necessitate a combined morphological and biochemical investigation, with the use of different periods (and methods) of alcoholization and withdrawal.

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IMMUNOHISTOCHEMICAL CHARACTERIZATION OF CHRONIC EROSIONS OF THE GASTRIC MUCOSA

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Chronic erosions are a special form of lesion of the gastric mucosa the verification and study of which has become possible as a result of progress in endoscopic techniques [1, 5, 10-12]. Endoscopic features and the histopathology of acute ("incomplete") and chronic ("complete") gastric erosions have now been sufficiently well studied, but the mechanisms of transformation of erosive defects into the chronic state remain unexplained [1]. The presence of a special form of fibrinoid necrosis, an essential component of erosions, its unusual relations with leukocytes [1, 12], the discovery of viruses [11, 12] and of bacteria [7] in the zone of erosive defects, and also the positive therapeutic effect of local application of leukocytic concentrate [7] are all evidence of the possible involvement of immunopathological reactions in the pathogenesis and morphogenesis of erosions.

The aim of this investigation was to study local immunity of the gastric mucosa in order to establish the role of an immunopathological component in the formation and chronic transformation of erosion lesions.

EXPERIMENTAL METHOD

Biopsy specimens from the stomach, taken during fiberoptic gastroscopy with direct vision biopsy from 85 male patients aged between 30 and 49 years, were studied by methods of light and electron microscopy and immunohistochemistry. In 36 patients with endoscopically diagnosed erosive gastritis, biopsy material was taken from the zone of erosions and the body and pyloric canal of the stomach. The comparison group consisted of 35 patients with

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TABLE 1. Quantitative Morphological Parameters of State of Local Immunity in Patients with Chronic Gastritis (M ± m)

Parameter	Unchanged mucosa	Superficial gastritis	Erosive gastritis
Number of plasma cells in 1 mm^2 of mucosa producing IgA	230±47	430±67*	140±36
» IgG	23±7	17±8	78±16**
Volume fraction of interepithelial lymphocytes in surface epithelium, %	12,0±1,6	6,3±0,2***	28,1±2.3**
Volume fraction of interepithelial lymphocytes in epithelium of gland neck and gastric pits (generative zone), %	9,0±0,3	11,7±0,1***	14,3±7,1

Legend. *p < 0.05, **p < 0.01, ***p < 0.001.

chronic superficial gastritis, the control group of 14 patients in whom histopathological investigation revealed an unchanged gastric mucosa. The biopsy material was fixed in a 4% solution of paraformaldehyde. After removal of the specimens for electron-microscopic investigation, the whole of the remaining material was postfixed in 10% neutral formalin solution and embedded in paraffin wax. Paraffin sections were stained with hematoxylin and eosin, alcian blue, by Brachet's method, and with the PAS reaction, with counterstaining with azure-eosin. Tissue specimens for electron microscopy were postfixed in 1% osmium tetroxide solution and embedded in a mixture of Epon and Araldite. Semithin sections were stained with azure II and the PAS reaction. Ultrathin sections were stained with uranyl acetate and lead citrate and examined in the JEM-100B electron microscope. Immunohistochemical investigations were conducted on paraffin sections. Immunoglobulins of the A and G classes were determined by the indirect Coons' method and immune complexes by the method of Goldwasser and Shepard. The bulk density of interepithelial lymphocytes in the surface epithelium and in the generative zones (the cervical part of the glands, the gastric pits) was measured by means of an ocular point grid. The number of globulin-producing plasma cells was counted in 1 mm^2 of the lamina propria of the gastric mucosa.

EXPERIMENTAL RESULTS

"Incomplete" erosions were found in the body of the stomach of three patients, but in the other cases from three to seven mucosal defects were located in the pyloric region in the form of a typical "track" and they were assessed as "complete" (chronic) erosions.

In three biopsy specimens from the body of the stomach the diagnosis of acute erosions was confirmed histologically. The epithelial defect lay at the apex of the rugae of the mucosa, spread to the floor of the pit, and consisted of a zone of fibrinoid necrosis (Fig. 1a). In one case an erosive defect occupied the area of several adjacent gastric rugae.

In areas bordering the zone of erosion marked degenerative changes were observed in the mucocytes: the cells had lost their microvilli and the whole apical zone was occupied by an extensive vacuole, displacing the mucoid granules and nucleus to the periphery — these were typical vacuolated cells described in the surface epithelium in chronic gastritis [14]. Polymorphonuclear leukocytes and lymphocytes were located between cells of the epithelial layer (Fig. 1b). "Distant" leukocytic infiltration of the epithelium of this type is so characteristic of all defects of the mucosa — from acute erosions to chronic ulcers — that it is suggested that it be interpreted as an indirect sign of an erosion (ulcerative) defect, which could not be excised at biopsy or which was not contained in the section because of incorrect orientation of the block [1]. However, besides indirect evidence of the presence of a pathological process, such material also gives information about the background against which the erosion develops. In such areas the integrity of the epithelial layer is considerably disturbed and the mucocytes preserved their tight junctions only in the apical zone. The surface epithelium lost its microvilli and their place was taken by clasmatotic outgrowths.

Many myelin figures were seen in the intercellular spaces of the basal portions of the epithelial layer and were in contact with lymphocytes, which had acquired the features of activated cells: the volume of their cytoplasm was increased, their nucleus showed predominance of euchromatin, with a developed lysosomal apparatus, and with myelin figures in the phagolysosomes (Fig. 1c). The bulk density of the interepithelial lymphocytes was much greater than that in other groups (Table 1).

Cellular infiltration in the zone of acute erosions and adjacent regions was polymorphocellular with predominance of plasma cells. No fixed immune complexes could be found in the lamina propria. Granular

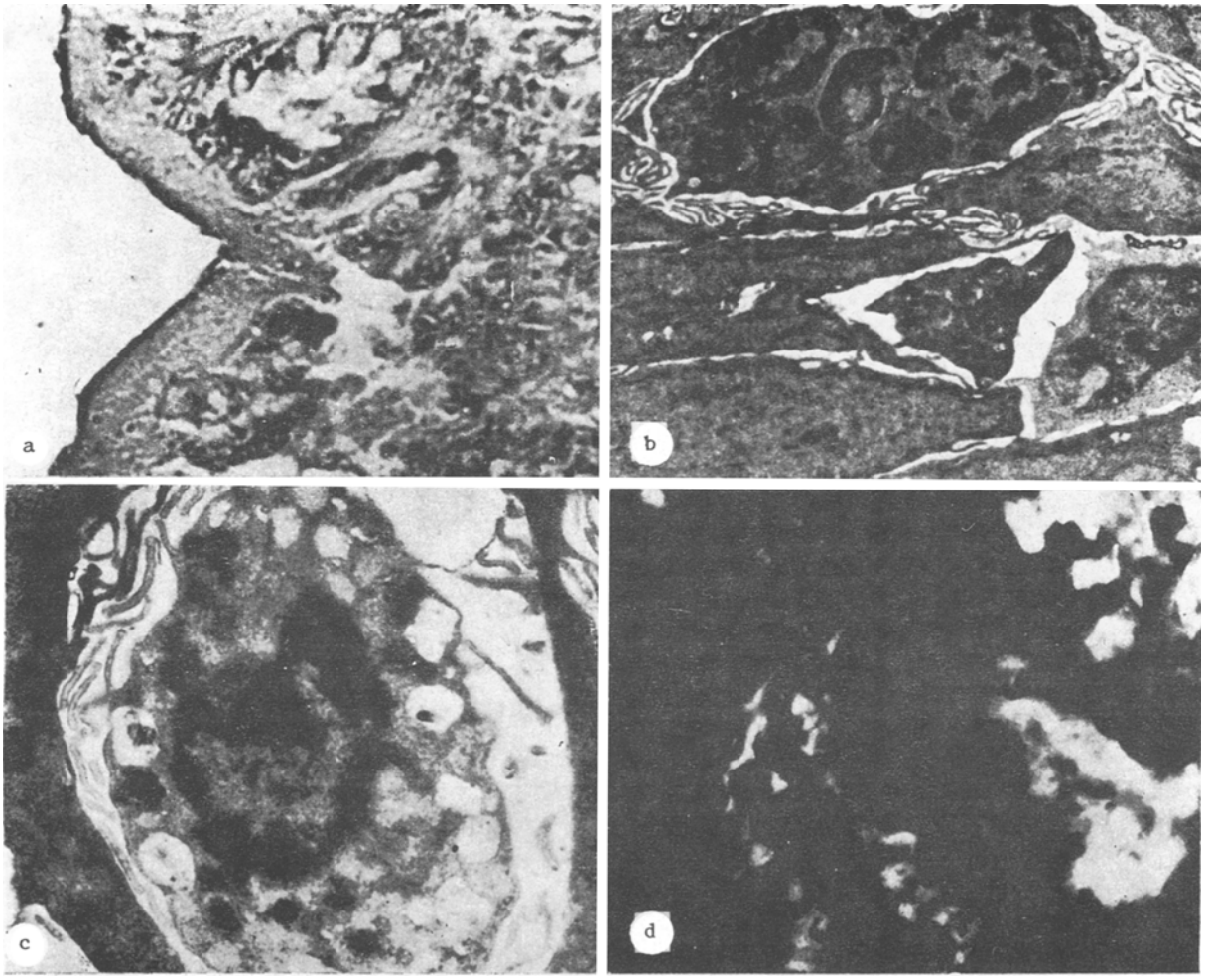

Fig. 1. Morphologic signs of acute erosion of gastric mucosa; a) triangular erosive defect consisting of fibrinoid necrosis of surface and pit epithelium. Hematoxylin and eosin. 200 ×; b) Polymorphonuclear leukocytes and activated lymphocyte in surface epithelium ("distant" infiltration). 5000 ×; c) Activated lymphocyte with numerous phagolysosomes. 6600 ×; d) Fixation of heterogeneous complement in zone of erosion (above) and on basement membrane of neighboring gastric pit (below). Method of Goldwasser and Shepard. 110 ×.

luminescence of IgG deposits and fixation of heterogeneous complement were found in the zone of fibrinoid necrosis (Fig. 1d).

Chronic erosions of the gastric mucosa were found on histologic investigation in 11 of 33 direct vision biopsy specimens. In the remaining cases, "distant" leukocytic infiltration of the surface epithelium was found. Chronic erosions consisted of a zone of fibrinoid necrosis with basophilic clumps of disintegrated nuclei, with an underlying strip of granulation tissue (Fig. 2a). In neighboring parts regenerating flattened cubical epithelium with basophilic cytoplasm could be seen. In its ultrastructural organization it resembled immature cells, such as are normally found in the isthmus of the glands or at the base of the gastric pits. Severe degenerative changes were observed during the study of the ultrastructure of the mucocytes in biopsy specimens with "distant" infiltration.

Synthesis of secretory IgA was disturbed in the degeneratively changed surface epithelium, and in the overwhelming majority of biopsy specimens it could be found only in single cells. In the comparison group, synthesis of secretory IgA was undisturbed. In the unchanged mucosa IgA gave diffuse luminescence in the form of a continuous layer in the apical zone of the mucocytes (Table 2). Consequently, a local IgA deficiency was formed in erosion gastritis.

This state of affairs is connected not only with the disturbance of synthesis of the secretory component and of assembly of secretory IgA in the mucocytes, but also with decreased production of IgA by plasma cells in the zone of erosion. Meanwhile the number of IgG-producing cells was increased here (Table 1). Deposits of IgG in the composition of immune complexes and ingestion of heterogeneous complement by them were found in the vessels of the

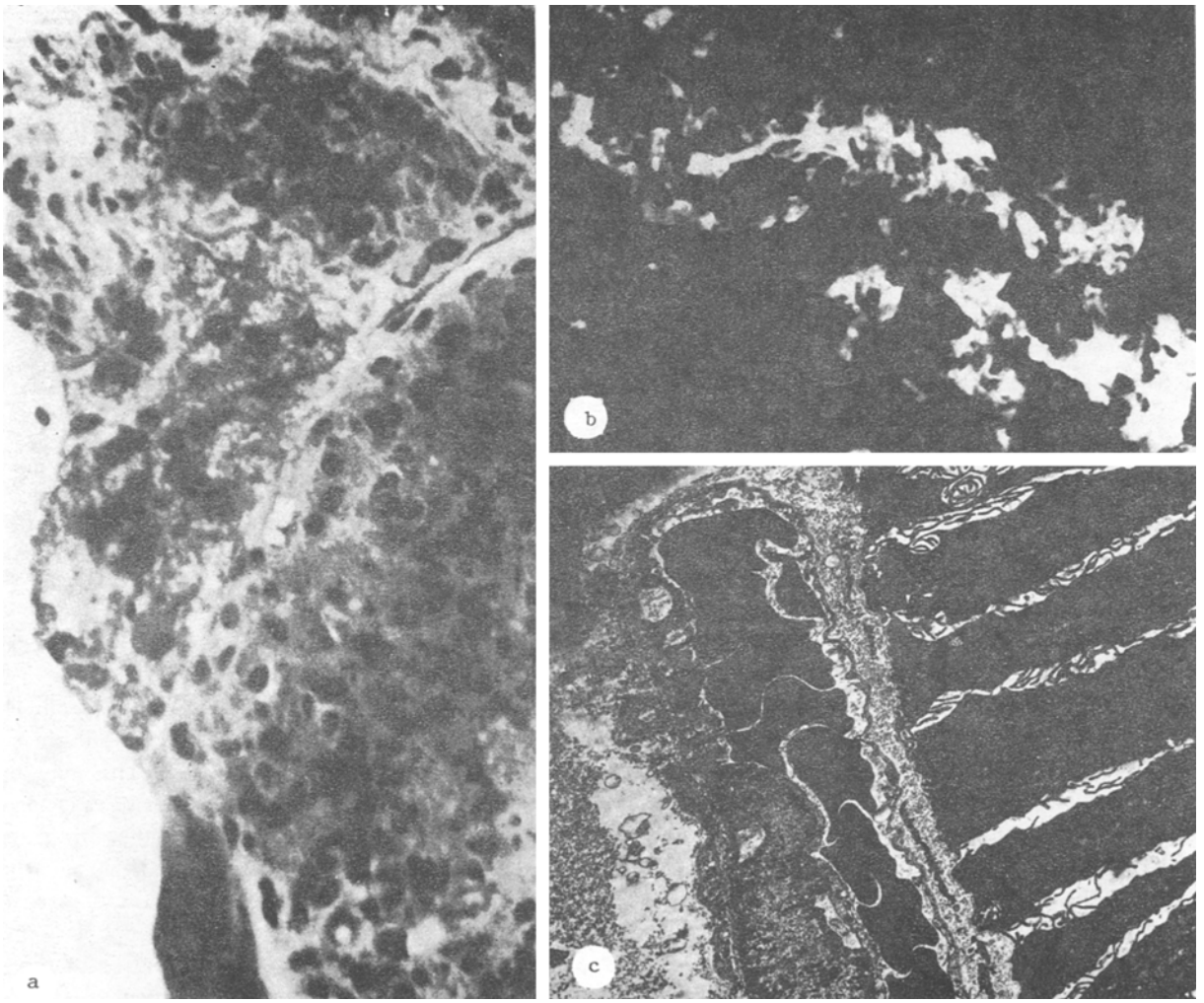

Fig. 2. Morphologic features of chronic erosion of gastric mucosa: a) fibrinoid necrosis with band of subjacent granulation tissue, regenerating epithelium along its edge. Semithin section. Azure II. 440 ×; b) fixation of heterogeneous complement in wall of small vessel and in cells in focus of infiltration of lamina propria of mucosa. Goldwasser—Shepard method. 440 ×; c) sludging of erythrocytes in venule in area bordering on erosion. 3200 ×.

laminar propria of the mucosa (Fig. 2b). In such vessels, chiefly venules, aggregation and sludging of erythrocytes developed (Fig. 2c).

Similar changes in immunoglobulin synthesis and in the state of the microcirculation were found in biopsy specimens with "distant" infiltration from the antral portion and body of the stomach, where no erosion defects were observed (Table 2). Reduction of the IgA concentration in the mucosal-epithelial barrier of the stomach greatly reduced its protective properties, for IgA (unlike IgG), interacting with antigen on the surface of the mucosal layer, as a rule does not activate complement, and in this way prevents the development of immunocomplex lesions [8].

A transient increase in the quantity of circulating immune complexes was found in the blood serum of patients with acute gastroenteritis [15]. Fixation of the immune complexes in the gastric mucosa, and also their local formation as a result of the arrival here of hetero- and autoantigens against the background of increased IgG synthesis, creates the conditions for realization of the immunocomplex mechanism of injury.

The mosaic nature of changes in the gastric mucosa can be fully explained by the concept of alternating activity of homologous tissue structures [2]. As a result of this, even in the case of total pathogenic action, the degree of damage to the tissue structures varies.

From the standpoint of the facts described above the evolution of local immunity in chronic gastritis can be pictured as follows. In superficial gastritis the protective properties of the mucosal-epithelial barrier are preserved due to hyperproduction of mucus and IgA. However, further progression of the degenerative changes in the surface epithelium leads to a disturbance of synthesis of the secretory component of IgA, and as a result of this, hetero- and

TABLE 2. Frequency of Immunomorphologic Features in Biopsy Material from Gastric Mucosa of Patients with Chronic Gastritis (in %)

Parameter	Unchanged gastric mucosa (n = 28)		Superficial gastritis (n = 70)		Erosive gastritis (n = 72)	
	body	antrum	body	antrum	body	antrum
IgA in apical parts of surface epithelium:						
forms a continuous layer	100	100	30	43	16	9,7
is found in most cells	—	—	10	14	9,7	4
in single cells	—	—	10	7	24	36
IgA in glandular epithelium	100	100	100	100	100	100
IgG in composition of immune complexes						
in wall of vessels	—	—	—	—	24	40
in cytoplasm of cells of focus of infiltration	—	—	—	4	12,5	50
subepithelially	—	—	1,4	6	5,5	22
in zone of erosions	—	—	—	—	5,5	32
Fixation of immune complexes by heterogeneous complement:						
in wall of vessels	—	—	—	1,4	24	40
subepithelially	—	—	—	4	—	—
in zone of erosions	—	—	—	—	5,5	40
in cytoplasm of cells of focus of infiltration	—	—	10	20	16,6	43

Legend. n) Number of biopsy specimens.

autoantigens enter the lamina propria. Hyperproduction of IgG against this background leads to the local formation of immune complexes.

Receptors of suppressor T cells in the mucosa, which can regulate the humoral immune response locally [13], are blocked by immune complexes [4, 9]. Blockade of lymphocyte receptors disturbs their production of lymphokines, which attract leukocytes and macrophages into the pathological focus, eliminating the immune complexes. This may probably explain the paradoxical integrity of the leukocytes in relation to fibrinoid in chronic erosions [1]. Fixation of the immune complexes in the microcirculatory bed leads to a disturbance of metabolism and to further progression of degenerative changes in the surface of the helium, and also in the generative zones, which disturbs the process of regeneration and differentiation of the epithelium even more and, consequently, behaves as a factor creating the conditions for recurrence of the erosive defect.

Thus a vicious circle is formed — one of the stereotyped mechanisms of chronic transformation of the disease [2, 3, 6], triggered by immune-complex reactions in the gastric mucosa. The immunopathological mechanism of injury is one of the components of pathogenesis. Its importance differs in different stages of evolution of chronic gastritis, but nevertheless it must be identified and taken into consideration when the disease is treated and its prognosis assessed.

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