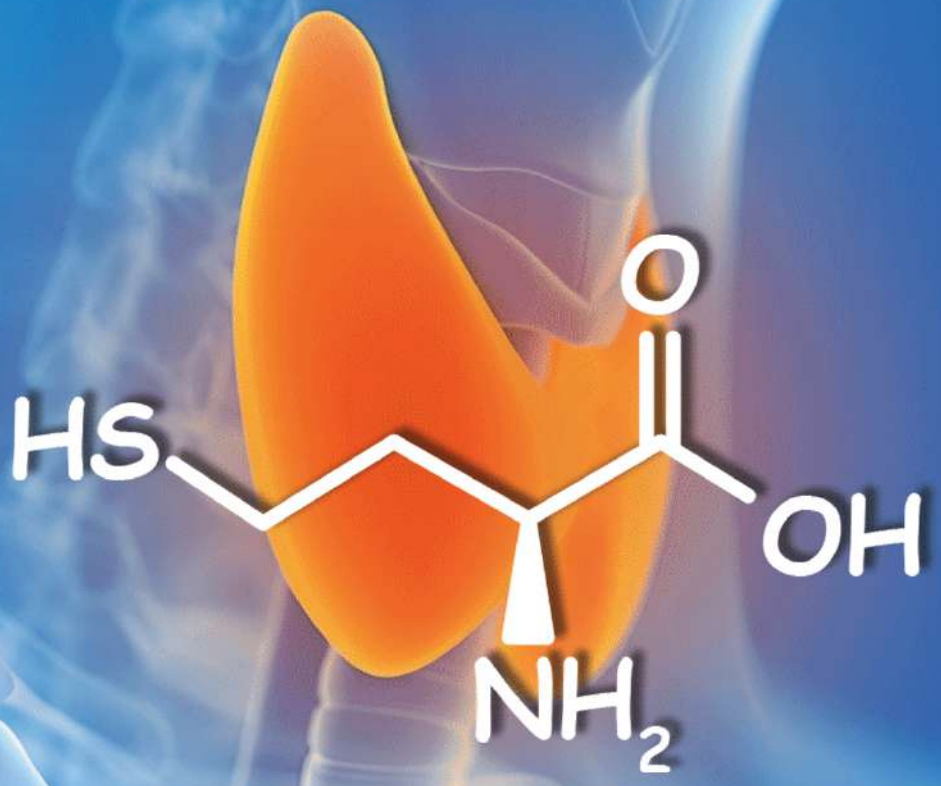
Yu. I. Bandazhevsky, N. F. Dubovaya

REGULATION OF THYROID GLAND FUNCTION IN CHILDREN LIVING IN AREAS AFFECTED BY THE CHERNOBYL NUCLEAR POWER PLANT



Coordination and Analytical Centre
«Ecology and Health»

Yu. I. Bandazhevsky, N. F. Dubovaya

REGULATION OF THYROID FUNCTION IN CHILDREN LIVING IN AREAS AFFECTED BY THE CHERNOBYL NUCLEAR POWER PLANT ACCIDENT

2025

UDC: 616-053.2:616.44+614.876

Bandazhevsky Yu. I., Dubovaya N. F.
Б19 Regulation of thyroid gland function in children living in areas affected by the Chernobyl nuclear power plant accident. Ivankiv: PI Coordination and Analytical Center «Ecology and Health», — Kyiv, FOP Samchenko A. M., 2025. 80 p.
ISBN 978-617-8413-19-4

The book is devoted to the regulation of thyroid function in children living near the Chernobyl exclusion zone. A scientific concept is presented that reflects the regulatory relationships of sulfur-containing amino acids and thyroid hormones under conditions of radiation exposure. The book is intended for doctors of all specialties, ecologists, researchers, specialists in the field of radiation protection, and for anyone involved in the consequences of the accident at the Chernobyl nuclear power plant.

ISBN 978-617-8413-19-4

UDC: 616-053.2:616.44+614.876

Authors

Yuri Bandazhevsky — Doctor of Medicine, Professor, Founder and first Rector of the Gomel State Medical University (1990-1999), Key expert № 1 of the European Commission project in Ukraine «Health and Ecological Programmes around the Chernobyl Exclusion Zone: Development, training and coordination of health-related projects», Head of the Board of PI Coordination and Analytical Center «Ecology and Health», Ukraine.

Nataliia Dubovaya — PhD, Senior Researcher, expert of the European Commission project in Ukraine «Health and Ecological Programmes around the Chernobyl Exclusion Zone: Development, training and coordination of health-related projects», Deputy Head of the Board of PI Coordination and Analytical Center «Ecology and Health», Ukraine.

CONTENTS

У ході реалізації в Україні у 2013-2017 рр. проектів Європейської Комісії «Програми охорони здоров'я та екології навколо Чорнобильської зони відчуження: розробка, навчання та координація проектів, пов'язаних зі здоров'ям» та Регіональної ради Рон Альп (Франція) у великої кількості дітей підліткового віку, які мешкають поблизу Чорнобильської зони відчуження, було виявлено підвищений вміст у крові сірковмісної амінокислоти гомоцистеїну, що визначається як гіпергомоцистеїнемія.

Згідно з численними зарубіжними дослідженнями, цей стан виникає при розвитку тяжких захворювань у дорослих осіб. При цьому гомоцистеїн розглядається як учасник патологічних процесів.

Тому важливо було визначити причини виникнення гіпергомоцистеїнемії у дітей, які перебувають в умовах постійного радіаційного впливу.

Автори публікації представили наукову концепцію, що ґрунтується на аналізі результатів кореляційного аналізу показників обміну речовин з урахуванням стану генів фолатного циклу у дітей, які проживають поблизу Чорнобильської зони відчуження.

Відповідно до цієї концепції гіпергомоцистеїнемія, що виникла внаслідок радіаційного впливу, стимулює гормоногенез у гіпоталамо-гіпофізарно-тиреоїдної осі.

При цьому в периферичних тканинах збільшується утворення трийодтироніну, здатного стимулювати клітинну енергетику та збільшувати синтез активних форм вітаміну B_9.

Таким чином, трийодтиронін є елементом захисту організму від руйнівної дії радіаційного фактора.

У зв'язку з цим, гомоцистеїн розглядається як учасник системи адаптації організму до зовнішнього впливу.

Однак при високих концентраціях в організмі, генетично обумовлених або пов'язаних з вираженою зовнішньосередовищною дією, гомоцистеїн порушує обмін речовин в організмі, викликаючи структурно-функціональні зміни в клітинах життєво важливих органів.

Preface

The book we present to readers contains information obtained as a result of many years of research conducted in areas bordering the Chernobyl exclusion zone.

Officially, the territory is not dangerous for human habitation.

However, during the implementation of the European Commission project in 2013-2016, it was established that the soils near populated areas contain large amounts of radioactive elements that penetrate the body of local residents, including children, through food chains.

At the same time, structural and functional changes occur in vital organs and systems of the body.

It is important to determine the nature of these changes, highlighting the elements of damage and compensatory and adaptive processes.

Considering the simultaneous incorporation of ^{137}Cs radionuclides into the internal organs and brain, an integrated approach was used to assess the metabolic changes that occurred.

The conducted assessment of the participation of homocysteine in the metabolism of thyroid hormones has scientific and practical significance.

The results of many years of work have allowed us to formulate a scientific concept that, according to the authors, reflects the regulatory links between sulfur-containing amino acids and thyroid hormones in the body of children and adults.

We hope that the information obtained will be used in practical healthcare when providing assistance to people suffering from radiation exposure.

We express our sincere gratitude to the French people.

With best wishes and gratitude for your attention,

Professor Yu. I. Bandazhevsky,

Senior Researcher N. F. Dubovaya

Chapter I.
The Chernobyl disaster and the thyroid gland

The thyroid gland (TG) is one of the vital organs of the human body.

Pathological processes associated with it, lead to death and disability.

The hormones produced by the TG participate in the main metabolic cycles of the human body, coordinating the activity of many organs and systems.

Their formation and metabolic transformation depend on the intake of iodine and selenium into the body.

The accident at the Chernobyl Nuclear Power Plant (ChNPP) in 1986 contributed to the contamination of the environment with short-lived radioactive isotopes of I: ^{131}I, ^{132}I, ^{123}I, ^{126}I, ^{130}I, ^{135}I, which, as some researchers believe, formed the total radiation dose of the TG. This was facilitated by the situation of iodine deficiency [1].

According to the official conclusion of the World Health Organization, it is radioactive iodine — ^{131}I, which ended up in the environment after the Chernobyl accident in April 1986, that is the main cause of malignant tumors of the TG in adults and children living in Ukraine and other countries of the former USSR [2].

However, 35 years after the Chernobyl accident, it was concluded that the ranking of regions, taking into account the thyroid dose due to ^{131}I, does not coincide with the results of ranking by the incidence of thyroid cancer [3].

In this regard, it should be noted that as a result of the explosion at the 4th reactor of the ChNPP, a huge amount of long-lived radionuclides were released into the environment, including ^{137}Cs and ^{90}Sr [4].

The results of radiometric studies conducted during autopsy of adults and children living in the Gomel region of the Republic of Belarus in the first decade after the Chernobyl accident indicate that the TG of children actively incorporates ^{137}Cs (Fig. 1) [5].

Subsequently, experiments on laboratory animals confirmed the ability of the TG to concentrate ^{137}Cs [6].

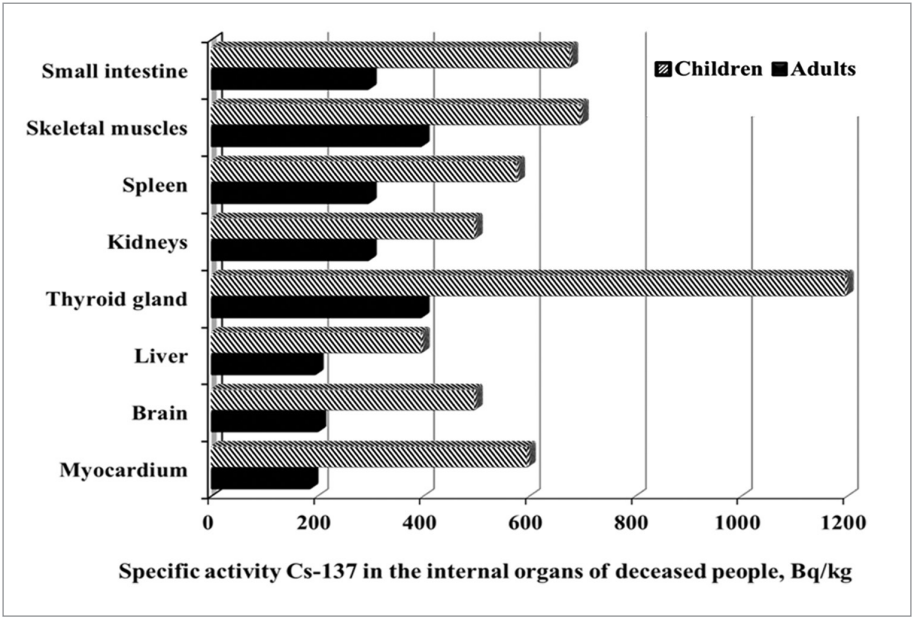


Fig. 1. Accumulation of ^{137}Cs radionuclides (Bq/kg) in the internal organs of adults and children – residents of the Gomel region of the Republic of Belarus who died in 1997 [5].

Based on this, attention should be paid to the participation of ^{137}Cs in thyroid cancer processes.

In Ukraine, an increase in thyroid cancer incidence, mainly among the female population, is noted many years after the tragic date of April 26, 1986 [7].

At the same time, the highest rate was recorded in areas with high levels of soil contamination with long-lived radioactive elements — in the Polessky and Ivankovsky districts of the Kyiv region [3].

In areas affected by the Chernobyl accident, an increase in non-neoplastic thyroid diseases was also noted, also mainly among the female population [8]. In children living near the Chernobyl Exclusion Zone (ChEZ), in the Ivankovsky and Polessky districts, in 2013-2017, structural changes in the TG were registered in 5.6% of cases, and impaired production of thyroid hormones — in 35.5% of cases [9].

Taking this into account, we can conclude that even many years after the Chernobyl accident, there is a real risk of pathological processes in the TG.

This is especially true for children and adults whose antenatal and postnatal development took place under conditions of constant radiation exposure.

An increase in thyroid pathology after the Chernobyl accident was also registered in areas that were not officially recognized as affected.

In particular, an increase in the incidence of thyroid cancer is noted in the 21st century, at a considerable distance from the site of the Chernobyl tragedy, in the Zaporizhia region [7].

When analyzing the causes of this phenomenon, it is necessary to pay attention to the migration of the population from Chernobyl areas to cleaner, in terms of radiation, areas.

It is also necessary to take into account the spread of ^{137}Cs, over huge distances from the original sources of radiation, in food products, wild berries and mushrooms, wood, air currents.

In this regard, as a source of radiation that currently exists, it is necessary to note the ChEZ, in which fires of radioactive forests often occur [10].

Insufficient iodine and selenium intake into the body are noted as causes of thyroid pathology [1].

Mild and moderate iodine deficiency is noted in the territory of the Ukrainian-Belarusian Polesie [1, 11], which undoubtedly contributed to the negative impact of ^{131}I on the TG of local residents in the first days after the Chernobyl accident.

However, it should be noted that the Gomel region, heavily contaminated with radioactive elements, has a lower level of iodine deficiency compared to other regions of the Republic of Belarus. At the same time, the highest number of thyroid cancer cases has been registered in the Gomel region [11].

We explain this by the impact of ^{137}Cs radionuclides on the population of this region, starting in the 60s of the last century [12].

For many years, attempts have been made to correct iodine deficiency in the population by iodizing food products, including table salt, bread and bakery products, as well as eating seafood, in particular seaweed [13].

However, it should be recognized that, despite the enormous attention to the TG after the Chernobyl accident, the etiopathogenesis of thyroid pathology has not been sufficiently studied.

This does not allow for the full implementation of effective preventive and therapeutic measures.

Chapter II.
Classical concepts of regulation of thyroid hormone metabolism

Thyroid hormones are iodinated amino acids L-thyroxine (T_4) and 3,5,3'-triiodo-L-thyronine (T_3) [14].

The TG produces mainly the prohormone T_4.

About 80% of T_3, the active form of thyroid hormones, is formed in peripheral tissues as a result of enzymatic deiodination of the outer ring of T_4, the so-called 5'-monodeiodination [15].

The process of T_4 deiodination is catalyzed by enzymes called iodothyronine deiodinases, or deiodinases.

Deiodinases of types 1 (D1), 2 (D2) and 3 (D3) have been identified. [16, 17].

These enzymes contain 250-280 amino acids, as well as a selenium-cysteine compound located in the center [17].

Deiodinases D1 and D2 perform deiodination of the outer ring of T_4.

Deiodinase D1 is localized on the plasma membrane of liver cells, proximal renal tubules, and follicular cells of the TG.

Deiodinase D2 is found in the endoplasmic reticulum of brain cells, the anterior pituitary gland, TG, skeletal muscles, and heart.

Deiodinase D3 catalyzes the process of converting T_4 into reverse rT_3 by deiodination of its inner ring.

Deiodinase D3 has been found in cells of the brain, skin, liver, intestines, fetus and placenta, as well as tumors, including malignant ones [16].

Deiodinases form a dynamic system, their activity changes depending on the functions performed by cells of various tissues [17].

An increase in the activity of deiodinase D1 in hyperthyroidism and deiodinase D2 in hypothyroidism has been noted [16].

T_3, acting on plasma membranes, regulates the penetration of calcium ions into and out of the cell [14].

T_3 is transported through the cell membrane by specific carriers, in particular, monocarboxylate transporter 8 (MCT8) [18].

Mitochondrial structures are exposed to T_3, resulting in a change in energy metabolism [14].

At the level of the cell nucleus, T_3 modifies gene expression by acting on nuclear receptors [16].

It is generally accepted that the regulation of thyroid function is carried out by structures of the central nervous system, in particular the hypothalamus and adenohypophysis (AH).

The main active element of the thyroid function regulation system is the pituitary thyroid-stimulating hormone (TSH), produced in the anterior pituitary gland.

In its structure, TSH is a glycoprotein consisting of alpha and beta chains, with a molecular weight of about 28,000 Da [15].

In the generally accepted regulatory scheme, the hypothalamic thyrotropin-releasing hormone stimulates the production of TSH in the AH, which in turn stimulates the production of thyroid hormones in the TG in the event of a decrease in the concentration of the latter in the blood.

It is believed that the main mechanism of thyroid homeostasis is a negative feedback loop between circulating thyroid hormone and the neuroendocrine system.

One of the triggers that initiates the process of activating the synthesis of hormones of the hypothalamic-pituitary-thyroid axis is iodine deficiency in the body [19].

TSH acts on specific receptors on the membrane of thyroid cells, stimulating the secretion of mainly T_4 [15].

In turn, an increase in the content of thyroid hormones in the blood is a blocking factor in the production of TSH in the AH [20].

However, there is a nuance that should be noted.

A decrease in TSH secretion is noted at a high level of the T_3/T_4 ratio, while at a low level of the T_3/T_4 ratio, an increase in TSH secretion occurs [15].

It is noted that the constant level of thyroid hormones in the blood depends on the state of the hypothalamic-pituitary-thyroid axis, as well as on the activity of tissue deiodinases [21].

The presented scheme does not reflect all the elements of the regulatory process in the pituitary-thyroid system.

It does not precisely define which other hormones and metabolites are involved in the regulation of hormonogenesis of the pituitary-thyroid axis.

Perhaps, therefore, there are problems in the clinic when providing medical care to people with altered thyroid status.

Chapter III.
Homocysteine and its role in the functioning of the body

The presented scheme does not reflect all the elements of the regulatory process in the pituitary-thyroid system.

During the implementation in Ukraine, in 2013-2017, of the European Commission projects "Health and Ecological Programmes around the Chernobyl Exclusion Zone: Development, training and coordination of health-related projects" and the regional council of Rhone Alpes (France), a large number of adolescent children from the Ivankovsky and Polessky districts of the Kyiv region were found to have elevated blood levels of the sulfur-containing amino acid homocysteine (H_{cy}) — the main participant in the metabolism of the essential amino acid methionine (Met) in the body [11].

a). Metabolism of sulfur-containing amino acids methionine and homocysteine in the body.

Met, entering the body from the outside, is a source of methyl groups used in methylation reactions, in the process of synthesis of proteins, phospholipids, biogenic amines.

However, for this, it must be converted into an active form — S-adenosylmethionine (SAM).

The process of formation of the sulfonium form of this amino acid occurs, under the influence of methionine adenosyltransferase, during the addition to the adenosine molecule, the source of which is ATP.

During the reaction catalyzed by methyltransferase, SAM gives up a methyl group and turns into S-adenosylhomocysteine (SAH).

The methylation potential determines the ratio of SAM and SAH.

Under the influence of hydrolase, SAH breaks down into H_{cy} and adenosine.

Reverse methylation of H_{cy} is carried out with the participation of enzymes of the folate cycle (FC) and active forms of vitamins B_9 (B_9) and B_{12} (B_{12}) [22-25].

The folic acid (folate) molecule includes a pterin derivative, para-aminobenzoic and glutamic acids.

This complex is converted in the liver, under the influence of folate reductase and dihydrofolate reductase, into tetrahydrofolate, which is capable of being an acceptor of one-carbon fragments in reactions with serine and glycine and transforming into 5,10, methylenetetrahydrofolate.

Under the influence of methylenetetrahydrofolate reductase (MTHFR), 5,10, methylenetetrahydrofolate is converted into 5 methyltetrahydrofolate (5-MTHF), which is capable of transporting a methyl group to an enzyme complex called B_{12}-methionine synthase (MS).

5-MTHF is the active form of vitamin B_9, transferring a methyl group to B_{12}, which directly interacts with the H_{cy} molecule.

As a result of this interaction, internal Met is formed.

This reaction occurs in all tissues. In addition to 5-MTHF, betaine, which is synthesized from choline by betaine-homocysteine-S-methyltransferase in the liver, kidneys, and lens, is a source of methyl groups for the formation of internal Met.

In a physiological state, about 50% of H_{cy} is methylated to form Met.

In the liver, kidneys, small intestine, pancreas, and lens, H_{cy} can also be utilized in the transsulfuration reaction cycle [22].

There is an opinion that the intracellular level of SAM affects the pathway by which H_{cy} is metabolized.

SAM is assigned the role of an allosteric activator of cystathionine-β-synthase (CBS) and an allosteric inhibitor of MTHFR, which produces 5-MTHF [23].

In the transsulfuration reaction cycle, H_{cy} condenses with serine, resulting in the formation of cystathionine (Cyst).

This irreversible reaction is catalyzed by CBS, the coenzyme of which is vitamin B_6 (B_6).

Cyst is converted into cysteine (Cys) by γ-cystathionase (CSE).

Cys, interacting with selenium, forms selenocysteine — a coenzyme form of deiodinase — an enzyme that catalyzes the process of T_4 deiodination.

In addition, Cys is involved in the formation of protein molecules, coenzyme A, sulfates and glutathione, which is a tripeptide L-γ-glutamyl-L-cysteinylglycine.

Antioxidant properties of glutathione have been noted. It is involved in reactions aimed at preventing the action of active forms of oxygen and free radicals [22].

Excess Cys is oxidized to taurine and can also be excreted from the body in urine.

H_{cy} and/or Cys catalysis results in the formation of H_2S, a gasotransmitter, one of the main regulators of physiological processes in the body [22].

Thus, the sulfur-containing amino acid H_{cy} is the main link in the body's metabolic processes.

b). Hyperhomocysteinemia and its association with pathological processes.

Based on the results of numerous studies, the level of H_{cy} in the blood was determined for each age group, the excess of which is characterized as a state of hyperhomocysteinemia.

In our studies, the state of hyperhomocysteinemia in adolescents was recorded if the level of H_{cy} in their blood exceeded 10.0 μmol/l.

Hyperhomocysteinemia — is it a pathological condition or an element / marker of the body's adaptive capabilities to certain environmental conditions?

It is not so easy to answer this question, despite the fact that a huge number of studies have been conducted related to the determination of H_{cy} in the blood.

For the most part, these were studies when the state of hyperhomocysteinemia was tied to a specific disease, or to an already developed pathological condition.

At the same time, H_{cy} was considered as an integral element of the pathological process.

Clinical and experimental studies have identified hyperhomocysteinemia as a risk factor for cardiovascular disease, stroke, and blood clotting disorders, with thrombosis and occlusion of peripheral vessels [26, 27, 28].

These pathological processes are associated with the toxic effects of H_{cy} on the body.

H_{cy} toxicity occurs when it covalently binds to proteins, resulting in structural and functional changes in the latter.

The process by which a new post-translational modification of protein molecules occurs is called N-homocysteinylation [22].

In this case, the resulting complexes acquire cytotoxic, pro-inflammatory, pro-atherothrombotic and pro-neuropathic properties [29].

H_{cy} is converted into H_{cy}-thiolactone, which carries out N-homocysteinylation of protein molecules.

In its chemical structure, H_{cy}-thiolactone is a five-membered form of the condensed H_{cy} ring.

With the development of atherosclerosis, this reactive anhydride-H_{cy} interacts with low-density lipoproteins, which ultimately leads to the deposition of cholesterol and other fats in atherosclerotic vascular plaques [30].

The interaction of H_{cy}-thiolactone with serum proteins promotes the formation of new protein antigens and autoimmune antibodies [29].

The toxic effect of H_{cy} on brain cells is associated with oxidative stress, overactivation of glutamate receptors, mitochondrial dysfunction, resulting in degeneration and death of nerve cells [31, 32, 33].

H_{cy} can not only penetrate the central nervous system through the damaged blood-brain barrier, but also be produced by nerve cells [34].

The neurotoxic properties of H_{cy} are based on its ability to react with the glutamate receptor subtype N-methyl-D-aspartate (NMDA) [33].

In this case, its oxidized form is isolated — homocysteine acid, produced by brain cells and is an excitatory neurotransmitter of NMDA receptors [35, 36].

Elevated H_{cy} levels in the blood are very often recorded among the elderly.

At the same time, H_{cy} in concentrations exceeding the physiological level (15.0 μmol/l) causes disruption of the hematological barrier of the brain and retina, which contributes to the development of neurodegenerative diseases and vision loss [31, 36].

By inducing neuronal degeneration, H_{cy} causes deterioration of cognitive functions and memory.

A link has been established between hyperhomocysteinemia and stroke, Parkinson's and Alzheimer's diseases [37].

The autonomic nervous system is also affected by hyperhomocysteinemia.

A correlation has been noted between the H_{cy} level in plasma and dysfunction of the autonomic nervous system of the heart in patients with obstructive sleep apnea syndrome [38].

In the elderly, high H_{cy} levels in the blood are associated with low bone mineral density and a high risk of fractures [39].

As a result, there is an opinion that H_{cy} is a predictor of bone fractures in the elderly [40].

An increase in the H_{cy} level in the blood has been noted in hypothyroidism [41].

Experimental studies have established that in the blood with hyperthyroidism there is a decrease in the concentration of H_{cy}, whereas in hypothyroidism an increase is recorded [42].

Very few studies have been conducted based on the determination of H_{cy} in the blood of individuals (adults and children) with no pronounced pathology.

This does not allow us to fully assess the role of H_{cy} as a participant in physiological processes or processes of adaptation to external conditions.

c). Hyperhomocysteinemia in Ukrainian children living near the Chernobyl exclusion zone.

The projects of the European Commission and the Regional Council of Rhone-Alpes (France), carried out in Ukraine in April 2015, made it possible to determine the level of H_{cy} in the blood of adolescents from the Ivankovsky and Polessky districts of the Kyiv region and identify the state of hyperhomocysteinemia in 48.8% of cases.

In December 2015, the state of hyperhomocysteinemia in children from these areas was determined much more often, in 75.3% of cases [11].

In January 2022, a laboratory genetic study conducted with the financial support of the French public organization "Children of

Chernobyl" revealed the state of hyperhomocysteinemia in a group of children from the Ivankovsky district in 65.44% of cases [43].

Undoubtedly, this information makes it necessary to look for the causes of hyperhomocysteinemia in children living near the ChEZ.

The participation of B_9 and B_{12} in the processes of H_{cy} methylation and Met synthesis is known [44].

In this regard, when determining the causes of hyperhomocysteinemia in children living near the ChEZ, genetic polymorphisms of FC that affect the formation of active forms of B_9 and B_{12} and the processes of H_{cy} methylation were studied.

In the general group of children, as well as in the groups of boys and girls, cases of the homozygous variant of the AMTR: 2756 neutral allele associated with the enzyme MS, which ensures the transfer of a methyl group from B_9 to B_{12}, and from B_{12} to H_{cy}, were more common.

At the same time, a significantly smaller number of children contained in their genome the homozygous variant of the neutral alleles of the MTHFR: A1298C, MTHFR: C677T and MTRR: A66G polymorphisms.

Cases with the CMTHFR: 1298 and TMTHFR: 677 risk alleles (Tables 1, 2, 3) are more common [45].

The MTHFR: A1298C and MTHFR: C677T polymorphisms affect the activity of the enzyme MTHFR, which catalyzes the formation of the active form of B_9 — 5-MTHF.

The prevalence rates of the TMTHFR:677 allele in the group of children from the Ivankovsky and Polessky districts corresponded to the rates of the European population [46], however, the proportion of variants with the GMTRR:66 allele was significantly higher than in the European population [47].

At the same time, the proportion of cases with the homozygous variant of the AMTRR:66 neutral allele was significantly lower than the proportion of cases with the homozygous variant of the GMTRR:66 risk allele (Tables 1, 2, 3).

The MTRR: A66G polymorphism is associated with methionine synthase reductase (MSR), which is part of a multiprotein complex that ensures the restoration of MS activity and the synthesis of methylcobalamin.

Table 1

The proportion of alleles of genetic polymorphisms of FC in the group of children living near the ChEZ

Gene, polymorphism	Genotype variants					
	«Neutral» allele homozygous variant		«Risk» allele heterozygous variant		«Risk» allele homozygous variant	
	n	%	n	%	n	%
MTR: A2756G	427	61.88	226	32.76	37	5.36
MTHFR: A1298C	328	47.54	297	43.04	65	9.42
MTHFR: C677T	320	46.38	311	45.07	59	8.55
MTRR: A66G	132	19.13	328	47.54	230	33.33

Note. n is the number of cases; % is the proportion of cases.

Table 2

The proportion of alleles of genetic polymorphisms of FC in the group of boys living near the ChEZ

Gene, polymorphism	Genotype variants					
	«Neutral» allele homozygous variant		«Risk» allele heterozygous variant		«Risk» allele homozygous variant	
	n	%	n	%	n	%
MTR: A2756G	193	59.94	111	34.47	18	5.59
MTHFR: A1298C	152	47.20	133	41.30	37	11.50
MTHFR: C677T	154	47.83	141	43.79	27	8.38
MTRR: A66G	58	18.01	157	48.76	107	33.23

Note. n is the number of cases; % is the proportion of cases.

The proportion of cases of hyperhomocysteinemia in the general group of examined children was 62.46% (431 of 690 persons), in the group of boys — 72.36% (233 of 322 persons), in the group of girls — 53.80% (198 of 368 persons).

The highest proportion of hyperhomocysteinemia cases was recorded in the subgroup with the main T/TMTHFR:677 genotype, the lowest in the subgroup with the main C/CMTHFR:1298 genotype.

Table 3

The proportion of alleles of genetic polymorphisms of FC in the group of girls living near the ChEZ

Gene, polymorphism	Genotype variants					
	«Neutral» allele homozygous variant		«Risk» allele heterozygous variant		«Risk» allele homozygous variant	
	n	%	n	%	n	%
MTR: A2756G	234	63.59	115	31.25	19	5.16
MTHFR: A1298C	176	47.83	164	44.56	28	7.61
MTHFR: C677T	166	45.11	170	46.19	32	8.70
MTRR: A66G	74	20.11	171	46.47	123	33.42

Note. n is the number of cases; % is the proportion of cases.

In the remaining genetic subgroups, its values did not have significant differences (Tables 4, 5, 6).

In most genetic subgroups of boys, the values of the proportion of hyperhomocysteinemia cases were higher than in similar genetic subgroups of girls (Tables 5, 6).

Table 4

The proportion of cases of hyperhomocysteinemia in the general group of children with genetic polymorphisms of the FC

Gene, polymorphism	Hyperhomocysteinemia					
	«Neutral» allele homozygous variant		«Risk» allele heterozygous variant		«Risk» allele homozygous variant	
	n	%	n	%	n	%
MTR: A2756G	271	63.47	137	60.62	23	62.16
MTHFR: A1298C	209	63.72	191	64.31	31	47.69
MTHFR: C677T	187	58.44	199	63.99	45	76.27
MTRR: A66G	75	56.82	209	63.72	147	63.91

Note. n is the number of cases; % is the proportion of cases.

Table 5

The proportion of cases of hyperhomocysteinemia in subgroups of boys with genetic polymorphisms of the FC

Gene, polymorphism	Hyperhomocysteinemia					
	«Neutral» allele homozygous variant		«Risk» allele heterozygous variant		«Risk» allele homozygous variant	
	n	%	n	%	n	%
MTR: A2756G	141	73.06	79	71.17	13	72.22
MTHFR: A1298C	112	73.68	100	75.19	21	56.76
MTHFR: C677T	104	67.53	107	75.89	22	81.48
MTRR: A66G	34	58.62	117	74.52	82	76.63

Note. n is the number of cases; % is the proportion of cases.

Table 6

The proportion of cases of hyperhomocysteinemia in subgroups of girls with genetic polymorphisms of the FC

Gene, polymorphism	Hyperhomocysteinemia					
	«Neutral» allele homozygous variant		«Risk» allele heterozygous variant		«Risk» allele homozygous variant	
	n	%	n	%	n	%
MTR: A2756G	130	55.55	58	50.43	10	52.63
MTHFR: A1298C	97	55.11	91	55.49	10	35.71
MTHFR: C677T	83	50.00	92	54.12	23	71.87
MTRR: A66G	41	55.40	92	53.80	65	52.84

Note. n is the number of cases; % is the proportion of cases.

The exceptions were the G/GMTR:2756, C/CMTHFR:1298, T/TMTHFR:677 and A/AMTRR:66 subgroups [45].

The range of H_{cy} values in the general group of children was 5.05-77.21 μmol/l, with the greatest number of cases associated with H_{cy} levels > 10.0 μmol/l.

A significantly smaller number of children had H_{cy} levels in the blood greater than 20.0 μmol/l.

The greatest number of cases with H_{cy} levels greater than 10.0 and 20.0 μmol/l were detected in the group of children with the T/TMTHFR:677 genotype (Table 7).

Table 7

Range of H_{cy} values and distribution of hyperhomocysteinemia cases in the analyzed groups of children

Analyzed group	N_1	N_2	H_{cy} > 10.0 μmol/L		H_{cy} > 20.0 μmol/L	
			n	%	n	%
General	690	5.05-77.21	431	62.46	20	4.49
C/C MTHFR:677	320	5.05-43.03	167	52.19	8	2.50
C/T MTHFR:677	311	5.81-71.27	199	63.99	8	2.57
T/T MTHFR:677	59	7.10-77.21	45	76.27	15	25.42

Note. N_1 is the number of cases in the group; N_2 is the range of H_{cy} values in the analyzed group (μmol/l); n is the number of cases; % is the proportion of cases.

The primary role of the MTHFR:C677T polymorphism in controlling the level of H_{cy} in the blood is confirmed by the direct correlation between the values of H_{cy} in the blood and the genetic risk index in children from rural settlements of the Polessky and Ivankovsky districts (Tables 8, 9) [48], as well as from the settlement of Ivankov (Tables 10, 11) [43].

Table 8

Correlations between H_{cy} and the genetic risk index (Risk) of analyzed polymorphisms in a group of children from Polessky district (April 2015) [48].

Parameter	Correlation coefficient	Parameters			
		[1]Risk MTHFR:C677T	[2]Risk MTHFR: A1298C	[3]Risk MTR: A2756G	[4]Risk MTRR: A66G
H_{cy}	Spearman's	0.283**	0.040	-0.109	0.170*
	Sign. (2-tailed)	0.0001	0.615	0.174	0.033
	N	158	158	158	158

Note. * — correlation is significant at the 0.05 level (2-tailed). ** – correlation is significant at the 0.01 level (2-tailed). [1]Risk MTHFR:677 — CC, CT, TT; [2]Risk MTHFR:1298 — AA, AC, CC; [3]Risk MTR:2756 — AA, AG, GG; [4]Risk MTRR:66 — AA, AG, GG.

Table 9

Correlations between H_{cy} and the genetic risk index (Risk) of analyzed polymorphisms in a group of children from Ivankovsky district (December 2015) [48].

Parameter	Correlation coefficient	Parameters			
		[1]Risk MTHFR:C677T	[2]Risk MTHFR: A1298C	[3]Risk MTR: A2756G	[4]Risk MTRR: A66G
H_{cy}	Spearman's	0.201**	-0.026	-0.108	0.177*
	Sign. (2-tailed)	0.007	0.728	0.151	0.018
	N	178	178	178	178

Note. * — correlation is significant at the 0.05 level (2-tailed). ** – correlation is significant at the 0.01 level (2-tailed). [1]Risk MTHFR:677 — CC, CT, TT; [2]Risk MTHFR:1298 — AA, AC, CC; [3]Risk MTR:2756 — AA, AG, GG; [4]Risk MTRR:66 — AA, AG, GG.

Table 10

Correlations between Hcy and the genetic risk index (Risk) of analyzed polymorphisms in a group of children from Ivankov (January 2022) [43].

Parameter	Correlation coefficient	Parameters			
		[1]Risk MTHFR:C677T	[2]Risk MTHFR: A1298C	[3]Risk MTR: A2756G	[4]Risk MTRR: A66G
H_{cy}	Spearman's	0.206**	- 0.165*	- 0.034	0.093
	Sign. (2-tailed)	0.002	0.015	0.618	0.172
	N	217	217	217	217

Note. * – correlation is significant at the 0.05 level (2-tailed). ** – correlation is significant at the 0.01 level (2-tailed). [1]Risk MTHFR:677 — CC, CT, TT; [2]Risk MTHFR:1298 — AA, AC, CC; [3]Risk MTR:2756 — AA, AG, GG; [4]Risk MTRR:66 — AA, AG, GG.

In this regard, the inverse correlation between the indicators reflecting the content of vitamin B_9 in the blood serum and the indicators of genetic risk (Risk) associated with the MTHFR:C677T polymorphism (Table 12) is logical [49].

Table 11

Correlations between H_{cy} and the genetic risk index (Risk) of the analyzed polymorphisms in the group of children with hyperhomocysteinemia from Ivankov (january 2022) [43].

Parameter	Correlation coefficient	Parameters			
		[1]Risk MTHFR:C677T	[2]Risk MTHFR: A1298C	[3]Risk MTR: A2756G	[4]Risk MTRR: A66G
H_{cy}	Spearman's	0.308**	- 0.161	0.098	0.146
	Sign. (2-tailed)	0.000	0.056	0.244	0.083
	N	142	142	142	142

Note. ** — correlation is significant at the 0.01 level (2-tailed). [1]Risk MTHFR:677 — CC, CT, TT; [2]Risk MTHFR:1298 — AA, AC, CC; [3]Risk MTR:2756 — AA, AG, GG; [4]Risk MTRR:66 — AA, AG, GG.

Table 12

Correlation relationships between H_{cy}, B_6, B_9 and B_{12} and the genetic risk indicator (Risk) of the MTHFR:C677T polymorphism in a group of children from Ivankovsky district [49].

Parameter	Correlation coefficient	Parameters			
		H_{cy}	B_6	B_9	B_{12}
Risk MTHFR: C677T	Spearman's	0.201**	0.060	- 0.218**	- 0.005
	Sign. (2-tailed), p	0.007	0.428	0.004	0.952
	N	178	178	178	178

Note. ** – correlation is significant at the 0.01 level (2-tailed); Risk MTHFR:C677T: CC, CT, TT.

It indicates the participation of MTHFR in the formation of the active form of B_9.

In the study of the causes of hyperhomocysteinemia, an assessment was made of the relationship between the number of polymorphisms with risk alleles and the proportion of hyperhomocysteinemia cases.

The population of children living near the ChEZ is characterized by a large number of cases with risk alleles of the FC polymorphisms.

Only 2.2% of children were not carriers of the risk alleles of the studied polymorphisms.

The largest number of children contained in their genome the risk alleles of two and three FC polymorphisms (Tables 13, 14) [50].

Table 13

The proportion of cases with risk alleles of genetic polymorphisms of FC and hyperhomocysteinemia in the general group of examined children [50].

Subgroup No.	N	Risk allele		Hyperhomocysteinemia	
		n	%	n	%
1	0	15	2.2	6	40.0
2	1	103	14.9	66	64.1
3	2	313	45.4	193	61.7
4	3	209	30.3	132	63.2
5	4	50	7.2	34	70.8
All cases		690	100	431	62.5

Note. N is the number of polymorphisms; n is the number of cases. % is the proportion of cases.

Table 14

The proportion of cases with risk alleles of genetic polymorphisms of FC and hyperhomocysteinemia in groups of boys and girls [50].

Subgroup No.	N	Risk allele				Hyperhomocysteinemia			
		Boys		Girls		Boys		Girls	
		n	%	n	%	n	%	n	%
1	0	5	1.5	10	2.7	0	0	6	60.0
2	1	50	15.5	53	14.4	38	76.0	28	52.8
3	2	138	42.9	175	47.6	98	71.0	95	54.3
4	3	111	34.5	98	26.6*	81	73.0	51	52.0
5	4	18	5.6	32	8.7	16	88.9	18	56.3
All cases		322	100	368	100	233	72.4	198	53.8

Note. N is the number of polymorphisms; n is the number of cases. % is the proportion of cases. * — statistical differences between boys and girls in subgroup No. 4 ($t=2.25$; $p=0.025415$).

At the same time, in the group of boys, the proportion of cases with risk alleles of three polymorphisms was significantly higher than in the group of girls (Table 14).

The proportion of hyperhomocysteinemia cases had the lowest values in the subgroup with the absence of risk alleles of all 4 FC polymorphisms (Table 13).

At the same time, in the group of boys, there were no cases of an increase in the H_{cy} level above the physiological level, whereas in the group of girls they occurred in 6 cases (Table 14).

The proportion of hyperhomocysteinemia cases in the remaining subgroups was not associated with the number of FC polymorphisms containing risk alleles.

In the general group, this indicator exceeded 60%, in the group of boys – 70%, in the group of girls – 50%.

Genotypes with the risk allele of one polymorphism were recorded in 15% of cases.

They are of scientific and practical interest in terms of assessing the role of one specific element of the FC enzyme system in the etiopathogenesis of hyperhomocysteinemia.

In the subgroup of boys with the T/TMTHFR:677 genotype, the proportion of hyperhomocysteinemia cases was 100%, in the subgroup of girls with the same genotype – 80%.

However, even in the absence of the risk allele of the MTHFR:C677T polymorphism (C/CMTHFR:677 genotype), the proportion of hyperhomocysteinemia cases in the subgroup of boys was 67.53%, in the subgroup of girls – 50.0% [45].

The highest proportion of hyperhomocysteinemia cases was recorded among all children and boys in the subgroup with risk alleles of all four FC polymorphisms [50].

This was facilitated by the compound heterozygosity of A/CMTHFR:1298 and C/TMTHFR:677 in combination with the A/GMTR: A2756G and G/G A66G genotypes.

The presence of risk alleles of FC polymorphisms in the genome of children was not always associated with an increase in the level of H_{cy} in the blood.

In 37% of cases with risk alleles of FC polymorphisms in the genome, the H_{cy} level in the blood did not go beyond the physiological parameters [50].

This fact, as well as the absence of reliable statistical differences in the proportion of cases of hyperhomocysteinemia in most genetic subgroups of boys and girls, with a different number of FC polymorphisms, and the occurrence of hyperhomocysteinemia in children whose genome did not contain the risk alleles of these polymorphisms, indicates a significant role of the environmental factor in controlling the functioning of FC.

The impact of the environmental radiation factor on the body of children is confirmed by the results of a study of the state of the cardiovascular system.

The specific activity of ^{137}Cs radionuclides in the body of children aged 6.0-18.0 years, living in 2014-2016 near the ChEZ, was determined in the range of 1.1-199.0 Bq/kg.

In this case, an inversely proportional relationship was recorded between the values of the specific activity of ^{137}Cs, systolic, diastolic and pulse arterial pressure (Table 15) [11].

Table 15

Correlation relationships between the indicators of specific activity of ^{137}Cs (Bq/kg), arterial pressure in the group of examined children aged 12.0-18.0 years [11].

Parameter	Correlation coefficient, r_{xy}	Parameters		
		SBP, mmHg	DBP, mmHg	PP, mmHg
Specific activity of ^{137}Cs, Bq/kg	Spearman's	- 0.318**	- 0.098**	- 0.228**
	Sign. (2-tailed), p	0.0001	0.008	0.0001
	n	719	719	719

Note. n is the number of cases; ** – correlation is significant at the 0.01 level (2-tailed). SBP – systolic blood pressure; DBP – diastolic blood pressure; PP – pulse pressure.

The damage to the mitochondria of heart cells and the disruption of the energy potential in the examined children was indicated by a direct correlation between the values of the specific activity of ^{137}Cs and the activity of serum aspartate aminotransferase (AST), the specific activity of ^{137}Cs and the De Ritis coefficient.

At the same time, this relationship was absent between the values of the specific activity of ^{137}Cs and the activity of serum alanine aminotransferase (ALT) (Table 16) [11].

Table 16

Correlation relationships between the values of specific activity of ^{137}Cs (Bq/kg) and the activity of transaminases in the blood serum of the examined children [11].

Parameter	Correlation coefficient, r_{xy}	Parameters		
		AST	ALT	AST/ALT
Specific activity of ^{137}Cs, Bq/kg	Spearman's	0.295**	- 0.027	0.285**
	Sign. (2-tailed), p	0.0001	0.328	0.0001
	n	1320	1320	1320

Note. n is the number of cases; ** – correlation is significant at the 0.01 level (2-tailed); n is the number of cases; AST – aspartate aminotransferase; ALT – alanine aminotransferase; AST/ALT – De Ritis coefficient.

Serum AST values exceeding reference values were recorded in 37.5% of cases, while serum ALT values exceeded reference values in 1.2% of cases.

De Ritis coefficient values exceeding 2.0 (upper physiological limit) were recorded in 26.29% of cases [11].

An increase in the H_{cy} level in the blood occurred in most children from the village of Radynka in the Polessky district after forest fires in the ChEZ in the spring and summer of 2015 [10].

At the same time, there was no correlation between the concentration of H_{cy} in the blood and the number of polymorphisms with risk alleles (Fig. 2a) [11].

At the same time, the mothers of these children showed a direct relationship between the number of genetic polymorphisms of FC with risk alleles and indicators reflecting the content of H_{cy} in the blood ($r=0.336^*$, $p=0.006$, $n=66$), as well as the proportion of cases of hyperhomocysteinemia (Fig. 2b) [11].

It can be reasonably stated that in children of the second Chernobyl generation, permanently residing in the territory affected by the Chernobyl accident, the increase in the level of H_{cy} in the blood is associated with a disruption in the implementation of the FC genes under conditions of constant environmental radiation exposure.

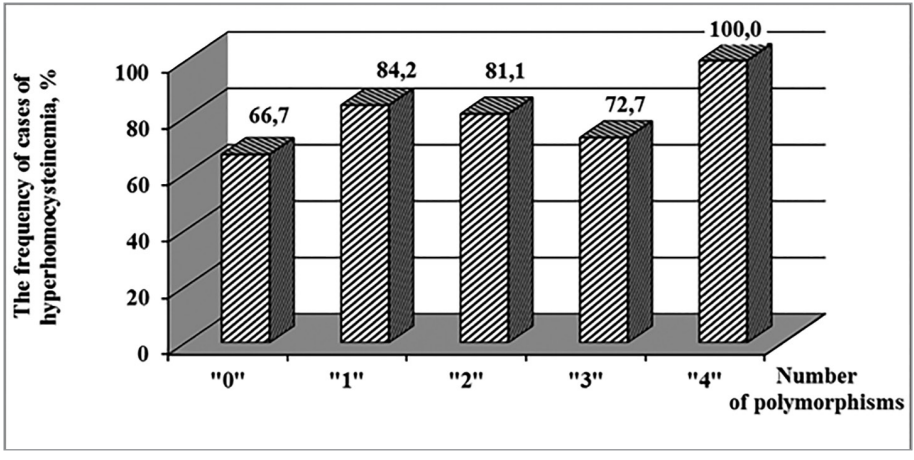


Fig. 2a. The proportion of cases of hyperhomocysteinemia depending on the number of genetic polymorphisms with risk alleles in subgroups of children from the Polessky district [11].

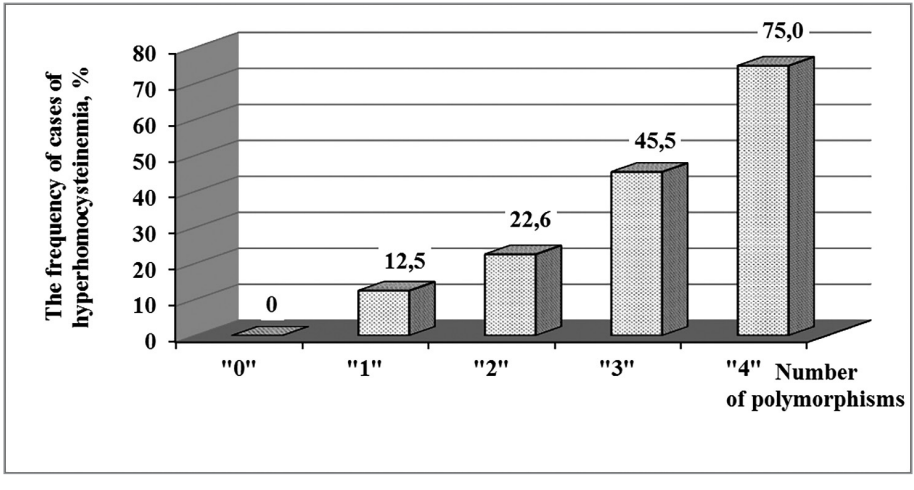


Fig. 2b. The proportion of cases of hyperhomocysteinemia in subgroups with risk alleles of genetic polymorphisms in the group of mothers of examined children from the Polessky district [11].

Chapter IV.
Regulatory associations between homocysteine, B vitamins and hormones of the pituitary-thyroid axis in children under conditions of radiation exposure

To clarify the cause-and-effect associations between FC, H_{cy} and the pituitary-thyroid axis under radiation exposure, statistical studies were conducted in genetic subgroups of children living in areas located near the ChNPP.

An important element of these studies was the analysis of correlations between H_{cy} and metabolic parameters reflecting the functioning of FC, the AH, the cycle of transsulfuration reactions, the process of T_4 deiodination with the formation of T_3.

In this case, the environmental radiation exposure caused by forest fires in the ChEZ was taken into account.

Variants of correlations of metabolic parameters in genetic subgroups of children in the Ivankovsky district are presented in Table 17.

Table 17

Variants of correlations of metabolic parameters in genetic subgroups of children of Ivankovsky district

Main genotype	Correlations	
	a	b
A/AMTR:2756	$-B_{12}$-H_{cy}, $-B_9$-H_{cy}, $+B_9$-B_{12}	$+B_9$-T_4, $+B_{12}$-T_4
A/GMTR:2756	$-B_{12}$-H_{cy}, $-B_9$-H_{cy}, $-B_{12}$-B_6	$+T_3$-B_9, $+B_{12}$-T_4, $-B_{12}$-TSH
G/GMTR:2756	$-B_{12}$-H_{cy},$+H_{cy}$-B_6	-
A/AMTHFR:1298	$-B_{12}$-H_{cy}, $-B_9$-H_{cy}, $+B_9$-B_{12}	$+B_{12}$-T_4
A/C MTHFR:1298	$-B_{12}$-H_{cy}, $-B_9$-H_{cy}, $-B_{12}$-B_6	$+T_3$-B_9, $+B_9$-T_4
C/C MTHFR:1298	-	$+B_{12}$-T_4
C/C MTHFR:677	$-B_{12}$-H_{cy}, $-B_9$-H_{cy}	-

Table 17 continuation

Main genotype	Correlations	
	a	b
C/T MTHFR:677	$-B_{12}$-H_{cy}, $-B_9$-H_{cy}, $+B_9$-B_{12}	$+T_3$-B_9 ,$+B_9$-T_4, $+B_{12}$-T_4, $-B_{12}$-TSH
T/T MTHFR:677	$-B_9$-H_{cy}	-
A/AMTRR:66	$-B_{12}$-H_{cy}	$+B_6$-T_4
A/G MTRR:66	$-B_{12}$-H_{cy}, $-B_9$-H_{cy}, $+B_9$-B_{12}	$+B_9$-T_4, $+B_{12}$-T_4
G/G MTRR:66	$-B_{12}$-H_{cy}, $-B_9$-H_{cy}	-
General group	$-B_{12}$-H_{cy}, $-B_9$-H_{cy}, $+B_9$-B_{12}	$+T_3$-B_9, $+B_9$-T_4, $+B_{12}$-T_4

Note. «+» direct correlation; «-» inverse correlation; a – Homocysteine and B vitamins; b – Pituitary-thyroid axis hormones and B vitamins.

Table 18

The proportion of cases with the T allele MTHFR:677 and the GMTR:2756 allele in genetic subgroups of children in the Ivankovsky district

Main genotype	N_1	Risk allele TMTHFR:677		Risk allele GMTR:2756	
		N_2	%	N_2	%
A/A MTR:2756	106	61	57.6	0	0
A/G MTR:2756	61	32	52.5	61	100
G/G MTR:2756	11	5	45.5	11	100
A/AMTHFR:1298	89	60	67.4	33	37.1
A/CMTHFR:1298	80	38	47.5	35	43.8
C/C MTHFR:1298	9	0	0	4	44.4
C/C MTHFR:677	80	0	0	35	43.8
C/T MTHFR:677	83	83	100	32	38.6
T/T MTHFR:677	15	15	100	5	33.3
A/A MTRR:66	27	14	51,9	14	51.9
A/G MTRR:66	93	53	57.0	39	41.9
G/G MTRR:66	58	31	53.5	19	32.8

Table 18 continuation

Main genotype	N_1	Risk allele TMTHFR:677		Risk allele GMTR:2756	
		N_2	%	N_2	%
General group	178	98	55.1	72	40.5
Group of boys	86	42	48.8	35	40.7
Group of girls	92	56	60.9	37	40.2

Note: N_1 is the number of children in a subgroup or group; N_2 is the number of cases with a risk allele. % is the proportion of cases.

a). Homocysteine and B vitamins.

The correlations between H_{cy}, B_9, B_{12}, B_6 were studied taking into account the genetic polymorphisms of FC.

In this regard, subgroups of children were identified in which one of the allelic variants of the genetic polymorphisms of FC was represented in 100% of cases.

The nature of the distribution of correlations in genetic subgroups does not allow us to draw a conclusion about the predominant influence of certain genetic polymorphisms of FC on the process of H_{cy} methylation.

In most of the analyzed subgroups, combinations of inverse B_9-H_{cy} and B_{12}-H_{cy} associations were found (Table 17), which indicates insufficient production of active forms of B_9 and B_{12} – the main participants in the process of H_{cy} methylation and the formation of internal Met.

The reason for this is the decrease in the functioning of MTHFR, the creator of the active form of B_9, as well as MS, which ensures the formation of the active form of B_{12} and the transfer of the methyl group to H_{cy}.

The most pronounced decrease in MTHFR activity (about 80%) occurs with the homozygous variant of the TMTHFR:677 allele.

In the subgroup with the main T/TMTHFR:677 genotype, the only inverse

B_9-H_{cy} association was recorded (r_{xy} = -0.674**, p = 0.006, n = 15), reflecting the primary importance of MTHFR for the process of H_{cy} methylation.

The direct correlation B_9-B_{12}, recorded in the general group and a number of genetic subgroups, reflects the dependence of the formation of the active form of B_{12} on the active form of B_9, and, in general, on the functioning of MTHFR.

The influence of MTHFR on the process of H_{cy} methylation can be observed in most genetic groups, given the proportion of the TMTHFR:677 allele represented in them (Table 18).

Partial dysfunction of MS, with the A/GMTR:2756 genotype, leads to a decrease in the formation of the active form of B_{12}, as a result of which the direct B_9- B_{12} association disappears.

At the same time, an inverse relationship appears between B_{12} and B_6, indicating an increase in the activity of CBS, the coenzyme of which is B_6.

The situation is aggravated with the G/GMTR:2756 genotype, when about 80% of MS activity is blocked.

At the same time, H_{cy} is almost not subject to methylation, since there is not enough B_{12}, as evidenced by the inverse B_{12}-H_{cy} association (r_{xy} = -0.918**, p = 0.0001; n = 11).

In this case, H_{cy} is utilized in a cycle of transsulfuration reactions with the formation of Cys and glutathione.

This is clearly illustrated by the direct H_{cy}-B_6 associations.

The disappearance of the inverse B_9-H_{cy} association – indicates the loss of the influence of MTHFR on the process of H_{cy} methylation.

In the subgroup with a combination of homozygous variants of AMTR:2756-CMTHFR:677 neutral alleles, the combination of direct B_9-B_{12} (r_{xy} = 0.328*, p = 0.028, n = 45) and inverse B_{12}-H_{cy} (r_{xy} = - 0.536**, p = 0.0001, n = 45) correlations reflects the participation of B_9 and B_{12} in the process of H_{cy} methylation.

The results obtained indicate that the formation of correlation links between H_{cy}, B_9, B_{12}, B_6 occurs under the influence of FC genes and environmental exposure, including the radiation factor.

As an example, a subgroup of boys with a combination of genotypes including only neutral alleles — A/AMTR:2756-C/C MTHFR:677-A/AMTRR:66, in which an inverse correlation was recorded between B_{12} and H_{cy} (r_{xy} = - 0.857*, p = 0.014, n = 7) is presented [51].

The high proportion of hyperhomocysteinemia cases in the general group and individual genetic subgroups allows us to reasonably assert the functional deficiency of FC enzymes associated with external radiation exposure.

At the same time, the genetic factor is not of primary importance.

b). Hormones of the pituitary-thyroid axis and B vitamins.

In the study group of children, direct associations were recorded between vitamins and hormones B_9-T_4, B_{12}-T_4, T_3-B_9, B_6-T_4, and an inverse B_{12}-TSH association.

In the subgroups with the main G/GMTR:2756, C/CMTHFR:677, T/TMTHFR:677, G/GMTRR:66 genotypes, the indicated correlations were absent (Table 17).

In the general group and most of the analyzed subgroups, there were direct B_9-T_4 and B_{12}-T_4 associations.

The inverse B_{12}-TSH association in the subgroups with the main A/GMTR:2756 and C/TMTHFR:677 genotypes (Table 17) indicates that cobalamin methylation promotes a decrease in TSH formation.

Accordingly, there is no stimulation of T_4 deiodination and T_3 formation.

In addition, B_9 and B_{12}, by enhancing H_{cy} methylation, reduce its utilization in the transsulfuration reaction cycle, which also promotes a decrease in T_4 deiodination with T_3 formation.

It is necessary to pay attention to the direct correlation between T_3 and B_9 in the general group and in the subgroups with heterozygous variants of the GMTR:2756, CMTHFR:1298, TMTHFR:677 risk alleles (Table 17) [52].

When combining genotypes that included risk alleles of the polymorphisms of the FC, a direct of T_3-B_9 association was also recorded. At the same time, this correlation was absent in subgroups with a combination of genotypes that included homozygous variants of neutral alleles of the indicated polymorphisms (Table 19).

The T_3-B_9 association was direct in all cases, regardless of the FC genotypes (Tables 17, 19), which indicates the influence of T_3 on the production of the active form of B_9.

Table 19

Correlation association T_3-B_9 in subgroups of children of Ivankovsky district with a combination of FC genotypes [52].

N	Combinations of genotypes	Correlation coefficient	T_3-B_9
1	A/CMTHFR:1298- C/TMTHFR:677	Spearman's	0.429**
		Sign. (2-tailed), p	0.007
		n	38
2	A/AMTHFR:1298- C/CMTHFR:677	Spearman's	0.186
		Sign. (2-tailed), p	0.335
		n	29
3	A/G, G/GMTR:2756- A/G, G/G MTRR:66	Spearman's	0.343**
		Sign. (2-tailed), p	0.008
		n	58
4	A/AMTR:2756- A/A MTRR:66	Spearman's	0.398
		Sign. (2-tailed), p	0.178
		n	13
5	A/G, G/GMTR:2756- A/CMTHFR:1298- C/TMTHFR:677- A/G, G/G MTRR:66	Spearman's	0.649**
		Sign. (2-tailed), p	0.009
		n	15
6	A/GMTR:2756- A/CMTHFR:1298- C/TMTHFR:677- A/G, G/G MTRR:66	Spearman's	0.594*
		Sign. (2-tailed), p	0.032
		n	13

Note. N – genetic subgroup number; * — correlation is significant at the 0.05 level (2-tailed); ** correlation is significant at the 0.01 level (2-tailed); n is the number of cases.

The more T_3 is formed in the process of T_4 deiodination, the more 5-MTHF is synthesized — the active form of B_9.

This connection cannot be interpreted differently, since B_9 is in direct connection with T_4 and cannot stimulate T_3.

At the same time, T_4 has an inverse connection with T_3.

Considering that the active form of B_9 is a product of a reaction carried out with the participation of MTHFR, it can be reasonably stated that T_3 has a stimulating effect on this enzyme.

This leads to increased methylation of H_{cy} and an increase in the formation of internal Met.

Thus, T_3 can be considered as an element of the compensatory-adaptive process in conditions of hyperhomocysteinemia caused by genetic disorders of the FC and forest fires in the ChEZ.

c). Homocysteine and hormones of the pituitary-thyroid axis.

The correlation links of H_{cy} and hormones of the pituitary-thyroid axis, in subgroups with different numbers of genetic polymorphisms of FC, illustrate the process of interrelations of FC and the endocrine system (Table 20).

In particular, in the absence of risk alleles of polymorphisms of FC in the genome, an inverse T_3-H_{cy} association was recorded (Table 20) [50].

Thus, the more T_3 is formed, the lower the level of H_{cy} in the blood.

The process of formation of T_3 occurs mainly in peripheral tissues, due to deiodination of T_4, the concentration of which in the blood decreases.

The inverse H_{cy}-T_3/T_4 association, confirming this, was revealed in the group of boys from Polessky (Table 21) and girls from Polessky and Ivankovsky districts (Table 22).

When risk alleles of 3 genetic polymorphisms of FC appeared in the genome, a direct correlation between H_{cy} and T_3 was revealed, indicating that H_{cy} stimulates the process of T_3 formation (Table 20).

The same relationship was recorded in groups and genetic subgroups of boys and girls (Tables 21, 22).

The direct TSH-T_3 and inverse TSH-T_4, T_4-T_3 associations appeared with risk alleles of polymorphisms of FC and reflected the participation of TSH in the process of T_4 deiodination and T_3 formation (Tables 21, 22).

The TSH-T_3 association was most pronounced in the subgroup of children from Ivankovsky district with the main T/TMTHFR:677 genotype (r_{xy}=0.693**, p=0.004, n=15).

A strong inverse TSH-T_4 association was recorded in the subgroup of children from Polessky district with the main C/CMTHFR:1298 genotype (r_{xy} = -0.781**, p = 0.0001, n = 16).

With risk alleles of 4 polymorphisms, there was an inverse T_4-T_3 association, reflecting the process of T_4 deiodination and T_3 formation (Table 20).

The same T_4-T_3 association was recorded in the subgroup of children from Ivankovsky district with the main C/CMTHFR:1298 genotype (r_{xy} = -0.977**, p = 0.001, n = 9).

After forest fires in the ChEZ, a direct H_{cy}-TSH association was found in subgroups of children in the Ivankovsky district with risk alleles of 2 and 4 polymorphisms of FC, confirming the stimulating effect of H_{cy} on the AH and TSH production.

It is especially pronounced with risk alleles of 4 polymorphisms of FC (Table 20).

Table 20

Correlation associations between hormones of the pituitary-thyroid axis and H_{cy} in subgroups of children with different numbers of polymorphisms of FC with risk alleles

Group of children	N	Correlation	Spearman's (r_{xy})	Sign. (2-tailed), p	n
1	0	T_3-H_{cy}	- 0.900*	0.037	5
1	1	TSH-T_3	+ 0.347*	0.048	33
1	2	TSH-T_4	- 0.336**	0.007	64
1	3	H_{cy}-T_3, TSH-T_4	+ 0.391** - 0.305*	0.005 0.031	50
1	4	T_3-T_4	- 0.829*	0.042	6
2	2	H_{cy}-TSH, TSH-T_3	+ 0.266* + 0.371**	0.016 0.001	82
2	4	H_{cy}-TSH	+ 0.771**	0.001	14

Note. 1 – children from Polessky district; 2 – children from Ivankovsky district; N – number of polymorphisms with risk alleles; «+» direct correlation; «-» inverse correlation.

The most pronounced stimulation of H_{cy} production of TSH was revealed in the subgroup of children from Ivankovsky district

with a combination of A/G, G/GMTR:2756-A/CMTHFR:1298-C/TMTHFR:677-A/G, G/G MTRR:66 genotypes (r_{xy} = 0.768**, p = 0.001, n = 15).

In the genetic subgroups of boys from Polessky district with the main A/AMTR:2756, A/C, C/CMTHFR:1298, C/CMTHFR:677 genotypes and H_{cy} level ≤ 10.0 μmol/l, a direct H_{cy}-T_4 association was found (Table 21), which can be assessed as an illustration of the physiological process of the association between H_{cy} and T_4 [53].

In the same subgroups, when the H_{cy} level in the blood was more than 10 μmol/l, an inverse TSH-T_4 association was recorded, reflecting the participation of TSH in the process of T_4 deiodination and T_3 formation (Table 21).

The presence of the TMTHFR: 677 risk allele in the genome of children may contribute to this (Table 23).

An increase in the H_{cy} level in the blood > 10.0 μmol/l in children living near the ChEZ was also detected with a homozygous variant of the CMTHFR: 677 neutral allele, which may indicate an environmental impact (Table 24).

Table 21

Correlation variants in genetic subgroups of boys

Main genotype	H_{cy} level, μmol/l	Correlations	
		Group 1	Group 2
A/AMTR:2756	≤ 10.0	+H_{cy}-T_4	-
	> 10.0	-TSH-T_4	-
A/G, G/GMTR:2756	≤ 10.0	-	-
	> 10.0	-	+TSH-T_3/T_4
A/AMTHFR:1298	≤ 10.0	-	-
	> 10.0	-	-
A/C, C/CMTHFR:1298	≤ 10.0	+H_{cy}-T_4	+H_{cy}-T_3/T_4
	> 10.0	-TSH-T_4	-
C/C MTHFR:677	≤ 10.0	+H_{cy}-T_4, -H_{cy}-T_3/T_4	-
	> 10.0	-TSH-T_4	-TSH-T_4, +TSH-T_3/T_4

Table 21 continuation

Main genotype	H_{cy} level, µmol/l	Correlations	
		Group 1	Group 2
C/T, T/T MTHFR:677	≤ 10.0	+TSH-T_3/T_4	-
	> 10.0	-	-
A/AMTRR:66	≤ 10.0	+ H_{cy}-T_4	-
	> 10.0	-	-
A/G, G/G MTRR:66	≤ 10.0	-	-TSH-T_3
	> 10.0	-	-
General group	≤ 10.0	+ H_{cy}-T_4, -H_{cy}-T_3/T_4	-
	> 10.0	-	-

Note. Group 1 – boys from Polessky district, examined on 02/04/2015; Group 2 – boys from Ivankovsky district, examined on 18/12/2015. «+» – direct correlation; «-» – inverse correlation.

Table 22

Variants of correlations in genetic subgroups of girls

Main genotype	H_{cy} level, µmol/l	Correlations	
		Group 1	Group 2
A/AMTR:2756	≤ 10.0	-H_{cy}-T_3/T_4, +T_3-T_4	-
	> 10.0	-	+TSH-T_3, +TSH-T_3/T_4
A/G, G/GMTR:2756	≤ 10.0	-	-
	> 10.0	-	-H_{cy}-T_3/T_4
A/AMTHFR:1298	≤ 10.0	-H_{cy}-T_3, -H_{cy}-T_3/T_4	-
	> 10.0	-	+TSH-T_3, +TSH-T_3/T_4
A/C, C/CMTHFR:1298	≤ 10.0	-	-
	> 10.0	-	+H_{cy}-T_4, -H_{cy}-T_3/T_4
C/C MTHFR:677	≤ 10.0	-	-H_{cy}-T_3/T_4
	> 10.0	-	+ H_{cy}-T_4, -TSH-T_4, +TSH-T_3/T_4

Table 22 continuation

Main genotype	H_{cy} level, µmol/l	Correlations	
		Group 1	Group 2
C/T, T/T MTHFR:677	≤ 10.0	$-H_{cy}-T_3/T_4$	$-TSH-T_4$
	> 10.0	-	-
A/AMTRR:66	≤ 10.0	$-H_{cy}-T_3$, $-H_{cy}-T_3/T_4$	-
	> 10.0	-	$+H_{cy}-T_4$
A/G, G/G MTRR:66	≤ 10.0	$-H_{cy}-T_3/T_4$	-
	> 10.0	-	$+H_{cy}-T_4$, $-H_{cy}-T_3/T_4$
General group	≤ 10.0	$-H_{cy}-T_3/T_4$	-
	> 10.0	-	$+TSH-T_3$, $+TSH-T_3/T_4$

Note. Group 1 – girls from Polessky district, examined on 02/04/2015; Group 2 – girls from Ivankovsky district, examined on 18/12/2015. «+» – direct correlation; «-» – inverse correlation.

Table 23

Correlations and proportion of the TMTHFR:677 allele in genetic subgroups of boys

Main genotype	H_{cy} level, µmol/l	Correlations	The proportion of cases of the TMTHFR:677 allele, %
A/A MTR:2756	≤ 10.0	$+H_{cy}-T_4$	28.6
	> 10.0	$-TSH-T_4$	60.0
A/C, C/C MTHFR:1298	≤ 10.0	$+H_{cy}-T_4$	7.1
	> 10.0	$-TSH-T_4$	39.3
A/A MTRR:66	≤ 10.0	$+H_{cy}-T_4$	25.0
	> 10.0	-	37.5

Note: «+» — direct correlation; «-» — inverse correlation.

Table 24

The proportion of cases of hyperhomocysteinemia in genetic subgroups of children in the study in April and December 2015

Subgroups, main genotype	The proportion of cases of hyperhomocysteinemia					
	Group1			Group 2		
	N_1	N_2	%	N_1	N_2	%
G/G MTR:2756	9	8	88.89	11	5	45.45
A/G MTR:2756	45	18	40.00	61	47	77.05
A/A MTR:2756	104	58	55.77	106	78	73.58
C/C MTHFR:1298	16	9	56.25	9	4	44.44
A/C MTHFR:1298	60	33	55.00	80	63	78.75
A/A MTHFR:1298	82	42	51.22	89	63	70.79
T/T MTHFR:677	19	15	78.95	15	12	80.00
C/T MTHFR:677	60	35	58.33	83	62	74.70
C/C MTHFR:677	79	34	43.04	80	56	70.00
G/G MTRR:66	54	35	64.81	58	45	77.59
A/G MTRR:66	72	37	51.39	93	68	73.12
A/A MTRR:66	32	12	37.50	27	17	62.96
A/CMTHFR:1298-C/TMTHFR:677	25	10	40.00	38	31	81.58
A/AMTHFR:1298-C/CMTHFR:677	28	10	35.71	29	20	68.97

Note. Group 1 – children of Polessky district, examined on 02/04/2015; Group 2 – children of Ivankovsky district, examined on 18/12/2015. N_1 – number of children in the subgroup; N_2 – number of cases of hyperhomocysteinemia.

d). Combinations of correlations between homocysteine, pituitary-thyroid axis hormones and vitamins in genetic subgroups.

In the general group there are complex combinations of correlation links of individual metabolic indicators (Fig. 3).

It is advisable to consider the formation of combinations of correlation links in subgroups compiled taking into account certain genotypes of FC.

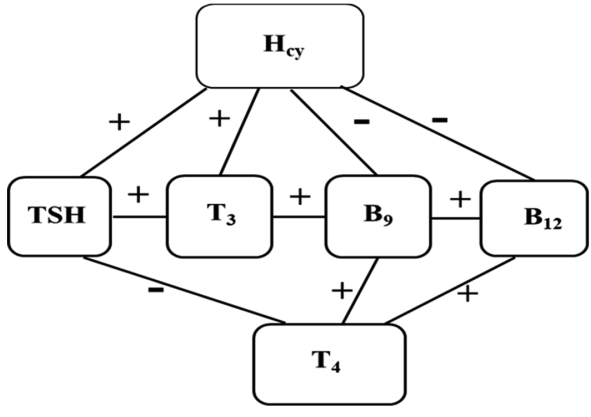


Fig. 3. Correlation links in the general group.

In the subgroup with the main A/AMTR:2756 genotype (Fig. 4), there is a combination of correlations reflecting the importance of B_9 and B_{12} for H_{cy} methylation and the formation of internal Met.

These vitamins maintain the concentration of T_4 at a physiological level.

The direct B_9-B_{12} association reflects the process of transferring a methyl group from B_9 to B_{12}.

The direct TSH-T_3 association indicates the influence of TSH on the process of T_4 deiodination and T_3 formation.

In the subgroup with the main A/GMTR:2756 genotype (Fig. 5), there is a combination of correlations of the analyzed indicators, in which two cycles can be distinguished with the participation of H_{cy} and TSH (Fig. 5a, 5b).

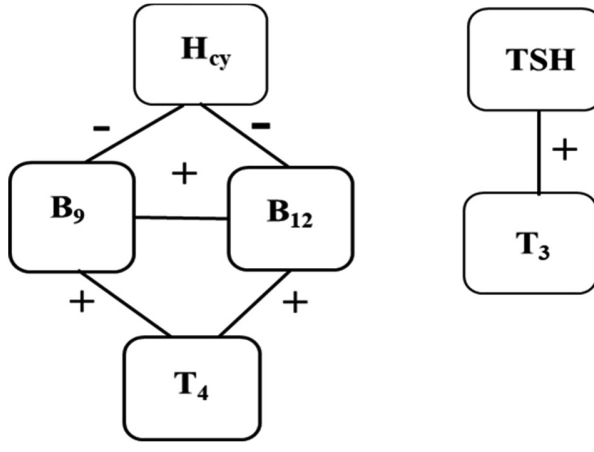


Fig. 4. Correlation links in the subgroup with the A/AMTR:2756 genotype.

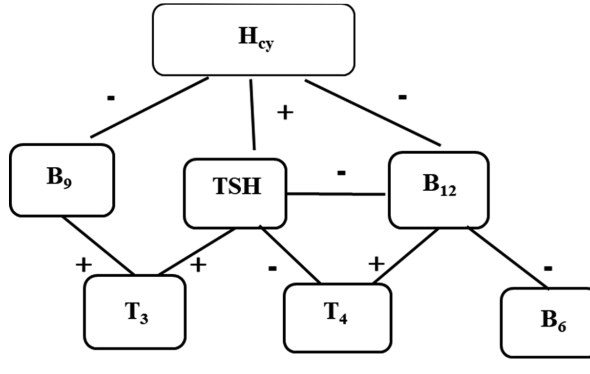


Fig. 5. Correlation links in the subgroup with the A/GMTR:2756 genotype.

A decrease in the formation of the active form of B_{12}, induced by a decrease in the activity of MS, leads to an increase in the level of H_{cy} in the blood and activation of the process of formation of TSH.

At the same time, the content of T_4 in the blood decreases. At the same time, there is an increase in the activity of enzymes of the transsulfuration reaction cycle, as evidenced by the inverse B_{12}-B_6 association.

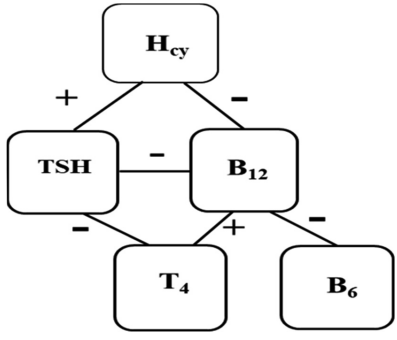


Fig. 5a. The cycle of correlation links based on the active form of B_{12}.

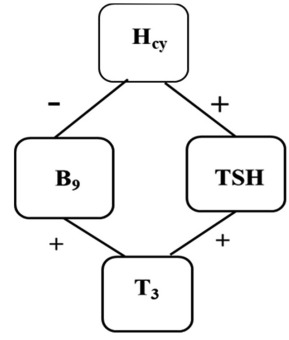


Fig. 5b. Cycle of correlations involving H_{cy} in the formation of TSH and T_3. In turn, T_3 promotes the formation of the active form B_9, which reduces the level of H_{cy} in the blood.

In the subgroup with the main G/GMTR:2756 genotype (Fig. 6), correlations are presented that reflect the influence of MS on the process of H_{cy} methylation and the cycle of transsulfuration reactions.

A decrease in MS activity with the G/GMTR:2756 genotype leads to a decrease in the formation of active forms of B_{12} and an increase in the level of H_{cy} in the blood.

As a result, the cycle of transsulfuration reactions is activated, as evidenced by the direct H_{cy}-B_6 association.

The direct T_3-B_9 association illustrates the influence of T_3 on the process of formation of the active form of B_9.

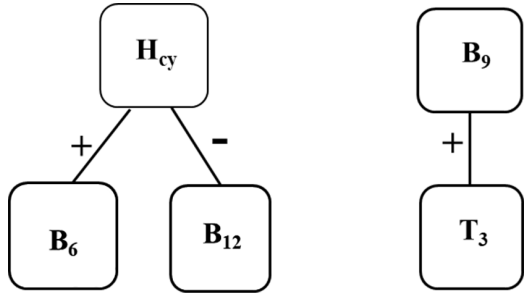


Fig. 6. Correlation links in the subgroup with the G/GMTR:2756 genotype.

In the subgroup with the main A/AMTHFR:1298 genotype (Fig. 7), there are two cycles of correlations involving H_{cy}:

a). Inverse associations — B_9-H_{cy} and B_{12}-H_{cy}, reflecting the influence of FC on the process of H_{cy} methylation;

b). Direct associations — H_{cy}-TSH, H_{cy}-T_3, TSH-T_3 reflect the stimulation of H_{cy} of the processes of TSH and T_3 formation.

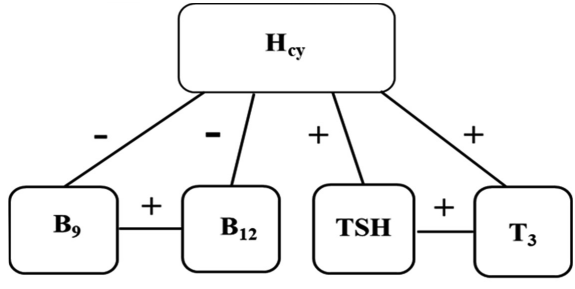


Fig. 7. Correlation links in the subgroup with the A/AMTHFR:1298 genotype.

In the subgroup with the main A/CMTHFR:1298 genotype (Fig. 8), the links characterizing the participation of B_9 and B_{12} in the methylation of H_{cy} are presented. In this case, the activation of the transsulfuration reaction cycle occurs, as evidenced by the inverse B_{12}-B_6 association.

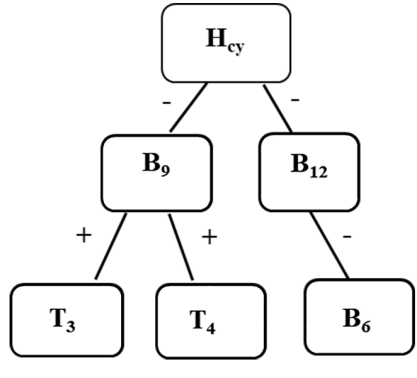


Fig. 8. Correlation links in the subgroup with the A/CMTHFR:1298 genotype.

Direct connections — T_3-B_9 and B_9-T_4 reflect the stimulating effect of T_3 on the synthesis of the active form B_9, which helps maintain the physiological level of T_4 (Fig. 8a).

T_3 stimulates the production of active forms of B_9, as a result of which the methylation of H_{cy} increases, the activity of enzymes of the transsulfuration cycle and deiodinases decreases, which helps maintain T_4.

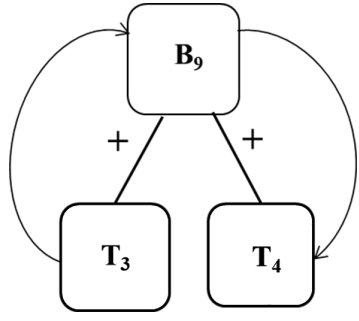


Fig. 8a.

In the subgroup with the main C/CMTHFR:1298 genotype (Fig. 9), a direct H_{cy}-TSH association is presented, indicating the participation of H_{cy} in the activation of TSH synthesis.

The complex of direct B_{12}-T_4 and reverse B_{12}-T_3/T_4 associations illustrates the role of B_{12} in the processes of thyroid hormone metabolism, combining FC, transsulfuration and deiodination cycles.

A deficiency of B_{12} promotes T_4 deiodination and T_3 formation in peripheral tissues.

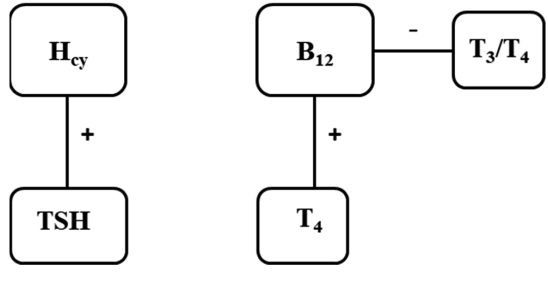


Fig. 9. Correlation links in the subgroup with the C/CMTHFR:1298 genotype.

In the subgroup with the main C/CMTHFR:677 genotype (Fig. 10), there are correlation links reflecting the influence of B_9 and B_{12} on the process of H_{cy} methylation, as well as the stimulating effect of H_{cy} and TSH in relation to the process of T_4 deiodination and T_3 formation.

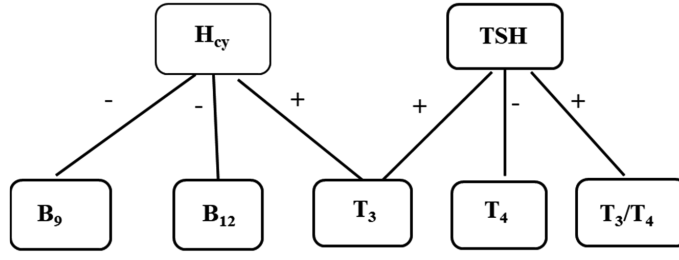


Fig. 10. Correlation links in the subgroup with the C/CMTHFR:677 genotype.

In the subgroup with the main C/TMTHFR:677 genotype (Fig. 11), the complex of correlations reflects the participation of B_9 and B_{12} in the processes of H_{cy} methylation, as well as in the regulation of thyroid hormone metabolism.

Direct connections — T_3-B_9 and B_9-T_4 reflect the stimulating effect of T_3 on the process of formation of the active form of B_9, which helps maintain the physiological level of T_4.

There are also connections reflecting the role of B_{12} and H_{cy} in the formation of TSH.

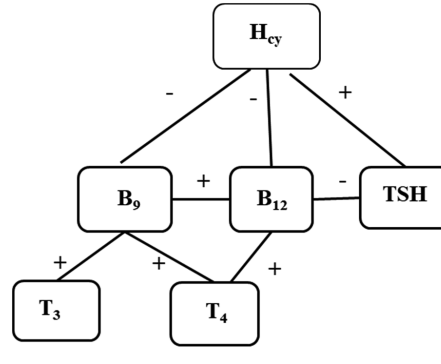


Fig. 11. Correlation links in the subgroup with the C/TMTHFR:677 genotype.

In the subgroup with the main T/TMTHFR:677 genotype (Fig. 12), the B_9-H_{cy} association reflects the dependence of the H_{cy} methylation process on the activity of MTHFR and B_9.

At the same time, there is a direct TSH-T_3 association, indicating the important role of TSH for the process of T_3 formation.

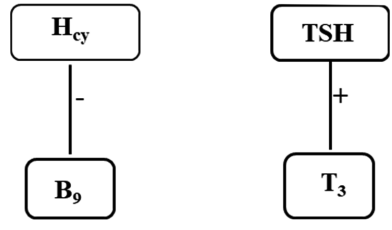


Fig. 12. Correlation links in the subgroup with the T/TMTHFR:677 genotype.

In the subgroup with the main A/AMTRR:66 genotype (Fig. 13), there is a direct T_4-B_6 association, indicating a connection between the cycles of transsulfuration and deiodination of T_4.

T_3, formed during the deiodination of T_4, reduces the level of H_{cy} and its utilization in the cycle of transsulfuration reactions. In this regard, the activity of enzymes of this cycle decreases and the content of B_6 in the blood decreases.

Thus, an increase in the utilization of T_4 during deiodination causes a decrease in the content of B_6 in the blood, as evidenced by the direct T_4-B_6 association.

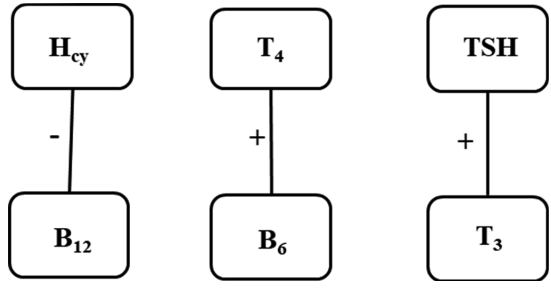


Fig. 13. Correlation links in the subgroup with the A/AMTRR:66 genotype.

In the subgroup with the main A/GMTRR:66 genotype (Fig. 14), there are elements of the connections presented in the previous subgroups.

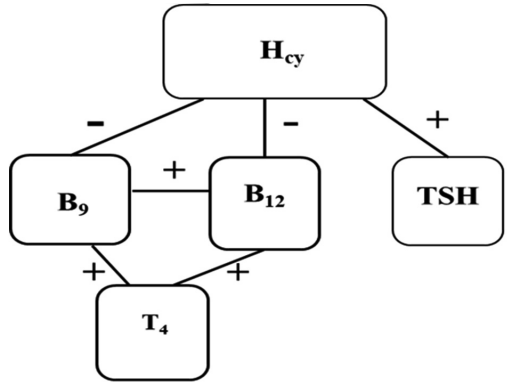


Fig. 14. Correlation links in the subgroup with the A/GMTRR:66 genotype.

In the subgroup with the main G/GMTRR:66 genotype (Fig. 15), there are correlations characterizing:

a) the dependence of H_{cy} methylation on the content of active forms B_9 and B_{12};

b) the role of TSH in the process of T_4 deiodination and T_3 formation.

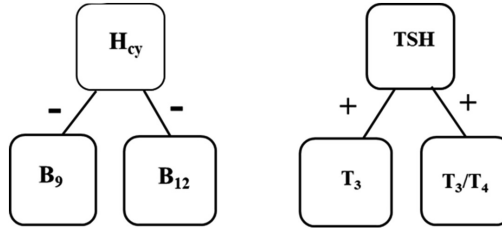


Fig. 15. Correlation links in the subgroup with the G/GMTRR:66 genotype.

In the subgroup with the combination of A/GMTR:2756-C/TMTHFR:677 genotypes (Fig. 16), which have a simultaneous negative effect on the activity of MTHFR and MS, there are connections reflecting the participation of H_{cy} in the formation of TSH, as well as B_{12}

in the functioning of the transsulfuration reaction cycle and the content of T_4 in the blood.

The direct T_3-B_9 association reflects the stimulation of the formation of the active form of B_9 under the influence of T_3.

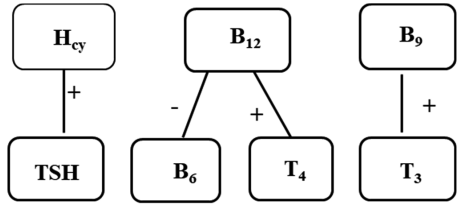


Fig. 16. Correlation links in the subgroup with the combination of A/GMTR:2756-C/TMTHFR:677 genotypes.

In the subgroup with the combination of A/AMTR:2756-C/CMTHFR:677 genotypes (Fig. 17), the direct B_9-B_{12} and inverse B_{12}-H_{cy} correlations reflect the participation of B_9 and B_{12} in the process of H_{cy} methylation. Thyroid hormones and TSH did not show any correlation.

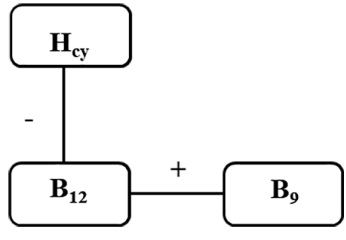


Fig. 17. Correlation links in the subgroup with the combination of A/AMTR:2756-C/CMTHFR:677 genotypes.

In the subgroup with a combination of compound heterozygosity A/CMTHFR:1298-C/TMTHFR:677 genotypes (Fig. 18), the associations are presented that characterize:

a) activation of the transsulfuration reaction cycle and an increase in the H_{cy} level with a deficiency of B_{12};

b) the stimulating effect of T_3 on the synthesis of the active form of B_9;

c) participation of B_9 in maintaining the physiological level of T_4 in the blood.

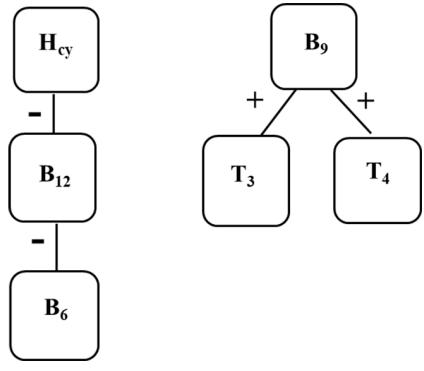


Fig. 18. Correlation links in the subgroup with the combination of compound heterozygosity A/CMTHFR:1298-C/TMTHFR:677 genotypes.

In the subgroup with the combination of A/AMTHFR:1298-C/CMTHFR:677 genotypes (Fig. 19), there are connections characterizing:

a) dependence of H_{cy} methylation on active forms of B_9 and B_{12};

b) stimulation of H_{cy} of the process of T_3 formation.

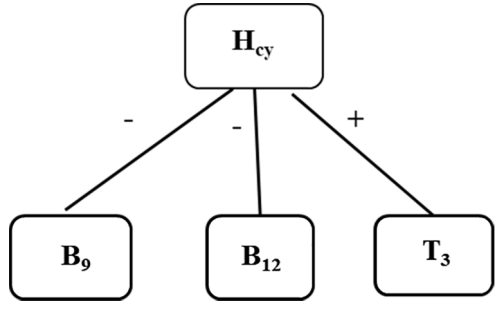


Fig. 19. Correlation links in the subgroup with the combination of A/AMTHFR:1298-C/CMTHFR:677 genotypes.

In the subgroup with the combination of A/GMTR:2756-A/GMTRR:66 genotypes (Fig. 20), there are correlations characterizing:

a) the effect of B_9 on the processes of H_{cy} methylation and TSH formation;

b) the effect of H_{cy} and B_{12} on the processes of TSH formation;

c) the effect of B_{12} and TSH on the level of T_4 in the blood;

d) activation of the transsulfuration reaction cycle with a deficiency of B_{12};

e) blocking of T_3 activity of transsulfuration reactions through the effect on FC.

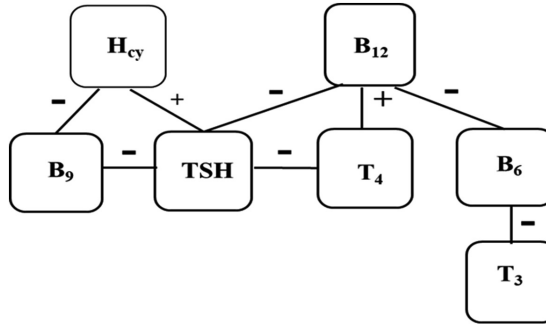


Fig. 20. Correlation links in the subgroup with the combination of A/GMTR:2756-A/GMTRR:66 genotypes.

In the subgroup with the combination of A/G, G/GMTR:2756-A/CMTHFR:1298-C/TMTHFR:677-A/G, G/GMTRR:66 genotypes (Fig. 21), there are relationships characterizing:

a) the effect of H_{cy} on the process of TSH formation;

b) the effect of B_{12} on the cycle of transsulfuration reactions;

c) the effect of T_3 on the process of formation of the active form of B_9.

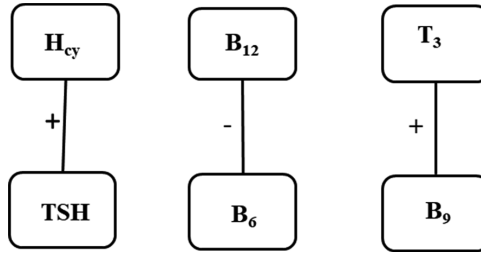


Fig. 21. Correlation links in the subgroup with the combination of A/G, G/GMTR:2756-A/CMTHFR:1298-C/TMTHFR:677-A/GG/GMTRR:66 genotypes.

In the subgroup with the combination of A/G, G/GMTR:2756-A/AMTHFR:1298-C/CMTHFR:677-A/G, G/G MTRR:66 genotypes (Fig. 22), there is a single connection characterizing the influence of B_{12} on the process of H_{cy} methylation.

At the same time, there is no disruption of the formation of the active form of B_9.

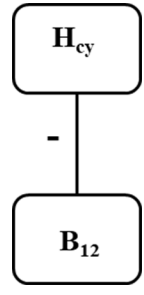


Fig. 22. Correlation links in the subgroup with the combination of A/G, G/GMTR:2756-A/AMTHFR:1298-C/CMTHFR:677-A/G,G/GMTRR:66 genotypes.

In the subgroup with the combination of A/AMTR:2756-A/CMTHFR:1298-C/TMTHFR:677-A/G, G/G MTRR:66 genotypes (Fig. 23), the associations are presented that characterize:

a) the influence of B_{12} on the process of H_{cy} methylation;

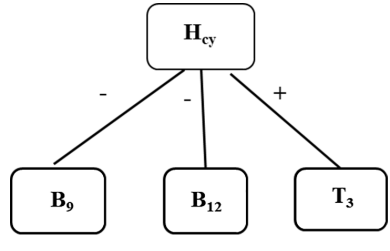


Fig. 23. Correlation links in the subgroup with the combination of A/AMTR:2756-A/CMTHFR:1298-C/TMTHFR:677-A/G,G/GMTRR:66 genotypes.

b) the dependence of the concentration of T_4 in the blood on the formation of the active form of B_9.

e). Gender differences in correlation associations.

One example of gender differences in metabolic transformations of H_{cy} was the subgroup with the main C/CMTHFR:677 genotype.

In the subgroup of boys with the main C/CMTHFR:677 genotype (Fig. 24), inverse B_9-H_{cy}, B_{12}-H_{cy} associations, as well as a direct B_9-B_{12} association were recorded, reflecting the association of FC with methylation of H_{cy}.

Blocking of the process of T_4 deiodination is reflected by the direct B_{12}-T_4 and the inverse B_{12}-T_3/T_4 associations.

TSH has the opposite effect on the process of deiodination.

An inverse TSH-T_4 and direct TSH-T_3/T_4 associations indicate stimulation of the process of T_4 deiodination and the formation of T_3 by TSH.

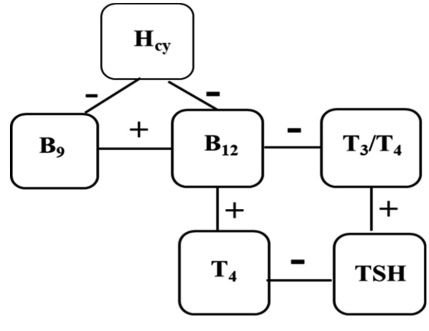


Fig. 24. Correlation links in the subgroup of boys with the C/CMTHFR:677 genotype.

In the subgroup of girls with the main C/CMTHFR:677 genotype, inverse B_9-H_{cy}, B_{12}-H_{cy} associations were also revealed (Fig. 25).

The inverse B_{12}-B_6 association reflects the process of stimulation of the transsulfuration reaction cycle.

The direct T_3-B_9, as well as the inverse T_3/T_4-H_{cy} associations indicate stimulation of the H_{cy} methylation process.

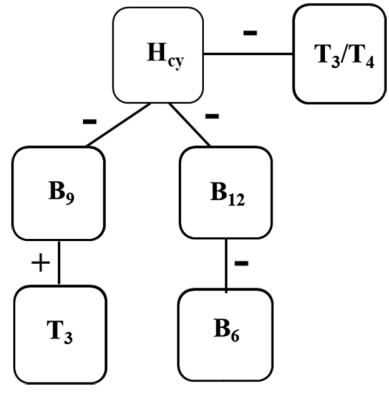


Fig. 25. Correlation links in the subgroup of girls with the C/CMTHFR:677 genotype.

Thus, in girls living in the territory of Ukraine, near the ChEZ, the mechanism of influence of thyroid hormones on the process of H_{cy} methylation is more pronounced, compared to boys.

f). Comprehensive assessment.

The conducted studies have established that the following are involved in the regulation of the functioning of the thyroid gland and the metabolism of thyroid hormones:

- Sulfur-containing amino acid H_{cy};
- Active forms B_9, B_{12}, B_6;
- FC enzymes involved in the production and utilization of active forms of B_9 and B_{12};
- Enzymes of the transsulfuration reaction cycle, in which the coenzyme is B_6;
- Deiodinase is a selenium-containing enzyme that carries out the process of T_4 deiodination and T_3 formation;
- TSH, the hypothalamus and AH, producing TSH.

It has been established that the process of H_{cy} methylation, with the formation of internal Met, is associated with the metabolism of thyroid hormones.

A key role in the process of H_{cy} methylation is played by MTHFR FC, catalyzing the reaction of the formation of the active form of B_9 — 5-MTHF.

A decrease in the functioning of MTHFR leads to a decrease in the formation of 5-MTHF and an increase in the level of H_{cy} in the blood.

5-MTHF induces, with the help of MS, the formation of the active form of B_{12} — methylcobalamin, as evidenced by the direct correlation between B_9 and B_{12}.

A decrease in MS activity leads to the fact that H_{cy} utilization occurs in the transsulfuration reaction cycle.

During the transsulfuration reactions, H_{cy} binds to serine and forms, with the help of CBS, Cyst, and then Cys.

Cys is a component of glutathione.

Also, Cys, when combined with selenium, is a coenzyme of deiodinase 5-Di, catalyzing the process of converting T_4 to T_3 outside the thyroid gland, in peripheral tissues.

The inverse B_9-H_{cy}, B_{12}-H_{cy} association, recorded in most genetic subgroups of children from the Chernobyl areas, indicate insufficient formation of active forms B_9 and B_{12} for the process of H_{cy} methylation.

A decrease in the production and utilization of B_9 and B_{12} during the methylation of H_{cy} leads to hyperhomocysteinemia and, accordingly, to a change in the functioning of the hypothalamic-pituitary-thyroid system.

Direct B_9-T_4, B_{12}-T_4 associations may indicate the dependence of T_4 formation in the thyroid gland on the active forms of B_9 and B_{12}.

In addition, the processes of thyroid hormone metabolism with the participation of H_{cy} in peripheral tissues should be considered.

Active forms of B_9 and B_{12} promote the methylation of H_{cy}, which limits its use in the transsulfuration cycle.

The consequence of this is a decrease in the formation of Cys and a decrease in the activity of deiodinase, which catalyzes the process of T_4 deiodination.

Thus, B_9 and B_{12} promote the preservation of T_4, preventing its conversion to T_3.

With a decrease in the formation of active forms of B_9 and B_{12}, the level of H_{cy} in the blood increases.

In this case, H_{cy}, under certain conditions, is utilized in the cycle of transsulfuration reactions, which ultimately leads to a decrease in the content of T_4 and an increase in the formation of T_3.

This is confirmed by the direct correlation between H_{cy} and T_4, recorded in the subgroups of boys in the Polessky district with the main genotypes A/AMTR: 2756, A/C, C/CMTHFR: 1298, C/CMTHFR: 677, A/AMTRR: 66, with a level of H_{cy} in the blood ≤ 10.0 μmol/l.

Thus, there is physiological parity between H_{cy} and thyroid hormones.

It is caused by a close connection between the cycle of transsulfuration reactions, in which H_{cy} is utilized, and the T_4 deiodination cycle, in which T_3 is formed.

Thus, an increase in the H_{cy} content in the blood creates conditions for the formation of T_3.

At the same time, under the influence of H_{cy}, the synthesis of TSH increases, the participation of which in the process of deiodination reflects the sequence of direct H_{cy}-TSH and TSH-T_3 associations.

A decrease in the H_{cy} content in the blood leads to a decrease in the formation of TSH.

The inverse correlation between B_{12} and TSH confirms the dependence of TSH formation on FC.

An increase in TSH formation, associated with an increase in the H_{cy} level in the blood, occurs when methylation of B_{12} is impaired due to a lack of 5-MTHF, as well as the functioning of MS, the role of a coenzyme of which is performed by B_{12}.

This negative relationship between the concentration of TSH and folates in the blood has been observed in patients with diabetes mellitus [54].

Under the influence of TSH, T_4 deiodination and T_3 formation occur, as evidenced by the correlations: direct TSH-T_3, TSH-T_3/T_4 and inverse TSH-T_4.

The ability of TSH to influence the production of hormones in the TG through a special receptor apparatus on the thyrocyte membrane has been proven.

There is a point of view that TSH regulates the formation of hormones in the TG by stimulating the activity of deiodinase D1, using cyclic AMP [16].

Also, the ability of TSH to increase the activity of deiodinase in many types of cellular experiments, increasing the formation of T_3, has been established.

At the same time, within the euthyroid range, a direct relationship has been established between TSH and the T_3/T_4 index.

Thus, TSH predominantly increases the production of T_3 and proportionally decreases T_4, which confirms its ability to stimulate the activity of D2 deiodinase [55].

This is one of its main functions.

Comparison of correlations in individual genetic groups allowed us to conclude that the formation of T_3 is associated with the activation of the transsulfuration reaction cycle.

In this cycle, H_{cy} is intensively converted to Cys, which, together with selenium, forms a cofactor for the deiodinase enzyme, converting T_4 into T_3.

The most pronounced activation of the transsulfuration reaction cycle occurs with impaired MS functioning.

However, the formation of the active form of thyroid hormones is enhanced with simultaneous dysfunction of MTHFR and MS.

A strong inverse T_4-T_3 association was recorded in a subgroup including cases with risk alleles of all 4 analyzed polymorphisms in the genome.

It is known that T_3, acting on mitochondria, is an active stimulator of the formation of cellular energy carriers [14].

Our studies have shown that T_3, acting on the enzyme systems of the FC, primarily on MTHFR, stimulates the process of H_{cy} methylation (a direct T_3-B_9, and inverse T_3-H_{cy} associations).

A decrease in the level of H_{cy} in the blood leads to a slowdown in the process of T_4 deiodination, as a result of which the concentration of T_3 in the blood decreases.

The consequence of this is an increase in the content of H_{cy} in the body, promoting the formation of TSH, which stimulates the deiodination of T_4 and the formation of T_3. In this case, H_{cy} is utilized in the cycle of transsulfuration reactions.

Thus, the metabolic cycle, including FC and the pituitary-thyroid axis, is repeated again.

Based on the obtained results, we can state the participation of T_3 in the control of H_{cy} utilization.

By ensuring the process of H_{cy} methylation, T_3 activates FC and the production of 5-MTHF, and therefore methylcobalamin.

A decrease in the H_{cy} content in the blood leads to a decrease in its utilization in the cycle of transsulfuration reactions.

With an increase in the T_3 content in the blood, there is a decrease in the activity of CBS, and therefore the use of vitamin B_6 as a coenzyme, as evidenced by the inverse T_3-B_6 association.

Thus, with the help of T_3, the concentration of H_{cy} in the blood is maintained, ensuring the physiological level of metabolic processes in the body.

Confirmation of T_3 participation in the regulation of H_{cy} metabolism is that in a state of hyperthyroidism (increased T_3 formation), the H_{cy} level in the blood decreases and the content of B vitamins involved in its methylation increases [56, 57].

In this regard, it is logical to know that MTHFR activity decreases in hypothyroidism and increases in hyperthyroidism, while MS activity increases in hypothyroidism and decreases in hyperthyroidism [58].

At the same time, the state of hypothyroidism is accompanied by a decrease in the content of folates and B_{12} in the blood [59].

T_3 directly affects the process of T_4 utilization.

If a lot of T_3 is formed, H_{cy} methylation increases, the TSH level in the blood decreases, the activity of the transsulfuration cycle decreases, and T_4 deiodination decreases.

With a decrease in the formation of T_3, the methylation of H_{cy} weakens, the level of TSH in the blood increases, the utilization of H_{cy} in the cycle of transsulfuration reactions increases, which leads to an increase in the deiodination of T_4.

Genetic factor in the regulation of thyroid hormone metabolism.

FC genes play an important role in the process of H_{cy} methylation, influencing the processes of synthesis of active forms of B_9 and B_{12}.

First of all, this concerns the MTHFR:C677T polymorphism, which affects the activity of MTHFR, an enzyme that provides the body with the active form of B_9 –5-MTHF.

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

The TMTHFR:677 allele reduces the formation of active forms of B_9, and thus increases the H_{cy} content in the blood.

In the examined group of children, this allele was recorded in 53.62% of cases.

The presence of the TMTHFR:677 risk allele in the genome causes an increase in the H_{cy} level in the blood and stimulates the participation of TSH in the process of T_4 deodination and T_3 formation.

The T/TMTHFR:677 genotype was found in 8.55% of cases, including 8.70% of cases in the subgroup of boys and 8.39% of cases in the subgroup of girls.

In 81.4% of cases, the T/TMTHFR:677 genotype is associated with the

G/GMTRR:66 and A/GMTRR:66 genotypes, which enhance its negative effect on the H_{cy} methylation process [51].

The heterozygous variant of the TMTHFR:677 risk allele, in the population of children living near the ChNPP, was found in 45.1% of cases.

In the subgroup of children, where the C/TMTHFR:677 genotype was the main one, direct T_3-B_9, H_{cy}-TSH, B_9-T_4, B_{12}-T_4, B_9-B_{12} associations, as well as inverse B_9-H_{cy}, B_{12}-H_{cy}, B_{12}-TSH associations were observed (Fig. 11).

Thus, in this case, there is a possibility of the effect of T_3 on MTHFR and the formation of B_9.

The presence of the GMTR:2756 risk allele in the genome suppresses MS activity and reduces the formation of the active form of B_{12}, as a result of which the enzymes of the transsulfuration cycle are included in the process of H_{cy} utilization.

A marker for this is the inverse B_{12}-B_6 association (Fig. 5a).

The H_{cy} level in the blood decreased in the case of the homozygous variant of the GMTR:2756 allele.

In this case, as well as in the G/GMTR:2756+A/G, G/GMTRR:66 association, a direct H_{cy}-B_6 association appeared (Fig. 6).

T_3 blocks the activity of enzymes of the transsulfuration cycle in the combination of A/GMTR:2756 and A/GMTRR:66 genotypes, as evidenced by the inverse T_3-B_6 association (Fig. 20).

Compound heterozygosity — A/CMTHFR:1298-C/TMTHFR:677, in combination with A/G, G/GMTR:2756 and A/G, G/GMTRR:66 genotypes, is a clear example of activation of TSH production, the transsulfuration cycle and the stimulating effect of T_3 on MTHFR under conditions of hyperhomocysteinemia (Fig. 21, Table 25) [52].

If compound heterozygosity — A/CMTHFR:1298-C/TMTHFR:677 was absent, then the connections confirming these processes were not manifested (Fig. 22).

If the group of children included cases with the absence of risk allele G of the MTR:A2756G polymorphism, with a combination of A/AMTR:2756-A/CMTHFR:1298-C/TMTHFR:677-A/G, G/GMTRR:66 genotypes, the associations presented in Table 25 were also absent (Fig. 23).

Table 25

Correlations in the subgroup of children with a combination of A/G, G/GMTR:2756-A/CMTHFR:1298-C/TMTHFR:677-A/G, G/GMTRR:66 genotypes

Correlation coefficient, significance p	Parameter		
	H_{cy}-TSH	B_{12}-B_6	T_3-B_9
Spearman's	0.768**	- 0.711**	0.649**
Sign. (2-tailed), p	0.001	0.003	0.009
n	15	15	15

Note. n is the number of cases; ** – correlation is significant at the 0.01 level (2-tailed).

The conducted studies have shown that the effect of T_3 on the FC cycle and MTHFR will be effective with heterozygous variants of the risk alleles of the analyzed FC polymorphisms.

However, a direct T_3-B_9 association was also present in the subgroup of girls with the C/CMTHFR:677 genotype (Fig. 25).

In this case, the cycle of transsulfuration reactions with the utilization of H_{cy} and deiodination of T_4 was also included (Fig. 25).

In the subgroup of boys with the C/CMTHFR:677 genotype this did not happen (Fig. 24), due to which the level of H_{cy} in the blood was higher than in girls from the same subgroup [45].

Environmental factors as a cause of H_{cy} and thyroid hormone metabolism disorders.

Disruption of H_{cy} methylation processes and changes in thyroid hormone metabolism in children living in areas affected by the Chernobyl accident are associated with environmental impacts.

The 1986 Chernobyl accident resulted in radioactive contamination of the environment.

Even many years later, the soils and forest trees in the ChEZ as well as in the adjacent territories of the Ivankovsky and Polessky districts of the Kyiv region of Ukraine, contain huge amounts of ^{137}Cs and other long-lived radionuclides [10, 11].

As a result, the population living near the ChEZ is under constant risk of radiation exposure.

Radioactive elements enter the body of adults and children through food chains, air currents and water.

Incorporation of ^{137}Cs into the cells of vital organs [5] causes damage to mitochondrial structures and energy deficiency [11].

As a result, the formation of active forms of B_9 and B_{12} decreases, leading to a state of hyperhomocysteinemia.

The radiation factor, in the form of radionuclides incorporated into the body, caused a state of hyperhomocysteinemia in adolescent children living near the ChEZ, regardless of the state of the FC genes.

In the case of forest fires, people living in settlements located near the ChEZ become victims of increasing radiation exposure.

After the forest fires in the ChEZ in the summer of 2015, the proportion of hyperhomocysteinemia cases increased significantly in most of the analyzed genetic subgroups of children in the Polessky district, including in subgroups with neutral alleles of the FC genetic polymorphisms [10].

In a subgroup of children from Ivankovsky district, with an association of homozygotes of AMTHFR:1298 and CMTHFR:677 neutral alleles, the proportion of hyperhomocysteinemia cases was 69.0% [52].

Hyperhomocysteinemia is a stress factor for the body and can cause a reaction from the central nervous and endocrine systems.

As a result, the production of TSH increases, which affects the synthesis of thyroid hormones in the TG and their metabolism in peripheral organs, increasing the formation of T_3.

In turn, T_3, by affecting MTHFR, stimulates the formation of the active form B_9, which leads to a decrease in the content of H_{cy} in the blood.

Increased production of T_3 is an adaptive response of the body aimed at increasing energy capabilities and the formation of nonspecific and specific protective reactions.

The obtained results indicate that environmental radiation exposure induces in the body of children living near the ChEZ, a violation of the H_{cy} methylation process, and the activation of TSH, which affects the metabolism of thyroid hormones.

Elevated levels of H_{cy} in the blood are recorded in individuals with hypothyroidism [41].

In areas affected by the Chernobyl accident, the occurrence of hypothyroidism may be associated with the radiation factor.

In addition to ^{131}I, which poses a danger to people in the first days after the Chernobyl accident, ^{137}Cs, throughout all the Chernobyl decades, is incorporated by vital organs, including the TG [5].

And this can cause a decrease in the production of thyroid hormones, defined as hypothyroidism.

The prevalence of clinical hypothyroidism in the world population is 0.5-5%, while subclinical hypothyroidism is much more common — 5-20% [60, 61].

Unfortunately, at present it is impossible to obtain objective statistical information on the prevalence of hypothyroidism in the post-Soviet space, including in the areas affected by the Chernobyl accident.

In hypothyroidism, the level of thyroid hormones, both T_4 and T_3, decreases in the blood.

Thus, the stimulating effect of T_3 on the enzyme systems of the FC, primarily on MTHFR, decreases.

The consequence of this is a decrease in the formation of active forms of B_9 and B_{12} and an increase in the content of H_{12} in the blood.

An increased concentration of H_{12} in the blood contributes to an increase in TSH in the blood serum.

Under physiological conditions, TSH causes an increase in the process of T_4 deiodination and an increase in the formation of T_3, which can affect the enzymes of the FC, stimulating the process of H_{cy} methylation.

However, under conditions of pronounced impact of ^{137}Cs on thyroid cells [5], this does not occur, since the formation of T_4 is reduced, which does not allow the formation of a regulatory cycle with the participation of T_3 and H_{cy}.

At the same time, an increased level of TSH is recorded in the peripheral blood, which negatively affects metabolic processes in the body.

Chapter V.
Scientific concept of regulatory associations between the folate cycle and the pituitary-thyroid axis. Its importance for protecting human health under conditions of radiation exposure.

Scientific concept of regulatory associations between the folate cycle and the pituitary-thyroid axis. Its importance for protecting human health under conditions of radiation

Analysis of correlations between H_{cy}, B_9, B_{12}, B_6, TSH, T_4, T_3, taking into account the state of the genes FC, in groups of children living near the ChEZ allowed us to formulate a scientific concept of regulatory associations between FC and the pituitary-thyroid axis under conditions of constant radiation exposure.

According to this concept, H_{cy} is a regulator of the metabolism of hormones of the pituitary-thyroid axis.

The intensity of production of THS and other hormones regulating the activity of endocrine organs depends on its concentration in the blood.

The level of H_{cy} in the blood of children from areas affected by the Chernobyl accident is directly related to the functioning of folate enzymes and the formation of active forms of B_9 and B_{12}.

The activity of FC enzymes depends on the state of their genes.

Genetic polymorphisms are known that significantly change the level of H_{cy} in the blood.

The most important in this regard is the genetic polymorphism MTHFR:C677T, which affects the activity of the MTHFR enzyme, which catalyzes the formation of the active form B_9 — 5 -MTHF.

The homozygous variant of the TMTHFR:677 allele is characterized by an increased level of H_{cy} in the blood, with a decrease in the level of B_9.

The heterozygous variant of this allele can be the cause of hyperhomocysteinemia when combined with the GMTRR:66 allele [62].

However, after forest fires in the ChEZ in the spring and summer of 2015, an increase in the H_{cy} level in the blood was recorded in most children, regardless of the state of their FC genetic apparatus.

Thus, an increase in the H_{cy} level in the blood of children living near the ChEZ is associated with genetic polymorphisms of the FC, as well as with the impact of the environmental radiation factor, causing a state of energy deficiency in highly differentiated cells of vital organs [11].

An increase in the H_{cy} content in the blood above the physiological level stimulates the synthesis of TSH in AH cells [10, 11, 48, 63, 64].

Correlation analysis shows the participation of THS in the process of T_4 deiodination and T_3 formation.

Stimulation of the process of T_3 formation is one of the most important functions of TSH.

In the body of children with the GMTR:2756 allele in the genome, activation of transsulfuration reactions occurs, in which H_{cy} is converted to Cys, followed by activation of the T_4 deiodination process with the formation of T_3 [11, 49].

In the group of children with the GMTR:2756 risk allele, the proportion of cases of elevated triiodothyronine levels in the blood is significantly more than in the group of children who do not have this allele in their genome (A/AMTR:2756 genotype) [65].

The connection between the cycle of trans-sulfuration reactions and the T_4 deiodination process ensures the participation of H_{cy} in the formation of T_3 — the active form of thyroid hormones.

T_3 stimulates the processes of cellular energy supply, which leads to increased activity of MTHFR and an increase in the synthesis of 5-MTHF [52].

As a result, methylation of H_{cy} and the formation of internal Met increase.

The direct T_3-B_9 association, as well as the inverse T_3-TSH and T_3-H_{cy} associations, confirm the participation of T_3 in this process and the blocking of TSH production [53].

But this happens under conditions of balanced metabolism, when the FC enzymes, including MTHFR, are able to respond to the effects of T_3 [53].

In the case of pronounced genetic disorders of the FC, in particular homozygous variants of the TMTHFR:677 allele, T_3 does not have a stimulating effect on the H_{cy} methylation process.

The most effective effect of T_3 on the FC and MTHFR occurs in the case of a heterozygous variant of the TMTHFR:677 allele.

T_3 reduces the H_{cy} content in the blood and reduces its effect on the pituitary-thyroid axis, which ultimately leads to a decrease in the formation of T_3 itself [53].

A decrease in the stimulating effect of T_3 on the FC leads to an increase in H_{cy} levels, promoting the activation of the process of converting T_4 to T_3.

The effect of T_3 on MTHFR is more pronounced in girls than in boys.

There is reason to believe that this is one of the main reasons for the lower level of H_{cy} in their blood.

Based on the proposed scheme (Fig. 26) [66], it can be concluded that T_3 is a stimulator of FC, promoting the methylation of H_{cy} and the formation of internal Met.

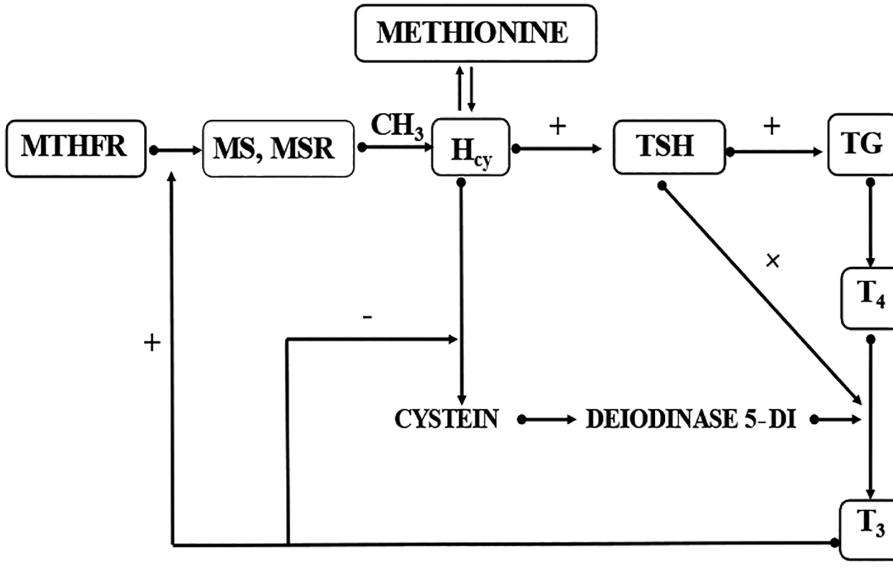


Fig. 26. Regulatory links between FC, H_{cy} and the pituitary-thyroid axis [66].

At the same time, H_{cy}, affecting hormonogenesis in the pituitary-thyroid axis, regulates T_4 metabolism.

In physiological concentrations, H_{cy} maintains the necessary level of T_4 in the blood.

In concentrations exceeding the physiological barrier, H_{cy} stimulates the synthesis of TSH, the process of T_4 deiodination and the formation of T_3.

The level of T_4 in the blood depends on how this metabolite is used by peripheral organs and tissues, and indicates, in particular, what the body's energy needs are.

It is the peripheral organs, including the liver and kidneys, that are responsible for the utilization of T_4 and the formation of T_3, the active form of thyroid hormones. In areas affected by the Chernobyl accident, radiation agents interfere with this process, significantly disrupting cellular energetics [11].

In the first decade after the Chernobyl accident, significant amounts of radioactive elements entered the bodies of residents of the affected areas.

Particularly pronounced incorporation of ^{137}Cs occurred in thyroid cells [5], which could be one of the main reasons for the decrease in the production of thyroid hormones, with clinical manifestations of hypothyroidism.

In the decades following the Chernobyl accident, the intake of radioactive elements by adults and children decreased.

However, the danger of radiation exposure for children of the second Chernobyl generation did not decrease.

According to laboratory tests, heart cell damage was recorded in 37.5% of cases in adolescents from the Ivankovsky and Polessky districts in 2015 [11].

This is associated not only with the direct impact of ^{137}Cs on the myocardium and TG [5], but also with the disruption of the regulatory mechanisms of H_{cy} and thyroid hormone metabolism that arose during antenatal and early postnatal ontogenesis.

In conditions of constant environmental radiation exposure, attention should be paid to how the body uses T_4, whereas, usually, attention is paid only to how the TG produces this hormone.

The increased concentration of H_{cy} in the blood of Chernobyl children induces chronic hormonal stress associated with the production of T_3 and cortisol [53].

The consequence of this is a disruption of the cardiovascular system.

In our studies, most of the examined children were found to have heart rhythm disturbances [11], as well as a decrease in functional reserves and adaptive capabilities of the circulatory system [67, 68].

The decrease in blood pressure and arrhythmia recorded in children with the incorporation of ^{137}Cs radionuclides into their bodies [11, 69] may be associated with T_3, given its effect on the cellular elements of the heart and blood vessels [70].

The disruption of H_{cy} methylation processes caused by genetic mutations of FC and environmental radiation exposure [51] may create a false impression of the existence of hypothyroidism.

In this case, to establish a correct diagnosis, it is necessary to evaluate not only the content of TSH and thyroid hormones (T_4, T_3) in the blood, but also H_{cy}, as well as the state of the genetic apparatus of FC.

In this case, it is imperative to determine the content of radionuclides in the body of children.

One should be careful when using thyroid hormones as a therapeutic agent, since their active form, T_3, may be present in sufficient quantities in the body.

In children exposed to radiation agents, elements of damage and compensatory-adaptive processes are recorded at the cellular, tissue and organ levels.

Sometimes it is difficult to distinguish them, and this creates difficulties in organizing treatment and preventive measures.

In this regard, the proposed scientific concept based on the analysis of the results of the correlation analysis of metabolic parameters, taking into account the state of the FC genes, in children living after the Chernobyl accident, in conditions of constant radiation exposure, may be useful.

The essence of this concept is that the feedback regulatory relationship between the hormones of the pituitary-thyroid axis functions with the participation of H_{cy} and FC enzymes.

This is most clearly manifested in unfavorable conditions for the body, including radiation expansion.

Exposure to ^{137}Cs leads to disruption of cellular metabolism and a decrease in the formation of active forms of vitamins B_9 and B_{12}.

Hyperhomocysteinemia, which occurs as a result, stimulates hormonogenesis in the hypothalamic-pituitary-thyroid axis.

At the same time, in peripheral tissues (liver, kidneys) the formation of T_3 increases, which is capable of stimulating cellular energy and the synthesis of active forms of B_9.

The consequence of this is an increase in the methylation processes of H_{cy}.

Thus, in this case, T_3 protects the body from the destructive effects of the radiation factor.

At the same time, H_{cy} is a participant in the body's adaptation system to environmental influences.

However, at high concentrations in the body, genetically determined or associated with pronounced environmental influences, H_{cy} disrupts the metabolism in the body, causing structural and functional changes in the cells of vital organs.

References

1. Кравченко В. І. Чорнобильська аварія та йодна недостатність як фактори ризику тиреоідної патології у населення постраждалих регіонів України. *Міжнародний ендокринологічний журнал*. 2016. № 2(74). С. 13-20.
2. Health consequences of the Chernobyl accident and special health programs: Reports of the expert group “Health” of the UN Chernobyl Forum. Geneva, 2006. 182 p.
3. Prysyazhnyuk A. Ye., Fuzik M. M., Gudzenko N. A., Bazyka D. A. et al. Incidence of malignant neoplasms among residents of small radionuclide-contaminated Chornobyl districts in a post-accident period. *Problems of Radiation Medicine and Radiobiology*. 2020. Вип. 25. P. 265-284. DOI: 10.33145/2304-8336-2020-25-265-284
4. 25 років Чорнобильської катастрофи. Безпека майбутнього : Національна доповідь України. К.: КІМ, 2011. 356 с.
5. Bandazhevsky Yu. I. Chronic Cs-137 incorporation in children’s organs. *Swiss Medical Weekly*. 2003. Vol. 133. P. 488-490. https://doi.org/10.4414/smw.2003.10226
6. Tourlonias E, Bertho JM, Gurriaran R, Voisin P, Paquet F. Distribution of 137Cs in rat tissues after various schedules of chronic ingestion. *Health Phys*. 2010 Jul;99(1):39-48. doi: 10.1097/HP.0b013e3181d4f00e. PMID: 20539123.
7. Сидоренко О. М., Сидоренко М. О., Тимошев М. П. Епідеміологія раку щитовидної залози наприкінці XX та на початку XXI століття в Україні та Запорізькій області. *Актуальні питання фармацевтичної і медичної науки та практики*. 2018. Т. 11, №3(28). С. 322–325.
8. Ткаченко В. І., Максимець Я. А., Видиборець Н. В., Коваленко О.Ф. Аналіз поширеності тиреоїдної патології та захворюваності на неї серед населення Київської області та України за 2007-2017 рр. *Міжнародний ендокринологічний журнал*. 2018. Т. 14, № 3. С. 272-277. DOI: 10.22141/2224-0721.14.3.2018.136426
9. Bandazhevsky Yu. I., Dubova N. F. Hyperhomocysteinemia in Ukrainian children living near the Chernobyl Exclusion Zone:

International scientific conference “New trends and unsolved issues in medicine”: conference proceedings (July 29–30, 2022. Riga, the Republic of Latvia). Riga, Latvia : “Baltija Publishing”, 2022. P. 263-266. DOI https://doi.org/10.30525/978-9934-26-226-5-69.

10. Bandazhevsky Yu. I., Dubovaya N. F. Forest fires in the Chernobyl exclusion zone and children’s health. Ivankov : PI Coordination and Analytical Center «Ecology and health», — Kyiv : «Aliant» LLC. 2021. 44 p. ISBN978-617-7819-10-2
11. Bandazhevsky Yu. I., Dubovaya N. F. Chernobyl catastrophe and childrens health. 35 years of world tragedy. Ivankov: PI Coordination and Analytical Center «Ecology and health», — Kyiv: «Alyant» LLC, 2022. 158 p. ISBN 978-617-7819-29-4
12. Марей А. Н., Бархударов Р. М., Новикова Н. Я. Глобальные выпадения Cs-137 и человек. М. : Атомиздат, 1974. 168 с.
13. Корзун В. Н., Воронцова Т. О., Антонюк І. Ю. Екологія і захворювання щитоподібної залози. К.: Мірегіональний видавничий центр «Медінформ», 2018. 743 с.
14. Louzada RA, Carvalho DP. Similarities and Differences in the Peripheral Actions of Thyroid Hormones and Their Metabolites. Front Endocrinol (Lausanne). 2018 Jul 19;9:394. doi: 10.3389/fendo.2018.00394. PMID: 30072951; PMCID: PMC6060242.
15. Pirahanchi Y, Toro F, Jialal I. Physiology, Thyroid Stimulating Hormone. [Updated 2023 May 1]. In: Stat Pearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK499850/
16. Peeters RP, Visser TJ. Metabolism of Thyroid Hormone. [Updated 2017 Jan 1]. In: Feingold KR, Anawalt B, Boyce A, et al., editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK285545/
17. Sabatino L, Vassalle C, Del Seppia C, Iervasi G. Deiodinases and the Three Types of Thyroid Hormone Deiodination Reactions. Endocrinol Metab (Seoul). 2021 Oct;36(5):952-964. doi: 10.3803/EnM.2021.1198. Epub 2021 Oct 21. PMID: 34674502; PMCID: PMC8566136.

18. Mebis L, van den Berghe G. The hypothalamus-pituitary-thyroid axis in critical illness. *Neth J Med*. 2009 Nov;67(10):332-40. PMID: 19915227.
19. Fonseca TL, Correa-Medina M, Campos MP, Wittmann G, Werneck-de-Castro JP, Arrojo e Drigo R, Mora-Garzon M, Ueta CB, Caicedo A, Fekete C, Gereben B, Lechan RM, Bianco AC. Coordination of hypothalamic and pituitary T_3 production regulates TSH expression. *J Clin Invest*. 2013 Apr;123(4):1492-500. doi: 10.1172/JCI61231. Epub 2013 Mar 25. PMID: 23524969; PMCID: PMC3613903.
20. Ortiga-Carvalho TM, Chiamolera MI, Pazos-Moura CC, Wondisford FE. Hypothalamus-Pituitary-Thyroid Axis. *Compr Physiol*. 2016 Jun 13;6(3):1387-428. doi: 10.1002/cphy.c150027. PMID: 27347897.
21. Luongo C, Trivisano L, Alfano F and Salvatore D (2013) Type 3 deiodinase and consumptive hypothyroidism: a common mechanism for a rare disease. Front. Endocrinol. 4:115. doi: 10.3389/fendo.2013.0011
22. Škovierová H., Vidomanová E., Mahmood S. et al. The molecular and cellular Effect of homocysteine metabolism imbalance on human health. *Int J Mol Sci*. 2016 Oct 20; 17(10): 1710 — 1733. doi: 10.3390/ijms 17101733
23. McCaddon A and Miller JW (2023) Homocysteine — a retrospective and prospective appraisal. Front. Nutr. 10:1179807. doi: 10.3389/fnut.2023.1179807
24. Moretti, R.; Giuffré, M.; Caruso, P.; Gazzin, S.; Tiribelli, C. Homocysteine in Neurology: A Possible Contributing Factor to Small Vessel Disease. *Int. J. Mol. Sci.* 2021, 22, 2051. https://doi.org/10.3390/ijms22042051
25. Koklesova L, Mazurakova A, Samec M, Biringer K, Samuel SM, Büsselberg D, Kubatka P, Golubnitschaja O. Homocysteine metabolism as the target for predictive medical approach, disease prevention, prognosis, and treatments tailored to the person. EPMA J. 2021 Nov 11;12(4):477-505. doi: 10.1007/s13167-021-00263-0. PMID: 34786033; PMCID: PMC8581606.
26. Ganguly, P., Alam, S.F. Role of homocysteine in the development of cardiovascular disease. *Nutr J* 14, 6 (2015). https://doi.org/10.1186/1475-2891-14-6

27. Gupta S.K., Kotwal J., Kotwal A., Dhall A., Garg S. Role of homocysteine & MTHFR C677T gene polymorphism as risk factors for coronary artery disease in young Indians. *Indian J Med Res*. 2012;135(4): P. 506-512.
28. Kolling J., Scherer E., da Cunha A. A., da Cunha M. J., Wyse A.T.S. Homocysteine Induces Oxidative-Nitrative Stress in Heart of Rats: Prevention by Folic Acid. *Cardiovasc.Toxicol.* 2011. Vol. 11, № 1. P. 67–73.
29. Jakubowski H. Homocysteine Modification in Protein Structure/ Function and Human Disease. *Physiol Rev.* 2019 Jan 1;99(1):555-604. doi: 10.1152/physrev.00003.2018. PMID: 30427275
30. Yilmaz N. Relationship between paraoxonase and homocysteine: crossroads of oxidative diseases. *Arch Med Sci*. 2012 Feb 29;8(1):138-53. doi: 10.5114/aoms.2012.27294. PMID: 22457688; PMCID: PMC3309450.
31. Tawfik A, Elsherbiny NM, Zaidi Y, Rajpurohit P. Homocysteine and Age-Related Central Nervous System Diseases: Role of Inflammation. *Int J Mol Sci.* 2021 Jun 10;22(12):6259. doi: 10.3390/ijms22126259. PMID: 34200792; PMCID: PMC8230490.
32. Shi Q, Savage JE, Hufeisen SJ, Rauser L, Grajkowska E, Ernsberger P, Wroblewski JT, Nadeau JH, Roth BL. L-homocysteine sulfinic acid and other acidic homocysteine derivatives are potent and selective metabotropic glutamate receptor agonists. *J Pharmacol Exp Ther*. 2003 Apr;305(1):131-42. doi: 10.1124/jpet.102.047092. PMID: 12649361.
33. Zieminska E, Stafiej A, Lazarewicz JW. (2003) Role of group I metabotropic glutamate receptors and NMDA receptors in homocysteine-evoked acute neurodegeneration of cultured cerebellar granule neurons. *Neurochem. Int*., 43(4-5), 481-492.
34. Ho P.I., Ashline D., Dhitavat S., Ortiz D., Collins S.C., Shea T.B. and Rogers E. (2003). Folate deprivation induces neurodegeneration: roles of oxidative stress and increased homocysteine. *Neurobiol. Dis.* 14, 32–42.
35. James SJ, Cutler P, Melnyk S, Jernigan S, Janak L, Gaylor DW, Neubrander JA. Metabolic biomarkers of increased oxidative stress and impaired methylation capacity in children with autism. *Am J Clin*

Nutr. 2004 Dec;80(6):1611-7. doi: 10.1093/ajcn/80.6.1611. PMID: 15585776

36. Obeid R, Herrmann W. Mechanisms of homocysteine neurotoxicity in neurodegenerative diseases with special reference to dementia. FEBS Lett. 2006 May 29;580(13):2994-3005. doi: 10.1016/j.febslet.2006.04.088. Epub 2006 May 6. PMID: 16697371.
37. Sibarov DA, Giniatullin R, Antonov SM. High sensitivity of cerebellar neurons to homocysteine is determined by expression of GluN2C and GluN2D subunits of NMDA receptors. Biochem Biophys Res Commun. 2018 Nov 30;506(3):648-652. doi: 10.1016/j.bbrc.2018.10.140. Epub 2018 Oct 27. PMID: 30454701
38. Liu L, Wu Q, Yan H, Zheng X, Zhou Q. Plasma Homocysteine and Autonomic Nervous Dysfunction: Association and Clinical Relevance in OSAS. Dis Markers. 2020 Jul 8;2020: 4378505. doi: 10.1155/2020/4378505. PMID: 32695242; PMCID: PMC7368224.
39. Fratoni V, Brandi ML. B vitamins, homocysteine and bone health. Nutrients. 2015 Mar 30;7(4):2176-92. doi: 10.3390/nu7042176. PMID: 25830943; PMCID: PMC4425139.
40. McLean R. R., Jacques P. F., Selhub J. and al. Homocysteine as a predictive factor for hip fracture in older persons. *N Engl J Med*. 2004 May 13 ; 350 (20) : 2042-2049. doi: 10.1056/NEJMoa032739.
41. Catargi B., Parrot-Roulaud F., Cochet C., et al. Homocysteine, hypothyroidism, and effect of thyroid hormone replacement. *Thyroid*. 1999. Vol. 9(12). P. 1163-1166.
42. Nechyporuk V. M., Zaichenko N. V., Korda M. M. Effect of thyroid gland functional state on the functioning of homocysteine remethylation cycle in rat organs. Deutscher Wissenschafts Herold • German Science Herald, N 4/2016. P. 45-48.
43. Bandazhevskyi Yu. I., Dubova N. F. Genetic control of homocysteine metabolism in children living nearthe Chernobyl exclusion zone. *Environment&Health*. 2022. № 2 (103). P. 10-15.
https://doi.org/10.32402/dovkil2022.02.010
44. Froese D. S, Fowler B., Baumgartner M. R. Vitamin B_{12}, folate, and the methionine remethylation cycle — biochemistry, pathways, and regulation. *J Inherit Metab Dis*. 2019; 42(4): 673-685. https://doi.org/10.1002/jimd.12009 .

45. Bandazheuski Yu., Dubovaya N. Hyperhomocysteinemia and folate cycle genes in girls and boys living near the Chernobyl Exclusion Zone // Traditional and innovative approaches to scientific research: theory, methodology, practice: Scientific monograph. Riga, Latvia: Baltija Publishing, 2022. P. 268-282.DOI: https://doi.org/10.30525/978-9934-26-241-8-12 (ISBN: 978-9934-26-241-8).

46. Yang B, Liu Y, Li Y, Fan S, Zhi X, Lu X, Wang D, Zheng Q, Wang Y, Wang Y, Sun G. Geographical distribution of MTHFR C677T, A1298C and MTRR A66G gene polymorphisms in China: findings from 15357 adults of Han nationality. PLoS One. 2013;8(3):e57917. doi: 10.1371/journal.pone.0057917. Epub 2013 Mar 5. PMID: 23472119; PMCID: PMC3589470

47. Rady PL, Szucs S, Grady J, Hudnall SD, Kellner LH, Nitowsky H, Tyring SK, Matalon RK. Genetic polymorphisms of methylenetetrahydrofolate reductase (MTHFR) and methionine synthase reductase (MTRR) in ethnic populations in Texas; a report of a novel MTHFR polymorphic site, G1793A. *Am J Med Genet*. 2002 Jan 15;107(2):162-8. doi: 10.1002/ajmg.10122. PMID: 11807892.

48. Bandazhevsky Yu. I., Dubova N. F. The state of folate metabolism and its link with thyroid system in children after forest fires in the Chornobyl exclusion zone. *Environment&Health*. 2019. № 2(91). P. 10-16.

DOI: https://doi.org/10.32402/dovkil2019.02.010

49. Bandazheuski Yu., Dubovaya N. Genetic regulation of the metabolism of methionine, homocysteine and vitamins B9, B12 in children living near the Chernobyl Exclusion zone // Theoretical and practical aspects of the development of modern scientific research: Scientific monograph. Part 2. Riga, Latvia: Baltija Publishing, 2022. P. 180-193. DOI: DOI: https://doi.org/10.30525/978-9934-26-195-4-22

50. Bandazhevskyi Yu. I., Dubova N. F. Genetic polymorphisms of the folate cycle and hyperhomocysteinemia in children from areas bordering the Chernobyl exclusion zone. *Environment&Health*. 2023. No. 3. P. 11-19.

https://doi.org/10.32402/dovkil2023.03.011

51. Bandazheuski Yu., Dubovaya N. Elements of etio-pathogenesis of hyperhomocysteinemia in children living in the regions affected from the accident at the Chernobyl nuclear power plant // The scientific

paradigm in the context of technological development and social change: Scientific monograph. Part 2. Riga, Latvia: Baltija Publishing, 2023. P. 140-163.

DOI: https://doi.org/10.30525/978-9934-26-297-5-25

52. Bandazheuski Yu., Dubovaya N. Hyperhomocysteinemia and pituiyary-thyroid axis among children living near the Chornobyl exclusion zone // Theoretical and practical aspects of science development : Scientific monograph. Part 2. Riga, Latvia : Baltija Publishing, 2023. P. 368-390. DOI: https://doi.org/10.30525/978-9934-26-355-2
53. Bandazheuski Yu., Dubovaya N. Folate cycle genes and the endocrine system in children living in the territory affected by the accident at the Chernobyl nuclear power plant //Science, technology and innovation in the modern world : Scientific monograph. Riga, Latvia : Baltija Publishing, 2023. P. 188-210.

DOI: https://doi.org/10.30525/978-9934-26-364-4
54. Lin, L., Du, Y., Niu, G. et al. Folate deficiency may increase the risk for elevated TSH in patients with type 2 diabetes mellitus. BMC Endocr Disord 23, 169 (2023). https://doi.org/10.1186/s12902-023-01422-2
55. So Young Park, Song Vogue Ahn, Hyun Seok Jin, Hyun-Jung An, Se Eun Park and Sihoon Lee. SUN-269: Increases in Thyrotropin Are Associated with Increased Triiodothyronine/Thyroxine Ratio in the Korean Healthy Adult Group. Endocrine Society's 98th Annual Meeting and Expo. Boston. 2016.April 1–4.
56. Nedrebø BG, Hustad S, Schneede J, Ueland PM, Vollset SE, Holm PI, Aanderud S, Lien EA. Homocysteine and its relation to B-vitamins in Graves' disease before and after treatment: effect modification by smoking. J Intern Med. 2003 Nov;254(5):504-12. doi: 10.1046/j.1365-2796.2003.01222.x. PMID: 14535973.
57. Demirbas B, Ozkaya M, Cakal E, Culha C, Gulcelik N, Koc G, Serter R, Aral Y. Plasma homocysteine levels in hyperthyroid patients. *Endocr J.* 2004 Feb;51(1):121-5. Doi: 10.1507/endocrj.51.121. PMID: 15004418.
58. Nair CP, Viswanathan G, Noronha JM. Folate-mediated incorporation of ring-2-carbon of histidine into nucleic acids: influence of thyroid hormone. *Metabolism*. 1994 Dec;43(12):1575-8. doi: 10.1016/0026-0495(94)90019-1. PMID: 7990714.

59. Tripathi Prashant, Saxena Nivedita, Verma Manish Kumar, Singh Anand Narayan. Association of Vitamin B_{12}, Folate and Ferritin with Thyroid Hormones in Hypothyroidism. Annals of International medical and Dental Research. 2019 Jan; 5(1): 1-6.

60. Juárez-Cedillo T, Basurto-Acevedo L, Vega-García S, Sánchez-Rodríguez Martha A, Retana-Ugalde R, Juárez-Cedillo E, Gonzalez-Melendez Roberto C, Escobedo-de-la-Peña J. Prevalence of thyroid dysfunction and its impact on cognition in older mexican adults: (SADEM study). *J Endocrinol Invest*. 2017 Sep;40(9):945-952. doi: 10.1007/s40618-017-0654-6. Epub 2017 Mar 25. PMID: 28343318.

61. Ferreira-Hermosillo A, Toledo J.O and Cordoba K (2024) Evaluation of the risk of hypothyroidism and its clinical manifestations using the Zulewski scale. Front. *Endocrinol*. 15:1416663. doi: 10.3389/fendo.2024.1416663

62. Bandazheuski Yu., Dubovaya N. The combination of folate cycle genotypes and hyperhomocysteinemia in children living near the Chernobyl Exclusion zone // Scientific space in the conditions of global transformations of the modern world: Scientific monograph. Riga, Latvia: Baltija Publishing, 2022. P. 21-37. DOI: https://doi.org/10.30525/978-9934-26-195-4-22

63. Bandazhevsky Yu. I., Dubovaya N. F. Associations between thyroid hormones and homocysteine in children living in areas affected by the Chernobyl nuclear power plant accident. *Гігієна населених місць*. 2018. Вип. 68. С. 177-183. https://doi.org/10.32402/hygiene2018.68.177

64. Bandazhevskyi Yu. I., Dubovaya N. F. Hyperhomocysteinemia in children and forest fires in the Chornobyl exclusion zone. *Environment&Health*. 2020. № 4(97). P. 21-26. DOI: https://doi.org/10.32402/dovkil2020.04.021

65. Bandazhevsky Yu.I., Dubovaya N.F. The role of folate metabolism genome in the formation of triiodothyronine in children living in areas affected by the Chernobyl nuclear power plant accident. Фактори експериментальної еволюції організмів: зб. наук. пр. / Національна академія наук України, Інститут молекулярної біології і генетики, Укр. т-во генетиків і селекціонерів ім. М.І. Вавилова; редкол.: В.А. Кунах (голов. ред.) [та ін.]. – К.: Укр. т-во

генетиків і селекціонерів ім. М.І. Вавилова, 2019. – Т. 24. – С. 197-201. DOI: https://doi.org/10.7124/FEEO.v24.1101

66. Bandazhevsky Yu., Dubovaya N. The concept of regulatory connections of the folate cycle and the pituitary-thyroid axis in children from areas affected by the accident at the Chernobyl Nuclear Power Plant // International Scientific Conference Science in the Modern World: Prospects and Directions of Development: Conference Proceedings, May 17-18, 2024. Riga, Latvia: Baltija Publishing, pp. 15-18. DOI: https://doi.org/10.30525/978-9934-26-438-2-4 pp/ 15-18
67. Dubovaya N., Bandazheuski Yu. Adaptation resources of the cardiovascular system of schoolchildren living near the Chernobyl nuclear power plant // Scientific space: integration of traditional and innovative processes: Scientific monograph. Riga, Latvia: Baltija Publishing, 2023. P. 147-170. DOI: https://doi.org/10.30525/978-9934-26-310-1-5.
68. Дубова Н. Ф., Бандажевський Ю. І. Оцінка адаптаційних можливостей серцево-судинної системи школярів, які мешкають поблизу Чорнобильської зони відчуження. *Environment&Health*. 2023. № 2 (107). P. 24-30. DOI: https://doi.org/10.32402/dovkil2023.02.024
69. Bandajevsky Y. I., Bandajevskaya G. Cardiomyopathies on cesium 137. *Cardinale. revue de cardiologie*. 2003. Vol. 15. № 8. P. 40-42.
70. Klein I, Danzi S. Thyroid disease and the heart. *Circulation*. 2007 Oct 9;116(15):1725-35. doi: 10.1161/CIRCULATIONAHA.106.678326. Erratum in: Circulation. 2008 Jan 22;117(3):e18. PMID: 17923583.

List of abbreviations

ChNPP	—	Chernobyl Nuclear Power Plant
ChEZ	—	Chernobyl exclusion zone
^{137}Cs	—	radioactive isotope of cesium
^{90}Sr	—	radioactive isotope of strontium
TG	—	thyroid gland
AH	—	adenohypophysis
T_3	—	triiodothyronine
T_4	—	thyroxine
ATP	—	adenosine triphosphate
AMP	—	adenosine monophosphate
TSH	—	pituitary thyroid stimulating hormone
SILR	—	syndrome of incorporated long-lived radionuclides
BP	—	blood pressure
SBP	—	systolic blood pressure
DBP	—	diastolic blood pressure
PP	—	pulse pressure
AST	—	aspartate aminotransferase
ALT	—	alanine aminotransferase
AST/ALT	—	de Ritis coefficient
H_{cy}	—	homocysteine
Met	—	methionine
FC	—	folate cycle
Cyst	—	cystathionine
Cys	—	cysteine
MTHFR	—	Methylenetetrahydrofolate reductase
MS	—	B_{12} methionine synthase
MSR	—	methionine synthase reductase
CBS	—	cystathionine β-synthase
SAM	—	S-adenosylmethionine
SAH	—	S-adenosylhomocysteine
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
NMDA — N-methyl-D-aspartate

Scientific publication

Yu. I. Bandazhevsky, N. F. Dubovaya

REGULATION OF THYROID GLAND FUNCTION IN CHILDREN LIVING IN AREAS AFFECTED BY THE CHERNOBYL NUCLEAR POWER PLANT ACCIDENT

Editing and release by O. S. Dubovaya
Computer typesetting by A. M. Samchenko

Signed for printing on 28.02.2025.
Format 60.84 1/16. Offset paper
Conditional printing. arch. 9,18.
Circulation 300 copies.

FOP Samchenko Anastasia Mykhailivna
Certificate of registration of the subject
of the publishing business
to the state register of publishers, manufacturers
and distributors of publishing products
DK No. 7906 of August 03, 2023.
Phone. (093) 860-62-21.