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CHERNOBYL CATASTROPHE AND CHILDREN'S HEALTH. 35 YEARS OF WORLD TRAGEDY

Coordination and Analytical Centre
«Ecology and Health»

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The book is devoted to the long-term medical consequences of the Chernobyl disaster.

The results of scientific research projects of the European Union and France in 2013-2018 on the assessment of the health status of children living near the Chernobyl exclusion zone are presented.

This book was written for medical doctors of all specialties, ecologists, scientists, specialists in the field of radiation protection, and for anyone involved in the consequences of the accident at the Chernobyl nuclear power plant.

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Книга присвячена віддаленим медичним наслідкам Чорнобильської катастрофи. У ній представлені результати наукових досліджень, виконаних у ході реалізації у 2013–2018 роках соціально-медичних проектів Європейської Комісії та Франції у районах Київської області України, що прилягають до Чорнобильської зони відчуження.

У ході проектів щорічно, протягом 3-х років, за допомогою лабораторних та інструментальних методів, було обстежено понад 3000 дітей. При цьому, у них також визначалися вміст радіоактивних елементів ^{137}Cs в організмі, рівень гомоцистеїну в крові, стан генетичного апарату фолатного циклу.

Аналіз отриманих результатів показав зв'язок між питомою активністю ^{137}Cs в організмі, фізичним розвитком та порушенням функції серцево-судинної системи дітей. В організмі більш ніж 70 % дітей з Чорнобильських районів рівень гомоцистеїну в крові перевищував фізіологічні межі, що свідчить про серйозні порушення обміну речовин. Показано зв'язок гіпергомоцистеїнемії з генетичними порушеннями фолатного циклу та вітамінами B_6, B_9 та B_{12}. Однак, більшою мірою цей стан був викликаний впливом чинником зовнішнього середовища у вигляді радіоактивних елементів та продуктів їхнього розпаду. У зв'язку з цим важливими є відомості про негативний вплив пожеж лісу в Чорнобильській зоні відчуження на обмін метіоніну та гомоцистеїну, в організмі дітей, які проживають у прилеглих населених пунктах. Підвищений рівень гомоцистеїну в крові свідчить про розвиток патологічних процесів, що призводять до інвалідності та летальних наслідків.

У книзі представлені матеріали про вплив генів фолатного циклу на стан мінерального обміну, гіпофізарно-тиреоїдні взаємини. Ця інформація може бути корисною для виявлення причин порушення фізичного розвитку дітей,

які проживають в умовах екологічного лиха, пов'язаного з аварією на атомній електростанції.

Книга призначена для лікарів усіх спеціальностей, екологів, науковців, спеціалістів у галузі протирадіаційного захисту, всіх, хто пов'язаний із наслідками аварії на Чорнобильській атомній електростанції.

Ключові слова: аварія на Чорнобильській атомній електростанції, Чорнобильська зона відчуження, питома активність ^{137}Cs, гомоцистеїн, гени фолатного циклу, радіаційний фактор, фізичний розвиток, порушення серцевої діяльності, пожежі лісу.

CONTENTS

FOREWORD

The book that we present to the reader is the fruit of many years of research into the effect of the environmental factor associated with the Chernobyl nuclear power plant accident on health of children. For reasons completely beyond his control, one of the authors was unable to conduct large-scale research in the Republic of Belarus in the 21st century at the Gomel State Medical University he established. However, owing to international support, the research was carried out in Ukraine. We express our deep gratitude to all those responsible representatives of the European community who contributed to the organization and implementation of a project to help the child population living near the Chernobyl Exclusion Zone and suffering from radiation exposure in the 21st century.

We hope that the results of our work will be used in the provision of medical and preventive care to people living under conditions of constant radiation exposure.

Yuri I. Bandazhevsky, Professor
Natalia F. Dubovaya, Associate Professor

INTRODUCTION

The accident at the Chernobyl nuclear power plant (ChNPP) in 1986 is of planetary importance. And the deeper we dive into the study of its consequences, the more questions we have. Huge doses of the rapidly decaying ^{131}I had hit the thyroid gland of adults and children — residents of Belarus, Ukraine, the Russian Federation, as well as of European countries, and therefore, the first cases of thyroid cancer of Chernobyl origin were recorded 4 years after the accident.

The first decade after the accident was characterized by high levels of ^{137}Cs and ^{90}Sr in the upper soil layers of the affected territories, and, consequently, in food products produced within them. It should be especially noted that the population of the southern and southwestern districts of Belarus has been in contact with ^{137}Cs radionuclides since the 60s of the last century, which is evidenced convincingly by an authoritative publication in 1974 [1]. After the accident at the ChNPP in 1986, this fact was carefully hidden. (This book was discovered by chance by the students of Professor Yu. I. Bandazhevsky in a small library in Gomel in 1998).

The state policy of the USSR and post-Soviet countries was aimed at concealing truthful information about the effects of Chernobyl radiation on the human body. Representatives of the nuclear lobby have minimized the importance of radionuclides incorporated into the body in the occurrence of pathological processes. In this regard, systemic monitoring of ^{137}Cs levels in the body of adults and children has not been carried out. The effect of this radionuclide, as well as of ^{90}Sr and transuranic elements, including ^{241}Am, on humans and animals has not been studied at the proper level.

A programme of the impact of the Chernobyl radiation factor on the human body was implementedat Gomel State Medical Institute since the first days of its existence (November 1990). At the same time, a study was carried out with regard to an association of incorporated ^{137}Cs radionuclides with the state of the vital systems of the body [2]. For this, beginning from 1992, radionuclide levels were determined in the body of children living both in areas officially recognized as affected by the accident and in areas with the status of radiation clean territories. In this work, Gomel State Medical Institute cooperated closely with the Belarusian Engineering Academy and Gomel Starting Engine Plant who organized facilities and resources for radiation monitoring of the population. In parallel with this, during autopsies, ^{137}Cs levels were measured in the organs of deceased children and adults — residents of the Belarusian affected territories, as well as in experimental laboratory animals.

In the course of experimental studies, a natural model of entry of ^{137}Cs and ^{90}Sr radionuclides into the body of laboratory animals as part of food products of plant and animal origin was used [2].

The studies, in which the employees of Gomel and Grodno Medical Institutes participated, revealed the role of the radiation factor in the impairment of metabolic processes, including the metabolism of amino acids. It was possible to determine the relationship between ^{137}Cs specific activity in the body and impaired cardiac activity. It was concluded that the entry of radioactive elements into the body of humans and animals leads to a significant metabolic abnormalities associated with damage to energy-dependent mechanisms in the cells of vital organs, including cardiomyocytes. At the same time, in the development of thyroid diseases one should take into account not only the effect of ^{131}I, but also ^{137}Cs which this organ incorporates intensively.

This process is especially pronounced in children, as evidenced by the results of measurements of autopsy material [2, 3, 4, 5].

Three decades after the Chernobyl tragedy, the radiation situation in the affected territories has not improved. ^{137}Cs radionuclide levels in locally produced food have significantly decreased, however, ^{90}Sr levels in them have significantly increased. Forest trees on the territory affected by the ChNPP accident have accumulated a huge amount of long-lived radionuclides over more than 30 years. These mini nuclear reactors are used by the population for domestic needs: heating houses and cooking. At the same time, people constantly breathe air containing radionuclides. The ash of burnt wood which concentrates huge amounts of ^{90}Sr, ^{137}Cs and other radioactive elements is used as fertilizer for the soils of vegetable gardens where vegetables and fruits are grown. Permanent forest fires in the Chernobyl Exclusion Zone (ChEZ) are also sources of radiation exposure to the population from adjacent areas. In addition to ^{137}Cs and ^{90}Sr, ^{241}Am which is hazardous to human health is widespread in the environment. 30 years after the Chernobyl accident, the amount of this transuranic element has increased due to the decay of ^{241}Pu.

The Chernobyl radiation expansion has led to an increase in morbidity and mortality of the population of the affected areas of Belarus and Ukraine from cardiovascular and cancer diseases. The number of children with congenital malformations and congenital metabolic diseases has increased [6].

Considering the continuity of the formation of a human body during the period of antenatal and postnatal ontogenesis, it is important to determine abnormalities that significantly affect the development of a child and continue in the adult state in the form of serious diseases. The most important is the study of the regulatory processes that ensure the vital activity of the body.

This will make it possible to develop effective medical and hygienic recommendations for prevention for the population suffering from the remote consequences of the Chernobyl disaster.

For more than 30 years, the authors have been studying the role of radioactive elements of the Chernobyl origin in the occurrence and development of pathological processes in humans.

This monograph presents the results of studies of health of Ukrainian children of the second Chernobyl generation, whose parents at a young age were exposed to large doses of radioactive agents in the first years after the accident.

The projects of the European Commission and the Regional Council of the Rhône-Alpes in Ukraine (2012–2018), initiated by the Coordination and Analytical Centre "Ecology and Health", allowed annually during 5 years to carry out medical examination of more than 3000 children living from the moment of their birth in districts bordering the ChEZ. At the same time, radiological, medical and genetic monitoring was carried out.

The purpose of the research conducted was to determine the cause and effect relationships of functional and metabolic disorders in a child's body, leading to the development of serious diseases in adulthood under conditions of constant exposure to the radiation factor associated with the ChNPP accident.

Chapter 1.
Incorporation of ^{137}Cs radionuclides into the body of children of the second Chernobyl generation. Associations between ^{137}Cs specific activity in the body of children and their age and physical growth

The 2014–2015 studies carried out in Ivankovsky and Polessky districts of Kyiv region, Ukraine, directly adjacent to the ChEZ showed that the average value of ^{137}Cs specific activity in the body of 3752 children living there was 3.48 Bq/kg, the median (Me) — 2.12; interquartile range (IQR) — 1.66–2.62 [7].

The ^{137}Cs specific activity was statistically significantly higher in children of the younger group (age 2.0–5.11 years) than in those from the middle and older groups. In turn, the ^{137}Cs specific activity was statistically significantly higher in children from the middle group (age 6.0–11.11 years) than in those aged 12.0–18.0 years, who made up the older group (Tables 1.1, 1.2) [7].

Table 1.1

Statistical characteristics of ^{137}Cs specific activity (Bq/kg) in the body of the examined children by age groups

Variables	Younger group		Middle group		Older group	
	Me	IQR	Me	IQR	Me	IQR
^{137}Cs specific activity, Bq/kg	3.00	2.79–3.31	2.41	2.06–2.62	1.63	1.51–1.85

Table 1.2

Results of statistically significant differences in ^{137}Cs specific activity in groups of children

Variables	Comparison groups	Comparison group size	Average rank	Mann-Whitney U test, significance level p
^{137}Cs specific activity, Bq/kg	1	323	1834.23	U = 69693.0; p = 0.0001
	2	1888	981.41	
	1	323	1521.07	U = 58765.0; p = 0.0001
	3	1541	809.13	
	2	1888	2220.05	U = 501170.0; p = 0.0001
	3	1541	1096.22	

Note. Group 1 — younger group (2.0–5.11 years), Group 2 — middle group (6.0–11.11 years), Group 3 — older group (12.0–18.0 years).

An inverse correlation dependence was found between the age of children and ^{137}Cs radionuclide levels in their body in the examined group (Table 1.3) [7].

Table 1.3

Results of correlation analysis between age and ^{137}Cs specific activity in the body of examined children

Parameter	Correlation coefficient	Parameter
		^{137}Cs specific activity in the body, Bq/kg
Age of children, (6–18 years)	Spearman's, r_{xy}	-0.658**
	Significance (2-tailed), p	0.0001
	N	3752

Thus, ^{137}Cs specific activity in the body of children is associated with their age in the districts of Ukraine directly

adjacent to the ChEZ. It is statistically significantly higher in the body of children of preschool and primary school age than in the body of older children. Consequently, they are exposed to more radioactivity. What are the reasons for this phenomenon?

First of all, it is necessary to determine the association between ^{137}Cs incorporated into the body and physical growth of children.

The physical growth of children reflects the state of metabolism in their body taking into account the role of internal and external factors. In most cases, abnormal physical growth of a child is a manifestation of a severe chronic disease. Under constant radiation exposure, an assessment of a child's physical growth is obligatory, as is an in-depth medical examination.

The Rohrer's index (RI), a universal physical growth index calculated by dividing weight in kilograms by the cubic of height in meters was used as a physical growth index [8].

The group of examined children was divided into subgroups: normal physical growth (RI = ≥10.7 — ≤ 13.7), abnormal low physical growth (RI < 10.7) and abnormal high physical growth (RI > 13.7).

Physical growth index (RI) values, as well as ^{137}Cs specific activity values, were statistically higher in children from the younger group than in those from the middle and older groups (Fig. 1.1) [9].

This means that younger children have more cellular elements per unit of body length that incorporate ^{137}Cs radionuclides in comparison with older ones.

However, no direct association was observed between ^{137}Cs specific activity and RI in certain age groups. On the contrary, an inverse association was recorded between these variables in the middle and older groups. It shows a negative effect of incorporated ^{137}Cs radionuclides on the physical growth of the children (Table 1.4) [9]. In this case, the results of studies of the

children in the older group, in which there was no association between RI and the age of children, were the most evidence based ones (Table 1.5).

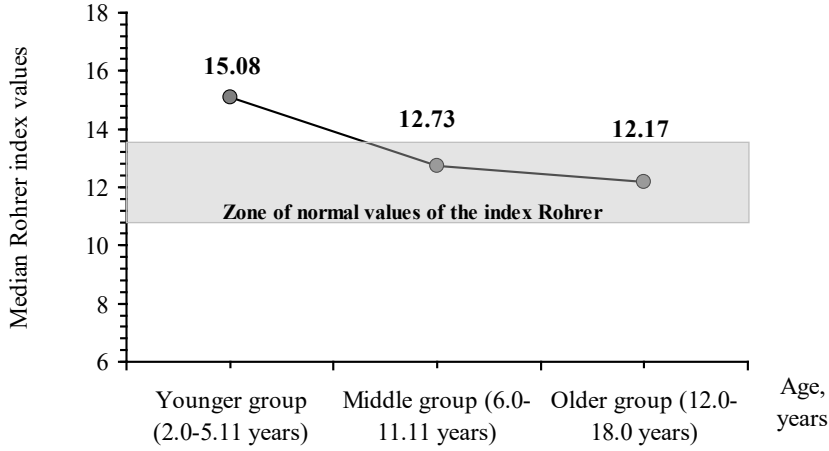

Fig. 1.1. Distribution of medians of RI values in children of different ages (3).

Table 1.4

Results of correlation analysis between RI and ^{137}Cs specific activity in the body of examined children

Groups of children	Correlation coefficient	Parameters	
		RI	^{137}Cs specific activity, Bq/kg
Total group	Spearman's	0.070**	
	Sign. (2-tailed), p	0.005	
	N	1656	
Younger group	Spearman's	0.120	
	Sign. (2-tailed), p	0.144	
	N	150	

Table No 1.4 continuation

Groups of children	Correlation coefficient	Parameters	
		RI	^{137}Cs specific activity, Bq/kg
Middle group	Spearman's	–0.094*	
	Sign. (2-tailed), p	0.009	
	N	782	
Older group	Spearman's	-0.326**	
	Sign. (2-tailed), p	0.0001	
	N	724	

Note. * — Correlation is significant at the 0.05 level (2-tailed). ** — Correlation is significant at the 0.01 level (2-tailed).

Table 1.5

Results of correlation analysis between age and RI in the groups of examined children

Groups of children	Correlation coefficient	Parameters	
		Age, years	RI
Total group	Spearman's	-0.325**	
	Sign. (2-tailed), p	0.0001	
	N	1656	
Younger group	Spearman's	-0.511**	
	Sign. (2-tailed), p	0.0001	
	N	150	
Middle group	Spearman's	-0.320**	
	Sign. (2-tailed), p	0.0001	
	N	782	
Older group	Spearman's	0.023	
	Sign. (2-tailed), p	0.532	
	N	724	

Note. * — Correlation is significant at the 0.05 level (2-tailed). ** — Correlation is significant at the 0.01 level (2-tailed).

In this group, in the absence of the effect of the age factor, a decrease in the RI values occurred with an increase in the ^{137}Cs specific activity in the body of children (Fig. 1.2).

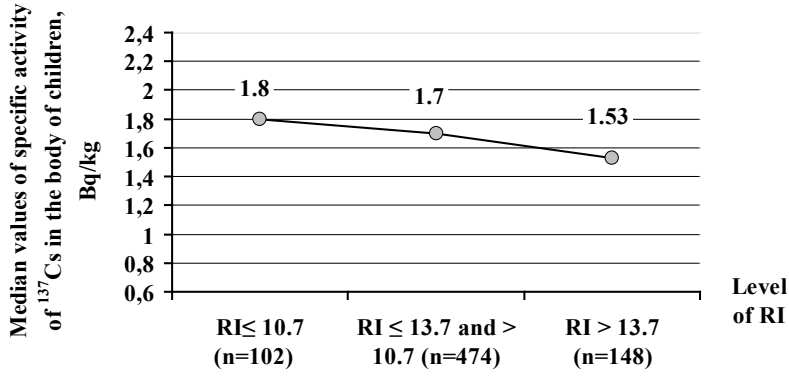

Fig. 1.2. Distribution of medians of ^{137}Cs specific activity values in the body of children of the older group with different levels of physical development (RI).

^{137}Cs specific activity values were statistically significantly higher in the subgroup of children with RI < 10.7 than in the subgroups of children with RI within the range of ≥ 10.7 — ≤ 13.7 and > 13.7 (Tables 1.6, 1.7).

Table 1.6

^{137}Cs specific activity (Bq/kg) in children of the older group (12–17 years) with different physical growth (RI) levels

Variable	Subgroups of children with different RI levels					
	Subgroup 1 (n = 89)		Subgroup 2 (n = 487)		Subgroup 3 (n = 148)	
	Me	IQR	Me	IQR	Me	IQR
^{137}Cs (Bq/kg)	1.81	1.65–2.01	1.70	1.57–1.97	1.53	1.43–1.70

Note. Subgroup 1 — RI < 10.7; Subgroup 2 — RI in the range of ≤ 13.7 and ≥ 10.7; Subgroup 3 — RI > 13.7.

Table 1.7

Results of comparison of variables by quantitative criteria (a non-parametric analysis) in children of the older group (12.0–17.0 years) with different levels of physical growth (RI)

Variable	Group number	Ivankovsky district		
		Number of cases	Average rank	Mann-Whitney U test, significance p
^{137}Cs (Bq/kg)	1	89	326.63	U = 18278.0; p = 0.019
	2	487	281.53	
	1	89	154.61	U = 3417.0; p = 0.0001
	3	148	97.59	
	2	487	346.7	U = 22062.5; p = 0.0001
	3	148	223.6	

Note. Subgroup 1 — RI < 10.7; Subgroup 2 — RI in the range of ≤ 13.7 and ≥ 10.7; Subgroup 3 — RI > 13.7.

The inverse association between ^{137}Cs specific activity and RI, as well as statistical differences in ^{137}Cs radionuclide levels in subgroups with different RI are an expression of the negative effect of a radiation factor on the metabolic processes of the child's body.

A child's physical growth is closely related to the state of vital systems of the body, in particular, the hematopoietic system.

Red blood cell and hemoglobin counts in the peripheral blood of children increases with age as proved by a direct association (Table 1.8).

The inverse association between values of ^{137}Cs specific activity and red blood cell and level hemoglobin counts in the blood also reflects the negative effect of radiation on the processes of cell proliferation.

This relationship is found in the group of children aged 12.0–18.0 years, when there is no pronounced influence of the age factor on the processes of hematopoiesis (Table 1.9).

Table 1.8

Results of correlation analysis between age, hemoglobin count, red blood cell count and ^{137}Cs specific activity in children from the total group

Parameter	Correlation coefficient	Parameters			
		RBC count, 10^{12}/L	HGB, g/L	^{137}Cs specific activity, Bq/kg	Age, years
Age, years	Spearman's	0.196**	0.364**	-0.599**	1.000
	Sign. (2-tailed), p	0.0001	0.0001	0.0001	,
	N	1606	1606	1601	1607
^{137}Cs specific activity, Bq/kg	Spearman's	-0.170**	-0.312**	1.000	-0.599**
	Sign. (2-tailed), p	0.0001	0.0001	,	0.0001
	N	1600	1600	1601	1601
HGB, g/L	Spearman's	0.715**	1.000	-0.312**	0.364**
	Sign. (2-tailed), p	0.0001	.	0.0001	0.0001
	N	1605	1606	1600	1606
RBC count, 10^{12}/L	Spearman's	1.000	0.715**	-0.170**	0.196**
	Sign. (2-tailed), p	,	0.0001	0.0001	0.0001
	N	1604	1605	1600	1606

Note. ** — Correlation is significant at the 0.01 level (2-tailed). RBC — red blood cell, HGB — hemoglobin.

Table 1.9

Results of correlation analysis between hemoglobin count, red blood cell count and ^{137}Cs specific activity in children aged 12.0–18.0 years

Parameter	Correlation coefficient	Parameters		
		RBC count, 10^{12}/L	HGB, g/L	^{137}Cs specific activity, Bq/kg
^{137}Cs specific activity, Bq/kg	Spearman's	-0.075*	-0.174**	1.000
	Sign. (2-tailed), p	0.044	0.0001	.
	N	721	721	721
HGB, g/L	Spearman's	0.739**	1.000	-0.174**
	Sign. (2-tailed), p	0.0001	.	0.0001
	N	721	721	721
RBC count, 10^{12}/L	Spearman's	1.000	0.739**	-0.725**
	Sign. (2-tailed), p	.	0.0001	0.044
	N	721	721	721

Note. * — Correlation is significant at the 0.05 level (2-tailed). ** — Correlation is significant at the 0.01 level (2-tailed).

Thus, the ^{137}Cs radionuclide incorporation into the body of children has a negative effect on metabolic processes, which is manifested in a decrease in RI values.

We believe that a higher level of ^{137}Cs accumulation in the children of the younger group compared to those from the older group cannot be associated only with physiological age characteristics.

Clarification of the peculiarities of home nutrition of children using the questionnaire method showed a closer association between children of the younger group and the consumption

of locally produced dairy products compared to those of the older group.

Statistical analysis of the respondents' answers showed that children aged 5.0–11.11 years statistically significantly more often ($t = 2.50$; $p = 0.013865$) consume milk every day compared to those aged 12.0–17.0 years [10].

Thus, the age dynamics of ^{137}Cs radionuclides can be associated with the alimentary factor. Younger children have a higher level of accumulation of ^{137}Cs radionuclides in the body in comparison with older ones, since in addition to physiological differences, they more often consume milk from cows obtained in the territory contaminated with radionuclides.

The existing state norms in Ukraine allow to consume milk of cows containing ^{137}Cs in the amount of up to 100 Bq/L for the adult population and up to 40 Bq/L for children [11]. In our opinion, this level is not safe. At the same time, it should be noted that the milk the residents of remote settlements have does not undergo regular radiological control in a territory contaminated with radioactive elements.

Based on this, it can be concluded that ^{137}Cs radionuclides contained in the soil of the territories affected by the ChNPP accident have been constantly entering the body of children via a biological chain which includes the milk of local cows.

It should be emphasized that even relatively small amounts of ^{137}Cs cause impaired functioning of vital organs and systems in a developing body.

Chapter 2.
The state of the cardiovascular system in children under conditions of constant incorporation of ^{137}Cs radionuclides into the body

In the first decade after the accident at ChNPP, employees of the Gomel State Medical Institute investigated the relationship between ^{137}Cs radionuclides incorporated into the body and cardiac disorders in children from the affected regions of Belarus. During this period, the specific activity of ^{137}Cs in the body of the inhabitants of the Gomel region amounted to tens, hundreds and even thousands of Bq/kg, as evidenced by the results of radiation monitoring of living people [4] and the study of the content of radionuclides in the internal organs of dead people [5].

During the research period (1992–1993), the frequency of occurrence of electrocardiograms without significant pathological changes ranged from 27.75 % of cases — in the group of children from the city of Gomel, to 44.67 % of cases — in the group of children from the city of Zhlobin. In these groups, the proportion of cases of arrhythmias was 40.0 % or more. In children with chronic pathology of the gastrointestinal tract, the frequency of cardiac disorders was 84.9 % [12].

It was revealed that with an increase in the content of ^{137}Cs radionuclides in the body of children aged 3–7 years, the number of cases with electrocardiographic changes increased (Fig. 2.1). To a greater extent, these were cardiac arrhythmias in the form of an incomplete blockade of the right bundle branch block [12, 13].

In 2014–2015 in areas of Ukraine bordering ChEZ, the average value of the specific activity of ^{137}Cs in the body of children was 3.48 Bq/kg, Me — 2.12; IQR — 1.66–2.62 [7], which

is significantly less than in the group of children from the Gomel region, examined in 1992–1993.

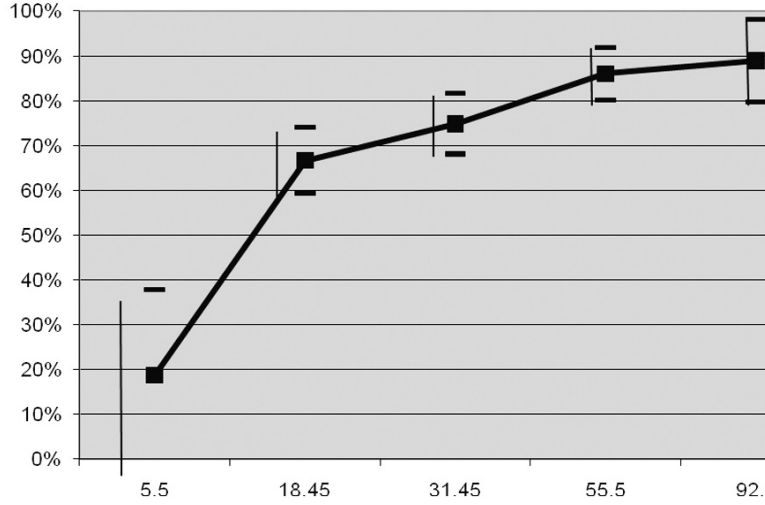

Fig. 2.1. The relationship between the frequency of electrocardiographic changes and the content of ^{137}Cs radionuclides in the body of children from the Gomel region aged 3–7 years (1993 study) (12, 13).

At the same time, electrocardiographic changes occurred in 81.9 % of cases. In particular, there were noted: sinus bradycardia (17.8 % of cases), sinus tachycardia (19.3 % of cases), unstable sinus rhythm (22.4 % of cases), early ventricular repolarization syndrome (14.2 % of cases), ectopic atrial rhythm (7.5 % of cases), incomplete blockade of the right bundle branch block (9.6 % of cases), migration of the pacemaker through the atria (4.7 % of cases), moderate changes in the ventricular myocardium (3.4 % of cases), syndrome shortened PQ interval (2.4 % of cases) [14].

Thus, the majority of cases of electrocardiographic changes in the examined children were cardiac arrhythmias. However, the proportion of cases with incomplete blockade of the right bundle branch block in the group of children from the Ivankovsky and

Polesye regions of Ukraine was significantly less than in the group of Belarusian children. The same differences were confirmed as a result of the analysis of electrocardiograms of 500 children from Minsk, obtained during the planned medical examination in 2014–2015 [15].

This issue requires further study, taking into account, first of all, the analysis of the genotypes of the studied groups of children that affect the state of the conduction system of the heart.

Blood pressure (BP) indicators in children from the regions of Ukraine bordering ChEZ, different from the age norm, were detected in 34.4 % of cases in the examined group of children [16].

BP above the established age norms was reported in 18.8 % of the examined children. An increase in BP was found in 8.5 % of cases in the group of children aged 3–6 years, in 7.9 % of cases in the group of children aged 7–11 years, and in 33.3 % of cases in the group of children aged 12–17 years.

BP below the established age norms was reported in 15.6 % of the examined children.

A decrease in BP was found in 33.3 % of cases in the group of children aged 3–6 years, in 18.4 % in the group of children aged 7–11 years, and in 7.3 % in the group of children aged 12–17 years [16].

The effect of the hypotensive action of ^{137}Cs radionuclides was detected in children of different ages.

During the studies of 1474 children, who comprised the age groups of 6.0–11.11 years (n=755) and 12.0–18.0 years (n=719), inverse associations were found between values of ^{137}Cs specific activity and values of systolic BP (SBP) and diastolic BP (DBP) and pulse pressure (PP) BP (Tables 2.1, 2.2) [17].

In the group of children of the age group of 6.0–11.11 years, a direct correlation was also determined between the values of the specific activity of ^{137}Cs in the body and the heart rate (HR) [17].

Table 2.1

Results of correlation analysis between values of ^{137}Cs specific activity, BP and HR in examined children aged 6.0–11.11 years from districts affected as a result of the ChNPP accident

Parameter	Correlation coefficient, r_{xy}	Parameters			
		SBP, mmHg	DBP, mmHg	PP, mmHg	HR, beats per minute
^{137}Cs specific activity, Bq/kg	Spearman's	-0.326**	-0.081*	-0.228**	0.126**
	p	0.0001	0.026	0.0001	0.001
	N	755	755	755	755

Note. * — Correlation is significant at the 0.05 level (2-tailed). ** — Correlation is significant at the 0.01 level (2-tailed).

Table 2.2

Results of correlation analysis between values of ^{137}Cs specific activity, BP and HR in examined children aged 12.0–18.0 years from districts affected as a result of the ChNPP accident

Parameter	Correlation coefficient, r_{xy}	Parameters			
		SBP, mmHg	DBP, mmHg	PP, mmHg	HR, beats per minute
^{137}Cs specific activity, Bq/kg	Spearman's	-0.318**	-0.098**	-0.228**	-0.043
	p	0.0001	0.008	0.0001	0.249
	N	719	719	719	719

Note. ** — Correlation is significant at the 0.01 level (2-tailed).

In the group of boys, the correlations between the values of the specific activity of ^{137}Cs in the body and BP are more pronounced than in the group of girls (Tables 2.3, 2.4).

The correlation analysis showed an inverse association between values of ^{137}Cs specific activity and lung capacity (VC), ^{137}Cs and SBP, ^{137}Cs and PP, ^{137}Cs and RI in the children aged 14.00 ± 0.07 years (Table 2.5) [18].

Table 2.3

The results of the correlation analysis between the values of the specific activity of ^{137}Cs, BP and HR in the examined boys aged 12.0–18.0 years from the areas affected by the ChNPP accident

Parameter	Correlation coefficient, r_{xy}	Parameters			
		SBP, mmHg	DBP, mmHg	PP, mmHg	HR, beats per minute
^{137}Cs specific activity, Bq/kg	Spearman's	-0,372**	-0,116*	-0,266**	-0,069
	p	0,0001	0,028	0,0001	0,191
	N	359	359	359	359

Note. * — Correlation is significant at the 0.05 level (2-tailed). ** — Correlation is significant at the 0.01 level (2-tailed).

Table 2.4

The results of the correlation analysis between the values of the specific activity of ^{137}Cs, BP and HR in the surveyed girls aged 12.0–18.0 years from the areas affected by the ChNPP accident

Parameter	Correlation coefficient, r_{xy}	Parameters			
		SBP, mmHg	DBP, mmHg	PP, mmHg	HR, beats per minute
^{137}Cs specific activity, Bq/kg	Spearman's	-0,231**	-0,044	-0,178**	0,025
	p	0,0001	0,401	0,001	0,637
	N	360	360	360	360

Note. ** — Correlation is significant at the 0.01 level (2-tailed).

Thus, with an increase in ^{137}Cs concentrations in the body of children, there is a decrease in the respiratory function of the lungs (a decrease in vital capacity), the level of systolic BP and a decrease in body weight.

Table 2.5

Results of correlation analysis between analysed variables in examined children

Parameter	Correlation coefficient, r_{xy}	Parameters					
		VC, ml	HR, beats per minute	SBP, mmHg	DBP, mmHg	PP, mmHg	RI, CU
^{137}Cs specific activity, Bq/kg	Spearman's	-0.267**	-0.045	-0.316**	-0.069	-0.255**	-0.397**
	p	0.000	0.304	0.000	0.117	0.000	0.000
	N	520	520	520	520	520	520

Note. ** — Correlation is significant at the 0.01 level (2-tailed). CU — conventional units.

The results of our previous studies indicate that ^{137}Cs radionuclides are incorporated by the myocardium and muscle cells, including myocytes of the respiratory system (intercostal muscles, diaphragm and abdominal muscles) [19]. At the same time, in them there occurs damage to energy supply systems — mitochondria, sarcoplasmic reticulum structures, which causes 'energy hunger' and inhibition of intracellular repair processes. Ca^{2+} accumulates in the cells and contracture changes in myofibrils occur. This results in a decrease in systolic BP and a decrease in vital lung function. A high concentration of Ca^{2+} in the heart cells leads to a heart rhythm disorder. This is due to peculiarities of the cardiac conduction system, in the cells of which the input current which is responsible for the action potential is mainly calcium [20].

The decrease in SBP and DBP, in the presence of an increase in HR, recorded by us in children aged 6–11.11 with an increase in ^{137}Cs specific activity in the body [17], can also be considered as an asympathicotonic variant of autonomic dysfunction, which

reflects unsatisfactory adaptation of the body [21]. This variant can be the case, since ^{137}Cs radionuclides were also observed in the structures of the central nervous system [19].

The activity of transaminases: aspartate aminotransferase (AST) and alanine aminotransferase (ALT) in serum is an indicator of damage to internal organ cells. ALT is a marker of liver cell damage, since it is present mainly in the cytoplasm of hepatocytes [22].

AST is predominantly found in the mitochondria of cardiomyocytes and hepatocytes, and therefore, its serum activity is an indicator of severe damage to liver and heart cells [23].

Simultaneous increases in serum AST and ALT values indicate that there is damage to liver cells, whereas an increase in AST values alone can be associated, to a greater extent, with injury to myocardial cells. To optimise the process of differential diagnostic assessment of damage to internal organ cells, the de Ritis coefficient — the quotient obtained when AST is divided by ALT — is used.

With the de Ritis coefficient of more than 2 (this level is the upper physiological limit for children), in case of an increase in the activity of serum AST, it is possible to state, with a greater degree of probability, is damage cardiomyocytes. At the same time, the state of other internal organs should be taken into account.

An examination of 1320 children (666 boys and 654 girls) living in Polessky and Ivankovsky districts of Kyiv region showed an increase in values of serum AST in 37.5 % of cases and serum ALT in 1.2 % of cases. The de Ritis coefficient of more than 2.0 was found in 26.29 % of cases of the number of children whose AST level was higher than 34.0 U/L (Table 2.6.).

In groups of children aged 2.0–5.11 years (younger group) and aged 6.0–11.11 years (middle group), the proportion of cases of elevated serum AST activity was greater than in the group

of children aged 12.0–18.0 years old — the older group (Tables 2.6, 2.7) [24].

Table 2.6

Proportion of cases of exceeding of reference values of transaminase activity and de Ritis coefficient in groups of examined children (24)

Groups	Number of children	AST > 34.0 U/L		ALT > 36.0 U/L		AST > 34.0 U/L — AST/ALT > 2.0	
		Abs.	%	Abs.	%	Abs.	%
Younger	91	48	52.8±5.2	3	3.30±1.9	43	47.25±5.2
Middle	580	271	46.7±2.1	6	1.03±0.4	181	31.21±1.9
Older	649	176	27.1±1.8	7	1.08±0.4	123	18.95±1.5
Total	1320	495	37.5±1.3	16	1.21±0.3	347	26.29±1.2

Table 2.7

Results of statistically significant differences in groups of children (24)

Comparison groups	Variable	T-test value, significance level, p	Variable	T-test value, significance level, p
1	AST>34.0 U/L	t = 1.09; p=0.277545	AST > 34.0 U/L — AST /ALT > 2.0	t = 2.88; p = 0.004381
2				
1	AST>34.0 U/L	t = 4.67; p=0.0001	AST > 34.0 U/L — AST / ALT > 2.0	t = 5.19; p = 0.0001
3				
2	AST>34.0 U/L	t = 7.09; p = 0.0001	AST > 34.0 U/L — AST / ALT > 2.0	t = 4.98; p = 0.0001
3				

Note. Group No. 1 — younger group; No. 2 — middle group; No. 3 — older group.

At the same time, the proportion of cases when the activity of serum ALT exceeded the reference range (36.0 U/L) had no statistically significant differences in separate age groups [24].

Age dependence was also traced in relation to the proportion of cases with an AST level above 34.0 U/l, in which the values of the de Ritis coefficient were greater than 2 (Tables 2.6, 2.7) [24].

The values of serum AST, the de Ritis coefficient and ^{137}Cs specific activity in the groups under study were also associated with the age of the examined children. They were statistically significantly higher in the younger group than in the older groups (Table 2.8) [24].

Table 2.8

Statistical characteristics of analysed variables of examined children (24)

Variable	Younger group (n = 91)		Middle group (n = 580)		Older group (n = 649)	
	Me	IQR	Me	IQR	Me	IQR
^{137}Cs specific activity, Bq/kg	3.0	2.8–3.2	2.5	2.1–2.7	1.7	1.5–2.0
AST, U/L	34.5	31.4–39.3	33.3	28.1–39.4	28.5	22.3–34.5
ALT, U/L	12.8	10.4–16.1	15.3	12.2–18.8	14.2	11.3–17.2
AST/ALT	2.7	2.2–3.2	2.3	1.9–2.7	2.0	1.7–2.4

Thus, myocardial cell damage was observed in the large percentage of children in the groups under study. The proportion of cases of such conditions is higher in the children of the younger group than in those of the older group.

In the general group, as well as in individual age groups, a direct correlation was determined between the values of the specific activity of ^{137}Cs and the activity of serum AST (Table 2.9), the specific activity of ^{137}Cs and the de Ritis coefficient (Table 2.10) [24].

Table 2.9

Results of analysis of associations between values of ^{137}Cs specific activity and AST activity in age groups (24)

Groups of children	Correlation coefficient	Parameters	
		^{137}Cs specific activity, Bq/kg	AST, U/L
Younger group	Spearman's	0.306**	
	Sign. (2-tailed), p	0.003	
	N	91	
Middle group	Spearman's	0.101*	
	Sign. (2-tailed), p	0.015	
	N	580	
Older group	Spearman's	0.207**	
	Sign. (2-tailed), p	0.0001	
	N	649	

Note. * — Correlation is significant at the 0.05 level (2-tailed). ** — Correlation is significant at the 0.01 level (2-tailed).

The findings indicate that in children living in areas affected by the Chernobyl nuclear power plant accident in the presence of incorporation of relatively small amounts of ^{137}Cs radionuclides into the body there occurs damage to mitochondrial structures of myocardiocytes with AST release into the blood.

The studies have shown a negative effect of ^{137}Cs incorporated into the body on the cardiovascular system of the children of the second Chernobyl generation.

Damage to cardiomyocytes and structures of the central and autonomic nervous systems caused by incorporated radionuclides leads to a decrease in BP and heart beat rhythm disorders which indicates that the adaptive capabilities of the child's body are unsatisfactory.

Table 2.10

Results of analysis of associations between values of ^{137}Cs specific activity and the de Ritis coefficient in age groups (24)

Groups of children	Correlation coefficient	Parameters	
		^{137}Cs specific activity, Bq/kg	AST/ ALT
Younger group	Spearman's	0.334**	
	Sign. (2-tailed), p	0.001	
	N	91	
Middle group	Spearman's	0.297**	
	Sign. (2-tailed), p	0.0001	
	N	580	
Older group	Spearman's	0.187**	
	Sign. (2-tailed), p	0.0001	
	N	649	

Note. ** — Correlation is significant at the 0.01 level (2-tailed).

Chapter 3.
Hyperhomocysteinemia in children from districts affected by the Chernobyl nuclear power plant accident

Studies conducted in Ukraine during 2013–2017, within the framework of projects of the European Commission and the Rhone-Alpes region (France), in Ivankovsky and Polessky districts of the Kiev region of Ukraine, located near ChNPP, made it possible to identify a large number of children with

hyperhomocysteinemia — increased blood levels of homocysteine (H_{cy}), a product of the essential amino acid methionine (Met). Its content in the body, in particular in blood serum, reflects the level of functioning of a number of metabolic processes, primarily the folate cycle (FC).

In the course of the study, a non-selective selection of children from families permanently residing in the territory contaminated after the ChNPP accident in 1986 with radioactive agents was carried out. The children were not officially sick and attended classes at school.

The state of hyperhomocysteinemia was recorded throughout 2015 with different frequency of occurrence.

Examination of 201 children, conducted on April 2, 2015, revealed an increase in the level of Hcy in the blood over 10 μmol/l in 98 cases (48.8 %). At the same time, this condition occurred among boys much more often than among girls — in 58.4 % and 39.0 % of cases, respectively ($t = 2.8$; $p = 0.006198$) [25, 26].

When examining 263 children conducted on December 18, 2015, the state of hyperhomocysteinemia was detected in 198 cases (75.3 %). And, just like during the examination on April 2, 2015, the frequency of its occurrence in the group of boys was higher than in the group of girls — respectively 86.5 % and 65.0 % ($t = 4.23$; $p = 0.000036$) [27].

Given the massive nature of hyperhomocysteinemia among the population of children living in areas affected by the ChNPP accident, it is important to investigate the causal mechanisms of this phenomenon, since its association with severe diseases is known.

A number of researchers recognize that H_{cy} is an independent modifiable risk factor for cardiovascular diseases [28, 29, 30, 31, 32] and atherosclerosis [33].

In the group of patients with acute myocardial infarction, with an increase in the level of H_{cy} in the blood above 15 μmol/l,

a positive correlation was found between the aggregation ability of platelets and the level of H_{cy}, as well as a direct relationship between the concentrations of total cholesterol and H_{cy} [34].

A strong direct correlation was found between the level of H_{cy} in the blood and the amount of brain damage in patients with the atherothrombotic subtype of stroke [35], as well as between the level of H_{cy} and the risk of developing Alzheimer's disease [36]. In this regard, it is proposed to consider H_{cy} as a predictive risk factor for stroke progression [37], an independent risk factor for the development of cognitive dysfunction (age-related memory loss) [38]. This conclusion is supported by the results of experimental studies with laboratory animals [39].

A high level of H_{cy} was stated in the development of oncological diseases [40], in particular, colorectal cancer [41].

Chapter 4.
Homocysteine and metabolic disorders

H_{cy} belongs to the group of thiols, and can form disulfides in the presence of cobalt or copper.

The main metabolic transformations of H_{cy} take place in the liver and, to a lesser extent, in the kidneys.

H_{cy} and Met are linked by methylation. It can be reasonably argued that H_{cy} is an intermediate link in biochemical transformations from Met to cysteine (Cys). An elevated concentration of H_{cy} in the blood indicates serious metabolic disorders.

H_{cy} is formed after Met donates its methyl group and is converted to adenosylmethionine (SAM). The H_{cy} is then remethylated to the same Met, using a methyl group from the FC. The main participants in the process of remethylation of H_{cy}

to Met are vitamins B_9 and B_{12} associated, respectively, with the enzymes FC methylenetetrahydrofolate reductase (MTHFR) and B_{12} methionine synthase (MTR) [42].

FC is one of the main metabolic cycles of the human and animal body. It is associated with metabolic reactions in all organs and systems.

In addition to FC, the resynthesis of Met from H_{cy} is carried out with the help of betaine (Bet), synthesized from choline. Bet is a methyl group donor for H_{cy} by betaine-homocysteine-S-methyltransferase, turning into dimethylglycine.

FC, which provides H_{cy} remethylation to Met, is present in all tissues, while H_{cy} remethylation using Bet occurs mainly in the liver, kidneys, and lens of the eye [37].

Only about 50 % of H_{cy} is remethylated to Met.

The complex of reactions for the conversion of H_{cy} to cystathionine (Cyst) and Cys is called trans-sulfurization. It is carried out in two stages. In the first step, with the participation of cystathionine-β-synthase (CBS), condensation occurs between H_{cy} and serine (Ser), leading to the production of Cyst. At the second stage, under the influence of cystathionine-γ-lyase, Cyst is converted into Cys.

Vitamin B_6 is involved in these reactions as a coenzyme CBS, the activator of which is the SAM-allosteric inhibitor of MTHFR [42].

Cells of the central nervous system (CNS), myocardium and endothelial cells, unlike the cells of most tissues, do not possess the CBS enzyme, and therefore, they are unable to utilize excess H_{cy} through the trans-sulfurization reaction. In these cells, only the H_{cy} remethylation system using FC is present, and therefore, they are more vulnerable to increased production of this metabolite [37].

Cys plays an important role in many anabolic processes, forms taurine and inorganic sulfates involved in the synthesis of direct

anticoagulants — heparin, heparan sulfate and chondroitin sulfate, is part of glutathione, which protects cells from oxidative stress.

During the process of transsulfuration, H_2S is produced, which, along with NO and CO, is a gas transmitter that regulates the physiological functions of the body [37].

The toxicity of H_{cy} is associated with its ability to form compounds with proteins, changing their structure. The severity of homocysteinylation — post-translational modification of proteins, is directly dependent on the level of H_{cy} in blood plasma [43].

In S homocysteinylation, H_{cy} binds via its free thiol group to another free thiol group from a Cys residue in the protein molecule. At the same time, the thiol-dependent oxidation and reduction status of proteins changes [44].

N homocysteinylation is the result of the formation of an isopeptide bond between the amino group of homocysteine-thiolactone (H_{cy} -TL) and the amino group of lysine, which leads to a change in the structure of the protein and a violation of its function. Fibrinogen molecules, low and high density lipoproteins, albumin, hemoglobin, ferritin undergo modifications. The consequence of this is the development of an autoimmune process, with the production of autoantibodies against N- H_{cy} -proteins, as well as increased thrombus formation caused by N- H_{cy} -fibrinogen.

Inactivation of free amino groups enhances oxidative stress of the endoplasmic reticulum [44]. Hydrogen peroxide (H_2O_2) and superoxide anion radical are formed, stimulating the processes of lipid peroxidation. Due to the inhibition of superoxide dismutase, the level of peroxynitrite increases, which significantly aggravates oxidative stress [37]. H_{cy} disrupts the formation of NO, the main gaseous regulator of endothelial homeostasis [45].

Homocysteine acid, a product of spontaneous H_{cy} oxidation, at concentrations characteristic of hyperhomocysteinemia, even with short-term exposure, causes cell apoptosis [46].

As a result of homocysteinylation, the formation of reactive oxygen species occurs, leading to the oxidation of lipids, proteins, carbohydrates and nucleic acids, followed by dysfunction and damage to the endothelium, with increased proliferation of smooth muscle cells in the walls of blood vessels.

In the course of thrombus formation, nonspecific inhibition of prostacyclin synthesis, factor V activation, inhibition of protein C activation, blockade of tissue plasminogen activator binding by endothelial cells, and platelet hyperaggregation occur. Hypercoagulability associated with H_{cy} underlies the development of ischemic stroke [47].

Thus, H_{cy} in high concentrations in the body is able to have both atherogenic and thrombovascular effects.

In experimental studies, damage to cardiomyocytes under conditions of hyperhomocysteinemia was revealed [48].

It has been established that Hcy is able to interact with glutamate receptors of neurons of the cerebral cortex and hippocampus (80 % of synapses) [49], and cells of the heart, liver, kidneys, lungs, testes, erythrocytes, neutrophilic leukocytes, lymphocytes, osteoblasts and osteoclasts [46, 50, 51].

The excitatory transmitter for this type of receptor is glutamic acid (glutamate), which plays one of the main roles in the regulation of many processes in the CNS, including during the period of intrauterine development of the embryo, as well as ensuring the processes of survival, migration and differentiation of neurons, the formation of neuronal connections [50].

There are ionotropic glutamate receptors associated with ion channels, and metabotropic, inducing a change in metabolic processes in neurons through a system of second messengers, and coupled with G-proteins. These receptors are interconnected [50].

Inotropic glutamate receptors provide fast transmission of nerve impulses. Among this class of receptors, N-methyl-D-aspartate (NMDA) receptors are the most studied.

The structure of the receptor is a tetrameric complex formed by two subunits forming an ion channel, which is blocked by the Mg^{2+} ion at rest.

Physiological activation of glutamate ionotropic receptors, lasting several milliseconds, leads to depolarization of the postsynaptic membrane (from –50 to –30 mV) and the opening of the channel, as a result of which K^+, Na^+, Ca^{2+} ions penetrate the cell. The result is the activation of Ca^{2+} dependent signaling pathways responsible for cell survival and preventing neuronal cell death [50].

Excessive activation of NMDA receptors promotes pathological impulses based on a sharp increase in transmembrane calcium current into the cell. At the same time, the concentration of Ca^{2+} in the cell increases, the activity of proteases, kinases, endonucleases, lipoxygenases, and phospholipase A2 increases, which leads to significant metabolic and genetic changes, uncontrolled action of free radicals, and apoptosis [50]. It is the influx of Ca^{2+} ions into the cell through the channels of NMDA receptors that is the main mechanism in the implementation of the toxic effects of glutamate [52], leading to damage to mitochondria and suppression of the production of adenosine triphosphoric acid (ATP).

Thus, superactivation of glutamate receptors induces excitation of brain structures, with the development of even convulsive conditions.

It was found that H_{cy} promotes overexcitation of NMDA receptors in the cells of the central nervous system, resulting in an increase in the level of intracellular ionized calcium [46], and as a result, the formation of reactive oxygen species [53]. The effect of H_{cy} exposure on NMDA receptors of immunocompetent cells was noted [51].

Since, under the influence of H_{cy}, there is no massive influx of extracellular Ca^{2+} into neurons, it is designated as a weak neurotoxin and a risk factor for neurodegeneration [54],

which, in particular, can disrupt the hypothalamic regulation of reproductive function [55].

Analyzing the results of studies conducted by various scientists, we can conclude that H_{cy} in amounts exceeding physiological levels can have a negative effect on metabolic processes in the cells of the nervous system, contributing to their death, as well as the occurrence of strokes, Alzheimer's disease, disseminated sclerosis, Parkinson's disease, epilepsy, and amyotrophic lateral sclerosis [36]. To do this, it uses receptors that are associated with glutamic acid, a unique regulator of metabolism in the body.

In adults, the state of hyperhomocysteinemia is defined when the H_{cy} level exceeds the level of 10 μmol/l [35].

For adolescent children, the physiological concentration of H_{cy} in the blood is considered to be a concentration of 5–6 μmol/l [56].

In our studies, the state of hyperhomocysteinemia was recorded in children aged 8–17 years, if the level of H_{cy} in their blood was above 10 μmol/l.

Chapter 5.
The state of the genetic system of the folate cycle in children from districts bordering the Chernobyl exclusion zone

The determination of the state of the genetic system of the FC is of great importance in finding out reasons for the methionine resynthesis from H_{cy} and occurrence of hyperhomocysteinemia.

The most frequently studied polymorphisms are C677T and A1298C MTHFR, A2756G MTR, A66G MTRR.

It should be noted that in our opinion, in order to assess the genetic potential of a population of a particular region, it is advisable to use the results obtained in a cohort of children from permanent families. It is even better if a genotype of even dead embryos would be taken into account. With age, the genotype of the population group under study may change due to high mortality especially in problem districts associated with the impact of environmental factors.

A similar situation of biased assessment develops in regions where there is a large migration of population. In particular, among the indigenous population of Amur region, the percentage of homozygotes consisted of neutral C alleles of the MTHFR: C677T polymorphism, which encodes the main enzyme of the folate cycle MTHFR, was 29.0 %, while in the group of expatriate subjects — 43.0 %, the percentage of C allele heterozygotes of the same polymorphism, 66.0 % and 50.0 % respectively [57].

Studies by D. A. Mikitenko and O. I. Timchenko [58] showed the prevalence of the MTHFR gene C677T polymorphism among parturient women in Kyiv region.

It was found out that in the examined group of women, the percentage of the 677CC genotype was 60.0 %, the percentage of the 677CT genotype was 31.11 %, and the percentage of the 677TT genotype was 8.89 % [58].

Thus, they identified the risk group of women who were recommended to conduct a molecular genetic analysis for the carriership of C677T of the MTHFR genetic polymorphism.

However, when compiling a genotype of a certain population, results of genetic analysis only for pregnant women cannot be used, since at present, a large number of women are unable to conceive a child, including due to genetic disorders.

In view of this, the most realistic information is the one based on the results of an examination of the child population.

In our project, children aged 8–17 years permanently living in Ivankovsky and Polessky districts of Kyiv region, Ukraine, comprised the examined group (n = 479).

The smallest number of cases was found in the group with no risk alleles. The largest number of cases occurred in carriers of two, a slightly smaller number of three polymorphic alleles. In 6.26 % of cases, there were persons carrying risk alleles for all four studied FC genetic polymorphisms. At the same time, in the group of girls, the relative number of these cases was higher than in the group of boys (Table 5.1).

Table 5.1

Frequency of genetic polymorphisms in the examined group of children (n = 479)

Number of polymorphisms, Subgroup No.	Total number of children		Boys		Girls	
	Abs. number	Percentage,%	Abs. number	Percentage,%	Abs. number	Percentage,%
«1» — Zero	10	2.09	4	1.75	6	2.39
«2» — One	75	15.66	38	16.67	37	14.74
«3» — Two	211	44.05	99	43.42	112	44.62
«4» — Three	153	31.94	78	34.21	75	29.88
«5» — Four	30	6.26	9	3.95	21	8.37*
Total	479	100	228	100	251	100

Note. The degree of confidence between boys and girls in the Subgroup 5 t = 2.03; p = 0.051987.

The MTR: A2756G polymorphism affecting the synthesis of B_{12}-methionine synthase had the highest prevalence of carriership of homozygotes consisted of neutral alleles in the group of children being studied, the MTRR: A66G polymorphism associated with methionine-synthase reductase (MTRR), an enzyme that

restores the activity of MTR, had the lowest prevalence. The largest percentage among values of homozygous carriership of risk alleles is related to the MTRR: A66G polymorphism.

The percentage of cases of carriership of risk alleles and neutral alleles (homozygotes) of the MTHFR: A1298C and MTHFR: C677T polymorphisms was the same (Table 5.2).

Table 5.2

Frequency of polymorphic alleles of FC genes in examined children in Ivankovsky and Polessky districts (n = 479)

Gene, polymorphism	Genotype variants					
	"Neutral" allele Homozygous variant		"Risk" allele Heterozygous variant		"Risk" allele Homozygous variant	
	Abs. number	Percentage,%	Abs. number	Percentage,%	Abs. number	Percentage,%
MTR: A2756G	299	62.42	153	31.94	27	5.64
MTHFR: A1298C	225	46.97	209	43.63	45	9.40
MTHFR: C677T	225	46.97	212	44.26	42	8.77
MTRR: A66G	89	18.58	227	47.39	163	34.03

There were no statistical differences in the percentage of determined genotypes between the groups of boys and girls (Tables 5.3, 5.4).

The results of the studies, with certain assumptions, indicate that there are no significant differences in the genetic system of the FC of the examined children from Ivankovsky and Polessky districts and people living in Ukraine and on the European continent [59, 60].

Table 5.3

Frequency of polymorphic alleles of FC genes in examined boys in Ivankovsky and Polessky districts (n = 228)

Gene, polymorphism	Genotype variants					
	"Neutral" allele Homozygous variant		"Risk" allele Heterozygous variant		"Risk" allele Homozygous variant	
	Abs. number	Percentage,%	Abs. number	Percentage,%	Abs. number	Percentage,%
MTR: A2756G	141	61.84	74	32.46	13	5.70
MTHFR: A1298C	101	44.30	101	44.30	26	11.40
MTHFR: C677T	117	51.31	94	41.23	17	7.46
MTRR: A66G	43	18.86	108	47.37	77	33.77

Table 5.4

Frequency of polymorphic alleles of FC genes in examined girls in Ivankovsky and Polessky districts (n = 251)

Gene, polymorphism	Genotype variants					
	"Neutral" allele Homozygous variant		"Risk" allele Heterozygous variant		"Risk" allele Homozygous variant	
	Abs. number	Percentage,%	Abs. number	Percentage,%	Abs. number	Percentage,%
MTR: A2756G	157	62.55	80	31.87	14	5.58
MTHFR: A1298C	122	48.61	110	43.82	19	7.57
MTHFR: C677T	109	43.43	117	46.61	25	9.96
MTRR: A66G	45	17.93	120	47.81	86	34.26

Carriership of a number of combinations of FC genotypes is studied in the genesis of a number of congenital and hereditary

diseases. In particular, compound heterozygosity for the 677CT/1298AC alleles of the MTHFR gene is widely known, and it significantly reduces the activity of the gene. It is set equal to the MTHFR: 677 T/T genotype by the degree of inhibition of the activity of the methylenetetrahydrofolate reductase enzyme and, accordingly, the degree of increase in the level of H_{cy} in the blood [61].

In the group of children under study, compound heterozygosity for the MTHFR gene 677CT /1298AC alleles was found in 21.5 % of cases, carriership of the homozygous T/T variant of the MTHFR 677 polymorphism was observed in 8.8 % of cases. Thus, there is a genetically determined predisposition to abnormal functioning of the FC and an increase in the level of H_{cy} in the blood in 30.3 % of cases in the population of children under analysis (Table 5.5.).

Table 5.5

Frequency of MTHFR genetic polymorphisms in the examined group of children

Number	MTHFR polymorphism genotypes					
	677CT /1298AC		677TT		677CT /1298AC + 677TT	
	Abs. number	Percentage,%	Abs. number	Percentage,%	Abs. number	Percentage,%
479	103	21.5	42	8.8	145	30.3

The percentage of carriership of the 677CT/1298AC heterozygous association of the MTHFR gene is statistically significantly lower in the group of children living in Polessky district affected by the accident at the ChNPP than in the group of their mothers (Table 5.6.) [62]. In this regard, we can assume that the radiation factor plays a negative role in processes of

prenatal development of human embryos in the presence of genetic factors in the form of the MTHFR 677CT /1298AC heterozygous association in the latter.

Table 5.6

Percentage of MTHFR genetic polymorphisms in groups (62)

Group	677CT /1298AC genotype		677CT+677TT genotype	
	Abs. number (n)	Percentage, %	Abs. number (n)	Percentage, %
Children	9	10.7*	40	47.6*
Mothers	20	30.3	42	63.6

Note. * Statistically significant differences between groups (P <0.05).

The literature contains combinations of carriership of genotypes with risk alleles of the MTHFR: C 677T and MTRR: A66G polymorphisms, as well as other polymorphisms recorded in a number of severe diseases in children and adults. Heterozygous associations of the MTHFR: C 677T and MTRR: A66G polymorphisms, as well as MTR: A2756G and MTRR: A66G have been noted in terms of an internal factor contributing to the occurrence of congenital malformations [61,63].

In the group of children examined by us, compound heterozygosity of the MTHFR: C 677T and MTRR: A66G polymorphisms was found in 23.17 % of cases, MTR: A2756G and MTRR: A66G polymorphisms — in 16.08 % of cases, MTR: A2756G and MTHFR: C 677T polymorphisms — in 12.94 % of cases (Table 5.7).

It should be noted that in the examined group, there were no cases of carriership of associations of the G/G MTR 2756 and T/T MTHFR 677 genotypes, a small number of cases of carriership of associations of T/T MTHFR 677 and G/G MTRR 66, G/G MTR 2756G and G/G MTRR 66 genotypes (Table 5.7).

Table 5.7

Frequency of combinations of FC genetic polymorphisms in the examined group of children

MTHFR: C 677T and MTRR: A66G polymorphism genotypes							
C/T677 — A/G66		C/T677 — G/G66		T/T677 — A/G66		T/T677 — G/G66	
n	%	n	%	n	%	n	%
111	23.17	67	13.99	17	3.55	15	3.13
MTR: A2756G and MTHFR: C 677T polymorphism genotypes							
A/G2756 — C/T677		A/G2756 — T/T677		G/G2756 — C/T677		G/G2756 — T/T677	
n	%	n	%	n	%	n	%
62	12.94	14	2.92	13	2.71	0	0
MTR: A2756G and MTRR: A66G polymorphism genotypes							
A/G2756 — A/G66		A/G2756 — G/G66		G/G2756 — A/G66		G/G2756 — G/G66	
n	%	n	%	n	%	n	%
77	16.08	50	10.44	13	2.71	3	0.63

Thus, combined carriership of homozygous variants of carriership of risk alleles of polymorphisms affecting the H_{cy} methylation process leaves no chance for the development of a human embryo.

Compound heterozygosity of these polymorphisms of folate cycle genes occurs in nature. However, under environmental exposure, the metabolism of H_{cy} and Met becomes disturbed.

In the area affected by the accident at ChNPP, such an impact is caused by the radiation factor.

Chapter 6.
Hyperhomocysteinemia and the state of the folate cycle genetic system

The initiation of hyperhomocysteinemia and a pathology related to it, is most often associated with the MTHFR: C 677T polymorphism which controls the synthesis of methylenetetrahydrofolate reductase, one of the main enzymes of the FC [64–70].

Studies conducted on the territory of Ivankovsky and Polesye districts showed that the presence of the T allele of this polymorphism in the genome of children contributed to the development of hyperhomocysteinemia in them.

The largest proportion of cases of hyperhomocysteinemia was found in the subgroup where the main genotype was the T/T MTHFR:677TT genotype (Fig. 6.1) [71].

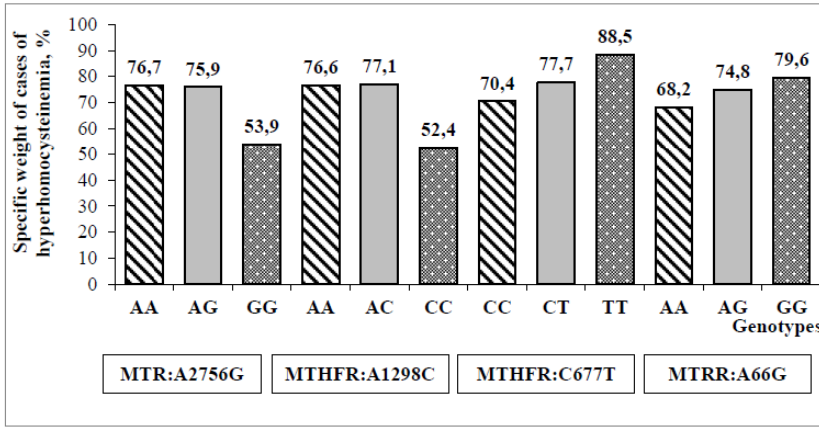

Fig. 6.1. The proportion of cases of hyperhomocysteinemia in subgroups of children. The subgroups MTR:2756GG, MTHFR:1298CC, MTHFR:677CC, MTRR:66AA have statistically significant differences $p<0.05$ with the MTHFR:677TT genotype (71).

In this subgroup, the blood level of H_{cy} is statistically significantly higher than in the subgroups with the C/C and C/T genotypes of the same polymorphism (Tables 6.1, 6.2) [8].

Table 6.1

Statistical characteristics of H_{cy} content indicators in genetic subgroups

Polymorphism, genotype	H_{cy}, µmol/L	
	Me	IQR
MTHFR: C677T		
TT	16.2	13.0–26.3
CT	11.7	10.2–13.3
CC	11.4	9.5–13.1

Table 6.2

Results of comparison of populations of H_{cy} levels (µmol/L) in genetic subgroups using a non-parametric Mann-Whitney U test.

Polymorphism, genotype	MTHFR:677		MTHFR:677		MTHFR:677	
	CC	CT	TT	CT	TT	CC
Number of cases	125	112	26	112	26	125
Average rank	113.4	125.3	98.6	62.7	112.0	68,5
Mann-Whitney U test	6395.5		699.0		689.0	
Significance p	$p = 0.181$		$p < 0.0001$		$p < 0.0001$	

It should be noted that the T allele was observed in children of all genetic subgroups, except for the subgroups with the C/C MTHFR:1298 and C/C MTHFR:677 genotypes (Table 6.3).

In all analysed genetic subgroups, with the exception of the subgroup where the base genotype was G/G MTR:2756, the phenotypic implementation of cases of carriership of the MTHFR:677 polymorphism T allele in the form of hyperhomocysteinemia occurred in more than 70 % of cases (Fig. 6.2).

Table 6.3

Proportion of cases of carriership of MTHFR:677 polymorphism alleles in genetic subgroups

Polymorphism, genotype	Number of children			
	T/T, C/T genotypes		C/C genotype	
	Абс.	%	Абс.	%
MTR:2756GG	6	46.2	7	53.8
MTR:2756AG	47	54.0	40	46.0
MTR:2756AA	85	52.2	78	47.8
MTHFR:1298CC	0	0	21	100
MTHFR:1298AC	47	44.8	58	55.2
MTHFR:1298AA	91	66.4	46	33.6
MTHFR:677TT	26	100	0	0
MTHFR:677CT	112	100	0	0
MTHFR:677CC	0	0	125	100
MTRR:66GG	48	54.6	40	45.4
MTRR:66AG	70	53.4	61	46.6
MTRR:66AA	20	45.5	24	54.6

However, it should be noted that, in the presence of carriership of the C/C MTHFR:677 genotype, the proportion of cases of hyperhomocysteinemia was quite large in the analysed genetic subgroups (Fig. 6.3).

The fact that, in addition to the genetic factor, an exogenous factor affects the level of H_{cy} in the blood is confirmed by the absence of statistically significant differences in the proportion of genetic polymorphisms in the groups of children with and without hyperhomocysteinemia (Tables 6.4, 6.5).

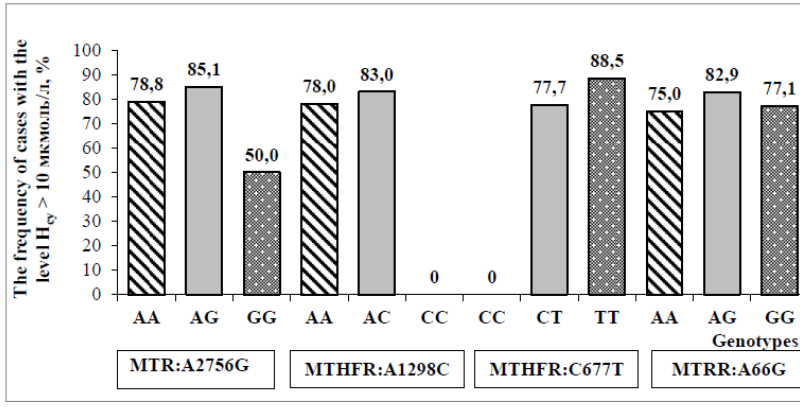

Fig. 6.2. The proportion of cases of hyperhomocysteinemia in genetic subgroups with the T allele of MTHFR:677 polymorphism

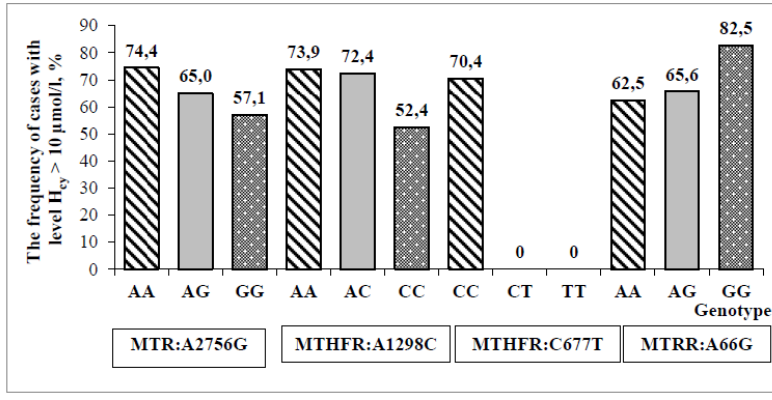

Fig. 6.3. The proportion of cases of hyperhomocysteinemia in genetic subgroups with the absence of the T allele (genotype C/C MTHFR:677)

The findings indicate that the genetic system of the FC has a significant impact on the blood level of H_{cy} in children living in districts affected by the ChNPP plant accident.

Table 6.4

The presence of polymorphic alleles of the FC genes in the examined children when the blood H_{cy} level is > 10 μmol/L, (n = 198)

Gene, polymorphism	«Neutral» allele		«Heterozygous variant» risk allele		«Homozygous variant» risk allele	
	Abs. number	%	Abs. number	%	Abs. number	%
MTR: A2756G	124	62.6	67	33.8	7	3.6
MTHFR: A1298C	105	63.0	82	41.4	11	5.6
MTHFR: C677T	88	44.4	87	44.0	23	11.6
MTRR: A66G	31	15.7	98	49.5	69	34.8

Table 6.5

The presence of polymorphic alleles of the FC genes in the examined children when the blood H_{cy} level is < 10 μmol/L, (n = 65)

Gene, polymorphism	«Neutral» allele		«Heterozygous variant» risk allele		«Homozygous variant» risk allele	
	Abs. number	%	Abs. number	%	Abs. number	%
MTR: A2756G	39	60.0	20	30.8	6	9.2
MTHFR: A1298C	32	49.2	23	35.4	10	15.4
MTHFR: C677T	37	56.9	25	38.5	3	4.6
MTRR: A66G	14	21.5	32	49.2	19	29.2

However, an increase in the blood H_{cy} level is associated not only with the T allele of the MTHFR:677 polymorphism, but also with the external environmental effect, that includes a radiation factor.

Taking into account the ability of ^{137}Cs radionuclides to disturb energy processes in the cell, it can be assumed that the increased formation of H_{cy} in children living under constant radiation pressure may be caused by a decrease in the activity of MTHFR and MTR due to their insufficient energy support.

Chapter 7.
Folate Cycle Genes and B Vitamins

Vitamins B_9 and B_{12}, participating in the metabolism of Met and H_{cy}, are closely related to the FC enzymes, the activity of which depends on the state of their genes. Thus, the FC genes and vitamins B_9 and B_{12} are closely tied.

Vitamin B_9 (folic acid) in a human body is converted into its main form circulating in the blood — 5-methyltetrahydrofolate (5-MTHF) [72], which is a donor of the methyl group for the resynthesis of Met from H_{cy}. The most important role in this process is played by the MTHFR, which is a flavoprotein according to its chemical structure. It catalyzes the formation of 5-MTHF from 5,10-methylenetetrahydrofolate (5,10-MTHF) involving vitamin C [73].

A blood H_{cy} level is a marker for the effectiveness of this process.

The activity of MTHFR depends on the MTHFR: C677T genetic polymorphism.

This current research showed that the body experiences the maximum vitamin B_9 deficiency in cases of a homozygous T/T variant of the MTHFR:677 polymorphism [74]. At the same time, the maximum level of H_{cy} is reported in the blood (Fig.7.1, Tables 7.1, 7.2) [27, 71].

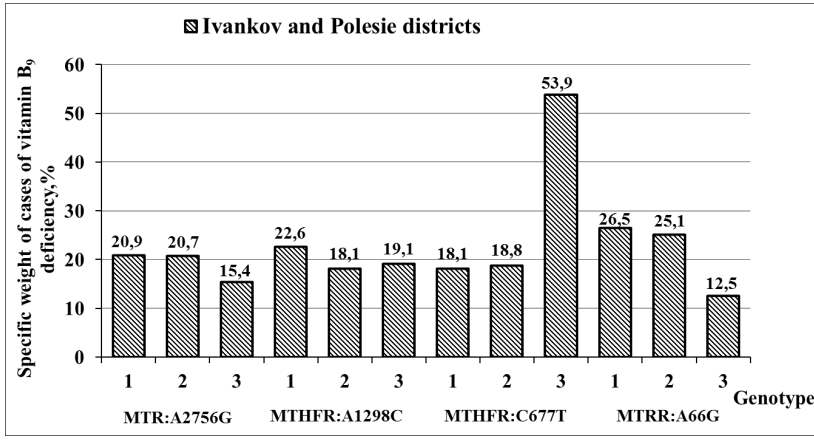

Fig. 7.1. Distribution of cases of vitamin B_9 deficiency in groups of children with different genotypes from Ivankovsky and Polessky districts.

Note.
MTR: A2756G: 1- AA; 2- AG; 3-GG;
MTHFR: A1298C: 1- AA; 2- AC; 3-CC;
MTHFR: C677T: 1-CC; 2- CT; 3-TT;
MTRR: A66G: 1-AA; 2- AG; 3-GG; [74].

Table 7.1

Statistical characteristics of H_{cy}, vitamins B_9, B_{12} in groups of children with genetic polymorphisms of the folate cycle (71)

Polymorphism, genotype	H_{cy}, µmol/L		B_{12}, pg/ml		B_9, ng/ml	
	Me	IQR	Me	IQR	Me	IQR
MTHFR:677T						
CC	11.4	9.5–13.1	315.5	266.5–469.0	6.6	5.4–8.0
CT	11.7	10.2–13.3	312.8	244.3–401.9	5.9	4.8–7.6
TT	16.2	13.0–26.3	317.6	254.7–446.1	4.5	3.6–6.5
Total group n=263	11.8	10.1–13.8	313.4	255.2–426.5	6.2	4.8–7.7

Note. Hcy — homocysteine, Me — median, IQR — interquartile range.

Table 7.2

Results of comparison of populations by quantitative criteria (non-parametric analysis)

Polymorphism, genotype		H_{cy}, µmol/L			B_{12}, pg/ml			B_9, ng/ml		
		Number of cases	Average rank	Mann-Whitney U test, significance p	Number of cases	Average rank	Mann-Whitney U test, significance p	Number of cases	Average rank	Mann-Whitney U test, significance p
MTHFR: C677T	CC	125	113.4	6295.5	125	123.2	6474.0	125	128.3	5839.0
	CT	112	125.3	p=0.181	112	114.3	p=0.318	112	108.6	p=0.028
MTHFR: C677T	CT	112	62.7	699.0	112	68.7	1365.5	112	74.3	918.0
	TT	26	98.6	p<0.0001	26	73.0	p=0.622	26	48.8	p=0.003
MTHFR: C677T	CC	125	68.5	689.0	125	76.4	1571.5	125	82.2	848.5
	TT	26	112.0	p<0.0001	26	73.9	p=0.792	26	46.1	p<0.0001

Correlation analysis confirms associations between H_{cy}, vitamins B_9 and B_{12}, and the MTHFR: C677T genetic polymorphism (Table 7.3) [27]. Thus, the greatest problems in the functioning of MTHFR occur in the case of presence of the genetic T allele of the MTHFR:677 polymorphism in the body. In the subjects with a homozygous variant of its inheritance (T/T MTHFR:677 genotype), the activity of MTHFR is significantly reduced. As a result, the formation of 5-MTHF, an active form of vitamin B_9, decreases, and therefore the delivery of methyl groups for the MTR enzyme system, in which vitamin B_{12} (cobalamin) acts as a cofactor. As a result, the blood concentration of H_{cy} increases.

Thus, the blood level of folic acid is determined by the state of the MTHFR genes.

MTR ensures the transfer of the methyl group from 5-MTHF to cobalamin and H_{cy} which results in the Met resynthesis. This enzyme is related to the MTR: A2756G genetic polymorphism.

In the case of homozygous carriage of the allele G MTR:2756, an enzyme is produced that, in most cases, is not capable of carrying out, with the help of cobalamin (vitamin B_{12}), the transfer of the methyl group to H_{cy}.

This is proved by a strong inverse association between H_{cy} and vitamin B_{12} in the group of children — carriers of the G/G MTR:2756 genotype. The less vitamin B_{12} in the blood, the more H_{cy} (Table 7.4). This group is characterized by a direct association between H_{cy} and vitamin B_6, illustrating the activation of a compensatory mechanism in the form of a trans-sulfuration reaction. The mechanism allows to convert the excess H_{cy} into Cyst with the help of the CBS. Vitamin B_6 is a cofactor for this enzyme. As the concentration of H_{cy} in the blood increases, the concentration of vitamin B_6 also increases (Table 7.4).

In the subjects with the G/G MTR:2756 genotype, in the absence of the MTHFR:677 genetic polymorphism T risk allele, a strong inverse association between H_{cy} and vitamin B_{12} remains,

and a direct association between H_{cy} and vitamin B_6 is enhanced. At the same time, there occur strong inverse associations between vitamins B_{12} and B_6, H_{cy} and vitamin B_9 (Table 7.5).

Table 7.3

Results of correlation analysis between H_{cy}, vitamins B_9, and B_{12}, number of polymorphisms, genetic risk variables in a total group of children (27)

Parameter	Correlation coefficient, significance p	Parameter			
		H_{cy}	B_{12}	B_9	Risk
H_{cy}	Spearman's (r_{xy})	1.000	- 0.377**	- 0.419**	0.227**
	Sign. (2-tailed)	.	0.0001	0.0001	0.0001
	N	263	263	263	263
B_{12}	Spearman's (r_{xy})	- 0.377**	1.000	0.245**	- 0.048
	Sign. (2-tailed)	0.0001	.	0.0001	0.435
	N	263	263	263	263
B_9	Spearman's (r_{xy})	- 0.419**	0.245**	1.000	- 0.234**
	Sign. (2-tailed)	0,0001	0.0001	.	0.0001
	N	263	263	263	263
Risk	Spearman's (r_{xy})	0.227**	- 0.048	- 0.234**	1.000
	Sign. (2-tailed)	0.0001	0.435	0.0001	.
	N	263	263	263	263

Note. The assessment of the analyzed genotypes MTHFR: C 677T in points (0–2) was carried out depending on their effect on the process of Hcy formation. Risk: "0" — C/C 677 genotype — no risk; "1" — C/T 677 genotype — low risk; "2" — T/T 677 genotype — high risk.
H_{cy} — homocysteine. N — number of observations. ** — Correlation is significant at the 0.01 level (2-tailed).

Thus, the normal functioning of MTHFR enhances the association between vitamins B_{12} and B_6, which are cofactors in the MTR and CBS.

Table 7.4

Results of correlation analysis between H_{cy}, vitamins B_9, B_{12}, B_6, in a group of children — carriers of G/G MTR:2756 genotype

Parameter	Correlation coefficient, significance p	Parameter			
		H_{cy}	B_{12}	B_9	B_6
H_{cy}	Spearman's (r_{xy})	1.000	**-.929****	-.385	**.674***
	Sign. (2-tailed)	.	.000	.194	.012
	N	13	13	13	13
B_{12}	Spearman's (r_{xy})	**-.929****	1.000	.429	-.531
	Sign. (2-tailed)	.000	.	.144	.062
	N	13	13	13	13
B_9	Spearman's (r_{xy})	-.385	.429	1.000	-.424
	Sign. (2-tailed)	.194	.144	.	.149
	N	13	13	13	13
B_6	Spearman's (r_{xy})	**.674***	-.531	-.424	1.000
	Sign. (2-tailed)	.012	.062	.149	.
	N	13	13	13	13

Note. H_{cy} — homocysteine, * — Correlation is significant at the 0.05 level (2-tailed). ** — Correlation is significant at the 0.01 level (2-tailed).

The decrease in the level of vitamin B_{12} in the blood, associated with the genetic mutation MTR:2756, stimulates an increase in the intake of vitamin B_6 in the body and the activation of CBS.

We tend to believe that it is the concentration of vitamin B_{12} in the blood, and not H_{cy}, that regulates the intake of vitamin B_6. Carriership of the MTHFR:677 polymorphism T allele also leads to an increase in blood H_{cy} levels, however, there is no association of the latter with vitamin B_6 (Table 7.6).

Table 7.5

Results of correlation analysis between H_{cy}, vitamins B_9, B_{12}, B_6, in a group of children — carriers of G/G MTR:2756 genotype in the absence of the T risk allele of the MTHFR: 677 genetic polymorphism

Parameter	Correlation coefficient, significance p	Parameter			
		H_{cy}	B_{12}	B_9	B_6
H_{cy}	Spearman's (r_{xy})	1.000	**-.964****	**-.786***	**.929****
	Sign. (2-tailed)	.	.000	.036	.003
	N	7	7	7	7
B_{12}	Spearman's (r_{xy})	**-.964****	1.000	.714	**-.857***
	Sign. (2-tailed)	.000	.	.071	.014
	N	7	7	7	7
B_9	Spearman's (r_{xy})	**-.786***	.714	1.000	-.643
	Sign. (2-tailed)	.036	.071	.	.119
	N	7	7	7	7
B_6	Spearman's (r_{xy})	**.929****	**-.857***	-.643	1.000
	Sign. (2-tailed)	.003	.014	.119	.
	N	7	7	7	7

Note. H_{cy} — homocysteine, * — Correlation is significant at the 0.05 level (2-tailed). ** — Correlation is significant at the 0.01 level (2-tailed).

In groups of children with neutral alleles of the studied polymorphisms, with a large number of cases of hyperhomocysteinemia, there is also no relationship between H_{cy} and vitamin B_6.

Based on the findings, it can be concluded that the state of the genetic apparatus of the FC determines the level of vitamins in the blood. This assertion indicates that it is necessary to take into account the state of the genetic apparatus of the folate cycle when determining vitamins B_9, B_{12} and B_6 status in a human body. There is an inverse association between H_{cy} and vitamins B_9 and B_{12} in the absence of serious mutations in the genes that control

the main enzyme systems of the FC: MTHR and B_{12} methionine synthase (a combination of C/C MTHFR:677 and A/A MTR:2756 genotypes in the same child in the research was observed in 29.7 % cases) (Fig.7.2). The occurrence of hyperhomocysteinemia in these cases may be associated with the insufficient intake of vitamins or with the effect of an external environmental factor(s) on metabolic processes at the post-transcriptional level. As such, one should consider ^{137}Cs and ^{90}Sr radionuclides incorporated into a human body, taking into account conditions of permanent residence of the studied children from the districts affected by the ChNPP accident.

Table 7.6

Results of correlation analysis between H_{cy}, vitamins B_9, B_{12}, B_6 in the group of children — carriers of T/T MTHFR:677 genotype

Parameter	Correlation coefficient, significance p	Parameter			
		H_{cy}	B_{12}	B_9	B_6
H_{cy}	Spearman's (r_{xy})	1.000	-.498**	-.545**	.066
	Sign. (2-tailed)	.	.010	.004	.750
	N	26	26	26	26
B_{12}	Spearman's (r_{xy})	-.498**	1.000	.303	-.135
	Sign. (2-tailed)	.010	.	.132	.509
	N	26	26	26	26
B_9	Spearman's (r_{xy})	-.545**	.303	1.000	-.013
	Sign. (2-tailed)	.004	.132	.	.950
	N	26	26	26	26
B_6	Spearman's (r_{xy})	.066	-.135	-.013	1.000
	Sign. (2-tailed)	.750	.509	.950	.
	N	26	26	26	26

Note. H_{cy} — homocysteine, * — Correlation is significant at the 0.05 level (2-tailed). ** — Correlation is significant at the 0.01 level (2-tailed).

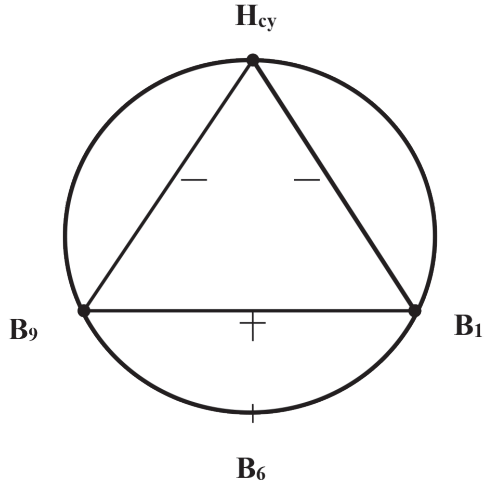

Fig. 7.2. Associations between metabolic variables in a group of children — carriers of a combination of A/A MTR:2756 — C/C MTHFR:677 genotypes (n=78).

The strength of an association was assessed according to a typical scale: weak — 0 to ±0.299; moderate — ±0.3 to ±0.699; strong — ± 0.7 to ±1.

Chapter 8.
Hyperhomocysteinemia in children and their mothers

This study involved 84 children (39 boys and 45 girls), whose average age at the time of laboratory examination in December 2015 was 15.5 ± 0.1 years, and 66 mothers, whose average age at the time of the examination was 42.61 ± 5.94 years [62].

The age of most mothers ranged from 7–11 years at the time of the ChNPP plant accident (April 1986) and 17–45 years at the time of birth of the children.

Taking into account the established age norms, hyperhomocysteinemia was observed in 79.8 % of cases in the group of children and in 31.8 % of cases ($p < 0.05$) in the group of their mothers. The involvement of the FC genes in this process was assessed.

The percentage of cases of hyperhomocysteinemia was found out to be statistically significantly higher in the subgroups of children with the absence or presence of one or two genetic polymorphisms with risk alleles than in the similar subgroups of mothers. At the same time, unlike the group of the children, a direct association between the percentage of cases of hyperhomocysteinemia and the number of genetic polymorphisms with risk alleles was observed in the group of mothers (Fig. 8.1, 8.2, Tabl. 8.1) [62].

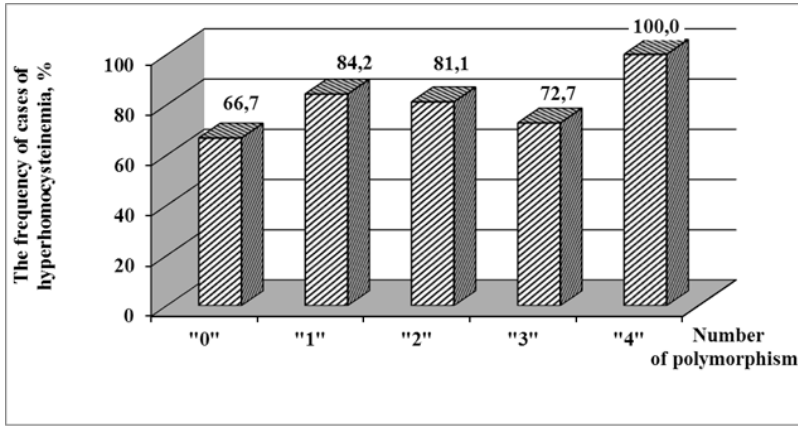

Fig. 8.1. The proportion of cases of hyperhomocysteinemia depending on the number of genetic polymorphisms with risk alleles in groups of children from the Polessky district who were examined on December 18, 2015 (62).

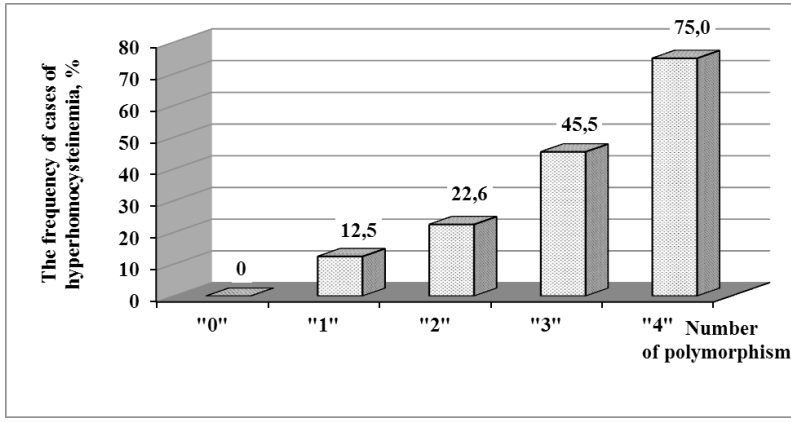

Fig. 8.2. The proportion of cases of hyperhomocysteinemia depending on the number of genetic polymorphisms with risk alleles in the group of mothers of children from Polessky district who were examined on December 18, 2015 (62).

Table 8.1

Results of correlation analysis between homocysteine and the number of genetic polymorphisms with risk alleles in groups of children and their mothers

Parameters	Correlation coefficient, r_{xy}	Parameters	
		Children	Mothers
H_{cy} and N pol.	Spearman's	-.060	.336*
	p	.590	.006
	N	84	66

Note. Hcy — homocysteine; N pol.— number of polymorphisms of folate cycle genes; * — correlation is significant at the 0.01 level (2-tailed).

No statistically significant differences were found in proportions of most polymorphic alleles of FC genes in the groups of children and their mothers. However, a MTHFR 677CT heterozygous genotype and a MTHFR 677CT/1298AC

heterozygous combination occurred statistically significantly more frequently in the group of mothers than in the group of children (Tables 8.2, 8.3, 8.4).

Table 8.2

Percentage of polymorphic alleles of FC genes in children

Gene, polymorphism	Neutral allele		Heterozygous risk allele		Homozygous risk allele	
	Abs. number	Percentage,%	Abs. number	Percentage,%	Abs. number	Percentage,%
MTR: A2756G	57	67.9	25	29.8	2	2.3
MTHFR: A1298C	47	55.9	25	29.8	12	14.3
MTHFR: C677T	44	52.4	29	34.5	11	13.1
MTRR: A66G	17	20.2	37	44.1	30	35.7

Table 8.3

Percentage of polymorphic alleles of FC genes in mothers

Gene, polymorphism	Neutral allele		Heterozygous risk allele		Homozygous risk allele	
	Abs. number	Percentage,%	Abs. number	Percentage,%	Abs. number	Percentage,%
MTR: A2756G	44	66.7	21	31.8	1	1.5
MTHFR: A1298C	34	51.5	29	43.9	3	4.6
MTHFR: C677T	24	36.4	34	51.5*	8	12.1
MTRR: A66G	10	15.2	30	45.5	26	39.4

Note. * — comparison between groups of children and mothers in the frequency of certain types of genetic polymorphisms presented in Tables 8.2 and 8.3, statistically significant differences ($p = 0.039864$) in the frequency of the heterozygous variant of the MTHFR: C677T polymorphism.

Table 8.4

Percentage of MTHFR genetic polymorphisms in groups

Group	677CT+677TT genotype		677CT/1298AC genotype	
	Abs. number (n)	Percentage,%	Abs. number (n)	Percentage,%
Children	40	47.6	9	10.7*
Mothers	42	63.6	20	30.3

Note. * — statistically significant differences between groups ($p < 0.05$).

Among carriers of T allele heterozygotes, the 677CT/1298AC compound heterozygous association was reported in 58.8 % (20 out of 34) of cases in the group of mothers and in 31.0 % (9 out of 29) of cases ($p = 0.028927$) in the group of children.

The compound heterozygosity for two 677T and 1298C alleles, as well as the homozygous variant of the MTHFR:667 genetic polymorphism T allele can lead to significant abnormalities in the process of homocysteine methylation [75, 76]. It is quite realistic that this was the cause of abnormal prenatal development and death of human embryos in the studied population of residents of Polessky district, which territory had been contaminated with the ^{137}Cs and ^{90}Sr radioactive elements after the ChNPP accident [77].

At the same time, both the germ cells of future parents at the stage of maturation, and prenatal embryos with combined 677CT/1298AC changes in the MTHFR gene could be damaged and die. This process resulted in the decrease in the birth of children with the 677CT/1298AC heterozygous association of the MTHFR gene.

The percentage of cases of carriership of the MTHFR:677 polymorphism T allele was statistically significantly higher in the MTR:2756AA and MTHFR:1298AC subgroups of mothers than in the similar subgroups of their children. No statistical differences in the percentage of cases of the T allele carriership were found in other FC genetic subgroups of children and their mothers (Table 8.5).

Table 8.5

Percentage of cases of carriership of MTHFR:677 polymorphism T allele in genetic subgroups of children and their mothers

Polymorphisms	Children		Mothers	
	Absolute number	Percentage, %	Absolute number	Percentage, %
MTR:2756GG	1	50.0	0	0
MTR:2756AG	15	60.0	12	57.1
MTR:2756AA	24	42.1	30	68.2*
MTHFR:1298CC	0	0	0	0
MTHFR:1298AC	9	36.0	20	69.0*
MTHFR:1298AA	31	66.0	22	64.7
MTHFR:677TT	11	100	8	100
MTHFR:677CT	29	100	34	100
MTHFR:677CC	0	0	0	0
MTRR:66GG	17	56.7	18	69.2
MTRR:66AG	17	46.0	17	56.7
MTRR:66AA	6	35.3	7	70.0
677CT+677TT	40	100	42	100
677CT/1298AC	9	100	20	100

Note. * Statistically significant differences between groups ($P<0.05$).

Despite this, the percentage of cases of hyperhomocysteinemia in most genetic subgroups of children was higher than in the similar subgroups of their mothers (Table 8.6).

An exception was the subgroups there the main genotypes were A/C MTHFR:1298 and the 677CT /1298AC MTHFR heterozygous association (Table 8.6).

A large number of cases of 677CT/1298AC compound heterozygosity of the MTHFR gene in the group of mothers were the cause of a high percentage of cases of hyperhomocysteinemia in the MTHFR:1298AC subgroup (Table 8.6).

Table 8.6

Number of cases of hyperhomocysteinemia in groups of children and mothers with FC polymorphisms

Polymorphisms	Children		Mothers	
	Absolute number	Percentage,%	Absolute number	Percentage, %
MTR:2756GG	2	100	0	0
MTR:2756AG	18	72.0	5	23.8
MTR:2756AA	47	82.5	16	36.4
MTHFR:1298CC	7	58.3	0	0
MTHFR:1298AC	19	76.0	15	51.7*
MTHFR:1298AA	41	87.2	6	17.7
MTHFR:677TT	11	100	4	50.0
MTHFR:677CT	25	86.2	14	41.2
MTHFR:677CC	31	70.5	3	12.5
MTRR:66GG	25	83.3	10	38.5
MTRR:66AG	29	78.4	9	30.0
MTRR:66AA	13	76.5	2	20.0
677CT+677TT	36	90.0	18	42.9
677CT /1298AC	8	88.9	13	65.0*

Note. * no statistical differences (p>0.05).

The percentage of the MTHFR gene A1298C and C677T risk alleles is statistically significantly higher in the group of mothers with hyperhomocysteinemia than in the similar group of children (Tables 8.7, 8.8).

The proportion of cases with the T allele in the group of mothers with hyperhomocysteinemia is statistically significantly higher than that in the total group of mothers (Table 8.9).

These differences are absent in the group of children (Table 8.10).

Table 8.7

Percentage of polymorphic alleles of FC genes in the group of children with hyperhomocysteinemia (n=67)

Genetic polymorphism	"Neutral" allele		"Heterozygous" risk allele		"Hetero- and homozygous" risk alleles	
	Abs. number	Percentage,%	Abs. number	Percentage,%	Abs. number	Percentage,%
MTR: A2756G	47	70.2	18	26.9	20	29.9
MTHFR: A1298C	41	61.2*	19	28.4*	26	38.8*
MTHFR: C677T	31	46.3*	25	37.3*	36	53.7*
MTRR: A66G	13	19.4	29	43.3	54	80.6

Note. *Statistically significant differences ($p<0.05$) in the frequency of neutral and risk alleles of MTHFR: C677T and MTHFR: A1298C polymorphisms between groups of children and mothers.

Table 8.8

Percentage of polymorphic alleles of FC genes in the group of mothers with hyperhomocysteinemia (n=21)

Genetic polymorphism	"Neutral" allele		"Heterozygous" risk allele		"Hetero- and homozygous" risk alleles	
	Abs. number	Percentage,%	Abs. number	Percentage,%	Abs. number	Percentage,%
MTR: A2756G	16	76.2	5	23.8	5	23.8
MTHFR: A1298C	6	28.6	15	71.4	15	71.4
MTHFR: C677T	3	14.3	14	66.7	18	85.7
MTRR: A66G	2	9.5	9	42.9	19	90.5

Thus, the genetic polymorphism MTHFR: C677T in mothers, to a greater extent, compared with their children, affects the level of H_{cy} in the blood.

Table 8.9

Percentage of risk alleles of MTHFR polymorphisms in the group of mothers

Group	MTHFR A1298C polymorphism C allele		MTHFR C677T polymorphism T allele	
	Abs. number (n)	Percentage,%	Abs. number (n)	Percentage,%
Total n=66	32	48.5	42	63.6
Hyperhomocysteinemia n=21	15	71.4**	18	85.7*

Note. * Statistical differences between the total group and the group with hyperhomocysteinemia — t= 2.31; P=0.024687. **There are no statistical differences between the total group and the group with hyperhomocysteinemia — t= 1.96; P=0.056298.

Table 8.10

Percentage of risk alleles of MTHFR polymorphisms in the group of children

Group	MTHFR A1298C polymorphism C allele		MTHFR C677T polymorphism T allele	
	Abs. number (n)	Percentage,%	Abs. number (n)	Percentage,%
Total n=84	37	44.0	40	47.6
Hyperhomocysteinemia n=67	26	38.8**	36	53.7*

Note. * There are no statistical differences between the total group and the group with hyperhomocysteinemia — t = 0.74; P = 0.460054. **There are no statistical differences between the total group and the group with hyperhomocysteinemia — t = 0.64; P = 0.521908.

At the same time, in mothers, even the carriage of the T allele of the MTHFR: C677T polymorphism does not always lead to a state of hyperhomocysteinemia. At the same time, in children, the state of hyperhomocysteinemia occurs even without the presence of the T allele in the genome.

In the absence of the C677T mutation in the MTHFR gene, the risk of hyperhomocysteinemia in mothers, compared with their children, is significantly lower.

It can be concluded that, in contrast to their mothers, children from areas located near the ChEZ have a disrupted mechanism of genetic control over metabolic processes in the body, in particular, over the exchange of Met and H_{cy}.

Congenital disorders of metabolic processes may be due to the impact on the reproductive system of future parents and developing fetuses of radioactive elements, primarily ^{137}Cs. Radionuclides present in the mother-fetal system have a negative impact on the processes of antenatal ontogenesis.

In this regard, the elimination of embryos with the genetic combination 677CT/1298AC MTHFR can be considered. This hypothesis is confirmed by congenital malformations of a multifactorial nature in the offspring of laboratory animals whose diet included products containing ^{137}Cs and ^{90}Sr radionuclides, in particular, oat grain grown in the Ivankovsky district (Fig. 8.3) [78, 79].

In addition to ^{137}Cs and ^{90}Sr radionuclides, grain grown in the fields of the Ivankovsky district contained, compared to grain grown on radiation-free soils, an increased amount of barium, manganese, strontium, and sulfur [79].

In the course of a project of the European Commission, a radiometric study of 362 placentas obtained in 2014–2017 during physiological childbirth by women in Ivankovsky district was carried out.

Fig. 8.3. Congenital malformations in 15-day-old embryos of Syrian hamsters. From left to right: exencephaly and cleft lip and palate; bilateral cleft lip; craniocerebral hernia (79).

^{137}Cs radionuclides with the specific activity of 0–5.9 Bq/kg were found in 105 placentas (29.0 %), with the specific activity of 6.0–10.9 Bq/kg — in 108 placentas (29.9 %), with the specific activity of 11.0–20.0 Bq/kg in 133 placentas (36.7 %), with the specific activity> 20.0 Bq/kg — in 16 placentas (4.4 %).

The disruption of the regulatory processes of the main metabolic cycles create conditions for the occurrence of pathological processes in the presence of a relatively weak external environmental impact, including ionizing radiation. In conditions of environmental distress, it is necessary to distinguish between the reaction of a human organism that has been exposed to radiation during antenatal ontogenesis and the reaction of a human organism being developed under physiological conditions. They are completely different in their essence and manifestations. The understanding of this will allow to develop effective measures to protect the population.

Chapter 9.
Changes in blood homocysteine levels in children after forest fires in the Chernobyl exclusion zone

As a result of the accident at the ChNPP in Ukraine, 4.0 million ha of forest lands were contaminated with radioactive elements, including 974.3 thousand ha in Zhytomyr region, 416.4 thousand ha in Kyiv region, 725.5 thousand ha in Chernigov region, 728.8 thousand ha in Rivne region [80].

During more than the 30-year Chernobyl post-accident period, soils of affected areas and, consequently, forest trees and bushes growing on them have accumulated a huge amount of radioactive elements. The greatest amount of radioactive fallout, in particular ^{137}Cs, fell within a 30-kilometer ChEZ [81].

In this regard, forest fires, frequently occurring here, being one of the most powerful sources of radioactive air pollution constitute a danger to human health.

At the same time, wood combustion products also have a negative effect on the human body [82]. Fine particles 0.1–2.5 μm in size (PM 2.5), including black carbon, penetrate the respiratory tract, reaching the bronchioles and alveoli [83]. This leads to elevated blood levels of a sulfur-containing amino acid H_{cy} and the development of oxidative stress in the presence of a certain genetic predisposition [84]. Long-term exposure to fine particles (PM 2.5) can be the cause of the development or exacerbation of cardiometabolic disorders, leading to fatal outcomes [85, 86].

H_{cy} is considered to be a participant in an intracellular oxidation process, which is the basis for the effects of the fine particles on the cardiovascular system [87].

One of the largest fires of forest and meadow vegetation in the ChEZ (spread area — 10127 ha) occurred on 26–29 April 2015 [88].

In addition, a forest fire affecting an area of 130 ha was recorded in the same territory during the period 29 May to 5 June 2015 [89].

In the areas of surface fire, the maximum density of the territory contamination in some divisions of Lubyanskoye forestry was 1040 kBq/sq. m — ^{137}Cs; 368 kBq/sq. m — ^{90}Sr; 11.4 kBq/sq. m — $^{238–240}$Pu and 14.4 kBq/sq. m — ^{241}Am [88].

To assess the effect of forest fires on the metabolism of H_{cy}, we used results of laboratory examination of 84 children (39 boys and 45 girls) living in Polessky district [90].

In order to measure the H_{cy} concentration and carry out genetic analysis of the FC, each child had blood drawn from the ulnar vein after fasting in the morning twice on 02/04/2015 and 18/12/2015. The blood samples were analysed at a laboratory certified under quality standards and were agreed with the parents. The average age of the children at the time of laboratory examination was 15.5 ± 0.1 years (95 % CI 15.4–15.7 years).

The proportion of cases of hyperhomocysteinemia was significantly higher in the total group of children, and in most of the separate subgroups compiled on the basis of 100 % inheritance of separate genotypes of the FC during Measurement 2 than during the Measurement 1 (Tables 9.1, 9.2). There were no statistical differences in the subgroups where the main genotypes were homozygous variants of risk alleles of the studied genetic polymorphisms of the FC: MTR:2756G/G, MTHFR:1298C/C, MTHFR:677T/T, MTRR:66G/G (Tables 9.1, 9.2). In addition, significant statistical dynamics of cases of hyperhomocysteinemia was absent in the subgroups where the main genotypes were the MTHFR:1298 A/C and MTHFR:677 C/T heterozygous variants.

The H_{cy} level was statistically higher in a total group of children and in most of the studied subgroups during Measurement 2 in comparison with Measurement 1. The exceptions were subgroups with the main genotypes: MTR:2756 G/G, MTHFR:1298 C/C и MTHFR:677 T/T (Tables 9.3, 9.4).

Table 9.1

Dynamics of hyperhomocysteinemia in subgroups of children with different genotypes (n = 84)

Polymorphisms, genotypes	Number of cases	Hyperhomocysteinemia					
		Measurement dated 02/04/2015		Measurement dated 18/12/2015		Increase	
		Abs. number	%	Abs. number	%	Abs. number	%
MTR:2756A/A	57	35	61.4	47	82.5	12	21.1
MTR:2756A/G	25	11	44.0	18	72.0	7	28.0
MTR:2756G/G	2	2	100.0	2	100.0	0	0
MTHFR:1298A/A	47	26	55.3	41	87.2	15	31.9
MTHFR:1298A/C	25	15	60.0	19	76.0	4	16.0
MTHFR:1298C/C	12	7	58.3	7	58.3	0	0
MTHFR:677C/C	44	20	45.5	31	70.5	11	25.5
MTHFR:677C/T	29	19	65.5	25	86.2	6	20.7
MTHFR:677T/T	11	9	81.8	11	100.0	2	18.2
MTRR:66A/A	17	7	41.2	13	76.5	6	35.3
MTRR:66A/G	37	20	54.1	29	78.4	9	24.3
MTRR:66G/G	30	21	70.0	25	83.3	4	13.3
MTR:2756A/A-MTHFR:677C/C	33	16	48.5	25	75.8	9	27.3
Total group	84	48	57.1	67	79.8	19	22.6

During the analyzed period, an increase in H_{cy} levels in the blood was observed in the total group in 67 out of 84 children (79.8 %), it was absent in 17 children (20.2 %), $p < 0.05$, including 33 boys (84.6 % of the number of boys in the group) and 34 girls (75.6 % of the number of girls in the group).

Table 9.2

Results of comparison of proportions of cases of hyperhomocysteinemia in subgroups of children with different genotypes in view of two measurements of H_{cy}

Genotype	t	p
MTR:2756A/A	2.57	0.011955
MTR:2756A/G	2.09	0.046276
MTR:2756G/G	-	-
MTHFR:1298A/A	3.63	0.000567
MTHFR:1298A/C	1.23	0.226711
MTHFR:1298C/C	-	-
MTHFR:677C/C	2.45	0.017846
MTHFR:677C/T	1.90	0.064163
MTHFR:677T/T	1.57	0.135081
MTRR:66A/A	2.24	0.038520
MTRR:66A/G	2.28	0.027220
MTRR:66G/G	1.23	0.225148
MTR:2756A/A- MTHFR:677C/C	2.37	0.023113
Total group	3.26	0.001481

The proportion of cases of an individual increase in the blood H_{cy} level was recorded at a level of over 70.0 % in each of the observed genetic subgroups (Table 9.5).

Thus, the largest increase in cases of hyperhomocysteinemia was recorded in children who had no risk alleles of FC polymorphisms in their genome, or who were heterozygous carriers of these alleles.

In this regard, the most vivid example was a subgroup, where the main genotype was a combination of neutral homozygotes of MTR:2756 and MTHFR:677 polymorphisms, which control the processes of H_{cy} methylation: MTHFR and MTR. The children of this subgroup showed an increase in the blood level of H_{cy},

the number of cases of hyperhomocysteinemia, as well as a very high proportion of cases of an individual increase in H_{cy}, which indicates the influence of an external environmental factor on the body of the examined children.

Table 9.3

Statistical characteristics of H_{cy} values in the blood of examined children

Genotype		H_{cy} 1, µmol/L			H_{cy} 2, µmol/L		
		N	Me	IQR	N	Me	IQR
MTR: 2756	A/A	57	10.7	9.0–14.1	57	12.8	11.2–15.8
	A/G	25	9.4	7.8–10.7	25	10.6	9.8–12.7
	G/G	2	12.0	8.5–9.5	2	13.0	9.7–9.8
MTHFR: 1298	A/A	47	10.3	8.0–13.3	47	12.6	10.9–14.5
	A/C	25	10.7	9.1–12.9	25	12.0	10.1–14.4
	C/C	12	10.3	7.8–12.6	12	10.8	9.4–16.9
MTHFR: 677	C/C	44	9.7	7.7–11.1	44	11.4	9.7–14.1
	C/T	29	11.0	9.1–12.9	29	12.0	10.6–13.4
	T/T	11	14.5	10.2–19.0	11	15.0	13.2–22.1
MTRR: 66	A/A	17	9.3	7.2–13.0	17	11.5	9.8–13.0
	A/G	37	10.3	7.9–12.6	37	12.0	10.4–14.3
	G/G	30	10.9	9.3–14.5	30	12.9	10.6–16.7
MTR:2756A/A-MTHFR:677C/C		33	9.7	7.5–12.2	33	12.5	10.0–14.9
Total group		84	10.3	8.0–13.1	84	12.3	10.4–14.5

This genetic combination is the most informative from the point of view of control over the state of the metabolism of H_{cy} and Met when the body is exposed to exogenous factors.

Carriership of homozygous variants of risk alleles of the studied FC polymorphisms, primarily the MTHFR: C677T genetic polymorphism, results in a high blood H_{cy} level, irrespective of the impact of environmental factors.

Table 9.4

Results of non-parametric analysis (Wilcoxon's T test) of comparison of two samples: H_{cy} "1" and H_{cy} "2"

Genotype	Standardized Wilcoxon's T test value	Asymptotic significance (2-tailed), p
MTR: 2756 A/A	- 4.660	0.0001
A/G	- 2.852	0.004
G/G	- 1.342	0.180*
MTHFR:1298 A/A	- 4.318	0.0001
A/C	- 2.866	0.004
C/C	- 1.804	0.071*
MTHFR:677 C/C	- 4.773	0.0001
C/T	- 3.081	0.002
T/T	- 1.156	0.248*
MTRR:66 A/A	- 2.391	0.017
A/G	- 4.186	0.0001
G/G	- 3.054	0.002
MTR:2756A/A-MTHFR:677C/C	-4.440	0.0001
Total group	-5.566	0.0001

Note. * — There is no statistical confidence ($p > 0.05$).

The proportion of cases of hyperhomocysteinemia in the group of children of Ivankovsky and Polessky districts was 48.8 % (98 out of 201) [25] when measuring on 02/04/2015, while when measuring on 18/12/2015 it was 75.3 % (198 out of 263) [27], which has a statistically significant difference: $t=5.99$; $p<0.000001$.

These differences are not associated with the FC genes, since the proportion of polymorphic alleles of the analyzed groups had no statistical differences (Tables 9.6, 9.7).

Table 9.5

Proportions of cases of an individual increase in the blood level of H_{cy} in subgroups of children with different genotypes

Genotype	Number of cases	An increase in a blood homocysteine level	
		Abs. number	%
MTR: 2756 A/A	57	44	77.2
MTR:2756A/G	25	21	84.0
MTR:2756G/G	2	2	100
MTHFR:1298 A/A	47	40	85.1
MTHFR:1298 A/C	25	19	76.0
MTHFR:1298 C/C	12	8	66.7
MTHFR:677 C/C	44	38	86.4
MTHFR:677C/T	29	21	72.4
MTHFR:677T/T	11	8	72.7
MTRR:66A/A	17	13	76.5
MTRR:66A/G	37	33	89.2
MTRR:66G/G	30	21	70.0
MTR:2756A/A- MTHFR:677C/C	33	29	87.9
Total group		67	79.8

There were statistical significant differences between the H_{cy} >10 μmol/L and H_{cy}<10 μmol/L subgroups in terms of the prevalence of a number of FC polymorphisms in the group of children examined on 02/04/2015 (Tables 9.8, 9.9).

This confirms the role of the genetic system of the FC in the induction of hyperhomocysteinemia. However, there were no differences between the H_{cy} > 10 μmol/L and H_{cy} < 10 μmol/L

subgroups in the prevalence of studied FC polymorphisms in the group of children examined on 18/12/2015 (Tables 9.10, 9.11).

Table 9.6

Frequency of polymorphic alleles of FC genes in a group of children examined on 02/04/2015 (25)

Gene, polymorphism	«Neutral» allele		«Heterozygous» risk allele		«Homozygous» risk allele	
	Abs. number	Percentage,%	Abs. number	Percentage,%	Abs. number	Percentage,%
MTR: A2756G	133	66.2	57	28.4	11	5.4
MTHFR: A1298C	99	49.3	80	39.8	22	10.9
MTHFR: C677T	103	51.2	78	38.8	20	10.0
MTRR: A66G	42	20.9	91	45.3	68	33.8

The findings show that during the period 02/04/2015–18/12/2015 an increase in the blood H_{cy} level in children living in the district bordering the ChEZ is not associated with the state of the FC genes.

Table 9.7

Frequency of polymorphic alleles of FC genes in a group of children examined on 18/12/2015 (27)

Gene, polymorphism	«Neutral» allele		«Heterozygous» risk allele		«Homozygous» risk allele	
	Abs. number	Percentage,%	Abs. number	Percentage,%	Abs. number	Percentage,%
MTR: A2756G	163	62.0	87	33.1	13	4.9
MTHFR: A1298C	137	52.1	105	39.9	21	8.0
MTHFR: C677T	125	47.5	112	42.6	26	9.9
MTRR: A66G	44	16.7	131	49.8	88	33.5

Table 9.8

Frequency of polymorphic alleles of FC genes in children with H_{cy} > 10 μmol/L (n=98). Analysis dated 02/04/2015

Gene, polymorphism	«Neutral» allele		Risk allele, heterozygous form of mutation		Risk allele, homozygous form of mutation	
	Abs. number	Percentage,%	Abs. number	Percentage,%	Abs. number	Percentage,%
MTR: A2756G	69	70.4	21	21.4	8	8.2
MTHFR: A1298C	47	48.0	41	41.8	10	10.2
MTHFR: C677T	40	40.8	42	42.9	16	16.3
MTRR: A66G	13	13.3	45	45.9	40	40.8

Table 9.9

Frequency of polymorphic alleles of FC genes in children with H_{cy} < 10 μmol/L (n=103). Analysis dated 02/04/2015

Gene, polymorphism	«Neutral» allele		Risk allele, heterozygous form of mutation		Risk allele, homozygous form of mutation	
	Abs. number	Percentage,%	Abs. number	Percentage,%	Abs. number	Percentage,%
MTR: A2756G	64	62.1	36	35.0[3]	3	2.9
MTHFR: A1298C	52	50.5	39	37.9	12	11.7[4]
MTHFR: C677T	63	61.2[1]	36	35.0	4	3.9[5]
MTRR: A66G	29	28.2[2]	46	44.7	28	27.2[6]

Note. [1] statistical differences in the analyzed subgroups of the proportion of the C/C genotype MTHFR:677: $p<0.01$; [2] statistical differences in the analyzed subgroups of the proportion A/AMTRR:66: $p<0.05$; [3] statistical differences in the analyzed subgroups of the proportion of the genotype A/GMTR:2756: $p<0.05$; [4] statistical differences in the analyzed subgroups of the proportion of the genotype T/TMTHFR:677: $p<0.01$; [5] statistical differences in the analyzed subgroups of the proportion of the G/GMTRR:66 genotype: $p<0.05$.

Table 9.10

The presence of polymorphic alleles of the FC genes in the examined children with the H_{cy} level > 10 μmol/L, (n = 198). Analysis dated 18/12/2015

Gene, polymorphism	«Neutral» allele		«Heterozygous» risk allele		«Homozygous» risk allele	
	Abs. number	%	Abs. number	%	Abs. number	%
MTR: A2756G	124	62.6	67	33.8	7	3.6
MTHFR: A1298C	105	63.0	82	41.4	11	5.6
MTHFR: C677T	88	44.4	87	44.0	23	11.6
MTRR: A66G	31	15.7	98	49.5	69	34.8

Table 9.11

The presence of polymorphic alleles of the FC genes in the examined children with the H_{cy} level <10 μmol/L, (n = 65). Analysis dated 18/12/2015

Gene, polymorphism	«Neutral» allele		«Heterozygous» risk allele		«Homozygous» risk allele	
	Abs. number	%	Abs. number	%	Abs. number	%
MTR: A2756G	39	60.0	20	30.8	6	9.2
MTHFR: A1298C	32	49.2	23	35.4	10	15.4
MTHFR: C677T	37	56.9	25	38.5	3	4.6
MTRR: A66G	14	21.5	32	49.2	19	29.2

The main reason for the increase in the blood level of H_{cy} in children should be considered the forest fires with an area of 10127 ha and 130 ha, officially recorded on the territory of the ChEZ in the spring-summer of 2015.

Wood combustion particles, including black carbon, ^{137}Cs and radioactive elements, spread with air currents from the fire

epicenters over significant distances and penetrated into the body of adults and children — residents of adjacent districts.

At the same time, an increase in H_{cy} levels occurred in the cells of their body [25, 27], leading to the formation of reactive oxygen intermediates and oxidation of proteins, lipids, carbohydrates and nucleic acids [87]. Oxidative stress caused disturbances in the state of the cardiovascular system in the examined group of children from Ivankovsky and Polessky districts [14, 16].

Despite the established association between wood combustion products and blood H_{cy} levels [83, 84], we are inclined to believe that the increase in the blood concentration of H_{cy} in children from the districts adjacent to the ChEZ — is to the fullest extent associated with radioactive elements distributed long distances with air currents from the place of burning of forest trees. The examined children lived in the settlements located near areas of a surface fire on the territory of the ChEZ a maximum density of contamination of 1040 kBq/sq. m for ^{137}Cs; 368 kBq/sq. m for ^{90}Sr; 11.4 kBq/sq. m for $^{238–240}$Pu and 14.4 kBq/sq. m for ^{241}Am [88, 91].

A negative effect of incorporated radioactive elements on H_{cy} methylation is confirmed by the results of experiments in which oats grown on the territory affected by the ChNPP accident, containing ^{137}Cs radionuclides at a concentration of 445.7 Bq/kg and ^{90}Sr at a concentration of 15.5 Bq/kg was used as food for experimental animals. The oats fed to the control group animals contained ^{137}Cs at a concentration of 44.2 Bq/kg, ^{90}Sr — 1.7 Bq/kg. The experiment lasted 28 days. An increase in ^{137}Cs levels and a decrease in Met levels in tissues of liver and skeletal muscles [92] were found in the body of animals of the experimental group in comparison with that of the control group; it may indicate an abnormality in the resynthesis of methionine from H_{cy}.

In light of the findings, a mandatory element of the programme for the protection of health of the child population

in districts affected by the ChNPP accident is regular monitoring of the blood level of H_{cy}.

Effects of exposure to combustion products are known to be enhanced in the presence of low blood plasma folate and vitamin B_{12} levels [87].

The inverse correlations of H_{cy}-B_9 and H_{cy}-B_{12} [93, 94] revealed by us predetermine the use of active forms of vitamins B_9 and B_{12}, as well as vitamin B_6 as measures to prevent the occurrence of hyperhomocysteinemia in children and adults during forest fires in the ChEZ.

Chapter 10.
Socio-economic factors as a cause of folic acid deficiency and an increase in the content of homocysteine in the body of children

The studies showed an association between the blood content of H_{cy} and vitamins B_9, B_{12}, B_6.

In order to determine the causes of hyperhomocysteinemia, it is important to identify how the socio-economic conditions in which children live affect the content of folic acid in their body, and, consequently, H_{cy}.

The comparison groups included children from two districts adjacent to the ChEZ. Ivankovsky district is more developed in terms of economy and has better infrastructure, its population as of January 1, 2020 was 29,174 people. It is located closer to Kyiv, in comparison with Polessky district, in which 5,456 people lived as of January 1, 2020 [95]. The social and living conditions of the adult and child population in Ivankovsky district are much better than in Polessky district [96].

The studies conducted on 18/12/2015 showed that the blood concentration of folic acid in children from Polessky district is statistically significantly lower than in those from Ivankovsky district. At the same time, the concentration of vitamin B_6 is statistically significantly higher (Tables 10.1, 10.2) as well as the proportion of cases where its values are above the physiological level (Table 10.3) [94].

Table 10.1

Statistical characteristics of blood values of H_{cy} and vitamins B_6, B_9, B_{12} in examined children

Variables	Polessky district		Ivankovsky district	
	Me	IQR	Me	IQR
H_{cy}, μmol/L	12.0	10.14–14.35	11.61	9.69–13.35
B_6, μg /l	21.55	17.80–25.70	18.90	14.9–22.4
B_9, ng/ml	5.87	4.54–7.04	6.53	5.10 - 7.95
B_{12}, pg/ml	316.2	255.8–434.7	309.10	255.10–422.40

Table 10.2

Results of statistically significant differences when comparing blood metabolic variables of examined children from Polessky[1] and Ivankovsky[2] districts

Variables	Comparison groups	Comparison group size	Average rank	U test value, significance p
H_{cy}, μmol/L	1	102	146.75	U = 8543.0; p = 0.371
	2	179	137.73	
B_6, μg /l	1	102	165.95	U = 6584.0; p = 0.0001
	2	179	126.78	
B_9, ng/ml	1	102	123.99	U = 7393.5; p = 0.008
	2	179	150.70	
B_{12}, pg/ml	1	102	142.92	U = 8933.0; p = 0.765
	2	179	139.91	

Note. 1 — Group 1; 2 — Group 2.

Table 10.3

Proportion of cases with values different from the reference values

Variables	Polessky district			Ivankovsky district		
	N[1]	Number of cases	Proportion,%	N	Number of cases	Proportion,%
H_{cy}, μmol/L	102	78	76.5	179	131	73.2
B_9, ng/ml	102	26	25.5	179	29	16.2
B_{12}, pg/ml	102	5	4.9	179	9	5.0
B_6, μg /l	102	23	22.6	179	19	10.6*

Note. * — significant statistical differences between the groups (p = 0.014720); ** — values below the reference values were taken into account when assessing B_9 — 4.6 ng/ml, B_{12} — 191 pg/ml; above the reference values — when assessing H_{cy} — 10 μmol/L, B_6 — 27.2 μg/l; N[1] — the size of the surveyed group.

No statistically significant differences in folic acid values were found in the subgroups of children from the both districts with a homozygous T/T variant of the MTHFR:677 genetic polymorphism.

In view of this, there were no differences between the children of two districts in the content of folic acid in the blood in case of the maximum blocking of the MTHFR function. These differences existed in the subgroups of children — carriers of the C/C and even C/T genotypes (Tables 10.4, 10.5).

Taking into account the fact that there were no differences in the proportion of polymorphic alleles of the FC genes [97] between the groups of children from Polessky and Ivankovsky districts we can assume that lower values of folic acid in the blood of children from Polessky district compared to children from Ivankovsky district are associated with social and living conditions of their residence. Thus, in addition to radiation exposure and gene mutations, the alimentary factor in the form of insufficient intake of vitamin B_9 should be noted among the

reasons for disturbed functioning of the FC in children living in areas affected by the ChNPP accident. The increased blood level of vitamin B_6 should be considered as a compensatory mechanism associated with transsulfuration reactions in which Cyst is formed from H_{cy} and Ser involving CBS, and then Cys is formed.

Table 10.4

Statistical characteristics of serum content of vitamin B_9 in children from Ivankovsky and Polessky districts, (ng/ml)

Genotype	Ivankovsky district			Polessky district		
	Number of cases	Me	IQR	Number of cases	Me	IQR
Homozygous TT	15	5.3	4.0–6.6	11	4.3	3.3–5.3
Other variants	164	6.5	5.2–8.0	73	5.8	4.6–7.1
With the T allele	98	6.1	4.8–7.6	40	4.9	4.0–6.6
Without the T allele	81	6.9	5.6–8.2	44	6.2	5.1–7.0

Table 10.5

Results of statistically significant differences when comparing serum values of vitamin B_9 in examined children from Ivankovsky and Polessky districts

District	Comparison groups	Comparison group size	Average rank	U test value, significance p
Ivankovsky	Homozygous TT	15	15.53	U = 52.00; p = 0.113
Polessky		11	10.73	
Ivankovsky	Other variants	164	127.05	U = 4666.50; p = 0.007
Polessky		73	100.92	
Ivankovsky	With the T allele	98	75.78	U = 1345.00; p = 0.004
Polessky		40	54.13	
Ivankovsky	Without the T allele	81	68.71	U = 1319.50; p = 0.0017
Polessky		44	52.49	

Vitamin B_6 is a cofactor of this enzyme. In the group of children from Polessky district, a direct association was found between values of vitamins B_9 and B_6 indicating activation of regulatory processes aimed at reducing the H_{cy} content in the blood (Table 10.6). In particular, this can occur in the case of blockage of MTR and disruption of the transfer of a methyl group from 5-MTHF to H_{cy}. At the same time, the excess of 5-MTHF is formed, which stimulates the intake of B_6, thereby activating CBS.

Table 10.6

Associations between H_{cy}, vitamins B_6, B_9, B_{12} in the group of children from Polessky district

Parameter	Correlation coefficient (r_{xy}), significance level (p)	Parameter			
		H_{cy}	B_6	B_9	B_{12}
H_{cy}	Spearman's	1.000	-.024	-.432**	-.320**
	Significance level, p	,	.814	.000	.001
	N	102	102	102	102
B_6	Spearman's	-.024	1.000	.453**	.086
	Significance level, p	.814	,	.000	.389
	N	102	102	102	102
B_9	Spearman's	-.432**	.453**	1.000	.232*
	Significance level, p	.000	.000	,	.019
	N	102	102	102	102
B_{12}	Spearman's	-.320**	.086	.232*	1.000
	Significance level, p	.001	.389	.019	,
	N	102	102	102	102

Note. * — Correlation is significant at the 0.05 level (2-tailed). ** — Correlation is significant at the 0.01 level (2-tailed).

Chapter 11.
Homocysteine and Calcium-Phosphorus Metabolism

It is of great importance to investigate mechanisms of regulation of calcium-phosphorus metabolism when organising therapeutic and preventive measures against osteoporosis, a metabolic skeletal disorder characterised by decreased bone mass and increased risk of fractures [98].

Gender/age dependence of this disorder has been noted [99, 100]. Epidemiological cohort studies have shown a strong direct association between the serum H_{cy} concentration and prevalence of bone fractures due to osteoporosis [101]. It has been inferred that H_{cy} affects mineral metabolism and is a predictor of bone fractures in adults [102].

Hyperhomocysteinemia in children's groups has not been diagnosed so far. However, studies conducted in 2013–2017 within projects of the European Commission and the Rhône-Alpes Regional Council (France) have found prevalence of hyperhomocysteinemia of more than 75 % for adolescents living in districts of Ukraine affected by the ChNPP accident [62, 97].

Taking this into account, the question on whether there is an association between H_{cy} and mineral metabolism in the human body developing under constant exposure to a radiation factor is of immediate interest.

Since the basis of a bone tissue is a combination of calcium (Ca) and phosphorus (P) in the form of calcium hydroxyapatite, first of all, it is necessary to assess associations of H_{cy} with these elements.

The regulation of the blood ionized calcium (Ca^{2+}) level is thought to be carried out through the synthesis of parathyroid hormone (PTH). The parathyroid gland detects serum Ca^{2+}

levels via a sensing receptor CaSR and regulates the synthesis and secretion of PTH [103].

High blood Ca^{2+} levels activate the CaSR leading to a decrease in PTH secretion. Under conditions of hypocalcemia, there is an increase in PTH secretion, which stimulates osteoclastic resorption of bone tissue, and also contributes to an increase in the reabsorption of Ca^{2+} by the kidneys [104].

However, in the group of examined children from a Chernobyl district, during a correlation analysis, a direct association was found between Ca^{2+} и H_{cy}, and at the same time there was no association of Ca^{2+} with P (Table 11.1), as well as with PTH and other hormones that affect mineral metabolism, including pituitary thyroid-stimulating hormone (TSH), triiodothyronine (T_3), thyroxine (T_4), cortisol (C), calcitonin (Ct) and testosterone (Tes) [105].

The effect of the direct association between serum H_{cy} and Ca^{2+} was associated with carriership of the T allele of the MTHFR:677 genetic polymorphism responsible for the synthesis of one of the main enzymes of the FC — MTHFR.

In the absence of the T allele in the genome of children (C/C MTHFR:677 and C/C MTHFR:1298 subgroups), or, with its minimal presence (the A/C MTHFR:1298 subgroup), there was no association between H_{cy} and Ca^{2+} (Fig. 11.1, Table 11.2) [106].

The maximum strength of the association between values of these metabolites was found in the subgroup of children with the T/T MTHFR:677 genotype [106].

At the same time, the proportion of cases of hyperhomocysteinemia was 79.0 %, while in the subgroup with the C/C MTHFR:677 genotype it was 43.0 % [107].

An inverse association was recorded between Ca and TSH (r_{xy} = –0.638**, p = 0.003; n = 19) in the subgroup with the T/T MTHFR:677 genotype [107].

In the presence of hyperhomocysteinemia, the direct association between Ca and H_{cy} may indicate that, first of all, bone

tissue demineralisation has occurred. This postulate is confirmed by the studies on establishing an association between H_{cy} and the development of osteoporosis in adults [108]. Persons with a high blood H_{cy} level had decreased mineral bone density [109].

Table 11.1

Results of correlation analysis between values of Ca^{2+}, P and metabolic variables in children examined (105)

Parameters	Elements of correlation analysis	Parameters	
		P, mmol/L	Ca^{2+}, mmol/L
H_{cy}, μmol/L	Correlation coefficient	Spearman's 0.046	Spearman's 0.314**
	Sign. (2-tailed), p	0.564	0.0001
	N	158	158
PTH, pg/mL	Correlation coefficient	Spearman's 0.301**	Spearman's –0.031
	Sign. (2-tailed), p	0.0001	0.703
	N	158	158
Tes, nmol/L	Correlation coefficient	Spearman's –0.050	Spearman's –0.090
	Sign. (2-tailed), p	0.530	0.261
	N	158	158
C, μg/dL	Correlation coefficient	Spearman's –0.172*	Spearman's 0.022
	Sign. (2-tailed), p	0.030	0.780
	N	158	158
TSH, μIU/mL	Correlation coefficient	Spearman's 0.178*	Spearman's 0.013
	Sign. (2-tailed), p	0.026	0.871
	N	158	158

Table No 11.1 continuation

Parameters	Elements of correlation analysis	Parameters	
		P, mmol/L	Ca^{2+}, mmol/L
T_3, pg/mL	Correlation coefficient	Spearman's 0.290**	Spearman's –0.009
	Sign. (2-tailed), p	0.0001	0.907
	N	158	158
T_4, ng/dL	Correlation coefficient	Pearson's –0.250**	Spearman's –0.079
	Sign. (2-tailed), p	0.002	0.326
	N	158	158
Ca^{2+}, mmol/L	Correlation coefficient	Pearson's –0.096	Pearson's 1
	Sign. (2-tailed), p	0.230	-
	N	158	158
P, mmol/L	Correlation coefficient	Pearson's 1	Pearson's –0.096
	Sign. (2-tailed), p	-	0.230
	N	158	158
Ct, pg/mL	Correlation coefficient	Spearman's –0.026	Spearman's 0.058
	Sign. (2-tailed), p	0.744	0.472
	N	158	158

Note. * — Correlation is significant at the 0.05 level (2-tailed). ** — Correlation is significant at the 0.01 level (2-tailed).

Thus, hyperhomocysteinemia in children from Chernobyl districts being combined with hypercalcemia may indicate that there is improper skeletal system formation associated with its demineralization. At the same time, there are no associations of Ca with hormones regulating mineral metabolism, first of all, with PTH.

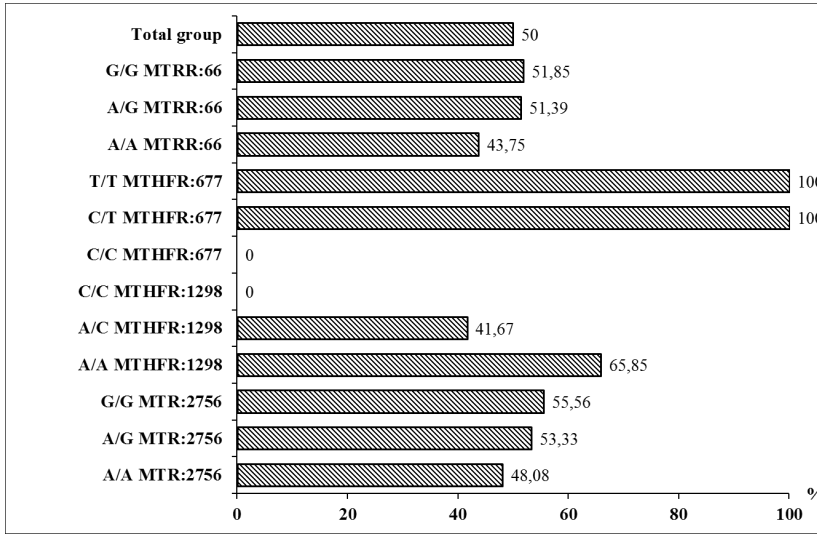

Fig. 11.1. The proportion of carriership of MTHFR: C677T polymorphism T allele in the genetic groups of children (106).

Table 11.2

Results of correlation analysis between values of H_{cy} and Ca^{2+}, H_{cy} and PTH in groups of children with genetic polymorphisms (106)

Polymorphism, genotype	Parame-ter	Correlation coefficient	Parameter	
			Ca^{2+} mmol/L	PTH, pg/mL
A/A MTR:2756	H_{cy}, μmol/L	Spearman's	0.319**	0.025
		Sign. (2-tailed), p	0.001	0.800
		N	104	104
A/G MTR:2756	H_{cy}, μmol/L	Spearman's	0.362*	-0.048
		Sign. (2-tailed), p	0.014	0.755
		N	45	45

Table No 11.2 continuation

Polymorphism, genotype	Parameter	Correlation coefficient	Parameter	
			Ca^{2+} mmol/L	PTH, pg/mL
G/G MTR:2756	H_{cy}, μmol/L	Spearman's	0.201	-0.767*
		Sign. (2-tailed), p	0.604	0.016
		N	9	9
A/A MTHFR:1298	H_{cy}, μmol/L	Spearman's	0.462**	-0.020
		Sign. (2-tailed), p	0.0001	0.858
		N	82	82
A/C MTHFR:1298	H_{cy}, μmol/L	Spearman's	0.216	0.126
		Sign. (2-tailed), p	0.097	0.338
		N	60	60
C/C MTHFR:1298	H_{cy}, μmol/L	Spearman's	-0.192	-0.389
		Sign. (2-tailed), p	0.476	0.137
		N	16	16
C/C MTHFR:677	H_{cy}, μmol/L	Spearman's	0.169	-0.099
		Sign. (2-tailed), p	0.136	0.386
		N	79	79
C/T MTHFR:677	H_{cy}, μmol/L	Spearman's	0.399**	0.073
		Sign. (2-tailed), p	0.002	0.580
		N	60	60
T/T MTHFR:677	H_{cy}, μmol/L	Spearman's	0.619**	0.326
		Sign. (2-tailed), p	0.005	0.173
		N	19	19

Table No 11.2 continuation

Polymorphism, genotype	Parameter	Correlation coefficient	Parameter	
			Ca^{2+} mmol/L	PTH, pg/mL
A/A MTRR:66	H_{cy}, μmol/L	Spearman's	0.403*	0.123
		Sign. (2-tailed), p	0.022	0.502
		N	32	32
A/G MTRR:66	H_{cy}, μmol/L	Spearman's	0.319**	0.074
		Sign. (2-tailed), p	0.006	0.537
		N	72	72
G/G MTRR:66	H_{cy}, μmol/L	Spearman's	0.276*	-0.067
		Sign. (2-tailed), p	0.044	0.633
		N	54	54
Total group	H_{cy}, μmol/L	Spearman's	0.314**	0.013
		Sign. (2-tailed), p	0.0001	0.869
		N	158	158

Note. * — Correlation is significant at the 0.05 level (2-tailed). ** — Correlation is significant at the 0.01 level (2-tailed).

The serum PTH level plays a key role in P homeostasis [110]. It is known that dietary P stimulates the secretion of PTH [111]. The kidneys are actively involved in regulatory processes [112]. Renal tubular P reabsorption increases when the blood PTH level is decreased, and its reabsorption decreases when the blood PTH level is increased [113].

Experiments on laboratory animals showed that hyperphosphatemia induced by phosphate infusion increased PTH values even when the serum Ca level was normal [114].

Under clinical conditions, during haemodialysis, high serum P concentrations prevented the inhibition of PTH secretion by Ca, and contributed to the increase in PTH blood level [115].

Unlike Ca, P formed no associations with H_{cy} in the examined group of Chernobyl children. Its values had direct associations with PTH, TSH and T_3 values, and inverse ones with T_4, C and Tes values in the total group of children (Table 11.1) [105].

The most pronounced association between P and PTH was reported in the subgroups where there was no carriership of risk alleles of the MTHFR: C677T and MTR: A2756G polymorphisms, and no such association was found in the subgroups with 100 % carriership of risk alleles of these (Table 11.3) [107].

Table 11.3

Associations between P and hormone values in groups of children with different genetic polymorphisms (107)

Group No.	Genotype	Variable	Correlation coefficient	Variable
				PTH, pg/mL
1	A/AMTR:2756	P, mmol/L	Spearman's	0.482**
			Sign. (2-tailed), p	0.0001
			N	104
2	A/GMTR:2756	P, mmol/L	Spearman's	-0.234
			Sign. (2-tailed), p	0.121
			N	45
3	G/G MTR:2756	P, mmol/L	Spearman's	0.150
			Sign. (2-tailed), p	0.700
			N	9
4	A/AMTHFR:1298	P, mmol/L	Spearman's	0.280*
			Sign. (2-tailed), p	0.011
			N	82

Table No 11.3 continuation

Group No.	Genotype	Variable	Correlation coefficient	Variable
				PTH, pg/mL
5	A/CMTHFR:1298	P, mmol/L	Spearman's	0.283*
			Sign. (2-tailed), p	0.029
			N	60
6	C/C MTHFR:1298	P, mmol/L	Spearman's	0.519*
			Sign. (2-tailed), p	0.039
			N	16
7	C/C MTHFR:677	P, mmol/L	Spearman's	0.411**
			Sign. (2-tailed), p	0.0001
			N	79
8	C/T MTHFR:677	P, mmol/L	Spearman's	0.115
			Sign. (2-tailed), p	0.380
			N	60
9	T/T MTHFR:677	P, mmol/L	Spearman's	0.394
			Sign. (2-tailed), p	0.095
			N	19
10	A/AMTRR:66	P, mmol/L	Spearman's	0.405*
			Sign. (2-tailed), p	0.021
			N	32
11	A/G MTRR:66	P, mmol/L	Spearman's	0.260*
			Sign. (2-tailed), p	0.027
			N	72
12	G/G MTRR:66	P, mmol/L	Spearman's	0.270*
			Sign. (2-tailed), p	0.049
			N	54

Note. * — Correlation is significant at the 0.05 level (2-tailed). ** — Correlation is significant at the 0.01 level (2-tailed).

In the subgroups with T/T MTHFR:677 and G/G MTR:2756 genotypes we found no associations of P with hormones regulating mineral metabolism as well [107].

Thus, the regulation of phosphorus metabolism in the examined children from the Chernobyl district is associated with the FC genetic system.

Based on the studies carried out, it can be concluded that the increased formation of H_{cy} stimulates the the breakdown of hydroxyapatite bone tissue and the release of Ca and P into the blood. This process is most pronounced in cases of a homozygous variant of the T allele of the MTHFR:677 polymorphism. The effect of H_{cy} on the Ca metabolic processes excludes the association of the latter with PTH and P.

While a direct association is recorded between H_{cy} and Ca^{2+}, no association is found between H_{cy} and P.

In the subgroups of carriers of risk alleles of the MTHFR: C 677T and MTR: A2756G polymorphisms where the process of H_{cy} remethylation is substantially blocked and the proportion of cases of hyperhomocysteinemia is very high, there are no associations between P and PTH, P and hormones [107].

Elevated blood H_{cy} concentrations suppress PTH production which is proved by a strong inverse association between these metabolites in the subgroup of children with the G/G MTR:2756 genotype (Table 11.2) [106].

Thus, the FC genotype affects the establishment of correlations between H_{cy} and the components of calcium-phosphorus metabolism.

Based on the results obtained, it can be concluded that the hormonal control of calcium-phosphorus metabolism depends on the state of the FC genetic system and the blood H_{cy} level.

Carriership of the T allele of the MTHFR:677 polymorphism contributes to the occurrence of hyperhomocysteinemia in which the body loses control over calcium-phosphorus metabolism.

It is important to stress that carriership of risk alleles of the MTHFR: C677T and MTR: A2756G polymorphisms, where an increase in the blood level of H_{cy} is possible, was seen in 65.8 % of cases (104 out of 158 children) in the examined group of children.

The children-carriers of the genotypes with the above alleles should be included in the bone and joint system disease risk group.

The data obtained allow to conclude that there is an association of hyperhomocysteinemia and the state of genome of FC with abnormal calcium-phosphorus metabolism and possible demineralization of bone tissue in children living in areas contaminated with radioactive agents due to the ChNPP accident.

In this regard, the state of mineral metabolism in these children should be assessed taking into account the blood H_{cy} level and FC genotypes.

It should be noted that the FC genotype is an internal factor affecting the state of calcium-phosphorus metabolism in a child's body.

However, at the same time, one should take into account an external environmental factor caused by the ChNPP accident, and which has a significant impact on methionine and H_{cy} metabolic processes. These are radioactive elements and their decay products.

The results of this study can be used when developing a prevention programme against calcium-phosphorus metabolic disorders among the child population living under conditions of constant radiation exposure.

In particular, this relates to the programmes where B vitamins (B_9, B_{12}, B_6) are used among children of different age groups to improve processes of H_{cy} remethylation and reduce its concentration in the blood.

Chapter 12.
The role of the folate cycle in the regulation of thyroid function under conditions of radiation exposure

The territory of the Belarusian-Ukrainian Polesie had been considered endemic in relation to the development of thyroid diseases in the local population even before the ChNPP accident. It was associated with insufficient iodine levels in soils, and as a result, its insufficient intake [116, 117, 118].

In particular, according to the results of a survey conducted under the auspices of the World Health Organization in 1997–1999, the Republic of Belarus was classified as a country with mild and moderate iodine deficiency [119].

It was noted that Gomel region, heavily contaminated with radionuclides, has a lower level of iodine deficiency than some other regions of the Republic of Belarus. At the same time, the soils of the districts of Ukraine affected by the ChNPP accident are poorer in iodine than that of the Republic of Belarus [120]. The iodine status of the population can change over time and this should be taken into account when assessing the risk of thyroid diseases.

Except iodine, deficiency of selenium, an element that plays an important role in metabolism, including in thyroid gland hormonogenesis, was recorded in most of the territory of the former USSR [121, 122].

After the accident at reactor 4 of the ChNPP on April 26, 1986, at least 180 million Ci of radioactive substances were released into the environment [123]. According to various sources, the release of ^{131}I was estimated to be about 260–1760 PBq, the ^{137}Cs release was estimated to be 38–85 PBq [124].

^{131}I — a fugitive water-soluble radioactive iodine isotope formed in nuclear reactors during the fission of uranium and

plutonium — easily entered the body and was intensively absorbed by the thyroid gland in adults and children where it quickly decayed to ^{131}Xe (half-life — 8 days) releasing beta and gamma radiation [125]. People living under conditions of natural iodine deficiency suffered from effects of radioactive iodine isotopes in particular.

30 years after the ChNPP accident, radiation expansion continues. ^{137}Cs and ^{90}Sr radionuclides enter the human body through biological chains and therefore, are incorporated by vital organs. Forest trees of the ChEZ and the territories adjacent to it accumulate these radionuclides in huge quantities. In this regard, forest fires in this areas, as well as the use of forest wood for heating homes and cooking pose a real threat of radiation exposure for children and adults.

The intensity of radiation exposure to the population of the districts adjacent to the ChNPP was so high that it caused thyroid cancer in children and adults 4 years after the accident [126, 127].

Of all regions of Ukraine, the largest number of cases of thyroid cancer in the period 1990–2010 was registered in Kyiv and Kyiv region [128].

30 years after the ChNPP accident, this situation remains, as well a larger proportion of cases of thyroid cancer in the group of women, in comparison with the group of men (Tables 12.1, 12.2) [129–133].

It is thyroid cancer which was officially recognized by the World Health Organization as a condition associated with ^{131}I released to the environment as a result of the ChNPP accident in 1986 [134].

But besides ^{131}I, a huge number of other radionuclides were released to the environment, including ^{137}Cs and ^{134}Cs whose role in the occurrence of thyroid diseases has not been studied, and, of course, has not been evaluated. Moreover, the official representatives of international radiation science had little desire to do this.

Table 12.1

Thyroid cancer incidence in Ukraine and Kyiv region per 100 000 people (Ukrainian standard) (129–133)

Years	Ukraine			Kyiv region		
	Both sexes	Male	Female	Both sexes	Male	Female
2014	8.0	3.6	11.8	12.3	7.0	17.1
2015	8.3	3.1	12.7	13.5	5.5	20.4
2016	8.0	2.9	12.3	13.8	4.2	22.5
2017	8.0	3.4	11.9	12.9	5.4	19.5
2018	8.7	3.8	13.0	15.1	6.9	22.2

Table 12.2

Thyroid cancer incidence in Ukraine and Kyiv region per 100 000 people (world standard) (129–133)

Years	Ukraine			Kyiv region		
	Both sexes	Male	Female	Both sexes	Male	Female
2014	6.3	2.8	9.5	9.9	5.4	14.0
2015	6.6	2.5	10.2	10.8	4.3	16.6
2016	6.3	2.3	9.9	11.4	3.1	19.1
2017	6.4	2.7	9.7	10.7	4.7	16.1
2018	7.0	3.0	10.6	12.3	5.7	18.1

During 1992–1999, employees of Gomel State Medical Institute measured during autopsies ^{137}Cs levels in thyroid glands, other internal organs, brains and skeletal muscles of adults and children that had lived in Gomel region of the Republic of Belarus. The children were found to have a higher ^{137}Cs specific activity in their organs than the adults. Moreover, the highest concentrations of this radionuclide were recorded in the thyroid glands (Fig. 12.1) [19].

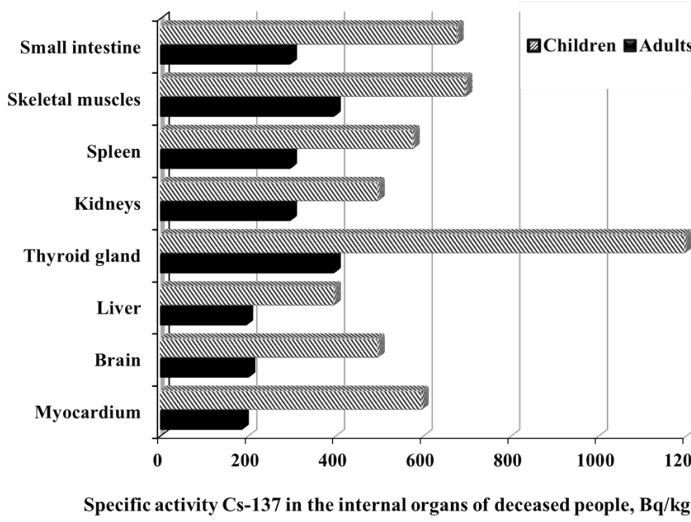

Fig. 12.1. Accumulation of ^{137}Cs radionuclides (Bq/kg) in the internal organs of adults and children who died in Gomel region in 1997 (19).

The findings allow us to conclude that the incorporation of ^{137}Cs into the thyroid gland and other organs occurs simultaneously; therefore, even small amounts of this radionuclide can cause serious metabolic changes in the body. These changes can be combined into the syndrome of incorporated long-lived radionuclides — SILR [3, 5].

Therefore, when characterizing structural and functional changes in the thyroid gland, changes in other organs and systems should also be considered.

A characteristic feature of the SILR is a decrease in the non-specific resistance of the body to exogenous factors of a biological, chemical and physical nature [135].

Results of studies conducted in Belarus by L. N. Astakhova et al. [126] suggest that in the first ten years after the ChNPP accident, thyroid glands of children of the first post-Chernobyl

generation were exposed mainly to ^{131}I and ^{137}Cs. The total number of the examined using a method of continuous screening was 20,785 people. As a result of the studies conducted in children and adolescents with increased incorporation of cesium in the body (the level of ^{137}Cs in the body in the presence of chronic incorporation was more than 1500 Bq/kg), there was found the suppression of normal thyroid gland growth rate relevant to their age and residence in an endemic goiter area, and the dissociation in the hypothalamus-pituitary-thyroid system. In particular, a decrease in the thyroid gland volume was accompanied by a decreased T_4 production and a decrease in the level of TSH in the blood [136].

Average TSH levels in the blood of the examined children had negative associations with rates of ^{137}Cs contamination of soils of the territory of residence of the children [126, 136].

The 2014–2015 of ultrasound scanning of 3088 children from Ivankovsky and Polessky districts of Kyiv region of Ukraine showed pathological changes in the thyroid gland in 6.7 % of cases.

The impaired production of thyroid hormones in the group of adolescents was recorded in 39.8 % of cases. At the same time, the blood T_4 levels below the established physiological level were noted in 32.3 % of cases, in which the proportion of boys was 61.5 %, and that of girls was 38.5 % ($p = 0.02$).

An excess of T_3 concentration in the blood above the established physiological barrier was found in 12.4 % of cases, of which boys made up 88.0 % and girls — 12.0 % ($p = 5 \cdot 10^{-5}$).

In the group of examined children, the level of TSH in the blood was within the permissible physiological parameters, which suggests impaired hormonal regulation in the pituitary-thyroid gland system [137].

It should be noted that we examined the children living in conditions of constant radiation exposure caused by the ChNPP accident and having risk alleles of FC genetic polymorphisms in their genome [Chapter No. 5].

In the group of children in whom the concentration of H_{cy} in the blood of more than 10 μmol/L was detected in 53.2 % of cases [105], the following associations were determined between TSH and thyroid hormones: an inverse one — between TSH and T_4, and a direct one between TSH and T_3 [138]. These associations are a manifestation of the physiological hypothalamic-pituitary regulation of the hormone producing function of the thyroid gland.

At the same time, TSH enhances the activity of 5'-deiodinase, and thereby causes an increase in T_3 production and a proportional decrease in T_4 production in peripheral tissues [139].

In the group of children in whom the concentration of H_{cy} in the blood of more than 10 μmol/L was recorded in 73.2 % of cases, in addition to the above associations, direct associations between H_{cy} and TSH, H_{cy} and T_3 were identified [138, 140]. At the same time, H_{cy} had inverse associations with serum vitamins B_9 and B_{12}, while T_4 had direct ones. Direct associations were found between vitamins B_9 and B_{12} (Fig. 12.2) [140].

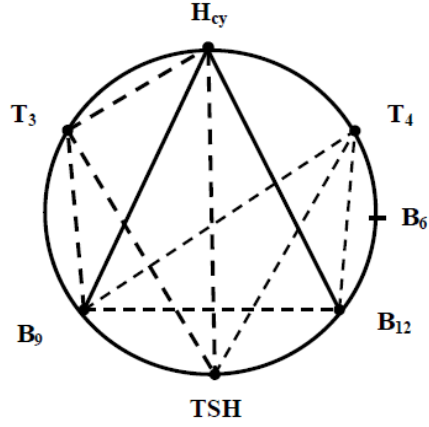

Fig. 12.2. Associations between metabolic variables in the group where the blood concentration of H_{cy} above 10 μmol/L was recorded in 73.2 % of cases.

It should be emphasized that this situation arose after a large fire in the ChEZ in the spring and summer of 2015 [138].

Thus, in the group of children with a predominant number of cases of hyperhomocysteinemia, direct associations of H_{cy} with the hormones of the pituitary-thyroid axis — TSH and T_3 — are determined. An increase in the level of H_{cy} in the blood adds to an increase in the production of TSH by the adenohypophysis.

H_{cy} did not form any direct associations with T_4; however, both of these metabolites had associations of the opposite direction with vitamins B_9 and B_{12}, reflecting the activity of the main FC enzymes [141, 142]. Insufficient activity of the latter leads to hyperhomocysteinemia and a decrease in the level of T_4 in the blood.

One of the mechanisms regulating the metabolism of T_4 and T_3 is the cycle of trans-sulfuration reactions, in which H_{cy} and Ser form Cyst, and then Cys, with the involvement of CBS. Cys, interacting with selenium, ensures the functioning of 5'deiodinase, which carries out the process of converting T_4 to T_3. An increase in the formation of H_{cy} leads to an increase in the formation of T_3 due to the loss of the iodine ion of T_4. TSH is also involved in this process, the synthesis of which stimulates H_{cy}. Thus, H_{cy} adds to the increase in T_3 production in peripheral tissues. At the same time, the level of T_4 decreases.

The genes of FC enzymes play an important role in the hormonal regulation of the thyroid gland, due to the fact that, under certain conditions, the level of H_{cy} in the blood depends on them.

The serum level of H_{cy} was higher in the group of children — carriers of the T risk allele of the MTHFR: C677T genetic polymorphism, encoding one of the main enzyme of the FC — methylenetetrahydrofolate reductase, than in the group of children who were not such carriers [143]. At the same time, the following associations were recorded: a direct association — between H_{cy} and TSH, inverse associations — between H_{cy} and

vitamins B_9 and B_{12}, with which T_4 was directly associated. TSH had a weak direct association with T_3, and had no association with T_4 [140]. It also had an inverse association with vitamin B_{12} (Fig. 12.3).

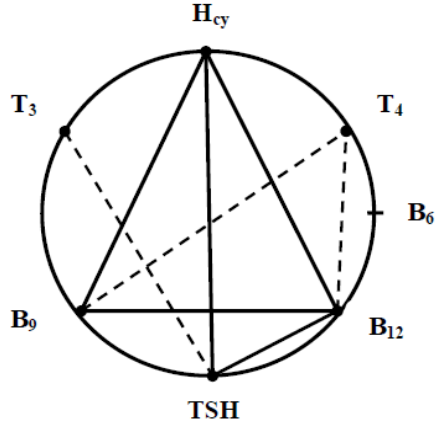

Fig. 12.3. Associations between metabolic variables in the group of children-carriers of the MTHFR: C677T polymorphism T allele

In the group of children with the C/C genotype MTHFR:677, there was no relationship between H_{cy} and TSH. A direct connection H_{cy}-T_3, and feedbacks H_{cy}–B_9 and H_{cy}–B_{12} were fixed. The following associations were the reflection of the physiological regulation processes: an inverse one — between TSH and T_4, a direct one — between TSH and T_3 (Fig. 12.4) [140].

The association between H_{cy} and T_3 results from the fact that the cases of carriership of the G allele of the MTR:2756 polymorphism were present in 43.75 % in this group of children. In the presence of such carriership, a block of H_{cy} methylation and the transformation of the latter into Met occurs [140].

In addition to MTHFR, other FC enzymes and related genes also participate in the regulation of metabolism of H_{cy} and hormones of the pituitary-thyroid axis.

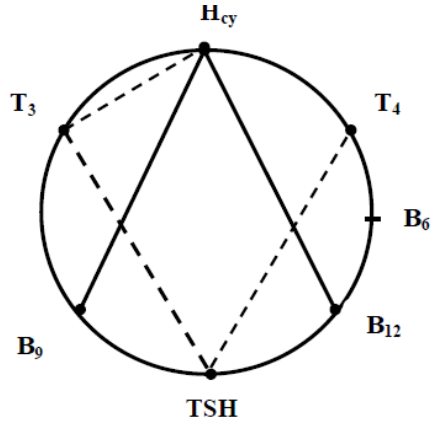

Fig. 12.4. Associations between metabolic variables in the group of children — carriers of the C/C genotype of the MTHFR: C677T polymorphism

The presence of the G risk allele of the MTR:2756 polymorphism in the genome reduces the activity of MTR, and, consequently, the level of vitamin B_{12} in the blood, while increasing the level of 5-MTHF, which cannot transfer the methyl group to vitamin B_{12}. As a result, the concentration of H_{cy} increases, and, as a consequence, the cycle of trans-sulfuration reactions is activated with the formation of T_3 from T_4. Direct associations between B_9 and T_3, B_{12} and T_4 are an illustration of this relationship. The inverse association between vitamins B_{12} and B_6 reflects the involvement of enzyme systems in the metabolic transformations of H_{cy}. A decrease in the level of B_{12} in the blood activates CBS, and leads to an increase in the level of vitamin B_6 in the blood. TSH has a direct association with H_{cy}, and an inverse association with vitamin B_{12} (Fig. 12.5) [144].

In the group of children with the G allele of the MTR:2756 polymorphism in the genome, in the absence of the T allele of

the MTHFR:677 polymorphism, the association between TSH and H_{cy} was not determined, however, an inverse association was recorded between vitamin B_6 and T_3 (Fig. 12.6).

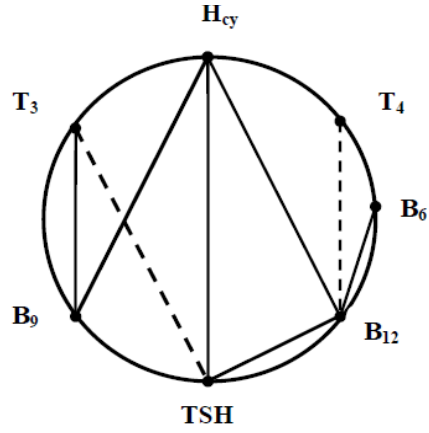

Fig. 12.5. Associations between metabolic variables in the group of children — carriers of the G allele of the MTR:2756 polymorphism

The increased T_3 level blocks under the inverse relationship principle the activity of CBS and naturally the utilisation of vitamin B_6 by it in the reaction of the formation of Cyst from H_{cy} and Ser. This compensatory mechanism prevents damage to the cardiovascular system in the presence of high levels of H_{cy} in the blood [140].

It should be noted that in the groups with the main genotypes, including the G allele of the MTR:2756 polymorphism there is no direct association between vitamins B_9 and B_{12} and, therefore between the enzyme systems in which they are involved.

In the case of simultaneous blocking of the FC enzymes MTHFR and MTR (carriership of risk alleles of MTHFR: C677T + MTR: A2756G polymorphisms) a pronounced direct association H_{cy}-TSH reflects the effect of H_{cy} on adenohypophysis cells producing TSH.

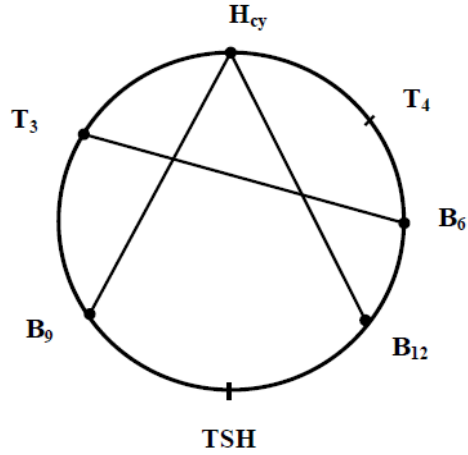

Fig. 12.6. Associations between metabolic variables in the group of children-carriers of the G allele of the MTR:2756 polymorphism in combination with the C/C MTHFR:677 genotype

At the same time, there are no associations between TSH and thyroid hormones [140].

The results of the studies carried out show a close relationship between the FC and metabolism of thyroid hormones.

It was found that the level of H_{cy}, as well as the genotype of FC enzymes, affect the hormonogenesis of the thyroid gland.

H_{cy} interferes with regulatory links of the hypothalamic-pituitary-thyroid axis, damaging its basic elements, which leads to the development of pathological processes in target organs.

Children with the C677TMTHFR mutation are most likely to develop hyperhomocysteinemia, which stimulates the synthesis of TSH.

Increased TSH production contributes to a decrease in body resistance [145]. There is a tenable hypothesis that serum TSH is associated with the development of thyroid cancer [146–148].

Blocking of H_{cy} remethylation processes due to a decrease in MTR activity (the genome contains the G allele of the MTR:2756

polymorphism) also leads to impaired metabolism of thyroid hormones in peripheral tissues, provided that the enzymes of the trans-sulfuration cycle function. Increased T_3 production may contribute to tachycardia and other heart rhythm disorders, especially atrial fibrillation [149]. This hormone indirectly affects the systemic vasculature, causing relaxation of vascular smooth muscles, leading to a decrease in diastolic blood pressure [150].

In addition to changes in the FC genes, the impact of an environmental factor in the form of forest fires containing ^{137}Cs and ^{90}Sr radionuclides in the ChEZ facilitates the occurrence of hyperhomocysteinemia.

The results obtained show that impaired Met and H_{cy} metabolism significantly alters hormonal regulation in the pituitary-thyroid gland system.

Based on this, children living in areas of environmental ill-being caused by the constant exposure to a radiation factor of Chernobyl origin, as well as the endemia for iodine and selenium, having risk alleles of the MTHFR: C677T and MTR: A2756G polymorphisms in the genome, should fall under a risk group for thyroid and cardiovascular diseases.

Chapter 13.
Folate cycle genes and ^{137}Cs incorporation into the body

Studies carried out at Gomel State Medical Institute in 1999 showed that the entry of ^{137}Cs into the body of a pregnant animal forms in the offspring the ability for increased incorporation of this radionuclide from food [78]. During pregnancy, white outbred female rats had an intragastric injection of 5 ml of a

^{137}Cs aqueous solution daily from the 10th to the 15th day of pregnancy.

In the control group, animals received intragastrically 5 ml of isotonic sodium chloride solution at the same period of pregnancy.

^{137}Cs radionuclide levels in females and newborn rat pups were measured on the 1st, 10th, 20th, and 30th days after birth. 19 females and 152 pups were examined in the experimental group, and 23 females and 224 pups were examined in the control group. During the transition to independent feeding (after the 20th day of life), significantly higher ^{137}Cs levels were recorded in the experimental group rat pups in comparison with those from the control group (Fig. 13.1). This effect was absent in the females (Figure 13.2). It should be noted that the rat pups and their mothers from the both groups received the same oat grain as food [78].

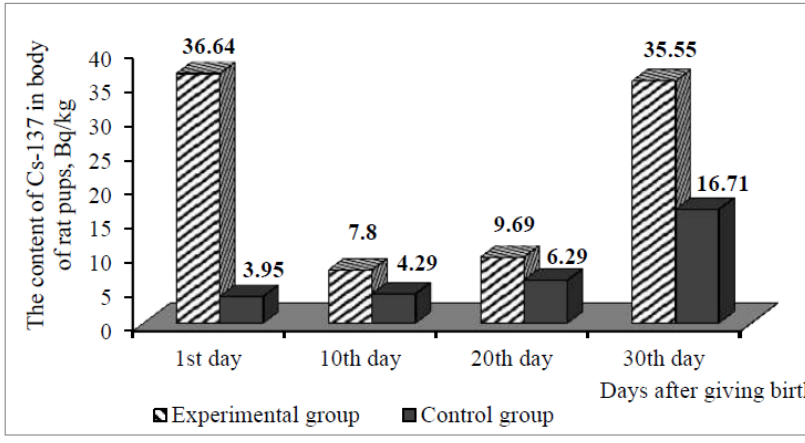

Fig. 13.1. ^{137}Cs levels in the rat pups from the experimental and control groups, Bq/kg (78).

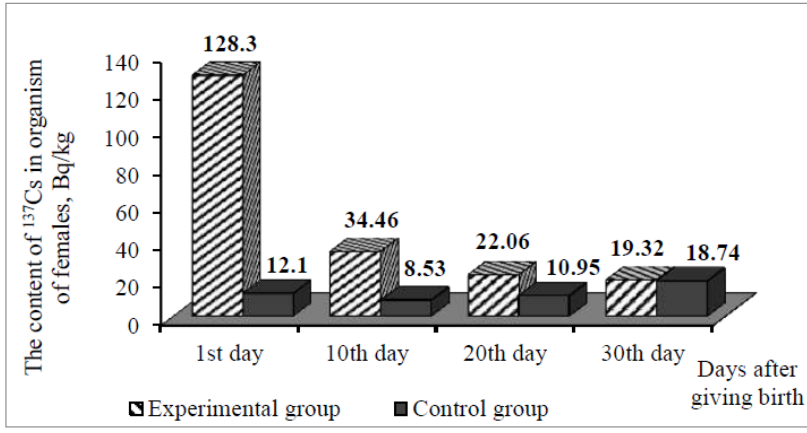

Fig. 13.2. ^{137}Cs levels in the female rats in the experimental and control groups, Bq/kg (78).

Thus, ^{137}Cs incorporation into the body depends on the state of the regulatory processes of metabolism and vital organs, which were laid down during the period of prenatal development. The contact of the mother-embryo system with radionuclides induces a certain reaction of the body in postnatal ontogenesis in the form of increased ^{137}Cs incorporation as compared to the control.

This is what can be characterized as an endogenous factor contributing to entering of radionuclides into the body, and naturally, the radiation exposure of the latter.

When identifying an endogenous factor, it is of considerable interest to assess the role of a genetic component. It was found that Rh-negative pregnant women accumulated ^{137}Cs in placentas in significantly smaller amounts compared to Rh-positive women [151].

We assessed a relationship between a MTHFR: C677T genetic polymorphism and incorporation of ^{137}Cs by a child's body in studies carried out in Ivankovsky and Polessky districts in 2018 [152].

We analyzed a group of children aged 8.0–11.11 years (Me – 9.1; IQR — 8.1–10.1). Carriership of the T allele of the MTHFR:677 genetic polymorphism was found in 57.6 % of cases of the number of children in the group. The level of ^{137}Cs was higher in the children with this allele than in those with the C/C MTHFR:677 genotype. At the same time, values of RI, which informs about the state of physical growth (PG) were lower (Tables 13.1, 13.2).

Table 13.1

Statistical characteristics of metabolic process and physical growth variables in the examined children of a younger group

Variables	A group of children with with a C/C MTHFR:677 genotype			A group of children with with a C/T + T/T MTHFR:677genotype		
	n	Me	IQR	n	Me	IQR
^{137}Cs specific activity, Bq/kg	14	2.52	2.39–2.83	19	3.07	2.75–3.29
RI	14	13.3	12.38–14.23	19	11.90	11.50–13.30

Table 13.2

Results of statistically significant differences when comparing variables of metabolic processes in the blood and physical growth in the examined children of the younger group

Variables	Comparison groups	Comparison group size	Average rank	U test value, significance level, p
^{137}Cs specific activity, Bq/kg	1	14	13.14	U = 79.0; p = 0.05
	2	19	19.84	
RI	1	14	21.43	U = 71.0; p = 0.024
	2	19	13.74	

Note: Group "1" — a group of children with the C/C MTHFR:677 genotype; "2" — a group of children with C/T + T/T MTHFR:677 genotypes.

Correlation analysis showed a inverse relationship between the values of ^{137}Cs association between the ^{137}Cs and RI values in the subgroup of children in the presence of 100 % carriership of the T allele, as well as in the subgroup with the main A/A MTHFR:1298 genotype, where the carriership of the T allele was the highest among the other analyzed genetic subgroups (Table 13.3, 13.4).

Table 13.3

Results of correlation analysis between values of ^{137}Cs and RI in groups of children with different polymorphisms

Genotype	Correlation coefficient	Parameters
		^{137}Cs and RI
A/G MTR:2756 + G/G MTR:2756	Spearman's	-0.242
	Sign. (2-tailed), p	p = 0.215
	N	28
A/A MTR:2756	Spearman's	-0.202
	Sign. (2-tailed), p	p = 0.217
	N	39
A/C MTHFR:1298+ C/C MTHFR:1298	Spearman's	-0.035
	Sign. (2-tailed), p	p = 0.826
	N	43
A/A MTHFR:1298	Spearman's	-0.435*
	Sign. (2-tailed), p	p = **0.033**
	N	24
C/T MTHFR:677+ T/T MTHFR:677	Spearman's	-0.330*
	Sign. (2-tailed), p	p = **0.049**
	N	36
C/C MTHFR:677	Spearman's	0.114
	Sign. (2-tailed), p	p = 0.541
	N	31

Table No 13.3 continuation

Genotype	Correlation coefficient	Parameters
		^{137}Cs and RI
A/G MTRR:66+ G/G MTRR:66	Spearman's	-0.233
	Sign. (2-tailed), p	p = 0.084
	N	56
A/AMTRR:66	Spearman's	0.094
	Sign. (2-tailed), p	p = 0.784
	N	11

Note. * — Correlation is significant at the 0.05 level (2-tailed).
** — Correlation is significant at the 0.01 level (2-tailed).

Table 13.4

Proportion of cases with the MTHFR: C677T polymorphism T allele among the studied genetic groups

Genotype	Number of cases	Number of cases of carriership of the MTHFR: C 677T polymorphism T allele	
		Absolute number	%
A/G MTR:2756 + G/G MTR:2756	28	16	57.1
A/A MTR:2756	39	20	51.3
A/C MTHFR:1298+ C/C MTHFR:1298	43	20	46.5
A/A MTHFR:1298	24	16	66.7
C/T MTHFR:677+ T/T MTHFR:677	36	36	100
C/C MTHFR:677	31	0	0
A/G MTRR:66+ G/G MTRR:66	56	31	55.4
A/AMTRR:66	11	5	45.5

Thus, the children who are carriers of the T allele of the MTHFR:677 genetic polymorphism have a tendency to accumulate large amounts of ^{137}Cs in the body, in comparison with the children who do not have this risk allele in their genome. This leads to a decrease in the level of their PG.

Chapter 14.
Folate cycle genes and predisposition to breast cancer in girls from districts bordering the Chernobyl exclusion zone

A study of the adult contingent showed that impaired functioning of the folate cycle is associated with the development of cancers, in particular, breast cancer [153, 154, 155]. The prevalence of this type of malignant neoplasms in Kyiv region with an annual increase (Fig. 14.1) [157–161] is the highest among all regions of Ukraine [156, 157].

The T risk allele of the MTHFR:677 genetic polymorphism, which controls the main FC enzyme the MTHFR, is associated with breast cancer [70, 155].

In this regard, it is of undoubted practical and scientific value to assess the prevalence of the T risk allele of the MTHFR:677 genetic polymorphism in the group of girls of Ivankovsky and Polessky districts located near the ChEZ, as well as variants of combined carriership of this allele with risk alleles of other genetic polymorphisms controlling the FC.

In the course of the studies, a PCR method was used. It enables to identify allelic variants of genetic polymorphisms that control the main FC enzymes: C677T and A1298C of the MTHFR, A2756G of the MTR and A66G of the MTRR gene.

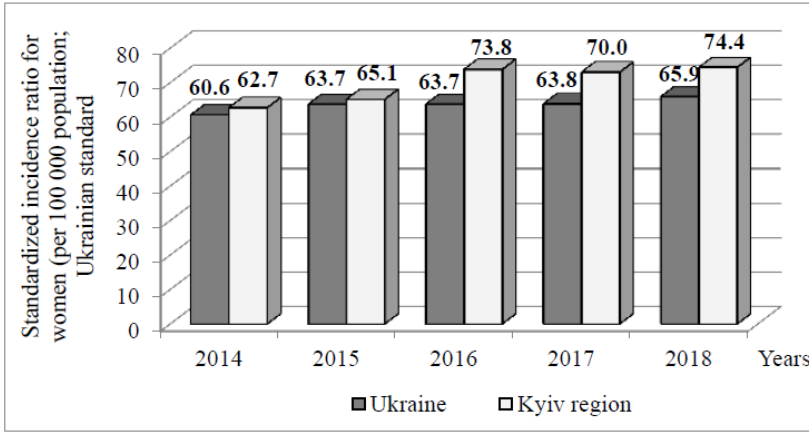

Fig. 14.1. Dynamics of the adjusted incidence rate (per 100,000 population; Ukrainian standard) of women with breast cancer in Ukraine and Kyiv region (158–162).

When examining 251 girls aged 8–17 years from the districts of Kyiv region bordering the ChEZ using this method, carriership of the T allele of the MTHFR: C677T polymorphism was observed in 142 girls (56,6 %).

The homozygous T/T variant, leading to a significant decrease in the MTHFR activity and an increase in blood H_{cy} levels [71] was found in 25 girls or in 10.0 % of cases (Table 14.1).

Attention should be paid to compound heterozygosity of the MTHFR gene 677CT/1298AC which is equal to the T/T genotype of the same polymorphism with regard to the degree of inhibition of the activity of the MTHFR, and accordingly, the degree of increase in the level of H_{cy} in the blood [163, 61].

The 677CT/1298AC compound heterozygosity of the MTHFR gene was seen in the study group in 60 girls or in 23.9 % of cases. Thus, there is a genetically determined predisposition to impaired FC functioning and an increase in H_{cy} blood level in the study population of children in 85 girls or in 33.9 % of cases (Table 14.2).

Table 14.1

Frequency of polymorphic alleles of FC genes in examined girls from Ivankovsky and Polessky districts

Gene, polymorphism	Genotype variants					
	"Neutral" allele Homozygous variant		"Risk" allele Heterozygous variant		"Risk" allele Homozygous variant	
	Abs. number	Percentage,%	Abs. number	Percentage,%	Abs. number	Percentage,%
MTR: A2756G	157	62.5	80	31.9	14	5.6
MTHFR: A1298C	122	48.6	110	43.8	19	7.6
MTHFR: C677T	109	43.4	117	46.6	25	10.0
MTRR: A66G	45	17.9	120	47.8	86	34.3

The heterozygous associations of the MTHFR: C677T and MTRR: A66G, MTR: A2756G and MTRR: A66G polymorphisms also contribute to the occurrence of severe diseases, including congenital malformations [61, 63].

Compound heterozygosity of the MTHFR:677CT/MTRR:66AG polymorphisms occurred in 61 girls, or in 24.3 % of cases, and compound heterozygosity of the MTR:2756AG/MTRR:66AG polymorphisms was seen in 37 girls, or in 14,7 % of cases in the study group of girls (табл. 14.2).

Compound heterozygosity of the MTR:2756AG/MTHFR:677CT polymorphisms found in 35 girls, or in 13.9 % of cases, leads to combined impaired functioning of the main enzyme systems of FC.

The environmental impact, including the radiation factor, will be a factor that affects the power supply of cells, and, as a result, provokes the manifestation of existing genetic defects. An increase in the level of H_{cy} in the children after forest fires in the ChEZ in 2015 may be an example of FC dysfunction.

Table 14.2

Frequency of FC genetic polymorphism combinations in a group of girls

MTHFR: C 677T and MTHFR: A1298C polymorphism genotypes							
CT677—AC 1298		CT677—CC 1298		TT677—AC 1298		TT677—CC 1298	
n	%	n	%	n	%	n	%
60	23.9	0	0	0	0	0	0
MTHFR: C 677T and MTRR: A66G polymorphism genotypes							
CT677 — AG66		CT677 — GG66		TT677 — AG66		TT677 — GG66	
n	%	n	%	n	%	n	%
61	24.3	41	16.3	11	4.4	8	3.2
MTR: A2756G and MTHFR: C 677T polymorphism genotypes							
AG2756-CT677		AG2756—TT677		GG2756—CT677		GG2756—TT677	
n	%	n	%	n	%	n	%
35	13.9	6	2.4	9	3.6	0	0
MTR: A2756G and MTRR: A66G polymorphism genotypes							
AG2756 — AG66		AG2756 — GG66		GG2756 — AG66		GG2756 — GG66	
n	%	n	%	n	%	n	%
37	14.7	29	11.6	8	3.2	1	0.4

Thus, there is a genetic predisposition to breast cancer in the examined group of girls from the districts bordering the ChEZ.

The manifestation of genetic defects will be facilitated by constant radiation exposure associated with entry of radionuclides. including ^{137}Cs and ^{90}Sr into a human body.

In this regard, it is necessary to identify a risk group of children to conduct early preventive measures for breast cancer.

Chapter 15.
Efficacy of measures to reduce the specific activity of 137Cs radionuclides in the body of children living near the Chernobyl Exclusion Zone

The project of the European Commission in Ukraine "Health and environmental programs associated with the Chernobyl exclusion zone. Preparation, training and coordination of health-related projects" (2012–2017), made it possible to assess the contamination of soils with ^{137}Cs and ^{90}Sr in the areas near the settlements of Ivankovsky district (Fig. 15.1, 15.2) and determine using stationary whole-body counters (WBC) annually for three years the specific activity of ^{137}Cs in the body of most children in Ivankovsky and Polessky districts. Schoolchildren prevailed among the examined children (Table 15.1) [164].

Table 15.1

Number of WBC-measurements carried out within the child population of Ivankovsky and Polessky districts of Kyiv region of different age groups depending on the study period

Measurement period, years	Number of measurements	Number of WBC measurements in age groups (years)				% of schoolchildren
		0–2	3–5	6–11	12–18	
2014–2015	3736	11	237	1742	1746	93.4
2015–2016	3423	5	114	1745	1559	96.5
2016–2017	3233	7	229	1498	1499	92.7
Total	10 392	23	580	4985	4804	94.2

In addition, the program of anti-radiation safety of children and adults of this project provided for radiation monitoring of food products and information support for the population.

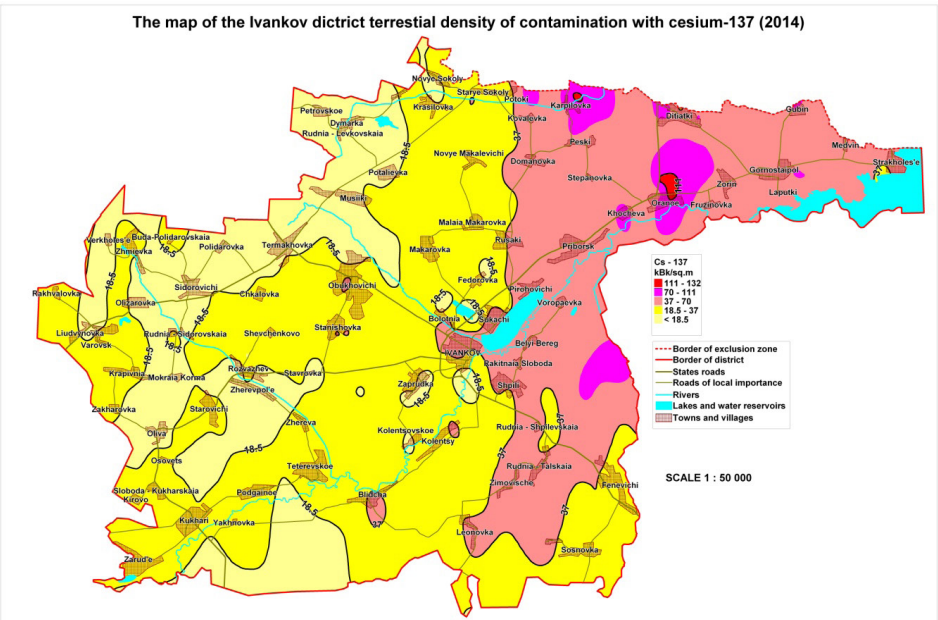

Fig. 15.1. Cartogram of density of contamination of soil of Ivankovsky district with ^{137}Cs as of 2014 (with half tones).
Scale 1:50 000

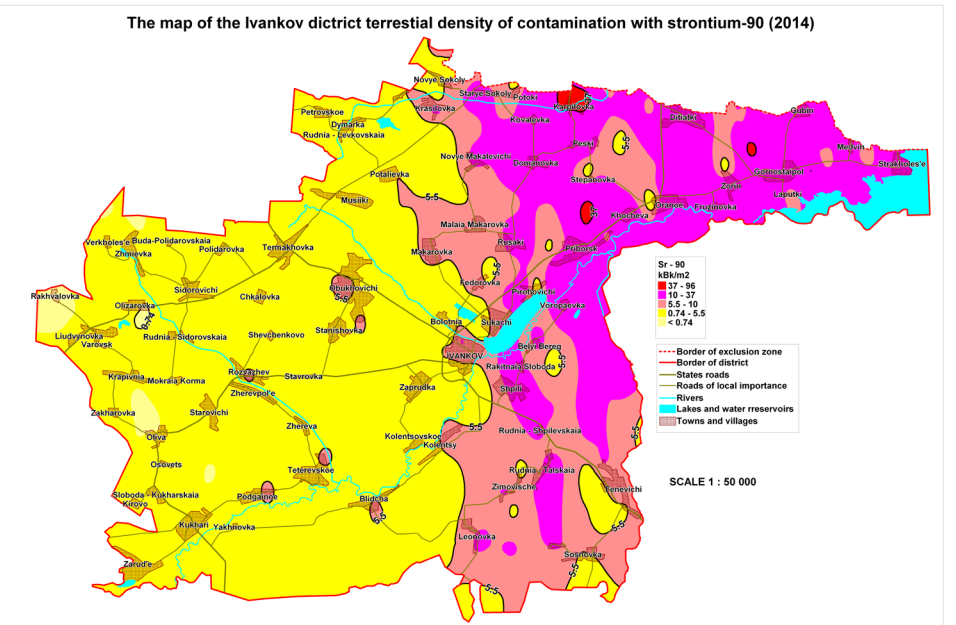

Fig. 15.2. Cartogram of density of contamination of soil of Ivankovsky district with ^{90}Sr as of 2014 (with half tones).
Scale 1: 50 000

For its implementation, a Hygiene and Nutrition Information and Consultation Center was established at the premises of Ivankov Central District Hospital, which should explain to the population of Ivankovsky and Polessky districts the rules of safe living and a healthy lifestyle.

If, during the radiation monitoring, increased ^{137}Cs levels in a child's body were found, all members of his family were recommended to undergo subsequent monitoring using a WBC.

We studied the most consumed foods within the child's family to find out a source of the child's body contamination with radionuclides.

Special emphasis was placed on conducting radiological control of locally produced products (milk, potatoes, vegetables, fruits) and "gifts of the forest": berries, mushrooms, as well as meat of wild animals and fish.

In most cases, the parent and older group's child questionnaire method was also used.

In the majority of children, the ^{137}Cs specific activity was not significant. However, during the measurement period 2014–2015, in the group of boys, a case was recorded when the ^{137}Cs specific activity in the body was 307.29 Bq/kg, and 126.4 Bq/kg in the group of girls.

Higher values of ^{137}Cs levels in the body of children were registered in October, November, December and January — the period of intensive harvesting and consumption of mushrooms (Fig. 15.3).

The use of various forms of informational work of the Center (Fig. 15.4) with medical workers, teachers, parents and children made it possible to lower significantly ^{137}Cs radionuclide levels in the body of children and to reduce the frequency of registration of cases with a specific activity of this radionuclide in the body of more than 5.0 Bq/kg among the examined children's contingent.

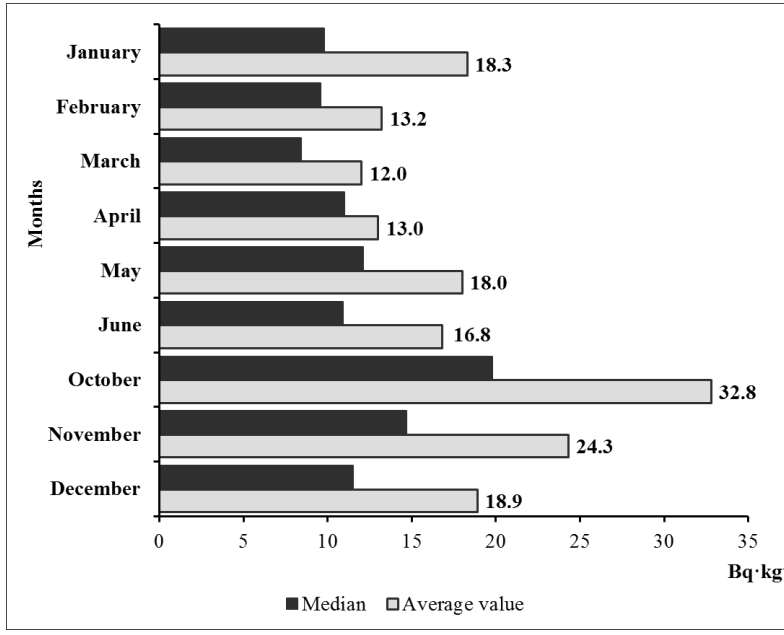

Fig. 15.3. Seasonal distribution of the results of WBC measurements in children with ^{137}Cs levels in the body over 5.0 Bq/kg

Radiation monitoring results suggest a decrease in ^{137}Cs radionuclide levels in the body of children when measured in the periods 2015–2016 and 2016–2017 in comparison with the period 2014–2015 (Tables 15.2, 15.3) [164].

The relative number of children with the ^{137}Cs specific activity in the body of more than 5.0 Bq/kg in the first year of measurements was statistically higher than in the subsequent years of measurements (Fig. 15.5).

Statistically significant differences were found between the specific gravity of ^{137}Cs levels in the body of children when comparing the data between the periods 2014–2015 and 2015–2016 ($t=4.74$; $p=0.0003$); and when comparing the data between the periods 2014–2015 and 2016–2017 ($t=6.5$; $p=0.00001$) [164].

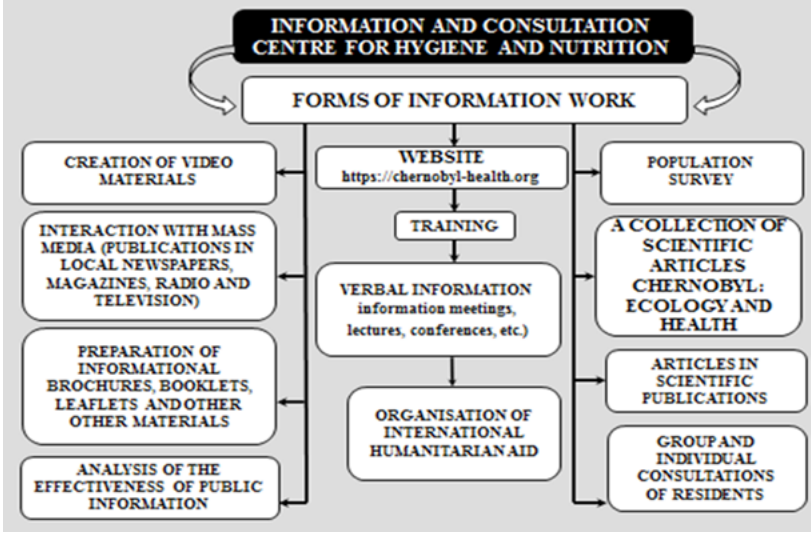

Fig. 15.4. Forms of work of the Hygiene and Nutrition Information and Consultation Center with the population of Ivankovsky and Polessky districts.

Table 15.2

Results of the statistical analysis of individual values of incorporated ^{137}Cs specific activity in children from Kyiv region's districts under study

Measurement period, years	Number of children	^{137}Cs levels in the body, Bq/kg^{-1}			
		Median	IQR	90 percent quantile	Largest observation
Both sexes					
2014–2015	3736	2.09	1.64–2.62	3.23	307.29
2015–2016	3423	2.05	1.63–2.54	2.92	199.38
2016–2017	3233	2.04	1.63–2.54	2.91	77.33
Boys					
2014–2015	1861	2.14	1.65–2.63	3.34	307.29
2015–2016	1714	2.08	1.64–2.54	2.90	199.38

Table No 15.2 continuation

Measurement period, years	Number of children	^{137}Cs levels in the body, Bq/kg^{-1}			
		Median	IQR	90 percent quantile	Largest observation
2016–2017	1617	2.06	1.66–2.54	2.87	45.82
Girls					
2014–2015	1875	2.02	1.63–2.61	3.14	126.4
2015–2016	1709	2.00	1.62–2.54	2.94	118.51
2016–2017	1616	2.02	1.62–2.53	2.93	77.33

Based on the results obtained, a conclusion should be drawn that there is a necesssity to carry out even 30 years after the ChNPP accident in the affected areas, anti-radiation measures, including radiological monitoring of the population and food, information distribution and medical examination of children and adolescents.

Table 15.3

Results of comparison of ^{137}Cs specific activity in the body of children who underwent a study in different years of screening using a non-parametric Mann-Whitney U-test

Variable	Comparison periods*	Mann-Whitney U-test value, significance level p		
		Total group	Boys	Girls
^{137}Cs specific activity, Bq/kg	I — II	U = 6109814.0; p = 0.001	U = 1509422.0; p = 0.006	U = 1544165.0; p = 0.061
	I — III	U = 5761112.0; p = 0.001	U = 1419325.5; p = 0.004	U = 1458358.0; p = 0.56
	II — III	U = 5525193.0; p = 0.918	U = 1381730.0; p = 0.884	U = 1379122.0; p = 0.950

Note. * — I (2014–2015); II (2015–2016); III (2016–2017).

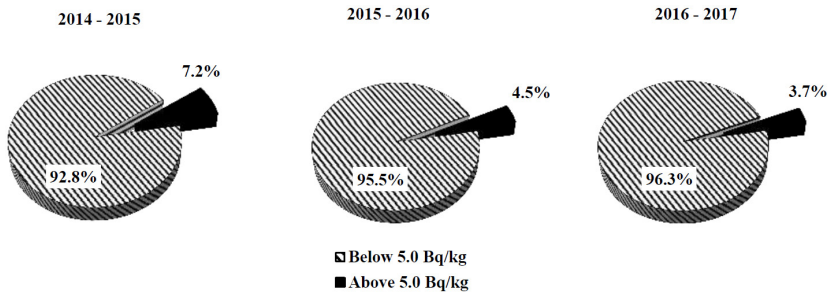

Fig. 15.5. Dynamics of the relative number of cases with different levels of specific activity of ^{137}Cs in children in 2014–2017.

Chapter 16.
Instead of a Conclusion. Cause-effect relations in abnormal growth of a child's body in areas affected by the Chernobyl nuclear power plant accident

It should be recognized that even 30 years after the ChNPP accident antenatal and postnatal human development in affected areas occurs under conditions of constant exposure to radioactive elements and their decay products.

It has been found that ^{137}Cs radionuclides entering the bloodstream through the gastrointestinal tract or respiratory tract are incorporated by cells of internal organs, nervous system, skeletal and smooth muscles.

As a result, mitochondrial damage occurs, leading to a deficiency in oxidative phosphorylation and insufficient production of energy carriers in the form of ATP.

In childhood, this is manifested by a decrease in body weight, due to the suppression of cell proliferation, impaired functioning of the vital systems of the body.

^{137}Cs radionuclides have a destructive effect on the mitochondrial structures of cardiomyocytes, as evidenced by an increase in serum AST activity. At the same time, an energy deficiency of the calcium-transport system develops and the contractile apparatus of the myocardium gets damaged, which manifests itself in the form of a decrease in SBP.

A decrease in the VC is the reflection of the effect of radioactive elements on the muscle cells of the respiratory system (intercostal muscles, muscles of the diaphragm and abdominal wall).

Studies carried out in Gomel region of the Republic of Belarus in the first ten years after the ChNPP accident showed that as the ^{137}Cs level in a child's body increases, the risk of arrhythmias, as well as cataracts increases (Yu. I. Bandazhevsky, 1995–1999).

30 years after this tragic event, more than 80 % of Ukrainian children living in the territories contaminated with radionuclides, near the ChEZ, also recorded electrocardiographic changes, including heart rhythm disturbances.

A relationship between the age of children and the specific activity of ^{137}Cs in their body was found. Younger children incorporate radionuclides more intensively compared to older ones. This is associated with both the physiological characteristics of their bodies and the high consumption of milk and dairy products obtained in areas contaminated with radioactive elements.

The genetic apparatus of the FC has an effect on the incorporation of ^{137}Cs by the child's body. In particular, the 677MTHFR point mutation which determines the activity of MTHFR contributes to the increase in the level of ^{137}Cs radionuclides in the body of children from families permanently residing in areas bordering the ChEZ.

Studies carried out 30 years after the ChNPP accident made it possible to draw an important conclusion that the physical growth of children, erythrocyte count and the level of hemoglobin in their blood are inversely associated with the ^{137}Cs radionuclide levels in the body.

The specific activity of ^{137}Cs in the group of children with disharmonious low physical development (body weight deficiency) was higher than in the groups of children with harmonious physical development and disharmonious high physical development.

Children with disharmonious low physical development represent a variant of the most pronounced medical and biological consequences of radiation exposure on the child population in the areas affected by the accident at the ChNPP.

In the conducted studies, they made up 14.0 % of the total number of children observed aged 12–17 years. These children had higher levels of H_{cy}, phosphorus (P) and T_3 in the blood compared to those with a greater body weight.

At the same time, they have lowered BP, reduced VC of the lungs and increased HR.

Along with ^{137}Cs radionuclides, ^{90}Sr, ^{241}Am and other long-lived radioactive elements enter the body of children and adults living near the ChEZ. Attention should be paid to the intracellular decomposition of ^{137}Cs and the formation, as a result of this, of barium (Ba) — a highly toxic element.

The entry of the above radionuclides into the body leads to a decrease in the blood level of an essential sulfur-containing amino acid Met, which ensures the functioning of vital metabolic cycles in the body.

Met, entering the body from outside, ensures the methylation — one of the most important metabolic processes, in which H_{cy} is an intermediate metabolite.

The concentration of H_{cy} in the blood, above the physiological level, indicates a violation of the functioning of the FC and / or transsulfurization cycle.

The state of hyperhomocysteinemia was found by us in 2015 in many adolescent children examined living near the ChEZ.

In adults, hyperhomocysteinemia is the cause of a blood clotting disorder that causes thrombosis of the vessels of the heart and brain with the occurrence of heart attacks and strokes, pathologies of intrauterine development of the embryo, including congenital malformations, oncological diseases, endocrine pathology, diseases of the nervous system, osteogenesis disorders, leading to to bone fractures.

H_{cy} interferes with nerve impulse transmission processes by acting on N-methyl-D-aspartate receptors, in which glutamic acid is an excitatory transmitter, a unique regulator of metabolism in the body. As a result, the concentration of Ca^{2+} in a cell increases sharply. This is accompanied by the formation of reactive oxygen species, damage to mitochondria, and suppression of ATP production. Overexcitation of glutamate receptors which occurs under the influence of H_{cy} results in the development of convulsive states, as well as neurodegeneration. Thus, H_{cy} in high concentrations affecting negatively metabolic processes in cells of the nervous system contributes to the occurrence of serious diseases, including Alzheimer's disease, multiple sclerosis, Parkinson's disease, epilepsy and amyotrophic lateral sclerosis.

The adverse effect of this sulfur-containing amino acid has been noted in relation to immunocompetent cells.

Diagnosing hyperhomocysteinemia in most of adolescent children examined excludes the individual reasons of this phenomenon and forces us to look for a common factor that causes impaired Met and H_{cy} metabolism.

Among the possible causes of hyperhomocysteinemia in most children, mutations in the genes responsible for the synthesis of

FC enzymes should be noted, as well as an environmental factor, including radioactive elements and their decay products, and insufficient intake of B vitamins.

It was found that hyperhomocysteinemia is associated with the T risk allele of the MTHFR:677 genetic polymorphism, which affects the activity of MTHFR, which is the main enzyme of the FC. The homozygous variant of carriership of this allele causes in comparison to other genetic variants of the FC the greatest increase in H_{cy} levels in the blood with the greatest decrease in the level of 5-MTHF, an active form of vitamin B_9.

MTR controls the process of transferring a methyl group from 5- MTHF to $H_{cy.}$

The G/G MTR:2756 genotype blocks the function of the enzyme and the involvement of vitamin B_{12} as its cofactor, resulting in an increase in the formation of H_{cy}. This is confirmed by a strong inverse association between the values of vitamin B_{12} and H_{cy}.

A decrease in vitamin B_{12} levels in the blood and an increase in H_{cy} levels at the same time, stimulates the activity of CBS, with the use of vitamin B_6 as its cofactor.

As a result of this, an excess of H_{cy} is converted into Cyst, followed by the formation of Cys.

High 5-MTHF concentrations also have a stimulating effect with regard to this enzyme.

It should be noted that in the cells of the CNS there is no possibility of utilizing an increased amount of H_{cy} through a cascade of trans-sulfurization reactions. In this regard, in individuals with increased H_{cy} formation due to genetic defects in the form of the T allele of the MTHFR:677 polymorphism and the G allele of the MTR:2756 polymorphism, there is a threat of impaired CNS functioning.

The conducted studies indicate that the level of active forms of vitamins B_6, B_9, B_{12} in the blood, reflecting their use in metabolic cycles, depends on the state of the FC genetic apparatus.

However, in the Chernobyl children examined by us, disturbances in the process of H_{cy} methylation and Met resynthesis were associated not only with mutations in the FC genes.

Hyperhomocysteinemia was recorded even in those cases when the genome contained no risk alleles of the above polymorphisms. At the same time, an inverse association was clearly observed between H_{cy} and vitamins B_9 and B_{12}.

In the studies carried out, it was found that blood levels of vitamin B_9 in the children depends on the socio-economic conditions in which their families live. The concentration of vitamin B_9 was statistically lower in children from Polessky district than in those from a more economically developed Ivankovsky district.

However, in the groups of children from both districts, H_{cy} level had no statistical differences and hyperhomocysteinemia was recorded in more than 70 % of cases. Thus, a deficit in the intake of vitamin B_9 in the studied children could not be the main cause of hyperhomocysteinemia in them. In addition, according to the reference values, vitamin B_9 deficiency was registered in 20 % of cases, and vitamin B_{12} deficiency was found in 5 % of cases.

Inverse associations of vitamins B_9 and B_{12} with H_{cy} suggest a functional deficiency of these vitamins in the body of children with hyperhomocysteinemia.

Forest fires in the ChEZ have played an important role in the induction of hyperhomocysteinemia in children. It was after the fires in the spring and summer of 2015 in the ChEZ forest area that the proportion of cases of hyperhomocysteinemia among schoolchildren aged 12–17 years from Ivankovsky and Polesky districts has increased from 48.8 % to 75.3 %.

An increase in the blood level of H_{cy} was recorded in 79.8 % of cases in the same children from Polessky district.

The greatest increase in the level of H_{cy} in the blood was observed in children with no homozygous variants of the risk alleles of the MTHFR:677 and MTR:2756 genetic polymorphisms.

In the group of mothers of these children, hyperhomocysteinemia was recorded only in 31.8 % of cases and, to a greater extent, was associated with the gene that controls the synthesis of MTHFR.

Thus, the FC genes did not fully regulate the process of the Met and H_{cy} metabolism in the body of children of the second Chernobyl generation, unlike their mothers. As a result of this, the effect of radiation agents and wood combustion products caused hyperhomocysteinemia in them.

Based on this, one should acknowledge that forest fires in the ChEZ are one of the most important etiological factors of a number of serious diseases of the adult and child population of the adjacent districts.

Radioactive elements, primarily ^{137}Cs, and wood combustion products spread with air currents over long distances from the epicenter of fire. In this regard, people who did not officially belong to the group of victims of the ChNPP accident, but who in fact are such, were exposed to radiation and toxic effects. In recent years, this issue has become especially acute, due to the increase in the number of forest fires in the ChEZ.

The use of wood containing radioactive elements in everyday life (heating the home, cooking) also creates conditions for constant radiation-toxic effects upon the body of children and adults.

Elevated concentrations of H_{cy} in the blood stimulate the synthesis of TSH, which regulates thyroid hormonogenesis. This is a very important element in the pathogenesis of a number of serious diseases, including tumor processes in the thyroid gland.

It was found that H_{cy} through a cycle of trans-sulfuration reactions participates in the formation of T_3 from T_4. The G allele of the MTR:2756 polymorphism plays a significant role in this process.

In the presence of the increased formation of H_{cy} and impaired regulatory mechanisms, the concentration of T_3 in the blood can be increased significantly, which has an adverse effect on the cardiovascular system, causing disturbances in the rhythm of heart contractions and relaxation of vascular smooth muscle fibers.

Under conditions of increased formation of H_{cy}, Ca metabolism in the child's body is being disturbed. At the same time, a direct association occurs between H_{cy} and Ca^{2+}, the regulatory links between Ca^{2+} and PTH, Ca^{2+} and P disappear. This is most clearly manifested in cases of the homozygous variant of the T allele of the MTHFR:677 polymorphism. A strong inverse association between H_{cy} and PTH was recorded in children with the G/G MTR:2756 genotype.

P has regulatory associations with PTH and hormones that affect mineral metabolism. However, we found no such associations in the subgroups where there are 100 % of carriers of risk alleles of MTHFR: C 677T or MTR: A2756G genetic polymorphisms where the largest proportion of cases of hyperhomocysteinemia was recorded.

The results obtained show that the hormonal regulation of calcium-phosphorus metabolism depends on the state of the FC genetic system and the level of H_{cy} in the blood.

With increased formation of H_{cy}, the body loses control over the processes of calcium-phosphorus metabolism, which leads to violations of osteogenesis and structural and functional changes in vital organs.

Genes regulating H_{cy} metabolism are an internal and endogenous factor of hyperhomocysteinemia.

At the same time, in the induction of an increased level of H_{cy} in the body, one should take into account the environmental — exogenous factor, in the form of long-lived radioactive elements and wood combustion products.

Thus, three decades after the ChNPP accident, the impact of incorporated radionuclides and their decay products on the human body during its antenatal and early postnatal ontogenesis leads to metabolic dysregulation, the manifestation of which, among other things, is the state of hyperhomocysteinemia, which occurs regardless of the state of the genetic system serving FC. At the same time, a latent deficiency of vitamins B_9 and B_{12} develops.

The incorporated radionuclides suppress the cellular energetics of the child's body, and therefore, the most important metabolic processes are blocked in the body, including those involving Met, vitamins B_9 and B_{12}.

The result of this is impaired functioning of the cardiovascular, nervous and endocrine and other vital systems of the body. It is necessary to underline the great vulnerability of the body of children of the second Chernobyl generation to the impact of external factors in comparison with their mothers. We tend to consider this a consequence of abnormal formation of regulatory systems that control metabolism, including the essential amino acid methionine.

Forest fires in the ChEZ should be considered as a source of powerful radioactive effects, in which ^{137}Cs and other radioactive elements enter the body of people living in adjacent settlements. Under appropriate conditions, they spread with air currents, water, food of animal and vegetable origin, wood over great distances from the accident site. In this regard, people who are unaware of the danger that threatens their health and life may be the victims of radiation exposure.

Recommendations

The results of the studies conducted suggest that the assessment of physical growth, endocrine, nervous, cardiovascular and hematopoietic systems, mineral metabolism in children living near the ChEZ should be carried out taking into account

the blood levels of H_{cy}, vitamins B_9, B_{12}, B_6, the state of the FC genetic system, specific activity of radioactive elements (^{137}Cs) in the body.

An increased level of H_{cy} in the blood of children calls for an in-depth examination of their health, with the determination of the specific activity of ^{137}Cs in the body, blood levels of TSH, T_3, T_4, Ca, the activity of AST and ALT and assessment of the state of the FC genetic system and the cardiovascular system.

Prevention of pathological processes, which are the main cause of mortality and disability in the adult population in areas affected by the ChNPP accident, should begin in childhood. It is obligatory to determine the genetic polymorphisms of the FC and the level of H_{cy} in the blood.

Children-carriers of the T allele of the MTHFR:677 genetic polymorphism, as well as the G allele of the MTRR:2756 polymorphism, should be identified as a risk group.

When determining the needs for vitamins and minerals in children being under constant radiation exposure associated with the accident at the ChNPP, or at other nuclear power plants, one should take into account the state of the FC genetic apparatus and the level of H_{cy} in the blood.

Preventive measures against hyperhomocysteinemia in children and adults during forest fires in the ChEZ should include the mandatory intake of active forms of vitamins B_9, B_{12}, B_6, as well as antioxidants — vitamins A, C, E.

In the event of large forest fires, children should be evacuated to radiation-free areas.

Antidotes and oxygen therapy are used to prevent poisoning of their body by combustion products.

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List of abbreviations

ChNPP	—	Chernobyl Nuclear Power Plant
ChEZ	—	Chernobyl exclusion zone
WBC	—	human radiation counter
^{137}Cs	—	radioactive isotope of cesium
^{90}Sr	—	radioactive isotope of strontium
Me	—	median
IQR	—	interquartile range (interval feature values containing the central 50 % of observations samples, i.e. interval between the 25th and 75th percentiles)
RI	—	Rohrer index — physical development index
HGB	—	hemoglobin
RBC	—	erythrocytes
BP	—	blood pressure
SBP	—	systolic blood pressure
DBP	—	diastolic blood pressure
PP	—	pulse pressure
HR	—	heart Rate
VC	—	vital capacity
CNS	—	central nervous system
PG	—	physical growth
SILR	—	syndrome of incorporated long-lived radionuclides
AST	—	aspartate aminotransferase
ALT	—	alanine aminotransferase
AST/ALT	—	de Ritis coefficient
H_{cy}	—	homocysteine
Met	—	methionine
Cyst	—	cystathionine
Cys	—	cysteine
Ser	—	serine

Bet	—	betaine
Chol	—	choline
FC	—	folate cycle
FA	—	folic acid
MTHFR	—	Methylenetetrahydrofolate reductase
MTR	—	B_{12} methionine synthase
MTRR	—	methionine synthase reductase
CBS	—	cystathionine β-synthase
SAM	—	S-adenosylmethionine
Allele C	—	neutral allele of the genetic polymorphism MTHFR: C677T
Allele T	—	risk allele of the genetic polymorphism MTHFR: C677T
Allele A	—	neutral allele of the genetic polymorphism MTHFR: A1298C
Allele C	—	risk allele of the genetic polymorphism MTHFR: A1298C
Allele A	—	neutral allele of the genetic polymorphism MTR: A2756G
Allele G	—	risk allele of the genetic polymorphism MTR: A2756G
Allele A	—	neutral allele of the genetic polymorphism MTRR: A66G
Allele G	—	risk allele of the genetic polymorphism MTRR: A66G
5-MTHF	—	5-methyltetrahydrofolate
5.10 MTHF	—	5.10 methylenetetrahydrofolate
NMDA	—	N-methyl-D-aspartate
ATP	—	adenosine triphosphoric acid
Ca	—	calcium
Ca^{2+}	—	ionized calcium
P	—	phosphorus
PTH	—	parathyroid hormone

TSH	—	pituitary thyroid stimulating hormone
T_3	—	triiodothyronine
T_4	—	thyroxine
Ct	—	calcitonin
C	—	cortisol
Tes	—	testosterone

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