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# EFFECT OF DESOXYCORTICOSTERONE ACETATE AND CORTISONE ON THE DEVELOPMENT OF CINCHOPHEN ULCER IN THE DOG

By

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In cinchophen-treated dogs, DOCA completely prevented duodenal ulceration and inhibited gastric ulceration. The harmful effect of cortisone on cinchophen ulcer was observed only in about half of the cases. Even exceptionally large ulcers were not necessarily associated with acute haemorrhagic gastritis and severe haemorrhagic gastritis was seen also in the absence of ulceration. Thus, ulceration and acute haemorrhagic gastritis are not strictly linked. It is suggested that the ratio of mineralocorticoids and glucocorticoids might play a role in the pathogenesis of gastric and duodenal ulceration.

In 1942 KÖHLER and FLECKENSTEIN [8] accidentally observed that DOCA promoted the healing of hepatogenic ulcers. Several authors [2, 3, 4, 6] have since described the favourable effect of DOCA on human peptic ulcer, while some authors found it of little therapeutic value [7]. It is difficult to evaluate clinical impressions and statistical evaluation of clinical observations would require in this case large numbers on account of the pronounced tendency of the disease to heal spontaneously. In our material about 80% of the hospitalized patients with deep penetrating ulcers recovered on placebo treatment.

The scattered favourable reports on the action of DOCA in peptic ulcer, in contrast with the ulcerogenic action of glucocorticoids, raised the possibility of an antagonism between these steroids in peptic ulcer. This suggestion was followed up by studying the action of DOCA and cortisone on cinchophen ulcer in the dog. In this paper our experiments will be described in detail.

## Materials and methods

A total of 58 dogs was used; 28 were treated with cinchophen alone, 18 with cinchophen + DOCA, and 12 with cinchophen + cortisone. One dog receiving cinchophen + cortisone died at the end of the 2nd week. No ulcers were found and pulmonary oedema was the only pathological process at autopsy. This animal has been excluded from evaluation.

The experiments were divided into five groups. In three of these the effect of DOCA, in two the effect of cortisone was compared with simultaneous controls receiving cinchophen only. The animals were kept in separate cages and fed a mixed diet. Cinchophen ulcers (VAN WAGONER and CHURCHILL [9]) were produced by injecting intravenously 100 mg/kg body weight of cinchophen sodium in 5% solution daily for three weeks. Administration of steroids was started simultaneously. DOCA (Decosteron, Richter, Budapest) and cortisone (Adreson, Organon—Oss, Netherlands) were injected intravenously in doses of 0.5 mg/kg and 5.0 mg/kg daily, respectively. Dogs, dying in the course of the experiment following perforation were

dissected within 2 to 8 hours. The surviving animals were sacrificed by intracardiac injection of chloroform on the 22nd day, 24 hrs after the last feeding and dissected immediately after death Contours of the ulcers were drawn to scale and are reproduced in the figures. Double lines in the figures separate groups observed at different times and permit the comparison of treated animals with their simultaneous controls. Single lines separate the ulcers of individual dogs. Animals without an ulcer are marked by Ø.

## Results

Post-mortem findings of 18 animals treated with cinchophen, and 18 treated with cinchophen + DOCA are demonstrated in Fig. 1. No duodenal ulcer was seen in the animals treated with cinchophen + DOCA, and consider-

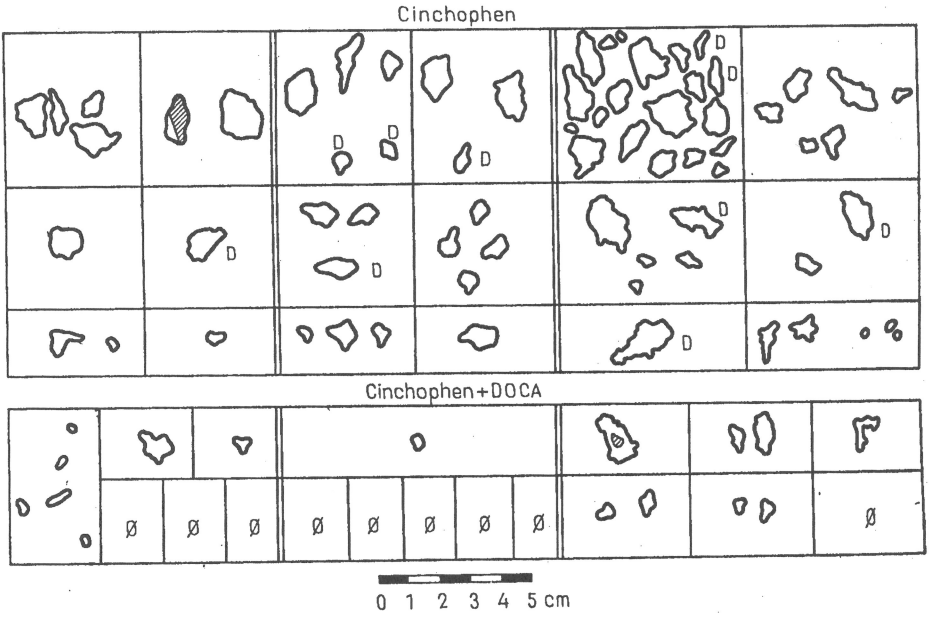


*Fig. 1.* Effect of desoxycorticosterone acetate on cinchophen ulcer development. D: duodena ulcer. Striped areas indicate perforations

ably fewer and smaller gastric ulcers were found than in the controls treated with cinchophen only. The most impressive observation was that while duodenal ulcers were absent in the dogs receiving cinchophen + DOCA, 10 duodenal ulcers were found in those treated with cinchophen only.

Fig. 2 shows the effect of cortisone in dogs treated with cinchophen. In 5 out of 11 dogs treated with cinchophen + cortisone exceptionally large ulcers were present. Three dogs died from perforation both in the group treated with cinchophen + cortisone and in that receiving cinchophen only. In one dog treated with cinchophen + cortisone an intact stomach was found.

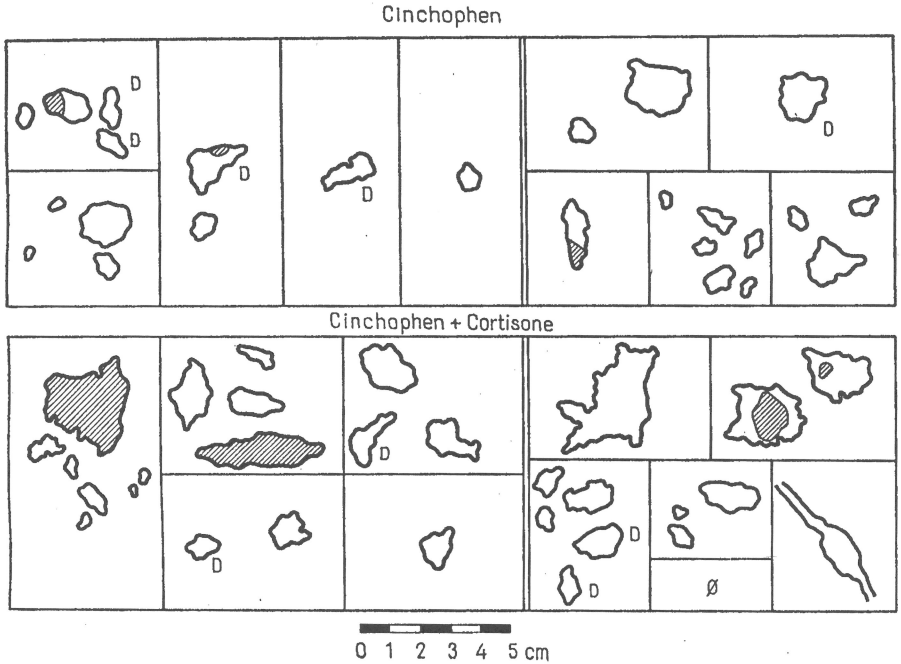


*Fig. 2.* Effect of cortisone on cinchophen ulcer development. D: duodenal ulcer. Striped areas indicate perforations

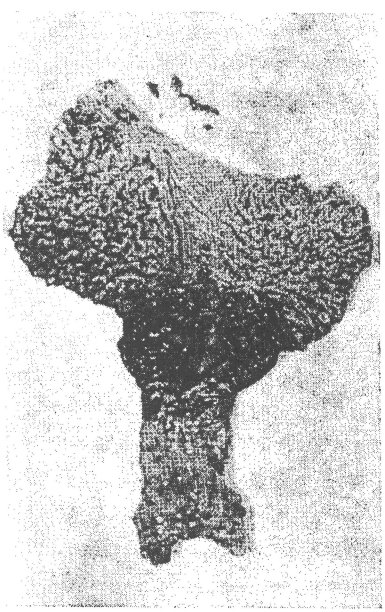

*Fig. 3.* Haemorrhagic antral gastritis in a dog treated with cinchophen + DOCA. No ulcer

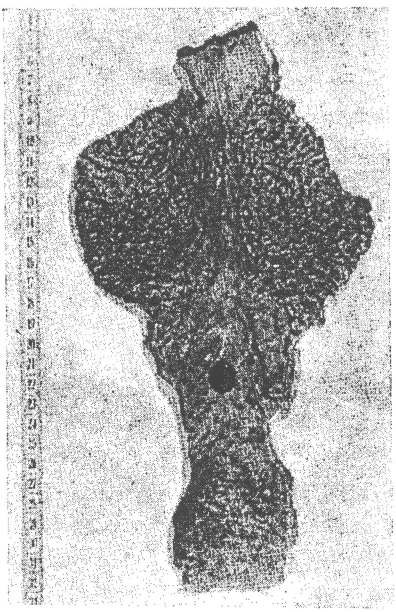

*Fig. 4.* Large ulcer following administration of cinchopen + cortisone. No haemorrhagic gastritis

About one third of the dogs developed acute haemorrhagic gastritis. In this respect no difference was found between the groups treated with cinchophen only, with cinchophen + DOCA, and cinchophen + cortisone. Fig. 3 demonstrates a severe antral haemorrhagic gastritis without any signs of ulceration in a dog treated with cinchophen + DOCA. Fig. 4 originates from a dog treated with cinchophen + cortisone; the animal displayed an exceptionally large ulcer without signs of haemorrhagic gastritis.

## Discussion

In the experiments, DOCA and cortisone produced opposite effects on the cinchophen ulcers in dogs. DOCA inhibited ulceration in the stomach, and prevented it completely in the duodenum, while cortisone aggravated ulceration in approximately half of the cases. Ulceration and acute haemorrhagic gastritis showed no parallelism. Ulceration was seen in the absence of acute haemorrhagic gastritis and severe inflammation was present in the absence of ulceration.

Similar observations were made by BERTI-RIBOLI and BELGRANO [1] who studied the combined effect of aqueous adrenocortical extracts and vitamins B and C on the cinchophen ulcer of dogs. The results were favourable, but were not suited to decide which of the employed agents was responsible for them. In addition, the composition of the aqueous adrenocortical extracts was undefined. Retrospectively, the effect was most probably due to mineralocorticoids contained in the extracts.

Ulcers are known to develop frequently, but not invariably, in Addison's disease. The beneficial effect of DOCA in cinchophen ulceration could suggest that the mineralocorticoids are somehow involved in the protection of the gastric and duodenal mucosa. The fact that DOCA was only partly effective, points to the involvement of other protective factors.

Several authors induced ulcers in different animals by vagotomy. HÁMORI et al. [5] observed giant gastric ulcers to develop in vagotomized dogs treated with cinchophen. These experiments seem to suggest that the intactness of the gastric mucosa requires an intact vagal innervation. In contrast, vagotomy prevented duodenal ulceration in cinchophen-treated dogs. Therefore the vagus apparently exerts opposite effects on the stomach and the duodenum. Excluding local factors, at least two defensive mechanisms have to be considered, a neural and a hormonal one. In the case of the duodenum, however, only the hormonal mechanism could be demonstrated and, in contrast to the stomach, vagotomy not only failed to enhance ulceration, but prevented the development of cinchophen ulcers.

Our experiments suggest that the ratio between mineralocorticoid and glucocorticoid secretion could be a significant factor in the genesis and the course of human peptic ulcer.

The present experiments have, moreover, shed some light on the interrelation between haemorrhagic gastritis and peptic ulcer. Neither DOCA nor cortisone have any significant effect on haemorrhagic gastritis. The incidence of severe mucosal inflammations was equal in both groups, although DOCA and cortisone produced opposite effects on the development of cinchophen ulcers. Haemorrhagic gastritis and the ulceration of the stomach depend, apparently, on two different mechanisms.

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