HISTOPATHOLOGICAL STUDY OF THE EFFECT OF ANTIRHEUMATIC DRUGS ON THE GASTRODUODENAL MUCOSA

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INTRODUCTION

The extensive use of antirheumatic drugs nowadays and their association with many gastrointestinal troubles stimulated the authors to study the histopathological changes which might affect the stomach and duodenum as a result of the administration of these drugs.

The occurrence of peptic ulcers was reported in man after the administration of endomethacin orally (Kamal and Ahmed, 1967; Gramajo and Salomane, 1976 and Loni and Ambrogi, 1968) and in the form of suppositories (Taylor *et al*, 1968). Peptic ulcers were also produced in experimental animals when endomethacin was given by injection (Djahanguiri, 1969).

Phenylbutazone was also reported to cause erosive gastritis and ulceration in man and animals, particularly on the greater curvature, and malignancy was suspected in the ulcers (Kirsner and Ford, 1955; Kern, *et al* 1957 and Kowalezuke, 1969).

Lyle (1974) reported the occurrence of bleeding peptic ulcers in patients receiving penicillamine.

Chabot *et al* (1974) noted the appearance of gastritis, gastroduodenal ulcers and melaena in patients receiving ketoprofene.

The aim of the present work is to further our knowledge about the histopathological effect of antirheumatic drugs on the gastroduodenal mucosa.

MATERIAL AND METHODS

Twenty adult male and female rabbits with average body weight 1.5 Kg. were used in this study. They were divided into four groups, five animals each. The first group was given endocid (endomethacin), the second curazolidine (phenyl butazone) the third atramine (penicillamine) at a daily dose of 16 mg., 50 mg. and 15 mg. respectively (according to Hanney Ball *et al* 1977). The fourth group was given alrheumate (Ketoprofene) at a daily dose of 6 mg. per Kg. body weight (according to Boyle *et al*, 1976). The

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animals were fed on green leaves and tap water and were kept under observation for 2 weeks. At the assigned time, the animals were sacrificed, specimens taken from the stomach and duodenum were fixed, dehydrated, cleared and embedded in paraffin. Sections were cut at 6 u and stained with haematoxylin and eosin and P.A.S. stains. Non-treated animals of the same body wiehgt were sacrificed. Their stomach and duodenum were examined and were used as control.

RESULTS

Naked-eye examination of the stomach and duodenum of animals given the four antirheumatic drugs used in this study showed multiple small ulcers scattered all over the mucous membrane. Larger ulcers (5-8 mm. in diameter) with inverted edges were occasionally found in the pyloric antrum (Fig. 1) and in the first part of the duodenum of animals receiving endocid and alrheumate. Most of these ulcers were perforated.

Microscopic examination showed that the surface epithelium and the epithelial lining of the gastric pits were denuded. Small ulcers with inverted edges and cellular infiltration at their bases were found (Fig. 2). Areas of squamous metaplasia were seen in all specimens (Figs. 3 & 4).

The fundic glands showed destruction of the mucous neck cells, but hypertrophy and proliferation of the oxyntic cells (Fig. 5). However, the peptic cells were normal in appearance.

P.A.S. stain of the pyloric glands of animals given endocid, curazolidine or atramine showed a weak positive reaction. However, a strong positive reaction was observed in the pyloric glands of animals given alrheumate (Fig. 6).

The mucous memberane of the duodenum showed the same appearance as that of the stomach. Most of the crypts of luberkuhn and Brunners' glands were found lined by stratified columnar epithelium (Figs. 7 & 8).

P.A.S. stain of the duodenal mucosa showed a weak positive reaction except in the cases receiving alrheumate.

DISCUSSION

The results of the present work showed the appearance of gastro-intestinal erosions and large prepyloric ulcers in all specimens obtained from animals receiving the antirheumatic drugs : endocid, curazolidine, atramine and alrheumate.

The appearance of gastro-intestinal ulcers, following the intake of antirheumatic drugs, was previously reported by Kamal and Ahmad (1967), Gramago and Salomon (1967) and Loni and Ambrogi 1968).

The present work also showed that the administration of antirheumatic drugs resulted in hypertrophy and proliferation of the oxyntic cells. This observation supports that of Kirsner and Ford (1955) who found that phenylbutazone increased the basal gastric acidity in man and dog. Hypertrophy of oxyntic cells could be explained in this study by assuming that the antirheumatic drugs might have an effect on the vagal gastric secretory fibres whereby they became hypertonus and thus resulted in hypertrophy of oxyntic cells and hypersecretion of the acid. This explanation is in agreement with Dragsted's view (1959) who suggested an intimate connection between the vagal neurogenic factor and the hypersecretion of the gastric juice in ulcer patients.

The mucinogen content of the gastric surface epithelium and of the mucous secreting cells of the fundic, pyloric and Brunner's glands was found less than normal as shown by the P.A.S. reaction, in animals receiving endocid, curazolidine and atramine. This observation indicated that the mucous-secreting cells, in these cases, became less active. As mucous normally forms a barrier that protects the lining epithelium against the chemical and enzymatic action of the gastric juice, it seems reasonable to assume that the diminution in mucous secretion, after the administration of the antirheumatic drugs, in the presence of high acid secretion plays the main role in the production of peptic ulceration. This view agrees well with that of Parke (1975) who stated that peptic ulceration might occur as a result of the reduced secretion of gastric mucous and its content of glucoproteins which normally protect the mucous membrane. In support of this is the occurrence of the large peptic ulcers in the prepyloric region and particularly on the greater curvature of the stomach. These areas were previously reported by Taylor *et al* (1968) to be the most common sites for the occurrence of peptic ulcers after the administration of antirheumatic drugs. Such areas, being most dependant, are more subjected than others to the chemical irritation of the gastric acid in the absence of enough mucous protecting barrier.

The mucous secreting cells in the pyloric and duodenal regions showed normal P.A.S. reaction in animals receiving alrheumate. Although this indicates the presence of a normal mucous protecting barrier, peptic ulcers were still found in these regions.

We can explain the occurrence of peptic ulcers in this case by assuming that the digestive power of the gastric juice increases to an extent that it corrodes the normally mucous protected mucosa. We can also assume that this drug may, according to the neurogenic theory of Cushing (1932), induce abnormal

vagal impulses, which produce vascular spasm and ischemia, thus lowering the resistence of the mucosa in these regions.

The most interesting findings in this study were the metaplastic changes in the surface epithelium and in the epithelium lining the gastric and pyloric pits and the hyperplastic changes in the pyloric and Brunner's glands. These changes, which are precancerous, probably occurred in response to the altered environment which resulted from the continued irritation by the increased gastric acidity and the absence of enough mucous barrier.

SUMMARY

The present study describes the histopathological effects of the antirheumatic drugs (endocid, curazolidine, atramine and alrheumate) on the gastroduodnal mucosa of rabbits.

The main findings were the occurrence of mutiple small ulcers all over the mucosa, large-occasionally perforated-ulcers in the pyloric antrum and duodenum, destruction of mucous fundic neck cells, hypertrophy and proliferation of oxyntic cells, metaplastic changes in the epithelium and hyperplastic changes in pyloric and Brunner's glands.

The continued irritation by the increased gastric acidity and the absence of enough mucous barrier, which result from the administration of these antirheumatic drugs, were concluded to be the main factors for the production of these pathological changes.

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EXPLANATION OF FIGURES

Fig. (1) Photograph showing the presence of a peptic ulcer in the pylorus of rabbit. (Endocid).

Fig. (2) Photomicrograph of a longitudinal section in the pylorus of rabbit showing the presence of pyloric erosions and the presence of stratified squamous epithelium lining the pyloric pits.
(Alrheumate) (10X10).

Fig. (3) Photomicrograph of a longitudinal section in the pylorus of rabbit showing the presence of stratified squamous equithelium on the surface as well as in the pilts (Artamine), (10X10).

Fig. (4) Photomicrograph of a longitudinal section in the pylorus of rabbit showing the presence of stratified squamous epithelium on the surface as well as in the pits. (Endocid), (20X10).

Fig. (5) Photomicrograph of a longitudintl section in the stomach of rabbit showing :

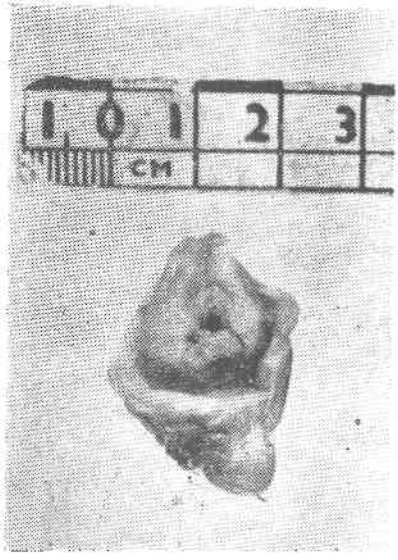
a) The presence of stratified squamous epithelium both on the surface and in the gastric pits.

b) Hypertrophy of the fundic glands and proliferation of the oxyntic cells. (Endocid) (20X10).

Fig. (6) Photomicrograph of a Longitudinal section in the pylorus of rabbit showing that the pyloric glands are distended with mucous. (Alrheumate), (20X10).

Fig. (7) Photomicrograph of a Longitudinal section in the duodenum of rabbit showing that the villi are covered by simple columnar, stratified columnar and stratified squamous epithelium.
(Alrheumate), (10X10).

Fig. (8) Photomicrograph of a transverse section in the duodenum of rabbit showing that the villi are covered by stratified squamous epithelium and that there is glandular hyperplasia.



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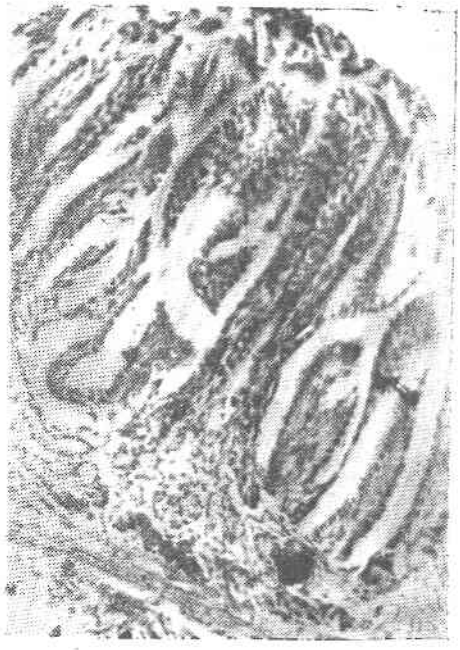

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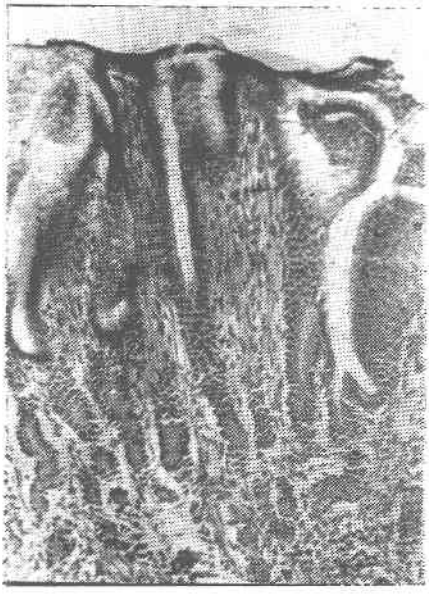

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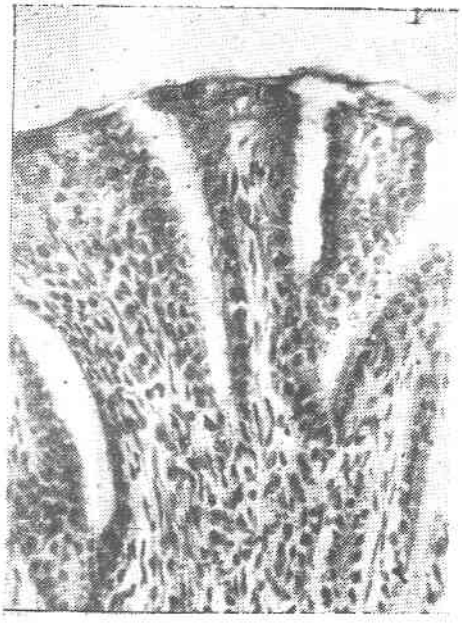

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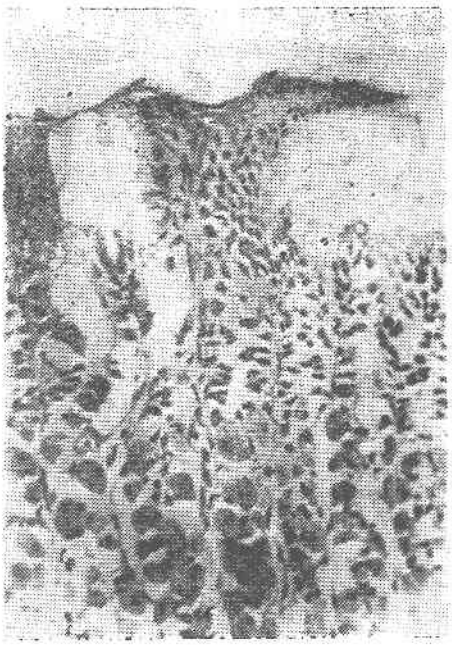

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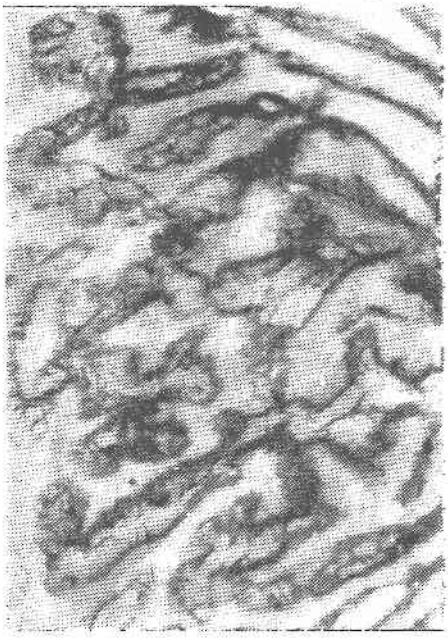

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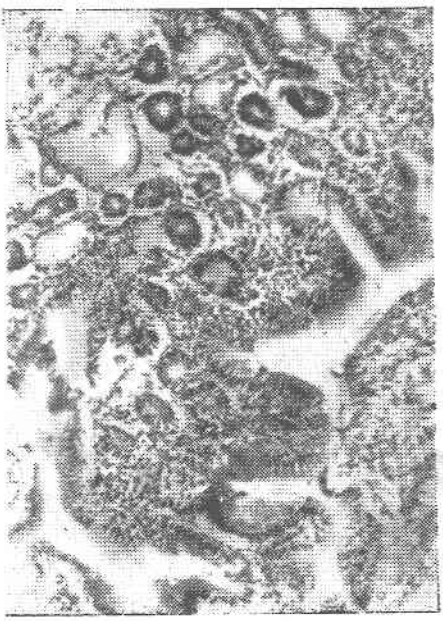

Fig. (8)