Ultrastructural Changes in Cells of the Gastric and Small Intestinal Mucosa during Bronchial Asthma

G. I. Nepomnyashchikh, G. M. Chernyavskaya, S. V. Aidagulova, and D. I. Korabel'nikov

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The complex of structural changes in the gastroduodenal mucosa in patients with bronchial asthma is considered as a polyetiological primary degenerative process with progressive atrophy of the epithelium and formation of erosions. Ultrastructural signs included degenerative changes in the endothelium of microvessels and surface and glandular epithelium, which were accompanied by compensatory hyperfunction of intact mucus-producing cells, hyperplasia, and increased functional activity of mast and immunocompetent cells. The development of destructive and erosive lesions was associated with hyperplasia of parietal and endocrine cells in the mucosa. We evaluated the specific structural reactions clinically typical of bronchial asthma of different severity. The data are interpreted in terms of a relationship between pathological changes in the mucosa of different localization.

Key Words: *bronchial asthma; stomach; duodenum; biopsy; electron microscopy*

Pathological changes of the digestive system in patients with bronchial asthma (BA) are pathogenetically related to the primary disease or precede its development and have no pathogenetic significance [3,11]. Hypoxemia and hypercapnia develop during respiratory insufficiency and local hypoxia that accompany microcirculatory disturbances and impairment of endocrine regulation. These disorders play a role in the pathogenesis of gastrointestinal disorders [7].

Particular attention is given to the role of the constitutional type in the pathogenesis of BA [8]. Hereditary predisposition is one of the major signs for atopic diseases, including atopic BA. Previous studies evaluated localization and specific relationship between various genes and signs of the atopic syndrome [2]. It should be emphasized that a variety of systems can be involved in the pathological process during atopic disorders [8].

Institute of Regional Pathology and Pathomorphology, Siberian Division of the Russian Academy of Medical Sciences, Novosibirsk; Siberian State Medical University, Russian Ministry of Health, Tomsk. ***Address for correspondence:*** pathol@cyber.ma.nsc.ru. Nepomnyashchikh G. I.

Here we studied ultrastructural changes in cells of the gastric (GM) and duodenal mucosa (DM) during BA.

MATERIALS AND METHODS

We studied structural changes in GM and DM in 24 patients with BA (women, 34-54 years). The duration of disease was 4-20 years. Pollen was the primary allergen. Signs of the systemic reaction observed in the mucosa included rhinitis and conjunctivitis. The patients were divided into groups depending on clinical severity of BA (mild, moderate, severe). Hormone-independent patients had mild or moderate BA. Severe BA accompanied the hormone-dependent process. Hormone therapy (prednisolone dose 10-30 mg/day) was performed for 1-3 years. The dose of drugs usually depended on the duration of BA.

Diagnostic procedures included clinical, laboratory, and instrumental assays. Esophagogastroduodenoscopy and biopsy of GM (fundus and pylorus) and duodenal bulb were performed if required. The staining procedure for paraffin sections included

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hematoxylin-eosin and Perls stain. Staining was performed by the method of van Gieson. Elastic fibers were stained with Weigert's resorcin fuchsin. The periodic acid-Schiff (PAS) reaction was performed. Semithin sections were stained with Schiff reagent and azure II. For electron microscopy ultrathin sections were contrasted with uranyl acetate and lead citrate and examined under a JEM 1010 electron microscope.

RESULTS

Endoscopy revealed diffuse hyperemia and focal atrophy of the mucosa in the esophagus, stomach, and duodenum in patients with BA. The degree of atrophy in the gastroduodenal mucosa increased with increasing the duration and severity of BA. It was accompanied by the formation of erosions. The number of erosions (including multiple lesions) was maximum in patients with moderate BA (40% patients, 15% patients with hormone-dependent BA).

Light microscopy of biopsy specimens from GM and DM of patients with BA revealed the following specific reactions: degeneration and atrophy of the surface, pit, cryptal, and glandular epithelium, metaplasia and dysplasia, diffuse lymphoplasmocytic infiltration of the mucosa, appearance of lymphoid aggregates, systemic vasculopathy, and moderate diffuse fibrosis of the stroma. The degree of specific structural reactions depended on the severity of BA.

Structural changes in the stomach and duodenum of patients with mild BA were least pronounced. Pathological changes in the secretory apparatus included mild degeneration, focal atrophy of the surface epithelium and fundal glands (Fig. 1, *a*), and lymphoplasmocytic infiltration of the stroma (Fig. 1, *b*). Moderate BA was accompanied by erosive destruction of the gastroduodenal mucosa (Fig. 1, *c*) and atrophy of the mucosa (22% patients) and fundal glands (56% patients). Severe BA was characterized by pronounced atrophy of GM and DM (75% patients), surface epithelium (88% patients), and glands (50% patients), appearance of single intraepithelial microabscesses, and diffuse disturbances in cell differentiation (intestinal metaplasia in the stomach and dysplasia in the duodenum, Fig. 1, *d*).

Particular attention was given to typical changes in cells of GM and DM. We evaluated not only alternative, but also compensatory reactions.

The surface epithelium in the gastric fundus was characterized by polymorphism of mucin granules. These granules were heterogeneous and osmiophilic in patients with mild BA (Fig. 2, *a*), but electron transparent during moderate and severe BA. Hormone-dependent BA was accompanied by the appearance of large intraepithelial lipid inclusions (Fig. 2, *b*). Secretory granules in surface epitheliocytes of the pylorus included eccentric round electronically dense areas. These changes reflect multicomponent composition of the secretory material. It should be emphasized that *Helicobacter pylori* was often found near the apical cytolemma of surface and pit cells, which is consistent with previous studies of other pathological processes [9]. However, these bacteria did not enter the epithelial layer (intercellular or intracellular space). We sometimes revealed the signs for adhesion of osmiophilic microbial bodies to epitheliocyte microvilli.

Epitheliocytes of fundal glands in patients with moderate and severe BA were primarily presented by mixt-cells with a considerable number of large mucin granules (predominance of mucus-producing activity). Zymogen secretory granules and/or elements of the tubulovesicular system typical of parietal cells were present in the cytoplasm (Fig. 2, *c*). The appearance of mixt-cells probably reflects not only delayed differentiation of glandular cells in fundal glands, but also the inhibition of protein synthesis due to progressive degeneration and "emergency" compensatory reaction (mucus hypersecretion).

Hyperplasia and hyperfunction of parietal cells were observed in most biopsy specimens of GM from patients with erosive lesions. However, the cytoplasm of many cells included heterogeneous myelin structures. It reflected intensive proliferation and degradation of parietal cells, which affected the development of erosive and necrotic changes.

Ultrastructural signs of cell specialization were absent in fundal glandular cells of patients with hormone-dependent BA. Instead of specific cytoplasmic organelles, epitheliocytes contained large polymorphic lipid inclusions bounded by strongly osmiophilic membranes (Fig. 2, *d*).

The study of biopsy specimens from the gastric pylorus of patients with moderate BA revealed hyperplasia of endocrine cells. They were presented by heterogeneous population of epitheliocytes classified by the type of secretory granules. Except for the apical region of gastrin-producing G-cells opening into the gastric lumen (exo-endocrine cells), other endocrine cells did not communicate with the lumen and had triangular shape, wide base, and sharply narrowed apex.

The most numerous gastrin-producing cells (G-cells) are large electron light epitheliocytes with the euchromatic nucleus. The specific feature of G-cells is the presence of specific secretory granules with typical ultrastructural characteristics (Fig. 3, *a*) and intermediary cytoplasmic organelles. The appearance of erosive lesions in the gastroduodenal zone of patients with BA is mediated by the gastrin mechanism, which underlies stimulation of parietal cells due to

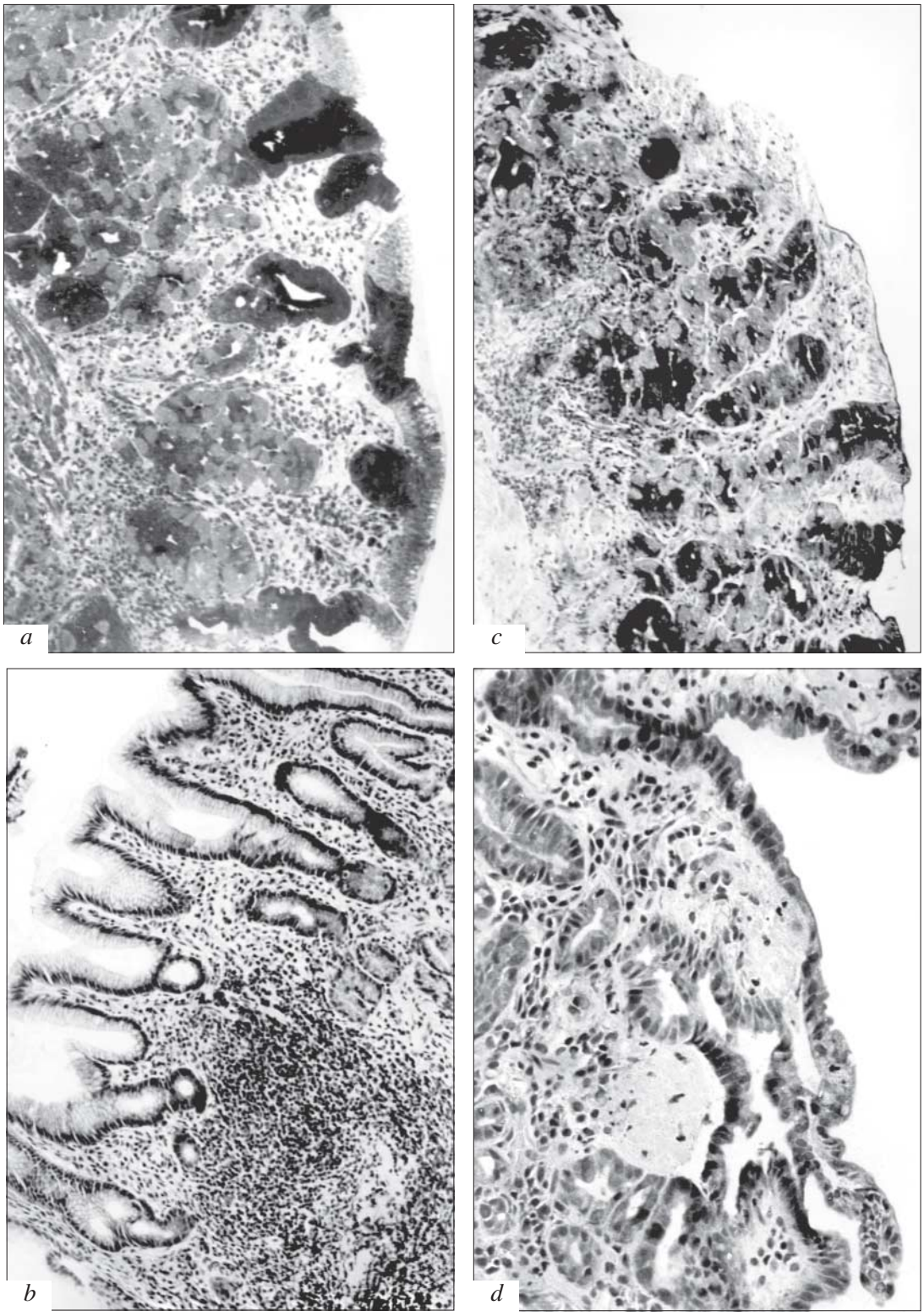

Fig. 1. Light microscopy of the gastroduodenal mucosa during bronchial asthma. Gastric fundus: reduction of folds, hypoplasia of glands, mononuclear infiltration of the stroma; semithin section, staining with Schiff reagent and azure II (×180, *a*). Gastric pylorus: atrophy of glands, large lymphoid follicle; staining with hematoxylin and eosin (×160, *b*). Gastric fundus: epithelialized erosion, hyperplasia of parietal cells; PAS reaction (×100, *c*). Duodenum: deformation of villi and crypts, atrophy and dysplasia of the epithelium, subepithelial hemorrhages; staining with hematoxylin and eosin (×250, *d*).

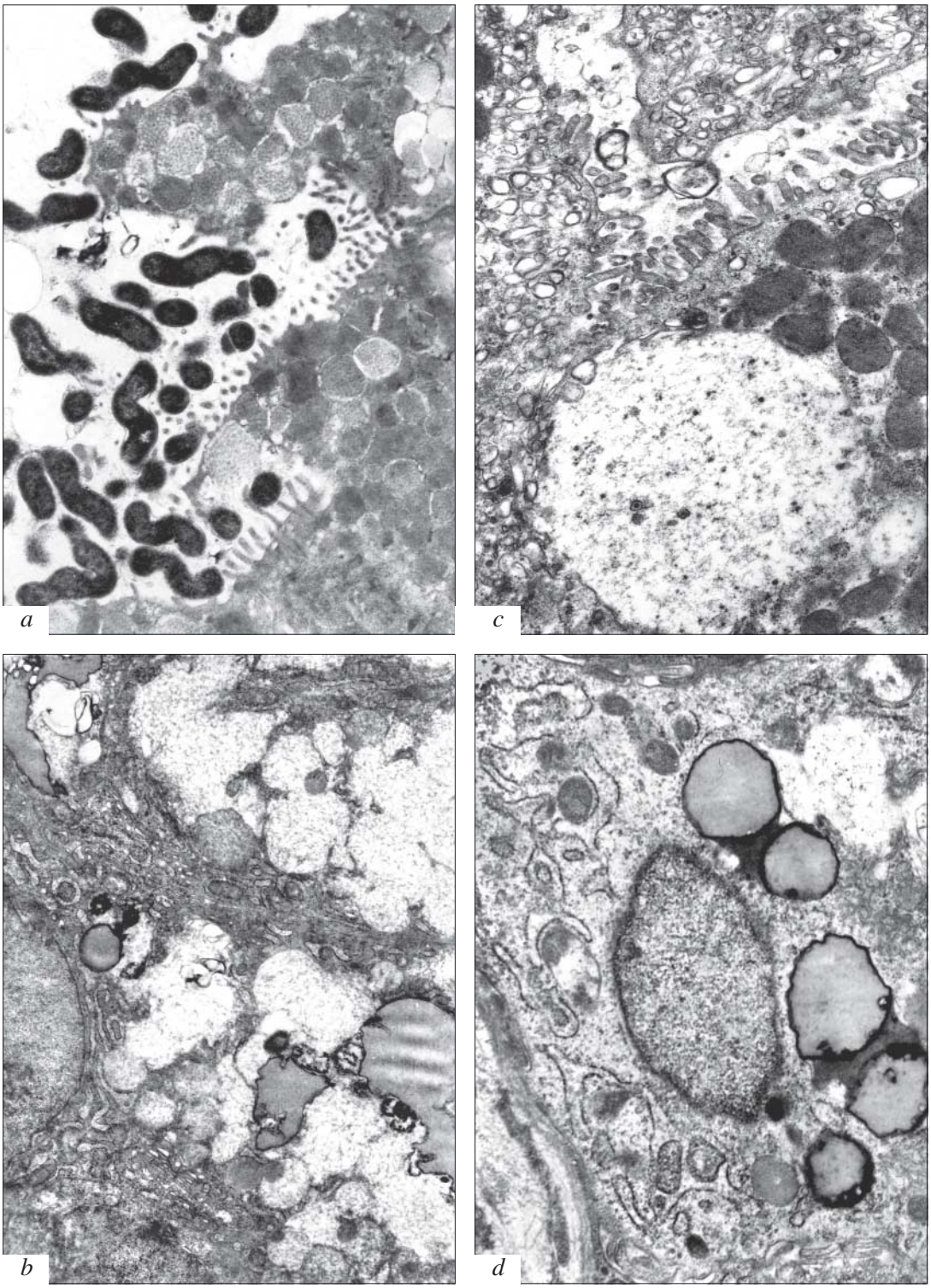

Fig. 2. Ultrastructural characteristics of epithelial cells in the mucosa of the gastric fundus during bronchial asthma: osmiophilic polymorphic *H. pylori* above surface epitheliocytes (×20,000, *a*); lipid inclusions and mucin-containing granules in the cytoplasm of surface epitheliocytes (×10,000, *b*); mixt-cell of the fundal gland with secretory canaliculus, large secretory granule, and mitochondria (×25,000, *c*); fundal glandular cell: large lipid inclusions, no signs of specialization (×10,000, *d*).

histamine hyperproduction by ECL and mast cells [10]. It probably determines the maximum number of erosions in patients with moderate BA.

We revealed a considerable number of somatostatin-producing D-cells (Fig. 3, *b*). They had smaller size and included moderately osmiophilic round

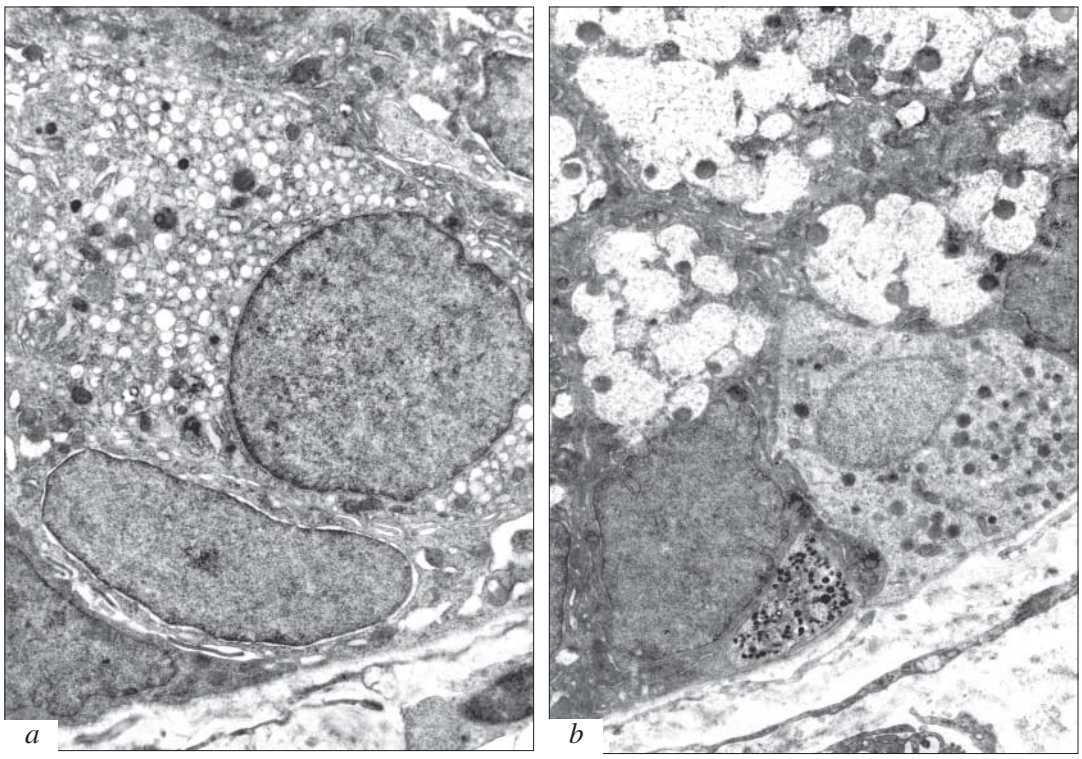

Fig. 3. Ultrastructural characteristics of endocrine cells in the mucosa of the gastric pylorus during bronchial asthma: G-cell with electronically transparent secretory granules (×5000, *a*); D-cell with electronically light cytoplasm, euchromatic nucleus, and secretory granules (*b*). Fragment of the endocrine cell with small osmiophilic granules is shown at the left (×4000).

secretory granules that were concentrated under the nucleus and contacted with the basal cytolemma. Endocrine cells with small, electron dense, and round or irregular granules were also present. Epithelial endocrine cells of various types differed in high transparency of the cytoplasmic matrix that included elements of the granular endoplasmic reticulum, Golgi complex, and single small mitochondria. Most cells were in the phase of synthesis of secretory material. Signs of excretion were revealed near the basal cytolemma. Long cytoplasmic processes sometimes extended along the epithelial basal membrane and were responsible for paracrine secretion and transport of regulatory substances to target cells. They sometimes penetrated the basal membrane and entered the subendothelial space.

Hemodynamic disturbances were revealed in patients with BA of different severity (hyperemia, stasis, hemorrhages, and aneurismal deformations). These changes primarily concerned the surface microcirculatory bed (gastric folds and intestinal villi). Endotheliocytes in these microvessels were structurally heterogeneous. Degenerative cells were predominant. A considerable number of mast (degranulated) and plasma cells was revealed in the subendothelial stroma of the gastroduodenal mucosa in patients with moderate and severe BA. Hyperplasia of these cells was accompanied by an increase in their functional activity.

Our results indicate that structural changes in the gastroduodenal mucosa of patients with BA are presented by progressive degeneration and atrophy of surface and glandular epitheliocytes and endotheliocytes in microvessels and moderate diffuse fibrosis. These signs reflect the development of primary degeneration. Compensatory and adaptive structural changes included the formation of polyfunctional mixt-cell and hyperplasia of immunocompetent cells (plasma cells and lymphocytes). Hyperplasia of endocrine cells associated with the development of erosive lesions was of particular importance. Hyperplasia of endocrine cells in the gastrointestinal tract was previously found in patients with peptic ulcer disease, chronic gastritis, and appendicitis [1,6].

The nonspecific mechanisms for atopic processes (BA, rhinitis, and dermatitis) include imbalance between the sympathetic and parasympathetic systems and increase in the ability of mast cells and blood basophils to release bioactive substances. These compounds are secreted spontaneously or in response to nonspecific stimulation, which does not trigger the reaction in healthy people.

Endocrine cells of the gastroduodenal mucosa play an important role in the neurohormonal regulation [12, 13]. They provide the neurohormonal regulation over structural and functional activity of the mucosa in the bronchial tree and gastrointestinal tract [14,15].

Diffuse systems of endocrine and mast cells realize the specific (immune) and nonspecific mechanisms of atopic diseases.

The data on pathological changes in the digestive system of patients with BA reflect the systemic type of this disease and confirm the existence of a relationship between structural changes in the mucosa [4,5].

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