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MORPHOLOGICAL CHANGES OF THE HEART WALL WHEN MEXIDOL IS USED IN EXPERIMENTAL HYPOTHYROIDISM

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Abstract.

Relevance. There are systemic consequences of hypothyroidism on the heart among other organs. It could cause modifications to heart rate, contractility, and relaxation, among other aspects of cardiac function. The structural alterations of the heart, such as the hypertrophy (enlargement) of the heart muscle cells, may be influenced by hypothyroidism. **Purpose of the study** identification of morphological and functional features of postnatal development and formation of the myocardium of offspring obtained under conditions of experimental hypothyroidism in the mother. **The object** of the study was female white outbred rats and their offspring on 3,7,14,21 and 30 days after birth. Experimental hypothyroidism in female rats was modeled by introducing mercazolil before pregnancy. The myocardium of the heart was studied using morphological, morphometric and electron microscopic research methods. Thus, analysis of the results of the study showed that the offspring of rats born to mothers with experimental hypothyroidism, starting from the 14th day after birth, develop vascular disorders in the myocardium, degenerative changes in the form of intracellular myocytolysis, disbandment of myofibrils, interstitial edema, and fragmentation of muscle fibers. **Conclusions**: experimental hypothyroidism reproduced in female rats leads to a pronounced disruption of the morphofunctional formation of the offspring myocardium and is a risk factor for the development of cardiovascular diseases.

Key words: Myocardium, heart muscle, hypothyroidism, experimental model, cardiomyocytes, immunohistochemistry, mexidol.

Introduction. There have been many experiments in the world related to the cardiovascular system and the thyroid gland [10]. Numerous literary data related to pathology in children born to mothers [9]. Some of these experiments are changes in the heart and blood vessels of offspring associated with hypothyroidism [7,8].

Increasing of thyroid hormones causes systemic changes in the body. Thyroid hormones regulate energy metabolism in the cells of organs, and their deficiency is manifested in a decrease in tissue oxygen consumption, a decrease in energy expenditure and the processing of energy substrates [3,5]. With hypothyroidism, the synthesis of various energy-dependent cellular enzymes necessary for the normal functioning of the cell is disrupted. In the case of advanced hypothyroidism, mucinous (mucous) edema occurs - myxedema, most pronounced in connective tissue. Myxedema develops as a result of excessive accumulation of glycosaminoglycans in the tissues, which, having increased hydrophilicity, retain water [1,2,4].

Every organ and system in the body has undergone changes, including the shape of the thyroid gland, hypothyroidism, heart wall morphology, myocardial lipid peroxidation products, and differences in the antioxidant system's activity. It is vital to do research on improved diagnostic methods for assessing the effect of mexidol therapy on the heart wall of experimental animals born with hypothyroidism [6].

This monograph serves as a partial supplement to the President of the Republic of Uzbekistan's Decrees Nos. PF-4947 of February 7, 2017, "On the Strategy for Further Development of the Republic of Uzbekistan" and PF-5590 of December 7, 2018, "On comprehensive measures to radically improve the health of the system of the Republic of Uzbekistan".

Material and methods. The research work reflected in this article was carried out in 2017-2020 in the clinic of Tashkent Medical Academy, Department of Anatomy, Clinical Anatomy, Vivarium of Tashkent Medical Academy, and Pathomorphological Laboratory IPSUM-Pathology. To achieve our goal, as well as to perform our tasks, we used 223 white laboratory rats as an object of study. Experiments on rat infants were approved by the Center of Bioethics and the experiments were conducted by the requirements of the center (excerpt from the protocol № 8 of the Ministry of Health of RUz from 18.10.2019 № 8/ 2-1222). White laboratory rats were divided into 3 groups.

In the monograph, the methods of morphometry, organometry, biochemical (ELISA), general histological, and transmission electron microscopy were used.

Results. Three-day-old rats' hearts did not look any different histologically from those of the control group. The internal endocardial layer of the ventricles of the heart consisted of single-layered oval-shaped endothelial cells. Longitudinally oriented collagen fibers were visible. Areas, where the longitudinal fibers are connected, were also visible. The collagen fibers close to the ventricular myocardium were intertwined with the connective tissue fibers located in the inner layer of the myocardium. In the ventricular endocardium, the longitudinally oriented bundle of elastic fibers was more dispersed than the collagen fibers. As the ventricles approached the myocardium, the density of elastic fibers increased.

The subepicardial myocardial layer is sparse, lumpy, with irregularly arranged cardiomyocytes (see Figure 1). In the intramural layer of the ventricular myocardium, muscle cells are arranged perpendicular to the subendocardial layer. In the interventricular barrier of the heart, the myocardium is relatively dense, and cardiomyocytes form relatively thick parallel bundles. The intramural layer of the myocardium consists of parallel cardiomyocytes in which myofibrils predominate over nuclear structures. The inner longitudinal myocardial layer covers the trabeculae and thoracic muscles in a more curved direction as they approach the endocardium.

Reticular and elastic fibers of myocardial connective tissue form loops of different shapes and sizes around multiple cardiomyocytes. The direction of connective tissue fibers is related to the direction of cardiomyocytes.

In this group of experiments with morphological changes in the heart of 7-day-old rats, there were observed full blood vessels, increased plasmorrhages and the appearance of fibrinoid tumors in the arterial wall. In hypothyroidism, small tumors began to appear around the veins after the start of mexidol application . Intracellular tumors were formed around some cardiomyocytes, and a vacuole filled with tissue fluid was formed in the cytoplasm of the cells. The intracellular tumor was found to be focal. Vascular changes in myocardial tissue were preserved, venous fullness and blood stasis persisted.

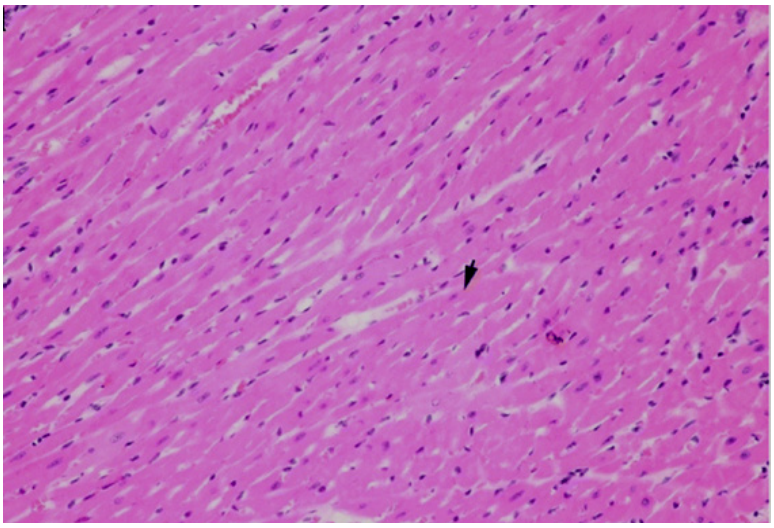


Figure 1. Subepicardial myocardial layer. Rare and clustered, misshapen cardiomyocytes. 3-day-old rat heart wall in experimental group 2. Staining: Hematoxylin-eosin. X: 10x40.

By the fourteenth day of the trial, myocardial enlargement was visible in specific areas, but it was less noticeable than in the first experimental group. The veins were the main area where tumors were seen. In the regions where the tumor is visible, collagen fibers may have swollen and homogenized.

In the cytoplasm of cardiomyocytes in some areas of the myocardium hydro peaked dystrophy is detected. It was discovered that vessel alterations had become less intense.

By day 21 of the experiment, focal myocardial swelling could be observed, but this swelling was focal and less pronounced than in group 1 of the experiment. The regions where the tumor is visible may exhibit collagen fiber swelling and homogenesis. In some sections of the myocardium, focal hydropic dystrophy was detected in the cytoplasm of cardiomyocytes. However, this change was less intense and focal than in the 1st group of

experiments. The severity of continuing changes in vessels was found to decrease (see Figure 2).

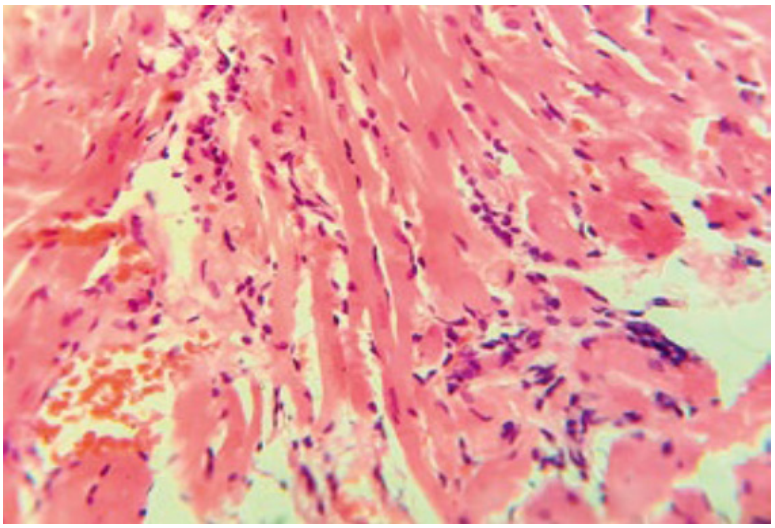


Figure 2. Heart tumor focalization. heart wall of the experimental group's 21-day-old rat. Hematoxylin-eosin staining. X: 10x40.

The daily dose of mexidol resulted in a partial resolution of the vascular abnormalities on the thirty-first day of the experiment. On this day of the experiment small focal infiltration by lymphocytes, histocytes and fibroblasts were observed for the first time. On this day of the experiment along with interstitial edema, there was observed an intensification of reparative processes. Fibroblast proliferation around the vessels and in the intermuscular connective tissue was revealed. The formation of focal fibrosis around the vessels and the appearance of thin connective tissue fibers were revealed.

Therefore, there were no pathohistological changes in the ventricular heart wall on the 3rd day of the experiment, because in the 2nd group of the experiment the mother rats with hypothyroidism were injected with mexidol as an antioxidant. Changes such as cardiomyocyte edema in the myocardium were noticed on the fourteenth day of the trial, seven days after the first set of participants. Diffuse edema in cardiomyocytes, a sign of significant alterations in hypothyroidism, was observed on day 30, which is later than in the first group of the trial. There were no obvious destructive changes and signs of necrosis accompanied by total fragmentation of muscle fibers. In the 2nd group of experiments, there was an acceleration of reparative processes with the occurance of thin connective tissue fibers instead of damaged muscle fibers. The above substantiate the protective effect of mexidol on myocardial damage in hypothyroidism.

As a peripheral component of the endocrine system, the thyroid gland is crucial to metabolic activities. Thyroid hormones enhance metabolic processes in cells and tissues, regulate the heart and vascular function, respiration, digestion, nerves, and reproductive organs. The deficiency of thyroid hormones leads to dysfunction of all organs. Hypothyroidism develops because of a deficiency of thyroid hormone. Cardiomyopathies are the most common pathology among thyroid disorders. Changes in hypothyroidism are manifested in the form of arrhythmias, arterial hypertension, heart failure. We chose to alter the dynamics of changes in the heart wall since our analysis of the literature revealed that changes in the heart in hypothyroidism are mostly focused on the clinical course and because there are no morphological alterations in the heart wall. Given the above, we set out to study the morphological changes in the cardiac wall of young rats during experimental hypothyroidism in mother rats. To achieve the goal, we induced experimental hypothyroidism in 223 white laboratory rats. We divided the white laboratory rats into 3 groups. The control group consisted of one hundred healthy rats. 20 white female laboratory rats were given mercazolil at a dose of 0.5 mg per 100 g body weight for 14 days in order to produce experimental hypothyroidism in experimental group 1 of group 2. The rats were subsequently given 0.25 mg of mercazolil for a month per 100 g of body weight. After the rats became pregnant and after the baby was born, we kept giving the lactating mothers rats mercazolil at a dose of 0.25 mg per 100 g body weight. In group 3 of our experiment, we called experimental hypothyroidism the same as in group 2. From the day of conception, we gave mother rats the antioxidant mexidol at a dose of 0.3 mg/

kg. Mexidol was given until the end of the lactation period when the rats were born.

The levels of triiodothyronine (T3), unbound thyroxine (T4) and thyrotropic hormone (TSH) in rat blood were determined to confirm that experimental hypothyroidism was induced in rats. Hormone level analysis in experimental hypothyroidism there was a significant decrease in the level of free thyroxine hormone (T4) in the blood of rats. A decrease in T3 and free T4 levels were noted from day 14, and by the last days of the experiment, the reliability of unbound T4 increased up to 4-fold and T3 increased 1.5-fold. After 14 days, compared to the control group, there was a 2-fold increase in TSH hormone due to the drop in blood levels of T3 and unbound T4 hormones.

There are many degrees of thyroid hormone deficiency-related metabolic diseases in the body that have been documented in the literature. Considering that it leads to disturbance of lipid peroxidation process in biomembranes, we considered it necessary to study some products of LPO. Our research's analysis revealed that, in comparison to the control group, the myocardium of mother rats born to hypothyroid moms had higher levels of LPO products.

The number of DC and TC in the single experimental group as well as MDA in the myocardium significantly increased, according to an analysis of the study's data. As the diagram illustrates (see Diagram 1), in 7-day-old rats there was a 41% increase in serum MDA levels, and in 14- and 21-day-old rats the reliability index was 89% higher in the control group than in the 14- and 21-day-old control group. By day 30, there was a gradual decrease in MDA, an intermediate product of lipid peroxidation.

Serum MDA levels were observed to be marginally higher in experimental group 2, or women born from rats that were given mexidol concurrently with experimental mercazolil hypothyroidism, than in the control group. This index was discovered to be substantially similar in 3-day-old rats when compared to the control group. A nonstatistically significant increase of 3% in MDA was observed in 7-day-old rats. It was 10–17% higher on days 14–21 than in the control group, and it was still 15% higher on day 30.

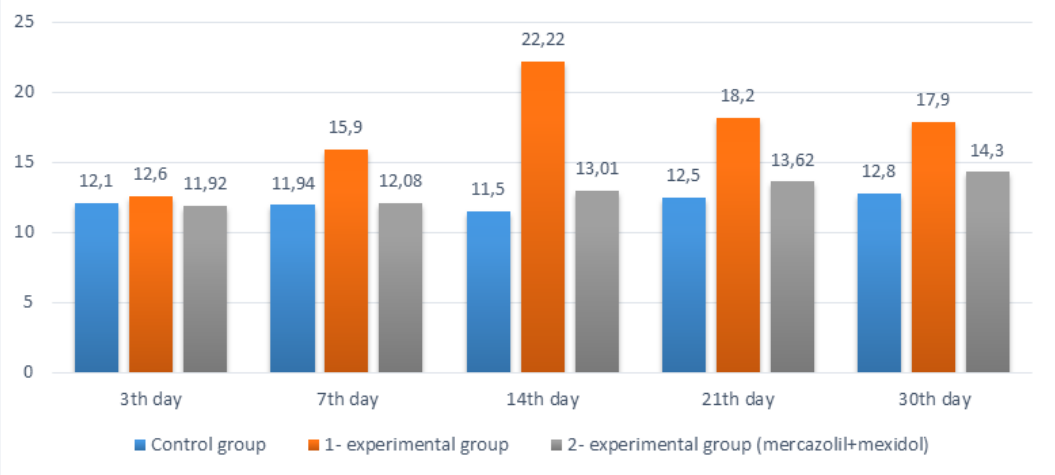


Diagram 1. Variations in the blood serum MDA concentration.

In testing serum DC levels in experimental group 1 rats, 3- and 7-day-old rats did not differ significantly from the control serum. On days 14-21, high levels of 20 to 28% were observed, and high levels of DC were maintained on day 30 (see Diagram 2).

Compared to the control group, the serum levels of DC in mother rats receiving mexidol concurrently with experimental hypothyroidism with mercazolil in experimental group 2 were shown to be not significantly higher. With an index that was 9% greater than that of the control group, the 21-day-old youngster had the highest index among the rats.

The delivery of mother rats receiving mercazolilol (experimental group 2) along with experimental hypothyroidism demonstrated that the levels of OH in the rats' serum did not vary considerably as compared to the control group. It was discovered that, in comparison to the control group, this index was substantially the same in 3-day-old rats. A nonstatistically significant shift in TS, or an 11% increase, was seen in 7-day-old rats. This index was 30% higher in rats that were 14 and 21 days old, respectively. It is evident that the 30-day-old rats' levels of TS rose by 15% in comparison to the control group.

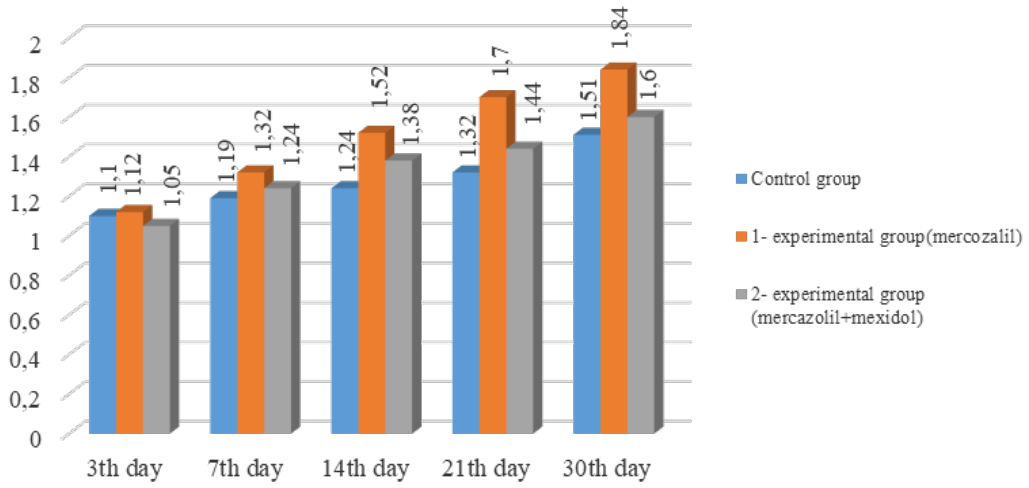


Diagram 2. Signs of variations in the concentration of DCs in blood serum.

Lipid peroxidation is a process that coexists peacefully with antioxidant system enzymes. In our study, we studied the modification of superoxide dismutase and catalase enzymes, which are the main enzymes of the antioxidant system. As a result of our studies, we observed a decrease in the activity of catalase and superoxide dismutase enzymes in the blood of young rats. Three-day-old rats in the experimental group's serum did not show a statistically significant difference in TC content from the control group. Rats aged 7 days had serum OX levels 38% higher than those in the control group; rats aged 14 and 21 days had higher levels by 73% and 71%, respectively; while rats aged 30 days had higher levels by 55% (see Diagram 3).

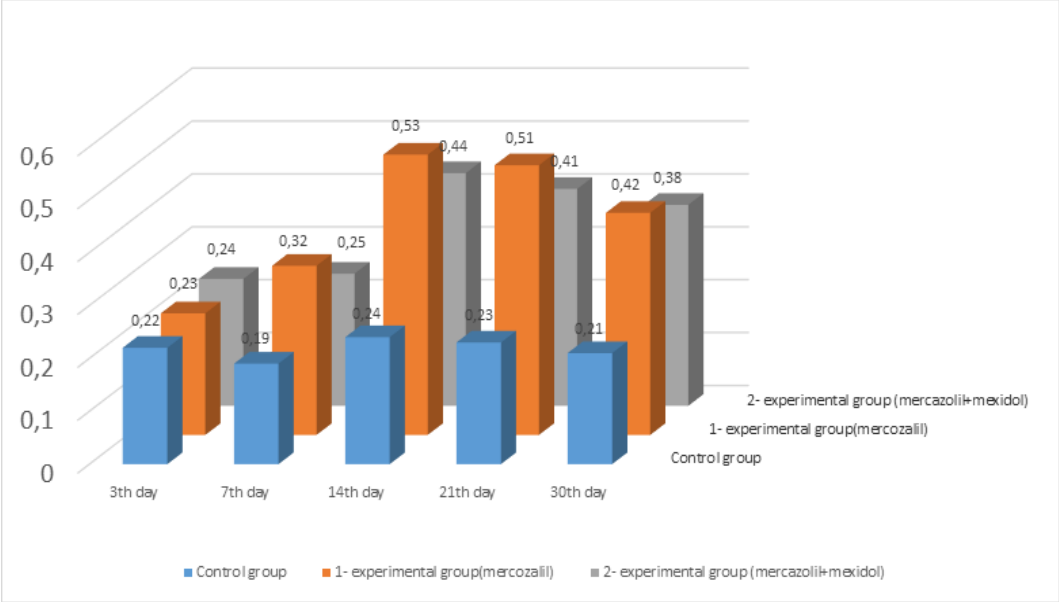


Diagram 3. Indicators of changes in the amount of DCs in blood serum.

The level of SOD in blood serum and cardiac tissue was found to be 1.0-fold in 3-day-old rats and 1.2-fold in 7-day-old rats. By the fourteenth day, these enzymes' activity was still reduced, and it had significantly decreased—by 2.4 times—when compared to the control group. Rats aged 21 days had serum superoxide dismutase activity that was almost 2.3 times lower ($p<0.001$) than that of the control group. 30 days later, this index was 2.0.

Infants delivered to mothers of rats in experimental group 2 who were concurrently treated with mexidol and mercazolil for experimental hypothyroidism had lower serum levels of SOD than the control group. In rats that were 3 and 7 days old, it was discovered that this index did not differ substantially from the control group. A 1.4-fold reduction in SOD was seen in 14-day-old rats, which was deemed a statistically significant alteration. Rats that were 21 days old and 30-days old had SOD levels that were 1.2 and 1.3 times

lower, respectively, than those in the control group.

That was established that the level of catalase in the blood serum and myocardial tissue decreased 1.2-fold in one-day-old rats and 1.9-fold in 7-day-old rats. By the fourteenth day, these enzymes' activity was still reduced, and it had significantly decreased—by 2.4 times—when compared to the control group. The 21-day-old rats' serum catalase activity was significantly maintained at 2.1-fold lower levels. Thirty days later, 2.0 was the index.

Serum levels of catalase were found to be lower in experimental group 2 rats' offspring whose mothers received mexidol and mercazolil concurrently with experimental hypothyroidism than in the control group. Rats that were 3 days old showed no significant difference in this index when compared to the control group, while rats that were 7 days old showed no significant change in catalase, which indicates a 1.1-fold drop. The index was 1.3 times lower at 14 days of age, and the amount of catalase in the rats at 21 and 30 days of age was 1.0 times lower than in the control group, although these differences were not statistically significant.

The acquired data's outcomes demonstrated that experimental hypothyroidism had an impact on the morphological structure of the thyroid gland. The emergence of big follicles in the thyroid gland's periphery on days 7–14 of the experiment served as the basis for morphological alterations in the gland's structure. During the course of the experiment, we saw changes in the vasculature, edema of the glandular tissue, rupture of the collagen fibers, the emergence of colloidal cysts, and dystrophic alterations in the cells of the gland's follicular epithelium. Despite the development of the mentioned changes, fragmentary development of the gland appeared to be preserved. In the first days of the experiment, there was observed plasmorrhagia due to the fullness of veins and increased permeability of vessel walls. Focal tumors were revealed in the stroma. Large follicles contained eosinophilic colloids. Immature follicles are covered with small cubic epithelium. An increased number of large follicles is observed in peripheral parts of the gland. In some parts of the gland, sharply enlarged follicles have a form of cysts. Flattening of epithelium can be seen in such follicles. Nuclei of follicular cells have an oval or elongated shape, somewhat smaller in size. In large follicles, the colloid appeared eosinophilic. Small follicles are lined by cubic epithelium. Focal overgrowth of fibroblasts, mainly around vessels, was observed in the stroma of the gland.

In 21 days after the beginning of the experiment the fragmentary structure of the gland is preserved, but the size of the fragments slightly decreases. Prevalence of large follicles in them, decrease in the number of small and medium follicles indicates the development of atrophic processes. At this stage of the experiment, protein hydropic dystrophy in the follicular epithelium and partial desquamation of damaged thyrocytes into the follicular cavity were manifested.

By the experiment's 30th day, the morphological changes previously noted had become more pronounced and diffused throughout the gland. There was no swelling and localization of collagen fibers. Reparative processes were intensified in the preserved stroma areas, the intensive proliferation of fibroblasts and formation of fibrils were revealed. On this day of the experiment, there were revealed characteristic structural changes in the thyroid gland: atrophy and deformation of follicles, wrinkling, and atrophy of follicular epithelium in the thyroid gland, dystrophic changes of thyrocytes, a rise in the quantity of large follicles, as well as the uneven exchange of large and small follicles. Tumor intensity was increasing in the stroma of the gland, which spread to the whole gland. In general, dystrophic changes developed in the thyroid gland, leading to disturbance of fragmentary structure of the gland, such as changes in size, shape, and structure of follicles.

The findings showed that hypothyroidism was also observed in the offspring when female rats were exposed to mercazolyl. On the 7th day of the experiment, T3 and T4 hormones of the hypothyroid and rat offspring in the control group did not differ significantly from each other. On day 14 of the experiment, there was a marked decrease in T4 and a slight decrease in T3. On day 21 of the experiment, we found that the level of T4 hormone decreased 2-fold and T3 hormone decreased 1-fold. Thyroid hormones in the blood of 30-day-old rats changed as follows: T4 decreased 4-fold and T3 decreased 2-fold.

Therefore, the analysis of the hormone index showed a significant decrease in the level of thyroxine hormone (T4) in the blood of rats with experimental hypothyroidism. The decrease of T4 hormone was evident from day 14 and decreased to a reliable time by the last days of the experiment (see Diagram 4).

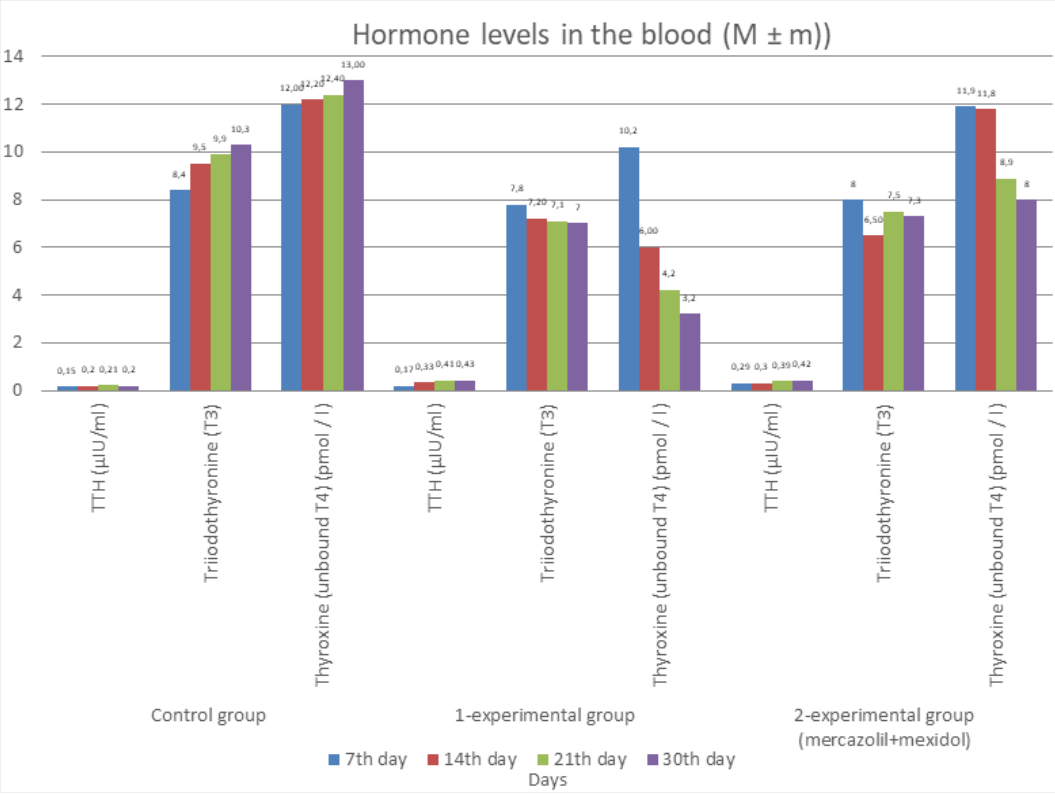
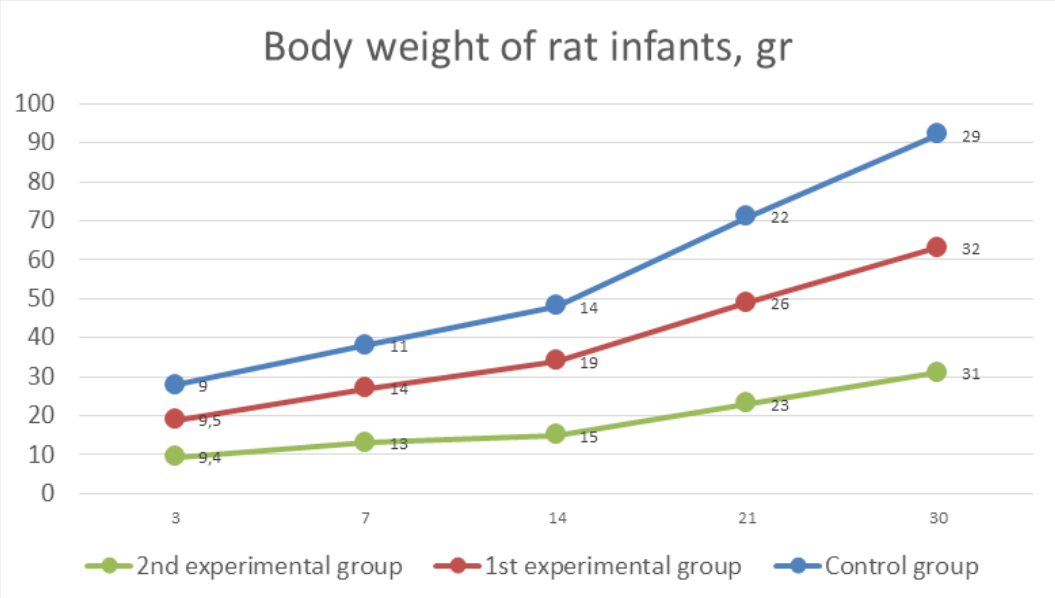


Diagram 4. Hormone levels in the blood of rats.

To achieve our goal and objective, we studied the anatomical and histological structure of the rat heart. The rat heart is located asymmetrically in the thorax and occupies a large area on the left side. With increasing body weight, the absolute weight of the heart increases significantly. The highest rate of weight gain in rats was observed on day 16 (50%). From birth to 21 days of age, rats gain 3-fold in weight and 1.7-fold in heart weight. In newborn rats, the heart weight is 1.75% of body weight. With age, the relative heart weight relative to body weight decreased to 1.1% at day 21 of postnatal ontogenesis (see Diagram 5).



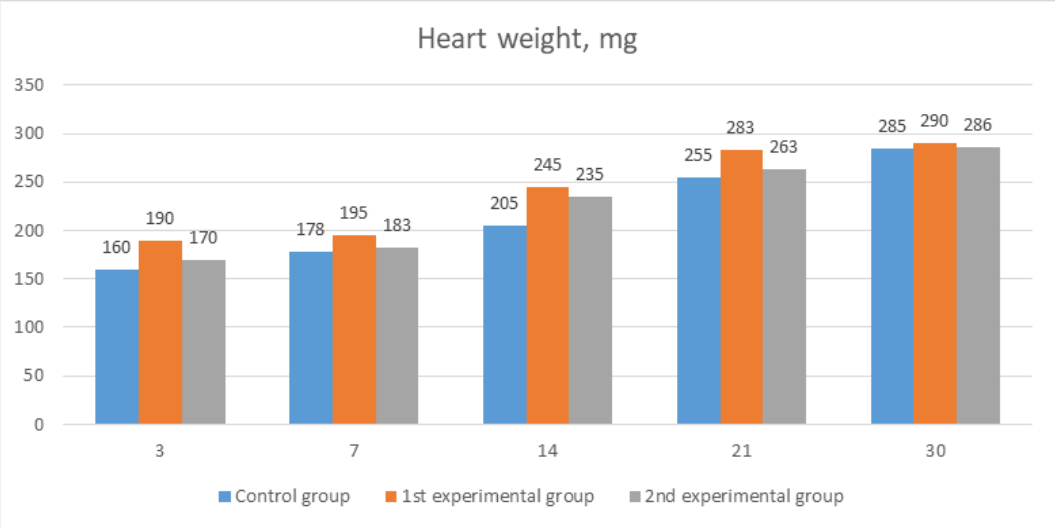


Diagram 5. Body and heart weights of rat infants.

The results show that the shape and size of the heart continuously change at different ages during postnatal ontogenesis. In newborn rats, because their anatomical features are almost identical, the heart is globular in most cases. During the first postnatal ontogenesis, the increase in length, width, and anteroposterior size of the heart occurs unevenly. From day 6, the length of the heart grows faster than its width and anteroposterior size, resulting in an elongated heart shape. The highest growth rate of anatomical parameters was observed in 6-day-old rats, and the increase in anteroposterior dimensions of the heart in 21-day-old rats ensured its conical shape. It was found that all dimensions of the heart of the experimental group rats were larger than in the control group.

Consequently, it was discovered that the experimental group's body weight and heart weight of cardiac rats were higher than those of the control group. Our study's findings indicated that on day 14, there was a discernible rise in both body and cardiac weight. The body weight was 35% higher and the heart weight was 19% higher than in the control group. When compared to the control group, these metrics increased body weight by 14% and heart weight by 10% in the second experience group, which involved the use of mexidol. There was a 1% to 9% increase in experimental group 1's heart's length, breadth, and anteroposterior dimensions when compared to the control group. Nevertheless, these values varied from 2% to 6% in the two experimental groups (see Diagram 6).

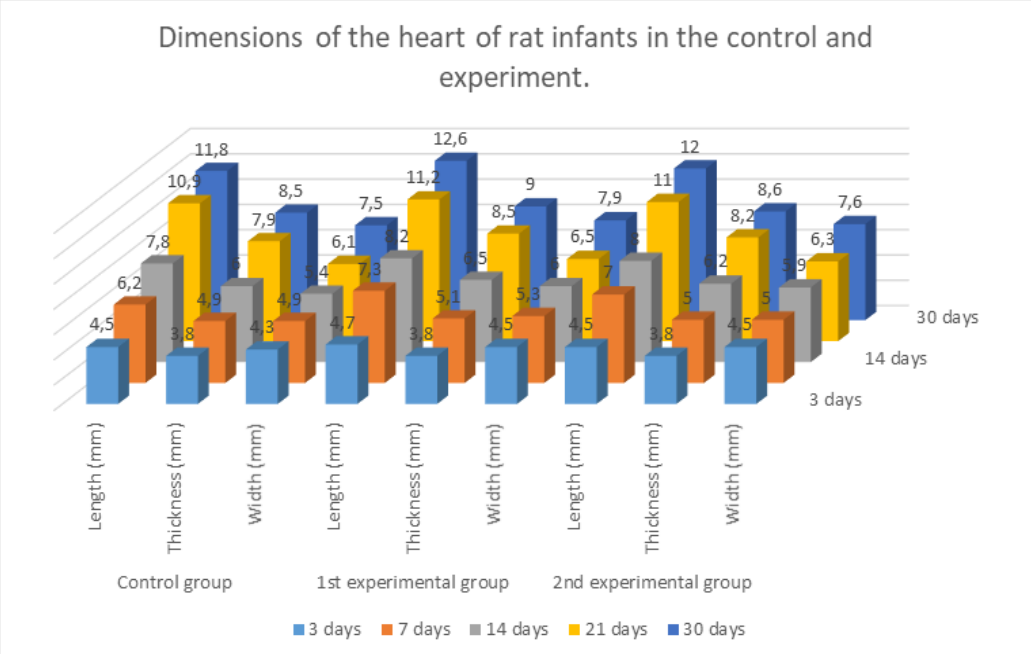


Diagram 6. Length, width, and anteroposterior dimensions of the heart of rat infants

In addition to the thyroid gland, we performed a morphological study of the ventricular wall. As a result of the histological study, the first signs of hypothyroidism appeared during the seventh day of the trial with fullness in the heart capillaries, stasis, and diapedesis, their perivascular tumors, swelling, and disorganization of connective tissue stroma. There were found dilated and full-blooded vessels in the subepicardial zone of the myocardium. There were primary tumors in the myocardial stroma. The tumor detected in the first days of the experiment was observed in the perivascular zone and manifested by its spreading to the myocardium during the following days of the experiment. The presence of edema in the myocardium resulted in swelling and rupture of collagenous fibers. Typical changes of the myocardium are edema of interstitial tissue, the fullness of vessels, dystrophic changes of the myocardium.

On the 14-21th day of the experiment, there was an increase in edema in the perivenous and pericapillary cavities. Collagen fibers were found to swell and signs of superficial disorganization of connective tissue began to appear. Blood vessels are rounded due to endothelial-cell swelling. In cardiomyocytes, a transparent cytoplasmic fluid appeared in the cytoplasm of small vacuoles. That is, it led to the development of hydrooptic dystrophy in cardiomyocytes. On the 14th day of the experiment, the cell tumor was focal, and on the 21st day, it was diffuse. It was noticed that fluid between cardiomyocytes caused the sliding of muscle fibers. Small infiltrates consisting of lymphocytes, histiocytes and fibroblasts appeared in myocardial tissue. The cardiomyocytes exhibit symptoms of protein hydropic dystrophy, many foci of plasmolysis are detected in the myocardium.

On day 30 of the experiment, the interstitial swelling intensified and spread throughout the myocardium. On this day of the experiment, cardiomyocyte damage was evident. The edema caused swelling of collagen fibers, which led to the rupture of their fibers. Myocardial tissue edema and disorganization of surrounding connective tissue fibers were revealed. Dystrophic changes of myocardium have diffuse character, increasing absorption of cytoplasm and tumor cells. Muscle twitches and focal tumors are revealed.

While using mexidol in the 2nd group of the experiment, the symptoms of hypothyroidism appeared later, i.e., on the 14th day of the experiment, and in the 1st group of the experiment - on the 7th day. These symptoms were manifested by edema around the vein and edema of some cardiomyocytes.

It appeared that the changes observed in the heart wall of rats of the 1st and 2nd experimental groups were characterized by a peculiar similarity when compared. These changes are diffuse interstitial swelling, diffuse intracellular swelling, myocytolysis, lymphocytic infiltration. At application of mexidol these changes had a focal character and were not reflected.

Consequently, there were observed adverse changes in the cardiac myocardium of rat infants born from hypothyroid mother rats. These changes are expressed in the form of hemomicrocirculatory bed, manifested by edema of interstitial stroma, destructive-dystrophic cellular changes. Mentioned changes are more pronounced on the 14th day of the experiment and deepen myocardial contractile dysfunction. In the experimental group, it also affects capillaries, leading to disruption of the transport function of the endothelium and other vascular wall structures, leading to the development of interstitial and intercellular tumors. During the following dynamic observation (14-21 days) we observed the appearance of fibroblasts and connective tissue fibers in the intermuscular and interstitial spaces, indicating the development of sclerotic processes in the myocardium.

Conclusion. Generation in the experimental group led to the development of intracellular and intracellular tumors as a result of disruption of the transport function of the rat cardiac vascular endothelium and exposure to other components of the vascular wall.

In the experimental groups of rats 1 and 2 the changes of diffuse interstitial edema, diffuse intracellular edema, myocytolysis, lymphocytic infiltration occured in the heart wall were peculiarly similar. When mexidol was used in the 2nd group of experiments, the symptoms of hypothyroidism appeared later, i.e., on the 14th day of the experiment, and in the 1st group of experiments - on the 7th day. As a result of implementing mexidol, these changes were focal and had no clear reflection.

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