vitro, were evidently intensified even more in vivo, where adhesion of the fungi prevents desquamation of the epithelium and their removal with food and saliva.

According to histological data CS have no marked effect on migration of neutrophilic granulocytes into a focus of information, and within the times studied they do not significantly inhibit their fungicidal mechanisms, thus leading to localization of the invading agent at the level of the epithelieum, followed by its destruction. In mucosal candidiasis induced in man by administration of Beclomet, the lesions also are relatively superficial in character, but they appear only after many weeks of use of the preparation [2]. A factor contributing to the comparatively rapid development of *Candida* infection in the present experiments was the larger doses of CS than are given to man, and the high concentration of fungal cells in the drinking water, many times greater than their concentration in human saliva (100 blastopores/ml [4]), in which *Candida* cells are often found in the form of saprophytes.

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## IMPAIRED EPITHELIAL REGENERATION IN THE MUCOSA AS A FACTOR IN THE PATHOGENESIS OF ACUTE GASTRIC AND DUODENAL ULCER


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KEY WORDS: acute ulcer, experimental model; vincristine


In the modern view the pathogenesis of acute gastric and duodenal ulcers is based on stress-induced ischemic damage to the mucosa, leading to a disturbance of cellular metabolism, to reduced formation and altered composition of the mucous, and to impaired reparative capacity of the epithelium [5, 6]. As a result the sensitivity of the mucosa, especially of the fundal part of the stomach, to bile acids and lysolecithin is increased and diffusion of hydrogen ions from the gastric contents (pH 1.0) into the interstitial fluid (pH 7.4) is intensified. Under normal conditions hydrogen ions diffusing into the tissue are neutralized by bicarbonate anions arriving from the blood or secreted by the parietal cells. If the mucosa is ischemic this does not happen and, as a result, cellular acidosis develops [2, 3, 5, 7]. Such cells are easily damaged by pepsin accumulating in the mucosa of the fundus of the stomach [4], as is confirmed by the protective action of its inhibitor in animals even at pH values of 1.3 [1].

Vincristine, widely used in clinical practice for the treatment of hemoblastoses, was used as a substance with direct action on cell regeneration processes. Binding with subunits of the protein tubulin, vincristine prevents the formation of microtubules of the spindle, so that divergence of the centrioles toward the poles of the cell is disturbed and mitosis


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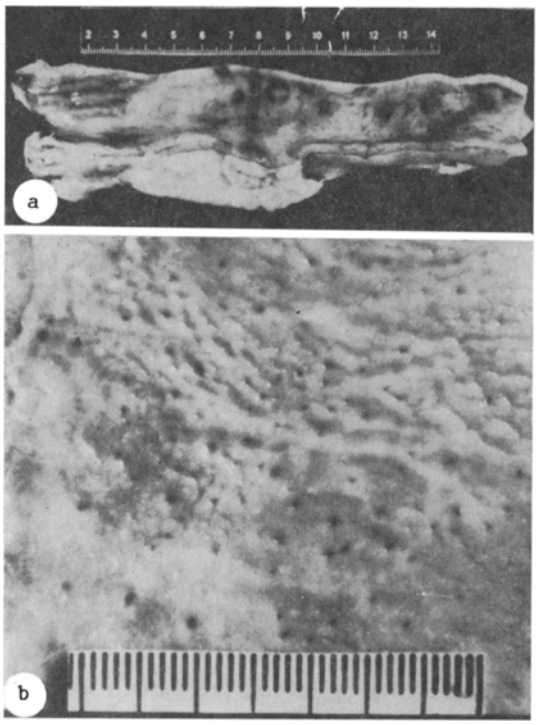

Fig. 1

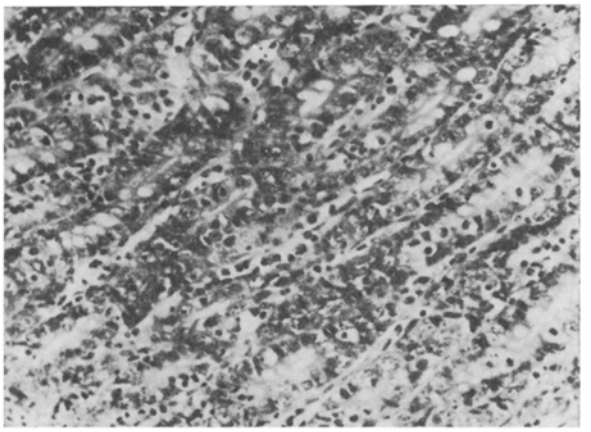

Fig. 2

Fig. 1. Structure of acute ulcer (naked-eye specimen). a) Multiple acute duodenal ulcers in a dog 3 days after injection of vincristine; b) multiple acute gastric ulcers in a dog 3 days after injection of vincristine.

Fig. 2. Epithelial cell nuclei in crypts of gastric mucosa of a dog 3 days after injection of vincristine. Hematoxylin and eosin. 100 ×.

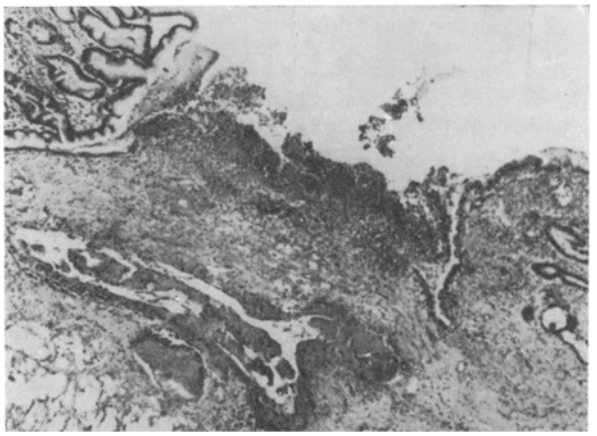

Fig. 3. Acute gastric ulcer in a dog 6 days after injection of vincristine. Hematoxylin-eoxin. 30 ×.

is stopped at the metaphase stage. As a result cell division ceases in the zones of growth and their physiological loss is not made good.

However, these data shed light on only one aspect ot the pathogenesis of acute ulcer formation, namely the effect of microcirculatory disturbances in the gastric mucosa and the state of metabolism of its cells on this process, but they do not give a complete picture of the role of mechanisms regulating regeneration of its epithelium in the formation of defects of the mucosa. The aim of this investigation was to study these problems.

## EXPERIMENTAL METHOD

Experiments were carried out on 20 mongrel dogs which were given an intraperitoneal injection of vincristine in a dose of 0.15-0.30 mg/kg body weight. The dose was determined

beforehand experimentally. After 1-6 days the experimental animals were killed by injection of a toxic dose of hexobarbital into the anesthetized dogs, which were then examined post mortem. Fragments of the stomach and duodenum containing ulcers were excised, fixed in 10% neutral formalin or Carnoy's fluid, dehydrated in alcohols of increasing concentration, and embedded in paraffin wax. Sections up to 6 μ thick were stained with hematoxylin and eosin and by Feulgen's and Samsonov's methods.

## EXPERIMENTAL RESULTS

In the control experiments after intraperitoneal injection of isotonic NaCl solution and sacrifice of the animal as described above, acute ulcer formation was not observed in the stomach and duodenum at the times specified. Meanwhile, on the 3rd day after injection of vincristine multiple acute ulcers were formed on the gastric and duodenal mucosa (Fig. 1a, b). Up to 15-20 were counted in the stomach: they were round, up to 1 mm in diameter, with clearly defined edges, and covered with mucous. Hematin hydrochloride mucous were present in the lumen of the stomach, and a very small quantity of bright red blood on the floor of individual ulcers and between folds of the mucosa. Up to 10 such ulcers appeared in the duodenum, but they reached a diameter of 0.5 cm and some of them (Fig. 1a) penetrated through all layers of the duodenum as far as the serous membrane, thus bringing the threat of perforation. The floor of the ulcers was covered with a brown deposit and a large quantity of mucus. Multiple petechial hemorrhages were seen in the subserous layer. These acute ulcers were still present on the 6th day (end of observation), but they were rather fewer in number and no longer showed any signs of bleeding.

Examination of histological sections showed that during the 3 days after injection of vincristine many nuclei in the metaphase stage appeared in the generative zones of the gastric and duodenal mucosa (Fig. 2). They showed a focal distribution on discrete parts of the mucosa. In these areas, as a rule, ulcer defects appeared and, on the 3rd day, they showed all the features of an acute ulcer.

Villi of the duodenal mucosa under these circumstances lost their normal PAS-positive border and desquamation of the brush-border and goblet cells was observed. In the superficial layers of the gastric desquamation of the surface epithelium could be seen. The ulcers present 5-6 days after injection of vincristine showed no tendency to heal, their floor was infiltrated with polymorphonuclear leukocytes, and around the edges of the defect there were regions of necrosis and no evidence of proliferation of the epithelium (Fig. 3).

It can thus be concluded from the results of this investigation that one of the leading factors contributing to the formation of acute gastric and duodenal ulcers is inhibition of regeneration of the mucosal epithelium in the zones of growth. Since physiological desquamation of the epithelial cells is not compensated under these circumstances, defects of the epithelial cover are formed. The action of the gastric and duodenal contents, digestive enzymes, and products of bacterial metabolism on these areas leads to the formation of superficial erosions, which later turn into acute ulcers, and as a rule, show no tendency to heal at least at the times studied. Epithelization of the defects also is prevented by the presence of necrotic areas around the edge of the ulcer. The focal arrangement of the cells with metaphase nuclei and the ulcer defects of the mucosa corresponding to these areas can probably be explained by the nonuniformity of functional activity of the mucosal cells and they may correspond to the zones of maximal intensity of proliferation at the moment of injection of vincristine.

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