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## Entropies of thymocytogram, splenocytogram, immunocytogram and leukocytogram in rats are regulated by sex and the neuroendocrine parameters while regulates immune parameters

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### Abstract

**Background.** We have previously shown that the Entropy (E) of the relative spectral power density (SPD) of the EEG rhythms is its quite relevant parameter. We also found significant relationships between the SPD E of individual EEG loci and the E of the Leukocytogram (LCG) and Immunocytogram (ICG) of the blood, as well as with their individual components. The **purpose** of this study was to clarify the relationships between E(s) of these four morpho-functional immune subsystem and sex as well as parameters of the neuroendocrine-immune complex in rats. **Materials and methods.** Experiment was performed on 108 healthy Wistar rats (48 male and 60 female) weighing 205-300 g ( $M \pm SD = 260 \pm 26$  g) divided into 8 groups. Animals of the first group remained intact, using tap water from drinking ad libitum. Instead, the other rats received various balneofactors for 6 days. The day after the completion of the drinking/application course in all rats the parameters of neuroendocrine-immune complex were registered. **Results.** The drinking/application course did not affect the E level of any morpho-functional immune subsystem, the relationships between which are insignificant. Females have less E TCG than males, whereas sexual dimorphism is insignificant for E SCG and ICG and absent for E LCG. The canonical correlation of mediocre force ( $R=0,675$ ) between sex index ( $M=1;F=2$ ) and neuro-endocrine parameters (HRV, calcitonin, parathyroid and mineralocorticoid

activities, corticosterone plasma, 17-KS urine) was revealed. Factors linked to female sex upregulates nine immune parameters ( $R=0,630$ ), while downregulates nine others ( $R=0,678$ ). The neuroendocrine constellation (testosterone plasma, HRV, calcitonin, parathyroid and mineralocorticoid activities) is associated with the constellation of entropies ( $R=0,533$ ). Entropy of a single morpho-functional immune subsystem is associated with a certain constellation of immune parameters. In particular, E SCG with 12 ( $R=0,721$ ), E TCG with 9 ( $R=0,615$ ), E ICG with 8 ( $R=0,586$ ), E LCG with 12 ( $R=0,631$ ). **Conclusion.** Entropies of thymocytogram, splenocytogram, immunocytogram and leukocytogram in rats are regulated by sex and the neuroendocrine factors while regulates immune parameters.

**Key words:** Entropy of thymocytogram, splenocytogram, immunocytogram and leukocytogram, autonomic nervous, endocrine and immune parameters, female and male rats.

## INTRODUCTION

We have previously shown that the Entropy of the relative spectral power density (SPD) of the EEG rhythms is its quite relevant parameter. In particular, judging by the portion of the explained dispersion of the information field of the neuro-immune complex, the Entropy in informativeness prevails over such common EEG parameters as rhythm deviation, rhythm index, its asymmetry and lateralization [31]. In other studies in this series, we found significant relationships between the SPD Entropy of individual EEG loci and the Entropy of the Leukocytogram and Immunocytogram of the blood, their individual components [32-36,55] as well as with parameters of gas-discharge visualization [1].

It is obvious that the Leukocytogram and Immunocytogram of peripheral blood reflect the redistribution of immune cells between bone marrow, thymus, spleen, lymph nodes, as well as non-encapsulated lymphoid tissue of mucous membranes, liver, skin, etc. by controlled migration and recirculation [19].

Due to the practical impossibility of analyzing the cellular composition of immune organs in humans (without punctio [3]), we resorted to an experiment in rats. On the other hand, we did not have the technical ability to record in rats the spectral parameters of EEG and HRV. Instead, it was possible to register the parameters of the autonomic nervous and endocrine systems [15,21,41,42]. From a previous study by IL Popovych [38], it is known that the Entropies of these four morpho-functional immune subsystems are virtually unrelated, ie not dependent on each other. Based on this, the purpose of this study was to clarify the relationships between Entropies of these four morpho-functional immune subsystem and sex as well as parameters of the neuroendocrine-immune complex.

## MATERIAL AND METHODS

Experiment was performed on 108 healthy Wistar rats (50 male and 58 female) weighing 205-300 g ( $M\pm SD=260\pm 26$  g) divided into 8 groups. Animals of the first group ( $n=20$ ) remained intact, using tap water from drinking ad libitum. Instead, the other rats received the same tap water ( $n=18$ ) as well as mineral waters Naftussya ( $n=20$ ), Sophiya ( $n=10$ ), Hertsa ( $n=10$ ) and its artificial salt analogue ( $n=10$ ) through the tube at a dose of 1,5 mL/100 g of body mass for 6 days. Another group of rats received together with Naftussya water three applications on the tail of ozokerite ( $t^0$  40-42 $^{\circ}$ C, duration 30 minutes, every other day) ( $n=10$ ), and the last - only ozokerite applications ( $n=10$ ).

The day after the completion of the drinking/application course in all rats, at first, a sample of peripheral blood (by incision of the tip of the tail) was taken for analysis of Leukocytogram (LCG), ie the relative content of lymphocytes (L), monocytes (M), eosinophils (Eo), basophils (Bas), rod-shaped (RN) and segmental (SN) neutrophils. Based on these data, the Entropy of the Leukocytogram (hLCG) was calculated according to the formula derived by IL Popovych [38] on the basis of the classical CE Shannon [48] formula:

$$hLCG = - [L \cdot \log_2 L + M \cdot \log_2 M + Eo \cdot \log_2 Eo + Bas \cdot \log_2 Bas + RN \cdot \log_2 RN + SN \cdot \log_2 SN] / \log_2 6.$$

Then they assessed the state of autonomous regulation. For this purpose, under an easy ether anesthesia, for 15-20 sec ECG was recorded in the lead II, inserting needle electrodes under the skin of the legs, followed by the calculation of the parameters of the HRV: mode (Mo), amplitude of the mode (AMo) and variational swing (MxDMn) as markers of the humoral channel of regulation (circulating catecholamines, steroids, glucagon etc), sympathetic and vagal tones respectively [2].

Animals were then placed in individual chambers with perforated bottom for collecting daily urine.

The experiment was completed by decapitation of rats in order to collect as much blood as possible.

The plasma levels of the hormones of adaptation were determined: corticosterone, triiodothyronine and testosterone (by the ELISA) as well as electrolytes: calcium (by reaction with arsenase III), phosphate (phosphate-molybdate method), sodium and potassium (flaming photometry), electrolytes were also determined in daily urine. The latter also determined the concentration of 17-ketosteroids (by color reaction with m-dinitrobenzene).

The analyzes were carried out according to the instructions described in the manual [13,17]. The analyzers "Tecan" (Oesterreich), "Pointe-180" ("Scientific", USA) and "Reflotron" (Boehringer Mannheim, BRD) were used with appropriate sets and a flaming spectrophotometer "CΦ-47".

According to the parameters of electrolyte exchange, hormonal activity was evaluated: parathyroide by coefficients  $(Cap/Pp)^{0.5}$ ,  $(Pu/Cau)^{0.5}$  and  $(Cap \cdot Pu/Pp \cdot Cau)^{0.25}$ , calcitonin by coefficients  $(1/Cap \cdot Pp)^{0.5}$ ,  $(Cau \cdot Pu)^{0.5}$  and  $(Cau \cdot Pu/Cap \cdot Pp)^{0.25}$  as well as mineralocorticoid by coefficients  $(Nap/Kp)^{0.5}$ ,  $(Ku/Nau)^{0.5}$  and  $(Nap \cdot Ku/Kp \cdot Nau)^{0.25}$ , based on their classical effects and recommendations by IL Popovych [41,42].

In the blood, the parameters of immunity were determined, as described in the manual [26]: the relative content of the population of T-lymphocytes in a test of spontaneous rosette formation with erythrocytes of sheep by M Jondal et al [18], their theophylline-resistant (T-helper) and theophyllin-susceptible (T-cytolytic) subpopulations (by the test of sensitivity of rosette formation to theophylline by S Limatibul et al [24]; the population of B-lymphocytes by the test of complementary rosette formation with erythrocytes of sheep by C Bianco [5]. Natural killers were identified as large granules contain lymphocytes. The content of zero-lymphocytes (0L) was calculated by the balance method. For these components, as well as plasma cells (Pla), the Entropy of the Immunocytogram (hICG) was calculated;

$$hICG = - [Th \cdot \log_2 Th + Tc \cdot \log_2 Tc + B \cdot \log_2 B + Pla \cdot \log_2 Pla + NK \cdot \log_2 NK + 0L \cdot \log_2 0L] / \log_2 6.$$

The blast transformation reaction of T-lymphocytes to phytohemagglutinin was performed separately [26].

About the condition of the phagocytic function of neutrophils (microphages) and monocytes (macrophages) were judged by the phagocytosis index, the microbial count and the killing index

for *Staphylococcus aureus* (ATCC N25423 F49). According to these parameters and the content of microphages and macrophages in the blood calculated their bactericidal ability [6,41].

After decapitation, the spleen, thymus and adrenal glands were removed from the animals. In the adrenal glands after weighing, the thickness of glomerular, fascicular reticular and medullar zones was measured under a microscope [6,41].

Immune organs weighed and made smears-imprints for counting Thymocytogram and Splenocytogram [3,4,6]. The components of the thymocytogram (TCG) are lymphocytes (Lc), lymphoblasts (Lb), reticulocytes (Ret), macrophages (Mac), endotheliocytes (End), epitheliocytes (Epi) and Hassal's corpuscles (Has). The Splenocytogram (SCG) includes lymphocytes (Lc), lymphoblasts (Lb), plasma cells (Pla), reticulocytes (Ret), macrophages (Mac), fibroblasts (Fib), microphages (Mic) and eosinophils (Eos).

For them Shannon's entropy was calculated too:

$$hTCG = - [Lc \cdot \log_2 Lc + Lb \cdot \log_2 Lb + Ret \cdot \log_2 Ret + Mac \cdot \log_2 Mac + En \cdot \log_2 En + Ep \cdot \log_2 Ep + Has \cdot \log_2 Has] / \log_2 7$$

$$hSCG = - [Lc \cdot \log_2 Lc + Lb \cdot \log_2 Lb + P \cdot \log_2 P + R \cdot \log_2 R + Ma \cdot \log_2 Ma + F \cdot \log_2 F + Mi \cdot \log_2 Mi + Eo \cdot \log_2 Eo] / \log_2 8$$

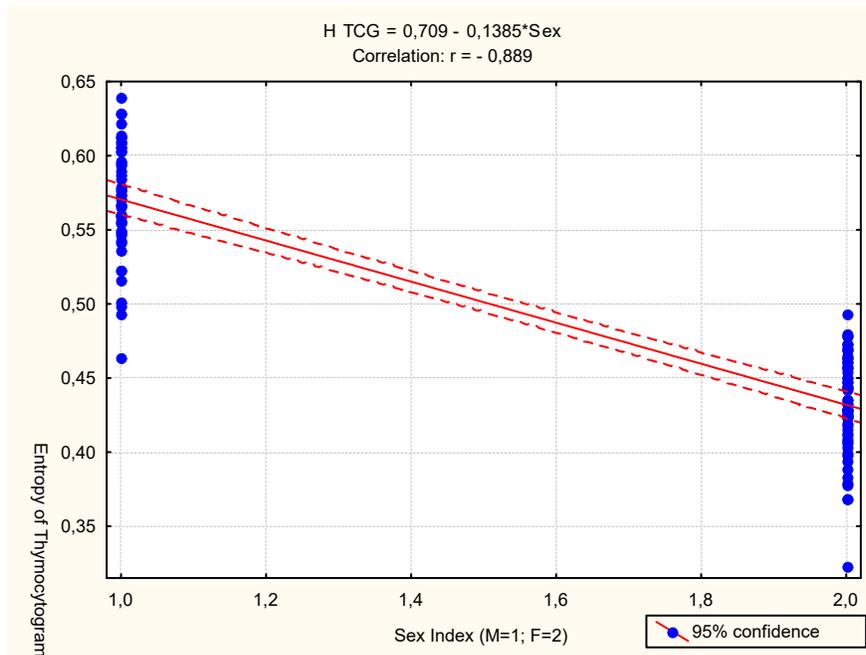
Digital material is statistically processed on a computer using the software package "Statistica 8.0".

## RESULTS AND DISCUSSION

The calculation of the Entropy of the peripheral blood Immunocytogram, as well as the Splenocytogram and Thymocytogram of smear prints in rats was first used by IL Popovych in 2007 [38], using the idea of OG Yushkovs'ka [51] to use the calculation of the Entropy of Leukocytogram of peripheral blood in athletes for estimation their adaptive responses. The creativity of this approach is demonstrated in subsequent studies by IL Popovych et al [10,14,16,21-23,25,29,30,39,40,43-47,49,50,52-54] and other representatives of the Truskavetsian Scientific School [11,12,20,37]. However, Entropy was not the focus of the analysis it occupied in this study.

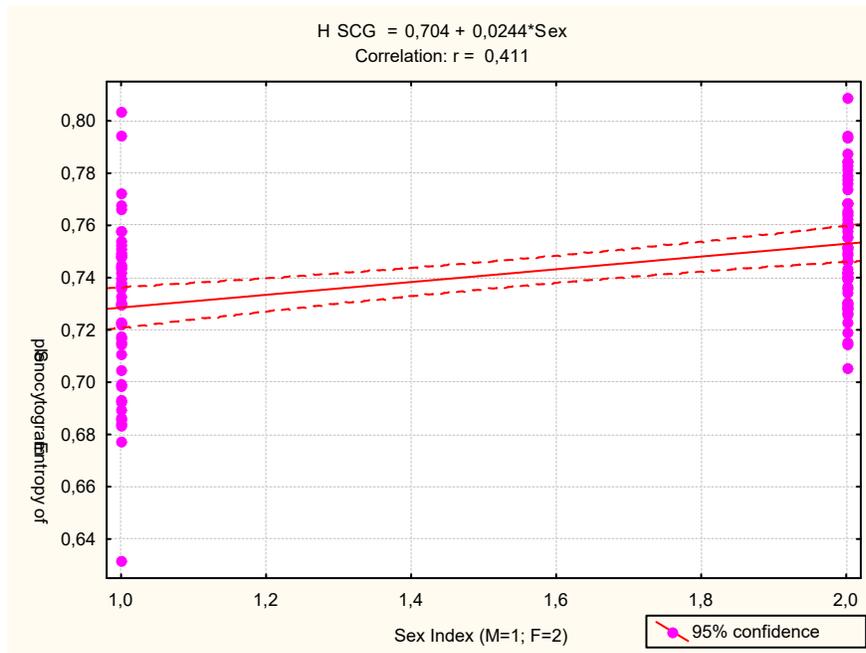
In the first stage of the analysis, we find out the sex differences in the Entropy of cytograms. To enable a quantitative assessment of the role of sex, males were given conditionally one point, and females two points.

Fig. 1 illustrates the significant sexual dimorphism of the Entropy cytogram of the central organ of immune system, which is documented by the correlation coefficient between Entropy and sex index.

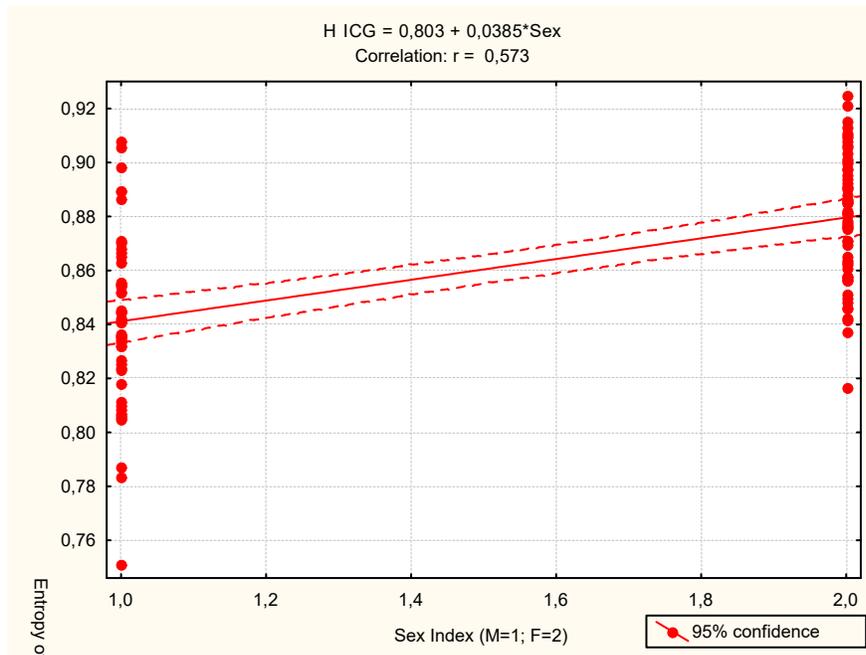


**Fig. 1. Sex differences Thymocytoqram entropy in rats**

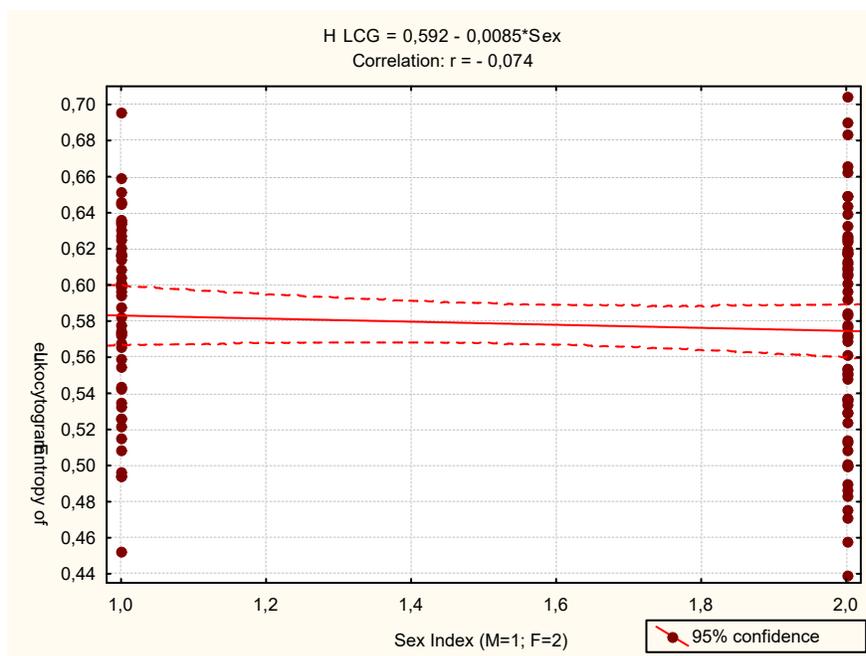
However, with respect to the Splenocytoqram (Fig. 2) and the Immunocytoqram (Fig. 3), the sex differences are insignificant, and with respect to the Leukocytoqram (Fig. 4) they are completely absent (although different variance draws attention).



**Fig. 2. Sex differences Splenocytoqram entropy in rats**

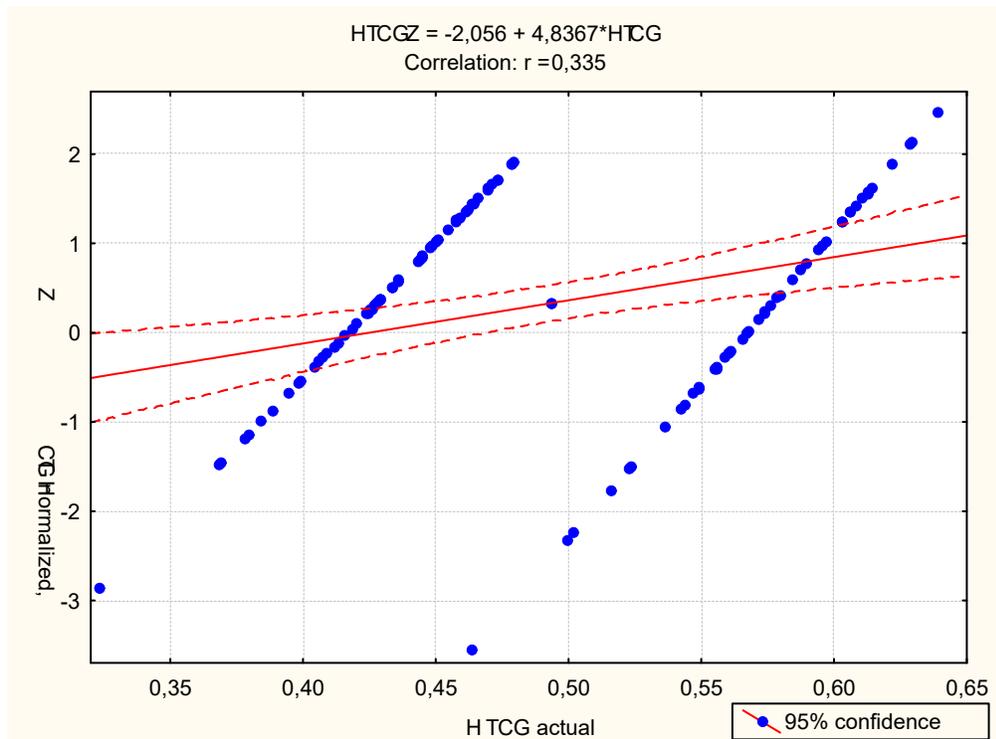


**Fig. 3. Sex differences Immunocytogram entropy in rats**

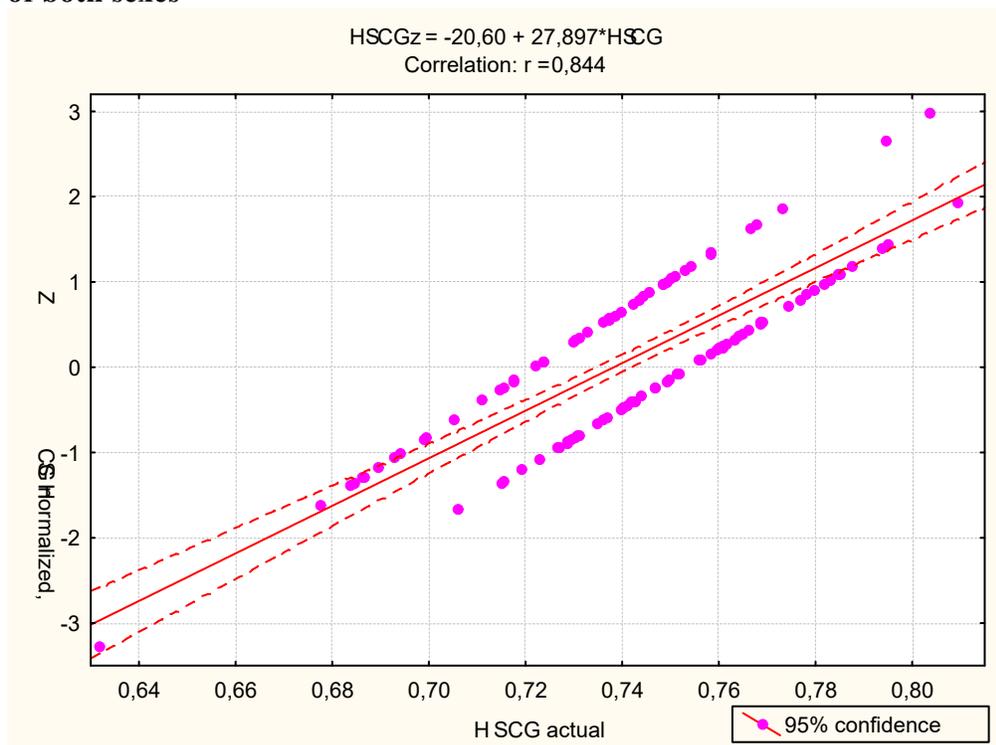


**Fig. 4. Sex differences Leukocytogram entropy in rats**

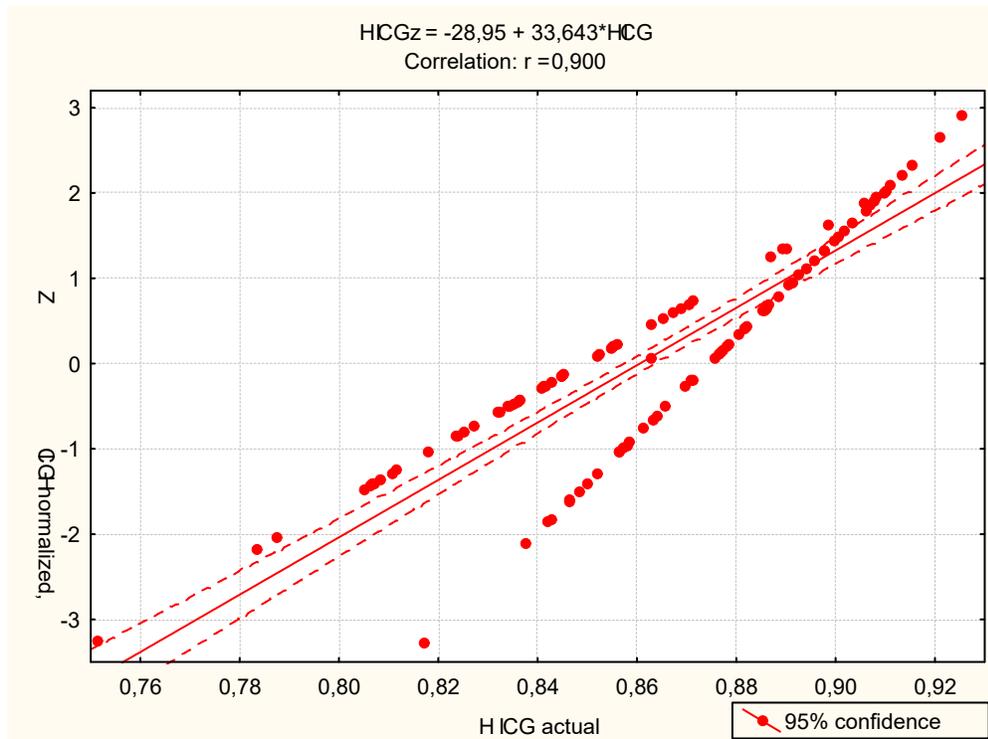
Given the information about the presence of sexual dimorphism in a number of parameters of the neuroendocrine-immune complex of rats [46], in order to level it, all registered parameters were calculated in Z-scores, ie normalized. Figures 5-8 illustrate the leveling (along the Y axis) of sex differences of cytograms of morpho-functional immune subsystems.



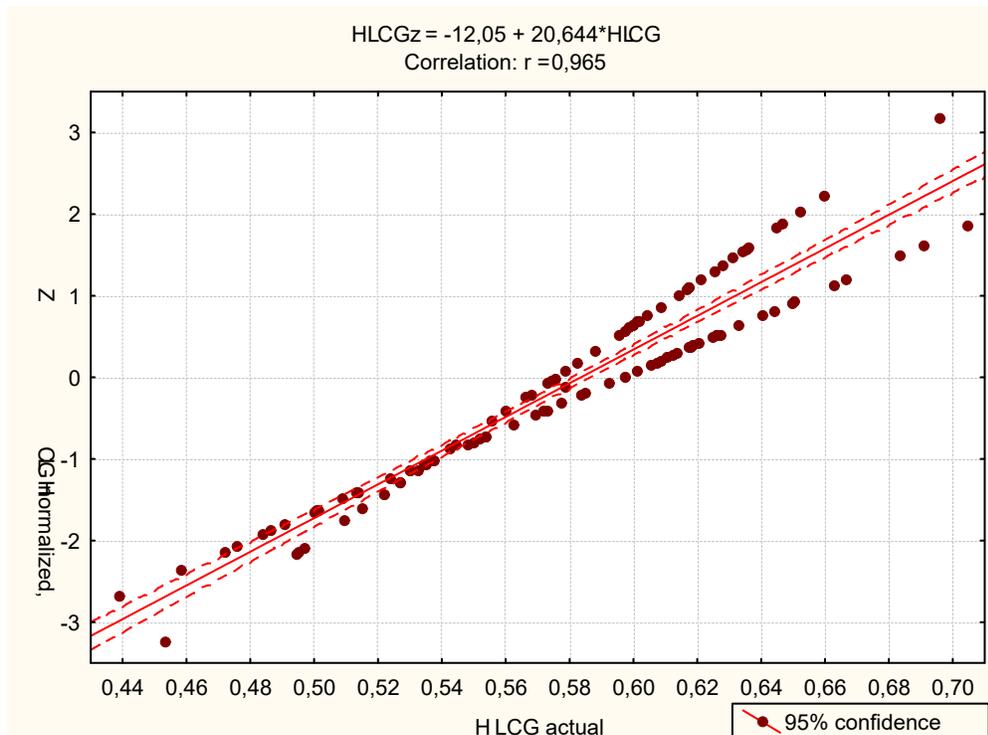
**Fig. 5. Actual (X-axis) and normalized (Y-axis) values of Entropy Thymocytogram of rats of both sexes**



**Fig. 6. Actual (X-axis) and normalized (Y-axis) values of Entropy Splenocytogram of rats of both sexes**

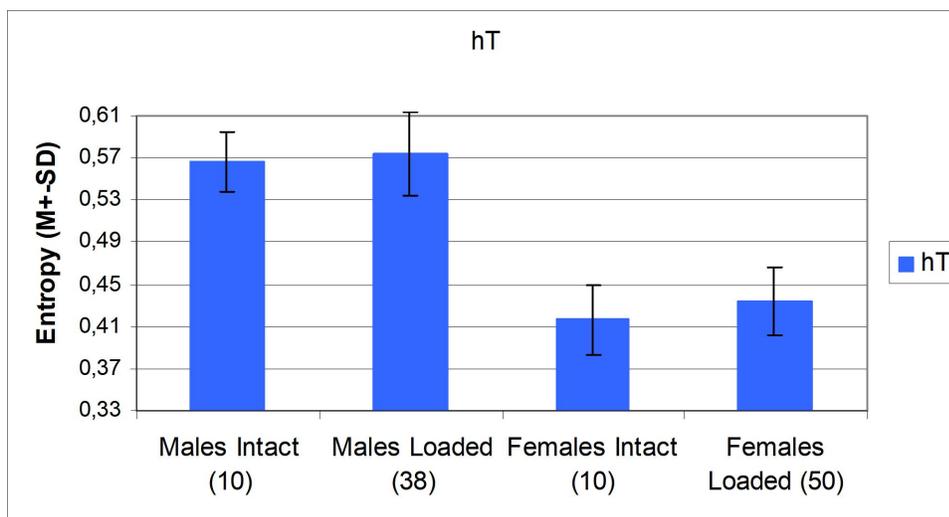


**Fig. 7. Actual (X-axis) and normalized (Y-axis) values of Entropy Immunocytogram of rats of both sexes**



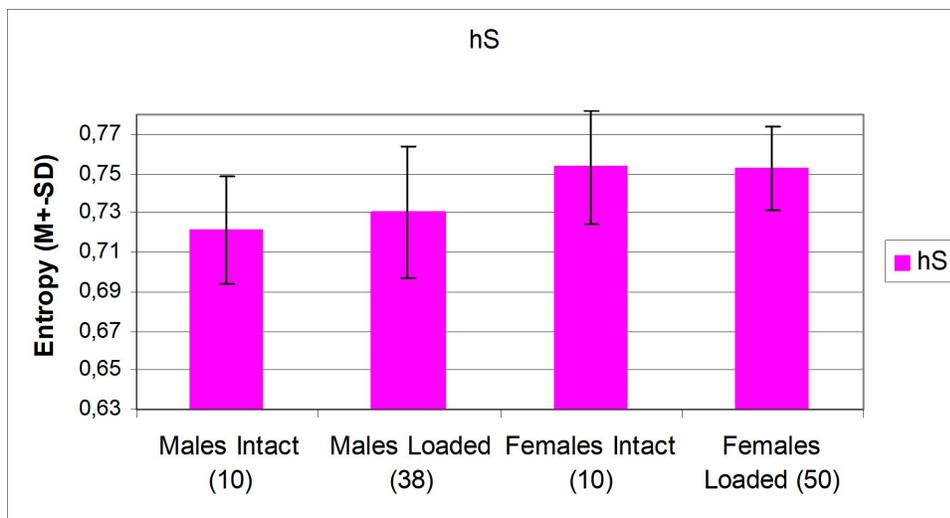
**Fig. 8. Actual (X-axis) and normalized (Y-axis) values of Entropy Leukocytogram of rats of both sexes**

When comparing the actual Entropy levels of the Thymocytogram, it was found that the applied course of balneofactors, judging by the average values, did not affect them in either males or females (Fig. 9).

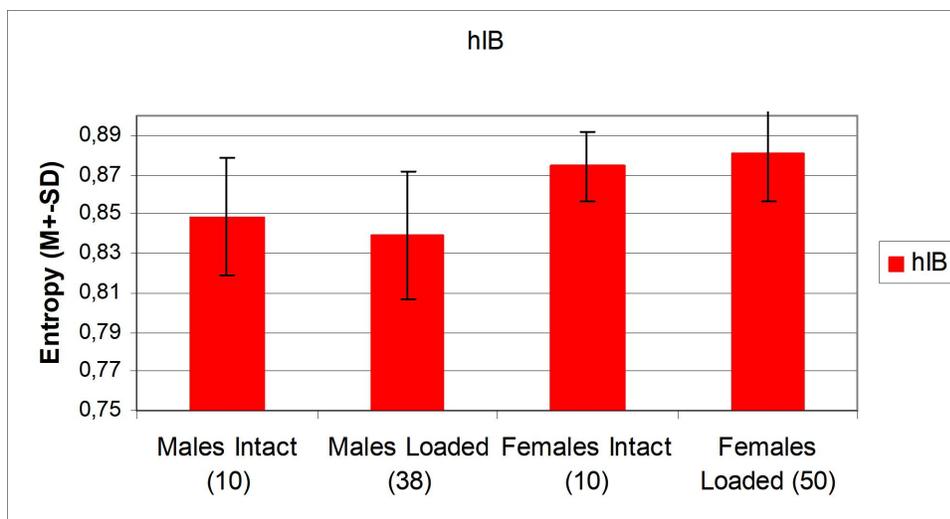


**Fig. 9. Actual levels of Thymocytogram entropy in intact and balneo-loaded rats of both sexes**

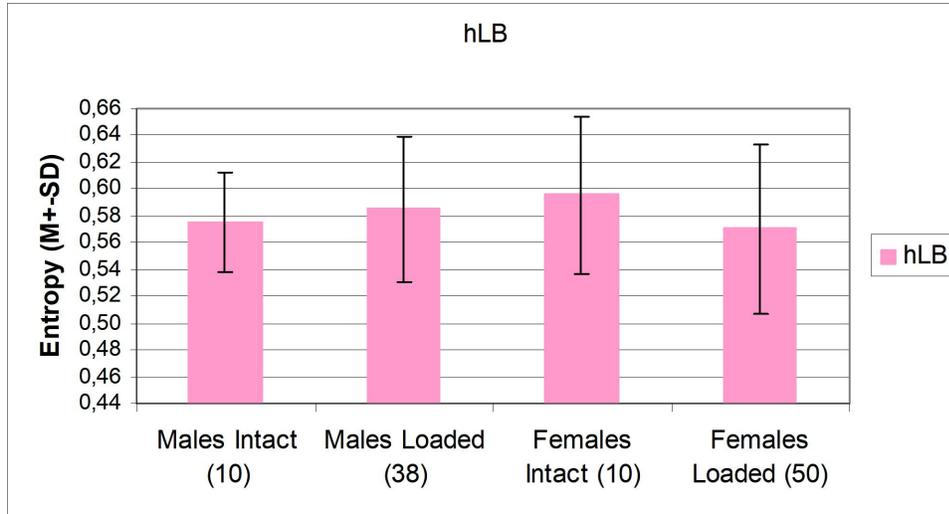
A similar situation occurs with respect to the Entropy levels of the Splenocytogram (Fig. 10), the Immunocytogram (Fig. 11) and the Leukocytogram (Fig. 12).



**Fig. 10. Actual levels of Splenocytogram entropy in intact and balneo-loaded rats of both sexes**



**Fig. 11. Actual levels of Immunocytogram entropy in intact and balneo-loaded rats of both sexes**



**Fig. 12. Actual levels of Leukocytogram entropy in intact and balneo-loaded rats of both sexes**

Thus, the Entropy of all four morpho-functional immune subsystems under the conditions of our experiment was found to be stable, in contrast to the actual parameters of the neuroendocrine-immune complex both in rats and humans [15,37,41,42,50].

Based on the screening of correlations of sex index with normalized neuro-endocrine parameters with step-by-step exclusion, a regression model was constructed (Table 1). It was found that sex determines the level of constellation of endocrine parameters by 43%. The negative correlation of the sex index with calcitonin and parathyroid activity and corticosteronemia indicates a lower level in females, while they have higher than in males, mineralocorticoid activity and daily excretion of 17-ketosteroids.

**Table 1. Regression Summary for Endocrine Variables vs Sex Index**  
 $R=0,675$ ;  $R^2=0,456$ ; Adjusted  $R^2=0,429$ ;  $F_{(5,1)}=17,1$ ;  $p<10^{-5}$

		Beta	St. Err.	B	St. Err.	t <sub>(102)</sub>	p-level
Variables, Z	r		Intercpt	1,347	0,045	29,9	10 <sup>-6</sup>
(Cau•Pu/Cap•Pp) <sup>0,25</sup>	-0,59	-0,322	0,097	-0,067	0,020	-3,33	0,001
(Cap•Pu/Cau•Pp) <sup>0,25</sup>	-0,40	-0,163	0,085	-0,071	0,037	-1,92	0,058
Corticosterone Plasma	-0,22	-0,087	0,075	-0,034	0,029	-1,16	0,249
(Nap/Kp) <sup>0,5</sup>	0,47	0,271	0,082	0,114	0,035	3,30	0,001
17-Ketosteroides Urine	0,31	0,181	0,076	0,064	0,027	2,38	0,019

Among the registered immune parameters, two networks were found, with positive and negative correlation with the sex index. The first set (Table 2) contains 6 parameters of **blood**, 2 parameters of the **spleen** and one parameter of the **thymus**, the levels of which are higher in females, ie subject to upregulation by factors associated with the female sex. Has the right to exist and an alternative statement about the subjectivity of these parameters to the

downregulation by factors linked to the male sex. Be that as it may, sex determines the level of this immune constellation by 34%.

**Table 2. Regression Summary for Upregulated Immune Variables vs Sex Index**

R=0,630; R<sup>2</sup>=0,397; Adjusted R<sup>2</sup>=0,342; F<sub>(10,0)</sub>=7,2; p<10<sup>-6</sup>

		Beta	St. Err.	B	St. Err.	t <sub>(98)</sub>	p-level
Variables, Z	r		Intercept	1,571	0,046	34,47	10 <sup>-6</sup>
Natural Killers Blood	0,35	0,132	0,086	0,040	0,026	1,54	0,127
Phi Monocytes Blood	0,33	0,278	0,085	0,130	0,040	3,27	0,002
Endotheliocytes Thymus	0,32	0,165	0,086	0,073	0,038	1,91	0,059
Reticulocytes Spleen	0,30	0,231	0,083	0,112	0,040	2,79	0,006
Killing Ind Neutr Blood	0,27	0,201	0,082	0,091	0,037	2,45	0,016
Basophiles Blood	0,26	0,193	0,102	0,090	0,047	1,89	0,061
Lymphoblastes Spleen	0,26	0,113	0,085	0,054	0,041	1,33	0,189
T-cytolytic Lymph Bloo	0,22	0,153	0,098	0,069	0,044	1,57	0,121
Plasmocytes Blood	0,21	-0,152	0,113	-0,058	0,043	-1,35	0,180

Instead, the second set (Table 3) consists of 5 other **blood** parameters, 2 parameters of the **spleen** and 2 parameters of the **thymus**, the levels of which are lower in females, ie subject to downregulation by factors linked to the female sex or activated by factors linked to the male sex. The degree of sex determination of this immune constellation is 41%.

**Table 3. Regression Summary for Downregulated Immune Variables vs Sex Index**

R=0,678; R<sup>2</sup>=0,460; Adjusted R<sup>2</sup>=0,410; F<sub>(10,0)</sub>=9,3; p<10<sup>-6</sup>

		Beta	St. Err.	B	St. Err.	t <sub>(98)</sub>	p-level
Variables, Z	r		Intercept	1,644	0,046	35,90	10 <sup>-6</sup>
Macrophages Thymus	-0,40	-0,192	0,087	-0,050	0,023	-2,21	0,029
Monocytes Blood	-0,39	-0,308	0,076	-0,172	0,042	-4,05	10 <sup>-4</sup>
0-Lymphocytes Blood	-0,30	-0,103	0,085	-0,042	0,034	-1,22	0,224
Microbian Count Monocytes Blood	-0,29	-0,130	0,088	-0,031	0,021	-1,48	0,143
Thymus Mass Index	-0,27	-0,179	0,077	-0,092	0,040	-2,32	0,022
Leukocytes Blood	-0,26	-0,191	0,075	-0,091	0,036	-2,54	0,013
Plasmocytes Spleen	-0,23	-0,160	0,078	-0,085	0,042	-2,05	0,044
Macrophages Spleen	-0,22	-0,093	0,081	-0,043	0,037	-1,15	0,252
Eosinophiles Blood	-0,20	-0,204	0,078	-0,106	0,040	-2,62	0,010

In order to assess the integral effect on the Entropy of immune subsystems from neuro-endocrine factors, a procedure of canonical correlation analysis was performed. The resulting (right) set is formed of partial Entropies. Within the set, a significant correlation was found only between the Entropies of the Thymocytoqram and the Immunocytoqram (Table 4). Interestingly, a fairly similar range of intrasystem correlation coefficients ( $r=-0,21\div 0,06$ ) was detected by IL Popovych [] in a completely different sample of 58 rats of both sexes, ie morpho-functional subsystems are sufficiently independent of each other.

**Table 4. Matrix of Correlation (Right set)**

Variables, Z	H LCG	H ICG	H TCG	H SCG
Entropy Leukocytoqram	1	0,140	-0,046	0,078
Entropy Immunocytoqram	0,140	1	<b>0,265</b>	-0,183
Entropy Thymocytoqram	-0,046	<b>0,265</b>	1	0,125
Entropy Splenocytoqram	0,078	-0,183	0,125	1

The factor (left) set is formed by the parameters of the autonomic nervous system, calcitonin, parathyroid and mineralocorticoid activities, as well as plasma testosterone (Table 5).

**Table 5. Matrix of Correlation (Left set vs Right set)**

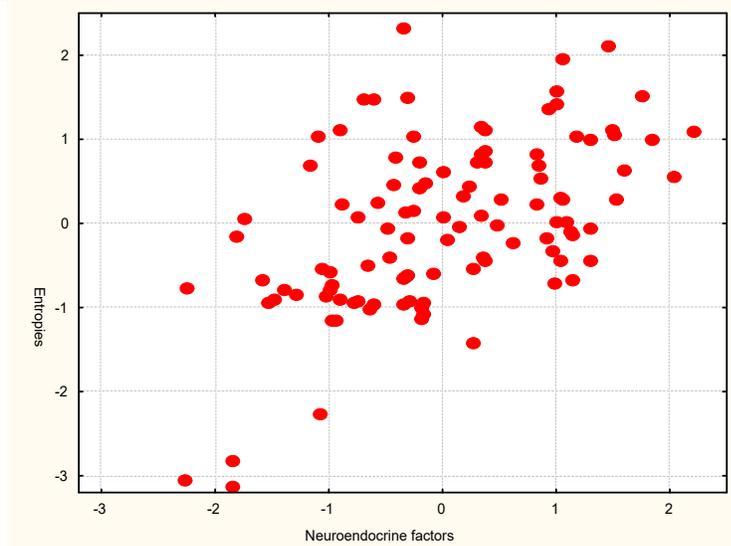
Variables, Z	AMo	DX	Mode	CTAu	PTAu	GloZAC	MCAp	Testost
Entropy Leukocytoqram	0,098	0,051	0,186	0,157	0,153	0,073	0,025	-0,172
Entropy Immunocytoqram	0,080	0,130	0,052	-0,189	0,026	-0,009	<b>0,284</b>	<b>0,205</b>
Entropy Thymocytoqram	<b>0,294</b>	<b>-0,221</b>	<b>-0,199</b>	-0,161	-0,138	-0,014	0,073	0,146
Entropy Splenocytoqram	0,155	-0,166	-0,170	<b>0,191</b>	<b>-0,205</b>	-0,184	-0,127	0,002

As a result, two pairs of canonical roots were identified (Table 6). The factor root of the first pair, judging by the received moderate negative loadings, represents inversely six endocrine parameters. The effective root of the first pair directly represents the Entropy of the LCG and the ICG, while inversely - the SCG. The canonical correlation between the roots of moderate strength, but significant (Fig. 13). The factor structure of the second pair of canonical roots has both common and distinctive features, compared with that of the first pair. The canonical correlation between the roots is somewhat weaker, but also significant (Fig. 14).

**Table 6. Factor Structure Matrix for Canonical Correlation between Endocrine parameters (Left set) and Entropies of Morpho-functional Immune Subsystems (Right set)**

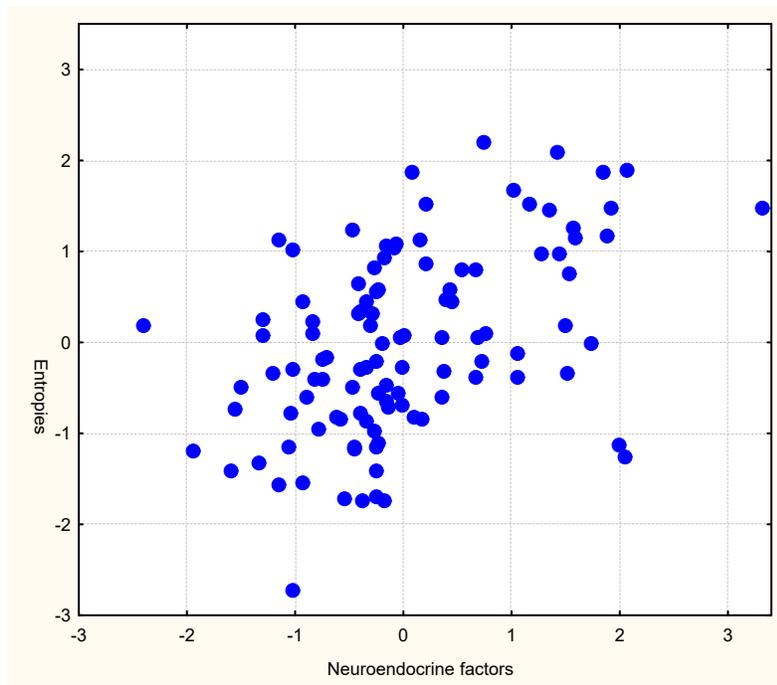
Right set	R 1	R 2
Entropy Leukocytoqram	<b>-0,918</b>	-0,262
Entropy Splenocytoqram	<b>0,170</b>	<b>0,175</b>
Entropy Immunocytoqram	<b>-0,419</b>	<b>0,770</b>
Entropy Thymocytoqram	-0,182	<b>0,651</b>

Left set	R 1	R 2
Mode HRV as Humoral channel	-0,338	-0,335
(Cap/Pp) <sup>0,5</sup> as Parathyroid Activity	-0,310	-0,323
AMo HRV as Sympathetic tone	-0,242	0,395
(Nap/Kp) <sup>0,5</sup> as Mineralocorticoid Act	-0,229	0,427
Glomerularly Zone of Adrenal Cortex	-0,197	-0,200
MxDMn HRV as Vagal tone	-0,123	-0,116
(Cau•Pu) <sup>0,5</sup> as Calcitonin Activity	-0,058	-0,450
Testosterone plasma	0,168	0,597



R=0,533; R<sup>2</sup>=0,284;  $\chi^2_{(32)}=83$ ; p<10<sup>-5</sup>;  $\Lambda$  Prime=0,413

**Fig. 13. First Scatterplot of Canonical correlation between Neuroendocrine factors (X-Line) and Entropies of Immune subsystems (Y-Line)**



$R=0,471$ ;  $R^2=0,222$ ;  $\chi^2_{(21)}=49$ ;  $p<10^{-3}$ ;  $\Lambda \text{ Prime}=0,611$

**Fig. 14. Second Scatterplot of Canonical correlation between Neuroendocrine factors (X-Line) and Entropies of Immune subsystems (Y-Line)**

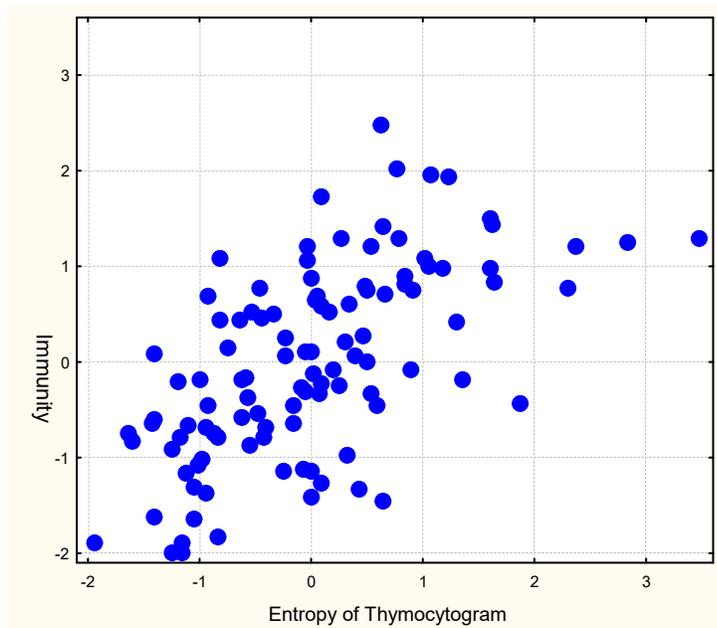
Thus, the entropy of each of the four immune subsystems is subject to the regulatory influence of a constellation of parameters of the autonomic nervous and endocrine systems.

Using the terminology of factor analysis, we consider Entropy as a hypothetical general factor. Taking this approach, we will consider what parameters of immunity are related to the Entropy of each of the immune subsystems.

It was found that the Entropy of the Thymocytogram has an activating effect on the content in the blood of plasma cells, basophils and B-lymphocytes, as well as the content in the Splenocytogram of reticulocytes and macrophages, instead of a suppressive effect on the relative mass of the spleen and intensity of blast transformation of T-lymphocytes to phytohemagglutinin. The degree of determination of the listed parameters of immunity makes 32% (Table 7 and Fig. 15).

**Table 7. Regression Summary for Immune Variables of Blood and Spleen vs Entropy TCG**  
 $R=0,615$ ;  $R^2=0,378$ ; Adjusted  $R^2=0,321$ ;  $F_{(10)}=6,6$ ;  $p<10^{-6}$

		Beta	St. Err.	B	St. Err.	t <sub>(98)</sub>	p-level
Variables, Z	r		Intercept	-0,006	0,107	-0,06	0,955
Plasmocytes Blood	0,33	0,129	0,112	0,110	0,096	1,15	0,255
Reticulocytes Spleen	0,29	0,282	0,095	0,308	0,104	2,97	0,004
Macrophages Spleen	0,25	0,230	0,093	0,237	0,095	2,48	0,015
Basophiles Blood	0,25	-0,114	0,113	-0,120	0,118	-1,01	0,314
B-Lymphocytes Blood	0,11	0,161	0,085	0,153	0,080	1,90	0,060
Blasttransformation T-Lym	-0,28	-0,393	0,094	-0,434	0,104	-4,17	10 <sup>-4</sup>
Spleen Mass Index	-0,27	-0,190	0,098	-0,258	0,132	-1,95	0,054
Lymphocytes Spleen	-0,23	-0,122	0,101	-0,134	0,112	-1,20	0,232
Leukocytes Blood	-0,17	-0,110	0,092	-0,118	0,099	-1,19	0,236



$R=0,615$ ;  $R^2=0,378$ ;  $\chi^2_{(9)}=48$ ;  $p<10^{-6}$ ;  $\Lambda$  Prime=0,622

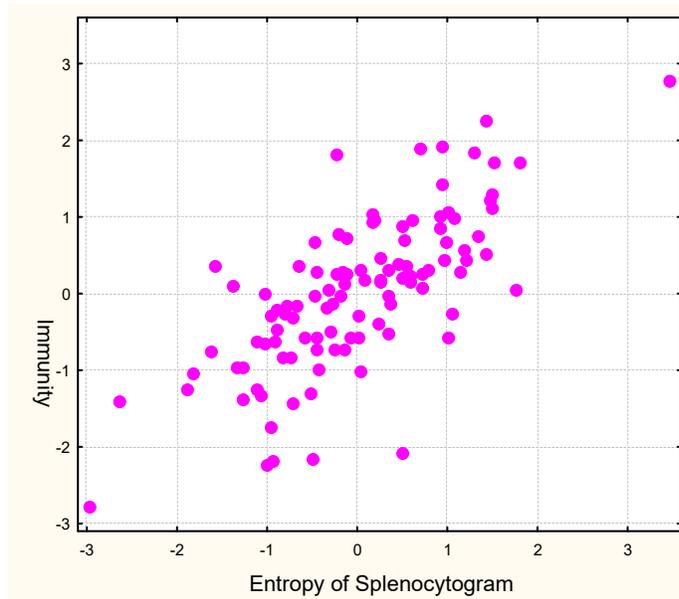
**Fig. 15. Scatterplot of canonical correlation between Entropy of Thymocytogram (X-Line) and parameters of Immunity (Y-Line)**

The hypothetical X-factor of Splenocytogram Entropy has an even stronger immunomodulatory effect (Table 8 and Fig. 16).

**Table 8. Regression Summary for Immune Variables of Blood and Thymus vs Entropy SCG**

R=0,721; R<sup>2</sup>=0,520; Adjusted R<sup>2</sup>=0,460; F<sub>(13)</sub>=8,6; p<10<sup>-6</sup>

		Beta	St. Err.	B	St. Err.	t <sub>(95)</sub>	p-level
<b>Variables, Z</b>	<b>r</b>		<b>Intercept</b>	-0,076	0,086	-0,88	0,378
<b>Phagocytosis Ind Monocytes</b>	-0,36	-0,375	0,091	-0,342	0,083	-4,13	10 <sup>-4</sup>
<b>Bactericidity Monocytes Blood</b>	-0,33	-0,338	0,088	-0,351	0,092	-3,84	10 <sup>-3</sup>
<b>Lymphoblastes Thymus</b>	-0,21	-0,127	0,075	-0,098	0,058	-1,69	0,094
<b>Plasmocytes Blood</b>	-0,20	-0,256	0,087	-0,191	0,065	-2,93	0,004
<b>Microbian Count Neutrophils</b>	-0,19	-0,112	0,084	-0,066	0,050	-1,32	0,190
<b>Reticulocytes Thymus</b>	-0,18	-0,108	0,080	-0,130	0,096	-1,35	0,180
<b>Macrophages Thymus</b>	0,19	0,103	0,091	0,052	0,046	1,13	0,263
<b>Microbian Count Monocytes</b>	0,17	0,339	0,102	0,157	0,047	3,33	0,001
<b>Segmentonucleary Neutr Blood</b>	0,16	0,298	0,089	0,326	0,098	3,33	0,001
<b>Hassal's corpuscles Thymus</b>	0,15	0,170	0,080	0,181	0,085	2,12	0,037
<b>Blasttransformation T-Lymphoc</b>	0,13	0,139	0,082	0,134	0,079	1,70	0,092
<b>0-Lymphocytes Blood</b>	0,11	-0,121	0,091	-0,096	0,073	-1,32	0,190



R=0,721; R<sup>2</sup>=0,520;  $\chi^2_{(12)}=73$ ; p<10<sup>-6</sup>;  $\Lambda$  Prime=0,480

**Fig. 16. Scatterplot of canonical correlation between Entropy of Splenocytogram (X-Line) and parameters of Immunity (Y-Line)**

At the same time suppressive influence prevails. In particular downregulated activity of phagocytosis of macrophages of blood and their bactericidal ability (despite increase in intensity of phagocytosis), instead of the last at microphages decreases. The content of plasma cells in the blood and lymphoblasts and reticulocytes in the thymus also downregulated. However, the X-factor of the Splenocytogram upregulates the content in the thymus of macrophages and Gassal's

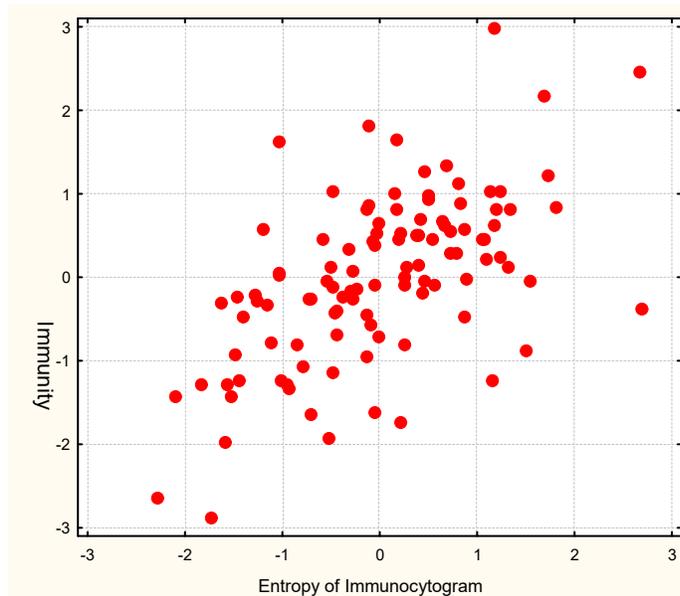
cells, polymorphonuclear neutrophils in the blood, as well as blast transformation of T-Lymphocytes. The degree of determination of these immune parameters by the Entropy of the Splenocytogram is 52%.

The Entropy of the Immunocytogram correlates positively with the content of basophils in the blood, endotheliocytes in the Thymocytogram and lymphoblasts in the Splenocytogram, while negatively with the content of leukocytes and pan-lymphocytes in the blood, the intensity of phagocytosis of monocytes as well as spleen mass indexes and content of plasma cells in the Splenocytogram. The degree of determination of the listed immune parameters from the Entropy of the Immunocytogram makes only 29% (Table 9 and Fig. 17).

**Table 9. Regression Summary for Immune Variables of Blood, Spleen and Thymus vs Entropy ICG**

R=0,586; R<sup>2</sup>=0,343; Adjusted R<sup>2</sup>=0,290; F<sub>(9)</sub>=6,5; p<10<sup>-5</sup>

		Beta	St. Err.	B	St. Err.	t <sub>(99)</sub>	p-level
<b>Variables, Z</b>	<b>r</b>		<b>Intercept</b>	0,135	0,114	1,19	0,238
<b>Basophiles Blood</b>	0,42	0,333	0,086	0,389	0,101	3,86	10 <sup>-4</sup>
<b>Endotheliocytes Thymus</b>	0,27	0,116	0,090	0,130	0,101	1,29	0,200
<b>Lymphoblastes Spleen</b>	0,17	0,151	0,089	0,181	0,108	1,68	0,096
<b>Microbian Count Monocytes</b>	-0,29	-0,169	0,086	-0,100	0,051	-1,97	0,052
<b>Plasmocytes Spleen</b>	-0,25	-0,199	0,087	-0,265	0,116	-2,29	0,024
<b>Spleen Mass Index</b>	-0,23	-0,196	0,091	-0,297	0,138	-2,15	0,034
<b>Pan-Lymphocytes Blood</b>	-0,13	-0,142	0,085	-0,160	0,096	-1,67	0,098
<b>Leukocytes Blood</b>	-0,12	0,119	0,096	0,142	0,115	1,23	0,221



R=0,586; R<sup>2</sup>=0,343;  $\chi^2_{(8)}=43$ ; p=10<sup>-5</sup>;  $\Lambda$  Prime=0,657

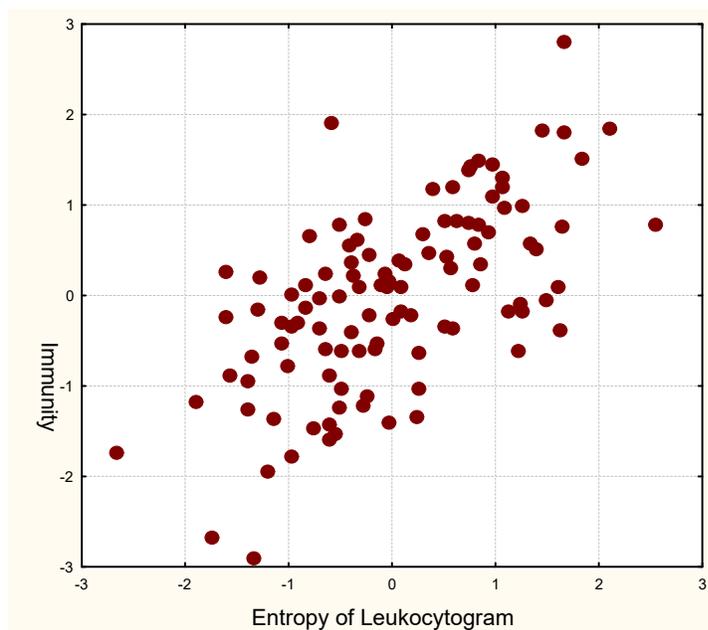
**Fig. 17. Scatterplot of canonical correlation between Entropy of Immunocytogram (X-Line) and parameters of Immunity (Y-Line)**

Finally, the regression model of the Entropy of the Leukocytogram includes as many as 12 immune parameters, but due to weak correlations, the degree of determination of this immune constellation is only 32% (Table 10 and Fig. 18).

**Table 10. Regression Summary for Immune Variables of Blood, Spleen and Thymus vs Entropy LCG**

R=0,631; R<sup>2</sup>=0,398; Adjusted R<sup>2</sup>=0,322; F<sub>(13)</sub>=5,2; p<10<sup>-6</sup>

		Beta	St. Err.	B	St. Err.	t <sub>(95)</sub>	p-level
Variables, Z	r		Intercept	-0,171	0,129	-1,32	0,189
Macrophages Spleen	0,24	0,122	0,105	0,138	0,119	1,16	0,249
Natural Killers Blood	0,18	0,235	0,086	0,176	0,065	2,72	0,008
Plasmocytes Blood	0,17	0,198	0,108	0,186	0,101	1,84	0,069
BactericidityNeutrophils Blood	0,16	0,399	0,109	0,648	0,177	3,66	10 <sup>-3</sup>
BactericidityMonocytes Blood	0,15	0,175	0,099	0,230	0,129	1,78	0,079
Eosinophils Spleen	-0,19	-0,130	0,090	-0,153	0,107	-1,43	0,155
Killing Index Neutrophils	-0,17	-0,243	0,091	-0,271	0,102	-2,67	0,009
Endotheliocytes Thymus	-0,16	-0,232	0,091	-0,254	0,099	-2,56	0,012
T-cytolytic Lymphocytes	-0,14	-0,113	0,101	-0,127	0,113	-1,12	0,265
Reticulocytes Spleen	-0,13	-0,152	0,089	-0,182	0,107	-1,70	0,092
Leukocytes Blood	-0,12	-0,418	0,119	-0,492	0,140	-3,53	0,001
Lymphoblastes Spleen	-0,12	-0,119	0,105	-0,141	0,125	-1,13	0,260



R=0,631; R<sup>2</sup>=0,398;  $\chi^2_{(12)}=51$ ; p=10<sup>-6</sup>;  $\Lambda$  Prime=0,602

**Fig. 18. Scatterplot of canonical correlation between Entropy of Leukocytogram (X-Line) and parameters of Immunity (Y-Line)**

It is known that in mathematics Entropy is a measure of the uncertainty of a random function; in information theory it is a measure of uncertainty of the situation, any experience (test), which may have different consequences; Entropy is also a measure of disorder, the degree of chaos present in the system (quoted in: [8,9]). SE Shannon [48] linked the mathematical dependence of the concept of information and entropy, which characterizes the degree of ordering of the system. This estimate of the amount of information coincides with the estimate of the quantitative measure of eliminating the uncertainty of entropy, the degree of organization of the system.

According to PV Biloshyts'kyi [7], the mathematical formula directly indicates the possibility of quantitative change of information to change the order of the system, which in relation to biosystems can mean a change in quality (sustainability, performance, health, etc.) and thus indicate the purposeful use of bioinformation in medical practice. Occasionally, the author proposes to use the term **reliability of the functioning of the organism** instead of the term Entropy, which is very impressive to us, as well as his assumption that the dependence of the reliability of the biosystem on information is elusive *vis vitalis*.

In our humble opinion, we have been able to demonstrate that Entropy has real *life force*, which is quantified by the canonical correlation coefficient of Entropy levels of morpho-functional immune subsystems with the immunity parameters of other subsystems. That is, Entropy is the subject of influence. On the other hand, Entropy is an object that is subject to the regulatory influence of the autonomic nervous and endocrine systems. Neuroendocrine-immune relationships in rats are analyzed in detail in our previous studies [15,27,28,41,42].

## CONFORMITY TO ETHICAL STANDARDS

Experiments on animals have been carried out in accordance with the provisions of the Helsinki Declaration of 1975, revised and supplemented in 2002 by the Directives of the National Committees for Ethics in Scientific Research.

The carrying out of experiments was approved by the Ethics Committee of the Horbachevskyy Ternopil' State Medical University. The modern rules for the maintenance and use of laboratory animals complying with the principles of the European Convention for the Protection of Vertebrate Animals used for scientific experiments and needs are observed (Strasbourg, 1985).

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