LESSON 3

MAN RADIATION DAMAGES

1. EXPERIENCE OF PEOPLE RADIATION DAMAGES

Radiation accidents that damaged considerable population contingents during the last century became a source of bitter but invaluable clinical experience in diagnostics, study of pathogenesis and course of radiation damage of people and search for remedies.

A  B 

Fig. 1. A) nuclear «mushroom» above Hiroshima on August 6, 1945; B) nuclear «mushroom» above Nagasaki on August 9, 1945

In the morning on August 6, 1945 the Enola Gay B-29 bomber dropped an A-bomb "Little Boy" equivalent to 13–18 kilotons of TNT on Hiroshima. Three days later the bomb "Fat Man" was dropped on Nagasaki (fig. 1). The number of deaths directly attributed to explosions in both cities made 70–80 thousands and 60–80 thousands accordingly. But this was not the end of the tragedy for inhabitants of the cities: explosions affected health and life of the second and third generations of the victims. Only during the first five years the number of people who died from effects of radiation exposure (combined bums, chronic radiation sickness, aplastic state of hematopoiesis, leukosis, cancer) could make more than 100 thousand in Hiroshima, and 60 thousand in Nagasaki. At that time there was no such concept as radioactive contamination, and that is why nobody was aware of the threat from everything that

surrounded them. People were not evacuated, they continued to live and restore the places, where they had lived before, and did not associate diseases with exposure to ionizing radiation.

Already in a few days after explosions doctors began to notice among victims manifestations of a new disease related to exposure to ionizing radiation, which was afterwards called *radiation sickness*. Death rate from this sickness peaked in 3–4 weeks after the explosion and began to subside only in 7–8 weeks. The doctors also noted an unusual course of skin burns, at first perceived as thermal ones from the light flash which accompanied explosions. But afterwards it became clear that those burns were combined — caused by the thermal action of light of extraordinary intensity and beta- and gamma-radiation.

The first serious radiation accident happened on June 19, 1948 in the USSR at the plant "Mayak" in Chelyabinsk region. Some uranium blocks of the nuclear reactor melted because of overheating, and since consequences were eliminated manually, all male personnel of the reactor and the soldiers involved in accident elimination were exposed. In March the following year, at the same plant due to discharge of high-activity liquid waste into the river Techa about 124 thousand people from 41 settlements were exposed, from which 28,100 persons got the highest dose. Being unaware of the accident the population continued using water from the river for daily living needs.

From 1946 to 1958 in the region of Eniwetok and Bikini atolls (Pacific Ocean) the USA tested nuclear weapon. On March 1, 1954 radioactive ash fell on the schooner Fukuru Maru (Lucky Dragon), which was at a distance of more than 91 miles from the place of hydrogen bomb explosion. Only in 2 weeks the schooner was able to reach the port of Yaizu, but by then all the crew, 23 persons, had radiation sickness. One member of the crew could not be saved. Except for radiation sickness signs the fishermen also had radiation burns of the skin (radiodermatitis of different gravity). And on March, 27 the same happened to another Japanese schooner — the ship was caught in the rain with radioactive ash in 10 days after the next nuclear explosion on the Bikini Atoll at a distance of 1500 km from the schooner and all its crew also returned home in grave condition with radiation damages.

On September 29, 1957 there was an explosion at the radioactive waste storage of the plant Mayak (Lighthouse). This catastrophe was later called Kyshtymsk tragedy. They began to evacuate population from the most polluted villages in 1–2 weeks. Thousands of people were forced to leave their place of residence, but many people refused to leave their houses and stayed to live on the land polluted by radionuclides under conditions of limited economic activity: water bodies, pastures,

forests and fields were contaminated. The consequences of radiation accident manifest themselves even in 50 years mainly as high leukosis incidence and solid malignant tumors.

On October 10, 1957 there was an accident in Windscale, Great Britain, on a nuclear reactor which produced plutonium for nuclear weapon. Radioactive contamination spread over considerable territories of England and Ireland and also reached Belgium, Denmark, Germany and Norway.

On July 3, 1961 there was a reactor accident on the submarine K- 19. Elimination of the accident cost lives of 8 crew members, and the others got high-dose exposure. Another accident happened on the same submarine on February 24, 1974 and took lives of 28 persons, the rest of the crew were imprisoned in the stem compartment for 23 days, but survived.

On January 18, 1970 at the plant Krasnoye Sormovo during building of a nuclear submarine there happened an unforeseen startup of the reactor, as a result of what the territory of the shop where the submarine stood underwent significant radioactive pollution. The majority of the thousand workers which were inside at that time went home without getting decontamination or medical assistance. Only the next day the workers were washed with special agents. Six hundred victims were taken to a Moscow hospital. Only 380 persons of the thousand victims survived until January 2005.

On March 28, 1979 at the nuclear power plant Three Mile Island on the river Susquehanna (Pennsylvania, the USA) the active zone of the nuclear reactor partially melted. This nuclear accident was considered the biggest in the history of nuclear power engineering before Chernobyl. Discharge of dangerous radionuclides (iodine-131, cesium-137, and strontium-90) into the environment was not considerable: protective structures of the APS sustained reactor explosion. A decision was made to recommend leaving the 5-mile area only to pregnant women and children of preschool age. An average equivalent dose for the population of the 10-mile area made 80 μSv and did not exceed 1 mSv for any inhabitant of the territory.

The accident with the biggest medical and socioeconomic consequences in the relatively short history of nuclear power engineering was the explosion of the 4^{th} block of Chernobyl NPP on April 26, 1986, which fully destroyed the reactor and entailed unprecedented radiation contamination of gigantic territories, for what this accident got the name of Chernobyl disaster. After the explosion 237 victims that got high doses of radiation were hospitalized. Acute radiation sickness developed in 134 persons, 28 of them died as a result of radiation sickness progress in combination with large radiation burns.

Except for the mentioned accidents with a significant number of victims there happened numerous local radiation accidents under different circumstances in different fields of radiation sources application, particularly in medical practice.

All sources of risk of radiation injury in man can be systematized in the following way:

- equipment for industrial defectoscopy,
- commercial radiation installations,
- sources in industrial processing lines,
- special-purpose radioisotope sealed sources,
- terrorism acts,
- nuclear fuel fabrication,
- nuclear reactors, and
- medical and therapeutic radiation.

Experience of physicians, obtained during observation and treatment of victims of bombed Japanese cities and radiation accidents, allowed classifying and describing the main syndromes of acute and chronic radiation injury, which, accordingly, got the name of acute and chronic radiation sickness. When medical aid was rendered to those first victims of radiation accidents, doctors first of all paid attention to the hematological complex as it became the main factor of patient's death threat. Radiation-induced skin injury was considered a secondary factor. Afterwards it was realized that radiation accidents are characterized by combined injury in which radiation damage of the skin and hypoderm is a big medical problem both as an independent object of doctors' attention and as a serious factor that makes the course of general radiation damage of the victim's organism severer. More than in half of people who died after the Chernobyl accident the cause of incurability of their disease and death was the combined nature of radiation injury. The way to understanding of this truth was long and required countless experiments on animals, detailed analysis of clinical observation and even mathematical modeling. Moreover, this search for the truth further led to understanding the reason for high incidence of cancer of superficial organs (breasts in women, testicles in men) after a considerable period of time after exposure.

Thus, the experience of observation of people exposed to high-dose ionizing radiation allowed differentiating three main specific pathological states, which were called:

- acute radiation sickness (ARS),
- chronic radiation sickness (ChRS), and

- local radiation injuries (LRI).

2. ACUTE RADIATION SICKNESS

Acute radiation sickness (ARS) can be defined as a constellation of specific clinical syndromes that appear sequentially after general homogeneous exposure as pathological changes are accumulated in the tissues, organs and systems of the victim's organism.

Circumstances of ARS development are:

1) external photon exposure of the whole or almost whole body,
2) relatively homogeneous exposure,
3) dose higher than 1 Gy,
4) short time of exposure.

ARS develops after brief exposure (from a few minutes to 1–3 days) of the whole body to a dose of 1 Gy and higher. It can happen if a person stays in the area of a radiation field or fall-out from a nuclear explosion, failure of powerful sources of ionizing radiation, application of total medical exposure of the body, etc.

In high-dose exposure of limited body areas there develop local radiation injuries but not ARS.

After lower levels of acute exposure of the whole body there are noted such consequences:

- if a dose is lower than 0.1 Gy, the state does not change, any laboratory signs are absent,
- at a dose of 0.1–0.2 Gy the incidence of chromosomal aberrations increases, but clinical signs are absent,
- at a dose of 0.12 Gy the sperm count minimizes approximately on the 45^{th} day, after what spermatogenesis recommences,
- at a dose of 0.5–1 Gy hemopoiesis in the bone marrow is substantially inhibited with development of lymphopenia without other signs of damage.

Radiation dose of 1 Gy is the *threshold dose* for the appearance of the first clinical sign of ARS — *vomiting.* The *minimal lethal dose* for man makes 1.5 Gy of external total photon exposure. It means that there are only isolated cases of victim deaths at such a level of exposure without treatment.

The indexes $LD_{50/30}$ and $LD_{50/60}$ denote doses which cause death of 50 % of people in a radiation-exposed group during 30 or 60 days, accordingly.

For man, $LD_{50/60}$ lies in the range 3.2–3.6 Gy, but victims make convalescence given minimum therapeutic support. The *absolute lethal dose* is the dose exceeding

5.5 Gy: after such exposure victims can hope to recover only under condition of transplantation of the autologous bone marrow or stem cells.

Reaction to exposure may not correspond to the one expected according to the obtained dose, that is why one should carefully estimate the dose obtained by the victim on the basis of clinical signs of disease in each isolated case. There has been described a documented case of total exposure of the whole body of a man of 5 Gy, whereupon there were practically no signs of ARS development.

In the course of the sickness the following periods are differentiated:

- *initial (prodromal, primary reaction),*
- *symptom-free (latent),*
- *height (manifestation) of disease,*
- *convalescence (recovery) and*
- *remote effects.*

The time of beginning and degree of transient symptoms of the initial period, duration of the latent period, the time of appearance of sickness height signs, the gravity of its course and the outcome completely depend on the cumulative dose of exposure and individual genetically determined relative radiosensitivity of cells of the victim's organism. To a certain extent, such factors, as exposure homogeneity and dose rate, victim's age and state of health can also have influence.

The *initial period* can last a few hours, and the *latent period* shortens as the dose increases.

In the clinical course of the disease the typical signs are united in three syndromes:

- *hematological (HS),*
- *gastrointestinal (GIS),* and
- *neurocirculatory (NCS).*

Hematological Syndrome

Exposure of 1–6 Gy inhibits bone marrow hemopoiesis with gradual development of pancytopenia.

The bone marrow has three hematopoietic cell lines differentiated by the rate of cell proliferation, the type of their distribution and, accordingly, reaction to exposure:

- erythropoiesis (production of red blood cells),
- myelopoiesis (production of leukocytes), and
- megacaryocytopoiesis (production of thrombocytes).

All three hematopoietic lines originate from the unique *polypotent stem cell,* which transforms into stem cells of *erythroid, myeloid* or *thrombocyte* lineages. The latter in the process of division are differentiated and grow into mature cells, accordingly: red blood cells, leukocytes (lymphocytes, granulocytes and monocytes) and thrombocytes, with proper functions.

It has already been mentioned that bone marrow stem cells are characterized by the highest radiosensitivity, which is connected with their high mitotic activity. However, even in exposure of 2.5 Gy and higher part of stem cells of every lineage survives, preserving the ability to reproduce. These cells begin accelerated division, replenishing not only the cell pool of their own lineage but also pools of precursors of other lineages.

The process of death and renewal of bone marrow stem cells develops according to a typical "scenario" — at first the number of cells of a population diminishes to the minimum level (nadir), whereupon there begins its gradual renewal, which means probability of patient's convalescence.

The gravity and duration of nadir and completeness of renewal are determined by the size of radiation dose, by individual genetically determined level of tolerance of the victim's bone marrow to radiation influence, and by adequacy of the administered therapy, which can both strengthen and accelerate renewal and inhbit it.

Radiation injuries of the genetic material of bone marrow cells and leukocytes of the peripheral blood can also develop at the level of exposure of 0.25 Gy, but clinically valuable hematological changes become apparent only in exposure at doses of over 0.5 Gy.

Thrombocytes. After IR action their count decreases simultaneously and parallel to a decrease in granulocytes; however, a subsequent reverse arbitrary increase in their count, which is observed in granulocytes, usually does not take place. They disappear from the peripheral blood completely or almost completely without subsequent renewal after action of IR at a dose of 5 Gy and higher.

In the period of hematological changes a patient also develops immunologic deficiency. During a week of nadir not only the number of neutrophils and thrombocytes changes in the blood, but also the functional ability of the remaining cells is violated, because they are either "old" cells at the end of their life cycle, or have sustained radiation damage and thus cannot function adequately.

If during 2 weeks of nadir a patient sustains febrile neutropenia, septic complications and uncontrollable hemorrhage, there is hope for his exit from the state of cytopenia and for convalescence (fig. 2). Consequently, the purpose of remedial mea-

sures during this period is decreasing the gravity of thrombocytopenia and neutropenia with simultaneous prevention and treatment of infectious complications.

Erythrocytes. After the action of IR there is usually no considerable decrease of the content of red blood cells in the peripheral blood, unless the state was complicated by bleeding (fig. 2, fig. 3).

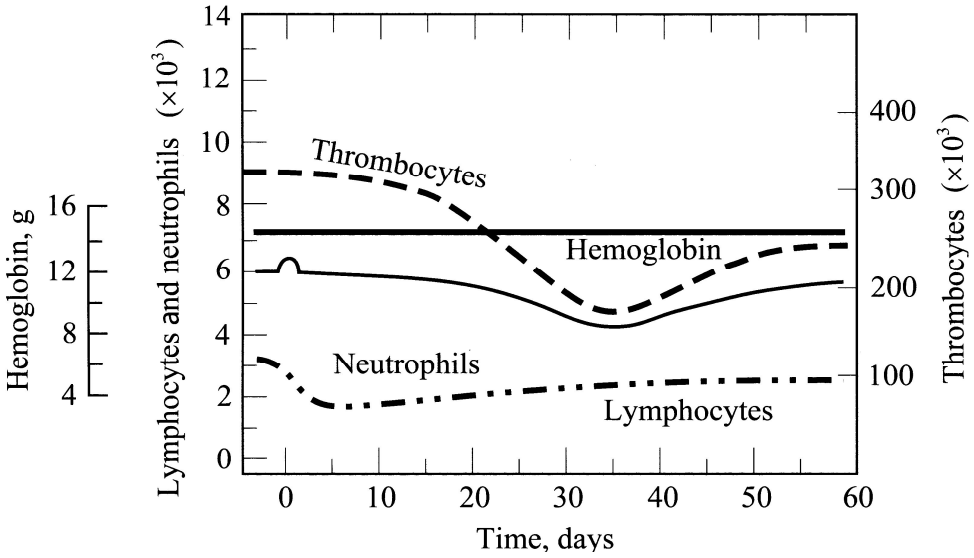

Fig. 2. Typical hematological reaction to total exposure of the body at a dose 1 Gy. Nadir was observed during the 30th–40th days after exposure. Remedial measures were taken to decrease the gravity of thrombocytopenia and neutropenia. The hemoglobin content in the blood did not change

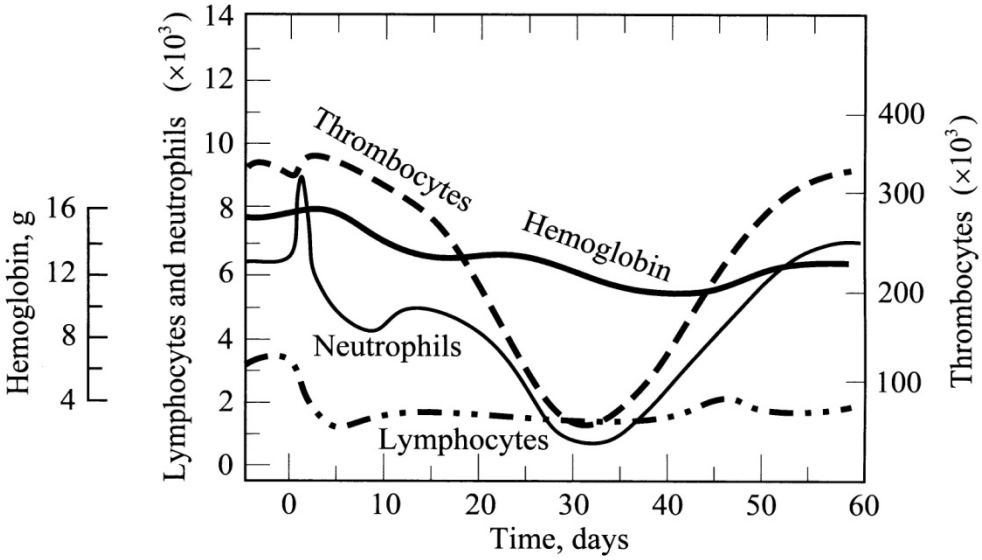

Fig. 3. Typical hematologic reaction to total exposure of the body at a dose 3 Gy. A decrease of hemoglobin content in the blood is characteristic of repeated massive bleeding. Intensive therapy adequate to hematologic violations was conducted right from the beginning of the period of disease manifestation

Granulocytes. Doses greater than 2 Gy cause a paradoxical initial, during a few hours or days, increase in the content of granulocytes in the peripheral blood, after which its abrupt decrease is observed. This phenomenon is predetermined by rapid redistribution of the pool of leukocytes. If in this period one conducts differentiated blood testing, its results can be mistakenly interpreted as signs of an infectious process.

In exposure at doses of 2–5 Gy there appears another abortive wave of increase of the level of leukocytes in the blood (fig. 3), conditioned by a release from the bone marrow of the final products of differentiation of polymorphonuclear leukocytes that do not further divide. The degree and duration of the second increase in the number of leukocytes may be different. Usually it lasts about one week, and the level of granulocytes increases to 50–70 % of the normal one. Later on the number of cells decreases again to nadir (0–20 % of the norm) on the 25^{th}–35^{th} day after exposure.

Gastro intestinal Syndrome (GIS)

Exposure with 8–30 Gy usually causes death of the victim, because in such exposure the stem cells of intestinal mucosal crypts are irreversibly damaged. In the absence of these cells nothing provides replenishment of the pool of functional cells of the intestinal mucosa, which quickly regenerates in its normal state because its cells have a short life cycle. Since normally cells of the small intestinal mucosa have the shortest life cycle, after exposure this very part of intestinal mucosa is affected the first and the most. Separate areas of the intestinal wall are bare, which, in its turn, predetermines another complex of pathophysiological phenomena, namely: bacterial penetration from the intestinal lumen into the circulatory bed, loss of fluid and electrolytes, and also absorption ability, massive gastrointestinal bleedings with development of acute bloody diarrhea, intestinal motility disturbance, anemia, dynamic intestinal obstruction, violation of electrolyte balance and malnutrition. In addition, there is violated nervous regulation of the intestinal function, the discharge of intestinal neurohumoral peptides increases.

Consequently, the pathogenetic bases of GIS are:

- exhaustion of epithelial cells that line the lumen of the GIT,
- free access of intestinal bacteria into the organism,
- bleeding through the bare areas of the mucus, and
- violation of the absorption function.

Prodromal period. In the interval from 30 minutes to 2 hours after exposure there are observed severe manifestations in the form of anorexia, nausea, vomiting,

sometimes — watery stool with abdominal muscle spasms, which make progress during 4–8 hours and are not always suppressed by antiemetic agents. Patients feel weakness, sleepiness and fatigability. Other prodromal symptoms are possible, such as pain in the parotid glands, metallic taste in the mouth, low blood pressure and tachycardia. Prodromal signs gradually weaken during the first 48 hours after exposure.

Latent period. It has no signs, lasts from a few hours to a few days. Fatigue and weakness are possible.

Then the *period of disease manifestation* begins: acute diarrhea returns, then there join vomiting and fever, intestinal bleeding with the development of shock and lethal termination without active medical assistance.

Massive penetration of opportunistic bacteria into the blood flow quickly depletes the ability of the victim's organism to fight infection. Absorption violation results in nutrition decrease; paralytic intestinal obstruction is accompanied with vomiting and flatulence; water and electrolyte balance is disturbed, which results in dehydration, acute renal insufficiency and cardiovascular collapse. Gastrointestinal bleeding results in anemia. Death ensues after sepsis and septic shock.

Thus, systemic symptoms of GIS are:

- insufficiency of absorption → malnutrition,
- water-electrolyte disbalance → dehydration, acute renal insufficiency, cardiovascular collapse,
- GI bleeding → anemia,
- sepsis,
- paralytic intestinal obstruction → vomiting, flatulence.

Exposure at a dose of 8–30 Gy usually leads to death as a result of GIS progress.

At the same time, such doses can lead to the development of potentially lethal damage of cells and tissues of the lungs, which clinically manifest themselves as respiratory insufficiency and pulmonitis in 14–30 days after exposure. Pulmonitis is caused by a complex of factors, such as damage of the tissue by biological and chemical toxins, inhalation of smoke and steam, increased vascular permeability, water-electrolyte disbalance, influence of free radicals on tissues, infection.

After exposure to a lethal dose of exposure, a patient can die from GIS before there appear signs of lung damage. However, if due to partial shielding of the body or uneven dose distribution the victim managed to avoid GIT damage, he can die from irreversible lung damage.

Neurocirculatory Syndrome

Acute exposure at a dose of 30 Gy and higher results in fatal outcome during the first 72 hours, usually within 24–48 hours, until there appear clinical signs of GIT or bone marrow damage. Such high doses exert a considerable direct influence on the structural molecules of cells and, moreover, induce surplus formation of free radicals in cells and basal membranes of vessels of the microcirculatory bed. As a result, except for other damages, there is massive output of plasma and electrolytes into the extravascular space which draws vascular collapse, edema, increased intracranial pressure and cerebral anoxia.

Less than in an hour, sometimes in a few minutes after exposure, the victim develops prodromal signs: burning sensation all over the body, and then pernicious vomiting. The signs of prodromal period can also include diarrhea, in particular bloody one, edema and erubescence (of burn type), low arterial blood pressure, high body temperature, disorientation and ataxia, prostration, sometimes cramps. Signs can last more than 24 hours.

After prodromal period the latent period ensues — clinical improvement, which lasts from a few hours to a few days.

Finally, there develops a complex of severe violations of CNS activity, total vascular collapse, which ends relatively soon in irreversible death.

Exposure doses of such level unavoidably result in lethal end regardless of treatment provided. Therefore active medical measures, in particular application of vasopressors, corticosteroids, infusion of liquids, etc., will produce short-time improvement and will only prolong suffering. Therefore in such situations therapy must be palliative, and a doctor who renders aid to such a victim must show mercy trying to alleviate victim's condition and not refusing to use opioid analgesics and sedatives.

Depending on the prevalence of a certain clinical syndrome of those which develop after acute external photon exposure such *clinical forms* of ARS are distinguished:

1) *bone marrow,*
2) *intestinal,*
3) *toxemic (vascular),*
4) *cerebral (fulminant or superacute).*

Table 1 gives the rate of doses, which induce development of that or another clinical form of ARS, and their clinical consequences. At super-high level of exposure and, as a rule, at super-high dose rate the victim can die directly at the moment of radiation effect. Such phenomenon was called "death under beam".

TABLE 1

Clinical Forms of ARS

Clinical Form	Dose (Gy)	Degree of Gravity, Consequences
Bone Marrow (typical)	1-10	From light to grave
Intestinal	10-30	Lethal end before the 16th day
Toxemic	30-80	Lethal end before the 8th day
Cerebral	Over 80	Lethal end before the 3rd day

Determination of Exposure Severity

Estimation of the degree of radiation damage of a victim is a hard and, at the same time, important clinical task which has decisive importance when one determines the approach to medical care.

The gravity of ARS course mainly depends on the total level of exposure of a victim. In accordance with this, four degrees of ARS severity are differentiated:

- I degree — *light* (1.0–2.0 Gy),
- II degree — *of moderate severity,* or *moderate* (2.0–4.0 Gy),
- III degree — *severe* (4.0–6.0 Gy),
- IV degree — *very severe* (6.0–8.0 Gy).

Minimum changes in the organism of a person explosed to 0.1–1 Gy are classified by some authors as *preclinical radiation sickness,* and the result of fatal exposure at doses which exceed 8 Gy as *lethal ARS.*

In most cases of the known radiation accidents and incidents there was no more or less certain data of direct physical dosimetry concering the degree of victim exposure. Moreover, even specifying the values of factors, which form exposure dose and are necessary for its reconstructive estimation, in particular time of victim's stay in the radiation field, intensity of radiation, distance from the source, etc. was problematic.

On the other hand, since the gravity of the clinical course of radiation damage and probability of victim's convalescence mostly depend on radiation level and dose rate, one should know at least estimated values of these very factors to make a clinical decision concerning patient management strategy and prognosis of possible disease outcome.

When it is impossible to approximately determine the physical dose, the patient's blood is sampled and sent to the nearest biological dosimetry laboratory, where according to the number and character of chromosomal aberrations one determines

the biological dose, which will become an adequate initial index of radiation damage degree.

In all other cases hematological and clinical data are used as indexes of severity degree.

The rate and degree of decrease in the content of cellular elements in the peripheral blood depends on the dose. The initial blood sample for clinical laboratory research should be taken as soon as possible after exposure. In future analyses are repeated not rarer than once a day during the first 2 weeks. Reliability of information during dose calculation rises as frequency of investigations increases.

There is a useful rule: if lymphocyte count reduces by 50 % of the initial one and it is less than $l \times l0^9$/L during the first 24–48 hours, it means that the victim has got at least an average dose of exposure (2.0–4.0 Gy).

During the whole period of observation one should consistently and continuously conduct diagnostic tests and estimate the patient's condition. Clinical signs are quite reliable landmarks of the level of radiation damage of organs and systems of the organism. Table 2 presents some clinical signs and their degree in different levels of radiation damage of the victim.

Table 2

Some Clinical Signs and Their Intensity Depending on the Degree of ARS Severity

Symptom	**1 Degree**	**II Degree**	**III Degree**	**IV Degree**
Vomiting	None or 1 in > 3 hours	In 1.5—3 hours, 2 and > instances	In 0.5—1.5 hours, repeated	In < 0.5 hours, indomitable
Headache	Periodic, moderate	Permanent, moderate	Periodic, strong	Permanent, strong; mental confusion
Weakness	No	Unsteady gait	Requires support	Stretcher
Temperature	Normal	Subfebrile	Subfebrile	Above 38° C
Skin Hyperemia	Reddening	"Tanned" look	Obvious hyperemia	Intensive hyperemia

First of all one should determine cases of absolutely lethal exposure, which require decision concerning administration of palliative treatment with anesthesia and sedation to alleviate patient's suffering. As clinical landmarks one can use signs appearing in the prodromal period.

Nausea and vomiting. *Vomiting that begins during the first hour after exposure, especially accompanied by sudden diarrhea, is connected with lethal exposure.* Vomiting that begins in 2 hours after exposure testifies to severe damage. But it should be remembered that these signs are transient and can arbitrarily temporarily calm down before a doctor begins patient's examination.

Hyperthermia. In victims with absolutely lethal exposure body temperature rises sharply already during the first hours. Appearance of fever and chill during the first day corresponds to severe and very severe degree of exposure. Hyperthermia can also be observed in persons which were exposed to rather high, but not lethal doses of exposure (2 Gy and more).

Erythema. In exposure of the whole body at a dose higher than 10 Gy during the first day skin erythema appears. It can be macular if separate areas of skin are exposed to an erythema dose of radiation — erythema develops on the exposed skin areas.

Hypotension. Low blood pressure testifies to total exposure at a lethal dose and usually means unfavorable prognosis.

Neurological disorders. Experience shows that appearance of obvious signs of CNS damage during the first hour after exposure is connected with lethal damage. These symptoms include *confusion of consciousness, cramps* and *coma.* Usually, these signs are accompanied by untreated hypotension. Introduction of vascular agents is ineffective, and a victim dies during the first 48 hours.

In victims, who most probably were not exposed or were exposed to small doses, nausea and vomiting can be episodic, and lymphocyte count can remain at a level not lower than 1.5×10^{9}/L when observed during 48 hours.

The Typical Patterns of ARS

Initial period (the period of primary reaction)

Patients that were exposed to doses of radiation within a range, which corresponds to the level of bone marrow damage, feel prodromal symptoms such as nausea and vomiting that can be controlled. They begin in 1–24 hours after exposure and last a few hours. Usually during this period there are no signs of CNS damage, except perhaps some instability of arterial blood pressure and moderate diarrhea. In

addition, victims complain of indisposition, fatigue, anorexia and sleepiness. These symptoms do not correlate with a dose as opposed to the time of beginning and severity of nausea and vomiting.

Latent period (symptom-free period)

The prodromal period changes into the latent one, whose duration can make 1 month. Specific signs are usually absent except for some indisposition and somewhat increased fatiguability.

This period is absent only in *very severe degree* of ARS. In this period any clinical signs of the disease are absent, but in the blood changes are taking place, after which it is possible to objectively define ARS severity.

Then there follows the period of disease manifestation, which is characterized by febrile neutropenia, bleedings, local and generalized infectious processes, sepsis.

(I) ARS OF LIGHT DEGREE (1–2.5 GY)

Moderate primary reaction (dizziness, sometimes vomiting) develops in 2–3 hours after exposure. The skin and mucous tunics usually do not change. The latent phase lasts for 25–30 days. In the first 1–3 days lymphocyte count in the peripheral blood decreases to 1.0– 0.5×10^9/L, leukocyte count — to 3.5–1.5×10^9/L, thrombocyte count on the 26^{th}–28^{th} day — to 60–40×10^9/L; ESR is moderately elevated. Infectious complications are rare, there are no bleedings. Recovery is slow, but complete.

(II) ARS OF MODERATE DEGREE (2.5-4 GY)

Primary reaction (headache, nausea, sometimes vomiting) develops in 1–2 hours. Skin erythema is possible. Latent phase — 20–25 days. During the first 7 days lymphocyte count decreases to 0.5×10^9/L, granulocyte count in the phase of disease height (20^{th}–30^{th} days) — to 0.5×10^9/L; ESR — 25–40 mm/hr. One usually observed infectious complications, reaction of the oral and pharyngeal mucous tunic. If thrombocyte count decreases below 40×10^9/L, insignificant signs of angiostaxis appear — petechiae on the skin. Lethal end is possible in belated and inadequate treatment.

(Ill) ARS OF SEVERE DEGREE (4-6 GY)

Primary reaction usually develops in 30–60 min and is characterized by acute course (repeated vomiting, fever, headache, skin erythema). Already during the first days lymphocyte count is 0.3×10^9/L, leukocyte count beginning from the 9^{th}–17^{th} day — less than 0.5×10^9/L, thrombocyte count < 20×10^9/L. Duration of the latent phase is

shortened to 10–15 days. In the phase of disease height one usually notes sthenic fever, damage to the oral and nasopharyngeal mucosa, infectious complications of different etiology (bacterial, viral, mycotic) and localization (lungs, intestine, etc.), moderate hemorrhages. Probability of lethal end rises (in the first 4–6 weeks).

(IV) ARS OF VERY SEVERE DEGREE (OVER 6 GY)

The signs are conditioned by severe damage to hematopoiesis which is characterized by early persistent lymphopenia — less than 0.1×10^9/L, by agranulocytosis, from the 8th day by thrombocytopenia — less than 20×10^9/L and then by anemia. The course of the disease becomes severer as the dose increases: duration of the latent period is shortened; there appear signs of damage to the intestine, liver, skin and general intoxication.

Treatment

Early clinical signs serve as a basis for decision making in relation to the volume of medical care provided to each victim.

The decision about the necessity of hospitalization after exposure of the whole body depends on the presence of early clinical signs, which are estimated according to the following chart:

- *vomiting is absent* → outpatient observation during 6 weeks,
- *vomiting in 2–3 hours after exposure* → admission to a general hospital or outpatient observation during 3 weeks with subsequent hospitalization,
- *vomiting in 1–2 hours after exposure* → admission to the department of hematology,
- *vomiting in less than 1 hour after exposure* → admission to a specialized clinic.

Victims with external exposure at a dose of less than 1 Gy must be under outpatient observation on conditions that absolute lymphocyte count and results of other methods of dose estimation do not contradict previously obtained information.

Treatment of hospitalized patients must correspond to ARS symptoms: nausea and vomiting are relieved by antiemetics, introduction of hypertensive solutions (in pernicious vomiting), dehydration signs require introduction of plasma expanders. One should create aseptic conditions of patient's stay to prevent exogenous infection: isolation ward, UV air sterilization, bactericidal solutions. One urgently begins treatment of infectious complications by means of broad spectrum antibiotics with obligatory inclusion of antimycotics. To increase effectiveness of antiinfective therapy immune preparations (for example, gamma globulin) are applied.

If there are signs of necrotizing enteropathy, complete starvation is prescribed up to elimination of clinical signs (during 1–1.5 weeks), the patient can only drink water. If longer starvation is necessary, the doctor administers parenteral nutrition, careful examination of the oral mucosa (oral rinsing), sterilization of the intestine by the use of antiseptics.

The treatment of hematological syndrome first of all includes transfusion of thrombocytes and leukocytes from one donor. RBCs are transfused only if there is considerable anemia (at the level of hemoglobin below 83 g/L). In exposure at doses of 8–12 Gy resort to transplantation of immunologically compatible bone marrow.

Local damage to the mucosa requires special systematic examination with sanation with bactericide, mucolytic, and anti-inflammatory agents. The pain syndrome caused by mucosa and skin damage is blocked by anesthetic aerosol sprays or bandages with antiseptics, corticosteroids, propolis. Nonhealing wounds and ulcers are excised with subsequent plasty. Metabolic and water-electrolyte disorders are corrected according to the rules of intensive therapy.

Prognosis

After elimination of all significant signs of the disease (bone marrow and intestinal syndromes, skin damage) the period of convalescence (recovery) begins. After first- and second-degree disease recovery is usually complete, although moderate asthenia may persist. After disease with a grave course considerable asthenia persists for a long time. In addition, cataract may develop in the patient, and after exposure at a dose of about 7 Gy — severe retinal damage, eye bottom hemorrhages, intraocular pressure increase and even total loss of vision is possible.

Recovery of the immune system can be complete, that is why susceptibility to infectious diseases is not usually observed. If one observes severe cytopenia or, on the contrary, leukocytosis in the remote period, it testifies to the development of a late complication as a new separate disease (aplastic anemia, leukosis, etc.).

3. CHRONIC RADIATION SICKNESS

Chronic radiation sickness (ChRS) is a result of long-term (for months, years) systematic external, internal or combined exposure of relatively low doses, but at the same time substantially higher (by 10–15 times) than the established limits.

The course of the sickness is typically polysyndrome dominated by changes in

the nervous and hemopoietic systems.

It is clear that one can become ill with ChRS only if he constantly blatantly violates the requirements of radiation safety during work with sources of radiation (X-ray units, accelerators of elementary particles, radiologic laboratories, ore-dressing and processing enterprises, flaw detection devices, technological processes which use powerful gamma-emitters, etc.).

Sometimes chronic exposure at substantial doses with development of ChRS is possible under living conditions if one loses control over industrial emission sources.

ChRS develops in external exposure with gamma- and X-rays, and in incorporation of radionuclides — with beta- and especially alpha-particles. Approximately, the minimum total dose, which results in ChRS development in exposure during 2–3 years, makes 1.2–1.8 Gy and higher. An increase in the intensity of exposure shortens the term of ChRS development.

Chronic radiation damage is mainly characterized by the same regularities of development of pathophysiological physico-chemical processes as the acute one. The only peculiarity of the pathogenic action of longterm exposure at relatively low doses consists in the fact that the basis of radiation damages of tissues under such conditions consists in repro ductive death of low differentiated mitotically active cells, i.e. it is not the radiation-exposed cell that dies, but its progeny in the next or later generation.

ChRS Classification

According to the *type of exposure* which resulted in the development of ChRS three types of the sickness are distinguished:

- *ChRS caused by external photon exposure* (gamma-radiation, x-rays),
- *ChRS caused by internal exposure* from incorporated radionuclides with variants of their tissue and organ affinity,
- *ChRS caused by combined external and internal exposure* in different variants of prevalence of one of the components of exposure.

According to course severity they distinguish three degrees of ChRS:

- *mild (I degree),*
- *moderate (II degree),* and
- *severe (III degree).*

Clinical Pattern of ChRS in External exposure

In the clinical picture of ChRS three periods are distinguished:

- *period of formation,*

- *period of recovery,*
- *period of consequences*.

The first period of ChRS is the *period of formation,* whose main peculiarity is gradual development and lingering undulating course. The character of damages to organs and systems, terms of their development, recovery features are predetermined by dose size and power, the type of exposure, the character of exposure distribution on areas of the body in external exposure and tissues and organs in internal one, and also by peculiarities of organism reactivity.

One should remember that clinical signs of ChRS, as well as of chronic infectious diseases, are preceded by a preclinical, prodromal period with unclear complaints of the patient (headache, rapid fatigability, enhanced irritability, general weakness, signs of depression) uncertain, nonspecific data of physical examination and instrumental and laboratory tests (signs of asthenia, functional vascular disorders, moderate changes in hepatic biochemical indices). If such a state develops in a person working with sources of radiation, in order to exclude possible overexposure it is necessary to remove this person from work under conditions of radiation effect with subsequent medical observation (with examination for possible incorporation of radionuclides at respective specific character of work) and thorough analysis of radiation conditions of the workplace. Such measures allow to weaken the severity of the disease course if the patient develops ChRS in the future.

After discontinuance of contact with radiation ChRS formation continues for some time — from 1 to 6 months depending on the degree of the accumulated dose.

The rate of disease formation is determined by the dose, its intensity and individual features of the organism. But under any circumstances neurological symptoms are brought to the foreground: asthenodepressive syndrome is forming, and in a significant cumulative dose — organic changes of encephalomyelosis type. First signs of ChRS can also include changes in the peripheral blood (hematological syndrome) — a consequence of bone marrow function suppression.

Irrespective of ChRS variety in the period of formation there can take place a decrease in the secretory and motor function of the digestive tract, dysfunction of the thyroid, lability of pulse and arterial pressure, functional vasomotor and secretory violations of the mucous of the upper airways. Sometimes there can develop changes of the skin (on hands in their prevailing exposure) in the form of chronic dermatitis.

It is significant that clinical signs of affection of different systems of the organism (nervous, cardiovascular or hemopoietic) can predominate in different cases.

The character of disease severity is determined on the basis of clinical and

laboratory findings in the period of formation and is not revised in the future, although the course and outcome of the disease can be different.

The beginning of the *recovery period* is the time of cessation of overradiation. Afterwards there begins gradual recovery of the impaired functions and alleviation of disease signs. The duration of the recovery period depends on the degree of ChRS severity and can last from 1–2 months to a few years. Recovery can be complete or with a defect. Hypoplastic and blastomogenic processes can develop in the future: acceleration of involution and development of tumors.

MILD ChRS (I DEGREE)

The first complaints of a patient are headache, increased fatigability, decreased efficiency, inversion of sleep (somnolence in the daytime and insomnia at night), unpleasant sensation in the heart, decreased appetite not connected with dietary habits, dyspepsia, constipation, exhaustion, low libido. In some cases patients present no clear complaints — the disease is diagnosed at a regular preventive examination on the basis of peripheral blood index change.

Nervous control violations prevail in the activity of organs and systems. Physical examination may show distal hyperhidrosis, hypodynamia, finger tremor, decreased skin reflex, persistent red dermographism. Low-energy x-ray exposure produces pigmentation, dryness, rhagades and desquamation, hair brittleness and loss. Respiration is vesicular. Low blood pressure is characteristic. Auscultation shows muffled I tone, sometimes — weak systolic murmur on the cardiac apex. There is moderate white fur on the tongue, palpation of the abdomen shows painfulness in the epigastrium, right subcostal area, and along the large intestine (manifestations of dyspepsia and dyskinesia of the gallbladder, stomach, and intestine).

Signs of organic changes in the internal organs are not revealed, but there is observed inhibition of the secretory and acid-forming functions of the stomach, dystonic state of the intestine (radiological investigation shows varied clinical presentation of alternation of spastic and atonic areas).

The system of blood is slightly changed: the content of erythrocytes and hemoglobin is usually normal, and thrombocyte count — on the lower limit of normal ($150–180\times10^9$/L), sometimes with formula changes (enlargement of old and appearance of gigantic forms of platelets). The most characteristic sign is marked tendency to leukopenia (up to $3.0\times l0^{12}$/L) due to a decrease in the count of neutrophils at relative lymphocytosis (35–45 %). Neutrophils partially have hypersegmented nuclei and toxic granulosity. Insignificant changes appear in punctates of the bone marrow:

inhibition of maturation of myeloid cells, plasmocytic and eosinophilic reaction at normal or almost normal count of myelokaryocytes.

As a rule, at this stage the disease ends with complete convalescence. Cessation of contact with ionizing radiation, adequate treatment, and rest lead to complete functional recovery of organs and systems during 2–3 months.

MODERATE ChRS (II DEGREE)

Moderate ChRS is characterized by more evident and diverse symptomatology, clear interdependence between subjective and objective signs of the disease, development of incompetence of the digestive glands, cardiovascular, and nervous systems. Morphological disorders of radiosensitive tissues develop against this background (hypoplasia of the hemopoietic organs, changes of the CNS pathways, metabolic disorders).

Patients typically complain of headache in the frontotemporal and frontotemporoparietal areas. The pain appears in different periods during the day, cannot be relieved with analgesics. Short-term memory (of current and recent events) is weakened. Sleep is interrupted, with bad dreams, patients wake up exhausted.

Fatigue, indisposition, and emaciation become constant and more evident, which decreases working capacity. Inconsiderable physical activity causes giddiness with nausea. A significant decrease in appetite leads to weight loss. There appears heart and stomach pain, paresthesia, extremity numbness, painfulness in the muscles of distal parts of extremities. There are often observed diencephalic disorders: paroxysmal tachycardia, subfebrile temperature, arterial pressure fluctuation. Patients complain of decreased potency, women have menstrual irregularities. Patients look older than their age. They are emotionally labile, irritable and whining.

Besides clear signs of asthenia and vascular dystonia of hypotonic type there are observed dysfunctions of internal organs, inhibited functions of the hemopoietic and immune systems. Patients complain of gingival hemorrhage, nosebleed, metrorrhagia, subcutaneous hemorrhages in insignificant traumas, pains in the skeleton and different sites of the abdomen. Examination of the patient shows either petechial subcutaneous hemorrhages or ecchymoses, dryness or hyperhidrosis, mottled skin, decreased turgor and elasticity of the skin, brittleness and thinning of nails, expressed acrocyanosis. The mucous of the upper respiratory tract are atrophic.

The patient's state is characterized by a persistent decrease of the secretory ability of the stomach and pancreas, dystonia and dyskinesia of the whole intestinal tract, sometimes enlargement of the liver with moderate partial impairment of its function

(transient bilirubinemia, hyperglycemia, hypercholesterolemia, depression of detoxication function, low albumin level and high globulin level in the blood). Not infrequently urobilin is found in the urine, occult blood in the feces, coprogram changes.

This degree of disease is characterized by marked inhibition of all levels of hematopoiesis — a decrease beyond norm in the peripheral blood of the content of hemoglobin (hypochromic anemia) and red blood cells (to 3.0×10^{12}/L) with possible poikilocytosis and anisocytosis with macrocytes and even megalocytes. Thrombocyte count decreases to 100×10^{9}/L and below, leukopenia reaches 1.5×10^{9}/L due to granulocytes. Hypersegmented nuclei, vacuolization, toxic granulosity are detected in neutrophils. In the bone marrow there are signs of inhibition of all types of hemopoiesis: granulocytopoiesis, erythropoiesis, megacaryocytopoiesis.

The course of the disease is prolonged, lasts for years, with exacerbations, not infrequently with incomplete recovery. Patients need repeated hospital treatment.

SEVERE ChRS (III DEGREE)

Severe ChRS is characterized by multiple syndromes with affection of practically all organs and systems. Complaints of patients are similar to those in second-degree ChRS, but severer. There prevail destructive processes in the hemopoietic tissue, atrophic and dystrophic microstructural changes develop in organs. CNS disorders take form of toxic encephalitis with areas of affection of the midbrain and interbrain: decreased tendon reflexes, violation of muscle tone and statics, appearance of nystagmus and optico-vestibular disorders. Examination of the cardiovascular system shows apparent dystrophic changes of the myocardium. Engorgement and signs of inflammatory process are found in the lungs. Laboratory tests show persistent and deep inhbition of functions of the stomach, liver, pancreas, and intestine.

Distinct hematological syndrome (profound inhibition of hemopoietic processes with grave hemorrhagic manifestations), organic disorders of the CNS and internal organs, deep trophic and metabolic disorders, infectious complications are noted. Patients, especially women, are emotionally unstable, whining. One observes memory impairment, decreased concentration of attention. In some cases diencephalic disorders appear in the form of thermoregulation violations, paroxysmal tachycardia, instability of arterial pressure.

Anemia reaches a severe degree (erythrocyte count $< 3.0\times10^{12}$/L), there is leukopenia with granulocytopenia up to agranulocytosis (leukocytes $< 1.0\times10^{9}$/L), thrombocytopenia to 50×10^{9}/L and less, bone marrow depletion with predomination of reticular, endothelial and plasma cells in its composition.

All ChRS patients due to suppression of the immune system lose resistance to any infectious and fungal diseases, for example, pneumonias of different etiology, which in such patients take a grave course with a tendency to suppuration, necrotizing of tissues, and slow reparation. Manifestations of septicemia can be observed.

Prognosis in severe ChRS is serious. The disease inevitably progresses to cachexia, it can end with fatal outcome as a result of hemorrhagic and infectious complications.

The diagnosis of ChRS is quite difficult, especially at the early stage, which is related to the absence of pathognomonic signs, i.e. symptoms specifically characteristic of ChRS, in its clinical picture. Diagnostics must include confirmation of the fact of radiation exposure at doses that can cause somatic (determined) effects, or, for persons of the personnel category, radiation hygienic examination of the workplace, CNS disorders take form of toxic encephalitis with areas of affection of the midbrain and interbrain: decreased tendon reflexes, violation of muscle tone and statics, appearance of nystagmus and optico- vestibular disorders. Examination of the cardiovascular system shows apparent dystrophic changes of the myocardium. Engorgement and signs of inflammatory process are found in the lungs. Laboratory tests show persistent and deep inhbition of functions of the stomach, liver, pancreas, and intestine.

Distinct hematological syndrome (profound inhibition of hemopoietic processes with grave hemorrhagic manifestations), organic disorders of the CNS and internal organs, deep trophic and metabolic disorders, infectious complications are noted. Patients, especially women, are emotionally unstable, whining. One observes memory impairment, decreased concentration of attention. In some cases diencephalic disorders appear in the form of thermoregulation violations, paroxysmal tachycardia, instability of arterial pressure.

Anemia reaches a severe degree (erythrocyte count $< 3.0\times l0^{12}$/L), there is leukopenia with granulocytopenia up to agranulocytosis (leukocytes $< 1.0\times l0^{9}$/L), thrombocytopenia to $50\times l0^{9}$/L and less, bone marrow depletion with predomination of reticular, endothelial and plasma cells in its composition.

All ChRS patients due to suppression of the immune system lose resistance to any infectious and fungal diseases, for example, pneumonias of different etiology, which in such patients take a grave course with a tendency to suppuration, necrotizing of tissues, and slow reparation. Manifestations of septicemia can be observed.

Prognosis in severe ChRS is serious. The disease inevitably progresses to cachexia, it can end with fatal outcome as a result of hemorrhagic and infectious complications.

The diagnosis of ChRS is quite difficult, especially at the early stage, which is related to the absence of pathognomonic signs, i.e. symptoms specifically characteristic of ChRS, in its clinical picture. Diagnostics must include confirmation of the fact of radiation exposure at doses that can cause somatic (determined) effects, or, for persons of the personnel category, radiation hygienic examination of the workplace, which also gives calculation of possible total dose for the whole period of work with sources of radiation.

If proper radiation hygiene documentation is available, in diagnostics of second- and third-degree ChRS the combined picture of hypoplastic anemia with trophic disorders and functional-morphological changes in the CNS has a decisive importance. It is much more difficult to accurately diagnose first-degree CRS, when there are only nonspecific functional changes in the nervous system, and hemopoiesis violations are insignificant. Functional test of hemopoiesis state is performed — after introduction of sodium nucleinate normally we see moderate leukocytosis with a left shift, while in ChRS such response is not observed.

From the point of view of differential diagnostics at first we should exclude diseases with similar clinical signs — hematological (in particular, secondary hematopoietic disorders in somatic pathology, e.g. kidney diseases, chronic hepatitis, chronic inflammations), chronic intoxication, asthenic states in somatic diseases, vegetative-vascular neurosis, organic disorders of the CNS, influence of other harmful occupational factors, remaining residual effects of earlier infectious diseases.

It should be emphasized that the final decision about the presence of ChRS in a patient can be made only after careful examination in a specialized medical establishment.

An example of severe chronic radiation sickness caused by longterm total exposure with gamma rays from a powerful cesium-137 source is the case of fatal radiation damage to members of 2 families, which happened in Kramatorsk. All the leading newspapers of the USSR wrote about this radiation accident in the end of 1989.

In August, 1980 a newly-built 9-floor panel house, which was standard at that time all over the Soviet Union, was moved into. In a year in one of the apartments of this house an 18-year-old girl died from anaplastic anemia, and a year later her 16-year-old brother died from the same disease. The children's mother also fell ill, and since severe anemia was diagnosed, doctors came to a conclusion that the family members suffered from hereditary disease. The parents of the deceased children exchanged apartments with a family that lived in a smaller apartment in that house, also with two children.

Now the same tragedy happened to the family which moved into the

apartment where children had died — their children also died one after another, the mother fell ill. The clinical picture of their diseases was similar to that which caused death of members of the previous family — anaplastic form of anemia. The children from this family lived in the new apartment longer than the predecessors. They repeatedly received treatment in sanatoria, where their state got much better, they put on weight, hematopoietic indexes improved. But when they returned home, so did their sickness. The elder teenager son died in 4 years after moving into the ill-fated apartment, and the younger son kept being sick despite treatment in Moscow and Germany and died in 1990. The mother of the children, who were the first victims of the ill-fated apartment, also died after moving to a new place.

It was 1989 — three years after the Chernobyl disaster. Presumably this circumstance suggested the father an idea of some connection of diseases of his family members with radiation, which was much talked about then. He appealed to the city sanitary epidemiological station with a request to check radiation background in his apartment. Head doctor M. Savchenko told that when the group of radiologists arrived in the territory of the house yard and switched on the dosimeter, it showed the level of radiation background that 20 times exceeded the normal one. On the threshold of the apartment the level of radiation was so high that radiologists had to find a dosimeter with a higher power range. The new dosimeter brought radiologists to the nursery and pointed at a place in a wall, from which a gamma-ray flux was exposured with the dose power of 200 R per hour.

The issue was given alert at all levels. To determine what kind of source was in the wall panel its irradiating piece was cut out with precautions and sent for analysis to Kyiv Institute for Nuclear Research. On the basis of analysis findings institute experts established that the source was a hermetically sealed capsule with radioactive cesium-137, which was asymmetrically located in the thickness of the concrete wall panel: the depth of its location made 1 cm on one side, and 14 cm — on the other side. It was also determined that the source earlier belonged to a macadam mining and producing enterprise in Donetsk region. The source was lost in 1979. A radiation device which measured the load level of a bunker was broken and the cesium source fell into a macadam container. The loss of the source was noticed only when macadam with the source was sent to a construction site, but since at this time sports facilities were built in Moscow for the 1980 Olympics, it was meticulously searched for at those very sites, but not at the neighboring house-building plant. Later everyone forgot about it.

The tragedy of the situation consisted in the fact that the wall panel with the source divided 2 nurseries in adjoining apartments. The height of source location in the wall corresponded to the height of beds, that is why the children

were exposed to exposure of a rather high level.

Experts from Kharkiv Institute for Medical Radiology of the Ministry of Public Health (presently S.P. Grigoriev Institute for Medical Radiology of NAMS of Ukraine) after reconstruction of exposure scenario estimated the doses, which the victims had got. They could make almost 5000 rem for the children and 1700 rem for the deceased mother.

TREATMENT OF ChRS

ChRS treatment must be complex and differentiated depending on the gravity of its course and prevailing affection of various systems.

In the mild form of the disease the doctor administers active regimen, remedial exercises, and balanced diet. Medications include adaptogens: preparations of ginseng, eleutherococcus, strychnine, multivitamins, hemostimulating agents, minor tranquilizers, etc. Physiotherapeutic procedures can be effective — first of sedative character, and then tonic (water procedures).

Patients with second-degree ChRS are prescribed bed rest, high-calorie but mechanically nonirritating diet rich in vitamins and antioxidants. Hemostimulating agents, especially stimulators of leukopoiesis (for example, pentoxyl, sodium nucleinate, vitamin B_{12}, folic acid, lithium carbonate), antihemorrhagic drugs (vitamins K, C, ascorutin), calcium preparations, anabolic hormones are obligatory. It is recommended to administer symptomatic treatment.

In case of concomitant infectious diseases broad-spectrum antibiotic therapy is administered.

Inpatient treatment duration is 1.5–2 months, during which bed rest is gradually relaxed as sickness signs decrease and the general patient's condition improves. Sanatorium and spa rehabilitation is recommended in the future.

In severe ChRS patients need similar treatment, but bed rest duration is prolonged accordingly. The main attention is focused on elimination of the hypoplastic state of hematopoiesis, for this one resorts to hemotransfusions, natural hemostimulating agents, and hematopoietic cells transfusions. Symptomatic therapy must take into account the importance of recovery of the functional state of the liver, pancreas, stomach and intestine. Special attention must be paid to intensive and balanced antibacterial, hemostatic and substitutive therapy: enzymatic preparations, spasmolytics, choleretics, laxatives. While performing medical manipulations in patients one must strictly follow the rules of asepsis and antisepsis, maintain hygienic regimen in wards to prevent infection.

It is clear that in the future patients require sanatorium and spa treatment and,

probably, registration as disabled persons.

Prognosis

ChRS itself in most cases does not actually threaten patient's life, its manifestations do not tend to progress. However, convalescence with complete recovery of quality of life is obviously not observed. ChRS is not a continuation of the acute form, although residual effects of the latter can remind ChRS.

In a few years after recovery from ChRS hemoblastosis and solid malignant tumors can develop. Consequently, such persons must have regular medical check-ups with obligatory oncologic examinations once a year and blood tests at least twice a year in order to prevent advanced stages of leukosis.

One should also remember that ChRS can lead to cataract and retinal angiopathy.

4. NONSPECIFIC LIFE SHORTENING

Some time ago experiments on small animals revealed a phenomenon which got the name "radiation ageing". Individuals exposured with sublethal doses survived, blood tests returned to normal, signs of gastrointestinal tract disorders disappeared, and their weight became almost normal. However, life span of these animals shortened, and animals behaved as though at the beginning of their life they lost part of their youth.

To counterbalance it, other thorough experiments proved beyond controversy that long-term exposure at low doses (1 rem per week) actually prolonged, even considerably, life of animals as compared with the control group.

This obvious contradiction of experimental data should be interpreted taking into account, firstly, that these series of experiments were conducted at substantially different levels and time characteristics of radiation (acute sublethal and chronic low-dose). Secondly, mechanisms and processes of organism ageing belong to a still little understood biological (and also medical) problem, thus no wonder effects of radiation on these natural processes are poorly known.

The only evidence for possible radiation-induced life shortening in humans was obtained from the study of duration of the term of professional activity of American radiologists. It turned out that in 1945–1954 this term in members of the Radiological Society of North America was shorter than in doctors of other specialties, with whom comparison was made. Unsupervised analysis of these results was performed, whereupon they were subjected to harsh criticism and doubt. In addition, a similar research

of radiologists of Great Britain over the period from 1897 to 1957 didn't find relative shortening of life. In fact the mortality rate among British radiologists over this period was lower than in general population even despite the fact that the research included many radiologists who had practiced before 1921, when radiation safety standards were insufficient. Besides, accelerated radiation-induced nonspecific ageing was not found in the Japanese, who survived after atomic bombing and did not develop cancer.

5. LOCAL RADIATION INJURIES

To the action of any factors of external environment the organism responds with changes in different organs and systems — *reactions*. In case of excessively powerful influence organism reactions become pathophysiological. One of such reactions, the most universal one, is inflammatory reaction or inflammation. *Inflammation* is a general pathologic reaction "directed at elimination of causes and blocking of the damage caused by them, and also at recovery of the functions impaired in the organism" (D.O. Alpern, 1959). Inflammation includes a complex of functional and structural changes: tissue alteration, blood flow disorder with exudation, proliferation of cells of the damaged tissues. Tissue alteration can be primary — under the action of a pathogenic agent (for example, ionizing radiation), and secondary, as a component of inflammatory reaction.

Clinical signs of inflammation are: *redness* (rubor), *edema* (tumor), *temperature rise,* or *fever* (calor), *sickliness* (dolor), *dysfunction* (functio laesa). Usually, these signs of inflammation are characteristic of its acute course.

To denote inflammatory reaction of certain organ the suffix *-itis* is usually added to its Greek or Latin name: dermatitis, esophagitis, epitheliitis, cystitis, etc.

Primary alteration of tissue is observed at the early stage of pathogenic agent action. In case of radiation injury such alteration carries a specific name — *radiation pathomorphosis.* It is a manifestation of lethal injures of tissue cells and destruction of its non-cellular structures under the action of radiotoxins. The gravity of this type of alteration depends almost exclusively on the degree of destructive action of the pathogenic agent, and in the case of ionizing exposure — on the dose size and power.

Secondary alteration develops as a result of subsequent biochemical and physicochemical violations and local blood and lymph flow disorders. Secondary alteration develops later than the primary one, but it is difficult to differentiate contribution of each of them into general morphological damage.

Obviously, the degree of secondary alteration must depend on the intensity of

primary injury. It is primary alteration that is the factor of triggering a cascade of biochemical violations in the tissue, which eventually entail secondary alternative changes.

At low doses of exposure alternative processes can be either practically absent, or so insignificant, that clinically their manifestations remain hidden. Appearance of clinical signs of inflammatory *radiation reaction* of tissue testifies to the fact that exposure exceeded the threshold of tissue tolerance. Usually such insignificant exceeding causes inflammatory reaction which ends with complete or almost complete recovery that does not need substantial therapeutic intervention. Clinically in such cases there is observed reddening, edema and sickliness, local temperature may rise on the damaged area of tissue or organ, i.e. typical signs of inflammatory reaction which subsides over time. One can accelerate this subsiding and provide complete recovery of organ tissues by means of minimum therapeutic measures and above all — by eliminating the action of factors, which can irritate tissue and thus increase inflammation.

Radiation reaction is a pathophysiological response of exposed tissues to the action of IR, which ends arbitrarily and that is why does not need considerable therapeutic measures for its elimination. It develops in exposure of moderate level and, as a rule, is of abortive inflammatory reaction type (for example, skin erythema, transient dermatitis, cystitis, proctitis, soft tissue edema, etc.). Recovery of the normal condition of a tissue or organ in radiation reaction can be accelerated by administering proper medications or hygienic measures.

Thus, at relatively insignificant exceeding of the tolerant dose of exposure which is observed almost in all cases of radiation therapy of malignant tumors, there develops the clinical picture of exposed tissue changes, which has all signs of aseptic inflammation. Alternative processes remain hidden in this case. Consequently, in such cases it is reasonable to call such a process *radiation reaction* in relation to its pathophysiological basis.

At considerable, and especially extraordinary levels of injury, the prevailing phenomena in the clinical picture are alternative processes of different degree up to ulcers and destructive necrosis. In such cases the pathological process acquires the character of radiation injury. The proliferative component of inflammation is suppressed, the recovery process becomes problematic, injury becomes chronic, inclined to malignization, and needs energetic therapeutic intervention, in particular removal of necrotic tissues and their replacement with healthy tissue transplant. Meanwhile it should be taken into account that injury edges, i.e. the zone of transition to the sites of

normal tissue, are composed of tissues with decreased viability and, consequently, with substantially decreased ability of arbitrary recovery. Therefore the volume of tissues which must be replaced considerably exceeds the area of visible damage.

The above mentioned data testify that it is clinically important to clearly differentiate *radiation reactions* and *radiation injuries*. This requirement is linked not only, as has already been noted, to the necessity of choosing different medical approaches in each of these two states, but also to the estimation of radiation therapy quality, which is now their main "supplier".

In publications devoted to the problem of radiation therapy complications, there is noted substantial difference between estimations of "radiation injuries" incidence after radiotherapy of malignant tumors — from 25 up to 95–98 %. These values of radiation therapy complications describe the latter as a too harmful method of treatment. Especially many insufficiently competent publications on this subject are found on the Internet, which disserves patients for whom radiation therapy is administered.

Consequently, since reactions to radiation therapy in the form of edema and hyperemia of tissues (erythema, reddening) are observed in a considerable part of treated patients, the importance of this phenomenon must be estimated by comparing it with another way of tumor removal — surgical. Surgical intervention is sure (one hundred percent) to damage healthy tissues in the form of a surgical wound. There is every reason to consider radiation reaction to exposure during radiotherapy similar to surgical wound, which is perceived as some acceptable and not frightening. Besides, radiation reactions develop not even in all treated patients.

As for *radiation injuries* after radiation therapy, they must be considered (in most cases) a manifestation of therapeutic error, which in each case requires analysis of its causes. In some patients radiation injuries develop as a result of either unpredictably high radiosensitivity of normal tissues or neglecting of the hygiene rules of care for exposed areas of the skin or mucous membranes.

In substantially uneven exposure of man the areas of body, which were exposed to high-level exposure, usually sustain injuries that under these conditions determine the type of radiation pathology of the victim. Such radiation injuries can be isolated, without substantial manifestations of general reactions of the organism if exposure was almost exceptionally of local action, as it is, for example, in radiation therapy of malignant tumors or under conditions of radiation incident, when total body exposure is insignificant. During radiation accidents in 90 % cases as a result of direct contact of a separate body area with a source the victim develops only local radiation injuries. But in total body exposure, which under certain circumstances is accompanied by

high-dose local exposure, local radiation injury becomes a precipitating factor of acute radiation sickness development.

Typical situations causing local radiation injuries are:

- errors committed during work with powerful sources of ionizing radiation:
  - —in industrial radiography (operators),
  - —in medicine (patients),
  - —in scientific work (operators, research workers);
- relocated, lost and stolen sources:
  - —finding a shielded source and opening it (ignorance or ignoring of threat),
  - —finding an unshielded source;
- lost and not found unshielded sources;
- other situations (in particular attempts of suicide, criminal acts with stolen sources).

General signs of local radiation injuries:

- clinical manifestations can develop right after an incident or relatively late after exposure,
- the earlier injury manifestations appear, the more significant the dose was,
- due to high penetrability of high-energy photons not only the skin but also all the underlying tissues and organs are usually damaged on the area of exposure,
- the range of manifestations: erythema, edema, blisters, ulcer, necrosis, inflammatory reaction of the radiation-exposed organ with subsequent fibrosis,
- the dose of radiation is as a rule unknown during the first examination of a victim by a doctor,
- dose can be estimated on the basis of results of observation over dynamics of the development of clinical manifestations of radiation injury,
- to make conclusions concerning the size of radiation dose one should reconstruct the incident scenario.

Internal factors that increase the risk of radiation injury development or transition of radiation reaction to injury can include:

- chronic inflammatory processes,
- allergy of any origin,
- skin diseases,
- obesity,
- exhaustion,

- endocrine diseases (diabetes mellitus, Addison's disease, thyroid diseases with thyroid dysfunction, etc.),
- kidney diseases,
- anemia,
- dehydration,
- peripheral blood flow disorders.

There are differentiated early (acute) and late (remote, long-term) LRIs. The former include injuries, which develop during the first 90–100 days after exposure cessation. Late LRIs develop in more remote periods, sometimes in dozens of years. These two types of LRIs differ not only by the terms of their origin but also by the pathophysiological peculiarities of their development. Early LRIs develop as a result of damage of cells with a short cell cycle, with a low potency of recovery from sublethal damage, but with a high capacity of repopulation. And vice versa, late LRIs are predetermined by damage of slowly dividing cell systems, with a high ability of sublethal damage recovery, but with low repopulation capacity. Late LRIs are rather unpredictable and, in addition, it is much more difficult to treat them.

LRIs of Skin and Hypoderm

Since in case of external exposure the skin and hypoderm are usually exposed to the largest absorbed dose, they are the organs that sustain radiation injuries most often.

The action of IR on the skin depends on the dose, its power and fractionation, and also on the type of radiation.

Development of radiation skin injuries is based on such factors:

- action of ionizing radiation on cells,
- inhibition of regeneration processes,
- disorders of local blood and lymph flow, microcirculation, and blood coagulation system,
- degeneration of nervous endings and fibers,
- death and substitution of cells with hyalinized connective tissue.

An important role is also played by immunoreactions and mechanisms of allergy.

The human skin is of stratified structure (fig. 4).

Epidermis is the external layer of skin of epithelial origin, biologically most active. It consists of five layers. Each layer of epidermis has its separate function. The

first layer — *comified* — consists of comified cells and performs protective function. The next layers consist of pigmented (under the action of ultraviolet they produce the pigment melanin) and immune cells. The deepest layer is *basal* (germinal), it provides the process of epidermis regeneration. Its cells are of homotypic structure and clear differentiation from more superficial ones and are characterized by high proliferative ability.

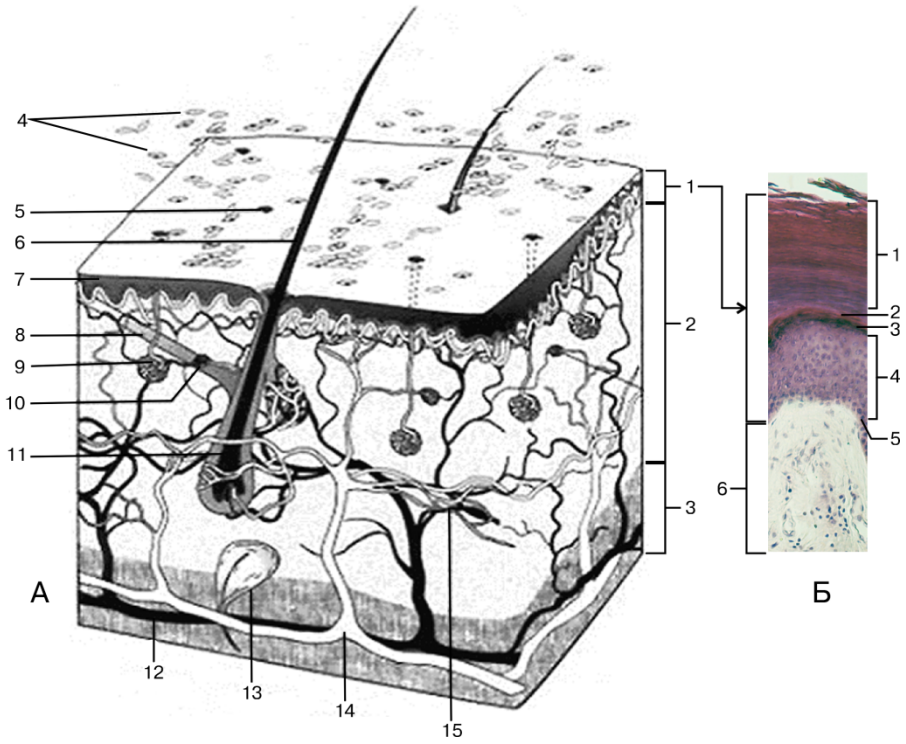

Fig. 4. Normal structure of human skin. A) Skin: 1 — epidermis, 2 — derma, 3 — hypodermic connective (fatty) tissue, 4 — desquamed cells of epidermis, 5 — opening of sweat-gland, 6 — hair, 7 — papillar loops, 8 — muscle-erector, 9 — sweat-gland, 10 — arteriovenous anastomosis, 11— follicle of hair, 12 — vein, 13 — Pacinian corpuscle, 14 — artery, 15 — nerve plexus; B). Epidermis: 1 — horneal layer, 2 — brilliant layer, 3 — grainy layer, 4 — acanthceous layer, 5 — basal layer

Derma is the connective tissue part of skin (skin proper), located between the epidermis and underlying structures, with which it is quite flexibly connected by hypodermic connective tissue, often rich in fat deposits. Thickness of the human derma is from 1 to 5 mm. It consists of two layers: *papillary {spongy, subepithelial)* and *reticular {compact).* The first of them mainly performs the function of nourishing the epidermis and its derivatives: hairs, glands, nails. Highly vascularized, it has a relatively loose structure. Its external surface forms protuberances (papillae), with which it connects to the epidermis. The deeper second layer makes the major part of

derma and mainly performs the supporting function.

According to severity radiation reactions are divided into three degrees:

- I — erythema;
- II degree — dry epidermitis;
- III degree — moist epidermitis.

Early radiation skin injuries (SRI) include the following**:**

- acute radiation dermatitis and
- early radiation ulcer (acute ulcerous dermatitis),

and the *late* ones:

- atrophic or hypertrophic dermatitis,
- radiation fibrosis of skin and subcutaneous tissue,
- late radiation ulcer,
- radiation cancer (malignization of radiation injury).

To a certain extent the last four types of skin injuries can be also considered as different degrees of severity of one pathological condition — *late radiation injury,* because late radiation ulcer is necessarily surrounded by a rim of skin fibrosis alternating with areas of atrophic and/or hypertrophic dermatitis, and in the thickness of tissue under the ulcer — by subcutaneous fibrosis, dystrophic changes in muscles and bones with areas of necrosis in the latter. In addition, the process of late radiation ulcer development usually begins with appearance of signs of atrophic and/or hypertrophic dermatitis, which gradually progresses and transforms by covering the lesion area with small erosions that later coalesce into ulceration.

Risk factors of skin LRI development can be external and internal.

External risk factors of skin LRIs in radiation therapy of malignant tumors:

- large fields of exposure,
- small number of radiation fields at a high total dose,
- overlapping or intersection of radiation fields,
- change of body relief above a tumor in the process of radiation therapy,
- absence of control over absorbed dose distribution,
- neglecting exposure of the skin by backward scattering and the dose at the output of the flux at exposure by opposite fields,
- repeated courses of radiation therapy.

Radiation treatment of tumors located above a bone (the lower jaw, skull, medial surface of the shin, etc.), extensive surgical intervention, traumas, bums, scratching, mechanical injuries in the area of exposure, hard physical load, over-

heating or overcooling in the period of exposure, application of irritant drugs on the areas of exposure, physiotherapeutic procedures, ultraviolet exposure, concomitant chemotherapy, bad hygiene care — all these are also external factors of skin LRIs risk.

Internal factors of skin LRIs risk at radiation therapy of malignant tumors:

- increased individual radiosensitivity,
- young or senile age,
- increased radiosensitivity of the exposed area (inguinal, vaginal, supraclavicular, subclavicular, etc.),
- chronic inflammatory processes,
- allergy of any origin, skin diseases (thinned skin),
- obesity,
- exhaustion,
- endocrine diseases (diabetes mellitus, Addison's disease, diseases of the thyroid gland with its dysfunction, etc.),
- diseases of the cardiovascular system (essential hypertension, hypotension, coronary heart disease, cardiac insufficiency),
- diseases of the kidneys,
- anemia,
- dehydration,
- peripheral blood circulation disorders,
- mental confusion (psychic diseases).

The clinical picture of LRIs depends both on the absorbed dose, energy and type of radiation, area and localization of injury, etc., and to a certain extent on individual peculiarities of the organism. The severest injuries that affect the hypoderm and other deeper anatomic structures develop in case of victim's exposure to photon and neutron radiation. Beta-particles are almost fully absorbed by the comified layer of the epidermis, therefore they can cause though extensive, but not deep injuries. The degree of local exposure can be really high, but due to the limited volume of radiation-exposed tissues in the majority of cases they do not constitute a threat to victim's life.

Pathogenesis of LRIs is complex. It is a sum of processes of damage and recovery in cells of the epidermis, derma, skin appendages (hair follicles, oil and sweat glands), in the vascular system of the derma and muscles, bones, joints, internal organs. Due to different radiosensitivity of organs and tissues, damage develops in them not simultaneously, but after a latent period of different duration.

Pathogenesis of early radiation injury is characterized by a special three-phase inflammatory reaction, whose gravity depends on the intensity of effect and a number of internal factors.

At the early stage vasoactive amines are released, while the two last phases ensue from destructive processes in the capillary walls and changes of vascular reactivity and microcirculation.

In the mechanism of *late radiation injuries* development the main role is played by vessel injuries caused by violation of their permeability and microcirculation. Plasma leakage and fibrinoid necrosis of vessel walls, occlusion of their lumen cause development of hypoxia. The most sensitive to the action of IR are the basal cells of epidermis, epithelium of hair follicles, endothelial cells of capillaries, mobile cells of connective tissue, and epithelial cells of sweat glands. Sebaceous glands, sweat glands, hair follicles are completely destroyed at exposure of 12–24 Gy. Variation of fibroblast function decreases collagen production and matrix organization is made considerably complicated. These changes are accompanied by trophism disorders, development of dystrophic and destructive processes of ischemic damage in tissues with transition to fibrosis or radiation ulcer, sometimes — to radiogenic cancer.

The process of postradiation recovery of radiation injury is compared to reparative regeneration, which takes place at many levels: cell, tissue, organ, and organism. Therefore this process depends on the physiological state of the latter, hormonal background, and many other conditions. Account of peculiarities of dose distribution of exposure and correct use of radiation therapy methods allow irradiating the skin at a total dose of 50–70 Gy during 3–4 weeks without the risk of radiation injury.

ACUTE RADIATION DERMATITIS

Acute radiation dermatitis has a couple of typical stages: primary erythema, latent period, height, outcome, and consequences. One should distinguish epidermitis as a manifestation of radiation reaction of the skin, which can disappear by itself, without serious treatment, and skin damage — dermatitis, or *radiation skin burn,* which is caused by exposure at a dose of 30–50 Gy. In this case on hyperemic edematous areas of skin there appear blisters containing serous or seropurulent fluid, itch and pain increase. Blisters break and an erosion surface is exposed. It is usually encrusted, and healing is very slow (2–3 months and more) under the crust. Afterwards the skin in the place of moist dermatitis becomes atrophic, dry, with alternating areas of depigmentation and hyperpigmentation, development of angieoctasia and

indurative edema.

EARLY RADIATION ULCER

Early radiation ulcer is an acute radiation skin injury. On the exposed area of skin there develops itch, redness, sharp painfulness, inflammatory edema, and blisters filled with serous fluid. After blisters break, there are exposed ulceronecrotic areas accompanied by pain increase, general malaise, fever, somnipathy, decreased appetite, headache. The edges of the ulceronecrotic area are edematous, hyperemic, unclear, surrounded by edematous skin, with phenomena of dry and moist dermatitis. A scab of dim gray color appears in the center of the focus. Necrotic masses of tight consistency do not detach from the surrounding tissues. Epithelization under the scab is slow — it may take years. The skin in the area of exposure undergoes cicatricial changes, it is atrophic, discolored, and telangiectatic.

Histological study of radiation ulcers shows necrosis of the epidermis and upper layers of derma, induration and fragmentation of argyrophilic fibers. The collagen fibers of derma swell, become homogeneous, lose structural properties. There develops endarteritis with hyalinosis of arteriole walls and dissociation of layers of the walls of large vessels with narrowing and obliteration of their lumen. Skin cells die, and the derma is substituted by fibrous tissue. In areas of skin around the ulcer there is observed hyperkeratosis and hypertrophy of the integumentary epithelium with focal round cell infiltration of the derma, atrophy of appendages, dystrophy and degeneration of the neuroreceptor apparatus. Nerve fibers are fragmented, unevenly colored. Perineuritis develops with neuroplasm depositing and neurofibril disintegration.

In the unclear demarcation line of radiation ulcer three zones of vascular bed microarchitectonics are conditionally differentiated:

- first — granulation tissue with an extensive network of capillaries and slow blood flow;
- second — arterioles and veins with arteriovenous shunts between them, whose presence causes blood diversion from arterioles into veins bypassing the capillary bed. The effect of shunting at the level of arterioles leads to venous congestion and, consequently, tissue hypoxia. At late terms (8–12 months) after radiation injury newly formed vessels alternating with pre-existing ones are seen in the radiation ulcer;
- the third — vascular zone is characterized by capillary bed depletion, development of telangiectasia, twisted vessels, absence of their peripheral narrowing, appearance of bead-like swelling. Marginal areas of the ulcer are almost

completely avascular. Such changes of vessels become the cause of necrosis of the skin surrounding soft tissues and development of hypodermal sclerosis.

ATROPHIC OR HYPERTROPHIC DERMATITIS

Back in 1929 the tolerant dose of chronic exposure for the hands skin was established at the level of 0.2 R per day. At greater doses characteristic signs of damage were observed: dryness, hyperkeratosis, cracks on the nail phalanxes, homogeneous or spotty pigmentation, telangiectasias, smoothing of papillary lines. Insignificant traumas of such skin could end with development of chronic ulcers or even late limited necrosis.

Atrophic or hypertrophic dermatitis is characterized by increased sensitivity of exposured skin to any external influences. It most often manifests itself through dryness of skin because of atrophy of its appendages. There often appear cracks which are accompanied by itching and hyperesthesia. Affected areas of skin are hyperemic alternating with depigmented ones. If the skin of the hand is affected, the nails are brittle, lusterless, marked with transversal or longitudinal lines and sulci.

RADIATION FIBROSIS OF SKIN AND HYPODERM

Radiation fibrosis of the skin and hypoderm develops in 4–6 months after exposure. The skin gradually thickens and together with the hypoderm becomes ligneous and painful. Impressions, hyperpigmentation, and telangiectasias are characteristic. The main pathogenetic factor of radiation fibrosis is lymphostasis and fibrosis of the skin and hypoderm.

CHRONIC RADIATION ULCER

The damage develops on the radiation-exposed area of skin in the period from 6 months to a few years. Long before its appearance there develops hyperpigmentation, itch, telangiectasias, skin erosion foci, which in the course of time are covered with large lamellar scales fused to the underlying tissues. Later crust is formed, which gradually becomes multilayer in the form of a scab. Usually the crust persists during many months without a tendency to separation. In the process of treatment the crust is separated exposing the base of the ulcer covered with necrotic masses of yellowish-white color, and in the central part — dim grey color. Edges of the ulcer are of different density, thick, bulging. Around the ulcer the skin is usually also considerably thickened, often ligneous, areas of hyperesthesia alternate with anesthesia. Usually the ulceronecrotic process after beginning has a tendency to both deepen and broaden. In

radiation ulcers a characteristic symptom is pain, often excruciating, and oppressive sensation of burning. Except pain patients also suffer from itch, sometimes unbearable, pulsating, it causes somnipathy and sometimes can not be eliminated by medicinal therapy. In most patients in early and late radiation injuries there develops paratraumatic eczema (edema, hyperemia, vesiculation, weeping) around ulcers, and in some of them eczema is accompanied by skin rash at a considerable distance from the main focus (allergids).

POST-EXPOSURE SKIN CARCINOMA

Post-exposure skin carcinoma is malignization of radiation skin injury. The period of time that passes from acute exposure to development of cancer can make from 5 to 60 years. At chronic exposure, which eventually leads to chronic dermatitis or ulcer, a malignant tumor appears against the background of characteristic hyperkeratotic changes of the damaged skin. Epidermoid cancer prevails among radiation skin tumors — it is observed in 90 % cases (of them 40 % — cornified), and in 10 % other forms of cancer develop. Very rarely sarcoma develops against the background of radiation dermatitis.

Clinically, radiation skin tumors are spots of different sizes deep in the skin and hypoderm, in some areas they are covered with crusts, or with a stellate ulcer with difficult-to-separate crust. The surrounding skin is dry, densely pigmented, lustrous, atrophic, not mobile, hairless.

LRIs of Mucous

LRIs of the mucous membranes to a great extent are similar to the course, pathophysiology, and forms of skin injuries. According to the anatomic sites of mucous membranes their injuries have respective names: rhinitis, stomatitis, esophagitis, cystitis, proctitis, etc.

LRIs of Lungs

Acute early radiation-induced lung injury is radiation pulmonitis of different severity.

An acute injury can become chronic with gradual development of fibrosis of pulmonary tissue structures *(late LRIs)*.

The RTOG scale (of the Radiation Therapy Oncology Group) according to the degree of severity divides acute radiation injuries of the lungs into:

0 — any signs of injury are absent,

1 — weak dry cough or dyspnea caused by physical load,

2 — permanent cough, which is relieved with narcotics only, dyspnea at minimum effort, but not at rest,

3 — cough can not be relieved with narcotics, dyspnea at rest, radiological signs of acute pulmonitis, oxygen therapy needed,

4 — evident respiratory failure, in need of long-term oxygen therapy or artificial ventilation of lungs.

Depending on the dose and volume of exposured tissue pulmonitis develops in 2–6 months after exposure. At total exposure the tolerant dose makes not higher than 10 Gy, but at exposure of the mediastinum alone the dose must not exceed 30 Gy for the adjacent areas of lungs.

LRIs of Heart and Vessels

The tolerant dose for the *myocardium* and *pericardium* makes about 40 Gy, but in some cases this dose causes myocardiodystrophy. Acute exposure of the heart (higher than 60 Gy) can cause death from pericarditis or pericardial hemorrhage. At such dose of exposure myocardial fibrosis can develop in the myocardium: contracting ability is im paired, stenocardia are intensified. Also there are observed His' bundle blockades, right atrial overload, etc. There is a strong probability that all this will lead to severe myocardial infarction.

Large blood vessels unlike capillaries are quite radioresistant. In early periods after fractionated exposure at a dose of 50–60 Gy vascular wall permeability increases, and in a few months there is observed degeneration of the endothelium, thickening of the basal membrane and sclerosis, which in future leads to vessel lumen narrowing and blood flow decrease.

LRIs of Breast

Exposure of the mammary gland, especially of the areola and nipple area, even at a dose of 10 Gy in prepubertal girls is quite often complicated with its hypoplasia.

The most important form of LRIs of the parenchymal structures of the breast is radiation-induced cancer, the risk of which, according to the data of observation over atomic bombing victims, increases by 3–4 % per 1 mGy. During high-dose mammography at 35 years and annual examinations after 40 years the risk of radioinduced cancer development makes 15 cases per each 100,000 examined women. The risk does not increase if exposure dose does not exceed 20 μGy, which corresponds to exposure during mammography with modem mammographs. But one should reme-

mber that the benefits of mammography after the age of 50 considerably exceed the risk of cancer development, because this method allows diagnosing breast tumors at curable stages.

LRIs of Thyroid and Parathyroid Glands

The parenchymatous cells of the thyroid gland are radioresistant. Their interphase death takes place after exposure within the dose range 50–100 Gy with further development of atrophy and hypothyroidism.

Exposure of the neck at doses higher than 20 Gy depresses functioning of the thyroid and parathyroid glands to different extent, which requires replacement therapy. In one of third of children with radiationinduced hypothyroidism spontaneous recovery of gland function is possible later. Other children have to undergo replacement therapy with thyroidin preparations, which is necessary not only to maintain the level of hormone in the blood, but also to stop hyperproduction of thyrotropic hormone that stimulates thyroid enlargement. Exposure can also cause formation of adenomas and even cancer of the gland.

Serious endocrine disorders also develop after exposure of the hypophysis and hypothalamic area of brain at doses of 50 Gy and higher.

LRIs of Nervous System

The tolerant dose for the brain and spinal marrow does not exceed 40 Gy. The threshold dose of radiation-induced *cerebral* necrosis development makes 55 Gy. The risk of necrosis development increases as the number of fractions decreases. Such brain damage after its total exposure develops gradually, the process can end completely in a couple of months or even years. Necrosis development is based on radiation-induced demyelinization of the brain and damage of vessels.

Single exposure during an accident within dose range 3–12 Gy, which usually leads to acute radiation sickness, in 3–10 years causes moderate demyelinization and cerebral blood flow disorder with phenomena of cognitive functions impairment.

Exceeding the tolerant dose of 40 Gy for the spinal cord after local exposure of maximum 3 vertebrae can cause radiation-induced myelitis over a period from 6 months to 2 years after exposure with neurological disorders of different severity to paraplegia inclusive.

Organic lesions of the CNS (leukoencephalopathy with intracranial calcifycations) sometimes develop after repeated exposure of the brain, especially combined with introduction of some cytostatic agents. However, even in the absence of severe

organic lesions of the CNS some patients can develop neurological complications after cranial exposure (problems in studies, psychological consequences). Mental retardation is a consequence of high-dose exposure of the child's brain in leukosis, and the younger the child, the more serious consequences. Age-related limitations are introduced for cranial exposure: children younger than two years get lower doses of radiation therapy in leukemias, and in brain tumors in children younger than three years radiation therapy is not performed at all.

LRIs of Organ of Vision

Cataracts were observed in survivors of the atomic explosions in Hiroshima and Nagasaki, and also in physicists working with neutron sources. In the past, when fluoroscopy was performed without an image intensifier, roentgenologists in mature age developed cataract much more frequently than other groups of people, because lead glass not always provided protection of the face, and consequently the eyes from a direct x-ray flux. The use of image intensifiers, especially with TV- systems, eliminates direct exposure of the face, and therefore prevents the risk of radiation cataract development.

Some information on radiation-induced cataract genesis was obtained from observation over patients treated with x- or gamma-rays with partial exposure of the eye if it gets into the zone of exposure without the possibility of protective shielding. After acute exposure of the eye at a dose 2 Gy cataract rarely develops, and at doses of 7 Gy and higher it almost always develops in a few weeks. The lowest dose, which causes cataract in 100 % cases at acute exposure, makes 5 Gy. At professional considerably protracted exposure this damage develops if the effective dose on the eye of 8 Gy is exceeded.

A unique feature of radiation-induced cataract, which differentiates it from other radiation effects, e.g. leukemia, is that in most cases it can be distinguished from cataracts caused by other factors. In ophthalmoscopy early radiation-induced cataract in man looks as a point located, as a rule, at the posterior pole of the eye lens. As it increases, small granules and vacuoles appear around it. As the zone of opacity increases to a few millimeters in diameter, it takes the shape of a roll. At the same time granular opacities and vacuoles can appear in the anterior subcapsular zone, usually in the area of pupil. At this stage opacification is often stabilized and fixed to the posterior subcapsular zone. If progression continues, then opacity loses specific features and cannot be differentiated from its other kinds.

At low doses opacity can be stabilized at the level, at which vision disorder is

practically unnoticeable. At higher doses opacity can progress, until it results in considerable loss of vision. After radiation therapy, during which patients got low levels of doses (2–6.5 Gy) on the eye, opacity progressed only in about 12 % cases. And vice versa, at higher doses (6.50–11.50 Gy) opacity stabilized only in 12 % patients.

The period between exposure and appearance of phacoscotasmus in people can vary from 6 months to 35 years. In patients, who were exposed to exposure of 2.5–6.5 Gy, the latent period made 8 years on the average. At higher levels of exposure — at doses between 6.51 and 11.50 Gy — an average latent period shortens by about 4 years. Thus, the latent period shortens as exposure dose increases.

The study of 233 case histories of patients, who underwent radiation therapy with influence of exposure on the eye lens and for whom dose estimation was possible, showed that cataract developed in 128 patients, and did not develop in 105 of them. There was no opacity at x-radiation doses less than 2 Gy. Two cases of minimum opacity without progress were observed in patients, who got this minimum dose in one fraction. The lowest single dose that caused progressing cataract was 5 Gy.

The lens can sustain higher doses as the degree of exposure fractionation and total treatment time increase. At multifractionated exposure lasting from 3 weeks to 3 months, and all the more so for its duration over 3 months, the minimum cataractogenic dose increases to 4 Gy and 5.5 Gy accordingly.

It has also been reported about 14 cases of radiation-induced cataract in 38 patients treated with gold grain implants of radon in eyelid tumors. Cataracts progressed from 6 to 11 years after treatment. Calculation of doses in the lens center showed that 40 Gy causes cataracts in all cases.

The results of observation over Hiroshima and Nagasaki survivors corresponded to the results of observation over patients who received radiation therapy. The available information obviously testifies to the existence of a threshold for induction of visible phacoscotasmus in man. However, this does not exclude the possibility that the least dose really causes some harm, but from the practical point of view doses of many Gy are necessary to lead to obvious effect, and it is large doses that cause cataracts which impair eyesight. Special care is necessary when one uses neutrons, and in general all types of radiation with high LET.

The retina is quite resistant to the action of radiation, but at its exposure at a dose of 50 Gy and higher late (in 1–3 years) diabetic-like retinopathy can develop. A higher level of exposure causes occlusion of the central retinal artery with loss of vision. At exposure of brain tumors localized in the area of optic nerve and/or chiasm,

if they get into the field of exposure at a dose of 50 Gy, there is a high probability of damage of these anatomic structures.

LRIs of Digestive Organs

Exposure of the *salivary glands* causes considerable, but recoverable, inhibition of their function already after exposure at a dose of 5–7 Gy. Irreversible ablation of the parenchymal elements of the salivary gland is caused by exposure doses of 25–30 Gy.

Signs of acute radiation-induced esophagitis at exposure of the neck and mediastinum at doses of up to 40 Gy can appear already in 1–2 weeks. But in such cases symptomatic treatment is usually sufficient to recover the esophageal mucosa. If the esophagus dose of 45 Gy is exceeded, exposure can end with the development of its permanent stricture. In 40–50 % patients exposure of the *esophagus* at a dose of 50 Gy and higher leads to stenosis of the esophageal lumen in 3–6 months.

The tolerant dose for the *stomach* is 30 Gy. A dose of 45 Gy causes acute reaction, which is accompanied by nausea, vomiting, epigastric pain. After exposure these phenomena subside without considerable special treatment. But there remains considerable risk of remote development of atrophic gastritis with all its typical symptoms: dyspepsia, anorexia, weight loss, and risk of secondary tumor formation.

Appearance of signs of acute enteritis depends on the volume of exposured intestine and the dose. *LRIs of the small intestine* develop in the early period after exposure at doses of 50–60 Gy in 60 % cases as atrophy of the mucous membrane with impairment of vitamin B_{12} absorption. Later on in most cases there develops diarrhea, fistulas and strictures, which ends with acute or subacute intestinal obstruction.

The large intestine is quite radioresistant: the minimum risk of developing early radiation injuries arises only from exposure to fractionated exposure of 45 Gy (and in the rectum — at a dose of 50 Gy). Complications declare themselves in the form of severe diarrhea, syndrome of low absorption, necrotic damage of the mucosa and underlying tissues, perforations. Stenoses, ulcers of rectum walls, rectovesical fistulas are observed in late periods.

After total exposure of the pelvis there can develop radiation-induced enteritises with chronic practically incurable diarrhea.

The *liver* is the least resistant to exposure of all parenchymal organs of the digestive tract, therefore its total exposure should be treated with caution. Fractionated exposure at a dose of 30 Gy can cause its functional insufficiency, even with ascites, at doses of 3050 Gy — radiation-induced hepatitis with thrombosis of venules

and capillaries. In the central and lobular veins there develops proliferation of intima cells with partial or full closure of vessel lumens, with subsequent closure of sinuses and atrophy of hepatocytes. In early terms after liver exposure (in 2–3 weeks), at doses of more than 40 Gy, radiation-induced hepatitis develops in almost 75 % cases. In future hepatocytes can renew due to proliferation of unaffected ones and the liver recovers its function.

Pancreas radioresistance makes 80 Gy of fractionation exposure. Alpha- and beta-cells are resistant to the action of radiation, and only vessel damage can cause secondary fibrosis of the gland with impairment of its function.

LRIs of Urogenital System

At late terms after total fractionated *kidney* exposure at a dose of 23 Gy and higher in most cases there develops radiation-induced nephritis accompanied by functional renal insufficiency and arterial hypertension. Part of nephrons are lost in this case, and renal function is partially recovered due to hypertrophy of the preserved ones. To prevent such a complication one should irradiate not more than 2/3 of the kidney.

The tolerant dose for the *urinary bladder* makes 55–60 Gy. After exposure at higher doses there develops radiation-induced cystitis, which disappears after proper treatment.

Testicle exposure even at high doses does not lead to the development of *impotence,* because the connective tissue is radioresistant. But in all cases of therapeutic pelvic exposure one should provide maximum protection of the testicles even from scattered radiation, because testosterone level decrease, oligo- and aspermia can develop as a complication.

However, the testicles and ovaries are critical organs from the point of view of other radiation effects — development of sterility and mutations in the next generations, because the germ cells are highly radiosensitive. A dose of even 0.1–0.2 Gy causes a decrease in sperm motility, and a dose of 2–3 Gy causes *temporary sterilization* with a considerable decrease in sperm count. Complete irreversible sterility develops after exposure of the testicles at a dose of 5 Gy.

In women the problem is different. Since the process of ovule development is of cyclic character, they are produced one at a time, the effect of sterilization appears at less doses of exposure and, as a rule, without recovery.

But there was a case, when after exposure of each ovary at 5 Gy a woman became pregnant and delivered a healthy boy.

The doses accepted as permissible for professional exposure do not reduce male fertility and do not influence the menstrual cycle in women.

LRIs of Connective Tissue, Muscles, Bones, and Cartilages

The signs of LRIs of the connective tissue can include contractures or decelerated wound healing. Damages develop too slowly due to peculiarities of cell pool recovery by the population, that is why they can be only late. Doses that can cause LRIs of the connective tissue exceed 60 Gy.

The bony and cartilaginous tissues are quite radioresistant in adults, but in children even a local exposure dose of 1 Gy can cause noticeable deceleration of growth. The bone growth plates are especially sensitive to the action of radiation, that is why exposure at a dose of 10 Gy can entail substantial delay in bone growth in little children.

Growth delay can also be a consequence of indirect action on growing tissues through hormonal regulation disorders as a result of exposure of the hypothalamic-pituitary region (decreased production of somatotropin and thyrotropin). The determining factors of the degree of growth delay are the dose of exposure and child's age in the period of exposure.

Consequences of local exposure include face asymmetry at orbital exposure in rhabdomyosarcoma, asymmetrical development of the soft tissues and skeleton of the shoulder girdle after high-dose neck exposure in lymphogranulomatosis.

Teeth growth disorders are noted at exposure of the jaw at doses over 24 Gy. Exposure of long tubular bones during treatment of Ewing's sarcoma causes disproportionate development of the extremities and bone fractures, especially if the epiphyses are exposured. Aseptic necrosis of the femoral head develops after exposure at a dose of 25 Gy, with especially high probability in children under 4 years.

In children exposured during Wilms' tumor treatment muscle atrophy can develop with scoliosis intensification. In addition, at exposure dose of 20 Gy there can be spine growth delay with its disproportionate development.

Radiation-Induced Hematological and Immune Disorders

As it has been already said, the hemopoietic system of the organism is the most susceptible to the action of ionizing radiation. Changes in hemopoiesis depend not only on the dose of bone marrow exposure but also on the volume of exposured bone marrow. The most severe, protracted and permanent hemopoietic disorders are obser-

ved during widefield radiation treatment of lymphogranulomatosis at doses over 40 Gy. The risk of severe hematological disorders is especially high during treatment of malignant diseases when radiotherapy is combined with chemotherapy, i.e. when exposure is applied together with cytostatic agents.

Spleen exposure at a dose over 40 Gy in lymphogranulomatosis or neuroblastoma results in the development of hyposplenism, which can promote such severe complication as pneumococcal sepsis.

6. CLINICAL EXAMPLES OF LRDs

LRDs of Skin Induced with Chronic Exposure

Patient Z., male, 56 years old, was hospitalized in the radiation pathology department of Grigoriev Institute for Medical Radiology of Ukrainian NAMS on 14 Jul 2008 with complaints of an ulcer of the palmar surface of the nail phalanx of the third finger of the right hand.

The patient is a roentgenologist by profession with 29 years of medical experience. During fluoroscopic investigations of the digestive tract and barium enema he regularly ignored the rule of putting a protective glove on his hand during palpation of the patient's stomach behind the screen under x-ray flux.

During the last 5 years he noted an increase in hyperkeratosis of surfaces of the II, III and IV fingers of the right hand, numbness and dermatalgia on them. Approximately 8 months ago cracks appeared in the thickened epithelium of the third finger, which gradually increased and grew into an ulcer.

Locus morbi: on the palmar surface of the nail phalanx of the III finger of the right hand there is an ulcer of irregular form with an area of approximately 2 cm^2. On the pads of the II and IV fingers of the same hand the skin coarsened, is covered with a layer of keratosis-like changed epidermis (fig. 5).

X-ray pictures of both hands (fig. 6 a) and enlarged x-ray picture of the right hand (fig. 6 b) show severe spotty osteoporosis of all phalanxes of the II, III and IV fingers, most expressed in the middle and especially the nail phalanxes, which testifies to bone trophic disorders with their destruction.

The general state of the patient is satisfactory, laboratory blood tests are within normal limits.

Diagnosis: chronic radiation-induced ulcer of the palmar surface of the skin of the nail phalanx of the III finger of the right hand. Hypertrophic radiation-induced dermatitis of the II and IV fingers of the same hand.

Reconstructive estimation of the dose of exposure of the affected hand was

conducted (25 years of working without a protective glove). It was established that the dose of exposure can make 400–450 Sv. Dose reconstruction was performed by the Central Laboratory of Radiation Hygiene of Medical Personnel (Grigoriev Institute for Medical Radiology of Ukrainian NAMS).

On 18.07.08 surgical amputation of the nail phalanx with the ulcer was performed. Fig. 7 shows the pathomorphological picture of changes of the skin and hypoderm of the damaged phalanx.

Fig. 5. The photoes of the fingers of the patient right hand: A) chronic radiation ulcer on the palmar surface of the nail phalanx of the III finger; B) the dorsum of the nail phalanx of the III finger: delay of nail growth and destruction of nail bed with hyperkeratosis; C) chronic hypertrophic dermatitis on the palmar surface of the IV finger

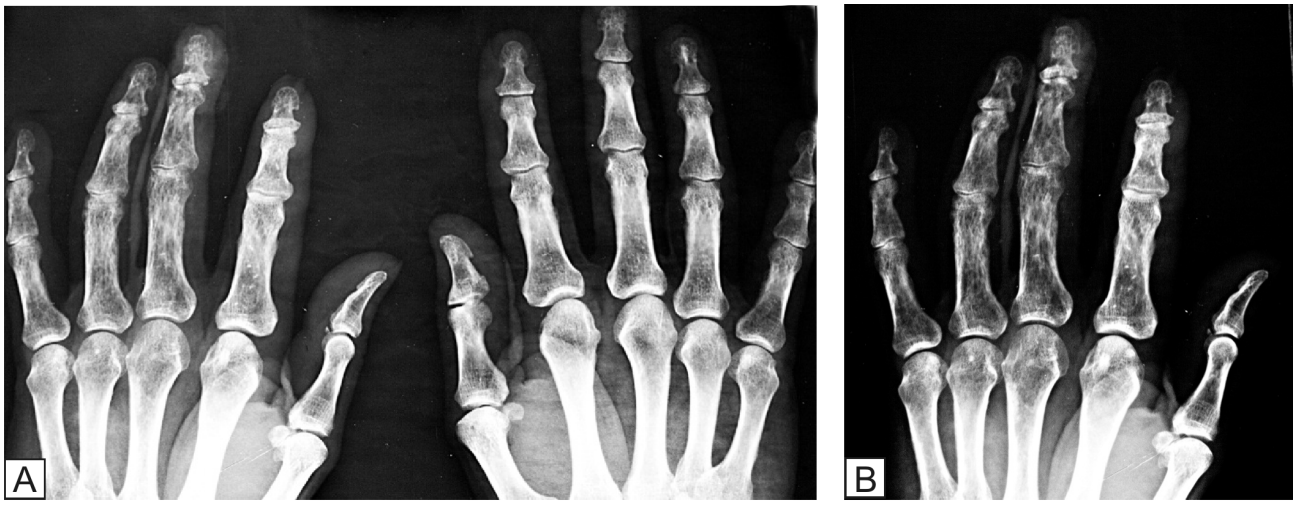

Fig. 6. A) Comparative x-ray picture of the patient hands. Severe spotty osteoporosis of the phalanxes of the II, III and IV fingers of the right hand is seen, which testifies to bony tissue trophism disorders with bony tissue destruction; B) x-ray picture of the right hand, which more clearly shows trophic changes of bones

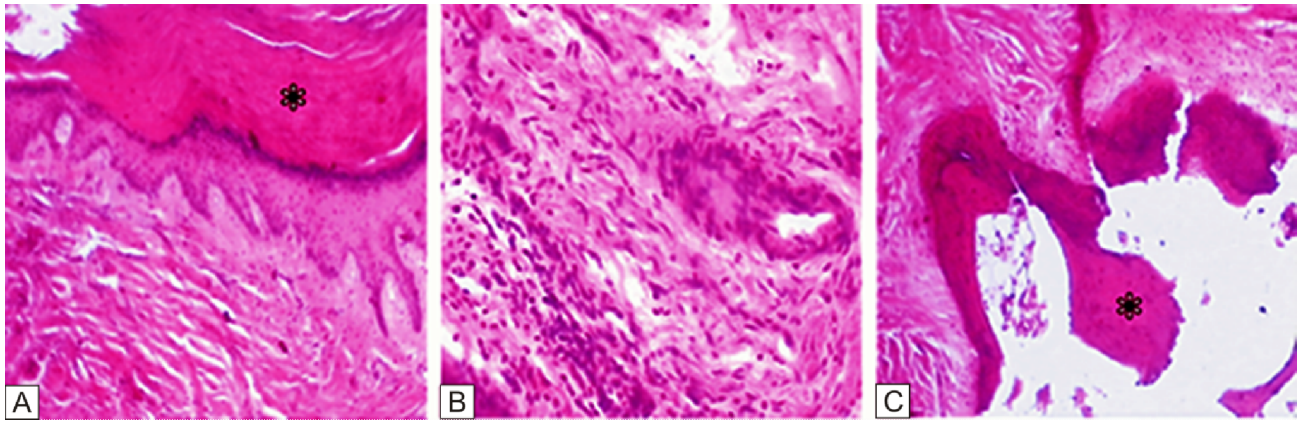

Fig. 7. The pathohistological pictures of tissues of the damaged phalanx of the patient: A) hyperkeratosis of skin (*) - excessive formation of homy substance as a result of chronic inflammatory process (hematoxylin and eosin staining, ×150 enlargement); B — granulations — excessive growth of connective tissue with focal lymphoid infiltration (hematoxylin and eosin staining, ×375 enlargement); C) destruction of the bony tissue (*) of the nail phalanx (hematoxylin and eosin attaining, ×150 enlargement)

Final diagnosis: chronic radiation-induced ulcer of the nail phalanx of the middle finger of the right hand with disorders of all tissue structures — the skin, hypoderm and bones; condition after surgical amputation of the affected phalanx. Chronic hypertrophic radiation dermatitis of the II and IV fingers of the same hand.

Radiation-Induced Fibrosis of Skin and Hypoderm after Radiotherapy of Rectal Cancer

Patient K., 59 years old, was hospitalized in the department of radiation pathology of the clinic of MRI of NAMS of Ukraine with complaints of general weakness, an expressed pain syndrome and reddening of the skin, presence of a fistula with purulent discharge in the sacrococcygeal region of the body.

Case history. At the age of 38 the patient was diagnosed rectal cancer $T_3N_0M_0$, II stage, concerning which resection of the affected area of the bowel was performed with preoperative telegammatherapy at a total focal dose of 46 Gy. Morphologically: differentiated adenocarcinoma. On the skin of exposure fields there was an early radiation reaction in the form of moist dermatitis. 4 years later there developed a radiation-induced ulcer 2 cm in diameter, which was surgically removed. In the next years the state of the patient remained satisfactory.

During May 2011 again an ulcer gradually developed on the same area of skin with a fistula in the hypoderm. With suspicion for sacral osteomyelitis the patient was hospitalized to the clinic of Sytenko Institute of Spine and Joint Pathology of NAMS of Ukraine.

Results of clinical examination of the patient. Microscopy of fistula discharge: characteristic signs of chronic purulent inflammatory process. Bacteriological examination of discharge: colibacillus and saprophytic staphylococcus were inoculated. Irrigoscopy findings: the rectum after surgery with a satisfactory function of anastomosis, chronic colitis.

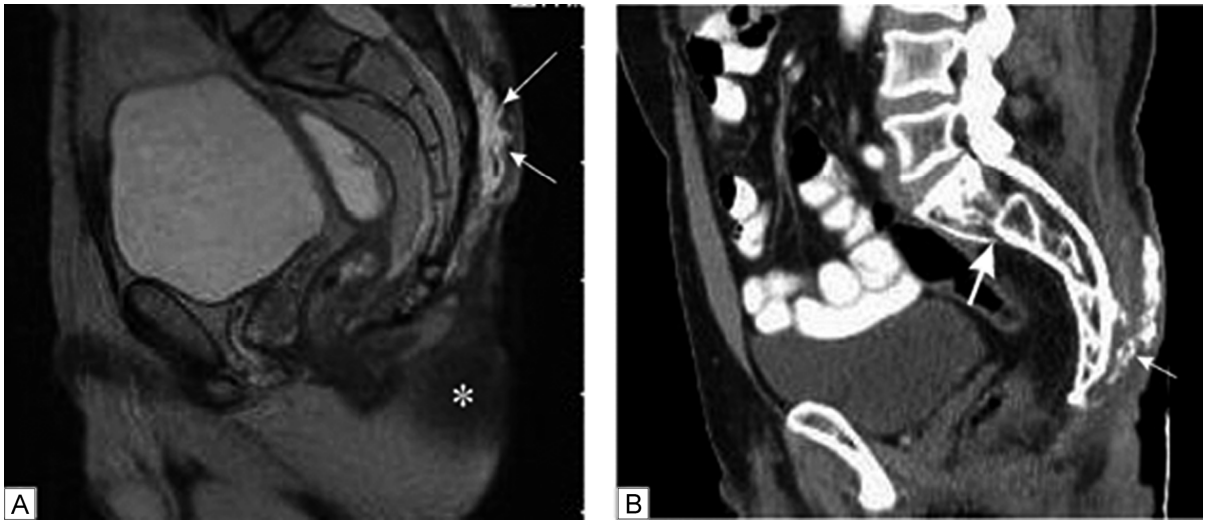

Fig. 8. MRI and CT images of the sacrococcygeal region of the patient K. in sagittal projection: A) MRI scan: hardening of the skin, hypoderm and gluteal muscles (*), presence of pus in the hypoderm above the sacrum (arrows); B) CT scan with fistula contrasting: destruction of the ***I*** sacral vertebra (large arrow), partial bone resorption of the bodies of the II and III vertebrae; the fistula reaches the coccyx (small arrow)

CT and MRI findings (fig. 8): fibrosis of the skin and hypoderm in the sacrococcygeal region as a result of chronic inflammation with the presence of a sinus tract to the sacral periosteum and small multiple cavities in the hypoderm with homogeneous content.

Fistula curettage was performed with draining. Detoxification and antibiotic therapy was provided. The state of the patient became better, but the fistula did not heal. For further treatment on 25.09.2011 the patient was transferred to the clinic of NAMSU IMR.

Findings of clinical examination of the patient upon hospital admission. The state of the patient is rather satisfactory, the nutritional state is sufficient, the peripheral lymph nodes can not be palpated, the heart and lungs — without pathology. Pulse rate 72 per min, arterial pressure 130/80 mm Hg. The abdomen is soft, painless. The liver and spleen are not enlarged.

Common blood analysis: red blood cells — 3.46×10^{12}/L; hemoglobin — 105 g/L; color index — 0.99; thrombocytes — 207×10^{9}/L; leukocytes — 6.0×10^{9}/L;

eosinophilic cells — 1 %; band cells — 2 %; segmented neutrophils — 52 %; lymphocytes — 42 %; monocytes — 3 %. ESR — 10 mm/hr.

Biochemical blood test: whole protein — 69.9 g/L; urea — 4.8 millimole/L; creatinine — 92.0 micromole/L; blood glucose — 5.4 millimole/L; AST — 19.3 IU/L; ALT — 17.2 IU/L; bilirubin — 18.0 micromole/L; calcium — 2.18 millimole/L; sodium — 141.8 millimole/L.

Coagulogram: thrombin time — 7.9 s; prothrombin index — 84 %; APTT — 28.0 s; clotting time — 5.05 min; fibrinogen — 3.21 g/L; SFMC — 3.5 mg%.

Clinical urine analysis: color — pale yellow, s.g. — 1017; reaction — weak-acid, protein— abs., sugar— abs., leukocytes — 2–4 in the field of view, red blood cells — solitary in the field of view, transitional epithelium here and there, salts — oxalates.

Ultrasound: signs of chronic cholecystopancreatitis, gallbladder polyp, chronic pyelonephritis with nephrosclerosis phenomena, salt diathesis, microlites in the left kidney.

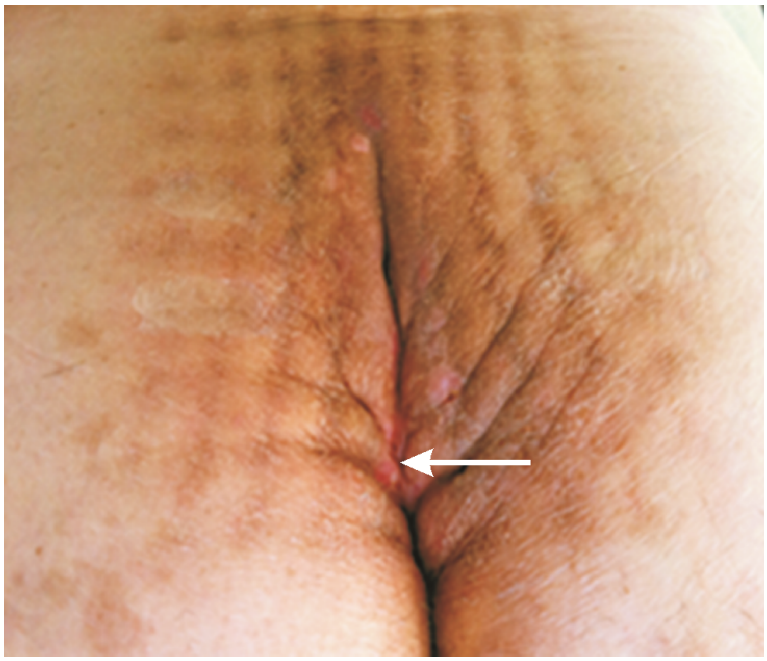

Fig. 9. Area of radiation injury to the skin of the patient K. The fistula opening on the skin surface is seen (arrow)

Locus morbi (fig. 9): in the sacrococcygeal area there is a region of congestive hyperemia 8×10 cm with a chronic ulcer in the center with a diameter about 1 cm; on the floor of the ulcer there is a fistula opening. Marked edema and fibrosis of soft tissues of exposure fields are observed.

Basic clinical diagnosis: rectal cancer $T_3N_0M_0$, II stage, condition after com-

bined treatment. Clinical group III. Radiation-induced fibrosis of the skin and hypoderm complicated by chronic purulent process with a fistula in the sacral area of the body.

General detoxication therapy and immunotherapy, and local treatment of radiation injury were provided. The patient was discharged with substantial improvement; recommendations were given in relation to medical follow up.

LRDs of Skin after Combined Therapy of Breast Cancer

Patient B., female, 44 years old, was hospitalized to the radiation pathology department on 15.09.2009 with complaints of an ulcer and pains in the area of scar after right-side mastectomy.

Life history: in November 2008, the patient was treated concerning breast cancer (T2N1M0). Madden's mastectomy was performed. Morphological research: low-differentiated ductal cancer with metastases in 3 lymph nodes. Receptors: estrogenic — negative; progesterone — negative; HER2/new — negative.

There was conducted a postoperative course of telegammatherapy on the inguinal, supraclavicular, parasternal fields and postoperative scar. During the course of radiation therapy there was a lymphorrhea in the area of the postoperative scar. In the period from January to April 2009 6 cycles of chemotherapy were conducted with doxorubicine and cyclophosphan.

Soon after treatment in the sternal part of the postoperative scar an ulcer developed, which was removed surgically (08.07.2009). Morphological research: ulcerous defect of the skin with fibrosis. Since surgical treatment of the ulcer appeared ineffective and skin injury continued to make progress, the patient was hospitalized to the radiation pathology department of Grigoriev IMR of NAMS of Ukraine.

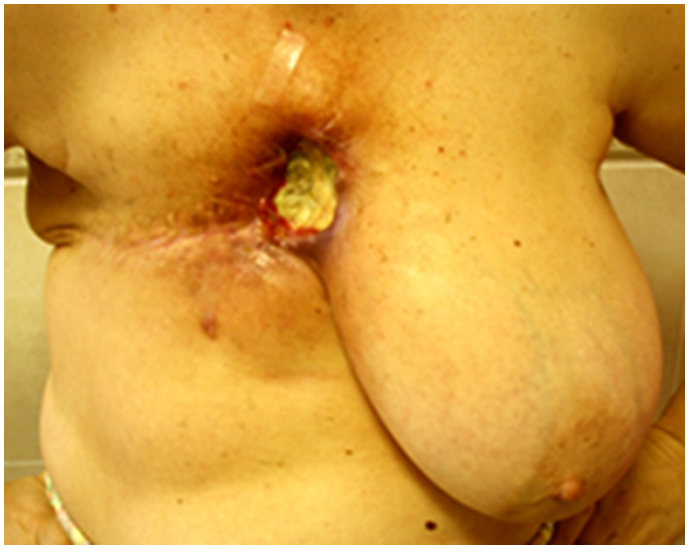

Fig. 10. Chronic radiation-induced skin ulcer of the patient B. before reconstructive surgical treatment

At the moment of hospitalization the general state of the patient was satisfactory. In the medial part of the postoperative scar there was a deep ulcerous defect up to 6 cm in diameter with uneven scalloped edges, whose bottom was the sternum and cartilaginous parts of the inferior ribs (fig. 10). The floor and edges of the ulcer were covered with dirty-gray fibrin film. The surrounding tissues underwent indurative changes, with phenomena of fibrosis and chronic inflammation. Signs of local cancer recurrence were not found.

Microbiological research of wound discharge: there was inoculated pseudomonia aeruginoza sensitive to gentamycin and tienam.

Diagnosis: radiation-induced ulcer of the postoperative scar after surgical excision (07.2009). Second-stage right-side breast cancer T2N1M0, after complex treatment (11.2008–04.2009). Clinical group 3. Hypochromic anemia. Myocardial dystrophy of mixed genesis, first-degree cardiac insufficiency.

Taking into account inefficiency of previously conducted therapy, concilium made a decision to provide surgical treatment of the radiation-induced skin injury: excision of the radiation-induced ulcer of the anterior chest wall with defect closure using the contralateral mammary gland as tissue donor.

Operation of excision of the radiation-induced ulcer of the anterior chest wall was conducted with skin defect plasty by means of the left breast. Viability of the tissues was determined by their bleeding and color. During excision of the ulcer there was found a sequestrum of the costosternal joint, which was removed.

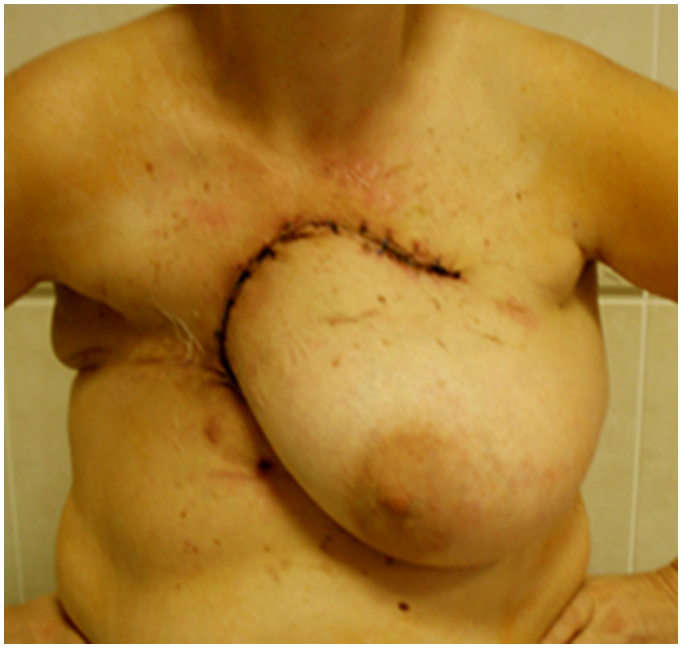

Fig. 11. The patient B. after reconstructive surgical treatment of chronic radiation-induced ulcer of the skin. The ulcerous skin defect is closed by the contralateral breast

The postoperative period had no complications (fig. 11). The stitches were taken out in 2 weeks. The patient was discharged from hospital on the 21st day.

Late Complications of Radiation Treatment for Hemangioma

During the 1940s–1970s radiation therapy with soft and orthovoltage x-rays was recommended and, accordingly, widely used in skin hemangioma treatment. When linear accelerators appeared in the clinical practice of Western Europe and North America, one began to use electron flows for this purpose, which allowed to adjust the dose according to the exposured tumor precisely concerning both the area and depth, which substantially decreased the risk of radiation damage to elements of the skin and hypoderm and allowed achieving better medical and cosmetic effects. Radiation therapy was also a method of treatment for vertebral hemangiomas. Mainly that was open-field gamma-therapy in the form of separate, sometimes repeated courses of exposure with intervals between them from 6 months to 1–2 years.

Except for independent primary treatment, x-therapy was also used to prevent possible relapses after surgical removal of skin hemangiomas, especially in cases of nonradical tumor excision. It should be noted that most patients were children even under the age of 5, and half of them — younger than 1 year. Most frequently x-therapy was conducted in hemangiomas of the orbital area, lips, cheeks, parotid area, i.e. where the volume of surgical intervention was limited and sometimes a surgeon was forced to refuse from this method of treatment at all.

Severe complications of radiation treatment for skin hemangiomas were radiation-induced exudative dermatitis, skin depigmentation, teleangiectasias, fibrosis, and chronic radiation-induced ulcers. Consequently, if RT cured patients of hemangiomas, cosmetic results were often bad, and complications even lead to permanent disability.

Telegammatherapy of vertebral hemangiomas was recommended at total focal doses (TFD) in the cervical spine — 26–32 Gy, thoracic spine — 28–30 Gy, lumbar spine — 30–34 Gy. At TFD less than 20 Gy long-term or permanent clinical effect was absent.

Patient S., female, 49 years old, was hospitalized with complaints of the presence of skin induration and burning pain in the left subclavicular region.

Life history: in 1961, at the age of 6 months, x-therapy was conducted concerning skin hemangioma of the anterior chest wall. The record about the conducted treatment was lost, the doses of exposure are unknown. During the last few

years (in almost 49 years after radiotherapy) there formed an induration of the skin in the area of exposure field, during the last 2–3 months pain began to disturb, an ulcer appeared. The patient, an inhabitant of Kharkiv, developed normally in childhood, got higher education, works as an engineer. She did not have chronic diseases, allergic history is not burdened. At the moment of hospitalization the state is satisfactory, body-build is correct, the skin and visible mucosa are pale pink, the peripheral lymph nodes are not enlarged. In the left subclavicular area on the skin a scar is present 3×4 cm with hyperkeratotic phenomena, with a centrally located ulcerous defect 0.5×0.9 cm. The chest is of normal form. Heart sounds are rhythmic, muffled, AP 130/80 Hg, pulse at rest is 66 beats per minute. There are no abnormalities in clinical and biochemical blood analyses, coagulogram, clinical urine analysis, and electrocardiogram. Ultrasound shows signs of autoimmune focal and diffuse thyroiditis. In the abdominal organs and kidneys signs of pathology are absent. Chest fluoroscopy: no infiltration and focal changes in the lungs. The roots are structural, the sinuses are free. The heart is in age-specific norm.

Diagnosis: late radiation-induced fibrosis of the left subclavicular area with hyperkeratotic phenomena and a centrally located ulcerous defect.

An operation of skin fibrosis excision was performed. After processing of the operative field under combined intravenous anesthesia two incisions were made on the skin, which edged the area of fibrosis. The fibrous area of skin and fibrous hypoderm were removed as one block. Subjacent muscles are not changed. The wound healed by first intention.

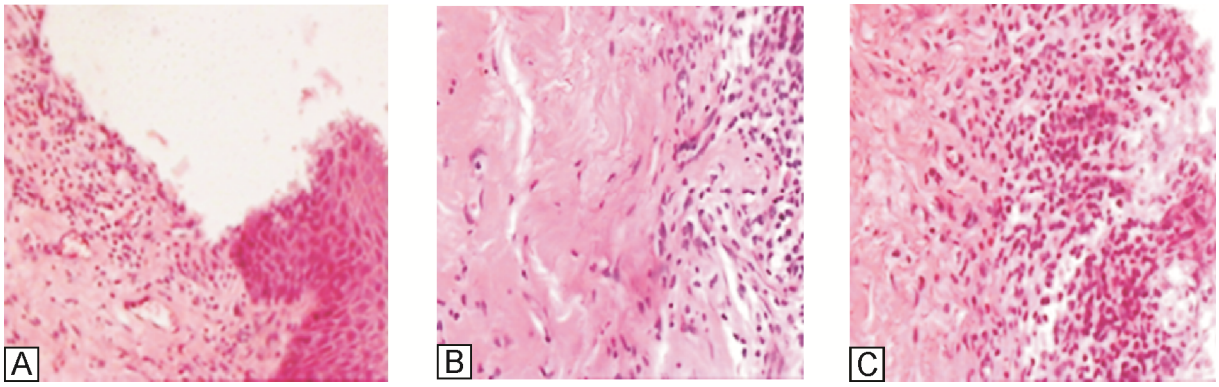

Fig. 12. Microslides of the removed area of skin of the patient S.: A) marked lymphocytic infiltration of the floor of chronic ulcer (hematoxylin and eosin staining, ×400 enlargement); B) overgrowth of connective tissue, focal edema (hematoxylin and eosin staining, ×200 enlargement; C) edge of the ulcer; absence of integumentary stratified squamous epithelium (hematoxylin and eosin staining, ×200 enlargement)

Gross specimen: a fragment of fibrous skin 4.5×2.0 cm with cicatrical changes

on the surface. Histopathological research: radiation-induced fibrosis of the skin with radiation-induced ulcer (fig. 12).

Thus, in this case a negative consequence of radiation treatment for skin hemangioma declared itself in 49 years after exposure in the form of typical fibrosis of the skin with a tendency to transformation to chronic ulcer. We can most probably prognose: in this case the revealed changes would afterwards pass into radiation-induced skin cancer.

Patient T., female, 67 years old, was admitted to the radiation pathology department with complaints of an ulcerous defect of the skin of the back with a pain syndrome in the area of projection of the XI thoracic vertebra (fig. 13).

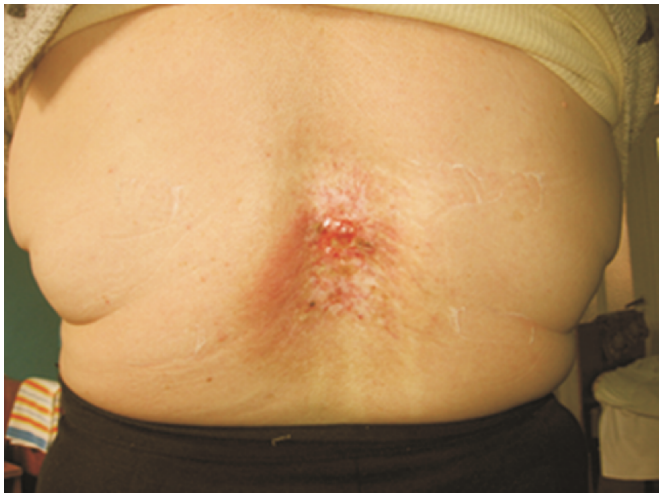

Fig. 13. Area of late radiation-induced ulcer of the skin in the projection of the XI thoracic vertebra of the patient T.

Case history: in 1973 radiation therapy of hemangioma of the body of the XI thoracic vertebra was provided. TFD is unknown (information was lost). After more than 25 years in the area of exposure there appeared itching, painfulness and hyperemia, and in some time — cracks, which were covered with dirty-gray scabs that lasted for many years. After their rejection in the center of the field of former exposure there formed an ulcer, which gradually broadened and deepened.

Examination: in the area of projection of the XI thoracic vertebra — on the skin of the back there is an ulcerous defect 5.0×5.0 cm. Around the ulcer there is an area of fibrosis of the skin and hypoderm 15.0×25.0 cm, tissues undergo eczema-like changes, become ligneous, with areas of hyperpigmentation, scaling, atrophy, hypoesthesia. The edges of the ulcer are flattened, elevated like rolls, tubercular, the floor is covered with fibrinopurulent yellow-grey necrotic masses.

Neurological examination shows diminution of strength mainly in the group of flexors of the lower extremities. Muscular tonus is weak. Tendon reflexes are of aver-

age vivacity, without asymmetry. Pathological reflexes are absent. There are radicular areas of hyperesthesia in the segments of Th X–XI.

Concomitant pathology: essential hypertension, CHD.

Cytology (wound surface scrape): many neutrophils, pavement epithelium in the state of radiation-induced pathomorphism.

There was performed bacteriological inoculation from the floor of the ulcerous defect to determine its sensitivity to antibiotics — aurococcus was inoculated sensitive to III–IV-generation cephalosporins, macrolides, nitrofurans.

X-ray pictures of the thoracic spine (fig. 14) show spongy structure of the body of Th XI with a decrease by 1/3 in its height in the anterior parts with manifestations of compression.

Conclusion: hemangioma of the body of Th XI, pathological fracture. There has been no dynamics since 1973.

In connection with the extension of radiation-induced fibrosis surgical treatment is not conducted at the present time. The patient received conservative therapy: disintoxication (reosorbilact, polarizing mixture), preparations that stimulate local reparative processes (actovegin, solkoseril ointment), angioprotectors (quercetin, troxevasin), preparations that improve rheological properties of the blood (dipiridamol), venotonics (detralex), locally bandages with 10–20 % dimethyl sulfoxide solution, levsin, tetracycline ointment, argedin; vitamins, microelements, antioxidants (mexidol), immunomodulators (cycloferon, immunofan), hypotensive, hepatoprotective therapy.

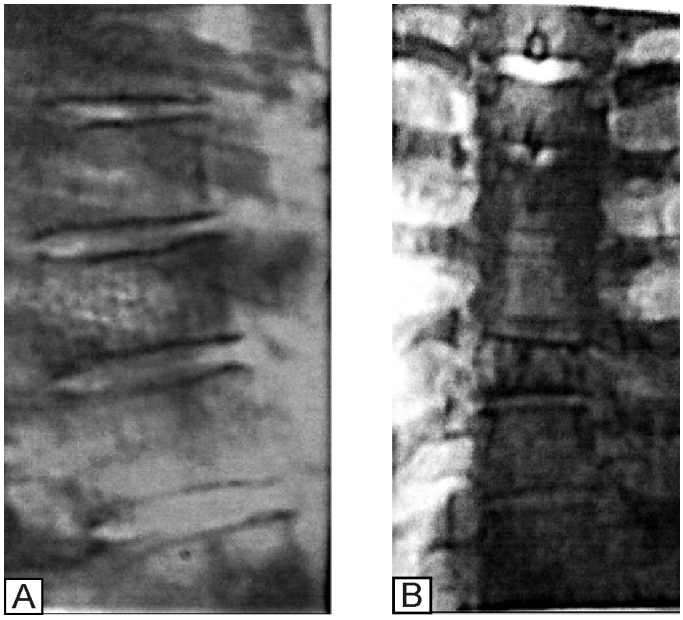

Fig. 14. X-ray pictures of the thoracic spine of patient T. A — lateral projection; B — frontal projection. There is determined spongy structure of the body of Th XI with a decrease in its height in the anterior parts with manifestations of compression

The patient was discharged in improved condition, positive dynamics in the area of damage — decreased intensity of clinical manifestations of late radiation-induced ulcer (a decline of manifestations of irritation, inflammatory reaction, a decrease in the area of fibrosis, ulcerous defect). It is recommended to continue treatment in a policlinic with application of hyperbaric oxygenation.

Thus, high-dose exposure characteristic of tumor treatment has a yearlong impact on exposured tissues, first of all on the skin which usually gets the maximum dose but it can not be considered an exceptional feature of radiation, because even a physical injury leaves locus minoris resistentiae in the affected tissues where a malignant tumor — osteosarcoma — can develop in many years.

Radiation injuries developed in treated patients in 26 and 49 years after high-dose therapeutic exposure, which reminds about the necessity of case follow up during the whole life of patients, in whom benign or malignant tumors were treated by means of radiation therapy. One should also call attention of the treated patients to the importance of permanent thorough care of the areas of skin, which were exposured, because it is known that physical and chemical irritants are among enhancers in the pathogenesis of late post-radiation injuries of the skin, in particular cancer.