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THE EFFECT OF STRESS ON THE HEMATOLOGICAL INDICATORS OF RATS RATTUS NORVEGICUS F. DOMESTICUS IN THE CONDITIONS OF THE BIOLOGICAL EXPERIMENT

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Ключевые слова: *лабораторные крысы, стресс, морфологические показатели, гематологические показатели*

Abstract. The effect of stress on the hematological indicators of rats *Rattus norvegicus f. domesticus* in the conditions of the biological experiment. Shevchyk L.O., Kravets N.Ya., Grod I.M. *The purpose of the work was the need to study the change in weight and hematological indicators of the rats as a reaction-response to being in difficult and unfavorable experimental conditions. The biological experiment was conducted in compliance with the normative conditions of keeping the rats, in accordance with ethical standards and recommendations for humanization of work with laboratory animals. In order to accomplish these tasks, rats were divided into two groups: control rats were housed in a spacious cage with comfortable living conditions and experimental animals were housed in a small cage with limited ability to move freely. For the purity of the experiment, the feed ration of animals of two groups was the same. Weight and hematological indicators were determined by conventional methods of physiology. It has been found that improper housing conditions, causing a stressful situation adversely affect the eating activity of the test animals, which explains the weak correlation of dynamics of the weight of animals in the control and experimental groups. The analysis of the absolute mass of the internal organs of rats showed their direct dependence on body weight and the correlation of these parameters between animals of both groups. The study found that the quantitative ratios of the main hematological parameters of each of the rodents are strictly different. The tendency to increase in the investigated parameters in the experimental group in comparison with the control one is symptomatic and can be explained by sympathetic-vegetative influences. The amount of hemoglobin directly correlates with the number of red blood cells. Comparison of the content of hemoglobin, erythrocytes, leukocytes with body weight showed inversely proportional relationship between them. The persistent predominance of leukocytes in the blood of rats in both groups is likely genetically conditioned.*

Реферат. Влияние стресса на весовые и гематологические показатели крыс *Rattus norvegicus f. domesticus* в условиях биологического эксперимента. Шевчик Л.Е., Кравець Н.Я., Грод И.Н. *Целью работы стала необходимость изучения изменения весовых и гематологических показателей крысы лабораторной как* *реакции-ответа на пребывание в сложных и неблагоприятных условиях эксперимента. Биологический эксперимент был проведен с соблюдением нормативных условий содержания крыс, в соответствии с этическими нормами и рекомендациями по гуманизации работы с лабораторными животными. С целью реализации поставленных задач крысы были разделены на две группы: контрольная – крысы находились в просторной клетке с комфортными условиями существования и экспериментальная – животные были расположены в малой клетке с ограниченной возможностью для свободного передвижения. С целью чистоты эксперимента кормовой рацион животных обеих групп был одинаковым. Весовые и гематологические показатели определяли по общепринятым в физиологии методикам. Было установлено, что ненадлежащие условия содержания, вызывая стрессовую ситуацию, негативно влияют на активность поедания кормов подопытными животными, что объясняет слабую корреляцию динамики веса животных контрольной и экспериментальной групп. Анализ абсолютной массы внутренних органов крыс продемонстрировал прямую зависимость их от веса тела и корреляцию этих параметров между животными обеих групп. В процессе исследования установлено, что количественные соотношения основных гематологических показателей каждого из грызунов строго индивидуальны. Тенденция к увеличению исследуемых параметров в экспериментальной группе по сравнению с контрольной носит симптоматический характер и может быть объяснена симпатично-вегетативными влияниями. Количество гемоглобина напрямую коррелируется с количеством эритроцитов. Сопоставление содержания гемоглобина, эритроцитов, лейкоцитов с массой тела показало обратно-пропорциональную зависимость между ними. Устойчивое преобладание доли лейкоцитов крови крыс обеих исследуемых групп, очевидно, генетически обусловлено.*

The relevance of the study follows from the goals of educational and professional training of graduates of medical universities of Ukraine and is determined by the content of knowledge and skills that must be mastered by future physicians: to gain knowledge about the mechanisms of resistance of living organisms at different levels of organization, to study the whole spectrum of their resistance to adverse factors of natural and man-made environment, the limits of their stability and ability to adaptation [8].

Throughout life, every living thing is affected by environmental factors, lifestyle and nutrition, behavioral sphere, physical and psychological stress, and so on. In fact, physical and psychological stress, disrupting metabolic processes in the body cause stress.

The scientific approach to the study of stress is most often reduced to its understanding as a "reaction-response" to the lack of "correspondence" between being and the environment. The term "environment" is used in the broadest sense and refers to both the physical and psychological state of a being [6, 15] and the external environment [4, 14].

The given data indicate the need to form in students of medical universities the skills of stress detection, mastering the methods of diagnosis and measures to prevent its negative impact.

It is important to note that the transition to a modern paradigm - adherence to biological ethics in conducting biomedical research using laboratory animals, brought to the fore the requirement to train a specialist who has the appropriate knowledge and skills to conduct procedure of medical-biological experiment and care of experimental animals [6].

Today, about 58.2 million animals in 179 countries of the world are involved in medical and biological research, the use of which is carried out with strict control over genetic, ecological, morphological traits, as well as the health status of experimental animals [5]. Depending on the purpose of the experiment, it is important to use purebred or heterozygous animals, because they differ in the stability of the reaction to the action of physical and pathogenic factors. That is why linear animals are used in research in the field of microbiology, parasitology, oncology, immunology, genetics, physiology, morphology, and others.

Purebred laboratory rats are a good material for studying the effects of stress on living organisms [9]. The changing environmental realities of today have caused a new outbreak of interest in such research.

As a hypothesis for analysis, we suggested that the peculiarities of feeding behavior of laboratory rats, due to different housing conditions, may act as a factor that simulates the psychosocial reactivity of the individual in response to stressful situations [7].

The aim of the work is to study the change of weight and hematological parameters of a laboratory rat as a reaction-response to being in difficult and unfavorable conditions of the experiment.

MATERIALS AND METHODS OF RESEARCH

The research was carried out during 2017-2018 using rats of the vivarium of I. Horbachevsky Ternopil National Medical University. In order to intensify the cognitive activity of students, students of 2-3 courses of higher medical establishment were involved in the experiment.

The experiment took place in a room with good ventilation, sufficient lighting and a stable temperature of 20-22°C. Humidity did not exceed 40-45%, which is fully consistent with the standards of laboratory rats. The study was conducted in accordance with ethical standards and recommendations for the humanization of work with laboratory animals, which are reflected in the "European Convention for the protection of vertebrate animals used for experimental and other purposes" (Strasbourg, 1986, 2010), as well as requirements of the commission on bioethics of I. Horbachevsky TNMU of Ministry of Health of Ukraine (Minutes N 59 of 5.06.2020). During the experiment, 10 specimens (five animals of the control and experimental groups) of purebred rats of the Wistar line with approximately the same body weight (m_c =214.5±3.8; m_e =194.7±13.3 t=1.74 p<0.1), placed in three cages were used. Two cages with sizes of 42×27×15 cm, where the animals were kept during the day for 9 hours, and one cage with sizes of 28×22×14 cm to accommodate experimental animals at dusk and at night [12]. The cages are equipped with drinkers and utensils for eating. The litter used in the experiment had the appearance of small pieces of hardwood, without the content of harmful impurities in the form of heavy metals, pesticides, herbicides, insecticides, etc. Litter was replaced every 2-3 days.

The amount of food was calculated by trial-and-error procedure. Feeding of animals at the rate of 87.6 g (485.18 kcal) of feed per day for one animal showed the ineffectiveness of this amount of feed, because the experimental animals did not eat all the food. More food remained in the cage of the experimental group of animals, less – in the control group. Due to this, the amount of food was reduced to 75.6 g (472.28 kcal) per day per animal, g/day (Table 1) [2]. For the purity of the experiment, the food ration of the animals for both groups was the same.

Table 1

Food ration of laboratory rats (g/day)

Name	Food ration		
	recommended	for animals under study	
		control group	experimental group
Different cereals	40	40	40
Carrot, cabbage, beet	20	15	15
Wheat bread	12	10	10
Green mass from sprouted oats	15	10	10
Feeding yeast	0.3	0.3	0.3
Salt	0	0	0
Feed, total, g	87.6	75.6	75.6
Caloric content, kcal	485.18	472.28	472.28

A variety of food was used, including a grain mixture of wheat, oats, barley cereals, and leavened bread. Cabbage and roots (beet and carrot) were fed to animals as a source of vitamins.

Animals were weighed using an electronic scale SF 400. For convenience during weighing a trap weighing 285 g was used. In order to avoid bites, all manipulations with animals were carried with using gloves.

Hematological indicators (content of erythrocytes, leukocytes and hemoglobin concentration) were determined according to generally accepted methods in animal physiology [13]. Internal organ indices were determined by the ratio of their weight to the body weight of the animal, expressed as a percentage. Statistical analysis of the results was performed using mathematical methods of biometrics using licensed software packages STATISTICA v.6.1 (StatSoft, USA, serial number AGAR909E415822FA) and Microsoft Excel (Microsoft Office 2010, license agreement) O14_RTM_VL.1_RTM_RU) [1] To establish the degree of probability of the results, the value of the criterion of probability according to the Student, with confidence thresholds $p<0.05$, $p<0.1$ was used.

RESULTS AND DISCUSSION

If the animals of the control group felt quite free and comfortable in a spacious cage, the animals of the experimental group, located in a small cage, were deprived of the opportunity to move freely. This inevitably led to a reduction in energy costs and, consequently, to a reduction in the amount of food consumed, which led to adjustments in the diet of animals.

During the experiment, the animals demonstrated different food preferences. Carrot and wheat bread were consumed the best, cabbage and a mixture of cereals – good, and beet and wheat – the worst.

Weighing of rats was carried out with an interval of 7 days (Table 2), the data showed a certain dynamics of animal weight both in the control and in the experimental group, weakly correlating with each other (r=0.45) (Fig. 1), and the found differences are insignificant ($0.2<t_{c-e}<1.6$ $p<0.1$).

Table 2

Dynamics of ratis weight in the conditions of experiment

Stage (weeks)	Dates	Control group			Experimental group			t; p
		n	X±m	C.V.	n	X ± m	C.V.	
1	7.09.18	5	171.47±2.8	28.4	5	164.2±2.2	23.4	$t_{k-e}=0.2$ $p<0.1$ $t_{k1-2}=0.6$ $p<0.1$ $t_{e1-2}=1.4$ $p<0.1$
2	14.09.18	5	150.63±1.9	22.3	5	132.3±3.8	17.6	$t_{k-e}=0.4$ $p<0.1$ $t_{k2-3}=0.58$ $p<0.1$ $t_{e2-3}=1.4$ $p<0.1$
3	21.09.18	5	166.3±1.8	19.4	5	167.97±2.5	25.7	$t_{k-e}=0.05$ $p<0.1$ $t_{k3-4}=1.53$ $p<0.1$ $t_{e3-4}=0.53$ $p<0.1$
4	1.10.18	5	250.3±5.2	35.6	5	165.5±1.8	18.3	$t_{k-e}=1.6$ $p<0.1$ $t_{k4-5}=2.47$ $p<0.05$ $t_{e4-5}=0.15$ $p<0.1$
5	9.10.18	5	172. 13±2.6	26.8	5	162.3±1.2	15.2	$t_{k-e}=0.15$ $p<0.1$

Notes: t – validity coefficient; p – Student's ratio; C.V. – coefficient of variation; c – control group; e – experimental group; 1-5 – stages (weeks) of the experiment.

During the first week, we observe a decrease in animal body weight, which is obviously explained by the stressful situation caused by the beginning of the experiment. Weight gain over the next week demonstrates the animals' adaptation to new living conditions. The tendency to weight gain during the third week is noticeable in both the control and experimental groups ($0.05<t_{c-e}<1.53$ $g<0.1$). The detected weight gain of animals in the control group during the fourth week of the experiment is still not significant ($t_{c4}=1.53$ $g<0.1$), and some decrease in this indicator in the experimental group is not significant ($t_{e4}=0.05$ $g<0.1$). By the fifth week, weight loss had been detected in both groups. However, if in the control group the differences are significant ($t_{c5}=2.47$ $p<0.05$), then in the experimental group there is only a tendency for this indicator to decrease ($t_{e5}=0.15$ $p<0.1$). In our opinion, the repeated weight loss (for the period from September 21, 2018 to October 4, 2018) is explained by the superimposement on the stressful situation of a certain lack of animal products in the diet: fishmeal, unsalted fresh lard, boiled eggs, cheese, etc.

The high value of the coefficient of variation (C.V.) in both groups throughout the study period indicates a high individuality of the genetically determined ability to change body weight in rats, and hence high variability in both groups.

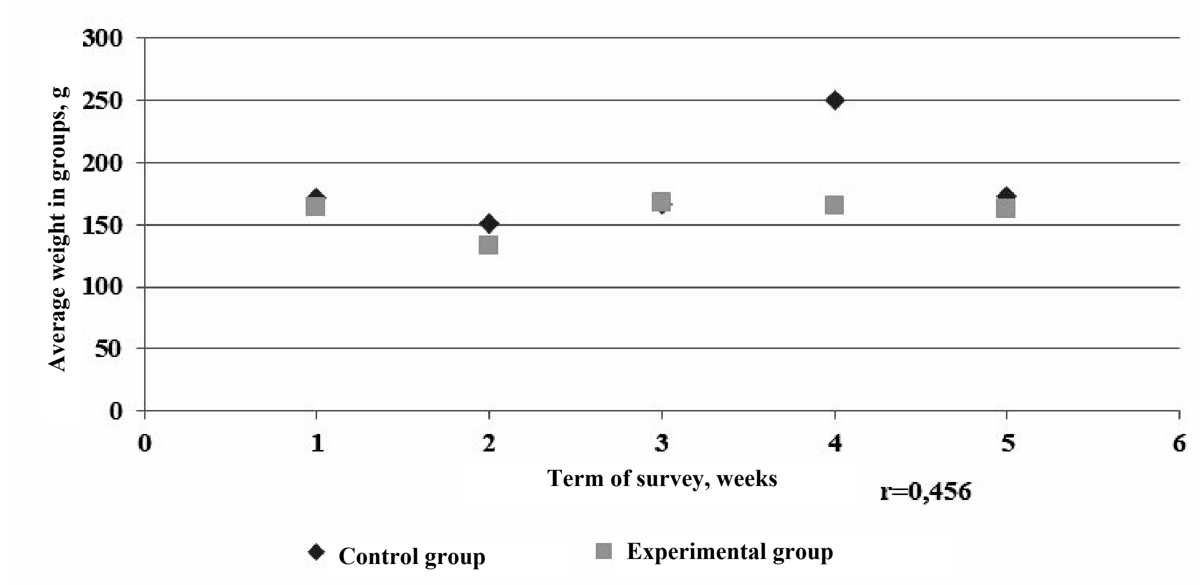

Fig. 1. Graph of correlation of dynamics of rats' weight of experimental and control group

The heart mass of laboratory rats in the experiment (M_h: 0.82±0.04) and control (M_h: 0.88±0.06) differ a little, while the cardiac indices in both groups of animals are identical (HI: 0.5%) (Table 3).

Table 3

Mass of inner organs of the laboratory rat

Indicator	Group	n	Xmin – Xmax	X±m	C.V. %%	Indices %%
Mass of heart	e.	5	0.76 – 0.94	0.82 ±0.04	9.9	0.5
	k.	5	0.78 – 0.99	0.88±0.06	12.5	0.5
Mass of liver	e.	5	5.86 – 7.0	6.5±0.26	8.1	4.0
	k.	5	5.41 – 8.55	6.96±0.9	22.6	4.0
Mass of kidney	e.	5	0.18 – 0.2	0.19±0.01	4.9	0.1
	k.	5	0.17 – 0.29	0.22±0.22	3.2	0.1

Notes: k. – control group; e.– experimental group.

Comparing the absolute mass of the liver $M_{l:}$ 6.5±0.26 and kidney M_k: 0.19±0.01 (at animal body weight in the experimental group M: 162.3±1.2) with the same indicators in the control (M_l: 6.96±0.9; M_k: 0.22±0.22; M: 172.13±2.6), we note their direct dependence on body weight and the correlation of changes in the mass of internal organs between control and experiment (r=0.99) (Fig. 2). In both groups of experimental animals, the liver index (LI: 4%) is significantly higher than the renal index (RI:0.1%).

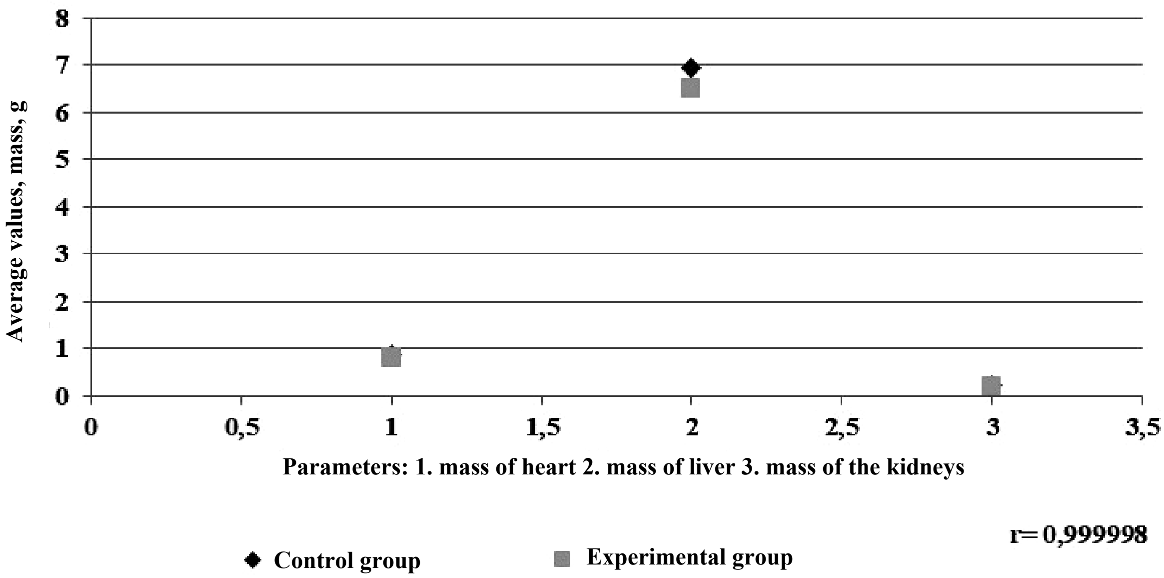

Fig. 2. Graph of the correlation between the mass of the internal organs of rats of the control and experimental groups

Comparison of the main hematological indicators (number of erythrocytes, leukocytes and hemoglobin concentration) showed a stable predominance of them in laboratory rats of the experimental group compared to the control. In both groups of animals, the number of leukocytes is 1.8 times higher than the number of erythrocytes (Table 4).

Table 4

Separate hematological indicators of laboratory rat in the conditions of biological experiment

Indicator	Group of animals	n	Xmin-Xmax	X ± m	C.V.	t ; p
Hemoglobin (mg/mm^3)	e	5	6.8–10.1	9.4±0.40	15.4	t=0.24, p<0.1
	c	5	7.2–9.6	8.26±0.70	13.8	
Erythrocytes (mln/mm^3)	e	5	1.8–4.3	3.8±0.60	11.7	t=1.5, p<0.1
	c	5	2.2–4.4	2.76±0.44	10.4	
Leukocytes ($thousnd/mm^3$)	e	5	6.2–7.6	7.0±0.29	8.4	t=2.1, p<0.05
	c	5	3.6–6.6	5.01±0.87	10.6	

Notes: c – control group; e – experimental group; C.V. – coefficient of variation; t – reliability factor; p – Student's ratio.

When assessing the role of the nutritional factor in the life of laboratory rats, one should take into account the pantophagy of animals, a certain percentage of plant and animal products, the ability of the species to switch to feed substitution. Actual and potential pantophagy of the studied species is basically due to the pantophagy of progenitor of laboratory rats – gray rat (with pantophagous-vegetational type of nutrition.

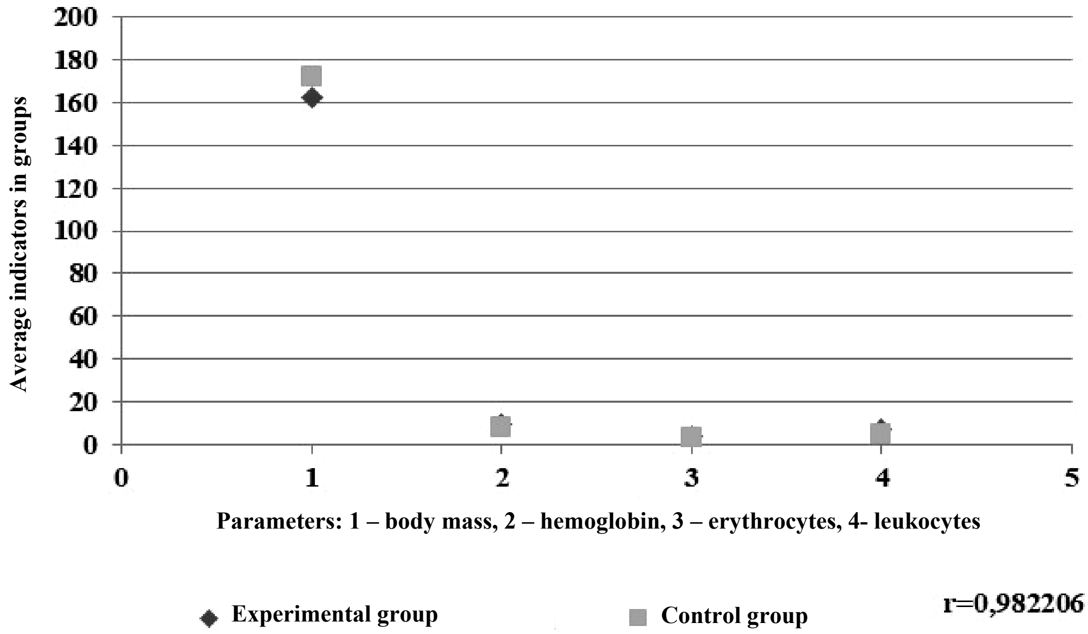

Fig. 3. Correlation between hematological indicatorsand body weight of rats of control and experimental groups

There is no doubt that the full life of animals is possible only if there is a sufficient amount of protein, fat, carbohydrates, water and vitamins in the diet. The absence of at least one component and the insufficiency or predominance of any of them leads to various disorders of the processes of animal life, because it negatively affects the process of energy supply.

The attempt of scientists to estimate the mass of the heart, liver and kidneys in terms of so-called somatic indicators led us to believe that they are not directly dependent on energy consumption, but are determined by the basic functions of the body and related to physiological and environmental features, able to make certain adjustments to these indicators.

Thus, the cardiac index is determined by the motor activity of animals, the liver index depends on the type of food and the ability of the body to deposit nutrients, while the renal index illustrates pronounced adaptive features to the microclimatic conditions of experimental animals. It should be noted that the absolute correlation of cardiac index, liver and renal in the one experiment and control is not accidental and is explained by the genetic homogeneity of linear animals [10].

Comparison of hematological indicators with the body weight of laboratory rats (Fig. 3) showed an inversely proportional relationship between them (r=0.9822).

The tendency to increase the number of erythrocytes in the experiment compared to the control, can be explained by symptomatic erythropoiesis caused by the body's compensatory response to hypoxia of tissues. Its occurrence is due to the keeping of animals in a tight cage during the entire period of the highest daily activity and is accompanied by insufficient lung ventilation due to superficial delayed, but rhythmic, respiration. Typically, this type of respiration causes an increase in carbon dioxide and a decrease in blood oxygen levels.

Some tendency to predominance of hemoglobin content in the experimental group over the control correlates with the content of erythrocytes in the blood of experimental animals (r=0.99).

The increase in the content of leukocytes is not always due to the disease of the animal, but may occur under the influence of physiological features. In our case, a significant predominance ($t=2.1$ $p<0.05$) of the number of leukocytes in the experimental group compared with the control (Table 4) is most likely due to sympathetic-vegetative effects associated with reactive dilation of the cutaneous vessels in overheating of animals. In this case, leukocytosis occurs as a result of vascular reactions with the eviction of leukocytes from blood depots [3].

CONCLUSIONS

1. The laboratory rat is a good object for modeling the impact of the environment on living

organisms. Its participation in the experiment requires humane treatment, and empathy is a mandatory ethical requirement for experimentalists.

2. The study found that improper housing conditions, causing a stressful situation, negatively affect the activity of eating food by experimental animals, which explains the weak correlation of the dynamics of weight of animals in the control and experimental groups. Analysis of the absolute mass of the internal organs of rats showed their direct dependence on body weight and the correlation of these indicators between animals of both groups.

3. In the course of the research it was established that the quantitative ratios of the main hematological indicators of each of the rodents are strictly individual. The tendency to increase the studied parameters in the experimental group in comparison with the control group is symptomatic and can be explained by sympathetic-vegetative influences. The content of hemoglobin directly correlates with the number of erythrocytes. Comparison of the content of hemoglobin, erythrocytes, leukocytes with body weight showed an inversely proportional relationship between them. The steady predominance of the proportion of leukocytes in the blood of rats of both study groups obviously is genetically determined.

Conflict of interest. The authors declare no conflict of interest.

REFERENCES

1. Antomonov MYu. [Mathematical processing and analysis of medico-biological data]. 2nd ed. Kyi: MIC "Medinform"; 2018. p. 579. Russian.
2. [Healthy eating: the calorie table of products]. Medfund. 2018;1. Ukrainian. Availabe from: https://medfond.com/static/tablicya-kaloriinosti-produktiv.html.
3. Kotsiumbas G, Tesarivska U, Humenetska M, Shumsk M. [Hematological parameters and morphological characteristics of the spleenin femalerats f1 underin fluense nanohermanium citrate, used indifferent doses]. Scientific Messenger Stepan Gzhytskyi NUVMBL. 2017;19:77:45-50. Ukrainian. doi: https://doi.org/10.15421/nvlvet7711
4. Litovchenko OL, Pertsev DP, Zavgorodnii IV, Mitelova TU, Chehovska IM, Abramova LP, Vekshin VO. [Biochemical mechanisms of mixed effect of electromagnetic radiation and low positive temperature on animals' organism]. Annals of Mechnikov Institute. 2015;2:119. Ukrainian. Availabe from: http://www.imiamn.org.ua/journal/2_2015/PDF/21.pdf
5. [Scientific and practical recommendations for keeping and working with laboratory animals: manual]. Kozhemyakin YuM, Khromov OS, Boldyreva NE, Dobrelya V, Saifetdinova GA, editors. Kyiv: Interservice; 2017;182. Ukrainian. ISBN 978-617-696-560-2.
6. [Order 01.03.2012 No. 249, dated 16th March, 2012 No. 416/20729 on approval of carrying out experiments on animals by scientific establishments]. 2012. Ukrainian.
7. Sorokman TV, Tkach VV. [Factors influencing the development of eating disorders. Prospects for the development of medical science and education: a collection of abstracts of the All-Ukrainian scientific and methodological conference, dedicated to the 25th anniversary of the Sumy State University Medical Institute]. Sumy: Sumy State University; 2017. p. 108. Ukrainian. Availabe from: https://essuir.sumdu.edu.ua/bitstream/123456789/64734/1/Sorokman_faktory.pdf
8. [Higher education standard of the second (master's) level, field of knowledge 22 Health care, specialty 221 Dentistry. Approved and implemented by the order of the Ministry of Education and Science of Ukraine No. 879 dated 24.06.2019]. 2019. Ukrainian. Availabe from: https://mon.gov.ua/storage/app/media/vishcha-osvita/zatverdzeni%20standarty/2019/06/25/221-stomatologiya-magistr.pdf.
9. Toziuk OYu, Kryvoviaz OV, Ivko TI, Voronkina AS. [Pharmacological effects of KB-28 compound under chronic immobilization stress conditions]. World of medicine and biology. 2018;1(63):160-3. Ukrainian. doi: https://doi.org/10.26724/2079-8334-2018-1-63-160-163
10. Barkasi Z. [Muroid Rodents of the Lowland Part of Transcarpathia: State of Populations and Morphophysiology]. Proceedings of the Theriological School. 2015; 13(13):3-10. Ukrainian. doi: https://doi.org/10.15407/ptt2015.13.003
11. Ju Hwan Kim, Jin-Koo Lee, Hyung-Gun Kim, Kyu-Bong Kim, and Hak Rim Kim. Possible effects of radiofrequency electromagnetic field exposure on central nerve system. Biomol Ther. 2019;27(3):265-75. doi: https://doi.org/10.4062/biomolther.2018.152
12. Makowska IJ, Weary DM. Differences in Anticipatory Behaviour between Rats (Rattus norvegicus) Housed in Standard versus Semi-Naturalistic Laboratory Environments Plos one. 2016;28:1-2. doi: https://doi.org/10.1371/journal.pone.0147595
13. Wilson Jacob Filho, Caio Cezar Lima, Marcos Rodolfo Ramos Paunksnis, Ariana Aline Silva, Mauro Sérgio Perilhão, Marina Caldeira, et al. Reference database of hematological parameters for growing and aging rats. The Aging Male. 2018;21(2):145-148. doi: https://doi.org/10.1080/13685538.2017.1350156
14. Shuren J, Patel B. FDA regulation of mobile medical apps. JAMA. 2018 Jul 24;320(4):337-8. doi: https://doi.org/10.1001/jama.2018.8832
15. The Laboratory Rat (Third Edition) A volume in American College of Laboratory Animal Medicine. Academic Press, 2019;215-42. doi: https://doi.org/10.1016/C2017-0-01188-6

СПИСОК ЛІТЕРАТУРИ

1. Антомонов М. Ю. Математическая обработка и анализ медико-биологических данных. 2-е изд. Київ: МИЦ «Мединформ», 2018. 579 с.
2. Здорове харчування: таблиця калорійності продуктів. *Медфонд*. 2018. № 1. URL: https://medfond.com/static/tablicya-kaloriinosti-produktiv.html (дата звернення 2018.).
3. Коцюмбас Г. І., Тесарівська У. І. Гематологічні показники та морфологічна характеристика селезінки самок щурів f1 за дії наногерманію цитрату, застосованого у різних дозах. *Науковий вісник ЛНУВМБТ імені С. З. Ґжицького*. 2017. Т. 19, № 77. С. 45-50. DOI: https://doi.org/10.15421/nvlvet7711
4. Літовченко О. Л., Перцев Д. П. Біохімічні механізми сполученого впливу на організм тварин електромагнітного випромінювання та позитивної низької температури. *Annals of Mechnikov Institute*. 2015. № 2. С. 119. URL: http://www.imiamn.org.ua/journal/2_2015/PDF/21.pdf
5. Науково-практичні рекомендації з утримання лабораторних тварин та роботи з ними: посіб. / ред.: Ю. М. Кожем'якін, та ін. Київ: Інтерсервіс, 2017. 182 с.
6. Про затвердження порядку проведення науковими установами дослідів, експериментів на тваринах: наказ МОЗ України від 16.03.2012 р. № 249 (№ 416/20729).
7. Сорокман Т. В., Ткач В. В. Фактори, що впливають на розвиток розладів харчової поведінки. Перспективи розвитку медичної науки і освіти: збірник тез доповідей Всеукр. наук-метод. конф., присвяч. 25-ти річчю медичного інституту Сумського державного університету. Суми: Сумський державний університет, 2017. С. 108. URL: https://essuir.sumdu.edu.ua/bitstream/123456789/64734/1/Sorokman_faktory.pdf
8. Стандарт вищої освіти другого (магістерського) рівня, галузь знань 22 Охорона здоров'я, спеціальність 221 Стоматологія: затв. та введено в дію Наказом Міністерства освіти і науки України від 24.06.2019 р. № 879. URL: https://mon.gov.ua/storage/app/media/vishcha-osvita/zatverdzeni%20standarty/2019/06/25/221-stomatologiya-magistr.pdf
9. Тозлюк О. Ю., Кривов'яз О. В. Івко Т. І., Воронкіна А. С. Фармакологічні ефекти сполуки КВ-28 за умов хронічного іммобілізаційного стресу. *Світ Медицини та Біології.* 2018. Т. 63, № 1. С. 160-163. DOI: https://doi.org/10.26724/2079-8334-2018-1-63-160-163
10. Barkasi Z. Muroid Rodents of the Lowland Part of Transcarpathia: State of Populations and Morphophysiology. *Proceedings of the Theriological School.* 2015. Vol. 13, No. 13. P. 3-10. DOI: doi: https://doi.org/10.15407/ptt2015.13.003
11. Ju Hwan Kim, Jin-Koo Lee. Possible effects of radiofrequency electromagnetic field exposure on central nerve system. *Biomol Ther.* 2019. Vol. 27, No. 3. P. 265-275. DOI: https://doi.org/10.4062/biomolther.2018.152
12. Makowska I. Joanna, Weary Daniel M. Differences in Anticipatory Behaviour between Rats (Rattus norvegicus) Housed in Standard versus Semi-Naturalistic Laboratory Environments. *Plos one*. 2016. Vol. 28. P. 1-2. DOI: https://doi.org/10.1371/journal.pone.0147595
13. Reference database of hematological parameters for growing and aging rats / Jacob Filho Wilson et al. *The Aging Male.* 2018. Vol. 21, No. 2. P. 145-148, DOI: https://doi.org/10.1080/13685538.2017.1350156
14. Shuren J., Patel B. FDA regulation of mobile medical apps. *JAMA*. 2018. 24 Jul. (Vol. 320, No. 4). P. 337-338. DOI: https://doi.org/10.1001/jama.2018.8832
15. The Laboratory Rat. (3 ed.) A volume in American College of Laboratory Animal Medicine. *Academic Press.* 2019. P. 215-242. DOI: https://doi.org/10.1016/C2017-0-01188-6

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