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## **MORPHOLOGICAL CHANGES OF THE PANCREAS AND LIVER DURING ACUTE EXPERIMENTAL PANCREATITIS AND CORRECTION OF CYTOCHROME C.**

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**Abstract.** The article describes morphofunctional changes of pancreas parenchyma and liver, in the modelling of acute experimental pancreatitis and its correction with cytochrome C, Sandostatin and their complex application. The treatment of experimental pancreatitis with cytochrome C has been associated with a decrease in the volume of discirculatory, dystrophy, destructive and inflammatory changes in both the pancreas and the liver.

**Keywords.** Acute pancreatitis, pancreas, liver, morphology, cytochrome.

In recent years, the incidence of acute pancreatitis (AP) has been steadily increasing worldwide, reaching 300-900 patients per million population per year, according to modern literature. [1]. Acute pancreatitis is one of the most severe illnesses in urgency abdominal surgery. In spite of the achieved successes in the improvement of diagnostics, intensive and antibacterial therapy, surgical methods of treatment the total lethality in severe acute pancreatitis during the last decade remains at a high level of about 10-30% and reaches 85% during the last decade [2]. In Europe and the United States, prevalence and mortality rates are lower and have remained stable over the past five years. In comparison, about 17 cases of acute pancreatitis per 100,000 people are reported annually in the United States. The number of hospitalized patients reaches 100,000 per year, of which 20 percent of clinical observations are of a severe and destructive nature. According to the American Gastroenterological Association, 1/5 patients develop severe forms of disease. The mortality rate among hospitalized patients with complicated forms of disease is 10-30% [3]. Excessive or prolonged stressors pose a risk of persistent dysfunction of homeostasis. Therefore, the liver, as the most multifunctional organ, which has a unique role in regulating the constancy of the body's internal environment, is highly sensitive to both acute and chronic stressors [4]. Due to the wide heterogeneity of the extremes and the influence of the initial state of the organism, the hepatropic effects of stressors are manifold and are expressed by both morpho-functional and metabolic alterations [5].

Recently, there has been a significant increase in the incidence of chronic and acute pancreatitis. Therefore, the study of the mechanisms of development, course, diagnosis and treatment of this pathology is becoming an extremely urgent problem today. The steady growth of this contingent of patients, the ambiguity of approaches to treatment tactics and unsatisfactory treatment results determine the need for further development of the clinical aspects of this pathology. Considering the above, the use of cytochrome C in the treatment of acute pancreatitis and the assessment of its effect on morphological changes in the liver and pancreas remains an urgent problem that needs to be addressed.

**The aim of research** – to study the morphological characteristics of pancreas and liver in acute experimental pancreatitis and cytochrome C correction.

**Materials and methods of research.** The experiments were carried out on 50 sexually mature outbred male rats with an initial body weight of 120-140 g. contained on a standard diet. The experiments were guided by the "European Convention for the Protection of Vertebrate Animals Used for Experiments and Other Scientific Purposes" (Strasbourg, 1985). Acute experimental pancreatitis was induced in rats by the method of P.S.Simovaryan [6]: local freezing of the surface of the pancreas with ethyl chloride.

To determine the degree of damage to the pancreas the activity of amylase in the blood was determined. The animals were slaughtered on the 10<sup>th</sup> day after the operation.

In the second series of experiments (10 rats), we studied the corrective effect of cytochrome C on the morphology of the pancreas and liver during the development of experimental acute pancreatitis. For this, the animals of the control and experimental groups were injected daily for 10 days with cytochrome C at a dose of 0.15 mg per day per kg of body weight. The drug was administered intramuscularly, the course of treatment was 10 days.

In the third series of experiments, the animals were injected (10 rats) with sandostatin - 0.007 mg per kg of body weight, and the morphology of the pancreas and liver was studied during the development of experimental acute pancreatitis.

In the fourth series of experiments, animals were simultaneously injected with cytochrome C and sandostatin, and studied indicators of pancreatic and liver morphology in the development of experimental acute pancreatitis. For this purpose, the animals of the control and experimental groups were daily administered cytochrome C at a dose of 0.15 mg per day per kg body weight, and a 0.007 mg per kg body weight inhibitor of the protease sandostatin.

Cytochrome C is a particularly important small heme-containing protein that transmits electrons from the cytochrome C reductase to the cytochrome C-oxidase between the internal and external membranes of the mitochondrial brane [7]. In the fourth series of experiments, the animals were simultaneously injected with cytochrome C and sandostatin, and the parameters of the morphology of the pancreas and liver were studied during the development of experimental acute pancreatitis. For this, the animals of the control and experimental groups were injected daily for 10 days with cytochrome C at a dose of 0.15 mg per day per kg of body weight, the protease inhibitor sandostatin at a dose of 0.007 mg per kg of body weight.

Cytochrome C is a particularly important small heme-containing protein that transfers electrons from cytochrome C-reductase to cytochrome C-oxidase between the inner and outer membranes of mitochondria [7].

The drug Sandostatin® is a synthetic octapeptide, which is a derivative of the natural hormone somatostatin and has similar pharmacological effects, but a longer duration of action. The drug suppresses the pathologically increased secretion of growth hormone (GH), as well as peptides and serotonin produced in the gastroentero-pancreatic endocrine system.

To establish a comparative assessment of cytochrome C and sandostatin, morphological studies of the pancreas and liver were carried out. Histological sections were prepared on a microtome 5-8  $\mu\text{m}$  thick and stained with hematoxylin and eosin and Van Gieson. The sections were examined under a light microscope.

**Results and discussions.** The tissue of the pancreas consists of different shapes and sizes of acini of the exocrine part, cellular-fibrous interstitial tissue and single islets of Langerhans (Fig. 1). Exocrine acini are more intensely stained with both eosin and hematoxylin. Prismatic acini cells are juicy, large, the cytoplasm is intensely eosinophilic, the nucleus is located on the basal part of the cells, the chromatin of the karyoplasm has hematoxylin concentrations in the karyoplasm. Interstitial connective tissue consists of randomly located fibrous structures, a few elongated nuclei of fibroblasts and fibrocytes. In some places in the interstitium there are blood vessels and excretory ducts of the exocrine part of the gland, which are covered with a single-layer densely located prismatic epithelium.

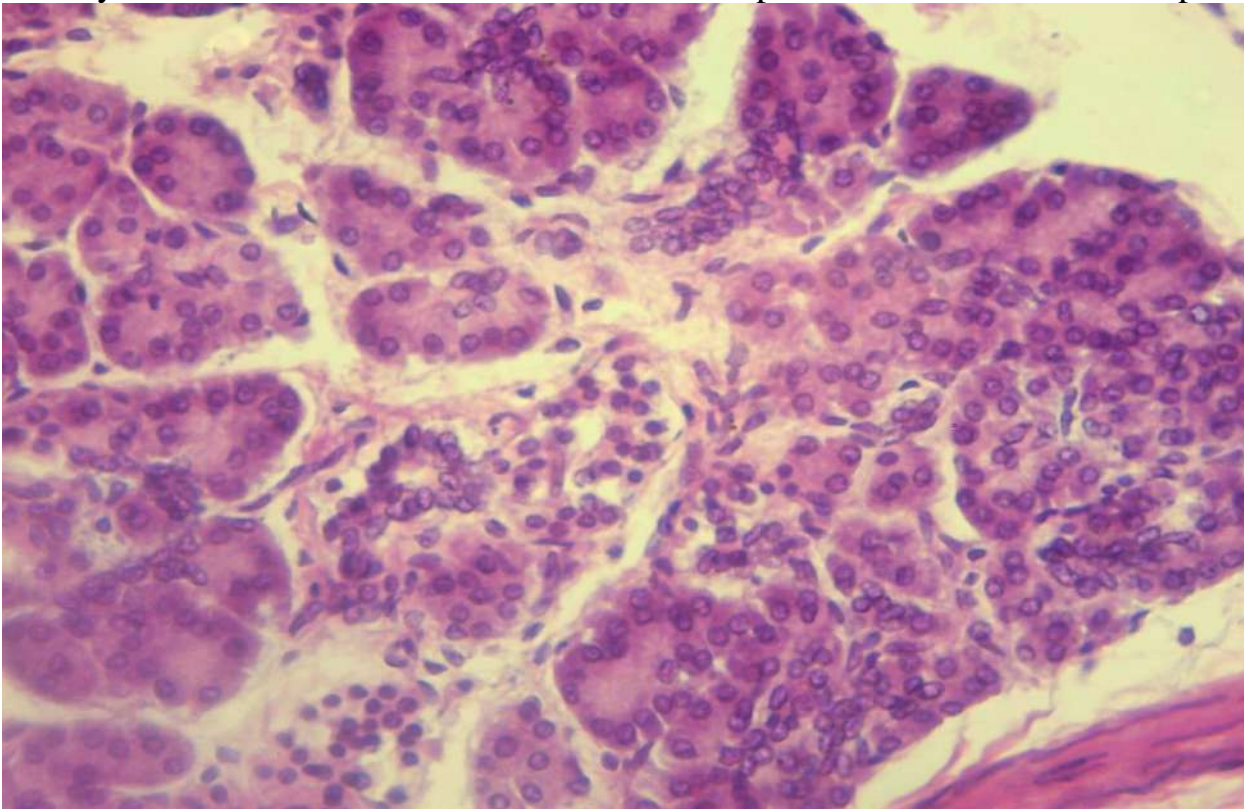


Figure 1. Pancreas gland of intact rat. Coloration: G. E.Uv: 10x20.

When analyzing the results of the study of intact animals, a typical morphological structure of the liver was noted. The organ is represented by lobules that do not have clear boundaries and are separated by a thin layer of connective tissue. The interlobular connective tissue of the rat liver is poorly developed; the outlines of the lobules can be judged by the location of the central vein and portal tracts. The parenchyma of the lobules is formed by the hepatic tracts radially located around the central vein (Fig. 2). Hepatocytes have a polygonal shape, the cytoplasm looks granular with one, rarely two

nuclei of a regular round or elongated shape. The nucleus is located in the center of the cell and contains one or more nucleoli. Portal tracts are represented by triads: arteriole, venule and bile ducts (Fig. 3). Arterioles have a well-defined intima, an internal elastic membrane and several layers of smooth muscle cells in the middle layer of the wall. The lumen of the veins is wide, limited by one layer of the endothelium, their wall is devoid of smooth muscle cells. Interlobular bile ducts are located in the center of the portal tracts, the wall is lined with cuboid epithelial cells. The nuclei of these cells are small, rounded, and the cytoplasm is poorly developed. The stroma of the portal tracts contains single macrophages, histiocytes, lymphocytes and polymorphonuclear leukocytes. Sinusoidal capillaries inside the lobules are very small vessels, their walls are lined with endothelium. Leukocyte infiltrates and connective tissue fibers are not detected in the parenchyma.

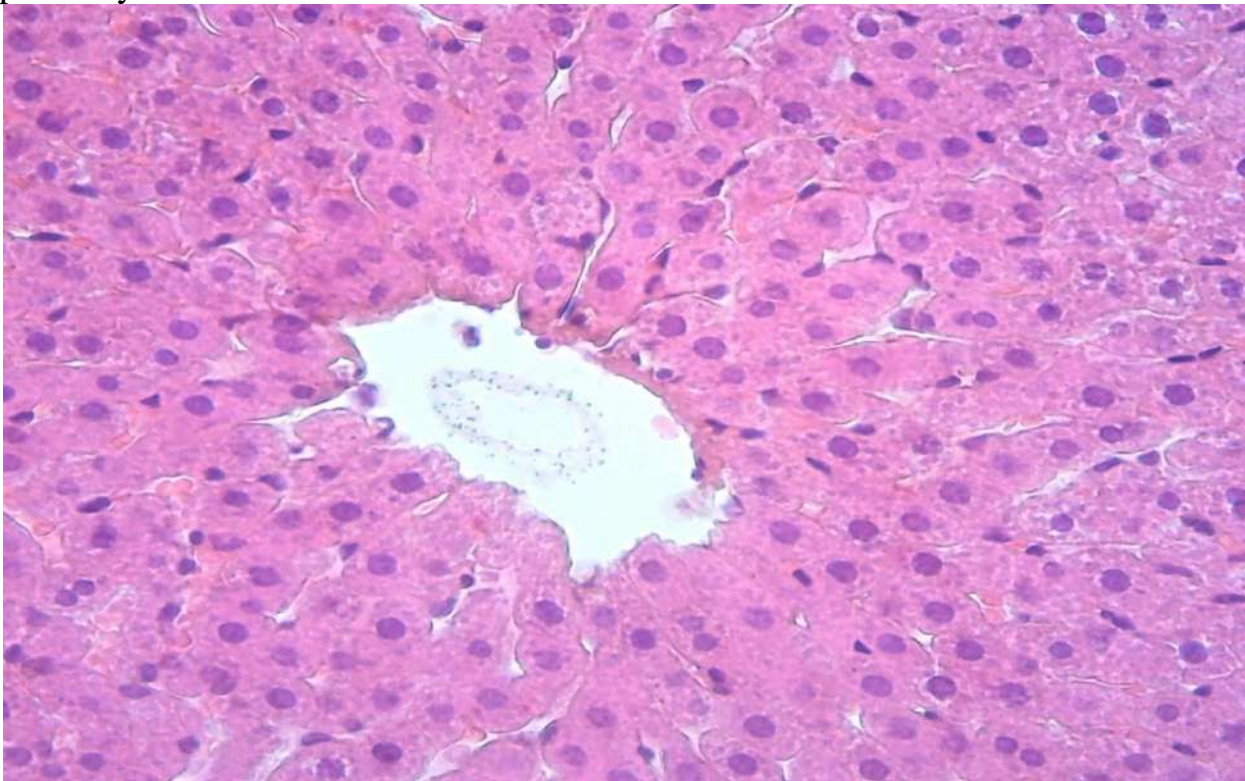


Figure 2. Central vein and radially positioned hepatocytes of the liver of intact animals.  
Coloration: G. E.

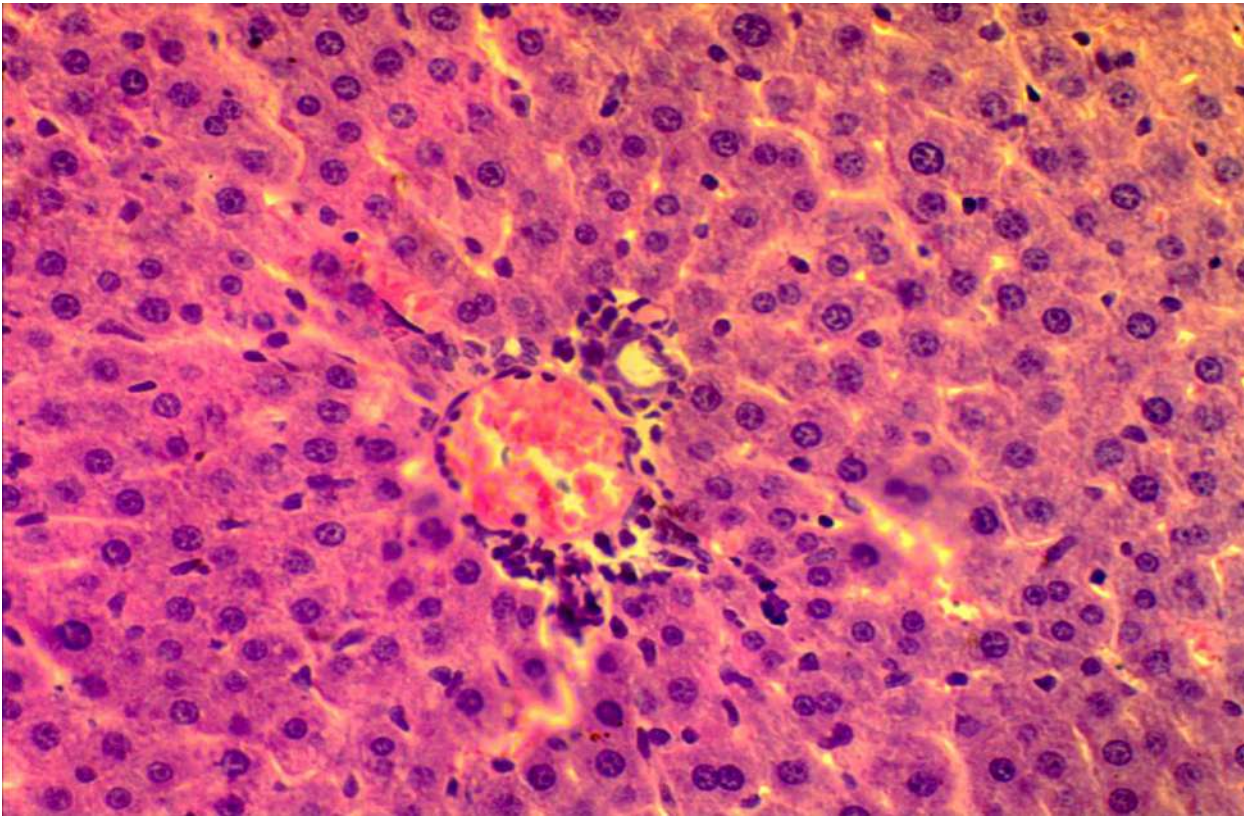


Figure 3. Triad of hepatic vessels of intact animals with small lymphoid infiltrate.  
Coloration: G. E.

The results of studying the tissue of the pancreas after modeling pancreatic necrosis showed the presence of foci of necrobiosis and necrosis of the parenchymal elements of the gland in the form of a non-structural mass. At the same time, the interstitial stromal tissue is edematous, loosened and infiltrated with inflammatory cells (Fig. 4). Examination of the pancreatic tissue on a large microscope objective showed that necrotic areas are represented by a structureless mass consisting of a homogeneous eosinophilically stained albuminous substance, in the thickness of which single remnants of cellular structures are determined (Fig. 5). In the circumference of necrosis, the interstitial connective tissue is in a state of severe edema, loosening of the fibrous-cellular structures. The cells contain inflammatory cells from leukocytes, lymphocytes and macrophages. Vessels of the interstitium are sharply dilated, full-blooded, their wall is thinned with diapedetic hemorrhages. Exocrine acini are loosened due to severe edema of the interstitial substance. Epithelial cells of acini have impaired histotopography in the form of denuded nuclei, vacuolization of the cytoplasm, and deformation of the acinar arrangement of cells.

In the tissue of the pancreas tissue, the focus of necrosis, interstitial tissue and exocrine acini are infiltrated by inflammatory cells. Macrophages and large connective tissue cells from fibrocytes and histiocytes predominate around necrosis in the inflammatory infiltration. At the same time, macrophages and lymphoid cells penetrate into the thickness of the necrotic mass, forming a diffuse and loose infiltration (Fig. 6).

The acini of the exocrine glands are loosened due to severe edema and infiltration of interstitial tissue by inflammatory cells. The epithelial cells of the acini retain the staining of the nucleus with hematoxylin, the cytoplasm with eosin.

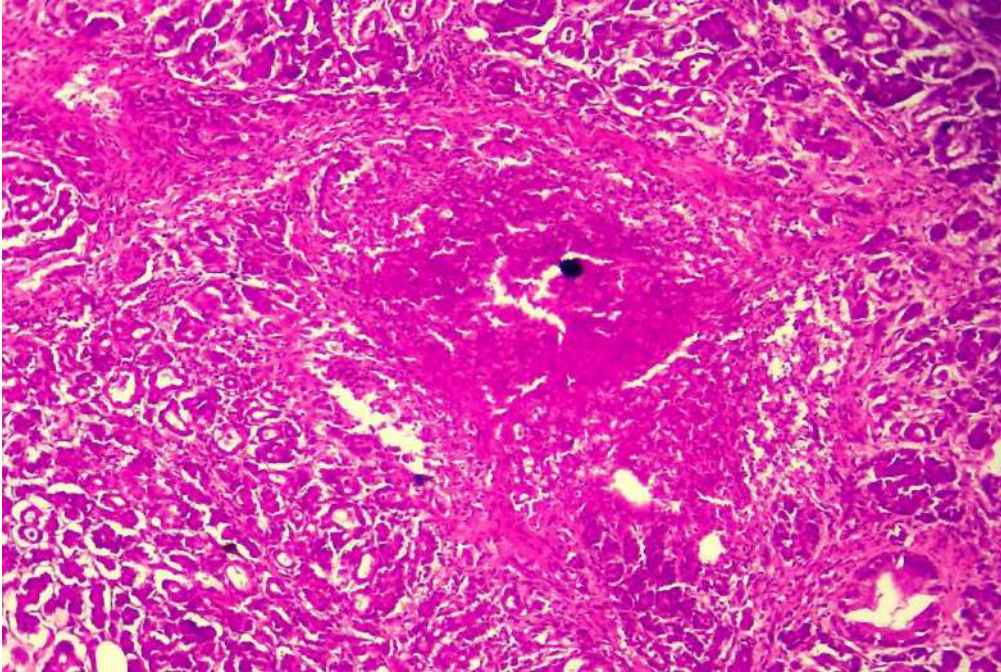


Figure 4. Pancreonecrosis unwarranted. Pancreole gland tissue has a source of necrosis.  
Coloration: G. E: 10x10.

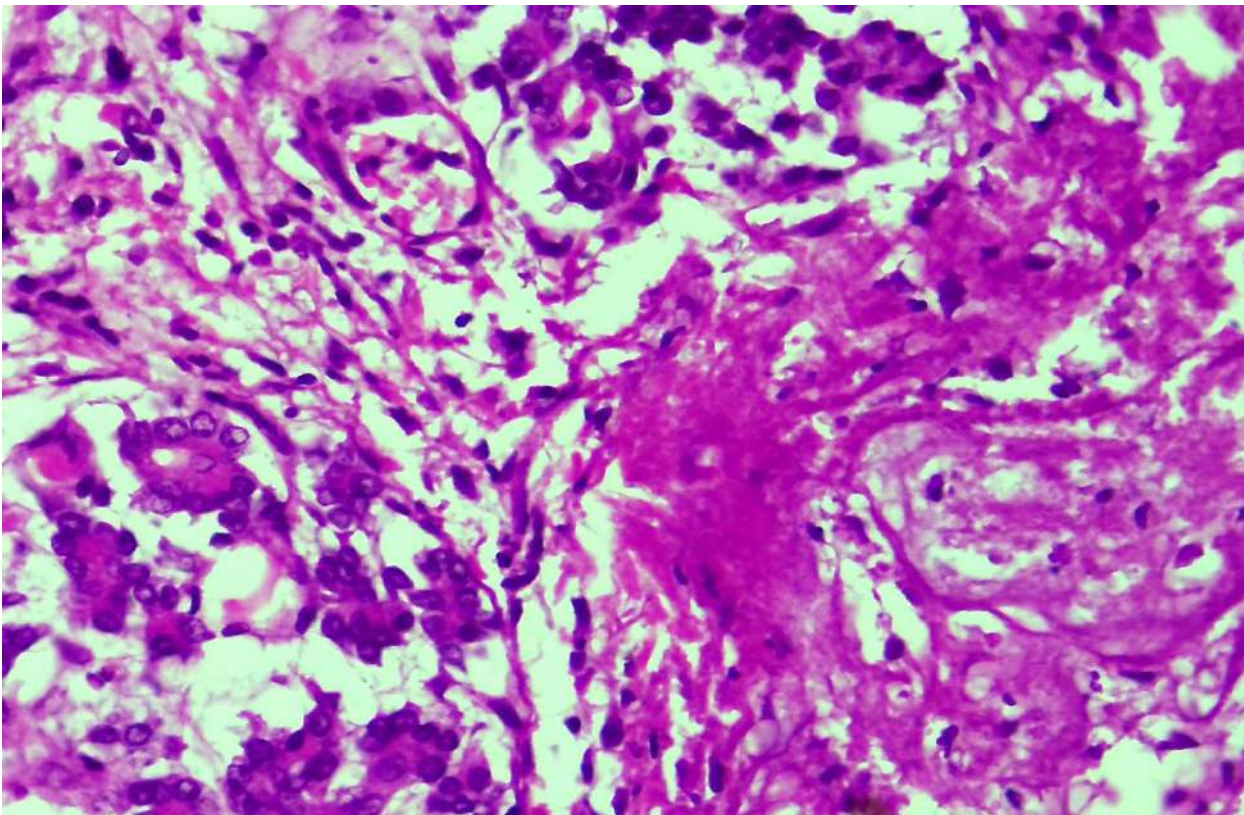


Figure 5. Pancreonecrosis non-prozen. Necrosis hotspot is represented by nonstructural mass and cellular residues. Coloration: G. E.Uv: 10x40.



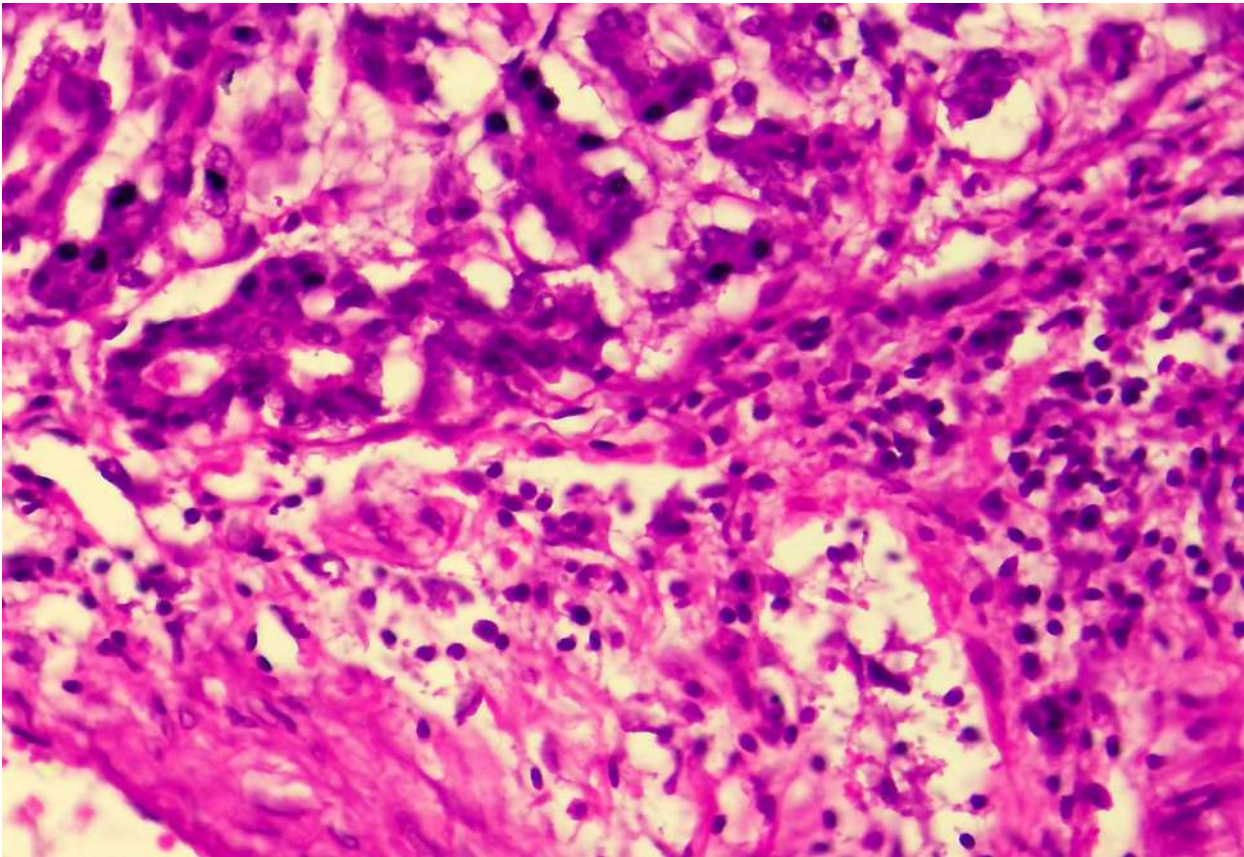


Figure 6. Pancreonecrosis non-proleptic. Infiltration by inflammatory cells of necrotic mass. Coloration: G. E: 10x40.

The results of a morphological study of the liver in experimental pancreatitis showed that discirculatory, dystrophic, destructive and inflammatory changes develop in the liver tissue. Dystrophic and destructive changes prevail in the liver parenchyma. In hepatocytes of all morphofunctional zones of the liver tissue, pronounced vacuolar degeneration is noted in the form of destruction of the matrix of the cytoplasm of hepatocytes. Due to vacuolization of the cytoplasmic matrix, the white protein contents are fragmented, denatured, some cells are in a state of necrobiosis and necrosis (Fig. 7). The nuclei of hepatocytes are round in shape with impaired chromatin concentration, some of them are in a state of karyolysis and karyopycnosis. Due to the swelling of hepatocytes, the space of Disse and the sinusoid is undetectable. In the periportal zone of the liver tissue, there is an increase in the proliferative activity of the connective tissue elements of the vascular wall in the form of hypertrophy and hyperchromasia of nuclear structures. Where the appearance of foci of hemorrhage and accumulation of neutrophilic leukocytes is also noted (Figure 8). The hepatocytes of this zone are also in a state of hydropic degeneration and necrobiotic changes.

**Conclusion.** Experimental pancreatitis was manifested by the appearance of foci of necrosis, inflammatory infiltration, disorganization of the parenchyma and stroma-vascular component of the gland. In the liver, the development of dystrophic, destructive

and inflammatory changes was noted, and in all morphofunctional zones of the organ.

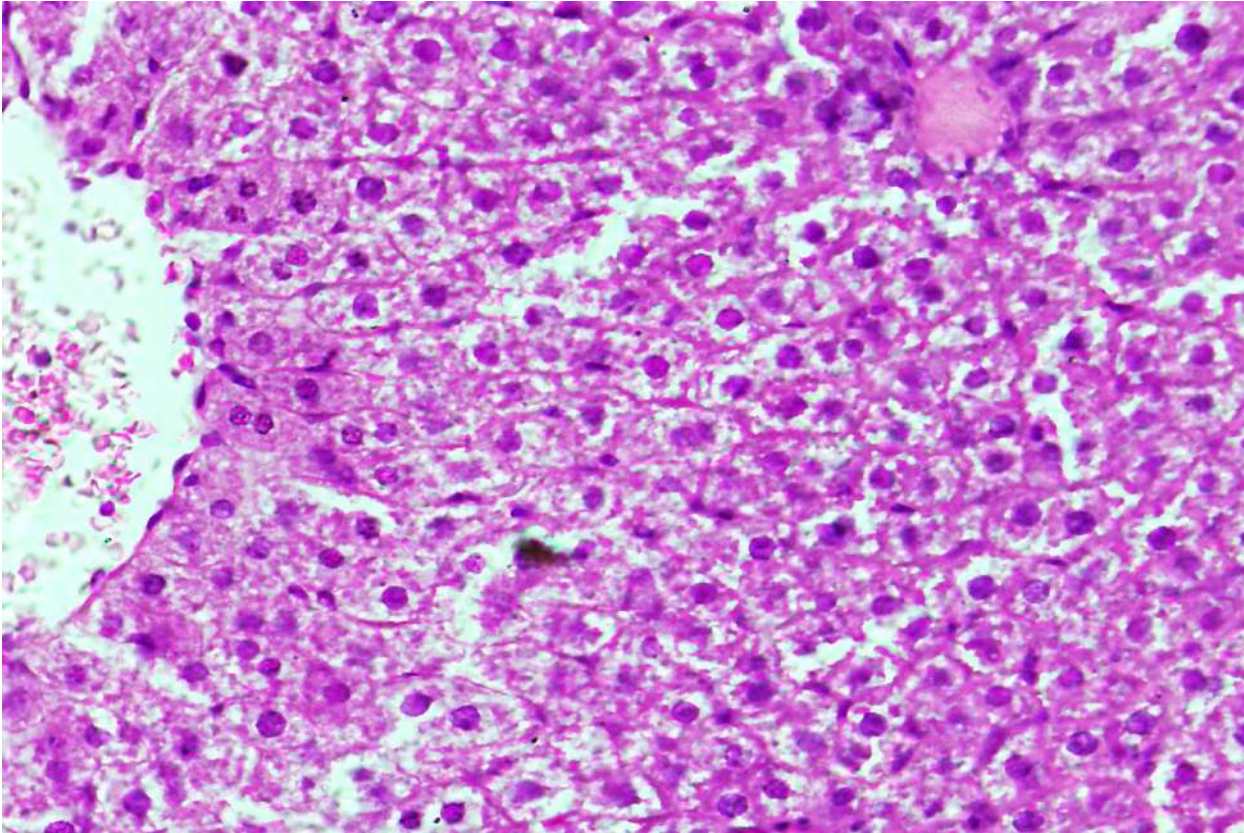


Figure 7. Pancreatitis, untreated. Central part of the liver, diffuse vacuolar degeneration of hepatocytes. Coloring: G-E. Uv: 10x40.

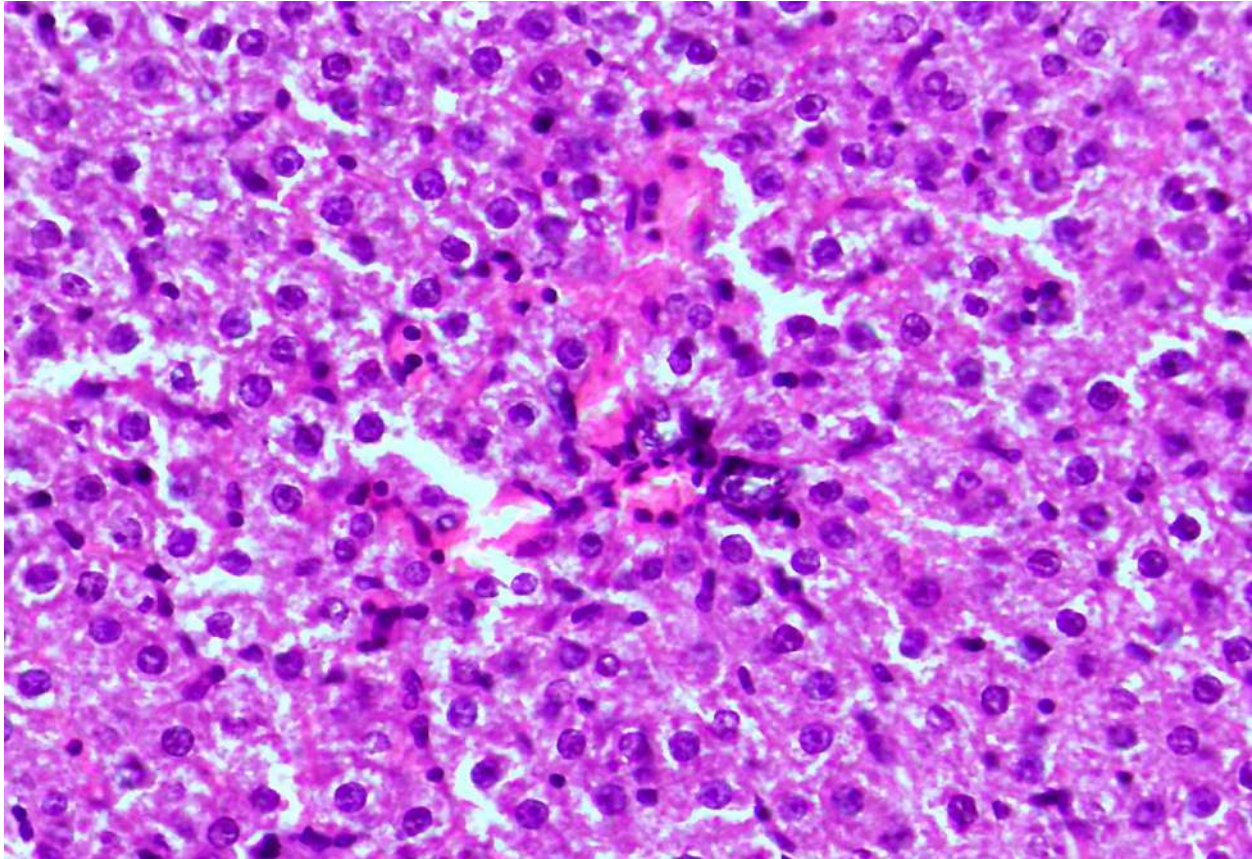


Figure 8. Pancreatitis non-performing. Periportal liver area, proliferative wall activity, hemorrhage centres. Coloration: G. E: 10x40.

The results of a morphological study of pancreatic tissue after treatment with cytochrome C of experimental pancreatitis showed a decrease in the volume of degenerative, destructive and inflammatory changes. At the same time, necrobiotic and necrotic foci disappeared, instead of them the proliferation of connective tissue was noted (Fig. 9). Moreover, connective tissue layers appeared not only at the site of necrosis, but in the interstitium of the exocrine part of the gland. The connective tissue layers were represented mainly by fibrous structures that are located around the acini of the gland and around the vessels. A small number of inflammatory cells are preserved in the thickness of the connective tissue. The acini of the exocrine part of the gland are randomly located with a violation of histotopography and a strong edema of the interstitium is determined between the acini. Examination on a large microscope objective showed that the connective tissue layers consist of separate bundles of fibrous-cellular structures, between which thin-walled blood vessels with diapedesic hemorrhages are determined (Fig. 10). Connective tissue cells are hypertrophied and hyperchromic, diffusely located. Inflammatory cells penetrate between the acini of the exocrine part of the gland. The epithelium of the acini are exposed to dystrophic and

edematous

phenomena.

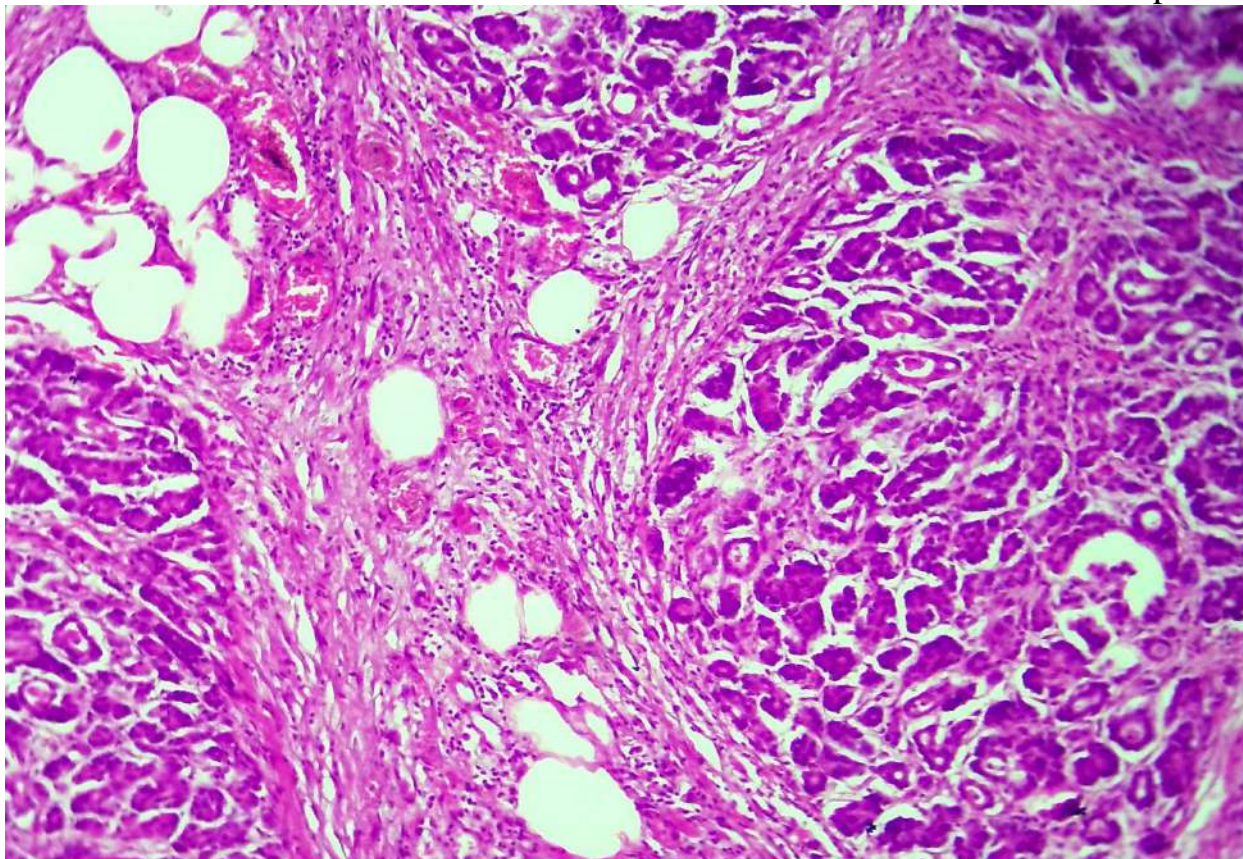


Figure 9. Pancreatitis, Treatment with cirrochre C. Interlaced connective tissue between gland. Coloration: G. E: 10x10.

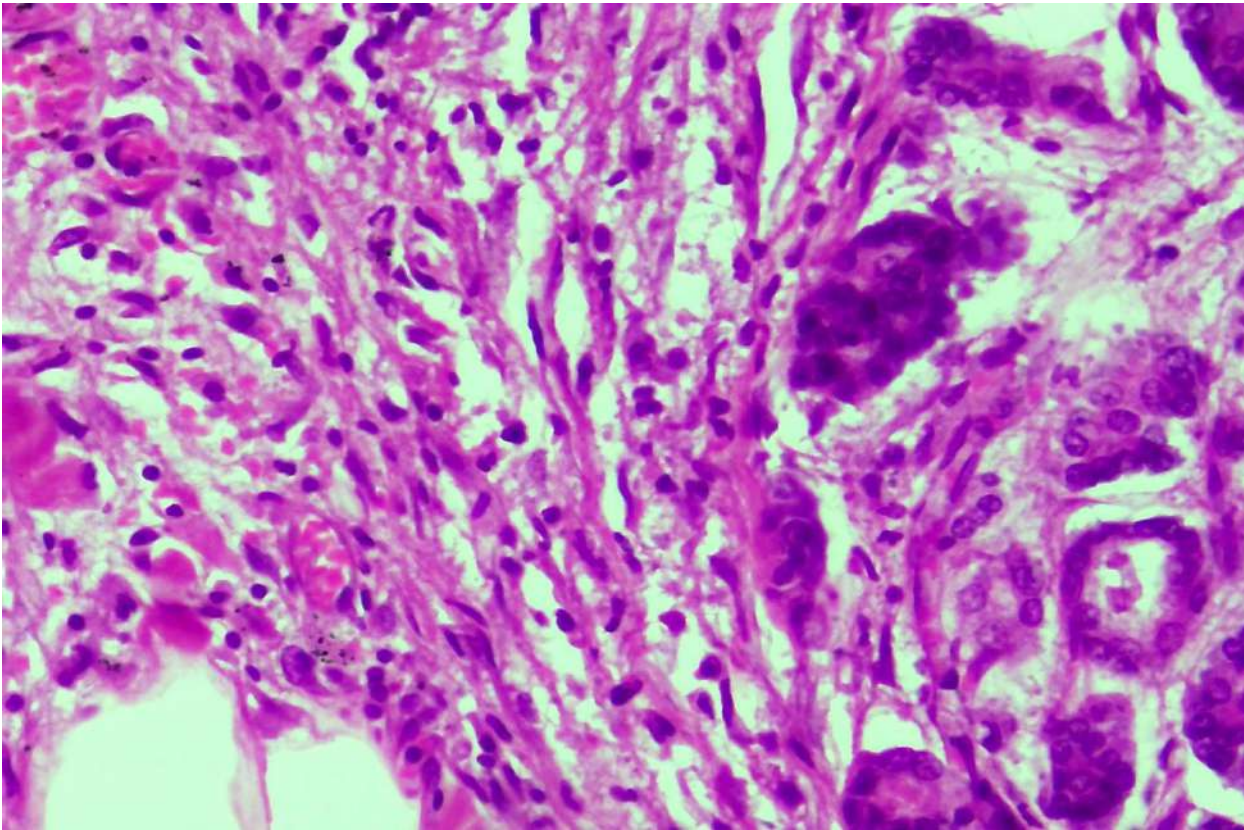


Fig. 10 Pancreatitis, cytochrome C. Connective tissue, inflammatory infiltrate in iron interstification. Oxark: G-E. Uv: 10x40.

The results of a morphological study of the liver in the treatment of experimental pancreatitis with cytochrome C showed that the pathomorphological changes in the group without treatment in the form of dyscirculatory, dystrophic, destructive and inflammatory changes are stabilized and less pronounced. Especially, dystrophic changes in the form of diffuse vacuolar dystrophy of hepatocytes disappear, only small-drop hydropic dystrophy of the second morphofunctional zone of the liver lobules remains (Fig. 11). In the third, central morphofunctional zone, hepatocytes have a normal structure, the cytoplasm is uniformly stained with eosin, the nucleus is located in the center of the cell with normal chromatin. Expansion of the Disse space and some hypertrophy of Kupffer's cells are noted.

Morphological study of the first morphofunctional zone showed that lymphoid infiltration persists in the periportal tissue and the proliferative activity of histiogenic cells in this zone is preserved (Fig. 12). Hepatocytes of the periportal zone are loosened due to focal vacuolar degeneration and edema of the Disse space. A single infiltration of inflammatory cells is determined between hepatocytes.

#### Conclusion.

When treating experimental pancreatitis with cytochrome C, it is noted that in the tissue of both the pancreas and the liver, the volume of dyscirculatory, dystrophic, destructive and inflammatory changes decreases. At the same time, the proliferation of connective tissue prevails in the tissue of the pancreas and some restructuring of the

gland parenchyma is noted. In the third central zone, hepatocytes are normalized, in the second zone, small droplet vacuolar dystrophy is preserved, the preservation of periportal lymphoid infiltration and hypertrophy of Kupffer cells are also determined.

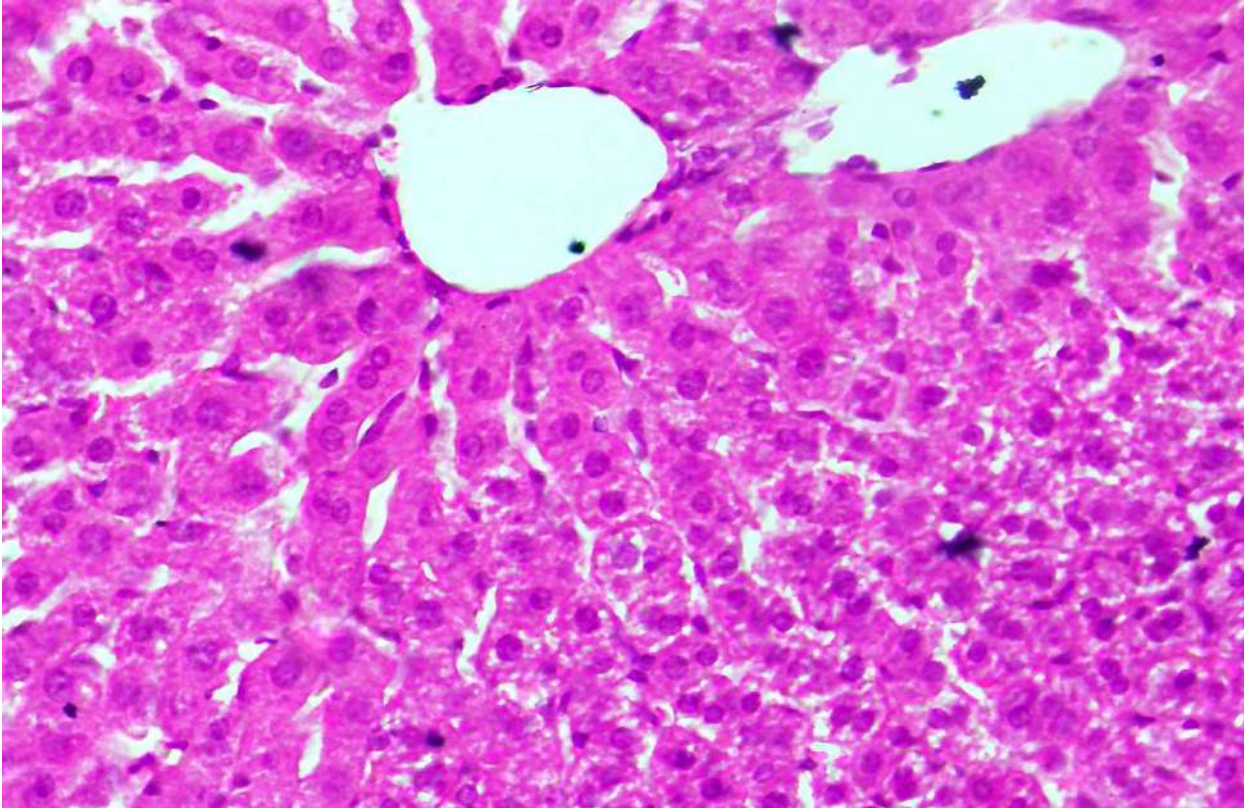


Figure 11. Pancreatitis, treatment with cytochrome C. Normalization of histopoporophy of hepatocytes of the central lobular zone, preservation of fine-capped vacuolar dystrophy in the second zone. Colour: G-E. W: 10x40.

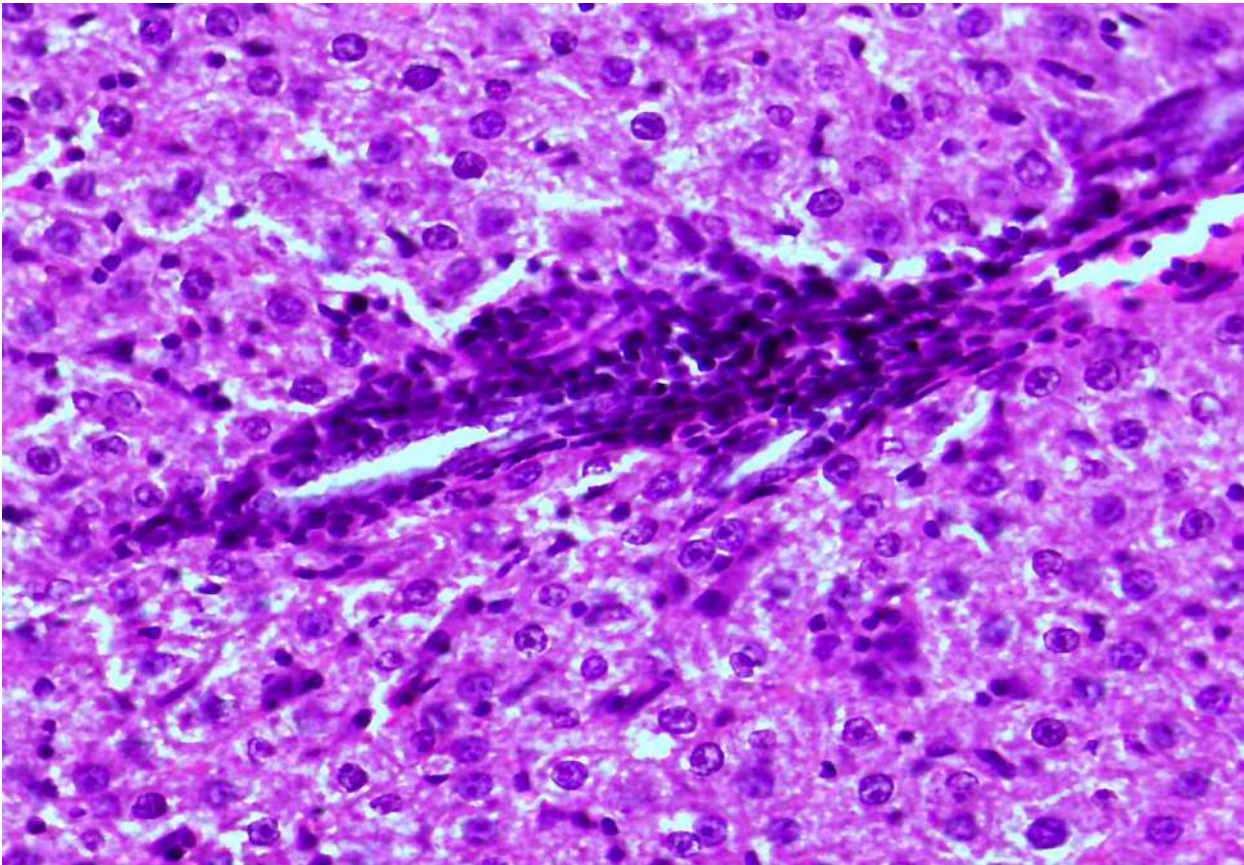
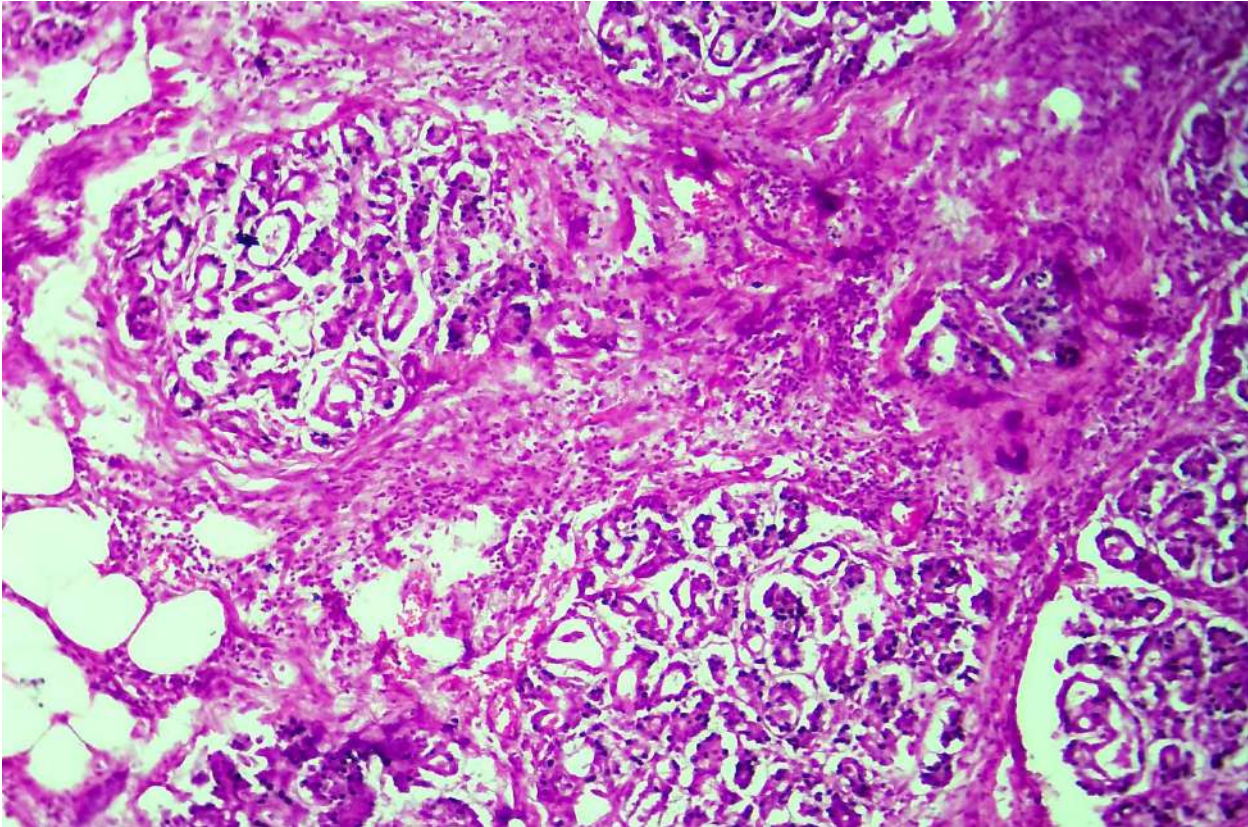


Figure 11. Pancreatitis, treatment with cytochrome C. Continuation of lymphoid infiltration in the periportal zone, infiltration by single inflammatory cells parenchyma liver. Colour: G-E. W: 10x40.

The results of the morphological study of the pancreatic tissue after the treatment of pancreatitis with sandostatin showed that of all general pathological changes dystrophic and destructive processes subside, and the inflammatory changes persisted and a combination of inflammatory changes with the growth of inflammatory granulation tissue was noted (Fig. 12). Microscopic examination reveals a diffuse environment of the acini and lobules of the gland with layers of inflammatory granulation tissue with a dense environment of the ducts of the gland. The interstitial tissue of the lobules of the gland is highly edematous, in places with inflammatory infiltration, the acini are deformed with a thinning of the size of the glandular epithelium. Examination under a large microscope lens shows that interstitial inflammatory granulation tissue consists of densely located inflammatory cells of lympho-histiocytic origin (Fig. 13) in the form of proliferative activity with hyperchromic nuclei. Fibrous structures of granulation tissue are represented by randomly located fibrils, intensely stained with eosin. The acini of the exocrine part of

the gland are deformed, edematous, the epithelium is concentrated in separate bundles.



Rice 12. Pancreatitis, sandostatin treatment. The pancreas are tightly surrounded by layers of inflammatory granule tissue. Colour: G-E. Ww: 10x10.



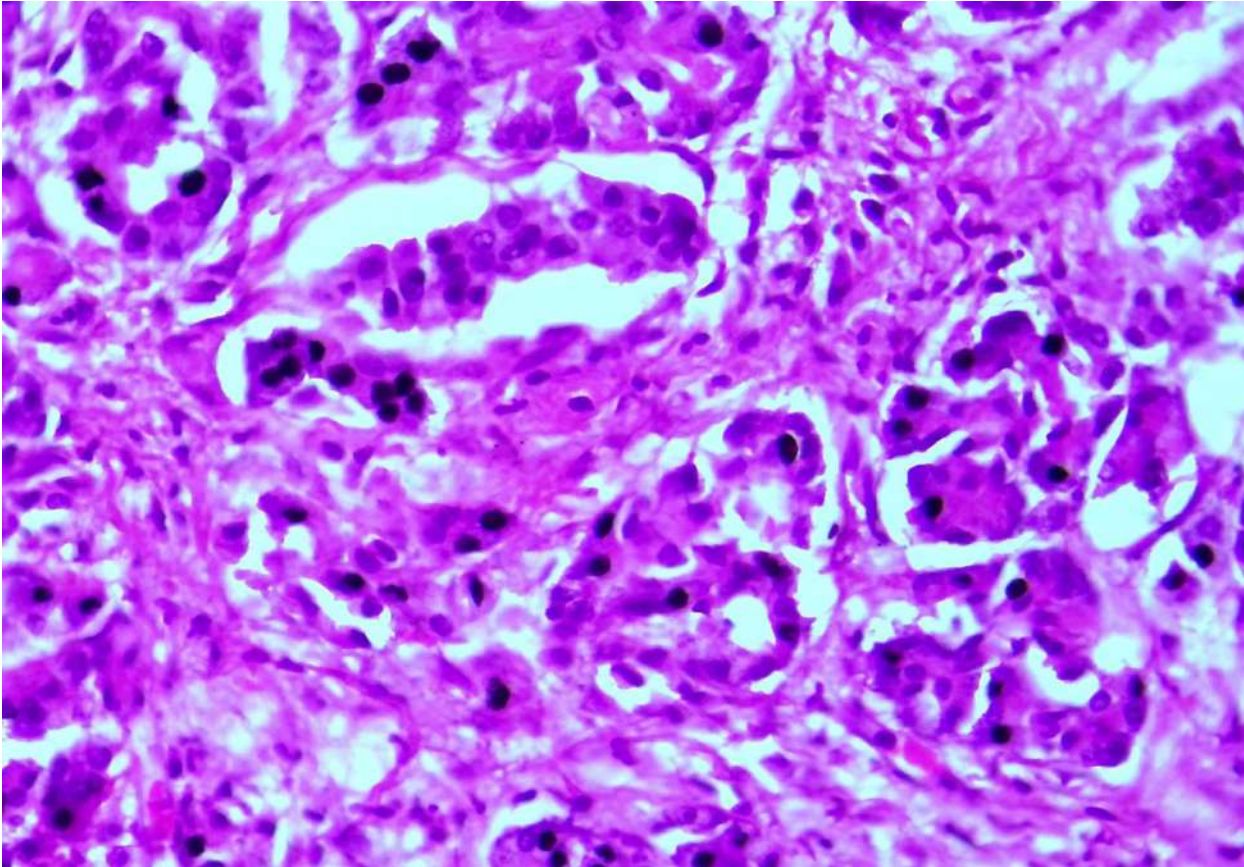


Fig. 13. Pancreatitis, sandostatin treatment. Iron interstification thickening from inflammatory granulation tissue. Coloration: G. E: 10x40.

When treating experimental pancreatitis with sandostatin, all general morphological processes are normalized in the liver tissue, only a slight small-drop vacuolar degeneration of hepatocytes of all morphofunctional zones remains. At the same time, the hepatocytes are swollen, the cytoplasm is motley due to small-drop hydration of the cytoplasm (Fig. 14). The nuclei of hepatocytes are relatively large, hyperchromic, rounded, located in the center of the cell. It should be noted that in this group of studies, Kupffer's cells are hypertrophied and the presence of single lymphoid cells is determined in the Disse space. The central vein and sinusoids are dilated and full-blooded. In some lobules of the liver, there is an expansion of the central vein with a rupture of the wall and hemorrhage into the surrounding tissue. In the vein wall, the appearance of inflammatory infiltration and hypertrophy of endothelial cells is noted (Fig. 15). Hypertrophy of Kupffer's cells, expansion of sinusoids, hemorrhages in the Disse space are also noted. At the same time, from the side of hepatocytes, a violation of the beam structure is noted, especially around the central vein are randomly located.

#### Conclusion.

When treating experimental pancreatitis with sandostatin, small layers of inflammatory granulation tissue and interstitial edema remain in the pancreatic tissue. From the side of the parenchyma of the gland, preservation of the histotopography of both the exocrine and endocrine parts is noted. In the liver tissue, the expansion of the

central veins and sinusoids, hemorrhages in the parenchyma and a slight vacuolar degeneration of the cytoplasm of hepatocytes are determined.

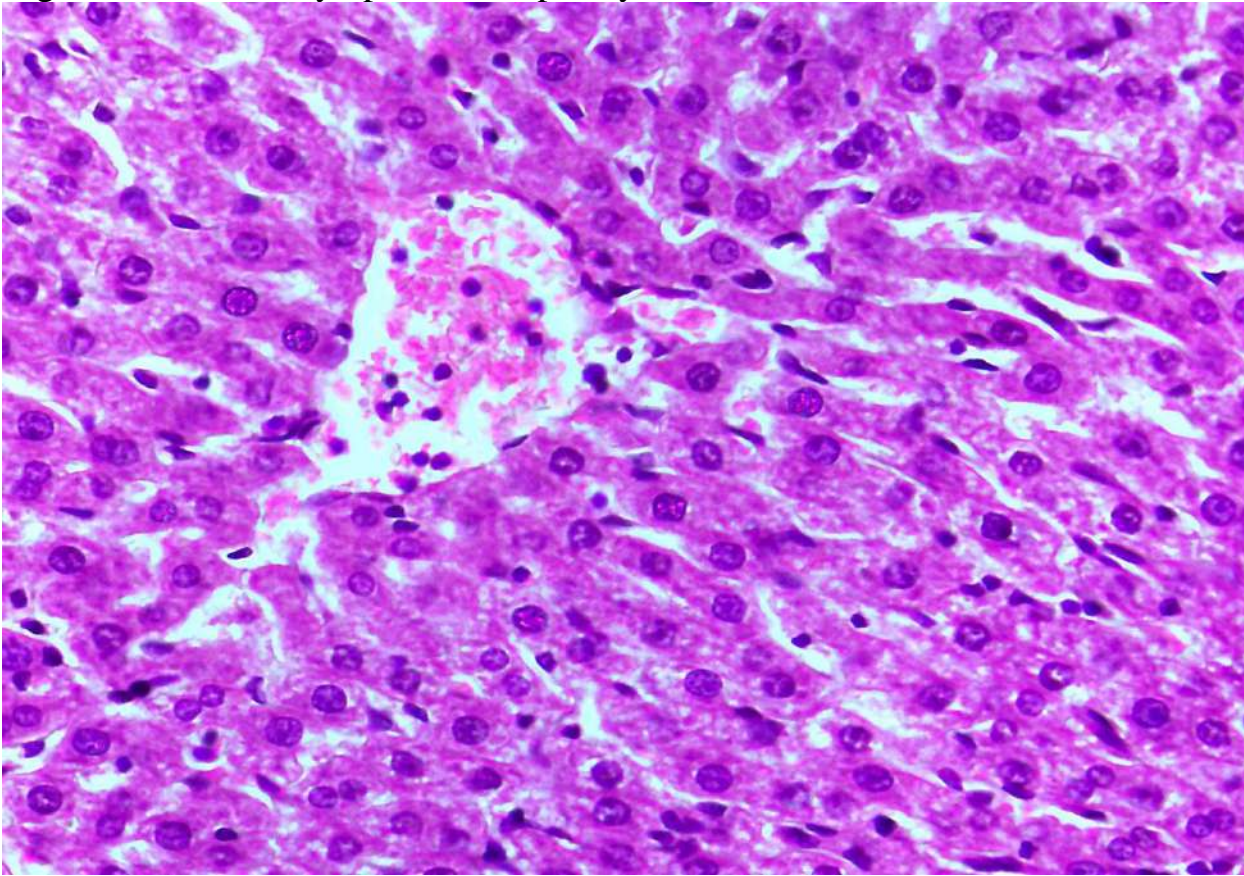


Fig. 14. Pancreatitis, treatment with sandostatin. Colour: G-E. W: 10x40.

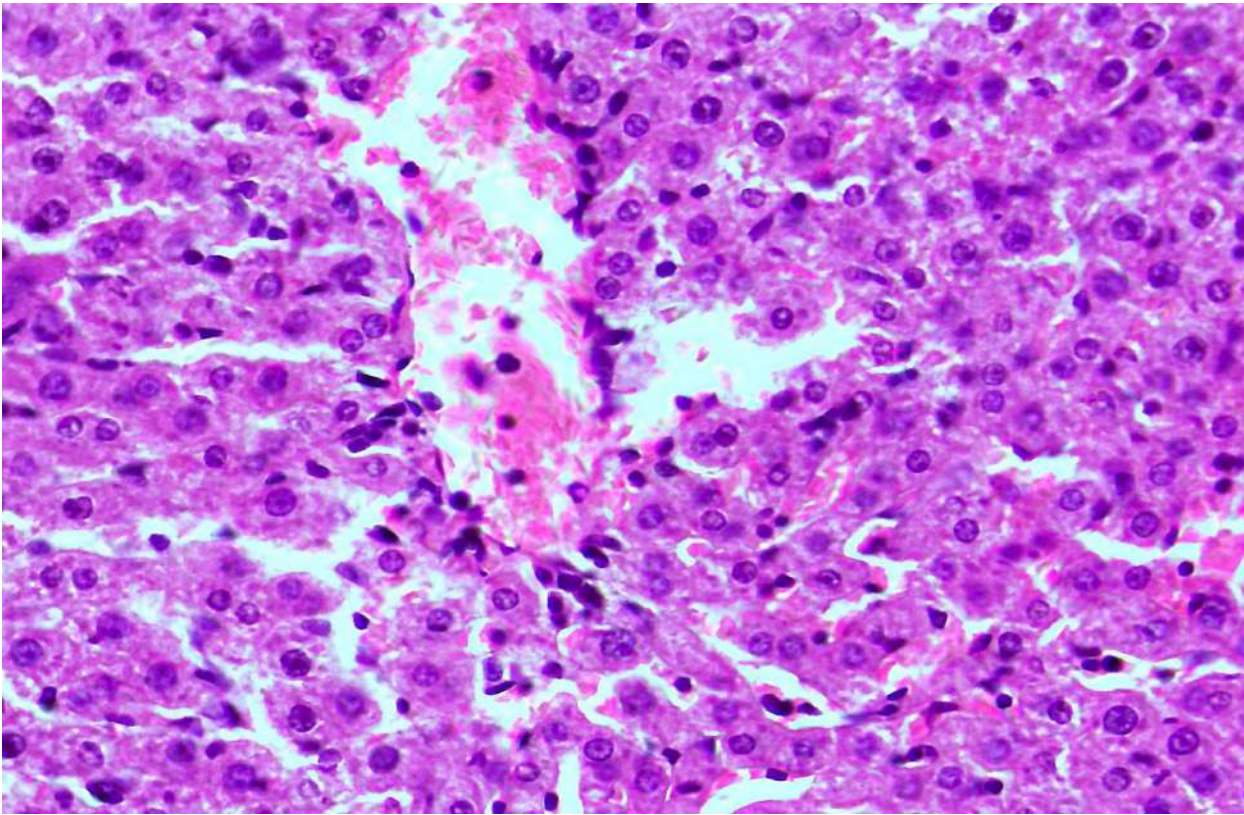


Fig. 15. Pancreatitis, Sandostatin treatment.

The results of a morphological study of the pancreatic tissue after combined treatment with cytochrome C and sandeostatin showed that, in comparison with the previous groups, all general pathological processes characteristic of experimental pancreatitis subsided in the gland. There is a preservation of the proliferation of connective tissue in the interstitium of the gland tissue with minimal signs of inflammation (Figure 16). At the same time, the layers of connective tissue consist of fibrous structures and small cellular elements. Moreover, in the interstitium of the small lobules of the gland, the connective tissue layers become thinner. In the parenchyma of the gland, there is a slight edema of the interstitial tissue. Acini glands of various shapes and sizes, some are in a state of expansion of the lumen. Examination of the gland tissue under a large microscope lens showed that signs of destructive and inflammatory processes were not detected in the interstitium, only a slight edema was detected (Fig. 17). At the same time, the histotopography and cellular content of the Langerhans islands are preserved, the endocrine cells have the usual structure with hyperchromic nuclei. The exocrine part of the gland also retains its histotopography against the

background of a slight edema of the intercellular substance.

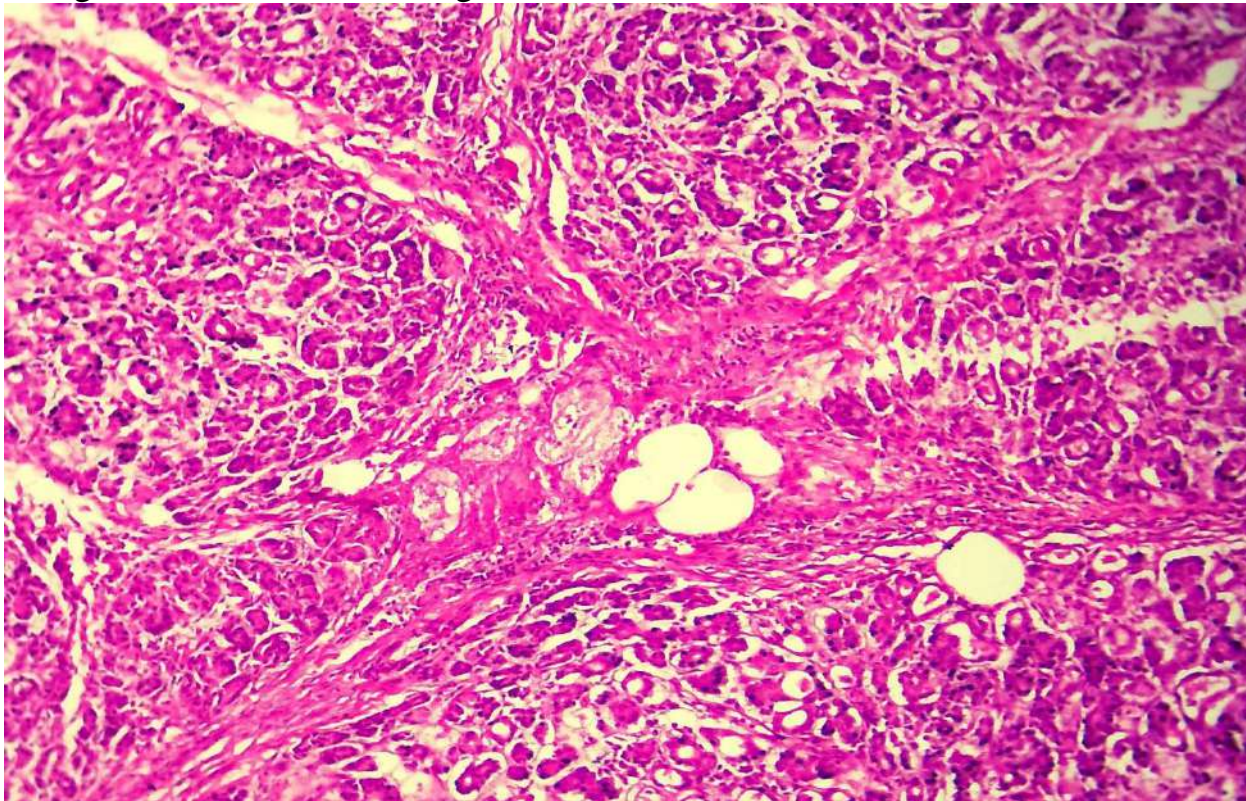


Figure 16. Pancreatitis, Combination Treatment. Reduction in gland tissue signs of inflammation. Coloration: G. E.Uv: 10x10.

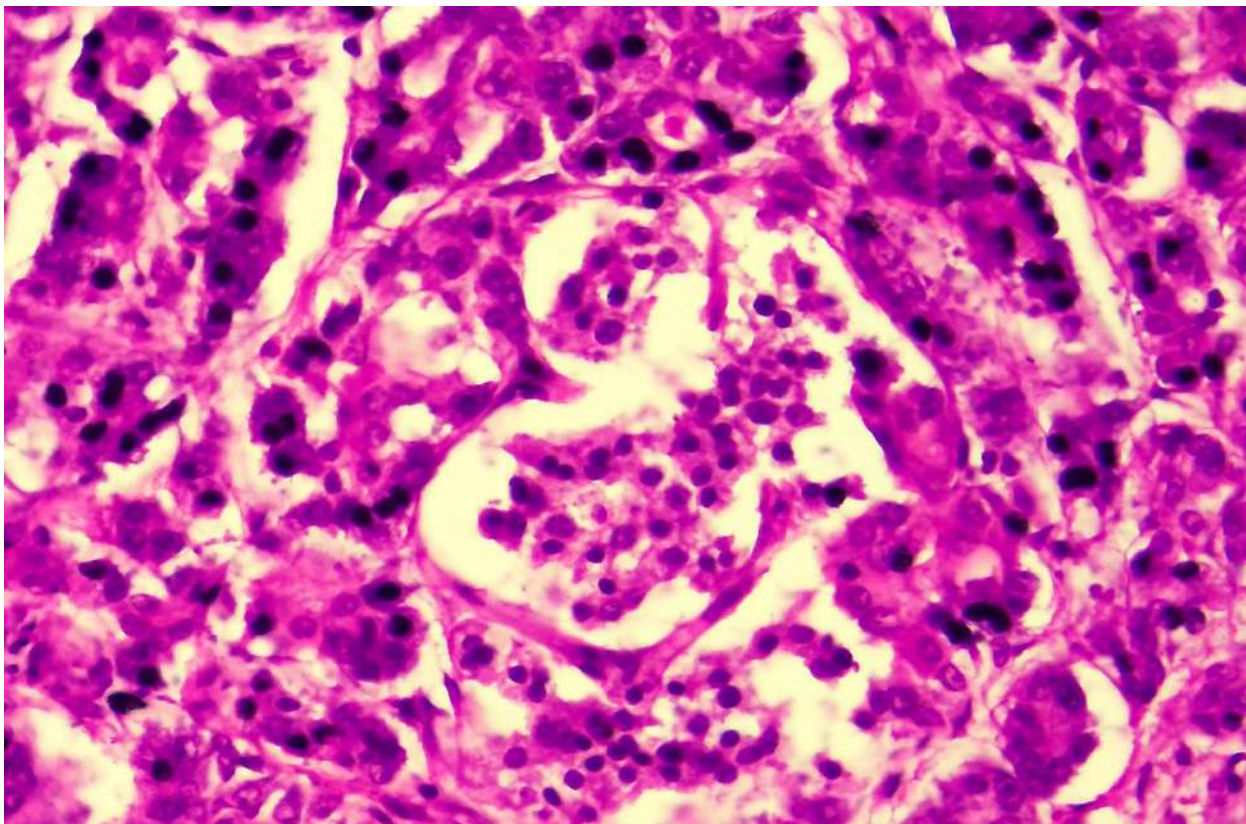


Fig. 17 Pancreatitis, combination treatment. Colour: G-E. W: 10x40.

With the combined treatment of pancreatitis in the liver tissue, normalization of all general pathological processes is also noted, only a slight edema of the Disse space and hypertrophy of Kupffer's cells remain. At the same time, hepatocytes retain a beam structure, the cytoplasm is expanded in volume, dyed by hyperchromic eosin, there are no pathomorphological changes (Fig. 18). Only in the second morphofunctional zone, where the metabolism of all products is intense, there is an uneven staining of the cytoplasm and an uneven size of nuclear structures. Examination of liver tissue under a large microscope lens showed that histotopography of the liver parenchyma has a normal structure, only a slight expansion of the central vein and hypertrophy of Kupffer's cells are noted. Hepatocytes are located along the beams, the cytoplasm is expanded and uniformly stained with eosin. The nuclei of hepatocytes are rounded, almost the same size, chromatin is intensely stained with hematoxylin (Fig. 19).

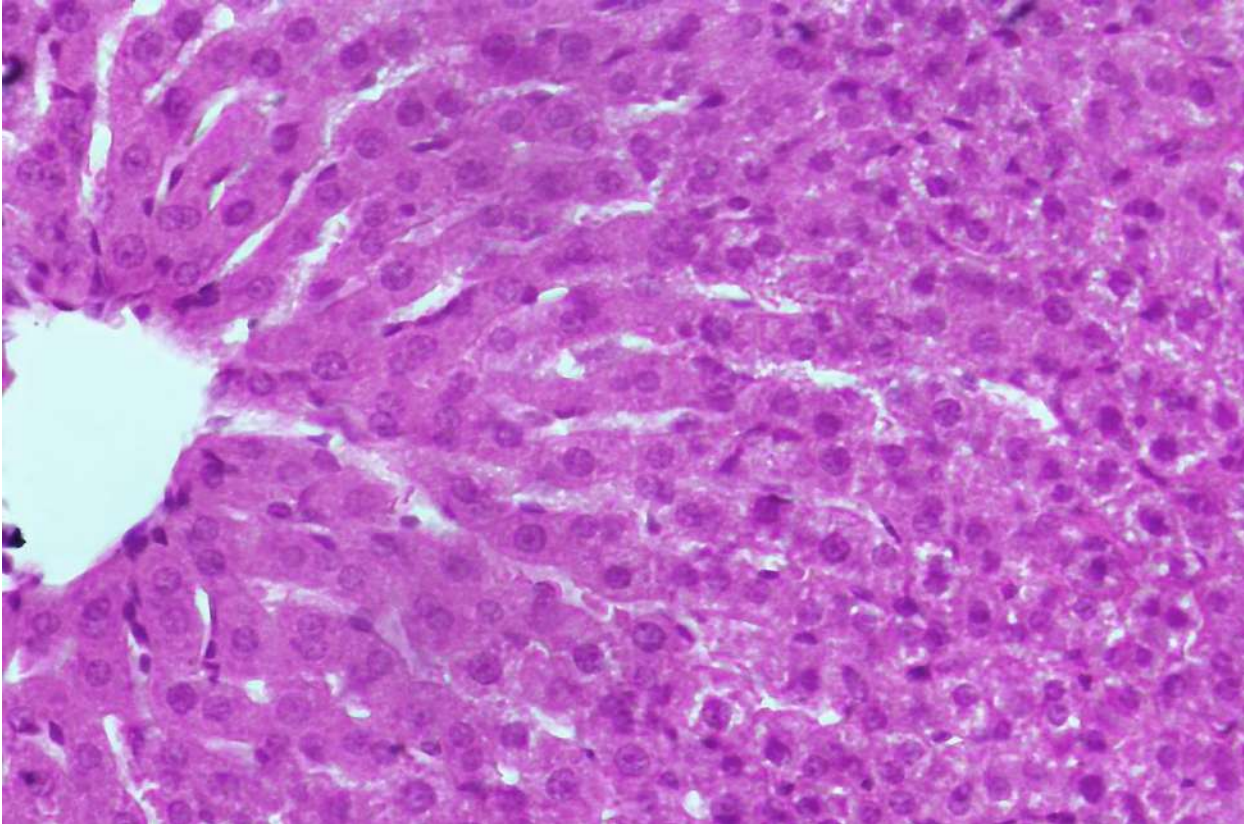


Fig. 18. Pancreatitis, Combination Treatment.

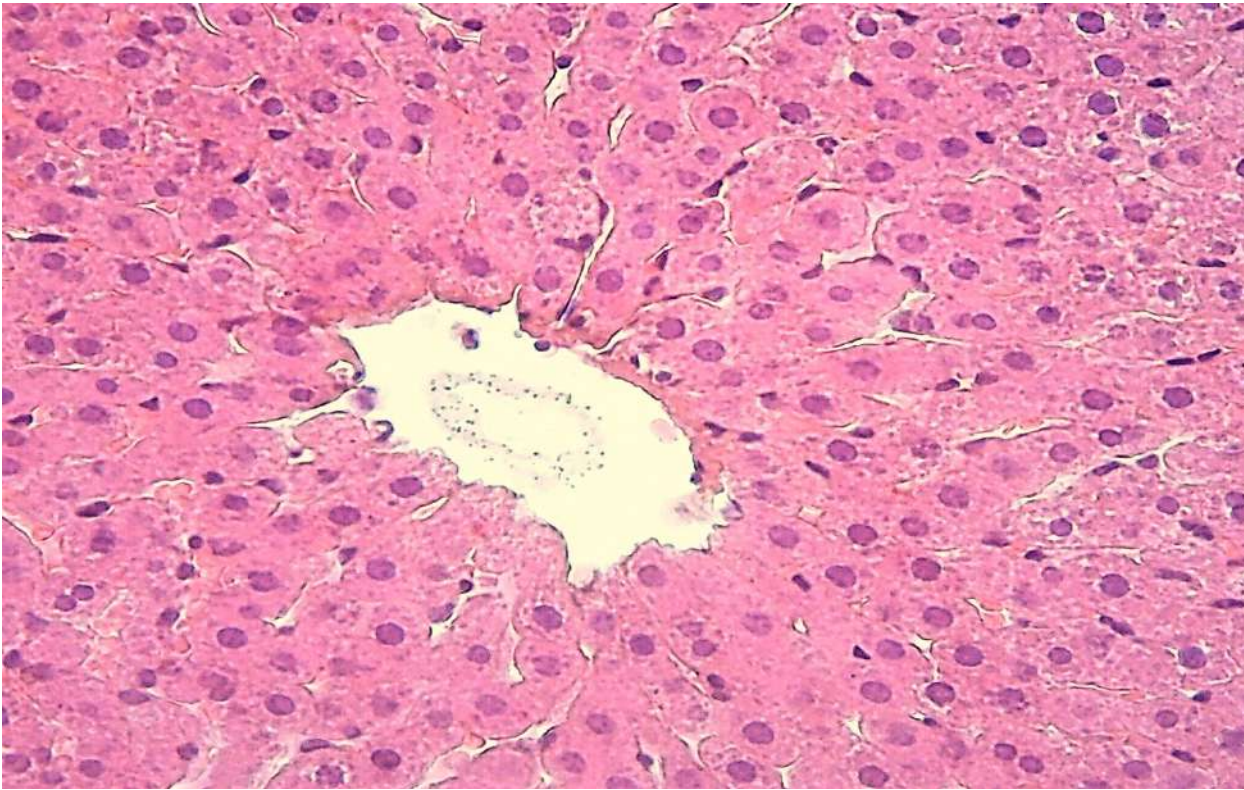


Figure 19. Pancreatitis, combination treatment. Hepatocyte cytoplasm is colored evenly by eosine, nuclei are hyperchromic. Coloration: G-E. W: 10x40.

#### Conclusion

Experimental pancreatitis was manifested by the appearance of foci of necrosis, inflammatory infiltration, disorganization of the parenchyma and stroma-vascular component of the gland. In the liver, the development of dystrophic, destructive and inflammatory changes was noted, and in all morphofunctional zones of the organ.

Treatment of experimental pancreatitis with cytochrome C was accompanied by a decrease in the volume of discirculatory, dystrophic, destructive and inflammatory changes both in the pancreas and in the liver. When treating experimental pancreatitis with sandostatin, small layers of inflammatory granulation tissue and interstitial edema remain in the pancreatic tissue. In the liver tissue, the expansion of the central veins and sinusoids, hemorrhages in the parenchyma and a slight degeneration of the cytoplasm of hepatocytes are determined.

Combined treatment of experimental pancreatitis with cytochrome C and sandostatin led to the normalization of both pancreatic tissue and liver. Preservation of a small proliferation of connective tissue in the interstitium and restoration of histotopography of both the exocrine and endocrine parts of the gland were noted. On the part of the liver tissue, there is a complete disappearance of general pathological processes, only the expansion of the central vein and hypertrophy of Kupffer's cells are determined.

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