8. J. C. Chachques, P. A. Grandjean, B. Vasseur, et al., Artif. Org., **9**(A), No. 6, 27 (1985).
9. J. C. Chachques, P. A. Grandjean, J. I. Tommassi, et al., Life Support Syst., **5**, No. 8, 227 (1987).
10. A. Kantrowitz, Trans. Am. Soc. Artif. Int. Org., **6**, No. 7, 305 (1960).
11. G. J. Magovern, S. B. Park, and G. J. Magovern, jr., Ann. Thorac. Surg., **41**, No. 1, 116 (1986).

ROLE OF PROSTAGLANDINS OF THE GASTRIC MUCOSA IN ULCER DEVELOPMENT IN CIRRHOSIS OF THE LIVER

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Among the different effects of prostaglandins (PG) in the digestive system one of the most important is their cytoprotective action on the gastroduodenal mucosa and their antiulcerative effect This cytoprotective effect is connected not only with the inhibition of acid secretion in the stomach, but also with mobilization of protective factors – stimulation of bicarbonate secretion, the formation and secretion of mucoglycoproteinss and mucus, and also the trophic action of PG, etc. [10]. In chronic liver diseases erosive lesions are frequently observed also in the gastroduodenal region, amounting in some cases to the development of so-called "hepatogenic" ulcers in cirrhosis, evidence of lowered resistance of the gastroduodenal mucosa in this pathology. The pathogenetic mechanisms of these lesions have not yet been adequately studied despite their evident urgency. It has recently been shown that disturbances of the function of the gastric mucosa (GM) in chronic liver disease are due to injury of the layer of mucus [6], in the synthesis and secretion of which an active role is paid by PGE and PGI_2 (prostacycline), which are of essential importance in the mechanism of gastric cytoprotection [14]. $PGF_{2\alpha}$ also has recently been shown to have a protective action on the gastroduodenal mucosa [5].

The aim of this investigation was to study the role of PG in the development of ulcers in the gastroduodenal region in cirrhosis of the liver, for which purpose the content of PG of the E, I_2, and $F_{2\alpha}$ groups was studied in GM of patients with cirrhosis of the liver, complicated or uncomplicated by gastric or duodenal ulcer, and also the PGE and $PGF_{2\alpha}$ content in the gastric juice of these patients.

EXPERIMENTAL METHOD

Tests were carried out on 104 patients with chronic liver diseases, divided into four groups. Group 1 (54 patients) had active cirrhosis of the liver of varied etiology: viral (HBsAg+), alcoholic, and primary biliary cirrhosis. The 13 subjects of group 2 and the 12 of group 3 were patients in whom cirrhosis of the liver was complicated by gastric ulcer or ulcer of the duodenal bulb respectively. For greater informativeness, patients with chronic active hepatitis (CAH) of viral and alcoholic etiology also were tested (group 4, 25 subjects). In all cases the diagnosis was confirmed by the usual clinical-biochemical, morphological, roentgenologic, and gastroscopic tests. The control group consisted of six persons with no disturbances of liver function, in whom the GM was unchanged on gastroscopy and on histological investigation, In some patients (10) of group 1 and in those of the control group, PG was determined in biopsy specimens of GM obtained during gastroscopy with direct vision biopsy from the gastric fundus, whereas in patients of groups 2 and 3, the material also was

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TABLE 1. Prostaglandin Content in Gastric Mucosa of Patients with Cirrhosis of the Liver (in ng/g tissue, M ± m)

Group of subjects	PGE	$PGF_{2\alpha}$	6-keto-$PGF_{1\alpha}$
Control	550,7±20,9	256,7±16,4	218,9±13,2
1 (Active cirrhosis of the liver)	341,7±42,2*	164,0±15,55*	141,9±28,4*
2 (Cirrhosis of the liver + gastic ulcer)	209,3±41,8*	112,1±14,0*	61,9±9,3**
Outside the ulcer	71,0±18,9**	59,5±14,4**	36,9±6,0**
Border of ulcer			
3 (Cirrhosis of the liver + ulcer of the duodenal bulb)	231,5±24,7*	128,7±13,9*	72,6±13,33**
	130,5±24,3**	81,5±13,4**	57,0±12,7**

Legend. *$p < 0.05$ Relative to control, **$p < 0.01$ relative to control.

taken from GM outside the region of the ulcer (from unaffected tissue of the same part of the stomach), and also from the borders of the ulcer defect (in the stomach or the duodenal bulb). In parallel tests on all patients with chronic diseases of the liver (groups 1-4) PG were determined in the gastric juice (basal and after histamine stimulation), obtained by means of a gastric tube. Quantitative determination of PGE, $PGF_{2\alpha}$, and 6-keto-$PGF_{1\alpha}$ (a stable metabolite of prostacycline) was carried out by radioimmunoassay using standard kits: PGE and $PGF_{2\alpha}$ – produced by Clinical Assays, USA, and 6-keto-$PGF_{1\alpha}$ – from the Institute of Isotopes, Hungarian Academy of Sciences. The results of the tests were subjected to statistical analysis by Student's t test.

EXPERIMENTAL RESULTS

As Table 1 shows, among the PG tested in GM of subjects of the control group, the highest level was characteristic of PGE (550.7 ± 20.9 ng/g). The PGE/$PGF_{2\alpha}$ ratio was 2.15, in agreement with the results of the few investigations described in the literature relating to the PG content in GM in man [11].

The content of PGE, $PGF_{2\alpha}$, and 6-keto-$PGF_{1\alpha}$ in GM in the patients of group 1 with active cirrhosis of the liver fell significantly: by 1.6, 1.56, and 1.5 times ($p < 0.05$) respectively. The greater decrease in the levels of all PG studied in GM in cirrhosis of the liver complicated by gastric or duodenal ulcer (groups 2 and 3) will be noted. A distinct and significant decrease in the PG content both outside the ulcer and, particularly emphatically, in the borders of the ulcer defect, was a regular feature in this case. For instance, in cirrhosis of the liver complicated by gastric ulcer levels of PGE, $PGF_{2\alpha}$, and 6-keto-$PGF_{1\alpha}$ in the borders of the ulcer were 3, 1.9, and 1.7 times lower respectively ($p < 0.01$) than outside the ulcer, whereas in cirrhosis of the liver combined with ulcer of the duodenal bulb, it was 1.8, 1.6, and 1.3 times lower respectively ($p < 0.01$).

As will be clear from Fig. 1, more substantial changes in the PG content in GM of patients with cirrhosis of the liver took place during exacerbation of the disease For instance, in patients with cirrhosis of the liver and ulcer of the duodenal bulb in the stage of exacerbation, levels of PGE, $PGF_{2\alpha}$, and 6-keto-$PGF_{1\alpha}$ in GM were 29, 30, and 22% lower respectively than in the stage of remission. This is evidence that the severity of the disturbances in the formation of PG in the gastroduodenal mucosa in chronic diseases of the liver depends on the severity of the illness.

It is stated in the literature that the state of PG biosynthesis in GM is reflected in the secretion of these substances with the gastric juice [10]. Taking these facts into consideration we studied the secretion of PG with the gastric juice in patients with cirrhosis of the liver and chronic active hepatitis.

It will be clear from the results in Fig. 2 that most of the patients studied were evidently characterized by a decrease in PGE and $PGF_{2\alpha}$ concentrations in the gastric juice, both basal and stimulated by histamine. This decrease was observed in 54% of patients with chronic active hepatitis of viral etiology (on average by 20-30%, $p > 0.05$), and was more marked (by 1.5-2 times, $p < 0.05$) in chronic active hepatitis of alcoholic etiology and cirrhosis of varied etiology (primary biliary, HBsAg+, alcoholic), and was greatest in cirrhosis of the liver combined with peptic ulcer. Similar changes in PG secretion with the gastric juice were observed also during histamine stimulation, but they were rather less marked.

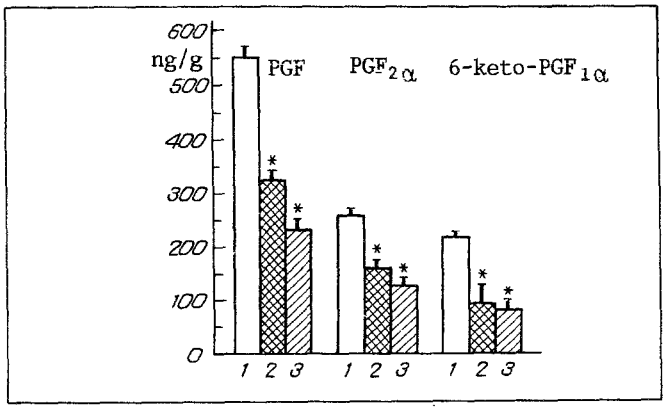

Fig 1. PG content in gastric mucosa (outside ulcer) in patients with cirrhosis of the liver combined with ulcer of the duodenal bulb: 1) control, 2) cirrhosis of the liver + ulcer of the duodenal bulb (remission), 3) cirrhosis of the liver + ulcer of the duodenal bulb (exacerbation) $p < 0.05$ Compared with control.

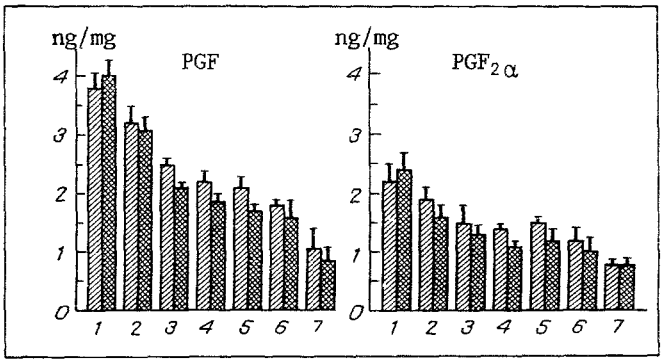

Fig. 2. PG content in gastric juice of patients with chronic liver diseases. 1) Control, 2) viral CAH, 3) alcoholic CAH, 4) primary biliary cirrhosis of the liver, 5) active cirrhosis of the liver HBsAg+, 6) alcoholic cirrhosis of the liver, 7) cirrhosis of the liver + ulcer of the duodenal bulb. Oblique shading – basal level, cross-hatching – after histamine stimulation.

Thus the results of investigations into the significant fall in the PG content in GM, correlating with lowering of their concentration in the gastric juice, in patients with chronic liver diseases lead to the conclusion that in this pathology and, in particular, in cirrhosis of the liver, considerable disturbances of endogenous PG biosynthesis are observed in GM, in agreement with the few data in the literature on PGE_2 insufficiency in GM in alcoholic cirrhosis of the liver [6]. PGE and prostacycline, and also $PGF_{2\alpha}$, as has recently been shown [9, 13], possess cytoprotective effects and play an exceptionally important role in maintenance of the integrity and high resistance of GM [8]. In this connection the discovery of insufficiency of these PG in GM for the gastric juice in pathology of the liver is of diagnostic and prognostic importance, for deficiency of PG, especially PGE and prostacycline, in GM is characteristic of peptic ulcer [14]. The mechanisms of the weakening of PG biosynthesis in GM in liver pathology may include: 1) possible changes in activity of the specific enzyme systems involved in PG biosynthesis, and coupled with changes in cyclase systems [3], 2) the deficiency of PG and their precursors (unsaturated fatty acids [2, 4] typical of chronic liver diseases, 3) the presence of alcohol, chronic intake of which inhibits processes of cyclooxygenase conversion of arachidonic acid into PG and induces ulcer formation [15], in the etiology of the disease, and 4) portal hypertension and congestive gastropathy, occurring in the majority of cirrhosis patients studied, etc.

Evidence was thus obtained that PG of GM play an essential role in the development of ulcers in patients with chronic liver diseases, especially cirrhosis. Taking into account the protective effect of PG against various lesions not only in the gastroduodenal mucosa, but also in the liver [7], changes in the formation and secretion of PG in the stomach may be one of the risk factors in the pathogenesis of hepatogenic ulcers [1].

LITERATURE CITED

1. N. Sh. Amirov, Z. D. Kondashova, and I. E. Trubitsyna, Diseases of the Hepatobiliary System and Pancreas [in Russian], Moscow (1984), pp. 79-83
2. R. A. Vysotskaya, A.S. Loginov, and E. V. Tkachenko, Byull. Éksp. Biol. Med., No. 8, 117 (1990).
3. A. S. Loginov, R. A. Vysotskaya, S. V. Sokolova, et al., Proceedings of the 4th All-Union Symposium on the Role of Cyclic Nucleotides and Secondary Messengers in the Regulation of Enzymic Reactions [in Russian], Petrozavodsk (1988), p. 134.
4. M. N. Markova, Patol. Fiziol., No. 3, 85 (1982).
5. A. Aly, K. Green, and C. Johansson, Scand. J. Gastroenterol., **22**, Suppl. 127, 35 (1987).
6. T. Arakawa, H. Satoh, T. Fukuda, et al., Gastroenterology, **93**, No. 2, 135 (1987).
7. E. Ballet, Gastroent. Clin. Biol., **13**, 712 (1989).
8. A. Bennett, Gastroent. Clin. Biol., **9**, No. 12, 30 (1985).
9. H. Grant, K. Palmer, R. Kelly, et al., Gastroenterology, **94**, No. 4, 955 (1988).
10. C. Johansson and S. Bergstrom, Scand. J. Gastroenterol., Suppl. No. 77, 21 (1982).
11. S. Konturek, T. Radecki, I. Piastucki, et al., Gut, **28**, 201 (1987).
12. M. Modard, V. Maxwell, T. Reedy, and J. Walsh, Gastroenterology, **93**, No. 1, 63 (1987).
13. C. Nicholl, G. Carolan, H. Sevelius, and S. Bloom, Digestion, **43**, No. 1-2, 47 (1989).
14. A. Robert, Gastroent. Clin. Biol., **9**, No. 12, 7 (1985).
15. D. Segarnik and I. Botrosen, Alcohol. Clin. Exp. Res., **11**, No. 1, 19 (1987).