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EFFECT OF PREDNISOLONE ON THE DEVELOPMENT OF CINCHOPHEN ULCER IN THE DOG

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Therapeutic doses of prednisolone administered over a period of three weeks gave rise to ulceration in 20% of the dogs so treated. The lesions were superficial and did not exceed 7 mm in diameter. These results raise the hope that human prednisolone ulcer may be detected in time, if the patient is subjected to X-ray examination every three weeks.

Prednisolone greatly promoted the progression of cinchophen ulcer. In some cases, giant ulcers developed resembling those seen in old age.

One of the possible explanations for the ulcerogenic action of prednisolone is a iatrogenic adrenal insufficiency.

The giant ulcers are not accompanied by gastritis, while in the group treated with prednisolone only haemorrhagic gastritis developed, mostly without ulcer. Consequently, peptic ulcer and gastritis result from two different mechanisms.

Among the untoward side effects of steroid treatment, gastrointestinal complications represent the gravest hazard. In the past years we, too, observed a number of cases of severe upper gastrointestinal haemorrhage and in one case there even occurred a perforation of the small intestine. We have therefore undertaken a study of the ulcerogenic effect of prednisolone under experimental conditions, to answer the questions,

(i) does prednisolone by itself induce gastroduodenal ulceration in the dog?

(ii) does prednisolone enhance the ulcerogenic effect of cinchophen?

Our results make it possible to discuss the correlations presumably existing between gastritis and peptic ulcer and to interpret the genesis of the giant ulcer of old age.

Materials and methods

Three groups of 12 dogs each were used. In each group four animals were treated with prednisolone alone, four with cinchophen alone, while four received prednisolone + cinchophen. The daily dose of cinchophen sodium was 100 mg per kg body weight, administered intravenously in the form of a 5% solution over a period of three weeks according to VAN WAGONER and CHURCHILL [8]. Prednisolone (Di-Adreson-F Aquosum, Organon) was injected intramuscularly in daily doses of 1 mg per kg. The animals were kept in isolation cages, fed a mixed diet not containing bones and were killed after 24 hours of fasting on the 22nd day of the experiment by intracardiac injection of chloroform. The animals succumbing to upper gastrointestinal haemorrhage of perforation before completion of the experiment were immediately subjected to study. The peptic ulcers were evaluated by planimetry, classifying them as small, medium and large. Medium size meant a longest diameter of 7 to 8 mm. In the presence of several ulcers the largest one was relied upon in classification. Three dogs succumbed to intercurrent disease; these were excluded from the analysis.

Finally, the normal weight of the adrenals was determined in 13 untreated control dogs.

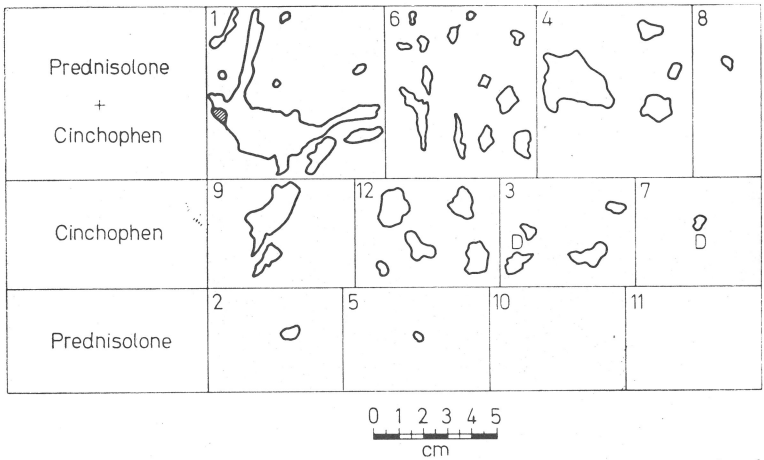

Fig. 1. Extent of ulcers in Group 1. Shaded area: site of perforation. D: duodenal ulcer

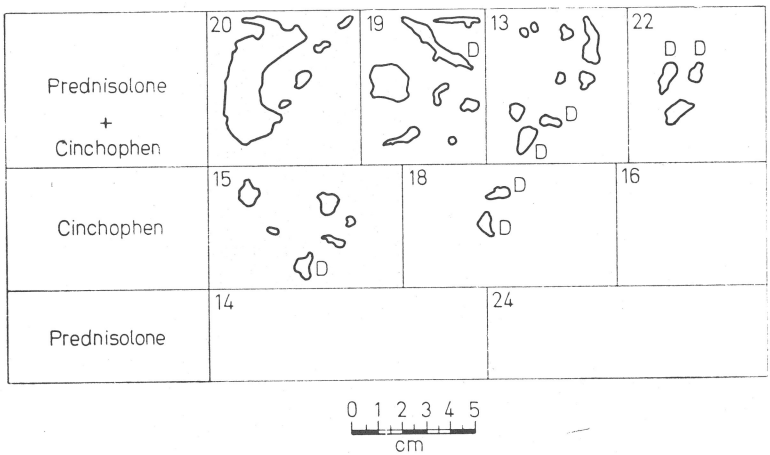

Fig. 2. Extent of ulcers in Group 2. D: duodenal ulcer

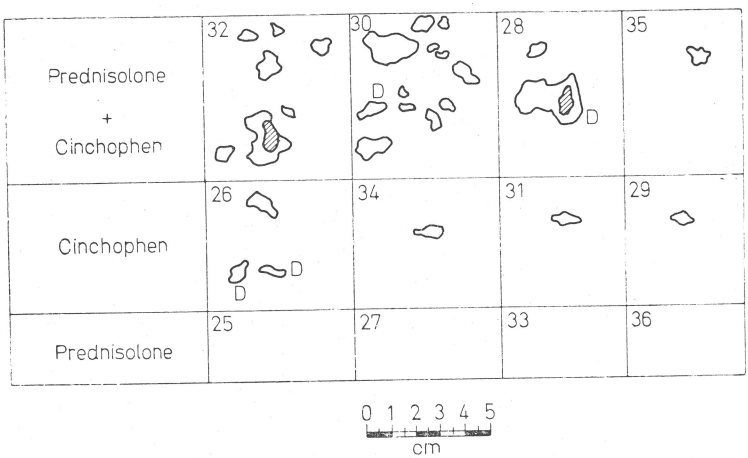

Fig. 3. Extent of ulcers in Group 3. Shaded area: site of perforation. D: duodenal ulcer

Results

Results are summarized in Table I. As visible, there was no negative finding.

Of the prednisolone-treated dogs ulceration occurred in two. The lesion was a small superficial ulcer in one case and a medium one in the other. A strik-

Table I

Results of prednisolone and cinchophen administration

Drugs used	No. of animals	Site of lesion	Inflammation	Size of ulcer			No lesions
				Small	Medium	Large	
Prednisolone + cinchophen	12	stomach	4			12	∅
		duodenum	6		1	4	
Cinchophen	11	stomach	6		1	8	∅
		duodenum	7		1	4	
Prednisolone	10	stomach	8	1	1		∅
		duodenum	8				

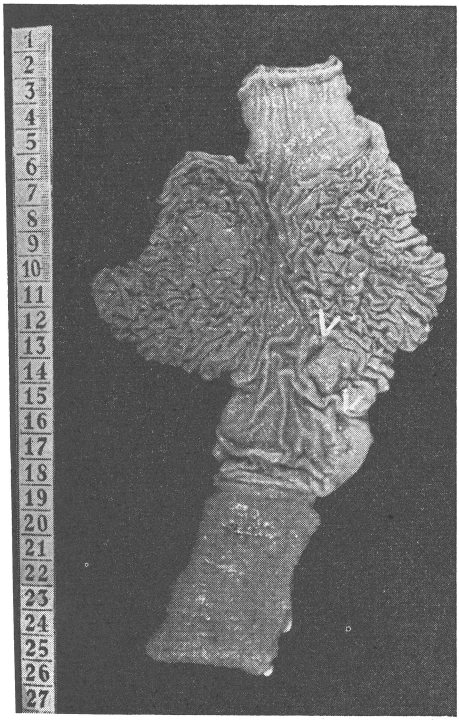

Fig. 4. Two common cinchophen ulcers

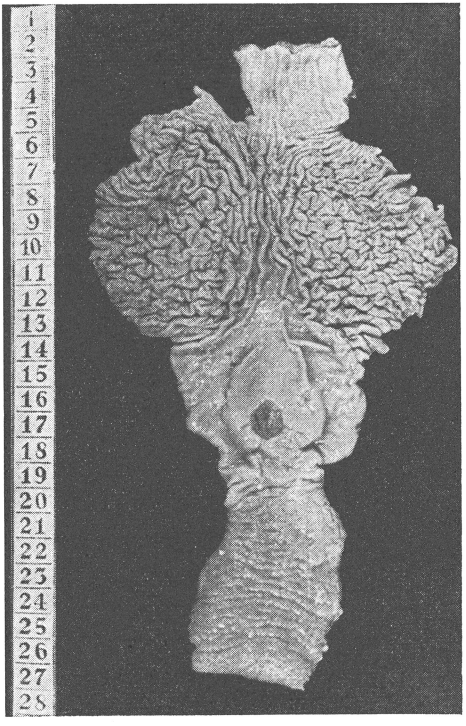

Fig. 5. Prednisolone+cinchophen ulcer. Type 1

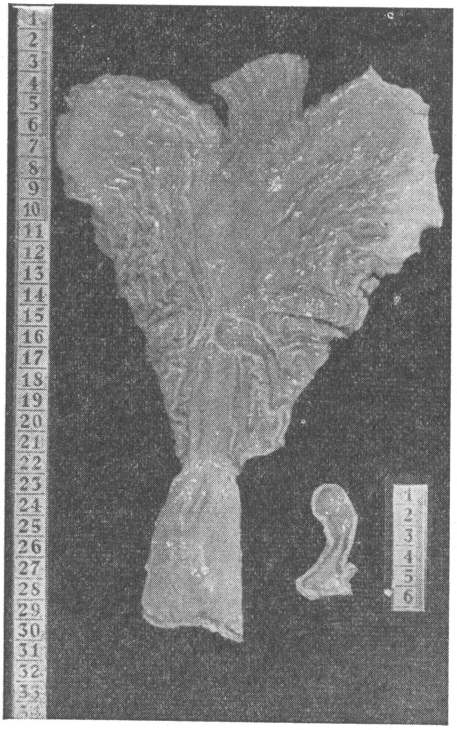

Fig. 6. Prednisolone + cinchophen ulcer. Type 2. The giant ulcer is not accompanied by gastritis

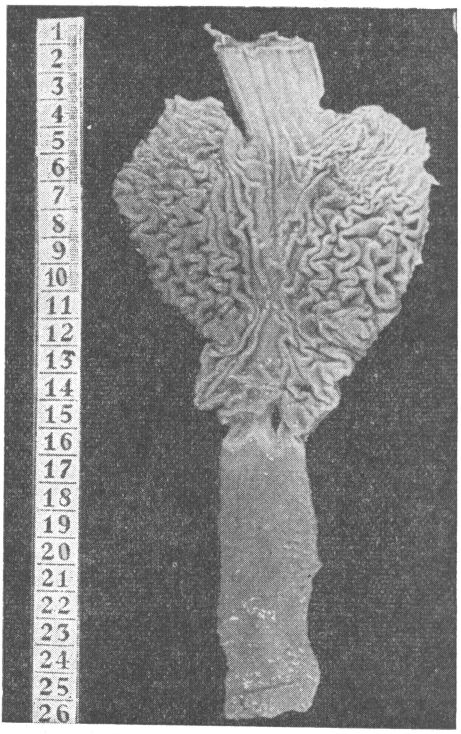

Fig. 7. Circular duodenal ulcer caused by prednisolone + cinchophen treatment. The animal died of perforation on the 17th day of experiment

ing and more or less regular change of the gastric and/or duodenal mucosa was its haemorrhagic tendency (haemorrhagic gastritis).

Cinchophen ulceration was greatly enhanced by the simultaneous administration of prednisolone. In this group there were three perforations and one death due to fatal haemorrhages; such complications did not occur in the control cinchophen ulcer group. In some cases giant ulcers were visible, similar to those found by us in earlier experiments in vagotomized and cinchophen treated dogs [4, 5]. The size of the ulcers can be seen in Figs 1, 2 and 3.

We distinguished two types of prednisolone + cinchophen ulcer.

Type 1. A large, deeply penetrating ulcer as if punched out.

Type 2. A less deep, but giant ulcer not accompanied by gastritis.

Progression of cinchophen ulcer is promoted by prednisolone not only in the stomach, but also in the duodenum. In this way circular penetrating duodenal ulcers may develop. A few ulcers are visible in Figs 4, 5, 6 and 7.

The adrenal glands were weighed at autopsy. In the prednisolone-treated group they weighed less than normal. The animals treated with both prednisolone and cinchophen displayed practically the same adrenal weight as those

treated with prednisolone alone (means, 0.077 and 0.072 g per kg body weight, respectively). Both these groups showed a highly significant difference from the group treated only with cinchophen (mean, 0.123). The statistical method applied was analysis of variance, the commont within-group S.D. 0.0327, ($P < 0.01$).

The control group with its mean of 0.099 differed from the three treated ones. The difference formally proved only borderline cases. Nevertheless, the economic efficiency of experimentation forbade to double the number of animals just to prove again facts well established in the literature.

Discussion

The ulcerogenic effect of prednisolone may be explained in various ways. Possible pathogenic factors are as follows:

1. Prednisolone increases the production of free hydrochloric acid and pepsin. BECK et al. [1] did not observe any significant change in gastric secretory activity in various patients and Heidenhain pouch dogs treated with high doses of prednisolone.

2. Prednisolone may slow down the regeneration of gastric mucosa. Using ^{3}H-thymidine, MYHRE [7] studied the healing of wounds of the gastric mucosa and the reaction of the intact mucosa in cortisone-treated rats. Autoradiography showed that the dynamics of cellular repair in the cortisone-treated animals lagged behind the control ones.

3. Iatrogenic adrenal atrophy. Prednisolone is known to reduce adrenal weight considerably, obviously by the negative feed-back mechanism. It is also known that peptic ulcer is common in patients suffering from Addison's disease. In our earlier experiments DOCA was found to prevent the development of cinchophen ulcer in the duodenum and to diminish it considerably in the stomach [2, 3]. According to our hypothesis prednisolone treatment gives rise to a iatrogenic hypomineralocorticism, which may be one of the factors in prednisolone-induced ulcerations.

If we compare our present results with those obtained in earlier experiments concerned with the effect of cortisone + cinchophen in the dog [2, 3], the ulcerogenic effect of prednisolone appears to surpass that of cortisone. We do not consider the question settled, because the experiments have not been carried out simultaneously.

From our results we have drawn the practical conclusion that prednisolone treatment should be preceded by X-ray examination of the patient's stomach and all those showing an ulcer in the stomach or duodenum should be excluded from such treatment. When higher doses are prescribed, the patient should be kept under close control. Prednisolone by itself may induce ulcer,

though its ulcerogenic effect is far less potent than that of cinchophen. In 3 weeks only 20% of the dogs developed ulcers, which were small and superficial. These results raise the hope that the prednisolone-induced ulcer may be detected in time, if the patients treated with large doses are subjected to X-ray examination at 3 week intervals. If there is ulceration, treatment must be discontinued immediately. As a result of this practice, we had no case of gastrointestinal bleeding or perforation at our Department during the past few years. As signs of iatrogenic adrenal insufficiency following the sudden interruption of steroid treatment we have observed headache, vertigo, weakness, tremor, tachycardia, anorexia and nausea. To prevent the interruption syndrome we suggest the administration of low doses of cortisone, which is less ulcerogenic. Experience has proved that daily 20 to 50 mg of cortisone injected intramuscularly is a suitable dose.

KONJETZNY [6] claimed that in man peptic ulcer would develop on the grounds of inflammation. His view has been adopted by many authors. In response to treatment with prednisolone and cinchophen giant ulcers may develop without gastritis. On the other hand, in other experiments we have observed the development of severe haemorrhagic gastritis without ulcer. In an overwhelming majority of cases prednisolone alone gives rise to haemorrhagic gastritis only. Earlier we found that in the dog DOCA inhibited the ulcerogenic action of cinchophen, but had no influence on gastritis and duodenitis [2, 3]. All these suggest that peptic ulcer and gastritis develop on the basis of two independent mechanisms. The relationship between the two diseases may be similar to that existing between arterial hypertension and arteriosclerosis. They often occur together, but may be present alone, too.

Recently, an increasing number of reports have described giant ulcers in old age. The pathogenesis of the condition is not clear. Earlier, HÁMORI et al. [4, 5] reported on the development of giant gastric ulcers in cinchophen-treated dogs following vagotomy. In the present study, similar changes have been observed following prednisolone + cinchophen treatment. We are fully aware of the fact that the results of model experiments cannot be applied directly to man, yet they offer two possible explanations. One of them is that the vagal nerve ensures eutropism of the stomach. In old age the vagus does not participate to a sufficient extent in the defensive mechanism of the gastric mucosa. Thus, ultimately, the senile giant ulcer may be considered a trophic one. The other explanation may be a significant role of endocrine factors in the pathological process. More closely: there may be a shift in the blood glucocorticoid and mineralocorticoid levels in favour of the glucocorticoids.

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