HEALTH EFFECTS
OF CHORNOBYL ACCIDENT
THIRTY YEARS AFTERMATH

Chapter 1
CHORNOBYL AND EVOLUTION OF RADIATION BIOLOGY AND MEDICINE

As a result of the accident at the fourth block of Chornobyl NPP on April 26, 1986 around 300 MCi (11×10^{18} Bq) of radioactive materials were released into the environment, which contaminated 50,500 km^2 of Ukrainian territory with a population of more than 2.4 million inhabitants. The most contaminated areas included a central part of Ukraine, south-east of Belarus and some regions of Russia. In total 17.5 million people inhabited in 2,293 settlements at the contaminated area including 2.5 million of children [1]. Around 600,000 of people were involved in the clean-up works. The accident was also unique by amount of radiation doses to clean-up workers and population. Collective dose in Ukraine for the first 10 years was around 50,000 man-Sv [2]. Collective dose to thyroid gland was 1.306 million man-Gy. Among that a total of 607,000 man-Gy were received by children and adolescents [3, 4].

The observed health effects of Chornobyl could be divided into major groups: effects due to ionizing radiation (high-dose and low-dose); effects due to a combined action of radiation and confounding factors and effects due to influence of psycho-social factors [5]. Such division thus providing a background to an assessment of radiation effects is to a great extent of artificial nature as the majority of clinical effects including the stochastic are now attributed to multifactorial origin and could be triggered by a set of mutations combined with an insufficiency of the homeostatic regulatory systems.

Radiological consequences of Chornobyl and their importance for radiation biology and protection became the subject of an increased interest and re-evaluation during the last years. Thus incomplete, health data obtained after Chornobyl provide a scientifically based scale for prognosis of effects of other accidents. Such approach showed its value after Fukushima and was used by different international groups [6–7].

1.1. RADIATION PROTECTION AND RADIATION HYGIENE AFTER CHORNOBYL

Radiation protection and hygiene before Chornobyl accident had a special status. Research was limited to special centers [8]. Available publications contained descriptions of early effects (acute radiation syndrome) and such stochastic effects as leukemia in hibakusha of Hiroshima and Nagasaki and also some groups exposed after nuclear tests at Marshall Islands. Experimental studies were directed to obtain information on the health effects during the space flights and changes in reactivity after continuous tritium incorporation. Radiation protection technologies were elaborated to minimize exposure after use of nuclear weapons. After the Chornobyl accident all health care and organizational resources were directed to the medical support of cleanup activities and treatment of heavily exposed. The large-scale measures of liquidation of consequences of accident required of mobilization of resources in medical sphere. Medical force involved in emergency teams, providing first aid to evacuees and treatment to exposed included 2,000 medical doctors, 4,000 nurses and other junior staff, 1,200 undergraduate medical students. At the first period after the accident 230 laboratory and dosimetry teams, over 400 medical teams including 212 special medical teams for children and pregnant women were created. Additionally 300 medical doctors, 600 junior staff and 125 special vehicles were recruited [3, 4, 9–10].

Fulfilling the tasks from the Ministry of Health Care the tens of thousands of exposed were examined by the created teams in a short time period the new methods of a large-scale population screening were implemented. From 1st of October 1986 the National Research Center for Radiation Medicine started its activities with the aim to provide research of the low-dose effects as well as the scientific and methodological support of population protection from the negative factors of the accident.

1.1.1. Protective and preventive measures

Before the accident for radiation protection of population that lived near the Chornobyl NPP the regulations of former USSR were used and temporary dose threshold were introduced after the accident. There are different views on effectiveness of medical response to this unpreceded challenge. A detailed analysis is presented in a previous edition and publications [5, 15].

A retrospective analysis of documents of the first emergency period enabled also to point to some of organizational shortcomings:

➤ The third main division of the USSR Ministry of Health did not promptly informed the Ministry of Health of Ukraine about the radiation situation and accepted measures for the protection of population at the NPP and adjacent Prypyat territories. Medical and sanitary support during the evacuation of people from the NPP zone was not sufficiently organized, as a result many staff workers and local residents received additional radiation doses;

➤ There were no available regulatory documents on actions in case of accidents at nuclear power plants. In addition to the delay in distribution the temporary instruction on iodine prophylaxis there were no other recommendations on this issue.

➤ Hygiene measures for supporting health well-being after an emergency evacuation of the population was not provided;

➤ Dosimetry and radiometry equipment of health service and healthcare facilities were unsatisfactory. Staff structure didn't meet the requirements to provide protection, water quality and food control.

The actions of the recruited health care services in general met the objectives set out in the specific circumstances of liquidation of medical consequences. In a short time in the three countries an effective system of early diagnosis of radiation induced diseases, including thyroid cancer. Due to the urgent need of comprehensive research and development to reduce and limit the adverse consequences in population of Ukraine, on 23/05/1986 the Republican Problem Commission was created on radiation medicine. The three countries created specialized scientific centers with in-and out-patient departments to monitor the health effects and provide qualified care. A system of free health care and rehabilitation treatment was implemented.

Chornobyl accident was followed by other accidents at radiation hazardous objects of which the Fukushima accident was the greatest by scale and influence on mankind. This shows that the lessons of the Chernobyl accident should not be forgotten. They must be well structured for preventing the fatal errors and finding of right solutions in future. Implementation of the basic principles of emergency planning of organizational, health, social actions and implementation them in practice of the population protection system will allow to minimize the risks of appearing an emergency situation, and the costs and efforts of healthcare facilities for the elimination of consequences of accident

Below some of considerations for population protection after a large-scale reactor accident are presented [15]:

➤ A decision-making system that works well in the case of small- or medium-scale accidents may not meet the needs of large-scale disasters;

➤ After the severe nuclear accidents in Chornobyl and Fukushima, the implementation of countermeasures was delayed. This delay could have been avoided by optimizing certain emergency countermeasures:

(1) pre-distribution of KI to communities in the vicinity of nuclear installations;

(2) early sheltering accompanied by distribution of simple-language instructions to the affected population. Lack of such instructions had a substantial negative impact after Chornobyl;

➤ In addition, national radiation protection reference levels adopted during the accident response were not driven by a scientific basis, but by political or emotional factors, or pressure from the population due to loss of trust in the authorities;

➤ Local hospitals and medical staff need to have sufficient resources to provide healthcare for a certain period after the accident without external support;

➤ Non-radiation effects outweigh the health effects caused by radiation exposure alone, in the range of low dose exposure resulting from a nuclear accident;

➤ Differentiation between the health effects caused by radiation exposure vs. those not directly related to radiation is a matter of competence of science and national legislation policies related to compensations. However, the origin of effects is not the central issue for the affected population needs for healthcare.

1.2. HEALTH EFFECTS

1.2.1. Dosimetry

Data on contamination and radiation exposure was collected in the first years after the accident. Dosimetry teams performed a huge amount of work in the 30-km area around the NPP and other contaminated areas. This work enabled to determine the scale of contamination and served for establishing the borders of contamination zones supporting the decision making strategies. Around 200 thousands of direct measurements of radioiodine incorporation to thy-

roid iodine isotopes and cesium incorporation by whole body counters enabled the creation of a Dosimetry register of the NRCRM and a background for further implementation of dosimetry settlement passportisation and research.

Dosimetry and radiation hygiene have quickly progressed during a further post-accidental period. Calculations of radiation dose loads were performed in different types of exposed. Dosimetry pasportisation was performed of more than 2,000 settlements at the contaminated areas. These results made possible government decisions on the status of exposed. The main regulatory document in the field of radiation hygiene was prepared and published – The Norms of Radiation Safety of Ukraine-97. [6, 7].

The problems of reconstruction and validation of irradiation doses of liquidators are still relevant. In the absence of a «gold standard» [13] for individual dosimetry the most reliable method seems be a reconstructive dosimetry with a combination of cleanup route or residential history questionnaires and computerized data on radiation fields at the area [11, 12]. The best results up to date were obtained implementing the RADRUE method [14]. In practice a method also has some limitations for epidemiology, i.e. in the NCI-RCRM leukemia study there was a wide distribution of the central estimates of the bone-marrow dose (from 3.7×10^{-5} to 3,260 mGy). The uncertainties in dose estimates are the subject of the subsequent research and new methods are in the process of elaboration. Recent thyroid cancer studies show also the necessity of the elaboration of a reliable reconstructive not only for external but inhalation exposure as well as estimates of radioiodine incorporation from foodstuffs for those who inhabited contaminated area.

European strategic research agenda recognizes also a need in new technologies of biological dosimetry especially in a low-dose range. At present the electron paramagnetic resonance of tooth enamel and fluorescent in situ hybridization in different modifications (WCP-1,2,4, COBRA etc.) conform the most reliable results thus showing not coinciding results at individual levels. Approaches of use of some other assays (T-cell receptor mutations, H2AX, cyclin D1, gene expression are presented in Chapter 8.

1.2.2. Scientific analysis

Chornobyl as a greatest nuclear energy accident was not only a challenge to national radiation protection system, but also to the basics of the radiation biology research paradigms. Among the main scientific issues was a question to scientists on the effects, if any of a low-dose radiation exposure and if these effects, if exist are comparable with the known health effects of A-bombing.

The main effects of A-bombing included deterministic (hematological, gastrointestinal syndromes, skin lesions cataracts); a dose dependent substantial increase in leukemia and cancer rates in children and adults, some excess was registered of benign tumors (digestive tract and gynecological),endocrine diseases including a 10% prevalence in diabetes mellitus rates, different somatic, psychoneurological and psychological effects [18].

Thus, the agenda for Chornobyl research during the thirty years after the accident addressed the problems:

➢ deterministic effects in heavily exposed;
➢ cataracts in clean-up workers;
➢ if there is an excess in incidence and mortality from leukemia, thyroid cancer and other cancers;
➢ if exist is there dose-effect relationship in incidence and mortality, in other words can the observed effects be attributed to action of ionizing radiation;

➢ if a relationship exists, is there any difference in radiation risks per unit of dose for the observed effects with data from A-bomb studies.

These questions couldn't be answered without the estimates of the differences in used disease classifications, quality of diagnoses and data harmonization enabling comparable biostatistic analysis.

A main scientific answer after 30 years of research is that health effects of Chornobyl when comparing per unit of dose are very similar to observed in hibakusha. Experience of radiation accident in Chornobyl as well as a chemical accident in Bhopal demonstrate that the accidental pollution from industrial infrastructure could have a hazardous effect on human population compared with the use of nuclear weapons.

Last radiation accidents show the existing necessity of a continuous assessment of the experience of Chornobyl at national levels as well as standardized approaches of the international scientific evaluation. Early response after the accident included estimation of the scale of the accident, reporting, prehospital care, patients sorting and timely evacuation of highly exposed patients to the specialized clinics. Radiological monitoring, started in 1986, made it possible to estimate internal exposure of children and adults from radiocesium and doses to thyroid.

After the accident reliable data were collected on the health effects of Chornobyl, the mechanisms of low-dose effects and treatment of radiation-exposed. As a result of accident the deterministic and stochastic health effects due to ionizing radiation were registered as well as the effects of the combined action of radiation and other factors.

Of special importance were studies of the early and late effects of the acute radiation syndrome, local radiation skin injuries and radiation cataracts.

Initially 499 patients were admitted to hospitals with the signs of acute radiation syndrome, from them diagnosis was confirmed in 237 patients. Diagnosis re-evaluation was performed three years after retrospectively and ARS diagnosis was confirmed in 134, including those 28 persons, who died within 11 to 96 days. For a substantial number of patients grade of severity also was changed. Amongst 103 patients with unconfirmed ARS for a group of 27 patients who exhibited typical clinical symptoms the main criteria for retrospective decline of diagnosis were incompleteness of early hematological data, and in the rest 76 – the atypical character of hematological parameters recovery after their initial decrease. [16].

Of 237 individuals, 190 were living in the territory of Ukraine, and the rest 19 outside of Ukraine. In the post-accidental 30-year period 52 patients died. Cardiovascular diseases caused the death of 20 people (38.5%), hematological malignancy and solid tumors of 18 patients (34.6%). The first included sudden cardiac death, heart failure and stroke. Myelodisplastic syndrome (MDS), acute and chronic myelogenous and myelomonoblastic leukemia, cancer of various locations belonged to the second group of death causes [17].

Radiation cataracts study led to a substantial progress in radiation epidemiology. Radiation risks were shown at lower doses and new 20 mSv eye lens dose limits were adopted for professionals by the ICRP. This study was based on the validated official dose records showing the possibility of such approach implementation for other studies. Results of a study of radiation-induced skin lesions were of limited value.

Important data on the radiation risks and molecular mechanisms were obtained by the Institute of Endocrinology and Metabolism in cooperation with the U.S. National Cancer Institute on radiation-induced thyroid cancer in children.

Comprehensive studies have been performed by a joint RCRM-NCI group on leukemia radiation risks in clean-up workers. A positive answer was obtained to a hypothesis that there

exists a dose-related increase in risk of leukemia among Chornobyl clean-up workers. Despite a previous assumptions it was found that the magnitude of an observed risk per unit dose is comparable to that seen in the atomic bomb survivors, exposed to essentially instantaneous radiation. The excess relative risk (ERR) of total leukemia for 15 years after exposure was 3.44 per Gy (95% confidence interval 0.47–9.78, $p < 0.01$). Study of risks at 20 years after exposure have shown the risk modifying effects of time since exposure but not age at exposure. A very important was non-expected similar dose response relationship for chronic (CLL) and non-chronic lymphocytic leukemia. Clinical studies have shown some peculiarities in the CLL natural history and response to treatment. These issues need further investigation due to importance for radiation protection. Later study has demonstrated the main role of Chornobyl dose for induction of leukemia while the non-radiation factors non-significantly interfere with radiation risks [19–23].

Nest two other prioritized directions of research include radiation risks of leukemia in children and of multiple myeloma (MM). At this book a new analysis is presented of the merged databases with more than 1,000 cases and some tendencies that have been registered due to an increased statistical power. For MM a study already shows increased standardized incidence rates (SIR) in clean-up workers for a period after 20 years [24]. A case-control study is of high priority.

Among two «early» solid cancer an extreme attention should be dealt to thyroid cancer in adulthood and breast cancer. The ecological study has demonstrated a significant SIR increase in cleanup workers with the highest values in those who participated in clean-up in 1986 [25]. Results of the case-control study performed by the IARC in Belarus, Russia and Baltic countries suggest presence of radiation risks in adulthood but have limitations due to heterogeneity of the study group and some dosimetry issues. A next case-control study performed in Ukraine will contribute additional information on the issue.

Studies of breast cancer radiation risks are of ecological type. The study cohort in Ukraine is presented by female cleanup workers from which about 8,000 have higher doses and in Belarus – by females inhabiting highly contaminated area. The attempts of constructing joint cohort failed and are for future.

For other cancers a substantial amount of data is collected but still there is no sufficient information or consensus on their radiation origin, due to longer period of induction after radiation exposure. These studies also have to be promoted.

Due to a wide prevalence in the unexposed population and multifactorial origin the data on circulation (cardiovascular and cerebrovascular) diseases radiation risks are evaluated with a special attention. Eight country meta-analysis has shown significant radiation risks of mortality of circulation diseases [26]. Additional suggestive information on cerebrovascular effects, cognitive function and their molecular background bridging clinical effects with radiation markers was added by CEREBRAD EU study.

Concluding, it's needed to mention that health effects of Chornobyl are far from final understanding. Some of effects will follow in future due to a long induction period, some have to be re-evaluated with a sufficient statistical power. Modern scientific approach enables to perform a search of radiation dose, radiation-induced disease markers at a remote period after exposure as well as at lower doses and dose rates, as well as to find the low-dose radiosensitivity markers. Next step available at this technology level will be an investigation of transgenerational effects. My personal feeling and hope is that the National Research Center for Radiation Medicine of Ukraine will be able to implement its skills and expertise to be at the front line of radiation research for basic science and care to radiation exposed.

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Chapter 2
DOSES OF EXPOSURE

2.1. IRRADIATION DOSES

Chernobyl radioactive release started on April 26th, 1986 and according to the existing estimates, lasted for 10–15 days. Short-lived radionuclides (niobium, zirconium, iodine, etc.) played a role of dose factors in the early phase of the accident. In course of time, the increasing role in dose formation was played by radioisotopes of cesium (^{137}Cs, ^{134}Cs) and, in a much less extent, by strontium (^{90}Sr). Radioisotopes of transuranium elements (^{238,239,240,241}Pu, ^{241}Am), though were present in radioactive release, the physical and chemical properties of the inactive carriers in which they were fixed, stipulated that the role of the transuranium dose was small.

During the emergency radioactive release the weather conditions had constantly changed, causing significant heterogeneity of radioactive fallout in Ukraine: ^{137}Cs fallout density varied from units to several hundred kBq x m^{-2}. ^{90}Sr contamination levels were approximately 10 times lower. In the area of population residence the levels of ^{239}Pu fallout varied from 0.004 to 0.9 kBq x m^{-2} (on average ^{239,240}Pu level of global fallout for Ukraine is estimated as 0.037 kBq x m^{-2}).

Although virtually all the residents of Ukraine were affected by the Chernobyl accident , but four critical cohorts had suffered the most impact, namely:
1) clean-up workers of ChernobylNPP accident known as «liquidators» – those who were directly involved in work on the industrial site or in the Chernobyl 30-km zone;
2) evacuated residents of Pripyat and Chernobyl, as well as other settlements of 30-km zone;
3) children and adolescents (age – at the time of the accident), whose thyroid gland received irradiation by radioactive isotopes of iodine, ingested with food or inhaled in May–June 1986;
4) rural residents living on contaminated territories.

The population of the contaminated areas *is the largest in number among the four contingents outlined above and makes millions of people in Ukraine*.

Doses were formed by two basic pathways of irradiation for population of contaminated areas:
1) *external* whole body *gamma irradiation* from the complex mixture of gamma-emitting radionuclides in the fall-out on the soil;
2) *internal irradiation* of thyroid gland from *radioiodine* (in 1986) and whole body irradiation from *radiocesium* (and to lesser extent – from other radionuclides) due to consumption of contaminated foodstuffs produced (grown) at the radioactively contaminated territories.

2.1.1. Radiation doses of clean-up workers of the accident. Retrospective dose reconstruction of clean-up workers of the accident.

Clean-up workers of the Chernobyl NPP accident (also known as «liquidators») compose one of the largest and probably the most exposed cohort affected by the Chernobyl accident. Despite the importance of this population – both in terms of medical and social aspects as well as systematic studying the consequences of accidental exposure – exposure pathways related to the liquidators for a long time remained uncertain. Thus, among the clean-up workers of years 1986–1990 included in the State Register of Ukraine (SRU) of persons affected by the Chernobyl accident only about a half have records of individual doses. Both the quality of available dosimetric data, and the overall success or failure of radiation protection during clean-up works remained unclear.

Traditionally there were ideas of almost total falsification of data on radiation doses and the mass excess of the standing dose limits. The situation with radiation doses of eye lens, one of the most radiosensitive organs, especially with respect to beta radiation from the Chernobyl radionuclide mixture remained unclear. Therefore a large scope of activities was planned and largely implemented for the past decades aimed at bringing clarity to the real exposure of clean-up workers and retrospective evaluation of dosimetric monitoring results during clean-up works.

A special place in the complex problems of exposure assessment for clean-up workers was caused by the need of dosimetric support of post-Chernobyl epidemiological studies. These studies require information on subjects'individual doses, and the problem of dosimetric support demanded the implementation of integrated approaches. The main methodology of individual retrospective dosimetry, which was developed in recent years and successfully used to reconstruct individual doses of clean-up workers is RADRUE (Realistic Analytical Dose Reconstruction and Uncertainty Analysis) – analytical calculation method jointly developed by Russia (Institute of Biophysics), Ukraine (National Research Centre for Rradiation Medicine, Chernobyl NPP), USA (National Cancer Institute) and France (International Agency for Research on Cancer).

An important feature of this method, which is based on personal interview with clean-up workers, evaluation of responses by an expert and the use of extensive databases of radiation (dose rate) conditions in the locations of clean-up activities, is that it can be universally applied to any clean-up worker, including the deceased ones (through interviewing the colleagues and relatives).

RADRUE method was widely used to reconstruct individual doses for whole body and bone marrow of subjects (cases and controls) of the Ukraine-US study of leukemia among liquidators. Altogether 1,000 doses were reconstructed for clean-up workers using RADRUE method, in particular, for 79 diseased subjects (through questioning colleagues and relatives of the deceased clean-up workers).

Taking into account that the study cohort included clean-up workers of 1986–1990, which have official status and are registered in the SRU, the dose range was from zero to about 3.2 Gy, arithmetic mean dose (expectation) – 90 mGy, geometric mean – 12 mGy. Such a huge range of doses is caused by extreme heterogeneity of cohort of clean-up workers composed at the same time with the people who received large doses in the first days after the accident, and household sector employees or persons who visited the 30-km zone during a short business trip.

Doses of certain occupational categories among the clean-up workers differ (Table 2.1.1). Thus, the employees of the Ministry of Internal Affairs (MIA) for which there were fewer opportunities to effectively influence on the levels of exposure, and nuclear power professionals

(NPP employees, workers of Administration of Construction No.605, AC-605) received relatively higher doses. It should be noted that the last group (nuclear power professionals) also includes so-called early liquidators, i.e. Chernobyl NPP personnel exposed at the initial phase of the accident, when there were no established effective system of radiation protection and radiation control.

Obviously, the highest doses had been received by clean-up workers for which no effective system of radiation protection and exposure management was in place, first of all, early liquidators (those who participated in the clean-up works during April-May, 1986) and certain categories of workers who carried out works on individual tasks, mostly outside the scope of attention of radiation monitoring services. Time course of military liquidators' exposure by years (Table 2.1.1) adequately reflects the evolution of the radiation situation in the 30 km zone and a gradual reduction of the dose limits within 1987–1988. It should be noted that the average dose of military liquidators were significantly lower than officially registered values and established in the public perception. This finding agrees well with the independent analysis of official dose records and qualitative considerations concerning radiation monitoring and radiation protection practices applied to the troops during the clean-up activities.

It should be noted that the cohort of subjects of Ukraine-US study of leukemia among liquidators is quite representative, because data on doses, typeы of work and distribution of professional groups (categories) of clean-up works (Table 2.1.2) are quite representative and can characterize the total set of Ukrainian clean-up workers.

A separate scientific and practical problem is to evaluate the lens exposure in clean-up workers, including assessment of individual doses of beta-radiation. The essence of the problem is that during the clean-up works beta-irradiation doses were not monitored (because of lack of logistical and methodological basis in place) while Chernobyl radionuclide mixture included hard beta emitters (^{144}Ce / Pr, ^{106}Ru / Rh, ^{90}Sr / Y), which could form a substantial remote beta-irradiation dose. Under certain conditions, beta doses to lenses of clean-up workers may exceed respective gamma radiation doses.

A large study on reconstruction of individual doses to lenses (beta plus gamma) of 8,607 participants of Ukrainian-American Chernobyl ocular study (UACOS) had been conducted by NRCRM specialists jointly with the Institute of Occupational Health, NAMS of Ukraine (the main contractor of the UACOS). Dosimetric model took into account the time elapsed after the

Table 2.1.1

Results of reconstruction of individual doses by RADRUE for some categories of occupational accident

Category	Number	Average dose (mGy)	Median dose (mGy)	Geometric standard deviation
Military (total)	218	76	54	2.1
Separately by year of participation in the clean-up works				
1986	99	105	82	1.89
1987	52	78	46	2.32
1988	44	29	17	2.41
1989	20	31	17	2.22
1990	3	60	24	2.89
Professional atomist	35	381	277	1.78
Staff of MIA	27	203	173	1.86
Sent in official journey	340	70	48	1.95
Drivers	213	64	41	1.99

Table 2.1.2
The structure of clean-up workers, who were the subjects of Ukraine-US study of leukemia

Category	All cohort study		Kyiv and Kyiv region		Other regions		Estimated for all Ukrainian liquidators (%)
	number (%)	duration of work – median (minimum, maximum)	number (%)	duration of work – median (minimum, maximum)	number (%)	duration of work – median (minimum, maximum)	
Witnesses of the accident	3 (0.5)	7 (1. 11)	2 (0.7)	6 (1. 11)	1 (0.4)	7 (7. 7)	< 1
Directly affected	2 (0.3)	2 (1. 2)	2 (0.7)	2 (1. 2)	0 (0.0)	– (–. –)	< 1
Early liquidators	66 (11.5)	7 (1. 185)	50 (17.1)	7 (1. 185)	16 (5.7)	7 (3. 16)	~ 10
Staff of Chornobyl NPP	9 (1.6)	317 (36. 1420)	8 (2.7)	379 (36. 1420)	1 (0.4)	225 (225. 225)	~ 1
Temporary submitted NPP staff	1 (0.2)	31 (31. 31)	1 (0.3)	31 (31. 31)	0 (0.0)	– (–. –)	< 1
Staff of AC–605	5 (0.9)	31 (19. 63)	1 (0.3)	24 (24. 24)	4 (1.4)	46 (19. 63)	~ 1
Staff of the Institute of Atomic Energy, named by I. Kurchatov	2 (0.3)	157 (138. 175)	0 (0.0)	– (–. –)	2 (0.7)	157 (138. 175)	< 1
Military clean-up workers	220 (38.5)	67 (6. 833)	33 (11.3)	65 (7. 366)	187 (66.8)	69 (6. 833)	48
Civil liquidators sent to the 30-km zone	181 (31.6)	19 (1. 1710)	121 (41.4)	18 (1. 1710)	60 (21.5)	21 (2. 103)	28
Staff of Industrial Association «Combinat»	4 (0.7)	458 (164. 1450)	4 (1.4)	458 (164. 1450)	0 (0.0)	– (–. –)	< 1
Mixed type	79 (13.8)	250 (4. 1710)	70 (24.0)	258 (4. 1710)	9 (3.2)	111 (9. 1710)	10
Total	**572**		**292**		**280**		

accident (and, accordingly, changes in the composition of the Chernobyl nuclide mixture), peculiarities of exposure (which were collected through questioning of liquidators) – nature of work, workplace characteristics, application of protective eyewear. In order to assess beta/gamma ratios, a specialized exposure model was used (phantom, taking into account the anatomical location of the lens, exposure from horizontal and vertical surfaces with different textures) and the method of calculating the doses of remote beta radiation by the Monte Carlo method.

Although the ultimate goal was to assess the total (gamma plus beta) doses to the lens, a correlation between doses of gamma and beta radiation is of paramount interest (Figure 2.1.2). It was found that approximately 32% of study subjects beta-irradiation doses were higher than the corresponding gamma doses (i.e., the total radiation dose in the lens was more than two times higher than the assessment of gamma dose only), while for about 53% of subjects of beta irradiation did not exceed a half of the corresponding dose of gamma radiation.

Parameters of total doses (beta + gamma) of lens irradiation in selected groups of clean-up workers – the study subjects are listed in the Table 2.1.3. The table shows that the largest radiation doses were received by so-called early liquidators, i.e. staff persons from the Chernobyl NPP and other organizations that were involved into the clean-up works during the first days and weeks after the accident. It should be noted that in view of the nature of exposure (gamma

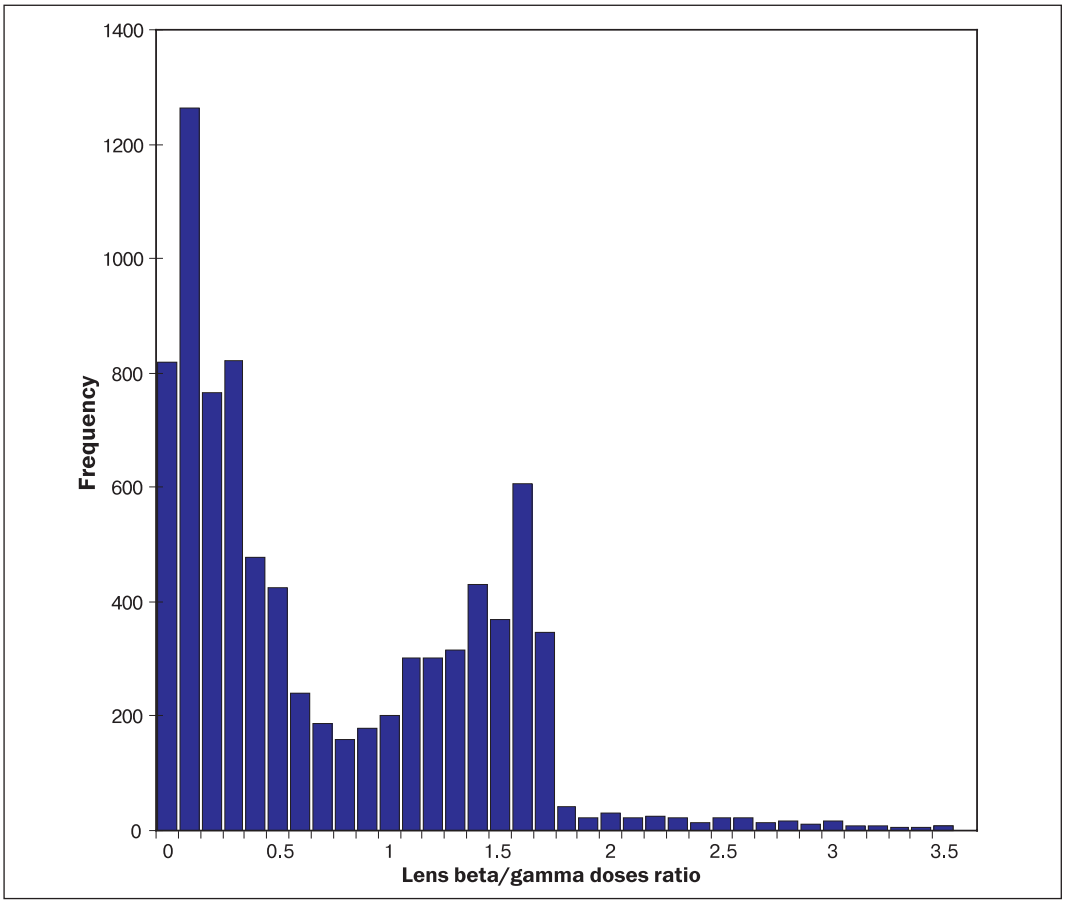


Figure 2.1.1. **The distribution of individual ratios of beta to gamma radiation doses for the 8,607 subjects of Ukrainian-American Chernobyl ocular research (UACOS)**

plus beta irradiation; see Figure 2.1.1) and characteristics of the cohort (clean-up workers of 1986– 1987) doses of the largest group of studied subjects – military liquidators – are in a good agreement with the dose reconstruction by RADRUE (Table 2.1.1).

Another original feature of ocular dosimetry was application of various methods of dosimetry that were calibrated against a single calibration standard («gold standard»). Thus, to assess individual doses of gamma irradiation the high-quality data of personal dosimetry monitoring (staff of Administration of Construction № 605-AC-605), as well as the results of calculation and analytical dose reconstruction (ADR), and the official dose records (ODR) of military liquidators were used as a source of raw dosimetric data.

Dose values from independent sources were calibrated against EPR dosimetry with tooth enamel as the most accurate and valid method for retrospective dosimetry ("gold standard"). This caused the introduction of calibration correction in the primary dose assessment. It appears that ODR of military liquidators approximately twice overestimate the actual levels of exposure in this category of clean-up workers.

To correct the original ODR and take into account of associated uncertainty, initial ODR was multiplied with stochastic correction factor of logarithmically normal distribution type with the

Table 2.1.3
Characteristics of lens exposure of certain groups of clean-up workers enlisted into the Ukrainian-American ocular Chernobyl research (UACOS)

Group of clean-up workers / dosimetry method	Number in the tested cohort	Dose distribution parameters of lens ($\beta + \gamma$) mGy: median (5% and 95% percentile)
Employees of AC-605 / individual monitoring by TLD dosimeters	410	16 (2, 235)
Representatives of various groups / EPR dosimetry in tooth enamel	104	94 (19, 426)
Early liquidators / analytical dose reconstruction (ADR)	712	502 (142, 1143)
Sent to the 30-km zone / ADR	126	16 (1, 242)
Military liquidators / Official dose records (ODR), received by the group and group-calculating method	7,255	121 (30, 287)
Total	**8,607**	**123 (15, 480)**

following parameters: geometric mean – 0.5, geometric standard deviation – 2.2. These options of the corrective distribution reflect large systematic bias of registered doses, as well as a considerable uncertainty of radiation monitoring data for military liquidators.

Serious attention was paid to assessing the quality and reliability of existing dose records of radiation levels of clean-up workers. These attempts were made areas along several lines:

➢ collection and unification of all existing databases on individual doses and the corresponding paper archives;

➢ studying practices of radiation protection and radiation control of various contingents of clean-up workers, including institutional and regulatory aspects;

➢ study of the dose record quality by statistical methods;

➢ retrospective evaluation of dosimetric uncertainty of SRU data by comparing the official results with the results of dose reference EPR dosimetry.

Towards the collection of available dosimetric information, all the electronic databases of radiation control during the clean-up work were acquired with funding from the National Cancer Institute (USA). Unfortunately, this information gathered with assistance of Russian colleagues from the Institute of Biophysics (Moscow) turned to be not useful for practical use due to lack of reliable identifiers for linking records in dosimetric databases with the data in SRU.

Noteworthy achievement was the transfer of dosimetric data archives of the Ministry of Defence of Ukraine into the electronic database. Results of this work, carried out jointly by specialists of Military Archive, Military Medical Academy and the RCRM was the database containing more than 45 thousand entries of Ukrainian troops (reguular and reserve), those that include the dates of participation in the clean-up works, military unit IDs and individual dose during the clean-up works. Comparison of data from the archive of Ministry of Defence (MOD) with ODR of the State Register of Ukraine proved to be very instructive. It appeared that the dose of military liquidators who are registered in the SRU practically coincide with the data contained in the military archive. Moreover, the degree of overlapping of the data sets and SRU and Military Archive was quite high – almost all the records contained in the Military Archive are reflected in the SRU. This conclusion confirms the high importance of SRU data as a source of dosimetric information for military liquidators, who are about 90% of individuals with registered dose in the SRU.

Table 2.1.4
Periods of dosimetric monitoring of clean-up activities

Period	Time Interval	Description
Pre-accidental	1978–26.04.1986	Normal functioning of Chornobyl NPP dosimetry service in accordance with Radiation Standards-76
Initial	26.04.1986 – about 10.05.1986	Inability of Chornobyl NPP dosimetry service, the use of the war-time approaches to dose control of forces
Interim	about 10.05.1986 – 01.06.1986	Parallel operation of dosimetry services Chornobyl NPP and the army, introducing a single exposure limit (250 mGy), AC-605 organization with its own dosimetric service
Main	June–October, 1986	Operation of dosimetry services of Chornobyl NPP, AC-605 and MOD units based on different approaches
Rutine	after November, 1986	Parallel operation of dosimetry services of Chornobyl NPP, AC-605, IA "Combinat" and MOD departments. Gradual return to normal operation, reduction of dose limits (1987–1988)

Study of regulations and practices of radiation protection and radiation monitoring during the clean-up works that has been done in the framework of French-German Initiative «Chernobyl», allowed better assessment of the quality, reliability and completeness of dosimetric data on clean-up workers. It was found that in terms of quality and level of contingent coverage by dose control, five periods can be identified (Table 2.1.4).

Although during the pre-accidental period the dosimetry and radiation safety service satisfactorily fulfilled its tasks, sudden accident revealed a complete failure of ability of the existing dosimetry to effectively determine individual dose of workers and provide the necessary level of personnel radiation safety under emergency conditions. It should be noted that the period of confusion was quickly overcome and since the second decade of May, 1986 dosimetry system in support of emergency workers began to be established gradually and in early June (about a month after the accident) the foundations of effective radiation protection and radiation control of the main forces involved into clean-up activities.

It was found that the quality of dosimetry data (and radiation monitoring practice) strongly depends on the fact which particular service or agency conducted radiation protection of liquidators and dosimetry control. During the clean-up works (1986–1990) in the 30-km zone four large independent dosimetry services (Table 2.1.5) and several smaller independent service providers (i.e. USSR Academy of Sciences, USSR Academy of Medical Sciences, Joint Expedition of Institute of Atomic Energy, etc.) were operating. These dosimetric services began at different times after the accident, covering various contingents and, most importantly, practiced radically different approaches to the assessment of individual doses of clean-up workers. Therefore the completeness, quality and reliability of their dosimetric data differ significantly (Table 2.1.5).

Dosimetry control of AC-605 staff of the Ministry of Medium Machinery (MMM) of the USSR, a specialized construction organization created to build a sarcophagus («Shelter» Confinement) was the best organized. The result of this exemplary work was 100% coverage of quality TLD individual control more than 20 thousand employees of AC-605, mostly temporarily assigned workers from MMM enterprises, based in Russia.

Dosimetric monitoring, performed by Chernobyl NPP Radiation Safety Service is characterized by a failure over the first weeks after the accident (when the regular dosimetric monitoring instrumentation have proved to be inadequate for measuring high levels of doses and dose rates), which was followed by gradual restoration of high-quality dose monitoring, which had been eventually achieved only in June-July, 1986. Negative consequence of such failure of the regu-

Table 2.1.5
Key dosimetric services that performed dosimetric control of clean-up workers

#	Service	Departmental affiliation	Period of function	Coverage of clean-up workers	Data quality
1	Chornobyl NPP Radiation Monitoring Service	Ministry of Energy and Electrification of the USSR, from July 1986 – USSR Ministry of Atomic Energy	May, 1986 – to present	NPP personnel and temporarily attached to the Chernobyl NPP personnel	Satisfactory-high (depending on the period after the accident)
2	Units of the of Ministry of Defence	USSR Ministry of Defence	May, 1986 – end of 1990	Military liquidators	Low
3	Division of Radiation Control AC-605	Medium Machine Building Ministry of the USSR	June 1986–1987	Civil and military constructors of AC-605	High
4	Office of Radiation Control of PA «Combinat» and its successors	USSR Ministry of Atomic Energy	November, 1986 – to present	Civilian personnel who worked in the 30-km zone outside the Chornobyl NPP site	Satisfactory

lar radiation monitoring at Chernobyl NPP was that doses of early liquidators - probably the highest among clean-up workers – remained unknown. Consequently, the completeness of dosimetry data of the Chernobyl NPP personnel was insufficient (in particular – in the sense of coverage by the dosimetric data for each liquidator during the entire period of clean-up work) causing the need for reconstruction of individual doses. Throughout the years 1986–1996 in total 1,600 individual doses of Chernobyl NPP workers and those temporarily assigned to the NPP were evaluated by the ADR calculation method. Since July, 1986 dosimetry monitoring and recording of individual doses were carried out at the Chernobyl NPP properly and that dosimetric information is characterized by high quality and completeness.

Dosimetric monitoring of the civilian personnel (permanent and temporarily assigned), working in the 30-km zone, due to organizational problems practically was not carried out during 1986 and a part of 1987, while this function gradually had been taken over by the Department of Dosmetric Control of PA «Combinat» / RPA «Pripyat». Thus, doses of this contingent, especially in 1986–1987, are characterized by a lack of completeness and not always are of high quality.

The largest contingent of clean-up works were military liquidators – cadre officers, conscripts (at the initial phases of the accident) and, the most, army reservists temporarily recruited to the army. The importance of this category particularly significant as about 95% of ODR in SRU belong to military liquidators (Figure 2.1.3).

Such a situation with ODR of military liquidators is the result of a 100% coverage of this contingent with the dosimetric control and also with the peculiarities of input of the dosimetric information to SRU – through the dose certificate (in case of military personnel – a supplementary sheet to military ticket), which were on hand of all military but only very few for civilian clean-up workers. However, despite excellent coverage with ODRs, dosimetry of military liquidators has the lowest precision of individual doses because of robust and inaccurate methods of dose assessment. For military liquidators generally group (one dosimeter per group) and group-assessment (when the dose of all group members was calculated in advance on the basis of dosimetric situation and the planned work) dosimetry methods were used.

It was found during the retrospective assessment of accuracy and bias of the dose estimates of military liquidators that on average the doses estimated by these methods exceeded the actual level of exposure two-fold, and geometric standard deviation (uncertainty) was quite high and comprised about 2.2. However, the positive note is that widespread interpretation of abnormal distribution of individual doses of the military liquidators (Figure 2.1.3) as the evidence of falsification

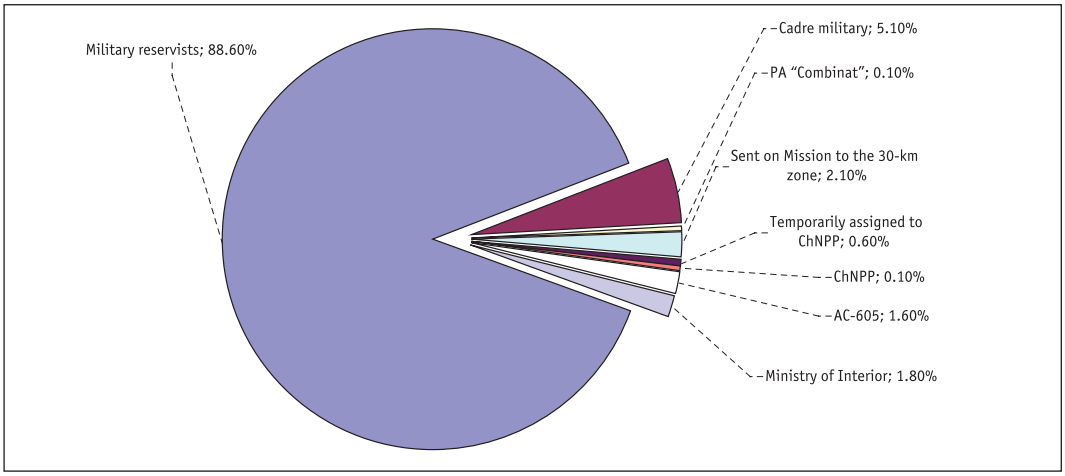


Figure 2.1.2. **Distribution of clean-up workers included in SRU according to their departmental affiliation (results of the survey)**

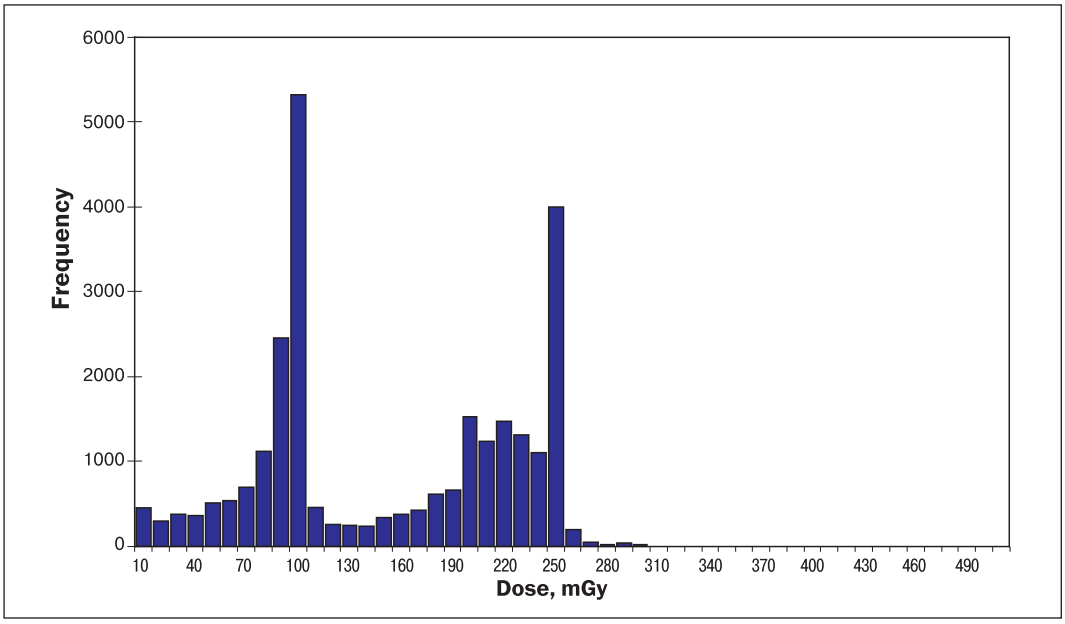


Figure 2.1.3. **The distribution of individual doses of military reservists (so called «partisans») of 1986–1987**

of the dosimetry information presumably done to bring the reporting of exposure levels of military personnel in accordance with the applicable dose limits (250, 100 or 50 mSv) not was confirmed.

Statistical methods showed that the possible contribution of the falsified dose values does not exceed 10% of the total, and the atypical form of distribution (left depleted and a sharp cut-off at doses above the limit) corresponds to fairly unusual practice of doses management when the person who received a dose close to the limit had been dismissed from the armed forces and simply replaced by a new (same unskilled) reservist.

In general, dosimetric monitoring, which was carried out for different groups of liquidators and the system of radiation protection of contingents involved in Chernobyl clean-up activities, allowed to comply with current norms and exposure limits. Mass overirradiation of clean-up workers happened only at the initial phase of the accident and was a problem for rather limited group of so-called early liquidators.

In the following periods (since late May, 1986) multi-thousand contingents were provided with adequate radiation protection, and cases of exceeding the established dose limits (250 mSv in 1986 and graduated limits of 100 and 50 mSv in subsequent years) were rare and usually occured in cases prescribed by the Radiation Safety Standard-76 being in force at that time.

* * *

1. The largest individual doses were received so-called early liquidators – people who participated in the clean-up activities in April-May, 1986, being exposed under conditions of poorly explored radiation situation and lack of adequate facilities for radiation control.
2. Doses of clean-up workers of later periods (since June, 1986) are largely in accordance with the dose limits established at the time. Radiation protection system, introduced during the clean-up works, mostly fulfilled its function and provided non-exceeding of permissible exposure limits.
3. The quality and completeness of dosimetric information significantly differ for different groups of clean-up workers, causing the need for a critical consideration prior to the use of existing dose records, retrospective assessment of individual doses and revision and correction of available dosimetric data.
4. Doses of military liquidators are not characterized by strong falsification, but are biased (towards overestimation of the actual exposure) and not accurate (are endowed with large uncertainty).
5. Studying health consequences of Chernobyl NPP accident among clean-up worker cohort requires extensiive application of retrospective dosimetry to determine individual doses of the study subjects.
6. Newly developed retrospective dosimetry methods, in particular instrumental EPR dosimetry with tooth enamel and analytical calculation method RADRUE are appropriate for supporting the post-Chernobyl epidemiological studies.
7. Beta-radiation caused a significant contribution to the lens doses of clean-up workers. Consideration of this factor is needed prior assessing risk of cataract in clean-up workers.

2.1.2. Dosimetry of evacuees

Individual effective dose of irradiation for 12,632 inhabitants of Pripyat (about 25% of the city evacuated population) and 14,084 residents of other villages of 30 km area were reconstructed and analyzed by the method of stochastic simulation based on direct measurements of dose rate and personal survey of evacuees. Evacuees represent 104 village of 30-km zone, including the towns of Pripyat and Chernobyl; 223 residents who lived in 40 settlements of the Belarusian part of the 30-km zone were also interviewed and included in the total number of investigated.

The average external exposure effective dose of Pripyat residents that was accumulated prior to evacuation, was 10.1 mSv. Doses of 534 persons from this group exceeded the level of 25 mSv and only 18 people received doses of 50 mSv or higher. Maximum value of effective doses among this group of inhabitants of Pripyat was 75 mSv.

Frequency distribution of individual effective doses is shown in Figure 2.1.4. Parameters of this dose distribution are shown in Table 2.1.6.

Table 2.1.6
Parameters of external exposure individual doses distribution for individuals evacuated from Pripyat. Results of deterministic calculation.

Parameter	Value
Number of persons in the group	12,632
The average portion of time outdoors	0.21
Distribution of effective doses of external gamma radiation exposure (mSv)	
➢ arithmetic mean	10.1
➢ median	8.93
➢ geometric mean	6.79
➢ geometric standard deviation	3.1
➢ 75 percentile	14
➢ 95 percentile	24
The coefficient of variation (%)	74

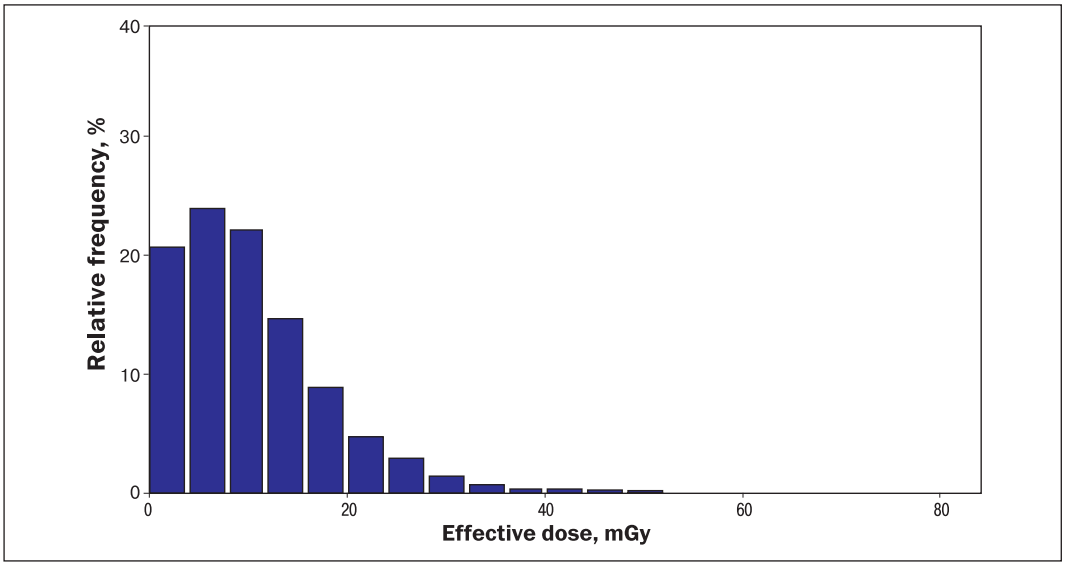


Figure 2.1.4. Distribution of individual doses of external exposure for 12,632 persons evacuated from Pripyat. Results of deterministic calculation.

Figure 2.1.4 shows that the distribution of individual doses is left-asymmetric and quite broad. This shape of dose distribution agrees well with the generally accepted model of logarithmically normal distribution of population exposure doses. 95% of the evacuated residents of Pripyat received a dose not exceeding 24 mSv.

2.1.3. The calculation of external exposure of people evacuated from thesettlements of the 30-km zone

Dosimetric models for the rural population were used to calculate individual doses of 14,084 persons evacuated from the settlements of the 30-km zone. The calculation covered the period from the beginning of the accident and till the moment of evacuation beyond the 30-km zone. The average effective dose among this group (about 25% of the evacuated population) was 15.9

Table 2.1.7

Parameters of the distribution of individual external exposure doses as a function of age of persons who were evacuated from Pripyat. Results of deterministic calculation

Birth years	1983–86	1979–82	1974–78	1970–73	1961–69	1931–68	before 1931
Age group (years)	0–3	3–7	7–12	12–16	16–25	25–55	>55
Number of persons in the group	1597	2104	2133	601	1159	4456	582
The average portion of time outdoors	0.14	0.17	0.18	0.21	0.25	0.25	0.21
Distribution of effective doses of external gamma radiation exposure (mSv)							
➢ arithmetic mean	8.32	9.09	9.0	10.5	10.8	11.5	10.2
➢ error in mean	0.15	0.15	0.14	0.31	0.24	0.12	0.32
➢ median	7.35	7.89	7.63	9.35	9.63	10.5	8.56
➢ geometric mean	5.50	6.15	6.32	7.16	6.77	7.85	7.07
➢ geometric standard deviation	3.18	3.04	2.79	3.02	3.6	3.13	2.74
➢ 75 percentile	11.2	12.2	12.2	15.1	15.3	15.6	14.2
➢ 95 percentile	20.0	21.2	21.3	24.8	25.9	25.8	23.9
➢ the coefficient of variation (%)	74	75	73	72	75	70	75

Table 2.1.8

Parameters of the distributions of individual doses of irradiation as a function of a professional affiliation of persons who were evacuated from Pripyat. Results of deterministic calculation

Professional group	Preschoolers	Schoolboys	Teachers	Medical workers	Consumers services	Workers	Engeneers	Municipal economy workers	Chornobyl NPP staff memberrs	Housewives	Pensioners
Number of persons in the group	3494	2945	376	202	799	2629	670	210	452	156	375
The average portion of time outdoors	0.16	0.19	0.22	0.23	0.23	0.26	0.24	0.27	0.28	0.20	0.20
Distribution of effective doses of external gamma radiation exposure (mSv)											
➢ arithmetic mean	8.81	9.4	10.2	11.5	10.9	11.5	10.8	12.6	13.0	8.94	9.51
➢ error in mean	0.11	0.13	0.36	0.59	0.28	0.16	0.30	0.73	0.40	0.54	0.35
➢ median	7.72	7.99	9.66	10.8	9.6	10.5	9.66	10.8	12.4	8.54	8.11
➢ geometric mean	5.92	6.51	7.35	7.57	7.66	7.7	7.11	8.27	8.39	5.74	6.92
➢ geometric standard deviation	3.11	2.88	2.72	3.16	2.86	3.21	3.46	3.09	3.84	3.25	2.53
➢ 75 percentile	11.89	12.8	13.7	16.5	14.5	15.9	14.9	16.7	18.0	12.8	13.4
➢ 95 percentile	20.64	22.6	22.4	27.4	25.1	26.2	24.7	29.7	28.2	20.1	20.4
The coefficient of variation (%)	74	74	68	73	72	71	72	84	66	75	70

mSv. Among this group the dose of 1,260 persons exceeded 50 mSv for 120 individuals the effective doses were higher than 100 mSv and only one person with a dose of 214 mSv dose exceeded 200 mSv. Calculated in the course of the revision (included cleansing of dose rate data, more soposticated interpolation in time and space, stochastic modelling of individual doses) the average dose of 15.9 mSv was slightly (14%) lower than the one that was identified in preceding study – 18.2 mSv. This difference has several reasons.

Firstly, 3,119 persons who lived in remote from Chernobyl NPP villages and whose doses were, respectively, quite small were excluded from this review. On the other hand, a critical review of dose rate measurement forced to reject some, perhaps, false values. In addition, a more sophisticated method of spatial interpolation (kriging, a geostatistical method) has prevented the devel-

opment of artificial unreasonably highest values of the interpolated dose rates. For these two reasons, number of persons with high doses slightly decreased. So, if according to the preliminary consideration 644 persons had dose more than 100 mSv, the results of the audit assessed the number of only 120 persons with doses of such magnitude. Moreover, same as in the problem of dose assessment of the urban population, use of age-dependent conversion factors to an effective dose also contributed to a certain reduction of effective doses received as a result of the audit.

Table 2.1.9 shows the general parameters of the effective doses distribution of 14,084 inhabitants of 30 km zone.

Table 2.1.9

Parameters of individual doses distribution of external exposure of individuals who were evacuated from villages of 30 km zone. Results of deterministic calculation (data of SI «RCRM of AMS of Ukraine»).

Parameter	Value
Number of persons	14,084
The average fraction of time spent outdoors	0.41
Distribution of effective doses of external gamma radiation exposure (mSv)	
➢ arithmetic mean	15.9
➢ median	7.77
➢ geometric mean	7.13
➢ geometric standard deviation	4.08
➢ 75 percentile	16.1
➢ 95 percentile	67.7
➢ coefficient of variation (%)	142

Noteworthy is a very large coefficient of variation of individual doses – 142%. Such a large variation can be explained by significant differences in dose rates in different villages of the 30-km zone, varying duration of the population in the zone of radioactive contamination (different time of evacuation), and individual differences in fraction of time spent outdoors. The distribution of individual doses (Figure 2.1.5) illustrates the heterogeneity of the population, comprising the residents of less contaminated villages and dwellers of localities with high dose rate.

The distribution of fractions of time spent outdoors is also quite broad. Figure 2.1.6 shows that half of the population spent more than 42% of time outdoors and about 5% of evacuees from rural areas spent more than 65% of the time outdoors. There are obvious differences between urban and rural populations: on average urban residents spent about 21% of time outdoors (Table 2.1.7), while for rural population this fraction was about 41% resulting in higher doses of external exposure. Another factor that has considerable influence on the resulting dose was the duration of stay of residents in the contaminated areas.

The parameters of individual doses distributions for same settlements included into the dose reconstruction are presented in Table 2.1.10. For villages with a number of surveyed less than 20, the median and 95% quantile were not determined. The table shows that for all sectors except Sector B (Figure 2.1.7), maximum (95% quantile) dose for the individual settlement exceeded the level of 50 mSv. On average, the highest doses were received in the villages Usiv – 154 mSv, Mashevo – 79 mSv (both – Sector C) and Chistogalivka – 70 mSv (Sector A). The parameters of the distributions are shown in the Table 2.1.11. For comparison, the table contains parameters of the distribution at Chernobyl town – much less affected and the second most populated settlement within the 30-km zone (after Pripyat).

It is seen that within the same locality the variation of individual doses is relatively small. Geometric standard deviation for small settlements is equal to 1.4–2.8 and supports the point

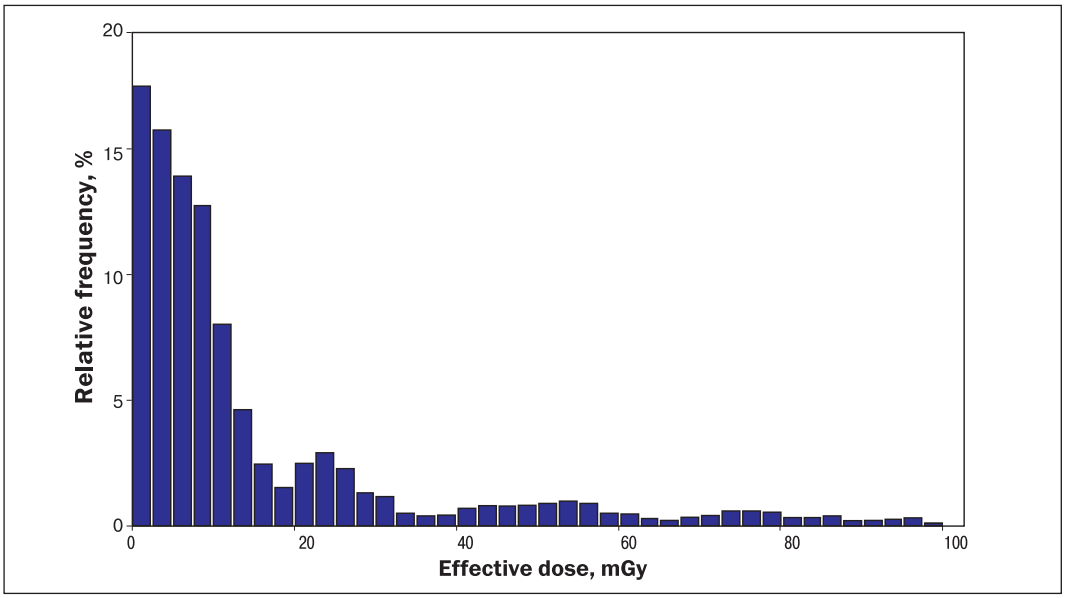


Figure 2.1.5. **Distribution of individual doses of 14,084 persons evacuated from the settlements of the 30-km zone. Results of deterministic calculation.**

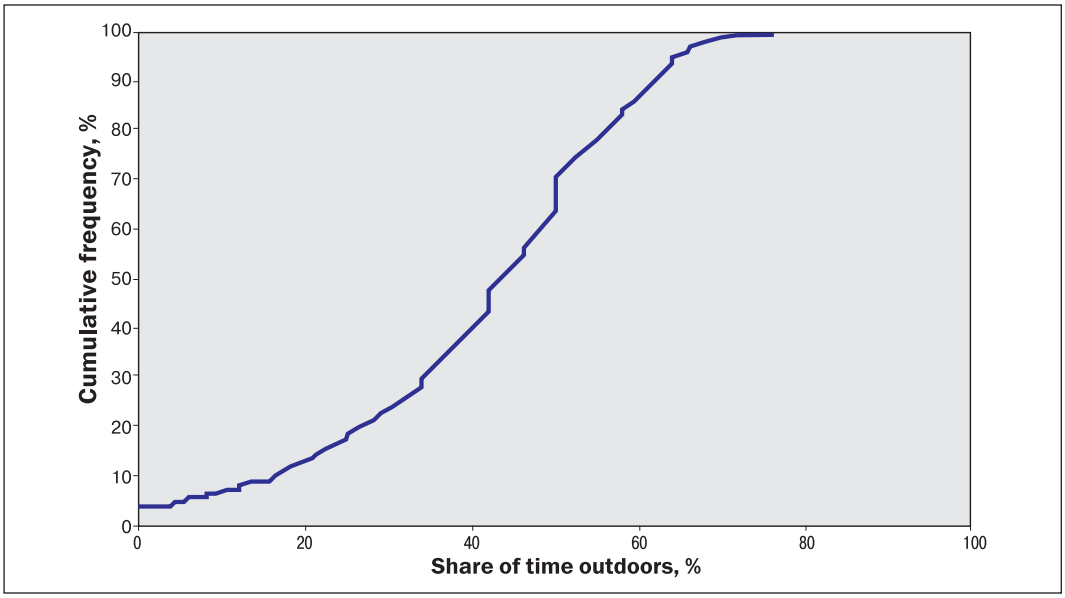


Figure 2.1.6. **Cumulative distribution of fractions (shares) of time outdoors for people who were evacuated from villages of 30 km zone**

that the population is quite homogeneous in terms of exposure and thus – behaviour patterns. The exception to this rule are such large settlements like Chernobyl, where population groups are characterized by a variety of behaviour patterns. In addition, the migration of Chernobyl residents out of the town, as well as self-evacuation of some of them resulted in significant

Table 2.1.10

Results of deterministic calculation of individual doses for selected settlements of 30-km zone. Location of settlements see Figure 2.1.7.

Code	Settlement	Quantity of persons	Day of evacuation	Part-time in the open airs, %	Average	Median	95% percentile
	Sector A						
14	Yaniv	63	3	34	22	9.5	84
20	Chystogalivka	331	7	44	61	70	98
15	Buriakivka	56	8	45	29	24	81
16	Nova Krasnytsia	89	8	48	23	23	29
18	Rechytsia	382	7	50	24	26	33
17	Tovsty Lis	408	8	51	52	60	81
19	Krasne (of Tovstolis rural district)	297	8	49	34	15	97
10	Rud'ky	43	7	32	10	12	19
22	Stara Krasnytsia	20	7	36	9.2	8.4	17
23	Vilshanka	24	10	34	10	11	13
24	Lub'ianka	304	10	46	12	12	16
	Sector B						
1	Novoshepelychi	815	6	37	15	13	31
2	Staroshepelychi	209	7	50	21	22	31
3	Beniovka	101	8	48	18	18	26
4	Bila Soroka	7	6	41	16	-	-
5	Dovliady	10	5	36	12	10	23
12	Khatky	19	9	44	10	9	12
	Sector C						
54	Mashevo	162	8	54	75	79	96
41	Usiv	89	8	48	150	154	165
43	Molochky	2	7	34	31	-	-
55	Zalissia	2	6	36	12	-	-
56	Kriuky	14	7	44	66	-	-
57	Kulazhyn	2	8	12	28	-	-
	Sector D						
51	Zymovyshche	431	7	37	37	42	56
52	Kryva Gora	146	8	40	47	51	67
74	Starosillia	100	8	40	3	3	4
73	Koshovka	126	8	45	9	8	12
76	Paryshiv	286	8	46	4	4	5
65	Chapaivka	211	8	39	6	7	8
75	Chykalovychy	3	8	50	8	-	-
	Sector E						
66	Copachi	432	8	40	45	53	66
67	Leliov	604	8	42	22	23	30
68	Chornobyl	4558	7	32	6	6	14
69	Zalisssia	1611	8	52	7	8	10
70	Zapillia	69	9	48	6	7	8
71	Cherevach	263	9	47	5	5	8
37	Novosilky	202	9	48	6	6	8
33	Korogod	601	8	52	4	5	6
29	Stechanka	333	8	43	4	4	5
30	Roz'yizzhe	49	8	37	3	3	4
31	Ilintsy	366	8	45	3	3	4
32	Rudnia Illinetska	15	11	36	4	4	5
34	Glinka	227	7	34	2	2	2

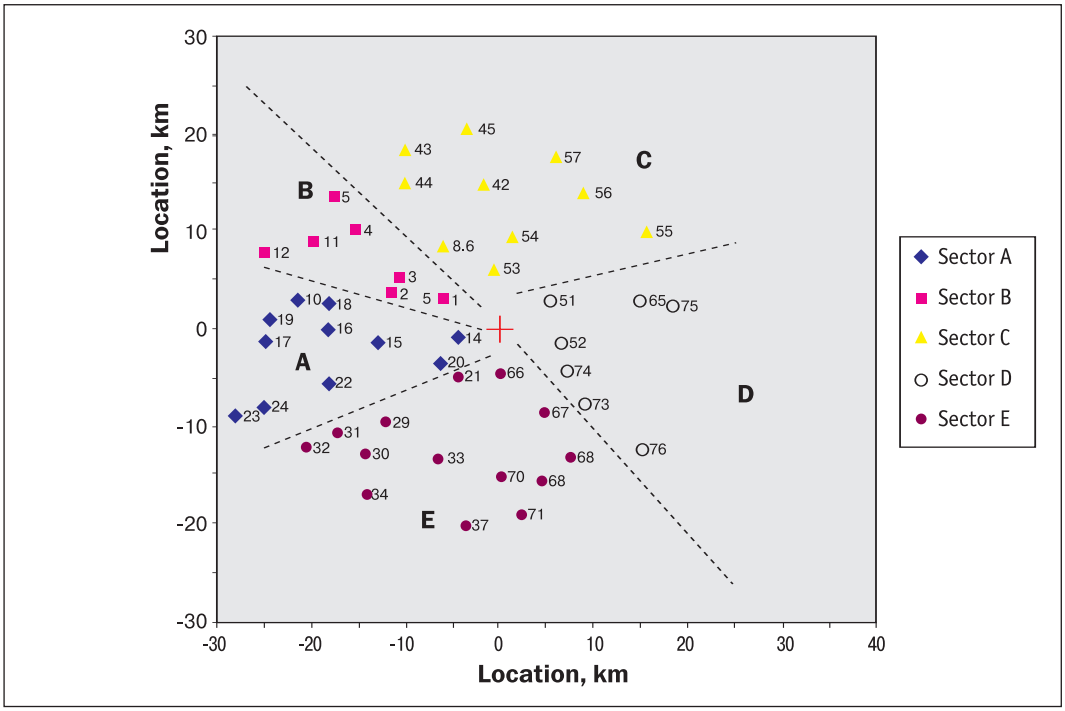


Figure 2.1.7. Schematic location of the 30-km zone settlements and their distribution by the sectors. Settlement codes and their full names see in Tables 2.1.10, 2.1.11.

Table 2.1.11

Parameters of distributions of individual external exposure doses in the most exposed villages of the 30-km zone abd Chernobyl town. Results of deterministic calculation.

Settlement	Usiv	Mashevo	Chystogalivka	Chornobyl
Number of persons	89	165	331	4558
Distribution of effective doses of external gamma radiation exposure, mSv				
➢ arithmetic mean	150	74.8	60.8	6.38
➢ median	154	78.7	69.7	5.84
➢ geometric mean	146	69.2	44.7	3.4
➢ geometric standard deviation	1,28	1.66	2.77	4.14
➢ 95 percentile	165	95.7	98.1	14.4
Coefficient of variation, %	15	27	52	85

expansion of the range of doses received by the residents of this town. Therefore, geometric standard deviation of the doses distribution of Chernobyl evacuees is very large (about 4.14), which is very close to the value of this index calculated for general distribution of doses of 30-km zone evacuees (Table 2.1.9).

In general, as it is seen from the above examples, the uncertainty of individual dose estimates of the rural population is slightly higher than for respective urban population doses, but even with uncertainty at the level of 60-80% (coefficient of variation), such precision is adequate for the purposes of retrospective assessment of individual doses of population evacuated after the accident.

2.1.4. Doses on evacuation route

The doses received by Pripyat residents during evacuation were estimated in a course of a special study. Analysis of route lists, completed in 1988-1989 during the large-scale survey of evacuees allowed to identify four main routes by which residents of Pripyat moved in the direction of evacuation points (Table 1.2.12).

The most significant itinerary was the road to Polisske which passed in the western direction. Prevalent quantity of evacuees took this route. Another, somewhat less important, was the route in Kyiv direction, the path of which went through the «Red Forest», Kopachi, Chernobyl, Cherevach and further to Kyiv. Other two less important itineraries were revealed: the railway in the direction of Chernigiv, and self-evacuation on their own vehiclest towards Belarus (the road to Bila Soroka village).

Table 2.1.12
Features of evacuation itineraries from Pripyat (data of the survey)

Route code	Direction of evacuation	Code of route	Number of persons	Percentage of total
1	Poliske	1	6831	42
2	Kyiv	2	4478	27
3	Chernihiv	3	938	6
4	Belorussian	4	612	4
5	The route is not specifically listed	5	2271	14
6	To the villages of the 30-km zone	6	1063	7
		Total:	**16193**	**100**

These data, in general, are not contradictory to information about the organization and realization of evacuation of Pripyat population.

Analysis of the radiation situation at the evacuation routes showed that the entire itinerary can be divided into two essentially different parts (phases): phase 1, which passed through the 5-km zone of Chernobyl NPP, and the rest of the route (phase 2) from the border of the 5-km zone to destination.

Crucial difference of phase 1 is that the evacuation route crossed several extremely high dose rate radioactive traces, the scale (typical size) of which sometimes reached only tens or hundreds of meters. The rest of the evacuation (phase 2) went through the less contaminated areas with much lower dose rate variations.

As a result, assessment of doses received on particular evacuation routes was carried out separately for phases 1 and 2. In the case of phase 1 doses reconstruction was conducted manually using cartograms of radiation situation data provided by Chernobyl NPP. In phase 2 dose was estimated by integrating the dose rate profiles along the route.

It appears from the estimation of doses received during each of the routes, that the main evacuation route, prescribed in the emergency preparedness plan, towards Poliske town was in reality less safe than the improvised Belarussian direction. On the other hand, a small change of route – leaving the Pripyat through the railway crossing near the plant «Jupiter» instead of travel through the contaminated area near the viaduct over the railroad, crossing Pripyat-Chernobyl NPP and cottages south of the station Yaniv - could significantly reduce en route doses of evacuees.

Route to Kyiv was also associated with significant doses due to travel cross a very active spot in the crossroad NPP-Chernobyl-Pripyat. While the rest of the route to the south was in less contaminated areas, doses formed at the first site were quite substantial.

En route doses were the highest on the route in the direction of Chernihiv. This route was taken by about 6% of the questioned evacuees. Evacuation in this direction was carried by rail, and electric trains leaved from relatively polluted station Yaniv, then headed north by the ChNPP site perimeter where the dose rates reached fairly large values. Finally, electric trains made scheduled stops at platform Semihody (north-eastern outskirts of Chernobyl NPP), resulting in further accumulation of dose. As a result, the doses received by evacuations of rail in the direction of Chernigiv were the largest among all possible routes of evacuation.

Thus, the doses of the majority of Pripyat dwellers, received during the evacuation, were within 11-19 mSv, comparable to pre-evacuation irradiation.

Individual doses before and during the evacuation were estimated and compared for each evacuee of those who had the ordinary behaviour mode (did not leave town limits before evacuation), left the town during the general evacuation and who clearly indicated the point of evacuation (in total 6,908 people met these criteria). Then the partial contribution of dose received en route of evacuation into the total dose of radiation was determined. The distribution of those dose partial contributions during evacuation is presented at Figure 2.1.8, showing that this value varies quite broadly, but most probable value is 0.5. The average (52±19)% of the total dose was received by evacuees from Pripyat just during evacuation.

Thus, it is obvious that the correct estimation of doses during evacuation significantly change the pattern of irraddiation of evacuated Pripyat population. For comparison, it should be emphasized that in case of evacuation of Pripyat in the direction of the Bila Soroka (Belarus route), the dose due to the evacuation would give the only contribution of about 6% of the total dose.

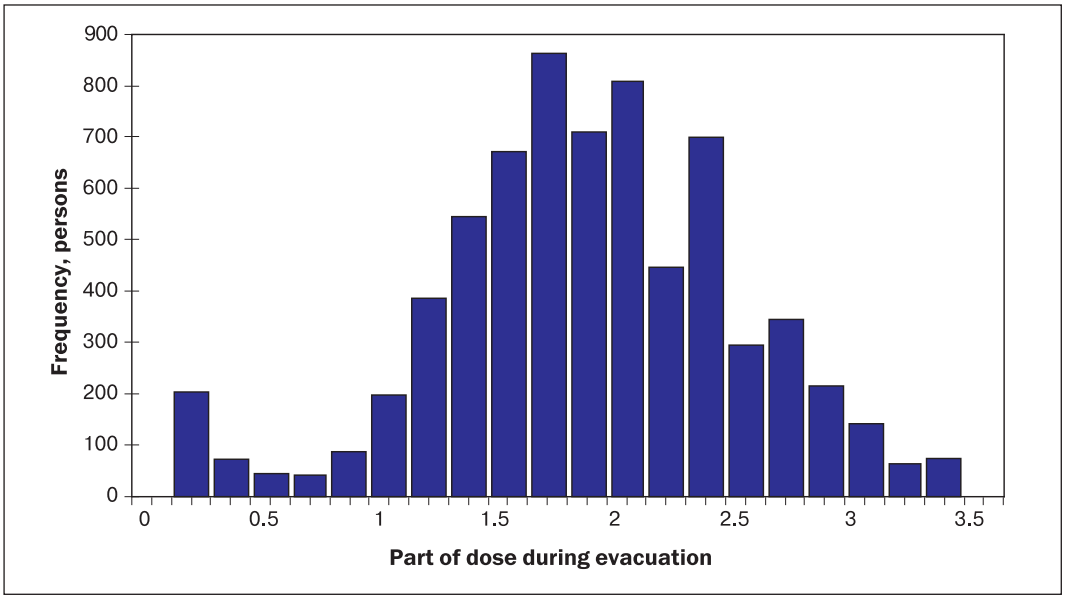


Figure 2.1.8. **Fractional contribution of dose received during the evacuation to the total dose of evacuees from Pripyat**

As a result of these efforts, integral dose was estimated separately for each of the four routes. It appeared that in terms of dose burden during evacuation, the most popular evacuation route towards Poliske, which was determined in the preparedness plan, was not the optimal one. Evacuation in the Belarussian direction resulted in the accumulation of an order of magnitude

smaller doses than any of the other routes. On the other hand, driving in the direction of Chernobyl-Kyiv and evacuation by train to Chernigiv gave even higher doses.

Comparison of individualized dose estimates on the evacuation route with individual doses received while staying within the Pripyat during the evacuation, showed that in many cases the doses at evacuation route were comparable or even larger than doses received prior to evacuation. In general, the dose at the evacuation route had given the contribution to the total dose of evacuees at around 50%. Thus, consideration of dose received at the evacuation route severely alters the overall picture of evacuees' irradiation.

2.1.5. Population irradiation doses

Radiological monitoring in 1986

In Ukraine in 1986 radiological emergency monitoring was organized so that literally since the first hours and days the mass measurement of *gamma-field dose rate* in the air from radioactive fallout on the ground, and later – *soil sampling* for gamma-spectrometric studies of radionuclide fallout on the basis of the most radioactively-contaminated areas were carried out.

As for the control of radiation exposure of the population-contaminated areas, the *radiometric monitoring* was conducted in large scale and had good enough quality, as in the earliest (acute) phase of the accident (May-June) when the main source of internal radiation were radioisotopes of iodine, which accumulate in thyroid gland, and at the beginning of the middle phase (August-December, 1986), when the basic role was played by radioisotopes of cesium, which are relatively evenly distributed in the soft tissues.

Total in Ukraine in May-June, 1986 more than 150 thousand direct measurements of radioiodine activity in the thyroid gland of residents of northern districts of Kyiv, Zhytomyr and Chernigiv regions (among them 130 thousand children and teenagers) were made. In addition, since July, 1986 till the end of the year about 23 thousand measurements of the current content of cesium isotopes in the body (^{137,134}Cs) using whole body counters (WBC) were taken in the residents of Kyiv and Zhytomyr regions.

2.1.6. Doses of irradiation in 1986

Whole body irradiation

Table 2.1.13 shows values of average doses of internal radiation from cesium intake residents of districts of Kyiv and Zhytomyr regions, assessed by results of measurements on whole body counters (WBC), conducted in summer and autumn of 1986.

Since WBC monitoring covered the population far from all settlements of radioactively-contaminated areas a simulation of the transfer of dose forming radionuclides from Chernobyl release was conducted via the links of trophic chains in the climatic conditions of Ukraine using non-stationary models that are traditionally used for retrospection and prognosis kinetics and levels of radioactive contamination of environmental objects (food in particular) as well as exposure doses of the population, which consumed these products.

As it was expected, the main source of internal radiation doses in 1986 was the contamination of two components of the diet: leafy green vegetables, and milk (and milk products).

Evaluations of effective doses of internal radiation from basic radionuclides in the emergency release (per 1 kBq x m^{-2} of ^{137}Cs in soil) obtained according to this model are presented in Table 2.1.14.

It should be noted that in terms of Western European countries, the calculated ratio between doses of first emergency year and doses accumulated over subsequent years, may reach 10 or more

Table 2.1.13

Individual doses of internal exposure of children and adults from radiocaesium in 1986 (Results of WBC measurements for areas with density of fallout ^{137}Cs in soil >37 kBq · m^{-2}) average by districts of Kyiv and Zhytomyr regions

Birth years	Children under 10 years			Children over 10 years			Adults		
	number of WBC-measurements	dose, mSv		number of WBC-measurements	dose, mSv		number of WBC-measurements	dose, mSv	
		GM	GSD		GM	GSD		GM	GSD
Zhytomyr region									
Korostens'kyi	-			-			34	0.13	2.9
Lugyns'kyi	-			-			12	0.32	4.8
Narodytskyi	1995	1.8	3.9	1120	1.8	3.9	2753	1.56	4.3
Ovruchskyi	134	1.1	2.8	28	0.43	2.5	18	0.19	3.5
Kyiv region									
Bilotserkivskyi	30	0.44	2.3	26	0.89	1.8	-		
Boguslavskyi	28	0.28	2.4	17	0.30	3.0	-		
Ivankivskyi	208	0.61	3.3	261	0.42	3.0	652	0.29	3.6
Kagarlitskyi	12	0.71	3.2	78	0.39	2.6	-		
Poliskyi	1323	1.2	3.5	1061	0.86	3.3	1872	0.81	3.5
Stavyshchenskyi				31	0.11	3.6	527	0.09	2.8
Chornobylskyi	1195	1.3	5.6	518	0.58	3.3	304	0.61	5.5

Notes. GM – geometric mean, GSD – geometric standard deviation.

Table 2.1.14

Effective doses of internal exposure in 1986 due to the main radionuclides of Chernobyl release (normalized to 1 kBq · m^{-2} of ^{137}Cs at the soil) in adult rural dwellers of Ukraine, caused by consumption of milk and leafy green

Radionuclide	Relative contributions to total dose of internal radiation dose components					
	«milk»		«leafy green»		total	
	µSv per 1 kBq x m^{-2} of ^{137}Cs at the soil^{-2}	relative contribution to dose (%)	µSv per 1 kBq x m^{-2} of ^{137}Cs at the soil^{-2}	relative contribution to dose (%)	µSv per 1 kBq x m^{-2} of ^{137}Cs at the soil^{-2}	relative contribution to dose (%)
^{89}Sr	0.1	0.16	0.064	1.6	0.16	0.26
^{90}Sr	0.39	0.7	0.094	2.4	0.48	0.8
^{95}Nb	9.8E-07	1.7E-06	0.021	0.5	0.021	0.03
^{95}Zr	4.8E-06	8.2E-06	0.042	1.1	0.042	0.07
^{103}Ru	0.002	0.003	0.11	2.8	0.11	0.18
^{106}Ru	0.015	0.026	0.37	9.5	0.39	0.6
^{125}Sb	0.39	0.7	0.015	0.38	0.41	0.7
^{134}Cs	6.8	12	0.26	6.6	7.1	11
^{137}Cs	10	17	0.36	9.2	10	17
^{136}Cs	0.08	0.1	0.014	0.35	0.10	0.16
^{131}I	41	70	2.3	57	43.3	69
^{141}Ce	1.0E-07	1.7E-07	0.038	1.0	0.038	0.06
^{144}Ce	2.5E-06	4.3E-06	0.21	5.3	0.21	0.34
^{140}Ba	0.001	0.002	0.099	2.5	0.10	0.16
All radionuclides	59	100	4,0	100	63	100

in favor of the first year. At the same time a variety of soil characteristics, both in Ukraine and Russia, which makes high (uncharacteristically for European countries) coefficients of radionu-

clides transfer from soil to vegetation and further into the milk, as well as an obsolete technology of dairy production in the private sector of Ukraine, identified a wide range of internal radiation dose ratios in the first and subsequent years.

In Ukraine (Table 2.1.15) the ratio of effective dose of internal radiation received in 1986 (the first year, 256 days) to the appropriate dose for the next nearly 20 years (1987–2005) essentially depends on the aggregate value of «soil-milk» transfer factor (TF-92) in a given settlement. In the areas where the value TF-92 does not exceed 0.5 Bq x l^{-1} per kBq x m^{-2}, the ratio of doses of the first and another 19 years is 8–50 in favor of the first year. For areas with TF-92 in the range 0.5–2 Bq x l^{-1} per kBq x m^{-2}, this ratio is 1–2, but still in favor of the first year. At the same time for the settlements, where the value of TF-92 is 2–20 Bq x l^{-1} per kBq x m^{-2} doses in the middle and late phases of the accident exceed the first year, so the first year dose is only 13–50% of the dose for further years. In the areas with very high values of TF-92 that exceed 20 Bq x l^{-1} per kBq x m^{-2} doses of the first year do not exceed 9% of the accumulated dose for subsequent years.

Table 2.1.15

The ratio of internal radiation doses in 1986 to the appropriate doses for the 1987-2005 depending on interval values of the aggregated transfer factor «soil-milk» (TF-92). Doses were estimated by the Method-97 (*total 4270 settlements of Ukraine*)

TF-92* Bq x l^{-1} per kBq x m^{-2}	D-86/D87-05 doses ratio	Number of settlements
< 0.05	49	269
0.05–0.1	48	261
0.1–0.2	15	1106
0.2–0.5	8.0	1097
0.5–1	2.6	478
1–2	1.1	354
2–5	0.51	404
5–10	0.25	146
10–20	0.13	115
20–100	0.09	40

Notes. * – TF-92 value was determined for a fixed time interval 1991-1993 based exclusively on results of monitoring radioactive contamination of soil and milk in every settlement.

Thus, under particular agro-ecological conditions (peat-swampy acidic soil of pastures) the population can receive significantly larger doses of internal irradiation in postaccidental period compared with doses of first year of the emergency (for example, a number of settlements Rokytne district, Rivne region, and Kamin-Kashirskyi district, Volyn region). On the other hand, where the black earth were prevailing, internal radiation doses accrued in subsequent years may be a small fraction of the first year dose (for example, a number of settlements in Cherkassy region).

Irradiation of the thyroid

The most significant in terms of radiation exposure and expected radioinduced consequences after Chernobyl accident was thyroid irradiation of children by radioiodine that came mainly from contaminated milk, dairy products and leafy green in May-June, 1986. A three-level system of reconstruction of thyroid doses developed and verified on the results of direct measurements allowed to evaluate the average gender-age settlement-specific doses of the thyroid gland for all settlements of Ukraine (Table 2.1.16).

Table 2.1.17 shows the distribution of children, adolescents and adults at intervals of absorbed radiation doses to the thyroid gland as a whole across Ukraine.

Table 2.1.16
Average regional thyroid doses (mGy) in different age groups of inhabitants of different regions of Ukraine

Region	The average thyroid dose (mGy) by age groups (years)				
	< 7	7–14	15–18	> 18	all
Vinnytsia	37	13	9.8	9.2	12
Volyn	87	33	25	21	31
Lugansk	12	4.0	3.1	3.1	4.1
Dnipropetrovsk	13	4.4	3.4	3.4	4.5
Donetsk	24	8.0	6.0	6.1	8.1
Zhytomyr	231	87	67	60	81
Transcarpathian	7.6	2.8	2.1	1.8	2.7
Zaporizhzhia	26	8.8	6.2	6.5	8.8
Ivano-Frankivsk	19	7.1	5.3	4.6	6.7
Kyiv	202	75	58	53	71
Kirovograd	89	31	23	23	30
AR Crimea	34	12	8.8	8.4	12
Lviv	14	4.9	3.8	3.5	4.8
Mykolaiv	20	7.1	5.4	5.0	7.0
Odesa	15	5.2	3.8	3.7	5.1
Poltava	54	19	15	13	18
Rivne	177	64	49	42	62
Sumy	71	25	19	19	24
Ternopil	18	6.4	4.8	4.5	6.2
Kharkiv	26	8.7	6.5	6.6	8.6
Kherson	30	11	7.8	7.3	10
Khmelnytsky	39	15	11	10	14
Chercasy	142	52	39	37	49
Chernivtsi	40	14	10	9.3	13
Chernihiv	151	55	43	37	50
Kyiv city	94	30	23	24	32
Sevastopol city	56	18	14	14	19
All Ukraine	**55**	**20**	**15**	**14**	**19**

Table 2.1.17
The relative distribution of child, adolescent and adult population with a mean absorbed doses of thyroid

Region	Relative (%) distribution of population				
	< 7 years	7–14 years	15–18 years	>18 years	entire population
< 0.05	72	93	95	95	92
0.05–0.1	15	4.4	3.5	3.7	5.0
0.1–0.2	8.2	2.2	1.3	1.1	2.0
0.2–0.5	3.7	0.76	0.40	0.21	0.65
0.5–1.0	0.77	0.08	0.05	0.04	0.12
1.0–2.0	0.15	0.03	0.02	0.01	0.03
2.0–5.0	0.04	0.007	0.005	0.004	0.008
>5.0	0.01	0.0005	–	–	0.001

2.2. DOSIMETRIC CERTIFICATION (PASSPORTIZATION) AND RADIOLOGICAL MONITORING AT THE INTERIM AND LATE PHASES OF DISASTER

«The Concept of the Annual Total Effective Dose», adopted in 1991, was important for planning and carrying out measures to reduce the impact of radioactive emissions on the population. Regulations of this concept were legalized in the Law of Ukraine № 791a-XII «On legal regime of territories which have undergone radioactive contamination as a result of the Chernobyl disaster» (1991) and in the Law of Ukraine № 796-XII «On the status and social protection of citizens affected by the Chernobyl disaster» (1991).

The basic principle of the Concept lays in that for the critical population group (children born in 1986), the value of calculated effective dose of additional radiation associated with the Chernobyl disaster, should not exceed 1.0 mSv (0.1 rem) per year and 70.0 mSv (7.0 rem) for life span (over the dose received by the population in pre-accident period in certain natural conditions).

The density of soil contamination with radionuclides was taken as a provisional criterion. These laws set a four territorial zone of radioactive contamination (Table 2.2.1).

Table 2.2.1

Areas of contamination according to criteria of the annual dose and density of radionuclides fallout determined by The Law of Ukraine № 791a-XII (1991)

Territorial zone		Zoning criteria			
		fallout density on soil, kBq x m^{-2} [(a)]			the annual dose, mSv x $year^{-1}$
		radiocaesium	radiostrontium	plutonium	
1	Exclusion zone	–	–	–	–
2	Zone of implicit (mandatory) resettlement	>555	>111	>3.7	>5
3	Zone of guarantee voluntary resettlement	185–555	5.5–111	0.37–3.7	>1
4	Zone of enhanced radiation monitoring	37–185	0.74–5.5	0.18–0.37	>0.5

Notes. [(a)] – in the text of the Law fallout density is given in units of «Ci x km^{-2}».

In Appendix 1 to the Decree of Cabinet of Ukraine № 106 from July 23, 1991 the list of 2172 settlements was given, which were formally assigned to one of four zones of radioactive contamination according to the Law of Ukraine № 791a-XII.

Annual dosimetric certification was held in Ukraine since 1991 until 2008. All dose calculations were based on results of annual measurements of radiocaesium contamination of milk and potatoes produced in those settlements, which were determined by the Decree of Cabinet of Ukraine № 106. In addition, for radiation monitoring of the residents of affected areas, the united WBC network of Ukraine was set up during the 1995–1997, providing operational control of the levels of radiocaesium in the body of the inhabitants of affected areas (Figure 2.2.1).

Medical organization of 12 most affected regions of Ukraine were provided with 57 units of WBC «Skrynner-3M» both stationary (40 units) and mobile (17 units) designed and manufactured by the Institute of Human Ecology (Kyiv) with the use of program-methodical and metrology software, developed by the Department of Dosimetry of SI «RCRM of AMS of Ukraine».

From 1995 to 2008 about 800 thousand WBC measurements was held within the network of WBC.

The Table 2.2.2 contains the relative distribution of all certified settlements according to established territorial areas as a result of dose certification within 2001–2008.

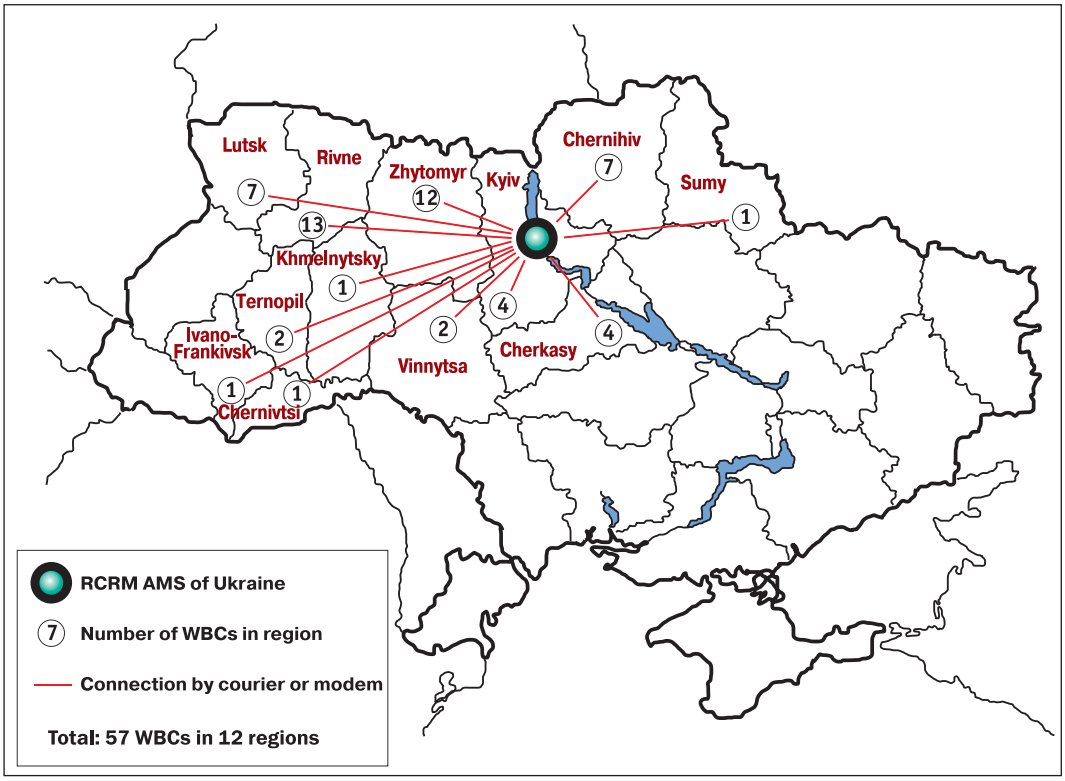


Figure 2.2.1. WBC Unified Network of Ukraine, established under the program of dosimetric certification

The evolution of the numbers of settlements attributed to the different zones in 2001, 2005 and 2008 for selected regions of Ukraine, where the largest number of settlements were dose certified, is shown in Table 2.2.2. As it is seen from the table data, since 2001 ~ 15–19% of all certified settlements were in the 4th zone of «Enhanced radiation monitoring», and 70–80% in general were outside the established territorial zones of radioactive contamination.

Table 2.2.2

Time evolution (2001–2008) of the distribution of settlements according to the magnitude of «passport dose»

Year	Number of certified settlements	Relative number (%) of certified settlements with the passport dose (mSv per year)			
		< 0.5	0.5–1	1–5	>5
		«safely»	4 zone	3 zone	2 zone
2001	2163	67	15	18	0,23
2002	2163	68	15	17	0,14
2003	2163	71	16	13	0,09
2004	2163	72	19	9	< 0,01
2005	1831	66	14	5	< 0,01
2006	1967	82	14	3,5	0,05
2007	1596	81	15	3,6	< 0,01
2008	1925	86	12	0,02	–

It should be noted that in Kiev and Zhytomyr regions in 2001–2008, the number of settlements in 2nd–4th zones continuously decreased in comparison with the official distribution by the Decree of Cabinet of Ukraine № 106 (Table 2.2.3). Most of the settlements in these areas were «moved» to the «safe» zone, where passport annual dose did not exceed 0.5 mSv. In the Rivne region, according to Decree of Cabinet of Ukraine № 106 the majority (~ 76%) of settlements was attributed to the third zone of «voluntary resettlement» (passport dose should be between 0.5 and 1 mSv). But in 2001 already, in this zone remained ~ 30% of the original number of settlements and in 2008 ~ 7% of the settlements. Most of the settlements «moved» to the 4th zone (passport dose – 0.5–1 mSv), or «safe» zone (passport dose <0.5 mSv).

In 2008, almost 82% of the settlements of Kyiv and Zhytomyr regions referred by the Decree of Cabinet of Ukraine № 106 to 2nd–4th zones actually have a «passport» dose of less than 0.5 mSv/year. That is, according to the dose criterion of the territory, these settlements have already lost the status of «victims». At Rivne region the passport doses below 0.5 mSv per year were estimated in 44% of settlements.

There is an annual reduction of the number ofsettlements, which according to the dose criteria can be attributed to 3rd zone (1–5 mSv x year^{-1}). For the 2nd zone (dose >5 mSv x year^{-1}), since 2000 in Kyiv and Zhytomyr regions there were actually no settlements belonging to that area, and in Rivne region in 2001 in this zone were to be only 5 settlements.

Table 2.2.3
Comparison of certification data of settlements of Ukraine in 2001, 2005, and 2008

Region	Quantity of inhabited localities with annual doses (mSv x year^{-1})											
	total	2001				2005				2008			
		≤ 0.5	0.5–1	1–5	> 5	≤ 0.5	0.5–1	1–5	> 5	≤ 0.5	0.5–1	1–5	> 5
Vinnytsia	89	89	–	–	–	88*	–	–	–	87	–	–	–
Volyn	166	–	3	163	–	107	55	3	–	121	40	3	–
Zhytomyr	698	472	135	93	–	524	96	43	–	569	74	14	–
Kyiv	469	441	23	5	–	428	13	3	–	383	9	–	–
Rivne	339	99	109	126	5	151	122	59	–	150	99	25	–
Cherkasy	103	101	2	–	–	100*	2*	–	–	100	2	–	–
Chernihiv	248	205	41	2	–	216	11	–	–	205	11	–	–

Notes. * – data for 2006 (in 2005 dose certification was not performed).

2.3. DOSES ACCUMULATED BY THE RESIDENTS OF UKRAINE FOR 25 YEARS AFTER THE CHERNOBYL ACCIDENT

Table 2.3.1 estimates averages (weighted by number of inhabitants in settlements) effective doses of external, internal and total (external and internal) exposure for all regions of Ukraine. Estimates of the relevant doses in 1986 accrued between 1987–2011 and for the whole post-accident period and the population distribution for each area are presented based on the density of fallout ^{137}Cs in soil. Table 2.3.2 presents similar data for Ukraine as a whole.

Table 2.3.3 estimates population-weighted effective doses in different time periods after the Chernobyl accident for all regions of Ukraine, Kyiv, Sevastopol, as well as Ukraine as a whole.

Table 2.3.4 shows the distribution of rural population in Ukraine, living in the areas where the density of ^{137}Cs fallout in 1986 exceeded 37 kBq x m^{-2}, with intervals of doses accumulated during the 1986–2011.

Table 2.3.1

Effective dose (mSv) external, internal and total irradiation for different regions of Ukraine depending on the density of fallout ^{137}Cs in soil in 1986

Region	Density of ^{137}Cs fallout kBq /m^2	% of population	Effective dose (mSv) according to years of exposure				
			external		internal		total
			1986	1987–2011	1986	1987–2011	1986–2011
Vinnytsia	< 37	94	0.24	0.47	0.51	0.25	1.5
	37–185	6.3	1.7	3.4	3.40	0.31	8.8
Volyn	< 37	97	0.19	0.38	0.43	2.4	3.4
	37–185	2.6	1.4	2.9	3.0	13	20.3
Lugansk	< 37	99	0.34	0.68	0.48	0.22	1.7
	37–185	0.69	1.0	2.1	1.7	0.33	5.2
Dnipropetrovsk	< 37	100	0.1	0.19	0.18	0.19	0.65
	37–185	0.02	1.29	2.6	2.8	0.40	7.1
Donetsk	< 37	94	0.2	0.39	0.29	0.21	1.1
	37–185	5.6	1.1	2.2	1.4	0.27	5.0
Zhytomyr	<37	75	0.2	0.4	0.37	0.58	1.5
	37–185	17	2.5	5.1	1.4	5.9	14.9
	185–555	7.2	6.8	14	1.9	3.4	25.8
	555–1440	0.69	20	39	8.2	12	79
	> 1440	0.06	52	103	22	32	208
Transcarpathian	< 37	100	0.12	0.25	0.24	0.19	0.80
Zaporizhzhia	< 37	100	0.07	0.15	0.15	0.16	0.52
Ivano-Frankivsk	< 37	95	0.26	0.52	0.55	0.36	1.7
	37–185	4.6	1.7	3.4	3.5	0.5	9.0
Kyiv	< 37	76	0.45	0.89	0.5	0.42	2.3
	37–185	22	1.9	3.8	1.5	1.0	8.2
	185–555	1.1	8.2	16	6.5	2.7	34
	555–1440	0.66	26	52	8.2	1.5	88
	> 1440	0.08	92	184	41	57	375
Kirovograd	< 37	99	0.20	0.40	0.37	0.15	1.1
	37–185	0.68	1.6	3.2	3.5	0.29	8.7
AR Crimea	< 37	100	0.12	0.23	0.20	0.17	0.72
Lviv	< 37	100	0.09	0.17	0.17	0.16	0.58
	37–185	0.008	1.2	2.4	2.6	1.5	7.7
Mykolaiv	< 37	100	0.12	0.24	0.22	0.15	0.73
	37–185	0.06	2.4	4.8	5.3	0.50	13
Odesa	< 37	100	0.19	0.38	0.34	0.15	1.1
	37–185	0.19	1.3	2.7	2.9	1.5	8.5
Poltava	< 37	100	0.17	0.33	0.31	0.22	1.0
Rivne	< 37	78	0.28	0.56	0.45	1.1	2.4
	37–185	21	2.2	4.3	1.9	14	22
	185–555	0.39	7.2	14	5.9	14	42
Sumy	< 37	99	0.21	0.42	0.41	0.32	1.4
	37–185	0.98	1.91	3.8	4.1	1.2	11
Ternopil	< 37	97	0.15	0.30	0.35	0.37	1.2
	37–185	3.0	1.6	3.1	3.3	0.77	8.7
Kharkiv	< 37	100	0.18	0.36	0.32	0.17	1.0
	37–185	0.01	1.12	2.2	2.4	0.54	6.3
Kherson	< 37	100	0.07	0.14	0.14	0.13	0.49
Khmelnytsky	< 37	98	0.16	0.33	0.35	0.26	1.1
	37–185	1.7	1.6	3.3	3.6	0.29	8.7
	185–555	0.003	6.7	13	15	0.15	35
Chercasy	< 37	84	0.30	0.59	0.59	0.27	1.7
	37–185	15	1.9	3.7	3.3	0.54	9.5
	185–555	0.37	7.3	15	15.8	0.12	38
Chernivtsi	< 37	92	0.36	0.72	0.74	0.35	2.2
	37–185	7.6	1.7	3.4	3.2	0.34	8.6
	185–555	0.31	5.9	12	13	0.25	31
Chernihiv	< 37	97	0.23	0.45	0.41	0.50	1.6
	37–185	3.2	1.8	3.6	2.3	2.2	9.8
	185–555	0.08	7.4	15	8.1	4.0	34
	555–1440	0.01	18	35	35	12	100
Kyiv city	< 37	100	0.48	0.96	0.28	0.13	1.9
Sevastopol city	< 37	100	0.2	0.40	0.34	0.14	1.1

Table 2.3.2

Distribution of population-weighted effective doses of total exposure of the inhabitants of Ukraine in general, depending on the density of fallout ^{137}Cs in soil

Fallout density of ^{137}Cs in soil kBq/m^2	% of population	Irradiation, mSv				
		external		internal		total
		1986	1987–2011	1986	1987–2011	1986–2011
< 37	96	0.20	0.41	0.33	0.29	1,2
37–185	3.7	1.8	3.7	2.1	3.3	11
185–555	0.29	7.0	14	3.5	3.4	28
555–1440	0.04	23	46	8.4	6.4	84
> 1440	0.005	77	154	34	47	313

Table 2.3.3

Population-weighted effective doses (mSv) of total whole body irradiation of the inhabitants of different regions of Ukraine

Region	Population-weighted effective doses (mSv) of total whole body irradiation according to time intervals (years)			
	1986	1987–1996	1997–2011	1986–2011
Vinnytsia	1.02	0.61	0.30	1.93
Volyn	0.72	2.34	0.81	3.86
Lugansk	0.84	0.60	0.31	1.75
Dnipropetrovsk	0.27	0.25	0.13	0.65
Donetsk	0.60	0.47	0.25	1.32
Zhytomyr	1.96	2.91	1.32	6.19
Transcarpathian	0.37	0.30	0.13	0.80
Zaporizhzhia	0.22	0.20	0.10	0.52
Ivano-Frankivsk	1.01	0.70	0.31	2.03
Kyiv	1.96	1.86	0.94	4.76
Kirovograd	0.61	0.38	0.19	1.18
AR Crimea	0.32	0.27	0.13	0.72
Lviv	0.25	0.22	0.11	0.58
Mykolaiv	0.35	0.26	0.13	0.74
Odesa	0.54	0.35	0.18	1.07
Poltava	0.48	0.38	0.17	1.04
Rivne	1.48	3.77	1.47	6.72
Sumy	0.67	0.53	0.25	1.45
Ternopil	0.63	0.54	0.23	1.40
Kharkiv	0.50	0.36	0.17	1.03
Kherson	0.22	0.19	0.09	0.49
Khmelnytsky	0.59	0.43	0.20	1.22
Chercasy	1.63	0.95	0.49	3.07
Chernivtsi	1.45	0.88	0.43	2.75
Chernihiv	0.77	0.79	0.34	1.90
Kyiv city	0.76	0.71	0.39	1.86
Sevastopol city	0.54	0.35	0.19	1.08
All Ukraine	0.71	0.69	0.32	1.72

Table 2.3.4

Relative (%) distribution of citizens of Ukraine living in rural areas with levels of fallout ^{137}Cs > 37 kBq × m^{-2} (in 1986), according to intervals of effective whole body dose accumulated at various times after the Chernobyl accident

Dose intervals (mSv)	Time intervals (years)			
	1986	1987–1996	1997–2011	1986–2011
	% of the whole population			
< 1	–	–	21	–
1–2	6.2	22	34	–
2–5	60	40	31	9.4
5–10	26	19	11	40
10–20	6.9	15	2.7	31
20–50	0.78	4.2	0.21	18
50–100	0.01	0.14	–	1.5
> 100	–	–	–	0.08

2.4. LARGE-SCALE AND LONG-TERM RADIOLOGICAL MONITORING OF THE POPULATION AFFECTED BY THE ACCIDENT AT CHORNOBYL NPP

The catastrophe at the Chernobyl Nuclear Power Plant (ChNPP) caused the contamination of 12 Ukrainian districts. 3 million persons living in these districts were under the radiological monitoring. The content of ^{137}Cs radionuclides in the body was measured by whole body counters (WBC) [1, 2]. Caesium is the most significant radionuclide, which forms the dose at currently post-accident stage.

Figure 2.4.1 presents a two-level currently operational monitoring system, which has been created in the NRCRM (National Research Centre for Radiation Medicine) dosimetry department. The first level has been designated for the current large-scale screening (with the help of the mobile and stationary WBC) of the population living in affected areas and patients included into the Radiation Registry of the NRCRM (liquidators and refugees who left the 30-km zone around the ChNPP, contaminated areas residents). The second one has been designed for an advanced monitoring of critical groups of population and workers using the expert WBC which combines the high sensitivity and the capability to detect a wide range of energy of photons emitted by radionuclides in the human body.

Figure 2.4.2 presents the stationary WBC «Super-Jemini» and «Screenner» installed in the polyclinics of the Radiation Registry. This equipment is used for patients of the Clinical and Epidemiological Registry (CER).

Figure 2.4.3 presents one of the mobile dosimetry laboratories mounted on the bus «UAZ» and «LAZ».

Table 2.4.1 demonstrates the main spectrometric and technical characteristics of facilities from NRCRM fleet of WBC for large-scale monitoring.

Since the ChNPP accident the NRCRM has performed more than 600 000 measurements.

In 1995 the necessity to fulfil the State program «The total dosimetric certification of settlements of Ukraine» led to the creation of a unified WBC network of Ukraine for individual monitoring of the internal exposure of members of the public (Figure 2.4.4). The network was working up to recent years.

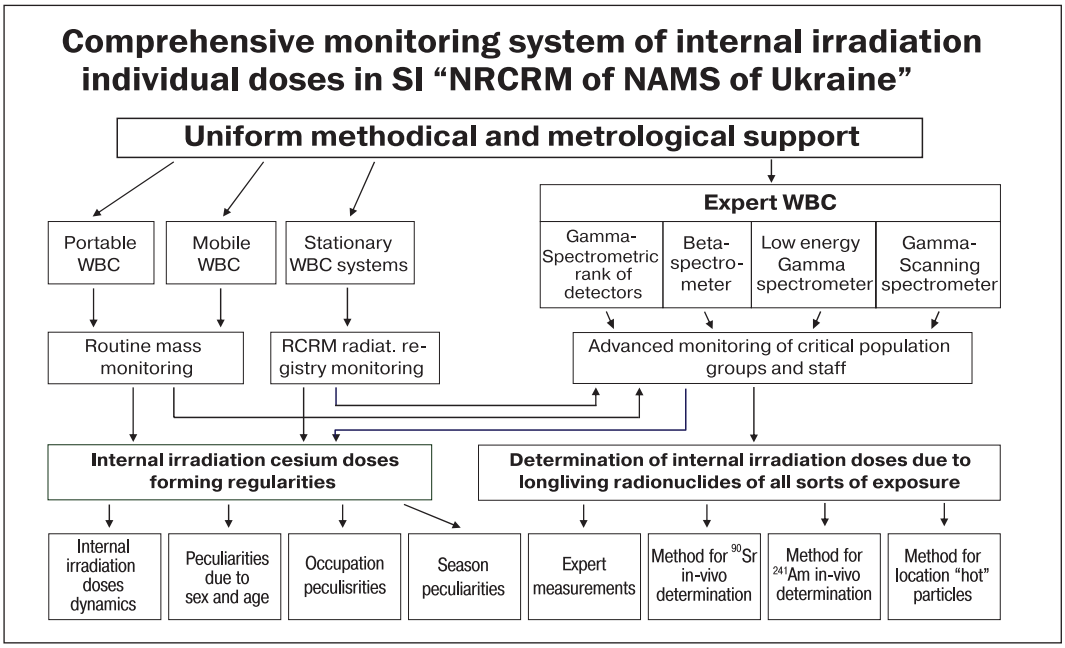


Figure 2.4.1. Comprehensive monitoring system of individual internal irradiation levels in the NRCRM



Figure 2.4.2. Stationary WBC «Screener» (left) and «Super-Jemini» (right) installed in the polyclinics of the Radiation Registry



Figure 2.4.3. External views of the mobile dosimetry lab mounted on the bus

The medical institutions in 12 districts of Ukraine affected by ChNPP accident were equipped with 57 facilities WBC «Screener-3M» both stationary type (40 units) and mobile type (17 units). The hardware was made in the Institute of Human Ecology (Kyiv), the metrological, methodical support and software was designed by NRCRM dosimetry department staff [3–5]. More than 100 operators were trained for working with facility «Screener - 3M» in the WBC laboratory during 1995–1999.

The facilities used in the program «The total dosimetric certification of settlements of Ukraine» were yearly undergone the comparison in the NRCRM with the help of the human

Table 2.4.1
WBC-system performance specification

Detector	Exposition, min.	Background, ppm	MDA*, кBq	Performance, persons per hour
Stationary (fixed) systems				
«Super-Jemini», France, 2 channels NaI(Tl) Ø76 x 76 mm	3 – 15	140	0.3	10 – 15
«Positronika», Holland, NaI(Tl) 210 x 140 x 70 mm	3 – 15	650	0.1	10 – 15
«Screener-3M» Ukraine, NaI(Tl) Ø150 x 100 mm	3 – 15	1180	0.4	10 – 15
Mobile radiation dosimetric laboratory (MRDL)				
MRDL based on I ch LAZ-42021 (bus) II ch NaI(Tl) Ø75x75 mm	1 – 3	600	0.2	20 – 30
MRDL based on UAZ (van) «Screener-3M» NaI(Tl) Ø100x100mm	1 – 3	1450	0.5	15 – 20

Note. * – This MDA fits with 3 minutes' exposition.

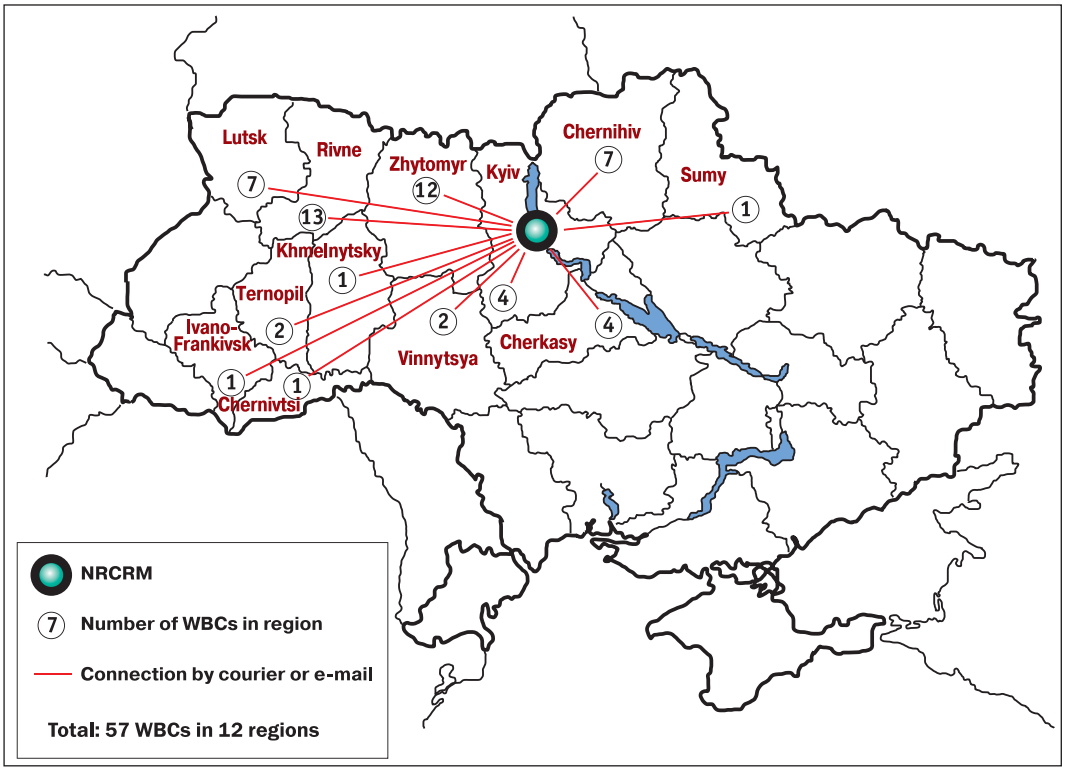


Figure 2.4.4. The unified WBC network of Ukraine for internal exposure monitoring

body phantoms filled up with dry radioactive component to ensure measurements standards (Figure 2.4.5). The phantoms have been designed and patented by NRCRM dosimetry department staff [6].



Figure 2.4.5. **The human body phantoms filled up with dry radioactive component to ensure the measurements standards**

The operators who served WBC facilities had been interviewed, consulted; sometimes they had been shortly trained to acquire skills for making WBC-measurements and for working with corresponding software Silbody5.02Net on the workplaces in the WBC laboratory of the NRCRM.

The unified WBC network resulted 50–100 thousand measurements yearly (Figure 2.4.6). Since 1995 to 2012 more than 700 thousands measurements were recorded in the database of the NRCRM and the Ministry of Emergency [7, 8].

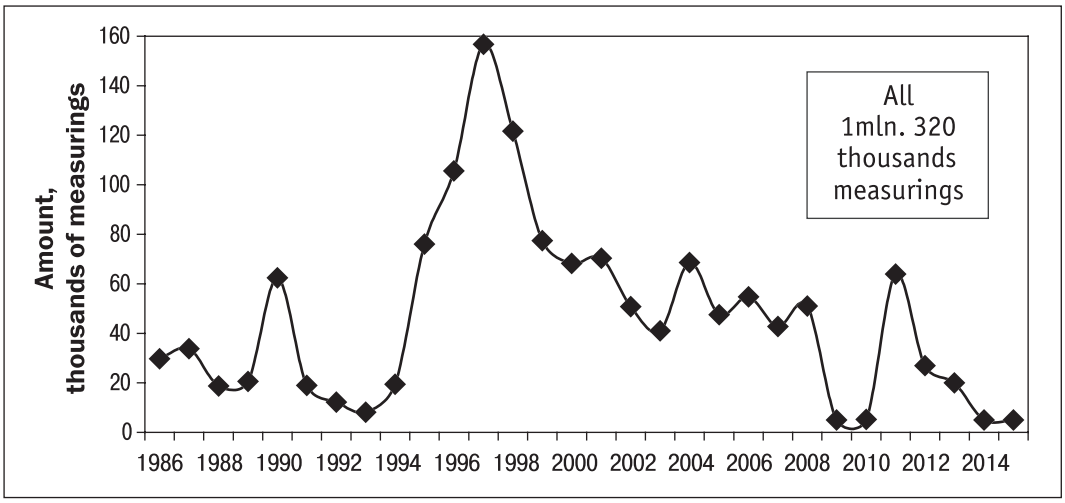


Figure 2.4.6. **Number of WBC-measurements performed in 1986–2015**

The internal exposure levels dynamics on contaminated areas were built on the basis of own measurements results and results collected from unified WBC network of Ukraine (Figure 2.4.7).

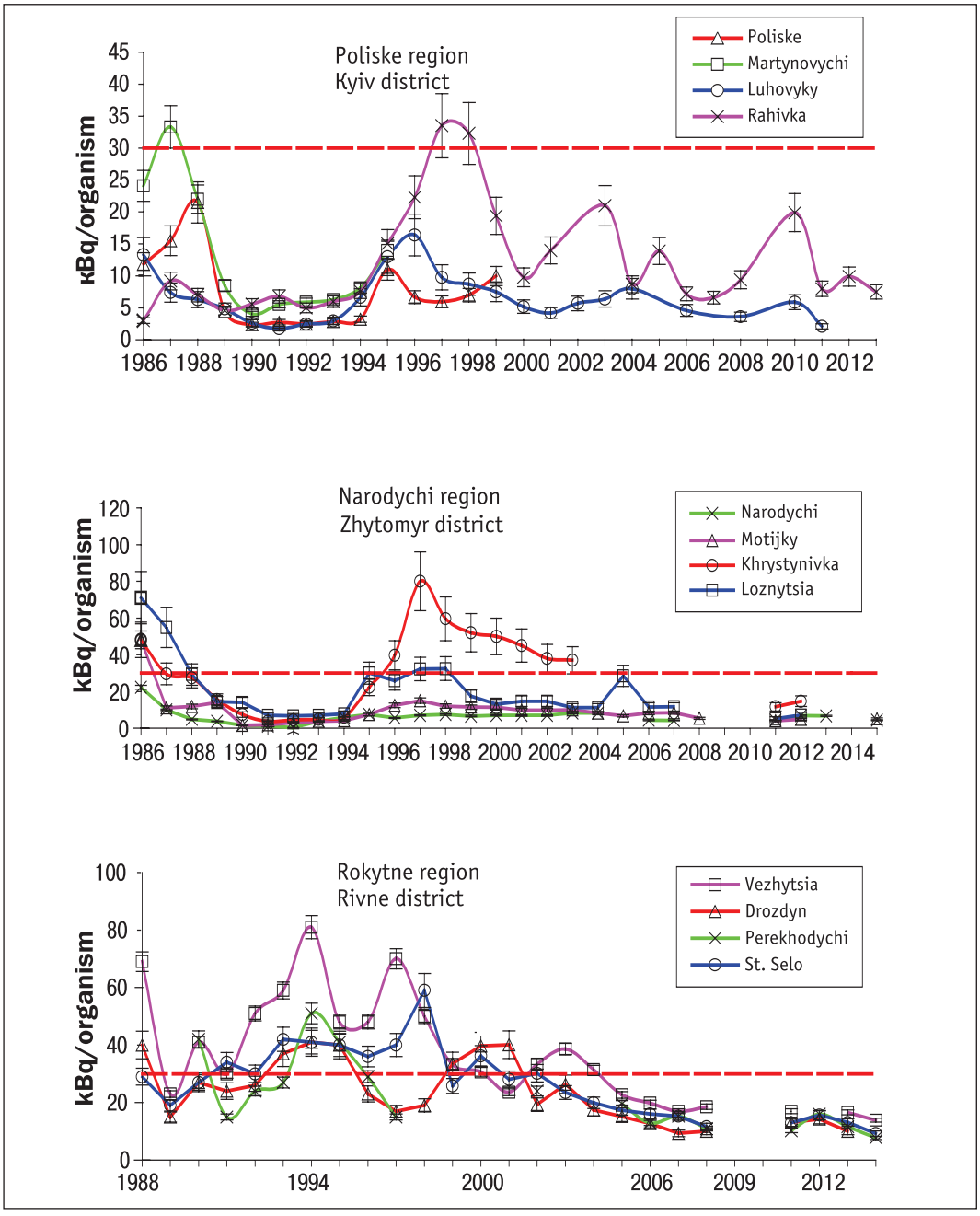


Figure 2.4.7. The trends of internal content of ^{137}Cs (medians) for the adults in the selected settlements in Ukraine within 1986–2008

The trends of doses are unstable. The doses varied within the range 0.01–2.0 mSv/year in the different years and obeyed the lognormal distribution law. It should be noticed the high irradiation levels which were hardly changing with time in Rivne district. They had been due to abnormally high transition of cesium to foodstuff.

It was revealed the effective countermeasures resulted the cesium content was systematically (35% yearly) decreasing up to 1992 practically in all the regions. Since 1992 the content grows 30–80% yearly and this fact can be explained by reducing countermeasures due to the economic recession in Ukraine which stimulated the population to consume the locally produced foodstuff. In some settlements in 1996–1999 the internal exposure doses were higher then the ones in the first years after the accident.

It was noticed last years the internal exposure doses from cesium were decreasing and became stable practically in all the regions.

It was marked out a number of settlements where internal irradiation levels were significantly higher then the assumed and estimated ones.

Figure 2.4.8 presents trends of internal exposure doses for the adults and the children from Rahivka village of Poliske region in Kyiv district. These residents' internal exposure doses in 1994–2001 were ones of the highest in Ukraine.

The caesium fall-out density in Motijky village of Narodychi region in Zhytomyr district was 6 Ci/km^2 (Figure 2.4.9).

As we can see in 1986 the internal exposure doses from caesium exceeded 3 mSv/year. The well-planned countermeasures significantly reduced the doses received before 1994. Since 1995 they grew that was true for whole Ukraine, but it should be noticed the considerable difference in doses for children and adults (1.2–5.8 times) which was observed still last years.

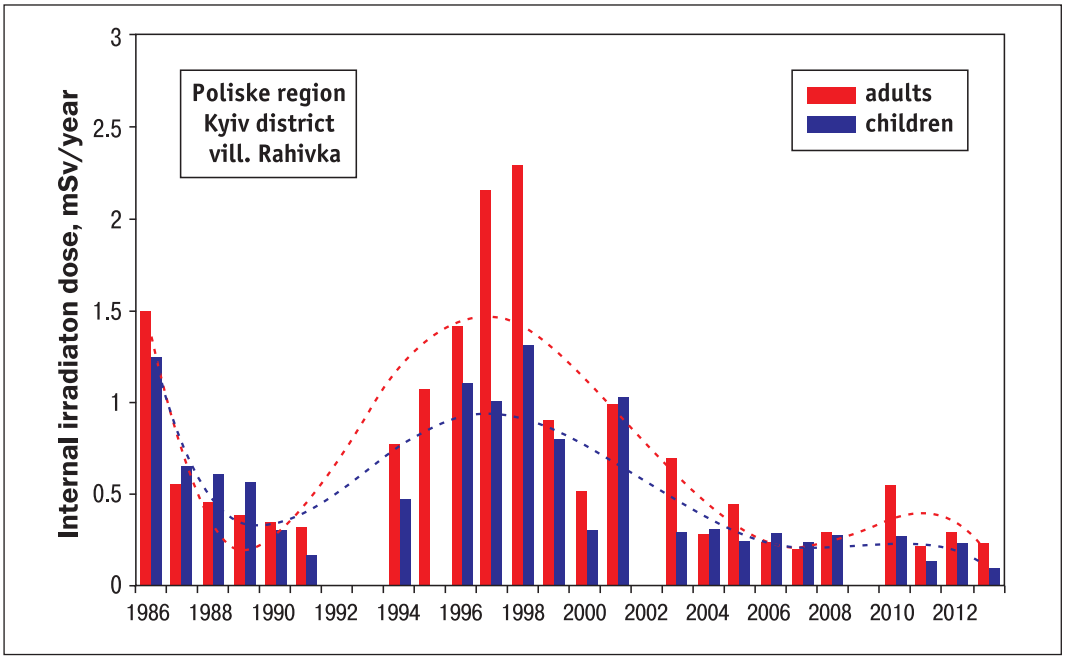


Figure 2.4.8. **The trends of internal exposure doses of inhabitants of Rahivka village of Poliske region in Kyiv district**

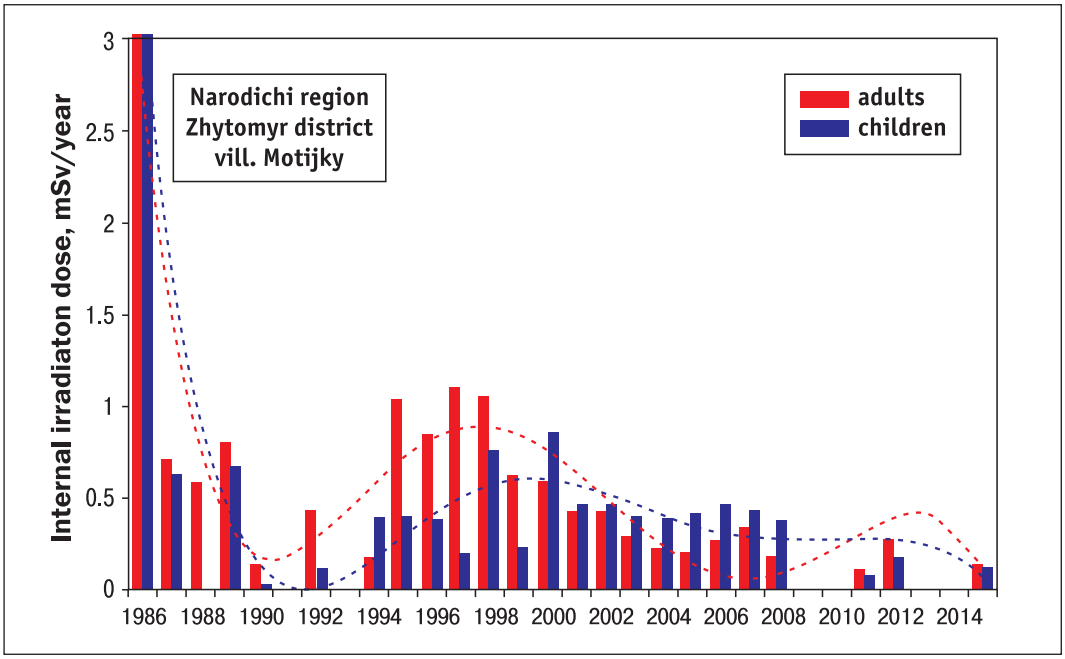


Figure 2.4.9. The trends of internal exposure doses of the inhabitants of Motijky village of Narodychi region in Zhytomyr district

According to the results of the State program «Dosimetric certification of settlements of Ukraine» which was carried out in 2011–2013, today there is about 200 settlements in Ukraine which need radiation monitoring, i. e. internal exposure doses in those settlements exceeds 0.5 mSv x year^{-1} [7, 8].

The carried out in 2010 researches in Kyiv district made possible to build the annual radionuclides accumulation dynamics. The internal content of ^{137}Cs for the inhabitants of settlements being under the monitoring from May to October grew 2–3 times.

The maximum of ^{137}Cs content that had been registered in Rahivka village was 150 kBq. This resulted the annual internal exposure dose of 4.5 mSv per year. In 2010 17.9% of inspected inhabitants of Rahivka village (3,2% of them were children) had internal exposure doses over 1 mSv x year^{-1}.

Figure 2.4.10 presents ^{137}Cs individual content statistical distribution for the adults from Rahivka village. The individual ^{137}Cs levels distribution for October is greatly drifted to the right in comparison with distribution for May. It is wider and it has long right «tail». It meant the ^{137}Cs content was increased for the most part of population of that village.

The advanced analysis of factors that form internal exposure doses for different cohorts in the inspected settlements led to the conclusion that the concentration of ^{137}Cs for the children is 1.2–2.8 times lower than for the adults. It is due to the care of diet for children. The concentration of ^{137}Cs for the males is 1.2–2.8 times higher than the one for the females. It is due to firstly males have the larger amount of muscles than females and secondly males are freer in a diet choice than females.

The content of ^{137}Cs and ^{90}Sr in main victuals (milk and potato samples) taken in settlements being under monitoring in Poliske region both in May and October is much lower than the one

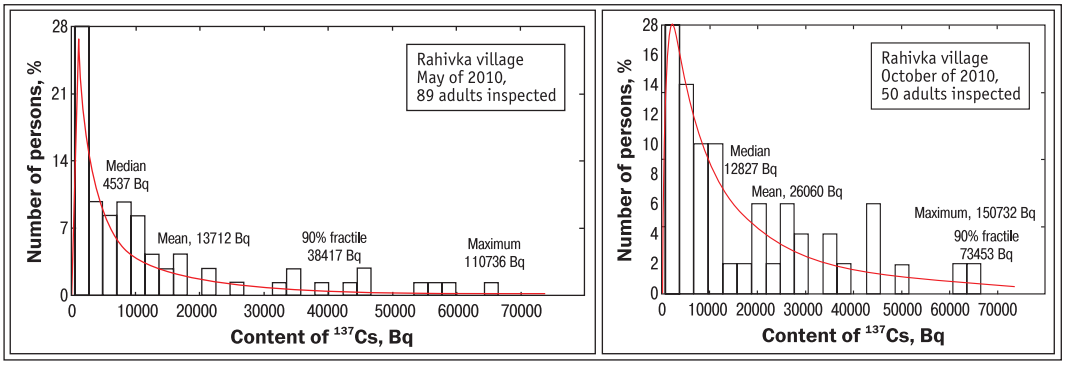


Figure 2.4.10. Statistical distributions of ^{137}Cs for the adults of Rahivka village in May and in October of 2010

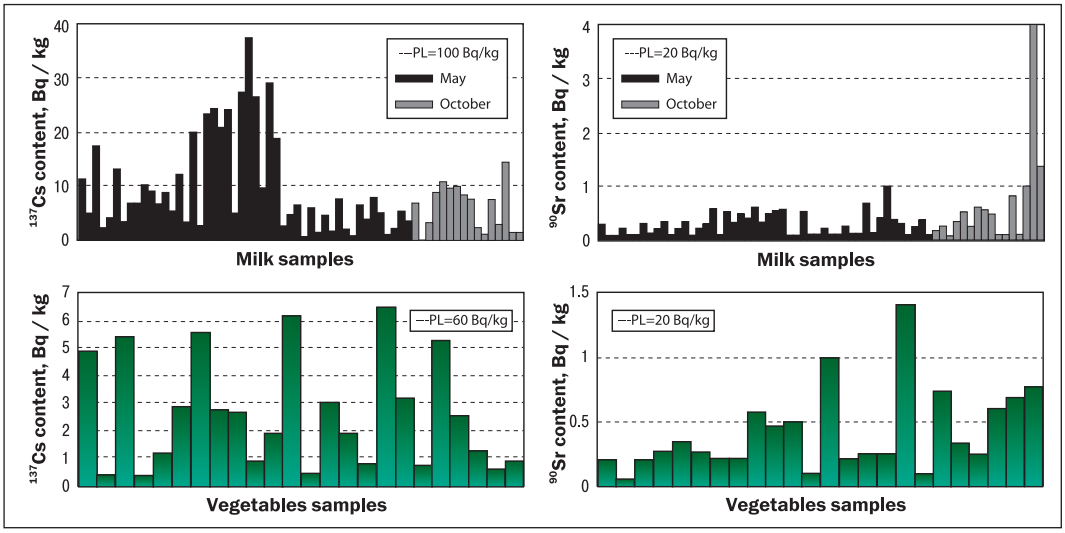


Figure 2.4.11. The ^{137}Cs and ^{90}Sr content in main food stuffs (milk and potatoes produced in the monitored farms from Polisky region of Kyiv district) in 2010

regulated by Hygiene Standards 6.6. 1. 1-130-2006. The contamination levels of main foodstuff (vegetables and milk) didn't have much effect on the internal exposure doses in those settlements (Figure2.4.11).

Food stuffs of forest origin are traditional for the residents. Their contamination levels are dozen times higher than permissible levels (PL) and even a small amount of their intake lead to high levels of internal exposure. Those facts took place in the settlements covered by the monitoring (Figure 2.4.12).

2010 was fruitful for foodstuffs of forest origin (mushrooms, berries). In 2010 the internal exposure doses for the adults increased twice in comparison to 2008. The doses for the children didn't considerably change because the child diet was of particular care. Figure 2.4.13 demonstrates the special regional peculiarities of the factors which form internal exposure doses. Thus, in the monitored settlements of Rivne district the internal exposure dose was induced by consumption of milk and foodstuffs of forest origin. The content of ^{137}Cs in the milk samples was 2–9 times

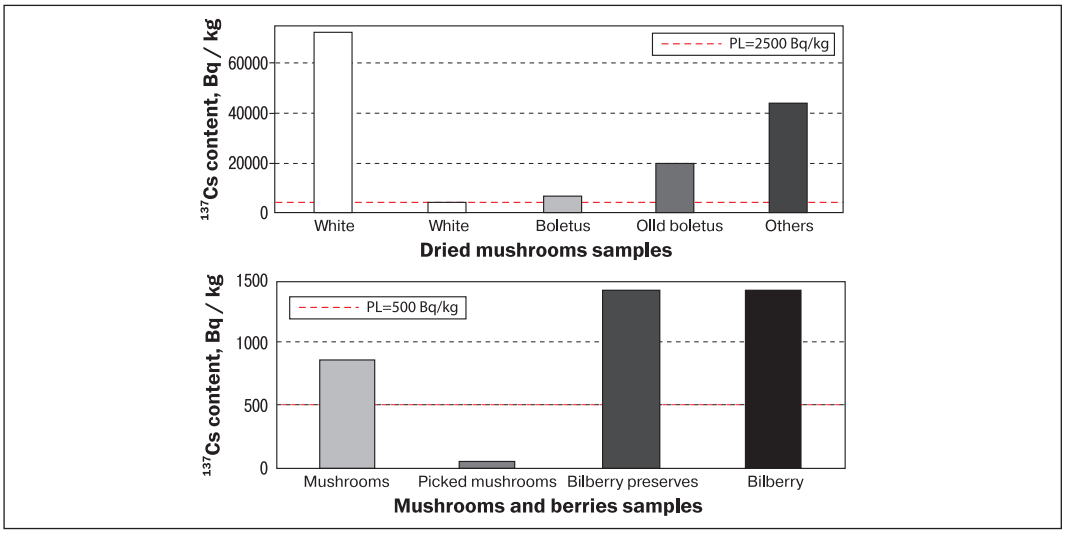


Figure 2.4.12. The ^{137}Cs content in the products of forest origin (mushrooms, berries) gathered by inhabitants from the monitored settlements of Polisky region of Kyiv district

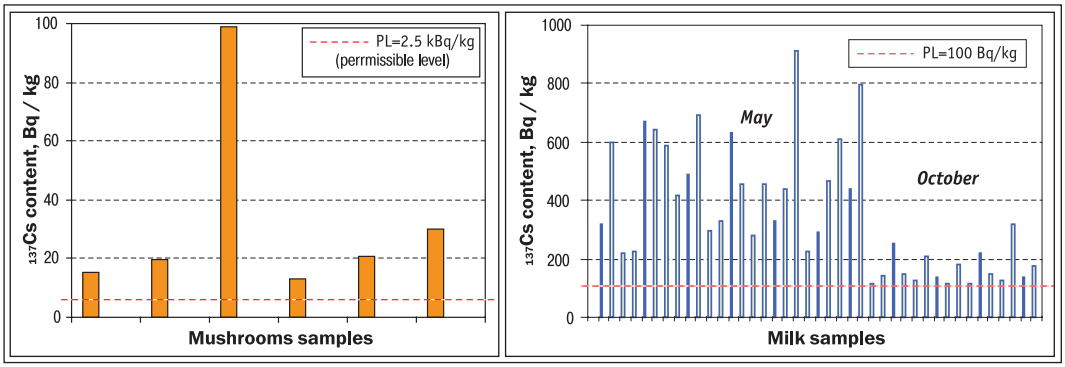


Figure 2.4.13. The ^{137}Cs content in locally produced food stuffs (milk and gathered natural products from neighborhood forests) in Rokytne region of Rivne district

higher than the permissible level prescribed by the Hygiene standards. The levels of contamination with cesium for mushrooms were dozen – hundred times higher than permissible level.

Thus, in order to minimize individual internal exposure levels of residents of contaminated areas it is extremely important to realize the following items:

➢ make the people to understand the factors which form internal exposure dose and its link with dietary habits;

➢ follow the radiation and hygiene safety rules on contaminated areas;

➢ the need for on-site inspection of radionuclides content and foodstuffs;

But the experience of the liquidation of accident at the CHNPP showed that the large-scale screening is not sufficient. The presence of nuclear and power complexes in Ukraine, activities of object «Shelter», the growing with time the relative contribution of strontium and transuranides in internal exposure dose, and others factors require facilities which extremely receptive to all kind of radiation. The created for expert tasks solving and for advanced moni-

toring the Expert Whole Body Counter (EWBC) in contrast to a WBC for large-scale monitoring is able to register alpha, beta, gamma radiation within a wide energy range. The Figure 2.4.14 demonstrates a general view of the EWBC.

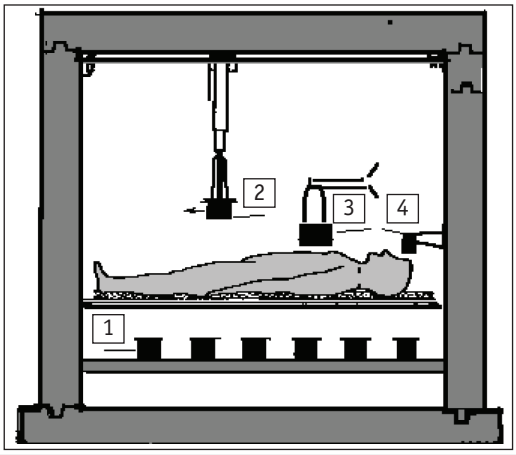


Figure 2.4.14. A general view of the EWBC

It includes the shielded chamber with low background and the system of detectors. The background inside the chamber is 100 times lower then outside. This fact made possible to reach the extremely high sensitivity – 20 Bq for ^{137}Cs and 100 Bq for ^{40}K per 10 minutes

The EWBC system includes the gamma-spectrometric row that is formed by 6 low background detection units, low energy gamma spectrometer presented by 2 double layers phoswich detectors, the measurement channel for beta-radiation. There is also a scanning system over spectrometric row which is able to locate radionuclides incorporated in a human body (Figure 2.4.15).

The main EWBC specifications are listed in Table 2.4.2.



1) the spectrometric row composed of 6 detectors NaI(Tl) 150 × 150 mm;

2) the scanner with detection unit NaI(Tl) 140 × 70 × 200 mm;

3) the low energy gamma radiation spectrometer of phoswich detectors NaI(Tl) CsI(Tl) 150 × 2 × 40 mm;

4) the beta detectors made of polysterene 52 × 2 mm.

Figure 2.4.15. The expert low-background WBC system in the shielding chamber

Table 2.4.2
The main EWBC specifications

Parameter	Value
Steel shield weight, tons	44.0
Size, m	2.4 x 2.2 x 2.0
Wall, floor, ceiling, thickness, mm	200.0
Multiplicity of weakening protection for ^{137}Cs, times	100
Reduction factor for energy range 0–2.0 MeV, times	83
Detectors:	
a) The row of 6 units, resolution at 662 keV (^{137}Cs), %	9.5
MDA (t = 10 min), Bq	20
b) The Scanner has a scintillation detector, resolution at 662 keV (^{137}Cs), %	6.5
MDA (t = 5 min), Bq	51
c) The lungs phoswiches, efficiency for ^{241}Am, %	4.6
MDA (point source, t = 30 min), Bq	25
d) The beta detector, resolution at E = 0.624 MeV, %	15.5
MDA for exposure at E = 2.25 MeV, t = 60 min, Bq	500
Number of channels for pulses analyzer	16384
Computer	IBM
Carrying capacity per 12 hours, persons	20–40
Measurement time of a person, min	5–60

The high registration sensitivity of the spectrometric row provides detection of minimal levels of accumulated sources of gamma-radiation with the high level of reliability. It allows studying of metabolism peculiarities and to determine comprehensive cases of intake at qualitatively new level. 3 thousands individuals passed through the expert WBC inspection.

Based on the EWBC researches revealed a number of individuals (clean-up workers, nuclear power plant staff (about 60 persons)) with «hot» particles (a fuel fraction in an insoluble form) and also with ^{60}Co content due to intake by inhalation.

The Figure 2.4.16 presents a usual normal case of caesium distribution. It was received through the scanning with the help of the spectrometric row and is due to the intake of ^{137}Cs by ingestion. Its curve looks like the distribution curve of ^{40}K. This is a typical form of curve for residents of contaminated areas which consume contaminated foodstuffs, i.e. for the case of intake by ingestion.

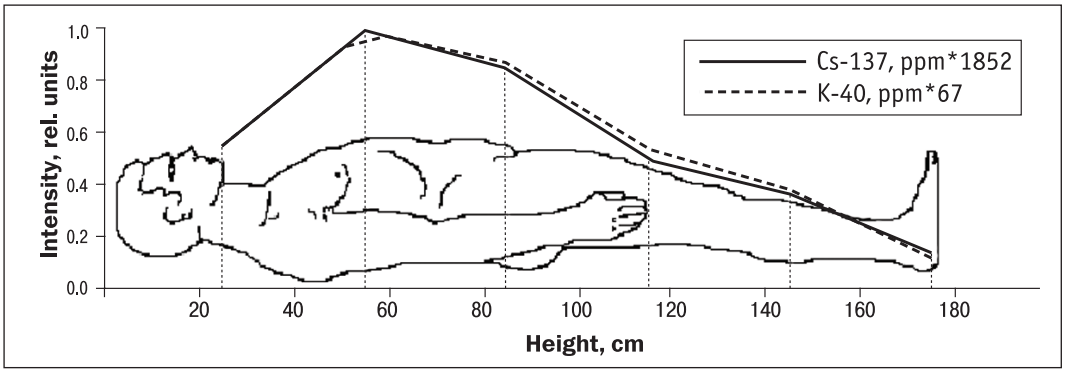


Figure 2.4.16. **Typical ^{137}Cs and ^{40}K distributions along a patient body with ^{137}Cs of «food» origin**

The Figure 2.4.17 presents the abnormal non-typical case of caesium distribution. Its curve form differs from the distribution form of ^{40}K in the described above case and was due to an intake by inhalation of a fuel fraction in insoluble form, called by «hot particle».

A «hot particle» can be located by the narrowly collimated mechanical scanner (Figure 2.4.18).

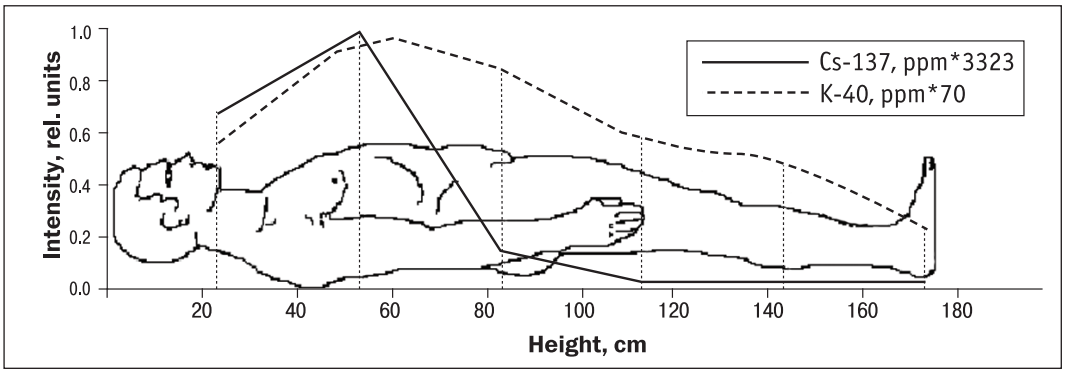


Figure 2.4.17. **The ^{137}Cs and ^{40}K distribution along the patient body with inhaled ^{137}Cs**

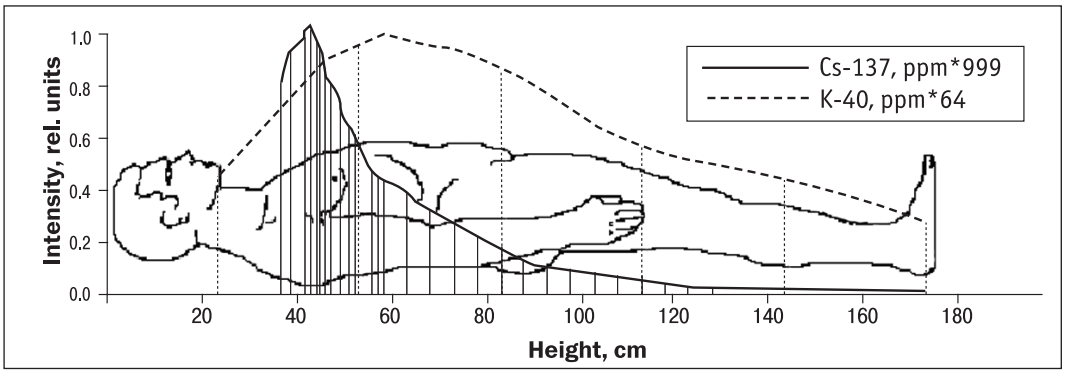


Figure 2.4.18. **The mechanical scanning over a patient (clean-up worker). He has got «hot particle» inside.**

Thus, the two-level system for monitoring of internal exposure equipped with the complex of whole body counters and with unified methodical and metrological support is able to implement both the large-scale screening of population (including the support of unified WBC network) and advanced research of critical groups of population, radiation registry patients, NPP staff.

More than 600 thousands of own measurements and 700 thousands measurements in unified network of WBC and Ministry of Emergency of Ukraine were performed.

The received information makes possible to correctly estimate the radiation situation countermeasures efficiency, and make decision to reduce harm to health and risks of long-term effects, to carry out epidemiological researches.

The work of EWBC made possible to solve expert tasks at a qualitatively new level in cases of complex incorporation of radionuclides mixture, of «hot particles». It also enabled to study metabolic processes and to provide the rest of WBC complex with the metrological support. It also allowed monitoring of critical groups of population and NPP staff.

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Chapter 3
ACUTE RADIATION SYNDROME

3.1. EVOLUTION OF HEALTH STATUS IN PERSONS WHO SURVIVED THE ACUTE RADIATION SICKNESS AS A RESULT OF ACCIDENT AT THE CHORNOBYL NPP (BASED ON 29-YEARS FOLLOW-UP)

Acute radiation sickness (ARS) belongs to deterministic radiation effects that attributed to cells death of mostly radiosensitive cellular systems of the human body, and it has well-defined clinical course. In dependence of radiation dose the severity of its symptoms changes from light, not threatened patient's life, to extremely severe, brings patient to death [1]. However, in the case of surviving after ARS, the risk for developing of stochastic consequences and late deterministic effects remains, which conditioned by dying out of functional cells in weakly proliferated tissues [2]. Therefor, medical supervision for victims of the Chornobyl accident and their health status monitoring are of great importance for the studying of radiation effects and effective treatment.

In a result of the Chornobyl NPP accident and subsequent radiation exposure ARS was diagnosed in 237 persons. However, the retrospective analysis of case histories, clinical and hematological symptoms [3] of ARS, performed in 1989, revealed the disease in only 134 patients, including 28 persons who died due to severe radiation damages. The 103 patients had no signs of radiation bone marrow syndrome, so we supposed that the exposed doses of ionizing radiation was less than 1 Gy. This group of patients (with non-confirmed ARS – ARS NC) constituted the cohort of priority follow up as well as ARS survivors.

At the beginning of October 1986 the 91 ARS survivors and 99 persons with ARS NC formed the group of patients under the follow-up. All of them were Ukraine citizens (Table 3.1.1.).

The groups of patients did not differ significantly by age at the moment of irradiation (table 1). On the contrary, average values of absorbed doses differed significantly ($p < 0.001$).

Before the Chornobyl accident gastrointestinal tract (GIT) diseases were diagnosed in 6 ARS grade 1–3 survivors and 9 patients of ARS NC, cardiovascular diseases – in 5 and 6 patients correspondingly. One patient of ARS grade 2 suffered from arachnoiditis in 1979 and a survivor of ARS grade 3 had brain contusion before his seventeenth, these patients were excluded from the analysis.

The absorbed radiation doses of external irradiation were determined in 1986 by analyses of chromosomal aberration in peripheral blood lymphocytes (number of dicentrics on 100 cells) [4].

Table 3.1.1
Age-gender and dosimetric characteristics of ARS survivors and ARS NC patients

Indices	ARS NC	ARS grade 1	ARS grade 2	ARS grade 3	ARS grade 1–3
Gender: f / m	10/89	2/36	1/40	0/12	3/88
Age at irradiation, years					
M ± SD[a]	35.9 ± 10.3	33.2 ± 8.2	38.5 ± 13.9	40.9 ± 16.5	36.6 ± 12.5
min – max	18.4–60.3	17.6–56.3	17.9–79.3	20.4–72.6	17.6–79.3
95% CI[b]	33.8–38.2	30.5–35.8	34.1–42.9	30.4–51.3	34.0–39.2
Absorbed radiation dose, Gy	n[c] = 15	n = 30	n = 37	n = 11	n = 78
M ± SD	0.4 ± 0.3	1.0 ± 0.6	2.4 ± 0.9	4.5 ± 1.4	2.2 ± 1.5
min – max	0.1–1.0	0.1–3.3	0.5–4.9	2.9–7.1	0.1–7.1
95% CI	0.2–0.5	0.8–1.3	2.1–2.7	3.6–5.5	1.9–2.5

Notes. [a] – mean ± standard deviation; [b] – confidence interval; [c] – number of patients for whom the adsorbed radiation dose was determined.

During entire post-accidental years every time when patients were admitted to NRCRM hospital such specialists as therapeutist, hematologist, cardiologist, gastroenterologist, pulmonologist, ophthalmologist, endocrinologist, neurologist, psychiatrist, dermatologist, urologist, and gynecologist examined them. Clinical-laboratory investigation included obligatory complex of blood and urine analyses, studying of cellular and humoral immunity, hormonal status, ultrasound investigation of abdominal and small pelvis organs, as well as thyroid gland and heart. Electrocardiography and electroencephalography recording, X-ray examination, endoscopy of GIT and bronchoscopy were also performed. The other special methods were used for patients' examination as well.

Though certain methods of patient's examination were improved during follow-up period, and exploited laboratory and diagnostic facilities were upgraded with new analogs the proceedings of patient's examination have the certificate of conformity to national and international medical standards. Statistical analysis was done based on SPSS 16 computer program.

3.1.1. The main reasons of patients' death during the post-accidental period

During post-accidental period 51 patients died. All lethal cases could be divided into four classes in dependence on the main reason of death: (1) cardiovascular diseases, (2) oncological and oncohematological pathology, (3) somatic and neurological diseases, as well as infections, and (4) trauma and accidents (Table 3.1.2).

As it is shown on the table 3.1.2, cardiovascular and oncological diseases brought 37 patients (72.5 %) to fatal outcome. More detail characteristics of these persons and every death case are submitted below. However, the number of patients who died due to oncological pathology is

Table 3.1.2
The main reasons of death during post-accidental period amongst ARS survivors and ARS NC patients

Reasons of death	ARS NC	ARS grade 1	ARS grade 2	ARS grade 3	Total
Cardiovascular diseases	8	3	5	3	19
Malignant blood diseases and solid tumors	10	3	3	2	18
Somatic and neurological diseases, infections	2	1	3	1	7
Traumas, accidents	2	2	2	1	7
Total	**22**	**9**	**13**	**7**	**51**

only a little less than from cardiovascular diseases. Somatic and neurological diseases and infections sat the third. Patients who survived ARS grade 2 died from liver cirrhosis (2 cases) and lung gangrene (1 case), one ARS NC patient died due to encephalitis finished with bulbar paralysis, for the three patients of ARS NC, 1st and 3rd grade of severity the reason of death was pulmonary tuberculosis. From traumas and accidents died 7 patients (13.7%).

3.1.2. Blood malignant diseases and solid tumors

The first case of malignant hypoplasia of hemopoiesis was revealed in August 1986 in a patient who has been working in the ChNPP zone in May and July. Hematological status is characterized by essential leukopenia and slight anemia. The debut of oncohematological pathology was mistakably assessed as ARS grade 1. However, further disease development eliminated any doubts concerning hematopoietic tissue pathology that was proved by bone marrow analysis.

During following years myelodysplastic syndrome (MDS) developed in two patients of ARS grade 3 and one who survived ARS grade 1. All cases brought these three patients to death (Table 3.1.3). One more ARS grade 2 survivor felt ill with myelomonoblastic leukemia in 11.8 years after irradiation and died in spite of treatment. In 2007 ARS NC patient developed polycythemia vera and died of thrombosis. The last malignant blood disease – chronic myeloblastic leukemia (CML) was diagnosed in ARS grade 1 survivor in 2012 and led to the lethal outcome two years later.

Table 3.1.3
Cases of malignant blood diseases in ARS survivors and persons of ARS NC group

#	Diagnosis	ICD-10 code	ARS grade	Firstly diagnosed	Age (years) at		Date of death
					diagnosis	death	
1	Hypoplasia of hematopoiesis	C96.9	NC	1986	48.6	49.3	1987
2	MDS	D46.1	1	1996	45.0	50.7	2002
3	MDS	D46.9	3	1993	52.1	52.2	1993
4	MDS	D46.4	3	1995	64.6	64.7	1995
5	Acute myelomonoblastic leukemia	C92.5	2	1998	59.9	60.7	1998
6	Polycythemia vera	D45	NC	2007	59.4	63.2	2011
7	CML	C92.1	1	2012	61.7	64.3	2014

All patients with oncohematological pathology were male of mean age 55.9 ± 7.3 years at the moment of radiation exposure and 57.9 ± 6.9 years old at the moment of death. The latent period since irradiation and to the first signs of disease was 14.2 ± 7.4 years. Today the relative number of persons, who felt ill and died from malignant blood diseases, is 3.7% in the group of 190 patients of primary follow-up and 5.5% – in ARS survivors.

The first case of malignant tumor was revealed in ARS NC survivor in 1992 (Table 3.1.4). At the end of 1993 he died. An autopsy revealed sarcoma of soft tissues of the hip (C49.2).

It is necessary to note that all following cases of solid tumors developed without any clinical symptoms and were revealed by chance during routine examination or followed by minimum non-specific compliances (so called «syndrome of minor signs») and revealed due to physicians' oncological alarm.

Totally during 23 years after the first diagnosis of sarcoma 18 cancers of different localization were revealed. Among them 4 cases of colon cancer (C18.7, C18.9), 3 cases of stomach (C16.9), 2 cases – thyroid gland cancer (C73), 2 cases of skin cancer (D04.4, D04.7), for one cases of

throat (C32.8), lung (D02.2), kidney (C64), urinary blood (C67.8), maxillary sinus (C31.0), and prostate (C61) cancers, and one case of neurinoma of lower jaw undergone malignant transformation (C72.5). In a patient of ARS NC of stomach cancer followed leiomyosarcoma of the left shin, which was surgically treated, fractionated radiation expose for the shin up to 52 Gy was applied.

The age at the time of firstly diagnosed oncological pathology and patients' age at the moment of death was 57.9 ± 13.0 and 62.1 ± 12.7 years old, correspondingly. The relative number of patients with oncological pathology was 8.8. So, in the group of ARS survivors, malignant tumors were revealed in 7.7% of patients, and in ARS NC group in 11.1% of persons.

3.1.3. Changes of eye

During post-accidental period the most common pathological changes of eye were radiation (H28.2) and involutional (H25) cataracts. Other changes, such as chronic conjunctivitis (H10.4) and different retinopathies (H35.8) were revealed in 63–82% patients.

Radiation (posterior subcapsular) cataract was diagnosed in 24 patients and involutional cataract in 118 ones (Table 3.1.5). In order to discriminate these types of cataracts we use criterion described by Choshi [5]. Combination of radiation and involutional cataracts was revealed in 12 ARS survivors and a patient of ARS NC.

Radiation cataracts significantly depended on ARS grade whereas a frequency of involutional lens opacification did not differ in patients of ARS NC and ARS grade 1. The lesser frequency of involutional cataracts in ARS grade 2–3 survivors in comparison with other patients could be explained by the fact of more radiation cataract cases. In all groups the radiation cataract latent period was shorter than involutional ones.

Table 3.1.4
Cases of oncological diaseases in ARS survivors and persons of ARS NC group

#	Diagnosis	ARS grade	Firstly diagnosed	Age (years) at		Outcome
				diagnosis	death	
1	Sarcoma of hip soft tissues	NC	1992	34.1	34.8	Died on 1993
2	Cancer of colon	1	1997	54.5		Operated on June 1997
3	Leiomyosarcoma of shin	NC	1998	72.5	75.9	Died on 2001
	Cancer of colon		1999	73.4		
4	Cancer of throat	NC	2000	59.3	59.9	Died on February 2001
5	Cancer of thyroid gland	2	2000	37.6		Operated on 2000
6	Cancer of thyroid gland	2	2000	42.9		Operated on January 2001
7	Cancer of kidney	NC	2000	44.4		Operated on January 2001
8	Cancer of colon	NC	2001	63.6	67.5	Died on October 2005
9	Cancer of prostate	NC	2001	71.7	73.3	Died on 2003
10	Cancer of lung	NC	2001	46.1		Operated on June 2003
11	Neurinoma of lower jaw	2	2003	52.7	53.9	Died on December 2004
12	Cancer of stomach	NC	2004	77.5	78.1	Died on January 2005
13	Cancer of stomach	NC	2004	65.7	65.9	Died on September 2004
14	Basal cell carcinoma of head	1	2006	51.9		Irradiation
15	Cancer of urinary bladder	2	2008	66.8	66.9	Died on August 2008
16	Cancer of maxillary sinus	1	2009	51.0	52.2	Died on April 2010
17	Cancer of colon	NC	2010	52.7	55.2	Died on 2013
18	Basal cell carcinoma of hip	3	2011	68.4		Operated on 2011
19	Cancer of stomach	NC	2013	69.1		Operated on 2014

Table 3.1.5
Frequency of radiation and involutional cataract in ARS grade 1–3 and ARS NC survivors

ARS		Radiation (abs. /%)	Involutional (abs. /%)
NC (na = 74)		3 / 4.1	61 / 82.4
Grade 1 (n = 34)		3 / 8.8	28 / 82.4
Grade 2 (n = 35)		8 / 22.9	24 / 68.6
Grade 3 (n = 11)		10 / 90.9	5 / 45.5
χ^2-test	F	66.7	8.18
	p	< 0.001	> 0.05

Notes. [a] – the total number of examined patients.

Survivors of ARS grade 3 demonstrated the minimal latent period for radiation cataracts – 5.1 ± 3.4 years that significantly differed ($p < 0.01$) from the same indices in ARS grade 2 (9.1 ± 3.3) and grade 1 (9.9 ± 5.2) survivors and ARS NC patients (7.2 ± 4.1 years). During first five years of follow-up radiation cataract was diagnosed in 10 patients whereas the rest 14 cataracts developed between 5 and 15 years after the irradiation. During the last 15 years no cases of lens opacity induced by radiation were revealed.

Analysis of survival function according to Kaplan-Meier showed that cumulative proportion survival of entire eye diseases did not differ in ARS survivors and ARS NC patients (log-rank test: χ^2=0.175, p=0.675) (Figure 3.1.1. A). The median of survival time for ARS grade 1–3 was equal 13 ± 0.8 years (hereinafter, where Kaplan-Meier method is described, mean or median ± standard error) whereas for ARS NC – 13±0.7 years.

3.1.4. Other somatic diseases

During the first 5 years after the accident, the increase of different somatic diseases in ARS convalescents as well as in ARS NC patients was found, first of all of the digestive, nervous and circulatory systems diseases. The survival median (the time to the exactly half of patients fill sick) for these systems was for 2, 3 and 5–6 years after exposure (Table 3.1.6).

In 29 years after radiation exposure cumulative incidence of cardiovascular diseases was 87% in ARS 1–3 grade survivors and 89.9% in ARS NC patients. Hypertensive heart disease (HHD, I10, I11.0, I11.9) and ischemic heart disease (IHD, I20, I25) with heart failure (I50) had been diagnosed more often. Atrial fibrillation (I48), atherosclerosis obliterance (I70.2) and veins varicose (I83.9) of lower extremities were not so common.

Table 3.1.6
Indices of survival function for different organ systems in ARS NC and ARS 1–3 grades

Organ systems	Log-rank test		Median for survival time ± standard error, years		Cumulative survival in 29 years after radiation exposure, %	
	χ^2	*p*	ARS NC	ARS 1–3 grades	ARS NC	ARS 1–3 grades
Cardiovascular	1.272	0.259	5 ± 0.6	6 ± 0.8	10.2	13.0
Endocrine	11.643	0.001	17 ± 0.3	13 ± 1.1	11.1	12.3
Digestive	0.099	0.753	2 ± 0.2	2 ± 0.1	1.7	0
Nervous	0.011	0.915	3 ± 0.3	3 ± 0.2	0	0
Respiratory	0.317	0.574	16 ± 0.8	15 ± 1.3	28.7	8.1

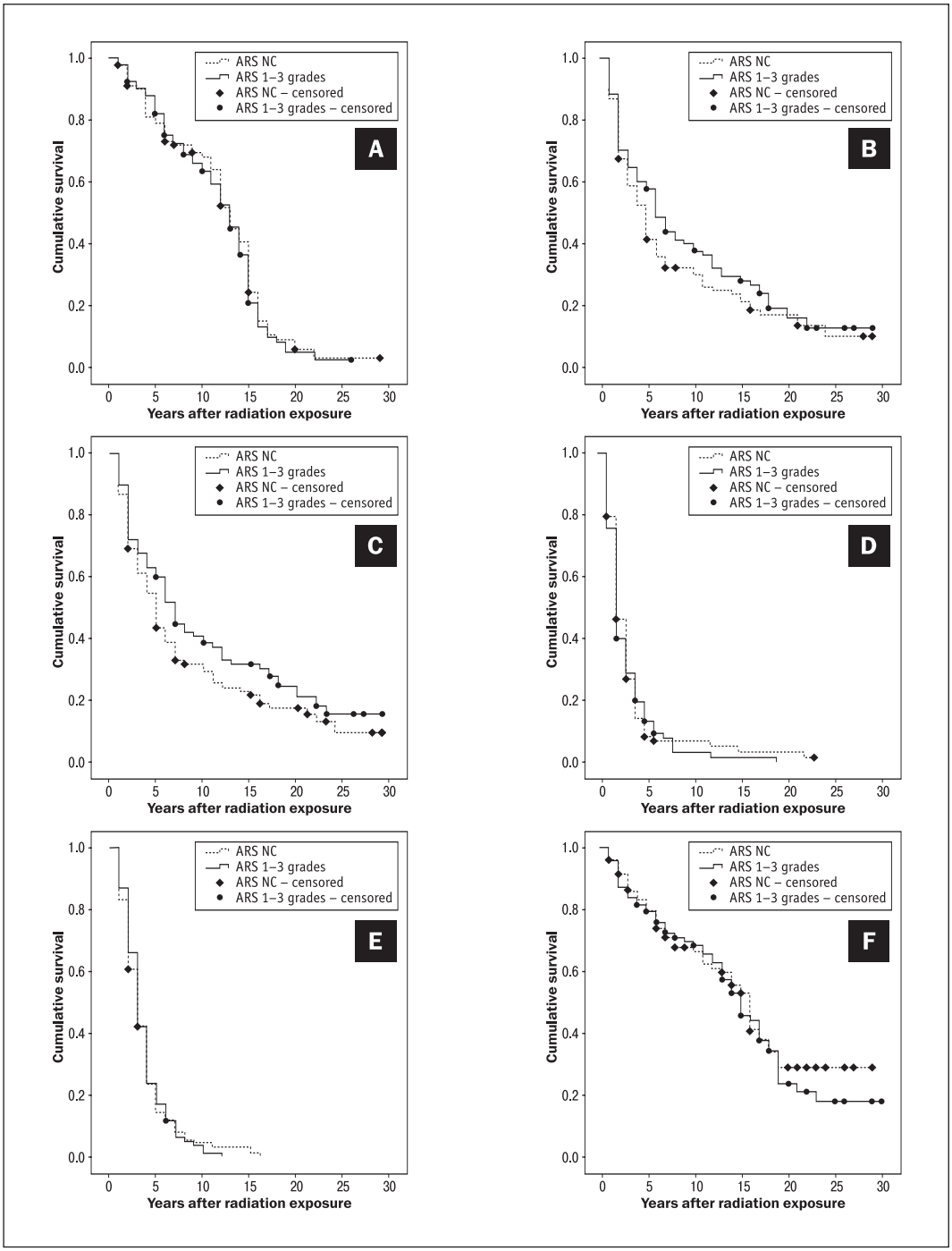


Figure 3.1.1. **The evolution of cumulative proportion survival for ARS grade 1–3 and ARS NC patients suffered from diseases of eye (A), cardiovascular (B), endocrine (C), digestive (D), nervous (E) and respiratory (F) systems before the till the end of third post-accidental decade.**

The value of median survival time for HHD in ARS 1-3 grades convalescents was 7 ± 0.7 and 5 ± 0.6 years in ARS NC group. At the end of 29 years follow-up period cumulative survival for HHD was 13 and 10.2% in ARS 1–3 grade and ARS NC patients whereas the cumulative proportion of diseased were 84.1 and 90.2% correspondingly. The same values for IHD were 27 ± 2 and 24 ± 2 years, 39.7 and 35.9%, and 60.3 and 64.1% correspondingly. The values difference between ARS 1–3 grades and ARS NC was insignificant.

During post-accidental period cardiovascular pathology led to death 19 patients. Sudden cardiac death (I46.1) happened in 7 patients of ARS 1–3 grades and 3 patients of ARS NC, chronic heart failure (I50.0, I50.1) was the reason of death in 3 and 2 patients correspondingly. Three ARS NC patients died from stroke (I64) and one ARS 2 grade convalescent – from acute myocardial infarction (I20.0). No significant difference in death reasons between ARS 1–3 grades and ARS NC groups was found.

During entire post-accidental period the cumulative survival for endocrine system pathology was significantly less in ARS NC group in compare with ARS 1–3 grades survivors. Most likely, this difference was due to a large number of diabetes mellitus cases (E11) in the ARS NC group (20 vs 11 patients, $p = 0.061$).

Goiter was the most often endocrine pathology in 37 persons (40.7%) of ARS 1–3 grades group and 40 (42.6%) – of ARS NC group. It subdivided in diffuse (E04.0), nodular or multinodular (E04.1, E04.2) and mixed one without hypothyroidism symptoms (Figure 3.1.2). Chronic thyroiditis (E06.5, E06.9), including autoimmune one (E06.3), was revealed in 16 patients (17.6%) of ARS 1–3 grades and 17 persons (17.2%) of ARS NC. Thyroid gland cysts were diagnosed in 9 (9.9%) and 4 (4%) patients correspondingly.

During the period of observation the cumulative incidence of endocrine diseases was 87.7% in ARS convalescents and 82.9% in ARS NC patients.

The dominative pathology of digestive system were chronic non-specific inflammatory disease of the gastrointestinal tract and gall bladder: gastritis (K29.3, K29.4, K29.5, K29.7), duodenitis (K29.8, K29.9), cholecystitis (K81.1) and cholangitis (K83.0). Their higher level of detection in the early post-emergency period could be explained by examination that was more thorough during hospitalisation with the use of endoscopy and ultrasound tests. By the end of the third decade after the Chornobyl accident abovementioned diseases were revealed in everyone ARS survivors and in 98.3% ARS NC patients. Chronic hepatitis (K73.0, K73.9) rank second by their frequency rate. Cumulated proportion of patients with chronic hepatitis was 77% in ARS 1–3 grade group and 74% in ARS NC. Gastric ulcer (K25.3, K25.7) and duodenal ulcer (K26.3, K26.7) met rarely as acute and chronic ulcers or as scar of the organ wall. Their cumulative incidence after 29 years was 44% among ARS convalescents and 42% in the ARS NC group.

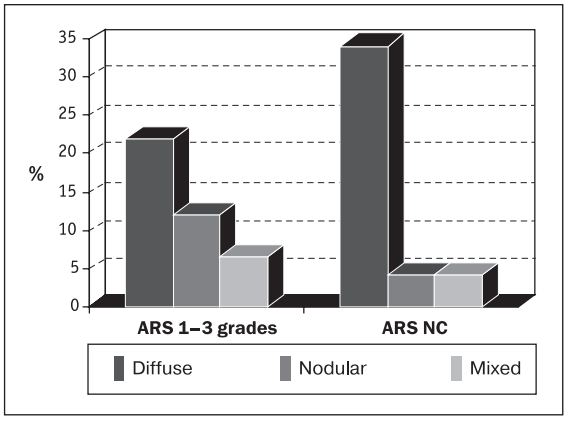


Figure 3.1.2. Proportion of different goiters in ARS 1–3 grades and ARS NC patients.

Already in the first months-years after radiation the most common disease of nervous system was vegetovascular dystonia (VVD, F45.3): median survival was 4 ± 0.3 years in ARS 1–3 grades and 4 ± 0.4 for ARS NC group. Altogether, this diagnosis was set for 87% ARS convalescents

and 68.7% persons of ARS NC. Almost everyone patient in both groups had transient phenomena of VVD, which gradually has been disappearing during 10–15 years. However, during this period there was an increase of another pathology of nervous system, which was called «organic»: cerebral atherosclerosis (I67.2) and discirculatory encephalopathy (I67.9). If in 5 ± 0.3 years after irradiation the disease was diagnosed in 25% patients of both groups, then in 10 ± 5 and 11 ± 0.7 years – in 75% patients of ARS 1–3 grades and ARS NC. Over 22 years after the accident, the cumulative incidence of cerebrovascular diseases was 98.7% in ARS 1–3 grades and 100% in ARS NC group.

The main respiratory system diseases observed in the patients were chronic bronchitis (J41.0, J42), the cumulative incidence of which amounted to 82.1% of ARS 1–3 grades patients and 71.4% ones of ARS NC. Half of the cases were chronic obstructive bronchitis (J44). All patients with bronchitis had signs of pneumofibrosis (J84.1) and lung emphysema (J43.9). During entire follow-up period bronchial asthma (J45) was diagnosed in one patient of ARS 3 grade and three patients of ARS NC.

* * *

There is an evidence of increased cancer incidence in post-emergency period in survivors [6–8] and experimental animals inhabited in «Chornobyl» zone. [9]. For others, no significant increase in cancers and, accordingly, mortality from malignant disease in exposed individuals due to Chornobyl accident compared with unexposed population was seen [10–12].

Such conflicting research results are likely because the doses of irradiation for cleanup staff of the Chornobyl accident were higher.

It is considered that a dose 0.1 Gy and above can cause a statistically significant risk of cancer incidence [13–15], and above 0.4 Gy – increase of leukemia by 100% between 1988 and 1998 [16]. Since people who suffered from ARS had radiation doses that exceeded the definite boundary, cancer and malignant blood diseases would have been revealed very likely.

Our studies have shown that malignant blood diseases in ARS convalescents preceded the appearance of solid tumors and had no wide variety of nosological forms (3 cases of MDS, acute and chronic leukemia and hypoplasia of hematopoiesis), while in victims of the atomic bombing in Hiroshima and Nagasaki there was found various forms of acute and chronic leukemia, lymphoma (Hodgkin and non-Hodgkin) and multiple myeloma from 1950 to 1987 [17, 18]. The peak of leukemia fell on 5–8 years after exposure [17].

Based on the analysis of leukemia in «hibakusha» and those that were irradiated with a health care purpose, Hall [19] found that the latency period for leukemia was 5 years. Other authors believe it longer – 7–10 years [20]. Our data is more in line with the latest opinion. Hypoplasia of hematopoiesis in patient with ARS NC arose in a very short time after the first exposure to ionizing radiation to consider that it was initiated by irradiation. Probably, he was sick before, and the first clinical manifestation fell on the period of his work in the Chornobyl zone.

After the Chornobyl accident among the 110,645 emergency workers (46% of all cleanup staff in Ukraine) MDS was diagnosed in 6 people, including 3 cases in ARS convalescents [21]. According to Sekine [22], among 93,700 victims of the atomic bombing 13 cases of MDS has developed during 50 years of follow-up that is much larger in absolute and relative meaning than in Chornobyl victims. However, health-monitoring period in our case is less than for the residents of Hiroshima and Nagasaki.

Accordingly to Romanenko and al. [23] cancers that arise in the emergency workers in the first years after the accident could be radiation induced promotion of existing tumors but not their induction. The increasing onset of radiation-induced cancer can be observed in 15-25 years period after exposure. The first case of cancer in ARS convalescents was diagnosed in 11

years after irradiation. This case, as well as other cases of malignant tumors, confirmed by Kato et al. [24] that affirmed that the minimum latency period for solid tumors is 10 years or more and could be followed by gradually increasing of their frequency rate.

Cancer referred to stochastic effects of radiation when higher absorbed dose increases the probability of their onset [2]. Based on these data, it should expect a higher yield of tumors in patients who had survived ARS in comparison with persons irradiated at doses less than 1 Gy. However, in our study, cancer met frequently (9.1%) in patients of ARS NC group than in ARS convalescents (7.7%), although these differences were statistically insignificant. There were not any differences between the frequency rate of cancer between patients of ARS 1, 2 and 3 grade.

Among ARS convalescents and patients of ARS NC group cancers of colon and stomach developed more frequently. Based on data observed in persons survived A-bombing during 1958–1987 these tumors were identified as having significant excess risk of onset and death [25]. Lung cancer and urinary bladder cancer also attributed to such class. The reliable increase of skin cancer cases (not for melanoma) was observed, but mortality from them did not exceed normal levels. Cancers of the larynx, prostate and kidney in «hibakusha» were not associated with radiation exposure.

No one research of A-bombing victims in Hiroshima and Nagasaki described increase of sarcoma appearance after radiation exposure. In our study two sarcoma cases were diagnosed in followed up group of patients, but this number is not enough for statistical analysis.

The early publications mentioned [26, 27] that the irradiation dose for radiation cataract development should to be at least 4 Sv. However, other researchers consider that the minimal cataractogenous dose of γ-radiation is much lower [28, 29]. In our study, posterior subcapsular cataracts were diagnosed in individuals with doses of external total body irradiation below 1 Gy. We believe that radiation cataract did not fit into the classic features of deterministic effects, but more consistent of the stochastic effects of radiation. If we accept this concept as a basis, it becomes clear that exposure having no threshold can lead to cataracts, even in patients with a very low dose. Thus, Fedirko has found signs of radiation cataracts in cleanup workers with radiation dose 0.02 Gy [29], but considered it marginal for this type of cataract, based on the classical concepts of determinism effect.

Puchkovskaya et al. [30] consider that under ordinary conditions a senile cataract is begun to develop after 45 years and in persons older 65 years its frequency increased from 7 to 60%. In our studies the relative number of patients with cataracts was essentially higher that aforementioned authors reported and 46.4% of patients were in their young and mature age. This fact let us to suppose a predominant contribution of radiation in involutional cataract forming. It was reported earlier before the Chornobyl catastrophe about frequent senile lens changes in employers who have been working under conditions of fixed irradiation that is did not go out of limits for acceptable doses [31, 32]. It is believed that radiation exposure can cause premature aging [33], which also finds reflection on eye lenses [34].

The incidence of nervous and somatic disease in patients who have undergone radiation exposure due to Chornobyl accident, was the same as for the rest of Ukrainian population accordingly to the age groups [35].

Cardiac muscle is a rather radioresistant tissue and its destruction occurs only at lethal doses of radiation for humans [36–38], but the vascular endothelium demonstrates high sensitivity to radiation [2, 39, 40]. In experimental animals death of endothelial cells occurs early after an external X-ray irradiation at a dose of 0.5 Gy and stored for a long period of observation [41]. Persistent homeostasis changes that lead to the formation of endothelial dysfunction, are called «oxidative stress» [42, 43]. Moreover, the nature of this stress does not play a significant role in

the onset of endothelial dysfunction. Direct and indirect radiation impact on endothelial cells launches a cascade of biochemical reactions that ultimately lead to the development of endothelial dysfunction and hypertension [44–48].

* * *

Our studies for the 29-year follow-up period allowed us to come to conclusions for relatively «closed» cohort of patients who survived ARS or exposed to radiation in dose below 1 Gy:

1. In the post-accidental period the most common cause of death in ARS survivors and patients exposed below 1 Gy were cardiovascular (37.3%) and cancer (35.3%) diseases. The first includes sudden cardiac death, heart failure, strokes, and the second MDS, acute and chronic myelomonoblastic and chronic myeloblastic leukemia, cancer of various organs, such as colon cancer, stomach and thyroid gland. Terms of malignant tumor occurrence and number of cases did not differ depending on ARS grades.
2. The relative number of radiation cataracts is directly depended on ARS grade. Their latent period was the shortest in patients with ARS 3 grade. All radiation cataract arose in the first 15 years after exposure.
3. In the first five years after exposure the significant increase of diseases of nervous, digestive and cardiovascular systems was revealed in ARS survivors and ARS NC patients. Diseases of the endocrine and respiratory systems developed more slowly throughout the post-accidental period. After 29 years cumulative incidence of diseases reached 71.3–100% but without any dependence from ARS grades.
4. Accumulated incidence of endocrine diseases during the post-accident period was significantly higher in ARS survivors compared with patients of ARS NC. Most likely this is due to the large number of diabetes cases in the group of patients with ARS 1–3 grades.

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16.3. ANTIPHOSPHOLIPID ANTIBODIES AND PARAMETERS OF LIPID METABOLISM IN RADIATION MEDICINE CLINIC

First antiphospholipid antibodies (APLA) were described at the last quarter of XX century. APLA are the antibodies against phospholipids of self-body. If APLA are present in high titers in the body, it leads to pathologic states – in obstetric practice to pregnancy losses [1], and in internal diseases clinic to pathologic state which was named antiphospholipid syndrome (APS) [2], which reveals by enhanced blood clotting and, in consequence, by arterial and venous thrombosis with relative results (strokes, infarctions, phlebitis) [3]. While our studies we have found APLA in Chornobyl clean-up workers in late terms after irradiation, and sometimes their clinical and laboratory data let us to suspect APS in these patients. Despite that in our previous studies we did not find correlation between exposure dose and APLA level [4], we cannot exclude its influence completely. In present work we show results of laboratory investigations in Chornobyl clean-up workers who received rather high exposure doses during first days and months of their work in Chernobyl nuclear plant after explosion on April, 26, 1986. We also compare our laboratory investigations of these patients with their suspected exposure dose and clinical state, according to their case reports analysis at the period 2004–2006.

We studied 84 patients Chornobyl clean-up workers, who received treatment at clinic of general and endocrine radioinduced pathology of NRCRM in 2004–2006. For comparison of laboratory data and clinical state 41 patients were chosen, for whom was possible to receive information about details of clinical state and dose of exposure. 17 patients from this group had acute radiation disease in anamnesis [5].

For studying of parameters of lipoprotein metabolism and APLA in accordance with exposure dose we formed two groups of patients – 1st group, who received less than 150 cGy and 2nd – who received more than 150 cGy. Mean dose of exposure of 21 patients from 1st group was (70.9 ± 8.5) cGy, and for 2nd group ($n = 19$) – (229.0 ± 19.6) cGy. In comparison of these two groups we found that triglycerides level is related to exposure dose. In patients of 2nd group (> 150 cGy) triglycerides level was 2 times lower than in patients of 1st group (< 150 cGy) ($p < 0.05$). Levels of cholesterol in lipoproteins of low density (LPLD, β-LP) tended to increase in patients with higher dose, and cholesterol in lipoproteins of very low density (LPVLD, pre-β-LP) tended to decrease in the same patients. Coefficient of aterogeneity, total cholesterol, apoproteins A-1 and B were not different in respect of exposure dose [6].

Also it has not been significant difference between groups of patients with different exposure dose in accordance with APLA occurrence. It relates either to anti-cardiolipin antibodies of isotypes IgG and IgM, or to anti-phosphatidylserine antibodies – IgG and IgM (Table 3.2.1).

However, measuring APLA in serum of 84 Chornobyl clean-up workers, we found positive APLA levels in 32 patients (38%), while among healthy donors this parameter is positive only among 8% [7]. In our irradiated patients anti-cardiolipin antibodies appeared more often (33%), than anti-phosphatidylserine antibodies (19%). These antibodies were of IgG and IgM isotypes (Table 3.2.2).

While performing of correlation analysis by Spirman criterion correlation between coefficient of aterogeneity with ratio apoprotein B / apoprotein A-1 (ApoB/ApoA-1) was found ($p < 0.0001$, $r = 0.6337$) [8]. Negative correlation was found between triglycerides level and exposure dose. High positive correlation was found between levels of anti-cardiolipin antibodies IgG and anti-phosphatidylserine antibodies of the same isotype (IgG) ($p < 0.0001$, $r = 0.7565$). Significant correlation also has been found among anti-cardiolipin antibodies IgM and anti-phosphatidylserine antibodies of the same isotype (IgM) (Table 2.2.3).

While making comparison between mean indices of dose of exposure and triglyceride levels in accordance with APLA levels, significant difference was not found.

As an example of influence of APLA on clinical state of our patients we quote case report of patient N.

Patient N, 64 years old. Exposure dose – 35.1 rem (BER), did not have acute radiation disease, took part in sarcophagus building at ChNPP, worked at industrial court of ChNPP from May, 9 till May, 13 1986. High levels of APLA IgG anti-cardiolipine – 23.5 U., anti-phosphatidylserine (IgG) – 35 U (normal level – < 10 U.). Diagnosis: hypertonic disease 2 stage, cerebral atherosclerosis. Dyscirculatory encephalopathy with disseminated neurologic microsymptomatic. Ischemic heart disease, stenocardia of tension, functional class 2. Atherosclerosis of aorta, coronary arteries, atherosclerotic cardiosclerosis, heart insufficiency of 1 degree, chronic obstructive bronchitis in remission stage, peribroncheal sclerosis, perspiration insufficiency of 0 degree. Chronic atrophic gastritis. Chronic hepatitis, active phase. Chronic cholecystitis in incomplete remission stage. Chronic pancreatitis in incomplete pancreatitis stage. Urinary-salt diathesis. Neuritis of right cannon-bone nerve with pares of right ream, walking disorders. Initial facosclerosis, maculodistrophia. Retinal angiopathy.

Table 3.2.1

Lipid and lipoprotein metabolism parameters and APLA in Chornobyl clean-up workers in late term after irradiation in dose 0.25–2.5 Gy

#	Parameter	Dose of irradiation, cGy	
		< 150; 70.9 ± 8.5; (n = 21)	>150; 229.0±19.6; (n = 19)
1	Triglycerides (mMol/L)	2.60 ± 0.89	1.27 ± 0.18*
2	Coefficient of aterogeneity	3.46 ± 0.30	3.48 ± 0.23
3	Anti-cardiolipin APLA class IgG (GPL)	7.49 ± 1.60	9.23 ± 2.43
4	Anti-phosphatidylserine APLA class IgG (GPL)	9.88 ± 2.9	7.31 ± 2.5
5	Anti-cardiolipin APLA class IgM (MPL).	9.02 ± 2.9	7.17 ± 2.0
6	Anti-phosphatidylserine APLA class IgM (MPL)	6.82 ± 2.43	6.56 ± 2.50
7	Total cholesterol (mMol/L)	4.89 ± 0.23	5.09 ± 0.26
8	Cholesterol in LPHD (β-LP) (mMol/L)	1.19 ± 0.07	1.22 ± 0.07
9	Cholesterol in LPLD (β-LP) (mMol/L)	2.96 ± 0.24	3.43 ± 0.23
10	Cholesterol in LPVLD (pre-β-LP) (mMol/L)	0.79 ± 0.10	0.58 ± 0.08
11	Apoprotein A1 (mg/dL)	137.70 ± 4.75	129.24 ± 5.82
12	Apoprotein B (mg/dL)	91.43 ± 6.86	92.49 ± 5.54

Notes. * – $p < 0.05$.

Table 3.2.2

Correlation analysis of lipoprotein metabolism parameters and APLA in dependence of age of patients and irradiation dose

No.	1st parameter	2nd parameter	*p*	*r*	Correlation degree
1	Ratio ApoB/ApoA1	Coefficient of aterogeneity	< 0.0001	0.6337	+++
2	Age	Coefficient of aterogeneity	0.4427	0.1284	----
3	Dose of irradiation	Coefficient of aterogeneity	0.9918	0.0018	----
4	Dose of irradiation	Level of anticardiolipin APLA class IgG	0.2641	0.1912	----
5	Dose of irradiation	Level of anti-phosphatidylserine APLA class IgG	0.9625	-0.0081	----
6	Level of anticardiolipin APLA class IgG	Level of anti-phosphatidylserine APLA class IgG	< 0.0001	0.7565	+++
7	Level of anticardiolipin APLA class IgG	Level of anti-phosphatidylserine APLA class IgM	0.7836	-0.0552	----
8	Level of anticardiolipin APLA class IgM	Level of anti-phosphatidylserine APLA class IgM	< 0.0001	0.6318	+++
9	Dose of irradiation	Level of triglyserides	0.0110	-0.4189	++
10	Level of triglyserides	Cholesterol in LPLD (β-LP)	0.6927	-0.0464	----

Incidence of different APLA isotypes in dependence of irradiation exposure doses during clean-up work at ChNPP is presented in Table 2.2.3.

Table 3.2.3

Mean levels of exposure doses in Chornobyl clean-up workers in dependence of presence of different APLA isotypes

No.	APLA isotype	n	Mean irradiation dose in rem (BER) (M ± m)	*p*
1	IgG	16	186.6 ± 16.5	1-2 = 0.02
2	IgM	13	108.4 ± 11.8	2-3 = 0.04
3	Without APLA	46	148.6 ± 13.4	1-3 = 0.09

Half of APLA-positive patients Chornobyl clean-up workers had both anti-cardiolipin and anti-phosphatidylserine antibodies. Only anti-cardiolipin antibodies were found in 6 patients, only anti-phosphatidylserine antibodies - in 5 patients. Distribution of APLA according to isotype is shown at the Figure 3.2.1.

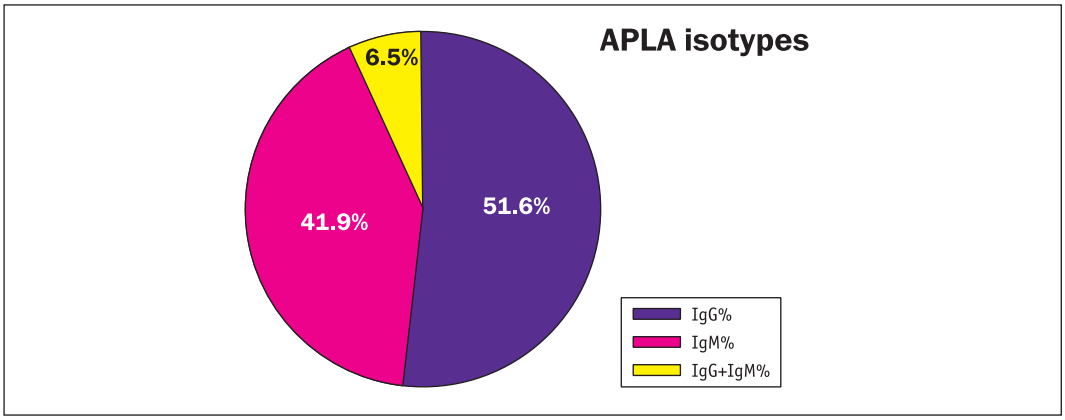


Figure 3.2.1. Distribution of APLA according to isotype.

As it shown at the picture, in Chornobyl clean-up workers among APLA prevailed antibodies of IgG isotype, but APLA IgM have been also found often.

* * *

Between 2004–2006 years in Chornobyl clean-up workers those who received treatment in clinic department of radio-induced general and endocrine pathology of NRCRM, neurologic syndromes, such as dyscirculatory encephalopayhy, pyramidal and extrapyramidal symptoms, were very often. Meanwhile, contemporary data suggest that neurologic disorders are among the most serious symptoms, associated with APLA [9]. Such disorders most of all are in local parts of CNS and reveal themselves with thrombotic occlusive events [10]. Different neurologic disorders may associate with APLA. Their basis is thrombosis. In some patients – it connects with big blood vessels, in majority – small ones. Patients with APLA usually have multiple disorders from nervous system, which are caused by micro infarctions of white substance of brain. In diagnosis of patient N. – disseminated neurologic micro-symptomatic may be connected with increased levels of APLA, class IgG, which were found in his blood. However, there was not found APLA IgM in his blood. Meanwhile, it is known that IgM antibodies point on body's

reaction on new pathologic process, but IgG – on long lasting. This finding showed old pathologic process with APLA in this patient. Eye diseases – thromboses of retinal arteries and veins are often the part of APS. We could not exclude that retinal angiopathy in our patient had connection with increased APLA levels in his blood.

In screening studies in blood donors it was shown that almost 8% of studied patients are APLA positive [7]. Among our patients – Chornobyl clean-up workers APLA had 38%. So, difference with these two cohorts is rather striking.

We found that decreased levels of triglycerides are connected with high exposure dose. These data are partially in agreement with results of work [11], where was revealed negative correlation between cholesterol level and probability of cancer development and positive correlation between exposure dose and incidence of cancers in patients who suffered from atomic bombarding of Nagasaki. It is possible to assume that radiation in our patients in dose (70.9 ± 8.5) cGy led to increase of triglyceride levels in blood, but high doses (229,0 ± 19,6 cGy) acted in opposite direction. Possibly, higher doses of irradiation lead to some kind of exhaustion of triglycerides reserves and more severe course of pathologic process related to the dose of exposure, and this fact is supported by negative correlation between dose of exposure and triglycerides which we found in our patients Chornobyl clean-up workers.

According to our results, there were no correlations between dose of exposure and lipid metabolism parameters, except negative correlation with triglyceride level. We shall admit that there was no increase of aterogeneity coefficient in association with increase of dose which was received by Chornobyl clean-up workers in 1986–1987.

Anticardiolipin antibodies of both classes (IgG and IgM) positively correlated with production of antiphosphatidylserine antibodies of the same classes ($p < 0.0001$). However, there was no correlation between two isotypes of antibodies, for example of anticardiolipin IgG antibodies with anticardiolipin IgM antibodies. Our data support opinion that in Chornobyl clean-up workers occurs production of auto-antibodies against many phospholipids but of one isotype. That's why it seemed important to study co-factor-dependent antibodies, which are direct pathogenic factors of intavessel clotting in different diseases.

We found that antibody level to co-factor protein – anti-β2GPI IgG was lower than 10 u/ml, in all studied patients, i.e. APLA in all Chornobyl clean-up workers were co-factor-independent [12]. There is opinion of one authors that in majority of patients such APLA do not lead to thrombotic events [13], but according to other authors they can provoke hypercoagulation state [14].

Thus, in Chornobyl clean-up workers APLA occurs quite often, and more often – IgG isotype and they are co-fator-independent and may take part in hypercoagulation processes exacerbating patient's state. Chornobyl clean-up workers, who had IgG APLA, received higher doses than those having IgM. It's possible to suppose that increased APLA in Chornobyl clean-up workers is a consequence of ionizing radiation effect on immunoregulatory mechanisms. Violation of controlling part of immunity may lead in long terms to activation of suppressed lymphocyte clones which are APLA producers.

It is important to admit, that increased incidence of APLA production is related to irradiation, but there was no direct «dose-effect» association.

The key fact is that higher doses of irradiation were in Chornobyl clean-up workers who had IgG APLA. Mean dose in Chornobyl clean-up workers with IgG APLA was higher than in Chornobyl clean-up workers with IgM, and higher than in group of Chornobyl clean-up workers without APLA, though it was not significant (tendency, $p = 0.09$). It is possible that statistic difference was not quite significant due to rather small number of the patients under our observation. 84% of APLA-positive Chornobyl clean-up workers were younger than 60 years old. IgG

anticardiolipin antibodies were found 2 times more often than antiphosphatidylserine in our patients Chornobyl clean-up workers.

We measured also anti-DNA antibodies but did not found any – either one- or two-spiral (data not shown).

Thus, in Chornobyl clean-up workers APLA, usually IgG, occur rather often, they are presumably cofactor-independent but they may take part in hypercoagulation processes and exacerbate patient's condition. Chornobyl clean-up workers with IgG APLA had higher exposure dose than Chornobyl clean-up workers with IgM APLA. We can suppose that APLA formation in Chornobyl clean-up workers is a consequence of irradiation effect on immunoregulatory mechanisms.

Though clinical state of our patients was not classical for APS, many of symptoms which they have are peculiar for APS. Lack of IgG antibodies against β2GPI does not exclude other co-factors participation, which may take part in APS formation also. That is why while estimating of Chornobyl clean-up workers' condition, possible presence of APLA should be taken into account.

There was not classic clinical picture of APS which described in the literature [15], in any our patient. But such nosology as pneumosclerosis, heart ischemic disease, hypertonic disease, obstructive bronchitis – which have had almost all the patients, retinal angiopathia (occurred in 1/3 patients with APLA), complains of practically all patients on migraine, dizziness in 1/3 – are considered, though indirectly, positive clinical manifestations of APS [16]. Among our APLA positive patients we had only one smoking person, only one patient had received treatment by α-interferon; other possible APS causes had not been found. Taking into account that other different causes of APLA are not found we can not exclude influence of radiation factor as a possible cause of APLA production in our patients.

* * *

1. In Chornobyl clean-up workers with dose of exposure > 150 cGy triglyceride level was 2 times smaller than in those who received radiation dose < 150 cGy. There was negative correlation between triglyceride levels and exposure dose.
2. In patients Chornobyl clean-up workers positive APLA levels are detected more often (38%), than in healthy donors (8%).
3. Increased level of APLA in Chornobyl clean-up workers is connected with irradiation but direct association «dose-effect» was not found.
4. In patients Chornobyl clean-up workers often occurs production of APLA against different phospholipids but of one class – IgG or IgM.
5. Lack of antibodies against β2GPI points on co-factor independent antibodies in Chornobyl clean-up workers.
6. IgG APLA appearance in Chornobyl clean-up workers in late terms after irradiation, especially in those younger 60 years, may point on immune regulation disturbances and possible APS formation.

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Chapter 4
LEUKEMIA

4.1. LEUKEMIA IN CLEAN-UP WORKERS: RADIATION, PROFESSIONAL AND LIFESTYLE RISKS

Despite the fact that the etiology of leukemia is not completely understood, the essential role of certain factors in its development has been proven. Importance of these factors may vary depending on the origin of disease – myeloid or lymphoid hematopoietic lineage, or even on the form of leukemia (acute or chronic).

The causal relationship of leukemia and ionizing radiation is not in doubt and proven in numerous studies [1–4]. Leukemia was recognized as an earliest and one of the most significant remote health effects of exposure to ionizing radiation decades before the Chornobyl NPP accident. The most comprehensive evidences are based on the follow up results on survivors after the A-bombing of Hiroshima and Nagasaki [2–4] and demonstrate the highest risk during 5-8 years after irradiation, declining but still existing along the decades. The highest relative risk was defined for the acute lymphoblastic and chronic myelocytic leukemia while there was no evidence of an excess risk for chronic lymphocytic leukemia

The leukemia risk increase was also demonstrated in groups of patients exposed to substantial doses of ionizing radiation due to either diagnostic or therapeutic medical reasons [5–8] with similar estimates for leukemia subtypes.

Results of the Chornobyl health consequences studies support these evidences and explored the elevation of the risk of different leukemia forms including the chronic lymphocytic one that was not traditionally considered as radio sensitive [9–12]. There are several occupational groups that are experienced or still undergoing exposure to ionizing radiation as a work condition for whom the causative relationship with leukemia is confirmed – medical staff, aircrews, underground hard-rock miners, nuclear weapons test participants, Mayak facility workers and other nuclear industry staff [13–19].

Along with ionizing radiation other potential causes including occupational or environmental exposure to several chemicals were proven or suspected.

Role of the certain chemical agents is well documented and proven to be causative in a case of at least some forms of the disease [20–26]. Among these first of all is benzene as a single compound, or as part of mixture of solvents [21, 22]. Benzene is the chemical with the well docu-

mented leukemogenic effect. The only malignant hematopoietic disease that has been clearly linked to benzene exposure is AML [22]. Although analysis of a large European dataset confirms a role of occupational exposure to solvents in the onset of CLL as well. It is suggested that benzene is most likely to be implicated [23]. Benzene could be responsible for toxic effect on hematopoetic tissue identified in several studies among persons occupationally exposed to petroleum products. Relatively low-level exposure to benzene experienced by petroleum distribution workers was associated with an increased risk of MDS, but not AML, suggesting that MDS (potentially previously reported as AML) may be the more relevant health risk for lower exposures [24]. While less toxic solvents have been substituted for benzene, it still is a component of petroleum products, including gasoline, though high exposures may exist in small, uncontrolled workshops in developing countries. Emissions from gasoline/petrochemical industry are its main sources to the ambient air, but a person's total inhalation exposure can be elevated from emissions from cigarettes, consumer products and gasoline powered engines/tools stored in garages attached to homes [25].

The results on the pesticides exposure are controversial to some extent. The majority of studies have recorded statistically significant excess risk of leukemia among agricultural workers exposed to pesticides in general, or several specific categories of pesticides such as phenoxy-herbicides, triazine herbicides, arsenic-containing pesticides, atrazine, gamma-hexachlorocyclohexane (lindane), dichlorodiphenyltrichloroethane (DDT), etc. [21, 26]. According to the recently published results of the Epilymph study [26] risk of chronic lymphocytic leukaemia (CLL) was elevated amongst those ever exposed to inorganic and organic pesticides with highest value amongst those ever exposed to organophosphates.

Several studies shown the rise of leukemia incidence after exposure to the chemicals used in the synthetic rubber industry, formaldehyde, butadiene and dimethyl-dithio-carbamateexisting [20, 21].

Certain role in the leukemia induction is reported for the non-radiation exposure. Small but statistically significant excess risk of leukemia was identified among workers highly exposed to extremely low frequency electromagnetic fields (ELF EMF) [27-29]. To date some evidences were received on environmental factors that could be responsible for leukemia incidence excess. Therefore ecological studies on environmental and domestic factors (residential exposure to radon, to heavy metals or extremely low frequency magnetic fields (ELF MF) are still relevant [22, 27–29]. Studies on the role of biological factors are still in progress to confirm the hypothesis on the viral nature of the disease [30].

Cytostatic drugs, and especially alkylating agents such as busulfan, chlorambucil, cyclophosphamide etc. used in the treatment of solid tumors represent another documented risk factor for developing of secondary leukemia, particularly AML [31–34].

There is some evidence on hereditary predisposition to leukemia development [35, 36]. CLL is estimated to have one of the highest familial risks among hematologic malignancies; this along with other evidence strongly supports an inherited genetic component [37].

As of dietary or lifestyle factors the weak association if any was identified according to the published data [38, 39]. Recent study confirmed the increase of myeloid leukemia with cigarette smoking and provides encouraging evidence of risk attenuation following cessation [40, 41]. Moreover smoking is estimated to be a large confounder to radiation risk estimates derived from the epidemiologic studies [42].

Thus, the scientific data obtained to date indicate a significant role of certain hazardous chemicals in the development of leukemia. To estimate this influence the analytical model used in joint NCI (USA) – NRCRM (Ukraine) study of leukemia included a block of data on occu-

pational exposures, as well as lifestyle factors besides the clean-up work characteristics for dose-dependent risk assessment. One of our tasks was to estimate if the influence of such factors could modify the effect of exposure to ionizing radiation after the accident.

The joint NCI (USA) – NRCRM (Ukraine) study of leukemia in Ukraine was realized in a cohort of 110,645 clean-up workers aiming to assess leukemia risks after exposure to ionizing radiation during emergency and clean-up activities after the Chornobyl catastrophe in 1986–2006 [9] and role of other factors influence. The study confirmed significant linear dose response for all leukemia with estimated ERR/Gy of 3.44 (95% CI 0.47-9.78, $p < 0.01$) for the period 1986–2000 [9] and ERR/Gy = 1.26 (95% CI: 0.03, 3.58) for the extended study period 1986–2006 [10].

These findings are consistent with either Japanese studies [4] or with the results of observation on the Russian clean-up workers [11, 12] (Table 4.1.1).

Table 4.1.1

Excess relative risk (ERR/Gy) of leukemia in clean-up workers (CW) in Ukraine and Russia and Life Span Study cohorts (Japan)

Cohort	Period of observation	Excess Relative Risk (ERR per Gy)	95% confident interval
Chornobyl clean-up workers, Ukraine,			
1986–2000 (A.Ye. Romanenko, [9])	1986–2000	3.44	0.47– 9.78
1986–2006 (L. Zablotska [10])	1986–2006	1.26	0.03–3.58
Chornobyl clean-up workers, Russia 1986–1997 pp.	1986–1997	4.98**	0.59–14.47#
(V. Ivanov [11])	1998–2007	-1.64**	(-2.55)–(-0.57)#
Life Span Study cohort, Japan (W.L. Hsu [4])	1950–2001	4.7**	3.3–6.5

Notes. ** excluding chronic lymphocytic leukemia (CLL); # 90% confident interval.

Study cohort of 110,645 male clean-up workers resided one of 5 oblasts of Ukraine or Kyiv city [9, 10] was formed based on the State Chornobyl registry data. The cohort was followed up during the 1986–2006 to identify cases of any type of leukemia. For retrospective dose reconstruction the time-and-motion RADRUE method was used [43, 44]. This method uses the results of personal interviews of clean-up workers conducted with a special questionnaire collecting the data on history of their exposure (including place, type, period, duration of clean-up work and residence in the 70-km zone around the Chornobyl NPP). The questionnaires were interviewers administered to collect the relevant information.

Besides the dose-related characteristics the questionnaire included sections designed to collect the data on the exposure to occupational or medical negative factors (radiation, petroleum products, pesticides), on social and lifestyle characteristics and also personal and family cancer history. Among these characteristics occupational group before and after clean up, education, marital status, type of residency settlement, history of medical diagnostic exposure, familial history of leukemia, certain lifestyle habits (tobacco and alcohol use) that were considered as potential risk modifying factors.

Majority of questions on non-Chornobyl work with ionizing radiation, occupational exposure to pesticides, organic solvents, petroleum products required «yes» or «no» answers. For questions on the X-ray examinations, alcohol consumption and smoking both general «yes/no» and categorical answers were included in questionnaire. Mostly descriptive nature of self reported answers were expected to be informative for identification the considerable risk modifying fac-

tors if any existed and defining the direction for the consequent detailed research. Participants smoking was categorized as «never versus ever smokers» and «never versus former smokers». For smoking intensity effect assessment study subjects were additionally categorized as «never smokers» versus «ever smokers < 1 pack a day», «never smokers» versus «ever smokers» ≥ 1 pack a day». Pack-years (pack/day times years smoked) categories were also compared.

Conditional logistic regression was used to estimate excess relative risk of leukemia per gray (ERR/Gy) of radiation dose and odds ratios (OR) for the effects of factors other than Chornobyl radiation on Leukemia risk with 95% confident intervals (CIs). Calculating ORs we examined the potential association between different factors: work at hazardous enterprises, contact with hazardous chemicals, including petroleum, occupational group, marital status, alcohol consumption, smoking, diagnostic X-rays (categorical variables) and the disease outcomes taking into the consideration estimated radiation dose (continuous variable). The estimates significance was tested using the likelihood ratio tests. The model was fitted using the EPICURE statistical package [45].

162 leukemia cases were confirmed by the International Diagnostic Review panel. Among these cases 89 were chronic lymphocytic leukemia (CLL) cases and 73 other (non-CLL) leukemia cases. Mostly due to the tracing problems it was possible to reconstruct the dose only for 137 of 162 confirmed leukemia cases with no substantial difference between leukemia subtypes (Table 4.1.2). The age at diagnosis of 137 cases ranged from 25 to 78 years (median, 56) and the corresponding age for 863 controls ranged from 25 to 79 years (median, 55). Mean ± SD estimated bone marrow radiation doses for cases and controls were (132.3 ± 342.6) mGy and (81.8 ± 193.7) mGy, respectively (Table 4.1.3). For all leukemias we found a significant positive association with continuous radiation dose with an estimated ERR/Gy = 1.26 (95% CI: 0.03, 3.58, p = 0.041). It was estimated that approximately 16% of all leukemia cases in our Chornobyl cleanup worker population over a period of 20 years of follow-up were attributable to radiation exposure from the Chornobyl accident [PAR = 16.4% (95% CI: 3.9, 32.6)].

As a result of testing the role of the social factors (marital status, education, type of residency settlement) none of them was identified as those playing significant role in leukemia risk (Table 4.1.3).

Table 4.1.2
Distribution of cases of leukemia among Ukrainian Chornobyl clean-up workers by subtype, 1986–2006

Cell Type	Confirmed[a] cases	Cases with doses[b] (% confirmed cases)
All leukemias	162	137 (84.6)
Non-CLL[c]	73	58 (79.5)
Including:		
Myeloid leukemia	48	40 (83,3)
➢ acute myeloid leukemia[d]	20	16 (80.0)
➢ chronic myeloid leukemia	28	24 (85.7)
Acute lymphocytic leukemia	8	6 (75.0)
Acute leukemia otherwise not specified	11	7 (63.6)
Other chronic leukemia[e]	6	5 (83.3)
CLL	89	79 (88.8)

Notes. [a] Cases confirmed by the International Hematolopathology Panel; [b] Bone marrow doses estimated by RADRUE method from dosimetric questionnaires of participants or their proxies; [c] CLL – Chronic lymphocytic leukemia; [d] Combined AML group includes 4 MDS RAEB-t cases; [e]1 Hairy cell leukemia initially was in CLL group and then was transferred to Other chronic leukemia group.

Table 4.1.3
Descriptive characteristics of cases and controls

Characteristic	Cases	Controls	*p*-value[a]
Mean age at first exposure	42.1 ± 9.6	41.9 ± 9.5	> 0.5
Mean attained age[b]	54.3 ± 9.95	54.2 ± 9.8	> 0.5
Radiation dose, mGy [mean ± SD (range)][c]	132.3 ± 342.6 (0-3220.0)	81.8 ± 193.7 (0-2600.0)	0.12
Type of residence at the time of interview[d]			0.09[e]
➢ Urban	101 (74%)	680 (79%)	
➢ Rural	19 (14%)	151 (18%)	
➢ Other	10 (7%)	32 (4%)	
Education[f]			0.47[e]
➢ 8 years or less	16 (12%)	131 (15%)	
➢ High school	46 (34%)	341 (40%)	
➢ Trade school	34 (25%)	200 (23%)	
➢ College	34 (25%)	188 (22%)	

Notes. [a] p-Value from the Wilcoxon rank sum test. unless otherwise stated; [b] For cases and reference year for corresponding controls; [c] Bone marrow radiation dose lagged by 2 years; [d] Data on type of residence is missing for 7 cases; [e] p value from the chi-square test; [f] Data on education is missing for 7 cases and 3 controls.

To study potential effect of the exposure to factors other than Chornobyl radiation we performed the categorical analysis by various variables adjusted for dose of irradiation.

Non-Chornobyl radiation exposure including army service and work in the nuclear energy facilities did not show any substantial risk deviation. We didn't receive the conclusive evidence on the role of the diagnostic X-ray examination in leukemia risk as well (not shown).

Similar results were received for those subjects worked in the hazardous industries including oil or chemical industry, electric industry, rubber production facilities, road construction, coal mining or metallurgy. Work at such facilities was estimated in a joint group of hazardous enterprises (Table 4.1.4). Exposure to hazardous chemicals including petrol, pesticides or organic solvents adjusted for the Chornobyl radiation dose was included to the leukemia risk analytic model. Exposure to hazardous chemicals as a group was not shown to elevate leukemia risk at whole (Table 4.1.4). The same was found for leukemia subtypes (not shown). However the increased non-CLL leukemia risk was estimated to be associated with petrol exposure adjusted for radiation dose mostly accounting for identified excess in chronic myelogenous leukemia cases (Table 4.1.4). It was not the same for all leukemia combined and for CLL leukemia separately.

Aiming to clarify the findings we tested the possible link between the case status and occupation factors, including self estimated occupational petroleum exposure. The preliminary estimates show no such dependency. None of the employment places dominated. Among 19 cases reported to be exposed to petrol 5 before Chornobyl accident were agriculture workers (including 1 CML case), 9 were industrial workers (including 2 AML and 3 CML cases), 3 cases were drivers (none of them was of myeloid origin). The rest of cases were office workers.

Taking into account the small number of exposed cases, the results should be interpreted with caution. Nevertheless our findings contribute to the understanding of the need to further examine the role of certain chemicals in the development of leukemia, first of all of non-lymphoid origin.

Smoking was not shown to be responsible for leukemia risk increase independently of radiation dose (Table 4.1.5) either for lymphocytic, or myeloid leukemia subtypes and total

Table 4.1.4

Odds Ratios and 95 % Confidence Intervals for hazardous factors exposure by subtypes of leukemia for 137 leukemia cases

Variable		Cases	%	Controls	%	OR[a]	95 % CI	*p*-value[b]
Radiation exposure[c]								
	No	113	87.6	749	87.1	1		
	Yes	16	12.4	111	12.9	0.82	0.46-1.49	> 0.5
Hasardous industry[d]								
	No	111	86.7	718	83.4	1		
	Yes	17	13.3	143	16.6	0.71	0.41-1.26	0.229
Hasardous chemicals[e]								
	No	102	78.5	666	77.5	1		
	Yes	28	21.5	193	22.5	1.03	0.64-1.65	> 0.5
Petrol[f]								
➤ All leukemias								
	No	115	85.8	765	88.7	1		
	Yes	19	14.2	97	11.3	1.56	0.86-2.81	0.153
➤ Non-CLL								
	No	45	81.8	339	89.4	1		
	Yes	10	18.2	40	10.6	2.28	1.13-6.79	0.03
➤ CLL								
	No	70	88.6	426	88.2	1		
	Yes	9	11.4	57	11.8	1.03	0.45-2.33	> 0.5

Notes. [a] OR from conditional logistic regression with adjustment for radiation dose to the bone marrow lagged by 2 years; [b] P-value from the likelihood ratio test testing addition of the variable to the model adjusted for radiation dose; [c] data on radiation exposure (other than Chornobyl) are missing for 8 cases and 3 controls; [d] data on hazardous industry factors exposure are missing for 9 cases and 2 controls; [e] data on hazardous chemicals exposure are missing for 7 cases and 4 controls; [f] data on petroleum exposure are missing for 3 cases and 1 control.

Table 4.1.5

Odds ratios and 95 % Confidence intervals for smoking categories and leukemia subtypes

Variable	All leukemias			CLL			non-CLL		
	Cases N (%)	Controls N(%)	OR[a] (95% CI)	Cases N (%)	Controls N(%)	OR[a] (95% CI)	Cases N (%)	Controls N(%)	OR[a] (95% CI)
Smoking status[b]									
➢ Never smoked[c]	35	217	reference	19	124	reference	16	93	reference
➢ Ever smoked	95	646	1.09 (0.72–1.67)	57	360	1.09 (0.62–1.92)	38	286	0.72 (0.38–1.37)
➢ Former smoker	65	311	1.25 (0.77–2.02)	35	191	1.08 (0.56–2.10)	30	120	1.46 (0.72–2.93)
➢ Current smoker	30	335	0.66 (0.37–1.18)	19	124	1.20 (0.57–2.53)	8	166	0.25 (0.09–0.69)
Regular smoking (ever smoked vs. never smoked)									
< 1 pack/day	53	281	1.11 (0.68–1.82)	31	157	1.27 (0.65–2.45)	22	124	0.94 (0.45–1.97)
> 1 pack/day	36	340	0.67 (0.39–1.14)	21	188	0.88 (0.43–1.80)	15	152	0.46 (0.20–1.05)
Pack-years for ever smoked[d]									
0	35	217	Reference	19	124	Reference	16	93	Reference
> 0–15	30	190	1.39 (0.82–2.36)	10	103	1.17 (0.60–2.30)	20	87	0.81 (0.38–1.70
> 15–30	32	207	1.38 (0.79–2.39)	23	112	0.79 (0.35–1.78)	9	95	0.43 (0.18–1.02)
> 30	25	221	0.98 (0.55–1.74)	17	128	1.04 (0.52– 2.07)	8	93	0.39 (0.15–0.98)
			p, trend > 0.5			p, trend = 0.281[b]			p, trend = 0.080[b]

Notes. [a]OR from conditional logistic regression with adjustment for radiation dose to the bone marrow lagged by 2 years; [b] data on smoking are missing for 7 cases; [c] reference group is «never smoked» for all models; [d] data on pack-years are missing for 8 cases and 28 controls.

leukemia. Categorical analysis of smoking intensity effect by packs per day and dose estimate (pack-years categories) brought similar results for all leukemia cases with no difference between CLL and non-CLL leukemia. We may suggest the significant decrease of the smoking intensity among cases at the time around the leukemia diagnose establishing. The received analysis results not contradict this assumption. Structure of the smoking data questionnaire section, mostly retrospective process of cases identification and interviewing did not allow to get a certain data on whether the smoking status and intensity were changed and to what extend due to the leukemia diagnose and hence to get clear picture of the possible pre-diagnostic cases/controls difference.

No difference in CLL clinical features was found in a group of clean-up workers in comparison with non-exposed patients. A significant increase in the risk of death with increasing radiation dose was observed in CLL patients ($p = 0.03$). It was shown that the younger was age at first exposure in CLL cases the shorter survival after diagnosis was observed even after accounting for the dose of exposure. Survival of CLL cases also was significantly shorter among those with higher peripheral blood lymphocyte count and the advanced clinical stage of disease (both $p < 0.05$) [46].

* * *

A large-scale study of leukemia in a 110,645 cohort of young and middle-aged males, exposed while the emergency or clean-up work after the Chornobyl accident, which was observed 20 years, has allowed reliably determine the effects of ionizing radiation as a major risk forming factor in the development of all forms of leukemia, including chronic lymphoid. Additionally to ionizing radiation it has been found that exposure to petrol is a significant independent factor increasing myeloid leukemia risk, although it is of no importance in chronic lymphocytic leukemia. The influence of other professional or lifestyle characteristics had no significant influence on the development of both CLL and non-CLL leukemia.

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4.2. CHILDHOOD LEUKEMIA IN UKRAINE AFTER THE CHORNOBYL NPP ACCIDENT

Childhood leukemia morbidity in Ukraine after the Chornobyl NPP accident adjusted to the status of the territory (contaminated, non-contaminated), time period (post-accident, 1987–2000), gender (male, female), and age subgroups (1–4, 5–10, 10–15, and 15–19 years old) was analyzed. During the elaboration of the French-German initiative for Chornobyl two groups from the NRCRM have collected data on leukemia cases for a 1987–2000 period in Kyiv and Zhytomyr regions (A. Prysyazhniuk et al.), and Chernihiv and Sumi regions (V. Bebeshko et al.). Separate descriptive analysis of data didn't reveal any changes in incidence rates.

A new approach to re-assess data was performed merging two databases to obtain better statistical power. Subsequent preliminary steps of a joint database formation included tables harmonization, data clearance and quality checks.

Objective of the study was to analyze the Ukrainian childhood leukemia morbidity after the ChNPP accident based on the data base (DB) of National Research Center for Radiation Medicine of the National Academy of Medical Sciences of Ukraine.

Subject of the study was the leukemia morbidity adjusted to the status of the territory (contaminated, non-contaminated), time period (post-accident – 1987– 2000), gender (male, female), and age subgroups (1–4, 5–10, 10–15, and 15–19 years old).

The DB included 1085 childhood leukemia cases in patients aged 1–19 years. Cases were diagnosed during 1980–2000 in 4 oblasts of Ukraine. Infant leukemia cases were excluded considering the disease peculiarities. Three target regions – Zhytomyr, Kyiv (except Kyiv city), and Chernihiv oblasts were included as contaminated areas after the Chornobyl accident, and Sumy region (oblast) was included as the control (non-contaminated) area. Radiation exposure doses were available as average values for the rayons (administrative units of regions) for each of three contaminated areas. However, as the study design is ecological, only two types of territory status have been taken into consideration for the subsequent analysis i.e. contaminated by radiocesium (1 to 15 Ci/sq.km of soil) with effective doses higher than 1.0 mSv per year; or non-contaminated – less than 1 Ci/sq.km radiocesium deposition density, and effective doses less than 0.5 mSv per year.

Disease codes were assigned according to the ICD-9. Usage of the ICD-9 codes (204–2089) allowed taking into account the degree of clonal cells maturation (acute or chronic leukemia), lineage specificity (myeloid or lymphoid) and possibilities of case verification in Ukraine at the time of diagnosis (the so-called group of unspecified leukemia).

The healthcare institutions of different level (oncological dispensaries, clinics, research institutes etc.) and Cancer Registry of Ukraine that began its functioning in 1995 were the data sources for leukemia diagnosis. Primary information included the medical records data and biological material (peripheral blood, bone marrow, trepanobiopsy smears). Retrospective clarification of diagnosis was not possible if only medical records were available thus the group of so called unspecified leukemia cases was put together.

Three categories of diagnosis were used before the verification procedure: definite, probable and possible. Criteria of probable cases were the following:

a) clinical information was convincing, but there was a lack or absence of biological material;
b) there were good biological smears but inadequate clinical information;
c) there were neither good clinical information nor biological material, but case was diagnosed by the very reliable hematologists;
d) there were adequate clinical and biological data, but the expert considered them doubtful.

Criteria of possible diagnosis were the following:
a) there was only a death certificate information;
b) both clinical and biological information was of unsatisfactory quality;
c) there were insufficient signs of the disease determined by all experts.

Cases with convincing clinical and biological data were diagnosed as definite and were input into DB after confirmation.

Gender and 5-year specific annual data for the population of each region were obtained from official publications of the State Committee of Statistics of Ukraine.

There were no individual doses for leukemia cases, so they were combined into exposed and non-exposed group each of which included 4 subgroups according to the age at diagnosis: 1–4, 5–9, 10–14, and 15–19 years old.

Three types of analysis were used. In the first analysis, cases were grouped according to the extent of leukemic cells maturity (acute leukemia (AL): ICD9 codes 2040, 2050, 2060, 2080; chronic leukemia (CL): ICD9 codes 2041, 2051, 2081; unspecified leukemia (UL (I)): ICD9 codes 204, 2048, 2049, 205, 2059, 206, 2069, 207, 208, 2089). For the second analysis, cases were combined according to leukemic cell lineage, i.e. lymphoid leukemia (LL): ICD9 codes 204, 2040, 2041, 2048, 2049; myeloid leukemia (ML): ICD9 codes 205, 2050, 2051, 2059, 206, 2060, 2069; unspecified leukemia (UL (II)): ICD9 codes 207, 208, 2080, 2081, 2089. In the third analysis all leukemia cases were analyzed.

The analysis was carried out using the standard methods of descriptive epidemiology: calculation of prevalence ratio (PR) and odds ratio (OR). To reveal possible trends the linear regression coefficients were calculated as well. Results of PR calculation for study areas are summarized in Tables 4.2.1–4.2.7. Cases were divided in subgroups according the criteria: gender (male, female, male & female), areas of residence (contaminated, non-contaminated), age at diagnosis (groups aged 1–4, 5–9, 10–14, 15–19 years), and study period (post-accident i.e. 1987–2000). Leukemia prevalence (PR) was analyzed taking into account three types of case distribution. Tables 4.2.1–4.2.3. compares the results of prevalence of leukemia divided into acute, chronic, and unspecified types (UL (I)). Tables 4.2.4–4.2.6 compares the results of dis-

Table 4.2.1
Prevalence of acute leukemia by sex, contamination of the territory and age at diagnosis (number of cases/number of inhabitants)

Gender	Contamination of the territory	Age at diagnosis, years				Total
		1–4	5–9	10–14	15–19	
Male	Yes	83/123213 (0.07)	92/177865 (0.05)	52/168311 (0.03)	50/168031 (0.03)	277/637420 (0.04)
	No	32/42668 (0.07)	19/51456 (0.04)	16/48545 (0.03)	18/48462 (0.04)	85/191131 (0.04)
Female	Yes	74/117714 (0.06)	69/172042 (0.04)	47/163748 (0.03)	32/164478 (0.02)	222/617982 (0.04)
	No	26/34252 (0.08)	16/41068 (0.04)	11/49826 (0.02)	11/46605 (0.02)	64/171751 (0.04)
Male and Female	Yes	157/240927 (0.07)	161/349907 (0.05)	99/332059 (0.03)	82/332509 (0.02)	499/1255402 (0.04)
	No	58/76920 (0.08)	35/92524 (0.04)	27/98371 (0.03)	29/95067 (0.03)	149/362882 (0.04)

Table 4.2.2
Prevalence of chronic leukemia by sex, contamination of the territory and age at diagnosis (number of cases/number of inhabitants)

Gender	Contamination of the territory	Age at diagnosis, years				Total
		1–4	5–9	10–14	15–19	
Male	Yes	5/123213 (0.00)	4/177865 (0.00)	6/168311 (0.00)	6/168031 (0.00)	21/637420 (0.00)
	No	0/42668 (0)	0/51456 (0)	1/48545 (0.00)	1/48462 (0.00)	2/191131 (0.00)
Female	Yes	3/117714 (0.00)	1/172042 (0.00)	2/163748 (0.00)	9/164478 (0.01)	15/617982 (0.00)
	No	1/34252 (0.00)	0/41068 (0)	2/49826 (0.00)	6/46605 (0.01)	9/171751 (0.01)
Male and Female	Yes	8/240927 (0.00)	5/349907 (0.00)	8/332059 (0.00)	15/332509 (0.01)	36/1255402 (0.00)
	No	1/76920 (0.00)	0/92524 (0)	3/98371 (0.00)	7/95067 (0.01)	11/362882 (0.00)

Table 4.2.3
Prevalence of unspecified leukemia (I) by sex, contamination of the territory and age at diagnosis (number of cases/number of inhabitants)

Gender	Contamination of the territory	Age at diagnosis, years				Total
		1–4	5–9	10–14	15–19	
Male	Yes	12/123213 (0.01)	14/177865 (0.01)	13/168311 (0.01)	10/168031 (0.01)	49/637420 (0.01)
	No	0/42668 (0)	0/51456 (0)	0/48545 (0)	0/48462 (0)	0/191131 (0)
Female	Yes	20/117714 (0.02)	7/172042 (0.00)	8/163748 (0.00)	11/164478 (0.01)	46/617982 (0.01)
	No	0/34252 (0)	0/41068 (0)	0/49826 (0)	0/46605 (0)	0/171751 (0)
Male and Female	Yes	32/240927 (0.01)	21/349907 (0.01)	21/332059 (0.01)	21/332509 (0.01)	95/1255402 (0.01)
	No	0/76920 (0)	0/92524 (0)	0/98371 (0)	0/95067 (0)	0/362882 (0)

tribution of cases as myeloid, lymphoid, and unspecified leukemia (UL (II)). The data of analysis of all leukemias are compared in Table 4.2.7.

In the first analysis (AL+CL+UL (I)) some peculiarities of PR were found. PR of childhood AL taking into consideration the territory status was not significantly different for contaminated and non-contaminated regions (Table 4.2.1). The same absence of any differences were obtained when compare PR for male, female, and both together. The comparison of PR of AL in different age subgroups found the most high level for the subgroup 1–4 (0.07–0.08), whereas for other subgroups the prevalence was lower and decreasing towards the subgroup 15–19 (0.03–0.04). When compare the subgroup 1–4 and the subgroup 15–19, PR for the second one was 2–3 times lower.

Table 4.2.4
Prevalence of lymphoid leukemia by sex, contamination of the territory and age at diagnosis (number of cases/number of inhabitants)

Gender	Contamination of the territory	Age at diagnosis, years				Total
		1–4	5–9	10–14	15–19	
Male	Yes	50/123213 (0.04)	45/177865 (0.03)	33/168311 (0.02)	19/168031 (0.01)	147/637420 (0.02)
	No	16/42668 (0.04)	11/51456 (0.02)	9/48545 (0.02)	1/48462 (0.00)	37/191131 (0.02)
Female	Yes	44/117714 (0.04)	39/172042 (0.02)	27/163748 (0.02)	19/164478 (0.01)	129/617982 (0.02)
	No	12/34252 (0.04)	6/41068 (0.01)	4/49826 (0.01)	0/46605 (0)	22/171751 (0.01)
Male and Female	Yes	94/240927 (0.04)	84/349907 (0.02)	60/332059 (0.02)	38/332509 (0.01)	276/1255402 (0.02)
	No	28/76920 (0.04)	17/92524 (0.02)	13/98371 (0.01)	1/95067 (0.00)	59/362882 (0.02)

Table 4.2.5
Prevalence of myeloid leukemia by sex, contamination of the territory and age at diagnosis (number of cases/number of inhabitants)

Gender	Contamination of the territory	Age at diagnosis, years				Total
		1–4	5–9	10–14	15–19	
Male	Yes	8/123213 (0.01)	12/177865 (0.01)	15/168311 (0.01)	10/168031 (0.01)	45/637420 (0.01)
	No	2/42668 (0.00)	2/51456 (0.00)	1/48545 (0.00)	2/48462 (0.00)	7/191131 (0.00)
Female	Yes	5/117714 (0.00)	7/172042 (0.00)	8/163748 (0.00)	12/164478 (0.01)	32/617982 (0.01)
	No	4/34252 (0.01)	5/41068 (0.01)	3/49826 (0.01)	6/46605 (0.01)	18/171751 (0.01)
Male and Female	Yes	13/240927 (0.01)	19/349907 (0.01)	23/332059 (0.01)	22/332509 (0.01)	77/1255402 (0.01)
	No	6/76920 (0.01)	7/92524 (0.01)	4/98371 (0.00)	8/95067 (0.01)	25/362882 (0.01)

Minimal PR of CL (0.01) was defined only for the female subgroup aged 15–19, and male and female subgroup aged 15–19 (Table 4.2.2). The insufficient number of cases for analysis in the most subgroups was the result of rare frequency of childhood CL.

For UL (I) the PR was low and fluctuated within 0.01–0.02 (Table 4.2.3) in inhabitants of contaminated regions: male subgroups in spite of age, female subgroups aged 1–4 and 15–19, and all male and female subgroups.

Second analysis (LL+ML+UL (II)) also disclosed the peculiarities of PR. PR of LL did not depend of territory status (contaminated, non-contaminated) and had similar tendencies to PR of LL subgroups (Table 4.2.4). The most high PR (0.04) was found in all subgroups aged 1–4 and minimal PR was revealed in subgroups aged 15–19 in spite of gender.

Table 4.2.6

Prevalence of unspecified leukemia (II) by sex, contamination of the territory and age at diagnosis (number of cases/number of inhabitants)

Gender	Contamination of the territory	Age at diagnosis, years				Total
		1–4	5–9	10–14	15–19	
Male	Yes	42/123213 (0.03)	53/177865 (0.03)	23/168311 (0.01)	37/168031 (0.02)	155/637420 (0.02)
	No	14/42668 (0.03)	6/51456 (0.01)	7/48545 (0.01)	16/48462 (0.03)	43/191131 (0.02)
Female	Yes	48/117714 (0.04)	31/172042 (0.02)	22/163748 (0.01)	21/164478 (0.01)	122/617982 (0.02)
	No	11/34252 (0.03)	5/41068 (0.01)	6/49826 (0.01)	11/46605 (0.02)	33/171751 (0.02)
Male and Female	Yes	90/240927 (0.04)	84/349907 (0.02)	45/332059 (0.01)	58/332509 (0.02)	277/1255402 (0.02)
	No	25/76920 (0.03)	11/92524 (0.01)	13/98371 (0.01)	27/95067 (0.03)	76/362882 (0.02)

Table 4.2.7

Prevalence of all leukemias by sex, contamination of the territory and age at diagnosis (number of cases/number of inhabitants)

Gender	Contamination of the territory	Age at diagnosis, years				Total
		1–4	5–9	10–14	15–19	
Male	Yes	100/123213 (0.08)	110/177865 (0.06)	71/168311 (0.04)	66/168031 (0.04)	347/637420 (0.05)
	No	32/42668 (0.07)	19/51456 (0.04)	17/48545 (0.04)	19/48462 (0.04)	87/191131 (0.05)
Female	Yes	97/117714 (0.08)	77/172042 (0.04)	57/163748 (0.03)	52/164478 (0.03)	283/617982 (0.05)
	No	27/34252 (0.08)	16/41068 (0.04)	13/49826 (0.03)	17/46605 (0.04)	73/171751 (0.04)
Male and Female	Yes	197/240927 (0.08)	187/349907 (0.05)	128/332059 (0.04)	118/332509 (0.04)	630/1255402 (0.05)
	No	59/76920 (0.08)	35/92524 (0.04)	30/98371 (0.03)	36/95067 (0.04)	160/362882 (0.04)

PR of ML was the most low (0.01) (Table 4.2.5) and did not depend of age and region of inhabitance.

PR of UL (II) was the most high (0.03–0.04) in subgroups aged 1–4, in another subgroups fluctuated 0.01–0.03 in spite of gender and region of inhabitance (Table 4.2.6).

Third analysis found the most high PR (0.07–0.08) for all leukemias in the most young subgroup (1–4 y. o.) and more lower PR (0.03-0.06) in another subgroups. There were no significant connection between the territory status and gender.

Summarizing all mentioned above, we haven't revealed any differences linked to gender and territory status. It is necessary to emphasize that prevalence level was the most high in children

aged 1–4 and decreased across the age towards the group 15–19 y. o., especially for AL, LL, and all leukemias.

Our study has also some limitations. No individual doses were available for childhood leukemia cases, so cases were combined into exposed and non-exposed groups, and therefore final estimation of how the low-dose exposure is linked to childhood leukemia risks is a subject of future analysis. Also, limitations were the results of insufficient number of cases necessary for analyses and peculiarities of childhood leukemia types (low number of CL and ML). So, all the mentioned above confirmed the necessity of further investigation of childhood leukemia after the Chornobyl accident.

Chapter 5
SOLID CANCERS

5.1. THYROID CANCER IN UKRAINE DURING 1986–2014

Thyroid malignancies are relatively rare worldwide, yet their incidence has increased over the last few decades [1, 2]. Epidemiology of thyroid cancer in the population of Ukraine exposed to radiation as a result of accident at the Chornobyl Nuclear Power Plant in April, 1986 is of a particular interest. Although the relationship between the Chornobyl radiation and increasing incidence of thyroid cancer among exposed children and adolescents in Belarus, Russia, and Ukraine is established in a number of studies and is the main proven health consequence of the accident [3, 4], a continued monitoring and analysis of temporal trends of this disease have important medical and scientific impacts [5–7].

The purpose of this Chapter is to overview data on thyroid cancer incidence for the period from 1986 to 2014 in specific groups of population of Ukraine exposed in childhood or adolescence and also prenatally (in utero). In addition, the group of subjects born after the accident is included in the study because it provides important information on thyroid cancer incidence in the population of Ukraine which had not experienced Chornobyl fallouts.

A tool for recording and storage of data on the incidence of any cancer are population-based registries [8–11]; information can be used for subsequent analysis of morbidity and mortality in certain age groups and geographical areas. Domestic sources of data on thyroid cancer incidence in Ukraine are the site-specific Clinico-morphological Registry (CMR) of the State Institution «VP Komisarenko Institute of Endocrinology and Metabolism of the National Academy of Medical Sciences of Ukraine» (IEM) [12], and a classic cancer registry, which keeps records on all types of cancer, The National Cancer Registry of Ukraine (NCR) of the National Cancer Institute of the Ukraine Ministry of Public Health [13, 14].

Specialized Clinico-morphological and National Cancer Registries of Ukraine

In the first half of the 1980-ies there were no personalized records of thyroid cancer cases in Ukraine [15]. Statistical summary of thyroid cancer could be derived from the archives of hospitals or from the reports of regional endocrinology services. After the Chornobyl accident in 1986, the Ministry of Public Health of USSR recommended to establish personalized registries of affected population and to improve recording system of patients with thyroid diseases which

were anticipated to be one of the possible health effects of the Chornobyl accident [16, 17]. In Ukraine, the collection of data on thyroid cancer incidence was coordinated by the Institute of Endocrinology and Metabolism (IEM) with participation of regional endocrinology services.

In 1992, a personalized Clinico-morphological Registry was established at the IEM for the first time in Ukraine, into which all cases of thyroid cancer in patients whose age at the time of accident did not exceed 18 years (i.e., born in 1968 and later) were entered. Creation of the Registry was promoted by the initiative of the Ukraine Ministry of Public Health in the Order No. 12 dated January 20, 1992 «On the improvement of endocrinological care to children and adults with thyroid diseases» in which the need for an increased attention to thyroid disorders after the Chornobyl accident and compulsory referral of children and adolescents with such diseases for surgical treatment to the Clinic of the IEM was formally stated. In addition, regional and municipal endocrinology and oncology clinics were imposed to collect and report complete information about thyroid cancer cases in corresponding age group to IEM, and to provide histological slides of tumors for additional expertise of the quality of pathomorphological diagnosis. Thus, IEM managed to collect the necessary data for comprehensive registry functioning.

In the post-Chornobyl period, the CMR has been continuously providing statistics on the number of cases and incidence of thyroid cancer among children and adolescents to the Ministry of Public Health and Academy of Medical Sciences of Ukraine, and also served as a source of data for a number of analytical studies on thyroid cancer incidence and assessment of radiation risks of thyroid cancer in the younger age groups of Ukraine [3, 5, 6, 12].

Statistical records of thyroid cancer as of a separate entity in the structure of oncological services of Ukraine were started in 1989 [14, 18]. At the same time, the Institute of Oncology of the Academy of Medical Sciences of Ukraine launched an automated National Cancer Registry (NCR) that covered all regions of Ukraine. NCR was based on a network of specialized cancer institutions and a State system of cancer registration. Practical realization and implementation of the information system in oncology at the regional level began in mid-90-ies receiving the government support according to the Order of the Ukraine Ministry of Public Health «On the establishment of a National Cancer Registry of Ukraine» dated December 30, 1996 [14]. In 2001, the creation of the system was completed by including all regions of Ukraine in the Registry [13, 14].

A close cooperation between the CMR and NCR began in 2005. Today, the CMR is in some way a part of NCR [19–21]. Note however, that cross-check of the registries reveals some differences. The CMR is a specialized Clinico-morphological Registry that includes particular age group (at high risk for developing thyroid cancer) and only operated cases with pathologically confirmed diagnosis. In contrast, besides the CMR records, National Cancer Registry also includes cases that had not been operated with only preoperative cytological conclusion about the possibility of thyroid cancer available. Moreover, the calculation of cases at the regional level in the CMR is based on the patient's place of residence at the time of Chornobyl accident, while the NCR system is based on the patient's place of residence at surgery. In other words, these differences should always be taken into account when comparing the two data Registries or analyzing the incidence according to the data of one or another registry.

Pathological verification of diagnosis is essential for the case to be included in the CMR. The detailed pathological report including tumor type, subtype, invasive properties and tumor size is mandatory for cases operated at the Department of Surgery of Endocrine Glands of the IEM, and for the material (paraffin blocks, histological specimens) from patients operated elsewhere in Ukraine but receiving radioactive iodine therapy at the Department of Clinical Radiology of the IEM [22].

Sources of information for the CMR are currently the reports of regional endocrinology services, data of regional oncological institutions (via the NCR of Ukraine), and clinical medical information system (MIS) of the IEM (www.therdep.com.ua). The principles of inclusion and recording of personal data coming from different sources correspond to the classical rules and procedures of cancer registries [23–25]. Automated procedures and control of completeness and quality of personal data play an important role [26].

Software realization of Clinico-morphological Registry

Entering and storage of Registry data is implemented using MS SQL Server software. This
➢ ensures data integrity;
➢ allows the use of a standard relational model for designing data structures and typical SQL for queries;
➢ provides a reliable import/export of data from most databases;
➢ allows performing application tasks using typical software tools (MS Access, Delphi, C + +, *. net , etc.).

The upgraded structure of registry databases provides some additional features:
➢ supports both Ukrainian and Russian versions of patient's surname and first name;
➢ implements a mechanism of saving changes or multiple patient's attributes' values (e.g. name, location, diagnosis);
➢ formalizes the place of residence according to the standard administrative territorial codifier «KOATO».

In addition, links have been established with databases with the geographical component at the regional, district and settlement level (MapInfo format), which extend the capabilities of data analysis and allow building various thematic maps. Today, the logical structure of the Registry includes three functional components: CaseRegist, CaseManager, and CaseReport.
➢ CaseRegist is a module of primary registration of data reported by the regional endocrinologists and IEM patients.
➢ CaseManager is a module of analysis, linkage, and verification of the Registry information. With this component, a comparative analysis of information from multiple sources is conducted including the search for and removal of duplicate records. A verified analytical version of the Registry record is generated that remains active for the year. A list of problematic cases to be verified by an expert morphologist and/or refined through queries to regional services could be created. The module also stores archives of the versions of analytical tables of the Registry from previous years; information about changes or refining of certain attributes of patients to be included in the next version of the Registry is accumulated.
➢ CaseReport component contains the current version of analytical tables of the Registry and a set of typical queries to generate standard numerical tables, charts and graphs that describe the available data for particular time and can be used for the preparation of reports, presentations, and publications.

The demographic component of the Clinico-morphological Registry

The demographic component of the Registry is based on a series of periodic publications of the State Statistics Committee of Ukraine; publications of regional statistics departments may be also involved detailing certain parameters for a specific region.

Census data represent the most reliable and detailed source of information on Ukraine population. Our study period (from 1986 to 2014) includes two censuses: Ukrainian SSR census of 1989 and the All-Ukrainian census of 2001 [27, 28].

Primary sources of demographic data also include publications on the distribution of population by age and sex [28–33], the number of current and permanent population of Ukraine at the regional level, and annual demographic data records.

General statistical collections and the official website of the State Statistics Committee (www.ukrstat.gov.ua) [34] may also be used as sources of current demographic information.

The demographic component of the Registry includes data on the population of Ukraine for the period 1986 to 2014, and the following age groups are selected for monitoring:

➢ children under 14 years old (born before 1987);
➢ children under 14 years old (born in 1987 or later);
➢ adolescents aged 15 to 18 years (born before 1987);
➢ adolescents aged 15 to 18 years (born in 1987 or later);
➢ adults aged over 19 years (born before 1987, beginning from 1968);
➢ adults aged over 19 years (born in 1987 or later);
➢ «in utero» cohort (born from April 27 to December 31, 1986).

Population observed in the Registry (i.e., population groups for which cases are registered) is growing from year to year: while for the first year of study (1986) it was slightly less than 14 million people, in 2014 it includes over 27 million subjects.

The demographic base of the Registry by attained age and ratio between exposed and unexposed subjects varies from year to year. The proportion of children and adolescents is monotonically decreasing (only that of born after Chornobyl remain practically unchanged), while the proportion of adults in the Registry is increasing (including those born both before and after Chornobyl).

The demographic base of the Registry allows assessing:

➢ annual dynamics of the age group from 0 to 14 years (born before and after Chornobyl separately);
➢ annual dynamics of the age group 15 to 18 years (born before and after Chornobyl separately);
➢ annual dynamics of the age group over 19 years who were aged from 0 to 18 years at the time of the accident or born after Chornobyl;
➢ annual dynamics in the «In utero» cohort.

Since the size of groups in each region and in the whole of Ukraine is known, it is possible to make arbitrary combinations of regions and to compare the indices for the regions with the Ukraine as a whole.

To calculate the incidence, the most adequate determination of the number of person-years in a given cohort for a particular year is to use the average population size. It should be taken into account that we are not dealing with an exact number but with estimates characterized by some uncertainty. Some worsening of the quality of demographic estimates by the end of the study period (1986–2014) could be expected due to postponement of the next census of Ukraine to 2020. A very informative overview of the problems of quality of demographic data, uncertainties in population parameters, and possible problems of their interpretation, was published in [35].

Methodology of descriptive analysis of the incidence

Current analysis of thyroid cancer incidence in younger age groups of the population of Ukraine represents methodologically, in general, a continuation of a series of previous publications [36-42]. By age at the time of accident and conditions of exposure, the study subjects are divided into the following three groups:

➢ exposed as children aged 0–14 years at the time of accident (0–14 AE);
➢ exposed as adolescents , aged 15–18 years at the time of accident (15–18 AE);
➢ exposed in utero, born in May–December 1986 (EIU).

The first group (0–14 AE) is the largest and includes about 11.1 million subjects; the second group (15–18 AE) about 2.2 million persons, and the size of the cohort exposed prenatally is estimated to be about 0.52 million. It should be noted that, according to the conditions of CMR establishment, registered population includes those born beginning from December 1, 1968, i.e. actually the second group includes the subjects aged from 15 to 18.32 years at exposure (the population aged 18.32–18.99 belongs to the age cohort born in 1967).

Subdivision of population into these three groups – besides general medical considerations – has dosimetric rationale as well. Radiation doses to the thyroid have strong age dependency [43–47]. Under similar radioecological conditions, the maximal radiation dose is received by the population of younger age. For regional estimates of mean radiation dose [43], the relative exposure dose (normalized to the dose in adults) for children aged one year is 4.5–6; for children aged 5 years – 3–4; for children aged 10 years – 1.7–2; and for children aged 14 – about 1.5.

Similar age relationships are also inherent to risk coefficients (ERRD, EARD) of developing radiogenic cancer per exposure unit [4,48]. These patterns, taken together, indicate the highest expected radiogenic effects in the younger age groups of 0–4 years old and 5–9 years old compared with those aged 10 years and older.

Effects of thyroid exposure in utero are markedly different from those of postnatal irradiation, and information on risks is very limited [4, 49, 50].

The group born from 1987 was also used in later analyses as a control because it was not exposed to Chornobyl fallout and therefore does not include Chornobyl radiogenic cancers.

For the analysis by age at diagnosis, cases are subdivided into those diagnosed in children (aged 0–14 years at diagnosis), adolescents (aged 15–18 years at diagnosis), and adults (aged $\geq$ 19 years at diagnosis). Such subdivision is traditional for oncoepidemiology that recons childhood cancers a particular category [51, 52]. A relatively new trend is to consider the group of adolescents and young adults (AYA) as patients requiring specific, tailored diagnostic procedures and streamlined procedures for cancer treatment [52–54].

Current analysis used a partition of 28 regions of Ukraine into two groups according to the level of thyroid exposure in children and adolescents [45,46]:

➢ 6 most contaminated regions (Zhytomyr, Kyiv, Rivne, Chernihiv, Cherkasy regions and Kyiv City; average thyroid exposure dose in the group 0–18 years at the time of the accident >35 mGy);
➢ 21 regions with relatively lower levels of contamination (average thyroid exposure dose in the group 0-18 years <35 mGy).

Childhood and adolescent population of 6 most contaminated regions accounted for 19–21% of the total population of corresponding age of Ukraine (Tables 5.1.1 and 5.1.2). It should be stressed that Zhytomyr, Kyiv, and Chernihiv regions are located at a distance up to 200 km from Chornobyl Nuclear Power Plant; the residents of northern areas of these regions received the highest thyroid doses [3, 55].

In this work, the period of study is 1986–2014 (preliminary results of 2014 not include data for Luhansk oblast and Sevastopol city). In the analysis of time trends, the two-year intervals are used. Also, periods under comparison are subdivided into six intervals: 1986–1989 – the period shorter than the minimal duration of latency of radiation-induced thyroid cancer [4, 48] when only sporadic thyroid cancers were diagnosed, and five subsequent intervals (1990–1994, 1995–1999, 2000–2004, 2005–2009, 2010–2014) when both sporadic and radiogenic thyroid cancers are diagnosed in the population.

Table 5.1.1

Thyroid cancer cases in selected groups of Ukrainian population in 1986–2014 (by periods of diagnosis)

	Population[a] million	1986–1989	1990–1994	1995–1999	2000–2004	2005–2009	2010–2014	1986–2014
0–14 years at exposure	11.1	59	386	830	1227	2028	3476	8006
6 regions	2.2	15	191	383	577	819	1302	3287
21 regions	8.9	44	195	447	650	1209	2174	4719
15–18 years at exposure	2.2	45	164	290	413	599	890	2401
6 regions	0.4	9	42	88	155	226	292	812
21 regions	1.8	36	122	202	258	373	598	1589
Subjects exposed in utero	0.5	0	3	5	26	56	112	202
6 regions	0.1	0	1	2	9	25	29	66
21 regions	0.4	0	2	3	17	31	83	136
Subjects born in 1987 and later	14.0[b]	0	0	12	104	292	878	1286
6 regions	2.9[b]	0	0	3	32	94	297	426
21 regions	11.1[b]	0	0	9	72	198	581	860
Total cases		104	553	1137	1770	2975	5356	11895

Notes. [a] – exposed population on 1 January 1987; [b] – estimation of unexposed population on 1 January 2015.

Table 5.1.2

Thyroid cancer cases in selected groups of Ukrainian population in 1986–2014 (by age at surgery)

	Population[a] million	Age at surgery			Total
		0–14 years	15–18 years	19+ years	
0–14 years at exposure	11.1	454	502	7050	8006
6 regions	2.2	276	246	2765	3287
21 regions	8.9	178	256	4285	4719
15–18 years at exposure	2.2	-	31	2370	2401
6 regions	0.4	-	5	807	812
21 regions	1.8	-	26	1563	1589
Subjects exposed in utero	0.5	13	27	162	202
6 regions	0.1	5	11	50	66
21 regions	0.4	8	16	112	136
Subjects born in 1987 and later	14.0[b]	256	339	691	1286
6 regions	2.9[b]	91	124	211	426
21 regions	11.1[b]	165	215	480	860
Total cases		723	899	10273	11895

Notes. [a] – exposed population on 1 January 1987; [b] – estimation of unexposed population on 1 January 2015.

Analysis of thyroid cancer incidence in 1986–2014 according to the data of Clinico-morphological Registry

Tables 5.1.1 and 5.1.2 summarize data on thyroid cancer in the defined groups, and show population size in the 6 and 21 regions. Table 5.1.1 shows the number of cases for the six study periods. Table 5.1.2 shows the distribution of cases by age at diagnosis, depicting cancers diagnosed in childhood, adolescence, and adulthood.

Thus, the current analysis involves 10,609 cases in the exposed population, including 8,006 exposed as children, 2,401 cases in irradiated adolescents, and 202 cases of prenatal exposure. In subjects born after Chornobyl, i.e. in the unexposed population, 1286 cases were diagnosed.

Data analysis for the groups by age at exposure takes into account that in each calendar year we are dealing with a virtual cohort with fixed characteristics of exposure that lived certain period after exposure. Thus, for a selected population group, over time, from year to year, the parameters of attained age change (increase) (minimum, maximum, median), as well as does the time after exposure. Attained age significantly affects the sporadic and radiogenic risks; time elapsed after exposure can also be an important parameter for calculating radiogenic risk. The attained age and time after exposure uniquely determine the age at exposure.

Detailed data on thyroid cancer cases and trends in the incidence among those exposed as children are shown in Figure 5.1.1. During the study period (1986–2014) in this group, the age varied from 0 to 14 years old in 1986 to 28–42 years old in 2014. Population size of this group was estimated to be 11.1 million persons at the beginning of 1987. This group showed the maximal number of cases (8,006) with about 41% of these (3,287 cases) registered in the 6 most contaminated regions. A significant increase in the incidence was observed in the first postlatent period (1990–1994) and continued until the end of the study (2014). Ascending trends are common to all four groups represented in Fig. 3.1 (males in six regions, females in six regions, males in 21 regions, females in 21 regions), although the growth rate and incidences are different for each group. For the low-dose regions, the increasing incidence is largely determined by the attained age; in the high-dose regions, there is an additional influence of radiogenic component and of the factor of intensive screening. The maximal incidence is expectedly observed in females from 6 contaminated areas (about 20 cases per 100,000 person-years). Incidence rates in the most contaminated areas are significantly higher than those in low-contaminated regions, although their ratio tends to be lower.

Rates in individuals exposed in adolescence are presented in Figure 5.1.2. The population size of this group was 2.2 million. In 2014, the age of this group reached 43–46 years old. The cumulative number of cases is 2,401, of which 812 (34%) were diagnosed in 6 regions with maximal thyroid doses. The main trends of incidence for males and females, in general, are similar to those in exposed during childhood. Due to differences in median attained age (about 9 years), the absolute values of the incidence for all four categories (males in six regions, females in six regions, males in 21 regions, and females in 21 regions) are somewhat higher than the corresponding values in exposed at childhood age. The incidence in females from 6 most contaminated regions reached 21-22 cases per 100,000 person-years at the end of the study period.

Figure 5.1.3 demonstrates incidence trends for those exposed at the age from 0 to 18 years old for different periods of study. Areas with the highest incidence (Kyiv, Chernihiv, Zhytomyr, and Kyiv-City) are located around the Chornobyl Nuclear Power Plant. Of note, there was a pronounced increase in the incidence in this group in low-contaminated regions during the last time period (2006–2014). Figure 5.1.4 presents ranked values of cumulative incidence [56] for those exposed at the age 0–18 years in postlatent period (1990–2014). High-dose regions,

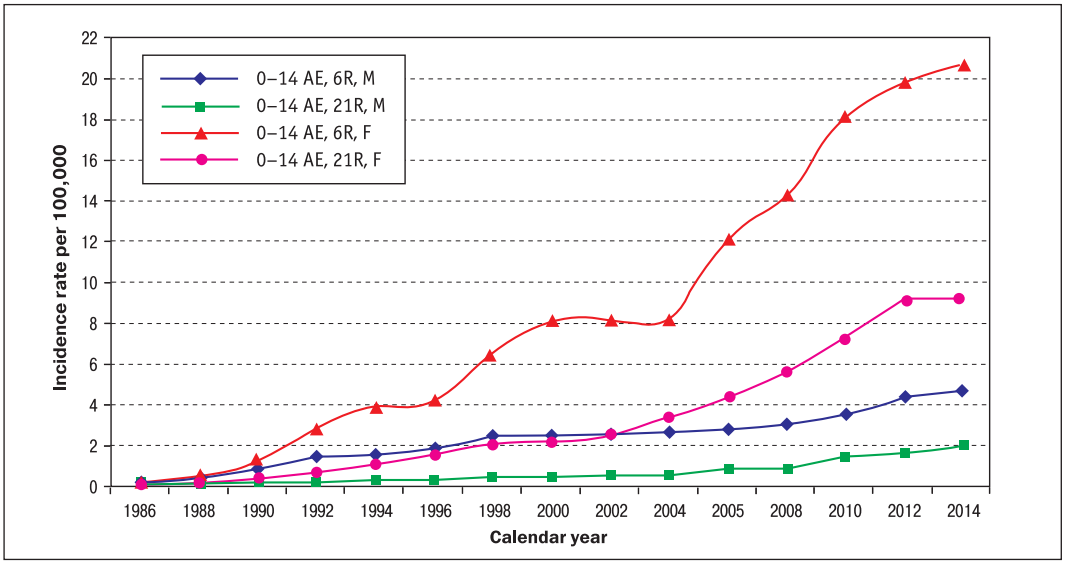


Figure 5.1.1. Time trends of thyroid cancer incidence in 6 and 21 regions of Ukraine for cohort aged 0–14 years at exposure. AE – age at exposure; 6R – 6 northern regions; 21R – other 21 regions; F – female; M – male.

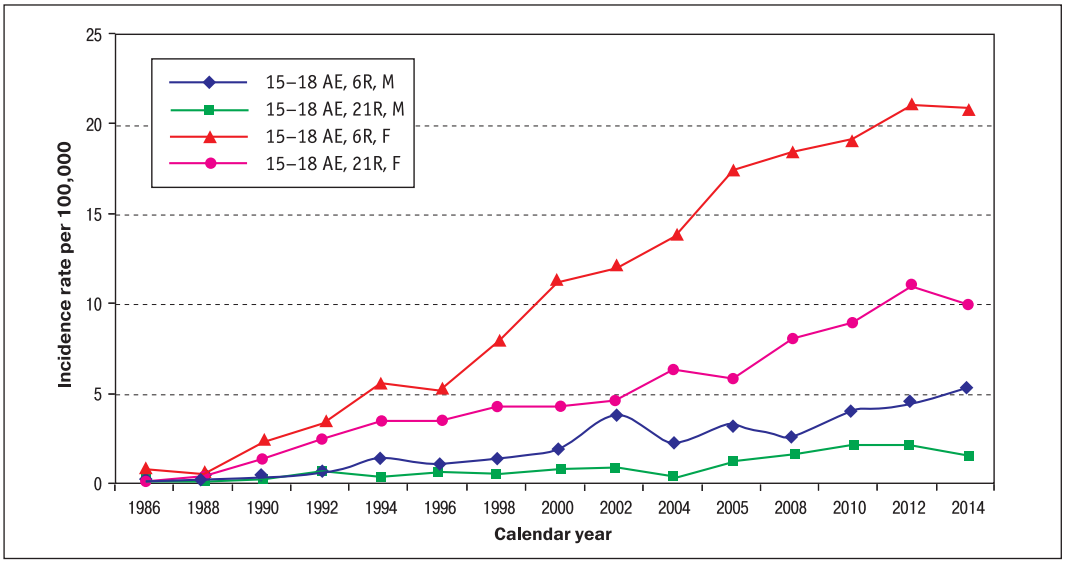


Figure 5.1.2. Time trends of thyroid cancer incidence in 6 and 21 regions of Ukraine for cohort aged 15–18 years at exposure. AE – age at exposure; 6R – 6 northern regions; 21R – other 21 regions; F – female; M – male.

except for Rivne, demonstrate a value above the average for Ukraine. Also, an increased incidence was noted in Kherson and Vinnytsia regions. It should be mentioned that a number of studies [57–60] found Polissia (Rivne, Volyn, Zhytomyr regions) to be an area with low incidence of sporadic thyroid cancer. The contribution of radiogenic cancers led to the increase in

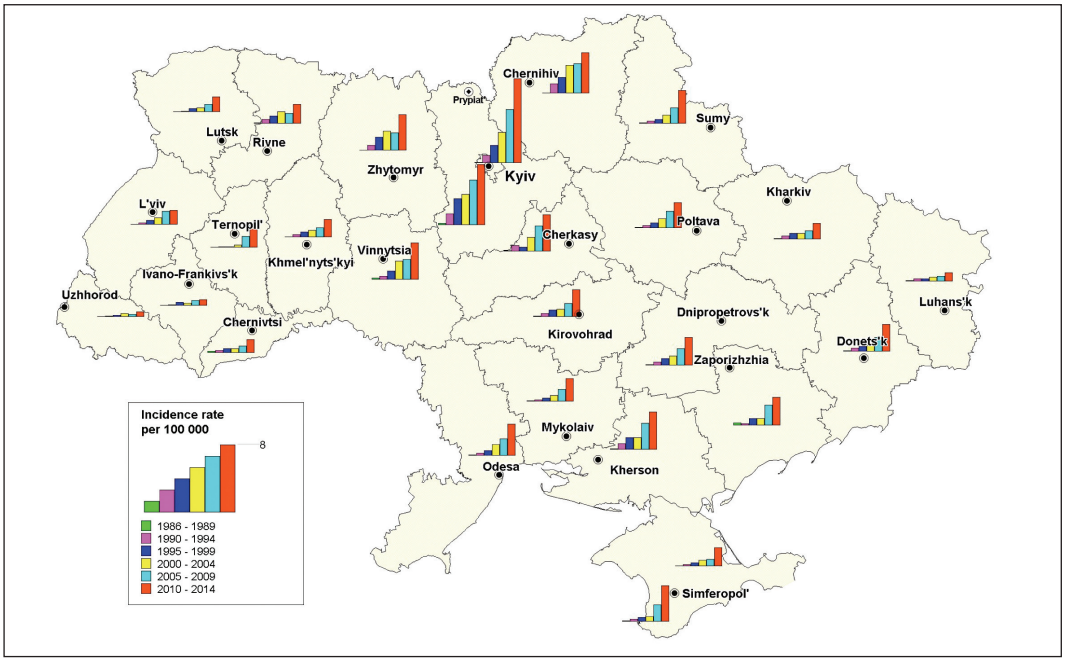


Figure 5.1.3. Region (oblast) specific time trends of thyroid cancer incidence in the cohort aged 0-18 years at exposure, both sexes.

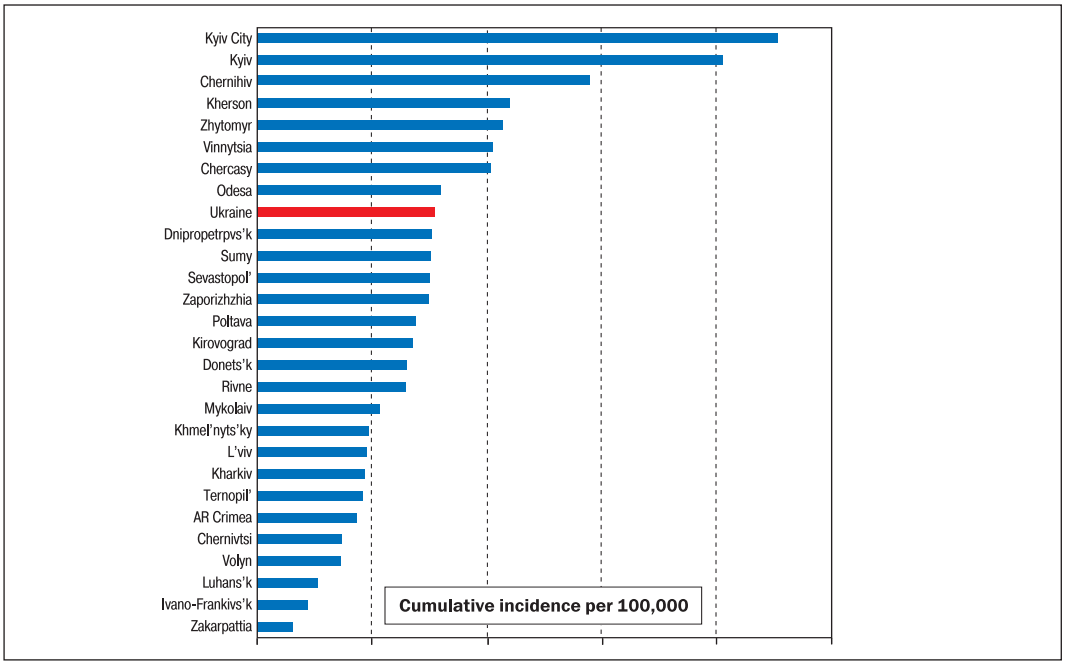


Figure 5.1.4. Ranking plot of region (oblast) specific cumulative incidence x 100 000 in 1990–2014 for the cohort aged 0–18 years at exposure, both sexes.

incidence in this region, but the values were found to be slightly below the average for Ukraine (Rivne region) or below the extreme values for Kyiv and Chernihiv regions (Zhytomyr region). The increased incidence in the industrial regions of Ukraine (Kherson, Odesa and Dnipropetrovsk) was mostly observed in 2000–2014, and does not seem to be associated with radiation factor.

An estimate of the proportion of cases due to radiation among the total number of cases in the study population is of particular interest. Since thyroid cancers induced by radiation do not have definite markers and cannot be isolated from the whole group, the estimate can only be obtained within a particular statistical model describing the dynamics of the disease depending on exposure doses (risk assessment model). So, the proportion of radiogenic cancers for the Ukrainian population aged from 0 to 18 years at the time of accident and for the study period 1990–1997 was estimated to be 30% [57]. A comparative analysis at the level of regions of the country for the period of 1990–2001 resulted in an estimate of the proportion of thyroid cancers attributable to Chornobyl radiation of 30% for the whole population of Ukraine and about 50% for the residents of the 3 most contaminated areas (Kyiv, Zhytomyr, and Chernihiv regions) [60]. Similar analysis performed in the individual cohort study for the residents (at the time of accident) of the 8 radiation-contaminated areas adjacent to the Chornobyl Nuclear Power Plant, yielded an estimate of excess cancer cases diagnosed during 1998-2000 of about 80% [61], and for the cases operated in 2001–2007 from 50 to 60% [62].

For individuals exposed in utero, data are presented in Figure 5.1.5. The population size of this group was estimated to be 0.52 million people. The number of diagnosed cases is 202. For the purpose of easier interpretation of data, Figure 3.5 also shows incidence trends for the cohort exposed at the age of 0–4 years old, and for the cohort of unexposed subjects born in 1987–1989 which could be considered a rough estimate of sporadic thyroid cancer incidence.

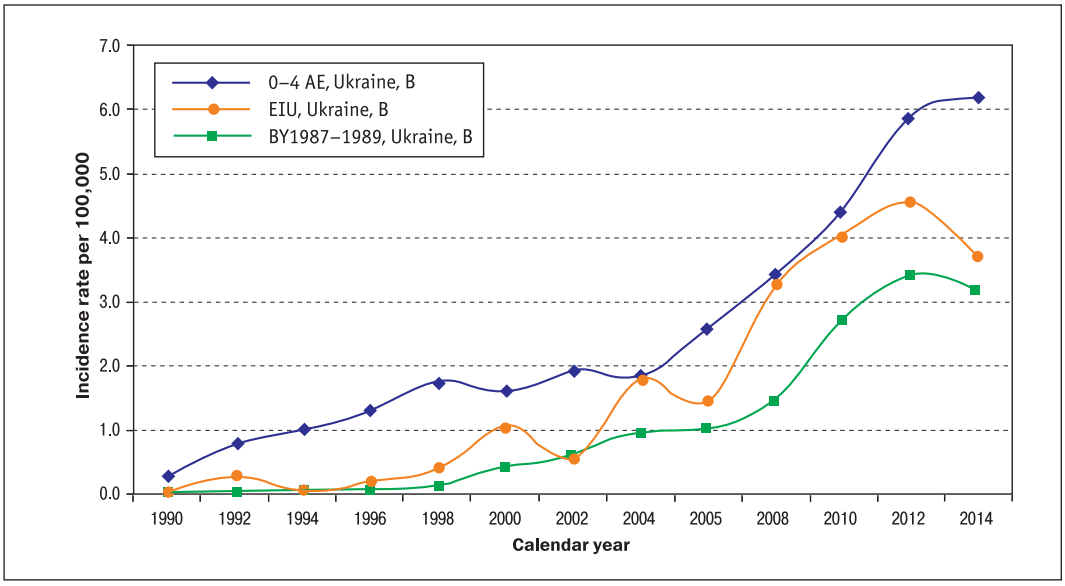


Figure 5.1.5. Thyroid cancer incidence in 3 birth cohorts, both sexes: aged 0-4 years at exposure (AE – age at exposure; Ukraine – whole Ukraine; B – both sexes); exposed «in utero» (EIU – exposed «in utero», Ukraine – whole Ukraine, B – both sexes); born in 1987-1989 (BY – year of birthday; Ukraine – whole Ukraine, B – both sexes).

The «in utero» group displayed an extremely low incidence for the period 1990–1999. During 2000–2014, however, the incidence increased sharply and reached values characteristic to the exposed subjects aged 0 to 4 years. If the increase in incidence in the «in utero» group was of radiogenic nature, it should be noted that the period of latency was substantially longer. Possible excess incidence for the «in utero» group was largely observed in the 6 contaminated regions where 66 cases were diagnosed (32%). Recently started, a study of radiation effects from in utero exposure is now actively carried out [49, 50] in the framework of prospective observations. Since the number of cases of thyroid cancer registered in these studies so far is very low (< 10), it would be promising to analyze the risks for this group in well-designed analytical ecologic or case-control studies using cases from the 6 contaminated areas.

Importantly, the interpretation of the number of cases and incidence in the groups defined by age at diagnosis (at surgery) should take into account that the composition of such groups changes from year to year as the cohorts become older. Both the size of the population and the proportion of exposed and unexposed subjects in the group are changing.

Figure 5.1.6 demonstrates the statistics of cases and incidence trends for the age group 0–14 years at diagnosis. The incidence in this group was approximately 0.1 case per 100,000 person-years of childhood population during the period of latency (1986–1989), and then displayed a sharp increase already noticeable in the early postlatent period (1990–1992). Incidence in females from the 6 most contaminated regions increased in 1992–1998 more than 20-fold as compared to the period of latency. The increased incidence in females and males from the 6 regions started to decline synchronously after 1998, with transition of the most exposed group (aged 0–4 years at the time of the accident) to older age categories.

Since 2001, this group does not include exposed subjects (even those potentially irradiated in utero) any more. Incidences in males from the 6 and 21 regions are not significantly different, while that in females from the 6 most contaminated regions is approximately 2-fold higher than

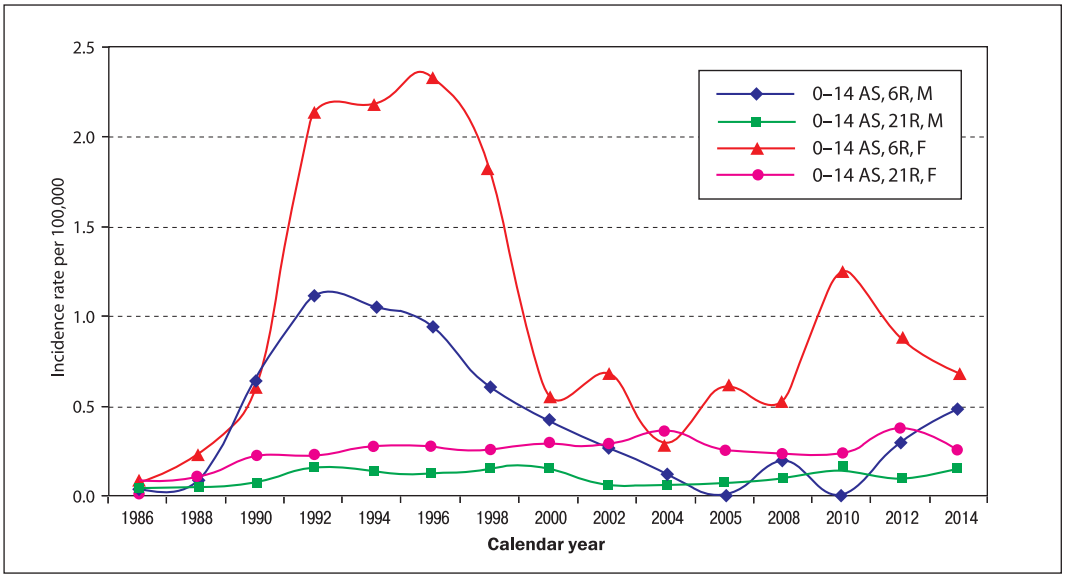


Figure 5.1.6. Time trends of thyroid cancer incidence among children aged 0–14 years at surgery. AS – age at surgery; 6R – 6 northern regions of Ukraine; 21R – other 21 regions of Ukraine; F – female; M – male.

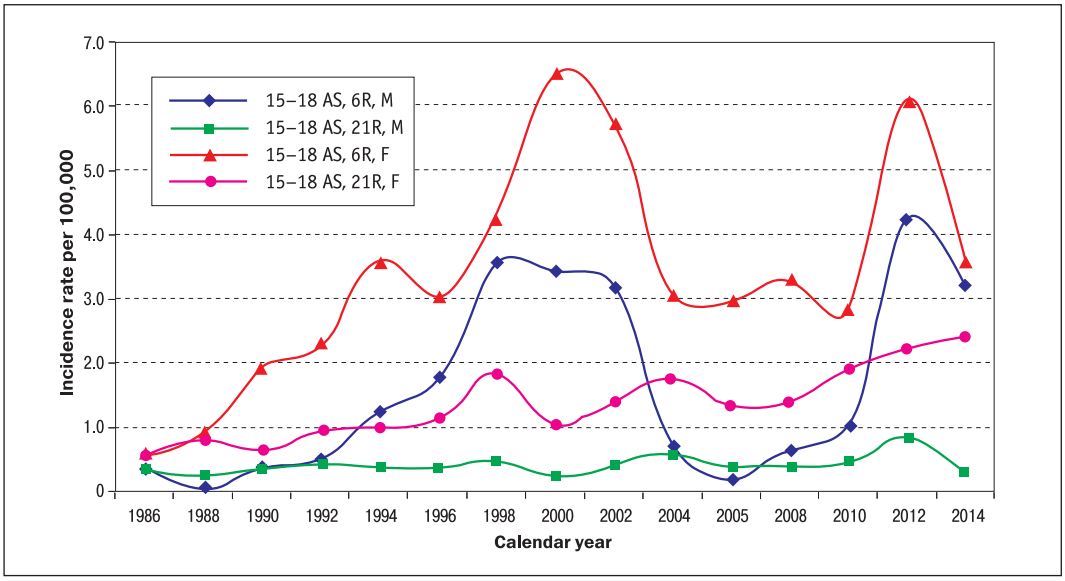


Figure 5.1.7. **Time trends of thyroid cancer incidence among adolescents aged 15–18 years at surgery. AS – age at surgery; 6R – 6 northern regions of Ukraine; 21R – rest 21 regions of Ukraine; F – female; M – male.**

in less contaminated regions. Incidence rate for the group aged 0–14 years is widely used in cancer statistics, and the observed values (0.2–0.4 cases per 100,000 person-years) for unexposed Ukrainian population can be compared with data from other countries and other registries. Such a comparison with the ranked data from 28 European countries [11] suggests that the incidence in Ukraine for the group 0–14 years in the period 2003–2014 was about the European average.

In the age group of 15–18 years old at diagnosis, the increasing incidence in the 6 high-dose regions was more gradual compared to the childhood group and reached maximal values both in females and males in 1998–2002 (Figure 5.1.7). Exposed population was not in the group since 2006, after which the incidence in males and females in the 6 and 21 regions became closer.

In the age group of 19+ years old at diagnosis, incidence trends were markedly different from the younger groups (Figure 5.1.8). This group has no upper age limit, and its size, median age, and age structure changes every year. Incidence rates in the four categories (males in 6 regions, females in 6 regions, males in 21 regions, females in 21 regions) show increasing trends. The maximal rates were observed in females from the 6 most contaminated regions, followed by that in females from 21 regions, then in males from the 6 regions and minimal one was in males from 21 regions. It should be noted that in the «adult cohort», the exposed and unexposed populations are «mixed» beginning from 2006.

As the next step, we consider in a descriptive analysis the birth cohort effect for exposed and unexposed populations by comparing the incidence trends in the three exposed cohorts (0–4, 5–9, and 10–14 years old at the time of exposure), and in the unexposed cohort (nearest by age to the exposed cohorts) born in 1987–1989. Time trends are considered separately for the 6 regions and 21 regions without subdivision by sex. The size of cohorts (0–4, 5–9, and 10–14 years old at exposure) were 0.75, 0.71 and 0.73 million for high-dose regions, respectively, and about 3 million in each age group for the 21 low-dose regions. The size of the unexposed cohort born in 1987–1989 for the whole of Ukraine was about 2.2 million.

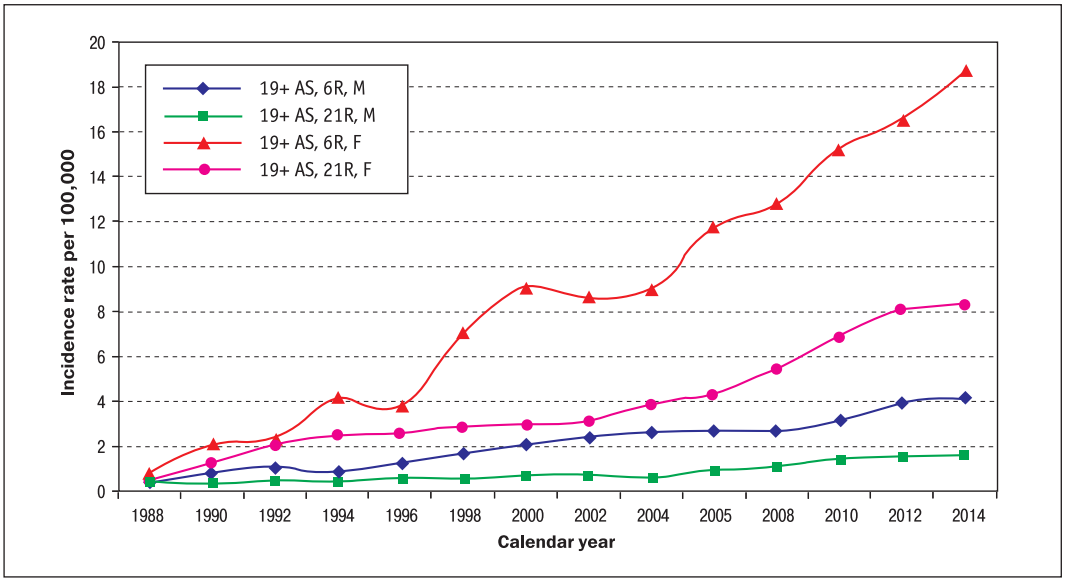


Figure 5.1.8. **Time trends of thyroid cancer incidence among adults aged 19+ years at surgery. AS – age at surgery; 6R – 6 northern regions of Ukraine; 21R – rest 21 regions of Ukraine; F – female; M – male.**

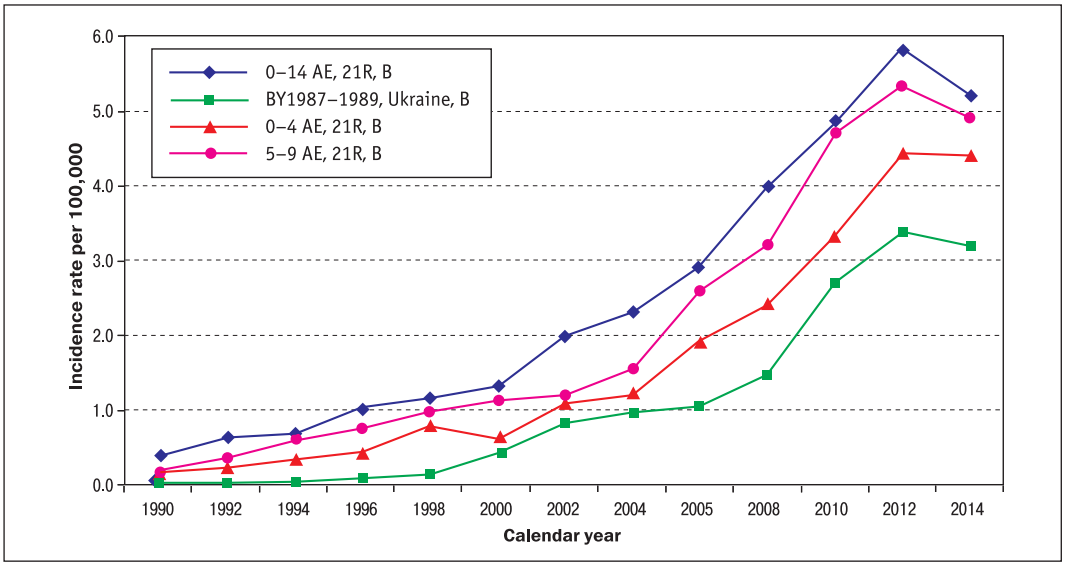


Figure 5.1.9. **Time trends of thyroid cancer incidence in 21 less contaminated regions of Ukraine among 3 exposed, and 1 unexposed birth cohorts. AE – age at exposure; 6R – 6 northern regions of Ukraine; B – both sex; BY – year of birthday; Ukraine – whole Ukraine.**

Figure 5.1.9 presents incidence trends in the postlatent period for these four cohorts in the 21 low-dose regions. At the beginning of the study period (1990–1992), the incidence in each cohort did not exceed 0.4 case per 100,000 person-years. In subsequent years, the cohorts showed a gradual growth of incidence, and at the end of the study incidence rates ranged from

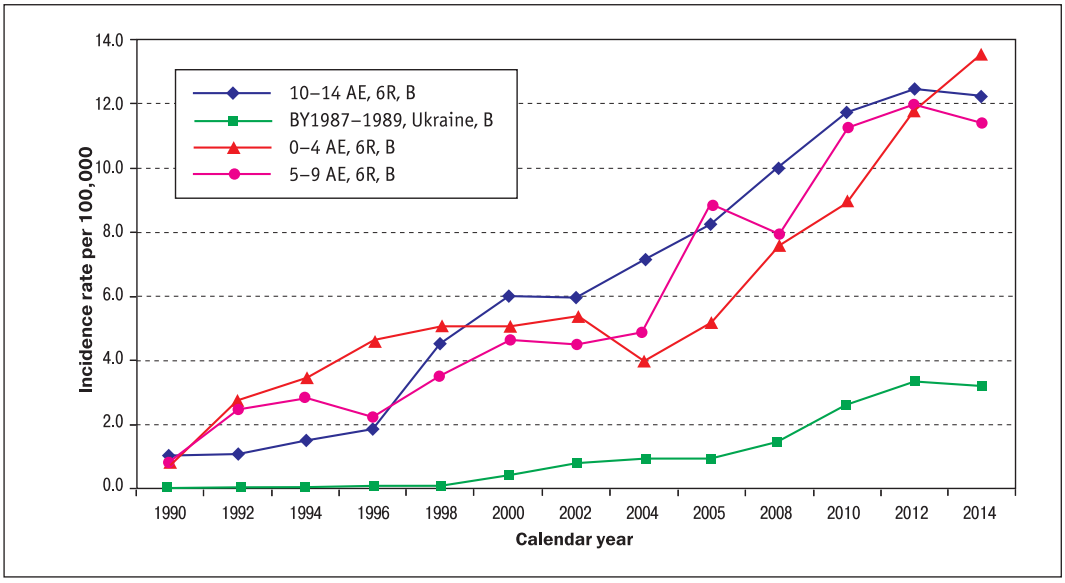


Figure 5.1.10. Time trends of thyroid cancer incidence in 6 northern regions of Ukraine among 3 exposed, and 1 unexposed birth cohorts. AE – age at exposure; 6R – 6 northern regions of Ukraine; B – both sexes; BY – birtnday year; Ukraine – whole Ukraine.

3.4 to 6.0 cases per 100,000 person-years. It is noteworthy that during the analyzed period of time the incidences displayed a strictly ordered character according to attained age. For each fixed period, the cohort born in 1987–1989 showed the lowest incidence; the next higher value of incidence was observed in the cohort aged 0-4 years at exposure (the difference in the attained age with the previous cohort was about 4 years); then in the cohort aged 5–9 years at exposure, and the maximal value was in the cohort of 10–14 years at exposure. The shapes of trends for all cohorts are similar and close to the exponential curves.

Figure 5.1.10 presents incidence trends in postlatent period for similar four cohorts in the 6 high-dose regions. The trend in the cohort of subjects born in 1987-1989 is the same as in Figure 5.1.9, and exponentially increases from 0 to 3.4 cases per 100,000 person-years. In the exposed cohorts, the sporadic incidence is supplemented by the radiogenic component and possibly by the factor of screening [58, 62, 63]. The trends in the exposed cohort are less «smooth», the values vary within the wide range (from 1 to 13.0 cases per 100,000 person-years) and do not show the «natural» ordering by attained age. Moreover, in the period of 1990–1998, the highest incidence was observed in the youngest cohort of 0–4 years old at exposure, which had accumulated maximal thyroid doses. From 1998 to 2006, the incidence in this cohort was almost stable: about 5 cases per 100,000 person-years, after which it continued to increase.

In the cohort aged 5–9 years old at exposure the incidence began to grow as rapidly as in the younger cohort in 1990, but until 2004 it was lower. The incidence in the older age group (10-14 years old at exposure) was slowly increasing until 1996, after which the growth accelerated and, beginning from 2000, it got a «natural» position with the highest incidence rate.

At the end of the study period (2012–2014), the rate ratios in the groups of 0–4, 5–9, and 10–14 years old at exposure for 21 regions to the cohort born in 1987–1989 were 1.3, 1.6, and 1.7 (Figure 5.1.9), respectively. The ratios for the 6 high-dose regions are remarkably higher: 3.5, 3.5, and 3.7, respectively.

Thyroid cancer incidence at the level of the whole population according to the data of National Cancer Registry

Finally, we will briefly discuss the incidence and mortality rates for the whole population of Ukraine in the period 2000–2014 according to the National Cancer Registry data [13]. During this period of time, the number of newly reported cases of thyroid cancer increased steadily from 2,093 (360 males and 1,733 females) cases in 2001 to 3,558 (571 males and 2,987 females) in 2013 (only preliminary data 2014 currently are available). The annual increase in the incidence was 112.7 cases; it was faster in females (96.5 cases) compared to 16.2 cases in males. The sex ratio (the ratio of the number of cases in females to the number of cases in males) was 4.7 on average for the period 2001-2014 ranging from 4.2 to 5.4.

Figures 5.1.11–5.1.12 represent the trends of thyroid cancer incidence and mortality due to thyroid cancer for the whole population of Ukraine for the period 2000–2014 according to the NCR [13]. During this period, the incidence showed an ascending trend both in females (from 6.5 to about 12 cases per 100,000) and males (from 1.9 to 2.9 cases per 100,000). At the same time, mortality rates vary within the ranges 0.9–1.2 per 100,000 in females and 0.5–0.6 in 100,000 in males with a tendency to a slow decrease. A similar relationship between the incidence and mortality is typical for the registries of other countries [1, 8, 9]. Such a ratio (declining trend of mortality and increasing incidence) reflects the fact that the increase in incidence is largely due to the growing number of curable well-differentiated tumors, and also due to improvements in the quality of diagnosis over time.

Age- and gender- specific incidence rates of thyroid cancer in the whole population of Ukraine in 2006 and 2010 pointed out in Figure 5.1.13. These figures show that the incidence of thyroid cancer as a function of age for both genders shows the minimum values in early childhood (0–9 years), has a period of rapid growth during the ages from 10 to 50–55 years with varying speed and magnitude for male and female. The maximum values of incidence are reg-

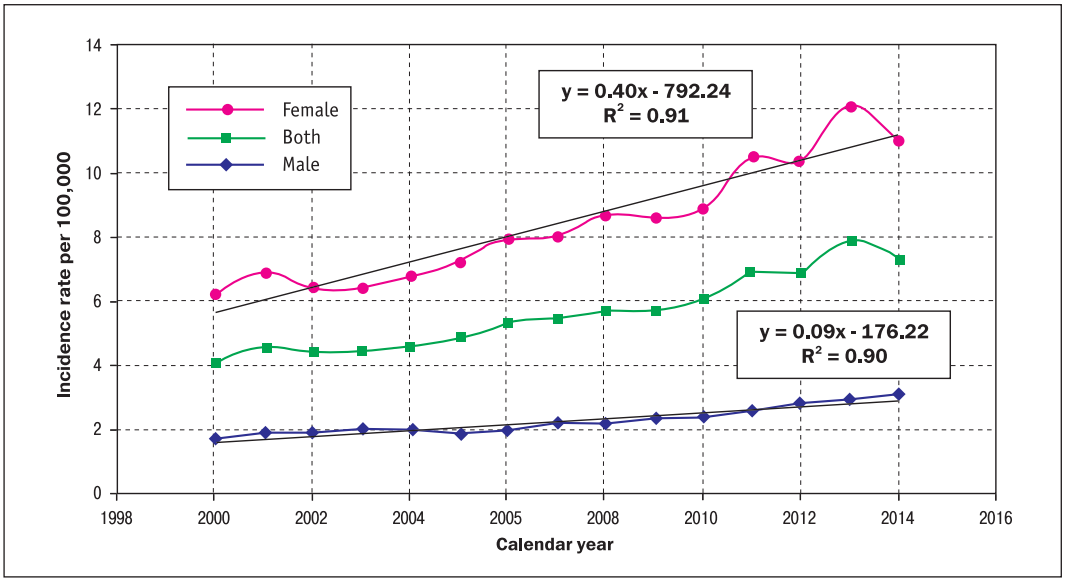


Figure 5.1.11. **Age-adjusted incidence rates of thyroid cancer per 100,000 general population of Ukraine in 2000–2014. Data from ref. [13].**

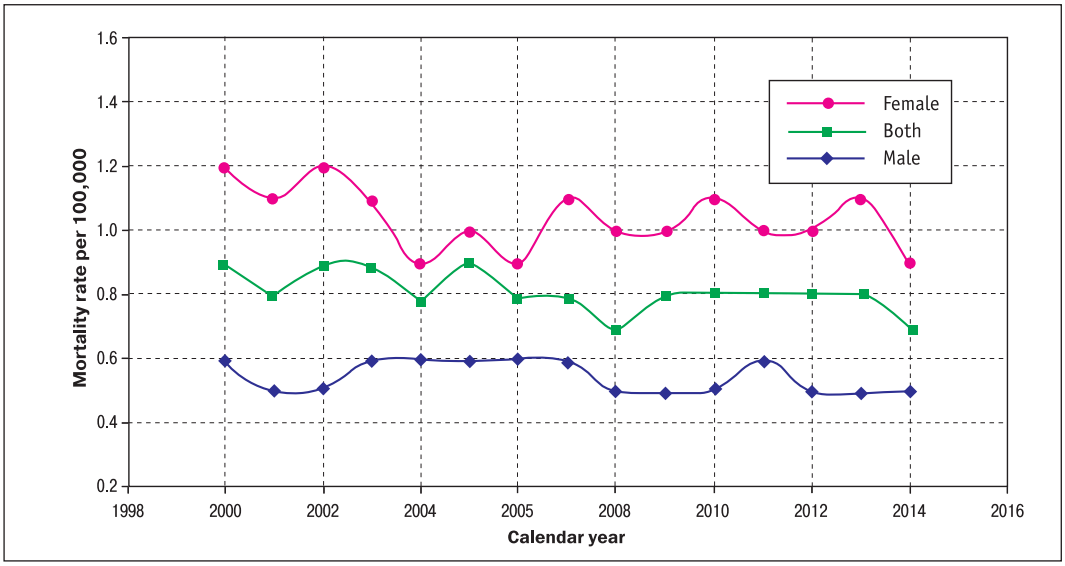


Figure 5.1.12. **Age-adjusted mortality rates of thyroid cancer per 100,000 general population of Ukraine in 2000–2014. Data from ref. [13].**

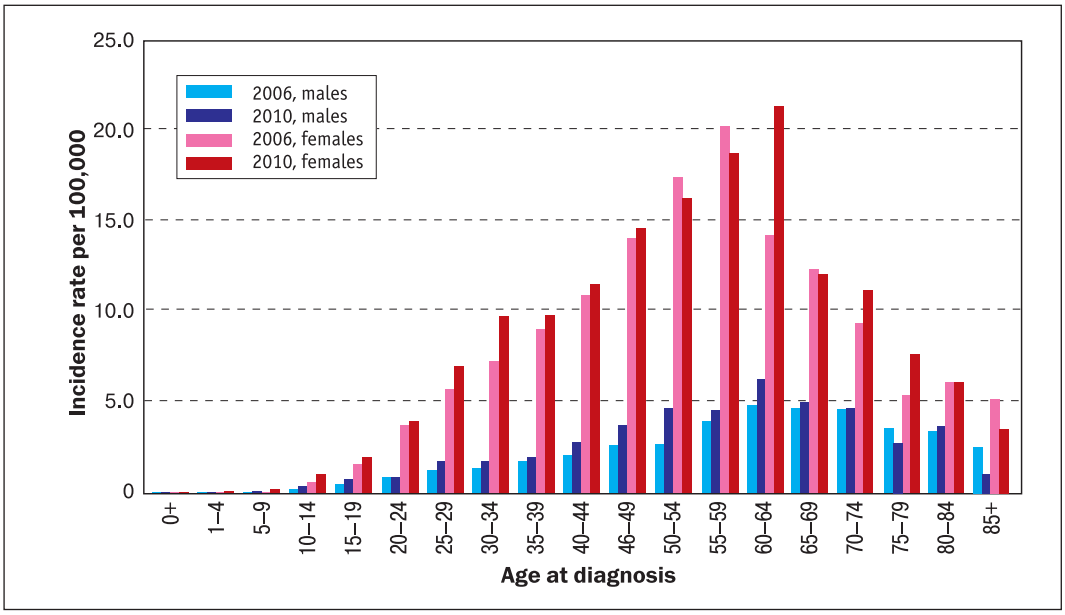


Figure 5.1.13. **Age- and gender-specific incidence rates of thyroid cancer per 100,000 general population of Ukraine in 2006 and 2010. Data from ref. [13].**

istered in the ages 55–65 years (4.5–6 cases and 19–22 cases per 100,000 population for male and female respectively). In older age groups (aged over 70 years), there was a decline in incidence. The dependence of the incidence from age and gender is important as for the interpretation of the observed incidence trends as well as the forecast of the expected values.

In summary, this chapter demonstrates that among the exposed population of children and adolescents (aged 0–18 years at the time of accident), there has been a significant increase in thyroid cancer incidence after the minimal period of latency; this tendency persists for the period of 24 years (1990–2014). At the same time, incidence rate in the 6 most contaminated regions exceeded that in 21 low-contaminated regions for all postlatent periods of study. However, in both high- and low-contaminated regions, incidence rate displays a descending tendency, perhaps indicating a gradual decrease in the contribution of radiation factor in the increased thyroid cancer incidence in the cohort aged 0-18 years at the time of Chornobyl accident. Among those exposed «in utero», a significant growth of incidence started after 15 years since accident and continued to grow during the further period.

By age at diagnosis, peak incidences in childhood and adolescent groups were observed in 1995–1997 and 2000–2002, respectively. Since 2002 there are no exposed subjects (including the «in utero» cohort) in the childhood group and since 2006 in the adolescent group. Thus, in these age categories all childhood and adolescent cases of radiogenic thyroid cancer have been realized. In the corresponding groups of unexposed subjects aged 0–14 and 15–18 years at the time of diagnosis, thyroid cancer incidence is comparable to the average rate in European countries.

Incidence of sporadic thyroid cancer markedly increases from the age of 25–30 years old; it may, therefore, be expected that the proportion of radiogenic cancers in Ukraine will decline, even in the regions with relatively high levels of radiation exposure. On the other hand, as shown in a recent study [65], a statistically significant contribution of radioinduced thyroid cancers developing after acute external irradiation can be observed even 50–60 years after exposure. This fact justifies the need for continuous monitoring and analysis of the incidence of thyroid cancer in the population groups exposed as a result of Chornobyl catastrophe.

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5.2. RESULTS OF 30 YEARS OF RESEARCH ON CANCER EFFECTS OF THE CHORNOBYL DISASTER IN UKRAINE IN NATIONAL AND INTERNATIONAL PROJECTS

Thirty years ago – on April 26, 1986 the world's largest radiation accident at the Chornobyl nuclear power plant happened. It caused great concern not only in scientists, the scope of which is focused on the study of negative medical and biologycal consequences of radiation exposure, but also in the international community as a whole. Since the first months after the accident considerable attention was paid to its possible health and especially cancer effects. A separate section approved by the government of the former USSR «Comprehensive environmental research program of the Chornobyl NPP in 1986–1990 years» was to study the incidence of malignant neoplasms in population of regions of Ukraine, Belarus and Russia that were most affected from radioactive contamination.

In Ukraine in 1987, as in Belarus and Russia, the State Register of persons affected by the Chornobyl disaster (SRU) was established, which operates to this day. It's main objective was the accumulation of personal information about the victims of the accident and their dose of exposure, registration diseases that were diagnosed during the annual clinical examination of the liquidators of the accident, people evacuated from the exclusion zone, residents of contaminated territories and children born in parents of these categories. The information was the basis for epidemiological studies. Further studies were carried out in the framework of the State program of elimination of consequences of the Chornobyl accident (1991–1992), State Programme on Medical and Biological Problems of the accident at Chornobyl (1993–1996), State Scientific and Technical Program «Protection of the gene pool of the population of Ukraine», program «Health of the Nation» (2010–2012), complex theme of the Ministry of Emergency situations (1996–1998), scientific research competition for the National Academy of Medical Sciences of Ukraine and others. The international scientific community has responded to the Chornobyl tragedy, initiating projects examining the environmental, medical and biological consequences of the accident. Considerable attention was paid to the study of epidemiology of malignant tumors

- in the framework of the international program of the Commission of the European Communities IPHECA, ECP-7: «Epidemiological studies, including evaluation and dose reconstruction»;
- in the framework of the French-German Chornobyl Initiative Project No.3: «Health Effects of the Chornobyl accident», sub-projects:
  - «The incidence of solid cancers in population of the most contaminated areas of Ukraine»
  - «Leukemia in Zhytomyr and Kyiv regions», «Leukemia in Chernihiv and Sumy regions»
  - «Thyroid cancer in adults and adolescents of Zhytomyr, Kyiv and Chernihiv regions»;
- in the project INCO-COPERNICUS:

«Cancer in population of new independent states after the Chornobyl accident».

Well-known foreign specialists, radiation epidemiologists: A. Kellerer, R. Pott-Born (Germany), M. Tirmarch, P. Verger (France), H. Storm (Denmark), E. Cardis (France) were involved in the guidance and execution of these projects.

Sasakawa Memorial Health Foundation provided financial and material support of the Chornobyl-Sasakawa project, which was mainly of practical orientation. 12 thousand cases of pathological changes of the thyroid gland were found in 64 thousand children that were surveyed. Prof. S. Yamashita, prof. K. Fujimura, prof. Y. Shibata, prof. M. Hoshi (Japan) participated in the project.

The main feature of these research projects is their narrative, descriptive character with some elements of environmental research. This situation was caused by the lack of domestic experience in conducting analytical studies and limited funds available for their implementation.

In the framework of Ukrainian-American cooperation:

➤ «The study on leukemia and related diseases in Chornobyl clean-up workers in Ukrine». Prominent American radiation epidemiologists G. W. Beebe, G. R. Howe, B. Wacholz, S. Finch were involved in the guidance and execution of this project.

➤ «The study of thyroid cancer in Chornobyl clean-up workers in Ukrine» This project, which continues to be performed today, involved famous epidemiologists K. Mabuchi, M. Hatch (USA). The latter two projects are of analytical nature with case-control design. Their implementation is based on the previous experience gained and financial support by the American side.

During this period, the following main research work was performed in scientific thems of the National Academy of Medical Sciences of Ukraine:

➤ «Epidemiological analysis of the incidence of malignant tumors in persons participated in the aftermath of the Chornobyl accident in 1986–1987, development forecasts for this disease and organizational measures to prevent» (term of execution 1996–1998);

➤ «To monitor malignant tumors in different groups of population affected by the Chornobyl accident (liquidators 1986–1987, evacuees), to analyze current trends, identify possible stochastic effects, and identify dependencies «dose-effect» (term of execusion 1999–2001);

➤ «Definition of stochastic oncology effects of radiation based on long-term monitoring of malignant tumors cases in the population living in the most contaminated areas of Ukraine» (term of execusion 2001–2003);

➤ «The results of mid-term stage of epidemiological monitoring on malignancies in key groups of population of Ukraine affected by the Chornobyl accident» (term of execusion 2004–2006).

➤ «Identify patterns of forming the incidence of malignant neoplasms in main groups affected by the Chornobyl accident, on long-term epidemiological monitoring stage» (term of execusion 2007–2009).

➤ «Identify patterns of formation of radiation associated cancer risk in the population affected by the Chornobyl disaster, the remote period after the emergency» (term of execusion 2010–2012).

➤ «To study the evolution of the incidence of malignant tumors in persons affected by Chornobyl catastrophe, the results of 25 years epidemiological monitoring» (term of execusion 2013–2015).

The above projects are dedicated to the study and analysis of dynamic models and the incidence of malignant tumors in general and by individual nosological forms in populations affected by the Chornobyl accident, for a long observation period that includes pre- and post-accident period. Most of them are of descriptive nature. Some of them have a cohort study design, others – «case-control». The study in adults focused on radiation risk in participants of the accident, or those with relatively high doses of radiation. Summary of the research are presented in Tables 5.2.1–5.2.4.

Table 5.2.1 summarizes conducted researches of origin of the Chornobyl radiation exposure to the risk of thyroid cancer in children and adults in the post-accident period. Most are descriptive ones and show the trends in the thyroid cancer incidence A small number have cohort study design, or «case-control» one. Along with the clear evidence of increased risk of thyroid cancer in children and adolescents who received radiation of the gland due to radioactive iodine, there are doubts as to adults. However, the study of certain groups of victims, especially liquidators of

Table 5.2.1
Results of researches of thyroid cancer risk in different age and gender groups of the population affected by the Chornobyl accident

The study area and cited source	Study design	The period of observation	Character comparisons	Features of the exposure data	The results
Three areas of the northern regions of Ukraine [1, 2]	Descriptive (incidence in children and adults)	1981–1990	The dynamics of disease during the observation period	In the study area one of the highest levels of contamination with radionucleades	The increase the incidence of thyroid cancer in children and adults
Ukraine, Belarus, Russia [3]	Descriptive (incidence)	1981–1994	The dynamics of disease during the observation period	Contamination with radionuclides territoriesof varying intensity	The increase in the incidence of thyroid cancer, particularly in Belarus
Zhytomyr, Kyiv, Chernihiv regions of Ukraine [4, 5]	Environmental (incidence in adolescents and adults)	1980–1999	The incidence of thyroid cancer in adolescents and adults in areas with different levels of radioiodine contamination	Three groups of districts in terms of radioiodine contamination: <100, 100–200, > 200 kBq/m^2	A direct correlation between intensity of radioiodine contamination and incidence of thyroid cancer
Zhytomyr, Kyiv, Chernihiv regions of Ukraine [6, 7]	Environmental (risk of thyroid cancer in children and at the adolescents (1–18 years time of the Chornobyl accident)	1990–2001	Comparison doses in patients with cancer of the thyroid gland and controls	This estimate of the average absorbed thyroid doses due to radioiodine	Excess relative risk per 1 Grey ERR = 8.0. (95% CI: 4.6–11.0); excess absolute risk EAR 10^4 person-Grey = 1.5 (95% CI: 1.2–1.9)
Zhytomyr, Kyiv, Chernihiv regions of Ukraine [8]	Analytical cohort study (13.2 thousand persons whose age at the time of the Chernobyl accident was less than 18 years)	1998–2007	Risk assessment of disease by comparing doses to patients with thyroid cancer and controls	Thyroid doses – direct measurements of thyroid I-131 radioactivity evaluated within two months after the Chornobyl accident	The excess relative risk in 1998–2000 ERR / Gy = 5.25 (95% CI: 1.70–27.5); in 2001–2007: ERR / Gy = 1.91 (95% CI: 0.4–6.34). The excess absolute risk EAR / 10^4 = 2.21 (95% CI: 0.04–5.78).
Cohort of 150,813 liquidators of the Chornobyl accident, residing in 6 regions of Ukraine [9]	Descriptive analytical study stage	1986–2010	Incidence	The dynamics of disease incidence during the observation period	Period 1995–1998: SIR=4.62 (95% CI: 3.47–6.15); 2000–2010: SIR = 4.80 (95% CI: 3.78– 6.10).

the Chornobyl accident, give grounds for conducting analytical studies in these groups, meaning of long-term observation of cohorts of adults, carry out of elimination of confounding to research factors such as screening, iodine deficit, lower adults sensitivity to radiation exposure of the thyroid gland.

Table 5.2.2 shows the results of epidemiological studies on leukemia risk associated with the Chornobyl disaster in children and adults. As in the previous case, a significant number of them are descriptive and focused on exposed children. In general, there is a little evidence of increased incidence of leukemia in children in Ukraine and Belarus due to at least partly the low radiation doses received by study subjects, In contrast to these results analytical studies in liquidators of the Chornobyl accident suggest that there is an increased risk of leukemia in this group of affected population in Ukraine and Russia. With the coincidence in time the risk gradually decreases. Note the first in Ukraine there is designated radiation dependence of chronic lymphocytic leukemia in liquidators.

Table 5.2.3 shows the results of epidemiological studies of breast cancer risk due to radiation exposure.

Table 5.2.2

Results of leukemia studies in different age and gender groups of the population affected by the Chornobyl accident

The study area and cited source	Study design	The period of observation	Character comparisons	Features of the exposure data	The results
Zhytomyr, Kyiv regions of Ukraine[10]	Descriptive – the incidence of leukemia in different age groups	1980–1999	The incidence during the period of observation	In northern areas of these regions the most significant precipitation of radionuclides	A moderate increase in morbidity during follow-up period
Sumy, Chernihiv regions of Ukraine [11]	Descriptive, the incidence of leukemia in different age groups	1980–2000	The incidence during the period of observation	In the Sumy region precipitation of radionuclides intensity is much smaller compared to Chernihiv	Incidence during the observation period did not exceed the national average
Zhytomyr, Kyiv, Chernihiv regions of Ukraine [12]	Cohort study 13.2 thousand persons whose age at the time of the Chornobyl accident was less than 18 years	1998–2009	The incidence of malignant neoplasms (other than thyroid cancer)	The average accumulated dose to the whole body for more than 20 years after the accident < 10mSv (rank from a few to hundreds of mSv)	The incidence of leukemia: SIR = 1.92 (95% CI: 0.69-4.13) tends to exceed the national level, which requires continued monitoring
Cohort of 110.6 thousand liquidators of the Chornobyl accident of 6 regions of Ukraine [13]	Analytical nested «case-control»	1986–2000	Risk assessment of disease by comparing doses in cases and controls	Radiation doses measured in a survey interviewer using the method RADRUE. Arithmetic average radiation dose to the bone marrow was 87 mGy (variations from 0.00004 to 3,300 mGy)	The excess relative risk of leukemia ERR = 3.44 / Gy (95% CI: 0.47–9.78)
Cohort of 110.6 thousand liquidators of the Chornobyl accident of 6 regions of Ukraine [14]	Analytical nested «case-control»	1986–2006	Risk assessment leukemia by comparing doses of radiation in cases and controls.	Radiation doses measured in a survey interviewer using the method RADRUE. Dose estimates are similar.	The excess relative risk of leukemia ERR = 1.26 / Gy (95% CI: 0.03–3.58) with time tends to decrease. Established a significant increased risk of chronic lymphocytic leukemia.
Belarus, Russia and Ukraine [15]	Analytical «case-control»	1986–2000	Risk assessment leukemia by comparing the dose in cases and controls	Doses of radiation children in the contaminated areas of the three countries evaluated by survey interviewers parents. The median radiation dose studied groups < 10mGy.	Risk assessments childhood leukemia in studies in Ukraine, Belarus and Russia differ considerably. It is not possible to make final conclusions based on the study results .
Rivne, Zhytomyr, Chernihiv regions of Ukraine [16]	Analytical «case-control» persons whose age at the time of the Chernobyl accident was less than 6 years.	1987–1997	246 – patients with acute leukemia and 492 – the control group.	The radiation exposure of investigated cases and controls personified assessed through interviews with parents.	Indicator – odds ratio OR = 2.4 (95% CI: 1.4–4.0) among those with exposure dose exceeded 10mGy, p = 0.01.

Table 5.2.3
The results of studies of breast cancer risk in different goups of population exposed to radiation

The study area and cited source	Study design	The period of observation	Character comparisons	Features of the exposure data	The results
A woman-residents of Hiroshima and Nagasaki (Japan), who survived the atomic bombing [17]	Analytical cohort study	1950–1985	A risk assessment conducted by comparing different dose groups	Instant acute high doses of radiation	The excess cases of breast cancer due to radiation impact was first found among women exposed as a result of the atomic bombing
Women participating aftermath of the Chornobyl accident in 1986–1987 [18–20]	Descriptive study	1994–2012	Comparison of the incidence of liquidators women with incidence of female population of Ukraine	Low-dose radiation exposure	The risk of breast cancer in women – liquidators 1.6 times higher than the female population level
The combined data for Belarus and Ukraine on breast cancer in areas contaminated with radionuclides [21]	Environmental epidemiological studies	1997–2001	Comparison of the incidence of breast cancer in the most contaminated areas compared to less contaminated	The average accumulated radiation dose in the most contaminated areas was 40 mSv or more	The relative risk of breast cancer in the most contaminated areas of Belarus amounted to RR = 2.24 (95% CI: 1.51–3.32); in Ukraine – RR = 1.78 (95% CI: 1.08–2.93)

Table 5.2.4
The results of the solid cancer risk in different age and gender groups of the population affected by the Chornobyl accident

The study area and cited source	Study design	The period of observation	Character comparisons	Features of the exposure data	The results
Malignant neoplasm in victims of the Chornobyl accident (residents of contaminated territories, evacuated from the exclusion zone, liquidators of the accident 1986–1987), Ukraine [22–24]	Descriptive study	1980–2012 in residents; 1990–2012 in evacuees; 1994–2012 in liquidators	Analysis of the level and dynamics of the incidence of malignancies during follow-up period.	The average external exposure dose of residents – 22.4 mSv; evacuees – 10–30 mSv; liquidators – 50–100 mSv	Excess cancer incidence (SIR) in liquidators of Ukraine amounted to – 1.17 (95% CI: 1.14–1.20). Indicators in residents and evacuees are below the national average
Participants of liquidation of the Chornobyl accident, Russia [25]	Analytical cohort study	1992–2009	Incidence and mortality during the period of surveillance and risk assessment	Estimated external exposure dose (0.1 to 1240 mGy), the median – 102 mGy	SIR = 1,18 (95% CI: 1,15-1,22). ERR = 0.47 / Gy (95% CI: 0.03–0.96, p = 0.034), attributive risk (ATR) = 5.8%.

Table 5.2.5
General characteristic of population groups involved in the study of frequqncy of malignancies

Cohort	Period of observation	Cohort size	Mean radiation dose*	Number of registered cases of cancer
Residents of the territories of Kyiv and Zhytomyr regions most heavily contaminated with radionuclides	1980–2012	1986 – 360.7 thousand. including 74.4 thousand of children; 2012 – 180.1 thousand. including 27.4 thousand of children	Average effective dose of external irradiation – 22.4 mSv, mean thyroid dose 187–221 mGy	24595
Evacuees from Prypyat town and 30 km zone	1990–2012	1990 – 50.2 thousand 2012 – 47.6 thousand	Average effective dose of external irradiation – 10–30 mSv; average thyroid dose – 184–857 mGy	3485
Liquidators 1986–1987 years of participation	1994–2012	1994 – 84.6 thousand 2012 – 95.0 thousand	Average effective dose of external irradiation – 50–200 mSv	10395

Notes. * – Information from National reports 2006, 2011 and UNSCER report 2011 [26, 27].

Increased risk of the breast cancer after exposure to ionizing radiation was first established in the Japanese cohort and later was confirmed in the study of the thyroid cancer incidence of women – participants of liquidation of the Chornobyl accident consequences (Ukrainian and Russian studies).

Table 5.2.4 shows the results of studies of solid malignancies risks after radiation exposure. These data suggest an increased risk of these diseases in Ukrainian and Russian liquidators of the Chornobyl accident. Risk of solid tumors does not exceed the national average in other groups of victims – evacuees from the exclusion zone and residents of contaminated with radionucledes areas.

Therefore results of mentioned studies suggest an actuality of long term monitoring of cancer incidence and its dynamics in the groups of population affected due to the Chornobyl accident to evaluate its factors in possible excesses of malignant tumours. Besides this review suggests significant difficulties in evaluation of carcinogenic effects of the Chornobyl accident. For arguments to be more substantial there is a need of clear estimation of radiation doses and exhaustive data on number of cancer cases in main groups of exposed population. These are liquidators who participated in recovery operation works in 1986–1987; evacuees from Prypyat town and 30-km exclusion zone; residents still living in the territories most heavily contaminated with radionuclides.

The goal of this study was to define cancer risk in groups of Ukrainian population affected by the Chornobyl accident during long-term period of observation.

The current study has been started to determine the frequency of malignancies after the exposure in a part of the Ukrainian population affected by the Chornobyl accident.

General characteristic of these groups is given in the Table 5.2.5.

A local personified database on all cancer cases was established in 1987 to study cancer incidence rate and its trends in the territories most heavily contaminated with radionuclides in order to perform a retrospective (since 1980) and current collection of information on all cancer cases in the Luginy, Narodichy and Ovruch districts of the Zhytomyr region, and the Borodyanka, Ivankov, and Polesskoye districts of the Kyiv region.

These six districts are referred to in the text below as territories most contaminated with radionuclides. In addition, information on all cancer cases in the former Chornobyl district during 1981–1985 was collected and included in the database as well.

At the time of the accident the total population of studied districts was 360.7 thousand including 74.4 thousand children aged 0–14 years. In 2012 the population of six districts excluding evacuated population of Chornobyl district was 180.1 thousand including 27.4 thousand children. For the data collection all relevant medical documents (including emergency notifications of new cancer cases as well as death certificates) were obtained from all medical institutions where these patients were diagnosed and treated. Since 1989 when the National Cancer Registry of Ukraine was established in Institute of oncology (now National cancer institute) this institution provides the on cancer cases data collection and storage in the whole state territory as well in mentioned districts. In 1980–2012 in these districts there were registered 24,595 new cases of malignant tumors (see Table 5.2.5).

Age-specific and age-standardized incidence rates were calculated for the period 1980–2012 and compared with respective data on Ukraine at whole and also on Zhytomyr and Kyiv regions those include most contaminated territories. Age distribution of the World Standard Population was used as a standard for direct standardization.

The data of the State Registry of the Ukraine on Chornobyl Victims (SRU) were used to investigate the cancer incidence among liquidators 1986–1987 and among evacuees. The data of the liquidators counted 95.0 thousand persons (including 11.2 thousand females) in 2012, namely those that reside in the Dnipropetrovsk, Donetsk, Kharkiv, Kyiv, and Lugansk regions, and in Kyiv city. In addition, there were the evacuees from the city of Prypyat and the 30-km exclusion zone, who resettled in other territories of the Ukraine, a group that included 47.6 thousand persons in 2012. The personified data of SRU on cancer patients were compared with the data base of the National cancer registry of Ukraine. After completing this procedure, all duplicates and cases without validated diagnosis were eliminated. During 1994–2012 there were 10,395 new cases registered among liquidators, and during 1990–2012 3,485 new cases among evacuees (Table 5.2.5).

Analysis was carried out with the standard methods of descriptive epidemiology: calculation of crude, age-specific and age-adjusted incidence rates with standard errors and confidence intervals. For indirect standardization (calculation of the standardized incidence ratio – SIR), the age-specific cancer incidence rates of the Ukrainian population were used.

All cancers incidence (ICD10 C00–C96)

Below the results of analysis of cancer incidence in population still living in the territories most heavily contaminated with radionuclides are presented (Figure 5.2.1). Data for Ukraine, Kyiv and Zhytomyr regions which includes mentioned territories are shown here for comparison too. In 1980-2012 cancer incidence rates in most contaminated territories were close to those in Zhytomyr region and lower than in Kyiv region and Ukraine in total.

To analyze peculiarities of dynamic trends the whole period of observation (1980–2012) was divided to separate time periods (1980–1992, 1993–2005, 2006–2012 pp.), those reflect existing trends most adequately. Regression coefficients and standard errors (b±m) for these periods are presented in the Table 5.2.6.

Time trends of cancer incidence rates were similar in all compared territories. Average annual cancer incidence rates increased till beginning of 90th and since 1993 rates were decreasing until 2005. Since 2006 the increasing trends were observed again. Such changes during the time were similar both for Ukraine in total and for the districts most contaminated with radionuclides

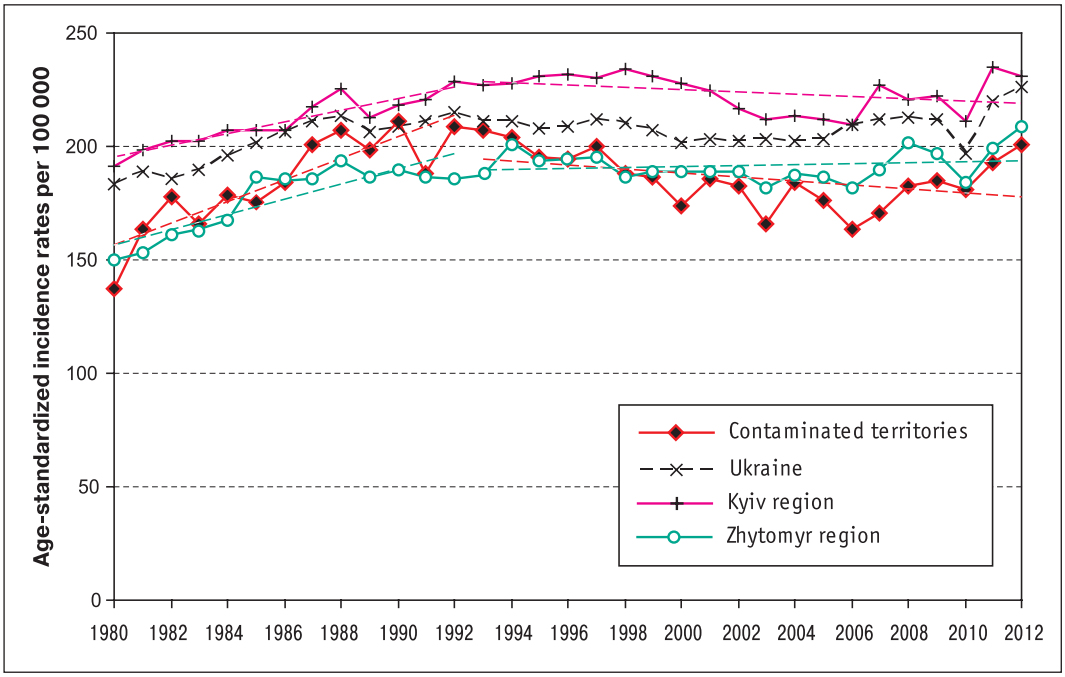


Figure 5.2.1. **Cancer incidence in population of Ukraine, Kyiv and Zhytomyr regions, and the territories most heavily contaminated with radionuclides in 1980–2012**

Table 5.2.6

Regression coefficients (b±m) of cancer incidence rates in the population of Ukraine, Kyiv and Zhytomyr regions, and the territories most heavily contaminated with radionuclides in different time periods of observation

Territory	Years		
	1980–1992	1993–2005	2006–2012
Ukraine	2.72 ± 0.32	-0.83 ± 0.16	1.80 ± 1.72
Kyiv region	2.59 ± 0.31	-1.62 ± 0.38	2.52 ± 1.59
Zhytomyr region	3.38 ± 0.58	-0.78 ± 0.30	2.96 ± 1.53
The territories most heavily contaminated with radionuclides	4.77 ± 0.82	-2.64 ± 0.48	5.57 ± 0.83

and those regions that include these districts. However it should be noted that increase of incidence rate in 1980–1992, 2006–2012 and its decrease in 1993–2005 are most pronounced in contaminated districts. Probably, mentioned tendency of cancer incidence is closely linked to the average life expectancy in the observed period.

Cancer incidence rates in three main groups of affected population are presented in Table 5.2.7.

Analysis of cancer incidence rates in these main groups of the affected population (Table 5.2.7) suggests the lower level of SIR in residents of contaminated territories and in evacuees comparing with national indexes. At the same time in recovery operation workers incidence rates of all malignant tumours significantly exceeded the national level – SIR = 107.5% (95% CI 105.4–109.6%). The decrease of the rate should be noted comparing with period of observation before 2004, when SIR was117.2% (95% ДІ 114.1–120.3) [23].

Table 5.2.7
Cancer incidence rate (ICD10 codes C00–C96) in the main groups of population affected by the Chornobyl accident (standardized incidence ratio SIR%)

Group of affected population (years of observation)	Actual No of cases	Expected No of cases	SIR, % (95% confidence interval)
Residents of the most heavily contaminated territories (1990–2012)	15977	19259.9	80.0 (78.8–81.3)
Recovery operation workers 1986–1987 years of participation (1994–2012)	10395	9671.1	107.5 (105.4–109.6)
Evacuees from Prypyat town and 30-km zone (1990–2012)	3485	4108.4	85.0 (82.1– 87.8)

Thyroid cancer (ICD10 C73)

Radiation origin of dramatic increase of thyroid cancer incidence is out of doubts at present time (Figure 5.2.2). In Ukraine this increase was two-fold in males and three-fold in females comparing with expected level.

Comparative analysis of thyroid cancer incidence in three main groups of affected population is presented in the Table 5.2.8. The significant excess of thyroid cancer in these groups above the national level is shown: 4.6-fold in recovery operation workers, 4.0-fold in evacuees and 1.3-fold in residents of the territories most heavily contaminated with radionuclides.

These data are the results of long-term observation of affected population groups. It should be noted that results of the first stage of this study [1] allowed even in 1990 to detect a dramatic increase of thyroid cancer incidence in youngest age group (0–4) resided in the territories most heavily contaminated with radionuclides surrounded Chornobyl (Narodychi, Ovruch, Poliske

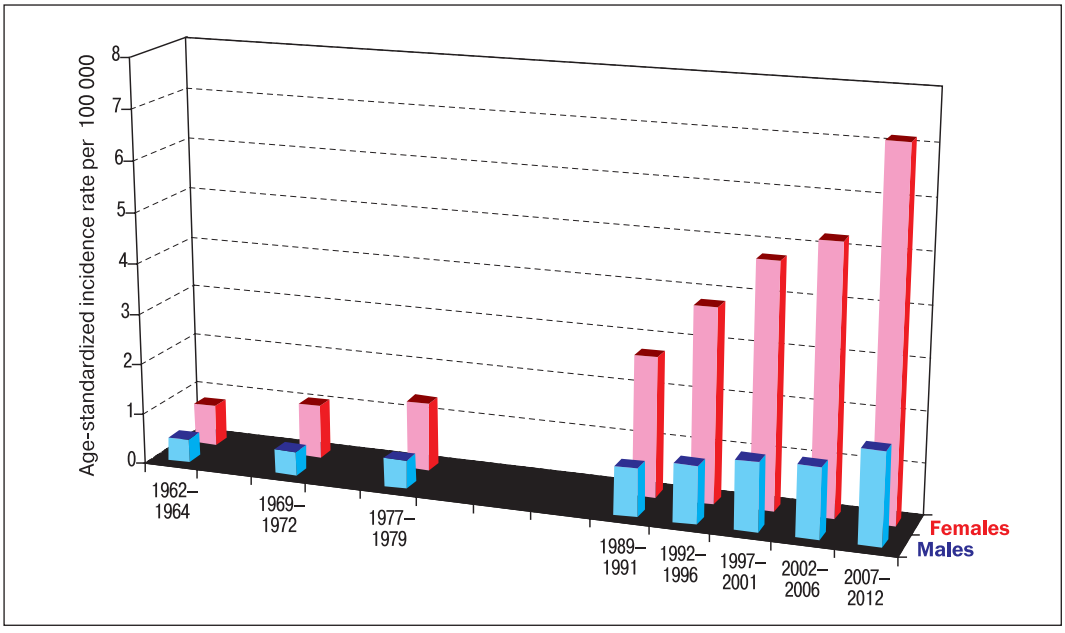


Figure 5.2.2. Thyroid cancer incidence in male and female population of Ukraine in 1962–2012 (age-standardized incidence rates per 100 thousand citizens of corresponding gender)

Table 5.2.8

Thyroid cancer incidence (ICD10 code C73) in the main groups of population affected by the Chornobyl accident (standardized incidence ratio SIR%)

Group of affected population (years of observation)	Actual No of cases	Expected No of cases	SIR, % (95% confidence interval)
Residents of the most heavily contaminated territories (1990–2012)	387	290.0	133.4 (120.2–146.7)
Recovery operation workers 1986–1987 years of participation (1994–2012)	360	77.6	463.9 (416.0–511.8)
Evacuees from Prypyat town and 30-km zone (1990–2012)	274	68.2	401.8 (359.2–449.3)

districts). It is notable that during previous decade (1980–1989) no one case of thyroid cancer was registered.

Ecological study of thyroid cancer incidence rates [28] in whole Ukraine showed differences in frequency of this pathology depending on gender and average (for each region) accumulated thyroid doses (Figure 5.2.3).

During the study period (1989–2012) age standardized thyroid cancer incidence rates in the female population of the «high exposure» regions increased from 3.34 to 12.47 per 100 thousand, i.e. 3.7 times. In females living in the «low exposure» regions the rates were correspondingly 2.51 and 7.20, i.e. a 2.9-fold increase was registered.

In males at the start of follow-up period (1989) the thyroid cancer incidence rates were similar both in «high» and «low exposure» regions, namely 0.87 per 100 thousand. Twenty six years after the accident in 2012 the rates increased to 3.55 in «high exposure» and 1.82 in «low expo-

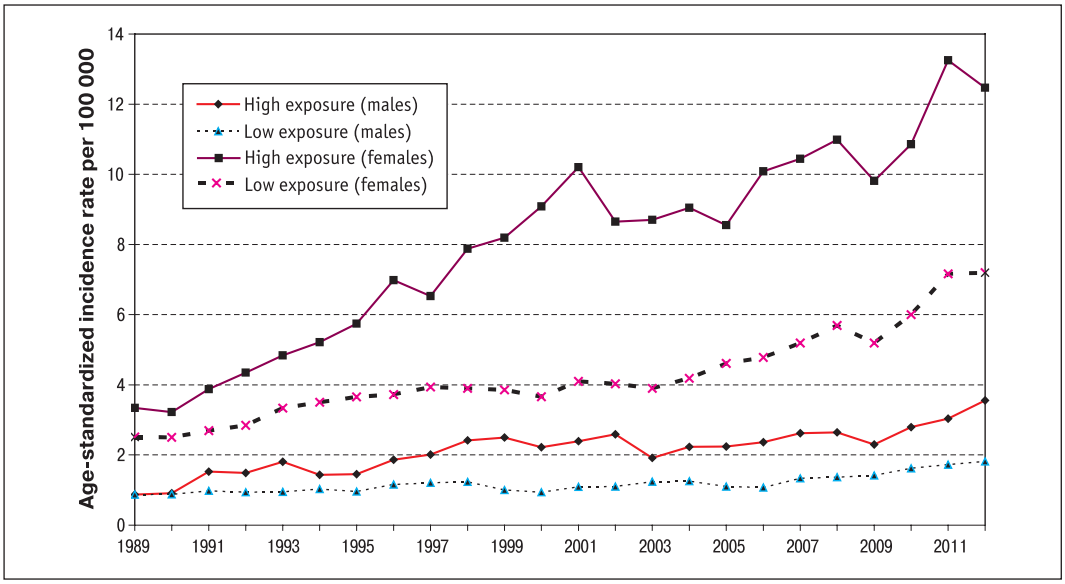


Figure 5.2.3. Thyroid cancer incidence in population of Ukraine living in the «high exposure» and «low exposure» regions in 1989–2012.

Regression coefficients b ± s.e (b): «High exposure» (males) 0.078 ± 0.009; «low exposure» (males) 0.032 ± 0.004; «high exposure» (females) 0.388 ± 0.017; «low exposure» (females) 0.169 ± 0.014.

sure» regions, i.e. 4.1 and 2.1 times respectively. Comparison of trends suggests a statistically significant difference ($p < 0.01$) between the regression coefficients. In «high exposure» territories the thyroid cancer incidence rates increased much faster both in males and females during the follow-up period.

Leukaemia and lymphoma incidence rate (ICD–10 C81–C96)

Indisputable interest is being attracted by analysis of frequency of other potentially radiation-associated malignant tumours first of all leukemia. Discriptive study results demonstrated the smooth increase of leukaemia incidence in residents of contaminated territories 7–8 years after the Chornobyl accident and significantly elevated incidence in clean-up workers and evacuees. These results helped to form the information ground for the hypothesis and consequent analytical study, realized in the frame of Ukrainian-American collaboration and joint study on leukemia and related deseases in liquidators. It was found out that radiation exposure in the range of small and medium doses is associated with a significant increase of leukemia risk.

Breast cancer incidence (ICD10 C 50)

Among another potential radiation exposure effects special attention should be drawn to female breast cancer, which previously considered to be the radiation sensitive form. Excess of radiation induced breast cancer cases was revealed in females in A-Bomb victims [17].

In the most contaminated territories under study moderate increase of the breast cancer incidence rate was observed in 1980–1991. At the same time observed levels were lower then the corresponding indexes in Ukraine at whole and in large regions under study (Kyiv and Zhytomyr) (Figure 5.2.4).

In 1991–1995 breast cancer incidence rate in contaminated territories became closely similar to those in large regions (especially in Zhytomyr region) due to the significant increase.

As to comparative evaluation of breast cancer incidence rate in three main groups of affected population (Table 5.2.9), it should be noted that significant exceeding over the national level was reported only in women participated in recovery operation works in 1986–1987. In 1994–2012

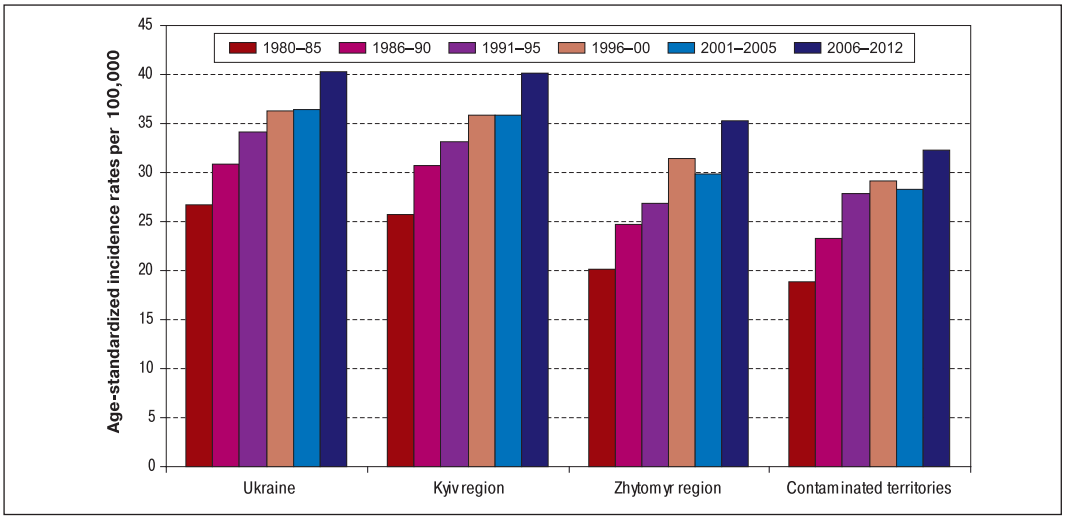


Figure 5.2.4. Breast cancer incidence in the female population of Ukraine, Kyiv, Zhytomyr regions and the territories most heavily contaminated with radionuclides in 1980–2012

Table 5.2.9
Female breast cancer incidence (ICD10 code C50) in the main groups of female population affected by the Chornobyl accident (standardized incidence ratio SIR %)

Group of affected population (years of observation)	Actual No of cases	Expected No of cases	SIR, % (95% confidence interval)
Residents of the most heavily contaminated territories (1990–2012)	1224	1912.3	60.0 (60.4-67.6)
Recovery operation workers 1986–1987 years of participation (1994–2012)	319	198.1	161.0 (143.4-178.7)
Evacuees from Prypyat town and 30-km zone (1990–2012)	330	427.4	77.2 (68.9-85.5)

SIR value in this group consisted 161.0% (95% CI 143.4–178.7%). Incidence rates in females, still living in territories contaminated with radionuclides, and evacuees were essentially lower. Interpreting these results one should take into account that two latter groups of the affected population lived before the Chornobyl accident in territories, where female breast cancer incidence was among the lowest in Ukraine. Significant increase of breast cancer incidence was found in liquidators females in Russia [29] – SIR=1.84 (95% CI: 1.23–2.45).

* * *

The epidemiological study of oncological consequences of the Chornobyl accident was promoted by developing and implementing national and international research programs. Due to limited funding research within national programs has been mostly descriptive in nature, while some international programs include analytical studies, which makes it possible to assess the risk of malignancies taking into account the radiation doses. Researches were conducted in the major population groups affected by the Chornobyl accident (residents of most contaminated areas of Ukraine; liquidators participated in recovery operation works in 1986–1987; evacuees from the exclusion zone) and made it possible to identify the characteristics of trend models of this pathology. Eearly radiation induced thyroid cancer cases in children – residents of the most contaminated areas – were detected even in four years after this tragic event. Before this time, over the past ten years mentioned pathology in children have not been registered. Therefore, these cases should be attributed to those that may indicate the onset of the so-called signaling events (sentinel events), preceding approximation of possible epidemic. Further observations confirmed this assumption.

International programs IPHECA (ECP-7), studies under French-German Chornobyl initiatives, INCO-COPERNICUS and others pushed long-term monitoring of malignant tumors in the affected groups with usage of databases of the State Register of Ukraine and the National Cancer Registry. This made it possible to establish that the incidence of all forms of cancer exceeds the national level only in the group of liquidators of 1986–1987. It was noted an increased incidence of thyroid cancer in residents of most contaminated territories, liquidators of 1986–1987 and evacuees. Increased risk of this disease was shown not only in children and adolescents but also in individuals exposed in adulthood, especially in females.

Descriptive studies of leukemia frequency, performed in two separate subcohorts of residents of contaminated territories, allowed to conclude about the lack of radiation risk excess of this disease.

As a result of Ukrainian-American project on leukemia and related diseases in liquidators it was found out that radiation exposure in the range of small and medium doses is associated with a significant increase of leukemia risk.

As tor other forms of malignant tumors, considerable attention was paid to the study of breast cancer incidence. An increase of this pathology frequency was observed in residents of contaminated territories and evacuees, but ultimately it does not exceeded the national average. However in female liquidators participated in Chornobyl operation works in 1986–1987 this rate was significantly higher (1.6 times) then the national level. There is a need of further research assessment of the role of radiation factor, as well as establishing the possible impact of screening effect and improve the quality of cases registration A small number of cases of some forms of cancer, as well as confounding effects and migration suggest the need to increase the power of the study. These issues could be achieved by extending the period of observation, using database of the State Registry of Ukraine and linkage between databases of the Registry and the National Cancer Registry of Ukraine. In addition, reliable assessment of cancer risk also requires comprehensive data on the doses of radiation exposure.

Because the latency period of various radiation induced tumors varies significantly profound attention is required to be paid not only for thyroid, breast cancers, leukemia, but also for malignant tumors of lung, stomach, bowl, ovary, bladder, kidney, multiple myeloma.

Particular attention should be drawn to groups of people who have suffered radiation exposure early in life – in utero, children and adolescence. Wider implementation of analytical epidemiological methods is required for reasonable quantitative estimates of the excess radiation cancer risk.

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5.3. MOLECULAR MECHANISMS OF THE MALIGNANT TRANSFORMATION IN THE URINARY TRACT EPITHELIUM, INFLUENCED BY CHRONIC LONG TERM LOW DOSE IONIZING RADIATION EXPOSURE

SI«Institute of Urology, National Academy of Medical Sciences of Ukraine»(IU), had accumulated the experience in the application of the modern clinical and histological methods for studies at the area of diagnostics, classifications, prophylactic measures and treatment of bladder cancer, renal-cell carcinoma, prostate cancer and testicular tumours over the several years before the Chornobyl accident in Ukraine. The pathogenesis as well as morphogenesis of precancerous lesions and the importance of some background states for bladder carcinogenesis were also investigated. This experience was represented in many articles, 7 monographs and some manuals that became a good background as well as they became the control groups for the investigations at the area of the new molecular peculiarities of the carcinogenesis after the Chornobyl accident.

5.3.1. Effects of chronic long term low dose ionizing radiation on the renal-cell carcinoma and the peritumoral tissue

Over the last 20 years we had investigated patterns of the renal-cell carcinomas (RCCs), renal oncocytomas and peritumoral renal tissue collected from Ukrainian patients with different exposure to ionizing radiation. The epidemiological, histological, immunohistochemical and molecular methods were applied. The immunohistochemical study and molecular genetic analysis were performed in the Department of Pathology, Medical School of Valencia University, Spain (Professor and Chairmen Dr. Antonio Llombart Bosch). We thank Luisa Morell-Quadreny, M.D. Ph.D., Jose Antonyo Lopez-Guerrero, Ph.D., Antonio Pellin, Ph.D. and Andriy Yurakh, M.D. for their kind assistance in our study.

Epidemiology of renal cancer in Ukraine after the Chornobyl accident

The epidemiological study showed the increasing number of patients with the primary found renal cancer from 3771 in 1998 to 4877 patients in 2009.

Morbidity of malignant renal tumors in adults during the period of 1986–2009 increased from 4.7 to 10.6 per 100,000 of total population in Ukraine (from 6.0 to 13.6 per 100,000 of the males and from 3.6 to 8.1 per 100,000 of the female population) [1]. Seventeen years of internal exposure to ^{137}Cs at low doses, which were constantly concentrated and eliminated by kidneys of about 10×10^6 dwellers of the radiation contaminated areas of Ukraine as well as Kyiv (over 3×10^6 people), could possibly influence the incidence of kidney tumors in Ukraine. The internal exposure is the most dangerous, ^{137}Cs constitutes 80–90% of it. This radionuclide is known to be concentrated and eliminated through kidneys and 90% of the more labile pool of ^{137}Cs is excreted via urine [2]

Radiometric measurement of ^{137}Cs was conducted using a Standard Y-Radiometer RUB-01 (Ukraine) with urine collected over 24 hours from all patients of groups I-III before surgery was performed. Significant relation of ^{137}Cs urine levels with level of radiocontamination residence territory was showed and possibility of group dividing was confirmed. Furthermore, apart from radionuclides, the synergetic effect influenced by the different chemical factors including potentially carcinogenic substances at the contaminated territories of Ukraine. The levels of the chemicals contamination in Ukraine is 6.5 times higher than in USA, and 3.2 times higher than in Europe.

Pathology and proliferative activity of RCCs in Ukrainian patients with different radiation exposure

An investigation of the histological and prevalence patterns of RCCs as well as tubular nuclear atypia and carcinoma in situ (CIS) of peritumoral kidney tissue in association with dose radiation exposure was performed. We selected five groups of patients with RCCs in Ukraine, which represented varying degrees of internal exposure to radiation and who were operated in 2 different periods of time (1993–1996 and 1997–1999) following the Chornobyl accident. The control group of analog patients with RCCs was selected in Valencia (Spain) for the present study. Three hundred forty-eight patients from Ukraine and Spain underwent radical nephrectomy due to RCC without previous treatment; 236 patients from Ukraine underwent surgery in the IU and were divided as groups I to V, according to the level of radiation contamination and duration of exposure. The Spanish group included 112 patients who underwent surgery in the University Clinic, Hospital of Valencia, thus representing control group VI. Characteristics of all patients are summarized in Table 5.3.1.

In all cases surgical specimens were revised with tumoral size as a variable for study. RCCs were classified in accordance with the clinical and histological criteria defined by the Heidelberg UICC classification

TNM stage and pathological features of RCCs and peritumoral kidney tissues in the different groups are summarized in Table 5.3.2. Mean and standard deviation of tumoral size was 7.7 and 4.9 cm, respectively, for the Ukrainian groups, and 8.6 and 4.4 cm, respectively, for the Spanish

Table 5.3.1
Patient characteristics

Group	I		II		III		IV		V		VI	
	male	female	male	female	male	female	male	female	male	female	male	female
Quantity of patients	30	27	30	25	43	29	11	3	22	16	74	38
Median age (range)	55 (27–79)		56 (34–75)		55 (18–77)		51 (27–75)		53 (41–75)		57 (26–77)	
Years of surgery	1993–1999		1993–1996		1997–1999		1993–1996		1997–1999		1975–1989	
Levels of soil contamination (Ci/km^2)	not contaminated		0.5–5		0.5–5		5–30		5–30		not contaminated	

Table 5.3.2
Incidences of clinical and pathological features of renal-cell carcinomas and peritumoral kidney tissues in different groups of patients

Patients		TNM stage				Histological type**						Grade			Sarcomatoid changes	Peritumoral changes***			
groups*	number of cases	I	II	III	IV	1	2	3	4	5	6	1	2	3		1	2	3	4
I	57	28	17	7	5	39	13	–	–	4	1	8	37	12	12	32	3	33	27
II	55	31	16	6	2	37	7	3	3	2	3	8	20	27	11	33	4	45	35
III	72	36	27	6	3	40	11	5	2	9	5	12	23	37	25	55	9	49	63
IV	14	7	5	1	1	10	1	1	–	–	2	3	8	3	4	10	1	9	10
V	38	21	11	6	–	18	6	1	1	8	4	10	16	12	10	30	6	22	37
VI	112	43	38	14	17	67	16	3	3	12	11	21	59	32	11	8	1	97	–

Notes. * I – , II –; **1 – conventional; 2 – papillary; 3 – chromophobe; 4 – collecting ducts – 5, oncocytoma; 6– others; *** 1 – nuclear atypia; 2 – carcinoma in situ; 3 – inflammation; 4 – radiation nephropathy.

Table 5.3.3
Incidence of urinary bladder dysplasias and carcinomas

Groups	Soil contamination, Ci/km^2	No. of cases	Dysplasia, %	Carcinomas		
				total (%)	carcinoma in situ, %	papillary urothelial carcinoma, %
1	5–30	73	71 (97)*	53 (73)*	47 (64)*	6(8)
2	0.5–5	58	48 (83)*	37 (64)*	34 (59)*	3 (5)
3	Non-contaminated	33	9 (27)#	0 (0)	0 (0)	0 (0)

Notes. * – significantly different versus group 3 at p< 0.0001 (χ^2 or Fisher's exact probability test); # – mild dysplasia.

group, without significant differences. Com-parative analysis between all Ukrainian and Spanish groups showed more frequent incidences of high grade RCCs in Ukrainian patients with the significant differences that depended predominantly on groups II and III. Analysis of statistical relations between different groups showed that the distributions by grade in group I and the Spanish group were similar, and tumors of both these groups were significantly more differentiated than those of groups II, III, IV and V.

It is interesting that RCCs from Ukraine presented more frequently sarcomatoid changes with significant differences, compared with the Spanish group. The high extent of sarcomatoid changes was seen in groups III, IV and V, with significant differences in groups I and II. Nevertheless, groups I and II also showed differences in sarcomatoid changes with the Spanish group ($\chi^2 = 4.99$; $p<0.05$). Peritumoral inflammatory response of Ukrainian RCCs was significantly less frequent than the Spanish group, which showed differences with all Ukrainian groups except group II.

Peritumoral medullar and cortical tubular nuclear atypia and CIS demonstrated significant differences between the Ukrainian and Spanish groups. Moreover, predominantly medullar nuclear atypia of collecting ducts occurred more frequently in groups III, IV and V, being less frequent and of low grade in groups I and II. Similarly, areas of CIS were detected more frequently in groups III and V, with significant differences against the other groups.

Irradiation-like lesions, predominantly of medullar and less cortical peritumoral tissue, were detected only and in all Ukrainian groups (Table 5.3.3). Microscopically they appeared in cortex patterns of radiation sclerosing, proliferative atypical nephropathy, with pyknotic epithelial cells of proximal and distal tubules. Furthermore, focally tubular degeneration and necrosis with glomerular changes, simulating membranous nephropathy, were detected. Large areas of pyknotic epithelial cells in collecting ducts with following epithelial detachment, degeneration, regeneration and desquamation with development of widened enlarged loops that were already naked and empty, resembling «cheese holes», were seen in medulla. It is important to note that the above mentioned irradiation nephropathy was more frequent in groups III and V than in other Ukrainian groups, with significant differences.

Molecular pathogenesis of renal-cell carcinomas in Ukraine after the Chornobyl accident

Our study shows the tumour suppression genes (and coded proteins) alteration associated with the high-level oxidative stress markers in tumor and peritumoral tissue which was caused by the influence of chronic low doses radiation. As it is known, the expression of $p16^{INK4A}$ gene is activated by oncogenic stress, whereas the expression of $p15^{INK4B}$ gene is related to the negative growth factor, transforming growth factor-beta [3]. The tumor suppressor activity of $p16^{INK4A}$ and $p15^{INK4B}$ is attributed to their biochemical ability to bind both cyclin-dependent kinase

(CDK) 4 and 6, thus inhibiting the catalytic activity of the CDK4-6/cyclin D enzyme complex required for retinoblastoma protein (pRb) phosphorilation and cell-cycle progression. The result is that both $p16^{INK4A}$ and $p15^{INK4B}$ prevent E2F-dependent transcription, blocking cell-cycle progression pathway and the Gl/S restriction point.

Recently, accumulated evidence indicated a close link between 5'CpG island methylation in the promoter region and transcriptional block of $p16^{INK4A}$ gene in various human tumors [4]. Extensive analysis of $p16^{INK4A}$ promoter methylation in human head and neck squamous cell carcinoma has also demonstrated a high level of inactivation that correlates exactly with the absence of $p16^{INK4A}$ protein expression that was immunohistochemically indicated [5]. Numerous additional studies have now established the importance of $p16^{INK4A}$ methylation as a major mechanism of carcinogenesis in many different tumors in human [6].

We try to determine whether there is any manifestation of oxidative stress associated with $p15^{INK4B}$ and $p16^{INK4A}$ genes alteration in renal cell carcinomas from patients continuously exposed to low doses of ionizing radiation in correlation with levels of ionizing radiation exposure, TNM stage and histological features of these tumors. Three groups of the Ukrainian RCCs with varying degrees of exposure to IR were selected for comparison.

Data from molecular analysis revealed no homozygous deletions of the $p16^{INK4A}$ and $p15^{INK4B}$ genes in any sample. However, aberrant hypermethylation of the 5'CpG islands in the promoter region of these genes was observed in seven (32%) and five (23%) cases for the $p16^{INK4A}$ and $p15^{INK4B}$ genes, respectively. A higher incidence of cases with hypermethylation of $p16^{INK4A}$ gene was observed in high-grade tumors. Three tumors of high stage and grade (one with sarcomatoid metaplasia and two with conventional renal cell carcinomas) showed a coincident hypermethylation of both genes. A high proportion of cases with hypermethylation of the promoter region of the $p16^{INK4A}$ gene were observed in tumors with CIS and cellular atypia in distal tubules and medullar collecting ducts of peritumoral kidney, particularly in undifferentiated tumors with sizes of more than 7 cm, all corresponding to patients from the radiation contaminated areas. No association between any of these parameters and hypermethylation of the $p15^{INK4B}$ gene has been found.

Thus, we have documented for the first time that RCCs from patients living in the radiation contaminated areas of the Ukraine showed aberrant hypermethylation of $p16^{INK4A}$, and fewer $p15^{INK4B}$ genes with immunohistochemically decreased expression of proteins, associated with dramatically increased expression of cyclooxygenase 2 (COX2), accompanied by the high incidence of radiation nephropathy in peritumoral tissues. This data confirmed that $p16^{INK4A}$/*pRb* pathway was damaged by oxidative stress during chronic long term low doses radiation exposure that leads to activation of the RCC progression and to the development of the more aggressive tumors.

The complex study of the molecular alterations of those tumor suppressor genes located on chromosome 9p21 (*INK4A/ARF* locus and $p15^{INK4B}$), MAPK signal transduction pathway's marker p38MAPK protein, alterations of p53 tumor suppressor gene and genetic amplification of the *cyclin Dl, mdm2* in association with the immunohistochemical protein expression of the same genes in the same samples of 26 primary renal-cell epithelial tumors and peritumoral kidney tissues from patients with different radiation exposure after the Chornobyl accident in Ukraine resulted to unique date.

Formalin fixed paraffin embedded 112 tissue blocks (approximately, 4 blocks per each case) and frozen material from 26 patients with RCETs (including the peritumoral kidney tissue), who underwent surgery at the Institute of Urology in Kyiv (Ukraine) were investigated. The control group I of patients from so called «clean» area (without indicated radiocontamination),

group II – from the less contaminated city of Kyiv; and group III patients were from heavily contaminated areas. All patients resided in the same areas during pre- and post- Chornobyl accident periods. Radiometric measurement of ^{137}Cs was conducted with urine collected over 24 hours from all patients before surgery.

P53 protein nuclear overexpression occurred in 3 (13%) conventional RCCs with >10% and <50% of stained nuclei and in 4 (18%) from 26 cases (one – papillary, one – Bellini and two conventional RCCs) with less than 10% of stained nuclei predominantly from groups II and III. RCCs from radiation contaminated areas expressed higher quantities of $p14^{ARF}$ protein, in relation to tumors from «clean» regions. There was direct relation between $p14^{ARF}$ protein and mdm2 expression in RCCs from groups I–III with the increased overexpression of $p14^{ARF}$ and mdm2 in radiation contaminated areas, associated with wild type p53 protein (negative staining).

Proliferative activity showed differences between groups with Ki67 stained nuclei and was the highest in groups II and III. Relationship between Ki67 immunostaining and histological variables demonstrated the increase of mean values of positive cells in high grade RCCs, with significant differences.

Regular homogenous or granular p38 MAPK cytoplasmic immunostaining in RCCs was detected in 100% and 78% of cases from groups II and III respectively. RCCs from radiation contaminated areas showed the highest frequency of *p14*^{INK4A} gene hypermethylation and strongest intensity of p38MAPK overexpression (p=0.003) to compare with RCCs from group I. Furthermore, $p16^{INK4A}$ protein immunostaining showed irregular tendency in relation to groups. Direct relation was presented between increased nuclear overexpression of cyclin Dl and cytoplasmic expression of p38MAPK in tumors from groups II and III. Moreover, relation between low or negative *p16*^{INK4A} protein expression in many cases of RCCs and cyclin Dl nuclear overexpression in the same tumors from groups II and III, accompanied by hypermethylation of the 5'CpG islands in the promoter region of *pl6*^{INK4A} gene in 10% of these tumors could be detected. Interestingly, hypermethylation of *p16*^{INK4A} and *p14*^{ARF} genes was never observed in the same samples. Hypermethylation of the promoter region of the *p14*^{ARF} and *pl6*^{INK4A} genes occurred eventually in peritumoral kidney tissues, predominantly in cortex with cellular atypia.

This study represents the first finding of a specific lesion in *INK4a/ARF* locus of chromosome *9p21* in primary human RCETs and peritumoral kidney tissues from patients chronically exposed to low doses of IR, as they lived in the radiation contaminated areas of Ukraine. The present radiometric study confirmed significant increase of ^{137}Cs in one-day urine of these patients, so the long-term radiation exposure of the kidney tissue could be easily supposed. There was no dose-response relationship in the range 2–12 Gy, suggesting that an instability phenotype may be induced by quite low radiation doses.

Our study has documented that RCCs from patients living in the radiation contaminated areas of Ukraine showed aberrant hypermethylation of *p14*^{ARF} and *p16*^{INK4A} genes associated with increased mdm2 and cyclin Dl proteins levels. Moreover, *p14*^{ARF} promoter hypermethylation occurs independently of the *p16*^{INK4A} methylation status, but in relation to the *p53* stable status, following by increased levels of nuclear mdm2 and $p14^{ARF}$ proteins in the same tumors. In the group of RCCs pl6INK4A promoter hypermethylation was never combined with *p14*^{ARF} promoter hypermethylation. The most common situation was the simultaneous absence of methylation in both promoters, but after this, the two possible scenarios (*p16*^{INK4A} methylated alone, *p14*^{ARF} methylated alone) were similarly represented. These data suggest the existence of multiple levels of «cross-talk» between the *p16*^{INK4A}*/pRb* and *p14*^{ARF}*/p53* pathways in RCCs.

We found significant relation between strong immunostaining against p38MAPK and RCCs of radiation contaminated areas. Constantly elevated p38MAPK activation leads to constitutive

elevation of nuclear factor – kappa B (transcription factor) response element transactivation in the malignant phenotype and furthermore, malignant progression [7, 8].

Our recent study, which use tissue microarray technique, include 56 Ukrainian patients with RCCs including 18 patients living in «clean» Ukrainian regions in control group and 41 patient living in contaminated regions of Ukraine. The similar group of 18 patients operated in University of Valencia's clinic (Valencia, Spain) was used as control. Significant increase of expression of the apoptosis promoter BAX and death receptor DR-5 in cytoplasm and cell membrane of tumour cells were detected. The same cells show reduced expression of apoptosis inhibitors Bcl-2 and Bcl-x combining with high expression of p65 and p50 subunits of nuclear transcription factor NF-κB. Our findings indicate that long-term low dose radiation exposure initiates the apoptosis regulation system alteration, thereby resulting to tumour progression and apoptosis resistance of tumour cells.

* * *

Significant increase of RCCs incidence in «contaminated» by radionuclides regions (CRR) of Ukraine combined with changing of tumors biological features gives the evidence for presence of ecological pathomorphosys in Ukraine after the Chornobyl accident. Increase of proliferative activity and aggressivity accompanied by hyperexpression of K-ras and PCNA in RCCs, especially in patients from CRR associated with chronic radiation nephropathy in peritumoral tissue are correlated with the duration of radiation exposure and confirms the influence of chronic and persistent radiation exposure on renal carcinogenesis.

The new histological form of nephropathy – radiation sclerosing proliferative atypical nephropathy, which was occured in association with the areas of epithelial nuclear atypia and CIS in patient living in CRR, was defined. Persistent oxidative stress inducted by long-term influence of low dose ionizing radiation exposure on renal cell carcinomas (RCCs) in patients living in CRR induces destruction of intracellular signal system, accompanied by inactivation of $p16^{INK4A}/p53$ pathway, plays a significant role in tumor progression

$p14^{ARF}$ promoter hypermethylation in peritumoral renal tissue could be explained by G1-S cell cycle regulation disorders and promotes the development of precancerous lesions in kidney as well as the progression of RCCs. Molecular promoters and inhibitors of apoptosis are the target for the long-term low-dose ionizing radiation exposure in renal-cell carcinogenesis.

5.3.2. Urinary bladder lesions induced by persistent chronic low-dose ionizing radiation

Urinary bladder lesions in male-patients with benign prostate hyperplasia (BPH) who underwent open transbladder prostatectomy were studied in the IU from 1993 until 2007. Multiple mapping biopsies of the bladder urothelium (including areas of bladder neck and both ureter orifices) were obtained from every patient. Furthermore, the histological and immunohistochemical studies were performed in collaboration with the Department of Pathology in the Uppsala Medical University, Sweden (Professor & Chairman Dr. Krister Busch) in 1993-1994, in collaboration with the Department of Pathology of the Innsbruck Medical University, Austria (Professor & Chairman Dr. Gregor Mikuz) in 1995–1996. Histological and immunohistochemical study accompanied by molecular biology were performed from 1996 until 2007 in collaboration with the Department of Pathology (Professor & Chairman Dr. Shoji Fukushima), Osaka City University Medical School in Japan.

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Chornobyl cystitis

We have documented for the first time that chronic long-term, low-dose IR in parts of the Ukraine leads to development of a previously unknown urinary bladder disease, radiation-induced chronic proliferative atypical cystitis or so-called Chornobyl cystitis [9]. This is characterized by multiple areas of dysplasia and CIS of the urinary bladder urothelium in strong association with sclerosis of connective tissue and strongly increased angiogenesis without a marked inflammatory reaction in the propria mucosa.

The incidences of urinary bladder dysplasias and carcinomas in 164 patients living in 5–30 Ci/km^2 (group 1), 0.5–5 Ci/km^2 (group 2) soil contamination areas or non-contaminated areas (group 3) are summarized in Table 5.3.3. Urinary bladder epithelium biopsied from 131 male patients with BPH from groups 1 and 2 demonstrated multiple areas of dysplasia with strong epithelial abnormalities such as extensive cellular pleomorphism and nuclear hyperchromism, frequently combined with increased thickness of urothelial epithelium. Foci of dysplasia were observed in 97% and 83% of cases in groups 1 and 2, respectively, and multiple areas of CIS with neoplastic changes of urothelium that frequently involved von Brunn's nests or cystitis cystica were detected in 73% and 64%. Nine small papillary or invasive transitional cell carcinomas (pTa-pT1) were also incidentally found in individuals from radiation contaminated areas.

Additionally, all cases in groups 1 and 2 exhibited proliferative cystitis, i.e. von Brunn's nests, cystitis cystica and squamous and glandular metaplasia, which were frequently combined and had marked features of chronic radiation cystitis rather than simple inflammation. Large areas of sclerosis of connective tissue in lamina propria with less prominent inflammatory cellular infiltration of lymphocytes, histiocytes and plasma cells were typical. Among these lesions, definite new vascularization, sometimes with the development of angiomatoid-like vessels full of erythrocytes and hemorrhage, was detected in 62%, 53% and 6% of groups 1, 2 and 3, respectively. Endothelial proliferation of new micro-vessels in lamina propria was markedly increased in 46% and 34% of cases in groups 1 and 2, respectively. In all female patients, large areas of sclerosis of connective tissue with some inflammatory infiltration and large areas of hypervascularization and patchy hemorrhage were detected in lamina propria. Patterns of chronic cystitis without proliferative changes but with clear cell urothelium and marked inflammatory cellular infiltration in lamina propria were found in patients of group 3. However, hypervascularization and development of angiomatoid-like vessels were not observed.

Unfortunately, we have no means to determine what radiation dose our patients received. However, we obtained results of ^{137}Cs measurement in daily urine of the same patients with BPH in groups 1 and 2; the values are summarized in Table 5.3.4. Significant elevation of ^{137}Cs levels was found in patients from group 1 (6.47 Bq/L) and to a lesser extent in patients from group 2 (1.23 Bq/L), as compared with group 3 patients (0.29 Bq/L). Our radiometric study showed significant increase of ^{137}Cs in urine of patients from groups 1 and 2, who suffered from BPH and

Table 5.3.4
^{137}Cs levels in urine of patients

Indices	Groups		
	1	2	3
Number of patients	55	53	12
Soil contamination levels, Ci/km^2*	5–30	0.5–5	non–contaminated
^{137}Cs levels in urine (Bq/l, Mean ± SD)	6.47 ± 14.30#	1.23 ± 1.01#	0.29 ± 0.03

Notes. * – data from Raes et al. [2]; # – significantly different versus group 3 at $p < 0.001$ (Steel–type separate ranking test).

presumably urinary retention, so that radiation exposure of the urothelium would be expected to have been high. Such male patients with BPH could be the group with the highest risk of Chornobyl cystitis. Our female patients with symptoms of chronic cystitis from groups 1 and 2, who were without urinary retention but with increased ^{137}Cs in urine, also demonstrated the same pattern of chronic proliferative atypical cystitis with less frequent mild dysplasia. These data strongly suggest the same pathway for development of urinary bladder lesions in male and female patients dependent on long-term exposure to low-dose IR.

^{137}Cs levels in urine of patients

However, synergistic effects of other ecological hazards (chemical pollution and cigarette smoking) in Ukraine, which is acknowledged to be an ecological disaster area, also have to be taken into consideration. The economic and social structures are very poor, and the majority of the Ukrainian population still is getting food from their private vegetable gardens (without any ecological control). Therefore, our patients (many of whom were smokers) living in the radiation contaminated areas could be synergistically affected by various hazards. The critical role of the Chornobyl accident (involving long-lived ^{137}Cs and possibly many other radionuclides, which were not taken into account in our study) is evident from the lack of such specific pathological lesions in analogous patients from Sweden and Austria.

It should be noted that classic descriptions of acute and chronic radiation effects on the urinary bladder do not coincide with the pathogenesis of human urinary bladder injury after long-term, low-dose exposure to IR. We did not observe reactive epithelial proliferation associated with fibrin deposits, fibrinoid vascular changes and multi-nucleated stromal cells, typical changes secondary to high doses of IR.

Pathogenesis of Chornobyl cystitis

Cell cycle regulation

Cell cycle check points function to maintain genetic stability by providing additional time for repair of DNA damage and completion of events that are necessary for accurate cell division. Some check points, such as the DNA damage G1 check point are dependent on p53, whereas others, such as the decatenation G2 check point, are not [10]. The molecular, genetic and cellular changes that occur in urothelial carcinomas are numerous and include loss of cell growth regulation. Several genetic alterations in bladder cancer have been linked with inactivation of tumor-suppressor genes [10]. In bladder urothelial carcinomas, one of the most frequently inactivated tumor-suppressor genes is the *p53* gene. Genetic alterations in *p53* occur in ?50% of bladder carcinomas and are associated with high-stage and high-grade urothelial lesions [11]. Spruck et al. have suggested the participation of two molecular pathways in urinary bladder carcinogenesis, with *p53* alterations occurring early in CIS and dysplasia before the development of non-papillary invasive lesions but occurring late in papillary urothelial carcinomas [12]. Thus, early detection of *p53* mutations in urinary bladder epithelial lesions (Chornobyl cystitis) may be strongly predictive of future urinary bladder cancer, especially of the non-papillary invasive type [13].

Our pilot studies indicated increased proliferative activity and possible genetic instability, with over-expression of p53, proliferating cell nuclear antigen (PCNA) and mdm2 in the bladder urothelium of exposed individuals with Chornobyl cystitis [ ]. The staining intensities of p53, PCNA, p21$^{WAF1/Cip1}$ and cyclin D1 were directly correlated with levels of radiation exposure and amounts of ^{137}Cs excreted in the urine by patients of groups 1 and 2. The patients from «clean» (not radiation contaminated) areas of Ukraine had significantly lower values for all parameters investigated [15].

It has been shown that wild-type p53 plays an essential role in transcription-coupled repair of DNA damage induced by oxidative stress, IR and some chemical carcinogens. The p53 protein expression in nuclei of bladder urothelium in both radiation contaminated groups 1 and 2 thus likely represents wild-type p53 accumulation in response to DNA damage. This speculation is supported by aberrant increases of PCNA, cyclin D1 and $p21^{WAF1/Cip1}$ in the same areas of urothelium, which could be explained by possible involvement of PCNA, cyclin D1 and $p21^{WAF1/Cip1}$ not only in DNA synthesis but also in DNA excision repair. An alternative explanation for the strong p53 protein expression observed in urothelium with Chornobyl cystitis is that it reflects mutations within *p53* gene.

Biopsied urinary bladder specimens were therefore analyzed for mutational inactivation of the *p53* gene by polymerase chain reaction-single strand conformation polymorphism (PCR-SSCP) analysis. In addition, urine sediments collected over intervals were examined by PCR-SSCP and assays of the ability of human p53 to activate transcription in yeast [13]. Because human *p53* cDNA polymerase chain reaction products can be cloned directly into the reporter yeast strain by homologous recombination without intermediate bacterial cloning steps, the percentage of positive red yeast colonies accurately reflects the mutant *p53* mRNA content of the starting material. Therefore, the assay can detect mutant *p53* in a minor fraction of cell clones such as those in urine sediments. Mutational analysis of the *p53* gene in DNA extracted from the urothelium of patients living in radiation contaminated areas of Ukraine revealed 9 of 17 cases (53%) to harbor one or more mutations within identical or separated samples [13]. This frequency is similar to values described for human high-grade, invasive urinary bladder cancers [12]. Although base deletions or insertions of the *p53* gene have been found in a certain proportion of human urinary bladder carcinomas [16], all *p53* mutations identified in this study were single-base-pair substitutions. The most striking feature was the predominance of G:C to A:T transition mutations at CpG dinucleotides, especially in codons 158, 245 and 248. Although IR has been reported to cause a variety of types of DNA damage including single- and double-strand breaks and cross-linking, direct *in vivo* evidence of radiation-induced base-pair substitutions is lacking. Thus, the underlying mechanism might be different from that responsible for the specific mutations observed in this study. In human urinary bladder carcinomas, no specific substitution pattern for the *p53* gene has hitherto been described, and there has been no pointer to any specific mutagen [16]. On the other hand, mutational analysis of schistosomal urinary bladder carcinomas (endemic in Egypt) gave results that are consistent with our findings; namely, a high proportion of base-pair changes at CpG dinucleotides (18 of 34; 53%). Chronic urinary infection with *Schistosoma hematobium* is a significant etiological factor in schistosomal urinary bladder carcinomas. Chornobyl cystitis was a common characteristic feature of cases in the present study. Recently, a close relationship between chronic infection and cancer risk has been suggested, with the production of nitric oxide (NO) during inflammatory processes playing a role [17]. It has been shown that NO can produce transitions at CpG dinucleotides by deamination of 5-methylcytosine [17]. In addition, endogenous formation of urinary *N*-nitroso compounds leads to O6-alkylguanine formation and G:C to A:T transitions [17].

Two patients of nine with *p53* mutations proved to have multiple *p53* mutations in the urinary bladder, in line with the report by Spruck et al. [12] and Goto et al. [18]. Different *p53* mutations in independent urothelial lesions (case 16) or in metachronous samples (case 17) indicate that a strong carcinogenic insult may have resulted in multiple transformation events in a large field of urothelium, as demonstrated previously in an animal model. The frequent (9 of 17 cases, 53%) *p53* mutations of altered urinary bladder epithelium in patients with Chornobyl cystitis suggest that prediction of induction of urinary bladder carcinoma may be possible.

Concerning the cell cycle transition regulation, it is necessary to note that activation of cyclin D1 and $p21^{WAF1/Cip1}$ occurs in response to activation of wild-type p53. It can be speculated that long-term exposure to low doses of ^{137}Cs induces chronic DNA damage in bladder urothelium. An increased level of $p21^{WAF1/Cip1}$ could thus be interpreted as a manifestation of cellular differentiation. $p21^{WAF1/Cip1}$ directly interacts with PCNA but the majority of studies show that it does not inhibit PCNA-dependent nucleotide excision repair. This suggests that $p21^{WAF1/Cip1}$ not only plays a critical role in negatively controlling proliferation but also could be activated in a p53-independent manner. About 75% of our cases in both groups 1 and 2 were cyclin D1 positive. It is possible that some of the observed cyclin D1 over-expression occurred in response to activation of wild-type p53 during radiation-induced DNA damage. The dramatic increase of PCNA staining in 88% of cases in groups 1 and 2 involving not only basal cells but also the suprabasal and superficial layers of bladder urothelium is indicative of increased cell proliferation.

In conclusion, the present finding of significant increases in p53, PCNA, cyclin D1 and to a lesser extent $p21^{WAF1/Cip1}$ expression in the majority of patients with Chornobyl cystitis in groups 1 and 2 chronically exposed to ionizing irradiation, associated with multiple *p53* gene mutations at CpG dinucleotides, is suggestive of a disregulated cell cycle transition that leads to increased chance of malignant transformation with the possible development of preferentially high-stage and high-grade bladder carcinoma among the population in Ukraine.

Increased oxidative stress, signaling cascades

Cellular stress is known to be a multifaceted condition generated by free-radical species, hypoxia and other factors that target the transcriptional factor nuclear factor-κB (NF-κB) with its two major subunit polypeptides, p50 and p65, and modulate their activity directly or indirectly by activating other signaling cascades. The p38 mitogen-activated protein kinase (MAPK) pathway is also involved in primary signaling activated by inducers of stress, such as IR inflammatory cytokines, mediating inhibition of cell proliferation and causing cell death. p50/p65 are the active transactivating species of NF-κB, responsible for induction of several genes involved in the control of cell proliferation, apoptosis and, hence, oncogenesis.

The pattern of Chornobyl cystitis, including four small incidentally detected pTa tumors in male patients with BPH of the radiation contaminated groups 1 and 2, was associated with strong p53 staining of the urothelial nuclei in the majority of cases (CIS and papillary urothelial carcinomas with severe dysplasia), overlapping with over-expression of the oxidative DNA damage marker, 8-hydroxydeoxyguanosine (8-OHdG), accompanied by elevation of cytoplasmic cyclooxygenase 2 (Cox2) and inducible NO synthase (iNOS). Therefore, our data suggest that the chronic low-dose irradiation could have at least two effects on the urinary bladder urothelium: (i) direct induction of oxidative stress due to irradiation DNA damage as IR is known to be a pure source of reactive oxidative species and (ii) indirect actions with possible consequences for homeostasis and reactions, involving inflammation following enhanced NO production, which triggers a cascade of oncogenic events, possibly initiated by *p53* mutations at sites involving CpG dinucleotides [13].

It is necessary to note that chronic infection and inflammation have become well recognized as risk factors for a variety of human cancers. It has been proposed that reactive oxygen and nitrogen species, both formed in infected and inflamed tissues, play roles in the multi-stage carcinogenic process. NO, a potential toxic substance with free-radical properties, is generated from L-arginine by constitutive NO synthase or iNOS.

One of the possible mechanisms underlying enhancement of initiation and promotion in carcinogenesis by oxidative stress is the ability to induce prostaglandin formation catalyzed by the

enzyme Cox, which converts arachidonic acid to prostaglandins. Presently two Cox enzymes are known Cox1 and Cox2, as important mediators of inflammation, whose synthesis can be stimulated rapidly by tumor promoters .

The marked increase of 8-OHdG, Cox2 and iNOS expression found in the majority of urothelium samples in groups 1 and 2 is an indicator of oxidative stress in its different manifestations. Murata et al. [19] demonstrated that NO induced mutations inactivating *p53* by causing deamination of cytosine, leading to G:C to A:T transitions *in vitro*. Our data, showing strong 8-OHdG, Cox2 and iNOS expression associated with *p53* mutational inactivation with frequent G:C to A:T transitions at CpG dinucleotides (in 73% of all mutations) with a hot spot in codon 245 in bladder urothelium of Ukrainian male patients with BPH [13], support the hypothesis that NO-mediated DNA deamination was induced by oxidative stress in groups 1 and 2 bladder urothelium.

Over-expression of p38 MAPK, p65 and p50 subunits of NF-?B by the same cells of urothelium in patients living in the radiation contaminated areas also strongly indicates a pivotal role of oxidative stress. Thus, our results point to low-dose radiation exposure acting on at least two distinct pathways:

cytoplasmic accumulation of NF-κB with p65 and p50 subunits as a result of protein synthesis,

➢ manifested by nuclear translocation;

➢ p38 MAPK-dependent transactivation of NF-κB.

Both of these are known to be required for full activation of NF-κB-dependent transcription.

Interestingly, the marked activation of angiogenesis in urinary bladder lamina propria observed in all cases of groups 1 and 2 with Chornobyl cystitis was associated with a dramatic increase of p38 MAPK and p65 cytoplasmic and nuclear expression as well as cytoplasmic iNOS and Cox2 in endothelial cells. These findings indicate a critical role for oxidative stress, as well as for the p38 MAPK signaling cascade and for the transcriptional factor NF-?B in endothelial cell activation, as an important component in the pathogenesis of Chornobyl cystitis. iNOS and Cox2 cytoplasmic expression in capillary endothelial cells of lamina propria, accompanied by the hypervascularization and the development of angiomatoid-like vessels, especially in group 1 patients, confirms the involvement of oxidative stress as a trigger of the angiogenic cascade, which is known to play a major role in human bladder carcinogenesis.

Furthermore, strong H-ras expression was evident in the bladder urothelium of patients from groups 1 and 2 [20]. Numerous cytokines and growth factors can activate the *ras* gene and H-*ras* expression may affect cell responses to chemical inducers of oxidative stress. This means that the H-*ras* expression in our material might reflect not only H-*ras* oncogene activation in bladder urothelium as an early event of human bladder carcinogenesis but also angiogenesis activated by oxidative stress.

In contrast to our results, it has been recently suggested that oxidative stress might play a key role in the inhibition of tumor initiation by p38 MAPK. Thus, Dolado et al.[ ] suggested that p38 MAPK acts to suppress tumor formation by H-*ras*. p38 MAPK pathway is implicated in suppression of tumorigenesis because it can inhibit cell growth by decreasing the expression of cyclin D, inhibit the activity of Cdc25 phosphatases and engage the p16/Rb and p19ARF/p53 tumor-suppressor pathways.

In conclusion, our findings point to a significant relationship between oxidative stress induced by long-term, low-dose IR in people living >20 years in radiation contaminated (^{137}Cs) areas of Ukraine and the development of Chornobyl cystitis, a possible pre-neoplastic condition in the urinary bladder.

Growth factors

Exposure of cells to a variety of stresses, including IR, induces compensatory activation of multiple intracellular signaling pathways. Change in expression of growth factor receptors such as fibroblast growth factor receptor 3 (FGFR3) and epidermal growth factor receptors (EGFRs) expressed by target cells due to radiation-induced signaling is therefore a question of interest. In our search for new markers of urinary bladder carcinogenesis, we recently were attracted by the FGFR3, a member of the receptor tyrosine kinase family, with heparin glycosaminoglycan as an important cofactor [22]. Recently, *FGFR3* mutations were found in >70% of non-invasive papillary urinary bladder carcinomas in humans [22]. The high frequency of *FGFR3* mutations in superficial urothelial carcinomas contrasts with the absence of *FGFR3* mutations in CIS and the low percentage of mutations in invasive urothelial carcinomas [22].

Recent studies showed that EGFR1 expression is increased in muscle-invasive carcinomas as compared with superficial bladder carcinomas and correlates with poor survival of patients with bladder cancer. Moreover, the ErbB2 proto-oncogene, also called HER2 or EGFR2*neu* located at 17q21, which encodes a 185 kDa transmembrane glycoprotein (p185HER2/*neu*) with tyrosine kinase activity, has been shown to be over-expressed in a variety of primary human carcinomas with a more aggressive clinical course, including breast, lung, ovarian and urinary bladder carcinomas [23].

Several signal transduction pathways have been implicated in EGFR-dependent cell survival as it relates to the anchorage-independent state. Primarily, these include the Ras/Raf/MEK/MAPK cascade. Raf-1 is a member of a family of serine-threonine protein kinases termed Raf-1, B-Raf and A-Raf, activated dependent upon Raf-1 translocation to the plasma membrane where phosphorylation occurs. Raf-1 activates MAP/ERK kinase (MEK), which in turn phosphorylates MAPK. Raf-1 protein expression is elevated in human breast carcinoma and it might be responsible for malignant progression. However, we were unable to find studies reporting the presence of Raf-1 protein in urinary bladder carcinomas, except one, related to Raf-1 amplification in urothelial cancers with mutation of the *p53* gene.

On the basis of these observations, we designed a study to compare alterations in signaling cell systems in different patient groups (with pre-neoplastic lesions, Chornobyl cystitis and already well-developed urothelial carcinomas) and relationships among three immunohistochemical markers of the growth factor receptors and Raf-1.

Molecular analysis of some growth factor receptors in urinary bladder lesions, described by our group as Chornobyl cystitis (groups 1 and 2), as well as urothelium from analogous patients from so-called clean areas (group 3) with primary urothelial carcinomas, revealed dramatic nuclear and cytoplasmic FGFR3 (isotype unknown) over-expression with a high score of 95% in group 1 cases [24]. Multiple areas of dysplasia and CIS were stained consistently and very strongly. Furthermore, because the *FGFR3* gene is known to be expressed both in normal urothelium and in bladder carcinomas, it is likely that the mutant gene has an oncogenic role in bladder carcinoma pathogenesis [22].

We have recently found *FGFR3* gene mutations in 30% of cases in the urothelial carcinoma patients (A. Romanenko, K. Morimura, A. Kakehashi, H. Wanibuchi, A. Vozianov, and S. Fukushima, unpublished data), the majority within the spectrum of oncogenic mutations (codon 249 TCC to TGC). Mutations were detected almost equally in both high- and low-grade/stage urothelial carcinomas, in contrast to recent reports of an absence of FGFR3 mutations in CIS and a very low percentage of mutations in invasive (pT2-4) urinary bladder carcinomas [22].

The marked increase of FGFR3 nuclear expression in 95% of urothelia in group 1 patients, associated with dysplasias and CIS, could be strongly related to the early events of the urinary bladder carcinogenesis in people living in the radiation contaminated areas of Ukraine. The majority (70%) of the primary bladder carcinomas in the additional urothelial carcinoma group (also from patients living in the radiation contaminated areas) demonstrated nuclear, membranous and more rarely cytoplasmic FGFR3 expression in both superficial and invasive carcinomas. These findings provide support for the idea that in the case of the presence (induction) of FGFR3 mutations, invasive carcinomas may arise from mutated superficial (pTa-pT1) carcinomas, which might progress from CIS.

It is necessary to note that FGFR3 cytoplasmic and nuclear over-expression was detected in both endothelial cells and fibroblasts of lamina propria of the same patients. Our results might suggest that mesenchymal cells are required for the induction of urothelial cell transformation. Evidence has accumulated that epithelial autocrine cells, constitutively producing and secreting the FGF and expressing FGFR3, have a highly aggressive mesenchymal phenotype [25]. Other studies demonstrated that FGFs can activate FGFRs that in turn can promote tumor cell proliferation in an autocrine fashion by stimulating the growth, survival and migration of stromal cells, including fibroblasts and smooth muscle cells, or, as demonstrated in our work, participating in the induction of tumor angiogenesis [26]. Importantly, the marked activation of angiogenesis in urinary bladder lamina propria in the majority of cases with Chornobyl cystitis was associated with a dramatic increase of FGFR3, EGFR1 and EGFR2*neu* expression in endothelial cells.

In our studies, EGFR1 and EGFR2*neu* immunoreactivity was found to be increased in the same cells of the bladder urothelium in group 1. Cytoplasmic over-expression in particular appears significantly associated with the Chornobyl cystitis pattern. This may also be the case for squamous cell carcinoma and pre-cancerous lesions of the lung [27], with prognostic importance for trafficking of EGFR1 between the Golgi apparatus and cell membranes and internalization of EGFR1 after interaction with an EGFR ligand. Moreover, cytoplasmic expression of EGFR has been correlated with a poor prognosis and increased metastatic potential in lung cancers [27].

EGFR and other receptor tyrosine kinases are immediate early response gene products that are activated by IR within minutes, as with their physiological growth factor ligands that cause complex cytoprotective responses including increased cell proliferation, reduced apoptosis and enhanced DNA repair. As repeated radiation exposure can induce a strong cellular proliferative response *in vitro*, evaluation of human response levels after sustained long-term, low-dose IR is clearly of interest.

Cell-cell contact inhibition is considered to contribute to control of cell growth, with involvement of molecules that mediate cell adhesion, such as cadherins. In addition to our finding of significant EGFR1, EGFR2*neu* and Raf-1 activation in urothelium of group 1 patients, transforming growth factor (TGF)-α over-expression and alteration in E-cadherin-β-catenin complexes in the analogous bladder lesions has been reported [28]. Since cell-cell contact inhibition is an important regulatory mechanism of cell growth, its loss due the MAPK activation could contribute to uncontrolled tumor growth and might correlate with an invasive phenotype. Collectively, our findings suggest that FGFR and EGFR signaling pathways associated with EGFR2*neu* and Raf-1 activation may contribute to several facets of multi-stage urothelial carcinogenesis, including auto- or paracrine growth stimulation, up-regulation of angiogenesis and stromal remodeling.

DNA damage and repair

Understanding the long-term effects of low doses of IR on living organisms requires identification of critical radiation-induced DNA lesions, measurement of their repair and determination of the consequences of misrepair or non-repair. Our results suggest that increased oxidative stress in the bladder urothelium of the Ukrainian population in Chornobyl radiation contaminated areas is accompanied by marked DNA damage and repair by 8-oxoguanine-DNA glycosylase 1.

Our recent studies showed mutational inactivation of the *p53* tumor-suppressor gene, with strong *p53* immunoreactivity of urinary bladder urothelium in this group of Ukrainian patients [13]. The *p53* gene in vivo modulates the base excision repair activity pattern after the oxidative stress generated by IR, suggesting a direct role in housekeeping base excision repair activity, with molecular cross-talk between the p53 protein and the DNA repair machinery. Furthermore, mutant *p53* seems to confer higher base excision repair activity in response to oxidative stress, in agreement with our observations of strong base excision repair enzyme expression in areas of urothelial dysplasia and CIS. However, activity is irregular in the background urothelium so that some cells may suffer inefficient base excision repair [29]. In contrast, nuclear over-expression of apurinic/apyrimidinic endonuclease 1 (APE1), a major endonuclease acting on apurinic/apyridinic sites after exposure to IR, appears homogeneous. Recently, nuclear APE1 expression was documented as a facet of increased cellular resistance to oxidizing agents [30], contributing to base excision repair of reactive oxygen species (ROS)-induced lesions. This finding is consistent with the previous observation that APE1 activation after ROS generation is accompanied by adaptive resistance of the cells to ROS [30]. Our data suggest that APE1 is also important for repairing oxidative DNA lesions in human urothelium as a result of long-term, low-dose exposure to IR [29].

The significant increase of nuclear xeroderma pigmentosum A (XPA) protein level evident in urothelium of group 1 patients is indicative of activation of transcriptional coupled repair and global genome repair pathways. Recent studies showed a major role of XPA protein in the early steps of nucleotide excision repair reaction with low-dose (0.2–2 Gy) IR exposure [ ]. A marked increase in nuclear 8-OHdG, APE1 and XPA, but not 8-oxoguanine-DNA glycosylase 1, was detected in the endothelial cells of micro-vessels, macrophages and lymphocytes close to the urothelium, also suggesting DNA repair in the bladder propria mucosa. Importantly, all detectable small invasive transitional cell carcinomas in our group 1 patients were mostly negative for 8-oxoguanine-DNA glycosylase 1, APE1 and XPA presumably, indicating the apparent disruption of the base and nucleotide repair machinery in these malignant cells. Whether oxidative damage does not occur in tumors is a question that requires further investigation.

Microenvironment-intercellular communications

Redox homeostatic processes in the microenvironment, involving signaling pathways and interaction between cells and also with the extracellular matrix, could be targets of chronic low-dose IR. Cellular interactions are modulated by cytokines and growth factors, which are known to be multi-functional molecules that orchestrate most aspects of the inflammatory response, eliciting their effects locally or systemically in an autocrine or paracrine manner. One of the TGF family multi-functional cytokines, the TGF-beta1 (TGF-β1), is known to regulate cell growth and differentiation, tissue remodeling, immune response and angiogenesis. Three major isoforms exist in mammals: TGF-β1, 2 and 3.

Alterations of cadherin-catenin complexes have also attracted interest as important for progression of many carcinomas in humans. Components of the E-cadherin-β-catenin complex, as well as TGF-β1 and iNOS, were evaluated in urinary bladder specimens in an attempt to detect molec-

ular lesions of cellular membranes with a possible role in urothelial changes in patients chronically exposed to low-dose IR after the Chornobyl accident in Ukraine. We thereby documented for the first time that Chornobyl cystitis with foci of urothelial dysplasia, CIS, and fibrosis of the lamina propria, is associated with activation of TGF-β1, as well as disruption of E-cadherin-β-catenin expression, which might be a result of chronic long-term, low-dose IR exposure.

Whereas excess ROS production clearly damages DNA, low levels might affect cell signaling, particularly, redox modulation. TGF-β1 is a major extracellular signaling sensor of damage, as it mediates redox homeostasis in cells and contributes to cell-cell communication. It is known as a mediator of tissue response to IR, pointing to a role in orchestrating changes due to oxidative stress. The present results indicate that alteration of TGF-β1 is a frequent event in background bladder urothelium of group 1 patients, with decrease observed in areas of dysplasia and CIS and little to no immunoreactivity in urothelial carcinomas. Furthermore, we found TGF-β1 immunostaining to be most pronounced in the lamina propria, in particular, in areas of sclerosis and fibrosis, where production of inflammatory cell cytokines is clearly important. IR appears to be one of a few exogenous agents that can cause TGF-β1 activation *in situ*.

Evidence has accumulated that gap junction intercellular communication is sensitive to oxidative stress. It was demonstrated that loss of Cx32/gap junction intercellular communication plays a significant role in radiation-induced tumorigenesis of the liver and importantly that Cx32 may also play a role in tumor suppression and/or tumor progression in other tissue types such as lung and adrenal gland [32]. Cx32 was demonstrated to function as a hepatic tumor suppressor in response to radiation-associated mutation events [32]. E-cadherin-β-catenin complexes are required for formation of gap junction intercellular communication, whereas mutations in the β-catenin gene have been described for various human cancers. Our findings indicate that alterations of E-cadherin-β-catenin are frequent in bladder urothelium of people living in radiation contaminated areas. Elevated protein levels of E-cadherin and β-catenin as well as their abnormal cytoplasmic localization detected in the urothelial cells could be the early event in urinary bladder carcinogenesis induced by long-term, low-dose IR exposure. Our results in line with other studies have suggested that oxidative stress causes internalization of E-cadherin from the plasma membrane to the cytosol [28]. Intracellular accumulation of ?-catenin might correspond to an increased level of hypophosphorylated β-catenin caused by a mutation, in turn leading to transduction of oncogenic signals and cancer progression. Over-expression may result in the premature reentry of cells into the cell cycle after γ-irradiation-induced DNA damage and thereby promote the accumulation of oncogene mutations and carcinogenesis.

Importantly, aberrant expression of β-catenin and E-cadherin in association with TGF-β1 up-regulation in lamina propria appears to be essential molecular alteration in pathogenesis of bladder urothelial carcinomas in the environment of continued chronic long-term, low-dose IR exposure, when compared with CIS and urothelial carcinomas which developed before the Chornobyl accident.

Ubiquitination and sumoylation

Recent evidence suggests that the ubiquitin (Ub)/proteasome system may play a critical role in responses to IR, controlling numerous physiological processes including signal transduction, DNA repair, cell cycle progression, cell survival and stress responses [33]. This is in addition to its more established roles in the removal of misfolded, damaged and effete proteins [33]. Ub, consisting of 76 amino acids, is an element within the Ub/proteasome system requiring initial activation by Ub-activating enzyme E1 in an ATP-dependent reaction. Ub is covalently bound to E1 and then passed to the E2 Ub-conjugating enzyme, where it forms a similar thiolester

linkage. Ubiquitinated proteins are then degraded by the 26S proteasome complex [33]. In addition to Ub, there are several Ub-like proteins. One of them, the small Ub-related modifier (SUMO), has been shown to covalently modify a large number of proteins with important roles in many cellular processes including gene expression, maintenance of chromatin structure and signal transduction . Post-translational modification by SUMO is not associated with protein degradation but rather plays role in determining protein localization and activity. In contrast to the Ub system where dozens of E2 enzymes have been identified, Ubc9 is the only known SUMO E2-conjugating enzyme. Many known targets for SUMO1 and Ubc9 (the integral players in sumoylation) are nuclear proteins with important roles in regulating transcription chromatin structure and DNA repair.

Classical examples are the tumor-suppressor proteins p53 and $p27^{Kip1}$ whose function is abolished in many tumors. Since ubiquitination and sumoylation are intimately involved in major cellular biological processes and many effects of IR involve changes in protein stability, it is reasonable to ask what effect these processes have on cellular responses to chronic long-term, low-dose radiation. Therefore, we examined the levels of ubiquitination and sumoylation elements in Chornobyl cystitis induced by long-term, low-dose IR in Ukraine. For this purpose, Ub, SUMO1 protein, the SUMO E2-conjugating enzyme Ubc9, the cell cycle inhibitor $p27^{Kip1}$ and the tumor-suppressor protein p53 were evaluated by immunohistochemistry in a series of radiation-exposed patients and controls. This revealed Ub, SUMO1 and Ubc9 over-expression, with high scores in 96, 96 and 72% of cases, respectively (Table 5.3.5). Steady-state accumulation of p53 protein in 60% cases was accompanied by loss or severe reduction of $p27^{Kip1}$ protein in 76% cases [34]. Over-expression of Ub, SUMO1 and Ubc9 might be related to the accumulation of the mutated p53, which is not degraded in IR-affected cells or, on the contrary, to the proteolysis of $p27^{Kip1}$ tumor suppressor.

Imunohistochemical scores for proteins of Ub/proteasome system

The Ub/proteasome system may have a critical role in rapid and late responses to IR with radiation-induced (through free-radical damage) impairment of proteasome function, which results in inhibition of proteolysis. Because repeated radiation exposure can induce a strong cellular proliferative response in vitro, human response levels after sustained long-term, low-dose IR are of interest.

The tumor-suppressor protein p53 is known to be rapidly turned over in unstressed cells by the Ub/proteasome-dependent pathway and it has been found to be covalently modified by SUMO1 in vitro and in vivo through direct interaction with the SUMO E2-conjugating enzyme Ubc9.

Table 5.3.5
Imunohistochemical scores for proteins of Ub/proteasome system

Protein/factor	Groups 1 and 2	Group 3
No. of patients	26	24
Contamination levels in soils (Ci/km^2)	0.5–30	NC[a]
Ub	$7.4 \pm 1.9^{b,*}$	1.7 ± 2.4
SUMO1	$7.6 \pm 1.8^{b,**}$	4.4 ± 2.9
Ubc9	$6.4 \pm 2.4^{b,*}$	2.6 ± 1.5
p53	$5.1 \pm 3.7^{b,*}$	0.7 ± 1.0
p27	$3.0 \pm 2.0^{b,*}$	6.5 ± 2.6

Notes. Data are mean ± SD (immunohistochemical scores); [a] – non–contaminated; [b] – significantly different versus group 3; * – $p < 0.0001$; ** – $p < 0.001$.

Accumulating evidence suggests an intrinsic role of sumoylation of p53 in stress-related processes, including DNA damage. Therefore, the fact that at least 60% of group 1 cases showed high scores for p53 protein over-expression is of clear interest [34]. Earlier, we reported defective regulation in cell cycling and DNA damage involving p53 and mdm2 expression, accompanied by specific *p53* gene mutations with G:C to A:T transitions at CpG dinucleotides and a hot spot at codon 245 in 53% of a series of patients with Chornobyl cystitis [9,13]. Therefore, our findings support the idea that increased p53 protein stability resulting from mutations prevents recognition by the Ub-mediated degradation machinery as well as by sumoylation modifying processes.

Destabilization of another Ub/proteasome target, the tumor-suppressor $p27^{Kip1}$ protein, has also been implicated in the pathogenesis of cancers [33]. Of our cases of Chornobyl cystitis, 36% showed loss or significantly decreased levels of $p27^{Kip1}$ expression in the nuclei and cytoplasm. However, in 44% of cases, we observed predominantly $p27^{Kip1}$ cytoplasmic staining. These observations suggest that decreased nuclear $p27^{Kip1}$ expression may be due to cytoplasmic translocation, known to be a result of mitogenic stimulation and has been claimed to be related to a poor prognosis.

Thus, our study suggests that ubiquitination and sumoylation processes are direct targets of long-term, low-dose IR exposure, leading to unscheduled protein degradation. Up-regulated ubiquitination and sumoylation processes might be an adaptive response to insufficient proteolysis of aberrant p53 and $p27^{Kip1}$ occurring due to long-term, low-dose IR exposure. These results are in line with recent findings that aberrant, unscheduled proteolysis of many cell cycle regulators contributes significantly to tumorigenesis, with increased protein stability as a result of mutations that prevent recognition by the Ub-mediated degradation and sumoylation machinery. If critically damaged cells with aberrant p53 protein escape from elimination, this would mean survival of cells with mutations in an environment of continued long-term, low-dose IR exposure.

* * *

Our data support the hypothesis of distinct molecular carcinogenesis pathways for bladder cancer in Ukraine before and after the Chornobyl disaster [35]. The biological effects of chronic low doses of IR and their relationships with chronic inflammation and carcinogenesis have received much attention in the last few years. Series of our recent studies point to a strong relationship between oxidative stress, accompanied by at least two signaling pathways (involving p38 MAPK NF-κB cascades) and growth factor receptor activation, induced by the IR exposure of people who have lived for $\geq$20 years in radiation contaminated areas of Ukraine, and the development of radiation chronic proliferative atypical cystitis, so-called Chornobyl cystitis, a preneoplastic condition in humans (Figure 5.3.1) [36]. Dramatic increase of iNOS, Cox2 and 8-OHdG expression is associated with the observed chronic inflammation; this may be mutagenic through NO-mediated DNA damage or hindrance to DNA repair and thus potentially carcinogenic, as suggested by p53 accumulation in urothelium of Chornobyl cystitis together with frequent G:C to A:T transitions at CpG dinucleotides in the *p53* gene [13]. Inflammation-induced reactive oxygen and nitrogen species cause damage to important cellular components (e.g. DNA, proteins and lipids), which can directly or indirectly contribute to neoplastic cell transformation. Over-expression, elevated secretion or abnormal activation of pro-inflammatory mediators, such as cytokines, chemokines, Cox2, prostaglandins, iNOS and NO, and a distinct network of intracellular signaling molecules including upstream kinases and transcription factors facilitate tumor promotion and progression. These enzymes may be acting as a 'landscaping tumor promoters' in the bladder urothelium and influence tumor growth according to the landscaping model proposed by Kinzler and Vogelstein (1998). On the other hand, DNA methylation and histone modifications are important epigenetic mechanisms of gene regulation

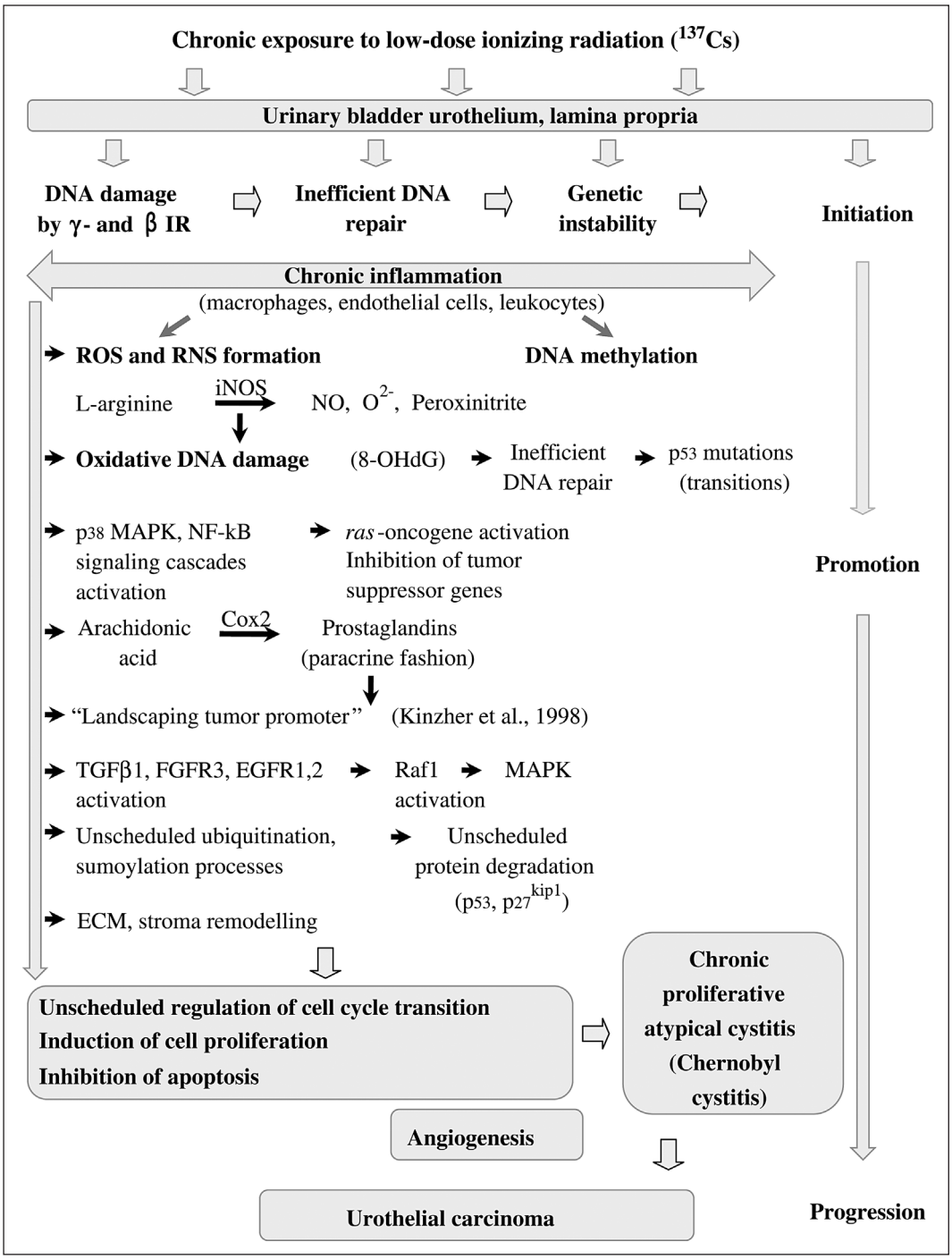


Figure 5.3.1. Schematic representation of cellular and molecular responses induced by exposure to chronic long-term, low-dose IR in the bladder urothelium of people living in ^{137}Cs-contaminated areas of Ukraine after the Chornobyl accident

and play essential roles both independently and cooperatively in tumor initiation, promotion and progression. Furthermore, recently, the possible mechanisms by which inflammation can contribute to carcinogenesis were reported to include induction of genomic instability, alterations in DNA methylation and subsequent inappropriate gene expression, enhanced proliferation of initiated cells, resistance to apoptosis, aggressive tumor neovascularization, invasion through tumor-associated basement membrane metastasis etc. Furthermore, significant alteration in regulation of cell cycle transition associated with increased activation of proliferative processes (p53, cyclin D1, mdm2, $p21^{WAF1/Cip1}$ and PCNA protein over-expression) has been documented [15], along with changes in ubiquitination and sumoylation processes in association with aberrant unscheduled proteolysis of many cell cycle regulators [34]. Moreover, DNA repair appears to be an early event in the radiation-induced adaptive response. Exhaustion of the capacity for base and nucleotide excision repair pathways associated with Chornobyl cystitis may be related to the carcinogenic potential of the urothelial lesions.

Bladder urothelium as well as endothelial cells, fibroblasts and immune cells in the microenvironment respond to chronic low-dose IR by activation of FGFR and EGFR signaling pathways in association with EGFR2*neu*, Raf-1 and stromal TGF-β1 activation with aberrant expression of the urothelial β-catenin-E-cadherin complexes, which may potentially contribute to several facets of multi-stage urothelial carcinogenesis, including auto- or paracrine growth stimulation, up-regulation of angiogenesis and stromal remodeling. It can be supposed that the microenvironment changes induced by IR, detected in our studies, could promote angiogenesis, remodeling the extracellular matrix to facilitate invasion as well as the progression of pre-existing initiated cells to malignancy. This hypothesis for chronic long-term, low-dose IR action is supported by the emerging concept that elements other than epithelial cells, and mechanisms other than genetic alteration, influence the processes of carcinogenesis. Based on now available IR-induced urinary bladder carcinogenesis markers in patients living in radiation contaminated areas, prediction and early detection of Chornobyl cystitis becomes very important. Moreover, patients from the radiation contaminated areas have to be followed up for many years with the cytological analysis of urine sediment as well as other clinical investigations. The targeting therapy might be used against some genes, growth factors and other important molecules, which are responsible for cell cycle transition, cell-cell communication and signaling cascades. Furthermore, it might be recommended to use some pectines and able to bind to ^{137}Cs and other radionuclides, thus eliminating them. Placing chronic low-dose radiation damage at the cellular level into the context of a dynamic multicellular system will provide a better basis for understanding and treatment of Chornobyl cystitis – the first step in a specific category of urinary bladder carcinogenesis in humans.

5.3.3. Prostate lesions induced by persistent chronic low-dose ionizing radiation

Ukrainian patients with benign prostate hyperplasia (BPH) were underwent open adenomectomy between 2007 and 2012, consisting of 30 patients from so called clean (without radio-contamination) areas (control group1) and 90 patients living in ^{137}Cs contaminated areas of Ukraine (group 2). These patients underwent surgery in the Institute of Urology, National Academy of Medical Sciences of Ukraine in Kyiv (Ukraine). It is necessary to note that these patients resided in the same areas during the pre- and post-Chornobyl accident periods. Furthermore, the histological and immunohistochemical studies were performed in collaboration with the Department of Laboratory Medicine, Tumor Biology (Professor and Chairman , Dr. Pirkko Harkonen M.D., Ph.D.) MAS University Hospital, Lund University, Malmo, (Sweden).

We thank professor Dr. Pirkko Harkonen, M.D., Ph.D., professor Sergey Vozianov, M.D., Ph.D., Anna Chekalova, M.D., Ph.D., Andriy Yurakh, M.D., Ph.D. for their kind assistance in our study.

The Chornobyl accident which occurred in April 1986 in Ukraine, was the first event to pose the problem of chronic long-term effects of low-dose ionizing radiation (IR) in humans.

As of now, 29 years after the accident, more than 10 million people who live in radio-contaminated areas of Ukraine, Russia and Byalorussia, are still exposed to low doses of persistent Cesium-137 (^{137}Cs) radiation, known to account for 90% of internal radioactivity, which is concentrated and eliminated through kidneys, and 90% of the more labile pool of ^{137}Cs is excreted via the urine [37, 38].

An increased incidence of renal cell carcinomas and urinary bladder cancer in adults in Ukraine after the Chernobyl accident has also been reported [39, 40].

Since, the prostate gland is adjacent to the urinary bladder, it is plausible that this gland may also be a target of radionuclides especially in benign prostate hyperplasia (BPH) patients with urinary retention as well as with the residual urine in the urinary bladder. During the 29 year period subsequent to the Chornobyl accident the morbidity of prostate cancer in Ukraine has increased from 12.0 to 33.4 per 100 000 of male population.

The present study investigated whether there is any increase in pre-malignant histological and molecular changes in prostates with BPH that can be associated with radiation exposure in the Ukrainian population. Two groups of the Ukrainian BPH patients which represent a varying degrees of internal exposure to irradiation were therefore selected for comparison. Patients characteristics were shown in Table 5.3.6. Radiometric measurement of ^{137}Cs was conducted with urine collected over 24 h. from patients of groups 1 and 2 before surgery. The results obtained from ^{137}Cs measurement in 1-day urine from patients in groups 1 and 2 were summarized in Table 5.3.6. Significant elevation of ^{137}Cs levels was evident in those from group 2 (6.4 Bq/liter or 102 micro Sievert/year) as compared with group 1 (0.29 Bq/liter or 5 micro Sievert/year).

Table 5.3.6
Imunohistochemical scores for proteins of Ub/proteasome system

Parameter	Group 1	Group 2
Number of patients	30	90
Median age (range)	65 (52–91)	66 (54–75)
Nutrition	Standard	Standard
Years of surgery	2007–2012	2007–2012
[1]Contamination levels in soils, Ci/km^2	NC[2]	0,5–30
Contamination levels in urine (Bq/liter)	0.29 ± 0.03	6.47 ± 14.30[3,4]

Notes. [1] – Data from Raes et al. (1991); [2] – Non-contaminated area; [3] – Mean ± SD; [4] – Significantly different vs. group 1 at $p<0/001$ (χ^2 or Fisher's exact probability test).

Prostate Intraepithelial Neoplasia (PIN) was classified into low and high grade according to the criteria defined by WHO Classification of tumors

Histopathology

Very specific histological lesions in group 2 prostates with BPH were found, in comparison with the group 1 control analogous specimens. Large areas of sclerosis and hyalinosis of connective tissue in stroma with less prominent inflammatory cellular infiltration of lymphocytes,

Table 5.3.7
Incidences of the inflammatory reaction, epithelial dysplasias and latent carcinomas in groups 1 and 2 BPH patients

Pathological features	Groups of BPH patients		Significance	
	I No of patients (%)	II No of patients (%)	χ^2	*p*
Inflammation	16 (53.3)	58 (64.4)	1.2	0.3
LG PIN	8 (26.7)	23 (25.6)	0.01	0.9
HG PIN	0	10 (11.1)	3.6	0.06
PIA	6 (20)	17 (18.9)	0.02	0.9
PIA with cellular atypia	2 (6.7)	22 (24.4)	4.4	0.035
BCH	7 (23.3)	32 (35.6)	1.5	0.2
BCH with cellular atypia	0	15 (16.7)	5.7	0.017
Latent prostate carcinoma	5 (16.7)	11 (12.2)	0.4	0.5
Total	**30 (100)**	**90 (100)**		

macrophages, hystiocytes and plasma cells were typical for group 2 BPH cases. Along with these lesions definite blood vessel walls thickness associated with their dilatation and endothelial proliferation of the new stromal microvessels were also detected. Multiple areas of proliferative inflammatory atrophy (PIA), less areas of prostatic intraepithelial neoplasia (PIN) as well as areas of basal cell hyperplasia (BCH) were rather frequently found in group 2 BPH cases, to compare with the control group 1. Incidences of the stromal inflammatory infiltration and epithelial dysplasias in groups 1 and 2 BPH patients were summarized in Table 5.3.7.

Significantly more frequent incidences of PIA and BCH with cellular atypia as well as areas of high grade PIN (HG PIN) were detected in group 2 BPH cases. However, incidences of intrastromal inflammatory response as well as the incidentally found areas of prostate latent carcinomas did not show the significant differences between groups 1 and 2.

Alterations of cell cycle and apoptotic regulatory molecules in benign prostatic hyperplasia after the Chornobyl accident in Ukraine

Immunohistochemical (IHC) analysis was performed in Tumor Biology Wallenberg Laboratory Malmo University Hospital (Department of Laboratory Medicine, Professor & Chairman Pirkko Harkonen, MD, PhD). Cancer – critical proteins were selected for our IHC study: tumor suppressor genes proteins (p53, p27Kip1), proliferation marker (Ki-67), DNA double-strand breaks marker which is known to be sensitive even to low doses of ionizing radiation (γ-H2AX), oxidative stress marker – inducible NO synthase (iNOS), basal cell marker (p63) and Bcl-2, proto-oncogene, a member of a family of genes known to inhibit apoptosis.

IHC results for γ-H2AX, iNOS, p53, Ki67, p27Kip1, p63 and Bcl-2 of BPH specimens in groups 1 and 2 are summarized in Table 5.3.8. Pathological and IHC findings in BPH from patients living in radio-contaminated areas (group 2) are illustrated in Figures 5.3.2 and 5.3.3.

Significantly increased nuclear γ-H2AX protein expression levels were obtained in areas of PIA and BCH (especially with cellular atypia), less in areas of PIN (scores 8.1, 8.4 and 3.5), respectively, to compare with group 1 cases (scores 2.3, 0, 1.9, respectively). Remarkably, the granular nuclear γ-H2AX staining was detected in acinar basal cells as well as in stromal fibroblasts, leyomiocytes, limphocytes, endothelial cells and macrophages in group 2 BPH cases.

The same correlations were obtained with cytoplasmic iNOS protein expression with highest levels of iNOS homogeneous cytoplasmic staining in areas of PIA and BCH with cellular atyp-

Table 5.3.8
Immunohistochemical results in relationship with groups and pathological features

Hystological diagnosis	Proteins expression indices (scores)													
	γH2AX		iNOS		p53		Ki-67		p27Kip1		p63		Bc1–2	
	Group1	Group 2	Group1	Group 2	Group1	Group 2	Group1	Group 2	Group1	Group 2	Group1	Group 2	Group1	Group 2
BPH	0,5±0,8	1,9±1,3***	0,5±0,8	1,4±0,9***	0,2±0,5	0,5±0,7*	0,4±0,8	1,1±1,1**	8,1±1,4	8,0±1,4	8,8±0,8	8,5±1,2	0	0
PIN	1,9±1,4	3,5±1,3**	1,1±1,4	2,8±1,2***	2,7±0,9	3,2±0,9	4,3±2,1	6,5±1,9**	3,8±0,9	4,2±1,3	5,2±1,2	4,0±1,0**	3,1±1,5	3,2±1,3
BCH	2,9±2,6	7,7±1,7***	1,5±0,7	3,0±1,0	2,0±0,8	3,0±1,8	3,3±0,7	4,0±1,1	6,3±1,9	5,8±1,7	8,3±1,4	3,8±1,0***	1,3±1,5	2,5±0,8**
BCH with cellular atypia	–	8,4±1,2	–	5,9±1,6	–	6,9±2,4	–	7,0±1,5	–	3,4±1,3	–	1,1±0,6	–	4,5±1,2
PIA	2,3±1,5	6,9±2,2***	2,7±1,9	4,4±2,2	3,0±0,8	6,2±1,8***	3,3±1,5	4,9±1,4*	5,7±0,8	4,0±1,1**	5,7±0,8	3,9±0,9***	1,7±0,8	3,5±0,9***
PIA with cellular atypia	2,3±0,6	8,1±1,4***	2,7±0,6	6,3±1,8**	5,0±1,4	8,5±1,2**	6,3±2,5	8,3±1,3*	3,7±2,1	3,9±1,2	4,7±1,2	2,4±0,8***	3,7±1,6	6,7±1,8**
Latent prostate carcinoma	0,4±0,8	1,8±0,8**	2,2±0,4	2,7±0,9	1,6±0,5	2,3±0,8	1,6±0,9	3,1±1,0*	4,6±1,3	4,0±1,2	3,8±0,5	2,5±0,8**	2,4±0,5	4,3±1,2**

Notes. The results are given as means ± SD; * – $p < 0,05$ compared with group 1; ** – $p < 0,01$ compared with group 1; *** – $p < 0,001$ compared with group 1.

ia ($p < 0.01$ and 0.001, respectively) as well as in stromal cells of the group 2 BPH cases, in comparison with the group 1 BPH cases.

The nuclear p53 protein overexpression (scores 9 and 6) was detected in 30 (33.4%) and 19 (21.12%) from 90 group 2 cases, respectively. However, the majority of these BPH cases showed areas of PIA and especially PIA with cellular atypia.

The same priorities were obtained with Ki-67 nuclear overexpression with scores 9, 6 and 4 in 15 (16.67%), 30 (33.4%) and 4 (4.45%) from 90 group 2 cases, respectively, especially in the areas of PIA and BCH with cellular atypia and areas of the incidentally found latent adenocarcinoma, less in PIN and BCH without cellular atypia.

The indicative tendency to lose p27Kip1 immunoreactivity was shown in areas of PIA, HGPIN and latent adenocarcinoma, especially in the areas of PIA and BCH with cellular atypia of group 2 patients. The p27Kip1 immunoreactivity scores of these areas were evaluated between 1–2, 2–3 and 4 in 3 (3.34%), 17 (18.89%) and 19 (21.12%) cases, respectively. It is necessary to note that p27Kip1 staining was predominantly cytoplasmic. There were no significant differences for p27Kip1 staining between groups 1 and 2.

Interestingly, the intensity of the granular nuclear p63 immunoreactivity gradually decreased in areas of BCH, PIA and less PIN in group 2 BPH cases, to compare with the BPH acinar epithelial cells, without significant differences between groups 1 and 2. BCH areas showed homogeneous nuclear staining in basal cells with scores 9–6 in 30 (33.4%) and scores 4 in 27 (30%) of group 1 cases. Areas of PIA and PIN in group 2 BPH cases demonstrated predominantly mosaic and weak p63 staining in 24 (26.67%) of 90 group 2 cases with scores 3. As for BCH and PIA areas with cellular atypia as well as in areas of incidentally found carcinoma, the p63 staining was negative or was scored as 1–2.

The homogeneous membranous and cytoplasmic Bcl-2 staining was the greatest in PIA and BCH areas with cellular atypia, less in areas of PIN and incidentally found adenocarcinomas. Bcl-2 scores 2, 3, 4 were detected in 17 (18.89%), 16 (17.78%) and 11 (12.23%) of group 2 BPH cases, respectively. Areas of PIA with cellular atypia were scored for Bcl-2 as 6

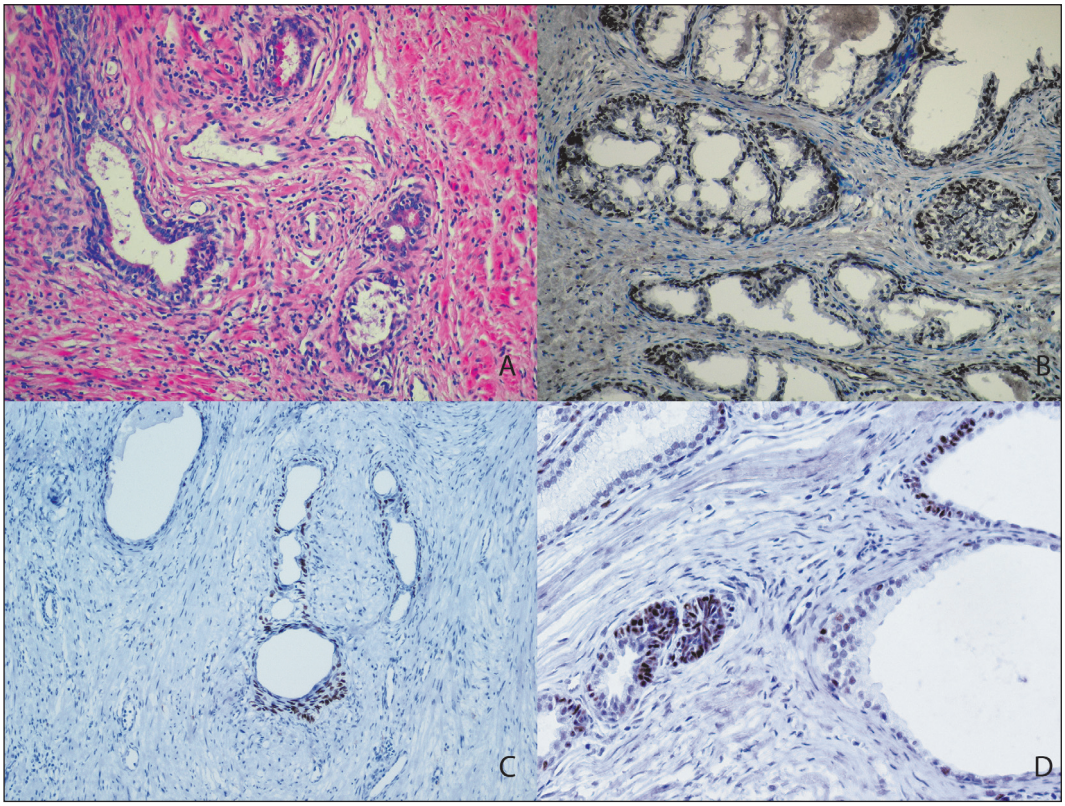


Figure 5.3.2. **Chronic proliferative atypical prostatitis. A – areas of proliferative inflammatory atrophy (PIA) associated with sclerosis of the stromal connective tissue without a marked inflammatory reaction. H-E; B – γ-H2AX expression; C – p63 expression; D – p53 expression. Magnification × 200.**

and 9 in 7 (7.78%) and 1 (1.12%) cases, respectively. The Bcl-2 scores in PIA as well as in PIA with cellular atypia in group 2 cases were significantly greater than in group 1 cases ($p < 0.001$ and 0.01, respectively). Adenocarcinoma areas of group 2 BPH cases showed also significantly greater Bcl-2 scores, to compare with group 1 analogous areas ($p < 0.01$).

* * *

In this report, we have documented for the first time that chronic long-term (about 29 years after the Chernobyl accident) low-dose ionizing radiation leads to the development of a previously unknown BPH lesions – radiation induced chronic proliferative atypical prostatitis in humans. This is characterized by multiple areas of PIA, BCH with cellular atypia, low and high grade PIN in strong association with sclerosis and hyalinosis of the stromal connective tissue, increased angiogenesis with dilated blood vessels, without a marked inflammatory reaction.

Our present radiometric study showed the significant increase of ^{137}Cs in urine of group 2 BPH patients, which suffered from urinary retention, so that radiation exposure of the prostate would be expected to have been enhanced. γ-radiation levels in urine of group 2 patients (6.3 Bq/liter or 10^2 micro Sievert/year) were 20 times higher than in control group 1. These data strongly suggest that the development of group 2 BPH lesions dependent on long-term exposure to low-dose ionizing radiation. However, it is necessary to add that Ukraine is acknowledged to be an ecological disaster area. The economic and social structures are still very poor,

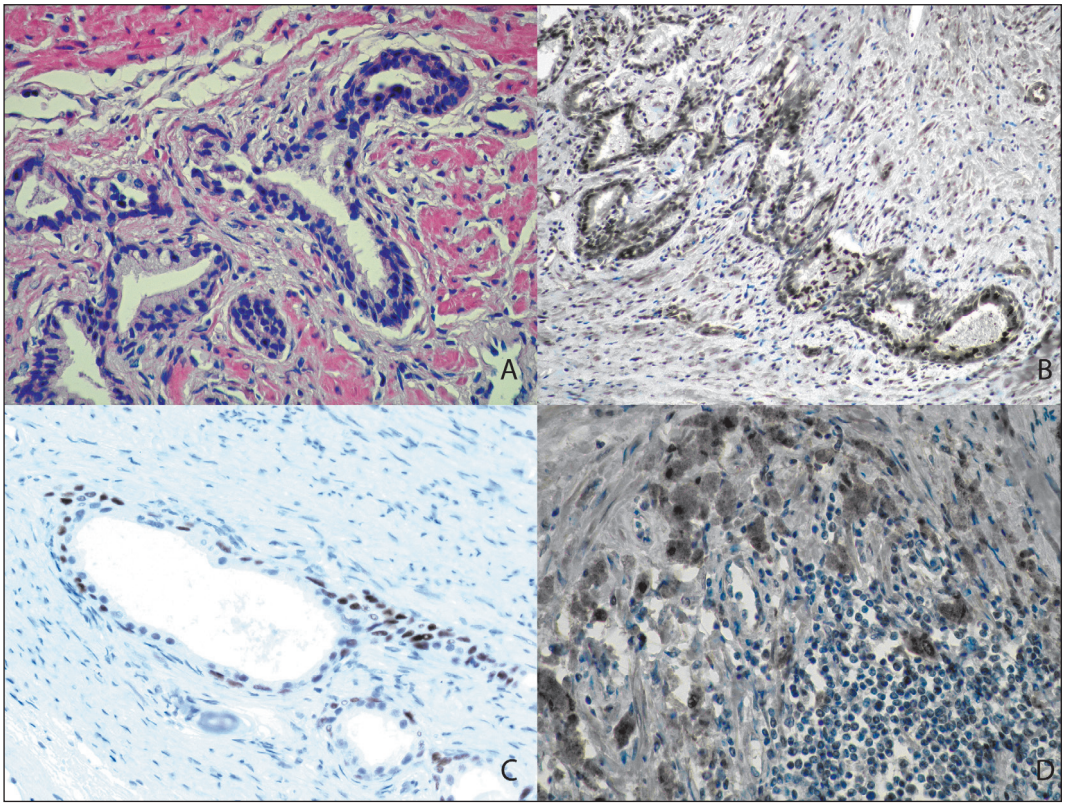


Figure 5.3.3. **PIA areas with cellular atypia in association with chronic proliferative atypical prostatitis. A – PIA with cellular atypia. H-E; B – γ-H2AX expression; C – p53 expression; D – iNOS expression. Magnification × 200.**

and the majority of the Ukrainian population still get food from their private vegetable gardens (without any ecological control). Therefore, our patients living in the radio-contaminated areas could be synergistically effected by various hazards. The critical role of the Chernobyl accident (involving long-lived ^{137}Cs and possibly many other radionuclides, which were not calculated in our study) as a part of synergistic effect for the development of specific atypical prostatitis was evident, because this specific pathological lesions were not detected in analogous group 1 BPH patients from so-called clean (without radio-contamination) areas of Ukraine.

It is important to note also that there is no dose-response relationship in the range of 0.1 to 1 Gy, suggesting that an unstable phenotype may be induced by a quite low radiation dose [41]. Moreover, the biological effect of chronic low doses of IR and its relationship with chronic inflammation and carcinogenesis have received much attention in the last few years [42]. Our recent studies also showed that the persistent chronic low doses of IR lead to the development of the similar urinary bladder lesions named as chronic proliferative atypical cystitis (or so called «Chernobyl cystitis») in humans [43].

Greatly increased nuclear γ-H2AX overexpression in PIA, BCH, less PIN areas, especially in cases with cellular atypia, associated with stromal leyomiocytes, fibroblasts, limphocytes, histiocytes γ-H2AX staining of group 2 BPH cases confirms the idea of radiation- induced DNA

damage with possible double strand breaks. Moreover, γ-H2AX is known as a very sensitive marker for low-dose IR and reactive oxygen spieces effects [44].

High levels of cytoplasmic iNOS expression that confirms the increased oxidative stress levels in group 2 BPH cases associated with proliferative atypical prostatitis possibly may be mutagenic through NO – mediated DNA damage or hindrance to DNA repair, and thus potentially carcinogenic [45].

Furthermore, areas of PIA, especially with cellular atypia at the background of chronic proliferative atypical prostatitis, that were detected in 43.34% of group 2 BPH cases demonstrated the significantly highest p53, Ki-67 and Bcl-2 proteins levels, to compare with others dysplasias and even latent prostate carcinoma. Anyway, these findings strongly showed the molecular alteration of genes, which control the processes of cell proliferation and apoptosis that may lead to prostate carcinogenesis. Moreover, the observed IHC findings support the interpretation that PIA may be caused by long-term low-dose internal ionizing radiation. These lesions supposed to be the earliest events of prostate carcinogenesis influenced by chronic long-term low-dose IR and could be evaluated as precancer lesions.

Development of prostate carcinoma is a multistep process [46, 47, 48]. PIA with cellular atypia, as well as HG PIN at microenvironment of chronic IR effects are associated with progressive abnormalities of phenotype and genotype, which are intermediate between the normal prostatic epithelium and cancer [49].

Interestingly, the significant differences were found between groups 1 and 2 latent adenocarcinomas in γ-H2AX, p63 and Bcl-2 protein expressions. These data support the suggestion that decrease of p63, as well as an increase of γ-H2AX and Bcl-2 expressions in latent prostate carcinomas are the important and earliest events that lead to prostate cancer activation induced by long-term low-dose IR exposure.

In conclusion, our data point a strong relationship between long-term low-dose ^{137}Cs radiation exposure of BPH patients, who have lived for about 29 years in radio-contaminated areas of Ukraine and the development of chronic proliferative atypical prostatitis, a possible preneoplastic condition in humans.

The presence in high frequency of histological and molecular changes associated with nuclear instability in the prostate of men exposed to IR following the Chernobyl nuclear accident suggests that this type of radiation exposure may be a cause of prostate carcinoma. Our study suggests that the alteration of cell cycle transition and apoptotic regulatory molecules in association with γ-H2AX and iNOS overexpression at the areas of PIA and BCH with cellular atypia could be also crucial early molecular events which may offer unique avenues for preventive or therapeutic intervention, as well as providing new insights into the mechanisms of prostate carcinogenesis.

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Chapter 6
FEATURES OF RADIATION-INDUCED CHROMOSOME INSTABILITY IN HUMAN SOMATIC CELLS IN LATE TERMS FOLLOWING THE CHORNOBYL ACCIDENT

The ability of the human genome stably operate in modern environmental conditions that are constantly changing, is one of the most important of its properties, which allows almost unerringly reproduce and transmit genetic information to the generations of cells and organisms. However, existing technogenic pollution of natural and working environment by different genotoxic agents, including factors of Chornobyl accident (main of which is ionizing radiation), led to increase of mutagenesis intensity in human somatic and germ cells and there to different forms of genome instability – a phenomenon in which over time the cells accumulated multiple changes on gene and chromosome levels that violates their normal functioning and can lead to increased incidence of pathology with mutationfl component – stochastic and non-stochastic (multifactorial).

As established in the last decade, under the action of such powerful mutagen as ionizing radiation somatic pathology in exposed individuals, especially in the remote period following radiation exposure, can be caused not only by direct damage of target cells, but radiation-induced untargeted effects, among which leading role played namely different forms of genomic instability (hidden, delayed, transmissible) and bystander effect [1–3].

Generalization and analysis of studies the various aspects of radiation-induced untargeted effects (including genomic instability) and assessing their value for future generations described in large section (Annex C, «Non-targeted and delayed effects of exposure to ionizing radiation») report UNSCEAR (2006), which indicates the urgency of the problem.

One of the manifestations of radiation-induced destabilization of the human genome at cytogenetic level is so called hidden chromosome instability (HCI) under normal or aberrant karyotype, which is defined as genetically caused or probably caused by some endogenous or exogenous genotoxic factors hypersensitivity of chromosomes in human somatic cells to the exposure of other mutagens (*in vivo* and *in vitro*) and regarded as propensity to induction and promotion of carcinogenesis [4–6]. Evaluation of HCI is a new direction of cytogenetic studies that ful-

filled in some cytogenetic laboratories around the world (including Cytogenetics Laboratory in NRCRM), mainly to determine the risk of spontaneous or induced cancer by chromosomes' hypersensitivity in human peripheral blood lymphocytes to exposure of certain reference mutagens in vitro in tests so called «Provocative mutagenesis» [5–7]. It had been found that individual sensitivity of chromosomes of human somatic cells to testing mutagenic exposure in vitro, as well as to exposure of environmental mutagens in vivo does not depend on gender and age and is genetically determined [7].

One from the most common tests of «Provocative mutagenesis» is «G2-bleomycin sensitivity assay», where as mutagen-provocateur radiomimetyk bleomycin had been used.

Given the need to assess the possible contribution of HCI to the realization of remote medical consequences of Chornobyl accident, we have adapted and applied this test under cytogenetic examination of the priority observation contingents, who had occupational contact with ionizing radiation to determine individual sensitivity to radiation exposure [8, 9]. As a result of research, materials of which were summarized and published, not only the reality of modification of genetically determined chromosome stability in human somatic cells due to ionizing radiation exposure *in vivo* had been established for the first time [10–12], but also the existence of the association between this phenomenon and the realization of the oncopathology (particularly lung cancer) in exposed individuals [13, 14].

However, it remained an open question regarding the duration of radiation-modified HCI (both *in vivo*, and *in vitro*) and its ability to be transmitted to future generations of cells that must be considered under prediction the delayed medical consequences of accidental human radiation exposure.

Several authors studied remote and delayed chromosome instability in human peripheral blood lymphocytes culture (without testing mutagenic exposure *in vitro*), mainly, *in vivo* – in different terms after radiotherapy of cancer patients with different localization of tumors [15, 16] and following chronic emergency exposure [17].

Persistence of radiation-induced chromosome instability had been investigated also in model cell systems *in vitro* under the long-term cell's cultivation [18, 19], particularly, in NRCRM – at cytogenetic examination the progeny of exposed parents [20–22], and at the research another of untargeted cytogenetic effects – bystander effect [23, 24]. As a result of these investigations had been found not only storage but also amplification of cytogenetic effect in long-term lymphocytes cultures because of radiation-induced remote chromosome instability.

In view of the above, the aim of our further studies of this phenomenon (2012–2014) was not only depth research of radiation-induced expression of HCI in human somatic cells following exposure to ionizing radiation *in vivo*, but also determining the possibility of its persistence over time and transmission capacity for the next cell generations.

To study the duration of radiation-modified HCI storage two previously improved by us test systems – «G2-bleomycin sensitivity assay» [8, 9] and method of two-termed (during three mitotic divisions) lymphocytes culturing [20] had been used. This allowed to evaluate the possibility of HCI expression in human somatic cells over time and to identify individuals hypersensitive to mutagens with increased risk of long-term health effects of radiation exposure.

With combined use of these both methods voluntary cytogenetic examination of two groups – comparison group (conditionally healthy volunteers who denied conscious contact with known or potential mutagens) and occupational group (individuals who participated in the transformation of «Shelter» «Chornobyl NPP» to the ecologically safe system) had been conducted.

The important quantitative characteristic of spontaneous mutagenesis intensity in humans is the background level of chromosome aberrations in somatic cells, significant excess of which

indicates the induction of cytogenetic effects by mutagenic factors *in vivo* or *in vitro*. In this direction a lot of research had been performed (special and at cytogenetical observation of control groups) using mainly classical uniform staining of metaphase chromosomes and much less – their differential G-banding staining and method FISH-WCP, resulting in a number of certain regularities of spontaneous somatic chromosome mutagenesis had been established [25–29]. In particular, it had been shown that with increasing the terms of lymphocytes cultivation there was a gradual elimination of the unstable and part of stable chromosome damages and change in the ratio of their spectrum.

Obviously, that under evaluation of background and/or induced level of chromosome aberrations do not desirable to use published data (one can only compare with them), because it is impossible to establish a uniform single control for different populations due unrealistic considering the entire complex of reasons that may affect the cytogenetic indicators [28]. It should be noted that under analysis of relatively small samples which are used in most cytogenetic studies both *in vivo* and *in vitro*, can be a random accumulation of the number of individuals with any unrecorded genotoxic or «confounding» factor modifying spontaneous frequency of chromosome aberrations. Therefore, every cytogenetic examination of irradiated human contingents must have its own data concerning intensity as spontaneous as well as induced by testing mutagenic exposure *in vitro* chromosomal mutagenesis in a relevant comparison group (matched control), especially when using two-term cultivation of lymphocytes.

Given the above, first of all we had been determined the values of background cytogenetic indicators in individuals from both groups surveyed under standard 48-hour and almost unused at cytogenetic examinations 100-hour lymhpocytes' cultivation – in the first and third mitosis, respectively.

Found that under short-term standard lymphocytes culturing the background cytogenetic effect did not differ between the groups in frequency and spectrum of chromosome aberrations (Figure 6.1) and corresponded as population indicators of spontaneous chromosome mutagenesis in human somatic cells (1.50% aberrant metaphases with variation in ranging from 1.00 to 3.00%) [25, 28] as well as own historical control – results of numerous cytogenetic examinations of other unexposed groups of people (1.12 ± 0.19)%, 0–2.00%, respectively) [10]. Lack of unstable and stable chromosome exchanges (dicentrics, centric rings, abnormal monocentrics) which are considered specific markers of human radiation exposure was evidence of the absence of such exposure in cytogenetically active doses not only to persons from unexposed group of comparison, but also from professional group.

Under the long-term lymphocytes' cultivation principal differences between the examined groups in the dynamic of background cytogenetic effect had been revealed (Figure 6.1). In the group of comparison with increasing duration of cells' incubation tendency to decrease of cytogenetic effect both in separate individuals and in group as a whole had been observed due to the elimination of dominant type of unstable chromosome damages (single acentric fragments) that are typical for spontaneous chromosome mutagenesis in successive mitosis *in vitro* [18, 28]. Individual and mean-group frequencies of exchange aberrations did not change, their overall level was (0.02 ± 0.01) per 100 metaphases that, as in the 48-hour cultures was lower than population control. However, because of the small values of these indicators it was impossible to establish the significant difference between them in the short-term and long-term cultures. It should be noted that similar results were obtained by us earlier at 144-hour (fifth mitosis) cultivation of lymphocytes from children lived in environmentally safe region in the study of delayed chromosome instability in progeny of exposed parents [21, 22, 30] and O.V. Shemetun at 120-hour (fourth mitosis) cultivation of lymphocytes from conditionally healthy volunteers at research of

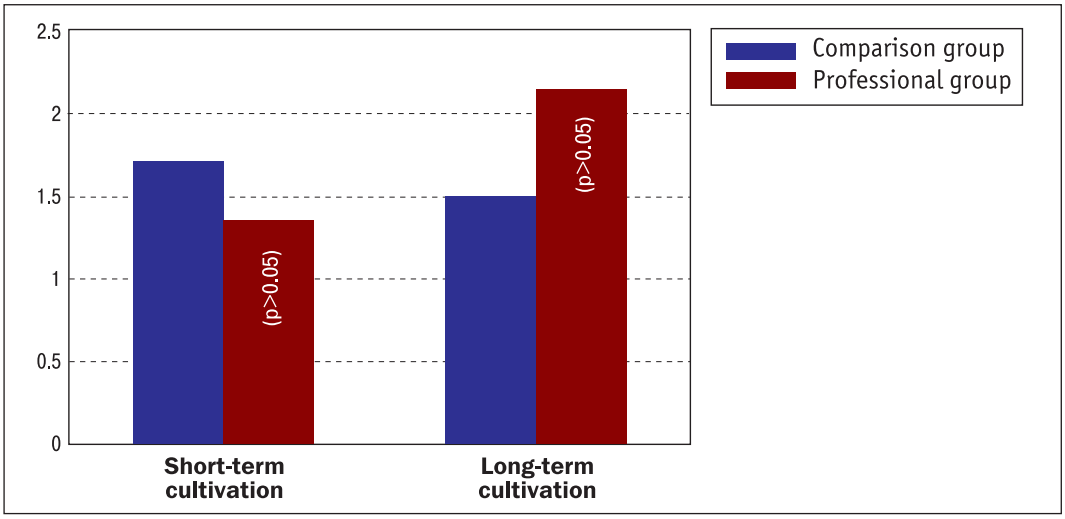


Figure 6.1. **Mean values of background frequency of chromosome aberrations in unexposed and occupational groups under short-term and long-term cultivation of peripheral blood lymphocytes**

bystander effect [23, 24] – the frequency of chromosome aberrations in long-term cultures had no statistically significant difference with those in the first mitosis obtained at standard 48-hour cultivation.

In occupational group significant increase of background cytogenetic effect in the third mitosis had been found – as in individuals (with interindividual fluctuations) as well as in group on average due to enhance the frequency of simple acentrics both chromatid and chromosome types (single and free double fragments that are considered cytogenetic indicators of delayed chromosome instability). In individuals from occupational group slightly changed the spectrum of «spontaneous» chromosome aberrations and their ratio in the third mitosis. In contrast to short-term cultures under the long-term cultivation of lymphocytes in 27% of the surveyed people have observed stable radiation-induced cytogenetic markers (abnormal monocentrics) with individual frequencies 0.20–0.40 per 100 metaphases and appropriate mean-group value 0.09 ± 0.04 per 100 metaphases that exceeded their population level, our own historical control, background values and their frequency in the short-term cultures [26, 29].

Under the short-term cultivation of lymphocytes with bleomycin in both examined groups had been established increase both individual and mean-group frequency of chromosome aberrations (mainly single acentric fragments) with significant interindividual fluctuations, the value of which did not depend on the values of background cytogenetic indicators which confirmed the established by us earlier distinction between different persons in chromosome sensitivity to mutagenic bleomycin exposure [10]. However, professional and unexposed groups differed among themselves in base cytogenetic indicators – mean frequency of aberrant metaphases and chromosome aberrations, as well as over-spontaneous levels of chromosome aberrations, which were significantly higher in the professional group (Figure 6.2). The difference observed between the groups monitored in the frequency of chromosome aberrations in the first mitosis, once again confirmed modifying effect of ionizing radiation on the induction of genetically caused HCI in human somatic cells [10].

Under the long-term cultivation of lymphocytes with bleomycin in both examined groups decrease of mean-group frequencies of chromosome aberrations had been observed (due to

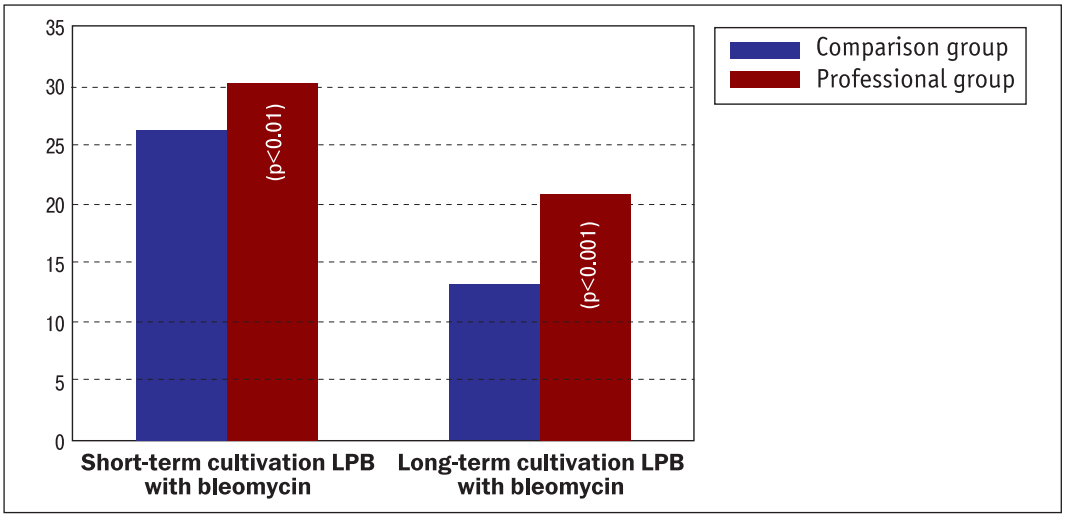


Figure 6.2. **Mean values of chromosome aberrations frequency in unexposed and occupational groups under short-term and long-term cultivation of peripheral blood lymphocytes with bleomycin**

simple acentrics with predominance of single fragments) and tends to increase the frequency of stable type chromosome aberrations (abnormal monocentrics). However, the values of all basic cytogenetic parameters were significantly higher in the professional group (Figure 6.2), confirming the modifying effect of ionizing radiation not only for induction, but also on the persistence of HCI in successive cell generations.

However, despite the unidirectionality the dynamics of induced by bleomycin cytogenetic effect in both observed groups (gradual elimination of unstable and trend to increase of stable chromosome aberrations in successive mitosis) surveyed groups differed in individual peculiarities of HCI persistence. So, in two persons from occupational group the level of chromosome aberrations in the third cellular division had not changed, while in three individuals hypersensitiv to bleomycin exposure under short-term cultivation of lymphocytes it increased compared with that in the first mitosis. In these persons KHCI value exceeded «1», indicating their increased sensitivity to mutagenic exposure [8, 9], and positively correlated with those in short-term cultures, which indicates the possibility of not only preservation, but even the growth of HCI with time. This may be due to a decrease in the intensity of reparative processes in aberrant cells or inhibition of their elimination in successive cell division. A similar phenomenon, but without testing bleomycin exposure, was established by us earlier under the cytogenetic examination the progeny of exposed parents [21, 22, 30] and in the study of radiation-induced bystander effect [23, 24]. As a result of these researches persistence of delayed chromosome instability in long-term cultures of human peripheral blood lymphocytes also had been revealed, which indicated the ability of somatic cells transmit it to their next generations.

Thus, by the magnitude and dynamics of as background as well as induced by bleomycin cytogenetic effects under both terms of lymphocytes' cultivation professional group significantly differed from the group of comparison towards the growth of HCI indicators with significant interindividual fluctuations that are in the professional group confirmed the possibility of not only the preservation but also increase of HCI with the passage of time.

Great interindividual range in the frequency of different types of chromosome aberrations induced by bleomycin in both surveyed groups, the individual peculiarities of their dynamics in

successive mitoses, independence the level of individual sensitivity of chromosomes to mutagenic exposure from the initial level of chromosome aberrations indicating the multifactorial nature (genetically caused and radiation-associated) of hidden chromosome instability.

The results obtained for the first time showed that under cytogenetic examination of persons who have (or will have) occupational contact with ionizing radiation even in small doses, it is expediently to use two-termed culturing of peripheral blood lymphocytes together with «G2-bleomycin sensitivity assay». It will allow to evaluate individual sensitivity to mutagenic exposure (including radiosensitivity) taking into account peculiarities of induction and persistence of hidden chromosome instability in human somatic cells. That can be used for developing and implementing of appropriate preventive measures aimed at the reduction the risk of consequences adverse health effects of ionizing radiation on humans.

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Chapter 7
EFFECTS IN THE IMMUNE SYSTEM

The problem of the radiation induced effects in human immune system in humans has been in focus of numerous studies and evaluations (UNSCEAR, 2006) [1]. Chornobyl resulted in external exposure of healthy humans in a wide range of doses and additionally in radionuclides inhalation and ingestion. Many publications using the modern research approach lacked information on doses, time after exposure and confounding factors. In the RCRM the studies of immune function were started in 1987 and directed to assess the effects in main groups – exposed to high doses, clean-up workers exposed to low and medium doses. General population groups included adults and children from Prypiat and 30-kilometer exclusion zone, and population from territories contaminated by radionuclides. Stress, environmental hazards, such as lead influence, individual radiosensitivity were studied among confounding factors.

7.1. IMMUNE DEFICIENCIES RATES IN EXPOSED GENERAL POPULATION

Long-term changes in the immune system during the first 10 years after the accident included the elements of compensation and impaired regulation of immune function. Compensatory changes were typical for 32% of exposed and were manifested with an increasing number of certain types of T-cells, increased activation and low levels of mutations in the loci of T-cell receptor. Dysregulation changes (37%) included the change in response to neurohumoral stimuli, the instability of immune function, also with the low levels of mutations in the loci of T-cell receptor. Manifestations of cellular immunity deficiency (31%) included the decreased levels of effector cells, preserving the number of T-cell receptor variant cells. Use of the adequate control groups recruited from the not-contaminated areas to the exposed was hampered in connection with lower immunological parameters compared with the reference international figures.

Study of the frequencies of the immune deficiencies was continued in a remote period up to 30 years after the accident and now based on the results in more than 200,000 of exposed. Changes in immune system indices in clean-up workers are associated with radiation dose and type of observed health effects, while in general population at the territories contaminated with radionuclides the main factors, that determine frequency of immune deficiencies are age, somatic pathology, and other confounding factors.

7.2. EFFECTS IN ACUTE RADIATION SYNDROME SURVIVORS

7.2.1. Early effects

The acute stage studies of the immune system in acute radiation syndrome survivors showed drop in concentrations of immunoglobulins, phagocytosis, nonspecific resistance and a significant reduction in anti-infectional immunity by an increase of the number of colonies of pathogenic microorganisms in the skin test [2]. In the RCRM the follow-up studies were launched one year after exposure. In total 183 patients were under immunologic follow-up including 96 with diagnosis of ARS not confirmed retrospectively three years after exposure. Detailed life statistics could be obtained from the recent publication [3]. Radiation doses in a group of ARS survivors under immune system follow-up are presented in Table 7.1. The period of recovery after irradiation was characterized by an acquired combined radiation-induced immune deficiency with inhibited T-cell immunity, failure of nonspecific resistance mechanisms and predominance of cytopenic reactions.

Table 7.1
Distribution of ARS patients by cytogenetic doses

ARS grade	Doses of irradiation in 1986, Sv		
	Mean	Minimum	Maximum
ARS-NC#	0.53	0.25	1.43
ARS-1	1.75	0.46	4.0
ARS-2	1.87	0.27	3.40
ARS-3	5.60	5.40	6.0

Notes. # – ARS – not confirmed in 1989.

Immune function analyses at 12–24 months, 25–36 months, 36–48 months after the accident showed tendencies to recovery. The highest inhibition of cellular immunity occurred in younger age. During the period from 3 to 5 years the wavy oscillations of expression of surface antigens related to the helper-inducer function, mitogen response, an increased expression of pan-B and activation antigens were registered. A detailed characterization is presented in previous publications [4–6].The severity of changes was associated with a grade of ARS and radiation dose.

In the recovery period a marked decrease in expression of antigens associated with helper-inducer function, increased presentation of cell surface pan-B and B-blast as well as activation antigens ($CD3^+Dr^-$; $CD4^+8^-$, $CD22^+$ $CD23^+$ subsets) was demonstrated. After 48 months of monitoring a temporary normalization was detected in the numbers of CD4-8^+ and $CD8^+57^-$ cells (Table 7.2). Content of $CD38^+$ cells, which are involved both to cytotoxic and activation reactions, was increased. It should be noted discrepancy in the first years of changes of $CD57^+$ and $CD15^+16^+$ cells, identified as highly active natural killer cells. The variations could be explained by a certain period of heterogeneity in cell recovery after radiation injury. During the whole first period, it was noted a strong tendency of increased counts of $CD4^+8^+$ and $CD1^+$ peripheral blood cells. Normally this phenotype is attributed to the intrathymic stages of differentiation interpreted as a manifestation of reparatory reactions.

For the estimation of the immune function in the ARS recovery period a complex of methods was applied, including DNA-cytometry, automated fluorescent activation assays to mitogens and different antigens, blast transformation, 3H-thymidine incorporation assay, index of leukocyte inhibition of migration. Cell activation studies demonstrated high spontaneous expression

Table 7.2
Distribution of ARS patients by cytogenetic doses

Study groups Mean	Years after radiation exposure	Percentage of lymphocytes (M ±m)				
		$CD3^+19^-$	$CD3^+$ HLA-DR^+	$CD3^+4^+$	$CD4^+8^+$	$CD3^-19^+$
Control	7–13	67.39 ±1.56	6.93 ± 1.22	41.84 ± 1.50	29.77 ± 1.29	7.90 ± 0.66
ARS–NC	7–8	67.78 ± 2.46	8.89 ± 1.99	36.63 ± 2.52	30.26 ± 2.17	6.79 ± 0.68
	9–10	70.16 ± 1.16	10.85 ± 1.31*	40.32 ± 1.35	33.99 ± 1.99*	9.12 ± 0.45
	11–13	66.15 ± 1.73	6.83 ± 1.28	39.25 ± 1.74	29.90 ± 1.68	8.95 ± 0.57
ARS grade 1	7–8	65.01 ± 4.65	6.72 ± 3.39	40.17 ± 4.33	26.74 ± 2.97	7.48 ± 1.36
	9–10	67.26 ± 1.57	7.99 ± 1.25	38.06 ± 1.76	33.59 ± 1.93	8.85 ± 0.97
	11–13	63.71 ± 2.02	4.07 ± 0.67*	37.56 ± 1.71	28.61 ± 0.85	10.80 ± 1.44*
ARS grade 2 & 3	7–8	65.17 ± 2.59	10.02 ± 2.15*	35.41 ± 1.87*	33.40 ± 1.40*	10.63 ± 1.21*
	9–10	65.86 ± 1.64	10.96 ± 1.81*	35.60 ± 1.29*	33.52 ± 1.47	10.16 ± 0.77*
	11–13	62.83 ± 2.33	5.21 ± 0.68	33.34 ± 1.85*	31.88 ± 1.64	10.22 ± 1.00*

Notes. # – non-confirmed ARS; * – significant differences with the control group, $p < 0.05$.

of activation T-cells antigens, and a decline of the mitogen-induced reactions, that was typical for ARS-NC and ARS 2–3 patients. These conformities repeated at the study of percent content of cells. Study of $CD4^+$ cells expressing IL-2 receptor, shows an increase of their number in ARS0 patients. In ARS 1–3 survivors, the spontaneous indices of $CD4^+25^+$ cells did not differ from control; the same was shown after Con A stimulation.

Dose dependency was observed for $CD3^+DR^-$ cells and to a lesser extent for $CD4^+$ lymphocytes. Reduced expression of CD3 receptor was crucial for the formation of response to exposure and rate of recovery of the immune system. Cell progeny of T-lymphocytes variant by T-cell receptor have a low density of surface functionally active receptor. In studies of patients with ARS survivors and clean-up workers exposed at low dose a correlation was determined between the number of TCR-variant cells and proliferative activity, in response to mitogens – PHA and Con A; and biologically active compounds, such as cortisol, epinephrine, 5-hydroxytryptamine. The use of flow cytometry with a number of counted cells up to 10^6 demonstrated

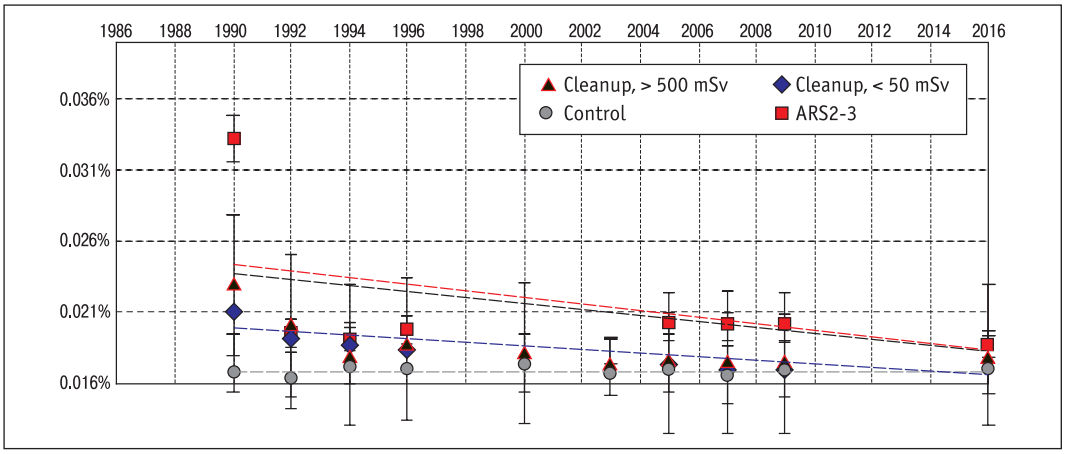


Figure 7.1. **Mean percentage of TCR-variant lymphocytes in ARS survivors and other groups of clean-up workers divided by radiation dose during the follow-up. A black solid line marks control values.**

that despite the negative selection of TCR-variant cells in vivo due to a half-life of 2 years, the radiogenic effects on T-cell receptor remain registered 10–15 years after exposure. Revision of TCR variant cells data showed that in patients who survived after ARS II–III degree, the increased numbers of TCR-variant cells were shown 20 years after exposure and more (Figure 7.1), and are associated with lower $CD3^+$ cell counts. In a $CD4^+$ subset $CD4^+8^-$ cells were determined in a reduced number with increasing the absorbed dose. The $CD4^+8^+$ cell counts were increased and differences between the groups of exposed over 250 mSv with a group of persons exposed in occupational limits, were significant. This subset was described earlier in different immune deficiencies and is known that transition through the stage of the simultaneous expression of these antigens is one of the stages of cell differentiation in thymus, so likely that $CD4^+8^+$ cells belong to those who have recently migrated from the thymus.

7.2.2. Late period after radiation injuries

In the late period the group parameters of the major regulatory subpopulations of T cells had a tendency to normalization. The number of T cells did not differ significantly from control values in all patients; after ARS grade 1 even a tendency to increasing the number of $CD3^+$ cells was shown (Figure 7.2). Noteworthy that after ARS grade 1 the restitution of total T cells counts was due to $CD4^+$ subset, whereas after ARS grade 3, the restoration of the $CD4^+$ cells number did not occur and the average remained significantly lower (Figure 7.3). Mean figures were decreased during all the follow-up period.

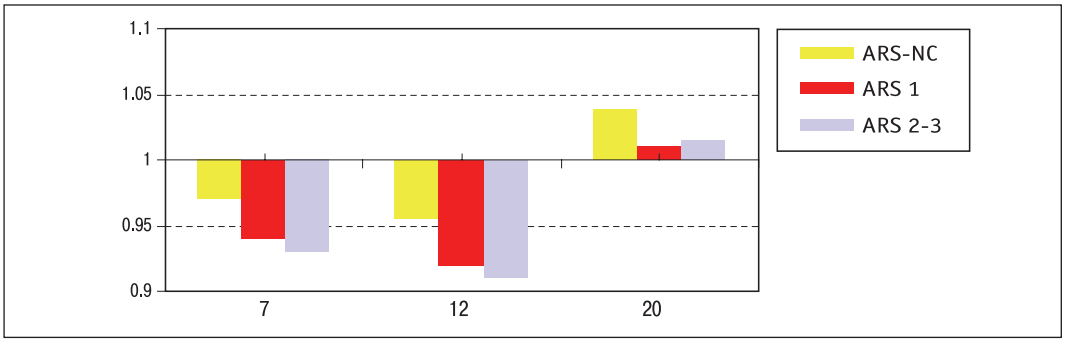


Figure 7.2. **Dynamics of mean peripheral blood $CD3^+$ cell counts in ARS survivors, depending on disease grade. Data are presented as a ratio to control values, taken for 1.**

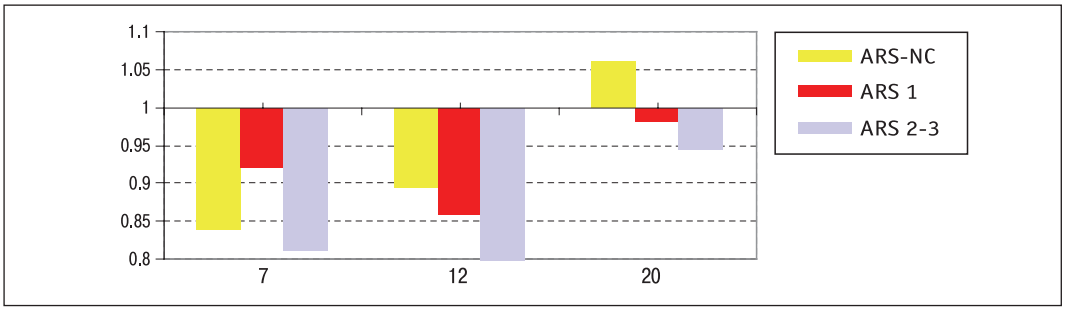


Figure 7.3. **Dynamics of mean peripheral blood $CD4^+$cell counts in ARS survivors, depending on disease grade. Data are presented as a ratio to control values, taken for 1.**

CD8$^+$ cells number varied according to other regularities (Figure 7.4). If after ARS grade 1 and ARS grade 3 there was a gradual reduction in the number of cells that becomes the significant within 20 years after exposure, in the ARS grade 2 convalescents we have recorded the opposite trend. The analysis is being continued.

The results of the ARS patients follow-up indicate at the remote period after exposure a certain exhaustion of the cell subsets compensatory abilities, still depending on the radiation dose. However, any results could be influenced by positive selection, i.e. a possibility to analyse data only in survivors. It was demonstrated for peripheral blood mature cells as well as for progenitor cells. For a subset of CD34$^+$ cells in total a significant correlation was found with Pearson and r of -0.48. This conclusion was confirmed by the analysis of the number of the CD34$^+$117$^+$ subset of stem cells and CD123$^+$ early progenitor cells, shown in Figure 7.5.

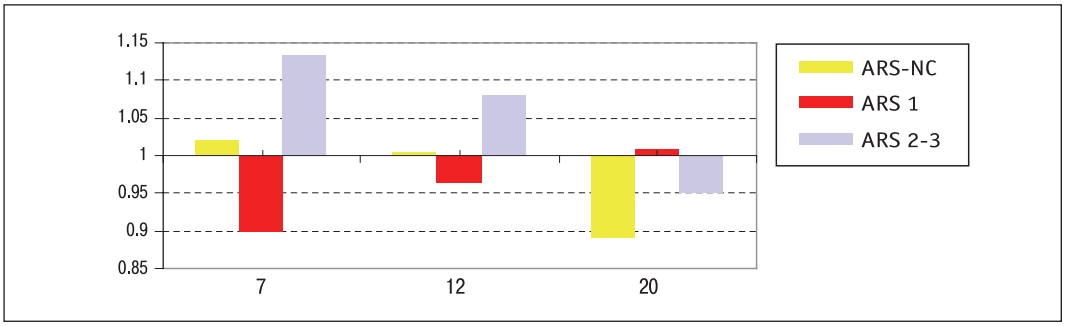


Figure 7.4. **Dynamics of mean peripheral blood CD8$^+$ cell counts in ARS survivors, depending on disease grade. Data is presented as a ratio to control values, taken for 1.**

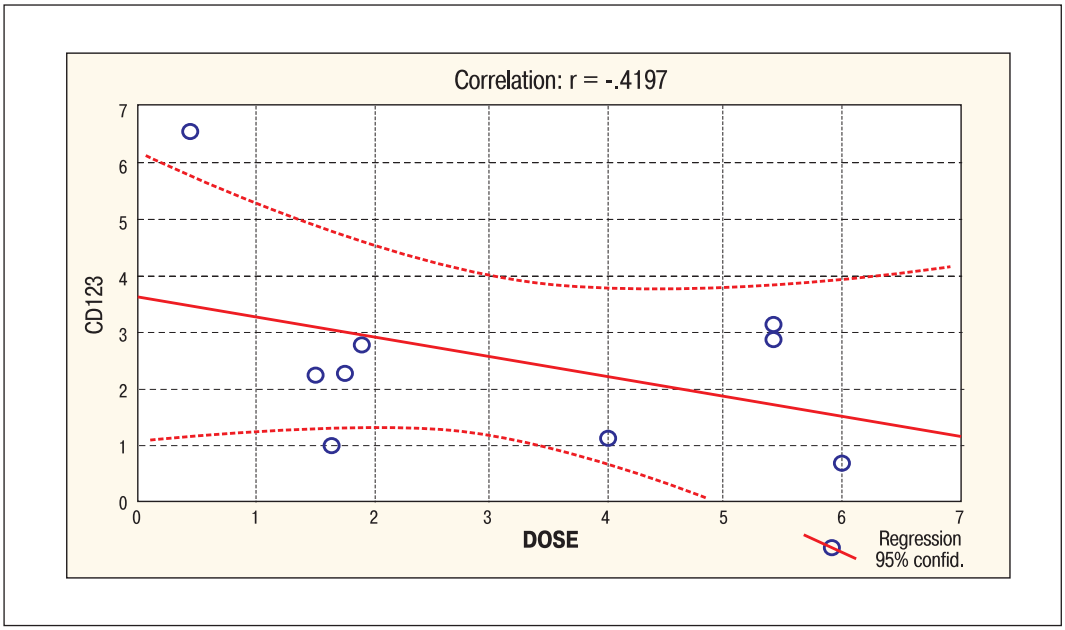


Figure 7.5. **Regression analysis plots of the dependence between the number of early haemopoietic progenitor cells and a dose of irradiation in ARS survivors 20 years after the exposure.**

7.2.3. Confounding factors

Influence of a radiation factor on the human body causes a number of adaptive and compensatory reactions, the most important of which are changes in the central and autonomic nervous system, metabolism, hormonal regulation. The results of follow-up of ARS survivors suggest that the presence of concurrent neurological disorders during the first years after the exposure resulted in impaired recovery of T-cell compartment. Later the effect could not be traced due to the high prevalence of vascular brain pathology and associated psycho-neurological disorders in ARS survivors. In detail data is presented in a previous edition [6].

7.3. Immune function after low and medium dose radiation exposure

Until now, no clear determination exists of ionizing radiation dose, which should be considered as low. Experts in the field of acute radiation pathology have defined low dose as the maximal dose that does not cause a specific response, such as bone marrow hematological syndrome, so is below 1 Gy. In nuclear emergencies such dose was considered as 0.25 Gy, which was used earlier as a dose limit for emergency radiation workers of Chornobyl in 1986 and in Fukushima in 2011. However, this limit, providing some safety from the view of radiation protection, is hardly substantiated with the regards to the low-dose effects described in the immune system during the last twenty-five year period. Other authors have defined as a low dose an absorbed dose of 0.1 Sv or less in a short period of time, or 0.5 Sv for a long time [7]. Similarly, from a standpoint of immunology it has been proposed to consider as a low dose such that did not cause significant changes in the immune system – 0.04–0.05 Gy [8]. The ICRP defines low doses, as less than 100 mSv. In the most recent UNSCEAR documents the low doses are defined as the doses of 200 mSv or less, and dose rates as 0.1 mGy·minute^{-1} or less for radiation with low LET value [1]. In the latter report an up-to-date evaluation the effects of ionizing radiation on the immune system is presented. The UNSCEAR considers the immune system as a modifier of cancers risks and concludes an impossibility at a current stage to get a clear answer, whether immune function is enhanced or weakened in the range of low doses and how it changes the ability of a human body to resist cancer. At the same time the Committee recognizes the accumulation of substantial new data on non-targeted and late effects of low doses.

Experimental data also exist in mice on the activation of immune function under chronic influence of low dose gamma-radiation. In contrast, an excessive damage to the immune response is described in mouse-models autoimmune pathology under the influence of chronic low-dose radiation. It remains unclear how these data can be extrapolated to humans including not only purely cellular response to radiation, but also changes of the microenvironment. The UNSCEAR suggests as a key direction the stem cell research with the use of modern analytical approaches, cell kinetics and the microenvironment. So far, according to international experts, the existing data on the impact of radiation in low doses on the immune system, and on dependencies of «dose-effect» type are not consistent and clear [1].

7.3.1. Early period of recovery after irradiation

Investigation of ionizing radiation effects after low-dose exposure in the early period was performed in several groups irradiated with different range of doses and duration of exposure – the clean-up workers of the Chornobyl accident, evacuees from Prypyat and 30-km zone of Chornobyl, adults and children living at the territories contaminated after fallout, staff of the

30-km zone of Chornobyl. These results are summarized in the monographs «Chornobyl disaster» (1997), «Chornobyl nuclear power plant-Slavutych: Medical aspects» (1996), the second volume of the monograph «Health effects of the accident at the Chornobyl nuclear power plant. (vol.2: Clinical aspects of the Chornobyl disaster (1999), «The effects of low and very low doses of ionizing radiation on human health» (2000), «Chornobyl: The Exclusion Zone»(2001), and other publications [9–11].

Research approach for study of the low doses effects included ensuring the homogeneity of study groups (exposed vs. comparison vs. controls), the same level of medical follow-up for the elimination of the screening effect, using, whenever possible, one source of information on radiation doses. For analysis mainly official doses specified in the Ministry of Health Form N-1 were used. Restrictions for radiobiology research include the lack of previous data on the analysis of the immune function and the uncertainty of official doses. For control groups the difficulties consisted in inability to select individuals, free from irradiation and concurrent diseases, according to the age characteristics and lifestyle. For control group the available opportunities were used. We examined healthy volunteers – residents of Kyiv, who were blood donors, have not participated in clean-up activities and not living on contaminated territories. Individual dose of external radiation and thyroid dose for residents of Kyiv from the control group were not considered. Group of comparison included the rural population of the Poltava region. While conducting research in parallel with the IAEA group (1990) the proposed approach of international group to inspect the near located settlements with different levels of radioactive contamination was applied. Analysis of the clean-up workers immune function data at that time was conducted by groups in accordance to limits of exposure approved by the USSR Ministry of Health. Clean-up workers irradiated in doses less than 0.05 Gy were selected as an internal comparison group.

During the clean-up period (1987–1990) a study group included 3010 clean-up workers of 1986–1989 (Table 7.3).

Table 7.3

Percentage of main subsets of lymphocytes in Chornobyl clean-up workers in the recovery period of 24–36 months after the exposure in dependence on the radiation dose

Lymphocyte subsets	Percent of antigen-bearing cells depending on a radiation dose interval, mSv					
	0–50		50–250		250–1000	
	M	±m	M	±m	M	±m
$CD7^+$	64.8	3.6	56.2*	3.9	49.7*	4.4
$CD5^+$	44.2	4.5	33.7*	5.0	33.9*	2.7
$CD3^+$	55.4	2.2	48.1	2.6*	41.6*	4.7
$CD3^+Dr^-$	46.5	2.8	30.6*	3.9	27.5*	5.1
$CD3^+Dr^+$	5.8	0.6	11.7*	1.6	10.0	4.2
$CD4^+8^-$	36.3	2.3	32.9	6.8	20.5*	4.1
$CD4^+8^+$	1.1	0.2	1.3	0.2	3.7*	0.4
$CD4^-8^+$	23.5	3.5	18.5	3.2	25.2	4.1
$CD38^+$	13.0	2.6	13.9	1.3	16.2	1.9
$CD11b^+$	11.5	1.4	16.2*	0.8	18.1*	2.1
$CD16^+$	11.0	1.3	8.5	1.1	10.2	1.3
slg^+	10.6	0.14	17.1*	1.01	17.3*	0.92
$CD19^+$	8.3	0.5	10.2	0.9	12.6*	0.5
$CD3^-Dr^+$	7.9	2.0	13.1	2.1	9.2	2.4
$CD23^+$	10.9	2.0	5.7*	0.6	8.1	1.6

Notes. *– significant difference, $p < 0.05$.

The decrease was demonstrated of the mean counts of the T-lymphocyte main subsets. Group values showed dose dependency, however a decrease in number of cells that expressed the earliest T-cell CD7 differentiation antigen was the smallest. The number of cells that express CD5 antigen, changed in parallel to content of CD3+HLA-Dr- lymphocytes, but not $CD3^+HLA\text{-}Dr^+$ cells. The cells of $CD4^+8^-$ phenotype were determined in a reduced number with increasing the absorbed dose. Number of $CD4^+8^+$ cells was increased and group values difference to a comparison group was significant in doses exceeding 0.25 Gy. Studies have shown heterogeneity of cytotoxic cell response. The number of cells that expressed CD38, had not changed and tended to increase. Designated was a threshold type of he changes of cytotoxic $CD11c^+16^+15^+$ lymphocytes. In patients with doses of 50–250 mSv the number of these cells was declining, at higher doses-not different from normal. Marked reduction was demonstrated for $CD8^+57^+$ and $CD8^-57^+$ lymphocytes.

According to the results of DNA flow cytometry an instability of cells traffic through the different phases of the cell cycle was observed. In the range of doses up to 250 mSv 24–36 months after the exposure an increased numbers of mononuclear cells were shown in S-and G_2+M phases. The growth of cell population heterogeneity was demonstrated by increased values of mean-square deviation and coefficient of variation indices. After irradiation at doses greater than 250 mSv, the presence of non-replicative DNA synthesis with blocking the cell cycle and G_2- or G_2- block was demonstrated. The frequency of changes also depended on some threshold: G_2-block was determined at doses above 250 mSv, G_1-block – at doses exceeding 1 Sv.

The registered variability could result from a different sensitivity to irradiation and recovery efficiency of various subsets of T-and B-lymphocytes. It was found that reducing the number of T-cells that express CD5 was not accompanied by activation processes and the increasing of cells in S-and G_2-M phases. In the CD57+ population with a high density antigen an accumulation of cells that entered the proliferative cycle was registered at doses lower than 250 mSv, and at doses exceeding this threshold the effect was not observed. The sIg^+ B-cells differed from the other by an elevated number of lymphocytes being in the proliferative cycle. At higher doses the increased average numbers of B-cells were accompanied by increasing of cells number in G2 and M-phases, without changing the number of cells in S-phase.

Study of exposed groups shows that the effectiveness of recovery mechanisms of cell subsets depend on the dose stepwise due to the different sensitivity of cellular compensatory mechanisms. Data on some contributive mechanisms revealed at the early period are presented in Table 7.4. Thus, the release of the immature $CD4^+8^+$ T-cells to the peripheral blood with concomitant decreased number of mature $CD3^+4^+$ cells became a substantial factor in the dose range above 250 mSv ($p < 0.02$). T-cell activation, by contrast, was depressed. Expression of CD25 antigen (interleukin-2 receptor) was increased, starting in the dose range from 50 mSv, but not accompanied by increased expression of T-cell class II major histocompatibility complex antigens, which was an essential factor of activation and promotion of cells to G2 and M phases of cycle. Last recovery mechanism seems to value at doses higher than 1 Sv.

Table 7.4
Variation of some T-cell indices in Chornobyl cleanup workers divided by dose groups

T-cell parameters	Ratio to control at different dose ranges			
	< 50 mSv	50–250 mSv	250–1000 mSv	> 1000 mSv
Increase of $CD4^+8^+$ lymphocytes number in peripheral blood	1.22	1.44	4.11	2.5
Number of activated $CD3^+$ $HLA\text{-}DR^+$ lymphocytes	0.34	0.67	0.59	0.92
Number of $CD25^+$ cells	0.88	2.45	1.56	0.76

7.3.2. Modification of effects in the immune system

Although the majority of clean-up workers especially in younger age groups provided sparse information on the diseases before clean-up and the clinical hematological counts were in a normal range the immunological analyses in the majority had not been performed before. After the exposure the different rates of the immune system recovery were observed in individuals with pathology of the early period. We performed a comparative analysis of the immune system restoration in the period from 6 to 32 months after irradiation in 872 clean-up workers. In healthy T-cell counts increased during this period from 38.2% to 50.3%, while in patients with pathology of the digestive tract – to 42.1%, vegetative-vascular disorders – to 41.8%. In a series of further studies a number of humoral factors modifying the immune response were revealed, as cortisol, epinephrine, 5-hydroxytryptamin, leu-enkefalin, interleukins (IL) 1, 2, 4, 10, alpha- and beta-endorphins, vEGF. In clean-up workers with cerebrovascular diseases and Th2 type of response domination, the in vitro interleukins 4 and 10 lead to paradoxical activation of Th1-cells. The opioid receptor agonists in doses up to 0.5 Gy inhibit the IL effects, and after doses higher than 0.5 Gy a potentiation effect was shown. Modifying influence of metabolites of arachidonic acid was shown: an inclusion of 12-HETE to lymphocyte membranes is associated with high $CD4^+$ and low $CD8^+$ counts, and the association of high content of 12-HETE with a low number of cytotoxic and natural killer cells, that can act as a factor for promotion of cell transformation [12].

Summary on early effects

As a result of the follow-up immune function studies it was, therefore, possible to formulate the main factors in the range of low doses effects:

➢ radiation-induced non-lethal damage of cells (proliferation of functionally defective offspring; spreading effect due to humoral factors);

➢ modification of the immune response (neuro-immune factors, lipid metabolism accompanying pathology);

➢ system adaptive response (transition to the radioresistant cell cycle phases; threshold type of dose-response recovery reactions including immature cells; nonspecific activation).

7.3.3. Effects in the immune system at the remote period after radiation exposure

Biological markers

Attribution of a late somatic pathology to radiation dose late pathology is disputable. Certain dependencies are recognized for radiation induced cancers, leukemia and cataracts and a lot of discussion is related to low-dose effects in circulation system. As for immune system, last UNSCEAR reports on the topic recommend studies of effects after exposure in high-dose range [1]. Other groups like IARC Research Agenda for Chernobyl Health (ARCH) recommend broader range of studies including biological markers of past exposure, disease and radiosensitivity [13].

At the late period after the accident a set of biological markers was tested at the NRCRM and connection to radiation dose determined by cytogenetic aberrations and/or dose reconstruction was evaluated. Among them were number of Glycophotin A and TCR-negative variant cells, telomere length, histone gamma-H2AX, p53, bcl-2, cyclin-D1 proteins and gene expression.

Glycophorin A

Research on the late effects in the immune system included the quantitative estimation of radiogenic mutations, studies of immune function and influence of confounding factors. From radiation markers at the late period we have studied somatic mutations in Glycophorin A (GPA) and T-cell receptor (TCR) loci.

GPA is present on erythrocytes in amount 5×10^6 per cell, is coded at 4q and it is determined as two allelic forms, according to M and N blood groups. Unlike variant lymphocytes, the red blood cells variant by GPA, do not pass selection in vivo, GPA mutation does not change life-span of red blood cells and is not associated with any clinical changes. Genotoxic effect is registered from erythroblast stage, it can be a marker of damage of early progenitors of red blood cells, including the polypotent stem cell. The assay was performed with analysis of 10^6 cells by two-color cytometry in Chornobyl clean-up workers, who were heterozygous by MN. Cells were stained with M-specific monoclonal antibody (moAb) 6A7B and N-specific moAb BricCF1. Detailed protocol was published previously. A satisfactory correlation was shown with the results of other methods of biological dosimetry. In healthy individuals from control group studied subsequently from 3 to 5 times a mean frequency of mutations (M ± SD) by variant hemizygote N0-erythrocytes was (12.3±4.8) per 10^{-6} cells. This data are compatible with results obtained in the RERF[14].

Studies of the individual parameters have shown weak correlations between the number of mutant erythrocytes, official radiation dose and number of dicentrics (Figure 7.6). Survey of Chornobyl 30-km exclusion zone staff showed the increased frequency of mutations up to 8.9–23 per 10^6 cells. The method is enough high informative for determining exposure, or biological indication. The limitation of this assay was a possibility to study only MN-heterozygote individuals, who represent from 1/4 to 1/3 of population.

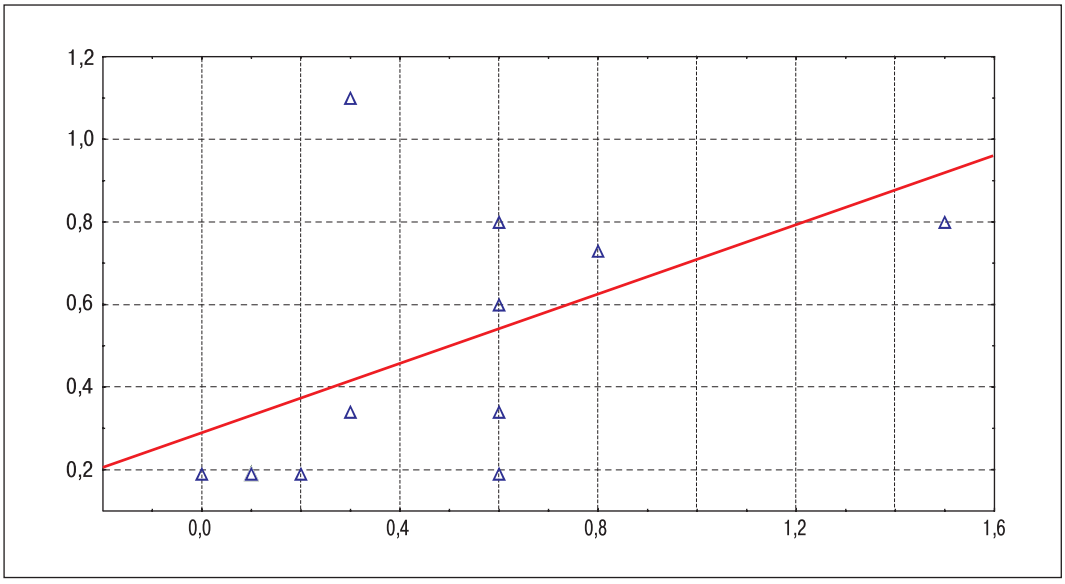


Figure 7.6. **Individual relationship between GpA and cytogenetic dose. X-axis – dose by chromosome aberrations method, Gy; Y-axis – GpA assay dose, Gy.**

T-cell receptor

Research of mutations in a locus of T-cell receptor/TCR gene showed that for Chornobyl clean-up workers with the doses of more than 500 mSv the dose dependent effects in the immune system were observed even through 15 and more years. In a period after 2000 the number of variant cells also exceeded the mean figures for control group, but a difference was not reliable (Figure 7.1).

Contrary to other radiation markers like GPA or chromosome aberrations the experimental studies with cloning of variant TCR-cells and analysis of their progeny have demonstrated relationship of TCR mutations with impaired immune function [15]. We conducted the analysis of correlative dependences between the number of variant T-cells, content of $CD3^+$ cells and expression of CD3 receptor. In a late period such dependence was not found, with an exception of group of patients who have survived after grade 3 acute radiation syndrome. At chronic irradiation in doses which not exceed professional limits, such dependencies were not shown. However, in workers with increased variant TCR-lymphocyte counts a number of T-cells was significantly lower but within the normal range.

Cyclin D1

Cyclin D1 is a protein controlled by PRAD1, CCND1 or bcl-1 genes on chromosome 11q13, which regulates transition from G1toS phase of cell cycle in complex with cyclin dependent kinase (cdk) by phosphorylating the product of the retinoblastoma gene (pRB), initiating release transcription factors with further DNA replication. Ionizing radiation induces the CCND1 gene overexpression and cyclin D1 protein releases that causes transformation to a malignant phenotype. However, the role of ionizing radiation in Cyclin D1 depended cell cycle impairment in a remote period is still to be clarified.

A study was performed in 36 clean-up workers (mean age M ± SD, 54.78 ± 5.31 years) with dose (D) of external exposure (M ± SD) 0.18 ± 0.16 Gy (from 0.01 to 0.80 Gy) were recruited in the test group. Chronical diseases of digestive, cardiovascular and nervous systems without tumorogenisis predominantly were present in the polymorbid structure of these patients. All examinees consisted of two groups according to the dose rage: I – (0.01–0.10) Gy; II – (0.11–0.80) Gy, which included 13 and 23 persons respectively. 18 healthy men in appropriate age, without radiation anamnesis were recruited in control group [16].

Cyclin D1 positive mononuclear cells were counted by flow cytometry (FACS Calibur, BD, USA) using FITC-stained Mouse Anti-Human Cyclin D1 Monoclonal Antibodies (BD Pharmingen). Obtained data shows that a percentage of Cyclin D1+ cells in exposed correlates with dose of radiation (r_s=0.518, p=0.001) and is higher in 1.66 times ($p<0.001$) in subjects with D>0.10 Gy against the normal range and I group of examinees with levels within a normal range. Elevated counts of Cyclin D1+ cells in II group is associated with a tendency to decrease T-NK cell numbers in 2.26 times ($p = 0.008$) together with $CD4^+$ level increase in 1.27 times ($p = 0.009$) on a base of increasing level of IgG in 1.27 times ($p < 0.001$) and low level of Ig A ($p = 0.025$) in compare to control group.

Increased level of Cyclin D1+ mononuclear cells correlated with IgG concentration ($r = 0.538$, $p = 0.039$) in II group of irradiated persons together with fond medium strength correlation between Cyclin D1+ cells and age (r=0.467, p=0.079) was revealed in exposed to doses over 0.1 Gy.

Thus, an increased expression of Cyclin D1+ in blood mononuclear cells at the late period after exposure points to possible radiation induced impairment of cell cycle.

Expression of γ-H2AX

To compare the effect of different doses of radiation on formation of γ-H2AX histone at different time intervals after radiation exposure and different radiation doses we have investigated the expression of γ-H2AX histone in peripheral blood lymphocytes of 68 patients, including 35 clean-up workers and 33 staff members working at the high radiation risk zone of the Shelter object.DNA reparation is a fundamental process which ensures the stability of the genome. It is believed that-double-strand breaks DNA are the most dangerous for cells because it can lead to its death. In humans and other eukaryotes DNA wrapped around the histone group consists of bark histones H2A, H2B, H3 and H4. H2AX is a histone of H2A family with a molecular mass of 14 kDa. One of the early stages of cell response to double-strand breaks DNA after ionizing radiation is the phosphorylation of histone H2AX on serine 139, which occurs around this breaks in chromatin domains. This phosphorylated form of H2AX is called γ-H2AX. At first, γ-H2AX foci are small and are already visible during 1–3 minutes after irradiation γ-H2AX accumulation in cell can be visualized using specific antibodies. The time which γ-H2AX foci are increased is directly proportional to the radiation sensitivity of cells. A flow cytometry method was developed for the diagnosis of Ataxia telangiectasia, which is based on measuring the phosphorylation of histone γ-H2AX [18]. Ataxia telangiectasia – is a progressive neurodegenerative disease that begins in early childhood and it is caused by mutations in the ATM gene (Ataxia telangiectasia mutated gene). Most of tests are not specific enough, need to much time or require a large number of blood samples. A method of flow cytometry is a very sensitive, specific, rapid and requires only 2 ml of peripheral blood and can therefore be used for regulation early diagnostic of Ataxia telangiectasia by determining changes in the γ-H2AX histones [19]. Research the impact of I-131 therapy on DNA breaks in peripheral blood lymphocytes by the method of flow cytometry was found that this therapy caused a large number of double-strand breaks of nucleic acid [20]. There are indications that determining the dose of tumors radiotherapy of different parts of the body also is possible using γ-H2AX analysis. The flow cytometry method is a very sensitive, specific and rapid, requires small quantity of peripheral blood cells [21, 22]. The aim of our study was to compare the effect of formation γ-H2AX histone with different doses of radiation in the Chornobyl clean-up workers and the people, who work on the project «Shelter» at different time steps by flow cytometry method using γ-H2AX antibody.

Individual doses in 35 Chornobyl clean-up workers of 1986–1988 varied from 200 to 1000 mSv, time after exposure 22–24 years. In the second group (staff) shift doses of external exposure were below 20 mSv, time after exposure - up to 2 weeks. Peripheral blood samples were stained with Alexa Fluor 488 mouse anti-γ-H2AX antibody (BD, USA) and analyzed using FACS Calibur flow cytometer (BD, USA).

The number of γ-H2AX positive cells in subjects, who work at the object «Shelter» was higher (0.7 ± 0.93) (M ± SD), than at clean-up workers ($0.51 \pm 0.27\%$) (M ± SD); $p < 0.001$. Clean-up workers group showed some heterogeneity with higher figures in subjects exposed to higher doses. In clean-up workers with history of exposure of 150–250 mSv the mean number γ-H2AX-positive cells was (0.49 ± 0.05)% in comparison with (0.55 ± 0.08)%, ($p < 0.01$) in samples from clean-up workers exposed in the interval of 250–1000 mSv [17].

Obtained data confirm the previous experimental conclusions that the expression of γ-H2AX histone increases with increasing radiation dose. The staff with recent history of low-dose exposure exhibits higher figures of γ-H2AX histone, than clean-up workers. Our findings show an preservation of an increased γ-H2AX expression later than in previous studies (days vs. minutes and hours), that could be explained by a higher sensitivity of assay. Such after exposure is later than in this can be explained by the fact that the structure of DNA has not yet stabilized, and the effect of radiation had not yet realized.

7.4. IMMUNE FUNCTION IN PATIENTS WITH CEREBROVASCULAR DISEASES (CVD) EXPOSED TO IONIZING RADIATION AS A RESULT OF THE CHORNOBYL ACCIDENT

Follow-up studies of the immune function in patients with vegetative dysfunctions (VD) of early period and cerebrovascular diseases of the later period after radiation exposure bridge the neuro-humoral regulation and radiogenic changes in the immune system. In patients with VD in the period of recovery after radiation damage the changes in expression of receptors for neuropeptides, messengers of neural signals and hormones, and hypersensitivity to brain tissue antigens were shown. Attempts were made to describe a post-irradiation systemic dysregulation of homeostasis, with a key role of the immune system in the formation of neuro-immuno-endocrine abnormalities.

In a late period such relationship is less obvious. According to studies of immune-mediated brain pathology a set of pathways can be proposed including:

➢ the secondary subset changes associated with disorders of the nervous-humoral regulation;
➢ cytotoxic mechanisms with a switch of antigen-dependent and natural killer reactions, apoptosis through Fas (CD95) and Fas-ligand (CD95-L);
➢ hypersensitivity immune complex and reagin type antibody and delayed type cellular reactions with an increase of hemato-encephalitic barrier permeability;
➢ an impaired lymphocyte regulation of a nervous system function by a release of lymphocytic neurotropic substances, accumulation or, to the contrary, decrease of consumption by lymphocytes of different neuropeptides (beta-endorphins, Leu-enkefalins, S-100 and others) due to receptory changes.

For a study of modifying role of CVD to immune system effects the official dose records from the State Chornobyl registry, the Chornobyl NPP dosimetry shop and Clinical epidemiological registry of the RCRM were used. Analysis of immunological parameters 10 years after exposure and later has shown dependence rather due to radiation dose than time after exposure and a presence of dose threshold of 250 to 350 mSv. However, for chronic exposure of staff of a 30-km exclusion zone, the major factor was the duration of work in the zone of high radiation risk. Examination of clean-up workers with CVD has demonstrated in 42.3% of cases the decreased $CD3^+$ and $CD4^+$ cell counts in peripheral blood. Depression of cellular immunity was association with the preservation of the increased variant TCR-cell counts.

The study of dose dependence and irradiation time showed that in 23.2% of patients in 11–13 years after exposure a stable depression of T-immunity was shown with a high degree of correlation of $CD3^+HLA\text{-}DR^-$ cell counts with radiation dose. The majority of these workers were exposed over 400–500 mSv. The second group included clean-up workers of the same period exposed below 250 mSv with prevalence of activation reactions and positive correlation between radiation dose and number of $CD3^-DR^+$ B-cells, the concentrations of circulating immune complexes and IgA..

In patients with doses over 500 mSv a decrease was demonstrated of the $CD3^+$ cell counts due to a lesser number of $CD4^+$ cells and also $CD3^+DR^+$ cells. In clean-up workers with doses below 0.5 Sv a similar tendency was accompanied by an increased number of $CD8^+$ cells. The number of cytotoxic T-cells and the NK-cells was decreased in both groups. B-cells have shown absence of substantial changes. The number of $CD19^+$ cells in exposed with doses below 500 mSv was (6.7±0.5)% , over 0.5 Sv - (8.19 ±0.6)%, in control – (8.45±0.17)%; for $HLA\text{-}DR^+$B-cells the counts were accordingly (8.78±0.9)%; (10.48±0,87)%; (9.89±0,34)%.

At the period of 15 to 20 years after exposure we have studied the immune function and influence of chronic somatic pathology in clean-up workers exposed to ionizing radiation. Research was carried out in 306 workers with doses exceeding 50 mSv (50–770 mSv) and the most common types of chronic disease of a late period (chronic obstructive pulmonary disease, chronic hepatitis, CVD). Analysis of immunological parameters have demonstrated that in acute exposure at the period after exposure greater than 10 years, the statistically significant differences depend on dose, not time. The threshold dose, the effect of which remains in the formation of long-term effects in patients with CVD, is 0.25 Sv. However, in chronic exposure at the 30-km zone, the major factor is the length of stay in the zone, and the threshold dose is reduced.

In the long-term period some changes were registered in immunity with a predominance of activation reactions, which probably indicate damage to the immune mechanisms. A substantial share of CVD pathways was a formation of hypersensitivity reactions, which were confirmed by cell activation by S-100 protein and other brain antigens.

7.5. GENE REGULATION OF APOPTOSIS AND TELOMERE LENGTH

Last progress in radiobiology, molecular biology and genetics, allowed to offer few theories in relation of biological senescence of cells which partly complement each other, and partly cause contradiction. Molecular-genetic theories describe genome changes at aging as programmed, or – as a result of accumulation of mutations. We have studied apoptosis as one of the system mechanisms of stability of cellular populations and telomere length in forming of cell response to ionizing radiation. Shortening of telomeres is regarded as one of the important stages in cell senescence [23–25]. Telomere shortening after irradiation could decrease proliferative abilities and thus influence the elimination of cells containing double strand breaks (DSB) and, possibly, dicentric chromosomes, mediate p53 pathways. A result could be an error-prone recovery of immune cells. To the contrary, experimental studies have shown that adding of telomerase to the genome of fibroblasts allows to elongate the life cycle [26]. Research on relative length of telomeres (RTL) was conducted in Chornobyl clean-up workers and staff of the Chornobyl 30-kilometer exclusion zone by flow-FISH assay. The analysis was performed in a FACS Calibur flow cytometer (Becton Dickinson Immunocytometry Systems, San Jose, CA) using the FL1 channel for detection of fluorescein signal and the FL3 channel for propidium iodide. No compensation was set on the instrument. List mode data from 10^4 cells in each experiment were collected and analyzed using CELL-Quest software (Becton Dickinson). The telomere fluorescence signal was defined as the mean fluorescence signal in G0/G1 cells after subtraction of the background fluorescence signal (i.e. FISH procedure without probe). The relative telomere length value was calculated as the ratio between the telomere signal of each sample and the control cell line (K562) with compensation for the DNA index of G_0/G_1 cells. This compensation was performed in order to «normalize» the number of telomere ends per cell. On Figure 7.7 an RTL analysis is illustrated by flow cytometry in the «Dot plot» mode. Sample after hybridisation with peptide nucleic acid (PNA) probe-FITC, show a significantly higher fluorescent FL1 signal (Figure 7.7 B), than base-line/autofluorescense signal from the cell samples, without PNA probe (Figure 7.7 A).

Analysis of relative telomere length in leukocytes of peripheral blood of Chornobyl clean-up workers with varying degrees of cognitive impairment was performed in comparison to the internal controls (persons with cognitive disabilities, exposed in low doses 0–2 cSv). It was found the increase of average RTL indexes in the study group compared to the internal control (Table 7.5).

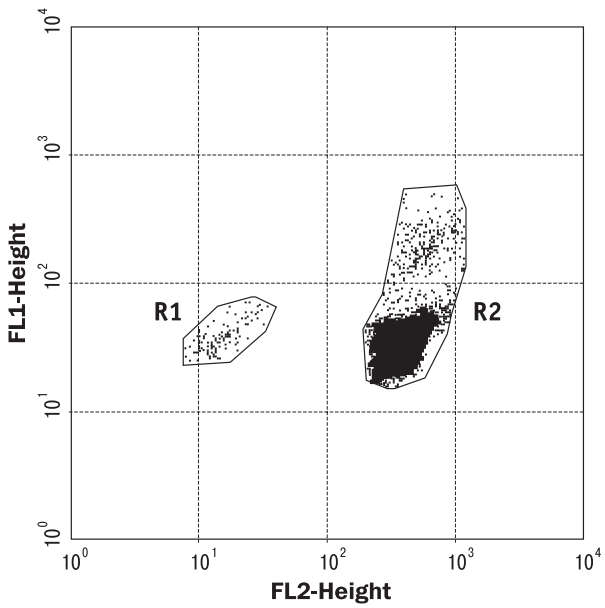


Figure 7.7. **Dot plot of the relative length of peripheral blood lymphocytes telomeres. R1 – experimental cells, R2 – control cells (K562 line).**

Table 7.5
Relative telomere length in peripheral blood leukocytes of examination groups

Groups by radiation dose	RTL		*t*-value	*p**
	M	SD		
Non-exposed control	17,21	2,21		
1 (0–2 cSv) internal control	14.16	4.17	–	–
2 (2–10 cSv)	16.80	4.21	-2.62	0.01
3 (10–25 cSv)	15.92	3.94	-2.02	0.04
4 (25–50 cSv)	16.88	3.96	-2.90	0.004
5 (>50 cSv)	17.64	3.64	-3.34	0.001

Notes. *– significant difference in comparison with the non-exposed group.

However, analysis of telomere length in dose group comparison with the healthy control showed the opposite result. It was established the decline of the RTL indexes in leukocytes of peripheral blood of Chernobyl clean-up workers in different dose ranges relatively of control ($p < 0.0006$).

The results of studies of telomere length in comparison with the control group confirmed our assumption about relationship between the telomere changes and radiation dose more than twenty years after the exposure. Our data suggest the relationship between the telomere changes and radiation dose more than twenty years after the exposure. The reduction of telomeric chromosomal sites may be a signal to start cell aging. In the presence of replicative aging reduces the effectiveness of the system, which detects DNA violations and participates in the repair of

genomic DNA. Such violations DNA reparation system in the remote period after irradiation can lead to pathological conditions, including malignant transformation.

Longer telomeres are related to a combined effect disease with cognitive impairment and ionizing radiation. Long telomeres representing a history of relatively low cellular proliferation wich may be associated with age-related changes. We presume, that the longer telomeres in persons more heavily exposed to ionizing radiation and the presence of cognitive impairment probably indicate dose-dependent activation of telomerase (as evidenced by increased TERT gene expression, which regulates telomerase activity (see below)) as a chromosome «reparative» mechanism following damage, and reflect defect in telomerase regulation.

In clean-up workers the length of telomeres depends on the dose of exposure and degree of cognitive disorders. The highest group values were registered in exposed over 500 mSv and among persons with severe degree of cognitive impairment. Pearson's correlations were not significant ($r = 0.13$).

7.5.1. Dependence of Relative telomere length from age

It is known that the telomere length of somatic cells shortens with age. It was inspect correlation analysis between the relative telomere length and age of the total cohort of persons. Established only a general trend that shows decrease in relative telomere length with age (Figure 7.8).

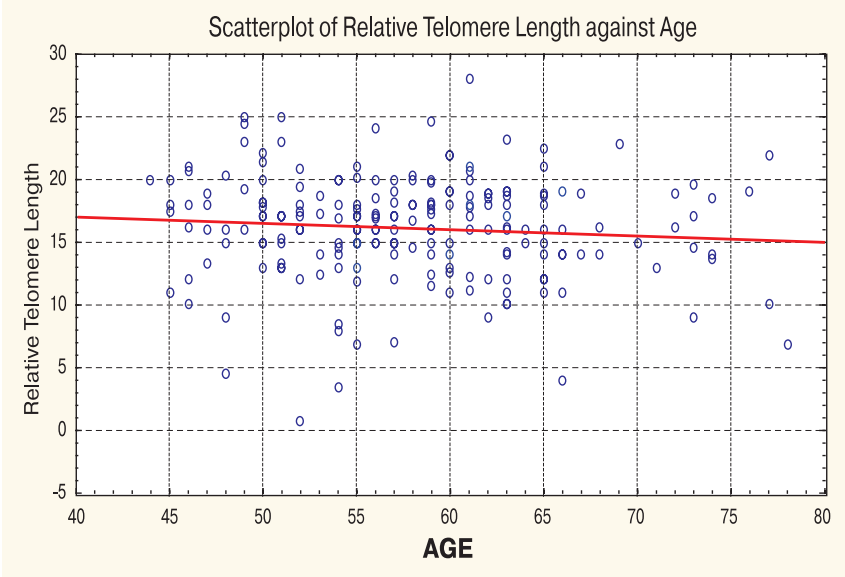


Figure 7.8. **Dependence between age and RTL in clean-up workers of Chornobyl accident**

Age of the total cohort of people examined was in the range of 44 (minimum) to 80 (maximum) years. It was formed 4 age groups to differentiation and characteristics changes of parameters in different age ranges. These are: 1st group – 40–50 years, 2nd group – 50–60 years, 3rd group – 60–70 years, 4th group – 70–80 years. This distribution showed that the rate of RTL reduced after 50 years (6.1%). The most significant reduction in telomere length shown after 70 years (11.7%). The results are shown in Figure 7.9.

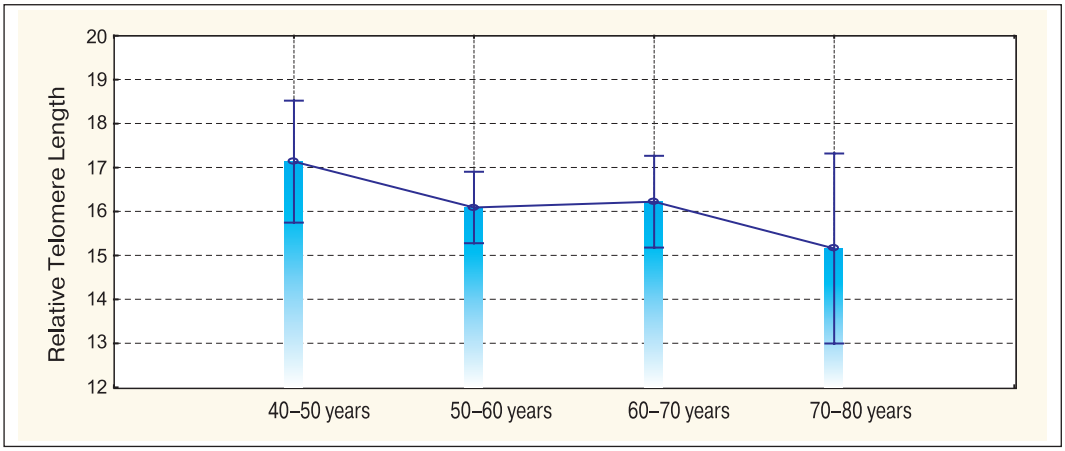


Figure 7.9. **Telomere length and age in Chornobyl clean–up workers 25–27 years after radiation exposure (M ± SD): X–axis – age groups; Y–axis – RTL**

7.5.2. Telomere length and cognitive deficit

Telomere length can be a potential diagnostic biomarker for differentiation between the degenerative and vascular cognitive impairment.A special study was performed by the NRCRM departments of clinical immunology and radiation psychoneurology in a frame of the EU FP7 CEREBRAD project «Cognitive and Cerebrovascular Effects Induced by Low Dose Ionising Radiation» (Grant agreement no: 295552). The project studies were dedicated to groups of clean-up workers exposed below 500 mSv and subjects exposed in utero. Results of cognitive function studies are presented at a special section of this book by prof. K. Loganovsky. Below we present data on gene expression and telomere length. In detail results of research are presented in the RCRM publications [26–41].

Cognitive functions decline with age, and telomere length is reduced. We observed this type of dependency in our study. Negative correlation was found between relative telomere length vs degree

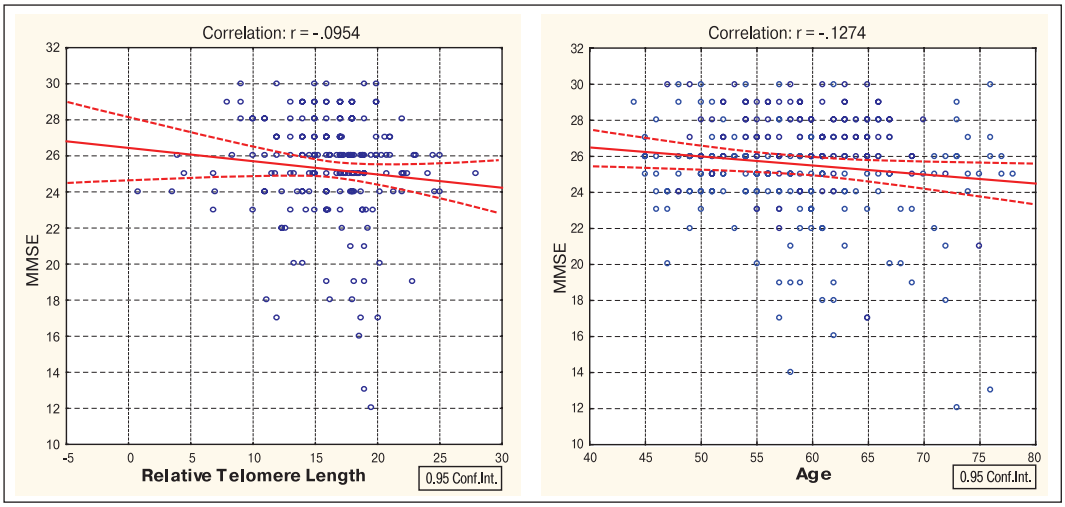


Figure 7.10. **Dependence between cognitive deficit according to the MMSE, age (A) and RTL (B) in clean-up workers of Chornobyl accident**

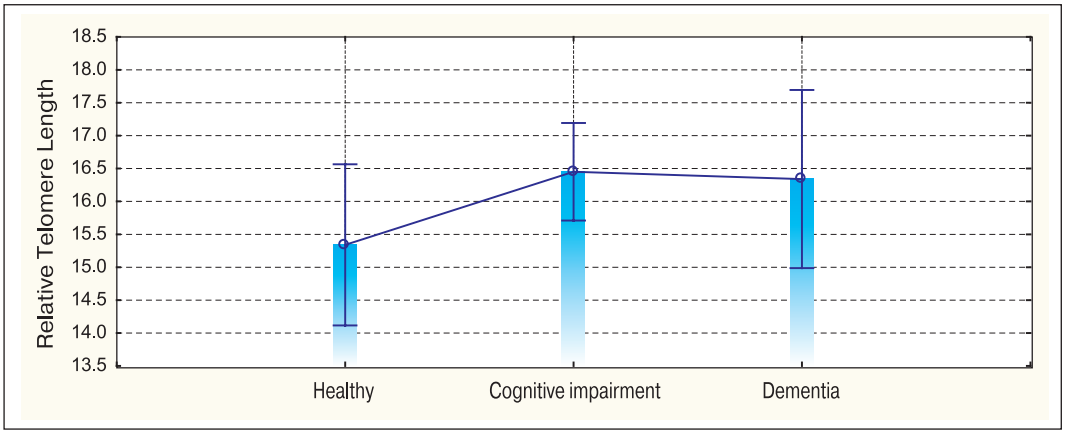


Figure 7.11. Changes of index of relative telomere length due to stage of cognitive impairment in Chornobyl clean-up workers 25–27 years after radiation exposure (M±SD): X–axis – stage of cognitive impairment; Y–axis – RTL

of cognitive deficit (MMSE scale) and between age vs. degree of cognitive deficit (Figure 7.10).

Cognitive deficits also accompanies the aging process and, therefore, may correlate with telomere length. In our study was confirmed the suggestion that telomere length correlates with different degrees of cognitive functions, and may be biomarkers of cognitive aging in patients before the onset of dementia. It was established that the RTL index increased in the group of persons with cognitive deficits and dementia (Figure 7.11).

However, comparative characteristics of telomere length in groups of persons with cognitive deficits of varying severity and in the control group demonstrated a decreased of RTL ($p<0.01$). This confirms the dependence of this parameter from the disease and inclusion of different mechanisms of regulation of telomere length in sick patients as compared to healthy, as well as within the cohort of patients with varying degrees of severity of cognitive impairment (Figure 7.12).

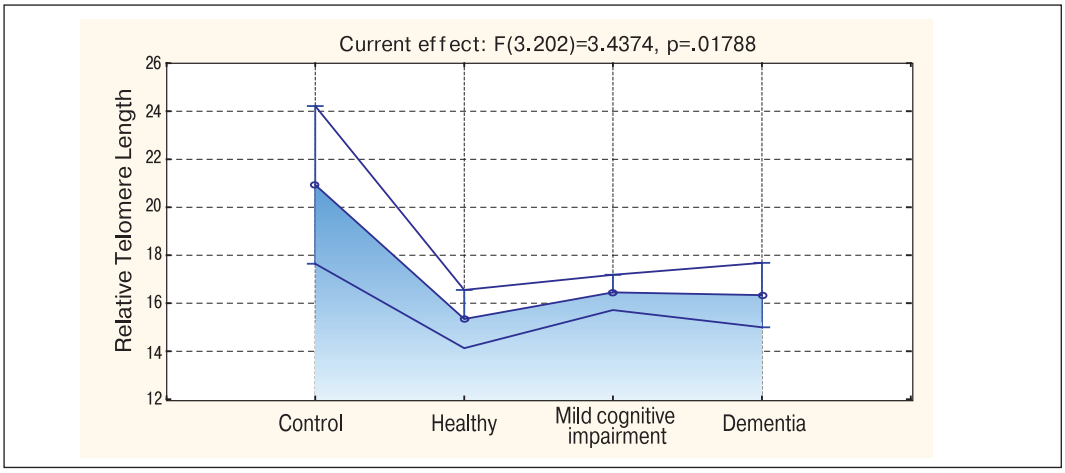


Figure 7.12. Changes of index of relative telomere length due to stage of cognitive impairment in Chornobyl clean–up workers 25–27 years after radiation exposure (M±SD): X–axis – stage of cognitive impairment ; Y–axis – RTL

7.5.3. Analysis TERF1, TERF2 and TERT gene expression due to radiation dose

Analysis of TERF1, TERF2, TERT gene expression was conducted comparatively to the internal control group and did not show statistically significant results. However, there were some trends and patterns (Table 7.6).

TERF1 gene expression characterized such features: the index of TERF1 RQ was not significantly altered compared with the internal control group. Considerable changes were observed in 4th (25–50 cSv) and 5th (> 50 cSv) groups with higher dose load (Figure 7.13, A). TERF2 gene expression in groups 2nd and 3rd was slightly reduced, but group of persons, exposed > 50 cSv characterized by overexpression of this gene (Figure 7.13, B). Most considerable changes are noted in the analysis of TERT gene expression. Average index of RQ of TERT grew with increasing radiation dose. The highest rate registered in the group of persons, exposed in > 50 cSv dose interval (Figure 7.13, C). Thus, there is a clear relationship between changes in expression of genes – regulators of telomeres length and dose.

Confirmation of this assumption is the established correlation between RQ of TERF1, TERF2, TERT and radiation dose). The Pearson correlation coefficient were $r = 1.17$ ($p < 0.05$), $r = 0.23$ ($p < 0.05$), $r = 0.48$ ($p < 0.05$) accordingly.

Thus, these data demonstrate the relationship between expression of genes-regulators of telomere-telomerase complex and radiation dose more than twenty years after the exposure. The results suggest that that at the late period there exists some difference in gene regulation at doses below and over 50 cSv.

7.5.4. Analysis TERF1, TERF2 and TERT gene expression and cognitive deficit

Telomeres play a role in regulation vascular aging and shorter leukocytes telomere length has been demonstrated to predict cardio-cerebrovascular disease and mortality. It has been postulated that TERF1 mainly involved in the regulation of telomere length, whereas TERF2 was

Table 7.6
Relative quantification of TERF1, TERF2, TERT gene expression

Groups	Gene symbol (Assay)	Relative quantification		*t*-value	*p**
		M	SD		
0–2 cSv	TERF1 (Hs00744634_s1)	1.78	0.90	–	–
	TERF2 (Hs00194619_m1)	2.38	1.05	–	–
	TERT (Hs00972656_m1)	0.91	0.60	–	–
2–10 cSv	TERF1 (Hs00744634_s1)	1.83	0.45	-0.05	0.95
	TERF2 (Hs00194619_m1)	1.17	0.31	1.44	0.15
	TERT (Hs00972656_m1)	1.79	1.01	-0.53	0.60
10–25 cSv	TERF1 (Hs00744634_s1)	1.64	0.38	0.16	0.86
	TERF2 (Hs00194619_m1)	1.63	0.44	0.73	0.46
	TERT (Hs00972656_m1)	2.94	1.22	-0.95	0.34
25–50 cSv	TERF1 (Hs00744634_s1)	2.90	0.70	-0.96	0.34
	TERF2 (Hs00194619_m1)	2.29	0.59	0.08	0.93
	TERT (Hs00972656_m1)	3.01	0.46	-0.57	0.57
> 50 cSv	TERF1 (Hs00744634_s1)	2.23	0.64	-0.42	0.67
	TERF2 (Hs00194619_m1)	3.94	1.23	-0.91	0.36
	TERT (Hs00972656_m1)	5.53	1.99	-1.73	0.10

Notes. *– significant difference in comparison with the internal control (0–2 cSv).

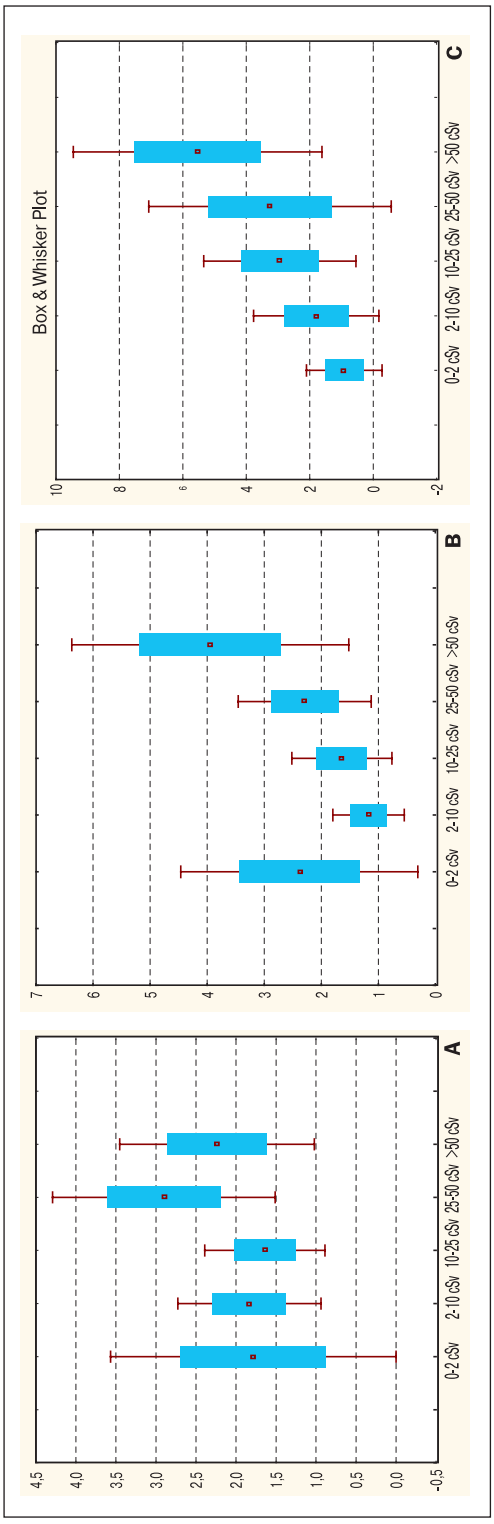


Figure 7.13. Description of TERF1, TERF2 and TERT gene expression in dose group comparative to the internal control (M ± SD): X-axis – exposure groups; Y-axis: A – RQ for TERF1; B – RQ for TERF2; C – RQ for TERT gene.

implicated in protectin chromosome ends. Recent reports have shown that both proteins play a crucial role in regulation telomere length as well as in protecting chromosome ends.

We studied the «sheltering» complex (TERF1, TERF2) and TERT gene expression depending on the degree of cognitive impairment. Analysis of features of TERF1 gene expression, showed the presence of overexpression of TERF1 in persons with cognitive deficits and dementia (Figure 7.13 A). On the background of increased RQ of TERF1, it was showed decreased TERF2 gene expression (Figure 7.13 B). Inhibition of TERF2 can induce either senescence or apoptosis of cells by destroying telomere loops. This assumption is supported by the established negative correlation between TERF2 gene expression and the expression of apoptosis marker CD95 ($r=-0.25$, $p<0.05$) (Figure 7.14). In addition, we found an increase of TERT gene expression (Figure 7.15 C), which partly explains the established fact of elongation of telomere length depending on the degree of cognitive deficit.

* * *

As a result of this study several conclusions could be made:

Cognitive function is influenced by the radiation dose and age at exposure. The level of subjective distress caused by traumatic event is higher in young adults exposed in utero. There is some increase of somatoform symptoms and levels of anxiety, insomnia and social dysfunction. Subjects exposed in utero during the check at age of 25–27 years exhibit an excess of the disorders of autonomic nervous system (ICD-10: G90). Neurological microsymptoms as well as neurotic, stress-related and somatoform disorders (F40–F48) dominate. Subjects exposed to ionizing radiation at adulthood as clean-up workers exhibit symptoms of mild cognitive impairment according to the operational

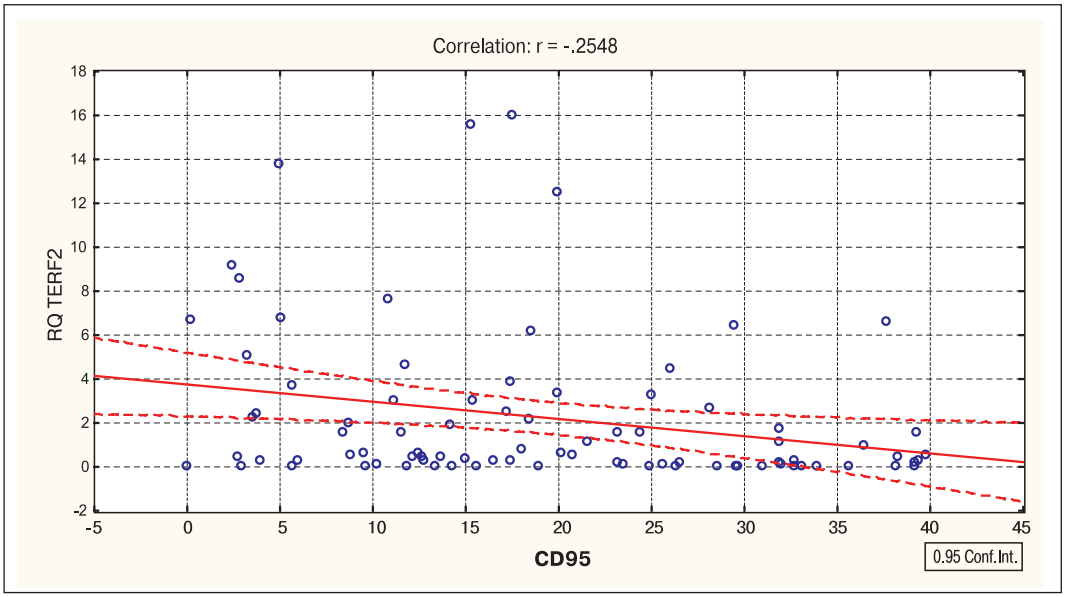


Figure 7.14. Dependence between RQ of TERF2 and expression of CD95 in peripheral blood leukocytes of clean-up workers of Chornobyl accident 25–27 years after radiation exposure

criteria of the MMSE (mean group scores range = 24–27). The clean-up workers have significantly higher level of mental disorders according to the BPRS in dose-related manner, than young adults. This could be the effect of the age and radiation dose. Clean-up workers exposed to doses over 250 mSv and, especially, 500 mSv demonstrate significant cognitive deficit in comparison with exposed below 250 mSv and non-exposed patients. In comparison with previous studies an excess of cognitive dysfunction was significant at doses of 250 mSv and higher. Analysis of relative telomere length in clean-up workers at the late period after radiation exposure shows a decrease radiation exposed comparing with healthy control. A significant telomere length decrease is demonstrated with age. Telomere length in clean-up workers is reduced after 50 years (6.1%). The most significant reduction in telomere length is shown after 70 years (11.7%).

This study shows a presence of a molecular mechanism supporting presence of a cognitive deficit at a late period after radiation exposure. Negative correlation was found between telomere length and degree of cognitive deficit (MMSE scale) and between age and degree of cognitive deficit. However, RTL index is significantly decreased in groups of persons with cognitive deficits compared to control group.Telomere length at the late period after radiation exposure is doenregulated by the high TERF2 gene expression combined with low expression of TERT gene. After exposure to doses over 250–500 mSv a considerable increase in TERT gene expression is demonstrated.Cognitive deficit and dementia in clean-up workers are associated with overexpression of TERF1 and TERT and decrease in expression of TERF2 gene. Other findings in clean-up workers include a relationship between the TERF2 gene expression and cell fraction susceptible to apoptosis ($CD95^+$) that has to be studied in future.

* * *

The performed study show a presence of the immune system cellular reactions after radiation exposure in a wide range of doses starting from high doses inducing radiation injuries to low doses and dose rates, which are determined both in the early period system and in a remote

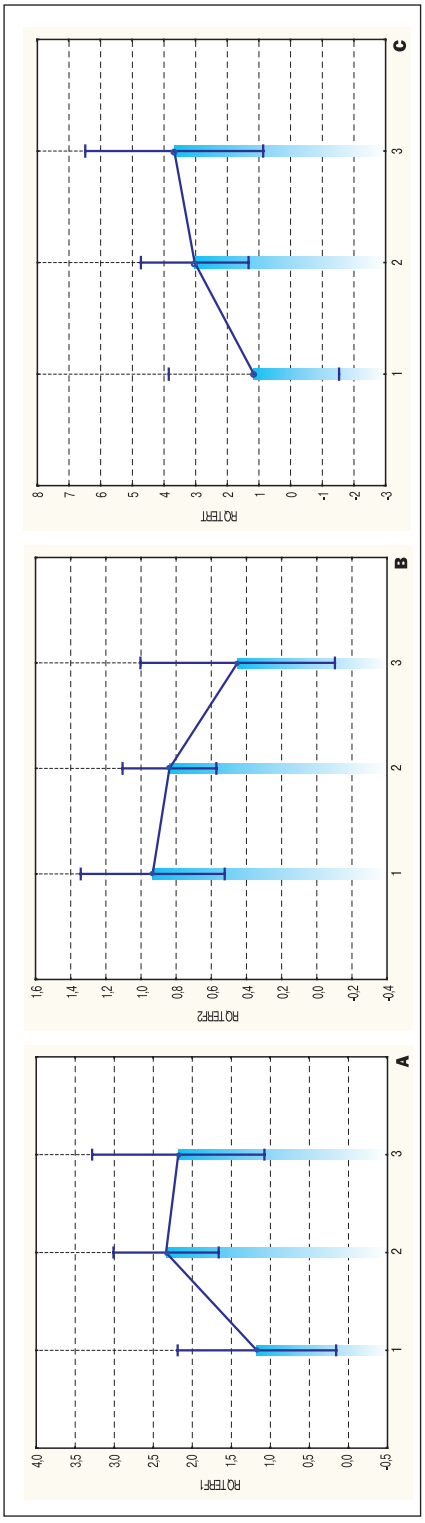


Figure 7.15. Description of TERF1, TERF2 and TERT gene expression in total cohort depending on the degree of cognitive impairment (M ± SD): X-axis – stage of cognitive impairment (1 – healthy; 2 – cognitive impairment; 3 - dementia); Y-axis: A – RQ for TERF1; B – RQ for TERF2; C – RQ for TERT gene.

period. The results allow to expand knowledge from the experimental data to humans, and testify the leading role of radiation factor in induction of the effects in immune system in exposed due to Chornobyl accident, and primarily – clean-up workers.

Unlike the experimental data of irradiation the cell lines, the cellular effects in human are modulated not only by a bystander and other non-targeted effects but by a set of confounding factors, from which the most important to our opinion are neuro-immune interaction and lipid metabolism especially the arachidonic acid metabolites. A substantial part of effects is of an adaptive type, like cells transition to the radioresistent phases of cycle with «early» G_1- and «late» G_2-blocks; dose-dependent entry of the immature T- and B-cells to peripheral blood and nonspecific activation.

At the same time both in recovery period and in a remote period the radiation induced unlethal cell damage was demonstrated, including a differentiation of early progenitor cells to a functionally defective progeny. At exposure in the professional limits a set of activation changes at the different stages of differentiation of immune cells was shown with an increased genome instability, which was revealed by an increase of non-replicative DNA synthesis, accumulation of S-G_2-M cells and enhanced expression of antigens of proliferating cells. The radiobiologic role of changes of apoptosis has to be understood in future.

A necessity is to fill the gap and find the link between the changes of immune function at low doses and formation of the late stochastic tumor effects as well as the non-tumor pathology of the late period.

The obtained findings enable the elaboration of strategies of staff selection and follow-up under low-dose exposure. First examples of such approach could be the staff of the 30-kilometer exclusion zone and Chornobyl «Shelter». On the basis of the experimental data an adaptation to ionizing radiation in doses up to professional limits is supposed for healthy individuals, while at latent tumor processes an increase of genotoxic

effects could be possible. It confirms the necessity of the thorougful staff entry checks to the radiation zone. So, in humans there is a relationship between violation of apoptosis, telomere shortening, parameters of cellular immunity and radiogenic somatic mutations due to ionizing radiation. At present the dependencies were described between the relative telomere length, dose of irradiation over 500 mSv, age and some types of chromosome aberrations. Future analysis is needed in humans expanding the studies on the role of gene regulation at the late period after low-dose exposure.

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Chapter 8
PERSISTENT INFECTIONS AND THEIR INPUT IN SOME POST-IRRADIATION ONCOLOGIC AND NON-TUMOR PATHOLOGIES

Since cooperative study of hepatitis C virus (HCV) infection among blood donors of Kyiv Municipal Blood Center under the supervision of Prof. H. Yoshizawa from Hiroshima University, Japan (1993–1995) revealing total 3.45% HCV^+ prevalence in these 'healthy' hosts [1] we were involved in the problem of persisting infections.

Our investigations were focused on the potential for a presence of persisting infections to contribute to the onset/progression of any observed changes in incidence of the various pathologies in different categories of exposed people [2], as a dose-effect ratio was not strictly evident in many of the documented cases of oncological diseases, and of non-tumor pathologies of the cardiovascular, bronchopulmonary, digestive, and urogenital systems as the effects of the 1986 Chornobyl nuclear power plant (NPP) accident,

Patients hospitalized in the in-patient clinic of the NRCRM or examined in the context of their biennial clinical-laboratory surveillance in the Clinical-Epidemiological Registry were entered into the study only after they had provided informed consent and full medical histories of any past/ongoing tumor- and/or non-tumor-based (i.e., somatic) diseases. All study designs used herein were approved by the Ethics Commission of the NRCRM.

The following groups of patients were recruited for these studies: convalescents of acute radiation syndrome (ARS), n = 155 (mean age 49.3 [± 0.82 {SE}] years); Chornobyl NPP clean-up workers, n = 1017 (mean age 47.6 [± 0.57] years); inhabitants of radiation-contaminated territories in the Ukraine, n = 578 (mean age 46.5 [± 0.37] years); and NPP workers, n = 122 (mean age 42.2 [± 0.73] years). While the «n» values noted here represent the total size of the various populations recruited, not every subject in a group was assessed for every endpoint outlined below. For comparison purposes, a group of patients with different somatic diseases, and who had not been exposed to ionizing radiation (IR; n = 367, mean age 44.8 [± 1.17] years) and the earlier blood donors of Kyiv Municipal Blood Center (n = 41,021, mean age 39.7 [± 1.17] years) were employed as controls.

For analyses of any relationship(s) between infection (past/ongoing) status and IR exposure history, 294 patients with chronic lymphocytic leukemia (CLL) and 4 with stable large granular

lymphocytosis [LGL]) were also recruited and studied. The diagnosis of CLL was based on clinical history, lymphocyte morphology, and immunophenotypic criteria. CLL patients were divided into two groups according to IR exposure: the first group included 63 IR-exposed CLL patients and the second group (the nosologic control group) consisted of 231 IR non-exposed CLL patients.

The group of IR-exposed CLL patients included 48 clean-up workers, 10 inhabitants of nuclide-contaminated areas, and 5 evacuees, who were observed in the Department of Hematology and Bone Marrow Transplantation (DHBMT) of NRCRM during June 2004-December 2008. Information about doses of clean-up workers was available from the State Registry of Chornobyl Catastrophe Sufferers of Ukraine. Among the clean-up workers, estimated doses ranged from 250–1200 mSv among those who were on site the earliest; doses for those who arrived later in 1986 and then over 1987–1989 ranged from 1.4 mSv to 99 mSv. Accumulated doses (since 1986 to the diagnosis of CLL; range 2.3–21.2 mSv) in the residents of contaminated areas were calculated on the basis of the data on ^{137}Cs soil contamination density (mean age dose typical for a given level of local contamination) and information on measurements of radioactive Cs in the body at the CLL diagnosis. The control (non-IR-exposed) group included CLL patients who were observed in the DHBMT (129 patients) and the Department of Hematology of Poltava Regional Hospital (102 patients) during the same period without special selection of patients.

Twenty two bronchial asthma patients were recruited for treatment of concomitant persisting infections.

Blood sampling was collected as part of any given patient's routine diagnostic protocol. Heparinised plasma or blood serum were used for serological investigations.

Anti-HCV (IgG) and/or anti-cytomegalovirus (CMV), herpes simplex 1/2 types, Epstein-Barr virus and *Toxoplasma gondii* (IgG and IgM) antibodies in an isolated serum sample were assessed using commercially-available ELISA diagnostics kits (Sanofi Diagnostique Pasteur, Marnes-La-Cosuette, France; RPC Diagnostic Systems, Nizhniy Novgorod, Russia; DiaProf Ltd., Kyiv, Ukraine; Vector-Best, Novosibirsk, Russia; and, Diagnostic Systems Laboratories (DSL), Webster, TX) and following manufacturer's instructions. HBs-antigen was determined by passive hemagglutination test.

Sub-populations of peripheral blood lymphocytes were quantified using two-color laser flow cytometry. The differential tagging of cells was performed with monoclonal antibodies of the Leu series obtained from Becton Dickinson (San Jose, CA) using standard protocols and following manufacturers' instructions. All data were then analyzed using the software provided by the manufacturer.

The presence of CMV DNA was investigated in the fraction of peripheral blood mononuclear cells by polymerase chain reaction (PCR). Briefly, DNA was extracted from the cells using a sorption method. PCR of the samples was then performed using kits from DNA-Technology JSC (Moscow, Russia) and the following regimen: 5 cycles of 94 °C for 90 sec, 94 °C for 50 sec, 67 °C for 45 sec, and 72 °C for 30 sec, then followed by 40 cycles of 94 °C for 20 sec, 67 °C for 20 sec, and 72 °C for 20 sec. The resulting PCR products were then electrophoresed over 1.5% agarose gels and visualized using standard ethidium bromide staining.

PCR analyses of *IgHV* genes rearrangements in CLL cell samples were studied according to the BIOMED-2 consortium rules [3] as described previously [4].

PCR products were then analyzed on a 1.5% agarose gel and visualized with ethidium bromide staining. Products were spin column-purified using a PCR purification kit (Promega, Madison, WI) and sequenced directly using forward and reverse primers in an automated DNA

sequencer ABI-310 (Applied Biosystems) using BigDye Terminator Cycle Sequencing Reaction Kit (Perkin Elmer, Foster City, CA). The closest germline *IgHV* gene for each B-CLL *IgHV* sequence was assigned using current databases, e.g., IgBlast (National Center for Biotechnology Information, Bethesda, MD), IMGT (International Immunogenetics Database; [5]), and JoinSolver [6]. The length of the HCDR3 was calculated followed established IMGT criteria. Sequences reported in this study can be found in GenBank database under accession numbers EF091900–EF091931, EF175384–EF175440, EF407822–EF407849, EF441744–EF441761, EF583659–EF583683. In some cases with homologous IgHV sequences, Ig variable light κ or λ chains (IgVκ and IgVλ) were amplified according to the BIOMED-2 protocol.

Data from all groups were analyzed using MANOVA (Multivariate Analysis of Variance) to evaluate the relation between groups and presence/absence of past/ongoing infection with the viral agent(s). Post-hoc LSD multiple comparisons procedures were conducted to simultaneously examine comparisons between all possible pairs of group means. All statistical analyses were conducted using the SPSS 11.0 software package (SPSS, Chicago, IL), general linear model.

Data about ages of the investigated persons are presented as their means ± standard errors (SE). The Chi-square test for categorical variables was used to compare characteristics between different sub-groups of patients. All p-values are two-sided, and significance was set at $p \leq 0.05$.

8.1. HCV INFECTION IN PERSONS SUFFERED DUE TO THE CHORNOBYL NPP ACCIDENT

The anti-HCV antibodies were found in 965 clean-up workers, 114 ARS convalescents, 578 inhabitants of radiation-contaminated territories of Ukraine, and 87 NPP workers. Samples from 41,021 blood donors at the Kyiv Municipal Blood Center were examined for comparison. As shown in Table 8.1, a very significant ($p < 0.0001$) greater prevalence of HCV infection was found in all groups of individuals who suffered from the Chornobyl incident as compared to that among the Kyiv blood donors. In a separate PCR analysis of the HCV found in the blood samples from HCV^+ subjects, a prognostically unfavorable 1b genotype of HCV – one associated with frequent development of cirrhosis – was the most prevalent form found (i.e., incidence of 86.92%) among all the sub-groups analyzed (PCR analyses were performed at the Department of Hygiene, in the School of Medicine of Hiroshima University, Hiroshima, Japan, under the supervision of Prof. H. Yoshizawa).

How and why these individuals became HCV^+ was also of interest to our investigation. For this purpose, groups of 199 male clean-up workers (71 persons received blood transfusions) and

Table 8.1

Presence of anti-HCV serum antibodies in individuals in the indicated populations

Groups of observed persons	Persons with anti-HCV antibodies		
	total[a]	men[a]	women[a]
Blood donors (n = 41,021; ♂ = 28990; ♀ = 12031)	1417 (3.45)	1145 (3.95)	272 (2.26)
Clean-up workers (n = 965; ♂ = 791; ♀ = 174)	#218 (22.59)	#169 (21.36)	#49 (28.16)
Convalescents of ARS (n = 114; ♂ = 106; ♀ = 8)	#31 (27.19)	#28 (26.41)	#3 (37.5)
Dwellers of radiation-contaminated area (n = 578; ♂ = 273; ♀ = 305)	#65 (11.24)	#37 (13.55)	#28 (9.18)
NPP workers (n = 87; ♂ = 64; ♀ = 23)	#22 (25.28)	#19 (29.68)	#3 (13.04)

Notes. [a] – first value shown is actual number of subjects with the antibodies; value in parenthesis is the calculated percentage among the respective population analyzed; # – reported value was significantly different ($p < 0.0001$) from that in the blood donor (i.e., IR non-exposed) persons.

140 male IR-non-exposed persons (75 persons received blood transfusions) were studied. In both groups we found a strong association ($p<0.001$) between the presence of anti-HCV antibodies and prior blood transfusion(s). Among persons who received blood transfusions, HCV-seropositivity was significantly higher ($p<0.001$) in the group of clean-up workers (39.4%) as compared with among the IR-non-exposed persons (14.3%). No significant differences were found among individuals who had not received blood transfusions (12.2% vs 6.7%; $p > 0.05$).

To analyze the prevalence of hepatitis B (HBV) virus and HCV 155 people who have suffered ARS in 1986, were supervised within 1987-2009, including 80 people with diagnosed non-verified ARS (ARS 0), 34 patients with ARS grade 1 (ARS 1), 31 with ARS grade 2 (ARS 2) and 10 people with ARS grade 3 (ARS 3). Infection with hepatitis B virus was found in 9 persons (5.8%), HCV – in 40 patients (25.8%), significantly higher than in the population of Kyiv Municipal Blood Center (respectively 0.28% and 3.45%, $p <0.01$). Three ARS convalescents had a dual infection: hepatitis B and C. Appearance of HBV carriers had following dynamics: in 1986 – 1, in 1990 – 1, in 1992 – 2, in 1997 – 1, in 1999 – 2, in 2002 – 1 and in 2005 – 1. HBV-positivity did not correlate with severity of ARS, patients were divided as follows: ARS 0 – 3 person, ARS 2 – 5 and ARS 3 – 1 patient.

Infection of ARS convalescents with hepatitis C virus began to occur since 2000 (8 persons) with a peak in 2001 (10 patients). In 2002, 2003, 2005, 2008 and 2009 annually identified 3 cases of new infection with HCV, no cases were in 2004, in 2006 registered 2, and in 2007 – 5 new cases of hepatitis C among ARS convalescents. No clear relationship between dose (grade of ARS) and the number of HCV infected patients was detected, out of a total of 40 HCV-positive individuals 15 (37.5%) were ARS 0 convalescents, 12 (30%) – ARS 1, 10 (25%) – ARS 2 and 3 (7.5%) – ARS 3. During the post-emergency health care ARS convalescents were regularly subjected to thorough examination, including the use of endoscopic investigations, which possibly can be a source of infectious risk [7].

The studies here also sought to determine, in part, if there was any association between persistence of HCV in exposed patients and selected somatic diseases. The data here shown that in a group of clean-up workers (specifically, 368 patients without malignant diseases), HCV infection was associated with active chronic hepatitis (32.4% vs. 11.0% among clean-up workers without anti-HCV serum antibodies; $p < 0.001$), chronic gastritis (40.9% vs. 27.4%; $p < 0.05$), acute myocardial infarction in anamnesis (7.6% vs. 2.6%; $p < 0.05$), thyroiditis and nodular goiter (28.6% vs. 12,5%; $p < 0.01$), thrombocytopenia (4.8% vs. 0.7%; $p < 0.05$), lymphadenopathy (14.3% vs. 4.9%; $p < 0.05$), and/or hemorrhagic vasculitis (2.8% vs. 0.4%; $p < 0.05$) (Figure 8.1). Thus, a significant prevalence of HCV infection among these IR-exposed persons appears to unfavorably influence their health in many manners.

8.2. CMV INFECTION IN PERSONS THAT SUFFERED DUE TO THE CHORNOBYL NPP ACCIDENT

As compared with the control group of IR-non-exposed persons, male subjects in each of the various groups of individuals that suffered from the Chornobyl incident (except for the dwellers of radiation-contaminated areas) had a significantly greater incidence of CMV infection as determined by the presence of anti-CMV IgG antibodies (i.e., values ranging from 79.4–85.6% vs. 69.2%; $p < 0.05$) (Table 8.2). Specifically, the level of significance of these differences in titers between the male IR-non-exposed persons and the male clean-up workers, ARS convalescents, and NPP workers were $p < 0.001$, $p < 0.001$, and $p < 0.05$, respectively. In addition, both the clean-up workers and ARS convalescents had significantly more frequent laboratory

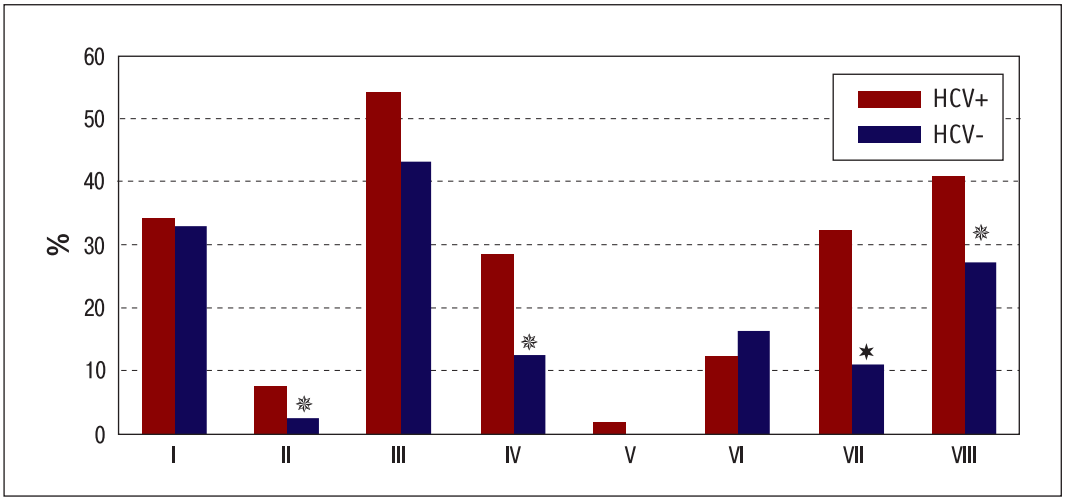


Figure 8.1. Frequency of some somatic disease in clean-up workers as related to HCV seropositivity.
I – coronary heart disease, II – acute myocardial infarction in anamnesis; III – essential hypertension; IV – thyroiditis/goiter; V – type I diabetes; VI – type II diabetes/impaired glucose tolerance; VII – chronic hepatitis; VIII – chronic gastritis. Differences between HCV^+ and HCV^- patients are significant at $p < 0.05$ (grey star) or $p < 0.001$ (black star).

signs of active CMV infection as determined by positive PCR measures for detection of viral DNA (i.e., 14.3% and 16.2%, respectively, vs. 5.51%; $p < 0.05$) (only male persons were included in this analysis). As a consequence of repeated viral activation, we estimated that there was likely to also have been a presence of high titres of anti-CMV IgG antibodies in the serum of the vast majority of these exposed subjects. Lastly, a correlation between IR absorbed dose and the level of CMV-seropositivity was found within the ARS convalescents group (i.e., $r = +0.3244$; $p = 0.028$).

In all groups of observed subjects (a total $n = 1017$), the presence of anti-CMV IgG antibodies was associated with somatic diseases (76.86% vs. 49.11% among persons without chronic somatic diseases; $p < 0.001$), especially with chronic gastritis, bronchitis, and different types of arthritis (Figure 8.2). Furthermore, a simultaneous existence of bronchopulmonary and diges-

Table 8.2
Presence of anti-CMV IgG serum antibodies in individuals in the indicated populations

Groups of observed persons	Persons with anti-CMV antibodies		
	total[a]	men[a]	women[a]
IR non-exposed persons (n = 367; ♂ = 162; ♀ = 205)	254 (69.2)	114 (70.37)	140 (68.29)
Clean-up workers (n = 505; ♂ = 428; ♀ = 77)	#401 (79.4) $p < 0.001$	#342 (79.9) $p < 0.01$	#59 (76.62) $p < 0.05$
Convalescents of ARS (n = 118; ♂ = 113; ♀ = 5)	#101 (85.59) $p < 0.001$	#96 (84.95) $p < 0.004$	5 (100)
Dwellers of radiation-contaminated area (n = 115; ♂ = 61; ♀ = 54)	89 (77.39)	48 (78.68)	41 (7.92)
NPP workers (n = 122; ♂ = 98; ♀ = 24)	#98 (80.32) $p < 0.01$	#80 (81.63) $p < 0.05$	#18 (75)

Notes. [a] – first value shown is actual number of subjects with the antibodies; value in parenthesis is the calculated percentage among the respective population analyzed; # – reported value was significantly different (at indicated *p*-value) from that in the IR non-exposed group.

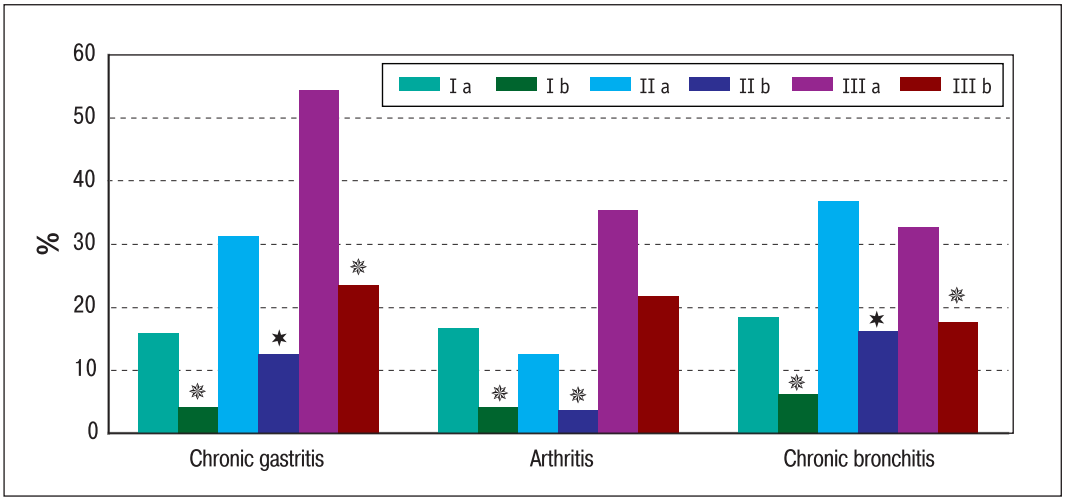


Figure 8.2. Frequency of some somatic diseases in the observed patients appears to depend on CMV seropositivity.

Group I = IR-non-exposed persons (Ia – CMV^+, Ib – CMV^-); Group II = clean-up workers (IIa – CMV^+, IIb – CMV^-); Group III = ARS convalescents (IIIa – CMV^+, IIIb – CMV^-). Differences CMV^+ vs. CMV^- patients are significant at $p < 0.05$ (white star) or $p < 0.001$ (black star).

tive system diseases was typical for the CMV^+ patients comparing with CMV^- patients. Such comorbidity was observed in 13.19% of the CMV^+ patients vs. 4.16% of the CMV^- patients among the IR-non-exposed subjects ($p < 0.05$) and in 36.84% vs. 11.24% of patients in a group of clean-up workers ($p < 0.01$).

The repeated reactivation of CMV significantly impaired the course of HCV infection (note: this analysis was performed in group of 105 HCV^+ clean-up workers). The clinical signs of active hepatitis (e.g., liver enlargement, elevated alanine and asparagine aminotransferase activities, and extra-hepatic symptoms) were observed in 44.4% of HCV^+CMV^+ patients, but only in 21.1% of HCV^+CMV^- patients ($p < 0.05$). In a one-way layout analysis the presence of anti-CMV antibodies ($r = 0.3418$; $p < 0.0001$), masculine gender ($r = 0.3553$; $p < 0.0001$), serological signs of viral hepatitis B in anamnesis ($r = 0.2896$; $p = 0.003$), and an increase in absolute $CD8^+$ T-lymphocyte counts (only in CMV^+ patients, $r = 0.5745$; $p = 0.005$) were the major risk factors for prediction of active HCV-associated hepatitis. It is possible to suppose that CMV may potentiate any hepatotropic action of HCV by the influence of the former on the liver parenchyma or be causing increases in the activity of cytotoxic T-lymphocytes.

Because there are some data that indicate that persistent CMV activation can trigger and maintain the clonal expansion of large granular T-lymphocytes [8], we also examined a small group ($n = 4$) of clean-up workers with LGL. In all of these patients, substrate cells were found that belonged to the class of mature post-thymic T-lymphocytes (i.e,. $CD3^+$, $CD8^+$, $CD4^-$, $CD16^+$, and/or $CD57^+$). A presence of CMV in blood mononuclear cells was found in two of these patients (by PCR). One of these patients who had stable LGL over the last 4 years (WBC 4.1–6.1 x 10^9/L, with a differential count of 56–68% lymphocytes, and 85–87% of these cells had a $CD3^+CD8^+CD16^+$ phenotype); after intensive anti-CMV therapy (i.e., anti-CMV IgG, ganciclovir), the patient's blood cell profile was completely restored and the patient displayed an improved general condition (i.e., no signs of chronic infections and episodes of febrile fever).

8.3. CHRONIC LYMPHOCYTIC LEUKEMIA (CLL) CELLS DISPLAY HOMOLOGY OF THEIR IG RECEPTORS WITH ANTI-VIRAL OR ANTI-MICROBIAL ANTIGENS

Over the previous decade, chronic lymphocytic leukemia (CLL) has been the subject of increasingly intensive research. Several research groups identified so-called homologous CLL cases that expressed immunoglobulins (Ig) composed from stereotyped combinations of heavy chain variable (*HV*), diversity (*D*), and joining (*J*) genes and very close heavy chain complementarity-determining region-3 (HCDR3) [9-13] Most of the CLL clusters were also characterized by specific Ig light kappa (κ) or lambda (λ) chain gene usage [14, 15]. Together with a biased repertoire of *Ig* genes [16], a similarity of CLL Ig sequences and antibodies against autoantigens and microbial/viral antigens [17] and some epidemiological data [18] has led to the hypothesis that there is a possible role of viral/microbial antigens in the development of this (and other non-somatic) disease(s).

In the studies here, we analyzed Ig gene rearrangements in 294 CLL sequences from Ukrainian patients (63 of them who suffered from the Chornobyl NPP accident) and identified 46 cases presenting a homology with antibody sequences of known specificity [21]. No differences were found between sequences from IR-exposed and IR-non-exposed CLL patients. Among the 46 CLL cases, 26 evidenced a HCDR3 homology with anti-bacterial or anti-viral Ig clones, namely, anti-PPS antibodies against *Streptococcus pneumonia* polysaccharides (12 cases), Igs that recognized capsular polysaccharide of *Neisseria meningitidis* (3 cases), anti-staphylococcal protein A Ig clones (2 cases), rotavirus-specific Ig clones (4 cases), anti-rabies Igs (4 cases), and anti-herpes simples virus type 1 (1 case). Additionally, 20 Ukrainian CLL cases demonstrated HCDR3 homology with auto-reactive clones. These included with homologies to: Igs in rheumatoid arthritis patients (5 cases); anti-cardiolipin antibody (6 cases); Igs peculiar to systemic lupus erythematosus (anti-Sm, 5 cases); Ig with autoantibody activity (2 cases), Ig from a bone-marrow transplant recipient with graft versus host disease (GVHD, 1 case), and Ig from B-cell lymphoma secreting anti-Pr2 erythrocyte autoantibodies (1 case) (see Table 8.3).

To explore the possibility of reducing the intensity of bronchial obstruction syndrome and asthma time-course relief by diagnosis and etiotropic treatment of persistent infections 22 persons with a diagnosis of asthma of different severity included in Clinical-Epidemiological Registry of NRCRM were selected during consultation of immunologist. Frequent colds, lymphadenopathy, comorbidities, fatigue, inefficient control of the asthma symptoms were main reasons of such consultations. Testing for antibodies to the CMV, herpes simplex viruses of first and second type, Epstein-Barr virus, HCV and Toxoplasma gondii was performed using commercial ELISA diagnostic kits.

All patients were carriers of persistent infections, at that only 2 people were monoinfected by CMV. In most cases there has been a mixed infection by CMV and herpes simplex viruses. As a third mixed infection antibodies were detected to Toxoplasma in 3 patients, to nuclear and capsid antigens of Epstein-Barr virus – in 2 patients, only to nuclear antigen – in 1 patient. Two patients have replicative form of hepatitis C infection with mixed cytomegalovirus and Toxoplasma.

Comprehensive course of causal treatment – consistent use of specific immunoglobulins, abnormal nucleotides and interferon inducers contributed primarily to reduce the frequency of acute viral respiratory infections in patients with asthma. After the treatment, the patients also noted a decrease in the number of asthma attacks and improvement of the asthma symptoms

Table 8.3
Ukrainian CLL cases showing HCDR3 homology with immunoglobulins of known specificity

IGHVgene	HCDR3 Amino acid sequence	Subset	Antigen specificity
3-30-3*01_2-2*01_6*02_UM_AY909636	-EVQDIVVPAAI--YYYYYGMDV		anti-PPS Ig
UA1-69*01_2-2*01_6*02_UM_D70_EF583683	-G-GDIVVPAEY--YYYYYGMDV	3*	
UA1-69*01_2-2*01_6*02_UM_D94_EF091906	PGPQDIVVPAAY--YYYYYGMDV	3	
UA1-69*01_2-2*01_6*02_UM_D3_EF175390	-EVQDIVVPAAI--YYYYYGMDV	3	
UA1-69*01_2-2*01_6*02_UM_C17_EF175388	-EVQDIVVPAAI--YYYYYGMDV	3	
UA1-69*01_2-2*01_6*01_UM_E94_EF175420	-EVQDIVVPAAI--YYYYYGMDV	3	
UA1-69*01_2-2*01_6*01_UM_F89_EU433873	-EVQDIVVPAAI--YYYYYGMDV	3	
3-33*01_3-3*01_4*02_UM_DQ535056	AG-SD-YDFWSGYPYYFDY		anti-PPS Ig
UA4-30-4*01_3-3*01_4*01_UM_E16_EF583678	VGPSGYYDFWSGYPYYFDY	Het‡	
3-48*03_2-21*01_4*02_UM_AY909680	DRTYCGGDCYGPYFDY		anti-PPS Ig
UA3-48*03_2-21*02_4*02_M_D76_EU814967	DVAYCGGDCYSGFFDY	Het	
3-33*01_3-10*01_4*02_UM_DQ322780	PQLWFGELN-YYFDY		anti-PPS human antibodies
UA3-11*01_3-10*01_4*02_UM_F85_EU433870	DTLWFGEFHAYYFDY	UA Ref13#	
3-11*03_3-3*01_5*02_UM_DQ322854	DTRPYDFWSGYYP-NWFDP		anti-PPS Ig
UA3-11*01_3-3*01_5*02_UM_G17_EU667604	--DRYDFWSGYIGYNWFDP	UA5#	
UA4-61*01_3-3*01_5*02_UM_E53_EF091926	HRGDYDFWSGYYPYNWFDP	UA5	
1-18*01_3-22*01_6*01_M_AF115133	--ADYYDSSGYYY-DYYYYGMDV		anti-Neisseria meningitides Ig
UA4-4*02_3-22*01_6*02_UM_D36_EF583668	ASGNYYDSSGYYYWNYYYYGMDV	N7**	
UA3-11*01_3-22*01_6*03_UM_F34_EF175439	APKNYYDSSGYYYWNYYYYYMDV	N7	
UA4-59*08_3-22*01_6*02_UM_D15_EU814956	--RPLYDSSGYYYVMNYYYGMDV	N7	
3-30-3*01_3-22*01_4*02_UM_AB021532	AR-NYYDSSGY-SFDY		anti-Staphylococcal protein A Ig
UA4-59*01_3-22*01_4*02_UM_F35_EF175440	AR-YYYDSSGY-YFDY	33	
UA4-b*01_3-22*01_4*01_UM_E99_EF175423	VKEYYYDSSGYYGFDY	33	
3-30*03_2-8*02_6*02_UM_EF177969	DHRYCTGGVCYDGYYYYGMDV		Rotavirus specific Ig
UA1-2*04_2-8*01_6*02_UM_F74_EU433868	PSFYCTNGVCYTDYYYYGMDV	Het	
UA1-2*02_1-26*01_6*02_UM_AY944713	VYSGSYPYYYYGMDV		Rotavirus specific Ig
UA1-2*02_1-26*01_6*02_UM_E70_EF091912	PYSGSYPWYYYGMDV	28	
UA1-2*02_nd*01_6*02_UM_G19_EU667602	LYSGSYFYYYYGMDV	28	
3-23*04_5-5*01_6*02_UM_AY944710	--ADTAMVIYYYYYGMDV		Rotavirus specific Ig
UA3-43*01_5-5*01_6*02_UM_F24_EF407840	GMVDTAMVIYYYYYGMDV	Het	
1-24*01_5-24*01_6*02_M_ Y17784	MKDGYNKVYYYYYGMDV		anti-Herpes simplex Ig
UA1-69*13_5-24*01_6*02_UM_GU358657	EGDGYNYGYYYYYGMDV	Het	
1-69*06_3-16*02_3*02_UM_AF460965	GGNYDYIWGSYRSNDAFDI		anticardiolipin Ig
UA1-69*01_3-16*02_3*02_UM_D34_EU814958	GGDYDYIWGSYRPNDAFDI	6	
UA1-69*01_3-16*02_3*02_UM_E77_EF091909	GGDYDYIWGSYRPNDAFDI	6	
UA1-69*01_3-16*02_3*02_UM_D89_EU814960	GGAYDYIWGSYRPNDAFDI	6	
UA1-69*01_3-16*02_3*02_UM_D73_EF175395	GGGYDYIWGSYRSNDAFDI	6	
1-3*01_3-10*01_3*02_M_AY393651	ASGRFWQSRG-DAFDI		rheumatoid arthritis Ig
UA3-21*01_3-22*01_3*02_M_B78_EF175385	VSGRNYDSSGTDAFDI	Het	
1-69*06_6-6*01_4*02_M_AY393692	GQGSSSSRFPFDY		rheumatoid arthritis Ig
UA3-74*01_6-6*01_4*02_M_E22_EF441750	EEGSSSLR-PFDY	Het	

Table 8.3 (continued)
Ukrainian CLL cases showing HCDR3 homology with immunoglobulins of known specificity

IGHVgene	HCDR3 Amino acid sequence	Subset	Antigen specificity
5-51*03_6-13*01_4*02_UM_AY393191	RADTSSWYYFDY		rheumatoid arthritis Ig
UA4-34*01_6-13*01_4*02_M_E49_EF441754	GGDGSSWYYFDF	UA Ref1#	
4-34*01_3-3*01_4*02_UM_X54441	GGSV-LRFLEWLLYPAFDY		rheumatoid arthritis Ig
UA1-69*06_3-3*01_4*02_UM_G12_EU667599	SGE--LRFLEWLLSADFDY	UA7#	
UA1-69*01_3-3*01_4*02_UM_F10_EF175428	EGSRPLRFLEWLL---FDY	UA7	
1-69*13_2-2*01_6-13*01_UM_U86795	TDIVVVPAAMIIYYYYGMDV		autoantibody activity
UA1-69*01_6-13_6*02_UM_E41_EF175412	VQGGGSAAAYENYYYYYGMDV	UA Ref2#	
UA1-69*01_2-2*01_6*01_UM_F3_EF175425	TLIGVPAAYTIYYYYYGMDV	UA Ref2	
4-31*03_3-9*01_6*02_UM_U80127	DGGN--YDILTGYYRADYYYGMDV		BMT recipient with GVHD
UA3-21*01_3-9*01_6*02_UM_E85_EF407825	DGGSLYYDILTGYYSLEYYYGMDV	Het	
1-18*01_2-15*01_4*02_M_X15611 Pr2 erythrocyte autoantibodies	APGYCSGGGCYRGDDY		B-cell lymphoma secreting anti-
UA4-34*01_2-15*01_6*02_M_F20_EF583679	GSGYCSGGSCYGGLDV	UA Ref9#	
AY942901	DFEYYYESSGY---PYYYYGMDV		anti-rabies Ig
3-33*01_3-22*01_6*02_UM_Z46379	DN-YYYDSSGY---YYYYYGMDV		anti-Sm Ig
UA1-2*04_3-22*01_6*02_UM_G2_EU433881	DLGHYYDSSGYSYPYYYYYGMDV	UA8#	
UA3-30-3*01_3-22*01_6*02_UM_E73_EF175415	DTTYYYDSSGY---YYYYYGMDV	UA8	
UA4-59*01_3-22*01_6*02_UM_D62_EF091925	GVGDYYDSSGY---LHYYYGMDV	UA8	
3-49*04_3-3*01_6*02_UM_AY941852	DRDGTYYDFWSGYPPPNYGMDV		anti-rabies Ig
UA1-69*01_3-3*01_6*02_UM_E92_EF583675	DWGTTYYDFWSGYFSP-YGMDV	Het	
3-23*01_4-17*01_3*02_UM_AJ305181	GDYGDYSFAFDI		anti-Sm Ig
UA3-33*01_4-17*01_3*02_UM_E13_EF407846	GVPGDYVMAFDI	UA9#	
UA3-30-3*01_4-17*01_2*02_UM_F42_EF407832	GPRGDYVSSFDL	UA9	

Notes. * – Subset nomenclature according [13, 19]; ** – New subsets according to [20]; # – New subsets according to [21]; ‡ – Het, heterologous sequences.

control, limited use of beta-blockers and inhaled corticosteroids up to complete abolition in some patients. However, treatment of patients comorbid with asthma and hepatitis C by interferon, contributed to the symptoms of asthma.

* * *

On the basis of our observations of several different groups of individuals who suffered during and after the Chornobyl NPP catastrophe, as well as a control group of persons without any previous direct exposure to IR, a high prevalence of HCV and CMV infections among the afflicted groups was established.

It is well-established that preceding blood transfusions are considered one major reason for HCV-seropositivity in epidemiologic studies of disease (i.e., HCV) incidence. The data from the current studies confirmed this phenomenon. Nevertheless, even if transfusions were a major source of infection, it is known that after the initial infection, HCV may be completely elimi-

nated in ~17–25% of the affected subjects. By comparing persons who received blood transfusions relative to IR exposure, these studies revealed that there was a significantly higher ($p < 0.001$) frequency of anti-HCV antibodies present among clean-up workers than in IR-non-exposed individuals. Based on our previous studies that revealed considerable disturbances in T-lymphocyte-mediated immunity among Chornobyl clean-up workers – and especially among ARS convalescents [22] it is possible to suggest that this state of immunomodulation may be one reason for the high level of HCV infection among these individuals – regardless of whether or not the initial infection was due to a transfusion or not.

Our data concerning the prevalence of anti-HCV serum antibodies in the clean-up workers and ARS convalescents were in agreement with data from Japanese investigators who had earlier concluded that radiation exposure may accelerate the progress of chronic liver disease associated with HCV in atomic bomb survivors [23]. Recently, it was shown that the non-structural protein 3 of HCV interacts with the ATM (ataxia-telangiectasia mutated) protein and, in turn, delayed dephosphorylation of phosphorylated forms of ATM [24]. These same investigators also showed that this HCV protein also impairs the efficiency of DNA repair and renders infected cells more sensitive to DNA damage after IR exposure [24]. This interaction may contribute to the observed HCV infection-associated pathogeneses among the IR-exposed patients here and in the Japanese studies. Specifically, among the group of HCV^+ Chornobyl clean-up workers monitored here, some diseases (e.g., chronic hepatitis, chronic gastritis, thyroid diseases, thrombocytopenia, and acute heart attack in anamnesis) were found to have occurred with greater frequently in comparison to that among HCV^- clean-up workers.

From the studies here and those of other investigators, some mechanisms to explain the potential for interactions between CMV and IR have been revealed as well. For example, it was shown (in different experimental models) that CMV gene expression was increased by exposure to oxygen radicals or after irradiation [25–27]. This may be a major reason for the observed increases in CMV-seropositivity and repeated CMV reactivation among our Chornobyl clean-up workers and ARS convalescents. The increases in CMV infectivity status (likewise HCV) were also found to be positively-associated with increases in the occurrence of somatic diseases, especially chronic gastritis, bronchitis, and different types of arthritis among the CMV^+ patients.

Studies here and elsewhere have also noted a significant homology between *IgHV* genes in the lymphoid cells of CLL patients with anti-viral and anti-microbial antibodies. Lanemo Myhrinder et al. [17] revealed that several CLL Igs reacted with bacterial components (*S. pneumoniae* polysaccharides and phosphorylcholine) as well as molecular structures exposed on apoptotic cells (e.g., vimentin, proline-rich acidic protein-1, and oxidized-LDL). These findings led to the suggestion that viral and bacterial infections in synergy with self-antigens or apoptotic cells could drive CLL. Among the CLL patient examined here, similar findings of CLL Igs that react with viral and bacterial components were proof that infections – even almost a quarter of a century after the nuclear accident – may contribute to CLL pathogenesis.

In summary, it appears that persistent viral infections, especially when accompanied by exposure(s) to ionizing radiation, can be quite deleterious. The worst-case scenario, where each of these factors have occurred/are ongoing, is one that appears to result in a modified (i.e., aggravated) clinical course of somatic diseases and/or to promote malignancies (i.e., CLL) among these hosts. Nevertheless, even under these seemingly 'dire conditions', the persisting infections can be transformed into «steerable/manageable constituents» with anti-viral treatments, even if the patient had been exposed earlier to an irradiation. In those cases, the patients can be medically steered to an eventually vastly improved general condition.

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Chapter 9
THIRTY YEARS OF EXPERIENCE IN RADIATION IMMUNOGENETICS SINCE THE CHORNOBYL ACCIDENT

Study of genetic basis of individual susceptibility or resistance to the negative impact of environmental factors from the standpoint of genetically determined predisposition to pathological process at various body systems level and risk of a particular disease as a result of genetic predisposition is one of contemporary human genome research areas.

Understanding of genetic polymorphism is a conceptual basis in this scientific field [1]. Unlike mutations that lead to abnormalities in organism the genetic polymorphism is more neutral, however with underlying appearance of protein-based products with a slightly altered physico-chemical characteristics and therefore altered functional activity. That is, the «predisposition genes» are the mutant genes (alleles) being compatible with birth and life in postnatal period, but contributing to occurrence of a particular disease under an impact of unfavorable environmental factors [2]. In specific circumstances the polymorphism can act as gene «triggers» or protectors inducing or preventing the initiation of a pathological processes . Over the 200 genetic tests on identification of genetic susceptibility markers of various body systems are proposed today in molecular predictive medicine [3].

Our studies of gene polymorphism in the Chornobyl accident survivors we have started on the genetic blood systems including major histocompatibility complex in comparison with hemopoietic and immunopoetic disorders because the immunogenetic factors are relevant for genetic control of immune homeostasis at a level of normal immune system function maintaining and implementation of human evolutionary tolerance to environment. On the other hand, the investigated nosological disease forms causally associated with irradiation (oncohematological, thyroid, and cardiovascular diseases) belong to a class of «multifactorial diseases» formation and development of which under the influence of unfavorable exogenous factors are largely associated not only with disorders in immune homeostasis [4] and molecular genetic abnormalities in genome but also with genetic predisposition of a person to the disease. Determining of each factor contribution to onset of these diseases is essential to calculate the disease risk in the late period after the impact of Chornobyl accident factors and predict the disease course.

Radiation exposure in the 0.75–2.0 Gy dose range was chosen as a negative exogenous risk factor of the above-mentioned diseases. The disturbances of immune homeostasis in patients was considered an endogenous factor.

Acute radiation sickness (ARS) Grade I survivors (n = 65) and patients with similar radiation history but no verified ARS diagnosis (ARS-NC, n = 88) were the study subjects. There were also ARS Grade II (n = 19) and ARS Grade III (n = 5) survivors, chronic coronary heart disease (CCHD) patients (n = 120), certified clean-up workers of the ChNPP accident (n = 73), and cleanup workers with no CCHD (n = 65) involved in the study both with multiple myeloma (MM, n = 54), chronic lymphoid leukemia (CLL, n = 58), acute lymphoid leukemia (ALL, n = 63), and myelodysplasia (MDS, n = 33) cases.

Almost healthy persons (n = 600) living in the Central Ukrainian geno-geographic zone were recruited as a population control.

Review of time pattern of immune homeostasis in childhood vs. HLA-polymorphism was conducted in children (n = 990) living in contaminated areas of Kyiv and Zhytomyr regions.

Genetic predisposition to these diseases was estimated through the assay of polymorphism of major histocompatibility complex [5]. Structural analysis of the antigenic/genetic polymorphism of genetic blood systems was conducted with taking into account main indicators of population immunogenetics i.e. prevalence, genetic representation, and linkage disequilibrium. Association factors (RR) with risk of studied ARS onset, radiation-associated diseases, and immunological disorders were calculated with assessment of the factor confidence level. Values of radiation doses in the most of patients were determined according to designation data from army recruitment bureaus. Doses in some of them have been confirmed by the biodosimetry approach [6].

Immunological screening was conducted using the card developed at the Department of clinical immunology of NRCRM given the radiation history [7].

Molecular genetic studies of exposed persons, namely of patients with leukemia included the identification of nature, frequency, and complexity of karyotype abnormalities, expression of chimerical genes, clonal rearrangement of immunoglobulin genes, and microsatellite DNA abnormalities (D9S171 and D12S98 loci).

Our early studies in radiation immunogenetics (1987–1990) were focused at evaluation of the issue if there is a genetically determined human body susceptibility to radiation from the standpoint of carriership of genetic markers of increased radiosensitivity or radioresistance. The received results clearly showed that individual sensitivity of human body to radiation is genetically determined at the level of blood genetic systems, especially the HLA (Human Leucocyte Antigen) system. Specifically, through the study of polymorphism of HLA genetic markers and other blood genetic systems in non-irradiated (n = 1600) and irradiated (n = 500) populations identical in genetic structure (the Central Ukrainian genogeographic zone) we defined the immunogenetic markers of human organism radiosensitivity and radioresistance at the model of bone marrow syndrome in ARS Grade I survivors. These included HLA-A10; HLA-A28; HLA-B38; HLA-B35; HLA-DR3, HLA-DR4, and homozygosity for Hp2-2 phenotype (haptoglobin system) (Figure 9.1) [8].

The HLA-B15; HLA-DR2; antigenic serotypes were assigned to the markers with protective function given the concentration and association rate. As molecular genetic techniques but no serological ones are used now for histocompatibility matching we had applied a repeated tissue typing in study subjects that allowed us to identify the radiosensitivity markers and predisposition to multifactorial disease at the level of allele genes specificity and confirmed the results of serological histocompatibility matching.

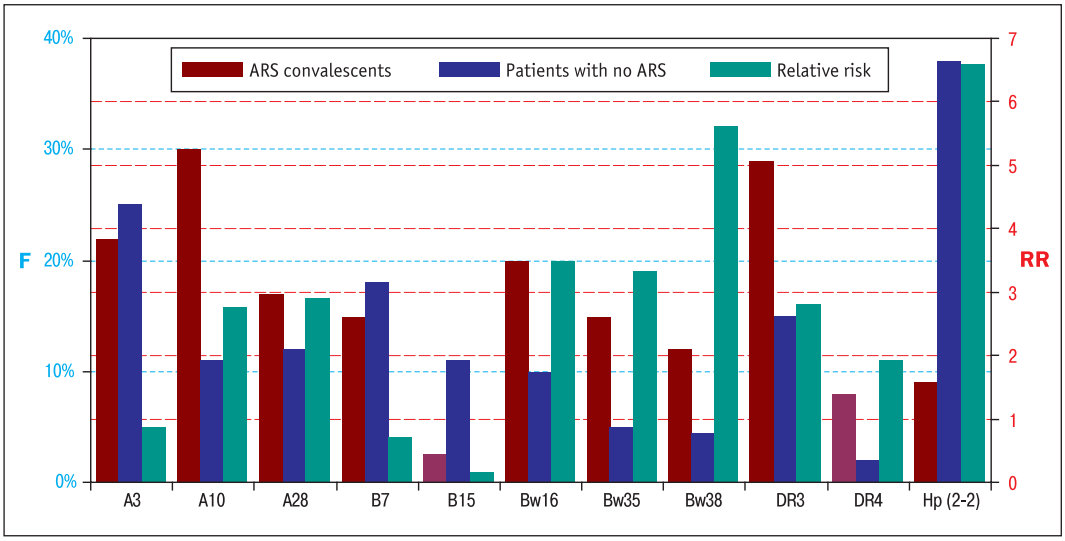


Figure 9.1. Association of some HLA-antigens with the risk of radiation-induced disease (ARS)

The immunogenetic risk of acute radiation syndrome was found associated with carriership of certain haplotypes and phenotypes (HLA-A/A; HLA-A/B; HLA-A/DR; HLA-B/DR; HLA-B/DQ), and the insulated specificities i.e. radiosensitivity markers are a part of them. However, there was a redistribution of RR association factor values depending on combinations of antigens. This fact demonstrates a complex relationship between antigenic determinants within the locus and whole system and the availability of synergism and antagonism between certain antigens in association with occurrence of pathological process pathways (Figure 9.2).

Given an association factor of all possible paired combinations of immunogenetic structures within a separate genetic blood system and between the systems the most pronounced synergistic and competitive relationships were identified between isolated radiosensitivity markers. Combinations of HLA-A1,28; HLA-A10,28; HLA-B8,16; HLA-A10,B13; HLA-A10,B38, HLA-DR3,4 antigens were regarded as having high synergism when the association factor RR is significantly higher. The HLA-A10,B16; HLA-A1,B16; HLA-B16,21; HLA-B13,DQ1; HLA-B16,DR3 combinations were regarded as having antagonistic interaction when the factor value is significantly reduced or if the reliability is lost under a high enough RR value.

In other words the performed studies demonstrate that an individual sensitivity of human body to ionizing radiation is genetically determined. The complexity of functional relationships of markers of blood genetic systems indicates the need to take account of such relationship for estimation of the real place of a subject in risk group of genetic predisposition to radiation-associated disease. Review of Rh-Hr, MNS, Kell, Duffy, Kidd antigen distribution in ARS survivors found no probable differences vs. the opposite and control groups. No probable associations for these systems with development of radiation disease were defined. But in this case also the correspondence with antigens of the main histocompatibility complex makes a bias in immunogenetically mediated realization of post-radiation effects at the level of the human organism. The most pronounced polysystemic associative links with ARS are identified for the HLA alleles in combination with Hp and MN phenotypes (Table 9.1).

Consequently, the contribution of isolated genetic blood systems to human radiosensitivity is ambivalent. Contribution of markers of different genetic blood systems to the individual human

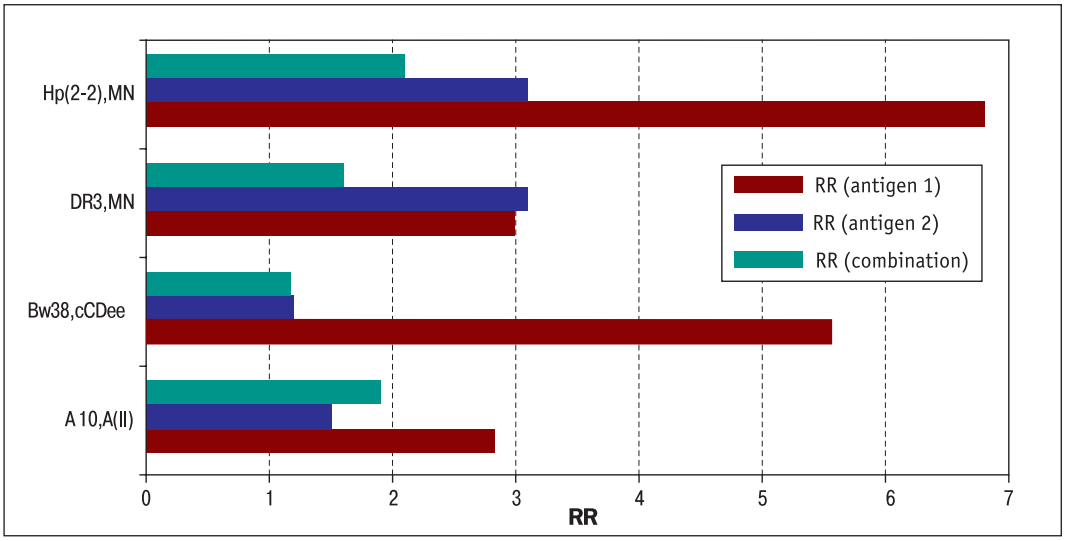


Figure 9.2. **Relative risks radiation injuries due to combination of different genetic blood factors**

radiosensitivity is also ambivalent and according to the analysis can be placed in the following order: HLA; ABO; Hp; Rh-Hr; MN ;Kell; Daffy; Kidd.

Appraisal of the immune system and closely connected hemopoietic one in correlation with immunogenic markers of predisposition to functional disorders in the spectrum of remote radiobiological effects in adults and children exposed to ionizing radiation in 0.01–1.5 Sv and more dose range we had considered as one of the urgent health issues of the Chornobyl accident. Some indices of hemopoiesis and immunopoiesis with total leukocyte count, lymphocyte count, and subpopulation content of immunocompetent cells in particular were attributed to specific features of the difference of irradiated and nonirradiated organism.

Table 9.1

Phenotypic antigen compositions of different blood genetic systems in associations with radiation disorders (ARS)

Phenotypic compositions	Incidence (%)		Relative risk (RR)	χ^2
	Control	ARS		
0(I);Rh+	30.00	18.87	0.54	1.564
B(III);Rh+	12.50	24.53	2.28	2.113
0(I);Hp1-1	16.67	5.66	0.30	1.669
0(I);Hp2-2	1.20	7.55	1.36	4.926*
A10;Hp2-2	1.12	6.60	4.30	4.675*
B15;MN	4.17	1.08	0.85	4.450*
A10;MN	0.64	4.72	1.21	2.177
A28;MN	0.08	3.77	1.16	2.934
Bw16;Hp2-2	0.80	2.83	1.12	3.695*
DR2;Rh+	10.00	2.00	0.67	4.74*
DR3;MN	0.20	10.87	1.56	2.35

Notes. * – significant associations ($p<0.05$).

Received data are indicative of redistribution of the normal, increased, and decreased values of studied parameters in populations of exposed and not exposed subjects. In such a way a significant relative decrease of leukocyte count and decreased lymphocyte and monocyte content is specific to the ARS-NC patients 6–8 months (1st period) upon the exposure event. Further in 5–6 years (2nd period) of survey the same values of leukocyte, lymphocyte, and monocyte counts remain in those groups. Later on in 12–14 years (3rd period) the leukocyte and monocyte counts remain the same along with somewhat increase of lymphocyte content. Number of the ARS Grade I patients having a decreased leukocyte count remains the same within first survey period, the lymphocyte content at that is increased whilst monocytopeny in the first period later evolves in monocytosis. Both lymphocytosis and lymphopenia are equally registered in the first period in ARS Grade II survivors, whilst lymphopenia exacerbated in second period and evolved in lymphocytosis in third one.

An associative link was established between the immunogenetic blood factors and risk of total leukocyte and lymphocyte count decrease in the comparison groups. Notably a significantly increased incidence of HLA-A10 antigen (24.7% vs. 9.8%, RR = 12.5) and HLA-Cw1 antigen (22.2 % vs. 7.6%, RR = 3,5) was found in ARS survivors having a decreased leukocyte count. The latter affords ground for the specificity data attributing to predictive markers of leukopenia risk. Incidence of an HLA-B8 antigene (3.7% vs. 19.5%, RR = 0.30) in the studied group of persons and value of association coefficient suggest the protective functions of this specificity.

A significantly increased prevalence of HLA-A10 antigen (17.8% vs. 7.79%, RR = 2.6) is seen in people with low lymphocyte content. Since this allele is a marker of radiosensitivity of the organism, this fact demonstrates a significant contribution of immunogenetic radiosensitivity component to the shaping of hematopoietic system dysfunction under the irradiation.

An interphase death of lymphoid cells in early period upon exposure results in a significantly different proportion and functional activity of cell populations that somehow determine the intensity and direction of immunological response of the organism. Radiation-induced mutations in the T-cell receptor locus affect the efficiency of cellular interactions that can be used as a marker of biological dosimetry considering elimination of the mutant cells [10]. It is known that under a radiation impact those diseases arise some complex immunological disorders are registered in which due to the fact that the immune system is highly sensitive to ionizing radiation. Particularly, the chromosomal aberrations in lymphocytes of survivors of the nuclear bombing in Hiroshima and Nagasaki are found even after 30 years, and bone marrow where the stem cells and precursors of immune cells are localized is the site of primary response to radiation factor [11, 12]. According to our data, an increased content of T lymphocytes with markers of intrathymic stage of differentiation ($CD4^+$; $CD8^+$; Thy1) was detected in ARS survivors 3-5 years after the accident, indicating the immunopoiesis strain and unstable level of the achieved compensation. The accumulation of cells with $CD4^+$; $CD8^+$ phenotype in the recovery period after a survived ARS against a decreased total $CD4^+$; $CD8^+$ lymphocyte count evidenced of a breakdown at the thymic and post-thymic stages of differentiation. No elevated levels of double-positive $CD4^+$; $CD8^+$ lymphocytes was found already in 1996. At the same time a $CD8^+$ lymphocyte count increased resulting in lowering of regulatory subpopulations in survivors of ARS grade II. Retrospective review data indicate that signs of depression of T- and B-parts of the immune system were observed during 3–6 years after the accident in ARS survivors or persons exposed to ionizing radiation at doses close to the origin of this disease. Forthwith in 6–12 years the immune homeostasis was characterized by further trend determined by interaction between the processes of adaptation and compensation on the one hand, and alternatively by degenerative abnormalities on the other. Development of myelodys-

plastic processes and leukemic transformation are a pathological syndrome that most of all threatens the health of ARS survivors in remote period. That is, the state of immune system depends largely on how the long-term effects of irradiation will occur in a spectrum of somatic disorders risk.

On the other hand, the immunogenetic component is responsible for genetic control of immune homeostasis at a level of maintaining of normal immunopoiesis. Violation of genetic control of immune response weakens the immune supervision, which in turn causes an uncontrolled proliferation of malignized lymphoid cells, and instead of elimination of mutated genetic structures off the body promotes the accumulation of them. In other words, there appears a pathogenic substrate of hematological diseases and distortions of immunological reactions in human and the formation of different types of immunopathology.

In a study of immune cell subpopulations the immunogenetic approach is important in assay of cells having a helper-suppressor function. It is believed that the degree of antigen recognition by T-lymphocytes depends on activity of binding with MHC molecules in membranes of antigen-presenting cells. Presentation of antigens to the T-lymphocytes can occur with participation of the MHC class I and II molecules. The $CD8^+$ T-lymphocytes recognize antigens synthesized in the presenting cell and linked with MHC class I molecules, whereas the $CD4^+$ T-lymphocytes recognize antigens internalized by the presenting cell combined with class II molecules. Actually such presentation is a key point in the immune response initiation.

Received data on HLA-monitoring in survived population groups having an immune dysfunction at a level of subpopulation content of immunocompetent cells compared to contingents not exposed to ionizing radiation but having the same immune disorders provide a robust evidence of associative link unidirectionally indicating the common nature of immunogenetic mechanisms (Table 9.2).

By reference to the prevalence ratios and associative connection markers of genetic susceptibility such specificities as HLA-B21 (RR = 7.54); DR2 (RR = 6.24); DR7 (RR = 4.23) and HLA-B7, DR2 haplotype (RR = 3.82) associated with a reduced number of CD4 cells were attributed to disturbances in the immune homeostasis at the level of immunoregulatory subpopulation of immune cells. The haplotype combinations of HLA-DR3, 7 (RR = 7.53) are associated with a decrease in the number of CD3 cells. It should be noted that HLA-A10; HLA-A28; HLA-DR3, HLA-DR4 allelic specificities identified as markers of increased radiosensitivity of the organism and presence of which in phenotypic combinations increases the association are attributed to immunogenetic markers of risk of abnormal subpopulation content. The risk of increased $CD19^+$ cell content is due to the HLA-B8 antigen carriership recognized in applied immunogenetics as an independent marker of high humoral response. Some interest was also found in pathways of perturbing of immunoregulatory cell subpopulation due to HLA-B35 allele, which is considered a marker of autoimmune processes.

The next phase of work (1990–2000) included a retrospective review of immune homeostasis in child population of contaminated territories in correlation with HLA-polymorphism.

Based on the assessment of immunological criteria required to identify the impact of the Chornobyl accident factors on children we have designed a conceptual framework to simulate the cellular mechanisms of immune system cell function in terms of adequate response to low radiation doses. Selection of external, internal, and outgoing variables was conducted on the basis of primary goals of the model, namely to determine the degree of differentiation and activation status of immune cells in children to reveal an individual type of immunological reactivity under the influence of radiation factor and specific somatic diseases and identify the adequate approaches of immune correction (Table 9.3–9.5).

Table 9.2
Coefficients of HLA-associative link with risk of abnormal population content of immunocompetent cells

Immune parameters	Antigens and combinations	Relative risk coefficients (RR)	
		ARS survivors	Not exposed subjects
Decreased $CD4^+$ cell number	HLA-B8	0.29	0.56
	HLA-B21	7.54	2.46
	HLA-DR2	3.44	5.00
	HLA-DR7	2.86	1.50
	HLA-A2,B7	7.30	2.85
	HLA-A9,10	5.79	2.50
	HLA-B7,DR2	3.85	3.00
	HLA-DR7,0(I)	3.28	1.34
Decreased $CD8^+$ cell number	HLA-DR3	2.30	1.50
	HLA-A28	3.24	1.90
	HLA-A1,B21	2.86	2.00
	HLA-B21,0(I)	6.55	3.44
	HLA-B21,DR3	7.20	1.50
	HLA-B21,cCDee	4.52	5.64
Decreased CD4/8 coefficient	HLA-A10	3.54	2.86
	HLA-B7	4.28	2.86
	HLA-B8	0.29	0.11
Decreased $CD3^+$ cell number	HLA-DR3	3.54	3.54
	HLA-DR3,7	7.23	3.54
	HLA-B8	0.53	0.41
	HLA-A2	0.42	0.38
	HLA-A10	0.61	0.52
Increased $CD19^+$ cell number	HLA-B8,DR3	3.46	1.34
	HLA-B8, DR7	7.20	3.16
	HLA-B35,DR3	2.96	0.56
Increased $CD38^+$ cell number	HLA-B17	3.47	1.50
	HLA-A1,DR3	4.48	2.52
	HLA-A9,A(II)	4.66	2.31

Table 9.3
Variables to assay the T- and B-cell differentiation

T-component	B-component
1	2
Number of $CD3^+$ peripheral blood lymphocytes (n3)	Number $C019^+$ peripheral blood lymphocytes (n19)
Average number of functionally active determinants of CD3 antigen per cell (fi3)	Average number of functionally active determinants of CD19 antigen per cell (fi19)
Number of $CD4^+$ peripheral blood lymphocytes (n4)	Number of $CD20^+$ peripheral blood lymphocytes (n20)
Average number of functionally active determinants of antigen per cell (fi4)	Average number of functionally active determinants of antigen per cell ((fi20)
Number of $CD8^+$ peripheral blood lymphocytes (n8)	Number of $CD22^+$ peripheral blood lymphocytes (n22)
Average number of functionally active determinants of CD8 antigen per cell (fi8)	Average number of functionally active determinants of CD22 antigens per cell (fi22)
Average number of functionally active determinants of CD57 determinants per $CD8^+$ cell (fi8/57)	Number of lymphocytes carrying surface immunoglobulins M (nM)

Table 9.3 (continued)
Variables to assay the T- and B-cell differentiation

T-component	B-component
1	2
Number of$CD4^+$ 8^+ peripheral blood lymphocytes (n4-8)	Average number of M-immunoglobulin determinants per cell (fim)
Average number of functionally active determinants of CD4 antigen per 4^+8^+ cell (fi4-8/4)	Number of lymphocyte carriers of surface immunoglobulins G (nG)
Number of $CO3^+16^+56^+$ peripheral blood lymphocytes (n16-56)	Average number of G-immunoglobulin determinants per call (fiG)
Average number of functionally active determinants of CD56 antigen per cell (fi16-56)	Number of lymphocyte carriers of surface immunoglobulins A (nA)
Number of active T-lymphocytes (n3/dr) Average number of functionally active HLA-DR determinants pet T-cell (fi3/dr)	Average number of A-immunoglobulin determinants per call (fiA)
Number of $CD5^+$ peripheral blood lymphocytes (n5)	Number of $CD5^+$ B-lymphocytes (n20/5)
Average number of functionally active determinants of CD5 antigen per cell (fi5)	Average number of determinants of CD5 antigen per B-cell (fi20/5)
Number of $CD7^+$ peripheral blood lymphocytes (n)	Average number of $CD23^+$ lymphocytes
Average number of functionally active determinants of CD7 antigen per cell (fi7)	
Number of $CD1^+$ peripheral blood lymphocytes (n1)	
Average number of functionally active determinants of CD1 antigen per cell (fi1)	
Average number of CD38 determinants per cell (n38)	
Number of $CD4^+$3-cells (n4/3)	

Table 9.4
Variables for monocyte and granulocyte series model

Monocytes / macrophages	Granulocytes
Number of $CD14^+$ 45^+ cells (n14)	Number of $CD45^+$ cells
Average number of CD14 determinants per cell (fi14)	Average number of CD13 determinants per cell (fi13g)
Average number of CD 13 determinants per cell (fi13)	Average number of CD33 determinants per cell (fi33g)
Average number of CD33 determinants per cell (fi33)	Average number of CD34 determinants per cell (fi34g)
Average number of HLA-DR determinants per cellfi14/dr)	Average number of HLA-DR determinants per $CD34^+$ cell (fi34/dr)
Average number of CD71 determinants per cell (fi14/71)	Average number of CD25 determinants per $CD13^+$ cell, namely a basophilic granulocyte (fi14b)
	Average number of CD11b cells in CD13 population
	Average number of $CD11b^+10^+$ neutrophilic granulocytes

The simulation approach helps to select some major biological regularities of membrane structure abnormalities, both with factors that affect the expression of specific antigens and DNA synthesis by cells of a child, their dependence on external environment and cellular interrelations under the immune response process (Figure 9.4).

Within our generation of simulation model we took in account development of non-specific activation reactions in loci CD10, CD25, CD71, HLA-DR. We considered both possibility of numeric increase of subpopulations and their functional activity increasing (Figure 9.5).

Table 9.5
Parameters of subsystem of activation-type principle variables

General nature parameters	
➤ Calcium channel transmembrane potential (nt) ➤ Number of cells in G0–G1 phases (ng0) ➤ Number of cells in S phase (ns) ➤ Number of cells in G2–M phases (ng2) ➤ Mitogenic effect per immunocompetent cell (t1)	
General nature parameters	
Average number of functionally active CD25 determinants per $CD4^+$ cell (fi4/25)	Average number of functionally active CD25 determinants per $CD19^+$ cell (fi19/25)
Average number of functionally active CD71 determinants per $CD4^+$ cell (fi4/71)	Average number of functionally active CD71determinants per $CD20^+$ cell (fi20/71)
Average number of functionally active CD25 determinants per $CD8^+$ cell (fi8/25)	Average number of functionally active HLA-DR determinants per B-cell (n19/dr)
Average number of functionally active CD71 determinants per $CD8^+$ cell (fi8/71)	
Average number of functionally active HLA-DRdeterminants per T-active cell (n3a/dr)	
Average number of functionally active CD25 determinants per T-active cell (n3a/25)	
Average number of functionally active CD71 determinants per T-active cell (n3a/71)	

Because of the lability of immune system in the processes of development of immune deficiency or its restoring after a negative impact the spatial and temporal shifts of nuclear-cytoplasmic relationship were taken into account, including DNA synthesis and cell distribution by cycle phases, differentiation degree of peripheral pool, expression of activation antigens and activity of calcium channel depending on leukocyte population characteristics. This approach just made it possible to examine some local disorders in immunocompetent cells with overall hematopoietic system response together. Study of the model showed that despite a diversity of «initial» system reactions, the principal types of response were caused not by accidental abnormalities of stem cell precursors, but by the systemic reactions of integrative response. It was established that abnormal T-associated parameters (n3; fi3; n4; fi4/25; fi4/71) are the source of reduced cooperative immune response and decreased immune barrier. Abnormal B-parameters (n19; fi19; n22; n19/dr; fi19/71) are less important in shaping of long-term effects, and shifts of parameters (n14; fi14dr; n4; fi4/25; fi14/71) reflect the formation of adaptive reactions.

Using the prepared simulation model it was possible to identify the principal gradations of cellular types relatively to pathogenetic pathways in immunopathology among children living in radiologically contaminated territories, namely:

➢ depression of T-cellular component with depression of T-helper subpopulation (n3; fi3; n4; fi4/25 ;fi4/71);

➢ depression of T-cellular component due to activation of T-suppressor subpopulation (n8; fi8; fi8/71);

➢ depression of B-component o immunity (n19; fi19; n20; fi20 ;fi20/71);

➢ combined peripheral-type immune depression (according to the features stated above);

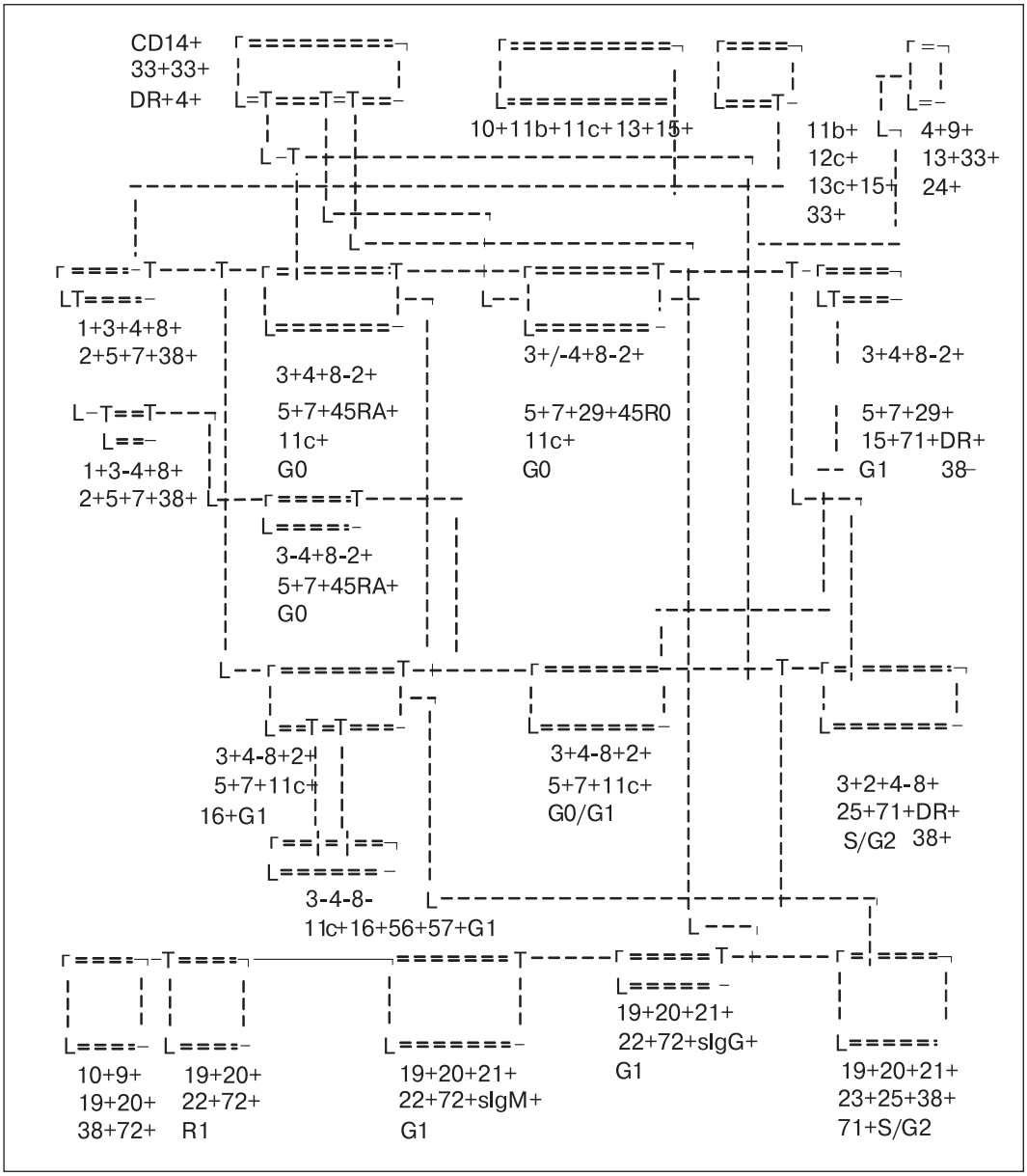


Figure 9.4. **Flow-chart of immune cell interactions**

➢ combined central-type immune depression (n3; n4; n4/8; fi4/8; n7; n19; n20; n38);
➢ disreguatory shifts (n3; n4; n4/8; fi4/8; n7; n19; n20; n38 general and population parameters of activation subsystem);
➢ activation of T-cellular component with depression T-suppressor subpopulation (n3; fi3; n8; fi8; fi8/25 ;fi8/71);
➢ activation of T-cellular component due to activation of T-helper subpopulation (n4; fi4; fi4/25 ;fi4/71);

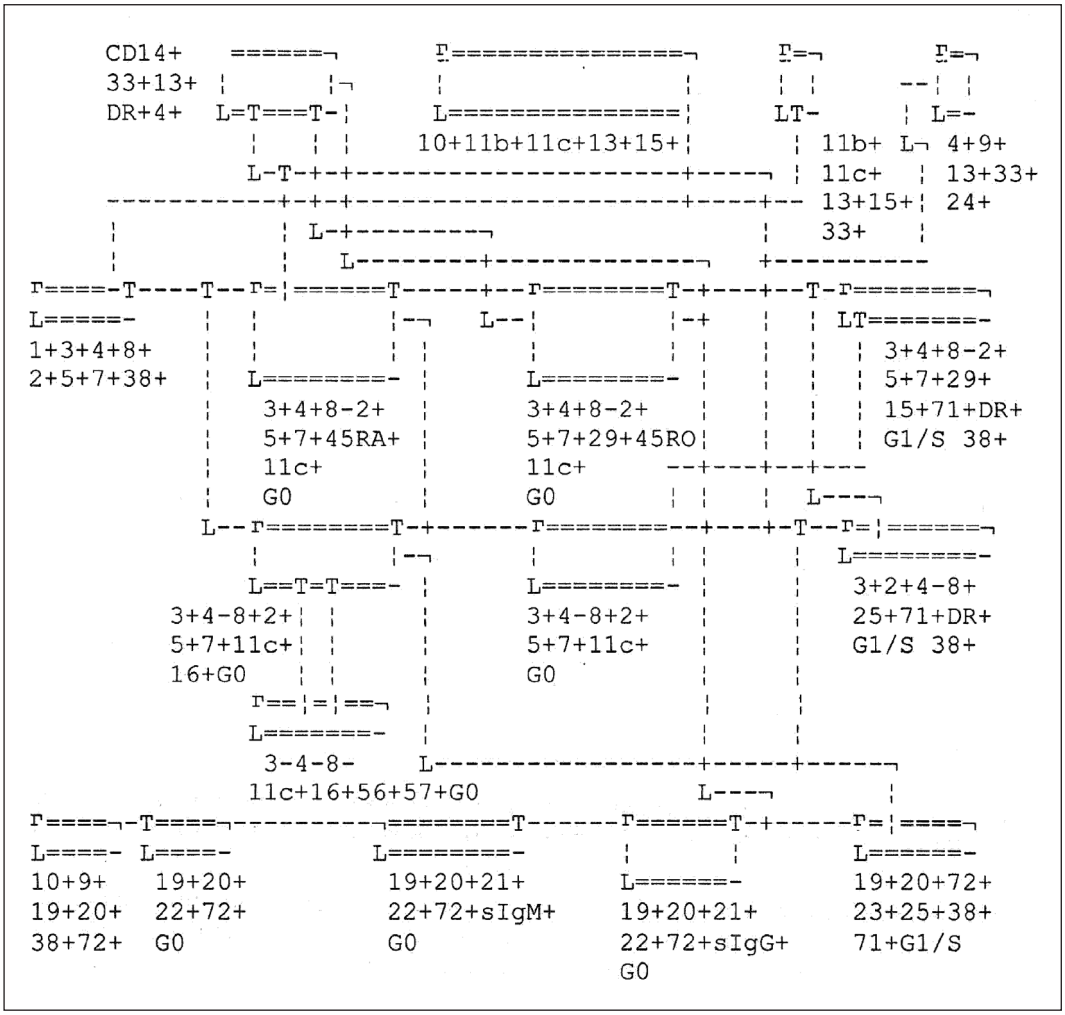


Figure 9.5. **Flow-chart of immunocompetent cell interaction under chronic radiation impact on a child at doses over the natural background**

➢ activation of B-component of immunity (n19; fi19; n19/71; n19/25; n20; n20/71);
➢ polyclonal activation (according to the features stated above and additionally n23, general and population parameters of activation subsystem);
➢ monoclonal activation (according to parameters of granulocytic, monocytic, and lymphoid series).

Model application (considering the WHO recommendations) makes it possible to establish the immunological diagnosis by the following types of immune disorders:
➢ transient immune deficiency;
➢ stable (refractory) immune deficiency with general syndromes;
➢ immunosupressive;
➢ severe combined immune deficiency;
➢ infective;

➢ infective-allergic;
➢ autoimmune;
➢ lymphoproliferative.

Retrospective review of immune homeostasis in children living in contaminated areas demonstrates the manifestation of immunodeficiency mainly of mixed type. Formation of respective immune response types mediated by both age and sex differences, as well as radiation history in children vs. non-irradiated ones necessitates the use of complex criteria for the assessment of immune homeostasis of a child when attributing him or her to a specific group of health.

Some alleles that control the strength and direction of immune response were identified in 65% of children with disorders in immune homeostasis been to the Chornobyl accident factors. Carriership of HLA-antigens HLA-A9; HLA-B7; HLA-DR2; HLA-DR4; HLA-B35 is usually associated with low immune responsiveness or with autoimmune processes. Moreover, the HLA-B8 antigen is involved, which is considered a marker of a high-level humoral response.

Study of association of HLA structures with risk of quantitative abnormalities of $CD4^+$ and $CD8^+$ subpopulations showed just identical results regarding the adult persons. There was also found an association of such haplotypes as HLA-A2, B7 DR2 (RR = 4.56); HLA-A9, B21, DR2 (RR = 4.88) and for HLA-DR7 antigen (RR = 5.0) with low immune reactivity (high activity of T-suppressors, low activity of natural killer cells, and abnormal clearance of immune complexes by macrophages). These data indicate the presence of one or more suppressor genes associated with HLA system. We note that an association of immunogenetic markers with immune homeostasis disorders in irradiated and non-irradiated persons is unidirectional in the context of associations with particular allele specificity. However the associative connection rates were in all cases higher in people exposed to radiation which indicates an increased risk of realization of genetic predisposition to a morbid process under the exposure.

Therefore, the HLA markers of genetic control of human immune homeostasis are important in shaping of immune response in both adults and children to a range of the Chornobyl accident factors. It increases the risk of realization of the post-radiation effects not only at the immune response level, but also at a level of somatic disease occurrence, pathogenetic substrate of which is largely including the immune system disorders. Use of a complex of immunogenetic approaches is the basis for early detection and prevention of immunodeficiency.

Immunogenetic monitoring of the ARS-NC patients with pronounced hematopoietic disorders indicates that isolated antigens, their combinations, certain alleles associated with oncohematological disease (HLA-A2; HLA-B35; HLA-B5; HLA-DRB1*11) and with reduced immunoreactivity (HLA-A24; HLA-A9; HLA-B7), (HLA-B35 association with autoimmune component) are present in 45% of individuals. That is, the similar association patterns are surveyed between the immunogenetic factors and disorders in immunopoiesis and hemopoiesis in exposed individuals regardless of the degree of exposure. It also indicates the increased risk of further realization of leukemic process in these individuals and is the basis of attributing them to the risk group of oncohematological diseases. It was established that the formation and realization of these diseases is associated with both genetic and molecular cytogenetic disorders in genome and genetic predisposition to a morbid process itself. On the one hand the basis of lymphoproliferative processes resides in uncontrolled proliferation of lymphoid cells, to which the lymphocytes of specific types and development stages are involved. And quite often the chromosomal rearrangements or changes in expression of specific genes and mutations occur. Despite the fact that function of malignant cells is partially preserved, the efficiency of immune surveillance in these diseases is weakened due to the nature of monoclonal proliferation. On the other hand, the major histocompatibility complex (MHC) carries the genetic control of

immunological surveillance at a level of foreign genetic material (mutated cells) recognition to eliminate the damaged hematopoietic cells from the body by the immune system cells.

Review of contribution in immunogenetic radiosensitivity markers to the formation of hematological diseases under the radiation exposure indicates the exacerbation of risk of the morbid process formation. Particularly, the association coefficient of relative risk RR was significantly increased under the carriership of HLA-specificities in genotype of patients with acute leukemia. These specificities are assigned to the markers of increased risk of oncohematological disease (*HLA-A*24* and *HLA-DRB1*11*) in combination with HLA radiosensitivity markers in genotype (Figure 9.6).

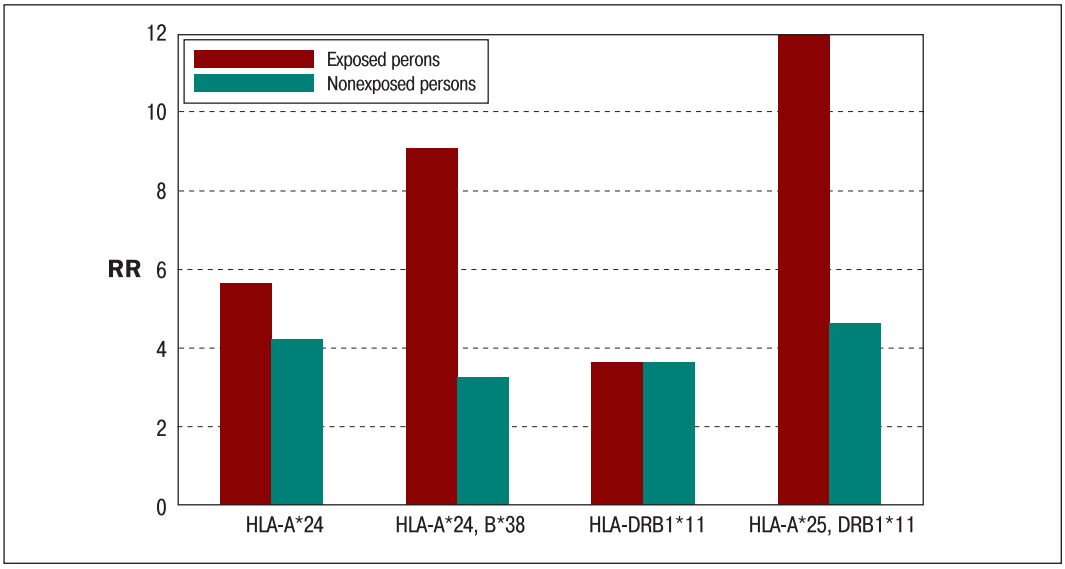


Figure 9.6. HLA-associations with oncohematological disease risk depending on presence of disease predisposition markers in combination with radiosensitivity markers in genotype of ARS survivors and non-exposed persons

Studies of immunogenetic passport in exposed and non-exposed persons having the hemopoietic system pathology show *HLA-A*24; HLA-B*18; HLA-B*35; HLA-B*51; HLA-C*03; DRB1*11* alleles and *DQA1*0101, DQB1*0501* haplotype attribution to acute leukemia, and *HLA-C*06; DQB1*0501; DQB1*0601* to multiple myeloma.

Effectiveness of therapy was found associated with certain HLA genotype in irradiated and nonirradiated patients with acute leukemia, regardless of patient's age. Presence of *HLA-A*02* and *HLA-B*51* specificities is associated with a favorable prognosis for duration of the first remission, and presence of *HLA-A*11* and *HLA-B*08* specificities is associated with life expectancy. Positive response to immunotherapy using transplantation of hematopoietic stem cells is associated with alleles *HLA-C*06* and *HLA-DQA1*0101* carriership, both of which can be considered as factors for predicting of treatment response.

Molecular-genetic testing in the exposed acute leukemia patients revealed no specific molecular genetic disorders associated with exposure to ionizing radiation. The nature, frequency, and complexity of karyotype disorders, expression of fusion genes, clonal rearrangements of immunoglobulin genes, and abnormalities in microsatellite DNA (loci D9S171 and D12S98) (Figure 9.7) in comparison with parameters of acute leukemia course is similar in irradiated and

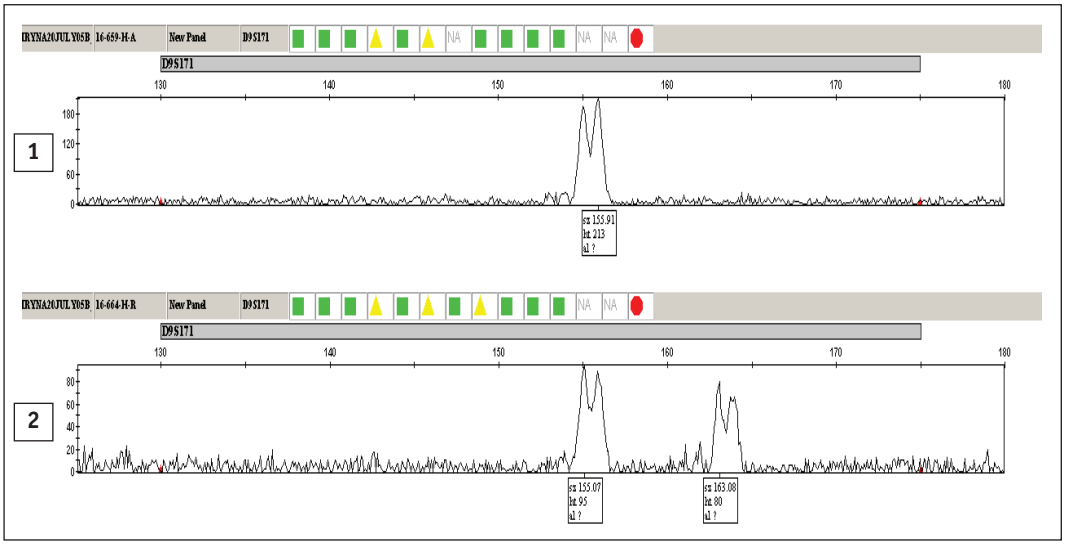


Figure 9.7. Microsatellite instability in D9S171 locus: 1 - constitutional DNA (buccal epithelium); 2 - tumor DNA (bone marrow)

non-irradiated individuals. In particular, the presence of cells with similar clones regardless of observation group is a prognostically unfavorable sign of acute leukemia progress, and complex clonal karyotype abnormalities in acute leukemia patients are an independent unfavorable prognostic factor of individual response to therapy. And finally, the chromosome 16 deletion in 16q13 segment is specific to the acute myeloid leukemia patients and does not worsen the disease. Loss of heterozygosity occurs more often than emergence of a new allele in D9S171 and D12S98 microsatellite loci in ALL patients.

No significant associative connection of data of molecular genetic disorders was found with immunogenetic factors.

Cytogenetic and molecular genetic testing of irradiated patients with chronic myeloid leukemia at the onset of the disease also shows no specific radiation-associated disorders. Namely, the t(9;22)(q34;q11) translocation and BCR/ABL fusion gene expression were the main genetic markers in both irradiated and non-irradiated patients. No increased frequency of related clones and additional chromosomal abnormalities called clonal evolution were found in patients with radiation history. Clonal evolution is considered a result of loss of control over the genomic instability and its intensification leads to disease progression [14, 15].

Clinical and laboratory monitoring with accounting of complete cytogenetic response (CCR) and major molecular response (MMR) achievement confirmed the high efficiency of Imatinib in treatment of CML patients exposed to ionizing radiation due to the ChNPP accident. Frequency of CCR achieving up to the 12th month of imatinib therapy was 35.7% and frequency of MMR was 8.3%, which corresponded to the respective parameters in patients with no history of irradiation. It should be noted that in some cases of no CCR achieved to the 12th month the continuation of therapy and imatinib dose increase resulted anyway in CCR and MMR at a later date, although the depth of response (i.e. the MMR achieving) was yet lower in the group of exposed subjects vs. the opposite group (Table 9.6).

In the group of patients who were exposed to ionizing radiation as a result of the accident, as well as in patients with no history of irradiation the complete hematological response was

Table 9.6
Response to Imatinib therapy in CML patients

Characteristics	Studied group*	Control group**
Total (n)	20	103
Complete hematological response at the 3rd month of imatinib therapy (%)	**100**	**98.0**
Complete cytogenetic response, n (%)	**10 (50.0)**	**50 (48.5)**
Pre–treatment period less than 6 months, n	5 out of 6	22 out of 28
Pre–treatment period 6–36 months, n	4 out of 10	24 out of 50
Pre–treatment period over 36 months, n	1 out of 4	4 out of 25
Major molecular response (%)	**23.5**	**27.6**
Pre–treatment period less than 6 months, n	3 out of 6	13 out of 22
Pre–treatment period 6–36 months, n	1 out of 8	9 out of 42
Pre–treatment period over 36 months, n	0 out of 4	2 out of 23
Primary resistance, n (%)	**10 (50.0)**	**52 (50.0)**
Pre–treatment period less than 6 months, n	1 out of 6	6 out of 28
Pre–treatment period 6–36 months, n	6 out of 10	26 out of 50
Pre–treatment period over 36 months, n	3 out of 4	20 out of 24
Secondary resistance, n (%)	**5 (25.0)**	**10 (10.0)**
Pre–treatment period less than 6 months, n	1 out of 6	1 out of 28
Pre–treatment period 6–36 months, n	3 out of 10	7 out of 50
Pre–treatment period over 36 months, n	1 out of 4	2 out of 24

Notes. * – CML patients exposed to ionizing radiation after the ChNPP accident; **– CML patients with no radiation history.

achieved after 3 month of imatinib therapy in 100% and 98% respectively. Complete cytogenetic response was recorded in 50% and 48.5% of patients in observation group and opposite group respectively. High molecular response in the compared groups was established in 20% of CML patients who had a history of radiation exposure and in 27.6% of patients in the control group. The best results in CCR and MMR achieving were found in patients with up to 6-month period of previous treatment (those in whom imatinib was administered as a first-line therapy). CCR and MMR were achieved significantly more often ($p < 0.05$) among patients with a history of radiation exposure who had received any previous treatment with other medicines in less than 6 months. The best therapy results (more patients with achieved CCR and MMR) were received under imatinib administration within 6 months upon the disease diagnosing. A significantly fewer cases of primary resistance to imatinib occurred in the same patient group.

These data are consistent with efficacy evaluation of imatinib treatment in the works of other authors [18, 19] depending on pre-treatment period duration (hydroxyurea compounds, interferon, busulfan) among the CML patients having no radiation exposure in a history. Moreover, these data confirm the fact that effectiveness of tyrosine kinase inhibitor (TKI) therapy depends on time elapsed between the CML diagnosis and TKI administration.

Prevalence of secondary resistance cases is noteworthy in CML patients who have a history of radiation exposure (25% of subjects). On the one hand, the most common mechanism of resistance is associated with kinase domain mutations of the *BCR/ABL* gene. The BCR/ABL-tyrosine kinase is a mutating factor itself. The longer a cell is under its influence, the more chances of mutation are including the *BCR/ABL* gene. This fact highlights possible mechanisms of increasing resistance to TKI therapy in patients who had received treatment with

other drugs for a long time. Given that the radiation factor somehow contributes to emergence of genomic instability [20], we can also assume that the increase in frequency of secondary resistance to some extent is due to preliminary genome destabilization under the impact of ionizing radiation.

On the other hand, the cytogenetic and molecular remission is a result of control of residual tumor clone by the immune system. If this control is not balanced, the residual cells begin to proliferate, which leads to the tumor clone growth and relapse. Since immune cells are critical to ionizing radiation, the effect of radiation factor can lead to attenuation of immune supervision and, consequently, to the loss of stable control over a residual tumor clone. Better understanding of the mechanisms of regulation of resistance evolvement, mutations emergency, genetic instability, and DNA repair systems promotes the development of new approaches to improve the effectiveness of therapy for patients with CML.

The received results give a reason to believe that it is appropriate to use a combination of TKI with immunomodulatory drugs for stabilization of remission in patients with CML, exposed to radiation as a result of the ChNPP accident.

We have conducted a comparative review of the existence of immunogenetic mechanisms of genetic susceptibility realization to other diseases that were casually associated with irradiation, including thyroid and cardiovascular disorders.

Retrospective review of associations between thyroid disease and HLA in ARS grade I survivors indicated that i 68.2 % of patients with benign thyroid disease expressed markers of genetic predisposition to thyroid disease in phenotype (HLA-A19; HLA-A1; HLA-B22; HLA-DR5). All that suggests a mechanism of realization of genetic predisposition to the disease under a radiation exposure.

A retrospective review of realization of remote post-radiation effects induced by the impact of the ChNPP accident also demonstrates a manifestation of secondary immune dysfunction, increased frequency of autoimmune endocrine diseases, growing number of radiation-induced malignant thyroid tumors among the irradiated cohorts [22, 23]. This risk group includes children and adolescents because the small size and higher than in adult functional activity of thyroid make it more predisposed to the development of radiation-induced diseases. Just the physiological state of thyroid attracts the attention under a compelling evidence about the lack of compensation of the gland function at the initial stages of its enlargement and possible further formation of stable thyroid disease in this context. Genetic predisposition to development of endocrine system disorders can be considered as a specific pathogenetic substrate of development of autoimmune endocrine diseases in children with diffuse nontoxic goiter (DNG) grade IA-IB associated with risk of DNG evolving into the severe clinical forms.

A widespread prevalence of HLA-A19, HLA-B8, HLA-B22, HLA-B35, HLA-DR5 antigens which are markers of thyroid disease was established in children with DNG regardless the nature of irradiation in comparison with exposed children having no DNG. Presence of markers of increased radiosensitivity of organism (HLA-A10; HLA-B38; HLA-DR4) in phenotype of children with DNG living in controlled areas increases the risk of realization of predisposition to thyroid disease. Thyroid disease diagnosed 5 years upon irradiation in 65% of exposed subjects vs. 15% in the control population is an argument here.

Increased association of thyroid disease with human histocompatibility antigens under the impact of radiation factor also shows the close relationship of radiation exposure with risk of realization of genetic predisposition.

A prospective analysis of clinical manifestations of thyroid disease in exposed children with DNG, whose phenotype included markers of thyroid disease and increased radiosensitivity

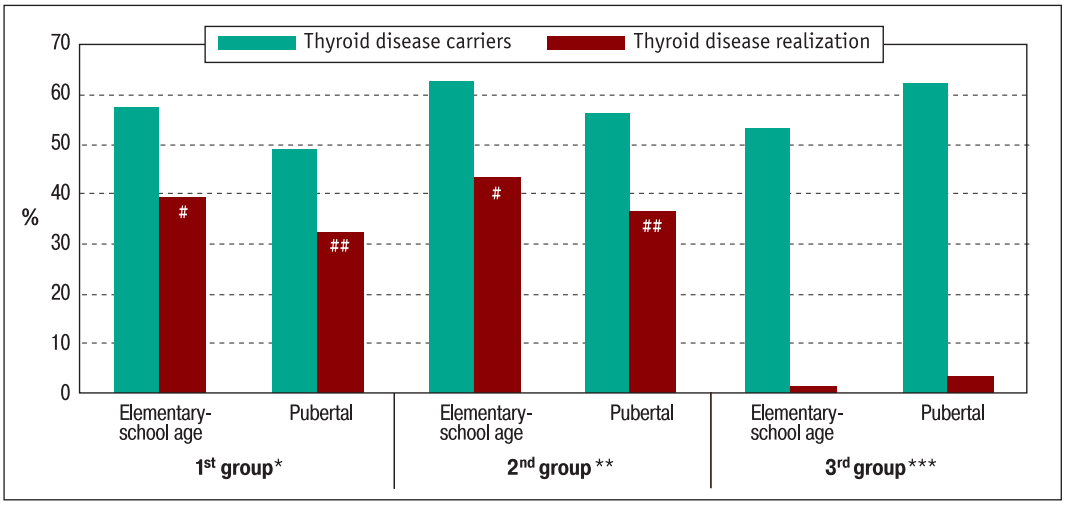


Figure 9.10. Carriership percentage of markers of thyroid disease and realization of hereditary genetic predisposition to thyroid disease in studied groups of children with DNG.

* – children evacuated from the 30-kilometer zone and exposed to a short-term irradiation and having a severe radiation burden on thyroid. ** – children living full-time in radiologically contaminated territories and exposed to long-term irradiation from a combined impact of radioactive iodine and cesium. *** – Children living in a conditionally "clean" region.

– difference vs. the elementary-school control group ($p<0.05$); ## – difference vs. the pubertal control group ($p<0.05$).

showed some significant differences in comparison with non-irradiated peers, namely there were 42.9% of evacuated children (87 persons) with DNG and overt thyroid disease born to the ChNPP accident clean-up workers (the first group), 54.2% of such pediatric patients living in contaminated territories, and 12.4% in control.

Thus, the results of accomplished studies indicate that the presence of genetic predisposition to formation of thyroid disease including chronic autoimmune thyroiditis is associated with immunogenetic factors and restricted with population and environmental features of the region. Radiation is an inducing factor in development of chronic autoimmune thyroiditis as the realization of genetic predisposition to thyroid disease in persons exposed to radiation as a result of the accident.

By analyzing the associative links of isolated antigen specificities of HLA system and their combinations with development of chronic autoimmune thyroiditis in exposed individuals it was determined that the highest risk of realization of genetic predisposition to this disease is specific to the people being the HLA-A29; HLA-B38; HLA-B21; HLA-Cw1, HLA-A25; HLA-B17,18; HLA-B8,38 HLA-DR5; HLA-DR3,7; HLA-DR5, DQ1; antigen carriers in their phenotype. Presence of one of such haplotypes as HLA-B5, Cw2; HLA-Cw5, DR2; HLA-B15, Cw1, in the individual's phenotype allows predicting the stability and low risk of realization of genetic predisposition to chronic thyroiditis under the irradiation.

Study results indicate that specificities considered as the markers of immune response strength and direction, namely the HLA-B7; HLA-A9; HLA-DR2; (low strength of immune response), HLA-B8 (high strength of immune response); HLA-B35 (autoimmune component) are among the composition of markers associated with risk of pathological process, regardless of the studied nosology (hematological, endocrine, or cardiovascular). This fact indicates that immune and immunogenetic components are the essential part of pathogenesis of multifactorial disorders [24].

Similar immunogenetic pathways of cardiovascular disease (CVD) development were surveyed in the studied contingents.

It should be noted that as for the time of formation after exposure the cardiovascular disease was realized by genetic predisposition much later (15 years or more, respectively).

The risk of realization of pathological process in the irradiated and non-irradiated persons in all cases was associated with similar by specificity HLA-genes that highlights common mechanisms of immunogenetic control, regardless of spectrum of endogenous factors. This fact gave us the basis to calculate the coefficient of relative risk of disease within overall group of patients with coronary artery disease (Figure 9.11).

A significant increase of concentration of HLA-29 and HLA-A33 specificities was established, which are equal to the frequency of occurrence. These specificities are a part of HLA-A19 split, which is considered a marker of the risk of endocrine disorders. The HLA-27 and HLA-B35 specificity concentration is significantly increased in locus B. These genes are considered a independent marker of risk for autoimmune processes.

A significantly increased prevalence of *HLA-DRB1*12* allele with positive value of index of associative connection with disease (RR = 3.45), reduced concentration of *DRB1*04* allele, and negative association coefficient (RR = 0.11) was determined in HLA-DRB1 locus in both studied groups, which gives rise to the assignment of this specificity to the genes-protectors.

The *DQA1*0103* and *DQA1*0501* alleles are also highly prevalent with positive coefficient of relative risk. By the degree of association these genes are attributed to the gene predictors. The DQB1*0303 specificity is attributed to genes-predictors. Received data indicate that the predictive function is performed by genes that according to the literature and our observations are associated with increased susceptibility to infectious factors and with risk of immunopathological reactions (IPR).

The HLA-markers of radiosensitivity in composition with antigens associated just with diseases were identified in 80% of irradiated patients with coronary artery disease. Increase in the numerical values of associative connection, confirming preliminary data on realization of increased risk of disease in terms of exposure was observed in these cases.

Review of a character of immunopathological reactions in patients with CCHD shows that the reduced proliferative capacity of lymphocytes, increased sensitization of lymphocytes to the

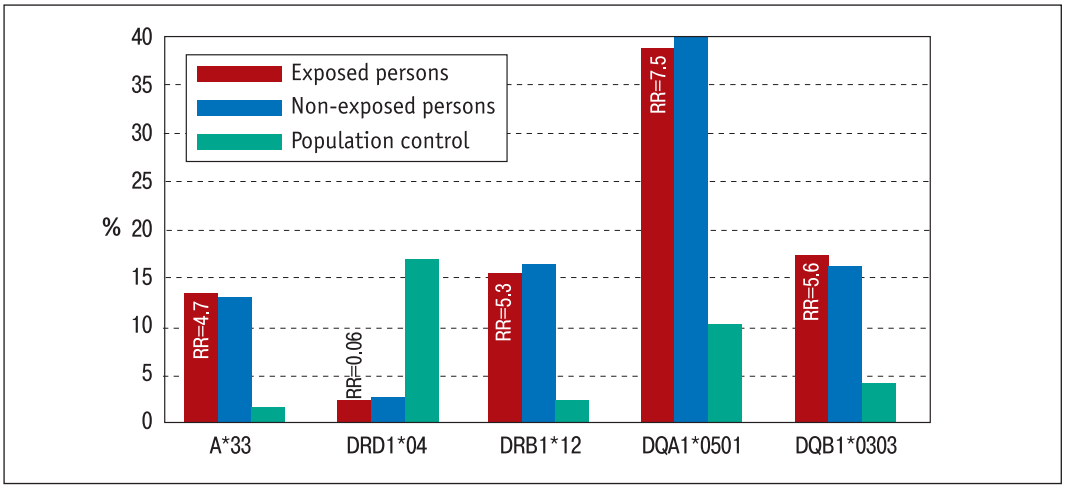


Figure 9.11. **HLA-associations with CVD development risk in exposed and non-exposed subjects**

Table 9.7
Incidence of some HLA-genes in CVD patients exposed to ionizing radiation

HLA-genes and their combinations	Control group (n = 100)	CVD patients (n = 60)	RR	X^2	CVD patients exposed to ionizing radiation (n = 48)	RR	X^2
1	2	3	4		5	4	
A*29	0.015	0.118#	3.36	4.252	0.132#	3.45	4.180
A*33	0.013	0.118#	3.36	4.110	0.121#	3.45	4.180
B*27	0.023	0.124#	2.94	3.933	0.145#	3.83	3.933
B* 35	0.071	0.213#	3.87	3.880	0.286#	4.12	3.980
B* 38	0.071	0.082	1.17	2.470	0.286#	3.51	3.870
DRB1*03	0.165	0.152	1.15	2.152	0.367#	4.24	4.252
DRB1*04	0.157	0.023#	0.11	3.980	0.031#	0.15	3.910
DRB1*12	0.023	0.152#	3.45	3.980	0.145#	3.62	3.980
DQA1*0103	0.069	0.191#	3.52	5.576	0.183#	3.58	4.276
DQA1*0201	0.140	0.023#	0.11	5.410	0.031#	0.15	3.910
DQA1*0501	0.106	0.383#	4.71	4.252	0.367#	3.68	3.880
DQB1*0301	0.203	0.191	0.87	1.860	0.183	0.72	1.240
DQB1*0303	0.032	0.164#	4.05	3.980	0.183#	4.25	4.210
DQB1*0602	0.128	0.023#	0.36	3.860	0. 031	0.46	2.860
B*35, DRB1*12	0.012	0.126#	5.24	4.730	0.145#	7.21	5.410

Notes. # – significant difference in the incidence vs. the control group, $p < 0.05$.

vascular wall tissue, and hypersecretion of IL-6 by the blood mononuclear cells are most common regardless of the survey group (irradiated, non-irradiated). Assessment of immunogenetic factors association with risk of these immunopathological changes allowed identifying the markers with regard to every type of immune responses (Table 9.8).

In 80% of patients with coronary artery disease the hyperactive type of immunopathological reactions was prevalent accompanied by severe atherosclerotic coronary vascular lesions. Both

Table 9.8
Probable associations of HLA-markers with immunopathological reactions in CVD patients

Immunological parameters	HLA-genes specificities	Incidence of HLA-specificities (F)		RR
		normal immune responses (n=30)	immunopathological responses (n = 29)	
Hypersecretion of IL-6 by the blood mononuclear cells	B*35	0.079	0.214	4.17
	DRB1*03	0.076	0.167	3.82
	DQA1*0103	0.077	0.286	4.23
Increased lymphocyte sensibilization to the vascular wall tissues	B*08	0.063	0.121	3.34
	B*14	0.035	0.100	4.69
	DQB1*0501	0.167	0.070	0.17
Decreased proliferative capacity of lymphocytes	B*35	0.057	0.153	2.97
	DRB1*03	0.050	0.143	4.23
	DRB1*16	0.025	0.107	3.68
	A*01	0.143	0.036	0.12
	B*07	0.163	0.036	0.11
	DQA1*0103	0.163	0.071	0.21

positive and negative associative factors of immune response were established in this group of patients. In this way the *HLA-B*08* (RR = 4.17); *HLA-DQA1*0103* (RR = 3.5); *HLA-DRB1*03* (RR = 3.7); *HLA-DRB1*16* (RR = 3.8) specificities were attributed to predictors by the frequency of occurrence and association coefficient.

The autoimmune type of IPR was prevalent in 30% of CVD patients, which correlated with early disease onset (up to 45 years old) and the development of complications. According to association coefficient the *HLA-B*14* (RR = 4.7); *HLA-B*35* (RR = 3.3); *HLA-DRB1*03* (RR = 3.8); *HLA-DRB1*16* (RR = 3.7) alleles were attributed to IPR predictors in CVD.

The *HLA-A*68* (RR = 4,7); *HLA-DRB1*01* (RR = 4.2) specificities were attributed to the IPR protectors. Their carriership promotes the late onset of atherosclerosis. The *HLA-A*01, B*07* (RR = 4,7); *HLA-DQA1*0101* (RR = 4.6) carriership is associated with no autoimmunity of a humoral type. Presence of *HLA-DQB1*0501* (RR = 7.2) alleles is associated with no autoimmunity of a cellular type.

Consequently, the received data altogether indicate that the realization of HLA-genetic predisposition to the disease both at a level of hematopoietic and imunopoietic disorders and at a level of disease in general is one of mechanisms of formation of radiation-associated multifactorial disease. The carriership of radiosensitivity markers in feno/genotype increases the risk of pathological process realization under the exposure. The available data also indicate the significant contribution of immunological and immunogenetic component to pathogenesis of multifactorial diseases as the endogenous risk factors of disease development. Moreover, there are common pathways of realization of generic predisposition under exposure to adverse environmental risk factors, regardless of their spectrum.

The study of genetic pattern of population of the Central-Ukrainian genogeographical zone showed a carriership of antigens associated with high radiosensitivity in 33.0% of individuals, carriership of antigens associated with radioresistance in 26.4%, presence of a competitive markers of radiosensitivity and radioresistance in phenotype in 8.2 % of persons, of markers of the immune dysfunction risk in genotype in 25.5%, combination of radiosensitivity and radioresistance markers with risk of immunological dysfunction in genotype in 7.4%, indicating a fairly high percentage of people who have markers of increased radiosensitivity in genotype and risk of disorders in immune homeostasis. And under the influence of radiation factor the latter people will constitute the risk group of realization of post-radiation effects at the level of immunopoietic and hematopoietic disorders that in turn may contribute to development of somatic disease causally related to irradiation (Figure 9.12).

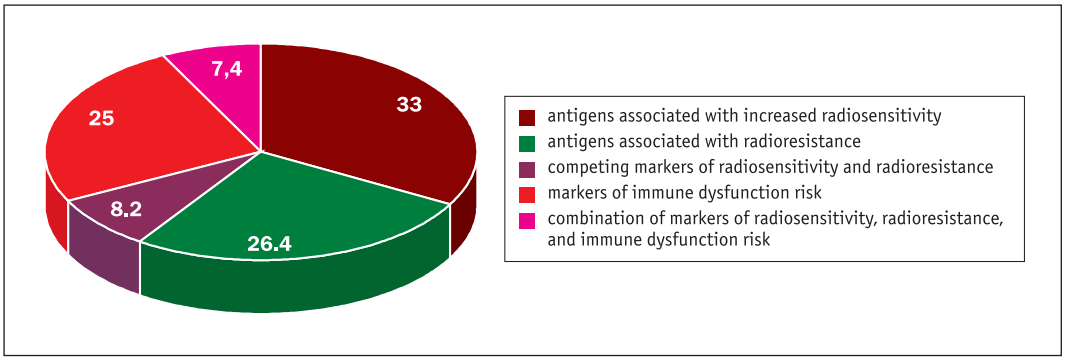


Figure 9.12. **The HLA-genetic structure of population of the Central-Ukrainian genogeographical zone by prevalence of markers for radiosensitivity and immune dysfunction risk**

The long-term health survey in the exposed contingents of people from a perspective of immunogenetics gives a reason to believe that immunogenetic research is an essential part of initial medical examination of individuals having occupational contact with radiation sources, or living in contaminated areas. The single genotype identification makes it possible to create an individual «immunogenetic passport», which contains data (i.e. genetic markers) of radiosensitivity or radioresistance of person, genetic risk factors of realization of hereditary predisposition to disorders in hemopoiesis and immune homeostasis and to specific diseases that can be causally linked to exposure. All that is the basis of decision-making in the choice of healthcare approach aimed at preventing of realization of radiation-induced risks.

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Chapter 10
DEMOGRAPHIC CONSEQUENCES OF THE CHORNOBYL CATASTROPHE IN UKRAINE

Thirty years' studies of NRCRM confirm that Chornobyl nuclear power plant accident is the largest in human history, man-made radiation catastrophe. According to INES scale it is of, seventh, the highest level of danger [1]. It subjected to radioactive contamination the northern hemisphere, more than 2 billion of earthlings were exposed [2].

In Ukraine, radioactive contamination with cesium-137 at 37 kBq x m^{-2} and above suffered 53,454 km^2 area (4.8% of the total). It seized 12 oblasts and 74 rayons. As radioactive polluted recognized 2293 settlements.

Status of sufferers of the Chornobyl catastrophe have received more than 3.4 million citizens, including 1.2 million children. [3]

The catastrophe and its aftermath caused enormous political, economic, social, agricultural, medical, demographic, medical and psychological damages.

All the years after the explosion of reactor residents live and work in increased over pre-accident level radiation and radioactive contamination of environment objects – soil, air, water, animal and plant world. The most harm to health cause contaminated food. It will remain the source of radionuclides in the human body, for many years.

Over the years, in the state a significant amount of work was done on overcoming consequences of the Chornobyl catastrophe. Radiation-ecological situation significantly improved and levels of human exposure decreased. However, the consequences of the catastrophe are not yet eliminated [4].

At 01.01.2015 the status of Chornobyl catastrophe sufferers in the country still had 2,025,141 person. Among them 222,498 liquidators of the accident, 1,802,643 victims of the accident, of which 442,343 – affected children. Among affected there are 35,033 persons who have the status of wife / husband of the deceased citizen whose death is related to the Chornobyl catastrophe.

Due to the high contamination still remain uninhabitable territories of exclusion zone and the zone of guaranteed (obligatory) resettlement. From these zones and other contaminated territories (RCT) of the country after the catastrophe were evacuated, relocated for compulsory resettlement and by oneselves in the guaranteed voluntary resettlement moved about 200 thousand people. In areas of contamination were deserted more than 120 settlements.

That is, catastrophe was the cause of uninhabitable land formation, the forced migration of hundreds of thousands of people, loss of settlement network. But scheduled for 1991-1992 resettlement of residents from the most RCT to clean continues still, and is being never completed.

Due to the location to clean areas mainly people of working age, pregnant women and families with children at the RCT been a changed of the population towards aging. All the years after the catastrophe at RCT were elevated levels of mortality (Figure 10.1), impaired reproductive behavior (Figure 10.2).

The birth rate declined particularly sharply during the first years after the Chornobyl catastrophe. As a result of violations of fertility to mortality ratio significantly deteriorated vitality of the population (Table 10.1, 10.2) and decreased its reproductive potential.

In the structure of RCT residents mortality far outweigh the diseases of cardiovascular system. More than 110 thousand of the Chornobyl catastrophe sufferers were disabled due to diseases related to the Chornobyl catastrophe or its consequences.

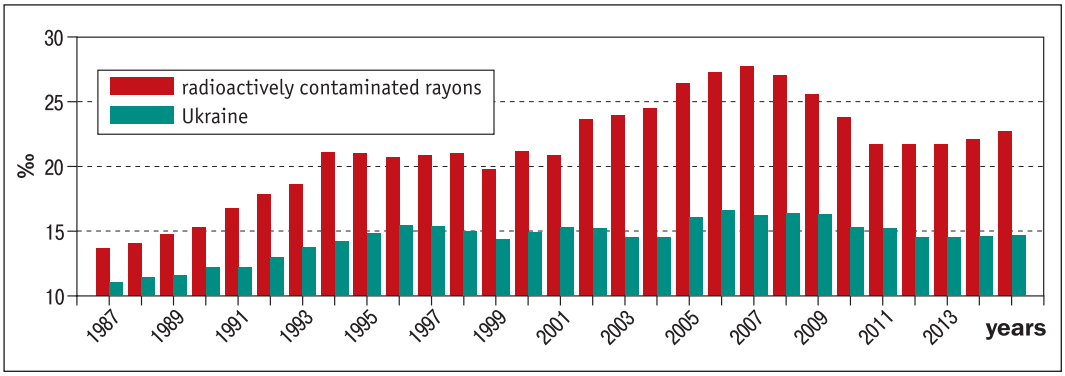


Figure 10.1. **Mortality at radiation contaminated territories of Ukraine, 1986–2014, per 1,000 population**

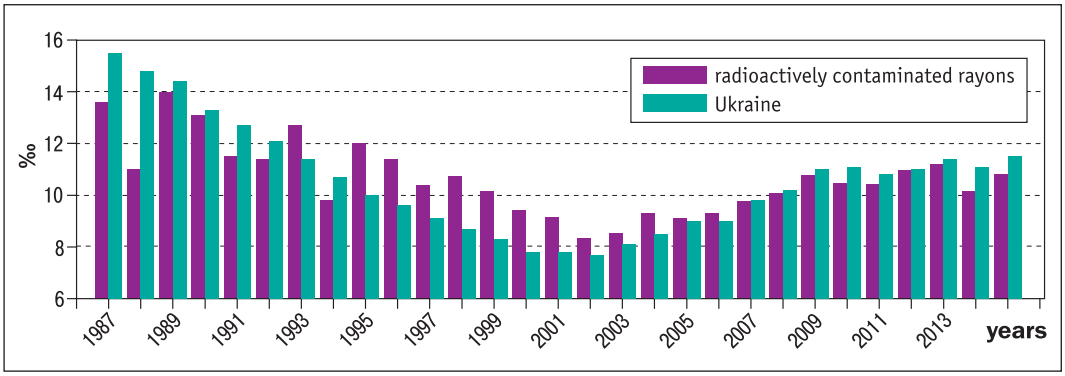


Figure 10.2. **Birth rate at radiation contaminated territories of Ukraine, 1986–2014, per 1,000 population**

Territorial differences in measures of radiation, health and social protection of RCT residents was noted and it was shown that their amounts was insufficient and not fully eliminated radiation health risks [5–8]. The data show not only the trouble in the expozed population in terms of fertility and mortality [9–11], but also to its reduced viability by low fertility and high mortality [12, 13].

Table 10.1
Viability index of the most contaminated regions and Ukraine as a whole in the years 1986–2012

Year	Zytomyr oblast	Kyiv oblast	Ukraine	Volyn oblast	Rivne oblast
1986	1.29	1.30	1.40	1.73	1.97
1989	1.04	1.11	1.15	1.49	1.67
1990	0.92	0.95	1.05	1.36	1.49
1991	0.89	0.83	0.94	1.16	1.35
1995	0.68	0.58	0.62	0.92	1.08
1997	0.65	0.55	0.58	0.89	1.05
1998	0.60	0.51	0.58	0.89	1.03
1999	0.54	0.46	0.53	0.80	0.94
2001	0.49	0.43	0.50	0.78	0.88
2005	0.52	0.51	0.54	0.79	0.88
2007	0.59	0.58	0.62	0.91	0.98
2008	0.62	0.65	0.67	0.99	1.05
2010	0.69	0.69	0.71	1.03	1.14
2011	0.74	0.75	0.76	1.06	1.24
2012	0.75	0.77	0.79	1.12	1.28

Note. Areas of unviable populations marked in gray, in bold figures – the minimum value of the index during the period of observation.

Table 10.2
Viability index of the contaminated rural territories residents and Ukraine by the size of grouping in the 1986–2009

Year	Distribution of regions by viability index, %						Viability index
	< 0.51	0.51–1.0	1.01–1.5	1.51–2.0	2.01–3.0	> 3.0	
Ukraine							
1986	1.9	57.8	24.9	9.4	5.6	0.4	1.04
1990	16.9	61.1	16.4	4.4	1.2	0.0	0.81
2000	65.5	30.2	3.5	0.8	0.0	0.0	0.49
2009	43.5	50.0	5.5	1.0	0.0	0.0	0.64
Radiation contaminated territories							
1986	4.1	69.9	9.6	8.2	6.8	1.4	0.98
1990	31.5	52.1	9.6	2.7	4.1	0.0	0.69
2000	78.1	13.7	4.1	4.1	0.0	0.0	0.47
2009	61.7	30.1	4.1	4.1	0.0	0.0	0.57

Forced migration of the population in situations of emergency (evacuation) and existing exposure (organized resettlement) contributed to a chain reaction of geodemographic and socio-economic changes not only in RCT (donor regions), but also in areas that received immigrants (region recipient), namely:

➢ increasing migration activity of the population of Ukraine, where the RCT during internal displacements have the status of migration donor for the recipient regions;

➢ spatial redistribution of the population;

➢ changes in population both individual regions and different types of settlements;

➢ change the quality of population (both in recipient region and RCT) in connection with participation in irregular migration movement of different socio-demographic groups (often migrated families that have young children, more active – people of young age than older age groups);

➢ change of reproduction of RCT population (short-term increase in the birth rate, the outflow of young people contributed to an aging population and as a consequence – increase in mortality, the average age of death rate and vitality of the population);
➢ demographic crisis in zones 3 and 4 and the demographic catastrophe – in zones 1 and 2;
➢ loss of RCT labor capacity (as people of economically active age migrate increasingly) and the growth of labor supply aggregate in the recipient region;
➢ changes in the settlement network (in zones 1 and 2 – to reduction the number of settlements and increasing poorly attended and deserted villages, reduction of all RCT population, in the region recipient – increasing population of settlements and territories);
➢ the improvement of social infrastructure in the recipient region (roads, schools, etc.) and the lack of socio-economic development of RCT;
➢ change the traditional way of life, namely for immigrants is a lack of information about the landscape and agro-climatic characteristics of land use, ethnic and cultural traditions and socio-economic conditions of the recipient region, for RCT residents – the need to fulfill radiation protection measures, changing culture of land use and so on. ;
➢ blur ethnic composition of the recipient region and at the RCT – loss of ethnic and ethnocultural traditions (zone 1 and 2) and the prospect of loss in zone 3;
➢ rupture of family, friendship, work and intersettlement bonds, difficulties in mutual adaptation with indigenous people;
➢ significant financial costs both the state and the individual, aimed at supporting life on RCT (including threats and risks in each zone) or resettlement in the recipient region.

Compiled information on population protection by distance after the catastrophe shows that organized evacuation and relocation led to a reduction of man-made radiation exposure of the population and were a difficult problem in organizational, socio-economic and psychological terms [14].

The most useful in terms of dose level averted for life were the evacuation and resettlement of contaminated territories residents in 1990 and 1991.

According to estimats calculated for Pereyizdivsky village council of Zhytomyr oblast [15] through resettlement diverted dose for the life ranged from 11.2 to 28.8 mSv for the most vulnerable cohort from radiobiological position (children aged 0 years at the time of the catastrophe.

Even at such levels it may be considered that resettlement reduced the level of stochastic effects.

After 2000 the relocation was almost not conducted and still is not implemented in amounts stipulated by law. Delayed relocation and its incompleteness reduced the effectiveness of the measure in the system of radiological protection.

Compiling data on the volume of organized migrations caused by the Chornobyl catastrophe shows that the absolute risk of territorial environmental migration for Ukraine is 3.2×10^{-3}, incl.: evacuation risk – 1.8×10^{-3}, the risk of organized resettlement – 1.4×10^{-3}.

It was shown that the value of regional risks to the contaminated administrative units has a significant range of values.

In particular, in Zhytomyr oblast – 3.3×10^{-2}, incl.: risks of obligatory resettlement – 1.2×10^{-2}, the risk of voluntary resettlement – 2.1 x 10, Narodychi rayon – 0.77; 0.62; 0.15, Ovruch rayon – 0.84; 2.6×10^{-2}; 0.82, Luhyny rayon – 4.0×10^{-2}; 0.16, respectively. For towns of Prypiat and Chornobyl evacuation risk was 1.

The degradation of zone 2 settlements, formed in the last 20 years because of the absence or insufficiency of funding for their socio-economic rehabilitation and low standard of living of its inhabitants, increase the risks from ionizing radiation and require the further implementation of anti-radiation measures, including resettlement moving to its completion.

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Chapter 11
HEALTH STATUS OF SURVIVORS. RISK FACTORS

11.1. HEALTH STATUS OF CHORNOBYL CLEAN-UP WORKERS

This section presents main results of epidemiological studies on health status of Chornobyl clean-up workers 1986–1987 carried out within post-accident period. We used database of the State Registry of Ukraine of the Persons Affected by the Chornobyl accident (SRU), which provides personalized health information on clean-up workers and disease registry. Throughout the study period we used in Ukraine two classifications to code diseases – ICD-9 (up to 2000) and ICD-10 (in later years), data sampling was carried out with both codes taken into account.

As of June 30, 2015 318,988 clean-up workers were registered in SRU. 196,423 males were involved in recovery operations in 1986–1987; 68,145 having information on whole body external doses.

Table 11.1 presents the total number of clean-up workers 1986-1987 who underwent medical examinations.

In the cohort, male clean-up workers 1986-1987 having whole body external doses (68,145 men) were divided into five dose subgroups (0–0.049; 0.5–0.099; 0.1–0.199; 0.2–0.249 and 0.25–0.7 Gy) and two age ones (18–39 and 40–60 years at the time of exposure). In these subgroups, we determined mean dose of external whole body radiation and average age at the time of exposure (Table 11.2). As apparent from Table 11.2, the average age-at-exposure among examined patients with various doses is 28.7–30.2 years in younger age group and 42.6–45.4 years for senior clean-up workers. Average doses in different age-dose groups are practically the same.

11.1.1 Integral indexes of health

A significant deterioration of the health of population affected by the Chornobyl disaster was found on the evidence derived from the previous epidemiological studies carried out at various stages of the post-accident period [1–3]. In 1988, the proportion of healthy and practically healthy persons among clean-up workers approximated 68%, while in 2012, i.e. 26 years after the accident, it fell to 5.5% (Figure 11.1). The decline in the proportion of the healthy people is due to a wide range of nontumor diseases, primarily circulatory, digestive, respiratory ones, diseases of the nervous, endocrine and genitourinary systems [4–7].

Table 11.1

Number of examined men in the cohort of clean-up workers 1986-1987 in five-year observation periods with regard for the age at the time of exposure (< 40 and ≥ 40 years old)

Observation periods	Cohorts, persons (abs.)		
	Total number	< 40 years old	≥ 40 years old
1988–1992	331761	281571	50190
1993–1997	519795	428774	91021
1998–2002	620620	499466	121706
2003–2007	651453	527299	124154
2008–2012	517629	439495	78134

Table 11.2

Distribution of male clean-up workers 1986–1987 in the cohort depending on the whole body external doses and age at the time of exposure (x±m)

Characteristics	Whole body external dose, Gy				
	0–0.049	0.05–0.09	0.1–0.199	0.2–0.249	0.25–0.7
Clean-up workers 1986–1987 aged 18–39 at the time of exposure					
Average age	28.8±5.4	30.2±5.1	28.7±5.2	28.8±5.1	28.8±5.2
Mean dose (Gy)	0.023±0.015	0.084±0.013	0.15±0.033	0.221±0.015	0.259±0.036
Total (persons)	6214	17777	14690	14618	6462
Clean-up workers 1986–1987 aged 40–60 at the time of exposure					
Average age	45.4±5.0	42.6±3.6	44.4±4.6	43.5±3.8	44.2±4.2
Mean dose	0.022±0.015	0.082±0.014	0.149±0.031	0.221±0.015	0.281±0.084
Total (persons)	922	1686	1390	1080	706

An increase of disability and mortality rates is attributable to nontumour diseases [8–9]. Nearly 90% of nontumor disability cases recorded among clean-up workers in 2012 were related to the Chornobyl accident. Within 26 post-accident years, disability has increased from almost 0 to 250 cases per 1000 persons (Figure 11.2). In 2012, circulatory diseases contributed mostly (63%) to the structure of causes of disability, the second place (13.3%) was occupied by diseases of the nervous system, and the third (6.7%) – by digestive diseases (Figure 11.3).

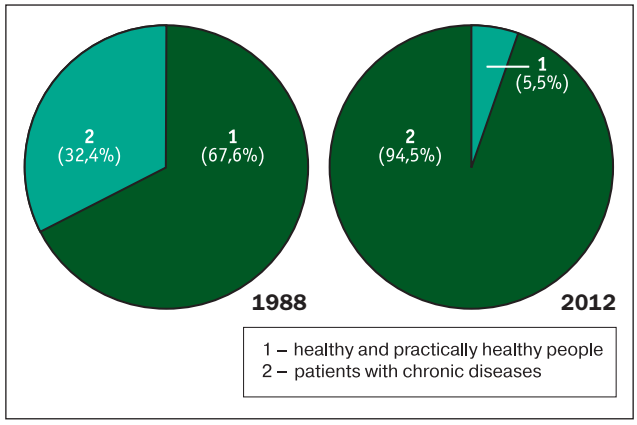


Figure 11.1. Distribution of the Chornobyl clean-up workers 1986–1987 by health indicators 1988 and 2012 (SRU data)

Within post-accident period, we observed a significant growth of the death rate: in 1988–2012, the overall death rate among clean-up workers has increased from 3.5 to 17.7 ‰. Some 70% of causes of death are those due to nontumor diseases. Figure 11.4 shows the dynamics of nontumor mortality in the cohort of clean-up workers depending on age at the time of exposure. Major contribution (82%) to the structure of causes of nontumor deaths made circu-

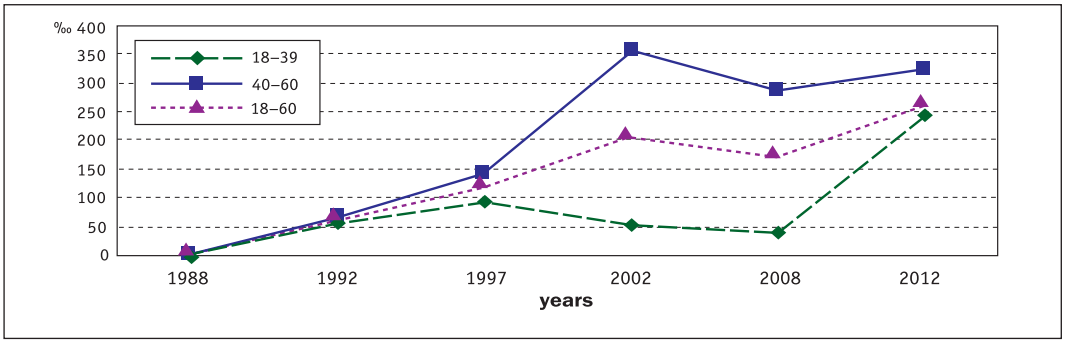


Figure 11.2. **Dynamics of disability among the Chornobyl clean-up workers 1986–1987 related to participation in recovery operations with regard for the age at the time of exposure (SRU data)**

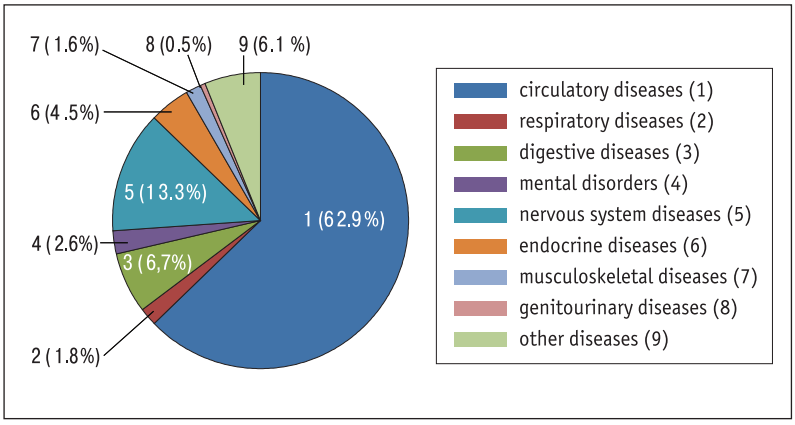


Figure 11.3. **Structure of causes of disability in the Chornobyl clean-up workers 1986–1987 for 2012 (SRU data)**

latory diseases, digestive diseases ranked second (9.7%), respiratory diseases – third (5.1%), and other nontumor diseases – fourth (3.2%) (Figure 11.5).

Figure 11.6 displays the dynamics of mortality from circulatory diseases among clean-up workers depending on age at the time of exposure for five-year periods. An increase in mortality was established in both age groups under study – people under age 40 at the time of exposure (increased by a factor of 16.7); those aged 40–60 at the time of exposure (by 13 times) as compared to the first (1988–1992) and the last (2008–2012) observation periods. As is evident from Figure 11.7, the following diseases (chronic ischemic heart disease, cerebrovascular diseases and myocardial infarction) make major contribution to mortality.

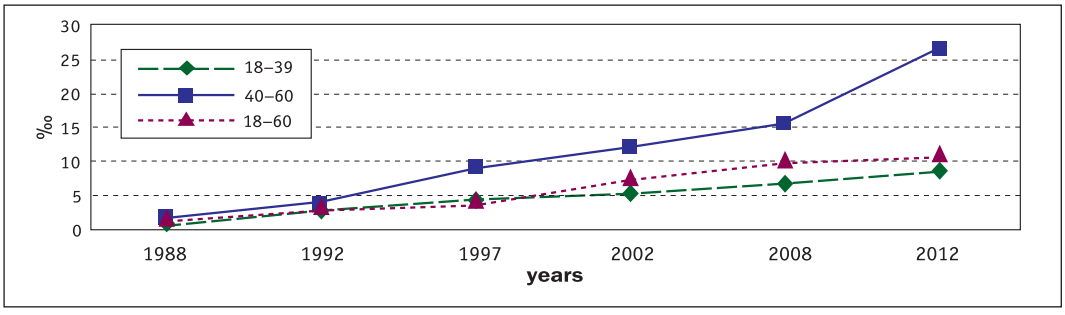


Figure 11.4. **Dynamics of nontumor mortality among the Chornobyl clean-up workers 1986-1987 with regard for the age at the time of exposure (SRU data)**

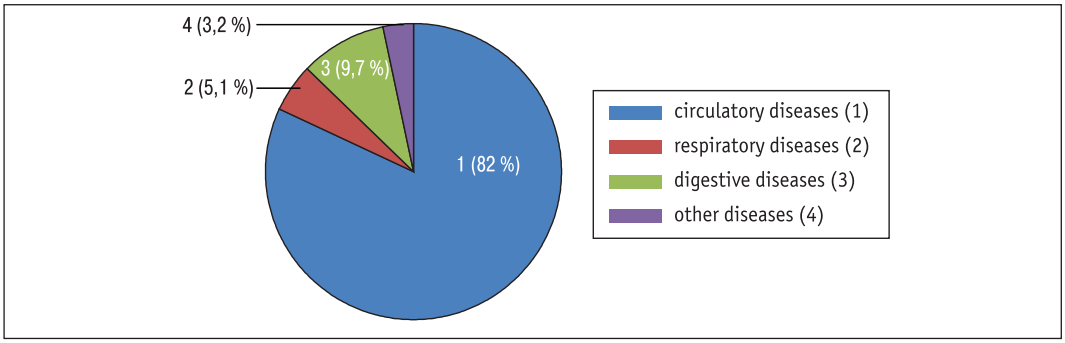


Figure 11.5. Structure of causes of death from nontumor diseases among the Chornobyl clean-up workers 1986–1987 for 2012 (SRU data)

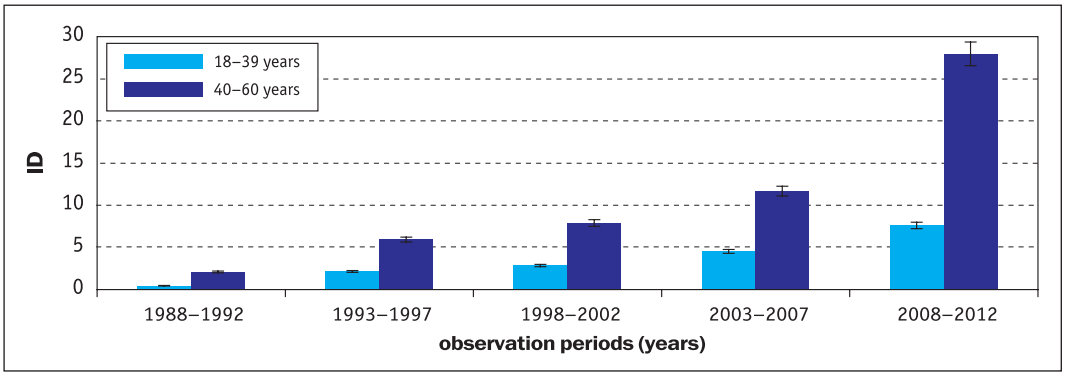


Figure 11.6. Dynamics of mortality from circulatory diseases among clean-up workers 1986–1987 depending on age at the time of exposure (cases per 10^3 person-years)

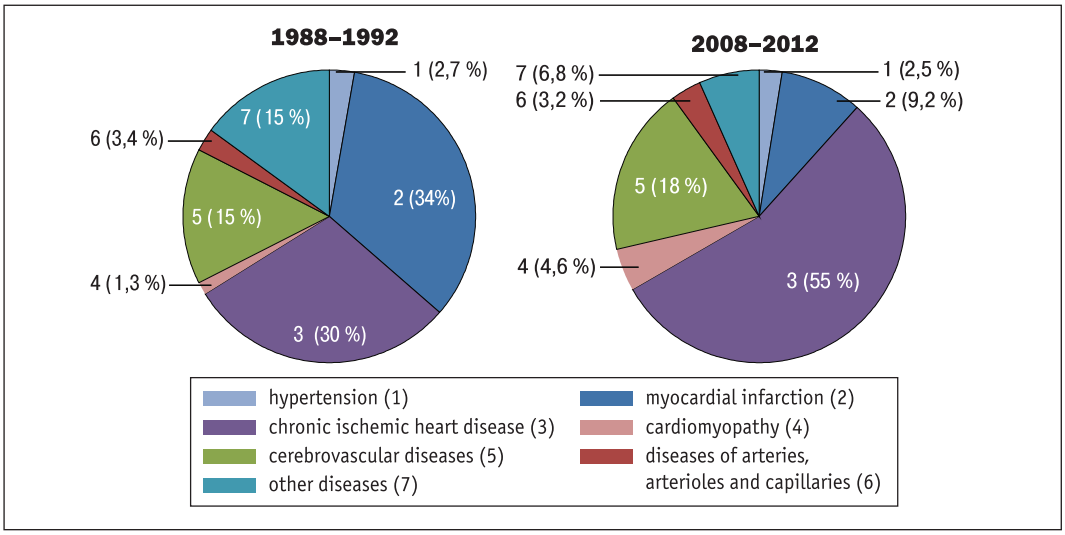


Figure 11.7. Structure of causes of death from circulatory diseases in the cohort of clean-up workers 1986–1987 for the periods 1988–1992 and 2008–2012 (%)

11.1.2. Nontumor incidence

Figure 11.8 shows the dynamics of nontumor incidence in the cohort of clean-up workers 1986–1987 depending on age at time of exposure by 5-year observation periods. The highest incidence was found in both age groups for the periods 1998–2002 and 2003–2007, i.e. 12–21 years after the Chornobyl accident. Pathology rates among people aged 40–60 are significantly higher than those of clean-up workers aged 18–39 at the time of exposure throughout the study. Figure 11.9 presents the structure of nontumor incidence among clean-up workers 1986–1987 with regard to the age at the time of exposure, observation periods 1988–1992 and 2008–2012.

In the first observation period, diseases of the nervous system, digestive and circulatory diseases made the greatest contribution to nontumor pathology in clean-up workers aged 18–39 at the time of exposure. Far less is the contribution of endocrine, nutritional and metabolic diseases, diseases of the musculoskeletal system, mental and behavioral disorders, respiratory and genitourinary diseases. In 2008–2012, an increasing proportion of digestive, circulatory and respiratory diseases, diseases of the musculoskeletal and genitourinary systems was noted. In the late period, we noticed a pronounced decrease in the proportion of diseases of the nervous system (from 23.4 to 6.5%), endocrine, nutritional and metabolic diseases (from 10.8 to 7.5%), a particular decline in percentage of mental and behavioral disorders (from 7.2 to 1.3).

Among clean-up workers aged 40–60 at the time of exposure (1988–1992), circulatory diseases are leaders in the structure of nontumor pathology, digestive diseases occupy the second place, the third are diseases of the musculoskeletal and nervous systems, followed by respiratory diseases. Other classes (endocrine, nutritional and metabolic diseases; mental and behavioral disorders; genitourinary diseases) made far less contribution. In 2008–2012, we noted the highest proportion of digestive and circulatory diseases; percentage of diseases of the nervous system has decreased from 12.2 to 6.4%, that of mental and behavioral disorders – from 3.9 to 1.1%. The contribution of other classes has remained virtually unchanged.

When comparing nontumor incidence structure of clean-up workers of different ages (1988–1992), we noted much higher percentage of diseases of the nervous system (23.4 vs. 12.2%), endocrine, nutritional and metabolic diseases (10.8 vs. 5.2%), mental and behavioral disorders (7.2 vs 3.9%) in people aged 18–39 at the time of exposure. At observation period 1, in those aged 40–60 at the time of exposure as compared to the other age group we revealed greater contributions of circulatory (32.1 vs. 17.8%), musculoskeletal (12.3 vs. 8.8%) and respiratory (8.3 vs. 6.9%) diseases. Within 2008-2012, no significant differences were observed in the structure of nontumor pathology in both study groups.

Figures 11.10–11.18 present the dynamics of major classes of nontumor diseases in post-accident period.

Figure 11.10 shows the dynamics of respiratory diseases. The highest incidence rates in both age groups were observed in 1998–2002 and 2003–2007, in the latest observation period (2008–2012) rate decreases almost twice.

The highest incidence of digestive diseases was established among clean-up workers aged 18–39 at the time of exposure for periods 1998–2002 and 2003–2007, among older people – in 2003–2007 (Figure 11.11). Rates recorded in the initial (1988–1992) and the last (2008–2012) observation periods are almost identical in both age groups. Incidence among clean-up workers aged 40–60 at the time of exposure far exceeds that in younger people. The following diseases (gastric and duodenal ulcers, gastritis and duodenitis, chronic liver disease, diseases of the gallbladder, biliary tract and pancreas) contribute mostly to the structure of digestive diseases in clean-up workers.

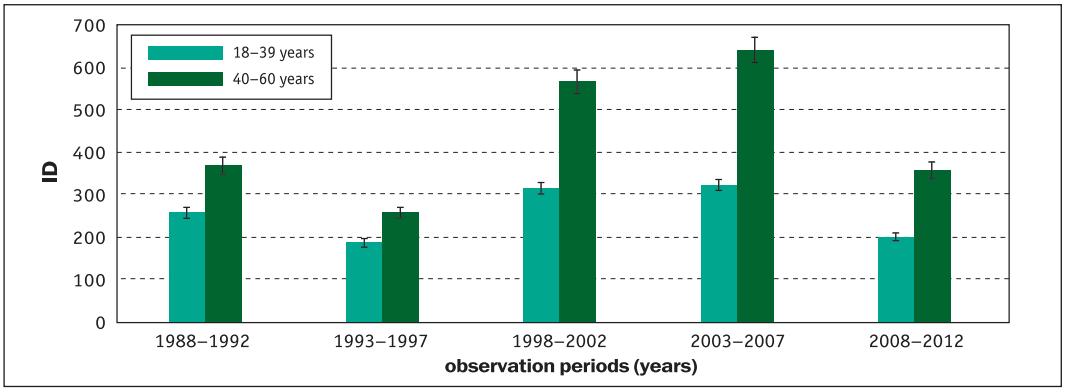


Figure 11.8. **Dynamics of nontumor incidence (ICD-9 code: 240.0-739.9, ICD-10 code: E00.0-N99.9) in clean-up workers 1986–1987 by five-year observation periods depending on age at the time of exposure (cases per 10^3 person-years)**

The dynamics of mental and behavioral disorders in clean-up workers depending on age at the time of exposure is shown in Figure 11.12. The dynamics of this class of diseases is quite different from that of other nontumor pathology. That is first due to higher rates in both age groups were revealed in an early observation period (1988– 1992), and with the passing of time after the accident the incidence drops dramatically. Second, the incidence in clean-up workers aged 18–39 at the time of exposure exceeded that of older people in all periods, with the exception of the last one (2008–2012). The following diseases (organic mental disorders, depression, anxiety and somatoform disorders, alcohol addiction etc.) dominate in the structure of the class.

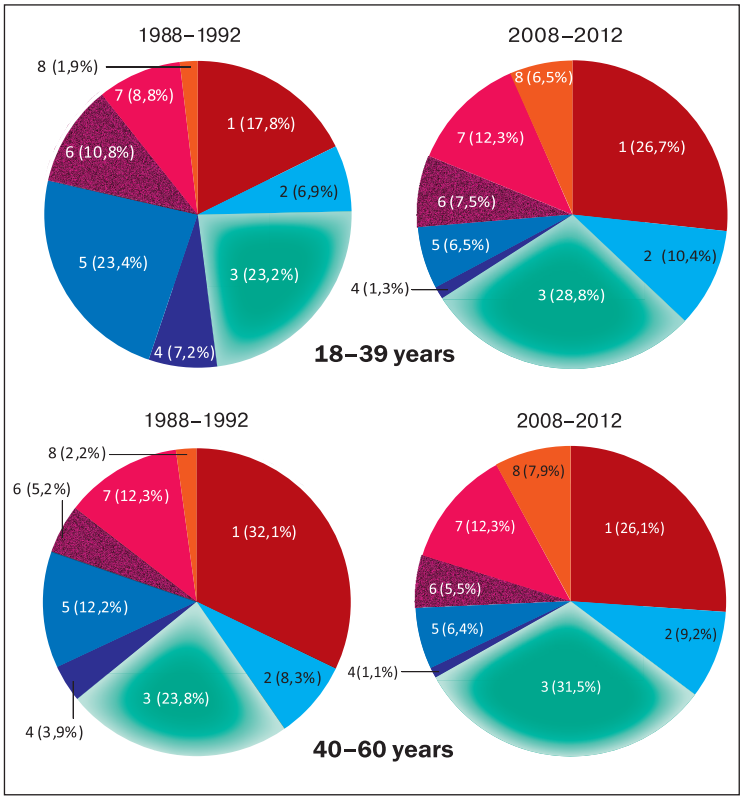


Figure 11.9. **Structure of nontumor incidence in clean-up workers 1986–1987 with regard for the age at the time of exposure, observation periods 1988–1992 and 2008–2012**

1 – circulatory diseases; 2 – respiratory diseases; 3 – digestive diseases; 4 – mental and behavioral disorders; 5 – diseases of the nervous system; 6 – endocrine, nutritional and metabolic diseases; 7 – diseases of the musculoskeletal system; 8 – genitourinary diseases.

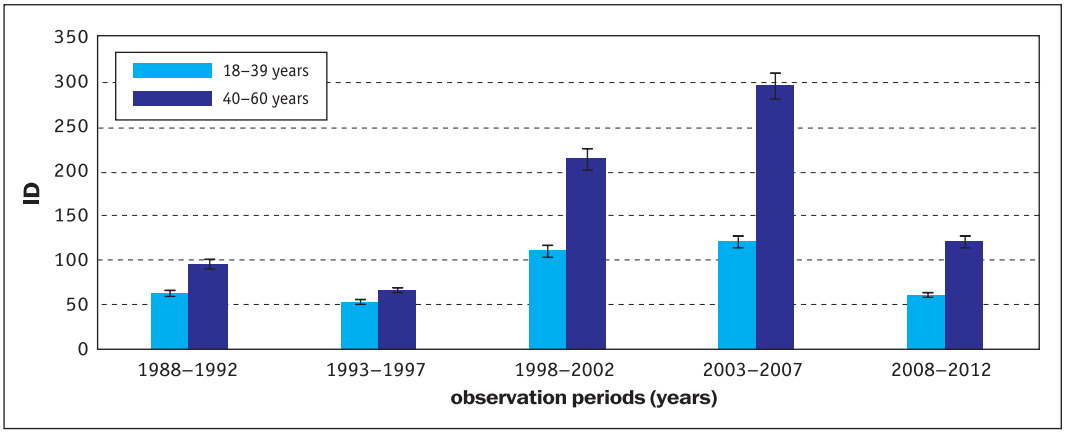


Figure 11.10. Dynamics of incidence of digestive diseases (ICD–9 code: 520.0–579.9, ICD–10 code: K00–K93) in clean-up workers 1986–1987 depending on age at the time of exposure

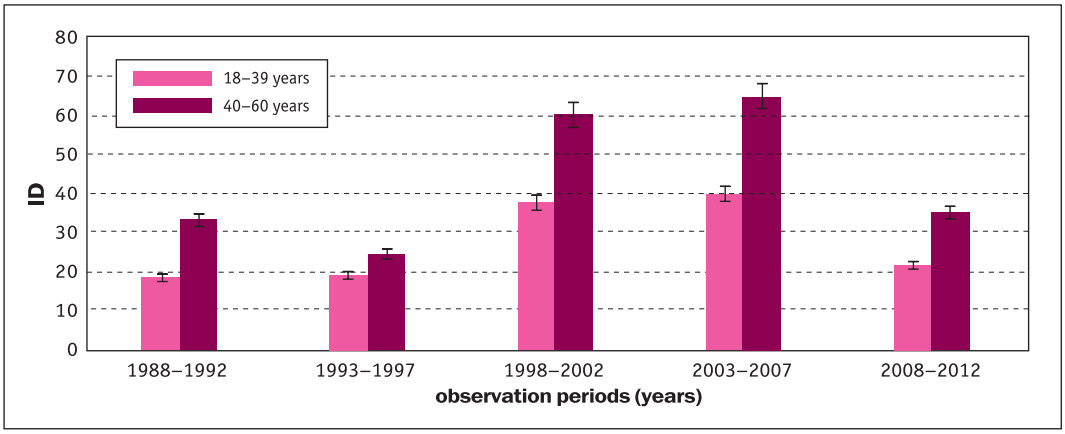


Figure 11.11. Dynamics of incidence of respiratory diseases (ICD–9 code: 460.0–519.9, ICD–10 code: J00–J99) in clean-up workers 1986–1987 depending on age at the time of exposure

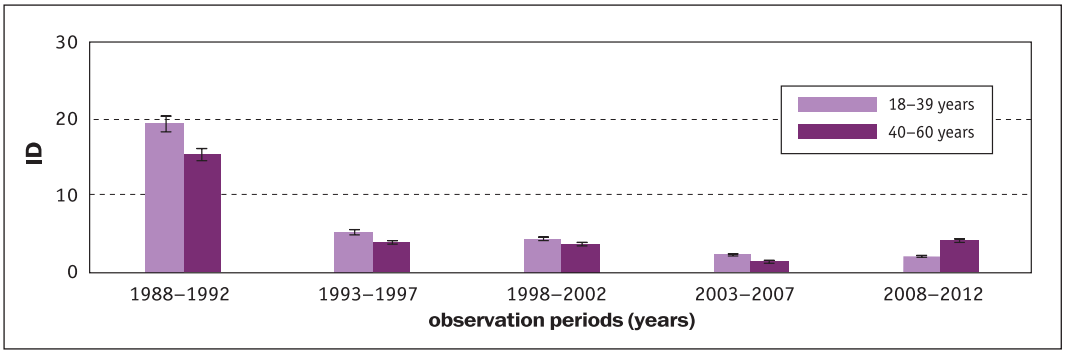


Figure 11.12. Dynamics of incidence of mental and behavioral disorders (ICD–9 code: 290–319, ICD–10 code: F00–F99) in clean-up workers 1986–1987 depending on age at the time of exposure

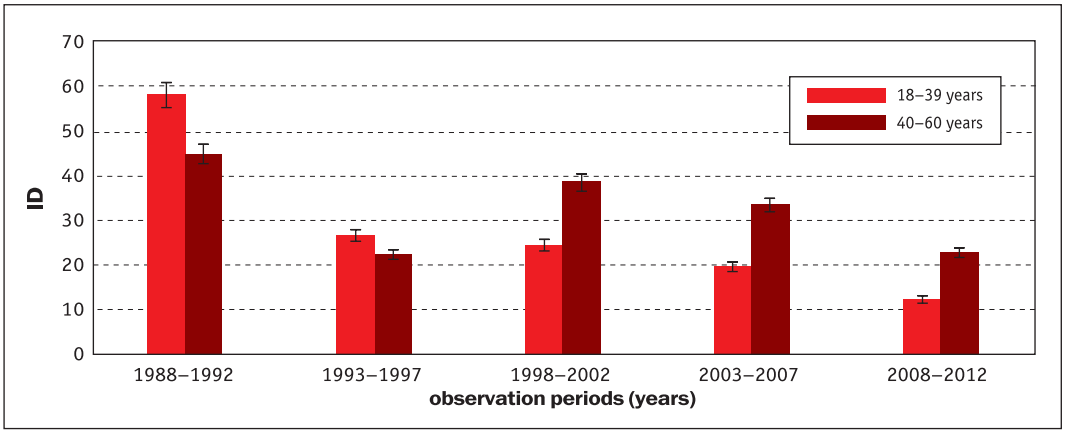


Figure 11.13. Dynamics of incidence of nervous system diseases (ICD–9 code: 320.0–359.9, ICD–10 code: G00–G99) among clean-up workers 1986–1987 depending on age at the time of exposure

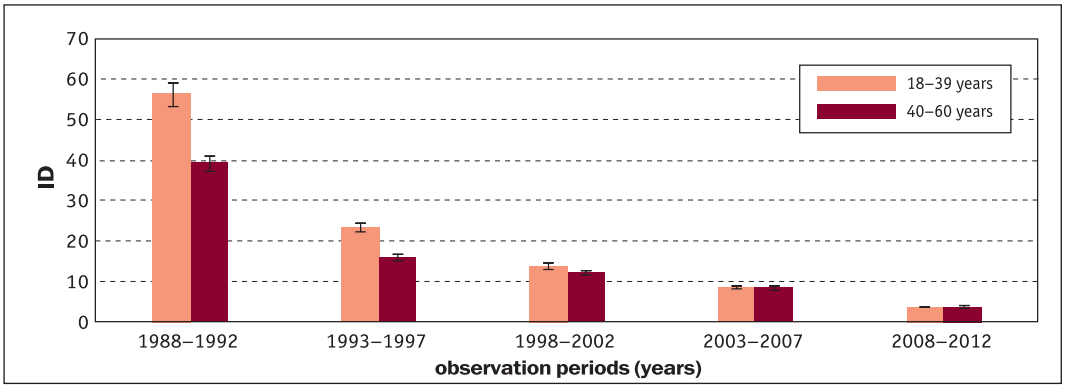


Figure 11.14. Dynamics of incidence of autonomic nervous system disorders among clean-up workers 1986–1987 depending on age at the time of exposure

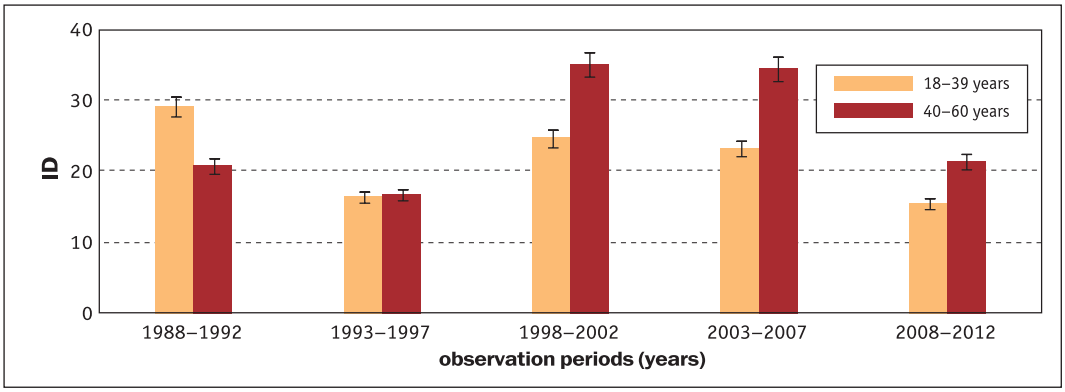


Figure 11.15. Dynamics of incidence of endocrine, nutritional and metabolic diseases (ICD–9 code: 240–269, ICD–10 code: E00–E90) among clean-up workers 1986–1987 depending on age at the time of exposure

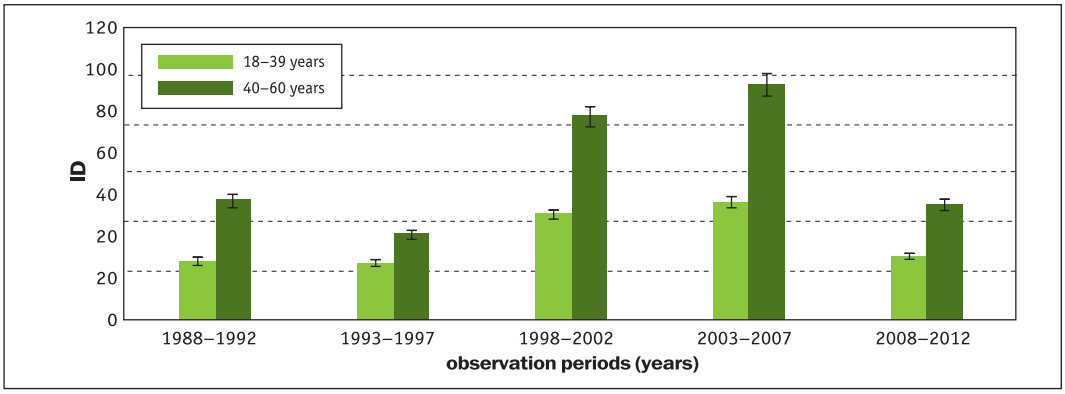


Figure 11.16. Dynamics of incidence of diseases of the musculoskeletal system and connective tissue (ICD–9 code: 710–739, ICD–10 code: M00–M99) in clean-up workers 1986–1987 depending on age at the time of exposure

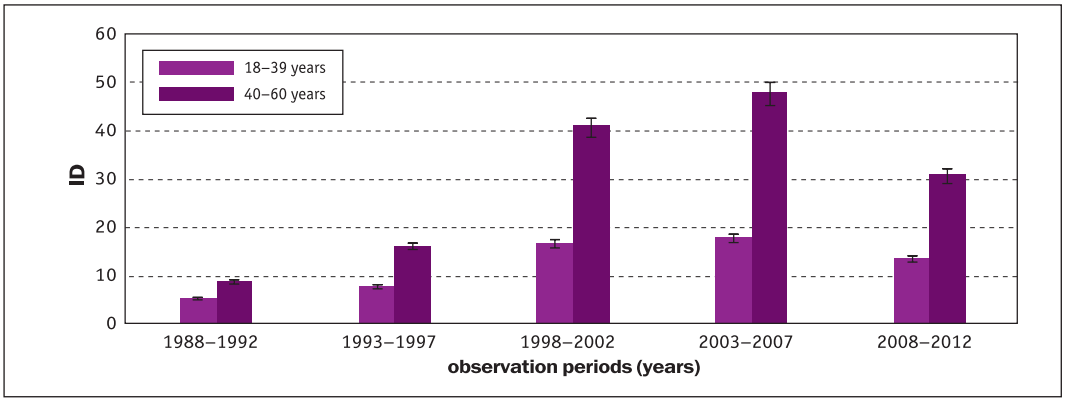


Figure 11.17. Dynamics of incidence of genitourinary diseases (ICD–9 code: 580–608.9, ICD–10 code: N00–N99) in clean–up workers 1986-1987 depending on age at the time of exposure

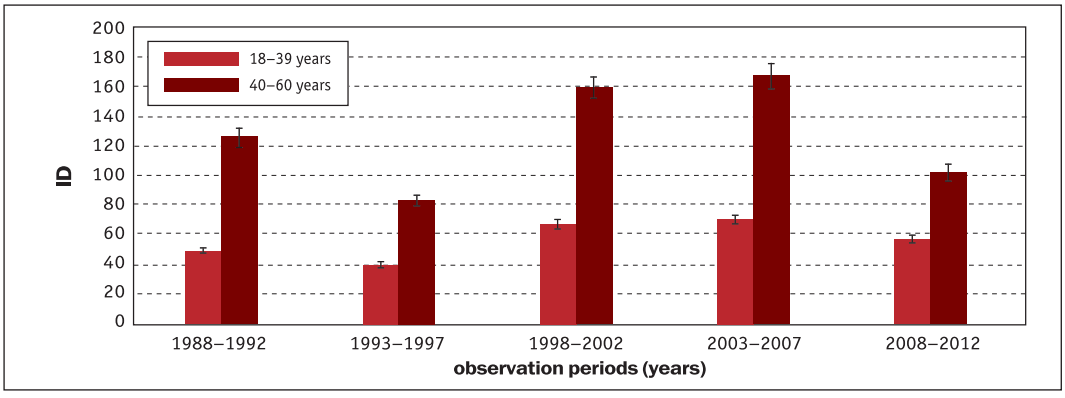


Figure 11.18. Dynamics of circulatory disease incidence (ICD–9 code: 390.0–459.9, ICD–10 code: I00–I99) among clean-up workers 1986–1987 depending on age at the time of exposure (cases per 10^3 person–years)

The highest rates of the nervous system diseases (Figure 11.13) in both age groups were observed in the first period (1988–1992). In clean-up workers aged 18–39 at the time of exposure, rates drop more than twice (1993–1997), and the downward trend in morbidity persists in subsequent periods. Among persons aged 40–60 at the time of exposure wave-like dynamics shows a decrease over the last period (2008–2012). It should also be noted that during the first 11 post-Chornobyl years (up to 1997) the rate of the nervous system diseases in younger age group of clean-up workers exceeds that in older people, while since 1998-2002 and up to date incidence in clean-up workers aged 40–60 at the time of exposure is much higher than that in younger people.

In the earlier periods of observation (1988–1992 and 1993–1997), disorders of the autonomic nervous system make up almost 90% in younger people and 80% in older clean-up workers (Figure 11.14). Since 1998–2002, rate of this pathology and its contribution to the structure of the class of the nervous system diseases (26% in younger and 15% in older age groups) has been reduced significantly. During 1988–2002, rate of the autonomic nervous system disorders in clean-up workers aged 18–39 at the time of exposure was higher than that among older people.

Figure 11.15 shows the dynamics of endocrine, nutritional and metabolic diseases. Among clean-up workers aged 18-39 at the time of exposure the highest rate is established in an early period (1988-1992). The rate decreases in 1993–1997, it is growing within 1998–2007 and drops again in the last period of observation (2008–2012). Similar dynamics is observed in older age group, whereas the highest rates were found in 1998–2002 and 2003–2007. In 1988–1992, incidence among clean-up workers aged 18–39 at the time of exposure is nearly 1.5 times higher than that in the older age group; in 1993–1997, rates are almost identical, while in periods 1998–2002, 2003–2007 and 2008–2012, incidence in older people exceeds that of younger age group. Thyroid diseases and diabetes are the major contributors to the structure of endocrine pathology.

Figure 11.16 presents the dynamics of diseases of the musculoskeletal system and connective tissue in clean-up workers 1986–1987 depending on age at the time of exposure. Among clean-up workers aged 18–39 at the time of exposure, rate of diseases of the musculoskeletal system and connective tissue has been growing over twenty post-Chornobyl years and peaked in 2003–2007, some decline was recorded in the last period of observation (2008–2012). Among people aged 40–60 at the time of exposure, the dynamics is represented by a wave curve, with the highest rate of incidence in 2003–2007, it fell in recent years. Throughout the study period, rate of diseases of the musculoskeletal system and connective tissue among older clean-up workers substantially exceeds that in younger people.

The dynamics of genitourinary diseases in clean-up workers 1986–1987 depending on age at the time of exposure is shown in Figure 11.17. In both age groups, a gradual increase in incidence rates is noted for the periods 1988–1992, 1993–1997 and 1998–2002, with the peak in 2003–2007, and decline in recent years of observation (2008–2012). Throughout the study period, the rate of genitourinary diseases in older clean-up workers substantially exceeds that in younger people.

As mentioned above, circulatory diseases make major contribution to the formation of non-tumor incidence among clean-up workers. The dynamics of circulatory diseases is shown in Figure 11.18. The highest incidence in both age groups of clean-up workers was observed in 1998–2002 and 2003–2007, i.e. 12–21 years after the Chornobyl accident. Throughout the study, rates of cardiovascular disease in people aged 40-60 are much higher than those among clean-up workers aged 18–39 at the time of exposure. In the early period (1988–1992), incidence in older clean-up workers was nearly three times higher than that for younger people. In the late period (2008–2012), incidence among clean-up workers aged 18–39 at the time of

exposure remains high, whereas in persons aged 40–60 at the time of exposure there is a slight decline; it is due to manifestation of the pathology in earlier periods.

The following diseases (ischemic heart disease, hypertension, cerebrovascular diseases, diseases of arteries, arterioles and capillaries, diseases of veins, lymphatic vessels and lymph nodes) dominate in the structure of circulatory diseases. Figure 11.19 represents the dynamics of rates for specified nosological groups among clean-up workers depending on age-at-exposure. Over 11 post-accident years (1988–1997), incidence of hypertension in people aged 18–39 at the time of exposure is much higher than that of other diseases. In the first period of observation (1988–1992), we recorded the highest rate of hypertension (nearly 27 ‰), which is five times higher than incidence of ischemic heart disease and venous diseases, and 18 times higher than that of cerebrovascular diseases and diseases of the arteries. In the remote post-accident period, the consistently high incidence of hypertension ranks second in the structure of cardiovascular pathology. A significant increase in rates of ischemic heart disease and cerebrovascular diseases was found throughout the observation period, with maximum rates recorded within the periods 1998–2002, 2003–2007 and 2008–2012. Since the third period of observation (1998–2002), ischemic heart disease is the leader in the structure of circulatory diseases in younger age group of clean-up workers. It is quite possible that rapid development of the disease started twelve years after the Chornobyl accident and is still in progress. Rates of diseases of arteries and veins also increased in the dynamics of observation but more slowly.

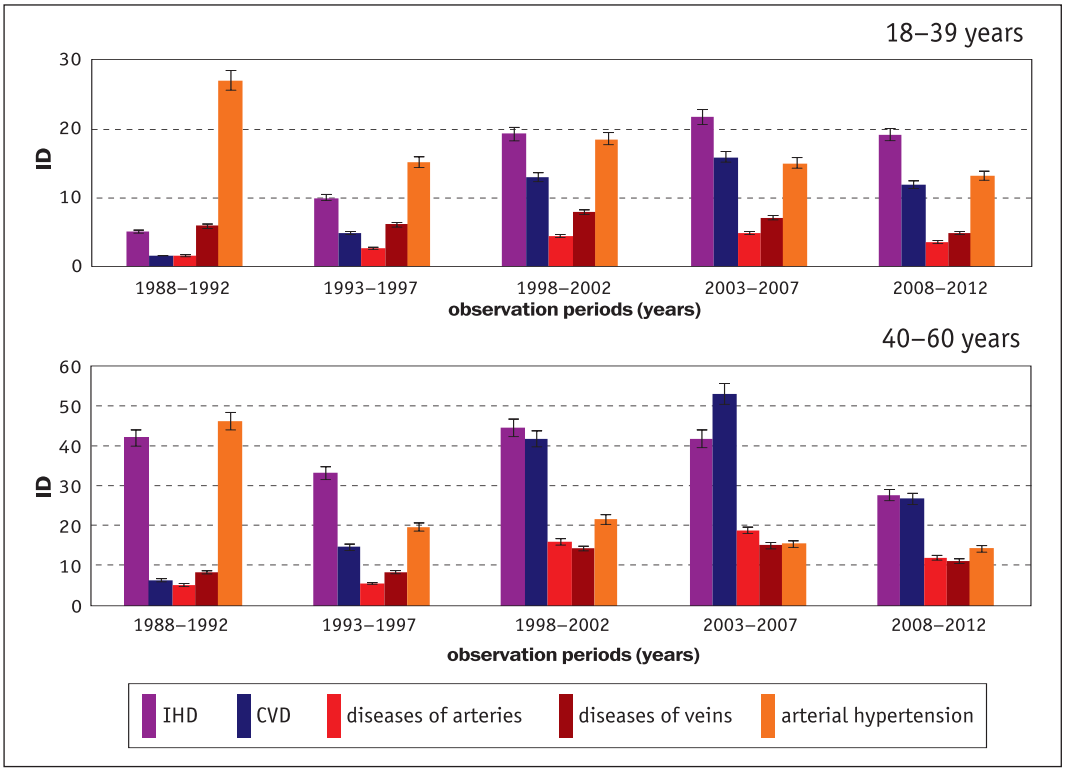


Figure 11.19. Dynamics of incidence of some nosological groups of circulatory diseases (ICD–9 code: 390.0–459.9, ICD–10 code: I00–I99) among clean-up workers 1986–1987 depending on age at the time of exposure (cases per 10^3 person–years)

In early post-accident period (1988–1992), incidence of hypertension and ischemic heart disease among clean-up workers aged 40–60 at the time of exposure was 4 to 7 times higher than that of cerebrovascular diseases and diseases of arteries and veins. In subsequent periods, incidence of hypertension decreased by a factor of 2–2.5. The highest rates of ischemic heart disease in older people, unlike the younger ones, were established in 1988–1992, 1998–2002 and 2003–2007, whereas in the late period (2008–2012) the rate slightly decreased. Within twenty years after the accident, cerebrovascular incidence has been growing and reached the maximum rate in 2003–2007; it decreased almost twice in 2008–2012. Rates of diseases of arteries and veins in the earlier periods (1988–1992, 1993–1997) are virtually unchanged, some increase was observed in 1998–2002 and 2003–2007, in the latest one, the incidence goes down.

11.1.3. Cardiovascular morbidity. Effects of radiation exposure.

Figure 11.20 presents the dynamics of circulatory disease incidence among clean-up workers 1986–1987 depending on whole body external dose and age-at-exposure. The highest incidence rates in both age groups of clean-up workers with different doses of whole body external radiation were established in 1998–2002 and 2003–2007, that is 12–21 years after the Chornobyl accident. The dynamics is represented by a wave curve with a gradual increase over 21 years after exposure and an evident decline in 2008–2012, which can be explained by manifestation of pathology in

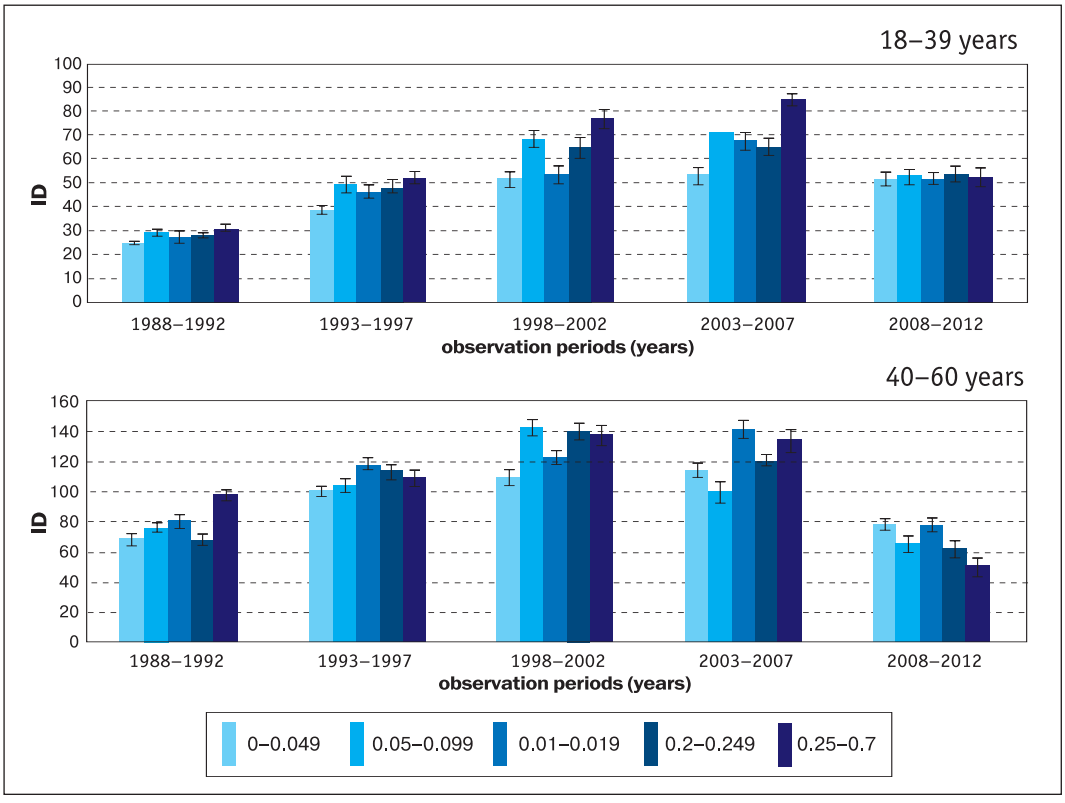


Figure 11.20. **Dynamics of circulatory disease incidence among clean-up workers 1986–1987 depending on whole body external dose and age at the time of exposure (cases per 10^3 person–years)**

earlier periods. Rates of cardiovascular pathology in people aged 40–60 are much higher than those for clean-up workers aged 18–39 at the time of exposure throughout the study, except for the late period (2008–2012) when they are virtually identical. In the first period (1988–1992), rate of incidence among older clean-up workers is almost 3 times higher than that in younger people. During 1988–2007, a significant increase in rates was found among clean-up workers aged 18–39 at the time of exposure (whole body radiation dose 0.25–0.7 Gy as opposed to dose group 0–0.049 Gy); in the late period of observation (2008–2012) incidence rates among patients with different radiation doses were nearly identical. A similar trend is observed among older people.

11.1.4 Results of risk-analysis

We conducted analytical study and risk assessment in the cohort of clean-up workers 1986–1987 to determine the effect of radiation and some non-radiation factors on the development of circulatory diseases over 25-year post-accident period. Subgroup with whole body external doses 0–0.05 Gy was taken as a control. The significant relative risks for ischemic heart disease, cerebrovascular diseases, diseases of arteries, arterioles and capillaries, diseases of veins, lymphatic vessels and lymph nodes were found in the range of whole body external doses 0.05–1.0 Gy. More stable risk estimates were obtained for clean-up workers under age 40 at the

Table 11.3

Risks for the development of circulatory diseases among clean-up workers 1986-1987 depending on whole body external dose and age at the time of exposure over twenty five postaccident years (in Italics RRY with 90% CI)

Dose (Gy)	under age 40 at the time of exposure		aged 40–60 at the time of exposure	
	RRY (95% CI)	ERR (Gy^{-1})	RRY (95% CI)	ERR (Gy^{-1})
Diseases of the circulatory system (ICD-10 code: I00.0–I99.9)				
0.05 – 0.099	**1.35 (1.32; 1.37**)	4.17 (4.13; 4.2)	1 (0.91; 1.1)	
0.1 – 0.199	**1.19 (1.11; 1.27)**	1.27 (1.25; 1.28)	**1.12 (1.1; 1.18)**	0.8 (0.75; 0.85)
0.2 – 0.249	**1.18 (1,16; 1,2)**	0.8 (0.74; 0.83)	*1.07 (0.96; 1.2)*	
0.25 – 0.7	**1.37 (1,14; 1,34)**	1.41 (1.39; 1.46)	**1.15 (1.02; 1.3)**	0.53 (0.47; 0.59)
Ischemic heart disease (ICD-10 code: I20.0–I25.0)				
0.05 – 0.099	**1.38 (1.33; 1.42)**	4.52 (4.49; 4.55)	0.87 (0.75; 1.0)	
0.1 – 0.199	**1.18 (1.02; 1.36)**	1.2 (1.18; 1.22)	0.99 (0.92; 1.1)	
0.2 – 0.249	**1.27 (1.23; 1.32)**	1.22 (1,2; 1.24)	0.95 (0.8; 1.13)	
0.25 – 0.7	**1.32 (1.27; 1.37)**	1.24 (1.2; 1.26)	0.96 (0.8; 1.16)	
Cerebrovascular diseases (ICD-10 code: I60.0–I69)				
0.05 – 0.099	**1.27 (1.22; 1.33)**	3.2 (3.18; 3.24)	0.92 (0.76;1.1)	
0.1 – 0.199	*1.01 (0.83; 1.22)*		*1.06 (0.95; 1.2)*	
0.2 – 0.249	**1.07 (1.02; 1.12)**	0.32 (0.3; 0.33)	*1.07 (0.86; 1.3)*	
0.25 – 0.7	**1.51 (1.44; 1.59)**	1.97 (1.93; 2)	*1.18 (0.9; 1.48)*	
Diseases of arteries, arterioles and capillaries (ICD-10 code: I70.0–I79.8)				
0.05 – 0.099	**1.48 (1.38; 1.59)**	5.71 (5,68; 5 75)	0.97 (0.7; 1.32)	
0.1 – 0.199	*1.22 (0.9; 1.65)*		*1.1 (0.9; 1.32)*	
0.2 – 0.249	**1.14 (1.07; 1.23)**	0.63 (0.62; 0.64)	0.92 (0.6; 1.32)	
0.25 – 0.7	**1.65 (1.52; 1.78)**	2.51 (2.47; 2.54)	**1.44 (1.01; 2.06)**	1.56 (1.47; 1.65)
Diseases of veins, lymphatic vessels and lymph nodes (ICD-10 code: I80.0–I89.9)				
0.05 – 0.099	**1.39 (1.32; 1.46)**	4.6 (4.61; 4.67)	*1.24 (0.93; 1.64)*	
0.1 – 0.199	*1.2 (0.97; 1.49)*		*1.3 (0.9; 1.72)*	
0.2 – 0.249	**1.18 (1.12; 1.24)**	0.8 (0.79; 0.83)	*1.25 (0.9; 1.72)*	
0.25 – 0.7	**1.4 (1.32; 1.48)**	1.54 (1.51; 1.57)	**1.45 (1.03; 2.02)**	1.6 (1.5; 1.69)

time of exposure with doses 0.05–0.7 Gy and in older age group at doses 0.25–0.7 Gy (Table 11.3). The results obtained support the conclusion that younger people are far more sensitive to ionizing radiation. However, this fact requires further investigation.

It is noted that risks for circulatory diseases are largely due to the impact of non-radiation factors such as adverse working conditions before the Chornobyl accident, emotional overstrain, physical activity, smoking, alcohol abuse, malnutrition and heredity. The combined effects of radiation and nonradiation factors may significantly exceed that of radiation itself.

* * *

Data submitted here is the result of long-term cohort epidemiological studies on health of clean-up workers 1986–1987. The subject matter of our investigation is nontumor morbidity, disability, nontumor mortality, effect of low doses of external ionizing radiation on the development of cerebrovascular pathology.

We used the database of the State Registry of Ukraine of Persons Affected by the Chornobyl accident as the source of information. Research period is 26 post-accident years (1988–2012).

Our findings are sufficient to allow definite conclusions.

Post-accident period was marked by significant health deterioration in the Chornobyl clean-up workers. Over 26 years after the Chornobyl accident, the proportion of healthy and practically healthy people has fallen from 68% in 1988 to 5.5% in 2012. The reduction is due to growth of a wide range of non-tumor diseases, especially circulatory, digestive, respiratory diseases, diseases of the nervous, endocrine and genitourinary systems.

We have found the increase in disability (up to 250 cases per 1,000 people in 2012) due to the development of nontumor pathology. Almost 90% of disability cases reported in 2012 were likely to be Chornobyl-related. Major contribution (63%) to the structure of causes of disability make circulatory diseases, diseases of the nervous system occupy the second place (13.3%), and the digestive diseases rank third (6.7%).

Death rate due to nontumor diseases has increased significantly in post-accident period. Circulatory diseases are the major contributor (82%) to the structure of causes of death, digestive diseases occupy the second place (9.7%), respiratory diseases rank third (5.1%), and the fourth (3.2%) come other nontumor diseases.

When studying the dynamics of nontumor diseases, we have found that in 1988–1992 the highest, throughout post-accident period, rate of mental and behavioral disorders, diseases of the nervous system was mainly due to disorders of the autonomic nervous system. Since 1993–1997, rate of this pathology has significantly reduced and remained stable in subsequent years of observation. Thus, we can assume that in the early post-accident period, stress factor in combination with radiation one had the greatest impact on health of clean-up workers; resulting in manifestation of other nontumor diseases in the remote post-radiation period.

Descriptive epidemiological studies found a significant increase in circulatory diseases among clean-up workers, primarily cerebrovascular diseases (due to the increase in stroke, cerebral infarction, cerebral atherosclerosis, hypertensive encephalopathy), ischemic heart disease (owing to the increase in chronic ischemic heart disease, acute myocardial infarction, angina pectoris), hypertension, diseases of arteries, arterioles and capillaries (owing to the increase in the incidence of atherosclerosis, embolism, arterial thrombosis), diseases of veins and lymphatic vessels (phlebitis and thrombophlebitis, thrombosis and venous embolism). An increased incidence rate was established 12–16 years after exposure, this has led us to believe that there might be a latent period for the development of this pathology.

The results of cardiovascular risk-analysis revealed certain dose-dependent effects. Significant values of relative risks were found in the range of whole body external doses 0.05–0.7 Gy.

However, it should be noted that more stable values of risks and excess relative risks were observed at doses 0.25–0.7 Gy.

It was found that younger people are more sensitive to ionizing radiation. However, this requires further investigation.

The data obtained are fully consistent with findings of the research on the results of health monitoring of hibakusha victims of the atomic bombings of Hiroshima and Nagasaki [10–11]; significant relative risks for some circulatory diseases among clean-up workers were confirmed by studies of Russian scientists [12–13]. Despite the fact that sufficient data has now been accumulated to serve as a reliable evidence of the effect of small doses of ionizing radiation (both external and internal) on the development of nontumor diseases (especially cardiovascular and cerebrovascular), there is no consensus on the issue. Therefore, further investigations are still relevant and important.

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11.2. RADIATION AND NON-RADIATION RISK FACTORS FOR THE DEVELOPMENT OF CIRCULATORY DISEASES AMONG CHORNOBYL CLEAN-UP WORKERS. RESULTS OF CLINICAL AND EPIDEMIOLOGICAL STUDY

Circulatory diseases (CD) being the leading causes of disability and mortality among population require substantial financial costs for treatment and rehabilitation. As a result of the Chornobyl accident, some other risk factors for circulatory diseases (primarily the radiation one) were added [1–2]. Assessment of the role of radiation and non-radiation factors as the causes of the pathology among Chornobyl survivors, causes of the increased nontumor incidence within postaccident period [3–4] is very important to determine medical and biological consequences of the accident and arguments in support of preventive measures.

Impact of radiation and nonradiation factors on the development of circulatory diseases among Chornobyl clean-up workers was determined using the data of clinical and epidemiological registry, NRCRM (CER). Under the unified protocol CER accumulates the results of long-term medical monitoring being held in Polyclinic of Radiation Registry since 1992. Monitoring program provides complex medical examinations, documented individual doses of whole body external radiation, standardized survey data on working and life conditions etc.

We investigated radiation and non-radiation risks for circulatory diseases in the cohort of clean-up workers 1986–1987 (8625 males, including 3623 men with whole body external doses). Observation period is 1993–2012. When estimating incidence and risks we accounted for the cases of newly diagnosed diseases. To calculate radiation risks we used person-years at risk since exposure, clean-up workers with doses < 0.05 Gy as a control.

The majority (63.1%) of clean-up workers started their activities in the area in April-June, 1986. Clean-up workers' mean age at the time of exposure was 37.8 years, 64.8% being younger 40. The average dose due to whole body external exposure was 0.254 Gy. Figure 11.21 presents cohort structure depending on age at the time of exposure and whole body external dose.

According to self-assessment, 94% of clean-up workers (respondents) considered themselves healthy before the accident. During observation the majority of clean-up workers assessed their health as satisfactory or poor; since 2003 percentage of people category 1 («satisfactory» health) exceeds that of category 2 («poor» health) (Figure 11.22).

In 1993, during the first medical examination in CER, cardiologist diagnosed cardiovascular disease among 43% of clean-up workers, neurologist identified cerebrovascular disease in 21%

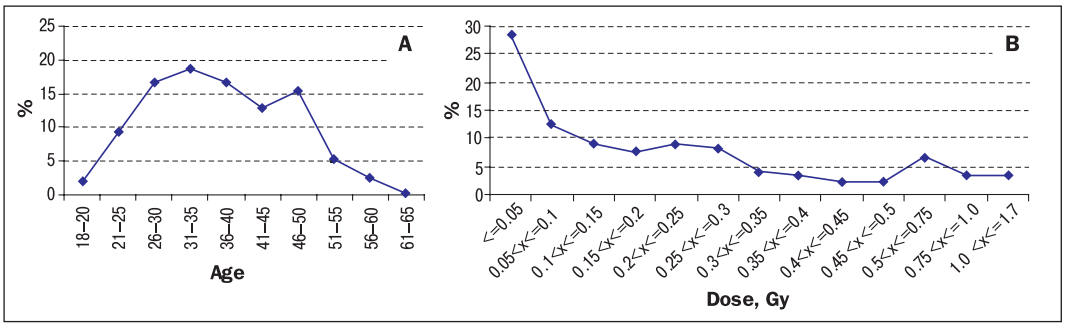


Figure 11.21. **Structure of clean-up workers cohort depending on age at the time of exposure (A) and dose of external radiation (B) (CER data)**

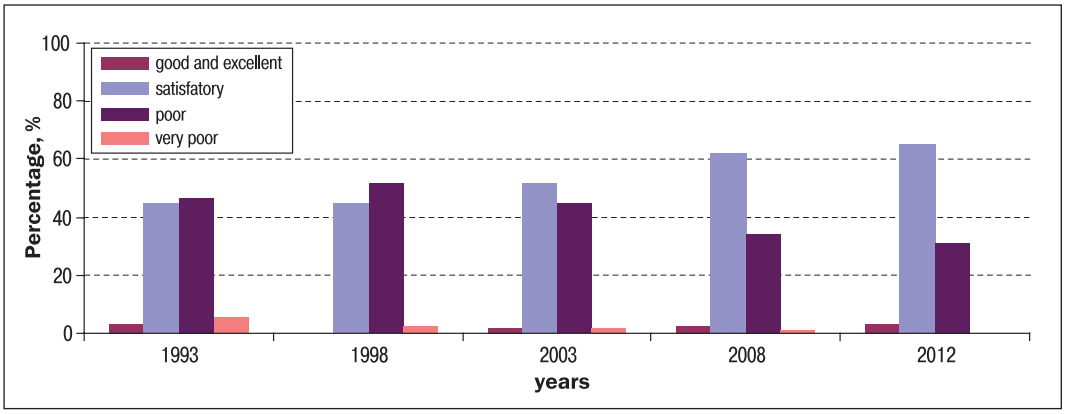


Figure 11.22. Self-assessment of clean-up workers' health over observation period in Clinical and Epidemiological Registry, NRCRM

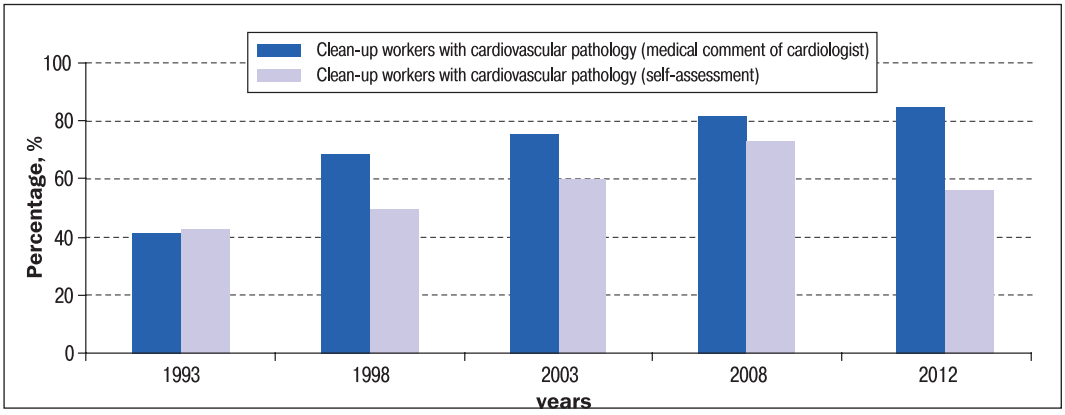


Figure 11.23. Percentage of clean-up workers with chronic circulatory diseases (CER data)

of them. That is about the same number of clean-up workers fell ill after exposure (relative to self-assessment before the accident). During follow-up in CER system about 90% of clean-up workers were found to be diseased (Figure 11.23). With respect to self-assessment, the percentage of unhealthy clean-up workers increases with time though it is less than that revealed by cardiologist (except for the initial period). As is apparent from the data, clean-up workers tend to underestimate their health problems.

Incidence

Over observation period, 8359 newly diagnosed circulatory diseases were recorded among male clean-up workers 1986–1987 (with and without doses) in Clinical and Epidemiological Registry. It is about 27% of all newly diagnosed nontumor diseases. Cerebrovascular diseases (CVD) and hypertention prevail in the structure of circulatory diseases. Cardiomyopathy, ischemic heart disease (IHD) and atherosclerosis rank third, fourth and fifth, respectively (Figure 11.24).

Among clean-up workers, the following diseases (essential hypertension (65.5%), hypertensive heart disease (19.8%) and secondary hypertension (14.7)) prevail among newly diagnosed

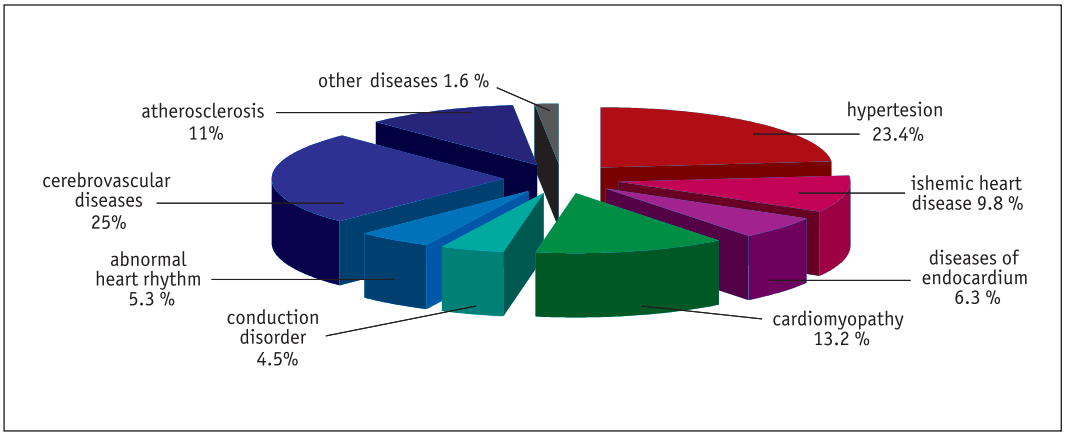


Figure 11.24. Structure of newly diagnosed circulatory diseases among Chornobyl male clean-up workers, follow-up period in CER system

cases of hypertension. IHD and CVD are represented by chronic forms of the pathology (94.6% and 98.1%, respectively). Atherosclerotic heart disease (66.2%) and angina pectoris (26.6%) are basic forms of IHD. There are cerebral atherosclerosis (27.6%), cerebral ischemia (18.1%), hypertensive encephalopathy (6.5%) and ill-defined and unspecified CVD (45.2%) in the structure of chronic CVD.

We determined differences in structure and rates of the incidence among clean-up workers of two age groups – those exposed under age 40 and at age 40 and older (Table 11.4). Incidence and percentage of essential hypertension among younger at the time of exposure clean-up workers are higher by the factor 3.5, and those of secondary hypertension, on the contrary, are 3 times lower. Among people exposed at age 40 and older as compared to those exposed under age 40, incidence and percentage of IHD, CVD and atherosclerosis are higher by the factor 1.7, 1.5, 1.3, respectively; while those of cardiomyopathy are lower by the factor 2.2.

An increase in the prevalence of circulatory diseases, primarily CVD, hypertension, IHD and atherosclerosis was recorded in the dynamics of monitoring of clean-up workers (Figure 11.25).

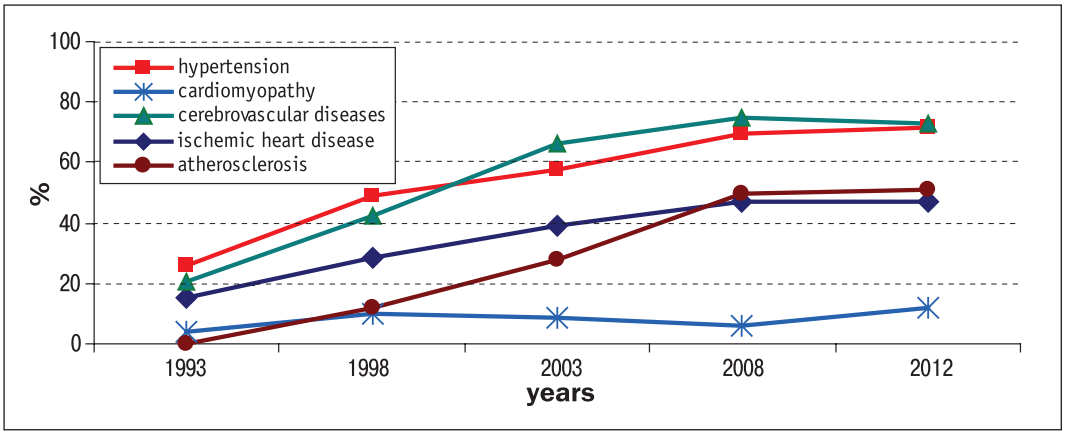


Figure 11.25. Prevalence of circulatory diseases among Chornobyl clean-up workers 1986-1987 in the course of monitoring within framework of CER, NRCRM

Table 11.4

Structure (%) and circulatory disease incidence rate among clean-up workers exposed under age 40, at age 40 and older (CER data)

Disease	ICD-9 code	IDC-10 code	Percentage,%		Incidence per 1000 person-years	
			Under age 40	40 years and older	Under age 40	40 years and older
CIRCULATORY DISEASES	390–459	I00–I99	100	100	164.9±4	169.6±5.4
Hypertension, including:	401–405	I10–I15	26.1	14.7	43.2±1.6	*24.8±1.5
➤ essential hypertension	401	I10	20.3	5.7	33.5±1.4	*9.6±1.0
➤ hypertensive heart disease	402	I11	4.0	3.6	6,6±0.6	6.0±0.8
➤ secondary hypertension	405	I15	1.8	5.4	3.0±0.4	*9.2±0.9
Ischemic heart diseases, including:	410–414	I20–I25	8.1	13.5	13.4±0.9	*22.8±1.5
➤ angina pectoris	413	I20	2.6	3.9	4.4±0.5	*6.6±0.8
➤ chronic ischemic heart disease, including:	414	I25	5.2	8.8	8.6±0.7	*14.8±1.2
➤ atherosclerotic heart disease	414.0	I25.0–25.1	5.0	8.5	8.2±0.7	*14.3±1.2
Other (chronic) diseases of endocardium	424	I34–I38	6.0	5.8	10.0±0.8	9.8±1.0
Cardiomyopathy	425	I42	17.7	7.9	29.2±1.3	*13.3±1.1
Conduction disorder	426	I44–I45	4.5	4.2	7.4±0.7	7.2±0.8
Abnormal heart rhythm	427	I47–I49	4.6	6.7	7.5±0.7	*11.3±1.0
Cerebrovascular diseases, including:	430–438	I60 – I69	22.4	34.4	36.4±1.4	*58.9±2.3
➤ other (chronic) CVD diseases, including:	437	I67	21.9	33.7	35.6±1.4	57.7±2.3
➢ cerebral atherosclerosis	437.0	I67.2	4.0	13.1	6.5±0.6	*22.5±1.5
➢ cerebral ischemia	437.1	I67.8	3.9	6.2	6.3±0.6	*10.7±1.0
➢ hypertensive encephalopathy	437.2	I67.4	1.5	2.1	2.4±0.4	3.6±0.6
Other ill-defined and unspecified CVD	437.8–437.9	I67.9	12.3	11.9	20.1±1.6	*20.4±2.0
Consequences of (acute) CVD	438	I69	0.4	0.7	0.7±0.2	1.2±0.3
Diseases of arteries, arterioles and capillaries, including:	440–448	I70–I79	9.0	11.5	14.8±0.9	*19.4±1.3
➤ atherosclerosis	440	I70	9.0	11.3	14.8±0.9	*19.1±1.3
Other newly diagnosed circulatory diseases			1.6	1.5	3.0	2.1

Notes. * – Statistically significant difference in incidence.

Non-radiation risk factors

Increased prevalence of circulatory diseases over time (Figure 11.25), and excess incidence in older age-at-exposure group of clean-up workers compared to those exposed under age 40 (Table 11.4) comply with age peculiarities of the disease development (Figure 11.26, Table 11.5).

Table 11.5 shows dependence of circulatory disease incidence on age at the time of examination.

The highest statistically significant relative risks were identified for hypertension, IHD and CVD. Dependence of circulatory disease incidence on age at the time of medical examination is tabulated in Table 11.5. As is apparent from the Table, among clean-up workers aged 50–59 as compared with those aged 30–39, absolute risk for IHD is higher by a factor of 7.4 and for CVD by a factor of 5.2.

The results of clinical and epidemiological study suggest probable impact of other non-radiation factors on the formation of circulatory diseases (Table 11.6).

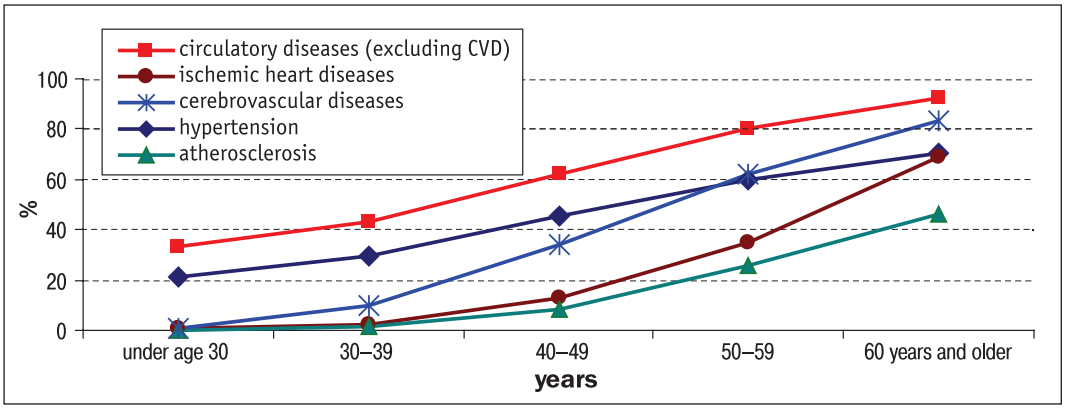


Figure 11.26. **Prevalence of circulatory diseases among Chornobyl clean-up workers 1986–1987 depending on age at the time of examination in CER system, NRCRM**

Table 11.5

Relative risks (RR and 95% CI) for some forms of circulatory diseases in different age groups of clean-up workers compared with that aged 30–39 (CER data)

Disease	Age at the time of medical examination, years		
	40–49	50–59	60 and older
Hypertensive heart disease	1.8 (1.3; 2.2)	5.3 (3.5; 19.0)	3.2 (1.95l 7.2)
Secondary hypertension	2.8 (1.2; 6.4)	10.3 (5.3; 20.1)	14.8 (8.05; 27.4)
Ischemic heart disease	4.6 (2.9; 10.7)	7.5 (4.9; 11.1)	7.9 (5.2; 11.8)
Angina pectoris	5.4 (2.2; 13.2)	14.5 (6.9; 30.4)	14.7 (6.9; 31.1)
Cardiomyopathy	1.3 (1.15; 4.2)	1.6 (1.4: 11.9)	1.3 (1.2; 5.5)
CVD	2.4 (1.8; 6.2)	5,2 (4.03; 23.8)	7.7 (6.1; 40.5)
Diseases of arteries and arterioles	6.0 (3.3–10.7)	14.3 (8.7–23.5)	16.1 (10.1–25.7)

Table 11.6

Statistically significant (95% CI) relative risks (RRs) for main circulatory diseases in the cohort of clean-up workers 1986–1987 depending on some exogenous non-radiation factors

Disease	Adverse working conditions before the accident	Emotional overstrain	Smoking	Alcohol abuse	Lack of physical activity	Malnutrition
Hypertension	2.3 (1.3; 4.4)	2.1 (1.4; 3.2)	1.6 (1.2; 2.3)	1.9 (1.5; 2.5)	1.4 (1,2; 1.5)	2.9 (2.6; 3.2)
IHD	1.7 (1.3; 2.2)	4.5 (2.9; 7.0)	2,6 (1.6; 4.6)		1.7 (1.1; 2.7)	
Cardiomyopathy	1.7 (1.1; 2.7)	1.4 (1.1; 1.8)		1.3 (1.2; 1.4)	1.4 (1.2; 1.6)	1,6 (1.3; 2.0)
CVD	1.5 (1.3; 1.8)	2.4 (1.6; 3.1)	1.9 (1.5; 2.3)		1.6 (1.4; 1.9)	1.5 (1,3; 1.9)

Incidence of cerebrovascular diseases, IHD and cardiomyopathy is significantly higher among clean-up workers with adverse working conditions in the past (mental stress, physical factors (noise, vibration, non-ionizing radiation), chemical factors etc.) compared with those having favorable working conditions.

Emotional overstrain increases frequency of some nontumor circulatory diseases under investigation. There are statistically significant (in the range 1.7–4.5) relative risks for CVD, IHD and hypertension among clean-up workers who are or were under stress due to constant conflicts at work or in the family, due to change of profession or job dissatisfaction. Among clean-up workers-smokers compared with nonsmokers or never smokers, incidence of CVD is higher by the factor 1.9, among ex-smokers that of hypertension is higher by the factor 1.6 and of IHD – by the factor 2.6. Among clean-up workers with alcohol abuse, significantly higher incidence of hypertension (by the factor 1.9) and of cardiomyopathy (by the factor 1.3) was reported. Dietary habits also contribute to the development of some forms of nontumor pathology. Higher occurrence of hypertension (by the factor 2.9) and cerebrovascular diseases (by the factor 1.5) was observed among salt food abusers. Physical overstrain out-of-work contribute essentially to the incidence of IHD and CVD (by the factor 1.7 and 1.6); an increased incidence of hypertention and cardiomyopathy was also observed. With lack of regular physical exercises such diseases as hypertension, IHD and CVD are most likely to occur (by the factor 1.3–1.7).

Endogenous risk factors contribute to the growth of circulatory diseases (Table 11.7).

Table 11.7

Some endogenous risk factors for circulatory diseases in the cohort of clean-up workers 1986–1987

Disease	Heredity	Identified diseases							RR range
		Hypertesion	CVD	IHD	Diabetes mellitus	Obesity	Thyroid diseases	Diseases of autonomic nervous system	
Hypertension (401–405)	1.5 (1.3; 1.7)				+	+		+	1.2–2.7
IHD (410–414)		+	+		+		+	+	1.2–2.7
Cardiomyopathy (425)	1.3 (1.03; 1.7)							+	1.3–2.7
CVD (430–438)		+		+	+		+		1.8–3.8

Significant excess of hypertension and cardiomyopathy was established in clean-up workers with hereditary load. Clean-up workers with elevated cholesterol levels are more likely to be diagnosed with hypertension, IHD and CVD. While those with hypertension are more likely to be diagnosed with cerebrovascular pathology and IHD.

When analyzed the data of standardized social and hygienic survey, we obtained estimates of the impact of exogenous non-radiation factors (Table 11.7). CER patients have the opportunity to suggest on the impact of factors contributed to their cardiovascular pathology (Figure 11.27).

In the initial period of CER monitoring, the clean-up workers considered a physical overstrain a major risk factor for cardiovascular diseases (1993–1994, 35.2%), in the late period it was an emotional overstrain (2004–2012, up to 79%). Respondents did not consider the

ionizing radiation effects to be a leading risk factor. The highest percentage of responses (29%) in which the radiation factor is believed to be a cause of the disease was recorded during the first survey (1993–1994). The following factors (i.e. vibration, high temperature, impact of harmful substances) were rarely mentioned.

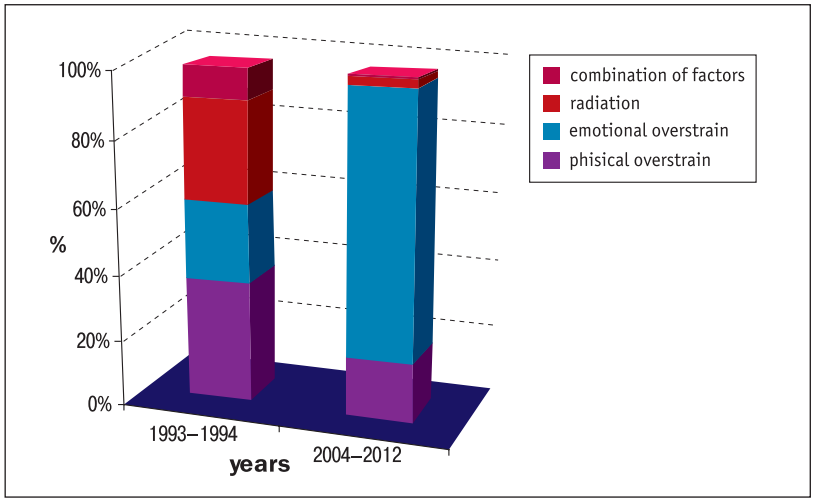


Figure 11.27. Factors that, according to self-assessment, caused the occurrence of cardiovascular disease among clean-up workers (CER data)

Radiation risks

Since a great number of non-radiation factors affect the development of circulatory diseases, we can assume the effect of confounder on the value of radiation risk. It is evident if groups (of exposed and control) were matched without regard to other factors. At the stage of analysis, confounder adjustment is carried out using Mantel-Haenszel weighted relative risks. This approach was applied in assessing radiation factor effect on the development of IHD and CVD (Table 11.8).

More fully differences between relative risks without regard to confounding («crude» relative risks) and with regard to age using Mantel-Haenszel procedure are described in [5, 6].

To minimize the potential corruption of radiation risk assessment due to uncontrolled effects of non-radiation factors, we excluded cases of earlier diagnosed diseases or groups of the diseases under study (because risk of the disease has already been implemented). Risks for the development of CVD and cardiomyopathy were calculated in view of the above (Table 11.8). When matching controls, to calculate radiation risks for IHD we excluded data containing diagnoses of all circulatory diseases. This diminishes potential «confounding effect» as the most common circulatory diseases have similar risk factors.

Statistically significant ($p \leq 0.05$) radiation risks for the development of CVD were estimated in the cohort of clean-up workers and subcohort of exposed at age 40 and older to whole body external doses 0.5 Gy and more, among younger at the time of exposure – in the range 0.25–0.99 Gy. Statistically significant relative risks were also obtained for some forms of CVD diseases (cerebral atherosclerosis, cerebral ischemia and hypertensive encephalopathy).

Statistically significant radiation risks for IHD development among clean-up workers were calculated at doses 0.15 Gy and more, with regard to younger age-at-exposure group. There were no statistically significant radiation risks in subcohort of clean-up workers exposed at age 40 and older.

No confounding due to age was found when determined relative risks for cardiomyopathy (Table 11.8). Statistically significant ($p \leq 0.05$) radiation risks for the development of cardiomy-

Table 11.8

Radiation risks for circulatory diseases in the cohort of clean-up workers (clean-up workers with doses less than 0.05 Gy as a control), in age-at-exposure subcohorts of clean-up workers (under age 40, at age 40 and older). CER data

Disease	Cohort as a whole	Under age 40		40 years and older					
	Dose, Gy	RR (95% CI)	p≤	ERR, Gy^{-1}	EAR*	RR (95% CI)	p≤	RR (95% CI)	p≤
IHD	0.05-0.09	1.2 (0.8; 1.8)				1.3 (0.5; 3.99)		1.2 (0.7; 2.0)	
	0.1-0.14	1.4 (0.8; 2.2)				1.3 (0.7; 2.5)		1.2 (0.6; 2.1)	
	0.15-0.25	1.5 (1.03; 2.2)	0.05	2.8 (1.1; 6.9)	87.7	1.9 (1.2; 3.1)	0.05	1.2 (0.7;2.1)	
	0.25-0.99	1.34 (1.0; 1.8)	0.05	0.8 (0.6; 1.0)	24.5	1.8 (1.1; 2.9)	0.05	1.1 (0.8; 1.6)	
	1+	2.1 (1.2; 3.8)	0.05	0.8 (0.6; 0.95)	25.0	3.2 (1.3; 7.8)	0.05	1.3 (0.6; 3.0)	
CVD	0.05-0.09	1.01				0.8 (0.5; 1.4)		1.1 (0.9; 1.4)	
	0.1-0.24	0.96 (0.8; 1.2)				1.01 (0.8; 1.2)		0.9 (0.7; 1.2)	
	0.25-0.49	1.3 (1.0; 1.5)	0.1	0.6 (0.3; 1.1)	13.8	1.4 (1.0; 1.8)	0.05	1.1 (0.9; 1.2)	
	0.5-0.99	1.4 (1.1; 1.8)	0.01	0.5 (0.3; 0.9)	12.6	1.4 (0.97; 2.1)	0.1	1.3 (1.05; 1.6)	0.05
	1+	1.6 (1.2; 2.3)	0.01	0.5 (0.3; 0.8)	10.8	1.3 (0.6; 2.7)		1.6 (1.2; 2.1)	0.01
Cardiomyopathy	0.05-0.09	1.3 (0.8; 1.85)		3.5 (33.6; 0.4)		1.1 (0.5; 2.3)		1.7 (0.9; 3.4)	
	0.1-0.24	1.2 (1.0; 1.34)	0.1	0.9 (0.8; 1.0)	25.9	1.1 (0.9; 1.3)		1.3 (0.6; 2.7	
	0.25-0.49	1.3 (1.0; 1.6)	0.1	0.8 (0.6; 1.0)	22.4	1.4 (0.9; 1.8)	0.05	1.3 (0.7; 2.3)	
	0.5-0.99	1.4 (1.1; 1.9)	0.05	0.6 (0.5; 0.9)	18.4	1.3 (0.9; 2.0)		1.2 (0,8; 2.0)	
	1+	1.8 (1.2; 2.8)	0.01	0.6 (0.4; 0.9)	16.5	1.9 (1.2; 3.1)	0.001	1.2	

Note. * – per 10^3 person-years, Gy^{-1}.

opathy were assessed at doses 0.5 Gy and more, whereas at doses 0.1–0.49 Gy confidence level is close to statistically significant ($p \leq 0.1$). In subcohort of younger at the time of exposure clean-up workers, statistical significance was observed at lower doses 0.25–0.49 Gy.

It should be noted that in this case measures to minimize unwanted confounding effect resulted in more plausible estimate «dose-effect» in terms of smoothed curve «dose-response» for CVD and IHD, replacement of statistically significant relative risks less than unity at doses 0.05–0.09 Gy for statistically insignificant (false hormesis), lower threshold of statistical significance of relative risks etc.

Radiation risks for the development of hypertension in study sample were statistically insignificant, with the exception of secondary hypertension at doses 1 Gy and more.

Thus, statistical confidence of radiation risks for circulatory diseases is much higher at doses 0.15 Gy and more. Statistical confidence threshold over 95% for CVD and cardiomyopathy was determined at doses 0.5 Gy and more, for IHD – at doses 0.15 Gy and more.

Contribution of radiation factor

Based on statistically significant excess relative risks (RR-1) in the first approximation, we can estimate contribution of radiation and non-radiation factors to the risk of circulatory diseases. The more factors taken into account comply with the rules of system analysis, more adequate is the assessment of their impact. Figures 11.27 and 11.28 present graphical solution to the problem for IHD and CVD. This specifies the percentage of relative risk factors.

Ageing (age at the time of diagnosis) and negative psychoemotional factors (frequent conflicts at work and at home, stress due to job or profession change, other causes of psycho-emotional overstrain) have the greatest influence on the development of ischemic heart disease.

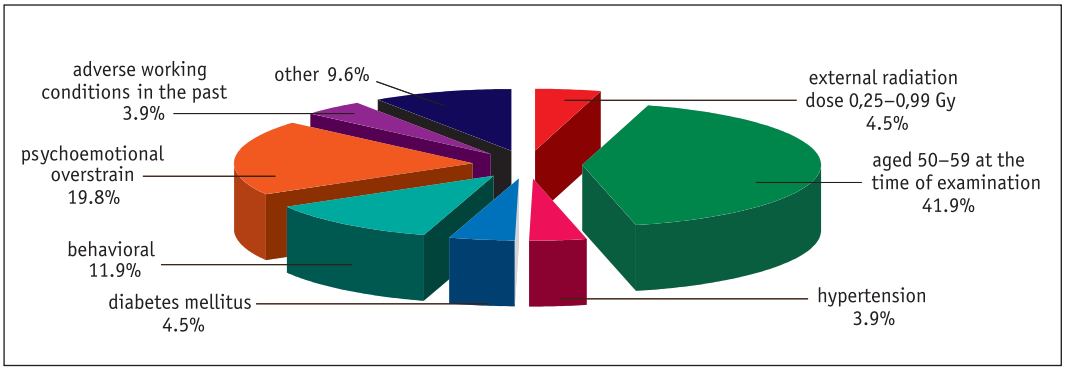


Figure 11.28. Structure and percentage of statistically significant risk factors for the development of ischemic heart disease among male clean-up workers 1986–1987 with radiation dose 0.25–0.99 Gy (aged 50–59 at the time of medical examination). CER data

In clean-up workers aged 40–49, leading risk factor for IHD is psychoemotional factors (32%) followed by age (22%), hypertension, hypercholesterolemia, obesity, diabetes and thyroid diseases (up to 15%), behavioral and other risk factors (24%), external radiation doses in the range 0.25–0.99 Gy (7%).

In the older age group (60 years and older) contribution of age is 53%, that of negative emotional factors – 19% and of external radiation doses in the range 0.25–0.99 Gy (4%).

Figure 11.27 illustrates impact of statistically significant risk factors on the development of IHD.

At the time of IHD diagnosis there were other diseases (atherosclerosis, CVD, hypertension, diabetes etc.) making a substantial contribution to the structure of risk factors. Given close relation between prevalence of atherosclerosis, CVD and age, these diseases were not considered.

Structure of statistically significant risk factors of the development of ischemic heart disease among clean-up workers is displayed in Figure 11.28. Among clean-up workers older at the time of exposure age (60 years and older), the percentage of risk factors for CVD is as follows: age (43%), radiation exposure (2.6%), behavioral (18%) and emotionally negative psychosocial factors (18%). Among those exposed under age 40, due to the smaller contribution of age the structure is completely different: age (14%), radiation exposure (4%), behavioral (28%) and psychosocial (27%).

It should be emphasized that one can reduce by one-third negative impact of statistically significant risk factors of CVD and IHD by lifestyle changes (stop smoking, be physically active, control for blood pressure and cholesterol etc.).

These data relate only to the specific risk factors. If risk factors form a system, the structure of risks, in the first approximation, represents regularities of the formation of the pathology under study. Such an approach is a quick complex analysis with regard to various factors.

Based on data of thorough clinical-and-epidemiological monitoring of male clean-up workers 1986–1987, statistically significant radiation risks for the development of circulatory diseases were established at whole body external doses 0.15 Gy and more. For CVD and cardiomyopathy we determined the statistical significance threshold of 95% at doses 0.5 Gy and more, and of 90% – at doses 0.25 and 0.1 Gy, respectively. For IHD, statistical significance of 95% was estimated at doses 0.15 Gy and more. In younger age at the time of the accident compared to those exposed at age 40 and older, statistically significant risks of CVD were found at lower doses; no statistically significant risks for the development of IHD and cardiomyopathy were

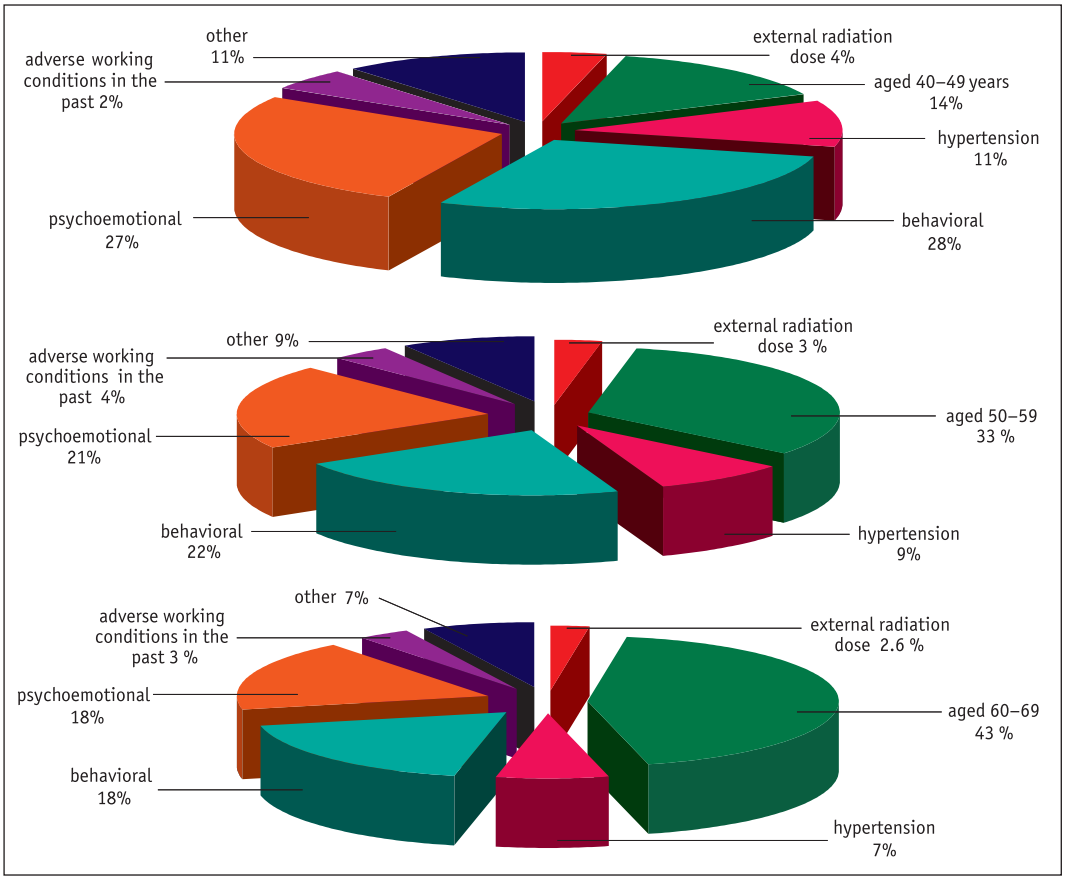


Figure 11.29. Structure and percentage of statistically significant risk factors for the development of cerebrovascular disease among male clean-up workers 1986–1987 with radiation dose 0.25–0.99 Gy (aged 40–49, 50–59 and 60–69). CER data

revealed among people exposed at the same age. It suggests that younger people are more sensitive to ionizing radiation.

Risk of circulatory diseases is largely due to non-radiation endogenous and exogenous factors. Lifestyle changes can reduce negative impact of risk factors by more than 40%. Ageing, stress and lack of physical training made major contribution to IHD and CVD development.

Using estimated risks of circulatory diseases it is possible to calculate an individual risk taking into account patient's risk factors (radiation dose, age, diseases, smoking etc.) [7], to predict risk subject to eliminating some of them and to implement as a «risk calculator». Based on the survivors' dose-age characteristics, it is quite possible to estimate risks of circulatory diseases over time, with ageing.

Multifactorial causes of circulatory diseases make it difficult to assess effect of radiation factor. To significantly change results of radiation risk assessment it is necessary in the analysis phase to clarify values of relative risks with regard to potential confounders using Mantel-Haenszel procedure, and at the stage of comparison group development to avoid confounding effects. Based on crude relative risks, without measures to control for potential confounders, dose-dependent characteristic may be incomplete or incorrect.

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11.3. HEALTH STATUS OF EVACUEES

The large scale of the Chornobyl disaster and the need to protect people from exposure to ionizing radiation resulted in the need for various research in radiation protection. Among them were evacuation and resettlement of residents.

The decision to evacuate residents was taken in the development and worsening of radiation situation in difficult situation when not only forecast the expected dose, and even dose assessment presented certain difficulties. The evacuation began the day and a half after the explosion and had two stages. 49,360 people from Prypyat and 254 people from Yaniv were evacuated the first. Then were evacuated residents from 10-km zone around the plant. However, secondary emissions from the destroyed reactor, which occurred on day 6 and lasted until day 10, made evacuation of the entire population of the 30-km zone inevitable [1].

Overall, by the end of 1986, 91,6 thousand people were moved from 81 settlements (including Prypyat) [2].

In medical and biological aspects, evacuated population, as well as those resettled later, were affected by two main factors – the psychosocial stress and prolonged radiation exposure, mainly in low doses.

Mental stress caused by sudden destruction of lifestyle, behaviour and communication that have been developed over decades and by vital solving-problem in new places.

As for radiation doses, according to available scientific publications [3–7], thyroid gland internal doses (April–May 1986) of adult evacuees were mostly in the range of 0.07 to 3.9 Gy, whole body external doses from gamma-irradiation – from 0.002 to 0.66 Gy.

From theoretical point, these factors could be the cause of psychosomatic disorders and somatic diseases.

The above is to a certain extent, generalization of the results of epidemiological studies on changes in health status of adult evacuees from 30-km Chornobyl zone.

Nontumor morbidity, disability and mortality are the subject of our study. Observation period: 1986–2012.

Data source is the State health-information system – the State Registry of Ukraine of Persons Affected by the Chornobyl Disaster (SRU) (Table 11.9).

Today there is reason to conclude that the health of victims of the Chornobyl disaster is unsatisfactory.

Based on SRU data, due to the development of nontumor diseases the number of healthy evacuees decreased from 67.7% (1988) to 12.04% (2012) and those with chronic diseases increased 2.8 times – from 31.5% to 87.7%. (Figure 11.30).

Table 11.9

Distribution of the cohort of evacuees from estrangement area on the data of prophylactic medical examination in 2012

Age group, years	Total number	% of total number of evacuees	Men	% of total number of evacuees	Women	% of total number of evacuees
Total	80480	100	34708	43.13	45772	56.87
0–17	0	0	0	0	0	0
18–29	6679	8.3	3355	4.17	3324	4.13
30–39	17291	21.48	8549	10.62	8742	10.86
40–49	11423	14.19	4831	6	6592	8.19
50–59	14797	18.39	6152	7.64	8645	10.74
60 years and older	30290	37.64	11821	14.69	18469	22.95

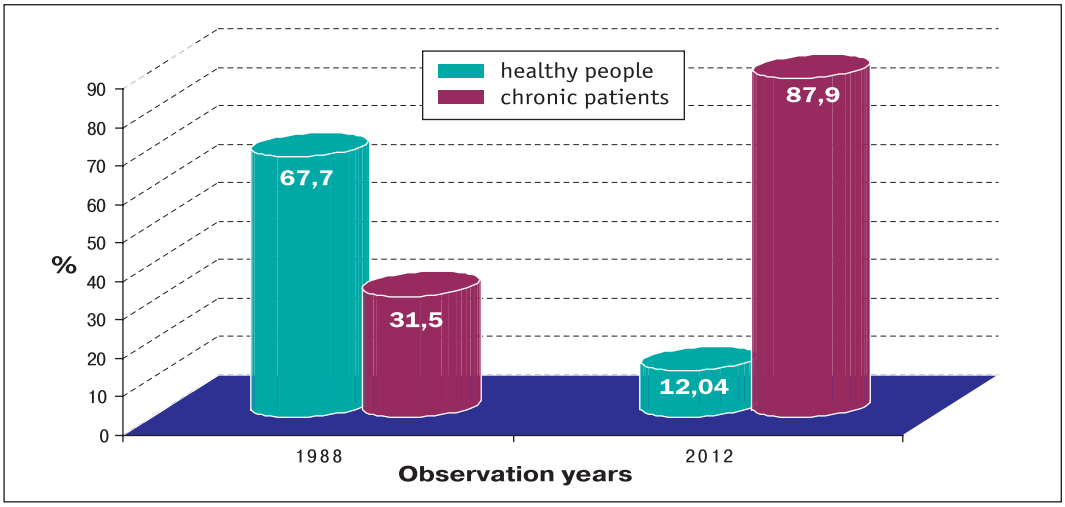


Figure 11.30. Integral indexes of health (%) of adult evacuees for 1988 and 2012

In the post-accident period an increase of the number of disabled persons was observed.

According to [8] from 1988 to 1994, rate of disability increased from 4.52 to 60.4 per 1000 persons, including up to 65.7 among men and up to 57.0 among women; with average republican rate being 3.7–4.9 per 1000 persons.

In 2012, Chornobyl-related disability among adult evacuees was 90% compared to 10% for systemic disease incidence (Figure 11.31).

Among adult evacuees, a higher rate of Chornobyl-related disability (disability groups 3 and 2) was noted.

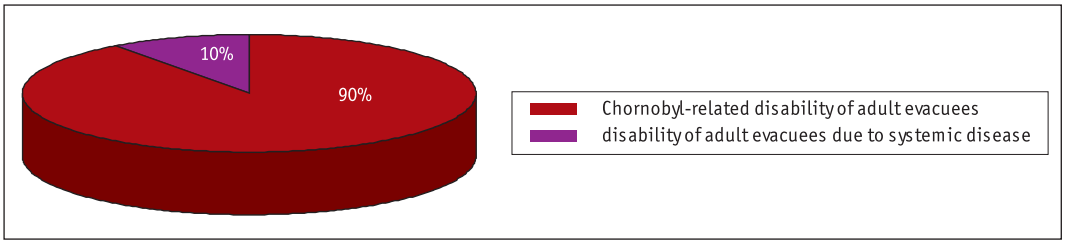


Figure 11.31. Distribution of Chornobyl-related disability of adult evacuees in 2012 (%)

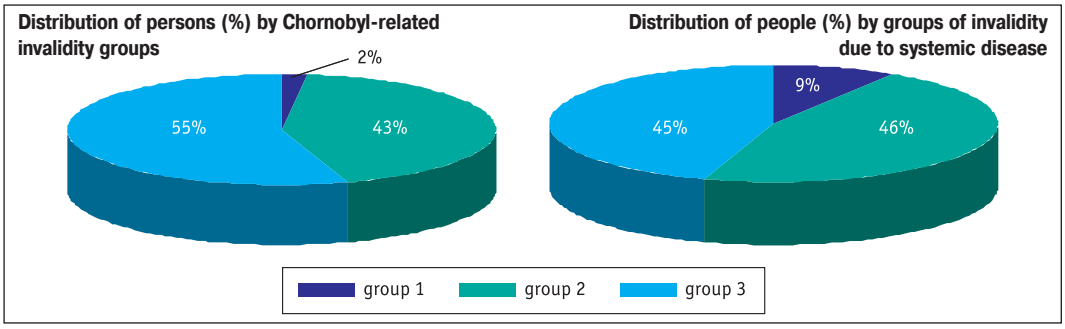


Figure 11.32. Distribution of adult evacuees by invalidity groups (SRU data, 2012)

To the structure of causes of disability associated with the Chornobyl accident, circulatory diseases make the highest contribution followed by diseases of the nervous system and sense organs, endocrine diseases. In the structure of disability causes due to systemic disease, a significant proportion also make circulatory diseases, somewhat larger part is occupied by digestive and musculoskeletal diseases, mental disorders. Rates of endocrine disease disability are similar (Figure 11.33).

Results of epidemiological studies of mortality from non-tumor diseases among adult evacuees over 1988–2012 are testimony to a gradual increase since period 3 (Figure 11.34). The highest mortality (18‰) was recorded in 2008–2012, that is 22–26 years after the accident.

Circulatory diseases prevail in mortality structure throughout study periods (Figure 11.35).

In 2012, percentage of cardiovascular pathology was 69.1%, second ranked deaths from digestive diseases (5.2%). Similar (1.1%) were death rates from respiratory diseases, diseases of the nervous and genitourinary systems.

In the structure of mortality from circulatory diseases, ischemic heart disease (IHD) occupies an important position – 74.70% (Figure 11.36). In recent years, rate of mortality from ischemic heart disease increased significantly. The growth rate of CHD mortality, on the one hand, is

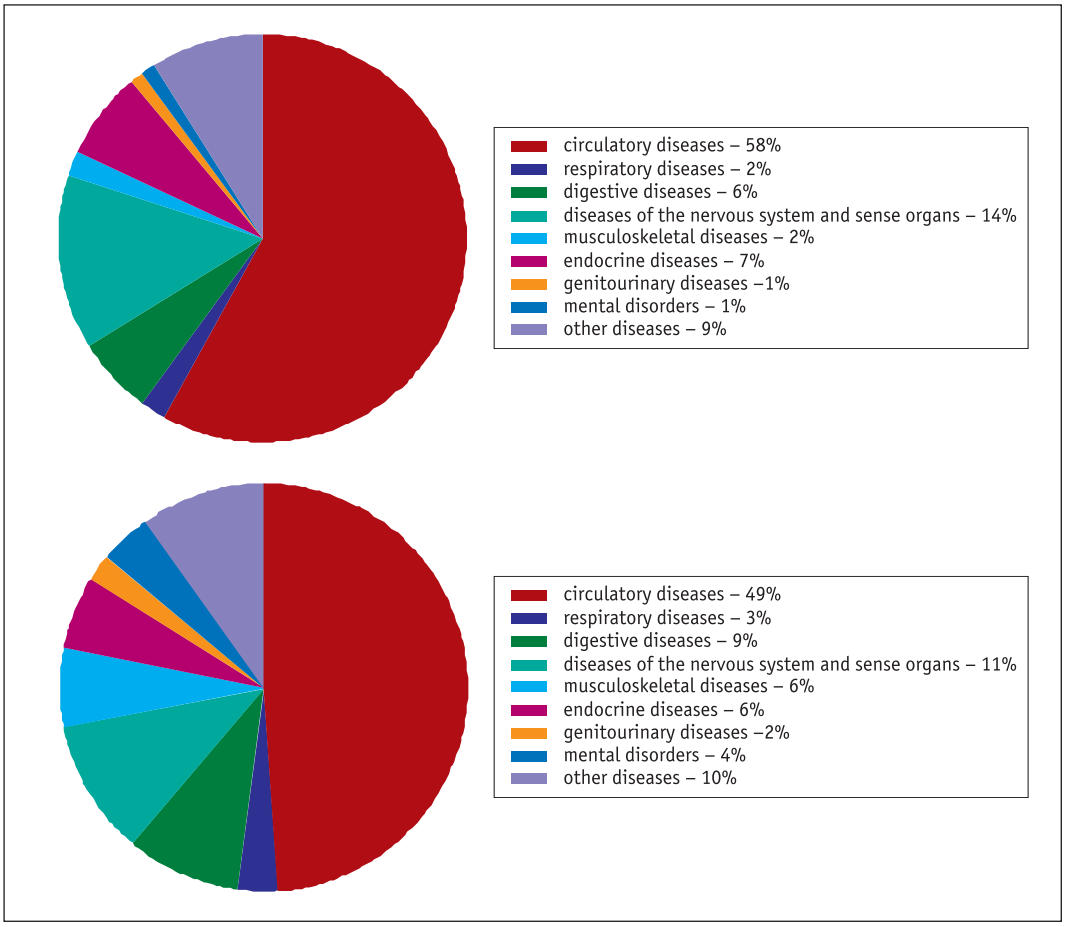


Figure 11.33. **Structure of causes of non-tumor disability (%) in adult evacuees (2012)**

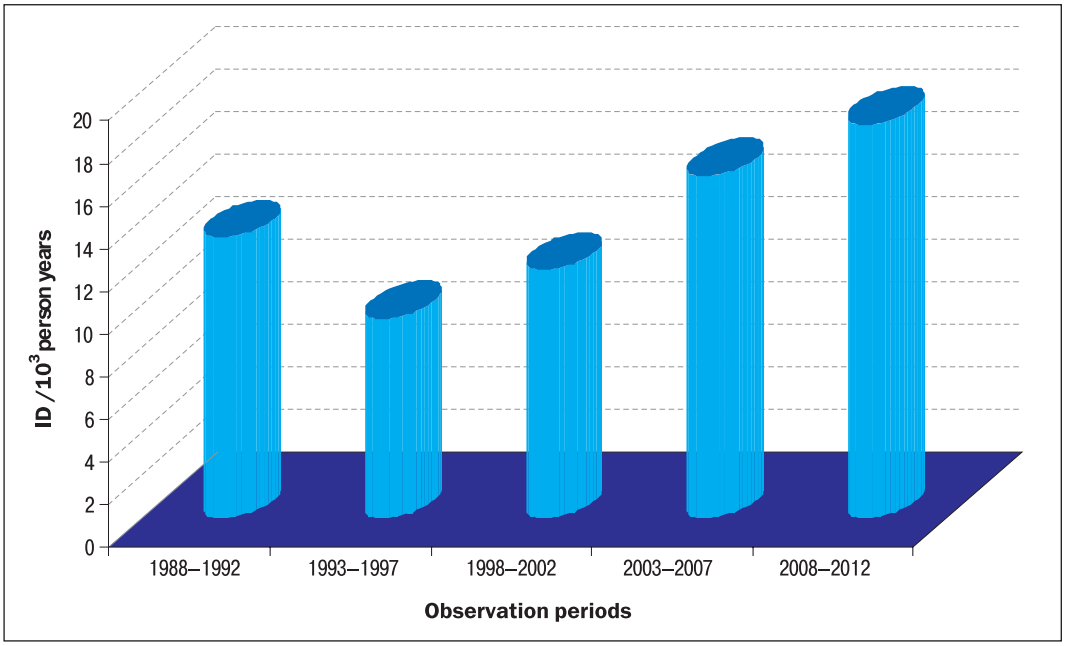


Figure 11.34. Dynamics of non-tumor mortality in adult evacuees for five-year periods of observation

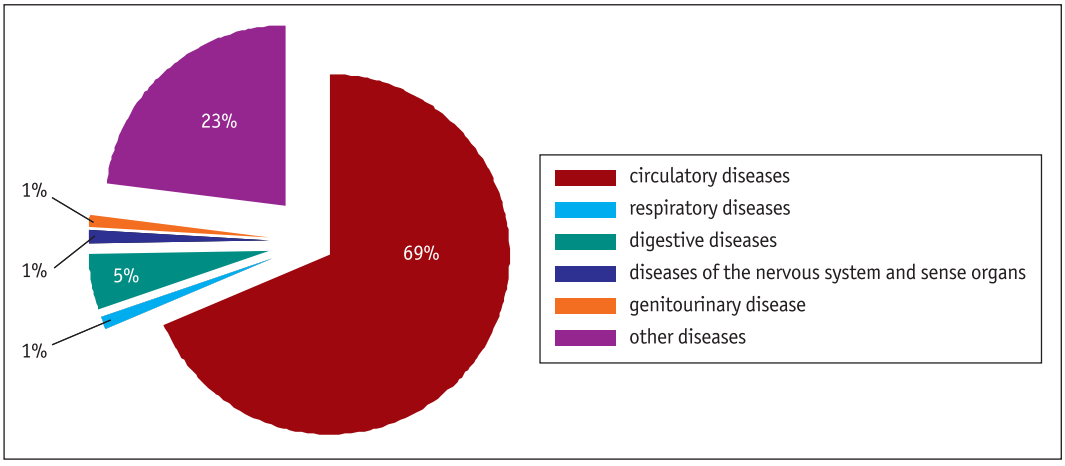


Figure 11.35. Structure of causes of death (%) from non-tumor diseases in adult evacuees, 2012

determined by the age of victims, and on the second – by the time elapsed since the accident. Chronic ischemic heart disease and acute myocardial infarction are the most common forms of the pathology.

Among causes of death, cerebrovascular diseases take an important place, being more pronounced in older men. Heart attack and brain stroke are among causes of death for cerebrovascular diseases.

The most important indicators that characterize health status – morbidity and mortality – are contravariant: when mortality increases morbidity, on the contrary, reduces (Figure 11.37).

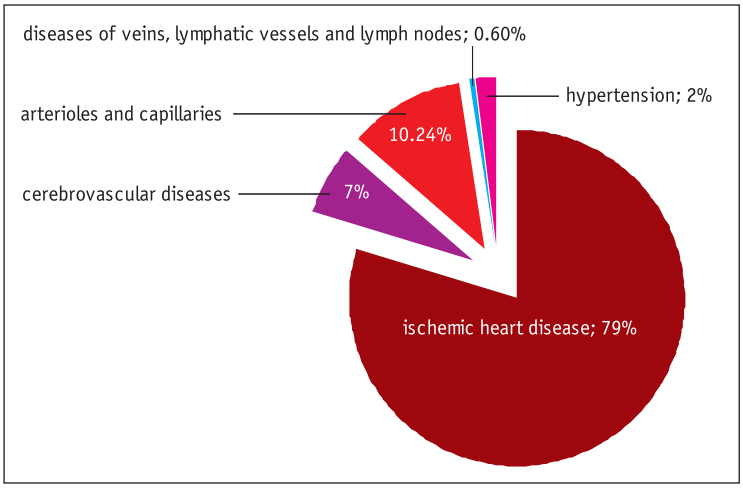


Figure 11.36. **Structure of mortality (%) from circulatory diseases in adult evacuees, 2012**

Epidemiological analysis of non-tumor morbidity by five-year observation periods demonstrates the undulating nature of changes.

Gradual increase in the incidence was found within 7–21-year period since the accident, peak being observed within 12–16 years after the accident. Significant reduction in the incidence occurred in 2008–2012, i.e. 22–26 years after the accident.

Reducing morbidity, especially in 22–26 post-accidental years, were possibly due to the influence of two main factors – effect «implementation of diseases» and «extinction» in the remote post-accident period.

In general, structure of non-tumor morbidity for adult evacuees over post-accident period did not change significantly (Figures 11.38 and 11.39). Carculatory, digestive, respiratory, musculoskeletal and endocrine diseases make major contribution. It should be emphasized that in early

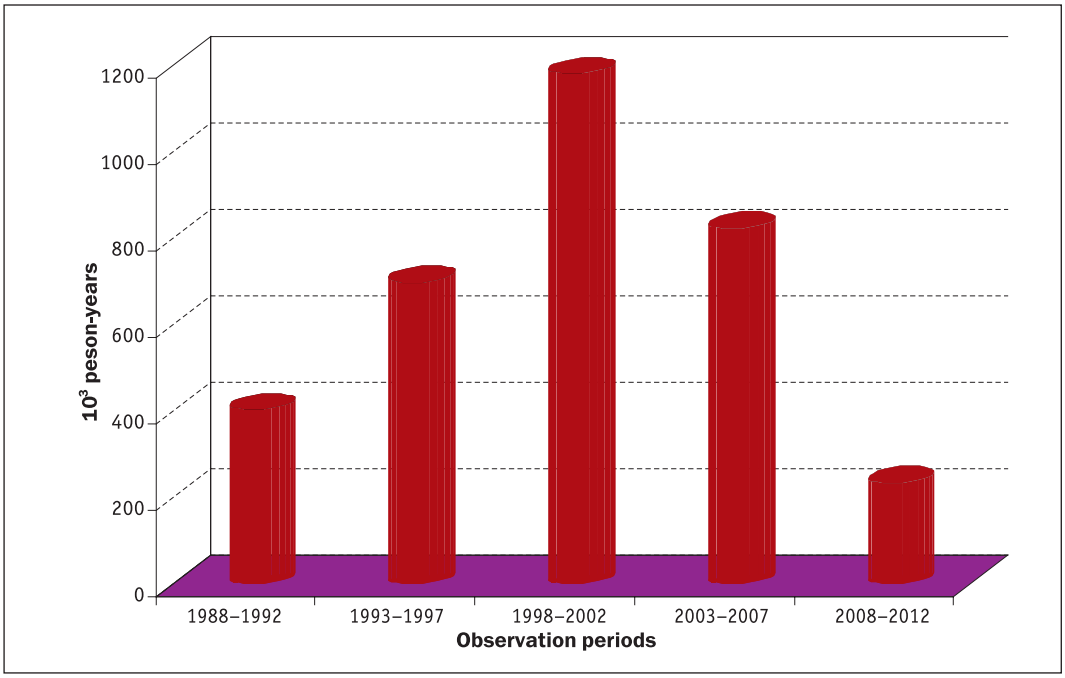


Figure 11.37. **Dynamics of overall non-tumor incidence in adult evacuees for five-year observation periods**

post-accident period endocrine diseases, mental disorders and circulatory diseases made up the bulk. In the last period, contribution of respiratory, digestive, musculoskeletal and genitourinary diseases increased. It is possible that these differences are in some way related to specific medical effects of such factors as «psychosocial stress», exposure in small doses. In the early post-accident period, «screening effect» may occur, particularly among older people (> 40 years).

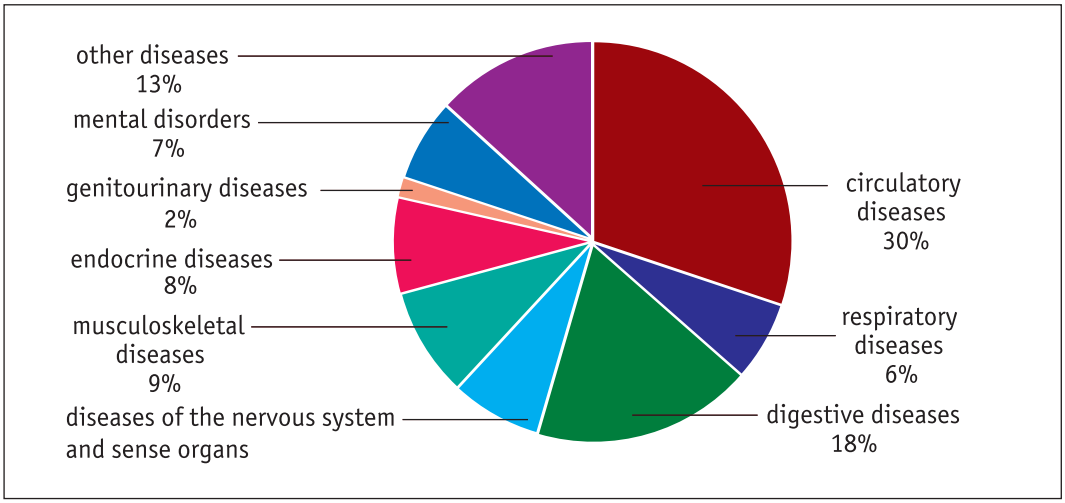


Figure 11.38. **Structure of non-tumor incidence (%) in adult evacuees for 1988**

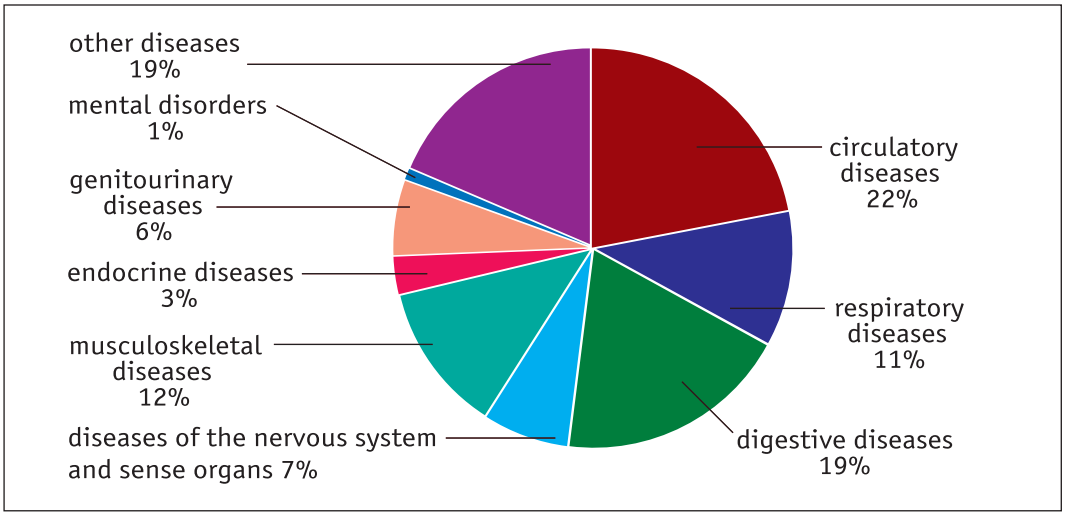


Figure 11.39. **Structure of non-tumor incidence (%) in adult evacuees, 2012**

Given that the main contribution to the deterioration of evacuees' health (morbidity, disability, mortality) made circulatory diseases, a detailed epidemiological analysis of this class of nontumor diseases has been conducted.

As evident from Figure 11.40, there are three main periods – early (1986–1992), remote (1998–2007) and the late (2008–2012) in the dynamics of circulatory diseases. Interim period (1993–1997) can be regarded as a «phase» pre-pathological changes.

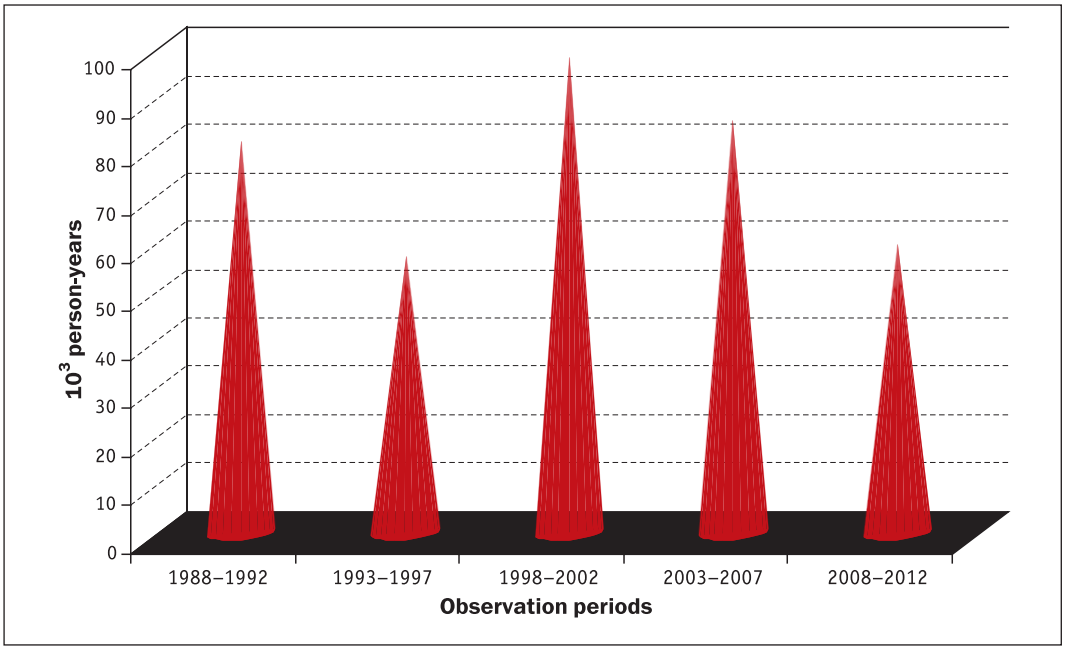


Figure 11.40. Dynamics of circulatory disease incidence in adult evacuees aged 18–60 at the time of the accident by five-year observation periods (ID / 10^3 person-years)

High cardiovascular morbidity in the early period is regarded not only as a «screening effect», but also as a consequence of acute psychosocial stress, as well as exposure of thyroid gland with ^{131}I.

Radiation exposure effects as well as nonradiation risk factors could occur in remote and late post-accident periods. Assumption is confirmed by the following data.

A significant difference is observed between the rates of circulatory diseases, depending on survivors' age at the time of the accident (Figure 11.41).

The highest incidence rates were established in persons aged 40–60 at the time of the accident, which can be explained, primarily, by the age factor – «age».

Based on the data presented in Fig. 12, the effect of «screening» manifested mainly in that age group – high incidence rate in the first post-accident years. Regardless of age, increased incidence occurred within 1998–2007, that is 12–21 years after the accident. In the last period (2008–2012), we recorded a clear downward trend in incidence, though higher rates still persist.

We found some differences in the dynamics of the overall level of circulatory diseases depending on sex (Figure 11.42).

Women have higher incidence registered during 1988–2002, i.e. 12–16 years after the accident, men – in the period 2003–2012, i.e. 17–26 years after the accident. These results are difficult to explain. We can assume effect of accelerated aging on Ukrainian men.

Figure 11.43 presents the dynamics of the most common cardiovascular diseases in the cohort of adult evacuees aged 18–60 at the time of the accident. Worthy of being noted, the high incidence of ischemic heart disease, with a peak 12–21 years after the accident, the growth of cerebrovascular diseases, diseases of arteries, arterioles and capillaries in 6–16 years after the accident, diseases of veins, lymphatic vessels and lymph nodes – in 12–21 years after the accident.

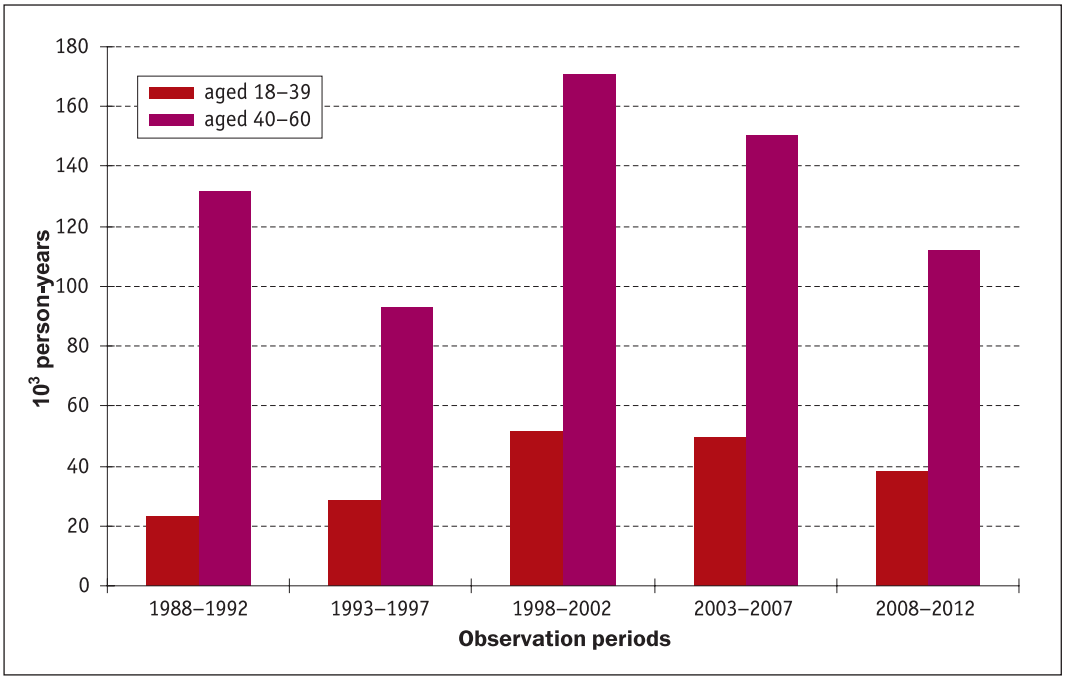


Figure 11.41. Dynamics of circulatory disease incidence in adult evacuees by five-year observation periods (ID / 10^3 person-years) depending on age at the time of the accident

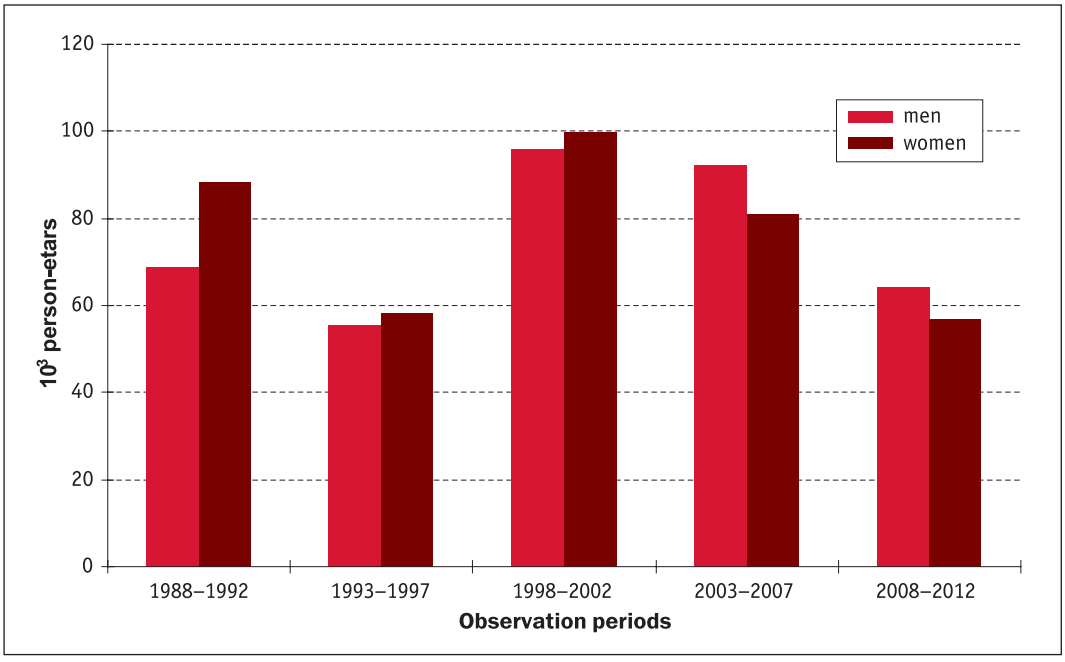


Figure 11.42. Dynamics of circulatory disease incidence in adult evacuees aged 18–60 at the time of the accident by five-year observation periods (ID / 10^3 person-years) depending on sex

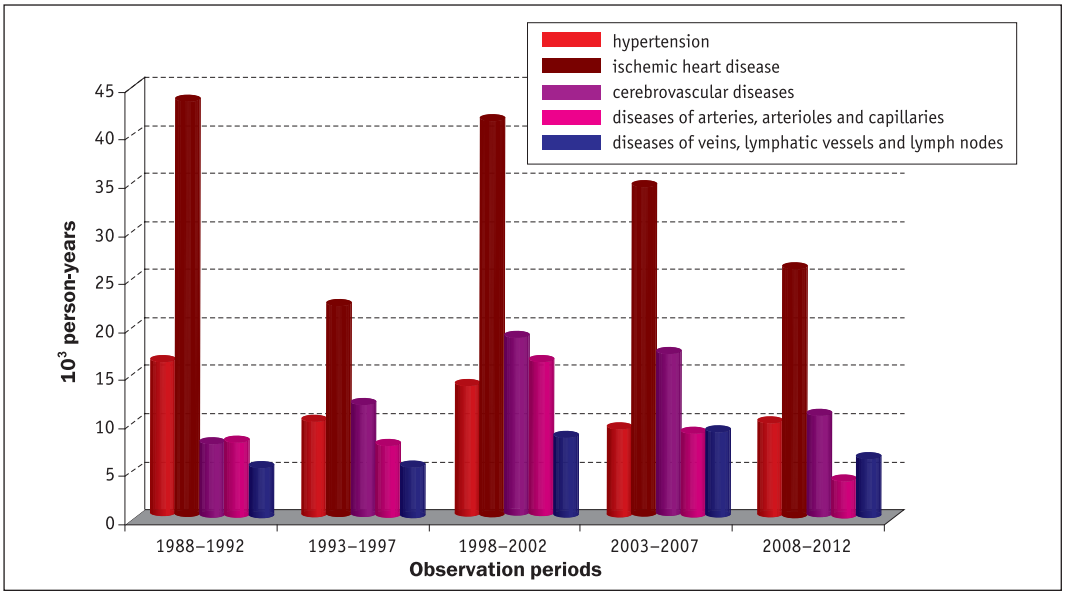


Figure 11.43. Dynamics of incidence of the most common circulatory diseases among adult evacuees (aged 18–60 at the time of the accident) by five-year observation periods (ID / 10^3 person-years)

In the early post-accident period – the first 6 years, an increased incidence of hypertension and ischemic heart disease was established. This is probably due to not only a «screening» effect but also the influence of social and psychological stress, which deserves special study.

A significant difference is observed in the rate and dynamics of some circulatory diseases depending on evacuees' age at the time of the accident (Figures 11.44, 11.45).

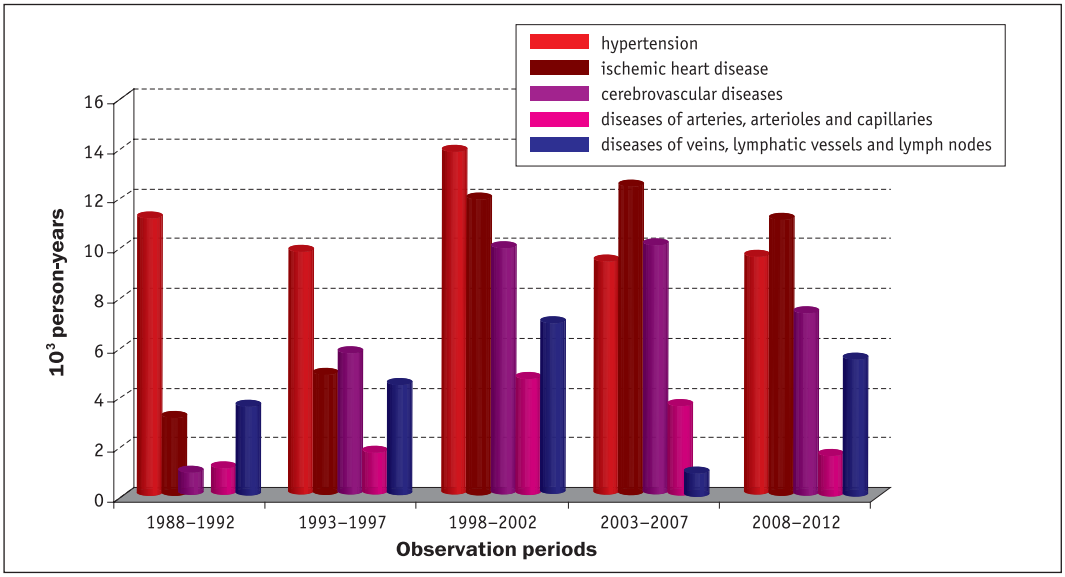


Figure 11.44. Dynamics of incidence of the most common circulatory diseases among adult evacuees aged 18–39 at the time of the accident by five-year observation periods (ID / 10^3 person-years)

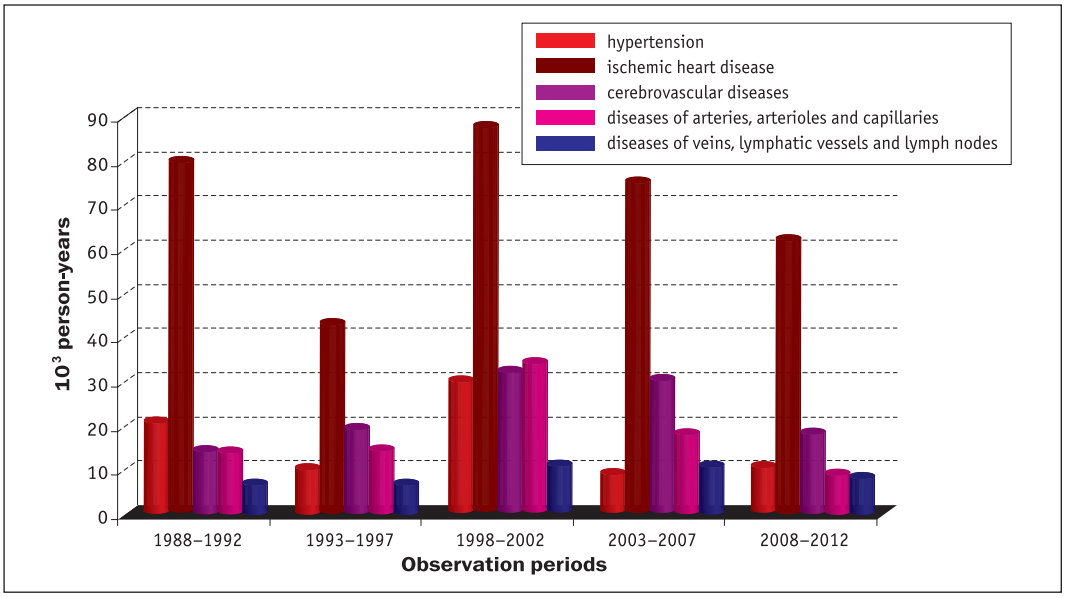


Figure 11.45. Dynamics of incidence of the most common circulatory diseases in adult evacuees aged 40–60 at the time of the accident by five-year observation periods (ID / 10^3 person-years).

Post-accident growth of circulatory disease incidence is mainly due to an increase in the incidence of hypertension, ischemic heart disease and cerebrovascular diseases among people of younger age group (18–39 years). In the last period, we noticed higher rates of the diseases of arteries, arterioles and capillaries, diseases of veins, lymphatic vessels and lymph nodes.

In the older age group (40–60 years), ischemic heart disease, cerebrovascular disease, diseases of arteries, arterioles and capillaries made the most contribution. The most significant growth of these diseases was observed in 1998–2007, i.e. 12–21 years after the accident. It cannot be attributed only to the effect of the «age» factor, but impact of exogenous factors, including exposure to radiation, is also quite possible.

In the initial post-accident period, a higher incidence of hypertension was found in the older age group (Table 11.10). No significant age and sex differences were revealed over the subse-

Table 11.10

Dynamics of hypertension incidence in adult evacuees depending on age and sex by five-year observation periods (ID / 10^3 person-years)

Sex	Observation periods, years				
	1988–1992 *ID ± m*	1993–1997 *ID ± m*	1998–2002 *ID ± m*	2003–2007 *ID ± m*	2008–2012 *ID ± m*
Aged 18–39					
men	13.22 ±0.75	10.66 ± 0.63*	14.37 ± 0.66**	9.37 ± 0.49*	9.21 ± 0.55*
women	10.04 ± 0.54	9.68 ± 0.48	14.0 ± 0.51*,**	9.75 ± 0.40	10.03 ± 0.45
Aged 40–60					
men	18.53 ± 0.88	9.94 ± 0.70*	13.93 ± 0.84*,**	6.79 ± 0.60*,**	11.99 ± 1.03*
women	21.24 ± 0.71	9.29 ± 0.50*	13.07 ± 0.60*,**	8.35 ± 0.48*	8.41 ± 0.63*

Notes. * – significant changes in rates relative to those of 1988–1992; ** – relative to those of 1993–1997.

quent post-accident periods. This is somewhat different from the modern view on the growth of circulatory disease incidence with age and requires more detailed epidemiological study.

According to the data (Figure 11.46), dynamics of IHD incidence in evacuees has significant time differences.

A gradual increase in the incidence was seen among persons aged 18–39 at the time of the accident. The highest rates were revealed in the third, fourth and fifth periods, i.e. 12–24 years after the accident.

In persons aged 40–60 at the time of the accident, an increased incidence of ischemic heart disease was observed 12–24 years after the accident, with a peak incidence in the third period (12–17 years after the accident).

It should be noted that the incidence in older age people, i.e. aged 40–60 at the time of the accident exceeds that of younger age group (18–39 years), which we attribute primarily to the impact of «age».

Higher IHD incidence in people aged 40–60 at the time of the accident, i.e. 6 years after the accident is remarkable. Obviously, in this case it is affected by two key factors – «age» and «screening effect».

In recent years, changes relating to the central nervous system are treated as one of the most tangible manifestation of the damaging effects of low-dose ionizing radiation [9, 10, 11].

Since 1993, there are negative trends in cerebrovascular diseases (CVD) among people in both age groups, with peak incidence growth in 1998–2002 (Figure 11.47). However, fairly high growth rate of the diseases among people aged 18–39 at the time of the accident deserves special attention.

Certain dependence of circulatory disease incidence on thyroid doses was found among adult evacuees (Table 11.11).

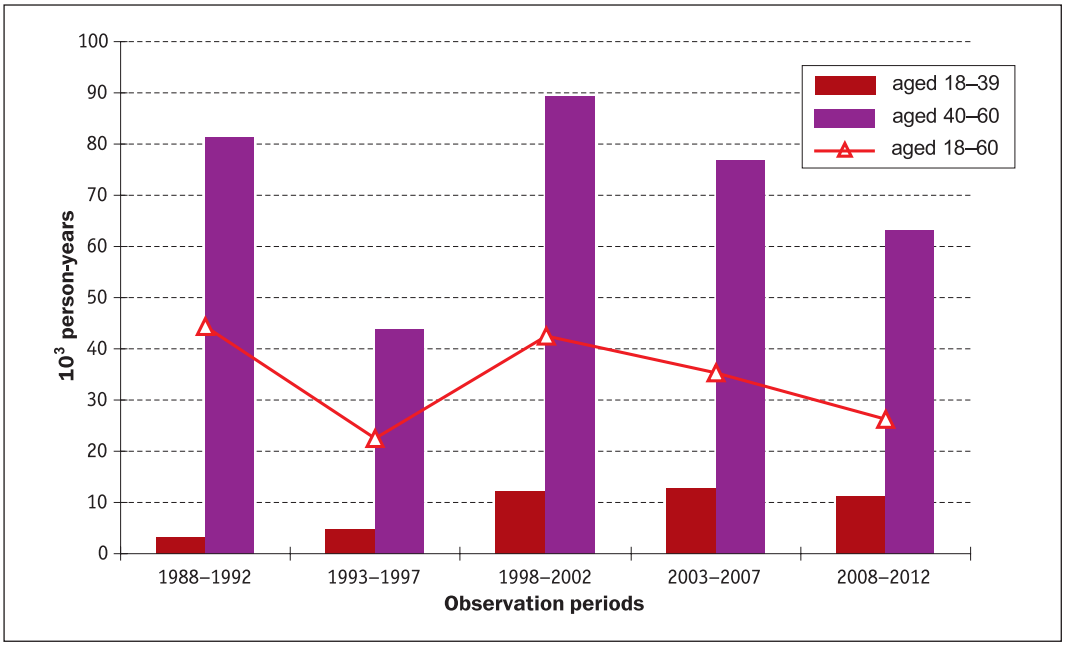


Figure 11.46. **Dynamics of ischemic heart disease incidence among adult evacuees by five-year observation periods with regard to the age at the time of the accident (ID / 10^3 person-years)**

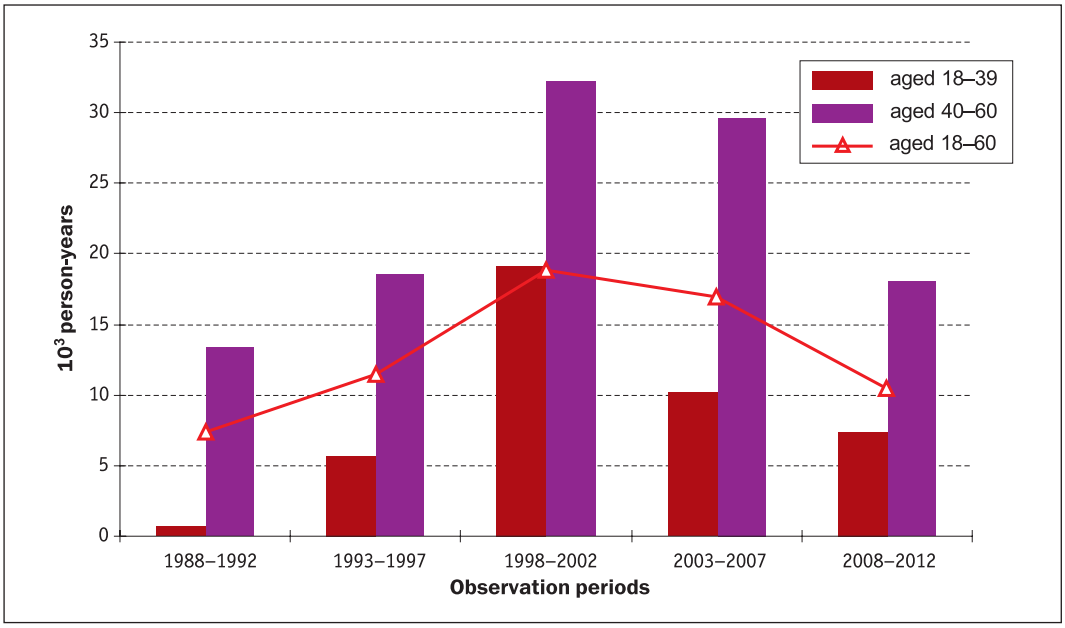


Figure 11.47. Dynamics of cerebrovascular disease incidence among adult evacuees by five-year observation periods with regard to the age-at-exposure (ID / 10^3 person-years)

Table 11.11

Dynamics of circulatory disease incidence among adult evacuees (aged 18–60 at the time of exposure) by five-year observation periods (ID / 10^3 person-years) depending on thyroid dose

Thyroid dose, Gy	Observation periods, years				
	1988–1992 *ID ± m*	1993–1997 *ID ± m*	1998–2002 *ID ± m*	2003–2007 *ID ± m*	2008–2012 *ID ± m*
0–0.3	41.43 ± 6.76	52.83 ± 7.84	78.26 ± 11,20*	35.21 ± 6.40**	64.69 ± 12.77
0.31–0.75	37.27 ± 6.68	68.38 ± 8.82*	125.00 ±12.33*,**	49.23 ± 8.11	80.21 ± 11.47*
0.76–2.0	47.66 ± 5.95	32.28 ± 4.68*	38.28 ± 5.63	17.40 ± 4.78*,**	32.95 ± 7.86
> 2.0	83.67 ± 12.36	20.30 ± 5.80*	29.18 ± 7.42*	44.12 ± 12.45*	45.71 ± 15.79

In the initial period (1988–1992), the highest incidence rates were recorded in adult evacuees exposed to thyroid dose > 2.00 Gy.

In the second period of observation, on the contrary, the highest incidence rates were recorded in dose range 0.31–0.75 Gy. The peak incidence of circulatory diseases occurred in observation period 1998–2002, with thyroid dose 0.31–0.75 Gy; i.e. 12–16 years after the accident.

Thus, a comparative analysis of circulatory disease incidence among adult evacuees at different dose intervals identified their main feature, namely, in the remote period after the accident (in 22–26 years), increased incidence rates of circulatory diseases in dose intervals 0–0.3 Gy and 0.31–0.75 Gy were observed. In the last observation period, the highest circulatory disease incidence rates were recorded in dose range 0.31–0.75 Gy. In the dose range > 2.0 Gy, the highest rates were recorded in the first period of observation.

Dynamics of IHD incidence among adult evacuees depending on thyroid doses is given in Table 11.12.

Table 11.12

Dynamics of IHD incidence among adult evacuees (aged 18–60 at the time of exposure) by five-year observation periods (ID / 10^3 person-years) depending on thyroid dose

Thyroid dose, Gy	Observation periods, years				
	1988–1992 *ID ± m*	1993–1997 *ID ± m*	1998–2002 *ID ± m*	2003–2007 *ID ± m*	2008–2012 *ID ± m*
0–0.3	10.36 ± 3.42	11.06 ± 3.67	15.65 ± 5.18	14.30 ± 4.28	18.87 ± 7.06
0.31–0.75	4.97 ± 2.48	26.89 ± 5.65*	44.44 ± 7.68*	14.06 ± 4.42	26.74 ± 6.81*
0.76–2.0	16.41 ± 3.55	18.95 ± 3.61	14.55 ± 3.50	– *,**	13.57 ± 5.09
> 2.0	31.87 ± 4.43	1.69 ± 1.69*	9.73 ± 4.33*	11.03 ± 6.33*	11.43 ± 8.03

Table 11.13

Dynamics of cerebrovascular disease incidence among adult evacuees (aged 18–60 at the time of exposure) by five-year observation periods (ID / 10^3 person-years) depending on thyroid dose

Thyroid dose, Gy	Observation periods, years				
	1988–1992 *ID ± m*	1993–1997 *ID ± m*	1998–2002 *ID ± m*	2003–2007 *ID ± m*	2008–2012 *ID ± m*
0–0.3	3.45 ± 1.99	4.91 ± 2.45	12.17 ± 4.57	13.00 ± 4.09*	21.56 ± 7.54*,**
0.31–0.75	7.45 ± 3.03	9.77 ± 3.44	36.11 ± 6.95*,**	23.91 ± 5.73*,**	23.17 ± 6.35*
0.76–2.0	2.34 ± 1.35	3.51 ± 1.57	10.27 ± 2.95*,**	6.69 ± 2.98	5.81 ± 3.35
> 2.0	9.96 ± 4.43	6.77 ± 3.37	3.89 ± 2.75	- *,**	17.14 ± 9.81

As evident from the table, over time, incidence steadily increased in adult evacuees received thyroid dose 0–0.3 Gy. Morbidity of population with dose 0.31–0.75 Gy has been increasing throughout three periods and reached maximum rate.

Analysis of CVD morbidity (Table 11.13) among evacuees aged 18–60 years depending on radiation dose shows that from the second to the last period, the highest incidence rates were recorded at doses 0.76–2.0 Gy but for the first period – with dose > 2.0 Gy.

At present, unfortunately, SRU does not contain sufficient information on radiation doses to evacuees. SRU presents data on thyroid doses to a total of 7589 people, including 957 adult at the time of the accident persons.

In this regard, data presented for possible dose-dependent effects of circulatory diseases due to thyroid radiation should be considered as preliminary. Epidemiological studies need special software provided SRU dosimetric information.

Results of special risk-analysis does not yet allow to express some thoughts on this issue.

Data presented in Table 11.14 are indicative of ambiguous rates of circulatory disease incidence relative to thyroid doses.

The most stable results were observed within dose range 0.3 to 0.75 Gy.

High rate of circulatory disease incidence was established in the early post-accident period among patients with thyroid dose > 2 Gy. However, size of this group is small – 138 people.

When analysing circulatory disease incidence for observation periods (Table 11.15), stable dose-dependent effects were found in dose range 0.31–0.75 Gy (virtually throughout the observation). At higher doses – only in the early post-accident period.

* * *

Table 11.14
Relative risks for main circulatory diseases among adult evacuees

Clinical entity	Dose intervals					
	0.31–0.75 Gy		0.76–2.0 Gy		>2.0 Gy	
	RR	CI	RR	CI	RR	CI
Circulatory diseases	1.39*	1.33-1.46*	0.70	0.67; 0.73	0.85	0.81; 0.90
Hypertension	0.82	0.79-0.86	0.48	0.46; 0.50	0.48	0.46; 0.51
Ischemic heart disease	1.73*	1.65-1.82*	1.06*	1.01; 1.11*	0.99	0.94; 1.05
Cerebrovascular diseases	2.06*	1.96-2.15*	0.58	0.55; 0.60	0.72	0.69; 0.76
Diseases of arteries, arterioles and capillaries	0.81	0.77-0.84	0.28	0.27; 0.30	0.71	0.67; 0.75
Diseases of veins, lymphatic vessels and lymph nodes	1.28*	1.22-1.34*	0.84	0.81; 0.88	3.16*	2.99; 3.34*

Note. * – $p < 0.05$.

Table 11.15
Relative risks for circulatory diseases among adult evacuees (aged 18–60 at the time of exposure) by five-year observation periods

Observation periods	Dose intervals					
	0.31–0.75 Gy		0.76–2.0 Gy		>2.0 Gy	
	RR	CI	RR	CI	RR	CI
1988–1992	0.90	0.82; 0.99	1.15*	1.06; 1.25*	2.02*	1.81; 2.25*
1993–1997	1.29*	1.17; 1.43*	0.61	0.56; 0.67	0.38	0.35; 0.43
1998–2002	1.60*	1.43; 1.78*	0.49	0.45; 0.54	0.37	0.33; 0.42
2003–2007	1.51*	1.37; 1.68*	0.54	0.48; 0.59	1.36*	1.18; 1.56*
2008–2012	1.24*	1.09; 1.41*	0.51	0.45; 0.58	0.71	0.59; 0.85
1988–2012	1.39	1.33: 1.46	0.70	0.67; 0.73	0.85	0.81; 0.90

Note. * – $p < 0.05$.

Thus, the health of adult evacuees has deteriorated over the past 20 years.

During 1988–2012, pathology of the circulatory system was the leader in the structure of non-tumor morbidity, disability and mortality of adult evacuees.

As for now, circulatory disease morbidity and mortality are the most important indicators of adult evacuees' health; an inverse relationship was observed: the circulatory disease incidence goes down and mortality, in contrast, increase. Reduced circulatory disease incidence 22–26 years after the accident does not suggest that the problem is solved, as within 1988 to 2012 the number of healthy evacuees has decreased 5.6 times, and chronic patients has increased 2.8 times. There is an increase of complications of some clinical entities and disability among the Chornobyl survivors. In 2012, the Chornobyl-related disability of adult evacuees was 90% compared to 10% of the systemic disease.

Gradual increase in the incidence was found 7–16 years after the accident. The highest incidence was registered in 1998–2002, i.e. 12–16 years after the accident. A significant reduction in the incidence occurred in 2008–2012, i.e. 22–26 years later. The decline in incidence since 2003, especially 22–26 years after the accident, is possibly due to the influence of two main factors – «implementation of disease» and «extinction» effects in the remote post-accident period.

Significant increase in mortality from circulatory diseases among adult evacuees in 2003–2007, i.e. 17–22 years after the accident. The highest mortality rates regardless age were estimated for men, particularly, 17 years after the accident. Among persons older 40 at the time of

the accident, at the end of the study (2012) there was a decline in mortality possibly due to the «extinction» effect. In persons under 40 at the time of the accident, no decrease in circulatory disease mortality was observed, so increase of its level is quite possible in subsequent years.

It was found that time elapsed after the accident made a significant impact on disease structure and clinical course. As for evacuees' incidence there were two waves of increased incidence – at the beginning of the study (1988–1992) and in the third period (1998–2002, that is 12 years after the Chornobyl accident). 26 years after the accident, the most significant changes in the incidence of adult evacuees affected circulatory diseases, primarily CVD. Early in the study, we recorded the highest rates for hypertension, since the second period permanent growth of IHD was observed.

Our results are indicative of difference in circulatory disease incidence rates between age groups. The highest rates of increasing incidence in age group 18–39 years (3.2 times compared with the initial period), whereas at age 40–60, incidence decreased.

The most characteristic feature in the remote period is increased incidence of chronic IHD in those aged 18–39. Growth of hypertension in young adults is of particular concern. After 26 years, CVD incidence has increased by a factor 3.3.

Comparative analysis of circulatory disease incidence among adult evacuees in different dose intervals allowed to allocate their basic feature, namely, in the remote post-accident period (within 22–26 years) increased circulatory disease incidence was revealed in dose ranges 0–0.3 Gy and 0.31–0.75 Gy. In the last period of observation, greatest incidence was observed in dose range 0.31–0.75 Gy. In dose range > 2.0 Gy, the highest values were recorded for the first period of observation.

Quick identification of people with initial signs of disease, impact on the risk factors that are amenable to correction, systematic drug and nondrug treatments will provide reducing risk of circulatory diseases among adult evacuees.

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11.4. HEALTH STATUS OF INHABITANTS OF CONTAMINATED AREAS

Twenty-nine years after the Chornobyl accident, numerous epidemiological, clinical and dosimetric studies have shown negative changes in the health status of population exposed to short-term (Chornobyl emergency workers, evacuees from the Chornobyl estrangement zone) and long-term (inhabitants of contaminated areas) radiation exposure [1-5]. Health deterioration among survivors is mainly due to increased nontumor incidence with circulatory diseases being a leader [6–8].

Health of inhabitants of contaminated areas is understudied except for medical demography [9–11] and cancer research [12–14]. In scientific literature, data on nontumor incidence among inhabitants are virtually unavailable. Some publications bear witness to the impact both high and low doses (less than 1 Gy) on the development of nontumor diseases, as well as dependence on sex and age at the time of the accident [15–18].

Here we present the results of epidemiological studies performed at the Institute of Radiation Hygiene and Epidemiology (IRHE), National Research Center for Radiation Medicine, NAMS of Ukraine in 2010–2015. We have carried out epidemiological studies on patterns of major nontumor diseases under long-term low-dose ionizing radiation among inhabitants of contaminated areas. To determine characteristics of nontumor diseases depending on passport doses of the settlement, we set up two cohorts of inhabitants listed on the State Registry of Ukraine (SRU) [19, 20]. Cohort 1 (a control group of 155,592 people) with effective dose accumulated over 1986–2010 approximated 5.6–20.99 mSv, cohort 2 (98,890 persons) with that 21–50.00 mSv. People aged 0–60 at the time of the accident were under study.

In view of reconstruction and individualization of the effective dose from long-lived radionuclides (^{137}Cs, ^{134}Cs and ^{90}Sr), epidemiological study on peculiarities of the development of nontumor diseases among inhabitants of contaminated areas depending on individual effective doses accumulated over 1986-2011. The study was conducted at the Department of Dosimetry and Radiation Hygiene, IRHE (Prof. I. A. Likhtarev et al.) [21].

In view of main tasks of the research, cohorts were formed with regard to the sex, age at the time of the accident and average individual effective doses accumulated over 1986–2011 (Table 11.16).

Epidemiological analysis of nontumor morbidity and mortality was carried out throughout observation period 1988-2011 and by periods (1988–1992, 1993–1997, 1998–2002, 2003–2007, 2008–2011).

To determine nontumor incidence among inhabitants of contaminated areas we calculated Incidence density (ID/10^3 person-years) and mean error (± m). To assess difference in morbidity between sex and age subcohorts and in dynamics by study periods Student's test (t) was used.

Table 11.16

Average (M ± δ) individual effective doses accumulated over 1986–2011 and number of inhabitants of contaminated areas with regard to the age at the time of the accident (SRU data)

Age of inhabitants of contaminated areas, years	Average individual effective doses, mSv	Number of persons in the cohort, absolute number (%)
Under 18	14.31 ± 8.69	33713 (34.08)
18–39	19.06 ± 12.20	34818 (35.20)
40–60	18.48 ± 13.36	30371 (30.72)
0–60	16.86 ± 11.61	98902 (100)

We calculated relative risks (RR) and confidence intervals (CI) for different doses to reveal relationship between circulatory diseases and radiation factor [22].

Statistical data processing was performed using software packages EXCEL 2007 (Microsoft Windows 2007).

Prospective cohort epidemiological study conducted in 1988–2010 revealed peculiarities of circulatory disease incidence among inhabitants of contaminated areas depending on age at the time of the accident and sex with regard to passport doses of settlements. Circulatory disease incidence was significantly higher among inhabitants with effective doses 21–50.00 mSv than among those with dose 5.6–20.99 mSv (Table 11.17). As evident from the table, incidence in both female cohorts was significantly higher than that of men. It is testimony of higher circulatory disease incidence among women against men in all age groups of both cohorts.

We estimated the highest incidence of circulatory diseases for inhabitants aged 40–60 at the time of the accident (Table 11.18). It evidenced to the impact of «ageing».

In both cohorts, regardless of age, sex and cumulative effective doses of radiation, we revealed increased incidence for the following groups of diseases: ischemic heart disease (ICD-10 code: I20–I25), hypertensive diseases (ICD-10 code: I10-I15), other forms of heart disease (ICD-10 code: I30–I52), cerebrovascular diseases (ICD-10 code: I60–I69), diseases of veins and lymphatic vessels (ICD-10 code: I80–I89). It should be noted that rates of hypertensive diseases, ischemic heart disease, other forms of heart disease, diseases of veins, lymphatic vessels and lymph nodes were significantly higher in cohort 2 (Table 11.19). Notice that in cohort 2 as compared to cohort 1 we observed a significant excess due to some nosologic forms.

Thus, in the group «hypertensive diseases» it is due to essential hypertension and hypertensive heart disease; «ischemic heart disease» – due to chronic ischemic heart disease; «other forms of heart disease» – mainly due to conduction disorders, heart arrest and heart failure; «diseases of

Table 11.17

Circulatory disease incidence in men and women, depending on effective doses for the period 1988–2010 (ID/10^3 person-years ± m)

Sex	Cohort 1 (5.6–20.99 mSv)	Cohort 2 (21–50.00 mSv)
Total	22.5±0.10	26.4±0.3*
Women	26.0±0.2	29.2±0.3*
Men	18.5± 0.2**	23.4±0.3*,**

Notes. * – significant difference in rates between cohorts 1 and 2; ** – significant difference in rates between men and women.

Table 11.18

Circulatory disease incidence in age groups of inhabitants of contaminated areas depending on effective doses accumulated over 1988–2010 (ID/10^3 person-years ± m)

Age, years	Cohort 1 (5.6–20.99 mSv)	Cohort 2 (21–50.00 mSv)
Total (aged 0–60)	22.5±0.10	26.4±0,2*
0–17	7.5±0.14	9.1±0.2*
18–39	18.6±0.21**	26.8±0.3*,**
40–60	41.1±0.30***	49.9±0.5*,***

Notes. * – significant difference in rates between cohorts 1 and 2; ** – significant difference in rates between age subcohorts 0–17 and 18–39; *** – significant difference in rates between age subcohorts 18–39 and 40–60.

Table 11.19

Circulatory disease incidence in inhabitants of contaminated areas under age 60 at the time of the accident depending on cumulative effective doses (ID/10^3 person-years ± m), 1988–2010

Class, group of the disease, clinical entity	ICD-10 code	Cohort 1	Cohort 2
Hypertensive diseases	I10–I15	5.017 ± 0.063	6.840 ± 0.102*
Essential hypertension	I10	1.767 ± 0.038	3.121 ± 0.069*
Hypertensive heart disease	I11	2.754 ± 0.047	3.488 ± 0.072*
Ischemic heart disease	I20–I25	8.346 ± 0.081	9.989 ± 0.123*
Other forms of chronic ischemic heart disease	I25.8	6.450 ± 0.072	8.012 ± 0.110*
Other forms of heart disease	I30–I52	3.063 ± 0.049	3.994 ± 0.078*
Cardiomyopathy	I42	1.517 ± 0.035	1.748 ± 0.051*
Conduction disorders	I44–I45	0.022 ± 0.004	0.127 ± 0.013*
Cardiac arrest	I47–I49	0.076 ± 0.008	0.446 ± 0.026*
Heart failure	I50	0.026 ± 0.005	0.169 ± 0.016*
Complications and ill-defined descriptions of heart disease	I51	1.236 ± 0.031	1.370 ± 0.045*
Cerebrovascular diseases	I60–I69	3.055 ± 0.049 *	1.710 ± 0.051
Subarachnoid hemorrhage	I60	0.014 ± 0.003	0.009 ± 0.004
Intracerebral hemorrhage	I61	0.031 ± 0.005	0.018 ± 0.005
Other non-traumatic intracranial hemorrhage	I62	0.014 ± 0.003	0.011 ± 0.004
Cerebral infarction	I63–I64	0.195 ± 0.012	0.222 ± 0.018
Occlusion and stenosis of precerebral and cerebral arteries, not resulting in cerebral infarction	I65–I66	0.099 ± 0.012 *	0.045 ± 0.010
Acute but ill-defined cerebrovascular disease	I67	0.051 ± 0.006	0.412 ± 0.025*
Cerebrovascular disorders in diseases classified elsewhere	I68	2,264 ± 0.042 *	0.904 ± 0.037
Sequelae of cerebrovascular disease	I69	0.386 ± 0.018 *	0.089 ± 0.012
Diseases of arteries, arterioles and capillaries	I70–I79	0.879 ± 0.026 *	0.625 ± 0.031
Atherosclerosis	I70	0.744 ± 0.024 *	0.530 ± 0.028
Other peripheral vascular diseases	I73	0.106 ± 0.009 *	0.054 ± 0.009
Arterial embolism and thrombosis	I74	0.002 ± 0.001	0.012 ± 0.004*
Disease of veins, lymphatic vessels and lymph nodes	I80–I89	1.642 ± 0.036	2.851 ± 0.065*
Varicose veins of lower extremities	I83	0.847 ± 0.026	1.887 ± 0.053*
Other noninfective disorders of lymphatic vessels and lymph nodes	I89	0.016 ± 0.004	0.035 ± 0.007*
Other unspecified disorders of the circulatory system	I95–I99	0.042 ± 0.006	0.121 ± 0.014*

Notes. * – significant difference in rates between cohorts 1 and 2.

veins, lymphatic vessels and lymph nodes» – due to varicose veins of lower extremities and other unspecified diseases of the circulatory system. Special attention should be paid to much higher rates for such clinical entity as «acute but ill-defined cerebrovascular disease» and «arterial embolism and thrombosis» in the cohort 2 compared to cohort 1; whereas rates for «cerebrovascular diseases» and «diseases of arteries, arterioles and capillaries» in the cohort 1 exceed significantly those in cohort 2.

Statistically significant relative risks (RR) of certain circulatory diseases in relation to cumulative effective doses are summarized in Table 11.20.

With relative risks presented in Table 11.20, we can observe dose-dependent effect in cohort 2 at doses 21.0-50.00 mSv.

Throughout observation period (1988–2010), overall mortality from circulatory diseases (ICD-10 code: I00–I99) among inhabitants of contaminated areas was estimated with regard to cumulative effective doses. It was found that overall death rate for cohort 2 was significantly higher than that of cohort 1 (Table 11.21).

Table 11.20

Relative risks (RR) for some circulatory diseases among inhabitants under age 60 at the time of the accident, cumulative effective doses in the range 21–50.00 mSv compared to those with doses 5.6–20.99 mSv. 1988–2010 observation period

Diseases of the circulatory system	ICD-10 code	RR	CI
Rheumatic aortic valve diseases	I06	2.02	1.27; 3.20
Essential hypertension	I10	1.77	1.09; 3.23
Other forms of chronic ischemic heart disease	I25.8	3.17	2.98; 3.36
Cardiomyopathy	I24	1.15	1.11; 1.19
Conduction disorders	I44–I45	5.77	2.73; 12.19
Cardiac arrest	I46–I49	5.87	1.58; 21.68
Heart failure	I50	6.50	2.13; 19.74
Arterial embolism and thrombosis	I74	6.00	2.13; 16.85
Varicose veins of lower extremities	I83	2.23	1.69; 2.92
Other non-infective disorders of lymphatic vessels and lymph nodes	I89	2.19	1.95; 2.45

Table 11.21

Overall mortality from circulatory diseases among inhabitants of contaminated areas with regard to age-at-exposure and cumulative effective doses (ID/10^3 person-years ±m). Observation period 1988–2010.

Age at the time of the accident, years	Cohort 1 (5.6–20.99 mSv)	Cohort 2 (21–50.00 mSv)
Under 18	0.75 ± 0.04	1.31 ± 0.08*
18-39	5.00 ± 0.11**	8.50 ± 0.19*,**
40-60	23.52 ± 0.24 #,##	48.95 ± 0.33*,#,##
0-60	6.29 ± 0.06	8.08 ± 0.10*

Notes. * – significant difference in death rates between age groups of both cohorts; ** – significant difference in death rates between age subcohorts under 18 and 18–39; # – significant difference in death rates between age subcohorts under 18 and 40–60; ## – significant difference in death rates between age subcohorts 18–39 and 40–60.

This is typical for all age groups under study. Mortality from circulatory diseases was particularly high among persons aged 40–60 at the time of the accident. The following diseases (ischemic heart disease, cerebrovascular diseases, other forms of heart disease, diseases of arteries, arterioles and capillaries, hypertension) are the main causes of death among inhabitants (Table 11.22).

The highest death rates were established in the older age groups (18–39 and 40–60 years at the time of the accident), it is primarily due to the effect of «age». Increased mortality in all age groups with cumulative dose in the range 21–50.00 mSv is worthy of notice.

During 1988-2011, we conducted prospective cohort epidemiological study among inhabitants of contaminated areas aged 0–60 (total cohort) depending on age at the time of the accident, sex and individual effective doses accumulated since April 26, 1986. As a result, we identified characteristic features of circulatory disease incidence Over this period, 120,405 cases of nontumor diseases were recorded in total cohort. The analysis of incidence structure found that digestive, respiratory and circulatory diseases are leaders accounting for 68.52 % (Figure 11.48).

Respiratory, digestive and circulatory diseases make major contribution to the structure of nontumor diseases among inhabitants regardless sex (Table 3.8). Large is contribution of the diseases of the endocrine and nervous systems. Among men and women, the least is percentage of mental and behavioral disorders.

Table 11.22

Death rates for main groups of circulatory diseases in age groups of inhabitants with different cumulative effective doses (ID/10³ person-years±m). Observation period 1988–2010.

Group of circulatory diseases	ICD-10 code	Age at the time of the accident (years)					
		Under 18		18–39		40–60	
		Cohort 1	Cohort 2	Cohort 1	Cohort 2	Cohort 1	Cohort 2
Hypertensive diseases	I10–I15	0.05±0.01	0.09±0.02	0.33±0.03**	0.55±0.02*,**	0.58±0.04**,#	1.17±0.08*,**,#
Ischemic heart disease	I20–I25	0.39±0.03	0.69±0.06*	2.67±0.08	4.5±0.14*,**	17.23±0.2**,#	36.14±0.43*,**,#
Pulmonary heart disease and diseases of pulmonary circulation	I26–I28	0.01±0.004	0.02±0.01	0.07±0.01**	0.1±0.02*	0.21±0.02**,#	0.44±0.05*,**,#
Other forms of heart disease	I30–I52	0.16±0.02	0.31±0.04*	1.06±0.05**	1.89±0.09*,**	1.25±0.06**,#	2.7±0.12*,**,#
Cerebrovascular diseases	I60–I69	0.1±0.01	0.1±0.02	0.6±0.04**	1.02±0.07*,**	3.01±0.08**,#	5.99±0.18*,**,#
Diseases of arteries, arterioles and capillaries	I70–I79	0.03±0.01	0.05±0.002	0.13±0.02**	0.2±0.03*,**	1.03±0.05**,#	2.06±0.1*,**,#

Notes. * – significant difference in rates between cohorts for each age subcohort; ** – significant difference in rates between age groups (under 18 years vs. aged 18–39 and 40–60) of the cohorts; # – significant difference in rates between age groups (40–60 vs. under 18 and 18–39) of the cohorts.

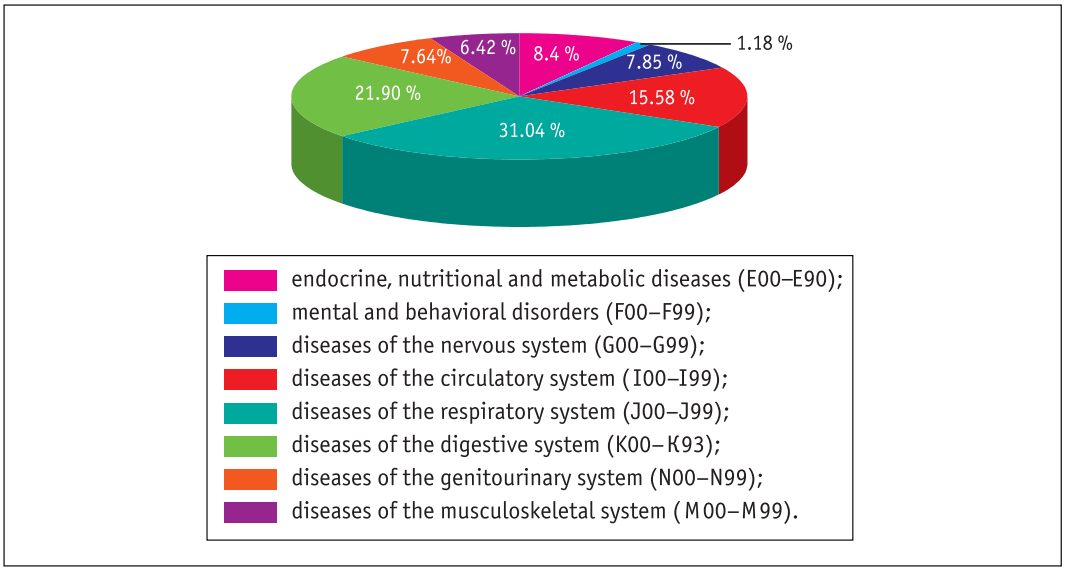


Figure 11.48. Structure of non-tumor morbidity among inhabitants of contaminated areas aged 0–60 at the time of the accident, observation period 1988–2011

It should be noted that percentage of respiratory and digestive diseases among men is much higher than among women, whereas percentage of genitourinary and circulatory diseases among women exceed that in men.

Table 11.24 gives the structure of nontumor incidence among inhabitants of contaminated areas depending on age at the time of the accident for 1988–2011.

Among inhabitants of contaminated areas under 18 years, the most common are respiratory, digestive and endocrine diseases; in age group 18–39, leaders are respiratory, digestive, circulatory and genitourinary diseases; among those aged 40–60 – circulatory, respiratory, digestive and musculoskeletal diseases.

Table 11.23
Structure of non-tumor incidence in the inhabitants of contaminated areas aged 0–60 at the time of the accident depending on sex, 1988–2011 (%)

Class of the disease, ICD–10	Men	Women
Diseases of the endocrine system (E00–E90)	9.14	8.19
Mental and behavioral disorders (F00–F99)	1.29	1.10
Diseases of the nervous system (G00–G99)	7.15	8.27
Diseases of the circulatory system (I00–I99)	14.00	16.55
Diseases of the respiratory system (J00–J99)	35.02	28.40
Diseases of the digestive system (K00–K93)	23.60	20.75
Diseases of the genitourinary system (N00–N99)	3.51	10.25
Diseases of the musculoskeletal system (M00–M99)	6.29	6.49

Table 11.24
Structure of non-tumor incidence among inhabitants of contaminated areas depending on age at the time of the accident, 1988–2011 (%)

Class of the disease, ICD–10	Age at the time of the accident, years		
	under 18	18–39	40–60
Diseases of the endocrine system (E00–E90)	20.10	2.66	1.95
Mental and behavioural disorders (F00–F99)	1.51	1.15	0.84
Diseases of the nervous system (G00–G99)	6.12	9.74	7.78
Diseases of the circulatory system (I00–I99)	5.05	11.99	30.52
Diseases of the respiratory system (J00–J99)	36.07	35.15	21.30
Diseases of the digestive system (K00–K93)	22.86	21.30	20.74
Diseases of the genitourinary system (N00–N99)	4.57	12.06	6.48
Diseases of the musculoskeletal system (M00–M99)	3.72	5.36	10.40

Table 11.25
Structure of non-tumor incidence among inhabitants of contaminated areas under age 60 at the time of the accident in the initial (1988–1992) and last (2008–2011) periods throughout observation (1988–2011), (%)

Class of the disease, ICD–10	Years of observation	
	1988–1992	2008–2011
Diseases of the endocrine system (E00–E90)	24.17	3.55
Mental and behavioural disorders (F00–F99)	2.54	1.03
Diseases of the nervous system (G00–G99)	4.22	2.12
Diseases of the circulatory system (I00–I99)	20.57	12.64
Diseases of the respiratory system (J00–J99)	17.34	65.02
Diseases of the digestive system (K00–K93)	19.72	13.09
Diseases of the genitourinary system (N00–N99)	2.35	5.84
Diseases of the musculoskeletal system (M00–M99)	9.08	0

We examined changes in the structure of non-tumor incidence among inhabitants aged 0–60 at the time of the accident; two observation periods – the late (2008–2011) and early (1988–1992) ones were compared. The results obtained are as follows. In the initial period of observation, large contribution to the structure was made by endocrine disorders, circulatory, digestive

and respiratory diseases, while in recent years – by respiratory, digestive and circulatory diseases. It should be noted that in the last period compared with the initial one, percentage of nontumor diseases has decreased significantly; while the proportion of genitourinary and respiratory diseases increased (Table 11.25).

Age-dependent difference in the structure of non-tumor incidence was observed between the early and recent periods of observation (Table 11.26). In the early period, major contribution to the structure of non-tumor incidence in men and women made endocrine, circulatory, digestive and respiratory diseases; in the late period – respiratory, digestive and circulatory diseases. It should be noted that percentage of nontumor diseases, particularly respiratory and genitourinary ones decreased substantially in the last period among both sexes (Table 11.26).

Analysis of the structure of non-tumor morbidity (1988–2011) in the total cohort of inhabitants and in age and sex groups revealed its characteristic features. Digestive, respiratory and circulatory diseases were and still are main contributors to the structure of nontumor morbidity; along with other nontumor diseases they accounted for a large percentage in the first (1988–1992) and last (2008–2011) periods of observation.

Over post-accident period (namely in the early and late ones), in the cohort under study, structure of non-tumor morbidity (respiratory, digestive, circulatory and endocrine diseases) has not changed significantly. There was insignificant percentage of diseases of the musculoskeletal and nervous systems, mental and behavioral disorders, genitourinary diseases among women.

In the last post-accident period (2008–2011), respiratory, digestive and circulatory diseases approximated 90% in the structure of non-tumor morbidity among men. Whereas proportion of respiratory and genitourinary diseases increased. Among women, respiratory, digestive and circulatory diseases approximated 90%. The proportion of genitourinary diseases increased three times in men and twice in women.

Peculiarity of the structure of non-tumor morbidity among inhabitants of contaminated areas is dependent on their age at the time of the accident. Among inhabitants under age 18, endocrine, respiratory and digestive diseases, diseases of the nervous system made major contribution, among people aged 18–39 – respiratory, digestive, circulatory and genitourinary diseases, among those aged 40–60 – circulatory, respiratory, digestive and musculoskeletal diseases.

The data obtained are essential in planning, organization and implementation of medical and preventive care for inhabitants of contaminated areas in the latest post-accident period.

Table 11.26

Structure of non-tumor incidence among male and female inhabitants under age 60 at the time of the accident in the initial and late periods of observation (%)

Class of the disease, ICD–10	Years of observation			
	1988–1992		2008–2011	
	Men	Women	Men	Women
Diseases of the endocrine system (E00-E90)	25.65	1.33	22.97	4.90
Mental and behavioral disorders (F00-F99)	3.03	0.00	2.16	0.06
Diseases of the nervous system (G00-G99)	4.03	1.58	4.35	2.56
Diseases of the circulatory system (I00-I99)	18.06	9.32	22.42	14.37
Diseases of the respiratory system (J00-J99)	18.96	68.14	16.35	57.60
Diseases of the digestive system (K00-K93)	20.36	12.40	19.18	13.04
Diseases of the genitourinary system (N00-N99)	0.91	3.08	3.44	7.47
Diseases of the musculoskeletal system (M00-M99)	9.00	0.00	9.13	0.00

Study of risks for non-tumor diseases among inhabitants of contaminated areas revealed the following. The overall non-tumor incidence among inhabitants aged 0–60 years at the time of the accident is 101.54±0.28 ID per 1000 person-years. In men, the overall non-tumor incidence was significantly lower (86.04±0.38) than that in women (114.69 ± 0.77). The overall non-tumor incidence in age groups is presented in Table 11.27.

Table 11.27

The overall non-tumor incidence (ID/10^3 person-years±m) among inhabitants depending on age at the time of the accident, 1988–2011

Age at the time of the accident, years		
under 18	18–39	40–60
104.40 ± 0.48	96.21 ± 0.46	116.0 ± 0.52

Significantly lower non-tumor incidence was found among people aged 18–39 compared with younger and older age groups, the highest – among those aged 40–60.

Figure 11.49 gives the overall non-tumor incidence depending on sex in age groups. As can be seen from the figure, the overall rates of non-tumor incidence in women of all ages are significantly higher than those in men.

Based on the data obtained it may be concluded that non-tumor incidence among women is significantly higher than that in men. But higher rates of non-tumor incidence in men and women in age groups under 18 and 40–60 years at the time of the accident are due to age-related characteristics of human body: first case – age periodization of human body, the second - irreversible changes associated with aging.

Dynamics of non-tumor diseases among inhabitants of contaminated areas aged 0–60 at the time of the accident by observation periods is illustrated in Figure 11.50.

The highest overall non-tumor incidence was determined in the first five years of monitoring. We have noticed a gradual decline in rates, especially in the last period (2008-2011).

The dynamics of overall non-tumor incidence depending on sex of inhabitants is similar in nature (Figure 11.51). The highest overall non-tumor incidence was observed within the first five years of monitoring, with gradual decline in each subsequent period and lowest rate in the last period (2008–2011).

Analysis of the structure and rate of non-tumor incidence, 1988–2011, revealed the following diseases (digestive, respiratory, circulatory, endocrine, genitourinary and musculoskeletal diseases) being the most common among inhabitants of contaminated areas.

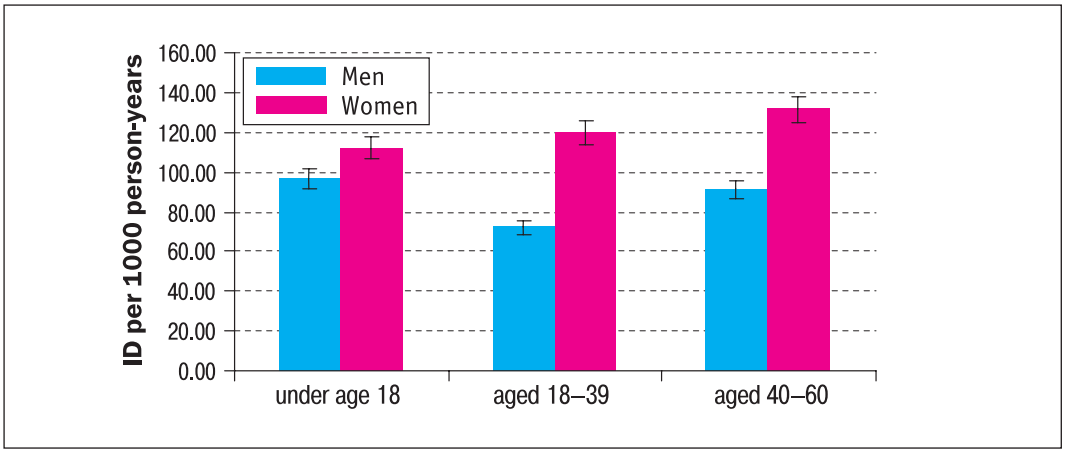


Figure 11.49. Overall non-tumor incidence among male and female inhabitants of contaminated areas depending on age at the time of the accident, 1988–2011

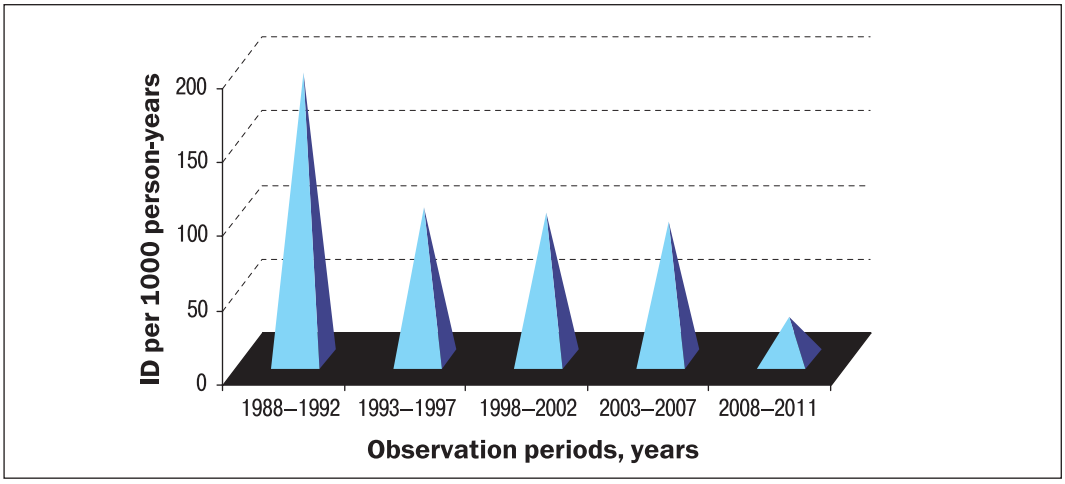


Figure 11.50. **Dynamics of overall non-tumor incidence among inhabitants of contaminated areas aged 0–60 at the time of the accident by post-accident periods of observation, 1988–2011**

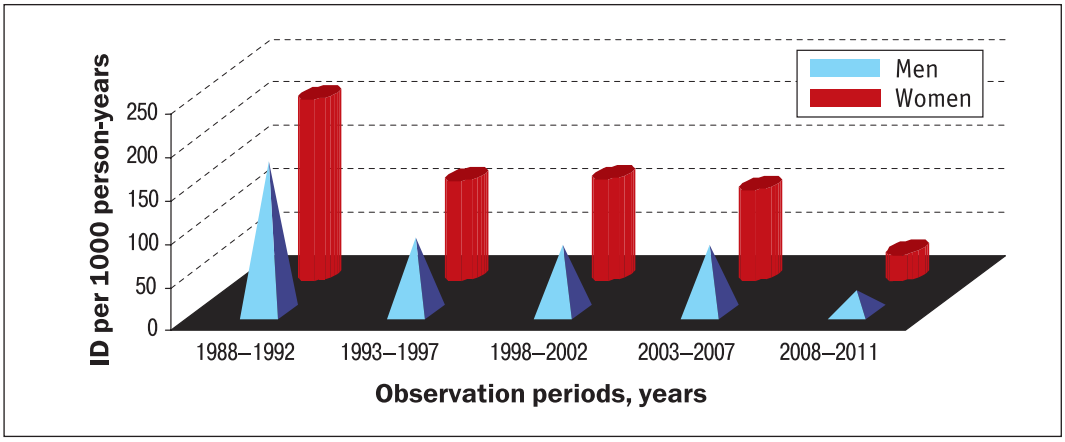


Figure 11.51. **Dynamics of overall non-tumor incidence in male and female inhabitants of contaminated areas by periods of observation, 1988–2011**

Considering that circulatory diseases make the major contribution to the structure of nontumor incidence and causes of death, there is a need for a detailed descriptive and analytical study on mechanism of development of these diseases.

Analysis of circulatory disease structure among inhabitants of contaminated areas has found that ischemic heart disease forms one third of overall morbidity (Table 11.28). IHD is followed by hypertensive diseases, cerebrovascular diseases, and diseases of veins, lymphatic vessels and lymph nodes, diseases of arteries, arterioles and capillaries. These diseases form nearly 80% of circulatory disease incidence structure, other diseases – 20%. Structure of circulatory diseases in men and women is practically identical.

Throughout the observation, ischemic heart disease and hypertensive diseases made a major contribution to the structure of circulatory diseases in cohort of inhabitants: 59.36% – in the initial (1988–1992) and 50.8% – in the late (2008–2011) periods (Figure 11.52).

Table 11.28

Structure of circulatory diseases among inhabitants of contaminated areas aged 0–60 at the time of the accident with regard to sex, 1988–2011 observation period

Diseases of the circulatory system	ICD–10	Men		Women		Total	
		abs. number	%	abs. number	%	abs. number	%
Total	I00.0–I99.9	6579	100	12224	100	18803	100
Hypertensive diseases	I10.0–I15.9	1162	17.66	2029	16.59	3191	16.97
Ischemic heart disease	I20.0–I25.9	2215	33.67	4440	36.32	6655	35.39
Cerebrovascular diseases	I60.0–I69.8	641	9.74	1699	13.89	2340	12.44
Diseases of arteries, arterioles and capillaries	I70.0–I79.8	372	5.65	570	4.66	942	5.01
Diseases of veins, lymphatic vessels and lymph nodes	I80.0–I89.9	704	10.70	1080	8.83	1784	9.48

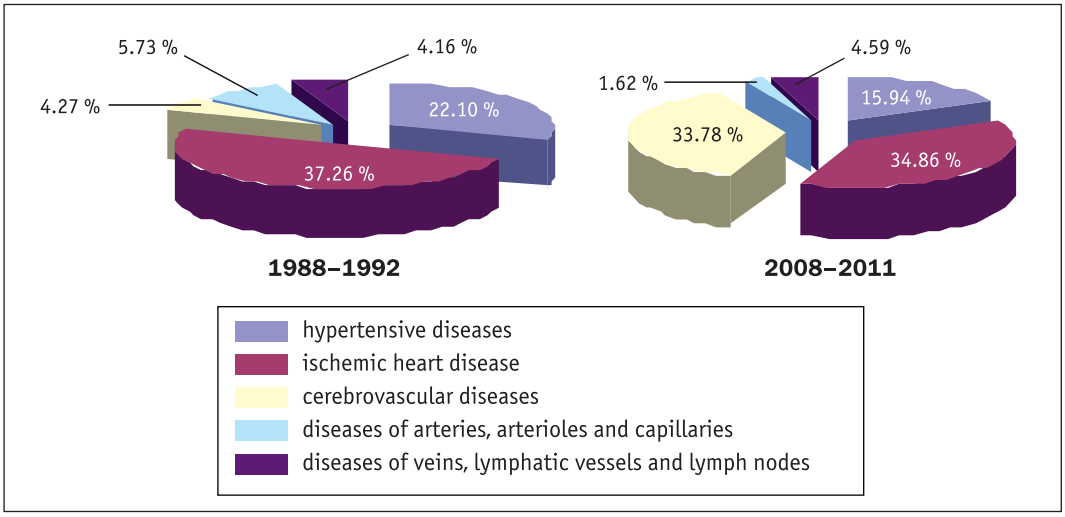


Figure 11.52. Structure of circulatory diseases among inhabitants of contaminated areas aged 0–60 at the time of the accident in the early and late periods of observation 1988–2011

While recently in the structure of circulatory diseases in total cohort of inhabitants, the percentage of cerebrovascular diseases has increased by almost 30 %. It is largely due to decrease of ischemic heart disease, hypertensive diseases, diseases of arteries, arterioles and capillaries.

Among men, ischemic heart disease and hypertensive diseases made major contribution to the structure of circulatory diseases during the first and last periods of observation (Table 11.29). In recent years, we observed a significant growth (by 23.61 %) of cerebrovascular diseases and ischemic heart disease.

Among women, in the early and late periods of observation, ischemic heart disease and hypertensive diseases are leaders in the structure of circulatory diseases (Table 11.30). In recent years, we have noted a substantially increased percentage (by 31.87 %) of cerebrovascular diseases.

Analysis of the dynamics of circulatory disease incidence among inhabitants of contaminated areas was conducted by periods of observation 1988–2011 depending on age at the time of the accident, sex and individual effective doses accumulated over 1986–2011.

Incidence rates for circulatory diseases among inhabitants depending on age at the time of the accident are given in Table 11.31.

Table 11.29
Structure of circulatory diseases among male inhabitants of contaminated areas aged 0–60 at the time of the accident, in the early and late periods of observation 1988–2011

Diseases of the circulatory system	ICD-10	Men			
		1988–1992		2008–2011	
		abs. number	%	abs. number	%
Total	I00.0-I99.9	1953	100	112	100
Hypertensive diseases	I10.0-I15.9	442	22.63	19	16.96
Ischemic heart disease	I20.0-I25.9	661	33.84	45	40.17
Cerebrovascular diseases	I60.0-I69.8	62	3.17	30	26.78
Diseases of arteries, arterioles and capillaries	I70.0-I79.8	89	4.55	5	4.46
Diseases of veins, lymphatic vessels and lymph nodes	I80.0-I89.9	69	3.53	5	4.46

Table 11.30
Structure of circulatory diseases among female inhabitants of contaminated areas aged 0–60 at the time of the accident, in the early and late periods of observation 1988–2011

Circulatory diseases	ICD-10	Women			
		1988–1992		2008–2011	
		abs. number	%	abs. number	%
Total	I00.0-99.9	3191	100	258	100
Hypertensive diseases	I10.0-I15.9	695	21.78	40	15.50
Ischemic heart disease	I20.0-I25.9	1256	39.36	84	32.55
Cerebrovascular diseases	I60.0-I69.8	158	4.95	95	36.82
Diseases of arteries, arterioles and capillaries	I70.0-I79.8	206	6.45	1	0.38
Diseases of veins, lymphatic vessels and lymph nodes	I80.0-I89.9	145	4.54	12	4.65

Table 11.31
Circulatory disease incidence among inhabitants of contaminated areas by periods of observation depending on age at the time of the accident (ID/10^3 person-years±m)

Age of inhabitants at the time of the accident (years)	Periods of observation, years				
	1988–1992	1993–1997	1998–2002	2003–2007	2008–2012
Under 18	32 ± 0.67	10 ± 0.38*	6 ± 0.23*,**	5 ± 0.20*,**	2 ± 0.25*,**
18–39	105 ± 1.88	17 ± 0.55*	15 ± 0.33*,**	13 ± 0.29*,**	6 ± 0.37*,**
40–60	208 ± 2.18	36 ± 0.73*	30 ± 0.49*,**	21 ± 0.40*,**	6 ± 0.43*,**

Notes. * – significant difference between the first and other observation periods; ** – significant difference between the first and second observation periods.

The highest incidence of circulatory diseases was observed in the earlier post-accident period among inhabitants of contaminated areas of all ages. The highest incidence rate was recorded among those aged 40–60 at the time of the accident. Gradual decline was observed in 1993–2007 and especially in the late period (2008–2011). The highest incidence of circulatory diseases in an early post-accident period is probably due to effective screening especially in age subcohort 40–60 years at the time of the accident. However, the impact of such factors as psychosocial stress, whole body irradiation and thyroid status cannot be excluded. An answer is yet to be found.

Circulatory disease incidence among inhabitants of contaminated areas depending on age and individual effective doses accumulated over 1986–2011 is given in Figure 11.53. Based on these

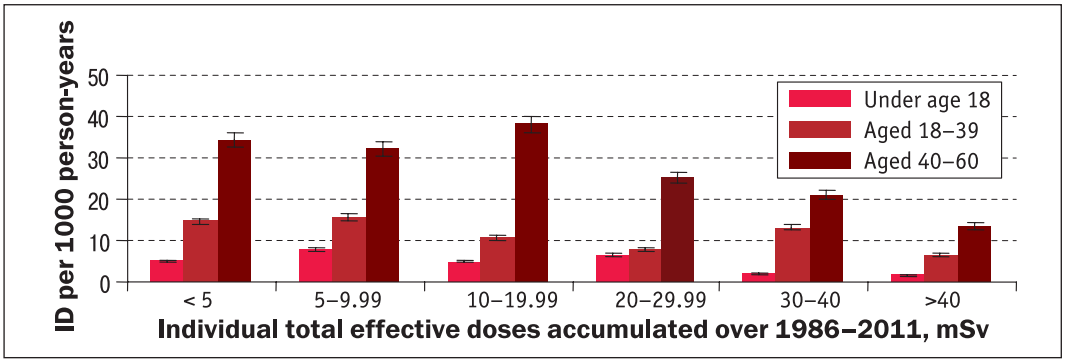


Figure 11.53. **Overall circulatory disease incidence in age groups of inhabitants of contaminated areas depending on individual total effective doses accumulated over 1986–2011, mSv**

data it may be concluded that there is no clear relationship between overall circulatory disease incidence and cumulative individual effective doses in all age groups.

Similar results were obtained in the analysis of circulatory disease incidence among inhabitants of different ages depending on sex (Figures 11.54, 11.55).

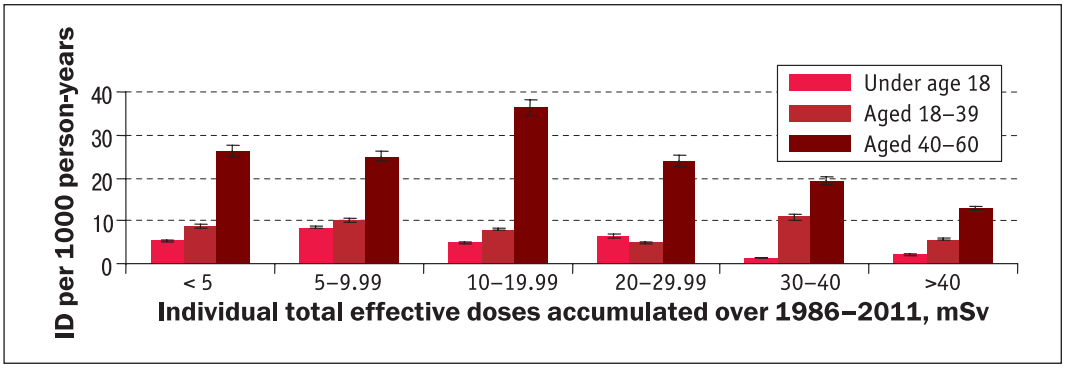


Figure 11.54. **Overall incidence of circulatory diseases among male inhabitants of all ages depending on individual total effective doses accumulated over 1986–2011, mSv**

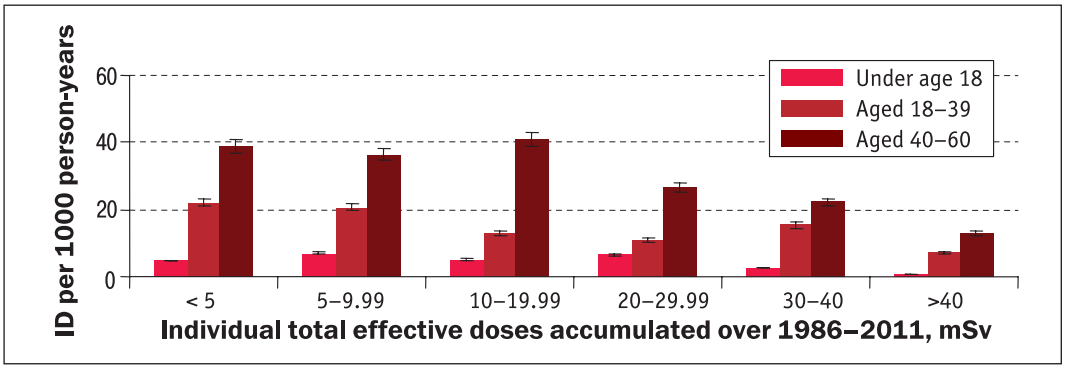


Figure 11.55. **Overall incidence of circulatory diseases among female inhabitants of all ages depending on individual total effective doses accumulated over 1986–2011, mSv**

To explain this result it can be assumed that low and very low doses of chronic radiation do not activate protective functions of the body and thus may be a risk factor for stochastic effects such as circulatory diseases. However, this assumption requires confirmation.

Circulatory disease incidence among older women is higher than that in younger age group within all dose intervals (Figure 11.55).

Figures 11.56–11.58 represent circulatory disease incidence among inhabitants of contaminated areas depending on age at the time of the accident, sex and effective doses accumulated over 1986–2011.

Figure 11.56 shows that the highest incidence of circulatory diseases among inhabitants under age 18 at the time of the accident was observed in the range <5 ... <29.99 mSv.

As seen from Figure 11.57, the highest incidence of circulatory diseases among inhabitants of contaminated areas aged 18-39 at the time of the accident is observed in the range <5 ... 40 mSv.

As illustrated (in Figure 11.58) the highest incidence of circulatory diseases among inhabitants of contaminated areas aged 40–60 at the time of the accident is observed in the range < 5...40 mSv.

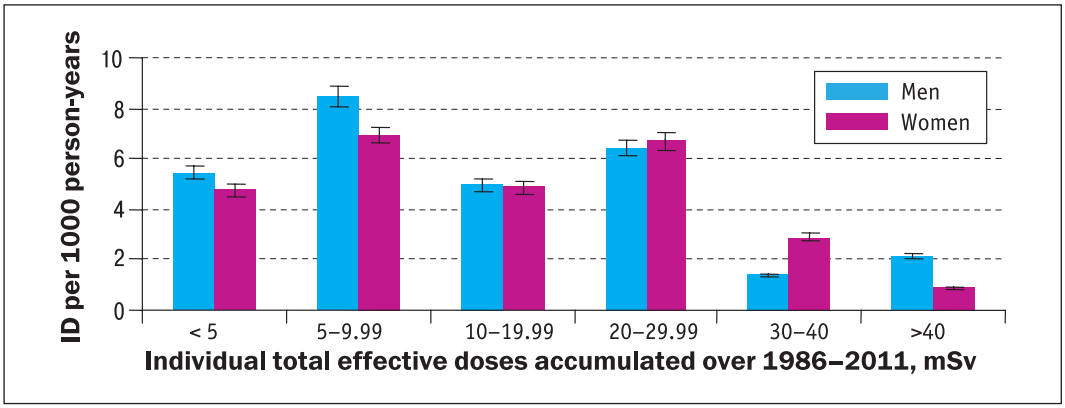


Figure 11.56. Overall incidence of circulatory diseases among inhabitants of contaminated areas under age 18 at the time of the accident depending on sex and individual total effective doses accumulated over 1986–2011

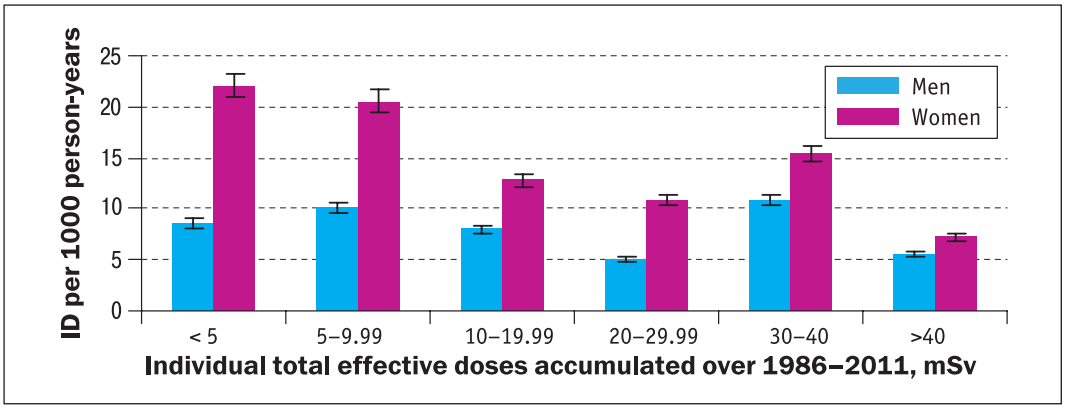


Figure 11.57. Overall incidence of circulatory diseases among inhabitants of contaminated areas aged 18–39 at the time of the accident depending on sex and individual total effective doses accumulated over 1986–2011

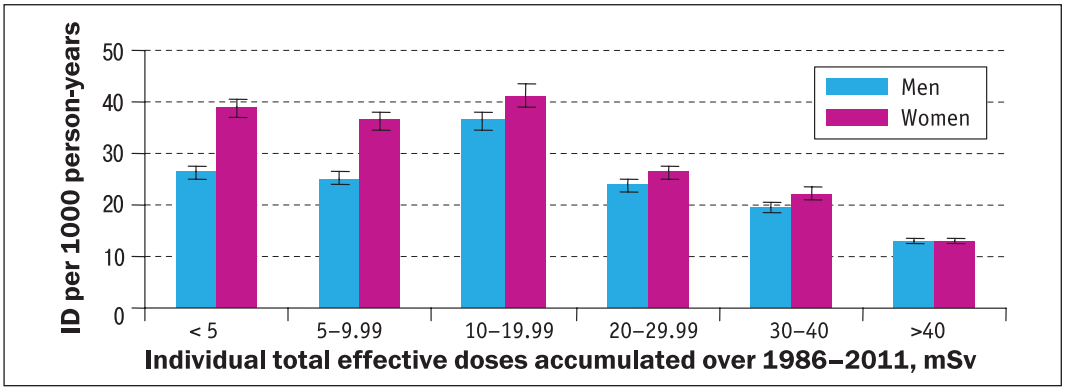


Figure 11.58. **Overall incidence of circulatory diseases among inhabitants of contaminated areas aged 40–60 at the time of the accident depending on sex and individual total effective doses accumulated over 1986–2011**

As evident from Figures 11.56–11.58, the highest circulatory disease incidence was due to low and very low doses (< 5...≥ 40 mSv), regardless of age at the time of the accident. This supports the above assumption as to the risk of low-dose radiation. Circulatory disease incidence among women exceeds that among men.

There is no doubt that the effects of low and very low doses of chronic radiation exposure might have not influenced on the overall rate of circulatory diseases. So there was an objective need for a detailed epidemiological analysis. Relevant data are given in Tables 11.32–11.35.

As a result, some unstable and ambiguous dose-dependent effects were identified.

We examined dose-dependent effects on the development of circulatory diseases depending on individual effective doses accumulated over 1986–2011. In Table 11.32 tabulated are relative risks (RR) with 95 % confidence interval (CI) for circulatory diseases in age groups of inhabitants of contaminated areas depending on individual effective doses accumulated over 1986–2011.

The interpretation of data obtained is far yet difficult. However, some preliminary conclusions can be made. Long-term (in this case 25 years) chronic whole body ionizing radiation under low and very low doses (average between 0.2 and 1.5 mSv) may be considered as additional risk factors for such circulatory diseases as hypertensive diseases, ischemic heart disease and cerebrovascular diseases.

Table 11.32

Relative risks (RR) and 95 % confidence intervals (CI) of circulatory diseases in age groups of inhabitants of contaminated areas depending on individual total effective doses accumulated over 1986–2011 (dose less than 5 mSv – control dose relative to other individual effective doses)

Individual total effective doses accumulated over 1986–2011, mSv	Age at the time of the accident (years)					
	Under 18		18–39		40–60	
	RR	CI	RR	CI	RR	CI
≥ 5 < 9.99	1.52	1.49; 1.53	1.08	1.07; 1.08	1.33	1.30; 1.34
≥ 10 < 19.99	0.97	0.95; 0.98	0.73	0.72; 0.74	1.11	1.09; 1.12
≥ 20 < 29.99	1.30	1.28; 1.31	0.50	0.50; 0.50	0.74	0.73; 0.74
≥ 30 ≤ 40	0.40	0.40; 0.40	0.90	0.90; 0.90	0.64	0.63; 0.65
> 40	0.30	0.30; 0.30	0.40	0.40; 0.40	0.39	0.38; 0.40

Table 11.33

Relative risks (RR) and 95 % confidence intervals (CI) of hypertensive diseases (ICD-10 code: I10–I15) among inhabitants with regard to age at the time of the accident and individual total effective doses accumulated over 1986–2011 (dose less than 5 mSv is a control dose)

Periods of observation, years	Intervals of individual total effective doses accumulated over 1986–2011									
	≥ 5–9.99		≥ 10–19.99		≥ 20–29.99		≥ 30–40		>40	
	RR	CI	RR	CI	RR	CI	RR	CI	RR	CI
Under age 18										
1988–1992	–	–	–	–	–	–	–	–	–	–
1993–1997	–	–	4.3	4.24;4.39	–	–	–	–	–	–
1998–2002	16	16.04;16.77	3.4	3.35;3.45	11.1	10.86;11.32	3.5	3.41;3.67	8.31	7.87;8.77
2003–2007	4.8	4.66;4.89	0.2	0.19;0.19	0.96	0.94;0.98	1.4	1.34;1.43	–	–
2008–2011	–	–	0.8	0.77;0.81	4.86	4.64;5.09	24	22.54;26.40	–	–
Aged 18–39										
1988–1992	3.0	2.88;3.16	4.9	4.78;4.94	3.00	2.82;3.17	1.7	1.54;1.82	0.81	0.77;0.85
1993–1997	3.0	2.97;3.06	0.9	0.88;0.92	0.41	0.39;0.42	0.4	0.42;0.45	0.65	0.63;0.68
1998–2002	1.0	0.93;0.97	6.3	6.19;6.40	5.55	5.45;5.64	5.6	5.45;5.71	1.35	1,32;1.39
2003–2007	1.7	1.64;1.72	0.6	0.56;0.59	0.41	0.40;0.42	0.9	0.85;0.89	0.82	0.79;0.84
2008–2011	0.2	0.15;0.16	0.7	0.69;0.72	1.28	1.24;1.32	2.4	2.29;2.51	–	–
Aged 40–60										
1988–1992	5.5	5.27;5.67	6.9	6.69;7.13	4.09	3.9;4.30	–	–	0.48	0.46;0.50
1993–1997	1.4	1.37;1.44	0.9	0.87;0.91	1.65	1.60;1.70	0.6	0.60;0.66	0.88	0.85;0.92
1998–2002	0.8	0.81;0.85	7.0	6.90;7.13	4.96	4.87;5.05	3.0	2.95;3.09	3.33	3.24;3.43
2003–2007	0.3	0.27;0.28	2.7	2.65;2.75	1.35	1.30;1.32	1.4	1.39;1.46	1.60	1,56;1.65
2008–2011	–	–	–	–	–	–	–	–	–	–

Table 11.34

Relative risks (RR) and 95 % confidence intervals (CI) of ischemic heart disease (ICD-10 code: I20–I25) among inhabitants with regard to age at the time of the accident and individual total effective doses accumulated over 1986–2011 (dose less than 5 mSv is a control dose)

Periods of observation, years	Intervals of individual total effective doses accumulated over 1986–2011, mSv									
	≥ 5–9.99		≥ 10–19.99		≥ 20–29.99		≥ 30–40		>40	
	RR	CI	RR	CI	RR	CI	RR	CI	RR	CI
Under age 18										
1988–1992	–	–	–	–	–	–	–	–	–	–
1993–1997	–	–	0.5	0.49;0.51	0.36	0.35;0.37	–	–	–	–
1998–2002	–	–	0.94	0.93;0.96	0.79	0.76;0.80	–	–	–	–
2003–2007	0.8	0.76;0.79	0.5	0.51;0.53	1.42	1.37;1.43	–	–	–	–
2008–2011	2.2	2.11;2.31	0.4	0.38;0.40	2.43	2.32;2.55	–	–	–	–
Aged 18–39										
1988–1992	2.89	2.76;3.04	2.94	2.83;2.93	0.69	0.65;0.73	–	–	0.17	0.17;0.18
1993–1997	1.83	1.79;1.85	0.27	0.27;0.28	0.46	0.44;0.47	0.22	0.21;0.23	0.39	0.38;0.41
1998–2002	0.23	0.22;0.23	0.4	0.39;0.41	0.29	0.29;0.30	0.26	0.26;0.27	0.17	0.17;0.18
2003–2007	0.51	0.50;0.52	0.21	0.21;0.22	0.15	0.15;0.15	0.17	0.16;0.17	0.32	0.31;0.33
2008–2011	0.31	0.30;0.32	0.19	0.19;0.20	0.21	0.20;0.22	0.58	0.56;0.61	0.24	0.23;0.26
Aged 40–60										
1988–1992	7.16	6.90;7.42	6.51	6.31;6.17	2.25	2.15;2.36	0.97	0.88;1.06	0.26	0.25;0.27
1993–1997	1.05	1.03;1.08	0.23	0.23;0.24	0.51	0.49;0.52	0.08	0.07;0.08	0.37	0.35;0.38
1998–2002	0.38	0.37;0.39	0.78	0.76;0.79	0.86	0.84;0.87	1.26	1.23;1.29	0.67	0.65;0.69
2003–2007	0.39	0.38;0.40	0.42	0.41;0.42	0.59	0.57;0.58	0.44	0.43;0.45	0.26	0.25;0.27
2008–2011	0.17	0.16;0.17	0.34	0.34;0.36	0.71	0.68;0.74	0.52	0.49;0.55	0.38	0.35;0.41

Table 11.35

Relative risks (RR) and 95 % confidence intervals (CI) of cerebrovascular diseases (ICD-10 code: I60–I69) among inhabitants of contaminated areas with regard to age at the time of the accident and individual total effective doses accumulated over 1986–2011 (dose less than 5 mSv is a control dose relative to other individual effective doses)

Periods of observation, years	Intervals of individual total effective doses accumulated over 1986–2011, mSv									
	≥ 5–9.99		≥ 10–19.99		≥ 20–29.99		≥ 30–40		>40	
	RR	CI	RR	CI	RR	CI	RR	CI	RR	CI
Under age 18										
1988–1992	–	–	–	–	–	–	–	–	–	–
1993–1997	0.71	0.69;0.73	0.96	0.94;0.97	–	–	–	–	–	–
1998–2002	0.19	0.18;0.19	0.03	0.03;0.03	–	–	–	–	–	–
2003–2007	–	–	0.07	0.07;0.07	–	–	–	–	–	–
2008–2011	–	–	–	–	–	–	–	–	–	–
Aged 18–39										
1988–1992	–	–	2.94	2.83;2.94	–	–	–	–	1.39	1.32;1.45
1993–1997	1.41	1.38;1.43	0.52	0.51;0.53	–	–	–	–	–	–
1998–2002	0.53	0.51;0.54	0.22	0.21;0.22	0.03	0.02;0.03	0.06	0.06;0.06	–	–
2003–2007	0.64	0.62;0.65	0.23	0.22;0.23	0.01	0.01;0.01	0.02	0.01;0.02	0.06	0.06;0.06
2008–2011	0.35	0.34;0.36	0.11	0.11;0.11	0.07	0.06;0.07	0.55	0.53;0.58	–	–
Aged 40–60										
1988–1992	1.72	1.66;1.78	1.53	1.48;1.58	0.37	0.35;0.39	1.36	1.24;1.49	0.14	0.13;0.14
1993–1997	1.09	1.07;1.12	0.28	0.27;0.28	0.3	0.29;0.31	0.04	0.04;0.04	0.03	0.03;0.03
1998–2002	0.29	0.29;0.30	0.12	0.12;0.12	0.16	0.16;0.16	0.11	0.10;0.11	0.05	0.05;0.05
2003–2007	0.36	0.36;0.37	0.10	0.10;0.11	0.02	0.02;0.02	0.06	0.06;0.06	0.07	0.06;0.07
2008–2011	0.13	0.13;0.14	0.03	0.03;0.03	–	–	0.14	0.13;0.15	–	–

In persons aged under 18 at the time of the accident (April 26, 1986), dose-dependent effects occur mainly in the remote period: hypertensive diseases 12–21 years after the accident (Table 11.33), ischemic heart disease – 17–21 years (Table 11.34), cerebrovascular diseases – no association with dose was found (Table 11.35).

Among persons aged 18–39 at the time of the accident (April 26, 1986), dose-dependent effects on the development of hypertensive diseases (Table 11.33) are typical for all observation periods. As for dose-dependent effects on ischemic heart disease (Table 11.34), the result is very ambiguous. Significant relative risks were established only in an early post-radiation period under low or very low individual total effective doses (5–29 mSv). Similar results were obtained concerning cerebrovascular diseases (Table 11.35).

Among people aged 40–60 at the time of the accident (April 26, 1986), we reported significant dose-dependent effects on the development of hypertensive diseases (Table 11.33) in an early period within the range of individual total effective doses 5–30 mSv; in remote period (12–21 years after the accident) – in dose range 10–40 mSv and more. As for ischemic heart disease (Table 11.34), cumulative individual total effective doses ranging from 5 to 30 mSv were observed in an early period. As to cerebrovascular pathology (Table 11.35), individual effective doses in the range from 5 to 40 mSv were recorded mainly within earlier post-accidental years (1986–1992).

* * *

Analysis was conducted to establish relationship between the development of circulatory diseases among inhabitants of contaminated areas and effective doses accumulated over 1986–2011 under chronic external and internal radiation exposure at low and very low doses (<5...>40 мЗв). Radiation was considered to be a significant risk factor for the development of respiratory, diges-

tive, circulatory, genitourinary and musculoskeletal diseases in survivors' sex and age subcohorts. Over study period, rapid (nearly double) increase in the percentage of circulatory diseases in the structure of nontumor diseases was recorded: 5.05% among inhabitants under age 18, 11.99% among those aged 18–39 and 30.52% in persons aged 40–60, while there was a decrease in the percentage of other nontumor diseases. This was an objective reason for further in-depth epidemiological study of circulatory diseases among inhabitants of contaminated areas exposed to effective doses accumulated over 1986–2011 with regard to age at the time of the accident and sex.

In the structure of circulatory disease incidence among inhabitants of contaminated areas, the highest were contributions of ischemic heart disease (ICD-10 code: I20.0-I25.0), hypertensive diseases (ICD-10 code: I10.0–I15.9), diseases of arteries, arterioles and capillaries, cerebrovascular diseases (ICD-10 code: I60.0–I69.8), and diseases of veins, lymphatic vessels and lymph nodes (ICD-10 code: I80.0–I89.9). It should be noted that rates for nearly all of the above nosological forms are significantly higher in the cohort 2 of inhabitants of contaminated areas; their cumulative effective doses (21–50 mSv) exceed those of the other cohort (5.6–20.99 mSv).

As is easy to see, the circulatory disease incidence among inhabitants of contaminated areas depending on age at the time of the accident, sex and effective doses accumulated over 1986–2011 were significantly higher in earlier post-accident periods as compared to the later ones. This is most probably due to effective screening particularly in the subcohort of people aged 40–60 at the time of the accident.

It was reported that throughout observation period the overall death rate for the cohort 2 was significantly higher than that of the cohort 1, regardless of age at the time of the accident. It is indicative of dose-dependent effect. Particularly high mortality from circulatory diseases was noted among people aged 40–60 at the time of the accident. The following diseases (ischemic heart disease, cerebrovascular diseases, other forms of heart disease, diseases of arteries, arterioles and capillaries, hypertensive diseases) are the main (in order of importance) causes of death among inhabitants of contaminated areas.

However, we cannot exclude the impact of the following factors: psychosocial stress, radiation exposure, thyroid status etc. But since we do not have the answer, further profound epidemiological study is needed to establish nontumor incidence patterns and to develop measures of medical care for victims of the Chornobyl accident.

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Chapter 12
NON-MALIGNANT ENDOCRINE DISEASE, ITS STAGES AND PATHWAYS IN CHILDREN AND ADULTS EXPOSED TO IONIZING RADIATION AFTER THE CHORNOBYL NPP ACCIDENT

The Chornobyl nuclear power plant (ChNPP) accident was followed by a fallout of numerous radioactive isotopes some of which been tropic to human endocrine tissues. The radioactive iodine was of especial role as upon incorporation it appeared a major dose contributor. The integral deleterious effect of the fallout on endocrine cells was exacerbated by external γ-radiation. Not unlike releases of iodine, cesium, and plutonium isotopes occurred at the Fukushima NPP in Japan in 2011. Moreover, the Fukushima meltdown resulted in a continuous leakage of multiple radioactive substances to the water of Pacific leading to contamination of marine food products potentially important for human nutrition in the regional countries. Radionuclide air emissions in the Northern hemisphere were also possible.

Such radiation impact resulted in a high prevalence of non-malignant endocrine disease in the ChNPP accident survivors, especially in the ChNNP accident clean-up workers (ACUW) [1–3]. Onset and distribution of such diseases lead to decrease of population workability, life quality and life span. All those require the substantial financial expenditures on further medical management, rehabilitation, and social adaptation of the patients. Our previous research indicated the progressing incidence and prevalence increase of hyperplastic, hypertrophic and autoimmune thyroid disease, type 2 diabetes mellitus, obesity, and metabolic syndrome with peak onset in 10–20 years upon a radiation impact [1–5].

For now the impact of ionizing radiation (IR) is proven only for thyroid cancer in children with incidence of 9 : 100000 (or 0.00001%) in children and 0.07% in adults. Thyroid cancer can be life threatening in some cases despite it is a rare disease. However in years before present the rather wide range of disorders with 13000–52000 : 100000 incidence was out of the scientific limelight featuring the nonmalignant endocrine disease. This fact is proven by a few available publications on the results of conducted research. Nevertheless the long-term clinical surveys managed by the SCRM staff and data from the SCRM Clinical-Epidemiological Registry for

1992–2015 period newly analyzed by years with contemporary diagnostic criteria application indicate to the high integral prevalence of nonmalignant thyroid disease in substantially all groups of survivors (85% in adults, and 62% in children and adolescents). It is substantially exceeding the prevalence values in a general public of Ukraine that had escaped the accidental exposure [1–3].

The cohort of 87,000 A-bombing survivors in Hiroshima and Nagasaki exposed to IR at doses under 0.5 Gy was the principal source of data on remote radiation risks to human health before the ChNPP accident. These Japanese data indicated the dose-effect dependence of mortality from nonmalignant diseases, thyroid cancer and nodular goiter, that arise more often in persons exposed to IR in childhood or adolescence [4–9] especially in children who had experienced a prenatal irradiation. The threshold radiation dose for onset of benign thyroid adenoma was < 0.25 Gy, and calculated average dose on chest for onset of breast cancer was 0.69 Gy. The dependence of «autoimmune hypothyroidism» on radiation dose was established in A-bombing survivors in Nagasaki [10] and in children exposed to radiation [11].

Thyroid disease as a result of A-bombing in Japan was diagnosed in 44.8% of males and 51.0% of females. Solid nodules were revealed there in 14.6% of cases, malignancies in 2.2%, benign nodules in 4.9%, and cysts in 7.7% [12]. Positive titers of thyroid antibodies were detected in 28.2% of hibakusha, antibody-positive hypothyroidism was diagnosed in 3.2%, and Grave's disease in 1.2% of cases. The strong linear «dose-effect» dependence was surveyed for all malignancies, benign nodules, and cysts ($p<0.01$). According to estimates of the authors of this study about 28.0% of solid nodules, 37% of malignant tumors, 31% of benign nodules, and 25.0% of cysts were related to radiation impact at medium (0.449 Sv) and low (0.078) radiation doses. At that, no any significant dependence was found between the radiation dose and thyroid effects in the spectrum of positive titers of thyroid antibodies, antibody-positive hypothyroidism, or Grave's disease [13].

Comparing the risk of overt hypothyroidism in subgroup of elderly Japanese A-bombing survivors the overt disease was four-fold more expectable in subjects with a subclinical form vs. euthyroid persons. The initial serum TSH content is a potential predictor of the further thyroid dysfunction. No dependence of hypothyroidism on radiation dose or dose of a replacement hormonal therapy was found by the authors [13].

Similar data were received upon 16 nuclear and 1 thermonuclear weapon testing on the Marshall Islands where the impact of 131I resulted in an increased incidence of nodular goiter in islanders exposed to radioactive fallout [14–17].

In a cohort study of persons exposed to ionizing radiation from the Hanford radioactive fallout in 1944–1956 (n = 3191, 0.29–2823 mGy dose range, 97 mGy median dose, 174 mGy average dose) [18] the chronic autoimmune thyroiditis was diagnosed in 18.2% (23.1% females, 13.1% males), thyroid cancer in 0.7% females and 0.4% males, hypothyroidism in 7.8% (11.7% females and 3.7% males), autoimmune thyroiditis with any kind of hypothyroidism in 5.1% (7.7% females and 2.4% males), autoimmune thyroiditis with stable hypothyroidism in 4.7% (7.0% females, 2.3% males). No any dose dependence was revealed however. Reviewing theese results the experts concluded that thyroid radiation effects were observed for up to 50 years and have not realized yet to a full extent [18].

The study of health and thyroid in particular in Belarusian children exposed after the ChNPP accident revealed an increase in thyroid antibody titer [17, 19]. Experts conclude that such a fact can be related to the extra amplification of radiation impact at the background of moderate iodine deficiency [20]. Nodular goiter and chronic thyroiditis making the 6.4% of follicular neoplasms were the principal nonmalignant thyroid diseases in 55,054 children. Adenomatous

goiter, chronic autoimmune thyroiditis, and thyroid cysts were diagnosed in 18.7%, 31.0%, and 24.0% respectively [21].

Review of the «dose-effect» in adult females subject to long-term radiation exposure indicated an increased incidence of chronic autoimmune thyroiditis (10.0% vs. 3.4% in control, $p < 0.05$, odds ratio is 3.46 in the 95% confidence interval) [10]. Significant values of relative risk of non-tumor diseases in the clean-up workers depend on the whole-body external radiation doses making from 0.5 to 0.99 Gy for the onset of chronic autoimmune thyroiditis and over 0.1 Gy for the spontaneous hypothyroidism [22].

12.1. STAGES OF REALIZATION OF ENDOCRINE SYSTEM DISORDERS

Major part of the absorbed radiation dose that affected the endocrine system after the ChNPP accident was accumulated within near months of emergency, whereas the rest one was formed for several years making it difficult to estimate its detrimental effect. The extremely high air concentration of iodine isotopes within near days and weeks upon the accident both with natural iodine deficiency resulted in a thyroid system strain i.e. the so-called «hungry thyroid» had predisposed to substantial accumulation of radioactive iodine causing the acute events such as some hormone-producing cell breakage in a close term upon the accident. As a result the acute radiation thyroiditis with transient hyperthyroidism, insulitis occurred etc. Induction of mutations had led in its turn to onset of some types of cancer. Upon irradiation at medium and low doses the radiation damage was postponed for years and decades occurring in survivors as chronic non-malignant diseases, namely first of all as nodular goiter, autoimmune thyroiditis, obesity, type 2 diabetes mellitus due to disorders in tissues of central and peripheral endocrine organs.

Transient elevation of peripheral hormone concentration in serum due to partial endocrine cell breakage occurred in a period of primary reaction to the unfavorable factor complex in April–July 1986. Increase of peripheral hormone concentrations under no response of central regulatory endocrine centers is a sign of abnormal feedback relationships due to the failure of synthesis of certain releasing factors and tropic pituitary hormones. It was peculiar for the period of compensatory hyperproduction of peripheral hormones since September 1986 till 1989.

Period of subclinical hormonal disorders (1990–1994) featured the renewal of central regulation of hormonal synthesis, decrease in functional capacity of peripheral endocrine tissues, and onset of subclinical disorders of thyroid and other hormone synthesis.

Later on in 1995–1999 the risk of thyroid disease in the ChNPP accident survivors increased ~9-fold, risk of the type 2 diabetes mellitus ~2.4-fold. The annual rate of endocrine disease incidence increase in the ACUW was ~3–5-fold more than in non-exposed adult population of Ukraine. Some king of endocrine disease «juvenation» was noticeable otherwise being typical for elderly persons. According to the State Registry of Ukraine (68,145 persons, 1988–2009 survey period) an increase of non-tumor thyroid morbidity mainly at the expense of chronic autoimmune thyroiditis, nodular goiter, primary i.e. spontaneous hypothyroidism was established (see Figure 12.1).

Prevalence of chronic autoimmune thyroiditis since 1997 till now in the accident clean-up workers is continuously increasing while in Kyiv city population it remains the same (Figures 12.2, 12.3). The most rapid rise of thyroid disease prevalence is established in the clean-up workers who had been under 20 years old in 1986. The whole-body total radiation doses within 0.25–1.0 Gy are found a substantial risk factor of chronic autoimmune thyroiditis and spontaneous hypothyroidism in the clean-up workers of 1986–1987 period and evacuees from the 30-kilometer exclusion zone.

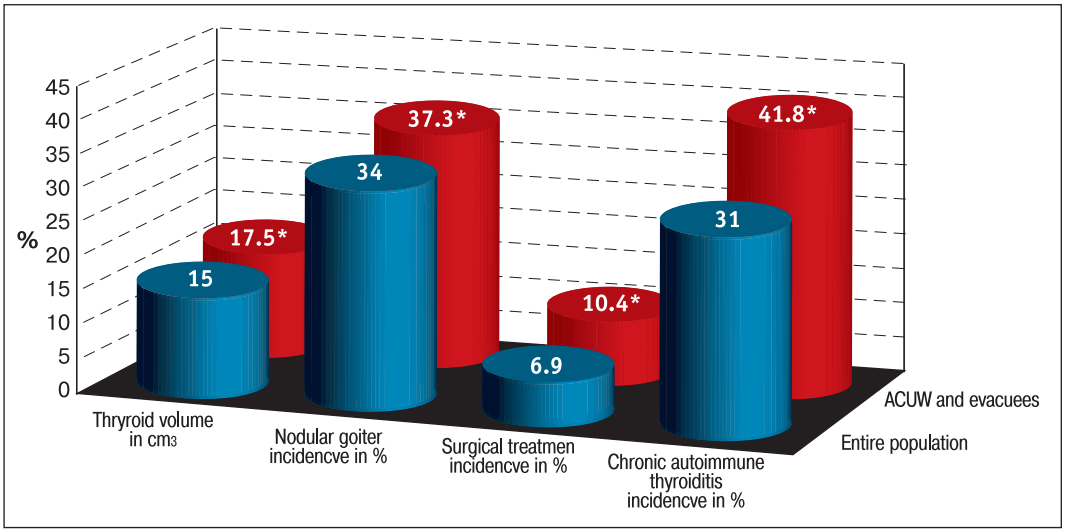


Figure 12.1. **Incidence of thyroid disease among the ChNPP accident clean-up workers (1986–1987 period) and evacuees from the 30-kilometer exclusion zone vs. the entire population of Ukraine not exposed to IR**

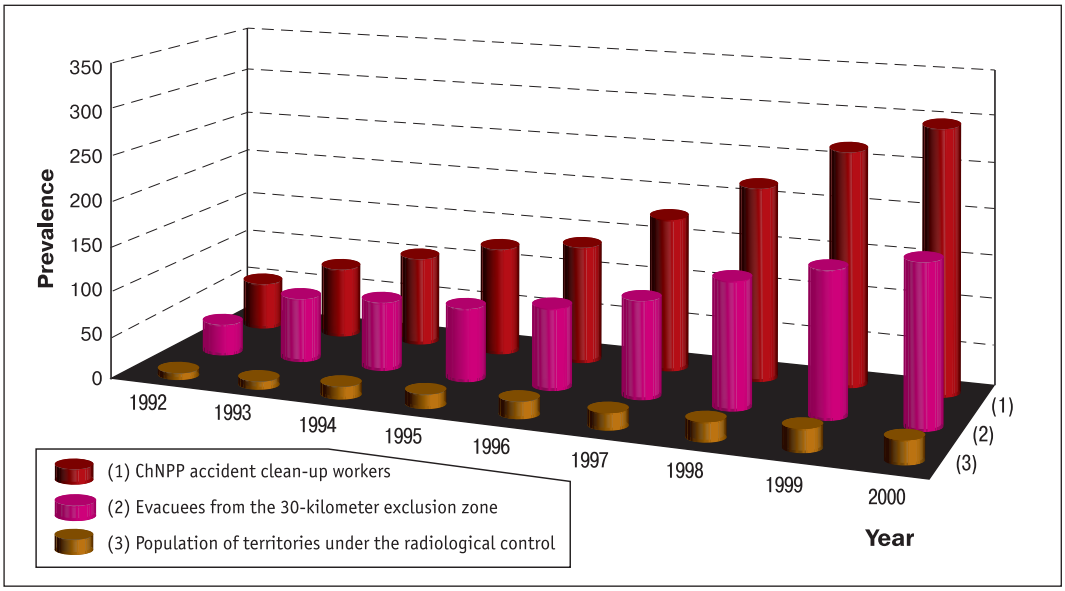


Figure 12.2. **Prevalence of chronic (autoimmune) thyroidits in Ukraine in subgroups of the ChNPP accident survivors (data from the Ministry of Health of Ukraine on adults and children, values calculated per 10,000 population**

Therefore prevalence of nonmalignant thyroid disease in the ChNPP accident survivors increased within 90th and continues to increase slowly till now especially in the clean-up workers of «iodine» period in 1986. Gradual development of non-stochastic endocrine disease is sur-

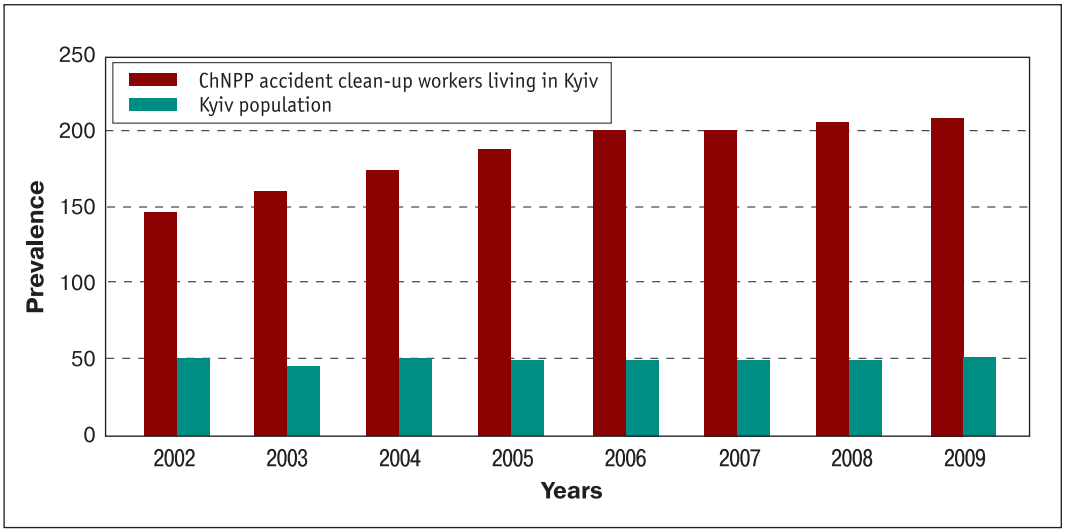


Figure 12.3. Prevalence of chronic (autoimmune) thyroiditis in the ChNPP accident clean-up workers versus population of the Kyiv city not exposed to ionizing radiation (per 10,000 population)

veyed corresponding to pathophysiological events in tissues of central and peripheral endocrine organs since the ChNPP accident (see Table 12.1).

Early thyroid reaction on radiation in the form of hyperthyroxinemia and a short-term «stressful» hyperthyrotropinemia with no clinical manifestations was surveyed in survived children within first year upon the accident. Serum content of thyroxin normalized in 12-18 months upon the accident followed by an undulating deviations of the value within normal range. Further there

Table 12.1
Integral characterization of stages of endocrine disease development after the ChNPP accident

#	Stage / period	Years	Disorders / abnormalities
1	*Functional strain* in consequence of qualitative alimentary deficiency (of iodine, selenium, other elements)	Up to 26.04.1986	Hypertrophy of the hormone-producing cells predisposing to higher accumulation of tropic isotopes
2	*Initial responses* to altering agents (complex of hazardous accident factors)	26.04.1986 – 08.1986	Transient elevation of peripheral hormone concentrations in serum in consequence of partial endocrine cell breakage
3	*Compensated hyperproduction* of peripheral hormones	09.1986 – 1989	Activated synthesis of peripheral hormones against absent response from central regulation bodies meaning the feedback disorders due to lack of hypothalamic releasing-factors and tropic pituitary hormones
4	*Subclinical disorders* of endocrine tissue functions	1990–1995	Renewal of central regulation of endocrine synthesis, decrease of functional capacity of peripheral endocrine tissues, onset of subclinical thyroid and other organ disorders
5	*Overt clinical presentation* of radiation-induced and radiation-associated endocrine disease	1996–2016	Upsurge of chronic nonmalignant endocrine disease against a decreased functional capacity of peripheral endocrine tissues, disorders of central regulation, and trend to further incidence increase of some disease classes, namely of nodular goiter, chronic autoimmune thyroiditis, obesity, type 2 diabetes mellitus.

were no differences in average values of thyreotropinemia from normal ones against the continued hyperthyroxinemia. At thyroid radiation doses over 1–2 Gy the average thyroxin content reliably increased along with a dose increase reaching the maximum values.

Hormonal disorders in the period of 1986–1989 have had no clinical presentation in the scope of endocrine morbidity in children and adolescents. Primary thyroid reaction on radiation, immune disorders in the coming years upon the accident, and structural thyroid abnormalities soon revealed with diagnostic ultrasound (beginning from 1990–1991) indicated an initiated development of chronic autoimmune thyroiditis. Decrease of the free thyroxin content was registered in 1992–1996 only in 0.8% of cases, increase of pituitary thyrotropic hormone with no any clinical presentation was revealed in 0.2% of cases.

Research on identification of the occult thyroid insufficiency was conducted in 1999-2003. Approaches in management and rehabilitation were elaborated for the children with thyroid disease who had survived after the ChNPP accident and inhabited the radiologically contaminated territories under the environmental iodine deficiency.

Strain in the central i.e. hypothalamic-pituitary regulation was found representative for the thyroid system function in children of the ChNPP accident clean-up workers (in first generation). It was revealed in 35.5% of examined persons indicating the TSH hypersecretion in response to the thyrotropine-releasing hormone challenging test and was supposed a sign of physiological inadequacy of neuroendocrine structures capable of further presentation of thyroid disease. The delayed in time cytogenetic effect revealed under a long-term lymphocyte culturing indicated the transmission of chromosome instability in descendants of irradiated parents. It can predispose to realization of thyroid disease in children with occult functional failure of hypothalamic-pituitary-thyroid system.

Clinical and hormonal studies in 2007–2014 showed the role of hypothalamic-pituitary functional instability, that can be both congenital and spontaneous, in shaping of unfavorable premorbid background for a range of neuroendocrine syndromes in children born from parents exposed after the ChNPP accident. Revealed strain in the function of hypothalamic-pituitary system is of high importance in thyroid disease onset. Long-term strain leads to decreased thyroid hormone production resulting in amplified pituitary thyrotropic hormone secretion. Under stimulation by TSH the thyroid volume is increased first leading to formation of the endemic goiter. Stable thyroid enlargement most often leads to appearing of nodular goiter and immune-inflammaory processes, namely the chronic autoimmune thyroiditis.

12.2. CLINICAL AND EPIDEMIOLOGICAL FEATURES OF NON-MALIGNANT THYROID DISEASE

12.2.1. The ChNPP accident survivors

Retrospective review of data on 24,588 persons from the NRCRM Clinical-Epidemiological Registry (CER) indicated that thyroid disease incidence among all the survivors in 1992–2014 was in average 40.29% rather exceeding ($p<0.0001$) the respective value (3.9%) in the entire population of Ukraine (Figure 12.4a).

Thyroid disease in the subgroups of survivors is revealed most often in the accident clean-up workers (35.37%, $p < 0.0001$) (Figure 12.4b) and in the exclusion zone evacuees (27.24%, $p < 0.0001$) (Figure 12.4c), population of radiologically contaminated territories (28.6%, $p < 0.0001$) (Figure 12.4d), and in 46.74% of children survived after the ChNPP accident (Figure 12.4d).

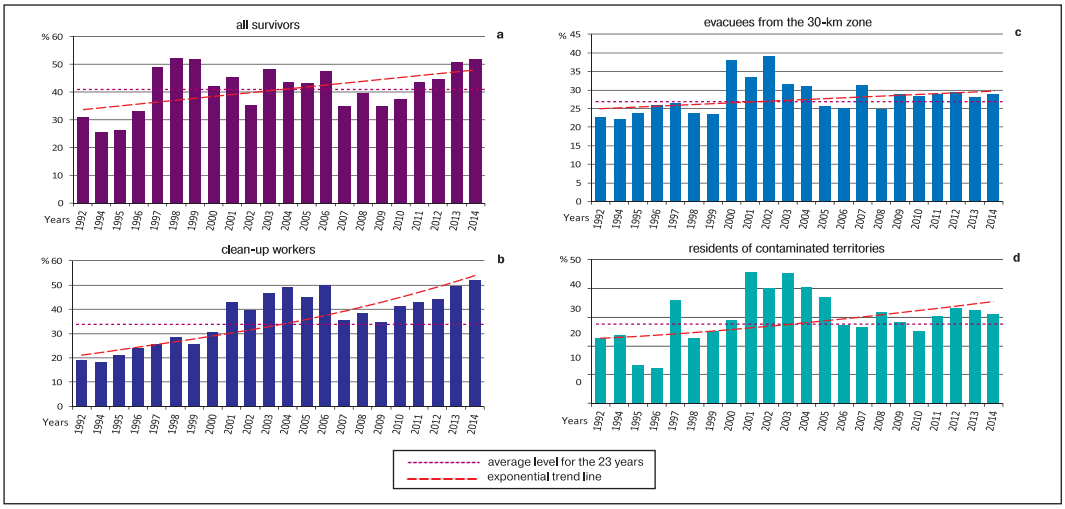


Figure 12.4. Time trends of thyroid disease in subgroups of the ChNPP accident survivors (adults; n=24,588; data from the NRCRM CER)

Incidence of thyroid disease in adults varied through the years from 17% to 53% with supreme increase in 10–15 years upon the radiation impact. Nodular goiter and chronic autoimmune thyroiditis are prevalent in survivors, clean-up workers, and exposed children that all is surveyed more often than in non-affected persons from the entire population of Ukraine (the control group).

Incidence of nodular goiter in survivors was in average by years equal to 14.35%, incidence of chronic autoimmune thyroiditis was ~8.0%. The lowest prevalence according to the CER data was typical for the non-toxic goiter and thyroid dysfunction i.e. hypothyroidism and hyperthyroidism including the occult disease forms. The received data indicate to the exponential trend in extensive increase of nodular goiter and moderate increase of chronic autoimmune thyroiditis onwards.

To specify the real prevalence of thyroid disease and other endocrine disorders in these persons the extra review was applied to verify in clinical settings the available data. The received data indicated prevalence of diffuse non-toxic goiter (40.4%; $\chi^2_{Yates} = 73.82$; $p = 0$) and nodular goiter (23.1%; $\chi^2_{Yates} = 14.13$; $p = 0.002$) in the ChNPP survivors vs. persons in the control group (4.8% and 17.6% respectively). No such difference was found for chronic autoimmune thyroiditis in the whole group of survivors ($\chi^2_{Yates} = 0.54$; $p \leq 0.46$), whereas hypothyroidism ($\chi^2_{Yates} = 4.24$; $p \leq 0.04$) and hyperthyroidism ($\chi^2_{Yates} = 16.68$; $p = 0$) were found contrariwise primarily in the control group (Table 12.2).

Incidence of thyroid disease was 1.5–2-fold higher in the ChNPP accident survivors vs. control group, especially it was relevant in persons with obesity. The TSH level in them was strongly associated with thyroid volume in euthyroidism ($r^2 = 0.62$) and hypothyroidism ($r^2 = 0.66$), but not in nodular goiter ($r^2 = 0.34$ and $r2 = 0.14$ respectively) indicating to the different pathways of development in both diseases.

A range of intersystemic hormonal links was revealed in the surveyed persons. Development of diffuse non-toxic goiter was under the impact of serotonin ($r^2 = 0.8$), leptin ($r^2 = 0.95$), cortisol ($r^2 = 0.95$), and phenomenon of insulin resistance (QUICKI by insulin, $r^2 = 0.79$). Correlation of the incidence of diffuse non-toxic goiter with non-hormonal factors was maxi-

Table 12.2
Thyroid disease incidence under the clinical data verification in the ChNPP accident survivors

Disease	ChNPP accident survivors (n = 606)		Control (n = 589)		Intergroup compare	
	n	%	n	%	Yates corrected χ^2	*p*
Diffuse non-toxic goiter	245	40.4**	104	17.6	73.82	< 0.01
Nodular goiter	140	23.1**	85	14.4	14.13	0.02
Chronic autoimmune thyroiditis	134	22.1	119	20.2	0.54	0.46
Hypothyroidism	60	9.9	82	15.1*	4.24	0.04
Post-operative hypothyroidism	28	4.6	29	4.9	0.1	0.91
Hyperthyroidism	4	0.7	27	4.6**	16.68	< 0.01
Thyroid cancer	6	0.99	5	0.8	0	0.96

Notes. *p* – statistical significance of difference between the compared group and control; * – $p \leq 0{,}05$; ** – $p \leq 0{,}01$.

mal for the indices of lipid metabolism ($r^2 = 0.68–0.92$) and related to that of lipase ($r^2 = 0.89$). Development of the nodular goiter was under a strong impact of α-melanostimulating hormone (α-MSG; $r^2 = 0.7$), melatonin ($r^2 = 0.99$), subclinical thyroid dysfunction ($r^2 = 0.63$), insulin resistance (QUICKI by C-peptide, $r^2 = 0.53$) and leptin resistance (leptin index, $r^2 = 0.59$). Dealing with non-hormonal factors the nodular goiter development depended upon the triglyceride level ($r^2 = 0{,}88$), total cholesterol content ($r^2 = 0.5$), and very low-density lipoproteins (r2 = 0.9). Development of chronic autoimmune thyroiditis was associated with insulin concentration ($r = 0.73$; $p \leq 0.01$), leptin ($r = 1$; $p \leq 0.01$), related leptin resistance ($r = 09$; $p \leq 0.01$) and insulin resistance (HOMA-IP, $r = 0.68$; $p \leq 0.01$), and also with cortisol ($r = 1$; $p \leq 0.01$), C-peptide ($r^2 = 0.61$) content, and HOMA by the C-peptide ($r = 0.87$).

Therefore, pathways of thyroid disease onset and development under the impact of ionizing radiation appear through the initial development of insulin resistance against an excessive accumulation of adipose tissue followed by increase of C-peptide and glucose content. Later it appear a background of onset of the type 2 diabetes mellitus against elevated level of total cholesterol ($p = 0.08$) and extracellular lipase activity ($p \leq 0.01$). Insulin resistance in most cases occurs a background for the later onset of thyroid disease, whereas the ionizing radiation promotes its onset especially under the iodine deficiency. It is supported by the presence of correlation of external radiation dose in the ChNPP accident clean-up workers of iodine period in 1986 and C-peptide ($r^2 = 0.504$; $p \leq 0.05$), insulin ($r^2 = 0.644$; $p \leq 0.05$), leptin ($r^2 = 0.658$; $p \leq 0.05$), and related indices of cellular resistance.

The accumulated clinical and epidemiological data indicate that exposure of the ChNPP accident survivors to ionizing radiation led to dramatic increase of non-malignant thyroid disease and non-thyroid endocrine disease prevalence in adults and children vs. persons not exposed to radiation.

The incidence of pre-obesity and obesity in survivors was 41.9%/36.8% ($p \leq 0.001$ vs. control i.e. 24.6%/31.1% respectively). The integral body weight excess observed in majority of the ChNPP accident survivors (78.7%), whereas in control it was in 55.7% of persons.

The CER data review for a 20-year period (since 1993–2012) on thyroid disease incidence in children indicated that diffuse non-toxic goiter we diagnosed in 50.5% children in the most study groups (Figure 12.5).

Examination of children exposed to ionizing radiation after the ChNPP accident revealed a most critical group of them, namely the evacuees from the 30-kilometer zone irradiated at an

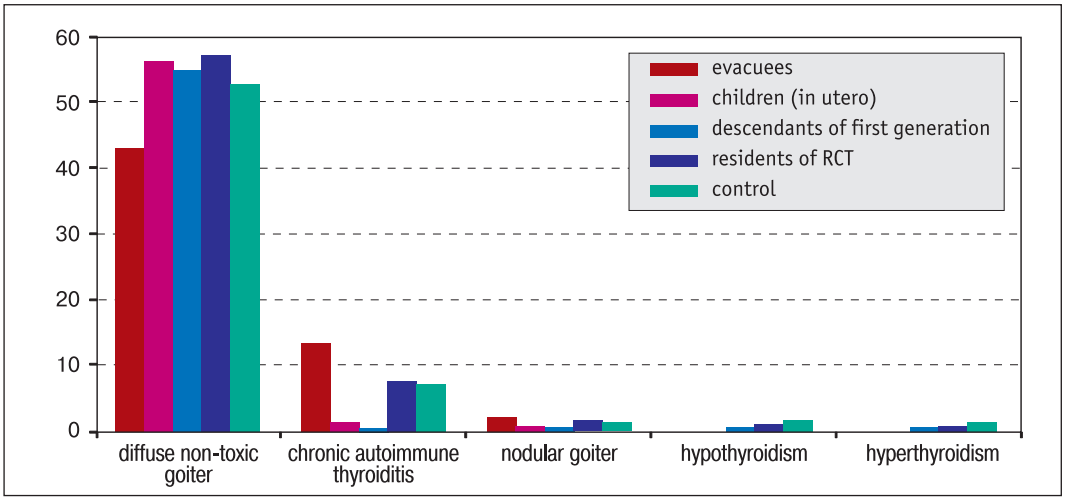


Figure 12.5. Incidence of thyroid disease in 20,087 children survived after the ChNPP accident (NRCRM CER data for 1992–2012)

age of 3–6 years old. The radiation impact provoked a development of DNT in 43.68% of them ($\chi^2 = 23.9$; $p < 0.0005$ vs. control), CAT in 1.74% ($\chi^2 = 31.6$; $p < 0.0005$ vs. control), primary hypothyroidism in 0.96% ($\chi^2 = 28.6$; $p< 0.0005$) (Figure 3.5.6), and NG in 2.57%. Peak of the CAT prevalence occurred in 2001–2003 i.e. in the period of intensive pubertal maturation of the survived children (Figure 12.6).

Thyroid disease was found in 42.64% children of parents exposed to ionizing radiation (first generation) that again exceeded the incidence in control ($\chi^2 = 10.6$; $p < 0.002$), the CAT was visibly rare i.e. in 0.45% of cases even vs. control ($\chi^2 = 8.68$; $p < 0.004$) (Table 12.3).

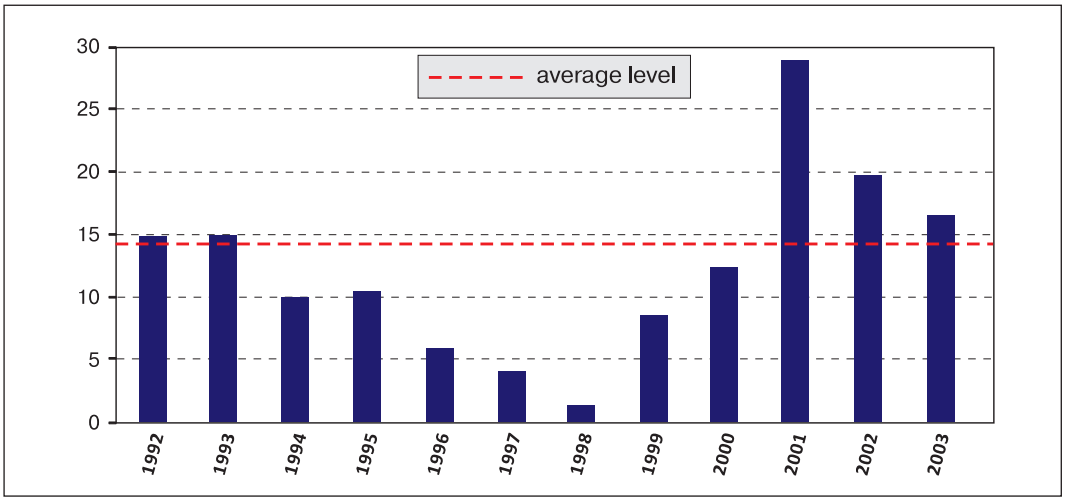


Figure 12.6. Time pattern of chronic autoimmune thyroiditis incidence in children evacuated from the 30-kilometer exclusion zone (n=20,087; NRCRM CER data for 1992–2012 up to the age of 18 years in each case)

Table 12.3
Incidence of thyroid disease in study groups of children (NRCRM CER data)

Disease	Groups, %			p_{1-2}	p_{1-3}	p_{2-3}
	1	2	3			
	Evacuees from the 30-km zone (n = 3331)	Children of the exposed parents (n = 4646)	Control group (n = 1410)	χ^2 (p value)		
Diffuse non-toxic goiter	43.68 ± 0.61	41.54 ± 0.49	37.83 ± 1.01	7.5 (0.007)	23.9 (0.0005)	10.6 (0.002)
Chronic autoimmune thyroiditis	1.74 ± 0.23	0.45 ± 0.1	1.21 ± 0.29	31.6 (0.0005)	1.5 (0.22)	8.68 (0.004)
Nodular goiter	0.36 ± 0.1	0.56 ± 0.11	0.64 ± 0.21	1.2 (0.27)	1.2 (0.28)	0.02 (0.89)
Hypothyroidism	0.96 ± 0.17	0.13 ± 0.05	0.28 ± 0.14	26.6 (0.0005)	5.2 (0.02)	0.8 (0.38)

Notes. p_{1-2} – significance of difference between group 1 & 2 values; p_{1-3} – between groups 1 & 3; p_{2-3} – between groups 2 & 3.

It stands to mention that since 2004 all the children exposed to ionizing radiation after the ChNPP accident were re-arranged in study group of "adult persons". Upon that, only children of the exposed parents (first generation) were subject to check-up. No significant incidence increase of the most thyroid disease was found in children exposed to ionizing radiation in utero vs. other study groups. The CAT incidence, however, reached in them 9.9–12.8%. The DNG was diagnosed in 9.5-13.8%, and NG in 1.7–4.2% in the first generation of children of survivors.

Children exposed to ionizing radiation after the ChNPP accident primarily from the ^{131}I. That is why the thyroid effects of IR were most prevalent in them. However, some kind of hypothalamic-pituitary functional instability was revealed in them comparing with agemates under the thorough hospital examination. Such instability results in onset of unfavorable premorbid background for a range of neuroendocrine syndromes and occult resistance to some hormones. It was relevant among other children (first generation) of the ChNPP accident survivors. Long-term persistence of such a strain led to decreased peripheral hormone synthesis resulting in dysfunctional secretion of tropic pituitary hormones in 26% of surveyed children. Such non-malignant diseases was the diffuse non-toxic goiter revealed in 43.68% and CAT found in 1.74% both with hypothalamic and metabolic syndromes. Abnormal sexual development and differentiation, and carbohydrate metabolic disorders were diagnosed in children exposed to ionizing radiation. Clinical examination of children exposed after the ChNPP accident indicated the pubertal hypothalamic syndrome prevalence in 25.4–28.9% persons that was accompanied by multiple striae distensae in 83.0% of such cases and blood pressure asymmetry in 36.8% of children. In the first generation of descendants of irradiated parents such disorders were found much more often i.e. in 41.5–52.3% of cases. Simplified screening procedure meaning the application of simplified protocol of thyroid and other endocrine systems examination with no challenge tests was incapable to diagnose such disorders. We focus our research now on identification of such peculiarities.

12.2.2. Clean-up workers of the ChNPP accident consequences

Nodular goiter and CAT were most prevalent within all thyroid disorders in the ChNPP accident clean-up workers compared to the entire population of Ukraine. Nodular goiter was diagnosed in 21.8% ($\chi^2 = 9602$, $p < 0.0001$), CAT in 12.95% ($\chi^2 = 5381$, $p < 0.0001$) (Figure 12.7), average values age shown in Table 12.4.

Diffuse non-toxic goiter was less prevalent (3.94%) among the thyroid disease. Functional thyroid dysfunction and thyroid cancer were of less impact on health in the clean-up workers.

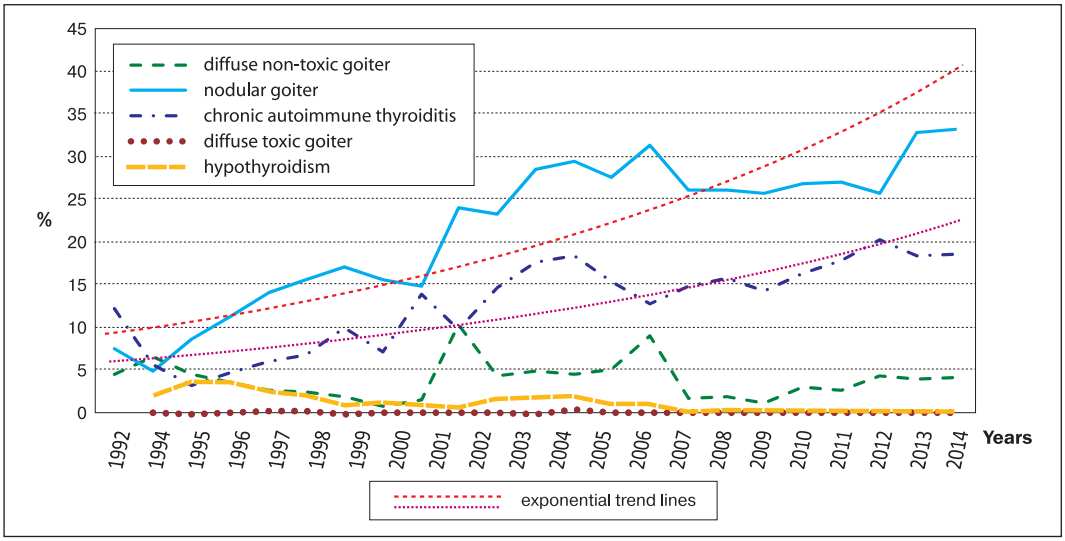


Figure 12.7. **Thyroid disease pattern by years in the ChNPP accident clean-up workers (n=10,771; NRCRM CER data) and exponent**

Table 12.4
Average incidence (%) of thyroid disease in the ChNPP accident clean-up workers (NRCRM CER data)

Disease	ChNPP clean-up workers	Control group	χ^2	*p*
Diffuse non-toxic goiter	7.90	2.50	743	<0.001
Nodular goiter	23.20	0.53	9602	<0.0001
Chronic autoimmune thyroiditis	13.37	0.35	5381	<0.0001
Hypothyroidism	2.84	0.18	895	<0.0001
Hyperthyroidism	0.40	0.12	36	<0.01
Thyroid cancer	0.42	0.07	75	<0.0001

Data received under the verification study with examination of survivors in hospital settings indicate the prevalence of diffuse non-toxic (40.4%; $\chi^2_{Yates} = 73.82$; $p \leq 0.001$) and nodular (23.1%; $\chi^2_{Yates} = 14.13$; $p = 0.0002$) goiter types vs. the intact persons in control group (4.8% and 17.6% respectively). No difference between groups was found for the CAT ($\chi^2_{Yates} = 0.54$; $p \leq 0.46$). Hypothyroidism ($\chi^2_{Yates} = 4.24$; $p \leq 0.04$) and hyperthyroidism ($\chi^2_{Yates} = 16.68$; $p \leq 0.001$) were found mainly in the control group as like as not due to iodine deficiency. However, in subgroups the clean-up workers of the «iodine» period of 1986 the thyroid disease incidence was 47.9% for diffuse non-toxic goiter ($\chi^2_{Yates} = 97.7$; $p \leq 0.001$ vs. control), 23.25% for nodular goiter ($\chi^2_{Yates} = 11.24$; $p \leq 0.001$), 21.6% for CAT ($\chi^2_{Yates} = 0.18$; $p \geq 0.05$), 7.6% for hypothyroidism ($\chi^2_{Yates} = 8.2$; p ? 0.01), and 0.6% for hyperthyroidism ($\chi^2_{Yates} = 10.8$; $p \leq 0.001$). In the clean-up workers of «non-iodine» period (1986–1987) the widely prevalent thyroid disease was represented by the diffuse non-toxic goiter in 49.1% of cases ($\chi^2_{Yates} = 28.76$; $p \leq 0.001$), nodular goiter in 27.3% of cases ($\chi^2_{Yates} = 5.38$; $p \leq 0.001$), CAT in 38.2% ones ($\chi^2_{Yates} = 8.53$, $p \leq 0.01$) that was revealed much more often than in persons from the control group. The statistically significant probability of nodular goiter development (23.8%, $\chi^2_{Yates} = 8.55$; $p = 0.003$) was esti-

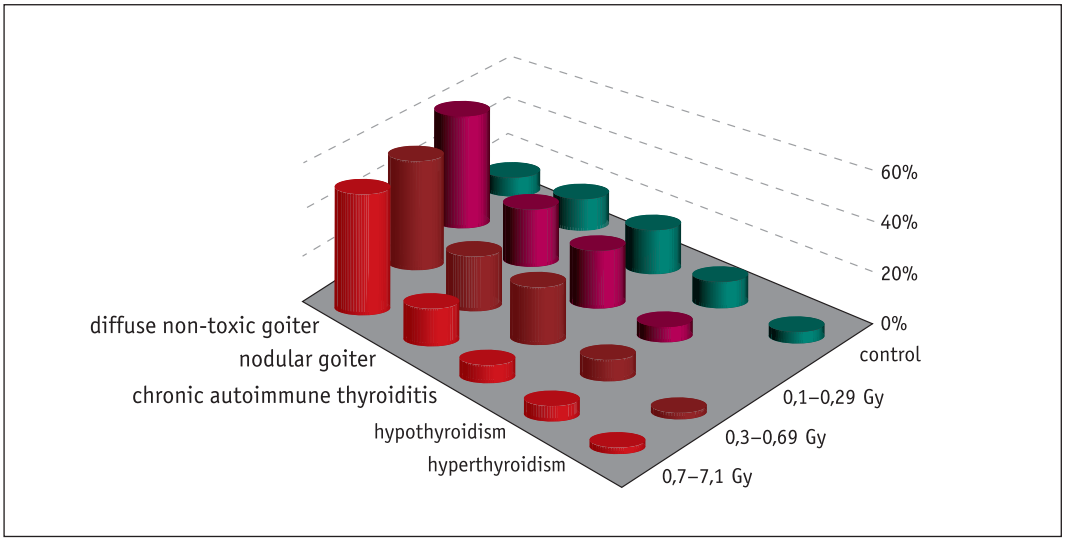


Figure 12.8. Thyroid disease pattern (%) in the accident clean-up workers of the «iodine» period by the external total-body irradiation dose range vs. the control group

mated in evacuees from the 30-kilometer exclusion zone exceeding the respective value in control. The diffuse non-toxic goiter prevalence at that in the former ones was 23.8%, (χ^2_{Yates} = 3.19; $p \geq 0.05$).

A statistically significant correlation of the nodular goiter onset ($r = 0.883$; p ? 0.05) was found in exposure dose group of 1.0–7.1 Gy and a weak one in lower radiation doses. According to clinical data a correlation was established between the thyroid status and external γ-irradiation in 0.2–0.49 Gy dose range. Namely, the thyroglobulin antibody titer was increased (p ? 0.01) followed by predisposition to thyroid hypofunction. In clinical settings the stated diseases correlated with external radiation doses in 0.2–0.5 Gy range (Figure 3.5.8).

In this group of the clean-up workers (average radiation dose 0.3 Gy) the highest incidence of CAT was found that could be explained by the effect of ?-irradiation.

Comparing the doses of external irradiation and thyroid volume a statistically significant negative correlation was established ($r^2 = 0.006$; $p \leq 0.01$). No statistically significant difference was found at that between a CAT incidence in the accident clean-up workers of the «iodine» period and persons from a control group ($\chi^2 = 0.43$; $p = 0.51$), but it was just found ($\chi^2 = 6.5$; $p = 0.01$) in the clean-up workers of «non-iodine» period of 1986–1987. It can be explained only by their long-term stay in the Chornobyl exclusion zone and hereto related to long-term impact of ionizing radiation despite in the narrower dose range.

According to the NRCRM CER data a significant increase of the CAT cases is followed in the ChNPP accident clean-up workers. Maximum of this excess occurred in 2002–2005 i.e. 15–20 years after the impact of ionizing radiation (Figure 12.9).

This post-accident period could be considered as a peak for the CAT and is associated with impact of radiation.

Consequently the combined impact of ionizing radiation on thyroid cells resulted in a statistically significant ($p \leq 0.01$) increase of hypertrophic and hyperplastic thyroid disease featuring the diffuse non-toxic goiter ($p \leq 0.01$) and nodular goiter ($p = 0.0002$) incidence among all population groups of the ChNPP accident survivors. The CAT incidence increase is present only in

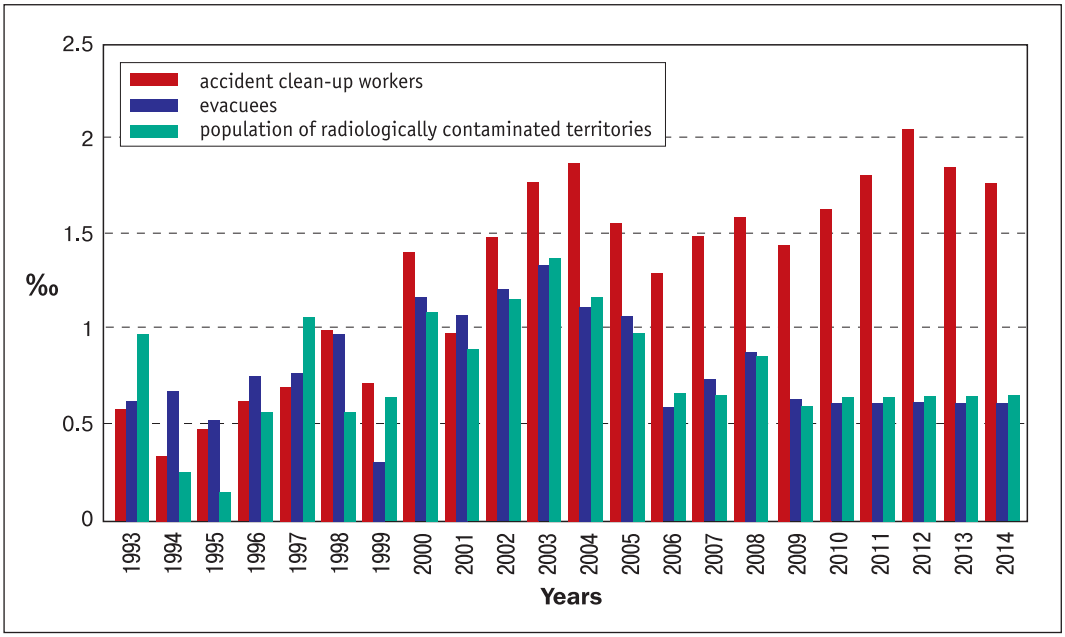


Figure 12.9. Time trends of annual prevalence of chronic autoimmune thyroiditis in subgroup of the ChNPP accident survivors (NRCRM CER data for 1993–2014 period)

clean-up workers of the «non-iodine» period in 1986–1987. The threshold dose of external irradiation for an increased probability of CAT onset in the clean-up workers was 0.32 Gy, the 0.37Gy was a threshold one for nodular goiter, and 0.7 Gy for obesity.

Comparing the incidence of endocrine disorders according to clinical data in the ChNPP accident clean-up workers of the «iodine» period in 1986 a double-natured trend is surveyed between the external radiation doses and manifestation of abnormalities of the hormone-producing tissues. Incidence of such abnormalities increased along with an external radiation dose up to 0.99 Gy for almost all diseases, namely diabetes mellitus, thyroid disease, and obesity. But upon exposure to radiation at doses over 1.0 Gy there was a contrariwise trend to its decrease (Figure 12.10).

Majority of the clean-up workers especially in the very first months of the ChNPP accident was subject to a combined impact of internal irradiation from the short-living iodine isotopes and external γ-exposure. Besides the irradiation the hormone-producing integral cerebral structures disorders of hormone secretion that precede obesity were identified. It concerns the α-MSH, leptin, insulin, and others inducing the central disorders with shift in energy balance and eating behavior in survivors.

Pre-obesity and obesity were revealed in the accident clean-up workers in 41.71% and 33.61% respectively ($p \leq 0.001$ vs. control) corresponding to a 75.32% integral body mass excess over the normal values (Figure 12.11a).

According to our research data the long-term impact of IR on neuroendocrine cerebral structures (arcuate nuclei in the periventricular zone) resulted to a breakdown of protective regulatory pathways in proopiomelanocortine system, namely of α-MSH synthesis (Figure 12.12).

Elevation of α-MSH took place in parallel with body mass and leptin level increase in persons not affected by the ChNPP accident that could be appraised as positive physiological event

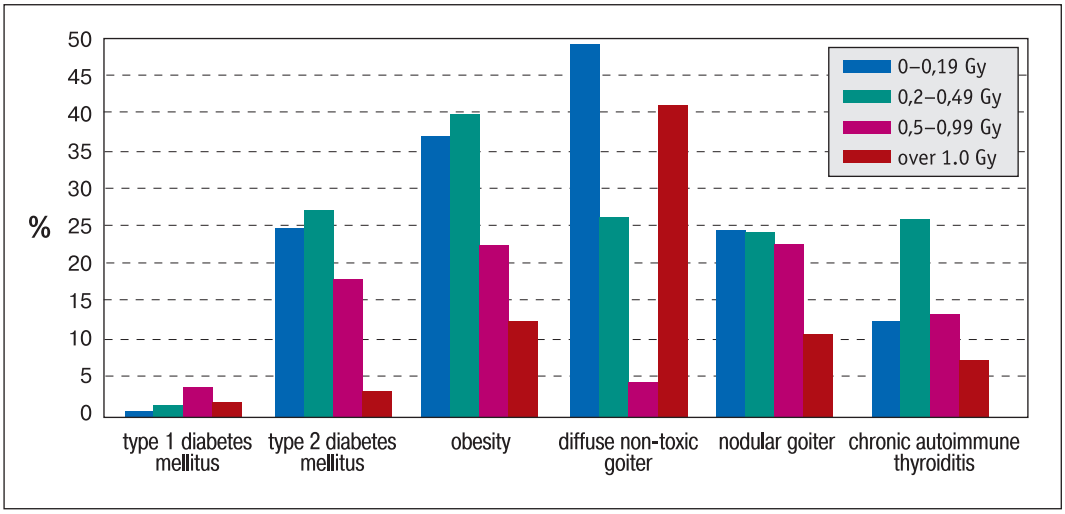


Figure 12.10. **Incidence of endocrine diseases by dose intervals in the clean-up workers of «iodine» period in 1986 (clinical data)**

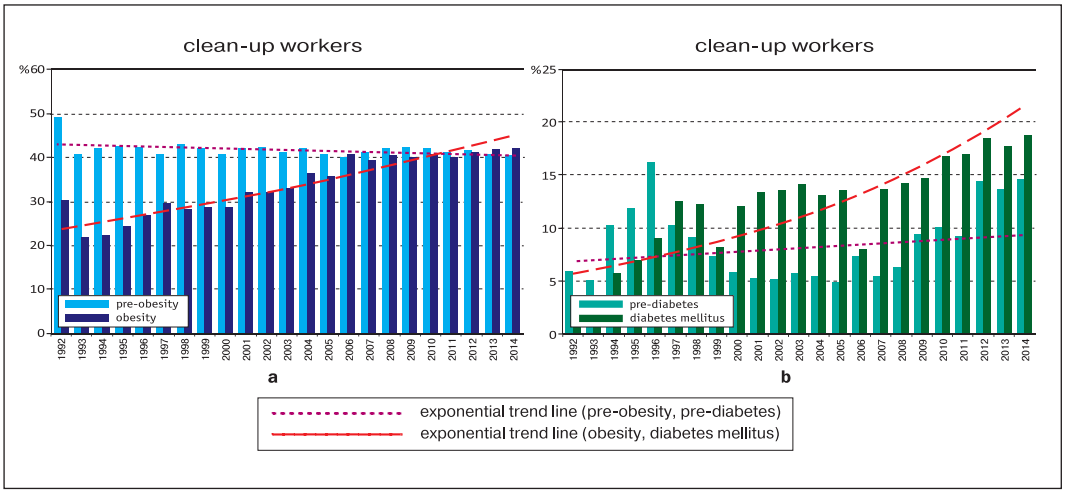


Figure 12.11. **Time trend of the body mass excess and obesity (a) both with pre-diabetes and diabetes mellitus (b) in the ChNPP accident clean-up workers (n=10,798; NRCRM CER data; 1992–2014 period**

focused at a decrease of food consumption. Under the same circumstances but in more pronounced hyperleptinemia an α-MSH secretion in the ChNPP accident survivors having body mass excess was unchanged ($p \leq 0.05$) (Figure 12.11a). Such deficiency results in an excessive accumulation of adipose tissue in the body followed by tissue leptin resistance and insulin resistance development, metabolic syndrome onset with associated abnormal states. Central disorders lead to alterations in the integral regulation of energy balance and eating behavior in the ChNPP accident survivors in combination with decreased concentrations of serotonin and melatonin. Lack of the latter predisposes to onset of depression, against which the obesity management will be ineffective.

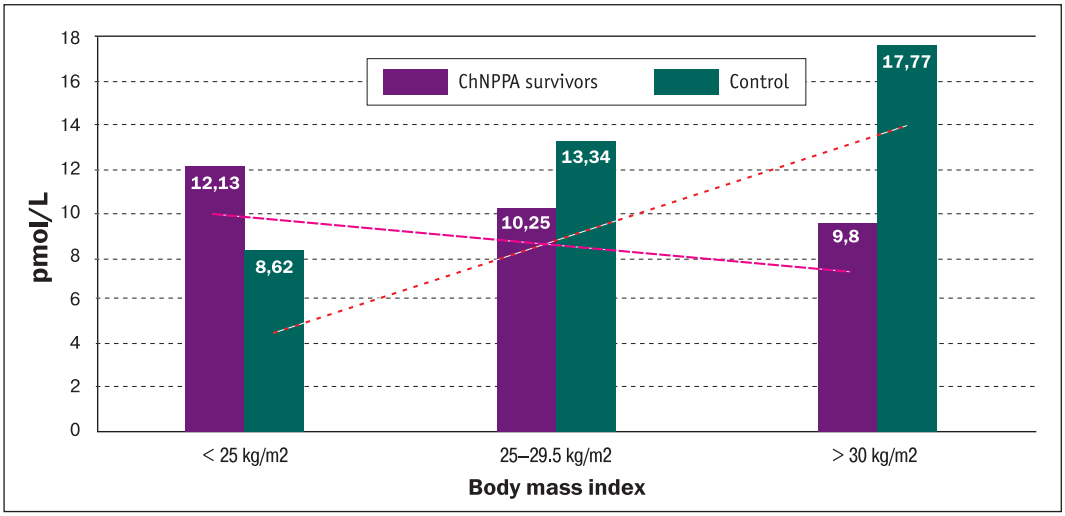


Figure 12.12. Abnormalities in the increase of α-melanocyte stimulating hormone concentration under body mass increase in the ChNPP accident survivors

Prevalence of pre-obesity and obesity in exposed children is much lower i.e. 3.2/1.1% vs. the adult persons indicating to the different irradiation pattern in both cases.

Impact of negative environmental factors range affected also the reproductive system in the ChNPP accident survivors. The incidence of menstrual cycle disorders increased 2–3-fold in females. In the early years an intensification of menstruation occurred, whereas in 5–6 years the incidence of oligomenorrhea, amenorrhea, infertility, and polycystic ovarian syndrome increased. Incidence of erectile dysfunction of various severity increased in men substantially (up to 60–70%). Serum content of peripheral sex hormones and their central regulation factors i.e. tropic pituitary hormones increased in early years upon the accident. Later on their concentration decreased to the threshold levels at a background of pituitary dysfunction onset i.e. increase of basal levels of follicle-stimulating and luteinizing hormones. Development of the premature hypohonadotropic hypogonadism was and now is the «final» in some of such cases. There is an increased incidence of elevated prolactin content or lactation cases incidence under its physiological serum concentrations.

Such situation (see Figure 5.3.11b) is characteristic for the onset of pre-diabetes and/or diabetes mellitus with median value of 15.5% and 21.4% respectively in survivors (up to 18.44% last years), and 8.6%/12.15% in clean-up workers (up to 18.44% last years). It reaches value of 23.5% in the clean-up workers of «iodine» period of 1986 ($p < 0.001$ vs. control). These values are much exceeding the IDF/FDA data for Ukrainian population [23–25]. We really agreed with an opinion of Vathaire et al. [26] about the oversensitivity of endocrine cells of the caudal part of the pancreas to IR contrary to the 99% of other cells of its caput and corpus constituting the exocrine part of a gland.

The profound clinical examination revealed a significant increase of type 2 diabetes mellitus in the ChNPP accident clean-up workers vs. the entire population of Ukraine, especially in the clean-up workers of 1986–1987 period in whom it reaches 60% ($\chi^2_{Yates} = 89.72$; $p < 0.01$). In the clean-up workers of «iodine» period it is 23.5% ($\chi^2_{Yates} = 25.21$; $p < 0.01$). No such dependence was found for the type 1 diabetes mellitus. It collaterally confirms the data on endocrine pancreatic cell sensitivity to IR.

12.2.3. Evacuees from the 30-kilometer zone and population of contaminated territories

Average yearly incidence of nodular goiter in adult evacuees from the Chornobyl exclusion zone was 13.4%, CAT was 8.43%, and of diffuse non-toxic goiter was 3.59%. In population of contaminated territories it was 14.17, 7.95 and 5.09% respectively. Dealing with thyroid dysfunction in survivors the hypothyroidism was most prevalent in the Chornobyl exclusion zone evacuees (3.37%), hyperthyroidism was most prevalent in residents of contaminated territories (0.48%).

12.3. SYSTEMIC CLINICAL AND METABOLIC DISORDERS IN THE CHNPP ACCIDENT SURVIVORS

To clinically characterize the pathogenetic pathways that follow insulin resistance and associated lipid and carbohydrate metabolic disorders both with the existing health risks the term «metabolic syndrome» was introduced.

Metabolic syndrome is a complex disorder i.e. a cluster of clinical and metabolic signs including the risk factors (genetic, lipid metabolic disorders, abdominal obesity, etc.), pathophysiological (insulin resistance, leptin resistance) and clinical manifestations of injury of several body systems (arterial hypertension, coronary heart disease, dyscirculatory encephalopathy and some other) in combination with disorders of carbohydrate metabolism (i.e. type 2 diabetes mellitus) that all lead to deterioration of life quality and shortening of life span in such patients. Decreased cellular receptor insulin sensitivity, tissue insulin resistance and leptin resistance are pathophysiologically realized through the disorders of lipid metabolism.

Gradual and staged development is characteristic for the metabolic syndrome. Decreased insulin sensitivity at a level of tropic tissues predisposes to basal hyperinsulinemia required to overcome the elevated threshold of sensitivity to endogenous insulin. Under a continuous dietary intake of proatherogenic lipids the breakdown of compensation mechanisms occurs with gradual exacerbation of insulin resistance later on leading to disorders of carbohydrate metabolism up to the overt type 2 diabetes mellitus.

Combination of mentioned above factors with hyperglycemia accelerates and exacerbates the development of atherosclerosis and fatal cardiovascular events, namely the myocardial infarction, cerebral stroke, or amputation of extremity. Basal hyperinsulinemia concomitant to insulin resistance despite its compensatory nature predisposes to increased blood pressure through activation of autonomous nervous system, kidney reabsorbtion of sodium ions, and their intracellular accumulation.

Clinical signs of metabolic syndrome diagnosed in accordance with IDF-2006 criteria were much often surveyed in the ChNPP accident survivors, namely in 49.8% (n = 271) (χ^2_{Yates} = 207.14; $p < 0.01$) vs. in control group (9.5%, n = 51).

Signs of metabolic syndrome were revealed in the accident survivors in 15.3% of normal body mass cases, in 25.3% of excessive body mass cases, and in 38.7% cases of obesity vs. in 4, 13.7, and 15.7% in control group respectively. Such data can indicate the extra role of radiation impact.

When comparing the systolic blood pressure in survivors having and having no metabolic syndrome signs the statistically significant difference ($p \leq 0.01$) was found. No difference between the groups was established for any other hemodynamic parameters.

Represented data imply an inextricable connection between the arterial hypertension and systemic metabolic disorders both in the main study and control groups, whereas the elevated sys-

tolic blood pressure is associated with insulin resistance. It possibly occurs through the proathrogenic dyslipidemia and immunogenic modification of serum lipoproteids despite all they develop to much extent independently one from other that probably indicate a leading role of systemic inflammation and oxidative stress in pathogenesis of those complex processes.

Metabolic syndrome is characterized not only by the elevated BMI and arterial blood pressure both with lipid and carbohydrate metabolic disorders, development of insulin resistance and leptin resistance syndromes, increased basal secretion of insulin and leptin, decreased receptor sensitivity to the latter in tropic tissues that all lead to gradual risk increase of related diseases e.g. type 2 diabetes mellitus ($\chi^2_{Yates} = 77.4$; $p < 0.01$) but also predispose to development of all classes on non-malignant thyroid disease that should be associated with metabolic syndrome (Table 12.5).

Table 12.5
Thyroid disease incidence under the clinical data verification in the ChNPP accident survivors

Disease	Associated with metabolic syndrome (n = 271)		No metabolic syndrome (n = 265)		Intergroup compare	
	n	%	n	%	χ^2_{Yates}	*p*
Type 1 diabetes mellitus	0	0	1	0.4	3.1	0.08
Type 2 diabetes mellitus	94	34.7*	11	4.1	77.4	< 0.01
Diffuse non-toxic goiter	132	48.7*	87	32.8	13.3	0.03
Nodular goiter	50	18.4*	29	10.9	5.4	0.02
Chronic autoimmune thyroiditis	83	30.6*	37	13.9	20.5	< 0.01
Hypothyroidism	39	14.4*	16	6.04	7.8	0.05
Hyperthyroidism	0	0	2	0.7	-	-
Thyroid cancer	3	1.1	3	1.1	0.07	0.9

Notes. * – significance of difference between groups 1 & 2.

Such association was revealed for the first time and was never reflected in scientific literature before. There was no type 1 diabetes mellitus found in the accident survivors with metabolic syndrome.

Research data in Ukraine and Republic of Belarus indicated some peculiarities of clinical presentation and course of musculoskeletal disorders in the ChNPP accident survivors and nuclear industry workers exposed to low radiation doses. Abnormalities of bone mineral density (BMD), namely of both spongy and compact substances were diagnosed in such persons indicating the wide prevalence of osteopenic syndrome, osteoporosis, secondary spinal osteochondrosis and arthrosis of large joints (degenerative joint disease).

Onset of osteopenic syndrome and osteoporosis in the ChNPP accident survivors in remote terms is related to a local impact of osteotropic and musculotropic radionuclides i.e. 90Sr, ^{134}Cs, ^{137}Cs that provoke a decrease of BMD and resistive characteristics of bone tissue, predispose to its accelerated aging more expressed in young and middle-aged persons.

In response to development and shaping of the systemic radiation-induced osteopenic syndrome the compensatory hypoparathyroidism arise followed by unincreased calcitonin synthesis against hypercortisolemia all being focused at preservation of mineral content of bone matrix and maintenance of stable calcium and phosphorus serum concentrations.

Such events are often complicated by vegeto-visceral and neuroreflectory syndromes, and by ambulant ossalgia. Disorders of calcium and phosphorus homeostasis with vitamin D deficiency and hyperparathyroidism are revealed in recent times in 5–22% of the clean-up workers.

Such complaints as stable cephalgia, cognitive disorders, joint pain and pain in extremities were most prevalent, they deteriorated the quality of life and exacerbated the disability in such persons.

Decreased BMD (T < -1) was revealed in ~31% of the clean-up workers with 0.5–1.0 Gy absorbed radiation doses. Osteoporosis (T < -2.5) was diagnosed in ~6,5% cases. In convalescents of acute radiation sickness of various grade the osteopenic syndrome and osteoporosis were revealed in 27.5% and 5.8% respectively.

To conclude there is no difference between the groups in osteopenia and osteoporosis incidence as well as in average value of bone strength index. So no direct dependence was found between the BMD and absorbed radiation dose values or age of survivors.

Osteopenic syndrome was diagnosed in ~10% female and ~4.5% male clean-up workers and population of radiologically contaminated territories exposed to IR at 5 mSv yearly doses.

* * *

Thus and so the received data indicate that pathways of non-malignant endocrine disease in the ChNPP accident survivors lies in abnormal effect of hormones at cellular receptor level featuring the pre-receptor, receptor and post-receptor interactions all leading to development of resistance to insulin, leptin, and other hormones. The latter pave the way for unswerving a progression of radiation-associated diseases. The revealed abnormal hormonal interrelations are exacerbated by the IR impact and lead to long-term disorders of a syndromic nature associating the involvement of various hormone-producing tissues i.e. thyroid disease and obesity, type 2 diabetes mellitus, etc.

Increased incidence of thyroid disease was predisposed by the impact of a complex of unfavorable accident factors nothing if not the effect of IR and deficiency of some microelements especially iodine and selenium. The integration i.e. combination of the external g-irradiation and internal radiation exposure of tropic hormone-producing cellular structures by radionuclides occurred that resulted to a damage of specific components of hormonal regulation system both in central and peripheral endocrine tissues. Radiation damage of these tissues occurred through activation of genetic predisposition through the interaction of unfavorable environmental factors.

Since 1986 in 30 years the prevalence of nodular goiter, CAT, obesity, and type 2 diabetes mellitus in the clean-up workers is still increasing, whereas in Kyiv city population the respective levels are stable. The most dramatic increase of thyroid disease prevalence was registered in emergency workers who were under 20 years old in 1986. The whole-body external radiation doses in a 0.1–1.0 Gy range showed to be an important risk factor of CAT and spontaneous hypothyroidism in emergency workers of 1986–1987 period and evacuees from the 30-kilometer zone.

Endocrine system in adult and children responds to ionizing radiation at high doses (over 1 Gy) within a short time upon an accident due to the peripheral hormone-producing cell breakage e.g. thyrocytes followed by a rapid onset of dysfunction e.g. such as transient normotropic hyperthyroxinemia. Later the stable hypofunction occurs, namely the hypothyroidism, obesity, diabetes mellitus, however in a limited number of persons.

In the most cases of man-made radiological accidents a human exposure occurs in medium radiation doses (0.1–0.5 Gy) thus radiation effects develop gradually and become evident only 10–15 years later when such consequences become expressed in majority of survivors and have a trend of further progression in terms over 30 years. Effect of IR on the hormone-producing cells is realized first of all through activation of hereditary predisposition, genetic variability, onset of immune system dysfunction stipulating the development of autoimmune inflammato-

ry processes (such as CAT, latent autoimmune diabetes in adults – LADA, and some others), and through the multiple mutations predisposing to non-malignant (more often) or malignant (more rare) tumors (such as nodular goiter, adenoma, cancer and some other).

* * *

Retrospective data review indicates that thyroid disease incidence in all the ChNPP accident survivors is 40.29%, in the clean-up workers is 35.37%, in persons evacuated from the exclusion zone is 27.24%, and in population of radiologically contaminated territories is 28.6% and significantly exceeding ($p < 0.0001$) the respective value for population of Ukraine (3.9%). Thyroid disease incidence in adult varied from 17% to 53% with dramatic elevation in about 10–15 years upon the impact of radiation factor.

The most prevalent endocrine diseases in the ChNPP accident survivors were nodular goiter (14.35%), chronic autoimmune thyroiditis (~8%), pre-obesity and obesity (41.9% and 36.8%), pre-diabetes and diabetes mellitus (15.5% and 21.4%).

The most prevalent endocrine diseases in the ChNPP accident clan-up workers were nodular goiter (21.8%), chronic autoimmune thyroiditis (12.95%), pre-obesity and obesity (41.71% and 33.61%), pre-diabetes and diabetes mellitus (8.6% and 12.15%).

Evacuees from the 30-kilometer zone who have been exposed to ionizing radiation at the age of 3–6 years old are a critical group of children. Incidence of diffuse non-toxic goiter was 43.68% in them, chronic autoimmune thyroiditis – 1.74%, primary hypothyroidism – 0.96%, and nodular goiter – 2.57%. Peak prevalence of chronic autoimmune thyroiditis occurred in 2001–2003 at the period if intensive pubertal maturation.

Thyroid disease was diagnosed in children of the irradiated parents (first generation) in 42.64% cases that exceeded the control values. Chronic autoimmune thyroiditis was much more rare disease diagnosed in 0.45%. Diffuse non-toxic goiter was revealed in 9.5–13.8%, nodular goiter in 1.7%.

Non-malignant endocrine disease in adult and children exposed to ionizing radiation is frequent just being surveyed in 3–53% of persons. It appear in the most part of survivors about 10–15 years upon radiation impact as a result of man-made accident and continues to increase slowly 30 years later.

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Chapter 13
RADIONUCLIDES INHALATION INFLUENCE ON BRONCHOPULMONARY SYSTEM OF CLEAN-UP WORKERS OF THE CHORNOBYL ACCIDENT

The accident at the Chornobyl nuclear power plant (ChNPP) resulted in radioactive environmental releases and fallout through the spreading of huge amount of radioactive substances by airborne-dust flows. Consequently the external and internal exposure (primarily inhalation) of the large contingents of population occurred in small doses.

According to various estimates inhalation of radionuclide's undergone at least 200,000 victims of different categories. Among them the most vulnerable and one of the largest categories are cleanup workers of Chornobyl NPP accident, especially those who were involved in the post-accident work in April and May 1986, and during the period prior to completion of the «Shelter» object – spring1987.

Under such circumstances radionuclides inhalation is one of the main ways of intake of the clean-up workers who worked in the 30-kilometer zone around the power plant. A very wide range of radioactive isotopes, including those belonging to the «hot» particles, causes difficulty of forecasting remote radiation effects.

Results of long-term (1996–2015) pulmonology monitoring of more than 16 thousand (16133) clean-up workers of ChNPP accident in 1986 in the policlinic of radiation register of NRCRM testify the reliable increase of chronic bronchitis and COPD morbidity among the marked contingent [1–8].

Parameters ofwhole body and bronchial system irradiation of people injured after the accident on the ChNPP, provided extreme distribution in time and space of the absorbed and effective equivalent doses at low levels, and the changes of physical and chemical structure of a mix inhaled radionuclides in various terms after the accident [9, 10].

Dose loadings on respiratory organs and, thus, expected consequences of an internal irradiation of clean-up workers of Chornobyl catastrophe defined by radionuclides air pollution from the first moment of failure up to the end of 1988. Thus, it is expedient to allocate some periods in clean-up work from the clinical-dosimetric point of view [6–8].

The first period – were the nearest post emergency days (from the moment of failure till May, 10, 1986). At that time a main role in formation of radioactive substance emission played the

dispersing of fulfilled nuclear fuel as a result of explosions on April, 26 and May, 3 1986 and the steam expiration of fragmental radionuclides from the fuel which stayed in a reactor pit, at its heating up to 1500–2000°C during the burning of graphite active zone.

The second period started from the second half of May, 1986 and finished with the termination of Object «Shelter» construction in November, 1986.

The third period included the end 1986–1988 when a leading role in air pollution played secondary dusting, caused by natural processes of wind rise of radioactive particles from the ground and people activity in the contaminated territories. At these stage significant receipts of radioactive substances in respiratory organs were expectedin persons, involved in deactivating works on the industrial site of ChNPP.

Not only fission products, but also nuclear fuel (^{238}U, enriched ^{235}U), and radionuclides with the induced activity thrown out into environment were the main distinctive features on the ChNPP accident. Thus, the radioactivity in air was gaseous, ionic-molecular kind, and radioactive aerosol – «hot particles». Last were formed by two ways: because of explosion of a reactor and subsequent it warming up («firm hot particles») and sedimentation thrown out in an atmosphere of radionuclides on pairs water («liquid hot particles») [9, 10].

The aerosols of radioactive substances formed after Chornobyl catastrophe, were extremely various on the physical and chemical properties and various biological transportability. Lungs were the critical body for aerosols of Zirconium, Niobium, Ruthenium, Cerium, Neptunium, Cesium [9,10].

The irradiation of bronchopulmonary system of clean-up workers during the first ten days occurred because of inhalation of radionuclides intake in the air. At that period the greatest value for bronchopulmonary system irradiation had ^{131}I, ^{106}Ru, ^{144}Ce [9]. The probability of radioactive particles admission into respiratory system was rather big as some particles reached the sizes of 1–5 microns; the same particles with sizes of 20–40 microns late in the upper respiratory ways [7–10].

The most essential value for bronchopulmonary system radiation safety in the remote terms had long-living transuranium elements (TUE): $^{238\text{-}241}$Pu, ^{241}Am, ^{242}Cm. Isotopes of these elements rarely meet separately and present in an environment in the combinations reflecting specificity of their reception [9]. One of most biologically significant and well-investigated elements is plutonium. The significant amount of radioactive substances is defined in lung parenchyma, in bronchial epithelium, and in lower parts of bronchial tree. Postponed TUE can leave the respiratory system in the several ways. One part of them will penetrate directly from lungs (after dissolution in a tissue liquid) into blood. This fraction of radionuclides is transported into other organs and tissues, mainly, into liver, bone, or excretes. The second fraction collects by macrophage, delivers lungs by bronchial and tracheal clearance, and swallows with sputum. The third fraction translocates through lymphatic vessels up to regional lymph nodes where it delays, but the part of it, eventually, can reach system circulation [9, 10].

The highest concentration of plutonium are always present in lungs and tracheabronchial lymph nodes [9]. The mentioned above mechanism of radioactive particles deducing for the account tracheobronchial clearance, is fair for many insoluble and poorly soluble compounds, and «hot» particles as well. At inhalation of radioactive short living aerosols, the bronchial epithelium is irradiated by the particles which stays in respiratory ways. About 90% of all radionuclides are concentrated in the lower layers ofbronchial epithelium, which makes possible of basal cells irradiation even by α-particles [10].

Analysis of relative radiation risks (RR) from data of deep clinico-epidemiological inspection (1992–2004) of 7665 men – COPD patients participants of liquidation of consequences of

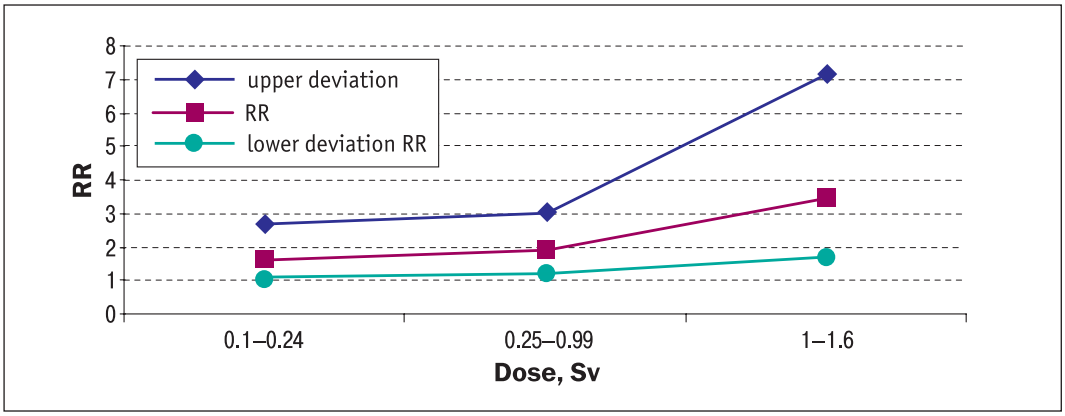


Figure 13.1. **Relative radiation risks(RR) and 95% confidential interval for COPD morbidityin patients – participants of liquidation of consequences of ChNPP accident 1986–1987**

ChNPP accident 1986–1987 with the different doses of total-body external irradiation (Figure13.1) in NRCRM of NAMS of Ukraine educed reliable connection of development of this pathology with influence of ionizing irradiation in doses higher 0.25 Sv (control group was formed by patients with doses lower then 0.05 Sv).

These data corresponds with the results of clinic-epidemiological researches on the base of Ukrainian national radiation register, that testify the one of the leading places of respiratory organs pathology in the structure of general morbidity of the outlined contingent of population [1, 2, 6, 7].

The «hot» particles incorporation into the lungs were verified by whole body counter technology for 10 individuals (predominately ^{137}Cs, ^{60}Co) (Table 13.1).

The analysis of radiation dose in clean-up workers showed the significantly higher level of various forms of bronchopulmonary disease, compared with those without bronchopulmonary pathology [(242.9 ± 82.0) mSv (median 117 mSv) to (145.8 ± 62.0) mSv (median 60 mSv), p = 0.001].

In clean-up workers smoking also showed reliable association with the presence of somatic diseases in general (r = 0,183; p <0.001), chronic bronchitis (r= 0.154; p <0.001) and COPD (r = 0.087; p <0.01). Smokers had twice higher incidence of bronchopulmonary diseases than

Table 13.1

Dosimetric characteristic of clean-upworkers of ChNPP accident and underwent inhalation incorporation of «hot» particles

#	Patient code	Year of birth	Radioisotope	Activity, Bq	Dose, mSv	Date of examination
1	A-v A.I.	1957	^{137}Cs	4300	250–1160	21.02.2002
2	B-ch Ya.O.	1940	^{60}Co	308	21–38	27.03.2002
3	G-i S.A.	1952	^{137}Cs	7226	400–1900	24.01.2002
4	K-ko I.M.	1961	^{60}Co	160	50–170	01.10.2002
5	K-t V.G.	1947	^{60}Co	585	40–65	08.02.2002
6	R-v V.V.	1945	^{60}Co	581	37–59	20.12.2000
7	T-b Yu.Yu.	1952	^{137}Cs	520	30–135	17.04.2002
8	F-v Yu.I.	1941	^{60}Co	464	25–42	10.06.1999
9	Yu-ko V.A.	1946	^{60}Co	804	55–90	14.01.2002
10	G-n S.N.	1958	^{137}Cs	120	10–37	08.05.2002

those who did not smoke, 46.23% and 27.46%, respectively, relatively to bronchopulmonary pathology in common ($p = 0.0001$); 33.49% and 19.01% compared to 10.2%in patients suffered with chronic bronchitis and 5.16% compared to COPD patients. Thus, if the risk of bronchopulmonary pathology in general for smokers was 2.909 (95% CI 2.526-3.349), and for those who did not smoke – 0.524 (0.479–0.573), $p < 0.001$, for those who stopped smoking, – 0.488 (0.419–0.567).

The manifestation of bronchopulmonary pathology in the early period after radiation exposure characterized by syndrome-complex, characteristic feature of which was the presence of distinct irritation of the upper respiratory tract. Overall, for the clean-up workers of the Chornobyl accident was typical «poverty» and «not patency» of clinical symptoms at onset, shortness of breath preceding the appearance of other symptoms. Prevailed hypo-reactive nature of COPD exacerbations.

Our studies demonstrated the prevalence in the structure of chronic nonspecific bronchopulmonary pathology morbidity in clean-up workers.

High comorbidity, the presence of multiple concomitant diseases were common in COPD victims of the Chornobyl accident. Concomitant diseases were registered in all the clean-up workers and only 35% of COPD patients from the control group. More common the combination of cardiovascular and nervous systems diseases (early vegetative disorders in the future – hypertension, coronary heart disease, early cerebral arteriosclerosis, encephalopathy), which during the first years was manifested in 63.4% of cases, and at latest periods was diagnosed almost in 100% of patients.

In COPD patients in the absence of difference in COPD stage (FEV1) in the clean-up workers compared to the control group significantly worse degree of dyspnea (MRC) [(2.3 ± 0.4) points against (1.6 ± 0.2) and control group, $p < 0.01$) was found, the frequency of exacerbations per year [(2.8 ± 0.8) and (1.7 ± 0.4) respectively, $p < 0.01$] were observed.

For the clean-up workers the gradual transformation of bronchial obstruction syndrome was also characteristic: at the beginning of the disease hypotonic dyskinesia of membranous part of the trachea and small bronchi obstruction was detected, which later turns into a total bronchial obstruction with a low level its recoverability.

It was established that the results of lung function tests in COPD clean-up workers of the Chornobyl compared with the group of nosology control patients detected a significant decrease in the maximum volumetric rate at 75% FVC (FEF 75), with no change in average group values other volume and speed indicators. The results of the body plethysmography in COPD clean-up workersidentified significant violations of lung volumes due to significantly higher levels of residual volume (RV), the internal volume of gas in the chest (ITGV) and expiratory reserve volume (ERV) in compare with the nosology control patients. These data indicated more severe respiratory problems in clean-up workers due to pulmonary emphysema and lung hyperinflation that accompanied the development of pulmonary hypertension, right ventricular dilatation and formation of its diastolic dysfunction.

The new data about the presence of dose interdependence between respiratory function tests and radiation dose of more than 500 mSv in COPD clean-up workers of Chornobyl in the remote period after exposure were received. That was proved by a significant decline in forced vital capacity (FVC) and FEF75 in clean-up workers with the highest level of deviation in individuals exposed to doses in the range of more than 500 mSv and a significant decrease in vital capacity of lungs (VC). FEF25 in the main groups of clean-up workers of the Chornobyl and nosology control group did not differ while exhaling at 50% FVC and 75% FVC significantly reduced relatively to nosology control group.

The lungs diffusion (DLco)reduction in COPD clean-up workers of the Chornobylwas one of the hallmarks of ionizing radiation and inhalation exposure of radionuclides emergency origin confirms more severe course of the disease and meet more frequency signs of the pneumofibrosis and emphysema in X-ray examination.

The results of endoscopic examination (877 COPD clean-up workers of the Chornobyl accident and 116 nosology control group patients were examined) showed the most common presence of chronic atrophic endobronchitis with significant fibrotic changes of bronchial mucosa. Endoscopic mucosal signs of trachea and bronchi change of clean-up workershad typical signs and, in general, were relevant to atrophic endobronchitis and significant catarrhal-sclerotic changes.Since 1996, the severe deformation of the bronchial tree was also found. In the nosology control group the level of atrophic and sclerotic changes in bronchial mucosa was significantly lower. During the first 10 years (up to 1996) the lower level of endobronchial inflammation activity was found in clean-up workers in compare with patients of nosology control group, who demonstrated the complete inflammatory response. The level of catarrhal-sclerotic endobronchitis cases was and remains significantly higher in clean-up workers of Chornobyl accident than in nosology control.

The results of bronchoalveolar washouts study showed the redistribution of cells in the T-link with a decrease in the relative content of major subpopulations of T cells. However, the relatively higher number of cytotoxic cells with high expression of functionally active surface antigenswere found.

In COPD clean-up workers of the Chornobyl groups exposed in dose ranges of less and more than 500 mSv were established dose the dependence of the changes in cellular immunity, including significant reduction in the number of $CD3^+$ T cells, mainly by CD8 + subpopulation. The number of $CD4^+$ cells probably were higher compared with the control group throughout the range of doses, decreased cytotoxic $CD3^+16^+56^+$ T-lymphocytes, increased $CD3^-16^+56^+$ natural killer cells, and increased CD 3^-19^+ B lymphocytes. These changes in humoral immunity, indicated the dependence of the immune status of the absorbed radiation dose.

We defined the direct connection of respiratory disorders in COPD patients, with a level of $CD3^+16^+56^+$ of cytotoxic T lymphocytes, such as FEV1, FEF 25, FEF 75 and DLco, which were the basis of more severe disease course.

In conducting the microbiological analysis of sputum and endobronchial content of clean-up workers was identified a range of microorganisms belonging to the resident and to pathogenic organisms. In clean-up workers of the Chornobyl accident in the bacteriological study of endobronchial washouts were identified microorganisms in associations 2-4 different kinds of families that have different sensitivity to antibiotics. In the first place by the frequency of detection in sputum of clean-up workers is *Staphylococcus aureus* (47.4 %). Second place is occupied yeast fungi genus Candida (26.9 %). Much less frequently were present *Streptococcus pneumoniae* (5.6%), *Haemophilus influenzae* (4.7 %), *Klebsiella pneumoniae* (2.8 %) in clean-up workers. Other microorganisms – *Moraxella catarrhalis, Proteus vulgaris, Proteus mirabilis, Streptococcus viridans, Streptococcus faecium, Neisseria perflava, Neisseria sicca, Enterobacter aerogenes, Enterobacter Iwoffi* – met sporadically. Noteworthy is atypical availability of the *Escheria coli* for the bronchi content. It can be associated with significant frequency of the gastroesophageal and duodeno-gastric reflux and digestive tract components intake to the bronchial tree on the background of vegetative regulation disorders and dysbiosis in these patients. It should also be noted that the study of endobronchial washouts usually defined several microorganisms (2-4) genera and species, often – association of *Haemophilus influenzae* and *Streptococcus viridans*, *Neisseria perflava* and *Streptococcus faecium* with different sensitivity to antibiotics. Moreover, according

to the morphological, in particular the ultrastructural, analysis of the clean-up workers presents deep penetration of microorganisms in the lamina propria of the bronchial mucosa[11–14].

According to the linkage of Cancer Registry of Ukraine in the cohort of clean-up workers (n = 7156) 50 lung cancer cases were recorded during 1993-2009 (17 years), first case was registered in 1993 (7 years after the Chornobyl accident), 4 cases – in 2009 (23 years after the Chornobyl accident). During 10 years after the Chornobyl accident 3 lung cancer cases were diagnosed, up to 15 years – 19 cases, up to 20 years – 18 cases, and up to 23 – 10 new cases of lung cancer. The peak of the morbidity occurred in 2000, when 11 cases of lung cancer in the surveyed cohort were found. The prevalence of lung cancer in this clean-up workers cohort was 7.9 ‰. The average age of men at the time of the accident, in which up to 2010 lung cancer has not been revealed, was (37.93 ± 0.12) years, was significantly lower than in lung cancer patients (43.0 ± 1.12) years; p = 0.001.

Among the male clean-up workers, with lung cancer (n = 50), significantly more frequently (to develop lung cancer) bronchopulmonary somatic diseases were determined, especially COPD, compared with those who did not become ill (n = 6257). Thus, all bronchopulmonary diseases detection rate was 72 and 47.01%, respectively, p <0.001; frequency of chronic bronchitis – 44 and 34.56%, respectively, p = 0.162; the frequency of COPD – 24 and 9.71% respectively, p <0.001; incidence of asthma was not significantly different – 2 and 1.96%, respectively, p> 0.05.

In clean-up workers with lung cancer the radiation dose was higher than in those without lung cancer and was accordingly (368.7 ± 90.8) mSv compared with (204.2 ± 56) mSv (p <0.05).

Smoking factor significantly influenced to the development of lung cancer. History of smoking was known in all lung cancer patients and 4227 men who are not sick. Only 6 of the 50 patients with lung cancer were never smokers, compared with 1439 (34.04%) clean-up workers with no lung cancer (p <0.001). The risk of lung cancer for smokers was 3.785 (95% confidence interval 1.609-8.903). If patients stopped smoking, it reduced the risk of lung cancer [15].

Thus, the detection rate of lung cancer among those who never smoked, was 0.41% (lung cancer appeared in 6 of 1445 surveyed) among those who stop smoking – 0.84% (9 of 1,064 surveyed), and smokers – 1.95% (35 of 1,794 surveyed) (p <0.001).

Among the 246 clean-up workers with dose over 500 mSv lung cancer developed in 6 people (2.43%), and among 2,151 clean-up workers with lower doses – only 13 people (0.60%), p <0.01. Lung cancer risk increased in 4.1 times (95% confidence interval 1.549-10.917) in radiation doses over 500 mSv.

Complex analysis showed the lung cancer development in association with the following factors: smoking, presence of chronic somatic bronchopulmonary diseases, radiation dose over 500 mSv. Lung cancer detection rate was highest among smokers with chronic bronchopulmonary diseases in radiation dose less than 500 mSv (Table13.2), which is significantly higher than in the no smokers clean-up workers and have no somatic pathology ($\chi^2 = 5.34$; p <0 01). Among the 66 clean-up workers with radiation dose over 500 mSv, lung cancer developed in 6 of 18 smokers individuals with bronchopulmonary diseases. Lung cancer not appeared in any of the 306 non-smokers clean-up workers with a lower dose, and have no bronchopulmonary diseases (highly probable differences, $\chi^2 = 103.92$; p = 0.0001). In addition, the presence of bronchopulmonary disease among the smokers risk of lung cancer was greater in clean-up workers when doses over 500 mSv compared with those who received a lower dose ($\chi^2 = 61.24$; p <0.001).

Thus, the greatest risk of lung cancer development was observed among people with radiation dose of more than 500 mSv, those with somatic diseases of bronchopulmonary system, smokers.

* * *

Table 13.2

The lung cancer detection rate among male's clean-up workers aged over 35 years, depending on the radiation dose, smoking, and bronchopulmonary diseases in history (%)

Radiation dose	Smoking status	Bronchopulmonary diseases	
		no diseases	existing diseases
< 500 mSv	Non-smokers	0 (0/306)*	1.5 (2/134)
	Smokers	0.69 (3/469)	1.73 (8/463)
>500 mSv	Non-smokers	0 (0/18)	0 (0/25)
	Smokers	0 (0/5)	33 (6/18)

Note. In the numerator – the number of lung cancer patients, and the denominator – the total number of patients in the subgroup.

In combined action of external exposure and inhalation of the clastic mixture of radionuclides in the Chornobyl catastrophe bronchopulmonary system became one of the main tissues – «target», later realized to chronic obstructive pulmonary disease, manifestation of which occurred during the first 3–5 years after patients participating in post-accident work.

The Chornobyl accident contributed to the growth of disease and morbidity of the pulmonary diseases among the clean-up workers of the accident.

The COPD progression in clean-up workers at Chornobyl in the early years was characterized by minimal clinical symptoms, in the future – the rapid development of fiber-plastic changes in the lungs and bronchial mucosa with progressive deformation of them, hypo-reactivity of the exacerbations and violation of bronchial secretions. In the remote period after exposure more severe clinical coursewas observed.

Broncho-obstructive syndrome in clean-up workers of the Chornobylaccident is modified from hypotonic dyskinesia of membranous part of the trachea and small bronchi obstruction to total low-reverse obstruction. For the clean-up workers of the Chornobyl established the significantly lower values of volume and speed indicators by spirometry results. The significant violations of lung volumes ratio due to significantly higher levels of residual volume. Established the dose relationship between the respiratory function indicators and radiation dose for the patient group among clean-up workers of the Chornobyl exposed at doses more than 500 mSv, compared with exposed at doses less than 500 mSv and nosology control. Significantly lower rates of lung diffusion capacity (DLco) in the group of COPD clean-up workers of the Chornobyl regarding of nosology control, confirming the severity of the disease, more frequent detection of signs of emphysema and pneumofibrosis by X-ray examination of patients of the main group.

Patients clean-up workers have several concomitant diseases, that COPD is a component of multiple organ pathology which caused greatly violations in integration systems providing homeostasis.

Verified in patients clean-up workers according to endoscopic studies chronic diffuse atrophic endobronchitis with significant fibrotic changes in bronchial mucosa morphologically relevant chronic inflammation disorders with distinct regeneration, damage to the mucociliary apparatus ciliary epithelial disorders of microcirculation and epithelial-connective relationships, transformed fibril-genesis, inability of local protection mechanisms and signs of the intensify of aging reactions in the bronchi mucosa.

Endobronchial environment of the COPD clean-up workers of the Chornobyl accident, contaminated preferably representatives 2–4 types of resident and pathogenic organisms with different sensitivity to antibiotics and typical invasion of microorganisms in the lamina propria

bronchial mucosa. In COPD clean-up workers of the Chornobyl in groups, exposed to dose ranges of less and more than 500 mSv, the dose dependence of the changes in cellular immunity, including significant reduction in the number of $CD3^+$ T cells, mainly by $CD8^+$ subpopulation, while the number of $CD4^+$ cells probably were higher compared with the control group throughout the range of doses, decreasing of the cytotoxic $CD3^+16^+56^+$ T-lymphocytes, increase $CD3^-16^+56^+$ natural killer cells, and increasing of the CD 3^-19^+ B lymphocytes and of changes in humoral immunity, indicating the dependence of the immune status of absorbed radiation dose was established. Defined the direct connection of respiratory disorders in COPD patients, with a level of $CD3^+16^+56^+$ of cytotoxic T lymphocytes, such as FEV1, FEF 25, FEF 75 and DLco, which is the basis of severe clinical currency.The greatest risk of lung cancer development was observed among people with radiation dose of more than 500 mSv, those with somatic diseases of bronchopulmonary system, smokers.

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Chapter 14
FEATURES OF DIGESTIVE SYSTEM DISEASES IN PERSONS EXPOSED TO IONIZING RADIATION UPON THE CHORNOBYL NPP ACCIDENT

Long-term clinical surveys and epidemiological research indicate a stable negative health transformation in the Chornobyl NPP accident clean-up workers.

Gastrointestinal tract is one of the principal routs of radionuclide incorporation and elimination. Radionuclide incorporation contributes to the equivalent radiation dose as an internal distant source. Long-term internal irradiation along with external radiation impact appears an important pathogenetic factor of the diseases of digestive organs. Long-term clinical observations and epidemiological studies prove the stable unfavorable health effects in the Chornobyl NPP accident clean-up workers [1].

According to the digestive system complex check-up results in the ChNPP accident clean-up workers some regularities were found in the onset and progression of digestive disorders. In the nearest time i.e. 1–1.5 years after the accident the inflammatory diseases of stomach and duodenum (gastritis and gastroduodenitis) were diagnosed most often. Soon the attention was drawn to the incidence increase of both inflammatory and erosive-ulcerative lesions of gastric and duodenal mucosa, disorders of gastric motor function with onset of reflux-esophagitis and duodenogastric reflux. Therewith some changes occurred in the clinical presentation of peptic ulcer disease. No pain syndrome was present in most cases of disease exacerbation, astheno-vegetative or dyspeptic syndromes were prevalent instead, whereas erosive-ulcerative lesions were just found under the esophagogastroduodenoscopy [2].

Astheno-vegatevive syndrome being identified in 49.7–85.3% of cases was prevalent among the clinical symptoms. General and pronounced asthenisation resulted in distortion of clinical presentation. Examination of vegetative tone indicated the parasympathetic tone prevalence.

Atrophy of gastric and duodenal mucous membrane was often registered in the clean-up workers having erosive-ulcerative diseases of gastroduodenal zone. Atrophy exacerbation occurred each time from one examination to the next (58.8–89.2% and 40.3–65% in comparison group). Trend was revealed of atrophic antral gastritis evolution to the atrophic pangastritis that had been diagnosed just in immediate period even in a young age more often than in comparison group (17.9–33.7% vs. 6.9–18.7%). Atrophy of gastric and duodenal mucous

membrane in the clean-up workers was diagnosed more often in comorbid cases of gastric and duodenal peptic ulcer disease (28.2–48.5%) and duodenal peptic ulcer (25.3–45.3%). Less often it was found in gastric peptic ulcer cases (12.0–17.5%). Atrophic processes in the clean-up workers having erosive-ulcerative lesions of gastroduodenal zone were almost the same as in clean-up workers with gastroduodenitis that was indicative to the common etiological issues and pathways of such disorders in both groups. Peptic ulcer disease developed at a background of the already existing gastritis with mucosal atrophy, exacerbating at that the degenerative and destructive lesions of mucous membrane.

Review of endoscopic pattern of gastric and duodenal mucosa in peptic ulcer disease in the ChNPP accident clean-up workers indicated a progression of atrophic mucosal lesions being more often revealed in all age groups. Atrophic pangastritis in particular was reliably ($p < 0.001–0.01$) more often diagnosed in the clean-up workers at the all survey points.

Atrophy of duodenal mucosa is of a key role in dysfunction of digestive system. This local atrophy leads to insufficient production of such hormones as motilin, cholecystokinin, pancreozymin, secretin, and others that all regulate bilious system and biliary excretion, exocrine pancreatic function, gastric secretion, and its evacuatory motor function. All that lead to cholestasis, biliary tract and gall-bladder dyskinesia, and then to development of cholecystocholangitis, cholangiohepatitis that even more suppress the exocrine pancreatic function both with gastric motor function and secretion [2, 3].

Motor dysfunction and evacuatory disorders and especially the duodenogastric reflux have a key role in development of erosive-ulcerative lesions.

Duodenogastric reflux was more often found in the clean-up workers who have had an erosive-ulcerative disease (18.7–46.0%), and less often in persons with gastroduodenitis (10.3–31.7%) as well as in comparison group (11.1–26.3%). In the clean-up workers with peptic ulcer disease a duodenogastric reflux was most often diagnosed at the age of 50–59 years old (52.4%).

Reflux-esophagitis was registered in the clean-up workers with erosive-ulcerative diseases at all survey points in 27.9–67.0% of cases that significantly exceeded the respective values in a comparison group (10.6–49.2%). But reflux-esophagitis with concomitant ulcers and hemorrhages (grade activity III) was revealed only in the emergency workers suffering peptic ulcer disease (in 9.1–21.1%) as against a comparison group.

Our findings give the evidence of interrelation of reflux-esophagitis with gastric and duodenal diseases especially pronounced in erosive-ulcerative lesions of gastroduodenal zone.

General morbidity pattern of erosive-ulcerative disease of stomach and duodenum was analyzed in the clean-up workers and a comparison group for the 1993–2006 period. Significant i.e. about a 2-fold excess of incidence was revealed in the clean-up workers (111.1–135.5 ‰ vs. 54.4–73.4 ‰).

Gastric ulcers of rare localization i.e. in forestomach (6.1–13.8%) and body of stomach (12.3–17.2%) were revealed at the all survey points in the clean-up workers as distinct from the comparison group. Such ulcers featured the prolonged scarring, treatment medicinal resistance, bleeding complications, penetration, and malignization.

Identification of multiple ulcers in stomach (5.3–7.1%) and duodenum (13.7–16.2%) both with large ulcers of the same localization (in 7.4–20.0% and 23.3–25.0% respectively) was featured in the clean-up workers.

An analytical «case-control» study was conducted to estimate the risk of erosive-ulcerative lesions of stomach and duodenum depending on radiation dose received under emergency works on the clean up of the ChNPP accident.

According to calculation results the 25-cGy level of dose burden was found being most correct to receive a precise relative risk estimates with narrow confidential interval indicating a statistical power of the study. Consequently the risk of erosive-ulcerative lesions is suggested in persons exposed to radiation doses over 25 cGy (Table 14.1).

Table 14.1
Odds ratio (OR) of erosive-ulcerative lesions under the exposure to ionizing radiation at doses over 25 cGy

Exposure presence	Lesion presence		Total	OR (95% CI)
	Yes (n)	No (n_1)		
Yes (≥ 25 cGy)	49	45	94	4,67 (2.84 – 7.71)
No (< 25 cGy)	79	339	418	
Total	**128**	**384**	**512**	

Organic narrowing of duodenal lumen in bulbus zone (8-19%) and compensated bulbus stenosis (32.6–35.2%) were revealed in disease remission phase in the clean-up workers that indicate a possible evolution of stenosis to subcompensation and decompensation stage with subsequent surgery and disablement.

Inflammatory disorders of stomach and duodenum in the clean-up workers suffering peptic ulcer disease were revealed not only in case of erosive or ulcerative defect but in absence of both of them (in 55.6–93.8% at various survey points). Thus an unstable remission stage can be suggested in such patients while the disease relapse any time should not be ruled out in its turn.

Study of hypothalamic-pituitary-adrenocortical system (HPACS) in the clean-up workers having erosive-ulcerative lesions indicated a significant activity increase of all system elements in the nearest postaccident years. Significant increase of corticoliberin, corticotropin (ACTH) and cortisol was found. Both ACTH and cortisol predispose to ulceration through the stimulation of hydrochloric acid and pepsin secretion and gastrin release, along with suppression of mucus production and trophism of mucous membrane, DNA synthesis and mitotic index decrease. The HPACS strain appeared being one of initiating factors of erosive-ulcerative lesions in gastroduodenal zone [4].

Basal concentration of ACTH and cortisol increased significantly in absorbed doses exceeding 25 cGy (Figure 14.1, 14.2). At that there was no normally present negative feedback in ACTH and cortisol production.

Increase of somatotropin (growth hormone – GH) and insulin content (Table 14.2) was revealed in the clean-up workers in years ahead the accident (1988–1992). GH and insulin as against the HPACS hormones make an anabolic effect on gastroduodenal zone. Together they stimulate synthesis of gastrin i.e. the principal hormone regulating hydrochloric acid and pepsin production and promote an elevated concentration of the latter hormone in the clean-up workers with amplification of acid-peptic aggression of gastric juice. Such disorders of hormonal regulation had led to aggression and protection factors imbalance, decrease of functional capacity of mucous barrier, failure of epithelial regeneration of stomach and duodenal mucosa, and ulceration.

Increased gastrin concentration was surveyed in blood of the clean-up workers in case of both hypoacidity and normo- or hyperacidity suggesting the gastrin mechanism predominance in acid production and disorder of local autoregulation system in gastroduodenal zone. The dependence of gastrin secretion on radiation dose was reveled in clean-up workers suffering the erosive-ulcerative lesions of stomach and duodenum (Figure 14.3).

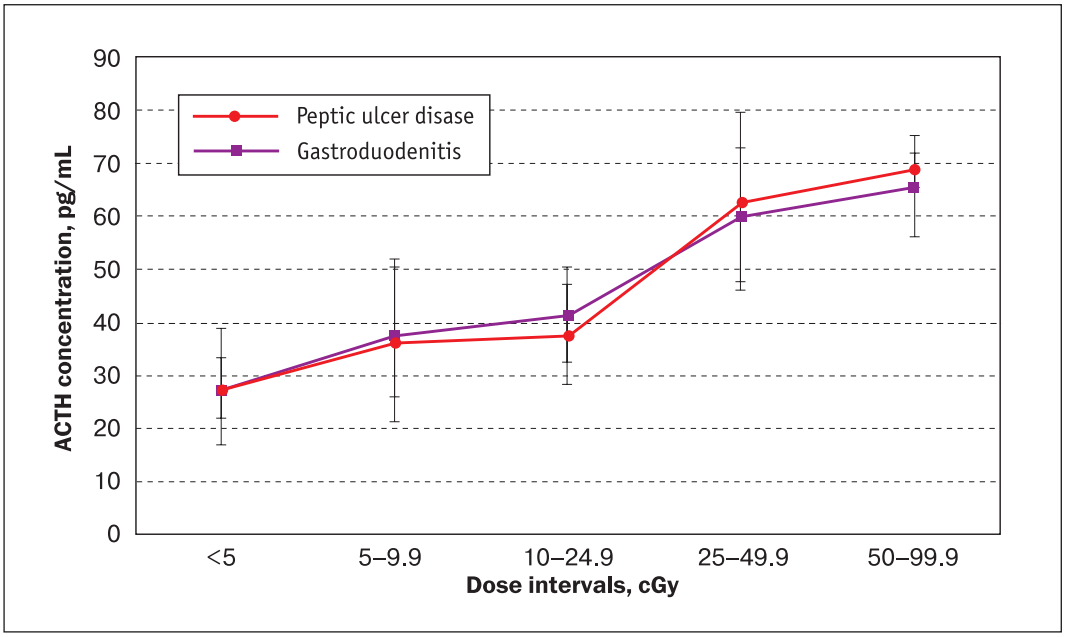


Figure 14.1. **Dependence of basal serum ACTH concentration (M ± m) on radiation dose in the clean-up workers with erosive-ulcerative lesions of stomach and duodenum and gastroduodenitis**

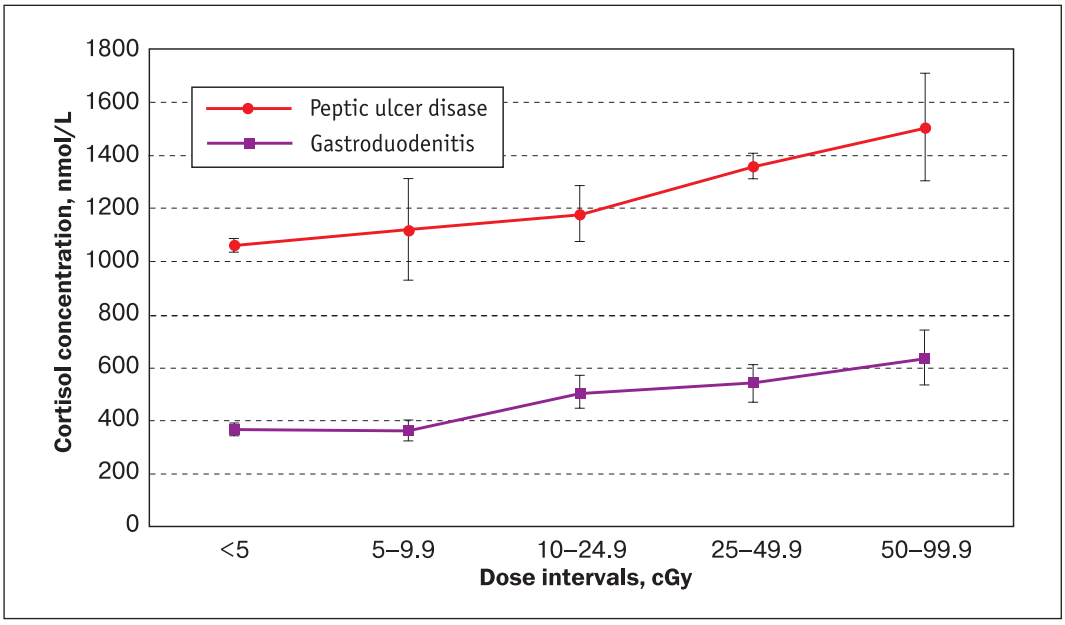


Figure 14.2. **Dependence of basal serum cortisol concentration (M ± m) on radiation dose in the clean-up workers with erosive-ulcerative and inflammatory lesions of gastroduodenal zone**
Note. * – significance of difference between groups ($p < 0.001$).

Table 14.2
Basal serum GH, insulin, and gastrin concentration in clean-up workers and comparison group (M ± m)

Hormones	Study groups		*p*
	clean-up workers	persons with no radiation exposure in the history	
GH, mg/L	2.0 ± 0.25 (62)	0.76 ± 0.07 (31)	< 0.01
Insulin, mmol/L	128.6 ± 8.7 (72)	63.2 ± 14.3 (25)	< 0.001
Gastrin, mU/mL	75.6 ± 4.97 (101)	57.47 ± 4.70 (24)	< 0.01

Notes. *p* – significance of difference between the groups; number of studied persons are shown within brackets.

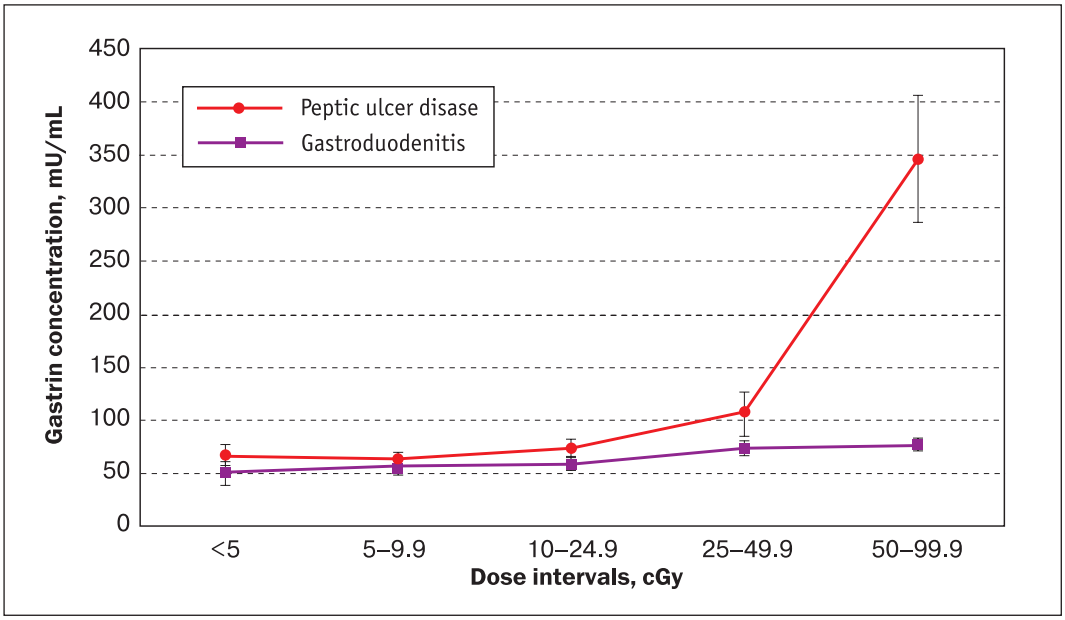


Figure 14.3. Dependence of basal serum concentration of gastrin (M ± m) on radiation dose in clean-up workers with erosive-ulcerative and inflammatory lesions of stomach and duodenum
Note. * – significance of difference between the groups (p < 0.001).

Basal concentrations of studied hormones i.e. ACTH and gastrin turned out to be rather low in the clean-up workers in remote period since the ChNPP accident. At the same time the cortisol concentration in these subjects was exceeding the normal range as before. At that a weak negative «cortisol-ACTH» feedback is surveyed as against in years ahead the accident. Therefore it can be stated that regulatory disorders of the pituitary-adrenocortical axis remain in the clean-up workers suffering the erosive-ulcerative lesions of stomach and duodenum, despite some trend to recovery.

Basal gastrin concentrations had significantly decreased in remote period upon the ChNPP accident in clean-up workers with erosive-ulcerative lesions of stomach and duodenum.

Elevated basal cortisol concentration remained at that with resulting stimulation of G-cells in stomach mucosa and intensified gastrin production featuring a significantly increased serum gastrin content is this group of survivors. No stimulating effect of glucocorticoids can indicate the pronounced mucosal atrophy in stomach antrum with some G-cells loss in the clean-up workers suffering the erosive-ulcerative lesions of gastroduodenal zone that is verified by endoscopic and pathology studies.

Serum gastrin concentration is decreased with radiation dose in remote period upon the ChNPP accident in the clean-up workers with erosive-ulcerative lesions of stomach and duodenum. The lowest values were found in case of 50–99.9 cGy dose range (Figure 14.4). In this case one can suggest more pronounced atrophy in stomach antrum of the clean-up workers with erosive-ulcerative lesions of gastroduodenal zone who had been exposed to more than 25 cGy radiation doses. It is confirmed by the pathology data of stomach mucosa in clean-up workers with peptic ulcer disease [5].

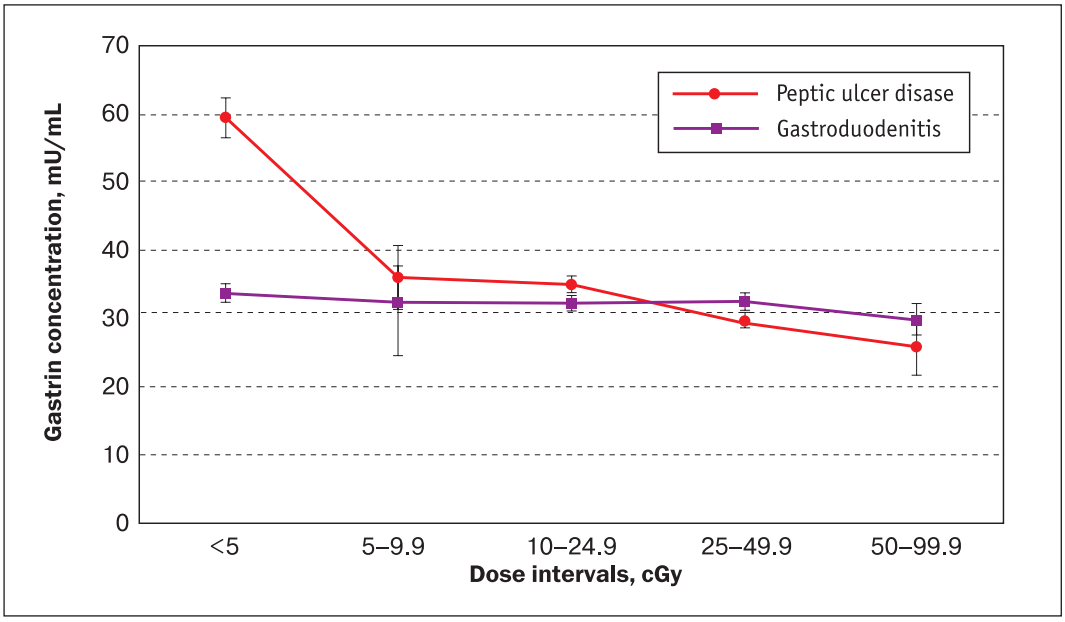


Figure 14.4. Dependence of basal gastrin concentration (M ± m) on radiation dose in clean-up workers with erosive-ulcerative and inflammatory stomach and duodenal lesions
Note. * – significance of difference between the groups ($p < 0.001$).

Structural features of Helicobacer pylori gastritis in the ChNPP accident clean-up workers lied in higher degree of Helicobacer pylori contamination, higher inflammation activity, and poor connections of epithelial cells with basal membrane of stomach mucosa. Higher strain of the local immune system was revealed. Higher percentage of plasma cells was registered in the inflammatory infiltrate, the eosinophilic granulocytes appeared, lymphoid follicles were more often seen in stomach mucosa proving an opinion about the more intensive antigenic stimulation of Helicobacer pylori in the clean-up workers. Atrophy was more widespread featuring a typical decrease of total thickness of stomach mucosa, thickness of glandular zone and volume ratio of glandular tissue.

Not only weakening of local immunity but also infection by highly toxigenic strains of Helicobacter pylori are important in disease process onset and development. Higher activity of chronic gastritis in stomach antrum was revealed in the clean-up workers vs. a comparison group ($p < 0.05$). Lymphoid follicles as a response to Helicobacter pylori colonization appeared significantly more often in the clean-up workers aged 40–49 years old. Higher spatial density of lymphoid follicles and their foci of growth correlated with increased plasma cell infiltration of lamina propria and intensified immunoglobulin synthesis indicating the activation of local immunity. In such a way an atypical mucosa-associated lymphoid tissue (MALT) had appeared in stomach under the impact of antigens and of Helicobacter pylori in particular. Such remodeling of mucosa can induce an autoimmune response [5].

Along with older age of the clean-up workers the structural abnormalities of stomach mucosa featured higher epithelial proliferative activity evident as the increased number of mitoses and interepithelial lymphocytes in generative zones. Connection of superficial epithelium with basal membrane was weaker being evident through the more frequent findings of desquamated epithelium in gastric pit pores ($p < 0.01$). Pronounced activity of chronic gastritis in stomach antrum against an abnormal ratio of proliferation and differentiation both with extrusion lead to increased risk of mass lesions at the age of 50 and more years old. Atrophic processes are associated with microcirculatory disorders in stomach mucosa. Amplification of thrombogenesis and higher incidence of subepithelial hemorrhages were evident (Figure 14.5).

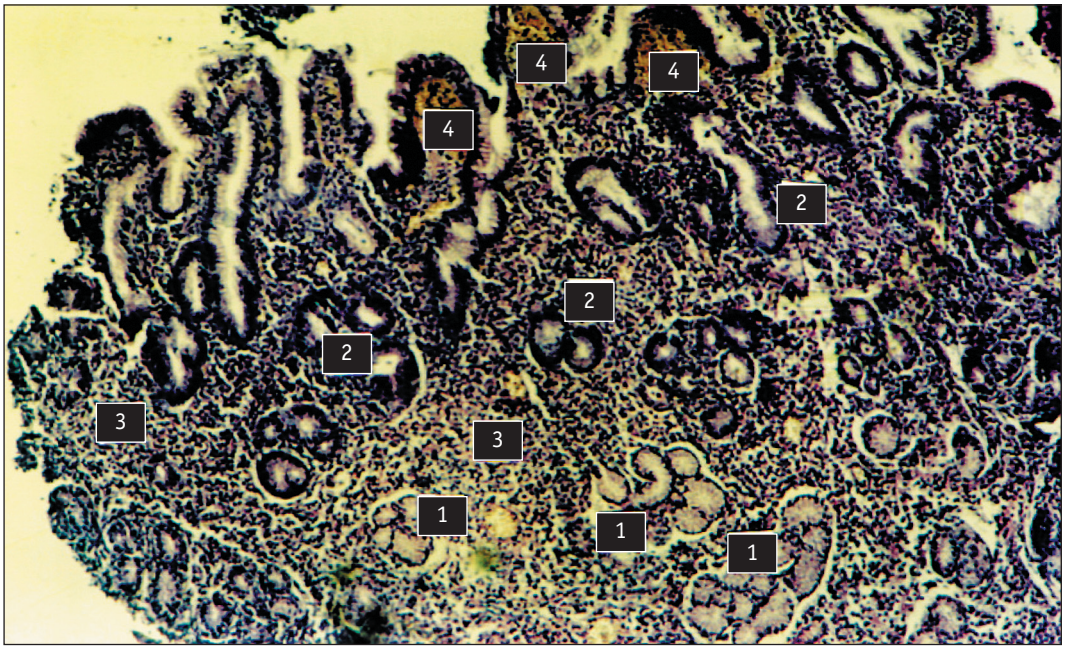


Figure 14.5. Patient P., 36 years old, the accident clean-up worker, 10 cGy external radiation dose. Chronic Helicobacter pylori gastritis. Locus of stomach mucosa. Hematoxylin and eosin staining. ×100. Moderate atrophy of stomach mucosa:

1 – groups of glands in gastric antrum;
2 – adenomeres of gastric pits;
3 – inflammatory infiltration cells of lamina propria of stomach mucosa;
4 – subepithelial hemorrhages.

Decrease of volume ratio of glandular epithelium in both stomach zones was more intensive in the clean-up workers. Index of epithelial volume ratio is one of the most meaningful characteristics of stomach mucosal atrophy under chronic inflammation induced by Helicobacter pylori. Atrophy becomes generalized and severe with age. Atrophic process is an integral interaction index of radiation modification of structures and normal aging processes.

Liver function disorders occurred upon a low-dose radiation impact in proximate period upon the accident. It was established that abnormal laboratory findings of liver function, namely total protein and total bilirubin content, alanin aminotransferase (ALAT) activity are significantly regressively dependent on radiation dose value [6].

According to contemporary opinions liver is a radiosensitive organ. Radiogenic injuries in human and animal organs and tissues occur through the free-radical oxidation, lipid peroxidation, oxidative modification of proteins and nucleic acids under the oxidative stress [7].

Results of the liver function assay just upon completion of the clean-up works at the ChNPP indicated a decrease of most serum protein fractions vs. normal values except the γ-globulin content that was increased. Soon a significant decrease of albumin occurred along with elevation of α1- and γ-globulins and a trend of β- and α2-globulins elevation that remained up to the end of iodine period of accident. Signs of hepatocyte functional insufficiency were revealed in 21.4–35% of surveyed clean-up workers in 1986–1987. Increased bilirubin concentration from 25 to 35 mmol/L was found in 10–25% of cases, values close to the upper limit of normal range i.e. 19–20.5 mmol/L were revealed in 21.4–35%. Radiation doses in these subjects were 25.1–73 cGy. Abnormal synthetic and excretory hepatocyte function was found. Under the elevated average values of total cholesterol content in the clean-up workers ($p < 0.05$) the significant hypercholesterolemia was diagnosed in 31.3–52.9% of cases and decreased serum content in 25–35.7%. Changes of the ALAT concentration were undulating, namely a decrease in the first months upon the accident was followed by elevation. Dehydratase activity was a sensitive marker of cytolytic syndrome, as a significant increase of L-serine dehydratase activity was found in 80% of persons and of L-threonine dehydratase in 93%. Regression analysis of abnormal biochemical parameters depending on radiation impact showed a significant dependence of total protein content, ALAT activity, and total bilirubin content on the absorbed radiation dose ($p < 0.05$). According to diagnostic ultrasound patterns the abnormalities of hepatobiliary system featured some moderate liver enlargement (39%), homogenous increase of its echogenicity (23.3%), and non-homogenous structure (26.4%) [8].

The long-lasting activation of reticular-endothelial liver system in immediate period after the accident was a predictor of chronic diffuse liver disease.

Studies within near five post-accident years i.e. in 1986–1991 showed a dose-dependent increase of chronic hepatitis incidence in the clean-up workers. Peak incidence values were found upon irradiation at a dose of 50 cGy and more (Figure 14.6).

There was a gradual increase in number of persons of working age recognized as disabled ones due to liver disease since the accident. Upward second decade after the accident an increase of chronic hepatitis incidence was marked, namely 28.6–36.1% in the clean-up workers, 16.0–22.3% in evacuees, and 22.0–24.0% in population of contaminated territories, both with incidence of liver cirrhosis cases.

The non-alcoholic fatty liver disease (NAFLD) was diagnosed in remote period after the accident in 86.6% (steatohepatosis – SH – in 50%) and nonalcoholic steatohepatitis (NASH) – in 36.6% of the ChNPP accident clean-up workers having liver disease [9].

The group of the ChNPP accident clean-up workers with NASH was different in radiation history from the group of SH patients. Namely the type and scope of works conducted within

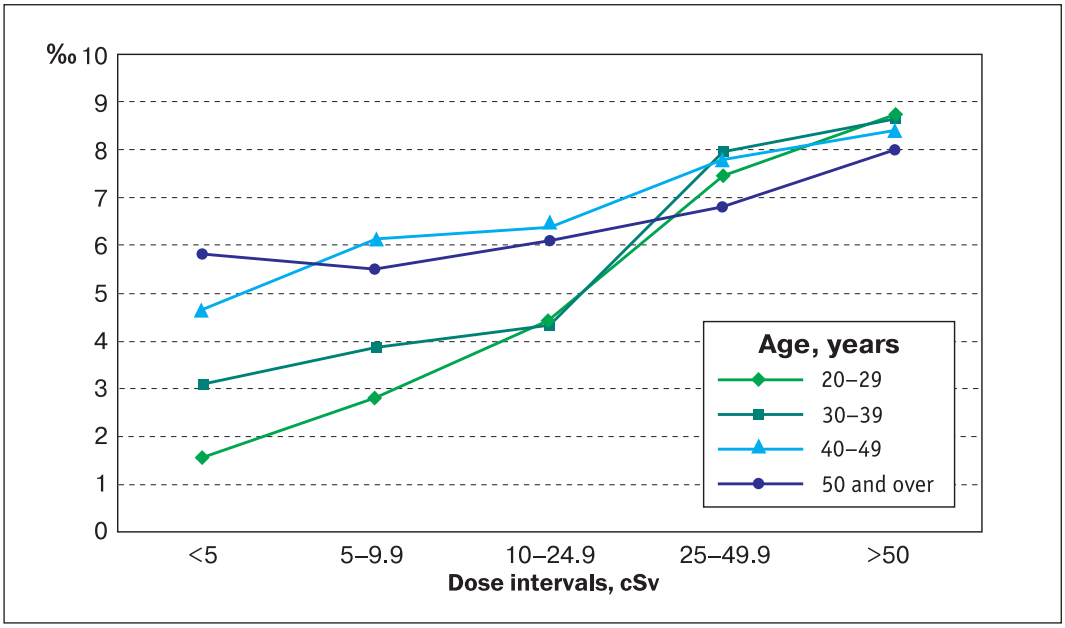


Figure 14.6. **Chronic hepatitis incidence in the ChNPP accident clean-up workers in 1986– 1991 depending on age and radiation dose**

clean-up activities and the absorbed external radiation doses i.e. (25.5 ± 4.6) vs. (13.5 ± 2.9) cGy were different ($p < 0.05$). NASH activity in the ChNPP accident clean-up workers correlated with absorbed dose values. Significant activity increase of aspartate aminotransferase (ASAT) ($p < 0.001$) and ALAT ($p < 0.05$), and decreased bilirubin ($p < 0.05$) and β-lipoproteid ($p < 0.001$) content were found in these patients under the absorbed radiation doses > 50 cGy vs. cases with exposure doses < 5 cGy. Abnormal liver function was more severe in the ChNPP accident clean-up workers exposed to radiation at higher doses. A direct correlation was revealed between the absorbed radiation dose and activity of γ-glutamil transpeptidase (GGT) ($r = 0.6$, $p < 0.02$), ALAT ($r = 0.39$, $p < 0.02$), and glucose concentration ($r = 0.5$, $p < 0.03$) in serum (Figures 14.7, 14.8).

Liver fibrosis was assayed using the FibroTest and APRI test in patients with chronic diffuse liver disease. The F1–3 liver fibrosis stage (unclassified fibrosis) was revealed in 17.1%, and F4 stage (advanced fibrosis) in 18% of cases in the ChNPP accident survivors.

Stage of liver fibrotic changes was correlated with indirect serologic markers of fibrosis i.e. ALAT and ASAT levels, ASAT/ALAT ratio, total bilirubin content, GGT activity, thymol test results, albumin and cholesterol concentrations, both with hemoglobin, platelet, erythrocyte, leukocyte content and blood sedimentation rate.

Increase over the reference values of the ASAT, ALAT, De Ritis Ratio, and GGT was surveyed in group F1–3, however a significant difference with Group F0 was revealed only for aminotransferase levels suggesting the presence of inflammation and cytolytic syndromes being among the triggers of fibrinogenesis. Significant increase of bilirubin, aminotransferase levels, De Ritis Ratio, thymol test results, GGT and alkaline phosphatase activity over the normal ranges was found in a group of advanced fibrotic lesions (F4) vs. Group F0 and Group F1–3. Subtle elevation of bilirubin content (21.1 ± 1.6 mmol/L), advanced cytolytic syndrome i.e. ASAT activ-

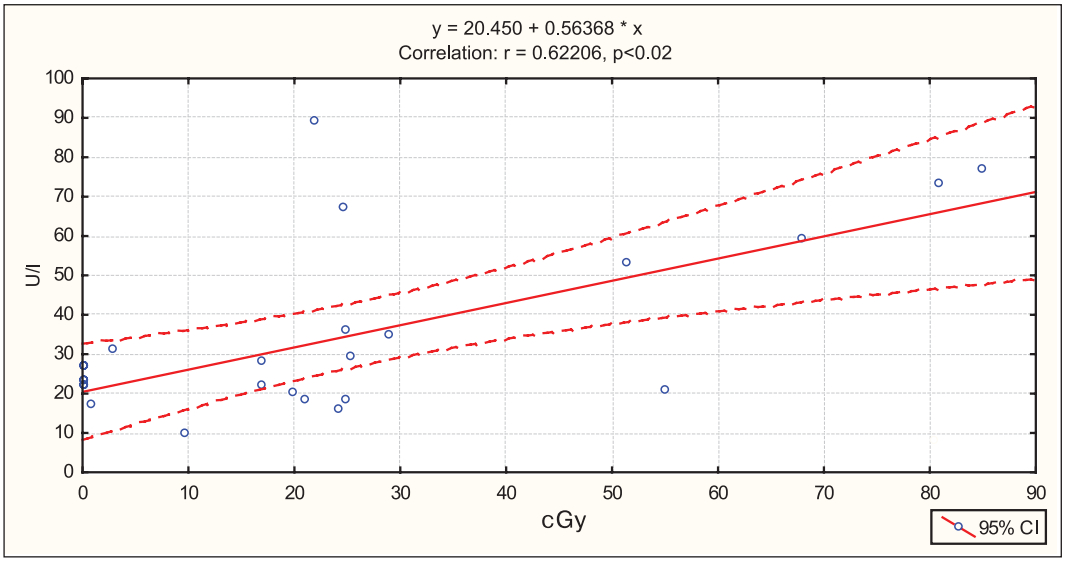


Figure 14.7. **Regression and correlation analysis between the absorbed radiation dose and γ-glutamil transpeptidase in serum of the ChNPP accident clean-up workers having chronic diffuse liver disease**

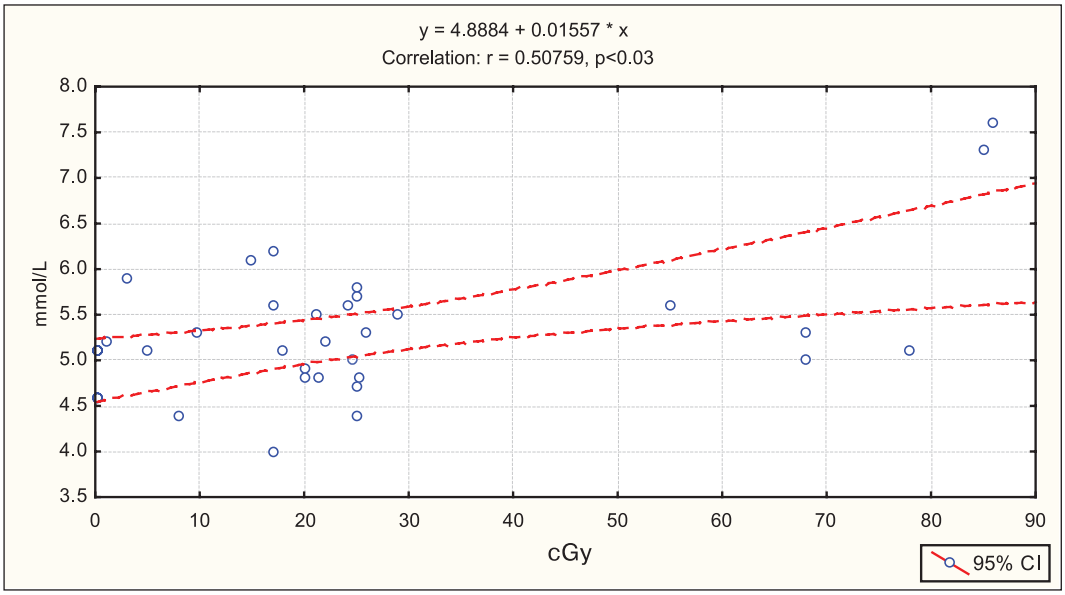


Figure 14.8. **Correlation and regression analysis between the absorbed radiation dose and serum glucose concentration in the ChNPP accident clean-up workers having chronic diffuse liver disease**

ity (128.1 ± 15.9) U/L, ALAT activity (107.7 ± 23.4) U/L, increased thymol test data over the normal range (6.1±1.1 U), and a 3-fold GGT activity increase vs. normal range with average value of (234.8 ± 106.2) U/L were revealed in persons from Group F4. Cholesterol and albumin levels were lower in this group vs. values in the groups F1-3 and F0. A direct correlation was

established of liver fibrosis stage with ASAT and ALAT levels, thymol test data, GGT, De Ritis Ratio ($p < 0.001$), total bilirubin, alkaline phosphatase ($p < 0.01$). A reversed correlation was found towards cholesterol and albumin ($p < 0.01$) (Table 14.3).

Table 14.3
Serologic markers of liver fibrosis in the main group of chronic diffuse liver disease at different stages of liver fibrosis

Indices	Fibrosis stage			*r*
	F0 ($n_1 = 72$)	F1–3 ($n_1 = 19$)	F4 ($n_1 = 20$)	
Total bilirubin, mmol/L	13.3 ± 0.8	17.2 ± 2.1	21.1 ± 3.6*	0.3 ($p < 0.01$)
ASAT, U/L	33.2 ± 1.1	57.4 ± 2.2$^{xxx.\ ^{^^^}}$	128.1 ± 15.9***	0.87 ($p < 0.001$)
ALAT, U/L	41.9 ± 3.0	69.5 ± 5.8^{xxx}	107.7 ± 23.4**	0.49 ($p < 0.001$)
De Ritis Ratio (ASAT/ALAT)	0.95 ± 0.04	1.04 ± 0.2^	1.64 ± 0.2***	0.4 ($p < 0.001$)
Thimol test, U	2.3 ± 0.3	2.1 ± 0.3^^^	6.1 ± 1.1**	0.5 ($p < 0.001$)
Cholesterol, mmol/L	5.8 ± 0.1	5.7 ± 0.3^	4.6 ± 0.3***	-0.26 ($p < 0.01$)
GGT, U/L	49.3 ± 8.4	77.7 ± 16	234.8 ± 106.2*	0.46 ($p < 0.001$)
Alkaline phosphatase, IU/L	146.6 ± 5.1	167.3 ± 11.4	203.7 ± 28.3*	0.3 ($p < 0.01$)
Total protein, g/L	74.3 ± 0.6	75.3 ± 0.9	75.9 ± 2.0	0.17 ($p > 0.05$)
Albumin, g/L	40.1 ± 1.9	39.1 ± 2.7	34.6 ± 1.4*	-0.34 ($p < 0.01$)

Notes. *r* – correlation index of APRI with biochemical markers ; * – $p < 0.05$, ** – $p < 0.01$, *** – $p < 0.001$ between groups F0 and F4; ^{xxx} – $p < 0.001$ between groups F0 and F1–3; ^ – $p < 0.05$, ^^^ – $p < 0.001$ between groups F1–3 and F4.

Calculation of average indices of total blood count by the liver fibrosis stages indicated a clearly surveyed significant decrease of erythrocyte count ($r = -0.37$, $p < 0.001$), hemoglobin content ($r = -0.32$, $p < 0.001$), and platelet count ($r = -0.49$, $p < 0.001$) both with elevated blood sedimentation rate ($r = 0.3$, $p < 0.01$) along the development of liver fibrotic injury (Table 4).

Table 14.4
Total blood count values in chronic diffuse liver disease patients from the main study group at different liver fibrosis stages

Indices	Fibrosis stage			*r*
	F0 ($n_1 = 72$)	F1–3 ($n_1 = 19$)	F4 ($n_1 = 20$)	
Erythrocytes, 10^{12}/L	4.7 ± 0.04	4.7 ± 0.07^	4.35 ± 0.1**	-0.37($p < 0.001$)
Hemoglobin, g/L	146.3 ± 1.4	149.1 ± 2.9^	136.4 ± 4.2*	-0.32($p < 0.001$)
Leukocytes, 10^9/L	6.03 ± 0.23	5.9 ± 0.4	5.4 ± 0.3	-0.15($p > 0.05$)
Platelets, 10^3/L	266.2 ± 3.6	253.2 ± 6.5^	222.1 ± 13.9**	-0.49($p < 0.001$)
Blood sedimentation rate, mm/hour	6.5 ± 0.6	10.2 ± 2.2	10 ± 1.9	0.3 ($p < 0.01$)

Notes. *r* – correlation index of APRI with total blood count values; * – $p < 0.05$, ** – $p < 0.01$ between groups F0 and F4; ^ – $p < 0.05$ between groups F1–3 and F4.

It should be emphasized that received data completely correspond to the contemporary opinions on indirect serological markers of liver fibrosis. Total protein concentration occurred being an exception here, as according to many authors it should be decreased along with developing fibrosis but in surveyed group it was assayed at equal levels in all stages of liver fibrosis. No relationship was found either in correlation analysis ($p > 0.05$).

Study of metabolic abnormalities and persisting hepatotrophic infection was conducted in the NAFLD patients exposed to ionizing radiation. A lot of concomitant diseases was diagnosed at that, namely more than 5 diseases were revealed in 42.9 % (vs. 21.4% in a group of nosological comparison, $p < 0.001$), and more than 10 diseases just only in the ChNPP accident survivors (6.6%). Cardiovascular and cerebrovascular diseases were most prevalent in comorbidity pattern (84.7% and 73.5% correspondingly, $p < 0.01$). There were also significantly more cases of locomotor and bronchopulmonary system disease (73.5%, $p < 0.001$ and 15.3%, $p < 0.05$ respectively). Elevated titers of antibodies to the Herpes simplex virus type 1 and type 2, cytomegalovirus, Epstein-Barr virus were registered in the NAFLD patients exposed to ionizing radiation after the ChNPP accident vs. groups of nosological control. There was a combination of Herpes virus infection types 1, 2, and 5 under the increased average indices in steatohepatitis patients with compromised radiation history ($p < 0.05$).

Metabolic abnormalities in the NAFLD patients exposed to ionizing radiation after the ChNPP accident at various disease stages (liver steatosis i.e. fatty liver and steatohepatitis) featured an absence of differences of incidence of carbohydrate metabolism disorders compared to values in survivors having no liver disease or patients in a group of nosological comparison (24.0, 15.2, and 21.6% respectively). Such metabolic disorders were however more frequent than in subjects having neither liver disease nor radiation exposure in a history (4.3%, $p < 0.05$). Time pattern of activity of cytoplasmic liver enzymes SDH and TDH in the patients from main study group was reverse to the trends in the NAFLD patients from group of comparison, namely the increased activity at steatohepatosis stage and relative decrease in steatohepatitis that can indicate an occult hepatocellular insufficiency. Abnormal indices of prooxidant-antioxidant equilibrium in the NAFLD patients from main study group particularly higher content of compounds with isolated double bonds ($p < 0.05$), higher relative content of diene and oxy diene conjugates, and decreased factor of anti-oxidant state were revealed in 60% of patients. In terms of review of correlation between all studied biochemical indices especially between specific enzymes activity (ALAT and GGT) and lipid peroxydation products (diene conjugates) the method of steatohepatitis risk assay in fatty liver patients was developed.

The conducted analysis led to the conclusion that clinical significance NAFLD is determined by the presence of a significant comorbid disease, progressing disorders of carbohydrate and lipid metabolism, abnormal balance in the hemostatic system, lipid peroxidation and antioxidant protection, disorders in regulation of blood pressure, activation of systemic inflammation pathways, and imbalance in proliferation-apoptosis system. These disorders can lead to development of irreversible processes and decompensation of homeostatic mechanisms. The state of anti-infective immunity and impact of viruses persisting in human body on development and progression of NAFLD remain unstudied both in general population and in the ChNPP accident survivors, which requires further research.

* * *

The long-term study of digestive system in persons exposed to ionizing radiation in low doses as a result of the ChNPP accident showed a steady increase of incidence of this system disease in the post accident years and revealed some features of pathogenesis and course of the most prevalent diseases.

The most frequent nosology forms of morphological and functional disorders of gastrointestinal tract under the Chornobyl catastrophe circumstances are chronic gastritis and peptic ulcer disease which can be characterized as an induced pathomorphosis featuring an atypical clinical course with predominance of asthenic-vegetative syndrome, association with Helicobacter pylori, altered secretory function of the stomach, disorders of vegetative regulation, accompa-

nied by a variety of concomitant diseases. Severe atrophic changes in mucosa progressing with time, a trend of atrophic antral gastritis transition in pangastritis diagnosed even in the younger age groups during the first years after the accident combined with reduced acid producing function of the stomach are the most dangerous in terms of stomach cancer development in survivors in the future.

Disorders in hormonal regulation of hypothalamic-pituitary-adrenocortical system played a significant role in pathogenesis of ulceration, namely led to imbalance between factors of aggression and defense, reduced functional capacity of mucosal barrier, failure of epithelial regeneration of stomach and duodenal mucous membranes.

Nonalcoholic steatohepatitis and steatohepatosis are the most prevalent diseases of hepatobiliary system in the ChNPP accident survivors. Contrary to established opinions of a benign course of nonalcoholic steatohepatitis in the ChNPP accident clean-up workers a progressive development of this disease is surveyed. Persistent character and minimal activity of cytolytic syndrome are the features of disease course. Liver function assay depending on the radiation dose indicated a dependence of pathological process activity in the liver on radiation dose that may indicate the role of radiation factor in development of chronic diffuse liver disease. Nonalcoholic fatty liver disease is a component of metabolic syndrome, systemic inflammation, supported by a persistent herpes infection in the ChNPP accident clean-up workers along with disseminated vascular involvement (cardiovascular and cerebrovascular disease) contributing to development of liver fibrosis and its final stage the cirrhosis in remote period after the accident.

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Chapter 15
MENTAL HEALTH AND NEUROPSYCHIATRIC EFFECTS

15.1. MENTAL HEALTH

The UN Chernobyl Forum experts have recognized mental health impact as the most public health and social burden of the Chornobyl accident not yet resolved till now, and outlined the main problems as follows: 1) stress-related disorders; 2) effects on a developing brain; 3) organic brain damage in the Chornobyl accident clean-up workers (liquidators) and 4) suicides [1]. In spite of the adverse long-term psychological-psychiatric and neuropsychiatric consequences are generally recognized, their genesis is still at issue [1–9].

Recent studies show that their rates of depression and post-traumatic stress disorder (PTSD) remain elevated two decades later. Very young children and those in utero who lived near the plant when it exploded or in severely contaminated areas have been the subject of considerable research, but the findings are inconsistent. Recent studies of prenatally exposed persons conducted in Kyiv and Scandinavia point to specific neuropsychological and psychological impairments associated with radiation exposure, whereas other studies found no significant cognitive or mental health effects in exposed persons grown up. General population studies report increased rates of poor self-rated health as well as clinical and subclinical depression, anxiety, and PTSD. Mothers of young children exposed to the disaster remain a high-risk group for these conditions, primarily due to lingering worries about the adverse health effects on their families. Thus, long-term mental health consequences continue to be a concern [2].

Mental health drives physical health. Research on mental health has led the development of new terminology to describe the health problems associated with stress (chronic fatigue syndrome [CFS], health anxiety). Radiation risk perception is the primary risk factor for health anxiety related to the accident. Mothers of young children and former liquidators are at highest risk of developing mental health effects [6].

Cognitive deficit, other neuropsychiatric disorders and cerebral damage following different scenario of radiation exposure together with possible its mechanisms, as well as mental health care at radiation emergencies is discussed in the next sub-chapters further.

The first official estimates of mental health in the Chornobyl disaster survivors were extrapolated from an experience of previous radiation accidents and of the Three Mile Island

Nuclear Generating Station (a civilian nuclear power plant, near Middletown, Pa., USA) accident on March 28, 1979 in particular. Such an experience was coming down to the psychological stress and radiophobia ascertainment as the crucial issue of the Chornobyl disaster by the former USSR officials [10]. We have never shared and do not share the opinion of the «radiophobia» epithet adequacy or appropriateness towards even just psychological consequences of the Chornobyl disaster when there was a real danger under insufficient and contradictory information. The IAEA International Chernobyl Project (1992) experts have underlined that «if the stress factor is a real danger it would be dishonest to say or pretend that feeling of disquietude appearing in a response to that danger is something abnormal». The term «radiophobia» is applied in the Western Europe and USA only in diagnostics of a fear towards an event usually considered as absolutely safe. However as the experts note, «only some people will regard the Chornobyl disaster to this category» [11]. «Radioanxiety» term was instead proposed [12] being more accurate in characterization of psychological reactions on the radiation danger.

Radiation accidents, radiological terrorist attacks, as well as nuclear conflict and war are substantially different from natural disasters and wars without the use of weapons of mass destruction. Clinical features include the major criteria of PTSD – «immersion» in the experience, «avoidance», «hyperexcitability», and «social functioning deficit» [13, 14]. The clean-up workers (liquidators) with PTSD have more general psychiatric symptomatology, state and trait anxiety, depression. There is the determining role of individual perception and assessment of radioactive hazard in the development of PTSD [15]. Psychological stress about the future (the risk of oncological and other diseases, congenital malformations in the descendants etc.), long-term radioactive contamination, evacuation and resettlement, as well as incomplete legislation regarding social benefits, to the victims, make a significant contribution to the development of psychopathological responses [13, 16–19].

It was conducted the standardized psychiatric interviews using the Composite International Diagnostic Interview (CIDI) with 295 clean-up workers and 397 controls 16–18 years after the catastrophe and report on common psychiatric disorders, suicide ideation and severe headaches. Prior to the Chornobyl accident, consistent with the healthy worker effect, the clean-up workers had significantly lower rates in anxiety and alcohol disorders. The clean-up workers had significantly higher post-Chernobyl rates of depression (18.0% vs. 13.1%) and suicide ideation (9.2% vs. 4.1%) after the catastrophe, but not alcoholism or intermittent explosive disorder. In the year preceding interview, rates of depression (14.9% vs. 7.1%), PTSD (4.1% vs. 1.0%), and headaches (69.2% vs. 12.4%) were elevated (Figure 15.1). Affected liquidators with depression and PTSD lost more work days than affected controls. Exposure level was associated with current somatic and PTSD symptom severity. Thus, long-term consequences of the Chornobyl accident on mental health were observed in clean-up workers [20].

However, at present there is an excess of alcohol abuse among liquidators considered to be the secondary to their current mental and behavioral disorders [21, 22]. These data were independently supported by Estonian liquidators' studies. The strongest difference was found for somatization, alcohol problems, sleep disorders, and symptoms of agoraphobia [23].

There are big differences in estimation of mental health. According to official data from the Ministry of Public Health of Ukraine the prevalence of mental disorders in Ukraine is 2-3% while as a result of the adequately designed epidemiological psychiatric study within WHO Initiative «World Mental Health Survey-2000» with application of the standardized psychiatric interview WHO-CIDI) it was revealed that in real the prevalence of only the «psychological» disorders (without cognitive and psychotic ones) in Ukraine is 20.5% (confidence interval: 17.7–

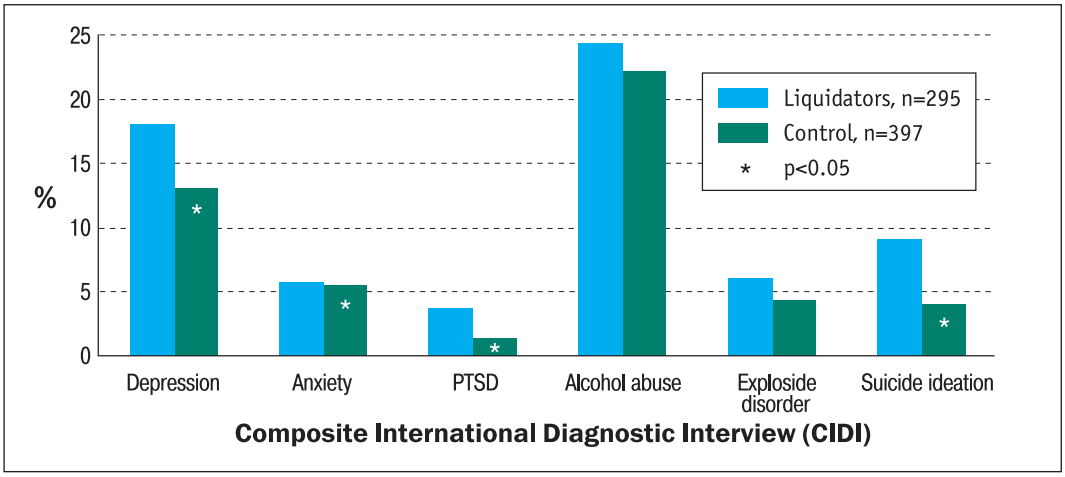


Figure 15.1. **Adverse long-term effect on mental health in clean-up workers (liquidators) [20]**

23.3%) [24]. Thus, the official (registry) data regarding mental health provide an about of one-order underestimation of the real state of things.

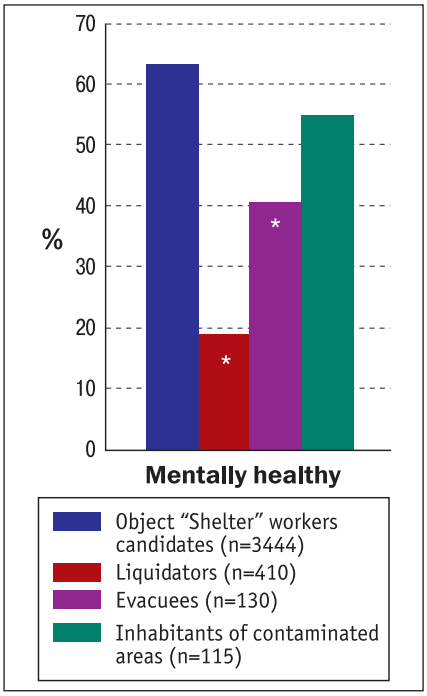


Figure 15.2. **Mental health in randomized samples of survivors, Clinical and Epidemiological Registry of SI «NRCRM of NAMS of Ukraine»**
Note. * – p < 0.001 in comparison with Object «Shelter» workers candidates.

Despite enough criticism about imperfection of the existing registries the State Registry of Ukraine on Persons Survived after the Chornobyl Disaster (SRU) and the Clinical-Epidemiological Registry (CER) of the State Institution «National Research Center for Radiation Medicine of NAMS of Ukraine» (NRCRM) remain the unique sources of epidemiological data acquisition on survivors in the country. Undoubtedly they require the state support and further updating.

The clinical-epidemiological evidence of incidence rise of mental disorders (organic, depressive etc.) and cerebrovascular disease in the liquidators with radiation risks in dose range > 0.25–0.5 Gy was received through the analysis of the CER data (NRCRM) [25, 26]. Mental disorders excess is 0.4 per 1 Gy (95% confidence interval 0.17; 0.64) [27].

Recent our mental health estimate within randomized samples from the representative liquidators and the Chornobyl exclusion zone evacuees cohorts (from the CER of NRCRM) compared to the applicants/candidates for employment at the Object «Shelter» transformation into environmentally safe system has testified the long-term mental consequences of the Chornobyl disaster. As it appears from the Figure 15.2 and Table 15.1 there are much more cases of mental and behavioral disorders in general, of vascular dementia, mental and behavioral disorders due to alcohol consumption, dysthymia, and PTSD

among the liquidators and evacuees. Additionally the incidence of the organic depressive disorder, organic emotionally labile (asthenic) disorder and organic personality disorder had increased in the clean-up workers. Received data correspond to the results of international epidemiological psychiatric studies.

The psychoneurological disorders prevalence in the Chornobyl exclusion zone personnel exposed to radiation doses over 0.25 Gy was 80.5% whereas under less that 0.25 Gy exposure the respective value appeared being much lower (21.4%) [28] actually corresponding the real population indices of mental disorders prevalence in Ukraine [24]. Since 1990 the substantial increase in schizophrenia incidence was found in the Chornobyl exclusion zone personnel (5.4 per 10,000 vs. 1.1 per 10,000 in Ukraine) [29]. Further epidemiological psychiatric research is required to identify the role of ionizing radiation in the origin of schizophrenia spectrum disorders [30–32]. At the

Table 15.1
Mental health in the randomized sample of liquidators and evacuees

Mental and behavioral disorder according to the ICD-10	Compare group (candidates to «Shelter», n=3444)	Liquidators (n=410)	Evacuees (n=130)
No mental and behavioral disorder	2180 (63.3%)	78 (19.0%)*	53 (40.8%)*
Vascular dementia, F01	0	6 (1.5%)*	1 (0.8%)*
Organic delusional [schizophrenia-like] disorder, F06.2	2 (0.06%)	2 (0.5%)	0
Organic depressive disorder, F06.32	7 (0.2%)	27 (6.6%)*	2 (1.5%)
Organic anxiety disorder, F06.4	0	2 (0.5%)*	0
Organic emotionally labile [asthenic] disorder, F06.6	479 (13.9%)	152 (37.1%)*	26 (20%)
Mild cognitive disorder, F06.7	284 (8.2%)	34 (8.3%)	19 (14.6%)
Organic personality disorder, F07.0	106 (3.1%)	89 (21.7%)*	7 (5.4%)
Postconcussional syndrome, F07.2	45 (1.3%)	2 (0.5%)	3 (2.3%)
Mental and behavioral disorders due to use of alcohol, F10	83 (2.4%)	57 (13.9%)*	13 (10%)*
Mental and behavioral disorders due to use of opioids, F11	1 (0.03%)	0	0
Residual schizophrenia, F20.5	0	1 (0.24%)	0
Schizotypal disorder, F21	0	0	1 (0.8%)
Moderate depressive episode, F32.1	1 (0.03%)	1 (0.24%)	0
Dysthymia, F34.1	1 (0.03%)	6 (1.5%)*	1 (0.8%)*
Specific (isolated) phobias, F40.2	1 (0.03%)	1 (0.24%)	0
Panic disorder [episodic paroxysmal anxiety], F41.0	0	1 (0.24%)	0
Generalized anxiety disorder, F41.1	0	0	1 (0.8%)
Post-traumatic stress disorder, F43.1	0	6 (1.5%)*	3 (2.3%)*
Adjustment disorders, F43.2	31 (0.9%)	0	0
Somatoform autonomic dysfunction, F45.3	8 (0.2%)	0	1 (0.8%0
Persistent somatoform pain disorder, F45.4	0	1 (0.24%)	0
Neurasthenia, F48.0	164 (4.8%)	5 (1.2%)*	9 (6.9%)
Nonorganic sleep disorder, unspecified, F51.9	2 (0.06%)	-	-
Specific personality disorders, F60	36 (1.05%)	1 (0.24%)	1 (0.8%)
Enduring personality change after catastrophic experience, F62.0	0	1 (0.24%)	0
Mild mental retardation, F70	6 (0.2%)	0	0
Moderate mental retardation, F71	1 (0.03%)	0	0
Nonorganic enuresis, F98.0	1 (0.03%)	0	0
Stuttering [stammering], F98.5	13 (0.4%)	2 (0.5%)	1 (0.8%)
Accentuation of personality traits, Z73.1	31 (0.9%)	4 (1.0%)	2 (1.5%)

Note. * – significant differences vs. candidates for employment at the Object «Shelter» by the χ^2 test or the double-sided Fisher's exact test. Differences were considered reliable according to Bonferroni correction if $p < 0.001$.

same time, irradiation in adulthood caused behavioral abnormalities relevant to schizophrenia, and that reduction of adult neurogenesis by irradiation may be associated with schizophrenia-like behaviors. Thus, irradiation in adulthood is considered as a new model of schizophrenia [33].

The UN Chernobyl Forum has defined the suicides in the clean-up workers as one of important issues within post-accident period [1]. Suicide is a leading cause of death in the Estonian liquidators [34] and in Lithuania the suicide mortality among the clean-up workers has exceeded the population level [35]. The major finding of epidemiological studies in the Estonian clean-up workers mortality is an increased risk of suicide [36, 37]. Whereas low radiation doses are the risk factor of exacerbated suicidal behavior or there is a purely socio-psychological phenomenon here s it is to be clarified under the forthcoming epidemiological studies [38].

There is an international consensus about the Chornobyl disaster impact on mental health as a top-priority healthcare problem in survivors. Given the prevalence and persisting resistance of their mental health disorders the educational, psychosocial and healthcare interventions both with further research are required [1, 2]. Therefore the long-term unfavorable consequences of the Chornobyl disaster regarding the mental health are found in the liquidators of the accident. Further research is required to receive more reliable data on radiation and somatic health, to review the cognitive disorders and psychotic symptoms, and to apply more precise psychiatric examinations [20].

15.2. NEUROPSYCHIATRIC EFFECTS AND BRAIN DAMAGE

15.2.1. Radiation brain damage current pathogenesis

If long-term unfavorable impact of the Chornobyl disaster on mental health is recognized worldwide [1–9], whereas the causes of neuropsychiatric effects still remain debatable [1–9, 39–45]. The potential cardiovascular morbidity/mortality excess was recognized by UN Chornobyl Forum in liquidators exposed to high radiation doses [1]. Contemporary experimental, clinical and epidemiological evidence disproves the canonic statement about the central nervous system (CNS) radioresistance. Precise analysis of the ionizing radiation neuropsychiatric effects, new data on the molecular-biologic pathways of radiation impact on the brain, review of contemporary evidence of the «low-dose» radiation effects and the debatable issues perscrutation regarding radiation and stress role in the genesis of mental health impact and neuropsychiatric effects of the Chornobyl disaster are outlined in a lot of scientific papers [46-57].

There is a strong and traditionally present opinion in the medical radiology field that radiation damage of the CNS is possible only under local exposure to the doses exceeding 10–50 Gy. Brain radiation necrosis was observed upon the local irradiation in doses over 70 Gy, after which the radiogenic dementia could occur. Brain tolerant dose is considered as 55–65 Gy, and fractional tolerant dose is believed as 2 Gy. Primary damage of CNS under the whole-body radiation exposure is orthodoxically diagnosed only if the doses exceed 100 Gy (cerebral Acute Radiation Sickness [ARS] form), while secondary radiation damage of CNS is diagnosed in case of 50–100 Gy respectively (toxemic ARS form). The total-body dose of 2–4 Gy was considered as a threshold for radiation-induced neuroanatomical abnormalities [58–60].

On the other hand, as we overviewed many times earlier [3, 28, 39, 43], since the 50s of the 20th century the neuronal morphology abnormalities were found just after exposure to 0.25–1 Gy of total-body irradiation, and dose value of 0.5 Gy has been called «the red line» of CNS radiation damage with primary neuronal injuries. Stable disorders of cerebral electrical activity were featured with 0.3–1 Gy threshold and with increment proportionally to the absorbed dose value. CNS dysfunction is possible under the impact of relatively low radiation doses. The mod-

ification of neurotransmission occurs under the irradiation leading to multiple cerebral and behavioral effects depending at most on radiation dose. The diagnostic entity of slowly progressing radiation sickness of CNS after 1–6 Gy total-body irradiation has been announced by A.L. Karpovsky (1985). It is stated in the UNSCEAR 1982 report that progressing cortex degeneration occurs after exposure to 1–6 Gy of radiation. The chronic progressing CNS damage is described in remote term after relatively low-dose exposure [3, 28, 39, 43].

It is believed now that CNS involvement was underestimated within classical ARS descriptions, while the nervous system is sensitive to radiation, and extent of its dysfunction has been quantified by means of electrophysiological, biochemical and/or behavioral parameters. CNS dysfunction was identified through the same parameters under the low-dose total-body irradiation too. They insist that evolving conception of radiation-induced syndrome of multi-organ injury in ARS provides a background for understanding of CNS damage [48]. A lot of newer neuroradiobiology data on molecular-biological pathways of radiation brain damage has recently become available. Thus even the apologists of CNS radiation resistance concept were forced to reconsider their opinion in favor of cerebral radiosensitivity [46].

Contemporary opinions about the radiation brain damage are no more focused only on the traditionally mentioned «glial-vascular union», where damage of cerebral vascular endothelium and injury of neuroglia are the cause of all radiocerebral effects. Nowadays both primary-neuronal pathways, i.e. neurogenesis inhibition, telomere changes, neuronal apoptosis, abnormal neurosignaling, modification of gene expression, damage of mitochondrial DNA and RNA not subject to reparation, lesions of neuromembranes and ion channels, «bystander effect», neuroinflammation, multiorgan dysfunction, autoimmune pathways, metabolic disorders and many others are in the focus of concern. It means that opinions on radiation neuropsychiatric effects and nervous system sensitivity do change [46–57] (Figure 15.3).

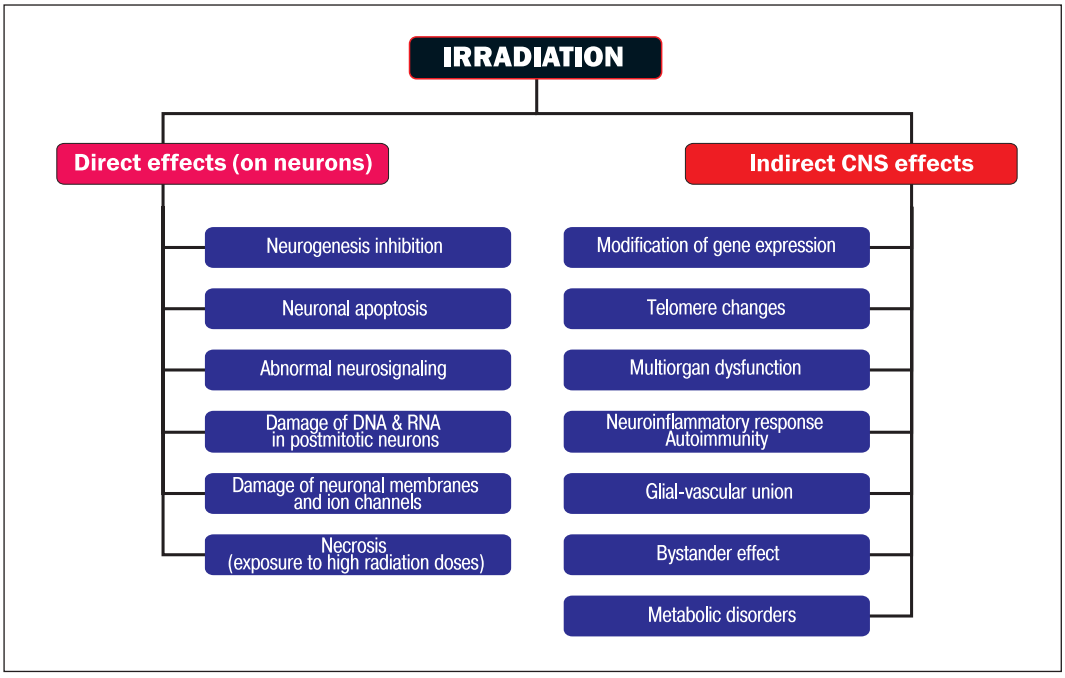


Figure 15.3. Pathogenesis of radiation brain damage

15.2.2. Epidemiological data

The clinical-epidemiological evidence of incidence rise of mental disorders and cerebrovascular diseases in dose range > 0.25–0.5 Gy was received through the analysis of the CER of NRCRM data [3, 25, 26, 42, 43]. Mortality from cardiovascular diseases in the clean-up workers is higher under the radiation doses exceeding 0.25 Gy [61]. Our data testify on higher radiation vulnerability of young adults up to 35 years old at exposure. This fact dictates the necessity of state control of admission to work with ionizing radiation sources (both under routine and emergency circumstances) of only the persons older than 35 years [62, 63].

As against the widespread false opinion of an excessive use of «vegetative-vascular dystonia» diagnosis as a marker of radiation exposure the mentioned diagnosis was established in proximate years upon the Chornobyl disaster only in about a quarter of the clean-up workers. It is clear from figure 15.4 that diagnostics of vegetative-vascular dystonia has reduced substantially within a post-accident years reaching nowadays just about 5% of the representative liquidators sample. Gradual increase of cerebrovascular disease prevalence occurred in the clean-up workers after the accident featuring the most pronounced rise of the chronic cerebral ischemia (ICD-10: I67.8), cerebral atherosclerosis (I67.2) and to the less extent of the hypertensive encephalopathy (I67.4). These disorders are traditionally classified as a «dyscirculatory encephalopathy» also not being perfect from the view of absolutization of only the vascular component of the organic brain damage pathogenesis, and also because of not enough strict diagnostic criteria. An international consensus on the optimal classification of such a kind of neuropsychiatric disorders will be certainly reached in the future.

Neuropsychiatric consequences of the Chornobyl disaster undoubtedly are etiologically heterogeneous due to the joint effect of disaster radiation and non-radiation factors with stress above all, and also because of social changes and traditional risk factors (age in particular). Radiation and age make a synergic impact resulted in an accelerated aging.

According to SRU data the dose-related growth of nervous system and sense organs diseases, vegetative-vascular dystonia, arterial hypertension and cerebrovascular disease was found in liquidators of 1986-1987 work period. According to SRU and CER data the excess relative risk

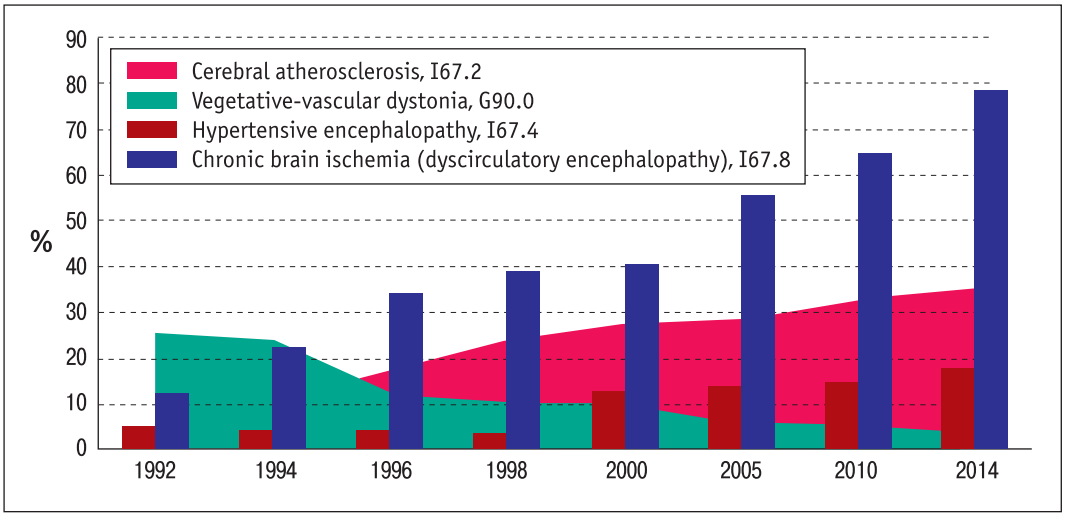


Figure 15.4. Cerebrovascular effects in liquidators

(ERR) per 1 Gy of radiation exposure was found out regarding the neuropsychiatric disease in the liquidators of 1986–1987 work period. Thyroid radiation doses over 0.3 Gy in adult evacuees are followed by the risk increase of cerebrovascular disease, whereas in case of thyroid doses exceeding 2 Gy the mental disorder risk excess takes place [25].

Dose-dependent increase of cerebrovascular morbidity in the Chornobyl accident clean-up workers of 1986–1987 period, specifically for cerebral atherosclerosis and especially for hypertensive encephalopathy was revealed. Incidence growth of other neuropsychiatric diseases with a dose-related rise of dizziness and other vestibular organ disorders in particular was revealed in the liquidators of 1986-1987 working period [26].

The conciliatory data have been received for the clean-up workers on the radiation risks of non-cancer diseases (of cardiovascular ones especially and cerebrovascular ones in particular). Mental disorders excess is 0.4 per 1 Gy (95% confidence interval 0.17; 0.64), excess for the nervous system and sense organ diseases is 0.35 (0.19; 0.52), and for endocrine system disorders accounts 0.58 (0.3; 0.87). The cerebrovascular disease is of highest excess here – 1.17 per 1 Gy (0.45; 1.88) where the radiation risk values are available for respective mortality. Coronary heart disease excess is 0.41 per 1 Gy (0.05; 0.78), arterial hypertension one reaches 0.36 per 1 Gy (0.005; 0.71), and excess relative risk (ERR) of cerebrovascular disease is 0.45 per 1 Gy (0.11; 0.80). The liquidators exposed to more than 150 mGy of external radiation within less than 6 weeks of work in the exclusion zone are the group of highest risk of cerebrovascular disease (relative risk (RR) = 1.18, 95% confidence interval 1.00; 1.40). The dose-related effect regarding cerebrovascular morbidity was revealed in 1986-2000 period studies featuring the ERR = 0.39 per 1 Gy (0.004; 0.77). There is a statistically meaningful cerebrovascular disease risk as an average radiation dose function under the exposure to 0.15 Gy and more (ERR per 0.1 Gy daily is 2.17 (0.64; 3.69) [25–27; 64, 65].

The UN Chernobyl forum has recognized the «Chornobyl» data on cerebrovascular mortality excess in the clean-up worker as corresponding to the published study results on A-bombing survivors [1, p. 76]. The latest publication on cardiovascular risk after the A-bombing states that radiation doses over 0.5 Gy are associated with an excessive risk of both stroke and «heart disease» (i.e. coronary artery disease, arterial hypertension etc.). At that the risk values under lower radiation doses are not defined yet. Stroke and «heart disease» cause about one-third of radiation-associated excessive deaths in A-bombing survivors [65]. An increased risk of non-neoplastic diseases in A-bombing survivors including the circulatory, respiratory and digestive systems was observed, but whether these are causal relationships requires further investigation [67].

The systematic reviews have not yet provided the undoubted evidence of cardiovascular risk dependence on radiation within dose range 0–5 Sv [68–70]. In the meantime the recently published data of an British epidemiological survey over the nuclear industry male workers testify the dose-related increase of cardiovascular mortality (ERR per 1 Sv is 0.65 with 90% confidence interval 0.36; 0.98) where the excess is meaningful in cumulative doses over 300 mSv [71]. It bears mentioning that these data correspond to our research results regarding the neuropsychiatric, neurophysiologic, neuropsychologic and neuroimaging effects in the liquidators just in radiation doses exceeding 0.3 Gy. Data analysis from studies in 15 countries among the nuclear industry personnel (average cumulative dose 20.7 mSv) revealed the ERR per 1 Sv of radiation for all non-cancer mortality as 0.24 (95% confidence interval –0.23; 0.78) and for cardiovascular disease as 0.09 (-0.43; 0.70). At that the highest risks were found in younger workers [72] that are also corresponding to our data on the liquidators. Further, it was also supported by an association between circulatory disease mortality and low and moderate doses of ionizing radiation (>0.5 Sv). It was suggested that overall radiation-related mortality is about twice that currently

estimated based on estimates for cancer end points alone (which range from 4.2% to 5.6%/Sv for these populations) [73].

High prevalence of multiple sclerosis (MS) in 2005-2010 was revealed in all regions of Ukraine. The highest level was revealed in Western (71.8 per 100,000), Central (59.0 per 100,000), and North (55.0 per 100,000) regions, which have the status of territories contaminated by radionuclides due to the Chornobyl catastrophe. At the same time the MS prevalence in low-contaminated regions of Ukraine is significantly lower: in Eastern region the MS prevalence is 41.4 per 100,000, and in Southern region – 36.4 per 100,000. In spite of radioactively contaminated areas had high prevalence of MS before the accident, it is reasonably to suggest that exposure to radionuclides is an amplifying risk factor of MS because of its prevalence is increasing in these areas after the Chornobyl disaster. The possible role of exposure to low doses of ionizing radiation in MS genesis is supported by the data concerning the differences in the MS prevalence in Kyiv and Zhitomir regions in dependence of the radiation contamination of the residence district. Thus, the MS prevalence in highly contaminated districts of Kyiv region is 37.6–61.5 per 100,000 while this is in low-polluted districts 11.0–22.8 per 100,000 only, as well as in Zhitomir region s 51,8- 95.2 vs 10.6- 33.0 per 100,000, correspondingly [74,75].

We proposed that the cerebrovascular diseases and some other neuropsychiatric disorders could be considered as the stochastic effects of a low-dose radiation [3], i.e. effects that occur by chance and which may occur without a threshold level of dose, whose probability is proportional to the dose and whose severity is independent of the dose.

15.2.3. Clinical studies

For the years immediately ahead the Chornobyl disaster an opinion was preponderated of only the psychogenic effect and of stress concept, vegetative-vascular dystonia, neurotic and psychosomatic disorders [76]. Vegetative-vascular dystonia and asthenoneurotic syndrome were the most prevalent neuropsychiatric diagnoses among the liquidators in that period [77], that was and remains being subject to criticism especially from the side of international experts who qualify such diagnostics as a discrepancy «between the East and West» [11]. Vegetative-vascular dystonia was considered being purely a «soviet» diagnosis reflecting the pathophysiological background of the disorders, whereas a pragmatic approach applied in the West features those conditions syndromologically as anxious with panic attacks or somatoform ones. In very deed the radiation disorders of nervous system were first described by the German researcher G. Riecker (1915) and the «vegetative dystonia» or «neurovegetative syndrome» terms were proposed by the German psychiatrist Berthold Wichmann (1934) who later (1963) have transformed them to the «psychovegetative syndrome». Nowadays the vegetative-vascular dystonia is attributed to the competence of psychiatrists and according to ICD-10 is diagnosed as the «F45.3 – Somatoform autonomic dysfunction».

As it was mentioned above the vegetative-vascular dystonia for the years immediately ahead the accident was diagnosed in about every one in four clean-up workers been in file of the CER of NRCRM. Later as against the reducing prevalence of vegetative-vascular dystonia in the liquidators the substantial growth of cerebrovascular disease occurred i.e. the cerebral ischemia (chronic) (I67.8), cerebral atherosclerosis (I67.2) and hypertensive encephalopathy (I67.4) all together traditionally diagnosed as a «dyscirculatory encephalopathy» (figure 15.4).

Neuropsychiatric disorders in the liquidators are peculiar by a progressive course with vegetovascular and vegetovisceral stage (up to 10 years upon the accident) consecutive exchange by the cerebroorganic and somatogenic disease stage (more than 10 years after). Vegetovascular and

vegetovisceral disorders in the clean-up workers were suprasegmental ones and combined with abnormalities of the central afferent pathways, peculiar with permanent-paroxysmal course type and diencephalic crises including the hysteroform ones that we consider being the symptomatic partial mediobasal limbic attacks. These disorders in combination with an increasing somatic disease stipulated the progressing origination of the cerebroorganic and somatogenic mental disorders in remote period upon the disaster. It is especially relevant to the persons who worked in the Chornobyl exclusion zone for a long time (more than 5 years)

Neurological symptoms in the liquidators in remote post-accident period (except severe organic diseases of the nervous system i.e. sequale of stroke, neuroinfection, trauma, intoxication, tumor etc.) are of microfocal and «open-work» type. The sensory-algetic, vestibulo-atactic, musculotonic and autonomous disorders with mild pyramid and extrapyramid symptoms, and also the paroxysmal states mainly as diencephalic crises (autonomous-visceral attacks) and sometimes temporal epilepsy and amygdalo-hippocampal (mediobasal limbic) attacks are peculiar to the clean-up workers of the Chornobyl accident. Neurological disorders are mainly observed within cerebrovascular disease structure (Cerebral atherosclerosis – I67.2, Hypertensive encephalopathy – I67.4, Cerebral ischemia (chronic) i.e. dyscirculatory encephalopathy – I67.8), Other demyelinating diseases of the central nervous system of encephalomyelosis type (G37), and Episodic and paroxysmal disorders (G40, G43, G44, G45)).

Incidence and intensity of hypochondriac symptomatology, «affective face» with neurosis-like and sthenic psychopathic-like manifestations had decreased in the liquidators within post-accident years; however the tendency to the negative psychopathologic symptomatology was surveyed especially in radiation doses exceeding 0.3 Gy. Time pattern of psychopathology in the clean-up workers lies in transformation of asthenoautonomic and hystero-hypochondriac manifestations, anxiotic and obsessive hypochondria into the senesto- and paranoic-hypochondriac formations, in exacerbating personality disharmony and regression, explosiveness and affective-volitional instability into the depressive and negative symptomatology with cognitive deficiency, autization and social dysadaptation. Clinical presentation of these disorders to the most extent corresponds to variants of psychoorganic syndrome (labile, apathetic, paranoid, and combined ones).

The negative psychopathic symptomatology is growing proportionally to radiation dose in doses exceeding 0.3 Gy and service record in the Chornobyl exclusion zone more than 5 years. PTSD manifestations on the contrary are reversibly related to radiation dose with a leading role of not the real danger of situation but its perception and realization. Personality defect in remote period upon the accident is featured by disintegration of intellectual and emotional spheres, shaping of psychopathic-like disorders with social dysadaptation and asthenic type of response. The Global Assessment of Functioning score (GAF Scale) here is not more than 70 points. Verbal memory deficit, mental working capacity decrease and cognitive decline compared both to normal range and to the premorbid IQ values testify the psychoorganic nature of mental disorders. Variants of the Organic personality disorder (F07.0 according to the ICD-10 and 310.1 according to the DSM-IV), the Organic emotionally labile [asthenic] disorder F06.6 and Organic Depressive Disorder (F06.32 according to the ICD-10 and 293.83 according to the DSM-IV) are the specific mental disorders in the clean-up workers in remote period after the accident. Aside from that the neurotic, related to the stress somatoform disorders (F40-F48), the Enduring personality change after catastrophic experience (F62.0) or the PTSD (309.81 in the DSM-IV) are surveyed in the liquidators [78, 79].

It is recognized that mental disorders in the Chornobyl disaster survivors have originated not only at the expense of direct or indirect impact of physical factors but also as a result of

somatopsychic or psychosomatic pathways involvement straightforwardly related to the impact of the Chornobyl accident It was proposed the systematization (classification) of mental disorders according to which the *pathological personality development* (posttraumatic, psychosomatic, schizotype, and organic one) is considered as a principal nosological (clinical) entity in remote period after the accident [78, 79].

PTSD is a key mental disorder as a result of a purely psychological impact of the Chornobyl disaster. The mentioned disorder is a postponed response on the negative impact of extreme events and situations been outside the scope of human daily experience. According to ICD-10 the PTSD (F43.1 diagnostic category) is diagnosed within 6 months of a stress situation otherwise at the end of a stress period. The Enduring personality changes after catastrophic experience (F62.0) can be the sequale of PTSD upon 2 years of its course. However according to the American psychiatric classification DSM-IV the PTSD (309.81 diagnostic code) is diagnosed irrespectively to the time since an experienced stress. The UN Chornobyl Forum experts have recognized the stress-related disorders, including PTSD, as the first among other main mental health problems in the Chornobyl accident survivors [1]. Psychological effect of ionizing radiation is the most powerful so-called «invisible» stress factor with an ahead-directed action [80]. Id est in radiation emergency the «flashback» symptom («cutback», «back shot», «back frame» or «backward look») as a typical psychopathologic PTSD manifestation undergoes transformation to a «flash-forward» i.e. «forelock» or «prospection». PTSD transformation has took place in the liquidators already 1.5–2 years upon the accident. Extreme agitation and irritability in response to elementary stress situations were noted at that, and the «flashback» symptoms featured a lack of brightness and had appeared indirectly [13, 14, 18].

Psycho-traumatic impact of the Chornobyl disaster is the result of not only the disaster itself but rather of a possible future effect perception. PTSD in the Chornobyl accident survivors unlike the Afghanistan war veterans featured fear and danger projection ahead that corresponds the concept of an «anticipatory stress» i.e. the stress of expectation or prediction. At that the PTSD in Chornobyl accident survivors comprise different semantic components. The radiation-associated PTSD component includes agitation with hypochondriac fixation elements related to the future «probable» own health disorders, cancer genesis, health deviations in children, congenital malformations in future generations etc. The socio-psychological PTSD block in survivors comprises the unwarranted (unguaranteed) future syndrome (fear to lose own social status, fear of socio-economic problems appearing and family disruption, the delicacy of perception of an unjust attitude from society (country) to the Chornobyl accident survivor), a subjective time space narrowing (lack of time to solve the daily living problems, permanent time handicap feeling, life perspective absence), the «runaway» or «flight» into illness (bad well-being and low working capacity, interest area narrowing, disability due to the illness, search of a serious disease in the own organism) and the acquired helplessness (helplessness feeling because of the Chornobyl accident, activity decrease, shifting of some own duties and responsibility on others, mood deterioration with own life worthlessness sensation) [18, 81-83].

Thus, «Radiation» PTSD includes «flash-forward» phenomena and anticipating stress (projection of fear and danger to the future); somatoform disorders (depression, trait and state anxiety); and neurocognitive deficit (impaired memory and attention, auditory-verbal memory and learning, proactive and retroactive interference, cerebellar and stem symptoms, intellectual changes). The intima-media component, thickness of common carotid arteries, and common and left internal carotid arteries stenosis rates are increased in the liquidators. Changes of bioelectrical brain activity as a decrease of beta- and theta-power, together with an increase of alpha-power, were found in the Chernobyl accident survivors with PTSD. PTSD following radi-

ation emergency is characterized by comorbidity of psychopathology, neurocognitive deficit, and cerebrovascular pathology with increased risk of cerebral atherosclerosis and stroke. The cerebral basis of this PTSD is proposed to be an abnormal communication between the pyramidal cells of the neocortex and the hippocampus, and deep brain structures. It is recommended that a system of emergency and long-term psychological and psychiatric care be organized for the survivors in Fukushima Daiichi, Japan [18, 81-83].

Depression is one of the most significant and long-term effect of the atomic bombings, nuclear testing and radiation emergencies [84–87]. The participants of the accident at the Chernobyl nuclear power plant increased prevalence of depression (18.0% and 13.1% in controls) and suicide rates. Depression is mainly observed in the structure of an organic mental disorder against cerebrovascular disease. The clinical pattern is dominated by asthenoadynamic and asthenoapathetic depression. Depressive disorders in radiation emergencies are multifactorial, that is the result of exposure to the complex psychogenic and radiological accident's factors, impact of traditional risk factors, somatic and neurological diseases, genetic predisposition, predisposition, etc. At the same time, exposure to ionizing radiation is a factor in the genesis of depression. This impact can be direct (to the Central Nervous System, CNS), and indirectly through the somatic and neurological abnormalities (multiorgan dysfunction) as well as by a variety of pathogenic mechanisms of ionizing radiation on the brain that have been discovered recently. It is strongly necessary analytical clinical and epidemiological studies with verification of depression and evidence-based establishment of the role of radiation and non-radiation risk [85].

Depression not only affects the quality of life and aggravate other diseases, but also can also lead to suicide. That is, depressive disorders potentially life-threatening. It is necessary analytical clinical and epidemiological studies with verification of depression and conclusive establishment of the role of radiation and non-radiation risk factors. Further researches of neuropsychiatric disorders in survivors of the Chernobyl and Fukushima disasters is needing [88-90].

15.2.4. Brain damage in liquidators

There are a lot of published consistent studies results on the characteristic neurophysiologic [91–97], neuropsychologic [98–100] and neuroimaging [101, 102] abnormalities in the clean-up workers of the Chornobyl accident. The organic brain damage in the liquidators was verified in such and some other studies with no dosimetry support and no dose-response estimations, however [39, 103–114]. At that the accelerated CNS aging is justified [95, 96, 115, 116].

Spontaneous and evoked bioelectrical activity and its topographic distribution in the liquidators, especially following long-term works in the Chornobyl exclusion zone, is substantially different from that in a population norm and the compare (control) groups [117–127]. Our first «blind» EEG brain mapping surveys 25–27 years ago had revealed the rigorous difference of exposed persons from the Afghanistan war veterans with PTSD by excess and lateralization of delta-power to the left frontotemporal zone both with beta-power excess (Figure 15.5).

There is a diphase cerebral electric activity pattern upon the exposure [78, 126]. The dose-dependent (in doses exceeding 0.3 Gy) cortico-limbic irritation with EEG spectral power amplification was surveyed in the clean-up workers 10 years immediately ahead the accident. The dose-related (again in doses over 0.3 Gy) signs of an organic brain damage with cortico-limbic inhibition and deficiency psychopathologic symptoms and cognitive deficit were observed in remote period (more than 10 years upon exposure). Irradiation to more than 0.3 Gy is followed mainly by the fronto-temporal zone involvement of the dominant (left) hemisphere,

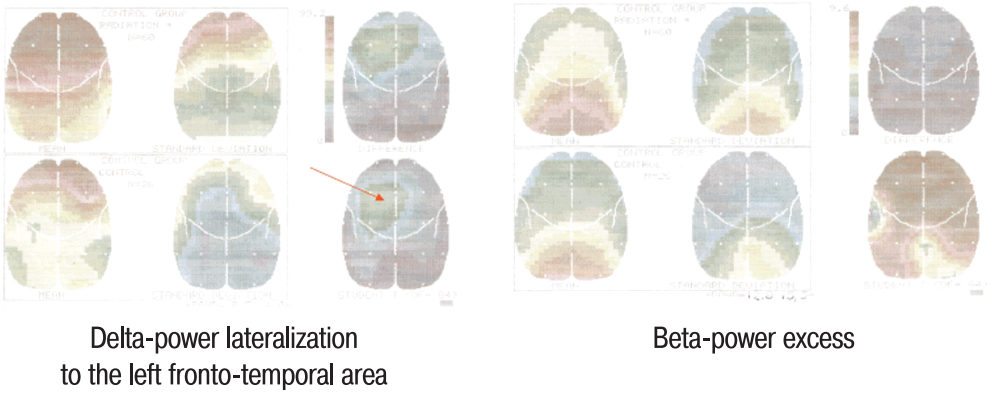


Figure 15.5. **The first Brain Mapping differences between the radiation exposure (clean-up workers, upper) and stress (Afghanistan war veterans with PTSD, lower)**
Unpublished data by A. Noshchenko & K. Loganovsky, 1991.

EEG's slowdown, progressing total decrease of an absolute spectral power («plain» polymorphous EEG) with delta- and beta-activity amplification along with theta- and alpha-activity decrease. The dose-dependence of neurophysiology effect is surveyed only in dose range over 0.3 Gy (Figure 15.6). Notably the dependence becomes significantly stronger after the long-term work (5 years and more) under the conditions of the Chornobyl exclusion zone that can testify the amplifying effect of a prolonged impact of zone factors including the chronic radiation. Dose contribution to the EEG pattern evolution (dose range 0.3 Gy and more) is 28%, cerebrovascular disease contributes here 29%, somatic disease –11%, and age – 19% respectively [29, 78, 123–125].

Study of the cerebral information processes through an evoked cerebral electric activity registration showed the following dose-related (under the radiation doses exceeding 0.3 Gy)

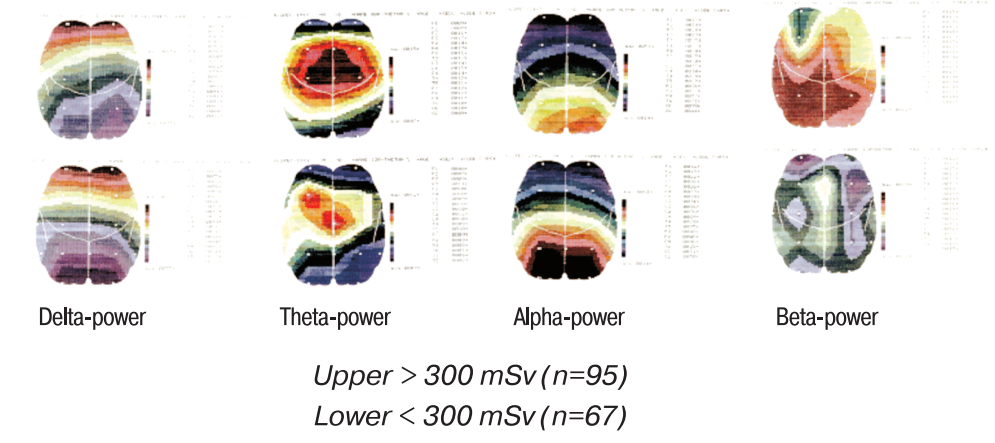


Figure 15.6. **Brain Mapping of EEG in clean-up workers after chronic exposure [39]**

neuro- and psychophysiologic effects: alterations of the central afferent pathways of all sensory modalities, overweight of sensory information processing by non-specific afferent systems over the depression of specialized ones, damage of the dominant hemisphere, cortico-limbic-reticular dysfunction with suppression of brainstem reticular formation resulted in a «sensory gate» dysfunction with a sharp increase of sensory afflux to the cerebral cortex that can lead to an origination of senestopathy and its hypochondriac experience [29, 78, 123–125].

As a result of acoustic evoked potentials survey, the dysfunction of the brain trunk sensoric integrative systems was revealed in 59.4% persons exposed to ionizing radiation. The disorders at the ponto-mesencephalic and mesencephalic levels are prevailing, which is the basis for the morphological and functional dysfunction of the autonomic regulation [128].

Cerebral circulation in the liquidators is peculiar with decreased vascular wall elasticity that is inconsistent with physiological age criteria especially under radiation doses exceeding 0.25 Gy and indicates the acceleration of a vascular wall involution, circulation reactivity decrease with formation of a «rigid» circulation, perfusion decrease in the extracranial parts of cerebral vessels, circulation asymmetry in the internal carotid artery due to more decrease of systolic velocity in the left internal carotid artery after exposure to more than 0.3 Gy, compensatory vasospasm of all cerebral arteries, no hemodynamically significant (over 65%) stenosis. Cerebral vessels are peculiar with an excessive arterial tortuosity and diffuse obliterating lesions [129–132].

Unlike a «classical» chronic cerebrovascular disease the brain atrophy prevails in the liquidators, whereas lacunar lesions are on the contrary less prevalent. The characteristic dose-related neuroimaging features of an organic brain damage reflecting cortical atrophy and the left (dominant) hemisphere pathways involvement were found through the magnetic resonance imaging (MRI) morphometry. These effects are observed upon exposure to the doses exceeding 0.3 Gy, whereas in case of more than 1 Gy irradiation the dependence on dose becomes stronger that can indicate to a radiation factor role in origination of the described characteristic neuroimaging pattern of a radiation brain damage [133–135].

The specific peculiarities of neuropsychiatric disorders in the liquidators reside in a tendency of the left hand predominance in right-handers, speech disorders, torpidity of the fine motor acts, sensory-motor memory abnormalities, direct memorization, short-term memory and interference decrease, memory function dissociation i.e. disorder of audioverbal memory along with preserved visual one, altered calculating operations, and specific abnormalities of an associative process. Neuropsychological study results in the clean-up workers highlight the localization of a pathological process in the frontal parts of the left brain hemisphere especially upon irradiation with doses exceeding 0.3 Gy [136, 137].

Cognitive disorders in the liquidators (except gross organic CNS lesions e.g. stroke, neuroinfection, trauma, intoxication, tumor etc.) do not reach the dementia level and correspond to the mild cognitive disorder (ICD-10: F06.7). The specific neuropsychological peculiarities of the cognitive disorders are found in the clean-up workers exposed to more than 0.3 Gy radiation doses. These cognitive disorders unlike such ones in vascular and demyelinating CNS disease reside in a verbal memory, speech, and intellectual abnormalities with regulation disorders of a voluntary activity along with preserved orientation ability and gnostical functions. The non-specific abnormalities of memory, dynamic praxis, visuospatial synthesis, thinking/brainwork and ability to plan were found in the liquidators exposed by doses under 0.3 Gy. Those abnormalities occurred being similar to cognitive disorders under the organic brain damage due to cardiovascular disease (hypertensive, atherosclerotic encephalopathy) and CNS demyelinating lesions [138–142].

The dose-related cognitive disorders lying in the decrease of a general intelligence quotient and verbal learning score proportionally to the radiation dose have been identified after expo-

sure by doses exceeding 0.3 Gy. Specific features of cognitive disorders in the dextromanual liquidators exposed by 0.3 Gy doses and more indicate to a predominant injury of the left temporal cortex zone, medial structures and frontal zone both with cortical-subcortical pathways mainly in the dominant (left) hemisphere. The young age (up to 35 years at exposure), low educational level, low occupational skills, and radiation dose over 0.3 Gy are the key factors of cognitive disorders in the liquidators given the excluded severe somato-neurological and mental disease. The «Diagnostic tool for the post-radiation cognitive disorders» has been developed for the probability estimation of a cognitive disorder radiation origin in remote terms after the total-body human irradiation under radiation accidents [143]. The post-exposure cognitive disorders (radiation dose 0.3 Gy and more) are featured by a mild and moderate cognitive deficit, deterioration of memory and attention, both with verbal learning disorder that in a whole can be attributed to the post-radiation injury of hippocampal neurogenesis especially in a dominant hemisphere (Figure 15.7) [138–143].

The post-radiation brain damage in the liquidators under 0.3 Gy and more radiation doses involves both white and gray brain matter. Revealed dependence of a cerebral electric activity on the state of its structures points at the each functional disorder of any brain structure correspondence to its structural disorders. Structure-functional pattern of the radiation brain damage features the abnormalities of the cerebral cortex (fronto-temporal zone atrophy), subcortical structures and pathways to the dominant hemisphere both with cortico-limbic system primarily in

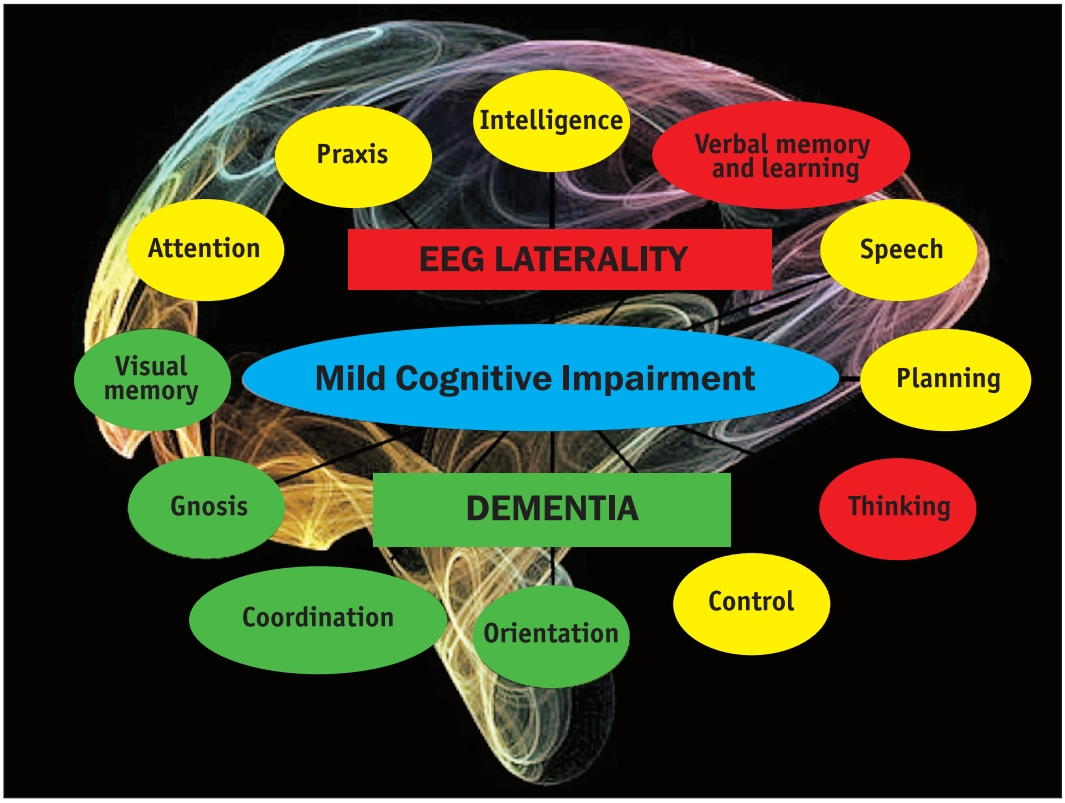


Figure 15.7. **Mild cognitive impairment as postradiation cognitive deficit [138–143]**
Note: red – severe disorders; orange – moderate disorders; yellow – mild disorders; green – no disorders.

the dominant (left) hemisphere [144–148]. Our data about the left hemisphere damage in the dextromanual liquidators are confirmed by an independent research with the cognitive auditory evoked potentials application [96, 97], however other authors notify that a left-hemisphere dysfunction is only the initial phase of a psychoorganic syndrome development [113].

Just due to the left-hemisphere pronto-temporal dysfunction and schizotype traits we have introduced the diathesis-stress hypothesis of the ionizing radiation as a risk factor of schizophrenia spectrum disorders [29–32, 148].

Among the major part of the liquidators exposed by low radiation doses (under 0.3 Gy), in the Chornobyl exclusion zone personnel, and in the «Shelter» unit staff members got employed in a recent few years the diseases are found corresponding to the chronic fatigue syndrome (CFS) criteria. The hypothesis has been introduced on the CFS origination and genesis under the synergic impact of low/very low radiation doses and stress. The left (dominant) hemisphere cortico-limbic dysfunction is a psychophysiologic background of the CFS following a radioecological disaster [149, 150]. At that the CFS incidence in the liquidators had decreased substantially (65.5% vs. 10.5% since 1990–1995 till 1996–2001), whereas the incidence of metabolic syndrome X (MSX) has increased as the years go by (15% vs. 48.2%). The CFS and MSX are considered as the neuropsychiatric and somatic pathology developmental stages where the CFS undergoes transformation to the MSX. The radiation-induced injury to the mitochondrial DNA (mDNA) in postmitotic tissues peculiar with a low proliferation can be one of the key pathways of a low-dose radiation effects towards a non-cancer morbidity elevation in the ChNPP accident survivors [151]. That is to say the CFS can be considered within the Chornobyl disaster model as an induced by the multiple environmental factors (acute and chronic external and internal irradiation, chemicals, viruses, psychological stress etc.) predisposition to neurodegeneration, cognitive injury and neuropsychiatric disorders [152–156].

Low-dose impact is a risk factor of the age-associated diseases with neurodegeneration in particular, and the aging and neurodegenerative processes can be exacerbated through the synergic effects of heterogeneous disturbing factors such as immune ones, oxidative stress and molecular-genetic abnormalities. Thus the radiation can accelerate aging and cause neurodegeneration [47, 157–160].

Cellular immunity and telomere length correlate with cognitive dysfunction in clean-up workers of the Chernobyl accident [53, 54]. There are parallel changes in decline of cognitive function and telomere length and differences in *TERF2*, *TERT* and *TERF1* gene regulation at the late period after low dose and over 500 mSv exposures [55]. Cognitive functions in cleanup workers exposed to ionizing radiation at adulthood are characterized by symptoms of a mild cognitive impairment according to the MMSE (mean group score 25.58±2.95) and a significantly higher level of mental disorders according to the BPRS in a dose related manner. Cleanup workers exposed to doses over 500 mSv demonstrate a significant cognitive deficit in comparison with those exposed below 500 mSv and especially non exposed patients. Relationship were revealed between the *TERT*, *TERF1*, *TERF2* genes expression, RTL, cognitive deficit and cerebrovascular pathology, radiation dose and age. Telomere length in cleanup workers is reduced after 50 years (6.1%). The most significant reduction in telomere length is shown after 70 years (11.7%). Negative correlation was found between telomere length and degree of cognitive deficit (MMSE scale) and between age and degree of cognitive deficit. The RTL is significantly decreased in groups of persons with cognitive deficit compared to a comparison group. Telomere length at the late period after low dose radiation exposure is downregulated by the high *TERF2* gene expression combined with low expression of *TERT* gene. After exposure to doses over 250–500 mSv a cognitive deficit and dementia were associated with a substantial increase in *TERT* gene expres-

sion, overexpression of *TERF1* and decrease in expression of *TERF2* gene. A relationship was revealed between the *TERF2* gene expression and $CD95^+$ cell fraction susceptible to apoptosis. Cognitive deficit in humans at a late period after radiation exposure is influenced by dose, age at exposure and gene regulation of telomere function [56].

The peculiarities of antioxidant enzymes activity and energy metabolism in demyelinating processes and vascular pathology of the CNS in exposed to low doses of ionizing radiation following the Chornobyl disaster have been revealed. In exposed patients neuroinflammation and energy deficit are increased, and catalase blood level decreased in cerebrovascular pathology [161].

Undoubtedly the neuropsychiatric effects in the liquidators are etiologically heterogeneous however the clinical and paraclinical research provides data on the probable role of ionizing radiation in their onset and genesis under total radiation doses exceeding 0.3 Gy.

The longitudinal psychiatric, psychometric, neuro- and psychophysiologic studies indicate to the development of organic mental disorders with an accent on the limbic system and its neurofunctional pathways' injury predominantly in the left (dominant) hemisphere (i.e. «limbic encephalopathy») in the liquidators. These disorders are of a polyetiological nature where the radiation dose impact is revealed only in a range above 0.3 Gy. Given the etiological heterogeneity of these disorders the «postradiation encephalopathy» diagnosis in such a case we consider inappropriate as absolutizing/overemphasizing the only single side of ethiopathogenesis. Diagnostic criteria of polyetiological including the radiation factor organic mental disorders are the following [162, 163].

A. Total radiation dose exceeding 0.3 Gy.

B. Somatoform (psychosomatic) disorder transformation to the organic brain damage.

C. Signs of polyetiological including the radiation factor organic mental disorders in the liquidators:

➢ microfocal organic neurological symptoms;
➢ paroxysmal states;
➢ mild cognitive impairment;
➢ depressive symptoms;
➢ manifestations of PTSD;
➢ hypochondriac symptoms;
➢ psychopathic-like manifestations;
➢ negative psychopathological symptoms;
➢ Global Assessment of Functioning score (GAF Scale) less than 70 points;
➢ disorganized or flat EEG pattern;
➢ dominant qEEG frequency decrease to less than 8 Hz in the occipital zone; delta- and beta-power excess with theta-power decrease in the frontotemporal zones especially in the dominant (left) hemisphere, alpha-power reduction;
➢ latency period (LP) deformation and shortening with an amplitude increase of the main components of visual evoked potentials (in response) to the chess(board) pattern reversion;
➢ LP deformation and elongation along with amplitude decrease of the main components of somatosensory evoked potentials (SSEP), contralateral LP increase and contralateral N20 i P25 amplitude decrease in the projection zone;
➢ lowered amplitude and absence or deformity of the main components of brainstem auditory evoked potentials (BAEPs), LP increase and interpeak intervals (IPI) elongation, BAEPs asymmetry increase;
➢ structure-functional brain damage with frontal zones, left temporal lobe and cortico-subcortical pathways both with deep cerebral structures involvement according to neuroimaging data;

➢ cerebral circulation abnormalities due to atherosclerotic lesions, vascular hypertonicity, brain interhemisphere asymmetry of a blood filling, and obliterating processes;
➢ cerebro-organic nature is testified by the brain structure abnormalities mainly as a ventricular atrophy and dilation both with focal brain lesions according to the magnetic resonance imaging data.

D. No mental disorders of any other origin.

The diagnosis of polyetiological including the radiation factor organic mental disorders is considered a substantiated one if A and B criteria are present both with at least 5 positions from criterion C. According to the ICD-10 multiaxial variant of mental disorders classification the typical complete diagnosis of polyetiological including the radiation factor organic mental disorders is the following:

Axis I – Clinical diagnosis. 1) Organic depressive disorder F06.32.2. Other cerebrovascular disease: Hypertensive encephalopathy I67.4.

Axis II – Disability. Loss of earning capacity >35% (averaged Global Assessment of Functioning score (GAF Scale) is 63 points, 37% loss).

Axis III – Situational factors: evacuation, work on the accident clean-up, experience (affection) of the Chornobyl disaster.

Verification of an organic brain damage in the liquidators is to be made on the basis of identification of structural-functional cerebral abnormalities through the clinical neuropsychiatric, neuropsychologic, neurophysiologic and neuroimaging methods application [164].

The developed diagnostic criteria of the post-radiation cognitive impairment are as follows [165]:

1) actual Intellectual quotient (IQ) decrease compared to premorbid IQ;
2) preponderance of the actual verbal IQ decrease compared to premorbid one;
3) short-term, long-term verbal memory and verbal learning decrease (deterioration) along with preserved visual memory;
4) abnormal retroactive interference of the verbal information;
5) speech disorders as the elements of an acoustic-mnestic aphasia;
6) disorders of regulation of the voluntary activity, associative thinking processes, activity planning, disorders of the voluntary movement and action organization (reciprocal coordination, dynamic tests, sensomotor coordination), switching disorders, voluntary attention weakness towards verbal stimuli;
7) preserved gnostical functions and visuospatial activity, body scheme, digital gnosis, space orientation;
8) EEG theta-range spectral power decrease in the frontotemporal zones;
9) EEG delta-range spectral power increase in the frontal zones with lateralization to a dominant hemisphere;
10) cognitive disorders combination with negative psychopathological symptoms.

15.2.5. Acute radiation sickness neuropsychiatric effects

According to UNSCEAR Report 2000 (Annex J) [166] the ARS was verified in 134 emergency workers in Chornobyl. Among them 41 persons had received the total-body external radiation doses under 2.1 Gy, while 93 patients were exposed to higher radiation doses resulting in more severe ARS, namely to 2.2–4.1 Gy in 50 cases, to 4.2–6.4 Gy in 22 men, and to 6.5–16 Gy in 21 of them.

The initial reactions and neurological disorders in ARS patients after the Chornobyl accident in wards of Moscow Clinical Hospital #6 have been described by F.S. Torubarov et al. (1989) [167].

In cases of mild ARS (Grade I, radiation doses 0.8-2.1 Gy) vegetative-vascular dystonia and neurotic disorders were diagnosed, in moderately severe ARS (Grade II, radiation doses 2–4 Gy) the vegetative-vascular dystonia was prevalent, in severe ARS (Grade III, 4.2–6.3 Gy of radiation exposure) the acute radiation and radiation-toxic encephalopathy, acute psychosis with visual and auditory hallucinations and cerebral edema were present, while in an extremely severe ARS (Grade IV, 6–16 Gy of radiation) the acute radiation and radiation-toxic encephalopathy, subarachnoidal/parenchymal hemorrhages both with pronounced cerebral edema were found [167].

A few years upon ARS convalescence the so-called «functional» disorders of nervous system were revealed neurocirculatory and vegetative-vascular dystonia with diencephalic paroxysms, and asthenoneurotic syndrome. No signs of organic brain damage were observed thereat [168, 169]. The decline in mental performance and the severity of asthenia were proportional to the survived ARS Grade. In case of doses over 2 Gy the signs of brain tissue microdestruction were revealed by means of neuroimmune tests [170]. The disorders of cerebral hemodynamics were considered as one among other reasons of neurological manifestations after the ARS [171]. The operator performance and cerebral electric activity abnormalities depended on severity of survived ARS. The electroencephalogram pattern slowdown due to theta-activity amplification was observed [172]. Extent of the evoked cerebral activity disorders was also proportional to ARS Grade. The brainstem, thalamocortical and intracortical disturbances were prevailing there. The signs of brainstem structures irritation in low-grade ARS evolved to their exacerbating depression of functional activity in ARS of intermediate and severe Grade [173].

In the nearest terms of ARS recovery period i.e. 4–6 months upon irradiation the mental state and intellectual performance were in close link to both ARS severity and premorbid personality traits, awareness level and extent of social issues resolving. Professional affiliation, adequate job placement and personality features of survivors had become of especial importance in more late terms of recovery period i.e. in 12–18 months. Later on in the proximal consequences period i.e. in 2.5–3 years the mental disorders with pronounced fatigability were found in survivors of more severe ARS and in older persons. Further the serious anxiety, depression, decline in mental working capacity both with specific alterations in personality semantic structure were revealed [174, 175].

Disorders of mental state and mental productivity were proportional to the severity Grade of survived ARS. The fatigability and anxiety-depressive disorders had exacerbated along with time, and formation of personality disorders occurred. At that if a tendency towards some amelioration of mental state was observed in 3 years upon exposure, then the recurrence of negative trend has become obvious 5-6 years later [176].

Prospective survey of ARS survivors provides data on origination and pathogenesis of the progressing structure-functional postradiation organic brain damage (postradiation encephalopathy) [3, 39, 106, 110, 111, 114, 122, 177-183]. Abnormalities in the cortical-limbic system and of its communications with mainly dominant (left) hemisphere accompanied by the pronounced alterations of central afferent pathways are the cerebral basis of postradiation organic mental consequences [29, 79, 124, 125, 127, 137, 138, 185]. Structure-functional brain alterations in remote period after the ARS appear as a damage of frontal zones and left temporal lobe with corticosubcortical links, and also of deep cerebral structures mainly through the atrophic type [134, 135, 145, 148].

The neuro-mental disorders in remote ARS period are peculiar with a progressing course with sequential change of autonomous/vascular and autonomous/visceral phase (3–5 years after exposure) by the phase of cerebroorganic disturbances and somatogenic lesions (5–10 years and more since the irradiation) (Figure 15.8).

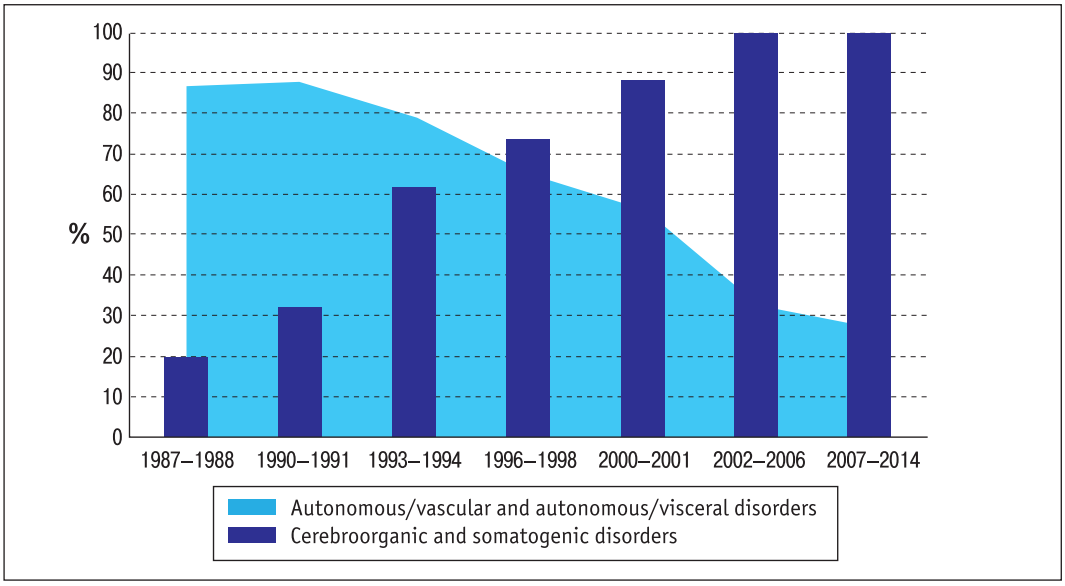


Figure 15.8. **Course of neuropsychiatric disorders in ARS survivors**

The autonomous/vascular and autonomous/visceral disorders in patients with diagnosed ARS were distinct in the suprasegmental type, combination with pronounced abnormalities of the central afferent pathways, intensity, resistance and permanent-paroxysmal course with accompanying diencephalic crises, which we classified here as symptomatic partial epileptiform limbic attacks. These abnormalities combined with exacerbation and multiplication of somatic diseases including cerebrovascular lesions have stipulated the progressive shaping of cerebroorganic and somatogenic mental disorders in remote period of ARS.

Along with years since ARS the psychopathological presentation has evolved to the most extent i.e. the «affective foreside» (neurosis-like and sthenic psychopathy-like symptomatology) decreased gradually in parallel with exacerbation of the negative psychopathological symptomatology. The mentioned psychopathological symptomatology in remote period upon ARS consists mainly from 1) negative psychopathological symptomatology i.e. energy potential decrease, personality disharmony and regression, affective flattening (flattening of affect), apathy, anhedonia, hypobulia, impoverished (scanty) speech, social withdrawal; 2) adynamic depressive symptomatology; 3) cognitive deficit and 4) characteristic psychopathy-like personality changes (personality disorders) with the general functioning scores under 70. As a whole the described above psychopathology can be classified as an apathetic variant of psychoorganic syndrome. According to ICD-10 criteria it should be diagnosed as an apathetic variant of Organic Personality Disorder (ICD-10: F07.0), corresponding to the apathetic type of Personality Disorder Due to General Medical Condition (310.1 code according to DSM-IV). This disorder is of progressing type of the course and its incidence depends on severity Grade of survived ARS and radiation dose respectively. Therewith some other organic mental disorders (F06, F07), both with neurotic, related to stress and somatoform disorders are found in ARS survivors [79, 80, 124, 146, 147]. The dose-effect relationship was fixed for mental working capacity decrease surveyed upon exposure to radiation doses exceeding 1 Gy [186, 187].

Neurological symptomatology in remote ARS period is of microfocal and «tracery» type. The sensory-algic, vestibulo-ataxic, musculotonic and autonomous (vegetative) disorders with soft

pyramidal and extrapyramidal symptoms, and also paroxysmal states mainly as diencephalic crises (autonomous-visceral attacks), and sometimes temporal epilepsy and amygdalohippocampal (mediobasal limbic) attacks are characteristic here. Neurological disorders are mainly observed within structure of cerebrovascular diseases (ICD-10: Cerebral atherosclerosis – I67.2, Hypertensive encephalopathy – I67.4, dyscirculatory encephalopathy within scope of Other specified cerebrovascular diseases – I67.8), demyelinating diseases of encephalomyelosis type (Other demyelinating diseases of central nervous system - G37) and paroxysmal disorders (G40, G43, G44, G45) [147, 182, 184].

In 3-5 years after irradiation the EEG abnormalities of irritative type with paroxysmal activity lateralized to the left frontotemporal zone were registered at that being estimated as hyperactivation of corticolimbic system. Along with time in 5–10 years these abnormalities have evolved to the low-amplitude EEG with an excess of fast (beta-) and slow (delta-) activity under the depression of alpha- and theta-activity indicating to the organic brain damage with corticolimbic system inhibition (Figure 15.9) [127].

The neurophysiologic markers of ionizing radiation (1–5 Gy dose range) were identified by means of quantitative electroencephalography (qEEG) application in patients with verified ARS diagnosis. They are the dominant frequency decrease in the left frontotemporal zone, the absolute delta-activity lateralization to the left hemisphere, relative delta-power increase in frontotemporal zones with lateralization to the dominant (left) hemisphere and diffuse decrease of absolute and relative alpha-power with lateralization of its depression to the left hemisphere. It can indicate that corticolimbic dysfunction is present being lateralized to the dominant hemisphere with cortical frontotemporal and hippocampal damage (Figure 15.10) [185].

Neurophysiologic studies (qEEG and evoked brain potentials registration) indicate to the damage of corticolimbic system mainly in the dominant i.e. left brain hemisphere and to the disorders of central afferent pathways of all sensory modularities with the prevalence of sensory information processing by non-specific afferent systems at the background of depression of specific ones in remote period upon ARS [79, 125].

Neuropsychology research has proved the pathological involvement of the frontal and temporal cortex of dominant hemisphere both with median cerebral structures and their cortical-subcortical links in remote period after the ARS. The left (dominant) hemisphere inhibition and

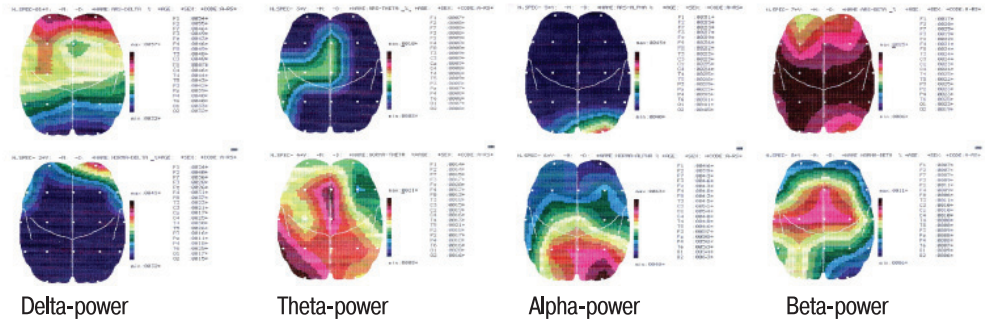


Figure 15.9. Brain Mapping of EEG in 10 years after ARS [39]

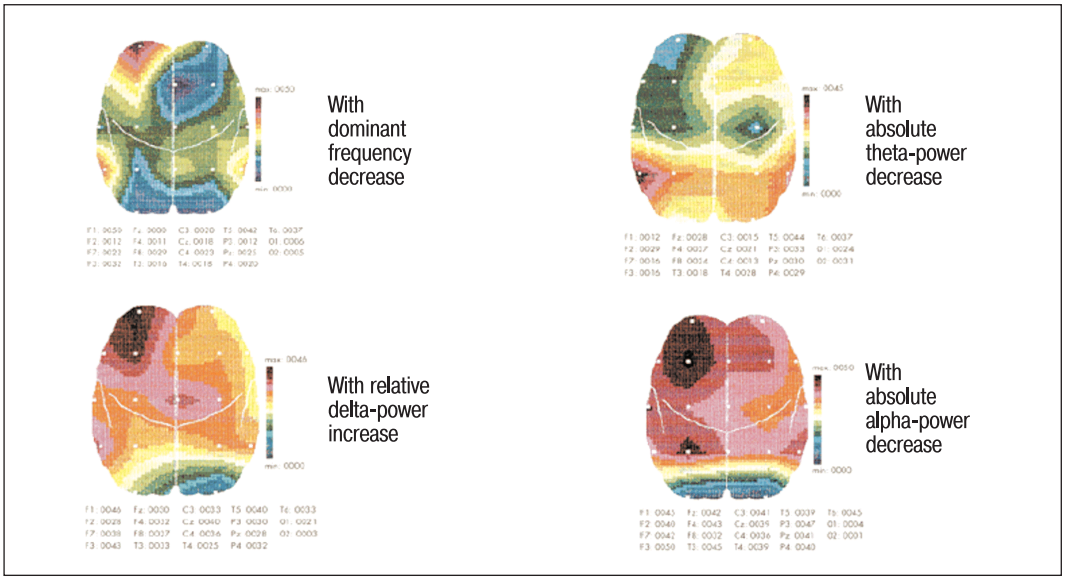


Figure 15.10. **Correlations between EEG Brain Mapping parameters and radiation dose (1–5 Gy) [185]**

compensatory hyperactivation of the right one were revealed. I means that damage of structures of the left brain hemisphere anterior parts responsible for verbal information reception and processing, planning, regulation and control is the cerebral basis of cognitive disorders after the ARS. On the opposite of those patients the diffuse brain damage with anterior (regulatory) and posterior (gnostical) parts of both hemispheres involvement and predominant injury of non-specific median structures are observed in the compare group i.e. patients suffering the dyscirculatory encephalopathy. Functional indices in associative brain zones responsible for the control and regulation of motor programs execution and speech-mediated mnestic (verbal) and complex intellectual activities were found being dose-dependent [137, 138].

Cognitive impairment in the remote period of ARS is an expected outcome. Regression-based estimates of premorbid IQ from demographic variables is the best way for estimation of intellectual impairment following accidental over irradiation, when any psychometrical information before the exposure is not available In 14–15 years after the Chornobyl accident verbal IQ (VIQ) and full IQ (FIQ) scores were lower in ARS-patients than in controls (M±SD: 103.2±13.5 vs. 113.8±9.4, and 102.2±11.4 vs. 110.2±8.6, correspondingly). Radiation dose of 1 Gy decreases FIQ of 4.1-6 scores at a dose range of 1-3.8 Gy. A reduction of 1 point of FIQ could be a result of exposure to 0.17-0.24 Gy. Discrepancy between pre- exposure and actual IQ (M±SD) in ARS-patients is dramatically severe as compared to controls: VIQ s 15.8±14.4 vs. 2.3±4.5, PIQ s 14.2±10.8 vs. 8.7±3.5, and 16.8±12.7 vs. 5.9±2.6, correspondingly. According to pre-exposure IQ estimations, IQ deterioration in ARS-patients, especially, in verbal and full intelligence, was observed. Such cognitive impairment could be evidence of a brain organic syndrome with an important involvement of the left dominant hemisphere, in the remote period of ARS [188].

Cognitive deficit is a base of brain damage clinical pattern in remote period of ARS. The specific dose-dependent abnormalities of cognitive functions were found being considered as a domain of post-radiation cognitive disorders. They include verbal IQ decrease compared to the premorbid verbal IQ, decline in cognition, memory and attention, deterioration of the short-term verbal memory and of the proactive and retroactive interference of verbal information.

Lowering of the relative theta-range power in the left frontal zone and decrease of the qEEG theta-range total relative power ratio to the alpha-range one accompany these cognitive disorders. The theta-range is known being a hippocampal rhythm. Therefore the revealed dose-dependent neurophysiologic and neuromental disorders can indicate to the injury of corticolimbic system, especially of hippocampus in the left (dominant) hemisphere. Therefore the revealed dose-related neurophysiologic and neuropsychological disorders can be the proof of corticolimbic system abnormalities especially of the left (dominant) hemisphere hippocampus. The post-radiation cognitive disorders are of mild and moderate severity here and feature memory, attention, and verbal learning abnormalities that can be attributed to the post-radiation alteration of hippocampal neurogenesis (especially in the dominant hemisphere) [139–143]. According to the Patent «Diagnostic tool for the postradiation cognitive disorders» [144] the probability of radiation cognitive disorders in remote ARS period is identified with 84.9% sensitivity, 81.8% specificity, and 83.4% accuracy.

The neuroimaging researches in remote ARS period have provided the verification of mental disorders cerebroorganic type by the presence of cortical atrophy, ventricular dilatation, and focal lesions. According to magnetic-resonance imaging (MRI) morphometry the neuroimaging markers of 1–5 Gy dose range ionizing radiation were identified featuring the contrast ratio decrease of the left internal capsule anterior limb (i.e. *crus anterius*) and genu, left parietal lobe in the radiate crown (i.e *corona radiata*) zone, and right parietal lobe white matter. Brain hemisphere cortical atrophy and dominant hemisphere pathways alterations are the quantitative neuroimaging particularities of ARS remote period [134–136, 145, 148].

Cerebrovascular Doppler ultrasound visualization (non-invasive angiography) have found the acceleration of vascular wall involution, diffuse decrease in hemodynamic reactivity with «rigid» circulation pattern appearing, and restriction of blood flow in the extracranial cerebral vessels. As a result the reactive compensatory vasospasm occurs in all cerebral arteries. The excessive arterial tortuosity with diffuse stenosis are the characteristic features of cerebral vessels. Therewith the asymmetry of blood flow was found in the internal carotid arteries (ICA) due to more pronounced left ICA systolic velocity decrease. The left ICA systolic velocity decrease is regarded as a marker of cerebral arteries' radiation damage, and just the left ICA as the target of deleterious action of ionizing radiation [130–133].

The specific and/or dose-related neurophysiologic, neuropsychologic and neuroimaging effects have occurred in remote period upon ARS. At that the mentioned effects are lateralized to the left (dominant) hemisphere indicating the increased vulnerability of dominant hemisphere to ionizing radiation [146]. Similar data for the left-handed persons unfortunately are not available. Thus, the post-radiation brain damage in the right-handed individuals is localized primarily in anterior zones of the left brain hemisphere. Upon ARS survivors the post-radiation abnormalities are found either in white and gray brain matter. The structure-functional markers of radiation brain damage have been identified, namely the abnormalities of big hemisphere cortex (frontoparietal zones atrophy), subcortical structures and dominant hemisphere pathways both with corticolimbic system mainly in the dominant (left) hemisphere [134-136, 184]. Therefore existence of the organic (i.e. structure-functional) cerebral damage in remote period upon ARS have been verified on the ground of neuropsychiatric, neuropsychological, neurophysiologic, and neuroimaging study results [182].

Despite the data presented above and studies results from other authors proving the existence of an organic radiation brain damage in remote ARS period [3, 28, 39, 43, 111, 180] some researchers considered that «response of the nervous system to less than 10 Gy of ionizing radiation occurs without a component of neuronal structures irreversible damage and is realized

through the biochemical reparation of a neuron and functional reorganization of neural activity» [189]. They insist on high regenerative capacities of human body under the radiation impact and psychoneurological disorders at that are regarded as «reactive neurotic changes» [190]. So more that centenary debates about the radiation sensitivity of nervous system are still going on.

The organic brain damage upon ARS is etiologically heterogeneous. In our opinion it is inappropriately to absolutize the radiation factor especially in case of low-dose radiation [104–106, 109] but we at that don't share the standpoint of ignoring the exogenous-organic impact of ionizing radiation on the human brain even at high radiation doses [189–192]. Our research data conclusively prove the existence of brain structure-functional alterations in remote period of ARS after the Chornobyl disaster. As it was outlined above the cerebral damage had occurred as a result of combined impact of exogenous and endogenous factors [112]. Undoubtedly the traditional risk factors and, in particular, age, cerebrovascular disease, somatic disorders, stress, psychoactive substance abuse, lifestyle and others do contribute to the organic brain damage after the ARS. However data are available on crucial importance of ionizing radiation in case of doses exceeding 1 Gy.

Therefore brain is sensitive to radiation, at that its vulnerability to ionizing radiation is different i.e. the radiation damage occurs ante omnia in neocortex, corticolimbic system and dominant hemisphere. The revealed neurophysiologic, neuroimaging and Doppler-sonographic radiation markers both with post-radiation neurocognitive deficit have been used as a background in elaboration of the «Diagnostic tool for radiation brain damage in remote period after the exposure». The tool is to be used in assay of probability of brain damage radiation origin in remote period after human exposure under radiation accidents. The complex of unified psychometrical, neurophysiologic (multichannel registration of brain electrical activity), neuroimaging (brain morphometric MRI), neuropsychological, Doppler-sonographic, and biochemical tests and examinations is applied. The tool sensitivity is 89.1%, specificity is 76.3%, and accuracy is 83.54% [193].

The diagnostics of post-radiation organic mental disorders (postradiation encephalopathy) is to be performed according to the following criteria [163, 164]:

1) radiation dose exceeding 1 Gy

2) progressive type of mental disorders course with transformation of neurosis-like states with pronounced asthenic, autonomous/vascular and autonomous/visceral abnormalities to the organic brain damage

3) signs of postradiation organic mental disorders:

➢ microfocal organic neurological symptomatology with sensory-algic, vestibulo-ataxic, and musculotonic syndromes, soft pyramidal and extrapyramidal symptoms, and progressing autonomous failure;

➢ paroxysmal states as diencephalic crises (autonomous/visceral attacks), temporal epilepsy and amygdalohippocampal (mediobasal limbic) attacks;

➢ cognitive deficit;

➢ senesto-hypochondriac symptomatology;

➢ negative psychopathological symptomatology i.e. energy potential decrease (lack of energy), personality disharmony and regression, affective flattening, apathy, anhedonia, hypobulia, impoverished (scanty) speech, social withdrawal;

➢ depressive symptomatology;

➢ general functioning score < 70;

➢ plane or disorganized EEG pattern with abnormal activity lateralization to frontotemporal zone of the dominant (left) hemisphere;

➢ dominant qEEG frequency decrease < 8 Hz in occipital zone; delta-power excess with theta-power reduction in frontotemporal zones especially of the dominant (left) hemisphere; alpha-power reduction;
➢ deformation and shortening of the latent periods (LP) and amplitude increase of the main components of visual evoked potentials (EP) to chess (chessboard) pattern reversion (VEPCP);
➢ LP deformation and prolongation with amplitude decrease of somatosensory EP (SSEP) main components, evoked response maximum (highest amplitude and shortest LP) not in projection zone but in associative ones under the right-sided stimulation;
➢ deformation of brain stem auditory EP (BSAEP) late components (i.e. III, IV, and V), elongation of component V latent period and III-V interpeak interval (IPI), component V amplitude decrease;
➢ structural-functional brain damage with frontal zones, left temporal lobe with cortical-subcortical links and deep brain structures involvement according to the neuropsychological tests;
➢ cerebral hemodynamics abnormalities due to atherosclerotic lesions, hypertonic type of vascular tone, interhemisphere asymmetry in brain perfusion with blood flow velocity decrease on the left, and obliterating processes;
➢ cerebral-organic nature is proved by the brain structure abnormalities according to MRI data (mainly as atrophy and brain ventricles dilatation, both with brain focal lesions)
4) no mental disorders of other origin.

The **diagnosis of organic mental disorders** is considered substantiated if **criteria #1** and **#2** are available both with at least 5 positions from criterion #3. In case of cerebrovascular disorders (hypertensive encephalopathy, cerebral atherosclerosis) with stable cerebral hemodynamic abnormalities the organic brain damage can be classified as a postradiation dyscirculatory encephalopathy.

In correspondence with multiaxial variant of ICD-10 mental disorders classification the typical complete diagnosis of postradiation organic mental disorders can be as follows:

Axis I – Clinical diagnosis. 1) Apathetic variant of the organic personality disorder F07.0. 2) Unspecified effects of radiation: Radiation sickness T66. 3) Other specified disorders of brain: Postradiation encephalopathy G93.8.

Axis II – Disability. Loss of earning capacity >40%.

Axis III – Situational factors: experience (affection) of the Chornobyl disaster.

Verification of organic brain damage after the irradiation is to be made on the basis of identification of structural-functional abnormalities through the clinical neuropsychiatric, neuropsychologic, neurophysiologic and neuroimaging methods application [165].

15.2.6. Brain damage *in utero*

The developing brain is extremely radiosensitive. Severe mental retardation, intellectual quotient (IQ) decrease, poor school performance, microcephaly, and seizures have been revealed in Hiroshima and Nagasaki A-bombing survivors exposed to radiation in prenatal period especially at 8–15th and 15–25th gestation weeks [194–199]. The latest re-appraisal of the dosimetry data showed the 0.06-0.31 Gy dose threshold of a mental retardation after exposure at week 8–15 and 0.28–0.87 Gy at week 16–25 respectively [200]. Despite schizophrenia cases number increase in prenatally exposed to radiation persons who had survived after the Nagasaki A-bombing the issue of an atomic radiation role in this excess remains open [201]. In the meantime schizophrenia risk excess upon prenatal diagnostic X-ray has been found in the Jerusalem cohort [202, unpublished data].

1 Sv prenatal irradiation at a gestation week 8-15 is believed resulting in the IQ decrease for 30 points. Every 100 mSv of prenatal exposure of an embryo or a fetus leads to respective IQ lowering for no more than 3 points. Severe mental retardation excess is estimated as 0.4 per 1 Sv at a gestation week 8-15 and to a less extent at a week 16–25 [203, 204].

Therefore the proven human radioneuroembryological effects are: 1) cognitive deficit i.e. the dose-related intellectual decline down to the severe mental retardation level, 2) microcephaly, 3) seizures. The IQ decrease depends on a cerebrogenesis period when the irradiation occurred. Other potential radioneuroembryological effects (e.g. schizophrenia) require further research.

Prenatal brain damage problem after the Chornobyl disaster is utterly debatable. The respective data are summarized in Table 15.2. It is clear from the table that cerebral effects had been found almost in all the studies, whereas their radiation origin remains a contradictory issue. At that it must be emphasized that the Japanese and total radiological experience extrapolation to the Chornobyl accident is impossible due to the internal prenatal irradiation by the radioactive iodine in the last case. The UN Chernobyl Forum experts had recognized the effects on a developing brain among the four priority neuropsychiatric issues of the Chornobyl legacy [1].

The World Health Organization in 1992–1995 had executed the Pilot Project «Brain Damage *in Utero*» within framework of the «International Programme on the Health Effects of the Chernobyl Accident» (IPHECA). Analysis of the data received in Belarus Republic, Russian Federation and Ukraine indicated the following: 1) mild cognitive retardation in prenatally irradiated children exceeds the respective value among the control groups (at the age of 5-6 years); 2) there was an increasing trend of the emotionally-behavioral disorders incidence in children irradiated *in utero* (at the age of 5–6 years); 3) prevalence rate of the borderline neuropsychic disorders in parents of the irradiated *in utero* children was higher than in control. However IPHECA was featured by several serious limitations where an absence of individual dosimetry was the leading one. Selection of the exposed and non-exposed study subjects was bases only on the value of soil radioactive contamination intensity at a place of residence irrespective to the individual radiation dose. Therefore an identification of prenatal irradiation role after the Chornobyl disas-

Table 15.2

Summarized principal results of the cerebral effect research in prenatally irradiated survivors of the Chornobyl disaster

Study	Cerebral effect	Radiation effect
International Programme on the Health Effects of the Chernobyl Accident (IPHECA), WHO, 1992–1995	++	?
Ukraine (Nyagu et al., 1999–2004)	+++	+
Belarus Republic (Igumnov et al., 1994–2015)	++ → ±	–
Russian Federation (Yermolina et al., 1994–1998)	+++	+
USA–Ukraine (Bromet et al., 1998–2010)	±	–
United Nations Scientific Committee on Effects of Atomic Radiation (UNSCEAR), 2000.	±	–
French–German Initiative for Chernobyl (FGI), 1998–2004	++	±
Israel (Bar Joseph et al., 2004)	±	–
UN Chernobyl Forum, 2006	+	?
Ukraine (Loganovsky et al., 2005–2015)	++	+
Finland (Huizink et al., 2007, 2008)	++	–
Sweden (Almond et al., 2007)	++	+
Norway (Sverdvik, Mednick et al., 2009)	++	+
France, USA, Norway (Moller et al., 2011)	+++	++
25 Years after Chernobyl, International Conference, 2011	++	+

ter in the genesis of neuropsychiatric effects in those children remained impossible [205]. The executors of this WHO Pilot Project «Brain damage *in utero*» have examined 4210 children born in the period from April 26, 1986 to February 1, 1987 in Byelorussia, Ukraine, Russia in contaminated and non-polluted (control) regions. In radiation-contaminated regions there was higher frequency of mental retardation and other mental disorders as well as deterioration of both mental and physic health of their parents. A preliminary character of the data obtained was emphasized as well as the necessity of more detailed follow-up of these groups [206].

A.I. Nyagu and collaborators (1992–2004) had paid high enough attention to the issue of prenatal brain damage as a result of the Chornobyl accident. Their initial reports featured the overestimated incidence of the mental retardation in prenatally irradiated kids (up to 77%). In was assumed that thyroid radiation dose *in utero* exceeding 0.3 Gy is a risk factor of neuropsychiatric effects [207, 208]. Further upon the international psychometric methodology application the incidence increase of mild mental retardation, borderline and low IQ, emotional and behavioral disorders was found. Both with that the number decrease of children with high IQ was revealed among the irradiated in utero. The radiation-induced dysfunction of pituitary-thyroid system after the 0.3 Gy and more thyroid dose irradiation *in utero* was considered as one among other biological pathways of neuropsychic disorders in prenatally exposed children. In conclusion the neuropsychic disorders among the prenatally irradiated children were recognized as a consequence of cerebral structure and function alterations resulted from interference of the pre- and postnatal factors against the present radiation effects in a developing brain [39, 209-213]. At the age of 10–12 years) the intellectual development disharmony due to the verbal IQ lowering, higher incidence of the EEG low-amplitude and epileptiform patterns with a left-hemisphere lateralization of the dysfunction, EEG delta- and beta-power increase along with alpha- and theta-power decline (Figure 15.11), incidence increase of the paroxysmal and organic mental disorders, somatoform autonomous dysfunction, psychological development abnormalities, both with emotionally-behavioral disorders were revealed in children irradiated in prenatal period after the Chornobyl disaster. The prenatal brain damage is considered etiologically heterogeneous [212, 213].

S.A. Igumnov and collaborators (1994–2015) hold their own that sociodemographic and sociocultural factors are the principal sources of mental disorders in prenatally irradiated children. The excessive incidence of the specific speech and emotional disorders both with lowered

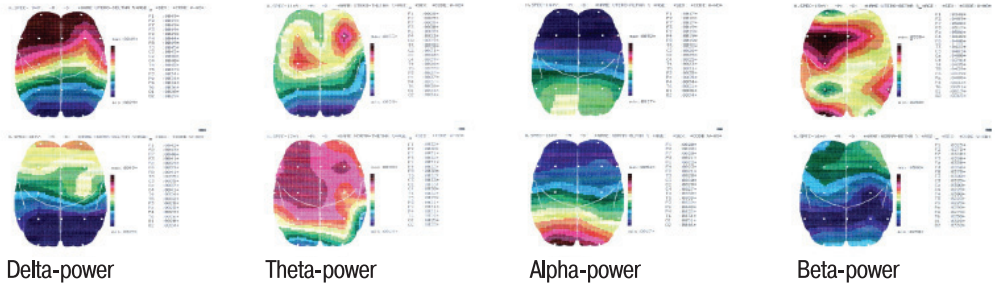


Figure 15.11. **Brain Mapping of EEG of in utero exposed children at age of 9–10 years [39]**

general IQ score and increased frequency of a borderline IQ cases among the exposed *in utero* habitants of the Belarus Republic were attributed to the impact of only the social and psychological factors. At that no associations had been found between the prenatal irradiation and decreased IQ as well as with mental health deterioration in children [214–216]. This stand was entirely supported by the UNSCEAR 2000 Report Annex J experts [167]. They had arrived at a decision that the unfavorable socio-psychological and sociocultural factors had a leading role in the origination of borderline intellectual functioning and emotional disorders among the prenatally irradiated children in Belarus Republic [217–219], despite the average IQ score in the most severely irradiated kids (thyroid doses *in utero* > 1 Gy) was lower vs. all exposed children [217]. The conclusion was reached in the last few years that neurophysiologic deviations in prenatally irradiated children in the Belarus Republic had mended and all those persons are not different from the non-exposed control according to the EEG data [220].

In the meantime the data were published on intellectual development retardation under the thyroid doses 0.5 Gy and more upon irradiation *in utero* and exposure up to 1.5 years of life [221]. More functional and organic disorders of the CNS, borderline IQ and abnormal EEG explained by the radiation and psychological factors were revealed in children irradiated prenatally especially at gestation weeks 8–15 [222]. Higher incidence rate of mental disorders, higher frequency of the borderline intellectual development and mental retardation had been revealed in children irradiated *in utero*. The mentioned phenomena they have associated with just a prenatal exposure [223–225].

As a result of the prospective American-Ukrainian research and the survey of emigrants to Israel no any signs of neurobehavioral or cognitive performance disorders were found through the applied tests in children exposed to prenatal radiation as a result the Chornobyl NPP accident [226–229]. The attention deficit hyperactivity disorder (ADHD) was revealed instead [229]. Noteworthy that evacuated mothers of the prenatally exposed children reported the memory disorders in their children 4 times more often, however no any difference from control was found according to the results of the applied neuropsychological tests and school performance estimates [227]. Alongside with that they have arrived at the conclusion that «Chornobyl anxiety» or mothers' risk perception was of a decisive role in general and mental health state of the children [230, 231]. It should be emphasized that study authors had no any dosimetry supplementation of the research and have assayed neither verbal intellect nor other functions of the dominant hemisphere (left one in dextromanual persons).

The opinion have been offered that the results of «Western» studies indicate to no cerebral disorders in prenatally irradiated persons, whereas «local» research data point out to the cognitive disorder excess in them. Nevertheless the UN Chernobyl Forum experts after all have attributed the effects of a developing brain to the key neuropsychiatric problems of the Chornobyl accident [1].

In view of the stated topic relevance the thorough study dedicated to the potential cerebral effects of prenatal irradiation was conducted in Ukraine within French-German Initiative for Chernobyl (FGI). The 154 children were examined that were born since April 26, 1986 till February 26, 2007 to mothers evacuated from Pripyat town to Kiev City. The 143 their classmates were involved as a control group members. All pediatric subjects were examined by means of the Wechsler Intelligence Scale for Children (WISC), Achenbach, and Rutter A(2) tests application. The verbal abilities and mental health including depression, anxiety and somatization were assayed in mothers. Both internal and external radiation was accounted within an individual dose reconstruction in children. Fetal effective doses and brain and thyroid equivalent doses in utero were calculated in both groups of children using the ICRP Publication 88 [232]. There were 52 children (33.8%) from Pripyat in whom the equivalent thyroid doses were over 1

Sv and 20 kids (13.2%) with fetal radiation doses exceeding 100 mSv. No cases of a severe mental retardation or microcephaly were identified in examined children, however much more psychological development abnormalities, emotional/behavioral and organic mental disorders, both with paroxysmal states were diagnosed there. The integral IQ in the exposed *in utero* children was lower at the expense of a decreased verbal IQ resulting in a higher incidence of disharmonic intellect. In case of the IQ disharmony (non-verbal IQ – verbal IQ) in prenatally exposed children that exceeded 25 points it correlated with fetal radiation dose. Mothers from both study groups have had equal verbal abilities, but the evacuees had experienced substantially more of the real stress events and had significantly higher levels of depression, post-traumatic stress and somatoform disorders, anxiety, insomnia and social dysfunction [233, 234].

It must be emphasized once more that as distinct from the atomic bombing of Hiroshima and Nagasaki the Chornobyl accident has resulted in an enormous environmental release of radioactive iodine (1,760 PBq of ^{131}I) [166]. For this reason the extrapolation of Japanese data regarding the prenatal brain exposure to the situation upon the Chornobyl accident runs into the considerable radiobiological limitations. The case is the embryo and fetal radiation doses after the Chornobyl accident are substantially lower whereas thyroid radiation doses *in utero* are much higher due to the radioactive iodine incorporation. Therefore the prenatal effects after the Chornobyl accident hardly can be predicted on the background of the Japanese experience because of a quite different radiobiological situation [234].

In correspondence to our study results the Chornobyl disaster impact was found being a stress factor towards the behavior of prenatally exposed to radiation adolescents in Finland. Those irradiated at the second trimester of pregnancy featured the 2.32-fold higher risk (95% confidence interval: 1.13; 4.72) of depressive symptoms and major depressive disorder according to the DSM-III-R criteria (odds ratio 2.48; 95% confidence interval: 1.06; 5.7), as well as of the attention deficit hyperactivity disorder. In a meantime no association of the prenatal impact of the Chornobyl accident with an anxious and an oppositional defiant disorder was revealed. In other words the abnormal development of a fetal brain can lead to prevalence increase of depression, attention deficit hyperactivity disorder upon the prenatal stress impact at the second trimester of pregnancy [235]. Also the potential effect of a prenatal stress associated with the Chornobyl disaster was surveyed within a framework of the current epidemiological study in Finland. Serum cortisol level in both boys and girls and testosterone level in girls were substantially higher after the prenatal maternal stress at the second trimester of pregnancy compared to the reference group of non-exposed adolescents. The prenatal impact to the abnormal cortisol level was 3% whereas contribution of testosterone reached up to 18%. At that there were no differences between the effects at the first or third trimester of pregnancy. The prenatal maternal status therefore can be reflected on the prenatal programming of physiological systems responsible for cortisol and testosterone levels maintenance [236].

The described above data stand together also with the results of a school performance survey in prenatally exposed persons in Sweden given the radiation contamination levels after the Chornobyl accident. The school performance occurred worse in people that were *in utero* at the time of Chornobyl disaster vs. other persons (the most complete database on 562,637 Swedish citizens born in 1983–1988). The poorest educational achievements were in persons exposed at week 8–25 upon conception and born in Swedish regions with most heavy radioactive fallout. Prenatal irradiation therefore alters the cognitive abilities at a level considered before as a safe one [237].

There were statistically lower general and verbal IQ both with more pronounced intellectual disharmony («asymmetry») due to the verbal IQ decrease in children prenatally exposed after the Chornobyl disaster as distinct from children-Kievites (compare group) (Table 15.3).

Table 15.3
Intelligence (WISC) of the examined children at the age of 10–12 years

Parameter	Prenatally irradiated (n=100)	t	p	Group of compare (n=50)
Full IQ (M±SD), points	112.2 ± 15.5	-2.7	< 0.006	119.1 ± 10.9
Verbal IQ (M ±SD), points	105.6 ± 13.6	-4.2	< 0.001	115.8 ± 14.3
Non-verbal IQ (M±SD), points	117 ± 18	-0.9	> 0.05	119.6 ± 9.4
IQ «asymmetry» (non-verbal IQ – verbal IQ) (M±SD)	11.4 ± 14.2	3.0	< 0.003	3.8 ± 14.1

The intelligence of children is a heterogeneous phenomenon defined by the combined effect of mental disorders and nervous system disease if any in a child, economical factors, traditional risk factors, parental educational level (of a father especially), mother's somatic and mental health as well as by prenatal irradiation and stress factors of the Chornobyl disaster. The prenatal radiation contribution to the child's intelligence is in average 11% ($p = 0.03$). At that the contribution of thyroid radiation dose *in utero* is the highest at the second critical period of cerebrogenesis i.e. week 16–25 at the time of the accident and amounts 20% in the complete IQ ($p = 0.04$) and 24% in the verbal one ($p = 0.014$).

In a case of the IQ disharmony («asymmetry») when non-verbal IQ – verbal IQ is > 25 points this disharmony goes worth in a statistically reliable dependence on embryo and fetal radiation dose (ICRP-88: (M±SD) 58.6±26 mSv; range: 24.4–116.9 mSv) ($r = 0.5$; $p = 0.029$) (Figure 15.12), as well as on a gestation week at the time of Chornobyl accident (since week 12: $r = 0,6$; $p = 0.027$). In prenatally exposed children suffering but more pronounced IQ disharmony

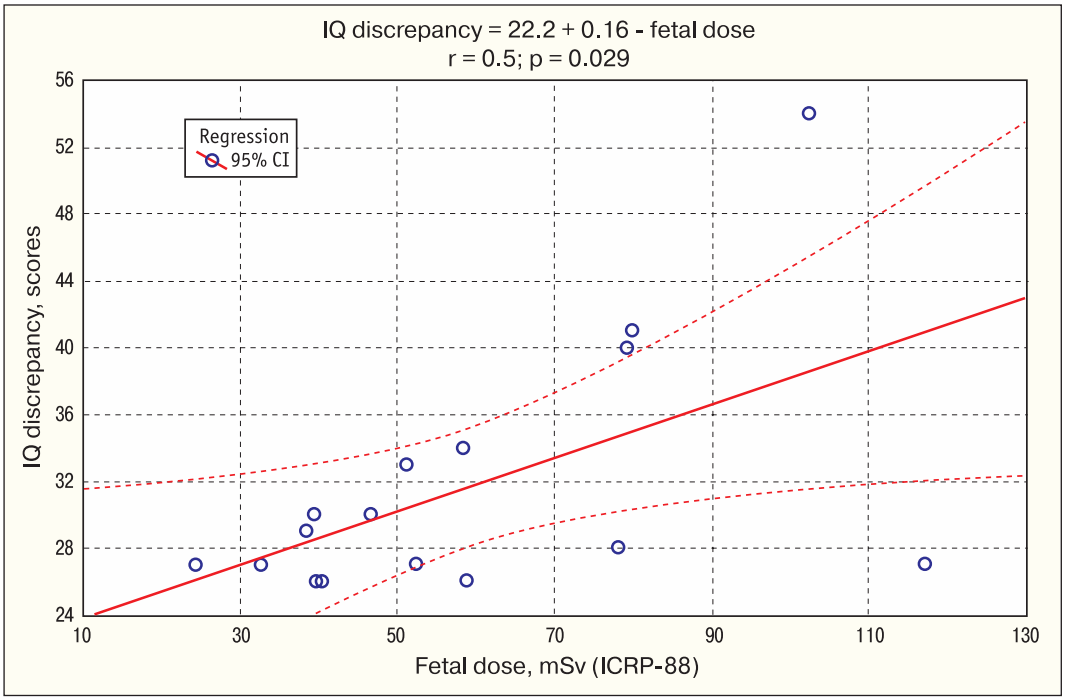


Figure 15.12. Intelligence disharmony relationship with embryo and fetal radiation doses (ICRP-88) in children prenatally exposed to radiation and suffering an IQ «asymmetry» (non-verbal IQ – verbal IQ) > 25 points [245]

(> 29 points) the dose-effect relationship becomes substantially stronger. In these cases the IQ disharmony exacerbation is proportional to the embryo and fetal radiation doses and is of a linear correlation pattern (69.5±21.3 mSv; range: 46.6-102.3 mSv; $r = 0.97$; $p < 0.001$). The power of a relationship between the intelligence disharmony and a gestation week at the time of Chornobyl accident goes stronger too (since week 14: $r = 0.8$; $p = 0.035$). The relation of an IQ disharmony in those children on a thyroid radiation dose *in utero* is surveyed too (871.3 ± 330.2 mSv; range: 421.3–1281.1 mSv; $r = 0.7$; $p \sim 0.05$) [238, 239].

The intelligence disharmony due to verbal IQ decrease can be considered the radioneuroembryological effect of a prenatal radiation after the nuclear reactor accident. The mentioned effect is surveyed in case of an exposure at week 8 of gestation and later with fetal and thyroid doses *in utero* exceeding 20 mSv and 300 mSv respectively, and in the terms of radiation exposure since week 16 till week 25 with doses > 10 mSv and > 200 mSv correspondingly. The EEG theta-range spectral power decrease (especially in the left frontotemporal zone), beta-activity amplification with lateralization to the dominant hemisphere as well as abnormalities of a normal asymmetry of visual evoked potentials and the vertex potential can be considered the neurophysiologic markers of a prenatal radiation. The relatively late gestation term (weeks 16–25) is the most critical period for cerebrogenesis under the nuclear reactor accident followed by an intensive environmental release of radioactive iodine compared to the circumstances of a uniform external radiation (weeks 8–15) [238–245]. The incidence of the organic mental disorders, psychological development abnormalities, paroxysmal states (headache, migraine, and epileptiform syndromes), somatoform autonomous dysfunction, childhood behavioral and emotional disorders was higher in children and adolescents prenatally irradiated after the Chornobyl accident. The IQ disharmony undergoes an exacerbation along with gestation term that can be explained with the thyroid growth and metabolism intensification. Specific features of radiation exposure after the nuclear reactor accident with an intensive environmental release of radioactive iodine stipulated also the differences in radioneuroembryological risks at cerebrogenesis periods.

Weeks 8–15 and 16–25 are the most critical periods of cerebrogenesis that entirely corresponds to radiocerebral effects under purely external exposure as it had been observed after the A-bombings. However after the Chornobyl accident, given the relatively low fetal radiation doses during the most critical period of cerebrogenesis (i.e. gestation weeks 8–15), there were no alterations in neuronal migration. Thyroid size in such a period is small and thyroid metabolism is at a minimal level. It means that the thyroid doses *in utero* and embryo/fetal radiation doses are correspondingly negligible too. At the next critical period of cerebrogenesis (i.e. gestation weeks 16–25) the activation of cellular differentiation and intensification of synaptogenesis occur, cerebral cytoarchitectonics takes shape, the development of main limbic structures both with its pathways is completing as well as cerebral asymmetry and hemisphere dominance appear (ICRP 49). The increase of thyroid mass with thyroid metabolism intensification leads to an *in utero* thyroid radiation dose increase and embryo/fetal dose increase respectively. That is just at the second critical period of cerebrogenesis (i.e. gestation weeks 16–25) the specific «overlap» of cerebrogenetic criticality occurs as well as the increase of prenatal radiation doses as shown at Figure 15.13. Just the abnormalities of neuroembryological events in this cerebrogenetic period can explain the revealed radioneuroembryological effect of IQ disharmony. They ought to consider that despite the radiosensitivity of a developing brain is lower during further periods of gestation the thyroid and fetal prenatal radiation doses on the contrary increase then resulting in an IQ disharmony also at the later terms of gestation i.e. weeks 26+.

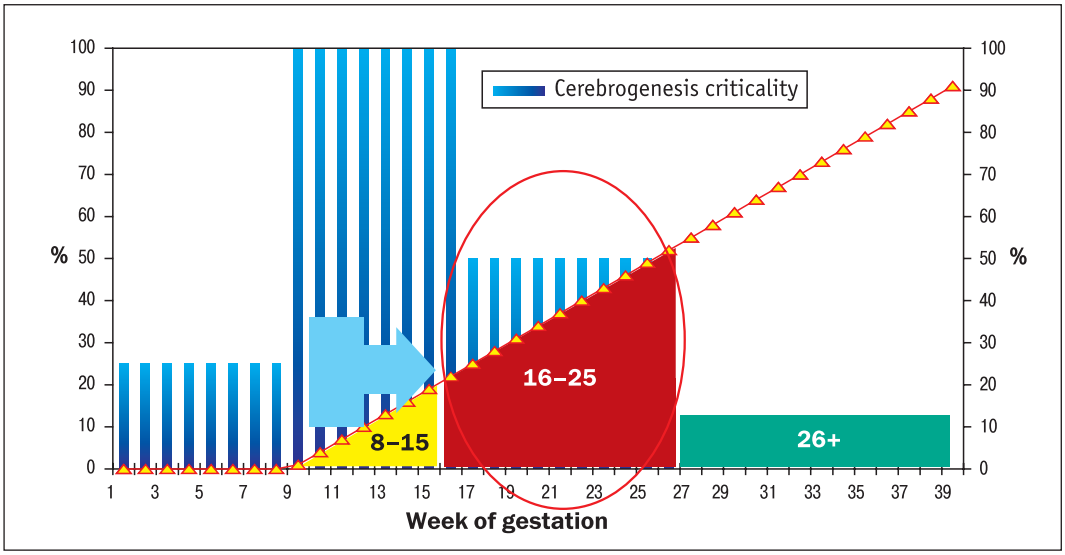


Figure 15.13. **Conventional pattern of relationships between critical stages of cerebrogenesis in relation to increasing thyroid doses in utero (ICRP-88) in prenatally exposed individuals as a result of the Chornobyl accident (gray spaces correspond to the degree of cerebral vulnerability to radiation from radioactive iodine) [245]**

Our initial publications suggested the prevalence of functional disorders of the dominant left hemisphere and especially of its cortico-limbic structures in children irradiated *in utero* after the Chornobyl accident [244]. Later we have concluded that there was an abnormal development of the dominant hemisphere after the prenatal exposure due to the Chornobyl disaster. More neuropsychic disorders, neurological signs of a left hemisphere involvement, decreased indices of the complete and verbal IQ, the IQ disharmony due to the verbal IQ decrease, disorganized EEG patterns, excess of the EEG delta- and beta-power lateralized to the left pronto-temporal zone along with theta- and alpha-power depression (Figure 15.14) and the interhemispheric

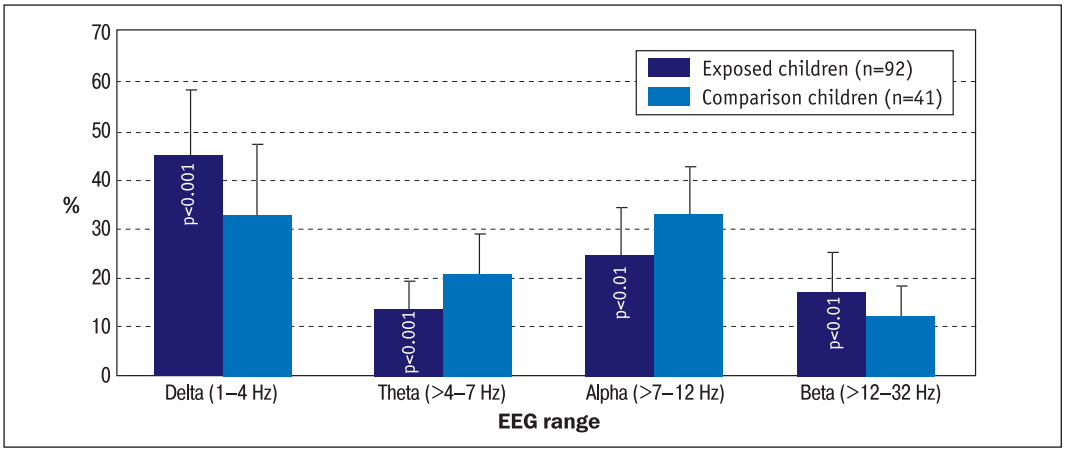


Figure 15.14. **Summarized relative spectral power of brain electrical activity in children without severe to very severe confounding factors at age 10–13 years [245]**

inversion of information processing were revealed in the exposed children. Maternal mental health deterioration, stress, prenatal irradiation and routine risk factors are the sources of those effects. The received results should be considered within of a current concern hypothesis on schizophrenia as a cerebral development disorder [44, 245].

Series of recent publications in radioneuroembryology field proves the hypothesis of a possible association of prenatal exposure and excessive schizophrenia risk in a further life. Schizophrenia is considered the neurodegenerative disease with possible brain development disorder [246–251]. Such experimental data have already received the clinic-epidemiological acknowledgement through inter alia schizophrenia risk increase after the prenatal diagnostic X-ray in the Jerusalem cohort [202, unpublished data].

Results of the Norwegian research are especially relevant for an unbiased understanding of the consequences of prenatal brain exposure after the Chornobyl disaster especially in the context of schizophrenia risk. The prenatally irradiated adolescents in Norway have the decreased indices of verbal operational memory, verbal learning and memory, information processing speed and executive function vs. non-exposed herd mates. It must be emphasized that study results of the Norwegian authors provide new and substantial support to our data on a selective damage to the dominant hemisphere after the prenatal exposure due to the Chornobyl accident [252–254].

The radiation damage of human embryo or fetus can therefore be presented with a cognitive deficit and other neuropsychiatric disorders. And these previously unrecognized neuropsychiatric effects can be stipulated by the relatively short-term effect of radioactive fallout levels of which previously had been considered safe [255]. The neuropsychiatric monitoring of people prenatally irradiated or exposed within first years of life after the Chornobyl disaster is surely required. These survivors remain under the risk excess of neuropsychic disorders including schizophrenia.

The developed diagnostic criteria of mental disorders as a result of prenatal irradiation after the nuclear reactor accident on the Chornobyl disaster model are as follows for children at age 10–12 years [238, 242]:

1. Irradiation *in utero* during the «iodine period» of a radiation accident at the nuclear reactor (within 1–2 months after the accident).

2. Clinically apparent mental disorders: Organic emotionally labile [asthenic] disorder (F06.6), Organic personality disorder (F07.0), psychological development disorders (Specific developmental disorders of speech and language, F80; Specific developmental disorders of scholastic skills, F81; Other disorders of psychological development, F88), Somatoform autonomic dysfunction (F45.3), children behavioral and emotional disorders (Hyperkinetic disorders, F90; Emotional disorders with onset specific to childhood, F93; Tic disorders, F95; Other behavioral and emotional disorders with onset usually occurring in childhood and adolescence, F98).

Neither severe mental retardation, nor microcephaly or severe epileptiform syndromes were revealed in a consequence of the prenatal irradiation after the Chornobyl disaster. The origination and development of such kind of neuropsychiatric disease after the prenatal exposure under similar radiological circumstances of a nuclear reactor accident should be considered in our opinion as improbable. The psychiatric effects of a prenatal cerebral irradiation after the nuclear reactor accident are possible if there are:

➢ embryo and fetal radiation doses exceeding 20 mSv and thyroid radiation doses *in utero* are over 300 mSv under the prenatal exposure after the gestation week 8;

➢ embryo and fetal radiation doses exceeding 10 mSv and thyroid radiation doses *in utero* are over 200 mSv under the prenatal exposure at the gestation week 16–25;

3. Cerebral abnormalities according to the data of an objective examination (psychometric, neurophysiologic etc.) of the brain. The specific cognitive and psychophysiologic presentations of the prenatal brain exposure in children after the nuclear reactor accident are:

➢ relative decrease of the verbal IQ vs. the non-verbal IQ;

➢ intellectual disharmony through the verbal IQ decrease vs. the non-verbal IQ for more than 25 points;

➢ low-voltage («flat») EEG (20-25 μV) with an excess of slow (delta-) and fast (beta-) activity as well as a depressed alpha- and theta-activity with paroxysmal activity lateralized to the left frontotemporal zone;

➢ epileptiform EEG type with «peak-» or «half-peak-wave» complexes in the frontotemporal zones especially of the left hemisphere, as well as bilateral oscillations of paroxysmal activity as delta-waves of a very high amplitude (> 100 μV);

➢ left-hemisphere dysfunction with lateralization of the slow and/or epileptiform activity to the left frontotemporal zone along with alpha-activity depression in the left hemisphere;

➢ cross-hemisphere dysfunction with an abnormal activity simultaneously in the frontotemporal zone of one hemisphere and the parietotemporal of another one;

➢ theta-power decrease and beta-power increase in the left frontotemporal zone;

➢ delta- and beta-range spectral power increase along with alpha- and theta-range power depression;

➢ abnormal vertex potential (the high-amplitude diphase potential in the Pz central parietal lead with a latency period (LP) P_{100} 42–152 ms, N_{145} 75–245 ms and P_{200} 115–302 ms) with the N145 component amplitude over 20 μV;

➢ LP elongation of all main components (P_{100}, N_{145}, P_{200}) of the visual evoked potentials (in response) to the chess(board) pattern reversion in the right occipital zone 02 along with the P_{100} LP component shortening and N_{145} component amplitude increase in the left occipital zone O1.

4. The specific cognitive and psychophysiologic presentations of the effects of prenatal brain irradiation in children after the nuclear reactor accident are indicative to the frontal and temporal brain zone function damage. At that there is a corticolimbic system dysfunction mainly in the dominant (left) hemisphere with an interhemispheric inversion of the maximum visual information processing from the non-dominant (right) hemisphere as it is normal to the dominant (left) hemisphere. The abnormal vertex potential at that is the sign of limbic system irritation and the neurophysiologic marker of paroxysmal disorders of epileptiform spectrum in children.

5. No pronounced routine risk factors (perinatal and postnatal complications, somatic disease, craniocerebral trauma, infection, and intoxication) that could affect the neuropsychic status of a child.

The course of mental disorders in prenatally exposed children is mainly of a development type with a gradual accumulation of psychopathological signs, unfavorable personality changes, character deformation and adaptation disorders with no psychic defect development. The most adequate diagnostics here is possible by means of application of the multiaxis classification systems.

Lifetime monitoring of potential neuropsychiatric effects in prenatally irradiated and exposed at the age 0–1 is continuing in the NRCRM. At the age of 23–25 years these exposed persons still have significantly more neuropsychiatric disorders (Figure 15.15) as paroxysmal disorders (G40, G43), including epilepsy and epileptic syndromes (G40), autonomic dysfunction and headache syndromes (G44, G90.9), dorsalgia (M54), neurotic and somatoform disorders (F40–F48). There is potentially higher risk of the neurodevelopment effects of exposure *in utero* as paroxysmal disorders (including epilepsy), organic mental disorders, demyelinating diseases of nervous system

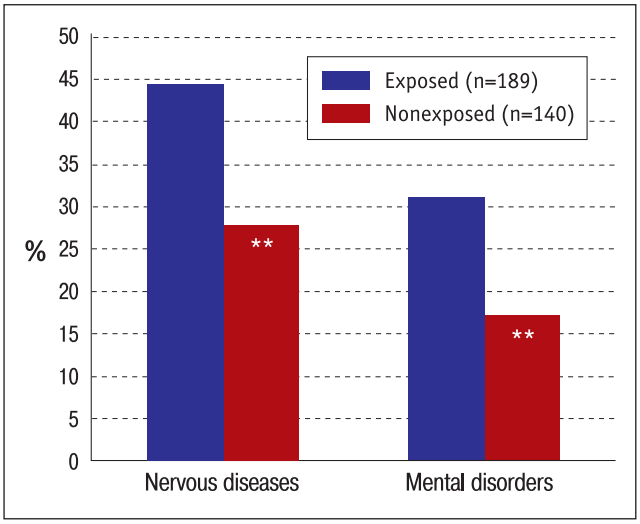


Figure 15.15. Frequency of neuropsychiatric disorders in prenatally and at 0–1 years exposed and non-exposed (at age of 23–25 years) [257]

and schizophrenia spectrum disorders. The specific neurocognitive deficit as verbal intelligence deterioration, left temporal lobe epilepsy, and left front-temporal cerebral lesions testified to the developmental disorders of the dominant (left) brain hemisphere. The microenvironment (family) of prenatally exposed persons provides a significant impact of their mental health. The atypical induced PTSD associated with the Chornobyl disaster was revealed in the prenatally exposed individuals, who born in Kyiv and had never been in the Chornobyl area. Moreover, *in utero* exposed persons have the more severe and increased rate of depression. (Loganovsky et al., 2011, 2013).

Cognitive features of prenatally exposed persons are IQ disharmony. Rate of abnormal electroencephalograms due to paroxysmal activity and interhemispheric asymmetry with changes in the left fronto-temporal region is increased. The risk factors of neurocognitive deficit in prenatally exposed individuals are as follows: residual-organic cerebral insufficiency; substance abuse; smoking experience more than 5 years; dose on embryo and fetus; thyroid dose *in utero*; gestational age at exposure. Reducing of $CD45^{+}4^{-}$ lymphocytes, $CD8^{+}4^{-}$, $CD3^{+}16^{-}56^{+}$ and increasing of $CD4^{+}25^{+}$, $CD4^{+}8^{+}$ cells in peripheral blood were associated with fetal dose (32.5–269 .2 mSv). Prenatal doses to the brain (0.001–101.56 mSv) correlated with intracellular p53 protein, increased expression of *TP53*, *TP53I3* genes and the level of CD95 lymphocytes, reducing the *BIRC5* gene expression, high frequency observations of telomerase *TERT* gene overexpression with positive dependence *BIRC5* expression and *VEGFA* genes. Such changes may lead to autoimmune processes, violations of anticancer and antiviral immune response. Thus, neurobiological mechanisms of brain damage due to exposure *in utero* and at the age of 0–1 years after the catastrophe, with the focus on violation of the dominant hemisphere of the brain, where the cortico-limbic system (hippocampus) is a target can include radiation-induced dysregulation of apoptosis, changes in gene expression profile, neuroinflammative reactions, autoimmune processes and changes of antiviral and antitumor immunity [54–57, 256, 257].

The Patent for Inventions of Ukraine №106419 (2014) «Method of retrospective differentiated designation of the human brain irradiation, which occurred in the early stages of developmental period» allow to distinguish exposure *in utero* and at the age of 0–1 years (at age of 23–25 years) by the discriminative neurobiological models (Figure 15.16). The invention relates to medicine, in particular to a method of retrospective differential determination of human brain irradiation at early stages of development which involves neuropsychiatric and molecular biological study, wherein degree of cognitive and affective disorders, intellectual consistency, parameters of brain electrical activity, gene expression and peripheral blood apoptosis indices are determined in patient, index of irradiation probability at early stages of brain development

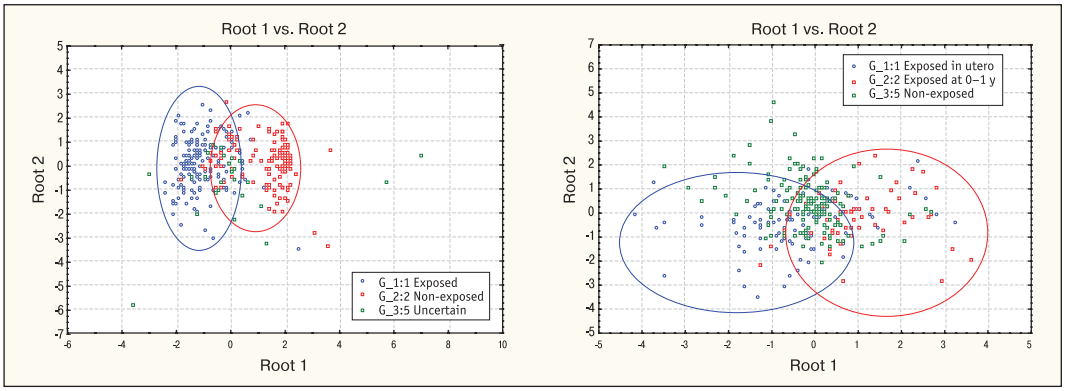


Figure 15.16. Differentiation (p<0.001) of exposure in utero and at the age of 0–1 years (at age of 23–25 years) by the discriminative neurobiological models [258]

is calculated. Then upon the determination of the fact of irradiation at early stages of brain development the differentiation of period of ionizing radiation effect is performed (prenatal period or at the age of 0–1 year).

The Chornobyl accident survivors exposed in utero and at 0–1 years are the unique cohort for the study of the neurodevelopment effects of low doses of ionizing radiation. These individuals must be under life span follow up at the frame of co-operative international studies

15.2.7. Object «Shelter»

Mental health protection of personnel and psychophysiologic service of work are the key issues development type with a gradual accumulation of psychopathological signs, unfavorable personality changes, character deformation and adaptation disorders with no psychic defect development within medical support of the Object «Shelter» of Chornobyl NPP transformation into the environmentally safe system [259–265]. Impact of radiation and harmful common industrial factors both with labor under the high psychoemotional strain do shape the unusual working environment of the Unit's personnel. Especial radiation danger from the scope of potential neuropsychiatric effects comes from the impact of uranium and transuranian elements (plutonium, americium). According to the data of uranium neurotoxicity the similar toxicity of transuranian elements is supposed. Cerebral electric activity abnormalities being basic for possible neuropsychiatric disorders were revealed under the neurophysiologic examination of personnel involved in work at the Object «Shelter». Low and very low doses of ionizing radiation, uranium neurotoxicity, stress and other industrial hazards are possible risk factors here. Study of biological effects of uranium and transuranian elements is an urgent radiobiology, radiation hygiene and radiation neuropsychiatry problem. Therefore the wide-scale interdisciplinary studies are required in this field. The Object «Shelter» transformation into the environmentally safe system provides a unique chance to explore the radiotoxic effects of uranium and transuranian elements on human [266–269].

Studies of cerebral information processes with application of the most perfect techniques of spontaneous and evoked bioelectrical activity analysis are the perspective approach of radiocerebral effects identification and of new tools elaboration of radiation exposure bioindication in human. Quantitative electroencephalography (qEEG) is the available and non-invasive method of screening and selection of persons not exposed, exposed, and overexposed to radia-

tion under occupational contact to the sources of ionizing radiation, after radiation accidents and radiation terrorist attacks. The works on the Object «Shelter» transformation into the environmentally safe system just provide the unique possibility to accomplish such a task [270–272].

In the period 2004–2008 there were 196 male workers aged 20–52 (35,9±8,2) years prospectively surveyed (before the initiation and after the dismissal from work) under the «BIOMED» program and the International Project «Chornobyl Research Service Project (CRSP) / International Consortium on Applied Radiation Research (ICARR)». External radiation doses for the work period from 1 to 4 years were 0–69.9 (20.4 ± 13.7) mSv, doses of internal irradiation were 0–2.4 (0.4 ± 0.5) mSv, and total radiation doses were 0–70.6 (19.4 ± 13.9) mSv [156, 157, 273–275].

Diseases of the nervous system, mental and behavioral disorders according to the ICD-10 before and after the work at the Object «Shelter» are shown in Table 15.4.

It is clear from the table that there was an increase of mental and behavioral disorders mainly due to the mild cognitive disorders and an elevated incidence of abnormal EEGs was registered after the work at «Shelter» Unit. This fact in general can be regarded as an onset of cognitive variant of the chronic fatigue syndrome after the impact of factors complex of work [156, 157]. Presence of cognitive disorder, namely of verbal learning deterioration after the work was verified with Rey Auditory Vernal Learning Test (RAVLT) (Figure 15.17).

According to the clinical assay of EEG data the decrease of organized EEG type (organized alpha-activity is the main component) and the increase of disorganized EEG type were found at the dismissal («output») control (Table 15.5).

The disorganized type was there of two principal variants. The first one was peculiar with disorganized high-amplitude alpha-activity prevalence being dominant in all cerebral zones, amplified amplitude of beta-activity, diffuse theta- and delta-activity of high enough amplitude in combination with bilateral paroxysmal activity. The second one featured theta- and delta-activity prevalence, weak expression of alpha-activity at the background of dysrhythmic irregular EEG of high or average amplitude.

Due to the qEEG application the substantial abnormalities of spectral content and dominant frequency of cerebral electric activity were revealed after work at the Object «Shelter» (Table 15.6

Table 15.4
Neurological, mental and behavioral disorders

Diagnosis	Before the work (n=196)	χ^2	p	After the work (n=196)
Diseases of the nervous system				
No diseases found	101 (51.5%)	0.37	> 0.05	95 (48.5%)
Disorder of autonomic nervous system, unspecified, G90.9	10 (5.1%)	0.5	> 0.05	7 (3.6%)
Osteochondrosis of spine, M42	3 (1.5%)	–	> 0.05	3 (1.5%)
Cerebral ischemia (chronic) I67.8	79 (40.3%)	–	> 0.05	88 (44.4%)
Sequale of injuries of head, T90.0	3 (1.5%)	–	> 0.05	3 (1.5%)
Mental and behavioral disorders				
No diseases found	155 (79%)	8.64	< 0.01	129 (65.8%)
Organic emotionally labile (asthenic) disorder, F06.6	21 (10.7%)	0.23	> 0.05	24 (12.2%)
Mild cognitive disorder, F06.7	7 (3.6%)	8.38	< 0.01	22 (11.2%)
Somatoform autonomic dysfunction, F45.3	2 (1%)	–	> 0.05	2 (1%)
Neurasthenia, F48.0	8 (4%)	–	> 0.05	6 (3%)
Function studies of central nervous system				
Abnormal EEG (convulsive readiness), R94.0	0	-	< 0,05	10 (5.1%)

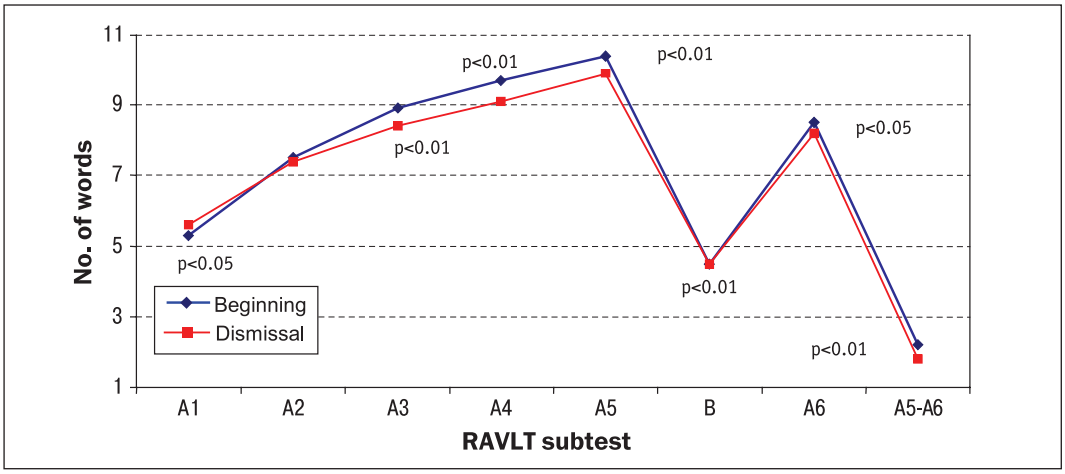


Figure 15.17. Verbal learning deterioration after the work at the Object «Shelter»

Table 15.5
Neurological, mental and behavioral disorders

EEG-syndrome	Before the work (n=196)	χ^2	p	After the work (n=196)
Organized EEG type	38 (19%)	9.33	<0.01	17 (9%)
Hypersynchronous EEG type	63 (32%)	0.43	>0.05	57 (29%)
Disorganized EEG type	25 (13%)	5.20	<0.05	42 (21%)
Plane polymorphous EEG type	70 (36%)	0.06	>0.05	80 (41%)

and Figure 15.18). Thus, there was an increase in relative and absolute spectral power of delta band mainly in frontal-temporal zones of the left (dominant) hemisphere after the dismissal from work. At that the absolute theta-power increased also however in parallel with somewhat lowering of theta band power in the right temporal zone, the absolute and relative alpha-power increased, the relative beta-power decreased with absolute beta-power augmentation, and dominant frequency decreased in the left temporal zone.

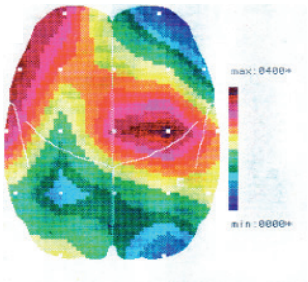
The revealed qEEG abnormalities indicate to dysfunction of the cortical-limbic system mainly at frontal-temporal zone of the left (dominant) hemisphere with substantial hippocampal involvement. Onset of cognitive disorders (cognitive variant of chronic fatigue syndrome, CFS) after the dismissal from work is possible due to reduced hippocampal neurogenesis resulted from low and very low radiation doses impact, uranium and transuranian elements neurotoxicity, stress etc. Discovery of neuroimmune and molecular biology pathways of those effects is one of the most urgent challenges in contemporary radiobiology and neuroscience [156, 157, 275].

The analysis of topographic charting spectral power and dominant frequency of brain activity after working at the Shelter showed the following changes: 1) increase in relative and absolute spectral power delta-activity, mainly in the anterior brain (frontal-temporal area), 2) reduction of relative θ-power in the right temporal area with increasing absolute theta-power mainly in the anterior brain, 3) an increase in absolute and relative alpha-power, especially in the temporal areas of the redistribution of alpha-activity to the front of the brain, 4) reduction of the relative beta-power in the right temporal area with an absolute increase beta-power in the anterior brain, and 5) reduction of the dominant frequency in the left temporal area . In general, changes

in brain activity after working at the Shelter can be interpreted as a damage of the cortico-limbic system with a key involvement of the hippocampus (Figure 15.18) [276, 277].

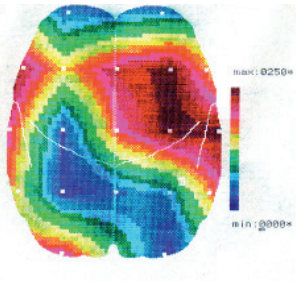
Table 15.6
Evolution of qEEG parameters

Parameters and leads	Beginning (entry) control (M ± SD)	*t*-paired	p	Dismissal (output) control (M±SD)
Relative delta power, %				
F7	20.78 ± 4.65	-2.49	< 0.05	21.81 ±5.46
T3	19.64 ± 4.59	-2.02	< 0.05	20.38 ± 4.82
T5	18.54 ± 4.35	-2.83	< 0.05	19.47 ± 4.97
Relative theta power, %				
T4	26.11 ± 3.63	2.67	< 0.05	25.37 ± 3.56
Relative alpha power, %				
T4	33.07 ± 6.43	-3.59	< 0.05	34.60 ± 7.30
T5	36.92 ± 8.43	2.23	< 0.05	35.83 ± 7.84
Relative beta power, %				
C4	19.64 ± 4.63	2.96	< 0.05	18.82 ± 4.35
T6	19.08 ± 4.34	2.42	< 0.05	18.42 ± 4.43
Absolute alpha power, $\mu V^2 \times Hz^{-1}$				
Fp1	10.58 ± 3.66	-3.54	< 0.05	11.79 ± 4.27
F3	8.01 ± 2.75	-2.79	< 0.05	8.69 ± 3.10
F4	8.13 ± 2.88	-2.21	< 0.05	8.69 ± 3.05
F7	8.08 ± 2.64	-4.67	< 0.05	9.23 ± 3.44
T3	6.26 ± 1.75	-3.56	< 0.05	6.92 ± 2.48
T4	6.95 ± 2.25	-2.59	< 0.05	7.43 ± 2.45
C4	5.70 ± 1.99	-4.39	< 0.05	6.49 ± 2.27
T6	9.11 ± 4.08	-2.37	< 0.05	10.02 ± 4.21
P4	7.13 ± 2.61	-1.98	< 0.05	7.60 ± 3.03
O1	10.11 ± 4.01	-2.49	< 0.05	10.84 ± 4.57
Absolute theta power, $\mu V^2 \times Hz^{-1}$				
Fp1	11.14 ± 3.42	-3.15	< 0.05	11.98 ± 3.96
F4	9.54 ± 3.18	-3.16	< 0.05	10.37 ± 3.71
F7	9.43 ± 3.17	-2.88	< 0.05	10.15 ± 3.36
T3	7.79 ± 2.45	-2.00	< 0.05	8.20 ± 2.89
T4	8.30 ± 2.69	-3.29	< 0.05	9.03 ± 3.08
C4	7.20 ± 2.54	-3.57	< 0.05	7.98 ± 3.11
T6	11.46 ± 5.08	-2.01	< 0.05	12.35 ± 5.59
O1	12.85 ± 5.57	-2.08	< 0.05	13.56 ± 6.11
Absolute alpha power, $\mu V^2 \times Hz^{-1}$				
Fp1	18.37 ± 9.60	-2.05	< 0.05	19.81 ± 10.59
F4	15.61 ± 8.19	-2.29	< 0.05	16.87 ± 8.67
T4	11.80 ± 5.46	-5.26	< 0.01	14.02 ± 7.39
C4	11.80 ± 6.12	-3.53	< 0.05	13.40 ± 7.54
T6	21.03 ± 12.94	-2.02	< 0.05	23.08 ± 13.68
Absolute beta power, $\mu V^2 \times Hz^{-1}$				
Fp1	7.82 ± 2.67	-2.28	< 0.05	8.25 ± 2.70
T4	7.04 ± 2.85	-2.65	< 0.05	7.56 ± 2.71
C4	6.05 ± 2.67	-2.19	< 0.05	6.43 ± 2.65
Dominant frequency, Hz				
T5	8.35 ± 0.54	3.24	< 0.05	8.22 ± 0.55



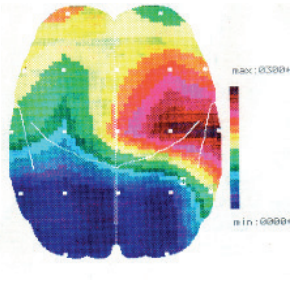
F1: 0354 Fz: 0250 C3: 0164 T5: 0191
T6: 0237 F2: 0000 F4: 0220 Cz: 0350
P3: 0105 O1: 0249 F7: 0466 F8: 0066
C4: 0438 Pz: 0150 O2: 0047 F3: 0279
T3: 0355 T4: 0259 P4: 0198

***t*-test increase in delta-absolute power**



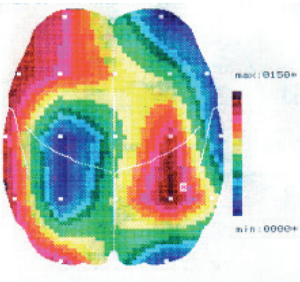
F1: 0035 Fz: 0225 C3: 0028 T5: 0168
T6: 0200 F2: 0051 F4: 0316 Cz: 0190
P3: 0019 O1: 0208 F7: 0288 F8: 0131
C4: 0357 Pz: 0045 O2: 0020 F3: 0155
T3: 0200 T4: 0329 P4: 0070

***t*-test increase in theta-absolute power**



F1: 0205 Fz: 0180 C3: 0087 T5: 0000
T6: 0202 F2: 0127 F4: 0228 Cz: 0220
P3: 0000 O1: 0005 F7: 0183 F8: 0188
C4: 0352 Pz: 0005 O2: 0000 F3: 0135
T3: 0141 T4: 0525 P4: 0011

***t*-test increase in alpha-absolute power**



F1: 0129 Fz: 0095 C3: 0003 T5: 0324
T6: 0067 F2: 0000 F4: 0070 Cz: 0065
P3: 0006 O1: 0129 F7: 0155 F8: 0000
C4: 0135 Pz: 0085 O2: 0003 F3: 0119
T3: 0133 T4: 0000 P4: 0180

***t*-test decrease in the dominant frequency**

Figure 15.18. **Brain Mapping of t-test on qEEG follow up before and after works in the Shelter «Object» [277]**

Workers on transformation of the Shelter «Object» of the ChNPP into an ecologically-safe system show qEEG abnormalities and cognitive dysfunctions. An increase of spectral delta-power in the left frontotemporal area, of theta- and alpha-power in the left temporal area, with redistribution of alpha-activity to the front and reduction of dominant frequency in the left temporal area, were registered. Further, neurocognitive tests revealed the presence of mild cognitive disorders after the works. Interestingly, those subjects previously exposed to radiation with no consequences, were more resistant to these detrimental effects. Taken together, the disturbances observed may be considered as cognitive symptoms of a chronic fatigue syndrome resulting from the exposure to ionizing radiation. Simple and non-invasive assessments, such as those performed by us, may be helpful to detect early brain changes caused by the presence of radiological risk factors. Personnel working at converting the Shelter into an environmentally safe system requires constant medical monitoring and rehabilitation [276, 277].

15.3. MENTAL HEALTH CARE AND PSYCHOSOCIAL REHABILITATION

The ICRP Publication 96 [278] states the mental health disorders as an important public problem in case of radiological attack using the dispersing (dispergating) radiation device (the «dirty bomb»). The WHO defines mental health not only as an absence of mental disorder but as a well-being when human can implement own potential, overcome routine life stresses, work fruitfully, and contribute to the life of own society. Impact of emergencies is a key risk factor of mental health disorders and origination of social problems [279]. Mental health care is one among other fields of healthcare response and management in radiological emergencies [280–282]. The integrity of somatic and mental health should be emphasized here stipulating the concept of social, biological, mental, and physical levels of life and adaptation of a human as of a biopsychosystem [283].

Issues of psychological-psychiatric and psychotherapeutic aid to survivors of the man-made accidents and disasters receive now rather serious relevance and actuality [284–286]. They recognize the necessity of general emergency/disaster psychiatric agency establishing within state emergency medical service. Accepting this standpoint in a whole it's worth mention the specificity of radiation impact and detrimental effect of its perception on mental health in society. Therefore there is an impelling need to establish the nationwide mental health service for the Chornobyl disaster survivors and potential sufferers of further possible radiation accidents and terrorist attacks [287, 288]. The mentioned service is to be based on the organizational principles and psychological/psychiatric aid providing algorithms integrating the best national and international experience and adjusted to local conditions, circumstances and possibilities.

According to WHO/MSD/MER/03/01 [279], general principles of mental health service in emergencies are as follows:

1. National Preparedness Planning before an emergency:
2. Estimation of population mental health and/or daily living detriment with urgent needs identification.
3. Coordinated and managed collaboration with governmental and non-governmental organizations.
4. Integration into the primary healthcare.
5. Accessibility of the psychological/psychiatric aid to all survivors without special services establishing for the specific population groups.
6. Training and supervision by mental health experts within a prolonged time period.
7. Primary right of the medium- and long-term strategy of social-psychological arrangements over the urgent and short-term aid.
8. Efficiency control.

Implementation of social and psychological/psychiatric arrangements is recommended. The strategic aim here is to update and improve the National system of mental health care with reinforcement of primary care and general services of hospital care both with strengthening the support to severe chronically mentally ill patients from family and surround.

Mental health care under the radiation emergency should be provided on the basis of IAEA-WHO/EPR-Medical approaches [280]. Knowledge about radiation and radiation effects do decrease the stress. If the stress factor is irremovable then efforts are to be focused on modification of its perception. Psychological reaction on radiation can be avoided, reduced or alleviated through the interventions before, during or after the radiation accident or radiological terrorist attack. In general the malicious act using radioactive substances will result in greatest psychological distress from all radiation emergencies.

The appropriate administrative officers at the National and local levels can apply adequate arrangements on psychological/psychiatric support. Those measures are to be planned at the preparation stage for radiation emergency.All the survivors (directly affected) and emergency/rescue personnel («liquidators») both with majority of population involved in radiation emergency require the psychological/psychiatric support.

The *psychological/psychiatric support at the preparation stage*. One should keep in mind that requirements at the preparation stage will meet no support both in population and in administrative officers. These requirements need effort application the necessity of what will not be obvious for most of those people. The named stage requirements are:

1. Launch and implementation of educational programs for the population.
2. Implementation of special educational programs for various categories of possible survivors.
3. Providing various categories of professionals (i.e. physicians, rescue staff, executive officers, healthcare managers, teachers, journalists) with educational tools and materials. Those professionals can be engaged in communication with population in emergencies aiming psychological stress reduction.
4. Avoiding violation of religious, cultural and social traditions under the emergency rescue activities. Help to both males and females should be provided. Providing of maximum privacy should be planned.
5. Informed persons having credibility are to be present in advisory/referral centers for communication with and calming of anxious survivors.
6. Strong avoidance of children separation from parents during the rescue activities. Clear understanding is required on extreme psychological damage to old people being relocated from their homes.

Psychological/psychiatric support during the radiation emergency. The wide-spread public anxiety about the severe radiation emergency may not correspond to radiation-induced health effects. It is especially relevant to the case of explosion of dispersing (dispergating) radiation device (the «dirty bomb»). The decision-making officers are to realize such issues under the emergency management, because public distress makes an impact on politicians, population health and healthcare staff.

Arrangements on minimization of the mental health disorders in an acute phase of emergency should include:

1. Issuing the simple and clear instructions on protective measures avoiding separation of families.
2. Guaranteeing the informed and having credibility leadership of healthcare service to provide psychological support during the emergency.
3. Foundation of advisory/referral centers at the evacuation routes.
4. Clear instructions and privacy/confidentiality guaranteeing during the decontamination of survivors.
5. Providing the specialized aid to patients already having mental disorders.
6. Foundation of medical advisory/referral centers for the pregnant survivors.
7. Honesty in communication and avoidance of conflict statements that can be disseminated by the mass media.
8. Persistent realization of the appropriate protective measures.

Upon an acute phase of emergency the following arrangements are to be applied:

9. Especial program implementation on social and psychological support providing aid to survivors. Most children do adapt in a rather good enough way if their parents do it first. Otherwise

in a case of parental dysadaptation the respective aid should be planned for kids. Mothers of young babies are subject to the long-term stress manifestations.

10. Long-term psychological support providing to the emergency/rescue personnel. Their family members can also require an aid. Some persons will be especially concerned by their health state and require the repeated health check-ups. Symptoms there can be despite presence or absence of signs of a specific disease. In disease absence the «health monitoring» should be recommended to them i.e. scheduled check-ups within national healthcare standards.

Psychological/psychiatric support to radiation emergency rescue personnel. The emergency/rescue activities are held under the stress conditions and circumstances. Rescue personnel («liquidators») will be necessitated to work despite deep anxiety and concern about the personal safety and safety of their families. Some mental health disorders especially the PTSD, substance abuse and depression can occur in liquidators that lose a grip on such a stress.

Arrangements on minimization of mental health disorders in emergency/rescue workers (liquidators) are to include:

1. Enough number of staff and teams planning to establish the rotating schedule. Adequate rest periods scheduling with their elongation availability.

2. Initial briefing with granting of protective gear and dosimeters use, description of mission tasks and purposes, possible dangers, radiation protection and contamination control procedures.

3. Briefings for rescue workers about the issues of emergency situation before each rotation shift and serially within its course. Liquidators should be kept in touch with their families.

4. Short briefing and initial aid under the new task setting to emergency worker (avoids stress related to indefiniteness of a new task).

5. Questioning after the emergency work with registration of the appeared psychological problems.

Psychological/psychiatric support in a radiological hospital. Survivors of a serious radiation emergency can face the series of problems stipulating stress and depression during the in-ward treatment. The in-ward stay can be rather long and require isolation from family and friends. Such patients are to undergo a lot of diagnostic procedures and privacy here can be violated. They can be afraid of death and changed own appearance. The survivors of radiation emergency may be afraid of sexual contacts and/or be concerned with having descendants. Pain syndrome, in its turn, can lead to analgetic drug abuse and require the prolonged respective rehabilitation. The healthcare staff is to listen-up the patient's complaints, discuss any problems with family members and provide honest replies with empathic concern on the patient.

Implementation of the described above arrangements will stipulate avoiding or minimization of an anxiety, fear, denial (unconscious protective response as a conflict situation and irritating event ignoring with purpose of anxiety and fear relief/abreaction), anger, depression, dependence etc. in survivors:

1. Providing the in-ward stay of a survivor in radiological hospital.

2. Assignment of a doctor that is in the confidence of the patient and his family.

3. Providing a patient with information on the emergency, results of his check-up and management.

4. Providing communication between patient and his family. Briefing the family about isolation procedures.

5. Persuading the family of exposed to external radiation patient regarding his safety for surrounding persons (i.e. his «non-contagiousness»).

6. Involvement of a patient himself (if possible) to decision-making in his health management.

7. Permission of self-care to a patient (if possible).

8. Providing the maximum privacy and confidentiality to a patient avoiding the mass-media contacts. Any of the lasts are to be available only by the survivor's permission [16, 17, 19, 289-291].

Principles of psychological/psychiatric aid to survivors in radiation emergencies and radiological terrorist attacks. Radiation accidents, radiological terrorist attacks both with nuclear conflicts and wars are quite different from natural disasters and wars with no mass destruction weapon use. The radiation emergencies entail the greatest mental response of people involved. Such emergencies have a beginning but have no end. They are rather unpredictable, whereas extent of detriment after them does not decline with time as environmental radioactive contamination can remain very long. Decontamination of radioactively polluted territories is not enough available and requires huge resources. The «non-therapeutic community» does appear in a society after the radiation emergencies and is characterized by proneness to conflict, negativism, dysadaptation reactions, behavioral disorders and annuity (pensionary) drives/sets [285]. The forward orientation of psychological stress (cancer and other diseases risk, congenital malformations in descendants etc.), duration of radioactive pollution, decontamination, evacuation and resettlement at the background of imperfect legislation in the field of social benefits to survivors shape the psychopathological response. That's why much more people will be involved to the radiation emergencies than were directly exposed (affected).

In virtue of the lessons of Chornobyl disaster and the experience of work on the Chornobyl NPP Object «Shelter» unit transformation into the environmentally safe system (as a «dirty bomb» model) the research/implementation essentials and organizational principles of psychological/psychiatric aid were developed for survivors of radiation emergencies and radiological terrorist attacks. Principal neuropsychiatric consequences of the Chornobyl disaster are: 1) psychological and psychosomatic disorders; 2) victimization; 3) necessity of radiological and social-psychological substantiation (i.e. feasibility evaluation) of resettlement; 4) effects on developing brain; 5) long-term mental health disorders; 6) suicides; 7) potential radiocerebral effects; 8) cerebrovascular diseases.

Research/implementation essentials of psychological/psychiatric aid for survivors of radiation emergencies and radiological terrorist attacks:

➢ neuropsychiatric approach;
➢ biopsychosocial paradigm;
➢ effective prophylaxis, social readaptation and rehabilitation.

Organizational principles of the psychological/psychiatric aid for survivors of radiation emergencies and radiological terrorist attacks [16, 17, 19, 285-291]:

1. Preparedness and planning.
2. Effective management based on flexible and coordinated structural-functional organization.
3. Adequate procurement.
4. Promptness, stringency and activity.
5. Availability to all population groups.
6. Continuous interaction and cooperation with radiological and dosimetric (biophysical) services.
7. Scientific substantiation, individualization and correspondence to the exact radiation emergency.
8. Effective interaction and cooperation with local authorities or government agencies, emergency reception center and administrations.
9. Control on mass media regarding the constructive curative-prophylactic presentation of information.

10. Avoiding panic and other socially negative consequences of radiation emergency and manipulation of survivors («mob-effect» prophylaxis in particular).

11. Teaching and supervision of the related/allied personnel.

12. Providing the maximum effective psychological/psychiatric aid.

Principal countermeasures towards mental health disorders in radiation accidents and radiologic terrorist attacks:

1. Operational (quick-prompt), consecutive and impartial informing of population about the radiation emergency;
2. Training of population about behavior in such situations;
3. Governmental preparedness to situation
4. Rational interventions
5. Psychological support
6. Social-economical superiority of «outlast» rather than being a «victim»
7. Constructive, professional and optimistic approach of the mass media
8. Psychoprophylaxis, psychorehabilitation and management
9. Social readaptation.

Implementation of the mentioned above is possible upon condition of the nationwide mental health care system establishing for survivors of radiation accidents and radiologic attacks [16, 17, 19, 285-291].

Approaches to optimization of curative-prophylactic and rehabilitation arrangements/measures

Basic principles of rehabilitation of survivors suffering neuropsychic disorders are:

a) unity/integration of biological and psychosocial interventions;

b) multi-vector nature of efforts with taking into account the variety of patient's life activity aspects and different fields of rehabilitation (psychological, social, family one, occupational);

c) appeal to the patient's personality and the «partnership» principle i.e. the patient's personality is to be involved in curative-renovation process with active participation in renewal of body functions an social intercourse;

d) stair-stepping principle (continuity/portability of interventions in healthcare institutions, day patient facilities and night ones, sanatorium and rest/recreation clinics).

Above-described approaches are implemented in the unique executive research-and-practice division – the Radiation Psychoneurology Department and Unit of the State Institution «National Research Center for Radiation Medicine of the NAMS of Ukraine» established in 2003 under the all-round support from NAMS of Ukraine and the Center administration. The division provides an integrated neurological, psychiatric and substance abuse relief aid to survivors, that has led to optimization of healthcare of survivors and has decreased the medico-social burden of the Chornobyl disaster aftermath.

Mental health care in survivors is to be in the focus of public attention under possible radiation accidents and radiological terrorist attacks in the future. National and international efforts are to be applied to enhance the mental health care and psychorehabilitation system for the Chornobyl disaster survivors. There is an international consensus about the Chornobyl disaster impact on mental health as a remaining top-priority issue within healthcare of survivors.

The following subgroups of survivors are to be authorized (i.e. legally established) for the life-long neuropsychiatric monitoring:

1) convalescents of the acute radiation sickness;
2) emergency/rescue personnel («liquidators»);
3) exposed to radiation in utero (in prenatal period);
4) exposed to radiation in childhood;

5) evacuees;
6) descendants of the exposed to radiation.

Risk excess of neuropsychiatric disorders can be expected from now onwards among persons exposed to radiation in utero, exposed in childhood, and in descendants of the exposed to radiation. Taking into account the prevalence and resistance of their mental health disorders the educational, psychosocial and healthcare interventions are required both with further research

Mental Health and Neuropsychiatric Effects of the Chornobyl Accident – a 30 years Aftermath and Fukushima Projections

There is an international consensus concerning severe long-term mental health adverse consequences of both Chornobyl and Fukushima accidents. These aftermaths were, are and will be the greatest medical and social burden to the society and public health.

There is also an international consensus concerning top mental/neuropsychiatric problems following the Chornobyl disaster:

1. Stress-related disorders (PTSD, depression, anxiety, somatoform and psychosomatic disorders, alcohol abuse) – full coherence, life-span studies recommend, psychological-psychiatric monitoring and care are strongly necessary;

2. Effects on the developing brain (cognitive impairment, emotional-behavioral disorders, attention deficit and hyperactive disorder (ADHD), neurodevelopment disorders) – discussion with contradictions, to be investigated further, life-span studies recommend interventions recommend if necessary;

3. Organic brain damage in liquidators (cerebrovascular pathology, neurocognitive deficit, demyelinating diseases of the nervous system, paroxysmal states etc.) – at issue, the further studies need; life-span studies recommend; constant neuropsychiatric monitoring and care are necessary;

Suicides – full coherence, further studies need and suicides prevention is strongly necessary.

Such mental health/neuropsychiatric problems as the Chronic Fatigue Syndrome, psychosis, stroke, multiple sclerosis, epilepsy, attention deficit and hyperactive disorder, etc. are still at issue. Further research is needed here. The biological mechanisms of cerebral effects due to the impact of low radiation doses are of great importance and are to be explored. All further studies should be conducted together with advanced biophysical (dosimetric) support on the base of analytical epidemiology.

Radiation exposure has multiple effects on the brain, behavior and cognitive functions. These changes depend largely on the radiation dose. The points of view on the genesis of the Chornobyl neuropsychiatric aftermath are extremely controversial. The cerebral effects of low doses of ionizing radiation, especially, cerebrovascular pathology and cognitive impairment are in the focus of research interest worldwide. An increasing pool of data supports the radiosensitivity of the CNS, mainly due to hippocampal neurogenesis. The cortical-limbic system is the target for radiation brain damage where hippocampal neurogenesis dysfunction is the crucial.

The psychological and neuropsychiatric lessons of Chornobyl are as follows: 1) information policy and risk communication issues; 2) stress-related disorders – radiation anxiety (NOT RADIOPHOBIA), panic reactions, depression, somatoform disorders, psychosomatic disorders, social disintegration, victimization, «learned helplessness», «pathological flight into illness», and disability at the inadequacy of social protection of Chornobyl survivors; 3) the necessity for radiological and socio-psychological justification of the resettlement of victims; 4) «postradiation» post-traumatic stress disorder (PTSD) with hypochondriac fixation to the

future (fear of premature death, cancer, congenital abnormalities in children, etc.); 5) disorders of the developing brain, particularly, at exposure during the prenatal period; 6) long-term mental disorders; 7) substance abuse (alcohol); 8) suicides; 9) cerebrovascular pathology; 10) radiocerebral effects of low doses of ionizing radiation.

There is a strong necessity to improve the system for neuropsychiatric care for the Chornobyl survivors. This system should include the crews/teams of intensive neuropsychiatric, emergency psychological and psychiatric care, networks of crisis and rehabilitation centers, neuropsychiatric outpatient and inpatient units in general hospitals.

It is necessary to organize a system of emergency and long-term psychological and neuropsychiatric care at radiation emergencies. The international joint studies on mental health and cerebral effects of the Chornobyl accident survivors exposed to the different radiological scenarios must be continued. At present these studies must be focused on neurocognitive deficit, emotional-behavioral and psychotic disorders with advanced biophysical (dosimetric) support on the base of analytical epidemiology (CO-CHER, Lyon, Loganovsky, 2015).

There are differences and community between Chornobyl and Fukushima. Without any doubts trio impact (earthquake, tsunami and Fukushima Daiichi NPP accident) resulted with dramatically greater psychological stress, than Chornobyl. At the same time, current dose estimations testify to the doses in Fukushima are significantly lower than that in Chornobyl. This demands verification.

What combines Chornobyl and Fukushima? There is the main unclaimed Fukushima psychological-psychiatric lesson of Chornobyl: equally inadequate information policy and risk communication: secrecy, untruthfulness, untimeliness, non-transparence, non-professionalism, contradictory, and politicization/commercialization. All together they are dramatically increasing stress, fear, anxiety and psychosomatic disorders, etc. Moreover, suicides, potential cerebrovascular pathology, cognitive deficit, neurodevelopment disorders, psychosis, and alcohol abuse should be monitoring

There is a strong necessity to develop and implement the system of emergency and long-term psychological and psychiatric care for the survivors of earthquake, tsunami, and radiation accidents in Fukushima. This system should include: emergency psychological and psychiatric crews, networks of crisis and rehabilitation centers, neuropsychiatric outpatient and inpatient units.

The further prospective studies on mental health and potential neuropsychiatric effects in Fukushima disasters clean-up workers and survivors with the radiation doses verification need.

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Chapter 16
EFFECTS OF IONIZING RADIATION ON THE BRAIN: EXPERIMENTAL STUDIES

16.1. EFFECT OF SMALL-DOSE RADIOACTIVE CESIUM INTERNAL RADIATION ON CENTRAL NERVOUS SYSTEM IN EXPERIMENT

The impact of ionizing radiation (IR) on a living body leads to considerable chemical impairments in cells, resulting in the development of various biologic effects. The extent to which these effects are pronounced depends, first of all, on the dose absorbed by the body tissues. High radiation doses received within a short time interval have been found to cause a major lesion to the living tissue [1–3]. An accident at the Chornobyl Nuclear Power Plant (ChNPP) was accompanied with a release of the great amount of radionuclides into the environment, leading to the radioactive contamination of the vast territories. In consequence, a problem has occurred associated with the penetration into human bodies of a great many of radionuclides, primarily in small doses, among which most important by today is ^{137}Cs – that is why its share in forming the dose absorbed in the contaminated «post-Chornobyl» territories is weightiest.

So, if the dose absorbed exceeds 1 Gy (in a single total exposure), a human develops the radiation disease. On exposure to medium doses there is observed the growth in the number of malignant neoplasms, cataract, nephrosclerosis, etc. The appearance and manifestation of biologic effects during the exposure to small doses of ionizing radiation has not yet been cleared up completely. In the literature prior to the Chornobyl period, there was a lack of data on this issue, and the data were somewhat controversial.

Some investigators are insisting on a harmful effect of IR in small doses on the body, while others, on the contrary speculating their stimulant nature [4, 5].

Interesting in this aspect is the theory by A.M. Kuzin (1990) [6] who put forward the notion of «radiation hormesis». Radiation hormesis is a favorable, in the author's opinion, biologic effect of small radiation doses that may be comparable by value to the Earth radiation background. He determined a small dose as a such one that caused to the improvement of the body condition, enhancement of the cell divisions and DNA synthesis, acceleration of the growth and development of whole flesh.

But the present world experience has proved the truth of the standpoint that «ionization is a destructive process and, most probably, is rather harmful than useful». U. Hagen et al. [7], sug-

gest 1 Gy to be consider as the upper limit of a small dose. Although this limit is substantially supersedes the limit admissible for professional radiation exposure (0.05 Sv/year), most of the authors share that particular viewpoint. Among the medical problems associated with ChNPP consequences for the central nervous system (CNS) diseases hold a specific place.

The appearing in the post-Chornobyl period of the great amount of people affected by small doses of radiation and having the symptoms of nervous-psychic disorders along with general somatic disorders, that did not fit the notion of an acute or chronic radiation disease, has brought to the forefront an urgent task to comprehensively study a small-dose radiation effect on CNS, both in experiments on animals and in people having suffered after the accident at ChNPP.

The studies of the recent years proved the CNS radiosensibility to radiation [1, 8, 9–14], and the CNS may be considered «a dose-limiting system in the clinical radiotherapy» [2]. A subchronic action of ^{137}Cs in the doses comparable to those resulted from ChNPP disaster, leads to molecular alterations of pro- and anti-inflammatory cytokins, NO-ergic pathways in the brain. The development of neuro-inflammatory reactions in the CNS during a small-dose radiation exposure leads to physiologic and chemical changes in the chronic action of ^{137}Cs [10, 11, 15–17].

Small doses of radiation cause changes in the expression of over 850 genes in the brain cells, that is 1.5 times more than in healthy animals. The first reaction is from the genes, responsible for the cellular cycle control, DNA reparation, stress, intra-neuronal intracellular signaling [18]. It is shown that the brain gene profile alterations after radiation exposure are complex and depend on the radiation time and dose. A dose of 0.1 Gy causes changes in the brain genes expression that differ qualitatively from those after 2.0 Gy [3, 18, 19]. Thus, a genome of the brain cells responds to the action of a small-dose radiation, thereby providing evidence of the complex physiologic, adaptive and pathologic alterations in the activity of different CNS compartments.

A small-dose radiation is shown to exert effect on neurogenesis in the hippocampus, on the stem nervous cells that are located in the hippocampal subgranular zone [20, 21]. The cognitive and memory disorders coincide with neurogenesis changes and inhibition of Ki-67 positive cells proliferation in the hippocampus [11, 22–24].

In the middle of 1950's , it was experimentally found that under the radiation exposure in a dose of 0.25Gy, the morphologic neuronal changes were seen, and a dose of 0.5Gy was considered as a threshold one that leads to the primary damage of the brain neurons [25–27]. Persistent alterations in the brain electric activity were observed also under radiation exposure of 0.3–1.0 Gy [20, 28, 29]. A small-dose radiation modifies the nervous signal transmission,thereby to the numerous manifestations of the clinical cerebral activity and changes in the behavioral reaction and cognitive functions [14, 28, 30, 31]. In the numerous literature before and after the Chornobyl, there exist minimum two controversial viewpoints as to the radiation effects on the CNS, its resistance and sensitivity to small doses of radiation [2, 4, 11, 13, 21, 28, 32–34].

These opposite viewpoints on the effect of radiation on the CNS, especially in the early period after the accident at ChNPP, and the lack of unity in their interpretation may have been the reason of erroneous or not sufficiently right solutions of not only the medical problems, but also the politico-social-measures in relation to the liquidators and persons living in the contaminated areas.

All this dictated the necessity to urgently carry out experimental studies on the laboratory animals and to investigate the effect of a small-dose radiation, in order to specify the mechanism of radiation action and determine the degree of the nervous system sensitivity to radiation. Such studies were performed in the Institute of Neurosurgery over 1988–1998 years, as reflected in three monographs and a great number of publications.

At present, 30 years following the accident at ChNPP, this problem still remains to be a red hot issue and requires new interpretation of the results obtained as well as contemporary explanations and comparisons with clinical observations made among the liquidators and persons, residing on the territories contaminated with radionuclides.

The purpose of the study was to elucidate a long-term effect of a small-dose radioactive ^{137}Cs radiation on metabolism of the nervous system cells and morphostructural organization of different brain regions in experiment.

* * *

According to regulatory documents, maximum allowable level of emitters in the basic human body deposits (body weight 70 kg) is for ^{137}Cs as high as 1221 kBq (RSN 76/87) or 1100 kBq (ICRP). If ^{137}Cs content in the human body comes to 1.2×10^6 Bq the dose absorbed will amount 0.05Gr/year. At the stage of experimental planning, both the dose of ^{137}Cs-chloride and the ways of its delivery to the body were selected. Taking into account a substantial difference in the life span of humans and experimental animals, kinetics of the cellular populations renewal, metabolic rate, reduction and reparation reactions, as well as sensitivity to IR effect [11, pp. 225–77], we selected activity of 600 Bq (for the white rats, daily during months 1, 3, 6 and 9).

A dose of 600Bq converted into the rat body weight exceeds by approximately 10 times the maximum allowable amount of ^{137}Cs in the food products and water if used daily according to the radiation safety norms, i.e. an equivalent amount of radionuclide may enter the human body with food products, water and dust, if he/she lives and works in the area of radioactive contamination. At that, a maximum allowable content of isotope ^{137}Cs in the human body, equaling as indicated above, to 1221 kBq per 70 kg of the body weight, or 3486 Bq per 200 g of the body weight, totally corresponds with our data obtained in the previous experiment. It was established that in 1 month after daily administration to animals of ^{137}Cs in a dose of 600 Bq its content in the rat body weighing 150–170 g amounted to (3314 ± 185) Bq.

To study the effect of ^{137}Cs routes of administration and accumulation in the white rat body, the animals from group 1 during 1 month were fed with the above mentioned amount of ^{137}Cs-chloride together with food, and that does not injure the animals at all and does not cause stresses, this being very important when investigating the nervous system.

Throughout the whole experiment the animals were in the same premise. The air temperature and humidity therein were kept at the same level. Each animal had its number and mark. The vivarium dietary included granulated mixed fodder, cereal, meat, cheese, bread and vegetables. It did not change during the whole experiment.

During the 1st month of experiment, radiometry of each animal was performed 2 times a week, during the 2nd and 3rd months – 1 time a week and further on – 1 time per 2 weeks.

In months 1, 3, 6 and 9 the animals were sacrificed via decapitation. After a 6-month daily administration of isotope a part of animals continued to be fed with the same dose, while other animals did not receive ^{137}Cs: under study in this group were the processes of isotope incorporation and the availability of repair processes in the nervous system and other organs and systems.

Control group included of intact animals of the same age. The second control group consisted of the animals receiving the same amount of nonradioactive cesium as that in the experiment. Such a control is necessary to exclude the impact of cesium microelement on the nervous system structure and function, as well as other organs and systems.

Calculation of isotope accumulation in the body and organs was made on radiometer Ortex (USA).

* * *

When studying the activity of free radical peroxidation reactions we used:
1. Determination of the brain content of malondialdehyde (MDA) – one of the end products of lipid peroxidation (LPO), MDA was determined by reaction with thiobarbituric acid (TBA) according to the TBA-active products.
2. The method to determine peroxidation resistance of erythrocytes was based on determining the percentage of erythrocytes hemolyzed under the action of standard hydrogen peroxide solution. The extent of hemolysis depends on antioxidant (AO) protection of erythrocytic membranes against peroxides. This indicator characterizes the body oxidation resistance [10, 11].
3. Determination of the content of endogenous peroxides in the brain tissue than gives an integral estimation to the amount of free radial peroxidation products in the tissue under study [10].
4. Determination of Schiff bases (LPO end products). After extraction from the brain by chloroform-methanol mixture, they were determined by the intensity of their fluorescence in the chloroform aliquot (λ-arousal 360–379 nM, λ-fluorescence 420–440 nM).
5. Activity of the blood plasma spontaneous chemiluminescence (SCL), the blood plasma chemiluminescence induced by hydrogen peroxide (ICL) and the homogenate supernatant was determined by somewhat modified method [10].
6. The method to determine triboluminescence of the blood serum and the whole blood [10].
7. The condition of physiologic antioxidant system (PAOS) was evaluated by the parameters of glutathione protective system: content of the reduced glutathione, activity of glutathione reductase and glutathione peroxidase [35].

* * *

The content of catecholamines was determined by the method of high-performance liquid chromatography on a microcolumn chromatograph «Muillichrom» [36].

Gamma-aminobutyric acid (GABA) content was determined by the method of spectrophotometry [37], based on the formation of high-fluorescent product when interacting with orthophthalic aldehyde and β-mercaptoethanol at high pH. GABA was extracted similarly to catecholamines, the extract pH was brought to 3 using 5N K_2CO_3. The frozen extract was stored at -20 °C for a few days.

* * *

Functional condition of the animals' CNS was evaluated by the indicators of behavioral shifts. Spontaneous behavioral reactions in animals were studied in the «open field» installation, inhibitory conditioned reflex reactions – by the «passive avoidance» test [38]. With regard for a considerable difference in the animals' behavior, all animals were divided into 4 groups: group 1 – males, group 2 – females with high locomotor activity (HLA), group 3 – males, group 4 – females with low locomotor activity (LLA).

To process the study results statistically, the Student's and Fischer's test was used.

* * *

The results of experiments give evidence that the dose selected does not lead to animals' death. The body weight of all animals, receiving and not receiving ^{137}Cs, grew permanently. At that, there were no probable differences between the study and control animals. Dosimetry data are presented in Table 16.1.

The results obtained give evidence that till day 50th of the observations the body reactivity of the white rats was increasingly growing up, and at day 50th it amounted for 3752.75±1076.1 Bq. From day 50th to day 84th of the experiment we observed the first plateau at the level of approximately 3700 Bq. From day 90 we noted the decrease in ^{137}Cs specific body weight of the animals to 2800 Bq, and the second plateau remained to exist till day 195 of the experiment.

Table 16.1
Body radioactivity in the white rats

Day of observation	Mean radioactivity, Bq	Standard error
3rd	378.24	255.26
7th	1169.84	588.82
30th	2728.87	881.07
65th	3741.55	997.28
90th	3112.72	1054.64
127th	2415.87	682.59
160th	2565,20	796.53
195th	2794.45	795.53
219th	4131.59	1125.16
262th	5067.56	1341.00
309th	3991.75	1343.74

After 210 days of observations and up to the end of a 9-month term, the content of ^{137}Cs began growing up again, remaining to be at the level of 4600 Bq. Such peculiarities of isotope ^{137}Cs accumulation in the body of animals may be due to the two reasons.

Firstly, they may be a consequence of the effect exerted on this process by biorhythms, since the decrease in ^{137}Cs content coincides with the increase in the day length, and the increase with its decrease. The content of ^{137}Cs in the body of rats started to reduce in March, and to increase – in July-August.

Secondly, the decrease in ^{137}Cs accumulation may be associated with the increase in the compensatory and detoxication possibilities of the body, and vice versa, the increase of this indicator may be a consequence of attenuation of these processes.

There exist several ways to calculate the dose absorbed from incorporated radionuclides. We selected the procedure that, in our opinion, is the most precise because it takes into account the two-component radionuclide elimination. The data obtained are presented in Table 16.2.

Thus, the dose absorbed was growing continuously and came to 3.0 rem/per animal on the average, upon completion of a 9th-month of experiment.

The experiment gives evidence that small doses of ^{137}Cs are accumulated in the body of the white rats with certain regularity. There exist individual specific features of isotope accumulation by some individual animals.

To evaluate the value of depositing, the activity (Bq) of radionuclide was studied during the experiment in the organs and tissues, which characterizes the specific activity of an organ weight part.

Table 16.2
The amount of ^{137}Cs in the body of rats and the dose absorbed in the different terms of experiment

Terms of experiment, day	Mean animal body weight, g	Mean amount of radionuclides in the body of animal, Bq	Dose absorbed, Gy
30th	150 ± 20	2728.87 ± 881,07	0.01 ± 0.00
90th	250 ± 25	3112.72 ± 1054.64	0.01 ± 0.01
180th	300 ± 25	2531.82 ± 908.81	0.02 ± 0.01
270th	320 ± 30	5067.56 ± 1341.00	0.03 ± 0.02

We identified the content of ^{137}Cs in the blood, liver, kidneys, spleen, femoral muscles, cardiac muscle, femoral bone, stomach, small intestine, brain, in different terms after the beginning of isotope incorporation. The main attention was paid to studying radionuclide activity in the different brain regions (cortex, cerebellum, medulla, mesencephalon, hypothalamus, hemispheres).

When investigating the amount of isotope in the organs and tissues of rats in 1st month after daily incorporation it was established that maximum indicators were noted in the skeletal muscles, where the levels of accumulation accounted for (27.4 ± 2.7) Bq/g, whereas in the parenchymatous organs (liver, kidneys, spleen) they were largely lower and amounted, respectively, to (11.7 ± 1.5), (15.7 ± 1.8) and (8.2 ± 0.7) Bq/g. In this period, the organs and tissues might be arranged by the amount of isotope ^{137}Cs in the following sequence: femoral muscle > kidney> stomach > small intestine > liver > cardiac muscle > mesencephalon > spleen > medulla > femoral bone > blood > cortex > cerebellum > cerebral hemispheres > hypothalamus. The relevant mean values of isotope amount (Bq/g) were accounted for: 27.4 > 15.7 > 14.3 > 12.8 > 11.7 > 11.5 > 9.5 > 8.2 > 8.2 >3 > 6.3 > 6.3 > 5.9 > 5.2 > 3.9. These data give evidence that by the content of 137Cs organs and tissues may be conditionally divided into three groups: with relatively high (27.4 Bq/g), medium (11.5–15.7 Bq/g) and low activity (3.9–9.5 Bq/g).

In all brain structures the content of ^{137}Cs was by 3–3.5 times smaller than in the skeletal muscles and by 1.5–2 times smaller than in the parenchymal organs. The content of ^{137}Cs in the brain was almost similar to analogous indicators for the blood (Table 16.3). The difference in indicators for the brain and blood in 6 months following the experiment is more than likely due to the seasonal fluctuations of ^{137}Cs content and its more rapid elimination from the blood than from the brain structures.

Table 16.3
Changes in ^{137}Cs content in the brain structures and blood of the white rats in a chronic experiment

Structures under study	Specific radioactivity of tissues depending on the term of experiment, Bq/g			
	1 month	3 months	6 months	9 months
Medulla	9.5 ± 0.3	7.4 ± 0.2	6.5 ± 0.1	5.3 ± 0.1
Mesencephalon	8.2 ± 0.2	6.9 ± 0.2	8.1 ± 0.2	6.0 ± 0.1
Cortex	6.3 ± 0.1	7.2 ± 0.2	4.6 ± 0.1	1.2 ± 0.0
Hypothalamus	3.9 ± 0.0	6.2 ± 0.1	2.0 ± 0.0	6.0 ± 0.1
Cerebral hemispheres	5.2 ± 0.1	6.9 ± 0.1	4.2 ± 0.1	8.0 ± 0.2
Cerebellum	5.9 ± 0.1	5.2 ± 0.1	3.8 ± 0.1	5.5 ± 0.1
Blood	6.3 ± 0.2	6.0 ± 0.1	1.5 ± 0.0	3.9 ± 0.1

Thus, when studying the content of ^{137}Cs in the innards, tissues and brain structures of the white rats during a 9-month chronic experiment we noted changes in its distribution, accumulation and elimination from different organs, tissues and structures. It is necessary to note one peculiarity: the content of cesium in the blood after the third month decreased and practically did not change in the brain, while in the hemispheres and hypothalamus we observed its further accumulation. This «dissociation» of radionuclide content points on the activation of certain compensatory reactions and adaptation of animals to the effect of a small-dose radiation. Investigations into the biochemical indicators of the blood and brain confirm such assumptions to a certain extent.

* * *

Studies of LPO dynamics under the internal radiation of rats with radionuclide ^{137}Cs showed the following.

From the results presented in Tables 16.4 and 16.5 it is seen that accumulation in the body of animals of radionuclide ^{137}Cs during months 1, 3, 6 and 9 brings about a substantial growth of LPO activity practically in all terms of experiment.

In the blood (see Table 16.4) the level of TBA-active products significantly exceeded control values by 34% in 30 days, by 22% – in 3 and 6 months, by 40% – in 9 months. In the brain (see Table 16.5) within the same term, the increment of TBA-active products accounted for 24, 37, 43 and 52%, and endogenous peroxides – 31, 35, 64 and 82%, respectively. The level of Schiff bases was especially high in at the end of the 1st month of radionuclide priming. It came to 234% of the control value. In 3 months this indicator was substantially lower than the initial one and in 6 months – exceeded the control values again. The studies carried out in 9 months of radionuclide priming, as well as in the case of a 6-month priming and further drug discontinuation, gave evidence of a substantial inhibition of Schiff bases accumulation in the brain: by 29% in the first instance and by 16% in the second. Those changes were accompanied with a notable decrease of the body antioxidant resistance. In all terms after ^{137}Cs incorporation to rats the level of erythrocytic hemolysis largely exceeded the control indicators. The body antioxidant resistance also reduced essentially after ^{137}Cs discontinuation.

Thus, feeding of ^{137}Cs to animals led to LPO activation in the body of rats. The most pronounced changes in the blood were revealed after months 1 and 9 of the experiment. In the brain, the activity of free radical peroxidation was also high, and after months 3, 6 and 9 it considerably exceeded that observed in the blood. Along with this, the effect of LPO activation was a longstanding. It persisted even after a 3-monts discontinuation of the drug.

Table 16.4

Effect of daily parenteral administration of radionuclide ^{137}Cs on LPO activity in the rat blood (M ± m, n = 5)

Priming term	Malondialdehyde μM/ml of the blood plasma	Peroxide resistance, % of destroyed erythrocytes	Blood ICL imp/s
Control	1.30 ± 0.03	32.30 ± 2.10	1842 ± 34
30 days	1.74 ± 0.10*	54.24 ± 2.40*	–
%	134	165	
Control	1.74 ± 0.02	7.52 ± 0.27	1842 ± 34
3 months	2.11 ± 0.11*	54.24 ± 2.40*	5009 ± 403*
%	121	165	271
Control	1.42 ± 0.01	15.02 ± 0.63	1842 ± 34
6 months	1.75 ± 0.04*	35.30 ± 1.52*	–
%	123	234	
Control	1.65 ± 0.15	31.60 ± 2.37	1842 ± 34
9 months	2.32 ± 0.20*	64.20 ± 8.90*	4860 ± I88*
%	140	203	263
Control	1.65 ± 0.15	31.60 ± 2.37	1842 ± 34
6 + 3 months without priming	2.34 ± 0.13*	47.70 ± 3.70*	4330 ± 103*
%	141	151	235
Control	1.46 ± 0.03	10.10 ± 0.50	1842 ± 34
3 months (stable cesium)	1.63 ± 0.06*	15.80 ± 1.27*	2727 ± 57*
%	111	156	148

Notes. * – the result significantly differs from the control values ($p < 0.05$; here and in the next tables).

Table 16.5
Effect of daily parenteral administration of radionuclide ^{137}Cs on LPO activity in the rat brain (M ± m, n=5)

Priming term	Malondialdehyde μM/ml of the blood plasma	Endogenous peroxides, % of destroyed RBC	ICL imp/s	Schiff bases, c.u. of fluorescence
Control	5.36 ± 0.17	13.07 ± 0.80	422 ± 36	11.80 ± 1.01
30 days	6.65 ± 0.18*	17.16 ± 0.12*	–	27.60 ± 2.80*
%	124	131		234
Control	4.50 ± 0.12	9.78 ± 0.19	422 ± 36	57.01 ± 3.70
3 months	6.20 ± 0.24*	13.20 ± 0.64*	705 ± 38*	42.60 ± 2.60*
%	137	135	167	74
Control	3.24 ± 0.15	5.52 ± 0.15	422 ± 36	32.00 ± 1.40
6 months	4.66 ± 0.17*	9.10 ± 1.00*	–	36.60 ± 1.60*
%	143	164		114
Control	2.75 ± 0.06	7.10 ± 0.17	422 ± 36	38.01 ± 2.30
9 months	4.18 ± 0.10*	12.96 ± 0.76*	691 ± 88*	27.00 ± 1.10*
%	152	182	163	71
Control	2.75 ± 0.06	7.10 ± 0.17	422 ± 36	38.00 ± 2.30
6 + 3 months without priming	3.43 ± 0.12*	9.26 ± 0.24*	531 ± 28*	32.10 ± 2.80*
%	126	130	126	84
Control	4.50 ± 0.19	9.78 ± 0.30	422 ± 36	27.60 ± 1.40
3 months (stable cesium)	5.80 ± 0.04*	11.60 ± 0.19*	573 ± 81*	28.01 ± 1.70*
%	129	119	136	101

Notes. * – the result significantly differs from the control values ($p < 0.05$; here and in the next tables).

Summarizing the results of these studies, one cannot pass over one more specific feature of the regularities revealed by us and conditioned by the body loading with a stable Cs isotope. As seen from the results presented, here again we observed a significant activation of the process of peroxidation – the level of TBA-active products by the blood and brain of the rats receiving ^{137}Cs, grew by 11 and 29%, respectively, the content of endogenous peroxides in the brain increase by 19% and erythrocyte peroxide resistance reduced by 56%.

That is, a long-term loading of rats with nonradioactive cesium salt also all by itself increased LLO activity in the body as a whole and in the brain in particular, but it may be surely stated that LPO activation effect in the rat blood and brain is undoubtedly associated with the action of «small doses» of internal radioactive exposure, since the increase in the level of the basic LPO products and decrease in the peroxide resistance of erythrocytes is more significant in this case. The same is evidenced by such indicators as the blood plasma and the brain supernatant ICL.

* * *

When determining the content of neuromediators in the rat brain structures exposed to the internal radiation, the changes revealed gave evidence that in the body reaction to the effect of internal radiation are actively involved neuroregulatory mechanisms, including both catecholaminergic and GABA-ergic systems. What is more, the structures of a limbic system, diencephalic and subcortical brain compartment appeared to be insensitive to radioactive impact.

Changes in the content of catecholamines under internal radiation exposure in the brain cortex of the experimental animals were revealed only in 6 months after receiving radionuclide (Figure 16.1).

The content of dopamine in the brain cortex of the rats receiving radionuclides during 1 and 3 months did not differ from the control values. In 6 months after radiation expose the content of this neuromediator increased 1.6-fold compared to control.

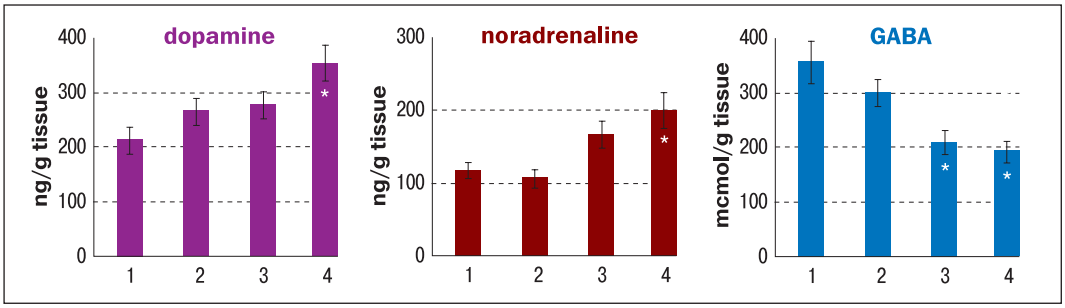


Figure 16.1. **Content of dopamine, noradrenaline and GABA in the brain cortex of the rats exposed to the internal (^{137}Cs) radiation. Along X-axis: 1 – control; 2 – internal radiation during 1 month; 3 – during 3 months; 4 – internal radiation during 6 months.* – $p < 0.05$.**

The content of noradrenaline in the brain cortex of the rats exposed to internal radiation changed in the same direction as that of dopamine. In the animals that received ^{137}Cs during 1 and 3 months, the content of noradrenaline did not differ from the control values. In 6 months the content of adrenaline in the brain cortex of the rats increased in 1.6 times as compared to control. The content of GABA in this brain structure of the rats exposed to internal radiation reduced in 1.7 and 1.9 times, respectively.

Thus, the results of investigations concerning the content of neuromediators (dopamine, noradrenaline, GABA) in the brain structures of the rats exposed to internal radiation evidence that individual neuromediator systems as well as individual brain structures have different sensitivity to IR effect.

* * *

The functional condition of animals' CNS was evaluated by indicators of shifts in the behavioral reactions. The studies in the "open field" installation revealed essential changes in the locomotor, emotional and exploratory activities of the rats exposed to ^{137}Cs radiation, as compared to the relevant control groups (Table 16.6).

Results of the studies give evidence that the CNS functional impairments in the long-term exposure to internal radiation with ^{137}Cs small doses are manifested by the complex of disorders of locomotor, emotional and exploratory activities, memory mechanisms, as well as by the increased convulsive readiness. At that, the CNS impairments have certain dose dependence and typical characteristic as well as sexual peculiarities.

Table 16.6

Exploratory reactions in the rats exposed to ^{137}Cs radiation and control rats (as per the «open field» test)

Group of animals	Latent period, s		Number of episodes, n		%
	3 months	6 months	3 months	6 months	
Males HLA	69.4 ± 17.8	328.3 ± 3,5**	5.7 ± 1.9	2.7 ± 0.5*	60.0 ± 0.2%
Females HLA	88.6 ± 20.3*	245.5 ± 22.2*	6.9 ± 1.3*	1.0 ± 0.2*	50.0 ± 0.1%
Males LLA	74.1 ± 8.1	546.3 ± 33.8**	2.0 ± 0.9*	1.0 ± 0.3*	16.7 ± 0.1%
Females LLA	79.1 ± 18.1**	105.5 ± 12.8**	3.1 ± 1.0	1.5 ± 0.2	33.0 ± 0.1%
Males HLA-C	70.2 ± 18.3	79.6 ± 8.8	4.3 ± 1.0	5.5 ± 0.6	100 ± 0%
Females HLA-C	147.5 ± 55.1	171.5 ± 21.3	5.3 ± 1.8	2.9 ± 1.1	100 ± 0%
Males LLA-C	81.8 ± 15.9	156.1 ± 20.1	3.7 ± 1.1	2.5 ± 0.8	100 ± 0%
Females LLA-C	182.8 ± 41.1	259.2 ± 28.3	2.7 ± 0.6	2.8 ± 0.9	100 ± 0%

Notes. HLA – high locomotor activity; LLA – low locomotor activity; C – control; s – seconds; * – $p < 0.05$, ** – $p < 0.01$ as compared to relevant control.

* * *

When histologically studying the brain bioptates of the rats fed with the food, containing 137Cs additives1 it was established that on the sites of the sensorimotor area of the hypothalamic cortex and nuclei (semi-fine slices were studied), the events of the disordered intra-organ capillaceous blood circulation were brought to the foreground. Under observation were the dilations and vascular congestions of the basic mass of microcirculatory vessels and the events of variously pronounced prerivascular edemas (Figure 16.2).

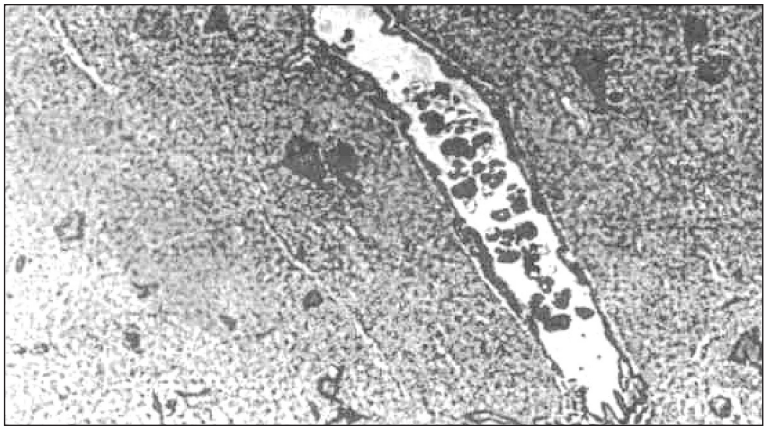


Figure 16.2. **First month after feeding rats with food, containing additives of radioactive ^{137}Cs. Abruptly dilated capillary in the brain cortex sensorimotor area. Semi-fine slice. Coloration with methylene blue pyronin. × 600.**

In the perivascular area of both sensorimotor cortical section and hypothalamic nuclei the aggregate of destructively changed neurons was revealed with the phenomena of a moderate cytoplasm hyperchromatism, blurred cellular contours and disordered integrity of the processes. Here one also could observe abruptly swelled neurocytes with clarified cytoplasm and solitary «shadow cells» (Figure 16.3).

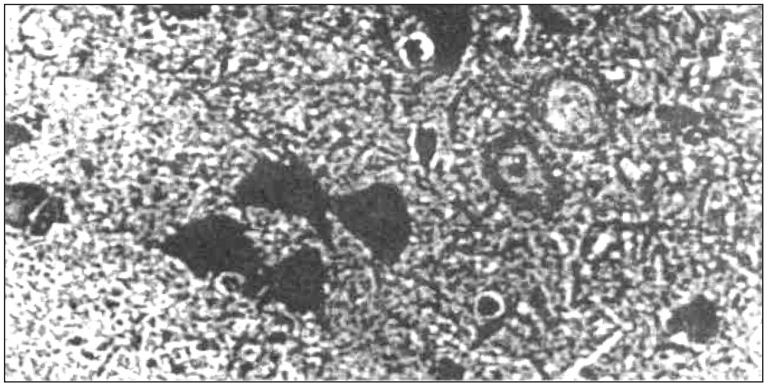


Figure 16.3. **First month after feeding rats with food, containing additives of radioactive ^{137}Cs. Dystrophically changed neurons in the cortical sensorimotor area. Semi-fine slice. Coloration with methylene blue pyronin. × 800.**

It should also be noted that the brain tissue swelling with dominating neuroglia changes in the section of hypothalamic nuclei was more pronounced than in the cortical sensorimotor area.

This was completely confirmed by the results of electron-microscopic analysis of the brain microcirculatory vascular blood-stream, where the pronounced edema and destruction of astroglia processes were observed around the basic mass of intracerebral capillaries. Here we also revealed the destruction of capillary walls due to the swelled marginal part of endoteliocytes, homogenization and clarification of the basal membrane substance, this undoubtedly evidencing the disordered permeability of membranous barriers of the intracerebral capillaries.

Electron-microscopic study of neurocytes gave evidence that in the majority of the nervous cells of both the cortical sensorimotor area and hypothalamic nuclei there was a dominance of cytoplasm edema with variously pronounced dystrophic-destructive changes of intracellular organelles (mitochondria, at the first place).

In the most mitochondria we observed vacuolization of cristae against the background of the clarified matrix. In the part of mitochondria due to the pronounced vacuolization, there was observed the disorder in their histoarchitectonics, destruction of both external and internal coats in the part of mitochondria. Near the destroyed mitochondria, there appeared lysosomes and autophagosomes (Figure 16.4).

Morphometric evaluation of the mitochondria swelling degree evidenced that the average size of mitochondria due to swelling increased against the norm in 2.6 times in the neutrocytes of the cortex sensorimotor area and in 3.2 times in neutrocytes of the hypothalamic site. The area occupied by the unchanged mitochondria in the neurocytic cytoplasm decreased, according to morphometric data, both in the neutrocytes of the cortex sensorimotor area and in the neurons of hypothalamic nuclei, in 1.5–1.6 times on the average (Table 16.7). Observed in neurons of the cortex sensorimotor area was not inconsiderable decrease in the chromatin content, due to its partial destruction and release into cytoplasm via the destroyed nuclear envelope.

Those processes were mostly pronounced in neuron nuclei of the hypothalamic section, where the area occupied by chromatin decreased more than 2 times and came to (26.3 ± 2.8) % at the

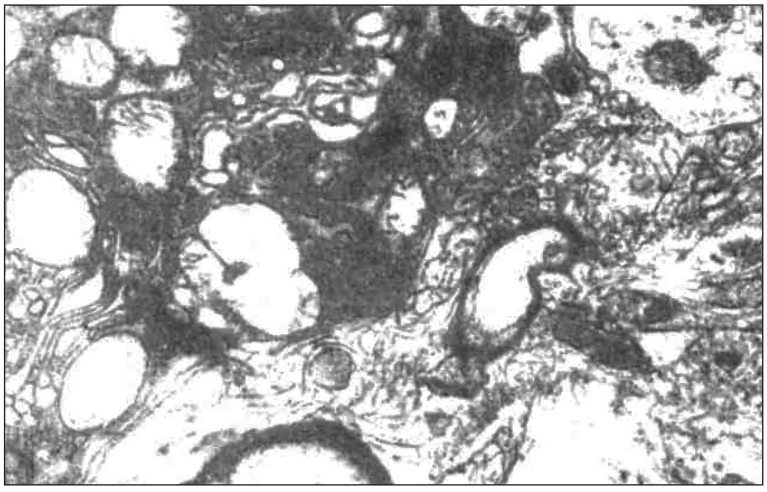


Figure 16.4. **First month after feeding rats with the food, containing additives of radioactive ^{137}Cs. Cytoplasm of destructively changed neuron. Swollen and destroyed mitochondria. Destruction of the reticular cisterns. Electron-diffraction pattern. × 17,000.**

Table 16.7

Morphometric parameters of morphofunctional condition of the nervous cells in 1 month after feeding rats with the food, containing additives of radioactive ^{137}Cs in a daily dose of 600 Bq

Parameters	Cortex		Hypothalamus	
	Control	1 month	Control	1 month
Chromatin, %	38.02 ± 3.01	21.90 ± 2.51*	54.01 ± 4.01	26.32 ± 2.81*
Mitochondria:				
swelling degree, %	0.36 ± 0.02	0.95 ± 0.03*	0.30 ± 0.01	0.98 ± 0.02*
area, %	26.01 ± 2.10	17.01 ± 1.80*	32.01 ± 2.60	20.31 ± 2.20*
Synapses:				
active area length / contact length, %	0.91 ± 0.02	0.33 ± 0.01*	0.80 ± 0.02	0.28 ± 0.01*
Synaptic vesicles, n	85.01 ± 6.00	47.00 ± 5.21*	102.02 ± 7.21	56.01 ± 5.40*

Note. * – significant as compared to control ($p < 0.05$).

rate of (45.0 ± 4.0) %. In the nuclei of the cortex sensorimotor area the percentage of decrease in the area occupied by chromatin was somewhat lower than in the hypothalamic nuclei and amounted to (21.9 ± 2.5) % against (38.0 ± 3.0) % in the norm, i.e. decreased in 1.7 times.

Sufficiently substantial changes were caused to the neuronal synaptic apparatus. Both pre- and postsynaptic endings were swollen and had expanded space, where one could notice destructively changed mitochondria and expanded cisterns of endoplasmatic reticulum. The decrease in the number of synaptic vesicles of presynaptic axon endings was conspicuous.

Morphometric determination of the average number synaptic vesicles gives evidence of the fact that the number of the latter decreased in 1.8 times in the synapses of both the cortex motor area and of the neurons of the hypothalamic nuclei, in 2.8 times as compared to the norm decreased the length of synaptic active area, this pointing to a partial synaptic apparatus destruction. Statistically significant differences between the study parameters of the cortical sensorimotor area and hypothalamic nuclei were not revealed.

* * *

Histological study of the brain cortical and hypothalamic area biopates on the series semi-fine slices after six- and nine-month feeding rats with food, containing additives of radioactive ^{137}CS, gave evidence, that the well-marked differences, as compared to the group of animals, who received three-month feeding with food, enriched with radioactive ^{137}Cs, were not observed.

In the microscope field of vision we noticed the full-blooded dilated capillaries with phenomena of perivascular edema and burned-out neurons. Changes in the brain histological structure had a pronounced mosaic character. Noticed in the brain cortex and in the area of hypothalamic nuclei were both the sections with practically unchanged or slightly burned-out nervous cells and the sections with sufficiently pronounced irreversible destructive changes of neurons, with the latter being the most pronounced in the area of hypothalamic nuclei (Figure 16.5).

In the electron-microscopic study of the brain tissue the dystrophic changes of different extent of pronouncement were revealed both in the system of microcirculatory vascular bed and in the brain neurons. The lumen of the main mass of intracerebral capillaries is expanded. The capillary wall relief is scallop-changed with numerous invaginations of cytoplasm endotheliocytes into the capillaceous lumen. Basal membrane of capillaries is unevenly thickened, homogenized (Figure 16.6).

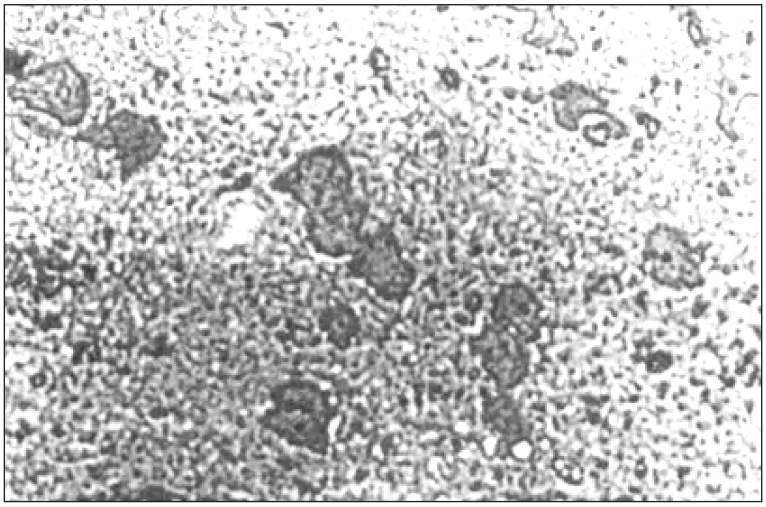


Figure 16.5. **Nine months after feeding rats with the food, containing radioactive ^{137}Cs. Dystrophicaly-destructively changed neurons in the hypothalamic section. Semi-fine slice. Coloration with methylene blue pyronin. × 800.**

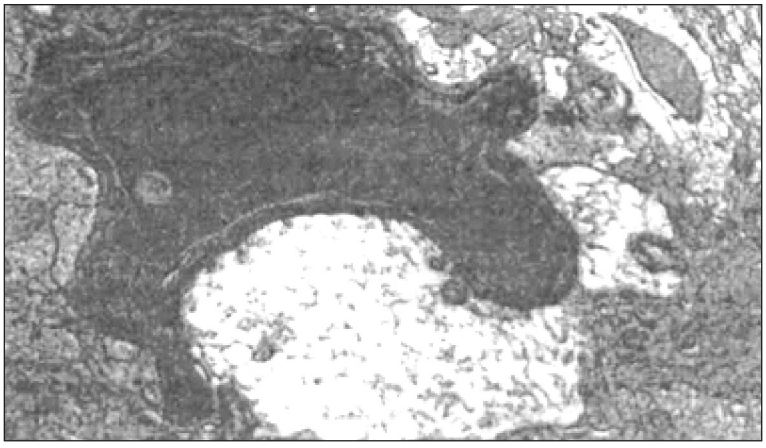


Figure 16.6. **Nine months after feeding rats with the food, containing radioactive ^{137}Cs. Destructively changed capillary in the brain cortex. Electron-diffraction pattern. × 17,000.**

Characteristic of the endotheliocytic cytoplasm, especially its marginal part, was the phenomenon of sufficiently pronounced plasmocytosis, i.e. bifurcation of the marginal part of endotheliocytic cytoplasm and protrusion of numerous cytoplasmic processes into the capillaceous lumen (Figure 16.7).

Ultra-structural peculiarities of the majority of the nervous cells were characterized by moderately clarified cytoplasm with dilated system of endoplasmatic reticulum and moderately hypertrophied mitochondria and clarified matrix, and vacuolated cristae.

In the cytoplasm of these cells there appeared numerous secondary lysosomes and autophagosomes. Free ribosomes and polysomes were in a very small amount (Figure 16.7).



Figure 16.7. **Nine months after feeding rats with the food, containing radioactive ^{137}Cs. Phenomenon of pronounced plasmocytosis of the endothelocytic marginal part. Electron-diffraction pattern. × 22,000.**

Encountered along with the aforementioned neurons were practically destroyed neurons and also the neurons, in whose cytoplasm ne could notice the processes of intracellular regeneration with enhanced protein-synthesizing and energy-producing function of these cells (Figure 16.8, 16.9).

Morphometric analysis of the condition of intracellular organelles and neuronal synaptic apparatus of the brain cortex and hypothalamic nuclei evidenced that the percentage quantitative indicators of the area occupied by mitochondria, content of nuclear chromatin and the number of synaptic vesicles in neuronal synaptic apparatus were not significant as compared to a three-month term (Table 16.8).

Thus, the performed complex morphostructural study of the brain cortex and hypothalamus by the methods of the light and electronic microscopy revealed sequential pathologic changes in the intracerebral capillaceous blood circulation with subsequent dystrophic-destructive

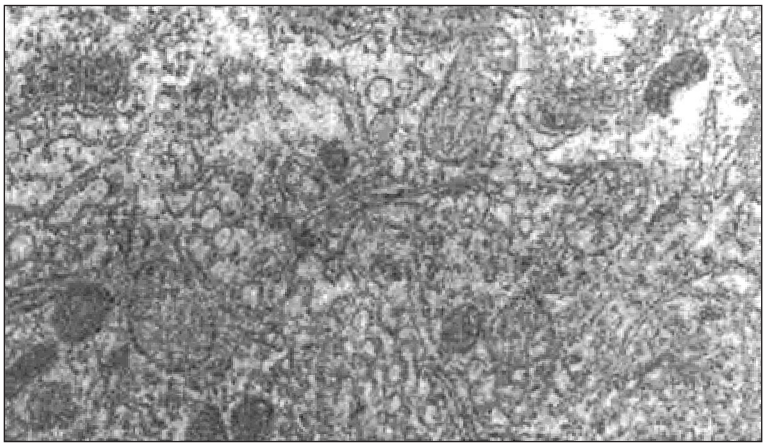


Figure 16.8. **Nine months after feeding rats with the food, containing radioactive ^{137}Cs. Section of dystrophically changed cytoplasm in the brain cortical sensorimotor area. Electron-diffraction pattern. × 17 000.**

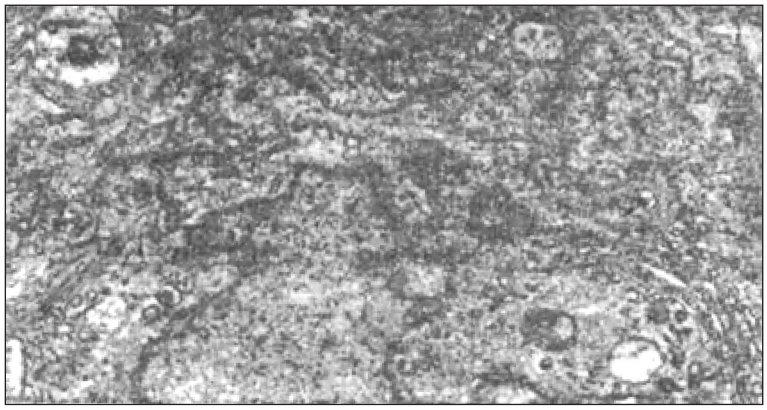


Figure 16.9. **Nine months after feeding rats with the food, containing radioactive ^{137}Cs. Neuron cytoplasm with pronounced phenomenon of intracellular regeneration. Electron-diffraction pattern. × 17 000.**

Table 16.8

Morphometric parameters of multifunctional condition of the nervous cells in nine months after feeding rats with the food, containing radioactive ^{137}Cs in a daily dose of 600 Bq

Parameters	Cortex		Hypothalamus	
	Control	9 month	Control	9 month
Chromatin, %	38.01 ± 3.00	14.00 ± 1.90*	54.00 ± 4.00	12.41 ± 1.20*
Mitochondria:				
swelling degree, %	0.36 ± 0.02	0.42 ± 0.02	0.30 ± 0.01	0.48 ± 0.05
area, %	26.01 ± 2.10	12.40 ± 1.50*	32.00 ± 2.61	15.41 ± 1.60*
Synapses:				
active area length / contact length, %	0.91 ± 0.02	0.61 ± 0.03	0.80 ± 0.02	0.55 ± 0.03
Synaptic vesicles, n	85.01 ± 6.00	22.01 ± 2,91*	102.00 ± 7.20	36.01 ± 3.00*,**

Note. * – significant as compared to control ($p < 0.05$); ** – significant between the cortex and hypothalamus ($p < 0.05$).

changes in the main mass sensorimotor cortex and hypothalamic nuclei. According to the data of morphometric studies, the most significant changes in the intracellular structure of neurons occur during 1 month of radiation exposure, and then the rate of their development diminishes. In the late terms of feeding after the radiation exposure the signs of repair process in neurocytes are revealed. Activation of these processes was seen only after the feeding of animals has been terminated. When comparing the changes in the neurocytes of the brain cortex and hypothalamus it may be stated that in hypothalamus they were more pronounced than in the brain cortex. Probably, it is associated with a long-term intake of radionuclides and their accumulation in hypothalamus with subsequent disorder of the body vegetative regulation.

* * *

Today there exist new proofs to evidence the effect of a small-dose radiation on the CNS, that are manifested starting from changes in the expression of a great many genes, disordered cytokine synthesis, development of neuroinflammatory reactions, impaired neurosignalling with further development of apoptosis and death of the brain cells, induced both by a direct effect of radiation and a secondary lesion of the cells [2, 9, 39]. Cytotoxic factors, humoral mechanisms (neuropeptides, neuroantibodies, activated immune cells, proinflammatory, apoptosis-inducing

cytokines) induced in a small-dose radiation exposure, lead to an organic lesion of the various brain cells [1, 9, 11, 39], mostly neurocytes and endotheliocytes of the brain blood vessels.

* * *

Based on the data presented, the following conclusions can be drawn.

1. During internal radiation exposure of rats to radionuclide ^{137}Cs in small doses of 600 Bq daily for 9 months, radionuclide is accumulated in different departments of the CNS, gradually growing structural-functional disorders developing in the micro-vascular and neuroglial compartments of the brain.
2. Radionuclide accumulation in the brain starts from the first days of exposure and has two rising peaks – at months 3 and 7–8, and falls – at months 5–6, this pointing to the existence of certain mechanisms to accelerate excretion of radioactive ^{137}Cs.
3. In terms of quantity, the CNS accumulates less radionuclides than other solid viscus, the highest amount being noted in the brain hemispheres and hypothalamus.
4. The studies of biochemical reactions in the blood and brain showed an early activation of peroxide reactions, phase derangement of catecholamine, GABA and dopamine metabolism in different brain sections. The most significant biochemical changes were revealed in the hypothalamus and hypophysis.
5 Changes in the behavioral reactions of rats start to be manifested from month 3 after the beginning of radiation exposure and grow up to month 9. These changes in the behavioral reactions depend also on the lability of the animals' nervous system and their sex.
6. Electron microscopic and morphometric studies of the different brain sections and structures revealed the step-by-step disorder increase in the CNS, being evident at first, at the level of arteriolovenular bridge structure and function and then via the development of progressing dystrophic-necrotic changes in neurons and glial cells in the various brain regions.
7. In parallel with the development of degenerative, dystrophic and dyscirculatory brain disorders, the development of reparative and regenerative processes in neurons and capillaries is noted over months 6–9, this being the evidence of the development of compensatory-reductive reactions in the CNS, despite the effect of radionuclides.
8. The termination of radiation exposure after month 6 leads gradually to a considerable renewal of the biochemical and morphostructural changes in the brain up to the activation of regenerative processes in the CNS, which evidences a partial reversibility of the disorders caused by small doses of radiation and points out the possibility to correct these disorders medicamentally.

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16.2. STUDIES OF Cs-137 LOW RADIATION EFFECT ON CATECHOLAMINERGIC CELLS OF RAT BRAIN *IN VIVO* AND *IN VITRO*

The importance of the problem concerning the effect of low doses of radiation on the nerve cell metabolism deals with an increase of neuropsychic disorders among the individuals who were exposed to ionizing radiation as a result of the accident at the Chornobyl nuclear power plant (Chornobyl NPP) [1–6]. The radiation effect of catecholamine metabolism on the nervous system deserves a special attention in the frame of studying radiation effects on the nervous system. An early response of catecholaminergic systems and increased catecholamine levels of dopamine and noradrenaline under ionizing radiation are revealed in the majority of studies [6–12]. It is believed that the reactions of catecholamine systems should promote the activation of antioxidant properties and radioresistance [13].

It is also known that catecholamine metabolism is associated with melanin synthesis [14]. Melanins are products of oxidative transformation of amino acid tyrosine first in dioxyphenylalanin and then in dioxyphenylalanin-chrome, the latter being polymerized into high-molecular water-insoluble melanins. Melanin of ectodermal origin performs the antioxidant and radioprotective function in the tissues [15, 16]. The neuromelanin pigment that is localized in neurons of substantia nigra and blue spot would also be released in the nervous tissue. The synthesis of neuromelanin is directly occurred with L-DOPA – the dopamine precursor. In the case of the cytosolic dopamine excess, preparation is primarily being in endosomes, then transported to mitochondria, converted into dioxyphenylalanin, an excess being oxidized to quinones and semiquinones that are reserving as neuromelanin. Neuromelanin performs the protective antioxidant action according to the current concepts.

Ce-144, Cs-137, Ru-106 were the main γ and β pollutants after the accident at the Chornobyl NPP. The transition of these elements through the trophic chains leads to the contamination of food products causing the internal exposure and various long-term metabolic reactions of the body.

The aim of our study was to investigate the influence of internal irradiation at a dose of 600 Bq Cs-137 per day, calculated from the average theoretically possible use of radioisotopes with food products to the level of catecholamines in the functional parts of the rat brain in vivo and in vitro, and also the accumulation of melanin-like substances in the nerve cells of substantia nigra in vitro.

The study was carried out using experimental animals – inbred rats weighing 160–180 g, which were kept on the isocaloric diet of vivarium and were subjected to Cs-137 exposure at a dose of 600 Bq per day for 30 days, that corresponds to the level of radioactive isotopes detected in the blood of clean-up workers who worked in the accident zone, within 3 months. The isotope was introduced in the diet with bread saturated with an aqueous solution of Cs-137 chloride (Cs-137Cl).

After finishing experiment, the rats were decapitated. The hypothalamus, the striatum, the hippocampus, the medulla, the midbrain and the cerebral cortex were removed. The resulting samples were stored in the liquid nitrogen.

Cs-137Cl in a concentration of 52 Bq per 1.5 ml of medium was added into the culture medium with the explants of substantia nigra on the fifth day to investigate the influence of the isotope on catecholamine synthesis in vitro, on the tenth day the explants were stained to detect catecholamines and neuromelanin. The culture with non-radioactive Cs in a concentration of 5.76×10^{-18} mol/l added to the culture medium was used for control.

The histofluorescent staining of the cells for melanin detection was carried out according to the Lilly method [18].

HPLC method with electrochemical detection was used for the quantitative determination of catecholamine content [19].

Studies *in vivo*

Conducted studies indicate (Table 16.9) that the tissue of the brain structures such as the hypothalamus, the striatum, the hippocampus, the cerebral cortex, where the most intensive metabolic processes [20] are occurred, responds more actively under the chronic internal exposure of experimental animals by Cs-137 at a dose of 600 Bq/day. Each of these structures plays a specific role in the system of the integrative brain connections. The mechanisms that underlie the fundamental processes of vital activity are associated with the hypothalamus: metabolism, homeostasis, adaptation processes. The most significant changes in the noradrenaline and dopamine contents were found in the hypothalamus of experimental animals as a result of the conducted studies (Table 16.9). The increase of noradrenaline level compared with control was 1.8 times and that of dopamine – 2.6 times.

The body dopaminergic neurons concentrated in the substantia nigra and ending of the ascending axons mainly localized in the striatum are the most important elements of the striatum nigra system that plays the central role in the organization of locomotion. The obtained data on the content of neurotransmitters in the striatum and the midbrain are indicative of the chemical equilibrium disorders in the striatum nigra system – the noradrenaline and dopamine levels of the midbrain in the experiment remains unchanged (Table 16.9), and in the striatum the dopamine level is increased by 1.6 times (Table 16.9).

The hippocampus is the structure of the limbic system of the brain [20, 21], which function is to organize the emotional and behavioral responses [22, 23]. The statistically significant increase in the noradrenaline content by 1.5 times was caused by the rat chronic exposure, and the tendency to increase the dopamine level was noted (Table 16.9).

The elevated level of catecholamines is also observed in the medulla oblongata of experimental animals: noradrenaline – by 1.5 times and dopamine – by 1.6 times. In the cortex tissue (Table 16.9) the noradrenaline levels compared with control are constant, and the dopamine levels are increased in 1.5 times.

Table 16.9

The catecholamine content in functional structures of the rat brain under chronic internal irradiation of Cs-137 (600 Bq dose/day)

Brain parts	Groups	Noradrenaline (ng/g tissue)	Dopamine (ng/g tissue)
hypothalamus	Control	1939 ± 189	108 ± 16
	Cs-137	3500 ± 449*	280 ± 43*
striatum	Control	-	3037 ± 258
	Cs-137	-	5077 ± 51*
hippocampus	Control	330 ± 17	18 ± 1
	Cs-137	500 ± 45*	28 ± 5
medulla oblongata	Control	786 ± 67	74 ± 8
	Cs-137	1073 ± 13*	119 ± 13*
midbrain	Control	764 ± 91	176 ± 19
	Cs-137	793 ± 60	254 ± 39
cerebral cortex	Control	439 ± 58	518 ± 39
	Cs-137	480 ± 53	804 ±102 *

Notes. * – $p < 0.05$.

Studies *in vitro*

To eliminate the influence of adaptation reactions on the content of catecholamines, its level was examined in culture of the midbrain nervous tissue. The active cell eviction from explants and the formation of growth zone were observed while culturing the explants of substantia nigra in both the control samples and the samples with isotope Cs-137 added to the nutrient medium. A large number of the neurons with fluorescent granules was noted under histochemical staining for catecholamines in a zone of growth (Figure 16.10). The level of noradrenaline per mg of cultivated tissue was increased by 2.4 times, and dopamine by 2 times that was demonstrated by the quantitative analysis. However, no statistically significant differences from control samples (without Cs addition) were observed in samples cultured with non-radioactive Cs (Table 16.10).

The black spots of round shape in the cytoplasm of dopaminergic neurons on the histofluorescent preparations that were subject to the influence of the isotope Cs-137 attract an attention (Figure 16.11). Several such spots are localized in one cell [18]. According to the literature data it can be the granules of lipofuscin, or neuromelanin [18]. The foci of destructive transformations can not be also excluded. The assumption that the detected spots were lipofuscin granules was excluded as lipofuscin under the action of ultraviolet rays has to fluorescence [18]. The fluorescence was not observed by us on the obtained preparations in the corresponding wave diapason. Regarding neuromelanin it is known that the preparation is deposited as the melanin granules which determine the pigmentation of the substantia nigra, while fluorescent complexes are revealed under histochemical staining.

The presence of corresponding green granules localized as the chains near the inner surface of the cytoplasmic membrane was demonstrated by staining of experimental and control samples for neuromelanin detection. Thus, their number was much higher in the experimental samples (Figure 16.12).

The balance of neurotransmitter content in different functional brain structures is one of the factors ensuring their functional and integrative activity. The results of our study indicate that the catecholamine level in the brain tissue is increased under internal radiation of Cs-137 at a dose of 600 Bq within 30 days, that coincides with the data obtained in other studies [6, 12, 13] where the change is interpreted by the authors as the activation of antiradical protection. Some studies suggest that the accumulation of neurotransmitters is a result of an imbalance between the rate of this synthesis and degradation [10] Thus, the rate of dopamine synthesis is increased by 3–5 times, and the decay (decomposition) rate – by 2 times, that is connected with the decrease of monoaminooxidase activity [10]. Many authors believe that the increase in the catecholamines has radioprotective significance connected with their ability to easily attach free electrons [6, 12, 13].

Table 16.10
The content of catecholamines in the brain cells after culturing with Cs-137

Groups	Noradrenaline (pg/mg tissue)	Dopamine (pg/mg tissue)
Control	9.1 ± 2.1	5.9 ± 1.8
Cs-133	9.8 ± 2.3	6.3 ± 1.5
Cs-137	21.5 ± 0.9 *	11.6 ± 1.5 *

Notes. * – $p < 0.05$.

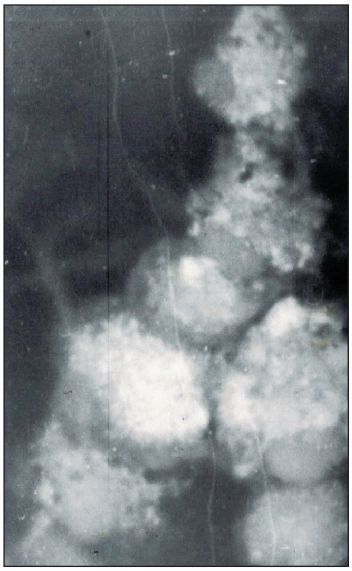


Figure 16.10. Catecholaminergic neurons of substantia nigra in culture. Control. Staining by Falk-Hillarp. Equal distribution of fluorescent granules in the body and cell outgrowthes (10 × 40).

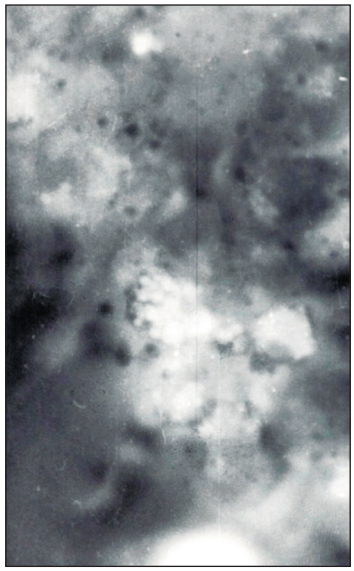


Figure 16.11. Catecholaminergic neurons of substantia nigra in culture under the influence of radiation. Staining by Falk-Hillarp. There are areas of destruction and black spots (10 × 40).

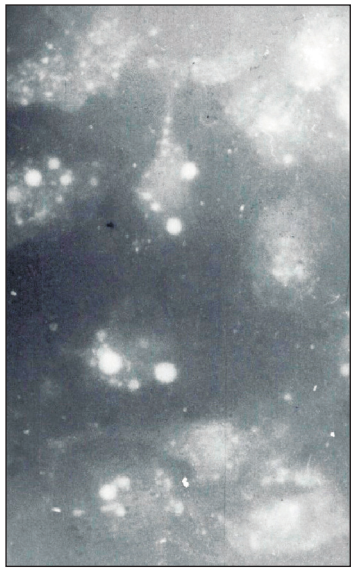


Figure 16.12. Histochemical detection of melanin in the cells of substantia nigra under the radiation effect. Increase in a number of neuromelanine granules on the background of destructive processess (10 × 40).

The obtained results indicate the different sensitivities of catecholaminergic systems to internal chronic irradiation in various functional structures of the brain in the experimental animals. So if you put the received changes in the order of increasing, the most expressed ones are in the hypothalamus, then in the striatum and the hippocampus, and the medulla oblongata, and the cortex, and midbrain, which correlate with data on the metabolic activity of these structures.

The high sensitivity of the hypothalamus to radiation exposure is manifested by the disorder of regulation in body adaptive systems, which are described in many works devoted to the studying the effect of small doses of radiation on the organism [7, 11, 22].

Data obtained under studying the radioisotope effect at a dose of 52 Bq on the catecholamine level in the explant cells of substantia nigra also indicate increasing their content under experiment conditions. The increase in catecholamine level is accompanied by the increased content of neuromelanin granules. It is known that this pigment is accumulated under an excess of catecholamines and in the presence of free radicals it can be recovered and oxidized reversibly and have radioprotective significance [14].

* * *

Internal radiation of Cs-137 at a dose of 600 Bq in the experimental animals within one month causes the increase in the noradrenaline content of the hypothalamus by 1.8 times and the hippocampus by 1.5 times and also that of dopamine in the hypothalamus, the striatum, the hippocampus, the medulla and the midbrain and the cerebral cortex by 1.5–2.6 times. The functional structures of the brain are characterized by the sensitivity to radiation effect. The structures of the hippocampus and the hypothalamus are the most sensitive ones.

The increase in neuromelanin granule content of the nerve cells in experimental samples indicates a link between increased catecholamine content and neuromelenin forming ability of catecholamine cells.

The increase in catecholamine and neuromelanin contents in the nerve tissue under small doses of internal exposure can be considered as a manifestation of adaptive processes aimed at radioresistance increase.

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Chapter 17
SENSORY ORGANS

A study of ionizing radiation effect on the sensory organs, fist of all, an organ of the sight, an organ of the ear and an organ of the equilibrium is one of the most essential directions of investigations connected with a study, an estimation and a prognosis of the remote medical consequences of radiation influence as a result of the Chornobyl catastrophe. In contemporary conditions the human working capacity is largely determined exactly by functional possibility of these sensory organs. Unfortunately, without regard to the several attempts of researcher collaboration in this field, this report is the first complex analysis of the state of sensory organs exposed to radiation as a result of the Chornobyl catastrophe.

The numerous reports of literature testify that functional disorders of sensory analyzers, first of all, visual, vestibular and auditory, occupy the leading places in the structure of pathology among those exposed to radiation after a catastrophe at ChNPP [1].

Presently there is practically a consensus that the functional state of sensory analyzers is one of reliable criteria of estimating human health, and their changes often result in the loss of occupational suitability, a decrease in working capacity and invalidity [1–6].

It is known that visual analyzer (VA), auditory analyzer (AA) and vestibular analyzer (VeA) anatomically, physiological and functionally are closely connected not only between themselves but also with the departments of the central nervous system, the circulatory system and with other body systems that cause their high sensitiveness to the changes in external and internal environments. Therefore a study of disorders of visual, vestibular and auditory functions, caused by IR as a result of the Chornobyl accident, has an important significance for clinical medicine additionally to scientific ones [1–7].

For estimating possible changes caused with radiation in VA, VeA and AA of radiation-exposed persons, and first of all in healthy and capable of Chornobyl clean-up workers we and other researchers went the mainly difficult way of realizing large-scale epidemiology researches on the basis of the long-term monitoring and careful analysis of clinical and electro-physiology indices of a state of the sense-organs.

The purpose of researches was to estimate the state of VA, VeA and AA in radiation-exposed persons, correlation between the IR dose and the effects caused by it in clean-up workers, the risk of visual, vestibular and auditory disorders, their character, a degree of manifestations and features of clinical course in the dynamics of postaccidental period.

Last years some aspects of a state of the sight organ in children, exposed prenatally (subsection 17.1.5) and children, born from the radiation-exposed persons, - clean-up workers - were

first studied (subsection 17.1.8). A problem for assessing state of the sensory organs in inhabitants of the territories contaminated with radiation remains not solved to the significant degree. Last researches (subsection 17.1.7) considerably extended our conceptions of eye development in children who were permanently exposed to ionizing radiation as a result of soil contamination with radiation substances.

17.1. EYE: CLINIC, DIAGNOSTICS, REGULARITIES AND RISKS FOR DEVELOPMENT OF EYE PATHOLOGY IN CHORNOBYL CATASTROPHE VICTIMS

An analysis of results of researches conducted for 20 years since the Chornobyl catastrophe testifies that just an eye is one of basic targets of radiation influence [1, 2, 6, 8, 9].

In this subsection the results of studyng regularities of the development and clinical features of eye illnesses are discribed in the radiation-exposed persons as a result of the Chornobyl catastrophe. A basis of this report is an information about the state of the sight organ in 25,344 persons among them 11,123 Chornobyl clean-up workers, 5270 were evacuated from zone of estrangement of ChNPP and 5297 inhabitants of the controlled territories, and also 3454 persons of other categories who were examined in SI «NRCRM of NAMS of Ukraine». Mainly an examination was carried out within the limits of CER (clinico-epidemiologic register of victims exposed at the Chornobyl catastrophe).

Data on the others researches are also involved, an information of all cases are reported in corresponding subsections.

As a result of the conducted researches, it was established, that eye diseases related to radiation are divided into two groups.

Radiation cataract which is examined as a deterministic effect [10-12]. Results of studying radiation cataract in radiation-exposed person in connection with the Chornobyl catastrophe are presented [4] was traditionally considered as a basic consequence of radiation effect on the eyes. The other known consequence of radiation influence is radiation retinopathy including two its new forms such as «syndrome of chestnut» (early and late) and «syndrome of diffraction grate» are described in victims as a result of the Chornobyl catastrophe.

At the same time the new radiogenic effects with deterministic signs were also found:

➢ Functioning of the eye as a complex of receptors is accompanied by the generation of retinal permanent potential. A radiation exposure disorders the generation of this potential, a threshold dose is 20 cGy.

➢ Radiation causes a dose dependent decrease in capacity for an accommodation. A threshold dose for this effect consists of 15 cGy.

It is also proved, that radiation influence substantially modifies the morbidity in some other illnesses of eye, it will be discussed in the corresponding subsection. In addition, the functional changes in the sight of radiation-exposed persons were revealed.

17.1.1 Specific radiation damages of the eye

Radiation cataracts

Same data are presented in [4, 6, 9, 13, 14] and soy will be presented in future.

During the primary examination of patients in 6–11 years after the catastrophe we have revealed both initial symptoms of radiation pathology of the lens and its expressed changes. The

following symptoms were taken to signify a threat of development of radiation cataract; appearance at the posterior pole of the lens of small spots of opacity (< 10), vacuoles (< 5) and areas of polychromatic changes [12].

The diagnosis of the radiation cataract was established by consultation of ophthalmologists in case of availability of the specific clinical picture [1, 11, 12, 14]. Such patient, beside an essential amount of spot opacities and vacuoles, have share posterior central subcapsular polychromatic opacity, oval opacity with a semi-transparent center and dark rims or granulated opacity clearly separated from the transparent part of the lens.

The stage of the cataract was determined, in concordance with our scheme by pronouncedness, localization, quantity and size of opacities, and while establishing the clinical diagnosis the most common international classification [12] was used. According to that classification:
1 stage – discrete opacity which can take the form of a small spot readily discernible with retroilluminated light; aggregates of dots (> 10) or vacuoles (> 5), cortical spokes, granulated opacities (Figure 17.1);
2 stage - more extensive cortical changes collectively occupying 25% of the noted area of the lens;
3 stage - advanced changes. Light does not reach vitreous;
4 stage - premature cataract;
5 stage - mature cataract.

Diagnosis of radiation cataract, stages 1 and 2, was made for 176 individuals, including 124 individuals – during the first time examination. In 43 cases diagnosis was made during the second time examinations of patients who did not demonstrate any radiation pathology before.

In case of cataract, stages 3-5, differential diagnostics between radiation and age cataracts are complicated. Radiation origin of mature or almost mature cataracts developed rapidly after Chornobyl accident in 26 relatively young liquidators, being healthy before, is highly probable (part of those people is already operated). This assumption is confirmed by that fact that some operated people had typical radiation cataract, stage 1 or 2, at the second eye. A.M. Petrunya [15] diagnosed radiation cataract in 1.4% participants of the Chornobyl NPP accident consequences elimination. As our prolonged observations have shown [1, 4, 6, 13, 14], the process of formation of the radiation cataract could be stopped at any stage of its development and acuity of the vision remains high enough, despite the presence of opacity. Meanwhile, in a part of patients very rapid progressing of the cataract was observed. So, during 3 years after diagnosis making opacities of the lens remained stable in 38% of patients; in 29% they progressed slowly; in 28% of patients they moderately rapidly; in 4.4% they rapidly up to complete opacity of the lens; in 2 cases partial regression of opacities was noticed. The acuity of the vision in initial stages was not decreased or decreased insignificantly, that is why patients did not express any complaints. During the progressing of the lens opacities the acuity of the vision was decreasing step by step or, seldom, abruptly.

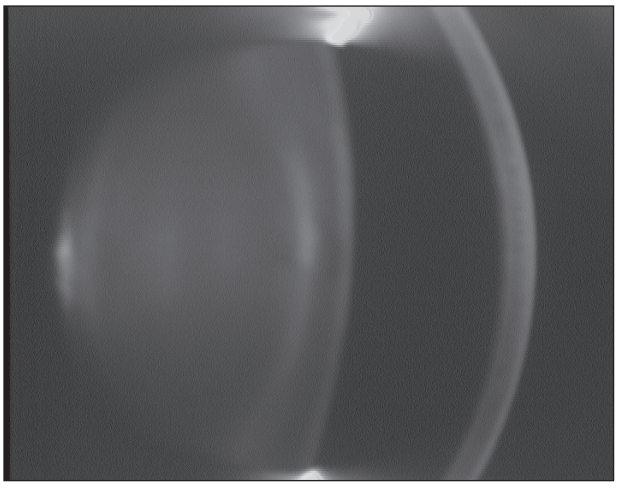


Figure 17.1. Radiation cataract, stage 1. The small posterior central subcapsular polychromatic opacity, Scheimpflug image.

It is common knowledge that the latent period of development of the radiation cataract varies depending on the dose loading and also the sensitivity of a patient in a wide range [1, 4, 9]. An prolonged observation allowed us to establish that the latent period of the development of the radiation cataract in survivors of the Chornobyl catastrophe can exceed 29 years. New cases continue to be revealed up to nowadays.

It has been shown that an appearance of non typical changes in the children and adolescent lens is possible as partial opacities and changes in optic infiltration without decreasing visual acuity by certain time and are only diagnosed in purposeful examination under chronic radiation effect [16, 17]. In long-term research was proved the presence of dose dependence for this pathology [6, 17].

Cataractogenic doses of ionizing irradiation are still not established accurately despite the considerable number of clinical observations and experiments.

Historically some authors consider 2.0–2.6 Gy [18] as the critical absorbed dose, other authors observed radiation cataracts under considerably lower doses [10, 19, 20].

Examinations performed after Chornobyl catastrophe proved that radiation cataract is appeared at the doses significantly less than it was early considered. The results of UACOS studies are evidence of possible presence of threshold but at the level nearly 0.1 Gy for some age groups, i.e. significantly lower than 2 Gy; a threshold is dependent on cataract form and can be higher than 0.7 Gy [9].

Officially registered doses in our patients with the radiation cataract varied from 0.02 to 2 Gy. The search for threshold level still continues along with the reconstruction of doses. A dose threshold for radiation cataract was not fixed in our study [1, 4, 6, 13]. Radiation cataract absolute risk for 1000 exposed persons, depending on the dose load presented in Figure 17.2.

Now ICRP established new dose limits to the lens for occupational exposure – 20 mSv in a year (old limits – 150 mSv) [22].

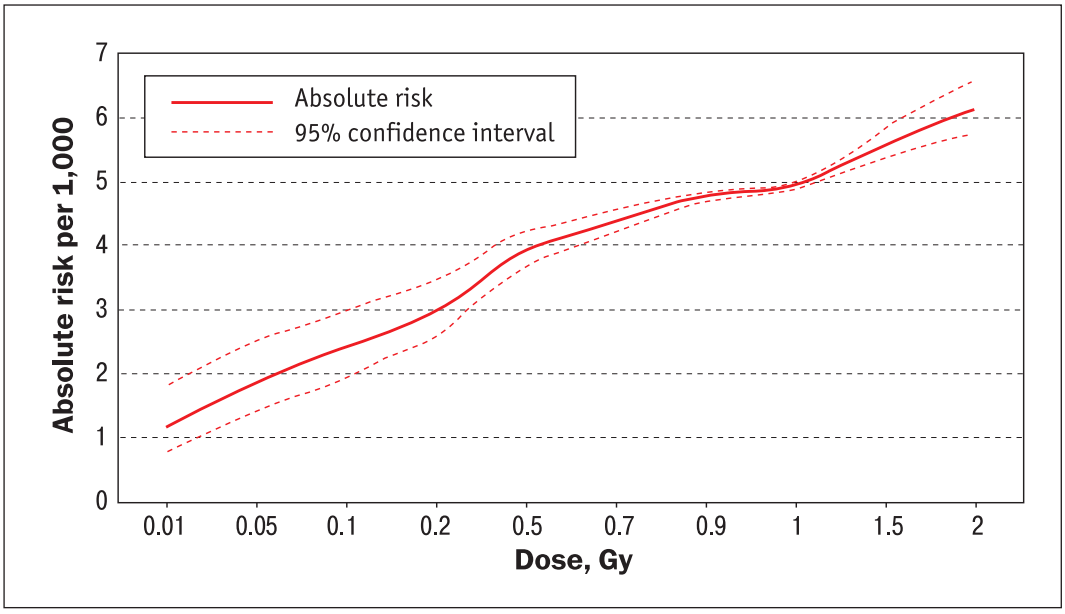


Figure 17.2. **Radiation cataract absolute risk for 1000 exposed persons, depending on the dose load [6]**

Radiation retinopathies

Hemorrhages on eye bottom, retinal edema, exsudate focuses were noted soon after a catastrophe in persons who were worked at its first days in the most contaminated areas with radiation. 2 forms of retinopathy, caused by the action of IR, with enough clear clinical pictures were detected by us among various changes in eye bottom. One of them was named by us «syndrome of chestnut», another – «syndrome of diffraction grate» [6, 23].

In the fall of 1986 we have observed certain changes in the retinal vessels – loss of tonus of venules and arterioles with appearance of huge number of aneurisms in the perimacular zone, and also sacculations having a stretched form which contacted with the extended veins. The picture resembled a crown of a tree or rather a leave of a chestnut tree. Macula was surrounded by such «leaves». We called such specific clinical picture the «early chestnut syndrome» [6, 23]. It could by observed till the end of 1986 – first months of 1987. Before 1996 we, however, continued to observe small number of aneurisms under condition of absence of diabetes mellitus and other somatic disease among separate acute period Chornobyl clean-up workers and evacuee's from the city of Prypyat'. Since 1993 in the locations of microaneurisms and extended venules under «early chestnut syndrome» loss of pigment was beginning, then sclerotic foci appeared. Macula was closely surrounded by a circle of ellipsoid foci of sclerotic character representing imprint of microaneurisms and sacculations. We called this clinical picture the «late chestnut syndrome» [6, 23].

In separate individuals exposed to irradiation under special condition during their stay within the field of direct vision of the bared active zone of the 4th reactor we observed a different clinical picture. Small round foci of white color appeared around the macula located behind the retinal vessels. As compared with the clusters of a vitreous plate a distinct order of location of those foci was observed: distances from each focus to neighboring ones was equal, it seemed that the foci appeared in foci of a diffraction grating. Near the macula foci were located closer to each other, and were bigger; beyond the fundus of the eye they looked rather like points on the periphery of a diffraction picture. We called this picture the «syndrome of diffraction grating» [6, 23]. Disruption of color perception, weakly pronounced metamorphopsias were observed under this syndrome. More often we found the weakly pronounced form with few foci.

Now it is impossible to find out the frequency of acute radiation retinopathies observed because the systematic examinations of victims in an early postaccidental period was not conducted by us and there were examined only those, who applied to ophthalmologic help [6].

Generation disorder of permanent potential in the retina

The epithelium of the retina, the photoreceptors and choroid take part in forming a permanent potential of the eye. As a disorder of the functional state of pigmented epithelium is one of main pathogenetic links in the development of retinal dystrophic processes, the method of electrooculography (EOG) – registration of permanent potential of the eye – was used by us during examination of persons exposed to radiation at the Chornobyl catastrophe [24].

An experimental group (44 eyes) was formed by the matching method. Matched liquidators were aged 40–60 years (middle age was 49.8±1.3 years). The officially registered doses of whole body irradiation were presented in 34 cases and ranged from 4.6 to 94.5 cGy. Middle dose of irradiation consisted of (27.24±4.1) cGy. EOG examination was also carried out on 22 clinically healthy eyes of control group persons (middle age – 49.1 ± 2.3 years), the inhabitants of Kyiv, without a contact with an ionizing radiation. Visual acuity 0.7–1.0 was in the persons of studied and control groups without a correction and 1.0 – with a correction, an ametropy did not exceed 3.0 D. An electrooculogram was registered by the method recommended by following authors [25].

The eyes of persons in control group were examined for clarifying the normal values of EOG indices. An Arden coefficient ranged from 200 to 299.5% in a control group with a mean value (245.99 ± 7.63) %. No significant changes in the Arden coefficient were noted in observed person depending on age.

The average Arden coefficient was (199.49 ± 8.20) % in the group of the radiation-exposed persons.

Analysing the results of examination the dependence of the Arden coefficient on a dose loading was found. A correlation analysis testified the presence of direct middle feed-back between the documented dose and the value of Arden coefficient ($r = 0.41 \pm 0.14$, $p < 0.05$), i. e. with increasing dose of irradiation a light dark coefficient is decreased.

No significant differences were revealed in EOG values of the majority of people with the dose loading up to 20 cGy. Mean value of the Arden coefficient was (219.94 ± 11.21) %, in this subgroup (16 eyes) – a difference with control was insignificant. At the same time, the significant changes in EOG indices were noted in persons exposed to radiation of the greater doses. The values of the Arden coefficient (173.36±15.22) % are significantly ($p < 0.05$) lesser in persons with the dose loading over 20 cGy, than in persons with a dose up to 20 cGy and significantly ($p < 0.05$) lesser than in control. The amplitude of dark minimum was insignificantly changed in radiation-exposed persons, while the amplitude of light maximum was significantly decreased in persons with the greater dose load comparing to control as well as dose group of patients irradiated up to 20 cGy.

In accordance with literature data, a decrease in EOG indices characterizing a state of the pigmental epithelium, the photocepters and the choroid, testifies the presence of pathological changes in these structures. The initial functional disorders can be detected by EOG before a clinical manifestation of pathology [6, 24].

The results of our research allowed to establish that without regard to absence of clinical symptoms in of the eye fundus pathology, presented disorders in generation of retinal permanent potential are connected with metabolic disorders in its external layers of radiation-exposed persons with the dose loading over 20 cGy. Changes found in EOG indices and their dose dependence is an objective argument of negative influence of ionizing radiation on the retina. A dose of 20 cGy is a threshold for arising this effect in accordance with our data [24].

A dose dependent decrease accommodation capacity

There is an idea, that one of ionizing radiation effects is decrease in duration of life. This effect appears, in particular, in quick-aging of radiation-exposed persons [26]. Because one of symptoms of age changes of eyes is decrease of power of accommodation [27], we considered to be necessary to conduct comparative study of accommodation ability of eyes in individuals exposed to irradiation [8]. With the purpose of study of accommodation condition from the massive of examined people by the way of random selection 456 individuals having taken part in works at the Chornobyl NPP after the catastrophe. Level of the absorbed doses of ionizing radiation was 4.0–0.001 Gy; mean 0.271±0.012. In group of individuals with absorbed external irradiation doses below 0.25 Gy – 249 persons (aged 20-66 years; mean 40.3±0.38); level of the absorbed doses of ionizing radiation was 0.249-0.001 Gy; mean 0.127±0.003. In group of individuals with absorbed doses of 0.25 Gy and more – 178 persons (aged 24–65 years; mean 44.5±0.5); level of the absorbed doses of ionizing radiation was 4.0–0.25 Gy; mean 0.476±0.024.

Control group consists of 136 industrial workers (aged 20–64 years; mean 43.9±0.72) who live in area with normal radiation conditions (more than 800 km from Chornobyl). Individuals with ametropia more then 2.0 D were excluded.

The examination was conducted in period of 1992 –1998 – more than 6 years after Chornobyl catastrophy. Volume of accommodation was measured by accomodometer AKA-01. Instrument AKA-01 is intended for monocular measuring of volume of accommodation. Range of measurement: 0–19 D; measurement error ±0.13 D.

Analysis of results of examination and statistical processing was implemented with the help of special program (CER 3.00 and CER 3.02); analysis was conducted for each of groups separately, for each of age groups separately and for age groups with intervals of 5 years; in all the cases average value of volume of accommodation was determined, error of average value, sigma deviation, trust interval and variation coefficient. Reliability of difference was evaluated by *t* criterium (Student). Regression analysis was conducted with determination of correlation coefficient r.

Both in group with various doses of absorbed external irradiation statistically reliable decrease of volume of accommodation was noticed in comparison with control in number of age groups (Figure 17.3). Volume of accommodation was reliably higher in group of individuals with absorbed external irradiation doses below 0.25 Gy in comparison with individuals with absorbed doses of 0.25 Gy and more in age groups of 28, 29, 34, 37, 38, 40, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58 years, $p < 0.05$ (in age groups 40 and 56 years $p < 0.001$).

During correlation analysis it has been noted that volume of accommodation depends first of all from age ($r = 0.83 \pm 0.01$; $p < 0.001$; relation is reliable reverse high). Refraction in examined group did not influence on volume of accommodation ($r = 0.0$; relation is absent). Reliable ($p < 0.001$) connection ($r = 0.25 \pm 0.03$; connection reverse, weak) is noticed for volume of accommodation with dose absorbed; more dose absorbed, less volume of accommodation.

However compared to controls it is clear that the ranges of accommodation in exposed group suffered greater decrements than did the control. To describe the changes of the accommoda-

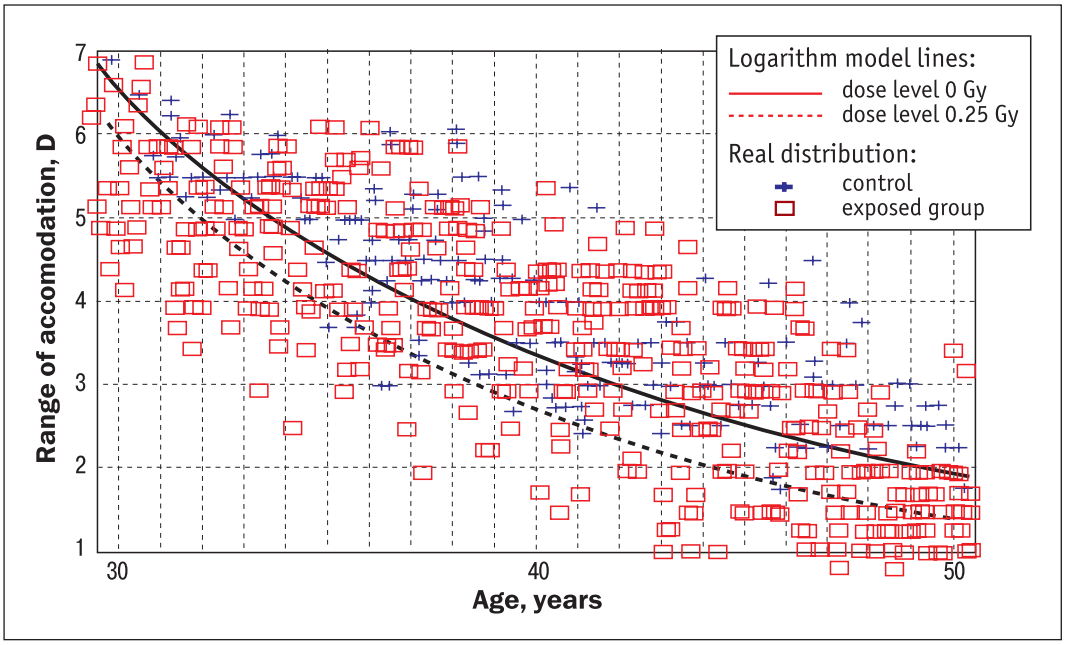


Figure 17.3. Range of accommodation, D, in control group and in the exposed group. Lines – logarithm model lines, symbols – real distribution [8]

tion ability in the entire irradiated persons group, beside the age of its members, the adequate ($p < 0.05$) linear model

$$RA = \beta_0 + \beta_1 \times age + \beta_2 \times dose \quad (17.1)$$

(where β_0, β_1, β_2 – coefficients; *age* – age, years; *dose* – doze, Gy) and logarithms model ($p < 0.05$) took account the dose loading (Figure 17.4). Excess of ranges of accommodation is -0.78 D/Gy, and -0.19 D/year (linear model).

A highly significant inverse correlation (Pearson) was found between the absorbed dose and the range of accommodation in the groups of patients of the same age, e.g. for age group 24 years r = -0.92 (95% CL -0.99; -0.61), 29 years= -0.89 (-0.99; -0.29), 38 years - r= -0.55 (-0.75; -0.26), 43 years - r= -0.55 (-0.76; -0.25), 47 years - r = -0.65 (-0.82; -0.37). Correlation coefficient r between the dose absorbed and the volume of accomodation in age qroups 26, 28, 30, 33, 34, 37, 41, 42, 44, 45, 46, 48 yrs. varied from -0.28 to -0.49 ($p < 0.05$, Pearson). In all the age groups the increase of the dose loading was accompanied by a decrease in the accommodative ability.

It has been established that model doses are thresholds for the factor, and threshold for this effect is a dose of 15 cGy.

17.1.2. Other pathology of the eye

Involutional cataract

An age cataract is a disease of elderly [1]. This is the most prevailed pathology of lens that causes a special actuality and social influence of researches regarding regularities of its development.

Data mentioned below are based on the results of examination within the limits of CER. A prevalence of involutional cataract (per 1000 persons) was increased for examination period from 294.3 ± 32.0 in 1993 to 766.7 ± 35.9 in 2004.

Its frequency is greater in elder age groups, in a group of clean-up workers as well as in a control group. But, as is shown below, an age prevalence of involutional cataract in liquidators is considerably exceeded a control level, a change in beginning of illness development into the side of more young age groups is observed. So, a relative risk made up 15.89 (CL – 2.22; 110.82) in clean-up workers under 40 years; in a group of 40-49 year old – RR=8.7, CL – 4.02; 18.85; in a group of 50–59 years – RR=3.86 and CL - 2.17; 6.88 comparing to the corresponding age group of control. A difference was also remained significant in an age group of 60 years and more (RR=2.98, CL – 1.57; 5.5), however a tendency to relative risk decrease caused by radiation has remained with an age: it can be an after-effect of greater sensitiveness of lens to radiation influence in relatively younger persons.

It has been established that a frequency of involutional type cataract was under influence of an age, a time of stay under a risk, and a dose.

A frequency of involutional cataract was studied in the groups of patients of different age and with the different dose loadings. The results are evidence of the presence of dependence between the prevalence of this disease and the dose loading.

The model of absolute risk of involutional cataract is shown below (P. Fedirko, 2002 [6]):

$$R = \frac{exp\,(\beta_0 + \beta_1 \times t + \beta_2 \times v + \beta_3 \times d)}{1 + exp\,(\beta_0 + \beta_1 \times t + \beta_2 \times v + \beta_3 \times d)} \quad (17.2)$$

where R – absolute risk; β_0, β_1, β_2, β_3 – coefficients; t – time of stay under a risk; v - age at the moment of examination; d – radiation dose.

A model of relative risk of involutional cataract (18.3) is as follows (P. Fedirko, 2002 [6]:

$$\lambda = \frac{e^{\beta_0 + \beta_1 v + \beta_2 doz + \beta_3 t}}{1 + e^{\beta_0 + \beta_1 v + \beta_2 doz + \beta_3 t}} \qquad (17.3)$$

where v – age, years; doz – $\sqrt{(d \times t)}$; t – time of stay under a risk, years; d – radiation dose, Gy.

Relative risks calculated by a model (18.1) from age factor was 2.89 (2.53; 3.31), from time of stay under a risk and radiation dose – 1.68 (1.03; 2.74) and from time of stay under a risk only – 1.14 ((1.06; 1.23). An influence of age factor was the greatest.

Relative risk of involutional cataract depending on the dose loading at time of stay under a risk 5 year shown in Figure 17.4.

The conducted modelling revealed that a statistically significant increase in a risk of involutional cataract is the most significant at fifth year stay under a risk. Thus, an absence of the significant difference of involutional cataract frequency has been found explanation in clean-up workers and non-irradiated persons before 1991.

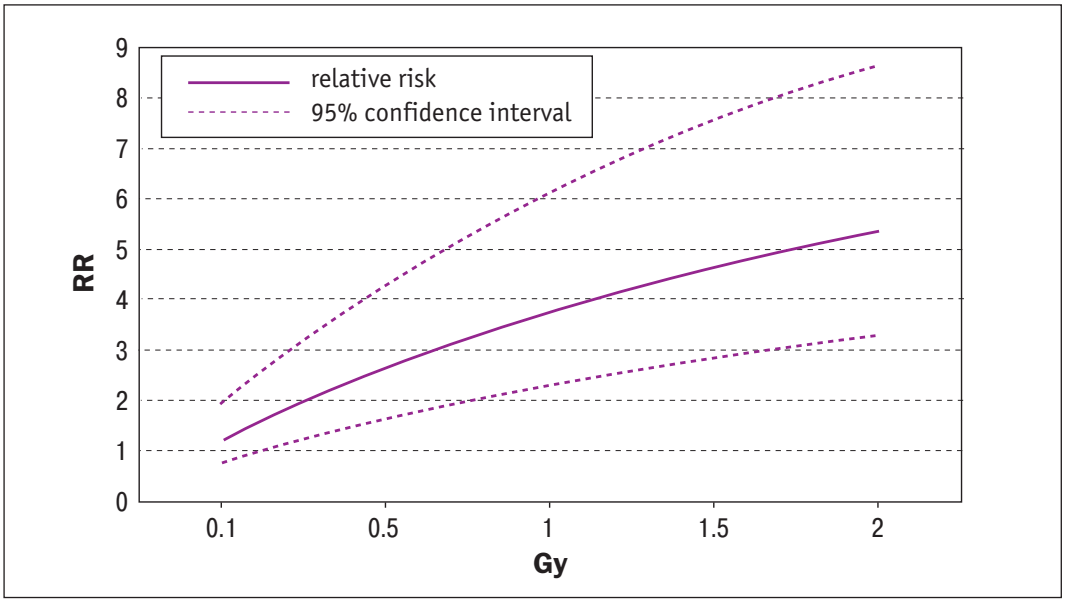


Figure 17.4. Relative risk of involutional cataract depending on the dose loading at time of stay under a risk 5 year

The results of our studies do not contradict the data of other researches. During an international study UACOS [9], in addition to typical radiation, cortical, i. e. involutional cataract was studied. An extract from the results of researches within the limits of UACOS is shown in Table 17.1.

Data of this table demonstrate that expressed cataracts were more frequently observed in a group with a dose over 400 mGy (40 cGy). The initial changes in lens are significantly detected already in a group with a dose exceeded 100–249 mGy; it is obvious that a risk of cataract in this dose group would be also confirmed by following observation [9].

Thus, our data and researches of other authors conducted after the Chornobyl catastrophe have been demonstrated, that an ionizing radiation is a risk factor of the development of involutional cataract.

Table 17.1

UACOS adjusted Odds Ratios (OR) and 95% Confidence Intervals by dose group and the estimated OR at 1 Gy for outcome variables observed. Reference – 0–99 mGy dose range (Worgul B.V., Kundiyev Y.I., Sergiyenko N.M. et al., 2007 [9])

Variable	OR at 1Gy	OR for dose range				
		100–249 mGy	250–399 mGy	400–599 mGy	600–799 mGy	800+ mGy
Early pre-cataract changes	1.15 (0.79–1.66)	1.19 (1.1–1.3)	1.12 (0.9–1.4)	1.16 (0.8–1.6)	0.85 (0.5–1.3)	1.07 (0.6–1.8)
Stage 1–5 cataract	1.70 (1.22–2.38)	0.94 (0.8–1.3)	1.02 (0.8–1.3)	1.07 (0.8–1.5)	1.55 (1.1–2.3)	1.77 (1.1–2.8)
Stage 1 cataract	1.49 (1.08–2.06)	0.92 (0.8–1.1)	0.97 (0.8–1.2)	0.89 (0.7–1.2)	1.46 (1.0–2.1)	1.65 (1.1–2.6)
Stage 2–5 cataract	1.57 (0.79–3.11)	1.04 (0.7–1.7)	1.56 (0.9–2.8)	2.37 (1.2–4.6)	1.29 (0.5–3.1)	1.26 (0.5–3.4)

Retinal angiopathy and angiosclerosis

In studies based on the CER an expressed growth of the prevalence of retinal angiopathy (314.8 ± 14.5 per 1000 persons in 1993 and 911.9 ± 19.7 per 1000 persons in 2004 years), and also an increase in a frequency of angiosclerosis were found in the cohort of clean-up workers. The similar results were obtained by other authors.

Risk of retinal angiopathy and angiosclerosis in groups with the different dose loading is shown comparing to control in Table 17.2.

Table 17.2

Relative risk of vascular pathology of retina in radiation-exposed persons in different doses comparing to control (Fedirko P., 2002 [6])

Variable	Dose range		
	< 0.1 Gy	0.1–0.249 Gy	0.25+ Gy
Relative risk	2.51	2.69	2.65
Confidence intervals	2.03; 3.1 *	2.17; 3.32 *	2.15; 3.26 *
χ^2	121.61	126.13	161.24
p	< 0.001 *	< 0.001 *	< 0.001 *

Notes. * – statistically significant, $p < 0.05$.

The model of absolute risk of retinal angiopathy resembed a formula (17.2) of relative and excess risks of angiopathies, risks were also described by dependences of logistic regression, for a relative risk (P. Fedirko, 2002 [6]):

$$\lambda = \frac{e^{\beta_0 + \beta_1 \log(d)}}{1 + e^{\beta_0 + \beta_1 \log(d)}} \qquad (17.4)$$

and excess risks [13]:

$$\pi = e^{\beta_0 + \beta_1 \log(d)} \qquad (17.5)$$

where d – dose, Gy.

Relative risks calculated by a model (18.4) from log (doze) are 1.29 (1.07; 1.56). Likelihood Ratio Statistic on 2 DF = 297.78, $p < 0.001$.

Thus, basic factors that cause the risk of retinal angiopathy are an age and a time of stay under a risk: a contribution of irradiation dose is lesser.

Subsequent researches in this direction could be based on involving other contingents. For involutional effects where radiation effect is a risk factor, it is important to conduct an examination at a certain period after radiation influence (so-called «window of risk analysis») that

was turned out by a research on the basis of CER. Therefore a large cohort study of retinal angiopathy morbidity including prolonged monitoring of Dnipropetrovsk region inhabitants, the Chornobyl clean-up workers with the known dose loadings (2892 radiation-exposed persons) was conducted. 15 annual stages of examination were conducted with a middle duration of examination 12.83±0.08 years. On the whole, there are 26605.24 men-years examinations [28, 29].

A middle ages of patients consisted of 35.46±0.13 years at a moment of the examination; a distribution according to the age was normal. Official dose loadings (dose of external whole-body irradiation) are known for all examined patients – from 0.01 to 0.7 Gy, middle dose loading – (0.21 ± 0.01) Gy, a distribution in accordance to the dose in groups is normal.

Morbidity of retinal angiopathy was increased with the increasing a time of stay under a risk, and a maximum was reached in 9 years after radiation influence. Then there was an insignificant decrease in morbidity, with the repeated increase in 13 years after radiation influence (Figure 17.5).

Such character of a curve is evidence of a significant effect of two factors as minimum on primary morbidity of retinal angiopathy. It is most likely, if a cohort, with above shown normality by the age, was only under effect of the age factor, we would look only one increase of morbidity.

An analysis of morbidity was conducted depending on a dose loading. Relative risk to fall ill was 1.65 (1.02; 2.67) at $\chi^2 = 4.15$; $p = 0.041$ in all group of radiation-exposed patients in a dose of 30–70 cGy comparing to radiation-exposed patients in a dose up to 0.3 Gy.

Thus, as a result of cohort analysis a statistically significant higher level of primary morbidity of retinal angiopathy was found in the group with greater radiation-exposed dose at a period after irradiation [29].

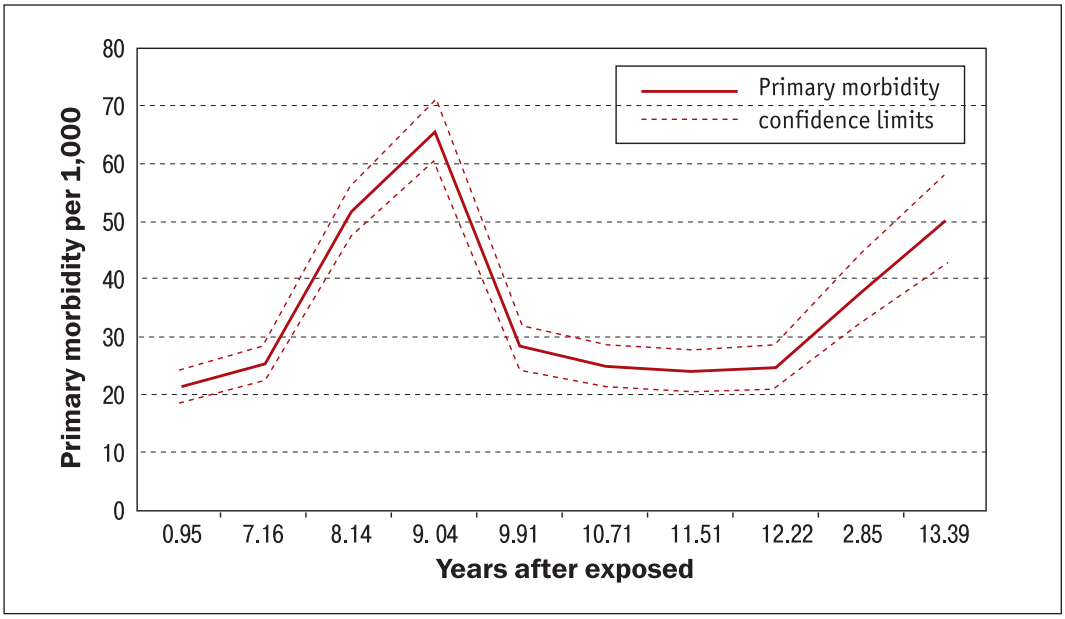


Figure 17.5. **Dynamics of primary morbidity of retinal angiopathy in the cohort of clean-up workers (Fedirko P., Garkava N.A., 2010 [28])**

Macular chorioretinal degeneration

The retina was considered to be relatively resistant to impact of ionizing radiation. Still before the Chornobyl catastrophe a number of authors expressed opinion based on their studies about extreme sensitivity of the retina to irradiation and showed that the retina can be damaged both under considerable and «low» doses of ionizing radiation. Experimental studies conducted after the Chornobyl catastrophe on rats constantly kept in the alienation zone around the Chornobyl NPP proved direct impact of ionizing irradiation on the retina. Photoreceptors appeared to be the most vulnerable ones; changes were also noticed in bipolar and ganglion cells and pigmental epithelium. Response of the vascular membrane of the eye on chronic impact of radiation factors of the Chornobyl NPP accident was studied in the similar series of experiments. Affection of collagen structures and basic substance of vascular membrane, dystrophic changes on endothelium of the vessels, increase of weight of connective tissue were detected [1, 6].

According to our data, the central chorioretinal dystrophy became a frequent type of pathology, well after the catastrophe. After the development of sclerosis of the retinal vessels, changes in the macular area appeared: fovea reflex was smoothed out; foci, blocks of pigment appeared.

In a few years after the catastrophe the frequent and premature development of macular chorioretinal degeneration in irradiated persons has been noted. The pathological changes of retina mainly were represented by drusen, dots of chorioretinal atrophy, pigment redistribution. Cases of «wet» form of this disease in our cohort were rare finds. Predominance of initial stage of disease in our patients is accounted by fact, that clean-up workers cohort consists mainly of young and middle-aged men, who were healthy at the moment of their participation in clean-up operation. Later on the pathological process was progressing slowly, mainly the progress of chorioretinal atrophy was observed. The eyesight was failing slowly, but irrevocable. It is necessary to take into account that repeated examinations were conducted under conditions of permanent medical treatment of the patients. It is possible, that this circumstance had an influence on course of disease [6].

Macular degeneration prevalence and primary incidence rate in our cohort exceeded population ones. A stable trend for the increase of this diseases frequency was observed. The macular chorioretinal degeneration frequency increased from 83.1 ± 57 per 1000 persons in 1992 to 585.7±23.8 per 1000 persons in 2004. Prevalence of this disease in cohort was 224.83 ± 5.8 per 1000, that considerably exceeds control level (55.56 ± 13.5 per 1000). The cohort research allowed to establish, that many new cases of macular degeneration had been appearing in groups which had examined before. A considerable raising of macular degeneration morbidity was noted in 6.5-7.0 years after irradiation, its maximum level was observed in 10 year after catastrophe. Detailed analysis in dose-age groups was performed. Some results are shown in Table 17.5. It was noted, that frequency of macular degeneration increased along with age both in basic and the control groups, but in the same age group the risk of developing this pathology was significantly greater in the basic one (Table 17.3). The increasing of macular degeneration incidence when increasing of dose loads were noted in every age group. For example, chorioretinal degeneration morbidity for the age group under 40 years was 120.17 ± 31.13 per 1000 men-years in dose-group of 0.25–0.499 Gy, and 47.29 ± 17.94 per 1000 men-years in dose-group below 0.05 Gy (difference statistically significant, $p < 0.05$). Thus, the morbidity level dependence on radiation dose was observed. The analysis of macular degeneration morbidity in different age-dose groups confirmed its level dependence on both the age and the dose load.

The computation of relative risk of chorioretinal degeneration in comparison with the control for various age group makes us to believe that risk of development of this disease is greater for per-

sons irradiated in more young age (Table 17.3). So, relative risk was 6.681 (1.68; 26.53) for age-group under 40; 4.21 (1.61; 10.99) for patient aged 40–49 and 3.61 (1.67; 7.79) for age group 50–59 years; 2.38 (0.96; 5.93) for persons aged 60 and over.

Table 17.3

Relative risks (RR) of macular chorioretinal degeneration in the examined clean-up workers of different age groups with different doses of external irradiation (Gy) in comparison with a control groups [6]

Age, years	Index	Doses of external irradiation (Gy)	
		< 0.25, n = 1138	0.25 J, n=956
Under 40	RR (CL)	5.81 (1.42; 23.79)*	7.89 (1.91; 32.57)*
40–49	RR (CL)	3.34 (1.25; 8.91)*	5.70 (2.15; 15.08)*
50–59	RR (CL)	3.60 (1.64; 7.89)*	3.86 (1.77; 8.44)*
60 and >	RR (CL)	3.60 (0.85; 5.63)	3.86 (1.77; 8.44)*
All	MHWRR (CL)	3.44 (2.12; 5.58)*	4.46 (2.76; 7.23)*

Notes. * – difference significant, $P < 0.05$.

The high level of morbidity in relatively young age groups of clean-up workers is indicative of an early beginning of this heavy pathology development.

The study and analysis of influence of some non-radiation factors on risk of macular chorioretinal degeneration development were conducted. Besides age such factors as chemical, physical and biological professional harmfulnesses, diet peculiarities, smoking, alcohol abuse, stresses ets.) were evaluated. As it turned out above-mentioned factors (except age) did not influence considerably on risk in our cohort. It should be took into account, that our cohort is representative of Chornobyl clean-up workers, but not all population. Therefore the results of this study are valid only for Chornobyl clean-up workers. We hope to report in future the results of study of non-radiation factors effect in detail.

An adequate non-linear multifactor model of macular chorioretinal degeneration prevalence was obtained, which follows [6]:

$$R = \frac{exp\,(\beta_0 + \beta_1 t + b_2 v + \beta_3 log(d))}{1 + exp\,(\beta_0 + \beta_1 t + b_2 v + \beta_3 log(d))} \qquad (17.6)$$

where R – absolute risk; β_0, β_1, β_2, β_3 – coefficients; t – time after exposure, years; v – age, years; d – dose, Gy.

An analysis of the results connected with an estimation of radiation-induced risk of maculodystrophy demonstrated that morbidity of maculodystrophy is time-dependent value, i. e. a disease risk related to human senility, is greater than a risk, induced by radiation effect, at the same time with increasing dose loading a reduction of latent period is observed.

The greater risk caused by radiation is noted in relative young age groups comparing to the «elder» after a stay under a 15 year risk. This results in «smoothing» frequency of maculodystrophy in the different age groups of radiation-exposed patients (Figure 17.6).

The nonlinear model of relative risk of maculodystrophy is as follows [6]:

$$\lambda = \frac{e^{\beta_0 + \beta_1 doz + \beta_2 v}}{1 + e^{\beta_0 + \beta_1 doz + \beta_2 v}} \qquad (17.7)$$

and the model of risk excess [6]:

$$\pi = e^{\beta_0 + \beta_1 \times v + \beta_2 \times doz} \qquad (17.8)$$

where β_0, β_1, β_2 – coefficients; $doze$ – $\sqrt{(d \times t)}$, where d – dose, Gy, t – time after exposure, years; a – age, years.

Summarizing the results of modelling relative risk and excess of relative risk of maculodystrophy, one can state that the greatest is an influence of such factors, as an age (relative risk – 1.727

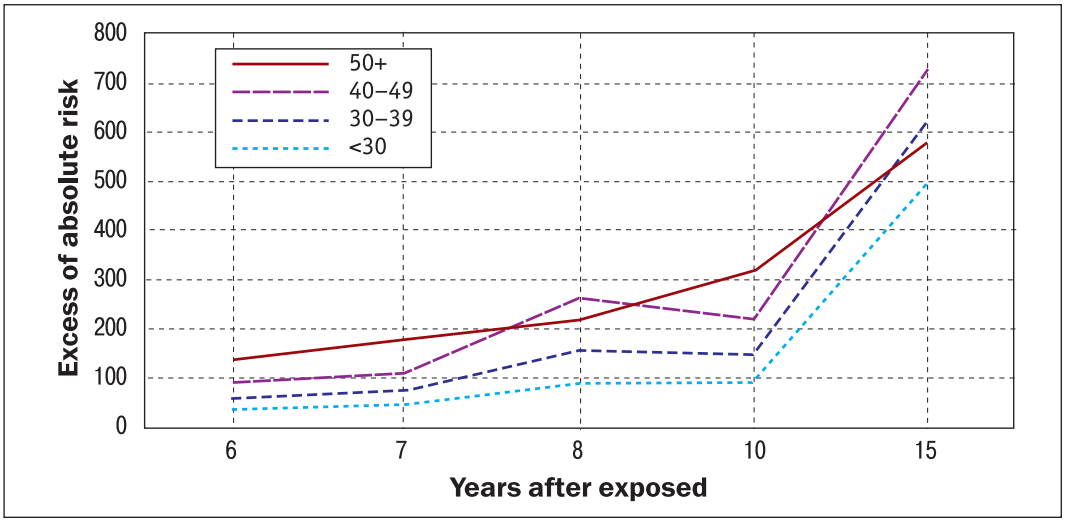


Figure 17.6. **Absolute risk excess of maculodystrophy by a trifactorial model in radiation-exposed patients at the doses of 50–200 cGy in the different age groups depending on time of stay under a risk (per 1000 persons) [6]**

(1.498; 1.727) per 1 year, an excess of relative risk – 1.076 (1.056; 1.095) per 1 year), a time of stay under a risk and a dose (relative risk 6.453 (3.115; 13.37), an excess of relative risk – 1.253 (1.137; 1.37) per 1 $\sqrt{(d \times t)}$, where d is a dose of whole-body irradiation, Gy, t is a time of a stay under a risk, years) [6].

The relative risk of maculodystrophy counted by a model depending on the dose loading at time of stay under risk 5 year is shown in Figure 17.7.

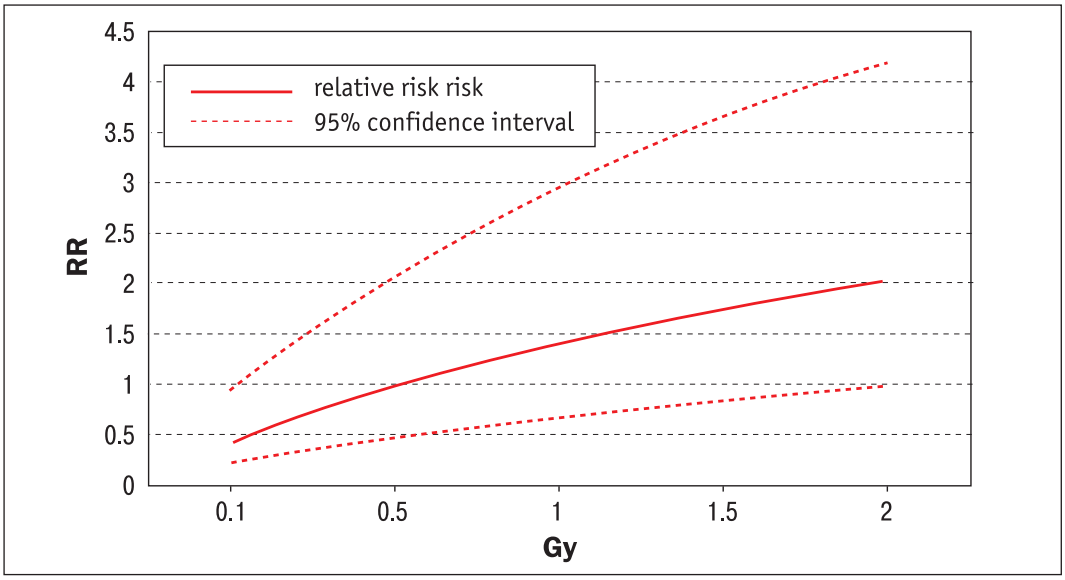


Figure 17.7. **Relative risk of maculodystrophy counted by a model depending on the dose loading at time of stay under risk 5 year [6]**

Thus, the results of cohort research and mathematical modelling allowed to establish that the risk of macular degeneration to the greatest degree depends on the age of radiation-exposed patients at the period of examination, a time of a stay under a risk, a dose of external irradiation. A significant increase in the prevalence of this ophthalmopathy is not expected during the first years of staying under a risk after an irradiation in a dose up to 2 Gy, its latent period consists of 6.5 years. These propositions coincide with presented in literature [1] data of examinations and allow to explain them.

17.1.3. Glaucoma

In the period from 25 to 30 years after the Chernobyl disaster incidence of glaucoma first increased in irradiated groups [30]. In earlier periods the incidence of glaucoma is not exceeded target figures. Increase of glaucoma morbidity with more high rate than in Ukraine as a whole is explained by after-effects of radiation influence [30].

Early development of dystrophic changes of structures of anterior chamber angle can be reason of development of open-angle glaucoma at radiation-exposed persons [31].

17.1.4. Changes in electrophysiologic indices of the eye in radiation-exposed persons

It is known that preclinical functional changes are preceded to the development of clinical pathology. The analysis of literary data testifies that an influence of ionizing radiation (IP) on the functional state of visual analyzer is not enough studied. All ophthalmologists who were examined the consequences of the Chornobyl catastrophe applied visometry and perimetry, the reports of using other methods are not numerous.

Data on the changes in electrooculogram of radiation-exposed persons are above shown.

The methods for determining a critical flicker frequency (CFF), an estimation of a limit of retinal electric sensitiveness (RES) by the phosphene phenomenon and critical flicker frequency by a phosphene (CFFP) were used for studying the functional state of macular zone, internal layers of retina and visual nerve. A group of 95 Chornobyl clean-up workers was matched among the patients of CER by the matching method. An age of examined patients was 30-60 years, a dose diapason of external irradiation consisted from 0.02 to 1.9 Gy. A control group included 42 persons at the age from 30 to 60 years who did not have a contact with an ionizing radiation. Clinically healthy eyes, visual acuity not smaller than 0.8, emmetropia or ametropy, no more than 3.0 D were revealed in all examined patients. CFF of the area in yellow spot was determined by perigraph. An electric stimulator was used for determinining RES and CFFP. An active electrode of this stimulator was placed on the upper eyelid, an indifferent ones - on the forearm of examined patient. An examination was carried out in a dark-room after 5-minute adaptation to darkness.

The results of analysing findings demonstrate the presence of substantial changes in the functional state of the sight organ in Chornobyl clean-up workers comparing to control group. Middle levels of CFF to the stimuli of different color for the Chornobyl clean-up workers are presented comparing to control in Table 17.4.

The significant decrease in CFF was observed independently on the color of twinkling stimulus in a group of clean-up workers comparing to control. This is an evidence of a decrease in functional capacity of macular retina in the radiation-exposed persons, despite an absence of organic changes. At the same time no significant differences were discovered in CFF, also independently on color of stimulus during comparing groups of clean-up workers with different dose loading.

Table 17.4
Levels of critical flicker frequency to the stimuli of different color for clean-up workers in comparison with control (Hz) [6]

Age, years	For the right eye		For the left eye	
	clean-up workers	control	clean up-workers	control
White color	32.7 ± 3.9 *	39.1 ± 0.9	32.0 ± 3.4 *	38.6 ± 1.2
Blue color	28.0 ± 3.7 *	35.0 ± 0.3	28.2 ± 3.2 *	34.3 ± 1.8
Green color	31.2 ± 2.9 *	35.1 ± 0.3	31.4 ± 2.9	34.9 ± 0.5
Red color	27.9 ± 3.2 *	34.4 ± 0.4	27.4 ± 2.9 *	33.8 ± 1.4

Notes. * – difference with control is significant, $p < 0.05$.

Electric sensitiveness of retina and CFF by a phosphene in the Chornobyl clean-up workers (66.2 ± 0.73 mcA) are significantly different in comparing to the control group (53.73 ± 0.89 mcA).

The decrease in an electric sensitivity of the retina (increase in tension current causing appearance of the phosphene phenomenon) and declined ability of distinguishing fluctuations by a phosphene in the radiation-exposed persons are evidence of disorders in internal layers of the retina and the visual nerve.

As a result of analysis of dose dependence of electric sensitiveness of retina and critical flicker frequency by a phosphene, it was found that the electric sensitiveness for persons with the dose loading up to 0.25 Gy and more was (65.06±1.14) mkA with the dose loading 0.25 Gy and more – (67.6 ± 1.2); CFTJ – (42.4 ± 1.1) and (40.1 ± 1.2) Hz, respectively. A difference was not significant.

Thus, the significant changes in electrophysiologic indices of the visual analyzer state, that is the sign of worsening functional state in the retina and the visual nerve, their pathological changes in a subclinical level were found in a group of those clean-up workers who did not have clinical manifestations of eye diseases.

17.1.5. Eye pathology in the exposed prenatally as a result of the Chornobyl disaster

An examination and long-term ophthalmological study of the closed cohort of 583 individuals, who were prenatally irradiated as a result of the disaster at the Chornobyl nuclear power plant was conducted. At the moment of acute irradiation the average gestational age of the patients was (21.07±0.48) weeks. The control group consisted of 808 Kyiv residents [32, 33].

The total effective irradiation dose is known for mothers of 160 persons, the average dose of mother's irradiation worked out (50.03±2.34) mSv, doses ranged from 3.1 to 168 mSv. Irradiation dose of embryo and fetus was reconstructed for 133 persons, individual doses of brain and thyroid gland irradiation in utero – for 134 persons [32, 33].

Total prevalence rate of eye diseases during the first examination of prenatally irradiated patients made up 855.9 per 1000 persons, in the control group - 414.6 per 1000 examined ($\chi^2 = 66.31$, $p < 0.0000001$).

In the visual organ pathology structure there was observed the predominance of refraction pathology (prevalence 449.4 ± 20.6 per 1000 persons in the group of antenatally irradiated and 266.1 ± 15,55 in the comparison group, $p < 0.05$), angiopathies (176.7 ± 15.8 and 51.98 ± 7.81 per 1000 respectively, $p < 0.05$), chronic conjuctivitis (84.1 ± 11.5 and 43.32 ± 7.16 per 1000

respectively, $p < 0.05$), congenital cataracts (17.15 ± 4.94 and 3.71 ± 2.14 per 1000 respectively, $p < 0.05$). Among diagnosed congenital eye developmental disorders congenital cataracts predominated (24.01 ± 6.34 and 4.95 ± 2.47 per 1000 respectively, $p < 0.05$) [32, 33].

Relative risk (RR) of eye disorders for individuals irradiated in utero compared with the control worked out 1.66, confidence interval (95% CI) 1.47; 1.88 and $\chi^2 = 66.48$, difference is significant, $p < 0.0000001$ [33].

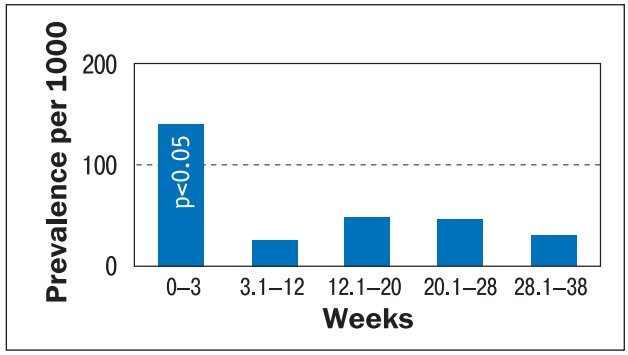


Figure 17.8. Dependence of congenital cataract prevalence on gestational age at the time of the Chornobyl accident

Prevalence of congenital cataracts in the group exposed in utero is significantly higher than in the comparison group, RR of congenital cataracts for exposed in utero was 4.6 (95% CI – 1.3; 16.7) [33].

Significantly higher was the prevalence of refractive errors in persons exposed in utero – RR = 1.7 (95% CI – 1.5; 1.9) on account of hypermetropia – RR = 2.8 (95% CI – 2.1; 3.6) and astigmatism – RR = 1.7 (95% CI – 1.1; 2.7).

Significant increase in the incidence of congenital cataracts (RR = 6.2, 95% CI – 1.34; 28.96) in those whose mothers were pregnant at the moment of Chornobyl disaster and received a total effective dose of 75 mSv and above compared with persons whose mothers' doses were less than 75 mSv was found.

Congenital cataracts were more often diagnosed in the exposed to radiation at gestational age up to 3 weeks ($p < 0.01$). Figure 17.8 illustrates the dependence of congenital cataract prevalence on gestational age at the time of the Chornobyl accident [32, 33].

Based on the long-term follow-up it was found that for individuals irradiated in utero while compared with the control there were significantly higher relative risks of: the development of retinal angiopathy 4.74 (95% CI – 3.3; 6.8), astigmatism 9.4 (95% CI – 2.2; 39.8), accommodation disorder 1.8 (95% CI – 1.3; 2.8), chronic conjuctivitis 2.98 (95% CI – 1.8; 4.9) [33].

An examination by OCT of the antenatally exposed individuals revealed a statistically significant increase in retinal thickness in foveola by 9.3% compared with the control, as well as the thickness increase of the retina in parafoveolar areas [34].

Parameters of retinal thickness in these areas are presented in Table 17.5 and Figure 17.9.

Table 17.5

Retinal thickness in the macular area in the exposed in utero group compared with the control group, μm

Retinal zone	Exposed in utero	Control	t
Foveola	197.75 ± 3.89*	181.0 ± 3.01	2.26
Foveolar zone	259.56 ± 5.67	248.29 ± 6.65	1.29
Parafoveal zone (upper segment)	317.13 ± 3.8	325.29 ± 2.85	1.72
Parafoveal zone (nasal)	326.63 ± 4.14	325.79 ± 3.49	0.16
Parafoveal zone (lower)	317.25 ± 4.38	321.0 ± 3.28	0.69
Parafoveal zone (temporal)	308.81 ± 2.6	310.29 ± 2.74	0.39

Notes. * – significant difference, $p < 0.05$.

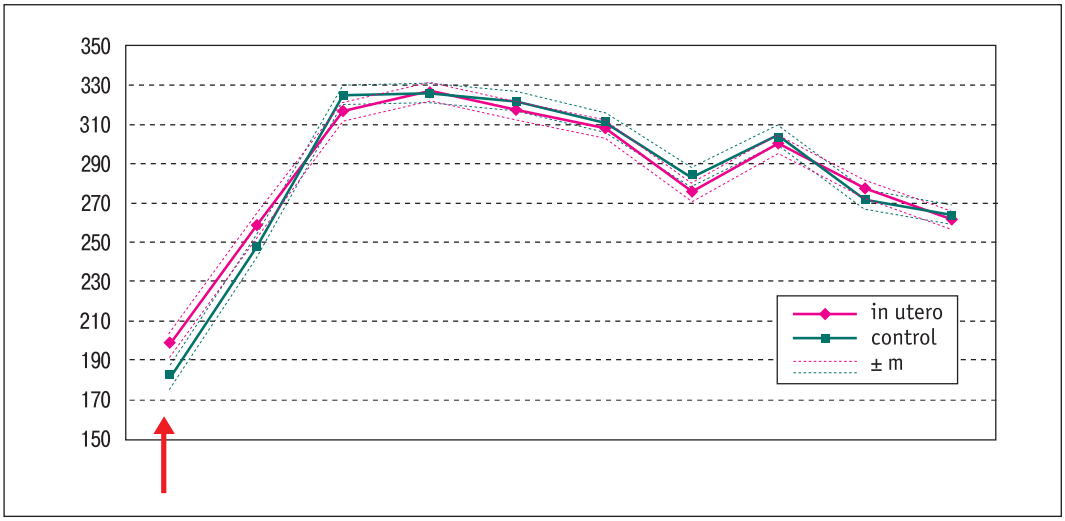


Figure 17.9. The average retinal thickness of the paramacular zone in the exposed in utero compared with control, μm. The arrow shows a significant difference in foveola thickness.

The thickness of the fibers of the optic nerve in the basic group was significantly higher compared with the control group.

Radiation effect in early gestational age – 2.8–19.9 weeks caused more significant changes in retinal thickness of the upper and lower parafoveolar zones compared with the exposure in later gestational age [34].

It has been established that prenatal radioactive irradiation is risk-factor for ophthalmopathology development. The necessity of medical observation of prenatalliy irradiated persons was noted [32].

17.1.6. Eye diseases in children who live in radiation contaminated territory

For the first time pathological changes in the eye of the children of contaminated zones were detected in 5–6 years after the Chornobyl disaster [16, 17, 35–37].

We analysed the results of the examination (in period 5–15 years after the Chornobyl disaster) at the of 1,487 residents of Boyarka (a town in the Kyiv region, 4th zone – tightened radiological control, density of soil ^{137}Cs contamination from 2 to 5 Ci/km^2, the average age of the examined – 11.09 ± 0.07 years) and 461 inhabitants of Ovruch (a town of the Zhytomyr region, 3rdzone – guaranteed voluntary resettlement, density of soil ^{137}Cs contamination from 5 to 15 Ci/km^2, the average age of the examined – 11.38 ± 0.16 years) [38–40].

The prevalence of eye diseases makes up among the children – inhabitants of radioactive contaminated areas – 475.04±24.23 per 1000 in 3 radioactive area and 531.26±25.78 per 1000 in 4 radioactive area and exceeds the control level by 2.79 (2.13; 3.67) and 3.12 (2.41; 4.05), respectively.

In zone 3 there were often observed: astigmatism (18.26% of all diagnoses), hyperopia (16.44%), myopia (11.42%), and asthenopia (11.42%). In zone 4 the most frequent diagnoses were hyperopia (22.35% of all diagnoses), then – astigmatism (11.49%), asthenopia (11.24%), and myopia (7.19 %).

Both in the 3rd and 4th zones diseases of the conjunctiva were in the second place in the structure of the examined eye prevalence – 12.79% and 25.25% respectively. The most common diagnosis was chronic conjunctivitis. In third place among diagnoses in children and adolescents of Ovruch (zone 3) – inflammation of the eyelids – 7.76%, in children from zone 4 – visual disturbances – 6.82% (due to amblyopia – 6.31%). Blepharitis in Boyarka (zone 4) accounted for only 2.27% of the diagnosed pathological changes.

The prevalence of refractive errors was 281.99 per 1,000 residents in the 3rd and 281.78 per 1,000 people in the 4th zones.

The prevalence of retinal diseases was 10.85 per 1,000 residents in radiation zone 3 and 2.02 per 1,000 for the 4th zones. As for the structure of retinal diseases: in the 3rd zone retinal diseases were represented by angiopathy (6.51 in 1000) and two cases of tapetoretinal degeneration, in the 4th area - only by angiopathy (2.02 per 1,000).

All groups showed an increasing tendency for refractive errors and retinal diseases to become more frequent with age.

Risk-analysis showed that the relative risk of having angiopathy in offspring of emergency workers compared with residents of Boyarka was 1.53, confidence interval – 1.36; 1.71 at $\chi^2 = 12.84$ and $p = 0.0003$, the difference is significant.

In the period from 25 to 30 years after the Chornobyl disaster incidence of eye lesions studied in the same areas. The prevalence of eye lesions was 475.04 ± 24.23 per 1000 inhabitants for three zone and 531.26 ± 25.78 per 1000 for 4 zone [41].

17.1.7. Peculiarities of refractogenesis in children who live in territory contaminated with radiation

The organ of sight is changed in children with an ageing, a process of refractogenesis is occurred. A subsequent relative refraction and, consequently, functional capacity of the eye are dependent on refractogenesis course. The features of refractogenesis in children with persistent irradiation influence were studied in long-term research. During 11 years, 989 pupils (born in 1981–1992) of 1–11 classes who were living in one of climate geographical zone of the Zhytomyr region, but in ecologically different districts were subjected to the repeated examinations [42].

The 1 group (main) consisted of 533 pupils from the radiation-contaminated settlements. It included two sub-groups: the 1 group – 485 pupils at the age of 6.5–16.5 years, who live in an area with radionuclide contamination (CZ) by ^{137}Cs 5–10 Ci/km^2; the 2 group – 48 pupils at the age of 8–15 from an area by ^{137}Cs contamination 10–15 Ci/km^2. The 2 group (control) was made of 334 pupils aged from 6.5 to 16.5 who live in «uncontaminated» zone – UZ. 3 group (additional) consisted of 164 pupils aged 16–17.5 years from settlement with radionuclide contamination by ^{137}Cs 5–15 Ci/km^2.

It has been established that refraction in children who were living in UZ ranged from –19.0 D to +8.75 D. Refraction variations from –14.0 D to +8.0 D was noted in children who were living in CZ. Hypermetropia of weak degree was prevailed in both areas. A middle refraction in pupils from CZ was equal to 0.47±1.29 D, that statistically does not differ from a middle refraction in children from UZ ($p > 0.3$). Emmetropia (29.6% and 34.3%, $p = 0.04$) was significantly rarely observed in CZ comparing to UZ and myopia of weak degree (5.9% and 2.3%, $p = 0.0003$) – significantly frequently.

For the first time the features of forming refraction (the process of emetropization) were diagnosed in children who were living in UZ and CZ: an emmetropia was diagnosed in 0.0–18.8% cases of pupils at the age of 7–12 years from an UZ, who were born in 1987–1992, and in

12.3–39.0% cases – in CZ. An emmetropia was more frequently diagnosed in pupils at the age of 13–16 years, who were born in 1981–1986 in UZ (60.0–81.8%) comparing to CZ (35.3–47.9%). From other side, hypermetropia was diagnosed in 70.0–100.0% children at the age of 7–12 years from UZ, and in 50.0–83.3% cases from CZ; in 6.8–27.5% and 35.3–53.4% in children aged 13–16 years, respectively (Figure 17.10).

Data obtained demonstrate the acceleration of emetropization process in children aged 7–12 years, who were born in 1987–1992, and are living in CZ comparing to children of analogical age from UZ, and at the same time the increased process of refractogenesis in children of 13–16 years from CZ, who were born in 1981–1986.

Risk of hypermetropia in the children of CZ, who were born before the Chornobyl accident is 22 times higher ($p = 0.0006$) at the age of 12–14 years, and in 2.3 times higher ($p = 0.015$) – at the age of 15–16.5 years than in children of analogical age from UZ.

The percent of myopia among children of the young school age is caused, as a rule, by the hereditary disposition. With the increase of age the percent of diagnosed myopia is increased in the «clean» as well as contaminated zones. A frequency of diagnosed myopia is 29.4% in children of 16 years from CZ comparing to 11.4% from a «clean» zone ($p = 0.049$). It has been established that risk of myopia development in children aged 15–16.5 years from CZ is 1.9 times higher, than in the children of identical age from UZ ($p = 0.01$).

It has been established that a frequency of all types of astigmatism (5.1% in UZ and 5.9% in CZ, $p > 0.3$), and also hypermetropic (3.6% in UZ and 3.3% in CZ, $p > 0.3$) and myopic astigmatism (1.05% and 1.03%, $p > 0.3$ respectively) in both zones was practically identical. However a frequency of mixed astigmatism (0.45% and 1.6%, $p = 0.03$ respectively) was higher in a radiation contaminated region. The mixed astigmatism was almost noted in all age groups of children in CZ, while it was diagnosed only in 13-years-old pupil from UZ.

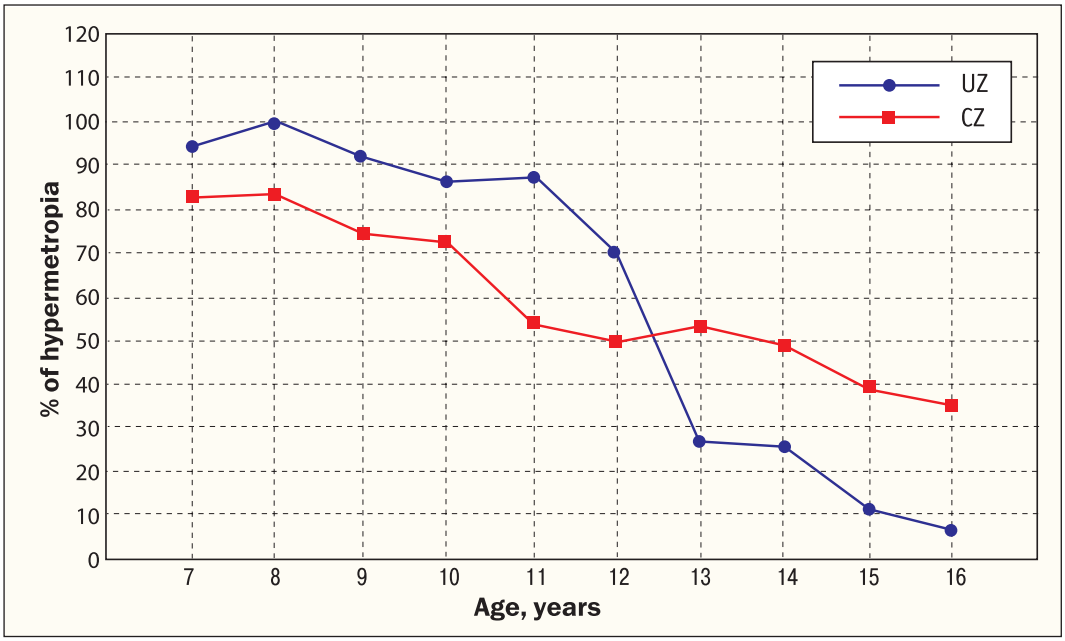


Figure 17.10. Percent of hypermetromia in children of different age category depending on the area of living [42]

The dynamics of changes in refraction was investigated during 5 years in children living in the contaminated with radiation and «uncontaminated» zones. Middle age of children at the moment of the first examination was 9.3 ± 1.6 in a «clean», and 9.4 ± 2.3 ($p = 0.45$) – in contaminated zone. Hypermetropic refraction was revealed in 91.5%, emmetropia – in 5.7%, myopia – in 2.8% children from UZ according to the data of the first examination. A frequency of hypermetropy was decreased 2 times as many (44%), a frequency of emmetropia was increased 8.5 times as much (48.4%), myopia – 2.5 times as much (6.9%), mixed astigmatism (0.6%) was found in 2 cases in 5 years. At the moment of the first examination the children with hypermetropia were also prevailed in CZ, but their number was less than in UZ (76.1%, $p < 0.05$); frequency of emmetropia was 19.7%, that is significantly higher than in children from UZ ($p < 0.05$), of myopias – 3.2%, of mixed astigmatism – 1.1%. In 5 years a hypermetropia frequency was also decreased 2 times as many (39.4%), a frequency of emmetropia was increased 2.6 times as much (51.9%), myopia – 2.3 times as much (7.2%), mixed astigmatism –1.5 times as much (1.6%). Noted reinforcement of refraction corresponds to the known data. At the same time, initial greater frequency of emmetropia in the children of CZ and lesser percent of its increase in 5 years confirm the fact of early emetropization in the pupils of zone contaminated with radiation.

Statistically significant strengthening of refraction took a place at all its initial types in the children of CZ, and only in initial hypermetropia – in the children of UZ.

Refraction distribution was studied in adolescents at the age of 16–17 years depending on a time of their birth regarding date of the Chornobyl accident. It is shown that a frequency of myopia was different: 11% was in those exposed to an irradiation in an embryo period or at the first year of life; 29% – in the age of 1–3 years, and 5% in children born in 4–6 years after an accident at ChNPP.

Thus, the conducted researches discovered that refraction forming i. e. a development of the eye differ between children who live in «uncontaminated» and contaminated with radiation zones: an emmetropia was marked in 9% children born after the Chornobyl at the age of 7–12 years from an «uncontaminated» zone, and in 26% children of a contaminated zone.

Hypermetropia is more frequently diagnosed in children at the age of 13–16 years who were born before the Chornobyl accident in a CZ with radiation (44%), than in an UZ (17%) that is the sign of refractogenesis deceleration.

Myopia frequency in the age interval 7–16 years is raised from 3.7% to 11.4% in the children of UZ and from 4.2% to 29.4% in the children of CZ. Risk of myopia development is 1.9 times as much in children aged 15–16 years who were born before the Chornobyl accident from the zone contaminated with radiation, than in the children from «clean» area.

It was first established that a myopia frequency was different in adolescents aged 16-17.5 years at a finishing phase of refractogenesis depending on birth time regarding the date of the Chornobyl accident: in those exposed to irradiation at an embryo period or at the first year of life – 11%; in radiation-exposed patients at the age of 1–3 – 29%; in children born in 4–6 years after an accident at ChNPP – 5% [42].

17.1.8. State of sight organ and its functional features in children, born from the radiation-exposed persons

The study of the eye state in children, born from the radiation-exposed persons, has an unordinary scientific significance, you know that the eye has extraordinarily difficult way of embryogenesis and contains the row of various structures that is the best a background for the study of

micromutations. That is why a research of the eye state in children, born at a postaccidental period from the Chornobyl clean-up workers, who live in Kyiv, was begun by us, partly in a collaboration with other scientific institutions.

2202 children, born from the Chornobyl clean-up workers took part in cohort research. The examined person lived in Kyiv and were not direct exposed to radiation influence. An age of examined patients was from 0.74 to 17.2, middle ages – 8.3±0.1 years. A period of examination included 1992–2006. A control group for ophthalmologic research consisted of 252 inhabitants of Kyiv of same age, including persons whose parents were not additionally exposed to (comparing to other inhabitants of Kyiv) radiation influence. An age of control group persons was from 0.5 to 17.58, middle ages – 8.42 ± 0.29 years.

It has been established that a prevalence of eye pathological changes was 229.34±10.62 per 1000 children of clean-up workers, 170.64 ± 23.69 per 1000 children of control group. The relative risk of pathological change presence for descendants of radiation-exposed patients was increased (due to an age group of 13 years and older) and consisted of 1.33 (CI – 1.0; 1.76, a difference is statistically significant, $\chi^2 = 4.12$, $p = 0.042$) in comparing to the control group. Prevailed majority of diagnoses belonged to disorders of refraction and accommodation – 53.88% from all diagnoses of children in clean-up workers, 65.79% from all diagnoses of children in control group. Prevalence of refraction anomalies was 123.07 per 1000 children in clean-up workers, 107.14 per 1000 children in control group, a relative risk 1.07 (0.74; 1.55), a difference is insignificant. Diseases of the conjunctiva (30.22%) took the second place in clean-up workers, a frequency of this pathology in them is 68.57 per 1000. Thus frequency of chronic conjunctivitis was 64.03 per 1000. A frequency of this pathology was 7.94 per 1000 in a control group, and a relative risk of this pathology for descendants of radiation-exposed persons comparing to the control group was 8.51 (2.12; 34.12). The presence of such substantial increase in frequency of conjunctiva chronic inflammations can be related to some unophthalmologic changes, an examination in main as well control groups were carried out under absence of acute diseases. Retinal diseases (6.56% diagnoses) with a prevalence of 14.99 per 1000 persons in the structure of morbidity in a basic group took the third place. Angiopathies (29 cases – 13.17 per 1000 persons) were prevailed in their structure in the children of liquidators, 2 cases of retinal central dystrophy and 2 cases of chorioretinitis – in 0.91 per 1000 persons were found. Retinal diseases (31.74 per 1000) are presented by angiopathies and by one case of retinal peripheral dystrophy in a control group. The difference between groups was insignificant. At last, a congenital pathology of the eye was found in 6.36 cases per 1000 in descendants of radiation-exposed patients and in 11.9 cases per 1000 – in a control group. Congenital cataracts were prevailed. Their relative risk was 0.34 (0.09; 1.26) for descendants of radiation-exposed patients and, thus, a difference between groups was insignificant ($p = 0.12$). It is necessary at once to note that minimum congenital changes in the lens while the diagnosis of a congenital cataract is not established, and were not included into this statistics data on such changes would be shown in future reports [41].

Thus, the results of primary examination in groups of clean-up workers were indicative of the greater risk of eye pathological changes for descendants of radiation-exposed patients, but not due to the expressed congenital changes in the eye.

Subsequent researches were connected with functional possibility of the eye in children of clean-up workers. 32 patients, whose parents informed of dose loading, were matched for studying dark adaptation. Middle age of examined patients by the data of an adaptometer was 15.91 ± 0.31, they were born in an interval from 2 to 8 years after an exposition of radiation effect on their parents, the middle dose of parent irradiation was (0.307 ± 0.06) Gy. The seven-minute

test using adaptometer (recording semi-automatic adaptometer) was conducted by a standard method.

The analysis of results witnessed that a sensitiveness for all examined persons was within the limits of permissible values. At the same time, an analysis of dependences on the dose loadings in the parents of examined patients revealed that some functional indices were worse in the group of children whose parents were exposed to the radiation doses over 0.24 Gy, than in children whose parents were exposed to radiation doses up to 0.21 Gy [43].

Thus, the analysis of dependences on the dose loadings in parents of examined patients, demonstrates that a sensitiveness was higher in the group of children whose parents were received the doses of irradiation in an interval from 2 to 21 cGy, for a time of adaptation 1 and 3 minutes, than in children whose parents were exposed to radiation in the doses of 24–120 cGy. Sensitiveness for time of adaptation 1 minute was 1.71 ± 0.07 in the group of descendants exposed to radiation in the lesser doses, and 1.46 ± 0.09, $t = 2.2$, $p < 0.05$ in the group of descendants exposed to greater doses. According values for adaptation time such as 3 minutes were 2.21 ± 0.04 and 1.95 ± 0.11, $t = 2.2$, $p < 0.05$.

Thus, a significant decrease in rate of adaptation to darkness is observed in the second group (radiation-exposed descendants in the doses of 24–120 cGy) [43].

The mechanisms of these changes require a subsequent verification. But now one can assert that the subsequent study of functional features of the sight organ in descendants of radiation-exposed patients can substantially extend our view of functioning visual analyzer.

* * *

Except a radiation cataract, severel effects with signs of deterministic ones were detected in radiation-exposed patients as a result of the Chornobyl catastrophe: radiation retinopathy – in the victims exposed as a result of the Chornobyl catastrophe – two its new forms such as «syndrome of the chestnut» and «syndrome of diffraction grate» and also disorder of generation in the eye permanent potential (threshold dose is 20 cGy) and dose dependent decrease in capacity to an accommodation (dose 15 cGy can be considered as threshold).

In addition, radiation influence substantially modifies a morbidity of other eye diseases; the functional changes in the sight of radiation-exposed patients were found.

It has been shown that a radiation exposure causes a significant dose dependent increase in the prevalence (369.9 ± 6.7 per 1000 clean-up workers versus 83.33 ± 16.3 per 1000 in control) and premature development of involutional cataract. In the risk model of involutional cataract the basic parameters are the age at the period of examination, the time of stay under a risk, absorbed dose of external irradiation. The relative risk of involutional cataract caused by radiation consists of 1.681 (1.033; 2.735) per $1 \sqrt{(d \times t)}$, where d is a dose of irradiation (Gy), t is time under a risk (years).

Effect of ionizing radiations causes a significantly increased risk of pathology in the eye vessels (694.3 per 1000 clean-up workers and 246.53 per 1000 persons of control group). By mathematical modelling it was established that the risk of basic factors in retinal angiopathy of clean-up workers population is the age of radiation-exposed persons, and a dose of external irradiation to the lesser degree.

In other cohort study it was revealed that morbidity of retinal angiopathy was increased with the increase of time for staying under a risk, and attained a maximum in 9 years after radiation influence in clean-up workers. Relative risk to fall ill in all group of radiation-exposed patients in the dose of 30–70 cGy in comparing to radiation-exposed patients in a dose to 0.3 was 1.65 (1.02; 2.67) at $\chi^2 = 4.15$; $p = 0.041$. Thus, the statistically significant higher level of primary morbidity of retinal angiopathy was found at a period after radiation influence in the group of radiation-exposed in a greater dose as a result a cohort analysis.

Radiation influence is a risk factor of premature development of retinal dystrophy at a remote period after irradiation. As a result of radiation the absolute risk of central chorioretinal dystrophy is increased; a prevalence of macular dystrophy among clean-up workers is 224.83 ± 5.8 per 1000 persons, that exceeds significantly control numbers (55.56 ± 13.5 per 1000). The risk basic factors of macular dystrophy development is the age of radiation-exposed patients, the time of stay under a risk, the absorbed dose of external irradiation in population of clean-up workers, by the data of examinations and mathematical modeling. The relative risk of maculodystrophy consists of 6.453 (3.115; 13.37) per 1 $\sqrt{(d \times t)}$, where d is a dose, t is time under a risk (years).

A significant decrease in the critical flicker frequency by phosphene was found in groups of clinically healthy clean-up workers comparing to control that is evidence of an increase in functional possibility of the macular retina in radiation-exposed persons, without regard to an absence of organic changes. There was also a decrease in electric sensitivity of the retina and a decrease in ability to distinct the fluctuations by a phosphene in the radiation-exposed persons that testify to disorders of functional capacity in the retinal internal layers and the visual nerve.

In the period from 25 to 30 years after the Chornobyl disaster incidence of glaucoma first increased in irradiated groups.

Prevalence of congenital cataracts in the group exposed in utero is significantly higher than in the comparison group, RR of congenital cataracts for exposed in utero was 4.6 (95% CI – 1.3; 16.7). It has been established that prenatal radioactive irradiation is risk-factor for ophthalmopathology development. The necessity of medical observation of prenatalliy irradiated persons was noted.

The prolonged observation of the refractogenesis process in children who live in the territories contaminated with radiation revealed that they have a delayed development of the eye refraction system, and an increased frequency of myopia that is diagnosed in children who were exposed a maximal irradiation at an embryo period or at the first years of life.

It has been established that a greater frequency of pathological changes in the eye were found out in the children of clean-up workers, born after radiation influence, but not due to congenital changes of the eye; their capacity to dark adaptation depends on the dose loadings of parents of examined persons, although it remains within the limits of permissible values.

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17.2. SENSORINEURAL DIMINISHED HEARING IN CLEAN-UP WORKERS EXPOSED TO RADIATION AS A RESULT OF THE CHORNOBYL CATASTROPHE IN THE DYNAMICS OF POST-ACCIDENTAL PERIOD

The results of our own scientific analysis are based on the standard clinical, audiometrical, electroacoustic and electrophysiologic examinations of the auditory analyzer (AA) in the clean-up workers of the Chornobyl nuclear power plant (ChNPP) who were exposed to short-term, relatively short-term and long-term ionizing radiation (IR) with different doses, under long monitoring during different years of post-accidental period.

There were 7812 Chornobyl catastrophe clean-up workers of male sex, who were sent to SI «O.S. Kolomiychenko Institute of Otolaryngology of National Academy of Medical Sciences of Ukraine» from SI «NRCRM of NAMS of Ukraine» for clinical observation and expert estimation of the AA functional state during 1986–2014 including also 8 months of 2015 year. Individual doses of ionizing radiation were used from the informative base of this institution as initial data.

The directed persons complained of auditory disorders, such as a noise in the ears of different spectrum of sounding and intensity (from low-frequency, high-frequency or mixed), and also a decreased hearing acuity and impaired perception of reversed speech during examination. Hearing within the normal age limits was registered in 55.5% cases among 1200 Chornobyl catastrophe clean-up workers at a primary audiometrical examination (1986-1987). A decrease in hearing acuity, that caused the manifestations of sensorineural diminished hearing (SNDH) of different degree was found in the other 44.5% cases. It was related to the diseases under the rubric H.90 by the ICD-10.

There are four degrees of decreased hearing acuity, detected in them by the V. G. Bazarov and A. I. Roskladka classification of 1995 [1]: the Ist degree – easy, the IInd – middle in 37.0% cases that are considered as a socially adequate hearing, and the IIIrd, the IVth degrees – diminished-hearing acuity in 7.5% cases that are regarding to socially inadequate significant hearing impairments.

In particular, there were 26.3% cases with the Ist degree of diminished hearing acuity, 10.7% – with the IInd degree, 6.1% – with the IIIrd degree and 1.4% – with the IVth degree among them. These data are shown in Figure 17.11.

325 Chornobyl catastrophe clean-up workers were matched by us from the general amount of examined patients for the prolonged examinations. The changes in the auditory analyzer of these persons were studied in a dynamics of 27–29 post-accidental years including 2014 and 8 months of 2015 year. They were divided into three groups depending on the dose and duration of IR effect.

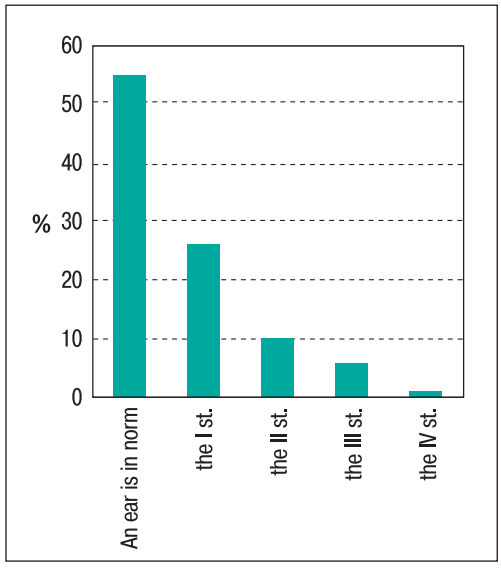


Figure 17.11. State of hearing acuity in accordance with data of audiometry in 1200 Chornobyl catastrophe clean-up workers at a primary examination (1986–1987)

57 Chornobyl catastrophe clean-up workers exposed to short-term ionizing radiation in the large doses and had acute radiation sickness (ARS) of the Ist and the IInd degrees) were included into the first group. 31 patients who had ARS of the Ist degree among them, were attributed to the I-A group; and 26 patients who had ARS of the IInd degree were included into the I-B group. The retrospective dose of IR made 1.3–2.0 Gy in patients of the I-A group and 2.1–3.5 Gy – in those of the I-B group by biological dosimetry (by chromosomal aberrations of peripheral blood lymphocytes).

The second group consisted of 120 Chornobyl catastrophe clean-up workers who were exposed to relative short-term IR at an early post-accidental period, namely: in the first 2 months of liquidating works. They were divided into the II-A and II-B groups at primary examination in 1986–1987. The II-A group included 64 clean-up workers whose IR dose made 0.20–0.25 Gy, and the II-B group consisted of 56 persons who were exposed to IR in the doses of 0.26–0.50 Gy that were retrospectively established after dosimetric calculation (by a occupational route letter).

148 clean-up workers who were exposed to long-term IR entered into the third group. They were examined before and after work during 6–8 years at Chornobyl the exclusion zone (*of estrangement*)in the dynamics of post-accidental period. Their IR dose is analogical to that of patients in the II group and made 0.20–0.50 Gy (by individual physical dosimetry). The III-A group included 79 clean-up workers whose IR dose was 0.20–0.25 Gy, and the III-B – 69 persons whose IR dose made 0.26–0.50 Gy.

The methods of clinical examination including the complex standard examinations of auditory function were used for studying the AA functional state: audiometry, electroacoustic examinations – otoacoustic emission of distorted products (OAEDP), dynamic impedancemetry; electrophysiologic examinations – the auditory induced potentials (AIP): short-latent (SL) or brain stem and long-latent (LL) or cortical ones.

In the first group hearing acuity was within the limits of age norm in 33 from 57 clean-up workers who had ARS, and SNDH of the Ist and the IInd decrees was found in 24 persons at a primary examination in 1986–1987. Impaired speech intelligibility was noted in 19 from 33 persons with a normal tonal hearing and in all 24 clean-up workers with SNDH of the Ist and the IInd degrees in the I group. In particular, their thresholds of 100% intelligibility of language tests were registered at the level of [(60.3 ± 0.5) dB (an expected level – (45.5 ± 0.7) dB].

The increase in a number of persons with SNDH and an increase in a degree of its manifestation was marked in the dynamics of different terms of post-accidental period among examined clean-up workers in the I group [2].

Thus, only 3 from 29 persons had hearing within the limits of age norm in the I-A group, 11 persons – SNDH of the Ist degree and 11 persons – SNDH of the IIIrd degree and 4 persons – the 3rd degree in the I-A group, and only 1 from 21 persons had had hearing within the limits of age norm, 4 – SNDH of the Ist degree, 10 – the IInd degree, 4 – the IIIrd degree and 2 – the IVth degree of the I-B group in 2008–2009. It should be noted that significantly more persons with manifestations of diminished hearing from IInd to IVth degree of SNDH were fixed in patients of the I-B group who had ARS of the IInd degree and were accordingly exposed to greater IR doses.

The audiometric examination included 32 persons of the first group in 2010–2014. 19 patients of them had ARS of the Ist degree, 13 – ARS of the IInd degree. SNDH of different degrees of manifestation was noted in all patients. Decreased hearing of the Ist degree was fixed in 3 persons of I-A group and in 1 person of I-B group. SNDH of IInd degree was fixed in 8 persons of I-A group and in 2 persons of I-B group. SNDH of the third degree was found in 7 persons of I-A group and 8 persons of I-B group. SNDH of IVth degree was found in 1 person of I-A group and in 2 persons of I-B group.

Impaired intelligibility of verbal tests was revealed in all the investigated persons with reduced hearing acuity according to tonal audiometry data.

The results of long term monitoring over 27–29 years in persons who had ARS of the Ist and the IInd degrees showed progressive SNDH of different degree of manifestation with impaired speech intelligibility including age-related changes in hearing acuity.

Hearing within the limits of physiologic age-related norm was noted in 64 persons from 120 clean-up workers of the II group, in 34 persons from them in the II-A group and in 30 persons – in the II-B group who were exposed to a greater dose of IR. Hearing acuity was decreased in other 56 clean-up workers; SNDH of the I^{st} degree was noted in 33 persons and SNDH of the IIst degree – in 23 ones.

In addition, the delayed intelligibility of language tests was noted in 13 from 64 clean-up workers with normal tonal hearing acuity and in 17 from 56 persons – with diminished hearing in the II group.

Hearing within the limits of age-related norm was registered in 32 persons from 10^6 clean-up workers in the II group, examined in 2008–2009. SNDH of different degree of manifestation was found in other 74 patients. In particular, SNDH of the Ist degree was registered in 22 clean-up workers from the II-A group, and in 16 persons of the II-B group; SNDH of the IInd degree was fixed in 16 persons of the II-A group and in 12 persons of the II-B group. SNDH of the IIIrd degree was diagnosed in 3 persons of the II-A and in 3 patients of II-B groups, and SNDH of the IV the degree was noted only in 1 person of the II-B group.

In addition, the delayed intelligibility of language tests was fixed in 16 from 32 clean-up workers with the normal hearing acuity in the 2nd group and in 53 from 74 patients with SNDH of different degree manifestation.

Hearing within the age norm was registered in 20 persons from 97 clean-up workers of the second group, in 12 of 20 persons from II-A group and in 8 persons from II-B group in 2010–2014. SNDH with different degree of hearing decrease was revealed in the remaining 77 patients. In particular, hearing decrease of the I^{st} degree was noted in 5 persons of II-A group and in 7 persons of II-B group. The IInd degree of hearing decrease was revealed in 16 persons of II-A group and in 11 persons of II-B group. The IIIrd degree of hearing decrease was fixed in 13 persons of II-A group and 19 people of II-B group. The IVth degree was fixed in 23 person of II-A group and in 4 persons of II-B group.

The results of audiometric surveys show that the number of patients with hearing within age norms was decreased in the second group and the number of persons with different degree of SNDH manifestation was increased in 27–29 years.

Hearing within the limits of age norm was observed in all 148 persons of the IIIrd group before the work at Chornobyl the exclusion zone (of estrangement) by audiometry results.

A number of persons with an ear within the limits of age norm was decreased up to 59 persons, and SNDH of the 1st and the 2nd degrees was registered in 89 patients after stopping an implementation of works at the area of estrangement.

In 2008–2009 36 persons had normal hearing among 141 examined patients of the III group, SNDH of different degrees was noted in 10^5 clean-up workers. Particularly, SNDH of the I^{st} degree was registered in 20 persons of the III-A group, and in 6 persons of III-B group; SNDH of the IInd degree – in 23 persons of the III-A group, and in 21 patient – of the III-B group; SNDH of the IIIrd degree – in 12 persons from the III-A group, and in 14 persons from the III-B group; SNDH of the IVth degree – in 3 patients from the III-A group, in 6 persons – from the III-B group, that is SNDH of the IIIrd degree was totally diagnosed in 26 clean-up workers, SNDH of the 4th degree – in 9 persons comparing to the IInd group where the number of per-

sons with the III[rd] and the IV[th] degrees of SNDH was less (SNDH of the III[rd] degree – in 6 persons, and SNDH of the IV[th] degree – in 1 person).

The audiometric examination was conducted in 116 clean-up workers of the third group in 2010–2014. Hearing within age norms was found only in 13 persons, in 8 of them in the III-A group and in 5 – in III-B group. SNDH with different manifestation was fixed in rest of 10^3 persons. Thus, hearing decrease of the I[st] degree was noted in 7 persons of III-A group and in 6 persons of III-B group. SNDH of the II[nd] degree was revealed in 15 persons of III-A group and in 20 persons of III-B group. The decrease in hearing acuity of the III[rd] degree was registered in 18 person of III-A group and in 26 persons of III-B group. SNDH of the IV[th] degree was noted in 4 persons of III-A group, and in 7 persons of III-B group.

In addition, it is interesting that further development of delayed intelligibility of verbal tests in individuals with the II–IV degree of reduction in hearing acuity, revealed by speech audiometry, can indicate the inhibitory processes in the central (cortical) structure of AA for 27–29 post-accidental years in particular in persons of III-B group.

Thus, an increase in hearing loss both by frequency and by the degree of manifestation was noted in clean-up workers of the III group comparing to the II group at a remote period after the Chornobyl accident under analogical small doses, but in considerably more short IR effect.

Temporal indices of dynamic impedasometry in Chornobyl accident clean-up workers at an early post-accidental period

At a primary examination the indices of acoustic reflex of entotic muscles (AREM) of clean-up workers aged 23–50 years with normal hearing as well as with SNDH of the Ist and the IInd degrees who received different doses of IR (from 0.23 to 2.0 Gy) have been presented in published works of 1990 and 1992 [3]. Especially interesting were AREM temporal indexes of clean-up workers, whose hearing acuity was within the limits of norm by an audiometry data in the two groups.

For comparison, 10 practically healthy non-irradiated persons (20 ears) with normal hearing were included in the Ist (control) group. The II group consisted of 10 clean-up workers (20 ears) exposed to short-time IR in the small doses (0.23–0.25 Gy). 13 persons (26 ears) – reconvalescents of the Ist degree ARS, received the large IR doses (1.0 to 1.9 Gy) were included in the 3 group.

Temporal indexes of AREM under ipsi- and contralateral stimulations in the persons of control (1) group and in clean-up workers of the II and the III groups are shown in the Table 17.6 and Table 17.7. The revealed changes in a time increase (Ti) of AREM are less in clean-up workers of the 2 and the 3 groups than the Ti size in the persons of control group under ipsi- and contralateral stimulations as it is shown by data of the Table 17.6 and 17.7.

Particularly, at the sizes of (136.8 ± 8.1); (176.0 ± 28.5); (220.0 ± 31.6) ms in control group a time increase was equivalent to (112.4±12.1); (157.1±19.1); (197.1±16.7) ms respectively under an ipsilateral stimulation at the studied frequencies 0.5, 1.0 and 4.0 kHz in the persons of the II group. The analogical decrease in size of AREM time increase was marked at contralateral stimulation, and also in clean-up workers of the 3 group under both types of stimulation.

No statistically significant changes in time of active action (Ta) of AREM at ipsi- and contralateral stimulations were fixed in two groups.

However, a time lengthening (Tl) of active after-effect was marked in both under ipsalateral and contralateral stimulations in persons of the 2 and the 3 groups comparing to control (Table 17.6 and Table 17.7).

As is evident from above-mentioned Table 17.6 and Table 17.7, a time slump (Ts) of AREM was noted in clean-up workers comparing to this index of control group at the studied frequen-

Table 17.6

Temporal indices of AREM under ipsalateral stimulation in clean-up workers with normal and diminished hearing at the different IR doses comparing to the control group

Groups	Stimul, kH	Terminal characteristics of AREM, ms					
		Tla	Ti	Ta	Tl.	Ts	TΣ
I (c)	0.5	126.2 ± 12.9	136.8 ± 8.1	1070.0 ± 41.6	116.0 ± 20.0	175.0 ± 22.7	1312.0 ± 66.0
	1.0	149.0 ± 6.1	176.0 ± 28.5	948.0 ± 64.4	131.0 ± 21.6	215.0 ± 28.0	1320.0 ± 81.0
	4.0	224.4 ± 9.3	220.0+31.6	789.0 ± 45.6	121.4 ± 13.1	205.0 ± 22.5	1249.0 ± 84.1
2	0.5	122.9 ± 9.5	112.4+12.1	1088.2 ± 20.4	110.0 ± 15.7	132.3 ± 18.7	1225.8 ± 30.4
	1.0	130.0 ± 7.1	157.1 ± 19.1	1058.0 ± 33.4	119.4 ± 18.4	191.3 ± 24.7	1258.0 ± 53.5
	4.0	220.0 ± 20.5	197.1 ± 16.7	898.6 ± 84.2	142.4 ± 22.1	177.8 ± 24.0	1160.0 ± 58.0
3	0.5	117.8 ± 12.6	86.8 ± 8.6	1091.7 ± 28.7	143.9+.20.9	118.7 ± 19.9	1270.8 ± 46.4
	1.0	118.26 ± 12.7	141.8 ± 11.1	1051.7 ± 47.5	137.8 ± 14.1	143.5 ± 19.8	1323.0 ± 76.1
	4.0	232.2 ± 22.2	181.1 ± 16.9	873.9 ± 42.0	154.5 ± 16.1	132.8 ± 12.2	1235.0 ± 87.5

Notes. In underlined figures a difference of AREM indices in CUW is significant in the two groups comparing to control, $p < 0.05$.

Table 17.7

Temporal indices of AREM under contralateral stimulation in clean-up workers with normal and diminished hearing at the different IR doses comparing to the control group

Groups	Stimul, kH	Terminal characteristics of AREM, ms					
		Tla	Ti	Ta	Tl.	Ts	TΣ
1 (c)	0.5	128.0 ± 13.6	144.4 ± 14.1	1044.0 ± 67.0	112.2 ± 16.0	245.0 ± 32.7	1442.0 ± 107.4
	1.0	171.0 ± 31.6	166.7 ± 18.1	896.0 ± 91.0	114.0 ± 9.5	251.0 ± 30.0	1320.0 ± 84.8
	4.0	247.5 ± 22.6	182.5 ± 24.7	744.4 ± 91.0	111.4 ± 9.5	247.5 ± 30.2	1211.1 ± 105.1
2	0.5	149.3 ± 26.3	136.3 ± 17.0	1019.4 ± 58.7	131.3 ± 11.0	130.6 ± 13.7	1237.5 ± 64.0
	1.0	135.6 ± 18.5	106.9 ± 28.3	1047.5 ± 59.1	152.5 ± 13.6	148.0 ± 17.0	1131.9 ± 99.1
	4.0	242.9 ± .26.1	170.7 ± 26.1	894.3 ± 78.6	160.7 ± 22.8	138.3 ± 20.1	1177.0 ± 100.1
3	0.5	132.3 ± 19.6	121.9 ± 12.1	1055.5 ± 49.3	150.0 ± 19.6	188.6 ± 15.2	1330.5 ± 66.5
	1.0	113.5 ± 15.3	122.6 ± 24.6	1018.7 ± 62.6	166.0 ± 23.9	220.9 ± 26.8	1336.9 ± 84.1
	4.0	190.6 ± 32.6	146.9 ± 25.5	966.2 ± 22.5	189.4 ± 22.9	157.1 ± 27.1	1334.4 ± 132.4

Notes. In underlined figures a difference of AREM indices in CUW is significant in the two groups comparing to control, $p < 0.05$.

cies under ipsi- and contralateral stimulations. These changes are more manifested in clean-up workers in the 3 group of patient with ARS. No differences of total time (TS index) of AREM under ipsi- and contralateral stimulations between the three groups were noted.

Thus, shortening of time increase (Ti), time slump (Ts) of AREM and time lengthening of active after-effect (Ta) of AREM specify the disorders of correlation between the stimulation and inhibition processes at the nuclear level of reflex arch of AREM in clean-up workers of the 2 and the 3 groups comparing to the persons of control group under ipsilateral stimulation.

Shortening of time increase (Ti), time slump (Ts) and lengthening of active after-effect (Ta) of AREM under contralateral stimulation, testify disorders of correlation between stimulation and inhibition processes at the nuclear level of reflex arch of brain stem structures of AA, that at the same time demonstrate early preclinical disorders in these structures comparing to control.

They are registered in clean-up workers, who received the small IR doses and are more manifested in persons with ARS, i.e. a dependence on the dose size is marked ($p < 0.05$).

Indices of the functional state of external Corti's cells in internal ear in clean-up workers by the data of otoacoustic emission of distorted products (OAEDP) at a remote post-accidental period

Registration of OAEDP was conducted in 93 in clean-up workers in the three groups (186 ears) in 15–20 years after an accident, and in 10 among them non-irradiated persons (20 ears) of control group with normal hearing acuity.

10 clean-up workers (20 ears) with hearing within the limits of age norm registered by audiometry were included in the I group.

The II group consisted of 31 clean-up workers (62 ears) with presbyacuzis praecox.

The III group included 52 clean-up workers, 27 from them (III-A group) with acute bilateral SNDH of the 2nd degree (44 ears) and 25 CUW (III-B group) – with acute unilateral SNDH of the 2nddegree (50 ears) as a result of hypertensive crisis. OAEDP examination was not conduct in clean-up workers with the 3nd and the 4th degree of SNDH, because its registration was impossible under considerable losses of hearing.

The values of acoustic range (AR) of OAEDP in clean-up workers of the three groups and persons of control group are presented in Table 17.8.

Data that are shown in Table 17.8 and in Figure 17.12 specify that AD value of OAEDP at the studied frequencies is less than 10 dB in clean-up workers with hearing acuity within the limits of norm and diminished hearing with presbyacuzis praecox in the Ist, the IInd, III-A and III-B groups in patients with unilateral and two-sided HSNP developed against a background of hypertonic crisis that is indicative of disturbed function in the external Corti's cells (ECC).

Thus, it was first established that the functional state of internal ear ECC in the hearing acuity within the limits of age norm and in SNDH by the type of presbyacuzis praecox was not impaired in clean-up workers at a remote period, but it was impaired in auditory disorders that have arisen on a background of hypertensive crises.

Changes in the functional state of brain stem structures of auditory analyzer in clean-up workers in the dynamics of post-accidental period

In 1990 the results of primary examinations of changes in indices of the brain stem structures of auditory analyzer, that were manifested by the significant increase in a size of LP in peaks of the third, fifth components of short-time latent hearing induced potentials (SHIP) and intervals between peaks of the I-V SHIP were analyzed not only in clean-up workers with revealed diminished hearing but also in patients with hearing acuity within the limits of norm [2]. These

Table 17.8

Values of OEDP acoustic range in control and three groups of in clean-up workers in 15–20 years after post-accidental period

Groups	The state of ear 2.0 кHz	Values of OEDP acoustic range, dB			
		4.0 кHz	6.0 кHz	10 кHz	
Control	Normal	14.5 ± 1.0	17.0 ± 1.2	17.5 ± 1.1	18.0 ± 1.2
I	Normal	15.5 ± 1.2*	17.5 ± 1.1*	16.5 ± 1.2*	16.5 ± 1.2*
II	Presbyacuzis praecox	15.0 ± 0.7*	16.5 ± 0.8*	17.5 ± 1.1*	17.1 ± 1.2*
III A	II degree acute SNDH	5.5 ± 0.9 **	6.5 ± 0.5**	6.5 ± 0.6**	5.0 ± 0.5**
III B	II degreeacute SNDH	4.1 ± 0.3**	4.9 ± 0.5**	5.0 ± 0.2**	6.5 ± 0.3**

Notes. * – indices between control. the I. and the II groups are insignificant, $p > 0.05$; ** – indices between control, the III-A. and the III-B groups are significant, $p < 0.05$.

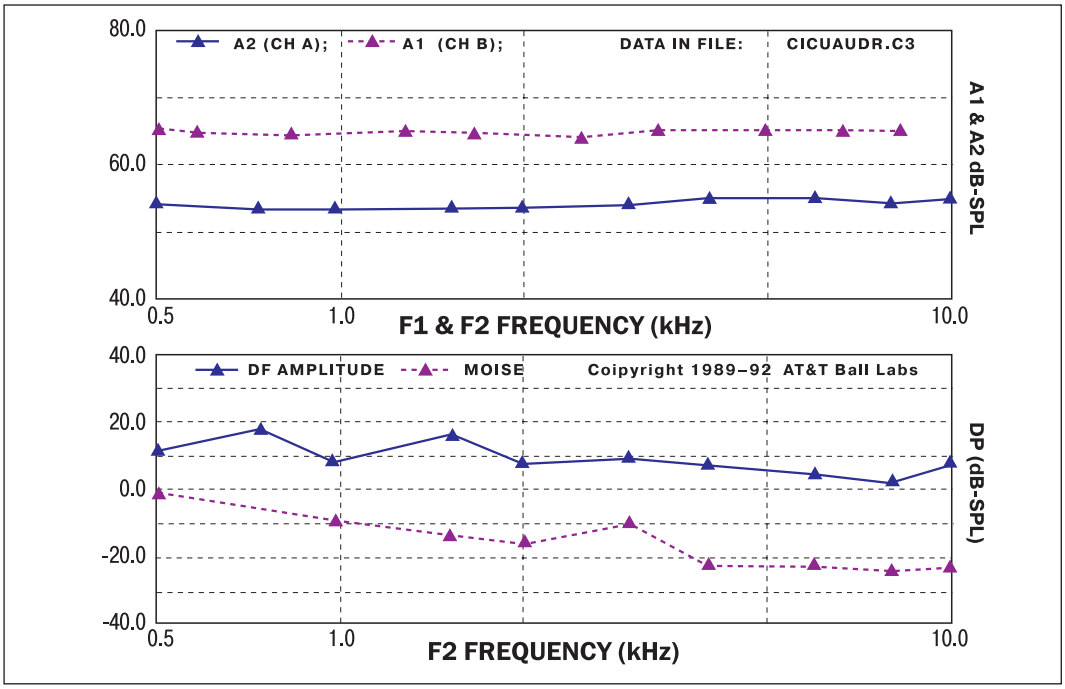


Figure 17.12. OAEDP of patient T., aged 54 years, who was clean-up workers, and had ARS of the 2nd degree with diminished hearing according to presbyacuzis praecox of corresponding age, AR between measuring noise level curve and that of OAEDP exceeds 10 dB

data testify the early initial changes in the brain stem structures of auditory analyzer before the clinical signs of auditory impairments detected audiometrically.

The changes in temporal parameters of brain stem or short-latent auditory induced potential (SHIP) components were analyzed in clean-up workers depending on state of hearing acuity comparing to the control group of the non-irradiated persons with normal hearing.

The qualitative and quantitative changes in basic components of SHIP were established in clean-up workers with the normal hearing of the 1 group, with the 1st degree of SNDH in the II group, as well as with the 2nd degree of SNDH in the III group comparing to control.

Qualitative changes are manifested with SHIP smoothing (by low amplitude) components. Quantitative sizes of IBP from I–III, III–V and I–V SHIP components in clean-up workers with normal hearing in the I group, and also with the 1st degree of SNDH in the II group and with the IInd degree SNDH in the III group, comparing to control – under ipsilateral sound stimulation with frequency of 1.0 kHz, are shown in Table 17.9.

Table 17.9

Indexes of IBP of SHIP components in persons of control group and clean-up workers of the three groups with the different state of ear under ipsilateral sound stimulation with frequency of 1.0 kHz

Groups	IBP, ms		
	I–III	III–V	I–V
control	2.15 ± 0.03	1.87 ± 0.01	4.02 ± 0.01
I	2.16 ± 0.01	2.06 ± 0.02*	4.22 ± 0.02*
2	2.18 ± 0.01	2.11 ± 0.02*	4.29 ± 0.02*
3	2.20 ± 0.01	2.16 ± 0.03*	4.36 ± 0.01*

Notes. * – a difference between the indices of CUW of the three groups and control group is significant, ($p < 0.05$).

No significant differences between the values of IBP from components I–III in clean-up workers of the three groups were marked comparing to control group by the data of Figure 17.13. However, lengthening of IBP indices in the III–V and the I–V components of SHIP were fixed in clean-up workers of the three groups, comparing to control ($p < 0.05$). For example, lengthening of IBP in the III–V and I–V components of SHIP was registered in the I group of clean-up workers with normal healing, that was equal to 2.06 ± 0.02 and 4.22 ± 002 ms respectively comparing to control group where the first index was 1.87 ± 0.01, and the second one – (4.02 ± 0.01) ms, $p < 0.05$.

The more prolonged are indices of IBP in the III–V and I–V components of SHIP comparing to control and between itself in clean-up workers with the 1st and the 2nd degrees of SNDH in the groups II and III: the above-named indices were (2.11 ± 0.02) and (4.29 ± 0.02) ms in the persons of the group II and (2.16 ± 0.03) and (4.36 ± 0.01) ms in patients of the group III ($p < 0.05$), respectively.

The increased values of IBP in the III–V and I–V components of SHIP in clean-up workers of the three groups testify the delayed impulse conducting by the auditory ways of the brain stem and at the same time underline early preclinical sensibility of the brain stem structures of AA under IR effect in clean-up workers with the normal hearing acuity.

The changes in IBP value of the III–V components of SHIP under ipsilateral sound stimulation with frequency of 1.0 kHz in clean-up workers exposed to short-term IR in the large doses (I-A and I-B groups), in relation to short-term IR (II-A and II-B groups), long-term IR (III-A and III-B groups) in small doses under the long-term monitoring studied by us [14] in the dynamics of post-accidental period comparing to the persons of the corresponding age in control groups are shown in Figure 17.13.

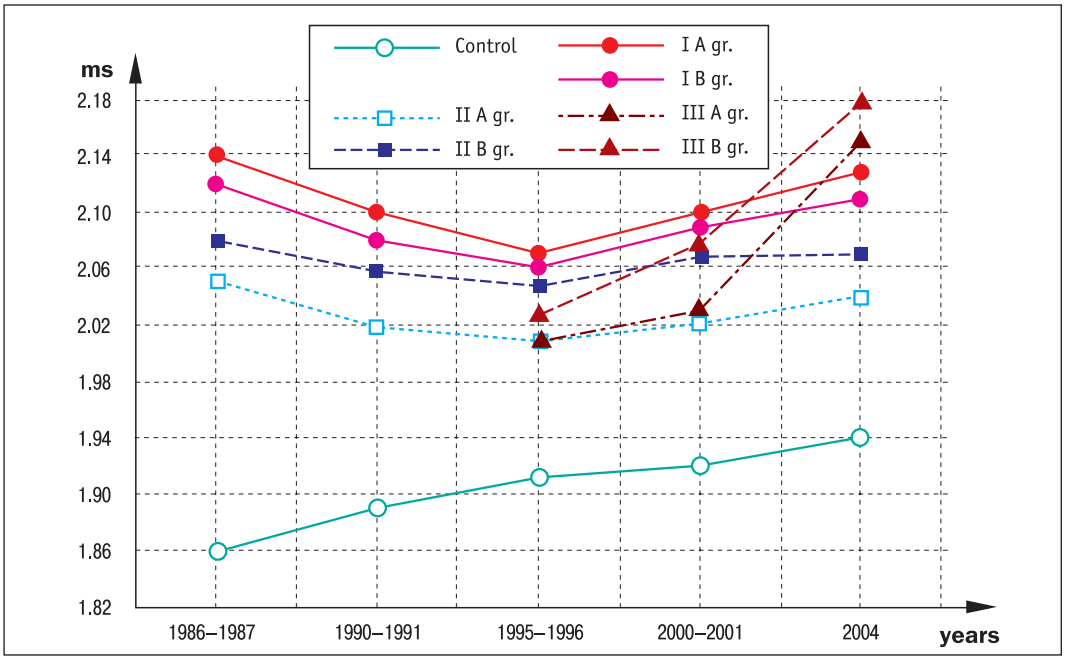


Figure 17.13. Indices of IBP in III-V components of SHIP in clean-up workers under ipsilateral sound stimulation with frequency of 1.0 kHz in clean-up workers of the I-A and I-B groups, the II-A and II-B groups, and the III-A and III-B groups, and also persons of corresponding age in control groups in 18 year dynamics after an accident

As shown data of Figure 17.13, a value of IBP in III-V components of SHIP made (2.12 ± 0.03) ms, at a control index – (1.86 ± 0.03) ms in the persons of the group I-A at a primary examination. This size was decreased up to (2.08 ± 0.01) ms in 5 years, and up to (2.06 ± 0.02) ms in 10 years.

A gradual increase of this index that made (2.11 ± 0.02) ms in 2004 have been noted at the second decade. Analogical changes were revealed in the persons of the I-B group in the dynamics of post-accidental period, but an above-named index was greater in them, i. e. it is dependent on IR dose.

A peculiarity of IBP index in the III–V components of SHIP in clean-up workers of the I group was its considerable increase at a primary examination, and following decrease during the first decade of post-accidental period. On the contrary the progressive increase of this index sizes, that in 18 years almost reached those values fixed at a primary examination, was marked in the second decade.

A feature of changes in sizes of IBP in the III–V components of SHIP in clean-up workers of the II group is the fact that they were lesser than sizes of IBP in clean-up workers of the I group at a primary inspection. So, it made (2.05±0.02) ms in the persons of the II-A group, and (2.08±0.03) ms in the persons of the II-B group, they were gradually decreased during the first decade, and were gradually increased in the second ones. The changes in SHIP parameters were fixed at short-term IR at 0.2 Gy that under this IR variety were also dependent on IR dose.

Other conformity of changes in index of IBP in the III–V components of SHIP was established in clean-up workers of the III group in the dynamics of post-accidental period. Its accelerated value was noted in them after stopping works at the Chornobyl zone of estrangement (taking into account age changes). So, in 2004 this index made (2.15±0.03) ms in the persons of the III-A group and (2.18±0.03) ms in the persons of the III-B group, and it consisted of (2.04 ± 0.02) ms and (2.07 ± 0.02) ms in clean-up workers of the II-A and the II-B groups who were received analogical doses, only during considerably more short time, respectively.

An accelerated increase in sizes of IBP in the III-V components of SHIP at the identical IR doses is a feature of long-term IR in clean-up workers of the III group comparing to the persons of the II group at a remote period. Long-term IR in small doses causes the more substantial manifestation of impairments in the AA brain stem structures.

Thus, as a result of the conducted examinations, the significance of dose size and duration of IR effect was established in clean-up workers of the three groups, that is manifested by the changes in SHIP parameters, and is indicative of early and progressive disorders in the brain stem structures of auditory analyzer in the dynamics of post-accidental period.

Changes in the functional state of auditory analyzer cortical structures in clean-up workers in the dynamics of post-accidental period

The sizes of LP in peaks of the P_2 and N_2 components of LHIP were studied by us [2] under sound stimulation with a frequency of 1.0 kHz in clean-up workers of the three groups with the different doses and duration of IR during different years (1986–2014) in the dynamics of post-accidental period, which are shown in Table 17.10.

Differences in clinical course of changes in LP of peaks in the P_2 and N_2 components of LHIP were fixed in clean-up workers of the three groups under long-term monitoring during different years after an accident, as it is shown by data of Table 17.10.

In particular, the feature of LP parameters of peaks of P_2 and N_2 components of LHIP is their considerable increase in clean-up workers of the I group at a primary examination, with following gradual decrease during the first decade after an accident and an a new increase – in the second and third decades.

Table 17.10

Latent periods in peaks of the P_2 and та N_2 components of LHIP were fixed in clean-up workers of the three groups under long-term monitoring during different years after an accident

Groups	Years of investigation					
	1986–1987	1990–1991	1995–1998	2001–2002	2003–2004	2013–2014
Sizes of latent periods of P2 component peak, ms						
Control	175.0 ± 3.1	178.0 ± 3.3	183.1 ± 2.6	186.5 ± 2.5	189.1 ± 2.1	190.1 ± 2.2
I–A	223.1 ± 2.1	196.7 ± 3.3	197.5 ± 3.2	199.6 ± 2.1	208.6 ± 2.6	218.0 ± 1.8
I–B	228.1 ± 3.5	206.5 ± 2.8	199.6 ± 3.9	203.7 ± 3.7	215.5 ± 3.6	224.3 ± 2.1
II–A	188.2 ± 2.8	195.5 ± 2.7	197.5 ± 2.9	198.9 ± 2.1	199.1 ± 2.5	201.2 ± 2.3
II–B	195.5 ± 2.6	199.5 ± 2.5	200.1 ± 2.7	201.5 ± 2.7	205.6 ± 3.1	207.1 ± 2.2
III–A	175.2 ± 3.1	–	187.2 ± 2.1	190.0 ± 2.0	198.5 ± 2.4	203.2 ± 2.3
III–B	179.0 ± 3.1	–	189.6 ± 2.5	194.0 ± 2.9	206.6 ± 2.7	215.3 ± 2.1
Sizes of latent periods of N2 component peak. ms						
Contro l	269.0 ± 4.8	272.2 ± 3.4	275.1 ± 3.0	278.6 ± 3.1	279.9 ± 3.2	217.0 ± 1.5.
I–A	319.5 ± 3.5	291.1 ± 3.1	287.3 ± 3.7	295.6 ± 3.6	310.6 ± 3.1	312.9 ± 1.7
I–B	326.1 ± 4.2	299.7 ± 3.6	289.2 ± 4.1	306.1 ± 3.3	318.6 ± 2.9	324.6 ± 1.9
II–A	288.5 ± 3.2	289.0 ± 2.9	290.0 ± 2.6	290.5 ± 2.1	294.7 ± 2.1	299.2 ± 2.0
II–B	290.7 ± 3.9	291.1 ± 3.0	293.0 ± 2.7	296.0 ± 2.6	301.5 ± 2.4	308.0 ± 1.8
III–A	268.0 ± 4.5	–	289.0 ± 2.6	291.0 ± 2.5	296.4 ± 2.7	305.1 ± 1.9
III–B	269.0 ± 4.6	–	292.3 ± 3.1	296.5 ± 2.4	306.6 ± 2.9	310.1 ± 2.3

The sizes of above-named indices of LHIP are greater in the persons of the I-B group that those in persons of the I-A group, i. e. they demonstrate a dependence on the size of IR dose.

The feature of LP indices in peaks of the P_2 and N_2 components of LHIP is their increase in clean-up workers of the II group at a primary examination comparing to control, however they are lesser than that in clean-up workers of the I group who were exposed to short-term radiation in large doses.

It is necessary to accent, that the changes in size of LP in peaks of the P_2 and N_2 components of LHIP in the persons of the II-A group were marked in a dose of 0.2 Gy, and in the persons of II-B groups who were received a small, but two times greater dose; the sizes of peak LP of the P_2 and N_2 components of LHIP are grater than those in the persons of II-A group, i. e. at this IR variety the LP size in peaks of P_2 and N_2 components of LHIP are also dependent on a dose.

The feature of changes in LP peaks of the P_2 and N_2 components of LHIP in clean-up workers of the II group is their gradual lengthening in the 1st as well as in the 2nd and 3rd decades of post-accidental period.

Other data have been obtained in radiation-exposed clean-up workers with analogical small doses in the III group as well as in the II group, but at the prolonged stay in the Chornobyl zone of estrangement. A size of their LP of peaks in the P_2 and N_2 components of LHIP did not differ from indices in the persons of the corresponding age categories in control group before work at Chornobyl the exclusion zone (*of estrangement*).

An increase in LP sizes of peaks in the P_2 and N_2 components of LHIP was marked after the prolonged work at the zone of estrangement in the different years of the long-term monitoring.

The feature of changes in LP peaks of the P_2 and N_2 components of LHIP is their accelerated lengthening in clean-up workers of the III group at a remote period. In 2003–2004 the indices of N_2 of LHIP were equal to (296.4±2.7) ms and (306.6±2.9) ms in the persons of the III-A and the III-B groups and above-named indexes were (294.7 ± 2.1) ms and (301.5 ± 2.4) ms in the persons of the II-A and the II-B groups in those years, respectively.

Particularly these figures were (305.1 ± 2.3) ms and (310.1 ± 2.3) ms compared to II-A and II-B groups respectively that had the value of (299.2 ± 2.0) ms and (308.0 ± 1.8) ms in 2013–2014. These data give basis to assert that prolonged IR is more harmful and causes considerable disorders in the subcortical and cortical structures of auditory analyzer, than relatively short-term exposure in analogically small doses at a remote period.

A direct correlation (r = 0.71) between the size of LP peak in the N_2 component of LHIP and thresholds of 100% legibility of linguistic tests, which specifies that with increasing size of LP peak of the N_2 component of LHIP, the thresholds of 100% legibility of linguistic tests are increased has been established by us [14]. That is the manifestation of inhibitory processes in the cortical structures of AA is synchronously demonstrated by electrophysiologic examinations as well as by speaking audiometry.

Thus, disorders of brain stem and cortical structures of auditory analyzer were found in all clean-up workers without an exception (in 100% cases) with normal as well as diminished hearing as a result of conducted examinations by the data of objective audiometry (by the indices of registration of AREM, SHIP and LHIP).

These data specify that the objective methods of examination allowed to find early changes in the central departments of auditory analyzer (in its brain stem and cortical structures) under radiation effect, before the development of clinical audiometrical signs and deviations in the indices of tonal and speaking audiometry that is very important for therapeutic and prophylactic measures, prognostic and expert tasks.

It is necessary to accentuate that revealed such changes in the indices of objective audiometry are deepening with the development of progressive impairments in hearing acuity. The analogical changes in the same brain structures were noted in radiation-exposed persons as a result of the Chornobyl catastrophe, by such authors as A.I. Nyagu [4], M.S. Kozak [5] and others who certify the progressive development of psychoneurologic pathology in the dynamics of post-accidental years.

The value of dose size and duration of IR action was established in clean-up workers of the three groups that is manifested by the changes in parameters of SHIP and LHIP, that is evidence of early and progressive inhibitory disorders in brain stem and cortical structures of auditory analyzer in the dynamics of post-accidental period.

Certain conformity of the obtained results was confirmed by different research groups with other actual clinical material of examinations in special contingents of persons exposed or who are exposing ionizing radiation as a result of the Chornobyl catastrophe, including V.V. Rymar [6], A.N. Golod [7], T.V. Shidlovska et al. [8].

In particular, T.V. Shidlovska et al. [8] presented the data of a number of deviations by psychoacustic audiometry and objective audiometry (APEM, SHIP and LHIP) in clean-up workers, the inhabitants of Narodytsky and Ivankivsky regions. Analogical deviation to our obtained results of APEM indices from a norm in clean-up workers, were revealed in 100% cases: in 43%, and 21% cases of Narodytsky and Ivankivsky region inhabitants, respectively.

According to the data of registration of SHIP and LHIP, the deviations from a norm were fixed in the brain stem and cortical structures of auditory analyzer in 100; 85.5; 19.7% and 100; 78.0 and 33.7% cases, respectively. The authors accent an attention that above-named changes were found in all clean-up workers exposed to radiation over 0.25 Gy without an exception. The considerable changes were especially noted in those patients who had acute radiation sickness.

In addition, the authors underline that the changes registered in the brain stem structures were more frequent and more significant in the inhabitants of Narodytsky region, than in the inhabitants of Ivankivsky region.

The results of our examinations indicate that study of APEM, SHIP and LHIP characteristics is important in the plan of objective determination of initial preclinical impairments in the central departments of auditory analyzer, that it is important for resolving some expert problems, and also for monitoring these parameters in the dynamics of post-accident period for treatment-and-prophylactic measures, rehabilitation and corrective events and also for prognosis.

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17.3. VESTIBULAR DYSFUNCTION IN THE CHORNOBYL ACCIDENT CLEAN-UP WORKERS IN THE DYNAMICS OF POST-ACCIDENTAL PERIOD. MORBIDITY AND RISKS FOR DEVELOPMENT OF VESTIBULAR DYSFUNCTION: RESULTS OF MATHEMATICAL MODELING.

17.3.1. Vestibular dysfunction in the Chornobyl accident clean-up workers in the dynamics of post-accidental period.

It is known that various pathological reactions of three kinds are occurred in the cases of impairing functional state of vestibular analyzer (VeA): vestibulo-sensory, vestibulo-somatic and vestibulo-vegetative with different degree of manifestations [1, 2, 3].

Vestibulo-sensory reactions cause the processes that take a place at the level of cerebral cortex. They are manifested by feeling of permanent or periodic dizziness and different manifestations of disorders connected with the orientation in space.

Vestibulo-somatic reactions are manifested by the reflexes on body muscular structures, that are accompanied by spontaneous disorders of staticokinetic equilibrium, resulting in disorder of walking and coordination of movements, and also pathological vestibulooculomotor reactions, as a spontaneous or positional nystagmus of different orientation and intensity.

Vestibulo-vegetative reactions are occurred under a decrease or an increase in sensitiveness of vestibular analyzer, and also under increased vestibular loadings. They are characterized by ephidrosis, the changes in skin staining – pallor or reddening, breathing disorders, disorders from the side of the cardiovascular system (the changes in pulse rhythm, arterial pressure) and gastrointestinal tract (nausea, vomiting), that cause infrequent development of severe symptom-complex – disease of movement.

The mentioned reactions have a different value in human life. In relation to its occupational activity the vestibulovegetative and vestibulosensory reactions are the most significant. The first ones, predetermine the state of vegetative discomfort disordering self-feeling, decreasing a working capacity; the others disorientate a man in space and can cause a serious danger in implementation of the works, connected with exact and coordinated movements.

From 10 to 20% of specialists, whose professions are related to the effect of the prolonged or increased irritants on vestibular dysfunction, can lose a working capacity or occupational adaptability as a result of VeD, according to data of literature [4, 5]. Different disorders of occupational activity promoting occurrence of technological accidents or even catastrophes can be provoked as a result of the un-coordinated movements or disorientation in space in those specialists.

For studying the functional state of vestibular analyzer a methodology of clinical examination was used: the complex of standard vestibulometric methods including determination of the state of staticokinetic equilibrium, electronystagmography (ENG) of spontaneous, positional nystagmus, and also experimental nystagmus, caused by caloric and rotary stimulations, taking into account the indices of electrooculography (EOG).

In sum 7812 clean-up workers were examined for post-accidental period (1986–2014).

One of the basic complaints were complaints to permanent dizziness of different intensity with equilibrium imbalance and pathological vestibulovegetative disorders in 91.3% cases simultaneously with complaint to head pain in 1200 clean-up workers at a primary examination (1986–1987).

Vestibular dysfunction (VeD) with different degree signs was found by primery vestibulometry in 1200 clean-up workers, including 325 patients who were matched for the long-term monitoring.

VeD was manifested by the type of central vestibular syndrome (H-81.4 by ICD-10) with prevailed affection of those or other structures of central department of VeA in the greater number of patients (97.0% cases) among them and by the type of mixed vestibular syndrome in accordance with I.B. Soldatov et al. classification (1980) [6] in considerably smaller number of patients (3.0% cases).

It was clinically manifested by progressive (85.7% cases) or remittent course (14.3%) with the various changes in vestibulosomatic, vestibulosensory and vestibulovegetative pathological reactions during the different years of post-accidental period.

The 1st degree VeD was registered in 252 persons (21.1% cases), the 2nd degree VeD – in 668 persons (55.7%), the 3rd degree VeD – in 246 persons (20.1%), the 4th degree VeD – in 34 persons (3.1% cases) from 1200 clean-up workers in 1986–1987 at a primary vestibulometric examination.

Indices of staticokinetic equilibrium in clean-up workers with the 1st degree of VeD were as follows: a static equilibrium made 3.7 ± 0.6 a. u. by the data of cephalography index (CGI), and a kinetic equilibrium (at an implementation of Fukuda stepping test – a body rotary around an own axis) consisted of 40.5 ± 1.9 deg. No spontaneous and positional nystagmus were found.

The insignificant symmetric, rare asymmetric hyperreflexia or hyporeflexia of experimental nystagmus with the signs of dysrhythmia, the presence of different duration of the «mute» fields, and also by the phenomena of its reversion were revealed under the caloric (circulating) and rotary stimulations.

The hyperreflexia of experimental nystagmus was accompanied by an inadequacy of vestibulosensory reactions, often more prolonged, than experimental nystagmus duration, and also vestibulovegetative reflexes of the Ist and the IInd degrees according to K.L. Hillov (prevailed intermediate subcortical and cortical levels of central vestibular syndrome) [7].

The moderate changes in staticokinetic equilibrium were diagnosed in clean-up workers with VeD of the 2nd degree. So, their CGI was equal to (5.4 ± 0.5) a. u. – a body rotation around an own axis using a stepping test – (64.3±3.5) deg., a deviation of writing test – (12.7 ± 1.3) deg.

Positional nystagmus was noted in a half of examined clean-up workers with VeD of the 2nd degree by phono (without stimulus) ENG that was low-amplitude horizontal nystagmus changing its direction depending on the head position (type I by Nylen) in 25.0% cases. An intensity and direction of positional nystagmus were inconstant in different head positions (type III by Nylen) in other 25.0% cases.

The considerable disorders (degree III) of staticokinetic equilibrium were registered in clean-up workers with diagnosed VeD of the 3rd degree: CGI made 6.1 ± 0.3 a. u., a stepping test – a body rotation around an own axis – (82.1 ± 5.1) deg., a writing test vertex – (15.5 ± 1.1) deg. (those patients required an outside assistance).

The significant deviations were registered under performing static and kinetic tests in clean-up workers with diagnosed VeD of the IVth degree. So, the cephalography index exceeded 6.5 ± 0.5 a. u., a body rotation around an own axis in stepping test was (115.5 ± 2.3) deg., the deviations in writing test – (20.6 ± 1.4) deg. (tests were difficult for performance and such patients could not neither stand nor move without assistance).

The indices of staticokinetic equilibrium in clean-up workers with VeD of the four degrees and those of control healthy persons are shown in Table 17.11.

In phone ENG the middle-amplitude nystagmus was diagnosed in the majority of patients with VD of the IIIrd degree (76.4% cases) and the low-amplitude, horizontal or diagonal spontaneous nystagmus of the IInd and the IIIrd degrees of manifestation – in the others.

More significant manifestation of symmetric or asymmetric hyperreflexia or hyporeflexia, and also dissociated experimental reactions with the prolonged vestibulosensory and

vestibulovegetative reflexes of the II[rd] and the III[rd] degrees – vomituration, increased sweating, changes in pulse rhythm, change in arterial pressure that are indicative of the disordered correlative processes in the brain stem, intermediate cortical and cortical structures in a central vestibular syndrome have been fixed under experimental (caloric) stimulations in VeD of the III[rd] degree (rotary ones were selectively conducted depending on a general feel after that of caloric).

Table 17.11

Indices of staticokinetic equilibrium in VeD of the four degrees in clean-up workers and healthy persons (control) without radiation

Degree of VeD	Indices of the studied tests		
	Static equilibrium	Kinetic equilibrium, deg.	
	CGI. a. u.	stepping (body rotation)[8]	writing (deviation)[9]
Control	3.2 ± 0.4	27.0 ± 2.1	5.3 ± 0.4
I	3.7 ± 0.6	40.5 ± 2.1	8.5 ± 0.3
II	5.4 ± 0.5	64.3 ± 3.5	12.7 ± 1.3
III	6.1 ± 0.5	82.1 ± 5.1	15.5 ± 1.1
IV	6.5 ± 0.5	115.5 ± 2.3	20. 6 ± 1.4

Spontaneous middle- or large-amplitude horizontal or diagonal nystagmus of the III[rd] degree was registered on phone ENG recording in VeD of the IV[th] degree in all cases.

Significant hyperreflexia of experimental nystagmus with considerable its dysrhythmia, prolonged reversion, vestibulovegetative reactions of the III[rd] degree (vomiting, ephidrosis, hypersalivation, disorders of pulse rhythm, a change in arterial pressure) was fixed under experimental (caloric) stimulation in VeD of the IV[th] degree. The rotary stimulation was not conducted in connection with patient feel worsening.

All structures of central department of VeD in the brain are included in pathological process in VeD of the IVth degree to the significant degree.

An analysis of results of vestibulometric researches in 325 clean-up workers revealed that the degree of VeD signs was changed with increasing spontaneous symptomatology in the dynamics of post-accident years: by increasing disorders of staticokinetic equilibrium, an appearance and increased intensity of positional or spontaneous nystagmus, the qualitative and quantitative indices of experimental nystagmus in caloric as well as in rotary stimulations.

The qualitative changes were manifested by progressive increase in dysrhythmia of experimental nystagmus, an appearance of toothed or bifurcated top of nystagmus, more frequent and more prolonged «mute» fields on ENG, the phenomena of nystagmus reversion.

The quantitative changes in experimental nystagmus were manifested by diminished frequency of nystagmus, increased middle angular rate of SFN.

The changes in these indices objectively indicate that experimental nystagmus had a clear tendency to transformation from clonic into clonicotonic, and then – into tonic in the dynamics of post-accidental period.

An increase in tonicity spontaneous as well as experimental nystagmus was observed as quantitative expression in clean-up workers with the different degree of VeD manifestation in the dynamics of post-accidental period. They were fixed in all clean-up workers, especially in patients with VeD of the III[rd] and the IV[th] degrees to the small or greater degree that testifies a prevailed progressive disorder of deep brain stem structures of VeA by the data of V.I. Babiyak et al. [1], N.S. Blagoveshchenskaya [3], I.B. Soldatov et al. [6] and other researchers.

The average statistic values of basic quantitative parameters of experimental nystagmus at the different degrees of VeD manifestation are shown in Table 17.12.

As is shown from, in long-term monitoring the key parameters of experimental nystagmus reaction were significantly changed into the side of tonicity development in clean-up workers with the increasing degree of VeD manifestations in the dynamics of 27–29-year examination:

Table 17.12
Indices of experimental post-caloric nystagmus in clean-up workers with VD at the different years of post-accidental period

Parameters of nystagmus	Degree,VeD	Values of OEDP acoustic range, dB			
		1986–1987	1993–1995	2005–2009	p
Frequency of nystagmus, Hz	I	2.3 ± 0.2	1.5 ± 0.1	1.3 ± 0.1	<0.01
	II	2.2 ± 0.3	1.3 ± 0.2	1.2 ± 0.1	<0.01
	III	2.2 ± 0.2	1.2 ± 0.1	0.9 ± 0.2	<0.01
	IV	1.9 ± 0.1	1.1 ± 0.2	0.8 ± 0.2	<0.01
Middle angular rate of SFN, deg./s	I	37.4 ± 2.5	45.9 ± 1.7	56.3 ± 1.2	<0.01
	II	43.3 ± 1.8	52.4 ± 1.7	59.5 ± 1.2	<0.01
	III	48.3 ± 2.3	56.3 ± 1.9	66.7 ± 1.5	<0.01
	IV	54.6 ± 3.1	63.3 ± 1.6	76.8 ± 1.3	<0.01

Notes. difference between the basic indices of experimental nystagmus in VeD of the 1st – IVth decrees is significant, $p<0.05$.

nystagmus frequency was decreased and the size of middle angular rate of SFN was increased aside of the tonicity.

The change in qualitative and quantitative indices of spontaneous and experimental nystagmus into the side of tonicity is indicative of developing general cerebral phenomena as hypertensive syndrome of nystagmus in clean-up workers that are gradually deepened in the first, second and third decades of post-accident period by the data of G.S. Zimmerman [10]; N.S. Blagoveshchenskaya [3], V.I. Babiyak et al. [1].

They are progressed against a background of development and deepening of organic cerebrovascular pathology of the brain – dyscirculatory encephalopathy that is conformed to other neurophysiologic and MRT examinations of A.I. Nyagu et al. [5] and other researchers.

Data obtained were confirmed with other actual clinical material by other researchers.

We established that the greatest VeD manifestations were observed in 57 persons of the group I with ARS of the 1st and the 2nd degrees at a primary examination in 1986–1987. So, VeD of the IInd degree was fixed in 26.7% cases of the group I-A, and the IIIrd degree – in 74.3%, and 15.3% cases with VeD of the II degree were only observed in the group I-B, and 84.7% – with VeD of the IIIrd degree. It is necessary to note that considerable spontaneous disorders such as staticokinetic disorders and spontaneous nystagmus of the IInd and the IIIrd degrees were found in clean-up workers with APS in I-A and I-B groups. Under functional stimulations the hyperreflexia of experimental nystagmus with its dysrhythmia accompanied by the prolonged vestibulosensory reactions and vestibulovegetative reflexes of the IInd and the IIIrd degree of manifestation, including vestibulovascular ones was noted. At early period the VeD signs were at the decompensation stage in clean-up workers of the I^{st} group [11].

A predominance of the irritation phenomena in brain stem (nuclear, under- and overnuclear), and also in the intermediate subcortical and cortical structures of VeA central department is the feature of clinical course of VeD in an early post-accidental period.

It is established that the degree of VeD manifestation was decreased in clean-up workers of the I group in 1.5–3.0 years after an accident. So, 45.1% cases with the 1st degree were noted in the I-A group in 1988–1989, and anyone person with easy degree of VeD was noted in 1986–1987. A decrease in a number of patients with VeD of the IIIrd degree up to 23.9% cases was fixed. There were 18.9% patients with the 1st degree of VeD in the I-B group, 22.7% – with VD of the IIIrd degree in the II group, with VeD of the IIIrd degree was decreased up to 58.4% cases.

A progress of VeD was noted since 1994–1996 and during 1997–2014. So, the percent of persons with VeD of the 2nd and the 3rd degrees was increased among 52 examined clean-up workers of the I group at the end of the second decade (2005–2006). In particular, there were 27.3% with VeD of the 2nd degree in the I-A group, and 25.1% – in the I-B group, 72.7% – with VeD of the IIIrd degree in the I-A group, and 74.9% cases – in the I-B group. They were manifested by an increase in disorders of equilibrium up to 83.9% cases, spontaneous nystagmus – up to 77.9%, changes in qualitative and quantitative parameters of experimental nystagmus – up to 71.8%. VeD of the IIIrd degree was registered in 79.9% cases in 2008–2009 among 50 examined persons.

VeD of the IIIrd degree was fixed in 85.5% cases among 32 clean-up workers of the 1 group in 2010–2014.

An increase in spontaneous vestibular symptomatology, the qualitative and quantitative changes in experimental nystagmus were indicative of the progressing disorders in the brain stem structures of VeA and a growth of hypertensive syndrome in the brain. At the same time a decrease in vestibulovegetative reactions up to 35.1% cases was fixed that can be obviously explained by a decrease in activity (by the increase of inhibition processes) of the brain cortical structures, including the cortical structures of VeA.

The VeD manifestations have been already registered at a dose of 0.2 Gy at a primary examination of 120 clean-up workers who were exposed to short-term IR in small doses in the II group. In particular, VeD of the Ist degree was in 18.3% cases, VeD of the IInd degree – in 21.6%, VeD of the IIIrd degree – in 7.5%, VeD of the IVth degree – in 5.0% cases in the patients of the II-A group. At that time VeD of the Ist degree was in 11.6% cases, VeD of the IInd degree – in 17.5%, VeD of the IIIrd degree – in 10.8%, VeD of the IVth degree – 7.5% cases in the persons of the II-B group. It has been established that the degree of VeD manifestation is greater in the patients of II-B group who were taken the greater dose of IR.

An increase of VeD manifestations was marked in the dynamics of post-accidental period. In particular, a number of persons with insignificant disorders is decreased, and with considerable – is increased. So, at the end of 2nd decade (2005–2006) VeD of the 1st degree was observed in 1.8% cases of the II-A group and in 0.9% – of the II-B group, VeD of the IInd degree – in 35.5% of the II-A group and in 24.4% – of the II-B group, VeD of the IIIrd degree – in 10.9% of the II-A group and in 11.9% of the II-B group, VeD of the IVth degree – in 7.5% of the II-A and in 8.3% cases of the II-B group. The same dependence of VeD manifestations on the IR doses was noted in the dynamics of post-accidental period. At the beginning of the third decade after an accident (2008–2009) 43.8% cases with VeD of the IIIrd and IVth degrees were registered.

In vestibular metrical examination of 97 clean-up workers at the end of the third decade after the accident (2010–2014) an increase in the degree of manifestation of vestibular disorders was recorded. Thus, VeD of the IIIrd degree was registered in patients of the II-A group (54.1% cases), and in patients of the II-B group (67.3% cases). VeD of IV degree – in patients of II-A group (11.7% cases) and in patients of II-B group (13.9% cases).

The feature of VeD clinical course in clean-up workers of the II group was characterized by two phases of development: at the first phase – VeD was mainly manifested by dissociated reactions, indicating disorders of correlation at the brain stem, subcortical and cortical levels to the end of the first decade after IR.

During the second and third decades after an accident (the second phase) a progressive growth of spontaneous symptomatology as follows: disorders of static and kinetic equilibrium, appearance of positional, and then spontaneous nystagmus, a change in their character and intensity, and also qualitative and quantitative changes in experimental nystagmus were revealed.

It is necessary to mark that VeD of different degree was registered in clean-up workers of the II group at the stage of subcompensation during 27–29 years of the long-term monitoring. This fact can be explained by slow growth of VD degrees from insignificant in 1986–1987 to considerable (the IInd and the IIIrd degrees) – in 2012–2014.

Obviously age changes play a considerable role in spite of active-therapeutic corrective measures aimed at activation of compensatory mechanisms VA were conducted. But it is interesting that the percentage of disorders is still more significant in patients of II-B group with larger radiation doses than group II-A.

In 148 persons of the III group exposed to long-term IR in small doses, a vestibular function corresponded to age limit variations that were fixed in the persons of control group before the work at the Chornobyl exclusion zone.

After leaving the exclusion zone VeD frequency and degree were grater in clean-up workers of the III group, than those in the II group at identical IR doses but received during different time that have been shown by examinations at remote period.

In particular, VeD of the IIIrd and the IVth degrees with heavy manifestations were registered in 58.5% cases in 2008–2009 among 141 clean-up workers of the III group in comparison with the II group of clean-up workers where VeD of the IIIrd and the IVth degrees was only fixed in 43.8% cases.

In 2010–2014 the increase of patients with VeD of the IIIrd and the IVth degree was also noted among 112 examined clean-up workers. VeD of the IIIrd degree was fixed in 61.9% persons including 27.1% of III-A group and 34.8% cases in III-B group.

The peculiarity of VeD development in clean-up workers of the IIIrd group in the distant post-accidental period is concluded in the rapid increase in both frequency and degree of manifestation compared with persons of the second group for the same total dose but the different IR duration.

Thus, the obtained results of vestibulometry in clean-up workers in the dynamics of post-accidental period allowed concluding as follows:

1) It has been established that VeD of different degree of manifestation has character of central vestibular syndrome in the majority (in 97% cases) of clean-up workers exposed to different doses of irradiation.

2) It was found that VeD as a result of IR effect is a consequence of disorders in compensative reactions from a side of the CNS at the level of central departments (the brain stem, intermediate subcortical and cortical structures) of VA in the brain that was already registered under the early preclinical manifestations.

3) It is marked, that progress of VeD signs was manifested by growth of spontaneous symptomatology, namely: by appearance or strengthening of positional or spontaneous nystagmus, strengthening of staticokinetic disorders in clean-up workers in the dynamics of all the studied post-accidental period.

4) The progressing changes in qualitative and quantitative parameters of experimental nystagmus were established in the dynamics of post-accidental period. The qualitative changes were manifested as strengthening of dysrhythmia, toothed or bifurcated tops of nystagmus, an increased frequency and duration of the «mute» fields, and quantitative ones – by the change in parameters of spontaneous and experimental nystagmus.

5) It was investigated, that the development of nystagmus tonicity manifested by the quantitative decrease in a frequency and an increase in the middle angular rate of SFN, arises against a background of forming the general brain phenomena in the progress of cerebrovascular diseases at remote post-accidental period.

6) The peculiarity of the VeD clinical course in clean-up workers of the 1st group who had ARS at primary examination is predominance of the irritation phenomena in the brain stem and also

in the intermediate subcortical and cortical structures of VA in the first 1.5–3.0 years of post-accidental period and a gradual progress of inhibitory processes in above-named structures at remote period (at the end of the 1st, and during the 2nd and 3rd decades).

➤ The peculiarity of VeD clinical course is characterized by two phases of development in clean-up workers of the II group: VeD was manifested by dissociation reactions that were indicative of impaired correlation at the intermediate subcortical and cortical levels at the first phase – to the end of the first decade after IR. The development of inhibitory processes was marked in the above-named structures of VA at the second phase (the second and third decades).

➤ The feature of VeD clinical course is consisted of a frequent growth of pathological reactions by the frequency as well as by the degree of manifestation in clean-up workers of the III group comparing to the persons of the II group at the remote period at the same doses but different duration of IR effect.

Detected above-mentioned manifestations of VeD and peculiarities of their clinical course in clean-up workers exposed to different doses and duration of IR under long-term monitoring in the dynamics of post-accidental period were used at medicosocial examination for studying an occupational adaptability and working capacity of clean-up workers, for the decision of prognostic problems, and also for realizing therapeutic-and-prophylactic and correcting measures.

17.3.2. Morbidity and risks for development of vestibular dysfunction in Chornobyl accident clean-up workers

An analysis of VeD morbidity was conducted by us [12] according to the results of vestibulometrical examination in of the clean-up workers drivers and the drivers of control group, at a calculation per 1000 persons.

For selecting radiation influence from the action of other occupational factors (males) from a number of all examined clean-up workers who worked as the drivers of motor transport were selected for working life during an analysis of 420 persons. A control group consisted of 102 drivers-professionals without radiation exposure.

A distribution by an experience and an age was identical in both groups. The majority of examined patients (88%) are the persons under 50.

The results of analysis are shown in Table 17.13.

Data, shown in Table 17.13 revealed that VeD of the Ist degree was prevailed in the persons of control group, and more severe VeD of the IInd and the IIIrd degrees – in a main group. Relative risk of VeD manifestations was 1.9–3.0 times greater in a main group than in the persons of control group.

Thus, it is established that degree of VeD morbidity in the drivers – clean-up workers is significantly higher, than in non-irradiated drivers of control group, i.e. a radiation factor is the most substantial in VeD disease at identical terms and age of persons in the two groups,

The next task of our researches was to study the size of IR dose effect on the risk of primary VeD morbidity by

Table 17.13

Vestibular dysfunction morbidity in the drivers-clean-up workers and drivers of the control group, per 1,000 persons

State of vestibular function	Drivers	
	Control group, n=102	Chornobyl clean-up workers, n=420
	Absolute number per 1,000 perons	
Normal	32 (314)	55 (132)*
VeD of the 1st degree	50 (490)	121 (288)*
VeD of the 2nd degree	13 (123)	149 (402)*
VeD of the 3rd degree	7 (69)	75 (178)*

Notes. * – difference with control is significant, $p<0.05$.

the type of central vestibular syndrome in clean-up workers, who worked at a zone of the Chornobyl accident at a post-accidental period in 1986–1987. A cohort analysis and risk-analysis were used for carrying out such researches.

The results of complex examinations of clean-up workers, that were conducted in the NRCRM in 1992–2001 and the results of own vestibulometric examinations, conducted in SI «O. S. Kolomiychenko Institute of Otolaryngology of NAMS of Ukraine», which are registered in CER were used for forming cohort. During the period up to 2001 the cohort of 4017 persons was formed from the general amount of clean-up workers who were clean-up workers in 1986–1987 using vestibulometric examinations. The middle dose of IR consisted of (0.220 ± 0.006) Gy. A distribution of examined patients by dose groups was realized by Pausson. Middle age at a time of exposition was 38.35 ± 0.22. A distribution of cohort of examined clean-up workers with the known dose loading by age groups was normal at a time of irradiation [13, 14].

The cohort study was focused on primary vestibular pathology incidence based on initial diagnosis identified at the first examination or at earlier stages of medical examination the diagnosis was absent.

The morbidity relative risks for all above-mentioned dose groups of recovery operation workers 1986–1987 were analyzed in comparison with those of the internal control group.

Figure 17.14 illustrates the relationship between the relative risk for vestibular disfunction and the radiation dose. Reliably higher risks for those exposed to doses 0.25–0.49 Gy (RR = 3.43, DI = 1.43; 4.13, $p < 0.05$), 1.0 Gy and over (RR = 7.76, DI = 4.18; 14.39, $p < 0.05$) were established.

It was established that the VeD risk was significantly higher for irradiated persons at a dose of 0.25–0.49 Gy (RR = 3.43; CI = 1.43, 4.13; $p < 0.05$) and at a dose of 1.0 Gy and more (RR = 7.76; CI = 4.18, 14.39; $p < 0.05$).

Determining VeD risk depending on dose loading and age for the period of irradiation it was established that the VeD risk was more increased in older age groups. If the relative risk of patients irradiated at the age of 30–39 years for a group with radiation dose loading of 1.0 Gy or more, compared to internal controls was 5.39 (2.03; 14.30), $p < 0.05$, and in the age group 40–49 years – 7.63 (2.56; 22.70), $p < 0.05$, but in the age group of 50–59 years – 16.30 (4.42; 60.16), $p < 0.05$.

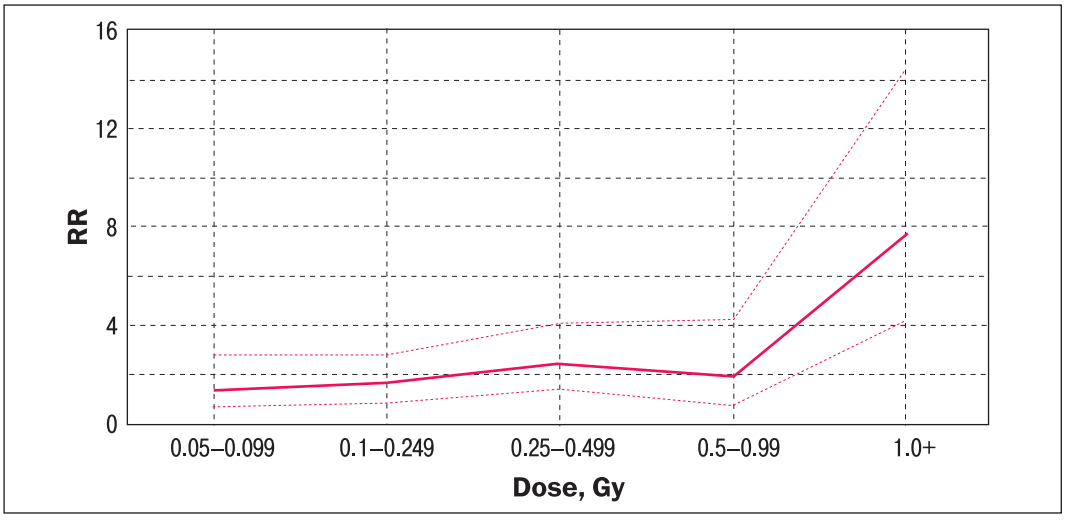


Figure 17.14. Relationship between the relative risk for vestibular disfunction and the radiation dose [12]

The relative VeD risk in group of patients aged 50-59 years, depending on dose accumulation is presented in Figure 17.15.

In this age group the relative risk is significantly higher even at a dose of 0.1–0.249 Gy. Central vestibular syndrome, as mentioned above by us, was dominated in 97.0% of cases (N.81.4 for ICD-10) among clean-up workers with VeD.

Central vestibular syndrome (H-81.4, ICD-10) was prevalent among vestibular analyzer diseases [5]. The relative risk here is reliably higher for those exposed to doses 0.25–0.49 Gy, 1.0 Gy and higher.

The manifestation relative risk of central vestibular syndrome was significantly higher for exposed persons at a dose of 0.25–0.49 Gy, 1.0 Gy and more as we can seen from Figure 17.16.

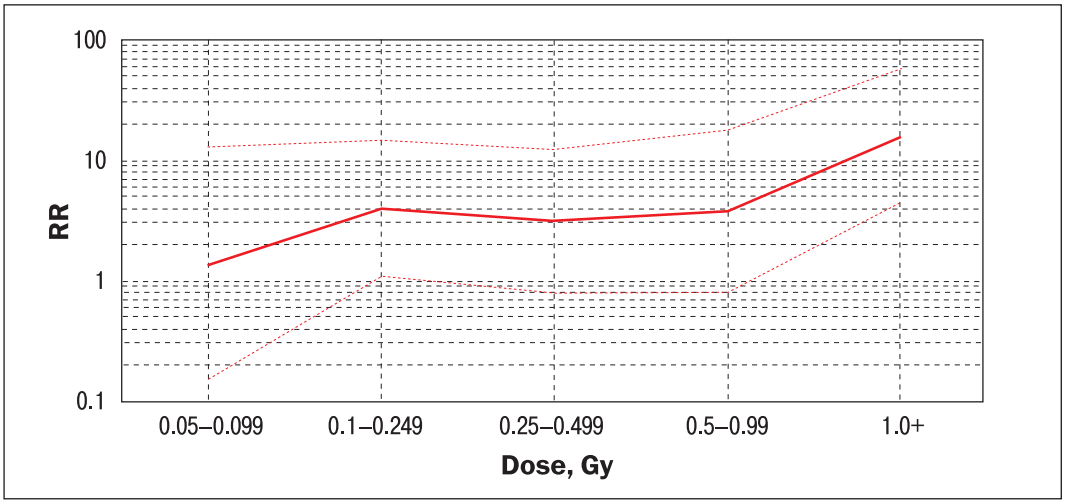


Figure 17.15. The relative risk of VeD morbidity in clean-up workers patients aged 50–59 years (1986–1987) at the time of IR depending on dose loading

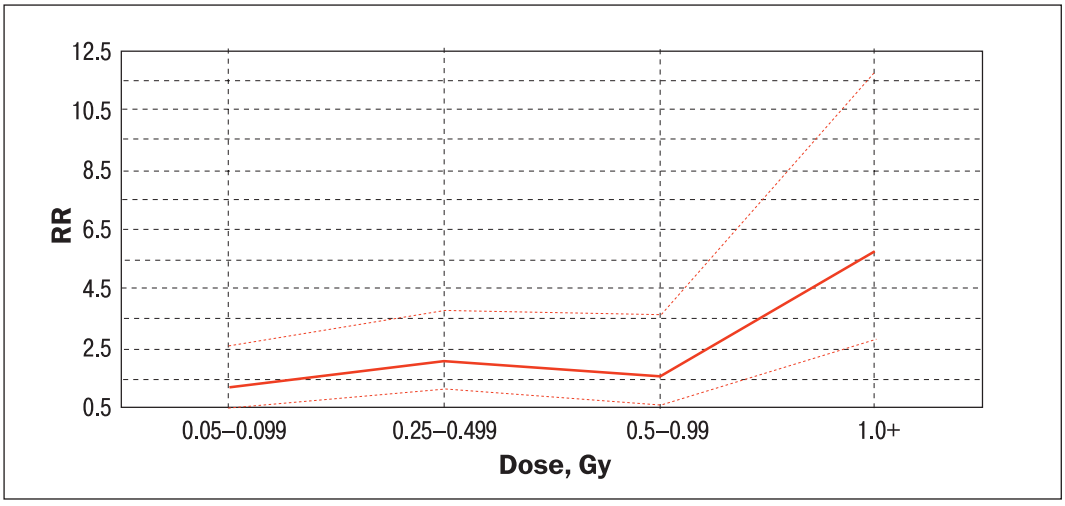


Figure 17.16. The relative risk for manifestation of central vestibular syndrome in a group of clean-up workers (1986–1987) depending on a dose loading

Analysis of some age groups revealed the reliable increase in risk for central vestibular syndrome relative to radiation dose. It was observed only for people aged 50-59 at the time of exposure (radiation dose 1.0 Gy and more) compared with those exposed to doses below 0.05 Gy (RR = 10.87, DI = 2.62; 45.1, $p < 0.05$).

Analyzing the distinct age groups the significant increased risk of central vestibular syndrome, depending on the dose of radiation was observed for persons aged 50–59 years during irradiation with radiation doses of 1.0 Gy or more compared with irradiated at a dose of 0.05 Gy (RR = 10 87; CI = 2.62, 45.10; $p < 0.05$).

As a result of the conducted researches prove for:

➤ A significant increase in risk of VeD primary morbidity was established in clean-up workers, who worked at ChNPP in 1986–1987.

➤ The risks of VeD disease were dose dependent in persons exposed to 0.25–0.49 Gy, 1.0 Gy, and more.

➤ Risk of vestibular impairment depended on age at exposure. Higher risk was observed in senior age groups, doses being equal.

17.3.3. Risks of VD morbidity in Chornobyl accident clean-up workers: results of mathematic modeling

The task of this research was to determine the dependence of VeD primary morbidity risk on the size of IR dose, age and other factors in clean-up workers of 1986–1987 by the method of mathematical modeling.

The results of studying risks of VeD disease appearance are presented by the method of mathematical modeling. The model of multiple logistic regression based on the method of maximal probability was used.

The model of multiple logistic regression was as follows:

$$Y = \frac{e^{\beta Z}}{1 + e^{\beta Z}} \tag{17.9}$$

where β – coefficients; Z – risk factors.

An analysis of VeD morbidity was first of all conducted in the dynamics. It has been established that VeD primary morbidity began to grow substantially in 6-7 years of stay under a risk after an irradiation, in 8.5 years reached a maximum, with temporal decrease and following increase.

The second maximum was observed in 10–11 years of stay under a risk. Farther a primary morbidity began to decrease. The dynamics of morbidity depending on time of stay under a risk reminds a parabola and is described by a formula [11]:

$$Y = -0.005 X^3 - 0.023 X^2 + 0.82 X - 1.17 \tag{17.10}$$

where Y – frequency of morbidity; x – time under a risk, years.

It has been supposed, that the dynamics of relative risk can be described by an exponential model. After a mathematical modeling the exponential model of relative risk of VD development was obtained.

A central vestibular syndrome was prevailed among VeD in 97.0% cases of clean-up workers by rubric H-81.4 (ICD-10). It was established that VeD morbidity was under effect of such factors as age at a time of exposure, dose of irradiation, a time of stay under a risk after irradiation. The formula of model for disease relative risk is below presented [18]:

$$RR = \frac{exp\,(\beta_0 + \beta_1 \times dose + \beta_2 \times age + \beta_3 / t)}{1 + exp\,(\beta_0 + \beta_1 \times dose + \beta_2 \times age + \beta_3 / t)} \qquad (17.11)$$

where *RR* – relative risk; β_0, β_1, β_2, β_3 – coefficients; *dose* (conditional designation) is a number of dose category, including this dose, Gy; *age* (conditional designation) is an age at the moment of work at the Chornobyl zone; *t* is a number of category including this term of stay under a risk (1 – it is 6 years after an accident; 2 – 7 years and so on).

As testify the calculations (17.11), a direct dependence between a IR dose, an age and a relative risk of VeD appearance is observed.

A relative risk of VeD occurrence calculated with a mathematical model at the IR dose (at the dose increase for every next dose group comparing to previous ones) is 1.24 (confidence interval 1.01; 1.39); at an age at time of irradiation (at an age increase for every next age group comparing to previous ones) – 1.28 (1.04; 1.59). A risk is significant, $p < 0.05$.

The results of calculations indicate that with the increase of dose the risk of VeD development is increased. A greater risk is observed in the older persons exposed, a smaller risk is in the younger ones.

A found conformity is interesting not only from scientific but also from the practical point of view. It is necessary to underline that a reverse conformity is observed in the majority of diseases regarding data of the risks dynamics depending on IR dose in different age groups by the data of P.A. Fedirko [15], i.e. a risk is greater for young age groups.

Since, as it was established, β_3 coefficient has a negative value, so primary morbidity with increasing time of stay under a risk is at first increased with following decrease. A relative risk of VD development (at 1/hour under a risk) is 0.099 (0.012; 0.82), $p < 0.05$.

Found conformities have a difficult nonlinear character. Obtained mathematical model of relative risk allowed to calculate the dynamics of VeD relative risk depending on a IR dose for different age groups and different time of stay under a risk after IR.

The corresponding graphs are shown in Figure 17.17.

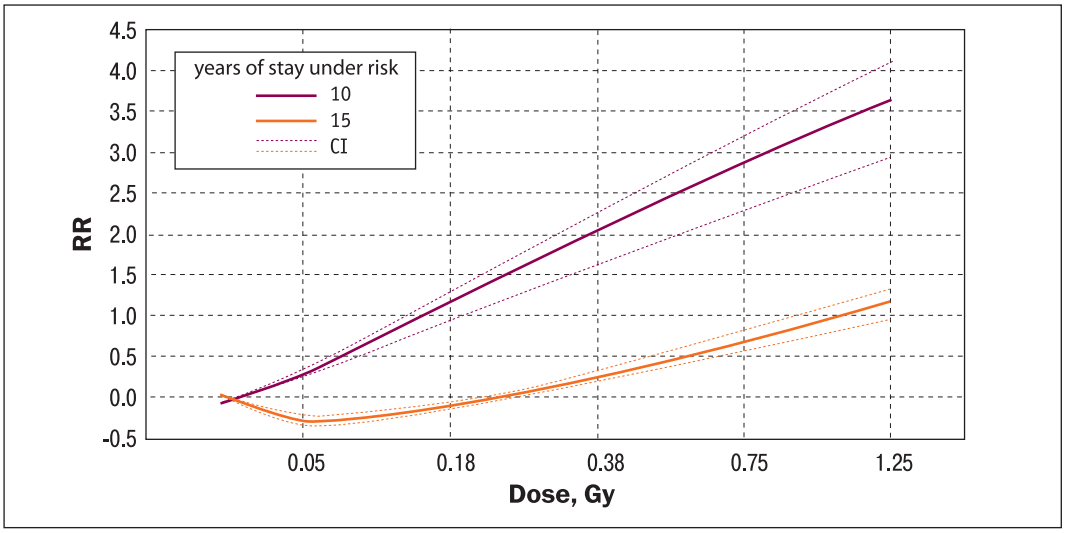


Figure 17.17. Relative risks of VeD disease and their confidence intervals are calculated by a model depending on the dose of irradiation in persons aged 41–50 years at the moment of exposition in 10 and in 15 years of stay under risk after IR influence

The graphs in Figure 17.17 illustrate a dose dependence of VeD risk (with increasing dose loading of IR a relative risk is increased). A risk becomes a significant at the doses over 0.2 Gy. The dynamics of relative risk shown in graphs depending on time of stay under a risk after an irradiation (10 and 15 years) had significal differences. A pronounced tendency of a decrease in relative risk with increasing period of stay under a risk is noted at a remote post-accidental period. These results agree with those obtained by P.A. Fedirko [15]: the presence of «window for analysing radiation risks», limited in time was established on the basis of risk dynamic analysis of other age-dependent diseases.

It has been established that change in VeD risk dependent on a size doses can not be diagnosed in 15 years after IR as testifies the graph in Figure 17.17. The calculations by model (17.11), revealed that VeD primary morbidity will slowly decrease in 20 years after a stay under a risk, and VeD morbidity due to cumulation of cases will be grow, although in less measure.

Thus, as a result of researches one can make following conclusions:

➢ the relative risk of VeD primary morbidity for clean-up workers is described by an exponential model which takes into account an age at time of irradiation, a dose of irradiation, a time of a stay under a risk after an irradiation.

➢ direct significant dependence between a dose of irradiation, an age and a relative risk of VeD appearance is shown, i. e. with an increase of a dose loading and with an increase of an age the risk of VeD development is increased at radiation period.

➢ VeD primary morbidity after IR is increased during 11 years with following decrease.

➢ as a result of mathematical modeling it has been established that the prognosis of VeD primary morbidity will be slowly decreased at a period after 20 years of a stay under a risk.

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Chapter 18
SOCIAL AND PSYCHOLOGICAL CONSEQUENCES OF CHORNOBYL CATASTROPHE

Thirty years passed, but the Chornobyl accident with its consequences is being a long-term stress factor. Accident and elimination of its consequences are firmly entrenched in the mass consciousness of the entire population, not just in the minds of the sufferers of accident. From time to time in certain time periods Chornobyl problem is actualized in mass consciousness, becomes the subject of attention (during any environmental, political actions, etc.), another time, this problem is dormant, that is «Chornobyl» represented in mass consciousness in so called, the background [1].

According to E. Golovakha (1997) research for Ukraine of the preaccidental period were characteristic: urbanization processes that shaped the culture of open public communications; relatively high levels of education, which created conditions for realization of critical perception of reality; as well as a large number of scientific, technical and humanitarian intellectuals interested in open channels of information and able to take advantage of them for the socio-political expression [2]. Only above factors, not to mention the loss of opportunities to system management, which had been considered controlled, and extrasensoric effects of radiation in the presence of any information about it, involved a significant social and psychological consequences. Unanticipated changes in the ecological environment, conditions and lifestyles, as the effects of the Chornobyl NPP accident, and the socio-political and economic transformation of society, which significantly worsened the level and quality of life become destructive to the social, mental and physical well-being not only affected population, but the population of Ukraine on the whole.

Despite existing materials of scientists from abroad about the social and psychological consequences of radiation accidents, public attention just after the accident was focused only on radio-ecological and health consequences and significantly later – on social and psychological. In the first years after the accident, few studies have been conducted [3–5]. Only since 1991 study of the psychosocial consequences as the problem becomes systemic. In the development and implementation of the socio-psychological monitoring were involved National Research Center for Radiation Medicine of National Academy of Medical Sciences of Ukraine, Institute of Sociology of National Academy of Scienses of Ukraine, Institute of Psychology of the Academy of Pedagogic Scienses of Ukraine and others. Analysis of monitoring allowed to allo-

cate specific time intervals in the post-emergency period and some groups, which were characterized by certain characteristics of social, psychological and medical losses. These were persons who participated in the clean-up works at Chornobyl NPP, the population evacuated in 1986 and relocated in 1991 and subsequent years, and people who were constantly living in areas with different levels of radiation contamination. The individual time intervals in the post-emergency period are characterized by: the participants of psychosocial monitoring; amount of received, analyzed and highlighted materials; study groups of the population, largely due to the interest of the authorities and the socio-economic situation in the country. In fact, the social and psychological monitoring of all studied groups ceased in 2007 with the termination of funding. Some studies of social and psychological consequences are in progress in NSCRM of the NAMS of Ukraine.

All matters covered in this section are mainly characterized population residing and working in the area of guaranteed voluntary resettlement in the dynamics of post-accident period and partly, to compare, – the population of the zone of obligatory resettlement.

Monitoring research was branched in directions according to the basic social and psychological problems of the population suffered from the consequences of the Chornobyl accident. Methodologically it highlighted key areas, which include the risk factors of the situation:

➤ Environmental sphere (state of environment and environmental awareness);
➤ Information and cultural sphere (availability of necessary knowledge, information on changes in the situation);
➤ The scope of health (their own health and the health of children);
➤ Social and psychological well-being;
➤ Economic sector (financial situation);
➤ Legal sphere (the efficacy of law).

During the post-accident period self-estimation of contaminated areas population for changes in these areas outlined social situations. Comparative analysis was carried out in view of the similar self-estimation of dwellers of conditionally clean areas.

The object of sociological research was monitoring of the adult population of contaminated territories of zone guaranteed voluntary resettlement (RCT) and conditionally clean territories (CCT) in Zhytomyr region. All studies were conducted with 2–3 years intervals in the same period of the year among the working population using the same methods. The samples sets in the dynamics of 1989–2013 was calculated based on the total population living in the study area. Random probable irreversible selection was applied [6]. During the years of research sampling error did not exceed the usual mistake of reliability. Selected totalities were: in 1989 – 1600 persons, from 1991 to1998 in 1200 persons, in 1999 – 400 persons, in 2001 – 319 persons, in 2003 – 400, in 2006 – 275 persons, in 2009 – 270 persons, in 2011 – 311 persons, in 2013 – 220 people. Allowable sampling error was 0.045–0.060. The number of samples for control territories amounted to 150–200 people.

The study of the living conditions of population was carried out using sociological and socio-hygienic methods. Structural-logical scheme of monitoring of social sphere was presented by groups of relatively independent but interconnected information blocks. Questionnaire was developed with relatively independent but interconnected blocks: assessment of the environmental situation, the level of radiation risk perception, social and psychological state of the population, behaviour aimed at preserving health in conditions of RCT, information of population, related to the development of nuclear power engineering. Methods applied: standardized questioning, test of integral index of social well-being [7], the self-assessment of health status [8]; «General Health Questionnaire GHQ – 28» [9], Spielberger's test by Y.L. Hanin modification [10].

To adequate assessment of the level of population's concern on radionuclide content in foodstuffs for comparisons, data from Ovruch sanitary-epidemiological service (SES) monitoring studies of food contamination from the private sector (P/S) and local production brands (B) from 2005 to 2011 were used in the settlements area of surveyed population and the data of NRCRM specialists NAMS Assessment of permissible levels of radioactive contamination of food in the studied settlements was carried out in accordance with hygienic standards that have been adopted in Ukraine by the Ministry of Health order No. 256 from 03.05.2006 [11]. Tests were conducted at one year intervals on basic food products, which form dose of internal radiation exposure (milk, meat of wild animals, honey, mushrooms and berries).

Measures to ensure the quality of medical care were analyzed using analytical and statistical methods. Official statistics on the resources and activities of medical institutions within years 2001–2011 and data of monitoring sociological studies on public opinion were analyzed. Statistical data collected in collaboration with the staff of the Regional Information and Analytical Center for Health Statistics of Zhytomyr region and central hospitals of Ovruch and Andrushivsky districts.

Expert questionings were held in 2002 and 2012 by specialists on three levels: district's, regional and state on the implementation of articles of the Legislative documents on medical support [12]. State level was presented by experts of Ministry of Health of Ukraine. Regional level group of experts was conventionally divided into two subgroups: specialization of treatment and prevention and specialists of SES. District level of experts was presented by the head doctors and heads of departments of district's SES. The group of experts consisted of 97 people, including 53 specialists in treatment and prevention and 44 SES experts.

During the processing of the data mathematical statistics methods were used as software packages Excel (comparison generalized of performance characteristics: relative size, means, reliability of pair differences by Student's *t*-criterion, interaction of factors with each other via the pair correlation *r*, factor analysis).

18.1. THE POPULATION'S PERCEPTION OF ENVIRONMENTAL AND RADIATION SITUATIONS

The question of the overall environmental situation is one of the most important concern of RCT population. However, it emerged in public of studied region much later. Fifteen years environmental factor was identical to radiation one. According to research of the Institute of Sociology of NAS of Ukraine, reflection of environmental issues in the public consciousness of different population categories during the first decade was very complex and controversial. Objective manifestation of mass awareness disorientation on environmental problems in conditions of socio-environmental stress have become passive social actions and acts [13].

Population assessment of environmental situations determined by several factors: the status of territory; its own assessment of radiation situation; changes occurring in the environment. Population of RCT estimates state of the environment more negatively than dwellers in relatively clean areas. In 2007, the ecological state of settlements as unfavourable were evaluated by 4% of conditionally clean areas residents and up to 58% of inhabitants of the zone of guaranteed voluntary resettlement and to 60% – in the zone of obligatory resettlement. Environmental well-being index amounted to 0.41; -0.25; -0.29 respectively [14].

In 2013, about 50% of inhabitants of zone of guaranteed voluntary resettlement considered the local environmental situation as disadvantaged, in particular, extremely unfavourable – 10.4%. The main causes of the current status of the respondents assessed differently. In RCT this was due

to radioactive and chemical contamination of soils (65.0%), food products (62.3%), drinking water (61.7%), deforestation and succession processes (54.5%). In relatively clean areas the main factors were the «indifferent attitude of people towards the protection of nature» (52%), pollution by domestic wastes (41%) and insufficient funding of nature-conservative measures (32%).

Only 38.4% of the RCT population believed that environmental situation was relatively safe. In the group of respondents who considered ecological situation as extremely unfavourable, the highest percentage was of those who considered the radiation situation dangerous to health (68.2%).

Among the difficult issues of social and psychological consequences of the NPP accident important is the question of radiation risk perception by population [15–18]. A situation of risk that has been established at RCT in 1986–1991, was due to the real risk factor – environmental contamination with radionuclides. It was characterized by high levels of anxiety of population for its own health, health of children and families in connection with possible exposure to ionizing radiation. In the early post accident years, most respondents (81.9%), regardless of the radiation situation in the community, believed that the deterioration of their health was due to the influence of radionuclides [19]. In 1992–1994 there was a decrease in the number of respondents who considered the radiation situation dangerous to the health with the trend to increase in 1997 (Figure 18.1).

The growth of this group was not due to the worsening of the radiation situation but the sharp economic changes in the country [20].

In the dynamics of the last ten years the number of respondents has decreased who believe that the radiation situation at residence is life threatening. In present conditions in the zone of guaranteed voluntary resettlement 41.7% of respondents believe that the radiation situation at residence is dangerous to health. For comparison – in 1997 the share of this population was 70.3%. Current index hazards to human health remains very low: in 2005 it amounted to 0.10 in 2010 – 0.16 in 2013 – 0.38 at the optimum 1 (scale from –1 to +1, where 1 – no danger to health). In CCT it amounted to 0.32; 0.33 and 0.57 respectively.

Attention is drawn to the fact that the level of public perception of the radiation situation in 2nd zone was significantly lower than in the population of 3rd zone: 36.5% of 2nd zone respondents do not feel anxiety, which is 4 times more than in the third zone (8.5%). Only 19.2% (26.6% – women, 11.9% – men) of respondents believe that the radiation situation at residence is dangerous for health.

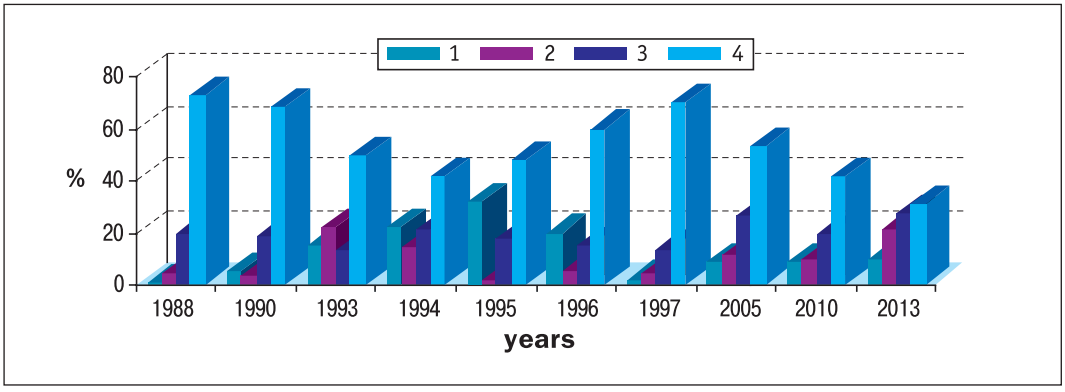


Figure 18.1. Dynamic for years distribution of respondents in terms of the perception of radiation situation (%)

1 – do not feel anxiety; 2 – generally feel anxiety; 3 – anxiety because they do not have information; 4 – consider the situation dangerous for health

The proportion of the population feeling anxiety due to the lack of information about the radiation situation grew from 13.7% in 1997 to 27.7% – in 2013. Calculated anxiety index due to the lack of thematic information in 1997 amounted to 0.72, and in 2010 – 0.61, and in 2013 – 0.45. This decrease is due to the dynamics of information flows, changing subjects and sources of information. Since 1993 started a decrease of information flows of press, radio and television in Ukraine. A dependence was established of indicators «general anxiety» and «anxiety because do not have information» on information flow saturation [21, 22].

The imprinting of negative consequences of the Chornobyl accident is manifested in public concern of their health and the health of children (Table 18.1). Estimates of the negative consequences of the Chornobyl accident were higher among respondents of 3rd zone compared to respondents in the 2nd zone. In the first place were concerns about their own health and the health of children (52% in 2nd zone, 68% in 3rd zone). The second place were concerns due to the lack of specific information about the health of the population affected by the Chornobyl accident (3rd zone) and concern about food used by people in everyday life (2nd zone). The problem of resettlement disturbed 7.6% dwellers of the 3rd zone and 10.0% of the 2nd zone.

In the dynamics of the last decade only the level of public concern about possible water contamination with radionuclides was decreased.

In towns surveyed population, According to SES and the Laboratory of Internal Dosimetry of NRCRM estimates, the greatest risk of internal exposure doses of ^{137}Cs through food consumption are fresh and dried berries, mushrooms, widelife meat, sometimes milk wihout, adequate radiation monitoring. In other food products, particularly potatoes and vegetables, honey, fish, poultry and poultry products content of ^{137}Cs was negligible [23]. The content of ^{137}Cs and ^{90}Sr in water samples within DHN (DR-2006).

Behaviour stereotypes turned out to be extremely stable for most people even in the first years after the accident. In 1989 57% of respondents continued to adhere to pre-accident life style, only 20% – fully performed hygienic advices in everyday life. During the first five years, most respondents (in 1986 – 59%, 1989 – 86.6%, 1991 – 61.7%) did not exclude anything from their diet, despite the restrictions on the use of certain products.

Analysis of respondents' responses of 2000–2011 on protective measures in the everyday life revealed that the population continued to declare concern about the negative consequences. Implementation of preventive measures to safeguard life due to living in contaminated areas for the population did not become a habit. A decline in preventive activity rate was fixed (Figure 18.2).

According to the survey in 2011, 57.0% of 2nd zone respondents and 59.2% of 3rd zone respondents never checked-risk products (milk, berries, mushrooms) for content of radionuclides before

Table 18.1

Negative consequences of the Chornobyl accident for respondents of RCT in 2013, %

The negative consequences of Chornobyl accident	Areas of RCT	
	2nd zone	3rd zone
Anxiety about food that may be contaminated	28.9	31.8
Concern about drinking water	26.4	28.0
Concern about their own health and the health of children	52.1	67.8
Concern about the lack of information about the health of the population affected by the Chornobyl accident	27.3	37.0
Resettlement problems	10.7	7.6
Change of traditional life style	3.3	4.3

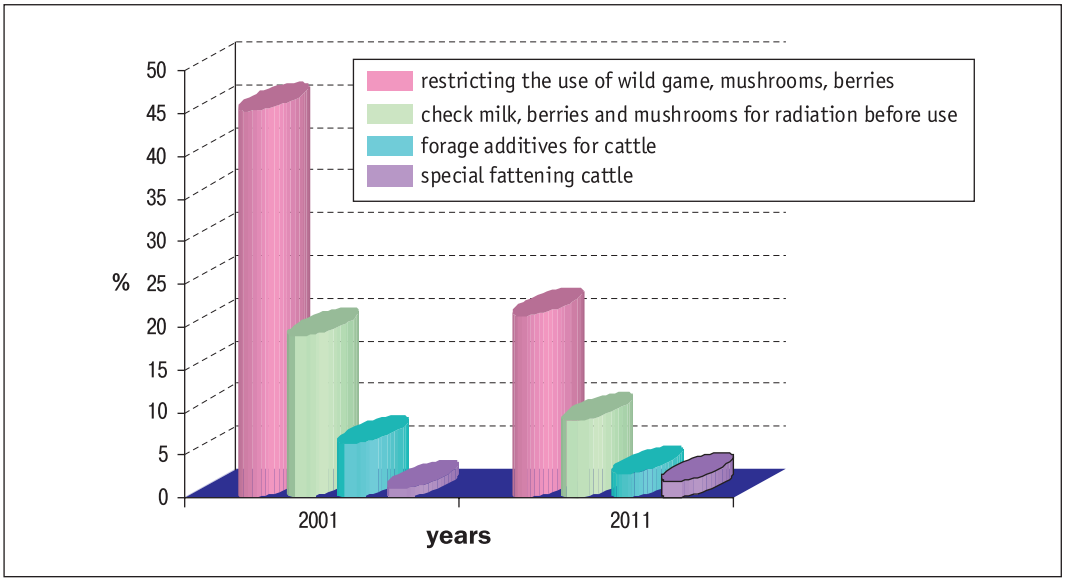


Figure 18.2. The list of countermeasures used in everyday life by RCT population in 2001 and 2011 (%)

use. At the 2nd zone number of respondents who limit themselves in the use of game, mushrooms and berries, was only 15.7%, in the territory of 3rd zone – 21.3% of respondents, which was extremely low, given the fact that in recent years in many settlements of Ovruchsky and Narodychsky districts experienced increased levels of internal exposure of people [23]. Among those who have cattle in households, 5.0% in the 2nd zone and 9.5% in the 3rd consider as necessary to keep and graze it according to the status of residence territory (Figure 18.3).

One of the indicators that characterized the behaviour of the population during the 1987–1991 was the relocation: of 46% of respondents would leave RCT, 28.5% – were undecided and 25.5% did not plan to leave the residence. For 20 years, from 1992 to 2010, the number of those wishing to leave the zone of guaranteed voluntary resettlement decreased to 7.3%.

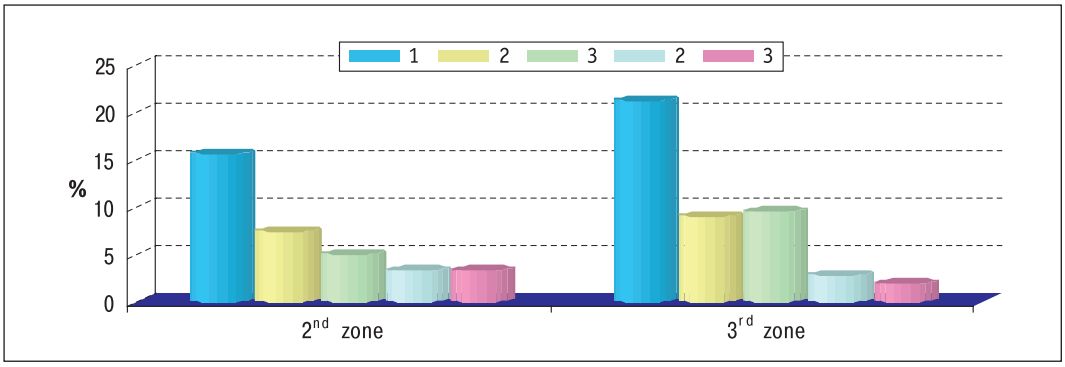


Figure 18.3. The list of measures that served population of 2nd and 3rd zones of RCT in 2011 (%)

1 – restricting the use of wild game, mushrooms, berries; 2 – check milk, berries and mushrooms on the content of radionuclides; 3 – grazing only in designated «clean» pastures; 4 – forage additives for cattle; 5 – special fattening cattle

18.2. VALUE PRIORITIES AND THE SOCIAL SECTOR OF THE POPULATION RCT

Comparing the hierarchy of life values of RCT population during 2001–2014 it was found that the «core» of the structure of consciousness value of people did not change, «health», «children», «family welfare» (Table 18.3). Due to environmental changes, the threat of consequences of the Chornobyl disaster and the increasing incidence the main position occupied health value, which refers to physical values. «Children» and «family welfare» form ethical part of general life values transmitted in the education from parents. «Core» included such values as «interesting work» (2001 and 2014) and «material wealth» (2007). According to the classification they were attributed to material and professional motivational values, but having one basis – vocational sphere of life.

«The structural reserve» of values-goals are a middle status values that can be displaced both to the «core» and the «periphery» (Table 18.2). For 14 years the composition of «structural reserve» was changed from purely material in 2001 («material wealth») to material and professional motivation in 2004, to the ethical – in 2007 and 2013 – «love», «friends» and « public recognition» – in 2014.

The «tail» of terminal values hierarchy are «freedom», «active creative life», «security», «public recognition».

Among RCT population was increasing awareness of «health value» category. The share of the population that believes that «Health is the most important thing in life» increased and decreased the share of those who «wants to live as they like without nothing limiting themselves»; «live like everyone else, regardless of radiation» (Figure 18.4). The proportion of respondents was decreasing who could ignore health for the material well-being of family and put it on a par with rest and entertainment. The percentage of respondents who did not want to limit anything themselves for the sake of health, decreased in the population of RCT, remained unchanged and among respondents of CCT.

A tendency to more responsible attitude to the health traced in dynamics (Figure 18.5).

Reducing of subjective radiation risk influences on motivation and preventive behaviour of population. The latter appears in reducing the number of those who were constantly watching their health dynamics in 2000-2010. In ten years, the number of those who care about their health when necessary increased by 12.4%. The positive trend is observed also in the group that did not care about his health, it decreased by 8%.

Though traditional guidelines have an impact on people, but another way of life, economic and social changes taking place in today's society, make significant adjustments in their behav-

Table 18.2

Dynamic change of structural sections life values of RCT population

Structural sections life values	Years			
	2001	2004	2007	2013
Core	- health - children - interesting work	- health - children - a happy family life	- health - a happy family life - material well-being	- health - a happy family life - interesting work
Structural reserve	- development - material well-being	- material well-being - interesting work	- interesting work - love - friends	- friends - public recognition
Tail	- freedom	- freedom - security - active creative life	- active creative life - public recognition	- material well-being - freedom

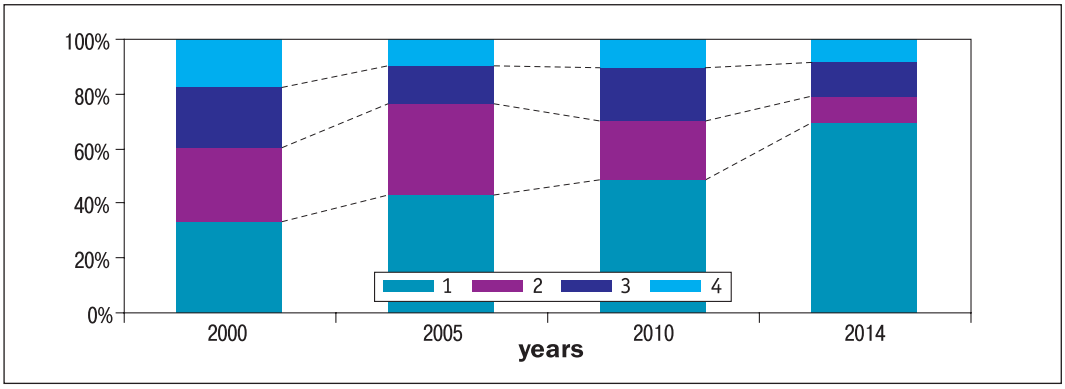


Figure 18.4. The value of health stance of respondents by the years' dynamics (%)

1 – health is the most important thing in life, decisions should be taken so as not to damage the health; 2 – health is important, but sometimes I can forget about it for material well-being of the family; 3 – health is important for me at the level of work, rest, and so on; 4 – I want to live the way as I like it

iour, in particular reproductive. Reproductive instruction are differentiated based on marital status. In men, the formation of reproductive orientations and guidelines was are formed before marriage, while in women this process occurs after marriage. The lowest rates of reproductive orientations found among young women who are in a civil marriage. The correlation relationship between the level of reproductive orientations and duration of marriage ($r = 0.219$ $p < 0.05$). Durable lasting marriage causes the growth of reproductive orientation.

Based on factor analysis the main conditions were found that hinder or help to increase the number of children in the family. Among inconvenient factors the greatest contribution to the overall variance terms of reproductive behaviour in RCT introduced eco-social factors (general environmental degradation in the country, radiation pollution, the likely negative impact of radiation on the offspring). At CCT – socio-economic factors (low income, inadequate infrastructure related to the care and upbringing of the child, insecurity, low social protection of chil-

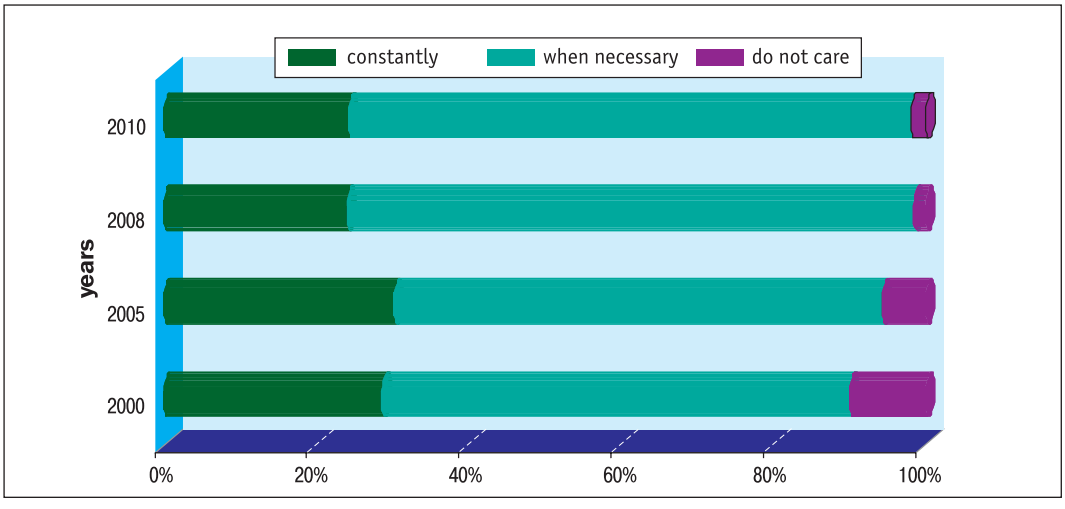


Figure 18.5. Distribution of RCT respondents by regular monitoring of their health, dynamics by years (%)

Table 18.3

Matrix loads on three main factors that characterize the reasons that motivate respondents to postpone child birth, depending on gender and place of residence (correlation coefficients > 0.4)

Indicator	Environmentally social				Socioeconomic				Interpersonal relationships			
	RCT		CCT		RCT		CCT		RCT		CCT	
	men	wom.	men	wom.	men	wom.	men	wom.	men	wom.	men	wom.
Contribution to overall variance%	30.0	25.5	16.7*	14.7*	15.9	12.8	22.9	25.2*	14.5	12.6	13.7	13.8
The general deterioration of the ecological situation	0.79	0.64	0.70	0.45	–	–	–	0.41	–	–	–	–
Environmental degradation that is associated with radiation contamination	0.76	0.71	0.86	0.71	–	–	–	–	–	–	–	–
A possible negative impact of radiation on posterity	0.75	0.58	0.77	0.81	–	–	–	–	–	–	–	–
Low income	0.44	0.51	–	–	0.70	0.65	0.69	0.75	–	–	–	–
Inappropriate infrastructure related to the care and upbringing of the child	–	–	–	–	0.48	0.69	0.59	0.49	0.66	–	–	–
Uncertainty about the future	–	–	–	–	–	0.42	0.52	0.67	–	–	–	–
Low social protection of children in our society	0.45	0.57	–	–	–	–	0.56	0.65	–	0.42	–	–
Bad living conditions	–	0.55	–	–	0.69	–	0.53	–	–	–	–	0.67
Poor health of his wife (husband)	–	–	–	0.59	–	0.73	–	–	0.67	–	0.78	–
Bad relations in the family	–	–	–	–	–	–	–	–	0.64	0.50	0.78	0.74
Great time at work, career	–	–	–	–	–	–	0.50	–	0.58	0.73	–	0.47

Note. * – $p < 0.05$ in relation to the corresponding sex respondents residing in RCT.

Table 18.4

Matrix loads on three main factors that characterize the conditions and safeguards that can affect the increase in the number of children in surveyed, according to sex and place of residence (correlation coefficients > 0.4)

Indicator	Social / economic guarantees				Social / environm. safeguards				Interpersonal relationships			
	RCT		CCT		RCT		CCT		RCT		CCT	
	men	wom.	men	wom.	men	wom.	men	wom.	men	wom.	men	wom.
Contribution to overall variance%	31.5	33.2	30.6	31.9	15.5	18.4	14.8	16.3	13.9	14.3	12.9	14.7
The ability to produce well	0.60	0.56	0.41	0.68	–	–	0.52	–	–	–	0.43	–
Confidence in job security in the future	0.66	0.62	0.68	0.76	–	–	–	–	–	–	–	–
Confidence in the future	0.75	0.54	0.65	0.62	–	–	–	–	–	–	–	–
Hope for improvement of ecological situation in the region	0.50	–	0.74	0.72	0.41	0.76	–	–	–	–	–	–
The increase in aid from the state to families with minor children	–	0.42	–	0.50	0.81	0.66	0.83	–	–	–	–	–
Significant improvement of living conditions	–	–	–	–	0.62	0.60	0.46	0.68	–	–	–	–
Improving health	–	–	–	–	0.45	0.68	0.41	0.47	–	–	–	0.53
Favorable family relationships	0.43	–	–	–	–	–	–	–	0.58	0.65	0.58	0.82
The emergence of opportunities devote to more time to family, children	–	0.47	–	–	–	–	–	–	0.75	0.52	0.78	0.75

dren; Table 18.3). Factor of interpersonal relations (bad relations in the family, over employment, career) introduced the smallest variance in the total contribution both at the RCT and at CCT. Among the conditions that help to increase the number of children the first place occupy socio-economic guarantees (opportunity to make good money, self- securing work in the future, confidence in the future), regardless of the place of residence of respondents (Table 18.4).

18.3. THE SOCIAL CONDITIONS OF LIFE

Satisfaction by the main spheres of life activity defines the state of social welfare of the affected areas population.

The level of adequacy in the socio-political sphere, which was in 2013 most dissatisfying for people of RCT has a close correlation with the position of a person who «figure on nobody» – pessimists ($r = -0.732$ $p \leq 0.05$) and with concern of the population in the events of social emergencies ($r = -0.185$, $p \leq 0.01$). That is, the lower the level of satisfaction in this area, the greater the fear on the emergence of social upheavals.

The level of adequacy in social security has a direct correlation with the level of anxiety regarding radiation situation residence ($r = 0.139$, $p \leq 0.05$). There is a lack of legal assistance to protect rights and interests of over 50% of the population living in the 3rd RCT zone. Long-term unsolved social problems under the Law of Ukraine «On the social status and social protection of citizens affected by the Chornobyl disaster» impact negatively on human society. During the 2001–2010 the number of people who wish to obtain financial compensation from the government for living on RCT almost doubled (36.1% in 2001 and 68.4% – in 2010).

The strategy for future plans of RCT population is defined by four lines of advance:

➤ Traditional preferential – seek increased compensation from the authorities for living on RCT;
➤ Migration – moving to permanent residence in the «clean zone»;
➤ Indifference – to live like everyone else, despite the radiation and talk about it;
➤ Conscious adaptation – all live as everyone performing certain recommendations in connection with living in this area (Figure 18.6).

Satisfaction of respondents by sphere of social relations depended on the quality of local authorities ($r = -0.164$ $p < 0.05$) and improved with the improvement of environmental conditions in the area ($r = -0.178$ $p < 0.01$) and with the growth of material well-being ($r = 0.235$ $p < 0.01$).

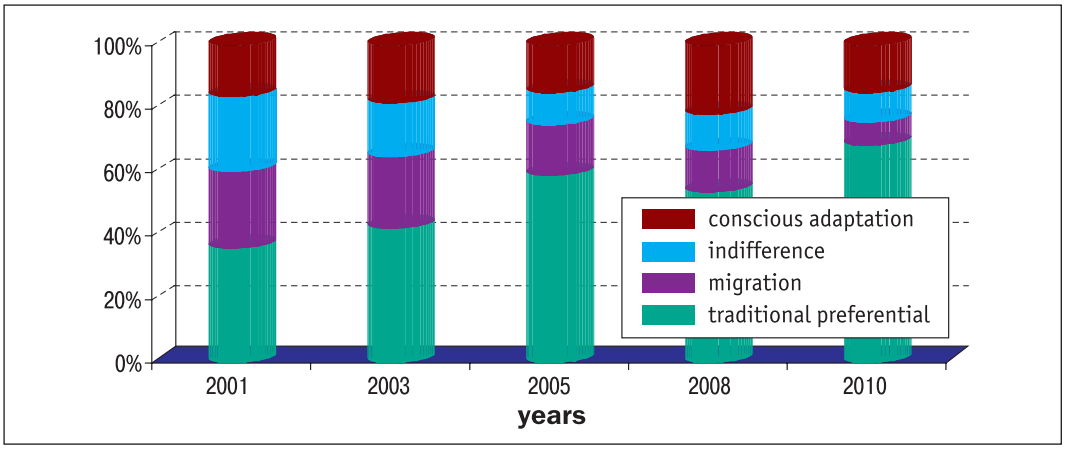


Figure 18.6. Dynamics of life plans of RCT population, %

Public satisfaction in recreational and cultural sphere tended to increase. The level of satisfaction of respondents in this area depended on the education of the respondent ($r = -0.167$ $p < 0.05$), the level of human well-being ($r = 0.241$ $p < 0.01$). There was a close correlation between satisfaction in recreational and cultural sphere and satisfaction by function of medical institution where the respondents were served, the number of specialists ($r = 0.138$ $p < 0.05$), working schedule ($r = 0.172$ $p < 0.05$), provision of necessary medicines ($r = 0.176$ $p < 0.01$), cost of medications, which prescribed doctor ($r = 0.187$ $p < 0.01$).

The positive impact on the social well-being with the satisfaction of material in the domestic sphere of 2nd and 1st levels, depended on the age of the respondent ($r = 0.200$ $p < 0.01$), the category of the Chornobyl accident sufferer identity ($r = -0.208$ $p < 0.01$). Besides the satisfaction of life in this area of grew with certitude in their prosperity ($r = 0.306$ $p < 0.01$) and health ($r = -0.293$ $p < 0.01$).

The level of satisfaction in material and everyday life was always dependent on the welfare of the family. The survey population RCT the last 15 years show the same trend: the number of respondents with an average standard of living has increased significantly due to the decrease in the proportion of very low and low, while in 2008 began to form small cohort of people who consider themselves as high levels of well-being (Figure 18.7).

In the distribution of household income food and clothing rank first. Over the past 15 years the family budget distribution structure has undergone minor changes (Table 18.5). With the increase in utility and gas tariffs, household expenses moved from 4th to 2nd place, increased budget item for treatment. Housing construction or improvement of housing conditions occupied the fifth position since 2010. Education in the budget of many families who had students with rising pay for it became almost a major item of expenditure.

Though improved the quality of RCT population life, but it was still not high enough for a normal existence of all segments of the population. The growth of material well-being of the population gradually reduced stress, which was associated with poverty.

A factor that supports social tension among the population is health care. According to official statements of Ministry of Health of Ukraine, the last ten years (until 2011) system of medical and preventive care infrastructure remained. Against the background of improving financial

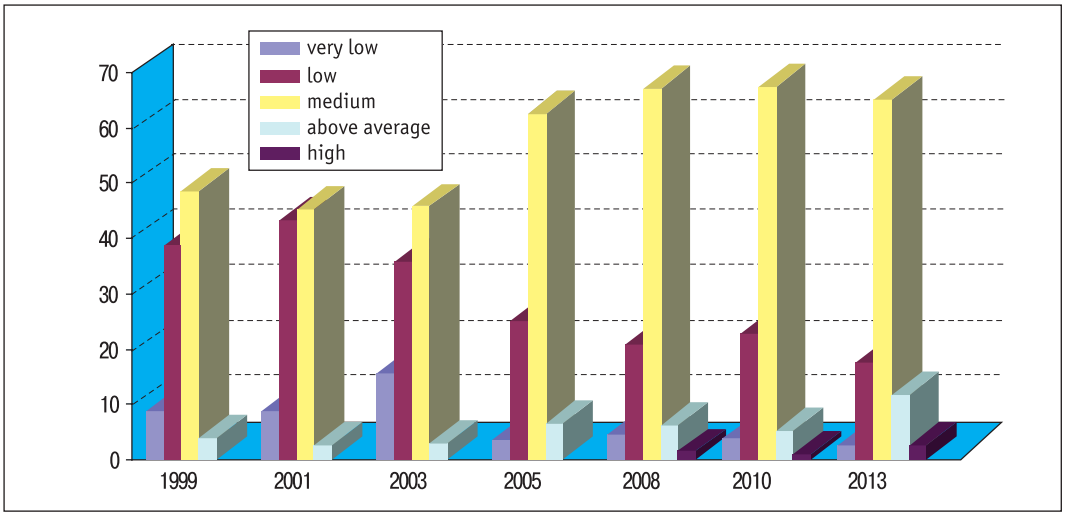


Figure 18.7. The level of family welfare ofrespondents living in RCT, dynamics by years (%)

Table 18.5
Distribution of the household budget of RCT population, dynamics by years (rank from 1 – most important, 10 – least important)

Expenses	1999	2010	2013
Nutrition	1	1	1
Clothes	2	2	3
Purchase of durable goods	7	7	6
Household expenses (utilities)	4	3	2
Treatment	5–6	4	4
Recovery	5–6	6	8
Housing construction or improvement of housing conditions	10	5	5
For leisure, holiday	8	10	9
Education	3	8	7
Purchase of newspapers, books, audio and video	9	9	10

support in the 2001–2011there are staffing problems, including providing doctors and paramedical staff. For 10 years the number of doctors at RCT decreased by 21.0% at CCT – by 14.3%, and the number of nurses – by 20.8% and 18.4% (Table 18.6).

In RCT level of physicians significantly decreased per 10 thousand of population by 16.3% in the dynamics of 2001–2006, in the CCT – by 4.0%. After 2006, the index increased in both areas to ensure physicians, but only in 2011 figures were close to those of 2001 (Table 18.7).

Table 18.6
Changes in the number of doctors (without stomatologists) and nurses in dynamics by years in the study area

Name of region	Years			2006 to 2001/ 2011 to 2001(%)
	2001	2006	2011	
The number of doctors (individuals)				
Andrushivskyi	70	62	60	88.6/85.7
Ovruchskyi	162	125	128	77.2/79.0
By region	4713	4538	4490	96.3/95.3
The number of nurses (individuals)				
Andrushivskyi	282	229	230	81.2/81.6
Ovruchskyi	673	562	533	83.5/79.2
By region	14923	13822	13514	92.6/90.6

Table 18.7
Dynamics of physicians and nurses per 10,000 population, dynamics for years

Name of region	Years			2006 to 2001/ 2011 to 2001(%)
	2001	2006	2011	
Physicians per 10 thousand people				
Andrushivskyi	17.5	16.8	17.1	96.0/97.7
Ovruchskyi	23.3	19.5	21.3	83.7/91.4
By region	33.0	34.1	35.1	103.3/106.4
Supply m / s 10 thousand population				
Andrushivskyi	70.7	62.1	65.6	87.8/92.8
Ovruchskyi	96.7	87.5	88.7	90.5/91.7
By region	104.6	103.9	105.6	99.3/100.9

Similar situation revealed for nurses. However, at the regional level, a slight increase was found, which could be due to depopulation and migration.

Shortage of individual physicians and nursing at all levels was observed (Table 18.8). Provision of staff positions of medical institutions was partially compensated by combining positions.

In absolute figures the bed fund within past 10 years decreased both at the RCT (by 10.5%), and the CCT (by 16.1%) and in the region (by 9.7%). At that provision of public by hospital beds for RCT increased by 7.1% and for CCT decreased by 3.9%. In RCT bed occupancy rate increased by 10.2% from 2001 to 2011 CCT. In 2001–2006 it wavy significantly increased (by 25.2%) and in 2006–2011 decreased slightly (by 1.4%). The average duration of stay decreased both in the study areas and the region.

In RCT and in the region increased activity of outpatient services. The number of visits per capita increased at RCT by 21.2% and in region – by 15.3%. In CCT indicator of visits per 1 inhabitant varied decreasing in 2006 to 13.4% and increasing by 21.2% in 2011.

According to the monitoring of public opinion polls, the general index of satisfaction with health care facilities has decreased rapidly in recent years (Figure 18.8). For 72.5% of the respondents RCT main reason for dissatisfaction was the lack of specialists in CCT – to 67.6%.

Table 18.8

Provision and staff positions of doctors and nursing individuals in dynamics by year (2001, 2006, 2011) without SES staffing

Districts	Head office physicians (absolute data)			Manning staff positions, individuals (%)		
	2001	2006	2011	2001	2006	2011
Andrushivskyi	83.50	84.50	83.50	83.83	73.37	69.5
Ovruchskyi	211.25	194.25	204.50	76.68	64.35	60.6
By region	6149.0	6218.0	5669.75	76.64	72.66	71.9
	Established nursing posts (absolute data)			Manning staff positions, individuals (%)		
Andrushivskyi	230.75	237.25	236.25	122.21	96.52	92.7
Ovruchskyi	518.00	509.00	507.50	129.92	110.41	105.0
By region	14095.0	13401.75	12475.0	105.87	103.51	94.0

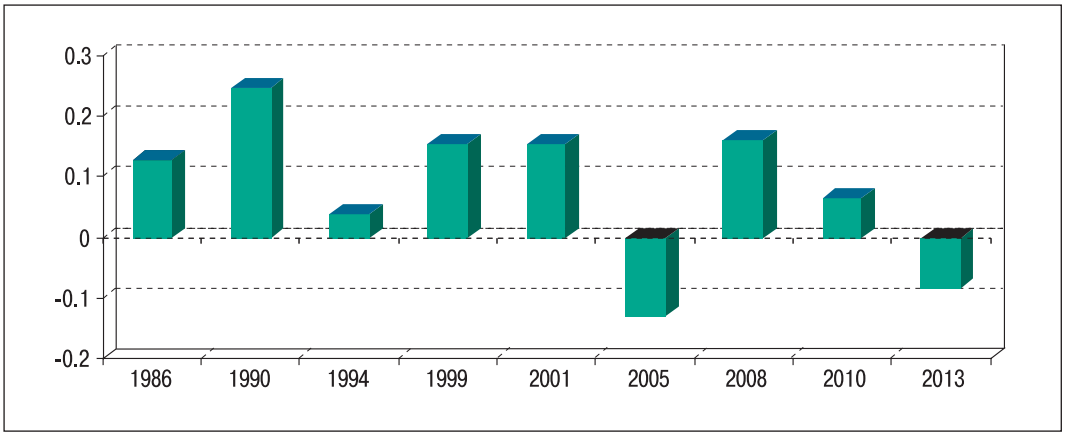


Figure 18.8. The index of satisfaction with medical institutions in dynamics (-1 to 1)

Table 18.9
Reasons for dissatisfaction with health care respondents in RCT and CCT, dynamics by years (%)

Age, years	1999		2010	
	RCT	CCT	RCT	CCT
Any lack of care in our village	5.3	3.4	12.3**	9.3*
Long distances to health institution	4.3	7.9	16.6**	16.7**
Lack of specialists	22.3	34.8	72.5**	67.6**
Inability to perform all doctor prescriotions (procedures, food, etc.)	25.5	34.8	41.7**	38.0
The inability to purchase medicines due to lack of funds	73.4	65.2	50.7**	52.8**
Other	6.4	2.2	4.7	1.9

Notes. * – statistically significant difference ($p \leq 0.05$) between indicators of the population in 1999 and 2010 to RCT and CCT; ** – statistically significant difference ($p \leq 0.01$) between indicators of the population in 1999 and 2010 to RCT and CCT.

In second place – the inability to purchase medicines due to lack of funds (Table 18.9). Third place occupied the inability to comply with all appointments and medical advices (procedures, food, etc.). The biggest complaints of the populationwas provided with the lack of necessary medicines and diagnostic equipment, including cabinets in clinics.

Despite all the problems of healthcare facilities, the vast majority of the population relies on public health (70.1% – at RCT and 61.1% – at CCT). But the percentage of people who procrastinate the visit to doctor until the last and relied on their own knowledge and abilities increased (from 25.7 to 52.1% – in RCT, from 39.0 to 60.2% – in CCT). In poorly developed private and insurance health care relied not more than one fifth of respondents. This service for the rural population with very low welfare was almost unattainable. Taking care of their own health, the people was forced to seek and rely on public hospitals.

According to the expert survey, the average expert assessment of the use of Fund to implement measures to eliminating the consequences of Chornobyl disaster and social protection in 2012 decreased compared to 2002. First of all it concerns the purchase of medical diagnostic equipment for specialized medical establishments (from 54 to 24 points respectively). On the low level was the acquisition of medications (38 and 36 points respectively).

On the issue of health care and rehabilitation focused their attention experts of 1991–1995. According to their forecasts, the Law of Ukraine «On status and social protection of citizens affected by the Chornobyl disaster» more or less satisfactorily determined the legal guarantees, but its implementation was highly questionable because of insufficient institutional arrangements and financial resources for further implementation [24, 25].

The implementation of the National Programme of overcoming Chornobyl accident consequences for 2006–2010, including medical component was evaluated by experts only 38 points out of 100 possible. The effectiveness of the Ministry of Health of Ukraine in solving a wide range of problems in liquidation of consequences of the Chornobyl accident was estimated at 48 points. Treatment of seriously ill was evaluated by various expert groups from 33 to 51 points. Health improvement of children and disabled worsened, its assessment has not exceeded 50 points and proving for a low level of patients rehabilitation [26]. Thus, the medical care of the population affected by the Chornobyl accident, was gradually losing public support.

18.4. SOCIAL AND PSYCHOLOGICAL STATE OF THE RCT POPULATION

Social feeling of RCT population steadily tended to improve and in 2013 was not significantly different from the social well-being of the CCT population. In the dynamics of post-accident period the general integral index of social well-being (ISWB) from 1997 to 2001 had a downward trend, and in the next years up to 2013 its significant growth and stabilization were found. In dynamics by years there was a significant reduction ($p \leq 0,05$) of respondents at RCT with an average level ISWB and growth with increased and high ($p \leq 0,05$).

Using factor analysis of social well-being indicators social needs were found that most influence the formation ISWB of the RCT population in different years of research (Table 18.10). If in 1999 and 2005 prevailed factor, in which the main burden formed socio-political and legal guarantees (social, political, social security, social relations, contribute to the dispersion of signs of 38.3% and 22.60%, respectively), in 2013 biggest factor (27.2%) was formed by the material, vocational, recreational and cultural, informational and cultural spheres.

Table 18.10

Matrix loads of three main components of social factors on health dynamics

Areas of life	1999			2005			2013	
	1	2	3	1	2	3	1	2
Social affairs	0.611	0.319	0.103	0.701	0.155	0.156	0.311	0.611
Social security	0.763	0.258	-0.044	0.688	0.093	-0.002	0.306	0.631
Social and political	0.777	0.015	0.213	0.673	-0.027	0.193	0.140	0.657
Professionally-labor	0.020	0.755	-0.149	0.165	0.565	0.480	0.575	0.255
Information and culture	0.186	0.675	0.057	0.235	0.108	0.757	0.475	0.227
Recreational and cultural	0.545	0.580	0.100	0.419	0.440	0.463	0.627	0.407
Material and household (1 level)	0.143	0.604	0.486	0.086	0.873	0.011	0.846	0.078
Material and household (2 level)	-0.347	0.658	0.309	0.133	0.849	0.050	0.864	0.072
Interpersonal relations	0.286	0.164	0.748	0.537	0.218	-0.490	-0.033	0.652
Personal qualities	0.600	0.057	0.655	0.519	0.272	0.207	0.314	0.544
Contribution to overall variance, %	**38.3**	**15.5**	**8.2**	**22.60**	**21.61**	**13.65**	**27.24**	**22.18**

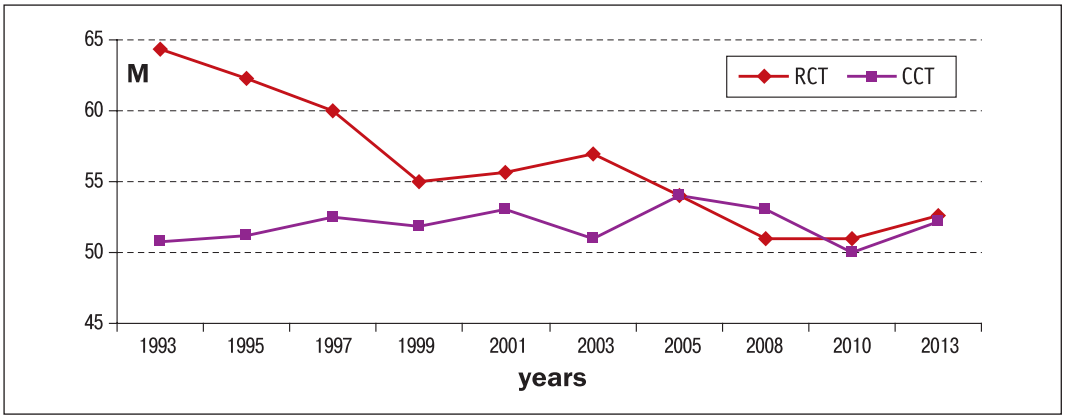


Figure 18.9. Average overall indicator of RCT and CCT population mental state in dynamics by years according to GHQ-28 test

Table 18.11
Dynamics of average performance scales GHQ 28 at RCT and CCT population (M ± m)

Scales		1993	1995	1997	1999	2001	2003	2005	2008	2010	2013
GHQ-28	RCT	64.3±2.0*	62.3±2.7*	60.0±1.3*	55.02±1.11*	55.64±0.91*	57.03±0.85**	54.07±1.19	51.47±1.09	51.31±0.71	52.60±0.68
	CCT	50.8±0.7	51.3±1.1	53.5±1.0	51.76±1.00	53.05±0.75	51.13±0.67	53.69±0.88	53.01±1.03	50.24±0.90	52.30±0.94
Somatisation	RCT	16.0±0.4*	18.0±0.9*	18.2±0.4*	15.67±0.44*	16.02±0.30**	16.69±0.30**	15.57±0.46	15.04±0.39	15.15±0.28	15.47±0.28
	CCT	14.7±0.3	14.7±0.4	15.5±0.4	14.26±0.4	14.26±0.3	14.42±0.28	15.51±0.36	15.16±0.35	14.56±0.34	15.07±0.35
Anxiety	RCT	14.2±0.3*	16.3±0.9*	15.9±0.5*	14.84±0.43	14.55±0.31	15.29±0.32**	14.36±0.46	13.24±0.45	13.35±0.27	13.85±0.30
	CCT	12.6±0.3	12.9±0.4	14.3±0.4	13.88±0.4	13.93±0.3	13.69±0.26	13.71±0.28	14.02±0.36	12.85±0.38	13.53±0.34
Socialdysfunction	RCT	15.3±0.3	17.1±0.8*	15.7±0.3*	15.87±0.22*	15.08±0.22	15.24±0.22**	15.17±0.28	14.30±0.29	14.46±0.17	14.94±0.15
	CCT	14.8±0.2	14.4±0.2	14.4±0.2	14.65±0.3	15.00±0.2	14.09±0.14	15.15±0.26	14.26±0.30	14.31±0.23	14.57±0.26
Depression	RCT	8.7±0.5	10.9±0.7	10.1±0.4	9.63±0.32	9.93±0.27	9.79±0.26*	8.98±0.29	8.89±0.33	8.41±0.17	8.35±0.16
	CCT	8.8±0.2	9.2±0.3	9.3±0.3	8.97±0.3	9.85±0.3	8.93±0.24	9.32±0.24	9.57±0.27	8.52±0.24	9.13±0.25

Notes. * – statistically significant difference ($p \leq 0.05$) between indicators of radioactively contaminated and relatively clean areas; ** – statistically significant difference ($p \leq 0.01$) between indicators of radioactively contaminated and relatively clean areas.

Improving of social well-being shows the gradual return of the RCT population to active life, ability to solve vital problems.

Mental and physical well-being of the population also improved, as indicated by data psycho diagnostic testing and self-estimate of health. Average overall rate of GHQ-28 estimating mental disorders of small depth and average scales of somatisation, anxiety, social dysfunction and depression tended to improve in the population of 3rd zone RCT dynamics of 1993–2013 (Table 18.11). From 1993 to 1997 for the RCT population were characteristic signs of psychological distress and small mental disorders. The percentage of people with neurotic disorders («event») in 1993– 1997 dynamics was quite high and tended to decline in later years. The group «no cases» was characterized by a high grade average point on a scale of social dysfunction, indicating that the problems were caused by daily activities.

After 1999 and until 2004 there was a gradual decrease in the average rate of total GHQ-28, while it was significantly different in the population of RCT from similar population in CCT. Since 2005 the figures were close in both study groups (Figure 18.9).

Average overall indicator of the GHQ-28 had a close correlation with the integral index of social well-being ($r = -0{,}500$ $p \leq 0{,}01$).

The analysis of data on the scales of GHQ-28 shows that the most significant throughout the post-accident period was somatisation scale. Since 1993, in population was dominated socio-economic problems of, as indicated by the opinion polls, giving second place to the social component – social dysfunction. Third place belonged to alarm scale except for 1995 and 1997, when she took 2nd place.

Indicator of somatisation scale GHQ-28, characterizing the state of physical health, has a strong tendency to improvement in the dynamics 1993–2013. From 1993 to 2003 the average somatisation in the RCT population significantly differed ($p \leq 0.05$) from that of the CCT population (Figure 18.10). Somatisation

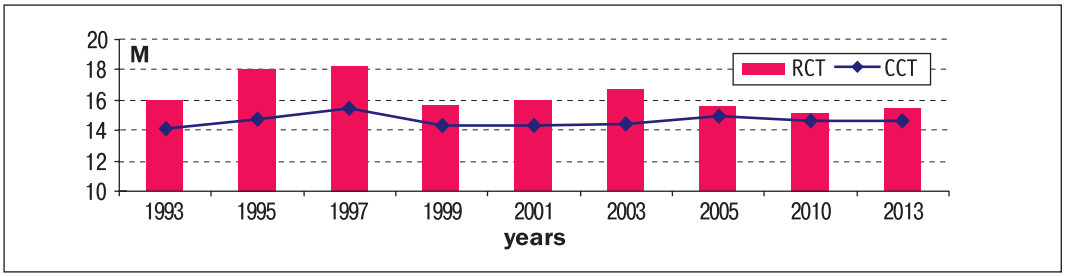


Figure 18.10. Dynamics of average somatisation scales of GHQ-28 people depending on place of residence (M ± m)

index had an average level of correlation with performance anxiety ($r = 0.644$, $p \leq 0.01$) and social dysfunction ($r = 0.342$, $p \leq 0.01$).

Average indices of anxiety and social dysfunction scales were significantly higher in the RCT population compared to the CCT population in dynamics from 1993 to 2003. The affected population more actively responded to the socio-political changes in the country and socio-economic problems than the population of CCT (Figure 18.11). All indices of scales that characterize the mental state of RCT population in dynamics of 2005–2013, did not significantly differ from similar indicators in CCT population.

State of mental health deteriorated with age (Figure 18.12). However, all age groups tended to improve performance GHQ-28 in the dynamics of post-accident period (Figure 18.13).

Analysis of GHQ-28 data using the method of gradual regression showed that the main contribution to the cumulative health index made psycho-emotional component that characterized the state of anxiety, nervous tension and fear (72.8%). Shares of of depression, physical conditions and social dysfunction indicators were respectively 12.3%, 2.2%, 1.2% ($p \leq 0{,}01$) [27].

Index of situational anxiety among the RCT population was significantly higher than in the CCT population in dynamics of 1991–1996. (Figure 18.14). In recent years, including the year 2013, the rate of situational anxiety in the RCT population was at the level of the control groups.

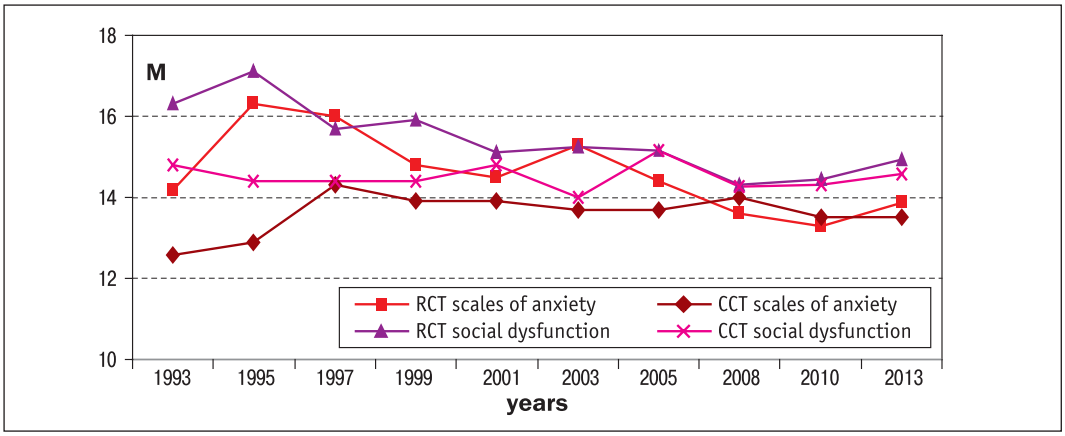


Figure 18.11. Dynamics of the GHQ-28 average scales of anxiety and social dysfunction of the population according to place of residence

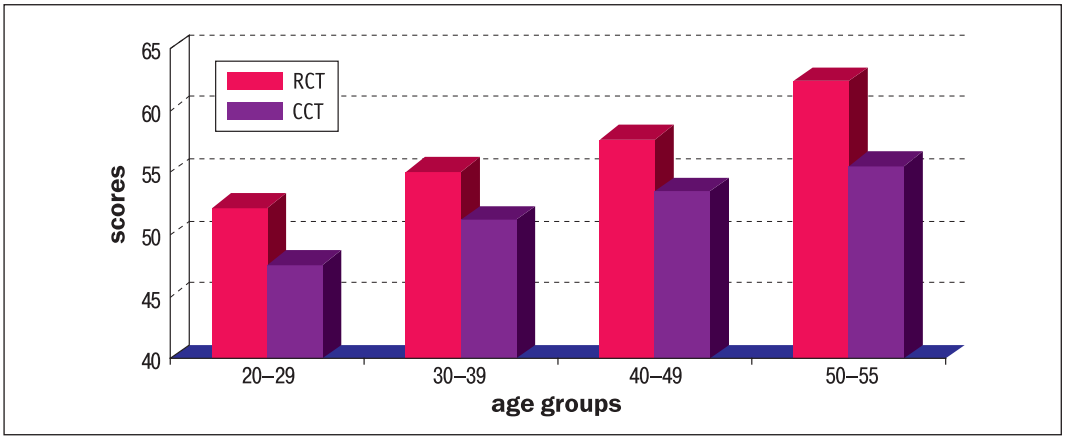


Figure 18.12. Average rate of GHQ 28 in different age groups depending on the residence

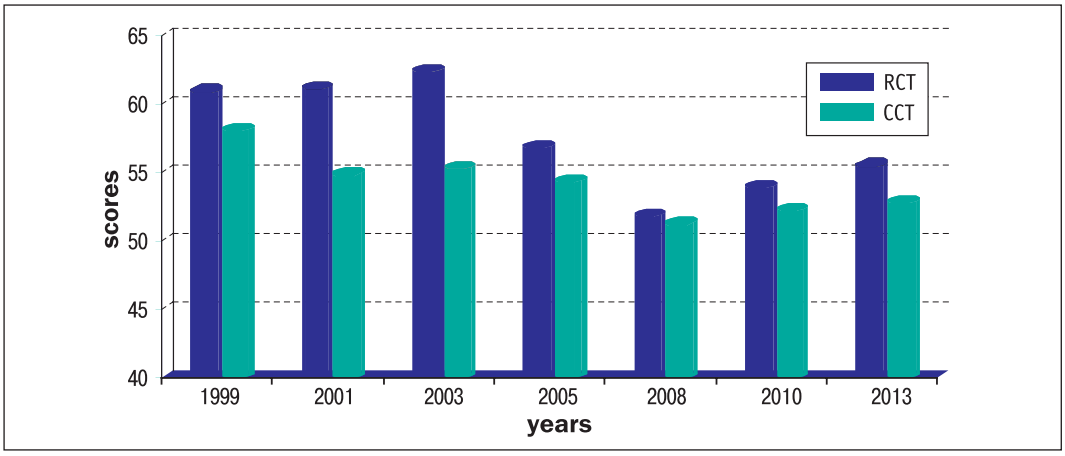


Figure 18.13. Evolution of the GHQ-28 people in the age group of 50–55 years depending on the residence

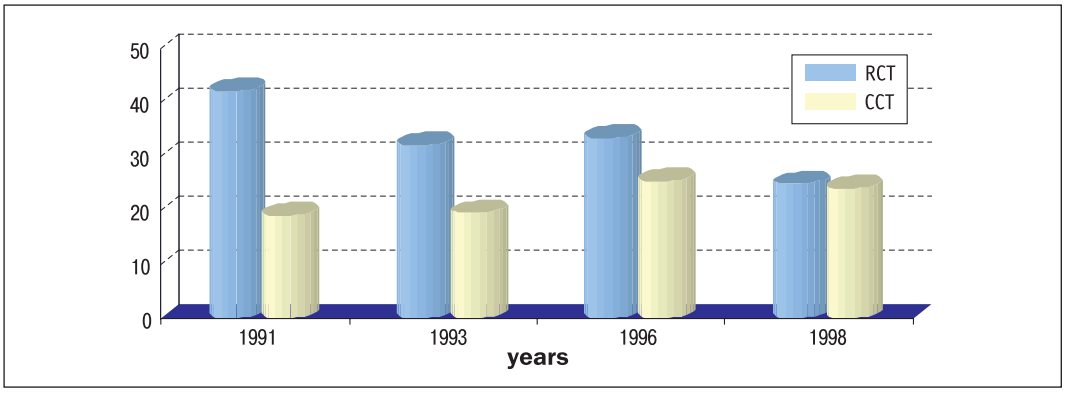


Figure 18.14. Dynamics of anxiety indicators of the population according to place of residence (1991–1998)

The most general trend that characterized the physical health of people living on RCT, according to the self-estimation, was inderstated. The index showed the general trend of worsening health in all studied areas from 1986 to 1997. Since 1999 to 2003 self-assessment of health on RCT was significantly lower than on CCT (Figure 18.15). For RCT was characteristic two ages dynamic curve with maximum number of «patients» and «very sick» in 1991, 1995–1997, and at the CCT we were seeing a steady increase. The physical state of RCT population health for the period of 1997–2013 tended to improve. The index of health by self-assessment to RCT inhabitants in 1999 made 0.54, at CCT it was 0.84, when the optimal is 1. In 1999 21.8% of RCT respondents felt «sick» and «very ill» when only 8% in CCT. In 2013 the number of RCT patients «sick» and patients «very ill»amounted to 8% at the health index of 0.83, and respectively – 4.6% and 0.91for the CCT. Data analysis of self-estimation by gender indicated significant improvement in the health of women since 1999 with almost constant performance in men in dynamics for years.

Using correlation analysis revealed to find relationships between averages situational anxiety, GHQ-28 and the factors that characterize living conditions: environmental conditions, chemical pollution, radiation situation, social well-being, health, etc. (Table 18.12).

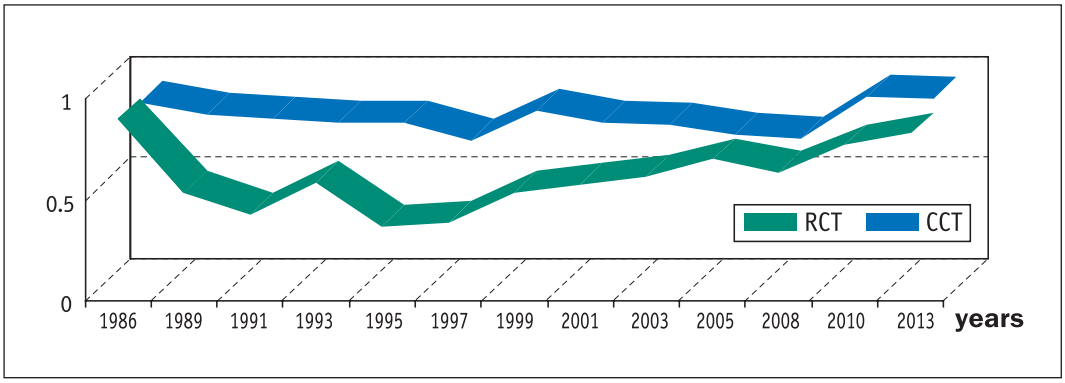


Figure 18.15. Indices of physical health on self-assessment at RCT and CCT

Table 18.12

Correlation performance of situational anxiety and GHQ-28 from the estimates of the population parameters characterizing the living conditions and health, 2013

Factors that characterize living conditions	PSA	GHQ-28
Ecological situation	-0.180**	-0.208**
Chemical pollution of the environment	0.238**	0.249**
Radiation situation	0.182**	0.122
The welfare of the family	-0.252**	-0.259**
Natural emergencies	0.184**	0.300**
Man-made emergencies	0.039	0.300*
Health status	0.453**	0.501**
Social health	-0.315**	-0.308*

Notes. * – correlation significant at $p \leq 0.05$; ** – correlation significant at $p \leq 0.01$.

18.5. INFORMATIONAL SUPPORT OF POPULATION

Perception of radiation situation by RCT population is due to several factors, it is proved by our monitoring study and research of scientists of the Russian Federation and Belarus [28, 29]. Impossibility of sense of ionizing radiation resulting in the inability to determine the extent of the danger and its limits and causes constant state of psychological stress and inadequate behaviour for living in RCT. The situation was worsening by the lack of provision with full information on radiation protection. Separate research on the social role of the media in the formation of remote social and psychological consequences of the accident, using content analysis material for the years 1986–1996, allowed to allocate two stages: the first – 1986 – August 1991 (till disintegration desintegration of USSR); second – since the country's independence, the adoption of Chornobyl laws and program of liquidation consequences of accident [30, 31]. First one was characterized by total control of information distributed to the population. The second phase was characterized by a large information flow. Analysis of changes in quantitative and qualitative characteristics of information flow within 1986 –1996 revealed some informational periods and different problem-thematic orientation of printed materials. Periods of information rises coincided with high levels of psychosocial stress: 1986 – the year of the accident; 1990 – information explosion after three years of artificial restrainment, the crisis of confidence in official information, social vulnerability of victims; 1993 – reducing benefits and compensation payments to victims as a result of the deepening economic crisis in the country.

Lack of profile structures, which would be responsible for informing the population on the problem of radiation situation and state of health, has not given sufficient opportunities to meet the needs of the population in particular information in the community. The volume of materials about dose limiting measures was insignificant and amounted in 1986 the total volume of 0.5%, in 1990–1991 – 2% in 1995 – 0.4%.

Among respondents of RCT 22.9% received the first information about the accident from friends, 19.8% – from family members, 18.0% – from colleagues at work, 14.4% – referred to the radio, 11.5% – on television, 8.0% – by neighbours, 7.9% – on foreign radio and only 2.3% from the authorities. That is, informal communication in the early post-accident period played a basic communicative role and carried false information with large defects on probability and objectivity [21]. Negative sides of informational influence on the suffered population manifested by stable psycho-emotional stress and other effects caused stable general information dissatisfaction, distrust thereto, information «hunger», ambiguity alerts.

Information field formed spontaneously, leading in this process were subjective factors and completely lacked not only the legal but documents regulatory for information process. Only in 1990 in Ukraine, Russia and Belarus began to publish available to the public policy papers that somehow defined certain principles and procedures for informing the public about the consequences of the accident, the protective measures and elimination of consequences. Due to political and conjuncture considerations and information field was inflicted great damage, lot of deformations were made, which negatively affected the future welfare and other living conditions. However, it should be noted that at the time of the Chornobyl accident was no generalized world experience how inform the population in case of global man-made disasters and society in general was not prepared for this situation.

Monitoring survey of population living on RCT points to structural changes in the sources of information in the dynamics of post-accident period. In the years 1986–2009 the main source of public information were the media (television, newspapers, radio), in second place – health

care institutions, the third – the local press, the fourth – place of work, on the fifth – experts on the issue (Figure 18.16).

After 2009 the main sources of information were the jobs, printed matters of experts on radiation issues, employees of medical institutions. A very small part of the population has information about: radiation situation at the residence (15.7% of the population), doses of exposure (13.2%), contamination of fruits and vegetables (15.7%), milk (14.9%), drinking water (13.7%). Despite the very low level of awareness, the last survey of RCT population (2013) showed that only 40% of respondents want to receive information on the content of radionuclides in fruits, vegetables, berries from the gardens, as well as the contamination of milk, meat, eggs and forest products (Table 18.13). Only 37.5% of the population wants to have information on the state of drinking water. As to social activity of the population in receiving information, this percentage was even smaller. Only 17.5% of the population wanted to know the addresses of laboratories where it was possible to determine the content of radionuclides in food from their own gardens.

Experts requests for information were distributed as follows: departmental, depending on the subordination, would get 84.4%. The need of a short analytical quarterly review on the radiation situation and public health felt most experts of the regional SES (64.7%). Semi annually want to receive information experts of medical institutions (71.4%).

Among other experts the intensity of obtaining such information was not determined by time period, and every third state-level expert and scientists wish to receive this information upon request.

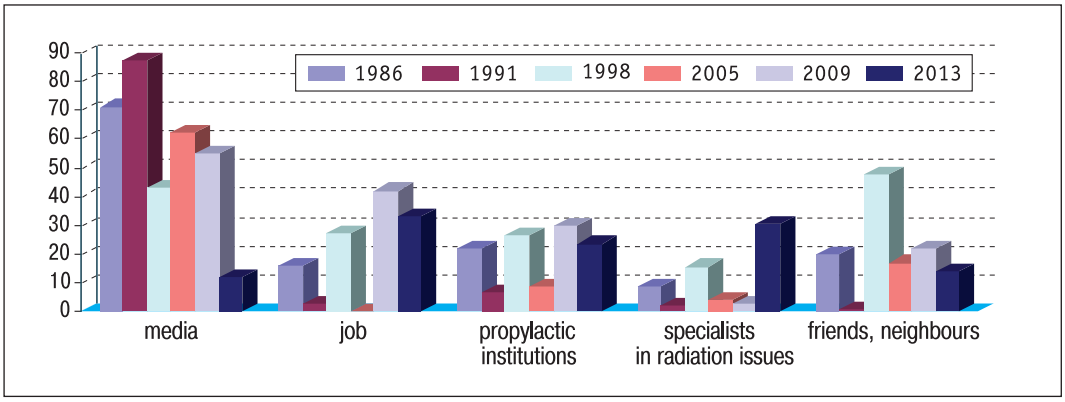


Figure 18.16. Respondents estimated sources in the dynamics by years (%)

Table 18.13

Distribution of the content of information that population wanted to receive (%)

Content of information	Men	Women	In general
Map of radiation contamination	35.7	31.6	33.1
Health status	38.1	31.6	33.9
Doses	45.2	29.1	34.7
Contamination by radionuclides vegetables, fruit, berries, gardens	28.6	49.4	42.1
Contamination of milk, eggs, meat with gardens radionuclides	31.0	44.3	39.7
Radionuclide contamination of forests	23.8	40.5	34.7
Water contamination with radionuclides	23.8	40.5	37.2
Laboratory where it is possible to determine the content of radionuclides in food	19.0	16.5	17.4

Table 18.14
Attitude to nuclear power depending on gender, dynamics in the years 1988–2013

Attitude	Men (%)		Women (%)		In general (%)	
	1988	2013	1988	2013	1988	2013
Positively, it must develop	13.4	27.5	7.4	16.4	10.3	20.5
I believe that it must be immediately removed from service	77.9	6.3	85.3	5.0	81.8	5.5
I believe that it takes place, but it is needed to develop other sources	6.5	63.8	6.1	77.1	6.3	72.3
Other	2.2	2.5	1.2	1.4	1.6	1.8

Other sources were named professional collections (45.8%), scientific publications (38.5%) and materials of scientific conferences (38.5%). Thus, professional affiliation, the intensity of work and status formed information needs and preferences.

The remoteness in time of the Chornobyl accident made a positive effect on the attitude of population to the development of nuclear power engineering. In 2013, compared with 1986, 12 times increased the population that believed that nuclear power engineering had a place, but it was needed to develop other sources of energy (Table 18.14). Two times increased population, supporting the development of nuclear energy. Only 5.0% of respondents believe that it should be immediately decommissioned. According to a study of the Institute of Sociology of NAS of Ukraine held in 2009 9% of respondents expressed for the immediate closure of all operating NPP [32]. Similar results were obtained in Belarus. The number of positive answers to the question «Belarus should develop nuclear energy?» increased by half since 2005, from 28.3% to 57.0% [33].

Among adolescents living in surveillance zone of Rivne NPP and the zone of guaranteed voluntary resettlement, 39.4% believed that nuclear energy should be developed, 50% supported the idea that it took place, but was needed to develop other sources and 9.6% adolescents were for the urgent need of the withdrawal of NPP operation. According to the data of O.M. Marzeev Institute of Hygiene and Medical Ecology, 55% of young people of Slavutych city considered possible construction of new reactors and approved it [34].

After the accident in Japan at «Fukushima-Daichi» in 2011, almost all countries have revised their policies in relation to nuclear power engineering [35]. The leading company of opinion polls, Globe Scan, conducted survey of the population of 23 countries after the devastating earthquake and tsunami in Japan, which led to a major accident in Fukushima-Daichi. Most of the world's population believes that itwas possible to dispense with the peaceful atom, through renewable energy and energy efficiency. Overall, only 22% of respondents agreed with the statement that «nuclear power was relatively safe and was an important source of electricity, so we need to build more new nuclear power plants». However, 71% of respondents believe that their country «in the next 20 years could almost completely abandon nuclear and coal power plants due to energy saving technologies and transition to solar and wind».

In general, 39% of the population were willing to continue the use of existing reactors but not to build new, and 30% would drown out all existing reactors. Thus Germany (90%); Mexico (82%); Japan (84%); France (83%), Russia (80%) were against the construction of new nuclear power plants.

Curiously enough, in Japan, despite the consequences of the disaster, the negative attitude towards nuclear energy compared to 2005 increased only slightly. But in Russia, Germany and even France, which have traditionally enjoyed the support of nuclear power plants, discontent nuclear power engineering increased markedly. Thus, more than half the population of Spain

(55%), Chile (55%), Ecuador (53%), Germany (52%) consider «nuclear power plants dangerous and that they must be closed as quickly as possible». Only Britain goes against all trends, there, on the contrary, is growing support for NPP. However, relatively high popularity this industry enjoyed in the US, China and Pakistan, remaining at the level of 40%.

The population preferred to generate electricity by any other way than nuclear power plants, even coal-fired power plants, and in the case of hydroelectric power or wind and sun energy, then for them fought 90% [36].

Among the RCT population of Ukraine accident at the «Fukushima-Daichi» has not caused particular concern.

* * *

One of the features of modern Ukrainian society is to strengthen the dominant ecological interest compared to the economic and social. This is largely due to the Chornobyl disaster, but no less important are the environmental literacy and awareness of population, their relation to quality of life.

Compared with previous years, among the RCT population is growing satisfaction by ecological situation in the community. The lack of clear environmental criteria for the assessment of environmental conditions in society affects the population's judgments on the environment. Depending on the habitat there are various factors of unfavourable ecological situation: for the RCT population – radiation and chemical factors, for the population relatively clean areas – indifference to environmental protection and financing of nature-conservation measures.

In the affected areas the level of public concern about the environmental consequences of the Chornobyl accident reduced. The number of respondents who believe the radiation situation at residence is dangerous to health decreased. However, the percent of the population preoccupied with own and children's health due to lack of information on health, radiation situation at residence in the present and future conditions.

In areas of the 2nd and 3rd zones of RCT in the dynamics of post-accident period formed communities which differ in relation to radiation situation, peculiarity of self-preservation behavior, social activity.

Both perceived levels of radiation situation and concern about the state of their own health and health of children in the population are significantly lower in the zone of compulsory resettlement of population compared to the 3rd zone (the zone of guaranteed voluntary resettlement). 86% of respondents 2nd zone are not going to set out on a new residence. Only 22% of respondents perform hygiene advices in connection with residence in the 2nd zone of RCT. That is, the dynamics of post-accident period in mandatory evacuation zone, formed a community, members of which are characterized by confidence in the correctness of their choice of residence and maintaining vital factors. Formed confidence may result due to incomplete environmental knowledge as well as medical, primarily hygienic knowledge.

The hierarchy of life values on population dynamics RCT does not change: «health», «children», «family welfare». Despite the fact that the aims population on the value of health are gradually increasing, they have no direct impact on preventive behaviours in the dynamics by years, due to a number of factors that affect the purposes. Another way of life, economic and social changes taking place in modern society, are making significant adjustments in reproductive behaviour. Among factors hampering to increase the number of children in family, the largest contribution to the overall dispersion of conditions in contaminated territories makes eco-social factor (environmental degradation, due to radiation contamination likely negative impact on descendants), in the relatively clean territories – socio-economic (low income, lack of confidence in tomorrow's day, low social protection of children).

Long-term unsolved social problems under the Law of Ukraine «On the social status and social protection of citizens affected by the Chornobyl disaster» negatively impacts on the stat of human being in society. During the years 2001–2010 almost doubled the number of people who wish to obtain financial compensation from the government for living on RCT (36.1% in 2001 and 68.4% – in 2010). The quality of life on RCT improved, but itwas still not high enough for a normal existence of all segments of the population. The growth of material well-being of this population gradually reduces stress, whichwas associated with poverty.

The system providing medical care for RCT population maintains its infrastructure, has serious staffing problems against the background of relative improvement funding. The effectiveness of health care is determined by complex factors, some of which lies in the socio-economic problems of the state. Availability of treatment of affected population significantly depends on its financial capacity. The ast causes high levels of dissatisfaction of the population, the overall index of satisfaction with health care institutions declined rapidly over the last decade. Most of all complaints are induced by the lack of needed specialists, provision of necessary medicines and diagnostic equipment, including cabinets in out-patient clinics.

The main factor that prevents the implementation of National Program is the lack of funding. Experts have identified organizational defects: decentralized funding from various ministries, the use of the wrong address, the lack of proper control by the state over the target use of funds. The root cause of failure of the program are: political and economic instability in the country, the problem of politicization of the Chornobyl accident, the restriction of public policy in the aftermath of the disaster, imperfect legislation, a large number of recognized victims and the possibility of the Cabinet of Ministers of Ukraine «manual» management of laws of Ukraine.

In solving the health problems of consequences of the Chornobyl disaster Verkhovna Rada of Ukraine a long period of time did not take conceptually new changes in the legislative framework on this issue, but only limits the action of a large number of articles of laws adopted in 1991, and this only exacerbates social tension, destroys the relationship «citizen-state».

RCT population social feeling health steadily tends to improve, indicating a gradual return to active life. The main burden of the total variance index of social well-being changed, the main contribution make socio-political sphere, social security and social relations.

Reducing of socio-psychosocial adaptation functions in the dynamics of post-accident period determines the state of health of affected population. Only in 24 years after the accident total GHQ-28 index, which characterizes the small depth of mental disorders and the average performance scales somatisation, anxiety, social dysfunction and depression in the population of contaminated areas, were not significantly different from that of conventionally clean areas. Index of somatisation, characterizing the state of physical health has an average level of correlation with indices of anxiety and social dysfunction. Index of situational anxiety among the RCT population was significantly higher than in the CCT population in the dynamics of 1991-1996. The health status of the RCT population for the period of 1989–2013 tends to improve. In the dynamics by years physical health index according to self-estimation of the RCT population remains lower than in the CCT population.

Studies of information field of the Chornobyl disaster and analysis of the literature on this issue suggests that the strategy of forming the information field of the Chornobyl at the initial stages of events and subsequent years was not perfect. Information flows documentaries were characterized by deformation on qualimetric, and semantic features that influenced the formation of lifestyles and, consequently, the health of the population, which lived in RCT. The organization of information technology did not take into account the information needs of different population groups, there was no feedback, information requests of individual consumer were not considered.

The information field of the Chornobyl accident have not performed the function of radiation-hygienic education of population and increase its health activity. The latter, based on the appropriate level of knowledge is one of the most important parts of the way of life. The models of the information field in case of large man-made disasters are implemented on the territory near critical infrastructure, including nuclear power plants. In contaminated areas there is no mechanism to ensure regular public awareness, as indicated by the survey on population as to growth anxiety due to lack of information and requests public and experts on the subject and time frames for information. It is necessary to continue study of information strategy and specific semantic and qualimetric properties of information processes of the Chornobyl accident for use in scientifically based information field models and saving human potential. In the dynamics of the studied period the structure of information sources changed of the amount of thematic information decreased. About 15% of the population RCT possess information about the radiation situation at residence. The need in the required information on food contamination, radiation doses, the incidence are experiencing not only the population, but medical specialists of district and regional levels. Official informing of RCT population about the contamination levels of soil, air, water, local food, vegetation, forest products, etc. should be a mandatory part of information activity of the local authorities, medical and educational institutions.

The remoteness in time of the Chornobyl accident effects positively on the attitude of population to the development of nuclear power engineering. In 2013, compared to 1986, 12 times increased the population believing that nuclear power has a place, but it is needed to develop other sources of energy. Only 5% of respondents believe that it must be immediately removed from service.

Government measures and means aimed at maintaining and improving the health of the population, should focus on: optimizing the legal and regulatory framework of the Chornobyl accident aftermath mitigation; continuous information support of managers and professionals implementing measures to eliminate the consequences of the regional, district and local levels; recovering of prompt information system through medical and educational institutions about the radiation situation and radiation protection; the formation of life style, aimed at preserving the health of the RCT population.

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Chapter 19
HEALTH CONSEQUENCES OF CHORNOBYL DISASTER IN CHILDREN EXPOSED TO IONIZING RADIATION AND CHILDREN BORN FROM EXPOSED PARENTS

Deterioration of child health is one of the most detrimental consequences of the Chrornobyl disaster [1, 2]. Despite vigorous efforts to preserve and restore child health, the proportion of apparently healthy children among survivors decreased. After the Chornobyl disaster, crude morbidity among children 0–14 years increased 3.1 times [1–4].

In Ukraine, the abnormal radiogeochemical environmental province is populated by 2,235,365 people, including 464,568 children. Due to radionuclide migration into crops, dairy, meat and fish, food becomes a source of internal radiation exposure for humans [5, 6].

Cesium-137 presents biological hazard for humans. Similar to potassium, it actively participates in biological turnover. Cesium-137 migrates through food chains and enters the human body. Consumption of food contaminated with radionuclides contributes 98–99% of the internal radiation dose. Milk provides about 80% of the internal dose, meat – 5–10%, potatos – 5–6%, vegetables – 1–6%, fish – 1.2%, mushrooms – 2–12.5%, and bread – 1–1.4%. Even today, availability of «clean» (i.e. free of radionuclides) dairy products is a problem at many private farms in some regions of Zhytomyr, Kyiv and Rivne provinces [4].

In people of all ages, intestinal absorption of ^{137}Cesium is 100%. Cesium-137 is accumulated predominantly in soft tissues, and only 4–8% is deposited in bones. This accumulation causes increase in internal radiation dose. Internal exposure to radiation in combination with poor diet may be among the main reasons for significant and persistent increase in incidence of diseases of digestive system [5, 6].

Most frequently (66.2%), several digestive organs are affected. Sub-atrophic and mixed type lesions occur in 22.6 and 26.4% of cases, respectively. Hyperplasic and catarrhal lesions are found less often (9.3% and 8.3%, respectively) [4].

The causes of child health deterioration are still unclear, and the role of radiation remains controversial. To large extent, this is due to a limited application of appropriate epidemiological methods and luck of dosimetry support in both clinical and epidemiological studies [7].

Future epidemiological studies utilizing individual measurements of incorporated ^{137}Cs, dose estimations from ecological model and findings from animal toxicological studies should help to elucidate health effects due to chronic internal exposure to low-dose radiation [7].

In 1992, an unexpected increase in incidence of noncancerous diseases among survivors of atomic bombing of Hiroshima and Nagasaki was reported by Shimizu and co-authors [8]. Several recent epidemiological studies explored the effects of exposure to low-dose radiation on the various body systems in children.

Stepanova and co-authors reported a significant reduction in red and white blood cell count, platelet count and hemoglobin concentrations associated with increased density of ^{137}Cs soil contamination at the place of residence [9]. Over the six-year observation period, the hematologic markers improved. This improvement was bigger for platelet count and smaller for red blood cell count and hemoglobin concentrations in children born before the disaster and thus exposed to higher levels of radiation [9]. There was no interaction with exposure time for white blood cell count in 702 children born after the accident. The initial exposure gradient persisted in this sub-sample of children. This was the first large cohort study in children following the Chornobyl accident. These findings suggest that residential exposure to ^{137}Cs may be associated with persistent adverse hematological effects [9] (Figure 19.1).

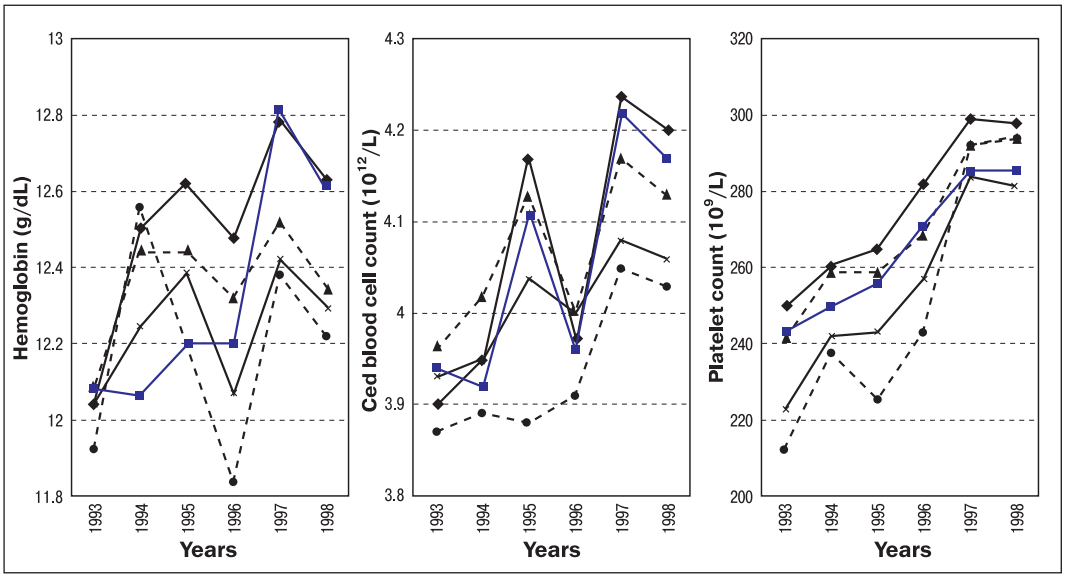


Figure 19.1. Dynamics of hemoglobin content in erythrocytes and thrombocytes of children who are residents of the territories with different density of contamination

A subsequent cross-sectional study used individual whole-body count (WBC) of ^{137}Cs (Bq/kg) for more comprehensive assessment of the exposure. The study sample consisted of 590 children from birth to 18 years of age who were examined in 2008–2010. Children with higher WBC had decreased concentrations of hemoglobin and lower counts of erythrocytes and platelets. The effect of increased activity of incorporated ^{137}Cs on decreased platelet count was only seen in children over the age of 12 years. The average village density of ^{137}Cs (kBq/m^2) soil contamination was associated with decreased blood count only indirectly, accounting for ^{137}Cs body content as an intermediate variable. Children in this study were born at least 4 years after

the accident, thus, have been exposed to low doses of ionizing radiation from ^{137}Cs. This cross-sectional study indicated that low levels of radiation exposure may be associated with decreased blood count [10] (Figure 19.2).

Another study explored serum concentrations of immunoglobulins A, G, M and E (IgG, IgA, IgM, IgE) in children residing in villages with various density of ^{137}Cs soil contamination. In 2008, residential soil contamination levels were strongly and positively correlated with individual body burden of ^{137}Cs. In the mentioned above study, serum concentrations of IgG and IgM increased between 1993 and 1998. Children with higher ^{137}Cs soil exposure had lower serum IgG levels. In a small cohort of children followed up between 1997 and 2010, serum concentrations of IgG increased over time. Between 1993 and 1998, children within the second highest quintile of ^{137}Cs soil exposure (266–310 kBq/m^2) had the highest concentrations of serum IgM compared to those within other soil contamination levels. However, between 1997 and 2010, levels of serum IgM in the highest exposure group (165–253 kBq/m^2) decreased. Changes in concentrations of serum immunoglobulins among children exposed to Chornobyl radiation described by McMahon at al. (2014) do not constitute any adverse health effects. Further investigations are needed to better understand how these deviations affect the health status [11]

Several other studies showed that children residing in areas contaminated with radionuclides had decreased levels of the main classes of immunoglobulins, imbalance between immunoregulatory T-cell subpopulations, depressed phagocytic activity of neutrophilic granulocytes and clinical symptoms of secondary immunodeficiency [12–16].

Immunoglobulin A plays a protective role on the surface of mucous membranes of the airways. Consequently, children and adolescents with low level of this immunoglobulin are at increased risk of development of respiratory diseases. After the Chornobyl nuclear disaster, the incidence of pulmonary disease steadily increased [17].

Children who survived the Chornobyl disaster frequently develop persistent pulmonary disease. Bronchial hyperresponsiveness, abnormal function of pulmonary surfactant, activation of free-radical reactions and suppression of local protective factors in respiratory organs were detected among children residing in areas contaminated with radionuclides. Analysis of the fatty acid content of exhaled breath condensate (EBC) using gas-liquid chromatography revealed increased lipid peroxidation, decreased antioxidant properties of pulmonary surfactant and impaired metabolism of polyunsaturated fatty acids at the stage of their conversion into eicosanoids [18].

Another epidemiological study showed that children residing in villages with soil ^{137}Cs contamination at the highest quintile (355.47 ± 6.84 kBq/m^2) were 2.6 times more likely to have forced vital capacity (FVC) < 80% of predicted [95% confidence interval (CI), 1.07–6.34] and 5 times more likely to have a ratio of forced expiratory volume in 1 sec (FEV_1) to FVC% < 80% (95% CI, 1.02–25.19) [19]. This study provided evidence of both airway obstruction and restricted forced vital capacity with increasing ^{137}Cs soil contamination [19]. In 2008–2010, a consecutive cross-sectional study conducted in the same pediatric population used whole body burden of ^{137}Cs as a refined measure of the individual exposure [20]. The decrements in percentage predicted FEV_1/FVC and an increased odds of bronchodilator responsiveness, restrictive impairment, and FVC less than lower limit of normal were associated with a log increase in weight-adjusted ^{137}Cs whole-body burden [20]. Thus, children in the region just outside of the Chornobyl contamination zone continued having radiation-related respiratory disorders as recently as in 2010.

Analysis of EBC revealed that children with respiratory disorders in addition had abnormalities of non-respiratory lung functions, such as reduction in moisture and aerosol excretion, along with

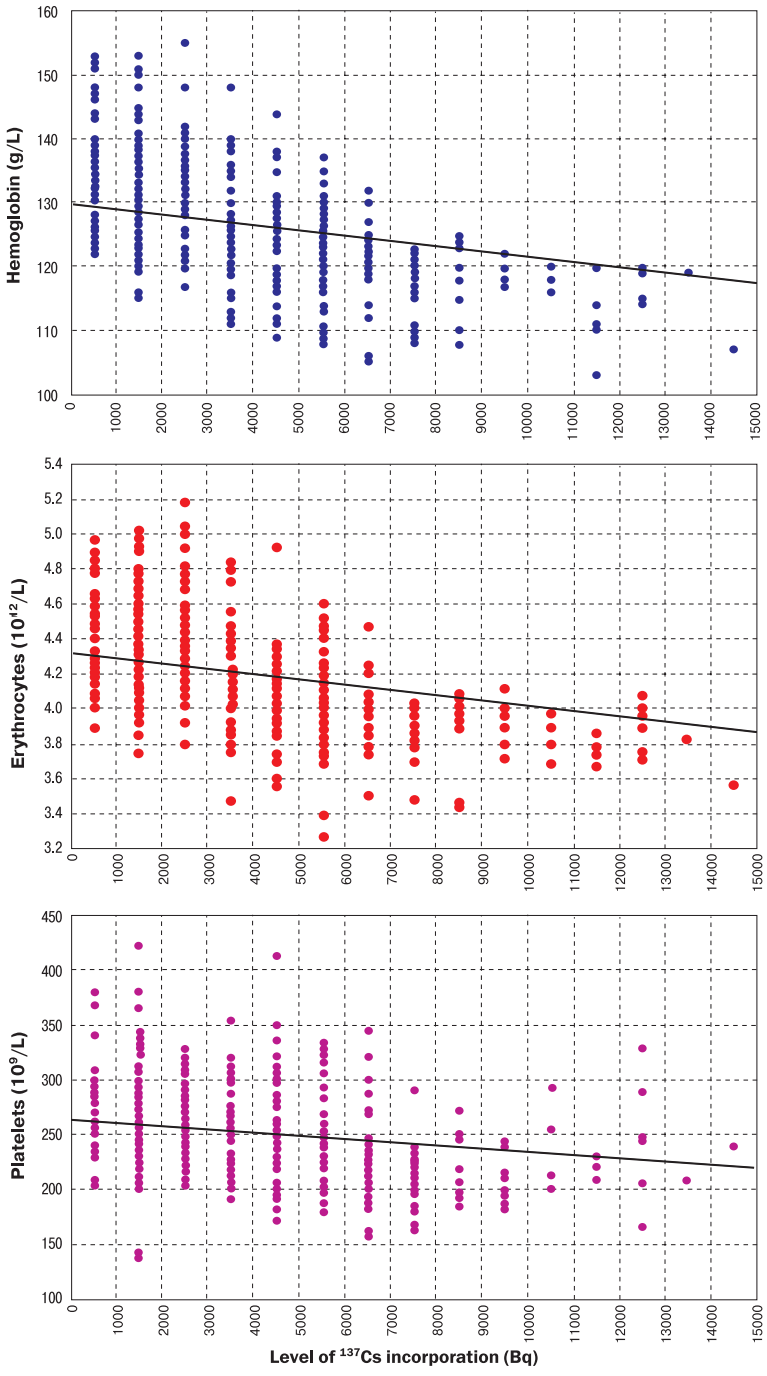


Figure 19.2. **The dependence of the indicators hemoglobin, red blood cells and platelets depending on the content of ^{137}Cs in the body**

decreased concentrations of phospholipids and total lipids in pulmonary surfactant. Increased activity of oxidative free radical processes became evident from increase in light sum indices and amplitude of flash-initiated chemiluminescent analysis of EBC. The inhibition of antitrypsin in EBC indicates decrease in the local defense of respiratory system [21–23] (Figure 19.3).

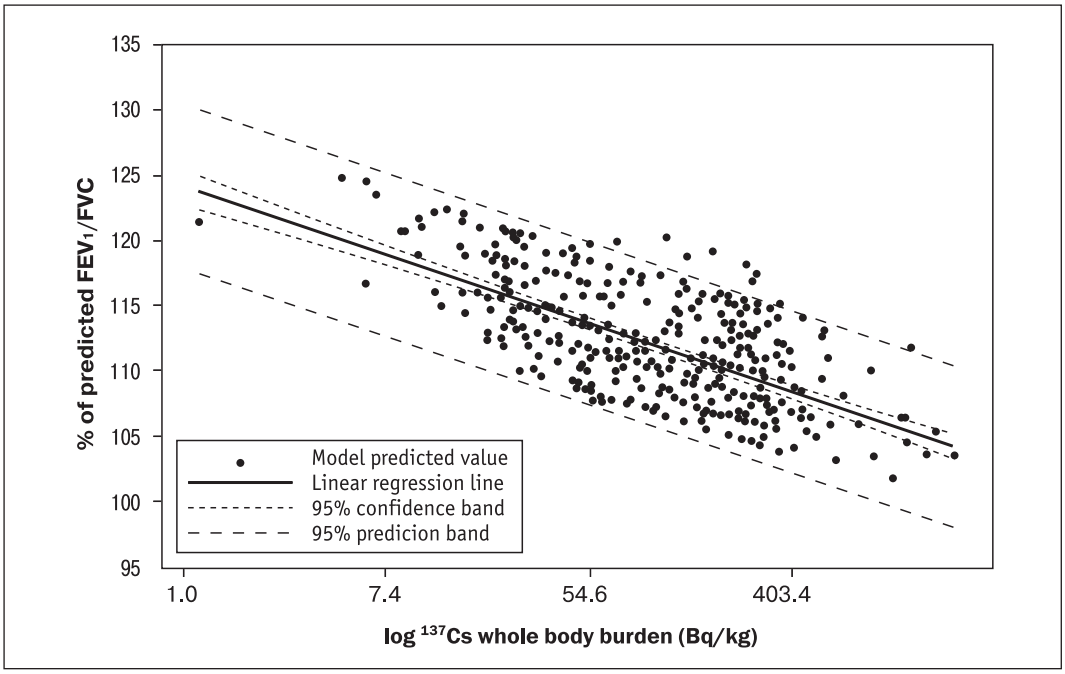


Figure 19.3. **Scatterplot and regression curve shoving the linear association of log-transformed weight-adjusted ^{137}Cs whole-body burden (Bq/kg) with percentage predicted FEV_1/FVC measures in the Narodichi Children Cohort, Narodichesky, Ukraine, 2008 to 2010 (n = 517). Models are adjusted for cigarettes/day, secondhand smoke, antibiotics, dog exposure, cat exposure, and coal/coke/wood store use.**

Functional abnormalities of cardiovascular system were observed in 40.0% of children. On the ECG, the sinus tachyarrhythmia was registered in 32.0% of these children and bradyarrhythmia in 45.0%. Moderate and severe metabolic disorders of the heart were diagnosed in 42.4% and 3.8% of children, respectively. Rheographic studies of regional hemodynamics detected dystonia and venous stasis often accompanied by an interhemispheric asymmetry of the blood flow, propensity to increased vascular tone, decreased pulse rate and rate of arterial circulation in the extremities. The following changes were established after controlled physical activity of average intensity: 1. decreased stroke and minute volumes of blood, 2. increased frequency of hypotonic and dystonic (reactions to loading (22.3 and 31.5%, respectively), 3. more intensive and less economic work of ventilation apparatus, and 4. reduction in some efficiency indices. These conclusions were based on detected 14.8% increase in oxygen deficit, 22.6% increase in total oxygen demand to perform work, 18.6% longer time to restore pulmonary ventilation to the initial level, and 20.1% increase in oxygen consumption after physical activity [4].

During physical exercise, the autonomic neural regulation of cardiovascular system in children was affected by the insufficient input from sympathoadrenal system which is characteristic feature in children since 1990 years. [24].

Several pathophysiological mechanisms have been proposed to explain health deterioration and increased incidence of variety of diseases among children exposed to ionizing radiation. Today, the most popular opinion is that nucleus and cellular membranes are the most sensitive targets for the ionizing radiation. The exposure to ionizing radiation activates free-radical reactions which produce reactive oxygen species. Lipid peroxidation is a key mediator between radiation exposure and a damage to cellular membrane followed by its structural reorganization and impaired functioning [25–26].

Red blood cells are ontogenically and phylogenically linked to many tissues of mesenchimal origin. Thus, they may serve as a universal model for evaluation of the impact of various factors including radiation on cellular membranes. The erythrocyte membrane is the most easily available study object that reflects the state of all cellular membranes is the human body.

An overall decrease in the number of discocytes along with increased proportion of prehemolytic and degenerative forms was observed in children residing in radiation-contaminated territories. A biconcave discoid shape of normal erythrocytes (i.e. discocytes) is optimal for gas exchange. (Figure 19.4). Structural abnormalities of membranes in erythroid cell population were most pronounced in a group of children whose ^{137}Cs body burden was between 6,845 and 16,522 Bq [27].

An abnormal shape and surface profile of the erythrocyte membrane, indicate membrane damage not only in erythrocytes but also in various cells throughout the entire human body.

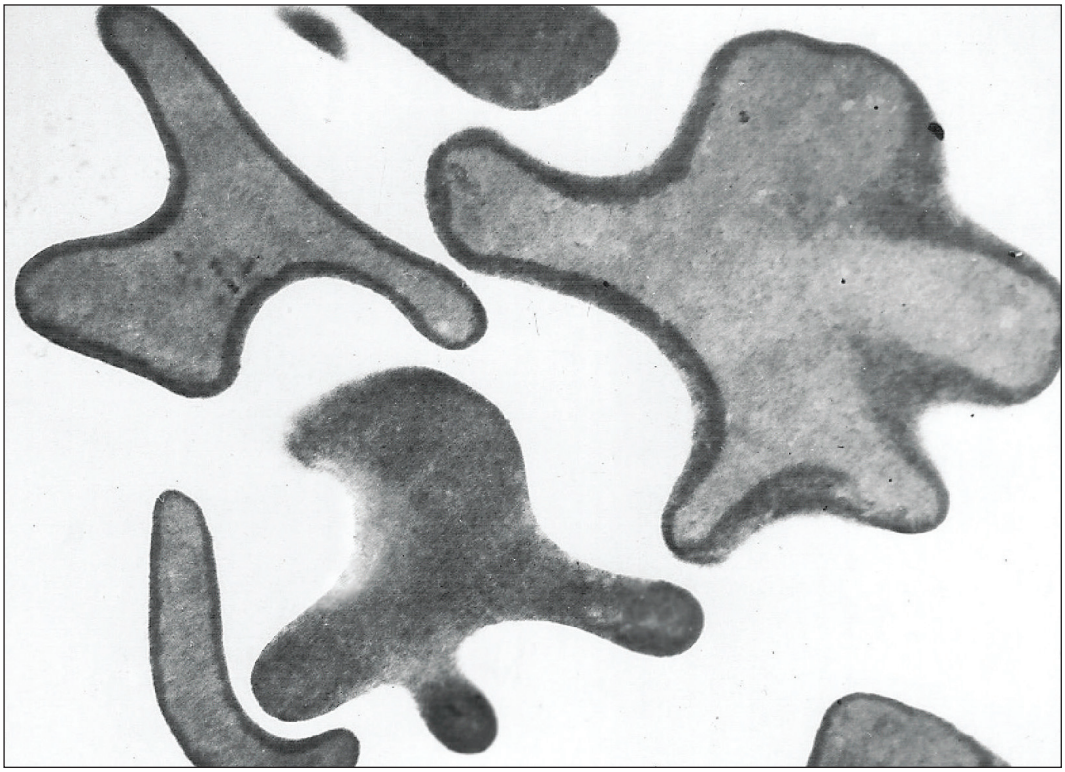


Figure 19.4. **PB erythrocytes of the child Z.I., 16 years old with 16,522 Bq of incorporated ^{137}Cs. Cells are of echinocyte-shaped with irregular density of cytoplasmic matrix and loosening of sections of superficial cell membrane. × 10,000.**

Significant changes in submicroscopic organization of organelles in circulating lymphocytes, especially in mitochondria, were found in children exposed to radiation over a long period of time. Children whose body burden of ^{137}Cs exceeded 6,845 Bq had the most obvious mitochondrial abnormalities. The latter included increased variability of structure and size, increase in the number of condensed-type mitochondria, decreased number of organelles of regular shape, and appearance of a giant forms. Electronic microscopy revealed «swollen» mitochondria, decreased contrast of outer membranes, flattened and abnormally oriented mitochondrial cristae, pale and homogenous matrix in organelles. Sometimes mitochondria almost completely lost their structure [28]. (Figure 19.5).

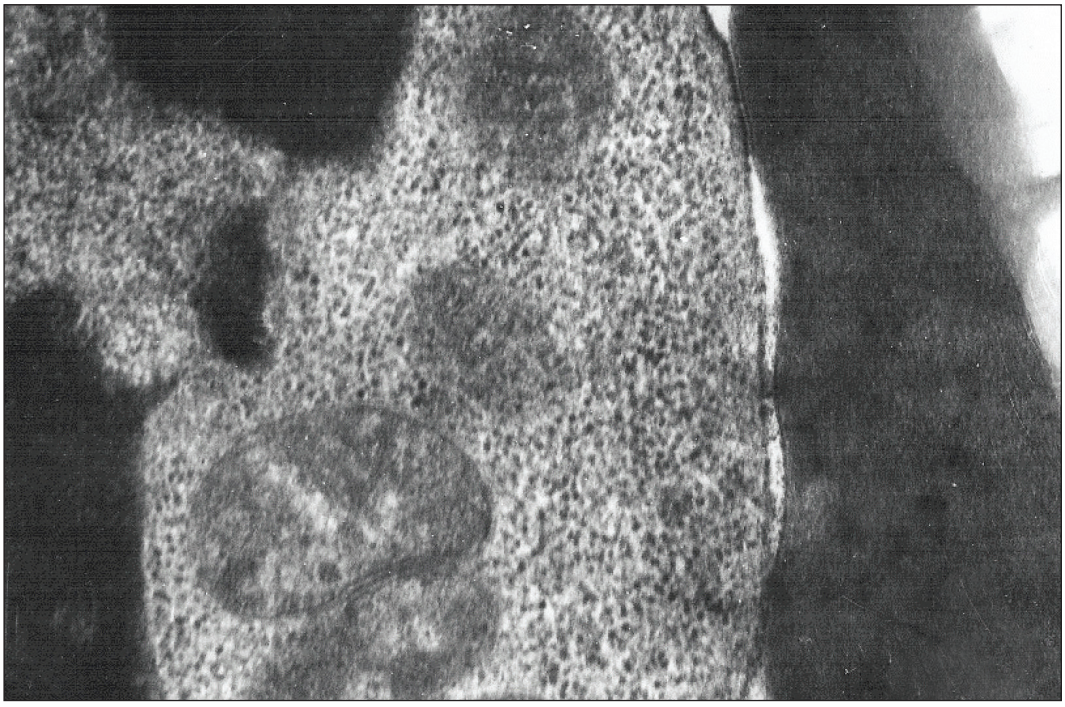


Figure 19.5. **Fragment of erythrocyte of the child T.L., 17 years old with 15,170 Bq of incorporated ^{137}Cs. Clearly seen mitochondrial swelling, damage of external membrane and cristae. Some mitochondria are almost completely disrupted. × 80,000.**

Ionizing radiation causes damage of mitochondrial DNA, an 80–90% reduction in activity of key enzymes involved in mitochondrial energy metabolism, and diminished regulation of enzyme activity in the Krebs cycle and anaerobic glycolysis. The emerging secondary mitochondrial insufficiency leads to shortage of energy and, consequently, to functional impairment of various organs and systems [29, 30, 31].

A cytochemical marker of impaired mitochondrial energy production is decreased activity of cellular enzyme succinate dehydrogenase while increased serum concentrations of lactate and increased ratio of lactate to piruvate are used as biochemical markers. In summary, the review of the recent studies shows that low doses of ionizing radiation received after the Chornobyl disaster can impair function of various organs and body systems which in turn may have detrimental effects on childrens health.

The issue of genetic effects in the first and consecutive generations of the offspring of the exposed parents is challenging and remains unresolved. Among survivors of the A-bombing of Hiroshima and Nagasaki, exposure to radiation during pregnancy did not increase the incidence of dysplastic congenital malformations in their offspring [citation]. However, in children exposed to radiation between 8 and 15th gestational weeks, the incidence of growth restriction and mental retardation increased. Some children with mental retardation had a small head size [32].

According to the report by the Chornobyl Forum, there was no reliable evidence of increases in the occurrence of genetic abnormalities among children born after the disaster [33]. In a separate epidemiological study by Wertelecki and co-authors, a contrary result was reported [35]. In this study, the incidence of neural tube malformations: blastopathy, microcephaly and microphthalmia in children born on contaminated regions of Ukrainian Northern Polessye (Rivne province) was one of the highest in Europe [35]. These findings warrant further studies of congenital malformations in regions of Ukraine where populations are chronically exposed to low doses of Chornobyl radiation.

To assess possible mutagenic and teratogenic effects of environmental factors including ionizing radiation, it is proposed to study the incidence of congenital birth defects, sentinel phenotypes, and minor birth defects as well [36]. It has been established that the exposure to radiation during organogenesis leads to development of morphogenetic variants with minor birth defects. The younger the gestational age and the higher the radiation dose, the more minor developmental abnormalities a child presented [36].

Cytogenetic studies indicated an increased incidence of stable and unstable chromosomal aberrations in children who were living in contaminated regions of Ukraine. The incidence of the chromosomal aberrations positively correlated with the level of radioactive contamination and radiation dose received by the fetal bone marrow [37, 38].

Children born to fathers who participated in clean-up work after the Chornobyl accident had multiple small birth defects in addition to dysplasia of connective tissue. More than one third of these children had a syndrome of connective tissue dysplasia in the heart. In addition, these children had various minor birth defects. Among these defects, the most prevalent were prolapse of mitral and tricuspid valves, and abnormal cords in the left ventricle. Children suffering from connective tissue dysplasia in the heart also had similar changes in musculoskeletal system [39].

In a study by Dubrova et al. (1996) it was found the that frequency of minisatellite DNA mutations in children born in Mogilev province, Belarus, heavily contaminated after the Chornobyl accident, was 2 times higher than in control group [40]. The incidence of these mutations positively correlated with density of ^{137}Cs soil contamination [40]. Similar observations were reported in families residing along Techa river [41].

In children born after the disaster to families of Chornobyl clean-up workers, incidence of mutations in DNA microsatellites was 5.6 times higher than in their siblings born before the disaster [42].

Radiation induced changes in parental germ cells can be detected at various stages of ontogenesis among the offspring. «Small» mutations that are present in heterozygous state and cause genomic instability have clinical manifestations during the postnatal period. This phenomenon leads to so-called «physiological inferiority» and decreased vitality of offspring of exposed parents [43]. In children of parents exposed to radiation, genomic instability causes multiple dysmorphisms, dysplasia of visceral organs, and increased incidence of chromosome aberrations and mutations in minisatellite DNA [44]. All these changes impair ability for adaptation and increase risk of various diseases.

Possible mechanisms of transgenerational genomic instability are currently under investigation. The goal of genetics during past fifty years of trying to predict the impact of radiation on human genome has not yet been accomplished. It is now considered plausible that transgenerational genomic instability may increase the risk of cancer and congenital malformations in offspring of parents exposed to radiation.

In the future, newly developed technologies may help to better answer important questions about detrimental health consequences among children exposed to low-dose ionizing radiation or to those born to parents exposed to radiation.

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Chapter 20
STATE OF BONE MARROW HEMATOPOIESIS OF CHILDREN IN POST-ACCIDENT PERIOD – 30 YEARS EXPERIENCE OF DYNAMIC ASSESSMENT

Hematopoiesis is one of the most radiosensitive systems. It is known that low doses of ionizing radiation can be promoters of genetic and carcinogenic effects in humans and in combination with other negative factors lead to the destabilization of proliferation and differentiation of hematopoietic stem cells. Due to prolonged exposure to low doses of ionizing radiation characteristic to the Chornobyl accident, there is a possibility of remote stochastic effects, one of which is leukemia.

Throughout the consecutive 30 years of post-accident period, we conducted qualitative analysis of hematopoiesis elements including stem cells and the bone microenvironment. The diagnosis of leukemia was established on the basis of morphological features and immunophenotype of bone marrow blast cells of patients in the Department of Clinical Immunology of NRCRM (Head – D.A. Bazyka, Corresponding Member of NAMS of Ukraine).

State of organic matrix and mineral component of bone structure and bone density were studied. Comprehensive assessment of the hematopoietic system in child population was based on quantitative and qualitative indicators of peripheral blood and bone marrow.

Morphological characteristics of erythrocytes (mean diameter and volume, the average content and average concentration of hemoglobin and their deformability) circulating and marginal pool of neutrophils, parameters of iron metabolism (levels of iron, ferritin, transferrin,), the content of alkaline phosphatase, state of acid-base balance and buffer systems of blood, porphyrin metabolism (koproporfiryn, Δ – aminolevulinic acid) were studied. The contents of Pb, Cr, Mn, Cu, Zn, Ni, Fe in nails, hair and blood of children were investigated.

The effectiveness of stromal fibroblast colony formation of bone marrow, their amino acid composition and influence on the processes of proliferation and differentiation of progenitor cells were evaluated.

Levels of cortisol, thyroid-stimulating hormone (TSH), osteocalcin, calcitonin and parathyroid hormone in the serum of children were defined.

We also analyzed the incidence of leukemia in children exposed to ionizing radiation in the dose range from 0.12 mSv to 36.0 mSv.

Evaluation of long-acting radiation and non-radiation environmental factors on the occurrence and course of hematological and oncohematological pathology in children was carried out using :

➢ data of «Total dosimetric certification of settlements of Ukraine, which suffered from radioactive contamination after the Chornobyl accident»;

➢ exposure doses to bone marrow and bone surface in patients with acute leukemia;

➢ data (2010) of the Ministry of Environmental Protection of Ukraine on the state of the environment (evaluation of integral degree contamination of territory) – air, soil, water (heavy metals, pesticides, ^{137}Cs).

Criteria for the formation of a risk-group of hematologic pathology among children of Ukraine and prophylactic measures aimed to reducing the incidence of diseases of the blood system in children were developed and improved.

Children born to parents affected by the Chornobyl disaster, including those who suffered acute radiation sickness; evacuated from Prypyat city and the 30 km zone in the first period after the accident and residents in the territories of Ukraine contaminated with radionuclides were examined as well.

Assessment of doses to patients with acute leukemia

Multifactor nature of carcinogenesis requires the integration of biochemical and molecular studies, especially in environmental disasters, including radiological and non-radiation etiology. We studied the effect of absorbed doses on the development and course of diseases of the blood of children in the remote period after emergency. Radiation doses in children with acute leukemia were estimated, depending on their age and gender specific, variants of the disease, clinical symptoms, terms of survival.

Two groups of patients with the consideration of ionizing radiation influence were formed: I group – irradiated (n = 55), II group – unirradiated (n = 57). Radiation doses of children were ranging from 0.12 mSv to 36.0 mSv (mean value equal to (4.25 ± 0.63) mSv. Depending on the variant of acute leukemia doses for children did not differ significantly and were in patients with acute lymphoblastic leukemia (ALL) (3.86 ± 0.63 mSv, for acute myeloid leukemia (AML) – (4.64 ± 0.82 mSv), $p > 0.05$.

The distribution of patients I and II groups by age and sex characteristics was uniform (the method of interval estimation – I gradation: 0.60–0.48–0.35; II gradation: 0.75–0.66–0.56).

No defined difference was found in the distribution of children according to acute leukemia variants depending on the effects of ionizing radiation (I gradation: 0.40–0.28–0.18; II gradation: 0.29–0.15–0.09) (Table 20.1).

The course of acute leukemia in children was assessed by the median survival of patients. Children with the median survival more than 60 months (mean 75.6 ± 3.5 months) were considered as favorable course, the unfavourable – patients with a median survival up to 60 months (mean 45.3 ± 2.1 months). No differences in the

Table 20.1

Distribution of patients with acute leukemia by disease variations

Variant of acute leukemia	Distribution of patients on disease variations (%)	
	I group	II group
T-ALL	5.3	7.2
B-ALL:	78.9	72.8
Pro-B	22.2	15.0
Common	62.2	65.0
Pre-B	15.6	20.0
AML	15.8	20.0

distribution of patients considering exposure and course of disease (ALL, AML) were established (I gradation: 0.90–0.84–0.75; II gradation: 0.91–0.83–0.69).

Radiation doses for children with acute leukemia, did not correlate with effectiveness of stromal fibroblast colony formation of bone marrow, the level of cortisol, TSH, alkaline phosphatase in serum and bone density.

Analyzing the results of the data on exposure doses in children with acute leukemia based on their sex and child's age at diagnosis, variants of the disease and median survival should be noted that the doses received by patients, were generally belonging to small and did not significantly affect the clinical data.

Thus, it was established, that between irradiated and non-irradiated children differences were minimal.

Dynamics of acute leukemia incidence among children in post-accident period

Since 1986–1991 hematopoietic condition and the incidence of leukemia were studied in children. It was shown that in the first period after the accident (45 days) there were quantitative changes in hemogram: in 63% – neutrophilic leukocytosis with concomitant eosinophilia elements in 21.0%, in 1.5% – thrombocytosis was recorded (platelet number greater than 450 G/L) .

Qualitative defects of hematopoietic elements were identified in 90% of children: increased activity of lipid peroxidation and redox enzymes in neutrophils, destabilization and violation of the integrity of erythrocyte membranes and their conformational reorganization, that do not depend on their age. During the next terms of observation changes in blood cells normalized and registered only in children with underlying comorbid somatic diseases.

Since 1988, we studied the incidence of acute leukemia in Kyiv, Zhytomyr, Chernihiv and Rivne regions of Ukraine and thoroughly analyzed cases of leukemia in children affected by the Chornobyl accident.

From 1992 to 2001 gradual uniform increase in the incidence of all forms of leukemia in children was noted with coinciding temporal trends in pre- and post-accident period. The increase of malignant neoplasms morbidity in the contaminated territories was at the same rate as in the other regions without radiation factors.

We did not note significant differences in the incidence rate of various forms of leukemia in 1986–2001 compared to 1980–1985 and averages on Ukraine as a whole (4–6 cases per 100,000 child population). After 1996 there was a redistribution of children leukemia by age, in particular the number of cases in children older than 12 years increased from 25% to 34%.

In this connection cases of disease were analyzed on the basis of soil contamination by ^{137}Cs from 37 kBq/m^2 to 555 kBq/m^2, where children lived.

Our results have not defined increase in the number of children with leukemia, both before and after the accident. There was no difference in the frequency of leukemia distribution by variants.

That is, the incidences of acute leukemia in children's population living in Kyiv, Zhytomyr, Chernihiv regions in the remote period after the accident, had some fluctuations, but they do not go beyond the average level in Ukraine as a whole.

On the example of Kyiv region conclusively proven impact of adverse environmental factors on the development of oncohematologic diseases in 325 children before (1980–1985) and after the accident (1986–2012). According to mapping the incidence of acute leukemia (ALL, AML) in patients within area of the region there are three cluster that correspond to the man-made pollution of nature.

Analysis of the survey of children born to parents, who have suffered acute radiation sickness (n = 30), did not revealed malignant diseases of the blood system, although in all individuals of

this group in peripheral blood were identified degenerative forms and aberrant cells. These changes may be due to the presence of somatic disease and the influence of unfavourable endo- and exogenous factors on the child's body, resulting in myelodysplastic changes in hematopoiesis.

Assessment of hematologic disease cases among children, born to parents clean-up workers of the Chornobyl accident, evacuated from Prypyat city and 30-km zone, residents of contaminated territories and this time living in different regions of Ukraine (total about 500,000 children) found no increase in the incidences of leukemia and lymphomas morbidity above the spontaneous level.

The impact of environmental factors on the development and course of hematologic pathology

The impact of unfavorable radiation and non-radiation factors on the state of hematopoietic system was assessed by the degree of territory integral contamination, frequency and peculiarities of anemic conditions, leukemoid reactions and acute leukemia in children.

It was shown, that after the emergency the share of children with deficient anemia (DA) was growing compared to iron deficient anemia (IDA). Thus, in 1996 the number of DA children was 25% in 2003 – 31%, in 2015 – 52%.

The causes of DA in children were changing processes of iron metabolism due to imbalance of micronutrients, toxic effects of heavy metals, prolonged exposure to low doses of ionizing radiation, the presence of chronic diseases, especially of gastro-intestinal tract, irrational nutrition, endocrine diseases. Hereditary porphyria was diagnosed in 5% of children.

Considering, that presence of DA with symptoms of ferrokinetyc performance disturbances is characteristic for patients with acute leukemia, children with anemic states require prolonged surveillance of hematologist and belong to the group of increased risk of oncohematologic diseases.

It should be noted, that with increasing degree of integrated contamination from moderately polluted to highly polluted, in children older than 12 years with the DA number of red blood cells decreased significantly (from (3.63 ± 0.02) T/l to $(3.41 \pm 0.02$ T/l) respectively, $p < 0.05$), proving for disturbances in erythrocyte link and changes in the functioning of hematopoiesis.

After the accident the number of children with leukemoid reactions (monocytosis, eosinophilia, lymphocytosis) did not increase, but the quantity of children with qualitative changes in the elements of hematopoiesis was noted to increase, especially growing percentage of degenerative and aberrant forms in peripheral blood (from 40% in 1999 to 69% in 2015).

Quantitative and qualitative changes in peripheral blood cells of children depended on the type of comorbid diseases, disorders in the endocrine status.

In 30% of children redistribution of granulocytes in the circulation and marginal pool was observed, depending on the presence of infection foci, activation of immune processes in the body of children and the state of proliferative processes in the bone marrow.

With the increase of the degree of territory contamination the number of children with monocytosis (number of monocytes in the blood of more than 0.8 G/L) grew.

One of the reasons for this effects is an overload of the body by iron and other metals as a result of ferokinetyc processes disturbance. In addition, the increase in the number of monocytes in the blood of children is a reflection of macrophage immunity processes. This can occur in the presence of chronic bacterial infections in children, infringement of control over the elimination of clones of malignant cells and so on. Monocytosis in a child with excess of iron may be one of the early diagnostic criteria of myelodysplastic syndrome.

It was proved that the proportion of acute leukemia patients with initial leukocyte count higher than 100 G / L was higher among persons, who lived at the intensively and extremely polluted

areas of contaminated territories, compared to those living in moderately polluted areas (interval estimation method – I gradation 0.34–0.32–0.38, II gradation 0.46–0.43–0.51).

These data suggest the influence of the environment, including ionizing radiation on children's health and development of diseases of the blood system, that allows to develop and apply adequate therapeutic and preventive measures, taking into account the pathogenesis and features of hematologic diseases.

Analysis of family history burden by risk factors occurrence and course of acute leukemia in children

Analysis of the frequency and type of pathology in the genealogy of children with AL, showed that the first frequency occupied the relatives with oncological diseases (24.5% versus 9.7% in the general population). Allergic reactions, endocrine disease in relatives of patients were found almost the same percentage and did not differ compared to the control group (17.6%, 11.9%, 13.4% respectively). Children born to these parents being born with a weight greater than 4.0 kg, with signs of constitutional lympatism.

Analyzing the course of oncohematological pathology in children, depending on the diseases in their families, we found that the presence of cancer in the genealogy was favorable survival prognosis recorded more often in children under 6 years with common-ALL and pre-B-ALL (median survival was 89.6 ± 3.7 months and 71.2 ± 3.6 months respectively). When relatives had allergic reactions, most children died from leukemia before 60 months from the time of diagnosis.

In children older than 12 years with T-ALL and pro-B-ALL and allergies and endocrine diseases in relatives unfavorable course of disease was observed (median survival was 32.7 ± 1.8 months and 31.4 ± 2.8 months respectively). AML more often observed in children having in pedigree endocrine diseases (U = 0.46).

The data received here prove for changes in the neuro-endocrine regulation of hematopoiesis, which are reflected in the occurrence and prognosis of AL in children.

State of stromal microenvironment and structure of bone in children with acute leukemia

Stromal fibroblasts of bone marrow are closely linked and make a physiological niche for hematopoietic elements. They provide the processes of collagen formation, support the structural integrity of connective tissue and are responsible for the state of hematopoietic microenvironment. We found changes in the functioning of stromal microenvironment in patients with acute leukemia.

In the initial period in patients with ALL and AML the effectiveness of stromal fibroblast colony formation of bone marrow was 5–6 times lower compared to controls, proving for the changes in the collagen formation from the early stages of the process (11.6 ± 2.2 and 52.4 ± 6.2 per 10^5 nucleated cells respectively).

However, the higher was the potential of cloning, the more aggressive was tumor process and the shorter median survival of patients.

Life expectancy was significantly higher in children whose fibroblast cloning efficiency in initial period of disease was ranged from 9 to 11 per 10^5 nucleated cells (65.4 ± 5.8 months) and shorter in children with high cloning proliferative potential – above 70 per 10^5 nucleated cells (18.1 ± 2.5 months).

Amino acid composition of fibroblasts influences on the elements of hematopoiesis. A direct correlation (rs = +0.84) was found between proline content in stromal fibroblasts, grown *in vitro*, and the number of erythroid progenitor cells in the bone marrow, according to myelogram

in patients with ALL. The results showed that the stromal fibroblasts are a source of essential factors for the functioning of the blood, including erythroid elements, starting with the development of progenitor cells of this line.

In children with acute leukemia changes were revealed in the organic matrix of bone structures, the main component of which is collagen.

Hydrophobicity of bone collagen molecule increases in an expanded phase of the disease, width of SLS-crystallites formed at leukemia is much smaller compared to the standard, collagen molecule 300 Å longer than physiological one (by ~ 100 amino acid residues), polar and unpolar loci appear along polypeptide chain (Figure 20.1).

In the collagen molecule the content of glycine (268.2 ± 12.2 against 319.5 ± 7.5), lysine (23.2 ± 0.5 against 28.3 ± 0.5 per 1000 residues) and the total amount of amino acids are reduced.

Oxyproline level is increased (122.9 ± 3.8 against 97.5 ± 3.7 per 1000 residues) compared with healthy children. Between urinary hydroxyproline and bone densitometry inverse relationship was established ($r = -0.34$; $T = -1.38$).

In the expanded phase of the disease these changes are progressing, increases the content of alkaline phosphatase. An imbalance of amino acids in urine appears due to 3.4 fold increase in aspartic and glutamic acids; increased the excretion of oxyproline.

Collagen composites are formed with collagen protein, non-protein components (polyamines), which shield certain loci along the length of the collagen helix, the activity of enzymes, prolyl- and lysyloxidase providing hydroxylation of lysine and proline residues reduces, enhanced conformational restructuring of isoforms α1- and collagen chains α2- leads to hypercalcination of bone matrix as a result of changes in the spatial configuration of individual chains.

Depending on the version of leukemia immunophenotype in children revealed changes in the mineral component of bone structures. The content of calcium dihydrophosphate and calcium

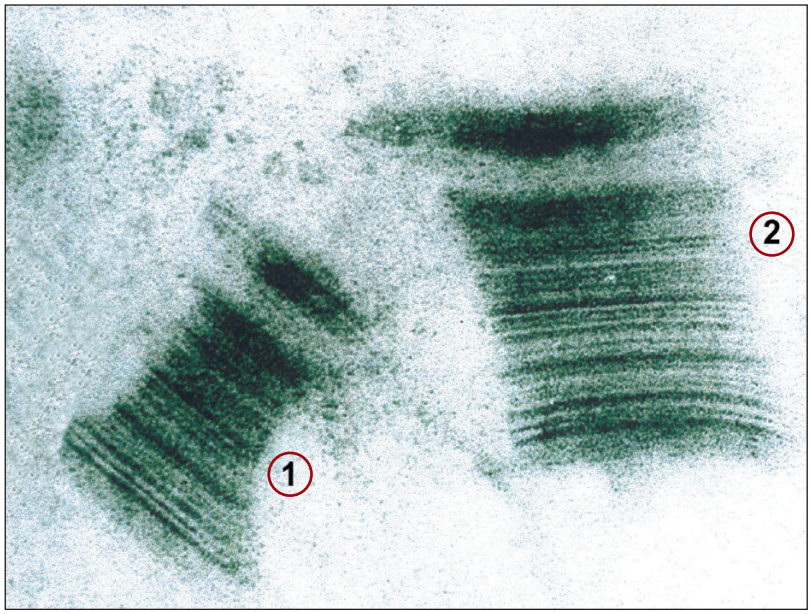


Figure 20.1. **Changes SLS-crystallites in children with leukemia (1 – a healthy baby, 2 – a child with leukemia)**

dihydrophosphate tetrahydrate in the urine was higher in patients with AML compared to ALL and practically healthy children.

Infrared absorption spectra of the dry sample of daily urine in children with AML, ALL and the comparison group are presented on charts (Figure 20.2–20.4). That is, in children with AL changes in bone metabolism indicators are revealed, accompanied by elimination of calcium phosphate and bone demineralization. Level of alkaline phosphatase is increased, the level of calcium in serum is reduced.

It was shown that micro hardness of bones at the early stages of leukemic process decreased, than increased with the progression of disease. Hydroxyapatite crystal lattice and the state of the crystal water changed. Alcaline phosphates passed into acidic (single- and twice-substituted) forms, high levels of pyrophosphate and manifestations of diffuse osteoporosis were appearing. At that, the excretion of salts was higher in children, whose median survival was shorter ($rs = -0.46$).

New data received on the structural features of bone tissue in acute leukemia patients with changes in indicators of endocrine status. Functional activity and effectiveness of stromal fibroblast colony formation of bone marrow depended on cortisol content.

It is proved, that in 26.1% of patients initial level of cortisol in the blood serum was lower than 200.0 nmol/l, unlike the children of the comparison group (8.1%, $p < 0.05$). In 5.8% of persons elevated above the 5.5 μMO/ml levels of TSH were registered (3.2% in the comparison group), the level of osteocalcin in the serum of patients was 2 times lower in comparison with the control group. The content of parathyroid hormone and calcitonin did not differ significantly by gender of the patient and disease variant. Exceptions were boys older than 12 years both with ALL and AML, whose level of calcitonin was higher compared with girls.

Changes in the endocrine status of patients negatively affect the prognosis of acute leukemia course in children. Reducing the level of cortisol in the body leads to osteopenic displays, and also affects bone density due to changes in the structure of collagen, phenomena of osteoporosis appear, which adversely affect the median survival of patients.

Children with low initial levels of cortisol had a median survival of 2.2 times shorter, than those of standard rates (31.0 ± 2.1 months against 73.4 ± 2.1 months).

Integral index of bone density is densitometry. Mean values of bone density in children with pro-B-ALL, common-ALL, pre-B-ALL and AML acute leukemia did not differ significantly. However, the distribution parameters densitometry in three gradations: 100–85; 84–65 and below 65 showed that people with pro-B-ALL had the index lower, than 65 and life expectancy of these patients was significantly shorter compared with patients, whose bone density was higher.

Table 20.2
Indicators affecting the median survival of patients with acute leukemia

Indicators	Rank scale according to Bayes formula
Bone density	1
Cortisol	2
Alkaline phosphatase in serum	3
Calcium in serum	3
Calcium phosphate in urine	3
Oxyproline excretion in urine	3
TSH in serum	4

Indicators that influence the course of the disease, according to their significance level are available in Table 20.2.

This cascade of reactions reveals one of the carcinogenesis mechanisms dealing with changes in the «stromal microenvironment – bone – bone marrow hematopoiesis – endocrine regulation», that occurs in children with acute leukemia, who undergo the unfavorable influence of Chornobyl accident.

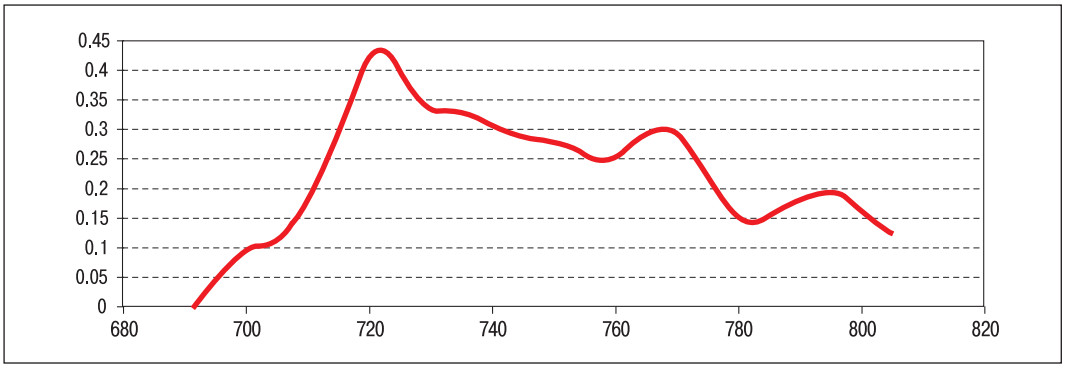


Figure 20.2. The infrared absorption spectrum of the dry sample of daily urine in the child (G.T., 14 years) with AML. On the horizontal axis delayed wave numbers, cm^{-1}; the vertical axis delayed absorption in relative units.

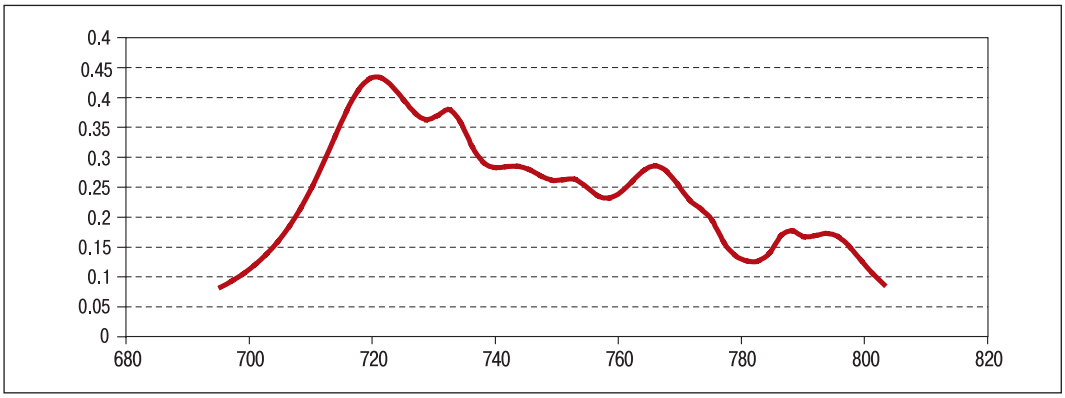


Figure 20.3. The infrared absorption spectrum of the dry sample of daily urine in the child (M.A., 11 years) with ALL. On the horizontal axis delayed wave numbers, cm^{-1}; the vertical axis delayed absorption in relative units.

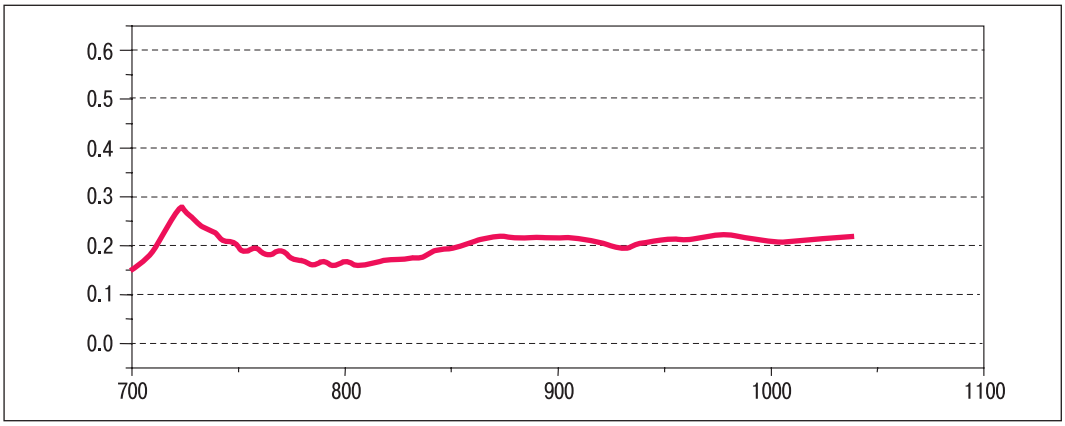


Figure 20.4. The infrared absorption spectrum of the dry sample daily urine a healthy child. On the horizontal axis delayed wave numbers, cm^{-1}; vertical axis delayed absorption in relative units.

Criteria for the formation of risk-group of onco hematological pathologies among children

Children's bodies are particularly sensitive to unfavorable factors due to the processes of growth, development, functional instability and staged hormonal changes. Summation and potentiation of the toxic effects lead usually to an earlier development of pathological conditions.

We were unable to establish the influence of isolated radiation in small doses on blood parameters in children and the incidence of acute leukemia, although have clearly seen combined impact of adverse environmental factors, including ionizing radiation, genetic factors on the child's body, acting as promoters of malignant diseases of blood system in children, which need treatment. Factors of Chornobyl accident that may influence on the development of hematologic diseases, including acute leukemias in children are presented at the Figure 20.5.

The results of studies have shown the importance of the microenvironment of bone and the need of early formation of groups at risk of oncohematologic pathology in children, whose treatment can prevent the development of acute leukemias.

The criteria for formation of priority supervision group were classified as follows: the presence of malignant tumors in the genealogy, age of children (from one to six years and older, than 12 years), DA with normative or elevated serum iron and ferritin, changes in endocrine status of the child, decreased bone density, body weight at birth surpassing 4.0 kg, the presence of ossalgia, arthralgia and symptoms of constitutional limphatism, living in ecologically unfavorable conditions.

From the total of 42,000 surveyed children, who have experienced adverse impact of complex radiation and non-radiation factors, a group of priority observation of 4243 children was formed. Within 30 years after the accident 13 cases of malignant blood diseases were realized in this group (9 ALL and 4 AML).

Therefore, the formation of the group of risk malignant diseases development of the blood system in children based on the evaluation of patient's genealogy, age and sex characteristics, clinical and hematological parameters under the influence of unfavorable environmental factors and improvement of treatment efficiency is actual.

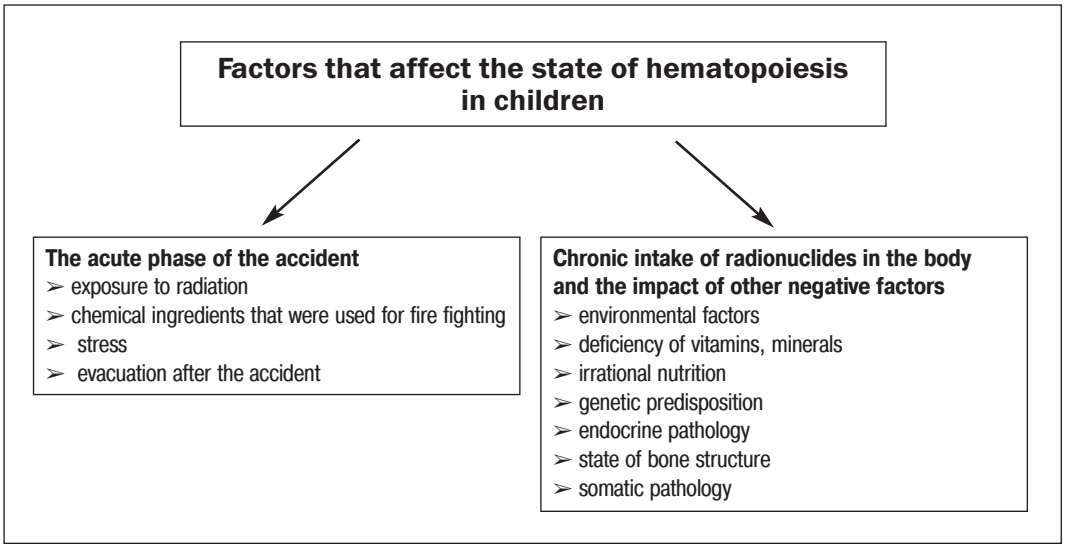


Figure 20.5. **Factors of Chornobyl accident that may influence on the development of hematologic diseases, including acute leukemias in children**

Treatment and prophylaxis measures

Children with changes in bone metabolism parameters form a group of risk hematologic diseases need long-term monitoring and implementation of treatment and preventive measures.

A set of preventive measures for correction of organic and mineral matrix of bones, that we have developed, provided for the children following activities:

➢ provided of calcium deficiency foods containing calcium and basic phosphates were appointed;

➢ subject to changes in composition of the mineral hydroxyapatite calcium diphosphate, dihydrophosphate drugs with ascorbic or citric acid were applied; mono-calcium phosphate preparations; Vitamins B_6, B_{15}, which are involved in the normalization of metabolic processes in the bone tissue;

➢ subject to changes in the collagen formation for normalizing urinary amino acid composition protein food mixes were administered, preparations based on glycine, which is a part of the bone collagen (33%) and helps eliminate acidosis;

➢ subject to changes in endocrine status correction of indicators was performed according to recommendations of endocrinologist;

➢ while lowered the pH of blood acid-base balance was adjusted using alkaline solutions (mineral water).

The received data showed that the complex medical measures in children at risk of malignant diseases of the blood system contributed to positive effect in 85.2% of cases. The effect of treatment was absent in 14.8%; these patients needed follow-up.

These data suggest the need for timely correction of the organic and mineral matrix of bone structures in order to reduce the frequency of hematological and oncohematological diseases in children population, subjected to adverse environmental factors.

Chapter 21
MEDICAL CONTROL AND RADIATION PROTECTION PERSONNEL THAT PERFORMING RADIATION-HAZARDOUS WORKS FOR TRANSFORMATION OF «OBJECT SHELTER» OF CHORNOBYL NPP INTO AN ENVIRONMENTALLY SAFE SYSTEM

Transformation of object of «Shelter» of SSE Chornobyl NPP (OS) into ecologically safe system is one of the most important state programs of Ukraine. The medical and dosimetric measures, aimed to care health of personnel, that participating in these works is occupied the main place among the most actual problems of modern clinical radiobiology, radiation hygiene and radiation protection [1, 2].

OS – destroyed by out of project accident block № 4 of ChNPP, «is building located on a earth's surface, which is specially equipped and construction designed so that the long protected isolation of radioactive waste (RAW) from the hit of them in a biosphere was guaranteed», and in its present OS state it is necessary to characterize as a «place of superficial storage of unorganized RAW («temporal depository of unorganized RAW, found in the stage of stabilization and reconstruction»)».

This qualification OS is obligatory for the use in the field of adjusting of radiation safety of personnel and population [3]. Now at the OS the «Shelter Implementation Project» (SIP) aimed for transformation of OS into the ecologically safe system is realized. The unicity of works that is conducted consists in fact that personnel, essentially, executes the work tasks in the conditions of action of high-activity open radionuclide sources of ionizing radiation in the indoors apartments of the destroyed 4th unit of SSE ChNPP or in a direct closeness to him on highly radioactively contaminated territory.

According to existent normal practice, works with such class sources must be performed in sealed rooms («hot chambers») with application of the distance controlled manipulators. It stipulates the substantial decline of levels of doses of external irradiation of personnel, also complete exception of contact of personnel with radioactive materials and possibility of their incorporation.

Due to the unique origination of the OS, radiation-hygienic conditions at the work execution zones cannot be brought into compliance with the world safety standards.

Works at OS are performed under multifactor occupational hazardous conditions with a dominant radiation factor that is increased with the general industrial hazardous and contaminated conditions, in difficult to access workplaces of destroyed nuclear reactor.

The all above-mentioned stipulates exceptional requirements to the somatic health and psychophysiological qualities of personnel. Thus, the performance of works by the staff to transform the OS is made in terms of common industrial and radiological risks synergy and psychoemotional high intensity of work. These radiation and non-radiation factors form the unique extreme environment for staff working at the OS.

The normative-legal documents of medical and sanitary-hygienic legislation in Ukraine require ensuring reliable providing of the check-in (initial) and check-out (final) medical and biophysical control of personnel, involved to work in conditions under influence of ionizing radiation and open sources of ionizing radiation (radionuclides), and also regular current medical and biophysical control of the personnel admitted to works.

Providing of all types of such control was and is the obligatory condition to receipt the permission of Ministry of Health of Ukraine (MHU), also special terms of concordance of UkrInvestExpertize.

Security works at the OS provides for measures to eliminate or minimize exposure to harmful factors, early detection of initial abnormalities in health of personnel, timely preventive measures or withdrawal of workers from the zone of influence. All of the above makes exceptional demands on physical health and physiological capabilities of staff.

According to the recommendations of MHU, to the SI «NRCRM of NAMS of Ukraine», as the primary medical research institution establishment of Ukraine in the field of radiation hygiene, dosimetria and clinical radiation medicine, that provides scientific medical and dosimetric accompaniment and executes the basic volume of works for minimization of medical consequences of the Chornobyl catastrophe and during all postaccidental years actively provides monitoring of health status and dosimetric control OS, ChNPP and execution zone personnel, and also as the center collaborating with WHO in international system for urgent reacting at radiation accident – The Radiation Emergency Medical Preparedness and Assistance Network (WHO – REMPAN), was incumbent to work out and lead program of medical and biophysical services of works for transformation of OS into environmentally safe system.

A system of medical and biophysical monitoring of health, working ability and radiation protection personnel performing work on converting the OS to an environmentally safe system was developed based on the unique experience of medical, biological and dosimetric and maintenance work on the impact of extreme radiation and non-radiation risk factors on the health and performance of staff [4–6] with the requirements of the basic normative-legal and regulatory documents [7–13], guidelines [14, 15], existing departmental standards of the Ministry of Health of Ukraine, as well as national and international consensus on the diagnosis of diseases that are contraindications to work in extremely dangerous and hazardous conditions – EDHC (ionizing radiation, radioactive substances and sources of ionizing radiation; works at height, general medical contraindications for work in EDHC).

The main interrelated elements of a comprehensive medical monitoring is input, periodic, special and final (including emergency) medical and psycho-physiological control, extra – individual inspection and routine (before shift) medical control (Figure 21.1).

The main purpose of medical support work on the SIP is to ensure radiation and general-industrial safety through compliance with Ukrainian legislation and the use of best internation-

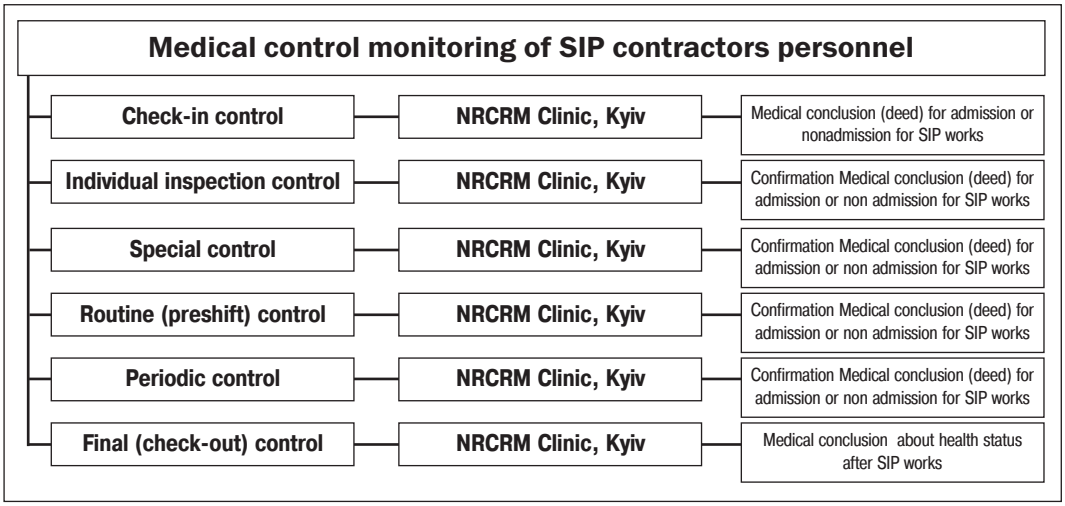


Figure 21.1. **The scheme of medical monitoring of SIP contractors personnel**

al practices with necessary measures to prevent or maximum possible reduce adverse factors, primarily radiation, influencing on health and aptitude of employees, early diagnosis of initial deviations in their health, the timely implementation of measures for preventive withdrawal of personnel from the zone of harmful factors influence on the basis of a comprehensive medical examination and subsequent peer review (medical supervision) the state of health on admission to work in EDHC at SO (ionizing radiation, general occupational hazards, work at height) required number of staff.

The main objectives of medical and biophysical control monitoring program for SIP personnel are:

1. Minimize the potential admission of personnel to work under extremely hazardous conditions that are not physically or mentally capable of performing the work. The legal basis for admission for work inside the Object Shelter and Local Zone;

2. To ensure that radiation exposure (internal and external) does not result in long term diseases;

3. To ensure that further occupational accidents do not occur because of the health of the workers. Specifically if an individual because of health reasons collapses during the performance of work the rescue efforts could lead to significant exposure to radiation and other hazardous conditions;

4. To verify that individuals are not exposed to internal radiation doses because of the hazardous conditions of Object Shelter. Personnel Protective Means although can be effective it requires a discipline and training to ensure that the individuals are not exposed to internal contamination. The program objective is to ensure that there are a means to independently verify the personnel exposure risk;

5. In the case of detection of internal contamination above a pre-set limit additional medical examinations will be conducted to ensure that the worker did no exceed the legal limits for radiation exposure (internal and external) and determine the capability of the worker to return to the work force at ChNPP;

6. To provide emergency care in case of industrial or radiation accidents that may occur during the performance of the work.

Implementation of these provisions also help to avoid possible lawsuits from staff about the loss of health in connection with participation in the work on the SIP. In addition, this approach provides for the Chornobyl NPP and contractors saving manpower required for work on the SIP.

In view of radiation hygiene and general-purpose features of works on OS, a set of comprehensive requirements for health and physiological qualities of candidates for admission to work, the only regulation of medical, physiological and professional selection was established, which was summarized in determining the categories of personnel's health.

Medical examination involves assessment of hematopoietic, immune, endocrine, respiratory system, eye, nervous system, mental and physiological adaptation, hearing and balance, circulatory, digestive, urogenital and the musculoskeletal system.

As part of the program admission and radiation safety works at the OS are biophysical control (Figure 21.2) – a complex physical and biodosimetric measures aimed to identify cases of radioactive substances incorporation into the body of workers, the calculation of the actual individual internal exposure caused by these events, and conformity radiation-hygienic conditions in the workplace sanitary requirements of Ukraine.

In terms of work for the SIP implementation biophysical monitoring includes collection of primary dosimetric information on employee and workplace and current radiation-hygienic and biophysical control. Input and output, special, urgent (emergency) biophysical control are performed in parallel and simultaneously with medical supervision.

Input biophysical control is a control before starting work as part of mobilization of personnel. Output biophysical control is a final control within demobilization personnel.

Biophysical monitoring – extended control that is performed when detecting excess respond to the contents of transuranic elements in samples of daily feces. The purpose of this control is to check the fact of radionuclides incorporation and determination of the exact value of the exposure of the worker.

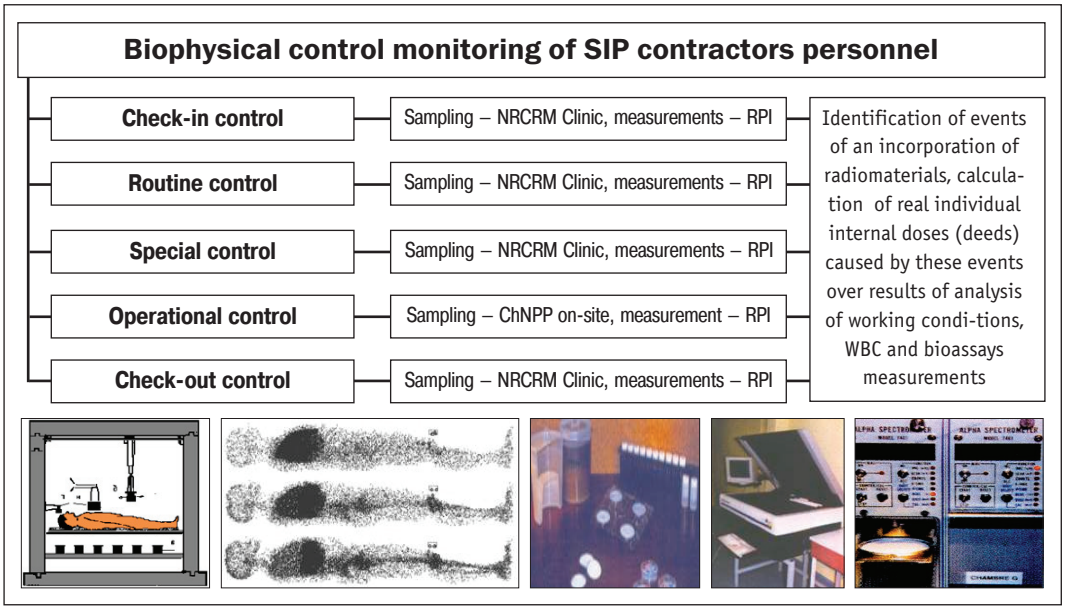


Figure 21.2. **Scheme of biophysical monitoring of SIP contractors personnel**

Current (routine) biophysical control – basic biophysical monitoring performed according to predetermined schedule of regular measurements. Current biophysical control consists of the following components: biophysical measurement before the shift; after the shift biophysical measurement; examination after the shift; intrashift biophysical measurements.

Evaluation and analysis of complex medical and psycho-physiological examination and dosimetric data of external and internal exposure are the basis for a decision by the expert commission of compliance with health, physiological characteristics and parameters of radiation-hygienic requirements to the personnel at work on the OS (Figure 21.3).

During the October 12, 2004 – October 1, 2015 the incoming medical and biophysical control was applied to 12,069 staff employees of contractors involved in the implementation of the SIP on admission to work at OS.

Among the staff involved in the SIP there are: 1) clean-up workers, evacuees from the 30 km zone of Chornobyl, residents of contaminated areas; 2) experts of nuclear energy industry;

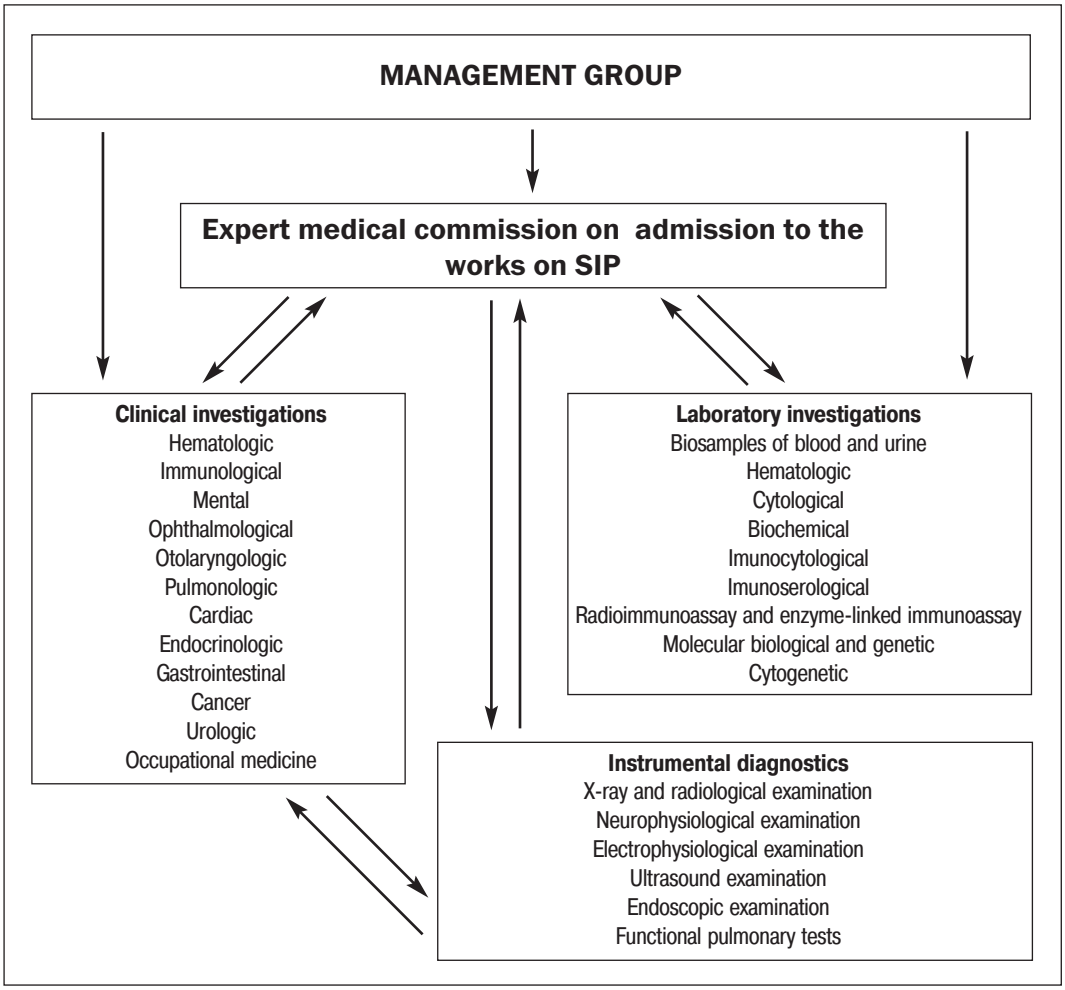


Figure 21.3. The organization of works to provide input, individual inspection, special and final medical examination

3) workers who had not been exposed earlier to ionizing radiation.

According to results of input medical supervision 6,082 people (50.4%) were allowed to work, 5,987 (49.6%) – not allowed.

Table 21.1
The results of medical monitoring of SIP contractors personnel for the period 12.10.2004 - 31.12.2009 (number of people)

Type of control	Allowed	Not allowed	Total
Check-In	6,082 (50.4%)	5,987 (49.6%)	12,069
Periodic	3,669 (74.2%)	1,261 (25.8%)	4,895
Inspective	4,449 (76.8%)	1,344 (23.2%)	5,793
Special		1,942 – individuals; 2,315 – cases	
Final		646	

The reasons for the non-admission were chronic diseases of digestive system (52.4%), eye – (15.0%), endocrine system (14.2%), circulatory system (6.4%), neoplasms (6.5%), respiratory system diseases (4.6%), pulmonary tuberculosis(1.6%) diseases of the nervous system, mental disorders and behavior (8.7%) mostly immune disease genesis (1.5%) blood and blood-forming organs (3.3%) urogenital system (2.1%), skin (4.0%), hearing (2.3%).

Staff of SIP contractor authorized to work, had 2 to 10 chronic diseases (respiratory, cardiovascular, digestive, nervous system). Stage and course of these diseases were not a contraindication for admission to work with SIP, but required complex rehabilitation.

In the periodic (annual) medical supervision allowed to work 3,669 employees (74.2%), not allowed – 1,261 (25.8%) (Table 21.1).

Non-admission to work on periodic monitoring results was due mainly to aggravation of existing course of chronic diseases of the digestive system (43.07%) respiratory system (24.16%) circulatory system (12.60%) diseases of the nervous system, mental and behavior disorders (18.69%), disorders of eye (1.47%). This suggests, first of all, not for the impact of hazards at the site of OS, but for a lack of work with staff to prevent relapse of these diseases.

Biophysical control with the definition of internal exposure doses over the 2004–2015 was promoted in general to 10,010 individuals – employees of contractors SIP. A 63,945 radiochemical analyzes were done for control of internal exposure. The analysis of distribution by type of biophysical control is shown in Figure 21.4. The structure of radiochemical analysis for

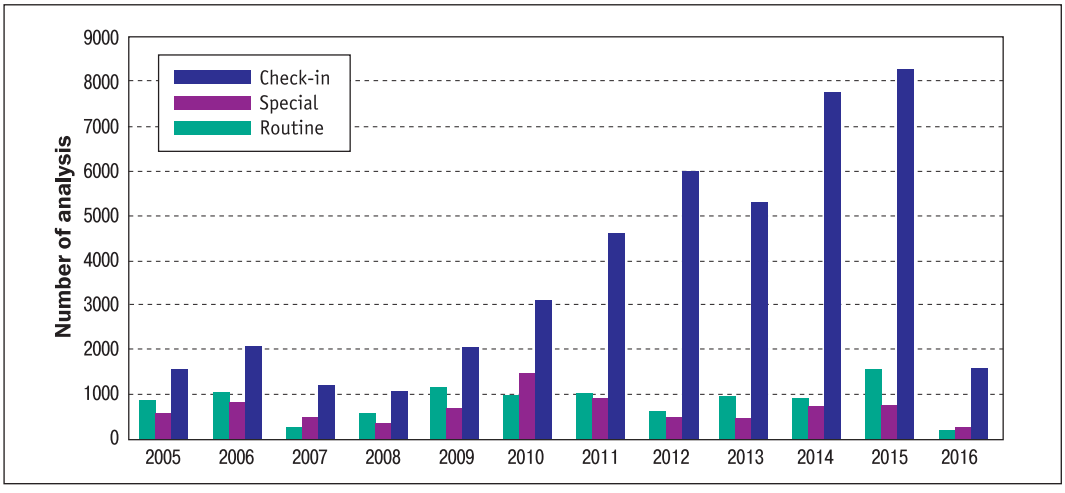


Figure 21.4. Distribution by type of biophysical control radiochemical analysis for monitoring internal dose of SIP contractors workers

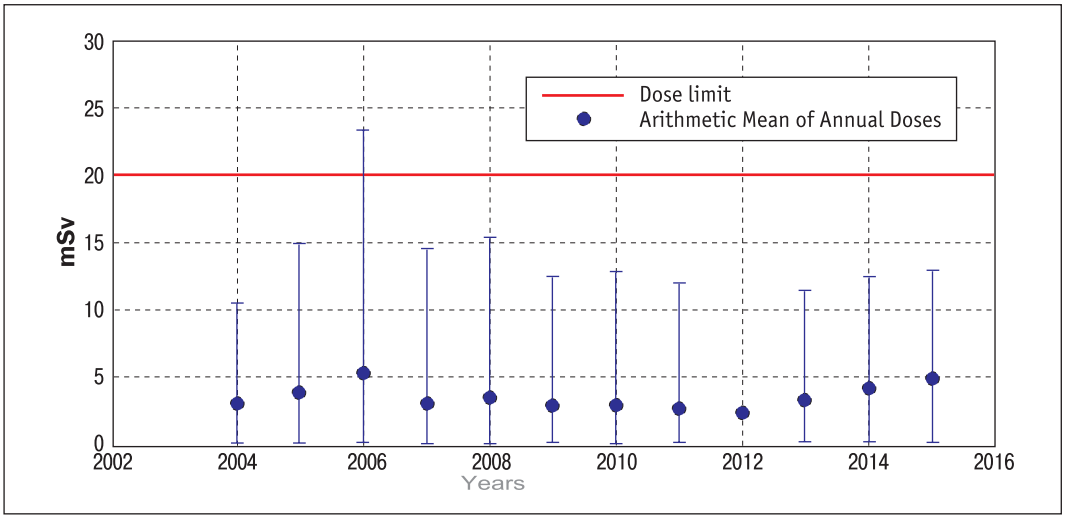


Figure 21.5. Distribution of yearly average external exposure of SIP contractors personnel within 2004–2016

monitoring internal dose was as follows: entrance control was 15%, routine – 68%, special – 16%, final – 1%.

During input biophysical control of candidates to participate in the work on the SIP, nor radionuclides in the body nor the radionuclide content in biosample (feces, urine) were practically not found. External doses were controlled by the radiation safety department of Chornobyl NPP. Distribution of average external exposure of personnel contractors for SIP 2004–2016 is shown in Figure 21.5. Average individual annual effective dose of external exposure of personnel during works is 3.73 mSv (STD = 4.02 mSv). Doses received by staff due to individual permission of Ministry of Health of Ukraine in 2006 and other years are not included.

Data obtained during the current (routine) biophysical monitoring of the personnel involved in the work of the OS (Figure 21.6) indicate that in samples of feces were measured levels of $^{239+240}$Pu, exceeding the level of response - and worker was sent to a special control (SC).

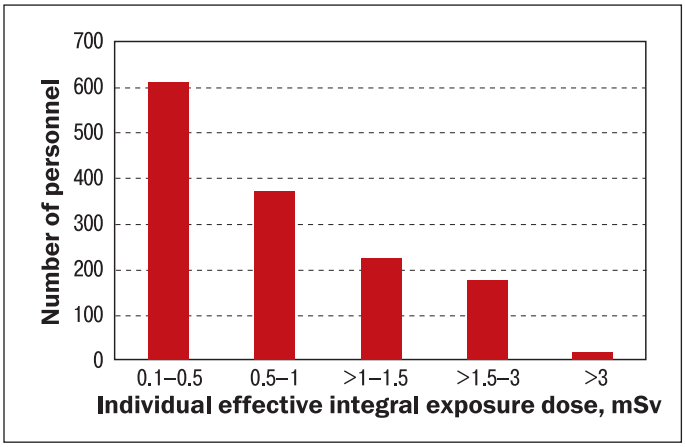


Figure 21.6. Distribution of internal exposure of personnel who passed the procedure of special biophysical and medical control

SC is exceptional and is done, when during the current biophysical monitoring in samples of feces $^{239+240}$Pu content level exceeding 1.5 mBq/test were found and there is a risk of exceeding individual exposure of 1 mSv x year^{-1}. This value corresponds to the reference level of annual individual internal exposure of the Chornobyl NPP set for the period of work in the OS. Quantity of workers called to IC serves as an indica-

tor of the radiation safety quality, measures concerning compliance with individual and collective protection of personnel, preventing radionuclides entrance into the body. Overall, in 2005–2015 there were 2,315 cases of initialization procedure of special medical and biophysical monitoring (some persons were submitted to IC 3 and more times).

The results of radiochemical analysis of biosamples selected under the special biophysical monitoring showed no systematic inflow of $^{239+240}$Pu to the body of workers and enable to conclude that the most likely way radionuclides influx were transit peroral route. Individual total doses of internal radiation (Figure 21.6), calculated by special biophysical monitoring, does not exceed 6 mSv and are, on average 0.85 mSv (STD = 0.69 mSv).

As the analysis has shown, the need to call workers for a special control at the initial stages of work on the SIP was primarily caused by insufficient organization of work and inconsistency of this type of work to radiation-hygienic requirements. However, as it turned out, at the current stage of work the main cause is low sanitary culture of workers.

That is why always there is intensive verification of radionuclides inflow ways in the body, characterization of radioactive aerosols, which are at the working place and recommendations provided on the use of personal respiratory protection, as well as to avoid external contamination when biosampling. A clean room was created and equipped at the Chornobyl NPP site to collect biosamples that preclude external contamination. Instructions and guidelines for the control of internal exposure of SIP personnel were developed and approved by regulators and implemented in practice at Chornobyl NPP.

In October-November 2005, after the first year of work on medical and biophysical support of work for SIP the Client (Chornobyl NPP) made an assessment of the program by the international audit. The audit team consisted of experts RTI International (Research Triangle Park, NC, USA), Battelle Memorial Institute (Richland, WA, USA) and Duke University (Durham, NC, USA).

According to the conclusion of the international audit, this project deserves appreciation and full support of both the methodology used and for the organization of work with some recommendations on how to optimize its management.

Audit work on the SIP, held by Mouchel Parkman Corporation in February 2007, noted in the final report that the program of medical and biophysical monitoring was extremely successful to achieve its main objective: ensuring medical fitness of SIP workers and prevent litigation in connection with damage to health from current and former employees involved in the SIP.

The above mentioned results of medical and biophysical monitoring indicate the critical importance of continued medical and biophysical maintenance of works on the SIP, because the problem of preventing personnel exposure is the key in the performance of works in these radiation-hygienic conditions.

* * *

The program of the medical and biophysical services for reconstruction works of OS witnessed its necessity and efficiency because results showed that in unique radiation-hygienical conditions the most critical are not engineer and technical problems, but – how to save the health and workability of people and prevent the overdose of personnel including and due to an internal irradiation.

The health status of workers that undergone check-in medical control is incompatible with requirements to participating in SIP works more than in 50% cases, regardless of previous regional medical examinations. Therefore, check-in and final medical control must be conducted only in high specialized, adequately equipped medical facilities that have practical experience of providing medicare and medical control to the persons, that undergone influence of ionizing radiation and, in particular, under radionuclides incorporation to the body.

As a result of realization of routine biophysical control were detected 1845 cases of $^{239+240}$Pu overlevel content in bioassays of faeces that is necessary to conduct the special biophysical and medical control for verification of ways of radionuclides intake to the body and estimations of dose of internal irradiation. Results of biophysical control also are basis for providing complex of organizational events on radiation protection and technical safety of personnel of SIP contractors enterprises and ChNPP, accurate keeping rules and measures that prevent radionuclides intake to the body.

Worked out and inculcated system for control of individual doses of internal irradiation by biophysical methods that responded requirements of sanitary legislation and provides the adequate level of radiation protection of workers from the internal irradiation during participation in SIP works. Development of the system for control of individual doses of internal irradiation of personnel foresees integration with radiation safety shop of ChNPP for control of both doses internal and external irradiation that agrees the requirements and corresponding instructional-methodical documents worked out and inculcated in practice of SSE ChNPP.

Protection of health and workability of personnel needs providing of complex of medicare and rehabilitation measures that must be realized within the framework of the special individual programs of treatment on a base of the highly specialized medical establishments.

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Chapter 22
THE CURRENT SYSTEM OF MEDICAL EXPERTISE TO ESTABLISH CAUSATION OF DISEASE, LEADING TO LOSS OF HEALTH, DISABILITY AND DEATH WITH THE INFLUENCE OF IONIZING RADIATION AND OTHER HAZARDOUS FACTORS OF THE CHORNOBYL ACCIDENT IN THE REMOTE POST-ACCIDENTAL PERIOD

One of the key issues to minimize the consequences of the Chornobyl NPP was the problem of medical and social expertise of victims [1].

According to the decision of the Government Commission # 539 from August 13, 1988 in agreement with the Trade-Unions and Goskomtrud of USSR the order of Ministry of Health # 731 from September 28, 1988 was issued «On the organization of the Central Interdepartmental Expert Council to establish causation of disease and disability with the works at the aftermath of Chornobyl accident and their professional nature at the All-Union Research Center for Radiation Medicine Academy of Medical Sciences» [2].

The basis of social protection of the Chornobyl accident victims was the Law of Ukraine «On status and social protection of citizens affected by the Chornobyl catastrophe» ratified by the Verkhovna Rada on April 1, 1991 [3]. Article 12 of this low is dedicated to «Establishing a causal link between the disease connected to the Chornobyl disaster, partial or complete disability of citizens affected by the Chornobyl disaster and the Chornobyl disaster». Of significant influence on making decisions in this issue are also articles 2, 14, 27 of this document.

On 01.01.2016 the status of victims of the Chornobyl disaster in Ukraine had 1,961,904 persons, among them: 210,247 liquidators of the Chornobyl accident (share in total is 10.7%);

1,751,657 victims of the Chornobyl accident (89.3%), of which 418,777 affected children (23.91%). The total number of affected people in 2016 compared to 2007 decreased by more than 564,312 people, or 22.34% (Figure 22.1). The number of victims of the Chornobyl disaster is constantly decreasing.

More than 35.6 thousand people have the status of wife / husband of the deceased citizen whose death was related to the Chornobyl catastrophe; 3,317 persons who participated in the liquidation of other nuclear accidents and referred to the relevant categories of victims.

At the same time, for the period of 1995–2014 a rapid increasing of number of people with disability category 1 was observed (from 40,106 to 118,108), that are persons who have the status of the Chornobyl accident victims and disabled due to illness for which a causal connection with the impact of the accident was established (Figure 22.2). During 2015 and 2016 a marked decrease in this category of persons to 108,530 at 01.01.2016.

The main cause that leads to these changes is the growing incidence of chronic diseases, leading to a rapid increase of morbidity and mortality of respective affected population.

Persons who have the status of the Chornobyl catastrophe victims under the current law are liable to expertise to establish causation of disease, disability and death causes of action of ionizing radiation and other harmful factors by the Chornobyl accident. Within expertise procedures compensatory and adaptive capabilities of person are revealed, implementation of which should contribute to the functional, psychological, social and professional rehabilitation and adaptation.

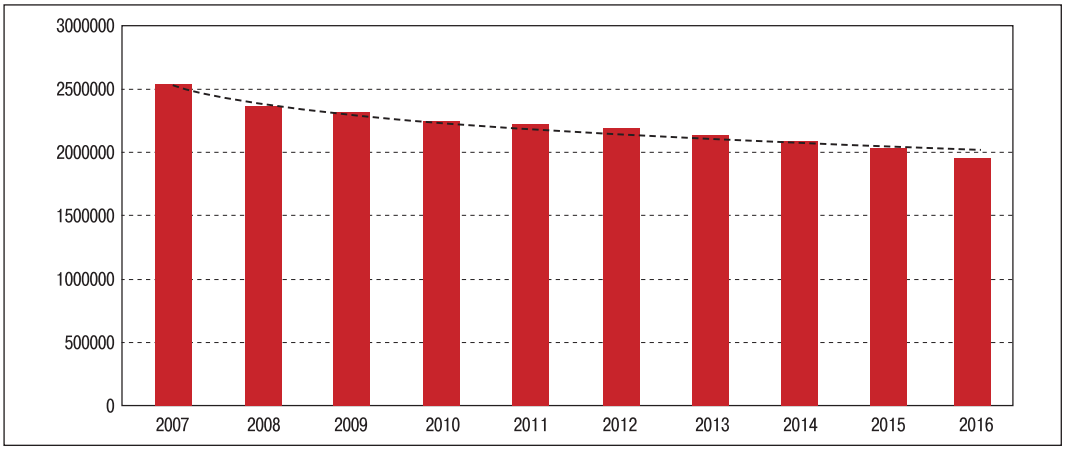


Figure 22.1. **Reducing the number of victims of the Chornobyl accident for the period of 2007–2016**

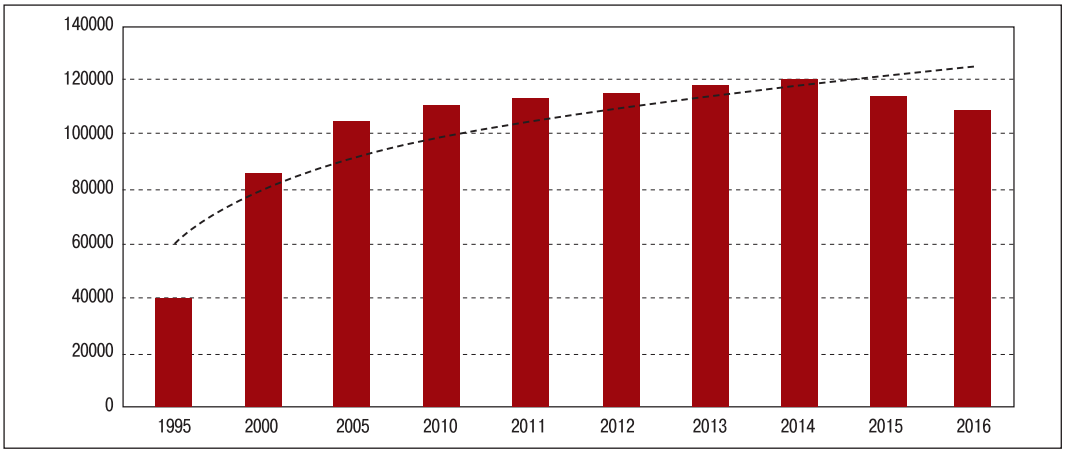


Figure 22.2. **Changes in the number of victims of the Chornobyl accident of category**

The main regulatory documents governing the connection of diseases with the impact of the Chornobyl disaster for 1997–2011 years was the order of MOH of Ukraine # 150 from 17.05.1997 «On approval of regulations on diseases in which causal links can be installed with the action of ionizing radiation and other harmful factors due to the Chornobyl NPP accident» [4] and joint order of the Ministry of Health and Ministry of Emergency of Ukraine # 166/129 from 30.05.1997 «On improvement of the system of expertise to establish causation of disease, disability and death with the effect of ionizing radiation and other harmful factors due to the Chornobyl NPP accident» [5].

By p. 3 of Resolution of the Cabinet of Ministers of Ukraine # 1210 from 23.11.2011 «On improvement of social protection of citizens affected by the Chornobyl disaster» [6] and subsequent joint decree of the Ministry of Health and Ministry of Emergency of Ukraine # 789/1248 from 10.10.2012 «On introduction changes to the order of the Ministry of Health of Ukraine and Ministry of Emergency of Ukraine from 30.05.1997 # 166/129» [7] regional specialized medical-advisory committees and regional inter-ministerial expert committee were eliminated except Central Interdepartmental Expert Commission, Donetsk and Lviv regional commissions (Table 22.1) made changes to the procedure of diseases lincage.

The order of Ministry of Health of Ukraine # 441 from 14.06.2012 «On amendments to the order of Ministry of Health of Ukraine # 150 from 17.05.1997» [8] defines the list of diseases for which can be determined relationship and instruction on its use.

Overall, during 2013–2015 in accordance with changes approved by the aforementioned documents, reviewed 22,764 medical expert dossiers of affected.

Including medical dossiers of 11,023 clean-up workers (48.42%), 456 evacuees (2.0%), 3,500 (15.37%) of 3rd category victims, 7003 (30.76%) residents in the area of enhanced radiation monitoring (4th category) and 782 (3.43%) victims who had category «D» before adulthood.

Today in the structure of medical expert dossiers cancer occupies a leading position – 60.3%, cerebrovascular diseases and their complications account for 10.0%, diseases of the cardiovascular system – 19.6%, respiratory diseases – 1.6%, endocrine disease (without thyroid cancer) – 1.4%, diseases of the digestive system – 1.1%, other diseases in general – 6.0%.

It is needed to notice that the legislative and regulatory basis of the medical-social expertise of connection of disease, disability and death causes to the impact of the Chornobyl NPP accident remains with defects requires clarification and improvement.

First of all the point is about amending the Law of Ukraine «On status and social protection of citizens affected by the Chornobyl catastrophe» [3] by articles to determine the status for children victims who lost this status at the age of adulthood and had fallen ill with cancer (primarily thyroid cancer) and hematological malignancies, as well as for guaranteeing medical support to descendants of victims of the second, third and future generations. It is needed to insist on clar-

Table 22.1

Distribution of regions from which persons affected by the Chornobyl disaster, documents submitted to the interdepartmental expert committees (IEC)

#	Commission	Regions
1	Central IEC	Zhytomyr, Kyiv, Cherkasy, Chernihivregion, Kyiv city and Donetsk regions that have been subordinated to Donetsk IEC – Dnipropetrovsk, Donetsk*, Zaporizhzhia, Kirovograd, Lugansk*, Mykolaiv, Odesa, Poltava, Sumy, Kharkiv and Kherson regions, the Autonomous Republic of Crimea* and Sevastopol city*, appeals and appealations from all regions
2	Lviv IEC	Lviv, Vinnytsia, Volyn, Ivano-Frankivsk, Lviv, Rivne, Ternopil, Khmelnytsky and Chernivtsi regions

Note. * – provided that the citizenship of Ukraine, residence and registration on the territory controlled by Ukraine.

ifying this law that the abolition of the status of the territory, which had a certain category of radioactive contamination does not provide abolition or loss of status for the affected residents of the area who have lived under the influence of radiation factor corresponding number of years.

Another issue arises as periodical update of the list of evidence-based diseases which may be a causal link of disease, disability and death causes to the impact of the Chornobyl NPP accident.

The latter requires consideration of many years experience of health effects minimization of medical effects of the Chornobyl NPP accident, the latest knowledge in the field of general and clinical radiobiology, radiation medicine, oncology and medical-social expertise.

If the case of disease that led to death, a causal link can be established if the diagnosis is listed and confirmed by pathological-anatomical, forensic investigation or, exceptionally, clinically proven at stationary inspection on the patient's life.

Direct known cause of death may be connected to the influence of harmful factors of the Chornobyl NPP accident without pathological-anatomical or forensic investigation if it is a consequence of the disease, which is listed and on which a causal link was installed within the life of patient.

Conducted in 2012, the reorganization of medical and social expertise of establishment causation of diseases, disability and causes of death to the impact of the Chornobyl NPP accident has proven its effectiveness and usefulness for medical and social protection of the victims of the accident.

There are pending issues (cancer of the thyroid gland in people who have lost the status of victims in adulthood) that require changes and amendments to legislation.

It is necessary to continue clinical and epidemiological studies patterns of development and course of diseases in affected population contingents in remote post-emergency period to develop scientifically based criteria due to ionizing radiation and other hazards of the Chornobyl disaster.

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Abbreviations

12-HETE	12-hydroxyeicosatetraenic acid
8-OHdG	8-hydroxydeoxyguanosine
AA	auditory analyzer
ACTH	corticotropin
ADHD	attention deficit hyperactivity disorder
ADR	analytical dose reconstruction
AE	age at exposure
AIP	auditory induced potentials
ALAT	alanin aminotransferase
AML	acute myeloid leukemia
AO	antioxidant
APE1	apurinic/apyrimidinic endonuclease 1
ARCH	IARC Research Agenda for Chernobyl Health
AREM	acoustic reflex of entotic muscles
ARS	acute radiation sickness
ARS NC	non-confirmed ARS
ASAT	aspartate aminotransferase
ATM	ataxia-telangiectasia mutated
AYA	group of adolescents and young adults
BAEPs	brainstem auditory evoked potentials
BCH	basal cell hyperplasia
BMD	bone mineral density
BPH	benign prostate hyperplasia
BSAEP	brain stem auditory evoked potentials
CCHD	chronic coronary heart disease
CCR	complete cytogenetic response
CCT	conditionally clean territories
CD	circulatory diseases
CDK	cyclin-dependent kinase
CER	Clinical and Epidemiological Registry, NRCRM
CFF	critical flicker frequency
CFFP	critical flicker frequency by a phosphene
CFS	chronic fatigue syndrome
CFTJ	complement fixation test
Chornobyl NPP (ChNPP)	Chornobyl Nuclear Power Plant
CGI	cephalography index
CI	confidence interval
CIDI	Composite International Diagnostic Interview
CIS	carcinoma in situ
CL	chronic leukemia
CLL	chronic lymphocytic leukemia
CML	chronic myeloblastic leukemia
CMR	Clinico-morphological Registry of the State Institution «VP Komisarenko Institute of Endocrinology and Metabolism of the National Academy of Medical Sciences of Ukraine»
CMV	cytomegalovirus
CNS	central nervous system
COPD	chronic obstructive pulmonary disease
COX1	cyclooxygenase 1
COX2	cyclooxygenase 2
CRR	«contaminated» by radionuclides regions
CRSP	Chornobyl Research Service Project

CUW	clean-up workers
CVD	cerebrovascular diseases
CZ	contaminated zone
DA	deficient anemia
DB	data base
DHBMT	Department of Hematology and Bone Marrow Transplantation of NRCRM
DHE	dihydroethidine
DLco	lungs diffusion
DNA	deoxyribonucleic acid
DNG	diffuse nontoxic goiter
DSB	double strand breaks
EBC	exhaled breath condensate
ECC	external Corti's cells
EDHC	extremely dangerous and hazardous conditions
EEG	electroencephalogram
EGFR	epidermal growth factor receptor
EIU	subjects exposed in utero
ENG	electronystagmography
EOG	electrooculography
EP	visual evoked potentials
EPR	electron paramagnetic resonance
ERR	excess relative risk
ERV	expiratory reserve volume
EWBC	Expert Whole Body Counter
FCM	flow cytometry
FEV1	forced expiratory volume in one second
FGFR	fibroblast growth factor receptor
FGI	French-German Initiative for Chornobyl
FIQ	full IQ
FISH-WCP	fluorescence in situ hybridization of human metaphase chromosomes
FITC	fluorescein isothiocyanate
FSH	follicular stimulating hormone
FVC	forced vital capacity
GABA	γ-aminobutyric acid
GAF Scale	Global Assessment of Functioning score
GGT	γ-glutamil transpeptidase
GH	growth hormone
GHQ	«General Health Questionnaire GHQ-28»
GIT	gastro-intestinal tract
GPA	glycophorin A
HBV	hepatitis B virus
HCDR3	heavy chain complemen-tarity-determining region-3
HCI	hidden chromosome instability
HCV	hepatitis C virus
HG PIN	high grade prostatic intraepithelial neoplasia
HHD	hypertensive heart disease
HLA	human leucocyte antigen
HLA-DR	MHC class II cell surface receptor encoded by the human leukocyte
HPACS	hypothalamic-pituitary-adrenocortical system
IAEA	International Atomic Energy Agency
ICA	internal carotid arteries

ICARR	International Consortium on Applied Radiation Research
ICD	International Classification of Diseases
ICD-10	International Classification of Diseases, 10th revision
ICRP	International Commission on Radiological Protection
IDA	iron deficient anemia
IEC	Interagency Expert Commission
IEM	State Institution «VP Komisarenko Institute of Endocrinology and Metabolism of the National Academy of Medical Sciences of Ukraine»
Ig	immunoglobulin
IHC	immunohistochemical
IHD	ischemic heart disease
IL	interleukin
IMGT	International Immunogenetics Database
iNOS	inducible NO synthase
IPHECA	International Program on the Health Effects of the Chornobyl Accident
IPI	interpeak intervals
IPR	immunopathological reactions
IQ	intellectual quotient
IR	ionizing radiation
IRHE	Institute of Radiation Hygiene and Epidemiology
ISWB	index of social well-being
ITGV	internal volume of gas in the chest
L-DOPA	dopamine precursor
LET	linear energy transfer
LGL	large granular lymphocytosis
LHIP	long-latent hearing induced potentials
LL	lymphoid leukemia
LLA	low locomotor activity
LP	latency period
LPO	lipid peroxidation,
MALT	mucosa-associated lymphoid tissue
MAPK	mitogen-activated protein kinase
MDA	malondialdehyde
mDNA	mitochondrial DNA
MDS	myelodisplastic syndrome
MEK	MAP/ERK kinase
MHC	major histocompatibility complex
MHU	Ministry of Health of Ukraine
MIA	Ministry of Internal Affairs
MIS	medical information system of the IEM
ML	myeloid leukemia
MM	multiple myeloma
MMR	major molecular response
MRDL	Mobile radiation dosimetric laboratory
MRI	magnetic resonance imaging
MS	multiple sclerosis
MSX	metabolic syndrome X
NAFLD	non-alcoholic fatty liver disease
NCI	National Cancer Institute, USA
NCR	National Cancer Registry of Ukraine of the National Cancer Institute of the Ukraine Ministry of Public Health

NF-κB	nuclear factor-κB
NRCRM	SI «National Research Center for Radiation Medicine of the National Academy of Medical Sciences of Ukraine»
OAEDP	otoacoustic emission of distorted products
ODR	official dose records
OR	odds ratio
OS	object of «Shelter» of the SSE Chornobyl NPP
PCNA	proliferating cell nuclear antigen
PCR	polymerase chain reaction
PCR-SSCP	polymerase chain reaction – single strand conformation polymorphism
PGE, PGF	prostaglandin E, prostaglandin F
PNA	peptide nucleic acid
PIA	proliferative inflammatory atrophy
PIN	prostatic intraepithelial neoplasia
PL	permissible levels
PNA	peptide nucleic acid
PR	prevalence ratio
PTSD	post-traumatic stress disorder
PV-2006	permissible levels of radioactive contamination
qEEG	quantitative electroencephalography
QUM	ultramorphological analysis
RADRUE	Realistic Analytical Dose Reconstruction and Uncertainty Analysis
RAVLT	Rey Auditory Vernal Learning Test
RCA	radioactively contaminated areas
RCCs	renal-cell carcinomas
RCET	renal-cell epithelial tumours
RCT	population of contaminated territories of zone guaranteed voluntary resettlement
RES	retinal electric sensitiveness
ROS	reactive oxygen species
RR	relative risks
RTL	relative length of telomeres
SC	special control
SEM	scanning electron microscopy
SHIP	short-time latent hearing induced potentials
SIP	Shelter Implementation Project
SIR	standardized incidence ratio
SNDH	sensorineural diminished hearing
SRU	State Registry of Ukraine of the Persons Affected by the Chornobyl accident
SSEP	somatosensory evoked potentials
SUMO	small ubiquitin-related modifier
TBA	thiobarbituric acid
TCR	T cell receptor
TEM	transmission electron microscopy
TGF-β1	tumor growth factor β1
TKI	tyrosine kinase inhibitor
TLD	term luminescent dosimetry
T-NK cell	natural killer T-cell
TSH	thyroid-stimulating hormone
TUE	transuranium elements
UACOS	Ukraine-American ocular Chornobyl research
Ub	ubiquitin

UICC	Union for International Cancer Control
UN	unspecified types of leukemia
UNSCEAR	United Nations Scientific Committee on the Effects of Atomic Radiation
UZ	«uncontaminated» zone
VA	visual analyzer
VC	lungs vital capacity
VD	vegetative dysfunctions
VeD	vestibular dysfunction
vEGF	vascular endothelium growth factor
VEPCP	visual evoked potentials to chess (chessboard) pattern reversion
VeA	vestibular analyzer
VIQ	verbal IQ
VVD	vegetovascular dystonia
WBC	whole body counter
WHO	World Health Organization
WISC	Wechsler Intelligence Scale for Children
XPA	xeroderma pigmentosum A