Effect of Acidification of Canine Duodenum on Gastric Secretory Response to Food Before and After Pancreatectomy.*† (29447)

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Acidification of duodenal contents both inhibits secretion of acid by the stomach and causes secretin to be released from duodenal mucosa. Commercially prepared secretin given intravenously to dogs inhibits gastric secretion in several experimental situations (1-4). The effects of secretin and of acidification of the duodenum on gastric secretory responses to different stimuli are being compared systematically to seek parallels and divergences that may provide evidence for or against the concept that secretin plays a role in regulation of gastric secretion.

Exogenous secretin (Vitrum, Stockholm, Sweden) inhibits the gastric secretory response of Heidenhain pouches in dogs to food after pancreatectomy has been performed(3). The present experiments were performed to learn whether the same was true of acidification of duodenal contents.

Methods. Surgical procedures. All operations were performed with aseptic surgical technic under anesthesia induced by pentobarbital given intravenously.

Each of 2 adult mongrel dogs was prepared by establishment of a Heidenhain pouch, division of the pyloroduodenal junction, cannulation of the duodenum, closure of the duodenal stump and gastrojejunostomy (Fig. 1). Thus, the duodenum was bypassed by the gastrointestinal stream and provided with a cannula near its proximal end through which fluid could be introduced. Care was taken to be certain that no antral mucosa remained in continuity with the duodenum.

In 4 other dogs, Heidenhain pouches were made at a first operation, and total pancreatectomy was performed at a second operation. At a third and final operation, the pyloroduodenal junction was divided, a cannula was placed in the duodenum opposite the entrance of the major pancreatic duct, the duodenal stump was closed and the antrum was anastomosed to the side of the first part of the jejunum to reestablish gastrointestinal continuity.

All Heidenhain pouches were drained by Vitallium cannulas.

Postoperative care. Penicillin G (500,000 units) was given intraperitoneally at the end of each operation, and 600,000 units of procaine penicillin was given intramuscularly daily for 5 days postoperatively.

When they recovered from the operations, the dogs were fed one can (426 g) of Hill's prepared dog food twice daily and given free access to water. Pancreatectomized dogs received, in addition, 50 g of raw beef pancreas twice daily. The beef pancreas was obtained at intervals from a nearby packing plant and preserved by freezing. Regular insulin was given subcutaneously twice daily in doses of 7 or 8 units. On this regimen, the weights of the animals remained stable. All animals were allowed 3 weeks to recover from the final operation before being tested.

Experimental procedure. Gastric secretory responses to food were compared when saline

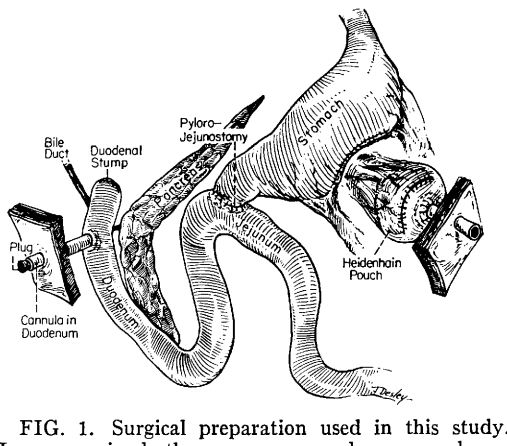

FIG. 1. Surgical preparation used in this study. In some animals the pancreas was also removed.

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solution or HCl was given intraduodenally.

A minimum of 48 hours elapsed between successive experiments on any one animal. All dogs were fasted for 24 hours before each experiment.

Animals stood on stands during experiments. A catheter for introduction of saline solution or HCl and the glass electrode and reference lead for a pH meter were passed through holes in a stopper that fitted the duodenal cannula and were inserted into the lumen of the duodenum. The pH of the duodenal contents was recorded continuously with a Beckman model R recording pH meter with a glass electrode. The instrument was standardized with buffer solutions of pH 4 and pH 7 before each experimental recording. Intraduodenal pH was recorded in half of the experiments, and was always recorded during the initial test on each animal.

Fasting secretion from Heidenhain pouches was collected for 30 minutes, after which gastric secretion was stimulated by feeding 400 g of partially cooked ground lean beef.

Thirty minutes after the meat meal, infusion of 0.15 N HCl (0.15 N NaCl in control experiments) into the duodenum was begun at a rate of 80 ml/hr and was continued for one hour. The liquid was introduced through a no. 10 polyethylene catheter whose tip was placed near the opening of the major pancreatic duct; rate of infusion was controlled by a motor-driven syringe. Additional amounts of HCl were added manually with the objective of maintaining the pH of duodenal contents at 2.5 or below except for brief periods. During experiments in which intraduodenal pH was not recorded, HCl was introduced into the duodenum in amounts and at rates identical to those used in the preceding test in which pH had been measured. A solution of 0.15 N sodium chloride was administered intraduodenally in comparable volumes during parallel control experiments.

Juice was collected from Heidenhain pouches at ½-hour intervals throughout all experiments. The concentration of free HCl in samples of gastric juice was determined by titration with 0.1 N NaOH, with Töpfer's reagent (dimethylaminoazobenzene) used as indicator, and output of acid was calculated and expressed as milliequivalents of HCl per ½-hour period.

Results. After division of the pyloroduodenal junction and pylorojejunostomy, the mean pH of fasting duodenal contents averaged 7.61 in 10 tests on 4 dogs that had undergone pancreatectomy, and 7.65 in 4 tests on two animals with the pancreas intact.

In 38 (74.5%) of 51 tests on the same 6 dogs, free acid was present in juice collected from Heidenhain pouches 24 hours after the last feeding. Free acid was noted more frequently when the pancreas was intact (87.5% of tests) than after it had been removed (68.6% of tests). Rate of secretion of free HCl during fasting ranged from 0.01 to 0.27 mEq per 30 minutes in the 2 dogs with the pancreas intact and averaged 0.05 mEq per 30 minutes. Comparable values for 4 pancreatectomized dogs were 0.01 to 0.19 with a mean value of 0.04 mEq per 30 minutes. The mean difference of 0.01 mEq per 30 minutes was not significant statistically ($p>0.5$).

During the hour in which 0.15 N HCl was infused into the duodenum with the goal of keeping the pH of duodenal contents 2.5 or less, the pH of 4 dogs with the pancreas removed was kept in this range for, on the average, 69% of the hour by instillation of 108 ml of acid, whereas the duodenal pH of 2 dogs with the pancreas intact was 2.5 or less for only 55% of the hour when an average of 184 ml of acid was used. Comparable figures for the percentage of the hour during which pH of duodenal contents was 4 or less were 94 for pancreatectomized dogs and 85 for the 2 dogs with the pancreas intact.

Comparison of gastric secretory responses to the meal of meat when 0.15 N NaCl or 0.15 N HCl was given intraduodenally for one hour from 30 to 90 minutes after feeding showed that in all cases, whether the pancreas was present or not, acidification of the duodenum was accompanied by a reduction in rate of secretion of HCl by the Heidenhain pouches. The mean percentage reductions in secretion of acid during the time HCl was infused into the duodenum, as compared with NaCl infusion, were —57.4 and

TABLE I. Effect of Instillation of HCl into Duodenum on Secretion of Acid by Heidenhain Pouches in Dogs in Response to a Meal in Presence and Absence of the Pancreas.*

		Output of HCl					
		30-90 min after feeding			0-180 min after feeding		
Status of pancreas	Dog No.	Control, mEq	HCl in duodenum, mEq	% Change	Control, mEq	HCl in duodenum, mEq	% Change
Intact	1	2.96	1.26	−57.4	7.13	7.87	+10.4
	2	2.16	1.25	−42.1	4.06	6.32	+55.6
Removed	3	.49	.14	−71.4	1.07	.94	−12.1
	4	1.40	.16	−88.5	2.98	1.56	−47.6
	5	.61	.25	−59.0	1.06	1.36	+28.3
	6	1.67	.48	−71.2	3.71	2.70	−27.2

* Data are mean values of 4 experiments (except for controls in dog 3, in which 7 tests were made).

−42.1 in the 2 dogs with the pancreas intact and −71.4, −88.5, −59.0 and −71.2 in the 4 dogs with the pancreas removed (Table I). After intraduodenal infusion of acid had been stopped, there was a tendency for the rate of secretion of HCl by the pouches to exceed that noted in control experiments. In 3 of the 6 dogs, more HCl was secreted during the 3 hours of experiments in which HCl was instilled into the duodenum than was the case in controls, despite the fact that during acidification of the duodenum, secretion was inhibited sharply.

Discussion. The dog, unlike man, does not secrete acid gastric juice continuously in the postabsorptive state. Although vagally innervated gastric pouches not infrequently secrete HCl during fasting, this sporadic secretion is interpreted as resulting from unidentified psychic stimuli and does not occur when vagally denervated (Heidenhain) pouches are used. The present experiments confirm those of Andersson(5,6), who noted that when gastric chyme was prevented from entering the duodenum and was passed directly into the jejunum, HCl was usually secreted by Heidenhain pouches during fasting. Andersson was able to inhibit this fasting secretion from vagally denervated gastric pouches by instilling HCl into the duodenum. As a consequence, he attributed the fasting secretion of HCl in these circumstances to loss of inhibition of gastric secretion that normally follows acidification of duodenal mucosa.

The observation that more HCl had to be instilled into the duodenum to keep the pH of its contents near 2.5 when the pancreas was intact than when the pancreas had been removed is readily explained by the assumption that in the presence of the pancreas, part of the acid was neutralized by the flow of pancreatic juice it stimulated.

The experiments on the 2 dogs with pancreases intact confirm the findings of Andersson that secretion of HCl by vagally denervated gastric pouches in response to food can be incompletely inhibited by infusion of acid into the duodenum. The mechanism involved could be liberation of a humoral agent from the duodenal mucosa, although acidification of the pyloric gland area could also play a role. The results of similar tests upon pancreatectomized dogs indicate that the mechanism of inhibition of secretion from Heidenhain pouches by acid placed in the duodenum does not require presence of the pancreas. The same is true of gastric secretory inhibition produced by parenteral injection of commercially prepared secretin(3).

These data harmonize with others gradually accumulating to support the concept that, assuming a humoral agent or agents inhibit gastric secretion after the canine duodenum is acidified, the agent may be secretin or other, closely allied, substances, or both.

Conclusion. The inhibition of the gastric secretory response of canine Heidenhain pouches to meat that follows acidification of the duodenum persists after removal of the pancreas.

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Histamine Forming Capacity of Human Wound Tissue.* (29448)

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During the last decade evidence has accumulated to show that there is a relationship between histamine forming capacity and rapid tissue growth(1,2). For example, in experimental studies on rats(3) it was found that excised wound tissue and granulation tissue grown into subcutaneously implanted polyvinyl sponges develop a high histamine forming capacity. Moreover, it was shown that the rate of repair of skin incisions determined by wound tensile strength could be influenced by altering experimentally the histamine forming capacity of the tissue of the wound. It has been suggested that a relationship exists between wound healing and histamine formation also in man(4). The present experiments were designed to investigate this problem further by studying histamine formation in normal skin and in tissue removed in the state of wound healing.

Material and methods. Wound tissue was obtained from 9 patients operated on for bilateral varicose veins under general anaesthesia (Fluothane). The patients were subjected to ligation of the long saphenous vein in the groin and stripping of the vessels in a 2-stage procedure in which the operation was performed on one leg at a time. At the first operation a portion of skin was excised from the leg just below the inguinal ligament and used for determination of histidine-decarboxylase activity. At the second operation performed at various intervals after the first one (1-11 days) normal skin was taken from a similar site of the other leg, the first wound was excised and resutured and histidine decarboxylase activity was determined in both specimens. In this way studies could be made of 1) normal skin (skin I) 2) normal skin after a previous operation (skin II) and 3) excised wound tissue.

The tissues were minced, suspended in phosphate buffer and incubated with ^{14}C-histidine and the amount of ^{14}C-histamine formed was measured by isotope dilution. The procedures used have been fully reported (5,6). Blank values were obtained by adding semicarbazide (10^{-2}M) to the incubation mixture.

Results. The results are listed in Table I where the amount of ^{14}C-histamine formed is expressed in counts per minute per gram tissue exceeding blank specimens. Normal skin only exceptionally showed any histamine forming capacity while wound tissue regularly had a high histamine forming capacity. This enzymic change seemed to reach a peak on the second and third day after the incision.

TABLE I

Age of patient	Sex	Wound age, days	Histamine forming capacity		
			Skin I	Skin II	Wound
53	♂	1	11.3	0	0
55	♀	1	0	5.6	27.5
39	♀	2	0	0	30.3
56	♂	2	30.4	15.3	65.8
67	♀	3	0	0	73.5
39	♂	3	0	0	48.5
61	♂	4	0	4.8	42.3
39	♂	4	0	0	15.3
69	♂	11	1.6	0	14.6

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