METHODS

A Model of Combined Gastroduodenitis and Hyperlipidemia in Rats

V. V. Knyshova, I. L. Ivanova, and V. G. Kapitonova

Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny*, Vol. 131, No. 2, pp. 237-240, February, 2001
Original article submitted October 2, 2000

We elaborated a model of gastroduodenitis combined with hyperlipidemia in rats. This model is based on alimentary lipid disturbances and morphological changes in the gastroduodenal mucosa caused by exogenous damaging factors. Morphological assay revealed gastroduodenitis; biochemical studies of the blood and liver demonstrated hyperlipidemia. This model holds much promise for evaluating pathogenetic mechanisms of combined gastroduodenal and heart diseases.

Key Words: *gastroduodenitis; hyperlipidemia; experimental models*

Pathogenetic mechanisms underlying concurrent system diseases of different systems are of considerable importance [4,6,11]. Ulcer disease and gastroduodenitis are often combined with coronary heart disease (12.0-33.3% patients with gastroduodenal diseases), which calls attention to the development of gastroduodenitis against the background of hyperlipidemia, the major risk factor for atherosclerosis [5,8]. The mononosological approach does not allow us to reveal the relationship between combined diseases at the tissue and cellular levels, which is important for elaborating new therapeutic and preventive methods.

We developed a model of gastroduodenal disease accompanied by metabolic lipid disturbances and reflecting the major morphological and pathophysiological changes in organs and systems of experimental animals.

MATERIALS AND METHODS

Experiments were performed on 100 male and female Wistar rats weighing 200-220 g and obtained from the Stolbovaya nursery. The rats were kept in a vivarium under standard conditions for 14 days. Gastroduodenitis accompanied by hyperlipidemia (model of combined gastroduodenal pathology, CGP) was modeled using a "step-by-step" approach. At stage 1, the animals were given an atherogenic diet containing sugar, cream butter, egg powder, dry milk, and cholesterol (2.5% food). At stage 2, cholesterol-treated (1% food) rats intragastrically received (through a probe) 100 mg/kg aspirin and 2.5 mg/kg indomethacin dissolved in 10% officinal bile for 8-10 days. The amount of bile corresponded to its physiological content (1% body weight). This model reproduced gastroduodenitis combined with hyperlipidemia in 90-95% animals. The animals were decapitated under ether anesthesia, and the blood, liver, and stomach were taken. Serum contents of total cholesterol (TCH), triglycerides (TG), and high-density lipoprotein cholesterol (HDL CH) were measured on a Cobas—Mira biochemical analyzer (Hoffman La Roche). The concentrations of TCH [12] and TG [13] in the liver were estimated. For light microscopy, stomach tissues were routinely fixed in 10% neutral formalin and embedded in paraffin. The slices were stained with hematoxylin and eosin. The results were analyzed by Student's *t* test.

Institute of Medical Climatology and Rehabilitation Therapy, Vladivostok Branch, Far-Eastern Research Center of Physiology and Pathology of Respiration, Siberian Division of the Russian Academy of Medical Sciences

0007-4888/02/1312-0199$25.00

RESULTS

A variety of pathogenetic mechanisms underlying gastroduodenal diseases contributes to the existence of numerous methods for their modeling, *e.g.*, application of necrotizing agents to the stomach wall, ligation of vessels impairing circulation in the stomach wall, and modulation of the central nervous system (CNS) [2,10,14]. Some complex methods, including ligation of vessels and modulation of the CNS, require the use of special devices or surgical treatment. Intragastric administration of necrotizing agents or irritants (aspirin, hydrochloric acid, and ethanol) is the most convenient method. These compounds should be administered for 12-15 days to produce steady changes in the gastroduodenal zone [9]. Experimental hyperlipidemia can be induced by giving cholesterol or a diet enriched with cholesterol, carbohydrates, and fats [1,3,7].

The sequence of steps in the proposed model of CGP was dictated by high incidence and severity of gastroduodenal complications developed against the background of lipid metabolic dysfunction [8]. A diet enriched with fats and cholesterol for 6-7 weeks changes not only serum cholesterol content, but also the concentration of lipoproteins and TG, which corresponds to hyperlipidemia in humans. Nonsteroid antiinflammatory drugs (aspirin and indomethacin) and bile serve as damaging factors. The use of these nonsteroid preparations accelerated the development of CGP from 12-15 to 8-10 days. Treatment with bile simulated duodenogastral reflux. Bile having detergent properties impairs the protective layer and the resis-

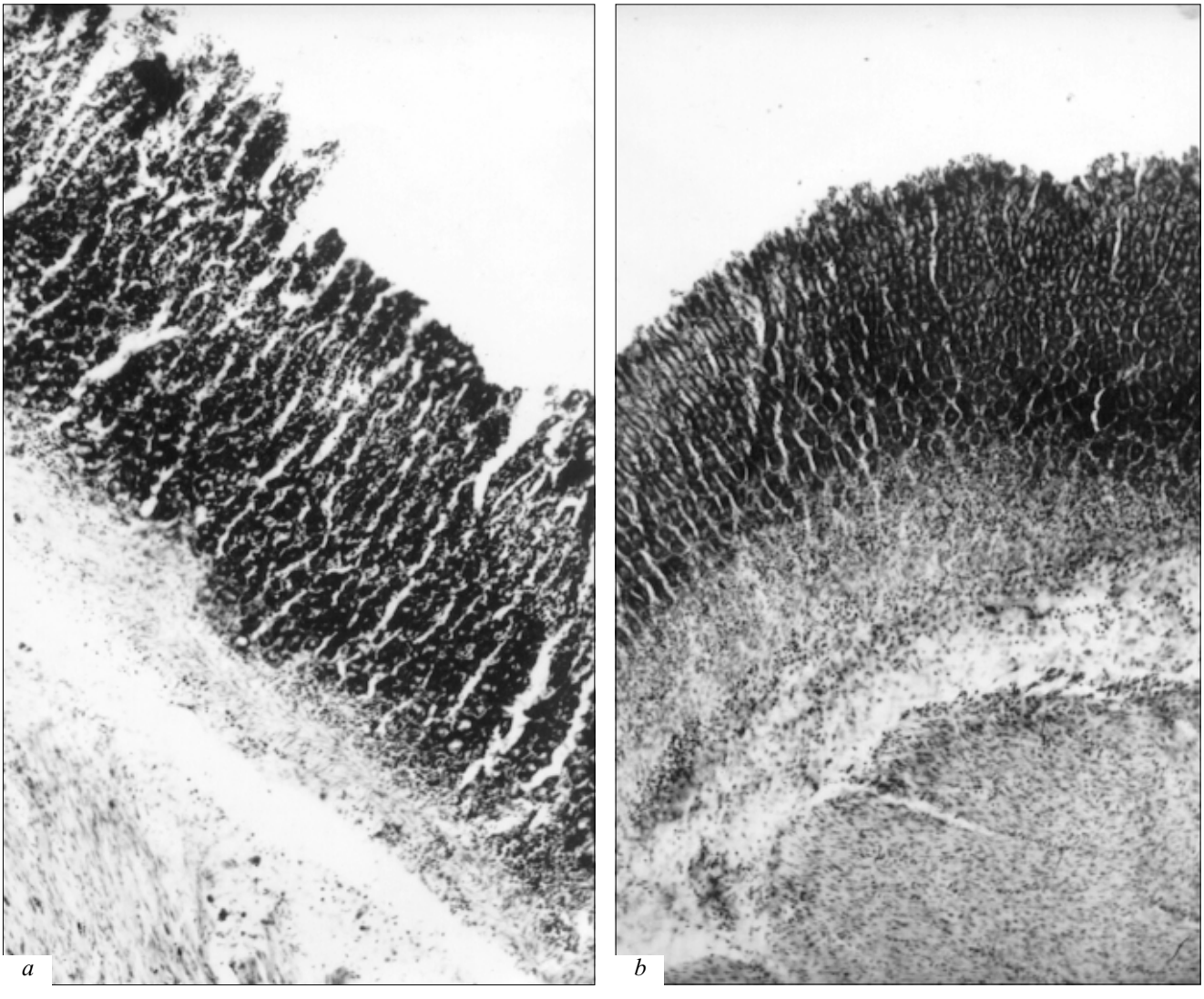

Fig. 1. Histological changes in the gastric mucosa in animals with experimental combined gastroduodenal pathology (lymphocyte-leukocyte infiltration and atrophy of the glandular epithelium, *a*) and gastroduodenitis (lymphocyte-histiocyte infiltration and transformation of the glandular epithelium, *b*). Staining with hematoxylin and eosin, ×250.

TABLE 1. Lipids in the Blood (mmol/liter) and Liver (μmol/g) of Animals with Experimental Combined Gastroduodenal Pathology and Hyperlipidemia (*M*±*m*)

Parameter		Control (*n*=10)	Combined gastroduodenal pathology (*n*=50)	Hyperlipidemia (*n*=20)
TCH	blood	1.27±0.02	1.28±0.03	2.77±0.11*
	liver	5.60±0.43	7.51±0.22*	7.94±0.44*
TG	blood	0.56±0.01	0.93±0.06*	1.28±0.07*
	liver	11.80±0.53	17.97±0.84*	18.27±1.01*
HDL CH	blood	0.110±0.004	0.25±0.01*	0.21±0.03*

Note. *p<0.01 compared to the control.

tance of the gastroduodenal mucosa to damaging factors. Since bile mixed with pancreatic juice bicarbonates and duodenal content is *in vivo* refluxed into the stomach, we used 10% bile for CGP modeling. In this case, pathomorphological changes are comparable with those observed in the gastric mucosa of humans with chronic gastritis.

Studies of the blood, liver, and stomach confirmed the development of persistent CGP. Metabolic disturbances were characterized by hypertriglyceridemia: TG concentration in the blood surpassed the control by 66.1%, and the contents of TCS and TG in liver cells were 1.3 and 1.5 times higher than in the control, respectively (Table 1). Cholesterol level 2.7-fold surpassed the control over 1 month of the experiment (p<0.01). Metabolic changes during experimental CGP were similar to those in animals with experimental hyperlipidemia (Table 1).

Morphological assay revealed focal lymphocyte-leukocyte infiltration of the gastric mucosa, cubic transformation, and focal necrobiosis of the epithelium in animals with experimental CGP (Fig. 1, *a*). Changes in the glandular epithelium were characterized by atrophy, cystic dilation of glands, and cell hyperplasia and dysplasia. Microcirculatory disturbances included paretic dilation of blood capillaries, stasis, microfocal hemorrhages, and perifocal inflammation. We found focal lymphoid infiltration and edema of the muscle layer. It should be emphasized that morphological changes during experimental CGP were similar to those in animals with experimental gastroduodenitis (Fig. 1, *a*, *b*).

The proposed model of gastroduodenitis combined with hyperlipidemia is characterized by lipid metabolic dysfunction and histomorphologic changes in the gastroduodenal mucosa, which corresponds to pathophysiological mechanisms of combined human diseases. This simple method reflects polyetiology of CGP.

REFERENCES

1. V. G. Baranov, N. F. Baranov, and M. F. Belovintseva, *Probl. Endokrinol*., No. 6, 58-62 (1972).
2. A. I. Voloshin, *Clinical and Experimental Substantiation of Successive Rehabilitation Therapy of Chronic Primary Gastroduodenitis*, Abstract of Doct. Med. Sci. Dissertation, Chernovtsy (1988).
3. I. Goranov, K. Avramova, N. Donchev, *et al*., *Vopr. Pitaniya*, No. 4, 71-73 (1990).
4. V. V. Knyshova, *Byull. Sib. Otd. Ros. Akad. Med. Nauk*, No. 4, 80-84 (1998).
5. V. V. Korzhikov, *Ulcer Diseases of the Stomach and Duodenum in Patients with Coronary Heart Disease*, Abstract of Cand. Med. Sci. Dissertation, Moscow (1994).
6. A. A. Krylov, *Ter. Arkh*., No. 2, 121-124 (1992).
7. M. F. Nesterin, V. F. Markemova, B. G. Lyapkov, *et al*., *Vopr. Pitaniya*, No. 1, 32-36 (1979).
8. A. N. Perevertkina, *Clinics, Diagnostics, and Therapy of Ulcer Diseases of the Stomach and Duodenum Combined with Coronary Heart Disease*, Abstract of Cand. Med. Sci. Dissertation, Moscow (1990).
9. N. D. Polushina, *Hormonal Mechanisms Underlying Primary Prevention of Gastroduodenal Ulcers by Drinking Mineral Water*, Abstract of Doct. Med. Sci. Dissertation, Pyatigorsk (1993).
10. N. I. Tutchenko, Ya. V. Goer, L. S. Belyanskii, *et al*., *Pat. Fiziol*., No. 5, 54-55 (1990).
11. N. V. El'shtein, *Rus. Med. Zh*., No. 6, 344-352 (1997).
12. G. Bradgon, *Lipids and the Steroid Hormones*, Philadelphia (1960), p. 7.
13. B. Nery and C. Frings, *Clin. Chem*., **19**, 1201-1202 (1973).
14. A. Robert, *Ann. Clin. Res*., No. 16, 335-338 (1984).