The Mechanism of Antral Regulation of Gastric Secretion *

Continuous Cross-Circulation

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THE UNPLEASANT side effects that may accompany gastric resection justify a continued search for a more physiologic operative approach to peptic ulcer. This requires a broader knowledge of the physiology of gastric secretion with emphasis on the manner in which secretion is regulated.

Dragstedt,[4] Wilhelmj,[9] Woodward [10] and others, have shown that the presence of acid in the antrum of the stomach regulates gastric secretion by paralyzing the further release of the antral stimulatory hormone: gastrin. However, others have suggested that a falling antral pH results in the elaboration of an inhibitor to further gastric secretion.[1-3, 6] The recent report that gastric juice contains a substance which, when given intravenously to dogs, inhibits the secretion of acid, indeed, results in atrophy of the gastric mucosa if the injections are prolonged, lends some support to the theory of active inhibition.[5]

All previous investigational efforts to distinguish between paralysis of stimulation and active inhibition have depended upon the interpretation of secretory responses of variously constructed pouches in dogs. This report describes an attempt to detect the hormonal aspects of gastric secretion in anesthetized cross-circulating dogs. The study had four objectives:

1. The production of a predictable stimulus to gastric secretion.
2. Inhibition of the secretion.
3. Detection of the hormonal nature of the stimulation, if any.
4. Detection of the hormonal nature of the inhibition, if any.

Twenty-seven dogs were used in single experiments, and 70 dogs were used in cross-circulation experiments.

Materials and Methods

Adult mongrel dogs, varying in weight from 12 to 20 kg., were used. When cross-circulation was planned, the animals were paired by weight within 1.5 kg. Each dog was starved for 24 hours, and prepared with morphine sulphate 10 mg./kg. intramuscularly, 30 minutes before operation. Anesthesia was achieved by a single intravenous injection of chloralose (50 mg./kg.) and urethane (500 mg./kg.). The abdomen was opened with a long midline incision. A flanged, plastic cannula was inserted through the posterior wall of the fundus of the stomach immediately above the highest short gastric arteries. The cannula was delivered through the eleventh intercostal space in the mid-lateral line of the flank and secured with an appropriate collar. Gastric outlet obstruction was produced by ligating the duodenum immediately distal to the pylorus. In animals which were to be stimulated, a straight, No. 18 French catheter carrying an inflatable balloon was passed through the pylorus prior to the ligation. The distal end of this catheter was delivered through a duodenostomy and to the outside through the abdominal wall. In the cross-circulation experiments, the abdominal aorta was mobilized, cross-clamped proximally and distally, (simultaneously in both dogs), and divided. Each proximal aortic stump was cannulated with an 18-inch length of one-quarter inch, nonwettable, plastic tubing. The tubing was filled with saline containing 0.5 cc. heparin and its distal end inserted into the distal aortic

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stump of the opposite dog. The cross-clamps were then removed simultaneously from both aortas (Fig. 1).

Following closure of the abdominal wall, the dog was turned on its left side. Gastric juice was collected from the fundus cannula at 15-minute intervals for the duration of each experiment. One cubic centimeter of each specimen was titrated with 0.1 sodium hydroxide using Toepfer's reagent as indicator. The number of cubic centimeters used was converted to milliequivalents per milliliter by dividing by ten, and expressed as total milliequivalents by multiplying by the 15-minute volume.

Stimulation of secretion was achieved by gently inflating the antral balloon using approximately 15 to 25 cc. of air. Inhibition of secretion was achieved by turning the dog onto its right side and introducing either 100 cc. of gastric juice, or saline adjusted to *p*H 1.0 with 0.1 N hydrochloric acid.

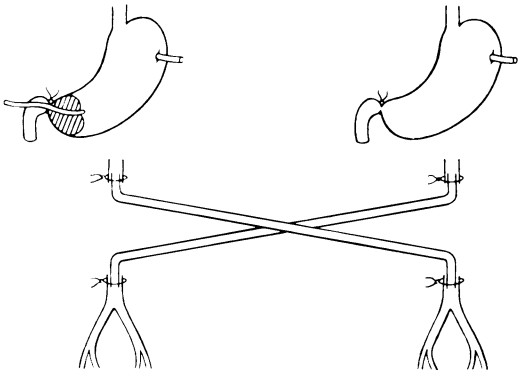

FIG. 1. Schematic view of the inter-connected aortas for cross-circulation between dogs. Note balloon in one gastric antrum.

Results

1. **The Production of a Predictable Stimulus to Gastric Secretion.** This was accomplished in three ways using 20 dogs. First, the basal secretion of a dog previously subjected to antrectomy was observed. The afferent and efferent limbs of the gastroenterostomy were ligated during the collection period. Second, the unstimulated secretion of intact dogs (with nothing in the antrum) was recorded. Third, the secretory response of the intact dog with an inflated balloon in the antrum was noted. Characteristic responses are reproduced in Figure 2.

2. **Inhibition of the Stimulus to Secretion.** Four dogs were prepared as described and stimulation of gastric secretion achieved with a balloon in the antrum of the stomach. After secretion was well established, and had continued without interruption for three hours, the dog was turned onto its right side and 100 cc. of gastric juice, or saline adjusted to *p*H 1.0, was introduced into the antrum (the balloon remaining inflated). Since the animal was on its right side, collections from the fundic cannula were not possible during this period. At the end of three additional hours, the experiment was concluded by turning the dog

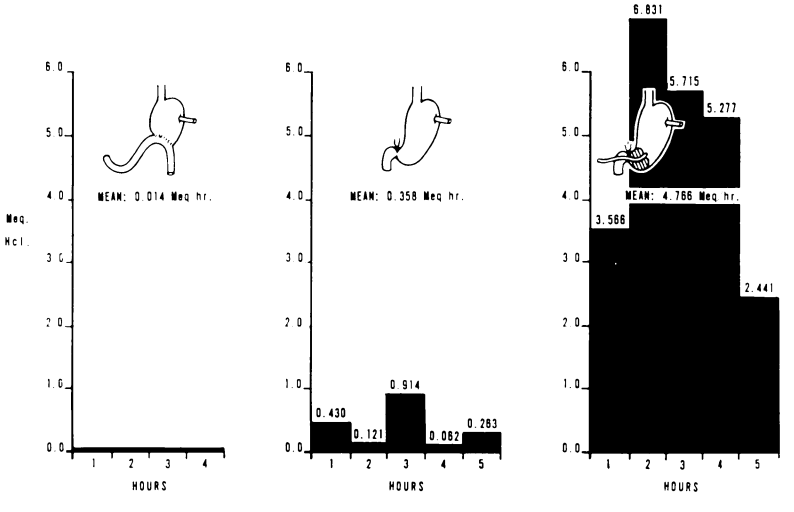

FIG. 2. Stimulation of gastric secretion with an antral balloon.

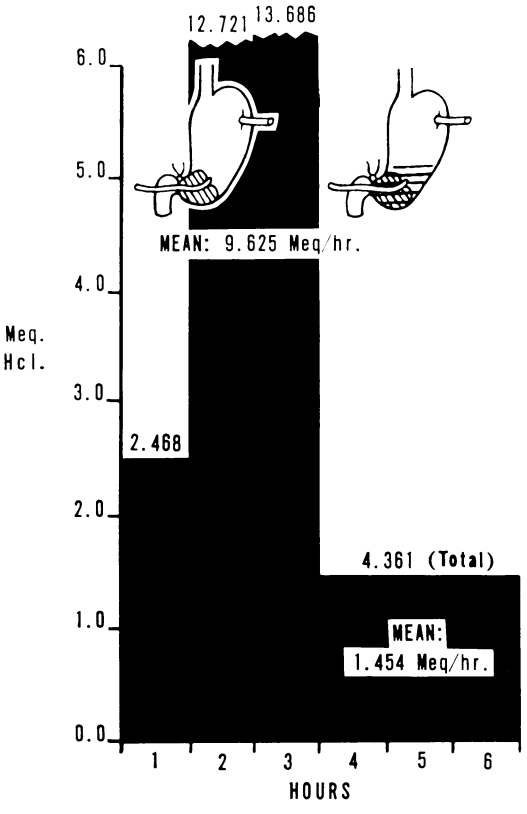

FIG. 3. The effect of acid in the balloon-stimulated antrum.

back to its left side, draining the stomach through the fundus cannula, and measuring the concentration of hydrochloric acid and the volume accumulated over the three hours. An example of this experiment is reproduced in Figure 3. Note that the mean volume during stimulation was 9.625 Meq./hr. prior to introduction of acid into the antrum. For the next three hours, in response to introduction of acid into the antrum, the mean secretion fell to 1.454 Meq./hr.

3. **The Hormonal Nature of the Stimulation.** This phase of the study was conducted in two ways. First, single dogs with previously constructed Heidenhain pouches were prepared in the usual manner. Gastric secretion was stimulated by inflating the antral balloon and the secretory response of both the fundus and the Heidenhain pouch recorded simultaneously at 15-minute intervals for six hours. The characteristic response of both is reproduced in Figure 4. The mean secretory response of the fundus was 2.641 Meq./hr. while that of the pouch was 0.595 Meq./hr.

Next, continuous cross-circulation was established between dogs, paired by weight, with a catheter-balloon in the antrum of one animal only. The secretory response of both animals was then observed at 15-minute intervals for six consecutive hours. Forty dogs were used. Figure 5 is an example of the response observed. The mean secretory response of the stimulated animal was 6.781 Meq./hr., while the mean secretory response of the unstimulated para-biotic mate was 2.327 Meq./hr.

4. **The Hormonal Nature of the Inhibition.** Two technics were used for this study. First, continuous cross-circulation was established between paired animals, the antrum of one containing a catheter-balloon. Following inflation of the balloon, the secretory response of that dog was followed consecutively for six hours. Meanwhile, the secretory response of the para-biotic dog was observed for the first three hours, at which time the latter animal was turned on its right side and its antrum filled with 100 cc. of gastric juice. This precluded observation of its secretory response for the last three hours. This experiment was attempted seven times, but four were not

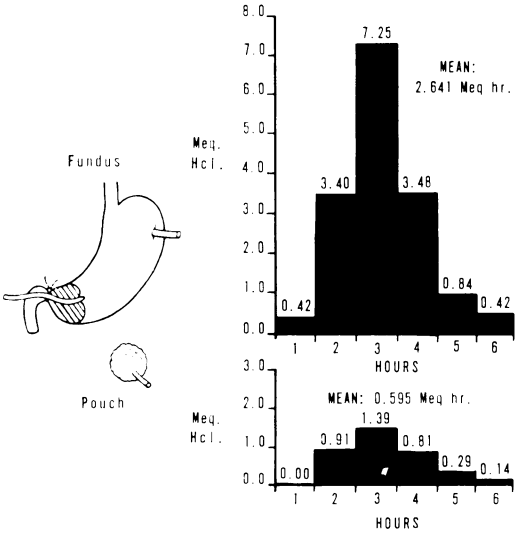

FIG. 4. The transfer of antral stimulation to a Heidenhain pouch.

completed due to the appearance of urticaria (once) and clotted cannulae (three times). Figure 6 is representative of this type of experiment. The mean secretory response of the stimulated dog over three hours was 4.595 Meq./hr. Following introduction of acid into the antrum of its para-biotic mate, the mean secretory response fell to 2.459 Meq./hr. for three hours.

Since deterioration of the animals could explain the decrease in secretion, the following experiments were done. Continuous cross-circulation was established between paired dogs as described. A catheter-balloon was placed in the antrum of only one dog. Following inflation of the balloon, the secretory response of this dog was observed at two hour intervals for six consecutive hours. Meanwhile, the secretory response of the para-biotic mate was observed for the first and last two hour segments of the experiment; however, during the middle two hours this dog was turned onto its right side and 100 cc. of gastric juice introduced into its antrum. This experiment was done eight times, four of which were never completed due to blood

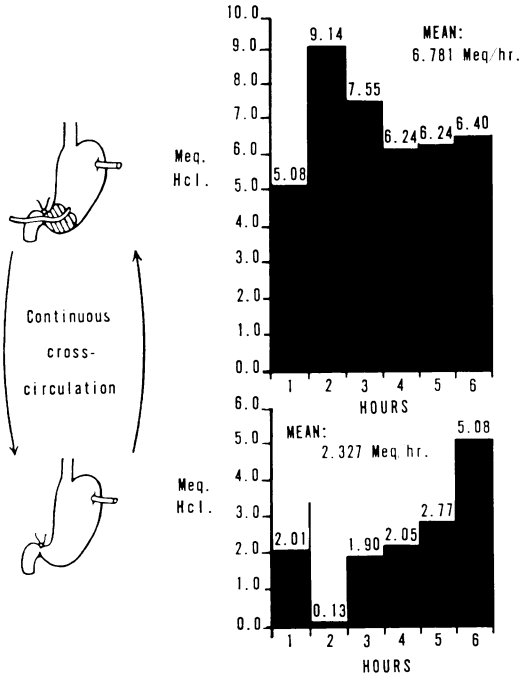

Fig. 5. The transfer of antral stimulation, between animals, by cross-circulation.

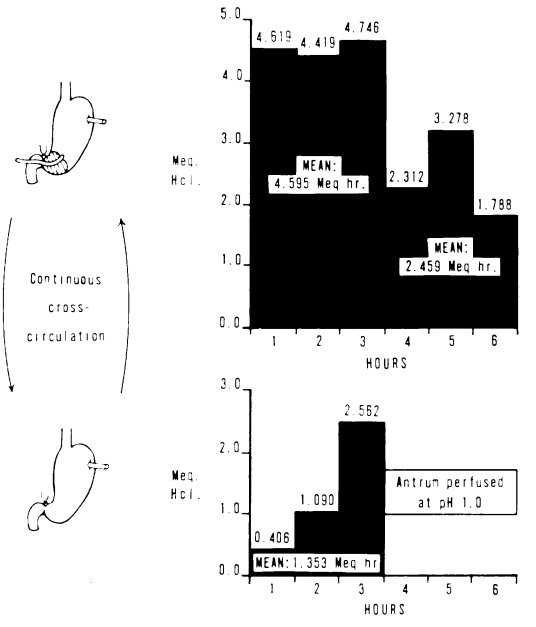

Fig. 6. The transfer of antral inhibition, between animals, by cross-circulation.

clotting and shock. A characteristic response for this experiment is reproduced in Figure 7. The effect of introducing acid into the antrum of the unstimulated dog during the middle one-third of the cross-circulation was to reduce the mean secretory response of the stimulated dog from 4.685 to 0.568 Meq./hr. That deterioration of the animals was insufficient as an explanation for this observation is apparent by the return of secretion to 6.386 Meq./hr. for the last two hours of the experiment.

Discussion

Method. Some of the technical features of the experimental method require comment. Since previous studies have been accomplished in pouch dogs, awake and normally responsive, the interpretation of comparable studies under anesthesia is hazardous. However, Uvnas [8] has reported successful observations of gastric function under the hypnotic agents: chloralose and urethane, following preoperative administration of morphine.

To lower the *p*H of the gastric antrum, isotonic saline adjusted below *p*H 1.5 with 0.1 N hydrochloric acid, is adequate. Fresh dog gastric juice proved equally effective,

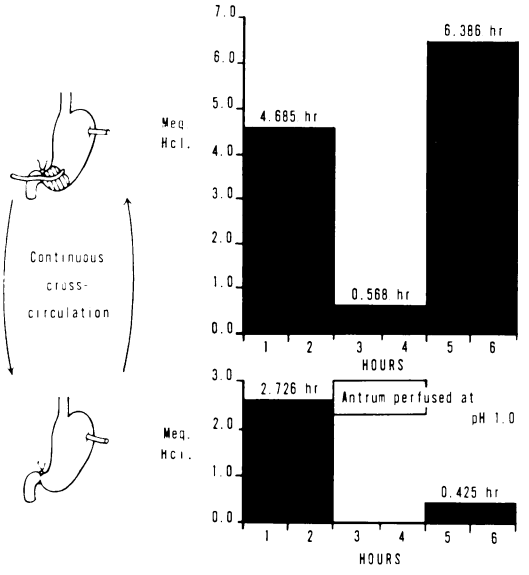

FIG. 7. The transfer of antral inhibition, between animals, by cross-circulation.

provided its *p*H was lower than 1.5 before use.

The mechanical and physiological factors involved in cross-circulation were many. Since the animals were not heparinized, many cross-circulations were abandoned due to clotting of the cannulae during the six to eight hour experiments. Blood subgroups were responsible for transfusion reactions, manifested under anesthesia by urticaria, tachycardia, gastric hypersecretion, and deterioration of the animals, in 15 to 20 per cent of the experiments.

These factors, plus the occasional appearance of shock, bleeding from one animal into the other, plugging of the fundus cannulae with food particles, leaves, etc., were a frequent threat to successful completion of each experiment.

Results. Gentle distention of the antrum is known to be an effective stimulus to gastric secretion in unanesthetized dogs. In these studies, the same stimulus proved successful under anesthesia. Since: 1) There was no secretion from a dog in which the antrum had previously been removed; 2) The stimulus was mechanical to the antrum; 3) The stimulus produced secretion from a Heidenhain pouch; and 4) The stimulus was transferable through the vascular system (at least in part) to the fundus of an unstimulated dog, it had many of the known characteristics of gastrin. Its elaboration with regard to the integrity of the vagus nerve has not yet been defined in this preparation.[7]

The inhibition achieved by cross-circulation under anesthesia also requires cautious interpretation. For example, the secretory response during the first and last two hours of the experiment depicted in Figure 7 might represent the combined stimulation of two animals, while the "inhibited" middle two hours represents the net stimulation remaining after paralysis of the parabiotic antrum with acid. Subsequent experience with discontinuous cross-circulation appears to eliminate this objection. Also, the shifts of blood volume from one animal to the other, made possible by prolonged cross-circulation, has an immediate and pronounced effect on the gastric secretory response. Indeed, it appears that hypersecretion is one of the responses to hypervolemia in the absence of direct antral stimulation. On the other hand, hypovolemia interrupts gastric secretion even in the presence of antral stimulation. This factor also has been carefully controlled in our recent experiments.

Summary

Distention of the antrum of the stomach of a dog, under morphine, chloralose and urethane anesthesia, results in stimulation of gastric secretion.

The antral stimulus is also manifest, in part, in a Heidenhain pouch, and is apparently transferable, by cross-circulation, to the intact fundus of a second dog.

The secretory response to antral stimulation, under the anesthesia used, ceases after introduction of acid into the stimulated antrum.

The secretory response of a stimulated dog can be inhibited by introducing acid into the antrum of a non-stimulated dog

with which it is cross-circulating, under the conditions of these experiments.

Some of the technical and physiological factors involved in experiments involving continuous cross-circulation have been discussed.

Bibliography

1. DuVal, M. K., W. E. Price and R. M. Fagella: The Mechanism of Antral Regulation of Gastric Secretion. I. Antral Pouch Studies. In preparation.
2. Harrison, R. C., W. H. Lakey and H. A. Hyde: The Production of an Acid Inhibitor by the Gastric Antrum. Ann. Surg., **144**:441, 1956.
3. Jordan, P. H. and B. F. Sands: Antral Inhibition of Gastric Secretion. Proc. Soc. Exper. Biol. and Med., **94**:471, 1957.
4. Longhi, E. H., H. B. Greenlee, J. L. Bravo, J. D. Guerrero and L. R. Dragstedt: Question of an Inhibitory Hormone from the Gastric Antrum. Am. J. Physiol., **191**:64, 1957.
5. Smith, W. O., M. K. DuVal, W. Joel and S. G. Wolf: The Experimental Production of Atrophic Gastritis Using a Preparation of Human Gastric Juice. Surgery, **46**:76, 1959.
6. State, D. and L. Morgenstern: The Inhibitory Role of the Pyloric Antrum on the Cephalic Phase of Gastric Acid Secretion in Dogs. Surg., Gynec. and Obstet., **106**:545, 1958.
7. Storer, E. H., E. J. Schmitz, L. R. Sauvage, E. A. Kanar, C. H. Diessner and H. N. Harkins: Gastric Secretion in Heiderhain Pouches Following Section of Vagus Nerves to Main Stomach. Proc. Soc. Exper. Biol. and Med., **80**:325, 1952.
8. Uvnas, B.: The Part Played by the Pyloric Region in the Cephalic Phase of Gastric Secretion. Acta Physiol. Scandinav. (Suppl.), 7:289, 1942.
9. Wilhelmj, C. M., F. T. O'Brien and F. C. Hill: The Inhibitory Influence of the Acidity of the Gastric Contents on the Secretion of Acid by the Stomach. Am. J. Physiol., **115**: 429, 1936.
10. Woodward, E. R., W. E. Trumbull, H. Schapiro and L. Towne: Does the Gastric Antrum Elaborate an Antisecretory Hormone? Am. J. Dig. Dis., 3:204, 1958.

Discussion

Dr. Lloyd M. Nyhus: The experimental study presented tonight by Dr. DuVal represents a phenomenal amount of hard work. Further elucidation and interpretation of these results will be necessary to realize their total significance. We must also understand the facets of acid stimulation to realize the complexity of the problems of inhibition.

It has become apparent recently that on the stimulatory side of gastric acid secretion the vagal release of gastrin has a significant role in the over all spectrum of gastric acid output.

Thus, there are found significant phases of acid stimulation instead of the formally postulated three phases: 1) direct vagal, for the direct action of the vagi upon the parietal cell; 2) vagal antral, or the effect of the vagus upon the antrum to release gastrin; local antral, the effect of chemical and mechanical stimulation of the antrum upon gastrin release; and, 3) the intestinal phase with its previous connotation.

Inhibition of gastric acid secretion from antral sources may be produced by vagotomy, or by perfusion of the antrum with acid or cocaine.

(Slide) This slide demonstrates the inhibition by acid of the vagal release of gastrin. As we well know, acid inhibits the mechanical and chemical phases likewise as does cocaine. It has been believed that this inhibitory effect upon acid secretion was due to the blockage of gastrin release at its point of origin in the antrum and since cocaine affects inhibition a neutral cut-off mechanism has been postluated, rather than inhibition due to an antagonistic hormone.

In the past four years three papers have been presented which indicated the presence of an inhibitory hormone. However, none has been confirmed. The work of DuVal and Price is the strongest evidence that such a hormone exists.

In canine gastric secretory studies simple nausea or retching in the animal can markedly inhibit the output of acid from an isolated gastric pouch, regardless of the stimuli. One wonders what the total effect of these acute experiments, under anesthesia, with the blood volume shifts, and so forth will be upon the output of acid in these animals.

We shall await with interest further work by Dr. DuVal, and I am sure of many others, in this fascinating area. I wish to thank Dr. DuVal for allowing me to see his manuscript in advance of his presentation and also the Association for the privilege of the floor.

Dr. Merlin K. DuVal (Closing): I wish to thank Dr. Nyhus for being kind enough to discuss this paper for me; and I appreciate the privilege of the floor.