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# TECHNICAL REPORT

## **Experiments on the Biological Action of Neutrons Performed in the Former Soviet Union: A Historical Review**

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October 2006

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# CONVERSION TABLE

Conversion Factors for U.S. Customary to metric (SI) units of measurement.

MULTIPLY  $\xrightarrow{\hspace{1.5cm}}$  BY  $\xrightarrow{\hspace{1.5cm}}$  TO GET  
 TO GET  $\xleftarrow{\hspace{1.5cm}}$  BY  $\xleftarrow{\hspace{1.5cm}}$  DIVIDE

|                                                  |                                   |                                                    |
|--------------------------------------------------|-----------------------------------|----------------------------------------------------|
| angstrom                                         | 1.000 000 x E -10                 | meters (m)                                         |
| atmosphere (normal)                              | 1.013 25 x E +2                   | kilo pascal (kPa)                                  |
| bar                                              | 1.000 000 x E +2                  | kilo pascal (kPa)                                  |
| barn                                             | 1.000 000 x E -28                 | meter <sup>2</sup> (m <sup>2</sup> )               |
| British thermal unit (thermochemical)            | 1.054 350 x E +3                  | joule (J)                                          |
| calorie (thermochemical)                         | 4.184 000                         | joule (J)                                          |
| cal (thermochemical/cm <sup>2</sup> )            | 4.184 000 x E -2                  | mega joule/m <sup>2</sup> (MJ/m <sup>2</sup> )     |
| curie                                            | 3.700 000 x E +1                  | *giga bacquerel (GBq)                              |
| degree (angle)                                   | 1.745 329 x E -2                  | radian (rad)                                       |
| degree Fahrenheit                                | $t_x = (t^{\circ}f + 459.67)/1.8$ | degree kelvin (K)                                  |
| electron volt                                    | 1.602 19 x E -19                  | joule (J)                                          |
| erg                                              | 1.000 000 x E -7                  | joule (J)                                          |
| erg/second                                       | 1.000 000 x E -7                  | watt (W)                                           |
| foot                                             | 3.048 000 x E -1                  | meter (m)                                          |
| foot-pound-force                                 | 1.355 818                         | joule (J)                                          |
| gallon (U.S. liquid)                             | 3.785 412 x E -3                  | meter <sup>3</sup> (m <sup>3</sup> )               |
| inch                                             | 2.540 000 x E -2                  | meter (m)                                          |
| jerk                                             | 1.000 000 x E +9                  | joule (J)                                          |
| joule/kilogram (J/kg) radiation dose absorbed    | 1.000 000                         | Gray (Gy)                                          |
| kilotons                                         | 4.183                             | terajoules                                         |
| kip (1000 lbf)                                   | 4.448 222 x E +3                  | newton (N)                                         |
| kip/inch <sup>2</sup> (ksi)                      | 6.894 757 x E +3                  | kilo pascal (kPa)                                  |
| ktap                                             | 1.000 000 x E +2                  | newton-second/m <sup>2</sup> (N-s/m <sup>2</sup> ) |
| micron                                           | 1.000 000 x E -6                  | meter (m)                                          |
| mil                                              | 2.540 000 x E -5                  | meter (m)                                          |
| mile (international)                             | 1.609 344 x E +3                  | meter (m)                                          |
| ounce                                            | 2.834 952 x E -2                  | kilogram (kg)                                      |
| pound-force (lbs avoirdupois)                    | 4.448 222                         | newton (N)                                         |
| pound-force inch                                 | 1.129 848 x E -1                  | newton-meter (N-m)                                 |
| pound-force/inch                                 | 1.751 268 x E +2                  | newton/meter (N/m)                                 |
| pound-force/foot <sup>2</sup>                    | 4.788 026 x E -2                  | kilo pascal (kPa)                                  |
| pound-force/inch <sup>2</sup> (psi)              | 6.894 757                         | kilo pascal (kPa)                                  |
| pound-mass (lbm avoirdupois)                     | 4.535 924 x E -1                  | kilogram (kg)                                      |
| pound-mass-foot <sup>2</sup> (moment of inertia) | 4.214 011 x E -2                  | kilogram-meter <sup>2</sup> (kg-m <sup>2</sup> )   |
| pound-mass/foot <sup>3</sup>                     | 1.601 846 x E +1                  | kilogram-meter <sup>3</sup> (kg/m <sup>3</sup> )   |
| rad (radiation dose absorbed)                    | 1.000 000 x E -2                  | **Gray (Gy)                                        |
| roentgen                                         | 2.579 760 x E -4                  | coulomb/kilogram (C/kg)                            |
| shake                                            | 1.000 000 x E -8                  | second (s)                                         |
| slug                                             | 1.459 390 x E +1                  | kilogram (kg)                                      |
| torr (mm Hg, 0° C)                               | 1.333 22 x E -1                   | kilo pascal (kPa)                                  |

\*The bacquerel (Bq) is the SI unit of radioactivity; 1 Bq = 1 event/s.

\*\*The Gray (GY) is the SI unit of absorbed radiation.

## Summary

Data on the research of neutron biological effects in the USSR, the organization of this research, and the main results are presented in this review. Particular attention is paid to data that are important for analysis of the underlying mechanisms of the biological effect of neutrons and their dissimilarity from mechanisms of photon effect. Particular emphasis has been placed on elaboration of new methods of recognition and prediction of neutron damage to an organism. Efficacy of chemical protection of an organism against neutron effect is established. These results supplemented essential knowledge on neutron effects by original data that are important for the theory and practice of neutron radiobiology and medicine.

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## Introduction

Within two to three months of Wilhelm Konrad Roentgen's discovery of x-rays the first radiation injury, dermatitis of the hand, had already occurred. The diagnostic potentials of ionizing radiation were realized almost immediately, and within four years radiation was being used to treat cancer, tuberculosis, and a variety of inflammatory conditions. With discoveries in atomic physics and the eventual ability to project a beam of neutrons onto a biological target, the logical extension was that the biological effects of neutrons be studied and compared with photons and electrons. This research was begun in the 1930's in the USA, and after WWII was continued in several other Western countries.

The major impetus for neutron radiobiology was provided primarily by the atomic weapons program, and Western scientists studied neutron effects on affected populations and conducted occupational health studies of workers in the weapons program (as well as workers with reactors, both military and civilian). Of course, with the development of the USSR weapons program, that country began its own neutron radiobiology program. A second stimulus for neutron radiobiology research, in both the West and the USSR, was the neutron contribution to total dose in spacecraft or high flying aircraft. (Production of neutron secondaries, primarily by high energy protons, is high at the altitudes used by strategic reconnaissance aircraft, though this was not recognized initially.) Though many of the results of Western investigators were confirmed by Soviet scientists (and vice versa), exchange of this scientific information was not widespread at all, for obvious reasons.

As one might expect, many of the findings of one group of researchers (Western or Soviet) were confirmed, intentionally or not, by scientists in the other group. For example, both realized that the relative biological effectiveness (RBE) of neutrons, using either cobalt gammas or 250 kVp x-rays as the reference radiation, depended significantly on the particular biological end point evaluated. (N.B. In this document, whenever experiments involving x-rays are mentioned, although the mean energy varied, it was generally 200 kVp [180-220 kVp].) In general, as the average neutron energy increased above 0.5-1.0 MeV, the RBE decreased. The "inverse dose rate" effect or "enhancement" was demonstrated by Western and USSR researchers (i.e., fractionating a given dose of radiation, or of lowering the dose rate and increasing the delivery time of the radiation, will increase a given biological effect of neutrons while decreasing it for photons). It was further noted that in intact animal models there was a very high hazard level for cancers, mutations and cataracts with neutrons. As a general rule, both groups noted that, at a given dose, the effect was greater for neutron radiation, injury occurred earlier, and repair of injuries was almost universally slower after neutron injury vs. photon.

This report documents some interesting findings with large animal models. Western doctrine has been that fission neutrons essentially have an RBE of near unity, owing to the falloff of absorbed dose as the depth of penetration increases. USSR studies cited in this report showed that, as Western researchers found also, that the RBE for intestinal cell damage for fission neutrons in mice is about four, though this is age-dependent. With dogs the RBE for intestinal

cell damage is 1.8-2.4. The LD<sub>99/30</sub> using 0.85 MeV neutrons drops from 2.8 in mice to only 1.2 in dogs (with uniform whole-body irradiation). The LD<sub>50/30</sub> for 14 MeV neutrons for mice decreases to 1.9, and with 22 MeV neutrons to 1.3. The authors hypothesized that as size increases, intestinal injury (where RBE is definitely elevated, in their studies, in both rodents and large animals), plays a smaller role relative to hematopoietic injury. Also, phantom data showed that damage of critical organs in large animals is mediated primarily by secondary photon production, which, in the author's opinion, means that, in principle, chemoprotection can be of value in neutron exposure as well as gamma exposure.

In some cases USSR investigators expended greater resources in selected areas of radiobiology than their Western counterparts. As the authors state, "In many instances they [USSR researchers] expanded and made more profound the knowledge base and even permitted approaches to the solution of actual problems, as, for example, in the case of chemical protection against neutron radiation, or of the use of new methods of recognition or predicting the outcome of neutron injury." Efforts were focused on possible radioprotectors, despite initial studies in the US and Germany not being very encouraging. The authors' own institute, the Petersburg Nuclear Physics Institute (PNPI) took the lead because of the unique characteristics of their reactor and the broad areas of expertise represented among their staff. They found that much of neutron damage comes not only from especially dense direct ionization but also from elastic collisions; secondary  $\gamma$ -radiation is also an important component of exposure to neutrons. Accordingly, they theorized that classic radioprotectors, e.g. sulfur-containing compounds and compounds inducing a hypoxic-like effect, should be useful in preventing or ameliorating injury. (The authors have provided one previous paper on this subject through Defense Nuclear Agency and AFRRI sponsorship. A follow on study on toxicity of these compounds in a canine model has been completed and accepted but not yet published)

In summary, this report provides a valuable review of important data that were not previously readily accessible concerning studies on the biological effects of neutrons conducted in the former Soviet Union. As such, it merits careful reading by Western scientists interested in this field.

Grateful acknowledgment is given to Dr. Ramesh C. Bhatt for review and advice, particularly on the physics and dosimetry portions of this paper.

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## Section 1.0 The Basic Lines of Investigations and their Organization

Studies of the biological effects of neutrons were started in the United States of America (USA) in the middle of the 1930s soon after the discovery of these particles. This research attracted particular emphasis in the whole world (USA, Germany, Great Britain, Japan, the Netherlands) in the post-war period in connection with the creation of atomic weapons and the evolution of nuclear technique. This problem was intensively worked out in the Soviet Union as well; however, results of this research (except for three or four reports) were published only in Russian, in Ukrainian, and in Belorussian. Because of language barriers these results are practically unknown in the West, although they concern many fundamental aspects of neutron radiobiology and not infrequently contain data which are useful for solving theoretical and practical problems of this branch of science. The object of this review is to introduce Western scientists to the scientific results obtained in the Union of Soviet Socialist Republics (USSR).

The first reports on investigations of the radiobiological effects of neutrons in the USSR appeared in the late 1950s and early 1960s [21, 53, 63]. The researchers did not indicate the institutions where these investigations were performed. However, appearance of these works during the period mentioned above demonstrates that in the USSR the investigations of the biological action of neutrons were performed as early as the 1950s. It is not inconceivable that they were performed earlier. The first industrial reactor in the USSR had been commissioned in 1948 [2] and it is entirely possible that they used their own data for setting hygienic and safety standards and methods of personnel security together with calculated and requested foreign data. However the number of studies in this field was relatively few until the beginning of the 1960s and information on their work is extremely scanty.

The situation completely changed when fifteen Atomic Scientific Centers with various types of nuclear reactors were built up in the country. Studies of biological action of neutrons were performed in five of them almost instantaneously after starting the reactor. Among them are the Petersburg Nuclear Physics Institute (PNPI) of the Russian Academy of Sciences (RAS) (Gatchina), the Institute of Nuclear Research of the Ukrainian Academy of Sciences (Kiev), the Institute of Nuclear Energetics of the Belorussian Academy of Sciences (Minsk), the Atomic Center of the Research Institute of Nuclear Physics at the Tomsk Polytechnic Institute (Tomsk), and the Physical-Energy Institute (Obninsk). In the mid 1970s a sixth center - the Joint Institute of Nuclear Research (JINR) (Dubna) - was added to these five Institutes. There were accelerators as well as reactors in many Atomic Centers that generated a neutron beam by application of appropriate targets (tritium, deuterium, lithium). These installations have been in service for biological investigations.

In the majority of these scientific institutions biologists and physicians were not staff members of the Center. Only in the PNPI of the RAS, in 1962, was a staff of biologists, physicians, physicists, and chemists assembled for study of the action of neutrons on biological organisms. After fifteen years the JINR also went this way. At the other Atomic Centers biological studies using the nuclear installation were made by scientists from other biological and medical

institutes. For example, in Kiev these users were staff members of the Institute of Physiology of the Ukrainian Academy of Sciences, subsequently the Institute of Oncology Problems, as well as of the Institute of Microbiology of the Ukrainian Academy of Sciences. In the Institute of Nuclear Energy of the Belorussian Academy of Sciences (Minsk) the biological actions of neutrons were studied by staff members of the Institute of Physiology and the Institute of Genetics and Cytology of the Belorussian Academy of Sciences, the Belorussian University, and the Institute of Developmental Biology of the RAS. At the Physics-Energetic Institute and the Branch of the Research Physics-Chemical Institute (Obninsk) such studies were performed by staff members of the Institute of Medical Radiology (IMR) of the Russian Academy of the Medical Sciences (RAMS). Also in Tomsk, at the reactor of the Polytechnic Institute, biological investigations were performed by staff members of the Tomsk University, and so on.

At first there was no integrated national program devoted to the study of the biological effects of neutrons, and the above-mentioned institutions planned and carried out their research activities in a climate approaching isolation, on the basis of their understanding of the scientific challenges in this field. A review of the studies carried out shows, however, that the research and practical development matters they covered were indisputably very topical ones. Moreover, these research activities were performed in a coordinated way. This coordination was provided by the Nuclear Energy Committee and the Council on Radiobiology, both bodies set up within the Presidium of the Academy of Sciences. The Nuclear Energy Committee was headed at one time by Academician Alexandrov, then President of the Academy of Sciences.

In the years 1960 to 1988 the Commission held biannual coordination meetings (conferences) where the studies performed in the nuclear research reactors were reviewed. Such meetings were convened in rotation at the institutions based in such centers of nuclear research as Moscow, Leningrad, Kiev, Tashkent, Alma-Ata, Tbilisi etc. The meetings were held both in plenary sessions and in working groups, and it should be noted that the Working Group on biological questions (headed by Dr. A. Sverdlov) has been meeting regularly from the very outset of the Commission's activities. This Working Group normally reviewed the research information originating from the various nuclear research centers. One session would normally comprise some 30 papers and presentations. The outlook for further research activities and the coordination of the efforts of various academic institutions were also discussed. The concrete decisions aimed at the development of particular activities, improvement of the working environment, funding, etc., were normally made at the conclusion of such sessions. These decisions were obligatory for Directors of the Atomic Centers and for the heads of the research laboratories.

More specific scientific issues were also discussed and their development was coordinated at the level of the Life Science Research Commission set up within the Interdepartmental Research Council for Complex Problems "Radiobiologia". This Commission was comprised of biologists from all the nuclear centers or institutions specialized in biological research operating within these centers. It organized research conferences and symposia on such subjects as neutron dosimetry, neutron radiobiology, etc. Prior to their regular all-Union coordination

meetings the Commission members visited every biological research institution with the purpose of familiarizing themselves with the research achievements and working conditions there and then identified any bottlenecks and hindrances. Their conclusions were then discussed and reflected in the decisions of the coordination meetings.

Studies of the biological effect of neutrons in the former USSR were aimed mainly at identifying the particular features of the effect of this type of radiation on the biological systems and developing rational methods for the prevention and treatment of neutron radiation-induced damages. This was the principal common guideline in the research activities of the various laboratories, within which each individual laboratory pursued more specific tasks.

### **1.1 The Institute of Nuclear Research of the Ukrainian Academy of Science**

Biological studies were carried out with the atomic reactor WWR-M (water-water moderated), which was put into operation in 1960 at a nominal power of 10 MWt [45]. The reactor utilized a horizontal channel. A U-120 cyclotron was also utilized. The principal line of investigation was the study of neutron injury of mammals, and the acute and late consequences of their irradiation by fast neutrons. In the majority of cases the investigations were performed on rats.

The changes of hemopoiesis and morphology of peripheral blood cells, the size and hemolytic stability of erythrocytes, the function of the thyroid gland, adenohypophysis, and adrenal cortex, the morphology of the testis, redox processes in the whole organism, the redox potential of blood, and the sugar content in blood and its luminescence were studied in animals during the period of acute radiation sickness.

Changes of DNA and its bases in the case of neutron irradiation *in vitro* were also studied. The recovery times for injury by neutrons vs. x-rays were compared.

The researchers developed special interest in the effects of fast neutrons on blastemagenesis. Their oncogenicity and effects on the various stages of tumor growth in different organs of animals were also studied. Many data on the influence of neutron irradiation upon the synthesis and content of DNA in organs of rats and on the protective and therapeutic action of exogenous DNA in the case of irradiation by fast neutrons were accumulated.

Based on study of the oxidation processes in organisms during neutron irradiation, Kiev's radiobiologists proposed a method of diagnosing and forecasting the clinical course and outcome of radiation injury with the help of registration of weak blood luminescence.

In addition to studies of the neutron effects in animals at the Ukrainian Atomic Scientific Center the influence of neutron radiation on microorganisms for the purpose of changing their properties and getting new bacterial strains for industrial use was also studied. They also studied the influence of fast neutrons on plants, including the possibility of modifying the effects of neutrons by means of various chemical compounds [5, 6, 7, 40, 43, 52, 57, 58, 59].

## 1.2 The Institute of Nuclear Energetics of the Belorussian Academy of Sciences

Biological studies were performed with the two MWt atomic reactor IRT-M. It was put into operation in 1962 [37]. Research was carried out in three basic directions:

- a) The study of genetic and physiological effects of intermediate energy neutrons on microorganisms, *Drosophila*, human lymphocytes *in vitro*, mice and in rats.
- b) The study of the shifts in metabolism of the brain, heart, and other organs under the influence of small doses of intermediate neutrons.
- c) The study of the role of the neuroendocrine system in the changes of bio-energetic processes, carbohydrate and protein metabolism in brain, liver, and spleen under the action of small doses of intermediate energy neutrons (ranging from several hundredths to tenths of a Gray). These experiments were performed in rats [13, 35, 36, 55, 60, 61, 62].

## 1.3 The Petersburg Nuclear Physics Institute

The WWR-M reactor with a thermal capacity of 20 MWt was commissioned in 1959 [22a]. The experiments were carried out in a large diameter vertical bio-channel, which provided better opportunities for research than the horizontal channel, particularly for tests with relatively large experimental animals (rabbits, dogs) or groups of smaller animals (mice, rats, guinea pigs). The neutron generator (neutron energy 14.1 MeV) was also used for this type of research. The main objectives of the experiments were: to identify the main mechanisms of neutron action in various biological species, to assess the specificity of neutron effects in animals, and, ultimately, to decide upon a possibility of providing an efficient chemical protection against neutrons and to assess the degree of additivity of the neutron and gamma-radiation effects in mammals.

To this end, a comparative study of neutron-induced effects in mice, rats, guinea-pigs, golden hamsters, rabbits and dogs was conducted, and space and energy distributions of neutrons in phantoms of a guinea pig, a rabbit and a dog were established. The RBE values were established for fission neutrons as based on the lethal effect observed in these animals, and the characteristics of the neutron-induced damage to the critical systems were studied. The RBE relations to the space-energy distribution of neutrons in the organism and the radiosensitivity specific to various species were established. The radioprotective effects of various aminothiols, indolylalkylamines, and hypoxia were studied in animals exposed to neutron radiation. The conclusion was made that efficient chemical protection against neutron irradiation was feasible.

Ways of improving the efficiency of chemical protection were studied by means of varying the combinations of radioprotectors, both among themselves and with unithiol. The particularities of neutron irradiation were studied as a function of age.

The influence of neutrons on the CNS, including that under high radiation doses, was studied [1, 8, 9, 10, 12, 20, 26, 27, 28, 38, 47, 48, 49, 50, 51, 54, 56].

#### **1.4 Physics & Energy Institute in Obninsk**

The fast breeder reactor BR-10 with sodium coolant and thermal capacity eight MW has been operated since 1959 [3]. The biological research started here in the mid-1970s whereby not only reactors but also accelerators were used, such as the cascade generator KG-25 with lithium and tritium targets, electrostatic generator DGP-10 with recharging and a tritium target, electrostatic accelerator EG-1 with a deuterium target. The researchers from the IMR of RAMS of Russia who have been working at these installations also use the neutron generator HG-150 M of the Obninsk subsidiary of the Scientific-Research Institute of Physical Chemistry.

These experiments were mainly aimed at studying the biophysical mechanisms of the neutron-induced damage to a cell. To this end, the reaction to neutrons with various energy levels was studied in terms of DNA release, bacterium, yeast, mammalian cells *in vitro* and plants.

The efficacy of fission neutrons was studied as expressed by the yield of free radicals in the DNA and the efficacy of neutrons with various energy levels was studied as related to the yield of gene and chromosomal mutations. The mechanisms of repairing neutron damage in human lymphocytes were studied as well as the other cellular level effects produced by neutrons in various biological species. The biophysical models of neutron-induced damage in living cells were developed on this basis.

The RBE values of fission neutrons were assessed on the basis of lethality and lesions in the critical systems in mice. Since 1986, the combined effects of neutrons,  $\gamma$ -radiation, other physical and chemical factors on yeast, *Drosophila*, mammalian cells *in vitro*, skin and tumors in rats have been studied [15, 18, 41, 42, 44, 54].

#### **1.5 Nuclear Center of the Scientific-Research Institute of Nuclear Physics at Tomsk Polytechnic University**

A reactor of the IRT type with a thermal rating of one MW has been operating since 1967 [13a]. Biological research has been conducted there since the end of the 1970s and was mainly oriented to the studying of neutron effects in mammals. The reaction of the gastro-intestinal tract (primarily the stomach) to neutron radiation has been studied in mice, rats, and dogs [23, 24]. Researchers also studied the significance of hyperglycemia as induced by x-ray and neutron radiation, the levels of 11-corticosteroids and 11-oxycorticosteroid-dehydrogenase activity in neutron-irradiated rats, and the effects of gamma-neutron radiation on leukocytes and their phagocyte activity [17, 34, 39, 46].

#### **1.6 The Joint Institute of Nuclear Research**

Here there is a fast breeder reactor, IBR-30 [3]. The biological actions of neutrons have been studied here since the early 1980s and have concentrated mainly on the cellular effects of neutron radiation. The neutron-induced effects in the DNA and the chromosomal apparatus of cells were studied, and the repair processes and oxygen effect were assessed in neutron-irradiated *E. coli* with various repair genotypes [22, 29, 30].

There are a few other interesting studies which have been carried out at these nuclear installations and without which the review of the main orientations of the experimental biological neutron research carried out in the labs and atomic research centers in the former USSR would be incomplete. Some of these research patterns deserve close attention. To summarize, they have covered a comprehensive study of the neutron doses in tissues, the doses absorbed by humans in gamma-neutron radiation fields, and also some works where the mutagenic effects of neutrons in cells were detected based on the lethality rate and hematological effects in various species [14,19,63,64,65].

Starting from the early 1980s, a substantial part of the research on neutron biological effects has been oriented towards the use of neutrons in the radiation therapy of tumors. Such studies have been and continue to be conducted at the Physics & Energy Institute (PEI) in Obninsk, the Institute of Nuclear Physics (INP) of the Ukrainian Academy of Sciences and Tomsk Polytechnic University. Not only are nuclear reactors used for the purposes of these studies, but also U-120 accelerators with a neutron energy of six MeV. As a result of these activities the parameters of the neutron beams were obtained, including those in phantoms, the performance of neutrons with this energy level was determined, the mechanism of repair of the damage caused by these neutrons was studied, and hyperthermia was assessed. These physical and radiobiological studies have allowed clinicians to set up and routinely perform neutron therapy at the PEI reactor facilities and the accelerators in Tomsk Polytechnic University and the Tomsk division of the Moscow Oncology Center, the Ukrainian INP and the Institute of Cancer Research in Kiev [4,11,16,25,31,32,33,42,59].

To summarize, the biological effects of neutrons were extensively studied in the former USSR in the 1960-1980s. Some of the results obtained were quite unique and gave a clue to both understanding the mechanism of these effects and meeting important practical objectives of the medical diagnostics, introducing modifications to neutron-induced lesions in mammals, treatment of tumors and creation of microorganisms with modified properties.

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## Section 2.0 Materials and Methods: The Basic Scientific Results

Ten monographs and approximately 230 papers on the biological effects of neutrons were published in the Soviet Union between 1960 and 1991. In this review results of the papers are considered according to the level of biological entity of the studied subjects (cells, organs, and so on), depending on the problem for which these results are important.

### 2.1 Cells

The lethal and mutagenic effects, the biological efficacy of neutrons with various energies, and the biophysical analysis of neutron effects were investigated.

### 2.2 Microorganisms

A greater efficacy of neutrons as compared with radiation of low LET was shown and values of the neutron RBE, using as an end point a lethal effect on bacteria and yeast cells, were established in the experiments with irradiation of microorganisms. The RBE of fission neutrons, assuming lethality, was  $2.02 \pm 0.16$  for *E. coli* K-12 [176]. In other experiments with *E. coli* (strains B/r and B<sub>s-1</sub>) the neutron RBE for the resistant strain B/r was  $2.1 \pm 0.2$ , and for the sensitive strain B<sub>s-1</sub> it was 1.1 - 1.5. The RBE of 0.35 MeV neutrons for the resistant strain was  $4.0 \pm 1.0$  and 1.1-1.5 for the sensitive strain [67]. For irradiation of *E. coli* cells of the wild strain WP2 the RBE of 0.85 MeV neutrons was equal to  $2.2 \pm 0.3$  [166].

Neutrons of 0.85 MeV lower the survival of yeast (diploid strain Megri 139B) with an RBE of 2.2. The RBE depends on ploidy; when passing from haploid strain to the diploid the neutron RBE is increased. The survival curve in the case of diploidy has a weakly expressed S-shaped form, whereas with other ploidities (haploid, tetraploid) it has an exponential one [62].

A greater ability of fast neutrons to inactivate microorganisms than radiations with low LET has been shown on other subjects too. So, in the result of irradiation of *Streptomyces griseus* spores by neutrons of 1.4-1.6 MeV, the RBE of these particles, assuming lethal effects, are 1 to 4 or more depending on dose; the RBE of neutrons with  $E_{ave}$  in the range of 22-50 MeV is even more - from four to six [122]. For irradiation of the spores of *Act. erythreus* the RBE of fast neutrons, assuming  $D_{37}$ , is 5 [52]. Fast neutrons with energy 1.4-1.6 MeV and 22-50 MeV inactivate spores of *S. kanamyceticus* with an RBE of 1.3-2.0; the RBE changes with dose. The same result has been arrived at in experiments with spores of *Streptomyces griseus* [123,124]. So, in experiments with microorganisms where the RBE values of neutrons with various energies was determined using an end point of cell inactivation, a higher efficacy of neutrons compared to  $\gamma$ -quanta and x-rays using an end point of lethality, RBE was found to be dependent on neutron energy, as well as on the ploidy of yeast cells (in one paper). [61, 62]

Dependence of RBE of neutrons on energy was observed in such microsubjects as the sperm of *Drosophila*: 0.35 MeV neutrons were more effective than 0.85 MeV and 0.1 MeV [4].

### 2.3 Mammalian Cells

It was shown, in studies of survival of cells depending on neutron dose, that for murine leukemia L cells and also for Chinese hamster cells the survival curve has an exponential character [53]. This dependence was established in experiments with cells of mice bone marrow cultivated in diffusion chambers, as well as in experiments with cells of Lewis carcinoma. Neutrons with energy 0.35 MeV and 0.85 MeV were used in all outlined experiments [71,73]. The RBE of neutrons, assuming lethality as the end point, on Chinese hamster cells is 4.5 for 0.35 MeV neutrons and 4.3 for 0.85 MeV neutrons; that is, it does not depend on energy. It was found in other experiments with the same L cells in non-synchronous culture that the RBE of 1.2 MeV neutrons, assuming lethality, on Chinese hamster cells is 2.8; for 22 MeV it is 1.3 [79]. The same dependence is revealed in the case of the effects of neutrons with various energies on dividing cells: fission neutrons more significantly inhibit mitotic activity of L cells than high-energy (22 MeV) neutrons and x-rays. The latter two inhibit mitotic activity uniformly [79]. Chronic irradiation over one to six days with neutrons of very high energy (30 GeV) up to 0.70 Gy on asynchronous cultures of Chinese hamster cells, assuming yield of cells with micronuclei, are equally effective as x-rays [163].

In the experiments with cells of mouse bone marrow in culture the RBE of neutrons was found to be dependent on neutron energy: for 0.85 MeV neutrons the RBE was 2.3, and for 0.35 MeV neutrons it was 3.7. For cells of Lewis lung cancer on  $\gamma$ -neutron irradiation from  $^{252}\text{Cf}$  the RBE of neutrons, assuming an end point of lethal effect, is 3.4 (calculated value) [71,73]. An unusually high value of 5.5 for the RBE of 0.75 MeV neutrons, assuming lethal effect, on Chinese hamster cells (strain 432) and on monkey cells (HMC), was found in another work [37].

Much attention was given to estimating the efficacy of neutrons in damaging chromosomes. So, in studies of the effects of neutrons formed upon bombardment of a beryllium target by 13.6 MeV deuterons, it was shown that in human lymphocytes irradiated in vitro the yield of chromosome aberrations depends linearly upon neutron dose, whereas their dependence on dose of x-rays corresponds to a linear quadratic function. The RBE of these neutrons, using as end points yield of chromosome aberrations and of numbers of aberrant cells, using a dose range from 0.40 to 2.20 Gy, changes from 5.2 to 2.1 for the yield of aberrations and from 5.7 to 2.6 for number of aberrant cells [39].

In the case of irradiation of Chinese hamster cells V-79 - 4 in the stationary phase by neutrons with  $E_{\text{ave}}$  0.7 MeV the RBE, assuming an end point of chromatid exchange, is equal to 5.5 [84].

The dependence of chromosome damage by neutrons on neutron energy was described. It was shown in experiments with lymphocytes that in the case of transition from fast neutrons to intermediate neutrons with energies of 144 and 24.5 KeV, the RBE of neutrons, using as end point chromosome damage, increases sharply. So, using as end points the number of aberrant metaphases, sum of aberration of all types, and yield of dicentrics, the RBE of monoenergetic neutrons of 24.5 KeV is more than the RBE of neutrons of 6 MeV by 9.5 times, 10.6, and 6.1 times respectively. The RBE of monoenergetic neutrons of 144 KeV is more than

the RBE of neutrons 6 MeV, using these same three end points, by 1.7, 2.2, and 1.8 times [86].

Damage of chromosomes by neutrons depends upon the stage of the cell cycle. So, respectively [48], the efficacy of neutrons with mean energy 1.2 MeV, assuming as end point chromosome aberrations in embryonic human cells *in vitro*, depends on time after exposure. The number of chromosome translocations from 0.01 Gy of neutrons or x rays is the same 4, 16, 18, and 30 hours after exposure, though at other periods the efficacy of neutrons may be more or less than that of x-rays. In the G<sub>1</sub> stage the yield of aberrations from 0.01 Gy of neutrons is twice that from 0.01 Gy of x-rays. The chromosome breaks after neutron irradiation are less apt to be rejoined than those after x-rays [48].

Dependence of the RBE of neutrons on stage of the cell cycle is described not only for chromosome damage but also for lethal effect. So, the RBE of fission neutrons assuming death of HeLa cells in synchronous culture in all stages of the cell cycle except the S stage is equal to one; however, in the S stage it is more than two, which occurs as a result of decreasing of sensitivity to x-rays [13]. The yield of the chromosome aberrations in lymphocytes as a result of their irradiation in culture by neutrons with energy six MeV depends on the stage of the cell cycle [40, 53, 87].

One study of the effects of neutrons on the chromosome apparatus brought unexpected results [157]. The human lymphocytes in the G<sub>0</sub> stage were irradiated by neutrons of  $E_{ave}$  0.35 and 0.85 MeV. It was shown by the authors that with  $\gamma$ -irradiation there is the characteristic Poisson distribution of chromosome aberrations of cells, but with neutron irradiation the distribution was significantly different from the Poisson distribution. With neutron irradiation a large number of cells do not have chromosome aberrations. The authors believe that lymphocytes in the G<sub>0</sub> phase consist of two fractions: there are no chromosome aberrations in the resistant fraction even at doses of 3.5 - 5 Gy, but in the sensitive fraction one can find six to eight aberrations per cell at these doses. In the case of  $\gamma$ -irradiation the resistant fraction is not found at all [157]. The resistant fraction was found in Chinese hamster cells, and in mouse thymocytes [38].

There were also studies of the influence of neutrons not only upon cell survival, but upon the differentiation of some cells in culture. So, it was shown that irradiation of muscle cell cultures by neutrons ( $E_{ave}$  1.5 MeV) inhibits formation of myoblasts even at doses of 0.25 Gy. However, complete inhibition of this process is not observed even with irradiation by a dose of two Gy [78].

The neutron effects in respect of cells were estimated not only in the experiments with cell cultures, but *in vivo* too. So, in the case of irradiation of mice by fast reactor neutrons it was shown that the RBE, using as an end point the yield of chromosome aberrations in cells of the eye cornea, was 4.6, but much less when delay of mitotic activity was used as the end point [98]. In another work the RBE of one MeV neutrons, assuming yield of chromosome aberrations of the mouse cornea, was found to be lower - 3.23 [43]. The dose-effect curve has an exponential character. The RBE of fission neutrons, using as an end point induction of chromosome damage in the intestinal epithelium, is equal to 3.6 [99].

The effect of fission neutrons upon the colony forming cells of bone marrow and intestinal epithelium was studied in detail. It was established that the D<sub>0</sub> for the

colony forming cells of bone marrow was 1.02 in the case of irradiation by  $^{60}\text{Co}$  gammas, and in the case of neutron irradiation it was 0.342 Gy; thus the RBE is equal to three, which is close to the RBE for bone marrow death. Experiments on determination of the RBE for intestinal death show an RBE value equal to 3.9, and calculations on a basis of the dose-survival curves for the stem cells of the intestinal epithelium show almost the same RBE value - 3,8 [72].

A considerable body of work, besides what was already cited, is devoted to the genetic effects of neutrons. It is primarily concerned with the cytogenetic effects at the cellular level. The cytogenetic damage from irradiation of human non-stimulated lymphocytes by neutrons with  $E_{\text{ave}}$  0.025 eV (thermal neutrons) and  $E_{\text{ave}}$  0.144, 0.35, 0.7, and 0.85 MeV, as well as by monoenergetic neutrons with energies of 0.6, 0.84, 1.07, and 14.7 MeV, was systematically studied. These works established a high neutron cytogenetic efficacy in comparison with  $\gamma$ -rays and a linear dependence of chromosome damages on dose for the majority of the neutron energies studied. The exceptions are fission neutrons and neutrons with energy 14.7 MeV for which, according to these data as well as for  $\gamma$ -rays, a linear-quadratic dependence on dose is characteristic. A high predominance of aberrations of the exchange type over deletions is characteristic for neutron damage in comparison with  $\gamma$ -ray damage. Also more aberrations of the chromatid type are formed; intermediate neutrons are more effective in this respect than fission neutrons. It was shown that the chromatid aberrations in lymphocytes irradiated in the  $G_0$  stage is not connected with induced radioactivity, as some authors believe.

In the region of doses greater than three Gy, for neutrons of energies of 0.35 and 0.85 MeV, the increase in number of aberrant cells slows down as the dose increases; the dose-effect curve forms a plateau and then slowly increases. For  $\gamma$ -rays the plateau is observed just at a dose of five Gy without further decrease in number of the damaged cells. The decrease of the number of aberrant cells with neutron irradiation is explained by the authors as a delay in mitosis. The same responses are noted in experiments with Chinese hamster cells [53].

Based on these results RBE values of neutrons with various energies, assuming chromosome damage in lymphocytes as the end point, as well as dose dependence of the RBE, were determined. Maximum values of RBE are observed at small doses. For example, for intermediate neutrons (0.35 MeV) the RBE is more than 20 with doses of 0.005-0.01 Gy. The RBE of neutrons with  $E_{\text{ave}}$  0.04 MeV does not depend on dose. The RBE values of neutrons of energies 0.35 and 0.85 MeV are tabulated in Table 1.

**Table 1.** Dependence of the RBE values on dose for intermediate (0.35 MeV) and fast (0.85 MeV) neutrons for various types of chromosome aberrations in human lymphocytes.

| Neutron Dose, Gy | Acentrics |          | Dicentrics |          | Dicentrics & Rings |          |
|------------------|-----------|----------|------------|----------|--------------------|----------|
|                  | 0.35 MeV  | 0.85 MeV | 0.35 MeV   | 0.85 MeV | 0.35 MeV           | 0.85 MeV |
| 0.005            | 18.0      | 5.8      | 25.5       | 11.0     | 25.6               | 11.2     |
| 0.01             | 17.0      | 5.6      | 22.0       | 10.7     | 24.0               | 11.2     |
| 0.025            | 16.0      | 5.4      | 18.6       | 9.2      | 21.2               | 10.4     |

Table 1. continued

| Neutron Dose, Gy | Acentrics |     | Dicentrics |     | Dicentrics & Rings |     |
|------------------|-----------|-----|------------|-----|--------------------|-----|
| 0.05             | 13.8      | 5.2 | 14.6       | 8.2 | 17.8               | 9.4 |
| 0.1              | 11.3      | 4.8 | 11.5       | 6.8 | 14.1               | 8.0 |
| 0.25             | 8.0       | 3.9 | 8.2        | 5.2 | 9.6                | 6.0 |
| 0.5              | 5.8       | 3.3 | 6.2        | 4.4 | 6.9                | 4.6 |
| 1.0              | 4.2       | 2.7 | 4.9        | 3.6 | 4.8                | 3.5 |
| 2.0              | 3.1       | 2.2 | 3.5        | 2.8 | 3.1                | 2.6 |
| 3.0              | 2.4       | 2.0 | 2.9        | 2.5 | 2.3                | 2.2 |

The RBEs of neutrons in the experiments with Chinese hamster cells (assuming yield of fragments as an end point) are tabulated in Table 2.

**Table 2.** The RBE of neutrons with various energies assuming yield of fragments in Chinese hamster cells.

| Energy of Neutrons, MeV | RBE |
|-------------------------|-----|
| Monoenergetic           |     |
| 0.04                    | 2.2 |
| 0.35                    | 5.0 |
| 0.6                     | 4.5 |
| 0.84                    | 4.4 |
| 1.07                    | 4.2 |
| From reactor, $E_{ave}$ |     |
| 0.35                    | 8.0 |
| 0.85                    | 5.9 |

The RBE coefficients do not depend on dose, since the yield of fragments changes linearly with dose. If one compares these data, two features of the experimental results with Chinese hamster cells in comparison with lymphocytes become obvious: a different effect of monoenergetic and reactor neutrons with the same energy, and less dependence of the RBE on the LET.

An attempt was undertaken by application of microdosimetric calculations to ascertain a reason of this almost twofold increase in efficacy of reactor neutrons of 0.35 MeV compared with neutrons of 0.85 MeV, because it is not explicable on the basis of the mean LET alone. The conclusion was made, on the basis of these calculations, that for 0.85 MeV neutrons the contribution to damage of cells by insiders is only 19%, but for 0.35 MeV neutrons it is 42%; that is two times more. This suggests that the tracks of the insider type are of considerable importance in the cytogenetic effect of intermediate neutrons [53,119].

It was shown in experiments with barley seedlings (*Crepis capillaris*) that the yield of aberrant metaphases does not depend on the time between irradiation by fast and intermediate neutrons; the spectrum of aberration in the case of fast neutrons

does not depend on time either. In the case of intermediate neutrons the spectrum of aberration changes during interphase, but differently than from  $\gamma$ -irradiation [53].

Point mutations in cells were studied less intensively than chromosome aberrations. It was observed in a former study that the mutagenic effect of fast reactor neutrons, assuming yield of recessive lethal sex-linked type mutations (RLSLM) as the end point, is roughly 1.5 times more than that of  $\gamma$ -rays [3]. Study of the mutagenic activity of intermediate neutrons, assuming as an end point the reversion of the methionine-dependent *E. coli* strain to the wild type, showed that it is higher than the mutagenic activity of  $\gamma$ -rays. However, this was established by calculation from a single dose [177]. In later work with irradiation of *E. coli* WP2 by neutrons with  $E_{ave}$  0.85 MeV the point mutation frequency (number of Trp+ revertants) using the same dose from  $\gamma$ -quanta and neutrons appears to be approximately equal, but if one counts the number of reverses at the same level of survival then the mutagenic activity of neutrons will seem to be much less. So, at a level of ten percent survival it does not exceed eight to ten percent of the mutagenic activity of  $\gamma$ -rays [166].

In studies of induction of the resistant mutation to 6-thioguanine in a culture of Chinese hamster cells the mutagenic activity of neutrons ( $E_{ave}$  0.7 MeV) was estimated through comparison of the mutagenic effect with the lethal effect. It was found that in the case of calculation of the mutation frequency at a single dose the mutagenic activity of neutrons is more than that of x-rays. If one determines it by calculation on the basis of lethal events, then there is no substantial difference from the mutagenic activity of x-rays [50].

The experiments in which irradiation of a prototrophic haploid strain of yeast 15B-P4 caused a mutation of the requirement for adenine led to the same conclusion on nonspecificity and to a practically quantitatively identical mutagenic activity between fission neutrons and x-rays. Difference in relationship of the mutants in the loci  $ad_2$  and  $ad_1$  was not statistically significant. There is no difference in the relationship of the number of noncomplementary mutants to the number of complementary mutants for radiation of both types [69].

In studies of the mutagenic activity of neutrons ( $E_{ave}$  0.1, 0.35, and 0.85 MeV) the set of visible and sex-linked mutations in the sperm of *D. melanogaster* were investigated (Table 3).

**Table 3.** The RBE value of neutrons with  $E_{ave}$  0.1(a), 0.35(b), and 0.85(c) MeV by means of the traditional method of evaluation\* and by means of isoeffectiveness, defining 15% survival ( $LD_{15}$ )\*\* doses (as relation of the effects).

| Tests                | Neutron RBE            |     |     |              |     |     |
|----------------------|------------------------|-----|-----|--------------|-----|-----|
|                      | Traditional Evaluation |     |     | By $LD_{15}$ |     |     |
|                      | a                      | b   | c   | a            | b   | c   |
| Gene mutations       | 1.0                    | 0.0 | 1.1 | 0.2          | 0.0 | 0.3 |
| Structural mutations | 3.3                    | 6.2 | 3.6 | 0.7          | 1.6 | 1.0 |
| RLSLM                | 2.4                    | 3.1 | .3  | 0.4          | 0.8 | 0.6 |
| Dominant lethals     | 5.1                    | 4.2 | 3.0 | --           | --  | --  |

\* As the ratio of the linear coefficients of the dose curves.

\*\* The  $LD_{15}$  for the specified neutrons and  $\gamma$ -quanta of  $^{60}Co$  are 7.8, 11, and 34 Gy respectively

As can be seen from Table 3, 0.35 MeV neutrons produce aberrant mutations and RLSLM more effectively than others, ranking slightly below 0.1 MeV neutrons in lethal effect. Neutrons of 0.35 MeV have extremely little effectiveness in induction of genetic mutations. By this standard the influences of neutrons of 0.35 MeV on the yield of genetic and chromosomal mutations is not merely unequal, but in diametrically opposite directions [4].

In the case of determination of the RBE of intermediate neutrons ( $E_{ave}$  0.2 MeV) it was found that for formation of double-hit chromosome aberrations in lymphocytes the RBE is 3.5. In the experiments on *Drosophila* the RBE was determined for the same neutrons (calculation to the same dose) by the RLSLM, by the RM (recessive mutations), and by the deletions in the X-chromosome of male *Drosophila*. With mature sperm the intermediate neutrons induced twice as many dominant lethals than x-rays, and 1.2 times more than fast neutrons. With spermatids the efficacy of intermediate neutrons is 2.3 times that of x-rays and two times more than for fast neutrons [177].

It was found in studies of the mutagenic effect of intermediate neutrons in mammals that, in mouse bone marrow cells in the stages of anaphase and telophase, these neutrons induce more chromosome translocations after 21 hours than do x-rays and fast neutrons (from 1.1 to 1.6 times more than fast neutrons, calculated to 0.01 Gy). The percentage of the translocations remaining after irradiation by intermediate neutrons decreases much more slowly than after x-irradiation [177]. Such evaluation of the efficacy of neutrons with various energies is given by other authors too. The RBE of fast neutrons ( $E_{ave}$  1 MeV), assuming as an end point the effect upon spermatids (estimation assuming yield of lethal mutation to the unit of dose), is  $3.6 \pm 0.04$  (to  $\gamma$ -rays), and the RBE of neutrons with  $E_{ave}$  0.19 MeV is approximately 6 [127, 128].

As a whole, a comparison of neutrons, assuming yield of point mutations and lethality as end effects, leads authors of the cited works to the conclusion that there are various mechanisms of damage, inasmuch as the RBE for different end points are different.

In a series of works the possibility of modification of the neutron effects at the expense of post radiation recovery, of the  $pO_2$  change, and other effects was investigated. So, on irradiation of stimulated lymphocytes *in vitro* by fast neutrons the dependence of yield of chromosome aberrations on dose rate, which indicate the role of repair in the ultimate outcome of neutron effects, was noted [88]. More evidence of this is in the fact that in case of fractionated irradiation of the non-stimulated lymphocytes by neutrons of  $E_{ave}$  6.0 MeV the yield of the chromosome aberrations is less than in case of a single exposure. By this means it is revealed that the repair processes are capable of influencing neutron damage, although to a lesser extent than in conditions of the effects of radiation with low LET [19].

As opposed to these data, no effect of dose fractionation of intermediate neutrons in the case of irradiation of the stimulated lymphocytes was detected, either in the  $G_1$  stage or in the S stage [156].

Different results were obtained in studies of DNA repair in hepatocytes stimulated by partial hepatectomy to divide. The DNA damages (one-strand breaks) after irradiation by 6 MeV neutrons were repaired, although significantly

less so than after x-irradiation. The RBE of neutrons, by calculating residual damages six hours after exposure, was 1.53, 1.39, and 1.33 after total neutron doses of 10, 20, and 30 Gy respectively. The authors conclude that the intensity of repair depends on the stage of cell cycle both for x-rays and for neutrons, although to a lesser degree for the latter [16].

Repair of potentially lethal damage in Chinese hamster cells was studied as well. Repair after irradiation by neutrons of 0.85 MeV, after four hours incubation in conditional culture medium, was not found: the  $D_0$  increased only from 0.69 to 0.72 Gy. On the other hand, with  $\gamma$ -irradiation the  $D_0$  increased under the same conditions from 1.97 to 2.34 Gy [53]. In cells of the *E. coli* K12 strain, which are deficient in excision and recombination repair, after irradiation by neutrons (0.85 MeV) the phenomenon of photoreactivation, characteristic of damage by low LET radiation, was not detected [53].

Data on repair of the DNA breaks in intestinal cells and in cells of rat bone marrow irradiated by fast neutrons ( $E_{ave}$  1.5 - 2 MeV) with doses from one to seven Gy are intriguing. Repair is not fully complete even after 18 hours (3.3-3.8 Gy), whereas after  $\gamma$ -irradiation (four to six Gy) it is finished after four hours or a little longer [139].

Neutron damage to cells can be enhanced by use of inhibitors of DNA and protein synthesis. Cycloheximide and oxyurea + fluorodeoxyuridine increase significantly the yield of chromosome aberrations in lymphocytes irradiated by neutrons (0.85 MeV); this result does not depend on the time of inhibitor administration into the culture media after irradiation (within the limit of five hours). The experiments were performed in the  $G_1$  stage, and cell fixation within 50 hours after stimulation of the phytohemagglutinin (PHA). The authors concluded that the repair of damaged chromosomes from neutron irradiation in  $G_0$  is completed within five hours or a little later. On the other hand, repair from  $\gamma$ -irradiation takes place in the first 1.5 hours after irradiation, because addition of the inhibitors following exposure does not influence the aberration yield. It is suggested that in the case of neutron irradiation we are dealing with repair of the double-strand breaks of DNA, and in the case of  $\gamma$ -irradiation the single-strand breaks [34].

In the experiments with irradiation of cells of Erlich ascites carcinoma by neutrons ( $E_{ave}$  6 MeV) by doses 10 - 52 Gy a reduction in the number of double-strand breaks of DNA during two to four hours of incubation was observed. 10-14% of the DNA damages remained non-repairable two hours after irradiation at 0° C. to a dose of 30 Gy. Addition of cytosine arabinoside (Ara-C) coupled with oxyurea (OU) into the incubation media before irradiation increased the yield of double-strand breaks as compared with irradiation without addition of Ara-C and OU. Two hours after irradiation repair in the experiments with Ara-C + OU was completely stopped. The DRF of the preparations irradiated to one Gy, assuming as an end point the number of double-strand breaks, is changed in relation to the dose of radiation and to time of incubation from 1.49 to 3.78. Nicotineamide gives the same effect [15].

The role of the oxygen effect in neutron damage of cells was not studied enough in the USSR. It was shown that the oxygen enhancement ratio (OER) for *E. coli* K-12 under irradiation by fast neutrons is much less than with  $\gamma$ -rays. In the latter

case the OER depends on the reparation genotype of cells: in the efficient repair strains (*recA*<sup>-</sup>, *uvrA*<sup>-</sup>) the OER is less than in the wild type, but with *polA*<sup>-</sup> it is more. In the case of neutron exposure ( $E_{ave}$  0.75 MeV) the OER does not depend on the reparation genotype [70]. With irradiation of the diploid strain by 0.85 MeV neutrons the OER is equal to 1.4 versus 1.9 in the case of  $\gamma$ -exposure [61].

The influence of hyperthermia was studied in some instances. So, it was observed in one experiment that the effect of neutrons (6.0 MeV) on Erlich carcinoma inoculated in a mouse thigh may be enhanced by local heating up to 43° C (by immersion in hot water of a mouse leg with inoculated tumour) for 30 min after irradiation. The neutron dose required for inhibiting growth of the tumour by 50% was decreased by such hyperthermia from 3.10 to 1.70 Gy [89].

It was shown that hyperthermia and irradiation with six MeV neutrons of lymphocytes in the S stage increases the yield of chromosome aberrations by a factor of 1.5, as compared with irradiation alone. The effect of irradiation in S stage is increased by caffeine [41].

An attempt to weaken the effect of fast neutrons ( $E_{ave}$  1.35 MeV) on stimulated human lymphocytes by addition of interferon into the culture medium was undertaken. According to the authors' data, the result of this influence was complete elimination of radiation induction of chromosome aberrations and sister chromatid exchanges; this would be extremely impressive [56]. However, other researchers using the same method could not confirm these results [158]. The reasons for this discrepancy are not clear.

A number of works were devoted to neutron effect on DNA *in vitro* and *in vivo* and on cell membranes. It was shown that neutrons with  $E_{ave}$  0.25 MeV on *E. coli* DNA in aqueous solutions cause formation of one-strand breaks with a yield that is approximately 2.5 times less than from  $\gamma$ -quanta [13a]. This accords well with the observation that the transformation of 2-deoxy-D-ribose (assuming yield of carbonyl compounds) in case of its irradiation *in vitro* by fast neutrons with energies of one, three, and five MeV takes place two times less effectively than under influence of  $\gamma$ -quanta of <sup>60</sup>Co [77].

The observation was made that one of the quantitative features of the effect of neutron irradiation on DNA as compared with the effect of sparsely ionizing radiation is decrease in content of purine nucleotides [137]. In the case of the effects of fast neutrons on the growth of DNA synthesized *de novo* in peas, decrease of the thymine content as well as deamination of adenine with its transformation to hypoxanthine was observed [173, 174]. Simultaneously inhibition of DNA synthesis, much more than from  $\gamma$ -rays, and abrupt depolymerization of DNA (by 50-60%) was observed. In the authors' evaluation, the changes of the A and T to G and C relationship (changes of DNA specificity) are a possible reason for the particularly expressed non-viability of cells irradiated by neutrons.

Differences in the changes of the melting point of rat spleen DNA after irradiation of the animals by fission neutrons versus by x-rays were also noted [82].

Irradiation by fast reactor neutrons to a dose of 100 Gy of solutions of the liver DNA, or mucous membrane of the rat small intestine, leads to a decrease of the melting point of DNA. The DNA from intestine of old rats was less resistant than from young rats [186].

The efficacy of neutron effects on DNA was evaluated by determination of the number of the DNA one-strand breaks in irradiated cells of the Erlich ascites carcinoma. It was shown in this case that yield of the one-strand breaks under conditions of neutron irradiation (0.85 MeV) is less than under  $\gamma$ -irradiation:  $1.21 \pm 0.09$  and  $0.727 \pm 0.073$  per 100 eV respectively [135]. It is interesting to compare these data with the formation of free radicals in thymus DNA and horseradish peroxidase under the effect of neutrons ( $E_{ave}$  0.85 MeV) and of  $\gamma$ -quanta. The identity of the radicals induced by radiation of both types was demonstrated by the ESR method. With respect to yield of the radicals,  $G_n \text{ DNA} / G_\gamma \text{ DNA} = 0.67$  and  $G_n \text{ peroxidase} / G_\gamma \text{ peroxidase} = 0.32$ . By this means the efficacy of radical formation by neutrons is essentially lower than in the case of  $\gamma$ -rays [165].

As the role of the DNA-membrane complex in cell activity was gradually elucidated, the need to study the influence of neutrons upon this structure became apparent. It was found that the dependence of the sedimentation rate of the DNA-membrane complexes from Chinese hamster cells on dose in the case of  $\gamma$ -exposure and neutron irradiation with  $E_{ave}$  1.0 MeV has the same character. However, in the case of neutrons at doses less than five Gy a drop of the sedimentation rate takes place significantly slower, and the plateau on the dose-effect curve is at a higher level than with  $\gamma$ -irradiation. At doses more than 80 Gy the sedimentation rate during neutron irradiation begins to rise earlier and more quickly than in experiments with  $\gamma$ -irradiation. The authors explain these features of the sedimentation curves by differing yields of single-strand and double-strand breaks of DNA from the effects of neutrons and  $\gamma$ -quanta; the RBE of neutrons using the end point of formation of double-strand breaks is approximately 2.5-3 [83].

Data on the effects of neutrons on cell membranes was also obtained. On irradiation of rat erythrocytes by fast reactor neutrons, membrane damages studied by the method of sedimentation are seen at doses well above of two Gy, but are not seen after  $\gamma$ -irradiation until doses higher than six Gy [105]. Changes of light-scattering in rat lymphocytes, which depends on the condition of the cell surface and the cell organelles, were already found by six hours after irradiation of the animals. After 24 hours the RBE of neutrons was three by this indication [25].

In one of these works the structure and function of cells of the Erlich ascites carcinoma at the level of cellular respiration, intensity of the lipid peroxide oxidation, and UV fluorescence of cells were evaluated. Thus it was found that neutrons of 0.85 MeV induce lipid peroxide oxidation less effectively than  $\gamma$ -rays; neutrons, unlike  $\gamma$ -rays, do not influence cell fluorescence. The authors demonstrated that peroxide oxidation and fluorescence of cells depend on the condition of the plasmatic membranes, and tissue respiration on the condition of the mitochondrial membranes. Activation of tissue respiration was found to be an effect of both  $\gamma$ -rays and neutrons; however, neutrons intensify tissue respiration twofold more than photons [160].

In studies of biochemical changes in the plasma membranes of rat lymphocytes at three and 18 hours after neutron (1.5 - 2.0 MeV) irradiation of animals with doses from two to six Gy it was found that neutron enhances lipid peroxide oxidation more than  $\gamma$ -quanta. During neutron irradiation the amino group content on the cell surface is also changed more than after  $\gamma$ -irradiation [106].

The effect of neutrons on the erythrocyte membrane was studied in experiments with hemolysis of these cells. A study of the hemolysis kinetics of irradiated rat erythrocytes in an alkaline buffer showed that lysis of the cells irradiated by fast reactor neutrons takes place considerably earlier than in the case of  $\gamma$ - or x-rays [175].

A number of works were also performed in the USSR in connection with the problem of additivity of effect of neutrons and low LET radiation. It is known that the problem is important for radiation therapy and for the biophysical analysis of the nature and interaction of damages induced by photons and neutrons. In studies of this problem two approach methods were used: 1) determination of the RBE of neutrons of mixed  $\gamma$ -neutron radiation for different relationships of  $D_n/D_\gamma$ , since changes of the neutron RBE with changing of the  $\gamma$ -radiation contribution to the total dose illustrates the non-additivity of radiation of both types; 2) an evaluation of the yield of damages from the simultaneous or sequential influence of different types of radiation. In the research performed by the first method it was shown that the RBE of fission neutrons, assuming lethal effect upon Erlich ascites carcinoma cells as the end point, is decreased as the contribution of  $\gamma$ -quanta to the total dose increases (Table 4).

**Table 4.** Influence of mixed  $\gamma$ -neutron radiation on survival of Erlich ascites carcinoma cells. Parameters of the dose-effect curves.

| Characteristic of mixed $\gamma$ -neutron radiation, $D_\gamma/D_n$ , relative units | n, extrapolation number, relative units | $D_q$ , value of "shoulder", Gy | $D_0$ , Gy | RBE of neutrons on the 50% survival level, relative units |
|--------------------------------------------------------------------------------------|-----------------------------------------|---------------------------------|------------|-----------------------------------------------------------|
| 0.03                                                                                 | 1.0                                     | 0                               | 1.7        | $6.5 \pm 0.6$                                             |
| 3.2                                                                                  | 1.05                                    | 0.4                             | 5.6        | $4.8 \pm 0.5$                                             |
| 5.6                                                                                  | 1.2                                     | 1.2                             | 8.4        | $1.8 \pm 0.6$                                             |
| $\gamma$ -quanta $^{137}\text{Cs}$                                                   | 1.2                                     | 1.8                             | 10.2       | -                                                         |

This demonstrates the non-additivity of the effects of neutrons and photons and the interaction of radiation of both types that, in the authors' opinion, is expressed in the early stages of damage [132].

Similar results were obtained with combined irradiation on *Crepis capillaris* seedlings by neutrons and  $\gamma$ -quanta: yield of aberrations of all types was less than would be expected in the case of summation of the effects of neutrons and  $\gamma$ -rays. Moreover, it was reliably less than in the case of neutron effect alone. The authors explain this by the failure of neutrons to induce SOS-repair [53].

Using the second method in experiments in yeast (haploid and diploid), it was observed that irradiation by neutrons of 0.85 MeV by doses decreasing survival to ten percent increases the cells' resistance to further (in 40-60 min) exposure by 20 MeV electrons with doses 200-1,200 Gy. If one changes the sequence of irradiation the effects are additive. Increasing the interval between the exposures up to 20 hours did not change the final effect [189].

In an experiment with *Drosophila* sperm during neutron ( $E_{\text{ave}} 0.85 \text{ MeV}$ ) and  $\gamma$ -quanta exposures separated by an interval of 40 minutes, the yield of point and chromosome mutations was also less than would be expected assuming additivity of the effects of neutrons and  $\gamma$ -quanta. Furthermore, for the overall yield of chromosome aberrations the effects of radiation of each type were shown to be antagonistic. However, cytogenetic analyses have revealed that for exchange reconstructions (inversions, translocations, transpositions) the combined effects were synergistic, especially at doses inducing death of most of the cells. As the analysis demonstrates, the basis for such synergism lies not so much in the increase of the probability of exchange of a uniquely damaged gene with other parts of the genome but in the appearance of new reciprocally interacting sites of damage, not connected to another part of the genome [5]. On exposure of lymphocytes to six MeV neutrons and  $\gamma$ -quanta in the sequence neutrons followed by  $\gamma$ -rays, and  $\gamma$ -rays followed by neutrons (neutron dose one Gy,  $\gamma$ -rays dose 2.7 Gy) the cytogenic effect was more than simply additive [41].

It was shown in more recent research performed in Russia (not the USSR) that in the different variations of fractionated irradiation of lymphocytes in the  $G_0$  by 0.85 MeV neutrons and  $\gamma$ -rays in various sequences and at various doses the entire gamut of variation of radiation interactions was observed: non-additive, sub-additive, and additive [125].

Thus, the problem of additivity and interaction of the effects of neutrons and  $\gamma$ -rays continues to be of interest to Russian research. This problem was mainly studied at the cellular level. If we are to complete the review we note that the problem is circumstantially examined on the level of the whole organism. Having followed the dependence of RBE of neutrons on  $D_n/D_\gamma$ , the authors noted that for all indicators studied (lethality, mass of thymus, spleen and liver, cellularity of bone marrow in mice and rats, and lethality in the golden hamster) the RBE of fission neutrons decreased as the contribution of  $\gamma$ -rays to the total dose increased, suggesting non-additivity of neutrons and  $\gamma$ -quanta [133, 153].

For the most part the exhibited data on values of the RBE of neutrons of various energies (assuming end points of cell inactivation, yield of gene mutations and chromosome aberrations) on the dependence of the RBE on the LET, on additivity and others, supplemented with microdosimetric studies [119, 120], were used for biophysical interpretation of the effects of neutron irradiation of cells.

In particular it was concluded that the genetic neutron effect is caused not only by ionization, but by elastic nuclear collision as well; the role of elastic collision increases as the neutron energy decreases. The role of elastic neutron collisions was calculated, and it was shown in experiments with slow neutrons that the dislocation of atoms by elastic collisions induces genetic damage five times more effectively than primary damage induced by ionization [177].

The biophysical model of radiation effect in DNA was also elaborated. Using this model as a basis, the yield of single strand and double strand breaks of DNA depending on LET and on neutron energy is calculated [112]. The calculated data on yield of one-strand breaks with irradiation of cells of mammals by neutrons of 0.85 MeV is equal to  $0.66 \cdot 10^{-10}$  breaks/Gy per g/mole; this accords well with the experimental findings of  $0.67 \cdot 10^{-10}$  breaks/Gy per g/mole [135].

On the basis of this proposed biophysical model [112, 113, 115] the convex shape of the curve describing the dependence of RBE, using as an end point the yield of chromosome aberrations, on neutron energy (a convexity of the curve in the zone of intermediate energy neutrons) is also explained. According to the Kellerer-Rossi theory this convexity is explained by the interaction of primary damages, each of which is induced by one ionization. The author of the model being considered believes that for double-strand breaks no less than two ionization events are demanded. The shape of the curve is explained by this. It is also suggested to take into account elastic nuclear collisions, which is not done in the Kellerer-Rossi theory.

On the basis of the same biophysical model the distributions of chromosome aberration in cells after irradiation of lymphocytes by intermediate neutrons were calculated; the experimental data are in good agreement with this, including presence of the previously mentioned resistant fraction of cells. This confirms the correctness of the biophysics ideas of the authors, though it may not explain the nature of such a strange phenomenon as the stability of cells to irradiation at doses that can produce hundreds of double strand breaks, the most severe type of DNA damage [113, 157].

An explanation of the effects of two to three Gy neutrons on mitotic delay to the cell at the  $G_0$  stage, which is not observed in  $\gamma$ -irradiation at doses up to ten Gy, was proposed; this also explains the absence of the dose rate effect and fractionation effect. It is associated with the fact that the nucleus of the cell is crossed by three to four particles (at two Gy), which form high density damages in their path. This leads to the fact that the probability of interaction of the primary damages along the track is significantly higher than between the tracks.

In the case of pulse neutron radiation (see below), independence of the effect (chromosome aberration in lymphocytes, RLSLM, and other genetic damages in *Drosophila*) with respect to pulse frequency can be explained when one takes into consideration that during the time of pulse on the average less than one charged particle passes through the nucleus of the cell. In this situation the duration of the pulse is not important.

As already indicated, a large role in the high efficacy of neutrons is attributed to elastic nuclear collisions. For example, this role is revealed on analysis of discrepancies between experimental values of the neutron RBE for inactivation of *E. coli* and calculated values, which are much less than the experimental values. Also the high experimental values of neutron RBE for *E. coli* inactivation do not conform with data obtained on the effect of fast heavy ions on these bacteria: the sensitivity of *E. coli* cells to them is not dependent on LET up to 50 KeV/ $\mu$ m. These discrepancies are attributable to the high efficacy of slow heavy recoil nuclei (H,N,O,C), which have about the same LET as fast heavy particles, but a slower speed. Actually, it was shown in the experiments with proton balance and without it, that the RBE of slow protons and heavy recoil nuclei, assuming inactivation of the *E. coli* B/r, is 3.5 - 6.6 [114, 134]. The RBE of elastic nuclear collisions can be calculated for the *E. coli* B/r: it is 20 - 60 for various energies and for various conditions of irradiation. Hence the explanation of experimentally established high values of RBE for fast and especially for intermediate neutrons, assuming inactivation of *E. coli* as the end point, follows. The calculation of the complete number of dislocated atoms on irradiation of a tissue-equivalent

substance by neutrons demonstrates that the RBE of neutrons and elastic nuclear collisions correlates with the number of the dislocated atoms. Because of this, although the dose contribution from recoil nuclei in the absorbed dose from fast neutrons is small (about ten percent), their contribution to the cytogenetic effect comprises 30 - 35%. It is suggested that the elastic nuclear collisions determine the high efficacy of neutrons that has been noted.

It was noted above that the main part of the experimental data obtained was used for the derivation of a theory. This was also true in regard to some works of a seemingly entirely practical trend. For example, in the interest of neutron therapy a comparison of the efficacy of irradiation by neutrons of various pulse frequencies was performed. It was shown that, assuming yields of chromosome aberrations in lymphocytes irradiated at the  $G_0$  stage, the pulse influence by neutrons of 0.7 MeV with pulse frequencies of one and five Hz is equally effective. The effect of this influence with a frequency of 100 Hz is somewhat higher. The biological efficacy of pulsed 0.7 MeV neutrons was intermediate between that of neutrons of energies of 0.35 and 0.85 MeV in the continuous mode. [159]. However, the results as indicated above were used for the above mentioned biophysical analysis. The results agree well with the theoretical ideas and therefore offer confirmation of their correctness.

However, a series of experiments was carried out directly in the interest of practical applications. The work, in which dependence of the yield of binuclear cells with micronuclei in human lymphocytes with doses of irradiation by neutrons of 0.85 MeV was studied using a cytokinetic block, relates to such research. It was shown that beginning with a dose of 0.05 Gy, the dose of neutrons to the cells may be estimated using these indications [7]. This test is useful for biological dosimetry.

A set of research studies on the change of hereditary properties of microorganisms under the influence of neutrons was carried out in Moscow, in Kiev and in Minsk. It was shown in these works that, for example, the morphology of *B. mesentericus* and the shape of these colonies in agar are changed, during which neutrons are more effective than  $\gamma$ -rays [14]. The morphological changes of *Act. erythreus* colonies as the result of neutron irradiation were also described [52]. Mutants with increased toxin formation were selected by irradiation with fast neutrons [101, 116]. However, the formation of toxins is depressed after a three to six times increase of dose (to 0.451 - 0.910 rad) [102].

Neutron irradiation, as being more effective compared with  $\gamma$ -radiation (fast and intermediate neutrons), was used for production of mutants - highly active producers of kanamycin, oleandomycin, erythromycin, biomycin, and streptomycin. It was shown, among other things, that super fast neutrons ( $E_{ave}$  20-50 MeV) bring into existence more stable variations of *S. kanamyceticus* with respect to the characteristic of production of antibiotics than do fast neutrons ( $E_{ave}$  1.4-1.6 MeV). The mutagenic activity of super fast neutrons is two to three times more than that of fast neutrons [123, 124].

Many works are carried out not only for solution of theoretical questions about neutron therapy, but for estimation of the possibility of using some of these experimental facilities for neutron therapy of cancer as well. These were primarily concerned with research on the effects of neutrons with energies 0.35 and 0.85 MeV. There is a need to add to research on these energies the research

on the neutron beam with 350 MeV energy from the accelerator at the Joint Institute of Nuclear Research (Dubna). On preliminary evidence the RBE of neutrons from this beam, as determined by decrease of survival of Chinese hamster cells to ten percent, is not changed with respect to depth in the phantom: one cm -  $1.6 \pm 0.1$ , ten cm -  $1.4 \pm 0.1$ , 39 cm -  $1.3 \pm 0.1$ . The OER, when the dose rate of the neutrons is ten mGy/min, is, at a phantom depth of one cm -  $1.0 \pm 0.1$ ; 13 cm -  $1.3 \pm 0.1$ ; 36 cm -  $1.5 \pm 0.1$ . The OER for  $\gamma$ -rays of  $^{137}\text{Cs}$  with dose rate 42 mGy/min was  $2.7 \pm 0.1$  [146].

Mathematical description of the distribution of the iso-effective neutron dose in irradiated tissue, of dependencies of the RBE and the gain factor on dose, and mathematical models of neutron and neutron-photon therapy on the basis of the Ellis-Field conception are presented in the works of Lisin [90-95].

## 2.4 Mammals

Studies of the neutron effects in mammals pursued three main goals:

1. To reveal the features of neutron damage of the organism and to promote elaboration of the most rational methods for treating humans injured from this kind of radiation.
2. To evaluate the danger from neutron influence on the organism, which was considered an equally important task; for this purpose it was important to determine the RBE of neutrons with respect to their damages on the organism as a whole and its crucial systems.
3. Finally, to elaborate the problem of modification of neutron effects, primarily chemical protection, as well as the problem of finding out and predicting neutron effects; this was also a major purpose.

Charged particle accelerators, the horizontal channels of some reactors, and the vertical channel of the reactor at the LNPI of the RAN, which was specially equipped to irradiate large laboratory animals or large groups of small animals simultaneously, were used in the USSR for the experiments with neutron irradiation of mammals. The channel of LNPI is equipped with a system of ventilation and of thermostatic control in the range from 20 to 22°C in the chamber for irradiation. The cages with animals are placed in this chamber on a rotary platform. This provides a circular irradiation of biosubjects and decreases irregularity of the radiation field with respect to radius. The irregularity of the height of the cage is corrected by the filters. The blocks of lead shield allow one to change the relationship  $D\gamma/Dn$  from 3/100 to 4/1. The cadmium filter inside the chamber decreases the flux of thermal neutrons.  $E_{\text{ave}}$  of neutrons in the channel is 0.85 MeV [66,154]. Analysis of the physical conditions in this channel and experience with its utilization allows one to propose the optimum variation of construction of similar vertical channels for biological research in reactors, when the thermal column is impossible to use for these purposes, and the horizontal channels do not meet the experimental requirements [131, 151].

The first publications on the neutron injury of mammals appeared in the Soviet press in 1958. In one work it was reported that rabbits were more severely injured by slow neutrons than by  $\gamma$ -rays. The animals were irradiated at a dose of approximately 360 rep of neutrons and 150 R of  $\gamma$ -rays, or by x-rays at a dose of 1,500 R (without filter) [65]. The results of a study on the influ-

ence of fast neutrons of 5.6 MeV on hemopoiesis in rabbits, irradiated on one side to a dose of 400 rep ( $LD_{100/80}$ ), was reported in another publication [64]. Erythropenia, microcytosis, decrease of hemoglobin content, full inhibition of erythropoiesis in animals were noted beginning from the first day and for the next five days after irradiation. Leukopenia and inhibition of myelopoiesis were even more severe. Simultaneously thrombocytopenia with inhibition of thrombocytopoiesis in bone marrow developed. Similar changes in the blood and bone marrow were observed with x-rays, but equal effects in terms of lethality required a dose of 1,200 rep. Five rabbits were irradiated by fast neutrons with a total dose of 600 rep for 40 days, and in parallel another group using the same scheme with x-rays. Changes of blood cell count were expressed less than after one time irradiation in both cases; neutrons caused more profound and longer lasting shifts than x-rays. Radiation of both kinds caused decrease of the bioelectric activity of brain cortex and of its reactivity; however neutron irradiation caused a more profound and longer lasting effect. The author came to recognize that there is a high efficacy of neutrons as compared with x-rays, even on equalizing doses assuming lethal effect [164]. It should be pointed out that the equalization of dose was performed approximately; they were not selected through comparison of the dose-effect curves but some single dose was selected. Certainly in this case significant effort is possible.

Nevertheless, the same differences in the changes of peripheral blood after fast neutron effect (4.00 Gy -  $LD_{50}$ ) and x-rays (600 R) were noted in the other experiment. In addition, neutrons diminished the hemolytic stability of erythrocytes; x-rays did not cause this decrease. The differences in effect of neutrons and x-rays on the heart were noted as well: on evidence from EKG x-irradiation causes dystrophic changes in myocardium, while neutrons cause not only dystrophic but focal damage, as confirmed by autopsy. On increasing the dose of x-rays to 8.00 Gy and on decreasing dose of neutrons to 1.75 Gy, the authors observed the same differences, though less pronounced [206]. However, it is not likely that the doses of x-rays and neutrons used were equally effective, because a neutron dose of 1.75 Gy caused death of all rats within three days, and 8.00 Gy of x-rays did not kill all the animals, even after a month.

The research on comparative radiation effects of both kinds of radiation in blood is described in the other reports as well. So, the post-radiation change of the erythrogram, (distribution of erythrocytes by hemolytic stability, characterizing their distribution by "age," reflecting intensity of hemopoiesis) was studied in rats for one month after irradiation by fast neutrons to a dose of 2.00 Gy and by x-rays to a dose of 6.00 Gy. The effect of both kinds of radiation turned out to be of a single type, though more pronounced in the case of neutron influence [190].

Also described were the oscillatory changes of sugar content in the blood of rats irradiated by fast reactor neutrons to a dose of 2.00 Gy, as well as some features of luminescence of the bone marrow cells in rats after such irradiation ( $LD_{50}$  - 2.15 Gy) [42, 188].

The biochemical and biophysical changes of the blood of animals irradiated by fast neutrons attracted the attention of certain researchers. So, it was observed that enhancement of the peroxidase activity of hemoglobin takes place under the influence of irradiation of rats by fast reactor neutrons and by x-rays to  $LD_{50/30}$  and  $LD_{100/30}$  dose levels. However after x-irradiation this takes place

on the first day of radiation sickness, whereas after neutron irradiation not until the 8th day. There are other differences in the dynamics of these changes as well, depending on the kind of radiation [207]. It was noted in another work that the changes of methemoglobin level are of a single type after irradiation by either neutrons or x-rays, but are expressed more in the case of neutron irradiation [208]. It was also described that the redistribution of potassium ions between erythrocytes and plasma, which has a phase character and depends on the dose of irradiation, takes place in rats after irradiation by reactor neutrons with doses of 2.00 Gy ( $LD_{50/30}$ ) and 3.00 Gy ( $LD_{100/30}$ ). The level of potassium in blood is not changed significantly during the course of radiation sickness, but increases appreciably before the animals' death [140].

Unilateral and bilateral  $\gamma$ -neutron irradiation (the neutron contribution 55% and 90% respectively) in dogs by doses up to 11.20 Gy produced rise of the proteolytic activity of blood serum in all groups of animals at the period of the height of the radiation sickness. The authors consider, on the basis of comparison of the survival of the dogs and of the changes of proteolytic activity of blood serum, that these changes are of a prognostic character: if increase of the proteolytic activity of blood serum takes place by a factor of only three to four, the death of animals is unlikely; death is more probable if this increase is more substantial [130].

Also studied was the influence of  $\gamma$ -neutron irradiation ( $E_{ave}$  0.9 MeV, neutron contribution 67%) on the composition of the metabolic foundation of amino acids and on anti-protease activity of blood in rats. Neutrons, as well as  $\gamma$ -rays of  $^{60}Co$ , cause a rise in the content of free amino acids in blood serum, but this rise from neutron effects is significantly more than from  $\gamma$ -irradiation: irradiation by photons with doses of three to six Gy raises this indicator by 40-42%, but neutron irradiation with a dose of one Gy raises this indicator 50%, and with a dose of three Gy by 63%. The levels of tryptophan and taurine in the blood are raised by radiation of both kinds, but this rise is more pronounced with neutrons. The level of glutamine is raised only after  $\gamma$ -irradiation. The authors point out that glutamine in the rat is, according to literature data, the final product of amino acid transformation in tissues. Therefore the rise in its level in rat blood may be considered as the compensatory reaction to the rise of the catabolic processes under the effect of radiation, aimed at restoration of the amino acid homeostasis. In the authors' estimation the absence of a rise in the glutamine level in blood from neutron irradiation is the result of more severe destructive processes in tissues and cells in the case of neutrons. Really,  $\gamma$ -neutron influence at a dose of one Gy inhibits activity of the anti-protease  $\alpha_2$ -MG, which protects proteins against proteolysis, whereas  $\gamma$ -rays, even with a dose of three Gy, do not cause such an inhibition.  $\gamma$ -irradiation with a dose of six Gy inhibits anti-protease  $\alpha_2$ -MG by 42%, and  $\gamma$ -neutron irradiation with a dose of three Gy by 51%.

Another difference:  $\gamma$ -neutron radiation causes, within 24 hours, an almost twofold rise of the alanine level in blood, whereas  $\gamma$ -rays do not cause such a change. The  $\alpha_1$ -AT level was not changed on irradiation. In accordance with the literature data the authors consider these results as a bad prognostic characteristic and report that shortening of the life span of irradiated rats correlates with the described metabolic changes. So,  $\gamma$ -neutron radiation with a dose of one Gy shortens the life span of these animals from  $611 \pm 21$  days to  $426 \pm 37$  days, but  $\gamma$ -rays do not similarly influence the life span. By this means the metabolic shifts

described are developed by neutron irradiation with a dose of one Gy and life span is simultaneously decreased, but  $\gamma$ -rays with a dose of one Gy do not cause either of these changes. The life span is shortened to  $204 \pm 33$  days with increasing neutron dose up to three Gy, and the changes of the metabolic foundation of amino acids and of the protease activity become more expressed [22].

The authors of this detailed study point out the severity of damage of the bone marrow by neutrons and the large expression in the changes of blood cells in the case of neutron irradiation ( $E_{ave}$  1.5-2.0 MeV) [145]. They observed these changes in rats irradiated by neutrons to doses of 0.5, 1, and 2.15 Gy. Unfortunately, data on the effects of radiation with low LET are absent from this work.

From other observations, hematological shifts in mice at the phase of depression of blood formation after irradiation by fission neutrons with a dose of 2.00 Gy and by x-rays with a dose of 6.00 Gy are the same. Hence it follows that the neutron RBE, in terms of influence on the blood cell count, is 3 during the phase of depression. However, the restoration after x-irradiation begins earlier and flows faster. The same situation takes place in the case of determination of bone marrow cellularity in mice. The RBE, using as an end point the decrease of bone marrow cellularity in these animals, is three [151]. Data on the RBE of fission neutrons, assuming as an end point the induction of chromosome damages in the bone marrow cells in mice, are close to these indications: the RBE is 3-4 [12].

Other values of the RBE with respect to bone marrow damage are obtained in dogs. In the case of unilateral neutron irradiation ( $E_{ave}$  1.5 - 2.0 MeV) the RBE of neutrons, using decrease of bone marrow cell number in a rib on the flux side, is 2.6, but on the opposite side it is 1.8. The RBE, using  $LD_{50/30}$ , is 1.8 [201]. The RBE of neutrons, assuming influence on hemopoiesis in dogs, was studied in an additional work. Relying on the literature data on the efficacy of neutron irradiation of dogs and using the concept of equal-effective dose, the authors defined the RBE of neutrons for these animals. As this takes place, it was postulated that dependence of bone marrow hemopoiesis on dose has two components; the second, more resistant, is expressed on irradiation at large doses. The author found generalized coefficients of neutron quality for such two-component curves and established the dependence of these on the mean LET for neutrons of various energies [32].

The effect of multiple neutron irradiations on hemopoiesis was studied as well. So, there is given a mathematical description of damage and reparation of hemopoiesis in mice upon fractionated irradiation by fast reactor neutrons (single dose 2.10 Gy, four-fold exposition with interval 60 days). As this takes place, the CFU value, content of karyocytes in the hip bone, and number of cells in circulating blood, was evaluated. It was shown that the regenerating potential of hemopoiesis is decreased as the fraction number and period of half-restoration  $T_{1/2}$  are increased. The restoration follows an exponential law, and the process of restoration involves fast and slow components. The first component takes four days in the case of a single exposure, and it is increased by a factor of 1.5 - 3 times upon repeated irradiation. The second component of restoration is three to four times as long as the restoration after a single exposure. By and large the  $T_{1/2}$  depends on the equivalent dose and is described by the equation:  $T_{1/2} = T_{1/2}^0 e^{-0.0009D}$ . The value of the coefficient of exponent as being  $0.009 \text{ mGy}^{-1}$  and the value of  $T_{1/2}^0$  as being equal to ten days in the case of small

doses were obtained by the authors earlier and are applicable, by their data, for the description of  $T^0_{1/2}$  in the hemopoietic system [181].

The rates of the processes of restoration were determined by the method of repeated irradiation. The equal effective doses were found for this purpose. The intensity of the restoration was evaluated by the magnitude of the remaining doses after repeated total irradiation at various intervals (1 - 30 days). The change of the  $LD_{50/30}$  on two-fold irradiation, as compared with this dose on single exposure, was the quantitative criterion for the degree of restoration [17, 49]. The effective dose corresponding to various periods of observation was found by the difference of the  $LD_{50/30}$  between single and repeated irradiation. With these data the  $T_{1/2}$  (time of decrease of the effective dose by one half) was determined. With irradiation of rats by 1.4 MeV neutrons the rate of reparation was approximately the same as with  $\gamma$ - and x-irradiation: the residual damage is  $14.76 \pm 0.26$  days, the restoration constant is  $0.062 \pm 0.6$  days, and the  $T_{1/2}$  is  $11.2 \pm 0.4$  [141].

Also described were the ultrastructural changes of the bone marrow cells in interphase after irradiation by fast neutrons of 1.6 MeV and by  $\gamma$ -rays. These changes are of a single type for both neutron and  $\gamma$ -irradiation, and they are observed mainly in the lipoprotein membrane of the cell nucleus, in mitochondrial and plasmatic membranes, as well as in nuclear nucleoproteins. Their expression and stability depend on the kind of cells, on stage of maturity, and on the dose and kind of radiation [57].

The weight and morphology of the spleen were studied. The spleen was removed and was cultivated *in vitro* at various periods after irradiation of mice by fast reactor neutrons to a dose of 6.00 Gy. It was noted that the effects of x-rays and of neutrons, taken according to equivalent mortality doses, are of a single type; but the stromal cells of spleen are more stable to the effect of neutrons than to Cobalt  $\gamma$ - and x-radiation. Increase in number of the polynuclear and gigantic cells with enormous nuclei, presence of mitosis, and retention of the ability to move are characteristic for the stromal elements growing after neutron irradiation. As for the free-moving cells of the spleen, they are damaged very rapidly after irradiation of mice by neutrons. This has developed already during the day of irradiation and leads to a sharp decrease in number of the normal migrating elements [58].

It was found in experiments on study of the spleen *in situ* that the character and periods of weight changes and morphology of spleen are the same after irradiation of mice and rats by fission neutrons with doses of 0.50-3.00 Gy and x-rays with doses of 5.00 Gy and 6.00 Gy ( $LD_{50/30}$ ) in the case of equivalent, according to lethality, doses of radiation of both kinds.

In studies of the features of neutron effects on bone marrow, researchers studied not only morphological changes but shifts in DNA metabolism as well. It was shown that in rats, irradiated by neutrons with  $E_{ave}$  1.5 - 2 MeV (using a pulse regimen) and by  $\gamma$ -quanta of  $^{60}Co$ , synthesis of DNA is inhibited. The dynamics of the inhibition has two phases. For the first it is characterized by decrease of synthesis within 2.5 - 4 hours after exposure, during which neutrons inhibit synthesis greater than  $\gamma$ -rays, at the same doses. The RBE of neutrons, assuming the effect of inhibition of DNA biosynthesis by 50% as the end point, is 2.7. The restoration of DNA biosynthesis or tendency to restora-

tion was observed at the second phase with doses from two Gy of  $\gamma$ -rays and to 1.13 Gy of neutrons within 18 hours after irradiation. However, in the case of neutron irradiation the restoration up to norm takes place only with doses less than 0.25 Gy. Thus, at higher neutron doses the inhibition of DNA biosynthesis is much longer than after  $\gamma$ -irradiation.

With  $\gamma$ -rays the effect on the activity of  $\alpha$ - and  $\beta$ -DNA-polymerases is decreased within 4 hours without any tendency toward restoration. However, the activity of  $\alpha$ -polymerase is not decreased until 18 hours after neutron irradiation, and then begins to decrease; the activity of  $\beta$ -polymerase is sharply decreased (to 25% of the initial level) immediately after the exposure. There is a strong correlation between the inhibition of DNA and the decrease of  $\beta$ -polymerase activity ( $R = 0.94$ ). The authors suppose that the inhibition of  $\beta$ -polymerase activity is the reason for low reparability of neutron damages, that is, for the high biological efficacy of neutrons [182]. The inhibition of DNA biosynthesis in bone marrow of rats on  $\gamma$ -irradiation (two, four, six Gy), according to some data, depends on animal age: it is less in young rats but is more stable than in mature adult animals. It is most significant in the group of mature animals, but by 18 hours after exposure the DNA synthesis is entirely or partially restored. Neutrons ( $E_{ave}$  1.5 -2 MeV, pulsed irradiation, with doses of 2.2 and 5.7 Gy) inhibit DNA synthesis in rats of all ages more than  $\gamma$ -rays; the inhibitory effect is similar in all age groups. Inasmuch as the proliferative activity in these groups varies, the authors consider that the presence of proliferation is essential for  $\gamma$ -rays to affect DNA biosynthesis, whereas it is not essential for the effect of neutrons [183, 187].

The special role of intestinal damage in neutron damage of an organism is known. Because of this, the attention of many researchers has been given to this organ. The morphological changes and changes of the mucopolysaccharide complexes in the epithelium of the mucous membrane of small intestine in rats were followed up after irradiation by fission neutrons to a dose of 2.80 Gy ( $LD_{100/4}$ ) from five hours to four days. Increase of the content of the glycoproteins and mucoproteins, which are positive by the SIA coloring method [209], are stable to ptyalin and to hyaluronidases, and which give  $\gamma$ -metachromasia with the toluidine blue is noted in the mucous membrane in every period. The SIA-positive substances are accumulated very early in the submucosal layer inside vessel walls and outside of them. The mitotic activity of the epithelium is entirely stopped within three to five hours after irradiation, and the cell population of crypts is sharply decreased. Aberrant mitoses are present in the crypts, and the migration of epithelial cells to the villi is retarded. These phenomena are almost entirely repaired by the fourth day.

Changes of the villus epithelium are also of interest. Towards the second day the cells in the lower part of the villus become polymorphic, their nuclei are increased, and alkaline phosphatase ceases to be detectable. Towards the third day already the entire surface of the villus is covered by fewer cells, the cells are increased in volume, and are vacuolized with large light nuclei. The epithelial flooring of crypts exists at all phases of evolution of the intestinal syndrome. The described phenomena testify to the changing of the functional condition of the epithelium, and its transformation to active secretory function with simultaneous full preservation of its protective cover function. It is

apparent that the mechanism of epithelial transformation is associated with radiation damage of the formative cells in crypts; the altered elements of the epithelial flooring of villus are their direct descendants. Another factor of the epithelial transformation is delay of the natural renewal of cells.

The same qualitative changes are observed upon irradiation of mice by x-rays to a dose of 1,000 R ( $LD_{100/4}$ ). These data allow one to determine the RBE of fission neutrons with respect to their ability to damage intestine in mice: the RBE is four [107]. A closely related value of the RBE - 3.6 - was determined in studies of the number of the chromosome aberrations in the duodenal epithelium of mice after their irradiation by fission neutrons to doses of 0.20-2.00 Gy [100].

Changes of not only the epithelium but the neural elements of the intestinal walls and the muscle layer as well are described in the acute intestinal syndrome in mice. So, damages of the intramural nervous cells, up to their disintegration, are discovered on irradiation by fission neutrons with a dose of 3.00 Gy ( $LD_{100/4}$ ). These damages remain even during the phase of restoration of the intestinal epithelial flooring: thinning of muscle layer of intestine wall, delay of secretion in crypts, and damage of neural cells is observed longer than the changes of the epithelial layer [179].

The intestinal damage in mice from neutrons is related to the age of the animals as well. So, on irradiation of mice of various ages by neutrons of 0.85 MeV and x-rays, within four hours after neutron irradiation the blocking of mitosis in crypts is not complete, although it is observed in four-week-old and mature animals. However, the crypts are most heavily damaged at this period in four-week-old mice after the effect of both kinds of radiation with doses corresponding to the  $LD_{100/4}$ . The age differences are especially marked within 48 hours after irradiation: the changed cells migrating from crypts to the villi are visible in newborn and two-week-old mice, whereas in four-week-old and mature mice the villi are almost entirely covered by anomalous cells. Apparently the rate of renewal of cells in the villi in animals of various ages is not the same. The long persistence of the differentiated cells in the villi, an insignificant number of anomalous cells migrating to them from the crypts, and the restoration of the crypts are necessary prerequisites for normal function of the intestine in newborn and two-week-old mice and promote their survival in the periods that are characteristic for development of the acute intestinal syndrome [18].

The acute intestinal syndrome in rats on neutron (1.5 Gy) and x-irradiation (six Gy) develops with a similar type of changes in intestinal morphology. They are almost the same as those described in mice, but they do have several differing features. Pyloric spasm is expressed more in rats, and indigestion is observed somewhat later [107].

The morphological study of internal organs in irradiated guinea pigs does not reveal the intestinal changes which are characteristic for the intestinal syndrome. This syndrome is not observed clinically either. In one experiment 97 guinea pigs of both sexes and of various weights were used. Of these 55 animals were irradiated by x-rays with doses of 3, 4, and 13 Gy; 22 animals were exposed to fission neutron irradiation with doses of two Gy, and 20 served as control.

With x-rays at a dose of 1,300 R the animals perished within six to seven days.

Enteritis against a background of hemorrhage was detected on dissection in one case; in the other six cases at these periods the hemorrhagic syndrome with several areas of hemorrhage, mainly in the hypodermic cellular tissue and in the lungs, without any manifestations of the intestinal syndrome, was clearly displayed. The time of the animals' death was shifted to 11 days on irradiation with a dose of 4 Gy. Multiple hemorrhages into the hypodermic cellular tissue, lungs, and gastrointestinal tract were detected in the four animals that perished at this time. The hemorrhagic syndrome and anemia were found in animals that perished by day 14 after irradiation with 3 Gy. The greatest decrease of hemoglobin content in blood (to 38-41%) takes place by day 14. Multiple hemorrhages into the hypodermic cellular tissue, lungs, and the gastrointestinal tract were detected in animals killed by six-seven days after the effect of various doses of x- and neutron-irradiation. The weight of the spleen is significantly decreased. The marked restoration of the organ does not take place, as opposed to rats and especially to mice. The structure of spleen is retained with a distinct picture of the red pulp sinus impoverished of cells. Migrated elements and the local formation of myeloid elements are not noticed in the spleen. The Kupfer cells of the liver did not undergo myeloid transformation and did not reproduce.

Observations show that the changes in guinea pigs have the same character with both neutron and x-irradiation. The gastrointestinal syndrome is not expressed at the doses used. The reason for the animals' death is hemorrhage and anemia. Disturbances in the hemopoietic system are developed during the time of passivity of reticular tissue and are poorly restored. The absence of the expressed intestine damages during neutron injury cannot be explained by features of distribution of the absorbed dose, since according to phantom measurements about 75% of the neutron dose on the surface is absorbed in the intestinal area [174a]. In addition, extremely large doses of x-irradiation were not successful in creating significant intestinal damage. It may be supposed that this is due to species specific features of radiosensitivity of guinea pigs, which have been indicated in the literature [136].

The changes in the intestine upon neutron irradiation were studied not only in rodents but in dogs as well. Under the effect of unilateral irradiation of dogs by  $\gamma$ -quanta and by neutrons of 1.5-2.0 MeV, beginning with dose levels of 1.50 Gy of neutrons and 2.50 Gy of  $\gamma$ -rays, a decrease in the number of cells of the jejunum takes place. The number of cells decreases down to 30% of the initial number on neutron doses of 3.50 Gy and  $\gamma$ -rays of 5.50 Gy; these doses cause acute intestinal syndrome in half of the cases. The rate of degradation of the mucous of the small intestine upon the effect of radiation of both kinds is approximately the same. The maximum decrease in cell number comes by the fifth to seventh day. The RBE of neutrons, using as an end point the decrease of cell number by day seven, is 1.8-2.4 [202].

The study of neutron effects on the digestive apparatus is not restricted to the intestine. It was found that neutron irradiation of the anterior abdomen causes phase changes of the secretion of gastric succus (juices) to food stimulus more so than on x-irradiation with a similar dose. The fermentative activity of gastric succus is decreased simultaneously, again more so by neutron effects. The excretion of dye introduced into the organism through the stomach wall is intensified after x-irradiation, whereas after neutron irradiation at the beginning it is

diminished, but by day five it is increased. The barrier functions of the stomach mucous membrane are enhanced after x-irradiation, but they are not preserved after neutron effects. Administration of atropine and dihydroergotamine before the study of stomach function in irradiated animals has varying influences on the radiation disturbances described, but in any case these changes are less modified with neutron effects. Atropine, as a whole, influences positively both the function of the stomach and the general condition of irradiated dogs, whereas the influence of dihydroergotamine is negative. Gastric lavage during the first six days of radiation sickness acts favorably, whereas administering exogenous bile to the stomach aggravates radiation sickness and negatively influences the function of this organ [74-76].

In studies of neutron damage of liver, changes of hepatic morphology in mice and rats were noted after irradiation by fission neutrons with doses of two to three Gy. Within seven to ten days after exposure the development of foci of hemopoiesis, variation of sizes of the hepatocyte nuclei, and appearance of gigantic forms of these cells were noted. On days 12-14 myeloid metamorphosis and reproduction of the Kupfer cells was described. This takes place even after a dose of 0.5 Gy, during which visible preceding changes in these cells were not observed. It is possible that the transfer of elements of bone marrow to the liver plays some role in this compensation reaction of forming of blood lines in the liver: this, in particular, explains the appearance of megakaryocytes in the intraglobular capillaries. As regards the parenchymal elements, which at the end of the second week after neutron exposure are still without visible initial damages, they begin the reproductive process of pathologic forms of cells. As a whole the condition of liver after neutron irradiation with doses of 2.50-3.00 Gy is not qualitatively different from the condition after x-irradiation with a dose of 10.00 Gy. The phenomena in hepatocytes described above have an adaptive, secondary character - they are caused by intensive functioning of the liver [107].

At large doses of fission reactor neutrons (six Gy) solitary damaged cells appear within one day after irradiation, resulting in disturbance of the microscopic hepatic architecture. In mice in the last periods of life irradiated with a dose of four Gy, and by five to ten days after three Gy, fatty membranes reminiscent of thick cords are found in hepatic parenchymal cells. Along with that, hepatic necrosis was not observed, which the author of this work had observed as an early effect of absolutely lethal doses of  $\gamma$ -rays [59].

It was found on biochemical analysis that total body irradiation of rats by fast reactor neutrons with a dose of 2.15 Gy leads to increase of the total quantity of cholesterol in the liver, and to delay of its etherification at early periods after irradiation. Local irradiation (3.00-15.00 Gy) causes increase of total and free cholesterol in this organ depending on dose. The disturbance of etherification with this kind of irradiation takes place only at the first day after the effect of 3.00 and 6.00 Gy, but after 15.00 Gy it is noted during all periods of observations [170].

Total irradiation of rats by fast neutrons with a dose of 2.30 Gy or by x-rays with a dose of 7.00 Gy decreases the ATPase activity in the liver tissue. During the first hours after neutron irradiation the ATPase activity is suppressed mainly in the nuclei of hepatocytes, but after the effect of x-rays ATPase activity suppression occurs in the cytoplasm [6].

Under the effect of neutrons of six MeV and x-rays the content of the adenine nucleotides in rat liver is changed. The level of ATP is decreased proportionally to the dose of radiation, but such a relationship is not observed with changing of the levels of ADP and AMP. The content of ATP is maximally decreased after three days, and the content of AMP after seven days. After 30 days all indicators have returned to the initial level. The RBE of neutrons, using as end points a 37% and 30% decrease of the ATP level, is 3.5 and 3.4, respectively. An effect of fractionation of the dose is noted: after single irradiation by neutrons with a dose of 1.00 Gy the ATP level is 55.2% with respect to the control value, but after a split dose (0.50+0.50 Gy with an interval of two days) it is 81.7%; increase of the interval up to seven days does not change the effect [85].

In several works an unusual effect of neutrons as regards hepatocytes was reported. In the first work it was reported that polyploidization of hepatocytes is detected after irradiation of rats by neutrons of 14 MeV and x-rays by use of flow cytometry. The authors bring forward evidence for the polyploidization taking place as a consequence of fusion of cells and their nuclei, and also as the result of blocking of mitosis in cells replicating DNA. The RBE of neutrons, assuming an end point of cell fusion, is 5,000 [30]. From data of the same authors, the neutron efficacy depends on the age of the rats and the energy of the neutrons: fission neutrons are more effective. Administration of uranyl acetate to rats before irradiation prevents fusion of hepatocytes [31].

These reports are very interesting; however, evidence for this result would be much greater, in our opinion, if the authors excluded the possibility of cell agglutination.

In studies of neutron effects on endocrine glands several works are devoted to the thymus. So, changes of this gland in mice are traced after the effects of fission neutrons and x-rays. A decrease of thymus weight up to 50% within one day after irradiation by neutrons with a dose of 0.50-2.60 Gy was noted. The loss of gland weight and its restoration depends on the dose of radiation. The character of changes of the thymus weight after x-irradiation is the same. Destruction of the thymus depending on the dose of irradiation is noted on histological investigation. Restoration of the architecture of the gland occurs at a sacrifice of restoration of the number of the gland's own cells and, it is conceivable, partially at a sacrifice of colonization by lymphocytes from blood. Within two weeks after irradiation by neutrons with a dose of 1.50 Gy the architecture of the thymus is almost returned to normal, but the size of the gland in this period is less than initially, and the weight is half that of the control.

The changes of mass and structure of thymus in rats is the same using equally effective (with respect to lethality) doses of x-rays and neutrons. This is observed in mice as well [107].

Influence of fast neutrons (1.5-2 MeV) on thymic lymphocytes of rats was evaluated by formation of polydeoxynucleotides (PDN) in the gland after total irradiation of animals. Dynamics of chromatin decay in the thymus cells (that is, dynamics of their interphase death), judging from the accumulation of the PDN, is the same under both neutron and  $\gamma$ -influence. However, intensity of chromatin decay under the effect of neutrons is higher. The RBE of neutrons, using as an end point this index, is changed from three to two on doses of 0.25-4 Gy. Decay

of the cells is begun at a smaller dose of neutrons than is the case with  $\gamma$ -irradiation. It was also shown that most of the accumulation of the PDN in the thymus after neutron irradiation is impossible to explain by the great decay of chromatin under the effect of neutrons; it is the result of decay of a large number of thymocytes [51].

The endocrine function of the thymus was studied as well. A study on the blood level of the thymus serum factor demonstrated that irradiation of rats by 6 MeV neutrons (1-2 Gy) and by x-rays (4-8 Gy) leads to inhibition of thymic activity, depending on the period of observation and on the radiation dose. The greatest inhibition is observed within three days after irradiation and is combined with the maximum decrease in the number of thymus cells: the RBE of neutrons, assuming as end point the duration of inhibition of thymic activity, is more than four; assuming as end point the severity of inhibition, the RBE is less than three. Shielding the thymus weakens the radiation effect, although to a lesser degree in the case of neutron irradiation than in the case of x-irradiation. By this means, the role of the abscopal effect ["bystander effect"] of radiation in inhibition of the thymus activity by neutrons was shown and evaluated [97a].

In studies of the effect of neutrons on the adrenal glands it was noted that the changes of their mass and structure after irradiation of mice and rats by fission neutrons and by x-rays was of the same type, using doses of equally effective lethality [107].

Studies of 11- $\beta$  oxycortico-dehydrogenase as an indicator of activity of the adrenal cortex demonstrated that, at the first two weeks after irradiation of rats by fast reactor neutrons, the activity of this enzyme in liver, thymus, spleen, and lymphatic ganglia is changed as well as in blood. Along with this, the expression of the reaction in each of these organs has own features. At the second half of the period of observation, after 15 days, the changes in the activity of this enzyme in these different organs varies [96].

In studies of the influence of 6 MeV neutrons (single irradiation with dose 1 Gy, or two fractions of 0.5 Gy separated by an interval of seven days), it was revealed that energy metabolism in rats is inhibited; the level of ATP and ADP decreases while the level of ATP/ADP in liver and in muscles increases. Simultaneously the development of hypercorticism, with increase of 11-oxycorticosteroids in the blood, was noted; the level of insulin increases as well, although to a lesser degree. Administration of hydrocortisone enhances inhibition of the energy metabolism by neutrons [167]. Fractionation of dose enhances the described changes in ATP and ADP levels [196].

Histologic changes in the thyroid gland and in the hypophysis of rats irradiated by fast neutrons with a sub-lethal dose are described [9,10]. They were not compared with the results of radiation with low LET, but they did not appear different from the changes caused by sparsely ionizing radiation, judging from the literature data.

Early changes of the ultra structure of the rat adenohypophysis after neutron ( $E_{\text{ave}}$  0.85 MeV) irradiation with an  $LD_{30/30}$  dose are studied in detail. An increase of function of corticotropic and thyrotropic hormones, as well as inhibition of activity of somatotropic hormone, is described, which is analogous to the previously described early inhibition after x-irradiation. The presence

of dark cells among corticotropic cells and thyrotropic cells is a distinction that the authors suppose is possible to explain by the direct effect of neutrons on cells of the gland [171].

The influence of neutron irradiation on some metabolic processes in an organism was investigated. So, the effect of fast reactor neutrons on DNA content in various structures of cells of the bone marrow, liver, and thymus was also studied. Similarly to what had been described in the literature, decrease of the DNA content in hepatocytes and in their nuclei was noted already within five min. after beginning neutron irradiation of rats to a dose of 2.15 Gy, but around days four to eight the DNA content in nuclei increases, while the total quantity of DNA in the cell decreases. The content of DNA in bone marrow cells changes as well. Changes of the biosynthesis of DNA in various organs are described: increase in DNA synthesis in mitochondria of hepatocytes is noted, and in bone marrow cells inhibition of DNA synthesis in nuclei is noted at early periods after onset of irradiation. The individual character of these changes has engaged our attention: in the data of the authors they were not infrequently diametrically opposite. This phenomenon remains unexplained.

The same authors traced the metabolism of DNA for two years after neutron irradiation of rats with a sublethal dose. In summing up their observations the authors note that neutron irradiation with an LD<sub>50</sub> dose (2.15 Gy) and with a sublethal dose (0.5 Gy) leads to decreasing of the total content of DNA in various organs, possibly due to the death of cells. In the surviving cells, after suppression of DNA synthesis comes its activation in excess of the initial level, and within 3 - 12 months there is instability of biosynthesis [195].

Increase of free DNAase 1 and its inhibitor in liver and spleen takes place after total irradiation of rats by fast neutrons, and after x-irradiation as well; but this increase is expressed more with neutron irradiation. In the course of six months after irradiation with a dose of 0.5 - 1 Gy these indices are normalized. Then around 9 - 12 months, when tumors appear in animals, the activity of free DNAase 1 and its inhibitor increases again; this takes place on a background of insignificant changes of bound DNAase 1. The dependence of these shifts on the character of the tumors is interesting. In the liver and spleen of rats, which carry benign tumors, the activity of free DNAase 1 is increased. In the case of malignant tumors the activity of free DNAase 1 and its inhibitor in liver and spleen does not differ from the control, whereas the activity of bound DNAase 1 is decreased in both organs [68].

The changes in the oxygen regime of an organism under the effect of fast neutrons from a nuclear reactor were studied. Oxygen consumption, number of erythrocytes, and content of hemoglobin and methemoglobin in blood were compared.

It was discovered, on the basis of analysis of the results of these studies, that the effect of fast neutrons, as compared with  $\gamma$ - or x-rays, causes earlier and more severe disturbance of the oxygen regime of an organism. Single irradiation of rats by fast neutrons (doses of 1.00, 2.15, and 3.00 Gy) leads to phase changes of respiratory metabolism and oxygen tension in the brain as part of the dynamics of radiation sickness. There is a sharp increase of  $pO_2$  occurring in the brain two hours after irradiation of animals by a dose of 2.15 Gy in the presence of insignificant changes of oxygen consumption; this indicates an early postradiation inhibition of oxidizing metabolism in the brain.

Irradiation by lethal and sublethal doses leads to a decreased number of erythrocytes and hemoglobin content in the blood of animals. The minimum values of the erythrocyte number and hemoglobin content are noted by the 8th – 12th days. A wave of increasing number of erythrocytes and quantity of hemoglobin in blood is observed with a dose of 3.00 Gy by two days after irradiation.

The phase changes of methemoglobin in blood of irradiated animals are noted during the course of radiation sickness. With doses of 2.15 and 1.00 Gy the maximum level of methemoglobin is observed around 12 - 16 days. With a dose of 3.00 Gy, an unswerving increase of methemoglobin beginning from two hours after irradiation up to the death of animals was noted. From four to six days after irradiation with 2.15 Gy until death the respiratory metabolism and the  $pO_2$  in brain are increased, following which a sharp decrease of these indices, observed until the time of death of the animals, takes place. A rapid increase in the methemoglobin level is noted during this period as well. These previously described changes of respiratory metabolism,  $pO_2$ , and methemoglobin content in blood may be considered as indicators of moribund changes in an irradiated organism. Fast neutron doses of 1.00 and 2.15 Gy cause an increase of affinity of hemoglobin to oxygen during the first seven days after irradiation, and during the period of the height of radiation illness a decrease of durability of the hemoglobin-oxygen bond takes place. The affinity of hemoglobin to oxygen successively decreases after an initial increase with a dose of 3.00 Gy. The decrease of durability of the hemoglobin-oxygen bond is to be considered as a compensatory reaction to disturbance of the respiratory function of blood.

The indicators studied--respiratory condition,  $O_2$  transfer,  $O_2$  consumption, oxidative phosphorylation, and so forth--bear witness to an essential and dose dependent decrease of the level of oxygen regime during the early period of radiation sickness caused by the effect of fast neutrons [47].

The free radical processes in tissues of animals irradiated by fast neutrons were also studied. For this purpose the formation of free radicals in lyophilic dried tissues of rats irradiated by x-rays and by neutrons with  $LD_{50/30}$  and  $LD_{100/30}$  doses as defined by the electron paramagnetic resonance (EPR) method was studied. It was noted that the number of free radicals in tissues within 0.5-3 hours after exposure is decreased and reaches minimum values by two to three days. By the seventh day their level begins to rise. Expression of these changes is not the same in different tissues and depends on the type of radiation. So, the effect of x-rays is expressed more in lung, liver, spleen, and thymus tissues, whereas it is not detected in muscles, kidneys, and in brain. The level of free radicals is virtually unchanged by the effect of neutrons on bone marrow and brain; the changes in the other tissues are about the same, but they are greater than after x-irradiation. The effect is increased as dose increases [185].

These results approximate the results obtained in earlier work: the number of free radicals in the liver and spleen of rats is found to be decreased in rats irradiated by 14 MeV neutrons to a dose of 5.00 Gy by 5 days after exposure. The investigation was not carried out before this time. About 30 days after irradiation the concentration of radicals in these organs and in blood exceeds initial values, but at days 10, 20, and 30 the differences from the control are not marked [26]. A qualitative similarity between the EPR spectra arising in tissues

from the effects of both kinds of radiation is shown on irradiation of samples of tissues of liver and of spleen by  $\gamma$ -rays and by neutrons in pulse mode ( $E_{n0} = 0.002 - 10$  MeV): the same radiation induced radicals and the same regularities of their formation and destruction on annealing are characteristic for both kinds of radiation. Values of the RBE are shown in Table 5.

**Table 5.** Radiation chemical yields  $G$  (spin/100 eV) of free radicals (FR) arising in tissues of liver and spleen on exposure to  $\gamma$ -radiation and neutrons, and the RBE of neutrons calculated as ratios  $G_n/G_\gamma$  for liver and spleen of mice.

| FR        | $10^2 \cdot G_\gamma$<br>liver | $10^2 \cdot G_\gamma$<br>spleen | $10^2 \cdot G_n$<br>liver | $10^2 \cdot G_n$<br>spleen | RBE<br>liver | RBE<br>spleen |
|-----------|--------------------------------|---------------------------------|---------------------------|----------------------------|--------------|---------------|
| $\Sigma$  | 60                             | 60                              | 100                       | 100                        | 1.7          | 1.7           |
| $OH\cdot$ | 10.0                           | 11.8                            | 16                        | 23                         | 1.6          | 1.9           |
| $K\cdot$  | 5                              | 5                               | 25                        | 23                         | 5            | 4.6           |
| $TH\cdot$ | -                              | 3.4                             | -                         | 3.9                        | -            | 1.1           |
| $Q\cdot$  | 18                             | 15                              | 36                        | 20                         | 2.0          | 1.3           |
| $Rs\cdot$ | 4.5                            | 11                              | 5                         | 13                         | 1.1          | 1.2           |
| $S1\cdot$ | 14                             | 13                              | 23                        | 14                         | 1.6          | 1.1           |

Total values  $G$  are equal to the number listed in Table 5 divided by  $10^2$ . For example, for  $OH\cdot$  in liver with  $\gamma$ -irradiation  $G = 10/10^2 = 0.1$

$\Sigma$  = value of total radiation chemical yield of primary radicals immediately after irradiation at  $77^\circ K$ .

The authors called attention to the high RBE for the radicals that are products of water radiolysis ( $OH\cdot$ ) and lipid radiolysis ( $K\cdot$  and  $Q\cdot$ ): in the first case, in connection with the role of hydroxyl radicals in the mechanism of radiation damage, and in the second case, in connection with the question of a possibly greater vulnerability of the cell membrane to neutrons [155].

Some data on effect of neutrons on the testicle are cited above, in the section on cells. However, the influence of neutrons on testicles as a whole, and not only to their cell structures, was studied in some works. So, decrease of testicular weight, reaching a maximum by 35 days after exposure, was observed on irradiation of mice by neutrons of 1 MeV with a dose of 1.00 Gy. Fractionation of the dose (0.25 Gy daily for four days) produces the same effect. Neutron irradiation is more effective than x-rays by a factor of five to six. Unlike testicles, the decrease of splenic weight from fractionated irradiation is less pronounced than from a single exposure.

A gradual disappearance of seminal cells beginning with the youngest, that is with spermatogonia, was observed on histological study. A full devastation of the spermatogenic channels was not noted, because along with the disappearance of mature cells, more young cells appear. The effect of fractionation is not noted on histological data as well [111].

The influence of fractionation on the effect of neutron irradiation regarding cells of testicles was studied in later works repeatedly and in greater detail. Mice were irradiated by neutrons of 1.58 MeV, determining within three

months the frequency of reciprocal translocations in spermatogonia and the frequency of dominant mutations. The influence of fractionated irradiation on the frequency of mutations was studied at two different levels of total doses (1.00 and 2.16 Gy), using various degrees of fractionation and various intervals between irradiation. It was shown that the frequency of mutations with fractionation is increased as compared with that from single irradiation. The obtained results testify to the higher genetic efficacy of fractionated irradiation by fast neutrons as compared to a single exposure with the same dose at both levels of dose. In contrast, with fractionated x-irradiation the increased mutation frequency was observed only with high doses [45]. [Editor's comment: *Presumably at a high single dose the cell killing is so great that few mutated cells survive; with fractionation, however, repair allows greater survival and consequently expression of more mutations.*]

It was shown on irradiation of mice by neutrons of 1.5 MeV with doses of 1.00 and 0.50 Gy and by neutrons of 0.19 MeV, that the sensitivity to neutrons of seminal cells at the various stages of maturation is arranged in the same order as by sensitivity to x-rays also. The RBE is about four for fast neutrons and is about six for intermediate neutrons [128].

In other research changes in the testicles of rats were observed for two years after total irradiation by fast neutrons to a dose of 4.00 Gy. As this occurred, quickly developing destructive changes in the epithelium of spermatic channels were noted, which led to stoppage of spermatogenesis and to atrophy of the testicles. The outlined changes took place against the background of abrupt damage to blood vessels; these changes are accompanied by hemorrhage and by interstitial tissue edema at all time points studied. Damage of the epithelium of spermatic channels was combined with development of hypertrophic and hyperplastic processes in interstitial tissue, which led in some cases to the development of tumors of the gonadal stroma, having characteristics of Leydig cells.

Histological research of the testicular tumors discovered integrity of their hormonal activity. It might also be well to point out the more frequent yield of testicular tumors from the influence of fast neutrons as compared with other kinds of irradiation.

The vulnerability of not only cells of the spermatogenetic epithelium, but also the special character of reaction of interstitial tissue at remote periods after irradiation as well, has engaged our attention. The observed interstitial changes apparently are connected not only with the direct effects of ionizing radiation, but with post-radiation damage of all neuroendocrine regulation of functions in the organism as well [29].

It was shown on cytogenetic study of the effects of 1.5 MeV neutrons on the cells of the testicle in mice receiving whole body irradiation with doses of 0.18-2.16 Gy, that, as on x-irradiation, the post-meiotic stages are genetically more radiosensitive, assuming frequency of dominant lethals as an end point, than are spermatogonia. The dependence of mutation frequency on dose has a linear character in mature sperms in the dose interval 0.18 – 2.16 Gy, and in spermatids and spermatocytes in the dose interval from 0.18 – 1.00 Gy. In spermatogonia the character of the dependence of the frequency of dominant lethals on dose differs from the character observed at post-meiotic stages. The frequency

of reciprocal translocations in spermatogonia increases linearly with dose up to 0.72 Gy. Further increase of the radiation dose does not lead to increase of the mutation frequencies, and an abrupt decrease of the translocation frequency is observed at a dose of 2.16 Gy. A similar difference in the character of the dose-effect curves, assuming yield of mutations, between post-meiotic stages and spermatogonia was obtained on x-irradiation as well. The RBE of fast neutrons with relation to x-rays is the same for the frequency of dominant lethals at post-meiotic stages. The frequency of reciprocal translocations in spermatogonia is also equal; its value is about 4.5 [44].

Research of damages of spermatogenetic epithelium by neutrons was combined with study of its restoration. Accordingly, mice were irradiated by fast reactor neutrons with single doses of 0.60 or 1.50 Gy, and with two doses of 1.50 Gy with an interval of 120 days. The contribution of  $\gamma$ -quanta to the total dose was 40%. Spermatogenesis was evaluated by the quantity of cells with various degrees of differentiation in a suspension of testicular tissue. The authors demonstrated that the relative decrease in the number of spermatocytes depends exponentially on dose. The  $D_0$  for neutrons is 0.35 Gy, and for  $\gamma$ -quanta – 1.20 Gy. The  $D_0$  is the same for spermatids and for spermatozoa: in the case of neutron irradiation it is 0.20 Gy for both cells, but in the case of  $\gamma$ -quanta – 0.55 Gy. The restoration of spermatogenetic epithelium is reduced as the dose increases. Dependence of the time for 50% restoration of the damage ( $T_{1/2}$ ) on equivalent dose is adequately described by the expression  $T_{1/2} = T_0^{1/2} e^{-0.0009D}$ . This expression describes the restoration from  $\gamma$ -damages as well as from damage by neutrons. The equivalent dose is calculated with use of the average value of the RBE, which is equal to three [184].

It is expedient to divide research on the effects of neutrons on the nervous system in accordance with the doses of radiation used: small (which does not cause radiation sickness), middle (sublethal and lethal doses), and high (supralethal, causing the CNS syndrome). Some results were mentioned earlier on the changes of nervous elements of the intestine wall by neutron irradiation at doses causing the acute intestinal syndrome. There is experimental evidence on the changes in brain at lethal doses in animals of various species. So, in studies of the effect of protons with energies of 120 and 660 MeV, (dose interval of 0.50 – 10 Gy), of neutrons with energies from 25 KeV to 10 MeV (dose of 3.00 Gy) and  $\gamma$ -rays in animals of various species - mice (8.30 Gy), rats (6.40 Gy) and rabbits (900 R), the damages induced in the brains of these animals at various periods from two hours to four days was studied. The author notes the mass death of oligodendroglia and microglia underneath the ependyma of the anterior horn of the lateral ventricle and in the olfactory lobes and bulbs within six to eight hours after exposure. Degeneration of the glia is started earlier and is finished by the end of the first day. Death of the glial cells is not observed at doses less than 100 R. These damages are described in animals of all species and are the same after irradiation of any kind [27].

Listlessness, refusal to eat, impossibility to keep the head stable, passive pose, tremor of extremities are noted at the height of radiation sickness (12 -13 days after irradiation with circular irradiation of dogs by fast reactor neutrons to a dose of 4.00 Gy). ("Circular irradiation" refers to rotating the dog's cage while being exposed so the animal receives a more uniform dose of radia-

tion.) Moreover, in most of the dogs lameness was noted; in some, aggressive behavior; and the day before death - tottering, inability to stand, lying on the side. Histological research shows that the number of normal neurons in irradiated animals is sharply decreased. In most animals less than ten percent of the neurons are normal, and in half only six percent were normal. Severe changes were observed in 25 - 45% of nerve cells, and 20 - 35% of the cells were dead. The changes in the pyramidal cells of the second layer of the cortex are similar to those in the hypothalamus in terms of severity. As time passes beyond the moment of irradiation the number and degree of severity of the changed cells grow, and the prognosis of restoration for the cells is doubtful [46].

The effects of neutrons on the nervous system was studied in experiments with whole body and local (head) irradiation of mice by fast neutrons with doses of 1.50 - 3.00 Gy as well, and the obtained results together with the literature data are summarized in a monograph [180]. Using a neurological classification, the authors define the picture of neutron damage of the nervous system as "radiation encephalomyelopolyganglioneuropathy with frequent variations of encephalomyelopathy and multiganglioneuropathy". Each case, depending upon the degree of extent of the process, is divided into microfocal, focal and total forms.

Noting the essential similarity in the damage of the nervous system by low LET radiation and by neutrons, the author shows that neutron damages differ by greater severity and multiformity of changes, and by greater expression of local changes of nervous elements in the side of the animal nearest the source of radiation.

In contrast to research studies of the effects of neutron irradiation at lethal doses, where fast neutrons were used and morphological changes in the condition of nervous system were studied, in studies of the influence of low doses intermediate neutrons ( $E_{ave}$  0.3 MeV) were used and biochemical shifts in the brain, as well as in myocardium, liver, and spleen were observed. The attention of the researchers was focused on carbohydrate-energy metabolism and on nucleotide metabolism, on activity of some enzymes (pyruvate dehydrogenase and other dehydrogenases, enzymes of the Krebs cycle, cytochrome oxidase and others), on metabolism of amino acids connected with the Krebs cycle, on enzymes of transamination and decarboxylation, and on others. The experiments were carried out in rats, and the doses of neutrons and x-rays used were about 0.10 - 0.40 Gy. It was shown, as the result of these studies, that single and fractionated irradiation by intermediate neutrons at low doses causes pronounced shifts in the energy and protein metabolism in the brain and other organs, by which is proved not only the direct influence of radiation on these processes, but the participation of the hypothalamus, hypophysis, and adrenal glands in these influences as well. Also shown were changes in the activity of the membrane-bound dehydrogenases of brain mitochondria under these conditions and correlation between changes in the dehydrogenase activity and changes of content of glucocorticoids in blood; as well as simultaneous changes in the ratios of ATP/ADP, NAD/NADH\*, and NADP/NADPH. By expression of these indicated effects in many cases it is possible to consider a dose of x-rays of 0.40 Gy as being approximately equal to a dose of intermediate neutrons of about 0.13 Gy. Within 90 days after exposure the majority of metabolic processes are returned to their normal level [28, 97, 104, 118, 121, 168, 169, 197, 198, 199].

The effect of high and super-high doses of neutrons on the central nervous system (CNS) was studied in experiments in rats irradiated by neutrons of 0.85 MeV with doses of 100 - 200 Gy and by  $\gamma$ -quanta of  $^{60}\text{Co}$  with doses of 100-400 Gy [80]. The  $\text{LD}_{100/1}$  in these experiments is 200 Gy for neutrons and 350 Gy for  $\gamma$ -rays. The authors note that death of rats at the first day can hardly be caused by brain edema. So, upon immersion of histological material into celloidin, an enlargement of the perivascular space, peculiar to brain edema, is rarely encountered, especially in the area of the third and fourth ventricles of the brain. Upon immersion of the same material into paraffin, dilatation of the pericellular and perivascular spaces, described under similar conditions by several authors, is found in most cases. This appears to be connected with certain features of this method.

The CNS syndrome at the indicated doses of radiation and the death of the animals within the first day appear against a background of relatively small damage to the neurons. The RBE of neutrons, assuming as end point the yield of irreversible changes in neurons, is 1.75. However two to three days are necessary for the appearance of widespread irreversible changes in neurons. Indeed, irreversible changes in large quantities of neurons are observed in rats killed within these periods after  $\gamma$ -irradiation by a dose of 140 Gy. On evidence derived from this work, a rise of permeability of the brain blood vessels can scarcely play an important role in the development of the CNS-syndrome on doses of hundreds of Gray, inasmuch as within four hours after  $\gamma$ -irradiation with a dose of 400 Gy the escape into brain tissue of intravenously administered uranine is not increased, but is decreased almost in half. The authors have supposed that a substantial role for development of the CNS syndrome in the conditions described pertains to disturbances in the metabolism of mediators. Increase of the GABA content, detected in cerebellar tissue studied specifically for its presence, gives evidence of such disturbance [80]. The authors subsequently studied the effect of super-high doses on the central noradrenergic formation of brain - the blue spot (BS) and on the mesencephalic nucleus (MN) of the trigeminal nerve, which have the most important role in the system, providing homeostasis in an organism-including one's own brain. It was shown that within 24 hours after  $\gamma$ -irradiation in rats with doses of 100 - 200 Gy and neutron irradiation (0.85 MeV) with a dose 100 Gy, in 55% of neurons of the BS severe chromatolysis develops. On irradiation with a dose of 100 Gy of neutrons and 300 Gy of  $\gamma$ -quanta (death of rats within one day after exposure) most of the neurons of the BS are found to be severely changed.

Neurons of the MN are more radioresistant: most of them are changed only to a small degree. Comparing damages of neurons in the nucleus dentatus of cerebellum with damages in the BS and the MN, the authors noted that on the same super-high doses of radiation the damage of nerve cells in different formation of brain is not the same: neurons of the BS are most highly damaged, neurons of the cerebellum to a smaller degree, and neurons of the MN to an even smaller degree. Therefore the authors infer heterogeneity of neurons of different parts of the brain with respect to radioresistance, even under conditions of super-high doses of radiation [81].

Noting the relatively low radiosensitivity of nerve cells under the conditions

of development of the CNS syndrome caused by super high doses of radiation, and demonstrating the disturbances in balance of mediators (GABA) and the changes in the central adrenergic substances of the brain, the authors tried to evaluate the functional condition of the membranes and cellular structures of neurons resulting from  $\gamma$ - and neutron effects with high doses, excluding the abscopal effect of radiation. With this in mind, the experiments were carried out with isolated sympathetic ganglia of frog, a somewhat exotic subject for radiobiological experiments. The results of electrophysiological research showed that irradiation of the ganglia by neutrons of 0.85 MeV and 14 MeV, and by  $\gamma$ -quanta of  $^{60}\text{Co}$ , with high doses (up to 200 Gy) caused depolarization of the membranes of the neuronal ganglia; this depends on dose. The RBE for decreasing the membrane potential is 1.0 for neutrons with energy of 14 MeV, and 1.3 with energy of 0.85 MeV. An increase of the threshold for synaptic activation of ganglia cells is observed as well. However these effects do not lead to the blocking of conductivity through the ganglia, proving the rather high radioresistance of the membrane structures which provide the conductivity of nerve impulses through the ganglia [20].

Histological, biochemical, and electrophysiologic research studies on the effects of high doses of neutrons on the CNS were completed by electron microscopic study of nerve cells and of the blood microcirculatory system of the sensorimotor cortex. It is stated that during the first six hours after whole body irradiation of rats by neutrons to a dose of 10 Gy there are changes of the ultrastructure of capillaries of the sensorimotor cortex, which give evidence of swelling of the capillary walls, of increase of their permeability, and of development of pericapillary edema. Coarse destructive changes in the wall of microvessels are not detected, which presumably indicates the reversible character of the observed changes and gives evidence of definite stability of the system of microcirculation of brain to the effects of radiation even at high doses.

Study of cortical neurons reveals that immediately after irradiation of rats by neutrons (0.85 MeV) with a dose of 10 Gy changes take place in nerve cells, which are explicable as indicators of their functional activity. The signs of suppression of nerve cells are noted within six hours after irradiation, and at the end of the first day the activation of intercellular compensatory processes may be noted. All changes within six hours after irradiation are apparently the result of direct effects of radiation on neurons. As time progresses this pathology is increased by damage of the microcirculatory system. The changes in neurons and blood circulatory capillaries do not qualitatively differ from analogous changes from the effects of low LET radiation [1, 2].

Development of the CNS syndrome from the effects of high doses of neutrons (0.85 MeV) is studied in guinea pigs irradiated with doses of 20 - 130 Gy as well. It is shown that death of 50% of these animals within the first 1.5 days (CNS syndrome) takes place at a dose of 75 Gy. The RBE of neutrons relative to electrons with an energy of 8 MeV, using the mean lethal dose as the end point criterion, is 1.87. A complete adynamia in all animals occurs with irradiation by neutrons at a dose of 130 Gy, but also occurs in 30% of cases at a dose of 65 Gy. By contrast, almost the same frequency of hypodynamia (other than adynamia) - 40% - on irradiation by electrons is observed only at a dose of 100 Gy. The convulsive syndrome is developed as an effect

of neutron irradiation with a dose of 65 Gy, at which level, as a rule, the radiation acts as an external irritant; only with a dose of 90 Gy does it occur in 100% of animals and have a spontaneous character. A similar picture is described with the effect of electrons at a similar dose of 80 - 100 Gy. It is interesting that convulsions develop in 100% of cases as an effect of electrons with a dose of 80 Gy, but death within the first 1.6 days occurs in only 20% of the cases. After neutron irradiation the situation is different: the convulsive syndrome is absent at doses of 25 and 40 Gy, whereas death of animals within 1.5 days occurs at about the same rate, 18 and 25% respectively [205].

Research on the remote consequences of neutron radiation effects included studies on the oncogenic, cataractogenic effects, and changes of life span of irradiated animals as well. In the latter case the average duration of life of rats (life span, or LS) was defined after x-,  $\gamma$ -, and neutron (0.9 MeV) single and fractionated irradiation. It was shown that the LS depends on the dose of radiation, during which neutrons influence this indicator to a large extent: for example, the LS of rats is shortened up to 15 months after neutron irradiation with a dose of 1 Gy, whereas for the same reduction of the LS in the case of x-irradiation a dose of about 3 Gy was needed. Fractionated irradiation by neutrons according to a schedule of 1 + 1 Gy with an interval of 24 hours between fractions produces the same effect as a single exposure of a dose of 2 Gy, but increasing the interval between fractions up to 72 hours increases the efficacy of irradiation; the LS is shortened more than in the case of single exposure [24]. This observation is difficult to explain, especially since in experiments where the interval of fractionation with low LET radiation was increased demonstrated the expected effect: the LS was not as significantly decreased as after a single radiation exposure [24].

The cataractogenic effect of neutrons with energy 0.85 MeV was studied in rats irradiated with doses from 0.20 to 4.00 Gy. Changes in the crystalline lens during the animals' life time, and the changes detected in it on histological study after the animals' death, allowed the author to conclude that it is expedient to distinguish two levels of doses. With doses in the first level morphological changes of the crystalline lens arise, but they do not lead to development of cataract; with doses in the second level, cataracts are developed. The first level of doses is 0.20 - 0.40 Gy, the second level is 0.40 - 1.00 Gy. In the latter case, within six to seven months clinically detectable opacities in the crystalline lens appear, which significantly progress as time goes on [103, 109].

The oncogenic effect of fast neutrons (1.4 - 1.6 MeV) with doses of 0.25 - 4.00 Gy was studied in 500 rats after single exposure: of the 225 rats which survived irradiation, 94 rats developed 117 tumors during the period between 6 and 25 months after irradiation. Mammary gland tumors were found in 48 of these rats; in some of these cases there were also neoplasms at other sites. Multiple mammary tumors occurred in five rats. Data on development of tumors are summarized in Table 6.

**Table 6.** Development of mammary tumors in rats (male and female) irradiated by fast neutrons.

| Group of animals | Dose (Gy) | Quantity of animals in exp. |    | Periods of formation of tumors during the 6th through 25th month interval |   |       |   |       |   |       |   |       |   |       |   |     |     |
|------------------|-----------|-----------------------------|----|---------------------------------------------------------------------------|---|-------|---|-------|---|-------|---|-------|---|-------|---|-----|-----|
|                  |           |                             |    | 6-9                                                                       |   | 10-12 |   | 13-15 |   | 16-18 |   | 19-21 |   | 22-25 |   |     |     |
|                  |           | m                           | f  | m                                                                         | f | m     | f | m     | f | m     | f | m     | f | m     | f | M,% | F,% |
| 1                | 0.25      | 50                          | 50 | -                                                                         | 2 | -     | 2 | -     | 1 | -     | 2 | 2     | - | -     | 1 | 4   | 16  |
| 2                | 0.50      | 50                          | 50 | 2                                                                         | 1 | 1     | 4 | 1     | 6 | -     | 1 | 2     | 3 | 1     | 4 | 14  | 28  |
| 3                | 2.00      | 17                          | 15 | 1                                                                         | 2 | -     | 1 | 1     | 1 | 1     | - | -     | 1 | -     | - | 17  | 28  |
| 4                | 4.00      | 18                          | 5  | -                                                                         | 1 | -     | - | 1     | 2 | -     | - | -     | - | -     | - | 5.5 | 60  |
| 5                | control   | 40                          | 60 | -                                                                         | - | -     | - | -     | - | -     | - | -     | 1 | -     | 2 | -   | 5   |

In studies of the functional condition of the endocrine glands in rats within various periods after irradiation an activation of the luteotrophic function of the hypophysis was noted. Later, six to eight months after irradiation, a suppression of thyroid activity was observed. Disturbance of thyroid function is noted in 55% of animals that had developed mammary gland tumors. Reactivity of the adrenal glands was decreased in individual rats, and in well differentiated tumors the daily excretion of 17-ketogenic steroids and 17-ketosteroids was increased.

Thus a significant number of neoplasms of various locations, but predominantly of mammary gland tumors, are produced upon irradiation of animals by fast neutrons. The blastomogenic effect of fast neutrons is increased with increase of dose. More tumors are formed in females than in males, but these are usually benign. In males there is almost the same number of benign as malignant tumors. The majority of the tumors arise between 10 - 15 months after irradiation. In non-irradiated animals the first tumors appear later than 20 months after beginning the experiment.

On histological examination the mammary gland tumors which developed in both males and in females were mainly of connective tissue origin [191]. In another work female rats were irradiated by neutrons of the same energy with a dose of 0.20 - 0.50 Gy. The mammary gland tumors in experimental rats irradiated once with a dose of 0.25 Gy developed in 16% of the animals within 25 months after beginning the experiment. On irradiation of the animals with a dose of 0.50 Gy mammary gland tumors developed in 24.4% within 25 months. In 38% of the rats the tumors developed within 25 months after the beginning of the experiment. In the control group the mammary gland tumors were observed in only five percent of the animals. In the irradiated rats the first tumors were detected within six months after irradiation, but in the control group at the age of 22 months. In many instances mastopathy preceded the development of tumors in the exposed rats. Mammary gland neoplasms are separable by histological type into two groups: benign (fibroadenomas, adenomas, adenofibromas, cystadenomas) and malignant (adenocarcinomas, solid cancers, fibrosarcomas). In all animals an increase of the content of luteotropic hormone, with undulating changes (during the first month and for the following year) of

the function of the thyroid, gonads, hypophysis, and adrenal cortex is noted. It is the author's opinion that this gives an indication of the role of disturbance of the neuroendocrine regulation in the carcinogenic effect of neutrons on the mammary glands [178].

Changes of DNA synthesis in nuclei and in mitochondria of liver cells and of bone marrow cells were studied at remote periods after irradiation of rats by fast neutrons with a sublethal dose. These changes are not identical at various periods, and are often the opposite between nuclei and mitochondria. Shifts of the DNA content in some organs at remote times after irradiation were studied as well. It was shown that during 6 - 9 - 12 months in animals with tumors the quantity of DNA in nuclei of the bone marrow cells is increased by 140%, whereas it is close to normal or significantly lower than normal in nuclei of hepatocytes [195]. Changes of activity of DNAase 1 and its inhibitor in the process of formation of tumors were studied as well. It turned out that the activity of the natural inhibitor of free DNAase 1 in spleen and liver is distinctly enhanced by 9 - 12 months after irradiation by neutrons of the same energies (1.4 - 1.6 MeV) with doses of 0.5 and 1 Gy; the period of formation of tumors in rats is around 9 - 12 months. The activity of free DNAase 1 itself simultaneously increases whereas the activity of bound DNAase 1 is not essentially changed. By the time of development of most of the tumors (within a year after irradiation) the inhibitor activity becomes less expressed. The shifts of activity of the enzyme and of its inhibitor in liver and spleen during the development of benign and malignant neoplasms are the reverse of each other: in the first case the activity of free enzyme is increased, but the activity of the inhibitor is decreased; the level of bound inhibitor is not changed. In the case of malignant tumors the activities of free DNAase 1 and its inhibitor are not changed, but the activity of bound DNAase is decreased [68].

There is a great interest in the possibility of early recognition of radiation (in particular neutron) damage and the prediction of its outcome in the evaluation of resistance of an organism to radiation. In connection with this the original research on the features of the effects of radiation with low LET and of fast neutrons with use of registration of super weak luminescence of blood and its components arrested our attention [161]. Registering the spontaneous super weak luminescence of blood and amplifying it by passing electric current through blood (electrochemiluminescence - ECL) or inducing of luminescence in blood plasma by using microquantities of  $H_2O_2$  (chemiluminescence - CL), the authors studied changes of this indicator in irradiated rats. Characteristics of ECL and CL kinetics and of changes in intensity of the super weak luminescence within various periods after irradiation of animals by fast neutrons with doses of 0.5 - 3 Gy were obtained. It thus appears that the changes of intensity of ECL after  $\gamma$ -irradiation and neutron irradiation are not the same: in the first case maximum of the luminescence for the  $LD_{50/30}$  was reached on the second day, and in the second case on the first day. There are differences in kinetics of the ECL as well. In rats which perished in early periods after  $\gamma$ -irradiation the level of luminescence was enhanced up to death, but in the case of neutrons it dropped by the fourth day to levels lower than in the control group. Furthermore, the authors describe a different character of changes in luminescence intensity within the first several days in animals that died later on from radiation sickness and in the surviving animals.

The authors elaborated a method of analysis of kinetic characteristics of che-

luminescence (KCC) in rats irradiated by neutrons with an LD<sub>50/30</sub> dose. As this takes place, changes of shape of the kinetic curves and their parameters are manifested.

The micromethod proposed by the authors needs only 0.01 ml of blood for measurement of luminescence, to give an opportunity to research the dynamics of this luminescence in a single animal. Using measurement of the dynamics of CL in intact rats and comparing the character of the CL with the resulting radiation injuries, the authors divided intact animals into three groups: 1 - with high radiosensitivity, 2 - radiosensitive, and 3 - radioresistant. The features of KCC presented are characteristic for the representatives of each group. In the authors' opinion, the radiosensitivity of intact animals may be determined by these methods, and thus predict results prior to irradiation [161].

These results are impressive. Together with these studies there is an obvious need for further research to determine how universal the regularities described are. It is reasonable, using these methods, to evaluate the radiosensitivity of animals of other species, to differentiate in them the damages induced by neutrons or by low LET radiation in the early periods of radiation sickness and to predict its outcome.

Estimations of the proteolytic activity of the blood of irradiated animals, of the amino acid composition of blood, and its content of protease inhibitors are proposed, as indicated above, for achievement of this last purpose. There are data indicating, from the perspective of this plan of research, fluorescence of lymphocytes in blood.

Research performed showed that the intensity of light scattering in lymphocytes of peripheral blood increases from 1.89 to 7.8, depending on dose, within the first day after  $\gamma$ -neutron irradiation in a reactor channel (Table 7):

**Table 7.** Influence of  $\gamma$ - and  $\gamma$ -neutron irradiation on the change of intensity of light scattering and connection of these changes with life span shortening in rats.

| Influence                     | Dose of irradiation, Gy | Intensity of light scattering of lymphocytes within 1 day after irradiation | Average life span, days | Criterion of statistical significance p compared with control |
|-------------------------------|-------------------------|-----------------------------------------------------------------------------|-------------------------|---------------------------------------------------------------|
| Biological control            | -                       | -                                                                           | 596±20                  | -                                                             |
| $\gamma$ -irradiation         | 1                       | 1.23±0.10                                                                   | 619±32                  | > 0.05                                                        |
|                               | 2                       | 1.89±0.12                                                                   | 459±34                  | < 0.05                                                        |
|                               | 4                       | 2.18±0.15                                                                   | 457±40                  | < 0.05                                                        |
| $\gamma$ -neutron irradiation | 1                       | 1.89±0.14                                                                   | 439±49                  | < 0.05                                                        |
|                               | 2                       | 2.25±0.20                                                                   | 354±40                  | < 0.05                                                        |
|                               | 3                       | 4.70±0.40                                                                   | 204±33                  | < 0.05                                                        |
|                               | 4                       | 5.95±0.50                                                                   | 5.0±0.1                 | < 0.05                                                        |
|                               | 6                       | 7.80±0.70                                                                   | 2.0±1                   | < 0.05                                                        |

The average life span of rats correlates with early changes of intensity of light scattering in lymphocytes and is accordingly  $439 \pm 49$  days when irradiated with a dose of 1 Gy, decreasing linearly as the dose increases. The life span of rats after  $\gamma$ -irradiation with a dose of 1 Gy is  $619 \pm 32$  days and does not significantly differ from the biological control ( $596 \pm 20$  days). The intensity of light scattering measured within one day after exposure is 1.23. With  $\gamma$ -irradiation with a dose of 2 Gy the intensity of light scattering was the same (1.89) as with  $\gamma$ -neutron irradiation with a dose of 1 Gy; accordingly the life span was  $459 \pm 34$  days. The RBE of  $\gamma$ -neutron radiation, assuming as an end point the parameter of the intensity of light scattering at an angle of 90 degrees, was two to three. It was previously shown that the RBE of mixed  $\gamma$ -neutron radiation, assuming as an end point the life span of rats, is 2.86 - 3.10 [55].

Based on experimental data obtained the authors came to the conclusion that it is possible to predict remote effects (i.e. survival) by the change of light scattering in lymphocytes of peripheral blood within one day after exposure [23].

The modification of neutron effects was one of the most intensively studied problems in the USSR. Stimulated by requirements of radiation therapy, researchers demonstrated a possibility of sensitization of animals to the effect of neutrons. It was observed in experiments in mice that boron-containing boronyl-acetic and methylboroncarbonic acids sensitizes these animals to the effect of neutrons of energy 1.3 MeV at a dose of 3.00 Gy, decreasing their survival by 20 - 40%. [138].

As for weakening of neutron effects, the opportunity of chemical protection of mammals against the effect of neutrons attracted our greatest attention. Studies of chemical protection against neutron radiation in the USSR were started during the first half of the 1960s against a background of disappointing results of the first experiments in the USA and in the Federal Republic of Germany (FRG) with the use of radioprotectors in conditions of neutron irradiation of mice [117]. In combination with data on the extremely high biological activity of neutrons, these results provided a rather hopeless outlook for the development of ideas of chemical protection against neutrons, or at least on the possibility of success for the investigation of special compounds capable of weakening the effect of neutrons.

Embarking on a study in this field, the authors - collaborators of the PNPI of the RAS - were of the opinion that the first necessity was to study the question, how do the neutron RBE values for mice correspond with those for animals of other species? It was equally important to find out what are the factors that define the RBE values. Furthermore it was necessary to realize what damages are specific to neutrons and what specific, hitherto unknown radioprotectors are required for their modification.

For solving the first task the values of the RBE of neutrons with energy of 0.85 MeV were defined for identical conditions in animals of various species (mice, rats, golden hamsters, rabbits, dogs) on circular irradiation; the contribution of  $\gamma$ -quanta to the total dose was less than 20% [147, 149, 151]. The results are shown in Table 8.

**Table 8.** The RBE of neutrons ( $E_{ave}$  0.85 MeV) using as end point lethal effect ( $LD_{100/30}$ ) in animals of various species.

| Animal species  | RBE, relative units |
|-----------------|---------------------|
| Mice            | 2.8                 |
| Rats            | 3.2                 |
| Golden hamsters | 3.4                 |
| Guinea pigs     | 1.9                 |
| Rabbits         | 1.9                 |
| Dogs            | 1.2                 |

Similar values of RBE for the  $LD_{100/30}$  end point in rats (2.8 and 2.9) and in mice (2.5 and 2.7) were obtained in several works [8,55,60,202]. The RBE decreases as the energy of neutrons increases: for an energy of 14 MeV the RBE, assuming as end point the  $LD_{50/30}$ , is  $1.9 \pm 0.32$  [148]; for an energy of 22 MeV it was 1.3 [60]. The RBE of fast neutrons of 1.5 - 2 MeV, assuming as end point a lethal effect in dogs, in another work was somewhat greater - 1.8 [202]. However this is quite easily explained, because the dogs in this experiment were irradiated unilaterally, from the right side, and the decrease in the depth dose coefficient from the right side to the left side was 2.5 - 4.5. The data in Table 8 were obtained from circular irradiation.

Analysis of the RBE values in animals of various species clearly shows dependence of this coefficient on size (mass) of the body of a biological subject; the RBE decreased from 2.8 in mice to 1.1 in dogs, that is by a factor of 2.5, as the body mass increased. A comparison of these facts with the coefficients presented in the literature for the RBE in large animals (sheep, goats, asses) led the author to conclude that the regularity observed in his experiments is universal [151].

There are important data about tissue doses of neutrons and loading doses for this explanation [33,200]. However, measurements of the space and energy distribution of neutrons of 0.85 MeV in tissue-equivalent phantoms of mouse, guinea pig, rabbit, and dog were carried out for analysis of the above results. During the course of this analysis it was shown that the absorbed dose in the phantoms of small animals changes little with depth, and along the axis of the phantom it practically coincides with the surface dose; when this happens it is mainly caused by reactions of elastic collisions. The mean absorbed dose falls only a little more than one percent in the reactions  $^1H(n,\gamma)^2H$  and  $^{14}N(n,p)^{14}C$ . In contrast to this, for a dog phantom the dose on the surface of body is more than the mean dose from reactions of elastic collisions by a factor of 1.7, and from all reactions by a factor of 1.3. In this connection the doses from reactions of elastic collisions along the phantom axis with a diameter of 15 cm (phantom of a rabbit) and 22 cm (phantom of a dog) differ by a factor of two, and for the entire doses by a factor of 1.5.

The relationship of the dose from heavy particles - protons, recoil nuclei, and protons - of the reaction  $^{14}N(n,p)^{14}C$  to the dose from fast electrons (from the reaction  $^1H(n,\gamma)^2H$  changes with depth. For a dog phantom this ratio:

$$\frac{D_n + D \text{ } ^{14}\text{N}(\text{n,p})^{14}\text{C}}{D \text{ } ^1\text{H}(\text{n},\gamma)^2\text{H}}$$

is 7.4 on the surface, 7.6 along the axis, and in an average dose 2.35 ( $D_n$  - dose from reaction of elastic collisions as measured by an ionization chamber).

The specific results of measurement are shown in Table 9.

**Table 9.** Distribution of the absorbed dose of  $\gamma$ -neutron irradiation in phantoms of animals of various species on uniform irradiation by pure neutrons from a nuclear reactor

| Specific absorbed dose                                                                                      | Phantom of                 |                            |                               |                         |
|-------------------------------------------------------------------------------------------------------------|----------------------------|----------------------------|-------------------------------|-------------------------|
|                                                                                                             | Mouse<br>(diameter 3,5 cm) | Rabbit<br>(diameter 15 cm) | Guinea pig<br>(diameter 7 cm) | Dog<br>(diameter 22 cm) |
| Full dose*<br>on surface of<br>phantom (is<br>taken to be<br>unity)                                         | 1                          | 1                          | 1                             | 1                       |
| Full dose along<br>the axis of<br>phantom (with<br>respect to the<br>surface dose)                          | 0.95                       | 0.69                       | 0.92                          | 0.45                    |
| Dose of $\gamma$ -ra-<br>diation** on<br>the phantom<br>surface (rela-<br>tive to the full<br>surface dose) | 0.013                      | 0.1                        | 0.07                          | 0.12                    |
| Dose of $\gamma$ -ra-<br>diation along<br>the phantom<br>axis (relative to<br>the full surface<br>dose)     | 0.015                      | 0.31                       | 0.10                          | 0.26                    |

\* Dose from reaction of elastic collision neutrons + dose from protons of reaction  $^{14}\text{N}(\text{n,p})^{14}\text{C}$  + dose from  $\gamma$ -radiation of reaction  $^1\text{H}(\text{n},\gamma)^2\text{H}$ .

\*\*Dose from reaction  $^1\text{H}(\text{n},\gamma)^2\text{H}$ .

These data explain why the RBE of neutrons changes with the size of the biosubjects. They testify that the damage of critical organs in large animals, in contrast to mice, is not primarily caused by densely ionizing radiation, but by secondary  $\gamma$ -radiation. The effect of the latter, as is known, is very effectively weakened by the classic radioprotectors - by sulfur-containing compounds and by compounds with a hypoxic effect - and by hypoxia by itself.

Along with that, as indicated in Table 8, changes of the RBE of neutrons in various species of animals do not take place monotonously according to increasing size of the biosubject. So, in rats and in guinea pigs the RBE differs by a factor of 1.7, although the mass of these animals is the same. The reason for this is

apparently in the features of organism, which are revealed upon more detailed analysis of neutron injury of these and other animals. It was shown that the period of occurrence of maximum lethality of rats corresponds to four to six days after irradiation, and for guinea pigs 10-12 days. These data and the previously reported results of morphological research of the intestine of these and other animals testify to the essentially lower sensitivity to neutrons of guinea pigs. This is confirmed as well by data from other work, in which it was shown that the RBE of neutrons, assuming intestinal damage as the end point, in guinea pigs is 1.87 [204], which is much less than in mice and rats - 4. The RBE for guinea pigs, assuming as end point the  $LD_{50/30}$ , as shown in other work of the same authors, is 2.2 [203]. It is higher than the value of 16% indicated in Table 8, but substantially less than for rats. Similarly, the second factor which determines the value of the neutron RBE for each species is the radiosensitivity of critical systems [151]. The high radiosensitivity of the intestine to neutrons is mainly inherent to mice and rats. In the other animals, better modeling of the anatomical-physiological features of injury of the intestine of high primates, including humans, shows that intestinal injury plays a much smaller role. Injury of the hematopoietic system becomes more prominent here; this is much more amenable to chemical protection, though still not a trivial problem. By this means, the studies conducted disclose biophysical and anatomical-physiological prerequisites for a more optimistic prognosis of the effect of chemical protection of mammals, and possibly of humans as well, than could be supposed up till now.

Researching the second aspect of the problem, the authors underline that they did not find considerable convincing evidence for qualitative differences in neutron damage of biological subjects from the damages by radiation with low LET, neither in their own data, nor from literature data. Most reports on such differences are almost always explicable by features of dose distribution in a subject. Nevertheless experiments were carried out in which the results of neutron irradiation and the effects of  $\gamma$ -rays were studied in conditions where this factor was entirely excluded. Changes in the hair bulb in rats exposed to x- and neutron (0.85 MeV) irradiation were studied in these experiments. 14-day old rats (the first and the most radiosensitive postnatal phase of hair growth) were used. Doses of neutron (1.5 Gy) and x-rays (6.37 Gy) were selected so that they induced synchronous (on day seven) complete epilation in all irradiated animals over the back area. Upon microscopic and ultrastructural study of cells of the hair follicle bulb it was noted that the changes detected in this formation are qualitatively the same from the effects of radiation of both kinds [21].

These and previously obtained data lead the authors to the conclusion that the differences between the effects of neutron irradiation and the effects of low LET irradiation are only quantitative: increasing the dose of low LET radiation or equalizing the doses of neutrons,  $\gamma$ - or x-rays required to cause a specific effect, the same changes in cells, in subcellular structures, in organs and organism are detected. This is entirely in agreement with biophysical and molecular biological observations which found out that neither in formation of free radicals, nor on induction of DNA breaks does the effect of neutrons qualitatively differ from the effect of low LET radiation. It follows that if, using some chemical compounds, the effect of low LET radiation is weakened, then, in all likelihood, the same effect will be achieved under the condition of neutron

irradiation as well.

All data presented demonstrate that there is no reason to doubt that an opportunity of effective chemical protection against neutrons exists. The experiments confirm this conclusion.

Mice were used for these experiments in accordance with usual radiobiological practice. In spite of the fact that neutron injuries of mice lack certain features enabling them to serve as a model for mammalian species in general, experiments with these animals ensures large enough numbers of observations, which are necessary for statistically justified conclusions. Moreover, a positive result with the use of radioprotectors in mice under conditions unfavorable for protection against neutron irradiation of mice allows one to hope not only for a similar positive effect of these compounds in animals of other species, but for a significantly better result. For experiments in mice radioprotectors of various kinds were utilized, primarily aminothiols and their derivatives, as well as indolyl alkyl amines and oxyacetonyl, which differ from aminothiols in their mechanism of effect.

A protective effect was not obtained in experiments using protectors with hypoxic effects: neither oxyacetonyl at various doses, nor indolylalkyl amines (serotonin, 5-methoxytryptamine, or mexamine) significantly enhance the survival of mice irradiated by neutrons. This is evidently explained by the small role of the oxygen effect in the biological effects of neutrons. In addition, special research studies demonstrate that the indolylalkyl amines protect well only a single critical system in an organism, the hemopoietic system. But its damage plays a significantly smaller role in the neutron injury of mice than does damage of the second critical system, the intestine, which is only poorly protected by these protectors. In these cases, when the contribution of the injury of this system to the overall damage to the organism is diminished (at certain periods of individual development, on fractionated irradiation with large intervals between exposures), certain radioprotective effects of mexamine may be observed [63, 172]. Furthermore, under conditions in which mice undergo extreme hypoxia or even complete deprivation of oxygen, anoxia essentially enhances their survival of neutron irradiation. So, anoxia protects newborn mice not only against x-rays with a DRF of 2.5, but also against fission neutrons as well with a DRF of 1.7 [154]. These data allow some hope that in animals of other species, with other relationships of the role of critical systems in survival from radiation injury, and especially where the contribution of secondary  $\gamma$ -radiation to the injury is relatively large, hypoxia and hypoxic agents alike can be effective. As for research in mice with irradiation by fission neutrons under the usual conditions, it was found, in experiments with derivatives of aminothiols (cystaphos), that this protector prevents radiation damage of the most sensitive critical system in mice - the intestine. The mitotic index in the intestinal crypts is not sharply decreased upon administration of cystaphos to animals before neutron irradiation and is restored much more quickly than in the control animals. This testifies to expression of protection of the stem cells of the intestine against 3 Gy - the  $LD_{100/4}$  dose - of irradiation [162]. (This dose was chosen because it exceeds the minimum absolutely lethal dose.) The same protection is detected with respect to the other critical system - blood formation [151]. The ability of ami-

nothiol protectors to enhance survival of mice lethally irradiated by neutrons was stated in other experiments. So, cystamine at the usual dose (150 mg/kg calculated to base) enhances their survival with a DRF of 1.2 and doubles the life span of the nonsurviving animals. With the use of aminoethylisothiuronium (AET) the DRF is 1.3, during which the protective effect is evinced even with a lethal dose of neutrons. Even more effective are cystaphos and S-2-(3-N-aminopropylaminoethyl)-phosphorothioate (gammaphos, WR-2721): the DRF in their use reaches 1.35 [151, 152]. Gammaphos protects golden hamsters effectively against fission neutrons as well [149].

These results allow one to conclude that the aminothiol radioprotectors have an expressed radioprotective effect during irradiation by fast neutrons as well. The greatest efficacy of protection in mice is observed at the range of radiation doses from the LD<sub>50/30</sub> to the LD<sub>80/30</sub>, which is one of the features of experiments in these animals. It was shown as well that the efficacy of protectors (cystamine and AET) is preserved with the use of the most important method of their administration - per os [151]. The other studies allow one to expand the list of thiol radioprotectors, which are effective on neutron irradiation of mice. So, 2-guanidinoethansulfenylthiosulfuric acid enhances their survival with a DRF of 1.2 [110].

The synthetic inductors of interferon - complexes of polyribonucleosinic and polyribocytidylic acids [poly(I) • poly(C)] and polyriboguanilyc and polyribocytidylic acids [poly(G) • poly(C)] - upon intraperitoneal administration in mice within three days before irradiation by fission neutrons enhance survival of the animals, with a DRF of 1.1 for [poly(I) • poly(C)] and with a DRF of 1.2 for [poly(G) • poly(C)]. The combination of [poly(G) • poly(C)] (administration two days before irradiation) and WR-2721 (administration just before irradiation) protects mice even more effectively against fission neutrons, and the DRF is equal to 1.33 [110].

Polysaccharide prodigiosane possesses a small radioprotective effect on neutron irradiation of mice; it enhances their survival more than 20% under the condition of exposure to a high dose of neutrons at the LD<sub>90/30</sub> level [108]. On the other hand, protection against neutrons is not observed with D<sub>2</sub>O replacing 25-30% of H<sub>2</sub>O in the tissues of mice, although it had been supposed that with a smaller cross section of reaction for neutron interaction with deuterium nuclei (D) than with hydrogen nuclei (H), this was grounds for expecting a weakening of the radiation effect. Moreover, the deuterating of an organism by the method of replacement of light water in the drinking bowl with heavy water influenced the radioresistance of animals negatively; this is possibly connected with D<sub>2</sub>O toxicity [151].

All these data, excluding the last, show the efficacy of chemical protection of mice, which are highly sensitive to radiation of this kind, against neutrons. As this takes place, it is significant that the protection is not carried out by some special protectors, but by the same agents as with exposure to low LET radiation. But the efficacy of protection of mice by cystamine, AET, cystaphos, and gammaphos is as much as 25% lower than under the condition of radiation by  $\gamma$ - and x-rays. So, even with this not very successful model which does not always adequately reproduce the total situation for most mammals because it presents radiation protection as being more difficult than it actually is, a high

level of chemical protection against neutrons can still be gained. However, it will not do to consider that the problem is solved. Research in subjects that allow better modeling of neutron injury in large animals and humans is necessary. We carried out such research in dogs with use of respiratory hypoxia (mixture of oxygen with nitrogen in the proportion 1:10) as a radioprotective agent. On circular irradiation of animals by neutrons with a mean energy of 0.85 MeV to a dose of 4 Gy only two of nine control dogs survived, but eight of ten protected animals survived. In these animals acute radiation sickness presented in a milder form in contrast to the control animals, with less leukopenia and with more rapid restoration of the content of leukocytes in peripheral blood [64,154]. Thus, in large animals such a method of weakening the radiation effect as hypoxia, which would seem to be less effective against the effects of neutrons, turns out to be extremely efficient. These observations are explicable only by the fact that the dosages to critical organs in dogs are caused to a substantial level by radiation with low LET; this, in turn, means that the chemical protection of large biological subjects against neutron radiation is also as practical as against  $\gamma$ - and x-rays, and is provided, not by some special class of radioprotectors, but by the classic radioprotectors. This entirely refutes the widespread ideas about the futility of chemical prophylaxis against neutron injuries and their lethality. A complete revision of these ideas, with removal of their corresponding formulations from the standard documents on the subjects, is a practical outcome of these research investigations.

Is it possible to further increase the efficacy of chemical protection against neutrons? Our experiments demonstrate that this is attainable by means of combining protectors of different kinds. In experiments in mice a combination of cystamine with AET and mexamine or of gammaphos with AET and mexamine provided survival of 80-100% in lethally irradiated animals [18a]. We stated in the other studies that combination of gammaphos with transplantation of bone marrow enhances the effect of the protector, and combined use of gammaphos, transplantation of bone marrow, and shielding of a small part of the marrow safeguards against death in more than 60% of the animals [151,152]. Another perspective is the combination of aminothiols with unithiol. As this takes place, an opportunity to increase the dose of the radiation protector and accordingly the effect of protection arises [35]. Thus, the DRF of AET in these experiments with irradiation of mice by fission neutrons increases up to 1.4, which is only 14% smaller than the DRF of x-rays.

Nontraditional methods were also used for increase of resistance of an organism to neutron exposure. True enough, in these research efforts the effect was evaluated not by change of the survival of animals but by decrease of some biochemical and physicochemical shifts induced by irradiation. So, for example, it was shown that administration of human ceruloplasmin in mice before their irradiation by fast neutrons with a dose of 2.5 Gy normalizes the content of lipids and the cAMP/cGMP index in liver, enhancing activity of catalase in this organ; in other words, administration of ceruloplasmin weakens the changes induced by irradiation [11].

Judging from the content of free radicals in tissues of rats, prolonged adaptation of animals to hypoxia enhances stability to neutron influence. The decrease in the level of free radicals under the influence of neutron irradiation in the

adapted animals is not so high as in the non-adapted ones [185].

The radioprotective effect of vitamin B6 during neutron irradiation was studied not in mammals but in yeast, during which the protective effect of this vitamin was demonstrated with respect to yeast cells [142].

A large cycle of research has been devoted to the radioprotective effect of DNA during neutron irradiation [192]. The authors demonstrated that isologous, homologous, and heterologous DNA and products of its enzymatic digestion decrease the damage of yeast cells by fast neutrons. The DRF of isologous DNA administered to a culture of yeast before irradiation is equal to 1.6; after irradiation it was 1.3 [143,144,193]. Heterologous DNA, homologous DNA, and the products of their heat denaturation, upon administration in small quantities (1-3 mg/kg) just before fast neutron irradiation, enhance survival of rats by one to three times. This enhanced effect with respect to survival continued to the end of the first year after exposure, although it was small in this case. The increase of survival of irradiated rats under the influence of exogenous DNA is combined with several parameters: less expression of radiation changes of hemopoiesis; immune reactivity; normalization of metabolism of DNA; and activity of DNAase 1 and its natural inhibitor [68,193,195]. The authors do not indicate the DRF of DNA, complicating the quantitative evaluation of the radioprotective effect of this biopolymer in animals. Undoubtedly, however, DNA, which attracted the attention of many scientists in the 1970s as a radio-protector, weakens the damage effect of not only low LET radiation but of fast neutron irradiation as well.

Finishing the review, it can be concluded that the results of research in the Soviet Union enriched to a significant extent knowledge about the biological effects of neutrons, being in agreement with the results of research in other countries and supplementing them as well. In many instances they expanded the knowledge base, made it more profound, and even permitted approaches to the solution of actual problems, as, for example, in the case of chemical protection against neutron radiation or of the use of new methods of recognition or predicting the outcome of neutron injury.

Unfortunately, most of the data obtained in labs of the USSR for many years were unknown to scientists of other countries\*. The object of this review is to familiarize them with the most substantial results obtained in the former Soviet Union.

*\* Publication of A.G. Sverdlov's book on chemical protection against neutrons translated into Chinese is an exception.*

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