MEANS OF PROTECTING THE BODY FROM THE EFFECTS OF IONISING RADIATION

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Poltava – 2018

UDC 615.849

ББК – 53.6я73

С75

«Рекомендовано вченою радою Вищого державного навчального закладу України «Українська медична стоматологічна академія» як навчальний посібник для студентів вищих навчальних закладів МОЗ України» (протокол №3 від 22.11.2017р.)

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Poltava, 2017. – 131 p.

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The manual is committed to provide current information about the human body protection against acute and chronic ionising radiation. The manual concerns the issues on applying radio-protective chemical agents and natural food items to increase the body resistance against the ionizing radiation in unfavourable environment as well as in the course of radiation therapy. Special attention is paid to the novel conception of radiation protection nutrition. This manual is designed in accordance with the Curriculum of Radiation Medicine and Radiology to meet the academic, professional needs of medical interns and medical residents of higher educational institutions of III – IV level of accreditation providing Ukrainian language training course. It is intended for use by delivering the course of Radiation Medicine and Radiology to medical students.

ISBN

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LIST OF SHORTENINGS AND ABBREVIATIONS

Gy – Gray

FRAD – Factor of Reduction of absorbed dose

AT – antioxidants

DNA – deoxyribonucleic acid

PAS – prooxidant-antioxidant system

FR LPO – free radical - lipid peroxidation

ROS – reactive oxygen species

LP – lipid peroxidation

Bq – becquerel

Ci – curie

LD – lethal dose

ICRP – International Commission on Radiological Protection

FPRP – fundamental principles for radiation protection

IRB – ionizing radiation background

INTRODUCTION

Ionising radiation has since the origin of life been part of the natural environment surrounding all living matter on Earth. Since 1945, when the atomic and later hydrogen bombs were developed, when their intense testing and the extensive development of nuclear energy has started and a range of modern human activities associated has expanded, the amount of energy causing irradiation has been gradually increasing. When released into atmosphere and reaching its upper layers in different ways, radionuclides can distribute fast throughout the globe, falling onto the land surface, oceans and seas.

This has resulted in an increase of environmental background radiation that, it is important to stress, has remained relatively stable over the last few thousand years. Thus, due to growing human activity, all living organisms throughout the planet began to experience additional radiation burden.

That is why the mankind inevitably faces the necessity to design and conduct measures aimed at providing effective radiation protection and safety. In this regard, the researchers worldwide are searching for the best ways to protect from both acute and chronic exposure to ionizing radiation, as well as working out the radio protective agents to decrease the side effects of radio therapy.

In Ukraine, the problem of the biological impact of ionizing radiation, particularly in small doses, and protection against is still remaining one of the fundamental issues of medical and biological sciences. Nowadays, the problem is extremely relevant because the Chernobyl nuclear power accident led to huge releases of radioactive materials into the atmosphere deposited over large areas of Ukraine. The consequences of this grievously known accident were associated with the significant environmental radiation pollution of different intensity.

Today we can confidently state that no one doubts the importance of using complex protection, which along with the methods of physical protection, and screening in particular, should involve the appliance of radiation protectors.

All radioprotective agents are divided into two classes - radioprotectants and agents for the treatment of radiation damages.

Radioprotectors - are drugs (mostly synthetic) that have the greatest effect when given within some period before the radiation exposure. They are present in the radiosensitive organs (often in the maximum tolerable and subtoxic doses) and prepare the body to develop high radio resistance. The agents for the treatment of radiation damages are usually applied following the irradiation and the development of the main syndromes. They are aimed at overcoming the potential damages by substitution and supportive therapy.

One of the new directions of radio protective researches is the medium of early pathogenic therapy. This is a special class of compounds that are able to influence on the development of pathologic process under the impact of ionizing radiation on early stages. Analysis of available literature allows us to consider a long-term chronic exposure to ionizing radiation as a lingering radiation stress, backed up by the set of environmental and psychosocial stress agents. Key role in the pathogenesis of the stress is played by the activation of free radical oxidation, increasing antioxidant deficit, immune and neuroendocrine deregulation. Effective means for correction of these changes include antioxidants, anti-stress drugs (adaptogens) and immunomodulators.

Currently, chemical methods of radiation protection embrace the following areas:

1. Individual prevention by using radiation protectors that protect the body from external irradiation that causes acute radiation syndrome.
2. Applying means that enhance human body radio resistance during radiation therapy.
3. Applying nutritional supplements and drugs that increase the resistance of biological objects during chronic exposure to ionizing radiation in natural conditions.
4. The removal of radionuclides from the body.

Existing radioprotectors and radio protection measures are far from being perfect. Literature review points out the fundamental properties in searching for new chemical agents, so-called perfect radioprotectors that must meet the following demands:

- To provide high efficiency causing no or little toxicity;
- To be manufactured in dosage forms, which are easy to use and are effective delivering the medication as needed;
- To be cost-effective and to have good storage stability;
- To be effective when used at different types of ionizing radiation
- To provide the protection that must start from the first minutes after the administration and last for a few hours.

Only few radio protective chemical compounds are widely used in medical practice, but they are ineffective at high lethal doses of radiation. Radioprotectors as means of individual chemical protection may be used in cases of emergency at nuclear power plants to make urgent repairs in conditions of increased radiation exposure or while being in a radiation contaminated environment, for example, during space missions and when taking the course of radiation therapy.

1. BIOLOGICAL EFFECTS OF IONIZING RADIATION

The main biological effects of ionizing radiation consist in its ability to induce functional, anatomical and metabolic changes at the molecular, cellular, organ and organism levels.

Biological effects of ionizing radiation are determined by the energy given to various tissues and organs.

The biological effects of ionizing radiation can be explained by the following processes as:

- ❖ Absorption and deposition of energy by living cells;
- ❖ Ionization and excitation of atoms and molecules with the following radiolysis and the formation of free radicals, the further development of primary radiation-induced chemical reactions and damage of large molecular compounds.

Primary radiation effects may be direct or indirect. Direct radiation causes excitation and ionization of molecules of tissues and organs.

Ionizing radiation energy transfer occurs in a very short period of time. The ionization and excitation of atoms and molecules of the irradiated tissue are the primary physical processes that trigger pathological changes.

The characteristics of the biological action of irradiation are the following:

1. The biological effect depends on the radiation dose absorbed. This dependence is direct, i.e. an increase in the dose intensifies the effect.

2. The effect of irradiation is also determined by the distribution of a dose in time line, i.e. by the rate of energy absorption. The distribution of the same total dose into separate fractions reduces the degree of radiation damage as the reparative (recovery) process starting immediately after the exposure to radiation, are capable at least to compensate disturbances caused by irradiation.

3. The extent and type of radiation damages depend on the radiation energy distribution throughout the body. The most marked effect is expected when the whole body is exposed to irradiation, so called the total exposure. Smaller changes

are caused by the action of the same dose, when they impact some parts of the body — local irradiation, when the part of the body exposed matters. Most adverse effects are observed in the abdominal irradiation. Less dangerous consequences are caused when limbs are irradiated.

4. The biological effect depends on the type of radiation. According to the value of the linear energy transfer (LET – it described how much energy an ionizing particle transfers to the material traversed per unit distance), ionizing radiation is divided into sparsely and densely ionizing radiation.

Sparsely ionizing radiation is irradiation of any physical nature characterized by LET of 10 keV/ μm, i.e. a more homogeneous dose distribution of relatively small energy depositions. Densely ionizing radiation exhibits a heterogeneous dose distribution with high local energy depositions, LET > 10 keV/μm. LET of ionizing particles increases with decreasing the speed of the particles, this means that at the end of distance the energy efficiency of any charged particle is maximal. This leads to a specific distribution of ionization that is described by the well-known Bragg curve, when the maximum, Bragg peak, is occurred immediately before the particles come to rest.

Mentioned characteristics of heavy nuclear particles interaction is used in the treatment of tumours, because it enables to focus sufficient energy on the depth of the affected tissue while minimizing its distribution through healthy tissues along the beam course. It has been found out that LET is proportional to the square of the charge: α-particle, which is formed due to the radioactive decay and containing two protons, it has a positive charge of two (+2), determines the appearance of ions 4 times more likely than other particles. In the air, α-particles depending on the primary energy form 40 000 - 100 000 pairs of ions, while ß - particles produce only 30 – 300 pairs of ions. The distance of particles increases with their energy.

Unlike charged particles, neutrons do not carry an electrical charge that allows them to penetrate without obstacles into atoms depth. Reaching nuclei, they are absorbed or spread throughout them. During the elastic scattering in carbon nuclei, nitrogen, oxygen, and other elements that make up the tissues, the neutron

loses only 10 - 15% of energy, and when collapses with hydrogen nuclei having almost the same mass - protons - the energy of the neutron decreases on average as much as twice by transferring protons recoil. Due to the elastic scattering of neutrons, highly ionizing protons are formed. Atomic nuclei in the process of the neutron absorption become unstable and, disintegrating, form protons, α-particles and photons of φ-radiation, and are capable of conducting ionization as well.

With such nuclear reactions, radioactive isotopes of elements can be formed and radioactivity arises, which, in turn, also causes ionization. The recoil nuclei, which arise in nuclear transformations, can ionize matter by themselves.

Consequently, in the case of neutron radiation, the ultimate biological effect is associated with ionization carried out directly by secondary particles or photons. Thus, the main contribution of one or another type of nuclear interaction of neutrons depends on their energy and composition of the matter emitted.

By the magnitude of energy, four types of neutrons are distinguished: fast neutrons (E> 100 keV), intermediate-energy neutrons (E = 100 - 1 keV), slow neutrons (E <1 keV) and thermal (E ≈0.025 keV).

Fast neutrons are of the most practical value in radiobiology. All others being formed during slowing down also contribute to the overall energy absorption process. Neutrons are counted as dense ionizing radiation because the recoil protons formed can ionize the matter to large extent. Protons arise at a large depth at the high penetrating capability of neutrons.

Thus, all types of ionizing radiation by themselves or indirectly result in the impairment or ionization of atoms or molecules of biosystems. However, irradiation of objects with different types of ionizing radiation in the same doses lead to quantitatively, and sometimes qualitatively different biological effects. Therefore, the concept of relative biological efficiency (RBE) of ionizing radiation was introduced. For example, fast neutrons in a dose of 1 Gy (100 rad) produce the same biological effect on humans as 10 Gy (1000 rad) during irradiation.

1. The presence of the latent period. The latent period is a period of time elapsed between the radiation insult and the onset of clinically registered effects.

The duration of the latent period is inversely proportional to the dose absorbed. The higher the dose, the shorter the latent period. It is necessary to remember that the latent period is a conditional clinical concept, and, in fact, the reaction to radiation starts developing immediately.

2. The property of cumulation. If a skin area is exposed to radiation in a dose of 1 Gy, no visible changes occur. If the irradiation is repeated for several consecutive days, erythema appears. In daily exposure to radiation for 2 - 3 months necrosis usually occurs. This can be explained by the fact that tissues gradually accumulate slight changes caused by each radiation event that ultimately lead to major damages.

Biological effects caused by irradiation are considerably determined by functioning of the integrative systems of the body - the nervous system, the endocrine apparatus and the humoral system that transport the toxic products resulted from radiation exposure throughout the body. Nerve receptors are sensitive to the impacts produces by toxins, and this leads to disorders in the processes of nerve regulation, and the emergence of self-accelerating chain reactions in the radiation-exposed body determines the further development of the stages of radiation damage with the characteristic periodicity of the course of the pathological process.

Thus, two important conclusions can be drawn from the above:

1. The interaction of ionizing radiation with living matter occurs in accordance with the laws of physics and is accompanied by impairment and ionization of atoms and molecules with primary radiochemical processes (reactions). But this is only the primary effect of radiation.

2. Ionization of atoms and molecules is only a trigger for secondary processes, which then develop in a living organism and occur in accordance with biological laws. Therefore, the effectiveness of the biological effects of ionizing radiation is assessed from the standpoint of the severity of these secondary injuries.

Effect of ionizing radiation on cells and organisms of warm-blooded animals. As a result of the cell irradiation consequences, it is possible to register a large number of various reactions, e.g. cell cycle delay, suppression of DNA syn-

thesis, damage to membranes, etc. The severity of these reactions depends on which stage of cell life cycle the radiation event occurs.

About 30 years ago DNA synthesis in a cell was found out to occur in the interphase covering a certain period of time. There are 3 stages of cellular interphase - the stage of DNA synthesis (5 years), the period (T), and post synthetic (C-2) periods. Mitosis (M) is the fourth stage. The duration of the life or mitotic cycle - the gap between two successive cell divisions - consists of individual stages, the duration of which varies in different tissues.

Some radiation reactions that cells can easily tolerate are the consequence of damaging multiple structures whose loss can be quickly recovered. Such transitional cell reactions are called physiologic, or cumulative, effects of irradiation (e.g. different metabolic disorders, suppression of nucleic acid metabolism and oxidative phosphorylation, chromosomes clumping, etc.).

Typically, such reactions are manifested within the immediate time after radiation exposure and eventually disappear. The most marked of them is the cell division delay. It is often called as the radiation-induced delay or blockage of mitoses. The cell division is stopped and then restored in some periods of time that differs in different objects, but that always increases in parallel with the increase in a dose of radiation. For most cell cultures, the division delay corresponds to about 1 hour per 1 Gy. The division delay time depends on the stage of the cell cycle during the radiation event. It is recorded as the longest in cases when cells pass through the stage of DNA synthesis or in the post-synthetic stage, and the shortest when the radiation event occurs in mitosis. The reaction of delayed cell division should be distinguished from total mitosis suppression. It typically results from the exposure to large doses of radiation. The cell continues to live for some time, but completely loses its ability to divide.

In 1906 I. Bergonie and L. Tribondeau mentioned that the radio sensitivity of tissues is directly proportional to the proliferative activity and inversely proportional to the degree of differentiation of the cells that make up the tissue. The suppression of cell ability to divide by ionizing radiation is the most significant factor.

In these terms, a cell death, or lethal effect caused by irradiation is regarded as the loss of cell capacity to proliferate. The cells that survived are those that preserve their capacity for unlimited proliferation, i.e. producing clones. Thus, we mean reproductive cell death. This form of radiation cell inactivation is known as the most common phenomenon in the nature.

Another type of reproductive death of the descendants of irradiated cells is the formation of so-called giant cells that arise as a result of the merger of two adjacent, more often sister cells. Such cells are capable of 2 to 3 divisions, after which they die. The main cause of reproductive cell death is the structural DNA transformation in the form of so-called chromosomal rearrangements, or chromosomal aberrations. The main types of the aberrations are the fragmentation of the chromosomes, the formation of chromosomal bridges, dicentric and ring chromosomes, the appearance of intra-and inter-chromosomal recombinations, etc.

Some aberrations (for example, bridges) mechanically interfere with cell division. The exchange within and between chromosomes, the appearance of acentric fragments leads to an uneven distribution of chromosomes and the loss of genetic material that results in the cell death due to insufficiency of metabolites, the synthesis of which was encoded by the DNA of the lost part of the chromosome.

The assessment of damages can be carried out by meta-analysis and anaphase analysis. At metaphase analysis, specially prepared specimen of metaphase cells are studied, in which structures of individual chromosomes are well distinguishable. This method enables to detect all types of aberrations, but it is quite laborious and time-consuming procedure. In anaphase analysis, it is easy to distinguish only “lethal” aberrations for cells — bridges and fragments. This method is used to assess radio sensitivity. Chromosomal aberrations causing the fragments formation are called deletions or end-points.

Another form of radiation-induced cell inactivation - interphase death – occurs prior the stage of cell mitosis. At a radiation dose of 10 Gy, death can occur immediately "under the beam" or soon after radiation exposure. At a radiation dose of 10 Gy death occurs within the first hours after irradiation and can be registered

in the form of various degenerative changes in the cell, more often pyknosis or chromatin fragmentation. For most somatic cells of mature animals and humans, interphase death is recorded only after irradiation with doses reaching dozens and hundreds of Gray. At lower doses, there is a reproductive form of death caused by structural chromosomal damages.

The nature of the radiation cell death

The sensitivity of the cell nucleus is about 6 units higher than that of the protoplasm. It is known that of all intra-nuclear structures, DNA is responsible for the cell vitality. It participates in the formation of chromosomes and in the transfer of genetic information. Radiation causes a variety of DNA transformations, formation of alkaline-labile bonds, loss of the base and change in their composition, change in the sequence of nucleotide arrangement, DNA-DNA and DNA-protein binding, and damage of DNA complexes and other molecules.

There are single breaks when the connection between individual atomic groups is broken in one of the strands of the double-stranded DNA molecule, and double when the break occurs immediately in the near areas of the two chains that leads the molecule disintegration. At any type of breakage, reading of information from the DNA molecule and the spatial chromatin structure is impaired. Single breaks lead to breakdowns of the DNA molecule, as the torn strand is firmly held in its place by hydrogen, hydrophobic and other types of bonds and by the opposite strand of DNA as well. Furthermore, the structure is well restored by the reparation system. Many radiobiologists believe that single breaks by themselves (if they do not turn into double) do not cause cell death.

At radiation doses up to 20 Gy double breaks are the result of simultaneous damage of both DNA strands. With an increase in the radiation dose, the probability of the transition of single breaks into the double ones increases.

Under the action of sparsely ionizing radiation, from 20 to 100 single breaks cause one double break. Densely ionizing radiation can cause a much larger number of double breaks immediately after the irradiation, as well as chromosomal aberrations.

In addition to breakage, the irradiated DNA shows the impaired structure of the bases, especially thymine, resulting in an increase in the number of gene mutations. The formation of cross-linking between DNA and proteins of the nucleoprotein complex is also observed.

The action rarely ionizing radiation (X-ray - fast electrons) 20 - 100 individual gaps predetermine one double. Densely ionizing radiation causes a much greater number of double breaks immediately after irradiation, and chromosome aberration.

Also the formation of discontinuities in irradiated DNA bases structure is broken, especially thymine, thereby increasing the number of gene mutations. There is a degree of cross-linking between DNA and proteins nucleoprotein complex.

Radiation-sensitive DNA -membrane complex is a complex structure formed at the site of the connection of DNA strands with the nuclear membrane. The disintegration of this complex and DNA degradation can be noticed after the exposure of cell culture to irradiation in a dose of 2 Gr.

Finally, an important consequence of the radiation exposure is the change of the epigenetic (non-nuclear material) cells heredity, the carriers which are various cytoplasmic organelles. This reduces the functional activity of the descendants of the irradiated cells. Perhaps this is one of the causes for the remote consequences of irradiation. However, the main cause of radiation-induced reproductive cell death is the damage to their genetic apparatus.

Post-irradiation cell recovery (reparation)

Many radiation-induced injuries can recover. Phenomenon of post-irradiation reparation is predetermined by the fact that the irradiation of cells causes the damage that usually leads to their deaths, but under certain circumstances they can be restored by enzymatic repair systems. Such damages are known as potential, they can develop in two ways – they can be restored (and then the cells sur-

vive), otherwise the cell die. By their timing there are pre-replication, post-replication and replication repair.

Pre-replication repair (prior DNA duplication phase) can occur through the reuniting breaks, or by removing (excision) of damaged bases. Several enzymes including lidase, endonuclease, exonuclease, DNA ligase are involved into reuniting of single breaks that provides the final act of reparation - ligase recovery.

Post-replication repair is a process in which the cell remains viable, notwithstanding the presence of the DNA defects.

Replication repair - the repair of DNA during its replication - is carried out in the process of replication by repairing damages within the growing point of chain by elongation passing through the damage.

As the post-irradiation repair is the enzyme process, its intensity and, consequently, the fate of the irradiated cells are dependent on the general cell metabolism. The cells that survived after a single exposure due to the repair after potentially lethal damage develop the same radiosensitivity as the non-irradiated cells. Cells are known to be the most radiosensitive during mitosis. Radiosensitivity in the 5th stage is significantly lower than during mitosis.

Free radical mechanisms of ionizing radiation

Radiation (as a natural background and the effect of man-made activity in the form of γ--radiation (wavelength < 0.02 nm) can lead to not only typical free radical pathologies as inflammation and stress, but to much more severe conditions. Pro-oxidant-antioxidant system (PAS) includes: the generation of active oxygen species (AOS: singlet, superoxidation radical, hydrogen peroxide, hydroxyl radical) that initiate and continue (with O2) non-enzymatic free radical peroxidation of biopolymers (FRPS, whose primary products - organic peroxide biochemiluminescence, diene conjugates, secondary products – 4-hydroxyenales, epoxides, Malone dialdegyde - MDA, end products – Schiff's bases and lipofuscine known as an aging pigment) that is limited by the antioxidant protection (AOP, which has the enzymes, superoxide dismutase with Cu, Zn, Mn, Fe -

SOD, glutathione reductase with FAD, glutathione with Se, glyutationtransferazu, ceruloplasmin with Cu, catalase and peroxidase the iron-heme metallothionein protein with 33% cysteine residues, amphiphilic hormone melatonin - a product of indispensable tryptophan, tripeptide glutathione, uric acid, vitamins E, C, F, A, is reduced by NADFH2 or NADH2).

γ-radiation possesses a very low quant energy, but commensurate with the chemical binding energy in a single molecule that cause it breakage (radical and ionic). Whereas the body contains about 80% of water, its radiolysis (H2O = H + .He) is of great importance that results in the formation of unstable, but very active hydroxyradical interacting with biopolymers. Therefore, bacterial spores, insects, having enough water in their bodies can tolerate high doses of radiation. Radiolysis of lipids produces hydrocarbon radicals, diene conjugates, hydroperoxides, which contribute to the formation of oxocompounds (including MDA) MDA forms a Schiff's bases and lipofuscine.

Theoretically, a dose of 10 Gy promotes the formation of 250 μm of lipid peroxides, 0.3 μm of TBA-active products, 0.03 μm of Schiff's bases. Amino acids produce peroxide, carbon and thiyle radicals, oxo-compounds. Most radiosensitivity is demonstrated by sulfur-containing and cyclic amino acids. Radiolysis of proteins and protein solutions gives the similar hydroxylation products, as well as radicals of the peptide group and its breaks.

The radiolysis of carbohydrates gives rise to deoxy sugars, breaks the ring and MDA, formed by ·OH; forms the breaks of the glycosidic bonds in polysaccharides. By amino groups, MDA may link protein filaments, DNA, RNA, glucose aminoglicanes. NAD, FAD, quinones, heme can be exposed to radiolysis.

Radiolysis of nucleoprotein contributes to linking of DNA-protein, DNA-DNA. Radiolysis of aqueous DNA solutions demonstrated 22 hydroxy- or oxoderivative thymine derivatives, 12 - cytosine, 5 - guanine (including 8-oG - 8-oxoguanine), 3 - adenine, 4 - deoxyribose, including MDA; thymine dimers, cross-linking of two DNA strands appear, as well as thymine hydro peroxide. Reparation of damages of pyrimidine links is more active than that of purine ones. Superoxide

anion radical or hydroxyl radical provide single-strand DNA breaks at phosphoester bonds; coincidence of two single-strand breaks under the action of two hydroxyl radicals or hydrogen peroxide produce double-strand breaks.

The single-stranded DNA breaks lead to cell apoptosis (small doses of radiation induce p53 protein synthesis - apoptosis promoter), double-stranded breaks lead to necrosis (effect of high doses induces peroxidation of membranes and DNA), contribute to the transposition (introduction of viral genome into DNA). Breaks can reunite randomly. Radiation cytosine deamination gives uracil and 5-methylcytosine – thymine that changes the coding. The irradiation breaks the hydrogen bonding between G and C, A and T.

In low dose irradiation, membranes are critical structures, and in large dose irradiation DNA experiences the considerable impact. In mammalians nuclear membrane is involved in controlling the cell cycle stage shifting and provides the signal transmission for the initiation and termination of DNA replication, this is the site of localization of ion-transport channels, receptors, enzymes, electric potential.

Lipids that make up chromatin are exposed to FRPS. γ-radiation causes the formation of 8-oG in liver DNA, and in the opposite DNA strand, cytosine complementary to guanine, is replaced by adenine, complementary 8-oG that is regarded in terms of mutation; this is especially dangerous for regulatory or structural genes; 8-oG is indicative of genomic instability and carcinogenesis. The leading role in the formation of chromosomal aberrations belongs to the secondary post-radiation processes; DNA repair system can correct a lot of the DNA damages, but can not correct double-strand breaks.

Poly (ADP-ribosyl) transferase is conjugate with DNA repair functions which substrates are histone and enzymes, co-substrates are presented by NAD and ATP. At severe radiation-induced damages, DNA activity of this enzyme leads to the exhaustion of NAD resources (reduced form of NADH2 provides hydrogen for oxidative phosphorylation) and ATP resources that leads to cell death due to energy exhausting (Korzone's effect). This system works as reparative by fixing the ends of the broken chromatin strands by cross-linking proteins with poly-ADP-

ribosyl bridges. With a lack of energy (or hypoxia) xanthine oxidase becomes more active giving uric acid and the AOF that induces apoptosis. Apparently, the protein biosynthesis system blockade as a consequence of radiation-induced damages reduces the activity of reparative processes.

Usually genes which should not be expressed, are methylated from cytosine into 5-methylcytosine (5mC). These loci with 5mC are hotspots (maximum of point mutations), and by the factors 5mC passes through deamination into thymine that is not predetermined by repair systems. Therefore, from the original G-C pair C may be replacing by T, and G may be replaced by A, and eventually there is the replacing of G-C pairs with T-A. Often certain sequences (STGG) experience mutations. Arisen from the AOF (or cytochrome P-450) and metabolites, epoxides produce a direct carcinogenic effect.

Usually, the DNA nitrogen bases are represented by amine- and ketoforms that are in equilibrium with small amounts of the enol and imino forms. UV, X-ray, gamma-irradiation increase the proportion of the tautomeric A and C forms, whereby adenine is paired with cytosine (A = C) that give rise the mutation frequency. Gamma radiation can break heterocyclic nitrogenous bases and pentoses in nucleic acids.

DNA is the only biomolecule that does not degrade and can repair its own damages (reparation).

1) Excision repair includes: a) detection and removal of the modified site from 5`-terminus with DNA-endonuclease and exonuclease (DNA polymerase 1); b) DNA polymerase 1 connects to 3`-terminus of DNA and complementary binds the empty site of the chain on the matrix of the second chain; c) DNA-ligase crosses the built-in site with the chain.

2) Dimers from adjacent thymines are destroyed by DNA-photoligase; DNA-alkyl transferase removes alkaline radicals on the base.

3) In post-replication repair, the completion of the second chain is interrupted in the site of the error of the previous type during the post-replication, then the error is corrected (by DNA-photolyase or DNA-alkyltransferase, often remains

for a long period for the excision repair), then site of the defect in the second chain is filled with fragment from the second homogeneous DNA strand.

4) SOS-repair occurs by interaction of proteins RecA and LexA in emergency situations that strongly induces the synthesis of various DNA repair systems, including those with DNA-glycolases.

The fact that the mechanisms of non-enzymatic free radical peroxidation of biopolymers are leading is demonstrated by the "oxygen effect" - a sharp increase in mortality of experimental animals with increasing O2 partial concentration in the environment under the radiation exposure with the equal doses. In general, quants of radiation have their targets - biomolecules of the body, but hitting them is an accidental stochastic process.

Radiation damage refers to a specific type of stress, and it has signs of inflammation. The threshold doses, which can cause stress syndrome and shift of the pro-oxidant-antioxidant homeostasis, are about 0.5 Gy. Dynamics of primary products of free-radical peroxidation after the irradiation is the following: first their concentration increases in the blood, liver, kidney, brain, spleen, but not in the lung tissue and heart, the normal values usually restore is months or years. Dynamics of the primary products of free-radical peroxidation (MDA) after the irradiation is next: having being formed in tissues, they may enter the bloodstream and accumulate in the spleen and kidneys, and normalization of their content occurs some time later. Products of free-radical peroxidation become accumulated in organs of the immune system and circulatory system.

Status of antioxidant protection changes as follows. Superoxide dismutase is radio resistant, but in high doses it becomes inactivated by hydrogen peroxide. Catalase activity firstly increases and then becomes suppressed that is associated with the induction of protease synthesis that destroys catalase. Large doses inhibit the synthesis of ceruloplasmin; small doses increase its activity. Glutathione peroxidase activity at first reduces and then under the influence of hydro peroxides rises. Heavy-dose or low-dose, but long-term radiation exposure promotes inhibition of glutathione-transferase, oxidation of sulfhydryl groups (including glu-

tathione) and ascorbic acid to dehydroascorbic acid, especially in living organisms that do not synthesize it (e.g., human body).

Low doses of radiation promote the mobilization of blood tocopherol, but chronic exposure leads to lowering of retinol and tocopherol. E- and A-hypovitaminoses contribute to an increase in mortality after irradiation and lysosome labilization. Irradiation accelerates the process of polyploidization of hepatocytes. Thorotrast (radiopaque substance containing radioactive thorium, stored in the liver) induces hematomas. In the experiments, single doses larger than 19.6 Gy or prolonged exposure to a total dose of 1 Gy induced hepatocarcinogenesis, which disguised itself as rapidly developing tumours of other tissues. Active forms of O2 generated by neutrophils can provoke malignant transformation of tissues. The action of carcinogens was observed to lead to the stimulation of the respiratory burst of granulocytes and formation of 8-oG in hepatocytes. Increased free-radical peroxidation contributes to carcinogenesis, as well as radiation, acting either directly on DNA, or indirectly through the activation of the production of active oxygen species.

Activation of calcium messengers system gives the tertiary NO mediator, which together with superoxide anion-radical form peroxynitrite ONOO-, the last with N + NO 2 forms OH (active hydroxyl radical-oxidant). NO inhibits ribonucleotide reductase, NADPH oxidase, superoxide dismutase, glutathione peroxidase, enzymes of the tricarboxylic acid cycle and oxidative phosphorylation, but activates guanylate cyclase, ADP-ribosyl transferase cyclooxygenase plasminogen activator. Peroxynitrite is known to be more toxic as it inhibits amino- and thiogroups of proteins, and 1 and 2 complexes of mitochondrial oxidation.

Irradiation contributes to hypercoagulation, induced by lipid hyperperoxidation. The anti-apoptotic Bcl-2 oncoprotein promotes antioxidant protection. Impairments in DNA activate its repair system, but extensive unrepairable damages lead to apoptosis. Some mutant cells survive, especially in the affection of the immune system, which controls the purity of the genotype of all body cells (each cell provides its receptors of MHC Class 2 with fragments of proteins synthesized from

amino acids 9-11; lymphocytes control the correctness of these fragments, and, if any changes occur, influence on the receptors of cells FAS / APO-1 - CD95, with tumour necrosis factor - TNF, which triggers cell apoptosis). The cells with activated adaptation systems survive and ready to divide, but only with the increased generation of active oxygen species. All this reinforces the genomic instability and increases the possibility of oncogenic transformation.

Increased free-radical peroxidation is hazardous for proliferating tissue cells, primarily for stem cells; therefore one of the approaches in cancer therapy is their irradiation. Immediately after the irradiation, necrosis or apoptosis kills a large number of cells that virtually determines the radiation sickness. However, in some cell types active oxygen species dramatically increase the rate of cell division, perhaps, due to the protein mutations of NF-kB with-Jun, p21ras, p44MAPK (mitogen activating protein kinase), C-FOS in genes; active oxygen species by themselves act as signalling molecules in a cell by causing expression of jun-B, D-jun, C-FOS, FOS-B (most of mentioned here is an immediate early response genes that promote the proliferation or apoptosis). That is, there are specific pathways and genes (sensors), which are affected by active oxygen species.

Irradiated cells release biologically active substances (cytokines, transforming growth factor c1 - TGF-b1 - activator NADFN2-oxidase membranes fibroblast, generator of superoxide and peroxide, or interleukin 8 - IL-8 - pro-mitogenic effect) that influence on cells that are not damaged by radiation. This is known as "bystander effect" that describes genomic instability of unaffected by radiation cells, and contributes to the development of remote effects of radiation.

Radiation exposure through the mechanisms stimulating active oxygen species, free radical peroxidation results in: a) cell apoptosis (programmed suicide); b) cell necrosis; c) delayed cell death; g) genome damage (unprogrammed and unwanted mutations, transpositions, and combinations of gene expression) of generative or stem cells that is reflected in their clones or descendants.

It is the impairment of the genotype of stem cells that causes the radiation – induced pathology in the remote periods after the radiation event, and a hundred-

fold increase in the incidence rate of thyroid cancer, especially in children since the Chornobyl disaster in 1986 is the evidence derived from sound data and information, and relevant research. Increased antioxidant protection promotes cell division, therefore the introduction of antioxidants is recommended before and during the radiation-exposure, but not in cases of uncontrolled cell division. It is sad to remark that genetic defects caused by irradiation in the testes may appear and become manifested by mutations in the offspring. Man, livestock, flora and fauna of the planet have being intensively exposed to high-dose irradiation for the last sixty years, the sources of which are primarily man-made. It can be assumed that the natural background radiation is one of the evolutionary factors for the biosphere, even though mankind seems do not need in this evolution.

2. FACTORS AFFECTING THE INTENSITY OF RADIATION DAMAGE

Final biological effects are determined and influenced by various factors, generally divided into physical, chemical and biological.

Among the ***physical factors*** the first position is placed by the irradiation characterized by the ***relative biological effectiveness (RBE)*.** The difference of biological effects is caused by linear energy transfer of ionizing radiation. RBE is defined as the ratio of a dose of standard radiation (60 Co isotope or X-rays of 220 kV) to the dose of test radiation to produce the same biological effects. Various biological effects can be chosen to compare. For the radiation test, there are several values of the RBE. If cataractogenic effect is chosen as the indicators of post-irradiation, RBE values for fission neutrons are within the range of 5 - 10, depending on the type of irradiated animals, while according to such important criterion as the development of acute radiation sickness - RBE fission neutrons is equal to about 1.

The other significant factor is the physical **dose of ionizing radiation** ii accordance to the International System of Units (SI) is expressed in Greys (Gy). 1 Gy = 100 rad, 1 rad = 0,975R. The magnitude of this dose absorbed determines the development of radiation syndroms and the life span.

While analyzing the correlation between the dose received by the mammalian body, and a certain biological effect, the probability of occurrence of biological effects is taken into account. If the effect occurs in response to the exposure regardless of the magnitude of the absorbed dose, it belongs to the category of **stochastic**. For example, hereditary radiation effects can be regarded as stochastic. In contrast, the non-stochastic effects are observed after reaching a certain threshold of radiation dose, for example: cataract, infertility.

The recommendations of the International Commission on Radiological Protection (№26, 1977), **stochastic effects have been defined as those for which the probability increases with dose, without a threshold. Nonstochastic effects are**

those for which incidence and severity depends on dose, but for which there is a threshold dose. These definitions suggest that the two types of effects are not related.

Chemical radioprotective agents depending on their biological effectiveness reduce the biological impact of radiation as much as in three times at best. But they can not prevent the occurrence of stochastic effects. The essential chemical factors, modifying the effects of ionizing radiation include the concentration of oxygen in the body tissues in mammals. Its presence in the tissues, especially during X-ray or gamma radiation, enhances the biological effects of radiation. The mechanism of oxygen effect is explained by the increased mainly indirect action of radiation. The presence of oxygen in the irradiated tissue following the radiation exposure produces the opposite effect.

To characterize the irradiation, along with the value of the total dose, it is important to know the duration of exposure. The dose of ionizing radiation, regardless of the time of its action causes the same number of ionization in an irradiated body. The difference, however, is in the extent of repair of radiation-induced damage. Therefore, low-energy radiation leads to less severe biological damage. The energy of absorbed dose is expressed in Greys (e.g., Gy / min mGy / h, etc).

Alterations in the radiosensitivity of body tissues are of great practical importance. According to the lowering of radiosensitivity of the tissues the following classes are distinguished: 1 - intermitotic stem cells (crypt cells of the intestine, precursors of blood cells in bone marrow, sperm cells and ova gonads, lymphocytes); 2 - rapidly dividing cells (spermatozoid, oogonia, intermediate cells and myeloma erythropoiesis); 3 - dividing multipotent irregular connective tissue cells (endothelial cells, fibroblasts, mesothelioma); 4 - resting postmitotic cells (cells of the liver, kidney, lung, pancreas, sweat and salivary glands, and endocrine glands); 5 - highly resistant (nerve and muscle cells, red blood cells, sperm cells). Lethal dose of gamma-radiation for humans makes up 10-100 Gy, acute radiation sickness is caused by doses of 1-10 Gy; doses of 0.25-1 Gy cause changes in the circulatory system and autonomic disorders, doses <0.25 Gy do not give noticeable changes;

natural radiation dose (<0.000015 Gy) can influence on individual cells causing mutations and unpredictable effects, including mutations determined by the evolutionary process.

This book is devoted to radioprotectors as well as substances that reduce the radio sensitivity of living organisms, but that does not mean that we underestimate the study of radiosensibilization; their study is especially important for clinical purposes, in radiotherapy, for example.

3. INFORMATION FROM HISTORY OF RADIOPROTECTORS

History of searching for radioprotectors has been around for 50 years 50 years. The development of this class of substances was considerably determined by the intensive growth of radio-biology researches throughout the world when the USA dropped nuclear weapons on the Japanese cities of Hiroshima and Nagasaki on August 6 and 9, 1945. At the beginning of the researches on radioprotectors a large group of sulphur-containing compounds was founded out to possess a marked radioprotective effect. The period from the end of 50th to the middle of 70th was devoted to extensive search among the sulphur- and nitrogen-containing radioprotectors and their and testing. Nowadays, a wide range of compounds including biologically active substances of natural origin have been known to possess radioprotective properties. Therefore, the conventional term "chemical protection" seems to be not exact for the descriptions of this group of substances.

The first hypothesis on the mechanism of radiation impact was suggested by G. Barron (1946), based on the prevailing in that time theory of indirect action of ionizing radiation: the initial formation of highly reactive agents that were able to transfer the energy of ionizing particles directly to molecules of bio substrate and thus damaging them. He proceeded from the fact that during the irradiation, radical particles damaged primarily the structure of sulfhydride enzymes that, in his opinion, was the cause of the development of all post-radiation alteration.

Then, in his laboratory, H. Patt (1949) and co-workers proved that the amino acid cysteine administered before the radiation exposure, protected the animals from the effects of X-ray lethal doses. H. Patt works have been recognized worldwide, and their results paid great attention to the radioprotective effect that gave rise to a rapid development and study of new materials in radiation pharmacology.

However, the accumulation of new experimental data gave the facts that did not fit into the framework of "SH-" Barron's hypotheses. Controversy or lack of some data on the decreased activity of thiol enzymes, as well as unsuccessful attempts to detect inhibition of anaerobic glycolysis immediately or after irradiation

with lethal doses were the weak points of Barron's theory. Since many enzymes of these processes contain the thiol group in the active centres, these data can be considered to refute the theory of Barron. Nevertheless, the works of Barron contributed much in the foundation and development of chemical protection.

The next stage in the development was the discovery of radioprotective properties of thiourea. Although, its effect is small, this discovery is noteworthy because it led scientists to suggest a possible involvement of amines in providing radioprotective effect. The results were not long in coming: a Belgian scientist Back (1952) synthesized ß-mercaptoethylamine, a compound containing amino decarboxylated cysteine. This event can be considered as a great discovery in chemistry of radioprotectors. ß -mercaptoethylamine provided high protection taken in concentrations of 5-6-fold less than the cysteine. At that time views on the mechanism of radioprotective effect consisted in the concept of the competition for the free radicals between the protective compounds and sensitive to radiation biological substrates. According to those conceptions, protector is a substance, which reacts with the active molecules of the environment and living cells before they start reacting with each other.

The programs on searching radioprotectors, studying their pharmacokinetics continually gained in scope in the United States. In 1955, the US radiobiologists founded S,ß-aminetilizotiurony. However, like all sulpha drugs, it was highly toxic, but demonstrated good protective effect. The main task the scientists considered was to discover or to create highly effective radioprotectors with no or little toxic effects and easy-to-use in daily routine.

By 1959, about 1500 compounds were proposed, and most of them were synthesized in Chicago radiobiological laboratory. It was shown that the best drugs, which at least partially met the requirements suggested to radioprotectors, were mercaptoethylamine and mercaptoethylamidine. These compounds were used as the basis for the synthesis of another 850 drugs, a half of which showed pronounced protective properties. Much attention was also paid to the combined effects of radioprotectors. Radioprotectors having different mechanisms of action

were the most often combined, for example, mercapto-compounds with methemoglobin producers. At the same time, scientists tried to find out ways to prolong protection. And one of those methods, an introduction of the lipophilic groups to radioprotector, still remains relevant for enhancing the temporary protection.

By 1969 in the USA, the programs on radiation protection research offered about 4000 compounds. However, only WR 638 (cystaphos) and WR 2721 (amifostine) were chosen for clinical trials. Their testing on volunteers was very successful. But soon it was found out that even those "outstanding radioprotectants" did not meet standards existing for pharmacological agents.

In our country, scientists carried out their studies in the way that made it possible to research the compound obtained in terms of modeling the effect of radiation on the chemical structure of the substance. This research method was very different from the American way according to which a massive screening of drugs was performed. It should be noted that the Soviet approach to a greater extent compared the US was instrumental in establishing a number of important laws and made considerable contribution to the theory of chemical protection against ionizing radiation.

4. CLASSIFICATION OF RADIOPROTECTIVE DRUGS

Nowadays, radioprotectors are presented by a wide range of substances different by their origin and chemical composition, thus their classification by pharmacological action seems to be very difficult. In this regard, in radiobiology protective drugs can be classified according to the duration of their effect and the timing of the development of radioprotective effect.

All radioprotectors are divided into two main groups: short-term and long-acting substances.

Short-term radioprotectors include drugs, which show their protective effect for 0.5 - 4 hours after the administration. They are the most effective when a body is irradiated to maximally tolerated doses. As an individual protection means, these drugs can be used to protect against nuclear weapons, before the session of radiotherapy, during space exploration missions with long-term protection from solar flares. The long-term protection drugs include agents with radioprotective effects lasting from one day to several weeks. They generally show less effectiveness than short-term radioprotection agents under pulsed ionizing radiation. Practical application of these protectors may be occupational and typical for professionals dealing with ionizing radiation, e.g. astronauts during long space flights, long-term course of radiotherapy. Thus, it is possible to select the appropriate class of radioprotectors for a particular case. But the selection and administration of the agents should keep some regulations.

1. The medicines must be sufficiently effective and do not induce adverse reactions.
2. The medicines must have a fast effect (within the first 30 minutes) and this effect must last for a relatively long period of time (at least for 2 hours).
3. The medicines must be non-toxic with the therapeutic ratio, a minimum is 3.
4. The medicines must not have a negative short-term impact on the ability to work or reduce the acquired skills.
5. The medicines must be manufactured in an easy-to -use dosage form.
6. They should not reduce the body resistance to other adverse environmental factors.

7. They should produce no harmful effects upon repeated administration or possess cumulative properties.
8. The medicines should have good storage stability preserving their protective and pharmacological properties for at least 3 years.

Radiotherapy raises less strict demands to radioprotectors. But they are complicated with an important condition, and namely the necessity to provide differential protective action. This means they are to provide the highest level of protection for healthy tissue and to produce minimal effects upon the tumor tissues. This separation makes it possible to enhance the action of topically applied therapeutic dose of radiation toward the tumors without serious damages to the surrounding healthy tissues.

The short-term medicaments are classified into the following groups, according to the structure and mechanism of their protective effect:

1. Sulfur-containing compounds (ß -mercaptoethylamine (IEA), cystamine, L-cysteine, gammafos, tsistofos, etc.).
2. Biologically active amines (serotonin, 5-methoxytryptamine, adrenaline).
3. Preparations than impair the oxygen transportation through the body or oxygen utilization by cells (cyanides, nitrites).
4. Imidazole derivatives.
5. Arylalkylamines.
6. Indolylalkylamines.
7. Other radioprotectors.

At present sulphur radioprotectors are known as the most effective. Most of the compounds of this group are derived from one of the first of radioprotective drugs - ß - mercaptoethylamine. Radioprotective effect of sulfur-containing radioprotectors is associated with the presence of free or easily released SH-group. More favorable pharmaceuticals are thiophosphates, derivatives of thiophosphoric acid. Their SH-group is “covered” with phosphoric acid residues that determine their slight hypotensive effect and less toxicity.

Indolylalkylamines (serotonin, tryptamine, 5-methoxytryptamine) yield to sulfur radioprotectors only when they are used to protect from the irradiated with neutrons. Their protective effect lasts for shorter time intervals compared with SH-radioprotectors. Obvious advantages of this group are the rapid development of the protective effects and greater efficiency in small doses. It should be noted that the study of derivatives of indolylalkylamines was conducted mainly by Soviet scientists. Cyanides are able to block the activity of iron-containing respiratory enzymes such as cytochrome oxidase, which provides the transfer of electrons from cytochrome to oxygen.

Radioprotectors of prolonged action. Disadvantages of available chemical radioprotectants (mainly toxic side effects and the limited duration of their action) served as the basis for the study of radioprotective properties of low-toxic substances of biological origin. The researches within this direction focus on searching substances and compounds, which would increase the overall body stability and resistance to infections and stimulate the active functioning of the hematopoietic system. Currently, metal-complexes of porphyrins can be regarded as substances demonstrating desired properties.

A wide variety of substances of natural origin have been studied to be used as possible radioprotective agents. Various extracts from plants, microorganisms and other biological objects without extraction of their active substances, and sometimes without control over their purity have been the most often in the scope of the scientists. For example, there were attempts to use such biologically potent substances as snake venom, bee venom, bacterial endotoxins, and estrogens in small doses to provide radiation prevention.

Melittin (polypeptide of bee venom, consisting of 26 amino acid residues, F-2840) demonstrated pronounced and statistically significant radio prevention action in both short-term and prolonged irradiation (low energy dose of 0,1Gy / min) .Bacterial endotoxin isolated from a Salmonella typhi, alleviated post-radiation damages when administered within 30 minutes after the radiation exposure.

Zymosan, a polysaccharide isolated from yeast cells and polysaccharides isolated from bacteria Salmonella paratyphi and Proteus vulgaris were also observed to have protective effects. The most statistically significant effect was demonstrated by estradiol when compared with methyl testosterone, diethylstilbestrol, and dipropionate estradiol.

As a radioprotective drugs and drugs used in combinations with effective radioprotectants, are often used Metabolite products including nucleic acids, vitamins, coenzymes, carbohydrates, lipids, flavonoids, amino acids, intermediates exchange are often used in combination with effective radioprotectors.

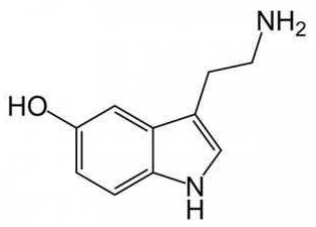
Intraperitoneal administration of 1.5 ml of boiled cow milk for 1-2 days to the total x-ray irradiation is known to have non-specific radioprotective effect. Other reports describe radioprotective effects resulted from parenteral administration of whole citrate blood, solcoseryl, benzene extract of human blood cells. Application of serum globulins with normal autoantibodies before the irradiation (or as a therapeutic measure after the irradiation) was proven to increase the survival of mice, guinea pigs, rats, rabbits, exposed to lethal γ-radiation in LD doses of 80-100 / 30 .

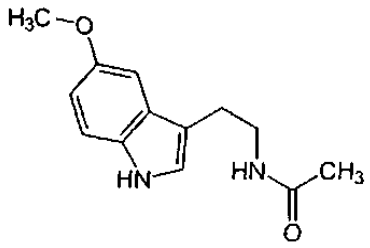
Radioprotective drugs of prolonged action also include natural adaptogens. Unlike radioprotectants, they produce a non-specific effect, enhancing the overall body resistance to various adverse factors. Adaptogens show radioprotective effectiveness when administered repeatedly over many days before the irradiation in doses lower than lethal. They are effective when used in cases of acute irradiation, but in cases of prolonged or fractionated irradiation they demonstrate

It is necessary to stress that there no adverse reactions caused by using radioprotective doses of adaptogens. The most effective drugs of this group are extracts of ginseng, Siberian Ginseng, Chinese lemongrass, Echinacea. The apparent decrease in the sensitivity of the laboratory animals was detected when dry extract of buckwheat was administered orally as well as by blockade of the reticuloendothelial system with coal particles, polystyrene, latex or glycogen.

However, the mechanisms of radioprotective effects provided by adaptogens are still unclear.

Таблиця 1. Деякі ефективні радіопротектори Ярмоленко С.П. (1969)

Препарат	Хімічна формула	Ефективні дози (внутрішньочеревинно, мг/кг)
β-Меркаптоетиламін (цистеамін, меркамін, MEA)	Меркаптоалкіламіни $SH-CH_2-CH_2-NH_2$	120—150
Дисульфід β-меркаптоетиламіну (цистамін)	$S-CH_2-CH_2-NH_2$ $S-CH_2-CH_2-NH_2$	150—180
β-Аміноетилізотіуроній (АЕТ)	-NH H2N-CH2-CH2-S- -NH2	200—250
2,3-Амінопропіл, аміноетилтіофосфат (гаммафос, WR 2721)	H2N-CH2-CH2-CH2-NH- -OH CH2-CH2-S-P =O -ONA	300—400
5-Окситриптамін (серотонін, 5-ОТ)	Індолілалкіламіни 	10—60

5-Метокситриптамін (мексамін, 5-МОТ)		10—60

*Досліди проводили на лабораторних мишах і щурах

It is worthy to say that a balanced diet has been proven to provide beneficial effects upon radioresistance of laboratory animals that offers the prospects of effective long-term protection of the body from the lethal effects of ionizing radiation.

5. BASIC METHODS OF EVALUATING THE EFFECTIVENESS OF RADIOPROTECTANT

More than 20 years the radiobiologists have been operating with the term "perfect radioprotectant", but its content has being constantly updated and enriched. It is believed that the main criteria for the applicability of radioprotectants should correspond to the purposes intended, taking into account how they can be used:

1. as means of personal chemical protection from the outside exposure to ionizing radiation at relatively intermittent irradiation doses with a large capacity (e.g. nuclear explosions, solar flares);
2. for protection from radiation during long-term low-dose exposure (e.g., passing through the radioactive clouds, in long term space flights);
3. as agents that increase the body resistance to radiation during the courses of X-ray therapy and radiotherapy.

There are different ways to evaluate the radioprotective capacity of radioprotective pharmaceuticals. Herewith, such criteria as radiation impact on life expectancy and survival rate can be applied.

The survival rate of the animals is the easiest way to determine protective capacity of the drug. Usually, the protective capacity is assessed by the difference between survival of a test group and control group within a months following the irradiation (calculates in percents) or by calculating ratio of these parameters (index of effect). The most precise results are typically observed in doses equal to or higher than the value of the LD 100 In cases, when the radiation dose is lower and not all animals of the control group die, radioprotective agent is characterized by 100% efficiency, the difference between test and control group decreases and hence data on protective capacity of the protective agent will be deflated.

Integral radioprotective efficiency index of radioprotectants is the value of so-called factor of reduction of absorbed dose - FRD, or factor of changing the dose – FCD, that show in how many times the value of equally effective doses of

radiation increases (changes) when radioprotectants are used. Half-lethal doses of radiation are usually taken as equally effective doses (denoted by LD 50), i.e. the dose causing death in 50% of irradiated animals, and therefore FRD is calculated by the formula:

FRD = LD50 (with radioprotectant) / LD50 (without radioprotectant).

FRD of the most effective radioprotectants reach the values of 1, 8 – 2, 0. This threshold can not be overcome by increasing the doses of drugs administered due to their high toxicity. Toxicity of radioprotectants is the main factor limiting their widespread practical usage. Some increase in the FRD values is obtained by combining two or more radioprotectants with different protective mechanisms. Half-lethal dose (LD 50/30) in this case is 4 Gy, i.e. the death of 50% irradiated animals (for 30 days after the irradiation) occurs at the radiation exposure in a dose of 4 Gy. The graph 2 shows the survival of irradiated animals, which received IEA 15 minutes before the irradiation. Half-lethal dose for this group made up 6 Gy, i.e., prophylactic administration of the drug had a marked radioprotective effect (FRD = 6/4 = 1.5).

The graph 3 relates to the animals, which received the IEA immediately after the irradiation.

The value of half-lethal dose here as well as in the control group made up 4 Gy, i.e. in the case of IEA administration after the irradiation it had no effects on the animals survival rate (FRD = 4/4 = 1). Ineffectiveness of the drug administration after the irradiation (as a therapeutic agent) is typical for the great majority of radioprotectants.

One of the quality indicators of radioprotectant effectiveness is a protection index (I). The advantage of this method of the evaluation of the radioprotective activity consists in calculation of therapeutic spectrum of their actions along with the degree of protection. The protection index is expressed by the following formula:

I = LD 50 / ED (1 + a / 100)

where LD 50 - dose of a substance that causes the death of 50% of the animals, the ED - dose of a substance providing protection effect, a - the percent of animals survived after the exposure to an effective dose, with 100% death of animals, irradiated without prevention with radioprotectants.

The current scale of the efficiency of radioprotectants allows us to evaluate their effectiveness differentially.

Scale of efficiency of radioprotectants

Table 1

0-1	2-5	6-10	11-14	>15
ineffective	low effect	moderately effective	effective	high effect

To calculate the toxic effect of radioprotectants the coefficient reflecting the probability of protecting the body against radiation death is applied:

ß = ß(Do, Da) = ALL(Do, Da) - (ALL)(Do.O) / (ALL)(0;0) - (ALL)(Do.O)

Where ALL (0.0) - the average life span of the animals in biological control;

ALL (D_0, 0) - the life span of animals exposed to irradiation in a dose D 0 (control);

ALL (D_0 , D_a) - the life span of animals exposed to irradiation in a dose D 0 when administering radioprotectants "a" in the dose D.

This index is used for determining the part (share) of subjects exposed to LD irradiation but can be protected from the death. In cases, when the studied objects are not living organisms, for example, cell cultures, while performing cytogenetic analysis the coefficient of protection A is used that reflects the probability of protection and is expresses by the ratio between difference between the indices of radiation damages without protection (a) and with protection (b) to the value of damages without protection

A = a - d / a

$$A = \frac{a - d}{a}$$

6. MECHANISM OF RADIOPROTECTOR ACTION

The first hypothesis, which could explain the radioprotective effect, was suggested by radiobiologists Z. M. Buck and P. Alexander (1955). According to their supposition, radioprotantants realize their protective functions by intercepting, neutralizing and inactivating free radicals, especially water radicals, which arise as a result of the interaction of radiation with substance and launch the chain of consecutive physical and chemical, biochemical and pathophysiological changes that eventually lead to the radioactive damage to the body. Oxidation of thiol radioprotectants neutralizes the active radicals and in this way mitigating radiation damage.

Such mechanism of the radioprotective seems to be quite possible, but it could not explain the entire scope of protection and the action of all radioprotective substances. But at the same time some serious objections were raised concerning this theory: the content of the protectors accumulated in the tissues is usually much lower than that required for launching this mechanism of radiation protection.

The development of the physical and chemical conceptions of the mechanisms of radioprotective protection is associated with the hypothesis of Norwegian researchers Eldyarn and Peel proved that thiol radioprotectors administered coild form mixed disulfides with thiol groups of proteins. Thus, thiol groups of proteins were protected from the destruction caused by radicals.

The hypothesis of Norwegian scientists did not disclose the mechanism for the protection of the genetic apparatus of the cell. The evidence of the protection did not always correspond to the number of generated mixed disulfides. Ant this hypothesis, therefore, was not able to explain all the facts.

A significant step forward in the understanding of the physical and chemical mechanisms of radioprotection was made by the Soviet radiobiologist N. A. Izmozherov (1984), who put forward the donor-acceptor hypothesis. The main physical effect resulting from the interaction of radiation with the matter is known as ionization, i.e. electron ejection that eventually leads to the inactivation of bio-

logical macromolecules. Obviously, the compensation of the lost electron by molecule can be considered as an elementary act of its recovery. He assumed the radioprotectors possessed such characteristics of the electronic structure that easily donate electrons, acting as their donor. Filling in the electronic gaps in the process of the donor-acceptor interaction, radioprotectans at the same tine mitigated radiation damage. Substances acting as electron acceptors, according to this point of view should enhance damaging effect by acting as a radio-sensitizer.

Thus, the donor-acceptor mechanism of protection consists in blocking the transition of the substance into the ionized state or transition of an ion into the radical. The intensity of donor activity of the compounds was measured by the ionization potential calculated by using the molecular orbital method. It has been proved that the majority of the protectors have electron-donating properties. On the other hand, new are being successfully carried out to find perfect protectors among the active donors. According to our data, phenolic compounds show high donor activity properties, while the products of their oxidation, quinones, are potent electron acceptors and radiosensitizers.

This hypothesis complements the others, and does not deny the existence of other mechanisms at higher levels of the organization.

According to the conceptions of the Soviet radiobiologist L.Ch. Èidus (1985), during irradiation in the target inside the cell two types of potentially lethal damages are triggered dependant and non-dependent on the presence of oxygen. Both can be reduced, but for the reparations of oxygen-dependent damage, radioprotectors, and particularly thiols are needed. The value of this hypothesis consists in concurrence of the action of protectors with the enzymatic reparation systems.

This author put forward a hypothesis of adsorption protection consisted in preserving the spatial structure of the irradiated macromolecule with adsorbed radioprotective molecules located over its surface. Developing this idea, Soviet researchers D. Spitkovsky and V. Andrianov suggested that the adsorbed molecules

of protectants also replaced a function of the radiation-damaged site of macromolecules ("structural" protection).

A number of hypotheses associate the protection mechanisms with a role of oxygen in radiation damage. The presence of oxygen approximately as much as three times increases the radiation damage of the cells of the body modeled systems, tissues, organs. Eliminating the oxygen effect or at least its mitigating can provide marked protection. This result can be achieved simply by reducing the amount of oxygen in the inspired air (hypoxic hypoxia). All protectors of indolealkylamines class, biogenic amines (adrenaline, histamine), and morphine, carbon monoxide, sodium nitrite, unitiol, para-amino propiofenon during its protective action significantly reduce the oxygen concentration in the radiosensitive organs (bone marrow, spleen) that apparently mitigate radiation damage.

But different groups of protectants achieve this result in different ways. Indolealkylamines cause vasoconstriction of the radiosensitive organs, thereby reducing oxygen amount at the time of irradiation (vascular hypoxia). Sodium nitrite converts a significant portion of blood hemoglobin into methemoglobin and limits the oxygen saturation of the blood. The same effect is achieved with the formation of carboxyhemoglobin by carbon monoxide (blood hypoxia). Opiates depress the respiratory center, and cyanide inhibits oxidative enzymes of the tissue (histotoxical hypoxia).

It is well known that by pressurized oxygen it is possible to enhance radiation damage and eliminate the protective effect of many radiation protectors. However, it is important, that the pressurized oxygen does not neutolize completely the protective action of serotonin, histamine and adrenalin, although the level of oxygen in the tissues thus even higher than normal. Apparently, the radioprotective effect of these compounds can not be reduced entirely to the hypoxic mechanism.

Numerous hypotheses are based on the physicochemical concepts about the mechanism of radio protection. However, a complex hierarchy, multi-level organization of the human body can not but influence on the nature and severity of radiation damage, and the ability to resist or tolerate it or to protect against it. That is

why the modern theory of radioprotective effect, one way or another, take into account the state of the cells, tissues, and a whole organism, the intensity of metabolic processes and their role in the stability against any harmful effects, including radiation.

As far back as 1964, Z. Buck and P. Alexander brought forward an idea of the cellular "biochemical shock", as a condition of increased radiation stability resulted from the action of radioprotectants. According to this hypothesis, thiol radioprotectors administered into the body bound to tissue proteins to form mixed disulfides. But it just only triggered the chain of transformations providing the protective effect. Due to the formation of mixed disulfides, a glutathione content and content of thiol compounds in cells increased. In this period cells responded to irradiation in other way than in normal conditions - they were in a state of "biochemical shock." What is the essence of this state? Metabolism in the cell is suppressed, membrane permeability increases. There is swelling of mitochondria, increasing the ascorbic acid content and other reduced compounds in the cell.

Based on these ideas, L.Ch. Èidus drew the conclusion that was underpinned with extensive factual material: the state of "biochemical shock" is typical not only for the administered thiol protectors; this is a common nonspecific response to any cell damage. This determines the membrane transport of substances, increase in the content of low molecular weight organic materials in the most vulnerable cell organelles. Their adsorption on macromolecules stabilizes the conformation of proteins and nucleic acids, restricts their functioning. Being in this state, the cells are more radio resistant.

The theories analyzed do not specify the details of the radiation protection mechanism, and do not clarify the nature of protectors. Their weak points are completed with other hypotheses.

E.F. Romantcev (1987) considers that the inhibition of synthesis of the DNA, RNA and proteins, the impairment of tissue respiration and separation of oxidative phosphorylation, delayed cell division are important in the mechanism of biochemical shock. Against this background, the enzymatic repair systems demon-

strate more intensity and more time for activities that contributes into cell survival after the radiation exposure.

S.E. Bresler and L. A. Noskin (1986) also believe that an important, even crucial role in the protection mechanism is played by an increase in the efficiency of intracellular repair systems as a result of the fact that the protectors link the DNA strands, prevent the formation of double-strand breaks and promote their recovery.

In the works of Soviet radiobiologist E. Y. Grajewski (1987) much attention was paid to ideas about the mechanism of "biochemical shock". According to his conception, based on a considerable experimental material, most radioprotectors cause in the cells the same response - increase in the content of its own (endogenous) thiol compounds. Moreover, their maximum content in the cell and maximum radioresistance coincide. Apparently, the level of endogenous thiol compounds to a large extent determines the natural radio sensitivity of the organisms. The composition of the natural endogenous thiols undoubtedly includes glutathione. However, the nature of most of these compounds is still unclear.

The most comprehensive general conception of the protective mechanisms of radioprotective effect is the hypothesis of endogenous radioresistance background, developed by Soviet radiobiologists E. N. Goncharenko and Y. B. Kudryashov (1985). The authors proceed from the well-established facts. On one hand, under the influence of radiation, a number of highly active free radical oxidation products as phenol (quinoid) and lipid radiotoxins are formed in the cells. Being administered into normal animals, these radiotoxins reproduce a number of important symptoms of radiation damage, simulating the clinical course of acute radiation sickness. Their administration into the irradiated animals increases the severity of radiation damages. Finally, the original amount of these substances in healthy animal tissues largely determines their natural radio sensitivity.

On the other hand, there are always a number of biologically active substances possessing radioprotective properties. They include glutathione, and other thiol compounds, biogenic amines (epinephrine, norepinephrine, histamine, dopa-

mine, tyramine, acetylcholine, serotonin), and others. The internal radioprotective resources of the organism also include such substances as antioxidants that slow down and stop the reaction of free radical oxidation and, conesquently, reduce the formation of endogenous radiosensitizers, radio toxins.

The mechanism of radioprotective action is associated with their participation in the suppression of inflammation, primary radiation-chemical reactions (in the interception of free radicals, in reducing the chain reactions of oxidation, in regenerative processes).

7. SULFUR-CONTAINING RADIOPROTECTORS

The most important from the point of view of practical application sulfur-containing radioprotectors are cysteamine, cystamine, aminoethylizothyuronium, gammophos, then cystaphos, cytryphos, adeturon and mercaptopropionylglycine (MPG).

Cysteamine

This is aminoethyol, p-mercaptoethylamin (MEA). Its formula in as follows:

$HS\text{-}CH_2\text{-}CH_2\text{-}NH_2$

Cysteamine is strong alkali. Its relative molecular weight is 77. It form salts with organic and inorganic acids. Melting temperature is 96 °C, pH of water solution is 8, 4. All MEA salts are hygroscopic, except salicylate, barbiturate, phosphate. Hydrochlorides and oxalates are most often used among them. Cysteamine hydrochloride is a white crystalline substance with unpleasant smell of mercaptane, water-soluble; melting temperature is 70-72 °C, pH of water solution is 3, 5-4, 0. MEA succinate melting temperature is 146-148°C, pH of water solution is 7, 3.

Aminoalkylthyols are strong reductants; they can be easily oxidized by the air oxygen and weak oxidants like Fe (III) forming disulfides. The rate of oxidation of aminoalkylthyols in air and in aqueous solutions depends on pH of medium, temperature and the presence of Cu and Fe ions. With the increase of pH, temperature and the quantity of ions in the medium, the oxidation rate increases as well. Strong oxidants can oxidize thyols and form derivative sulfinic or sulfonic acids.

The radioprotective effect of cysteamine was discovered by Bacq and co-authors in 1951, at the Institute of Pharmacology, Lutheran University in Belgium.

Cysteamine is the chemical compound with the formula:

$S\text{-}CH_2\text{-}CH_2\text{-}NH_2$

$S\text{-}CH_2\text{-}CH_2\text{-}NH_2$

Cystamine is white crystalline substance, poorly soluble in water, but well soluble in alcohol, benzene and other organic solvents; it is relative molecular weight is 152. It has properties of alkalis, forms salts reacting with the acids, of which cystamine dihydrochloride is the most commonly used. It is also a white crystalline, hygroscopic, water-soluble, but sparingly soluble in alcohol substance. Water solutions of cystamine dihydrochloride is pH 5, 5.

MEA and cystamine was synthesized by Gabriel in 1889. The radioprotective effect of cystamine was first described by Bacq and co-authors in 1951.

Aminoethylizothyuronium

This is a derivative of thiourea, S-2-aminoethylizothiourea, which is commonly used in the form of hydrobromide bromide. This formula is:

$H_2N\text{-}CH_2\text{-}CH_2\text{-}S\text{-}C\text{-}NH_2$

I I

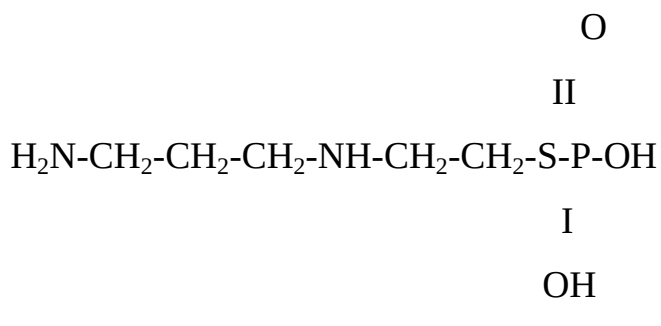
NH

Its relative molecular weight is 119. AET bromous salt is a white crystalline hygroscopic substance, bitter in taste, unstable under the light, water-soluble, but unsoluble in alcohol. Water solutions have an acid reaction. AET turns into 2-mercaptoethylhuanidine (MEH) in neutral solution, unstable *in vitro* and easily oxidized into disulfide.

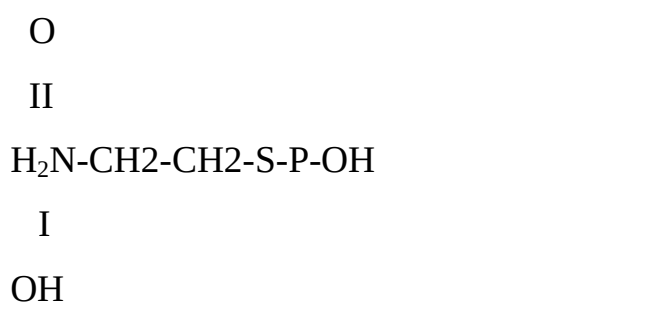
The information about radioprotective effect of AET was first published by the US radiobiologists Doherty R.I. and Burnett K. in 1955. 80% of lethally irradiated mice survived after administration of AET in a dose of 250-450 mg/kg. Shapira I. and co-authors described the AET synthesis in 1957. Irrespective to this data, the soviet scientist V. D. Lyachenko synthesized AET in 1954. According to his report Semenov B.K. (1955), 18% of lethally irradiated mice survived after the administration of AET in a dose of 150 mg/kg that was less than by using cystamines. Therefore, this radioprotector was not given much attention.

Gammophos

It is the aminoalkyl-derivative of thiophosphoric acid, 8-2-(3-aminopropylamine) ethyl ether of thiophosphoric acid. Its formula is as follows:



It is white water-soluble crystalline substance of garlic smell. Its melting temperature ranging from 145 to 147°C was determined by Sverdlov O.K. and co-authors (1947). Gammophos synthesis was first described by Pipper D. and co-authors in 1969. At the same year Yuhas K. and Storer H. described its radioprotective effect on mice. Special attention was paid to the protective effect of cystaphos (WR-638) S-2-aminoethylphosphoric acid.



This substance was first synthesized by Akerfeldt M.M. in 1959. At the same time its radioprotective effect was described. It was found out to be quite effective under neutron irradiation of mice. Some worth mentioning low-toxic substances were synthesized by Panteev and co-authors in 1973. By mixing cysteamine and adenosine triphosphate (ATP), a new radioprotector, cytryphos, was developed, and by mixing AET and ATP molecules, adeturon was obtained.

2- Mercaptopropionylglycine (Mill’), which is effective in the case of prolonged low-dose exposure arose considerable interest among radiobiologists. It is non-toxic radioprotective substance. MPG protective dose in mice is 20 mg/kg for intra-abdominal injection. The median lethal dose is 2100 mg/kg. Many modern

scientists consider this substance alongside gammophos to be the most prospective sulfur-containing radioprotector for clinical use.

8. AMINES

The main representatives of this group of radioprotectants are serotonin and mexamine. *Both substances* are derivatives of tryptamine. Indolylalkylamines are formed from the tryptophan amino acid; one out of every 60 molecules of tryptophan is used for the synthesis of vitamin PP (its derivatives NAD and NADP); at that it should be noted that tryptophan is an essential amino acid. Serotonin is a neurotransmitter in the brain, increases the production of liberines of the hypothalamus, and serves an inflammation mediator. Mexamine is hypoxanthom. Serotonin and mexamine are precursors of melatonin, a hormone of the pineal gland and the diffuse neuroendocrine system. Radiation (II), round-the-clock lighting (individuals with inborn blindness do not develop cancerous diseases); radio waves and electromagnetic fields suppress melatonin production. Melatonin is known as a neurotransmitter (in the hippocampus, produces somnogenic effect), a hormone (blocks the synthesis and secretion of pituitary gonadotropins), a immunomediator (activates the immune system, the decrease in melatonin secretion causes involution of the thymus), an anti-carcinogenic agent (inhibits cell proliferation), an antioxidant, which has receptors on all cells (membrane and nuclear) that generally slows down aging and improves body adaptation. As antioxidant, melatonin is endogenous, mainly released at night, amphiphilic (and water- and fat-soluble), more active than tocopherol and glutathione, but unlike other low molecular weight antioxidants, its excess does not cause prooxidant effect. Melatonin gives hydrogen from imino, activates synthesis of SOD, catalase, glutathione peroxidase, glucose-6-phosphate dehydrogenase at the gene level.

Serotonin has amphoteric properties. Under physiological conditions, it behaves like a base and only at pH> 10 demonstrates its acid properties. Unbound serotonin is readily soluble in water, while is sparingly soluble in organic solvents. It easily becomes crystallized into white crystalline salt in the form of creatinine, which relative molecular weight of 405.37. Due to the considerable instability there is constant necessity to prepare fresh serotonin solutions to protect them from

light and heat impacts. Radioprotective effect of serotonin was described as far back as in 1952 by two laboratory researchers independently from each other (Vasq, Herve; Gray et al)

Mexamine

Its chemical formula is very similar to the formula of serotonin. Mexamine is 5-methoxytryptamine (5-MOT).

Mexamine readily forms salts. Hydrochloride 5 – methoxytryptamine is a form the most commonly used. It is white crystalline substance, readily soluble in water; its melting temperature is 240-243 ° C and a relative molecular weight is 226.72. Radioprotective effect of mexamine was first described by Krasnykh et al. (1962). The main reason for the separation of short-term chemical radioprotectants into two groups is the difference in the chemical structure of substances; another important factor is the conception of the different mechanisms of their action. Schematically, one can imagine that the radioprotective effect of sulfur-containing substances realizes depending on the concentration obtained in the cells of radio-sensitive tissues, whereas derivatives of indolylalkylamines increase radio re-sistance of tissues and the entire human body mainly due to the development of hypoxia caused by the pharmacological vasoconstriction effect of serotonin and mexamine. The idea of the different mechanisms of radioprotective effect of two types of protectors confirmed the protective effect of different combinations of radioprotectors. They might be administered simultaneously with single solution (so-called cocktail) or in portions of the same or different methods. Thus, the third largest group resulted from the combination of radiation protectors and designed for single short-term protection against radiation.

The combination of radioprotective substances

Usually researchers study and test radioprotective effect of two-component combinations, however, multi-component formulations are not completely exclud-ed. All combinations are tested in order to reduce to acceptable dose of acting

agents to minimum to lower their adverse effects and to achieve maximum protective effect. Most often a combination of protectants is introduced with the solution and by using a particular rout of administration. However, a number of reports describe the combination of different routs of parenteral administration or oral and parenteral administration of different radioprotectants. In this case all components should not be administered simultaneously, but only at certain intervals.

Combination of sulfur-containing and derivatives of indolylalkylamines.

Two-component formulation of protectants with different mechanisms of action is logically well-grounded. In the late '50s a number of combinations with sulfur-containing and indolylalkylamines protectors were tested. One of the first those combinations consisted of cysteine and tryptamine was tested by Romantsev and Savich in 1958. If by using the separate protecants before the lethal radiation exposure only 20-30% of rats survived, the combined use of these protectors increased survival of animals up to 70 %.

This study gave rise the analysis of a number of two-component protectors combining two major groups of chemical radioprotective substances.

For most dosage formulations doses of individual components were selected empirically for several years. Then pharmacological method was introduced. Initially, by using the method of determining isoboles the qualitative ratio between toxicity and protective effect of the combined radiation protectors was determined. Thus, in this way we can evaluate whether the combinations produce synergic protective action, or it is only of additional or potential character, whether the toxicity of protectors increases or decreases by their join or separate application.

Co-administration of various sulfur-containing radioprotectants

The first combination of cysteine and cysteamine was offered by Straube H.H. and Patt N.Y. in 1953. The administration of half doses from optimal doses of these protectants demonstrated summation of the protective effects.

However, many scientists did not observe pronounced protective effects following intraperitoneal administration of combinations of AET with cysteamine or cystamine to mice. Oral co-administration of cystamine and AET confirmed only additive protective effect of the individual components. Combinations of AET with AET gammafos and tsistafos enable to reduce the effective dose even in 4 times compared to the equally effective protective doses of the protectants received.

Since the separate application of effective doses of sulfur-containing radioprotective can cause adverse pharmacological effects, one of the main tasks of radiobiology within the scope of issues discussed is to investigate these combinations in order to minimize adverse manifestations. It seems to be quite difficult task because side effects produced by sulfur-containing radioprotectants and non-specific and include nausea, vomiting, decreased blood pressure, bradycardia, and others.

Multi-component combinations of radiation protectors

In the late 60-ies the protective effects of multi-component combinations of radiation protectors were tested in the experiment on mice by Maisin Y.R. and Mattelin R. (1967), MaisinY.R. and Lambiet B.E. (1967), MaisinY.R. et al (1968). They administered AET, glutathione, serotonin and cysteine intraperitoneally either combined or in various 3-component combination, sometimes in combination with post-irradiation bone marrow transplantation.

Earlier, in 1962, Wang A.M. and Kereiakes T.L. published a report on the protective effect of a single co-administration of AET, cysteamine and serotonin to supralethally irradiated mice. Intraperitoneal administration of the combination of AET, IEA and 5-HT was observed to be highly effective even in total irradiation of rats.

Significant effect was obtained by using 3-component combination of mexamine, AET and tsistafos that was described in details by Pugacheva O.P. et al (1973). If in this formulation tsistafos was replaced by cystamine, it became even more effective.

According to Schmidt B.L. (1965), American astronauts were prescribed a combination of radiation protectors made up of seven components: reserpine, serotonin, AET, cysteamine, glutathione, paraaminopropiofenona and chlorpromazine.

Oral co-administration of three sulfur radioprotectors (gammafos, tsistafos and AET) is considered to be more beneficial mainly because their total effectiveness is approximately equal to the effectiveness of a dose of individual components, and compared with them is less toxic and thus safer.

9. ANTIBIOTICS

A particular group within metabolic modifiers is made up with antibiotics, among which there are antioxidants (penicillin) and pro-oxidants (antitumor antibiotics: bleomycin, adriamycin). They were studied as potential protectors against the genetic effects induced by radiation in animals. Two antibiotics were studied in details: actinomycin D and penicillin. Actinomycin D administered with growth medium, was by 40% more effective in reducing the incidence of the recessive lethal mutations in the X chromosome of Drosophila after X-ray irradiation in a dose of 3000 R. Penicillin also reduced the incidence of radiation-induced recessive lethal mutations in all stages of germ cell development. These results were interesting, especially because penicillin does not have high toxicity like sulfur-containing radioprotectors (but some researches have shown that penicillin by itself slightly increases the frequency of spontaneous mutations).

Some scientists investigated such antibiotics as actinomycin D, and chloramphenicol. It turned out that both antibiotics reduced the frequency of mutations induced by irradiation at the stage of late spermatids and spermatocytes, but their number increased in the mature sperm.

Similar results in testing an actinomycin D Redd P.P. (1985) were obtained in another work that showed the drug was able to reduce the frequency of sex-linked recessive lethal mutations in Drosophila caused by φ-rays in a dose of 600 R at the stage of spermatids and spermatocytes.

However, the first positive results were followed by a series of works about the radioprotective effect of antibiotics, demonstrating the same contradictory situation as when studying of genetic protection with SH-containing protectors. Thus, when investigating actinomycin D it was detected not a protective but a reinforcing effect of this compound. In 1965 Olivieri M. published an article describing sensitizing effect in Drosophila spermatocytes produced by the effect of actinomycin D (used B-radiation). The study of this compound on the frequency of radiation-induced losses and the non-disjunction of X-chromosomes in Drosophila showed

the actinomycin D enhanced the induction of both types of mutations in all stages of spermatogenesis, moreover not only in radiation-exposed, but also in non-irradiated animals. Herewith the frequency of X-chromosome doubled under the effect of actinomycin D as compared to the control group.

After the administration of actinomycin D, DLM frequency in male mature spermatozoa was increased 4 times as compared to the control group. This high sensitizing effect was statistically reliable in all the experiments.

As for penicillin, further researches have demonstrated that it reduces the frequency of radiation-mutations not at all the stages, but only at certain stages of spermatogenesis. One of the reports showed that penicillin protected only spermatids, while other work stressed on the radioprotective effect of this drug in the Drosophila sperm cells. Both Fry R.I. in Storer I.B. (1986) studied the rate of lethal recessive mutations in the ring X-chromosome. The only difference in methods of researching was the way of introducing substances into the body: in one case the substance was injection, in the other case it was fed with the growth medium. This made it possible to suggest that the difference between the conclusions drawn was due to the fact that the effect of penicillin was determined not by the direct protection against radiation, but by the secondary effect on the metabolic activity of developing germ cells. That is why, for the manifestation of a protective effect in mature spermatozoa, penicillin should be administered far long before the irradiation, that' happens when breeding flies on the growth medium containing the drug.

In addition to penicillin another antibiotics were studied - chloramphenicol and streptomycin. All these three drugs are equally (by 30-50%) reduced the rate of radiation-induced mutation on spermatid stage. However, according to some reports, streptomycin is not able to protect the Drosophila germ cells from the risk of radiomutations. In these works, the injections of the drugs in similar concentrations were given to male Drosophilae before the irradiation with the same dose of 1000 R and the same index was tested - the frequency of sex-linked recessive lethal mutations in all stages of spermatogenesis in Drosophila. Moreover, in one of the

works streptomycin were fed with growth medium, but this method did not reveal the ability of the drug to reduce the frequency of mutations induced by irradiation.

The impact of antibiotics on the genetic effects of irradiation in mammals was first studied in the work of Schao Wang Wei, Du Gul, and Chtom Han. Streptomycin taken in low concentrations (0.5-1 mg / mouse) induced decrease in chromosomal aberrations in the germ cells in an average by 50% and higher (3.5 mg / mouse), was ineffective in protecting against radiomutations, and increased frequency of spontaneous mutations.

Chloramphenicol and mitomycin C were studied on mice. The studies found out that chloramphenicol increased DLM output in sperm cells by more than 50% without affecting on the radio sensitivity of spermatids and without exerting mutagenic action. At the same time, mitomycin C produced mutagenic effect for all stages of spermatogenesis and showed an expressed synergistic effect in spermatocytes. Since mitomycin is an inhibitor of DNA biosynthesis, it has been suggested that a synergistic effect in spermatocytes is a consequence of interaction between ionizing radiation and mitomycin during DNA synthesis. It is also shown that intraperitoneal injection of mitomycin C increases the frequency of specific loci mutations in mice spermatogonia, induced by irradiation.

Mitomycin C was studied additionally on the Drosophila. The results showed that the antibiotic itself caused a high frequency of mutations in all stages of spermatogenesis. Applied before the irradiation, mitomycin showed an additive effect. However, in the later stages of early spermatids and spermatocytes the total amount of mutations decreased, while on the spermatogonia stage increases. Based on this, the Hahn F.F. (1983) concluded the reducing of radiomutations level under the influence of mitomycin C as well as actinomycin D, on a stage of spermatids and spermatocytes was a consequence of the inhibition of DNA replication. It is interesting, that the opposite effect obtained by studying mitomycin C (synergistic effect on the spermatocyte stage) was explained by the Dobson R.I. (1984) as the

ability of this antibiotic to inhibit the DNA biosynthesis. In this case the synergistic effect, according to the author, was a consequence of the interaction between ionizing radiation and mitomycin during DNA synthesis. Further studies of mitomycin C demonstrated that it was able to reduce the frequency of the partial visible mutations in twelve loci, but did not affect the total yield of this type of mutation. The results obtained in testing antibiotics as possible protectors against genetic effects induced by irradiation are difficult to compare, because most studies have used various techniques, and in particular, different genetic tests. But even in those rare cases when the experimental conditions were fairly uniform, the results were different.

10. BIOLOGICAL ROLE OF MELANIN PIGMENTS

Melanin is a polymer, derivative of oxidized tyrosine, found in most organisms in the aggregate with proteins. They are present in the tissues of plants, animals and many microorganisms. In a human body this pigment gives color to hair, eyebrows, eyelashes, iris, and skin. In the skin of animals and humans, presence and formation of melanin is a protective response of the organism to the action of ultraviolet radiation. The influence of ultraviolet radiation intensifies the formation of melanin from tyrosine and other monomers (that is known as a protective reaction of the organism to the exposure of sunlight). The appearance of black skin in humans due to the migration of the originally white race to the tropical regions resulted in, according to Lengraydzh R.M. (1986), the selection of many small mutations that eventually led to the formation of darker and darker skin that is of a great adaptive value in these areas. The formation of melanin in the body provides body resistance not only to ultraviolet, but to ionizing radiation as well.

Thus, in many species of microscopic fungi, actinomycetes, and some bacteria brown and black melanin pigments perform protective function against the hazardous electromagnetic radiation and is a major cause of high resistance of pigmented microorganisms not only to ultraviolet (including the short-wave), but also to X-rays.

Strains of microorganisms that contain melanin pigment are known to be exceptionally resistant to the action of solar ultraviolet radiation and cosmic rays and can live and breed in the high layers of the atmosphere, in the mountains, the deserts, the Arctic and Antarctic, in areas where other microorganisms die. Melanin in certain conditions even increases survival after absolutely lethal dose (LD100) of radiation. Growth of the natural radiation background caused by utilizing radioactive substances, improper storage and decontamination of radioactive wastes, etc, promotes preferential development of dark-pigmented fungi, some of them survive after exposure of the soil by dose of 6400 Gr. There is evidence of occur-

rence of the melanin-containing species of fungi in the soil samples, taken after the explosion of the atomic bomb near Bikini Atoll.

A number of works show an increase in radio resistance of black mice, as well as the appearance of hyper pigmentation in white and gray mice as a result of prolonged exposure to low doses of gamma-rays. The comparative study of survival rate between gamma irradiated white and black yeast strains revealed a difference due to the presence of the black pigment of melanin nature in the cells. Hamster melanoma transplanted cells containing melanin are twice more resistant to the lethal effects of radiation than the same cells lacking pigment. According Adams E.E. (1983) to some reports, exposure of the axolotls by doses of 500, 1500, 3000 R stimulated melanization process in the liver, head and eyes. The authors point out that this hyper pigmentation is a protective body response to radiation. Similar data obtained by irradiation of the frog pituitary gland by gamma rays: there was increased formation of melanin in the skin melanophores resulted from releasing the intermedin from the middle lobe of the pituitary and the changes in tyrosine metabolism. In the first hours after the irradiation the oxidation of tyrosine in the tissues of irradiated animals was observes.

Melanins of animal origin are able to interact with many radioactive elements: cesium, radium, cobalt, ruthenium, strontium, thorium, and radioactive isotopes of zinc, cadmium, lead, chromium, manganese and iron. It has been found out melanin effectively absorbs ions of various metals. In the same way, melanins of fungal origin adsorb ions of Pb, Th, Hg, La, Zn, Cz. Apparently, similar properties of animal melanin are mainly responsible for accumulation of ^{226}Ra in pigmented animal tissues, as well as in melanoma.

As noted by N. I. Vavilov, in the centres of plant development (centers of origin of the plants - by N. I. Vavilov) heavily pigmented forms dominate. Selecting light-colored plant forms by humans for promoting their cultures in the northern areas means, according to Shcherbakov B.M. (1983), that selection of forms are less protected against mutagenic factors compared to pigmented wild forms. Apparently, not accidental is the fact that plant tissues surrounding the generative

tissue contain colored pigments, which are likely to have to provide protection against mutagens. The presence of forms with a high content of pigment is typical for alpine areas with high levels of ultraviolet radiation and cosmic rays.

In some experiments, there were made attempts to use melanin to enhance biological radio resistance. In one of the experiments four fractions of melanin from fungus Pullularia prototropha were extracted; they differed by their solubility in alkali and ethanol. Two of them produced a protective effect onto mice, irradiated by X-rays, and the average lifespan of mice increased by 1.5 times. Introducing melanin into growth medium significantly increased the survival of the irradiated mice cultured connective tissue cells; the intraperitoneal administration of melanin to white mice before the radiation exposure in a dose of 800 R significantly increased their lifespan.

No data on the effect of melanin upon the mutagenic effects of radiation prior to the beginning of our research were available. However it has been found out phenols can bind with DNA, and especially with thymine. Radiation damage of DNA just starts with damaging thymine, and melanin is able not only to capture and neutralize free radicals, but also to regulate the concentration of unpaired electrons. Moreover, a number of phenols (Na-gallate, propylgallate, catechins and coumarins) show antimutagenic activity. One of the hypotheses explaining their antimutagenic ability assumes that phenols interact with the functional groups of DNA, which can shield the important parts of the DNA from the action of a mutagen or divert excess energy. This was a precondition for studying melanin ability to protect hereditary structure of the body from mutations induced by irradiation.

11. ANTIOXIDANTS

In 1954 - 1957 Emanuel M.M. and his disciples developed the doctrine about the role of chain reactions of self-oxidation in lipids, then applied it toward radiation damage and carcinogenesis, and successfully applied such food antioxidants as butyloxyanisole, butyloxytoluene (ionol), n-propyl ester of gallic acid, to inhibit pathological free radical reactions during irradiation. Later on, other scientists proved that such antioxidants of phenolic nature, such as nordihydroguaaretic acid, pyrogallol derivatives, galascorbin, can provide protection against radiation damage.

It has been shown that there is a direct correlation between the antiradical activity of the drug in model studies and its anti-radiation effect in the experiments with animals.

By the mechanism of their action, antioxidants are divided into:

- Antiradical inhibitors, and phenols are first among them;
- Antioxidants that destroy peroxides - sulfur-containing substances;
- Substances that bind catalysts of free radical processes - ions of metals of variable valence;
- Substances that quench, i.e. those inactivate singlet oxygen - tocopherols, carotenoids.

11.1. Ascorbic acid

Ascorbic acid (vitamin C) is a dienol, a hydrogen donor that, during oxidation into dehydroascorbic acid, passes through the stage of the monodehydroascorbinate radical; decomposes into oxalic acid, therefore when taken in heavy doses, renal tubules are clogged with calcium oxalate. Vitamin C participates in hydroxylation during the synthesis of steroids (cholesterol and hormones), serotonin, catecholamines, collagen maturation, and oxidation of Fe + 2, and folate reduction. It is a powerful water-soluble AO that inactivates free radicals and non-enzymatically reduces tocopheryl quinone into tocopherol, and itself is

regenerated by glutathione. When in excess, it produces prooxidant effect.

Favorable action of ascorbic acid on animals of different species (guinea pigs, rabbits, hamsters) in acute and sub-acute forms of radiation sickness caused by X-ray irradiation, administration of radioactive isotopes of phosphorus and polonium consists in increasing lifespan and survival rate. Improvement of peripheral blood parameters and acceleration of hematopoietic reparation, less pronounced changes in permeability and strength of vascular walls, carbohydrate metabolism and liver glycogen functioning (Prane L.Y., Belousov O.I.)

Additional, and in particular, preventive administration of ascorbic acid to rats increases its content in the retina and reduces the destruction of rhodopsin and photoreceptor-cell nuclei induced by radiation Yarmolenko S.P. (1969). The radioprotective effect of ascorbic acid was demonstrated in the experiments, in which adding of the ascorbic acid to aqueous glucose solutions protected the last from its destruction, which might result from the irradiation. The same authors showed that ascorbic acid protects cells from radiation damage enhanced by antibiotics. However, the attempt of therapeutic and protective application of ascorbic acid as the only agent for treating severe radiation damage in dogs was unsuccessful.

Many authors (Maksimovich Y.B., Petrov R.V., Rogozin V.D.) report about positive results of using ascorbic acid in the treatment of radiation damages in people exposed to radiation therapy. The therapeutic use of ascorbic acid in X-ray therapy improved the overall condition of patients, their peripheral blood parameters, produced favourable effect upon some aspects of carbohydrate metabolism, reduced the level of lactic acid in the blood and increased the accumulation of glycogen in the liver, promoted the normalization of the functioning of the reticuloendothelial and epithelial cells in the liver, as well as urobilin and stercobilin excretion.

K.A. Skulme (1987), observing 202 cancer patients undergoing radiotherapy, showed that the regular administration of 200-300 mg of ascorbic acid per day contributed to mitigating the radiation syndrome by reducing hematopoietic disor-

ders, increasing capillary permeability, and enhancing the antitoxic functioning of the liver. A moderate dose of 100 mg per day is effective. Nevertheless, to achieve the optimal effect, the author recommends increasing the doses.

This opinion is shared by many other authors, especially emphasizing the fact that only high doses of ascorbic acid help to remove cations of strontium, cadmium, chromium and mercury from the body. There are reports of the beneficial effect of high doses of ascorbic acid, administered before and after irradiation of rats, with daily irradiation (10R per day up, a total dose of 600 R) of guinea pigs, as well as a single administration of a high dose of this vitamin to mice soon after irradiation. Interest to the use of high doses of ascorbic acid may be partly due to the available reports of their stimulating effect on the immune system. Along with this, Perepelkin S.R. presents data on the effectiveness of the vitamin used in doses according to daily requirements, and in minimum therapeutic doses. Nevertheless, the overwhelming majority of researchers point out the appropriateness of using elevated doses of ascorbic acid for mitigating radiation sickness. At the same time, there are several reports about adverse effects on the course of acute radiation sickness produced by heavy doses of ascorbic acid (40-100 mg/kg) administered immediately before or during the first hours after irradiation of mice, rats and rabbits.

11.2. Bioflavonoids (polyphenols, vitamin P)

Bioflavonoids are a class of water-soluble plant pigments with antioxidant, anti-inflammatory, antiallergenic, antiviral, and anti-carcinogenic properties. This is the collective name given to rutin, hesperidin and quercetin and a range of other naturally occurring compounds including the oligomeric pro-cyanidins found in red wine. Strictly speaking, bioflavonoids are not true vitamins, though they are sometimes referred to as vitamin P.

Bioflavonoids are proven to be one of the first nutrients, the antiradiation properties of which were introduced into medical practice. In 1944 rutin was successfully used to reduce hemorrhagic syndrome in patients with radiation therapy.

Bioflavonoids as antiradiation agents used for protective and therapeutic purposes in different animal species, including dogs, demonstrate clear positive effects: an increase in lifespan and survival rate, mitigation of hemorrhagic syndrome, increase in resistance of the vascular walls. Synthetic polyphenols as futorusid and venaurin are used to prevent and treat radiation damage to the skin, by stimulating the healing of irradiated areas and reducing edemas.

According to some reports, the effect of P-vitamin preparations is manifested mainly by their preventive use, whereas the therapeutic effectiveness of these drugs is low.

There are few works reporting the lack of a positive effect of bioflavonoids in radiation sickness. The isolated use of citrine for severe radiation sickness in dogs was unsuccessful. As in other cases, this discrepancy between the results is obvious. It can be determined by the differences in experimental conditions, doses of preparations and radiation, the supply of animals with vitamins, and especially ascorbic acid, as well as other factors affecting the survival rate of irradiated animals.

The favorable effect of bioflavonoids in radiation pathology is determined mainly by the weakening of the severity of the hemorrhagic syndrome due to the protection of the vascular wall, primarily the capillaries. Some authors believe that this effect is associated with the effect of bioflavonoids on the hyaluronic acid-hyaluronidase and with the inhibition of the processes of depolymerization of the basic substance of connective tissue initiated by radiation.

The undoubted influence of flavonoids on intracellular membranes, which permeability and damage are significantly reduced during the irradiation has also been revealed. Flavonoids are considered to stabilize membranes of perivascular mast cells by preventing the release of vasoactive amines and interrupting one of the most important links in the pathogenesis of radiation vascular lesions. At the basic of radioprotective and membrane-strengthening action of bioflavonoids are their antioxidant properties, their ability to act as a "trap" for free radicals and inhibitors of the peroxide oxidation of membrane lipids. A certain role in the mecha-

nism of the positive effect of bioflavonoids is played by their ability to alleviate the disturbances in energy metabolism associated with the inhibition of oxidative phosphorylation in the irradiated organism.

Bioflavonoids are especially effective in combination with ascorbic acid, which potentiates their antihemorrhagic properties. Galaskorbin (complex preparation of gallic and ascorbic acids) promotes normalization of energy metabolism in irradiated animals, reduces the disturbance of water-electrolyte equilibrium, improves the functional state of the liver, hemopoiesis processes, increases skin tolerance to local radiation exposure and accelerates the healing of radiation dermatitis.

The data on the positive influence of bioflavonoids, ascorbic acid and galascorbine on radiation damage are convincing enough to ground their inclusion in the complex therapy of acute radiation sickness.

Due to the ability of bioflavonoids to form complexes with heavy metal ions, they can be used to reduce the absorption of heavy radioisotopes entering from food and to accelerate their removal from the body that deserves special attention.

Food and medicinal plants containing various polyphenols

(Trachtenberg I.M., 1986)

Classes of polyphenols	**Food**	**Medicinal plants**
Phenolic acids	Wheat, corn, rice, cabbage, tomato, white grapes, pears, cherries, apples, blueberries, walnuts, coffee, cider, tea, white wine.	Chinese tea bush, grapes cultural
Flavonols	Onions, cabbage, broccoli, tomatoes, radishes, olives, apples, cherries, grapefruit, tea, chicory, red wine.	
Flavones	Parsley, thyme, celery, olives, lettuce.	
Flavonones	Citrus	
Catechins	Apples, tea, red wine, cherry, black currant, strawberries, grapes, dark chocolate.	

Isoflavones	Soybeans, beans.	Japanese Sophora
Stilbenes	Red wine, grapes.	Grapes cultural
Lignans	Wheat, soy, beans, sesame oil, black pepper.	Echinopanax elatum, sesame, lemongrass, black pepper, Eleutherococcus.

11.3. Retinol (vitamin A)

Vitamin A (retinol) is formed by oxidative rupture of β-carotene, oxidizes into retinal (plays a role in vision by affecting the membrane channels of nerve endings; is deposited in the liver lipocytes) and then into retinoic acid (a hormone that activates at the gene level the synthesis of connective tissue proteins, division of epithelial cells, growth as a whole). Due to the system of double bonds, it inactivates singlet oxygen, takes on the attack of APK, competing with PUFA. Excess of retinol is toxic because of the formation of peroxides and epoxides of retinol.

Retinol successfully mitigates a lot of adverse effects caused by the radiation: it reduces leucopenia, thrombocytopenia, delays the involution of the thymus, accelerates the healing of ulcers within the gastrointestinal tract and radiation damage to the skin.

When treating radiation damage to the skin with 0.5-1% retinol ointment, a pronounced positive clinical effect was obtained. Enriching the ration of rats with vitamin (150,000 IU per 1 kg of feed) increased their survival rate, increased the life span of animals exposed to the lethal doses of irradiation (in the range of 175-850 R), and promoted healing of local radiation damages.

This effect can be explained by the occurrence of early inflammatory reactions, i.e. by increasing in the number of monocytes and macrophages in the wound surface, and, possibly, by changing in the collagenase activity. It is believed that retinol acts on the thymus, stimulating immune responses, and also on epithe-

lial cells, improving their differentiation. Retinol is proven to be effective in the preventive and therapeutic application in cancer patients undergoing radiation therapy. Good therapeutic efficacy is a significant advantage of retinol over other drugs (like sulfhydryl compounds), which demonstrate their most marked effects only when administered as preventive measures. A necessary condition for the effective treatment with retinol is, perhaps, the early start of its usage, immediately after the irradiation. The positive effect is observed, albeit to a lesser extent, in 2 to 3 days after the exposure and almost completely disappears in 6 days.

The mechanism of the retinol protective action has not been sufficiently studied yet. An important role belongs to its ability to prevent damage to the cell components produced by radiolysis products, which is due to the peculiarities of its chemical structure with a large number of conjugated double bonds.

It is shown that the double bond of the ß-ionic ring of the vitamin easily interacts with the products of the water radiolysis - the free hydroxyl OH radical and hydrogen peroxide H2O2, while being oxidized to epoxide derivatives. This reaction can be a part of the natural mechanism of detoxification of H2O2 and free radicals of hydroxylase. Radioprotective effects of retinol not only do not interfere with the antitumor effect of X-rays, but also significantly complement it. In this case, the resistance to the neoplastic process is enhanced by stimulation of high-dose vitamin immune responses against tumor antigens.

The ability of retinol to strengthen (at certain concentrations and conditions) immunological defense of the body is also an important point of its radioprotective action. A key role in its radioprotective action belongs to the activation of lymphocytes and monocytes in lymph caused by retinol.

Some authors believe that the mechanism of the radioprotective action of retinol can be associated with the intensification of the processes of cell differentiation as opposed to cell division. The effect of retinol on these processes can be realized at the level of ribonucleoside diphosphate reductase, an enzyme that catalyzes the conversion of ribonucleotides to deoxyribonucleotides, which play a key role in the regulation of DNA synthesis and cell proliferation. In excessive doses,

retinol reacts with the dithiol group of the active center of ribonucleoside diphosphate reductase. This reaction has two important physiological effects:

1. conversion of the radiosensitive dithiol form the enzyme into a more radioresistant form - thioacetal;

2. suppression of the biosynthesis of DNA precursors of deoxyribonucleotides from ribonucleotides. This promotes the synthesis of RNA and cell differentiation in opposition to the synthesis of DNA and cell proliferation.

11.4. Carotenoids

Along with retinol, much attention has been focused on studying radioprotective properties of retinol precursors, e.g., carotenoids, especially ß-carotene. Large doses of the ß-carotene were successfully used in the treatment of patients with the skin radiation damage. The advantage of ß-carotene in comparison with retinol is its extremely low toxicity, even in the heaviest doses. Yarmolenko S.P., Bajnson A.A. (1969) numerous works reported on the antitumor effect of carotene that is of great clinical importance in the treatment of long-term effects of radiation. Anti-radiation and anti-tumor properties of carotene were also reported by A.M. Kuzin and M.M. Vilenchik. These researchers recommended increasing the intake of food rich in carotenoids (ß-carotene) in order to reduce the risk of radiation-induced and spontaneous carcinogenesis. The authors emphasized on the safety of high doses of carotene, which were many times higher than those currently accepted for human health. Experiments of A.M. Kuzin and M.M. Vilenchik on mice and rats, as well as trials conducted in the United States on volunteers, showed that the use of ß-carotene in quantities, which 100-fold or more exceeded the standard doses did not have any negative impact on human health. In the opinion of these authors, even slight alimentary deficiency of ß-carotene or retinol that does not lead to any clinical manifestations of hypovitaminosis, should be regarded as a factor that increases the sensitivity of the human body to radiation and increases carcinogenic risk.

11.5. α -Tocopherol (vitamin E)

Tocopherol (vitamin E) has several vitamers with predominant antioxidant (α, β) and antiradical (γ) effects. It has a chromane ring that bears aliphatic carbon chain derived chain from isoprene units, nuclei, mitochondria. This is a fat-soluble AO phenolic type that inactivates APK and organic peroxides. As a hormone, it influences the exchange of heme, ubiquinone through the nuclear receptors. When taken in excess, it inactivates neutrophils, inhibits proteinkinase C, and produces a prooxidant effect.

α -Tocopherol, as a powerful antioxidant would seem to be a strong radioprotector. However, experimental data on the prophylactic activity of tocopherol are contradictory. Along with reports on the radioprotective properties of the vitamin, there are publications, in which these effects can not be Burlakova O.B. (1975), in particular when using mega doses of tocopherol. These contradictions can be explained by the fact that chemical antioxidants demonstrated the optimal effect within narrow dose limits.

The lack of effect and even the adverse effect of mega doses of tocopherol is determined by the formation of radical that promotes free radical oxidation. The lack of protection against the radiation is explained not only by the severity of the radiation sickness, but by possible radio sensibilization due to the deficiency of selenium, an indispensable nutritional factor closely related to tocopherol. In clinical practice, it is recommended to use tocopherol in moderate doses and, in some cases, in co-administration with selenium. This point of view is supported by other researchers. Increased survival rate was obtained with parenteral administration of tocopherol to rats immediately after the irradiation, and in this case the radioprotective effect is associated with increased immune response or with accelerated bone marrow recovery.

Electron microscopy showed in the endothelial cells of the vessels that the administration of tocopherol after 1 day - 9 months after total (4-5Gy) or local (9-30 Gy) irradiation led to a decrease or disappearance the membrane defects, like

myelin-like transformation, enhanced the reparation of endotheliocytes, growth of autophagosomes and lysosomal bodies. The data obtained may indicate the essential role of lipid peroxidation not only in the mechanisms of initial radiation damage to epithelium, but in the development of long-term effects of radiation damage, although the antioxidant effect of tocopherol is of the greatest importance in the early period after irradiation. The protective effect of tocopherol on the hemostasis system is confirmed by the ability of rats, which received this vitamin and then were irradiated, to synthesize anti-aggregant substance actively during the all the period of observation. The weakening of the carcinogenic effects induced by the radiation when using tocopherol in a dose calculated ranging from 5 to 50 mg per 100 g of body weight is of particular interest.

11.6. Selenium

Selenium is an essential trace element, an important component of antioxidant enzymes, such as glutathione peroxidase (GPx), thioredoxin reductase (TrxR) and iodothyronine deiodinases (IDD).

The key mechanism of the biological effect of selenium, its inorganic and organic compounds is the antioxidant activity of its ions and compounds that has been proven by a large number of reports. Selenium stimulates the conversion of methionine into cysteine and the synthesis of glutathione that also contributes to the overall increase of body AO potential and the detoxification of lipoperoxides. Excess glutathione, like other AO (vitamins E, C, A, ubiquinone) partially weakens the deficiency of selenium.

It is the high AO-activity that promotes the protection against toxic effects of oxygen under pressure, provides the ions and selenium compounds with the capability of radiation protection, higher than that of thiol compounds. AO-activity of seleno-L-methionine (10-100 μg / kg) in the experiments on rats correlates with the radioprotective effect, with a decrease in the level of peroxidation products in the irradiated organism. Selenium, added to the mice diet as organic compound (1 - 2 μg per day per os), increases survival after UV and gamma irradiation and poison-

ing with aflatoxin B1 known as a very potent carcinogen. Selenium in little and medium doses performs an effective mitochondrial AO-defense, even against the deficiency of glutathione that is stronger than a-tocopherol protection. AO-activity of selenium underlies its hepato- and cardioprotective action with the participation of glutathione.

Selenium protects proteins from peroxynitrite attacks, accompanied by the nitration of tyrosine present in their composition. There is a correlation and interchangeability (partial) between selenium and other AO-membrane protectors in the protection of plasma and mitochondrial membranes from the attacks of free radicals and peroxidation. It should be especially stressed that selenium, like zinc, and unlike other metals with variable valency, acts as AO and almost never acts as a prooxidant.

The content of selenium in the human blood and tissues depend of its content in food and drinking water, in plants, soils, and, initially, in rocks. In its highest concentrations, selenium is found in seafood (mollusks, crustaceans, fish, algae), liver, kidneys (0.4-1.5 mg /kg of wet weight); in meat - 0, 1 - 0, 4 mg / kg, milk 0, 1 - 0, 3 mg / kg; in grain and grain products (bread) - 0, 8 mg / kg; in fruit and vegetables is less than 0.1 mg / kg. Brewer’s yeast is rich in selenium. Among vegetables relatively rich in selenium there is garlic, onion, squash, cabbage and other crucifers, especially broccoli.

12. PHYTOADAPTOGENS

In 1957, Brekhman S.E. put forward the conception on the biological effect of plant adaptogens (phytoadaptogens) capable of regulating homeostasis by stimulating and toning up the human body. Using extracts of ginseng and eleutherococcus (liguanic glucosides), he showed that both drugs administered to rats and mice with diet had protective action (13 - 30%) against acute and chronic irradiation. According to Rogozkin (1969), oral or subcutaneous administration to mice for 7 to 10 days before the total single-session irradiation with lethal dose of 5 Gy led to an increase in survival by 20%. An important peculiarity of the action of phytoadaptogens is their ability to regulate brain activity, expressed by normalizing the reactions of excitation and inhibition, improvement in learning and memorizing, as well as restoring a number of biochemical disorders, including the metabolism of biogenic amines.

The increase in the CNS reactivity is accompanied by the activation of neurohormonal regulation of the functions of internal organs, mainly the hematopoietic system and an increase in the accuracy of the dynamic correction of homeostasis. At the same time, it is known that stimulation of biogenic amines production under the influence of phyto-adaptogens can contribute to an increase in the radio resistance of animals. There is also evidence that phytoadaptogens are often unable to provide protective effects to animals irradiated with high lethal doses. Thus, the extract from the ginseng root loses its effectiveness when with mice are exposed to radiation in a dose of 6 Gy. Other domestic phytoadaptogens obtained from magnolia-vine (polymethoxyphenols) wolfberry, and aralia of the Menshujurian (glucosides), do not protect rats irradiated with a dose of 7 Gy. Only agents isolated from some highly radio-resistant plants show marked anti-radiation properties in acute radiation sickness.

For example, the extract from Turkistan mint (Lagochilus inebrians), a plant of Central Asian is characterized by a high content of trace elements balanced by nature, antioxidants, antiradicals and can markedly increase the endogenous back-

ground of radio resistance as well as to protect laboratory animals from acute irradiation. In general, the radioprotective effect of many phytoadaptogens is most clearly manifested under low-dose radiation that causes disturbances in the immune homeostasis of animals. Despite its low efficiency (FID = 1.25), these drugs attract much attention by a number of their qualities: they are nontoxic, can be used as food supplements under chronic exposure and repeated intake, are able to increase the overall nonspecific body resistance.

13. USE OF RADIOPROTECTIVE AGENTS IN RADIOTHERAPY

Radioprotectors are widely used in the clinical practice for cancer radiotherapy. For the purpose of radiation sterilization of tumors, local irradiation is sometimes used in such heavy doses that it can cause radiation damage to the patient's body. Therefore, to protect the body, radioprotectors, developed for selective protection of the healthy tissues, are used.

These drugs are used in combination with radio sensitizers, which increase the sensitivity of tumors themselves to irradiation that enables the sterilization of cancer tissue even with lower doses of ionizing radiation.

In addition to preparations for radiotherapy, the technique of applying special oxygen regimes that is based on the known in radiobiology oxygen effect, confirming the fact that the irradiation becomes less effective when its procedure occurs under hypoxic conditions (see of Fig. 3).

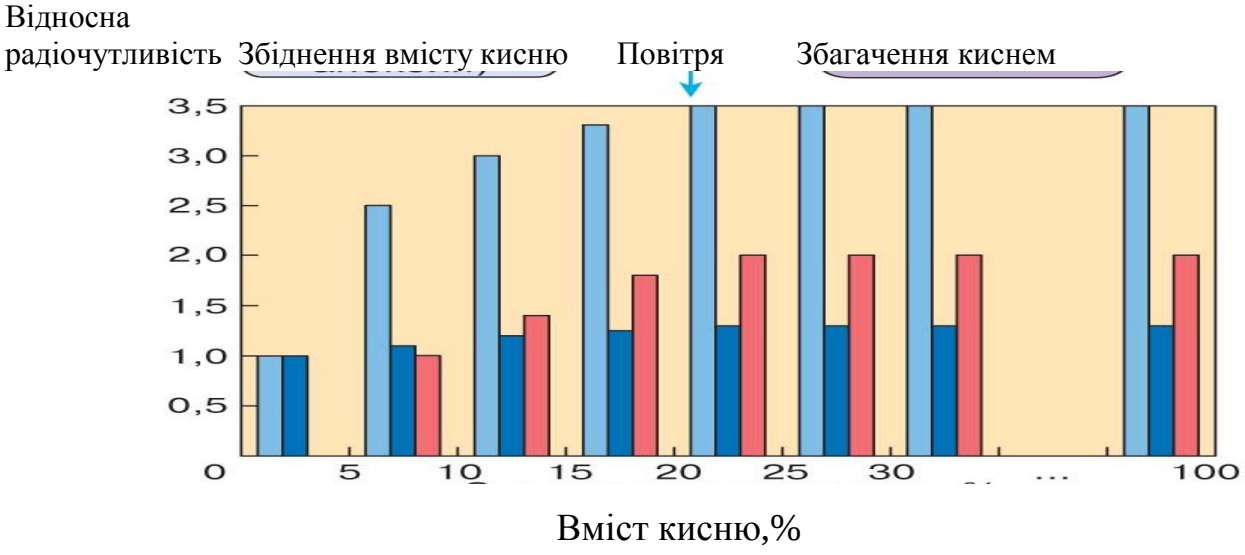


Fig. 3. Dependence of the radiosensitivity of biological objects on the oxygen content in the environment: 7 - single cells, 2 - cancerous cells, 3 - animal organism. LD_{50}: when irradiating cells in anoxic conditions (0% of O_2) or animals in hypoxic conditions (5% of O_2).

With a decrease in the oxygen content in the inhaled air, healthy tissues are depleted of oxygen to a greater extent than tumor tissues. Gas hypoxia has a differ-

entiated effect: the organism with tumour develops greater resistance to irradiation than the tumor itself. It is known that an individual at rest is able to breathe normally for a certain period under reducing the oxygen content to 10% (instead of 21% in normal atmospheric air). Inhalation of gas mixture with 8-10% of oxygen for 10-15 minutes (immediately before and during the radiation session) leads to a significant increase in the effectiveness of radiotherapy. The differentiated effect of gas hypoxia enables to increase the radiation dose for some tumors and to apply the method of hypoxic radiotherapy in the medical practice.

14. REMOVAL OF RADIONUCLIDES FROM THE BODY

Special protection against radiation damage includes measures to speed up the removal of radionuclides found in organs and tissues from the body. The radionuclides incorporated into the body lead to so-called internal irradiation that has some peculiarities in comparison with external irradiation, in which the source of radiation acts onto the organism, being in the external environment. In particular, under internal irradiation, not only the easily penetrating gamma radiation (as in the case of external action) is dangerous, but also beta and especially alpha radiation, less penetrating into the body under external irradiation. Under internal irradiation, radiation damage also depends on the half-life of the radionuclides, their tissue distribution and the rate of excretion from the body. Accelerated excretion (decorporation) of radionuclides from the body can prevent or interrupt further irradiation to a greater or lesser extent, and therefore such measures can only be considered conditionally preventive. In addition to mechanical methods (baths that stimulate sweating, gastric and intestinal lavage), such techniques of radionuclides removal as a special diet in combination with the intake of laxatives and diuretics, preparations of stable isotopes, which replacing radioactive ones, sorbents (including complex agents) that bind radionuclides into structures that are rapidly eliminated from the body, are commonly often used. Of the sorbents, the most promising are ferrocin and polysurmine that absorb cesium and strontium, alginates (con-

taining polysaccharides released from algae), highly active cellulose, preparations of activated carbon, barium sulfate and other sorbents.

Among the actual directions of modern radioecology there are attempts to develop anti-radiation drugs of complex action. Thus, the drug extracted from marine mollusks, MIGI-K mussels (mussel hydrolyzate, acid) not only sorbs and removes radionuclides from the body, but also detoxifies the antioxidant activity of the adaptogen by stimulating the general body resistance to radiation and chemical effects. Recently, it has also been found that ethereal treated pectins, used as food additives, are capable of removing cesium, plutonium and americium from the body.

When choosing drugs for the removal of radionuclides from the body it is important to take into account many factors related to the physicochemical properties and migration of radioactive substances. The main of these factors are:

- ❖ the way of primary intake into the body (respiratory, gastrointestinal or skin);
- ❖ dynamics of distribution of radionuclides in the organs and tissues, their concentration in critical structures and natural isolation;
- ❖ the duration of internal exposure that depends on the period of radioactive half-life and the dynamics of biological excretion of radionuclides;
- ❖ magnitude of dose loads on irradiated organs and tissues;
- ❖ pathological consequences of internal irradiation for the whole organism.

Measures to remove radionuclides from the body consist in the interruption of internal irradiation. But more effective method of protection is actually not interruption, but prevention of irradiation. Among the measures of such prevention there is the iodine technique.

Having enterd the body, radioactive iodine is concentrated in the thyroid gland and is capable to cause serious structural and functional disturbances in it up to the formation of a cancerous tumor. In contrast to radioactive iodine, its stable isotope is vitally important as a microelement necessary for the synthesis of thyroid hormones. Daily intake of stable iodine by an adult human in a dose of 3 mg

causes saturation of the thyroid gland, which in this case loses its ability to absorb new portions of iodine. It is clear that the radioactive isotope of iodine, which gets into the blood later, is not able to be absorbed by the thyroid gland and is quickly excreted from the body. This is the basis of the principle of iodine prophylaxis - preliminary saturation of the thyroid gland with stable iodine prevents the entry of radioactive iodine into it.

15. THE MODERN CONCEPT OF RADIOPROTECTIVE NUTRITION

Among the three main ways of entering radionuclides into the human body (inhalation, alimentary, dermal), the alimentary route is of paramount importance.

In the first 20-40 days after the accident, critical foods were milk, fresh vegetables and berries. During this period, the iodine-131, which determined 60-70% of the dose of internal irradiation, had the largest radioprotective danger to the human body. Its content in milk reached 37-370 kBq / l, in fresh vegetables - 27-300 kBq / l, in strawberries - 50-215 kBq / l. After 40 days, part of the iodine-131 in milk accounted for 30-40% of the total radioactivity, and the first place was released from the radionuclides of cesium, whose contents in the milk of the northern regions of the Zhytomyr, Kiev and Rivne regions reached 4 kBq / l.

The degree of radioactivity of contaminated meat was somewhat less. The content of cesium-137 in this product was 0.1-0.8 kBq / l and was the highest in meat of wild animals (wild boars, elks, goats). In freshwater fish, depending on remoteness from the Chernobyl nuclear power plant, the cesium content was 0.1-0.7 kBq / l. By August of 1986. Radioactive iodine-131 completely disintegrated. The importance of ruthenium, barium, and cerium diminished.

Since 1989, 95-98% of the dose of internal exposure for people who live in the contaminated area were formed at the expense of cesium-134 and cesium-137, 3-4% - due to strontium-90, all other radionuclides represented no more than 1 - 2%; Their part was further reduced by decay.

Fortunately, the density of contamination by plutonium of agricultural lands outside the 30 km zone is insignificant (no more than 8.7 kBq / l). In addition, in the soil-plant system the plutonium compounds are inactive, the absorption in the digestive tract is not more than 0.01-0.003%.

Therefore, plutonium radionuclides do not pose a significant threat as food contaminants. Thus, 25 years after the accident, the main dose-forming nuclides that come with food are cesium-137 and strontium-90.

There are 18 radioactive isotopes of strontium. Most of them are short-lived, only four radionuclides have a half-life from 1 day to 2 months, and one, the most common - strontium - 90 - over 29 years.

When it enters in the digestive tract, strontium is absorbing rapidly into the bloodstream (by 20-70%). Its absorption depends on the species, age, physiological condition and nutritional status of the animal or human. In an adult, strontium is absorbed by 20-30%, in children, depending on age, the absorption of the radionuclide reaches to 30-50%. In the case of a lack of calcium and protein in the diet, absorption of the isotope may increase to 50-60% in adults and up to 60-100% in children.

Regardless of the route and mode of ingestion, soluble strontium compounds selectively accumulate in the bones. In soft tissues, less than 1% of strontium-90 is retained. Accumulating in bone tissue, it is practically not excreted from the body.

The content of the radionuclide in crop yields may differ significantly. Most intensively, it accumulates in leguminous plants. Strontium is found in seeds, fruits, root crops in a much smaller quantity than in other parts of the plant (leaves, stems). In plant products, 50-80% of Sz-90 is in the fraction of hemicellulose and starch, 6-40% is in a readily soluble form.

In animals during lactation, a significant amount of Sz-90 is excreted in milk. The Sz-90 transition from the bird's diet to the egg constitutes 39-60% of the daily intake, while up to 96% of the strontium is concentrated in the shell, 3.5% in the yolk and 0.5% in the albumen.

A special threat to Sz-90 is for children, in the body of which the nuclide comes with milk, meat and grain products. The greatest biological threat is cesium - 137.The properties of cesium are similar to those of potassium, like potassium it is actively involved in the biological cycle, migrates through biological chains and reaches the human body. The source of cesium intake into the human body is more often food, into the animal body - milk, meat, eggs.

The modern concept of radioprotective nutrition is based on three main provisions: 1) the maximum possible reduction in the intake of radionuclides from

food; 2) inhibition of the absorption and accumulation of radionuclides in the body and 3) adherence to the principles of rational nutrition.

To reduce the intake of radionuclides into the body with food we can achieve by reducing their content in products using various technological or agro-industrial methods, as well as by modeling food, ie, using rations that contain their minimum quantity. This can be achieved by consuming "clean" products, or replacing very contaminated products with less contaminated products, or by freeing products from radionuclides.

Milk, cream, sour-milk products are able to accumulate radionuclides. Most of them are combined with proteins and contained in protein-lipid shells. Therefore, the radioactive strontium content is 90, cesium is 137 lower in dairy products with a high content of fats and low proteins, and vice versa. In the production of milk from dairy products, an oiler and whey are formed, in which the main part of the radionuclides that are contained in the milk remains. Therefore, before using them, it is necessary to specially treat with the precipitant of radioactive substances. So you can extract up to 90% of strontium -90.

In the production of cream, a lot of radioactive substances (strontium, cesium) passes into the oil tank. Washing cream with water, and then with skim milk, which does not contain radionuclides, allows to reduce the content of radioactive substances by almost 10 times. In the production of melted butter, it is possible to extract almost all the protein-lecithin shells, and with them radioactive substances. Cheese from fat and skim milk has a high content of proteins that concentrate radionuclides, especially a strong complex with proteins forms strontium - 90. Cheese produced by the most common rennet-acid method contains more radionuclides than those made by acid method. At the last method of cheese production from milk more than 90% of the initial content of cesium is extracted - 137.

Meat can immobilize radioactive strontium. In the bones, its concentration can be 1000 times higher than in the muscle tissue. Studies have shown that when you cook meat into broth, about 80% of cesium passes - 137, and strontium - 90 - hundredths of a percent. This is especially important in connection with the fact

that for the preparation of the first dishes, up to 30% of the daily intake of meat is used.

The concentration of cesium - 137 in adipose tissue is 4-10 times lower than in muscle. In overturned fat, it is 20 times less than in raw, so melted fats can contain few radionuclides at high content in meat. Milk with a high content of radionuclides is used for the production of butter, rennet cheese and dry condensed milk, provided that they are stored for a long time. Eggs accumulate most of the radionuclides in the shell, from which they can be converted into edible parts during cooking, which must be taken into account when use them in food. Potatoes with a lower radionuclide content from the established level are used after thorough washing with water for further purification. Green vegetables - lettuce, spinach and early cabbage - in the case of establishing high levels of radionuclides are not allowed in the market, they are utilized locally. Cucumbers and tomatoes with a low degree of soiling can only be used after removing the top fruit bowl.

Berries (black currants, gooseberries, blueberries) which grow in areas of radioactive contamination significantly absorb radionuclides and therefore can not be used for food. To process on compotes, jam, jams they also do not follow, as the content of radionuclides in these processing products does not change.

The content of radionuclides in foodstuffs is significantly reduced during the appropriate technological and culinary processing. At home, it is necessary to remove the top leaves from vegetables, it is good to wash vegetables, fruits, berries in running water and clean; Mushrooms, forest berries soak in cold water for 2-3 hours, and in the conditions of increased contamination with radionuclides cook, as part of radionuclides, as well as nitrates and heavy metals passes into a decoction. Pre-soaking contributes to the reduction of activity of radionuclides, for example, in carrots - 30%, table beet - 29%, apples - 39.8%, zucchini - 17.8%, pumpkin - 20.9%.

Radionuclides that enter the body, especially accumulating in separate organs, are a source of ionizing radiation for a long time, sometimes for years and decades. Therefore, in such cases, the preliminary application of radioprotectors,

even the longest acting ones, is meaningless. In these conditions, prevention can pursue another goal: to prevent the absorption of the radionuclide into the body. So, in connection with the selective accumulation of radioactive 131I thyroid, it is advisable to ensure the intake of stable iodine by daily administration of 5-6 drops of a 5% solution of iodine alcohol or a solution of potassium iodide 1-3 times a day, while there is a risk of penetration into the body (in the first 40 Days after the accident).

Absorption of radionuclides depends on the state of nutrition. When 90Sr enters the food, the majority of it in the stomach passes into a soluble state, regardless of the initial forms of the radionuclide in the food product. Data are received on the same assimilation of 90Sr from milk and bread. Radioactive, iodine is equally assimilated regardless of its form in food. In the stomach, radionuclides are in a "free" state, do not interact with the chemical components of the chyme. This creates relatively favorable conditions for the absorption (binding) of their radioprotective substances. In the intestine due to the preferential binding of radionuclides with proteins of intestinal juice and bile, the availability of their radioprotective substances is reduced. In this connection, it can be assumed that the uptake of radionuclides associated with proteins will be mainly determined by their ability to adsorb proteins. Iodine, unlike other fission products of heavy nuclei, weakly interacts with bile and intestinal juice proteins, and this indirectly indicates its high mobility and possible accessibility for radioprotective drugs.

The influence of various food products and food additives on the absorption of radionuclides in the digestive canal has been studied. It is shown that tannins rich in tannin do not influence the resorption of 90 Sr in the digestive canal. Activated carbon, widely used in medical practice as an adsorbent for various food poisoning, proved to be ineffective as a means of absorbing 90Sr, 238U, 2I0Po, fission products of uranium. Egg protein, starch, agar, carboxymethylcellulose turned out to be ineffective as a means of reducing the absorption of radioactive strontium in the gut.

Effective compounds, the mechanism of action of which is based on various types of sorption interactions and their combinations (so-called enterosorbents). With respect to 204Te, the strongest acid cations (KU-2, Dowex-50, Amberlite-120), activated carbon and silica gel turned out to be the most effective in the environment of the stomach and intestine. The effective sorbents of radioactive cesium are ferrocyanides, alginates. Highly acidic celluloses effectively absorb radioactive strontium in the digestive canal. In recent years, work has been done on the study of the specific activity of drugs designed to prevent the absorption of radionuclides of cesium and strontium in the digestive canal. The efficacy of Berlin azure and ferrocin is shown. The use of ferrocin reduces the absorption of radioactive cesium by 70-88%. It has been established that sodium alginate reduces strontium absorption (by 30-70%) and deposition of it in the body (approximately 3.4 times). It is shown that sodium alginate, added to milk, decreases absorption in the digestive channel of radioactive strontium, taken with milk 6 times. It is assumed that the absorption of radioactive strontium from liquid products by alginates occurs more efficiently than from solid ones. The ability of aluminum compounds to bind radioactive strontium (by 50%) is established. A moderate effect of phosphate (in the form of glycerophosphate) in the binding of radioactive strontium in the human digestive channel (by 23%) is shown. The absorption of radioactive strontium in the digestive canal essentially depends on whether the radionuclide is delivered on an empty stomach or on a full stomach. When food is present, 20-30% of radioactive strontium is absorbed in the stomach, when administered on an empty stomach (after 12 hours of fasting), the radionuclide absorption rises by 2-3 times. The presence of food in the stomach contributes to a temporary delay in the evacuation of radionuclides into the lower intestine and slowing the rate of their absorption into the blood. Thus, conditions are created for some prolongation of the effective action time of protective preparations. Therefore, when examining the victims, it is recommended to gather relevant information about the time of ingestion and the nature of the food.

Since the late 50-ies of the last century, the search began for funds that block the absorption of radionuclides in the digestive tract and (or) accelerate their removal from the body. All nutrients were studied: proteins and individual amino acids, fats, and fatty acids, simple and complex carbohydrates, including dietary fiber, pectins, hemicellulose, phytates, lignin; All macro- and microelements, vitamins and provitamins, phytoncides; Chelators, chelates, zeolites, clays, coal, many medicinal plants. It is established that in the conditions of long-term intake of radionuclides into the body, the possibility of using blockers is limited. Thus, the use of polysurmine, vokacite, and adsobar is permissible only in case of acute poisoning with strontium radionuclides. The same applies to certain drugs (activated charcoal, laxatives, etc.). Therefore, an intensive search for radioprotective agents among food and plant products.

In the problem of minimizing the radiation loads of the population that lives on areas contaminated with radionuclides, reducing the level of contamination of food products and restricting their absorption in the digestive tract is of primary importance.

Measures to reduce absorption, accumulation and acceleration of radionuclide removal are complex, sometimes ineffective, but they must be introduced.

These measures are implemented in two ways:

1. Providing a balanced diet, especially protein (especially proteins of animal origin, carbohydrate (fiber, pectin), mineral (calcium, phosphate, potassium, iron, iodine, cobalt, copper, zinc) and vitamin (retinol, beta-carotene, Tocopherol, ascorbic acid, cyanocobalamin).

2. The use of drugs, food and additives that reduce the absorption and accumulation of radionuclides (sorbents, complexones, as well as the means that accelerate their removal).

The use of these tools should not be uncontrolled. In the case of long-term use of such funds must meet more stringent requirements than in the case of short-term use. They should be sufficiently effective, easy to use, economical, with long-term use - not to violate the mineral metabolism and exchange of other substances.

The selected remedy should not be toxic for long-term use, or such that the risk from its use is lower than from the possible effects of irradiation.

The effectiveness of various drugs (potassium, iron, hexacyanoferrate, sodium and calcium alginate, barium sulfate, phosphoric acid calcium), nutrients (proteins, carbohydrates, vitamins, potassium, calcium, phosphorus salts), various pectins and dietary fiber natural products (fruit and Berry juice products, bakery products, marine algae products, mussels, etc., as well as special foods that contain blocking agents for the absorption of radionuclides of cesium and strontium (potassium, iron, hexacyanoferrate, and Ligands, food fibers, pectins, etc.) .The range of such products is very wide - meat and canned fruits, tinned meat, sausages, bakery, confectionery, dairy products.

It has been established that of all the drugs studied-cesium-137 absorption blockers-ferrocin is the most effective (the iron potassium hexacyanoferrate.) The chemical names of the active substance are Berlin blue, ferrous-cyanide iron.

This drug was tested in acute and chronic (throughout the life of the animal) experiments in rats, as well as in clinical and field observations in humans. If the product is included in the composition of the food product, its effectiveness not only does not decrease, but also increases somewhat due to an increase in the possible contact area of the drug and cesium. The optimal dose of the drug is 50 mg per day for a rat and 3 g per day for a person - it provides 95-99% reduction in cesium absorption (preventive use) and a 3-fold acceleration of radionuclide removal (therapeutic use).

The salts of alginic acid (sodium alginate from laminaria of the White Sea, Japanese, from Japanese laminaria rizoid, cystariium, cystocira, calcium alginate from the laminaria of the White Sea, Japanese, equatorial) have been thoroughly studied as blockers or decorporators of strontium and cesium. The addition of alginates to the test (0.5 - 2.0% to the weight of flour), dairy, confectionery, meat and fruit preserves (0.5 - 2.5%) improves the physicochemical properties of the finished product and provides 2-3 single decreases in the absorption of radioactive strontium.

The results of the studies indicate that the optimal intake of sodium alginate, which does not violate the exchange of the strontium-calcium analogue, is the daily intake of 6-8 g (for an adult). This amount of sodium alginate reduces the absorption of strontium-90 in 3-3.5 times, and the dose in 20 g provides - 5-7 –time higher "protection". Viscosity, the ability to gel formation, the absorption of radionuclides and heavy metals, the good manufacturability of alginates, the use of them (products with them) in the ecologically contaminated areas.

It is known that calcium deficiency in the diet of animals and humans leads to an increase in absorption and accumulation in the body of radionuclides of strontium. So, in the case of normal maintenance of laboratory animals with calcium, strontium absorption becomes 20-30% of the amount entered into the intestine, in case of its deficiency, 60-70%.

The inclusion in the diet of increased amounts of this element (in 1,5-2p above the norm) helps to reduce absorption and increase the removal of strontium by 30-40%. The main sources of calcium, especially for children - milk and dairy products. To ensure the daily requirement of a person in calcium, you need to consume at least 500ml of cow's milk or fermented milk products. Therefore, the composition of food products included such sources of calcium as milk, sea cabbage, blood, liver. The use of calcium-enriched products during the experiment reduced the absorption of strontium-85.

In addition, these products enrich the diet with a complete protein, which increases the overall resistance of the body and reduces the accumulation of radionuclides.

Potassium salts are known to play an important role in intracellular metabolism, in the regulation of water-salt metabolism, osmotic pressure, necessary for the normal activity of muscles and myocardium. Potassium promotes the excretion of water and sodium, activates a number of enzymes. In case of its deficiency, the accumulation of cesium radionuclides in the body increases. The results of the research show that the use of fruit and vegetable dishes in the diet prevents the accumulation of this radionuclide and accelerates its excretion in the urine. There-

fore, in the diet of the population living in contaminated areas, it is necessary to include a sufficient number of potassium-bearing products: vegetables, fruits, dried fruits, juices with pulp, sea kale, peas, beans, potato. The content of potassium in the daily ration should not be less than 4 grams per day.

Among the means of individual protection from the accumulation of radionuclides in the body, great importance is attached to the use in nutrition of the population of substances possessing radioprotective action. In this case, it is preferable to use food substances of natural origin or close to those in their chemical structure, which do not have a side effect on the body and exhibit a sufficiently pronounced radioprotective effect. Such pesticides include pectins, organic compounds capable of forming gel (jelly) in the presence of organic acids and sugars. The basis of these compounds is a polygalacturonic chain consisting of anhydrogalacturonic acid residues. Individual chain links-the residues of galacturonic acid can either be sieved with methyl alcohol, or some of the hydrogen atoms of the carboxyl groups can be replaced by metal cations in them. The presence of free carboxyl groups of galacturonic acid in pectic substances determines their ability to bind metal ions in the digestive channel, followed by the formation of insoluble complexes (pectinates, pectata) that are not absorbed and removed from the body. Consequently, pectins belong to complex-conforming compounds (chelators, chelators), the main property of which is the ability to form stable, slightly dissociating complexons with many divalent and trivalent heavy metals and rare earth elements, as well as their salts. When forming such complexes in the body, they are relatively quickly excreted in the urine. The protective effect of pectins is also explained by the fact that together with other dietary fibers they improve the intestinal motility, contributing to the faster excretion of metals with feces.

Table. Pectin content in fruit juices, g / 100ml (I.M. Trakhenberg, 1986)

Juice	Pectin content	Juice	Pectin content
Redcurrant	0, 436	Peach	0,445
Blackcurrant	0.657-0.077	Orange	0,03 – 0,37

Gooseberry	0.652-2.25	quince	0,332
Wild rose	0,242	Raspberry	1,22
Bilberry	0.429	Cranberry	1,3
Cowberry	0.388	Grape	0,11 – 0,152
Cherry	0.09 to 0.98	Strawberry	1,63
Apricot	0.335	Apple	0,43 – 1,2

These properties of pectin substances allowed them to be used in preventive nutrition of persons exposed to toxic elements in the production environment, which is regulated by the "Methodology recommendations for the organization of preventive nutrition for workers dealing with heavy metals" approved by the USSR Ministry of Public Health (No. 3084-84) Preventive application of pectin substances in conditions of radioactive contamination approved by the Ministry of Health of the Ukrainian SSR on 12.12.86. Experimental studies have shown that when a radioactive 90Sr is introduced into the digestive canal, pectin binds it and reduces absorption and deposition in the bones of the skeleton.

Pectin substances are contained in fruit, vegetables, root crops and other vegetable products in the amount of 0.5-3.8% (Tables 66, 67). The richest in pectins are beetroot, radish, carrots, sweet pepper, pumpkin, eggplant, apples, apricots, quince, cherries, plums, pears, citrus fruits. The high content of pectin is also characterized by fruit and vegetable juices with pulp (apple, carrot, apple-carrot, apple-cranberry, quince, peach, tomato), fruit and berries, rubbed with sugar (apples, strawberries, gooseberries, plums, currants) and others(Table 68).

The main raw material for industrial production of pectin is beet pulp and apple squeezes. Let out dry food pectin represents a powder grayish or brownish color, without a smell, swelling in water with formation gelatinous weight. The content of pure pectin in the powder ranges from 16 to 25%. Finished canned fruits and vegetables, enriched with pectin (pepper cut with vegetables, eggplant caviar), fruit purees, jelly drinks, syrups recommended containing from 2.3 to 6.4%. With the preventive purpose enrichment with pectins of diets of an adult and children's

population can be spent both at public catering establishments, and in house conditions. In the summer-autumn period, the daily introduction of salads from fresh vegetables and fruits to a considerable extent enriches the body with pectin.

Taking into account the duration of administration, the recommended daily preventive dose of pectin is 2-4 g for adults, 1-2 g for children (I.M. Trakhtenberg et al., 1986). In a daily diet, this amount of pectin can be included either in the form of finished pectin-containing industrial products or in the form of a dry powder added to the dishes after it has swelled. The daily dose of pectin can be calculated for a one-time meal (lunch) or two meals (breakfast - lunch, lunch - dinner). With a one-time intake of pectin, its daily amount is diluted with boiled water at room temperature (1 glass) and after swelling (after 1 hour) half of the resulting mass is added to the first dishes (soups, borsch, rassolnik) at the end of cooking, not allowing boiling. The second half of the swollen pectin is added to the third dishes (jelly, jelly, mousse) also at the end of their preparation. With a two-time administration of pectin, the daily dose of the powder must be divided into two equal parts, and then used as indicated above. However, one should not allow their boiling after the introduction of swollen mass. At home, the dry powder of pectin can also be added to the first and third dishes in the swollen form at the end of their preparation. As in public catering establishments, pectin powder can be divided into two meals or taken in one go.

It should be taken into account that pectin, obtained from various plant products, has unequal gelling properties. Dry pectin from sugar beet is most suitable for adding to dishes, since its gelling capacity is the lowest, and therefore the dishes are less exposed to the uneducated student. Pectin substances contained in apples and quince have a high gelling ability. It should be taken into account that in the food basket for people exposed to radionuclides, the content of products - sources of pectin substances slightly increases: potatoes - 350 g, vegetables - 650 g, fruits and fresh juices - 370 g.

For example, we give several recipes for preparing dishes with pectin (I.M. Trakhtenberg et al., 1986).

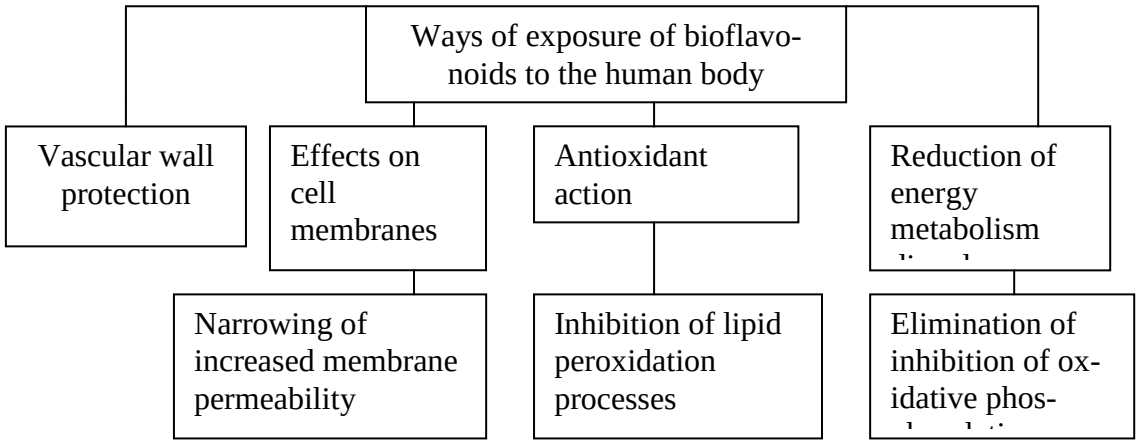
Kissel (jelly) with pectin. A portion of pectin, equal to its daily dose (2-4 g for an adult, 1-2 g for a child), is taken in a glass of water, or fruit, or berry broth for 1 hour. The mass obtained is poured with an equal volume of hot water or broth and boil. Here add 3 g of starch, and boil again. Cool after finishing, divide into two equal parts and taken in two stages.

Jelly with pectin. 2-4 g of pectin are mixed with 100 ml of water at room temperature and left for 1 hour for swelling. Then add 40 ml of water, 90 g of sugar and cook for 4 minutes. At the end of cooking, add 6-8 drops of citric acid and mix thoroughly. Pour into molds and cool to room temperature. After 1 hour, jelly can be consumed. Portion is calculated on 2 receptions.

Apple-pectin drink: apple-natural juice - 470 g, beet or apple pectin - 2-4 g, sugar-¬ 50 g, water - 510 g. This amount of dry pectin is poured into 200 g of boiled water at room temperature And after swelling (after 1 hour) is added to the remaining components of the beverage. In this case, the specified amount of water in the beverage recipe will be correspondingly lower by 200 g. The drink can not be boiled.

Influence of bioflavonoids on the human body

(I.M. Trakhenberg, 1986)



Among plant-based products, which can also have a radioprotective effect, plant phenolic compounds and plant polymers, in particular polysaccharides, take a special place (Fig. 7). Vegetable phenols are able to provide antioxidant, vasoconstrictive, P-vitamin and anti-inflammatory effects and, thus, influence the

course of recovery processes under radiation exposure. Vegetable polysaccharides have a detoxifying and complexing effect that promotes the excretion of radionuclides from the body. In recent years, natural phyto-chemical complex preparations containing flavonoids and polysaccharides have been created, as well as compositions of individual flavonoids with natural and synthetic polymers capable of binding radionuclides in biological fluids and providing a preventive and curative effect on local and general responses (G.P. Sivachenko Et al., 1989).

It has been established that plants such as plantain containing a complex of polymers of galacturonic structure with mucous substances and flavonoids affect the general radiation reaction. As a result of clinical tests of lyophilizate from plantain leaves (plantatin) their ability to reduce the damaging effect caused by radiation effects is shown.

The basis for the use of vitamins in the prevention and treatment of radiation damage is the negative effect of their deficiency on the body's resistance to ionizing radiation and the aggravation of their deficiency when exposed to it. The use of vitamins is aimed at filling their deficiency and optimizing the functions performed by vitamins inherent in them and in a healthy, non-irradiated organism. The most important are the specific mechanisms of the effect of vitamins associated with their ability to inactivate free radicals and inhibit the processes of lipid peroxidation, which are sharply activated upon irradiation. It is with this mechanism that the enhancement of the damaging effect of radiation can be associated with the deficiency of p-tocopherol and ascorbic acid. A similar effect is possible with insufficient carotene and retinol. A number of vitamins are effectively used for the prevention and treatment of radiation lesions in doses exceeding the physiological need of 10-100 times and certainly exceeding those that are necessary to fill the deficit that arises during irradiation. The basis for their use is the presence in some vitamins of valuable physicochemical features that impart radioprotective properties to them. This includes the ability of a number of vitamins (tocopherols, carotene, ascorbic acid, bioflavonoids, vitamins containing sulfur, thiamine, coenzyme derivatives of pantothenic acid, biotin) to interact with free radical forms of oxygen

and active radiolysis products, inactivating them. In addition, coenzyme derivatives of vitamins containing SH-group can be used for regeneration of SH-groups of proteins oxidized upon irradiation. No less valuable is the ability of a number of vitamins and vitamin-like compounds, in particular bioflavonoids, to bind radionuclides, hindering their absorption and accelerating their excretion from the body. In some cases, these properties are directly related to the specific function of the vitamin (tocopherols, carotene) in the body, but more often they are not directly related to the primary mechanism of action of the vitamin in metabolism, but are based on the use of the properties of its molecule, which are valuable in the irradiated organism.

The use of significant amounts of ascorbic acid can be justified by the available reports of its stimulating effect on the body's immune system. It is expedient to use ascorbic acid in combination with thiol compounds that restore dehydroascorbic acid. The mechanism of the positive effect of ascorbic acid with increased radiation exposure is multifaceted. Of great importance is not only the replenishment of this vitamin deficiency in tissues of the irradiated organism, but also the normalization of the collagen synthesis processes depending on it, with which the beneficial effect of ascorbic acid on the permeability and strength of blood vessels can be associated. The improvement in the pattern of peripheral blood may be due to the participation of ascorbic acid in hemopoiesis, the mechanism of which is probably connected with the exchange of folic acid. The most important role in the mechanism of the radio-protective effect of ascorbic acid is played by its antioxidant properties: the ability to inactivate free-radical oxygen species, to maintain the SH group of proteins and low molecular weight thiols in the reduced state. The beneficial effect of ascorbic acid in the ionizing effect is associated with its participation in the processes of cell division. According to one hypothesis, ascorbic acid, by blocking hyaluronidase, inhibits cell division, thereby reducing the radiosensitivity of the tissues. In accordance with the assumption of the synergistic effect of high doses of ascorbic acid and cyclic nucleotides, ascorbic acid, together with adrenaline, probably activates adenylate cyclase and inhibits

the cleavage of cycloadenine monophosphate, which is the activator of many metabolic processes. It should also be taken into account the stimulating effect of ascorbic acid on the immune system.

Under the conditions of radioactive exposure, gala-scorbin (a complex preparation of gallic and ascorbic acid) useful to normalize energy metabolism, reduce violations of water-electrolyte equilibrium, improve the functional state of the liver and hematopoiesis are useful.

Among the nutrients that are of great practical application due to their radioprotective properties are bioflavonoids. The favorable effect of bioflavonoids under ionizing radiation is due mainly to the protective walls of the vessels, primarily the capillaries. Some authors believe that this effect is associated with the effect of bioflavonoids on the hyaluronic acid-hyaluronidase system and inhibition of the depolymerization of the basic substance of connective tissue initiated by ionizing radiation. The beneficial effect of flavonoids on intracellular membranes and a decrease in their increased permeability was also revealed. It is believed that flavonoids stabilize membranes of perivascular mast cells, preventing the release of vasoactive amines and interrupting one of the most important links in the pathogenesis of vascular lesions under ionizing radiation. The basis of radioprotective, including membrane-strengthening action of bioflavonoids, is their antioxidant properties, the ability to act as a "trap" for free radicals and inhibitors of the processes of peroxide oxidation of membrane lipids (A.L.Kondrusev et al., 1990). A certain value in the mechanism of the positive action of bioflavonoids has also their property to soften the disturbances in energy metabolism associated with the inhibition of oxidative phosphorylation in the irradiated organism. Bioflavonoids are especially effective in combination with ascorbic acid, which potentiates their antihemorrhagic properties.

As a result of modern research, it is becoming increasingly clear that p-carotene can protect phagocytic cells from auto-oxidative destruction, enhance the proliferative response of T and B lymphocytes, stimulate T cell effector functions, enhance the activity of cytotoxic T cells and natural killer cells, Their ability to de-

stroy tumor cells, and to stimulate the formation of certain types of interleukins. It is shown that low consumption of fruits and vegetables, carotenoids leads to an increased risk of lung cancer. It is assumed that carotene fulfills its protective function without its preliminary transformation into vitamin A.

An adequate supply of the organism with selenium is of great importance, which is due to its multifaceted protective effect when exposed to ionizing radiation (*Fig. 8*). The greatest amount of selenium is found in meat and grain products: 0.28 mg / kg in legume beans, 0.29 m g / kg in meat, 0.3 mg / kg in cheese, cheese and cheese. Vegetables and fruits contain less (0.004-0.14 mg / kg). The need for an adult in selenium is 0.4 mg / day.

Widely applied enrichment of food products by some elements and substances seems to be an effective way of obtaining products with increased biological value. Suffice it to recall salt iodization in endemic goiter regions fortification products synthetic vitamin preparations enriched flour certain amino acids, salts of calcium, phosphorus, iron, fluorination water and others. Currently, are products to prevent absorption of cesium and strontium radionuclides in the intestines by additives various substances in the formulation of food products and the creation on the basis of the latest diets with optimal content of substances that reduce the absorption and accumulation in the body, these radionuclides.

The need for an adult in selenium is 0,4 mg / day.

The prevalence of iron deficiency anemia among children and women in the controlled areas of Polesie testifies to the need to enrich the diets not only with high-grade protein, ascorbic and folic acid, but also microelements involved in the process of blood formation (iron, copper, manganese, cobalt). The source of easily digestible forms of hematopoietic microelements includes some meat products, especially liver, blood, and also apples. The daily requirement for menis 10 mg; for women - 18 mg; copper - 2 mg, manganese - 5 mg, cobalt - 0.05-0.2 mg.

Enrichment of food products with some elements and substances is widely used as an effective way of obtaining products with increased biological value. Suffice it to recall the iodization of salt in endemic regions, the vitaminization of

products with synthetic vitamin preparations, the enrichment of flour with certain amino acids, calcium, phosphorus, iron, fluoridation of water, etc.

At present, products are being created to prevent the absorption of cesium and strontium radionuclides in the gut by adding various substances to the formulation of food products and creating on the basis of the last diets of nutrition with the optimal content of substances that reduce absorption and accumulation in the body of these radionuclides. The main requirements for such special purpose products are: harmless with long-term use, good organoleptic properties (taste, smell, color, consistency, appearance); High nutritional and biological value; Possibility of long-term storage; Convenience of transportation.

Formulations of a large number of food products have been developed, including ferrocin (0.1-0.5%), sodium alginate food (1-5%), individual amino acids (lysine, methionine, phenylalanine), a complex of vitamins, calcium salts Dry fat-free, calcium phosphate), bran as a source of dietary fiber. The assortment of products is rather wide: different kinds of bread (with bran, from the padded grain from the wallpaper flour); several kinds of cookies, marmalade of sweets, sausages, canned meat and meat and vegetable; concentrate jelly; processed cheese.

New food compositions based on meat are created; Raw materials, which include sodium ferrozinc sodium alginate, as well as sea kale. The results (V.N. Korzun 1990). of the study indicate a significant increase in the use of excretion from the body of 137Cs and 85Sr, which confirms the possibility of incorporating radio-protective substances into food products, which are recommended to reduce the dose of accumulation in the body of radioactive substances.

Sea cabbage is especially promising in this respect. It can be used as a component in the creation of many food items, combining with meat raw materials, cereals, skim milk (V.N. Korzun et al., 1990). When ferrocin was added 1 g 3 times a day for 10 days (total dose 30 g), the half-life of radioactive cesium from the children's body was reduced from 50.6 to 24.4 days, according to the measurements of the human radiation counter.

This confirms that ferrocin has a rather pronounced specific efficacy (L.A. Buldakov et al., 1989).

Experimental studies by E.P. Podrushnyak and co-authors (1988) showed that the biologically active product Kosmol, containing about 70% skimmed milk, lactose, calcium lactate, magnesium and trace elements, tocopherol, ascorbic acid, calciferol, when used on the eve and At the time of irradiation contributes to the removal of 10-23% of radioactive strontium.

AP Tarasenko (1988) shows the modifying effect of the "Okean" paste applied before irradiation on the cell repair system, which increases the radioresistance of the organism, partially prevents radiation damage to the liver cells. At the same time, the yield of aberrant mitoses decreases by an average of 30.8%. B.V. Ochronchuk and co-authors (1988) found that the constant use of polysalt extracts "Polysol" and "Antihypoxin" reduces the accumulation of 137Cs.

Radionuclide-binding activity with respect to 137Cs, in addition to ferrocin and sodium alginate, has citrus, beet, apple low-melted pectins; And in relation to 85Sr - sodium alginate, citrus, beet, apple low-methylated pectin.

The radioprotective effect of polysaccharides of microbial origin has been revealed (A.P. Duplishcheva et al., 1972). It has been shown that three particle-bound polysaccharide particles derived from Saccharomyces cerevisiae and one soluble polysaccharide extracted from Rhodotorula rubra are effective radioprotectors. When administered intravenously to mice 15 minutes before irradiation, LD50 increased by a factor of 2 (J. R. Maisin, G. Mattenlin, 1987).

The ability of alcohol extracts of propolis to protect mice from gamma-irradiation has been established (S. Schel-ler et al., 1989). The preparation of ginseng with oral administration to mice for 7-10 days at doses of 100-150 mg / kg increased the survival rate of animals by 20% with a total irradiation dose of up to 5 Gy (V.D. Rogozkin, 1990). Dry buckwheat extract may be administered orally for 1 to 18 days twice a day, 1 or 5 mg / kg, increased the radio-resistance of mice after a total irradiation of 6.7 Gy (I.N. Usacheva et al., 1981).

A clear decrease in the sensitivity of mice to total irradiation was established by M. Pospisil and co-authors (1980) with an increase in the content of potassium and magnesium salts of aspartic acid in drinking water.

Increased radioresistance also causes prolonged feeding of dry thyroid preparations (M. Pospisil et al., 1975, A. Vacek et al., 1978). Developments of the Kiev Trade and Economic Institute and the Institute of Nutrition Hygiene showed that the additive for sausage products containing tissue of the thyroid gland of cattle has radioprotective properties (a pp. 1515437). Products containing pigmented substances - anthocyanins (chokeberry, beet and grape juice).

This is also noted by Dr. R. Gale in his recommendations. You can also agree with his recommendations to use garlic, horseradish, which are sources of ascorbic acid and phytoncides, as well as preparations of ascorbic acid or a complex including retinol, B vitamins, ascorbic acid. When choosing meat products, it is advisable to give preference to meat of poultry and rabbit, which contains less fat.

Among cereals, buckwheat and oatmeal should be preferred, since their radioprotective effect is indicated. Both croups contain a large amount of high-grade protein, essential amino acids, in oat groats - and a significant number of polyphenols, which have antiradiation effect. From dairy products it is preferable to use cottage cheese containing a lot of high-grade protein and easily digestible calcium.

Calcium salts are known to possess similar properties with 90Sr properties and therefore can prevent its deposition in the skin. Vegetables after thorough washing should be cleaned from the skin, as radionuclides can accumulate in it. Anti-radiation effect is a vegetable oil. Useful walnuts, rich in high-grade protein and vegetable fats, containing polyunsaturated fatty acids, as well as tocopherols.

For prevention of harmful effects of radioactive radiation to people working with radioactive substances and ionizing radiation, therapeutic and preventive ration No. 1 is included, which includes products with a high content of lipotropic substances (methionine, cystine, phosphatides, vitamins, polyunsaturated fatty ac-

ids) , Improving metabolism in the liver and increasing its antitoxic function (liver, eggs, milk and dairy products, fish and vegetable oils, vegetables, fruits, etc.), as well as products with high co Keeping of sulfur-containing amino acids, calcium salts (milk, cottage cheese, cheese, sour-milk products, legumes) and pectin substances (vegetables, especially carrots, fruits, especially apples, plums, berries and juices with pulp of these products).

According to the "List of industries where work entitles them to receive free medical and preventive nutrition", ration No. 1 is received by workers engaged in the production of radioactive salts of uranium and thorium, loparite concentrate at mining and processing plants, processing loparite concentrate, and also working with radioactive substances And sources of ionizing radiation.

In conditions of an increased background of ionizing radiation, it is important to supply the organism with adaptogens. Adaptogens are the means that create in the body a state of unspecific increased resistance, i.e., accelerating adaptation to a variety of environmental factors. Adaptogens must meet three main criteria: do not have a noticeable negative effect on the body, ie, have low toxicity; Act nonspecifically, that is, protect the body regardless of the nature of the detrimental factor; To show a normalizing, i.e., protective, effect on the body, regardless of the direction of the physiological changes.

The use of adaptogens increases the general resistance of the organism to the action of a great many damaging agents, including ionizing radiation. Among the most effective adaptogens are preparations of Eleutherococcus prickly, ginseng, magnolia vine, vitamins, flavonoids, vitamin-amino acid complexes, protein-vitamin complexes, some trace elements, especially in combination with vitamin-amino acid complexes, bio-stimulants, coenzymes and a number of other substances.

An antihypoxin prepared on the basis of polysol, obtained from malt extract from sprouted wheat seeds, oats and maize, containing macro- and microelements, amino acids, digestible carbohydrates, proteins, vitamins (C, group B, E), flavo-

noids, phytohormones, enzymes, rose hips extract and tea leaves (B.V.Ochronchuk et al., 1989).

Examination of special food products with radioprotective properties indicates that it is impossible to include the optimal dose of alginates, laminaria, pectins in one product without changing organoleptic and physico-chemical properties. In addition, in the case of long-term use of products with radioprotective action, it is necessary to have a sufficient set of such products in order to minimize the frequency of the dishes, and not to interfere with the optimal set of nutrients.

Experience shows that the use of such radioprotective agents as alginates, pectins, dietary fiber, calcium salts (within reasonable limits) does not cause negation, since their harmlessness has been extensively studied both in animal experiments and in human observations that traditionally use them Throughout life. Dietary fibers, pectins, alginates can not only reduce the incorporation of radionuclides, but also the risk of constipation, diverticulum, polyposis and cancer of the colon and rectum, hemorrhoids, atherosclerosis, diabetes, cholelithiasis.

At the same time, excessive consumption of dietary fiber and pectin leads to fermentation in the large intestine, increased gas production with the phenomenon of flatulence, deterioration in the absorption of proteins, fats, calcium, iron and other minerals. It is recommended to use dietary fiber not more than 25-30g per day, pectin - 2-3g per day, alginates - 6-10g per day.

The second way to use of potassium iron of hexacyanoferrate both in the form of a drug and in the composition of food products must be addressed individually.

Taking into account the poverty of Polesie soil for microelements, as well as data on the biological effect of sea products (fish and especially sea kale), in animal experiments and in clinical trials on the population, the radioprotective and general therapeutic effect of products with seaweed (laminaria, cystoseira , Fucus, ascofilium, etc.) - salads "Far East", "Health", salad from cucumber, spicy, jam sticks.

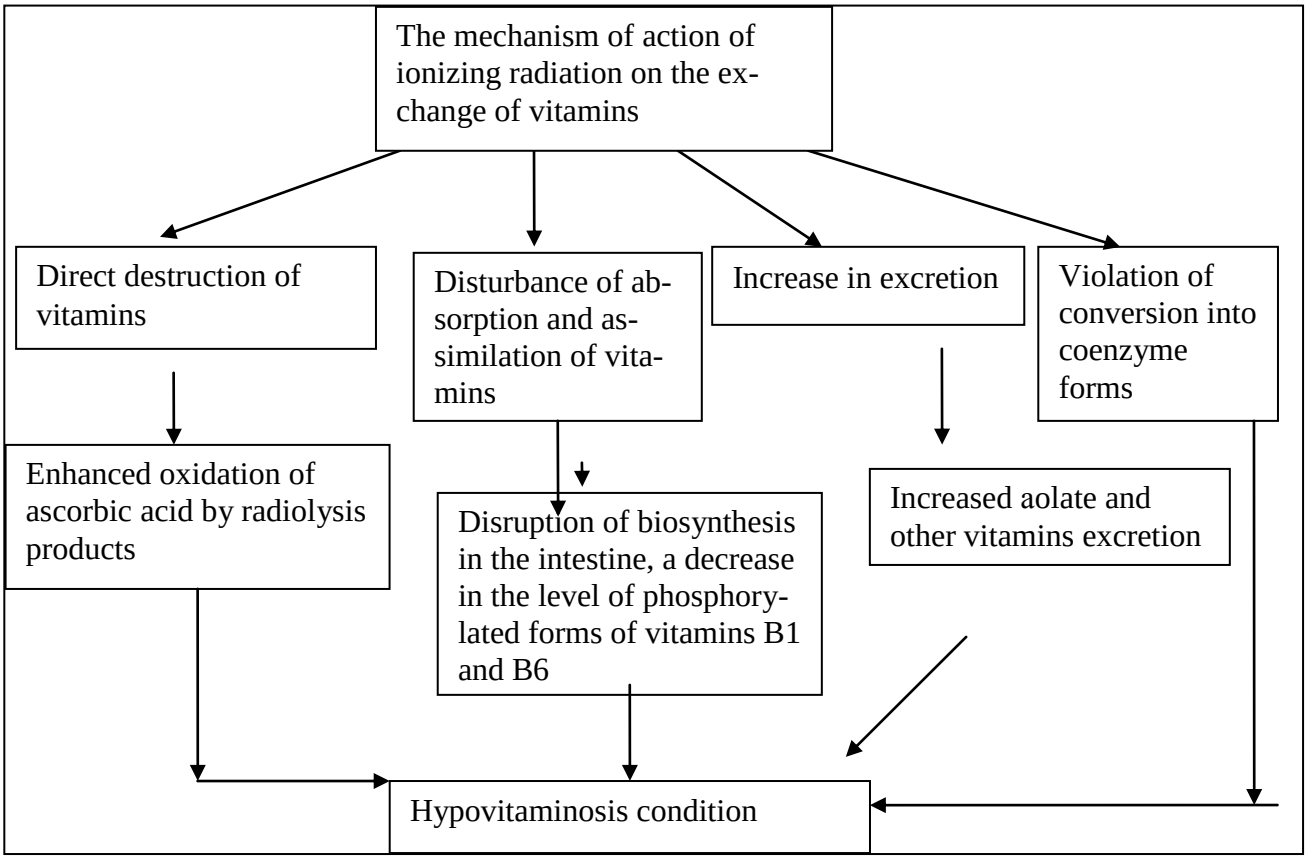
It was found that the inclusion of these products in the diet of animals reduces the accumulation in the body of cesium - 137 and strontium - 85. Their use in feeding children who live in contaminated areas, contributed to a more intensive removal of the radionuclide.

In addition, a positive therapeutic effect was noted in 80% of the children examined. Pain syndrome disappeared in 72%, dyskinetic phenomena in 68%, cavity digestion normalized in 64%, there was also an improvement in the state of the gastric mucosa in children with pathology of the gastroduodenal zone, red blood with normalization of hemoglobin level and red blood cells in children who had iron deficiency Anemia of mild degree.

The results of laboratory and clinical studies allowed us to recommend products with seaweed in the diet of the population that lives in contaminated areas. Developed also tableted preparations from algae, 2 tablets (1g) provides a daily human need for iodine, manganese and selenium.

Particular attention requires monitoring the content of vitamins in the diet. The lack of vitamins increases the radiosensitivity of a person. The negative effect of vitamin deficiency on the body's resistance to radiation is reinforced by the fact that ionizing irradiation can itself lead or enhance vitamin deficiency.

Scheme. Influence of ionizing radiation on vitamin metabolism (for V.I. Smoljarom 1997)



Deficiency of vitamins in the case of irradiation is created by the destruction of their primary products of radiolysis, as well as by disruption of the processes of utilization and exchange of vitamins: an increase in excretion under stress (primarily ascorbic acid), a disruption of conversion to coenzyme forms and binding to apoenzymes due to damage to the corresponding protein Structures, and also because of the violation of absorption processes in the intestine.

Reducing the resistance of the body to radiation exposure in conditions of vitamin deficiency, the increase in this deficit under the influence of ionizing radiation is the basis for widespread use of multivitamin preparations by the population of contaminated areas, which contributes to the preservation of vitamins in the body and positively affects the overall condition. However, do not increase the daily physiological dose of ascorbic acid by more than 2 times, because This can lead to a pro-oxidant effect.

Alimentary prevention of the separated effects of the action of radiation is based on the reduction of the processes of excess lipid peroxidation.

It is known that the formation of free radicals and peroxide compounds increases under the influence of radiation.

The substrate of free radical oxidation (CPO) is unsaturated lipids. The consequence of these reactions is an increase in the products of lipid peroxidation (LPO), which lead to oxidation of the structural components of biomembranes, inactivation of enzymes, changes in the structure of macromolecules, disruption of the integrity of cell membranes.

All these processes underlie the pathophysiological mechanisms of the action of radiation and are subject to alimentary correction. In the human body, the intensity (LPO) regulates the antioxidant system (AOS). It provides binding and modification of free radicals, prevents the formation of peroxides, protects the functional groups of proteins and other biosubstrates. AOS includes such specialized enzymes as superoxide dismutase, glutathione peroxidase, succinate dehydrogenase, catalase and natural antioxidants: tocopherol, glutathione, selenium, ascorbic acid, etc.

To improve the radioresistance of the body, the principles of nutrient use in the diet have been developed.

№	Principles	Nutrients
1.	Reduction of the dose of internal exposure and the entry into the body of other contaminants, which may cause additive effect.	Use of environmentally friendly raw materials and products
2.	Reducing the absorption of radionuclides.	Enrichment of the diet: nonspecific enterosorbents (dietary fiber);
3.	Acceleration of excretion of cesium-137 and strontium -90.	specific antagonists of cesium-137 and strontium-90 (potassium, calcium, ferrocin);
4.	Increase in the antioxidant status of the	tocopherol, selenium, bioflavo-

	body.	noids.
5.	Restoration of the plasticity of membranes.	retinol, beta-carotene, lecithin.
6.	Stimulation of blood.	Microelements (iron, zinc, cobalt).
7.	Increased immunological reactivity.	Retinol, protein.

The results of numerous experimental studies indicate that the state of nutrition has a modifying effect on the development of the body's reactions to long-term internal irradiation with small doses. This effect is realized by reducing the dose of internal radiation to the action of radiation.

CONCLUSION

New period in radiobiological research focuses on challenges arisen from radio ecological crises, demands new approaches in developing methods and techniques for chemical protection against ionizing radiation. Extensive research of Radio protective agents except of pharmaceutical radioprotectors, is aiming at the investigation of protective properties of natural food, study of adaptogens, capable of reducing or preventing the effects of chronic low-intensity irradiation combined with other extreme natural and man-made factors. Much attention is also paid to the research of the substances to remove radionuclides from the body.

At present, in Ukraine the project of the National concept of curative and preventive nutrition has been developed. The domestic industrial production of special foodstuff (food, beverages, confectionery with therapeutic and prophylactic properties) is expanding. This foodstuff is planned to be produced according to the state order and with following targeted distribution (school and preschool settings, orphanages, boarding schools for children and disabled people). The Institute of Experimental Radiology of the Scientific Centre of Radiation Medicine, the National Academy of Medical Sciences of Ukraine, founded from the moment of the Chornobyl nuclear power disaster, is searching, developing and testing therapeutic and prophylactic agents for the prevention and protection of population against the radiation.

Particular attention is paid to adaptogenic types of natural origin, which are non-toxic and suitable for long-term use. These products are the source of the most nutritious food and regulatory substances essential for a human body. They are manufactured in the form of tablets, powders, dragees, balms, infusions. Biologically active supplements contain complexes of biologically active substances, macro- and trace elements, alginates, pectins, essential amino acids, vitamins, carotenoids, anthocyanins, flavonoids, glycosides, sanonins that contribute to reduce or remove radionuclides from the body, improve metabolic processes, and stimulate the digestive tract functioning. These substances also normalize the functioning of

the endocrine and nervous systems, increase the adaptive capabilities of the body in conditions of irradiation aggravated with other unfavourable environmental factors.

The Institute has developed and tested beverages "Vidrodzhdennia", balm "Monomakh", "Crimean", "Black coral", oils from seeds of dill weed, pumpkins and watermelons, wheat germs; fiber, multivitamin pectin tablets, spirulina, meat and caviar of slug Ampoules, quail eggs, sauces prepared from pumpkins with various vegetable and fruit additives; tincture of birch mushroom "Chama", lyophilized powders of calendula, nettle, chokeberry, waffle "Rowan tree branch" containing lyophilized powder of chokeberry; food solution of beta-carotene from carrots in oil "Carotele" and the recipe of dishes (more than 50 recipes) with "Carotele"; "Elamin" produced from brown seaweed and food with "Elamin" including more than 20 names: bakery products, mayonnaise, pasta and meat products, as well as many other nutritious and useful products; developed recipes for dishes (over 100 recipes) with "Elamin" for therapeutic and preventive purposes as well as for introducing into public catering.

Food, beverages and food additives possessing appreciable radioprotective, antioxidant and adaptogenic properties are in the centre of numerous researches and having shown their effectiveness are recommended as a preventive measure for people who work in harmful and difficult working conditions, or experience nervous overstrain; also for residents, especially children who live in radiation-polluted and ecologically unfavourable areas. They promote the removal of radio nuclides and other toxic substances from the body, provide the body with the necessary vitamins, trace and macro elements, biologically active substances, as well as normalize the hormonal state and strengthen the nervous and immune systems, that is, contribute to the maintaining body homeostasis.

APPENDIXES

1. RADIOPROTECTORS COMMONLY USED IN RADIOTHERAPY

BATYLOLUM

Synonymic name: Batyl alcohol.

Pharmacological effect. Stimulates erythro- and leukopoiesis (formation of erythrocytes and leukocytes). It inhibits a decrease in the number of leukocytes (white blood cells) and a decrease in the level of haemoglobin (a red protein responsible for transporting oxygen in the blood) under radiation exposure and promotes rapid recovery. It has little toxicity. **Indications**: to prevent and treat radiation sickness during X-ray therapy and radiotherapy.

Dosage and Administration.

An oral dose of 0.02 g is taken 30 min before meal twice a day from the beginning of radiation therapy to prevent, in radiation sickness it should be taken 3-4 times a day. The course of treatment lasts 4-6 weeks, periodic blood testing (1 every 7-10 days) is needed. Pediatric dosage is reduced according to the age. Side effects: not found. Contraindications: not found. Dosage form: Tablets of 0.02 g, 50 tablets / a blister pack.

Storage conditions. List B. Keep in dry and dark place.

DIETHON OINTMENT (Unguentum Diaethoni)

Pharmacological effect. Diethon in the form of 5% ointment possesses radioprotective properties. When applied onto the skin before irradiation, it increases its radioresistance and prevents or reduces the manifestation of radiation dermatitis (inflammation of the skin due to irradiation), eliminates edema, hyperaemia (redness), itching and burning of the skin, promotes its healing. The radioprotective effect of the drug is determined by its ability to prevent lipid peroxidation and stabilize membranes, as well as the ability to absorb free radicals.

Indications: applied for preventive and curative purposes to protect the skin of patients undergoing radiation therapy, or to protect the hand skin of personnel working with sources of ionizing radiation. The drug has low toxicity and does not cause irritation.

Dosage and Administration: as a preventive measure, a thin layer the ointment is applied onto the skin areas planned to be exposed to irradiation for 30-40 minutes before the irradiation session and in 1-2 hours after it. Then the ointment is applied 2-3 times daily for 5-10 days. For a therapeutic purpose it is applied 3 times daily for 10-20 days, depending on the severity of the lesion. Side effects. Some patients may experience individual during the first 30 minutes after the application that which quickly goes away and is not a contraindication to its use.

Dosage form. A tube of 30 g.

Storage conditions. Keep in a cool place.

"LIOXAZOLE" AEROSOL (Aerosolum "Lioxasolum")

Pharmacological effect. 2-Allyloxyethanol, an active agent of the drug, has the ability to prevent spasms of the skin vessels, to improve blood circulation and to enhance the reparation in the epithelium.

Indications. Applied for the prevention and treatment of acute local radiation damage of the skin of 1 and 2 degrees.

Dosage and Administration. Aerosol is sprayed with a thin layer (from a distance of 10-15 cm) to the affected areas of the skin. During radiotherapy it can be applied after each irradiation session (no later than 1 hour) during the entire course of treatment. For a therapeutic purpose, the drug is applied when the first signs of lesion (oedema, erythema / limited reddening of the skin, etc.) appear. Aerosol is sprayed daily for 10-20 days, depending on the severity of the lesion.

Side effect. In cases of skin allergic reactions discontinue treatment; antihistamines may be prescribed.

Dosage form. Aerosol system.

Storage conditions. Keep at temperatures up to + 35°C; avoid heating and direct sun lights.

MARINYL QU 10 (Marinil Q1O)

Pharmachologic effect. A medicine that protects the skin from the irritating effects of radiation. It also has immuno stimulating (enhancing protective forces of the body) and antioxidant (protecting the body from the effects of aggressive forms of oxygen) properties.

Indications. Radiation dermatitis (inflammation of the skin due to irradiation), weakening of immune processes.

Dosage and Administration. When there are no other prescriptions, 1 capsule is taken twice a day. Ointment is applied on the affected skin 1-2 times a day.

Dosage form: Ointment in a tube of 100 ml; 30 capsules are in a plastic tube.

Storage conditions. Keep in dry cool, place protected from the light.

SAMIN (Mexaminum)

Pharmacological effect. An important property of mexamine is its radioprotective activity. Under the experimental conditions, it lowers the mortality of animals exposed to X-ray or gamma irradiation, as well as to high-energy proton irradiation. The mechanism of radioprotective action can be explained by the hypoxia caused by the medicine in the "critical" body organs (bone marrow, spleen, etc.). This effect is due to the narrowing of the blood vessels in these organs. Taking mexamine by the patients who underwent X-ray therapy for malignant neoplasms before the therapy reduces the manifestations of radiation reaction.

Indications. Applied for the prevention of general radiation reaction during radiation therapy.

Dosage and Administration. 0.05 g (1 tablet) is taken per os 30-40 minutes before each session of radiotherapy. In good tolerability, the dose can be increased to 0.1 g.

Side effect. The drug is usually well tolerated. In some cases, mild nausea, dizziness, pain in the epigastric region, rarely vomiting is observed. Adverse events may be relieved with caffeine. If the tolerance is poor, further administration of the drug is stopped.

Contraindications. Contraindicated in the marked sclerosis of the vessels of the heart and brain, cardiovascular insufficiency (deterioration of the blood supply of organs and tissues due to lowering the pumping function of the heart), bronchial asthma, kidney disease with the impairment of their functioning, during pregnancy.
Dosage form. Coated tablets of 0.05 g (50 mg),.

Storage conditions. List B. In vials of dark glass in dry place protected from the light.

METHYLURACILE (Methyluracilum)

Synonyms: Metacil.

Pharmacological effect. Promotes the processes of cellular regeneration (recovery); enhances the wound healing, stimulates cellular and humoral (tissue) factors of protection. It also has an anti-inflammatory effect. A key characteristic of the drug is the stimulation of erythro- and especially leukopoiesis (the process of formation of erythrocytes and especially leukocytes); therefore it is usually referred to the group of leukopoiesis stimulants.

Indications. As a stimulant of leukopoiesis, methyluracil is prescribed in X-ray and radiotherapy and other conditions accompanied by leukopenia (a decrease in the level of leukocytes in the blood).

Dosage and Administration. Methyluracil is taken per os during or after meal. Adult patients are to take 0.5 g 4 times per day (if necessary, up to 6 times a day); children aged from 3 to 8 years are prescribed to take 0.25 g, over 8 years - 0.25-0.5 g 3 times a day. The course of treatment of the diseases of the gastrointes-

tinal tract lasts usually 30-40 days; in other cases it can be less prolonged. For local injuries (skin lesions, rectum / inflammation of the rectum /, sigmoiditis / inflammation of the sigmoid colon, etc.), arising from radiation therapy, is prescribed per orally and topically. Topical application of 10% methyluracil ointmen in prescribed to heal wounds, burns, trophic ulcers (long-lasting non-healing skin defects). To treat proctitis, sigmoiditis, ulcerative colitis (inflammation of the colon with the formation of ulcers) suppositories containing methyluracil (1-4 suppositories per day for adults) are used. Microclysters (0.2-0.4 g of methyluracil on a starch paste in a volume of 20-25 ml) can also be used.

Side effect. Methyluracil is usually well tolerated; when suppositories are introduced into the rectum, slight burning sensation may develop. In rare cases allergic skin reactions (urticaria rash / skin rashes /), sometimes headache, dizziness may develop.

Contraindications. The drug is contraindicated in acute and chronic leukaemia, lymphogranulomatosis (malignant disease of lymphoid tissue), and malignant diseases of bone marrow. Dosage form: Powder; Tablets of 0.5 g, 50 in a blister pack; Suppositories with 0.5 g of methyluracil, 10 suppositories in a pack; Ointment with methyluracil 10% in an aluminum tube, 25 g.

Storage conditions. Keep in dry, dark place at room temperature.

PENTACIN (Pentacinum)

Synonyms: Calcium trisodium penetate, Pentamyl.

Pharmacological effect. Refers to complexing compounds.

Indications. Applied in acute and chronic poisoning with plutonium, radioactive sodium, cesium, zinc, lead, and a mixture of uranium fission products, as well as to determine the carriage of these radioisotopes. It has no significant effect on the excretion of uranium, polonium, radium, radioactive strontium, and lead. The drug does not affect the content of calcium and potassium in the blood.

Dosage and administration. Apply intravenously in the form of a 5% aqueous solution. A single dose is 0.25 g of the preparation (5 ml of a 5% solu-

tion). In acute cases, a single dose can be increased up to 1.5 g (30 ml of a 5% solution). Introduce by slow intravenous injection or infusion, observing the state of the cardiovascular system. Injections are given in 1-2 days; the course consists of 10-20 injections. With long-term use of pentacin, its effectiveness with regard to excretion of radioactive isotopes is observed to reduce; after discontinuation of the drug, its effectiveness gradually renews. In this regard, the treatment is carried out by separate courses with intervals of 3-4 months between them. In acute conditions of lead intoxication (lead colic / lead poisoning), 1-2 g (20-40 ml of a 5% solution) are administered intravenously.

To detect carriage of radioactive isotopes and lead, pentacin is administered for 3 consecutive days in therapeutic doses, the isotope and lead content in urine is examined. A preliminary control test is carried out. During the therapy with pentacin, a urinalysis should be done at least once a week to determine the excretion of radioactive isotopes with urine. To avoid damage to the kidneys and electrolyte imbalances (balance of the ionic composition), it is important to maintain a time interval between the courses of treatment with pentacin.

Side effect. In rare cases, dizziness, headache, pain in the extremities and in the chest area. These manifestations usually go away by themselves. In case of nausea and vomiting, reduce the dose or discontinue treatment. When signs of impaired coronary circulation appear, discontinue treatment.

Contraindications. Pentacin is contraindicated in feverish conditions (a sharp increase in body temperature), lesions of the parenchyma (functional elements) of the kidneys, hypertension (persistent increase in blood pressure) with impaired renal function, and also in patients with spasms (periodic sharp narrowing of the lumen) of the heart vessels.

Dosage form. 5% solution in ampoules of 5 ml, 10 / a pack.

Storage conditions. Keep in cool and dark place.

TESANAPINIMENT (Unimentum Thesani)

Synonym: Emulsion of the thesan.

Pharmacologic effect. The drug has bactericidal (killing bacteria), antiseptic (disinfecting) effects. It stimulates regenerative (restorative) tissue processes.

Indications. Applied for the prevention and treatment of skin lesions with radiation therapy, ulcers, pressure sores, and burns. With the preventive purpose, an emulsion (a liquid dosage form, which is an externally homogeneous system of two immiscible liquids), smears the irradiated surface of the skin after each X-ray therapy session.

Dosage and Administration. To treat the skin lesions that have already arisen, liniment is applied with a spatula on a thin layer to the affected area after each irradiation, covered with a gauze cloth, through which additional lubrication is performed - only 2-3 times a day. After the end of the course of radiotherapy, liniment continues to be applied for another 7-10 days. When treating ulcers, burns, etc. on the treated surface, apply a gauze cloth, abundantly lubricated with liniment. Napkins are changed in a day or less depending on the indications.

Side effect. Dryness and itching of the skin, dermatitis (skin inflammation).

Contraindications. Dermatitis, hypersensitivity to the drug.

Dosage form. In glass jars of 30 g.

Storage conditions. List B. Keep in a dry, cool, sheltered from the world place.

TRIMEPHACIN (Trimephacinum)

Pharmacological effect. Trimefacin is a complexing compound containing a diethylenetriamine pentamethylphosphonic acid hexahydrate. Enhances the excretion of uranium, beryllium, plutonium, yttrium, zirconium, and niobium with urine.

Indications. Applied for first aid in acute poisoning with uranium and beryllium, as well as in the secondary intake of beryllium to identify its carriage.

Dosage and Administration. Administered intravenously or by inhalation in the form of a 5% aqueous solution. To prepare the solution, into a vial containing 0.226 or 0.9 g of diethylenetriamine pentamethylphosphonic acid hexanoate, 5

or 20 ml of a 2.5% aqueous solution of CaCl2 is added. The suspension should be shaken (for 20-30 seconds) until a completely clear solution is obtained. In acute poisoning with uranium or beryllium, a single dose of 40 ml of the solution is injected intravenously, and in the next 2-3 days - 20 ml daily. When uranium and beryllium entered the respiratory tract and there are no signs of pulmonary edema, trimephacin is co-administered intravenously and in the form of inhalations. Aerosol therapy (aerosol / gas treatment or a mixture of gases in which solid or liquid particles of the drug substance are suspended) is carried out 1-2 times a day by ultrasonic aerosol generators. Duration of inhalation - 15-20 minutes, consumption of a solution of trimephacin for 1 inhalation - 15-20 ml. Duration of treatment - 2 - 4 weeks with 1-2-day intervals between weeks. In chronic pulmonary processes due to the deposition (accumulation) of beryllium, the treatment is carried out according to the same scheme. When using the drug, the functioning of the kidneys should be monitored.

Dosage form. Vials containing 0.226 g or 0.9 g of diethylenetriamine pentamethylphosphonic acid disodium salt (lyophilized), with an ampoule of 2.5% aqueous calcium chloride solution (5 or 20 ml respectively).

Storage conditions. Under normal conditions.

FERROCIN (Ferrocinum)

Pharmacological effect. Complexing compound.

Indications. Used to provide the first aid and subsequent treatment of intoxication (poisoning) with radioisotopes of cesium and rubidium, as well as uranium fission products containing these radioisotopes.

Dosage and administration. Taken per orally in the form of an aqueous suspension of 1 g (in half a cup of water) 2-3 times daily for 5-10 days. The drug is low-toxic (little harmful), not absorbed in the gastrointestinal tract.

Dosage form. Vials of 1 g.

Storage conditions. Keep under normal conditions.

CYSTAMINE DIHYDROCHLORIDE (Cystamini dihydrochloridum)

Synonyms: 2-Aminoethyl Dislufide Dihydrochloride, Cystamine.

Pharmacological effect. Cystamine belongs to the group of aminothiols. Aminothiols have a preventive radio protective effect in acute radiation sickness by increasing the body resistance to the action of ionizing radiation. The action of aminothiols is based on their ability to reduce the number of radicals, ionized and excited molecules formed in tissues under irradiation, as well as on the ability of these compounds to interact with certain enzymes and to impart stability to them in relation to radiant energy. The action of the aminothiols is more pronounced when administered within a short time (10-30 min) prior to irradiation. The protective effect after a single administration lasts about 5 hours.

Indications. Cystamine is used to prevent and reduce the manifestations of radiation sickness (general malaise, nausea, vomiting, etc.) that occur when using large doses of radiation for radio and X-ray therapy.

Dosage and Administration. Taken perorally in the form of tablets 1 hour before the irradiation session. The dose depends on the nature of the disease, the state of the hematopoietic system of the patient, and the radiation dose. Daily doses range from 0.2 to 0.8 g. The drug is used during the entire course of radiation therapy. At the same time, patients should receive general restorative therapy.

The use of cystamine in advanced radiation sickness (with pronounced leucopenia) has no therapeutic effect. The drug does not prevent the development of leukopenia. With a significant decrease in the number of leukocytes (blood cells) in the blood during the period of irradiation and the need to continue treatment, it is possible to use cystamine in combination with stimulants of leukopoiesis (the process of formation of leukocytes); when necessary, blood transfusion is recommended.

Side effects. After taking cystamine in some cases, burning in the esophagus, nausea, stomachache may develop; these manifestations usually do not serve as an obstacle to continue the therapy. It should be taken into account that the drug has an antihypertensive effect; in cases of essential hypertension (persistent in-

crease in blood pressure), a significant decrease in blood pressure may be observed.

Contraindications. Relative contraindications to cystamine dihydrochloride include acute diseases of the gastrointestinal tract, acute failure of the cardiovascular system (impairment of blood supply to organs and tissues due to decreased pumping function of the heart), impaired liver functioning. **Dosage form**. Tablets of 0.2 and 0.4 g.

Storage conditions. List B. In dry, sheltered from the world place.

ESTRODIOL DIPROPIONATE (Oestradioli dipropionas)

Pharmacological effect. Steroidal hormone.

Indications. Estradiol dipropionate is used as a hemostimulating (stimulating hemopoiesis) means in men with acute radiation damage. The drug increases the number of leukocytes (neutrophils) and promotes the regeneration of their number in the course of myelodepression (oppression of the hematopoietic function of the bone marrow) associated with radiation damage.

Dosage and administration. As a gastrointestinal agent, estradiol dipropionate is used when the number of leukocytes is lower than 2000 in 1 μl of blood (usually in 10-20 days after irradiation with severe lesions and from 15^{th} - 18^{th} day with milder lesions). 1 ml of 0.1% solution is administered every 1-2 days. The course consists of 10 injections (if necessary - up to 15 injections).

Dosage form. 0.1% (1 mg) oil solution in 1 ml ampoules.

Storage conditions. Keep in a cool, dark place.

2. ESSENTIAL MEDICINES AND NUTRITIONAL SUPPLEMENTS, POSSESSING RADIOPROTECTIVE, ANTIOXIDANT AND ADAPTOGENIC PROPERTIES

Name	Composition
Rutin (birutan, rutozide)	Flavonoid
Quercetin (flavin, quercetol) tab. 0.02	3,4,7,3,4-pentahydroxyflavone
Ascorutin (table 0.05 + 0.05)	Ascorbic acid, rutozide
Revit (dragees)	Carotene, ascorbic acid, B1, B2
Aevit (capsules 100,000 IU + 100 mg)	Retinol palmitate, Tocopherol acetate
Undevit (dragees)	Retinol acetate, thiamine bromide, riboflavin, pyridoxine hydrochloride, cyanocobalamin, ascorbic acid, tocopherol acetate, nicotinamide, rutin, folic acid, calcium pantothenate
Decamewith (dragee)	Retinol acetate, tocopherol acetate, thiamine bromide, folic acid, riboflavin, pyridoxine hydrochloride, rutin, methionine
Tri-vi-plus (Table)	D-carotene, tocopherol, ascorbic acid, zinc oxide, selenium, copper
Flamikar	The preparation of mountain ash ordinary
Polifitol - 1	Grassy wormwood grass, corn stigmas |, oak bark, rhizome root of a carrot | Erect, leaves peppermint | pepper |, St. John's wort, sugar and 40% ethyl alcohol
Extract Ginkgo biloba (tanakan, memo, bilobil, etc.) caps. 0.04	Ginkgo biloba leaf extract
Extract of Echinacea (immunal, Echinacea compositum)	Polysaccharides, biflavonoids, echinaposide, Zn, Se o
Ceruloplasmin pore 0.0 ll. № 5, pores. 0.1 ampoules. №10	Ceruloplasmin
Ionol (dibunol) - 10% liniment	Dibunol (2,6-Di-t-butyl-4-methylphenol)

Thiatriazolin	Tiatrizolin
Emoxipine (amp 1% - 1 ml)	Emoxipine
Fruit thistle spotted	Flavonoids
Legalon (karsil, silymarin)	Silymarin
Silibor	Silibinin
Gepabene (capsule 0.275 + 0.05 No. 30 No. 100)	Extract of a medicinal smoking lime, fumarin, a thistle syrup extract, silymarin, silibinin
Polyphepane	Modified natural natural Lignin
Flacarbine	Complex of flavonoids from the root and rhizome of licorice
Flamin	The sum of flavons Immortelle sand
□-tocopherol (capsule 0,1, capsule 0,2)	□-tocopherol acetate
Retinol (Table 33000 MO, capsule 0.86% - 2 ml)	Retinol acetate
Ascorbic acid (Tables 0.25, 0.5, rn 5%, amp 1 ml, 2 ml, 5 ml 10% amp 1 ml)	Ascorbic acid
Nicotinic acid (Table 0.05, amp. 1% - 1 ml)	Pyridinecarboxylic acid - 3 acid
BAD "Phytosorbin"	Great plantain leaves, dandelion roots, licorice root, naked, sea kale, dried carrots
Elerosbin	Eleutherococcus spiny
Diosorbin	Diascoria Japanese
Lyosorbin	Chinese magnolia seed
Pectin supplements: apple apple, vitapekt, pectolact, medopect	Pectin
Ginseng (tincture in a 50 ml bottle)	Glycosidi-panaxosidides A, B; Panaxylon, panaxin, saponins, essential oils

Rhodiola rosea (extract liquid, 30 ml)	Salidroside, tyrosol, phenol-alcohols, flavonoids, tannins
Eleutherococcus (extract liquid, 50 ml)	Coumarin derivatives
Leuzea (extract liquid 40 ml) 7	Essential oils, resins, salts of organic acids

Recommendations for persons receiving radiotherapy

1. Rational balanced nutrition (meat, fish, cheese, dairy products)
2. Daily stool
3. Decoctions of laxative herbs, prunes, dried apricots, raisins, figs, persimmons
4. Plenty drinking (mineral water, compote of dried fruits, fruit drinks). Sweet soda drinks ("Fanta") should be excluded.
5. Juices with coloring pigments (grape, tomato, pomegranate, pumpkin)
6. Juice of beets, carrots, red wine ("Cabernet" 50.0 ml per day)
7. 4 - 5 walnuts daily
8. Grated black radish (to grate in the morning – to eat in the evening)
9. Horseradish, garlic
10. Buckwheat, oatmeal, millet
11. Ascorutin (3 times a day)
12. Activated charcoal (1 - 2 tablets before meals)
13. Pectolact (3 tablets per day), or 3 apples daily
14. Ground seeds of milk thistle spotted (1 teaspoonful 3 times a day 40 minutes before meals - plenty of mineral water)
15. Laminaria (sea kale) p) (every day 2 teaspoons in any form (dry, canned, pickled)

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GLOSSARY

Activity - the quantity of a radionuclide; defined as the number of spontaneous nuclear transformations from the given energy state per second.

Alpha decay - the radioactive decay process resulting in emission of alpha particles (two protons bound to two neutrons, a charge of +2, mass 4) and turning into the nucleus of another, "daughter", element, which decays in Periodic Table of the Elements by 2 positions left, i.e. its charge is lower by 2 units than in the "parent" nucleus.

Apoptosis - a process of programmed cell elimination that occurs through the events leading to characteristic cell changes and death. These changes include cell fragmentation into "apoptosis corpuscles" that are then engulfed by phagocytes and neighbouring cells.

Becquerel (Bq) – the SI unit of radioactivity, corresponding to one nucleus disintegration per second.

Beta decay – the radioactive decay of an unstable atomic nucleus accompanying the emission of either a beta-particle (electron or proton), or additionally gamma-quantum as well.

Internal radiation exposure – results from radioactive material that gets inside the body (when you breathe it or eat it) and usually is accompanied by passing the same radioactive material through the skin.

High doses of radiation exposure – doses exceeding the level at which the most of biological events deviate from the linear dose dependence. The conventional border value between low and high doses is more than 1 Sv / h (USA, 2013)

Gamma radiation (ray) – a form of electromagnetic radiation, when photons of nuclear origin result from the radioactive decay of nuclei of unstable nuclides. Usually photons of gamma radiation are characterized b sufficiently high energy, ranging from tens of kilo electron-volts and more.

Gray (Gy) – the SI unit of the absorbed dose of ionizing radiation, corresponding to one joule per kilogram.

Irradiation dose – the quantity of energy transmitted to a unit of substance mass by irradiation beam.

Law of radioactive decay - the likely regularity of nucleus decay of unstable nuclides that consists in a given radioactive substance decreases in the course of time.

Closed sources of radiation - sources of ionizing radiation of different types depending on the radionuclides used, goals, radiation intensity, size of the radiation-generating machine, structure and physico-chemical characteristics of a radionuclide insulated within the enclosure.

Sievert (Sv) – the SI unit of dose equivalent (the biological effect of ionizing radiation), equal to an effective dose of a joule of energy per kilogram of recipient mass.

Earth's crust radiation – mostly consists of gamma-rays of the main contributors as natural deposits of uranium-235, uranium-238, thorium-232 and the by-products of their natural decay as radium-226, radium-224, and rubidium-87.

Isotopes - atoms that have the same number of protons and electrons but different numbers of neutrons and therefore have different physical properties.

X-rays (x-radiation, roentgen radiation) an electromagnetic wave of high energy and very short wavelength (between ultraviolet light and gamma rays), which is able to pass through many materials opaque to light. In the field of atoms of the environment, electrons brake, their kinetic energy is emitted as photons that is known as 'braking radiation'.

Ionizing radiation - radiation consisting of particles, X-rays, or gamma rays with sufficient energy to cause ionization in the medium through which it passes

Radioactivity decay constant - proportionality between the size of a population of radioactive atoms and the rate at which the population decreases because of radioactive decay.

Artificial radioactivity - the radioactivity of radionuclides obtained artificially.

Constant collapse - relative nuclei of radionuclide decays per unit time.

Curie (Ci) – a unit of radioactivity, corresponding to 3.7 × 10 10 disintegrations per second.

Latent period - the period between exposure to radiation and the appearance of signs of radiation damage

Lethal effects of radiation, or **cell death** – the loss of cells ability to proliferate and form many generations. This is actually the reproductive cell death that is the most common form of radiation cell inactivation.

Luminescent dosimeter (scintillation counter) - an instrument for detecting and measuring ionizing radiation; it it consists of a scintillator, which generates photons in response to incident radiation, a sensitive photomultiplier tube (PMT), which converts the light to an electrical signal and electronics to process this signal.

International organization (**intergovernmental organization**) - an international intergovernmental organization, including specialized agencies and organizations of the United Nations, as well as programs, departments and offices of the United Nations; does not involve non-governmental organizations.

Minimum lethal dose of radiation - the dose of radiation expected to cause death to 1 – 5% of an exposed population. Typically, the LD is 1,5 Gy of total external total photon irradiation. This means that such levels of exposure can cause only a few deaths of exposed individuals if they are not given medical care.

Mitosis (M) – a type of cell division that results in two daughter cells each having the same number and kind of chromosomes as the parent nucleus, typical of ordinary tissue growth.

Change in radiosensitivity - the weakening or strengthening of the radiosensitivity of cells, tissues, or whole body due to chemical or physical factors.

Neutron (n) - a subatomic particle of about the same mass as a proton but without an electric charge, present in all atomic nuclei except those of ordinary hydrogen (rest mass 940 MeV/c 2).

Indirect biological effect II - the transmission of own energy by X-rays, gamma rays, charged and uncharged particles of water molecules of tissue,

followed by radiolysis of water molecules to form oxidative radicals that become damaging are factors of cells macromolecules.

Nuclide - a distinct kind of atom or nucleus characterized by a specific number of protons and neutrons (synonymic to isotope).

Nucleon – the general name for one of the elementary particle, the proton and the neutron, which are the constituents of the atomic nucleus.

Acute radiation syndrome (ARS), also known as **radiation toxicity** or **radiation sickness** - a collection of specific clinical signs, which appear consecutively after total external even ionizing radiation exposure due to the accumulation of pathological changes in the tissues, organs and systems of the body of the victim.

Half-life (T1/2) – the time taken for the radioactivity of a specified isotope to fall to half its original value.

Absorbed dose - the quantity of the energy absorbed from ionizing radiation per unit mass.

Positron (e+) – a subatomic particle, the antimatter counterpart of the electron, has an electric charge of +1, rest mass 511 MeV/c 2. In fact, this is a mirror to the electron particle, which comes paired with an electron when braking a photon with energy of not less than 1.022 MeV, because the mass of each of these particles is 511 MeV. In addition, positrons can be of nuclear origin.

Natural background radiation (NBR) - is a constant source of ionizing radiation present in the environment and emitted from a variety of sources, e. g. cosmic radiation, Earth's crust radiation, natural radionuclides from the food we eat, the air we breathe and the water we drink.

Proton (p) - a stable subatomic particle (nucleon) occurring in all atomic nuclei, with a positive electric charge +1 and rest mass 938 MeV.

Rad - a unit of absorbed dose of ionizing radiation, corresponding to the absorption of 0.01 joule per kilogram of absorbing material.

Radioactivity – disintegration of the nuclei of certain elements, with the emission of energy in the form of alpha, beta, or gamma rays.

Radiation safety – enforcement of mandatory requirements and promotion of safety measures providing the protection of people and their descendants from possible adverse effects of ionizing radiation.

Radiation protection - a collection of legal, medical, technical and organizational measures to ensure radiation safety.

Radioisotope (radionuclide) - an isotope (nuclide) of an element with n unstable nucleus that emits alpha, beta, or gamma radiation during its decay into another element.

Radiometry - a set of techniques for measuring electromagnetic radiation

Radioprotector – a substance when administered into the body prior the radiation exposure provides some protection against the harmful effects of ionizing radiation.

Radiosensitizory - a chemical compound that can enhance the sensitivity of the biological object to ionizing radiation.

Radiosensitization - the relative susceptibility of cells, tissues, organs or organisms to the injurious action of ionizing radiation.

Radioactive toxins – resulted from the radiolysis of water and hydrogen peroxide H2O2 and radical HO, products of oxidation of unsaturated fatty acids and phenols (lipid and chionic radioactive toxins).

Radioactive toxins inhibit the synthesis of nucleic acids, affecting DNA molecule as chemical mutagens, change the activity of enzymes, react with lipid-protein intracellular membranes.

Radiotoxicity - the toxicity of radionuclides, usually caused not by their chemical, but physical properties as the ability to irradiate cells during radioactive decay.

Radiosensitivity - the relative sensitivity of the biological object to the harmful effects of ionizing radiation.

Roentgen (R) – a unit of ionizing radiation, the amount producing one electrostatic unit of positive or negative ionic charge in one cubic centimetre of air under standard conditions.

Chromosomal aberrations – structural damages of DNA due to ionizing radiation that are the leading cause of reproductive cell death.

Chronic radiation sickness – results from long-term (months, years) systematic external, internal or combined exposure to relatively low radiation doses, but significantly higher (in 10-15 times) than the specified dose limits.

Electron – a stable subatomic particle with a charge of negative electricity (-1) and rest mass 511 MeV, found in all atoms and acting as the primary carrier of electricity in solids. Electrons can also be of nuclear origin, they are produced during the radioactive decay of nuclei in unstable nuclides by converting one of the neutrons in the nucleus into proton and electrons. The electrons of such origin ae called beta particles.