Physiologic Scope of the Antral Inhibitory Hormone *

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Introduction

THE NORMAL FLOW and ebb of acid gastric secretion in response to a meal is clear evidence of regulatory mechanisms designed initially to stimulate and later curtail acid output. Pavlov [24] separated the stimuli governing gastric secretion into three phases, cephalic, gastric, and intestinal. The post-prandial cut-off of gastric secretion has been attributed to withdrawal of these stimuli, but current evidence suggests that acidification of the pyloric antrum, as well as the duodenum, may also liberate an inhibitory hormone (chalone) which acts to suppress further acid production.[34]

Sokolov [31] first noted that introduction of hydrochloric acid into the stomach decreased the acid secretion from a Pavlov pouch, and Wilhelmj, O'Brien, and Hill [38] reported inhibition of the antral phase of gastric secretion following instillation of acid into the stomach. The careful studies of Dragstedt [8, 9, 22] and Woodward [40, 41] and their associates have shown that acidification of the antral mucosa will suppress the release of the antral hormone, gastrin. Whether the total inhibitory effect of antral acidification is due to this suppression is controversial.[37]

Harrison, Lakey, and Hyde [15] in studies on dogs with divided antral pouches gave the first evidence for a separate antral inhibitory hormone. Although this preparation appears ideally suited to the study of antral inhibition, its subsequent use yielded contradictory results, some supporting an inhibitory hormone,[10, 14, 17] others denying it.[9, 20, 26, 42]

This disagreement has stimulated the development of other means of differentiating between simple suppression of gastrin formation and the action of a separate inhibitory hormone. Attempts at this purpose (with varying success) have been made with cross-circulation experiments,[11, 12, 36] with studies on the inhibition of secretory stimuli other than gastrin,[13, 21, 25, 29, 33, 41] and by demonstrattion of the protective (anti-ulcer) role of the antrum.[5, 18, 32]

Resolution of the uncertainty surrounding antral inhibition is of obvious importance. The demonstration and possible future isolation of a naturally-occurring material which inhibits gastric acid production would aid greatly in the understanding, and perhaps in the treatment, of the peptic ulcer diathesis.

In the following report we present data from two experimental approaches to antral inhibition. In the first category, evidence is given that the antral-gastrin mechanism

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of one animal may be suppressed by the administration of blood draining the acidified antrum of another animal. In the second group, antral inhibition of gastric secretion stimulated by the cephalic phase (partially dependent on gastrin release) and by the intestinal phase and by histamine (stimuli not dependent upon gastrin) is demonstrated.

Segments of this work have been previously reported.[35, 36] Our knowledge of the range of action of the antral chalone is summarized here.

Materials and Method

Thirty-six healthy adult, 20 to 25 kg., female mongrel dogs with chronic gastric fistulas were used. Paired test and control secretory studies were carried out on the same dogs on alternate days, and the sequence of the test and control studies was varied. Only animals in good health were used; any sign of illness would exempt an animal from study. The experiments were carried out with the dog in the Pavlov stand, and collections were made from the gastric pouch every 30 minutes following the stimulus. The volume of the secretion was measured and the acidity determined using Töpfer's reagent. Samples of less than 1.0 cc. were not titrated. Studies were carried out only on fasting animals in a basal secretory state. (Criteria for basal state: 15-minute pouch output of less than 0.5 cc. with acidity of less than 20 clinical units.)

Operative Technic. The operative technics used in preparing various gastric pouches were those in standard use, described briefly for clarity. We have developed a method for chronic cannulation of the portal vein which has proved to be simple and useful.

A. Fundic Pouches

1. Heidenhain. Large denervated fundic pouches (Heidenhain) were constructed from the greater curvature of the stomach using a technic similar to the one described by DeVito and Harkins.[7] These pouches were drained by stainless steel cannulas brought through the body wall.

2. Pavlov. Large pouches of the innervated gastric fundus (Pavlov) were constructed by first incising the fundus across the distal greater curvature and later completing the superior division between pouch and main stomach with a double internal mucosal barrier, thereby leaving the serosa over the proximal fundus (and vagal innervation) intact. These pouches were drained by stainless steel cannulas brought through the body wall.

B. Antral Pouches

In the construction of antral pouches (innervated and denervated), the distal division was made immediately proximal to the pylorus in order to exclude duodenal mucosa. The duodenum was divided just beyond the pylorus and the intervening tissue was discarded. The pH of the mucous secretion from both innervated and denervated antral pouches was routinely tested.

1. Denervated. In preparing denervated antral pouches, the stomach was cut entirely across at the level of the *incisura anqularis* taking care to denervate completely the lesser curvature. Gastrointestinal continuity was restored with a gastroduodenostomy. The proximal end of the antrum was oversewn and the distal end brought through the body wall as a cutaneous fistula.

2. Innervated. Vagally innervated antral pouches were constructed by partially dividing the stomach with an incision across the greater curvature just opposite the *incisura angularis,* leaving the lesser curvature intact. The gastric and antral lumens were separated with a double mucosal barrier and gastro-intestinal continuity was restored with a gastroduodenostomy.

C. Thiry-Vella Fistulas

An isolated loop of jejunum (Thiry-Vella) was constructed in some animals. The small bowel was divided in two places, approximately 36 and 68 cm. from the ligament of Treitz, thereby creating an isolated loop of upper jejunum measuring 32 cm. Intestinal continuity was restored with a jejuno-jejunostomy and the two ends of the isolated loop were brought through the body wall as cutaneous fistulas. The serosa of the bowel was sutured to the parietal peritoneum to prevent prolapse.

D. Venous Catheters

1. Portal vein. Portal vein cannulation was accomplished by inserting a previously siliconized soft plastic catheter (accepts 14-gauge needle) into a large vein in the splenic pedicle. The cathe-

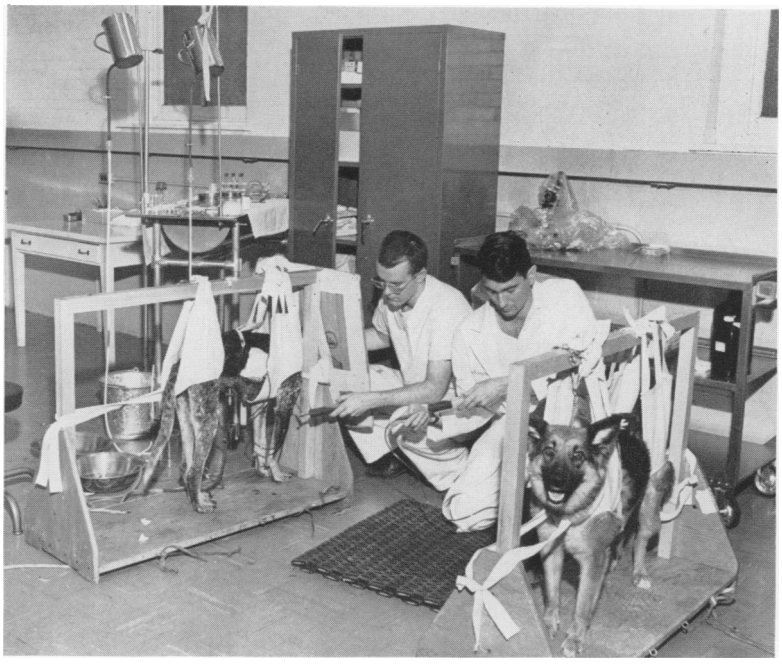

FIG. 1. Cross-transfusion in progress. 150 ml. of blood withdrawn from each dog every 15 minutes and immediately transferred to the opposite animal. Donor Dog A at left receiving antral irrigation of N/10 hydrochloric acid for test cross-transfusion study. All animals used in cross-transfusion experiments were healthy and alert.

ter was usually threaded into the portal vein without difficulty although on occasion the tip would be deviated into one of the vasa brevia. In such event, repositioning was accomplished without difficulty. The end of the catheter was positioned about 1.0 cm. from the entrance of the portal vein into the liver and could be palpated easily at this site. Prior to insertion five or six holes about 0.5 cm. apart were made at the end of the catheter. The catheter was tied in place at its emergence from the splenic vein and was brought obliquely through the body wall and tunneled under the skin of the thorax to emerge dorsally at about the level of the eighth rib. A slow drip containing 5.0 mg. of heparin * was administered through the portal venous catheter until the operation was concluded at which time a small amount of concentrated heparin was placed within the plastic cannula itself. The external portion of the catheter was fixed to the body wall with adhesive, and the dog was placed in a canvas jacket to protect the catheter.

2. *Inferior vena cava.* Cannulation of the inferior vena cava was accomplished by inserting a large-bore soft plastic catheter (described above) through the femoral vein. A length calculated to place the tip of the catheter near the diaphragm was used. The external portion of the catheter was fixed to the thigh with adhesive.

* Supplied by Upjohn Company

Cross-Transfusion Studies

Cross-transfusion experiments were carried out between pairs of alert, healthy, nonanesthetized dogs. The *donor* animal (A) was prepared with an isolated antral pouch (innervated or denervated) and an indwelling cannula in the portal vein. The *recipient* animal (B) was prepared with an Heidenhain pouch and an indwelling femoral cannula leading into the inferior vena cava. The venous catheters were inserted 30 days following the preparation of the gastric pouches, and cross-transfusion studies were usually begun one or two days after the catheters were placed. Cross-transfusion studies were carried out with the animals in adjacent Pavlov stands (Fig. 1). One hundred and fifty ml. of blood was withdrawn simultaneously from the portal vein of Dog A and the femoral vein of Dog B and was immediately administered to the opposite dog. The cross-transfusions were begun shortly before the onset of antral stimulation and were repeated every 15 minutes for the duration of the study so that an average of 10 ml. of blood per

minute was exchanged for three to four and one-half hours. Each cross-transfusion was completed in three to five minutes. In test experiments, the isolated antrum of Dog A was gently and continuously perfused with N/10 hydrochloric acid at about 3.0 ml. per minute beginning 30 to 60 minutes prior to antral stimulation of Dog B. In control studies, the antrum was either gently irrigated with saline (pH 7, 1.0 ml./min.), or was not irrigated at all. Except for these differences in the antral perfusants of Dog A, the paired test and control studies were identical and were performed on the same animals on adjacent days. All animals received identical daily doses of heparin, a portion of which was given through the catheter to maintain the high concentration within its lumen.

A. Antral Phase, Food Stimulus

Sixteen experiments were carried out on eight separate pairs of dogs. Five donor dogs were prepared with an innervated antral pouch while in three other donors, the antrum had been denervated. All donor animals had an indwelling plastic cannula in the portal vein. Dog B had a Heidenhain pouch and a femoral vein catheter. Gastric secretion was stimulated by feeding Dog B 400 Gm. of Pard (Fig. 2, 3).

B. Antral Phase, Acetylcholine Stimulus

Six experiments were carried out on three separate pairs of dogs. Two donor dogs were prepared with an innervated antral pouch, while in one donor the antrum had been denervated. Both types of donor ani-

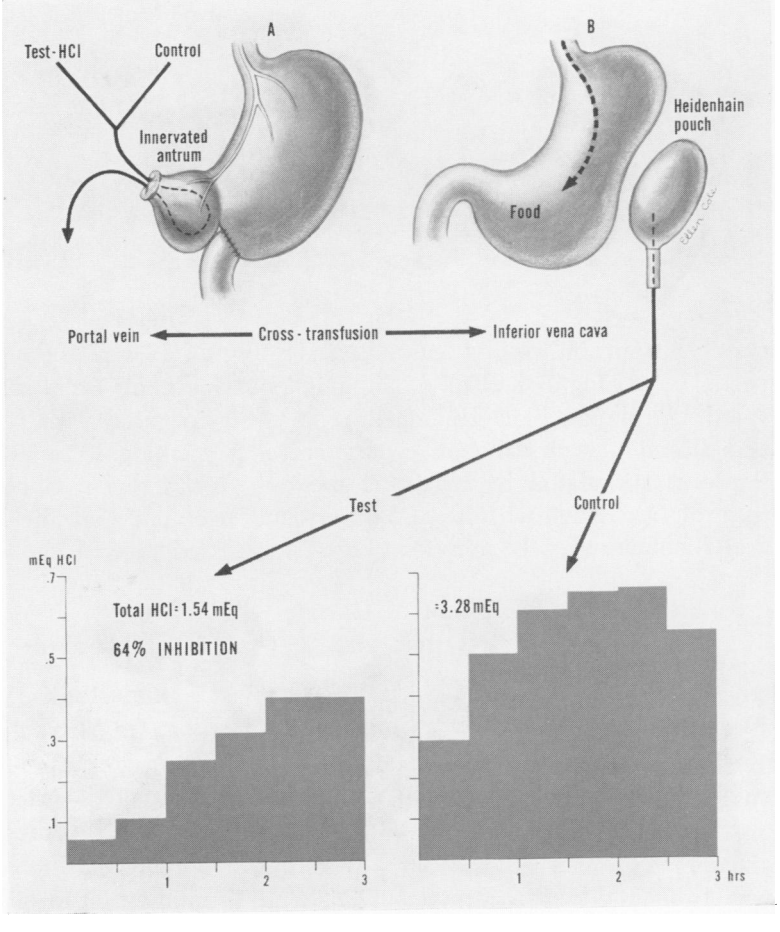

FIG. 2. Antral phase—cross-transfusion—food stimulus—donor animal with innervated antrum. Heidenhain pouch acid output of Dog B in milliequivalents. Average of 10 control–10 test cross-transfusion studies on 5 separate pairs of dogs, using 400 Gm. Pard as stimulus.

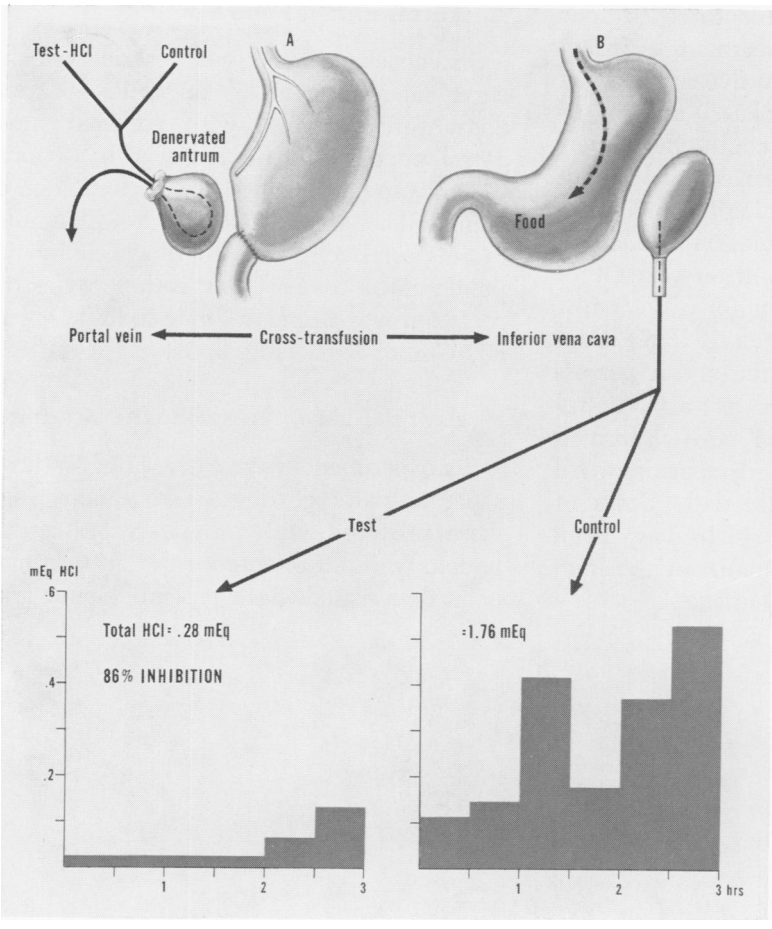

FIG. 3. Antral phase—cross-transfusion—food stimulus—donor animal with denervated antrum. Heidenhain pouch acid output of Dog B in milliequivalents. Average of 6 control–6 test cross-transfusion studies on 3 separate pairs of dogs, using 400 Gm. Pard as stimulus.

mals had an indwelling cannula in the portal vein. Dog B had an isolated innervated antral pouch, a Heidenhain pouch and a femoral vein catheter. Gastric secretion was stimulated by irrigating the antrum of Dog B with 10 ml. of 1.0 per cent acetylcholine every 10 minutes (Fig. 4).

Studies on the Inhibition of Gastric Secretory Stimuli Other than Gastrin

A. Cephalic Phase, Insulin Stimulus

Nineteen studies were carried out on six Pavlov pouch dogs. Three of these had an innervated antral pouch and in three the antrum was denervated. Gastric secretion was stimulated by the intravenous injection of 15 units of regular insulin. In test studies, the isolated antrum was continuously irrigated with N/10 hydrochloric acid beginning 30 to 60 minutes before the insulin was given. Control studies were identical except that the antrum was either gently irrigated with saline or not irrigated at all (Fig. 5).

B. Intestinal Phase, Food Stimulus

Nine studies were carried out on four dogs prepared with Heidenhain and denervated antral pouches. Gastric secretion was stimulated by feeding 400 Gm. Pard. In test studies, the antrum was continuously irrigated with N/10 hydrochloric acid beginning 30 to 60 minutes prior to feeding.

In control studies, the antrum was not irrigated (Fig. 6).

C. Intestinal Phase, Distention Stimulus

Seventeen studies were carried out on four dogs prepared with Heidenhain pouches, Thiry-Vella fistulas, and isolated antra, two of which were innervated and one denervated. Gastric secretion was stimulated according to the method of Sircus [30] by inflation of a balloon within the small bowel loop. The balloon was inflated to 30 mm. Hg pressure and left in place throughout the collection. In test studies, the antrum was irrigated continuously with N/10 hydrochloric acid beginning 30 minutes before the inflation of the balloon. In the control studies, the antrum was not irrigated (Fig. 7).

D. Histamine Stimulus

Forty-four studies were carried out on 12 Heidenhain pouch dogs prepared with isolated antra, six of which were innervated and six denervated. Gastric secretion was stimulated by the subcutaneous injection of 1.0 mg. of histamine base. In test studies, the antrum was continuously irrigated with N/10 hydrochloric acid beginning 30 to 60 minutes before the administration of histamine. In control studies, the antrum was not irrigated (Fig. 8).

Results

Secretion from the isolated antral pouches was found to be uniformly alkaline on testing, even following the administration of histamine. The pH of the saline used to

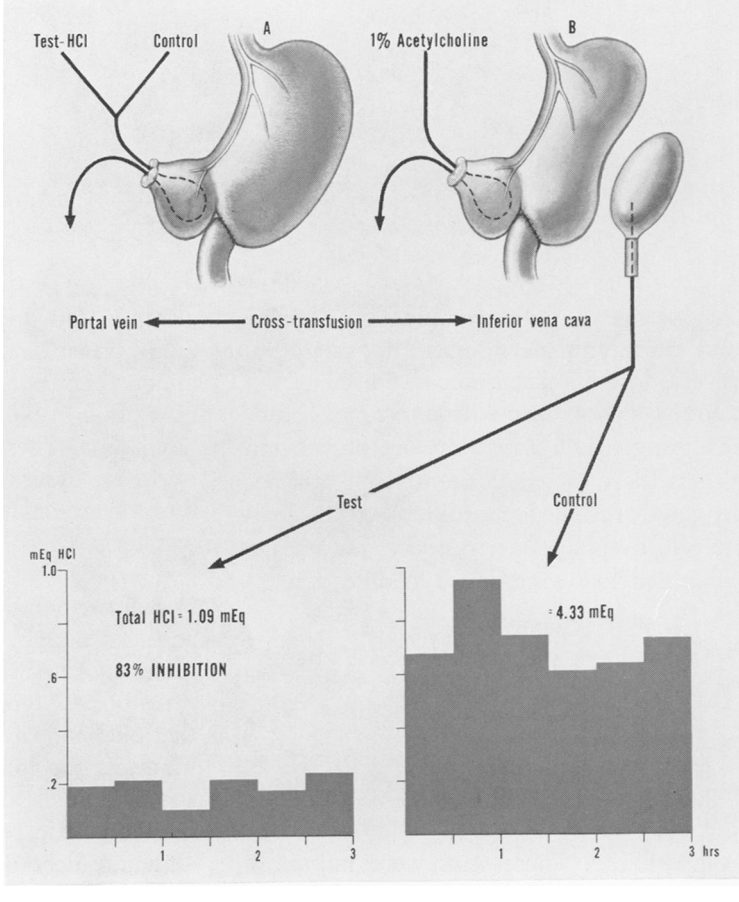

FIG. 4. Antral phase—cross-transfusion—acetylcholine stimulus. Heidenhain pouch acid output of Dog B in milliequivalents. Average of 6 control–6 test cross-transfusion studies on 3 pairs of dogs, using local acetylcholine as stimulus. Two of the donor dogs had innervated antra and one of the donor dogs had a denervated antrum.

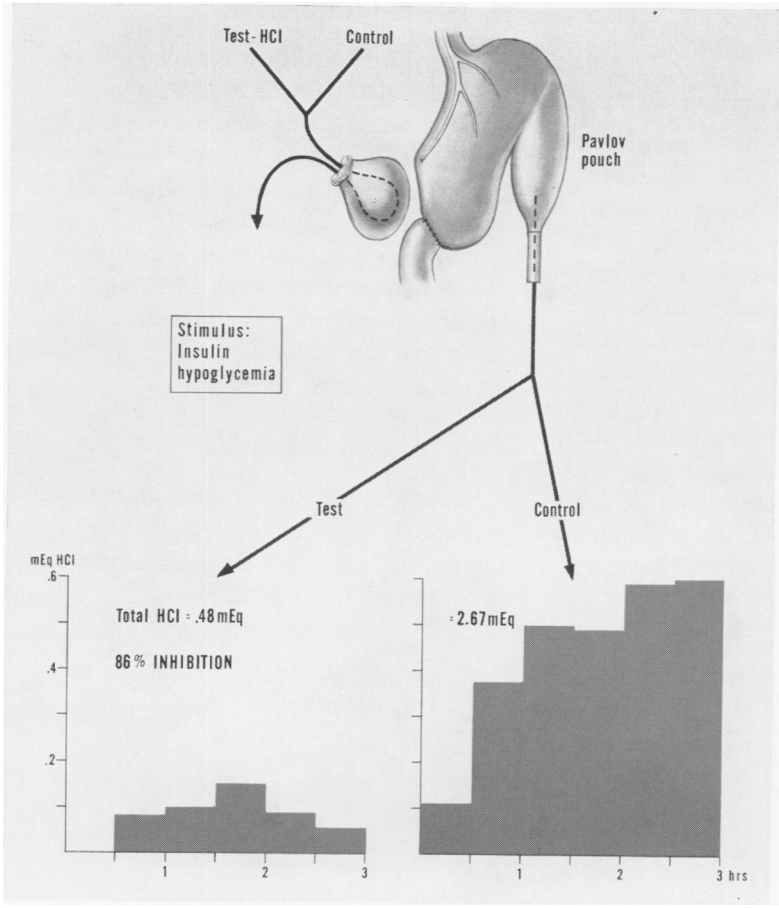

FIG. 5. Cephalic phase—insulin hypoglycemia stimulus. Pavlov pouch acid output in milliequivalents. Average of 19 control–19 test studies on 6 dogs using insulin hypoglycemia as stimulus. Three dogs had innervated antra and three had denervated antra (as shown above).

irrigate the antra was found to be 7 before and after antral perfusion. Autopsy studies revealed no duodenal mucosa in any of the antral pouches. Comparison of control studies using saline irrigation of the antrum versus those in which the antrum was not irrigated revealed no difference in acid output. Results are expressed as percentage inhibition following antral acidification.

$$\frac{\text{Control-test}}{\text{control}} \times 100$$

Cross-Transfusion Studies

Early in the cross-transfusion experiments, attempts were made to cross-match the dogs by *in vitro* agglutination test for compatibility. These tests were uniformly negative, but despite that there were three fatal transfusion reactions and several minor aberrations that were interpreted as being due to blood incompatibility or contamination. These usually were manifested by fever, dyspnea, or vomiting. Whenever these symptoms occurred, the experiment was terminated. Ota, Camishion, and Gibbon [23] recently suggested that such reactions may actually be due to filarial antigen-antibody anaphylaxis rather than to blood-group incompatibility.

Autopsies were performed on all animals that died and small pulmonary emboli were found in the lungs of two recipient dogs. In one animal, antral acidification failed to inhibit gastric secretion. Autopsy revealed an acute ulceration of the antrum suggest-

ing that antral as well as duodenal[28] inhibition may be obtunded by mucosal ulceration.

On a regimen of daily irrigation which kept the catheter filled with concentrated heparin solution, it has been possible to keep portal catheters patent for as long as eight weeks. The average period of patency is two weeks. We have found that large intravenous doses of heparin will at times acutely suppress gastric secretion although chronic administration of subcutaneous heparin has no apparent effect. Care has been taken to use small amounts of heparin intravenously and to match exactly heparin doses in all paired test and control studies.

The pH of portal venous blood was not altered by irrigation of the antrum with N/10 hydrochloric acid.

A. Antral Phase, Food Stimulus

Cross-transfusion of blood from animals with acidified antra resulted in the inhibition of Heidenhain pouch acid secretion of the recipient dog following the stimulus of a test meal. The degree of inhibition was similar in cross-transfusion studies involving donor dogs with innervated or with denervated antrum (Fig. 2, 3). The average percentage inhibition secured in ten paired test-control studies on five pairs of dogs in which the antrum of Dog A was innervated was 64 per cent. This difference had a P value of less than 0.01. In six studies on three separate pairs of dogs in

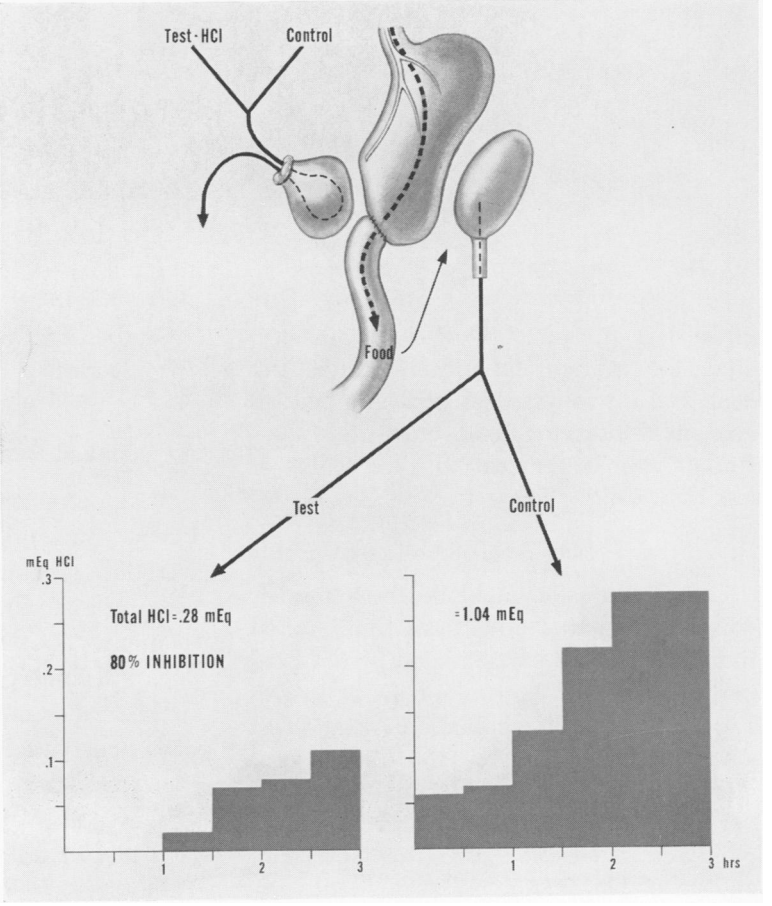

FIG. 6. Intestinal phase—food stimulus. Heidenhain pouch acid output in milliequivalents. Average of 9 control–9 test studies on 4 dogs using 400 Gm. Pard as intestinal phase stimulus. All animals had denervated antra.

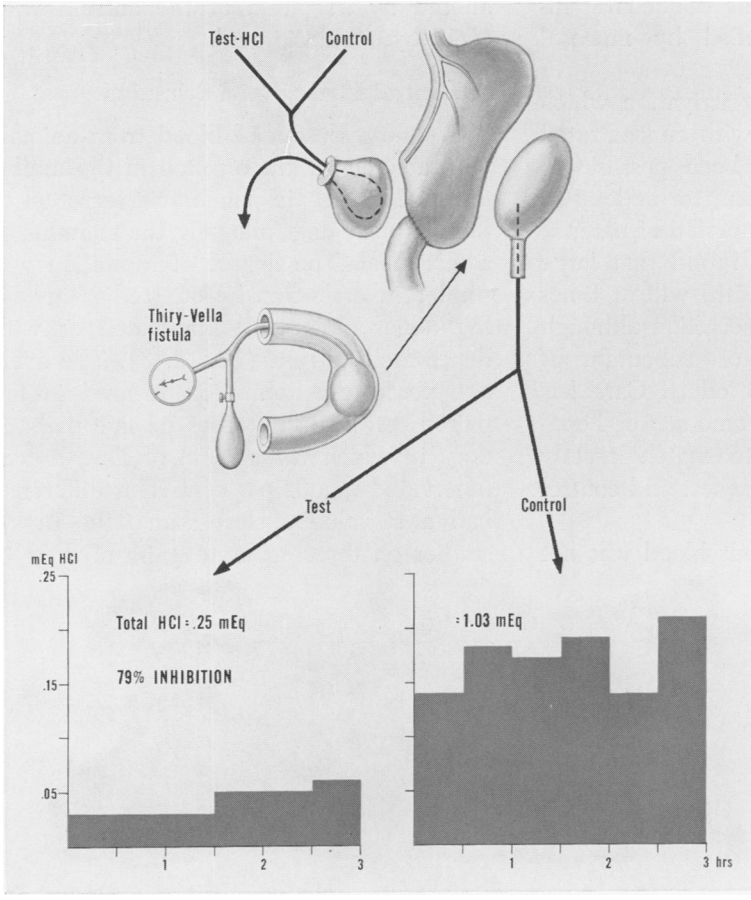

FIG. 7. Intestinal phase—distention stimulus. Heidenhain pouch acid output in milliequivalents. Average of 17 control–17 test studies on 4 Heidenhain pouch, Thiry-Vella fistula dogs, 2 with innervated antra and 2 with denervated antra. Distention of Thiry-Vella jejunal loop used as stimulus to gastric secretion.

which the antrum of Dog A was denervated, the average inhibition was 86 per cent, and P was less than 0.02. The over-all acid inhibition for food cross-transfusion studies was 74 per cent with a P value of less than 0.001 (Table 1).

B. Antral Phase, Acetylcholine Stimulus

Cross-transfusion of blood from animals with acidified antra (A) similarly inhibited the gastric secretion stimulated by the local perfusion of the antrum of Dog B with 1.0 per cent acetylcholine (Fig. 4). Test studies showed from 60 to 100 per cent less acid, for an average inhibition of 83 per cent in six studies in three separate pairs of dogs (Table 2; note the *denervated* antrum of Dog 11A).

Studies of the Inhibition of Gastric Secretory Stimuli Other Than Gastrin

A. Cephalic Phase, Insulin Stimulus

Acid perfusion of the isolated antra of Pavlov pouch dogs uniformly inhibited acid secretion stimulated by insulin hypoglycemia (Fig. 5). The average inhibition seen in seven studies on three Pavlov pouch dogs with innervated antra was 89 per cent. In 12 studies on three Pavlov pouch dogs with denervated antra the average inhibition was 83 per cent. The over-all inhibition of the cephalic phase stimulus was 86 per cent in 19 studies on six dogs ($P < 0.001$; Table 3).

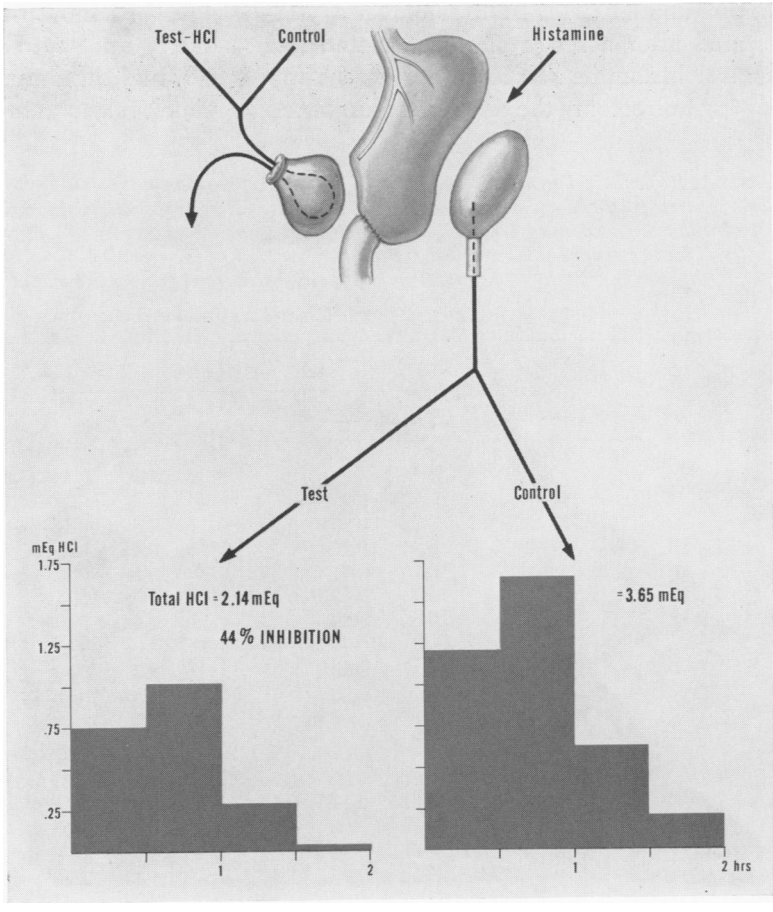

FIG. 8. Histamine stimulus. Heidenhain pouch acid output in milliequivalents. Average of 44 control–44 test studies on 12 dogs using 1 mg. histamine base as stimulus. Six dogs prepared with innervated antra, 6 with denervated antra (as shown above).

B. Intestinal Phase, Food Stimulus

Antral acidification uniformly diminished Heidenhain pouch acid secretion in response to food in animals with denervated antral pouches (intestinal phase secretion) (Fig. 6). The average inhibition was 80 per cent in nine studies on four dogs ($P < 0.02$; Table 4).

C. Intestinal Phase, Distention Stimulus

Antral acidification inhibited gastric secretion stimulated by distension of a Thiry-Vella loop of jejunum (Fig. 7). Twelve studies on two animals with innervated antra demonstrated an average inhibition of 69 per cent, and five studies on two animals with denervated antra showed an average inhibition of 90 per cent. The over-all inhibition was 79 per cent in 17 studies on four animals (Table 5).

D. Histamine Stimulus

Antral acidification following subcutaneous administration of 1.0 mg. of histamine resulted in an inhibition of gastric secretion (Fig. 8). The average suppression of acid secretion demonstrated in 27 studies on six Heidenhain pouch dogs with innervated antra was 46 per cent ($P < 0.01$). The average inhibition in 17 studies on six dogs with denervated antra was 41 per cent ($P < 0.05$). The over-all inhibition of histamine-stimulated gastric secretion noted on antral acidification in 44 studies on 12 dogs was 44 per cent ($P < 0.01$; Table 6).

In one animal (T-47) antrectomy was performed after a series of five test and five control histamine studies. Four weeks following antrectomy the dog was again tested with histamine in five secretory tests. The average pre-antrectomy control response to 1.0 mg. histamine base was 4.70 mEq. which fell to an average level of 2.98 mEq.

TABLE 1. *Heidenhain Pouch Acid Output in Milliequivalents. Summary of 16 control-16 test cross-transfusion studies on 8 separate pairs of dogs, using 400 g. Pard as stimulus. Results of studies using donor animals with innervated antra and with denervated antra presented as subtotal figure with over-all average of both groups combined.* P *value given for difference of innervated and denervated groups as well as for over-all difference. If more than one study performed on each pair, figure represents average output.*

Antral Phase—Cross-Transfusion—Food Stimulus

Dog Pair	Studies per Pair	Periods (30-min.) 1	2	3	4	5	6	3-hr. Total	% Inhibition	*P* Value
Control										
Innervated										
1A-1B	3	0.18	0.19	0.26	0.42	0.49	0.53	2.07		
2A-2B	2	0.11	0.21	0.30	0.34	0.41	0.28	1.65		
3A-3B	1	0.20	0.11	0.09	0.21	0.28	0.41	1.30		
4A-4B	1	0.36	0.47	0.52	0.86	1.01	0.66	3.88		
5A-5B	3	0.60	1.52	1.88	1.45	1.14	0.91	7.50		
Subtotal		1.45	2.48	3.05	3.30	3.34	2.79	16.41		
Average		0.29	0.50	0.61	0.66	0.67	0.56	3.28		
Denervated										
6A-6B	3	0.24	0.28	0.34	0.17	0.20	0.18	1.41		
7A-7B	2	0.08	0.17	0.68	0.25	0.46	0.77	2.41		
8A-8B	1	0	0	0.23	0.12	0.45	0.63	1.43		
Subtotal		0.32	0.45	1.25	0.54	1.11	1.58	5.25		
Average		0.11	0.15	0.42	0.18	0.37	0.53	1.76		
Total		1.77	2.93	4.30	3.84	4.45	4.37	21.67		
Average		0.22	0.37	0.54	0.48	0.56	0.55	2.72		
Test										
Innervated										
1A-1B	3	0	0.05	0.04	0.03	0.03	0.04	0.19	91	
2A-2B	2	0	0	0	0	0.24	0.18	0.42	74	
3A-3B	1	0.15	0	0	0.08	0	0.17	0.40	69	
4A-4B	1	0.12	0	0.19	0.28	0.42	0.48	1.49	62	
5A-5B	3	0.06	0.51	0.99	1.22	1.29	1.14	5.21	30	
Subtotal		0.32	0.56	1.23	1.61	1.99	2.01	7.72		
Average		0.06	0.11	0.25	0.32	0.40	0.40	1.54	64	<0.01
Denervated										
6A-6B	3	0.06	0.04	0.03	0	0.06	0.04	0.23	84	
7A-7B	2	0	0	0.04	0.07	0.16	0.35	0.62	74	
8A-8B	1	0	0.02	0	0	0	0	0.02	99	
Subtotal		0.06	0.06	0.07	0.07	0.22	0.39	0.87		
Average		0.02	0.02	0.02	0.02	0.07	0.13	0.28	86	<0.02
Total		0.38	0.62	1.30	1.68	2.21	2.40	8.59		
Average		0.05	0.08	0.16	0.21	0.28	0.30	1.08	74	<0.001

following antral acidification. The average output following antrectomy was 4.29 mEq.

Discussion

Demonstration of the release of an inhibitory hormone from the acidified antrum requires experimental differentiation from simple suppression of gastrin formation.

In the cross-transfusion experiments on alert healthy dogs presented here, blood draining the acidified antrum of one dog inhibited acid production in the recipient animal. The intact antral-gastrin mechanism of the recipient dog was stimulated by food or local acetylcholine, both potent activators of the antral phase. As the gastric secretory mechanism of the recipient dog was not altered in any manner, and since the only difference in the test and control studies was the presence or absence of acid in the antrum of the donor animal, these studies indicate the presence of a humoral inhibitor of gastric secretion liberated by the acidified antrum.

DuVal and Price reported continuous [11] and discontinuous [12] cross-circulation studies which noted similar humoral inhibition of gastric secretion in acutely parabiotic anesthetized dogs. In a preliminary report, Danhof [6] indicated that lyophilized material prepared from blood draining the *acidified* antrum, when given intravenously to another dog, would inhibit histamine-stimulated gastric secretion.

Results of previous studies on the antral inhibition of stimuli other than gastrin have not been so uniform.[34] Dragstedt and co-workers [9] and Woodward and colleagues [41] were unable to inhibit insulin-stimulated gastric secretion by antral acidification. There are several reports of profound inhibition of the cephalic phase following the acidification of the isolated innervated antrum [1, 16, 35, 36] which is also

TABLE 2. *Heidenhain Pouch Acid Output in Milliequivalents. Summary of 6 control-6 test cross-transfusion studies on 3 pairs of dogs, using local acetylcholine as stimulus. Two donor dogs had innervated antra and one had a denervated antrum. If more than one study performed on each pair, figures represent average output.*

Antral Phase—Cross-Transfusion—Acetylcholine

Dog	No. Studies	Periods (30-min.) 1	2	3	4	5	6	3-hr. Total	% Inhibition
Control									
Innervated									
9A- 9B	1	0.35	0.90	1.01	0.82	0.67	0.54	4.29	
10A-10B	1	0.18	0.20	0.30	0.20	0.30	0.35	1.53	
Denervated									
11A-11B	4	1.46	1.77	0.91	0.79	0.93	1.30	7.16	
Total		1.99	2.87	2.22	1.81	1.90	2.19	12.98	
Average		0.67	0.95	0.74	0.60	0.63	0.73	4.33	
Test									
Innervated									
9A- 9B	1	0.12	0.09	0	0.04	0.09	0.10	0.44	90
10A-10B	1	0	0	0	0	0	0	0	100
Denervated									
11A-11B	4	0.42	0.54	0.33	0.59	0.42	0.58	2.85	60
Total		0.54	0.63	0.33	0.63	0.51	0.68	3.29	
Average		0.18	0.21	0.11	0.21	0.17	0.23	1.10	83

reported in the present study. As vagal stimulation is known to release gastrin from the innervated antrum, however, it has been suggested [16] that the action of antral acidification is simply to block the release of gastrin following vagal stimulation. It is important, therefore, to note that in the present study as well as in the work of Shimizu, Morrison, and Harrison [29] and of State and Morgenstern,[33] clear evidence is presented that acidification of the *denervated* antrum will inhibit profoundly insulin-stimulated secretion of the innervated fundic pouch. Since vagal stimulation does

TABLE 3. *Pavlov Pouch Acid Output in Milliequivalents. Summary of 19 control-19 test studies on 6 dogs, using insulin hypoglycemia as stimulus. Results of studies using animals with innervated antra and with denervated antra presented as subtotal figure with over-all average of both groups combined. P value given for over-all difference. If more than one study performed on each animal, figure represents average output.*

Cephalic Phase—Insulin Hypoglycemia

Dog	No. Studies	Periods (30-min.) 1	2	3	4	5	6	3-hr. Total	% Inhibition	*P* Value
Control										
Innervated										
T-17	4	0	0.59	0.68	0.68	0.71	0.66	3.32		
T-50	2	0.17	0.32	0.45	0.47	0.60	0.49	2.50		
T-93	1	0.38	0.66	0.30	0.18	0.25	0.32	2.09		
Subtotal		0.55	1.57	1.43	1.33	1.56	1.47	7.91		
Average		0.18	0.52	0.48	0.44	0.52	0.49	2.63		
Denervated										
T-110	6	0.07	0.09	0.16	0.11	0.15	0.20	0.78		
T-129	3	0.03	0.59	0.82	0.84	0.73	1.06	4.07		
T-145	3	0.01	0.06	0.57	0.66	1.12	0.84	3.26		
Subtotal		0.11	0.74	1.55	1.61	2.00	2.10	8.11		
Average		0.04	0.25	0.52	0.54	0.67	0.70	2.70		
Total		0.66	2.31	2.98	2.94	3.56	3.57	16.02		
Average		0.11	0.38	0.50	0.49	0.59	0.60	2.67		
Test										
Innervated										
T-17	4	0	0.15	0.18	0.18	0.09	0.05	0.65	81	
T-50	2	0	0	0	0	0.02	0	0.02	99	
T-93	1	0	0	0.17	0.02	0.02	0.06	0.27	87	
Subtotal		0	0.15	0.35	0.20	0.13	0.11	0.94		
Average		0	0.05	0.12	0.07	0.04	0.04	0.32	89	
Denervated										
T-110	6	0	0	0	0	0	0	0	100	
T-129	3	0	0.30	0.22	0.31	0.29	0.15	1.27	69	
T-145	3	0	0	0.02	0.36	0.14	0.11	0.64	80	
Subtotal		0	0.30	0.24	0.67	0.43	0.26	1.91		
Average		0	0.10	0.08	0.22	0.14	0.09	0.64	83	
Total		0	0.45	0.59	0.87	0.56	0.37	2.85		
Average		0	0.08	0.10	0.15	0.09	0.06	0.48	86	<0.001

TABLE 4. *Heidenhain Pouch Acid Output in Milliequivalents. Summary of 9 control-9 test studies on 4 Heidenhain pouch, denervated antral pouch dogs, using 400 g. Pard as intestinal phase stimulus. P value given for difference. Figure represents average output of multiple studies performed on each animal.*

Intestinal Phase—Food Stimulus

Dog	No. Studies	Period (30-min.) 1	2	3	4	5	6	3-hr. Total	% Inhibition	P Value
Control Denervated										
T-118	2	0.10	0.12	0.13	0.31	0.28	0.22	1.16		
T-144	2	0.04	0.07	0.18	0.35	0.39	0.44	1.47		
T-150	3	0.01	0.11	0.19	0.20	0.39	0.30	1.20		
T-152	2	0.07	0.09	0	0.02	0.06	0.14	0.38		
Total		0.22	0.27	0.50	0.88	1.12	1.10	4.21		
Average		0.06	0.07	0.13	0.22	0.28	0.28	1.04		
Test Denervated										
T-118	2	0	0	0	0	0	0	0	100	
T-144	2	0	0.01	0.06	0.18	0.24	0.27	0.76	48	
T-150	3	0	0	0	0.09	0.09	0.16	0.34	72	
T-152	2	0	0	0	0	0	0	0	100	
Total		0	0.01	0.06	0.27	0.33	0.43	1.10		
Average		0	0	0.02	0.07	0.08	0.11	0.28	80	<0.02

not release gastrin from the denervated antrum, this suppression is further indication of a separate inhibitory substance.

The effect of antral acidification on the intestinal phase was studied by Woodward and co-workers [41, 42] who initially were unable to demonstrate inhibition of the intestinal stimulus, but later, in a single animal with an innervated antrum, did produce significant suppression of gastric secretion stimulated by the intestinal phase. Margolus and Harrison [21] blocked the intestinal phase secretion following food in Heidenhain pouch, *denervated* antral pouch animals by acidifying the antrum. We have confirmed this observation in similar studies (Table 4). As there is no evidence that the stimulus of a meal releases gastrin from a denervated antrum, suppression of gastric secretion noted on antral acidification in these animals gives further indication of an inhibitory antral hormone.

Sircus [30] demonstrated that distention of the isolated Thiry-Vella fistula resulted in gastric secretion from a denervated fundic pouch. The nature of this humoral secretagogue is unknown, but it is certainly not gastrin of antral origin. Inhibition of this stimulus by antral acidification, therefore, is a further indication of a separate inhibitory hormone.

The antrum, left in continuity following partial gastrectomy, has been shown experimentally to protect against histamine-induced ulcer.[5, 18, 31] Despite this clear evidence for the release of an inhibitory hormone by a histamine-stimulated gastric secretion, there is disagreement on the effect of antral acidification on histamine-induced gastric secretion; some studies report inhibition [6, 13, 17, 42] while other investigators have been unable to obtain such evidence.[2, 9, 16, 25, 38, 41] Gillespie [13] reported effects of antral acidification on three pa-

tients in whom the antrum had been surgically excluded and intubated. He noted inhibition of the gastric secretory response to a maximal histamine stimulus when the antral pH was 1.5 or less. Suppression of histamine-stimulated gastric secretion was uniformly demonstrated in the dogs reported in this study. This difference averaged 44 per cent in 44 separate tests on 12 different animals and was statistically significant at the 1.0 per cent level.

There is strong evidence that histamine is the final common pathway for all gastric secretory stimuli.[4] It is an extremely potent secretagogue, and it may be that previous failures to secure inhibition following antral acidification have been due to the overriding or cancelling of physiologic amounts of inhibitory material by pharmacologic doses of histamine. We believe that the failure to standardize histamine stimulus and the current inability to quantitate antral inhibition probably explain the previously noted contradictory results in the study of the effect of antral acidification on histamine-stimulated gastric secretion.

The results noted in the animal subjected to antrectomy following histamine secretory studies also strongly support the concept of an antral inhibitory hormone. Antrectomy reduced histamine-stimulated gastric secretion only 0.9 per cent, but antral acidification lowered it 36 per cent. Antrectomy or isolation of the antrum in dogs has been shown repeatedly to have no effect on gastric secretion stimulated by

TABLE 5. *Heidenhain Pouch Acid Output in Milliequivalents. Summary of 17 control-17 test studies on 4 Heidenhain pouch, Thiry-Vella fistula dogs, 2 with innervated isolated antra and 2 with denervated isolated antra. Distention of Thiry-Vella intestinal loop used as stimulus to gastric secretion. Figure represents average output of multiple studies performed on each animal.*

Intestinal Phase—Distention Stimulus

Dog	No. Studies	Periods (30-min.) 1	2	3	4	5	6	3-hr. Total	% Inhibition
Control									
Innervated									
T-11	6	0.02	0.03	0.01	0.02	0.01	0.02	0.11	
T-52	6	0.23	0.49	0.34	0.36	0.41	0.46	2.29	
Denervated									
T-111	3	0.21	0.15	0.31	0.32	0.16	0.26	1.41	
T-137	2	0.08	0.04	0.02	0.07	0.08	0.09	0.38	
Total		0.54	0.71	0.68	0.77	0.56	0.83	4.19	
Average		0.14	0.18	0.17	0.19	0.14	0.21	1.03	
Test									
Innervated									
T-11	6	0	0	0.01	0.01	0.01	0.01	0.04	64
T-52	6	0.06	0.10	0.11	0.14	0.10	0.10	0.61	73
Denervated									
T-111	6	0.04	0.03	0	0.03	0.08	0.12	0.30	79
T-137	2	0	0	0	0	0	0	0	100
Total		0.10	0.13	0.12	0.18	0.19	0.23	0.95	
Average		0.03	0.03	0.03	0.05	0.05	0.06	0.25	79

TABLE 6. *Heidenhain Pouch Acid Output in Milliequivalents. Summary of 44 control-44 test studies on 12 dogs, using 1 mg. histamine base as stimulus. Results of studies using animals with innervated antra and with denervated antra presented as subtotal figure with over-all average of both groups combined. P value given for innervated and denervated groups as well as for overall difference. Figure represents average output of multiple studies performed on each animal.*

		Histamine						
		Periods (30-min.)						
Dog	No. Studies	1	2	3	4	2-hr. Total	% Inhibition	*P* Value
Control								
Innervated								
T-16	6	0.12	0.39	0.13	0	0.64		
T-63	5	0.35	0.98	0.76	0.27	2.36		
T-84	5	0.31	0.82	0.85	0.37	2.35		
T-85	5	0.17	0.76	0.76	0.32	2.01		
T-93	3	0.85	2.00	0.95	0.17	3.97		
T-97	3	2.89	1.62	0.37	0.50	5.38		
Subtotal		4.69	6.57	3.82	1.63	16.71		
Average		0.78	1.10	0.64	0.27	2.79		
Denervated								
T-47	5	1.58	2.72	0.40	0	4.70		
T-98	3	0.26	1.27	1.29	0.29	3.11		
T-112	2	3.63	1.64	0	0	5.27		
T-115	2	2.93	5.04	1.86	0.42	10.25		
T-137	3	0.63	0.56	0	0	1.19		
T-143	2	0.80	1.61	0.18	0	2.59		
Subtotal		9.83	12.84	3.73	0.71	27.11		
Average		1.64	2.14	0.62	0.12	4.52		
Total		14.52	19.41	7.55	2.34	43.82		
Average		1.21	1.62	0.63	0.19	3.65		
Test								
Innervated								
T-16	6	0.01	0.12	0.04	0	0.17	73	
T-63	5	0.17	0.58	0.29	0	1.04	56	
T-84	5	0.18	0.69	0.64	0.28	1.79	24	
T-85	5	0.01	0.41	0.31	0.10	0.83	59	
T-93	3	0.79	1.19	0.32	0	2.30	42	
T-97	3	2.38	1.75	0.13	0	4.26	21	
Subtotal		3.54	4.74	1.73	0.38	10.39		
Average		0.59	0.79	0.29	0.06	1.73	46	<0.01
Denervated								
T-47	5	1.42	1.19	0.23	0.14	2.98	37	
T-98	3	0.16	0.84	0.68	0.07	1.75	44	
T-112	2	1.68	1.64	0	0	3.32	37	
T-115	2	0.82	3.11	0.93	0	4.86	53	
T-137	3	0.37	0.38	0.05	0	0.80	33	
T-143	2	0.95	0.50	0	0	1.45	44	
Subtotal		5.40	7.66	1.89	0.21	15.16		
Average		0.90	1.28	0.32	0.04	2.54	41	<0.05
Total		8.94	12.40	3.62	0.59	25.55		
Average		0.76	1.03	0.30	0.05	2.14	44	<0.01

histamine.[3, 16, 19, 39] Therefore, the inhibition demonstrated in these 44 tests on 12 dogs would seem to be due to some action other than gastrin suppression.

The suggestion has been made that the reactivity or secretory tone of the parietal cell is maintained by sub-threshold stimuli (cephalic, antral, intestinal) and that antral acidification, by removing gastrin from circulation, acts to depress this reactivity, leading to a smaller secretory response to *any* gastric secretory stimulus. Once invoked, this syllogism is difficult to prove or disprove, since the study of any single phase of gastric secretion requires that other stimuli be altered or abolished. The results of the cross-transfusion studies provide the only evidence for an antral inhibitory hormone which is not at least partially vitiated by the foregoing concept. Since the gastrin mechanism of the recipient dog is intact, the secretory tone of the parietal cell mass is not impaired. Inhibition of gastric secretion is due to infusion of blood draining the acidified antrum of the donor dog.

Since our cross-transfusion studies demonstrate that this material can be transferred from one animal to another in blood, it is clearly humoral in nature. As it is not absorbed from food but is apparently elaborated by the antrum, it fits the definition of an *autocoid* as suggested by Sharpey-Schafer.[27] *Hormones* are autocoids which act to stimulate activity. This material is properly a *chalone,* or inhibitory autocoid.

The antral chalone has been demonstrated in these studies to be capable of inhibiting the cephalic, antral, and intestinal phases of gastric secretion stimulated by histamine itself. Although the site of action of the chalone is unknown, such a wide physiologic range would point to a locus at or near the parietal cell.

Summary

Demonstration of the release of an inhibitory hormone from the acidified antrum requires experimental differentiation from simple suppression of gastrin formation. This has been accomplished in two separate experimental approaches.

In cross-transfusion studies, gastric secretion stimulated by the intact antral-gastrin mechanism of one animal has been inhibited by the infusion of blood draining the acidified antrum of another animal.

In studies dealing with secretory stimuli other than gastrin, antral acidification has been shown to inhibit gastric secretion stimulated by the cephalic and intestinal phases and by histamine itself.

Evidence for a separate inhibitory hormone was elicited in studies on animals with both innervated and *denervated* antra, illustrating that such inhibition is not secured by suppression of vagally-released gastrin.

This demonstration of a humoral inhibitory material (liberated from the acidified gastric antrum) that is capable of suppressing gastric secretion stimulated by the cephalic, antral, and intestinal phases, and by *histamine,* supports the existence of a separate antral chalone. The wide physiologic scope of this chalone suggests a site of action at or near the parietal cell.

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Discussion

Dr. Lester Dragstedt (Gainesville): I had the privilege of visiting Dr. Thompson's laboratory and was greatly impressed with the skill and care with which this difficult experiment was carried out.

I am also impressed by the experiments of Dr. DuVal and those of Dr. Harrison, and as a result I am persuaded that there is an inhibitory agent liberated from the antrum of the stomach when acid of sufficient concentration is applied long enough to the antral mucosa.

How can we harmonize these data with the data from our own laboratory which led us to draw a conclusion almost opposite to the one here presented? (slide) Here is an experiment Dr. Edward R. Woodard and I reported some years ago, which was performed on an animal with a vagus denervated Heidenhain pouch and a vagus denervated antrum pouch. We found that when we put neutral food in the antrum we got an abundant secretion of gastric juice from the Heidenhain pouch, but when we acidified that food we got no stimulation of secretion.

It occurred to us that the interpretation of the experiment might be either that acid prevented the release of gastrin just as cocaine does when cocaine is applied to the antrum mucosa, or that an inhibitory hormone might be released from the antrum.

It seemed to us that if an inhibitory hormone was released, we ought to get an immediate stimulation, followed at some later period by inhibitions. The fact that we got inhibition immediately made us prefer the interpretation that acid had prevented the release of the hormone gastrin.

(slide) In a similar experiment we found that distention of the antrum with neutral salt solution would produce a stimulation of secretion from the Heidenhain pouch, but distention of the antrum with acid solutions caused no stimulation at all.

In a later experiment with two antrum pouches and a Heidenhain pouch the data decidedly favor the interpretation that acid in contact with the antrum prevents the release of the hormone gastrin. We prepared two pouches of the antrum, A and B. We could stimulate the secretion of gastric juice by putting food in either pouch A or B. While we had a secretion stimulated continuously by putting food in pouch A, we introduced acid in pouch B. But as you see, we got no inhibition of gastric secretion.

It seemed to us that if an inhibitory hormone of significance were liberated from pouch B, it should have inhibited the secretion induced by putting the food in pouch A. We then reversed the experiment putting food in pouch B, and acid in pouch A and again failed to demonstrate inhibition.

Prof. Schofield of Newcastle, England, has repeated this experiment and confirmed it in every respect, and in addition has done one rather important experiment that I regret we neglected to do. He pointed out that if he put food in pouch A and got a sustained plateau of secretion, and then put acid in pouch B, he got no inhibition of secretion; but if then he put the acid in pouch A containing the food there was prompt and immediate inhibition.

I cannot get away from the interpretation that under the conditions of this experiment, acid has inhibited the release of gastrin from pouch A that had been stimulated previously by the contact with food.

A possible harmony in these conflicting experiments is suggested by the work of Dr. Paul Jordan. He has pointed out that in a similar type of experiment a sustained plateau of secretion