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Received August 25, 1966. P.S.E.B.M., 1966, v123.

Effect of Hydrocortisone on Secretion of Acid and Pepsin by Heidenhain Pouches.* (31581)

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In a previous study(1) in dogs with Heidenhain pouches, bilateral adrenalectomy reduced significantly gastric acid secretion stimulated by histamine. Small doses of hydrocortisone not only restored acid output to normal but caused a transient elevation to levels above pre-adrenalectomy control. Subsequently acid output returned within the range of pre-adrenalectomy control and remained at this level. This study was undertaken to determine the effect of hydrocortisone on gastric secretion in dogs with their adrenals intact.

Materials and methods. Three mongrel dogs weighing between 14 and 18 kg were used. A pouch of the oxyntic gland area (Heidenhain) was made in each animal and a Gregory cannula(2) was inserted. Studies were started 3 weeks later.

The animals were fasted 18 hours before each test. A continuous intravenous infusion (30 ml/hr) of 0.15 M NaCl was given throughout each experiment. Gastric juice was collected for two 15-minute periods to obtain basal levels of secretion. At the end of this period either gastrin or histamine was added to the saline to give desired dosage. Doses were doubled every 60 minutes for histamine and every 75 minutes for gastrin.

Gastric juice was collected by gravity drainage every 15 minutes. The volume was recorded to the nearest 0.1 ml and the acid concentration determined by titrating 0.2 ml of juice with 0.2 N NaOH to pH 7 using a glass electrode and an automatic titrator (Radiometer, Copenhagen). Pepsin activity was determined by the method of Grossman and Marks(3).

Gastrin extracts were prepared from the mucosa of the pyloric gland area of the hog stomach by the method of Gregory and Tracy (4) carried only through the stage of fractionation with isopropanol. All the gastrin used was from the same batch. Doses of gastrin are expressed in terms of the wet weight of mucosa from which the extract was obtained. Histamine doses are recorded in terms of the dihydrochloride salt.

After control studies, each animal was given 50 mg of hydrocortisone intramuscularly every day and secretory responses to gastrin and histamine again determined.

Results. Effect of hydrocortisone on histamine-stimulated acid and pepsin secretion. During control studies, as the acid output increased with increasing doses of histamine, the pepsin concentration decreased (Fig. 1). Maximal pepsin output occurred with a dose of histamine (1.5 mg/hr) that was submaximal for acid output.

During the period when hydrocortisone was being given the mean maximal acid output

* This work was supported in part by USPHS Grant AM 08354.

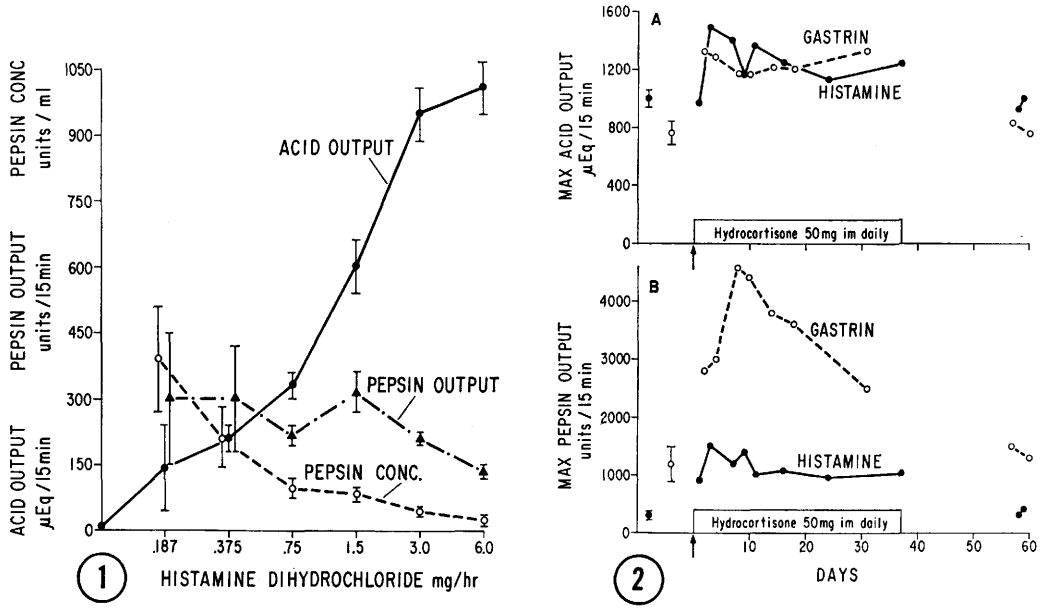

FIG. 1. Dose response curve to histamine dihydrochloride. The scale for dose of histamine is logarithmic. Each point is the mean of the last two 15-minute periods at each dose level, the vertical bars the SEM. Each line is the mean of 9 experiments in 3 dogs.

FIG. 2. Effect of hydrocortisone on acid output (A) and pepsin output (B) in response to histamine and gastrin. Each point represents the mean maximal output on the day studied for 3 experiments in 3 dogs. The control studies represent the mean of 9 experiments in 3 dogs, the vertical bars the SEM.

increased (Fig. 2A). The peak value occurred on the third day (1.48 × control) and then fell over the ensuing days. However, acid output was still greater than control values on the 37th day.

Maximal pepsin output during hydrocortisone treatment increased (Fig. 2B). The mean peak pepsin output was reached on the third day (4.76 × control) and remained elevated throughout the treatment period. As during the control period, maximal pepsin output during hydrocortisone administration occurred with doses of histamine that produced submaximal acid output (1.5 to 3.0 mg/hr). Maximal acid and pepsin output returned to control levels 3 weeks after stopping hydrocortisone.

Effect of hydrocortisone on gastrin-stimulated acid and pepsin secretion. Pepsin concentration and output increased in parallel with acid output during control studies (Fig. 3). Maximal pepsin output in response to gastrin was approximately 4 times that obtained in response to histamine. Maximal acid output coincided with maximal pepsin concentration and output (20 g/hr).

During hydrocortisone treatment all 3 animals behaved similarly. The mean maximal acid output increased above pretreatment values (Fig. 2A). The peak acid output occurred on the second day (1.73 × control). This value was not so high as that obtained with histamine stimulation (Fig. 2A), but other values during the treatment period were within the range found with histamine.

Mean maximal pepsin output increased during hydrocortisone administration (Fig. 2B). The peak output was 3.83 × control. Maximal pepsin output occurred when acid output was at its maximum (20 or 40 g/hr). Maximal acid and pepsin output returned to control limits 3 weeks after stopping hydrocortisone injections.

Discussion. There have been a number of studies of the effect of chronic corticosteroid administration in dogs with intact adrenals. Evidence has been reported for(5-16) and against(17-20) an increase in acid secretion. With the exception of the studies of Clarke *et al*(5), Plainos *et al*(6,7) and Wein-

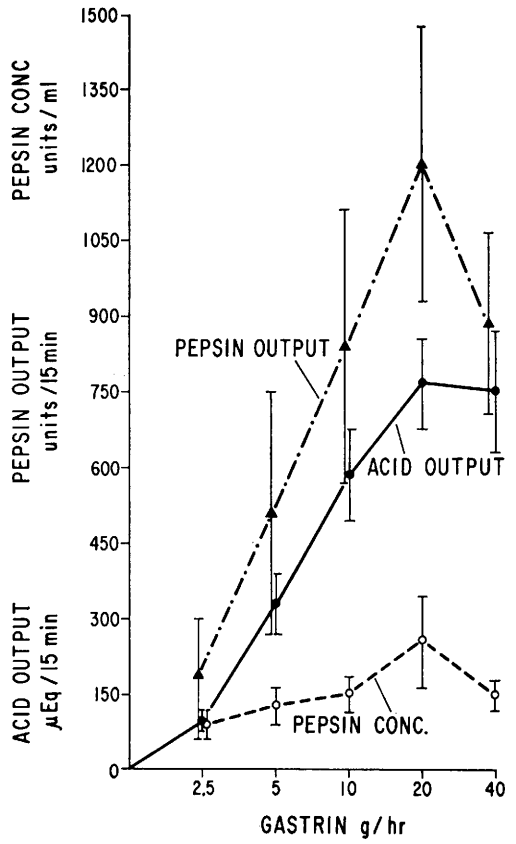

FIG. 3. Dose response curve to gastrin. The scale for dose of gastrin is logarithmic. Each point is the mean of the last two 15-minute periods at each dose level, the vertical bars the SEM. Mean of 9 experiments in 3 dogs.

shelbaum *et al*(11), all the other reports were concerned with 24-hour secretion(8-10,12,14, 15,17-19) or an inadequate method of stimulation(13,16,20). With the 24-hour secretion method acid output fluctuates markedly from day to day since such variables as quantity, rapidity and time of food ingestion are not taken into consideration. Plainos *et al*(6,7) studied secretion in gastric fistula and Weinshelbaum *et al*(11) in Heidenhain pouch dogs using submaximal histamine stimulation. The only report in which maximal histamine stimulation was used is that of Clarke *et al*(5). All 3 groups(5,6,7,11) found glucocorticoids increased gastric secretion significantly.

In the present study we have found that the maximal acid output increased significantly (1.48 × control) following hydrocortisone administration. Both the latent time interval of response and the size of the increase in acid output (Fig. 2A) were similar to the findings of Clarke *et al*(5).

There have been no previous studies of the effect of corticosteroids on gastrin stimulated gastric secretion. During the control period maximal acid output in response to gastrin was less than in response to histamine (Fig. 2A) as previously reported from this laboratory(21). The effect of hydrocortisone was to cause the mean maximal output in response to gastrin to increase significantly so that it was not only above control values but also within the range of histamine stimulated maximal acid output (Fig. 2A). These findings would suggest that the action of glucocorticoids cannot be due to an increase in parietal cells alone as suggested by Reid and coworkers(22), since such an increase would be expected to act equally on stimulation by histamine and gastrin.

There have been 5 previous reports of the effect of chronic administration of glucocorticoids or ACTH on pepsin secretion in dogs (5,6,7,16,17). Plainos *et al*(6,7) using gastric fistula animals found basal pepsin secretion was significantly increased. In Heidenhain pouch dogs neither Clarke *et al*(5) (antral stimulation and basal) nor Nicoloff *et al* (16) (antral stimulation) nor Wiederanders *et al*(17) (24-hr secretion) could find any effect of ACTH or glucocorticoids on pepsin secretion. None of these studies measured maximal pepsin secretion in response to histamine or gastrin. We have found that the mean maximal pepsin output was increased significantly in response to both histamine and gastrin during administration of hydrocortisone. Pepsin secretion in response to gastrin was greater than in response to histamine during the control period and remained so throughout hydrocortisone administration (Fig. 2B). In contrast, maximal acid output in response to histamine and gastrin was approximately equal during hydrocortisone administration although histamine stimulated acid output was greater in the control studies (Fig. 2A). This suggests that hydrocortisone has an effect on the parietal cell that differs from that on the chief cell.

Summary. Hydrocortisone (50 mg intra-

muscularly daily) was given to 3 dogs with Heidenhain pouches for a period of 37 days. Maximal acid and pepsin output in response to histamine and gastrin increased during hydrocortisone administration. During control studies, the mean maximal acid output in response to gastrin was lower than to histamine but the maximal responses to these 2 stimulants were generally equal during hydrocortisone administration. In contrast, mean maximal pepsin output was higher with gastrin during control studies and remained higher than histamine during administration of hydrocortisone.

The authors wish to thank Ray Linford for technical assistance.

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Received August 25, 1966. P.S.E.B.M., 1966, v123.

Effect of Non-Steroidal Anti-Inflammatory Drugs in the Evans Blue Pleural Effusion. (31582)

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The Evans Blue pleural effusion method has been suggested and used as a test for anti-inflammatory compounds. As generally used(1,2,3) drug effect is studied by measuring the volume of pleural fluid 6 hours following the intrapleural injection of the dye. Further investigation of the method indicated that the exudative response obtained later than 12 hours after injection of the irritant was significantly greater than at 6 hours, and that there were certain advantages to using the volume at this time in assaying drug activity. Results obtained with this modification are presented here for acetylsalicylic acid, phenylbutazone, indomethacin, mefenamic and flufenamic acids.

Methods and materials. Male Holtzman rats (250-400 g) were randomized into the control and experimental groups using random tables(4). Compounds were administered by

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