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COMPARATIVE CHARACTERISTICS OF HISTOLOGICAL CHANGES IN THE KIDNEYS OF INTACT RATS AND UNDER THE INFLUENCE OF THE *LEIRUS MACROCTENUS* SCORPION VENOM

Abstract. A comparison and analysis of histological changes in the kidneys of intact rats and under the influence of the *Leiurus macroctenus* scorpion venom were carried out.

The aim of the study. To determine the differences in the histological organisation of the kidneys of intact rats and under the influence of the *Leiurus macroctenus* scorpion venom.

Materials and methods. The study used 10 white male laboratory rats weighing 200 g (±10 g). The rats selected for the experiment were divided into two groups: control group – 5 rats; no venom was administered, the material was collected one hour after the administration of saline solution; experimental group – 5 rats, histological material was collected 1 hour after the administration of the scorpion venom. The venom of scorpions of the Buthidae family, genus Leiurus, species Leiurus macroctenus, was administered to rats once intramuscularly (0,5 ml of venom solution previously dissolved in saline; 28,8 μg/ml; LD_{50}=0,08 mg/kg. Rats were euthanised by carbon dioxide inhalation. Rat kidneys were isolated at 4 °C immediately after euthanasia.

Kidney samples from animals of all groups were collected for microscopic examination. Histological samples of rat kidneys were stained with hematoxylin and eosin. Histological slides were studied using an SEO SCAN light microscope.

Results of the study. Microscopic examination of the kidneys of white laboratory rats of the intact group showed a typical histological organisation of the organ. Histological analyses of kidney samples 1 hour after the introduction of scorpion venom to the experimental animals established the onset of acute renal failure as a result of acute damage of the glomerular apparatus of nephrons, the onset of significant hemodynamic disorders and the initiation of inflammatory processes in the organ, in contrast to the control group of rats. Oedema was noted in the fibrous capsule. Hypertrophied renal corpuscles were found in the renal cortex. Initial signs of focal endothelial dystrophy were observed in the wall of the glomerular capillaries. In the proximal and distal renal tubules, the lumens were unevenly dilated with thinning of the walls. Epithelial damage was noted in the proximal and distal tubules.

Conclusions. In the group of intact rats, general patterns of the structural organisation of the kidneys were noted. Under the influence of the Leiurus macroctenus scorpion venom, toxic substances cause the development of significant hemodynamic disorders and the initiation of inflammatory processes in the organ in experimental rats, acute renal failure as a result of acute damage of the glomerular apparatus, disruption of the cytoskeleton of podocytes and the tubular apparatus of nephrons with manifestations of desquamation, hydropic, hyaline-droplet dystrophy of the tubular epithelium.

Keywords: venom, scorpions, kidneys, inflammation, rats.

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ПОРІВНЯЛЬНА ХАРАКТЕРИСТИКА ГІСТОЛОГІЧНИХ ЗМІН НИРОК ІНТАКТНИХ ЩУРІВ ТА ЗА УМОВ ДІЇ ОТРУТИ СКОРПІОНІВ *LEIRUS MACROCTENUS*

Анотація. Проведено порівняння та аналіз гістологічних змін нирок інтактних щурів за умов дії отрути скорпіонів *Leiurus macroctenus*.

Мета дослідження. Визначити відмінності гістологічної організації нирок інтактних щурів та за умов дії отрути скорпіонів *Leiurus macroctenus*.

Матеріали та методи. У дослідженні використано 10 білих лабораторних щурів-самців масою 200 г (±10 г). Відібрані для експерименту щури були розподілені на дві групи: контрольна – 5 щурів, введення отрути не проводилось, забір матеріалу через годину після введення фізіологічного розчину; експериментальна – 5 щурів, відбір гістологічного матеріалу через 1 год після введення отрути. Отруту скорпіонів родини Buthidae роду Leiurus виду Leiurus macroctenus вводили щурам одноразово внутрішньом'язово (0,5 мл розчину отрути попередньо розчиненому у фізіологічному розчині; 28,8 мкг/мл; $ЛД_{50}$=0,08 мг/кг. Щурів піддавали евтаназії за допомогою інгаляції вуглекислого газу. Виділення нирок щурів проводили при 4 °С відразу після евтаназії.

Для мікроскопічного дослідження забирали зразки нирок тварин всіх груп. Фарбування гістологічних препаратів нирок щурів здійснювали гематоксиліном та еозином. Гістологічні препарати вивчали за допомогою світлового мікроскопа SEO SCAN та фотодокументували за допомогою відеокамери Vision CCD Camera з системою виводу зображення з гістологічних препаратів.

Результати дослідження. Проведене мікроскопічне вивчення нирок білих лабораторних щурів інтактної групи показало типову гістологічну

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організацію органу. Дослідження гістологічних препаратів нирки через 1 годину після введення піддослідним тваринам отрути скорпіона встановили початок розвитку гострої ниркової недостатності як наслідок гострого ураження гломерулярного апарату нефронів, початку значних гемодинамічних розладів та запуску запальних процесів в органі на відміну від контрольної групи щурів. У фіброзній капсулі відмічали набряк. В кірковій речовині зустрічалися гіпертрофовані ниркові тільця. В стінці гломерулярних капілярів спостерігалися початкові ознаки вогнищевої дистрофії ендотелію. В проксимальних та дистальних ниркових канальцях просвіти були нерівномірно розширені з витонченням стінок. В проксимальних та дистальних канальцях відмічали пошкодження епітелію.

Висновки. В групі інтактних щурів відмічали загальні закономірності структурної організації нирок. За умов введення отрути скорпіона *Leiurus macroctenus* через 1 годину токсичні речовини спричиняють в експериментальних щурів початок розвитку значних гемодинамічних розладів та запуску запальних процесів в органі, гострої ниркової недостатності як наслідок гострого ураження гломерулярного апарату, порушенням цитоскелету подоцитів та тубулярного апаратів нефронів з проявами десквамації, гідропічної, гіаліново-крапельної дистрофій епітелію канальців.

Ключові слова: отрута, скорпіони, нирки, запалення, щури.

Statement of the problem. To date, there is data on about 2000 species of scorpions. Most are dangerous to humans, especially representatives of the Buthidae, Scorpionidae and Hemiscorpionidae families. Clinical manifestations of poisoning with scorpion toxins vary significantly, depending on their species and the amount of poison that has entered the victim's body [1, 2, 3, 4]. Researchers note that the content of their venom is highly complex and heterogeneous. Its most studied components are currently small peptides due to their diversity and broad pharmacological properties. According to the structure, small peptides are classified into three large superfamilies: peptides containing cysteine (CS) stabilised α / β motifs with the presence of disulfide bridges, calcins and peptides that do not contain disulfide bridges [5, 6, 7, 8, 9]. However, it has been established that the toxic components of scorpion venom, enzymes, mixtures of inorganic salts, free amino acids, nucleotides, and lipids are also distinguished [10, 11, 12].

Connection of the publication with planned scientific research works. Among the currently known pathological processes associated with scorpionism, according to experimental studies, kidney damage is considered one of the most critical complications, which is often fatal [13, 14, 15]. In particular, it is noted that Hemiscorpius lepturus and Androctonus australis exhibit a pronounced nephrotoxic effect. Toxic compounds of their venom can directly or indirectly affect the kidney tissue, causing mesangiolysis, the development of glomerulonephritis, vasculitis, interstitial nephritis, cortical, tubular necrosis, as well as hypoxia and renal

infarction [16, 17]. Of the indicated pathologies, tubular necrosis is most often observed in victims, which is characterised by a decrease in reabsorption and an increase in the secretion processes of Na+, K+, and CL^-. It has been demonstrated that inoculation of venom affects Na+ channels in the kidneys. At the same time, there is an increase in the blood levels of catecholamines in the victims. In the cytosol of nephron tubular cells, under conditions of poisoning with scorpion toxins, the concentration of Ca2+ ions increases. The body's protective mechanisms contribute to the growth of pro-inflammatory cytokines in the renal parenchyma, namely IL, TNF-α, NO, platelet aggregation factor, PG, leukotrienes, kinins, angiotensin and ET. Clinical cases of bites accompanied by rhabdomyolysis, hemolysis and disseminated intravascular coagulation are known to date. These processes contributed to the development of acute renal failure due to damage to the glomerular apparatus and were associated with haemoglobin and proteinuria. The action of PLA2 poison can also cause acute kidney injury. The enzymes in these conditions exhibit hemolytic and cytotoxic effects on the organ. In addition, it promotes the growth of arachidonic acid and, accordingly, the synthesis of eicosanoids. There is also evidence of increased activity of the hypothalamic-pituitary-adrenal system, which stimulates the production of corticosteroids. At the same time, an increase in the levels of acute phase proteins and significant hemodynamic disorders are recorded. It is known that the accumulation of a substantial number of hemoproteins accompanies hemolysis phenomena. Under these conditions, heme groups increase the production of free radicals that accumulate in the renal cortex, having a toxic effect. An increase in the activity of NADPH oxidase facilitates the production of ROS. In this case, apoptosis or necrosis of kidney cells is a frequent consequence [18].

Movahed A. et al. [19], studying the effect of the venom of the scorpion Hemiscorpius lepturus on the morphology of the kidneys, histological examination revealed the expansion of the lumen and thinning of the walls of the proximal tubules of the nephron, the accumulation of fibrin in the glomerular apparatus. The glomerular capillaries contained clusters of erythrocytes, and the endothelium of their walls was swollen 4 hours after the introduction of the venom to laboratory animals. In the proximal tubules, flattening of the epithelial cells of their inner membrane, loss of their brush border, and an atypical reaction of the nuclei of these cells were noted, which indicated the development of acute tubular necrosis.

A careful analysis of the scientific literature demonstrated the participation of macrophages in the development of acute kidney injury in scorpion bites. Thus, the level of MCP increases in the victim's body, which indicates the launch of an inflammatory process in the organ and signals the risk of complications since it directly affects the migration of macrophages, proliferation and differentiation of leukocytes in the epithelium of the human kidney tubules. MCP-1 stimulates the secretion of IL-6 and the intercellular expression of ICAM-1. In addition, binding to chemokine receptors CC2 on the surface of podocytes can reduce the expression of

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both microRNA and nephrin protein. The latter forms filtration gaps, so defects in this protein lead to renal failure, disruption of the podocyte cytoskeleton, and disorders of the filtration process [20].

The purpose of the article. To determine the differences in the histological organisation of the kidneys of intact rats and those exposed to the venom of the scorpion Leiurus macroctenus.

Research objects and methods. The venom of scorpions of the Buthidae family, genus Leiurus, species Leiurus macroctenus, was administered to rats once intramuscularly (0.5 ml of venom solution previously dissolved in saline; 28.8 μg/ml; LD50=0.08 mg/kg) [21, 22].

The study used 10 white male laboratory rats weighing 200 g (±10 g), grown in the vivarium of the Educational and Scientific Center "Institute of Biology and Medicine" of Taras Shevchenko National University of Kyiv (agreement on scientific and practical cooperation between Taras Shevchenko National University of Kyiv, Vinnytsia National Medical University named after M. I. Pirogov and Ternopil National Medical University named after I. Ya. Horbachevsky of the Ministry of Health of Ukraine, dated February 1, 2021). Rats were kept on a standard diet in an accredited vivarium by the "Standard Rules for the Arrangement, Equipment and Maintenance of Experimental Biological Clinics (Vivaria)". The experiments were conducted according to the current regulatory documents regulating the work organisation with experimental animals and compliance with the principles of the "European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes" [23]. Also, all work with animals was carried out by the Law of Ukraine No. 3447-IV of February 21, 2006, "On the Protection of Animals from Cruelty and Ethical Norms and Rules for Working with Laboratory Animals". The rats selected for the experiment were divided into two groups: control - 5 rats; no poison was administered, the material was collected one hour after the administration of saline; experimental - 5 rats, histological material was collected 1 hour after the administration of poison. Rats were euthanised by carbon dioxide inhalation. Kidneys were isolated at 4 °C immediately after euthanasia.

Kidney samples from animals of all groups were collected for microscopic examination. The pieces were fixed in a 10% formalin solution for 1 day. They were then dehydrated in alcohols of increasing concentration and embedded in paraffin blocks. Histological preparations of rat kidneys were stained with hematoxylin and eosin [24, 25]. Histological preparations were examined using an SEO SCAN light microscope and photographed using a Vision CCD Camera with a system for displaying images from histological preparations.

Presentation of the primary material.

Research results and their discussion. Microscopic examination of the kidneys of white laboratory rats of the intact group showed a typical histological organisation. The stroma of the kidney is represented by a fibrous capsule of dense

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fibrous connective tissue and the interstitium - thin layers of loose connective tissue. In the interstitial stromal tissue of the organ, there is a dense network of vessels of the hemomicrocirculatory bed (peritubular capillary network). The kidney parenchyma is formed by tortuous, thin, straight and collecting tubules lined with epithelial cells. The structural and functional unit of the kidney is the nephron, which includes the renal corpuscle and tortuous and straight tubules. The renal corpuscle is formed by a glomerulus of hemocapillary loops, mesangium and Shumlyansky-Bowman capsule. Near the urinary pole of the renal corpuscle, the tortuous part of the proximal tubule begins, lined with a single-layered prismatic epithelium lying on a continuous basement membrane. A characteristic feature is that the lumen of the tubule is not contoured or slit-like due to the microvilli of the brush border. The distal tubules have a clear lumen lined with a single-layered cubic epithelium. At the apical pole of the epithelium, there are single microvilli and well-pronounced basal striation. Epitheliocytes have one round nucleus in the centre and a weakly oxyphilic cytoplasm. The collecting tubules in the cortical substance are lined with a single-layered cubic epithelium, and in the medulla – with a single-layered prismatic epithelium (Fig. 1).

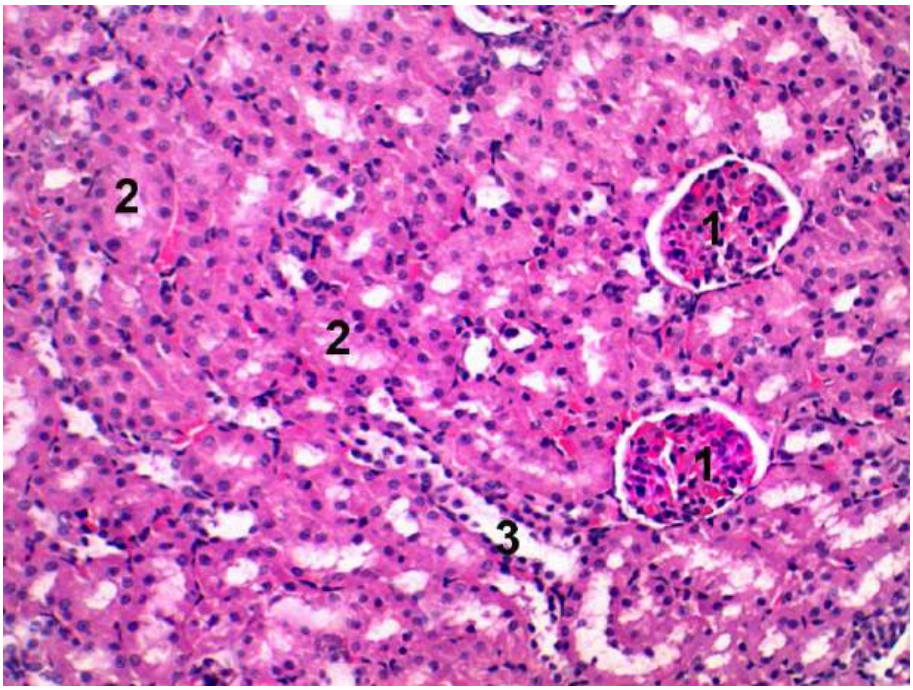

Fig. 1. Microscopic organisation of the kidney of an intact group of animals. 1 - renal corpuscles, 2 - proximal tubules, 3 - distal tubule. Staining with hematoxylin-eosin. x 200

Histological studies of kidney preparations 1 hour after the introduction of scorpion venom into the experimental animals established the onset of acute renal failure as a result of acute damage to the glomerular apparatus of nephrons, the onset

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of significant hemodynamic disorders and the initiation of inflammatory processes in the organ, in contrast to the control group of rats.

The fibrous capsule was edematous and easily peeled off from the organ. Dilation and engorgement of the venous vessels and ischemia of the arterial vessels were observed. In the interstitium of the organ around the vessels of the microcirculatory bed, perivascular oedema with infiltration by lymphocytes, macrophages, and histiocytes was noted. The hemocapillaries were spasmodic and engorged with increased intracapillary aggregation of erythrocytes.

In the cortical substance, next to the renal corpuscles, which retained a typical histological structure, hypertrophied renal corpuscles were found, in which the lumen of the afferent and efferent arterioles was spasmodic with moderate anaemia. In their lumens, increased erythrocyte aggregation was detected. The wall of the arteries and arterioles was thickened due to hypertrophy and slight leukocyte infiltration of the media, smooth myocytes, losing their spindle-shaped shape, became rounded, their nuclei were hyperchromic, and the cytoplasm was brightly oxyphilic. Slight oedema and lymphohistiocytic infiltration were noted in the subendothelial layer of the intima and adventitia. The endothelial cells of their intima had a cubic shape, and there was slight oedema in the cytoplasm. The nuclei were hyperchromic, and their plasmalemma was indistinct and formed significant protrusions into the lumen and invaginations. The basement membrane is continuous, but in some places, there are signs of endothelial desquamation (Fig. 2).

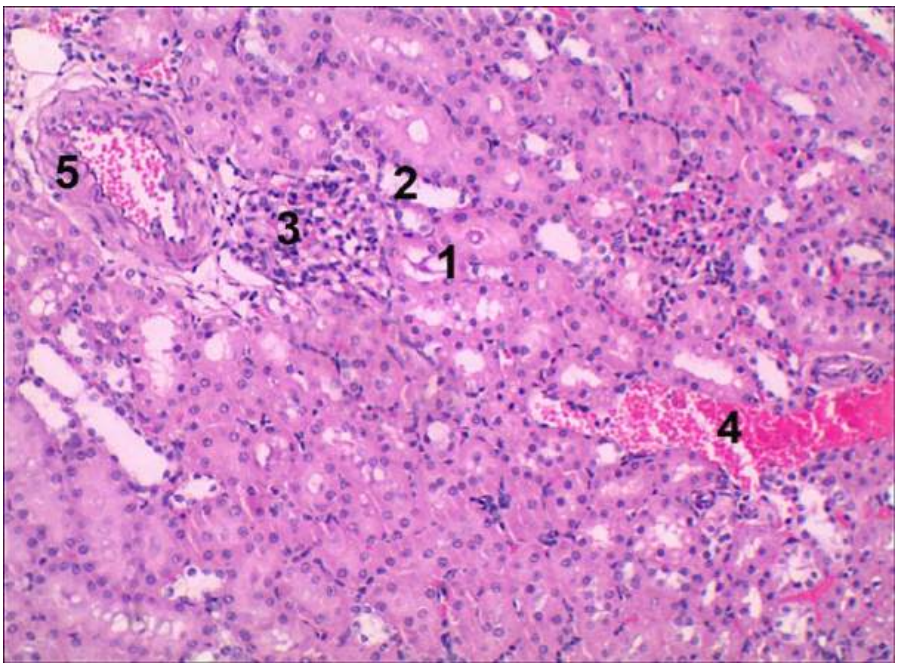

Fig. 2. Microscopic organisation of the kidney of white rats 1 hour after the introduction of scorpion venom. 1 - dystrophy of proximal tubules with an accumulation of cellular detritus in the lumen, 2 - the destruction of distal tubules, 3 - hypertrophied renal corpuscle, 4 - an area of haemorrhage, 5 - destructured artery. Staining with hematoxylin-eosin. x 200

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In the glomerular vascular glomeruli, there was anaemia; in their lumens, there was stasis. In some places, their lumens collapsed due to spasms of the afferent arteriole. The urinary spaces were sharply dilated. In the wall of the glomerular capillaries, initial signs of focal endothelial dystrophy were observed. The cytoplasm of endothelial cells was swollen, and the nuclei were hypertrophied, hyperchromic, and significantly protruded into the vessel's lumen. The basement membrane was thickened and swollen. Due to the increased proliferative activity of mesangiocytes, the mesangium expanded, and the amount of matrix increased. Hyperplasia of the mesangium and pleurisy of the glomerular capillaries caused a sharp narrowing of the urinary space of the renal corpuscles; in most fields of view, it looked slit-like or was not visualised at all (Fig. 3). The cells of the outer leaf of the Shumlyansky-Bowman capsule are sharply flattened, their nuclei are hyperchromic with invaginations of the karyolemma, the basement membrane is thickened. The growth of the mesangium leads to disruption of the cytoskeleton of podocytes of the inner leaf of the capsule. Disorganisation of cytopodia and cytotrabeculae of podocytes occurs, resulting in the beginning of the process of filtration disorders. In the proximal and distal renal tubules, the lumens were unevenly expanded with thinning of the walls. Damage to the epithelium was noted in the proximal and distal tubules. The brush border and basal striation are especially noticeable dystrophic changes. Focal cells almost completely lose them, and the epithelium's desquamation into the tubule's lumen is observed. The cells show signs of hydropic and hyaline-droplet dystrophy, characterised by the appearance of vacuoles and single acidophilic granules in the weakly oxyphilic cytoplasm, indicating cytoplasmic oedema. The nuclei are hyperchromic, compacted, and have indistinct contours. Fibrin accumulations were detected in the lumens of the tubules. In thin tubules, hyperplasia of epithelial cells is due to oedema of their cytoplasm. On the cross-section, thin tubules with slit-like lumens. When tubules with moderately dilated lumens are collected, epithelial cells almost completely lose microvilli and basal striation in their cytoplasm, oedema, and single vacuoles in the weakly oxyphilic cytoplasm. The nuclei are hyperchromic and compacted. Along the course of the vessels of the microcirculatory bed of the interstitium, both in the cortex and the medulla, local single haemorrhages occur (Fig. 3).

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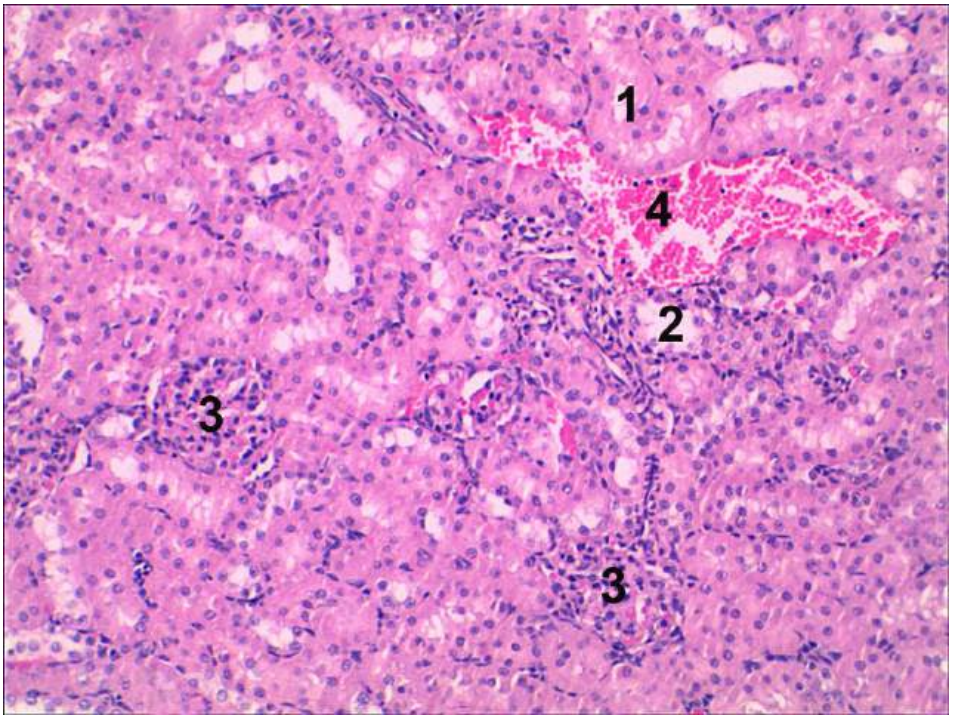

Fig. 3. Microscopic structure of the kidney of white rats 1 hour after the introduction of scorpion venom. 1 - dystrophy of proximal tubules, 2 - destruction of distal tubules, 3 - renal corpuscles with no urinary space, 4 - area of hemorrhage. Staining with hematoxylin-eosin. x 200

Conclusions. In the group of intact rats, general patterns of the structural organisation of the kidneys were noted. Under the conditions of administration of the venom of the scorpion Leiurus macroctenus, after 1 hour, toxic substances cause the development of significant hemodynamic disorders and the initiation of inflammatory processes in the organ in experimental rats, acute renal failure as a result of acute damage to the glomerular apparatus, disruption of the cytoskeleton of podocytes and the tubular apparatus of nephrons with manifestations of desquamation, hydropic, hyaline-droplet dystrophy of the tubular epithelium.

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