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"All-Russian Nikiforov Center of Emergency and Radiation Medicine"

# 30 YEARS AFTER CHERNOBYL:
# PATHOGENETIC MECHANISMS OF DEVELOPMENT OF SOMATIC PATHOLOGY, EXPERIENCE OF MEDICAL ASSISTANCE FOR PARTICIPANTS OF LIQUIDATION OF ACCIDENT AFTERMATH AT THE CHERNOBYL NUCLEAR POWER PLANT

**MONOGRAPH**

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**30 years after Chernobyl: pathogenetic mechanisms of development of somatic pathology, experience of medical assistance for participants of liquidation of accident aftermath at the Chernobyl nuclear power plant: monograph. Issue 2** / Edited by Prof. Aleksanin S.S. - Saint Petersburg: Politekhnika-print, 2018. - 270 p.

The present scientific publication is a result of many-year studies performed by the collective of the Federal State Budget-funded Institution “All-Russian Nikiforov Center of Emergency and radiation Medicine of the Ministry of Emergencies of Russia for investigating the problem of medical consequences caused by the accident at the Chernobyl NPP in long term period. The monograph summarizes the data on peculiarities and pathogenetic mechanisms of development of somatic pathology in the participants of liquidation of accident aftermath at the Chernobyl nuclear power plant and also the experience in providing them specialized medical aid including high-technology medical aid. Special attention is paid to innovative technologies for laboratory diagnostics and treatment of somatic pathology, assessment of psychological status and life problems experienced by participants of liquidation of accident aftermath at the Chernobyl NPP and the population living on radioactively contaminated territories.

The present monograph has been prepared within the limits of the Program of Joint Activities for Overcoming the Aftermath of the Chernobyl catastrophe for the period to 2016. It is intended for the wide circle of specialists: cardiologists, neurologists, internists, surgeons, radiologists, specialists in functional, radiation and laboratory diagnostics, public health officials.

ISBN ?

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## LIST OF ABBREVIATIONS AND SYMBOLS

| | | |
|---|---|---|
| BMD | – | bone mineral densitometry |
| cFT | – | calculated free testosterone |
| COL1α1 | – | receptor of collagen alpha 1 chain, type I |
| $CT_x$ | – | cross-linked C-telopeptide of type I collagen |
| DEXA | – | dual energy X-ray absorptiometry |
| DHEA | – | dehydroepiandrosterone (dehydroepiandrosterone sulfate) |
| DPA | – | dual photon absorptiomentry |
| Dpyr (DPD) | – | Desoxypyridinolin |
| DAI | – | free androgen index |
| IFN | – | Interferon |
| IGF I (II) | – | insulin-like growth factor type I (type II) |
| IL | – | Interleukin |
| ME | – | magnifying endoscopy (visualization system with magnifying optics) |
| NBI | – | narrow band imaging |
| NBI−ME | – | narrow−band imaging system with magnifying endoscopy (NBI using magnification) |
| $NT_x$ | – | cross-linked N-telopeptide of type I collagen |
| OPG | – | Osteoprotegerin |
| P1CP | – | C-terminal serum propeptide of type I collagen |
| P1NP | – | N-terminal serum propeptide of type I collagen |
| PADAM | – | partial androgen deficiency of aging men |
| PGE 2 | – | prostaglandins E2 |
| Pyr | – | Pyridinolin |
| RANK | – | receptor activator of transcription nuclear factor kappa B |
| RANKL | – | receptor activator of transcription nuclear factor kappa B ligand |
| SD | – | standard deviation |
| SHBG | – | sex hormone-binding globulin |
| TGFβ | – | transforming growth factor β |
| VDR-3 | – | vitamin D receptor |
| β-CrossLaps | – | collagen cross-links and C-terminal telopeptides of type I collagen |
| BP | – | blood pressure |
| BPd | – | diastolic blood pressure |
| BPs | – | systolic blood pressure |
| ACE | – | angiotensin-converting enzyme |
| ATMA | – | anti-thyroid microsome antibodies |
| ATgA | – | anti-thyreoglobulin antibodies |
| NPP | – | nuclear power plant |
| MMC | – | military medical commission |
| ARCERM | – | All-Russian Nikiforov Center of Emergency and Radiation Medicine of the Ministry of Emergencies of Russia |
| GERD | – | gastroesophageal reflux disease |
| DHT | – | 5α-dihydrotestosterone |
| DM | – | Densitometry |
| DE | – | dyscirculatory encephalopathy |
| $E_2$ | – | Estradiol |
| GIT | – | gastrointestinal tract |

HRT – hormone replacement therapy
CHD – coronary heart disease
IR – ionizing radiation
BMI – body mass index
PPI – proton pump inhibitor
AHI – anterior horn index
IEA – immune enzyme assay
EDD – end-diastolic dimension
ISIC – intrathyroid stable iodine concentration
QCT – quantitative computed tomography
IM – intestinal metaplasia
CT – computed tomography
CRAF – complex of radiation accident factors
bALP – bone isoenzyme of alkaline phosphatase
LH – luteinizing hormone
LHBB – left His bundle branch
HDL – high density lipoproteins
LDL – low density lipoproteins
VLDL – very low density lipoproteins
LAA – participant of liquidation of accident aftermath
IAEA – International Atomic Energy Agency
ICD-10 – International Statistical Classification of Diseases and Related Health Problems (10th revision)
BMM – bone mineral mass
ICRP – International Commission on Radiological Protection
MO – metabolic osteopathy
BMD – bone mineral density
MRI – magnet-resonance imaging
MSCT – multi-slice spiral computed tomography
IDEC – Interdepartmental Expert Council
UNSCEAR – United Nations Scientific Committee on the Effects of Atomic Radiation
HP – Helicobacter pylori
RSS – radiation safety standards
NRER – National Radiation Epidemiologic Register
NEFA – non-esterified fatty acids
OC – Osteocalcin
ACVA – acute cerebrovascular accident
UNO – United Nations Organization
OP – Osteoporosis
OPS – osteopenic syndrome
GPVR – general peripheral vascular resistance
CCA – common carotid artery
RT-PCR – reverse transcriptase polymerase chain reaction
CBV – circulating blood volume
BE – Barrett esophagus
PTH – parathyroid hormone (intact)
PCR – polymerase chain reaction
TSHR – thyroid-stimulating hormone receptor

RCT – radioactively contaminated territories
TC – thyroid cancer
CNTR – calcitonin receptor
DM-2 – diabetes mellitus type II
SIM – specialized intestinal metaplasia
MCS – mucous coat of stomach
POTS – postural orthostatic tachycardia syndrome
CRP – C-reactive protein
FRO – free radical oxidation
SSBG – sex steroid-binding globulin
STH – somatotropic hormone (growth hormone)
T – total testosterone
Tf – free testosterone
$T_3$ – triiodothyro nine
$T_4$ – Thyroxine
LVPWT – left ventricular posterior wall thickness
TCDG – transcranial dopplerography
TMDF – transmitral diastolic flow
TRAP – tartrate-resistant isoenzyme of acid phosphatase
USODM – ultrasound osteodensitometry
PDM – Photodensitometry
TNF-α – tumor necrosis factor –α
FPS – farnesyl-pyrophosphate synthetase
FSH – follicle-stimulating hormone
CCVD – chronic cerebrovascular disease
COPD – chronic obstructive pulmonary disease
CVD – cerebrovascular diseases
CVD – cerebrovascular diseases
ChNPP – Chernobyl nuclear power plant
HR – heart rate
TG – thyroid gland
ECG – electrocardiography; electrocardiogram

## INTRODUCTION

A radiation accident, which was the greatest in the whole modern history of the mankind and resulted from an explosion of the nuclear reactor at the Chernobyl nuclear power plant (ChNPP), occurred 30 years ago. This catastrophe changed the environment and interrelations in the system "man - nature" for a significant population. It affected the destinies of millions of people living on the vast territories of the former USSR. Radiation exerted an effect on the staff of the power plant, fire fighters and participants of liquidation of the accident aftermath (LAA) and also the population on the radioactively contaminated territories. The Chernobyl catastrophe intruded into the life of more than 20 mln people and caused significant ecologic, social and economic, political, psychological and medical consequences.

Medical consequences of the accident at the ChNPP are a subject of close attention of the medical community in the whole world because the exposure of the population to radiation associated with the Chernobyl catastrophe has no analogues either by its nature, or by its scale. The matter concerns a multi-component and prolonged effect of the ionizing radiation in combination with various factors of social, psychological and anthropogenic origin.

The state policy of the Russian Federation in the field of overcoming the aftermath of the catastrophe at ChNPP is aimed at lowering negative medical, social, ecologic and psychological consequences of this catastrophe for the population and LAA at the ChNPP. Overcoming the aftermath of the accident at the ChNPP required to solve very complex and large-scale problems affecting nearly all spheres of the social life, many aspects of science, technics, production, morals and law. Such problems include medico-demographic, ecologic and rehabilitation, social and economic aspects of overcoming the aftermath of the radiation accident. These problems are solved in RF basing on Federal Targeted Programs and also the targeted programs of the Union State (Russia – Belarus). The large-scale work for health protection and medical and social rehabilitation of citizens exposed to radiation, social and economic rehabilitation of the territories contaminated with radionuclides was carried out over the last decades. And while during the first years after the accident at ChNPP the main forces were directed to minimization of the radiation accident aftermath, in the last decade a problem of rehabilitation of the territories contaminated with radionuclides and biota recovery and also medical measures for health preservation of ChNPP accident liquidators and the population on the contaminated territories becomes increasingly urgent.

Most scientific reports of the last years make an unambiguous conclusion on the complex effect on the human organism of factors associated with the accident at ChNPP among which the role of the radiation component should not be overstated.

In order to improve medical assistance of LAA, the All-Russian Nikiforov Center of Emergency and Radiation Medicine of the Ministry of Emergencies of Russia performs regularly their deep investigation, analyzes the materials of the North-Western Branch of the National Radiation Epidemiologic Register on morbidity, develops methodical materials for adopting regulatory documents on overcoming the medical consequences caused by the accident at ChNPP. The collective of ARCERM published more than 150 research papers and monographs, prepared more than 20 regulatory and methodical documents, defended more than 30 theses only over the period from 2010 to 2017.

Research results extended the range of knowledge about long-term consequences of the large-scale radiation accident. At the same time, the problems of overcoming the aftermath of the accident at ChNPP still remain urgent because years which elapsed after the accident established a

range of unsolved problems. The variety of tasks, first of all, associated with victims' health preservation requires the knowledge of pathogenesis of the somatic pathology in LAA at ChNPP in the long-term period. Just this should be the base for providing addressed specialized medical aid and also developing new diagnostic, treatment and rehabilitation technologies for LAA at ChNPP. The above problems were reflected in the monograph in preparing of which the authors based, first of all, on very rich experience and extensive clinical and research materials. It is intended for physicians (public health officials, epidemiologists, specialists in radiation hygiene and radiologists, physicians of all specialties) participating in medical provision of large-scale technogenic catastrophes and radiation accidents.

## CHAPTER 1

## THE WORK EXPERIENCE OF THE FEDERAL STATE BUDGET-FUNDED INSTITUTION ALL-RUSSIAN NIKOFOROV CENTER OF EMERGENCY AND RADIATION MEDICINE OF THE MINISTRY OF EMERGENCIES OF RUSSIA IN DIAGNOSTICS, TREATMENT AND REHABILITATION OF THE PARTICIPANTS OF LIQUIDATION OF ACCIDENT AFTERMATH AT THE CHERNOBYL NUCLEAR POWER PLANT AND CITIZENS LIVING (HAVING LIVED) ON RADIOACTIVELY CONTAMINATED TERRITORIES

More than 1.7 mln citizens, whose health was affected to some extent by the aftermath of the catastrophe at the Chernobyl NPP, live today on the territory of the Russian Federation. This number includes participants and disabled persons of Chernobyl, children of the 1st and subsequent generations, citizens living permanently on the contaminated territories and evacuated persons, other citizen categories (in total 14 categories). More than 700 thousand people are registered in the Russian State Medical Dosimetric Register; the number of accumulated records on diagnoses of diseases of registered persons is more than 31 mln.

The analysis *of current* morbidity rates in participants of liquidation of accident aftermath at the Chernobyl NPP (hereinafter referred to as LAA at ChNPP) is evidence of the fact that the highest morbidity levels over the last 5 years were observed in the following disease classes: "Diseases of circulatory system", "Diseases of digestive system", "Diseases of musculoskeletal system and connective tissue" and "Diseases of eye and its appendages".

The average number of diseases per 1 LAA at ChNPP increased from 1.4 to 10.5 over the last 20 years. The peculiarity of the somatic pathology in this cohort consists in simultaneous affection of several systems what requires a complex approach to diagnostics and treatment. Their health condition is characterized by polypathology, long course of chronic disease exacerbations accompanied with lowered organism immune system activity levels.

Diseases of the circulatory system (25%), musculoskeletal system (18%) and digestive system (14%) take the leading places in the structure of the somatic pathology revealed in LAA.

Permanent disability (invalidism) is established in more than 50% of LAA at ChNPP, i.e. every second person of them is invalid and among these people subjects with disability group II predominate. Diseases of the circulatory system (55% of cases) and diseases of the nervous system (12%) are the most often causes for disablement.

The role of diseases of the circulatory system and neoplasms increases in the mortality structure of LAA at ChNPP over the last years. Changes in morbidity and primary disablement are

associated, mainly, with diseases of the circulatory system, nervous, musculoskeletal, digestive and respiratory systems.

This causes the need to provide specialized (therapeutical and surgical) and high-technology medical aid to LAA at ChNPP.

More than 30 thousand persons who suffered from radiation accidents, mainly, participants of catastrophe liquidation at the Chernobyl NPP from different constituent entities of the Russian Federation (predominantly, from the North-Western region) underwent expert investigation, diagnostic investigation, received treatment and rehabilitation at our multi-field institution, the Federal State Budget-funded Institution All-Russian Nikiforov Center of Emergency and Radiation Medicine of the Ministry of Emergencies of Russia founded in 1991 during the period of its existence.

Our work is based on complex monitoring of the health condition, introduction and use of new medical technologies for diagnostics, treatment and rehabilitation of victims suffering in radiation accidents and close associations between science and practice.

Over the last 25 years, the employees (who form a large collective of physicians, genetetists, biologists, psychologists, research workers) of our Center have been studying consequences of radiation accidents in liquidators of accident aftermath at the Chernobyl NPP; they carry out health condition monitoring, diagnostics, treatment and medical rehabilitation of these persons.

A North-Western Regional Center of the National Radiation Epidemiologic Register with subregisters of leucoses, thyroid cancer and oncologic register has been functioning since 1993 on the base of ARCERM for monitoring of the health condition of victims who suffered in the accident at ChNPP. A research clinical register including the data on 12.5 thousand LAA was established and is constantly widened basing on results of deep medical investigations of LAA.

The Saint Petersburg Interdepartmental Expert Council for establishing the cause-effect relation between diseases, disablement and death in persons exposed to radiation has been functioning at ARCERM since 1991. Twenty two administrative territories of the Russian Federation were assigned to the Expert Council by spheres of its activities.

More than 5000 applications of citizens were considered over the last 5 years with performing the expert assessment of the cause-effect relation between diseases, disablement and death and exposure to radiation factors; the cause-effect relation with exposure to radiation was established in 54% of citizens having participated in liquidation of the accident aftermath at the ChNPP or in nuclear tests (54% of expert cases with final expert decision).

Diagnostics, treatment and rehabilitation of LAA at ChNPP have been carried out by our Center from 2007 within the “Program of Joint Activities for Overcoming the Aftermath of the Chernobyl Catastrophe within the Limits of the Union State” (Russia-Belarus).

***In 2007-2010 within the “Program of Joint Activities for Overcoming the Aftermath of the Chernobyl Catastrophe within the Limits of the Union State for 2006-2010”*** approved by the Resolution of the Council of Ministers of the Union State No. 33 dated September 26, 2006, our Center provided specialized medical aid to 2535 LAA at ChNPP with different somatic pathology (of cardiological, neurological, pulmonological, endocrinological, gastroenterological profile) using the advanced medical technologies.

The use of advanced medical technologies in the investigation allowed to perform not only treatment but also differential diagnostics of different somatic pathology, determine predictors of

unfavorable cardiovascular prognosis, reveal the most significant factors for progression of cerebrovascular pathology.

Prevalence of Helicobacter pylori gastritis was assessed, high rate of intestinal metaplasia was revealed.

The use of up-to-date investigation technologies made it possible to reveal the earliest stages on oncologic pathology, brain tumors, tuberculosis process reactivation.

Differential diagnostics was performed between chronic obstructive pulmonary disease, chronic bronchitis and asthma what allowed to differentiate the administered therapy.

The assessment of the immune status revealed not only predisposition to development of autoimmune pathology but also presence of secondary immune deficit which is the grounds for administering the replacement and immunostimulating therapy.

A new multi-field specialized clinic No. 2 (for providing high-technology medical aid) for 410 beds (250 beds out of them are intended for surgical patients) was commissioned in 2011; this makes it possible to provide specialized and high-technology medical aid to more than 15 thousand people annually including citizens exposed to radiation because of accidents and catastrophes.

The advanced medical equipment, highly qualified staff (1889 established posts, 54 posts out of them are doctors of science and more than 200 posts are candidates of science) allow the Federal State Budget-funded Institution All-Russian Nikiforov Center of Emergency and Radiation Medicine of the Ministry of Emergencies of Russia to provide specialized and high-technology medical aid in a wide range of pathology including LAA at ChNPP and citizens living on radioactively contaminated territories.

The new multi-field clinic as the whole our center including the Clinic No. 1 for 120 beds and the Outpatient Clinic for 460 visits per shift took part actively in fulfilling the ***"Program of Joint Activities for Overcoming the Aftermath of the Chernobyl Catastrophe within the Limits of the Union State for the period to 2016"***.

Which new work do we carry out within the limits of the Program of Joint Activities?

This work includes, first of all, outpatient screening. This involves diagnostic programs: screening for gastrointestinal cancer pathology, thyroid cancer, urologic cancer pathology, cerebrovascular disorders, genetic disorders, assessment of dysbiosis and dyselementosis, screening for vascular disorders in the lower extremities and carbohydrate metabolism disturbances.

These screenings allow to diagnose early different diseases, first of all, oncologic pathology for formation of the "risk group", further monitoring and inpatient investigation and treatment. More than 1000 LAA at ChNPP and citizens living (having lived) on radioactively contaminated territories undergo such screening investigations annually on the base of out Center.

The second characteristic feature in the activities of ARCERM within the limits of the new program Russia-Belarus consists in directing the attention towards providing not only specialized medical aid to patients with somatic pathology but also high-technology types of medical aid to surgical patients and medical rehabilitation using the medical and diagnostic resources of the new multi-field clinic No. 2 (for providing high-technology medical aid) of ARCERM.

Providing specialized and high-technology medical aid not only to LAA at ChNPP but also citizens having lived (living) on radioactively contaminated territories has been the third characteristic feature in the activities of ARCERM since 2014.

**In 2014 within the limits of the program Russia-Belarus on the order of the Ministry of Emergencies of Russia, our Center provided medical aid to 1785 LAA at ChNPP and citizens having lived (living) on radioactively contaminated territories** including:

- specialized medical aid in outpatient settings [including screening for oncologic pathology, thyroid cancer, genetic disorders, assessment of dysbiosis and dyselementosis, deep investigation before hospitalization to somatic departments, deep investigation (selection) for providing high technology medical aid, investigation before surgical intervention with providing high-technology medical aid] to 1245 patients;

- specialized medical aid in inpatient settings to 386 patients out of citizens living (having lived) on radioactively contaminated territories in Russia and LAA at ChNPP from the North-Western Federal District with different somatic pathology (of cardiovascular, pulmonological, gastroenterological, endocrinological profile) using advanced medical technologies;

- high-technology medical aid to 109 patients and 45 patients received medical rehabilitation;

- our Center prepared and tested unified medical and diagnostic standards for LAA at Chernobyl NPP and residents of radioactively contaminated territories in Russia and Belarus who suffer from chronic obstructive pulmonary disease, coronary heart disease, dyscirculatory encephalopathy and chronic atrophic gastritis.

Our Center provided medical aid to 1234 LAA at ChNPP and citizens living (having lived) on radioactively contaminated territories in Russia in 2015 within the limits of the program Russia - Belarus on the order of the Ministry of Emergencies of Russia. And a significant portion of this aid was provided in inpatient settings using the advanced medical and diagnostic equipment by very different pathology profiles including expensive high-technology medical aid (55 patients) and early postoperative medical rehabilitation.

So, specialized medical aid in outpatient settings was provided to 885 patients out of LAA at ChNPP and citizens living (having lived) on radioactively contaminated territories in 2015. Specialized medical aid (to subjects with therapeutic and surgical pathology) in inpatient settings was provided to 294 patients of above categories. High-technology medical aid (in neurosurgery, traumatology and orthopedics, ophthalmology, cardiovascular surgery, oncology) was provided to 55 patients.

In 2015 our Center developed and tested methodical recommendations on laboratory diagnostics of microecological status (microbiota) using the method of chromato-mass-spectrometry in citizens exposed to radiation because of the accident at ChNPP.

It should be mentioned that amounts of financing of medical aid are very low with high need of LAA at ChNPP in specialized and high-technology types of medical aid.

Our Center provided specialized and high-technology medical aid to 1175 LAA at ChNPP and citizens having lived (living) on radioactively contaminated territories in 2016.

Thus, ARCERM performed complex diagnostics and specialized treatment in more than 4000 LAA at ChNPP and citizens having lived (living) on radioactively contaminated territories in 2014-2016 as per the “Program of Joint Activities for Overcoming the Aftermath of the Chernobyl Catastrophe within the Limits of the Union State for the period to 2016”.

Besides that, in 2016 within the limits of a separate measure of the Union State “Providing complex medical aid to certain citizen categories of Belarus and Russia exposed to radiation

because of the catastrophe at the Chernobyl NPP", our Center provided specialized medical aid to 753 LAA at ChNPP and citizens living (having lived) on radioactively contaminated territories; 118 persons out of this number received high technology medical aid and 492 subjects received specialized medical aid using advanced medical technologies and 143 patients underwent medical rehabilitation in inpatient settings.

*The results obtained during many-year follow-up of LAA at ChNPN were summarized in methodical recommendations, cycles of lectures and monographs*. The employees of our Center prepared the following methodical recommendations:

"Antioxidant therapy in the treatment of somatic pathology in participants of liquidation of accident aftermath at the Chernobyl NPP" (2007).

"Cancer prevention in participants of liquidation of accident aftermath at the Chernobyl NPP suffering from gastric diseases" (2008).

"Diagnostics and treatment of sleep disorders in participants of liquidation of accident aftermath at the Chernobyl NPP suffering from somatic pathology" (2008).

"Diagnostics and methods fr correction of metabolic syndrome in participants of liquidation of accident aftermath at the Chernobyl NPP" (2008).

"Clinical and immunologic aspects of diagnostics and differential diagnostics of autoimmune pancreatitis in participants of liquidation of accident aftermath at the Chernobyl NPP and modern approaches to their treatment" (2009).

"Modern diagnostics and treatment of acid-dependent diseases in liquidators of accident aftermath at the Chernobyl NPP" (2010).

Komlev A.D., Kuzyaev A.I., Kolosova M.V., Markova I.A. The experience in long-term use of Tiotropium Bromide (Spiriva) in participants of liquidation of accident aftermath at the Chernobyl NPP suffering from chronic obstructive pulmonary disease (methodical recommend-ations) / edited by prof. Aleksanin S.S. - Saint Petersburg: Politekhnika-Service, 2011. - 20 p.

Khirmanov V.N., Kireyenkov I.S., Doinikov D.N., Pavlysh E.F. Heart valvular disease in participants of liquidation of accident aftermath at the Chernobyl NPP: screening, verification, principles of conservative and surgical treatment: Methodical recommendations / Edited by prof. Aleksanin S.S. - Saint Petersburg: Politekhnika-Service, 2011. - 42 p.

Shantyr I.I., Rybnikov V.Yu., Rodionov G.G. et al. Laboratory diagnostics of microecologic status (microbiota) using the method of chromato-mass-spectrometry in citizens exposed to radiation because of the accident at ChNPP: methodical recommendations. - Saint Petersburg: Politekhnika-Service, 2015.

*The following cycles of lectures and manuals were prepared, published and are used in the medical and diagnostic work and educational process:*

"The latest technologies for diagnostics of somatic pathology" (2008).

'Modern medical technologies in diagnostics and treatment of somatic pathology in participants of liquidation of accident aftermath at the Chernobyl NPP: theory and practice" (2009).

Radiation medicine: manual / Grebenyuk A.N., Legeza V.I., Yevdokimov V.I., Sidorov D.A.; edited by Aleksanin S.S., Grebenyuk A.N.; All-Russian Nikiforov Center of Emergency and Radiation Medicine of the Ministry of Emergencies of Russia. - Saint Petersburg: Politekhnika-Service, 2013. - Part I: Fundamentals of biological effect exerted by radiation. - 124 p.

Radiation medicine: manual/ Grebenyuk A.N., Legeza V.I., Yevdokimov V.I., Salukhov V.V.,

Timoshevsky A.A.; edited by Aleksanin S.S., Grebenyuk A.N.; All-Russian Nikiforov Center of Emergency and Radiation Medicine of the Ministry of Emergencies of Russia. - Saint Petersburg: Politekhnika-Service, 2013. - Part 2: Clinical picture, prevention and treatment of radiation damages. - 156 p.

Radiation medicine: manual / Baltrukova T.B., Barinov V.A., Grebenyuk A.N., Yevdokmov V.I., Legeza V.I., Tarita V.A.; edited by Aleksanin S.S., Grebenyuk A.N. - Saint Petersburg: Politekhnika-Service, 2013. - Part 3: Principles of radiation safety. - 151 p.

Korolev A.A., Sobolevskaya Yu.A., Rudakova S.M., Kukelev Yu.V., Kamayeva A.V., Shipulina G.V., Martynyuk M.D. Medical rehabilitation: manual / edited by Aleksanin S.S.; All-Russian Nikiforov Center of Emergency and Radiation Medicine of the Ministry of Emergencies of Russia. - Saint Petersburg: Politekhnika-Service, 2014 - 184 p.

*The following bibliographic indices were prepared and published:*

Yevdokimov V.I. Abstracts of theses in the field of liquidation of accident aftermath at the Chenobyl NPP (1990-2010): bibliographic index / Yevdokimov V.I.; All-Russian Nikiforov Center of Emergency and Radiation Medicine of the Ministry of Emergencies of Russia. - Saint Petersburg: Politekhnika-Service, 2011. - 117 p. - (Radiation. Radioactivity. Chernobyl; issue 1).

Yevdokimov V.I. Liquidation of accident aftermath at the Chenobyl NPP: bibliographic index of books (1987 - 2010) / Yevdokimov V.I., Yermolenko T.V.; All-Russian Nikiforov Center of Emergency and Radiation Medicine of the Ministry of Emergencies of Russia. - Saint Petersburg: Politekhnika-Service, 2011. - 158 p. - (Radiation. Radioactivity. Chernobyl; issue 3).

Yevdokimov V.I. Neutralization of radioactive substances, prevention and treatment of radiation damages: annotated index of home patents for inventions (1994-2010); All-Russian Nikiforov Center of Emergency and Radiation Medicine of the Ministry of Emergencies of Russia. - Saint Petersburg: Politekhnika-Service, 2011. - 196 p. - (Radiation. Radioactivity. Chernobyl; issue 2, Part 2).

Yevdokimov V.I. Scientometric analysis of information materials on liquidation of accident aftermath at the Chernobyl NPP (1987 - 2010) / Yevdokimov V.I., Yermolenko T.V.; All-Russian Nikiforov Center of Emergency and Radiation Medicine of the Ministry of Emergencies of Russia. - Saint Petersburg: Politekhnika-Service, 2012.

*The following monographs were prepared and published:*

Rybnikov V.Yu., Marchenko T.A., Melnitskaya T.B., Simonov A.V. Information and psychologic safety and social-psychologic rehabilitation and adaptation of the population. Monograph. Russian-Byelorussian Information Center for Problems of Overcoming the Aftermath of the Chernobyl Catastrophe. - M., 2008. - 81 p.

Khirmanov V.N., Tikhomirova O.V. Metabolic and hemodynamic mechanisms of development of cardiac ad cerebral diseases in participants of liquidation of accident aftermath at the Chernobyl NPP in long-term period / edited by Aleksanin S.S. - Moscow: Politekhnika-Service, 2010. - 344 p.

25 years after Chernobyl: health condition, pathogenetic mechanisms, experience of medical assistance for liquidators of accident aftermath at the Chernobyl nuclear power plant: Manual for physicians / edited by prof. Aleksanin S.S. - Saint Petersburg: ELBI-SPb, 2011. - 736 p.

Melnitskaya T.B., Rybnikov V.Yu., Belykh T.V. Psychological culture conception of life safety of the population on radioactively contaminated territories. Monograph. - Saint Petersburg: Politekhnika-Service, 2014. - 169 p.

Melnitskaya T.B., Rybnikov V.Yu., Khavylo A.V. Social and psychological life problems and

stress reactions of the population in long-term period after the accident at the Chernobyl NPP. - Moscow: Politekhnika-Service, 2015. - 148 p.

# CHAPTER 2

# CLINICAL LABORATORY DIAGNOSTICS IN ASSESSMENT OF THE HEALTH CONDITION OF PARTICIPANTS OF LIQUIDATION OF ACCIDENT AFTERMATH AT THE CHERNOBYL NUCLEAR POWER PLANT

## 2.1. CLINICAL LABORATORY DIAGNOSTICS IN THE INVESTIGATION AND TREATMENT PROGRAMS FOR PARTICIPANTS OF LIQUIDATION OF ACCIDENT AFTERMATH AT THE CHERNOBYL NUCLEAR POWER PLANT SUFFERING FROM DISEASES OF THE CIRCULATORY SYSTEM

Diagnostics, treatment and prevention of cardiovascular and cerebrovascular diseases take the central place among medical problems associated with victims who suffered during accident liquidation at the Chernobyl nuclear power plant (ChNPP). Epidemiologic studies evidence the leading role of the cardiovascular system pathology in LAA at ChNPP. Gradual growth of the number of persons with chronic vascular pathology and increase of morbidity with CHD are observed lately. Besides that, diseases of the cardiovascular system (CVS) are one of the main causes for death of LAA (25 years after Chernobyl..., 2011).

Pathogenesis of vascular diseases in liquidators of accident aftermath at ChNPP exposed to low radiation doses remains debatable what makes it difficult to distinguish the most significant diagnostic criteria which would allow to follow the process changes, administer the pathogenetic therapy and estimate treatment efficiency. Some authors report a damaging effect exerted by radiation on blood vessels what results in development of essential hypertension (EH) and CHD. Early development of carotid atherosclerosis and high rate of EH and CHD in liquidators are reported. Dyscirculatory encephalopathy is a dominating concomitant pathology in LAA with diseases of CVS what suggests common mechanisms for development of vascular pathology both in the brain and heart. Many-year studies performed at ARCERM demonstrate that in liquidators of accident aftermath specific molecular mechanisms form which are able to exert a pronounced effect on the vascular endothelium what may be materialized in its dysfunction, activation and damage and, therefore, also in development of vascular pathology. At the same time, there is no sufficient data which allows to associate undoubtedly variants of vascular pathology with endothelial dysfunction and damage markers. Solution of this problem, which is insufficiently studied both in our country and abroad, will make it possible to substantiate measures for prevention of vascular diseases in liquidators of accident aftermath at ChNPP.

Close attention is being paid to investigation and treatment of liquidators suffering from diseases of the circulatory system at ARCERM within the limits of the Federal Targeted Program over many years. The list of diagnostic investigations is extended constantly in accordance with recommendations of professional communities and advances of medical science.

A significant place in the investigation programs for liquidators suffering from diseases of the circulatory system (DCS) is taken by laboratory tests results of which are used with the purpose of

diagnostics, for monitoring of disease course, assessment of treatment efficiency and also for establishing the mechanisms of development of vascular pathology in this patient category. The investigation of more than 60 laboratory parameters makes it possible for a clinician to assess closely the metabolism and oxygen regimen state, disturbed organ functions, diagnose metabolic syndrome and concomitant pathology, prescribe the pathogenetically substantiated therapy and follow changes in the test parameters. At the same time, a large body of diagnostic information makes it difficult to select markers of metabolic disorders which are the most significant for the patient. Therefore, an important task for clinical laboratory diagnostics is to substantiate the use of the most significant laboratory parameters basing on analysis of investigation results of numerous liquidator groups with DCS taking into account findings of clinical examination, concomitant pathology and administered treatment.

As coronary and cerebral circulation disorders develop either in subjects with atherosclerotic and hypertonic vascular damage or because of changed vascular tone, revealing the mechanisms of vascular pathology is based on investigation of those metabolism parameters which underlie the development of atherosclerosis, vascular endothelium permeability and intactness disturbances and vascular tone regulation. Therefore, parameters of the hemostasis system, fibrinolysis, lipid metabolism, homocysteine metabolism, free radical oxidation processes, inflammation reactions, endothelium condition were investigated in liquidators with vascular pathology, i.e. CHD, EH and CCVD.

More than 350 liquidators of the accident at ChNPP suffering from DCS were investigated in the period from 2004 to 2014.

### *Assessment of dyslipoproteinemia as risk factor for cardiovascular and cerebrovascular diseases in liquidators*

Atherosclerosis resulting from disturbed lipid metabolism is considered, undoubtedly, one of the main factors for development of vascular pathology. Diagnostic significance of lipid metabolism parameters and assessment of their atherogenicity are studied, mainly, in patients with diseases of the cardiovascular system. Numerous epidemiological studies showed convincingly an association between the cholesterol level in the blood plasma and development of CHD. Such investigations in patients with cerebrovascular diseases are significantly less numerous but they also demonstrate etiological role of atherosclerosis and dyslipidemia in development of vascular diseases of the brain. According to modern concepts, assessment of atherogenicity is not limited by determination of total cholesterol but includes measurement of cholesterol level of different lipoprotein classes, triglycerides, lipoprotein apoproteins, oxidized lipoprotein forms and also inflammatory process markers. This is caused by established independent significance of these parameters as risk factors of atherosclerosis. Atherogenicity risk increases in case of low levels of high density lipoproteins (HDL), hypertriglyceridemia, increased lipoprotein (a) content (LPA). A special role in increased atherosclerosis risk belongs to oxidized lipoproteins (LP) which are produced as a result of free radical attack.

We investigated the following lipid metabolism parameters in order to elucidate the role of disturbed lipid metabolism in LAA in development of vascular diseases: total cholesterol, cholesterol of high, low and very low density lipoproteins, triglycerides, coefficient of atherogenicity, apoprotein A and apoprotein B. All parameters were measured in the blood serum of LAA with diagnoses of coronary heart disease (CHD), essential hypertension and dyscirculatory

encephalopathy (DE) after 12-hour fasting using a biochemical analyzer DxC 600 ("Beckman-Coulter", USA).

The nature of changes in lipid metabolism parameters during the whole investigation period remained constant though the age of investigated patients increased. Similar to earlier years, the patients investigated in 2014 had no differences in dyslipidemia degree when patients with mainly cardiovascular diseases were compared to those with cerebrovascular diseases.

Dyslipidemia is permanently revealed approximately in 70% of LAA. The content of total cholesterol, HDL-, LDL- and VLDL-cholesterol, triglycerides remained on average within the normal range in all liquidators. And value distribution showed that cholesterol content exceeded the upper limit of the normal range in 40.5% of LAA but this value was higher than 7.0 mmol/l only in 10.1%. HDL-cholesterol level was lowered in 29.8% of LAA. Coefficient of atherogenicity was higher than 3.6 in a half of patients, and it was within the normal range or insignificantly increased in others.

Changes in lipoprotein apoprotein content and ratio were noticeable. The data on measurement of lipoprotein apoprotein levels performed in the period from 2004 to 2006 showed that while apo A (HDL-protein) level was within the normal range in all investigated patients suffering from DCS, apo B (LDL and VLDL protein) level, which is considered as an independent risk factor of atherosclerosis, was increased in 68% of patients in the LAA group. Therefore, the ratio of apo A to apo B was lower than 1.5 in most patients both the cardiovascular and cerebrovascular diseases.

The liquidator group investigated in 2014-2015 had on average lower apo B content (1.08±0.04 g/l vs. 1.52±0.06 g/l in 2004 (reference range: 0.46–1.42 g/l)) and apo A content (1.35±0.04 g/l vs. 1.86±0.08 g/l (reference range: 0.73–2.1 g/l)). But apo A / apo B ratio remained the same and was on average 1.34±0.05 (1.32±0.09 in 2004-2006), i.e. apo A / apo B ratio was lower than 1.5 in about 70% of all subjects during the whole follow-up period of this patient category.

While analyzing the obtained results, one should evidently take into account liquidators' age but to a greater extent the fact that implementation of many-year deep investigation programs results in the larger number of liquidators for whom it is possible to receive the treatment based on medical care standards and advances of modern medicine.

Sixty five percent of liquidators with DCS undergoing the investigation and treatment at ARCERM lately received the therapy using statins, beta-blockers, ACE inhibitors, anticoagulants, antiaggregants, Ca-channel blockers, and 35% did not take any drugs. The lowest total cholesterol, LDL-cholesterol levels and CA were revealed regularly just in the patient group receiving only statins or statins in combination with beta-blockers. The most pronounced atherogenic shifts were observed in patients receiving no pharmacotherapy or receiving only ACE inhibitors and beta-blockers. Administration of statins had a pronounced effect on apo A / apo B ratio (1.63±0.13 (median: 1.7)) due to increased apo A-protein content. But HDL-cholesterol level did not show any dependence on the pharmacotherapy nature. The median of value distribution of apo A / apo B ratio was 1.2 in the patient groups receiving no pharmacotherapy or receiving only ACE inhibitors and beta-blockers, i.e. most patients of these groups had apoprotein ratio below 1.5.

Thus, apo A / apo B ratio is one of laboratory indicators of atherogenicity which are observed the most often in liquidators with DCS. But just this parameter is used in the daily clinical practice

significantly rarer that other ones characterizing atherogenic shifts. This is associated partially with high correlation of apoprotein level and their ratio with all lipidogram parameters irrespective of pharmacotherapy nature. Therefore, coefficient of atherogenicity (CA) is the main informative parameter in the assessment of dyslipidemia degree in the LAA group and the apo A / apo B ratio may be used for patients with minimum changes in the lipid metabolism parameters having the high risk of atherosclerosis basing on the findings of the clinical and instrumental investigation.

The results of our previous studies demonstrated the dependence of atherogenic shifts on clinical signs of the disease, i.e. the deeper the pathologic process was, the more pronounced changes in lipid metabolism parameters were (Zybina N.N. et., 2011). In contrast to earlier studies, the patient group with DCS investigated in 2014-2015 had no considerable differences in the lipid spectrum depending on the disease severity. It was possible that this was caused with increasing age of investigated liquidators.

Characteristic features in just liquidators consist in considerable changes in lipoprotein apoprotein composition, increased apoprotein B content forming the structure of the most atherogenic lipoproteins and lowering of apo A / apo B ratio which is considered as an independent and serious risk marker of vascular atherosclerosis. It seems also important that lipid metabolism disorders have the single-type nature both in the groups with cardiovascular and cerebrovascular pathology.

### *Diagnostics of plasma and thrombocyte hemostasis disorders in liquidators with cardiovascular and cerebrovascular diseases*

Disturbed hemostatic reactions play the leading role in formation of DCS. Thromboses are the main cause for complications in DCS. They result from excessive coagulation mechanism activation, disturbed state and functioning of the vascular wall, slowed down blood flow and form ischemic vascular events. In addition to disturbed lipid metabolism, a significant role in atherosclerotic vascular involvement is played by hemostasis system disorders which also may have independent significance for the development of vascular pathology as the factors favoring lowered blood flow because of increased blood viscosity and thrombus formation.

Therefore and also taking into account the significant prevalence of DCS in this patient category, it is urgent to develop problems of laboratory diagnostics with finding the optimum methods for revealing hemostatic disorders in liquidators of the accident at the Chernobyl nuclear power plant in a long-term period and for controlling the administered therapy.

Any changes in plasma hemostasis parameters were not revealed in the liquidator group with DCS investigated in the period from 2004 to 2008. Liquidators also had no significant changes in the anticoagulant system parameters as compared to the normal ranges. But 30% of liquidators had low antithrombin III levels and 25% had low concentration of protein C, the important anticoagulant system component, and the higher fibrinogen content what in combination may become a precondition for increased thrombus formation and lowered thromboresistance in every third patient with the vascular pathology. The thrombocyte hemostasis parameters also did not differ from the normal ranges on average. The analysis of value distribution showed that more than 50% had some or other thrombocyte aggregation disturbances. Increased spontaneous thrombocyte aggregation was observed the most often what indicated the presence in the blood flow of active

thrombocytes able to thrombus formation. Forty three percent of patients had increased aggregation to low aggregation inductor concentrations and more than 60% had increased aggregation to collagen what was an indirect indicator of the vascular endothelium damage.

The shifts in the hemostasis system were of one type for all patients with the vascular pathology irrespective of its localization, similarly to revealed changes in the lipid metabolism.

Our recent studies found that liquidators of the accident at the Chernobyl NPP with diseases of the circulatory system (DCS) had high functional thrombocyte activity which was manifested by significantly increased number of active thrombocytes expressing P-selectin on their surface and also by significantly enlarged aggregates in the non-induced thrombocyte aggregation test. Besides that, we revealed that the increased number of thrombocytes expressing P-selectin at the level of more than 10% was observed more often in liquidators with DCS (47.1%) as compared to patients from the non-liquidator group (17.4%). Enlarged thrombocyte aggregates (higher than 1.5 U) in the test without aggregation inductors in patients of the test group was revealed in 39.4% of cases while exceeded upper limit of the reference range was observed in none of the subjects in the control group.

The group of subjects suffering for DCS but not having participated in liquidation of the accident at the Chernobyl NPP on the whole had lower functional thrombocyte activity as compared both to the group of healthy subjects and to liquidators. This was manifested in significantly lowered parameters of ADP- and adrenalin-induced thrombocyte aggregation (thrombocyte aggregate size, thrombocyte aggregation rate, percentage of thrombocytes involved in aggregation) and explained by the more active antiaggregant therapy administered in the control group.

The comparative analysis of thrombocyte activity parameters in patients with DCS taking into account the risk of cardiovascular complications (CVC) showed that liquidators with moderate and high vascular risk had the high thrombocyte activity which was manifested in significantly increased number of thrombocytes expressing P-selectin and enlarged thrombocyte aggregates in the test without induction as compared both to the group of healthy subjects and to control group.

An undoubted cause for these differences consists in more active use of antihypertensive (71.4% of patients) and antiaggregant (40% of patients) drugs what was also confirmed by further follow-up of patients in the process of the treatment and correction of the pathogenetic therapy.

The analysis of the influence exerted by risk factors of cardiovascular diseases on the functional thrombocyte activity parameters showed that high functional activity was typical of liquidators with arterial hypertension and patients aged above 55 years. The control of the groups with other risk factors of vascular diseases (obesity, dyslipidemia, smoking, disturbed carbohydrate metabolism) and with brachiocephalic artery stenosis within the test group did not reveal any statistically significant differences.

At the same time, the correlation analysis of clinical laboratory parameters revealed strong and confident associations between thrombocyte number expressing P-selectin and intima-media thickness ($r=0.49$, $p=0.03$), between cholesterol content and thrombocyte aggregate size when using high ADP inductor concentrations ($r=0.61$, $p=0.003$), between coefficient of atherogenicity and thrombocyte aggregate size when using low ADP inductor concentrations ($r=0.40$, $p=0.04$) and the negative correlation between HDL-cholesterol and thrombocyte aggregation rate when using low ADP inductor concentrations ($r=0.57$, $p =0.009$).

The follow-up of liquidators with DCS, whose pathogenetic therapy was corrected, revealed considerably improved thrombocyte activity parameters in patients with moderate and high vascular risk what was evident by lowered thrombocyte number expressing P-selectin on their surface and lowered induced thrombocyte aggregation parameters.

The results of the comparative analysis of plasma and endothelial activation markers showed that liquidators with DCS had endothelium dysfunction and plasma hemostasis activation. It should be mentioned that the results of screening coagulation tests in the test groups were with the reference range and did not differ significantly. Inability of these tests to reveal increased coagulation activity and thrombinemia is known.

Out of analyzed parameters, the most significant changes were observed in fibrinogen and tissue plasminogen activator antigen concentrations. We did not find any considerable changes in D-dimer level in spite of the fact that many studies showed its increased concentration in patients with cardiovascular diseases and its prognostic significance not only regarding vascular events but also death.

Hyperfibrinogenemia in the test group was observed significantly more often as compared to non-liquidators: 42.3% vs. 15.3%, respectively, and increased tissue plasminogen activator (t-PA) concentration in the blood plasma exceeding 8.0 ng/ml in liquidators was observed in 48.3% of cases while the exceeded upper limit of the reference range was not found in the control group. The most pronounced endothelium dysfunction was observed in liquidators with disturbed carbohydrate metabolism what corresponded to pathogenetic mechanisms of vascular disorders in diabetes mellitus. The concentration ratio of t-PA and plasminogen activator inhibitor (PAI) in the blood plasma was shifted towards intensified fibrinolysis inhibition process.

Endothelium dysfunction manifested in significantly increased t-PA concentration in the blood plasma was typical of liquidators with high and moderate risk of CVC. Liquidators with the high vascular risk had increased t-PA concentration in the blood plasma significantly more often as compared to liquidators with moderate vascular risk (80 vs. 42.8%, respectively). These changes were eliminated in the process of therapy correction.

The comparison of groups with different vascular risks showed that significantly increased fibrinogen and fibrinopeptide A (FPA) concentration in the blood plasma was typical of liquidators with the highest vascular risk as compared to healthy donors. The FPA concentration in the blood plasma of more than 12.0 ng/ml was observed in liquidators of this group significantly more often (35.7%) as compared to liquidators with moderate (13.3%) and high vascular risks (10.0%).

In spite of absence of a considerable difference in Willebrand factor content which is considered as one of the leading biochemical markers of endothelium dysfunction, the correlation analysis revealed a statistically significant positive association between Willebrand factor and intima-media complex ($r=0.48$, $p=0.03$) in the compared groups. Besides that, a positive significant correlation was revealed between the PAI antigen and body mass index.

This data confirms the interrelation between morphological and functional laboratory parameters of the vascular wall condition and makes the latter an important evidence of endothelium dysfunction. Any other important differences in coagulation activation and endothelium dysfunction markers in the process of correction of the pathogenetic therapy were not revealed.

Basing of these studies we characterized the peculiarities of the hemostasis system in patients with DCS who participated in liquidation of accident aftermath at the Chernobyl NPP, determined the most informative laboratory methods for assessment of the vascular-thrombocyte and plasma hemostasis components which were included in the investigation program for this patient group (Fig. 2.1). These parameters may be used both for primary and single assessment and in the follow-up and estimation of the therapy efficiency over time.

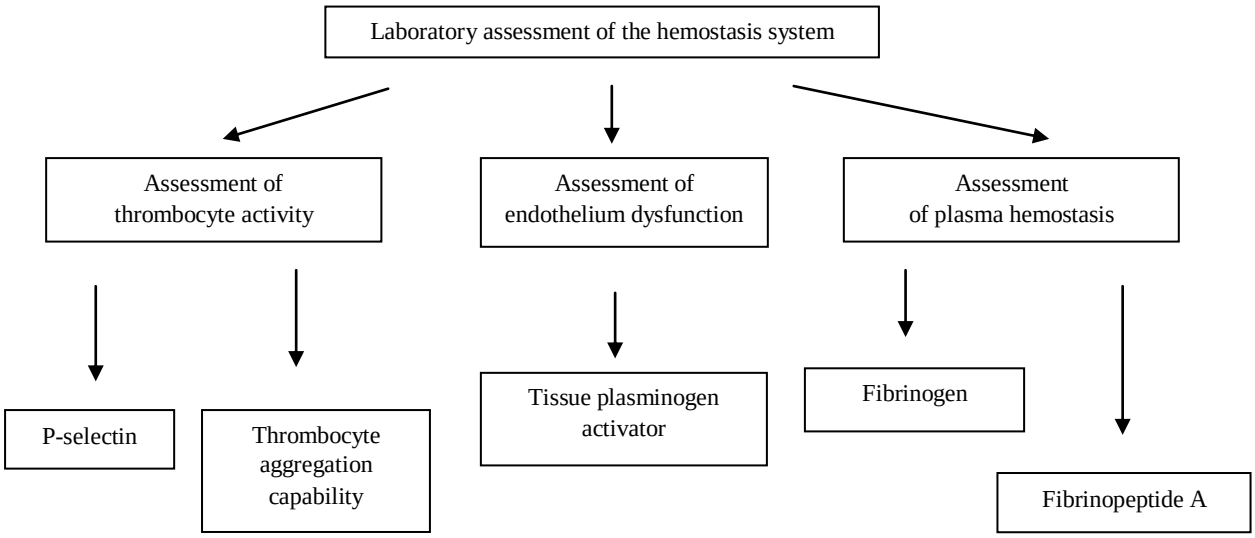


Fig. 2.1. Laboratory investigation and hemostasis system assessment program for patients with DCS who participated in liquidation of accident aftermath at the Chernobyl NPP.

### *The potential of laboratory diagnostics of vascular endothelium damage in liquidators*

The lowered local blood flow, reduced heart or brain blood supply with subsequent function or organic affection of the organ are the main cause for onset and development of the cardiovascular and cerebrovascular pathology. The thrombus formation process, which as a leading factor in vascular lumen decrease, is closely associated with damage of the vascular internal membrane. The integrity damage of the endothelium, which fulfils important homeostatic functions in the normal condition, may become a starting point in the sequence of pathophysiologic reactions resulting in small vessel occlusion what is observed in liquidators.

Liquidators with the vascular pathology develop a whole complex of pathochemical changes, which are evidence of the key role of endothelium damage as an important pathogenetic factor of this pathology in liquidators.

Free oxygen radicals and some cytokines, hyperproduction of which is constantly revealed in liquidators with the vascular pathology (Zybina N.N. et al., 2011) can interact directly with endothelium cells damaging it and changing the vascular tone. The inflammation, signs of which include increased C-reactive protein and pro-inflammatory cytokine levels in liquidators, is also a powerful factor of endothelium damage. Disturbed lipoprotein apoprotein metabolism typical of liquidators exhibits its atherogenic properties also by the influence on the vascular endothelium.

Disturbed homocysteine (HC) metabolism revealed by us in 24% of liquidators is a powerful factor for endothelium damage.

Clinical trials revealed the following proatherogenic effects of increased homocysteine level: development of endothelium dysfunction; increased circulation adhesion molecule level; effect of

thrombus formation process; intensified cholesterol synthesis in hepatic cells; intensified lipid peroxide oxidation (Khibutia M.Sh., Shevchenko O.P., 2004).

The liquidators (140 subjects) with the cardiovascular (EH and CHD) and cerebrovascular (CCVD) pathology investigated by us had HC concentration in the blood plasma of 15.0±0.6 μmol/l (median (Me): 14.2 μmol/l) what exceeded the set discrimination normal value for this parameter.

One may not rule out that increased HC level in males-liquidators results from smoking as nicotine lowers the blood pyridoxal phosphate (vitamin B6) content. As hyperhomocysteinemia may be corrected by administration of folic acid and vitamins of group B, timely revealing of increased HC content in the liquidators' blood plasma may promote lowered risk of complications caused by vascular diseases.

Endothelin-1 (ET-1) is a significant marker of endothelium dysfunction; its synthesis is regulated by several factors which are important in functioning of the cardiovascular system. For example, such factors as vascular wall pulse distension, its damage and pH intensify ET-1 production. Physical activities and hypoxia increase its myocardial expression. Oxidized VLDL, glucose, insulin and thrombin stimulate ET-1 synthesis. ET-1 synthesis is also stimulated by such vasoconstrictors as angiotensin-2, catecholamines, growth factors and cytokines. Nitrogen oxide, prostacyclin, estrogens and atrial natriuretic peptide inhibit ET-1 synthesis.

It is especially important that ET-1 gene expression and its synthesis are stimulated by increased low density lipoprotein content. Increased ET-1 concentrations are revealed in atherosclerotic plaques of human vessels what is evidence of the fact that ET-1 may play an important role in the pathogenesis of atherosclerosis and coronary heart disease.

The investigation results of liquidators showed that the patient group with EH and CHD had ET-1 content of 5.46±0.37 pmol/l and this parameter value was 5.61±1.63 pmol/l in the group with CCVD what was significantly higher that the values in the group of healthy subjects (1.62±0.75 pmol/l, $P < 0.05$).

Willebrand factor is the most known marker of vascular damage. It belongs to molecules secreted by endothelium and mediates the initial stage of thrombocyte adhesion. A significantly increased Willebrand factor level in the blood serum is revealed in patients with diseases associated with acute and chronic endothelium damage (e.g., diabetes mellitus, atherosclerosis). Its increased content is evidence of endothelium dysfunction.

According to our data, 23.5% of liquidators with vascular pathology has increased Willebrand factor activity. Besides that, correlation analysis showed a significant positive association between Willebrand factor activity and ADP-induced thrombocyte aggregation (r=0.67), LPO product content in the blood serum (r=0.47), active oxygen form (AOF) production by neutrophils and mononuclear leukocytes of the peripheral blood (r=0.49 and r=0.37, respectively) and also coefficient of atherogenicity (r=0.32). This data confirms the supposition that more pronounced atherogenic shifts, increased functional thrombocyte activity and AOF hyperproduction by leukocytes of the peripheral blood in liquidators with the vascular pathology serve as actual causes for vascular endothelium damage which, in its turn, forms a morphologic base for lowered coronary and cerebral blood flow and, finally, results in development of the cardiovascular and cerebrovascular pathology.

This is also evidenced by revealed correlations between the tested metabolic parameters and depression level, thinking and cognitive function disorders, worsened visual memory, lowered cerebral functions. Thus, e.g., a significant inversely proportional dependence was revealed between

HDL, apoprotein B, total cholesterol, LPO product levels and coefficient of atherogenicity and the depression level, thinking disorder, disturbed functional brain activity, i.e., aggravation of atherogenic shifts and FRO process activation resulted in development of depressive conditions, worsened cognitive functions and memory.

This data confirms involvement of the studied mechanisms in development of the vascular pathology and allows to develop pathogenetic methods for prevention and medicinal correction of the cardiovascular and cerebrovascular pathology.

### *Metabolic syndrome markers in liquidators of the accident at the Chernobyl NPP*

Metabolic syndrome is an integral risk factor of cardiovascular diseases what determines its great clinical significance. The presence of this pathologic condition increases the risk of coronary heart disease 3-4 times and the risk of death from it 2.5-3 times, risk of death because of any cause (total mortality) 2 times; the risk of diabetes mellitus type 2 increases 3-6 times as compared to patients without metabolic disorders (Flegal K.M., 2012; Martin B. J., 2013). This fact was reflected in the recommendations of the All-Russian Scientific Society of Cardiologists (ARNSC) on prevention, diagnostics and treatment of arterial hypertension, in which metabolic syndrome was included in the stratification system of cardiovascular risk along with diabetes mellitus (Diagnostics and treatment..., 2009). The role of metabolic syndrome in the pathogenesis of cerebrovascular diseases is discussed much rarer. But the need to study metabolic syndrome markers also in patients with cerebrovascular pathology is evident because the mechanisms of vascular pathology are common.

The data obtained at ALCERM is evidence of high (75%) prevalence of metabolic syndrome in liquidators with DCS. More than a half (55.6%) of liquidators with metabolic syndrome have clinically pronounced obesity. Almost all these patients have arterial hypertension (95%) (Khirmanov V.N. et al., 2011).

The high prevalence of metabolic syndrome in the liquidator group may be associated only partly with elderly age of these patients which was on average 66 years, although most subjects had typical risk factors including hypodynamia, incorrect nutrition and smoking. Along with genetic predisposition and also a complex of specific factors associated with the radiation accident, these factors favored the development of metabolic syndrome.

The investigation results of liquidators with metabolic syndrome and predominantly cardiovascular pathology were presented in the monograph “25 years after Chernobyl: health condition, pathogenetic mechanisms, experience of medical assistance for liquidators of accident aftermath at the Chernobyl nuclear power plant” (2011). Lately we analyzed the laboratory markers of metabolic syndrome in a group comprising 74 liquidators with CCVD.

Similarly to patients with the cardiac pathology, liquidators with CCVD and metabolic syndrome had a body mass index (BMI) on average of 30.3±0.6 kg/m² (Me: 30.5 [28.4; 32.0]) what was considerably higher than that in patients without metabolic syndrome (25.3±0.6) kg/m² (Me: 24.7 [24.0; 26.5]). And 53.2% of liquidators from this group had obesity of degree I (BMI = 30–34.9 kg/m²); obesity of degrees II and III was not revealed. The mean waist circumference in liquidators with CCVD and metabolic syndrome was 105.4±1.8 cm and this parameter in patients with the cardiovascular pathology was 106.5±10.4 cm.

Changes in the lipid spectrum also were identical to those revealed in liquidators with the cardiovascular pathology and metabolic syndrome. Metabolic syndrome in patients with CCVD was characterized by deeper atherogenic shifts of the lipid metabolism parameters relative to the control group (patients with CCVD without metabolic syndrome). These differences were the most pronounced in the triglyceride and HDL-cholesterol level because just these parameters were more often used as a criterion of metabolic syndrome. Considerable differences in the integral parameters of atherogenic shifts, i.e. coefficient of atherogenicity and apo A / apo B ratio were revealed, respectively (Table 2.1).

Table 2.1

Coefficient of atherogenicity and apo A / apo B ratio in liquidators with CCVD, Me [25%; 75%]

| **Parameters** | Liquidators with CCVD | |
|---|---|---|
| | without metabolic syndrome | with metabolic syndrome |
| Coefficient of atherognicity | 3.2 [2.7; 4.0] | 4.4 [4.0; 5.4]* |
| apo A / apo B ratio | 1.6 [1.23; 2.03] | 1.2 [1.01; 1.36]* |

The presented data shows that 50.0% of patients had coefficient of atherogenicity of more than 3.1 and 37.9% had apo A / apo B ratio of less than 1.5 in the liquidator group with metabolic syndrome. In this situation certain lipid spectrum parameters may be within the limits of the reference range, what is evidence of greater informativeness of just the integral parameters characterizing atherogenic shifts in the lipid metabolism.

In addition to dyslipidemia, the C-reactive protein (CRP) level as an inflammation indicator in the vascular wall is an important risk factor of atherosclerosis. The CRP level measured by the high sensitivity method (CRPhs) in the blood serum of liquidators with metabolic syndrome and CCVD is evidence of the higher risk of vascular atherosclerosis relative to the control group (Me: 2.0 mg/l [1.3; 3.5] and Me: 0.7 mg/l [0.4; 2.8], respectively) and patients with the cardiac pathology had the considerably higher CRPhs level (4.2±0.3 mg/l).

Carbohydrate metabolism disorders in liquidators with metabolic syndrome and cardiovascular pathology were revealed in 81.1% of cases. Out of these cases diabetes mellitus type 2 accounted for 43.3%, disturbed glucose tolerance accounted for 36.7% of liquidators and glycemia deviations after fasting were revealed in 20% of liquidators (Khirmanov V.N. et al., 2011). Only 12.3% of liquidators with metabolic syndrome in combination with CCVD had diabetes mellitus, disturbed glucose tolerance was revealed in 32.2%, and hyperglycemia after fasting was found in 10.5% of patients and in the group without metabolic syndrome there were no patients with diabetes mellitus and only 19.3% showed disturbed glucose tolerance.

Any patients with hyperinsulinemia were not revealed in the liquidator group with CCVD. But higher insulin levels were found more often in the group with metabolic syndrome that in the control group (Me: 9.8 mIU/l [5.5; 11.2] and Me: 5.5 mIU/l [3.9; 7.8]).

The values of baseline insulinemia in liquidators with metabolic syndrome in the group with the cardiovascular pathology varied significantly and mean baseline insulinemia was 9.9±0.5 mIU/l.

HOMA index (homeostatic model assessment), calculation of which considers both glucose and insulin concentrations, is more indicative for diagnostics of insulin resistance underlying the pathogenesis of metabolic syndrome. Median of HOMA index distribution was 2.52 [1.39; 3.06] in patients with metabolic syndrome and CCVD and 1.63 [0.85; 1.89] in the group without metabolic

syndrome, i.e. 96% of patients had this index value of more than 1.0, what corresponded to insulin resistance. It is important to mention that insulin resistance could be diagnosed also in 65% of cases in patients without metabolic syndrome.

Hyperleptinemia was revealed in patients with CCVD much more often than in liquidators with the cardiac pathology in whom leptin concentration in the blood plasma was on average 12.7±1.4) ng/ml in presence of metabolic syndrome and 2.8±0.3 ng/ml without it what corresponded to the reference values (2.0-5.6 ng/ml).

Metabolic syndrome in patients with CCVD was associated with hyperleptinemia with the mean leptin level of 16.2±2.1 ng/ml (Me: 12.0 ng/ml, [8.8; 21.5]) and this value in the group without metabolic syndrome was 9.0±1.3) mg/ml (Me: 6.5 [3.8; 11.7], i.e. more than 50% of patients also in this group had leptin level exceeding the upper limit of the reference range (2.0–5.6 mg/ml). Thus, hyperleptinemia in liquidators with CCVD was observed in nearly 75% of cases what indicated frequent presence of leptin resistance in this patient category. The adiponectin concentration in the blood plasma in liquidators with metabolic syndrome and CCVD was on average 10.5±0.6) mg/ml (Me: 9.8 [7.9; 12.2] what corresponded to normal values in most patients (8-30 mg/l). Hypoadiponectinemia was revealed in 25% of cases.

Patients with CCVD were characterized by increased type 1 plasminogen activator inhibitor (PAI-1) level in more than 75% of investigated liquidators. Median of PAI-1 value distribution even in patients without metabolic syndrome was 44.5 ng/ml [30.6; 60.4] and it was even higher in patients with metabolic syndrome (65.6 ng/ml [45.3; 95.6] (reference interval: 7.0 – 43 ng/ml).

Adipose cells secrete PAI-1 which at first inhibits plasminogen activity and, consequently, influences the rheological blood properties. The association between PAI-1 and visceral obesity and insulin resistance is of special importance for assessment of prothrombogenic changes. The blood plasma PAI-1 level in increased in patients with obesity and correlates directly with the degree of metabolic syndrome being a predictor of DM2 and cardiovascular diseases. PAI-1 may not only favor the thrombogenic state of readiness in patients with metabolic syndrome (MS) but also cause lowered sensitivity to insulin in the adipose tissue. Therefore and taking into account frequent revealing of increased PAI-1 concentration in liquidators with CCVD, one may recommend to include this parameter in the diagnostic algorithms of DCS in this patient category, especially in presence of metabolic syndrome.

Among often revealed markers of metabolic syndrome, hyperuricemia is also considered; it was found in 30.1% of cases in the liquidator group and was more pronounced just in patients with metabolic syndrome in combination with the cardiac pathology (409±5.6 μmol/l) while liquidators without this syndrome had significantly lower uric acid concentration in the blood plasma: on average 347±74 μmol/l [(in patients with CCVD: 383±15.5) (314.9±9.6) μmol/l, respectively)].

New markers of metabolic syndrome include fructose and non-esterified fatty acids (NEFA). We showed earlier that investigated liquidators with metabolic syndrome had fructose concentration in the blood plasma after fasting of 0.8±0.98 mmol/l on average [(confidence interval (CI): 0.46±1.14 mmol/l what significantly exceeded the normal values: plasma fructose concentration in healthy subjects after fasting is less than 1 mg/dl or 0.03 mmol/l)]. NEFA concentration in the blood plasma was on average 0.55±0.26 mmol/l in liquidators with metabolic syndrome. Increased plasma

NEFA concentration after fasting (more than 0.9 mmol/l) was observed in 16.9% of liquidators (Khirmanov V.N. et al., 2011).

An important role in the pathogenesis of metabolic syndrome may be played by disturbed melatonin production what is evidenced by recent publications. The diagnostic significance of melatonin and its derivative in insomnia, which is quite often present as a clinical sign of DCS, especially CCVD, is the most well-studied. The melatonin preparations are widely used in the clinical practice. Therefore, assessment of excretion of the main melatonin metabolite, 6-sulfatoximelatonin (6-COMT), was included recently in the investigation program of liquidators with DCS. As melatonin synthesis is considerably influenced by administration of beta-blockers, we used the data on patients not receiving these drugs to analyze 6-COMT excretion.

We revealed significantly lower excretion level of night 6-COMT in patients with dyscirculatory encephalopathy of stage II (DE II) (8.8 μg [4.1; 17.3] (15.1 μg [9.5; 25.3] in patients with DE I, $p<0.05$) what was combined with high CRPhs level, pronounced microalbuminuria and disturbed glucose tolerance. The 6-COMT excretion below 8.0 μg was associated with older age, greater intensity of the pathologic process and signs of metabolic syndrome in the patient group with DCS. Not only decrease of the peak melatonin synthesis level but also the pronounced shift of this peak from the night to evening was significant. In this situation, the percentage of evening 6-COMT excretion was on average 2 times higher than that in the group with the night 6-COMT excretion of more than 8.0 μg (28.9±8.3% vs. 11.9±2.7%, $p<0.05$), and the ratio of the night and day 6-COMT excretion was more than 2 times lower. The high day 6-COMT excretion level in more than 30% of cases was also typical of investigated patients.

We revealed a significant correlation between night melatonin synthesis and sleep characteristics in liquidators with CCVD. Increased 6-COMT excretion in evening time due to lowered night excretion was found in patients with metabolic syndrome (Table 2.2). Patients with metabolic syndrome and CCVD were characterized by considerably increased melatonin metabolite excretion in the evening, lowered night excretion percentage and lowered night and day 6-COMT ratio what was combined with sleep structure disturbances in these patients.

Table 2.2

6-Sulfatoxymelatonin excretion parameters in liquidators of the accident at ChNPP, Me [25%, 75%]

| Parameter | Liquidators with CCVD | |
|---|---|---|
| | without metabolic syndrome | with metabolic syndrome |
| 6-COMT, μg, night | 16.1 [7.4; 25.7] | 12.9 [3.9; 19.7]* |
| 6-COMT, μg, day | 7.8 [5.5; 23.2] | 7.6 [2.9; 24.2] |
| 6-COMT, μg, evening | 1.04 [0.4; 1.87] | 2.6 [1.06; 5.76]* |
| 6-COMT, night/24 h, % | 62.4 [47.1; 74.3] | 36.1[21.0; 54.1]* |
| 6-COMT, evening/24 h, % | 3.4 [2.5; 4.0] | 14.3 [7.1; 21.8]* |
| 6-COMT, night/day, % | 1.8 [1.1; 3.2] | 0.8 [0.36; 2.0]* |

The data on 6-COMT excretion may become the grounds for establishing the additional indications for administering melatonin for the treatment of insomnia in patients with CCVD and in the therapy regimens of DCS, especially in subjects with metabolic syndrome. The level of day and evening excretion and the ratio of these parameters may be important in the assessment of melatonin metabolism in the clinical practice in addition to night excretion level of its metabolites.

The selection of diagnostically significant laboratory parameters (basic and additional ones) for assessing the efficiency of the administered pathogenetic therapy was one of the main results of our study.

Along with the standard investigation, it is advisable to determine additionally markers of thrombocyte and plasma hemostasis activation, parameters characterizing insulin and leptin resistance, melatonin metabolite excretion in liquidators with MS and DCS.

Thus, searching for additional diagnostic tests and their introduction into the clinical practice will favor the timely revealing of MS in LAA. Understanding of the true causes for MS and pathogenetic mechanisms of insulin resistance will make it possible to develop the more effective methods for prevention and correction of this metabolic disorder what finally may promote the lowered risk of cardiovascular morbidity and mortality in this patient category.

It seems evident that diagnostics, treatment and prevention of the vascular pathology in liquidators should be carried out taking into account the revealed mechanisms of its development. Our investigation allowed to understand not in the least all mechanisms of the pathologic process in the vessels in liquidators. Nevertheless, already today we have sufficient information in order to formulate general principles of diagnostics of vascular diseases in liquidators basing on which it becomes possible to implement pathogenetically substantiated medical and preventive measures.

First of all, one should take into account the common pathogenesis of vascular diseases in liquidators both with cardiovascular and cerebrovascular pathology what is confirmed by the results of our studies. This is also evidenced by significant percentage of liquidators in whom CHD and DE are diagnosed simultaneously. All these facts enable us to speak about mechanisms and prevention of vascular diseases without indicating the belonging to a specific system.

The analysis of the pathogenetic variant of the vascular pathology type in every specific patient should become an important stage preceding measures for the treatment and prevention of vascular diseases. As the results of our work show, only approximately 60% of liquidators have pronounced atherogenic shifts and the oxidative stress condition, 43% of them develop hemostasis system disorders and only 25% have hyperhomocisteinemia and signs of endothelium damage. Therefore, the selection of preventive complex should be based both on the general ideas about mechanisms of vascular pathology in liquidators and on the individual analysis of clinical and pathophysiologic signs of the vascular pathology, patient's psychophysiological condition, laboratory markers evidencing some or other prevailing variant of metabolic changes.

The second important principle following from the results of our work consists in involvement of all revealed molecular mechanisms in development of the pathologic process in the vascular bed based on vascular endothelium damage. Free oxygen radicals modify the chemical structure of lipoproteins which increase their atherogenic properties in the oxidized form and become able to influence the endothelium function. Chemically modified lipoproteins (oxidized, glycated etc.) can initiate an autoimmune response. This is associated with formation of LDL-containing autoimmune complexes, which, in their turn, activate macrophages and damage endothelial cells. Cytokines induce leukocyte adhesion to endothelial cells, promote synthesis and secretion by the endothelium of compounds having procoagulant properties and also growth factors favoring smooth muscle cell proliferation. Besides that, thrombocyte activation in the vessels is one of effects exerted by TNF-α. Mutual damaging action of free radicals, cytokines and apo B-containing lipoproteins results in

increased adhesive properties of thrombocytes adherence of which to the vascular wall triggers the thrombus formation process which may develop without limitation if antithrombotic endothelium potential is lowered because of its damage by some or other factors.

Basing of the results of our many-year studies one may state with certainty that the laboratory diagnostic algorithms for liquidators with the vascular pathology should include:

- investigation of lipoprotein metabolism parameters with obligatory determination of apo A / apo B ratio;
- assessment of both plasma and thrombocyte hemostasis systems;
- estimation of parameters characterizing the oxidative stress intensity;
- revealing the inflammatory reaction markers, i.e. determination of C-reactive protein level by the high sensitivity method and pro-inflammatory cytokines;
- assessment of endothelium dysfunction or damage.

The therapeutic measures preventing dyslipidemia, restricting free radical oxidation processes, inhibiting inflammation reactions including the excessive synthesis and secretion of pro-inflammatory cytokines, lowering the functional thrombocyte activity, maintaining the structural integrity and functional activity of the vascular endothelium should become, evidently, the main directions in the vascular disease prevention program in liquidators.

An important precondition for efficiency of such measures consists in the use of adequate laboratory diagnostic methods allowing to establish a required pathogenetically substantiated plan of medical and preventive measures for every specific patient and also obtain the objective information on efficiency of the administered therapy.

### *The role of laboratory diagnostics in assessing the efficiency of the pathogenetic therapy of chronic vasculocerebral insufficiency in liquidators*

The modern conception of heterogeneity of ischemic cerebral damage causes the need to determine a pathogenetic variant of vasculocerebral insufficiency more precisely on case-by-case basis because only such approach to diagnostics makes it possible to administer the effective therapy aimed at the treatment and prevention of disease progression. Besides that, selection of the therapy taking into account the effect on the prevailing factors favoring CCVD progression allows to use a minimum number of drugs and avoid polypragmasia.

When performing the studies we determined the most important clinical, instrumental and laboratory parameters allowing to reveal the pathogenesis peculiarities on case-by-case basis and select individually a minimum number of drugs required for the effective treatment and prevention of the disease.

Special attention should be paid to BP normalization in patients with hypertonic encephalopathy. The correction of metabolic disorders (lipid metabolism, blood sugar, nutrition and physical activities regimen) becomes the most important in patients with atherosclerotic encephalopathy. The complex therapy in patients with venous dyscirculation include venotonic drugs and medicines lowering the intracranial pressure. The endothelium dysfunction and microcirculation disorders may be observed in all pathogenetic variants of vascular encephalopathy what makes it necessary to include antiaggregants, antioxidants and angioprotectors in the treatment

regimen. A psychopathological defect is of critical significance for the disease course, social and professional deadaptation what makes it necessary to select the therapy depending on its variant.

As a rule, each patient has a whole disorder complex requiring correction. At the same time, simultaneous administration of several drugs may change the action of each of them and intensify side effects. Therefore, it is preferred to administer the drugs having several mechanisms of action or the course treatment with staged prescription of 1-2 drugs influencing successively on different components of pathogenesis. The drugs exerting a combined effect on the cerebral blood supply and metabolism and also on the central hemodynamics and rheological blood properties become especially important.

The use of the complex method for diagnostics of DE allowed us to reveal the pathogenesis peculiarities in 100% of investigated liquidators what became the grounds for selection of individual therapeutic regimens with a minimum number of drugs. In this situation, the clinical efficiency of the therapy was 87%. The group on the whole showed significantly improved cognitive functions, lowered anxiety and depression, improved parameter values of cognitive potentials P300, lowered amplitude of pathologic theta-beta-waves in EEG, increased cerebral blood flow and improved cerebrovascular reactivity what reflected the adequacy of the suggested pathogenetic therapy.

The complex diagnostics and treatment control algorithm allowed us not only to confirm the well-known mechanisms of action of the drugs used for treatment of DE but also reveal new positive and side effects. Our use of an antiaggregant Curantyl (in combination with Mildronate or Triovit) in the treatment of patients with atherosclerotic encephalopathy and considerably increased thrombocyte aggregation showed that the significant improvement of the clinical picture observed in 100% of cases was associated not only with antiaggregant effect but also with lowered fibrinogen level, decreased coefficient of atherogenicity and increased reduced glutathione level. The significant effect of Curantyl on these parameters was confirmed by the results of variance analysis (Figs. 2.2, 2.3, 2.4).

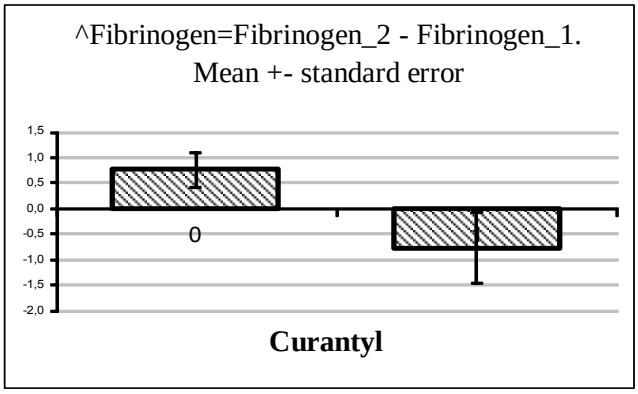


Fig. 2.2. Changes in fibrinogen level depending on the therapy.

0 - Increased fibrinogen level when Curantyl is not included in the treatment regimen (therapy with Stimuloton in combination with Trivit or Mildronate); 1 - lowered fibrinogen level when Curantyl is included in the treatment regimen (Curantyl in combination with Triovit or Mildronate).

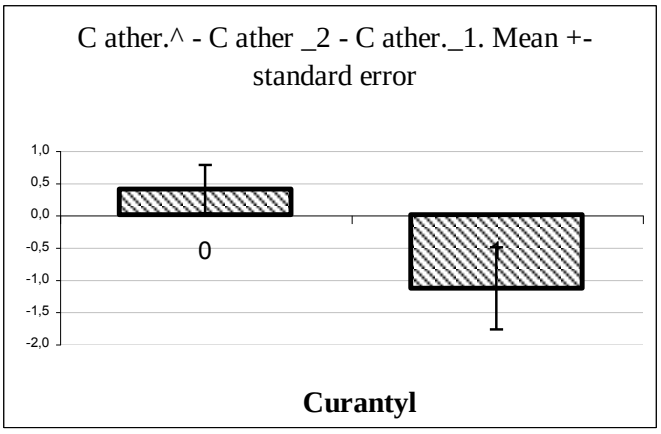


Fig. 2.3. Changes in coefficient of atherogenicity depending on the therapy.

0 - Increased coefficient of atherogenicity when Curantyl is not included in the treatment regimen (therapy with Stimuloton in combination with Trivit or Mildronate); 1 - lowered coefficient of atherognicity when Curantyl is included in the treatment regimen (Curantyl in combination with Triovit or Mildronate).

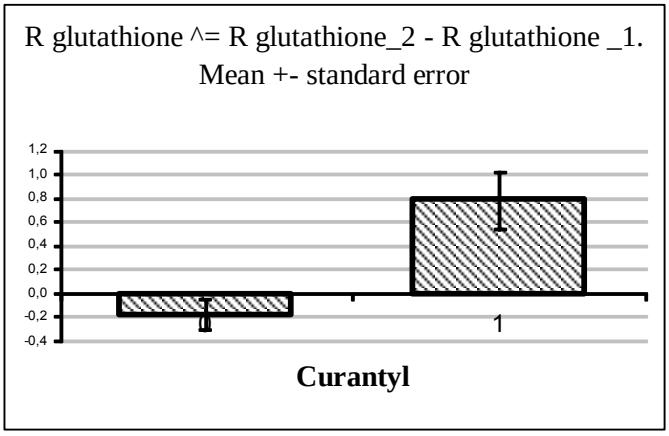


Fig. 2.4. Changes in reduced glutathione level depending on the therapy.

0 - lowered reduced glutathione level when Curantyl is not included in the treatment regimen (therapy with Stimuloton in combination with Trivit or Mildronate); 1 - increased reduced glutathione level when Curantyl is included in the treatment regimen (Curantyl in combination with Triovit or Mildronate).

Administration of the antidepressant Stimuloton (in combination with Triovit or Mildronate) to patients with pronounced affective disorders resulted in significantly improved cognitive functions and lowered anxiety-depressive disorders in 71% of cases. It should be noted that some positive psychotropic effects were associated just with the effect of Stimuloton. This concerned, first of all, the improved memory and lowered depression. At the same time, the improvement of parameters of cognitive potentials P300, some parameters of the cerebral bioelectric activity, lowered personal anxiety were observed equally in all administered drug combinations. Thus, not only psychotropic drugs but also the treatment aimed at microcirculation improvement resulted in the significant improvement of the cognitive functions and psychic status. At the same time, we paid attention to significantly activated lipid peroxide oxidation which was observed in 100% of patients receiving Stimuloton (Fig. 2.5). While not disproving the pronounced positive effect of Stimuloton, this data makes it necessary to follow-up patients further and is evidence of the need to select the adequate antioxidant therapy in patients receiving Stimuloton.

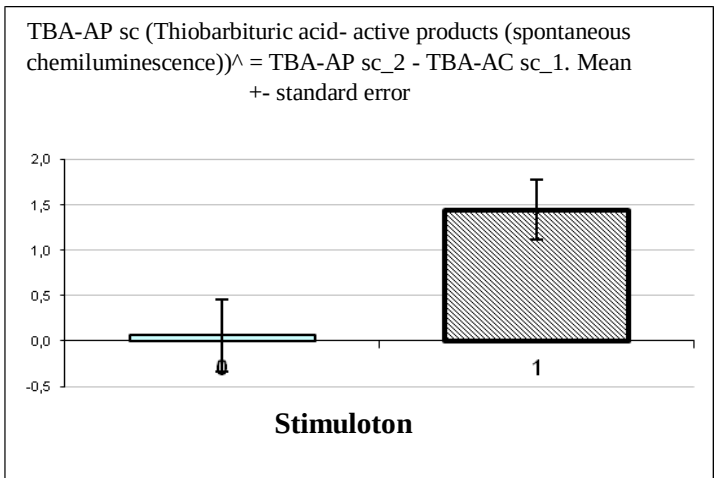


Fig. 2.5. The comparative assessment of changes in lipid peroxide oxidation depending on the therapy.

0 - Stimuloton is not included in the treatment regimen (Curantyl in combination with Trivit or Mildronate); 1 - Stimuloton is included in the treatment regimen (Stimuloton in combination with Triovit or Mildronate).

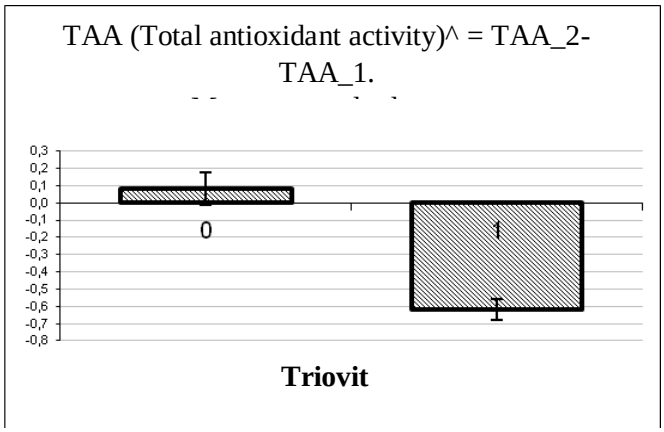


Fig. 2.6. Changes in the plasma total antioxidant activity level depending on the therapy.

0 - increased plasma antioxidant activity level when Triovit is not included in the treatment regimen (Stimuloton + Mildronate and Curantyl + Mildronate); 1 - lowered plasma antioxidant activity level when Triovit is included in the treatment regimen (Triovit + Stimuloton and Triovit + Curantyl).

Assessing the clinical efficiency of Triovit as per the suggested investigation algorithm did not confirm its antioxidant effect but revealed, on the contrary, that this drug had an unknown and usually not controlled side effect in the form of significantly decreased plasma total antioxidant activity level which was observed in all patients receiving Triovit (Fig. 2.6) and increased apo B level (Fig. 2.7) what reflected the intensification of oxidative stress and atherogenic shifts. This was the grounds for refusing from the use of this drug in the treatment of DE. In the literature there are reports on the high antioxidant activity of many drugs (Mexidol, Espa-Lipon, Cavinton etc.) what requires further studies.

Any hypolipidemic and antihypoxant effect expected from the use of Mildronate was not obtained what made it necessary to perform further studies to select the effective drugs normalizing metabolic processes. On the whole, one may speak of the high efficiency of treatment of DE based on the selection of the pathogenetic therapy but the mechanism of action exerted by most drugs used in the treatment of DE requires further studies.

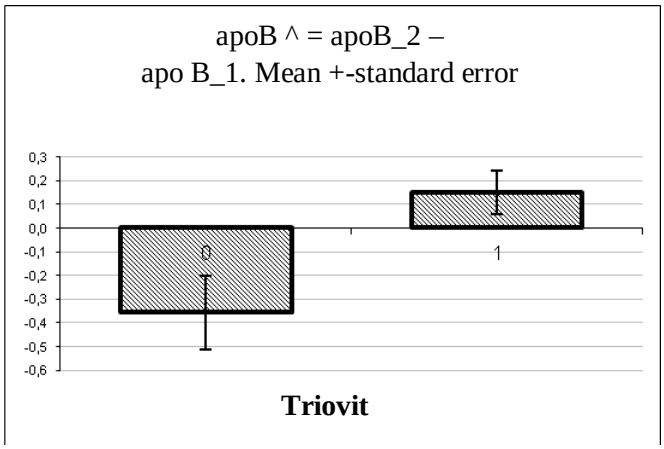


Fig. 2.7. Changes in the apo B level depending on the therapy.

0 - lowered apo B level when Triovit is not included in the treatment regimen (Stimuloton + Mildronate and Curantyl + Mildronate); 1 - increased apo B level when Triovit is included in the treatment regimen (Triovit + Stimuloton and Triovit + Curantyl).

The results of this work section are evidence of the fact that it is advisable to use methods of laboratory diagnostics in order to assess the efficiency of the administered therapy, especially if several drugs with different mechanisms of action are combined and that it is urgent to perform research in this field.

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## 2.2. NONINVASIVE METHODS FOR DIAGNOSTICS OF PRENEOPLASTIC CHANGES

As it is known, radiation effects, especially in a long-term period after exposure, result in increased risk of malignant transformation. Therefore, today prevention of cancer diseases remains a key issue when investigating the victims who suffered because of the accident at ChNPP.

Cancer prevention includes the direct screening of conditionally healthy Chernobyl liquidators and revealing the risk groups regarding cancer diseases and also prophylaxis of recurrences in persons who made a complete recovery at early stages. Therefore, noninvasive laboratory investigations in LAA (liquidators of accident aftermath at ChNPP) seem urgent and timely.

Most advances in the field of clinical medicine over the last two decades are associated with innovation laboratory resources for determination of specific proteins which are markers of the somatic and cancer pathology. Such diagnostic approach favors effective revealing of a disease.

Today stomach cancer (SC) still remains the 2nd most frequent cancer disease in males and 3rd most frequent cancer disease in females in the oncologic disease structure in Russians what leaves behind not only European but also Afro-American countries (Merabishvili V.M., 2007). Stomach cancer is primarily diagnosed in more than 80% of cases already at the stage of severe tumor progression and this fact keeps SC in the group of poorly curable diseases (Simonov N.N., et al., 2001).

According to modern conceptions, stomach tumor develops very rarely in patients with unchanged mucous coat of the stomach (MCS). The development of SC is much more often preceded by certain pathologic changes. Helicobacter pylori plays a trigger role in the development of these changes.

Taking into account the high prevalence of malignant neoplasms, the problem of early diagnostics of precancer conditions: atrophy, metaplasia, dysplasia using modern clinical laboratory methods becomes greatly important.

The interrelation between atrophic changes and preneoplastic changes in MCS is based on the fact that *H. pylori* (HP) causes inflammatory and dystrophic changes in the mucous coat of the stomach with disturbed cell regeneration processes with formation of focal or diffuse atrophy, metaplasia and dysplasia (Correa P., 1988, 1992).

It is proven that the risk of SC grows with increased severity degree of atrophic gastritis. The risk of SC in persons with atrophic gastritis of the stomach body is 3-5 times higher than that in the

other population (Sipponen P., 2002). Epidemiologic studies showed that about 99% of the total number of patients with malignant stomach tumors was represented by primary SC, metastases with stomach involvement in patients with tumors of other localization and non-epithelial stomach tumors accounted for less than 1% (Danilova I.A. et al., 2008). The comparative assessment of SC percentage, patients' gender and age revealed higher prevalence of the disease in males aged 55-59 years as compared to females of the same age (Danilova I.A., et al., 2008). All this data is evidence of the fact that it is urgent to search for simple noninvasive methods for clinical laboratory analysis which could be included in the screening programs for risk groups regarding this pathology.

At present the investigation of gastric bioptates by the morphologic method is the only one way for diagnostics of atrophic and preneoplastic changes in the mucous coat of the stomach. But taking into account the non-uniformity and focal nature of these changes in the stomach, it may be very difficult to assess the pathology type in MCS with the help of the histologic method. The histological analysis of gastric bioptate cannot be a screening method for diagnostics and prevention of SC because of the invasive nature of the investigation and the need of high morphologist's professional competence. Another problem consists in the fact that it is difficult to make a histological diagnosis because there is no a single approach to stomach tumor verification (Hermanek P., at al., 1994). Therefore, the main task for a physician is to be alert regarding those gastrointestinal diseases which cause complications or predispose to possible development of a malignant tumor.

A new noninvasive diagnostic approach is based on determination of four biomarkers in the blood serum or plasma: pepsinogen I (PG I), pepsinogen II (PG II), gastrin-17 (G-17) and anti-HP antibodies (anti-HP), quantification of which provides the information about the functional state of different regions of MCS (Sipponen P., et al., 2002).

Pepsinogen I, pepsinogen II, gastrin-17 are determined using the sandwich ELISA (enzyme-linked imunosorbent assay). Vaananen H. et al. (2003) performed a multicenter study on the use of this method for diagnostics of stomach diseases.

When investigating 404 patients with dyspepsia, the authors showed the comparable data on verification of atrophic gastritis basing on both gastroscopy with histological investigation of bioptates and serological blood analyses with the help of the noninvasive ELISA test. The positive prognostic significance was 64% for ELISA, 54-75% for the histological investigation, and the negative prognostic significance was 93% and 90-96%, respectively. The authors also obtained the identical results in determination of healthy MCS.

### *Gastrins and pepsinogens*

At present ***gastrins*** are a well-studied group of compounds having the identical pentapeptide structure and stimulating hydrochloric acid production.

Gastrin synthesis is stimulated both by alimentary proteins and stomach distension. This results in production of α-amidated bioactive gastrins having identical sections at C-end of polypeptide sequence. The greater portion (90%) of amidated gastrins is represented by 17-member peptide amide which is little gastrin (G-17); big gastrin G-34 (34 residues) accounts for 5%; other 5% is represented by the mixture of big-big gastrin (71 and 52 residues), mini-gastrin (14 residues) and short hepta- and hexapeptide amine fragment. Amidated gastrins are produced mainly by antral

G-cells and are very active regarding histamine release. The shorter gastrin forms prevail in mucous coat extracts of the antral region of the stomach and longer gastrin forms predominate in the serum. Amidated gastrin-17 accounts for 90% in the mucous coat in the antral region of the stomach while gastrin-34 is mainly contained in the small intestine. Amidated gastrin synthesis and release to the blood flow occur maximum in 20 min after the protein loading, at this time G-17 stimulates hydrochloric acid secretion. High acidity (pH < 2.5) inhibits further G-17 secretion by the negative feedback mechanism.

The gastrin biosynthesis process results in production of about 5-10% of unamidated hormones; the amino acid sequence of these compounds terminates with glycine. Unamidated gastrin forms have no biological activity and enter mainly the blood. Unamidated gastrins may be synthesized by TG-cells in the distal section of the small intestine, large intestine cells, EC-cells in the fetal and neonatal pancreas, hypophyseal cells, cerebellar and vagus nerve neurons, ovaries in the postmenopausal period and spermatogenic cells. Tumors develop from the cells or tissues which express gastrin gene in the normal condition. Gastrinoma or Zollinger-Ellison syndrome are associated with hypergastrinemia caused by gastrin hyperproduction by tumor G-cells. Gastrinoma may be localized in the region of the pancreas, duodenum (DUO) or other organs and tissues.

Bioactive products have different elimination time from the organism what influences their hormonal significance. The larger a molecule is, the longer its elimination time from the organism is. Gastrin-17 has a pronounced effect on acid production in the stomach body, and G-17 activity, the hormone of the antral region of the stomach, is the highest of all known gastrins. Besides that, gastrins regulate the stomach mucous coat regeneration, stimulate ECL-cell proliferation, gastric motor activity, cholecystokinin secretion, pancreatic secretion, stimulatemalignant transformation.

In case of exposure to stress factors, G-cells intensify the gastrin secretion with changed molecular structure: unamidated gastrins are synthesized predominantly; cells produce less quantity of sulphated amidated gastrin forms.

Gastrin-17 is synthesized mainly by antral G-cells; this is a dominating and potent gastrin form in health MCS, therefore, it was suggested to use this parameter as a biological marker of atrophy in the antral region of the stomach. G-17 secretion is lowered in patients with mucous coat atrophy in the antral region.

***Pepsinogens I and II*** are pepsin precursors. PG I is synthesized by the chief cells of the mucous coat in the stomach body. Pepsinogen I level correlated significantly with the chief cell number in the mucous coat of the stomach body. Chief cells are being lost in case of severe atrophic gastritis what results in lowered PG I level. The cells secreting PG II are present nearly in each gastric gland and Brunner's glands in the duodenum. The serum pepsinogen II level reflects the condition of MCS. Thus, PG I is secreted exclusively in the region of the body and fundus while PG II is produced in all stomach regions. Therefore, determination of PG I and PG II levels and also their ratio may provide the important information on the histological and functional condition of the mucous coat of the stomach.

G-17 production is regulated by the negative feedback between pH in the gastric lumen and pepsinogen level. The presence of high G-17 level in combination with low PG I level confirms the diagnosis of atrophic gastritis with involvement of the stomach body. The high G-17 concentration may be evidence of hypo- and achlorhydria, on the other hand. In contrast to this, the low serum G-

17 level is observed in patients with atrophic gastritis in the antral stomach region; such patients are most often infected with *H. pylori*. The low G-17 and PG I concentrations may confirm the diffuse involvement of the gastric wall. The risk of stomach cancer and ulcer (SU) increased if the serum G-17 level is anomalously low.

The determination of the serum or blood plasma gastrin-17 level may be used for verifying the diagnosis of hypergastrinemia of tumor or non-tumor nature. In the latter case, the G-17 level does not increase in contrast to gastrin forms with high molecular weight. The measurement of G-17 level may be used also to follow up patients who underwent the surgical treatment. The G-17 secretion in the general circulation is nearly equal to zero after successful antrumectomy.

A clear positive association is observed between serum PG I levels and hydrochloric acid production. Most diseases of the upper gastrointestinal tract are acid-dependent pathology and the adequate treatment consists in administration of the drugs inhibiting gastric secretion. Thus, determination of PG I provides the information about treatment efficiency of these diseases. Numerous studies showed a significantly increased PG I level in patients with non-atrophic HP-associated gastritis. Nevertheless, it is important to rule out factors which may influence PG I secretion, e.g. proton pump inhibitors, in order to assess PG I level objectively. According to some reports, PH I level is increased in smokers and those consuming alcohol, especially in subjects not infected with HP.

Thus, serum pepsinogen (I and II) and gastrin-17 levels reflect quantitatively the condition of the whole mucous coat of the stomach, its functional activity and severity of atrophic changes.

The general picture of variations in markers of inflammation and functional changes in MCS in investigated liquidators of accident aftermath at ChNPP with acid-dependent diseases is presented below (Table 2.3).

Table 2.3

Functional state markers of MCS in liquidators with acid-dependent diseases (n=94)

| | Designation | PG I, µg/l | PG II, µg/l | PG I/II | G-17, pmol/l | Anti-HP, Relative Units |
|---|---|---|---|---|---|---|
| Atrophic gastritis of stomach body (n=7) (7,4%) | C | 13.4±1.8* | 12.0±0.9 | 0.99±0.8* | 25.3±1.3 | 90.9±0.0 |
| Atrophic gastritis of antral region of stomach (n=1) (1,1%) | A | 86.3±0.0 | 2.8±0.0 | 30.8±0.0 | 0.8±0.0** | 121.5±0.0 |
| Atrophic gastritis of stomach body and antral region (n=7) (7,4%) | AC | 26.4±2.0* | 16.0±1.6 | 1.5±0.7* | 4.4±0.9 | 109.2±0.0 |
| Non-atrophic gastritis (n=67) (71,3%) | S | 137.7±2.8*** | 24.9±1.5 | 5.4±1.1 | 4.9±1.4 | 122.6±0.0 |
| Normal condition (n=12) (12,7%) | N | 83.1±1.5 | 12.5±1.1 | 7.8±1.2 | 1.4±0.8 | 22.3±0.0 |

* Differences with subgroups A, S, N are significant ($p < 0.05$)

** Differences with subgroups C, AC, S are significant ($p < 0.05$)

*** Differences with subgroups C, A, AC, N are significant ($p < 0.05$).

The analysis of blood marker concentration in investigated patients allowed to predict different conditions of MCS with high probability: 1) Normal condition (N); 2) atrophic gastritis of antral region (A); 3) atrophic gastritis of stomach body and antral region (AC); 4) atrophic gastritis of stomach body (C); 5) non-atrophic gastritis (S).

It was shown that either local atrophic changes in the mucous coat of the stomach body, or multifocal changes (the body and antrum) prevailed in liquidators with acid-dependent diseases. Atrophic gastritis in the antral region of the stomach was revealed only in 1 subject.

The concentration of Helicobacter pylori CagA antigen IgG antibodies (relative units - rel.u) in patients with Helicobacter gastritis differed significantly from the patient group not infected with HP ($p < 0.05$). G-17 level in patients investigated by us ranged from 0.1 to 70.8 pmol/l and was on average 10.2±1.4 pmol/l. The positive correlation between anti-HP antibodies and G-17 concentration in the blood serum ($r= +0.60$) was shown. The PG I level in liquidators investigated by us ranged from 1.9 to 269.8 μg/l [on average, 101.4±5.8 μg/l]. The PG I levels of more than 120 μg/l were revealed in 28 (29.8%) of males. The PG II concentration was on average 24.7±1.6 μg/l; the PG II level of higher than 10 μg/l was observed in 84 (89.4%) of subjects what was evidence of MCS inflammation.

It is known that the PG I level depends on the number of chief cells in the stomach body and is the basic atrophy marker in the stomach body. Several authors proved clearly that not only pepsinogen I but also pepsinogen II concentrations and also their ratio lowered as atrophic gastritis in the stomach body became more severe. Basing on calculation of ROC-characteristics (receiver operating characteristic) sensitivity-specificity performed by T. Tiusanen (2006), it was shown that PG I/II ratio was the second choice marker of stomach body atrophy (www.gastropanel.net). The lowered PG I concentration (less than 30 μg/l) and PG I/II ratio (below 3.0) are evidenced of pronounced stomach body atrophy. Our study revealed the PG I level of less than 30 μg/l in 9 (9.5%) of investigated liquidators; the lowered PG I/II ratio (below 3.0) was observed in 24 subjects (25.5%).

G-17 may be considered as the third marker in patients with atrophic gastritis in the stomach body. Gastrin plays the key role in regulation of acid production. As it was mentioned above, the gastrin-17 level depends on acidity by the negative feedback mechanism. As oxyntic cells are being lost in patients with atrophic gastritis of the stomach body, the lower the hydrochloric acid is, the higher G-17 concentration is; 29.5% had G-17 level of higher than 10 pmol/l.

Chronic helicobacter gastritis of different activity degree, which was diagnosed by anti-HP titer in 81.9% of cases (77 subjects), was the predominant pathology in investigated patients; the other 17 patients (18.1%) had chronic non-helicobacter gastritis. As follows from Table 3.3., liquidators with non-atrophic HP-associated gastritis have significantly increased PG I level what is in agreement with the results of numerous studies (Reshetnikova O.V. et al., 2007; Sipponen P. et al., 2002; Genta R. et al., 2006).

In addition to assessment of functional activity of MCS using noninvasive ELISA test, all patients underwent esophagogastroduodenofibroscopy with simultaneous of MCS. MCS biopsy material for used for histological studies. Table 2.4 presents distribution results of dysregeneratory changes in MCS revealed by us in patients.

Dysregeneratory changes (disturbed cell regeneration) of the stomach mucous coat epithelium manifested in different types of intestinal metaplasia and atrophy of the mucous coat were diagnosed in 45 patients (i.e. 47.9% of all stomach biopsies); two patients of them had stomach ulcer (SU) and stomach cancer (signet ring cell carcinoma) was revealed in 1 case.

Table 2.4

Distribution of dysregeneratory changes in MCS and their different combinations in investigated liquidators (n = 94)

| Patient number (%) | Atrophy (body and/or antrum) | Enteric metaplasia | Colonic metaplasia | Stomach cancer | Stomach ulcer |
|---|---|---|---|---|---|
| 9 (9.5) | + | | | | |
| 7 (7.4) | + | + | | | |
| 1 (1.1) | + | | + | | |
| 1 (1.1) | + | + | + | | |
| 2 (2.1) | | + | + | | |
| 4 (4.3) | | | + | | |
| 18 (19.1) | | + | | | |
| 1 (1.1) | | + | | + | |
| 2 (2.1) | | | | | + |
| 49 (52.1) | No dysregeneratory changes in MCS | | | | |

It should be mentioned that only one subject out of all patients with morphologically confirmed cell regeneration disturbances of MCS (n=49) had no anti-HP. This patient had intestinal metaplasia of MCS, abnormally low G-17 level and high PG II concentration what was a sign of gastritis of non-Helicobacter nature. Patients with stomach ulcer were characterized by PG I concentration increase of more than 260 μg/l, and according to some authors, PG I concentration of more than 120 μg/l increases the risk of SU 3 times (Reshetnikova O.V. et al., 2007).

A patient with primarily diagnosed stomach cancer had PG I concentration in the blood serum 5 times lower than the limit of acceptable reference range (4.4 μg/l).

The comparison of results obtained by using the noninvasive ELISA test and histological investigation of MCS bioptates is presented in Table 2.5.

Table 2.5

Results obtained by using the noninvasive ELISA test and histological investigation of MCS bioptates

| "Biohit GastroPanel" | Histological investigation of MCS bioptates | | | |
|---|---|---|---|---|
| | Atrophy | Dysregeneratory changes in MCS | NA | Total |
| Atrophy | 5 | 8 | 2 | 15 |
| NA | 13 | 17 | 49 | 79 |
| Total: | 18 | 25 | 51 | 94 |

NA - non-atrophic (superficial) gastritis or normal MCS

We showed that analysis results on revealing MCS atrophy in investigated patients coincided in 5 subjects, results of diagnosing non-atrophic (superficial) gastritis or revealing normal MCS were in agreement in 49 subjects. Atrophic changes of MCS were revealed in 16% of cases (n = 15) according to findings of noninvasive analysis and in 18 subjects (19%) basing on the results of the histological investigation.

At present there is no data on determination of noninvasive ELISA test parameters in patients with different metaplasias of MCS.

We showed (Table 2.6) that liquidators with histologically confirmed preneoplastic changes in MCS (enteric and/or colonic metaplasia) had significantly increased PG II concentration as compared to the patient group with non-atrophic gastritis and/or unchanged MCS.

Table 2.6

Variations in noninvasive ELISA-test parameters in patients with dysregeneratory changes in MCS (n=94)

| Subgroups | PG I, μg/l | PG II, μg/l | PG I/II | G-17, pmol/l | Anti -HP |
|---|---|---|---|---|---|
| 1) Enteric and/or colonic metaplasia (n=25) (26.6%) | 98.4±2.5 | 30.5±0.9* | | 10.4±2.7 | +/- |
| 2) Non-atrophic gastritis or normal MCS (n=49) (52.1%) | 110.4±3.9 | 18.7±1.2 | 6.6±1.1 | 3.15±0.9 | +/- |

* Differences with subgroups 1 and 2 are significant ($p < 0.05$).

One may conclude that noninvasive diagnostics with determination of biochemical markers (gastrin, pepsinogens and anti-HP antibodies) is a safe method for observing the possible changes in MCS, therefore, it is advisable to use this method before prescribing endoscopy. Such method will allow to optimize endoscopy and take the biopsy material from critical regions in MCS revealed initially using the laboratory methods.

### *Biochemical markers characterizing functional activity of MCS and oncoprotein production in patients with HP-infection*

Gastrin-17 (G-17), pepsinogen I (PG I) and pepsinogen II (PG II) concentration was assessed depending on Helicobacter infection and MCS atrophy degree. HP-positive patients with chronic gastritis (CG) had significant changes in PG I ($p<0.01$), PG II ($p< 0.001$) and G-17 ($p<0.01$) levels as compared to HP-negative subjects (Fig. 2.8-2.10).

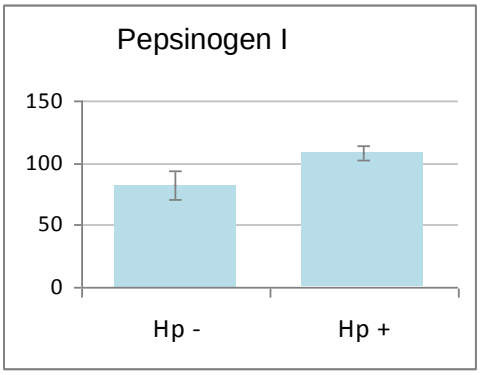


Fig. 2.8. The serum PG I level depending on HP CagA status.

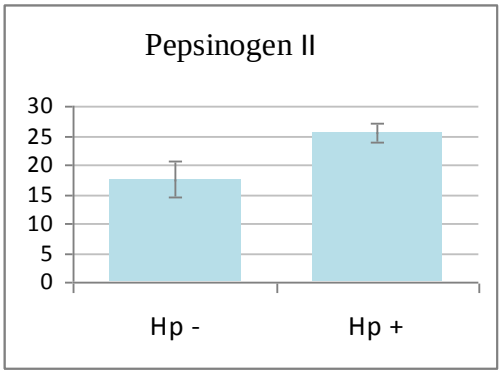


Fig. 2.9. The serum PG II level depending on HP CagA status.

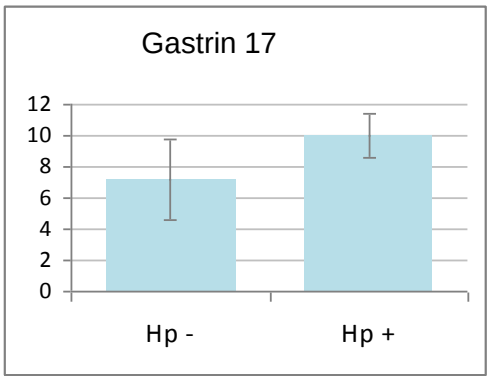


Fig. 2.10. The serum G-17 level depending on HP CagA status.

The PG I, PG II and G-17 concentrations were significantly higher in HP CagA infected subjects. HP-positive patients showed significant Spearman's rank correlations and γ between PG I, PG II, G-17 and oncoprtein Ki-67 and IgG level (Table 2.7).

Table 2.7

Spearman's rank correlations and γ with IgG level in HP-positive patients

| Parameter | Spearman's rank correlation | γ |
|---|---|---|
| PG I | 0.230 | 0.152 |
| PG II | 0.229 | 0.166 |
| G-17 | 0.221 | 0.149 |
| Ki-67 | 0.282 | 0.305 |

Spearman's rank correlations and γ were insignificant in HP-negative patients.

The histological investigation of gastric bioptates showed that inflammatory and dystrophic changes in MCS in liquidators are localized, mainly, in the antral region. The stomach body is involved rarer and to a less extent. The inflammation and atrophy do not affect the zone of chief and oxyntic cells synthetizing pepsinogen and hydrochloric acid. The intensified pepsinogen production revealed by us may be mediated by increased gastrin secretion in patients with Helicobacter infection. High gastrin concentrations cause intensified hydrochloric acid secretion by parietal cells what leads to increased concentration of PG II produced by mucoidal cells and simulation of chief cells results in increased PG I release.

Helicobacter pylori has a double effect on intragastric pH. On the one hand, urease secreted by it alkalizes the stomach content and, on the other hand, chronic inflammation in the antrum (the basic region of HP colonization) stimulates hydrochloric acid production by parietal cells through a gastrin-mediated mechanism. As parietal cell atrophy progresses intragastric pH value increases naturally.

There is strong evidence that HP participates directly in signaling path control of the gastric epithelium and triggers hyperproliferation process. This results in disturbed physiology of gastric epitheliocytes with signs of malignant transformation: activated growth factor receptors; suppressed apoptosis; unlimited replication potential; intensified angiogenesis; cell dissociation and tissue invasion. So, HP-positive patients had significantly increased production of oncoprotein Ki-67, the proliferative activity marker (Table 2.8).

Table 2.8

Ki 67 oncoprotein production depending on HP-status

| Ki-67, % | HP-positive patients | HP-negative patients | p |
|---|---|---|---|
| Surface epithelium | 17.65±3.87 (n=66) | 5.00±3.66 (n=24) | 0.028 |
| Gastric pits | 78.3±3.05 (n=56) | 68.9±3.57 (n=22) | 0.003 |
| Bottom regions of glands | 5.36± 1.94 (n=56) | 0.46±0.31 (n=22) | 0.022 |

The studies showed that oncoprotein HER-2/neu was revealed significantly more often in HP-positive patients; according to some authors, this oncoprotein is involved in transmission of the mitogenic signal (Fig. 2.11).

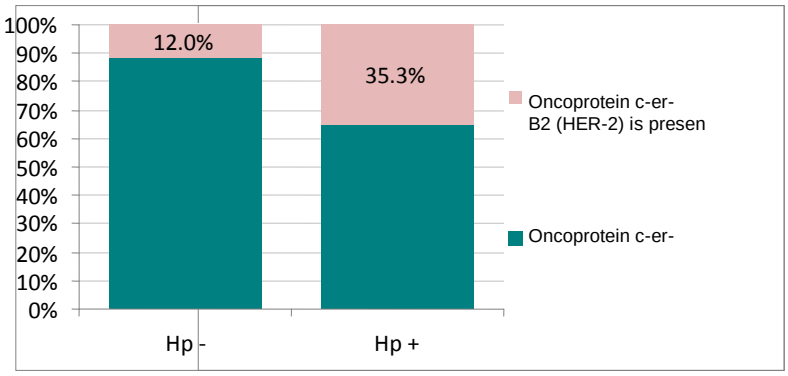


Fig. 2.11. Frequency of revealing HER-2/neu depending on the HP-status.

Any significant differences in p21 and apoptosis marker Bc1-2 between the groups of HP-positive and HP-negative patients were not revealed.

### *Variations in biochemical markers characterizing the functional activity of MCS over time and changes in histological parameters in the period of the therapy for Helicobacter pylori eradication*

Lately a hypothesis has been developed (Mirodzhov G.K. et al., 2008), according to which HP leads disturbance of the ratio between G-cells producing gastrin and D-cells producing somatostatin and playing an important role in regulation of parietal cell function; HP exerts this effect directly or through cytokines. Hypergastrinemia associated with HP-infection causes growth of the parietal cells mass and increased acid production and also influences pepsinogen secretion. The effective antimicrobial treatment normalizes these parameters.

This hypothesis became a precondition for use of noninvasive ELISA-test in order to assess the efficiency of the therapy for HP eradication in liquidators of accident aftermath at ChNPP with diagnosis “chronic gastritis”.

The immunocytochemical method, histological method (hematoxylin and eosin staining) and PCR (“AmpliSense Helicobacter pylori”, Russia) were used for revealing HP in gastric bioptates. Anti HP IgG antibody content in the blood serum exceeding 42 EIU was considered as the positive result and was evidence of the organism infection.

Seventy liquidators with chronic HP-associated gastritis received the eradication therapy as per the line I standard regimen including Omeprazole (20 mg twice daily), Clarithromycin (500 mg

twice daily) and Amoxycilline (500 mg 4 times/day) for 14 days.

Six patients without HP infection received the monotherapy with Omeprazole (20 mg twice daily).

In total 76 liquidators were investigated in the process of treatment: ad admission to the hospital, 2 and 12 months after completion of the therapy.

All patients were divided in 4 groups 2 months after completion of the treatment. The first group (HP0, n=6) included HP-negative patients with chronic gastritis. The second (E+, n=31) comprised patients in whom HP was eradicated. Patients of the third group (E+/-, n=19) had the infection revealed only by the PCR-method. The fourth group (E-, n=20) included patients in whom HP was not eradicated (the infection was revealed by all methods used in the study).

As follows from the data presented in Table 2.9, the anti-HP IgG level in the patient groups with Helicobacter gastritis before the treatment differed significantly from that in the group of HP-negative patients ($p < 0.05$).

Table 2.9

Changes in anti-Helicobacter pylori IgG level (rel. u.) in the blood serum in patients with non-ulcer dyspepsia before and after treatment, medians

| Groups | Before treatment | 2 months after treatment | 12 months after treatment |
|---|---|---|---|
| HP0 | $32.5^{a}$ | $43.8^{n}$ | $52.6^{m}$ |
| E+ | $84.7^{a1}$ | $66.4^{n1}$ | $49.1^{m1}$ |
| E+/- | $78.4^{a2}$ | $68.1^{n2}$ | $31.9^{m2}$ |
| E- | $115.2^{a3}$ | $132.8^{n3}$ | $89.7^{m3}$ |

*Note:* differences between a3 and a are significant ($p<0.05$);
differences between n3 and n, n1, n2 are significant ($p<0.05$);
differences between m3 and m, m1, m2 are significant ($p<0.05$).

The groups (E+, E+/-) showed significant decrease of the antibody level by 21.6 and 13% 2 months after the treatment and by 42 and 59%, respectively, after 12 months. It is known that anti-HP antibody level decreases to the minimum value within 1 year after the successful treatment of infection (Kishkun A.A., 2000). We showed that the IgG level was close to the reference value (42 EIU) and did not exceed 60 EIU in patients (HP0, E+, E+/-) in 1 year. The anti-HP antibody level in the group (E-) changed insignificantly during the whole observation period but on the whole it remained significantly high as compared to HP-negative patients. The immunologic IgG threshold did not exceed 60 EIU after the effective treatment of HP-infection and this value may be taken as a threshold for assessment of the treatment efficiency.

Fig. 2.12 shows changes in PG I concentration over time depending on the results of treatment of HP-infection.

The PG I level in the group HP0 before the treatment was 66.0 ±17.5 μg/l and this value was significantly lower than that in HP-positive patients (E+, E+/-, E-) (107.1 ±12.9 μg/l ($p< 0.05$).

It was found that the increased PG I concentration was preserved after 2 months only in the group HP0 which received the monotherapy with proton pump inhibitor (PPI). The patient groups with positive (E+, E+/-) and negative (E-) treatment results showed by this time the decrease of the PG I concentration on average by 20-30% as compared to baseline values.

The PG I levels in the groups of HP-negative patients and with positive therapy results (E+ and E+/-) corresponded to the baseline value in 12 months and did not exceed the upper reference limit of 120 μg/l. The PG I concentration in patients with persisting infection (E-) increased significantly in 12 months as compared to the previous follow-up period and was 175.8±18.3 μg/l

what exceeded the upper limit of the reference range (30 – 120 μg/l).

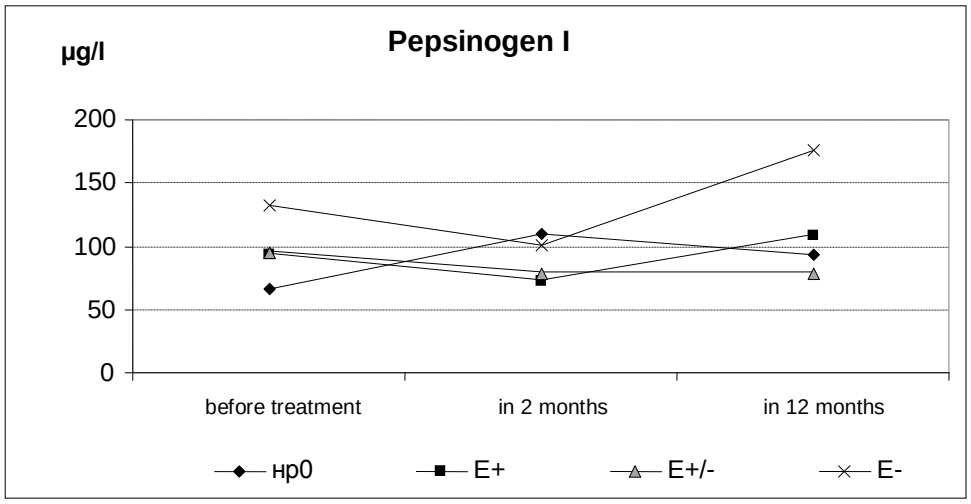


Fig. 2.12. The pepsinogen I level in the blood serum in patients with chronic gastritis before and after treatment.

Thus, we showed that determination of PG I concentration in a long-term period (after 1 year-follow-up) is one of the criteria of the treatment efficiency. The PG I values do not exceed the threshold level of 150 μg/l in case of the effective treatment and they remain significantly higher than this limit in patients with persisting infection.

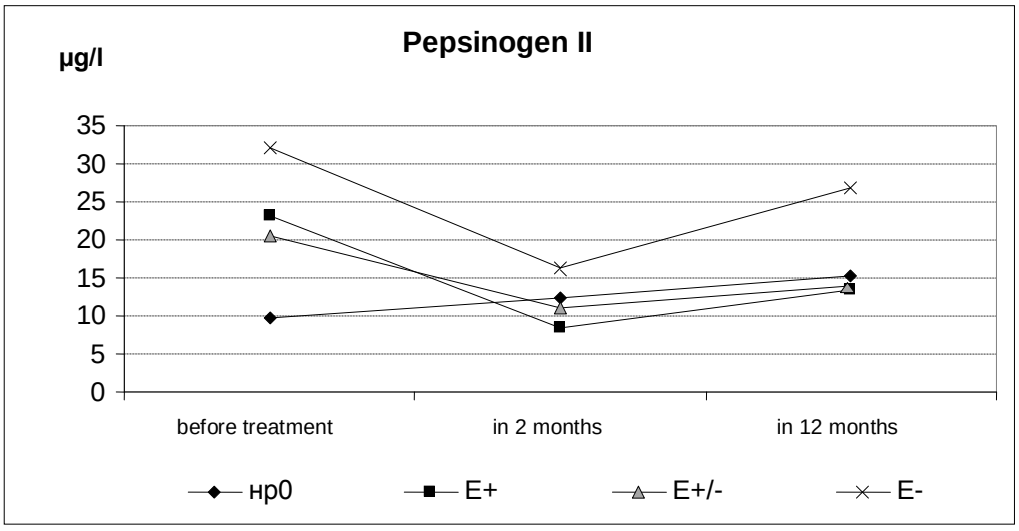


Fig. 2.13. The pepsinogen II level in the blood serum in patients with non-ulcer dyspepsia before and after treatment.

Before the treatment, the PG II concentration was significantly lower in HP-negative patients (HP0) than that in HP-positive patients ($p<0.05$) (Fig. 2.13). HP-negative patients receiving the treatment with PPI showed insignificantly increased PG II concentration during the whole follow-up period ($p>0.05$).

The PG II concentration in the groups of HP-positive patients (E+, E+/-, E-) before the treatment exceeded the reference values of 3-10 μg/l 2 times and the PG II level decreased 1.5-2 times after 2 months of the treatment.

The PG II concentration in the groups (E+, E+/-) in 12 months remained at the normal level and was 13.3±3.52 μg/l and 13.9±8.12 μg/l, respectively, what may be evidence of the

inflammatory process regression, and this value in the group (E-) increased up to 26.8±0.56 μg/l exceeding significantly the upper limit of the reference range (10 μg/l).

The PG II level in patients with effective eradication after 1 year-follow-up did not exceed the threshold value of 15 μg/l. This value may be recommended as a criterion for assessment of the treatment in a long-term period.

The measurement results of gastrin-17 level are presented in Fig. 2.14.

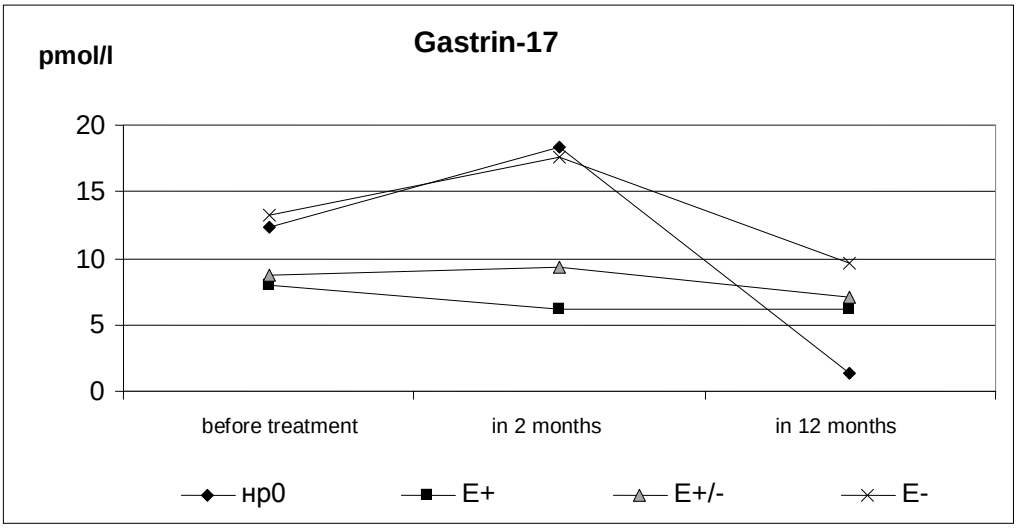


Fig. 2.14. The gastrin-17 level in the blood serum in patients with non-ulcer dyspepsia before and after treatment.

The gastrin-17 concentrations in the groups of HP-negative and HP-positive patients did not differ considerably in the follow-up period. The G-17 levels in the groups E+, E+/- varied within the reference range from 2 to 10 pmol/l and did not differ significantly.

A trend to G-17 concentration increase was observed in the groups HP0, E- 2 months after the treatment, and the gastrin-17 concentration became normal in 1 year.

We found that decrease of the IgG, pepsinogen I and II level may serve as a criterion of the therapy efficiency for HP eradication in a long-term period. The threshold value is 60 rel. u. for anti-HP IgG level, 150 μg/l for pepsinogen I and 15 μg/l for pepsinogen II. Those patients, in whom HP-infection was revealed only by PCR method after the treatment, require longer follow-up in order to rule out reinfection.

The assessment of pepsin proenzyme concentration (pepsinogen I and pepsinogen II) in combination with gastrin-17 allowed to reveal the liquidator groups with atrophic changes of different degree and different localization in the mucous coat of the stomach and estimate the efficiency of HP eradication.

In addition, lowered pepsinogen I and/or gastrin-17 concentrations make it possible to reveal the liquidator groups with functional insufficiency of the mucous coat of the stomach, i.e. with atrophic gastritis, which is considered as “an initial link” in the chain of precancer changes. The combination of precancer conditions (chronic gastritis, ulcers, stomach polyps etc.) with precancer changes in the mucous coat of the stomach (atrophy, intestinal metaplasia, dysplasia) increases actually the risk of cancer. The development of criteria for revealing precancer changes in the mucous coat of the stomach or stomach cancer by determining the blood serum parameters at curable stages, when it is potentially possible to reverse atrophic changes in the mucous coat by pharmacotherapy, allows to prevent stomach cancer.

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## 2.3. IMMUNOINFLAMMATORY SYNDROME AND SECONDARY IMMUNE DEFICIT

The complex investigation of quantitative and functional parameters of immunocompetent cells, namely, the proliferative, regulatory and cytotoxic functions, production by them of

intercellular interaction mediators, the cytokines, and also parameters of the humoral immunity and innate immunity system allows to determine the contribution of this regulatory integral system in the pathogenesis of the somatic pathology in LAA (liquidators of accident aftermath) at ChNPP.

The literature provides the data on changes in the immunity cytokine system caused by exposure to low doses of the ionizing radiation (Timoshevsky A.A., 2010). Nevertheless, changes in the cytokine production in liquidators of accident aftermath at the Chernobyl NPP in a long-term period and the role of these changes in development of the somatic pathology are also described insufficiently (Kalinina N.M., et al., 1997).

The investigation of post-radiation consequences in vitro revealed high sensitivity of the cytokine system to exposure to the ionizing radiation. The study in vitro found that the ionizing radiation modulated the TNF-α gene transcription rate in myelocytes and stimulated cytokine gene expression (Neta R. et al., 1991, 1992, 1997). Low radiation doses induced TNF-α production by astrocytes and microglia cells (Neta R. et al., 1991, 1992, 1997). The intensified IL-1β, IL-6 and TNF-α production by the immune system cells in response to the ionizing radiation is associated, first of all, with the marcoorganism protection against the damaging radiation effect.

The investigation of patients exposed to the ionizing radiation revealed that increased production of pro-inflammatory cytokines IL-1β, IL-6 and TNF-α by peripheral blood mononuclear cells (PBMC) in the remote period after the irradiation stimulated astrocyte, endothelium cell proliferation and increased hematoencephalic barrier permeability (Kureshi S.A. et al., 1994; Rubin P. et al., 1995).

In the last decades there appeared many studies concerning the investigation of peculiarities of intercellular mediator (cytokine) synthesis and their role in the pathogenesis of different diseases of the cardiovascular system, namely, atherosclerosis, essential hypertension and coronary heart disease. It was shown that patients with essential hypertension had increased interleukin -1β (IL-1β) content in the blood serum. The positive correlation between this cytokine level and blood pressure was revealed (Dalekos G.N. et al., 1997). According to the authors, the interrelations between the high serum IL-1β level and increased blood pressure may be explained by the fact that this cytokine stimulates smooth muscle cell proliferation in the vascular wall. Another possible mechanism of the effect exerted by IL-1β on the blood pressure level consists in its stimulating influence on the hormone and hypothalamic-pituitary-adrenal system mediator production (Dinarello C.A., 2009, 2010). IL-1β stimulates smooth muscle cell and fibroblast proliferation in the vascular wall by activating the PDGF-thrombocyte growth factor (Raines E.W., et al., 1989). Addition of IL-1β to the vascular wall myocyte culture increases angiotensin receptor type I expression. At the same time, the combined addition of IL-1β and TNF-α (tumor necrosis factor alpha) to the culture results in lowered expression of these receptors (Sasamura H. et al., 1997). It was found that activated T-lymphocytes in atherosclerotic plaques produced IL-4 (Hansson G.K., et al., 1988). IL-8 mRNA was revealed in the cells forming atherosclerotic plaques (Apostolopoulos J. et al., 1996). This cytokine acts as a mitogen and chemoattractant for the smooth muscle cells in the vascular wall (Yue T. et al., 1994). The investigation of this cell culture found that IL-4 induced VCAM-1 adhesion molecule expression (Li H. et al., 2003), the same effect was caused by TNF-α (Iademarco M.F. et al., 1998). Addition of IL-1β, IL-4 and IL-8 to the vascular wall myocyte culture results in intensified 12-lipooxygenase production, the enzyme favoring migration and proliferation of these cells (Clinton S.K. et al., 1992; Natarajan R. et al., 1997).

It is known that IL-1β and TNF-α inhibit myocardium contractility (Finkel M.S. et al., 1992) but such inhibition mechanisms remain unclear. The induction of active oxygen forms inhibiting the myocardium contractility by pro-inflammatory cytokines is considered as one of the possible explanations for this effect (Chandrasekar B., et al., 1997; Epperly M., 1999). Free radicals are produced in the organism constantly but their increased production or antioxidant system insufficiency may result in formation of conditions for cell damage. Free radicals are formed in the organism, in particular, during prostaglandin synthesis which may be induced by IL-1β and TNF-α. Thus, the above mechanism of the pathogenic effect exerted by active oxygen forms may be mediated by IL-1β and TNF-α hyperproduction and may be of great importance in progression of coronary heart disease (Emerit et.al., 1997). It is known that changed antioxidant status leads to lipid peroxide oxidation (LPO) activation and AOF formation. TNF-α hyperproduction plays its role not only in development of oxidation stress but also in cardiomyocyte apoptosis. TNF-α influences also endothelium cells in which this cytokine increases nitrogen oxide production, induces oxidation stress and apoptosis (Ferrari R. et al., 1998). Patients suffering from chronic heart failure (CHF) have increased TNF-α concentration in the blood plasma (Komajada M. et al., 1998). The correlation between TNF-α concentration and the degree of clinical, hemodynamic and neuroendocrine disorders in patients with CHF was revealed (Ferrari R. et al., 1995, Testa M., et al., 1996). TNF-α favors increased production of induced NO-synthase (iNOS), the enzyme ensuring nitrogen oxide synthesis, the metabolite involved in cardiomyocyte signal transduction. Nitrogen oxide also favors lowered cardiomyocyte contractility and may cause their apoptosis (Packer M. et al., 1995; Narula J. et al., 1996).

The investigation in vitro showed that IL-1β and cardiotropin (protein from IL-1β family) favored the cultured cardiomyocyte proliferation. This effect is materialized after binding of IL-1β with its receptors on the cardiomyocyte surface what results in activation of phosphorylation/ dephosphorilation reaction cascade which stimulate cardiomyocyte proliferation through activation of nuclear transcription factors (NFKB, NF-AT) (Hefti M.A. et al., 1998).

It was found that cytokines (IL-1β, IL-6, TNF-α) could favor lowered myocardium contractility. The monocytes/macrophages and endothelial cells synthesize iNOS under the influence of IL-1β, IL-6, TNF-α, after that these cells produce NO inhibiting cardiomyocyte contractility (Fig. 2.15). The effect of IL-1β makes T-lymphocytes and NK-cells to produce INF-γ which also suppresses myocardium contractility. IL--1β, IL-6 and TNF-α have a damaging effect on cardiomyocytes both through NO synthesis and NO-independent path (Kelly R.A. et al., 1997). TNF-α suppresses myocardium contractility inhibiting penetration of $Ca^{2+}$ ions in cardiomyocytes (Squadrito F. et al., 1993; Krown K. et al., 1995). This cytokine favors increased production and lowered excretion of triglycerides the higher level of which increases the risk of coronary artery atherosclerosis. It was found that severity of heart failure correlated with TNF-α in the peripheral blood (Torre-Amione G. et al., 1996). The investigation of the interrelation between TNF-α and IL-6 level in the blood plasma and heart failure degree revealed the positive correlation between heart failure symptoms intensity and TNF-α and IL-6 level in addition to increased level of these cytokines in patients as compared to the control group (Hasdai D. et al., 1996). Studying the IL-1β level in the peripheral blood serum in patients suffering from diseases associated with coronary artery pathology showed that the maximum IL-1β level was observed in patients with angina pectoris and mild (< 50% of artery lumen) coronary stenosis (Colucci W.S. et al., 1998).

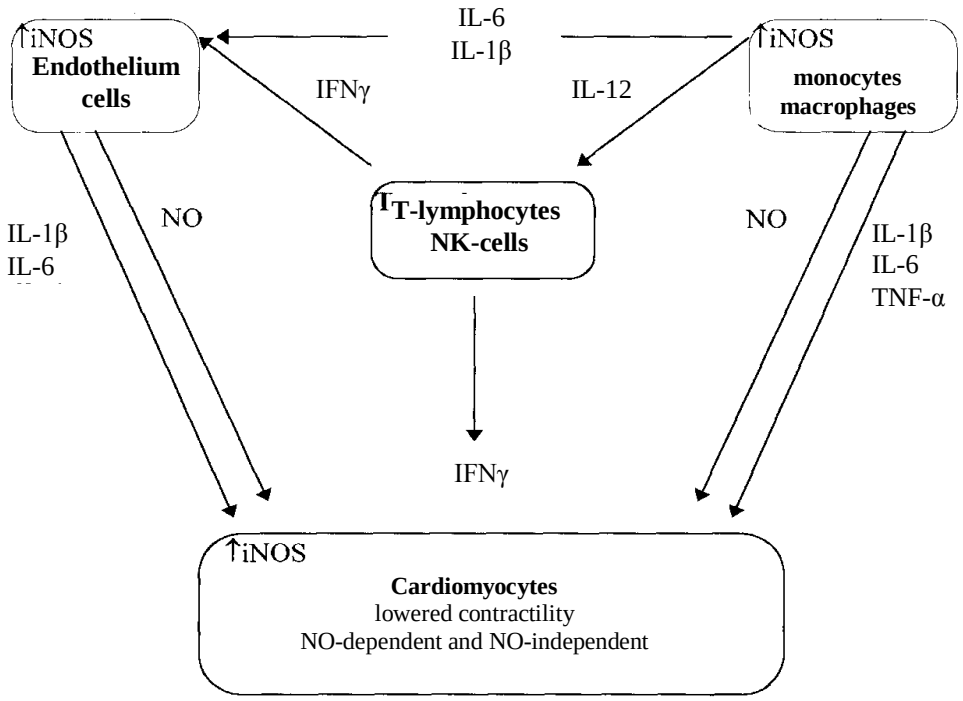


Fig. 2.15. Mechanisms of myocardium contractility inhibition by cytokines
(Kelly R.A. et al., 1997, with modifications).

The change in myocardium structure because of cardiomyocyte hypertrophy caused possibly by IL-1β hyperproduction is one of the reasons for functional myocardial insufficiency in CHD (Thaik C.M. et al., 1995). It was found that cardiac myocyte hypertrophy resulted in their apoptosis. The myocardial structure is maintained by extracellular matrix components which include collagen, proteoglycans, fibronectin and proteases. At present there is evidence that myocardial fibroblasts and endothelium cells play the key role in postischemic myocardium transformation by producing the extracellular matrix components under the influence of different factors. These factors include noradrenaline, the neurotransmitter of the sympathetic nervous system, which is able to stimulate the collagen production by fibroblasts when it binds with the adrenergic receptor. Endothelin produced, mainly, by endotheliocytes can both stimulate and suppress the collagen synthesis (Burgess M.L. et al., 1994). Some extracellular matrix components (collagen, fibronectin, osteopontin) may play an important role in the development of myocardial structural reorganization when they bind with adhesion molecules (ICAM-1, VCAM) expressed on the cardiomyocyte, fibroblast and epithelium cell surface (Ikeda U. et al., 1994). Hemodynamic heart overload is the most known stimulating effect favoring cardiac muscle hypertrophy (Colucci W.S. et al., 1997); such overload activates the secondary messenger system (proteinkinase C synthesis, increased intracellular $Ca^{2+}$ ion concentration) what results in activation of transcription factors and stimulation of hypertrophic processes.

The role of cytokines in all above intermolecular and intercellular interactions observed in patients with CHD (Fig. 2.16) is not established finally but it is evident that cytokines cannot but influence the mentioned processes directly or through an intermediary system being intercellular cooperation mediators.

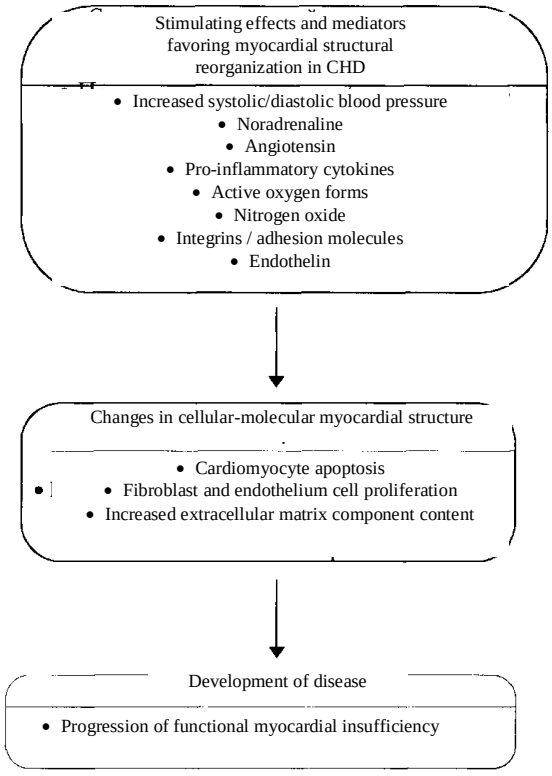


Fig. 2.16. Intermolecular and intercellular interactions observed
in patients with CHD (Colucci W.S. et al., 1997, with modifications).

When investigating liquidators of accident aftermath at ChNPP 30 years after the accident, we included males, the residents of Saint Petersburg and the Leningrad region, who participated in liquidation of accident aftermath at the Chernobyl NPP in 1986, in the test group (n=132). The age of investigated liquidators ranged from 45 to 65 years (mean age: 55.65±0.64 years). The documented absorbed radiation dose was not more than 20 cGy. The somatic pathology in subjects of the investigated category was characterized by multiple organ involvement at the time of examination taking account the age and exposure to a complex of radiation accident factors. The leading place by morbidity and disablement was taken by diseases of the circulatory system. The control group included patients not exposed to a complex of radiation accident factors (CRAF) who were comparable by gender, age and diagnosis.

The study of spontaneous and induced TNF-α production by peripheral blood mononuclear cells (PBMC) and the assessment of the cytokine content in the blood serum revealed the following peculiarities in patients of the compared groups. The study data is presented in Table 2.10.

Table 2.10

Levels of TNF-α production in vivo and in vitro (M±m, pg/ml)

| | Spontaneous production | Induced production | Blood serum |
|---|---|---|---|
| Liquidators (group I), n=33 | 170±18* | 310±45 | 120±33* |
| Control group (group II), n=18 | 130±26 | 429±87 | 33±15 |
| Reference values | 0-30 | 500-1500 | 0-30 |

*p<0.05

As one can see in Table the spontaneous TNF-α production was maximum in the liquidator group, it exceeded significantly the values in the control group and was more than 5 times higher that than the upper limit of the reference range. We paid attention to considerably lowered induced TNF-α production in the liquidator group as compared to the reference values. The lowered cell ability to produce TNF-α in response to an antigen stimulus is revealed the most clearly by studying the stimulation index (SI). TNF-α SI was 1.8 in the liquidator group and 3.2 in the control group.

Thus, TNF-α production disturbance in response to antigenic stimulation revealed in the liquidator group may be associated with long-term TNF-α hyperproduction by the peripheral blood cells, subsequent disturbance of the autocrine cytokine regulation and refractory condition of cells-producers to an antigen stimulus. A characteristic feature of the investigated liquidator group consisted in significantly increased TNF-α level in the peripheral blood as compared to patients of the control groups and reference values.

The cytokine synthesis and production were investigated at the level on one cell because of the need to elucidate more precisely the mechanisms of disturbed TNF-α production by PBMC in liquidators with the cardiovascular pathology. The data is presented in Table 2.11.

Table 2.11

The number of cells (%) synthesizing TNF-α in patients of the compared groups (M±m, pg/ml)

| Parameter | Liquidators, *n* = 42 | Control group, *n* = 14 |
|---|---|---|
| TNF-α, intracellular form | 8.9 ± 1.1* | 4.4 ± 0.3 |
| TNF-α, surface form | 7.4 ± 0.6* | 4.8 ± 0.7 |

*p<0.05

As it is seen from the data presented in Table, the 1st liquidator group had a significantly increased number of cells with intracellular and surface TNF-α forms. The changes in TNF-α synthesis revealed in the test patient groups with cardiovascular pathology are in agreement with the literature data evidencing that TNF-α is involved in the development of this pathology (Hargreaves R.G. et al., 1997). More pronounced disturbances revealed in the liquidator group confirm the literary data on the fact that exposure to low radiation doses intensifies significantly TNF-α production (Natarajan R. et al., 1997) which favors intensified apoptotic processes in immonocompetent cells (Yarilin A.A., 1996).

We revealed also changes in IL-4 synthesis in the liquidator group (in contrast to the control group). The data is presented in Table 2.12.

Table 2.12

The number of cells (%) synthesizing IL-4 in patients of the compared groups, (M ±m, pg/ml)

| Parameter | Liquidators, *n* = 40 | Control group, *n* = 14 |
|---|---|---|
| IL-4, intracellular form | 18.30±1.93* | 3.28±0.98 |
| IL-4, surface form | 1.62±0.19 | 1.3±0.19 |

* p<0,01.

As follows from Table, the liquidator group had significantly intensified IL-4 synthesis as compared to PBMC in the control group (p0.01) what may be evidence of switching the immune response from Th1 to Th2, which is less effective in pathogen elimination.

The characteristic features of IL-6 synthesis in liquidators of accident aftermath at ChNPP as compared to subject group not exposed to CRAF in the past are presented in Table 2.13.

Table 2.13

The number of cells (%) synthesizing IL-6 in patients of the compared groups, (M ±m, pg/ml)

| Parameter | Liquidators, *n* = 43 | Control group, *n* = 14 |
|---|---|---|
| IL-6, intracellular form | 13.10±1.21* | 2.08±0.62 |
| IL-6, surface form | 1.40±0.17 | 2.89±0.49 |

*p<0.001 as compared to the control group.

The study of IL-6 synthesis and production in liquidators revealed significantly increased cell number synthetizing Th-2 cytokine relative to the control group. The revealed increased number of cells synthetizing IL-6 which, as it is known, favors the lowered myocardium contractility, is one of the components in the pathogenesis of the cardiovascular pathology in liquidators.

Thus, the studies found that the exposure to the complex of accident factors at ChNPP including ionizing radiation caused changes in the number of cells synthetizing and producing cytokines spontaneously.

The intensified TNF-α synthesis favors the development of the cardiovascular pathology in liquidators and patients of the control group. It is known that TNF-α causes changes in endothelial cells and leads to multiple vascular pathology due to adhesion molecule activation. TNF-α influences also the coagulation processes favoring thrombosis (Ketlinsky S.A., 2008). Basing on this data one may suppose that the development of the cardiovascular pathology is more pronounced in the liquidator group due to intensified synthesis of this cytokine.

The fundamental studies of the last years are evidence of a significant role played by immune inflammation in the pathogenesis of atherosclerosis. The progression of atherosclerosis process in the vascular wall is associated with formation of immune complexes (IC) containing unchanged or modified low density lipoproteins (LDL-IC) and with increased pro-inflammatory cytokine production. The studies revealed biologic differences between LDL-IC and other IC types, clinical and pathogenetic features of the humoral autoimmune response associated with anti-LDL- antibody isotype. It is known that increased cytokine production by monocytes, the numerous regulatory effects of which are significant for the pathogenesis of atherosclerosis, is one of the consequences associated with the interaction between LDL-IC and monocytes. The results of studies performed by both home and foreign authors are evidence of a significant correlation between increased cytokine production and the degree of clinical symptoms of CHD, significantly increased TNF-α and IL-1β content in the serum in patients with destabilized CHD course; one of the consequences of the increased cytokine level consists in the fact that they induce expression of adhesion molecules sICAM-1. In addition to the direct hypolipidemic action, statins widely used by the internists, have several pleotropic effects. These effects include anti-inflammatory effects: statins lower the serum C-reactive protein level. Besides that, the investigations in vitro demonstrated that statins lowered IL-1β, TNF-α, IL-6, IL-8 pro-inflammatory cytokine secretion by endothelial cells and macrophages.

The investigation of liquidators in a long-term period after the accident (in 30 years) revealed the preserved activation in the T-cell component of the immune system, the increased spontaneous production and blood serum content of pro-inflammatory cytokines. While pro-inflammatory

cytokine hyperproduction by peripheral blood mononuclear cells in LAA was a compensatory macroorganism's reaction to exposure to a complex of radiation accident factors (CRAF) and it was aimed at maintaining the homeostasis (results of numerous studies proved radioprotective effects of IL-1β, TNF-α, IL-6, INF-γ and other pro-inflammatory cytokines) during the first years after the accident at ChNPP, subsequently, maintaining the immune inflammation favored the formation of characteristic features of cardiovascular diseases in this subject category (Bychkovskaya I.B., et al., 2000; Petrichshev N.N., Vlasov T.D., 2003).

The investigation results of the immunity parameters in patients with cerebral vascular diseases in the liquidator (n=31) and control (patients with the similar pathology no exposed to CRAF previously, n=19) groups are presented in Table 2.14.

Table 2.14

The comparative characteristics of the basic immunological parameters in LAA and patients of the control group

| Parameter | Liquidators | Control group |
|---|---|---|
| Lymphocytes, % | 28.4±1.55* | 36.1±1.4 |
| Lymphocytes, abs. number | 2079±114* | 2539±132 |
| CD3+, abs. number | 1470±88* | 1829±132 |
| CD3+ HLADR+, % | 6.6±0.4* | 2.2± 0.3 |
| CD4+, abs. number | 878±54* | 1090±110 |
| CD16+CD56+, abs. number | 273±35* | 406±68 |
| CD16+CD56+HLADR+, % | 1.4±0.1 | 0.9±0.1 |
| CD25, % | 11.8± 0.6* | 3.6±0.6 |
| CD25, abs. number | 245± 27* | 102±23 |
| CD95, % | 6.7±0.9 | 7.6±1.0 |
| CD95, abs. number | 130.0±18 | 190 ±28 |
| CD4+CD8+, % | 2.5±0.4* | 0.8±0.1 |
| CD19+CD5+, % | 3.6±0.7* | 1.5±0.3 |
| IL-1β serum, pg/ml | 93±20* | 35±3 |
| IL-6 spont., pg/ml | 217±26* | 59±5 |
| IL-10 serum, pg/ml | 24±18 | 20±6 |
| IL-l induced, pg/ml | 80±12* | 417±15 |
| TNF-α serum, pg/ml | 120±33* | 39±10 |
| TNF-α induced, pg/ml | 262±59* | 542±91 |
| INF-γ serum, pg/ml | 324±119* | 51±8 |
| INF-γ spont., pg/ml | 140±37* | 37±5 |

*p<0.05 between groups I and II, Wilkoxon - Mann – Whitney test.

The liquidator group has lowered absolute lymphocyte number of the following subpopulations: CD3, CD4, CD16, CD95 (what is associated with significantly lower lymphocyte number in the liquidator group) relative to the control group.

The lymphocyte number expressing CD25, the early activation marker (11.8±0.6%), number of activated T-lymphocytes (CD3+HLA DR+) (6.6±0.4%), activated NK-cells (CD (16+56) + HLADR+) (1.4±0.1%) were higher than these in the control group. The number of "double-positive" T-lymphocytes (CD3+CD4+) was higher than that in the control group and exceeded the upper limit of the population reference range. The autoreactive B1-lymphocyte (CD19+CD5+) number also exceeded the values in the control group and the limits of the population reference range.

When comparing the investigation results of patients of both groups, we paid attention to activated pro-inflammatory cytokine production in the liquidator group in contrast to the control group which did not show significant deviations from the reference values in the spontaneous

production of pro-inflammatory cytokines. Liquidators had increased serum IL-1β ($p<0.05$), TNF-α ($p<0.01$) content. The lowered induced TNF-α production ($p<0.05$) was observed. We found the increased spontaneous IL-6 production ($p<0.01$), increased serum content and higher spontaneous production of INF-γ as compared to the control group.

Similar to the control group, liquidators had normal serum IL-10 content. The lowered induced IL-1β, TNF-α, IL-10 production allows to suppose chronic immune inflammation with absence of its suppression mechanisms.

On the whole, the observed changes in the cytokine production are of significant importance for development of the vascular wall pathology because pro-inflammatory cytokines are mediators of endothelium damage (Khirmanov V.N., Sidorov M.G., 2009). The effect of the pro-inflammatory cytokines TNF-α, IL-1, INF-γ makes endothelium cells to express actively adhesion molecules and leukocyte to express their ligands. The increased adhesiveness to the endothelium walls precedes the coming out of cells from the vascular bed to the tissues. IL-1, IL-6, TNF-α activate leukocytes and, thus, favor leukocyte infiltration of the myocardium in patients with myocardial infarction. The pro-inflammatory cytokines are involved in the development of atherosclerosis because cholesterol metabolism is regulated by them. The activation of endothelium and smooth muscle cells in vessels, cardiomyocytes, neutrophils, marcophages, micro- and astroglia cells by the proinflammatory cytokines TNF-α, IL-1, INF-γ results in induction of production of NO-synthase, the enzyme involved in nitrogen oxide synthesis, by these cells. Nitrogen oxide causes activation of guanylate cyclase in smooth muscle cells in the vessels and, thus, increases, cyclic GMP concentration (Epperly M., 1999; Petrichshev N.N., Vlasov T.D., 2003).

The development of secondary antiphospholipid syndrome with production of antiphospholipid antibodies in liquidators is another mechanism of vascular damage.

The antiphospholipid antibody level exceeded the normal values in 65% of liquidators out of 120 investigated subjects, what, probably, evidences the development of secondary antiphospholipid syndrome in this patient cohort.

As it is known, disturbed endothelium function is one of universal pathogenesis mechanisms of many diseases. Endothelium dysfunction influences significantly the development of uncontrolled blood coagulation. Such pathology may develop in patients with diseases of autoimmune genesis united in a symptom complex under a general name of antiphospholipid syndrome (APS). Antiphospholipid antibodies (APA) are serologic markers of APS. APA are revealed more often as the age increases, especially in elderly subjects with vascular diseases. The vascular pathology in 50-70% of patients with APA may develop during a long period of 20 years. Clinical symptoms of APS, specificity and physiologic activity of APA, their effects, when they bind to the targets, are described in numerous studies (Kalinina N.M. et al., 2004; Grumbach I. et al., 2005).

The endothelium, the internal vascular lining, has pronounced metabolic activity and fulfills different functions. Endothelium dysfunction, which is being formed also under the effect of pro-inflammatory cytokines IL-1β, TNF-α and others, favors the development of thromboses, intravascular thrombocyte activation etc. The vascular wall is directly involved in regulation of the blood coagulation potential by producing different endothelial factors which may be divided conditionally to thrombogenic and athrombogenic ones. The production of athrombogenic

substances prevails over production of thrombogenic ones in the physiologic state what serves as a precondition for thromboresistance. The luminal endothelium surface has receptors to many biologically active substances including cytokines which exert not only local but also systemic effect on the vessels and blood cells. The disturbed vascular wall integrity or changed functional properties of endothelium cells is accompanied by imbalance between thrombogenic and athrombogenic vascular factors and leads to hemostasis system disorders.

### *Diagnostics of autoimmune diseases in liquidators*

Endogenic factors, which are able to disturb the vascular wall integrity or cause endothelium dysfunction, include autoimmune antibodies. They can exhibit membrane-aggressive properties what favors thrombus formation (Kalinina N.M. et al., 2004; Grumbach I. et al., 2005).

The pathogenesis of APS is associated with disturbed integrity and/or functional activity of endotheliocytes because of immune complex formation with endothelial and thrombocyte proteins involved in hemostasis. There are different theories which explain cellular and molecular mechanisms through which APA initiate thromboses. One of these theories supposes endothelium cell activation after binding with APA what is manifested in adhesion molecule expression, intensified cytokine secretion and prostacyclin metabolism. The second one is based on the oxidative damage of the vascular endothelium. Oxidized low density lipoproteins (LDL) are captured by macrophages what leads to their activation, cytokine production and subsequent endothelium cell damage. This is confirmed by the fact that autoantibodies against oxidized LDL circulate in association with APA and some APA cross-react with oxidized LPL. APA differ from other coagulation inhibitors in the fact that they bind the antigens immobilized on the anion phospholipid membrane surface and, as a rule, do not lower their level in the blood.

Antiphospholipid antibodies, the increased level of which was observed in 65.1% of liquidators of accident aftermath at ChNPP, play the leading role in the pathogenesis of antiphospholipid syndrome. The wide antigen range causing production of APA guarantees various supposed pathophysiologic mechanisms and heterogeneous clinical symptoms of this syndrome.

Autotolerance failure in liquidators became the materialization of the long immune inflammation characterized by pro-inflammatory cytokine hyperproduction and activation of cells involved in the immune response.

When assessing liquidators' immunity parameters 30 years after the accident, we selected the parameters which on the whole are evidence of autotolerance failure. The studies revealed increased number of autoreactive T- and B-lymphocyte clones in the blood, lowered number of regulatory T-cells and anti-inflammatory cytokine production exerting an inhibiting effect on the autoimmune response. The increased number of "double-positive" T-cells in the blood and also autoreactive B-lymphocyte clones is considered as precondition for autoaggression (Yevstratova I.V., 2004; Sugumar, 2009).

The humoral indicators of the autoimmune process include increased IL-6 production providing for B-cell differentiation to plasmacytes, INF-γ increased production of which favors presentation of own tissue antigens. The lowered synthesis and production of transforming growth factor β (TGF-β) and interleukin-10 (IL-10), the anti-inflammatory cytokines, are the indicators of low suppressor activity in the immune response (Komarovskaya M.E., 1992; Sugumar, 2009). The

investigation of liquidators included determination of “double-positive” T-lymphocytes (CD4+ CD8+) the number of which exceeding the limit of the population reference range was considered as one of the preconditions for development of the autoimmune process because it evidenced the immunologic tolerance failure. The increase of this parameter was revealed in 30% of subjects.

B-cells are divided in two main subpopulations, namely: B-1, B-2 and two types of memory B-cells (CD27+ CD5+, CD27+CD19) are formed after completion of the immune response (Savitsky D. et al., 2006). The B-1 and B-2 subpopulations may be distinguished by presence of the surface marker CD5. CD19+CD5+ or B-1 lymphocytes are cells which are responsible for autoantibody production. The high content (one third and more of the total B-lymphocyte number) is observed in patients with systemic and uncompensated organ-specific autoimmune diseases. The presence of autoreactive B-lymphocyte clone number exceeding the upper limit of the reference range is also a precondition for autoaggression and evidences the immunologic tolerance mechanism failure.

Such parameters as T-regulatory cells with CD4+CD25+CD127 phenotype (Baecher-Allonc et al., 2006), which, according to present views, are the chief cells suppressing the autoimmune response, were also investigated in liquidators. Besides that, antinuclear, antiphopholipid antibodies, anti-DNA (native and denaturated) antibodies, antibodies against parietal cells were determined.

The investigation of peripheral blood B-lymphocyte subpopulations in liquidators revealed the increased number of cells expressing CD19+CD5+ in 15%.

T-regulatory cell number with phenotype CD4+CD25+CD127 was lowered in 10.1% of investigated liquidators (Baecher-Allonc et al., 2006).

Thus, the investigation of the peripheral blood lymphocyte subpopulation composition allowed to reveal preconditions for autoimmune pathology in about 30% of liquidators: increased number of autoreactive both T- and B-lymphocyte clones, lowered T-regulatory cell number what was evidence of immunological tolerance failure.

Gastrointestinal diseases have been described among organ-specific diseases of autoimmune nature; the determination of specific antibodies, the concentration of which, exceeding the reference value, may precede manifestation of clinical symptoms, is of great importance in their diagnostics (Lapin S.V., Totolyan A.A., 2010).

As it is known, autoimmune diseases result from tolerance loss regarding own organism antigens. The autoimmune response to alloantigens is antigen-specific.

At present, the number of autoimmune diseases of the endocrine organs is quite high. They include insulin-dependent diabetes mellitus type I, Addison’s disease, autoimmune thyroid diseases, namely, diffuse toxic goiter (DTG), Hashimoto’s disease, atrophic autoimmune thyroiditis (AIT) and also polyglandular syndromes of type I and II.

According to many authors, AIT is one of the most frequent TG diseases; it is observed in 20-40% of the adult population with the thyroid pathology and is a main cause for primary hypothyroidism. The problem of the thyroid autoimmune pathology became especially urgent after the Chernobyl catastrophe.

The patient group had no increased spontaneous production and higher serum content of IL-1β, but the investigation revealed increased spontaneous interleukic-1α, β receptor antagonist production (IL-ra). The induced production of interleukin-2 growth factor produced by T-helpers of

type I was 10.17 ±5.02 pg/ml and this level was lower than the mean values of this parameter in the healthy population (27.7±6.4). The high spontaneous INF-γ production was observed in the investigated patient group (181.4±87.5). INF-γ produced, mainly, by T-helpers of type I and natural killers can intensify antigen HLA and transport protein expression required for antigen presentation including that to autoreactive T-lymphocytes. Liquidators with AIT had high spontaneous interleukin-6 (IL-6) production; according to literature data, its hyperproduction is considered as a peripheral mechanism for immunologic tolerance recovery. Liquidators with AIT still have the high serum content of pro-inflammatory cytokine TNF-α 30 years after the accident.

The changes revealed in the immune system may be considered as unstable balance of the factors maintaining the autoimmune process (high spontaneous interferon γ production level, high serum TNF-α content) and factors aimed at the immunologic tolerance recovery (high spontaneous IL-6, IL-1ra production, low induced IL-2 production).

The investigation algorithm of immunologic parameters in liquidators with AIT should include the following basic methods:

1. Determination of peripheral blood lymphocyte subpopulation composition with investigation of:
   - activated T-lymphocytes (CD3+ HLAII+);
   - B-lymphocytes (CD19+ HLAII+);
   - autoreactive T- (CD3+ CD8+ CD4+) and B- (CD19+ CD5+) lymphocyte clones.
2. Determination of spontaneous and induced production and serum content of IL-1, IL-2, IL-6, TNF-α, interferon-γ, IL-1 receptor antagonist.

It is advisable to recommend the additional methods:

- Determination of the number of professional effector cells with double markers. Determination of the number of professional effector cells (CD16briht CD56 dim), (CD3+CD8+).

### *Autoimmune pancreatitis (AIP) is an organ-specific autoimmune disease developing also in liquidators*

A significant revolution in investigation of AIP was achieved in 2001 when H. Hamano et al. reported the high serum $IgG_4$ level in patients with AIP. Later T. Kamisawa et al., (Kamisawa T. et al., 2004, 2005, 2006) described the intensive $IgG_4$-positive cell infiltration not only in the pancreas but also in other organs in patients with AIP. It was supposed basing on these observations that AIP may be a link of the systemic disease known as $IgG_4$-associated system disease (ISD) (Kamisawa T. et al., 2003).

The typical changes in serologic tests include increased plasma γ-globulin or immunoglobulin level, in particular $IgG_4$, presence of antinuclear antibodies and also antibodies against lactoferrin, carboanhydrase II and smooth muscles. The histological criteria of AIP include periductal lymphoplastocytic infiltration or fibrosis, obliterating phlebitis, increased $IgG_4$-positive plasmocyte cell content in the pancreatic tissues.

The diagnosis of AIP in all patients was verified using all clinical data in combination with immunologic and instrumental (ultrasound investigation, computed tomography) methods by suggested criteria (Aoki S. et al., 2005). For this purpose, the following immunologic diagnostic

methods were used: a) determination of C-peptide, antinuclear antibodies (ANA), anti-mitochondrial antibodies (AMA), anti-thyreoperoxidase antibodies (anti-TPO), anti-thyroglobulin antibodies (anti-TG), anti-parietal cell antibodies, anti-gliadin antibodies; b) assessment of immunoreactive insulin (IRI). When investigating patients with AIP, we revealed the following laboratory markers of autoimmune pathology:

- anti-TPO antibodies in 32.1%;
- anti-parietal cell antibodies in 5.1%;
- antinuclear antibodies in 25.6%;
- rheumatoid factor in 7.7%;
- anti-hepatic, renal and gliadin antibodies – 1.3%.

The literature concerning the problems of immunological tolerance pays close attention to lymphocyte differentiation and apoptosis processes in the central immunogenesis organs, especially double-positive T-lymphocyte subpopulations, the low-differentiated T-cells among which autoreactive T-clones may be present with extremely high probability. The increased level of these immature T-cells in the blood is considered as one of preconditions for autoaggression. At present, two basic subpopulations, namely B-1, B-2, are distinguished among B-cells. According to the literature data, B-1 cells are relatively long living cells, have the low-affine B-cell receptor on its surface, prevail in the abdominal and pleural cavities and also tonsils as compared to B-2 cells. The immune response results in formation of two memory cell populations with markers CD27+CD5+ and CD27+CD19+.

B-1 cells attract significant interest due to the fact they are associated with autoantibody production including cases with the autoimmune pathology. According to the literature, B-1-cells are responsible for production of circulating natural antibodies which are a kind of autoreactive antibodies. Natural antibodies are polyspecific, form a significant part of the autoreactive repertoire and are represented by different immunoglobulin subclasses. They bind with structurally heterogeneous epitopes of "foreign" or own molecules with low or moderate affinity; thus, they are involved in protection against bacterial pathogens in the beginning of the immune response, in autoantigen recognition and apoptosis product elimination. Increased concentrations of natural autoantibodies may be revealed in the blood of patients with autoimmune diseases without induction of normal tissue damage. The significantly increased CD19+CD5+-cell number was observed in patients with rheumatoid arthritis, systemic lupus erythematosus, Sjögren's sicca syndrome, myasthenia, insulin-dependent diabetes mellitus and Hashimoto thyroiditis.

Close attention is paid to regulatory cells which have the suppressor activity. T-regulatory cells have the following phenotype: $CD3^{+}CD4^{+}CD25^{bright}CD127^{dim\text{-}to\text{-}neg}$FOXP3+ CD45R0+CD95+. Studies showed that FOXP3, which codes scurfin transcription factor, was the main regulating gene for development and functioning of $CD4^{+}CD25^{high}$ regulatory T-cells. CD127 is α-chain of IL-7 heterodimer receptor, which consists of CD127 and common γ-chain which is available also in other cytokine receptors (IL-2R, IL-4R, IL-9R, IL-15R and IL-21R). Cd127 is expressed on thymocytes, T- and B-precursors, mature T-cells, monocytes and some other lymphoid and myeloid cells. It was shown that IL-7R plays an important role in mature T-cell proliferation and differentiation.

The high T-regulatory cell content in the peripheral blood is observed in patients with the hyperreactive immune response. It is probable that this situation reflects attempts of the immune

system to restrict the excessive cell activation. The lowered T-regulatory cell number in the peripheral blood in patients with autoimmune diseases is one of unfavorable signs and is associated with exacerbation.

Natural killer cells are the effector cells involved not only in the anti-infection but also in the autoimmune response. Their role in autoaggression is associated with their ability to materialize antibody-specific cytotoxicity relative to target cells including pancreatic cells the antigens of which gain immunogenicity properties and are involved in the autoimmune response. This lymphocyte subpopulation may kill target cells materializing ligand-receptor, perforin and granzyme- mediated apoptosis. The ability of NK- cells to activate autoreactive B-lymphocytes is proven.

According to foreign authors, immunologic indicators of the local immunity in patients with autoimmune pancreatitis include pancreatic lymphoplasmocytic infiltration, especially in the paraductal region, presence of $G_4$-expressing plasmocytes, T-helper and HLA DR-expressing cytotoxic T-lymphocyte subpopulations in the infiltrate. Revealing the HLA DR-expressing own cells in the infiltrated wall of the grand duct is a generally accepted autopresentation criterion, especially in combination with high interferon-γ production.

The analysis of results obtained during the immunological investigation of the liquidator cohort (n=62) examined at the All-Russian Nikiforov Center of Emergency and Radiation Medicine of the Ministry of Emergencies of Russia in 2008-2010 showed that the quantitative characteristics of mature T-lymphocytes (CD3+), T-lymphocyte (CD3+CD4+, CD3+CD8+), T-regulatory cell (CD4+CD25+CD127-), TNK-cell CD3+CD(6+56)+), B-lymphocyte (CD19+) and NK-cell [CD3-CD(16+56)+] subpopulations and also activated NK-cells (CD3-CD8+) were comparable with normal values for this population. But the immunoregulatory index exceeded the normal values for this population. The number of CD25-expressing lymphocytes (early activation marker), activated T-lymphocytes (CD3+HLA DR+) and activated NK-cells [CD (16+56) +HLA DR+] was increased. The number of double-positive autoreactive T-lymphocytes approximated to the upper limit of the population reference range. The autoreactive B-1-lymphocyte (CD19+CD5+) number exceeded the limits of the population reference range and was combined with high spontaneous interleukin-6 production, spontaneous production and serum content of interferon-γ which exceeded significantly these parameter values in healthy subjects. Exacerbation of chronic pancreatitis was confirmed by the high secretory immunoglobulin A level in the blood serum (factor of local protection for mucous coats) which exceeded the upper limit of the reference range 2 times. The mean serum immunoglobulin E level in this subject cohort exceeded the upper limit of the reference range 2 times.

So, the presented data is evidence of activation of different links in the immune system and prevailing of T-helper type II response, i.e. confirms exacerbation of chronic inflammatory process at the time of the investigation.

In order to analyze the obtained data in more details, we distributed all investigated liquidators in two groups: group 1 included liquidators suffering from chronic pancreatitis with endocrine insufficiency (n=20); group 2 comprised liquidators with exacerbation of chronic pancreatitis without pancreatic endocrine insufficiency (n=42).

The comparative analysis of immunologic parameters showed significantly increased spontaneous interleukin-6 production in the group 2. The liquidator group suffering from combination chronic pancreatitis and diabetes mellitus was characterized by increased serum

interleukin-6 levels, high spontaneous interferon-γ production exceeding the reference values while the lowered serum interferon-γ level was revealed in the group 2. The relative and absolute number of double-positive T-lymphocytes (CD3+CD4+CD8+), autoreactive memory B-cell clones in the group 2 was significantly higher than those in liquidators of the group 1. The activated T-lymphocyte (CD3+HLA DR+) number in the peripheral blood exceeded the reference values in both groups by any significant difference between the groups was not revealed. The activated NK-cell number in the liquidators group 2 exceeded this parameter value in the patient group 2 but differences were insignificant.

The secretory immunoglobulin A and total immunoglobulin E levels in both groups exceeded the limit of the reference range for this population. The liquidator group without diabetes mellitus had significantly increased anti-gliadin antibody A and G levels as compared to the group 1. The anti-gastric parietal cell autoantibody level was significantly higher in the patient group with pancreatitis with endocrine insufficiency than that in the group 2 and is exceeded significantly the limit of the reference range.

Thus, patients with exacerbation of chronic pancreatitis (group 2) had significantly increased number of low-differentiated double-positive T-lymphocytes, autoreactive memory B-cells as compared to the group 1. Significantly increased activated T- and NK-cell number, higher interleukin-6 and interferon-γ, secretory immunoglobulin A, immunoglobulin E levels were observed in both groups.

The liquidator group 1 had significantly increased anti-gastric parietal cell autoantibody level; this parameter and anti-gliadin autoantibody content corresponded to the upper limit of the reference range in the group 2.

Celiac disease is one of autoimmune gastrointestinal diseases. Celiac disease is an autoimmune disorder which involves the gastrointestinal tract; it is characterized by chronic inflammation of the enteric mucous coat and, as a consequence, by morphologic destruction and disturbed function.

Serological tests were suggested for diagnostics of celiac disease. They are very sensitive and specific. The determination of class A autoantibodies against tissue transglutaminase is one of available tests. At present, anti-gliadin antibody testing is recommended only in combination with determination of anti-tissue transglutaminase antibodies because of low sensitivity and specificity of the test-systems used. The diagnosis of celiac disease can be made if the results serological antibody tests and positive results of biopsy are in agreement. In case of correct diagnosis symptoms of the disease disappear when using gliadin-free diet (Lapin S.V., Totolyan A.A., 2010).

The presence of clinical symptoms with negative results of serological tests may be observed in patients with selective immunoglobulin A deficit. In this situation it is recommended to determine anti-tissue transglutaminase class G antibodies. Revealing the genetic markers (DQ2 and/or DQ8) may be recommended to diagnose celiac disease because of their high prognostication significance (the prevalence of these markers reaches 97% in patients with celiac disease and it is 40% in the general population).

ANCA are the second antibody group which are used for diagnostics of autoimmune gastrointestinal diseases. ANCA (anti-neutrophil cytoplasmic antibodies) are antibodies which are specific to cytoplasmic granulocyte and monocyte antigens. The immunofluorescent methods are

classical methods for revealing ANCA. The two basic luminescence types are revealed using the method of indirect immunofluorescence:

- cytoplasmic (c-ANCA);
- perinuclear (p-ANCA).

Basic antigens for c-ANCA and p-ANCA were identified. Proteinase 3, PR3-serin protease from neutrophil α-granules is the target antigen for c-ANCA in 80-90% of cases; these antibodies are directed against other proteins in 10-20%. p-ANCA are formed against antigens of positively charged perinuclear proteins.

p-ANCA antibodies are directed against myeloperoxidase (MPO) localized in neutrophil granulocyte granules in 90% of cases; antibodies against following antigens: lactoferrin, elastase, cathepsin G and lysozyme are revealed in 10% of cases. But the immunofluorescent method does not allow to differentiate granulocyte-specific antinuclear antibodies (GS-ANA). When p-ANCA are revealed, it is recommended to confirm the obtained results by IEA (immune enzyme assay) method which is more specific and reproducible (Lapin S.V., Totolyan A.A., 2010).

Anti-PR3-antibodies correlate with the patient's clinical status, their level decreases during the therapy and they may be absent in remission. Anti-MPO-antibodies also correlate with the clinical status, their level is always higher in the active disease phase and they do not disappear in remission.

Such autoimmune gastrointestinal diseases and nonspecific ulcerous colitis, Crohn's disease are indications for revealing specific ANCA.

Detection of the autoantibody complex, which includes anti-SLA/LP class G antibodies, makes it possible to confirm this supposition. Recently an opinion was expressed that SLA antigen (soluble liver antigen/liver-pancreas) is identical to hepatic cytokeratins 8 and 18 or enzyme glutathione-S-transferase. It is known at present that the target antigen SLA/LP is a cytoplasmic molecule involved in biosynthesis regulation of the protein associated with UGA codon suppressor of tRNA (transport ribonucleic acid) (Zhang L. et al., 2007).

In addition to anti-SLA/LP antibodies, autoimmune hepatitis is associated with antibodies against cell nuclei (ANA), native DNA, smooth muscle tissue (SMA with the most important target antigen F-actin), liver-kidney microsomes (LKM-1; cytochrome P450IID6 is a target antigen) and granulocytes (pANCA). Anti-SLA/LP antibodies are evidently the most diagnostically reliable among all autoantibodies synthesized in patients with autoimmune hepatitis. Anti-SLA/LP antibodies alone or in combination with other autoantibodies may be revealed in the patients' serum. Anti-SLA/LP antibodies are detected in 10-30% of patients with autoimmune hepatitis. Revealing anti-SLA/LP autoantibodies in the serum makes it possible to confirm availability of autoimmune response.

Autoantibodies against cell nuclei and smooth muscles are also often revealed in subjects with autoimmune hepatitis but they are found also in 10-20% of patients with other diseases. Anti-LKM-1 autoantibodies were revealed in only 1% of adults with autoimmune hepatitis (Lapin S.V., Totolyan A.A., 2010).

Primary biliary cirrhosis developing in the form of nonsuppurative destructive inflammatory process in the biliary ducts (chronic nonsuppurative destructive cholangitis) is characterized by detection of anti-mitochondrial M2 autoantibodies (AMA M2) and anti-SP100 acidic protein antibodies. The process becomes autoimmune-like in approximately 10-15% patients with primary

biliary cirrhosis what is confirmed by revealing autoantibodies of other specificity, in particular anti SLA/LP antibodies.

Antibodies against α- and β-subunits of $H^+/K^+$-ATPase of gastric parietal cells are revealed in patients with pernicious anemia, which is a final stage of chronic atrophic gastritis of type A. Pernicious anemia is caused by vitamin $B_{12}$ deficit resulting in disturbed DNA synthesis and, as a consequence, in functional and morphologic disorders in erythrocytes and their precursors (Lapin S.V., Totolyan A.A., 2010).

Anti-gastric parietal cell autoantibodies are revealed in 80-90% of patients with pernicious anemia and in 50% of patients with atrophic gastritis without pernicious anemia. Autoantibodies of this specificity are often found in patients with other organ-specific autoimmune diseases such as diabetes mellitus type I, autoimmune thyroiditis, primary Addison's disease.

The determination of anti-parietal cell antibodies is less specific for pernicious anemia than investigation of antibodies against the internal factor, glycoprotein, synthesized exclusively by gastric parietal cells. It is essential for transport and absorption of vitamin $B_{12}$ in the small intestine. There are two types of antibodies against the internal factor: antibodies of type I block the cobalamin-binding site on the internal factor molecule thereby preventing vitamin binding; antibodies of type II block the site involved in binding of the complex internal factor – cobalamin with intestinal receptors (Mazurov V.I., 2005).

The immunologic investigation was performed in a liquidator group with exacerbation of chronic pancreatitis. At present there is a sufficient number of studies indicating the development of autoimmune pancreatitis in case of immunologic tolerance failure in patients with the gastrointestinal pathology (Batskov S.S. et al., 2010; Okazaki K. et al., 2005; Kamisawa T. et al., 2008; Sugumar A. et al., 2009).

Autoimmune pancreatitis is an organ-specific autoimmune disease but there is no literature data on specific immunologic criteria confirming the autoimmune nature of inflammation. The immunologic parameters determined in combination with clinical, biochemical, X-ray investigation findings in patients are indirect signs, the whole complex of which is evidence of disturbed autotolerance. The mechanisms of immunologic tolerance failure are different: disturbed central mechanisms of immunologic tolerance formation (selection processes) result in increased autoreactive T-helper, B-lymphocyte clone number in the blood and disturbed peripheral mechanisms lead to insufficient suppressor effects in the immune response. The lymphocyte differentiation and apoptosis processes in the central immunogenesis organs are still being studied; autoreactive clones are present among T-lymphocytes with the phenotype of "double-negative" – "double-positive" cells, i.e. low-differentiated, immature T-cells, with high probability. The increased number of these immature T-cells and also autoreactive B-lymphocyte clones in the blood is considered as preconditions for autoaggression.

The peripheral humoral parameters of the autoimmune process include increased level of IL-6, the cytokine providing for B-cell differentiation to plasmocytes, interferon-γ, the factor influencing autopresentation of own tissue antigens, including the pancreas. The indicators of low suppressor activity in the immune response include lowered synthesis and production of TGF-β (transforming growth factor-β) and IL-10 (interleukin-10), the anti-inflammatory cytokines.

The foreign literature presents a complex of immunologic parameters confirming autoimmune nature of inflammation in the pancreas including the parameters of both systemic and local

immunity. The systemic parameters include increased γ-fraction, immunoglobulin G and immunoglobulin G4 subclass levels in the blood serum (Taguchi M. et. al., 2005).

According to foreign authors, the indicators topical inflammation in patients with autoimmune pancreatitis include pancreatic lymphoplasmocytic infiltration, especially in the paraductal region, presence of G4-expressing plasmocytes, T-helper and HLA DR-expressing cytotoxic T-lymphocyte subpopulations in the infiltrate. Revealing the HLA DR-expressing own cells in the infiltrated wall of the grand duct is a generally accepted autopresentation criterion, especially in combination with high interferon-γ production.

We investigated 70 liquidators with the gastrointestinal pathology. We did not reveal any changes in quantitative characteristics of mature T-lymphocytes (CD3+), T-lymphocyte (CD3+CD4+, CD3+CD8+), T-regulatory cell (CD4+CD25+CD127-), TNK-cell [CD3+CD(16+56)+], B-lymphocyte (CD19+) and NK-cell [CD3-CD(16+56)+] subpopulations and also activated NK-cells (CD3-CD8+) as compared to normal values for this population. The immunoregulatory index exceeded the reference (1.9±0.1). The number of CD25-expressing lymphocytes (early activation marker) (11.8±0.6%), activated T-lymphocytes (CD3+HLA DR+) (6.6±0.4%) and activated NK-cells (CD(16+56)+HLA DR+) (1.4±0.1%) was higher than the reference values. The number of "double-positive" T-lymphocytes, the low-differentiated cells, approximated to the upper limit of the population reference range. The autoreactive B-1-lymphocyte (CD19+CD5+) number exceeded the limits of the population reference range and was combined with high spontaneous interleukin-6 production, spontaneous production and serum content of interferon-γ which exceeded significantly these parameter values in healthy subjects. Exacerbation of chronic pancreatitis was confirmed by the high secretory immunoglobulin A level in the blood serum (factor of local protection for mucous coat) which exceeded the upper limit of the reference range 2 times. The mean serum immunoglobulin E level in this subject cohort exceeded the upper limit of the reference range 2 times and anti-gastric parietal cell autoantibodies concentration exceeded it nearly 3 times.

So, the presented data is evidence of activation of different links in the immune system and prevailing of T-helper type II response, i.e. confirms exacerbation of chronic inflammatory process at the time of the investigation. Thus, as there are no specific immunologic criteria for diagnostics of autoimmune pancreatitis, it becomes especially important to investigate the complex of immunologic parameters evidencing failure of central and peripheral immunologic tolerance mechanisms, namely: autoreactive T- and B-lymphocyte clones, autoantibodies of different specificity, interferon-γ and IL-6. It is advisable to determine G4 subclass, specific antibodies against pancreatic antigens in the blood serum when following up these patients in order to confirm autoimmune nature of chronic pancreatitis (Taguchi M. et al., 2005).

The findings of the immunologic investigation of liquidators (n=70) and patients of the control group (n=20) with exacerbation of chronic pancreatitis are presented in Table 2.15. The reference of the investigated immunological parameters revealed significantly increased spontaneous IL-6 production by peripheral blood mononuclear cell in the liquidator group as compared to patients of the control group (see Table 2.15). The increased IL-6 level in the blood serum was observed. The spontaneous interferon-γ production exceeded the reference values and the spontaneous production level in the control group. The activated T-lymphocyte (CD3+HLA

DR+) number in the peripheral blood in the liquidator group exceeded also the reference values and values of the similar parameter in the control group.

Table 2.15

The comparative characteristics of the basic immunologic parameters in liquidators with chronic pancreatitis and patients of the control group

| Parameters | Liquidators | Control group |
|---|---|---|
| IL-6, spontaneous production (pg/ml), [0-50] | 120±18* | 63±5 |
| IL-6 in blood serum (pg/ml), [0-50] | 59±23* | 29±13 |
| INF-γ, spontaneous production (pg/ml), [0-50] | 95±21* | 35±17 |
| INF-γ in blood serum (pg/ml), [0-50] | 100±45* | 31±14 |
| CD4+CD8+, % [0.1-1.5] | 2.4±0.2* | 1.2±-0.5 |
| CD19+CD5+, % [0-2] | 3.5±0.7* | 1.2±0.6 |
| CD3+HLADR+, % [0-5] | 7.2 ±0.5* | 1.9±0.4 |
| Anti-gastric parietal cell antibodies (U/ml), [0-10] | 79±47* | 11.7±2.9 |

*p<0.05 between the liquidator group and Control group, Wilkoxon - Mann – Whitney test.

The relative number of "double-positive" T-lymphocytes (CD4+CD8+), autoreactive B-cell clones was increased what was evidence of disturbed immunologic tolerance in subjects of the test group and these parameters can be considered as prognostication markers of autoimmune diseases in liquidators.

The polyclonal immune system activation is confirmed by significantly increased autoantibody levels revealed in the liquidator groups. The screening revealed anti-gastric parietal cell antibodies in the blood serum in 67 out of 234 liquidators with gastrointestinal diseases what was 29% of the whole subject cohort. It is known that anti-parietal cell autoantibodies are revealed in patients with atrophic gastritis.

Five out of 70 liquidators had increased anti-gliadin class A and G antibody levels, 23 subjects (32.8%) showed increased anti-gliadin class A antibody level, 10 liquidators (14.3%) had increased anti-gliadin class G antibody level, anti-transglutaminase class A antibodies were revealed in 2 patients (2.8%) anti-transglutaminase class G antibodies were found in 10 persons (14.3%). The increased level of these antibodies is a laboratory diagnostic criterion of secondary celiac disease, the autoimmune disorder which is characterized by chronic inflammation of the enteric mucous coat and, as a consequence, by morphologic destruction and disturbed function.

Immunologic disorders in liquidators with chronic pulmonary diseases were investigated in 30 liquidators (chronic obstructive bronchitis, chronic non-obstructive bronchitis, chronic obstructive pulmonary disease, asthma) in remission period 24 years after the accident.

When investigating liquidators with chronic pulmonary diseases (n=30) we compared the immune system parameters with those in the control group which included 15 subjects. The activation (increased relative T-helper number accompanied with increased mature T-lymphocyte CD3+ number) was revealed in the cellular link in 24 liquidators with the respiratory pathology (80%). The number of "double-positive" T-lymphocytes with the phenotype CD4+CD8+ in the peripheral blood exceeded the reference values in 5 (16.7%) subjects of this category what was evidence of disturbed autotolerance.

The investigation of B-lymphocyte number in the peripheral blood revealed the increased number of cells expressing CD19+CD5+ in 20.0% of liquidators, i.e. increased autoreactive B-lymphocyte number (Yevstratova I.V., 2004; Suzuki N., 1990).

Thus, the investigation of the peripheral blood lymphocyte subpopulation composition allowed to reveal preconditions for autoimmune pathology, i.e. increased autoreactive T- and B-lymphocyte number, in 26.6% (10% of LAA had increased autoreactive T- and B-lymphocyte number, 6.6% of LAA showed increased "double-positive" T-cell number, 10% has increased autoreactive B-lymphocyte number) what was evidence of central mechanism failure of immunologic tolerance formation (Yevstratova I.V., 2004; Oradovskaya I.V., 2007; Suzuki N., 1990).

The antiphospholipid antibody level exceeded the normal values in 13 liquidators (37%) out 30 investigated LAA with chronic pulmonary diseases what confirmed, evidently, presence of secondary antiphospholipid syndrome; 4 subjects (13.3%) had the high anti-gastric parietal cell antibodies what was consistent with the data obtained by I.V. Oradovskaya (2007). Sixty percent of investigated liquidators had the increased relative and absolute TNK-lymphocyte number. TNK-lymphocytes can not only realize the cytotoxic activity but they are characterized by the high interferon-γ production required for fulfilling this function. The increase of this subpopulation is observed in patients with autoimmune diseases and also with chronic recurring viral infections and neoplastic processes (Yamamura T., 2007).

The studies performed in the liquidator group with the respiratory pathology did not reveal lowered natural killer cell number; 30% of subjects had increased activated NK-cell pool. As known these cells belong to the innate immunity system, provide for nonspecific antiviral and antitumor protection in the organism (Sepiashvili R.I. et al., 2005). The adequate interferon-α and –γ production is also required for realization of this protection. But 50% of subjects had lowered induced interferon-α production in response to a standard inductor what was evidence of inadequate antiviral and antitumor protection in this liquidator cohort.

All investigated liquidators suffered from frequent acute upper respiratory tract infections, herpes infection exacerbations. The T-helper number was increased in 66.6% of all investigated liquidators; the number of specific cytotoxic lymphocytes corresponded to the reference values or was lowered, i.e. the immune response, mainly, of type Th2 developed (with antibody formation), which was less effective regarding viral pathogen elimination. This was confirmed by the results obtained in the study of immunoglobulin production.

The investigation of immunoglobulins showed that IgM, IgG levels were increased nearly in all liquidators at the time of the examination; such findings were revealed in combination with increased secretory Ig A level in 50% and in combination with increased IgE level in 30%.

The studies revealed lowered number of natural killer cells which belong to the innate immunity and provide for antiviral protection in the organism.

The viral pathogen persistence was confirmed by natural killer activation; 30 of subjects had increased cell pool with the phenotype CD3(-)CD8(+). The adequate interferon-α and –γ (INF-α and INF-γ) production is also required for the effective antiviral immune response.

The peripheral blood cells did not produce adequate IFN-α and IFN-γ quantities in vitro in response to the standard virus in 50% of all investigated liquidators of accident aftermath at ChNPP what was evidence of viral pathogen persistence and lowered functionality of cells producing interferons in response to the antigenic stimulus (Korobko I.V. et al., 1996).

Sixty percent of investigated liquidators had increased both relative and absolute NKT-lymphocyte number (CD3+CD16+CD56+); the increased number of this subpopulation is evidence

of the additional involvement of compensatory mechanisms under conditions of quantitative and functional insufficiency of effector cells killing target cells affected by viruses.

Thus, when assessing the immunity parameters in liquidators 30 years after the accident we determined the parameters which on the whole are evidence of autotolerance failure. The disturbed central mechanisms of immunologic tolerance results in increased autoreactive T- and B-lymphocyte clone number, lowered regulatory T-cell number and production of anti-inflammatory cytokines inhibiting the autoimmune response. The increased number of "double-negative" and "double-positive" T-cells and autoreactive B-lymphocyte clones in the blood is considered as a precondition for autoaggression (Yevstratova I.V., 2004; Oradovskaya I.V., 2007; Suzuki N., 1990).

The humoral indicators of the autoimmune process include increased IL-6 production providing for B-cell differentiation to plasmacytes, INF-γ increased production of which favors presentation of own tissue antigens. The lowered synthesis and production of transforming growth factor β (TGF-β) and interleukin-10 (IL-10), the anti-inflammatory cytokines, are the indicators of low suppressor activity in the immune response (Komarovskaya M.E., 1992; Oradovskaya I.V., 2007; Suzuki N., 1990).

The revealed characteristic features of the immune response, chronic immune inflammation contribute to specific course of cardiovascular, respiratory and gastrointestinal diseases in the liquidator group of accident aftermath at ChNPP.

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# CHAPTER 3

# INNOVATION MEDICAL TECHNOLOGIES FOR DIAGNOSTICS OF HEALTH CONDITION PARAMETERS IN PARTICIPANTS OF LIQUIDATION OF ACCIDENT AFTERMATH AT THE CHERNOBYL NUCLEAR POWER PLANT AND RESULTS OF THEIR USE

## 3.1. INNOVATION METHODS FOR ASSESSMENT OF THE BIOELEMENT STATUS

The influence exerted by a complex of environmental factors results in pathological functional and morphologic changes in different organs and systems. Therefore, when considering the medical consequences of the accident at ChNPP we have to consider not only the exposure to radiation but also negative chemical factors accompanying liquidation of the accident at ChNPP. One should take into account the possible additional effect exerted by the factors of radiation and non-radiation nature during the everyday life of liquidators of the radiation accident in a long-term period.

It is known that liquidators were exposed to chemical substances already at the early stages of accident liquidation. The destroyed reactor was covered with about 5000 t of different materials including 40 t of boron compounds, 600 t of dolomite, 1800 t of clay and sand, about 2500 t of metal lead. Lead melted and evaporated in the form of superfine steam-gas phase in the incandescent zone (2000 °C) and contaminated the environment. The lead concentrations exceeded MPC 10-12 times in some settlements at a distance of 80-120 km from ChNPP in the first month after the accident (Shubik V.M. et al., 2006).

Studying the element "portrait" of the population in individual biogeochemical regions and occupational groups in order to develop and introduce measures for elimination of revealed microelementoses is one of the perspective innovation directions in the modern medicine.

According to results of the recent research, disturbed macro- and microelement homeostasis leading to lowered health resources is one of the risk factors for development of functional and somatic disorders. Cases of increased morbidity with infectious, respiratory diseases, functional gastrointestinal and cardiovascular disorders were described in subjects exposed to toxic factors; the authors explained this fact by changed hormonal and immune status in functioning of which bioelements play a significant role (Microelements, 1991; Shubik V.M. et al., 2006; Kudrin A.V. et al., 2007). Therefore, when considering the causes for increased morbidity in liquidators of the accident at ChNPP we have to consider not only the exposure to radiation and stress but also the effect of adverse ecologic factors.

In connection with the above, the employees from the research laboratory of elemental analysis studied the bioelement status in 332 liquidators of the radiation accident at ChNPP. For this purpose, researchers performed the quantitative assay of vital and toxic bioelement content in the hair samples of above subjects from the biomaterial bank established at the Federal State Budget-funded Institution All-Russian Nikoforov Center of Emergency and Radiation Medicine of the Ministry of Emergencies of Russia in order to investigate the effect of low radiation doses on the human organism (grant No RSS 2145/1705/2000).

The study included biosamples of subjects resident on the following territories of the North-Western region of Russia: Saint Petersburg (n=124), city of Kaliningrad (n=155), town of Velikiy Novgorod (n=53). The mean age of subjects was 48.2±9.5 years.

The content of 30 bioelements was determined in the hair samples of all subjects using the method of inductively coupled plasma mass spectrometry (ICP-MS). Basing on the obtained data, the most significant bioelement ratios were calculated.

The reference ranges for the adult population obtained at the laboratory of elemental analysis at the Federal State Budget-funded Institution All-Russian Nikoforov Center of Emergency and Radiation Medicine of the Ministry of Emergencies of Russia were used as criteria for assessment of the organism provision with vital chemical elements and the content of toxic chemical elements.

The obtained results were analyzed depending on the parameters of the radiation history (year of participation in the emergency recover works, duration of stay in the accident zone, registered exposure), medical history and region of residence.

The subjects were divided in three dose groups depending on the obtained external irradiation dose: up to 10 cGy (93 persons), from 10 to 20 cGy (67 persons ), more than 20 cGy (41 persons ). There was no data on the external irradiation dose for 131 subjects included in the study.

Out of the subjects, 176 persons participated in the emergency recovery works at ChNPP in 1986, 113 subjects in 1987 and 43 subjects in 1988. The stay duration in the accident zone at ChNPP varied from 5 to 210 days.

The information on the medical history of investigated liquidators was obtained from the electronic data base of the North-Western Regional Center of the Russian State medical Dosimetric Register at the time of sampling.

On the whole, the subjects' hair samples were characterized by insufficient concentration of several vital bioelements: cobalt (in 90%), iodine (in 84%), selenium (in 76%), zinc (in 53%), copper (in 29%), magnesium (in 27%) and calcium (in 25% of subjects). The deficit of other vital bioelements (potassium, sodium, manganese etc.) was revealed in relatively small number of cases (less than 10% of subjects).

When performing the comparative analysis of the assessment results of the bioelement status in LAA at ChNPP living in different districts of the North-Western region, we revealed several territorial features (Table 3.1).

Table 3.1

Significant values of vital bioelement concentration in the hair samples of investigated LAA at ChNPP living on different territories (μg/g)

| Elements | Saint Petersburg | | | Velikiy Novgorod | | | Kaliningrad | | | p<0.05 | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1 | | | 2 | | | 3 | | | 1–2 | 1–3 | 2–3 |
| | Me | q25 | q75 | Me | q25 | q75 | Me | q25 | q75 | | | |
| **Iron** | 31.28 | 12.33 | 50.28 | 18.50 | 12.81 | 28.66 | 13.830 | 11.23 | 18.13 | + | + | |
| **Iodine** | 0.048 | 0.028 | 0.084 | 0.026 | 0.020 | 0.035 | 0.029 | 0.020 | 0.046 | + | + | |
| **Calcium** | 402.1 | 237.6 | 803.3 | 278.2 | 235.6 | 514.8 | 705.9 | 443.3 | 1136.0 | | + | + |
| **Magnesium** | 39.08 | 28.53 | 84.72 | 24.30 | 14.34 | 51.37 | 38.48 | 25.40 | 57.85 | + | | + |
| **Copper** | 8.440 | 6.650 | 10.69 | 4.670 | 2.970 | 6.730 | 7.500 | 5.460 | 9.710 | + | + | |
| **Selenium** | 0.365 | 0.210 | 0.700 | 0.200 | 0.130 | 0.300 | 0.230 | 0.120 | 0.400 | + | + | |
| **Phosphorus** | 111.8 | 61.07 | 158.9 | 61.31 | 56.14 | 72.39 | 111.7 | 97.49 | 136.9 | + | | + |
| **Zinc** | 80.18 | 59.19 | 97.45 | 38.57 | 32.25 | 51.59 | 76.49 | 60.78 | 94.32 | + | | + |

Note: Me = median; q25 = lower quartile; q75 = upper quartile.
+ Groups are marked , differences between which are significant.

As follows from the data presented in Table, iron, iodine, copper and selenium content in the liquidator group resident in Saint Petersburg was significantly higher ($p < 0.05$) as compared to that in other two test groups (LAA at ChNPP from Velikiy Novgorod and Kaliningrad). Calcium content in the hair samples of liquidators from Kalinigrad was significantly higher than that in LAA at ChNPP resident in Saint Petersburg and Velikiy Novgorod. We found that magnesium, zinc and phosphorus concentration in liquidators living on the territory of Velikiy Novgorod was significantly lower than that in the respective citizen category from Saint Petersburg and Kaliningrad.

Fig. 3.1. (colored inlay) shows the data reflecting the territorial differences in liquidator percentage without vital element deficit.

The presented data shows that selenium deficient was the least prevalent in Saint Petersburg (it was revealed in 58% of subjects) in contrast to other territories of the region where selenium deficit was found in 83 and 91% of LAA at ChNPP (in Kaliningrad and Velikiy Novgorod, respectively). At the same time, we established that the liquidator ratio with calcium deficit in Kaliningrad (in 9% of subjects) was considerably lower than that in Saint Petersburg (34%) and Velikiy Novgorod (51%). Liquidators of radiation accident aftermath at ChNPP living in Velikiy Novgorod were characterized by the lowest organism provision with vital elements. Magnesium deficit was revealed in more than a half of investigated LAA at ChNPP from Velikiy Novgorod, while its deficit was found in 23% of subjects in Kaliningrad and in 19% in Saint Petersburg. Zinc deficit was observed in 92% of liquidators from Velikiy Novgorod in contrast to two other territories of the North-Western region of Russia where zinc deficit was revealed in less than a half of subjects. LAA at ChNPP living in Velikiy Novgorod had copper deficit significantly more often

(in 62% of subjects) while this parameter was lowered in 14 and 29% in Saint Petersburg and Kaliningrad, respectively.

Thus, we revealed several territorial features of vital bioelement content in the hair samples of LAA at ChNPP living on different territories of the North-Western region of Russia. The liquidators of the radiation accident living in Saint Petersburg were characterized by the highest provision with several vital elements (iron, copper, selenium). LAA at ChNPP living in Kaliningrad were the second most provided with vital elements. Liquidators of radiation accident aftermath at ChNPP living in Velikiy Novgorod were characterized by the lowest content of vital elements in the organism.

When investigating toxic chemical element accumulation in the hair samples from liquidators of the accident aftermath at ChNPP living in the North-Western region of Russia, we revealed excessive cadmium content in 30% of subjects, 28% of subjects had excessive arsenic content and 23% had excessive lead content; in this situation we found differences in the levels of these bioelements depending on the region of residence (Table 3.2).

Table 3.2

Statistical values of toxic bioelement concentration in the hair samples of investigated LAA at ChNPP living on different territories (μg/g)

| Elements | Saint Petersburg | | | Velikiy Novgorod | | | Kaliningrad | | | p<0.05 | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1 | | | 2 | | | 3 | | | 1–2 | 1–3 | 2–3 |
| | Me | q25 | q75 | Me | q25 | q75 | Me | q25 | q75 | | | |
| **Aluminum** | 10.05 | 7.185 | 16.30 | 7.510 | 6.470 | 9.930 | 21.99 | 19.13 | 25.63 | + | | + |
| **Arsenic** | 0.100 | 0.014 | 0.216 | 0.037 | 0.001 | 0.090 | 0.058 | 0.015 | 0.098 | + | + | |
| **Nickel** | 0.520 | 0.310 | 0.930 | 0.320 | 0.240 | 0.570 | 1.210 | 1.020 | 1.460 | + | | + |
| **Mercury** | 0.480 | 0.280 | 0.900 | 0.250 | 0.140 | 0.500 | 0.340 | 0.230 | 0.480 | + | + | |
| **Lead** | 1.555 | 0.705 | 4.530 | 2.110 | 0.760 | 4.480 | 2.720 | 1.300 | 5.000 | + | | + |

Note: Note: Me = median; q25 = lower quartile; q75 = upper quartile.
+ Groups are marked , differences between which are significant.

As follows from the data in Table 3.2, significantly higher aluminum, lead and nickel content was revealed in the hair samples of LAA at ChNPP from Kaliningrad. The mercury and arsenic concentration was significantly higher in the hair samples of LAA at ChNPP in Saint Petersburg as compared to that in subjects from Kaliningrad and Velikiy Novgorod.

Fig. 3.2 (colored inlay) present the data reflecting cases when concentrations of certain toxic bioelements in LAA at ChNPP exceeded the reference ranges.

It was found finally that increased cadmium content was observed practically in every third liquidator living in Kalinigrad and Velikiy Novgorod and in every fourth one in Saint Petersburg. It should be mentioned that excessive arsenic content in the hair samples was observed considerably more often (in 44% of cases) in subjects from Saint Petersburg that in those in Kaliningrad (18%) and Velikiy Novgorod (17%). At the same time, subjects living in Velikiy Novgorod had increased content of nickel (21%), strontium (14%), aluminum (11%) considerably more often as compared to other regions where there parameters exceeded the reference values in less than 10% of subjects. Other dyselementosis groups due to increased toxic chemical element content were observed in LAA at ChNPP from the North-Western region rarer (less than 10%). We revealed the excessive lead content in the subjects' hair against a background of existing differences in the content of several toxic chemical elements in LAA at ChNPP. This pattern was observed in all groups of LAA

at ChNPP approximately with equal rate (about 20%) what enabled us to conclude that lead content in the hair of LAA had no territorial features.

When comparing the revealed (toxic and vital) chemical element concentrations in the hair of LAA at ChNPP and the data on the external irradiation dose and participation period in the emergency recovery works we could not find any significant relationship. Significantly ($p < 0.05$) higher levels of lead content revealed by us in the hair samples in the group of subjects performing the works at ChNPP in 1988 as compared to 1986 and 1987 were the exclusion (Fig. 3.3).

The increased lead load in LAA at ChNPP, who participated in the works in 1988, was associated, probably, with the fact that immediately after the accident the destroyed reactor was covered with about 2500 t of metal lead which was gradually included in the food chain (Malenchenko A.F. et al., 1997; Shubik V.M. et al., 2010). This is additionally confirmed by the revealed significant positive correlation between the participation period in the emergency recovery works and lead concentration in the hair samples of LAA at ChNPP (r=0.24).

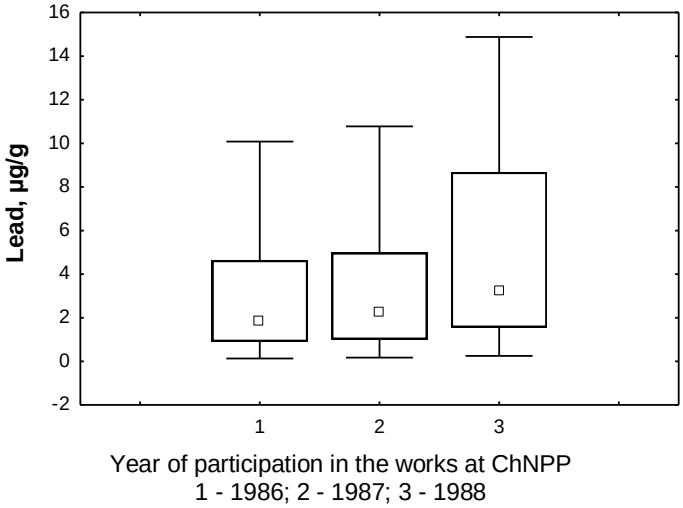


Fig. 3.3. Comparison of lead content in the hair samples from LAA at ChNPP depending on the year of participation in the works at ChNPP.

When analyzing the structure of the most frequent diseases in investigated liquidators basing on the data of the North-Western Reginal Center of the Russian State Medical Dosimetric Register, we distinguished 5 main disease classes: diseases of the circulatory system (in 49% of subjects), digestive diseases (in 42%), diseases of the musculoskeletal system (in 39%), respiratory diseases (in 33%) and diseases of the nervous system (in 22%). When analyzing the percentage of the somatic pathology in LAA at ChNPP depending on the region of permanent residence, we found some features in the distribution of disease classes (Table 3.3).

Table 3.3

Territorial features in the percentage of the main somatic pathology classes in investigated LAA at ChNPP

| Pathology class (code as per ICD-10) | Saint Petersburg | Kalini ngrad | Velikiy Novgorod |
|---|---|---|---|
| | Percentage of pathology, % (n=332) | | |
| Diseases of the circulatory system (I0–I99) | 69 | 36 | 40 |
| Digestive diseases (K0–K93) | 42 | 28 | 51 |
| Diseases of the musculoskeletal system and connective tissue (M0–M99) | 36 | 40 | 50 |
| Respiratory diseases (J0–J99) | 38 | 27 | 28 |
| Diseases of the nervous system (G0–G99) | 15 | 30 | 15 |

As follows from the data in Table 3.3, the percentage distribution of the somatic pathology in investigated liquidators was different: the cardiovascular pathology and respiratory diseases were revealed more often in LAA from Saint Petersburg. The liquidators living in Velikiy Novgorod were characterized by more frequent digestive diseases and diseases of the musculoskeletal system but the percentage of diseases of the nervous system was higher in Kaliningrad than that in other regions of residence of LAA at ChNPP.

The presented data indicates that Saint Petersburg and Velikiy Novgorod are the least "safe" cities from viewpoint of subjects' health.

When analyzing the relationships between the percentage of disease classes and disturbed bioelement status of subjects, we revealed a significant ($p<0.05$) negative correlation between the percentage of diseases of the circulatory system and the ratio of calcium content to magnesium content ($\gamma$=–0.2). This is presented as a graph in Fig. 3.4. The more detailed analysis confirmed significant correlations ($p<0.05$) between calcium concentration, ratio Ca/Mg and percentage of several diagnosed diseases of the circulatory system (cerebrovascular diseases, coronary heart disease and essential hypertension). According to obtained data, all subjects with above diseases had the lowered calcium level in the hair samples and the change in the ratio Ca/Mg was caused, first of all, by the lowered calcium content. This fact enables us to substantiate scientifically the fact that it is advisable to diagnose calcium-magnesium balance disorders in subjects with the cardiovascular pathology in order to develop the medical and preventive measures.

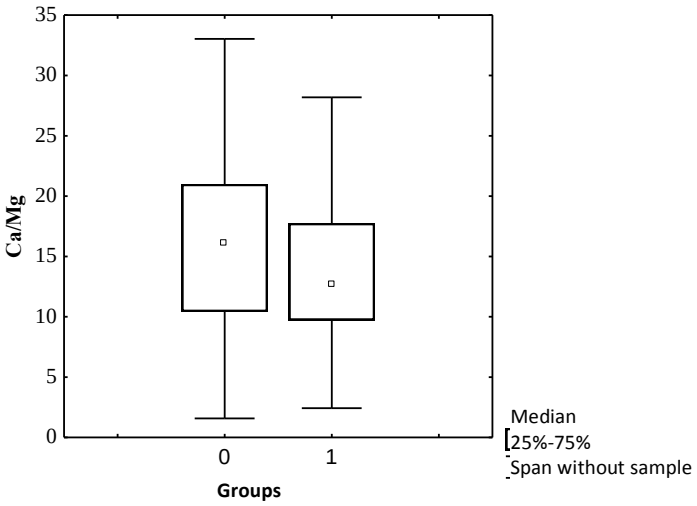


Fig. 3.4. The comparison of the ratio of calcium concentration to magnesium concentration in LAA at ChNPP depending on the percentage of the circulatory pathology.
0 – subject group without the circulatory pathology;
1 – patient group with the circulatory pathology.

The statistical analysis revealed significant ($p<0.05$) correlation between percentage of diseases referred to disorders of the vegetative nervous system (G90) and lead ($\gamma$=0.15) and cadmium ($\gamma$=0.19) content in the hair samples. The investigated liquidators of the radiation accident aftermath with disorders of the vegetative nervous system had high lead and cadmium concentrations in the hair samples and, consequently, changed ratios of cadmium to its main essential antagonists (zinc, calcium and copper).

Basing on the obtained data we may state that LAA at ChNPP with disorders of the vegetative nervous system need diagnostic measures for more precise assessment of the organism load with toxic bioelements, first of all, lead and cadmium.

The obtained data make a significant contribution in the clinical picture, especially, of the somatic pathology and should be taken into account when carrying out medical measures.

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## 3.2. THE ASSESSMENT OF INCORPORATED RADIONUCLIDE COMPOSITION AND ACTIVITY

The accident at the Chernobyl NPP, which is considered as a largest technogenic radiation accident, took place of the 26th of April, 1986. In total approximately 1018 Bq of radioactive substances was discharged to the environment; these substances include: $^{85}$Kr, $^{133}$Xe, $^{131}$I, $^{132}$Te, $^{95}$Zr, $^{144}$Ce, $^{103,106}$Ru, $^{134,137}$Cs, $^{90}$Sr, $^{238,239,240,241}$Pu and other short- and long-lived radionuclides with the half-life from several minutes to decades. Four elements (about 70% of the total amount) out of all radionuclides discharged from the active zone determined the radiation situation in the short-term and long-term period: iodine (mainly, iodine-131) (about 20%), cesium (cesium-134, 137) (22%), strontium (first of all, strontium-90) (8%) and plutonium (plutonium-239? 240) (about 20%). The contamination with strontium and plutonium was limited, mainly, by the 30-kilometer zone and neighboring districts. As the distance from the station increased, the role of volatile cesium isotopes became more significant in the radiation situation in the area. (Sources..., 1993, Large-scale..., 2001).

The external irradiation is, as a rule, the leading dose-forming factor in radiation accidents (RA). At the same time, the contribution of the internal irradiation may reach 20-25% in some types of RA (Emergency..., 1998).

The main paths for entrance of radionuclides into the human organism during RA are as follows (Analysis..., 2006):

• inhalation path (through the respiratory organs by breathing in the polluted air);

• peroral path (through the gastrointestinal tract by ingesting radionuclides or consuming the contaminated water or food);

•percutaneous (through unprotected skin, mucous membranes and wound surfaces).

The distribution of incorporated radionuclides in the human body depends on their chemical properties, paths of entrance into the organism and metabolism peculiarities.

The problems concerning dosimetry of the internal irradiation consist in the fact that it is impossible to record the internal irradiation dose of the body or critical organ by direct instrumental

methods. The whole process of its determination may be divided in 2 stages: measurement of radionuclide activity (quantity) assimilated by the organism and subsequent calculation of the integral energy release in the organ taking into account metabolism of this radionuclide for some or other period.

It is generally recognized that direct measurement of the radioactive substance content in the body or organ using human radiation spectrometers (SICh) is the most convenient, rapid and precise method for assessing the radionuclide incorporation and internal irradiation dose (Measurement..., 1999). The entrance of iodine radionuclides and first of all, $^{131}$I, which formed, mainly, the thyroid irradiation doses, was the main factor determining the internal irradiation level in the early period after the accident. The iodine threat lowered significantly in a month after the accident and became negligible by the middle of July: radioactivity caused by this isotope not exceeding 1% of the content in the reactor discharge was preserved by the 50th day (6 half-lives). While the hazard of internal irradiation caused by the entrance of $^{131}$I, lowered, the role and significance of irradiation due to $^{134,137}$Cs incorporation increased. So, at the end of May, 1986 the first measurements using the scanning human radiation spectrometer (SSIChZh) were started, which revealed certain comparatively high levels (up to 10-15 μCi ($3.7\cdot10^5$-$5.5\cdot10^5$ Bq) of cesium content in the organism (Basic ..., 1987).

Besides that, the internal irradiation dose in liquidators of accident aftermath at ChNPP was formed due to $^{90}$Sr, $^{239}$Pu and other radionuclides which were not recorded by SICh types used (Large -scale..., 2001, Radioecological..., 1995).

About 500 subjects from different staff categories in the 30-kilometer zone around the ChNPP were investigated in 1.5 year using SICh. The maximum $^{137,134}$ Cs content in the whole body was 0.74-1.2 μCi ($2.7\cdot10^4$-$4.4\cdot10^4$ Bq). The SICh-investigation of about 1200 residents from the settlements in the 30-kilometer zone around ChNPP and adjacent regions of Ukraine and Byelorussia for measurement of cesium content was performed in 1989-90. The mean incorporated $^{137,134}$Cs activity was 60 nCi (2200 Bq) (Maintaining ..., 1991).

The population of the territories contaminated with radioactivity because of the accident at ChNPP, namely, Bryansk, Tula and Kaluga regions, was investigated as per the German-Russian project in 1991. Twenty SICh units were used to measure the body radioactivity in more than 150,000 subjects. All adults were distributed in three categories by the cesium activity level in the body: up 7000 Bq (190 nCi), from 7000 to 25000 Bq and more than 25000 Bq (670 nCi). The overwhelming majority of subjects was included in the first category even in the most contaminated regions what corresponded to individual doses due to the internal irradiation of not more than 0.3 mSv/g. Only less than 1% of subjects were included in the third category and could obtain a dose of more than 1 mSv (Medical..., 1993).

Thus, investigations of different liquidator groups of accident aftermath at ChNPP and the population of the adjacent regions found the presence of incorporated radioactive substances.

Since 1993, when a laboratory for human radiometry equipped with human radiation spectrometers of SIB-1, SIB-2, UDEG-01T types for measurement of the content (activity) of gamma-radiating radioactive substances in the whole human body, thyroid and lungs was founded

at the All-Russian Center of Ecological Medicine (ARCEM, then ALCERM of the Ministry of Emergencies of Russia from 1997), more than 2500 subjects were investigated, out of whom liquidators of the accident at ChNPP accounted for about 85%, veterans of special risk departments accounted for about 5% and residents of the contaminated regions are others - 10%.

$^{137}$Cs in the whole body was confidently revealed in 63.5% of investigated liquidators in 1993. The activity was higher than the background values and equal to 0.012-1.5 μCi (440-55500 Bq) what did not exceed the maximum permissible levels of the radionuclide content in the whole body for this contingent in accordance with the regulatory documents which were valid at that time. The percentage of such patients was about 20% in 1994 and later cesium was not revealed in their organism. In our opinion, the results obtained, first of all, in 1993 are evidence of the internal contamination with radioactive substances in a significant number of liquidators and are fully consistent with the biological and physical patterns of the natural radionuclide excretion from the organism and its decay (Harmful..., 1990).

A dosimetric diagnostic complex, the highly sensitive low-background human radiation spectrometer for expert investigations (SICh-E) was commissioned at ALCREM in 2008. The unit is intended for direct determination of the radioactive substance content in the human organism, i.e. their presence, quantity and distribution in the organs and tissues it makes it possible to reveal the most radiologically significant radionuclides (Complex..., 2008).

More than 450 of liquidators of accident aftermath at ChNPP were investigated in the linear longitudinal scanning mode from November, 2008 to December, 2016 since commissioning of the SICh-E unit. None of them had radionuclides of the Chernobyl accident origin in the organism (i.e. possible incorporation during the works at ChNPP). This is quite explainable by the natural decay and excretion processes ($T_{ef}$ = 110-120 days) regarding cesium. As concerns other long-lived radionuclides, e.g., plutonium and strontium, which are tropic to the pulmonary or bone tissue, they were not revealed even by targeted local detection of the lungs, frontal bone and shin bones. At the same time, the presence of $^{137}$Cs i the organism was recorded in 86 subjects. And while the activity was from 70 to 2300 Bq (2-60 nCi) in 2009-2010, it was 50 - 400 Bq in 2011-2015. $^{137}$Cs with the activity of 50 - 100 Bq was revealed in 3 liquidators in 2016.

It is established that this results from using for food the gardening products or gifts of forest, first of all, mushrooms in the western districts of the Leningrad region which fell in the zone of radioactive precipitations after the accident at the Chernobyl NPP in 1986 (Radiation..., 1999). At present the radiation situation in the region became normal on the whole, what is confirmed, among other facts, also by the lower incorporated activity levels in the last years but at the same time there are areas (lowlands, marshlands) with the increased radiation background associated with $^{137}$Cs content in the soil and plants.

Fig. 3.5 presents a radiation spectrum from the patient K. investigated in 2010; the energy peak of 661.7 keV corresponding to radionuclide $^{137}$Cs is clearly seen in it. The calculation showed that the activity was 2300 Bq (60 nCi). As we established, this subject lived in the Kingisepp district of the Leningrad region and actively used for food large quantities of the products cultivated on the farmland and mushrooms. The incorporation occurred, evidently, in the summer and autumn approximately 2 months before the investigation; the internal irradiation dose for this period was

about 1.5 μSv (1.5 mRem). Even if we assume that this radionuclide quantity is permanently contained in the organism over a year, the effective dose for this period will be 0.1 mSv (0.01 Rem). This value does not exceed the irradiation dose limit for the population (NRB-99/2009). Taking into account that $^{137}Cs$ has a relatively short period $T_{eff}$ (110-120 days), we may consider that the actual radiation exposure for the organism is significantly lower. The radionuclide activity and, consequently, the dose were 10-15 times lower in other patients in whom $^{137}Cs$ was present in the organism.

Thus, the following conclusion can be made basing on the above facts:

- the accident at the Chernobyl NPP resulted in incorporation of radioactive substances, first of all, gamma-radiating radionuclides iodine, cesium, cerium and others in different categories of accident liquidators and residents of the adjacent radioactively contaminated territory what was confirmed by radiometric and spectrometric investigations performed both during the first 1.5-2 years in the districts adjacent to the ChNPP zone and in the later period, including investigations in the early-mid 90s at the laboratory of radiometry at ARCEM;

- the investigation of liquidators performed at the Clinic No. 1 at the Federal State Budget-funded Institution All-Russian Nikiforov Center of Emergency and radiation Medicine of the Ministry of Emergencies of Russia more than 20-25 years after the accident using the highly sensitive low-background human radiation spectrometer SICh-E did not reveal radionuclide presence in the organism, i.e. the consequences of possible incorporation during the works at ChNPP;

- low radionuclide cesium-137 activities not exceeding the standard maximum permissible levels revealed in some patients are explained by the use of foodstuffs or gifts of forest, first of all, mushrooms gathered in the districts of the Leningrad region with the residual radioactive contamination after the accident at ChNPP.

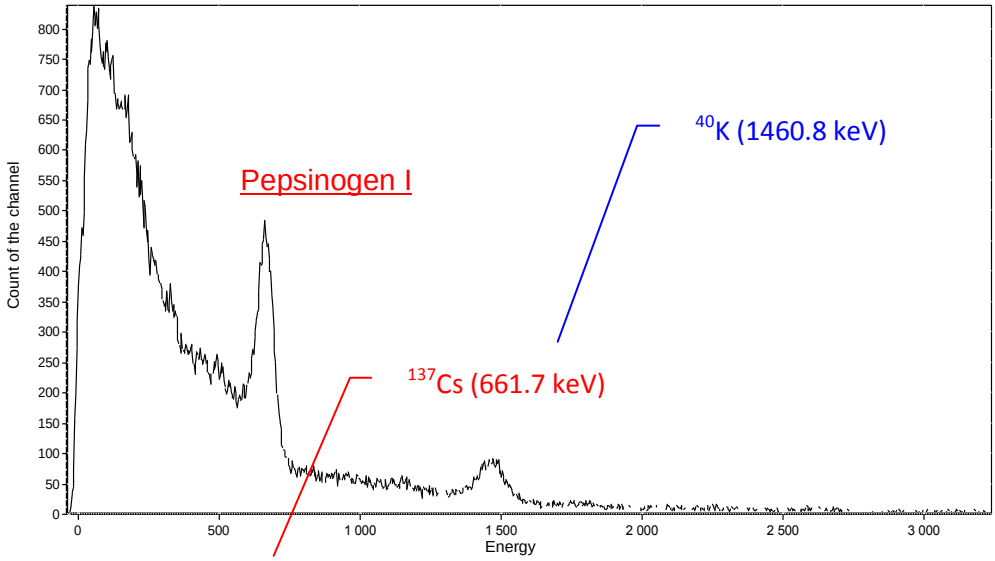


Fig. 3.5. The gamma-radiation spectrum obtained by the system of four scintillation detection units Ø160x160 mm large over 750 s from a subject (patient K.).
$^{137}Cs$ radionuclide content in the whole body is 2300 Bq.

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## 3.3. CYTOGENETIC PARAMETERS OF RADIATION-INDUCED GENOME INSTABILITY IN LAA AT CHNPP

### Concept of radiation-induced genome instability

The assessment of the biological effect exerted by the ionizing radiation on the human organism has been the subject of interest for researchers for several decades. Lately the problem of long-term consequences caused by the radiation becomes especially important. By now researchers have obtained the extensive data showing that the action exerted by the radiation on the cellular genetic material is not restricted by disturbances revealed immediately after the irradiation; genetic disturbances are revealed in the irradiated subjects many decades after the exposure to the radiation.

Numerous studies showed that some cells, which survived after the irradiation, could produce the functionally changed progeny and genetic changes observed in the cells of the filial generations differed from those occurring in the parent exposed cell. This phenomenon was named as radiation-induced genome instability. It results from direct action of the radiation on cells, and its manifestations include delayed reproductive cell death (long-term lethal mutations), chromosome destabilization, somatic mutations and apoptosis [17, 34, 55].

The experiments using unicellular murine embryos exposed to X-ray or neutrons revealed a surprising effect: chromosome aberrations could be preserved after irradiation instead of expected and natural reduction in frequency of induced chromosome aberrations and elimination of disturbances. In this situation the increased frequency of aberrations per cell in the first, second and third mitoses after the exposure to the radiation was observed. The relatively high aberration frequency revealed in subsequent mitoses after the exposure enabled the authors to suppose that new aberrations occurred in the cellular cycles in the post-exposure period [58, 59]. The analysis of the clonal progeny from the irradiated cells showed that chromosome instability could be manifested in the form of increased frequency of different cytogenetic disturbances, i.e. chromosome aberrations of different types, frequency of micronuclei and sister chromatid exchanges [13, 18, 19, 21, 25, 32, 47, 48, 54, 22, 34, 35]. In spite of the fact that most revealed

disturbances belong to the type of instable ones, i.e. those disturbances which are eliminated in the cell division process, chromosome destabilization was observed in the experiment over the period of many cell divisions, namely, up to 72 mitotic cycles [22]. The clones with chromosome instability could recover the their stability, keep the same instability level or became even more instable. In researchers' opinion, instable aberrations can lead to gene amplification, apoptosis and contribute to formation of delayed reproductive cell death although there are no direct correlation and simple relations between these parameters [21, 29, 32, 45, 33].

Researchers tried to find a minimum irradiation dose which can cause expression of genome instability and for this purpose they used a method of microbeam and human peripheral blood lymphocyte immobilization, in which only one alpha-particle track passed through a cell [23]. The progeny of the lymphocytes irradiated in a such a way showed significantly increased frequency of chromosome aberrations of chromatid type after 12-13 doubling cycles what was evidence of induction of the instable phenotype. Thus, it was found that passage of a single alpha-particle track through a cell was sufficient for induction of chromosome instability in human lymphocytes and induction could depend on the radiation type and genetic peculiarities of the object [22, 53]. Some studies suggested the availability of a threshold dose (<500 mGy) below which instability was not induced [33, 38]. The radiation can induce point mutations, deletions of gene parts and even whole genes in cells. Deletions account for 75% of radiation-induced mutations. Most delayed mutations (up to 80%) are point mutations and may affect many genes. Partial and complete gene deletions in the progeny of irradiated cells account for not more than 20% of all disturbances [20].

Exact mechanisms for development of genome instability have not been studied by now. Maintenance of genome stability at the cellular level is ensured by three systems disturbed functioning of which may result in development of instable genome:

1) mechanisms of DNA reparation recovering the damaged chromosome material in cells;

2) cell cycle control system in check points which provides for emergency elimination of the cell with pathologically changed DNA;

3) oxidation-reduction homeostasis system producing different cytotoxic factors including also active oxygen forms involved in elimination of genetically foreign material;

4) chronic inflammation manifested as activation of the innate immune processes leading to inhibition of mechanisms for reparation of DNA and disturbed cell cycle control points [11]. The mechanisms leading to genetic process disturbances as a result of chronic inflammation are not clear yet and researchers focus their attention on them today [11, 15, 31, 50].

The genetic inheritance implies transmission of the information recorded in DNA and required for reproduction of certain biological structures from the parents. The epigenetic inheritance is understood as transmission of the information about the functional state of genetic programs, i.e. about inherited changes in the activity of any gene or gene totality after exposure of cells to internal or external modifying factors. According to some researchers, just this path of inheritance is of importance in transmission of genome instability: change in the gene expression model typical of unirradiated cell, transmission of the changed model to filial cells and its reproduction in next generations at the epigenetic level [36, 37].

Lately, researchers attempt to find the possible explanation for mechanism of genome instability by studying the so-called “witness effect”. This phenomenon was revealed for the first time in experiments performed by [49] when intact cells were introduced to the culture medium from irradiated human keratinocytes. They and their progeny soon began to exhibit some signs typical of genome instability; experiments revealed, in particular, lowered clonogenic capability of cells (by 40%) what evidenced the transmission of any unknown signal about damage from the irradiated cells to unirradiated ones through the culture medium starting from the signal about DNA damage to its transmission to the plasma membrane of intact cells.

Most studies to investigate genome instability were performed in in vitro system. Therefore, a question may arise on whether there exists induced instability under in vivo conditions. The studies are available, which confirm the existence of this phenomenon in the in vivo system. So, murine embryos at the zygote stage were exposed to X-rays, and specimens were prepared using the biopsy material from the skin of these embryos on Day 19 after the exposure [41]. The considerably increased frequency of chromosome aberrations and micronuclei was revealed in fibroblasts of the irradiated embryos. The researchers noted that zygote irradiation induced structural chromosome aberrations which were preserved over many cell divisions what was evidence of genome instability. The studies showed induction of genome instability in the form of the increased level of single chromatid and paired fragments in the clonal cultures of embryo hepatic cells exposed to X-ray in the dose of 1 Gy on Days 13-14 of the intrauterine development. The degree of instability expression grew as the time (2-5 days) after the exposure to radiation increased [46]. The mice, which underwent transplantation of the bone marrow cells exposed to alpha-particles in vitro, were observed for a period of a year [57]. The prevalence of non-clonal instable aberrations in the recipient animals over the the period of 12 months was significantly higher that the frequency of stable translocations and deletions. Two and more cells with identical stable aberrations were revealed at month 8 and 12 after transplantation what was evidence of the fact that they had clonal origin and originated from the irradiated bone marrow.

As concerns humans, the radiation-induced chromosome instability was revealed for the first time in the experiments after exposure of the bone marrow cells to X-rays and alpha-particles [22]. Subsequent experiments showed that instability could be manifested as the high frequency of chromosome aberrations of chromatid and chromosome type and in the cell cultures of clonal and non-clonal origin [21]. In this situation, the radiation of different type was characterized also by different type of revealed disturbances: X-rays induced, mainly, aberrations of chromosome type.

Thus, the radiation-induced genome instability is a special condition of the progeny from irradiated cells in which they differ considerably from normal, unirradiated cells. At present this condition is characterized by cytogenetic, molecular-biological, cytological and biochemical phenomena which are not typical of normal cells [7]. These phenomena at the cytogenetic level consist in transmission of the tendency to form chromosome aberrations and point mutations *de novo* to the progeny. These phenomena at the molecular-biological level include transmission to the progeny of epigenetic and conformation changes in the chromatin structure including expression and production of proteins involved in functioning of check points in the cell cycle. At the cytologic

level these phenomena are manifested in lowered viability and clonogenic capability of the progeny from irradiated cells. Biochemical features of such condition include changes in the oxidation-reduction homeostasis system.

The genome instability occurs after the irradiation in a wide dose range including also low doses (up to 20 cGy); it depends on the irradiation dose and persists in the progeny of irradiated cells for many tens of cell cycles.

The genome instability exists both under *in vitro* and *in vivo* conditions, it is revealed both in animals and humans. Besides that, the data was obtained, which was evidence of the association between the radiation-induces genome instability and tumor cell transformation [44]. But the information on induction of this human genome condition is restricted by single studies which do not allow to make final conclusions about the pathogenetic significance of this phenomenon what confirms the need to perform further studies of this phenomenon, especially in subjects exposed to factors of the accident at ChNPP.

## The characteristics of subjects and investigation methods

The observation of the chromosome complex condition of peripheral blood lymphocytes in LAA was started in 1992. We investigated in total 595 LAA who participated in the liquidation works in the accident zone in 1986-1990. The stay duration in the accident zone was from one week to several months (on average 125±17 days). The irradiation doses were documented in 70% of subjects. Most of them received the doses of up to 25 cGy but 30 subjects received the doses from 25.1 cGy to 1 Gy. Thus, the mean irradiation dose was 20.2±0.10 cGy for liquidators who worked at the power plant in 1986, 13.4 ± 1.70 cGy for those who worked at the power plant in 1987 and 5.2 ± 0.9 cGy for those who worked in 1988-1990. The comparison group including 68 subjects of similar age and health condition but without history of contacts with the ionizing radiation was investigated.

In addition to the clinical investigation, all subjects underwent the computed survey in order to reveal any additional, potentially mutagenic factors influencing the organism. The questionnaire considered the effect of everyday, industrial factors, bad habits etc. The survey was conducted in the form of questioning by an employee of the laboratory. All collected information was stored in the computer data base developed specially for this purpose by he programmers of the ALCERM.

The cytogenetic investigation was performed using a method for analysis of instable chromosome aberrations in the peripheral blood lymphocyte culture as per the standard procedure [5]. From 200 to 500 metaphases at the stage of the first mitotic division were analyzed. We recorded all types of chromosome aberrations, i.e. single and paired fragments, chromatid exchanges, dicentric and circular chromosomes. We considered also the total aberration frequency, aberration frequency of chromatid and chromosome type.

In addition to the cytogenetic analysis, 95 liquidators of accident aftermath at ChNPP underwent the investigation of several biochemical parameters of “oxidative stress”.

The "oxidative stress" parameters were assessed using the following materials: blood serum (ser.), erythrocytes (er.), neutrophils (n), mononuclear cells (mon.c.) and thrombocytes (tr.) of the peripheral blood. leukocytes and thrombocytes were isolated from the peripheral blood using ficoll-verografin gradient. The following parameters were determined to assess free radical oxidation (FRO) and the antioxidant system (AOS): production of hydrogen peroxide ($H_2O_2$) [baseline (bas.) and stimulated (stim.) levels] by neutrophils and peripheral blood mononuclear cells [43], product content of lipid FRO by the test with thiobarbituric acid (TBA-AP or TBA-active products, i.e. products of lipid FRO reacting with thiobarbituric acid [the spontaneous level (TBA-AP sp.) and the level stimulated by bivalent iron (TBA-AP stim.) were determined for the serum] [16], reduced and oxidized glutathione content [27], superoxide dismutase SOD) activity in erythrocytes [14], catalase activity [9] in erythrocytes. When assessing deviations from the norm in the "oxidative stress" parameters in liquidators, we used the values of the laboratory parameters in healthy individuals.

The Mann-Whitney criterion, analysis of gamma- and Spearman correlations, regression analysis were used for the mathematical processing of the investigation results. The calculations were performed using the application program package Statistica 5.0 for Windows.

**Assessment of the somatic cell genome condition in LAA**

The analysis of chromosome aberrations revealed that 84% of subjects had different disturbance types evidencing the effect of genotoxic factors of endogenic and exogenic nature. So, 57% of subjects had cytogenetic radiation markers: dicentric, tricentric, circular chromosomes and also atypical chromosomes induced by the action of the ionizing radiation. Chromatid exchanges, the markers of exposure to chemical factors, were revealed in 20% of patients. 16% of subjects had cells with multiple disturbances in the genetic material which were typical for the acute irradiation period. Moreover, the analysis of obtained results demonstrated the increasing number of genetic disturbances in patients as compared to the results of many-year monitoring of the subject group involved in liquidation of accident aftermath at the Chernobyl NPP obtained at the laboratory during the previous years. It was found earlier that 27.3% of LAA had chromosome markers, but the number of LAA with markers increased up to 48.8% after 28 years. The results of the cytogenetic investigation are presented in Table 3.4. Table shows the increased level of different chromosome aberration types relative to the comparison group. The significantly increased percentage of radiation markers (dicentric and circular chromosomes) was revealed even many years after the irradiation.

Liquidators were divided in several groups depending on the time period between the cytogenetic investigation and irradiation. Figs. 3.6 and 3.7 present changes in the frequency of different chromosome aberration types over time. It was revealed that the frequency of chromatid exchanges did not change depending on the time but the total number of chromosome aberrations, paired fragments, chromatid fragments and radiation markers were influenced by the time (Wilks lambda=0.71, $F(84, 2715.2)=2$, $p<0.001$).

The results obtained in the assessment of the genetic status of patients exposed to the ionizing radiation because of the Chernobyl accident by chromosome aberrations are evidence of the need to perform monitoring of the patients' health condition, especially the patients with chromosome disturbances because radiation markers and also other disturbances associated with risk of cancer diseases are revealed with frequency exceeding the control values in spite of a long period after the irradiation.

Table 3.4

The frequency and types of chromosome aberrations in LAA at ChNPP in a long-term period after irradiation and in the comparison group

| Frequency, % | Comparison group, n=68 | LAA at ChNPP, n=595 |
|---|---|---|
| Chromosome aberrations | 1.96±0.21 | 2.82±0.10* |
| Chromatid fragments | 1.59±0.18 | 1.70±0.09 |
| Chromatid exchanges | 0.01±0.01 | 0.13±0.01*** |
| Paired fragments | 0.29±0.05 | 0.69±0.04*** |
| Dicentric, circular chromosomes | 0.04±0.02 | 0.21±0.02*** |
| Atypical chromosomes | 0.05±0.02 | 0.10±0.02 |

Significant differences at the level of * $p < 0.05$, *** $p < 0.001$

When comparing empiric distributions of control subjects and liquidators by the frequency of chromosome disturbances using the criterion $\chi 2$ we revealed significant differences between them ($p<0.001$) what was evidence of the fact that the investigated (liquidator and control subject) samples did not belong to a single total population. In addition to studying chromosome aberrations and finding their frequency, we analyzed the distribution of different types of chromosome aberrations among subjects. For this purpose, patients were divided in three groups depending on the type of aberrations revealed in them: donor group whose lymphocytes had no chromosome aberrations; the second group included patients who had only single and/or paired fragments; the third group involved subjects with exchanges of chromatid and chromosome type. Fig. 3.8. presents the analysis results of distribution of chromosome disturbances in patients. The analysis showed that the subject sample (both the comparison group and liquidator group) included subjects without cytogenetic disturbances (17.6% in the control group and 12.0% in the LAA group, $\chi 2=1.76$, $p>0.05$). Single and/or paired fragments were revealed in 66.2% of control patients. At the same time liquidators with only this disturbance type were found significantly rarer and accounted for 44.9% of all irradiated subjects ($\chi 2=11,1$ $p<0.001$). The significantly increased number of subjects with exchanges was observed (43.1% vs. 16.2% in control patients; $\chi 2=18.4$, $p<0.001$). The increased number of exchange mutations in LAA was associated with the increased number of dicentric, circular chromosomes and chromatid exchanges. In some cases several types of exchange aberrations were revealed simultaneously in one patient. Among LAA there were 11 subjects who had aberrations of only exchange type. 27.3% of LAA were radiation marker carriers. The control group included 11 subjects with dicentric and atypical chromosomes and 1 patient with chromatid exchange.

**THE FREQUENCY OF CHROMOSOME ABERRATIONS, CHROMATID AND CHROMOSOME FRAGMENTS IN A LONG-TERM PERIOD AFTER IRRADIATION**
(SE± 95% confidence interval)

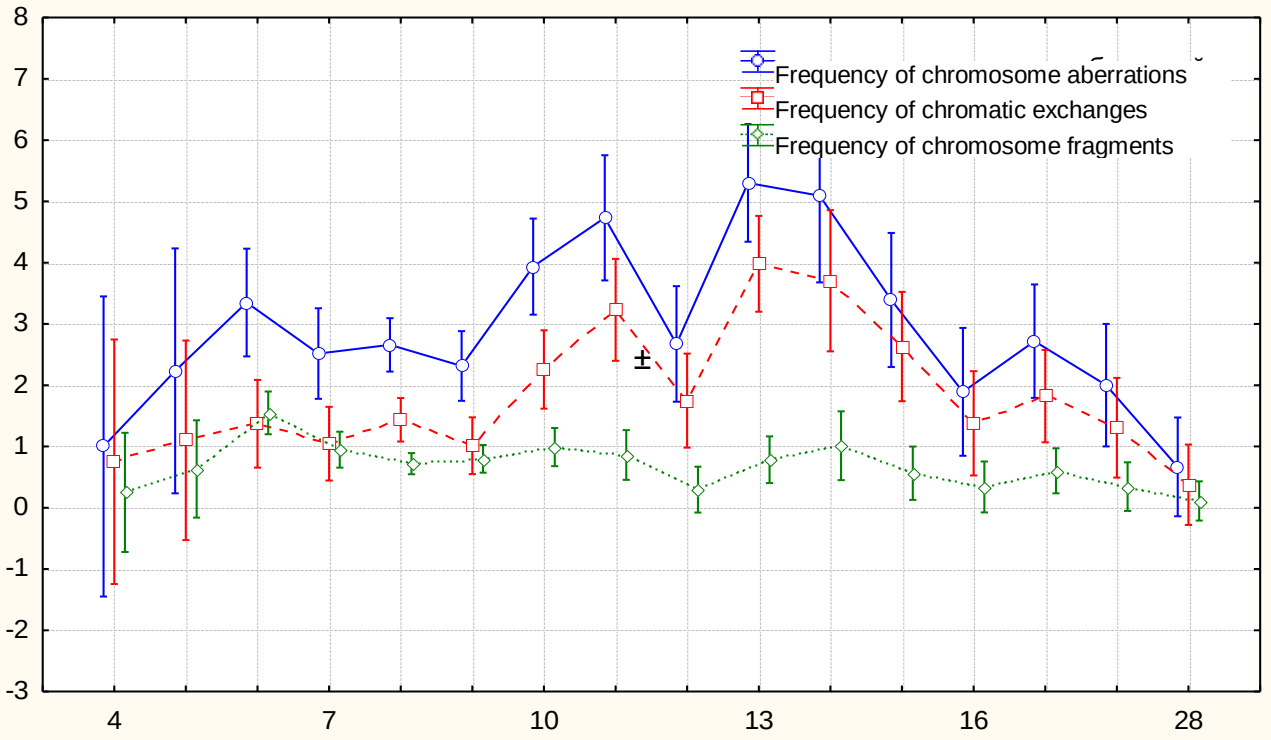


Fig. 3.6.

**CHANGES IN THE FREQUENCY OF CHROMATID EXCHANGES AND RADIATION MARKERS IN A LONG-TERM PERIOD AFTER IRRADIATION**
(SE± 95% confidence interval)

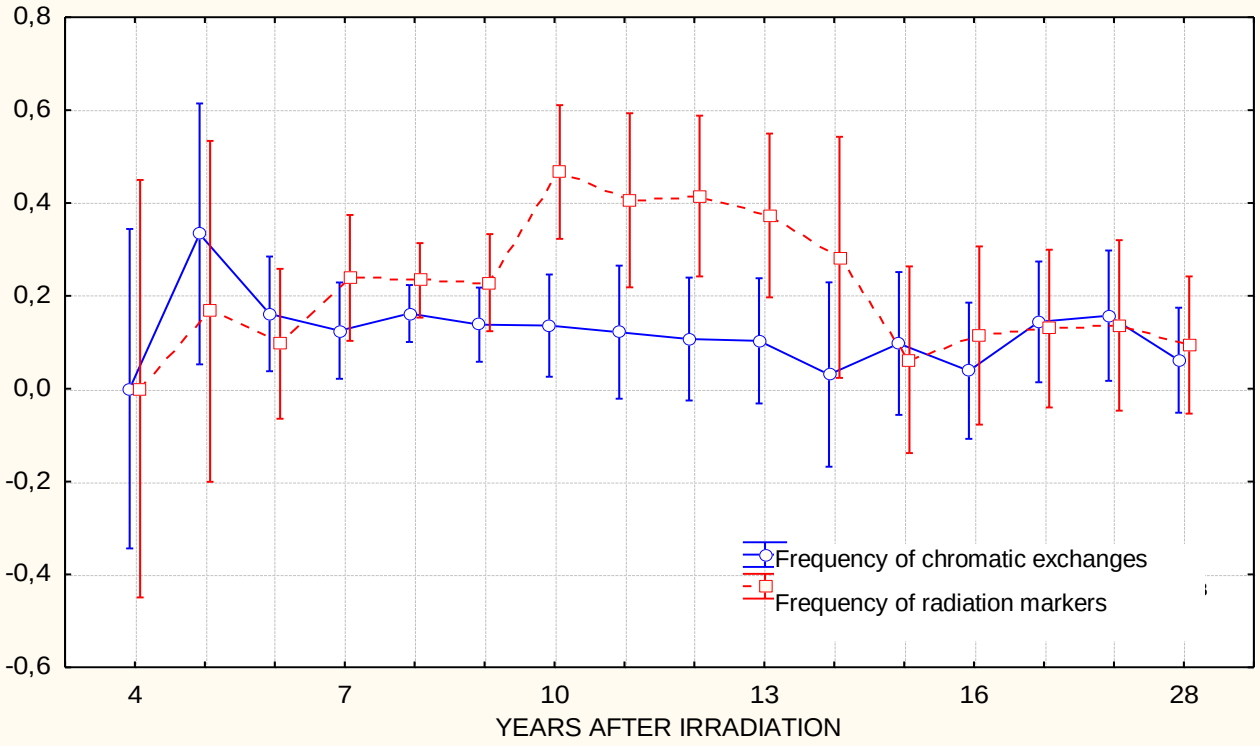


Fig. 3.7.

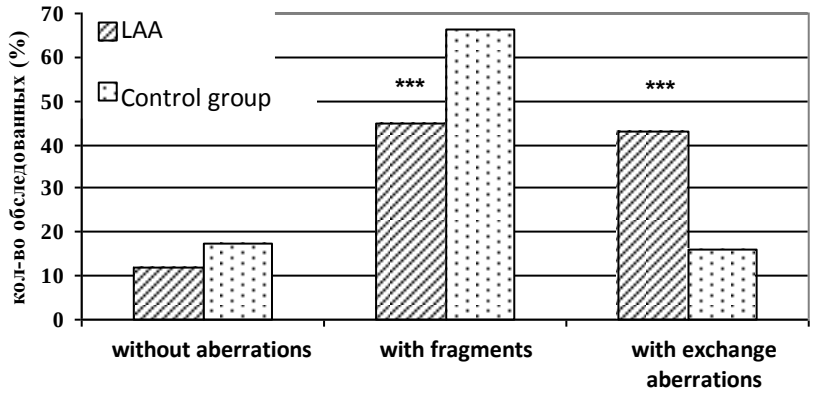


Fig. 3.8. The range of chromosome aberrations in LAA at ChNPP and in the control group

The correlation analysis between the recorded irradiation dose and number of revealed aberrations was performed. All LAA were divided in 5 groups depending on the recorded irradiation dose. The sixth group included LAA for whom there was no data on the obtained irradiation dose (Table 3.5). The data presented in Table 3.5 demonstrates that the frequency of dicentric and circular chromosomes in the long-term period exceeded significantly the control values in the whole range of recorded doses. The correlation analysis showed a significant positive association between the test irradiation parameters ($r=0.14$, $p<0.05$). The dependence of the radiation marker frequency on the irradiation dose was described by the equation of regression $Y=0.113+0.008*D$ where Y was the radiation marker frequency per 100 cells and D was the dose (cGy). Thus, the dependence on the irradiation dose was preserved in spite of a considerable interval between the irradiation and cytogenetic analysis typical of such parameter as chromosome aberrations.

Table 3.5

The chromosome aberration frequency in liquidators depending on the recorded irradiation dose in a long-term period after the accident

| Dose (cGy) | Subject number | Frequency of aberrant cells (%) | Frequency of dicentric and circular chromosomes (%) |
|---|---|---|---|
| Below 5 | 48 | 2.64±±0.34*** | 0.18±0.06* |
| 5-10 | 44 | 2.58±0.32* | 0.17±0.06* |
| 10-20 | 60 | 2.87±0.41* | 0.20±0.06* |
| 20-25 | 96 | 3.05±0.25*** | 0.35±0.05*** |
| more than 25 | 31 | 2.44±0.38* | 0.39±0.17** |
| Unknown | 112 | 2.75±0.21** | 0.30±0.04*** |
| Control group | 50 | 1.67±0.21 | 0.03±0.02 |

*p<0.05; **p<0.01; ***p<0.001 as compared to the control group

Our many-year observation of induced mutagenesis parameters in somatic cells in liquidators of accident aftermath at ChNPP exposed to low doses of the ionizing radiation showed chromosome disturbances in a long-term period after the exposure to the radiation. These findings are not consistent with the classical concepts of radiobiology according to which elimination of damaged cells should take place as a result of their death or ageing in a long-term period. One may express several suppositions considering the causes and mechanisms of long persistence of the increased mutagenesis parameter level including also detection of radiation markers in liquidators.

### The investigation of radionuclide incorporation

In addition to the external irradiation, the internal irradiation resulting from radionuclide incorporation which enter the organism by the inhalation path or through the gastrointestinal tract may also contribute to the radiation load on the organism in emergencies such as the accident at ChNPP. As known, chromosome aberrations in peripheral blood lymphocytes may be induced not only as a result of the external irradiation but also radionuclide incorporation; consequently, the internal irradiation may be also one of the mechanisms favoring preservation of chromosome disturbances in liquidators. The investigation of radionuclide incorporation in liquidators of accident aftermath at ChNPP started in 1993. Researchers assessed the presence of gamma-radiating radionuclides (by Cs-137) and also other the most radiologically significant radionuclides (plutonium and strontium). The results of these investigations are presented in detail in a special section of the present monograph. The data obtained within the limits of this work is evidence of gamma-radiating radionuclide incorporation in the organism in a significant percentage of liquidators revealed during the first years after the accident. But incorporated radioactive substances were revealed only in 20% of investigated liquidators by mid 90s and presence of incorporated radioactive substances was not established after 20-25 years what was evidence of the natural radionuclide excretion from the organism and their decay.

Thus, the investigations of the incorporated radionuclide composition and activity in the organism of liquidators do not confirm the supposition on induction and persistence of generic disturbances in somatic cells in liquidators as a result of radioactive substance incorporation.

### The genome condition and “oxidative stress” parameters in LAA

In the modern literature high emphasis is placed on the “oxidative stress” and a supposition is expressed that intensified production of active oxygen forms as a result of exposure to the radiation may be a source for genome instability in a long-term period after the irradiation. The present study compared the analysis results of chromosome aberrations and some “oxidative stress” parameters in liquidators of accident aftermath at ChNPP in order to check this supposition. The results of this study are presented in Table 3.6 and are evidence of the shift in some biochemical parameters in LAA as compared to the healthy subject group.

First of all, the data presented in Table 3.6 is evidence of significant variability of the test parameters in the LAA group. So, hydrogen peroxide production by peripheral blood neutrophils

ranged from 0 to 180.0 nmol/$10^6$ cells per hour, therefore, one may not speak of significant increase of this parameter in the group on the whole. At the same time, hydrogen peroxide generation by neutrophils and mononuclear cells was increased in 75% of LAA. Such activation was accompanied with significantly increased generation of LPO products (TBA-AP) in leukocytes with considerably lowered reduced glutathione content in erythrocytes. The antioxidant enzyme activity in erythrocytes in the group on the whole did not differ from the normal level. Thus, in accordance with our earlier data [5], we may speak of the "oxidative stress" condition in LAA due to activation of leukocyte systems generating AOF with oxidative lipid damage simultaneously with considerably lowered reduced glutathione level.

When comparing the chromosome complex condition in the peripheral blood lymphocytes and biochemical blood parameters in LAA at ChNPP in the liquidator group, we showed a correlation between some "oxidative stress" parameters and cytogenetic parameters (Table 3.7; only those parameter pairs are presented, the correlations between which are significant).

Table 3.6

The comparison of the "oxidative stress" parameters
in LAA and the group of healthy subjects

| Parameters | Group of healthy subjects | | LAA | |
|---|---|---|---|---|
| | n | X±SD | n | X±SD |
| $H_2O_2$ n. nmol/$10^6$ cells per hour | 31 | 32.2 ±±7.6. | 54 | 83.44±92.11** |
| $H_2O_2$ mon.c. nmol/$10^6$ cells per hour | 31 | 18.3±±3.4 | 60 | 37.25±39.89** |
| TBA-AP sp. μmol/l | 41 | 3.1 ±±0.48 | 89 | 4.16±1.18*** |
| TBA-AP stim. μmol/l | 41 | 2.1±±0.3 | 88 | 3.13±1.83*** |
| TBA-AP n. nmol/$10^6$ cells | 23 | 0.12±±0.019 | 35 | 0.40±0.17*** |
| TBA-AP mon. c. nmol/$10^6$ cells | 23 | 0.069±±0.018 | 46 | 0.29±0.16 |
| TBA-AP tr. nmol/mg of protein | 31 | 0.38±±0.04 | 49 | 0.88±0.36*** |
| Reduced glutathione, er μmol/l | 39 | 2.71±0.06 | 88 | 1.59±0.38*** |
| Oxidized glutathione, er μmol/l | 39 | 0.35±0.15 | 76 | 0.40±0.39 |
| Catalase U/ml er. | 32 | 7.85±2.65 | 59 | 6.06±1.68*** |
| SOD er. U/mg of protein | 36 | 5.45±1.34 | 86 | 4.60±1.50 |

Significant differences with the group of healthy subjects: * - $p<0.05$; ** - $p<0.01$; *** - $p<0.001$.

Table 3.7

The analysis results of correlations between cytogenetic parameters and "oxidative stress" parameters in LAA

| Parameters | Subject number | Coefficient of correlation gamma |
|---|---|---|
| TBA-AP sp. and XPT | 81 | -0.17* |
| TBA-APsp. and CCE | 81 | -0.33** |
| TBA-AP stim. and CCE | 80 | 0.34** |
| TBA-AP mon.c. and DC | 42 | -0.32* |
| TBA-AP n. and XPT | 31 | -0.35** |
| TBA-AP n. and SF | 31 | -0.34** |
| SOD er. and TCAF | 77 | -0.21** |
| SOD er. and XPT | 77 | -0.19** |
| SOD er. and SF | 77 | -0.20** |
| $H_2O_2$ n. and DC | 50 | 0.25* |

Significance of correlations: * - $p<0.05$, ** - $p<0.01$,*** - $p<0.01$.

When analyzing the data presented in table 3.7, attention is drawn to the following relationships:

direct correlation between: radiation marker frequency and quantity of hydrogen peroxide, frequency of chromatid-chromatid exchanges (CCE) and stimulated TBA-AP level;

reverse correlation between the frequency of different types of aberrations: single fragments (SF), chromatid exchanges, dicentric and circular chromosomes (DC) and lipid peroxide oxidation product level;

reverse correlation between SOD level and total chromosome aberration frequency (TCAF) and frequency of single fragments.

The cytogenetic radiation markers (dicentric and circular chromosomes) occur as a result of exposure to the ionizing radiation. The frequency of these disturbances depends on the irradiation dose. The number of the radiation markers should decrease as the time after the exposure passes but our studies [51, 52] showed that the frequency of dicentric chromosomes in LAA did not lower over the period of many years after the irradiation. Consequently, there exist mechanisms favoring the preservation of the stable radiation marker level. Therefore, the revealed direct correlation between the frequency of dicentric chromosomes and hydrogen peroxide concentration is of great interest. It is known that exposure to the ionizing radiation intensifies AOF production in irradiated cells both due to occurrence of radiation-induced radicals and as a result their enhanced metabolic generation. According to modern concepts, AOF hyperproduction may persist also in a long-term period after the irradiation [1]. The data concerning the possible direct induction of dicentric chromosomes associated with the effect of hydrogen peroxide is not numerous and contradictory. [40] showed in 1986 using the human embryonic fibroblast culture that a short-term single exposure to $H_2O_2$

induced aberrations of chromosome type including dicentric chromosomes. The authors made a conclusion that hydroxyl radical played the key role in induction of chromosome aberrations after adding $H_2O_2$. Later the same group of authors [39] performed experimental studies and confirmed their previous results.

But other authors, who studied the effect exerted by the "oxidative stress" on the chromosomes, did not reveal aberrations of chromosome type in the form of dicentric and circular chromosomes. So, generation of free radicals was induced in the model system in the Chinese hamster cell culture in the study performed by Uggla [56]. The author showed that free radicals induced only aberrations of chromatid type irrespective of the cell cycle stage at which the cells were exposed. Aberrations of chromosome type including dicentric chromosomes occurred only after the additional exposure to X-rays. When assessing the cytogenetic effect exerted by active oxygen forms on human lymphocytes Duell et al. [12] revealed chromosome disturbances belonging exclusively to the chromatid type. The presence of dicentric and circular chromosomes in liquidators is not, evidently, a direct consequence of the exposure to hydrogen peroxide or its derivatives. The correlation between the frequency of dicentric chromosomes and $H_2O_2$ concentration is evidence of fact that there exist common biological mechanisms for maintaining the increased level of both AOF hyperproduction and radiation markers. The modern literature considers the radiation-induced genome instability as such mechanism. This genome condition develops in the progeny of irradiated cells and is manifested differently at the cellular (delayed cell death, apoptosis), biochemical (active oxygen form hyperproduction) and genetic (increased frequency of gene and chromosome mutations) level [6].

The present study shows a reverse correlation between the frequency of different aberration types in LAA: single fragments, chromatid exchanges, dicentric and circular chromosomes and the lipid peroxide oxidation product level.

Mutagenicity of LPO products is known [3], therefore, revealed reverse correlations between cytogenetic disturbances and LPO parameters in liquidators are to be explained. Our previous studies [4] and also the investigations of other authors [2, 24, 42] demonstrated that LPO parameter values changed greatly depending on the disease stage: the high LPO level was followed by its rapid lowering down to zero values. Because of this, LPO levels in subjects experiencing the stage of massive release of LPO products may be even lower than the normal values. Therefore, the revealed cytogenetic disturbances may be associated both with the preceding effect exerted by LPO products and with direct exposure to the factors leading to organism destabilization (stress, viral infection etc.). The obtained results are consistent with the data of Michshenko et al. [8] who observed the lowered blood peroxidation level and respiratory burst intensity of active neutrophils after 5 years in subjects involved in liquidation of the accident at ChNPP. The lowered neutrophil and also mononuclear cell activity may be associated with changes in the DNA structures. This supposition may be indirectly confirmed by significantly increased frequency of chromatid-chromatid exchanges in the LAA group with lowered TBA-AP production level sp. as compared to the normal production values (Table 3.8).

The present study showed the decrease of the frequency of single fragments in LAA as SOD concentration increased. The dependence of the frequency of single fragments on SOD quantity was described by the equation of linear regression y = 4.452-0.465x ($p<0.01$). The frequency of single fragments (4.30±0.41%) in the LAA group with SOD quantity of less than 3 rel.u./mg of protein exceeded 2 times the frequency of single fragments in subjects with SOD quantity of more than 3 rel.u./mg (2.01±0.25%, $p<0.001$) (Table 3.9). Consequently, SOD may be considered as an agent protecting the cell genome from damaging action of clastogenic factors.

Table 3.8

The frequency of chromosome aberrations in LAA with different level of TBA-AP sp.

| Type of chromosome aberrations | Frequency of chromosome aberrations (X±m, %) | |
|---|---|---|
| | TBA-AP sp. is lower than the normal value (less than 2.5 μmol/l); N=7 | TBA-AP sp. is normal and higher (more than 2.5 μmol/l; N=74 |
| TCAF | 4.53±1.09 | 3.28±0.27 |
| SF | 3.21±0.78 | 2.28±0.24 |
| CCE | 0.24±0.09* | 0.07±0.02* |
| ΠΦ | 0.74±0.40 | 0.65±0.09 |
| DC | 0.40±0.18 | 0.28±0.05 |

* - significant differences between the groups at the level $p<0.05$.

Table 3.9

The frequency of some types of chromosome aberrations
in the LAA groups with different SOD er. level

| Type of chromosome aberrations | Frequency of chromosome aberrations (X±m, %) | |
|---|---|---|
| | SOD er. >3 U/mg of protein (N=67) | SOD er. ≤3 U/mg of protein (N=10) |
| TCAF | 3.01±0.26*** | 5.32±0.68*** |
| SF | 2.01±0.25*** | 4.30±0.41*** |
| CCE | 0.09±0.02 | 0.10±0.06 |
| ΠΦ | 0.62±0.09 | 0.88±0.31 |
| DC | 0,28±0.05 | 0.04±0.04 |

* - significant differences between the groups at the level $p<0.001$.

The protective action of SOD relating induction of chromosome aberrations was shown earlier by Lipecka et al. [38]. They revealed a negative correlation between SOD activity in cultured lymphocytes from different donors and the sensitivity of these cells to clastogenic effect exerted by gamma-radiation (2 Gy). The mean number of dicentric and circular chromosomes in subjects with the high SOD activity was 2-3 times lower than that in subjects with the low enzyme activity. But

later these authors could not confirm the revealed effects [10]. Larramendy et al. [26] showed a reverse correlation between chromosome sensitivity to Bleomycin (manifested in the increased frequency of dicentric chromosomes) and SOD concentration in the blood, plasma and erythrocytes of donors' cells in the experiments in vitro using the blood from 10 different donors.

Thus, the comparison of analysis results of chromosome aberrations and some "oxidative stress" parameters in liquidators of accident aftermath at ChNPP in a long-term period after exposure to the radiation revealed the direct (for some cytogenetic characteristics) and reverse (for other ones) correlation with the "oxidative stress" parameters. Evidently, the revealed interrelations are not the direct cause-effect associations but reflect the complex processes developing in the organism of those exposed to the ionizing radiation.

**Conclusion:**

The radiation-induced genome instability is a special condition of the progeny from irradiated cells in which they differ considerably from normal, unirradiated cells. This condition is characterized by cytogenetic, molecular-biological, cytological and biochemical phenomena which are not typical of normal cells. The information on induction of genome instability in humans is restricted by sporadic studies.

Our many-year observation of genetic material condition in somatic cells in liquidators of accident aftermath at ChNPP exposed to low doses of the ionizing radiation showed chromosome disturbances in a long-term period after the exposure to the radiation. This phenomenon is not consistent with the classical concepts of radiobiology according to which elimination of damaged cells should take place as a result of their death or natural ageing in a long-term period. The obtained data is evidence of occurrence of radiation-induced genome instability in LAA. The genome instability is manifested in increased cell disposition to formation of chromosome aberrations at the cytogenetic level, in the form of changes in the oxidation-reduction homeostasis system at the biochemical level; these phenomena may be a pathogenetic base for long-term consequences caused by the ionizing radiation.

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## 3.4. ASSESSMENT OF THE MICROECOLOGICAL STATUS IN LIQUIDATORS OF ACCIDENT AFTERMATH AT THE CHENOBYL NUCLEAR POWER PLANT USING THE METHOD OF CHROMATO-MASS-SPECTROMETRY

The results obtained by the epidemiological analysis of the health condition of citizens exposed to radiation because of the accident at ChNPP in a long-term period (Astafiev O.M. et al., 2011) are evidence of the fact that the percentage of digestive diseases in the morbidity structure is 11%.

The percentage of cancer diseases of the gastrointestinal tract is 38% of all cancer diseases in this citizen category.

The long-term radiation digestive pathology may develop as a result of exposure to external radiation sources and radionuclide incorporation for which GIT is one the most important paths for entering and excretion from the organism. In the small intestine there are actively mitosing cells which are the progenitors (stem cells) for all functioning blood and enteric cells. The dose of 45 cGy causes complications in 1-5% of cases, and the doses of 50-60 cGy cause complications in up to 60%. The dose of 30 cGy leads to mucous membrane atrophy and disturbed vitamin $B_{12}$ adsorption. Subjects exposed to low-intensive occupational radiation develop clear dysbiotic changes in the form of lowered anaerobic microbial count (bacteroids, peptostreptococci, fusobacteria, lacto- and bifidoflora).

According to some authors (Batskov S.S., Staroselskaya N.A., Pronina G.A., 2011) the percentage of functional intestinal diseases in these subjects is 37% and 51% of patients have signs of colic mucous membrane inflammation. The authors made a conclusion about more pronounced inflammatory changes in the colic mucous membrane with insignificant clinical symptoms and more frequent revealing of bacterial overgrowth syndrome. This data confirms that it is urgent to determine the intestinal microbiota using the latest technology.

The metabolism disturbance in the organism as a result of changed intestinal microflora and related intestinal wall permeability variations are one of the consequences caused by any human organism exposure to stresses. This results in disproportion in entering of biologically active substances produced by microorganisms into the hoist's organism and disturbed functioning of its organs. The consequences may be pathologic because the intestinal wall microbiota influences the production of more than a half of vitamins, enzymes, factors, signal molecules, mediators and other hormone-like compounds which are necessary for humans and required for metabolism and reproduction of its own cells and systems (immune, nervous, endocrine and other systems). Cell wall peptidoglycan of gram-positive microorganisms (the absolute majority of the human intestinal wall microbiota is represented by them) is involved actively in regulation of the host's immune status at the local and systemic levels. It is considered that just microecological changes in the host's organism are a triggering mechanism for a great majority of pathologic processes and there are as many variants of human microbiocenosis imbalance as the number of known nosologic forms of diseases (Shenderov B.A., 1998).

Therefore, the human microecological status, more exactly, maintenance of its homeostasis, is an essential precondition for stable functioning of all its organs and systems. The control and recovery of the microbiocenosis, if it is disturbed, should be, consequently, one of the first stages in rehabilitation of persons suffering from emergencies because of peculiarities of their professions (rescuers, fire fighters, participants of military operations, liquidators of accidents and emergencies aftermath and others).

The methods for assessment of the microecological status and also diagnostics of infections used today in the clinical practice have certain restrictions and defects. For example, in addition to expensiveness and long duration (7-10 days), a considerable defect of the classical bacteriological testing consists in the fact that it is impossible to assess the role of uncultured microorganisms in the infection-inflammatory process, first of all, anaerobes. The immunoserological method used as an addition to the classic testing, is indirect as it reveals not a pathogen but an immune response to it, which may have individual variations. The known molecular-biological methods along with their undoubted advantages (direct pathogen detection, high specificity and sensitivity, versatility, rapidity, possibility to diagnose chronic and latent infections) have such serious defects as frequent false-positive results and impossibility of adequate quantification (Persing, 1991; Fenollar et al., 2006; Mikhailova D.O. et al., 2008).

All above facts show evident need in a reliable quantitative express-method for diagnostics of dysbacteriosis and determination of infectious pathogens.

Microorganism chemodifferentiation using gas chromatography (GC-MS) based on quantification of microbial marker substances (fatty acids, aldehydes, alcohols and sterols) is such a method. As a medical technology, this method allows not only to monitor these compounds in samples but also to calculate the microorganism number of one or other taxon in a sample. This fact determines the principal distinction of the method giving it a qualitatively new property, namely, the possibility to analyze superposition of the whole microbial marker pool what allows to assess the contribution made by each of hundreds of microorganism species which are present, e.g., in the feces (Luckey, 1987; Suau et al., 1999).

The suggested method of gas chromatography combined with mass-spectrometry (GC-MS) allows to detect markers, cell components of the wide microorganism spectrum of the normal and pathogenic human microbiota in test samples. The GC-MS method makes it possible to detect many microbial markers simultaneously when analyzing one sample. The introduction of GC-MS allows to reduce the test duration and cost escaping the stage of repeated passages of primary colonies and test fermentations which are especially difficult, labor-intensive and long for anaerobes. The method allows not only to determine marker substances (fatty acids, aldehydes, alcohols and sterols) in pure microbial cultures isolated from the clinical material (Weiant F. et al., 1999) but also to reveal and quantify the composition of the microbial association which hides behind the series of markers in a specific sample (Osipov G.A., Demina A.M., 1996; White, 1988).

In 2010 Roszdravnadzor allowed to use it as a new medical technology “The assessment of the human microecological status using the method of chromate-mass-spectrometry” on the territory of the Russian Federation (Authrization FS 2010/038 dated 24.02.2010. Authors:

Baranov V.M., Academician of the Russian Academy of Medical Sciences; Osipov G.A., Dr. Biol. Sci.; Mukhamedieva L.N., MD; Beloborodova N.V., MD, Prof.; Pakhomova A.A.; Ilyin V.K., MD; Rodionova T.A., Cand. Biol. Sci.).

When investigating patients with suspected changes in the microecological status (intestinal or skin disorders, allergy, sepsis, fever of unclear genesis and etc.) we revealed the following types of changes in the normal microbiota of patients' organism:

- general and partial microorganism overgrowth;
- total deficit;
- heteropolar changes in individual microbiota components;
- appearance of microorganism groups not typical for the norm.

One hundred and twenty-nine blood samples (assessment of wall microbiota) and 30 feces samples (assessment of luminal microbiota) were taken in 129 liquidators of accident aftermath at ChNPP (LAA) within the limits of providing the specialized medical aid in outpatient settings. The microbial marker content in these samples was determined by the method of gas chromatography with mass-spectrometric detection.

Paired comparison of the groups was performed using Mann-Whitney U-test.

### *The investigation results of microbial markers in the blood*

The total microbial marker count in the blood in the normal condition should be within the range from 15,752 to 31,504 cells/g·$10^5$ including the beneficial microflora (from 9013 to 18 029 cells/g·$10^5$), opportunistic microflora (not more than 13 475 cells/g·$10^5$). The ratio of the beneficial microflora to the opportunistic flora is 1.34 (Fig. 3.10).

When investigating the wall microbiota in LAA we revealed that mean microbial marker count in the blood in 129 liquidators was 43825 cells/g·$10^5$ (including the beneficial microflora (up to 19353 cells/g·$10^5$), opportunistic microflora (24 472 cells/g·$10^5$), and their ratio was 0.79).

The total microbial marker count in the blood in LAA was within the normal range (variations from mean values ± 20%) in 39 subjects (30.2%), exceeded the normal value in 78 persons (60.5%) and was lower than the normal value in 12 subjects (9.3%) (Fig. 3.9).

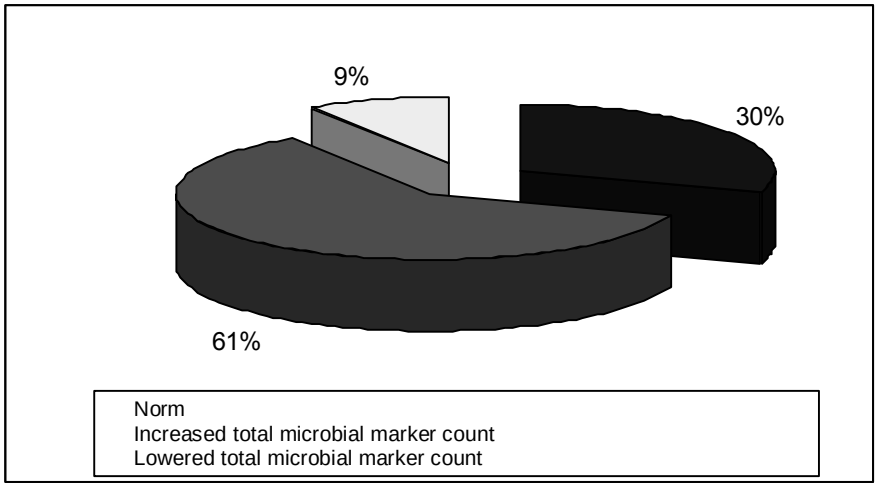


Fig. 3.9. Distribution of liquidators of accident aftermath at ChNPP by the total microbial marker count in the blood.

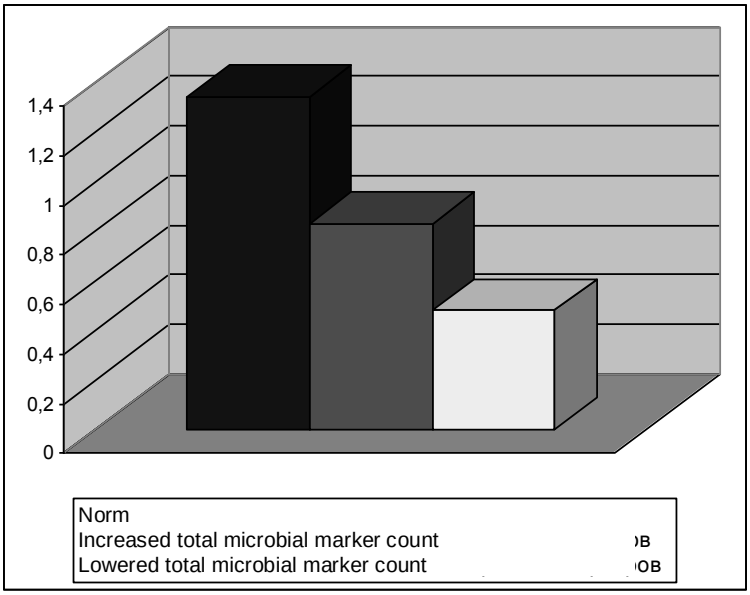


Fig. 3.10. The ratio of microbial marker count of the beneficial microflora
to microbial marker count of the opportunistic microflora
in liquidators of accident aftermath at ChNPP depending on the total microbial marker count in the blood.

It should be mentioned that liquidators of accident aftermath at ChNPP with lowered total microbial marker count in the blood (12 samples) had doubly lowered microbial marker count of the beneficial microflora in combination with count of the opportunistic flora similar to the norm (their ratio was 0.48) (Fig. 3.10). The quantitative and qualitative composition of the wall microbiota changed. So, we revealed that the microbial marker count of the beneficial microflora *Eubacterium/ Cl. coccoides* and *Bifidobacterium* was lowered 1.8-2 times as compared to the norm with simultaneous slight compensatory increase of the microbial markers *Propionibacterium/ Cl. subterminale* and *Lactobacillus* by 50 and 70%, respectively (Fig. 3.11, 3.12).

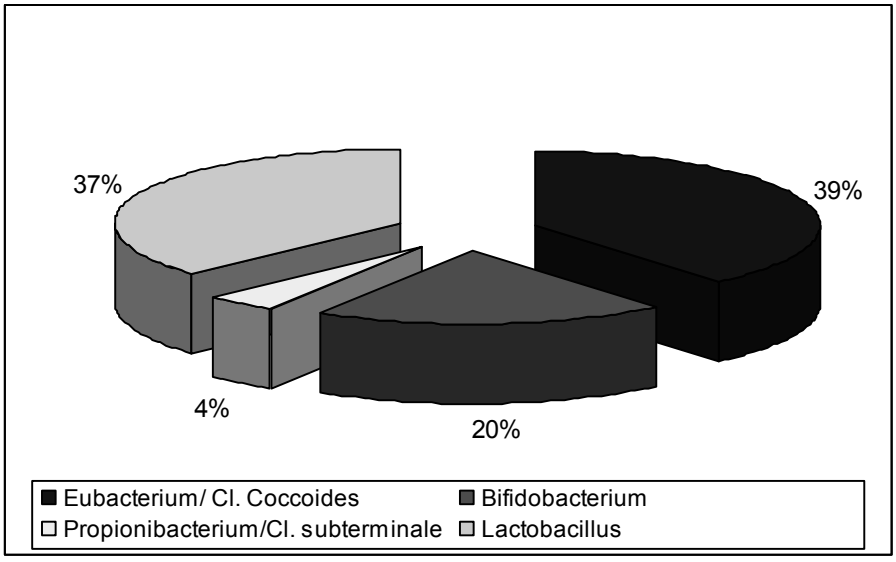


Fig. 3.11. The microbial marker composition of the beneficial microflora in the blood in the normal condition.

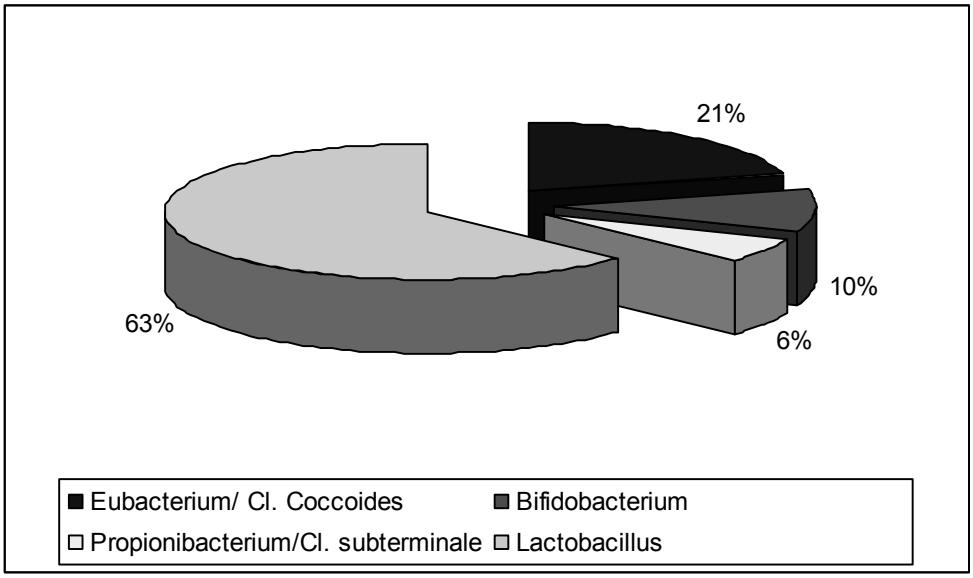


Fig. 3.12. The microbial marker composition of the beneficial microflora in liquidators of accident aftermath at ChNPP with lowered total microbial marker count in the blood.

The microbial marker count of the opportunistic microbiota increased 10 times for *Streptococcus (peroral)*, 8.5 times for *Nocardia*, *14:1d11*, 4 times for *Clostridium hystolyticum*, 3 times for *Streptomyces*, 2 times for *Clostridium ramosum* and *Propionibacterium jensenii*, 1.5 times for *Nocardia asteroids* with the lowered count of microbial markers *Actinomyces viscosus* (4 times), *Herpes* (2 times) and other specimens of the opportunistic flora (4 times) (Table 3.10, Fig. 3.13-3.16).

Table 3.10

Microbial markers of the opportunistic and pathogenic microflora in the blood in LAA at ChNPP

| No. | Opportunistic and pathogenic microflora | Microbial marker parameter, n (%), g · $10^5$ | | |
|---|---|---|---|---|
| | | LAA | | |
| | | low (1) (n=12) | normal (2) (n=130) | high (3) (n=78) |
| Aerobic or facultative gram-positive cocci | | | | |
| 1 | Streptococcus (peroral) | 2522 (17.0) | 249 (1.8)* | 3154 (10.8)** |
| 2 | Staphylococcus intermedius | 791 (5.3) | 756 (5.6) | 1389 (4.8)** |
| 3 | Streptococcus mutans | 177 (1.2) | 229 (1.7)* | 367 (1.3)** |
| Anaerobes | | | | |
| 4 | Clostridium hystolyticum | 396 (2.7) | 95 (0.7)* | 1,080 (3.7)** |
| 5 | Clostridium ramosum | 4197 (28.4) | 2000 (14.8)* | 7262 (24.9)** |
| 6 | Propionibacterium jensenii | 431 (2.9) | 185 (1.4)* | 1,113 (3.8)** |
| 7 | Propionibacterium acnes | 84 (0.6) | 0* | 155 (0.5)** |
| 8 | Actinomyces viscosus | 305 (2.1) | 1190 (8.8)* | 1221 (4.2) |
| Aerobic or facultative gram-positive bacilli | | | | |
| 9 | Nocardia, 14:1d11 | 2376 (16.1) | 262 (1.9)* | 4393 (15.1)** |
| 10 | Nocardia asteroides | 731 (4.9) | 448 (3.3)* | 1457 (5)** |
| Fungi, viruses and others | | | | |
| 11 | Streptomyces | 190 (1.3) | 62 (0.5)* | 343 (1.2)** |
| 12 | Herpes | 797 (5.4) | 1648 (12.2)* | 2929 (10.1)** |
| 13 | Microscopic fungi, campesterol | 0 | 842 (6.2)* | 82 (0.3)** |
| 14 | Microscopic fungi, sitosterol | 0 | 384 (2.8)* | 61 (0.2)** |
| Others | | | | |
| 15 | Others | 1762 (12.1) | 4835 (38.0)* | 4123 (14.1)** |
| **Total count** | | **14 792 (100)** | **13 765 (100)** | **29 129 (100)**** |

* Differences with group 1 $p<0.05$;
** Differences with group 2 $p<0.05$

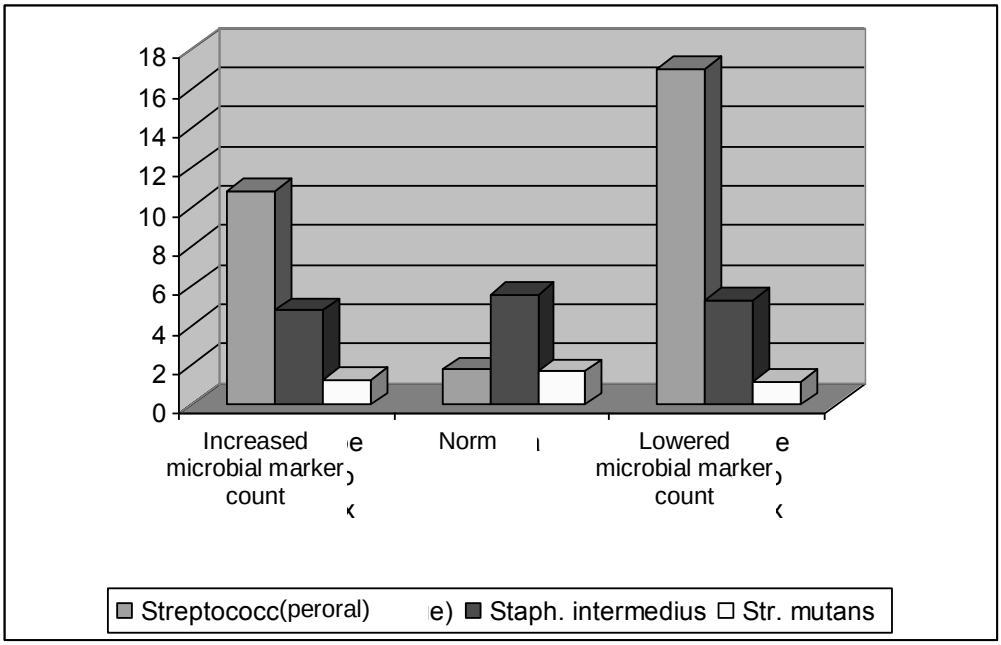


Fig. 3.13. The microbial marker composition (%) of the opportunistic flora [aerobic or facultative gram-positive cocci] in liquidators of accident aftermath at ChNPP with lowered and increased total microbial marker count in the blood.

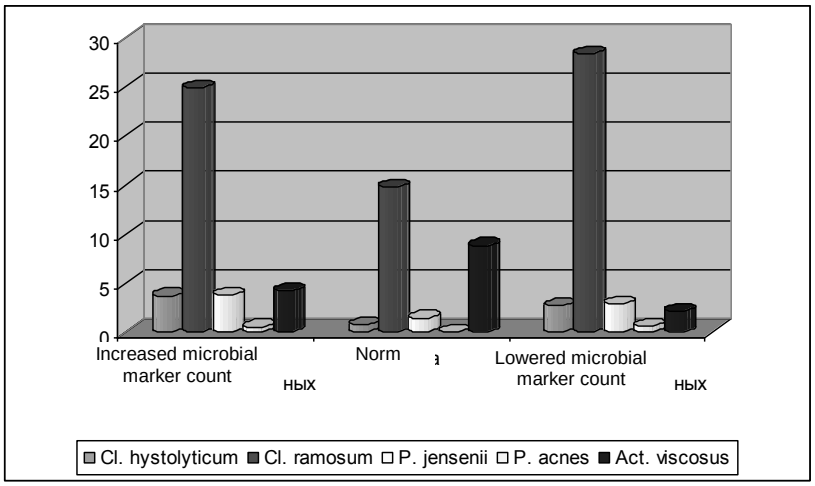


Fig. 3.14. The microbial marker composition (%) of the opportunistic flora (anaerobes) in liquidators of accident aftermath at ChNPP with lowered and increased total microbial marker count in the blood.

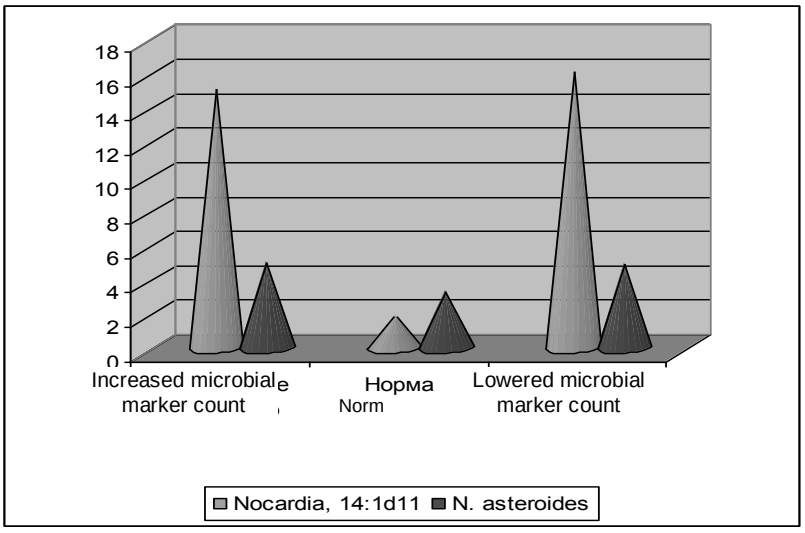


Fig. 3.15. The microbial marker composition (%) of the opportunistic flora [aerobic or facultative gram-positive bacilli] in liquidators of accident aftermath at ChNPP with lowered and increased total microbial marker count in the blood.

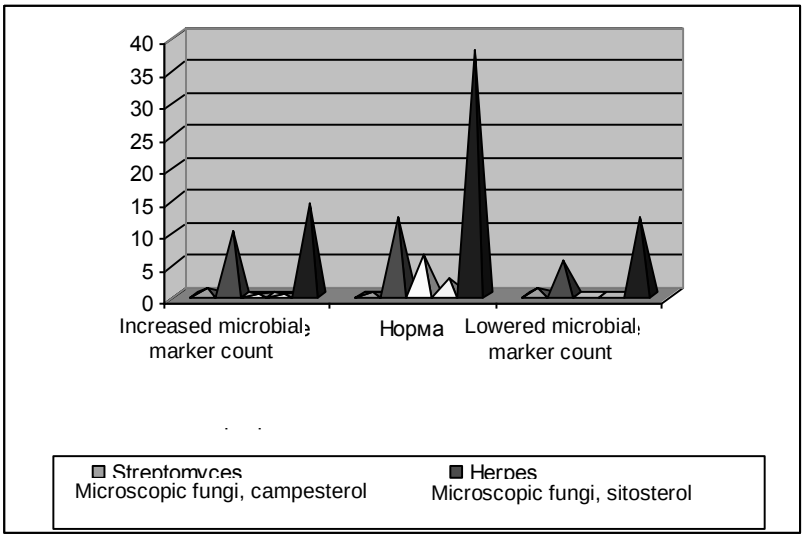


Fig. 3.16. The microbial marker composition (%) of the opportunistic flora [aerobic or facultative gram-positive cocci] in liquidators of accident aftermath at ChNPP with lowered and increased total microbial marker count in the blood.

It should be mentioned that liquidators of accident aftermath at ChNPP with increased total microbial marker count in the blood (78 samples) had doubly increased microbial marker count of the opportunistic flora in combination with moderately increased (by 34%) microbial marker count of the beneficial microflora (their ratio was 0.83) (see Fig. 4.11). The quantitative and qualitative composition of the wall microbiota changed. So, insignificantly lowered microbial marker count of the beneficial microflora *Eubacterium/* Cl. coccoides and *Bifidobacterium* (by 8-15%) was combined with twofold increase of microbial markers *Propionibacterium/Cl. subterminale* (Fig. 3.17).

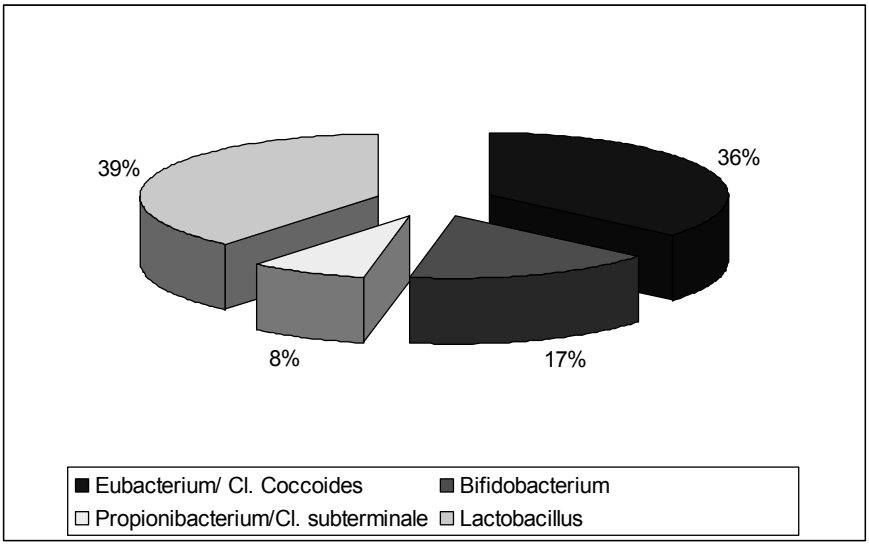


Fig. 3.17. The microbial marker composition of the beneficial microflora in liquidators of accident aftermath at ChNPP with increased total microbial marker count in the blood.

The microbial marker count of the opportunistic microbiota increased 8 times for *Nocardia, 14:1d11,* 6 times for *Streptococcus (peroral),* 5 times for *Clostridium hystolyticum*, 3 times for *Streptomyces* and *Propionibacterium jensenii*, 1.7 times for *Clostridium ramosum*. 1.5 times for *Nocardia asteroids* with the lowered count of microbial markers *microscopic fungi (campesterol)* (21 times), *microscopic fungi (sitosterol)* (14 times), *Actinomyces viscosus* (2 times),

*Staphylococcus intermedius, Streptococcus mutans* and *Herpes* (1.2 times) and other specimens of the opportunistic flora (3 times) (Table 3.10, Fig. 3.13-3.16).

The fact attracts attention that there are crucial differences in the composition and count of individual microbial markers in the blood of liquidators of accident aftermath at ChNPP with different total microbial marker count. Liquidators of accident aftermath at ChNPP with lowered total microbial marker count had decrease of the markers *Eubacterium/ Cl. coccoides, Bifidobacterium* 2 times and *Nocardia asteroids* 4 times. At the same time, liquidators of accident aftermath at ChNPP with increased total microbial marker count showed increased markers *Propionibacterium/Cl. subterminale* (2 times) and *Nocardia asteroids* (1.5 times) and lowered markers *microscopic fungi (campesterol)* (21 times), *microscopic fungi (sitosterol)* (14 times).

***The investigation results of microbial markers in the feces (luminal microbiota)***

The total microbial marker count in the feces in the normal condition should be within the range from 135,261 to 270,523 cells/g·$10^5$ including the beneficial microflora (from 28453 to 56,907 cells/g·$10^5$, opportunistic microflora (not more than 213616 cells/g·$10^5$). Their ratio is 0.27.

The mean microbial marker count in 30 feces samples in liquidators of accident aftermath at ChNPP was 209440 cells/g·$10^5$ including the beneficial microflora (up to 68,636 cells/g·$10^5$) and opportunistic microflora (140804 cells/g·$10^5$). Their ratio was 0.48 (Fig. 3.18).

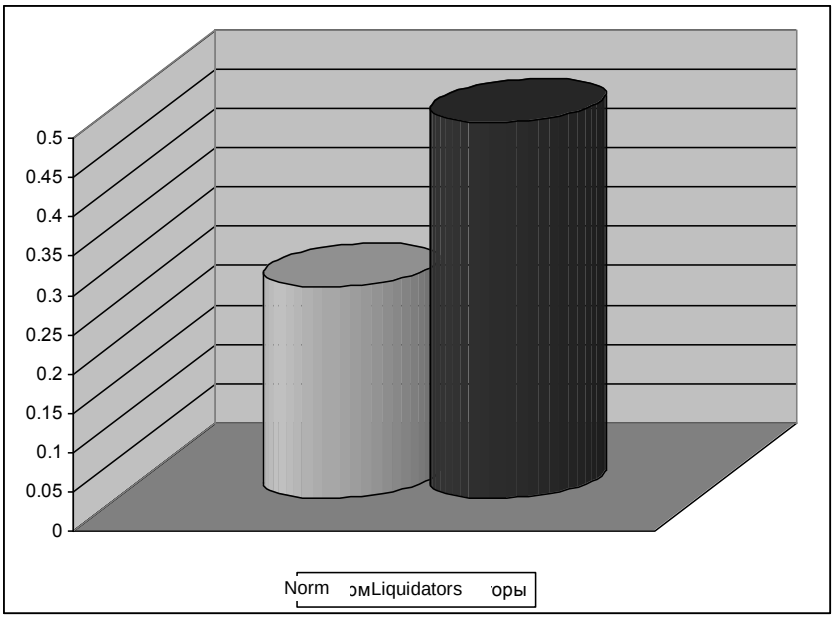


Fig. 3.18. The ratio of microbial marker count of the beneficial microflora
to microbial marker count of the opportunistic microflora
in liquidators of accident aftermath at ChNPP depending on the microbial marker count in the feces.

The total microbial marker count in the feces of LAA was within the normal range (variations from the mean values ± 20%) in 10 subjects (33%) and lower than the normal value in 20 subjects (67%) (Fig. 3.19).

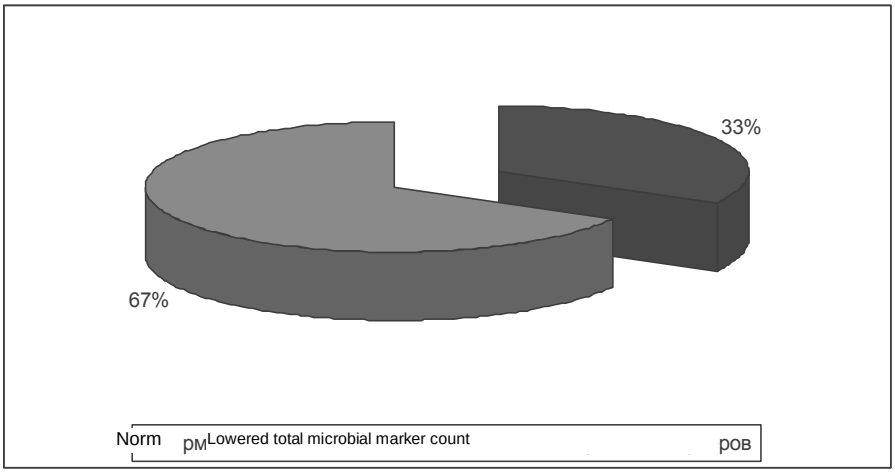


Fig. 3.19. Distribution of liquidators of accident aftermath at ChNPP by the total microbial marker count in the feces.

The fact attracts attention that liquidators of accident aftermath at ChNPP had doubly increased microbial marker count of the beneficial microflora (mainly due to *Eubacterium/Cl. Coccoides*) in the feces in combination with lowered count of the opportunistic flora (their ratio was 0.48). The quantitative and qualitative composition of the beneficial microbiota changed. So, the count of microbial markers *Eubacterium/ Cl. coccoides* increased 3 times with simultaneous decrease of the microbial marker count of the beneficial microflora 1.5-1.7 times for Bifidobacterium and Propionibacterium/Cl. subterminale and also 3 times for Lactobacillus (Fig. 3.20, 3.21).

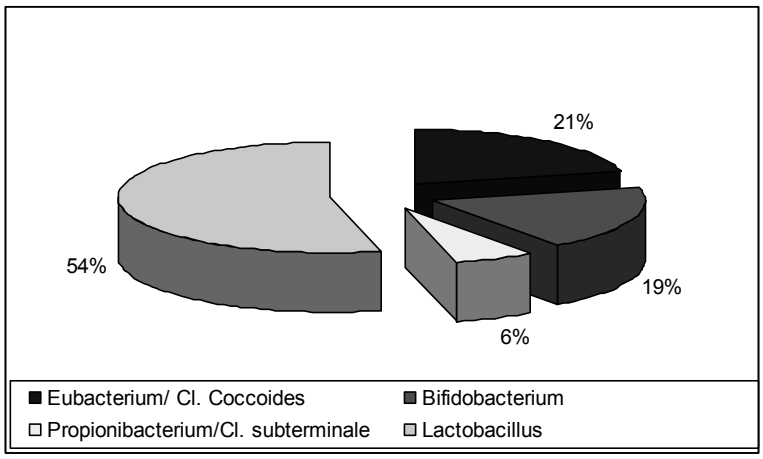


Fig. 3.20. The microbial marker composition of the beneficial microflora in the feces in the normal condition.

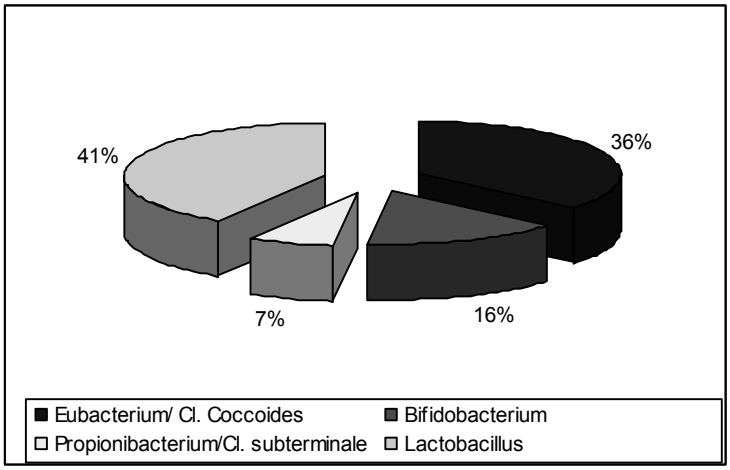


Fig. 3.21. The microbial marker composition of the beneficial microflora in liquidators of accident aftermath at ChNPP with lowered total microbial marker count in the feces.

We revealed the increased microbial marker count of the opportunistic microbiota: 4-9 times for aerobic or facultative gram-positive cocci (*Strreptococcus group A, Staphylococcus intermedius, Streptococcus mutans*), 6 times for *Streptomyces*, 4 times for microscopic fungi (sitosterol), 2 times for Propionibacterium jensenii. The considerably increased count of microbial markers *Nocardia, 14:1d11* (80 times), *Clostridium ramosum* (22 times), *Herpes* (24 times), *Nocardia asteroids* (11 times) was observed. We revealed also the lowered count of microbial markers *Clostridium perfringens* (2.6 times) and *Eubacterium (metabolism)* (1.3 times). It should be mentioned that liquidators of accident aftermath at ChNPP had no microbial markers *Clostridium propiopicum* in the feces (less than $10^5$) (Table 3.11, Fig. 3.22-3.25).

Table 3.11

Distribution of individual microbial markers of the opportunistic microflora in liquidators of aftermath at ChNPP with lowered total microbial marker count in the feces.

| No. | Opportunistic and pathogenic microflora | Microbial marker parameter, n (%), g · $10^5$ | |
|---|---|---|---|
| | | LAA | |
| | | Low (1) (n=20) | Normal (2) (n=70) |
| Aerobic or facultative gram-positive cocci | | | |
| 1 | Streptococcus of group A | 5473 (3.9) | 1691 (0.8)* |
| 2 | Staphylococcus intermedius | 6088 (4.3) | 2061 (1)* |
| 3 | Streptococcus mutans | 2732 (1.2) | 641 (0.3)* |
| Anaerobes | | | |
| 4 | Clostridium hystolyticum | 271 (0.2) | 388 (0.2) |
| 5 | Clostridium ramosum | 3116 (2.2) | 0 (0.1)* |
| 6 | Clostridium propionicum | 0 (0) | 13942 (6.5)* |
| 7 | Clostridium perfringens | 11124 (7.9) | 44698 (20.9)* |
| 8 | Peptostreptococcus anaerobius of group 1 | 10656 (7.6) | 15192 (7.1) |
| 9 | Eubacterium (metabolism) | 46315 (32.9) | 93218 (43.6)* |
| 10 | Propionibacterium jensenii | 12953 (9.2) | 9725 (4.5)* |
| 11 | Actinomyces viscosus | 1643 (1.2) | 2769 (1.3) |
| Aerobic or facultative gram-positive bacilli | | | |
| 12 | Nocardia, 14:1d11 | 11188 (7.9) | 7 (0.1)* |
| 13 | Nocardia asteroides | 1479 (1.1) | 108 (0.1)* |
| Fungi, viruses and others | | | |
| 14 | Streptomyces | 5602 (3.9) | 1522 (0.7)* |
| 15 | Herpes | 3344 (2.4) | 0 (0.1)* |
| 16 | Microscopic fungi, campesterol | 651 (0.5) | 1430 (0.7)* |
| 17 | Microscopic fungi, sitosterol | 2115 (1.5) | 888 (0.4)* |
| Others | | | |
| 18 | Others | 16054 (11.4) | 25336 (12)* |
| **Total count** | | **140804 (100)** | **213616 (100)** |

*Differences with the normal value $p<0.05$

The total microbial marker count in the blood of LAA was within the normal range (variations from the mean values ± 20%) in 14 subjects (47%) and exceeded the normal value in 16 subjects (53%). The total microbial marker count in the feces of LAA was within the normal range (variations from the mean values ± 20%) in 10 subjects (33%) and lower than the normal value in 20 subjects (67%).

The investigation of microbial markers showed that if LAA had the increased total microbial marker count in the blood, as a rule, the lowered total count was revealed in the feces.

Liquidators of accident aftermath at ChNPP (16 samples with increased total microbial marker count) had doubly increased count of microbial markers *Propionibacterium/Cl. Subterminale* in the blood with simultaneous lowering of *Lactobacillus* count by 14%.

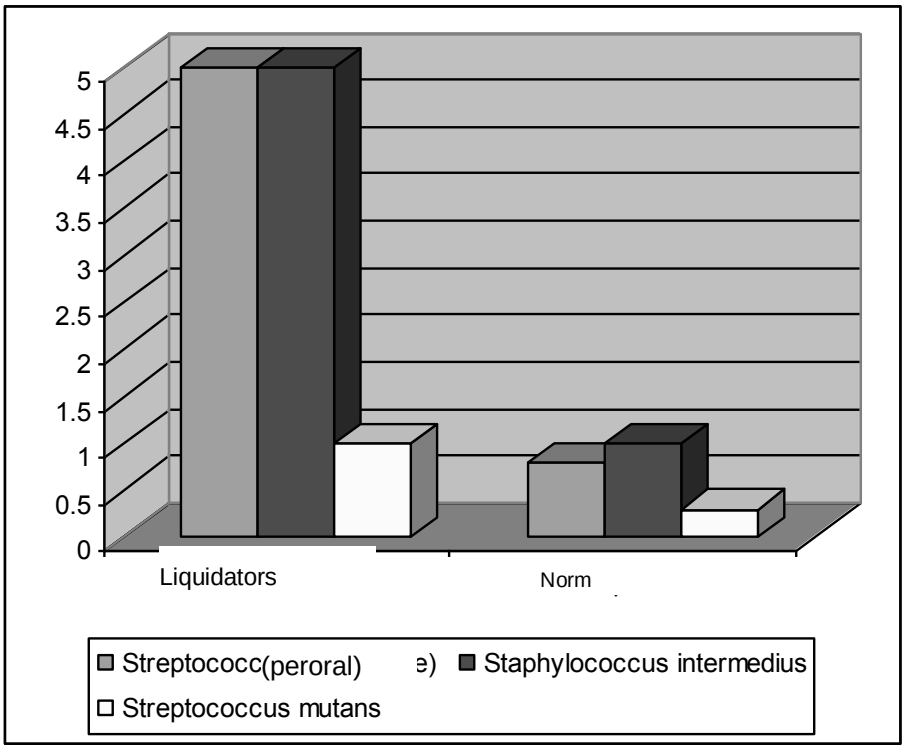


Fig. 3.22. The microbial marker composition (%) of the opportunistic flora [aerobic and facultative gram-positive cocci] in liquidators of accident aftermath at ChNPP with lowered total microbial marker count in the feces

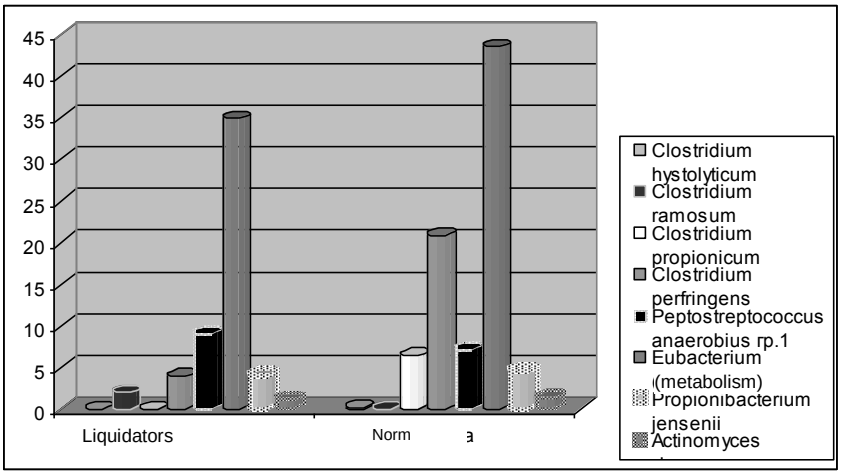


Fig. 3.23. The microbial marker composition (%) of the opportunistic flora (anaerobes) in liquidators of accident aftermath at ChNPP with lowered total microbial marker count in the feces

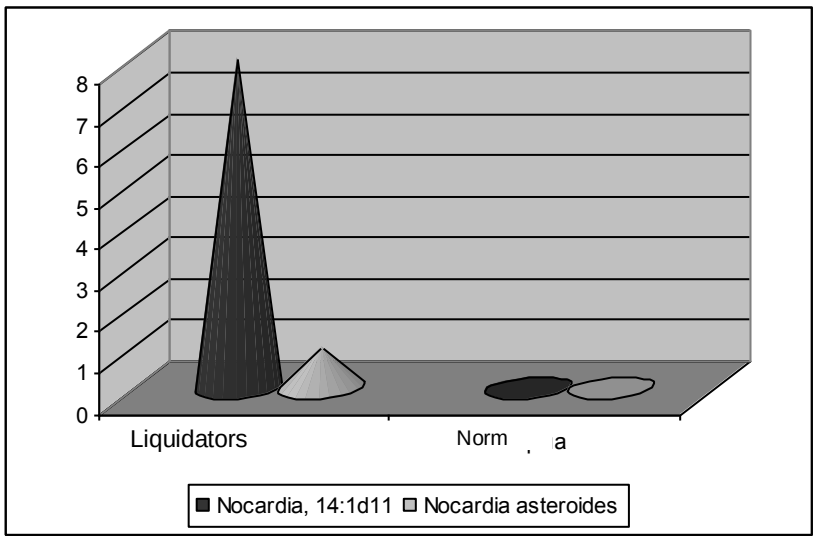


Fig. 3.24. The microbial marker composition (%) of the opportunistic flora [aerobic or facultative gram-positive bacilli] in liquidators of
aftermath at ChNPP with lowered total microbial marker count in the feces.

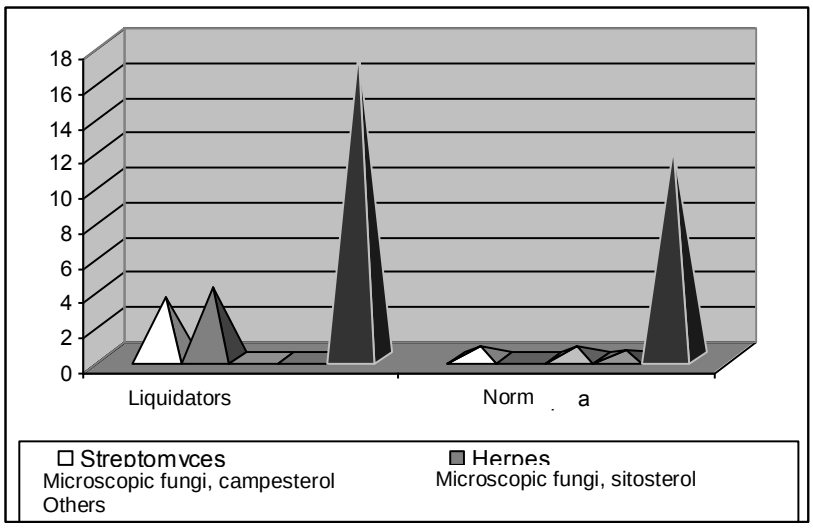


Fig. 3.25. The microbial marker composition (%) of the opportunistic flora [aerobic or facultative gram-positive cocci] in liquidators of accident aftermath at ChNPP
with lowered total microbial marker count in the feces

### *The investigation results of microbial markers in the blood and feces in 30 liquidators of accident aftermath at ChNPP*

At the same time, the increased count of microbial markers *Eubacterium/ Cl. coccoides* (by 71%) and lowered count of markers *Lactobacillus* (by 24%) were revealed in the feces (20 samples with lowered total microbial marker count) (Fig. 3.26).

The microbial marker count of the opportunistic microbiota in the blood was increased 7.4 times for *Nocardia, 14:1d11,* 5 times for *Streptococcus of group A,* 4 times for *Clostridium hystolyticum* and *Propionibacterium jensenii,* 1.7 times for *Clostridium ramosum* and *Streptomyces.* At the same time the lowered count of the following microbial markers was also revealed: *Actinomyces viscosus* (1.8 times), *microscopic fungi (campesterol)* (7 times), *microscopic fungi (sitosterol) (*5 times), and other markers of the opportunistic flora (2.3 times) (Table 3.12).

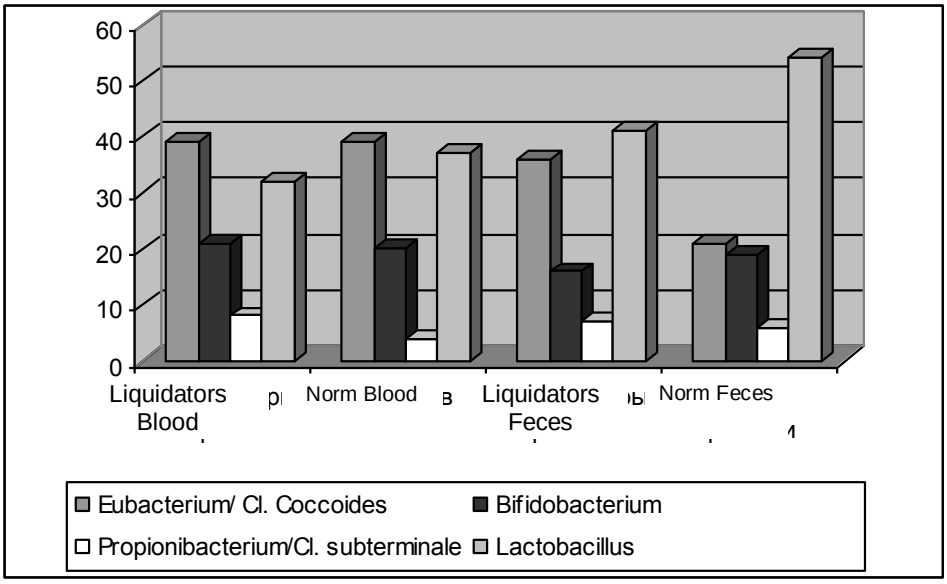


Fig. 3.26. The microbial marker composition of the beneficial microflora in liquidators of accident aftermath at ChNPP with increased total microbial marker count in the blood and lowered total microbial marker count in the feces.

At the same time, the microbial marker count of the opportunistic microbiota was increased in the feces: aerobic or facultative gram-positive cocci *(Streptococcus of group A, Staphylococcus intermedius, Streptococcus mutans*) (3–6 times), *Streptomyces* (6 times), other markers of the opportunistic flora (1.5 times).

Table 3.12

The microbial markers of the opportunistic and pathogenic microflora in the blood with increased total microbial marker count and in the feces with lowered total microbial marker count in LAA at ChNPP

| No. | Opportunistic and pathogenic microflora | Microbial marker level, % | | | |
|---|---|---|---|---|---|
| | | in the blood, % | | in the feces, % | |
| | | LAA | Norm | LAA | Norm |
| Aerobic or facultative gram-positive cocci | | | | | |
| 1 | Streptococcus of group A | 9* | 1.8 | 5* | 0.8 |
| 2 | Staphylococcus intermedius | 4.4* | 5.6 | 5* | 1 |
| 3 | Streptococcus mutans | 1.4 | 1.7 | 1* | 0.3 |
| Anaerobes | | | | | |
| 4 | Clostridium hystolyticum | 3* | 0.7 | 0 | 0.2 |
| 5 | Clostridium ramosum | 24.8 | 14.8 | 2* | 0.1 |
| 6 | Clostridium propionicum | 0* | 2.1 | 0* | 6.5 |
| 7 | Clostridium perfringens | 0 | 0.1 | 4* | 20.9 |
| 8 | Peptostreptococcus anaerobius of group 1 | 0 | 0 | 9* | 7.1 |
| 9 | Eubacterium (metabolism) | 0* | 0.4 | 35* | 43.6 |
| 10 | Propionibacterium jensenii | 5.7* | 1.4 | 4 | 4.5 |
| 11 | Actinomyces viscosus | 5 | 8.8 | 1* | 1.3 |
| Aerobic or facultative gram-positive bacilli | | | | | |
| 12 | Nocardia, 14:1d11 | 14* | 1.9 | 8* | 0.1 |
| 13 | Nocardia asteroides | 3.5* | 3.3 | 1* | 0.1 |
| 14 | Bacillus megaterium | 0* | 0 | 3.5* | 0.1 |
| Fungi, viruses and others | | | | | |
| 15 | Streptomyces | 0.8 | 0.5 | 4* | 0.7 |
| 16 | Herpes | 11.1 | 12.2 | 0* | 0 |
| 17 | Microscopic fungi, campesterol | 0.9* | 6.2 | 0* | 0.7 |
| 18 | Microscopic fungi, sitosterol | 0.6* | 2.8 | 0* | 0.4 |
| Others | | | | | |
| 19 | Others | 15.8* | 35.7 | 17.5* | 11.6 |
| **Total count** | | **100** | **100** | **100** | **100** |

*Differences with the normal value $p<0.05$

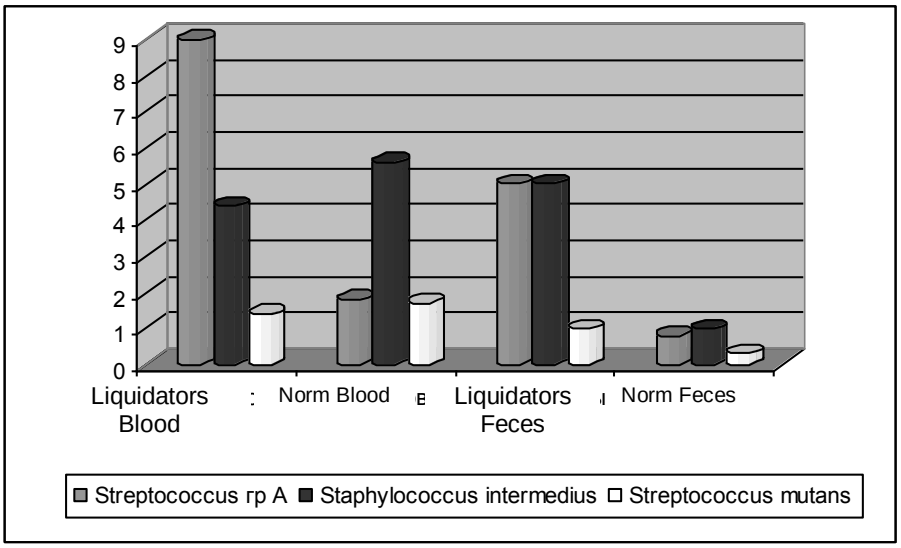


Fig. 3.27. The microbial marker composition (%) of the opportunistic flora [aerobic and facultative gram-positive cocci] in liquidators of accident aftermath at ChNPP with increased total microbial marker count in the blood and lowered total microbial marker count in the feces.

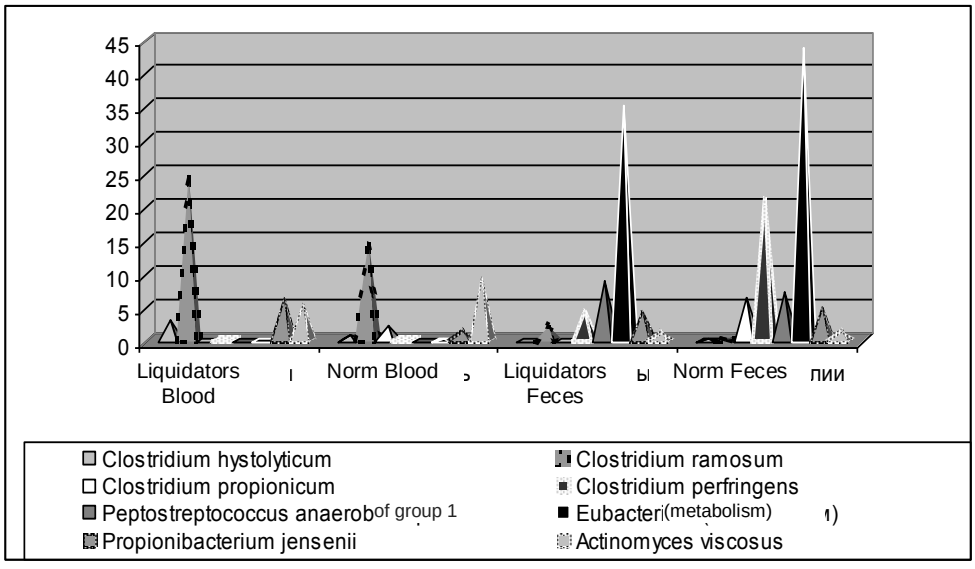


Fig. 3.28. The microbial marker composition (%) of the opportunistic flora (anaerobes) in liquidators of accident aftermath at ChNPP with increased total microbial marker count in the blood and lowered total microbial marker count in the feces.

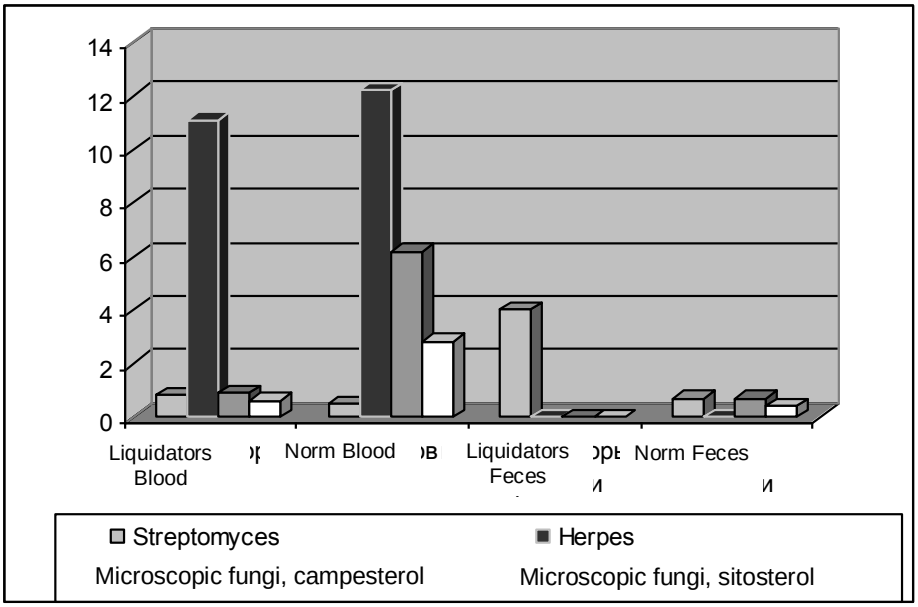


Fig. 3.29. The microbial marker composition (%) of the opportunistic flora (fungi, viruses etc.) in liquidators of accident aftermath at ChNPP with increased total microbial marker count in the blood and lowered total microbial marker count in the feces.

We observed considerably increased count of microbial markers *Nocardia, 14:1d11* (80 times), *Clostridium ramosum* (20 times), *Bacillus megaterium* (35 times). We revealed also the lowered count of microbial markers *Clostridium perfringens* (5 times) and *Eubacterium (metabolism)* (1.2 times) (Table 4.8, Fig. 3.27-3.29). Attention is attracted by the increased count of microbial markers of the opportunistic microbiota *Streptococcus of group A, Clostridium ramosum, Nocardia, 14:1d11, Streptomyces* both in the blood and feces.

Thus, the investigation of the blood and fecal microbiota using the method of chromato-mass-spectrometry of microbial markers is evidence of the fact that investigated liquidators of accident aftermath at ChNPP have pronounced intestinal dysbiosis which is manifested in the following microbiota change:

1.The total microbial marker count in the blood in liquidators of accident aftermath at ChNPP was within the normal range in 30.2%, exceeded the normal value in 60.5% and was lower than the normal value in 9.3%.

2.Liquidators of accident aftermath at ChNPP with lowered total microbial marker count in the blood had doubly lowered microbial marker count of the beneficial microflora in combination with count of the opportunistic flora similar to the norm with changed quantitative and qualitative microbiota composition.

3.Liquidators of accident aftermath at ChNPP with increased total microbial marker count in the blood had doubly increased microbial marker count of the opportunistic flora in combination with moderately increased microbial marker count of the beneficial microflora with changed quantitative and qualitative microbiota composition.

4.The total microbial marker count in the feces of LAA was within the normal range in 33% and lower than the normal value in 67%. Liquidators had doubly increased microbial marker count of the beneficial microflora (mainly, due to *Eubacterium/ Cl. coccoides*) with simultaneously lowered count of the opportunistic flora with changed quantitative and qualitative microbiota composition.

5.Chromato-mass-spectrometry of microbial markers in the blood and feces revealed the following changes in the same liquidators of accident aftermath at ChNPP:

- increase of total microbial marker count in the blood and its lowering in the feces;

- doubly increased count of microbial markers *Propionibacterium/Cl. subterminale* with simultaneously lowered count of *Lactobacillus* in the blood and increased count of microbial markers *Eubacterium/ Cl. coccoides* and lowered count of markers *Lactobacillus* in the feces;

- increased count of microbial markers of the opportunistic microbiota in the blood and feces.

The obtained individual microbiotic status profiles served as the base for targeted correction of revealed disorders the main principles of which are: dietetic correction, decontamination of the opportunistic microflora, eubiosis recovery, treatment of the pathology which resulted in dysbiosis.

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## CHAPTER 4

## METHODOLOGY FOR EPIDEMIOLOGICAL STUDIES OF MEDICAL AND SOCIAL CONSEQUENCES AT THE CHERNOBYL NUCLEAR POWER PLANT

The investigation of the influences exerted by exposure to the radiation on the health condition of liquidators of accident aftermath (LAA) at the Chernobyl NPP (ChNPP) started from the first days of the works in the ChNPP zone. An All-Army Register of Military Men Exposed to the Radiation in the Accident Zone at ChNPP was initiated in June, 1986 in order to collect the information on the health condition of LAA, and the Ministry of Health of the USSR established an All-Union Distributed Register of Persons Who Suffered because of the Accident at ChNPP. The Russian State Medical Dosimetric Register (RSMDR) became the successor of this register in 1991

and in 1993 it underlay a National Radiation Epidemiologic Register (NRER) of persons exposed to the radiation as a result of the Chernobyl and other radiation catastrophes and incidents.

The main tasks of the NRER are as follows:

- long-term personal registration and follow-up of the health condition of persons exposed to the radiation;

- information support of medical preventive examinations of persons included in the register in order to provide for the optimum strategy for reducing the medical consequences caused by the accident at ChNPP;

- large-scale radiation epidemiologic studies to assess objectively the dose-effect dependence and radiation risks.

The NRER system provides for obtaining the personal medical and dosimetric information from the whole territory of the Russian Federation, for which purpose four main registration forms are used:

- registration card of a person exposed to the radiation as a result of the accident at the Chernobyl NPP;

- coding coupon of a person exposed to the radiation as a result of the accident at the Chernobyl NPP;

- registration card of cancer disease of a person exposed to the radiation as a result of the accident at the Chernobyl NPP;

- death cause card of a person exposed to the radiation as a result of the accident at the Chernobyl NPP.

The NRER data base contains the information on more than 700 thousand people; the whole data set of registered diseases is more than 18 mln pathologic conditions; the received external radiation doses were registered for 450 thousand people included in the register (Russian National Report). The data collected in NRER allows to accumulate the information for subsequent analysis by the workers of the practical health care system and research workers of the following data bases:

- main base containing the registration, dosimetric and medical information on persons exposed to the radiation because of the accident at ChNPP;

- cancer subregister data base on cases of cancer diseases in persons registered in NRER;

- death cause data base of persons registered in NRER;

- children subregister data base of LAA at ChNPP;

- data bases of the subregister of thyroid cancer cases in persons living or having lived on the Russian territories and exposed to increased radiation levels as a result of the accident at ChNPP.

The complex analysis of the material contained in the above data bases with the participation of clinicians, epidemiologists, radiologists, hygienists and other specialists allows to assess the influence exerted by the radiation factor on the health condition of LAA at ChNPP, provide the targeted medical aid, prognosticate long-term medical radiological consequences and develop the purposeful measures for reducing the medical consequences.

It should be mentioned that the characteristics of the main public health parameters (morbidity, prevalence of diseases, disablement, mortality) of LAA in a long-term period after the accident differ considerably on the different territories of the country because these parameters are influenced by many factors (climate, condition of environmental objects, economical situation,

medical provision, etc.). Therefore, a special role is played no so much by the determination of the prevalence of the pathology revealed in LAA as by methodological aspects of the epidemiological investigation and search for arguments for and against the radiation genesis of the revealed health disorders in order to assess objectively the long-term consequences of LAA exposure to the radiation.

The effects exerted by low radiation doses received by LAA at ChNPP are still being studied till today in spite of the fact that 30 years elapsed after the accident. The action of low doses is not manifested in specific affections in contrast to direct effects of exposure to the radiation (acute and chronic radiation sickness, radiation cataract, radiation burn). The clinical and epidemiological methods have been traditionally used as the main ones to investigate the influence exerted by any unfavorable factors on the population health. The analysis is performed with comparing the frequency of the clinical, laboratory and instrumental characteristics or public health parameters in LAA and the comparison group.

The clinical method is used to reveal and study the features of pathogenesis, clinical picture, treatment and prevention of diseases. When performing the scientific clinical studies, the use of the above NRER data bases allows to form the test group (LAA group) with the prescribed required parameters (underlying and concomitant diseases, sex, age, year of participation in the works at ChNPP, received external irradiation dose, etc.).

It should be mentioned that when the clinical method is used, the study is performed, as a rule, in a specially formed restricted sample, and, therefore, its result depends much on the size and homogeneity of groups being compared. If there is a statistically significant difference between the compared groups by the frequency, degree and other signs of the clinical course of the given pathology, a conclusion is often made that this difference is a consequence either of the influence exerted by the radiation factor on LAA, or, rarer, of the participation of LAA in the works in ChNPP zone in 1986–1991. Besides that, in those cases, when a correlation between the test phenomenon and received irradiation dose is established, a conclusion is also made on the effect of the radiation factor on LAA irrespective of the correlation strength.

It should be specially emphasized that the above facts contradict to some extent to the recommendations of the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) R.686 “Possibility to attribute the risks and effects to exposure to the radiation” (2011) (Kiselev, M. F., Azizova, T. V., Akleyev, A. V. et al., 2012). According to this document, it is possible to attribute an effect to exposure to the radiation only in those cases when there exist tissue reactions (determined effects) and a diagnosis is made, which rules out other possible causes. In this situation special attention is paid to the fact that “when the population is exposed to low radiation doses, even significant exceeding of stochastic effects cannot be attributed to exposure to the radiation because the natural dispersion of these effects caused by non-radiation factors exceeds considerably their any expected growth associated with exposure to the radiation.” The cited statement does not exclude the need to continue the studies of long-term medical consequences in LAA, especially because the document mentions only determinate and stochastic effects.

Therefore, the expediency of clinical investigation of the consequences caused by the exposure of LAA to low radiation doses does not raise doubts but the following conditions are of

fundamental importance in order to reduce the probability of erroneous conclusions when performing the clinical studies:

- maximum possible homogeneity of the LAA group and the comparison group by the factors influencing the prevalence of diseases (sex, age, bad habits, heredity, administered X-ray investigations, etc.);

- exclusion of the influence exerted by accidental factors on the study results by enrollment of the test group, which is representative by its size, and exceeding of the comparison group size not less than 3 times as compared to the test group size;

- performing the clinical investigation of LAA and persons from the comparison group by the same medical team shortly and carrying out the laboratory tests and instrumental investigations at one base;

- use of adequate methods for statistical analysis with assessing not only the statistical significance of value differences in LAA and the comparison group but also their medical and biological significance;

- use of only strong association between the test parameters for interpretation of the correlation relationship.

The NRER data bases are created, undoubtedly, predominantly for epidemiological studies of the medical and social consequences in persons exposed to the radiation because the epidemiologic method is intended for revealing and studying the causes, preconditions and prevalence of any pathologic states in the human population. This method represents a specific complex of approaches and procedures including observation, investigation, historical and geographic description, comparison, experiment, statistical and logic analysis with subsequent professional interpretation of obtained results.

The retrospective epidemiological analysis of such public health parameters as morbidity, prevalence of diseases, morbidity rate, disablement and mortality calculated basing on the data of official statistical reports is used the most often at the first stage of epidemiologic study of the health condition. The analysis includes the frequency, changes over time, structure and territorial distribution of the given pathology in the group of persons exposed to the test factor and in the group of persons not exposed to the test factor. The marked difference in the test parameters in the compared groups is evidence of the possible cause-effect association between the test unfavorable factor and the population health and allows to continue the study in order to obtain more reliable evidences of such associations.

It should be mentioned that the significant exceeding of these parameters in LAA group is often considered as the consequence caused by their exposure to the radiation factor. At the same time, the design of epidemiologic studies and interpretation of their results applicably to LAA are extremely difficult as it is impossible to enroll a reliable comparison group because:

- ninety-eight percent of LAA are males, i. e. the sex structure principally differs from that of the population;

- the test group for participation in the emergency-recovery works in the ChNPP zone was enrolled, mainly, by military registration and enlistment offices from among those liable for military service and also specialists of the nuclear industry, i. e. initially the healthier part of the population;

- young people prevailed in the age structure of LAA at the time of their involvement in the works in ChNPP zone and “ageing” of the test group takes place as years pass in contrast to the relative stability of this parameter in the population;

- in contrast to the registration documents of NRER which keep personal records of diseases, disablement and mortality of LAA, the forms of official statistical reports on diseases revealed in the population do not contain the division by sex and age but include the adult population aged above 18 years on the whole; the exclusion is only “The information on causes for temporary disability” (form No. 16—VN) which contains this data but only for those who received a sick-list (it is clear that this information reflects only partially the true situation);

- the existing system of special preventive medical examinations of LAA with their assignment to a certain health care facility (deputed physician) with obligatory annual examination (or once in 2 years) cannot come up with the efficiency of revealing the pathology by visits to physicians including non-state health care facilities ( the materials are available, which confirm that the number of diseases revealed by preventive medical examinations of the population is 3 times more than that assessed by visits to physicians);

- verification of the pathology revealed in LAA is significantly better because one visit to the outpatient clinic leads on average to one hospitalization or a course of sanatorium-and-spa treatment what distinguishes them considerably from other population groups;

- aims of LAA concerning their diseases differ principally from that in the population because of the benefits granted to this category (putting a law “On Monetization of Benefits” in force resulted in the increase of disablement rate in the population 1.5 times over 1 year; according to the data of Rosstat, the number of disabled persons decreased nearly by 500 thousand people in Russia from the beginning of 2014 to September, 2015 after adopting of the Law of the Ministry of Labor and Social Protection No. 664n.

The above circumstances should be taken into account when performing the epidemiologic studies of the medical and social consequences in LAA and assessing the obtained results.

The results obtained at the first stage of the epidemiologic study reveal the systems or target organs affected by the possible influence of the radiation factor in LAA, i. e. those classes of diseases and nosologic forms for which the public health parameters in LAA differ significantly from that in the population.

The cause-effect associations between the possible causative factors and the pathology in revealed systems or target organs are searched for at the second stage of the epidemiologic study. It should be mentioned that the range of these factors is determined in many respects by the researcher’s qualification and the best results are provided by the combined work of epidemiologists, clinicians, hygienists, and health officials with involvement also of other specialists including those of non-medical profile, if necessary.

Taking into account the above, it is advisable to use the following two approaches in order to search for the cause-effect associations between exposure to the radiation factor and LAA health conditions:

a) use of such method of formal logics as combined method of similarity and difference. In this specific case, it consists in searching for identical signs of disturbed public health in LAA

living on different territories and who are united only by their participation in the works in ChNPP zone;

b) comparative analysis of the test health parameters in persons exposed to given unfavorable factor of different intensity. In our case these persons are LAA who received a different external irradiation dose or involved in the works at ChNPP in different years.

As concerns the second approach, we should mention the uncertainty of dosimetric data contained in the NRER data base and associated with the method for measurement of the irradiation dose (Table 4.1). It should be mentioned that, in spite of the fact that both the "Registration Card" and "Coding Coupon" contain items for indicating the measurement method of the received dose, it is indicated only for 2 persons out of 7,630 LAA with recorded irradiation dose in the North-Western Region of Russia.

Table 4.1

Uncertainty of Dosimetric Data Contained in the NRER Data Base
(from the Russian National Report "25 Years After the Chernobyl Accident—
Final Results and Perspectives for Overcoming its Consequences in Russia, 1986–2011," 2011)

| Dose category | Measurement method | Maximum error |
|---|---|---|
| Exposure or absorbed | Use of individual dosimeter | 50 % |
| Group | Assigned to all persons of the group by reading of the dosimeter used by 1 person | Dispersion up to 3 times in the group |
| Route | Calculated by mean power of the exposure dose in the working zone and duration of stay in it of the person group | Dispersion up to 5 times in the group |

We should add to the above that, as a rule, neither clinical nor epidemiologic studies consider the doses received during X-ray investigations. This circumstance is of extreme importance applicably to LAA because detectability of the pathology in them during special preventive medical examinations including modern methods for radiation diagnostics is higher than that in the population and differs among LAA themselves what may distort considerably the investigation results concerning the dependence of the pathology in LAA at ChNPP on the dose.

Using the own experience in the model of the North-Western Region including the territories of five constituent entities of the Russian Federation (Saint Petersburg, Kaliningrad, Leningrad, Novgorod, and Pskov Regions), we present some methodical techniques for the epidemiological study of long-term medical consequences in LAA at ChNPP. The total learning sample size for the region was more than 11 thousand LAA distributed in the following groups by the received external irradiation doses: 70 % of LAA received the external irradiation dose of less than 20 cSv, the dose from 20 to 24 cSv was recorded in 27.4 %, and 25 cSv and more was received by 2.8 %. Thus, according to definition of UN SCEAR, which was valid till 2011, most LAA were exposed to so-called low ionizing radiation doses (up to 20 cSv). At the same time, the accumulated scientific data on long-term medical and biological consequences allowed UN SCEAR to approve a new classification of dose ranges in 2011 (Kiselev, M. F., Azizova, T. V., Akleyev, A. V. et al., 2012). The following dose ranges were distinguished according to this classification: very low doses—up to 10 mGy; low doses—10–100 mGy; medium doses—0.1–1 Gy; high doses—1–10 Gy. According to this classification, 81.6 % of LAA from the North-Western Region of the country received the medium irradiation dose, 15.7 % received the low dose, 2.6 % very low dose and 0.1 % high

irradiations dose in 1986 (Fig. 4.1). More than 90 % received low (56.5 %) and very low (38.7 %) irradiation doses among LAA of 1987–1991.

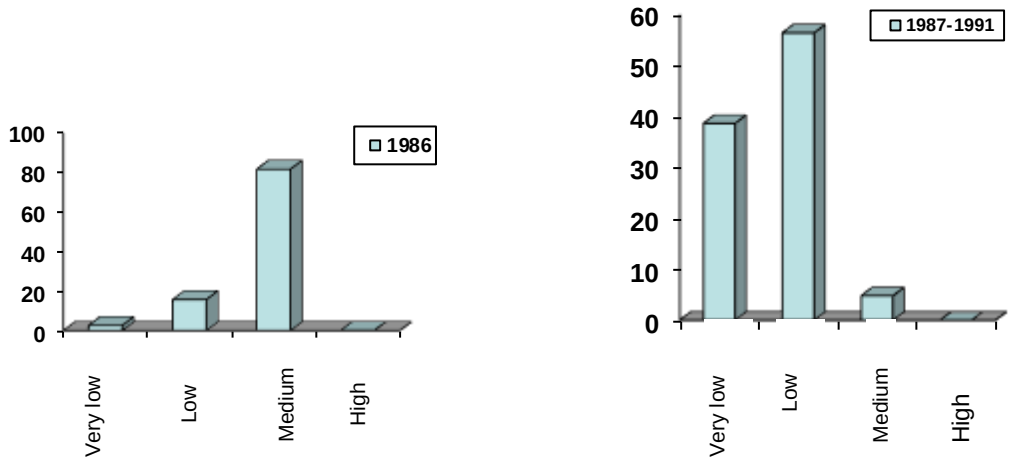


Fig. 4.1. Distribution of LAA from the North-Western Region of Russia by the Received External Irradiation Doses

The above data are the additional evidence of the fact that, firstly, it is advisable to analyze the health condition of LAA depending on the year of their participation in the works in ChNPP zone within the epidemiologic studies and, secondly, it is necessary to assess the informativeness of the new ranges of irradiation doses basing on the results of epidemiologic studies.

When interpreting the results of the epidemiologic study aimed at revealing the cause-effect associations between the effect of unfavorable factors during liquidation of accident aftermath at ChNPP and LAA health condition, we should proceed from the fact that if this effect was significant, it should be manifested similarly and synchronously in LAA on all territories of the region. Otherwise, any changes in the health of LAA living on different territories should be recognized as a consequence caused by the action of local causative factors of non-radiation genesis.

We used the analysis results of morbidity, prevalence of diseases, disablement and mortality of LAA from the North-Western Region of the country in order to demonstrate the techniques for epidemiologic diagnostics of medical consequences. The morbidity and prevalence of diseases are the most frequent medical statistical parameters used for the analysis of the population health condition. But their significance in the assessment of the health condition differs considerably. So, morbidity characterizing the frequency of diseases revealed for the first time per year is more sensitive to changed conditions of the habitat and is evidence of the action strength exerted by unfavorable factors on the population health. The value of morbidity is a medical statistical parameter is especially high when a new unfavorable factor appears on the given territory or the action of already existing factors is intensified significantly. The analysis of this parameter over several years allows to understand changes in the action intensity of unfavorable factors and the efficiency of medical and preventive measures.

As the prevalence of diseases considers not only newly registered diseases but also already existing diseases because of which persons took medical advice during a calendar year, this parameter is more stable to environmental factors. So, the prevalence of diseases will grow in case of the stable morbidity with chronic diseases due to “accumulation” of persons registered for obligatory preventive medical examinations and also in case of higher efficiency of the medical

measures and associated increase of the lifespan, etc. (*Materials for Preparation and Qualification Certification, 2005*). The prevalence of diseases in LAA at ChNPP should be interpreted taking into account the cohort ageing by 25–30 year by now.

Disablement and mortality as medical statistical parameters of the population public health differ from morbidity and prevalence of diseases in the higher verification degree of the existing pathology. This is associated with the fact that a citizen is referred for medical and social expert examination for his (her) recognition as a disabled person by a health care facility after carrying out the necessary diagnostic, medical, and rehabilitation measures. This health care facility is responsible for the confidence and completeness of the information indicated in the referral for the expert examination. The decision on recognition of the citizen as a disabled person is made by specialists of the office for medical and social expert examination by a simple majority after the investigation of the citizen, studying the submitted documents, analysis of social, occupational and labor, and other data (*Rules for Recognition of a Person as Disabled Person, 2006*). Persons recognized as disabled persons are fully registered by social security bodies.

Mortality is a medical statistical parameter having no alternative and the final cause of death is established as a result of the pathologicoanatomic (medicolegal) investigation in a significant percentage of cases. The "Death Cause Card of a Person Exposed to the Radiation as a Result of the Accident at the Chernobyl NPP" (registration document of NRER) contains several items, describing in details both death causes and presence of other pathology in LAA: final clinical diagnosis; pathologicoanatomic diagnosis; direct cause of death, disease producing the direct cause of death; other important diseases. Unfortunately, the diseases revealed in LAA at autopsy (except for malignant tumors) are not recorded in the NRER data base and, therefore, they are not included in the analysis of morbidity and prevalence of the diseases in LAA what distorts the study results of medical and social consequences caused by LAA exposure to the ionizing radiation as a result of the accident at ChNPP.

Then several specific examples were used to show the diagnostic technique and significance of analysis results of the traditional epidemiologic signs (intensity, changes over time, structure, spatial characteristic) of public health in order to assess the effects exerted by the radiation factor on LAA. Each of these signs has its diagnostic significance, methods for assessment and units of measurement, informativeness degree and techniques for graphic presentation (*Epidemiologic Diagnostics. Semiotics*).

The diagnostic value of the intensity consists in the fact that it reflects the action strength exerted by causative unfavorable factors and conditions under which they act. The intensity may characterize morbidity, prevalence of diseases, morbidity rate, disablement, mortality, temporary disability, and other parameters of the population public health. Proceeding from the study objectives, this sign may be assessed in different age, sex, social, territorial, dose and other population groups. The intensity analysis allows to reveal the rate of pathologic conditions, determine the systems and target organs, risk groups for further search for cause-effect associations between the action of unfavorable factors and the population health condition.

The spatial characteristic uses the parameters of intensity, dynamics and structure to reflect the differences in the strength, time and pattern of influencing causes and conditions on different

territories. The use of cartographic method extends considerably the resources and informativeness of the spatial analysis and cartograms ensure demonstrativeness of the obtained results.

Dynamics characterize changes in the population public health conditions over time. This sign is of extreme importance because it reflects the intensification or reduction of the action strength of unfavorable causes and conditions over time and, consequently, allows to determine the risk time. The diagnostic value of dynamics consists just in this whether this concerns many-year, monthly, or other intervals. Dynamic signs may be studied in different aspects just as the intensity: for individual nosologic forms, territories, different population groups, etc.

The diagnostic value of structural parameters consists in the fact that they indicate the correlation between separate parts of the phenomenon being studied, and their change over time or difference in the compared groups are evidence of the difference in the causative factors determining them. The structural parameters are used to study the age, social, nosologic, and other characteristics of the public health condition in the process of analysis.

Thus, the use of epidemiologic methods for studying long-term medical and social consequences caused by participation of LAA in the emergency recovery works at ChNPP basing on the materials of the data bases of NRER allowed to make the following main conclusions:

- epidemiological analysis of the intensity, dynamics, territorial distribution and structure of the public health parameters makes it possible to reduce the probability of erroneous conclusions on long-term consequences in LAA at ChNPP;

- all test parameters of the public health in LAA are significantly influenced by local cause factors of non-radiation nature;

- the relationship between the dose and pathology in LAA should be studied taking into account the method for determination of the irradiation dose and doses received during X-ray investigations.

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# CHAPTER 5

# SOMATIC PATHOLOGY AND ITS PATHOGENETIC MECHANISMS IN LIQUIDATORS OF ACCIDENT AFTERMATH AT THE CHERNOBYL NUCLEAR POWER PLANT IN A LONG-TERM PERIOD

## 5.1. CEREBROVASCULAR DISEASES: PATHOGENETIC MECHANISMS, DIAGNOSTICS, AND TREATMENT

Since 2002 till today the Federal State Budget-Funded Institution All-Russian Nikiforov Center of Emergency and Radiation Medicine of the Ministry of Emergencies of Russia has been

continuously involved in the research and practical work in accordance with the "Program of Joint Activities for Overcoming the Aftermath of the Chernobyl Catastrophe within the Limits of the Union State." Many-year follow-up of the health condition of LAA at ChNPP showed that diseases of the cardiovascular and nervous systems (CHD, EH, dyscirculatory encephalopathy) are a main cause for their invalidization.

The morbidity with cerebrovascular diseases (CVD) and mortality because of CVD are increasing constantly both according to home and foreign data. The studies concerning the investigation of chronic cerebrovascular disease in liquidators indicate the high prevalence of dyscirculatory encephalopathy and its more frequent development than in the population on the whole. In total, 310 liquidators of accident aftermath at ChNPP with diagnosed dyscirculatory encephalopathy (DE) underwent the in-depth investigation and received treatment at the clinic of ARCERM in the period from 2002 to 2015. This allowed to investigate in detail peculiarities of the clinical course of DE, determine pathogenetic mechanisms of chronic cerebral ischemia, assess the dynamics of the disease and efficiency of the administered therapy.

The data of epidemiologic studies is evidence of the fact that the considerable growth of morbidity with cerebrovascular diseases (CVD) and invalidization because of diseases of the nervous system is observed in a long-term period in liquidators of accident aftermath at ChNPP (Legeza, V. I. et al., 1996; Nyagu, A. I., Loganovsky, K. N., 1997; Ivanov, V. K., et al., 1999; Shantyr, I. I. et al., 2000; Suvorov, I. M. et al., 2002).

The clinical investigation over a certain period revealed transformation of vegeto-vascular dysfunction observed in the earlier period after the accident, in DE seen later (Krasnov, V. N. et al., 1993; Kovtun, A. V., 1998; Bronsky, V. I. et al., 1999; Zhavoronkova, L. A., 2001). The changes in prevalence of diseases in liquidators in the North-Western Region are characterized by the intensive growth of morbidity with cerebrovascular diseases (CVD). "Other CVD," which mean DE, prevail in the CVD structure. The prevalence of "Other CVD" increased 32.5 times over the last 20 years (Astafiev, O. A., Makarova, N. V., 2010). The morbidity with acute cerebrovascular accidents (ACVA) in liquidators resident in Saint Petersburg ranges lately from 5 to 7 per 1,000 liquidators aged at present above 40 years who underwent preventive medical investigation. Undoubtedly, this value is lower than morbidity in the population of the city which was 5.2 per 1,000 people, i. e. per all age groups in Saint-Petersburg in 2014. Thus, in spite of the higher prevalence of chronic CVD in the liquidator group, ACVA are observed in them rarer than in the population what may be associated with the higher quality of medical assistance and prevention of stroke in LAA at ChNPP.

The complex of all factors accompanying the anti-damage works including low radiation doses, psychogenic and physical stress during the emergency works, social and psychologic strain associated with obtaining benefits after completing the works, chronic alcoholism, tobacco smoking and their combinations is considered as possible causes determining the high morbidity with chronic CVD in liquidators.

The absorbed dose from the external gamma-radiation was not more than 30–50 cGy (total dose for 1–2 months) for most liquidators. This dose does not cause acute radiation sickness and is called "low" dose. There are many publications which analyze the contribution of low radiation doses as a possible risk factor for the development of cerebrovascular diseases. Most studies did not reveal any interrelationship between the work duration in the region of ChNPP, external irradiation dose and

morbidity with CVD. At present there is no direct evidence that low ionizing radiation doses are a cause for onset of the cerebrovascular pathology. Along with the reports disproving the effect of low radiation doses on development of the vascular pathology (Lelyuk, V. G., Lelyuk, S. E., 2003; Guskova, A. K., 2010) several authors still advocate the determining role of low ionizing radiation doses in formation of specific cerebrovascular damage (Nyagu, A. I. et al., 1992; Zhavoronkova, A. A. et al., 1996; Taranov, S. V., and Kartashova, S. S., 1999).

We analyzed the results of the in-depth investigation of 190 liquidators hospitalized to the clinic of ARCERM in 2007–2010 and 70 liquidators hospitalized in 2014 with the basic diagnosis "DE" in order to reveal the peculiarities of the clinical picture and basic factors influencing the development of CVD in liquidators at ChNPP. The diagnosis of DE, mainly stages I and II, was confirmed in all investigated liquidators; 42 liquidators were included in a separate group because of the history of ACVA.

The analysis of complaints in liquidators with diagnosed DE showed that they corresponded to personive disorders which are typical for this pathology. The frequency of complaints in liquidators depending on DE stage is presented in Table 5.1. Headache characterized by different intensity degree (from mild to severe), meteo-dependency, increased intensity under conditions of psychoemotional stress or physical activities, different localization, not associated with blood pressure increase in most cases was the most often personive disorder in liquidators with DE at all stages of the disease. The frequency of headache was from once a week to daily what was associated with uncontrolled frequent use of analgesics. Headache was classified as chronic tension-type headache in most cases.

Table 5.1

The Prevalence of Complaints (%) in Liquidators Depending on the Stage of DE

| Complaints | DE I, n = 50 (%) | DE II, n = 107 (%) | DE III, n = 6 (%) |
|---|---|---|---|
| Headache | 84 | 95 | 83 |
| Sleep disorders | 50 | 65 | 83 |
| Emotional instability | 40 | 55 | 33 |
| Increased fatigability | 70 | 93 | 83 |
| Dizziness | 44 | 74 | 83 |
| Hypomnesia | 52 | 77 | 100 |
| Loss of consciousness | 10 | 20 | 33 |

Most liquidators complained of general asthenia, absence of rest sensation after sleep, rapid fatigability, lowered capacity for work, inattention and memory impairment for recent events already at early stages of the disease. The typical complaints included nonrotary vertigo, sleep depth and duration disturbance, emotional instability with changed mood, increased irritability, aggressiveness, more pronounced anxiety.

As the disease progressed, liquidators developed a trend to more frequent complaints of dizziness, memory impairment, sleep disorders and loss of consciousness.

In order to reveal the features of the clinical course of DE (without history of ACVA), we assessed the prevalence of basic syndromes in the liquidator group and comparison group which included patients comparable by their age, sex, and DE stage but not involved in liquidation of accident aftermath at ChNPP. As the number of liquidators with DE of stage III was not large, both groups included only patients with DE of stages I–II. The prevalence of the most frequent neurological syndromes in the patient groups is presented in Table 5.2.

Table 5.2

The Prevalence of Basic Neurological Syndromes in the Liquidator Group of Accident Aftermath at ChNPP and the Comparison Group

| Syndromes | Liquidators, n = 157 | Comparison group, n = 37 | Student' s test |
|---|---|---|---|
| | Abs. number (%) | Abs. number (%) | p |
| Vestibular-atactic | 41 (28 %) | 4 (11 %) | <0.05 |
| Intellectual-mnestic | 109 (69 %) | 8 (22 %) | <0.001 |
| Asthenoneurotic | 82 (52 %) | 11 (30 %) | <0.05 |
| Asthenodepressive | 53 (34 %) | 6 (16 %) | <0.05 |
| Paroxysmal | 26 (17 %) | 1 (3 %) | <0.001 |
| Microfocal | 39 (25 %) | 8 (22 %) | – |

Both groups had neurological syndromes typical of chronic cerebrovascular disease (CCVD) (Yakhno, N. N., 2003) but the prevalence of syndromes was different in the groups. Attention is drawn by the fact that the clinical picture of CCVD in most liquidators was represented by intellectual-mnestic, asthenodepressive or asthenoneurotic disorders while these syndromes were observed considerably rarer in the comparison group. It should be mentioned also that vestibular-atactic and paroxysmal syndromes were observed significantly more often in the test group as compared to the comparison group. The diffuse microfocal symptoms were revealed rarer, with equal probability in both groups.

One hundred and ninety liquidators with CVD underwent the neuropsychologic testing in order to assess more precisely the features of cognitive, emotional and volitional impairments.

The degree of cognitive impairments was assessed using standard tests: Mini-Mental State Examination (MMSE) with the maximum score of 30 points, Frontal Assessment battery (FAB) with the maximum score of 18 points, 10-point clock drawing test and 5 word memory test. MMSE is intended for investigating the cognitive capabilities of a person basing on assessment of his(her) orientation in the time and space, perception, attention, memory and speech functions. FAB was used to reveal the capability for generalization and determining the similarity and difference, the features of speech and motor activity. The clock drawing test allowed to assess preservation of executory functions and visual-spatial perception. The testing results confirmed the high prevalence of cognitive impairments in the test group with predomination of moderate disturbances (Table 5.3).

Table 5.3

The Prevalence and Degree of Cognitive Impairments in Liquidators with CVD in A Long-Term Period After Liquidation of the Accident at ChNPP

| Group characteristics | Cognitive impairments | | |
|---|---|---|---|
| | None | Moderate | Dementia |
| Liquidators with DE and with history of ACVA (n = 30) | 0 | 24 (80 %) | 6 (20 %) |
| Liquidators with DE (n = 160) | 17 (11 %) | 131 (82 %) | 12 (7 %) |

Isolated memory impairment also as isolated non-amnestic impairment was observed rarer that the mixed impairment type in the test group (Table 5.4). The executory functions were lowered in all persons with non-amnestic and mixed impairment types. Impairment of visual-spatial gnosis was observed rarer, namely in 50 % of patients with history of ACVA, and only in 23 % of liquidators with DE.

Table 5.4

The Prevalence and Degree of Cognitive Impairments in Liquidators with Cerebrovascular Diseases in a Long-Term Period After the Accident at ChNPP

| Group characteristics | Type of cognitive impairment | | | |
|---|---|---|---|---|
| | No impairment | Amnestic | Non-amnestic | Mixed |
| Liquidators with DE and with history of ACVA (n = 30) | 0 | 3 (10 %) | 1 (3 %) | 26 (87 %) |
| Liquidators with DE (n = 160) | 17 (11 %) | 13 (8 %) | 30 (19 %) | 100 (62 %) |

The condition of the emotional and volitional sphere was assessed using Beck Depression Inventory, Hospital Anxiety and Depression Scale. The prevalence of anxiety and depression in liquidators with history of ACVA and in liquidators with DE was identical, namely 80 % in both groups with predomination of combined anxiety-depressive disorders (Table 5.5).

Table 5.5

The Prevalence of Anxiety-Depressive Disorders in Liquidators with Cerebrovascular Diseases in a Long-Term Period After the Accident at ChNPP

| Group characteristics | Nature of emotional and volitional disturbances | | | |
|---|---|---|---|---|
| | No disturbances | Isolated anxiety | Isolated depression | Anxiety-depressive disorders |
| Liquidators with DE and with history of ACVA (n = 30) | 20 % | 27 % | 7 % | 46 % |
| Liquidators with DE (n = 160) | 20 % | 26 % | 6 % | 48 % |

The neuropsychological testing allowed to confirm the high prevalence of cognitive impairments and emotional and volitional disturbances in liquidators with CVD and to quantify these disturbances. Cognitive impairments and emotional and volitional disturbances took the leading place in the clinical picture of the disease and their severity increased significantly as the disease progressed (Table 5.6).

Table 5.6

The Degree of Cognitive Impairments and Emotional and Volitional Disturbances in Liquidators Depending on the Stage of DE

| Neuropsychologic scales (scores) | DE of stage I, n = 50 | DE of stage II, n = 107 |
|---|---|---|
| MMSE | 28 ± 1.7** | 26 ± 2.6 |
| FAB | 16.9 ± 1.20** | 15.6 ± 2.26 |
| 5 words remembering test | 4.78 ± 0.54 | 4.57 ± 0.75 |
| Clock drawing test | 9.51 ± 0.98 | 9.19 ± 1.11 |
| Hospital anxiety scale | 7.5 ± 3.4 | 7.8 ± 3.6 |
| Hospital depression scale | 6.2 ± 3.9* | 7.9 ± 3.5 |

* - significant differences between the groups at the level $p < 0.05$.

** - significant differences between the groups at the level $p < 0.01$.

The correlation analysis showed that the degree of anxiety was not associated with cognitive impairments while depression could intensify cognitive defect. We revealed a significant correlation between depression level and MMSE ($r = -0.24$), depression and 5 word remembering test ($r = -0.26$).

It was found that affective disorders and cognitive impairments were determinants in invalidization and social deadaptation of liquidators of accident aftermath at the Chernobyl NPP in a long-term period (Levin, O. S., Tsyganenko, E. V., Chesalin, P. V., 2007; Ivanchuk, E. G., Orudzhev, Ya. S., 2009), but the problem of basic causes for these impairments is not solved finally. The data are available that the high emotional strain level can result in disturbed thinking processes, attention, memory and emotional and volitional functions (Levin, O. S., 2006; Chermyanin, S. V., Korzunin, V. A., Yusupov, V. V., 2008; Reshetnikova, E. M., Rusanovsky, V. V., Rudkevich, L. A., 2010; Ashanina, E. N., Bukhvostov, A. V., 2011; Granovskaya, R. M., Shingaev, S. M., 2013; Kolotilchshikova, E. A., 2014). A large body in information has been accumulated on the effect of cardiovascular diseases (essential hypertension, atherosclerosis) on the cognitive functions (Yakhno, N. N., Levin, O. S., Damulin, I. V., 2001; Zakharov, V. V., 2006; Odinak, M. M., Yemelin, A. Yu., Lobzin, V. Yu., 2006; Romazina, T. A., 2007). It was also established that the active mental activity and high educational level also favored preservation of the cognitive functions (Velichkovsky, B. B., 2009; Slobodin, T. A., Gorev, A. V., 2012; Scarmeas N., Stern, Y., 2003). The contribution of medical and social factors in the development of cognitive impairments and affective disorders remains the least studied.

Most investigated liquidators of accident aftermath at the Chernobyl NPP aged under 60 years are disabled persons (76 %). Sixty-five percent of liquidators of accident aftermath at able-bodied age are unemployed although the established disablement group (III and IIa) allows to continue the labor activities.

The comparison of the degree of cognitive impairments and emotional and volitional disorders in the groups of employed and unemployed LAA at ChNPP aged under 60 years revealed significantly more significant disturbances in unemployed liquidators of accident aftermath at the Chernobyl NPP (Table 5.7).

Table 5.7

The Degree of Cognitive Impairments and Emotional and Volitional Disturbances in LAA at ChNPP Depending on Availability of Professional Activities (M ± SD)

| Name of tests and their parameters (scores) | Employed LAA at ChNPP (n = 35) | Unemployed LAA at ChNPP (n = 64) | p < |
|---|---|---|---|
| MMSE | 28.6 ± 1.3 | 27.2 ± 2.2 | 0.001 |
| FAB | 17.3 ± 0.7 | 16.4 ± 1.9 | 0.001 |
| Clock drawing test | 9.7 ± 1.0 | 9.4 ± 1.1 | - |
| Range of attention | 5.2 ± 1.5 | 4.8 ± 1.4 | - |
| Attention concentration | 8.9 ± 1.4 | 8.2 ± 1.8 | 0.05 |
| Auditory-verbal memory | 4.1 ± 0.8 | 3.7 ± 1.1 | 0.05 |
| Visual memory | 10.8 ± 02.3 | 9.7 ± 2.5 | 0.05 |
| Anxiety | 6.9 ± 3.3 | 8.0 ± 4.0 | - |
| Depression | 5.7 ± 3.6 | 7.2 ± 3.9 | 0.05 |

Liquidators of accident aftermath at the Chernobyl NPP were divided in subgroups exposed to very low and low radiation doses in order to reveal the possible role of the received radiation dose (Table 5.8).

Table 5.8

Characteristics of the Subgroups of LAA at CNPP
Depending on the Received Radiation Dose, n (%)

| Risk factors | Radiation dose of less than 10 cSv (n = 26) | Radiation dose of more than 10 cSv (n = 36) | p < |
|---|---|---|---|
| No labor activities | 15 (57.7) | 27 (75.0) | - |
| Disablement | 21 (80.8) | 34 (94.4) | - |
| Smoking | 16 (61.5) | 19 (52.8) | - |
| Alcohol | 15 (57.7) | 14 (38.8) | - |
| Essential hypertension | 17 (65.4) | 18 (50.0) | - |
| Atherosclerosis | 6 (23.1) | 11 (30.5) | - |
| Disturbed glucose metabolism | 17 (65.4) | 20 (55.5) | - |
| Overweight of the body | 18 (69.2) | 22 (61.1) | - |
| Anxiety | 14 (53.8) | 16 (44.4) | - |
| Depression | 10 (38.5) | 18 (50.0) | - |
| Cognitive impairments | 18 (69.2) | 28 (77.7) | - |

The comparison of these subgroups by social, vascular, emotional and volitional and cognitive factors did not reveal any significant differences.

Our study did not provide any data confirming the effect of low radiation doses on the development of cognitive impairments and affective disorders.

The correlation analysis was performed in order to determine the significant risk factors for lowering of the cognitive functions (Table 5.9).

Table 5.9

Correlations Between Social, Vascular and Emotional and Volitional Risk Factors and
the Cognitive Functions in the Group of LAA at ChNPP

| Parameter | MMSE | FAB | Hours | Attention | | Memory | |
|---|---|---|---|---|---|---|---|
| | | | | range | concentration | auditory-verbal | visual |
| Age, years | −0.233 | | | | −0.204 | | −0.219 |
| Disablement | −0.209 | | | | | −0.240 | |
| Education | 0.379 | 0.234 | | 0.372 | 0.319 | 0.292 | 0.447 |
| Smoking | | | | −0.279 | −0.235 | −0.226 | |
| Alcohol | | | | | | | |
| Essential hypertension | | | | | | | |
| Intima-media thickness (IMT), mm | −0.293 | −0.322 | | | −0.379 | −0.206 | −0.563 |
| Glucose, mmol/l | −0.276 | −0.268 | −0.256 | | | | −0.245 |
| BMI | | | | | | | |
| Anxiety, score | | | | | −0.211 | | |
| Depression, score | −0.266 | | −0.199 | | −0.275 | −0.233 | −0.234 |

*Note:* Table presents values with $p < 0.05$.

A significant correlation of the basic screening scales (MMSE, FAB) with IMT, disturbed glucose metabolism and educational level was revealed in the liquidator group of accident aftermath

at the Chernobyl NPP. The decrease of MMSE results was influenced also by the age, disablement and emotional and volitional disorders.

We summed up the scores of the screening scales (MMSE, FAB, "clock" test) in order to determine the basic factors which influenced the development of cognitive impairment in liquidators of accident aftermath at the Chernobyl NPP. Affective disorders were revealed by summing up the questionnaire results concerning anxiety and depression. The correlation analysis was used to obtain the leading risk factors of cognitive impairment and affective disorders in liquidators of accident aftermath at the Chernobyl NPP in a long-term period (Fig. 5.1).

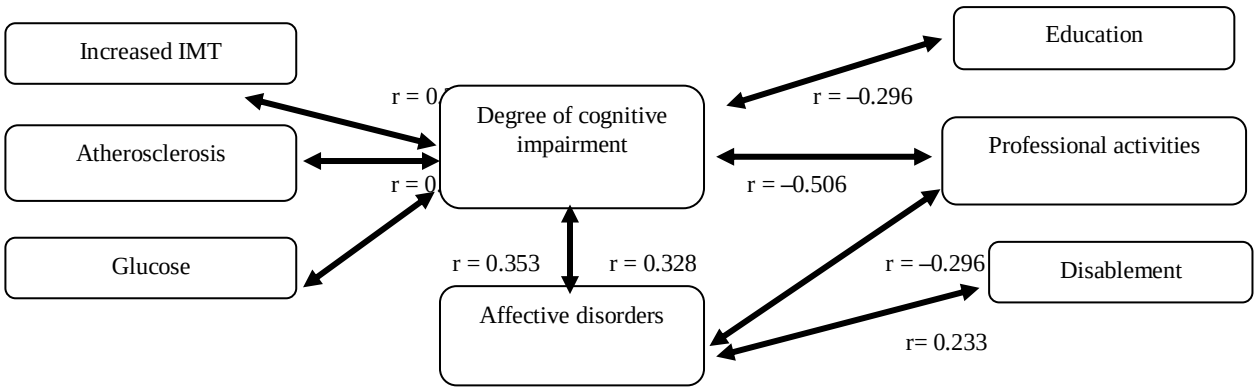


Fig. 5.1. The influence of Risk Factors on Development of Cognitive Impairments and Affective Disorders in Liquidators of Accident Aftermath at the Chernobyl NPP (Arrows Designate Significant Correlations)

We revealed a significant influence of both vascular and social risk factors on development of cognitive impairments of accident aftermath at the Chernobyl NPP. The vascular factors influencing the lowering of cognitive functions include increased intima-media thickness, presence of atherosclerotic plaques in the brachiocephalic arteries and disturbed glucose metabolism. The social risk factors include the educational level, emotional and volitional disturbances and absence of labor activities. The most significant correlation of lowered cognitive functions was revealed with absence of labor activities (r = –0.506).

### *The Role of Atherosclerosis in Development of the Cerebrovascular Pathology in Liquidators*

Atherosclerosis is a multi-factor vascular disease with predominant involvement of medium and large caliber arteries as a result of focal vascular wall infiltration with lipids and proliferative connective tissue changes.

Diagnostics of the degree and extent of atherosclerosis is of fundamental importance for selection of the therapeutic tactics. Non-stenosing atherosclerosis characterized by locally increased intima-media thickness (IMT) and stenosing atherosclerosis with formation of atherosclerotic plaques are distinguished. Hemodynamically insignificant and hemodynamically significant stenosing atherosclerosis is distinguished depending on the plaque size and changes in

hemodynamics. Hemodynamically significant stenosis leads to blood flow changes above stenosis and is, as a rule, 70–99 % by diameter.

Before the ultrasound investigation methods were put into practice, intravital diagnostics of atherosclerosis was possible only by performing angiography. Introduction of ultrasound diagnostic methods, CT- and MR-angiography allowed to perform low-invasive diagnostics of atherosclerosis. Dopplerography ("blind Doppler") makes it possible to diagnose only hemodynamically stenoses of extra- and intracranial arteries with high degree of accuracy. The appearance of duplex scanning method extended significantly the resources for diagnostics of atherosclerosis and allowed to assess objectively the process intensity starting from its initial stages. Atheromatous plaques develop, mainly, in the large and medium arteries in the points of their division and tortuosity. It is proven that atherosclerotic plaques are localized the most often in the ostium of the internal carotid arteries (ICA), in the ostium of the vertebral arteries (VA), in ICA siphon and in the region of ICA division in the medial cerebral artery (MCA) and anterior cerebral artery (ACA). Comparing the resources of duplex scanning and the knowledge of atherosclerotic plaque localization allowed to distinguish the bifurcation zone of CCA to ICA and ECA as the most informative one for screening assessment of atherosclerotic involvement of the vessels supplying the blood to the brain.

The disturbance of the intima-media structure in the form of heterogeneous changes in echogenicity, layer differentiation in combination with pathologic thickening in the standard assessment zones is a criterion of non-stenosing atherosclerosis of the brachiocephalic arteries (BCA). According to the Recommendation of the European Society of Hypertension (ESH), European Society of Cardiology (ESC) on arterial hypertension (2007) and Russian Society of Arterial Hypertension, the IMT in the common carotid artery of 0.9 mm is considered as the upper limit of the norm. The increased IMT (1.5 mm and more), revealing a local protrusion of the vascular wall in the lumen to not less than 50 % and/or to 0.5 mm as compared to IMT in the adjacent areas are considered as a criterion of plaque presence (Touboul, P. J. et al., 2012).

The mechanism of chronic cerebrovascular disease in patients with atherosclerosis depends on the process stage. The parameters of the cerebral blood flow at rest remain, as a rule, within the normal range in persons with non-stenosing atherosclerosis. At the same time, there are many publications evidencing that isolated increased IMT is an independent risk factor of chronic and acute cerebral ischemia. As the stenosis degree increases constant hypoperfusion, which is intensified considerably in case of any changes in the external and internal environment [changes in the blood pressure (BP), physical activity, mental activities, etc.], becomes increasingly significant, the risk of arterio-arterial microembolism underlying both acute and chronic cerebral ischemia grows.

The prevalence and degree of atherosclerotic involvement in liquidators with CVD were assessed basing on the findings of duplex scanning of BCA. The prevalence of atherosclerotic involvement in liquidators with the history of ACVA was significantly higher than that in the patient group with DE (Table 5.10). The mean IMT values in the whole group were higher and hemodynamically significant ICA involvement was observed more often in liquidators with the history of ACVA. Thus, hemodynamically significant stenosis was an additional risk factor of

ACVA in liquidators what was consistent with the data of numerous population studies showing the increased risk of stroke in patients with stenoses of more than 70 % (Beletsky, V. et al., 2000; Eliasziw, M. et al., 2000).

Table 5.10

Characteristics of Atherosclerotic Involvement of the Carotid Arteries Basing on Findings of Duplex Scanning of BCA in Liquidators with Chronic Cerebrovascular Disease and Acute Cerebrovascular Accident

| Characteristics of atherosclerosis | Liquidators with DE, n = 98 | Liquidators with the history of ACVA n = 34 |
|---|---|---|
| Age, years (M±SD) | 60 ± 8.8 | 63 ± 6.1 |
| Intima-media thickness (IMT), mm | 1.14 ± 0.22 | 1.22 ± 0.19* |
| Increased IMT (more than 0.9 mm) | 66 (67 %) | 24 (70 %) |
| Presence of ICA plaques with stenosing of up to 70 % by diameter | 35 (36 %) | 15 (44 %)* |
| Presence of ICA plaques with stenosing of more than 70 % by diameter | 0 (0 %) | 4 (12 %)* |

* - significant differences between the groups at the level $p < 0.05$.

Comparing the investigation results of liquidators in 2007–2010 and 2014 showed significantly increased prevalence of atherosclerosis what was associated with the age (Table 5.11).

Table 5.11

Characteristics of Atherosclerotic Involvement of the Carotid Arteries Basing on Findings of Duplex Scanning of BCA in Liquidators with DE Investigated in Different Periods

| Characteristics of atherosclerosis | Liquidators with DE investigated in 2007-2010, n = 98 | Liquidators with DE investigated in 2014, n = 58 |
|---|---|---|
| Age, years (M ± SD) | 60±8.8 | 67±9.6 |
| Intima-media thickness (IMT), mm | 1.14 ± 0.22 | 1.12 ± 0.26 |
| Increased IMT (more than 0.9 mm) | 66 (67 %) | 37 (64 %) |
| Presence of ICA plaques with stenosing of up to 70 % by diameter | 35 (36 %) | 35 (60 %) |
| Presence of ICA plaques with stenosing of more than 70 % by diameter | 0 (0 %) | 1 (2 %) |

We distinguished two subgroups of LAA at ChNPP differing by the received “radiation” dose in order to assess the possible effect of radiation on the development of atherosclerotic plaques (ASP). The results of the ultrasound investigation in the subgroups of LAA at ChNPP are presented in Table 5.12. The distinguished groups were comparable by the age. Any differences in the cerebral hemodynamic parameters, IMT and extent of atherosclerosis between the subgroups were not revealed. The correlation analysis confirmed absence of any correlation between the received “radiation” dose and the degree of atherosclerotic involvement.

Table 5.12

Comparison of the Ultrasound Investigation Results of the Cerebral Blood Flow in LAA at ChNNP (M ± sd)

| Parameter | Subgroup 1 (up to 10 cSv) | Subgroup 2 (more than 10 cSv) |
|---|---|---|
| Age, years | 57.8 ± 7.62 | 55.2 ± 7.12 |
| IMT in the carotid arteries, mm | 1.05 ± 0.21 | 1.06 ± 0.21 |
| Linear blood velocity (LBV) in MCA, cm/s | 56.1 ± 10.2 | 56.03 ± 9.26 |
| PI in MCA | 0.79 ± 0.10 | 0.79 ± 0.13 |
| Kr+ | 1.34 ± 0.10 | 1.32 ± 0.10 |
| Kr– | 0.31 ± 0.06 | 0.29 ± 0.07 |
| Prevalence of atherosclerotic plaques, % | 37 | 36 |

Our data are consistent with the results obtained by other researchers who showed that the prevalence of hemodynamically significant stenoses in patients with DE of stages I–II in the population did not exceed 8 % while the initial signs of atherosclerosis were observed in 68–76 % of patients (Martynov, Yu. S. et al., 1998; Vizilo, T. L. et al., 2001; Anisimova, A V. et al., 2003). The similar results evidencing that the prevalence and degree of atherosclerosis in LAA at ChNPP did not exceed their frequency in the population were obtained at the Institute of Biophysics (Lelyuk, V. G., Lelyuk, S. E., 2001) what contradicted to the studies confirming the early development of atherosclerosis in liquidators (Voloshin, P. V. et al., 1995; Babadzhanova, M. A. et al., 2000). According to results of the population study PESA (Fernández-Friera, L. et al., 2015), which was completed recently and included 4,184 participants at the middle age (40–54 years old) without the history of cardiovascular diseases, the prevalence of subclinical AS of the carotid arteries was 36 % in males and 24 % in females. Thus, atherosclerosis of the carotid arteries is a significant factor for the development of dyscirculatory encephalopathy in liquidators but its prevalence is not higher than that in the population and is not associated with the received radiation dose.

When discussing the mechanisms of atherosclerosis in liquidators, we should assess the prevalence and significance of the main risk factors, which include, first of all, dyslipidemia, increased glucose level, increased CRP level, hyperhomocysteinemia, smoking, chronic stress and arterial hypertension.

Since times of R. Virchow and classical studies performed by Anichkov, N. N., the pathogenic role of hyperlipidemia in the development of atherosclerosis has been established and it was characterized more precisely and developed further in the last decades (Klimov, A. N. et al., 1009; Gavrisheva, I. A., Gavrishev, N. A., 1999). Researchers revealed the damaging effect exerted on the vascular wall by atherogenic lipoproteins referred to classes of low density lipoproteins (LDL) with increased cholesterol content (dyslipoproteinemia type IIa as per Frederickson classification) or increased content of both cholesterol and triglycerides (type II b). The pathogenic role of increased very low density lipoproteins (VLDL) content with increased triglyceride concentration (dyslipoproteinemia type IV) is equally significant. Other rarer dyslipidemia variants are distinguished. The lowered cholesterol content in high density lipoproteins (HDL), which are antiatherogenic, is of special importance. It is proven at present that different atherogenicity degree in patients with disturbed lipid metabolism depends also on the qualitative change in circulating lipoproteins which are bound with glycoproteins (apoproteins). Apo-A favors the reverse transport of cholesterol from the periphery to the liver and is a basic protein in HDL in 90 % of cases. Apo-B is included in LDL and VLDL composition determining their atherogenicity. Apo-B belongs to a group of multifunctional proteins providing for lipid-protein interactions. The increased content of this protein and lowered ratio apo-A/apo-B is considered as an early marker of the coronary risk. Its level may increase as a response to emotional stress. Besides that, lipoprotein atherogenicity increase significantly when they are oxidized. Thus, oxidized LDL and VLDL and also the independent lipoprotein (a) fraction are associated, first of all, with the development of atherosclerosis.

The basic causes for hyperlipidemia include hereditary predisposition (family hyperlipidemia), disturbed lipid metabolism in patients with diabetes mellitus, hypothyroidism, irrational nutrition. The studies performed by Gubachev, Yu. M. and Makienko, V. V. (2000)

showed the wide prevalence of psychogenic hyperlipidemia. The convincing data are available on the correlation of dyslipidemia and metabolic syndrome with permanent stress at work (Janczura, M. et al., 2015).

Not only hypercholesterolemia but also hyperglycemia is a risk factor for cerebrovascular diseases. It is necessary to measure glucose level in order to reveal diabetes mellitus or disturbed glucose tolerance resulting in macro- and microangiopathy.

Activated free radical oxidation (FRO) processes observed in persons with increased catecholamine production, in stress conditions or in case of arterial hypertension may also serve as a cause for damage of the vascular wall. On the other hand, degenerative and destructive processes in the vascular wall cause the release of such factors as collagen, ADP, adrenaline, thrombocyte factor 3, thereby activating the production of procoagulant prostaglandins, thromboxanes, leukotrienes from arachidonic acid, intensifying the processes of lipid peroxide oxidation and free radical oxidation (Bills, T. K. et al., 1978; Weiss, M. I., Turitto, V. T., 1979) what forms a vicious circle. Activated FRO processes cause increased oxidative destruction of proteins and lipids in cell structures. This circumstance is of great importance in the assessment of the degree of atherogenic shifts. Today it is considered as generally recognized that only lipoproteins oxidized as a result of FRO reactions are actively absorbed by macrophages what leads to formation of a plaque saturated with cholesterol. From this viewpoint, the combination of activated lipid peroxide oxidation (LPO) and hypercholesterolemia reflects the highest risk of atherosclerosis.

The increased C-reactive protein (CRP) level and hyperhomocysteinemia are considered as independent factors causing endothelium damage and atherosclerosis. The subacute inflammatory process in the endothelium, as a rule, is not associated with infections. The CRP concentration increases in the high sensitive range from 0.1 to 10 mg/l in these cases. It was shown that even insignificantly increased CRPhs level enhances the risk of stroke and cognitive impairment. The increased homocysteine level is associated with activated thrombocytic aggregation function and also with blocking of endothelial NO-synthase what is manifested in disturbed regulation of the vascular tonus, increased IMT, smooth muscle tissue hyperplasia and favors growth of atherosclerotic plaques (Lentz, S., 1997; Stein, J., McBride, P., 1998; Hoffman, M., 2001). Besides that, homocysteine has a neurotoxic effect (Bisschops, R., 2004).

The results obtained by the laboratory tests in liquidators with CVD which include measurement of glucose, lipids, apoproteins levels, parameters of free radical oxidation, C-reactive protein and homocysteine are presented in Table 5.13.

Table 5.13

Parameters of Metabolism, Free Radical Oxidation and Vascular Risk Factors in Liquidators with and Without Signs of Atherosclerosis

| Metabolism parameters | Limits of reference ranges | Percentage of persons with disturbances | Degree of atherosclerosis | | |
|---|---|---|---|---|---|
| | | | 0 | i | II |
| Glucose, mmol/l | 3.5–5.8 | 40 | 5.58 ± 1.06 | 5.50 ± 0.85 | 6.25 ± 2.00* |
| Total cholesterol, mmol/l | 3.3–5.7 | 38 | 5.27 ± 0.65 | 5.74 ± 1.03* | 5.48 ± 1.21 |
| Triglycerides, mmol /l | 0.60–2.28 | 10 | 1.14 ± 0.45 | 1.34 ± 0.76 | 1.45 ± 0.98 |
| LDL-cholesterol, mmol/l | 1.03–2.00 | 39 | 1.18 ± 0.42 | 1.16 ± 0.29 | 1.09 ± 0.33 |
| LDL-cholesterol, mmol/l | 2.5–4.0 | 35 | 3.56 ± 0.58 | 3.97 ± 0.84* | 3.72 ± 0.99 |
| VLDL-cholesterol, mmol/l | 0.27–1.04 | 12 | 0.52 ± 0.20 | 0.62 ± 0.35 | 0.66 ± 0.45* |
| Coefficient of atherogenicity | up to 3.0 | 69 | 3.89 ± 1.69 | 4.26 ± 1.54 | 4.32 ± 1.64 |
| Apoprotein A, g/l | 0.73–2.10 | 0 | 1.18 ± 0.39 | 1.21 ± 0.25 | 1.19 ± 0.27 |
| Apoprotein B, g/l | 0.46–1.42 | 14 | 0.88 ± 0.28 | 0.98 ± 0.32 | 1.03 ± 0.34 |
| Apo-A/Apo-B | > 1.5 | 64 | 1.38 ± 0.35 | 1.32 ± 0.36 | 1.24 ± 0.43 |
| FRO parameters | | | | | |
| TBA-AP sp. in serum, μmol/l | 2.62–3.58 | 44 | 3.42 ± 0.57 | 3.45 ± 0.49 | 3.64 ± 0.80 |
| TBA-AP stim. in serum, μmol/l | 0.58–2.40 | 20 | 1.81 ± 0.66 | 1.69 ± 0.61 | 1.99 ± 0.64 |
| TBA-AP in mononuclear cells, nmol/mln cells | 0.05–0.11 | 81 | 0.14 ± 0.05 | 0.13 ± 0.06 | 0.16 ± 0.06 |
| Vascular risk factors | | | | | |
| CRP hs, mg/l | 0–2.5 | 41 | 2.2 ± 2.2 | 2.32 ± 2.02 | 3.08 ± 2.38 |
| Homocysteine, μmol/l | <15 | 31 | 12.5 ± 2.82 | 13.7 ± 6.76 | 14.01 ± 4.67 |

* Significant difference with the group with atherosclerosis degree 0, $p < 0.05$.

Atherosclerosis degree in points (0 = no signs of atherosclerosis, I = increased IMT (more than 0.9 mm) without plaque formation, II = presence of atherosclerotic plaques).

Liquidators without and with atherosclerotic involvement of vessels had significant differences by glucose, total cholesterol, LDL and VLDL levels. The lower ratio Apo-A/Apo-B, higher TBA product levels in the serum and CRP hs in liquidators with atherosclerosis should be mentioned as clear trends.

The correlation analysis (Table 5.14) showed that the effect exerted by risk factors of the development of atherosclerosis (AS) depended on the age. So, increased C-reactive protein and LPO product levels influence the development of atherosclerosis at the mature age and become less significant n elderly persons. It is possible that disappearance of the correlation at elderly age is associated with the considerable influence on atherosclerosis exerted by the age itself and high prevalence of atherosclerotic involvement in patients aged above 65 years. The increased glucose level is a risk factor of atherosclerosis at any age. At the same time, according to the data of

correlation analysis, the influence of hyperglycemia on the development of AS turned to be insignificant.

Any significant influence exerted by smoking and abuse of alcohol on atherosclerosis in the investigated liquidator group was not revealed.

Table 5.14

The Dependence Between Atherosclerosis Degree and Clinical, Morphologic and Laboratory Parameters in Liquidators with the Cerebrovascular Pathology Basing on the Results of the Correlation Analysis

| Parameters | Liquidators aged 40–80 years (n = 125) | | Liquidators aged 40–65 years (n = 83) | | Liquidators aged 66–80 years (n = 42) | |
|---|---|---|---|---|---|---|
| | IMT | AS | IMT | AS | IMT | AS |
| Age, years | 0.48** | 0.47** | | | | |
| Degree of DE | 0.48** | 0.35** | 0.49** | 0.32** | 0.16 | 0.14 |
| Smoking | 0.17 | 0.08 | −0.05 | −0.06 | 0.17 | 0.08 |
| Alcohol | 0.03 | 0.10 | 0.03 | 0.05 | 0.20 | 0.11 |
| Parameters of metabolic disturbances | | | | | | |
| Glucose | 0.13 | 0.19 | 0.09 | 0.22* | 0.12 | 0.20* |
| Cholesterol | 0.06 | 0.04 | 0.10 | 0.06 | −0.07 | −0.18 |
| LDL | 0.08 | −0.06 | 0.10 | 0.11 | −0.18 | −0.15 |
| HDL | 0.06 | 0.09 | 0.15 | −0.21 | −0.18 | −0.15 |
| Coefficient of atherogenicity | 0.04 | | −0.09 | 0.19 | 0.13 | 0.02 |
| | 0.06 | | 0.14 | | -0.12 | −0.15 |
| Parameters of free radical oxidation | | | | | | |
| TBA in serum, sp. | 0.13 | 0.13 | 0.26* | 0.15 | | |
| TBA in serum, stim. | 0.13* | 0.04 | | 0.13 | | |
| TBA in mononuclear cells | 0.08 | 0.12 | 0.25* | 0.31** | | |
| | 0.00 | | 0.12 | | | |
| Vascular risk factors | | | | | | |
| CRP hs | 0.04 | 0.12 | 0.15 | 0.21* | 0.03 | 0.10 |

* - significant differences at the level $p < 0.05$.
**- significant differences at the level $p < 0.01$.

Summarizing the obtained results we may conclude that atherosclerotic involvement of the vessels is one of considerable causes for dyscirculatory encephalopathy in liquidators but it is observed not more often that in the population. Bad habits (smoking, abuse of alcohol) are insignificant for the development of atherosclerosis in liquidators. The basic risk factors for AS in liquidators include the age, hyperglycemia, dyslipidemia, increased C-reactive protein level and free radical oxidation activation. The absence of the significant correlation between cholesterol level and AS degree suggests that independent role of isolated hypercholesterolemia is, evidently, insignificant for the development of AS in liquidators and this process requires additional risk factors, which include, first of all, FRO activation and nonspecific inflammation the criteria of which comprise increased high sensitive C-reactive protein level and hyperglycemia.

### *The Role of Microangiopathy in Development of the Cerebrovascular Pathology in Liquidators*

The involvement of microcirculatory vessels with the development of arteriolosclerosis and lowered cerebrovascular reactivity results in hypoperfusion in the terminal circulation zones where the pial arteries of the cortex of the hemispheres join with the penetrating branches of large cerebral vessels. The terminal blood supply zones include basal ganglia, subcortical white matter. Chronic ischemia in these zones causes rarefaction of the periventricular and/or subcortical substance, i. e. leukoaraiosis (LA,) which represents a demyelinization zone, gliosis and dilated perivascular spaces by its pathomorphology. Besides that, ischemia in these regions may develop also in case of acute occlusion of the penetrating arteries what results in lacunar infarctions.

The main cause for involvement of small arteries consists in arterial hypertension, especially in presence of crises with high pressure levels. The natural ageing is also associated with progressing changes in the walls of small arteries and development of hyalinosis. Amyloid small artery angiopathy, which results in repeated cortical hemorrhages, observed rarer. Genetically determined involvement of small arteries accompanied by diffuse white matter affection and cognitive impairment (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL)) is distinguished separately.

Diagnostics of small vessel involvement is based on the clinical data, cerebral morphologic changes confirmed by neurovisualization (MRI and CT) and diagnostics of cerebral hemodynamic disorders. Transcranial dopplerography (TCDG) is a basic method for assessment of the cerebral blood flow. This method allows to measure the linear blood velocity in the extracranial and basal cerebral arteries. Changed linear blood velocity is diagnostically significant only in presence of hemodynamically significant stenoses (spasm) of the located arteries and provides little information for assessing the condition of small arteries. The increased pulsatility index (PI), which is calculated using ratios of the systolic and diastolic velocities, is an indirect criterion of the higher tonus of small arteries or their hyalinosis. The parameters of cerebrovascular reactivity are the most sensitive indicators of disturbed cerebral hemodynamics. The reactivity of the cerebral vessels is indicated by their ability to modify their diameter in response to changes in the external and internal environment. In order to determine the quantitative characteristics of autoregulation, changes in the blood flow are investigated using functional tests causing the vasodilating or vasoconstricting reaction.

Two test types are used more often in the clinical practice when assessing the cerebrovascular reactivity (CVR) with the help of TCDG:

1) tests causing changes in the arterial blood gas composition which include hypercapnic (inhalation of 5–7 % $CO_2$, voluntary breath-holding, intravenous injection of 1 g of Acetazolamide) and hypocapnic-hyperoxic (hyperventilation, oxygen inhalation) stresses;

2) tests with changed perfusion pressure in the cerebral arteries: orthostatic and anti-orthostatic stresses, common carotid artery (CCA) compression test, non-pharmacologic arterial hypotension test.

Hypercapnic tests lead to progressive dilation of the cerebral arteries and arterioles of mainly small diameter. The resulting decrease of the peripheral resistance provides for increased blood volume supplied to the brain what is reflected in the increased linear blood velocity (LBV) in the cerebral basal arteries. It is a standard practice to assess the degree of the vasodilating reaction by change of LBV in the medial cerebral artery (MCA). Under conditions of hypercapnia the maximum increase of the blood velocity in the medial cerebral artery may reach 52.5 % as

compared to the initial level. The voluntary breath-holding test, which provides for the increase of endogenous $CO_2$ level or the test with intravenous injection of 1 g of Acetazolamide (carbonic anhydrase inhibitor which causes decrease of blood pH value and reflex arteriole dilation) are used more often in practice. The reaction to all types of stresses is similar, the results are quite comparable what allows each researcher to calculate the coefficient of reactivity (Kr+) selecting the optimum stress type.

The hypocapnic tests (hyperventilation, oxygen inhalation) lead to opposite changes: lowered $CO_2$ level, vasoconstriction of the pial-capillary system, increased peripheral resistance, lowered volume blood flow. These processes are reflected in lowered LBV in MCA what allows to calculate coefficients of reactivity to hypocapnic stress (Kr-).

Transcranial dopplerography was performed in 198 liquidators with CVD. The linear blood velocity was within the reference ranges in most persons, the increased pulsatility index (higher than 0.9) was observed only in 15 % of cases. Disturbed cerebrovascular reactivity was diagnosed considerably more often: lowered Kr+ (less than 1.31) was revealed in 51 %, lowered Kr- (less than 0.3) was observed in 49 %.

The results of dopplerography in liquidators with cerebrovascular pathology aged 40–65 years and the control group of healthy persons of comparable age are presented in Table 5.15. Significant differences between the groups were revealed only by the parameters of cerebrovascular reactivity.

Table 5.15

The parameters of Cerebral Hemodynamics in Liquidators with DE and the Control Group

| Parameter | Group | |
|---|---|---|
| | Liquidators, n = 60 | Control group, n = 30 |
| Age, years | 55 ± 4.810 | 53 ± 4.963 |
| Mean LBV in MCA, cm/s | 57.3 ± 8.9 | 60.8 ± 6.6 |
| PI in MCA | 0.79 ± 0.14 | 0.72 ± 0.12 |
| Kr+ | 1.31 ± 0.091* | 1.39 ± 0.084 |
| Kr– | 0.31 ± 0.079* | 0.34 ± 0.056 |

* Significant differences with the control group at the level $p < 0.01$.

The results of the correlation analysis revealed correlations between Kr+ and DE degree ($r = -0.3$), EH degree ($r = -0.23$) and CRP hs ($r = -0.23$). Any significant correlations between Kr+ and other laboratory parameters, smoking and abuse of alcohol were not revealed. PI values correlated only with DE degree ($r = 0.23$). Any significant correlations of LBV with other parameters were not revealed. The obtained data are evidence of the higher diagnostic significance of Kr+ for assessment of microangiopathy as compared to other dopplerographic parameters.

Essential hypertension and increased CRP hs level were the most significant risk factors of microangiopathy in liquidators, and the lowered vasodilation reserve was the earlier sign of small vessels involvement.

The significance of essential hypertension for the development of CVD is generally recognized. The prevalence of EH in the investigated liquidators with CVD was 79 % what determined a considerable role of arterial hypertension in the development of DE and its main clinical symptoms in liquidators. The results of the correlation analysis confirmed a significant

correlation between EH and both DE degree (r = 0.45) and degree of cognitive impairments (r = 0.28). In order to compare the contribution of EH in the involvement of small and large arteries in liquidators, we performed the correlation analysis which showed the more significant influence of EH on the development of atherosclerosis than microangiopathy. The coefficient of correlation of EH was 0.33 with atherosclerosis degree, 0.35 with IMT, 0.23 with small arteries reactivity, 0.25 with the degree of microfocal white matter affection. At the same time, all correlations were significant what confirmed the considerable role of EH in involvement of both large and small arteries.

The presence of morphologic changes in the cerebral structure is an obligatory criterion for diagnostics of DE. The morphologic changes were assessed only by findings of autopsy in 60-70s. The intravital comparison of the morphologic and clinical data became possible after introduction of the methods for brain visualization, i. e. computed tomography and magnet-resonance imaging, into the clinical practice.

The occurrence of areas with lowered white matter density around the cerebral ventricles is one of the early morphologic signs of DE. The cause of the high white matter sensitivity to ischemia consists in the peculiarity of its blood supply. It is known that the periventricular white matter is a territory with adjoining blood supply where the pial arteries of the hemispheric cortex join with the penetrating branches of the large cerebral vessels. The changes in the brain matter density around the ventricles are caused by the white matter rarefaction. V. C. Hachinsky et al. (1987) suggested to call this phenomenon as "leukoaraiosis." The strong correlation between presence of leukoaraiosis, ageing and arterial hypertension was established. It was shown that leukoaraiosis had only slight effect on performing the simple neuropsychologic tests but resulted in slowed rate of the complex psychic processes associated with information processing. The cause of these disturbances is associated with bilateral involvement of corticofual fibers occurring in patients with leukoaraiosis, especially in the subcortical matter in the cerebral frontal lobes. The white matter involvement results in disturbance of cortico-cortical and cortico-subcortical connection and, as a consequence, to dysregulatory and neurodynamic disorders of the cognitive functions. The main manifestations of dysregulatory syndrome include slowed thinking, inability to concentrate the attention.

Already at the stage I of DE, CT and MRI reveal mildly pronounced changes in the liquor-containing spaces which progress as the disease develops. In opinion of some researchers (Karlov, V. A. et al., 1997; Burtsev, E. M., 1998), hydrocephalus and disturbed liquor circulation play a significant role in pathogenesis of the nervous and psychic disorders in patients with DE, namely, paroxysmal disturbances of consciousness, memory, orientation in the surroundings, ataxia, etc. As DE progresses, the cerebral ventricles enlarge, atrophic changes become more pronounced. It is considered that progression of internal hydrocephalus is a more reliable criterion of presence and changes of dyscirculatory encephalopathy than an attempt to visualize ischemic foci.

Broadened sulci of the cerebral hemispheres (locally or focally) which reflect atrophic changes in the cortex are an indirect sign of vascular encephalopathies. As the process develops, single cystic-focal cerebral changes become multiple foci.

After wide introduction of MRI into the clinical practice, this method showed the high prevalence of the cerebral white matter involvement in the form of gliosis foci in the subcortical, periventricular and deep regions of the hemispheres, which were hyperintensive in TIRM and T2-weighted images, and microhemorrhages in persons having no neurological symptoms and without history of transient ischemic attack or stroke. Such changes are often called “silent” or “latent” infarctions because they have no clinically evident symptoms but at the same time they significantly increase the risk of stroke and dementia in future. The proven risk factors of latent infarctions include the age, arterial hypertension, diabetes mellitus and atherosclerosis.

Thus, the following parameters of CT (MRI) are significant for diagnostics in patients with DE: cerebral ventricles dimensions; dimensions of the subarachoidal spaces and cortical atrophy degree; leukoaraiosis; presence of small focal changes in the white matter.

All liquidators with CVD underwent cerebral CT or MRT in order to assess the cerebral morphologic changes. The probability to reveal leukoaraiosis and small foci in the white matter depended considerably on resolution of the equipment used and was significantly higher when performing MRI with the field strength of 3 T which was administered to 117 patients. The probability to reveal small foci was 90 % in this group and the probability to find presence of leukoaraiosis was 42 %. The dilation of the subarachnoidal spaces was revealed practically in all persons irrespective of the diagnostic method used. The presence of internal hydrocephalus was assessed by the width of the ventricle III and lateral ventricles. The width of the ventricle III ranged from 0.4 to 1.29 cm and exceeded the reference values in 31 % of persons. Anterior horn index (AHI) of the lateral ventricles varied in the range of 0.24–0.35 cm. The lateral ventricles dilation was observed more often than that of the ventricle III and was revealed in 57 % of persons.

The correlation analysis revealed a considerable correlation between morhometric parameters, degree of cognitive impairments and cerebral hemodynamics condition (Table 5.16).

Table 5.16

The Interrelationship Between Morphometric Parameters, Cognitive Impairments and Parameters of Cerebral Hemodynamics in Liquidators with Cerebrovascular Diseases

| Parameters | Morphometric parameters | | | |
|---|---|---|---|---|
| | Foci in the white matter | Leukoaraiosis | AHI | Ventricle III |
| Degree of DE | 0.46** | 0.16 | 0.16 | 0.21 |
| Degree of cognitive impairments as per testing results | | | | |
| MMSE | −0.25* | 0.01 | −0.23 | −0.20 |
| FAB | −0.21 | 0.14 | | |
| Clock drawing test | −0.14 | 0.01 | −0.12 | −0.09 |
| | | | 0.07 | −0.17 |
| Parameters of cerebral hemodynamics | | | | |
| Kr+ | −0.25* | −0.21 | −0.18 | −0.22 |
| IMT | 0.29* | 0.22 | | |
| AS | 0.21 | 0.38** | 0.33* | 0.25* |
| PI | 0.28* | 0.12 | 0.37* | 0.32* |
| | | | 0.04 | 0.25* |

*- Significant differences at the level $p < 0.05$.
**- Significant differences at the level $p < 0.01$.

The changes revealed by cerebral CT and MRI were associated both with the degree of small and large vessel involvement and with clinical symptoms of dyscirculatory encephalopathy including the degree of cognitive impairments.

### *Basic Factors Influencing the Cerebrovascular Pathology in Liquidators in a Long-Term Period After the Accident at ChNPP*

The long-term follow-up of liquidators of accident aftermath at ChNPP, their complex investigation including all modern methods for diagnostics of cerebrovascular diseases confirmed the high prevalence of the vascular pathology in liquidators and allowed to determine basic factors which had a considerable effect on its development.

The liquidators' age correlated with atherosclerosis degree, cerebrovascular reactivity and degree of dyscirculatory encephalopathy. At the same time cognitive impairments, which were one of the basic clinical manifestations of encephalopathy, did not correlate significantly with the age. The basic risk factors of cognitive impairment included the increased intima-media thickness, presence of atherosclerotic plaques in the brachiocephalic arteries, disturbed glucose metabolism, educational level, emotional and volitional disorders and absence of labor activities.

Smoking and abuse of alcohol had significant correlations neither with DE degree not with degree of cognitive impairments in spite of the wide prevalence of these bad habits in liquidators.

Atherosclerotic changes exerted a considerable effect on the development of DE and cognitive impairment in LAA at ChNPP but AS prevalence did not exceed that in the population. In addition to dyslipidemia, a considerable role in the pathogenesis of atherosclerosis in liquidators was played by activated FRO and nonspecific vascular wall inflammation evidenced by the increased CRP hs level which served as a marker.

As it was shown above, essential hypertension diagnosed in 79 % of liquidators with CVD resulted in involvement of the small and large arteries and correlated significantly with the degree of DE and cognitive impairments. The lowered vasodilation reserve diagnosed by dopplerography and microfocal damage of the subcortical white matter revealed by MRI were the most significant diagnostic criterion of small arteries involvement. The damage of small arteries was associated not only with EH and age but also the nonspecific inflammation. Evidently, the increased CRP hs level played a considerable role in endothelium damage in resistive vessels what resulted in disturbed cerebrovascular reactivity. The significant correlation between CRP hs level and Kr+ ($r = -0.24$) was the grounds for such supposition.

Hyperglycemia was a significant factor influencing the large and small arteries involvement, dyscirculatory encephalopathy and cognitive impairment in liquidators irrespective of their age.

Anxiety-depression disorders diagnosed in 80 % of liquidators with CVD reduced considerably their social adaptation and life quality but did not correlate significantly with vascular pathology. The use of antidepressants in the therapy improved significantly the liquidators' condition what was manifested in regress of daily headaches and improved cognitive functions.

The obtained data was assumed as a basis for a developed standard for diagnostics of dyscirculatory encephalopathy in liquidators and effective therapeutic regimens aimed at correction of revealed risk factors. The revealed laboratory and instrumental changes, peculiarities in the clinical picture of the disease allow to substantiate the need to administer the permanent pharmacotherapy including hypotensive therapy, constant use of antiaggregants or anticoagulants, correction of disturbed lipid metabolism, intake of antioxidants, neurometabolic drugs and antidepressants.

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## 5.2. CLINICAL FEATURES OF THE VASCULAR AND CARDIAC PATHOLOGY: PATHOGENESIS, SYMPTOMS, DIAGNOSTICS, AND TREATMENT

### 5.2.1 Cardiovascular Continuum: from Metabolic Syndrome to Diabetes Mellitus, Atherosclerosis, and Calcinosis

The greater part (about 55 %) of all death cases in Russia is associated with cardiovascular diseases, and our country leaves behind significantly all European countries by the total mortality (World Health Organization, *http://www.who.int*). The problem of morbidity and mortality in a special Russian subpopulation, which is quite numerous and very important socially, i. e. liquidators of accident aftermath at the Chernobyl nuclear power plant, seems very serious under these unfavorable conditions.

The prevalence of cardiovascular diseases in LAA at ChNPP registered by the beginning of this century on the whole exceeded that in the control group of the same age category 4 times (Ministry of Health and Medical Industry of RF, 1999). The registered morbidity increased more than 3 times in 1987–2003 what was associated only partially with ageing of this human contingent. On average 2.3 cases of registered diseases of the circulatory system are observed per one LAA at present. Essential hypertension, coronary heart disease and cerebrovascular disease predominate by their prevalence.

Which is the cause for such significantly increased cardiovascular morbidity in LAA? The in-depth analysis of morbidity among these persons performed at the All-Russian Nikiforov Center of Emergency and Radiation Medicine of the Ministry of Emergencies of Russia showed that a very unfavorable effect was caused by a complex of factors associated with participation in liquidation of accident aftermath: long psycho-emotional stress, subsequent psychic and psychosomatic defects, concomitant diseases aggravating each other, and social costs. The effect of these factors was the most intensive in 1986. At the same time, it was found that the external irradiation dose received by LAA had a moderate negative effect which caused the growth of cardiovascular morbidity. This is confirmed also by the data obtained when studying (in 1950–2003) a person cohort who survived after the atomic bombing in Hiroshima and Nagasaki (in total more than 86.5 thousand people) and were exposed to radiation in the dose of up to 3 Gy (86 % of them received the dose of less than 0.2 Gy). The studies proved the dose-dependent increment (due to irradiation in this exposure range, taking into account other risk factors) in probability of stroke and infarction and death because of them, the number of which was 1/3 of the number of lethal tumors caused by the radiation. The probability of death because of stroke increased by 9 %/Gy and that because of cardiac disease increased by 14 % (Shimizu, Y., 2010).

The medical consequences for persons who suffered because of the Chernobyl catastrophe, including because of the involvement in the emergency recovery works, cannot be considered outside the general medical and biological patterns of diseases and death. A modern conception of cardiovascular continuum may serve as a reliable scientific platform for such analysis.

A Latin word *continuum* is translated in Russian as an uninterrupted association, succession of events. Even several decades ago, such typical and frequent diseases as arterial hypertension, diabetes mellitus, atherosclerosis were described in the textbooks on internal diseases as independent or concomitant pathologies regarding their diagnosis wordings and, finally, selection of

the methods for their prevention and treatment. But some outstanding clinicians (first of all, Lang, G. F. and his disciple Myasnikov, A. L. in our country) noted the interrelationship between above conditions and some laws of their progression already by the middle of the last century. At that time this interrelationship was guessed, mainly, when comprehending the clinical experience.

The decades and significant efforts of many researchers working in the field of, mainly, clinical epidemiology and cardiology were required so that their outstanding representatives (Braunwald, E., Dzau, V. J. et al.) could formulate and substantiate a scientific conception called by them as "cardiovascular continuum" by 1991 (Fig. 5.2). Today this conception is known to most physicians and considered by them as classical one because of its consistency and strength. The risk factors associated or not associated between each other are a starting point in the continuum. Some of them are present from birth (genetical predisposition to a disease) or start their adverse influence quite early (family habits to overnutrition or smoking since juvenility). The first evident clinical signs of atherosclerotic vascular constriction (e. g., angina pectoris) are formed after many years. A sudden outburst of atherosclerosis (plaque occurrence and rupture in the coronary artery complicated with thrombosis) or hemodynamic intima damage (e. g., in case of sudden significant change of blood pressure) lead to the development of acute coronary syndrome, myocardial infarction. The hazard of death, other complications occurs (failure of a significant myocardium area, mitral valve, rhythm disturbances are the most typical complications). Later the anatomic and functional heart restructuring (remodeling) takes place: its dilation, relative valve insufficiency, arrhythmias; chronic heart failure progresses gradually and it inevitably results in death.

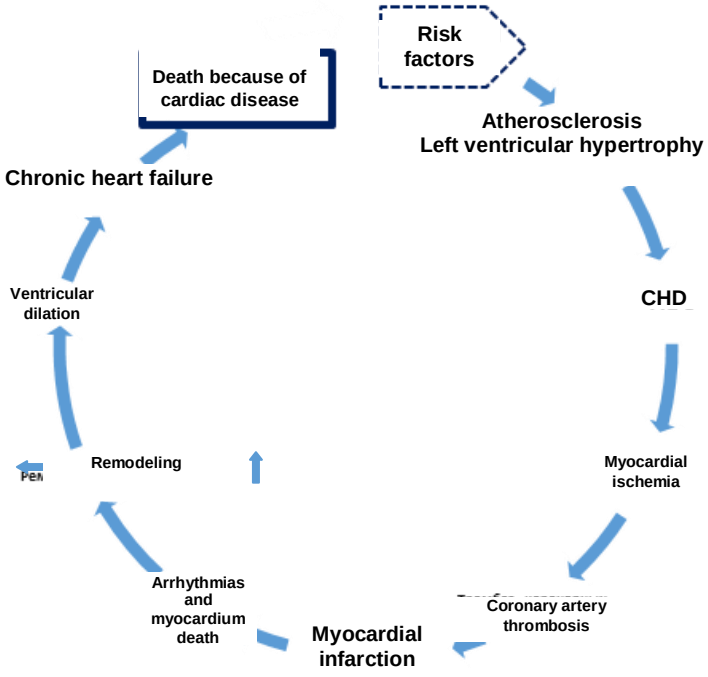


Fig. 5.2. Cardiovascular Continuum (Braunwald E. et al., 1992)

The wide prevalence of risk factors of cardiovascular diseases, their frequent co-existence, association with social factors and age underlie the high morbidity with these diseases. A significant part of risk factors in their combination form the so-called cardiovascular metabolic syndrome. The WHO experts characterized metabolic syndrome as a "pandemic of XXI century." According to the data of the State Research Center of Preventive Medicine the prevalence of metabolic syndrome is about 20 % in Russia. But the prevalence of metabolic syndrome is 75 % in liquidators of accident aftermath at ChNPP hospitalized to the cardiological department of ARCERM. This may be partially associated with not young age of these patients (from 42 to 80 years) which on average was 61 years. The typical risk factors, which include hypodynamia, incorrect nutrition and smoking, as a rule, already appear at this age. In addition to genetic predisposition and also a complex of specific factors associated with exposure to radiation accident, these factors favor the development of metabolic syndrome.

**Metabolic syndrome** is an integral risk factor of cardiovascular diseases what determines its great clinical importance. If this pathologic condition is present, the risk of coronary heart disease increases 3–4 times, and the risk of death because of it increases 2.5–3 times, the risk of death because of any cause (total mortality) grows 2 times, and the risk of onset of diabetes mellitus type 2 increases 3–6 times (Cornier, M. A. et al., 2008) as compared with patients without metabolic disorders. This fact was reflected in the recommendations on diagnostics and treatment of arterial hypertension (3rd revision) suggested by the All-Russian Scientific Society of Cardiologists, where metabolic syndrome was included in the stratification system of cardiovascular risk along with diabetes mellitus.

As a rule, metabolic syndrome develops much earlier than future diseases with their evident clinical picture and is a potentially reversible condition. Well-timed revealing and treatment of metabolic syndrome result in significant improvement and often in complete removal of its symptoms and cardiovascular diseases caused by it.

### *Determination of Metabolic Syndrome*

There are no generally accepted diagnostic criteria of metabolic syndrome because of absence of a single opinion about its pathogenesis. The first diagnostic criteria of metabolic syndrome were formulated by the WHO Working Group in 1998 (Alberti, K. G., Zimmet, P. Z., 1998). Alternative versions were suggested later (Table 5.17).

The All-Russian Scientific Society of cardiologists suggests to use the following criteria for diagnostics of metabolic syndrome which are described in the special "Recommendations of experts of the All-Russian Scientific Society of cardiologists on diagnostics and treatment of metabolic syndrome. Second revision (2009)":

**The basic criterion** is abdominal (central) obesity: waist circumference of more than 80 cm in females and more than 94 cm in males.

**Plus two additional criteria:**

- arterial hypertension (BP ≥ 130/85 mm Hg),
- increased triglyceride concentration in the plasma (≥1.7 mmol/l),

• lowered HDL cholesterol concentration in the plasma (<1.0 mmol/l in males; < 1.2 mmol/l in females),

• increased LDL-cholesterol concentration in the plasma (>3.0 mmol/l),

• hyperglycemia after fasting (blood plasma glucose after fasting ≥6.1 mmol/l), and

• disturbed glucose tolerance (blood plasma glucose 2 h after glucose load is within the range from ≥ 7.8 to ≤ 11.1 mmol/l).

Table 5.17

Diagnostic Criteria of Metabolic Syndrome

| WHO (1998) | NCEP/ATP III (2001) | ACE (2003) | IDF (2005) | AHA/NHLBI (2005) |
|---|---|---|---|---|
| **DM/hyperglycemia after** fasting or **GDT**, or **IR** (hyperinsulinemic euglycemic test) **plus two or more** of the following factors:<br>*abdominal obesity:* BMI > 30 and/or waist/thighs index < 0.9 (M) and < 0.85 (F)<br>*dyslipidemia:* TG ≥ 1.7 mmol/l and/or *HDL-CH* < 0.9 mmol/l (M), < 1.0 mmol/l (F)<br>*arterial hypertension*: BP > 140/90 mm Hg;<br>*MAU:* microalbumin excretion > 20 μg/min albumin/creatinine ≥30 mg/g | **Three and more factors:**<br>*Abdominal obesity:* WC > 102 cm (M) > 88 cm (F);<br>TG ≥ 1.7 mmol/l;<br>*HDL-CH* < 1.0 mmol/l (M) and < 1.3 mmol/l (F)<br>Arterial hypertension: BP ≥135/85 mm Hg or its treatment<br>*Plasma glucose after fasting:* ≥ 6.1 mmol/l | **Availability of two basic criterion plus 1 additional criterion**<br>Basic criteria:<br>*IR or abdominal obesity* WC > 102 cm (M), > 88 cm (F)<br>*HDL-CH* < 1.0 mmol/l (M), < 1.3 mmol/l (F)<br>*TG* > 1.7 mmol/l<br>*Arterial hypertension:* BP > 130/85 mm Hg<br>*Disturbed glucose tolerance*<br>*Hyperuricemia*<br>Additional criteria: Hypercoagulation, polycystic ovaries, endothelial dysfunction, MAU, CHD | **Abdominal obesity** (Caucasians): WC ≥ 94 cm (M) and ≥ 80 cm (F) plus two or more of the following factors (or treatment because of them):<br>TG ≥ 1.7 mmol/l<br>*HDL-CH* < 1.0 mmol/l (M) and < 1.3 mmol/l (F)<br>*Arterial hypertension* (BP ≥ 135/85 mm Hg)<br>Plasma glucose after fasting: ≥ 5.6 mmol/l or diagnosed DM type 2, GTT is advisable in this situation but *it is not obligatory* | **Three factors or more** (or treatment because of them)<br>*Abdominal obesity* (Caucasians): WC ≥ 120 cm (M) and ≥ 88 cm (F)<br>TG ≥ 1.7 mmol/l;<br>*HDL-CH* < 0.9 mmol/l (M) and < 1.1 mmol/l (F)<br>*Arterial hypertension:* BP ≥ 135/85 mm Hg<br>*Plasma glucose after fasting:* ≥ 5.6 mmol/l |

Note. ACE—American College of Endocrinology; AHA/NHLBI—American Heart Association/ National Heart, Lung, and Blood Institute; IDF—International Diabetes Federation; NCEP/ATP III—National Cholesterol Education Program. Adult Treatment Panel III; BP—blood pressure; WHO—World Health organization; F—for females; BMI—body mass index (Quetelet); IR—insulin resistance; M—for males; MAU—microalbuminuria; DGT—disturbed glucose tolerance; WC—waist circumference; DM—diabetes mellitus; TG—triglycerides; GTT—glucose tolerance test; HDL-CH—high density lipoprotein-cholesterol.

### *Formulation of Diagnosis*

The International Classification of Diseases, 10th revision (WHO, 1998), does not contain a diagnosis "metabolic syndrome." This is associated with the fact that the first definition of metabolic syndrome and its diagnostic criteria were published later. There are only rubrics "Arterial hypertension (essential hypertension)" (code I 10) and "Obesity (code E 66.9); double coding (I 10 and E 66.9) is possible. All components of metabolic syndrome are listed in the diagnosis.

The "Recommendations of the experts of the All-Russian Scientific Society of Cardiologists on diagnostics and treatment of metabolic syndrome. Second revision (2009)" note that it is inappropriate to use additional definitions of metabolic syndrome, i. e. *not full* or *full* and also *compensated* and *decompensated*, in the diagnosis. If signs of atherosclerosis or diabetes mellitus are revealed, it is advisable to consider the situation as metabolic syndrome complicated with atherosclerosis or diabetes

mellitus. In patients with this syndrome, arterial hypertension is usually a consequence of abdominal obesity, insulin resistance and hyperinsulinemia and it is secondary, i. e. symptomatic pathology. Exclusions are cases when essential hypertension developed before the signs of metabolic syndrome occurred.

### *Diagnostics of Metabolic Syndrome*

Metabolic syndrome may be supposed already when obtaining the case history and examining the patient. Abdominal (synonym: visceral, central) obesity which is characterized by fat deposition in the region of the abdomen and superior shoulder-girdle (of "apple" type) is the first sign which should be considered. It is necessary to elucidate in more details, how the body weight changed lately and in the past, nutrition pattern (regularity, number of food intakes, food composition, portion volume), degree of physical activities (both at work and at leisure time), duration of stay in sitting position per day. Hereditary predisposition to obesity, diabetes mellitus, coronary heart disease, arterial hypertension, bad habits (smoking and abuse of alcohol) should be revealed obligatorily. It is necessary to pay attention to the following typical complaints: frequent headaches, fatigue, irritability, asthenia, lowered working capacity, sleep disorders, discomfort in the region of the heart, dry mouth, thirst, increased body weight, excessive appetite.

### *Revealing Obesity*

The calculation of the *body mass index according to Quetelet (BMI)* is used the most often in order to assess the presence and degree of obesity and also associated cardiovascular risk:

BMI = body weight (kg)/[height (m)]$^2$ (Table 5.18).

Table 5.18

Classification of Obesity by BMI (WHO, 1997)

| Types of body weight | | BMI (kg/m$^2$) | Risk of concomitant diseases |
|---|---|---|---|
| Body weight deficit | | <18.5 | Low (increased risk of other diseases) |
| Normal body weight | | 18.5–24.9 | Usual |
| Overweight of the body (obesity precursor) | | 25.0–29.9 | Increased |
| Obesity, degree | I | 30.0–34.9 | High |
| | II | 35.0–39.9 | Very high |
| | III | ≥40 | Extremely high |

Liquidators with metabolic syndrome investigated at ALCERM in 2007–2009 had the mean body mass index of 30.0 ± 4.6 kg (n = 71); exceeding of the normal ranges of the body mass index was observed in 91.1 % of liquidators. The overweight of the body (BMI = 25–29.9 kg/m²) was revealed in 35.6 % of liquidators and obesity (BMI ≥ 30.0 kg/m²) was diagnosed in 55.6 % of liquidators; obesity of degree I was observed in 40.0 % (BMI = 30–34.9 kg/m$^2$), obesity of degree II in 8.9 % (BMI = 35–39.9 kg/$^2$), obesity of degree III in 6.7 % (BMI > 40.0 kg/m$^2$).

The abdominal (central, visceral) type of obesity is of the most significance in patients with metabolic syndrome. It may be confirmed by *measurement of the waist circumference* which is performed in upright position at the end of usual expiration. The measurement point is located in

the middle of the distance between the crest apex of the iliac bone and the inferior lateral margin of the ribs (not obligatorily at the level of the umbilicus) If the waist circumference is more than 94 cm in males and more than 80 cm in females, we may speak of abdominal obesity type in a patient (International Diabetes Federation, 2005). If we measure additionally the thigh circumference, we may calculate *the ratio of the waist circumference (cm) to thigh circumference (cm)*. This parameter is more than 1.0 in males and more than 0.8 in females in persons with abdominal obesity. The waist circumference is considered as an independent sign of abdominal obesity and indicates indirectly presence of insulin resistance. The coefficient waist circumference / thigh circumference has lower diagnostic significance.

According to data of ARCERM (2007–2009), abdominal obesity is revealed in 67.1 % of liquidators with cardiovascular diseases basing on the measurement results of the waist circumference. Patients with metabolic syndrome (abdominal obesity observed in 100 % of cases) had mean waist circumference of (106.5 ± 10.4) cm (n = 168).

Computed tomography and magnet-resonance imaging, densitometry allow to determine the abdominal fat weight more accurately.

### *Diagnostics of Disturbed Lipid Metabolism*

The plasma concentrations not only of total cholesterol but also triglycerides, high and low density lipoprotein cholesterol should be measured in all patients with metabolic syndrome because changes of just these lipid parameters are typical of metabolic syndrome. According to data of ACRERM (2007–2009) the exceeded optimum cholesterol concentration was observed in 69 % of liquidators with metabolic syndrome not receiving any hypolipidemic drugs and it was on average 5.7 ± 0.9 mmol/l. The lowered HDL-cholesterol playing the "protective" role in atherogenesis processes was observed the most often in liquidators with metabolic syndrome (in 69 % of cases) [ the mean HDL-cholesterol concentration in liquidators with metabolic syndrome was 1.06 ± 0.33 mmol/l, n = 183]. The triglyceride concentration in the blood plasma was on average 1.9 ± 1.7 mmol/l (n = 183), hypertriglyceridemia was observed in 25 %. The increased LDL-cholesterol concentration was found in 37.5 % [mean value was 3.8 ± 0.9) mmol/l, n = 184], and the increased VLDL-cholesterol concentration was revealed in 25 % of cases [mean value was 0.83 ± 0.52 mmol/l]. The increased index of atherogenicity (higher than 3.1) was observed in 88 % of cases. Thus, overwhelming majority of liquidators with metabolic syndrome (87.5 %) needed correction of dyslipidemia.

### *Diagnostics of Disturbed Carbohydrate Metabolism*

The standard peroral glucose tolerance test is used to diagnose disturbed carbohydrate metabolism. This test allows to reveal and distinguish clearly diabetes mellitus, disturbed glucose tolerance (considered as pre-diabetes condition), disturbed glycemia after fasting and normal condition. The glucose concentrations in the blood plasma after fasting and 2 h after peroral intake of 75 g of dry glucose dissolved in 200 ml of water are significant for diagnostics (Table 5.19).

Table 5.19

Diagnostic Criteria of Diabetes Mellitus and Other Types of Hyperglycemia (WHO, 2006/2011)

| Test conditions | Glucose concentration (mmol/l) | | |
|---|---|---|---|
| | Whole blood | | Plasma |
| | venous | capillary | venous |
| **Norm** | | | |
| After fasting | 3.3–5.5 | 3.3–5.5 | 4.0–6.1 |
| 2 h after GTT | <6.7 | <7.8 | <7.8 |
| **Diabetes mellitus** | | | |
| After fasting | ≥6.1 | ≥6.1 | ≥7.0 |
| 2 h after GTT or 2 h after meals (postprandial glycemia) | ≥10.0 | ≥11.1 | ≥11.1 |
| Accidental revealing of glycemia at any time of the day irrespective of the meals time | ≥10.0 | ≥11.1 | ≥11.1 |
| Disturbed glucose tolerance | | | |
| After fasting (if revealed) | <6.1 | <6.1 | <7.0 |
| 2 h after GTT | 6.7–10.0 | 7.8–11.1 | 7.8–11.1 |
| Disturbed glycemia after fasting | | | |
| After fasting | ≥5.6<br><6.1 | ≥5.6<br><6.1 | ≥6.1<br><7.0 |
| In 2 h (if revealed) | <6.7 | <7.8 | <7.8 |

Note. GTT = glucose tolerance test.

According to the data of ARCERM, disturbed carbohydrate metabolism in liquidators with metabolic syndrome was revealed in 81.1 % of cases. Out of this number, diabetes mellitus type 2 accounted for nearly a half of cases, i. e. 43.3 %, disturbed glucose tolerance was found in 36.7 % of liquidators and disturbed glycemia after fasting was revealed in 20 % of liquidators.

### *Diagnostics of Insulin Resistance and Hyperinsulinemia*

Both direct and indirect methods are used for revealing and assessing insulin resistance and hyperinsulinemia.

Indirect methods are aimed at assessment of the effects caused by endogenous insulin. They include peroral glucose tolerance test, intravenous glucose tolerance test and different indices.

Direct methods assess the effects of exogeneous insulin on glucose metabolism. They include insulin tolerance test, euglycemic hyperinsulinemic “clamp” test and insulin suppressive test.

The *euglycemic hyperinsulinemic ‘clamp” test* is a gold standard for measurement of the tissue sensitivity to insulin. The method essence consists in a continuous infusion of insulin with the rate of 1 IU/min per 1 kg of body weight with simultaneous repeated infusions of glucose maintaining its concentration in the blood plasma at the euglycemic level. After the equilibrium is reached (not earlier than in 2 h), when the administration rate of glucose becomes equal to the rate of its consumption by the organism, the coefficient of utilization (M-index) is calculated as a mean arithmetic of 10–12 discrete values of glucose infusion rate divided by the person’s body weight per 1 min. This parameter characterizes the tissue sensitivity to insulin. The advantage of this method consists in the possibility to quantify accurately the insulin sensitivity index under conditions of stable glycemia level. But this method is not suitable for wide clinical use because of its complexity, invasiveness and need in specially trained staff and special equipment.

The peroral glucose tolerance test consists in measurement of plasma glucose and insulin concentrations after fasting and 30, 60, 90, and 120 min after peroral intake by the patient of 75 g of dry glucose dissolved in 200 ml of water. The insulin concentration is assessed after fasting and after the load. Increased plasma insulin concentration is evidence of insulin resistance.

*Intravenous glucose tolerance test* or *insulin-modified intravenous glucose tolerance test*. The advantage of this test consists in the fact that glucose absorption occurs more rapidly and does not depend on the condition and functioning of the intestinal wall in contrast to the peroral glucose tolerance test. The test is performed not less than 12 h after the last food intake. The procedure of the test is as follows: 40 % glucose solution is administered by intravenous bolus for 2 min on the basis of 0.3 g/kg of body weight; short-acting insulin is administered by intravenous bolus on the basis of 0.03 U/kg of body weight 20 min after administration of glucose. The blood is sampled to measure plasma glucose, insulin and C-peptide concentrations 10 and 5 min before administration of glucose and at minute 2, 4, 8, 19, 22, 25, 27, 30, 40, 50, 70, 90, and 180 after administration of glucose. This allows to reproduce the normal physiologic model of insulin action and makes it possible to assess both insulin secretion phases.

*HOMA IR index* (Homeostatic Model Assessment Insulin Resistance):

$$HOMA\ IR = \frac{\text{Insulin after fasting (μU/ml) x glucose after fasting (mmol/l)}}{22.5}$$

This value is about 1 in the normal condition and, as a rule, it exceeds 2.5 in persons with insulin resistance. This parameter is used the most often because it is easily calculated, it correlates well with clamp-test. The calculated HOMA IR index was on average 2.88 in liquidators with metabolic syndrome and this parameter value exceeded 2.5 only in 34 % of liquidators.

*Caro glycemic index:*

$$Caro = \frac{\text{glucose after fasting (mmol/l)}}{\text{Insulin after fasting (μU/ml)}}$$

The reference value is more than 0.33.

*QUICKI* (quantitative insulin sensitivity check index):

$$QUICKI = \frac{1}{[\log \text{Insulin after fasting (μU/ml)} + \log \text{glucose after fasting (mg/dl)}]}$$

The reference value is more than 0.300. It is used to measure insulin sensitivity.

*FGIR index* is specific for assessment of insulin sensitivity.

$$FGIR = \frac{\text{glucose after fasting (mg/dl)}}{\text{Insulin after fasting (μU/ml)}}$$

FGIR index is less than 7 in persons with insulin resistance.

The *baseline insulin concentration in the blood plasma (basal insulinemia)* also may be considered as indirect sign of insulin resistance: the higher this value is, the more pronounced tissue insulin resistance is. The mean basal insulinemia in liquidators with metabolic syndrome was 9.9 ± 7.9 mmol/l (n = 118).

### *Diagnostics of Arterial Hypertension*

The arterial blood pressure is assessed by the generally accepted method according to Korotkov or by 24-h monitoring method. In contrast to Korotkov's method, 24-h blood pressure monitoring allows to investigate the 24-h profile, variability, degree of blood pressure decrease at night and its increase in the morning, and also reveal the "white-coat" phenomenon what reduces the risk of hyperdiagnostics. The typical features of arterial hypertension in patients with metabolic syndrome include significantly pronounce day and night disturbances in the blood pressure rhythm, increased variability of the blood pressure and absence of its adequate lowering at night. According to data of ARCERM (2009), liquidators with metabolic syndrome had arterial hypertension practically in all cases (95 %) (basing on the data of 24-h blood pressure monitoring); the blood pressure was about 150/88 mm Hg (n = 111).

### *Diagnostics of Other Diseases and Pathologic Conditions Associated with Metabolic Syndrome*

According to recommendations suggested by the experts of the All-Russian Scientific Society of Cardiologists on diagnostics and treatment of metabolic syndrome (2009), hyperuricemia is not referred to basic metabolic syndrome criteria. But hyperuricemia is observed quite often in patients with this disease what was reflected in diagnostic criteria of metabolic syndrome developed by the American College of Endocrinology (ACE, 2003) in which hyperuricemia is one of the basic criteria. Therefore, the plasma uric acid concentration in persons with metabolic syndrome should be measured in all patients in order to reveal hyperuricemia. Liquidators with cardiovascular diseases investigated at the department of cardiology at ACRERM in 2007–2009 had hyperuricemia in 30.1 % of cases. But in patients with metabolic syndrome, hyperuricemia percentage was 54 % and uric acid concentration in the blood plasma after fasting was on average 409 ± 84 μmol/l ($p < 0.001$, n = 66) while the blood plasma uric acid concentration in persons without this syndrome was considerably lower: mean value was 347 ± 74 μmol/l (n = 58).

The excessive fructose consumption in food becomes important as an etiologic factor of metabolic syndrome lately because it leads to numerous unfavorable metabolic consequences: progression of diabetes mellitus and its complications, obesity, hypertension, hypertriglyceridemia, nonalcoholic fatty liver disease, hyperuricemia (Gaby, A. R., 2005).

The *blood plasma fructose concentration after fasting* may be measured to reveal hyperfructosemia which is evidence of the excessive consumption of this food ingredient. The blood plasma fructose concentration after fasting in liquidators with metabolic syndrome hospitalized to the cardiologic department of ARCERM was on average 0.8 ± 0.98 mmol/l (n = 35) what exceeded considerably the normal levels: the plasma fructose concentration after fasting in healthy persons was less than 1 mg/dl or 0.03 mmol/l (Cheil, V. et al., 2001).

The increased nonesterified fatty acids concentration in the blood plasma is a risk factor of cardiovascular diseases, diabetes mellitus type 2, arterial hypertension and sudden death. The increased NEFA concentration in the blood plasma is often observed in patients with metabolic syndrome. *The measurement of nonesterified fatty acids concentration in the blood plasma after* fasting may be used for diagnostics of metabolic syndrome (as an additional criterion) and also for assessment of disease prognosis. The NEFA concentration in the blood plasma was on average 0.55 ± 0.26 mmol/l (n = 177) in liquidators with metabolic syndrome hospitalized to the cardiologic department of ARCERM in 2007–2009. The increased NEFA concentration in the plasma after fasting (more than 0.9 mmol/l) was observed in 16.9 % of liquidators.

If a patient has atherogenic dyslipidemia, it is possible to measure additionally *the blood plasma content of apoprotein B* (*or non HDL-cholesterol*), *small low density lipoprotein particles* because metabolic syndrome is characterized by the increase of these parameters. The mean apoprotein B concentration in the blood plasma is 1.09 ±0.28 g/l in liquidators with metabolic syndrome (the normal apoprotein B content is 0.46–1.42 g/l), the increased apoprotein B concentration in the blood plasma is observed only in 12.5 % of cases in this patient category.

It is advisable to measure the blood plasma content of fibrinolytic factors (*plasminogen-I activator inhibitor*) and coagulation factors (*fibrinogen*) in order to assess the prothrombotic status. The increase of their levels is observed in patients with metabolic syndrome.

It is expedient to measure the blood plasma concentrations of *C-reactive protein and also inflammatory cytokines* (*interleukine-6, tumor necrosis factor*–α) in order to estimate the pro-inflammatory status. The increase of their levels is observed in patients with metabolic syndrome. The C-reactive protein concentration in the blood plasma exceeds the normal level for the patients with the cardial pathology (less than 2.5 mg/l) in 50 % of liquidators with metabolic syndrome and it is on average 4.3 ± 5.1 mg/l (n = 181). This indicates the high cardiovascular risk and frequent presence of chronic subclinical inflammation in this patient category.

*Endothelial dysfunction* may be investigated and *microalbuminuria* may be revealed in patients with metabolic syndrome in order to assess vascular disorders more precisely. Liquidators with metabolic syndrome often had microalbuminuria (more than 15 mg/l) (in 30 % of cases). This value on average was 21 ± 36 mg/l (n = 177).

The measurement of leptin and adiponectin concentration in the blood plasma is used to assess regulation of the alimentary behavior, course of the disease and risk of complications. According to data of ARCERM (2008–2009), liquidators without metabolic syndrome had mean blood plasma leptin concentration of 2.8 ± 3.5 ng/ml (n = 39) what corresponded to the normal values (2.0–5.6 ng/ml). But liquidators with metabolic syndrome had the mean blood plasma leptin concentration of 12.7 ± 21.3 ng/ml (n = 121) what exceeded considerably the normal values. Hyperleptinemia in liquidators with metabolic syndrome was observed in 75 % of cases what was often evidence of leptin resistance in this patient category. The blood plasma adiponectin concentration was on average 11.5 ± 9.8 mg/ml (n = 58) in liquidators with metabolic syndrome was corresponded to normal values (12–30 mg/l in females and 8–30 mg/l in males in the blood plasma). Hypoadiponectinemia was observed not often (in 12 % of cases).

The methods of computed tomography, magnet-resonance imaging or densitometry (Total Body program) are used for detailed assessment adipose tissue distribution pattern.

The measurement of hepatic enzyme levels and ultrasound investigation of the liver are required for diagnostics of nonalcoholic steatosis/steatohepatitis.

The ultrasound investigation of small pelvis organs and measurement of sexual hormone concentrations are used for diagnostics of polycystic ovaries syndrome in women.

The sexual hormone concentration is measured to reveal androgenic deficit and age-related hypogonadism in males.

### *Differential Diagnostics*

Many symptoms typical of metabolic syndrome are observed also in patients with Cushing's syndrome, hypothyroidism and other endocrine diseases. These diseases may be differentiated basing on the typical signs, which are specific for them (signs associated with hypercortisolism, aldosteronism, etc.) or unusual course of the disease (progression, sometimes with crises, etc.). The additional investigations are used provided that there are sufficient grounds for this: methods for visualization of the adrenal glands and hypophysis (computed tomography, magnet-resonance imaging), and also it is possible to measure hormone concentrations (depending on the supposed disease, i. e. adrenocorticotropic hormone, cortisol, aldosterone, catecholamines, thyroid-stimulating hormone) which exceed the normal values tens of times and more in patients with the endocrine pathology.

The data obtained at ARCERM in 2007–2010 is evidence of high (75 %) prevalence of metabolic syndrome in liquidators suffering from cardiovascular diseases. More than a half (55.6 %) of liquidators with metabolic syndrome had clinically pronounced obesity. Practically all these patients had arterial hypertension (95 %). Hyperleptinemia was observed quite often (75 %). Most of these patients needed correction of dyslipidemia (87.5 %), dysglycemia (81.1 %) and hyperuricemia (53.7 %). The lowered concentration of HDH-cholesterol playing the "protective" role in atherogenesis was the most typical of dyslipidemia in liquidators with metabolic syndrome. Diabetes mellitus type 2 was observed the more frequently among other carbohydrate metabolism disturbances (43.3 %).

### *Treatment of Metabolic Syndrome*

In its essence, the treatment of metabolic syndrome is prevention of cardiovascular diseases and their complications and depends in many aspects on the fundamental understanding of the nature of metabolic syndrome by a physician, his (her) knowledge of mechanisms of action exerted by drugs used for its treatment. The selected tactics for management of patients with metabolic syndrome should depend on the degree and dominating of its some or other manifestations and degree of cardiovascular risk. The purpose of the treatment of metabolic syndrome consists in reaching the target values of its main components (Table 5.20).

The paramount significance in the treatment of metabolic syndrome is attached to elimination of life style defects: overweight of the body, incorrect nutrition, hypodynamia, smoking and abuse of alcohol, psycho-emotional overstresses. These measures may be often sufficient for gradual complete elimination of all manifestations caused by metabolic syndrome. But if non-medicinal therapeutic

methods are insufficiently effective, there are complications of metabolic syndrome or a patient does not wish to change his(her) life style as much as it is necessary, it is advisable to start pharmacotherapy. When selecting a drug, we should take into account its metabolic effects, we should not administer those drugs which lower tissue sensitivity to insulin and we should try to correct associated metabolic disorders. If there are specific complications, their treatment and secondary prophylaxis should be started.

Table 5.20

Therapeutic Purposes and Tactics for the Treatment of the Main Metabolic Syndrome Components (Eckel, R. H. et al., 2005)

| Metabolic disorder | Therapeutic purposes | Recommendations |
|---|---|---|
| Abdominal obesity | Reduction of body weight by 10 % within a year, then subsequent its reduction or maintaining | Restriction of calories, change of the life style* |
| LDL-cholesterol | Target values:<br>*in case of high risk-*<br><2.6 mmol/l (without hypolipidemic therapy);<br><1.8 mmol/l (with hypolipidemic therapy);<br>*in case of moderately high risk-*<br><3.4 mmol/l (without hypolipidemic therapy);<br><2.6 mmol/l (with hypolipidemic therapy);<br>*in case of moderate risk* < 4.1 mmol/l | Patients with *high risk* should change the life style* with simultaneous administration of hypolipidemic drugs (statins) for reaching the recommended target values.<br>Patients with *moderately high risk* should change the life style*; if necessary (if LDL-cholesterol > 3.4 mmol/l) they should receive hypolipidemic drugs (statins) for reaching the recommended target values.<br>Patients with moderate risk should change the life style*; if necessary (if LDL-cholesterol > 4.1 mmol/l) they should receive hypolipidemic drugs (statins) for reaching the recommended target values. |
| Hypertriglyceridemia or lowered HDL-cholesterol concentration | No convincing data for setting a target | Patients with *high risk* should receive the treatment with fibrates (fenofibrate is preferred) or nicotinic acid |
| Increased blood pressure | Target values:<br><130/85 mm Hg;<br><130/80 mm Hg for patients with diabetes mellitus or chronic kidney diseases | Patients should change their life style* and if it is necessary to reach the BP target values, patients should receive antihypertensive therapy (monotherapy or combined antihypertensive therapy if monotherapy is not effective) |
| Increased glucose concentration in the plasma after fasting | Glucose after fasting ≤ .5 mmol/l (capillary plasma) or ≤6.1 mmol/l (venous plasma);<br>glycated hemoglobin <7 % for patients with diabetes mellitus | Patients should change their life style* and if it is necessary, to reach target values of glucose after fasting and glycated hemoglobin patients should receive hypoglycemic pharmacotherapy. |
| Predisposition to thrombosis | Elimination of predisposition to thrombosis | The therapy with low doses of Aspirin should be started in patients with *high risk* (if there are contraindications, administration of Clopidogrel should be considered).<br>Administration of Aspirin in low doses should be considered in patients with *moderate risk* |

*Change of the life style includes: reduction of the body weight, regular physical exercises, antiatherogenic diet.
*Note.*
*High risk*: presence of diagnosed atherosclerotic cardiovascular disease, diabetes mellitus or risk of CHD within 10 years ≥ 20 %;
*moderately high risk*: risk of CHD within 10 years = 10–20 %;
*moderate risk:* patients with metabolic syndrome but risk of CHD within 10 years < 10 %.

### *Non-Medicinal Methods for Treatment of Metabolic Syndrome*

Numerous studies showed convincingly that reduction of the body weight in patients with metabolic syndrome resulted in significantly lowered cardiovascular risks: decreased blood pressure, improved parameters of lipid metabolism, considerably lowered risk of diabetes mellitus type 2.

Therefore, modification of the life style plays a very important role in the treatment of metabolic syndrome.

But many patients understand the whole hazard of their condition and the need to change their life style not completely and most of them even cannot master a new healthy life style without assistance. The physician's purpose in this case is to form the steady patient's motivation aimed at long-term fulfillment of recommendations concerning nutrition, exercise stress, use of drugs. It is necessary to instruct patients; it is better to conduct such instruction at schools of health life style. Such schools should be established at health centers which follow-up liquidators of the accident at ChNPP.

### *The Motor Activity and its Medical Effects*

The tissue insulin resistance is observed in approximately 25 % of persons having the sedentary life style. Regular physical trainings promote enhanced tissue sensitivity to the action of insulin (due to improved muscle blood supply, development of microvessels in them, intensified glucose consumption by the muscles, increased number of insulin receptors), reduction of the body weight and normalization of the blood pressure. Even if regular trainings do not result in reduced body weight and it is not possible to intensify them this should not cause their stopping. Regular physical trainings, which do not promote the body weight reduction in patients with prediabetes, lower the risk of diabetes mellitus type 2 by more than 50 % (Duncan, G. E. et al., 2003).

Walking is the simplest but quite effective way to increase physical activity. Four hundred kilocalories are consumed during 1 h walking. It is sufficient to walk intensively every day for 30–40 minutes outdoors or practice 20–30 min runs 3–4 times a week to achieve the therapeutic effect. Besides that, daily walking for 20-30 min outdoors results in decrease of the systolic/diastolic blood pressure by 5–7/2–3 mm Hg for the next 6–8 h. In this situation, the hypotensive effect is associated with recovered ability of the arteries to tone self-regulation, in particular due to improved endothelium function.

For example, it is possible to give a patient a specific advice to go to work and back home on foot (or part of this distance), to walk during lunch break and before going to bed. Days off should be used for journeys to the country, i. e. to the forest (ski trips, hike for mushrooms, depending on a season), to a cottage (work on the farmland). Sport plays, bicycle trips and swimming are very useful. Patients should be encouraged to perform exercises for overcoming the resistance (i. e. isometric stresses) twice a week. The physician should not only give such advices but also check their fulfillment, i. e. to ask about this at the next visit of the patient and also welcome positive changes in the life style.

### *Nutrition of Persons with Metabolic Syndrome*

The correct nutrition is of importance to correct all metabolic syndrome components without exception. The diet of such patients should not only provide body weight reduction but also favor normalization of existing metabolic disorders and blood pressure. It is necessary to restrict the food calorie content but such restriction should be acceptable for long-term use (for many years and even

for life): it should not cause an unpleasant sensation of hunger, depression, lowered working capacity and worsened general well-being and not do harm to the health. It should be emphasized especially that fasting and even single misses of food intake are inacceptable. Fasting is hazardous because rapid disintegration of the adipose tissue is accompanied by increasing unesterified fatty acid concentrations in the blood what results in numerous unfavorable metabolic effects. Besides that, the basal metabolism rate lowers as a compensatory reaction, therefore, when patients stop fasting their body weight usually increases rapidly so that it soon already exceeds the initial body weight.

The optimum practice is to lower the food calorie content by 500–600 kcal from the daily patient's caloric requirement taking into account his(her)physical activity. In order to calculate the daily patient's caloric requirement, we should estimate the basal energy expenditure (BEE) using the Harris-Benedict equation:

males: BEE (kcal) = 66.47 + (13.75 x *W*) + (5.0 x *H*) − (6.77 x *A*);

BEE (kJ) = 278 + (57.5 x *W*) + (20.92 x *H*) − (28.37 x *A*);

females: BEE (kcal) = 65.51 + (9.56 x *W*) + (1.85 x *H*) − (4.67 x *A*);

BEE (kJ) = 274.1 + (40.0 x *W*) + (7.74 x *H*) − (19.68 x *A*),

where *W* is actual body weight (kg); *H* is height (cm); and *A* is age (years).

1 kcal = 4.184 kJ; 1 kJ = 0.239 kcal.

When calculating the actual energy expenditure, we should take into account the factor of activity. BEE is increased by the coefficient of 1.2 for patients with low physical activity, by 1.4 for persons with moderate activity and by 1.6 for persons with high activity.

The most optimum practice is to reduce the body weight by 7–10 % of the initial value but not by more than 2–4 kg per month during the first year of the therapy.

The nutrition should include frequent, small portions (usually 3 basic food intakes and 2–3 intermediate food intakes). The last food intake should be not later than 1.5–2 h before going to bed.

When selecting the ration, you should use tables of foodstuff calorie content. Fats should account for not more than 30 % of the total calorie content, and fats of animal origin should account for one third and the share of vegetable oils should be two thirds. The percentage of carbohydrates should be about 50 %, mainly due to complex carbohydrates with low glycemic index (whole grain products, vegetables, fruits with high content of dietary fibers). Proteins should account for the remaining 15–20 % of the daily ration. Fish should be used not less than 1–2 times weekly, fruits and vegetables should be consumed daily (it is advisable to use them with every meals). The permissible quantity of sweet fruits depends on the degree of carbohydrate metabolism disturbance: they should be greatly restricted in patients with diabetes mellitus type 2. It is also expedient to reduce the consumption of Table salt to 2–3 g/day.

It is necessary to recommend a patient with metabolic syndrome to keep a diary of nutrition in order to assess actually the nutritional behavior, reveal and correct nutrition defects. It should describe (once-twice a week) the number and time of food intakes during a day, size and composition of portions and also body weight and waist circumference.

Table 5.21

Practical Recommendations for Changing the Life Style in Patients with Metabolic Syndrome (Deen, D., 2004)

| Metabolic disorder | Measures for changing the life style | Practical recommendations |
|---|---|---|
| Abdominal obesity | Reduction of body weight | Reduce the portion size in order to lower the quantity of consumed calories |
| | More intensive physical activity | Physical exercise stress with moderate intensity for 30 min daily |
| Hypertriglyceride-mia | Reduction of body weight | Reduce the portion size in order to lower the quantity of consumed calories |
| | More intensive physical activity | Physical exercise stress with moderate intensity for 30 min daily |
| | Increase the consumption of foodstuffs with low glycemic index | Replace refined carbohydrates (white bread, potatoes, and spaghetti) with legumes, whole grain products and monounsaturated fats (nuts, avocado, olive and rapeseed oil) |
| | Decrease the total quantity of consumed carbohydrates | Replace carbonated beverages and juices with ordinary water, mineral water and dietetic drinks |
| | Increase consumption of omega-3 fatty acids | Consume fish at least once a week |
| | Restrict the use of alcohol | Maximum 2 portions of alcohol* daily for males and 1portion of alcohol* daily for females |
| Low HDL-cholesterol concentrations | Reduction of body weight | Reduce the portion size in order to lower the quantity of consumed calories |
| | More intensive physical activity | Physical exercise stress with moderate intensity for 30 min daily |
| | Increase consumption of monounsaturated fats | Use fish, nuts and avocado. Use olive or rapeseed oil for preparing salads and cooking other food |
| | Stop smoking | Join the smoking refusal program |
| Increased blood pressure | Reduction of body weight | Reduce the portion size in order to lower the quantity of consumed calories |
| | More intensive physical activity | Physical exercise stress with moderate intensity for 30 min daily |
| | Reduce consumption of saturated fats | Prefer diary products with low fat content and reduce consumption of red meat, butter and products of whole milk |
| | Reduce sodium consumption | Restrict consumption of sodium to 2.4 g (or 6 g of salt) daily due to use of larger quantity of flavorings; use foodstuffs with low sodium content; take the salt-cellar away |
| | Increase consumption of fruits | Use more than 5 portions of fruits and vegetables daily |
| | Increase consumption of fat-free dairy products | Use 3 portions of fat-free or low-fat dairy products daily |
| | Restrict the use of alcohol | Maximum 2 portions of alcohol* daily for males and 1 portion of alcohol* daily for females |
| Increased glucose concentration in the blood plasma after fasting | Reduction of body weight | Reduce the portion size in order to lower the quantity of consumed calories |
| | More intensive physical activity | Physical exercise stress with moderate intensity for 30 min daily |
| | Reduce the total quantity of consumed carbohydrates; replace carbohydrates with monounsaturated fats | Replace flour products with whole grain products (oat flakes, brown rice, corn and whole grain wheat) and monounsaturated fats (nuts, avocado, rapeseed and olive oil) |
| | Increase consumption of dietary fibers (more than 30 g daily) | Add legumes and fruits with high content of soluble fibers |

*1 portion of alcohol is equivalent to 20 ml of ethanol or 40-45 ml of vodka (cognac) or 360 ml of beer or 150 ml of wine.

Very moderate consumption of alcohol (mainly, this concerns red dry wine in the quantity of up to 1-2 wineglasses daily) in those cases when this is not contraindicated (hepatic diseases, diabetes mellitus, high risk of life-threatening rhythm disturbances, instable angina pectoris, severe heart failure) may increase the tissue sensitivity to insulin and have a positive effect on prognosis of cardiovascular complications. But consumption of large quantities of alcohol promotes worsened course of metabolic syndrome and diseases associated with it. Therefore, it is more reasonably to

recommend absolute refusal from alcohol consumption to patients with predisposition to abuse of alcohol who are often seen among liquidators. The recommendations for changing the life style of patients with metabolic syndrome depending on prevalence of some or other metabolic disorders are summarized in Table 5.21.

### *Pharmacotherapy—Drugs Used for Treatment of Obesity*

The drugs reducing the body weight are used as a rule when intensified physical activity and diet with low calorie content proved to be insufficiently effective or ineffective.

At present a drug with peripheral action Orlistat or a drug with central action Sibutrain are used mainly for pharmacotherapy of obesity in patients with metabolic syndrome.

Thanks to its similarity to triglycerides, when taken perorally, Orlistat binds with pancreatic lipase and inhibits it reversibly. This results in disturbed breakdown of alimentary fats and their absorption from the gastrointestinal tract is reduced approximately by 30 %. The administration of Orlistat to patients with obesity and metabolic syndrome leads to considerable reduction of the body weight and waist circumference, lowering of the blood pressure, total cholesterol concentration in the plasma, increased high-density lipoprotein cholesterol concentration and also decreased plasma insulin concentration after fasting and lowered risk of diabetes mellitus type 2. The administration of Orlistat to patients with diabetes mellitus type 2 improves compensation of diabetes mellitus (Torgerson, J. S. et al., 2004). The drug is used for those who prefer fatty food, it is ineffective in case of overeating carbohydrates. the drug is administered perorally in the dose of 120 mg 3 times daily.

Sibutramin is a selective noradrenaline and serotonin reuptake inhibitor, the anorectic drug with central action. It lowers the appetite and reduces the quantity of consumed food and also intensified thermogenesis. The reduction of the body weight associated with the use of Sibutramin is accompanied with increased high-density lipoprotein cholesterol concentration in the blood serum and lowered quantity of triglycerides. The mean glycated hemoglobin level decreases in patients suffering from diabetes mellitus type 2 with obesity. Sibutramin is used in patients with increased appetite for whom it is difficult to restrict themselves permanently in food intake. The antidepressive effect of Sibutramin the mechanism of which is similar to mechanism of action of antidepressants exerts an additional beneficial influence on patients suffering from obesity because many of them have lowered baseline mood and are predisposed to depression. the drug should be taken perorally in the dose of 10 mg once a day.

A new drug Rimonabant for pharmacotherapy of obesity appeared recently. This drug is the selective endocannabinoid receptor (CB1 type) inhibitor. The treatment with Rimonabant lowers appetite, reduces obesity and waist circumference, decreases the blood pressure, glycated hemoglobin content and triglyceride concentration in the blood plasma, increases high-density lipoprotein cholesterol concentration. The drug is also effective for treatment of tobacco smoking dependence.

### *Drugs used for Correction of Dysglycemia*

The progression of vascular diseases, risks of their complications and premature mortality are considerably influenced by hyperglycemia, especially postprandial hyperglycemia (developing after food intake). Correction of insulin resistance, hyperglycemia, even mild hyperglycemia, decreases considerably risks of cardiovascular complications and death.

The use of the drugs influencing the tissue sensitivity to insulin and carbohydrate metabolism (mainly, Metformin and Acarbose) is indicated to patients with disturbed carbohydrate metabolism in the form of disturbed carbohydrate tolerance or hyperglycemia after fasting if the effect of non-medicinal measures is insufficient.

*Biguanides (metformin)* lower gluconeogenesis in the liver, inhibit glucose absorption in the small intestine, increase the tissue sensitivity to insulin due to suppressed free fatty acid oxidation and their lowered concentration in the plasma, reduce the degree of hyperinsulinemia. At present, the only one drug from this group, i. e. *Metformin*, is used because it is associated with minimum risk of lactic acidosis. When Metformin is used, hypoglycemic episodes are practically not observed because it does not influence insulin secretion.

The therapy with Metformin lowers plasma concentrations of triglycerides, low-density lipoprotein cholesterol and glucose after fasting, reduces postprandial hyperglycemia, decreases the blood pressure and body weight, improves endothelium function, increases high-density lipoprotein cholesterol concentration.

The study USDPP involving 3,234 patients with high risk of diabetes mellitus type 2 found that the administration of Metformin lowered the morbidity with diabetes mellitus type 2 by 31 %, resulted in reversal of symptoms of metabolic syndrome by 17 % as compared to placebo (Knowler W. C. et al., 2002). It may be administered to patients with disturbed glucose tolerance.

The side effects of Metformin include diarrhea and other dyspeptic disorders and also lactic acidosis. Contraindications for administration of Metformin include hypoxic conditions: coronary insufficiency, heart, respiratory, renal, hepatic failure, and abuse of alcohol.

The drug is taken in the dose of 500–850 mg 1–3 times daily under control of the glucose concentration in the blood.

*Acarbose (Glucobay)* is a reversible intestinal α-glycosidase inhibitor. It disturbs the enzymatic breakdown of poly- and oligosaccharides and absorption of monosaccharides what prevents postprandial hyperglycemia and favors lowered insulin concentration in the plasma. It is one of the safest drugs influencing the postprandial glucose level and insulin resistance. The multicenter randomized study STOP-NIDDM revealed that when Acarbose was administered to patients with disturbed glucose tolerance, metabolic syndrome and high risk of cardiovascular complications, the relative risk of diabetes mellitus type 2 reduced by 36 %, the relative risk of new cases of arterial hypertension decreased by 34 %, this parameter lowered by 91 % for myocardial infarction and by 49 % for any cardiovascular event (Chiasson, J. L. et al., 2003). The Russian study “APRIL” demonstrated the positive effect of the main factors of cardiovascular risk, i. e. overweight of the body, postprandial hyperglycemia and arterial hypertension (Chazova I. E., Mychka V. B., 2005).

Acarbose is administered in the dose of 50 mg 3 times daily just before or with meals for the first 2 weeks, then the dose is increased gradually up to 100 mg 3 times daily taking into account the tolerance. The main side effects include meteorism and diarrhea which, as a rule, may be avoided by gradual increase of the dose. If a patient develops intestinal disorders associated with administration of the drug, it is necessary to keep to a diet strictly with restriction of carbohydrate consumption and to decrease the dose of Acarbose. Contraindications for administration of Acarbose include intestinal diseases associated with disturbed absorption, ulcers, diverticula, fissures, stenoses. Acarbose should not be administered to persons aged under 18 years, pregnant women and in the lactation period.

According to the data of ARCERM (2009), the treatment with Acarbose in the full dose (300 mg/day) in liquidators suffering from metabolic syndrome with disturbed carbohydrate metabolism, i. e. disturbed glucose tolerance or diabetes mellitus type 2 (n = 33), resulted already on Day 7 of the treatment in significantly lowered plasma concentration after fasting of uric acid [before treatment: 414.5 ± 85.2) μmol/l, after treatment: 388.6 ± 80.3 μmol/l, $p < 0.01$], fructose [before treatment: 1.01 ± 1.27 mmol/l, after treatment: 0.25 ± 0.47 mmol/l, $p < 0.05$] and also postprandial blood plasma concentrations of glucose [before treatment: 8.2 ± 3.9 mmol/l, after treatment: 8.05 ± 3.76 mmol/l, $p < 0.001$] and insulin [before treatment: 61.3 ± 42.9 mIU/l, after treatment: 45.4 ± 35.9 mIU/l, $p < 0.05$]. The use of Acarbose (for 2 months) in this patient category also has a beneficial effect on the carbohydrate (lowered glycated hemoglobin concentration and reduced degree of insulin resistance basing on changes in the waist circumference) and purine [significantly lowered uric acid concentration in the blood plasma (on average by 5.8 %): before treatment: 403.5 ± 90.3 μmol/l, after treatment: 380.1 ± 79.6 μmol/l, $p < 0.05$).

The hypouricemic effect of Acarbose is associated with the influence of this drug on fructose absorption. If fructose enters the organism in excessive quantities, it activates adenosine monophosphate disintegration to uric acid what favors hyperuricemia. The administration of Acarbose favors reduced fructose absorption (due to lowered rate of sucrose hydrolysis which consists of glucose and fructose), consequently, decrease of its entrance to the organism.

If the effect of the above therapy types is unsatisfactory, in patients with severe diabetes mellitus type 2, it is rational to administer secretogenic drugs (e. g., sulfonyl urea products) or insulin therapy in spite of the unfavorable pathogenetic influence of insulin in patients with metabolic syndrome. The main purpose of the therapy in this case is to control postprandial glycemia and achieve compensation of the carbohydrate metabolism at any cost what will promote lowered cardiovascular morbidity and mortality.

### *Hypolipidemic Therapy*

Statins (Atorvastatin, Simvastatin, Pravastatin, and Rozuvastatin) are the main class of hypolipidemic drugs used for correction of dyslipidemia in patients with metabolic syndrome. The advantage of these drugs consists in the combination of pronounced hypolipidemic efficiency with considerably reduced risk of cardiovascular complications with absence of negative effects or even with some positive influence on other metabolic syndrome components (moderate lowering of the blood pressure, increased insulin sensitivity, improved endothelium function, anti-inflammatory effect). The beneficial clinical effect of statins is confirmed in several clinical trials. These drugs are

indicated to all patients suffering from metabolic syndrome with manifestations of atherosclerosis, with history of its complications (myocardial infarction, stroke) and/or with diabetes mellitus.

When considering the administration of statins to patients with metabolic syndrome with the purpose of primary prophylaxis of atherosclerosis (i. e. when its clinical signs are absent yet) you should assess the risk of cardiovascular complications as per the SCORE system. It is recommended to administer statins usually to patients with risk of more than 5 %. But it is advisable to lower this conditional limit for liquidators of the accident at ChNPP; it is usually lowered by 1 % and even by 2 % if a liquidator was involved in emergency works in 1986 (Khirmanov, V. N., Sidorov, M. G., 2009). This is associated with the fact that the participation in liquidation of the accident at ChNPP may be considered as the risk factor of diseases. It is necessary to lower LDL cholesterol concentration to a same degree as in patients with diagnosed coronary heart disease (CHD): LDL cholesterol <2.5 mmol/l (<100 mg/dl), in liquidators with metabolic syndrome because of the high risk of CHD.

*Fibrates* also have a marked hypolipidemic effect. Their especially important advantage as compared to statins consists in the fact that these drugs lower considerably blood triglyceride content, increase HDL cholesterol concentration in the blood, may intensify the action of hypoglycemic drugs. But the treatment with these drugs leads to side effects more often than the therapy with statins. Besides that, there is no sufficiently convincing data on the beneficial effect of fibrates on the final outcomes of cardiovascular diseases and the long-term prognosis in patients with metabolic syndrome.

*Nicotinic acid* preparations have a considerable hypolipidemic effect, they are similar to fibrates in their influence on the blood lipid composition but, when used for a long period, they may lower glucose tolerance, increase uric acid concentration in the blood plasma and intensify insulin resistance. Therefore, they are administered to patients with metabolic syndrome only in special cases in the dose of not more than 2 g/day with frequent control of the glucose concentration in the blood plasma.

*Bile acid sequestrants have* a quite moderate effect on the low density lipoprotein cholesterol concentration in the blood plasma and may cause the increase of the plasma triglyceride concentration. Therefore, they are used quite rarely, mainly, as a component of the combined therapy when it is necessary to lower additionally the low density lipoprotein cholesterol concentration in the blood plasma.

*Ezetimib (Ezetrol)* is a selective cholesterol absorption inhibitor. When used in combination with statins, it favors considerable decrease of the low density lipoprotein cholesterol concentration in the blood plasma.

One also should remember that the treatment with hypolipidemic drugs may lead to side effects. In particular, the typical side effects caused by statins include increased level of hepatic enzymes and myopathy; fibrate cause such side effects as myopathy, dyspepsia and concrement formation in the gallbladder; side effects of bile acid sequestrants include gastrointestinal disorders, constipation, disturbed absorption of other drugs; finally, nicotinic acid preparations cause reddening of the face and superior half of the body, dizziness, hot flush in the head, urticaria, unpleasant sensations of numbness, tingling, burning, formication, hyperglycemia, hyperuricemia and upper gastrointestinal disorders and hepatotoxicity (the latter is caused by some drugs).

### *Antihypertensive Therapy*

The treatment of arterial hypertension is referred to pathogenetic therapy because it may contribute to onset and progression of metabolic syndrome. One should prefer drugs, which have at least a neutral effect on the metabolic processes; it is even better if they will promote lowered insulin resistance, improved carbohydrate, lipid and purine metabolism parameters and also have organ protective properties (cardio-, nephro- and vasoprotection) with the beneficial influence on the endothelial function, throbocytic and vascular hemostasis, fibrinolysis and also the proven effect on cardiovascular endpoints. The combined therapy is should be used often with the effect on different pathogenesis components of arterial hypertension which are typical of metabolic syndrome.

Diuretic drugs are not the medicines of the first choice for normalization of the blood pressure in patients with metabolic syndrome. Nevertheless, they may be used in some cases in patients with this pathology because one of the basic mechanisms for development of arterial hypertension in patients with metabolic syndrome consists in hypervolemia resulting from increased sodium and water reabsorption in the proximal sections of renal tubules in persons with simultaneous hyperinsulinemia. One should have in mind the possible serious side effects caused by these drugs: hypokaliemia (it, in its turn, may lower the tissue sensitivity to insulin with compensatory hyperinsulinemia), disturbed carbohydrate, lipid and purine metabolism.

*Thiazide (Hypothiazide)* and thiazide-like *diuretics (Indapamid, Indapamid-retard)* are the most suitable for long-term therapy. Many multicenter prospective studies revealed more frequent development of diabetes mellitus and gout when arterial hypertension was treated with *thiazide* and *thiazide-like diuretics* (the study INSIGHT, etc.) as compared to the use of other groups of antihypertensive drugs. It should be mentioned that the described effects were dose-dependent. Therefore, when Hypothiazide is used regularly its dose should not exceed 25 mg/day and the advisable dose is 6.25–12.5 mg/day what lowers considerably the risk of adverse metabolic effects.

Indapamid combining the properties of diuretic and vasodilator influences the metabolic risk factors to a lesser extent what makes it a drug of choice in this drug group. The recommended dose is 1.25–2.5 mg/day (non-retard form) or 1.5 mg/day (retard form: Arifon-retard).

It is rational to combine low doses of thiazide diuretics with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers which neutralize some side effects caused by diuretics.

The use of *potassium-sparing diuretics* is restricted for patients with diabetes mellitus due to high risk of hyperkaliemia. At present there is no convincing data on any unfavorable metabolic action of potassium-sparing diuretics although their influence of the carbohydrate and lipid metabolism is studied insufficiently.

The use of *β-adrenoblockers* for correction of arterial hypertension in patients with metabolic syndrome is rational because of hypersympathicotonia observed in this condition. But when used in high doses, these drugs, especially those with nonselective action, may lower insulin secretion, cause hyperglycemia, prolong hypoglycemic conditions, mask hypoglycemia symptoms and also have an adverse effect on the lipid composition of the blood plasma. Therefore, one should prefer highly-selective β-adrenoblockers such as Bisoprolol, Betaxolol, Metoprolol succinate, Nebivolol, and Carvedilol, the efficiency and safety of which in patients with metabolic disorders and diabetes mellitus type 2 is proven. The latter two drugs, in addition to high $\beta_1$-selectivity have additional

advantages. Nebivolol influences nitrogen oxide production what results in lowered general peripheral vascular resistance and improved peripheral tissue sensitivity to insulin. In addition of block of $\beta_1$-adrenoreceptors, Carvedilol blocks also $\beta_2$- and α-adrenoreceptors. Such combination of effects in favorable in respect of metabolic disorders which are typical of metabolic syndrome. Thus, highly-selective β-adrenoblockers (Betaxolol, Bisoprolol, Nebivolol, etc.) should be used as a component of the combined therapy and high doses should not be administered in patients with metabolic syndrome.

Dihydropyridine *calcium channel antagonists* (Nifedipine (only retard form)) and non-dihydropyridine calcium channel antagonists (Verapamil, Diltiazem (also retard forms)) are effective and safe for correction of arterial hypertension in patients with metabolic syndrome. The lowered insulin resistance, absence of the negative effect on the carbohydrate, lipid and purine metabolism, vasoprotective and nephroprotective action (proven for non-hydropyridine drugs) and also the beneficial effect on the endothelium function are observed when these drugs are used.

*The angiotensin-converting enzyme inhibitors and angiotensin receptor blockers (angiotensin receptor antagonists*) are drugs of the first choice for the treatment of arterial hypertension in patients with metabolic syndrome. They have a pronounced hypotensive property, cytoprotective and organ protective action on the endothelium, kidneys, heart, brain, they are neutral for metabolism or even have a beneficial effect on it; they influence positively on the endothelium function, thrombocytic hemostasis and fibrinolysis. The angiotensin receptor blockers can lower the uric acid level (Losartan).

The use of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers favors the lowered number of new cases of diabetes mellitus type 2 in patients with arterial hypertension.

The treatment with Telmisartan (Micardis) in the dose of 80 mg/day administered to liquidators with metabolic syndrome and arterial hypertension (n = 34) resulted in considerable decrease of the blood pressure in 93 % of patients already after 1 month and the target BP values were reached in 65 % of patients. We revealed significant decrease of uric acid concentration in the blood plasma on average by 6.8 % [before treatment: $426.7 \pm 64.3$ μmol/l, after treatment: $397.6 \pm 72.7$ μmol/l, $p < 0.05$]. Thus, taking into account its hypouricemic effect, metabolic neutrality and pronounced hypotensive effect, Telmisartan may be used for the treatment in patients with arterial hypertension and metabolic syndrome in combination with moderate hyperuricemia.

Another drug, which is the first direct renin inhibitor, *Aliskiren (Rasilez)* deserves attention. This drug lowers the blood pressure effectively, it is well tolerated by patients, it does not exert any unfavorable influence on lipid and carbohydrate metabolism and has an organ protective property. At present large-scale clinical trials (ALTITUDE, ASPIRE HIGHER) are in progress in order to study the effects of Aliskiren on the outcomes of cardiovascular diseases. Aliskiren is used both as the monotherapy and in combination with other antihypertensive drugs.

The treatment with Aliskiren (Rasilez) in the dose of 300 mg/day in liquidators with metabolic syndrome and arterial hypertension for 1 month favors considerable decrease of the blood pressure in 80 % of cases; in this situation the target blood pressure values were reached in 54 % of cases. Besides that, the use of Aliskiren in this patient category promotes additionally significant lowering

of plasma concentration of triglycerides ($p < 0.05$), VLDl-cholesterol ($p < 0.05$) and uric acid ($p < 0.01$).

As concerns the drugs with central action, only *$I_1$-imidazoline receptor agonists* are used mainly at present. They have a moderate hypotensive effect, are tolerated rather well, they exert a beneficial influence on the tissue sensitivity to insulin and carbohydrate metabolism due to lowered central sympathetic pulse rate, decrease the activity of the renin-angiotensin-aldosterone system, promote reduction of the body weight and have a pronounced cardioprotective property. The long-term effects of the risks of serious cardiovascular complications are to be investigated yet, therefore, it is the most advisable to use them as a component of the combined therapy in patients with metabolic syndrome.

In addition to a considerable hypotensive effect, *α-adrenoblockers* have several metabolic advantages which are of importance in patients with metabolic syndrome: they increase the tissue sensitivity to insulin, thereby improving the carbohydrate and lipid metabolism, have a beneficial effect on hemostasis and endothelial function. Besides that, they suppress effectively signs of prostatism. But these drugs may cause intensified sympathetic heart stimulation, postural hypotension and favor the development of heart failure. Therefore, these drugs should be used with caution, it is better to combine them with β-adrenoblockers.

### *The Combined Antihypertensive Therapy in Patients with Metabolic Syndrome*

The combined antihypertensive therapy is used if the monotherapy of arterial hypertension is ineffective in patients with metabolic syndrome, especially in presence of arterial hypertension of degree II-III and also diabetes mellitus type 2. The combination of angiotensin-converting enzyme or angiotensin receptor antagonists with calcium channel antagonists is the most rational for patients with metabolic syndrome and diabetes mellitus type 2 because this combination exerts the most beneficial effect on the carbohydrate and lipid metabolism in this patient category. The combination of a β-adrenoblocker and thiazide-like diuretic should be avoided because both these drugs have an unfavorable effect of the metabolism of these substances.

### *Antiaggregant Therapy*

Patients with metabolic syndrome are characterized by the lowered activity of the fibrinolytic system resulting from increased concentration and activity of the tissue plasminogen-I activator inhibitor what increases considerably their risk of thombotic complications. Therefore, Aspirin in the dose of 75–100 mg/day should be administered for primary prophylaxis in patients with moderately high risk and for treatment in patients with the high and very high risk. If patients with high and very high risk have contraindications to Aspirin, Clopidogrel may be administered.

The morbidity with metabolic syndrome acquires the nature of epidemic which does not leave aside also liquidators of accident aftermath at ChNPP. Only timely (early) diagnostics of metabolic syndrome and reaching the target levels of its main parameters may prevent the risk of cardiovascular complications and diabetes mellitus.

## *The problem of Cardiovascular Calcinosis*

The calcification process, i. e. deposition of calcium salts in the vascular walls or cardiac structures, was considered for a long time mainly as a result of passive involution changes and described from this viewpoint for the first time by I. Menkenberg in 1904. Lately the concepts concerning the nature of cardiovascular calcification process changed considerably.

According to WHO, the number of persons aged above 65 years in the world will be 690 mln people and the mortality from on-infectious diseases (first of all, cardiovascular diseases) will reach 49.7 mln cases annually by 2020. In Russia the percentage of elderly people in the population exceeds 20 %, therefore, diseases developing at elderly age arouse special interest in clinicians (The Second World Assembly on Ageing Problems, 2002). Nevertheless, in spite of the fact that calcification is revealed the most often in senior age groups, the influence of the risk factors predetermines significantly the onset and progression of the process at earlier age. The risk factors for early calcification of the coronary arteries are similar to those for development of atherosclerosis and include arterial hypertension, increased body mass index and low HDL level (Mahoney, L. T. et al., 1996). The risk of coronary calcinosis is significantly increased by presence of concomitant diseases such as diabetes mellitus and the terminal stage of chronic renal failure leads to marked calcium accumulation in the arteries due to considerable deviations in the calcium and phosphorus homeostasis. Recently a close correlation was shown between atherosclerosis of the aorta and coronary arteries, arterial and cardiac valvular calcinosis and osteoporosis. The analysis of the rate of lower extremity amputation, mortality and prevalence of coronary complications confirms that arterial calcinosis is a powerful predictor of these complications and significance of calcification is preserved even after correction of the traditional risk factors. For example, when coronary artery calcinosis is revealed by electron beam CT or multi-slice spiral CT, the risk of severe coronary complications increases 5–7 times and is preserved irrespective of the age. Femoral artery calcinosis causes nearly threefold increase of the risk of amputation. The data obtained recently suggests that coronary complications and involvement of the target organs are associated with lowered arterial elasticity rather than with occlusions (Lehto, S. et al., 1996; Iribarren, C. et al., 2000; Leoncini, G. et al., 2006).

According to ARCERM (2008–2009), absolute absence of coronary artery calcinosis was revealed only in 13.4 % of liquidators with cardiovascular pathology while 86.6 % of patients had coronary artery calcinosis of different degree. It should be mentioned that coronary artery calcinosis was combined with calcification in other arterial systems (involvement of the aortic arch branches and calcinosis of the abdominal aorta and iliac arteries) in 25 % of cases.

### *Pathogensis*

It becomes evident that calcification is an actively regulated process associated partially with atherosclerosis and its risk factors (Jeziorska, M. et al., 1998; Raggi, P. et al., 2000).

A complex of humoral and cellular components is the main pathogenetic mechanism for development of arterial calcinosis. It is considered that disturbed balance between the factors, which are responsible for calcification stimulation and inhibition, underlies the development of calcinosis.

The expression of several collagen and non-collagen matrix proteins such as osteocalcin, bone syaloprotein, osteopontin, osteonectin, type I collagen, alkaline phosphatase, bone morphogenetic protein-2, Msx-2, Cbfa-1, matrix Gla-protein, osteoprotegerin and others being the position calcinosis regulators is shown in the human atherosclerotic plaques at present.

The calcinosis process itself develops due to deposition of calcium hydroxyapatiie crystals by osteoblast-like cells the appearance of which in the vascular wall is a known and proven fact today.

The arterial calcinosis process is stimulated by the factors causing osteogenesis and transformation of the vascular wall cells, especially media smooth muscle cells (SMC) to osteoblasts. They include such factors as bone morphogenetic proteins (BMP): BM2, BMP4. Proteins BMP2 and BMP4 are involved in the mineralization process and local induction of inflammation and, on the contrary, BMP7 inhibits the process of calcium deposition in the vessels (Johnson R. C., Jane A., 2006).

Several cells within the vascular wall may be differentiated to osteoblast-like cells. The media smooth muscle cells may express osteoblastic phenotype under the influence of the bone morphogenetic proteins BMP2 (synthesized by endothelial cells exposed to hypoxia, oxidative stress, turbulent blood flow, high pressure and inflammation) and BMP4 (synthesized by foam cells after their stimulation by oxidized low density lipoproteins). The same process takes place when phosphate level is lowered, and this causes the transition of smooth muscle cells to osteoblastic phenotype. These osteoblast-like cells are characterized by increased production of transcription factors and also intensified synthesis of alkaline phosphatase.

A significant role in genesis of calcinosis is played by the phosphate content in the blood and activity of the parathyroid hormone secretion and also long use by a patient of such drugs as Warfarin or corticosteroids.

The alkaline phosphatase activity is one of humoral markers of calcification (Whyte M. P., 1994). Bone alkaline phosphatase (AP) is a functional phenotypic marker of osteoblasts and is often used as a molecular marker of vascular calcification. It is considered that AP destroys calcification inhibitors and hydrolyses phosphoric esters with formation of free phosphates which are required for bone tissue mineralization. Evidently, mineral structures are deposited in the vascular wall in a similar way under the influence of AP. The experiments showed that classical activators of atherocalcinosis, i. e. morphogenetic protein BMP2 and oxidized LDL increased the activity of AP in the culture of vascular smooth muscle cells (VSMC). This results in lowered inorganic pyrophosphate level which is used as a substrate for AP and a powerful inhibitor of vascular calcification.

Importance is attached also to the influence of such factors and oxidative stress, apoptosis and neoangiogenesis.

There exist also substantiated suppositions on the possible involvement of infectious agents such as Chlamydia pneumoniae in calcification of the peripheral arteries and cardiac *valves.* Chlamydia persistence is revealed in the cartilage, bone tissue and ectopic calcinosis foci. As some researchers suppose, immune inflammation, fibrosis and calcification play the role of a protective, restricting reaction in the point of penetration of a pathogen, in particular chlamydia (Glader, C. A. et al., 2003).

The data on analysis of immunoglobulins of class G against *Chlamydia pneumoniae* obtained at ARCERM is evidence of the fact that antibodies of this class are present in 48.5 % of liquidators with atherocalcinosis.

The inhibiting effect of calcinosis is confidently known for:

**- inorganic phosphate** (Rutsch, F. et al., 2003);

- **matric GLa protein (MGP)** (Jono, S. et al., 2004), the powerful vascular calcification inhibitor synthesized by chondrocytes and media smooth muscle cells. The role of MGP in calcification is complex. MGP modulates both cell differentiation and calcification due to mechanisms which are not fully understood. It was shown that MGP could suppress directly calcium crystal formation. It was demonstrated recently that MGP inhibited smooth muscle cell differentiation in the osteogenic path due to binding a powerful factor of osteogenic and chondrogenic differentiation, BMP2, thereby preventing its interaction with receptors. The effect of MGP on BMP2 is associated with the degree of vitamin K-dependent γ-carboxylation of MGP. The risk of intensified calcification is determined not by the MGP quantity but by its insufficient functional activity due to disturbed γ-carboxylation. Thus, MGP, the vitamin K-dependent protein, is a powerful arterial calcification inhibitor in vivo. The low circulating MGP level and disturbed γ-carboxylation in sites of its tissue expression are associated with the onset and progression of the cardiovascular pathology;

- **osteopontin (OPN)** which is adhesion phosphorylated glycoprotein expressed by some cell types. It is one of the main non-collagen proteins of bone matrix in the bone tissue and is synthesized by osteoblasts, osteocytes and osteoclasts. OPN is involved in the bone homeostasis both inhibiting mineral deposition and stimulating osteoclast differentiation and intensifying their activity. The presence of repetitions with many electronegative residues of glutamic and aspartic acids and also the calcium-binding site allow OPN to bind strongly with hydroxyapatite. Besides that, OPN protects cells against apoptosis. Histologic investigations showed that the highest OPN concentration was observed in the regions where calcified atherosclerotic plaques were formed. OPN is expressed by macrophages, media smooth muscle cells and endotheliocytes in the zone of a plaque. It was shown recently that the OPN level in the blood plasma was considerably higher in patients with coronary disease irrespective of traditional risk factors and depended on the condition severity (Steitz, S. A. et al., 2002);

- **osteoprotegerin (OPG)** which is referred to the family of TNF-α receptors and is an indirect osteoclastogenesis inhibitor. It was shown that OPG expressed in the smooth muscle cell culture of the coronary artery media. OPG expression is revealed in the endothelial cells lining vascular walls in early atherosclerotic lesions at the stage of fatty streaks. OPG was expressed in intima cells in the marginal plaque zones at the fibroatheroma stage and in fibrocalcified plaques on the border of bone structures and in inflammation cells. The OPG presence on the border of bone structures proves its function of bone resorption inhibitor. The results of the first clinical trial of OPG confirmed its ability to act as a therapeutic agent slowing down osteoporosis (Hofbauer, L. C. et al., 2001);

- **fetuin** which is also known as $\alpha_2$-Heremans-Schmid glycoprotein, Ahsg in contrast to OPN, OPG and MGP functioning within the vascular wall. Fetuin is a circulating calcification inhibitor. In experiments in vitro fetuin suppresses hydroxyapatite crystal formation de novo not influencing

already formed crystals. The experimental data confirms the important role of fetuin in calcification; so mice with deficit of this protein develop extensive soft tissue calcification in the myocardium, kidneys, tongue and skin (Ketteler, M., 2005).

**BMP7** prevents transition of SMC to osteoblast phenotype by intensification of smooth muscle α-actin expression. Proteins p21, Smad 6, and Smad 7 are involved in this process. The experimental studies with vascular atherocalcification modeling found that adding MP7 to the cell culture prevented progression of vascular calcification. This effect correlated with lowered osteocalcin expression of atheromathous plaques and vascular wall (Davies, M. R., Hruska, K. A., 2003).

### *Morphologic Forms of Calcinosis in the Cardiovascular System*

*Atherocalcinosis.* Calcinosis of arteries affected by atherosclerosis in the most common form of cardiovascular calcinosis. Calcification develops often in those zones of atherosclerotic plaques where there is combination of cell necrosis, inflammation and cholesterol deposition. After their oxidation, low density lipoproteins (LDL) stimulate migration of T-lymphocytes and macrophages to the affected zone. Atherosclerotic calcinosis develops through a process which is similar to endochondral ossification, chondrogenesis (cartilage metaplasia in this case), it is preceded by osteoblast induction and splenial osteogenesis.

*Calcinosis of arterial media*. In contrast to atherosclerotic calcinosis, calcinosis of arterial middle coat (also known as Mönckeberg sclerosis) develops as a process which is similar to intramembrane osteogenesis potentiated by matrix bubbles without intermediate cartilage formation. This variant is common in patients with diabetes mellitus, chronic renal failure and at senile age (Davies M. R., Hruska K. A., 2003).

*Uremic calcifilaxia.* In contrast to other types of vascular calcinosis, vascular uremic calcifilaxia or calcifying uremic arteriolopathy, is a systemic process characterized by diffuse calcinosis of the arteries of small and middle caliber and arterioles with proliferation of their intima layers and resulting in tissue necrosis. This variant is observed, in particular in patients with extensive subcutaneous soft tissue calcinosis, which develops when the physiologic threshold of calcium phosphate solubility (60 $mg^2/dL^2$) is exceeded and does not depend on active osteogenic processes. This is a rare complication of chronic renal failure and secondary hyperparathyroidism, diabetes mellitus, obesity and hypercoagulation conditions (Mathur R. V. et al., 2001). It is often preceded by the therapy with Warfarin or significant body weight loss and also the use of immunodepressants.

*Cardiac valvular calcinosis.* Cardiac valvular calcinosis is a process which is similar to both atherosclerotic calcinosis and calcification of arterial middle coat. Elements of bone metaplasia, foci of mature spongy bone tissue and endochondral ossification are revealed in affected cusps in patients with aortic valve calcinosis (Mazzone, A. et al., 2004).

### *Diagnostics of Calcinosis*

The basic methods for diagnostics of vascular calcinosis are aimed, first of all, at revealing zones of calcified vessels in the organism and subdivided in invasive and noninvasive ones and they are also characterized by different sensitivity and specificity.

*Roentgenography and roentgenoscopy* make it possible to reveal regions of marked calcinosis and roentgenoscopy may also be used for detecting foci of moderate and extensive calcinosis. It is impossible to reveal minimum calcification signs using these methods. They are also characterized by low sensitivity as compared to modern radiation diagnostic methods (electron beam computed tomography) (about 52 %) although their specificity is sufficiently high (Agatston, A. S. et al., 1990).

*Transthoracic echocardiography* is an excellent tool for revealing cardiac valvular calcinosis. Unfortunately, this method is used vary rarely for visualization of the coronary arteries and does not allow quantification of calcinosis (Wexler, L. et al., 1996).

When performing the *intravascular ultrasound investigation* (IVUS) it is possible to reveal vascular calcinosis in the form of hyperechogenic regions within the vascular wall (including also atherosclerotic plaques, intima, media and adventitia) although hyperdiagnostics is also possible because of hyperechogenicity of compact fibrous plaques. This method has excellent sensitivity and sensitivity (90 and 100 %, respectively) when identifying, e. g., coronary calcinosos (Friedrich G. J. et al., 1994; Escolar E. et al., 2006). In spite of the fact that IVUS is an extraordinarily sensitive and specific method for revealing vascular calcinosis, it is invasive and provides semi-quantitative results allowing to visualize vessels of a certain caliber and only a restricted part of the coronary system. Besides that, the use of this method is associated with increased risk of arterial dissection in the zones of calcified atherosclerotic plaques and it is more valuable for detecting zones of extensive calcinosis. The invasiveness of this method means its restricted use as a screening diagnostic method.

*Electron beam computed tomography* (EBCT) is a noninvasive and effective method for investigation of the vascular, and especially coronary system. EBCT allows to obtain the unique information about presence of coronary artery calcinosis, i. e. the so-called calcium score (CS) reflecting the degree of coronary artery calcinosis. This score is closely associated with the severity of coronary atherosclerosis and degree of coronary artery occlusion (Rumberger, J. A. et al., 1995).

Lately clinics began to actively acquire apparatuses *for multi-slice spiral computed tomography* (MSCT). Therefore, the procedure for estimation of CS was adapted for MSCT devices which are now produced extensively. This noninvasive test is simple and not unpleasant for a patient and can reveal confidently the possible development of CHD irrespective of presence of traditional risk factors. This is of special importance for patients without clinical symptoms and persons whose profession is associated with increased responsibility (pilots of aircraft, engine drivers, drivers of public transport, etc.). According to data obtained at ARCERM (2008–2009), patients underwent multi-slice spiral computed tomography (MSCT) of the thorax with assessment of calcinosis using the program CALCIUM SCORING with estimation of calcium score as per Agatston's method and assessment of the degree of the coronary artery involvement and coronary risk. Then CS was less than 10, the coronary risk was considered low, CS values from 10 to 100 indicated moderate risk and if CS ranged from 100 to 400 and exceeded 400 the coronary risk and coronary artery calcinosis was assessed as high and extremely high, respectively. 11.9 % of patients had low coronary risk and 20.9 % had moderate coronary risk among liquidators investigated at the department of cardiology at ARCERM. The high and extremely high coronary risk was revealed in 31.3 and 22.4 % of patients, respectively. It was found also that the high and extremely high

coronary risk was characterized by clinical symptoms of coronary atherosclerosis in the form of exertional angina pectoris of functional class II in 59 % of patients and angina pectoris of functional class III in 7 % of patients.

### *Principles for Prevention and Treatment of Vascular Calcification*

The prevention and therapeutic treatment of calcinosis will be the most effective at its early stages and especially in case of presence and early detection of risk factors if calcification. The basic principles for prophylaxis and therapy are aimed at pathogenetic components of calcinosis process and calcium homeostasis, lipid metabolism and organism immune reactivity and consist in prevention of endothelial dysfunction, preclusion of inflammatory reaction cascade activation, reduction of lipid infiltration, prevention of angiotensin-mediated effects and slowing down the progression of ectopic calcification and osteoporosis.

According to the latest data, the most effective therapeutic strategy for patients with calcification is to use several pathogenetically active drug classes: ACE inhibitors, calcium channel blockers and HMG-CoA-reductase inhibitors (statins) and drugs correcting phosphorus and calcium metabolism.

The administration of ACE inhibitors favors the improved left ventricular systolic and diastolic function, lowered left ventricular myocardium mass, reduced inflammatory infiltration and slowed LDL accumulation in the cardiac valves (O'Brien, K. D. et al., 2002).

Lately several pleiotropic effects were revealed in statins in addition to direct hypolipidemic action; they may be used to influence the calcification process. These effects include anti-inflammatory effects: statins lower the C-reactive protein level in the serum irrespective of the LDL level decrease. Besides that, the studies in vitro demonstrated that statins reduced the pro-inflammatory cytokine secretion by endothelial cells and macrophages. The recent studies allowed to suppose the significance of another alternative mechanism of action of statins regarding the decrease and restriction of the calcinosis process, namely apoptosis inhibition.

Many experts recommend the therapy with statins when cardiac valvular calcinosis is combined with coronary artery atherosclerosis or hypercholesterolemia (Rajamannan, N. M., Otto, C. M., 2004; Quinn, D. W., Spinler, S. A., 2005).

As concerns calcium channel blockers, large-scale studies to assess progression of vascular calcinosis were performed using a drug OSMO-Adalat (studies INSIGHT and ENCOR). The development of this process over a period of 3 years was assessed in patients with initially pronounced coronary artery calcinosis in a special fragment of the study INSIGHT using multi-slice spiral computed tomography. It was found that the treatment with OSMO-Adalat prevented progression of arterial calcinosis (Motro M., Shemesh J., 2001).

Besides that, the results of the studies suggest the efficiency of the drugs aimed at improvement of calcium absorption and restriction of phosphate entrance with food (calcium preparations and/or their combination with vitamin D) and slowing down the bone resorption (bisphosphonates) for prevention of mineral metabolism disturbances and progression of calcification. In addition to restricted phosphate entrance with food, as a rule, patients receive different drugs binding phosphates in the intestines, thereby preventing their absorption. Such substances include: aluminum salts, calcium salts (alginate, acetate, carbonate, citrate), magnesium

carbonate and hydroxide and also Sevelamer (Rena-Gel) which is a new drug binding phosphate and not containing calcium and aluminum. The randomized studies found that Sevelamer slowed down progression of coronary arteries and aortic calcinosis in patients receiving programmed hemodialysis (Terai, K. et al., 2009).

Thus, we may conclude that cardiovascular calcinosis is a complex, regulated process, which is an independent predictor of cardiovascular complications and common in the group of liquidators of accident aftermath at ChNPP. It is a multifactor process controlled by many closely associated activators and inhibitors; this process includes inflammatory cells localized in the arterial wall and also infectious agents. Modern diagnostic methods allow to reveal calcinosis early and reliably and to quantify it. The problem of calcinosis still remains urgent and requires further studies to investigate more precisely the molecular mechanisms leading to calcinosis and development of therapeutic methods basing on knowledge of these mechanisms for prevention of its onset and progression.

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### 5.2.2. Diseases of Arterial Pressure Regulation: Essential Hypertension, Hypotensive Conditions

Arterial hypertension is heterogeneous and multiform. Sometimes it may be a consequence and symptom of certain diseases (symptomatic hypertension) but it is significantly more often an independent primary disease (essential hypertension or primary hypertension) which is rooted, as a rule, in numerous risk factors (genetic and acquired ones). Arterial hypertension (it is more and more often called so, not defining its causes concretely), in its turn, has a pathogenic effect playing a double destructive role. On the one hand, it causes gradually chronic damages of target organs

(myocardial hypertrophy, hypertonic arteriopathy, hypertensive nephropathy, hypertensive encephalopathy, etc.), on the other hand, it "bursts" targets suddenly (causing directly or indirectly myocardial infarction, cerebral stroke, aortic dissection, etc.). Both the complexity of the causes and hazards of arterial hypertension deserve special consideration.

***Essential hypertension*** is a frequent diseases caused by a combination of several genetic and acquired causes the basic manifestation of which is arterial hypertension. Because of its prevalence and morbidity, essential hypertension is a main risk factor of cardiovascular complications and death in the population of our country and, in particular, in is subpopulation, i. e. in liquidators of the accident at the Chernobyl NPP. At the same time essential hypertension is a correctable (modifiable) risk factor. the effective treatment of this diseases allows to reduce the development of severe complications and mortality.

According to the data of the investigation performed within the limits of the targeted Federal Program "Prevention and treatment of arterial hypertension in the Russian Federation," the prevalence of essential hypertension in adult citizens of our country is 40 % (Shalnova, S. A. et al., 004). At present essential hypertension is registered in 35 % of cases in liquidators of the accident at the Chernobyl NPP (according to the data of the North-Western Regional Center of the National Radiation Epidemiologic Register) (Aleksanin, S. S. et al., 2010). At first sight, this value is only somewhat lower. But if we take into account that the mean age in the liquidator subpopulation exceeds considerably that in the whole population, we should make a conclusion that the disease is revealed not in all liquidators. The awareness of patients with arterial hypertension about their disease grew up to 77.9 % recently in Russia (Shalnova, S. A. et al., 2004). At the same time, in approximates to 100 % in liquidators hospitalized to the clinic of ARCERM. Sixty percent of patients with arterial hypertension in the general population take antihypertensive drugs, the treatment is effective in 22 % of patients out of them (Shalnova, S. A. et al., 2004); these parameters are 75 and 60 %, respectively, in patients of our clinic. One can make a conclusion that the patient group with yet not recognized essential hypertension is the most urgent from viewpoint of the active preventive intervention.

### *Causes for arterial hypertension.*

It is necessary to distinguish the origin of secondary arterial hypertension and primary disease (essential hypertension). Symptomatic forms account for 3–5 % in the total number of patients with arterial hypertension. They are caused by infrequent diseases of those organs which are involved in maintenance of the normal arterial pressure, i. e. kidneys, endocrine organs, central nervous system, heart, and major arteries (aorta). Nevertheless, serious importance should be attached to purposeful search for these "causative" diseases because they often have a malignant course and at the same time they may be radically eliminated together with hypertension. Iatrogenic hypertension is also referred to symptomatic hypertension.

*Diseases causing symptomatic hypertension syndrome:*

- nephrogenic hypertension,
- endocrine hypertension,
- "hemodynamic" hypertension,

- neurogenic hypertension, and
- iatrogenic hypertension.

Nephrogenic symptomatic hypertension is observed the most often. Its forms are so numerous and various that they are to be classified. Three groups of nephrogenic arterial hypertension are distinguished: prerenal (caused by obstruction of the arteries supplying the kidneys), renal (caused by diseases of their parenchyma) and postrenal (consequences of the pathology of the urinary tracts) hypertension.

***Endocrine arterial hypertension*** is not very rare and is caused by diseases associated with hyperproduction of hormones having a hypertensive effect. The hormone-active lesions of the adrenal glands are the most significant: hypertension may be caused by pheochromocytoma (chromaffin tissue tumor in the adrenal medulla), aldosteroma (aldosterone-producing tumor in the adrenal cortex) and also corticosteroma (glucocorticoid-secreting tumors in the adrenal cortex), Cushing's hypophyseal disease. Other endocrinopathies may be also complicated with hypertension.

**"Hemodynamic" hypertension is caused** by certain diseases of the heart, major arteries or the blood flowing in them, which influence directly the main hemodynamic parameters predetermining the blood pressure level (Table 5.22).

Table 5.22

The Diseases Causing "Hemodynamic" Hypertension and its Pathogenetic Mechanisms

| Causative diseases | Leading pathogenetic mechanisms |
|---|---|
| Aortic atherosclerosis, aortic hypoplasia, aortic coarctation, aortitis | Lowered aortic elasticity, baroreflex sensitivity, renovascular mechanism |
| Aortic valve insufficiency, patent ductus arteriosus, bradycardia (atrioventricular blocks) | Increased stroke volume and general peripheral resistance |
| Polycythemia | Increased blood viscosity, general peripheral resistance and circulating blood volume |

***Neurogenic arterial hypertension*** includes traumatic brain injuries (including those in a long-term period), tumors and other intracranial mass lesions, some psychic disorders, in particular panic attacks.

***Iatrogenic hypertension*** is usually caused by drugs, namely, adreno- and sympathomimetic agents (including drops against rhinitis), peroral contraceptives, steroidal and non-steroidal anti-inflammatory drugs, some drugs lowering the appetite.

### *Causes of essential hypertension*.

Etiology of the disease under consideration is complex. This concerns not only the enormous number of illnesses but also to specific cases of this disease.

*Genetic predisposition* to essential hypertension is observed in most patients. But this is associated not with any specific gene but with different combinations of multiple gene anomalies which are responsible for blood pressure regulation; each of these genes makes only a facultative (depending, particularly, on the environment and person's life style) and insignificant contribution to the

development of this disease (polygenic type of recessive inheritance). At present the molecular genetic analysis in patients with essential hypertension does not provide a significant benefit for the clinical practice. Nevertheless, it is important from clinical viewpoint that presence of arterial hypertension at least in one parent means the increased risk of the disease for the descendants and it is most likely that this disease will manifest relatively early. Elementary medical knowledge, prophylactic skills (which, in particular, should be disseminated by "schools of health"), habits of healthy nutrition, physical culture and sports, keeping the medical archives should be especially important for maintaining the health of members in such families. A tonometer and medical balance should be available in their house.

*The condition of the nervous system and higher nervous* activity is of importance for origination of essential hypertension. The neurogenic theory of the disease in its classical form was formulated by Lang, G. F. in the middle of the last century (Lang, G. F., 1948). It contains three basic postulates:

- concept of single psychogenic etiology of the disease: "psychogenic overstress with negative emotions and psychogenic traumatization are an initiating factor of essential hypertension and factor determining its further development in the first period"; and constitutional predisposition is a precondition for development of the disease (the concepts "genetics," "genetic" was anathematized in Lang's time);

- description of the onset and mechanisms of the pressor effect: "...we may consider that disturbance in the function of the system regulating the blood pressure, which underlies essential hypertension, occurs, first of all, in the cortex of the cerebral hemispheres and then in the hypothalamic centers and consists in the condition of their increased excitability";

- indication to the direct cause of increased BP: "the arteriole muscles contract at the neurogenic stage of the disease, first of all, by means of transmission of pulses to the arteriole muscles by the sympathetic vasoconstrictor nerves..."

On the whole, validity of this theory does not raise doubts after decades and it was confirmed by the extensive experimental and clinical data (Shlyakhto, E. V. et al., 2008), except one principle. The categorical statement on the unity of psychogenic etiology did not pass the test. It is clear today that psychologic traumatic events, psychosocial stress belong to risk factors but they are neither only one nor obligate cause for hypertension. At the same time, undoubtedly, they played a quire significant role just in liquidators of the accident at ChNPP. The rapid changes in the morbidity with essential hypertension observed after participation in liquidation of the Chernobyl accident aftermath in 1986–1988 and the high rate of clinically evident psychogenic disorders in liquidators (mainly, anxiety-depressive disorders) are the most important arguments confirming this.

There are several clinical forms of arterial hypertension, in which neurogenic mechanisms play an especially important role: arterial hypertension associated with panic attacks and also sleep apnea syndrome, "white-coat" syndrome (syndrome developing when a patient sees a white coat). White-coat syndrome is observed in patients, who are predisposed to emotional reaction, at the moment of their examination (measurement of blood pressure) by a health care professional (e. g., a physician) and is manifested in the significant deviation of the blood pressure at this moment (usually its increase up to hypertension level but sometimes its decrease (masked hypertension or hypotension)). In spite of its transient nature, hypertensive white-coat syndrome cannot be

considered a completely benign phenomenon (Khirmanov, V. N., 2000) because it is associated with involvement of the target organs. This phenomenon may distort the assessment of the blood pressure level, cause diagnostic errors and provoke incorrect treatment. It is observed in relatively healthy individuals, in patients with essential hypertension (approximately in 20 % of cases at the initial stages of this disease) and also in patients with a predisposition to hypotension. There several possibilities to verify this syndrome. The simplest method is to compare the results of pressure measurements performed by a patient many times at home and at repeated visits to the health care facility. The data analysis of the blood pressure monitoring is also useful (Khirmanov, V. N., 2000).

The enormous body of scientific arguments is evidence of the fundamental role played by the sympathetic nervous system hyperactivity in the onset and progression of arterial hypertension (Shlyakhto, E. V. et al., 2008). At the same time, this phenomenon is one of the components in the complex mechanism of blood pressure neurohumoral regulation (the system including renin, angiotensin and aldosterone, natriuretic hormones, prostaglandins, kinins, etc.). In addition to sympathoadrenal hyperactivity, a well-studied phenomenon of the renin-angiotensin-aldosterone activation is very important today for the clinical practice. The fundamental concepts of this phenomenon underlie the modern treatment of arterial hypertension using the agents inhibiting the sympathetic nervous system activity (β- and α-adrenoblockers, sympatholytic drugs with central mechanism of action) and also the renin-angiotensin-aldosterone system (ACE inhibitors, angiotensin receptor blockers, aldosterone synthesis and action blockers).

*Arterial hypertension and life style*. By now, in addition to chronic psychosocial stress, the unfavorable influence of other several life style factors was demonstrated: low physical activity, abuse of alcohol, overnutrition. Several large-scale studies and their subsequent meta-analysis found that the sedentary life style increased the risk of hypertension and regular dynamical physical trainings under aerobic conditions provided for a marked although moderate hypotensive effect (Cornelissen, V. A., Fagard, R. H., 2005a, 2005b; Fagard, R. H., 2006). It is important to emphasize that this preventive and therapeutic effect is mediated by the lowered activity of the sympathetic nervous system, renin-angiotensin system, improved autoregulatory endothelium function and also by the reduced body weight. Besides the low physical activities, obesity is associated also with the excessive caloric value of food, preference for meat and fatty food over the vegetarian nutrition style. Each of the above circumstances tells upon blood pressure increase, which is especially marked in elderly people. It should be mentioned that these features of the life style are associated directly with the onset and progression of so-called cardiovascular metabolic syndrome.

*Essential hypertension and the kidneys.* A certain (quite normal) blood pressure level and blood supply to the kidneys correspond to any (normal) quantity of sodium entering the organism with food in the normal condition. The increased entrance of salt (sodium) is accompanied by liquid accumulation in the organism and results in transient increase of the blood pressure, intensified renal blood supply and enhanced sodium excretion. This, in its turn, leads to blood pressure normalization by the feedback mechanism. Thus, the kidneys play the role of a barostat, i. e. the organ involved in maintenance of the blood pressure. The disturbance of this regulatory association is always present in patients with arterial hypertension, i. e. sodium balance can be maintained provided that the blood pressure is increased. The

initial renal dysfunction is absolutely necessary for onset of arterial hypertension, its stabilization and progression.

The nature of primary renal dysfunction consists in lowered kidney weight and number of their functional subunits, i. e. nephrons, decreased renal functional reserve by the time of birth of a human (because of prenatal development defects). This congenital phenomenon is called oligonephopathy and it is the risk factor of essential hypertension (Mackenzie, H.S. et al., 1996; Baum, M., 2010). At the same time, a concept of chronic kidney disease as a multi-factor pathologic process, which is quite common in the population, was formed lately (Levey, A. S. et al., 2003). A considerable role in its formation is played also by many acquired risk factors which are nearly identical to those causing the typical atherosclerotic changes in the cardiovascular system. Arterial hypertension, smoking, obesity, dyslipidemia, diabetes mellitus, hyperhomocysteinemia favor chronic kidney disease, i. e. gradual failure (atrophy) of nephrons. Besides this, renal tissue damage, alcoholization, administration of some (nephrotoxic) drugs and also nephron atrophy associated with biological ageing are significant. The age plays a considerable role as the exposure duration to any damaging risk factors is of importance. The everyday clinical practice is evidence of the fact that the above factors co-exist quite often. None of the patients of the cardiological department at ARCERM out of liquidators of the accident had less than three risk factors over the last 5 years.

Renal damages are not only a cause of nephrogenic hypertension but also essential hypertension and it, in its turn, aggravated the renal damage. Their morphologic analysis shows that all patients with essential hypertension have some or other vascular changes starting from signs of vasospasm in practically normal arterioles to their pronounced hyalinosis and intima fibrosis. Arterial hypertension favors renal major artery atherosclerosis what may be complicated with ischemia and renal atheroembolic infarctions. Ischemia causes damage of glomerular capillaries, hyalinosis and shrinkage. The preserved glomeruli are hypertrophied compensatorily, hypertension, hyperfiltration develop in them. This is accompanied, in its turn, at first by microalbuminuria (this is a relatively early sign of renal damage), then by proteinuria. Nephrosclerosis is formed. The damage, i. e. chronic kidney disease, is progressing steadily irrespective of its prime cause under conditions of hypertension.

*"Mosaic" conception of arterial hypertension genesis*. It became evident lately that many factors influencing the regulation, function and structure of the heart and vessels were involved in origination of steadily increased blood pressure (including also essential hypertension). This fact was noticed and clearly characterized for the first time by I. H. Page more than 40 years ago (Page, I. H., 1967). According to this scientist's conception which is of interest also today, hypertension compensates the trend to tissue hypoperfusion and depends on the effect exerted by a combination of factors: disturbed stroke volume, artery reactivity, their elasticity and size of their lumen, blood viscosity, circulating blood volume, influence of nervous factors and chemical blood composition (Fig. 5.3).

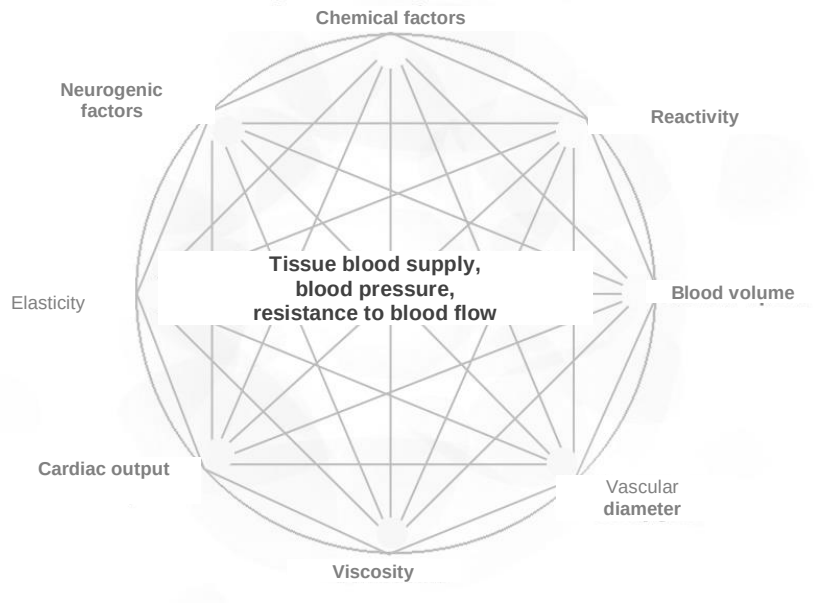



Fig. 5.3. Schematic Mosaic of Factors
Involved in Pathogenesis of Arterial Hypertension

The practical significance of the considered theory for modern physicians consists in the fact that one should understand the pathogenesis of essential hypertension as a complex and recognize in details the totality of risk factors and their targets, the influence on which may result either in progression of hypertension or in its correction.

***Consequences of arterial hypertension, i. e. target organ involvement in patients with hypertension.*** The complications associated with arterial hypertension seem not less complex than their causes. When analyzing them, one should emphasize, first of all, that although the nature and severity of target organ involvement in patients with arterial hypertension depend on hypertension degree and duration but they are also predetermined by the common pathogenetic mechanisms of affection of the cardiovascular system on the whole, separate vascular systems and by arterial hypertension itself. Sympathicotonia causes indeed hypertension, myocardial involvement, renal damage and influences unfavorably the prognosis for life on the whole. The long renin-angiotensin system activation is accompanied by generalized involvement of the vessels, myocardium, kidneys, brain, increased risk of complications and death because of cardiovascular diseases and the complex of other causes. Metabolic syndrome, for which hypertension is so typical, is also a universal damaging mechanism. The prognosis for life depends significantly on interaction of organ damages, e. g., the heart and kidneys, the heart and brain. Both hemodynamic and nervous, hormonal, metabolic factors act as mediators in this situation.

The ability to assess secondary damages of the heart, vessels, brain and kidneys is important for a general practitioner in order to interpret the symptoms, explain the disease picture, estimate the prognosis but especially to select a successful therapeutic tactics and secondary prophylaxis. The considered pathologies include a wide range of damages. They may be conditionally subdivided in preclinical changes (not manifested in clinical symptoms but revealed only by instrumental investigation methods or laboratory tests), relatively early clinical affections (they are referred to as target organ

damages, especially in hypertension classification) and, finally, late affections or complications (they are often designated by the term "associated conditions" in hypertension classification) (Table 5.23).

Table 5.23

**Early and Late Consequences of Arterial Hypertension**

| Target organs | Subclinical affections | Early clinical affections of target organs | Late affections and associated complications |
|---|---|---|---|
| Aorta | Initial atheromatosis signs, minimum diffuse dilation, initial signs of aortic valve involvement | Nearly absent. The murmur may be auscultated along the aorta. | Stenosed aortic branches ostia. Aneurysms, aorta dissection, severe aortic valvular heart disease |
| Major arteries | Endothelial dysfunction. Thickened intima-media layer of arteries | They are manifested sometimes in vascular murmurs with presence or absence of minimum ischemic symptoms | Acute ischemic syndromes and organ (extremities) infarctions |
| Heart | Myocardium remodeling. Myocardium hypertrophy, minimum atriomegaly, diastolic or systolic dysfunction | Initial signs of CHF, benign rhythm disturbances | Progressing heart failure and coronary insufficiency. Severe arrhythmias (atrial fibrillation is especially typical) |
| Brain | Nearly absent if not to consider general cerebral complaints which are typical even for initial arterial hypertension and depend on BP level (headache, asthenia) | Initial stages of hypertonic encephalopathy (cognitive dysfunctions) | Transitory cerebral ischemic attacks, ischemic and hemorrhagic strokes |
| Kidneys | Microalbuminuria. Initial stages of chronic kidney disease | | Late stages of chronic kidney disease |

The subclinical and early symptoms of damages, e. g., microalbuminuria, thickened intima-media layer of arteries are especially valuable for primary prophylaxis of complications (Khirmanov, V. N., 2004). But they are not numerous and it is difficult to reveal or differentiate them in some cases.

It should be noted in summary that arterial hypertension is a very important risk factor, the basic cause of lethal complications. The thorough meta-analysis of the enormous body of scientific data is evidence of the fact that systolic blood pressure of higher than 115 mm Hg leads to steady increase of the risk of death because of basic cardiovascular complications (myocardial infarction, cerebral stroke‖) in a long-term perspective by 50 % with reference to every 20 mm Hg (Lewington S. et al., 2002). According to the World Health Organization, the increased blood pressure is responsible for 36 % of early deaths of Russian citizens. Therefore, this risk factor deserves close attention when carrying out primary and secondary prophylaxis also in liquidators of accident aftermath at the Chernobyl NPP.

***Diagnostics***. When performing the diagnostic assessment of each patients suffering from stable arterial hypertension we should answer four basic questions:

1. Is arterial hypertension a primary disease (i. e. essential hypertension) or is it a symptomatic form of the disease?
2. Which is the degree of blood pressure increase?
3. Which is the stage of the disease?
4. How high is the risk of cardiovascular complications?

First of all, one should have a data base on the blood pressure levels in a given patient for the effective treatment and prophylaxis. It includes its measurements presented in the outpatient's medical record, inpatient's case report (or extract from it), in the report on 24-h blood pressure monitoring but

also in the patient's medical self-control diary. Active, motivated participation of the patient in observation of own health condition is very important. It is not easy to achieve this in a significant percentage of patients-liquidators of the Chernobyl accident (insufficient cultural level, patient's dependent stand in life but also inadequate physician's professionalism may be interfering factors). But if a physician succeeded in this, the medical effect will be much better. The assessment of management quality of any patient with essential hypertension at any health care facility, in particular a liquidator of the accident at ChNPP at a specialized health center, should be started from the analysis of this data base informativity (it should include also the information on changes in risk factors, especially modifiable ones, on the treatment and its efficiency).

The degree of blood pressure increase is established by comparing the blood pressure levels (measured by a physician using Korotkov's method), which are the most typical for the patient at present, with stages generally recognized today (Table 5.24). One should take into account also the data on the blood pressure obtained using other methods, under other conditions (measurement by the patient him(her)self at home, 24 h monitoring in outpatient settings or at the clinic) and consider their natural difference (Table 5.25). As concerns stages of essential hypertension, the classification of WHO experts (1993) is still used in our country to distinguish them (Table 5.26).

Table 5.24

Classification of Blood Pressure Levels (BP, mm Hg)
Within the Normal Range and Degrees of Arterial Hypertension

| BP levels | Systolic BP | Diastolic BP |
|---|---|---|
| Normal blood pressure | | |
| Optimum | <120 | < 80 |
| Normal | 120—129 | 80—84 |
| High normal | 130—139 | 85—89 |
| Arterial hypertension (AH) | | |
| Degree I | 140—159 | 90—99 |
| Degree II | 160—179 | 100—109 |
| Degree III | ≥ 180 | ≥ 110 |

Note. Exceeding for one of BP parameters is sufficient in order to classify the BP level as the higher stage.

The risk of cardiovascular complications is assessed in our country usually in accordance with the Framingham scale developed using a model of the American population (such assessment concerns not only essential hypertension but the whole totality of risks and diseases). According to our viewpoint, it should be modified, at least, regarding the liquidator subpopulation of the accident at the Chernobyl NPP (Khirmanov, V. N., Sidorov, M. G., 2009).

Table 5.25

Threshold BP Levels (mm Hg) for Diagnostics of
Arterial Hypertension Basing on the Date of Different Measurement Methods

| Measurement method | Systolic BP | Diastolic BP |
|---|---|---|
| Measurement at the clinic (outpatient clinic) | 140 | 90 |
| 24-h monitoring: | | |
| on average for 24 h | 125—130 | 80 |
| on average for the day | 130—135 | 85 |
| on average for the night | 120 | 70 |
| Measurement at home | 130—135 | 85 |

Note. Exceeding for one of BP parameters is sufficient for diagnostics of arterial hypertension.

Table 5.26

Characteristics of Essential Hypertension Stages

| Stages | Characteristics of disease stage |
|---|---|
| I | Arterial hypertension is present but the patient has no signs of target organ involvement |
| II | The patient with arterial hypertension has signs of target organ involvement |
| III | The patient with essential hypertension has associated complications |

It is necessary to analyze in detail causes for hypertension, in particular, rule out its symptomatic nature in patients with arterial hypertension revealed for the first time or with its significant change over time (progression). The problem of the disease nature is solved basing on the special investigation program which includes the history, findings of the physical examination, laboratory tests and instrumental investigations. The unified recommendation on this problem are provided in the recommendations "Diagnostics and treatment of arterial hypertension" (3rd revision, 2008) suggested by the experts of the Russian Medical Society on Arterial Hypertension and the All-Russian Scientific Society of Cardiologists.

**Recommendations on Obtaining the Case History in Patients with Arterial Hypertension (All-Russian Scientific Society of Cardiologists, 2008)**

1. **Medical history of arterial hypertension**, level of BP increase, presence of hypertensive crises.

2. **Diagnostics of secondary forms of arterial hypertension**:

• family history of renal diseases (polycystic kidneys);

• medical history of renal diseases, urinary bladder infections, hematuria, abuse of analgesics (renal parenchymatous diseases);

• use of different drugs or substances: peroral contraceptives, nasal drops, steroidal and nonsteroidal anti-inflammatory drugs, cocaine, erythropoietin, cyclosporines;

• episodes of paroxysmal sweating, headaches, anxiety, palpitations (pheochromocytoma);

• muscular weakness, paresthesia, cramps (aldosteronism).

3. **Risk factors**:

• hereditary load regarding arterial hypertension, cardiovascular diseases, dyslipidemia, diabetes mellitus;

• medical history of cardiovascular diseases, dyslipidemia, diabetes mellitus;

• smoking;

• irrational nutrition;

• obesity;

• low physical activity;

• snoring and data on apnoe episodes during sleep (information according to patient's relatives);

• patient's personal features.

4. **Data evidencing the involvement of target organs and complications associated with hypertension**:

• brain and eyes: headache, dizziness, visual impairment, speech disturbances, transitory ischemic cerebral attacks, sensory and motor disorders;

• heart: palpitation, chest pain, dyspnea, edemas;

• kidneys: thirst, polyuria, nycturia, hematuria, edemas;

• peripheral arteries: coldness of extremities, intermittent claudication.

5. **Drug history**: previous antihypertensive therapy; drugs used for this purpose, their efficiency and tolerance.

6. **Assessment** of the possible effect exerted by the environmental factors, marital status, working situation on arterial hypertension.

**Findings of the Physical Examination Indicating the Secondary Nature of Arterial Hypertension and Organ Pathology (All-Russian Scientific Society of Cardiologists, 2008)**

**Signs of secondary arterial hypertension:**

• symptoms of Cushing's disease or syndrome;

• skin neurofibromatosis (may indicate presence of pheochromocytoma);

• kidney enlargement revealed by palpation (polycystic kidneys, mass lesions);

• auscultation of the abdomen: murmurs above the region of the abdominal aorta, renal arteries (renal artery stenosis, consequently, vasorenal arterial hypertension);

• auscultation of the heart, thorax (aortic coarctation, diseases of the aorta);

• weak or delayed pulse on the femoral artery and lowered blood pressure on the femoral artery (aortic coarctation, atherosclerosis, nonspecific aortoarteriitis).

**Signs of involvement of target organs and complications associated with hypertension:**

• brain: motor or sensory disorders;

• retina of eye: vascular changes in the fundus of eye;

• heart: displaced cardiac borders, intensified apex beat, cardiac rhythm disturbances, assessment of symptoms of heart failure (rales in the lungs, peripheral edemas, liver dimensions);

• peripheral arteries: absence. weakening or asymmetry of pulse, coldness of the extremities, symptoms of skin ischemia;

• carotid arteries: systolic murmur.

**Signs of visceral obesity:**

• increased waist circumference (in upright position): >102 cm in males and >88 cm in females;

• increased body mass index: overweight of the body: ≥25 kg/m$^2$, obesity: ≥30 kg/m$^2$.

**Laboratory and Instrumental Methods for Investigation of Patients Suffering from Arterial Hypertension (All-Russian Scientific Society of Cardiologists, 2008)**

**Obligatory investigations:**

• complete blood count and general urine analysis;

• glucose content in the blood plasma (after fasting);

• total cholesterol, HDL-cholesterol, triglyceride, creatinine content in the blood serum;

• determination of creatinine clearance (using Cockcroft-Gault equation) and glomerular filtration rate (using MDRD formula);

• ECG.

**Additional recommended investigations:**

• uric acid, potassium content in the blood serum;

• echocardiography;

• microalbuminuria testing;

• investigation of fundus of eye;

• ultrasound investigation of the kidneys and adrenal glands;

• ultrasound investigations of the brachiocephalic and renal arteries;

• X-ray of the thoracic organs;

• 24-h monitoring and measurement of arterial blood pressure at home;

• determination of ankle-brachial index;

• determination of pulse wave velocity (indicator of magistral artery rigidity);

•peroral glucose tolerance test: if glucose level in the blood plasma is more than 5.6 mmol/l (100 mg/dl);

• quantification of proteinuria (if diagnostics strips show positive result).

**In-depth investigation:**

• complications of arterial hypertension: assessment of the brain, myocardium, kidneys, magistral arteries condition;

• revealing secondary forms of arterial hypertension: investigation of aldosterone, corticosteroid concentration, renin activity in the blood; revealing catecholamines and their metabolites in 24-h urine and/or blood plasma; abdominal aortography; computed tomography or magnet-resonance imaging of the adrenal glands, kidneys and brain, computed or magnet-resonance angiography.

### *The Treatment of Essential Hypertension*

The main objective of the therapy is to lower the risk of cardiovascular complications. For this purpose, it is necessary to decrease the blood pressure (as a rule, to below 140/90 mm Hg) and carry out all other measures for possible primary prophylaxis.

**Non-medicinal treatment**. The blood pressure level in the range of 120–140/80–90 mm Hg considered earlier as the norm is estimated today as *prehypertension condition*. It is the first sign of the fact that it is necessary to change the life style in order to prevent true arterial hypertension. The difficulty consists in the fact that not only these patients with the trend to disease but even many patients with true arterial hypertension are asymptomatic or they have minimum symptoms. But the non-medicinal methods are an integral part in the treatment of all patients with arterial hypertension. It is important to reduce the body weight in patients with obesity, moderate restriction of salt consumption (to 5 5 of sodium chloride daily) is useful. This results in moderate decrease of the blood pressure (He, F. J., MacGregor, G. A., 2002). The diet with low calorie content, large quantity of fruits and vegetables is favorable. The patient should intensify physical activity outdoors (Appel, L. J. et al., 2003). Finally, it is important to avoid abuse of alcohol. Each of these measures provides for decrease of the blood pressure which is comparable with the effect of one standard antihypertensive drug. Finally, one should have in mind that smoking is an independent risk factor of coronary heart disease and stroke and it should be strongly discouraged in patients with arterial hypertension who run the hazard of cardiovascular complications as it is. The above hazards are typical of liquidators of accident aftermath at the Chernobyl NPP and, therefore, such recommendations are very urgent for them although it is usually difficult to fulfil them.

**Pharmacotherapy**. As a rule, patients with arterial hypertension should take certain drugs in order to reach the target blood pressure level. The selection of drugs depends on the risk degree, severity of the target organ involvement and presence of concomitant diseases and conditions

associated with hypertension. At least in some cases, the pharmacotherapy may worsen the life quality and cause adverse changes in lipid concentration and other plasma composition parameters. It is recommended to be careful of excessive decrease of the blood pressure (the diastolic pressure of lower than 65-70 mm Hg is dangerous) especially if the matter concerns elderly people (Hansson L. et al., 1998).

In their latest official recommendation for physicians, the Russian and European experts in problems of arterial hypertension consider antihypertensive drugs of all five basic groups (thiazide diuretics, calcium channel antagonists, ACE inhibitors, angiotensin receptor blockers and beta-blockers) as a rational choice for starting the treatment of these patients and its continuation.

In order to achieve the optimum blood pressure level, a physician should select just that drug which ensures advantages for the given patient, i. e. the drug of "preferred choice" (Chobanian, A. V. et al., 2003; Mancia G. et al., 2007) or a combination of such drugs (Table 5.27).

Table 5.27

Recommendations for Selection of Drugs for Treatment of Arterial Hypertension
(Chobanian A. V. et al., 2003; Mancia G. et al., 2007)

| Drug classes | Conditions for which this drug class has advantages | Absolute contraindications | Relative contraindications |
|---|---|---|---|
| **Diuretics** (low doses of thiazides) | Chronic heart failure, elderly age of the patient with arterial hypertension, systolic hypertension | Gout | Metabolic syndrome, disturbed glucose tolerance, pregnancy |
| **Diuretics** (loop) | Chronic heart failure, severe renal failure | Hypokaliemia | |
| **Diuretics** (aldosterone antagonists) | Chronic heart failure. Postinfarction period. Hyperaldosteronism (primary or secondary) | Hyperkaliemia, renal failure | Renal failure, hyperkaliemia |
| **B-adrenoblockers** | Angina pectoris, tachyarrhythmia, heart failure, postinfarction period, glaucoma, pregnancy | Asthma, atrioventricular block of degree II-III | Metabolic syndrome, disturbed glucose tolerance, chronic obstructive pulmonary disease, sports and physical activity, pathology of peripheral arteries |
| **ACE inhibitors** | Left ventricular dysfunction or heart failure, postinfarction period, diabetic nephropathy, non-diabetic nephropathy, proteinuria and microalbuminuria, atrial fibrillation, metabolic syndrome | Pregnancy, angioneurotic edema, hyperkaliemia, bilateral renal artery stenosis | pronounced cough, aortic stenosis |
| **Angiotensin II antagonists** | Heart failure, postinfarction period, diabetic nephropathy, proteinuria and microalbuminuria, left ventricular hypertrophy, metabolic syndrome, cough associated with administration of ACE inhibitors | Pregnancy, bilateral renal artery stenosis, hyperkaliemia | |
| **Calcium channel blockers** | Angina pectoris, elderly age of the patient, systolic arterial hypertension, supraventricular tachycardia (Verapamil or Diltiazem), left ventricular hypertrophy, carotid/coronary arteries atherosclerosis, pregnancy | Atrioventricular block of degree II-III, heart failure (verapamil or Diltiazem) | Tachyarrhythmia, heart failure |

The treatment may be started from the use of a single hypotensive drug in low dose. If the required effect is not observed, either the dose should be increased or a drug of another group should be preferred (if any side effect is seen additionally). But it should be mentioned that lowering of the blood pressure to below 140/90 mm Hg using one drug belonging to any of five basic groups may be achieved in not more than 20–30 % of cases in the patient population with

arterial hypertension (Mancia G. et al., 2007) if the matter does not concern arterial hypertension of degree I. But it is actually hazardous to delay achievement of the result, especially in patients with high risk of complications because they may be manifested already within the next few months (Julius S. et al., 2004).

The initial combined therapy is justified by its higher efficiency (especially, in case of additive interaction) and better tolerance (also due to mutual neutralization of side effects when drug components are combined rationally); it should be used for patients with arterial hypertension of degree II and III or with very high risk of cardiovascular complications. It is possible to use two drugs in low doses at first. The increase of the doses and number of drugs may be required in order to achieve the target values.

Fixed drug combinations considerably simplify the treatment, their number is increasing (Table 5.28). The combinations of thiazide diuretic in a low dose with ACE inhibitor or angiotensin receptor blocker were the most numerous and relevant type lately. In the meanwhile, already today the whole body of new scientific arguments, in particular the results of the studies INVEST (Pepine C. J. et al., 2003), ASCOT (Dahlöf B. et al., 2005), ACCOMPLISH (Jamerson K. et al., 2008) make physicians to prefer more often combinations of ACE inhibitors or angiotensin receptor blockers with calcium channel blockers. The typical trend consists also in appearance of statin component in the fixed antihypertensive combined drugs (Caduet). Finally, it is necessary to emphasize again that the combined pharmacotherapy should always be supplemented with measures for changing the life style.

Table 5.28

Drug Combinations for Treatment of Arterial Hypertension

| Drug combinations | Trade Name |
|---|---|
| *Beta-adrenoblockers and diuretics* | |
| Atenolol 50 or 100 mg + Chlortalidon 25 mg | Tenoretic, Tenoric |
| Bisoprolol 2.5, 5 or 10 mg + Hydrochlorothiazide 6.25 mg | Lodoz |
| *ACE inhibitors and diuretics* | |
| Enalapril 10 mg + Hypothiazide 25 mg | Enap |
| Enalapril 10 mg + Hypothiazide 12.5 mg | Enap HL |
| Enalapril 20 mg + Hypothiazide 12.5 mg | Corenitec |
| Prestarium 2 mg + 2/4 + Indapamid 0.625 mg | Noliprel |
| Prestarium 4 mg + Indapamid 1.25 mg | Noliprel-forte |
| Captopril 25 or 50 mg + Hydrochlorothiazide 12.5 or 25 mg | Capozid |
| *Angiotensin II receptor blockers and diuretics* | |
| Losartan 50, 100 mg + Hydrochlorothiazide 12.5–25 mg | Hyzaar |
| Telmisartan 40 or 80 mg + Hydrochlorothiazide 12.5 mg | Micardis-plus |
| Valsartan 80 or 160 mg + Hydrochlorothiazide 12.5 mg | CoDiovan |
| Calcium channel blockers and ACE inhibitors | |
| Verapamil (slow release) 180 mg or 240 mg + Trandolapril 1, 2, or 4 mg | Tarka |
| Amlodipine 5 mg + Lisinopril 10 mg | Ekvator |
| Calcium channel blockers and β-adrenoblockers | |
| Felodipine 10 mg + Metaprolol tartrate with controlled release 100 mg | Logimax |
| Atenolol 50 mg + Amlodipine 5 mg | Tenotec |
| *Combinations including rauwolfia alkaloids* | |
| Reserpine 0.1 mg + Hydrolasine 10 mg + Hydrochlorothiazide 10 mg | Adelphane, Triresid |
| Reserpine 0.1 mg + Dihydroergocrystine 0.6 mg + Brinaldix 5 mg | Crystepin |
| *Diuretic combinations* | |
| Triamterene 25 mg + Hydrochlorothiazide 12.5 mg | Triampur |
| *Calcium channel blocker and angiotensin II receptor antagonist* | |
| Valsartan 80 or 160 mg + Amlodipine 5 or 10 mg | Exforge |
| *Calcium channel blocker and statin* | |
| Amlodipine 5 or 10 mg + Atorvsatatin 10 mg | Caduet |

For patients with arterial hypertension which is resistant to all possible drugs and their combinations the following questions (probable causes) should be considered:

1) Is the patient actually adherent to the treatment?

2) May hypertension be a "white-coat" reaction, i. e. the reaction to the procedure of measurement of the blood pressure by a health care professional itself? Do the blood pressure levels during the visit to a physician actually correspond to those observed in the patient's everyday life? Revealing a significant difference is very probable.

3) Does the patient have some manifestations of symptomatic arterial hypertension, i. e. atherosclerotic involvement of the renal arteries or renal insufficiency?

4) Is the table salt or alcohol content in the ration increased or is it possible that the patient took sympathomimetic drugs, nonsteroidal anti-inflammatory drugs or a drug belonging to a relatively new group of cyclooxygenase-2 inhibitors?

5) Is the patient in the condition of temporary psychologic stress?

6) Is any latent cause for arterial hypertension present?

7) Finally, is the therapy actually maximum, in particular, regarding diuretic dose? The conception of the therapy with low doses of diuretics is not applicable in this situation.

The answers to this complex questions allow to find the correct tactical solution.

**Faints Acute** short-term losses of consciousness (or faints) are conditions accompanied as a rule by sudden decrease of the blood pressure. Syncope syndromes are observed in liquidators of accident aftermath at ChNPP than in the general population (Aleksanin, S. S., 2008).

Syncope condition (faint, syncope) is a transitory loss of consciousness and postural tone because of general cerebral hypoperfusion characterized by fast development, short duration and spontaneous stopping.

Some conditions may be similar to a faint. Sometimes the loss of consciousness occurs actually but its mechanism is not associated with general cerebral hypoperfusion. Such conditions include epilepsy, intoxications, several metabolic disorders including hypoxia, hypoglycemia, hyperventilation with hypocapnia and transient ischemic attack (TIA) of vertebrobasilar genesis. Other conditions are not associated with complete loss of consciousness as in case of cataplexy, syncope vertebrogenic syndrome, falls, psychogenic pseudo-faints or TIA of carotid genesis. Differential diagnosis is usually not complex in such cases but sometimes it may become more difficult because of insufficiently detailed history, atypical symptoms or problem to diagnose the faint itself. Differential diagnosis is important for a clinician who observed sudden loss of consciousness (actual or false) due to causes not associated with the global cerebral hypoperfusion such as cramps and/or conversion reaction.

**Classification and pathophysiology of syncope conditions**

The following pages present pathophysiologic classification of the basic causes for faints subdividing them in large groups of conditions having common clinical symptoms and associated with different risks (Table 5.29). The pathophysiologic approach focuses on decrease of the systemic blood pressure (BP) what is associated with lowered general cerebral blood flow as a direct cause for the syncope condition. The sudden stopping of the cerebral blood flow for 6–8 s can already result in complete loss of consciousness. The decrease of systolic BP to 60 mm Hg and lower also leads to a faint (Brignole, M. et al., 2004). The systemic BP is determined by cardiac

output (CO) and general peripheral vascular resistance (GPVS), and rapid decrease of both BP and GPVS may cause a faint.

Table 5.29

Classification of Causes for Syncope Conditions (ESC, 2001, 2004)

| |
|---|
| ***I. Reflex (neurogenic) faints:*** |
| *1) vasovagal:*<br>*- because of emotional stress: fear, pain, view of blood, medical manipulations or instruments;*<br>*- orthostatic load.*<br>*2) situation-related:*<br>*- sneezing, cough;*<br>*- stimulation of GIT: swallowing, defecation, visceral pain;*<br>*- reaction to urination;*<br>*- after exercise stress;*<br>*- postprandial (after food intake);*<br>*- other (laughing, play on brass, lifting heavy objects);*<br>*3) stimulation of the carotid sinus;*<br>*4) trigeminal or glossopharyngeal neuralgia;*<br>*5) atypical (unidentified trigger or atypical symptoms).* |
| ***II. Faints associated with orthostatic hypotension*** |
| *1) primary vegetative insufficiency;*<br>*- true vegetative insufficiency, multiple system atrophy, Parkinson's disease with vegetative insufficiency, dementia with Lewy bodies;*<br>*2) secondary vegetative insufficiency:*<br>*- diabetes mellitus, amyloidosis, uremia, spinal cord injury;*<br>*3) orthostatic hypotension provoked by chemical substances/drugs:*<br>*- alcohol, diuretics, vasodilators, phenothiazides, antidepressants;*<br>*4) circulating blood volume deficit:*<br>*- bleeding, diarrhea, vomiting, etc.* |
| ***III. Cardiogenic faints:*** |
| *1) arrhythmogenic (primary cause):*<br>*a) bradycardia:*<br>*- sinus node dysfunction including tachy-brady syndrome;*<br>*- disturbed atrioventricular conduction;*<br>*- implanted pacemaker dysfunction;*<br>*b) tachycardia:*<br>*- supraventricular;*<br>*- ventricular (idiopathic, pathology of ion channels function, because of structural cardiac pathology);*<br>*c) drug-induces brady- and tachy-arrhythmias;*<br>*2) structural pathology:*<br>*a) cardiac pathology: heart valvular disease, acute coronary syndromes, hypertrophic cardiomyopathy, intracardiac mass lesions (myxoma, tumors, etc.), pericarditis/ tamponade, congenital coronary artery malformations, valvular prosthesis dysfunction, etc.;*<br>*b) other: pulmonary circulation embolism, acute aortic aneurysm dissection, pulmonary hypertension.* |
| ***IV. Cerebrovascular faints:*** |
| *1) vertebral arteries atherosclerosis in combination with cervical osteochondrosis (Sistine chapel syndrome);*<br>*2) vertebral-subclavian steal syndromes (steal syndrome);*<br>*3) pathological tortuosity of brachiocephalic vessels;*<br>*4) craniocervical transition malformations* |

Low or inadequate GPVR may be a consequence of abnormal reflex activity which causes vasodilation and bradycardia and is manifested in vasodepressor, cardioinhibitory or mixed reflex faint. Other causes for low or inadequate GPVR include functional or structural disturbances in the function of the vegetative nervous system (VNS) in the form of drug-induced, primary or secondary vegetative insufficiency (VI). The sympathetic vasomotor nerves cannot increase GPVR in response to transition in the upright position in patients with VI. The gravitation load in combination with vasomotor insufficiency results in venous blood pooling below the diaphragm, reduced venous return and, consequently, lowered CO.

There exist three main causes for transient lowering of CO. The first one is associated with a reflex causing bradycardia and known as a reflex faint of cardioinhibitory type. The second cause consists in cardiovascular genesis; CO is lowered due to arrhythmias and structural pathology

including pulmonary circulation embolism and pulmonary hypertension. The third cause consists in inadequate venous return due to lowered circulation blood volume (CBV) or venous pooling. Three final mechanisms of faints (reflex, cardiogenic mechanisms and mechanism associated with orthostatic hypotension (OH) underlie the pathophysiologic conception.

**Reflex syncope conditions (syncope conditions caused by the influence of the nervous system** Reflex faints are traditionally understood as a heterogeneous group of conditions, in which cardiovascular reflexes controlling the adequate circulation in the norm are manifested temporarily inadequately in response to a respective trigger what results in vasodilation and/or bradycardia and, consequently, BP decrease and general cerebral hypoperfusion (Albina, G. et al., 2004).

Reflex faints are usually classified basing on the most significant mediating types of efferent influences, e. g., from the sympathetic or parasympathetic nerves. The term "vasopressor type" is used usually if hypotension predominates due lowered vasoconstricting postural tone. A faint because of prevailing bradycardia or asystolia is called cardioinhibitory faint. Both mechanisms play their role in faints of mixed type.

Reflex faints may be classified also basing on the causes provoking them (triggers), i. e. basing on the afferent component. It should be recognized that this classification is simplified because several different mechanisms may be present in a given specific situation. Trigger situations may vary considerably in one person or in different persons. The information about different triggers are important because their recognition may be critical for diagnostics of the faint (Khirmanov, V. N. et al., 2006).

Vasovagal syncope (VVS) also known as ordinary faint are induced by emotional or orthostatic stress. They are usually preceded by prodromal symptoms of vegetative hyperactivation (sweating, paleness, nausea).

A situation faint is usually associated with reflex faint occurring under certain conditions. A faint after exercise stress may develop in sportsmen of young age in the form of reflex syncope and persons of middle and elderly age as early manifestation of VI before development of typical OH.

Faints associated with carotid sinus hypersensitivity in their rare spontaneous form are potentiated by mechanical influence on the sinocarotid region; diagnosis is made basing on the positive result of the carotid sinus massage test (Brignole, M. et al., 2004).

The term "atypical forms" is used to describe those situations when a reflex faint develops with unclear provoking factors or in their absence. In such case the diagnosis is based to a lesser extent on the history but to a greater extent on exclusion of other causes for syncope condition (absence of structural cardiac pathology) and an attempt to reproduce such conditions by the tilt table test. Such unclear cases may be combined with faints of known origin in same patients.

The classical form of VVS develops usually in young persons as isolated episodes and differs clearly from other forms but it often may occur atypically in elderly individuals what is often associated with cardiovascular or neurologic pathology manifested in orthostatic or postprandial hypotension (Tyurina, T. V., 2005). In the latter case a reflex faint is manifestation of the pathologic process associated mainly with the inability of VNS to activate the compensatory reflex. Consequently, the reflex faint develops in this case with simultaneous existence of VI (Tonkin, A. et al., 1999).

**Orthostatic hypotension and orthostatic intolerance syndromes**. OH is defined as abnormal BP decrease when moving to an upright position. In contrast to reflex faints, VI results in chronic disturbance of sympathetic activation, i. e. vasoconstriction deficit.

From pathophysiologic viewpoint, reflex faints and VI have many distinctions but their clinical symptoms coincide often what makes the differential diagnosis more difficult sometimes. Orthostatic intolerance syndrome belongs to symptoms manifesting in the upright position due to disturbed circulation. A faint is only one the symptoms. Other symptoms include: 1) dizziness; 2) general asthenia, inertia, somnolence; 3) palpitation, sweating; 4) visual disorders including "mist" in the eyes, increased perception brightness, great decrease of visual fields); 5) acoustical disturbances (hearing impairment, crackling or ringing in the ears); pain in the neck (occipital-cervical and cervical zones), loin or cardialgia (Barsukov, A. V. et al., 2009).

– Classical OH is revealed clinically as decrease of systolic BP by more than 20 mm Hg and diastolic BP by more than 10 mm Hg within 3 min after movement to the upright position; it is described in patients with "true" VI, hypovolemia and other forms of VI.

– Initial OH (Mathias, C. et al., 1997) is characterized by immediate BP decrease by more than 40 mm Hg after movements to the upright position. Then BP returns to the normal level spontaneously and rapidly i. e. the hypotension period and duration of symptoms are short (<30 s).

– Delayed (progressing) OH is observed quite often in elderly patients. It is considered that it is caused by age-related disturbances of compensatory reflexes myocardial remodeling provoking the sensitivity to lowered preload. Delayed OH is characterized by slow progressing decrease of systolic BP when a patient moves to the upright position. Absence of bradycardia (vagal reflex) makes it possible to differentiate delayed OH from a reflex faint.

– Postural orthostatic tachycardia syndrome (POTS). Some patients, mainly young women, complaint of orthostatic intolerance with significant increase of HR (>30 beats/min or >120 beats/min and instable BP but they do not develop a faint in such situation. POTS is often associated with chronic fatigue syndrome. pathophysiology of this syndrome is unclear.

**Syncope conditions of cardiovascular genesis. Arrhythmias.** Arrhythmias are the most frequent causes for cardiogenic faints. They cause hemodynamic disturbances resulting in critical decrease of CO and cerebral blood flow. Besides that, such factors are of importance as degree of acceleration or slowing of HR, arrhythmia type (supraventricular or ventricular arrhythmia), LV myocardial function, position of the body and adequacy of vascular compensatory reactions. The latter include baroreceptor nervous reflexes and also the reflex response to OH induced by arrhythmia (Kardos, A. et al., 2001). If arrhythmia is a primary cause of syncope condition, a patient needs specific therapy.

Sick sinus syndrome (SSS) is associated with sinoatrial node damage because of its disturbed automatism or disturbed sinoatrial conduction. In this situation, syncope conditions are caused by long pauses resulting from sinus node stops or sinoatrial block and insufficiency of replacing centers of the second order. Such pauses develop the most often after a sudden stop of atrial tachyarrhythmia paroxysm (tachy-bradycardia syndrome) (Kapoor, W. et al., 1996).

As a rule, the severest forms of acquired atrioventricular (AV) block (Mobitz II type, blocks of "high grade" and complete AV-block) are associated with syncope conditions. In these cases, the cardiac rhythm depends on replacing pacemakers of the third order which often unreliable.

Syncope conditions develop because of a long interval until a pacemaker of the third order starts to function. Besides that, the replacing rhythm of pacemakers of the third order is typically too slow (25–40 beats/min). Bradycardia also extends repolarization and predisposes to onset of polymorphous ventricular tachycardia, especially of torsade de pointes type.

Syncope may accompany paroxysmal tachycardia attacks (Brembilla-Perrot, B. et al., 2001). The consciousness recovers, as rule, already before stopping of tachycardia.

Brady- or tachyarrhythmia may be caused by administration of some drugs. Many antiarrhythmic drugs may cause bradycardia due to their specific action on the function of the sinus node and AV-conduction. Syncope conditions develop usually with simultaneous tachycardia of torsade de pointes type, especially in females. Their development is associated with administration of *QT*-prolonging drugs. Therefore, syncope is often observed in persons with long *QT* syndrome. The *QT*-prolonging drugs are represented by different agents, in particular: drugs with antiarrhythmic and psychotropic action, antimicrobial properties, vasodilators, non-sedative antihistamine agents, etc.

In addition to arrhythmias, the classification of syncope conditions lists cardiovascular diseases which result in syncope the most often. A faint may develop in conditions accompanied with fixed or dynamic occlusion of outflow paths from the left ventricle. But in some cases syncope is associated not only with lowered cardiac output but also with orthostatic hypotension. For example, patients with aortic valve stenosis develop syncope because of both lowered cardiac output and reflex vasodilation and/or primary arrhythmia. Thus, there are many mechanisms of syncope conditions including combined ones.

**Prognosis.** The presence of cardiac structural pathology or primary electric myocardial instability is the most significant prognostication marker of mortality in patients with syncope syndromes (Kapoor, W. et al., 1983). So, the mortality within 1 year in patients with cardiac syncope is from 18 to 33 % as compared to mortality of 6 % in patients with faints of unclear etiology or 0–12 % in patients with faints of non-cardiac nature. So, e. g., the risk of sudden death within 1 year was 45 % in a group of patients suffering from congestive heart failure with low ejection fraction and syncope conditions, while this risk was 12 % in the control patient group with HF but without faints.

On the other hand, it is possible to distinguish the following patients with favorable prognosis (Martin, T. et al., 1997):

- Young healthy persons without cardiac disease and with normal ECG; neurogenic faints or faints of unclear etiology are diagnosed in them.
- Patients with orthostatic hypotension. The mortality of patients with orthostatic hypotension depends on the causes of this disorder. The causes are temporary, may be removed by the treatment and have no long-term consequences in some cases (e. g., in patients with hypovolemia, side effects of drugs).
- Patients with neurogenic and reflex syndromes.

- Patients with faints of unclear etiology (mortality within the first year of follow-up is 5 %).

**Characteristics of the patient group with syncope conditions.** The investigated group included 30 males aged from 44 to 78 years (mean age: 59±8 years) who suffered from different syncope syndromes and underwent the scheduled investigation and treatment at the department of Cardiology of the Division of Cardiovascular Pathology at ARCERM. They all were involved in liquidation of accident aftermath at ChNPP in the period from 1986 to 1988, stayed in the affected zone from several weeks to several months and fulfilled the wide range of functions from direct construction of the protective sarcophagus to assessment of the environmental contamination intensity. Fourteen investigated patients were disabled persons (group II-III) because they were exposed to the radiation as a result of the catastrophe at the Chernobyl NPP. All persons developed syncope syndrome at different terms (from several months to several years) after their return from the affected zone.

The nosologic characteristic of the group was represented by the following pathology. All patient except for one suffered from essential hypertension (EH) and stage II of EH was diagnosed in 14 persons and stage III was observed in 15 persons. Coronary heart disease (CHD) was diagnosed in a half of patients: 11 of them suffered from stable exertional angina pectoris of functional class I-II, 4 persons had history of myocardial infarction in different periods (on average, more than 5 years ago). One third of the investigated patients suffered from chronic heart failure (CHF), 6 persons of them had stage I, and stage II of CHF was diagnosed in 4 patients. Sixteen patients of this group had different gastrointestinal pathology: chronic gastritis, peptic ulcer, chronic cholecystitis and chronic pancreatitis. Eight persons suffered from chronic respiratory pathology. Diabetes mellitus was diagnosed in 8 patients.

Patients of the test group lived in Saint Petersburg (18 persons), Velikiy Novgorod (3 persons) and settlements of the Leningrad Region (9 persons) in separate apartments and own cottages; they all assessed their dwelling conditions as good. Sixteen persons had higher education, others had secondary and secondary special education and the greater part of persons with higher education were employed at the time of the investigation (10 persons). Seventeen persons in the patient group with faints smoked actively (not less than 1 pack daily) at the time of the investigation, all patients consumed moderate amount of alcohol (not less than 50 ml/day). Seventeen patients received β-adrenoblockers, 19 persons used angiotensin-converting enzyme inhibitors permanently because of the underlying pathology.

**Peculiarities of taking the history in patients with syncope syndromes.** The investigation program included a detailed inquiry to take the case history, which, in addition to traditional items, elucidated the information about clinical features, circumstance of onset, course and consequences of faint episodes using a special Torsten-Schwalm “syncope questionnaire” (Table 5.30) (Schwalm, T., 2006).

Table 5.30

Torsten-Schwalm Questionnaire (2006)

| 1. Did you ever develop losses of consciousness? | ES | O |
|---|---|---|
| 2. If yes, how long was the unconscious period (s)? | | |
| 3. Was this accompanied by sudden muscular weakness up to sitting on the floor? | | |
| 4. Did you have any injuries because of falling which made you to seek medical attention? If yes, which injuries you had? | | |
| 5. Did you experience sudden fear, sharp pain, unpleasant odor or loud sound before the loss of consciousness? | | |
| 6. Did you lose consciousness after staying in the upright position for more than 5 min? | | |
| 7. Did you lose consciousness after significant exercise stress and do you suffer from cardiac diseases? | | |
| 8. Did you lose consciousness during significant exercise stress and do you suffer from any cardiovascular disease? | | |
| 9. Are there cases of sudden death associated with cardiac cause or death because of unknown cause among your relatives? | | |
| 10. Did your loss of consciousness develop suddenly, without previous clinical symptoms, do you have cardiac diseases and implanted pacemaker? | | |
| 11. Do you experience intermittence or sensation of irregular heartbeat before a faint? | | |
| 12. Do you experience difficult breathing or chest pain before a faint? | | |
| 13. Did you lose consciousness immediately after urination, cough, swallowing or after defecation? | | |
| 14. Did you develop a faint several seconds after getting up from the lying position? | | |
| 15. Do you have losses of consciousness when lying, sitting or turning in the bed? | | |
| 16. Did you ever have loss of consciousness after the abrupt turning of the head or after pressing on the neck because of shaving, wearing tight collars or the load on the shoulders (rucksack)? | | |
| 17. If you use pharmacotherapy, was the dose of the drug changed recently? | | |
| 18. Was the loss of consciousness accompanied with biting your tongue, facial cyanosis or cramps? | | |
| 19. Was there a period of feeling unwell for more than 5 minutes after consciousness recovery? | | |
| 20. Did you feel an unusual odor or taste before loss of consciousness? | | |
| 21. Did you ever lose consciousness when working with one or two hands? | | |
| 22. Did you ever lose consciousness in the throng or crowded place? | | |
| 23. Do you experience presyncope symptoms more frequently than monthly and was the investigation for this condition successful? | | |
| 24. Was dizziness the main symptom before a faint? | | |
| 25. Was a faint accompanied with speech disorder or diplopia? | | |
| 26. Was the loss of consciousness associated with intensive pain in the facial region? | | |
| 27. Did a faint develop within 1 h after meals? | | |
| 28. Was the loss of consciousness associated with intense headache? | | |

The successive analysis of answers in the presented questionnaire helped us to orient in the search for etiology in each case. So, questions 1–4 help to differentiate a faint from non-syncope conditions, questions 5–7 reveal more accurately vasovagal nature of a faint, questions 8–12 concern faints associated with structural cardiopulmonary pathology (e. g., they help to suspect heart valvular disease, pulmonary hypertension, pulmonary embolism, hypertrophic cardiomyopathy, brady- and tachyarrhythmias).

The following questions suggest: situation faint (question 13), orthostatic faint (question 14); thrombosis of atrial myxoma (question 15); carotid sinus hypersensitivity (question 16); drug-related faint (question 17); epilepsy (questions 18-20); subclavian steal syndrome (question 21); psychic disorders (questions 22, 23); transient ischemic attack in the vertebrobasilar system (questions 24–25); trigeminal or glossopharyngeal neuralgia (questions 26); postprandial hypotension (question 27); migraine (question 28).

**Psychologic investigation.** The complex of psychodiagnostic methods included a life quality (LQ) questionnaire “Medical Outcomes Study Short Form” (SF-36) reflecting such components as

physical functioning, role physical functioning, pain, general health condition, viability, social functioning, role emotional functioning and psychic health; clinical questionnaire "Module" for assessment of neuropsychic stability, self-report questionnaire "The Coping Strategy Indicator" ("CSI") developed by D. Amirkhan and assessing the degree of coping-strategies in the structure of coping behavior; Spielberg-Hanin Reactive and Personal Anxiety Scale and Beck Depression Inventory.

**Physical examination.** In addition to the standard medical methods of investigation, physical examination program for a patient included obligatory measurement of the blood pressure in lying and upright position (active orthostasis test0, auscultation assessment of extracardial murmurs, revealing the hypersensitivity in the exit points of the trigeminal nerve.

**Laboratory diagnostics.** The laboratory diagnostics included the minimum set of clinical tests (complete blood count with estimation of the thrombocyte number and general urine analysis), biochemical parameters [glucose, lipidogram, transaminase activity, total bilirubin, creatinine, albumin, uric acid and electrolytes (potassium, sodium, chlorides, total calcium] and immunochemical tests ( thyroid-stimulating hormone, free thyroxine, total testosterone, aldosterone, adrenocorticotropic hormone, cortisol and C-peptide).

**Instrumental diagnostics.** Patients with syncope syndrome underwent the following instrumental investigations: electrocardiography (ECG), echocardiography, duplex scanning of the brachiocephalic arteries, combined 24 h ECH and BP monitoring, treadmill-test, electroencephalography, magnet-resonance imaging (MRI) of the brain with contrast enhancement of arteries and veins, MRI- angiography of cervical arteries, tilt table test and carotid sinus massage test.

**Electrocardiography.** The following changes in ECG (Table 5.31) allowed us to suspect the arrhythmical nature of the faint:

Table 5.31

ECG Changes Allowing to Suppose Arrhythmogenic Faint

- *Bifascicular block (left bundle branch block or right bundle branch block in combination with anterosuperior or posteroinferior semi-block);*
- *other intraventricular conduction disturbances QRS duration ≥0.12 s);*
- *atrioventricular block of degree II, type Mobitz I;*
- *asymptomatic sinus bradycardia (<50 per min) or sinoatrial block;*
- *ventricular preexcitation syndrome;*
- *long QT syndrome;*
- *right bundle branch block in combination with ST segment elevation $V_1$-$V_3$ leads (Brugada syndrome);*
- *negative T-waves in the right thoracic leads, "epsilon waves" and late ventricular potentials indicative of arrhythmogenic right ventricular dysplasia;*
- *Q-waves indicating myocardial infarction*

### *Combined 24-h ECG and BP Monitoring*

The apparatus-program portable complex with digital recording for 24–72 h ECG and BP Holter monitoring "Cardiotekhnika-04" (Inkart, JSC, Russia) was used for diagnostics of intermittent brady- and tachyarrhythmia.

Establishing a clear interrelationship between symptoms and documented arrhythmia was the gold standard for diagnostics of arrhythmic faint (Kenny R. et al., 2000). The revealed asymptomatic bradyarrhythmia with asystolia episodes for more than 3 s, supraventricular tachycardia (more than 160 beats/min) or ventricular tachycardia were considered as an additional

diagnostic criterion. Absence of recorded arrhythmia during syncope allowed to exclude it as a cause for faint but it was a specific diagnostic indicator.

As a rule, ECG monitoring is indicated in cases when arrhythmic etiology of faint is highly probable. But it is known that arrhythmia (as a rule, asystolia) during syncope is observed practically in 50 % of persons aged above 40 years with repeated syncope episodes, without confident structural heart pathology and with normal ECG picture.

**Tilt table testing.** We used the orthostatic test with rotating table or tilt table testing as a simple noninvasive test which is generally recognized by the medical community for assessing the vegetative regulation of the cardiovascular system (Benditt, D. et al., 1991).

Tilt table testing allows to reproduce a neurologically mediated pathologic reflex which may be provoked by blood pooling and reduced venous return due to orthostatic stress and patient's immobility. Insufficient vasoconstricting stimulation resulting from inhibition of sympathetic pulses and vagal hyperactivity leads to hypotension and usually concomitant slowed cardiac rhythm.

As a rule, the clinical situation, when reflex syncope develops due to long stay in the upright position, corresponds to tilt table testing. But this test may be positive also in patients with other forms of reflex faint and sick sinus syndrome.

The classical "Westminster" protocol of tilt table testing chosen by us includes monitoring of hemodynamic parameters and cardiac signal in the initial horizontal position of the a patient (for 10 min) with subsequent observation of the patient in the orthostatic position (60˚, 45 min). Testing was stopped after occurrence of significant hemodynamic reactions (BP decrease, slowed HR, appearance of pauses in the heart functioning) causing syncope symptoms provocation of which was considered as a positive investigation outcome (Table 5.32). Testing was performed in the morning in quiet conditions of an isolated room 2 h after light breakfast and detailed explanation of the procedure and the need of the investigation to the patient.

Table 5.32

Classification of Positive Responded to Tilt Table Testing (Sutton, R., 1992)

- ***Type 1. Mixed***. During a faint, the heart rate is slowed down but the ventricular rhythm is not less than 40 beats/min or it is slowed down to less than 40 beats/min but this lasts for not more than 10 s with asystolia for less than 3 s or without it. Blood pressure decrease leaves behind slowing of heart rate.
- ***Type 2A. Cardioinhibition without asystolia.*** The heart rate is slowed down to less than 40 beats/min what lasts for more than 10 s but asystolia for more than 3 s is not observed. The decrease of the blood pressure leaves behind slowing of the heart rate.
- ***Type 2 B. Cardioinhibition with asystolia.*** Asystolia lasts for more than 3 s. The decrease of the blood pressure coincides with slowing of the heart rate or leaves it behind.
- ***Type 3. Vasodepression.*** The heart rate is not slowed down by more than 10 % of the initial value during a faint.
- ***Addition 1. Chronotropic insufficiency.*** There is no increase of the heart rate during tilt table testing (i. e., acceleration is less than 10 % of the initial HR).
- ***Addition 2. Excessive increase of the heart rate.*** The heart rate increases excessively (i. e. more than 130 beats/min) both in the beginning of orthostasis and during the whole orthostasis before a faint.

ECG monitoring in 12 leads and measurement of the blood pressure according to Korotkov's method were performed using the portable recorder "Cardiotekhnika-04-0" (Inkart JSC, Russia).

The intracranial blood flow was assessed using the apparatus "Angiodin-2K" (BIOSS, Russia) allowing to monitor the cerebral circulation by dopplerographic method with the help of two pulse sensors with frequency of 2 MHz. The system is fitted out with a head-piece with external clamps allowing to change freely orientation of the ultrasound beam relative to the investigated vessel. The linear blood velocity (LBV) and Gosling's pulsatility index (PI) were used to assess the blood flow and peripheral resistance in the medial cerebral arteries located at a depth of 50–55 mm.

So, BP, HR, ECG (12 leads), LBV and PI and also personive symptoms were assessed continuously during the whole investigation. The blood was sampled from the vein for determination of the following parameters: insulin, BNP and NT-proBNP, noradrenaline and dopamine, three times during the test, i. e. at minute 10 of the initial period in lying position (point 1), during the first minutes of orthostasis (point 2) and at the response peak in case of positive test or at minute 20 in case of negative response (point 3).

The results of tilt table testing may be indicative of either reflex hypotension/ bradycardia or late OH associated with syncope or presyncope conditions. The nature of the response to the provoked reflex is assessed depending on the dominating component, i. e. vasodepressor or cardioinhibitory variant (cardioinhibotory, vasodepressor response or response of mixed type, respectively) (Fitzpatrick, A. et al., 1991). In this situation the negative result of tilt table testing is not the grounds to rule out the diagnosis of reflex syncope. Loss of consciousness without hypotension and/or bradycardia may be considered as a diagnostic marker of psychogenic pseudosyncope.

Tilt table testing is a safe diagnostic method. Not a single case of death during it is known. But the data are available on the possibility of life-threatening ventricular arrhythmias in patients with CHD or sick sinus syndrome. In spite of low risk of complications and side effects, the resuscitation set of drugs and equipment and switched on defibrillator Cardioserv (General Electric, USA) were always readily available during our investigation.

### *The Results of Clinical and Instrumental Investigation*

The material was analyzed in accordance with the positive or negative result of tilt table testing. The first group ("tilt-positive" patients) included 6 patients and the second group ("tilt-negative" patients) comprised of 15 persons, i. e., a faint could be provoked by tilt table testing in more than one third of patients who underwent the investigation. There were no significant differences in the age of these patients and also in mean values of all biochemical parameters.

When analyzing the pathology structure in both groups, we revealed the following peculiarities. Most (66.7 %) "tilt-positive" patients have stage II of EH while "tilt-negative" patients more often have stage III of EH. We revealed a negative correlation between the result of tilt table testing and stage of essential hypertension ($r = –0.44$; $p = 0.05$).

Most patients of both groups (66.7 and 53,3 %, respectively) had no diagnosed CHD, moreover, not a single patient with post-infarction cardiosclerosis was among "tilt-positive"

patients. Practically nobody among patients with CHF was included in the first group (positive outcome of tilt table testing). Moreover, the group of "tilt-positive" patients did not include patients with diabetes mellitus, respiratory and gastrointestinal diseases ($r = –0.50$; $p = 0.02$).

Thus, absence of significant cardiac diseases and also concomitant diseases (diabetes mellitus, gastrointestinal and respiratory diseases) in the pathology structure in "tilt-positive" patients was more likely evidence of reflex nature of faints what was reproduced with the help of passive orthostasis. Although it is known that, e. g., post-infarction cardiosclerosis or diabetes mellitus may promote occurrence of pathologic neurogenic mechanisms and, consequently, increase the probability of positive investigation outcome.

It should be mentioned that faints were more frequent in the group of "tilt-negative" patients. This fact may support the supposition that "tilt-negative" patients included persons with pseudo-faints including those of psychiatric nature.

Analysis of clinical symptoms revealed by a special inquiry found the following peculiarities. The typical manifestations of a classical vasovagal faint (nausea, paleness, hyperhydrosis) were not characteristic of patients with positive response to tilt table testing. It is hard to say whether this may be explained by prevalence of atypical clinical forms among reflex faints in this patient group or by small sample size.

Besides that, overwhelming majority (83.3 %) of "tilt-positive" patients reported relatively good general personive condition after a spontaneous syncope episode as compared to the second group what just was pathognomonic for ordinary reflex faint. We did not obtain any confident results regarding injuries resulting from spontaneous falling because of loss of consciousness in patients of both groups. At the same time, "tilt-positive" patients lost consciousness irrespective of the initial position of the body, i. e., when standing, sitting or lying, with equal frequency. Moreover, we did not see a clear dependence of loss of consciousness on the specific situation preceding a faint: changed position of the body, physical activity, urination, cough, etc.

Strangely enough that smoking patients demonstrated the higher resistance in orthostasis that non-smokers. Patients receiving beta-blockers more often had the positive result of tilt table testing while patients receiving ACE inhibitors were more often included in the group of "tilt-negative" patients ($r = –0.45$; $p = 0.04$). It is known that angiotensin-converting enzyme inhibitors improve orthostatic tolerance and beta-blockers may worsen it, thus, this result was expectable.

The compared groups did not differ in the result of treadmill exercise stress test: both "tilt-negative" and "tilt- positive" patients had approximately equal rate of actual ischemic changes during exercise stress.

When comparing changes in ECG in both groups we revealed that different findings (blocks and cardiac arrhythmias) were somewhat more often in "tilt-negative" patients, consequently, they more often had concomitant cardiac pathology.

According to echocardiography findings, cardiac chamber dilation was found with equal frequency in both patient groups just as hydrocephalus visualized by cerebral magnet-resonance imaging with contrast enhancement of arteries and veins. The signs of dyscirculatory encephalopathy were also characteristic of most patients with faints irrespective of the outcome of the tilt table testing. The signs of disturbed venous outflow, on the contrary, were revealed somewhat more often in "tilt-negative" patients. All brachiocephalic artery stenoses and atherosclerotic plaques visualized in the

arteries were also found in patients of this group. Vertebral artery malformations were revealed only in one third of cases in both groups. This may be evidence of insignificant clinical contribution of revealed pathologic vascular changes in the development of faints in this patient category.

Strangely enough, stem structure dysfunction was revealed somewhat rarer in "tilt-positive" patients basing on findings of electroencephalography.

The result analysis of Holter monitoring demonstrated the following features. There were no pauses and significant cardiac rhythm disturbances in 24 h-records in patients with positive tilt table testing and in contrast to "tilt negative "patients they had normal variability of the cardiac rhythm. Ischemic changes were revealed in ECG to an equal but insignificant extent in both groups.

### *Changes in the Clinical, Hemodynamic and Laboratory Parameters During Tilt Table Testing*

As it was mentioned above, the investigated patients were divided in two groups depending on the result of tilt rest. Differences in the clinical, hemodynamic and laboratory parameters were revealed in both groups.

Six patients with the positive test were distributed as follows in accordance with R. Sutton classification (1992): one person had reaction type IIB (cardioinhibition with asystolia for more than 3 s), one patient had type IIA (cardioinhibition without asystolia), vesodepressor type (type III) of hemodynamic reactions was revealed in four persons.

The following hemodynamic phenomena were revealed in patients with negative test (15 persons): two patients had asymptomatic orthostatic hypotension, 3 patients developed chronotropic insufficiency and postural orthostatic tachycardia syndrome was found in 3 patients.

#### *Clinical case 1*

**Medical history.** Patient L., 54 years old, lost consciousness two times over the period of 3 years. It was not possible to reveal any causes provoking a faint. He describes the presyncope period not clearly. The unconscious condition lasts for 3-4 min during which skin paleness, dyspnea periods are observed. The general well-being normalizes quickly and consciousness recovery.

At the same time the patient experiences attacks of arrhythmic palpitations occurring up to 3 times per month; the provoking factors include emotional experience, raising his hands, inclinations forwards, physical activities; these attacks are accompanied with worsened general personive condition, chest discomfort, sweating. These attacks last for up to 30 min and are stopped spontaneously or after peroral and intravenous administration of Verapamil. The vagus tests are not effective for stopping the attacks. He has been suffering from arrhythmia since 1996. He takes Verapamil in the dose of 80 mg twice daily and Cardiomagnyl permanently.

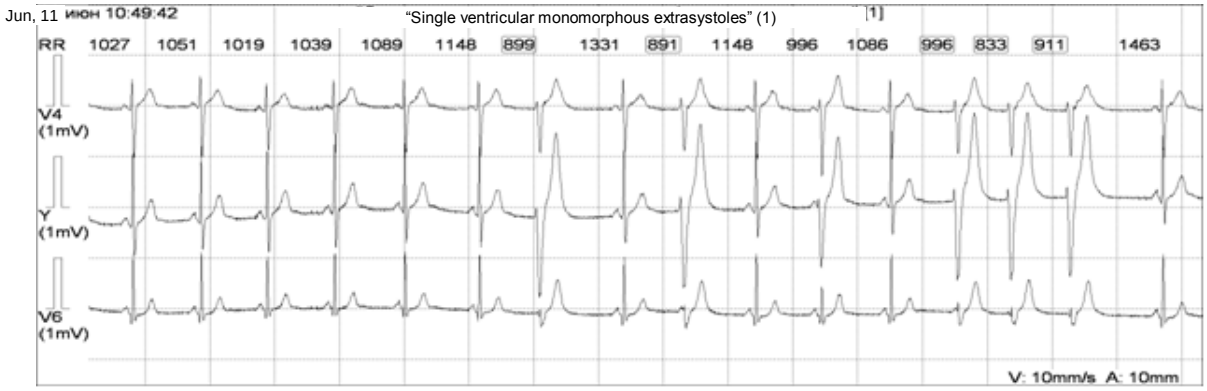
The patient underwent the investigation in 2008 after two episodes of loss of consciousness: EEG revealed a focus with pathologic activity in the posterotemporal-parietal-occipital region in the left hemisphere at rest and when performing the hyperventilation test. MRI did not find any focal changes but showed initial signs of dyscirculatory encephalopathy.

**Supposed diagnosis:** arrhythmogenic faint, differential diagnosis with epilepsy.

**Plan of the investigation:** ECG, echocardiography, Holter monitoring, stress-test, EEG. Tilt-test in case of intact results.

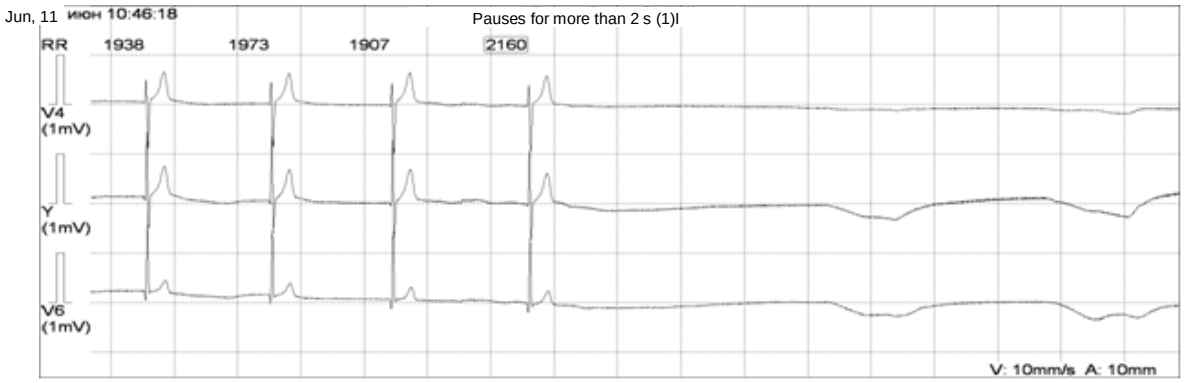
**Findings of the investigation.** Active orthostatic test was negative. ECG was without pathologic changes. Holter monitoring (ECG) recorded an episode of group monomorphous ventricular extrasystoles, instable atrial tachycardia paroxysm with heart rate of 110 beat/min. Electroencephalography revealed signs of lowered threshold of readiness for convulsions.

**Tilt-test:** *initially:* normotension, normosystolia, unremarkable ECG, single and group ventricular monomorphous extrasystoles, normal general personive condition.

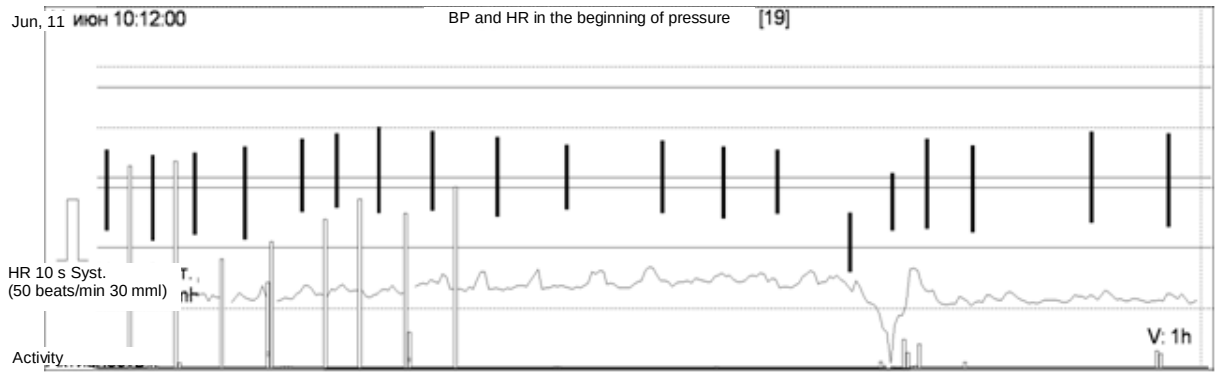



*Orthostasis:* the general personive condition, ECG parameters and BP did not change during 20 min of stay in the upright position. At minute 21 the patient suddenly felt unwell because of drop of BP and bradyarrhythmia (sinus bradycardia, nodal escape rhythm with heart rate of 30 per min changing to asystolia for 13.669 ms). Any ischemic changes were not observed.

*Cause for stopping the test:* acute arterial hypotension, arrhythmia, asystolia. The orthostasis period was 21 min.




*Recovery period:* recovery of sinus rhythm, normalization of hemodynamics. The general personive condition improved gradually. No chest pains, headaches, dizziness, and focal symptoms after 15 min. Unremarkable ECG.




Conclusion: the test is positive; cardioinhibition with asystolia (type 2B according to R. Sutton, 1992).

**Comments**. The peculiarity of the case consists in the fact that the tilt table testing results changed understanding of final diagnosis. Not arrhythmogenic mechanism but a very intensive vasovagal reflex underlay syncope syndrome. This changed the therapeutic tactics fundamentally: implantation of a permanent pacemaker was indicated to the patient taking into account the clinical features of the faint (asystolia for more than 13 s).

### *Clinical case 2*

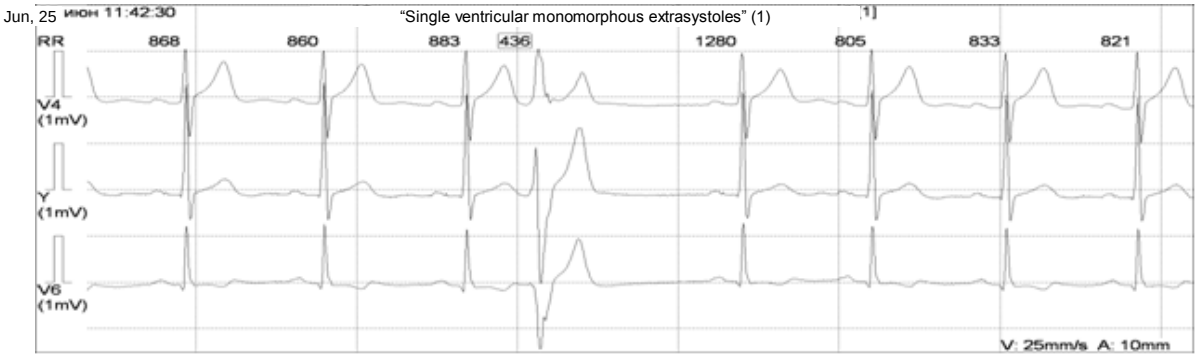
**Medical history.** Patient O., 58 years old, was hospitalized with complaints of pronounced dizziness when turning his head, unsteady gait, episodes of "mist in the eyes" and sudden weakness. He did not experience full loss of consciousness earlier but when he attempted to stand up quickly from the bed he fell on the floor six months ago. He did not seek medical attention. Since that time he has become unsure of himself when he changes the position of his body, he needs a support in order to stand up successfully. It is known that the patient has been suffering from arterial hypertension for 20 years, he had a stroke in the left hemisphere 5 years ago. He did not receive any pharmacotherapy at the time of hospitalization.

**Supposed diagnosis**: cochleovestibular syndrome? Vertebrobasilar insufficiency? Orthostatic hypotension?

**Plan of the investigation:** ECG, MRI of the brain, cervical arteries, duplex scanning of the brachiocephalic arteries, encephalography, consultation by a neurologist, and tilt table testing.

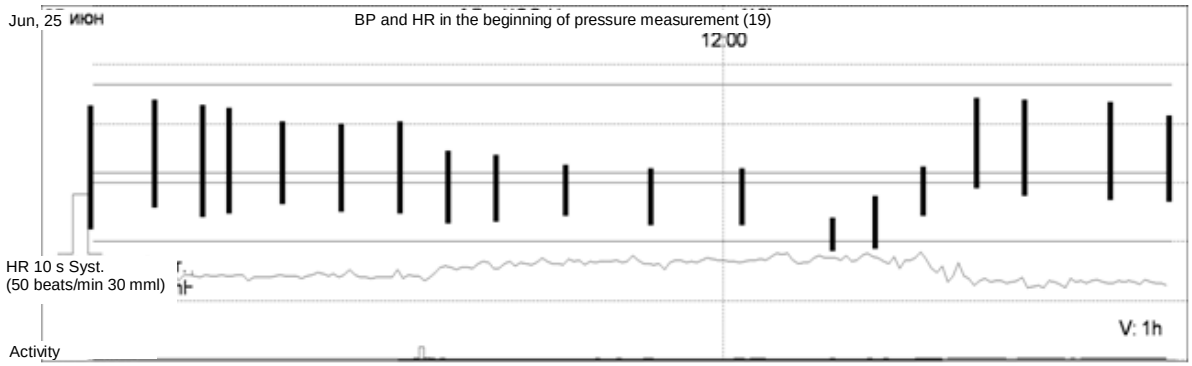
**Findings of the investigation**: electroencephalography did not reveal any focal, paroxysmal, specific epileptiform activity; stem structure dysfunction was detected. Duplex scanning of the brachiocephalic arteries showed signs of marked atherosclerotic involvement of the arterial walls at the whole their length complicated by plaque formation on the right side; there was no data indicative of hemodynamically significant stenoses and occlusions. MRI detected cystous-gliosis changes in the parietal lobe of the left hemisphere (ACVA outcome), signs of dyscirculatory encephalopathy and replacement hydrocephalus of mixed type. There were no MR-findings indicative of stenosing or occluding processes in the cerebral arteries and also vascular malformations and aneurysms; MR-picture of left vertebral artery hypoplasia was seen. Conclusion of a neurologist: dyscirculatory encephalopathy of stage II-III of mixed genesis with diffuse organic symptoms. Condition after ACVA in the system of the left medial cerebral artery. Osteochondrosis of the cervical, thoracic and lumbosacral spine with muscular-tonic syndrome.

**Tilt table testing:** *initially:* normotension, normosystolia, ECG was unremarkable; single ventricular extrasystoles; no complaints.




*Orthostasis*: the patient showed progredient lowering of blood pressure down to critical values immediately after turning the Table what required to stop the investigation. The patient developed increasing orthostatic symptoms (asthenia, dizziness, visual impairment, obnubilation) simultaneously with lowering of BP. Any ischemic changes, rhythm and conduction disturbances were not revealed. HR increment was insufficient.

*Recovery period*: gradual normalization of hemodynamics and general well-being. No complaints.




CONCLUSION: the test is positive, vasodepression is observed (type 3 as per R. Sutton, 1992). Single ventricular extrasystoles. Orthostatic hypotension. Chronotropic insufficiency.

**Comments**. In this situation, the clinical picture in combination with the data of the medical history orientated the diagnostic search in the direction of vascular neurologic disorders. The tilt-test results revealed significant orthostatic hypotension. This allowed to recommend the patient non-medicinal measures for increasing the orthostatic stability and to correct vasoactive therapy.

### *Clinical case 3*

**Medical history.** Patient Kh., 52 years old, was hospitalized with complaints of repeated syncope conditions developing without any provoking factors. The patient has been suffering from essential hypertension for 10 years, he uses Lisinopril permanently. He had in total four episodes of full loss of consciousness during a year. Presyncope period lasts for several minutes: he develops headache, seeing spots. The unconscious period lasts for several tens of seconds. The general personive well-being is normalizing quickly in the post-syncope period. There were no injuries when he lost consciousness. It is

known that after the last syncope episode the patient was hospitalized to a hospital where atrioventricular block of degree I and aortic valve insufficiency of degree II were revealed.

**Supposed diagnosis**: cardiogenic faint? Migraine?

**Plan of the investigation:** ECG, EchoCG, treadmill test, Holter ECG and BP monitoring, MRI of the brain, cervical arteries, duplex scanning of the brachiocephalic arteries, electroencephalography, consultation by a neurologist. If there are no findings, tilt table testing will be performed.

**Findings of the investigation**: the active orthostasis test was negative. ECG was without pathologic changes. Holter monitoring: "pressure load indices" at daytime were typical of stable hypertension. Echocardiography showed that the left ventricle was not enlarged. Left ventricular hypertrophy by myocardium mass index was found. Any local contractility disturbances were not revealed. Global contractility was not disturbed. The left atrium was insignificantly enlarged. The ascending aorta was dilated up to 42 mm. The walls, demilunes were indurated. Aortic ring calcification was observed. Blood flow at the valve was accelerated. Aortic valve insufficiency of degree II was diagnosed. The mitral valve cusps were indurated. Mitral insufficiency of degree I was found. The right cardiac chambers were not dilated, the tricuspid and pulmonary valves were unremarkable. Any pathologic flows at the valves were not revealed. The calculated pulmonary pressure was normal. Treadmill test was negative.

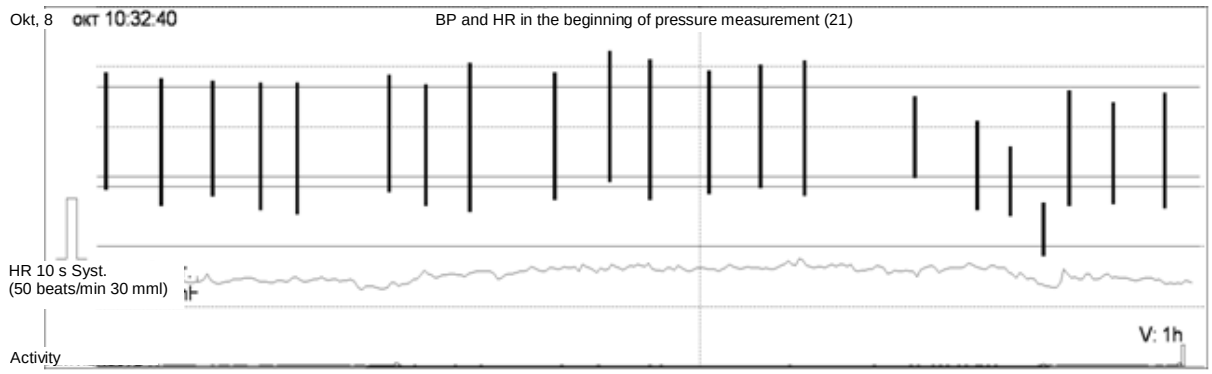
Electroencephalography revealed transient local changes (with presence of pathologic slow-wave activity) in projection of the left temporal lobe; any paroxysmal, generalized undoubted epileptiform activity was not found. Duplex scanning of the brachiocephalic arteries showed signs of initial atherosclerotic involvement of the arterial walls at the whole their length complicated by plaque formation on the right side; there was no data indicative of hemodynamically significant stenoses and occlusions. MRI revealed signs of dyscirculatory encephalopathy and internal hydrocephalus, cystous dilation of the posterior horns of the lateral ventricles; there were no MR-findings indicative of stenosing or occluding processes in the cerebral arteries and also vascular malformations and aneurysms; there were no MR-signs of stenoses and vascular malformations of the cervical arteries. Conclusion of a neurologist: dyscirculatory encephalopathy of degree I of mixed genesis (associated with atherosclerosis, hypertension and disturbed liquor circulation) with cephalgia, asthenoneurotic syndrome, psychophysiologic insomnia, paroxysmal conditions.

**Tilt table testing:** *initially:* moderate arterial hypertension, normosystolia. Unremarkable ECG; no complaints.

*Orthostasis:* slight increase of BP in orthostatic position was observed, then a phasic BP reaction with moderate amplitude excursion without significant reduction was seen. HR increment was adequate.

*At minute 30 of orthostasis*: quite sudden lowering of blood pressure was observed, what was accompanied with hyperhydrosis, paleness, complaints of weakness, sickness, nausea, blackout. Moderate secondary HR decrease was seen. Any ischemic changes, rhythm and conduction disturbances, pauses in the heart function were not revealed.

*Recovery period*: fast normalization of hemodynamics and general well-being. No complaints.




CONCLUSION: the test is positive, vasodepression is observed (type 3 as per R. Sutton, 1992).

**Comments**. The complex investigation allowed to rule out significant cardiac and neurological causes for faints. Tilt Table testing was of critical importance among all performed investigations. The clinical picture and hemodynamic profile in orthostasis corresponding to the neurogenic mechanism of syncope coincided completely with episodes experienced by the patient before the present hospitalization.

BP was higher in the group with the negative result of tilt table testing than that in the group of "tilt-positive" patients (138.1 ± 4.8/83.9 ± 2.8 and 121.7 ± 4.3/ 77.7 ± 1 mm Hg, respectively; p = 0.035 for systolic BP). "Tilt-negative" patients similarly had higher mean hemodynamic pressure (101.9 ± 3.2 and 92.3 ± 1.3, respectively; p =0.039). This is consistent with the logics that "tilt-negative" patients had the more severe degree of essential hypertension than "tilt-positive" patients.

One may suppose that the tilt table testing result depended on the initial blood pressure level. We revealed a negative correlation between the test outcome and systolic (r = −0.47; p = 0.03) and mean hemodynamic pressure (r = −0.46; p = 0.03).

The blood pressure in both groups differed approximately to a same degree (138.9 ± 4.6/ 86.7 ± 2.9 and 123.5 ± 6.7/80.7 ± 2.8 mm Hg, respectively; p = 0.043 for systolic BP) immediately after transition to orthostasis (point 2).

The degree of BP difference in both groups increased (133.8 ± 4/89 ± 2.5 and 69.3 ± 4.9/48.2 ± 2.9 mm Hg, respectively; p = 0) by the time when the patient developed syncope condition (point 3); considerable decrease of blood pressure at the moment of faint was observed.

The differences in the systolic pressure levels in the recovery period were insignificant (130.6 ± 9.5 and 121.7 ± 3.9 mm Hg for "tilt-negative" and "tilt-positive" patients, respectively). At the same time, diastolic pressure in "tilt-negative" patients was higher (84.9 ± 2.2 and 74.3 ± 1.8 mm Hg, respectively; p = 0.01) just as the mean hemodynamic pressure (102.5 ± 2.6 and 90.2 ± 2.2 mm Hg, respectively; p = 0.01), probably, due to more severe initial hypertension.

Initial HR did not differ significantly in both groups (72.6 ± 3.3 and 74.2 ± 3.6 beat/min). Any difference between mean HR also was not observed after transition to orthostrasis (79 ± 4.2 and 77.7 ± 4.1 beat/min). But chronotropic insufficiency in orthostasis was observed 2.5 times more often in the group of "tilt-positive" patients what might be evidence of autonomous disorders in these patients. When HR was compared just before the faint or at minute 20 of the test, its mean value was significantly lower (86.4 ± 4.7 and 62.7 ± 6.9, respectively; p = 0.01) in the group of "tilt-positive" patients; it was the natural vagal reaction in a patient with reflex faint. Any significant difference in mean HR was not revealed in the recovery period (70.27 ± 3.29 and 63.83 ± 1.78 beat/min).

Cardiac rhythm disturbances at minute 20 of orthostasis were found more often in "tilt-negative" patients and disturbed conduction was observed more often in "tilt-positive" patients before the faint due to pauses or bradycardia of vagal nature.

The profile of changes in the linear blood velocity (LBV) in the medial cerebral arteries was similar to variations of the blood pressure during the tilt table testing. LBV values in two groups ("tilt-negative" and "tilt-positive" patients) were initially 50.3 ± 1.9 and 54.2 ± 5.5 cm/s, respectively. These values also did not differ significantly in point 2 (46.1 ± 1.9 and 51.2 ± 5.4 cm/s). Mean LBV decreased considerably in patients with provoked faint (43.4 ± 1.7 and 29.0 ± 2.9, respectively; $p = 0.003$).

At the same time, changes in the peripheral resistance parameters in "tilt-positive" patients were reciprocal to LBV variations in the same group. The mean Gosling's pulsatility index was significantly higher (0.77 ± 0.06 and 1.86 ± 0.55) in the patient group with faint in the test point 3.

When syncope is provoked by tilt table testing, these reactions of intracerebral hemodynamics are completely within the limits of pathophysiology of a reflex faint: short-term cerebral hypoperfusion because of lowered systemic blood pressure and/or bradycardia.

When conducting the tilt table testing, in addition to hemodynamic changes we also analyzed variations of laboratory parameters: insulin, BNP, NT-proBNP, noradrenaline and dopamine.

During the test, the group on the whole showed a trend to lowered insulin level which was clearly manifested by minute 20 of orthostasis or before the faint. The insulin levels in points 1, 2, 3 were 25.6, 21.6 and 13.9, respectively. The difference in the insulin level in points 2 and 3 was significant ($p = 0.03$). In other words, the longer the orthostatic stress lasted, the larger insulin consumption was. When considering the changes of this parameter separately in "tilt-positive" and "tilt-negative" patients we found that the change trend remained the same, but differences were not significant any more (Fig. 5.4, 5.5).

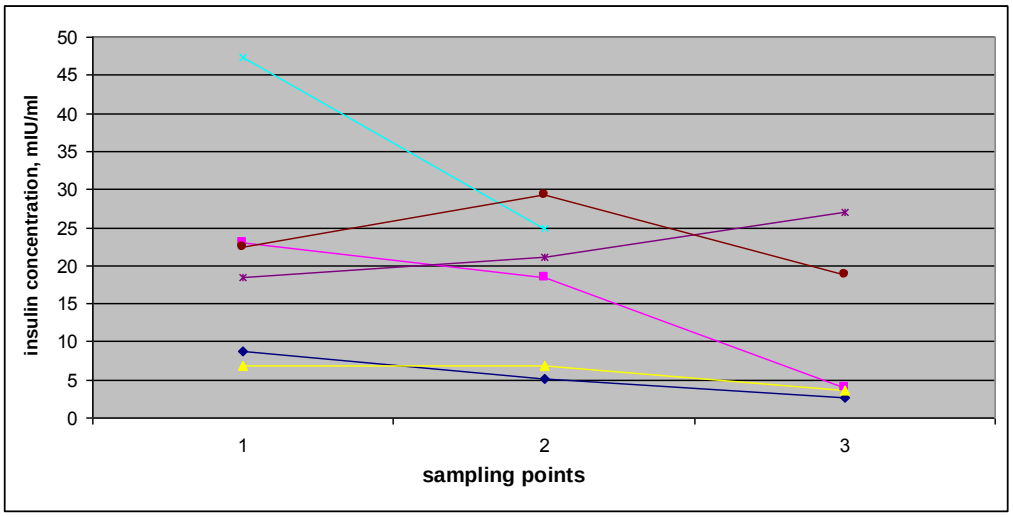



Fig. 5.4. Changes in Insulin Concentration in the "Tilt-Positive" Patient Group

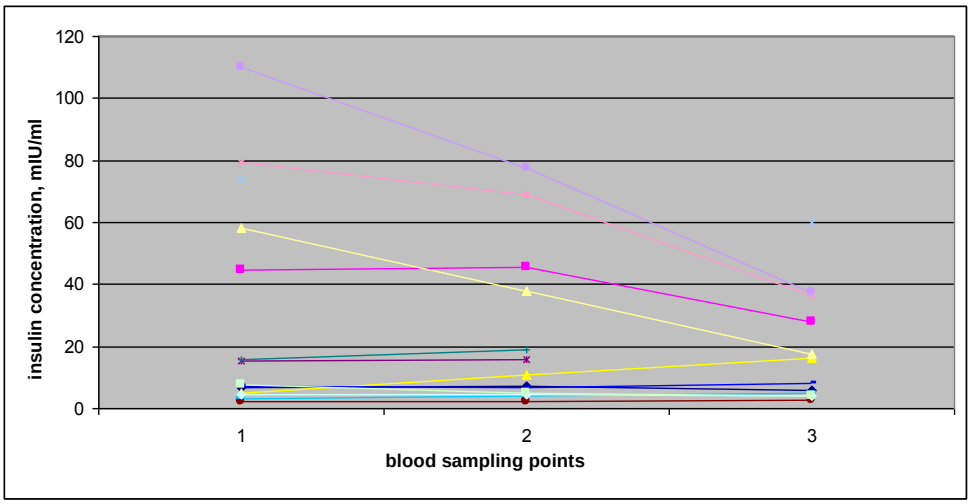



Fig. 5.5 Changes in Insulin Concentration in the "Tilt-Negative" Patient Group

The changes in BNP level during the tilt-test in the general patient group with faints was as follows: 57.0, 60.3, and 53.7, respectively, in three time points and the increase of BNP level after turning the Table was significant (p = 0.03). The separate analysis of the parameter changes in two groups confirmed the trend of changes in each of them but the initial and subsequent BNP levels were approximately 2 times lower in the "tilt-positive" patient group (29.33; 36.5; 26.4) as compared to "tilt-negative" patients (68.9; 70.5; 65.0) (Fig. 5.6) and the difference between points 2 and 3 was significant (p = 0.04).

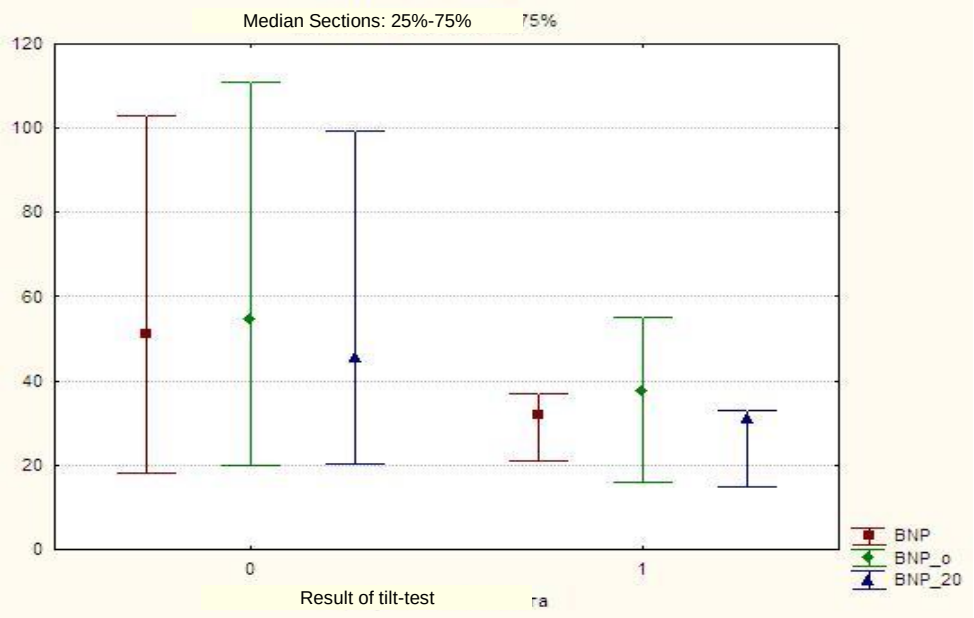



Fig. 5.6. Mean BNP Values During the Tilt-Test in
"Tilt-Negative" (0) and "Tilt-Positive" Patients (1)

Any difference in NT-proBNP levels practically was not observed in three different points during the tilt-test both in the general patient group (13.17; 13.16; 13.26) and when considering the test results, i. e. in "tilt-negative" (15.97; 15.96; 15.38) and "tilt-positive" (6.62; 6.61; 8.16) patients. Attention is drawn by the fact that the level of this factor was also lower in patients with provoked faint than that in "tilt-negative" patients (Fig. 5.7). This fact allows to consider the supposition on involvement of natriuretic peptides in pathophysiology of reflex syncope conditions.

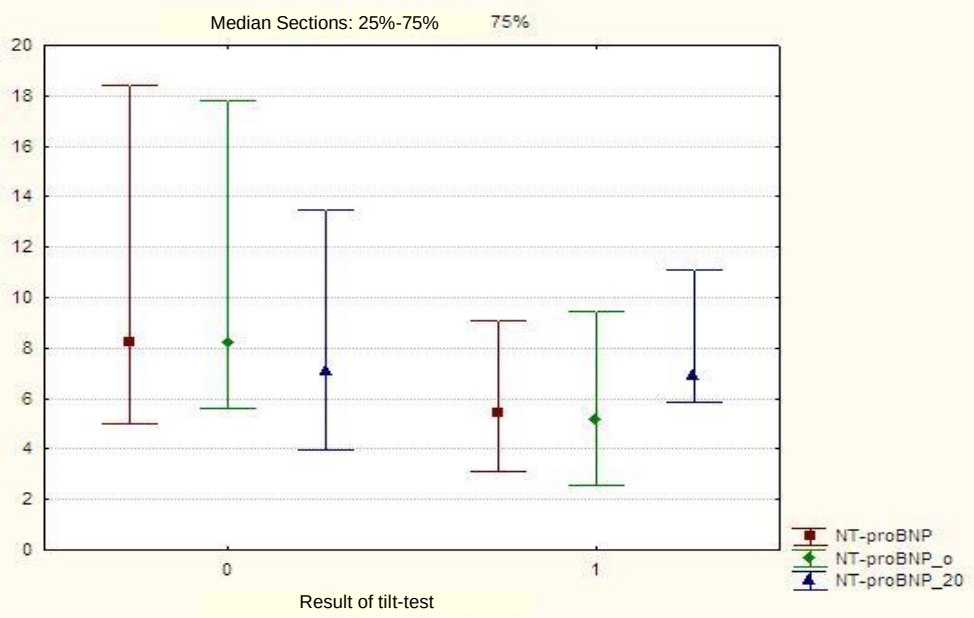



Fig. 5.7. Mean NT-proBNP Values During the Tilt-Test in
"Tilt-Negative" (0) and "Tilt-Positive" Patients (1)

When describing the changes in catecholamine level, it should be mentioned that the baseline noradrenaline levels were characterized by considerable dispersion, they somewhat increased in orthostasis (point 2) and lowered again in point 3 (4.07±3.57, 6.16±4.31 and 4.54±2.86, respectively). Such pattern was seen especially clearly in "tilt-positive" patients and had a reverse trend in most patients in the group with the negative test result. Besides that, "tilt-positive" patients had the lower baseline noradrenaline level than "tilt-negative" patients (Figs 5.8 and 5.9). It is probable that such changes reflected changes in HR in orthostasis. A strong positive correlation between noradrenaline concentration and HR was revealed in point 3 ($r = 0.86$, $p = 0.01$).

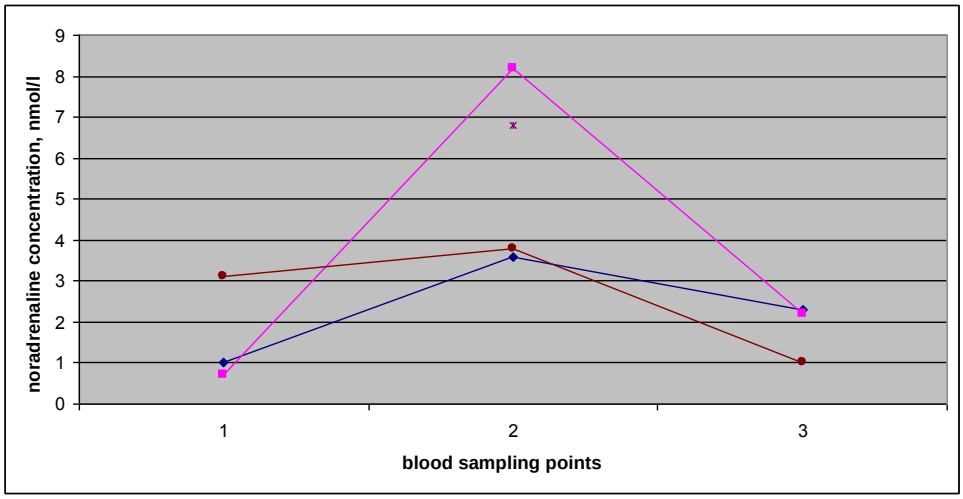



Fig. 5. Changes in Noradrenaline Concentration in the "Tilt-Positive" Patient Group

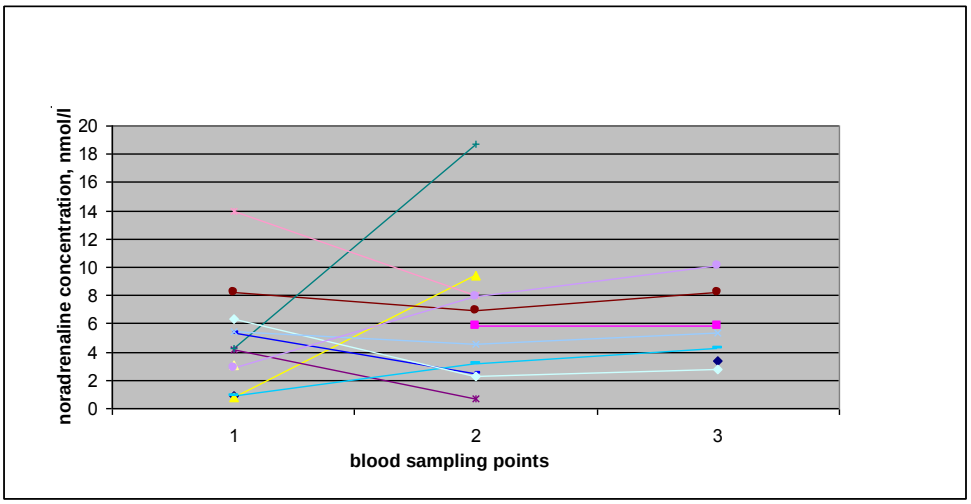



Fig. 5. Changes in Noradrenaline Concentration in the "Tilt-Negative" Patient Group

Approximately the same pattern was observed when assessing changes if dopamine concentration in orthostasis. The mean values of this parameter in three points in the general patient group were 0.27 ± 0.10, 0.60 ± 1.22 and 0.23 ± 0.09, respectively (Fig. 5.10 and 5.11).

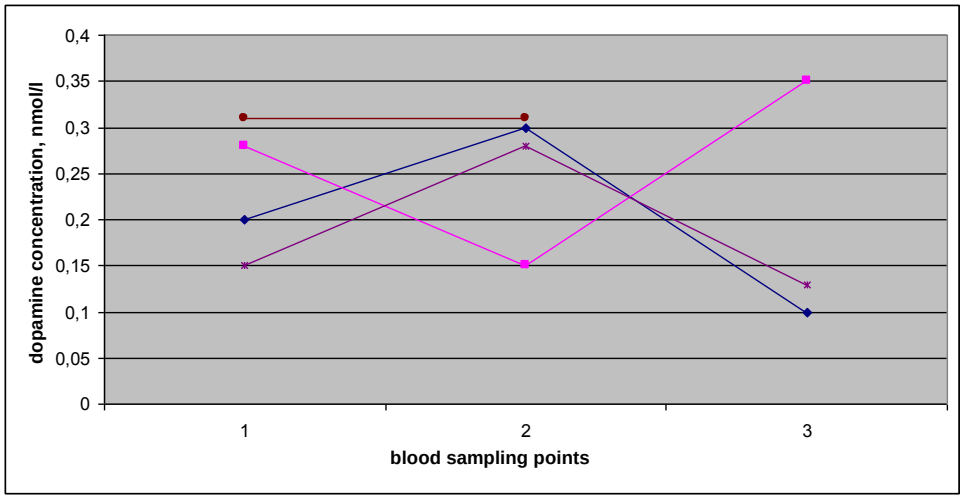



Fig. 5. Changes in Dopamine Concentration in the "Tilt-Positive" Patient Group

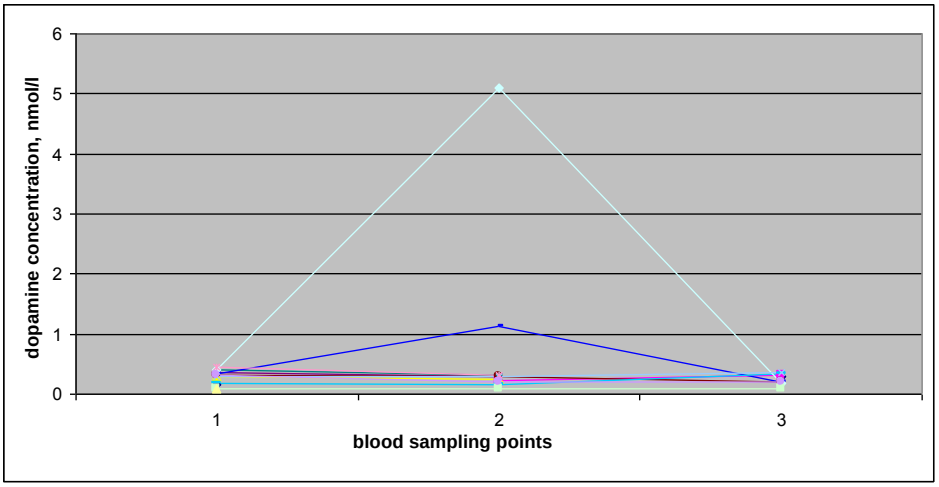



Fig. 5.11. Changes in Dopamine Concentration in the "Tilt-Negative" Patient Group

Thus, the analysis of the investigation results enables us to draw some generalizations.

We obtained the data confirming the high prevalence of syncope syndromes in the nosological structure in liquidators of accident aftermath at ChNPP. When analyzing the causes for syncope conditions, we revealed that a considerable percentage of persons had reflex nature of faints (13 persons) and most of them (9 persons) had a combination of syncope episodes with different cardiac pathology (CHD, cor pulmonale, pulmonary embolism, permanent form of atrial fibrillation, aortic insufficiency) and only 4 persons had no structural cardiac and pulmonary pathology. Secondary orthostatic hypotension because of diabetic, drug and intoxication neuropathy was diagnosed in 3 patients; this pathology was observed in combination with CHD in 1 case. Attention is drawn by the fact that it was very difficult to establish an isolated cause for faints in the liquidator group in most cases; syncope conditions had the most often the multiple, combined etiology. So, e. g., patients with the reflex nature of faint proved by the tilt table testing often had different signs of vegetative insufficiency (POTS, OH, chronotropic insufficiency), cardiac arrhythmias. Presyncope conditions in 2 persons correlated clearly with the vascular pathology of the brachiocephalic arteries (vertebral artery hypoplasia). We could not reveal an evident cause for faints in more than one third of patients with syncope syndromes (12 persons). It is probably that these cases could include psychogenic pseudosyncope, transient loss of consciousness referred to non-syncope conditions.

Undoubtedly, the investigation of patients with syncope syndrome should be started from thorough obtaining of the case history with precise elucidation of the circumstances associated with the faint. One should exclude, first of all, the cardiologic pathology because it has the most unfavorable prognosis as a cause of faints. Then, if the cause for syncope condition remains unclear, it is necessary to perform the tilt table testing the result of which will help to prove the reflex nature of the disorder. The special expensive methods such as cerebral computed tomography, MRI of the cervical vessels, electroencephalography prescribed without direct indications have a low diagnostic final result.

We obtained undoubted evidences of the interrelationship between different neuromediator systems and orthostatic stability. Nevertheless, it is too early to make definite conclusions about specific mechanisms of hormone involvement in pathophysiology of syncope conditions. This may be a task for future studies.

Our study revealed some features of the life quality and psychological status of liquidators of accident aftermath suffering from syncope conditions. The parameters of liquidators' life quality were considerably lowered as compared to healthy persons what was manifested in disturbed both physical and emotional well-being. The everyday functioning, professional activities were disturbed in persons to a maximum extent due to pronounced influence of existing physical and emotional problems. Their exercise stress was restricted, social activity was lowered, their interests were narrowed. More than 50 % of persons had the high level of personal anxiety what caused the high anxiety level on average for the whole sample and indicated the emphasis of the sensitive, psychasthenic and asthenoneurotic features in the personality structure, difficulties in self-actualization, lowered stress tolerance.

The neurasthenic and paranoiac types of attitude to the disease were the predominant ones; they were characterized by hypernosognosia, i. e. this patient category overestimated the severity and danger of existing disorders, they do not believe in recovery. The revealed types of the reaction

to the disease were characterized by disharmonicity, lowered psychic adaptation associated with the disease. The active behavioral strategy for "solving problems," by which a person tries to use the available personal resources for searching the possible methods for effective solution of problems, predominated to some extent in case of low level of the coping behavioral strategies. The level of neuro-psychic stability was somewhat lowered, mainly, due to the anamnestic scale and neurotic and somatomorphous disorder scale and the individual characterologic features reached the accentuation level what was evidence of the formed vector of possible deadaptation disturbances and required more close attention to their psycho-emotional condition.

Thus, the analysis of the investigation results revealed that liquidators suffering from syncope conditions needed the medical and psychological assistance and psychocorrection measures aimed at lowering the anxiety level, reducing the disharmonicity of the internal picture of the disease, improvement of neuro-psychic stability and adaptation potential. This will allow to optimize significantly the treatment process and improve their life quality.

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### 5.2.3. Coronary Heart Disease

The greatest danger for patients with coronary heart disease is associated with myocardium ischemia. Hypoperfusion, even if it lasts for a relatively short period, may cause arrhythmia including life-threatening arrhythmia, sudden cardiac death. Acute and long-term stopping of myocardium area blood supply leads naturally to development of its infarction. Repeated or chronic extensive myocardium ischemia is accompanied with the development of ischemic cardiomyopathy and heart failure, in particular, because of post-ischemic, partially reversible local contractility disturbances, i. e. myocardium hibernation and stunning. Cardiomegaly and heart failure develop.

**Chronic painful and painless myocardium ischemia**. Anginal pains (or discomfort) are a sign of myocardium ischemia, which is the most recognizable one. They are characterized by retrosternal

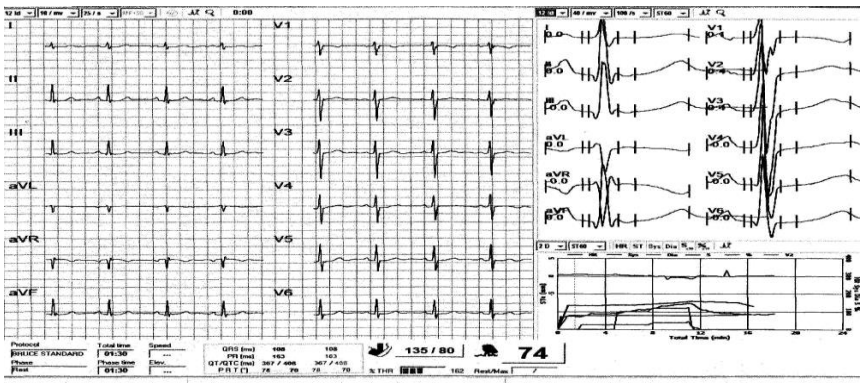
localization, burning, constricting, compression nature; irradiation is also possible. Sometimes respiratory discomfort develops simultaneously, and severe pain is accompanied by typical profuse sweating. Exertional angina pectoris syndrome is a kind of anginal pains. This phenomenon is reversible, it develops usually in persons with significant fixed (atherosclerotic) stenosis of one or several subepicardial arteries and is manifested at a certain exercise stress level, when the resources for myocardium blood supply and its demand do not correspond anymore.

**Exertional angina pectoris** is manifested at the moment of the stress, i. e. at its peak. Stable angina pectoris is usually provoked by approximately equal stress load which determines its functional class (Campeau, L., 1976) (Table 5.33). Angina pectoris often develops earlier at the start of the exercise stress than after a period when the patient has "gathered speed." Angina pectoris is often more intense in the morning than in the evening. It is very typical that it is more intense in the cold, in case of contrary cold wind. The sensitivity of angina pectoris to the cold and some variability in the stress tolerance over a day may be clinical signs of diffuse coronary vasospasm (i. e. general increased tonus and diffusely lowered patency of the coronary arteries). But the problem of coronary vasospasm and vasospastic angina pectoris deserves special consideration.

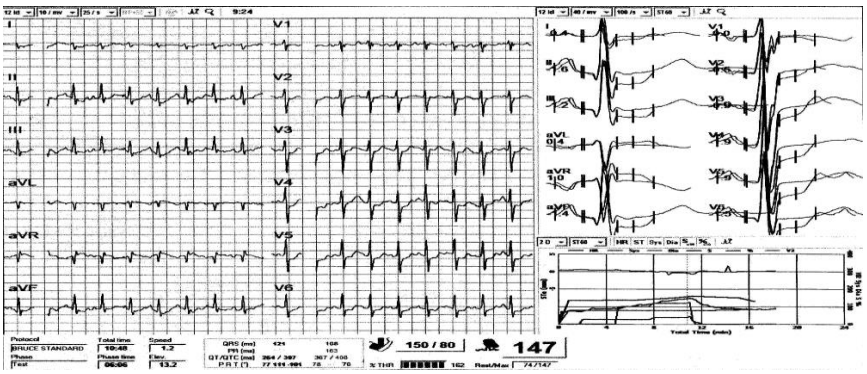
Table 5.33

Functional Classification of
Stable Exertional Angina Pectoris Severity (Canadian classification)

| Functional class (FC) | Signs |
|---|---|
| I | The usual everyday physical activity (walking or going upstairs) does not cause angina pectoris. Pains develop only if the person performs very intensive or very fast or long exercise stress |
| II | Slight restriction of usual physical activity: angina pectoris develops in case of fast walking or when going upstairs, after meals or in the cold, or in windy weather, or in condition of emotional stress, or within the first several hours after awakening; when walking in an even area for a distance of more than 200 m (two blocks) or when going upstairs for more than one flight in a usual tempo under normal conditions |
| III | Significant restriction of usual physical activity: angina pectoris develops when walking quietly on an even area for a distance of one or two blocks (100–200 m) or when going upstairs for one flight in usual tempo under normal conditions |
| IV | Impossibility to perform any exercise stress without unpleasant sensations or onset of angina pectoris at rest |




a

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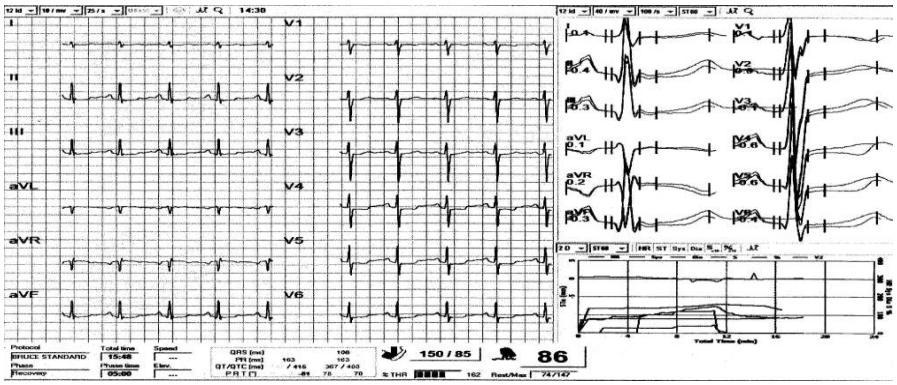


c

Fig. 5.12. ECG with Ischemia When Performing the Bicycle Ergometry Test (a—Baseline ECG; b—ECG at Stress Peak; c—ECG During the Recovery Period)

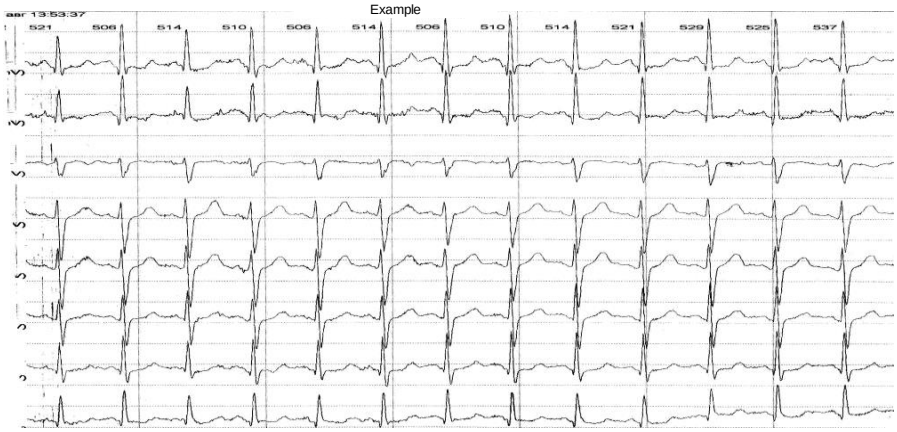


Fig. 5.13. Fragment of ECG Recorded During 24-h Monitoring (Painless Myocardium Ischemia)

It is possible to assess objectively angina pectoris severity (class) using the stress ECG-tests (bicycle ergometry, treadmill test). The stress allows to reveal occurrence of typical ischemia ECG-signs, sometimes also arrhythmias, and to analyze them in association with pain syndrome (Fig. 5.12, 5.13). It is useful to use the objective equivalents angina pectoris functional classes, i. e. the number of metabolic units, double product and stress power (Aronov, D. M., Lupanov, V. P., 2007) (Table 5.34).

Table 5.34

Characteristics of Angina Pectoris Functional Class
by Objective Results of the Stress Test

| Parameters | Functional class of exertional angina pectoris | | | |
|---|---|---|---|---|
| | I | II | III | IV |
| Number of metabolic units (treadmill-test) | ≥7.0 | 4.0–6.9 | 2.0–3.9 | <2.0 |
| Double product (HR x BPs x $10^{-2}$) | >278 | 218–277 | 151–217 | <150 |
| Power of the last stress stage (bicycle ergometry, W) | ≥125 | 75–100 | 50 | 25 |

The expert analysis shows that the diagnosis of angina pectoris syndrome in liquidators of accident aftermath at the Chernobyl NPP quite often was made not precisely (from 10 to 40 % of cases) let alone the angina pectoris functional class. This depends on the patients' region of residence (where health care facilities have some "own," more or less strict, style for making this diagnosis). A physician often does not see the strict correspondence between pain syndrome and well-known criteria and overstates the diagnosis believing that he (she) acts "for the sake of a patient." But this is not medical valor at all. Diagnosis of atypical angina pectoris or atypical cardialgia syndrome is justified in certain atypical cases (Table 5.35). If a physician still doubts in presence of myocardium ischemia itself, he (she) should try to verify it using special methods. These include stress ECG-tests (bicycle ergometry, treadmill-test) (see Fig. 5.12), stress-echocardiography, stress myocardial perfusion scintigraphy and also (in some special cases) ECG-monitoring (see Fig. 5.13). The latter of the above methods became readily available, its benefit is incontestable. This method is of importance for patients with angina pectoris in order to analyze the interrelationship between angina pectoris and arrhythmia, reveal vasospastic angina pectoris; besides that, it allows to detect painless myocardium ischemia. But one should remember that its sensitivity, specificity and also reproducibility of obtained results concerning presence of myocardium ischemia are considerably lower than these of ergometric ECG-tests. At present stress-echocardiography is one of the most informative methods for noninvasive diagnostics of latent coronary insufficiency (both physical and drug stresses causing ischemia are used). Stress-echocardiography surpasses the stress ECG-tests in its prognostic significance. It is more sensitive and specific in diagnostics of myocardium ischemia.

Table 5.35

Clinical Classification of Chest Pain
(Diamond, G. A., 1983)

| |
|---|
| Typical angina pectoris (diagnosed) |
| • retrosternal pain (discomfort) of typical nature and duration (up to 10 min);<br>• develops during exercise stress or in case of emotional stress;<br>• relief occurs at rest and (or) after administration of Nitroglycerine. |
| Atypical angina pectoris (probable) |
| • Only two of above signs are available |
| Cardialgia (not associated with myocardium ischemia) |
| • Only one of above signs is available or there are no such signs at all |

**Vasospastic (variant) angina pectoris (Prinzmetal's angina)** is observed in isolated form in insignificant percentage of patients with CHD. It is usually difficult for a physician to make a diagnosis just because of absence of the association with stress. A patient experiences a short-term spontaneous pain attack. If ECG can be recorded during the pain sensation or an attack develops during ECG-monitoring, this usually helps significantly in diagnostics because ECG shows typical

ST segment elevation (not depression revealed in patients with exertional angina pectoris) (Fig. 5.14). The mechanism of these attacks is associated with episodes of coronary artery local spasm (just this restricts the local myocardium supply with oxygen). Spasm may develop both in case of presence and absence of evident atherosclerotic involvement of the coronary arteries. The vasospasm mechanisms are not clear. It may be provoked by smoking, cold, electrolyte disturbances, autoimmune diseases (vasculitis). The prognosis for patients with vasospastic angina pectoris is uncertain and disturbing. A significant percentage of patients, especially young people, develops infarction or sudden death. Therefore, if vasospastic angina pectoris is suspected, the investigation should be drastic. It is advisable to perform coronarography in addition to ECG, stress tests (they often show negative result) and ECG-monitoring. In particular, this is of importance because it is possible to verify spasm and concomitant fixed (atherosclerotic) obstructions influencing the prognosis negatively and removable by a surgical intervention in some cases.

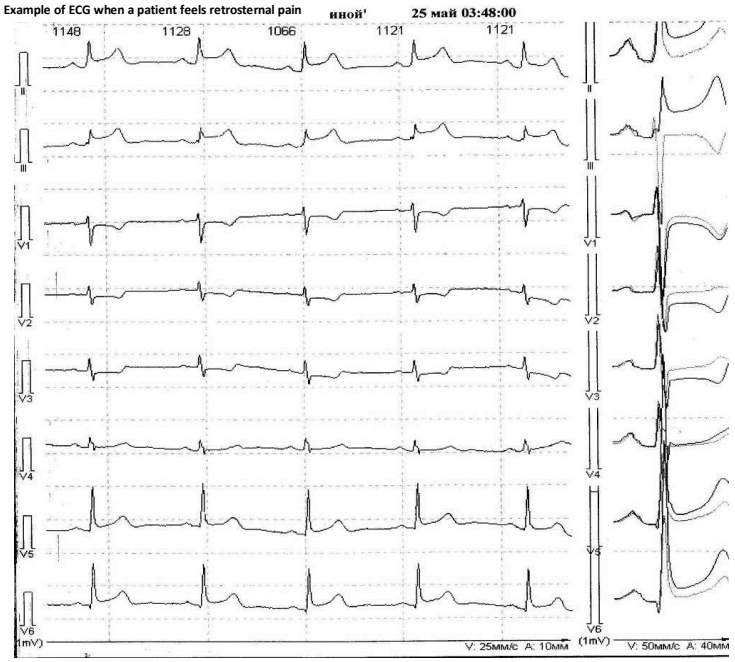


Fig. 5.14. ST Elevation in ECG

**Paroxysmal painless (silent) myocardium ischemia**. Coronary heart disease may develop without any symptoms or with few symptoms for a long time. The large-scale and very important Framingham epidemiologic study showed that myocardial infarction was identified by the retrospective ECG analysis nearly in every fourth case and is was asymptomatic in a half of cases. Painless ischemia is more typical for females (than for males), patients with diabetes mellitus, persons abusing alcohol.

When analyzing the case reports of liquidators in whom diagnosis of angina pectoris was made without sufficient grounds, we could note approximately in a half of cases that this hyperdiagnostics was based on the justified physicians' concern about coronary heart disease. The obstructive affection of the coronary arteries is indeed probable at a certain age and in persons with typical risk factors. It may be verified as an anatomic phenomenon only with the help of coronarography (including also digital, computed tomographic version). But this investigation as also some other investigations, which are useful for revealing myocardium ischemia (from scintrigraphy to stress-echocardiography, but often even standard stress ECG-tests) is feasible only at well-equipped medical centers.

At the preliminary (outpatient) stage of the investigation, way out of the difficult situation should consist evidently not in making a false diagnosis but in objectivization of the risk of cardiovascular complications (including those associated with the cardiac pathology), adequate investigation (at least, stress ECG test and ECG monitoring) and immediate administration of the treatment lowering the risk (if it is high).

As concerns painless forms of coronary heart disease and episodes of painless myocardial ischemia (they are observed not rarely and quite expected in typical cases or risk groups), it is advisable to distinguish isolated forms of painless cardiac ischemia and their combination with pain syndromes (in particular, angina pectoris. Painless cardiac ischemia may be revealed either in exercise stress tests or with the help of monitoring (it is better if findings of these investigations supplement each other) and this may be done only very rarely by scheduled ECG recordings. As concerns patients with angina pectoris, painless ischemic episodes are quire typical for them. Painless myocardial ischemia, especially long-term, pronounced (according to the degree of repolarization changes) ischemia complicated with ventricular rhythm disturbances is an unfavorable prognostic sign (including prognosis regarding sudden death). Very active tactics of the investigation and treatment is required in such cases.

**Cardiac syndrome X** is syndrome of typical exertional angina pectoris or more often atypical angina pectoris without occlusion changes in the coronary arteries revealed by angiography. The probability of such situation is about 10–20 %. Moreover, positive results of stress tests in patients the normal coronary arteries are revealed approximately in the same percentage of cases. Cardiac syndrome X is observed more often in young persons (aged 30–45 years) and also in women.

The mechanisms of the considered syndrome are not established precisely. First of all, it should be stated that myocardial ischemia in patients with syndrome X can be confirmed not always by special methods. Evidently, this syndrome is a multifactor condition. The following explanations, which are applicable only to certain patients suffering from syndrome X, are the most convincing:

- microvascular affection manifested in the lowered functional resource for dilatation of the peripheral coronary vessels during the stress and associated, possibly, with endothelial dysfunction; the organic stenosing changes in the arterioles are not ruled out also;

- lowered pain perception threshold in combination with psychic disorders or psychologic features of a patient and also with cardiac vegetative innervation disbalance (predomination of sympathicotonic trends).

The prognosis for patients with syndrome X is favorable, it is better at any case than for patients with occlusion changes in the coronary vessels. But if patients have positive results of stress tests and multiple risk factors of complications, significantly disturbed endothelium function, prognosis is not so comforting.

Patients with syndrome X need the thorough investigation to rule out extracardiac causes of pains including those associated with the esophagus, thorax, pericardium, pleura and spine. A neurologist, psychologist and even psychiatrist should be involved in the diagnostic process in some cases. The information about the initial condition of the endothelial vasomotor function and its changes in the process of treatment of the disease is of critical importance.

**Coronarography** may be performed *with diagnostic purpose* in stable patients in whom angina pectoris is suspected (if noninvasive investigation methods allow neither rule out nor confirm the involvement of the coronary arteries but the judgement concerning this is critical for selecting the tactics of the patient management) or in patients with evident angina pectoris in order to assess more precisely the possibility of myocardial revascularization and the nature of the intervention [by open (surgical) or catheter (endovascular) method].

**Indications for coronarography in a patient with stable exertional angina pectoris when solving the problem of the possibility to perform a catheter intervention or open surgical revascularization**:

• severe angina pectoris of FC III-IV persisting with the optimum antianginal therapy;

• signs of pronounced myocardial ischemia (according to findings of noninvasive investigation methods);

• history of sudden death episodes or dangerous ventricular rhythm disturbances;

• disease progression according to changes in findings of noninvasive tests;

• early development of severe angina pectoris (FC III) soon after myocardial infarction or myocardial revascularization; and

• doubtful results of noninvasive test in persons having socially significant professions (drivers of public transport, pilots, etc.).

Thus, the more pronounced the clinical symptoms are, the worse prognosis is regarding the clinical picture, the more grounds are available for prescribing coronarography to a patient and solving the problem of myocardial revascularization.

**Indications for coronary angiography in order to make a diagnosis in patients with stable angina pectoris.** The investigation is evidently justified in patients with severe stable angina pectoris with high probability of coronary heart disease, especially if there is no acceptable effect of the pharmacotherapy and also if the history contains information about clinical death, malignant ventricular arrhythmias, early onset of moderate or severe angina pectoris after myocardial revascularization (transcutaneous intervention on the coronary arteries or coronary artery bypass graft surgery). Coronarography is more likely advisable in case of ambiguous or contradictory results of noninvasive tests, in patients with moderate or high risk of coronary heart disease and also in persons with high risk of repeated stenosis after the catheter intervention on the coronary arteries.

**At present the treatment of stable angina pectoris and other pain and painless manifestations of myocardial** ischemia is based mainly on the use of well-known antianginal drugs (this treatment is predominantly aimed at improvement of the life quality due to elimination of disease symptoms). But the basic modern directions, which should be supported by Russian physicians including those providing the medical and preventive aid to liquidators of accident aftermath at the Chernobyl NPP, include cardiac revascularization and also active prophylaxis of atherosclerosis progression. These measures combined with the antianginal therapy are aimed at increase of the lifespan, mainly, due to prevention of myocardial infarction and death. Special attention should be paid to formation of the healthy life style and fight against risk factors.

**Medicinal correction of angina pectoris**. Nitrates are the most effective and used the most often among different drugs administered for relief and prevention of pain in patients with angina pectoris. But one should have in mind that there is no evidence of the fact that they lower mortality

of patients with coronary heart disease. Nevertheless, the symptomatic efficiency of nitrates, their ability to improve exercise stress tolerance due to reduction of angina pectoris symptoms justify their use as the standard therapy in combination with β-blockers and calcium channel blockers. Addition of long-acting nitrates is indicated to patients with progressing disease. Nitrate tolerance developing often when they are administered for a long period is a considerable clinical problem. The most practicable method to avoid tolerance is to take the drug with irregular intervals of 8–12 h. It is possible to use also long-acting mononitrates; if they are taken once daily in the morning the effect is preserved for the whole day but the drug is not acting at night.

**β-adrenoblockers or calcium channel antagonists** are used in combination with nitrates in most cases. The meta-analysis of 90 randomized or crossover studies which compared the use of β-blockers, calcium channel blockers and long-acting nitrates in patients with angina pectoris did not reveal any significant difference in the probability of cardiac death and myocardial infarction by these drug groups (Heidenreich, P. A. et al., 1999).

Beta-adrenoblockers are preferable in patients with left ventricular dysfunction and insufficiency and also in the post-infarction period, in persons with sinus tachycardia and arrhythmia. But the drugs of this class have many contraindications: pronounced bradycardia, atrioventricular block of degree II and III, sick sinus syndrome, asthma and decompensated heart failure. Adverse events associated with β-blockers may include lowered exercise stress tolerance because of asthenia, impotence and obesity and also disturbed glucose tolerance. Caution should be exercised when using these drugs in patients with chronic obstructive pulmonary disease without evident bronchospasm, in patients with depression and peripheral vascular atherosclerosis. β-blockers may be administered to most patients with diabetes mellitus but special caution should be exercised in patients suffering from insulin-dependent diabetes mellitus with hypoglycemia symptoms.

If calcium channel blockers are administered to patients with angina pectoris, the drugs from non-dihydropyridine group (Isoptin, Diltiazem) are usually preferred. As concerns dihydropyridines, the convincing evidence of their efficiency (especially in patients with concomitant arterial hypertension) was obtained when using Osmo-Adalat in combination with β-adrenoblockers in a large-scale study ACTION (Heidenreich, P. A. et al., 2004). If angina pectoris is caused by coronary artery spasm, i. e. the matter concerns Prinzmetal's angina pectoris, β-blockers are not advisable, ineffective and even may cause worsening but calcium channel blockers including also dihydropyridine drugs are used successfully.

**The three-component antianginal therapy including nitrates**, calcium channel antagonists and β-adrenoblockers is administered if the two-component therapy is insufficiently effective. It is more safe to use in such combination calcium channel blockers of dihydropyridine group such as long-acting Nifedipine or Amlodipine and β-adrenoblocker with simple pharmacokinetics such as Atenolol which is not metabolized in the liver. The study ACTION found that addition of long-acting Osmo-Adalat to the combination of antianginal drugs improved outcomes of coronary heart disease (Heidenreich, P. A. et al., 2004).

If angina pectoris is still resistant to the pharmacotherapy it is possible to reckon on Trimetazidine (Preductal) and also Ivabradine (Coraxan). Trimetazidine has a beneficial effect on fatty acid and glucose metabolism thereby reducing the cardiac demand in oxygen and blood

supply. In accordance with the recommendations of the All-Russian Scientific Society of cardiologists “Diagnostics and treatment of stable angina pectoris (second revision)” (2008), it may be used in patients with exertional angina pectoris as an additional agent for improvement of antianginal efficiency of nitrates and other antianginal drugs. But the use of this drug does not influence outcomes of the disease.

Ivabradine (Coraxan), the $I_f$ current inhibitor providing for rhythm generation in the sinus node, has an antianginal effect due to lowered heart rate. The decreased myocardial contractility, bronchoconstriction, erectile function suppression, sleep disorders or depression are not typical of its action. The investigation BEAUTIFUL following up a quite large patient group with combination of stable coronary heart disease and systolic dysfunction (ejection fraction <40 %) receiving 5–7.5 mg of Ivabradine daily (as a rule together with β-adrenoblockers) for up to 2 years did not reveal on the whole any improvement of basic outcomes of the underlying disease when sinus rhythm was slowed down. The additional result analysis in the subgroups of this study showed that the treatment with Ivabradine, possibly, influenced the outcomes when the heart rate was more than 70 beats per min (Fox K., 2008).

The positive effect of the long-term therapy with ACE inhibitors and angiotensin receptor blockers in patients with coronary heart disease was confirmed by the results of the studies HOPE, EUROPA и ONTARGET which were evidence of fact that the drugs of above groups, when administered continuously for a long period, could favor prevention of cardiovascular complications in patients with CHD having multiple risk factors. But on the whole they play an auxiliary role and are more appropriate in patients with concomitant arterial hypertension.

**Hypolipidemic and antiaggregant** drugs are the key components for treatment of CHD. The target low density lipoprotein concentration (2.5 mmol/l or even lower) may be often achieved by keeping to a diet and using sufficiently high doses of statins. Aspirin should be administered to all patients having no contraindications to it. The efficiency of Aspirin regarding the decrease of the number of cardiovascular complications in patients with stable angina pectoris was confirmed by the meta-analysis of 287 randomized studies (Antithrombotic Trialists' Collaboration, 2002). Clopidogrel is recommended as an alternative for patients with Aspirin intolerance although this drug was never tested in patients with chronic stable angina pectoris. It is noteworthy that both statins and Aspirin have anti-inflammatory properties and influence positively the course of the atherosclerotic process. But the efficiency of use of antibiotics for treatment of coronary heart disease was not confirmed (Baker, W. L., Couch, K. A., 2007), and moreover, an attempt of such treatment may exert an unfavorable effect on outcomes (Gluud, C. et al., 2008). But at the same time influenza vaccination has a beneficial effect on risks of complications and mortality of patients with CHD.

**Refractory angina pectoris. Revascularization surgeries.** The multicomponent pharmacotherapy is not inferior to catheter interventions regarding its influence on the mortality and probability of myocardial infarction and other, the most significant cardiovascular complications in patients with stable but not the most severe exertional angina pectoris associated with multiple involvements of the coronary arteries and without sharp decrease of the cardiac systolic function. Such conclusion may be made basing on the results of the studies COURAGE (Boden, W. E. et al., 2007) and MASS II. In total about 4.5 thousand patients were prospectively followed up for

approximately 4.5 years within these studies. The large-scale meta-analysis (61 studies and more than 25 thousand patients) also did not show any influence on prognosis and risk of myocardial infarction (Trikalinos, T. A. et al., 2009). Thus, the modern pharmacotherapy administered to stable patients with CHD allows to achieve good results and the minimally invasive interventions on the coronary arteries make it possible to expect improved outcomes only in thoroughly selected patients taking into account many circumstances and with obligatory subsequent intensive pharmacotherapy.

*Open surgical revascularization* is the tactics of choice in patients with severe exertional angina pectoris responding not completely to the pharmacotherapy, especially in persons with progressing symptoms, involvement of the trunk of the left coronary artery or affection of three main coronary branches, diabetes mellitus and left ventricular dysfunction.

Catheter *plasty of the coronary arteries.* The appearance of drug-coated stents and the use of antiaggregants of new types such as glycoprotein IIB/IIIA receptor inhibitors administered intravenously and Clopidogrel and also the use of new anticoagulants including Bivalirudin and Fondaparinux (Arixtra) were the main advances in this field lately. These drugs lowered considerably the number of perioperative complications, especially in patients with severe involvement of the coronary arteries. The use of stents decreased much the need in emergency coronary artery bypass graft surgeries and lowered the probability of restenoses requiring repeated interventions.

But the basic outcome parameters such as prevalence of myocardial infarction and mortality did not change when using stent of early design (without special coating) as compared to catheter plasty of the coronary arteries without stenting (Serruys, P. W. et al., 1994; Rankin, J. M. et al., 1999). The introduction of drug-coated stents resulted in considerably lowered probability of early restenosing (Moses, J. W. et al., 2003) in the studies with long-term follow-up summarized in a large-scale meta-analysis (Kastrati, A. et al., 2007). But there were no differences in late outcomes (death, myocardial infarction) when the use of standard metal stents were compared to drug-coated stents. It turned out that the former were more predisposed to early stenoses (therefore, repeated angioplasty surgeries were required more often because of angina pectoris recurrence) and the latter could be person to extremely dangerous late thromboses in a long-term period (Curfman G. D. et al., 2007). However, drug-coated stents provide more reliable results in patients with diabetes mellitus (Daemen J. et al., 2008; Iijima R. et al., 2009) and in several nonstandard difficult situations (arteries of small caliber, restenoses including those in bypasses and anastomoses, involvement of the trunk, bifurcations and ostia, complete coronary artery occlusions (as compared to ordinary stents) (Brodie, B. R. et al., 2008; Marroquin, O. C. et al., 2008).

**Comparisons of catheter plasty of the coronary arteries with coronary artery bypass graft surgeries** in the randomized studies performed in different period showed different results. A relatively early study AWESOME revealed that outcomes of catheter plasty of the coronary arteries (without the use of drug-coated stents) and coronary artery bypass graft surgeries were comparable regarding the mortality and prevalence of myocardial infarction in patients with angina pectoris refractory to pharmacotherapy with high risk of complications (Morrison, D. A. et al., 2001; Sedlis, S. P. et al., 2002). Later a systematic review of 23 randomized controlled studies (performed in 1966–2006 at the leading clinics and involving approximately 10 thousand patients) made a

conclusion that coronary artery bypass graft surgeries removed angina pectoris more efficiently than catheter plasty of the coronary arteries. Repeated interventions were required rarer but strokes in the perioperative period developed more often after the surgeries. But when patients were followed up for the period up to 10 years, their survival rate was approximately equal (Bravata, D. M., 2007). Finally, a first-rate study SYNTAX (Serruys, P.W. et al., 2009) was completed recently; it was aimed at comparison of the efficiency of catheter angioplasty interventions and coronary artery bypass graft surgeries in all patients with multiple occlusions of the coronary vessels and/or involvement of the left coronary artery trunk hospitalized successively without any special selection (in total more than 4.3 thousand patients underwent revascularization). It was found that the rate of all the most significant cardiovascular complications (deaths because of any cause, strokes, myocardial infarctions or repeated revascularizations) was considerably higher in case of catheter interventions than in case of surgeries (risk ratio: 1.44) by the end of the first year after the intervention. The rate of repeated revascularizations was higher also when the minimally invasive procedure was used. The prevalence of strokes was higher in case of surgeries. Deaths because of cardiac causes were less probable when using the surgical method. The combined probabilities of death because of any cause or because of myocardial infarction and also death because of any cause, stroke or myocardial infarction were equal in the compared groups. The prevalence of stent and bypass thromboses was also equal. The conclusion of this important modern study is as follows: coronary artery bypass graft surgeries remain a standard of treatment for patients with the involvement of three coronary arteries or coronary trunk because the main cardiac and cerebrovascular complications develop rarer on the whole during the first year when using this revascularization method as compared to catheter angioplasty.

**Acute coronary syndrome and myocardial infarction.** Acute coronary syndrome is a preliminary diagnosis for designation of clinical situations in which myocardial infarction or instable angina pectoris should be suspected. Such designation (similar to the term “acute abdomen” accepted in surgery) is expedient for selection of a rational investigation plan and maximally early prescription of the differentiated treatment. The coronary catastrophe may lead to sudden death or myocardial infarction but may not result in such severe consequences due to the favorable natural course or thanks to active treatment. The following pathogenetic mechanisms may underlie the catastrophe: endothelium tear or atheroma rupture with (mural or total) thrombosis in this zone of the coronary artery, coronary artery embolism (revealed rarely as an independent phenomenon) or severe and long coronary artery spasm (observed quite rarely). Finally, myocardial infarction may develop in case of excessive load on the heart with compromised magistral blood supply (tachyarrhythmia in a patient with occlusive coronary atherosclerosis). All above situations are accompanied with severe myocardial ischemia the long existence of which causes necrosis (myocardial infarction). But myocardial infarction will not develop under certain conditions: this is possible in case of spontaneous thrombus lysis or its restricted size, removal of another reversible cause for ischemia including that due to the treatment.

***Tactics of initial actions in case of acute coronary syndrome***. The standard medical actions to be performed by a physician providing the first-line aid in such cases are regulated in a modern

international manual for physicians prepared by the expert group of the European Scientific Society of cardiologists (Fig. 5.15).

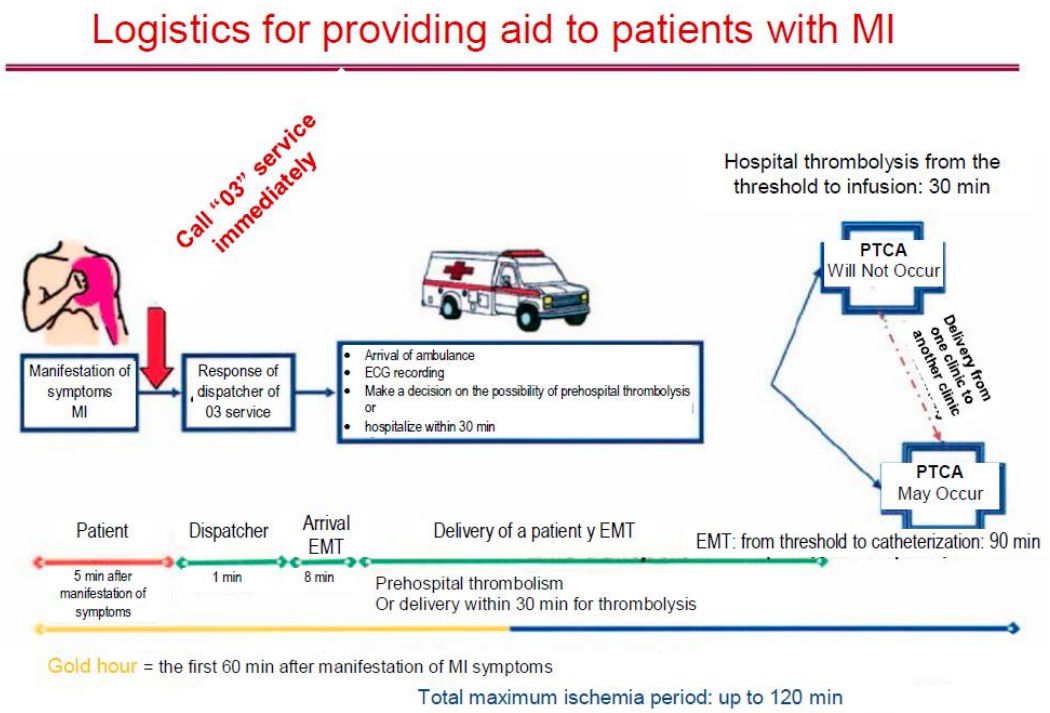


Fig. 5.15 Tactics of Emergency Measures in Order to Recover the Blood Flow in the Myocardium in Patients with Acute Myocardial Infarction (Antman, E. M. et al., 1999)
PTCA = percutaneous transluminal coronary angioplasty;
MI = myocardial infarction; EMT = emergency medical team.

***Tactics of Initial Actions in Case of Acute Coronary Syndrome***
***(according to recommendations of the European Scientific Society of Cardiologists)***

- **Oxygen inhalation** is required **only** for patients with hypoxia (it may be recognized basing on cyanosis or results of pulse oximetry).
- **Nitrates are administered** to patients with persisting pain: at first, sublingual spraying of a nitrate drug is administered usually (caution should be exercised, especially in case of repeated applications if systolic blood pressure decreases to below 90 mm Hg).
- **Aspirin is administered per os** (if there is no its intolerance): a patient should take tablets without protective coating after preliminary chewing; the dose should be 150–300 mg.
- **Clopidogrel in saturating dose** (300 (or even 600) mg is considered today as an essential starting measure in addition to Aspirin.
- **Anticoagulants are administered**: a subcutaneous injection of Enoxaparin (Clexan) in a single dose of 1 mg/kg is the most convenient.
- **Administration of Morphine** or another potent analgesic is required if the pain is still not stopped.
- **Administration of β-blocker** (it is usually Metaprolol per os) is also a standard measure, which is especially indicated in patients with tachycardia or hypertension but without marked heart failure.

In 2007 the European Society of Cardiology, American College of Cardiologists, American Heart Association and World Heart Federation adopted jointly a coordinated document providing a universal definition of the concept “myocardial infarction” (Thygesen, K. et al., 2005). The new universal definition of myocardial infarction is based on a basic criterion, namely the criterion of increased blood concentration of troponin which is a specific peptide molecule contained in cardiomyocytes and released from them to the blood in case of necrosis. According to the new definition, diagnosis of this disease is appropriate when there are signs of myocardial necrosis in the clinical situation corresponding to myocardial ischemia.

It is rightful to use one of the following five criteria in order to make this diagnosis:

1.New left bundle branch block; appearance of pathologic *Q* wave in ECG; visualization of newly occurring loss of viable myocardium or a zone with its disturbed mobility.

2.Sudden and unexpected cardiac death, i. e. circulation stops usually with simultaneous symptoms of myocardial ischemia in combination with ST segment elevation or new left bundle branch block or fresh thrombus revealed by coronarography and/or autopsy and in this situation death may take place before blood sampling or biomarker release to the blood.

3.Special diagnostic troponin levels are set for patients who underwent the catheter plasty of the coronary arteries or coronary artery bypass graft surgery.

4.Pathomorphologic evidence of AMI.

The basic strategic line in the treatment of patients with myocardial infarction is to recover maximally early the myocardial blood supply, i. e. to achieve its revascularization with the help of thrombolytic drugs, catheter interventions (today they are the perfect means for this) and even open surgeries. The complex problems associated with the selection of the medical tactics for cardiac revascularization are discussed in details in modern recommendations on cardiac revascularization prepared by the Working Group for myocardium revascularization of the European Society of Cardiology (ESC) and European Association of Cardio-Thoracic Surgery (EACTS) (2014). After a new clinic of ARCERM having the most up-to-date medical and diagnostic equipment and high-skilled specialists was opened in 2013, several tens of patients underwent successful surgeries for cardiac revascularization including cases of acute coronary syndromes.

Today chronic forms of CHD are one of the mot mass and significant forms of diseases in liquidators of the accident at ChNPP. Taking into account this circumstance, we have developed the management standards for these patients (they are presented in Appendix to this monograph).

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### 5.2.4 Chronic Heart Failure

Chronic heart failure (CHF) is one of urgent medical and social problems. The interest in this problem is associated with the prevalence of CHF, difficulties in diagnostics of its early stages, recent review of the pathogenetic conceptions and therapeutic principles, absence of reliable methods of therapy and unfavorable prognosis.

In Russia, the prevalence of CHF in the population is 7 % (Ageyev, F. T., Ovchinnikov, A. G., 2002); the annual mortality of patients with clinically evident heart failure reaches 12 % (Danielyan, M.O., 2001). The prevalence of CHF grows considerable as the age increases. When analyzing the statistical data, one should take into account that CHF is a progressing syndrome and those patients, who have asymptomatic heart dysfunction during the investigation, may be included in the group of

serious cases within several years. Therefore, early diagnostics of CHF and left ventricular dysfunction and, consequently, early beginning of the treatment of such patients are very important preconditions for achieving a socially significant result of the medical aid.

### *Definition of Chronic Heart Failure*

The wording provided in the recommendations on diagnostics and treatment of CHF given by the European Society of Cardiology defines heart failure as a "pathophysiologic syndrome in which one or other cardiovascular disease results in the lowered pumping ability what leads to imbalance between the organism hemodynamic demand and the cardiac resources." The modern neurohumoral pathogenesis model proved that CHF developed as per the single pathophysiologic laws irrespective of etiology of the damage. From clinical viewpoint, this gives "formal" grounds to designate CHF not only as a symptom complex complicating the course of one or other cardiovascular disease but also as an independent nosologic form.

Thus, from modern clinical viewpoint, CHF is a disease with a complex of typical symptoms (dyspnea, fatigability, lowered physical activity, edemas, etc.) which are associated with inadequate organ and tissue perfusion at rest or during exercise stress and often with liquid retention in the organism.

The prime course consists in the worsened heart ability to filling or ejection associated with myocardium damage and also with imbalance between the vasoconstricting and vasodilating neurohumoral systems.

CHF may complicate the course of practically all cardiovascular diseases. But in the Russian Federation, the main etiologic causes of CHF include arterial hypertension (AH) (88 % of cases) and coronary heart disease (CHD) (59 % of cases) or combination of these diseases (Fomin, I. V., 2007).

Systolic and diastolic types of heart failure are distinguished. Heart failure and its severity are traditionally associated with lowered heart contractility (systolic heart failure) which is assessed more often by the left ventricular ejection fraction. But a significant percentage of patients with heart failure has the normal or nearly normal left ventricular ejection fraction. It is advisable to speak of heart failure with preserved systolic function in such cases. It should be taken into account that while diastolic heart failure may be isolated, systolic heart failure develops, as a rule, not only with systolic but also with diastolic disturbances, i. e. has mixed nature.

### *Classification of Chronic Heart Failure*

Classification of CHF (Table 5.36) suggested by the Society of Specialists in Heart Failure and approved by the Russian Congress of cardiologists in 2003 unites the current Strazesko-Vasilenko classification of CHF stages and functional class of the New York Heart Association (NYHA).

Table 5.36

Classification of CHF

| Stages of CHF (may worsen in spite of the treatment) | | Functional classes (FC) of CHF (may change in the process of the treatment both in one and other direction) | |
|---|---|---|---|
| | Initial stage of the cardiac disease (damage). Hemodynamics is not disturbed. Latent heart failure. Asymptomatic left ventricular dysfunction. | | No restrictions of physical activity: habitual physical activity is not accompanied with high fatigability, dyspnea or palpitation. The patients tolerated the increased exercise stress but it may be accompanied with dyspnea and/or slowed recovery. |
| IA | Clinically evident stage of cardiac disease (damage). Moderate hemodynamic disturbances in the systemic or pulmonary circulation. Adaptive heart and vessel remodeling. | I | Insignificant restriction of physical activity: there no symptoms at rest, habitual physical activity is accompanied with fatigability, dyspnea or palpitation. |
| IB | Severe stage of the cardiac disease (damage). Evident hemodynamic changes in the systemic and pulmonary circulation. Deadaptive heart and vessel remodeling. | II | Noticeable restriction of physical activity: no symptoms at rest, physical activity with lowered intensity as compared to habitual exercise stresses is accompanied by symptoms. |
| II | Final stage of heart damage. Pronounced hemodynamic changes and severe (irreversible) structural changes in the target organs (heart, lungs, vessels, brain, kidneys). Final stage of organ remodeling. | V | Impossibility to perform any physical activity without occurrence of discomfort; symptoms of heart failure are present at rest and become more pronounced during the minimum physical activity. |
| Example : CHF, stage IIB, FCII; CHF, stage IIA, FC IV | | | |

Staging of the disease (heart damage), which may be aggravated over time in spite of the administered treatment, is not directly associated with FC (patients' capability for performing exercise stresses, i. e. physical activities). The classification of the Society of Specialists in Heart Failure (2002) implies that a physician should establish the disease stage (degree of heart damage) and FC (patients' dynamical capability for activities). Establishing the CHF stage and FC allows to separate the disease severity and patient's personive general well-being. Thus, as a rule, the disease stage and FC are not parallel.

### *Comments to Classification of CHF*

**Firstly**, the classification does not include CHF of stage 0 because a patient has no heart failure if there are no symptoms and heart damage. Asymptomatic left ventricular dysfunction corresponds already to stage I of the disease or FC I depending on the symptom intensity.

**Asymptomatic left ventricular dysfunction (corresponds to stage I)**

1. No symptoms of CHF at rest and during usual physical activity.

2. Systolic dysfunction: left ventricular ejection fraction is <45 % and/or left ventricular end-diastolic dimension (EDD) is >5.5 cm [left ventricular end-diastolic dimension index (EDDI) is >3.3 cm/$m^2$].

3. Diastolic dysfunction: IVST (interventricular septum thickness) + LVPWT (left ventricular posterior wall thickness) are >1.3 cm and/or LVPWT is >1.2 cm and/or hypertrophic spectrum type of Doppler transmittal flow (DTMF) (E/A < 1.0).

4. In this situation relative left ventricular wall thickness (IVST + LVPWT/EDD) does not differ from the normal value and is >0.45.

5. Left ventricular sphericity index in systole (ratio of the left ventricular short axis to its long axis) does not differ from the normal value (<0.70).

**Adaptive left ventricular remodeling (corresponds to stage IIA)**

1. Symptoms (corresponding to stage IIA).

2. Systolic dysfunction (see stage I) + left ventricular sphericity index in systole (ratio of the left ventricular short axis to its long axis) >0.70 and/or relative left ventricular wall thickness (IVST + LVPWT/ LV EDD) >0.30 and <0.45.

3. Diastolic dysfunction (see stage I) + pseudonormal spectrum type of DTMF > 1.1 and < 2.0.

**Deadaptative left ventricular remodeling (corresponds to stage IIB)**

1. Symptoms (corresponding to stage IIB).

2. Systolic dysfunction (see stage I) + left ventricular sphericity index in systole (ratio of the left ventricular short axis to its long axis) >0.80 and/or relative left ventricular wall thickness (IVST + LVPWT/ LV EDD) <0.30.

3. Diastolic dysfunction (see stage I) + restrictive spectrum type of DTMF >2.0.

**Secondly**, any special procedures and investigations (e. g., bicycle ergometry) are not required to determine CHF stage as it was in the Vasilenko-Strazesko classification and also to establish CHF FC as it is accepted in the classification of the New York Heart Association (NYHA).

**Thirdly**, the six-minute walk test (SMWT) and Clinical Condition Assessment Scale (CCAS) are used for the objective estimation of CHF FC.

Epidemiologic studies are evidence of the fact that diseases of the circulatory system take the first place in the morbidity structure and are a dominating cause for disablement and mortality in liquidators of accident aftermath at the Chernobyl NPP in a long-term period (Shantyr, I. I. et al., 2002). According to the data obtained by ARCERM (2005), their morbidity with the cardiovascular pathology increased more than 3 times only over the last decade. We studied the prevalence of HCF in liquidators.

## *Epidemiology of Chronic Heart Failure in Liquidators of Accident Aftermath at the Chernobyl NPP*

***Prevalence of chronic heart failure.*** Heart failure was revealed practically in every fifth liquidator registered at the North-Western Regional Center of RSMDR (in 2,338 liquidators out of 11,087, i. e. 210.9 per 1,000 persons) over the follow-up period from 1986 to 2003. In this situation EH (99.2 %) was the main cause for CHF, and CHF was associated with CHD or the cause for heart failure was not established only in 0.8 % of cases.

The analysis of CHF prevalence by the age showed that that the rate of this pathology in the oldest age group (70 years and older) was 7.8 times higher than that in the youngest (35–39 years) age group (583.3 and 74.8 %, respectively; $p < 0.0001$). And we observed the uniform growth of this parameter value with increasing age (Fig. 5.16).

The analysis of CHF prevalence depending on the year of participation in the emergency-recovery works at ChNPP showed that the highest level of this pathology was revealed in liquidators involved in the works in 1986; it exceeded the respective levels in liquidators involved in the works in other years 1.3–2.1 times ($p < 0.0001$) (Fig. 5.17). They were followed by

liquidators involved in the works in 1987 in whom the rate of CHF was 1.5–1.7 times higher ($p < 0.0001$) than that in those who participated in the works later (1988–1990).

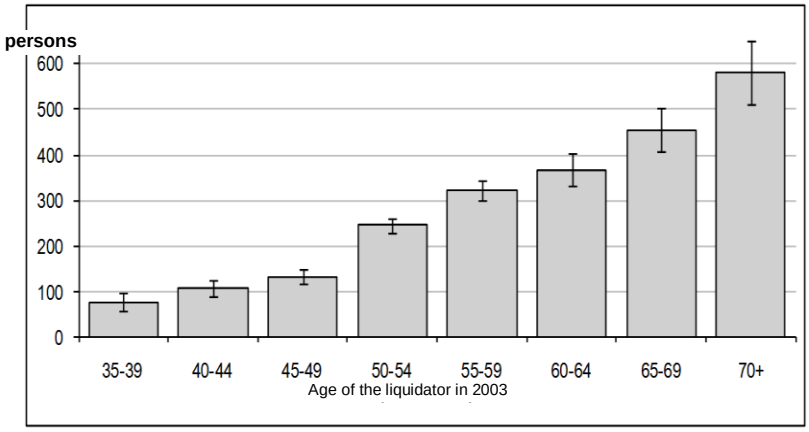


Fig. 5.16. CHF Prevalence in Liquidators of Accident Aftermath at ChNPP of Different Age Groups (per 1,000 Persons with 95 % Confidence Interval)

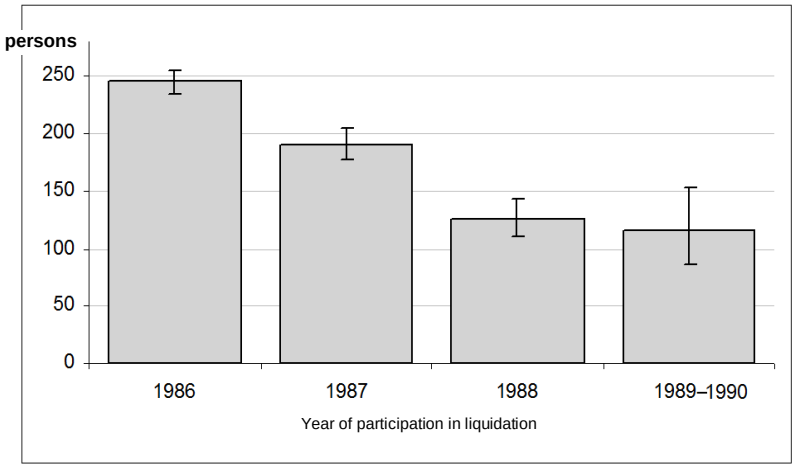


Fig. 5.17. CHF Prevalence in Liquidators Depending on the Year of Participation in the Works at ChNPP (per 1,000 Persons with 95 % Confidence Interval)

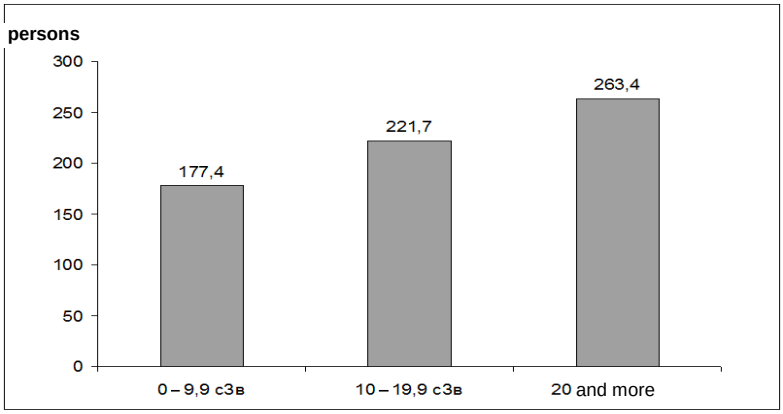


Fig. 5.18. CHF Prevalence Depending of the External Irradiation Dose (per 1,000 Persons)

When analyzing CHF prevalence depending on the received external irradiation dose we found that the highest prevalence of heart failure was revealed in liquidators with irradiation dose of 20.0 cSv and more over the whole follow-up period (Fig. 5.18). This value exceeded 1.5 times that in liquidators with the external irradiation dose of 0–9.9 cSv and 1.2 times that in liquidators with the irradiation dose of 10.0–19.9 cSv ($p < 0.05$, $p < 0.0001$).

When analyzing CHF prevalence depending on the received external irradiation dose we found that the highest prevalence of heart failure was revealed in liquidators with irradiation dose of 20.0 cSv and more over the whole follow-up period (Fig. 2.19). This value exceeded 1.5 times that in liquidators with the external irradiation dose of 0–9.9 cSv and 1.2 times that in liquidators with the irradiation dose of 10.0–19.9 cSv ($p < 0.05$, $p < 0.0001$).

***Mortality of liquidators of accident aftermath at the Chernobyl NPP with chronic heart failure.*** The mortality of liquidators with CHF was 144 persons (6.2 %) over the whole follow-up period; 58.3 % out of this number died directly because of a cardiovascular disease complicated with heart failure. Other diseases including oncologic ones were the cause of death of other liquidators. Most lethal outcomes were observed in the period from 2000 to 2003 (90.3 %). The number of the departed during these years was similar: from 28 to 37 persons annually (Fig. 5.19).

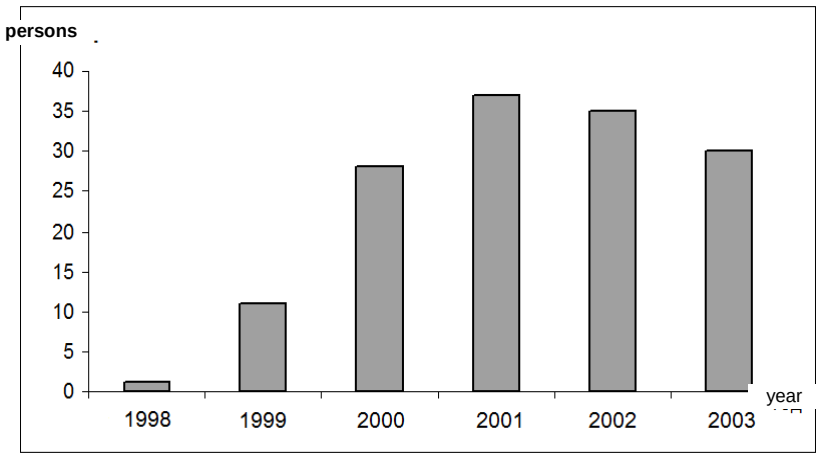


Fig. 5.19. The Distribution of the Departed Liquidators with CHF by Years (abs. numbers)

The results of the epidemiologic study showed high prevalence of CHF in liquidators from the North-Western Region of Russia which reached 21.1 % by 2003. At the same time, the results of the epidemiologic analysis indicated that the exposure of liquidators to accident factors at ChNPP including the received external irradiation dose increased their risk to develop heart failure.

We investigated the structural and functional changes in the heart and peculiarities of CHF course in liquidators with cardiovascular diseases. The study included 79 patients aged from 34 to 62 years (mean age was 51.29 ± 0.75 years) who participated in the emergency-recovery works at ChNPP in 1986–1987 and received the irradiation doses (as per dose registration records) from 5 to 30 cSv and more. Among the investigated liquidators, EH of stage II was diagnosed in 19.1 %; CHD: exertional angina pectoris of FC I-II was revealed in 2.5 %; the combination of CHD and EH was found in 78.5 %; 14 persons (17.7 %) of them had the history of myocardial infarction. The comparison group included 56 males aged from 37 to 64 years (mean age was 51.32 ± 0.07 years) with the similar pathology. CHF was diagnosed 2 times more often in the liquidator group that in the control group (in 41.8 and 19.6 %, respectively).

### *The Peculiarities of Clinical Symptoms of Heart Failure in Liquidators of Accident Aftermath at the Chernobyl NPP*

It is possible to make a diagnosis of CHF provided that two key criteria are available (Table 5.37):

• typical symptoms of heart failure (mainly, dyspnea, fatigability and restricted physical activity, edemas on the malleoli);

• objective evidence of the fact that these symptoms are associated with damage of the heart but not any other organs (e. g., pulmonary diseases, anemia, renal failure).

It should be emphasized that symptoms of CHF may be present at rest and/or during exercise stress. At the same time, objective signs of heart dysfunction should be revealed obligatorily at rest. This is associated with the fact that such sign as low left ventricular ejection fraction during exercise stress (e. g., in a patient with CHD) may be a symptom not of heart failure but coronary insufficiency. This concerns also other objective signs of myocardium damage. The diagnosis of heart failure may be confirmed by the positive response to the therapy in doubtful cases.

Table 5.37

**Criteria used for making a diagnosis of CHF**

| Symptoms (complaints) | Clinical signs | Objective signs of heart dysfunction |
|---|---|---|
| • Dyspnea (from insignificant to asthma)<br>• Increased fatigability<br>• Palpitation<br>• Cough<br>• Orthopnea | • Pulmonary congestion (rales, X-ray picture)<br>• Peripheral edemas<br>• Tachycardia (> 90-100 beats/min)<br>• Swollen jugular veins<br>• Hepatomegaly<br>• Gallop rhythm<br>• Cardiomegaly | • ECG, X-ray of the thoracic organs<br>• Systolic dysfunction (lowered contractility)<br>• Diastolic dysfunction (Doppler-echocardiography, increased left ventricular filling pressure)<br>•Brain natriuretic peptide hyperactivity |

It is known that the most frequent complaints in patients with heart failure include dyspnea and increased fatigability which are observed in 98.4 and 94.3 %, respectively, according to the data of the study IMPROVEMENT (2000). They are followed by palpitation (80.4 %) and also symptoms of congestion, i. e. peripheral edemas, cough and orthopnea (from 73 to 28 %).

These trends were confirmed in our study. The clinical subjective symptoms in investigated liquidators were reduced to complaints of lowered physical working capacity (70 %), increased fatigability (60.9 %), dyspnea during physical activities (56.5 %), palpitation (41 %), peripheral edemas (13 %). At the same time, clinical signs of heart failure (peripheral edemas, pulmonary congestions, cardiomegaly and hepatomegaly) were revealed only in 11 % of patients what was associated with the initial stages of the disease. We noticed that liquidators without signs of heart dysfunction also often complained of dyspnea, increased fatigability, palpitation and peripheral edemas.

All liquidators complained of frequent headaches, 81 % of them complained of dizziness, 71 % of liquidators had memory impairment, vegetative disorders were revealed in 59 %. All persons had asthenic and neurosis-like symptoms (increased fatigability, lowered attention concentration, sleep disorders, emotional instability, high anxiety, irritability, self-doubt.

The spiroergometryc test was performed in order to assess the patients' physical working capacity and establish objectively the functional class of CHF using the parameter of the maximum oxygen consumption (MOC). It is known that stress tests in patients with heart failure are justified not for diagnostics but for assessment of the functional status and risk degree (National recommendations on diagnostics and treatment of CHF, 2009). Nevertheless, the normal result of

the stress test in a patient not receiving any specific treatment rules out the diagnosis of CHF nearly completely.

Performing the stress test for a long time (8–12 min up to reaching stoppage criteria) with the minimum stress increment when changing from one stage to another is justified in patients with CHF. For this purpose, it is better to use the stresses modelling the gradually increased gradient of slope of the conditional distance (treadmill or bicycle ergometer) especially under control of gas exchange (spiroergometry). The oxygen consumption at the stress maximum ($VO_2max$) reflects the stress tolerance and functional class of CHF more precisely than any other parameter including the stress time or performed work load (Table 5.38). The value $VO_2max$ of less than 10 ml/($kg^{-1}\times min^{-1}$) indicates the high prognostic risk while the value of more than 18 ml/($kg^{-1}\times min^{-1}$) corresponds to the minimum risk.

The 6-minute waking test corresponding to the submaximum stress may be used in the routine praxis and if there is no special equipment for assessment of physical tolerance and obtaining the objective data on the functional status in patients with HCF. The conditions for this test are very simple: the corridor marked with an interval of 1 m, a clock with a second hand and clear explanation of the task to a patient who should walk along this corridor the maximum distance over 6 min as fast as it is acceptable for him (her) (if the patient stops for rest, this time is also included in the total count). This test correlates with the functional class of heart failure and prognostic significance (Florya, V. G. et al., 1992): the traversed distance of less than 300 m corresponds to unfavorable prognosis. Performing the stress test by patients with CHF is quite safe and is not associated with the risk of serious complications.

Table 5.38

The Parameters of Physical Activity and Oxygen Consumption in Patients with Different Functional Classes of CHF

| Functional class of CHF according to NYHA | Six-minute walk distance, m | Oxygen consumption, ($VO_2max$) ml/($kg^{-1}\times min^{-1}$) |
|---|---|---|
| 0 | > 550 | > 22.1 |
| I | 426–550 | 18.1–22.0 |
| II | 301–425 | 14.1–18.0 |
| III | 151–300 | 10.1–14.0 |
| IV | <150 | <10 |

Taking into account multiplicity of complaints in liquidators, we compared the functional class of CHF diagnosed by patients' complaints with the functional class of CHF established basing on the oxygen consumption at the stress maximum when performing the spiroergometric test. It was found that heart failure in liquidators was diagnosed significantly more often and the higher functional class was established basing on clinical symptoms that this was confirmed by the spiroergometric test (Table 5.39). There were no such differences in the control group.

Extracardial complaints such as general fatigue, pain in the legs, dizziness, difficult breathing are an often cause for stopping the stress test in liquidators. The refusal from continuation of the test may be explained partially by presence of psychoneurologic and vegetative disorders. On the one hand, this makes it more difficult to perform the spiroergometric test and interpret the obtained results. On the other hand, it is necessary to perform the stress tests taking into account polymorphism of complaints in this patient category and the impossibility of accurate diagnostics of heart failure basing only on the clinical picture.

Table 5.39

The Comparison of the Functional Class of CHF Established by Complaints and Oxygen Consumption in Liquidators of Accident Aftermath and Patients of the Control Group

| Diagnostics of CHF | Liquidators (n = 79) | | | | Control group (n = 56) | | | |
|---|---|---|---|---|---|---|---|---|
| | By complaints | | By MOC | | By complaints | | By MOC | |
| | Abs. number | % | Abs. number | % | Abs. number | % | Abs. number | % |
| Total number of persons with CHF | 50 | 63.3 | 33 | 41.8 | 13 | 23.2 | 11 | 19.6 |
| Out of them: FC I | 16 | 32 | 14 | 42.4 | 6 | 46.2 | 5 | 45.5 |
| FC II | 34 | 68 | 19 | 57.6 | 7 | 53.8 | 6 | 54.5 |

∗Difference between the groups is significant ($p < 0.05$)

In our opinion, the 6-min walk test is more sensitive and simple-to-perform test for assessing the functional status in this patient category. This test is referred to the tests with continuous submaximum stress which is usually below the anaerobic threshold in contrast to other stress tests with the maximum stress increasing more often up to the level of the anaerobic threshold which not always can be reached by liquidators. It has less pronounced emotional effect on the person because there is not mask and the tempo is not imposed.

The multiplicity and polymorphism of complaints, presence of vegetative dysfunction and psychoneurological disorders in liquidators aggravate the clinical picture of the disease and are evidence of the need to use instrumental methods for confirming the association between clinical manifestations and presence of CHF, especially for revealing its initial stages.

### *Peculiarities of the Structural and Functional Changes in the Heart in Liquidators of Accident Aftermath at the Chernobyl NPP*

It is known that structural and functional changes occurring in the heart and vessels in patients with cardiovascular diseases are a separate cause for further progression of the disease and an independent negative prognostic factor also for the development of CHF. The concept of remodeling includes a complex of changes in the dimensions, shape, structure, biochemical and functional properties of the myocardium and vessels under the influence of different factors. According to modern views, heart remodeling in patients with arterial hypertension means not only left ventricular hypertrophy but also changes of its diastolic function reflecting myocardial fibrosis, modified left ventricular geometry, changes in the right ventricle and atriums. The results of many recent studies demonstrated that morphologic and functional changes in the heart and vessels were associated not only with the level of hemodynamic load but they depended considerably on activation of several neurohumoral systems and also had genetic predisposition. The main hemodynamic and neurohumoral mechanisms of the heart and vessel remodeling are similar and aggravate each other.

We investigated the role of structural and functional changes in the heart in the development of heart failure in liquidators with CHD and EH in a long-term period after the accident. The parameters of echocardiography (EchoCG) characterizing the left ventricular diastolic and systolic

function were investigated in order to establish more precisely the degree of morphologic changes in the heart and assess the myocardial functional properties.

EchoCG is a visualizing procedure which is of primary importance in diagnostics of CHF because it is easy-to-perform, safe and widely used at all health care facilities. EchCG allows to solve the basic diagnostic problem, i.e. to assess more accurately the fact of dysfunction itself and its nature and also to perform the dynamic estimation of the heart condition and hemodynamics.

The left ventricular ejection fraction reflecting the left ventricular myocardial contractility is the most important hemodynamic parameter. The assessment of the left ventricular ejection fraction allows to differentiate patients with systolic dysfunction from those with preserved systolic function. The level of the left ventricular ejection fraction of more than 50 % calculated using the method of two-dimensional EchoCG according to Simpson may be recommended as a criterion evidencing the preserved systolic function with high probability. The degree of decrease of the left ventricular ejection fraction is associated with the intensity of systolic dysfunction and used for assessing the risk of the surgical treatment; its changes indicate the disease progression and efficiency of the therapy. The low left ventricular ejection fraction is a marker of negative prognosis. It is important to have in mind that the normal left ventricular ejection fraction does not exclude presence of heart failure. More than a half of all patients with heart failure in the Russian population have the left ventricular ejection fraction of more than 50 %.

When heart failure is suspected, the left ventricular diastolic function is assessed in addition to estimation of the left ventricular ejection fraction. The combined assessment of the transmittal diastolic flow (TMDF) and mitral valve ring movement velocity is used for the judgment about presence and severity degree of the left ventricular diastolic dysfunction. Three types of left ventricle filling are distinguished: type with slowed relaxation, pseudonormal and restrictive types which correspond to mild, moderate and severe diastolic dysfunction.

The Working Group of the European Society of cardiology suggests the following ultrasound diagnostic standards for assessment of diastolic dysfunction:

• the increased left ventricular isovolumic relaxation time (IVRT): IVRT < 30 l > 92 ms, IVRT 30–50 l > 100 ms, IVRT > 50 l > 105 ms;

• slowed left ventricular filling in early diastole: *E/A* < 50 l < 1.0 and *DT* < 50 l > 220 ms; *E/A* > 50 l < 0.5 and basic therapy (BT) > 50 l > 280 ms and/or *S/D* < 50 l > 1.5; S/D > 50 l > 2.5;

• decreased diastolic compliance of the left ventricular chamber: *PV–A* > 35 $cm \cdot s^{-1}$ and/or *PVAt* > MV–At + 30 ms where MV–At is duration of atrial A-wave of TMDF.

Three conditions are required for diagnostics of primary diastolic heart failure:

- presence of symptoms and signs of heart failure;
- normal or insignificantly disturbed left ventricular systolic function (left ventricular ejection fraction > 50 %);
- revealing disturbed left ventricular relaxation and/or its compliance.

Revealing the disturbed cardiac diastolic filling is important not only for elucidation of the pathogenesis of heart failure: it is proven that diastole disturbances are more closely associated with the severity of the patients' clinical condition, degree of exercise stress tolerance lowering and life quality than systole disturbances. Changes in the diastolic parameters may serve as a criterion of the treatment efficiency and prognostication marker for patients with CHF.

We showed that liquidators developed myocardial diastolic dysfunction significantly more often than persons of the control group with the similar pathology: 73 and 38 % of patients, respectively. The results of our study coincide with the data obtained by other authors who demonstrated that disturbed diastolic function was often observed in liquidators with initial stages of essential hypertension and even in those without any cardiovascular disease (Ektova, T. V. et al., 1997; Katelnitskaya, L. I., Makarenko, E. S., 2000). We revealed myocardial systolic dysfunction in 5.0 % of liquidators and 1.8 % of patients of the control group. Mean values of the basic parameters characterizing the systolic function were within the normal range in patients of both groups. But differences between the groups were significant by such parameters as ejection fraction, left ventricular end-diastolic dimension and left atrial diameter what indicated the presence of latent systolic function disturbances in liquidators.

As it is known, left ventricular hypertrophy is the basic cause of disturbed left ventricular diastolic function and belongs to independent factors of cardiovascular risk including onset of congestive heart failure (Kannel, W.B. et al., 1981). It is revealed in the general population in 16 % basing on EchoCG findings (Levi, D., 1988). Basing on EchoCH findings, left ventricular hypertrophy is revealed in patients with EH in 50 % of cases and even more often according to different data and this parameter varies within the wide range from 12 to 96 % depending on peculiarities of the sample and criteria used (Savage, D. D. et al. 1979). It was shown that predictors of myocardial hypertrophy include age, duration of arterial hypertension, BP level and body weight (Konradi, A. O., et al., 2005).

Liquidators significantly more often had myocardial hypertrophy and it was significantly more pronounced than in the control group in spite of absence of differences between patients of the compared groups in the age, nosologic forms of diseases, blood pressure level, body weight in our study (Table 5.40). In this situation diastolic dysfunction was revealed in 77.5 % of liquidators and 65.0 % of patients of the control group with left ventricular myocardial hypertrophy what enabled to consider myocardial hypertrophy as the basic cause for disturbed diastolic function in both groups.

Diastolic dysfunction is one of the main components in the remodeling process. According to modern conceptions, there exist four variants of left ventricular remodeling typical of patients with arterial hypertension: normal geometry, concentric and eccentric hypertrophy and concentric remodeling. This division is based on the value of left ventricular mass index and left ventricular relative wall thickness in respect to the cavity diameter (Ganau, A. et al., 1992). The Framingham study analyzed for the first time the prognosis for patients with different types of left ventricular geometry and revealed that patients with concentric hypertrophy had the more unfavorable prognosis than patients with eccentric hypertrophy and patients with concentric remodeling developed complications more often than patients with normal left ventricular geometry.

When studying the structural and geometric changes in the left ventricle we found that left ventricular remodeling took place in liquidators more often than in patients of the control group. The concentric and eccentric hypertrophy predominated and the most unfavorable remodeling variant, concentric hypertrophy, was observed significantly more often than in the control group (Fig. 5.20).

Table 5.40

Echocardiographic Parameters Characterizing Myocardium Hypertrophy
in Liquidators and Patients of the Control Group

| Parameter | Liquidators (n = 79) | Control group (n = 56) |
|---|---|---|
| Myocardium hypertrophy, abs. (%) | 49 (62.0) | 20 (35.7)* |
| Interventricular septum, cm | 1.14 ±± 0.02 | 1.10 ±± 0.02 |
| Posterior wall, cm | 1.09 ±± 0.02 | 1.04 ±± 0.01* |
| Myocardium mass index, g/m$^2$ | 122.5 ±± 3.14 | 114.1 ±± 3.26* |

*Difference between the groups is significant ($p < 0.05$)

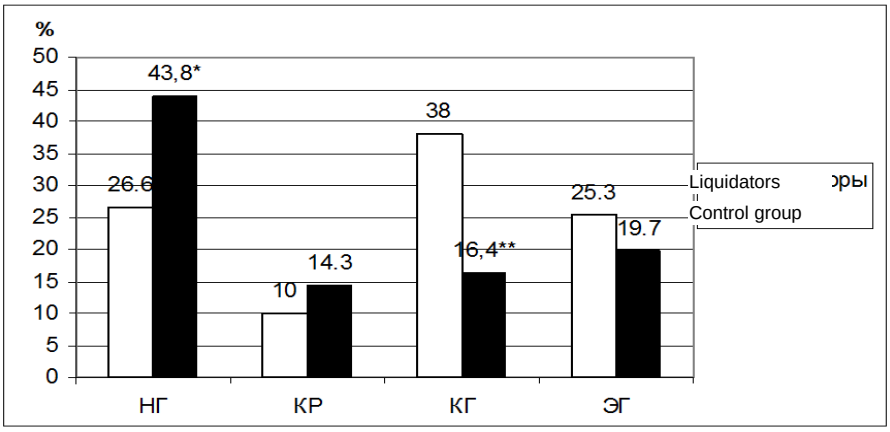


Fig. 5.20. Types of Left Ventricular Geometry in the Groups
* - Difference Between the Groups Is Significant ($p < 0.05$); **- Difference Between the Groups Is Significant ($p < 0.01$)
NG—Normal Geometry; CR—Concentric Remodeling; CH—Concentric Hypertrophy; ECH—Eccentric Hypertrophy.

The peculiarity of the liquidator group consists in significantly more frequent development of diastolic dysfunction in patients with concentric remodeling and normal left ventricular geometry than that in persons of the control group.

Thus, the performed studies showed that liquidators developed the more pronounced structural and functional changes in the left ventricle as compared to patients of the control group. And cardiac morphologic changes develop in them, mainly, in the form of concentric hypertrophic myocardial remodeling which is an unfavorable variant. These changes accompanied, mainly, by disturbed myocardial diastolic function underlie the development of diastolic heart failure. At the same time, we revealed changes in some echocardiographic parameters which were evidence of more pronounced disturbances of also systolic function in liquidators.

### *Neurohumoral Factors of Cardiovascular Remodeling in Liquidators of Accident Aftermath at the Chernobyl NPP*

A considerable role in the processes of cardiovascular remodeling is played by the sympathetic nervous system, renin-angiotensin system, insulin and also cellular and rheological factors among non-hemodynamic factors (Konradi, A. O. et al., 2005).

It is accepted to call catecholamines as “hormones of myocardial hypertrophy” (Manolis, A., 1993). It is known that the simpatico-adrenal system hyperactivation is accompanied by increased noradrenaline level in the blood plasma and causes vasoconstriction, tachycardia, salt and liquid retention in the organism; myocardium contractility is intensified and its hypertrophy is stimulated. The sympathetic nervous system is closely associated with other neurohormonal systems in the organism, in particular, with the system renin-angiotensin-aldosterone. In spite of the fact that renin

itself is not a stimulator of myocardial hypertrophy, it was shown that angiotensin II stimulated myocardial hypertrophy and fibrosis in experimental animals (Ageyev, F. T., Ovchinnikov, A. G., 2002; Baker, W. L., Couch, K. A., 2007). Aldosterone also plays the role of the stimulator of cellular hypertrophy and fibrosis (Weber, K., 1993).

Several studies (Paleyev, N. R. et al., 1994; Ovchinnikov, Yu. V., 1997) revealed sympathetic nervous system hyperactivity already at initial stages of development of the cardiovascular pathology in liquidators; according to the authors, such hyperactivity favored earlier development of the pathology and structural and functional changes in the heart (myocardial hypertrophy, diastolic dysfunctions).

The psychologic traumatic factor is a recognized unfavorable influence exerted on liquidators which acted both in the first years after the accident and acts at present. Psychopathologic conditions manifested in vegetative and somatic disorders are materialized through changes in the neurohumoral regulation, intensified lipid peroxide oxidation processes and are factors predisposing to hemodynamic disorders (Vinokur, V. A., 2002).

It is noteworthy that any correlation between diastolic dysfunction and received ionizing radiation dose was not revealed in liquidators what might indicate that the radiation factor was not the leading one in formation of these changes (Ovchinnikov, Yu. V., 1997).

### *Other Factors of Cardiovascular Remodeling in Liquidators of Accident Aftermath at the Chernobyl NPP*

Metabolic disorders. Most patients with arterial hypertension and CHD have other factors of cardiovascular risk involved in affection of the cardiovascular system. Arterial hypertension is often combined with several metabolic disorders what is manifested in some or other metabolic syndrome components involved in cardiac and vascular remodeling. Undoubtedly, diabetes mellitus or only insulin resistance predisposes to CHF and the combination of CHF and diabetes mellitus aggravates the unfavorable prognosis in patients.

The prevalence of metabolic syndrome ranges from 10 to 60 % of populations in different countries of the world. At the same time, the percentage of metabolic syndrome is about 75 % in the sample of patients, liquidators of the accident at ChNPP, hospitalized to the cardiologic clinic of ARCERM. In this situation, disturbed carbohydrate metabolism was revealed significantly more often in liquidators in a long-term period after the accident than in patients of the control group. Diabetes mellitus dominated in the structure of carbohydrate metabolism disturbances in liquidators, while disturbed glucose tolerance prevailed in patients of the control group.

The lipid metabolism in the liquidator group on the whole and in patients with diastolic dysfunction and heart failure is characterized by more pronounced atherogenic shifts what is manifested in the higher apoprotein B level and lowered ratio Apo-A/apo-B.

***Immunologic changes.*** It is impossible to consider pathophysiologic patterns of development of the cardiovascular pathology and heart failure in liquidators of accident aftermath at ChNPP not taking into account the role of the immune status in this subject category. It was shown long ago that pro-inflammatory cytokines (IL-1, TNF-αα, IL-8, IL-6) have very wide range of properties being involved practically in all physiologic processes in the organism. The role of cytokines in development of cardiovascular diseases (CHD and EH) and progression of CHF is well known.

The stimulating effect exerted by the ionizing radiation of production of pro-inflammatory cytokines IL-1, TNF-α, IL-6 is proven convincingly. IL-1 and TNF-α have a radioprotective property realized with involvement of IL-6. Evidently, stimulated production of these cytokines is aimed at reduction of consequences caused by the ionizing radiation.

We revealed considerably increased spontaneous production of IL-1β in liquidators and patients of the control group. We observed more pronounced lowering of its induced production in liquidators what could be evidence of reduced reserves for production of this cytokine in a long-term period after the accident in contrast to the data obtained by the investigation in earlier period. The long IL-1β hyperproduction played a considerable role in early onset of EH in liquidators, in development of more pronounced myocardial hypertrophy due to vascular remodeling and stimulated production of hormones and mediators of the hypothalamo-hypophyseal-adrenal system.

Our study found significantly higher level of spontaneous TNF-α and IL-8 production in the liquidator group as compared to the control group. These differences were also found in patient with myocardial dysfunction and CHF. It is known that TNF-α hyperproduction stimulates myocardial hypertrophy, myocardial interstitial component remodeling what is a cause for disturbed diastolic function (Colucci, W. S., 1997; Azzawi, M., Hasleton, P., 1999). TNF-αα has a suppressive effect of the myocardial contractility (Goldhaber, J. I., 1996). Induction of active oxygen forms by pro-inflammatory cytokines is one of the possible mechanisms for cardiomyocyte damage (Chandrasekar, B., 1997) what is an additional factor aggravating structural and functional changes in the cardiovascular system in the liquidator group.

Basing on the results of our study it may be considered that long pro-inflammatory cytokine hyperproduction along with changed neurohumoral regulation, intensified lipid peroxide oxidation process and development of metabolic disorders is a cause for early occurrence of more pronounced structural and functional myocardial changes.

Thus, our investigations showed that liquidators with cardiovascular diseases developed CHF in a long-term period after the accident 2 times more often than patients with EH and CHD at the same age and with similar pathology and disease severity but not involved in liquidation of accident aftermath at ChNPP.

Cardiac structural and functional changes in the form of myocardial hypertrophy underlie the development of CHF; these changes are accompanied with mainly diastolic dysfunction and latent disturbances of myocardium systolic function, they develop earlier and are more pronounced in liquidators than in standard patients. Probably, these changes result from not only diseases of the circulatory system themselves but their development is associated with the exposure to the complex of damaging accident factors: received external irradiation dose, long psychoemotional stress, subsequent psychic and psychosomatic defects. The exposure to damaging accident factors leads to free radical hyperproduction, disturbances in the cytokine component of the immunity and changed neurohumoral regulation. On the one hand, these disturbances favor the development of cardiovascular diseases and, on the one hand, cause directly myocardial dysfunction.

Evidently, it is practically impossible to divide preconditions for heart failure in those associated with a cardiovascular disease and those caused directly by the exposure to damaging

accident factors. But the common pattern of myocardial structural and functional changes suggests that the risk of development and more rapid progression of CHF is higher in liquidators suffering from cardiovascular diseases than that in patients not exposed to damaging factors associated with the accident.

### *General Principles of Pharmacotherapy of Chronic Heart Failure in Liquidators of Accident Aftermath at the Chernobyl NPP*

"Evidence-based medicine" underlies the principles of pharmacotherapy of any disease and CHF. In other words, only those drugs the efficiency (including the effect of patients' prognosis) and safety of which was proven by long-term multicenter double blind, placebo-controlled studies may be recommended for wide use in the clinical practice. The modern principles of pharmacotherapy of CHF are based on available current data.

Table 5.41

Drugs for Treatment of CHF

| Basic (their effect on the clinical picture, life quality and prognosis is proved and does not raise doubts) | Additional (their efficiency and safety were studied but should be assessed more precisely) | **Secondary** (their effect on the prognosis is not known, their use is dictated by clinical picture) |
|---|---|---|
| ACE inhibitors<br>β-adrenoblockers<br>Aldosterone antagonists<br>Diuretics<br>Glycosides<br>Angiotensin receptor antagonists | Statins<br>Anticoagulants (for patients with atrial fibrillation) | Peripheral vasodilators<br>Calcium channel blockers<br>Antiarrhythmic drugs<br>Aspirin<br>Non-glycoside inotropic drugs |
| A | B | C |

All drugs for treatment of CHF may be divided in three basic categories according to the degree of evidence (Table 5.41). Taking into account the neurohormonal conception of the development and progression of CHF, four out of six classes of the basic drugs for treatment of CHF, i. e. angiotensin-converting enzyme inhibitors (ACEi), β-adrenoblockers, aldosterone antagonists and angiotensin II receptor antagonists, belong to neurohormonal modulators.

***Basic drugs*** are medicines the effect of which is proven, does not raise doubts and which are recommended just for treatment of CHF (evidence degree A):

• ACE inhibitors which are indicated for all patients with CHF irrespective of etiology, process stage and decompensation type;

• β-adrenoblockers are neurohormonal modulators used "from above," i. e. additionally to ACEi;

• aldosterone receptor antagonists used in combination with ACEi and β-adrenoblockers for patients with pronounced CHF;

• diuretics are indicated for all patients having clinical symptoms of CHF associated with excessive sodium and water retention in the organism;

• cardiac glycosides are administered in low doses and with caution to patients with sinus rhythm but they remain a drug of choice for patients with atrial fibrillation;

• angiotensin receptor antagonists may be used not only in cases of ACEi intolerance but also in combination with ACEi as a first line drug in order to block the renin-angiotensin-aldosterone system in patients with clinically evident decompensation.

***Additional drugs*** the efficiency and (or) safety of which was demonstrated in several large-scale studies but should be assessed more precisely (evidence degree B):

• statins recommended for use in all patients with CHF of ischemic etiology; besides that, they can prevent CHF in patients with different forms of CHD;

• indirect anticoagulants indicated for use in most patients with CHF developing in patients with atrial fibrillation and also in some cases in patients with CHF and sinus rhythm.

***Secondary drugs*** whose effect and influence of the prognosis for patients with CHF are unknown (not proven) what corresponds to recommendation class III or evidence level C. These drugs should not be used for treatment of CHF (and this is impossible) and their administration is dictated by certain clinical situations complicating the course of decompensation itself:

• peripheral vasodilators, i. e. nitrates used only in patients with concomitant angina pectoris;

• calcium channel blockers (long-acting dihydropyridines) are used in patients with persistent angina pectoris and stable AH;

• antiarrhythmic drugs (except for β-adrenoblockers, mainly, of class III included in the category of basic drugs) are used for treatment of life-threatening ventricular arrhythmias;

• Aspirin (and other antiaggregants) are used for secondary prevention after MI;

• non-glycoside inotropic stimulators are used in patients with exacerbation of CHF with low cardiac output and resistant hypotension.

The pattern of CHF in liquidators of accident aftermath at the Chernobyl NPP make is advisable to use, first of all, drugs referred to neurohormonal modulators and those improving the myocardial diastolic function for prevention and treatment of CHF. As left ventricular hypertrophy is more pronounced in liquidators it is necessary to check the blood pressure level more strictly and observe whether the administered antihypertensive therapy causes the reversal of left ventricular hypertrophy if this is possible.

### *Pharmacotherapy of Diastolic Chronic Heart Failure*

The first and obligatory precondition consists in revealing and correction of all factors and diseases favoring diastolic disorders such arterial hypertension and left ventricular hypertrophy, CHD, diabetes mellitus, obesity, etc. An adequate decision should be made concerning prevention, recovery and maintenance of sinus rhythm in patients with tachysystolic atrial fibrillation. If permanent form of atrial fibrillation is preserved, the ventricular contraction rate should be normalized.

At present there is no convincing evidence of improved survival rate when using any specific pharmacotherapy in patients with diastolic heart failure. Nevertheless, the efficiency of some drugs was shown in certain studies (evidence level B) and it is still being investigated now.

ACE inhibitors can improve directly myocardial relaxation and compliance and also exert an indirect action on the diastolic properties of the left ventricle due to their hypotensive effect and ability to reduce myocardial hypertrophy and fibrosis degree.

Angiotensin II receptor antagonists are not inferior to ACEi in the intensity of their positive effect on left ventricular hypertrophy and fibrosis degree and may even surpass them in their ability to eliminate diastolic disorders.

β-Adrenoblockers may be administered in order to reduce HR (to increase the LV diastolic filling period) and degree of left ventricular hypertrophy (to decrease the rigidity of the left ventricular chamber). Taking into account multiplicity of factors influencing the development of CHF in liquidators, it seems expedient to use the drugs having additional properties. So, Carvedilol, the β-adrenoblocker having the properties of αα1-blocker (vasodilating activity), marked antioxidant and antiproliferative activity, may be recommended for prevention and treatment of CHF in this patient category. It is justified to use Nebilet, the β-adrenoblocker exerting a vasodilating effect due to modulated relaxing factor (NO) release from the vascular endothelium, to eliminate endothelial dysfunction which is more pronounced in liquidators than in patients not exposed to the accident factors.

The administration of Verapamil to a patient with diastolic heart failure in order to decrease the heart rate may be recommended only in case of β-adrenoblocker intolerance and in patients without pronounced heart failure because its efficiency is not proven.

Diuretics may be required in case of liquid retention in the organism but they should be used with caution in patients with diastolic heart failure so that they should not cause excessive reduction of the left ventricular preload and significant decrease of cardiac output.

Aldosterone antagonists administered to patients with diastolic disorders should be considered not so much as potassium-sparing diuretics but as antifibrotic drugs. Thanks to this effect of the drug it is advisable to use it in liquidators already at initial stages of CHF.

The effect of heart rate slowing caused by cardiac glycosides (Digoxin) may be useful for patients with atrial fibrillation which is observed in approximately 30 % of patients with diastolic heart failure. The drug dose should not exceed 0.25 mg/day. Nevertheless, Digoxin should not be used routinely in this patient category and if it is necessary to reduce the heart rate, beta-adrenoblockers should be preferred.

The "cytokine" model of CHF pathogenesis enables us to suppose the possibility to influence effectively the disease course using new classes of drugs, i. e. TNF-αα synthesis inhibitors (Vesnarinone, Pentoxyphylline) or TNF-αα activity inhibitors (Enterasept). But these drugs are yet tested in patients with CHF and may not be recommended for use today. Nevertheless, this objective can be achieved using ACE inhibitors. One of the mechanisms of the positive effect exerted by ACE inhibitors in patients with CHF consists in their ability to influence the cytokine synthesis, and ACE inhibitors can lower the TNF-αα level not only due to hemodynamic myocardium unloading and lowered diastolic stress but also due to suppression by the drug of pro-inflammatory cytokine synthesis both in cardiomyocites and other sources (Savage, D. D., 1979).

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# CHAPTER 6

# THE PSYCHOLOGICAL STATUS AND SOCIAL AND PSYCHOLOGICAL LIFE PROBLEMS OF PARTICIPANTS OF LIQUIDATION OF ACCIDENT AFTERMATH AT THE CHERNOBYL NUCLEAR POWER PLANT AND THE PUBLIC RESIDING ON THE RADIOACTIVELY CONTAMINATED TERRITORIES IN A LONG-TERM PERIOD

## 6.1. PSYCHOLOGICAL STATUS OF PARTICIPANTS OF LIQUIDATION OF ACCIDENT AFTERMATH AT THE CHERNOBYL NUCLEAR POWER PLANT IN A LONG-TERM PERIOD AND FEATURES OF THEIR MEDICAL AND PSYCHOLOGICAL REHABILITATION

According to the current experience, data from various medical, psychologic and clinical psychiatric studies indicated the significant growth of psychic deadaptation of subclinical level and border-line neuropsychic disorders in LAA at ChNPP and the population in all age categories in the regions affected by the accident at ChNPP. Changes in the psychologic status in this victim category in a long-term period after the accident are observed in the form of stable symptom complexes of personal disorders (mainly, asthenic, neurosis-like, depressive and intellectual-mnestic disorders). They have several specific features which should be considered when

organizing a complex of medical and preventive measures, performing psychocorrection, medical and psychologic expert examination and rehabilitation.

The following important aspect should be mentioned while considering the etiology of negative personal changes and neuropsychic disorders in LAA at ChNPP. The impact of the factors of the ChNPP accident on the human body should be referred to as the extreme one.

It is known that all the extreme factors are divided into physical and chemical (including radiation exposure), informational (based on insufficiency, excess or falsity of the available information) and semantic (which threaten the biological and social motives of the human life acivities). Liquidators of the accident at ChNPP were exposed to a unique combination of extreme factors from all groups. It includes the prolonged exposure of the body to the low radiation doses, absence of reliable information about the accident, availability of distorted and sometimes falcified data on the impact of the radiation on the human body, significant public and social interest to this population group.

Extreme factors have both specific (radiation exposure in this case) and nonspecific (psychoemotional stress) effects on the organism.

The contribution of the specific and nonspecific components in the increased morbidity of LAA at ChNPP by psychosomatic (somatoform) diseases observed in 30 years after the accident, signs of increase of the psychic deadaptation have not been settled yet. But there is no doubt that the excitators of information and semantic genesis form the perception of threat for the individual's life (health) and well-being and, therefore, are a powerful factor of emotional stress.

As a consequence, LAA at ChNPP, even exposed to radiation doses not exceeding the threshold level, have different lingering unfavorable psychic conditions of emotional strain, anxiety and sometimes fear which gradually transform to stable psychopathologic disorders from neurosis-like disturbances to stable depressive and intellectual-mnestic disorders with restricted professional working capacity and disturbed social adaptation. The absence of rough personal changes in most cases, preserved positive social values and orientation (striving for family preservation, mutual support, orientation to socially acceptable behavior forms and social employment) may be mentioned as a positive factor.

The more rapid growth of severe forms of psychologic disorders is observed when individuals that are exposed to low radiation doses abuse alcohol. This additionally requires to form the individual life behavior programs for LAA not only by the methods of psychocorrection but also by providing them social and psychologic aid at specialized social and psychologic rehabilitation centers.

The results of many-year follow-up indicate that two fundamentally different groups with various peculiarities of changes in the psychologic status depending on the type of social and personal behavioral strategy and goal-directedness for continuation of the labor activity were determined in LAA at ChNPP.

The first group has the positive social and personal behavioral strategy. Even if the psychosomatic pathology is present, the representatives of that group are striving to achive an expert association between the existing disease and involvement in liquidation of accident aftermath

and to receive a disablement group; at the same time these individuals are focused on the continuation of their work, i. e. solution of medical and social problems has adaptive format.

The second group has the negative social and personal behavior strategy. These individuals having mild forms of psychosomatic pathology are not focused on the continuation of their work, they are extremely concerned with their health condition, have unfavorable changes in the psychic status and personal features and, therefore, need specialized psychologic and psychiatric and psychotherapeutic aid.

Hence, practically all LAA at ChNPP have changes in their psychologic status of different degree in the form of stable personal symptom complexes which significantly complicate not only the course of the somatic diseases but also the life of a liquidator as a social individual itself. It is necessary to provide psychologic aid both within the limits of medical actions and in the process of social and psychologic rehabilitation. The measures of psychological aid should be carried out by specially trained staff (psychologists, physicians-psychotherapists). But medical specialists working with LAA in inpatient and especially outpatient settings should know and consider the features of the psychologic status, rehabilitation and psychologic correction of this cohort.

The analysis of the results of the psychological investigation of personal peculiarities of LAA at ChNPP in a long-term period performed at ARCERM indicated that practically all patients had signs of personal deadaptation and emotional stress.

The conversation preceding the psychological investigation revealed a range of the most urgent personal problems realized by LAA. Overwhelming majority of LAA reported irritability, hot temper, absence of life pleasure sensation, vulnerability, lack of self-confidence, mistrustfulness, passivity.

The experimental psychologic investigation using Spielberg-Hanin test and Minnesota Multiphasic Personality Inventory (MMPI) revealed that most LAA had considerably increased reactive anxiety and anxiety as a stable personal characteristic. That can indicate the individual personal predisposition to the development of neuroses and psychosomatic diseases or correlate with already existing pathology.

The performed psychological investigation (MMPI test) allowed revealing the main individual personal features of LAA at ChNPP in a long-term period.

First of all, a pronounced trend to dramatization of existing circumstances and own attitude to them, i. e. a certain orientation to emphasizing the available problems, dramatization of difficulties, aggravation of the condition (which is often unrealized) should be mentioned.

The analysis of the psychologic profile in this group indicates the leading symptoms of depressive-hypochondriacal range (increased scores in the scales “hypochondria,” “depression” exceeding the limits of the norm) and reveals a protective mechanism of the type of “escape into disease.” In this situation the disease (evident or imaginary) is an original screen masking the striving to shift the responsibility for existing problems to the others. This psychologic phenomenon can be considered as a single socially acceptable way to justify own passivity. The psychologic investigation of LAA (MMPI test) often revealed increased score in the scale “hypochondria” that is commonly associated with the predisposition to psychosomatic diseases.

The increased score in the scale “hypochondria” was observed in 70 % of cases in the LAA cohort. The high scores in the scale “depression” were typical to 61 % of LAA and indicated the presence of depressive reaction within the limits of personal deadaptation. That was revealed by the predomination of a passive personal position with leading motivation directivity to avoid failures and such personal features as trend to intensive emotions caused by failures, agitation, aggravated sense of guilt with self-critical attitude to own drawbacks, lack of self-confidence. Frustrated need in understanding, love, friendly attitude should be mentioned as well.

The scores obtained in these tests reflect the problem of suppressed hostility, at the same time including the characteristics of mixed reaction type irrespective of the other profile structure.

The high score in the scale “hysteria” indicated the accentuation of hysteroid type, emotional immaturity and trend to excessive dramatization of circumstances. That condition was characterized by pronounced emotional lability with striving to please others, somewhat demonstrative behavior with tangentiality of emotions, self-rating instability, “childness.”

The high scores in the scale “anxiety” revealed emphasized anxious and mistrustful and sensitive personal features indicating the high anxiety within the limits of depressive- hypochondriac condition. This condition is characterized by sleep disorders, obsessive fears, feeling of confusion, unrest, sensation of oncoming misfortune.

The relatively low scores in the scale “optimism” emphasized the depth of depressive mood color and indicated chronic nature of difficulties in adaptation what was the most often associated with neurotic condition.

The clinical and psychologic analysis of the condition of LAA at ChNPP performed based on the data of the conversation, follow-up and experimental psychologic tests indicates that majority of the LAA were in the condition of extreme internal (psychic) strain. Such condition negatively influenced the intellectual and cognitive sphere in which the very low interference immunity, serious difficulties in distinguishing significant indications, in differentiation of the main and secondary issues, increased trend to consideration of improbable possibilities and very close attention to negative stimuli were revealed.

The emotional sphere of LAA at ChNPP was characterized by anxiety, internal emotional torments, multiple unmotivated misgivings, sensation of vague threat and high concern about the health condition. Obsessive fears characterized by rich emotional experience, lowered motivation for achieving success due to fixation to failure avoidance, lowered sensation of reality, skepticism and also constant need in the help and support from the others were frequently observed as well.

The following features were revealed in the character: timidity, aspontaneous behavior (fear to demonstrate own emotions), responsibility, rigid behavioral stereotype, impressionability up to mistrustfulness, scrupulousness, irresolution, lack of initiative.

The mixed reaction type was observed, which combined the high demand in self-realization with the high self-control and trend to retain behavioral reactions. That impacted the general overstrain and manifested in somatization of the internal conflict, i. e. psychosomatic variant of deadaptation, with the target being the weakest component of any of the functional system in the

human body. It is important to emphasize the established structure of personal attitude to the existing situation, chronic psychic deadaptation and deficit of compensatory personal resources.

Consequently, the results of psychologic studies on LAA at ChNPP indicate their stable condition of general deadaptation and emotional stress that is developing within the limits of asthenoneurotic state with pronounced hypochondria and trend to increased excitability. It is important to emphasize the existing probability of somatization of anxious-depressive strain and problem of suppressed hostility as well as the deficit of compensatory personal resources.

The results of investigation of cognitive psychic processes allowed revealing psychic function disturbances in LAA. 86.4 % of persons had attention impairments (changeover and concentration, trend to exhaustion); decreased operative and short-term memory capacity was observed in 60.0 % of cases. A general trend to the decrease in the generalization level was observed in the cogitation in 84.3 % of liquidators. Attention-mnestic impairments characterized by the dereased operative memory capacity and active attention, instability and exhaustion of psychic processes were observed in 77.2 % of cases.

The revealed types of cognitive psychic process disturbances in LAA (decreased generalization level up to establishing the functional and specific associations between persons and phenomena, memory impairments with the defects of memory acquisition, retention and reproduction with the complications in memory acquisition with simultaneous general reduction of retention of stimulus series) indicated the possible organic nature of the impairment.

Hence, the revealed changes in the psychologic status of LAA at ChNPP can be traced in the form of stable symptom complexes of personal disorders, mainly, of asthenic, neurosis-like, depressive and intellectual-mnestic range. The decreased cognitive psychic functions, motor activity, physiologic resources and reduced working capacity were observed in nearly 90.0 % of cases. That was the evidence of the necessity to carry out actions for psychologic correction for the majority of the cohort.

A course of psychologic correction was set up for the consent participants considering their individual psychologic features. The results of the previously conducted interviews indicated that 85 % of LAA confirmed the requirement to conduct “special” trainings to educate them in the rational behavior and ability to remove excessive nervous and emotional strain.

The efficiency of psychologic correction measures was confirmed by the results of the subjective assessment of well-being and psychophysiologic investigation. In particular, 95.0 % of respondents reported improved general subjective health condition and mood as well as reduced sensation of anxiety and internal strain after the trainings. Only 5.0 % of respondents reported that their general subjective health condition did not change.

The results of the psychophysiologic investigation indicated that psychological correction measures administered to LAA resulted in a significantly decreased Robinson index, trend in a decrease in HR and BP; the degree of these changes progressed through the sessions. At the same time the breath-holding time (Stange's test) increased significantly after trainings. It should be noted that the individual reactive anxiety level decreased by 10 conventional units after the course of

psychologic correction measures. That was thr evidence of relatively normalized psychic condition as well.

These in-depth psychologic investigations allow obtaining the additional information about features of LAA psychologic status (depressive-hypochondriac type of personal reaction with the trend to emotional lability and predisposition to impulsivity in the behavior). Then it is possible to select the methods for their medical and psychologic rehabilitation.

Revealing the psychologic causes for deadaptation condition in LAA at ChNPP after many years is one of the most important factors in solving the problem of their medical and psychologic rehabilitation. The results of our investigations indicated the considerably increased prevalence of borderline neuropsychic abnormalities in LAA. Hence, frustration of the significant personal needs was one of the causes for neuro-emotional strain in 80.0 % of LAA. Their typical compensation forms included the flight into the world of internal emotional experience with "infaltilization" of relations with avoidance of responsibility; in other cases, frustration was compensated by active actions, aimed at changing the current conditions, or attempts to numb the emotional dissatisfaction by vigorous, risky activity and elements of poorly controlled social aggression. The third, the most prevalent compensation form included striving to achieve safety due to certain social guarantees (establishment of the association between the disease and the works for liquidation of the accident and obtaining a disablement group).

The obtained results indicate that LAA have a specific pattern of pathopsychologic changes which causes certain homogeneity of clinical symptoms observed in their cohort and typical stereotype of syndromokinesis. This is the evidence of fact that a certain way of psychologic adaptation typical to this contingent was formed during the period since the accident at CHNPP.

The analysis of obtained results indicates that the increased severity of psychic process disturbances in the investigated population sample is directly associated with the intensity of neuropsychic strain. That reflects a considerable role of the effect exerted by the psychologic status (personal structural features) on the general functional condition, behavior, activity and adaptation resources. It is important to emphasize the existing probability of somatization of anxious-depressive strain and the problem of suppressed hostility, established structure of person's attitudes to current situation, chronic psychic deadaptation and also deficit of personal compensatory resources.

The investigations of the actual emotional condition indicate that the main demands determining the LAA behavior were associated with sensation of fatigue, spiritual bankruptcy, isolation. That resulted in decreased mood, passivity, escape from social contacts, lack of confidence in the behavior. The internal strain developing in this situation caused borderline neuropsychic disorders with subsequent possible formation of the somatic pathology, diseases of the nervous and cardiovascular diseases in particular. These personal features indicated difficulties in the psychologic correction activities with this contingent. While their condition is characterized by general intellectual-mnestic impairment and personal changes, most of them have a "rent" attitude to own disease, i. e. they strive for being more socially protected and supported by different

public institutions (health care facilities, trade-union organizations, social security bodies) as chronic patients.

The psychological investigations of LAA revealed a focus on obtaining social benefits which promoted stamping in the mechanism for protection against problems by "escaping into the disease."

The stable and weak components of the intrapersonal structure are a risk zone regarding break of the adaptation barrier. The clear changes in psychic process disturbances (memory, attention, thinking) were observed with increase of their severity with the stream of time from the moment of exposure to a complex of unfavorable accident factors at ChNPP. These changes develop as organic pathology with predomination of asthenic symptoms.

The analysis of specific typological features of LAA at ChNPP indicates that their psychologic profile is similar to psychologic profile (condition) of persons with history of psychologic traumatic situations from military conflicts, terrorist acts, different catastrophes of natural and technogenic origin which are referred to consequences of posttraumatic stress disorders (PTSD) according to modern concepts [13, 16–21].

The psychocorrection measures accelerate adaptation to professional activity and favor prevention of PTSD in LAA at ChNPP. Their general subjective health condition and mood improve; cardio-respiratory system parameters are optimized and psychoemotional stress tolerance increases.

The medical and psychologic rehabilitation program developed by the specialists of ARCERM includes a multi-level, constant system with obligatory participation of psychologists and physicians-psychotherapists at all stages of the medical and preventive measures. The current experience indicated the expediency of these measures in outpatient settings. Physicians-specialists working with LAA in inpatient and especially outpatient settings should know and consider features of the psychologic status and medical and psychologic rehabilitation of this contingent.

The combination of activities for medical and psychologic rehabilitation should include the following methods: social and psychological, psychologic (hetero- and autorelaxation technologies, suggestotherapy, rational psychotherapy, psychoanalysis, neurolinguistic programming, art therapy, etc.) and physical (special trainings) methods.

The medical and psychologic rehabilitation should consist of three main stages:

1. Diagnostic stage: clinical and psychologic investigation to assess the functional condition, psychologic features and strain of psychic adaptation mechanisms in LAA at ChNPP.

2. Medical rehabilitation stage: formation of the individual approach based on existence of the psychoemotional disorders in a specific individual, selection of the psychotherapeutic tactic (rational psychotherapy, relaxation technologies with suggestive elements, etc.).

3. Social adaptation stage (professional rehabilitation). Special trainers, equipment and computer methods for recovery of lost skills are used at this stage.

Hence, results of the studies indicated that after many years the majority of the LAA at ChNPP had had changes in their psychologic status, which, commonly, negatively developed in the form of stable personal symptom complexes significantly complicating the course of somatic

diseases as well as the process of social adaptation. The stable condition of general deadaptation and psychoemotional stress with simultaneous deficit of personal compensatory resources of the LAA at ChNPP requires providing aid to such individuals within the system of measures for medical and psychological and social rehabilitation.

The measures for medical and psychological rehabilitation should be aimed at normalization of the psychoemotional condition, enhancement of the personal adaptation potential, formation of the optimal behavioral stereotype for the professional activities and private life, development of communicative capabilities, training in basic methods of psychic self-regulation and removal of somatoform disorders. It is possible to solve the problem of rehabilitation by creating the state system for medical and psychological support for the victims of different emergency situatons in dedicated medical and psychologic rehabilitation centers with obligatory involvement of psychologists and physicians-psychotherapists at all stages of medical and preventive measures.

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## 6.2. SOCIAL AND PSYCHOLOGIC LIFE PROBLEMS AND STRESS REACTIONS IN THE POPULATION OF RUSSIAN RADIOACTIVELY CONTAMINATED TERRITORIES AFTER THE CHERNOBYL NUCLEAR POWER PLANT ACCIDENT

The large-scale technogenic accident at the Chernobyl NPP (ChNPP), which took place on the 26th of April, 1986, resulted in emission of a significant quantity of radioactive substances to the environment leading to the radioactive contamination of several areas in the Russian Federation, Ukraine and Belarus and some areas in the Eastern and Western Europe. In addition to the ecologic, social-economic and medical and social consequences caused by the radiation, the ChNPP accident impacted the psychic health of the population residing on the radioactive contaminated territories (RCT).

The mass psychologic stress for the population immediately after the ChNPP catastrophe in 1986 and the consequent legislative recognition of millions of citizens residing on RCT and being involved in liquidation of accident aftermath as "victims" of Chernobyl resulted in social and psychologic strain which was determined by inadequate information on the accident consequences, implemented countermeasures , social benefits and compensations (Abramova, V. N., 1988; Alexandrovsky, Yu. A., 1989; Rumyantseva, G. M., 1996, etc.).

According to some studies (Abramova, V. N., 1988, 2001; Tarabrina, N. V., 2001; Melnitskaya, T. B., 2009, etc.), the basic problems from the ChNPP accident result in psychologic stress reactions associated with radioanxiety, inadequate perception of information on the consequences of the radiation exposure on the human body and social-economic conditions of life of the population residing on RCT.

Marchenko, T. A., Rybnikova, V. Yu. (2004) evaluated the problems of medical and psychologic rehabilitation and medical and social aspects of the improvement of life safety of the population after the large-scale radiation accidents. Melnitskaya, T. B. (2009) established a conception of informational and psychological safety of the population in the presence of the radiation risk. Rumyantseva, G. M. et al. (2009) assessed psychological and psychiatric consequences of radiation catastrophes. Simonov, A. V. (2010) established the principles, structural and functional model and organizational and methodical provision of the informational-psychological protection of the population residing on RCT in Russia and Belarus. The PhD thesis by Reshetnikova, E. M. (2012) is focused on the individual psychologic status of liquidators of accident aftermath at ChNPP in a long-term period. The PhD thesis by Belykh, T. V. (2014) develops the problem of psychological assessment and formation of life safety culture of the population residing on RCT.

The social and psychologic life problems of the population affected by the accident at ChNPP were considered in the studies performed by Abramova, V. N. (1988, 1992), Tarabrina, N. V. (2008), and others.

The population of RCT is characterized by associating all unfavorable life situations with the radiation factor (Zykova, I. A., Arkhangelskaya, G. V., 2007). This may cause false paradigms of having the diseases associated with exposure to the radiation and "rent" idea that consisits of the expectation of the moral and material aid from the wider public, society and state (Marchenko,

T. A., 2003). The population on the whole is guided not by own resources but by social support from the authorities (Melnistkaya, T. B., Belykh, T. V., 2014). That favors the development of feeling of being helpless and the loss of control of own life in public. The long frustration and life conditions close to the extremal situation result in social apathy of the population on RCT; cases of neuropsychic pathologies become more frequent. Several researchers report prevalence of reactions of neurotic type in the population on RCT (Tarabrina, N. V., 2008; Rumyantseva, G. M., 2009).

In addition to medical and ecologic consequences, the Chernobyl catastrophe caused many negative social and psychologic processes associated with mass resettlement of the people from the contaminated territories, changes in established conditions of residence, work, nutrition, changes in the economic activity in the regions (Liberman, A. N., 2002). According to several experts, the most complex problems caused by Chernobyl are hidden in the field of psychology (Alexandrovsky, Yu. A., 1990; Summarizing report of UNO, 2003–2005).

The experience in overcoming radiation catastrophes confirms that the threat of the radiation exposure can be considered as acute or chronic stress influence leading to several psychologic stress reactions (Abramova, V. N., 1988; Rumyantseva, G. M., 1996).

That results in the reduction in the quality of life and can result in a wide range of alterations of the somatic and psychic health Vishnevskaya, V. P., 2004). The analysis of the studies assessing stress reactions after the radiation accidents indicated that the threat of the exposure of the population to the ionizing radiation frequently resulted in the development of acute or chronic stress disorder accompanied with neuropsychic strain and anxiety (Tarabrina, N. V., 2008). Such condition can cause systemic disturbances in the psychic and physical health and result in the reduction in the quality of life in a long-term period (Rumyantseva, G. M., 2009; Rybnikov, V. Yu., Marchenko, T. A., Melnitskaya, T. B., Simonov, A. V., 2009).

Even if people have no physical health damage resulting from the accident, the anxiety associated with possible consequences causes long psychologic distress in residents of contaminated territories. It was estimated that symptoms of “immersion” into a traumatic situation were observed more frequently compared to the escape reactions even several years after the accident (Rumyantseva, G. M., 1996).

The results of the many-year analysis of psychopathologic disorders in the population on RCT indicated that the asthenic symptoms gradually replaced anxious stress reactions (Rumyantseva, G. M. et al., 1996). This phenomenon may be considered as sign of chronization of neurotic disorders under the conditions of long stress.

We have studied the social and psychologic life problems and stress reactions in the population of radioactively contaminated territories of Russia in a long-term period after the accident at ChNPP.

In order to investigate social and psychologic life problems and stress reactions in the population of radioactively contaminated territories (RCT) of Russia after the accident at ChNPP, a monitoring of social and psychologic strain and social and psychologic life problems, stress reactions and coping-strategies of the population on RCT was performed based on the data obtained by the comparative analysis of similar parameters in the population of radioactively non-contaminated territories and status residence zones on RCT (residence zone with privileged social-

economic status (RZPSES); zone with right for resettlement (ZRR); resettlement zone (RZ)) in the Bryansk, Kaluga, Orel and Tula Regions of Russia.

This monitoring was included in the list of activities of the Programs of Joint Activities for Overcoming the Aftermath of the Chernobyl Catastrophe within the Boundaries of the Union State (for the period of 2006–2010, to 2016) and the Federal Targeted Program "Overcoming the Aftermath of Radiation Accidents for the period of up to 2015."

The raw data was collected under the leadership of Melnitskaya T.B. together with specialists of the regional information and analytical centers (cities of Bryansk, Tula, Kaluga, town of Bolkhov of Orel Region) and social and psychologic rehabilitation centers (settlement of Nikolskaya Sloboda of Bryansk Region, town of Bolkhov of Orel Region, town of Uzlovaya of Tula Region). The sample representativeness was ensured by the use of the quota method (multi-staged quota sample).

The empirical material was based on the sample including the investigation results of 5,988 people aged 16–89 years; 4,003 persons resided on RCT, 1,985 persons resided on RNCT.

The investigation was performed using the following methods:

– Method for the research on social and psychological problems of population (MRSPP) (Abramova, V. N., Marchenko, T. A., Melnitskaya, T. B., Khavylo, A. V., Antonova, E. V., 1989–2004);

– Impact of Event Scale—Revised (IES-R) (Gorovitz, M., adapted by Tarabrina, N. V., modified by Belykh, T. V., Melnitskaya, T. B., Khavylo, A. V., 2004-2011);

– Strategic Approach to Coping Scale (SACS), S. Hobfoll, 1989, adapted by Vodopyanova, N. E., Starchenkova, E. S.).

The comparison of the social and psychologic strain level in 2004–2014 in three similar periods allowed concluding that this parameter lowered significantly but was considerably higher in the population on RCT compared to the population on RNCT (Fig. 6.1).

The results of the study indicated as well the lowered general level of concern about social and psychologic life problems of the population on RCR over the last 10 years.

Fig. 6.2 presents the changes of parameters reflecting the concern of the population on RCT with problems of health, personal changes and interrelationships.

The signs of asthenia: high fatigability, weakness, lowered working capacity were the most frequent complaints of the population on RCT concerning their own health condition. It was determined that a significant percentage of persons associated their health problems with increased radiation level.

While describing changes in their own personality, residents of RCT often reported signs of excessive responsibility, were concerned about manifestation of emotional lability: insomnia, deficit of forces, increased uneasiness. The problems of interrelations observed in the population of RCT were manifested mainly in increased irritability, disappointment in the people, negation of generally accepted standards and rules. It was determined that the hierarchy of symptoms within each factor did not change considerably during the whole monitoring period.

The comparative analysis of the concerns of the residents of RNCT and RCT indicated that the integral parameters of three analyzed factors of social and psychologic deadaptation were significantly higher for the residents of RCT: they were more concerned about health problems, more troubled by negative personal changes and problems of interrelations with the others.

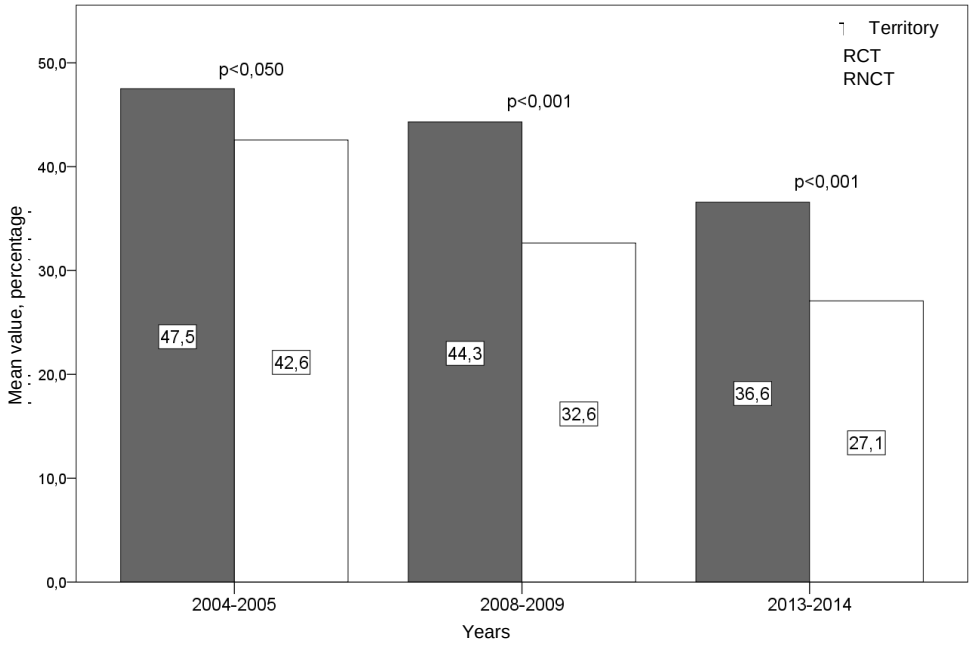


Fig. 6.1. Changes in the Level of Social and Psychological Strain over Time in the Population of the Radioactively Contaminated and Non-Contaminated Territories in a Long-Term Period After the Accident at ChNPP

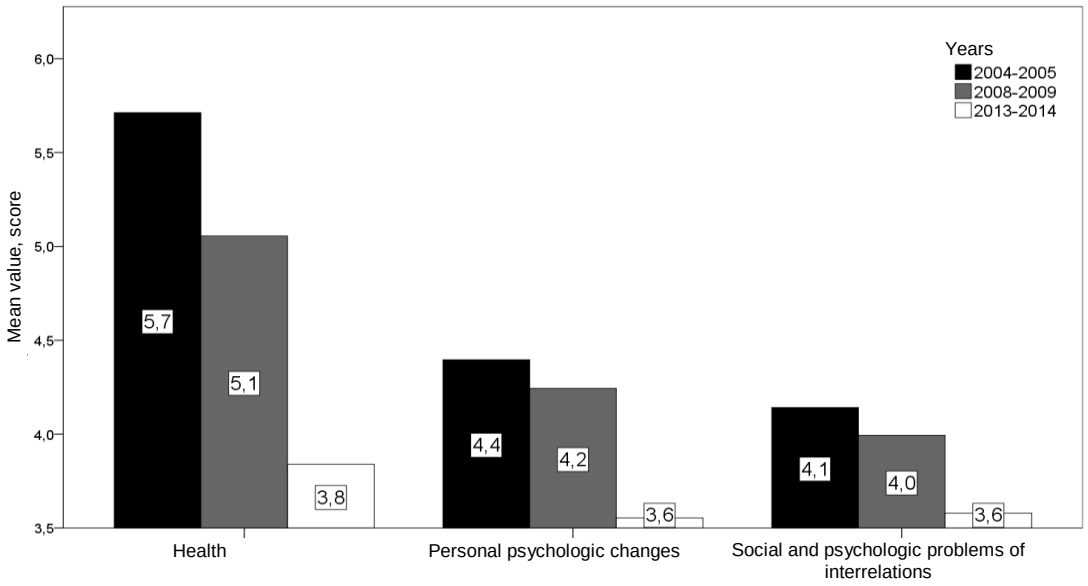


Fig. 6.2. Social and Psychologic Life Problems of the Population on RCT Basing on the Monitoring Results

In order to assess the changes in the population concern on social and psychological life problems over time we performed the comparative analysis of these parameters on the territories with different status over the last decade. Fig. 6.3 presents a diagram with the mean scores of significance of the social and psychologic life problems in the population of the investigated areas with different radioactive contamination level based on the 2013–2014 monitoring data.

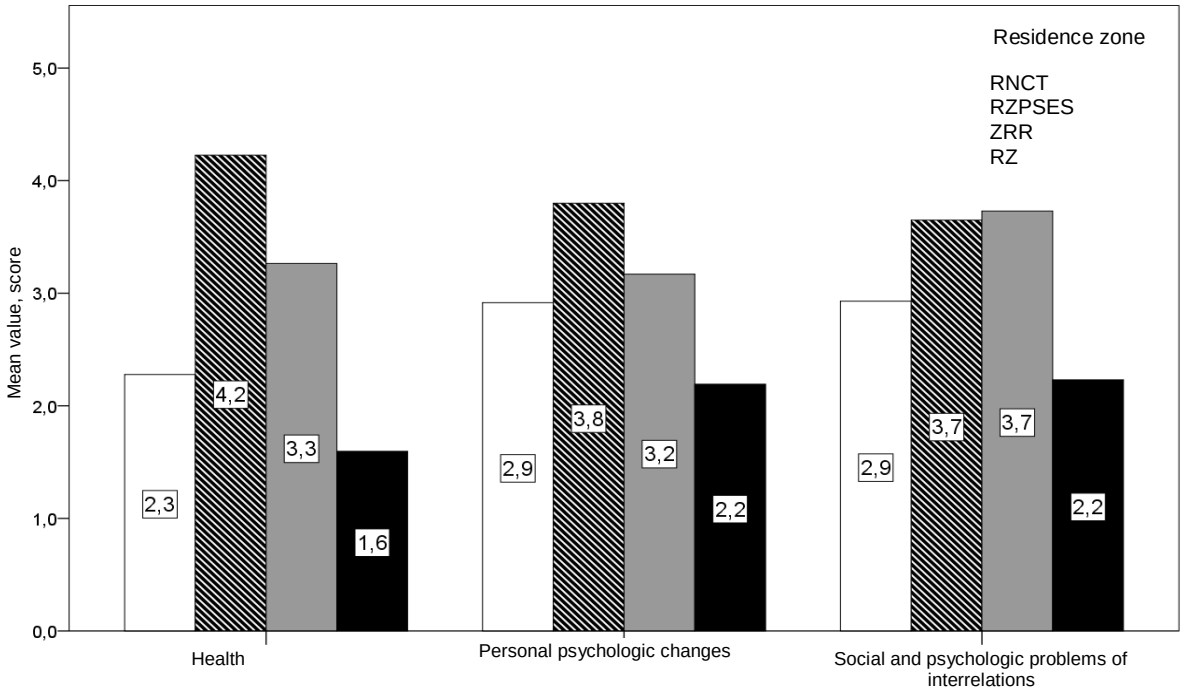


Fig. 6.3. Social and Psychologic Life Problems of the Population on
Different Status Areas Basing on Monitoring Results over the Period of 2013–2014

A lowered population concern level was revealed for each problem block in all analyzed residence areas.

It was indicated that residents of the resettlement zone were the least concerned with the social and psychologic problems. It can be explained by the resettlement of residents, that were maximally influenced by the stressogenic factors, from the contaminated districts of this region. Additionally, it is necessary to consider differences in the gender and age composition of the sample on this territory. The level of concern with social and psychologic life problems was slightly higher in the population of the radioactively non-contaminated territories. The resident sample of RNCT was used as the control sample in that study.

The residents of the districts with privileged social-economic status and zone with right for resettlement had the maximum degree of concern with health problems and personal psychologic changes. We consider that this is caused by the concerns associated with the threat to lose the privileged status. Lately the policy of granting benefits is being reviewed at the state level. Residents of the districts with privileged social-economic status and relatively low radioactive contamination level may be deprived of benefits. We consider this as an additional stress-factor acting on RCT at the current time.

Factor analysis was performed using the MRSPP method in order to determine the key blocks of social and psychologic life problems associated with each other. As a result, four blocks of social and psychologic life problems were determined: “concern about health condition” (F1, ДП = 19.5 %), “emotional discomfort” (F2, ДП = 7.3 %), “disapproval of family” (F3, ДП = 4.9 %) and “estrangement” (F4, ДП = 4.0 %) combining close and interrelated life problems on RCT.

We considered the impact of gender and age characteristics of residents of RNCT and RCT on the concern level with distinguished problem blocks. The influence of gender and age characteristics on concern on the social and psychologic life problems on radioactively

contaminated and “clean” territories was different. The concern about personal health condition in the population of RCT increased at the middle age and subsequently remained relative stable. Gender differences in the intensity of this problem in the investigated population of RCT were observed only in the middle age category: the concern level was slightly higher in females.

The assessment of the data obtained on RCT revealed that gender and age characteristics had no significant effect on the “emotional discomfort” problem block. It can be explained by the strong impact of the factor of residence on the radioactively contaminated territory that neutralized the impact of individual differences that, according to our data, were observed in residents of RNCT.

the analysis of the “disapproval of family” problem block indcated a relatively high concern about the problems of this group in young age. Evidently, that is associated with problems of separation from the parent family which are typical for this age and concerns about the problem of developing their own family life.

The assessment of the impact of the gender and age characteristics on the intensity of the “estrangement”problem block indicated differences in the concern level about the problems of this block between elderly persons and young and middle age residents of RCT. Elderly persons had considerably higher concern level about this problem. It was indicated that females were significantly more concerned about the problem of estrangement in all age groups.

As a result, it was indicated that the social and psychologic life problems of the residents of RCT had their specifics. The degree of problems differed in the residents of the territories with different status.

We determined the basic blocks of the social and psychologic life problems and analyzed the effect of gender and age and educational characteristics on the concern level of the population.

The assessment was performed using one-dimensional analysis of variance. It was revealed that the social and psychologic strain level in RCT was associated with persons’ educational level, age and interaction of these two factors. It was indicated that the gender of the investigated residents of RCT had no significant effect on the social and psychologic strain level considering the factors of age and education.

The social and psychologic strain in young age was slightly higher for individuals without secondary or higher vocational education. Evidently, this is associated with difficulties in social adaptation for the individuals without a vocational education or only undergoing education.

The social and psychologic strain in middle-aged individuals was higher for those having secondary vocational and higher education.

The growth of the social and psychologic strain with the increase of the educational level was determined for the group of elderly individuals.

The analysis of the stress reaction intensity in the population of RCT indicated the following. The sample was divided in three groups by the stress reaction intensity using the method of cluster analysis. Comparison of the results of sample division with the recommendations of the authors of the method IES-R allowed providing the informative interpretation of obtained groups.

According to the monitoring results, the stress reaction intensity in the population of RCT of Russia has been lowering steadily over the last 10 years. The percentage of persons referred to the risk group decreases.

We proved the existence of differences in the level of stress reactions associated with the radiation factor in the population of RCT and RNCT. It was indicated that the highest stress reaction level was observed on the territory with privileged social-economic status. Slightly lower intensity of stress reactions was indicated in the zone with right for resettlement. Residents of RNCT and RZ were to the least extent exposed to stress reactions associated with the radiation factor.

The assessment of the effects exerted by the gender, age and combined effect of these two characteristics on the intensity of stress reactions associated with the radiation factor allowed revealing the following. The degree and nature of the influence exerted by the gender and age characteristics on the intensity of psychologic stress reactions differed on RCT and RNCT. Residents of RNCT were characterized by pronounced gender differences regarding stress reactions associated with the radiation factor. The stress reaction intensity in females was significantly higher compared to males.

The assessment of interrelationship between the gender, age and intensity of intrusion reaction in the population of RCT indicated low intensity of the stress reaction in young age and its abrupt growth in the middle and elderly age. No significant differences between males and females were determined in the intensity of intrusion reaction and its changes over time .

It was estimated that the intensity of escape reaction increased with the increase in the age as well; changes of this parameter over time did not differ significantly in females and males, and the intensity of this stress reaction in females was higher in all age groups.

There were practically no differences in the intensity of stress reactions in males and females on RCT. The intensity of psychogenic stress reactions increased with the increase in the age both on RNCT and RCT. The analysis of interrelationship between the gender, age and intensity of physiologic excitability reaction in the population of RCT with the help of analysis of variance indicated that only age factor influenced the intensity of escape reaction.

The analysis of data obtained on RCT did not reveal any significant impact of gender characteristic and combined influence of gender and age characteristics on the intensity of stress escape reaction. It was possible to observe relatively low intensity of physiologic excitability reaction in young age and higher intensity in the middle and elderly age both in males and females.

The analysis of the impact of the individual educational level, age and gender on the intensity of stress reactions indicated that the intensity of stress reactions on RCT was associated with the persons' age, educational level and interaction of these two factors: according to the results of the analysis the gender of investigated residents of RCT had no significant influence on the total intensity of stress reactions.

The intensity of stress reactions increased with the increase in the age. The differences in the intensity of stress reactions of persons with different educational level became more pronounced as well. Hence, the maximum intensity of stress reactions was observed in residents of RCT with higher education in the group of elderly persons, in persons with the higher and secondary special education in the group of middle-aged persons and in persons with the higher and secondary education in the group of young persons.

It was indicated that the intensity of all stress reactions had positive correlations with the concern level on social and psychologic problems. Intensification of stress reactions in the

population of RCT was accompanied with more pronounced concern of the population on social and psychologic life problems.

The results of the studies on protective and coping behavior and coping-strategies in the behavior of the residents of RCT indicated differences in the degree of escape-copingstrategies between the groups representing different status zones. Significant differences were determined between the degree of escape-coping strategy of the residents of ZRR and the population of other status zones. Residents of ZRR used this coping-strategy more more frequently compared to other groups.

It was indicated that the gender factor had a significant impact on the degree of such behavioral coping strategies in RCT as search for social support, getting in social contact and asocial actions. The first two strategies were used more frequently by females, and the latter was more frequently used by males. The studies on the population of RNCT did not reveal any impact of the gender factor on the features of the protective and coping behavior of the population. Respondents with high degree of coping-strategy "search for social support" need the support of scientists, physicians, teachers, ecologists and other specialists. That is associated with the fact that residents, especially in zones with ecological problems, are mainly concerned with their own health and ecological problems.

Hence, it is necessary to continuously improve the information and psychologic work with the population. One on the ways to organize such work results in information interaction between the representatives of science and motivated primary specialists at the local level working directly with the public. That was implemented in the form of training courses or seminars for groups of primary specialists. During their professional activity, these specialists informed the population on the data obtained in the process of the measures mentioned above. That allowed providing consultative aid to the population of the affected territories. Such two-staged system for informing the population of RCT was called "distant consulting."

The results of the social and psychologic monitoring concerning the degree of social and psychological life problems and stress reactions of the population living in different zones on RCT should be considered when preparing and correcting social decisions (standard acts), federal and regional programs aimed at the development of a complex of effective technologies, implementation and improvement of the system of measures for social and psychologic adaptation of the population and formation of the culture of life safety.

In summary, the results of the study allowed making two important conclusions.

First, the degree of social and psychologic life problems and social and psychologic strain in the population on the radioactively contaminated territories in Russia lowered considerably in a long-term period (2004–2014) after the accident at ChNPP. But the level of this parameter is significantly higher in the population of RCT compared to RNCT. In this situation the structure and leading factors (signs) of the problems mentioned above have specific features for the population of radioactively contaminated and not contaminated territories, in different resident zones, depending on gender, age and educational characteristics.

Second, the degree and structure of stress reactions and strategies of coping-behavior of the population of different status zones of radioactively contaminated territories in a long-term period after the accident at ChNPP have their features compared to the population of not contaminated territories and are significantly determined by the age, educational level and social and psychologic life problems of the population. This should be considered when organizing the social and psychologic work with the population of RCT.

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## CONCLUSION: MEDICAL CONSEQUENCES OF THE ACCIDENT AT THE CHERNOBYL NUCLEAR POWER PLANT IN A LONG-TERM PERIOD: RESULTS OF long-term MONITORING, PATHOGENETIC MECHANISMS OF DEVELOPMENT OF SOMATIC PATHOLOGY; EXPERIENCE OF DIAGNOSTICS, TREATMENT AND REHABILITATION OF PARTICIPANTS OF LIQUIDATION OF ACCIDENT AFTERMATH AT THE CHERNOBYL NUCLEAR POWER PLANT

Thirty years have passed after the large-scale radiation accident at the Chernobyl nuclear power plant that resulted in millions of people being exposed to the ionizing radiation on a different level, vast territories were contaminated with radioactive substances.

In addition to ecologic, social-economic and medical and social consequences caused by the radiation, the accident at ChNPP influenced the somatic and psychic health of the population residing on the radioactive contaminated territories (RCT) as well as the liquidators of accident aftermath at ChNPP.

LAA at ChNPP are a special citizen category who performed a heroic deed. They included firefighters who extinguished the fire occurring during the accident that prevented further

development of the catastrophe; Pilots, who dropped about 5,000 t of different materials into the shaft of the destroyed reactor from helicopters under high radiation levels, hence preventing radionuclide discharges. Additionally, they included military men, workers of the Ministry of Internal Affairs of Russia, employees of civil institutions and departments who risked their health carrying out the deactivation of NPP, settlements on the contaminated territories, building the covering above the 4th destroyed power-generating unit of NPP. That resulted in the improved radiation situation, reduced exposure of both the NPP staff and the population residing on the contaminated territories.

The state policy of the Russian Federation and the Russia-Belarus Union State in the field of health care is aimed at lowering the negative medical consequences of the Chernobyl catastrophe for the population of the territories affected by the radioactive contamination and liquidators of accident aftermath at ChNPP. This monograph is aimed on the analysis of the medical consequences of LAA due to the accident at ChNPP. Additionally, it contains the data on the experience and features of the provision of the specialized medical aid to LAA at ChNPP and citizens residing (having resided) on the radioactively contaminated territories.

Health problems of LAA involved in liquidation of accident aftermath at ChNPP became one of the main negative results of the Chernobyl catastrophe.

The increased morbidity and disablement rate due to the different somatic pathologies is particularly observed in liquidators that worked at ChNPP in 1986. It should be mentioned that the negative consequences caused by the accident at ChNPP are associated with the increased exposure of the people to the radiation as well as with the excessive stress and anxiety promoting the development of different psychosomatic disorders. The analysis of available studies and scientific reports on the problem of the effects caused by accident factors at ChNPP on humans evidences that the radiation factor is not a determining one in the assessment of medical consequences of the accident at ChNPP. Hence, today it is considered common to consider not only the radiation factor but a complex of accident factors at ChNPP among all the causes of health problems as a result of the accident at ChNPP.

The complex of factors influencing the LAA includes:

- external esposure and incorporation of radionuclides and several toxic substances which entered the environment and the food chain when the liquidation of accident aftermath at ChNPP was carried out;

-long-term psychoemotional overstress associated with the fact of «waiting for health hazard";

- changes in the life style, social strain in the society due to the economic and social causes.

The increased rate of cancer diseases over the period of next 30 years and above (colon, larynx, paranasal sinus, uterus, ovary, testis, stomach, thyroid, lung cancer) was referred to long-term consequences after the exposure of the individuals that survived after the atomic bombing in Hiroshima and Nagasaki, in doses exceeding significantly those after the accident at ChNPP. . It should be mentioned that this trend is observed also in LAA at ChNPP.

This chapter summarizes the results of many-year work performed by the collective of the All-Russian Nikiforov Center of Emergency and radiation Medicine of the Ministry of Emergencies of Russia on the assessment of the impact exerted by the radiation accident factors in Chernobyl on

the human organism and the introduction of new diagnostic, treatment and rehabilitation technologies for LAA at ChNPP in a long-term period.

Medical consequences caused by radiation accidents are quite various and complex; they may be conditionally distributed in two groups:

- radiological and toxic-radiologic consequences resulting from indirect effect of the ionizing radiation and toxic components during liquidation of the accident at ChNPP;

- different causes of general health problems associated with other accident factors of non-radiation nature.

Today it is a standard practice for most scientific reports concerning the accident at ChNPP to speak of the complex influence of the accident factors on the human organism. All these factors resulted in health reduction of LAA. The many-year changes in total morbidity of LAA over the studied period (from 1987 to 2015) are characterized by gradually increasing morbidity from 1991 to 1999 with subsequent sudden decrease and relative stabilization in 2001–2016 at a slightly higher level compared to the initial years (1987–1991).

The North-Western Branch of the national Radiation Epidemiologic Register (NWB-NRER), a division of the Federal State Budget-funded Institution "All-Russian Nikiforov Center of Emergency and Radiation Medicine" of the Ministry of Emergencies of Russia analyzed long-term changes in morbidity in LAA with diseases of the main classes allowing revealing the following features:

- most disease classes are characterized by relative monotonicity and autonomy of morbidity changes;

- there are morbidity variations in LAA by individual nosologies and classes over different years (e. g., synchronous rapid growth of morbidity with diseases of the cardiovascular and musculoskeletal systems was observed in 1999 with abrupt decrease after 2000) what enables to predict the influence of not only ethiopathogenetic but social factors as well (e. g., the law on benefits for LAA at ChNPP) on these processes based on the experience obtained with other similar cases;

- morbidity structure in LAA in different regions of permanent residence in RF differs considerably over the same period;

- morbidity with diseases of the cardiovascular, respiratory and nervous systems correlated directly with the age of LAA.

Considering the above patterns for the 30 years after the accident at ChNPP It is possible to make a conclusion on the dominating influence exerted by the factors of non-radiation nature on the prevalence of diseases in LAA. In this situation, population studies on the influence of the radiation factor expressed by the slight dependence of morbidity on the dose are incommensurable with the strength of the effect exerted by non-radiation factors. Results obtained by the dosimetric investigation of different LAA categories indicated that all persons had radioactive substance incorporation, mainly short-lived gamma-radiating iodine, cesium radionuclides, etc.

The studies on LAA at our Center using the highly-sensitive low-background whole bosy counter SICh-E that have been performed for more than 20–25 years after the accident did not reveal radionuclides in the organism. Low cesium-137 activities not exceeding the standard maximum permissible levels revealed in some patients can be explained by the use of food products

, mainly, mushrooms gathered in the districts of the Leningrad region with the residual radioactive contamination after the accident at ChNPP.

The epidemiologic analysis of disablement intensity, structure, dynamics and severity in LAA residents on the territory of the North-Western Region Russia over the period of 1987–2016 allowed revealing certain patterns:

- differences in diseases and disablement rate, dynamics, structure and severity by the territories of permanent residence in RF;

- dose-effect dependence of disablement which has a significantly higher effect of LAA invalidization compared to the influence of causative factors of non-radiation nature;

- structure of primary disablement by causes and cause severity predetermining this process including also the causes associated with everyday activities.

According to data of NWB-NRER, any dependence of mortality on the received irradiation dose in LAA at ChNPP have not been determined over the 30-year period; the lower average annual mortality of LAA is preserved in Saint Petersburg and other industrialized regions compared to other territories of Russia.

Epidemiologic studies of disablement and mortality of LAA residents in the North-Western Region of Russia and the results of the analysis of morbidity and prevalence of the diseases are the evidence of the predominating effect exerted by local causative factors of non-radiation genesis on all above statistical parameters.

The dynamical investigation of LAA health condition allows making the following conclusion:

- there is a dependence of disablement and mortality of LAA on morbidity with somatic diseases and malignant neoplasms;

-the effect exerted by causative factors of non-radiation genesis on the LAA public health parameters is considerably stronger compared to the exerted by the dose from the external exposure received over the period of participation in the works at ChNPP.

A typical feature of the somatic pathology in LAA consists in its comorbidity. So, the mean number of diseases per one LAA at ChNPP increased from 1.4 to 12.1 over 30 years. Simultaneous involvement of several systems is a feature of the somatic pathology in this cohort requiring a complex approach to the diagnostics and treatment. Their health condition is characterized by polypathology, lingering exacerbations of chronic diseases accompanied with reduced parameters of the immune system functioning in the organism. The leading roles in the structure of the somatic pathology revealed in LAA are played by diseases of the circulatory system (25 %), musculoskeletal system (18 %) and gastrointestinal tract (14 %).

Permanent disability (invalidism) is determined in more than 50 % of LAA at ChNPP, i. e. every second person of them is invalid with the predominance of the group II. Diseases of the circulatory system (55 % of cases) and diseases of the nervous system (12 %) are the most frequent causes for disablement.

The role of diseases of the circulatory system and neoplasms increases in the mortality structure of LAA at ChNPP over the last years. Changes in morbidity and primary disablement are

associated, mainly, with diseases of the circulatory system, nervous, musculoskeletal, digestive and respiratory systems.

That requires increasing the extent of specialized and high-technology medical aid provided to LAA at ChNPP.

The pathology of the thyroid should be mentioned separately. According to the majority of researchers, increased morbidity with thyroid cancer is associated with the internal exposure due to the selective accumulation of radioactive iodine. These processes are especially active in case of iodine isotope incorporation in districts which are endemic by goiter and iodine deficit in the water and food prducts. Just the territories of the Bryansk, Kaluga, Smolensk and other regions of RF and the territory in the south-east of Belarus comply to these conditions, and the pathology of the thyroid was observed before 1986 on the above mentioned territories more frequently compared to other regions.

The TG diseases in LAA at ChNPP may be characterized by two syndromes: TG enlargement syndrome (nodular or diffuse enlargement) and TG disturbed function syndrome (hyperthyroidism or hypothyroidism). Hyperthyroid conditions were revealed in 20.2 % of cases and hypothyroidism was indicated in 13.9 % in LAA at ChNPP involved in the works in the 30-km zone from April 1986 to November, 1987. Hyperthyroidism was revealed in 14.9 % of persons and hypothyroidism was indicated in 5.6 % of cases in persons involved in liquidation of accident aftermath in 1988-1990. The percentage of persons staying in the 30-km zone in May, 1986 with revealed iodine incorporation in TG was estimated to be 55.7 % . TG irradiation was accompanied with acute, then chronic inflammatory reaction. It is known that radiation mutagenesis, carcinogenesis and ageing are the main long-term consequences caused by exposure to the ionizing radiation, they can trigger autoimmune processes in exposed persons with simultaneous genetic determination. The high frequency of mutations in hypervariable mini-satellite gene loci is revealed in LAA at ChNPP.

The ionizing radiation even in low prolonged doses leads to the delayed reproduction death (long-term lethal mutations), chromosome destabilization, somatic mutations and gene amplification, changed radiosensitivity of modified cells. The investigation of TG function in LAA at ChNPP in long-term periods after the accident (1993-2015) revealed the high rate of thyroid dysfunction and diseases. “Low T3” syndrome was the leading disorder. Monitoring of the hormone balance by the level of total T3 allowed considering the a general trend to its normalization associated with changed peripheral conversion of T4 to T3 from 2000–2015. At the same time, deviations in ratios of all three hypophysis-thyroid system hormones (TSH, T3, T4) from the reference values were revealed in 20 % of persons of the total number in LAA even after decades after the accident. Besides that, a significant percentage of LAA at ChNPP has dissociation of hypophyseal tropic functions, lowered activity of the functional associations in the system “hypothalamus- hypophysis- thyroid-adrenal glands- gonads.” Changes in the hormone status are accompanied by the disturbance of other metabolic processes.

As our studies indicated, the pattern of changes in the lipid metabolism parameters remained constant over the 10-year period of follow-up of LAA and did not depend on the age. We did not confirm any differences in dyslipidemia degree between patients with mainly cardiovascular or cerebrovascular diseases over the above period and dyslipidemia was permanently found in 70 % of LAA. A typical feature of lipid metabolism disturbances consists in considerable changes in

lipoprotein apoprotein composition, increased apoprotein B level with lowered ratio apoA/apoB. At present the latter is considered as an independent and serious risk marker of vascular atherosclerosis.

The comparative analysis of thrombocytic activity parameters in patients with cardiovascular diseases considering the risk degree of cardiovascular complications (CVC) indicated that liquidators with moderate and high vascular risk had high thrombocytic activity. The latter was manifested in significantly increased number of thrombocytes expressing P-selectin and enlarged thrombocyte aggregates.

The analysis of the effect exerted by risk factors of cardiovascular diseases on the parameters of thrombocyte functional activity indicated that the high functional activity was typical for the liquidators with arterial hypertension and aged above 55 years.

At the same time, we confirmed signs of endothelium dysfunction manifested in significantly increased concentration of t-PA (plasminogen activator), fibrinogen and fibrinopeptide A (FPA) in the blood plasma in liquidators with high and moderate degree of cardiovascular complications.

Hence, in addition to the disturbed lipid metabolism, liquidators with the vascular pathology develop a whole complex of biochemical shifts which are evident of the role of endothelium damage as an important pathogenetic factor of atherosclerosis.

This pathogenetic mechanism is supported by the activated lipid free radical oxidation and some cytokines, homocysteine metabolism disturbances which are indicated in liquidators with the vascular pathology. These factors can interact directly with endothelium cells damaging it and changing the vascular tonus. The inflammation phenomenon revealed by increased C-reactive protein levels and growth of pro-inflammatory cytokine concentrations in liquidators favors damage of the vascular endothelium. Endothelin -1 (ET-1), the level of which is increased in LAA, is a significant marker of endothelium dysfunction. One should take into account that ET-1 gene expression is stimulated by increased low density lipoprotein content.

Hence, dyslipidemia and disturbed lipoprotein apoprotein metabolism, disturbed thrombocytic activity and inflammation phenomenon, typical for the LAA, induce atherogenesis influencing the vascular endothelium and are a pathogenetic mechanism of atherosclerosis and cardiovascular diseases in LAA at ChNPP.

Summarizing the obtained results, we may conclude that the atherosclerotic involvement of the vessels is one of considerable causes for dyscirculatory encephalopathy, arterial hypertension and CHD in liquidators but it is observed not more often that in the population.

The basic risk factors for atherosclerosis in liquidators include the age, hyperglycemia, dyslipidemia, increased C-reactive protein level and free radical oxidation activation. The absence of the significant correlation between cholesterol level and atherosclerosis degree suggests that independent role of isolated hypercholesterolemia is, evidently, insignificant for the development of atherosclerosis in liquidators and this process requires additional risk factors, which include, first of all, FRO activation, nonspecific inflammation and hyperglycemia.

The prevalence of metabolic syndrome is high in LAA at ChNPP 30 years after the accident. This only partially may be associated with elderly age of patients (on average 66 years). Most persons had typical risk factors of metabolic syndrome which included hypodynamia, incorrect nutrition and smoking.

LAA at ChNPP had disturbed carbohydrate and lipid metabolism in a long-term period after the accident in 81.1 % of cases. Out of this number diabetes mellitus type 2 was revealed in 43.3 % of liquidators, disturbed glucose tolerance was found in 36.7 %, and disturbed glycemia after fasting was observed in 20 % of LAA. At the same time 96 % of patients had HOMA index of more than 1.0.

Hyperleptinemia was found in 75 % of cases in liquidators with CCVD and metabolic syndrome confirming the leptin resistance in this person category.

The observed trend og the increased rate of oncologic pathology in LAA required serching for and developing the oncoprevention methods due to the well-knownrole of H. pylori as a carcinogen of the first order. Besides that, we revealed the increased frequency of micronucleus formation in the stomach mucous coat in LAA at ChNPP. These processes developed simultaneously with increased frequency of atrophic changes in the mucous coat of the stomach and duodenum. These phenomena increase the risk of oncologic pathology.

Lately an extensive information base has been accumulated, which confirms the interrelationship between stomach cancer and polymorphism of cytokines IL-1, IL-10 and TNF. The external factors exert a negative effect in carcinogenesis; they include consumption of salty food, nitrose compounds in food, tobacco smoking, ascorbic acid deficit, insufficient consumption of fresh vegetables and fruits, alcohol, etc.

The development of oncoprevention methods and H. pylori eradication by administering the triple or quadrotherapy allow reducing both the oncologic risk and the frequency of micronucleus formation in the gastric mucous coat in LAA at ChNPP and residents of RCT.

This fact does not solve completely the problem of oncoprevention in LAA at ChNPP due to the confirmation of the increased lead and cadmium content, which are toxic and carcinogenic factors, in the liquidators' organism.

The increased cadmium and lead concentration in the hair of 30 % of LAA at ChNPP did not depend on the region of residence, LAA age but these changes were frequently observed in LAA involved in the works at ChNPP in 1986. Our investigation of the intestinal microbiota by the method of chromato-mass-spectrometry of microbial markers in the blood and feces and the investigation of the feces using the classical microbiologic method indicate the pronounced intestinal dysbiosis in investigated liquidators of accident aftermath at ChNPP. Currently the interrelationship between macro- and microelementoses and the intestinal microbiota in LAA at ChNPP is proven.

Hence, oncoprevention, prophylactic medical examinations and follow-up and provision of the targeted specialized medical aid including high-technology medical aid to LAA at ChNPP are the most important factors in the work of the medical community.

Persons exposed to the radiation moved to the age period, when involution metabolic changes began, over the time elapsed after the Chernobyl catastrophe. Natural ageing is accompanied by the loss of the bone mineral, change in bone tissue density and predominant disintegration of the bone trabecular architecture.

Age-dependent factors explain the development of senile osteoporosis in males. The age had an insignificant effect of the intact parathyroid hormone concentration the median of which

increased in elderly LAA at ChNPP. Most factors associated the calcium metabolism (DHEA-sulfate, calcitriol, 25-hydroxyvitamin D), modified hormone and metabolic parameters of calcium metabolism (ratios of estradiol and total testosterone in the blood serum, free and bioavailable testosterone, growth hormone and calcitonin) changed in the process of physiologic ageing in LAA at ChNPP and resulted in the development of osteoporosis and osteopenic syndrome.

Increased level of the antiphospholipid antibodies was revealed in 65.1 % of liquidators of accident aftermath at ChNPP. 20–25 years after the event they still play the leading role in pathogenesis of antiphospholipid syndrome and microcirculation disorders.

The wide range of antigens, which induce production of APA (antiphospholipid antibodies) suggests diverse supposed pathophysiologic mechanisms and causes heterogeneous clinical symptoms of syndrome associated with activation of endothelial cells, expression of adhesion molecules, intensification of cytokine secretion and prostacyclin metabolism. Another mechanism consists in oxidative damage of the vascular endothelium. Oxidized low density lipoproteins (LDL) are captured by macrophages what results in their activation, cytokine production and subsequent damage of endothelial cells.

The long immune inflammation in liquidators described above and characterized by pro-inflammatory cytokine hyperproduction, activation of the cells involved in the immune response resulted in autotolerance failure. LAA at ChNPP had the increased number of autoreactive T- and B-lymphocyte clones in the blood, lowered number of regulatory T-cells and pro-inflammatory cytokine production.

The increased number of “double-positive” T-cells in the blood and autoreactive B-lymphocyte clones is considered to be a precondition for autoaggression. The investigation of lymphocyte subpopulation composition in the peripheral blood allowed revealing the preconditions for autoimmune pathology (increased number of autoreactive both T- and B-lymphocyte clones, lowered number of T-regulatory cells) in approximately 30 % of liquidators.

The study on liquidators in a long-term period after the accident (30 years after the event) revealed intensified spontaneous production and increased blood serum content of pro-inflammatory cytokines. During the first years after the accident at ChNPP pro-inflammatory cytokine hyperproduction by peripheral blood mononuclear cells in LAA was a compensatory reaction of the macroorganism to exposure to a complex of radiation accident factors and was aimed at homeostasis maintenance (the results of numerous studies prove radioprotective effects of IL-1β, TNF-α, IL-6, IFN-γ and other pro-inflammatory cytokines).

The subsequent follow-up of LAA health condition indicated that persisting immune inflammation favored the development of cardiovascular diseases in this category. The changes revealed in the immune system may be considered as the instable equilibrium of factors maintaining the autoimmune process (high spontaneous interferon-γγ production level, high TNF-α content in the serum) and factors aimed at recovery of immunologic tolerance (high spontaneous IL-6, IL-1ra production level, low induced IL-2 production).

The memory about the previous exposure to the radiation is preserved in the form of stable chromosome aberrations (translocations), i. e. cytogenetic disturbances not resulting in the cell death and not preventing its division. If such disturbances occur in precursor cells (in the

hemopoietic tissue) lymphocytes carrying stabile chromosome aberrations enter the blood flow regularly.

Twenty-three percent of investigated LAA at ChNPP had aberrations of stable type (translocations) what allowed to perform biologic retrospective cytogenetic dosimetry and estimate the dose at the level from 14 to 34 cGy for these patients (mean dose was 24.25 cGy).

The investigation of LAA at ChNPP at our Center indicated that the frequency of chromatid exchanges did not change depending on the period elapsed after the participation in liquidation of accident aftermath but the total number of chromosome aberrations, paired fragments, chromatid fragments and radiation markers were influenced by the time.Evaluation of the changes in frequency of chromatid radiation markers over the period of 29 years after the accident at ChNPP indicated their growth from 27 to 48.8 %. At the same time, the increased radiation marker level (dicentric and circular chromosomes) in LAA at ChNPP was stable and it was revealed even many years after the irradiation.

The genetic heterogeneity of the human population and genotoxic effects exerted on humans during their life may influence the nature and course of the somatic and oncologic pathology.

The genetic status of LAA has been assessed at our Center for many years. We revealed certain dependencies between liquidators' diseases and polymorphous gene variants. The association of ACE (I/D) gene with dyscirculatory encephalopathy, which is often observed in liquidators, was estimated for the first time. The dependence of metabolic syndrome severity in LAA on the number of predisposing genotypes and alleles was revealed. It was estimated that more pronounced signs of metabolic syndrome in LAA at ChNPP were observed in carriers of 4 and 5 unfavorable candidate genes of cardiovascular diseases (ACE, MTHFR, PPARG2, LPL, AT2R1, ApoE-y) and in those who were homozygous by two unfavorable alleles (DD-genotype of ACE gene and TT-genotype of C677T polymorphous marker of MTHFR gene). Significant hemostasis disturbances in LAA at ChNPP were revealed in persons with gene polymorphism of the system F5, F2, MTHFR (C667T and A1298C), FGB; GP IIIa, PAI-I and homocysteine level correlated with mutation frequency in genes controlling the folate metabolism: MTHFR (methylenetetrahydrofolate reductase, polymorphism of C677T and A1298C, MTR (vitamin $B_{12}$-dependent methionine-synthase), polymorphism of A2756G, MTRR (methionine-synthase reductase), polymorphism of A66G.

The assessment of the psychologic status in liquidators of the accident at ChNPP evidences of their stable condition of general deadaptation and emotional stress developing within the limits of asthenoneurotic state with pronounced hypochondria and the trend to increased excitability.

Over the last years, the research collective of ARCERM has accumulated rich experience and scientific data on the mechanisms of development of the somatic pathology in LAA.

Such mechanisms may include:

- dissociation of hypophyseal tropic functions and changes in the hypothalamus—hypophysis—thyroid gland, hypothalamus—hypophysis—adrenal gland, hypothalamus—hypophysis —gonads systems in the form of modified interrelations between the central and peripheral regulation components of the endocrine function;

- activated lipid free radical and peroxide oxidation, disturbed protein metabolism, changed parameters of plasma hemostasis and blood anticoagulation system;

- disturbed immune (instable equilibrium of factors maintaining the autoimmune process and factors aimed at recovery of the immunologic tolerance) and cytokine systems, activated apoptosis processes;

- dependence of the test metabolic parameters on the anxiety, depression level, disturbed thinking and cognitive functions, visual memory impairment, lowered cerebral functions;

- increased frequency of gene mutations caused by the genotoxic effect of the accident factors at ChNPP and genetic heterogeneity of LAA at ChNPP favor the persistence of revealed metabolic and functional disorders.

It should be mentioned that a single conception of pathophysiologic mechanisms of the effect exerted by the complex of accident factors at ChNPP on the human organism does not exist until now. At present the scientific community assess more and more critically the existing paradigms (from Greek παράδειγμα—example, model, standard) in radiobiology which could explain the mechanisms of somatic pathology in LAA at ChNPP.

The theory of "punctual heat" or "punctual warming-up" (Desauer, F., 1922), stochastic (probabilistic) hypothesis of the direct effect caused by the ionizing radiation (Hug, O. and Kellerer, A., 1966), theory of "lipid radiotoxins" (Tarusov, B. I. and Kudryashov, Yu. B.), structural and metabolic theory (Kuzin, A. M., 1976) are accepted in radiobiology in the historical and scientific aspect.

At present the paradigm changed from the target theory to "bystander" effect and radiation-induces genome instability (RIGI). The "bystander" effect means affection of the cells located outside the zone of radiation exposure but contacting with the irradiated cells. The "bystander" effect may be associated, at least, with two mechanisms: gap junctions including Tp53-mediated path for conduction of the damage signal and secretion of biologically active factors to the culture medium (similarly to action of cytokines). The recent experimental studies allowed formulating the theory of radiation-induced genome instability (RIGI) as an example of non-target effect of the ionizing radiation. The RIGI essence consists in increased probability of unpredictable defects (revealed, mainly, as unclonable genome damages) in the progeny of irradiated cells. Such genome damages may occur also spontaneously, the radiation only increases their frequency. The main feature of RIGI consists in the fact that the progeny cells have no damage which can be revealed in the irradiated progenitors. By definition, radiation-induced genome instability results in increased mutation frequency and, finally, may lead to the accumulation of carcinogenic mutations resulting in an increased risk of malignization and oncogenic transformation. Contradictions between radiobiological paradigms and problems of clinical medicine in the investigation of LAA and residents of RCT consist in the phenomenon of radiation hormesis, radioadaptive response. Overestimation of radiobiological patterns in the epidemiological and medical interpretation results in even more deplorable consequences that underestimation. It is very difficult to interpret the results of in vitro experiments using cell cultures for the possible situation in vivo.

Several recent fundamental studies explain the changes in the health of persons exposed to the extreme factors (including the accident factors at ChNPP) with chronic adaptive (adaptation) overstrain syndrome (CAOS). The most typical symptoms of this syndrome include: various complaints of worsened general well-being, pronounced psychoemotional strain, lowered mental

and physical working capacity, reduced functional efficiency of energy-supplying processes, dysfunction of the immune system and nonspecific protective factors, depressed organism general resistance, increased total morbidity. Our investigation of LAA allows establishing CAOS in them. This agrees well with the published scientific data describing certain mechanisms of development of the somatic pathology in LAA at ChNPP and the population of radioactively-contaminated territories.

Fundamental endocrine and metabolic reorganizations in the organism form the pathogenetic base for CAOS. We revealed these changes both at the organ and organism levels. At present it is proven that certain changes in the function of the endocrine and immune systems correspond to changes in the psychoemotional status. Disintegrated action of the hormones in the system hypothalamus—hypophysis—adrenal glands and hypothalamus—hypophysis- gonads is a significant fact revealed by our investigation. In this situation, changed ratios of sexual hormone levels favors intensified catabolic processes. This results in the higher role of lipids in the energy generation process as compared to carbohydrates and, as a consequence, in activation of LPO processes with simultaneous overstrain and exhaustion of the antioxidant system. In this case the changed hormone regulation favors the persisting role of lipids in energy generation. Any increased energy consumption, which is ensured due to aerobic oxidation as per classical scheme, is accompanied absolutely synchronously by increased generation of free radical oxidation products.

This is manifested especially clearly in stress conditions when the more extreme the effect of a harmful factor is, the more intense activation of peroxide oxidation is and the more probable and more pronounced membrane damage of intensively dividing cells (first of all, the cells of the immune system and digestive organs epithelium) and adaptation process failure are. The activity of the antioxidant system including the enzymatic and non-enzymatic components is aimed at neutralization of peroxide oxidation products in the organism.

As it was mentioned above, accumulation of lipid peroxide oxidation products in the organism plays a significant role in cell membrane damage including immunocompetent cells and thereby results in immune deficit conditions.

The increased lipid peroxide oxidation product concentration in the organism with simultaneous disintegration in functions of the endocrine and immune systems, strained mechanisms of energy production and differentiation underlie pathogenesis of diseases in LAA. That confirms as well that the above pathogenetic mechanisms are supported by the increased toxic microelement level revealed in the organism of LAA.

Today we may state that the technogenic catastrophe at ChNPP caused a great complex of problems concerning radiation protection, health preservation of those who suffered because of the radioactive contamination of territories, development of the safe residence conception, radiobiology of the environment, etc.

The 30-year stage of overcoming the consequences is ending, and the problem of health preservation of LAA at ChNPP becomes even more urgent. In our opinion, the priorities in further policy for overcoming the accident aftermath at ChNPP should be highlighted from this viewpoint:

improvement of ecology, development of measures for early revealing of diseases caused by the exposure of an individual to a complex of accident factors at ChNPP.

While summarizing the results of the work aimed at overcoming the medical consequences of the accident at ChNPP we should make some conclusions:

1. The radioactive contamination of the territory after the technogenic catastrophe at ChNPP, exposure of victims and influence on the health caused by non-specific factors of the accident at ChNPP are, undoubtedly, hazardous for humans and biota. The complex of accident factors is the main cause resulting in health problems in LAA at ChNPP and among its components radiation factor is not the leading one.

2. The formation of chronic adaptation overstrain syndrome, which may be referred to the mechanism of "nonspecific" effect caused by technogenic radiation accident, is one of the basic mechanisms for development of the somatic pathology in LAA.

3. The state policy for overcoming the accident aftermath at ChNPP should be aimed at minimization its medical consequences, providing the targeted specialized medical aid to LAA at ChNPP and population living on the radioactively contaminated territories.

The features of the development of the somatic pathology and its pathogenetic mechanisms determined in LAA are used in the medical and diagnostic work of our Center when providing them with specialized medical aid in outpatient settings and at the hospital.

The advanced medical equipment, highly qualified staff (1,889 established posts, 54 posts out of them are doctors of science and more than 200 posts are candidates of science) allow the Federal State Budget-funded Institution All-Russian Nikiforov Center of Emergency and Radiation Medicine of the Ministry of Emergencies of Russia to provide specialized and high-technology medical aid in a wide range of pathology including LAA at ChNPP and citizens living on radioactively contaminated territories.

Out multi-field medical center including the Clinic No. 1 (specialized therapeutic clinic), clinic No. 2 (for providing high-technology medical aid), Outpatient Clinic for 460 visits per shift functions actively in fulfilling the "Program of Joint Activities for Overcoming the Aftermath of the Chernobyl Catastrophe within the Limits of the Union State."

Which new work do we carry out within the limits of the Program of Joint Activities? This work includes, first of all, outpatient screening. This involves diagnostic programs: screening for gastrointestinal cancer pathology, thyroid cancer, urologic cancer pathology, cerebrovascular disorders, genetic disorders, assessment of dysbiosis and dyselementosis, screening for vascular disorders in the lower extremities and carbohydrate metabolism disturbances.

These screening programmes allow diagnosing early diseases, first of all, oncologic pathology for formation of the "risk group," further monitoring and inpatient investigation and treatment. More than 1,000 lAA at ChNPP and citizens living (having lived) on radioactively contaminated territories undergo such screening investigations annually on the base of out Center.

The second characteristic feature in the activities of ARCERM within the limits of the new program Russia-Belarus consists in directing the attention towards providing the specialized medical aid to patients with somatic pathology as well as the high-technology types of medical aid to surgical

patients and medical rehabilitation using the medical and diagnostic resources of the new multi-field clinic No. 2 (for providing high-technology medical aid) of ARCERM.

Providing specialized and high-technology medical aid not only to LAA at ChNPP but also to the citizens having lived (living) on radioactively contaminated territories has been the third characteristic feature in the activities of ARCERM since 2014. **Nikiforov Russian Center for Emergency and Radiation Medicine EMERCOM of Russia (NRCERM EMERCOM of Russia)** is a modern medical, scientific and educational institution with over 25 years of experience. The Center is rapidly developing new fields of medical, research and education activities. Clinics of the Center are equipped with high-tech diagnostic and treatment facilities for providing emergency and scheduled medical assistance, high-specialized examinations and treatment, preventive measures and rehabilitation under conditions of outpatient polyclinic, day and 24/7 inpatient hospital. Our staff includes highly qualified specialists with the first and second doctoral degrees (PhDs) who underwent training in the leading world medical centers. We care for our patients and partners 24 hours a day so that they could feel comfortable and confident.

**NRCERM is:** World Health Organization Collaborating Center (WHOCC) for Treatment & Rehabilitation of Nuclear &Other Disasters Recovery Workers; Leading medical institution EMERCOM of Russia; Multidiscipline medical diagnostic center with a full complex of the newest facilities and high-tech medical technologies; Specialized and high-tech medical assistance; Highly qualified personnel; Member of the international Radiation Emergency Medical Preparedness and Assistance Network (REMPAN); More than 5,000 different medical services; Scientific and educational center.

Hence, our many-year experience in monitoring of the health condition of LAA at ChNPP allows forming new knowledge of possible pathogenetic mechanisms of development of the somatic pathology in this cohort. This data is used in the practical work when developing new technologies, regulatory and methodical documents and diagnostics, treatment and rehabilitation standards for LAA at ChNPP and, first of all, when conducting the screening investigations, providing the targeted specialized medical aid, including high- technology medical aid.

## ABOUT THE CENTER

**Nikiforov Russian Center for Emergency and Radiation Medicine EMERCOM of Russia (NRCERM EMERCOM of Russia)** is a modern medical, scientific and educational institution with over 25 years of experience. The Center is developing rapidly new fields of medical, research and education activities. Clinics of the Center are equipped with high-tech diagnostic and treatment facilities for providing emergency and scheduled medical assistance, high-specialized examinations and treatment, preventive measures and rehabilitation under conditions of outpatient polyclinic, day and 24/7 inpatient hospital. Our staff includes highly qualified specialists with the first and second doctoral degrees (PhDs) who underwent training in the leading world medical centers. We care for our patients and partners 24 hours a day so that they could feel comfortable and confident.

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qualified personnel; Member of the international Radiation Emergency Medical Preparedness and Assistance Network (REMPAN); More than 5,000 different medical services; Scientific and educational center.

## OUR HISTORY

**The history of the Center started September 12th, 1991 when Russian Center of Ecology Medicine (RCEM) was founded at the Military Medical Academy (under the resolution of the State Committee on the USSR National Economy Management in Saint-Petersburg). Since 1993 RCERM was the head organization providing medical assistance to Chernobyl accident recovery workers.**

Emergency medical assistance, ambulance (including air ambulance); Specialized inpatient medical assistance; Outpatient polyclinic assistance; Intensive care; Urgent and elective surgery; 24/7 multipurpose laboratory; Telemedicine; Rehabilitation; Dental service; Psychological assistance; Consultative diagnostic assistance.

March 14th, 1997 RCEM was reformed into the Federal State Institute of Public Health "Russian Center of Emergency and Radiation Medicine" The Ministry of Russian Federation for Civil Defence, Emergencies and Elimination of Consequences of Natural Disasters (RCERM EMERCOM of Russia) which became medico-diagnostic, research and education institution. In 1999 Emergency Psychological Assistance Center was created at RCERM; since 2003 it is an independent institution of EMERCOM of Russia. August 2006 RCERM EMERCOM of Russia received the name of its founder and first director professor Aleksei Mikhailovich Nikiforov (1991-2006), MD, Corresponding Member of the Russian Academy of Medical Science (under the order of the Russian Federation Government) – Nikiforov Russian Center of Emergency and Radiation Medicine EMERCOM of Russia (NRCERM EMERCOM of Russia). May 2008 the construction of new multidiscipline Clinic No 2 of high-tech medical assistance (surgery) with a rehabilitation complex started in Saint-Petersburg. November 2011 Clinic No 2 opened its doors for the first patients.

## OUR CAPACITY

Emergency medical assistance, ambulance (including air ambulance); Specialized inpatient medical assistance; Outpatient polyclinic assistance; Intensive care; Urgent and elective surgery; 24/7 multipurpose laboratory; Telemedicine; Rehabilitation; Dental service; Psychological assistance; Consultative diagnostic assistance.

## MAIN OBJECTIVES

Multidiscipline specialized medical and psychological care to people with different diseases, including victims of radiation accidents, technogenic catastrophes and natural disasters;

Basic and applied research in the fields of radiation medicine, radiobiology, industrial pathology; implementation of high-tech medical technologies;

Education activities in the sphere of post-graduate and advanced professional education (post-graduate training, residency, advanced training, professional retraining).

## OPERATIONAL PRINCIPLES

***Aid and mercy; Professionalism and quality; Introduction of world leading hospitals experience; Patient-oriented care and attention.***

Center is staffed with highly qualified specialists, many of which underwent advanced trainings in the world leading medical institutions (in Austria, the United Kingdom, Germany, the Netherlands, Israel, Spain, Italy, Korea, China, the USA, Finland, Sweden, Switzerland). There are over 50 specialists with the first doctoral degree (PhD), over 45 of them are professors; and over 150 specialists with the second doctoral degree (so called Candidate of Science). Over a half of doctors and nursing staff have the highest qualification categories. Many specialists are rewarded with the following titles of honor: "Honored Doctor of the Russian Federation", "Honored Worker of the Health Care System of the Russian Federation", "Honored Scientist of the Russian Federation".

## CLINIC № 1

***Multidiscipline 24/7 inpatient hospital for 120 beds.***

***It includes:*** Clinical Department of Gastroenterology and Hepatology (Gastroenterology Unit, Clinical Hepatology Unit, Dietology Unit and Ultrasound Diagnostics Room); Clinical Department of Pulmonology and Allergology (Pulmonology Unit, Allergology Unit and External Respiratory Functions Research Room); Clinical Department of Therapy and Industrial Pathology (Therapy Unit and Industrial Pathology Unit); Clinical Department of Cardiology; Intensive Care Department. Comfortable wards are equipped with all the necessary (nurse call button, WC and shower, telephone, radio, TV, refrigerator, ventilation system).

***Gastroenterology and Hepatology:*** Specialists of the Department diagnose and provide high quality treatment for people with diseases of pancreatic gland, gall bladder and bile passages; with non-specific ulcerative colitis, hepatopathy and intestinal tract disorders. They also develop individual programmes for correction of different nutrition problems.

***Pulmonology and Allergology:*** Modern equipment and advanced technologies allow our specialists to diagnose and successfully treat different infectious inflammatory diseases of the respiratory system (bronchitis, pneumonia etc.) and allergic diseases (bronchial allergy, chronic obstruction lungs disease, urticaria fever, atopic dermatitis etc.).

***Therapy and Industrial Pathology:*** Patients can be diagnosed and treated by qualified specialists of the Department of Therapy and Industrial Pathology.

***Cardiology:*** Specialists of Cardiology Department carry out complex diagnostics and treat patients with coronary artery disease, arterial hypertension including endocrine system diseases, essential arterial hypertension and heart rhythm disorder.

## CLINIC № 2

***Multifield 24/7 inpatient hospital for 450 beds***

***It includes:*** Unit of Emergency Surgery; Unit of Anesthesiology, Resuscitation and Intensive Care (38 beds); Operational Block (14 ORs); Unit of Dialysis and Gravitational Blood Surgery

Techniques; Unit of Hyperbaric Oxygen Therapy; Unit of Functional Diagnostics; Unit of Ultrasound Diagnostics; Department of Laboratory Diagnostics; Department of Radiodiagnostics; Department of Endoscopy; Department of Traumatology and Orthopedics; Department of Cardiovascular Pathology; Unit of Neurosurgery; Burns Unit (with Plastic Surgery); Unit of Urology; Unit of Gynecology; Unit of Ophthalmology; Unit of ENT and Maxilla-Facial Surgery; Unit of Thoracoabdominal Surgery; Department of Therapy and Integrative Medicine; Department of Clinical Neurology; Department of Rehabilitation; Department of Radiation Medicine, Hematology and Toxicology.

***Also, there are:*** Outpatient polyclinic (460 visits per shift); Department of Transfusiology (harvesting donor blood and its components); Ambulance Station (Unit of Emergency Medical Assistance with air medical service); Anatomical Pathology Department.

***Polyclinic:*** Delivers specialized highly qualified medical assistance in the following fields: Allergology and Immunology; Gastroenterology; Infectious Diseases; Cardiology; Neurology; Psychiatry; Rheumatology; Endocrinology; Oncology; Breast Care; Phlebology; Endoscopy; Stomatology; Orthodontia, etc. High-tech equipment from the world leading manufacturers is used for diagnostics and treatment. Continuity is observed on different stages of specialized medical assistance.

***Central Operation Unit:*** Delivers selective specialized as well as emergency surgical assistance to patients in life-threatening conditions using endovideosurgical and endoscopic methods.

**ADVANTAGES**

High level of preparedness for providing emergency surgical assistance; Professionalism of our specialists who have experience of working in emergencies; Multidisciplinary approach; Responsibility for life and health of each patient.

***Surgery departments:*** Unit of Emergency Surgery; Central Operation Unit; Unit of Neurosurgery; Unit of Cardiosurgery; Burns Unit; Unit of Traumatology; Unit of Orthopedics; Unit of ENT and Maxilla-Facial Surgery; Unit of Thoracoabdominal Surgery; Unit of Ophthalmology; Unit of Urology; Unit of Gynecology; Department of Endoscopy Research; Unit of X-ray Surgery Methods of Diagnostics and Treatment.

***Emergency specialized medical assistance***
***provided 24/7 by the highly qualified personnel.***

**POTENTIAL**

Accompanying of patients with injuries of varying severity during transportation by air, sea, train, car; Evacuation and accompanying of patients on the territory of Russia, neighboring and far foreign countries; Visits to any district of Saint-Petersburg and Leningrad Region; Medical accompanying of mass events; 24/7 hospitalization to the clinics of the Center and other inpatient hospitals of the city; Resuscitation, monitoring, infusion therapy at home and during transportation; Installation of temporary cardio stimulator, counterpulsation at home and during transportation; Thrombolytic therapy using the newest equipment.

## DEPARTMENTS OF CLINIC № 2

***Department of Anesthesiology, Resuscitation and Intensive Care is:***

Modern global technologies; Highly qualified specialists; 24/7 availability of all services.

***Emergency specialized medical assistance provided 24/7 by the highly qualified personnel.***

**POTENTIAL**

Accompanying of patients with injuries of varying severity during transportation by air, sea, train, car; Evacuation and accompanying of patients on the territory of Russia, neighboring and far foreign countries; Visits to any district of Saint-Petersburg and Leningrad Region; Medical accompanying of mass events; 24/7 hospitalization to the clinics of the Center and other inpatient hospitals of the city; Resuscitation, monitoring, infusion therapy at home and during transportation; Installation of temporary cardio stimulator, counterpulsation at home and during transportation; Thrombolytic therapy using the newest equipment Wards equipped with the most modern facilities allow highly qualified anesthesiologists and resuscitation specialists carrying out intensive care for emergency states such as myocardial infraction, arrhythmia, acute heart and respiratory failures, cerebral hemorrhage, disorders of stomach, pancreatic gland, gall bladder, intestinal tract disorders, coma, etc.

***Three specialized units (Unit of Cardio-Resuscitation, Unit of Neuro-Resuscitation, and Unit of General Surgery Resuscitation) are able to receive up to 38 patients at one time.***

### *Department of Clinical Neurology*

**POTENTIAL**

Emergency 24/7 neurology assistance to patients with brain circulation disorders; Diagnostics and treatment of patients with diseases of central and peripheral nervous systems; Complex diagnostics of all kinds of sleep disorders, vascular diseases of central nervous system; Brain functional state assessment. Complex approach is applied using medication, physiotherapeutic, psychotherapeutic treatment methods, acupuncture, biological feedback methods, remedial blockade, and manual therapy. The treatment is carried out in the Unit of Neurology with capacity for 25 beds. Comfortable rooms are equipped with monitors, special facilities for the disabled people, monitoring video cameras. Specialists of the Department work also in the outpatient polyclinic providing continuity of outpatient and inpatient stages of treatment.

### *Traumatology and Orthopedic Department*

**POTENTIAL**

Specialized emergency medical assistance for trauma patients and victims of traffic accidents, emergencies and catastrophes; Treatment of patients with acquired and congenital diseases, deformations of musculoskeletal system; High-tech care (including replacement arthroplasty) for patients with traumas.

### *Burns Unit (with Plastic Surgery)*

### ADVANTAGES

Operative treatment of burnt patients at the earliest stages; Quick regeneration of skin using cell technologies; Complex approach to treatment of patients with the consequences of burns using reconstructive and plastic surgery; Early rehabilitation.

***Department of Urology:*** Complex diagnostics and treatment of genitourinary system using the following methods: Laparoscopy (operative treatment of the disease through small punctures without dissection of skin); Remote lithotripsy (non-surgical elimination of stones from kidneys and ureters).

***Department of Gynecology:*** Surgical treatment of female reproductive system cancer, endometriosis; reconstructive and regenerative operations using low-invasive technologies.

### *Department of Radiation Medicine, Hematology and Toxicology*

### MAIN OBJECTIVES

Providing high-tech and specialized medical care to victims of radiation accidents, natural disasters and technogenic catastrophes; Treatment of acute and chronic radiation disease as well as oncohematological diseases as a result of radiation and chemical effect on the human genome; Creation of the Register of HLA-typed donors of EMERCOM of Russia and stem cell bank for providing radiation safety for Russian population; Transplantation of hematopoietic stem cells for treatment of hemopoiesis depression, leukemias, lymphomas, hereditary and genetic disorders; Preparation of mesenchymal stem cells, keratinocytes and skin fibroblasts for the treatment of burn disease in patients with thermal injury; Using positron emission tomography for targeting high-dose chemotherapy and immunotherapy for cancer; Efferent and barotherapy for toxicological complications; Support therapy and cell therapy of medullar and multiple organ failure in victims of natural disasters and technogenic catastrophes.

***Laboratory of Toxicology and Medication Monitoring provides with:*** Chemical and toxicological studies for alcohol and its substitutes, narcotic and psychotropic drugs and other toxic substances; Therapeutic medication monitoring (medications bioequivalence and pharmacokinetics); Microbe markers mass-spectrometry; Studies of neurally mediated metabolism and adrenal bodies hormones; “Oxidative stress” monitoring and development risk; Analysis of amino acids and metabolism markers; complex analysis of water- and fat-soluble vitamins; Proteomic and metabolomic analysis.

### *Nuclear medicine*

### ADVANTAGES

The Center possesses the most modern radio-diagnostic equipment (PET/CT and SPECT/CT) that allows carrying out diagnostics according to the European standards; Diagnostics methods for cardiovascular, nervous systems and oncologic diseases allow early diagnostics of diseases. Radiopharmaceuticals are used that are analogues of the natural substances of a human body or inert organotropic agents marked by short-living and ultrashortliving radioactive isotopes that give low radiation load to patients; Highly qualified personnel engaged in producing radioisotopes and tracers (radiopharmaceuticals) on their basis.

***Positron emission computed tomography, cyclotron:*** Positron emission tomography (PET), a diagnostic procedure of visualization of space-temporal distribution of positron-emitting radiopharmaceutical in a patient's body under the annihilation radiation, is widely used in oncology (90%) as well as in neurology (5.5%) and cardiology (4.5%).

***Laboratory of Human Radiation Spectrometry:*** Unique dosimetry diagnostic unit, high sensitivity low-background spectrometer of human radiation (SHR), is designed to directly determine radioactive substances in human body – their presence, type, quantity and distribution in organs and tissues; it allows detecting the most radiologically important radionuclides that enter an organism with air, water, and food.

***Bio-elemental analysis:*** Individual pre-nosological diagnostics and correction of conditions associated with deficiency, plethora or disbalance of chemical elements in human body.

### *Department of Rehabilitation*

Rehabilitation in the Center is carried out in the Unit of Clinical Rehabilitation (capacity for 50 beds in Clinic No 2), Unit of Restorative Treatment (Clinic No 2), Unit of Physiotherapy and Exercise Therapy (Clinic No 1).

## MAIN OBJECTIVES

Early rehabilitation of patients with neuro-trauma, after cardiovascular operations, after arthroplasty of large movable joints, spinal cord trauma and joints, after burns; Complex bio-mechanical diagnostics of body motor functions; Robotized equipment for restoration of motor skills; Instrumental physiotherapy; Manual therapy and different kinds of massage; Acupuncture; Speech therapist assistance; Psychological and psycho-physiological rehabilitation; Programmes for body correction and fitness; Education seminars for patients and their relatives; Selection of orthopedic goods; Social worker assistance.

## POTENTIAL

Developing complex programmes of extended preventive medical examination for sportsmen; Developing individual rehabilitation programmes regarding type of sport; Rehabilitation after traumas; Assessment of rehabilitation treatment effectiveness.

## UNITS OF DIAGNOSTICS

***Radiodiagnostics:*** Gives opportunity to carry out full spectrum of diagnostic research such as X-ray examination (including digestive tract, urinary system), multispiral X-ray computer tomography, MRI on MR tomographs with magnetic field intensity of 1.5 and 3 tesla, mammography (including aspiration biopsy), fluorography, echocardiography, Doppler sonography, etc.

***Laboratory diagnostics:*** Gives opportunity to examine more than 200 metabolism parameters, special proteins, ferments, hormones, oncomarkers, coagulation parameters, specific allergens, infectious diseases markers. It also provides with a wide range of cytological, hematological, general clinical, bacteriological and chemical toxicological research. 45 parameters of immune system can be assessed in the Department.

***Genetic diagnostics:*** Gives opportunity to determine the radiation doses using cytogenetic methods, genetic diagnostics in the aspect of personalized medicine, diagnostics of oncological

diseases, qualitative and quantitative evaluation of a wide spectrum of bacterial and virus infections using PCR method.

***Innovation spheres of NRCERM medical technologies development:*** Developing of modern minimally invasive endovideoscopy and endovascular surgeries; Robot-assisted surgeries; Telemedicine; Cell technologies implementation into treatment; Nuclear medicine (diagnostics and treatment, based on using isotopes); Simulation and other e-technologies for education of medical personnel; Medical evacuation of victims using medical airplane/helicopter modules.

## RESEARCH AND EDUCATION

Conducting fundamental, exploration and applied research in the most perspective areas of medico-biological science and clinical practice; Developing perspective fields of scientific research, conducting scientific, research, design and experimental and technological works; Carrying out preclinical and clinical research of drugs, testing of medical devices, approbation and expertise of new medical technologies. Training of Russian and foreign specialists in post-graduate course, residency and courses of advanced education. The training is conducted by more than 30 professors and PhDs, 10 associate professors and candidates of science. NRCERM is a founder and publisher of reviewed research journals **"Medico-Biological and Socio-Psychological Problems of Safety in Emergency Situations"**, "Herald of Psychotherapy" included in the register of the State Commission for Academic Degrees and Titles under the Ministry of Education and Science of Russia. 2009-2013, over 180 doctors, nurses and specialists of the Center underwent advanced training in leading foreign medical and education institutions of Austria, Brazil, Germany, Holland, Israel, Spain, Italy, China, Korea, the USA, Finland, France, Switzerland, and Sweden. NRCERM has a license of the Federal Education and Science Supervision Agency for performing education in post-graduate studies, clinical residency, advance training courses and professional retraining. In NRCERM over 150 specialists undergo training annually. NRCERM includes the Institute of Extended Professional Training "Emergency Medicine" consisting of Scientific Department and three Schools: Life Safety, Emergency and Radiation Medicine; Surgery and innovation Technologies; Therapy and Integrative Medicine.

**CLINIC № 1** Multidiscipline 24/7 inpatient hospital for 120 beds. 4/2 Academic Lebedev St., Sant-Petersburg, Russia


**Polyclinic**. 54 Optikov St., Sant-Petersburg, Russia

Ambulance

Conference hall

**CLINIC № 2** Multifield 24/7 inpatient hospital for 450 beds (250 beds – surgery, 80 – therapy, 50– clinical rehabilitation). 54 Optikov St., Sant-Petersburg, Russia

Traumatology and ortopedics

Cardiovascular surgery

Meeting of the Scientific Council

Graduation of postgraduates and residents

There are 480 doctors, 600 nurses, 60 professors, and 180 medicine doctors working in the Center