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# Histochemical and histopathological study of the gastric mucosa in the portal hypertensive gastropathy

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**Abstract**

It has been studied "in situ" the action of NADH2-cytochrome C reductase, an aerobe oxidative enzyme, in comparison to lactate dehydrogenase, a glycolitic enzyme in the gastric mucosa and with portal hypertensive gastropathy (PHG) accompanied by morpho-pathological observations. In the normal gastric mucosa, the aerobe oxidative metabolism is predominant over the anaerobe one in all types of cells, but in different intensities (medium in the surface epithelium and low in the vascular endothelium, weak, medium, intense and very intense in fibroblasts and in secretory cells of fundic glands and macrophages). In the portal hypertensive gastropathy, this type of metabolism decreases and the anaerobe metabolism increases, tending to equal the first, especially in the glandular cells. The oxidative activity decreases in the surface epithelium and in the vascular endothelium, increases in cells of the inflammatory infiltrate and in fibroblasts and mast cells.

***Keywords*:** stomach, PHG, histochemistry, histopathology.

## Introduction

The portal hypertensive gastropathy (PHG) and gastric antral vascular ectasia (GAVE syndrome) are recently characterized entities which can be associated with hemorrhages of the gastro-intestinal tract at patients with hepatic cirrhosis.

About 65% of the portal hypertensive patients, owing to the hepatic cirrhosis, develop PHG; this could also appear in the initial stages of the portal non-cirrhosis hypertensions. At the portal hypertensive patients, the PHG is mostly associated to the presence of the esophagus varix not the gastric one.

The mechanisms involved in the PHG pathogenesis are not entirely elucidated. Nevertheless the disorder of the secretion of the NO, TNF-α (tumoral element of necrosis) [2, 3], prostaglandins [4–6], and EGF (epidermal element of growth) [7, 8], could be involved in this process.

The mechanism involved in the appearance of the GAVE syndrome are also vague. The ectasic signs of this syndrome include red injuries, most frequently hemorrhages, injuries mostly situated in the "gastric antrum" which can lead to the loss of important quantities of blood. Over 70% of the patients with GAVE syndrome do not suffer of cirrhosis or portal hypertension.

In the initial phases of hepatic cirrhosis the difference between PHG and GAVE syndrome may be difficult. The distinction is distinguished by the type of response to a treatment which follows the decrease of the portal hypertension, more exactly is ascertained a general positive response at the patients with PHG in comparison to those suffering of GAVE syndrome or a coexistent form of portal hypertension, which usually does not respond to this kind of therapy.

## Material and methods

The work has been done on human normal and gastritis portal hypertensive stomach fragments, ingathered through surgical techniques by the specialized services, as well as on gastric mucosa fragments, as on mucous gastric from rat. The 4–5 μm thick cryosections, taken from cryotome, have been studied with histochemistry methods to emphasis "in situ" the activity of $NADH_2$-cytochrome C reductase and of the lactate-dehydrogenase [9, 10]. Sections obtained from the ingathered fragments were colored also with Hematoxylin–Eosin for the histopathology exam [11–13].

## Results

### Histochemical results

#### *Normal gastric mucosa*

#### *$NADH_2$-cytochrome C reductase*

The upper epithelium of the stomach's bottom of the pyloric area presents enzimatic reactions of medium intimacy, so the zymogene granules are present between the cytoplasm of the cells, with a tendency of concentration in the ectoplasm.

In the fundic glands, the principal cells, pepsinogen appear with a diaphorase activity of different degrees (weak, medium, intense and rarely very intense) under the shape of dark violet, isolated granulations and

equally distributed in the cytoplasm. The parietal cells are intensely and very intensely reactive (the most numerous) with big zymogene granulations.

In "*lamina propria*", the blood vessels present a medium and intense enzymatic activity in the endothelium, as the mast cells and macrophages (connective tissue cells). The fibroblasts are very diversified by their enzimatic intensities, with weak, medium, intense and very intense reactions (Table 1).

***Lactate dehydrogenase***

The mucous epithelium presents a weak or a medium activity, the fundic glands present a medium intensity both the principal and parietal cells. The capillaries and arterioles had a weak and sometimes medium enzymatic activity in the endothelium cells, in the same way with the surrounding fibroblasts. Mast cells and macrophages are medium reactive.

**Table 1 –** ***Gastric mucosa. Normal and portal hypertensive gastropathy (PHG)***

| Enzyme | Epithelium | | Lamina propria | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | *Gland* | | | | *Blood vessels* | | *Connective tissue cells* | | | | | |
| | | | *CC* | | *PC* | | *End* | | *F* | | *Ma* | | *Mac* | |
| | N | PHG | N | PHG | N | PHG | N | PHG | N | PHG | N | PHG | N | PHG |
| *$NADH_2$-cytochrome-C-reductase (diaphorase)* | + | –+<br>+ | –+<br>+<br>++<br>+++ | +<br>++ | ++<br>+++ | ++ | +<br>++ | –+<br>+ | +<br>++<br>+++ | +<br>++<br>+++ | +<br>++ | +<br>++ | ++ | +++ |
| *Lactate-dehydrogenase* | –+<br>+ | –+ | + | + | +<br>++ | +<br>++ | –+<br>+ | +<br>++ | –+<br>+ | –+<br>+ | + | + | + | + |

*CC – Chief Cell; PC – Parietal Cell; End – Endothelium; F – Fibroblast; Ma – Mast cell; Mac – Macrophage; Reaction: (–) negative; (–+) weak; (+) medium; (++) intense; (+++) very intense.*

***Portal hypertensive gastritis***

***$NADH_2$-cytochrome C reductase***

In general, enzyme's activity falls in all the types of mucous gastric cells. The epithelium presents unequal weak and medium reactions. In the gastric glands the enzymatic reaction appears equal, intense, in both principal and parietal cells. Diaphorase activity is of a weak or medium intensity in the vascular endothelium cells and usually in all kinds of conjunctive cells from "*lamina propria*".

***Lactate dehydrogenase***

The upper epithelium, capillary and arterioles endothelium are weak. The main cells from the fundic glands, the perivascular mast cells and macrophages appear with medium intensity reactions. The parietal glandular cells are medium and intensity reactive, and the weak and medium positive fibroblasts. Around the blood vessels in the conjunctive of *lamina propria* appear frequently inflammatory infiltrations (neutrophils, eosinophils, lymphocytes and macrophages/monocytes) with oxidative enzymatic activities both aerobe and anaerobe also very intense.

## Histopathological results

They are characterized by accented modifications at conjunctive-vascular level of the gastric mucous. These manifest through chronic and acute infiltrations of inflammatory cells, and mostly trough alteration gastric micro-circulation in which prevails the congestion, the capillary and precapillary dilatations, through the rise of the number of arterial-venous communications, vascular wall thickened through fibrosis. There may appear partial exulcerations, epithelium desquamation, superficial hemorrhages (Figures 1–5).

## Discussions

The normal gastric mucous presents an intense oxido-reductive metabolism predominant aerobe, more intense in the fundic glandular cells with a high concentrated level in parietal cells and with different glands from a principal cell to another or from a cellular group to another, marking this way the existence of a cellular cycle of synthesis and secretion in the pepsinogen cells. Periglandular, the connective tissue cells are very active enzymatic, especially those involved in the fibrilogenesis process, as the fibroblasts, and those engaged in the synthesis of macromolecules of the extracellular matrix, and that together intervene in the turn-over of collagen, glycosaminoglycan and proteoglycans.

The portal hypertensive gastropathy, through its predominant vascular-conjunctive injuries, lead to a decrease of the gastric mucous oxygenation, a fact which determines a decrease of the aerobe oxidative metabolism and its approaching to the anaerobe metabolism, which suffers soft, unpeculiar changes. It tends to equalize the enzymatic aerobe/anaerobe reactions in all the cellular mucosal component structures. The experimental studies made on animals and fragments of rezected stomachs taken from cirrhosis subjects, performed on optical and electronically microscopes, have established with quite a good precision the injuries of the gastric mucous, principally with the alteration of the sanguine microcirculation which have permitted to define the PHG as a process where the congestion predominates, the hemorrhages the inflammations and also the fibrosis.

Recent studies say that the hemodynamic systemic alterations present at the patients with cirrhosis are materialized through the increase of pressure in the portal vein, of the cardiac flow and the sanguine systemic and splanchnic flux. These are phenomena have appeared because of the endogenous vasodilatation processes (glucagon, prostacyclin, endothelin, etc.) and the diminution of vascular sensitivity to the endogenous vasoconstrictors. All these lead to a decrease in the vascular diameter, to the forming of arterio-venous shunts in the mucosa, to a decrease in the sanguine flux of the gastric mucous which makes it susceptible to the aggressive agents.

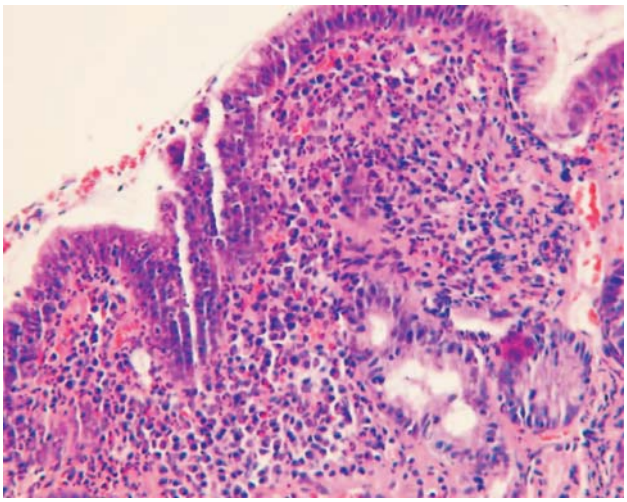

**Figure 1** – ***Portal hypertensive gastropathy. Stomach, antral region. Congestion, vascular ectasia, chronic and acute inflammatory infiltrate; discrete fibrosis at the level of lamina propria, with dissociation of the remaining glandular elements (HE staining, ×180)***

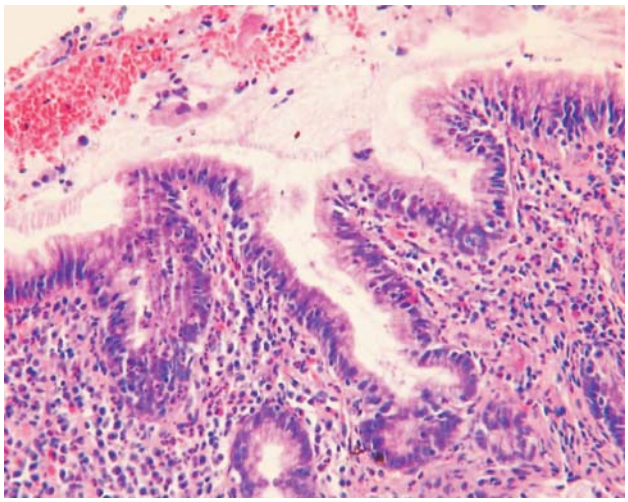

**Figure 2** – ***Portal hypertensive gastropathy. Gastric mucosa. Epithelial desquamations, mucus and superficial hemorrhage, rich inflammatory infiltrate, vascular ectasia, partial and regional epithelisation (HE staining, ×200)***

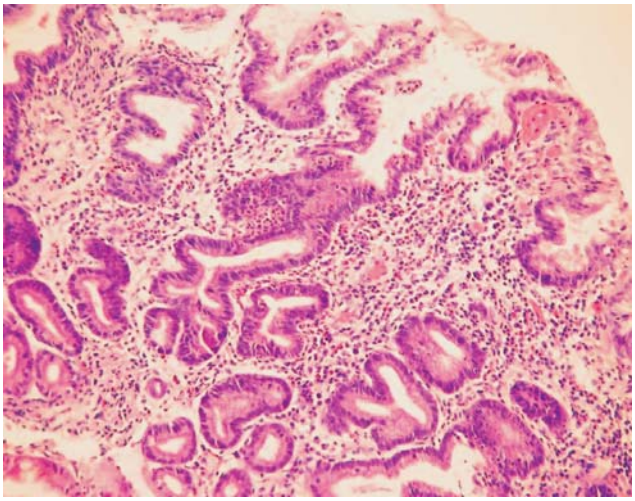

**Figure 3** – ***Portal hypertensive gastropathy. Gastric mucosa. Regional exulcerations, edema, blood vessels with wall thickening by medio-intimal sclerosis of monocytic type; chronic inflammatory infiltrate; glands with preserved architecture (HE staining, ×100)***

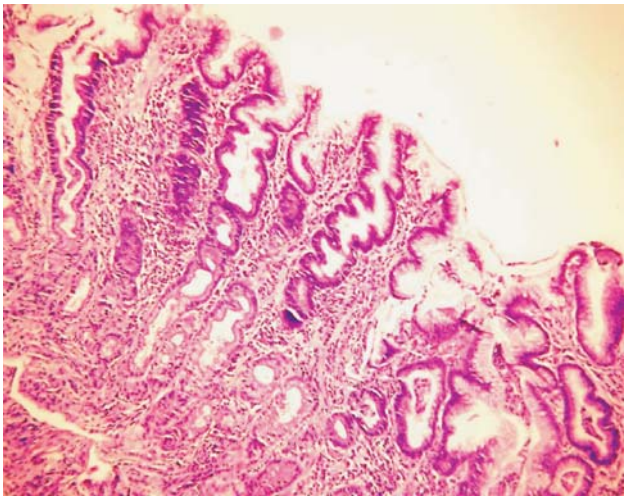

**Figure 4** – ***Portal hypertensive gastropathy. Gastric mucosa. Fibrosis in lamina propria, submucosa, residual inflammatory infiltrate and regional foveolar hyperplasia (HE staining, ×40)***

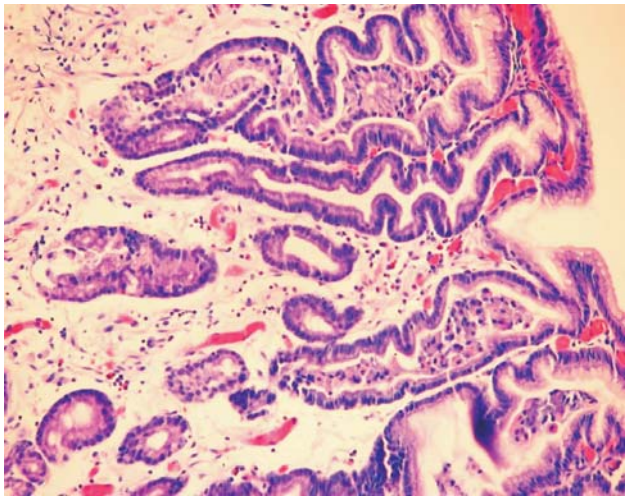

**Figure 5** – ***Portal hypertensive gastropathy. Gastric mucosa. Superficial vessels, subepithelial, of different calibers; edema, discrete inflammatory infiltrate and fibrosis with focal hyalinisations; dalliant process (HE staining, ×200)***

It produces a deficiency of oxygenation, of nutrition, it reduces the secretion of gastric mucus and the capacity of the ions neutralization, it increases the production of free radicals, and it is more easily injured by agents like aspirin, ethanol and bile acids. There are signaled functional alterations like achlorhydria, hypergastrinemia and the diminution of the seric pepsinogen levels in the severe gastropathy [14–16].

PHG appears as multifunctional process, in which interfere alterations of the gastric microcirculation, of the oxidative aerobe metabolism. The gastric mucous injuries in all its structures (epithelium exulcerations, erosions, and fibrosis) lead to the alteration of the integrity and its functionality.

## Conclusions

In the normal gastric mucous, the two studied enzymes, $NADH_2$-cytochrome C, a mitochondrial, aerobe, oxido-reductive enzyme and the lactate-dehydrogenase, a cytosolic enzyme of the glycolitic anaerobe metabolism, have positive activities but with different degreases of intensity depending on the type of component cell.

The aerobe metabolism is predominant in comparison to the anaerobe one. The most intense activity takes place in the fundic glands and in the frequent connective tissue cells (fibroblasts, mast cells, macrophages). In portal hypertensive gastropathy the most important modifications are present in the periglandular conjunctive and in the walls of the blood vessels (frequent capillaries with thickened endothelium, capillary and precapillary ectasia).

In the *lamina propria* sanguine microcirculation alterations, congestion, superficial hemorrhages, inflammatory chronic and acute infiltrate, fibrosis and glandular elements dissociation could be observed.

Oxidative cellular metabolisms are decreased and diversified (especially the aerobe one), and the degree of vascular injury, with very low enzymatic endothelial activities, indicates also an alterations of bidirectional exchanges between blood and interstitial fluid.

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