Structural and Functional Changes in Gastric Epithelium in *Helicobacter Pylori*-Associated Chronic Gastroduodenal Pathologies

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Complex structural analysis of the gastric mucosa was carried out in patients with *Helicobacter pylori*-associated chronic gastroduodenal ulcers, chronic gastritis, and vibration gastropathy. Microscopic examination showed stereotypical changes in the epithelium in all diseases: degeneration, focal intestinal metaplasia, dysplasia, and glandular atrophy. The severity of these changes depended on the disease entity. The most typical ultrastructural modifications of epitheliocytes were damage to the apical plasmalemma, heterogeneity of the secretory compartment of the cytoplasm, dilatation of the cytoplasmic reticulum, vacuolation, and signs of cytolysis. Plastic reactions of the gastric epithelium reflected disproportional changes in all cell metabolites caused by increased proliferative activity of the epithelium under conditions of uneven inhibition of intracellular protein synthesis.

Key Words: *chronic gastroduodenal diseases; gastric epithelium; Helicobacter pylori; electron microscopy; autoradiography*

Helicobacter pylori is considered to be one of the main etiopathogenetic factors of chronic gastroduodenal diseases [1,3,11]. Invasion of *H. pylori* initiates a cascade of inflammatory and immune reactions [8, 12,13,15] and is associated with complex pathomorphological changes in the gastric mucosa [1,6,7]. Molecular genetic markers of *H. pylori*, virulence factors, and mechanisms of bacterial persistence were intensely studied in recent years [2,7,9,10,14]. However, the data on the biology and pathology of the infectious process induced by *H. pylori* are contradictory. Structural modifications, processes of injury and recovery of the gastric mucosa, and the role of the host organism in the development of *H. pylori*-associated diseases are still not quite clear.

We studied restructuring of the gastric epithelium in chronic diseases of different origin associated with *H. pylori*.

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MATERIALS AND METHODS

A total of 527 clinical cases with chronic gastroduodenal diseases (379 men and 148 women aged 16-78 years) were analyzed: 185 cases of chronic gastritis, 100 chronic gastric ulcers, 156 chronic duodenal ulcers, and 86 cases with vibration gastropathology. Common clinical and laboratory biochemical studies were carried out in all patients; fibrogastroscopy with spot biopsy of the gastric mucosa was carried out, when indicated. Biopsy specimens were collected from the fundal and pyloric compartments, from the ulcer defect, and from the periulcer area.

After standard histological processing of the biopsy specimens, paraffin sections were stained with hematoxylin and eosin in combination with Perls reaction, Van-Gieson staining, and periodic acid-Schiff reaction. *H. pylori* was detected in Giemsa-stained preparations. Semithin sections were stained with Azur II and Schiff reagent. Ultrathin sections were contrasted with uranyl acetate and lead citrate and examined under a JEM 1010 electron microscope. *In vitro*

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autoradiography was carried out using ^{3}H-thymidine (100 μCi/ml, specific radioactivity 24 Ci/mM) and ^{3}H-uridine (200 μCi/ml, specific radioactivity 26.6 Ci/mM). The label index and density were estimated on semithin sections.

RESULTS

Bacterioscopy of biopsy specimens showed high prevalence of *H. pylori* infection in gastric diseases of different origin. The bacteria were detected in 73.8% cases of chronic gastritis, 87.5% chronic gastric ulcers, and 82.8% chronic duodenal ulcers. Moreover, vibration gastropathy was also associated with high rate of *H. pylori* infection (73.3%). The bacteria were found in biopsy specimens from both pyloric and fundal parts of the stomach. The degree of mucosal colonization greatly varied increasing mainly in the distal direction; high contamination of both compartments of the stomach with the bacteria was often observed.

Microscopic examination of biopsy specimens of *H. pylori*-colonized gastric mucosa showed degenerative changes of different severity in the epithelium (Fig. 1, *a*). Production of the mucus is intense in some cases and suppressed in others. Active secretion of the gastric epithelium was usually associated with high degree of *H. pylori* colonization of the gastric mucosa.

An important structural characteristic of the gastric epithelium is its intestinal metaplasia type transformation (Fig. 1, *b*). Foci of metaplasia most often developed in chronic gastric ulcers (45.7%), particularly in the marginal zone of the ulcer defect (52.1%), more rarely in duodenal ulcers (24.4%), chronic gastritis (26.3%), and vibration gastropathy (27.7%). *H. pylori* can be present in high amounts in the immediate vicinity of the metaplastic epithelium. However, extensive metaplastic involvement of the mucosa, most typical of vibration gastropathy, seemed to be a factor limiting propagation of *H. pylori* in the stomach.

Epithelial dysplasia developed most often in the marginal zone of chronic gastric ulcer (45.8%; Fig. 1, *c*). In other chronic gastroduodenal diseases associated with *H. pylori* foci of epithelial dysplasia were detected in 30.3% cases of chronic gastritis, 22.2% chronic duodenal ulcers, and 21.5% cases of vibration gastropathy. The bacteria were located mainly on the epithelial surface with signs of slight and moderate dysplasia, in contrast to zones of severe dysplasia with pronounced deficiency of secretory function.

Atrophic changes in the epithelial structures infected with *H. pylori* manifested most intensively in the glandular compartment of the mucosa. Atrophies of different severity developed in pyloric (Fig. 1, *d*) and fundal glands of the stomach. Irrespective of the degree of bacterial colonization, glandular atrophy of the stomach was more incident in chronic gastritis (44.7%) and vibration gastropathy (67.7%) than in chronic gastric (31.4%) or duodenal ulcer (40.0%).

Electron microscopy showed that epitheliocyte population was characterized by peculiar heterogeneity determined by different functional activity of epitheliocytes on the one hand, and by different degree of cytoplasmic organelle alteration on the other. Slightly modified epitheliocytes retained polarity of intracellular organization. Numerous secretory granules occupying the supranuclear compartment of the cytoplasm slightly varied in size and electron density. Deformation of the apical surface relief with reduction of microvilli was sometimes paralleled by microclasmatosis (Fig. 2, *a*). Destabilization of cell contacts, mainly interdigitation, manifested in dilatation of intercellular spaces with free disposed lateral processes of the plasmalemma.

Progression of cytopathic changes is associated with epitheliocyte depletion of secretory granules, which were detected only in the apical zone of the cytoplasm. Characteristic features of this process were uneven dilatation of cisterns of the cytoplasmic reticulum and elements of the Golgi complex (Fig. 2, *b*); "swollen" mitochondria with focal matrix clarification, sometimes large cytolysosomes were seen.

Epitheliocytes (solitary or grouped) with signs of appreciable destruction were detected everywhere in the epithelial layer. They were characterized by pronounced disorganization of the ultrastructure with signs of cytolysis. The cell nuclei contained loose chromatin sometimes with compact nucleoli. There were virtually no secretory granules in the electron-clear cytoplasm, but dilatation and degranulation of the cytoplasmic reticulum, mitochondrial edema with destruction of the cristae were sharply expressed; many small vacuoles were seen (Fig. 2, *c*).

The status of plastic reactions of the epithelium reflected changes in DNA synthesis (according to autoradiography data); modulations of the label index varied from 3.9 to 16.7% (Fig. 2, *d*). Activation of DNA synthesis in the epithelium correlated with the progress of structural changes in the mucosa and seemed to be aimed at preservation of the epitheliocyte population under conditions of intensive cell damage and death.

The protein-producing activity of the epithelium evaluated by RNA production varied within a wide range, the percentage of labeled cells being 22.2-88.1%. The intensity of the radioactive isotope incorporation in the epithelium in chronic gastritis and vibration gastropathy was lower than in chronic ulcer, which resulted from more grave cytopathic reactions and from atrophic changes in the gastric mucosa.

Hence, the prevalence of *H. pylori* infection is high in gastroduodenal diseases irrespective of their

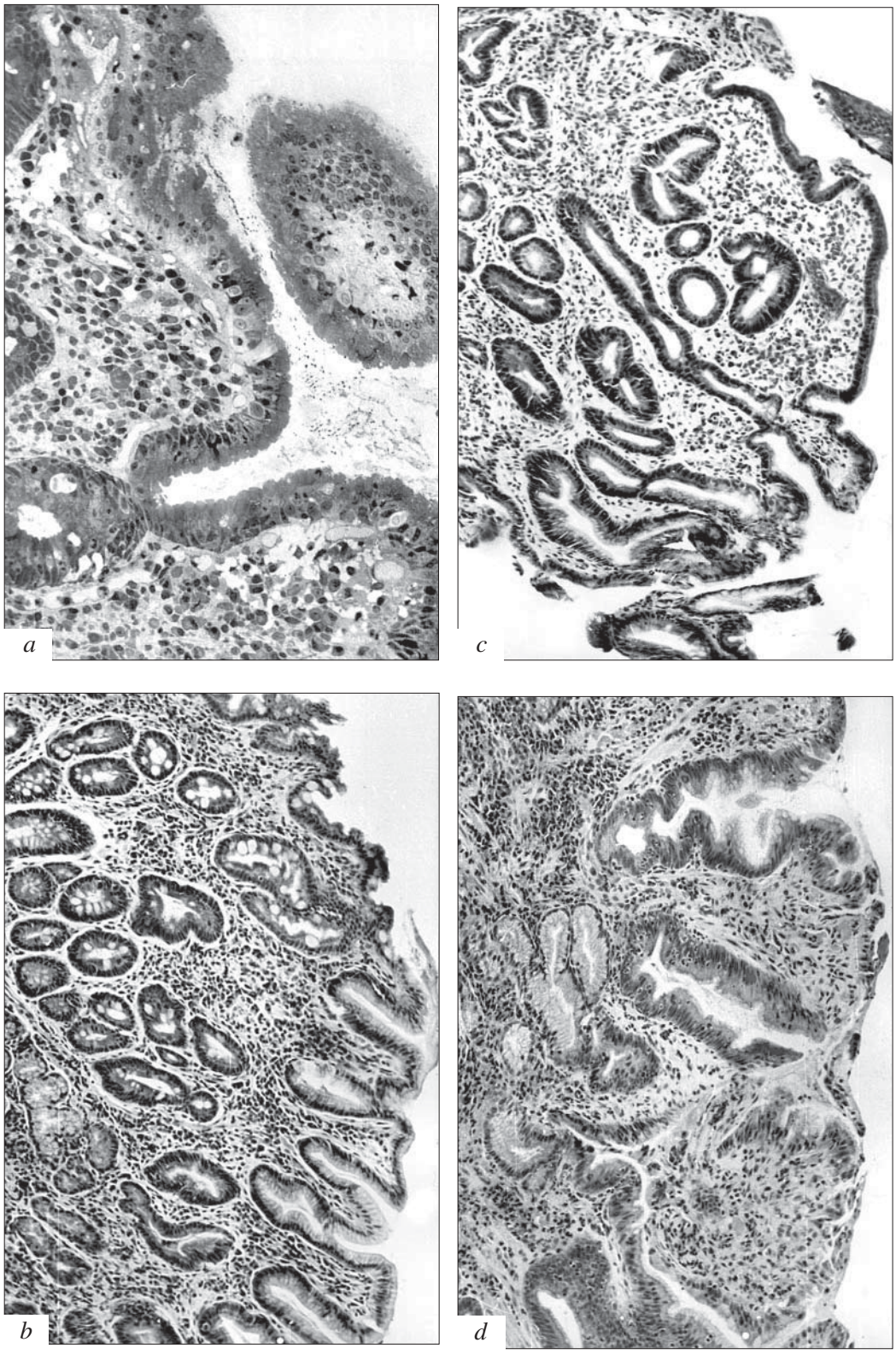

Fig. 1. Pathomorphological changes in the gastric mucosa epithelium in *H. pylori*-associated gastric pathologies. *a*) degeneration of the epithelium. *H. pylori* on the surface of cell layer. Semithin section, Azur II staining, ×400; *b*) intestinal metaplasia of surface and glandular epithelium; *c*) gastric epithelial dysplasia; *d*) degeneration of the surface epithelium, atrophy of pyloric glands. *b-d*) hematoxylin and eosin staining, ×160.

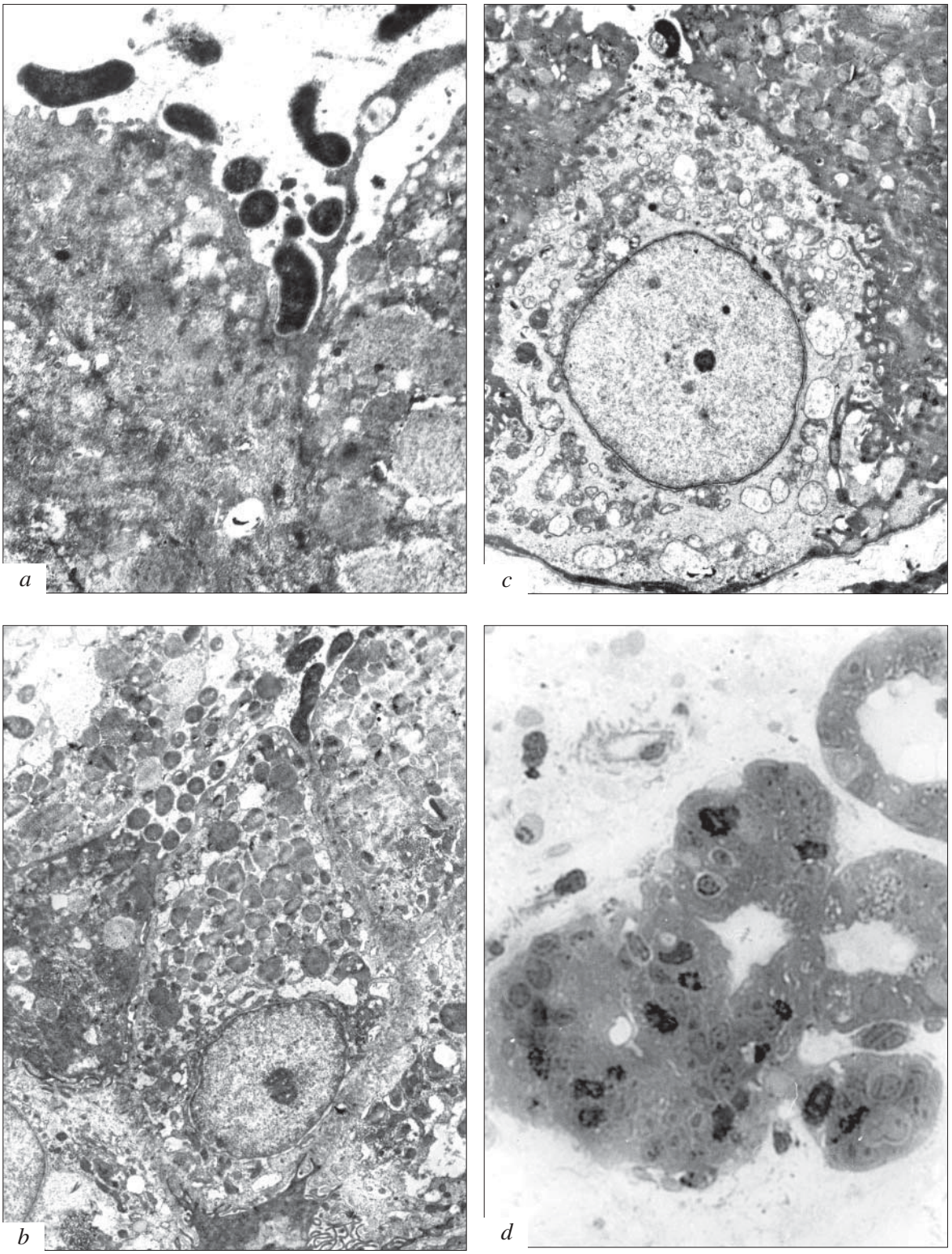

Fig. 2. Ultrastructural changes in gastric epitheliocytes in *H. pylori*-associated gastroduodenal disease. *a*) fragments of two epitheliocytes, *H. pylori* on cell surface, destruction of plasmalemma apical relief, ×4500; *b*) *H. pylori* on epithelial surface, heterogeneous secretory granules in epitheliocytes, dilatation of cytoplasmic reticulum, reduction of microvilli, ×2340; *c*) epitheliocyte with signs of destruction and vacuolation of cytoplasmic organelles, ×2340; *d*) DNA synthesis in the epithelium of a gastric pit. Semithin section, incubation with ^{3}H-thymidine, Azur II staining, ×720.

pathogenesis. The gastric epithelium undergoes stereotypical pathological changes during colonization of the mucosa with *H. pylori*, the main of which are diffuse degeneration, impaired cell differentiation, partial atrophy of the glandular components. The severity and prevalence of these changes depend to a great measure on the disease. Epitheliocyte ultrastructure is characterized by impairment of the apical plasmalemma, heterogeneity of the secretory compartment, dilatation of the cytoplasmic reticulum, vacuolation of the cytoplasm, and cytolysis. Biosynthesis of the main cell metabolites in the gastric epithelium is paralleled by disproportionate changes reflecting the intensification of the proliferative function in conjunction with uneven inhibition of protein synthesis.

The detected structural changes in the gastric epithelium in *H. pylori*-associated gastroduodenal pathologies are not specific, because they can develop in chronic diseases not associated with bacterial infection. Nevertheless, they indicate intricate interactions between the host and microorganisms. The cytopathological effect of *H. pylori* seems to be compensated mainly due to proliferative reaction of the epithelium maintaining the total number of these cells. On the other hand, the deficiency of intracellular regeneration can promote attenuation of the protective characteristics of epitheliocytes and the entire epitheliocyte layer, which augments the development of pathological process in the mucosa.

On the whole, the pathogenic potential of *H. pylori* is realized in complex with other factors, which have an unfavorable impact on the gastric mucosa, leading to the development of a certain disease, and depends largely on the individual characteristics of the host [4,5].

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