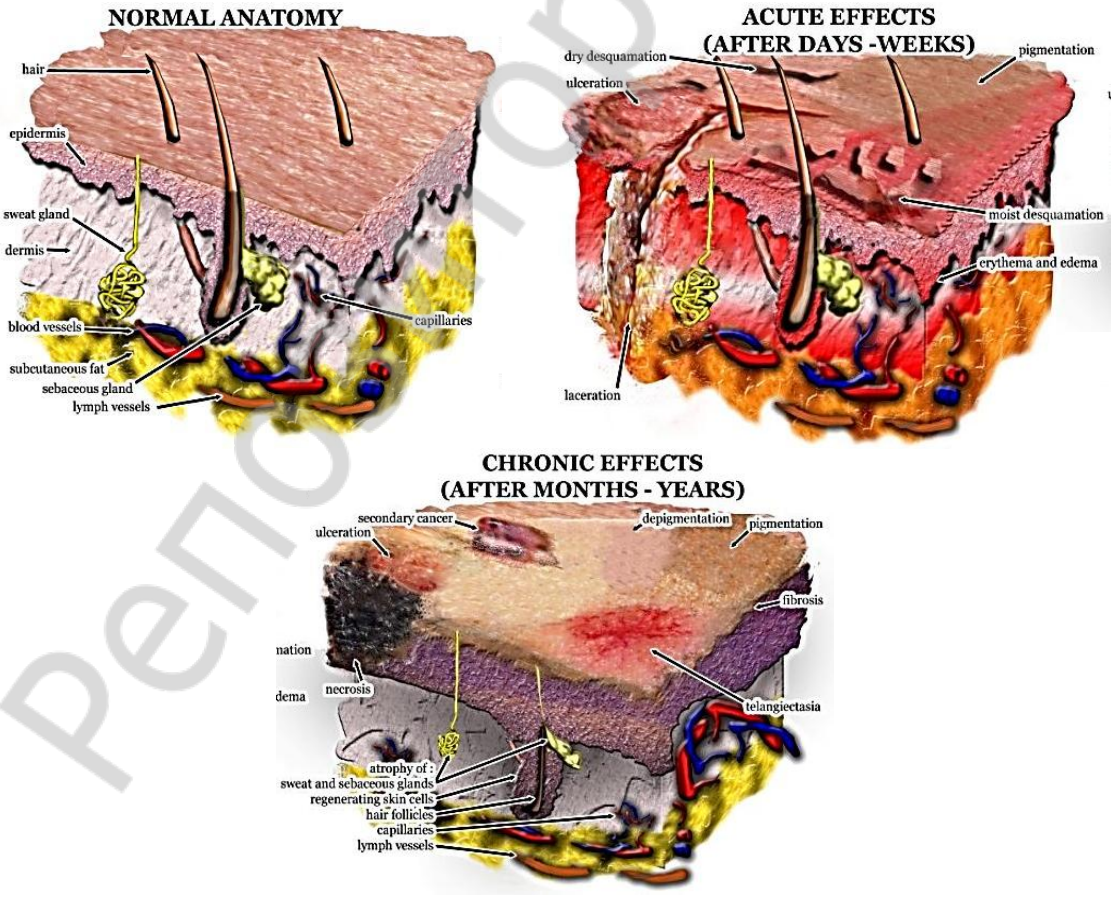


Fig. 9. Effects of ionizing radiation on the skin (http://en.academic.ru/dic.nsf/enwiki/11595994)

According to the severity there are three degrees of radiation burns: *easy, medium, severe.* In the latter case, not only the skin dies but also the subcutaneous tissue, fascia, muscles and bones; spot hemorrhage, necrosis, phlebitis, venous thrombosis, recurrent erosions and ulcers, severe pain, high leukocytosis, fever appear.

At the site of healed ulcers scars which are prone to ulceration and malignancy are formed.

MEDIATED EFFECTS OF IONIZING RADIATION

Nervous and endocrine systems injury. In the irradiated organism damages of some organs, tissues and systems will inevitably cause changes in others, and indirect effects usually associated with a local radiation exposure are developed. Basic regulatory systems of the body — the nervous and endocrine are involved in their formation. An example of mediated reactions may be the painful condition which is similar to alcohol intoxication, developing in the local radiation therapy — «beam hangover».

Marked changes are observed in non-critical organs and tissues — the sense organs, nervous, endocrine, immune, cardiovascular, respiratory, digestive (except the small intestine), musculoskeletal systems, liver and excretory organs, reproduction, and others which are not responsible for the outcome of radiation injury.

Immune system damage. A special role in the pathogenesis of Radiation Sickness belongs to the changes of the immune system, which occupies an intermediate position between the critical and non-critical systems of the body. The immunosuppression and immunodeficiency appear; resistance to infectious agents due to the loss and dysfunction of the white blood cells decreases, as well as autoimmune processes develop.

Changes in metabolism. Radiation exposure affects metabolism. In radiosensitive tissues cells undergoing interphase death, metabolic changes mainly occur in the inhibition of DNA synthesis and activation of glycolysis; the oppression of the biosynthetic process and a sharp increase of catabolism take place in the late stage.

Thus, impairments of various organs and systems in the far-off periods after the irradiation are determined not only by direct changes in the cells of these systems; they may be the result of the damages of the neuroendocrine regulation determining an adaptive-compensatory reduction of the body.

PROTECTIVE AND ADAPTIVE RESPONSES AND RECOVERY PROCESSES IN THE IRRADIATED ORGANISM

Along with signs of damage and dysfunction in the irradiated organism the recovery intra- and intercellular compensatory-adaptive processes are developed.

First of all, this is a *proliferation of cells saving their vitality*. Due to this a cell population of critical organs and their functional activity are restored.

Reserve for cell proliferation of critical organ and tissues can be both unaffected cells and cells partially reversible damaged which restored their ability to reproduction.

At the same time there is reparation at the tissue, cellular and subcellular levels, the most important mechanism of which is the *hyperplasia and hypertrophy of cells and cell ultrastructure*.

Recovery of the body after exposure is largely associated with the regeneration of remaining viable hematopoietic pluripotent stem cells. *Active regeneration of the bone marrow* results in a quantitative normalization of its cellular elements. The increase in the number of cells occurs as sooner as the dose is lower.

Depending on the severity of Radiation Sickness recovery period lasts from 2 weeks to 1 month or more. Actively proliferating tissues have the highest rate of reparation. Reparation of weak renewed tissues comes slower. Residual effects may remain until the end of life (general weakness, unstable hematopoiesis, reduced resistance, etc.). But even a full recovery does not guarantee absence of long-term effects at patient and the genetic and congenital disorders at posterity.

DISTANT CONSEQUENCES OF RADIATION EXPOSURE

Distant consequences of exposure — various changes which occur in long-term period (10–20 years or more) after the RS in the body, apparently completely «cured» and recovered from radiation damage.

It is distinguished generic and somatic effects (tumor and non-tumor). It is necessary to take into consideration *stochastic and non-stochastic effects* in assessing the possible effects of exposure.

Stochastic effects are effects of probable and accidental character. Probability of their manifestations exists at low doses of IR and increases with the dose, but the severity of a radiation manifestation does not depend on the radiation dose.

The consequences of stochastic effects include:

a) Cancer, leukemia contributing to the development of somatic effects of exposure in low dose. They are identified only by a prolonged follow-up (15–30 years) of large groups of people (dozens, hundreds of thousands of people);

b) Hereditary pathology manifested in offspring of exposed individuals is the result of the genome damage of sex cells. Changes in the genetic apparatus — «genetic load» is now found in infants in many countries. Conditions increasing the «genetic load» in 2 times are dangerous to the viability of the society.

Non-stochastic effects are consequences appearing after the accumulation of dose greater than the threshold. In this case, the severity of damage is changed depending on the dose (radiation cataracts, reproductive disorders, dyshormonal status, obesity, panhypopituitarism, cosmetic skin defects, sclerotic and degenerative destruction of connective tissue, liver cirrhosis, nephrosclerosis, damage of the embryo and fetus, reduction of life expectancy).

Thus, in assessing the mutagenic action of IR is necessary to distinguish the genetic effects of radiation occurring in somatic cells, from those in the sex ones.

The damage of the somatic cell genome leads to leukemia, cancer and premature aging, i. e. affects only the irradiated organism, and it is not transmitted to the next generation.

Radiation effects in the germ cells lead to the formation of genetically abnormal gamete. It may lead to death of zygote or embryo at different stages of development, to the birth of individuals with congenital anomalies or individuals having new unfavorable genes in the heterozygous state. Thus, the mutagenic effect caused by radiation in sex cells, is transmitted from generation to generation.

So, there are the following mechanisms of long-term exposure effects formation: 1) the accumulation of damage in the genetic apparatus of somatic and sex cells, 2) violation of gene activity, 3) disorders of neuroendocrine regulation determining the reduction of the body adaptation.

CORRECTION OF VIOLATIONS OF ORGANS AND SYSTEMS AT RADIATION DAMAGE

- Supportive care in clean environment;
- Stimulation of hematopoiesis (use of growth factors, i. e., GCSF, GMCSF, interleukin 11);
- Recovery hematopoiesis (stem cell transfusions: cord blood, peripheral blood or bone marrow transplantation); Platelet transfusions if bleeding occurs or if platelet count too low;
- Eliminate the infection, intoxication, hemorrhagic phenomena;
- Restoration of the function of the nervous, endocrine, digestive, cardiovascular system;
- Recovery cellular processes; increase tissue respiration;
- Stabilization of cell membranes;
- Decrease lipid peroxidation processes and intensity of the oxidation process;
- Inhibition of chain radiation-induced reactions;
- Liquidation immunodeficiency (drugs thymus, immunomodulators);
- Psychological support.

Appendix

Table 1

Signs and symptoms of prodromal phase

Signs and symptoms	Mild (1–2 GY)	Moderate (2–4 GY)	Severe (4–6 GY)	Very severe (6–8 GY)	Lethal (> 8 GY)
Vomiting Onset % of incidence	≥ 2 h after exposure 10–50	1–2 h after exposure 70–90	< 1 h after exposure 100	< 30 min after exposure 100	<10 min after exposure 100
Diarrhea Onset % of incidence	None	None	Mild 3–8 h <10	Heavy 1–3 h >10	Heavy Within min 100
Headache Onset % of incidence	Slight	Mild	Moderate 4–24 h 50	Severe 3–4 h 80	Severe 1–2 h 80–90
Consciousness Onset % of incidence	Unaffected	Unaffected	Unaffected	May be altered	Unconsciousness/min 100 at >50 Gy
Body temperature Onset % of incidence	Normal	Increased 1–3 h 10–80	Fever 1–2 h 80–100	High fever <1 h 100	High fever <1 h 100

Table 2

Signs and symptoms of latent phase

Signs and symptoms	Mild (1–2 GY)	Moderate (2–4 GY)	Severe (4–6 GY)	Very severe (6–8 GY)	Lethal (> 8 GY)
Latency period	21–35 days	18–28 days	8–18 days	≤ 7 days	None
Lymphocytes g/l (days 3–6)	0.8–1.5	0.5–0.8	0.3–0.5	0.1–0.3	0.0–0.1
Granulocytes g/l	>2.0	1.5–2.0	1.0–1.5	≤ 0.5	≤ 0.1
Diarrhea	None	None	Rare	Appears on days 6–9	Appears on days 4–5
Depilation	None	Moderate, beginning on day 15 or later	Moderate, beginning on day 11–21	Complete earlier than day 11	Complete earlier than day 10

Table 3

Signs and symptoms of critical phase

Signs and symptoms	Mild (1–2 GY)	Moderate (2–4 GY)	Severe (4–6 GY)	Very severe (6–8 GY)	Lethal (> 8 GY)
Onset of symptoms	>30 days	18–28 days	8–18 days	<7 days	<3 days
Clinical manifestations	Fatigue, weakness	Fever, infections, weakness, depilation	High fever, infections, bleeding, depilation	High fever, diarrhea, vomiting, dizziness, disorientation, hypotension	High fever, diarrhea, unconsciousness
Lymphocytes g/l (days 3–6)	0.8–1.5	0.5–0.8	0.3–0.5	0.1–0.3	0.0–0.1
Platelets g/l	60–100	30–60	25–35	15–25	<20
% of incidence	10–25	25–40	40–80	60–80	80–100
Lethality	0 %	0–50 %	20–70 %	50–100 %	100 %
Onset time		6–8 week	4–8 week	1–2 week	1–2 week

Table 4

The time course and severity of clinical signs and symptoms

Absorbed dose level	Prodromal phase	Latent phase	Manifest illness	Final phase
0.5–1.5 Gy	Absence of symptoms or nausea and vomiting for 1 day	1 day – several weeks	No symptoms or weakness, nausea and vomiting, temporary hair loss	Recovery
1.5–4 Gy	Nausea, vomiting, fatigue, weakness, diarrhea for up to two days	1–3 weeks	Hematopoietic syndrome (HS): leucopenia and trombocitopenia, hair loss	Recovery possible with supportive care
4–6 Gy	Nausea, vomiting, weakness, diarrhea for up to two days	< 1–3 weeks	HS: bleeding, immunosuppression and sepsis, permanent hair loss	Death without supportive care
6–15 Gy	Severe nausea and vomiting, diarrhea in shorter period of time	Several days	HS + gastrointestinal syndrome: diarrhea, bleeding, fluid loss and electrolyte imbalance	Variable with supportive care
>15 Gy	Immediate severe nausea and vomiting	Non-existent	Neurovascular syndrome	Death within 48 h

Table 5

Acute Radiation Syndromes

Syndrome	Dose	Prodromal Stage	Latent Stage	Manifest Illness Stage	Recovery
Hemato-poietic (Bone Marrow)	> 0.7 Gy (> 70 rads) ***(mild symp-toms may occur as low as 0.3 Gy or 30 rads)***	Symptoms are anorexia, nausea and vomiting. Onset occurs 1 hour to 2 days after exposure. Stage lasts for minutes to days	Stem cells in bone marrow are dying, alt-hough patient may appear and feel well. Stage lasts 1 to 6 weeks	Symptoms are anorexia, fever, and malaise. Drop in all blood cell counts occurs for several weeks. Primary cause of death is in-fection and hemorrhage. Survival de-creases with increasing dose. Most deaths occur within a few months after exposure	In most cases, bone marrow cells will begin to repopulate the marrow. There should be full recovery for a large per-centage of indi-viduals from a few weeks up to two years after exposure. Death may occur in some indivi-duals at 1.2 Gy (120 rads). The LD50/60[‡] is about 2.5 to 5 Gy (250 to 500 rads)
Gastroin-testinal (GI)	> 10 Gy (> 1000 rads) ***(some symp-toms may occur as low as 6 Gy or 600 rads)***	Symptoms are anorexia, severe nausea, vomiting, cramps, and diarrhea. Onset occurs within a few hours after exposure. Stage lasts about 2 days	Stem cells in bone marrow and cells lining GI tract are dying, although patient may appear and feel well. Stage lasts less than 1 week	Symptoms are malaise, ano-rexia, severe diarrhea, fever, dehydration, and electrolyte imbalance. Death is due to infection, dehy-dration, and electrolyte imbalance. Death occurs within 2 weeks of exposure	The LD100[‡] is about 10 Gy (1000 rads)
Central Nervous System (CNS)	> 50 Gy (5000 rads) ***(some symp-toms may occur as low as 20 Gy or 2000 rads)***	Symptoms are extreme nervous-ness and confu-sion; severe nau-sea, vomiting, and watery diarrhea; loss of conscious-ness. Onset occurs within minutes of exposure. Stage lasts for minutes to hours	Patient may return to partial func-tionality. Stage may last for hours but often is less	Symptoms are return of watery diarrhea, con-vulsions, and coma. Onset occurs 5 to 6 hours after exposure. Death occurs within 3 days of exposure	No recovery is expected

Note to the table 5

* The absorbed doses quoted here are “gamma equivalent” values. Neutrons or protons generally produce the same effects as gamma, beta, or X-rays but at lower doses. If the patient has been exposed to neutrons or protons, consult radiation experts on how to interpret the dose.
† The LD50/60 is the dose necessary to kill 50 % of the exposed population in 60 days.
‡ The LD100 is the dose necessary to kill 100 % of the exposed population.

REFERENCES

1. *McPhee, S. J.* Pathophysiology of Disease : An Introduction to Clinical Medicine / S. J. McPhee, W. F. Ganong. 5th ed. 2006.

2. *Porth, C.* Essentials of Pathophysiology : Concepts of Altered Health States / C. Porth, K. J. Gaspard, G. Matfin. 2nd ed. 2007. 1149 p.

3. *Crowley, L.* An Introduction to Human Disease : Pathology and Pathophysiology Correlations (The Jones and Bartlett Series in Health Sciences) / L. Crowley. 7th ed., 2007.

4. *Чантурия, А. В.* Повреждающее действие ионизирующей радиации : учеб.-метод. пособие / А. В. Чантурия, Ф. И. Висмонт. Минск : БГМУ, 2012. 40 с.

5. *Литвицкий, П. Ф.* Pathophysiology: Concise Lectures, tests, clinico-pathophysiological situations and clinico-laboratory problems / П. Ф. Литвицкий, С. В. Пирожков, Е. Б. Тезиков. М. : ГЭОТАР-Медиа, 2012. 432 р.

6. *McConnell, T. H.* The Nature of Disease : Pathology for the Health Professional / T. H. McConnell. Lippincott Williams & Wilkins, 2007.

7. *General* and Clinical Pathophysiology: textbook for students of higher educational institutions / A. V. Kubyshkin [et al.] ; ed. A. V. Kubyshkin. Vinnytsia : Nova knyha publishers, 2011. 651 p.

8. *The Editors* of Encyclopaedia Britannica. www.britannica.com/science/radiation-injury

9. *Nicholas, J. Jr.* Biological Effects of Irradiation / J. Jr. Nicholas RT(R), P. Jeffrey M.D. https://www.ceessentials.net/article3.html

10. *Taylor, R. C.* Apoptosis : controlled demolition at the cellular level / R. C. Taylor, S. P. Cullen, S. J. Martin // Nat. Rev. Mol. Cell Biol. 2008. N 9. P. 231–241.

11. *Radiation* sensitivity and apoptosis in human lymphoma cells / J. Rudner [et al.] // Int. J. Radiat. Biol. 2001. Vol. 77. P. 1–11.

12. *Eriksson, D.* Radiation-induced cell death mechanisms / D. Eriksson, T. Stigbrand // Tumour Biol. 2010. Vol. 31. P. 363–372.

13. http://dx.doi.org/10.3389/fonc.2012.00116.

14. *International* Atomic Energy Agency. IAEA; Vienna, 1998. Diagnosis and treatment of radiation injuries. Safety reports series 2.

15. *Currance, P. L.* Medical response to weapons of mass destruction // P. L. Currance. Elsevier eBook on VitalSource, 2005. 256 p.

16. http://emergency.cdc.gov/radiation/arsphysicianfactsheet.asp. Acute Radiation Syndrome: A Fact Sheet for Clinicians.

CONTENT

Учебное издание

Жадан Светлана Анатольевна
Висмонт Франтишек Иванович
Меленчук Екатерина Вячеславовна

ПОВРЕЖДАЮЩЕЕ ДЕЙСТВИЕ ИОНИЗИРУЮЩЕЙ РАДИАЦИИ

DAMAGING ACTION OF IONIZING RADIATION

Учебно-методическое пособие

На английском языке

Ответственный за выпуск Ф. И. Висмонт
Переводчик С. А. Жадан
Компьютерный набор С. А. Жадан
Компьютерная верстка Н. М. Федорцовой

Подписано в печать 21.05.15. Формат 60×84/16. Бумага писчая «Снегурочка».
Ризография. Гарнитура «Times».
Усл. печ. л. 1,63. Уч.-изд. л. 1,61. Тираж 150 экз. Заказ 134.

Издатель и полиграфическое исполнение: учреждение образования
«Белорусский государственный медицинский университет».
Свидетельство о государственной регистрации издателя, изготовителя,
распространителя печатных изданий № 1/187 от 18.02.2014.
Ул. Ленинградская, 6, 220006, Минск.