Multidisciplinary Studies of the Thyroid Gland's Synthetic Activity under Conditions of Iodine Deficiency Using Correlation Analysis

Olha Ryabukha (PhD in Medical Sciences, Associate Professor, Lviv Medical University, Ukraine)
*Corresponding author: Olha Ryabukha

Received: June 16, 2023
Published: July 13, 2023

Abstract. The article examines the results of a multidisciplinary study of the thyroid follicular cells' synthetic activity of male albino rats using the author's methods for determining the profiles of hormonopoietic cells' special capacities and semi-quantitative analysis of electronograms, a package of mathematical methods using the principle of fuzzy logic, the cluster approach to grouping data, the principle of phase interval, correlation analysis using Pearson's formula and evaluating the results according to the Chaddock scale, interpreting the obtained results from the standpoint of cytophysiology. A comparative study on the effect of low, moderate, and high doses of organic and inorganic iodine on changes in correlations between protein-synthesizing organelles of follicular cells under conditions of dietary iodine deficiency was carried out. Based on the data on the number, strength and direction of correlations, a comparative study on the effect of low, moderate, and high doses of organic and inorganic iodine on the thyroid follicular cells' protein-synthesizing organelles under conditions of dietary iodine deficiency was carried out. The information on the peculiarities of thyroid hormonopoiesis under the action of iodine of different chemical nature was deepened and the greater activating effect of organic iodine was proved, which is of scientific interest and has practical significance for the development of personalized preventive measures for dietary iodine deficiency.

Keywords: thyroid gland, follicular cells, synthetic activity of follicular cells, organic iodine, inorganic iodine, dietary iodine deficiency, Pearson correlation analysis.

Introduction. Thyroid hormones are critical for the coordinated activity of all organs and systems of the body [1-11]. In view of this, the growth of thyroid pathology is a serious medical and social problem of our time [12,13], the solution of which requires a multidisciplinary and multi-vector approach [14]. The most common thyroid pathology is hypothyroidism [15,16], caused by dietary iodine deficiency. Iodine deficiency is largely a hygienic and environmental problem [17]. The basic method of prevention and correction of such hypothyroidism is the use of iodized products [18,19], the use of iodine-containing supplements [20,21]. According to a number of scientists, inorganic iodine compounds can no longer be recognized as the only and optimal way to prevent and overcome hypothyroidism [22-25]. At the same time, despite information about the confirmed efficacy of taking organic iodine with reduced functional activity of the thyroid gland, the specifics of its influence have not been sufficiently studied. This actualizes the need to study various aspects of the processes that occur in follicular cells of the thyroid gland in case of alimentary hypothyroidism. Since the in-depth study of thyroid hormonopoiesis goes beyond the scope of any single branch of medicine, it should involve the coordinated application of physiological, morphological, biochemical [26,27], histochemical [28,29], clinical and other fields of scientific research at different levels of integration of the thyroid gland into the body [30]. The need for an in-depth study of the thyroid gland's state, in particular thyroid hormonopoiesis, has become especially important under conditions of the COVID-19 pandemic, which is characterized by multiorgan damage [31,32]. In this case, the application of mathematical methods to study the features of the thyroid gland's activity [33-45], whose hormones are important for the functioning of the body's regulatory systems and are responsible for the reproduction of tissues, is extremely appropriate.

The purpose of the study was multidisciplinary research using electron microscopy and a package of mathematical methods (principle of fuzzy logic, cluster principle of data grouping, principle of phase interval, and Pearson correlation analysis) to study the effect of different doses of organic and inorganic iodine on the features of relationships between organelles of the thyroid follicular cells' synthetic direction of activity under the conditions of dietary iodine deficiency.

Materials and methods. The study was carried out on non-linear male albino rats with an initial body weight of 140-160 g, which were fed a standard starch-casein diet in the summer period in a vivarium. All food ingredients and vitamins were given to rats in the amounts recommended for animals of this species and age. To create a model of dietary iodine deficiency, potassium iodide was removed from the recipe of the standard J.H. Jones & C.Foster salts' mixture (the background iodine content in such a diet was within 13-15 μg/kg of body weight). Dietary iodine deficiency was corrected by taking organic and inorganic iodine in histologically determined minimally effective dose, optimal dose (2.5 times greater than minimally effective) and excessive dose (2 times greater than optimal one). These doses were designated by us as "low" (21 μg/kg of body weight for groups 1 and 4), "moderate" (50 μg/kg of body weight for groups 2 and 5) and "high" (100 μg/kg of body weight for groups 3 and 6).

The source of organic iodine was an iodine-protein supplement [46] produced of iodine-protein components [47] of the Black Sea red algae Phyllophora nervosa (*Phyllophora crispa*) at the A.V. Bogatsky Physico-Chemical Institute of the National Academy of Sciences of Ukraine. Inorganic iodine came with a potassium iodide (Darnitsa Pharmaceutical Company, Ukraine). Given the high sensitivity of the thyroid gland to stress, which is possible when iodine-containing agents are introduced into the stomach through an orogastric tube, they entered the body physiologically with food.

The study was carried out on 60 rats, of which 6 groups of 10 animals each were formed by random sampling. After the 30-day observation period, the rats were decapitated under ether anesthesia, their thyroid glands were carefully separated from the connective tissue and prepared for electron microscopy examination according to the standard technique. Experiments with the use of laboratory animals were carried out in compliance with the Law of Ukraine "On Protection of Animals from Cruel Treatment" (Kyiv, 2006), and the provisions of the "European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes" (Strasbourg, 1986). The Statistica 6.0 Microsoft Office software was used to calculate the digital database.

Electron microscopy [48-52] and mathematical methods were used to study the characteristics of changes in the ultrafine structure of the thyroid gland under the influence of organic and inorganic iodine.

• *Electron microscopy*. After fixation in a 2% osmium tetroxide solution, the thyroid glands were dehydrated in alcohols of ascending contraception and acetone, followed by polymerization in epoxy resins according to standard methods. Ultrathin sections were made from the tissue blocks with the LKB Bromma 8800 Ultrotome III (Sweden) appliance, which were additionally contrasted with solutions of uranyl acetate and lead citrate salts. Electronograms were obtained using a PEM-100-01 transmission electron microscope (Selmi, Ukraine).

The study of the relationships features between the follicular cells' protein-synthesizing organelles was carried out using the author's morphological methods for determining the profiles of the hormonopoietic cells' special capacities [53] and semi-quantitative analysis of electronograms [54], based on mathematical methods – the principle of fuzzy logic [55-57] for the objectification of qualitative information, cluster approach to data grouping [58], phase interval principle [59,60] for comparing the state of follicular cells' structural elements, Pearson correlation analysis [61,62] to establish relationships and interdependencies between structural elements of thyroid follicular cells.

• *O.Ryabukha's method for determining the profiles of hormonopoietic cells' special capacities*. If each activity field of a hormonopoietic cell (synthesis, secretion, transportation of the produced hormones by perifollicular capillaries, energy supply of these processes) is qualified as an "capacity", then the result will be the creation of appropriate clusters, the implementation of which is provided by specialized cell components. We call such clusters "profiles of special capacities". The arrangement of the cluster/profile's determined elements of the investigated capacity is achieved by using special symbols that we use to denote ultrastructural cell components. The composition of cell components of the profile of thyroid follicular cells' synthetic capacity presented in Table 1.

Table 1. Profile of follicular cells synthetic capacity [63].

Cell components	Data	Status	Symbol
Cytoplasm	electron density	insignificant	B1
		moderate	B2
		significant	B3
Rough endoplasmic reticulum (rough ER)	form (structures' width)	constricted	J1
		moderate	J2
		expanded	J3
	number of fixed ribosomes	decreased	J4
		moderate	J5
		increased	J6
Free ribosomes and polysomes	number	decreased	K1
		moderate	K2
		increased	K3
Golgi body	form (structures' width)	constricted	L1
		moderate	L2
		expanded	L3

• *Semi-quantitative analysis of electronograms according to O.Ryabukha*. Electronograms are analyzed according to the defined algorithm [64]. According to it, the ultrastructural cell components of the special capacity profile on electronograms of the rat thyroid glands in the study group are first visually divided into the categories "few", "moderately", and "many". After that, in electronograms, they are compared to the same structural cell components of the glands in normal conditions and in the studied pathology (uncorrected dietary iodine deficiency). When studying electronograms, non-numerical results (qualitative or binary data) are transformed into numerical (quantitative) indices by the method of their digital assessment according to a point scale developed by us in the range from 0 to 4 points (percentage scale with gradation from 0 to 100% is also possible). The absence of a feature was assessed as 0 points, the low degree of feature severity – 1 point, moderate – 2 points, high – 3 points; the very high value corresponded to a score of 4 points (Table 2). It should be noted separately the features of assessing the number of ribosomes. Under conditions of thyroid follicular cells' normal synthetic activity, the highest score is 4 points. At the same time, when synthetic processes are stimulated, the number of ribosomes (fixed and free) can significantly increase. In this case, with the maximum degree of activation of hormonopoiesis by organic or inorganic iodine, an increase in the index to 8 points (200%) is possible.

Table 2. Assessment scale of features severity in cell components' semi-quantitative analysis of electronograms.

Feature severity degree	**Symbol**	**Numerical assessment**	
		(points)	(percentage)
feature absent	–	0	0
low	+	1	25
moderate	++	2	50
high	+++	3	75
very high	++++	4	100

Further, the obtained digital parameters are averaged and used for correlation analysis when determining the relationships and interdependencies between the ultrastructural components of the studied fields of activity (cluster-profiles) of follicular cells.

• *Pearson Correlation Analysis*. The bivariate Pearson Correlation produces a sample correlation coefficient, which measures the strength and direction of linear relationships between pairs of continuous variables. To find out the presence of correlations between the components of the profile of the synthetic capacities of follicular cells, the Pearson correlation coefficient r is calculated.

When assessing the results, the number of correlations, their strength and direction are indicated. An *r* value of positive one (+1) indicates a perfect [65] positive correlation, while an *r* value of negative one (−1) indicates a perfect negative correlation. An *r* value of zero indicates no correlation. A positive value of the Pearson's *r* coefficient indicates an increase in both associated indices, a negative value indicates that as one of the indices increases, the other index associated with it decreases. In the structure of correlations between profile components, the most significant are very high and high correlations, which according to the Chaddock scale [66] are, respectively, within the range of $1.00 \geq r \geq 0.91$ and $0.90 \geq r \geq 0.71$; in the absence of such correlations, we consider marked correlations $0.70 \geq r \geq 0.51$ and moderate correlations ($0.50 \geq r > 0.31$). The obtained data were interpreted from the standpoint of cytophysiology [67].

The study is a fragment of research works of Lviv Medical Institute LLC on the topic of "Improving the system of circulation of drugs during pharmacotherapy on the basis of evidentiary and forensic pharmacy, organization, technology, biopharmacy and pharmaceutical law" (state registration number 0120U105348, implementation period 2021-2026).

Results and discussion. Analysis of significant correlations showed that when rats of group 1 (Table 3) received a low dose of organic iodine, moderate (normal) of structures' width of the rough endoplasmic reticulum (rough ER) formed positive correlations of moderate strength (hereinafter referred to as "moderate positive") with moderate (normal) and with a decreased number of fixed ribosomes (r = 0.535) and positive correlations of high strength (hereinafter referred to as "high positive") with moderate (normal) of structures' width of the Golgi body (r = 0.791). This nature of connections between protein-synthesizing cellular components indicates sufficient synthetic activity of the thyroid follicular cells. However, at the same time, the separation of the processes of formation and maturation of the thyroglobulin molecule was also observed, a sign of which is very high negative correlations of expanded Golgi body structures with a moderate (normal) number of free ribosomes (r = −1.000), as well as certain disorders of protein synthesis, a sign of which are very high negative correlations of the rough endoplasmic reticulum's expanded structures with a decreased number of fixed ribosomes (r = −1.000).

Table 3. Correlations of the synthetic capacity profile of follicular cells in the correction of alimentary iodine deficiency with a low dose of organic iodine.

Data of the cell components for correlation analysis	Symbols of correlations	Pearson's *r* coefficient
insignificant electron density of cytoplasm — expanded structures of the rough ER	B1—J3	0.791
insignificant electron density of cytoplasm — decreased number of fixed ribosomes	B1—J4	−0.791
insignificant electron density of cytoplasm — moderate number of fixed ribosomes	B1—J5	0.791
insignificant electron density of cytoplasm — moderate (normal) structures' width of the Golgi body	B1—L2	0.500
moderate electron density of cytoplasm — moderate (normal) structures' width of the rough ER	B2—J2	−0.423
moderate electron density of cytoplasm — decreased number of free ribosomes and polysomes	B2—K1	0.791
moderate electron density of cytoplasm — moderate number of free ribosomes and polysomes	B2—K2	0.791
moderate electron density of cytoplasm — moderate (normal) structures' width of the Golgi body	B2—L2	0.500
moderate electron density of cytoplasm — expanded structures of the Golgi body	B2—L3	−0.791
moderate (normal) structures' width of the rough ER — decreased number of free ribosomes and polysomes	J2—K1	−0.802

expanded structures of the rough ER — decreased number of fixed ribosomes	J3—J4	−1.000
moderate number of fixed ribosomes — moderate (normal) structures' width of the Golgi body	J5—L2	0.791
moderate number of free ribosomes and polysomes — moderate (normal) structures' width of the Golgi body	K2—L2	0.791
moderate number of free ribosomes and polysomes — expanded structures of the Golgi body	K2—L3	−1.000
moderate (normal) structures' width of the Golgi body — expanded structures of the Golgi body	L2—L3	−0.791

When rats of group 4 (Table 4) received a low dose of inorganic iodine, a decreased number of fixed ribosomes formed high positive correlations with expanded structures of the rough ER and Golgi body ($r = 0.802$), indicating the presence of functional stress. Under these conditions, the high positive correlations between the moderate (normal) of structures' width of the rough ER and the expanded structures of the Golgi body ($r = 0.791$) can logically be considered an adaptive mechanism aimed at maintaining the synthetic activity of follicular cells in adverse conditions.

Table 4. Correlations of the synthetic capacity profile of follicular cells in the correction of alimentary iodine deficiency with a low dose of inorganic iodine.

Data of the cell components for correlation analysis	Symbols of correlations	Pearson's *r* coefficient
insignificant electron density of cytoplasm — moderate electron density of cytoplasm	B1—B2	−0.764
insignificant electron density of cytoplasm — moderate (normal) structures' width of the rough ER	B1—J2	0.408
insignificant electron density of cytoplasm — decreased number of fixed ribosomes	B1—J4	0.408
insignificant electron density of cytoplasm — moderate number of fixed ribosomes	B1—J5	−0.612
insignificant electron density of cytoplasm — decreased number of free ribosomes and polysomes	B1—K1	−0.612
insignificant electron density of cytoplasm — moderate number of free ribosomes and polysomes	B1—K2	−0.612
insignificant electron density of cytoplasm — moderate (normal) structures' width of the Golgi body	B1—L2	−0.612
insignificant electron density of cytoplasm — expanded structures of the Golgi body	B1—L3	0.646
moderate electron density of cytoplasm — moderate (normal) structures' width of the rough ER	B2—J2	−0.534
moderate electron density of cytoplasm — expanded structures of the rough ER	B2—J3	−0.429
moderate electron density of cytoplasm — decreased number of fixed ribosomes	B2—J4	−0.534
moderate electron density of cytoplasm — decreased number of free ribosomes and polysomes	B2—K1	0.802
moderate electron density of cytoplasm — moderate number of free ribosomes and polysomes	B2—K2	0.802
moderate electron density of cytoplasm — expanded structures of the Golgi body	B2—L3	−0.422
moderate (normal) structures' width of the rough ER — expanded structures of the rough ER	J2—J3	−0.534

moderate (normal) structures' width of the rough ER — expanded structures of the Golgi body	J2—L3	0.791
expanded structures of the rough ER — decreased number of fixed ribosomes	J3—J4	0.802
expanded structures of the rough ER — decreased number of free ribosomes and polysomes	J3—K1	−0.534
expanded structures of the rough ER — moderate number of free ribosomes and polysomes	J3—K2	−0.534
expanded structures of the rough ER — expanded structures of the Golgi body	J3—L3	0.422
moderate number of fixed ribosomes — moderate (normal) structures' width of the Golgi body	J5—L2	1.000
moderate number of fixed ribosomes — expanded structures of the Golgi body	J5—L3	−0.791
decreased number of free ribosomes and polysomes — moderate number of free ribosomes and polysomes	K1—K2	1.000
moderate (normal) structures' width of the Golgi body — expanded structures of the Golgi body	L2—L3	−0.791

Taking a moderate dose of organic iodine by rats of group 2 (Table 5) contributed to normalization of protein synthesis [68]. This was indicated by a very high positive correlation between the moderate (normal) of structures' width of the rough ER and moderate (normal) of structures' width of the Golgi body ($r = 1.000$); free ribosomes, which formed two significant positive correlations and four significant negative correlations with other elements of the cluster, played a major role in maintaining sufficient functional activity of follicular cells.

Table 5. Correlations of the synthetic capacity profile of follicular cells in the correction of alimentary iodine deficiency with a moderate dose of organic iodine.

Data of the cell components for correlation analysis	Symbols of correlations	Pearson's *r* coefficient
insignificant electron density of cytoplasm — moderate electron density of cytoplasm	B1—B2	−0.802
insignificant electron density of cytoplasm — moderate number of fixed ribosomes	B1—J5	0.791
insignificant electron density of cytoplasm — increased number of free ribosomes and polysomes	B1—K3	−0.534
moderate electron density of cytoplasm — moderate (normal) structures' width of the rough ER	B2—J2	−0.534
moderate electron density of cytoplasm — moderate number of fixed ribosomes	B2—J5	−0.845
moderate electron density of cytoplasm — increased number of free ribosomes and polysomes	B2—K3	0.786
moderate electron density of cytoplasm — moderate (normal) structures' width of the Golgi body	B2—L2	−0.534
moderate (normal) structures' width of the rough ER — moderate (normal) structures' width of the Golgi body	J2—L2	1.000
moderate number of fixed ribosomes — increased number of free ribosomes and polysomes	J5—K3	−0.845
increased number of fixed ribosomes — moderate number of free ribosomes and polysomes	J6—K2	−1.000
increased number of fixed ribosomes — increased number of free ribosomes and polysomes	J6—K3	0.534

moderate number of free ribosomes and polysomes — increased number of free ribosomes and polysomes	K2—K3	−0.534

The interdependence of the states of protein-synthesizing cellular components was also observed when consuming a moderate dose of inorganic iodine by rats of group 5 (Table 6): moderate (normal) of structures' width of the rough ER and moderate (normal) of structures' width of the Golgi body had moderate positive correlations with a moderate (normal) number of free ribosomes (r = 0.408). However, although the interdependence of the rough endoplasmic reticulum's morpho-functional state and the Golgi body as the main protein-synthesizing organelles is logically considered a prerequisite for the sufficient intensity of synthesis processes in follicular cells; marked positive correlations between their expanded structures (r = 0.612) against the background of negative correlations of the same strength between their normal structures (r = −0.645) are a sign of a certain functional stress. The same is indicated by moderate positive correlations of expanded structures of the rough ER with a moderate (normal) number of fixed ribosomes (r = 0.408) and a decreased number of free ribosomes (r = 0.408).

Table 6. Correlations of the synthetic capacity profile of follicular cells in the correction of alimentary iodine deficiency with a moderate dose of inorganic iodine.

Data of the cell components for correlation analysis	Symbols of correlations	Pearson's *r* coefficient
insignificant electron density of cytoplasm — expanded structures of the rough ER	B1—J3	0.408
insignificant electron density of cytoplasm — decreased number of fixed ribosomes	B1—J4	−0.612
insignificant electron density of cytoplasm — moderate number of free ribosomes and polysomes	B1—K2	−0.612
insignificant electron density of cytoplasm — moderate (normal) structures' width of the Golgi body	B1—L2	0.645
moderate electron density of cytoplasm — moderate (normal) structures' width of the rough ER	B2—J2	1.000
moderate electron density of cytoplasm — expanded structures of the rough ER	B2—J3	−0.612
moderate electron density of cytoplasm — decreased number of fixed ribosomes	B2—J4	0.408
moderate electron density of cytoplasm — moderate number of free ribosomes and polysomes	B2—K2	0.408
moderate electron density of cytoplasm — moderate (normal) structures' width of the Golgi body	B2—L2	−0.645
moderate electron density of cytoplasm — expanded structures of the Golgi body	B2—L3	1.000
moderate (normal) structures' width of the rough ER — expanded structures of the rough ER	J2—J3	−0.612
moderate (normal) structures' width of the rough ER — decreased number of fixed ribosomes	J2—J4	0.408
moderate (normal) structures' width of the rough ER — moderate number of free ribosomes and polysomes	J2—K2	0.408
moderate (normal) structures' width of the rough ER — moderate (normal) structures' width of the Golgi body	J2—L2	−0.645
moderate (normal) structures' width of the rough ER — expanded structures of the Golgi body	J2—L3	1.000
expanded structures of the rough ER — moderate number of fixed ribosomes	J3—J5	0.408

expanded structures of the rough ER — decreased number of free ribosomes and polysomes	J3—K1	0.408
expanded structures of the rough ER — moderate (normal) structures' width of the Golgi body	J3—L2	0.791
expanded structures of the rough ER — expanded structures of the Golgi body	J3—L3	−0.612
decreased number of fixed ribosomes — moderate number of fixed ribosomes	J4—J5	0.408
decreased number of fixed ribosomes — decreased number of free ribosomes and polysomes	J4—K1	0.408
decreased number of fixed ribosomes — moderate number of free ribosomes and polysomes	J4—K2	1.000
decreased number of fixed ribosomes — moderate (normal) structures' width of the Golgi body	J4—L2	−0.791
decreased number of fixed ribosomes — expanded structures of the Golgi body	J4—L3	0.408
moderate number of fixed ribosomes — decreased number of free ribosomes and polysomes	J5—K1	1.000
moderate number of fixed ribosomes — moderate number of free ribosomes and polysomes	J5—K2	0.408
decreased number of free ribosomes and polysomes — moderate number of free ribosomes and polysomes	K1—K2	0.408
moderate number of free ribosomes and polysomes — moderate (normal) structures' width of the Golgi body	K2—L2	−0.791
moderate number of free ribosomes and polysomes — expanded structures of the Golgi body	K2—L3	0.408
moderate (normal) structures' width of the Golgi body — expanded structures of the Golgi body	L2—L3	−0.645

When group 3 (Table 7) rats received a high dose of organic iodine, eight significant correlations were observed between the fixed ribosomes and other profile elements, indicating their importance for ensuring the synthetic activity of follicular cells. However, high, and very high positive correlations of insignificant cytoplasm electron density with moderate (normal) number of fixed ribosomes (r = 0.791), moderate (normal) number of free ribosomes (r = 1.000) and expanded Golgi body structures (r = 1.000) is a sign of functional stress, which can be caused by intensive stimulation of hormonal synthesis.

Table 7. Correlations of the synthetic capacity profile of follicular cells in the correction of alimentary iodine deficiency with a high dose of organic iodine.

Data of the cell components for correlation analysis	Symbols of correlations	Pearson's *r* coefficient
insignificant electron density of cytoplasm — moderate electron density of cytoplasm	B1—B2	0.612
insignificant electron density of cytoplasm — moderate number of fixed ribosomes	B1—J5	0.791
insignificant electron density of cytoplasm — moderate number of free ribosomes and polysomes	B1—K2	1.000
insignificant electron density of cytoplasm — increased number of free ribosomes and polysomes	B1—K3	−1.000
insignificant electron density of cytoplasm — expanded structures of the Golgi body	B1—L3	1.000
moderate electron density of cytoplasm — moderate (normal)	B2—J2	−0.612

structures' width of the rough ER		
moderate electron density of cytoplasm — moderate number of fixed ribosomes	B2—J5	−0.645
moderate electron density of cytoplasm — increased number of fixed ribosomes	B2—J6	−0.612
moderate electron density of cytoplasm — moderate number of free ribosomes and polysomes	B2—K2	0.612
moderate electron density of cytoplasm — increased number of free ribosomes and polysomes	B2—K3	−0.612
moderate electron density of cytoplasm — moderate (normal) structures' width of the Golgi body	B2—L2	−0.645
moderate electron density of cytoplasm — expanded structures of the Golgi body	B2—L3	0.612
moderate (normal) structures' width of the rough ER — increased number of fixed ribosomes	J2—J6	1.000
moderate (normal) structures' width of the rough ER — moderate (normal) structures' width of the Golgi body	J2—L2	0.791
moderate number of fixed ribosomes — moderate number of free ribosomes and polysomes	J5—K2	−0.791
moderate number of fixed ribosomes — increased number of free ribosomes and polysomes	J5—K3	0.791
moderate number of fixed ribosomes — expanded structures of the Golgi body	J5—L3	−0.791
increased number of fixed ribosomes — moderate (normal) structures' width of the Golgi body	J6—L2	0.791
moderate number of free ribosomes and polysomes — increased number of free ribosomes and polysomes	K2—K3	−1.000
moderate number of free ribosomes and polysomes — expanded structures of the Golgi body	K2—L3	1.000
increased number of free ribosomes and polysomes — expanded structures of the Golgi body	K3—L3	−1.000

In rats of group 6 (Table 8), which consumed a high dose of inorganic iodine, there is a very high positive correlation between the moderate (normal) numbers of fixed and free ribosomes (r = 1.000) and marked positive correlations of moderate (normal) of structures' width of the rough ER with moderate (normal) numbers of ribosomes fixed on its membranes and free ribosomes in the cytoplasm (r = 0.612) indicate a sufficient level of functional activity. At the same time, moderate positive correlations between the expanded structures of the rough ER with moderate (normal) numbers of fixed and free ribosomes (r = 0.408), as well as marked negative correlations between the moderate (normal) of structures' width of the Golgi body and moderate (normal) numbers of fixed and free ribosomes (r = −0.667) may be signs of functional stress preservation [69]. Dissociations (inconsistencies) in the morpho-functional states of protein-synthesizing organelles, between which the following correlations were traced, can be considered signs of this: marked positive (r = 0.408) between the expanded structures of the rough ER and a moderate (normal) number of fixed ribosomes; marked positive (r = 0.408) between the expanded Golgi body structures and a moderate (normal) number of free ribosomes; marked negative (r = −0.408) between the moderate (normal) of structures' width of the rough ER and moderate (normal) of structures' width of the Golgi body [70]. However, these connections may also be a sign of adaptation of follicular cells to activity in conditions of enhanced protein synthesis against the background of residual functional stress.

When studying electronograms, attention was drawn to the correlations of the thyroid follicular cells cytoplasm's electron density, as their nature indicated the peculiarities of the activating synthetic process by different doses of iodine. When taking a low dose of organic iodine, high positive

(r = 0.791) correlations were observed between the cytoplasm of moderate (normal) electron density and free ribosomes, which were in moderate (normal) quantity, and moderate (normal) of structures' width of the Golgi body, at the same time, cytoplasm of insignificant electron density had high positive (r = 0.791) and moderate positive (r = 0.500) correlations, respectively, with a moderate (normal) number of fixed ribosomes and moderate (normal) of structures' width of the Golgi body. Consumption by group 2 rats of a moderate dose of organic iodine contributed to the formation of high positive (r = 0.786) correlations of moderate (normal) electron density cytoplasm with an increased number of free ribosomes, while cytoplasm of insignificant electron density had high positive (r = 0.791) correlations with a moderate (normal) number of fixed ribosomes. In rats of group 3, which received a high dose of organic iodine, marked positive (r = 0.612) correlations were observed between the cytoplasm of moderate (normal) electron density and the moderate (normal) number of free ribosomes, while the cytoplasm of insignificant electron density had high positive (r = 0.791) and very high positive (r = 1.000) correlations with moderate (normal) numbers of fixed and free ribosomes, respectively. Thus, the study of the correlations of the cytoplasm electron density showed that free ribosomes, fixed ribosomes, and the Golgi body are important participants in thyroid hormonopoiesis when taking organic iodine.

Table 8. Correlations of the synthetic capacity profile of follicular cells in the correction of alimentary iodine deficiency with a high dose of inorganic iodine.

Data of the cell components for correlation analysis	Symbols of correlations	Pearson's *r* coefficient
moderate electron density of cytoplasm — moderate (normal) structures' width of the rough ER	B2—J2	−0.408
moderate electron density of cytoplasm — expanded structures of the rough ER	B2—J3	−0.612
moderate (normal) structures' width of the rough ER — moderate number of fixed ribosomes	J2—J5	0.612
moderate (normal) structures' width of the rough ER — moderate number of free ribosomes and polysomes	J2—K2	0.612
moderate (normal) structures' width of the rough ER — moderate (normal) structures' width of the Golgi body	J2—L2	−0.408
moderate (normal) structures' width of the rough ER — expanded structures of the Golgi body	J2—L3	−0.612
expanded structures of the rough ER — moderate number of fixed ribosomes	J3—J5	0.408
expanded structures of the rough ER — moderate number of free ribosomes and polysomes	J3—K2	0.408
expanded structures of the rough ER — moderate (normal) structures' width of the Golgi body	J3—L2	−0.612
expanded structures of the rough ER — expanded structures of the Golgi body	J3—L3	0.612
moderate number of fixed ribosomes — moderate number of free ribosomes and polysomes	J5—K2	1.000
moderate number of fixed ribosomes — moderate (normal) structures' width of the Golgi body	J5—L2	−0.667
moderate number of free ribosomes and polysomes — moderate (normal) structures' width of the Golgi body	K2—L2	−0.667

When taking inorganic iodine in a low dose, the follicular cells cytoplasm of moderate (normal) electron density had high positive (r = 0.802) correlations with a moderate (normal) number of free ribosomes, while the cytoplasm of insignificant electron density formed moderate positive (r = 0.408) correlations with moderate (normal) of structures' width of the rough ER. Consumption of a moderate dose of inorganic iodine contributed to the formation of very high positive (r = 1.000) correlations between the cytoplasm of moderate (normal) electron density and moderate (normal) of structures' width of the rough ER against the background of marked positive (r = 0.645) correlations of insignificant electron density cytoplasm with moderate (normal) of structures' width of the Golgi body. At the same time, moderate and marked correlations of cytoplasm of moderate (normal) electron density with moderate (normal) of structures' width of the rough ER and moderate (normal) of structures' width of the Golgi body were negative: r = −0.408 and r = −0.612, respectively. In general, when taking inorganic iodine, thyroid hormonopoiesis was largely determined by the rough ER, the Golgi body, and free ribosomes. Therefore, the presented studies established that the degree of electron density of the cytoplasm in the thyroid follicular cell can be considered a marker of the majority of changes (marker of the significant changes), which occur in the cell during etiopathogenetic correction of iodine deficiency [71].

Thus, our research has established that under conditions of dietary iodine deficiency, the synthetic capacity of the thyroid follicular cells is determined by the intake of iodine, its chemical nature and dose. Addition of organic and inorganic iodine to the diet activates hormone synthesis, as indicated by the correlations traced between the structures of the rough ER and the Golgi body with the same functional state, the same amounts of free and fixed ribosomes, and the correspondence of the degree of follicular cells cytoplasm electron density to the status of protein-synthesizing cellular organelles. Under the discussed conditions, ribosomes located on the membranes of the rough endoplasmic reticulum (fixed ribosomes) play a leading role in ensuring the synthetic activity of follicular cells. It was noticed that the change in the number of ribosomes correlates with the change in the intensity of the synthesis process and is its morphological feature. An increase in the number of ribosomes in the cytoplasm (free ribosomes) is the first sign (marker) of an increase in the intensity of thyroid hormonopoiesis, while an increase in the number of fixed ribosomes indicates the achievement of a sufficient level of hormonopoiesis intensity and can be considered as a marker of the stability of the follicular cells' synthetic activity.

The processes of hormonal synthesis are usually accompanied by the phenomena of functional tension, which is indicated by correlations between protein-synthesizing organelles which are in opposite functional states. The correlations between the structures of the rough endoplasmic reticulum and the Golgi body in different functional states (different combinations of ultrastructural signs of functional stress) are not constant and depend on the dose and chemical nature of consumed iodine. The degree of electron density of follicular cells' cytoplasm depends on the level of their synthetic activity.

Conclusions. The study of the thyroid follicular cells activity by the author's methods of determining the profiles of hormonopoietic cells' special capacities and semi-quantitative analysis of electronograms for creation of digital databases and using Pearson correlation analysis permits to research in-depth the peculiarities of thyroid hormonopoiesis under the influence of iodine of different chemical nature, which is of undoubted scientific interest and has practical significance for the development of personalized preventive measures for iodine deficiency.

Acknowledgements. We express our sincere gratitude to PhD, Associate Professor Taras Lahotskyi (Department of Economic Cybernetics of Ivan Franko National University, Lviv) for assistance in using of Pearson correlation analysis.

Conflict of interests. The author reports no conflict of interests.

Funding. The author state, that this research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

References.

1. Warner A., Mittag J. Thyroid hormone and the central control of homeostasis. *Journal of Molecular Endocrinology*. 2012. Vol. 49. No. 1. P. R29–R35. DOI: https://doi.org/10.1530/JME-12-0068.

2. Bernal J. Thyroid hormones in brain development and function. *Endotext* [Internet]. Last update: 2022, January 14. URL: https://www.ncbi.nlm.nih.gov/books/NBK285549/.

3. Yamakawa H., Kato T.S., Noh J.Y. et al. Thyroid hormone plays an important role in cardiac function: from bench to bedside. *Frontiers in physiology*. 2021. Vol. 12. Article ID 606931. DOI: https://doi.org/10.3389/fphys.2021.606931.
4. Deligiorgi M.V., Trafalis D.T. The intriguing thyroid hormones-lung cancer association as exemplification of the thyroid hormones-cancer association: Three decades of evolving research. *International journal of molecular sciences*. 2021. Vol. 23. No. 1. Article ID 436. DOI: https://doi.org/10.3390/ijms23010436.
5. Piantanida E., Ippolito S., Gallo D. et al. The interplay between thyroid and liver: Implications for clinical practice. *Journal of Endocrinological Investigation*. 2020. Vol. 43. No. 7. P. 885–899. DOI: https://doi.org/10.1007/s40618-020-01208-6.
6. Kim S.H., Min H.K., Lee S.W. Relationship between thyroid and kidney function: Analysis from the Korea National Health and Nutrition Examination Survey between 2013 and 2015. *Kidney and Blood Pressure Research*. 2020. Vol. 45. No. 3. P. 442–454. DOI: https://doi.org/10.1159/000507290.
7. Chen C., Xie Z., Shen Y. et al. The roles of thyroid and thyroid hormone in pancreas: physiology and pathology. *International journal of endocrinology*. 2018. Vol. 2018. Article ID 2861034. DOI: https://doi.org/10.1155/2018/2861034.
8. Namulema J., Nansunga M., Kato C.D. et al. Thyroid hormones increase stomach goblet cell numbers and mucin expression during indomethacin induced ulcer healing in Wistar rats. *Thyroid Research*. 2018. Vol. 11. No. 6. DOI: https://doi.org/10.1186/s13044-018-0050-0.
9. Bassett J.H., Williams G.R. Role of thyroid hormones in skeletal development and bone maintenance. *Endocrine reviews*. 2016. Vol. 37. No. 2. 135–187. DOI: https://doi.org/10.1210/er.2015-1106.
10. Bloise F.F., Cordeiro A., Ortiga-Carvalho T.M. Role of thyroid hormone in skeletal muscle physiology. *Journal of Endocrino*logy. 2018. Vol. 236. No. 1. P. R57–R68. DOI: https://doi.org/10.1530/JOE-16-0611.
11. Wondisford F.E. A direct role for thyroid hormone in development of the adrenal cortex. *Endocrinology*. 2015. Vol. 156. No. 6. P. 1939–1940. DOI: https://doi.org/10.1210/en.2015-1351.
12. Taylor P.N., Albrecht D., Scholz A. et al. Global epidemiology of hyperthyroidism and hypothyroidism. *Nature Reviews Endocrinology*. 2018. Vol. 14. No. 5. P. 301–316. DOI: https://doi.org/10.1038/nrendo.2018.18.
13. Moini J., Pereira K., Samsam M. *Epidemiology of thyroid disorders*. Elsevier; 2020. 320 p.
14. Ryabukha O. Mathematical methods in biomedical studies: The need for new approaches to study of follicular thyrocytes. *SSP Modern Pharmacy and Medicine*. 2022. Vol. 2. No. 2. P. 1–17. DOI: https://doi.org/10.53933/sspmpm.v2i2.47.
15. Unnikrishnan A.G., Kalra S., Sahay R.K. et al. Prevalence of hypothyroidism in adults: An epidemiological study in eight cities of India. *Indian journal of endocrinology and metabolism*. 2013. Vol. 17. No. 4. P. 647–652. DOI: https://doi.org/10.4103/2230-8210.113755.
16. Strikić Đ. I, Pleić N., Babić L.M. et al. Epidemiology of hypothyroidism, hyperthyroidism and positive thyroid antibodies in the Croatian population. *Biology* (Basel). 2022. Vol. 11. No. 3. Article ID 394. DOI: https://doi.org/10.3390/biology11030394.
17. Ryabukha O.I., Fedorenko V.I. Environmental determinants of thyroid pathology. Medicni perspectivi. 2021. Vol. 26. No. 3. P. 169–178. DOI: https://doi.org/10.26641/2307-0404.2021.3.242253.
18. Iacone R., Iaccarino Idelson P., Russo O. et al. Iodine intake from food and iodized salt as related to dietary salt consumption in the Italian adult general population. *Nutrients*. 2021. Vol. 13. No. 10. Article ID 3486. DOI: https://doi.org/10.3390/nu13103486.
19. Niero G., Visentin G., Censi S. et al. Invited review: Iodine level in dairy products – A feed-to-fork overview. *Journal of dairy science*. 2023. Vol. 106. No. 4. P. 2213–2229. DOI: https://doi.org/10.3168/jds.2022-22599.
20. Dineva M., Fishpool H., Rayman M.P. et al. Systematic review and meta-analysis of the effects of iodine supplementation on thyroid function and child neurodevelopment in mildly-to-

moderately iodine-deficient pregnant women. *The American journal of clinical nutrition*. 2020. Vol. 112. No. 2. P. 389–412. DOI: https://doi.org/10.1093/ajcn/nqaa071.

21. Kamal A., Mahmood A., Zaman M. et al. Evaluation of Renessans (iodine complex molecule) safety in human deings: An Open-Labeled Clinical Study. *Dose-Response*. 2022. Vol. 20. No. 4. DOI: https://doi.org/10.1177/15593258221129777.

22. Korzun V.N., Kotikovich Y.S., Derkach A.V. A new method to overcome the iodine deficiency and iodine deficient diseases. *Problems of Radiation Medicine and Radiobiology*: collection of scientific papers. Kyiv; 2011. Iss. 16. P. 171–180. URL: http://radiationproblems.org.ua/16_2011/171Vypusk_16_2011.pdf.

23. Kravchenko V., Orlova V., Laryanovska Yu. et al. Investigation of Laminaria aqueous extract effect on thyroid gland morphological status in rats with experimental hypothyroidism induced by sodium perchlorate. *Ukrainian biopharmaceutical journal*. 2017. No. 6. P. 50-55. URL: http://nbuv.gov.ua/UJRN/ubfj_2017_6_10.

24. Pati M.P., Sharma S.D., Nayak L. et al. Uses of seaweed and its application to human welfare: A review. *International Journal of Pharmacy and Pharmaceutical Sciences*. 2016. Vol. 8. No. 10. P. 12– 20. DOI: https://doi.org/10.22159/ijpps.2016v8i10.12740.

25. Lebedynets V., Buriachenko L., Bagrii L. et al. The scientific search for the over coming of iodine in Ukraine. *Tovaroznavchiy Visnik*. 2017. Vol. 1. No. 10. P. 14–22. URL: http://tovvisnik.lutsk-ntu.com.ua/index.php/tovvisnik/article/view/72.

26. Ryabukha O.I. The content of ascorbic acid in the liver and adrenal glands of rats during correction of alimentary hypothyrosis by an iodine of a different chemical nature. *Medical and Clinical Chemistry*. Vol. 20. No. 1. P. 51–58. DOI: http://doi.org/10.11603/mcch.2410-681X.2018.v0.i1.8841.

27. Ryabukha O.I. Iodine content in white rats thyroid glands in organic and inorganic iodine administration under the conditions of subclinical hyperthyroidism. *Medical and Clinical Chemistry*. Vol. 22. No. 1. P. 91–98. DOI: https://doi.org/10.11603/mcch.2410-681X.2020.v.i1.11060.

28. Ryabukha O.I. Peculiarities of thyroidal colloid hormonal activity of white rats' thyrocytes during consumption of organic and inorganic iodine in conditions of potentiated alimentary iodine deficiency. *World of Medicine and Biology*. 2020. No 4. P. 193–198. DOI: https://doi.org/10.26724/2079-8334-2020-4-74-193-198.

29. Ryabukha O.I. Hormonal activity features of intrafollicular colloid of white rat's thyroid gland in common disorders of its function. *Bulletin of Problems in Biology and Medicine*. 2021. No 1. P. 245–250. DOI: https://doi.org/10.29254/2077-4214-2021-1-159-244-250.

30. Ryabukha O.I. Conceptual approaches to the study of the thyroid gland at different levels of its integration into the body. *Endocrinology and Disorders*. 2020. Vol. 4. Iss. 1. DOI: https://doi.org/10.31579/2640-1045/047.

31. Ryabukha O. COVID-19 Pandemic encourages to deepen the study of the thyroid gland: Correlation portraits as a means of research in different directions of follicular thyrocytes activities. *SSP Modern Pharmacy and Medicine*. 2022. Vol. 2. No. 1. P. 1–21. DOI: https://doi.org/10.53933/sspmpm.v2i1.40.

32. Shapovalova V. Alcoholic hepatitis: An Experimental Meta-Analysis. *SSP Modern Pharmacy and Medicine*. 2023. Vol. 3. No. 1. P. 1–11. DOI: https://doi.org/10.53933/sspmpm.v3i1.77.

33. Degon M., Chait Y., Hollot C.V. et al. Quantitative model of the human thyroid: development and observations. *Proc. Amer. Control Conference*, Portland, OR, USA. 2005. Vol. 2. P. 961–966. DOI: https://doi.org/10.1109/ACC.2005.1470084.

34. Degon M., Chipkin S.R., Hollot C.V. et al. A computational model of the human thyroid. *Mathematical Biosciences*. 2008. Vol. 212. Iss. 1. P. 22–53. DOI: https://doi.org/10.1016/j.mbs.2007.10.009.

35. Tiwari M.A mathematical applications into the cells. *Journal of Natural Science, Biology and Medicine*. 2012. Vol. 3. No. 1. P. 19–23. DOI: https://doi.org/10.4103/0976-9668.95937.

36. Riabukha O. Application of new information technologies for the study of cell activity. In: *Proceedings of the XIth International Conference on Perspective Technologies and Methods in*

MEMS Design (MEMSTECH); 2015 Sep 2-6; Lviv, Ukraine. New York (NY), United States: IEEE; 2015. P. 69–71. URL: http://ieeexplore.ieee.org/document/7299458.

37. Ryabukha O.I. Perspectives of applying new approaches to the implementation of mathematical technologies in the study of cell activity. *Medical Informatics and Engineering*. 2018. No. 1. P. 67-75. DOI: https://doi.org/10.11603/mie.1996-1960.2018.1.8894.

38. Ryabukha O.I. Substantiation of conceptual apparatus for mathematical studies on the hormone-producing cell activity. *Bulletin of problems in biology and medicine*. 2018. Iss. 3. No. 1(145). P. 234–237. DOI: https://doi.org/10.29254/2077-4214-2018-3-145-234-237.

39. Ryabukha O.I. Application of mathematical approaches in medicine on the example of follicular thyrocytes secretory activity study. *World of Medicine and Biology*. 2019. No. 1. P. 181-187. DOI: https://doi.org/10.26724/2079-8334-2019-1-67-181.

40. Ryabukha O., Greguš ml M. Correlation analysis as a thyroid gland, adrenal glands, and liver relationship tool for correcting hypothyroidism with organic and inorganic iodine. *Procedia Computer Science*. 2019. Vol. 160. P. 598-603. DOI: https://doi.org/10.1016/j.procs.2019.11.041.

41. Ryabukha O., Dronyuk I. Applying of information technologies for study of the thyroid gland follicular thyrocytes' synthetic activity. *CEUR Workshop Proceedings-Series*. 2020. Vol. 2753. P. 323–337. URL: http://ceur-ws.org/Vol-2753/paper23.pdf.

42. Ryabukha O., Dronyuk I. Modern approaches to the applying of mathematical methods in the analysis of the transport direction of follicular thyrocytes. *CEUR Workshop Proceedings-Series*. 2021. Vol. 3038. P. 302–316. URL: http://ceur-ws.org/Vol-3038/paper19.pdf.

43. Ryabukha O.I. Study of ultrastructure profile of follicular thyrocytes' transport capabilities by means of correlation analysis. *Medical Informatics and Engineering*. 2022. No. 3-4. P. 28–38. DOI: https://doi.org/10.11603/mie.1996-1960.2021.3-4.12638.

44. Ryabukha O. Features of relationships between ultrastructures of the energy capability profile of follicular thyrocytes in the correction of alimentary iodine deficiency with a low dose of organic and inorganic iodine. *The Medical and Ecological Problems*. 2022. Vol. 26, No. 3-4. P. 16–29. DOI: https://doi.org/10.31718/mep.2022.26.3-4.03.

45. Ryabukha O.I. Potentiated alimentary iodine deficiency: Features of relationships between the follicular thyrocytes' energy capability profile ultrastructures when corrected by different doses of organic iodine. *Hygiene of Populated Places*. 2022. Iss. 72. P. 68–83. DOI: https://doi.org/10.32402/hygiene2022.72.068.

46. Ryabukha O.I. To the problem of application in hypothyrosis inorganic and organic iodine (review). *Actual problems of transport medicine*. 2018. No. 2. P. 7–21. DOI: https://doi.org/10.5281/zenodo.1319531.

47. Gazha P.A., Andrianov A.M., Stepaniuk I.A. et al. Isolation of iodine-protein components from sea algae. *Prikl Biokhim Mikrobiol*. 1976. Vol. 12. No. 4. P. 597–601. URL: https://www.ncbi.nlm.nih.gov/pubmed/1026942.

48. Wissig S.L. The anatomy of secretion in the follicular cells of the thyroid gland. I. The fine structure of the gland in the normal rat. *J Biophys Biochem Cytol*. 1960. Vol. 7. No. 3. P. 419–432. DOI: https://doi.org/10.1083/jcb.7.3.419.

49. Petrovici A., Lupulescu A. Ultrastructure of the normal thyroid gland. In: *Ultrastructure of the Thyroid Gland*. Basel, Karger; 1968. pp. 4–34. DOI: https://doi.org/10.1159/000389735.

50. Petrovici A., Lupulescu A. Ultrastructural changes of the thyroid gland in different experimental conditions. In: *Ultrastructure of the Thyroid Gland*. Basel: Karger; 1968. pp. 50-63. DOI: https://doi.org/10.1159/000389738.

51. Lupulescu A., Petrovici A. Ultrastructure of the thyroid gland. *Archives of Internal Medicine*. 1969. Vol. 123. Iss. 1. Article ID 111. DOI: https://doi.org/10.1001/archinte.1969.00300110113041.

52. Gordienko V.M., Kozyritsky V.G. Thyroid Gland. In: *Ultrastructure of the Endocrine System Glands*. Kyiv: Zdorov'ya; 1978. pp. 83–99.

53. Ryabukha O.I. O.Ryabukha's method for determining the profiles of hormonopoietic cells' special capacities (Certificate of State Intellectual Property Service of Ukraine No 7966, Kyiv). *Bulletin of Copyright and Related Rights*. 2004. Iss. 4, 2003. P. 72.

54. Ryabukha O.I. Semi-quantitative analysis of electronograms according to O.Ryabukha (Certificate of the Ukrainian Agency of Copyright and Related Rights No 2769, Kyiv). *Catalog of State Registration*. 2000. Iss. 4. P. 11.

55. Zadeh L.A. The roles of fuzzy logic and soft computing in the conception, design and deployment of intelligent systems. *BT Technology Journal*. 1994. Vol. 14. No 4. P. 32–36. DOI: https://doi.org/10.1109/FUZZY.1997.616336.

56. Zadeh L.A. Can mathematics deal with computational problems which are stated in a natural language? *Logic Colloquium*. San Francisco, USA: UC Berkeley; 2011. URL: http://philosophy.berkeley.edu/events/detail/793.

57. Dev U., Sultana A., Saha D. et al. Application of fuzzy logic in medical data interpretation. *Bangladesh Journal of Scientific and Industrial Research*. 2015. Vol. 49. No. 3. P. 137–146. DOI: https://doi.org/10.3329/bjsir.v49i3.22127.

58. Mintser O.P., Karlenko V.P., Shevchenko Ya.O. et al. Clusterization of functional states of the organism. Pilot study. *Medical Informatics and Engineering*. 2021. No. 2. P. 4–13. DOI: https://doi.org/10.11603/mie.1996-1960.2021.2.12449.

59. Kolmogorov A.N., Fomin S.V. *The Elements of the Theory of Functions and Functional Analysis*. Moscow: Nauka; 1976. 544 p.

60. Plashchevaya E.V., Smirnov V.A., Nigei N.V. et al. The main types of medical logic. In: *Textbook for practical training in medical informatics*. Blagoveshchensk: Amur State Medical Academy; 2014. p. 176.

61. Miot H.A. Correlation analysis in clinical and experimental studies. *Jornal vascular brasileiro*. 2018. Vol. 17. No. 4. P. 275–279. DOI: https://doi.org/10.1590/1677-5449.174118.

62. Uurtio V., Monteiro J.M., Kandola J. et al. A Tutorial on canonical correlation methods. *ACM Computing Surveys*. 2018. Vol. 50. No. 6. Article ID 95. DOI: https://doi.org/10.1145/3136624.

63. Ryabukha O.I., Dronyuk I.M. Application of correlation analysis in cytology: Opportunities to study specific activity of follicular thyrocytes. *Regulatory Mechanisms in Biosystems*. 2019. Vol. 10. No. 3. P. 345–351. DOI: https://doi.org/10.15421/021953.

64. Ryabukha O., Dronyuk I. The portraits creating method by correlation analysis of hormone-producing cells data. *CEUR Workshop Proceedings-Series*. 2018. Vol. 2255. P. 135–145. URL: http://ceur-ws.org/Vol-2255/paper13.pdf.

65. Perfect correlation. *Merriam-Webster.com Dictionary*. Accessed 28 Jun. 2023. URL: https://www.merriam-webster.com/dictionary/perfect%20correlation.

66. Chaddock R.E. Interpretation of the coefficient of correlation. In: *Principles and Methods of Statistics*. Boston: Houghton Mifflin; 1925. pp. 303–304. URL: https://babel.hathitrust.org/cgi/pt?id=uc1.b3257183&view=1up&seq=323.

67. Caplan M.J. Functional organization of the cell. In: W.F. Boron, E.L. Boulpaep (Eds.). *Medical Physiology*, 3rd ed. Philadelphia: Elsevier; 2016. pp. 8–46.

68. Ryabukha O.I. Ultrastructural features of the follicular thyrocytes’ synthetic activity while taking organic iodine under conditions of alimentary iodine deficiency. *Bulletin of Problems in Biology and Medicine*. 2017. Iss. 4. No. 2(140). P. 134–139. URL: https://vpbm.com.ua/ua/vipusk-4-tom-2-(140),-2017/9557.

69. Ryabukha O. I. Study of the follicular thyrocytes’ synthetic activity while taking inorganic iodine under conditions of alimentary iodine deficiency. *Bulletin of Problems in Biology and Medicine*. 2017. Iss. 4. No. 3(141). P. 218–223. DOI: http://dx.doi.org/10.29254/2077-4214-2017-4-3-141-218-223.

70. Ryabukha O., Dronyuk I. Applying of information technologies for study of the thyroid gland follicular thyrocytes’ synthetic activity. *CEUR Workshop Proceedings-Series*. 2020. Vol. 2753. P. 323–337. URL: http://ceur-ws.org/Vol-2753/paper23.pdf.

71. Ryabukha O. I. Search for markers of changes of the synthetic activity of thyrocyte under the influence of iodine reception in iodine deficiency conditions. *World of Medicine and Biology*. 2018. No. 3. P. 179–185. DOI: http://doi.org/10.26724/2079-8334-2018-3-65-179-185.