Mechanism of Antral Regulation of Gastric Secretion: Discontinuous Cross-Circulation *

MERLIN K. DUVAL, JR., M.D., WILLIAM E. PRICE, M.D.

From the Department of Surgery, University of Oklahoma Medical Center, Oklahoma City, Oklahoma

THE PROMPT cessation of gastric secretion which follows the lowering of antral pH to 1.5 or below is thought to be due to interference with the release of the antral stimulating hormone: gastrin.[3, 5] However, some evidence suggests that, at the lower pH, the antrum elaborates a second hormonal agent, specifically: an inhibitor of gastric secretion.[2, 4]

Experimental efforts to distinguish between paralysis of stimulation and active inhibition have depended upon interpretation of the secretory responses of variously constructed pouches in dogs. The limitations of such studies have prompted a recent effort to detect the hormonal character of the regulation of gastric secretion by attempting passive transfer of both stimulation and inhibition of gastric secretion between dogs made acutely parabiotic by interconnection of their aortas.[1] In those experiments, stimulation was achieved by continuous balloon-distention of the gastric antrum of one dog for a six-hour period. During the middle two hours of the experiment, acid was introduced into the antrum of the dog with which it was cross-circulating, the effect of which was to reduce the gastric secretory response of the stimulated dog. Figure 1 demonstrates this sequence of events.

Although this was interpreted as evidence favorable to the thesis of hormonal regulation of gastric secretion, reservations were expressed regarding such an interpretation until two experimental artifacts could be studied further. First, the secretory response during the first and third two-hour periods may have represented the cumulative response to stimuli from both dogs; and the fall in secretion during the middle third of the experiment, due to simple withdrawal of stimulation from one dog by lowering the pH of its antrum. Second, turning the second dog under general anesthesia (in order to introduce acid into its antrum) may have produced a disturbance of its homeostatic regulating mechanisms resulting in a shift in blood volume between the animals.

In an effort to clarify and interpret the significance of these experimental artifacts, the following studies were done.

Materials and Methods

Adult mongrel dogs varying in weight from 12 to 20 kg., but paired within 1.5 kg. of each other, were used. Each member of each pair was starved for 24 hours, given morphine sulfate (10 mg./kg.) intramusculary 30 minutes before operation and anesthetized with a single intravenous injection of chloralose (50 mg./kg.) and urethane (500 mg./kg.). The abdomen was entered through a long midline incision. A flanged, plastic cannula was inserted through the posterior wall of the fundus of

* Submitted for publication September 2, 1960.

This work has been supported by grants #A-3221 & A-2121 from the United States Public Health Service.

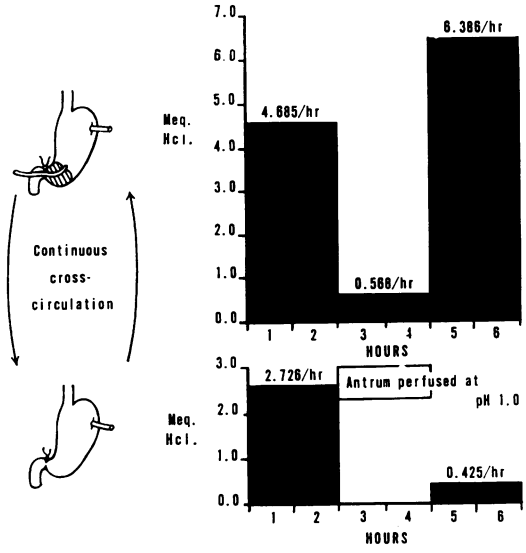

FIG. 1. The transfer of antral inhibition, between animals, by cross-circulation.

the stomach immediately above the highest short gastric vessels, secured with a purse-string suture, and delivered to the exterior through a stab incision in the mid-lateral line of the flank. Gastric outlet obstruction was produced by ligating the pylorus (or both afferent and efferent limbs of the gastrojejunostomy if previously subjected to antrectomy). A straight No. 18 French catheter carrying an inflatable balloon was passed into the antrum of one dog through the pylorus just prior to its ligation. The distal end of this catheter emerged to the exterior through a duodenostomy and abdominal wall-stab incision.

The abdominal aorta of each dog was then mobilized, cross-clamped and divided. The proximal stump of each aorta was cannulated, using an 18-inch length of one-quarter inch, nonwettable, plastic tubing. The tubing was filled with isotonic saline and the distal end inserted and tied into the distal stump of the aorta of the same dog. The abdomen was then closed around the projecting loop of cannula. This is illustrated in Figure 2.

The dog with the antral balloon was turned onto its left side and placed on the platform of a 50-kg. scale (accurate to changes of 20 Gm.). Gastric juice was collected from its fundus cannula at 15-minute intervals after inflation of the rubber balloon with 15 to 25 cc. of air. At the same time, the non-stimulated dog was turned onto its right side (no gastric juice collections from it) so that it lay face-to-face with its mate, and 100 cc. of 0.1 N HCl instilled into its antrum through the fundus cannula.

No less than one hour after the appearance of a good secretory response from the fundus of the stimulated dog, the loop of projecting aortic cannula of each dog was cross-clamped and divided. The proximal end of each was joined to the distal end of the other inside a tight-fitting collar of plastic tubing, and the cross-clamps removed. During this period of cross-circulation, blood volume shifts were prevented by regulating flow through the cannulas as needed to keep the scales in balance. Cross-circulation continued for a period of time equal to that which had preceded cross-circulation, after which the cannulas were again cross-clamped, unjointed, and each proximal stump rejoined to its own distal stump.

Control studies were done in the same manner except that each "non-stimulated" dog had been subjected to antrectomy between two and four weeks earlier. All gastric secretions were assayed by titra-

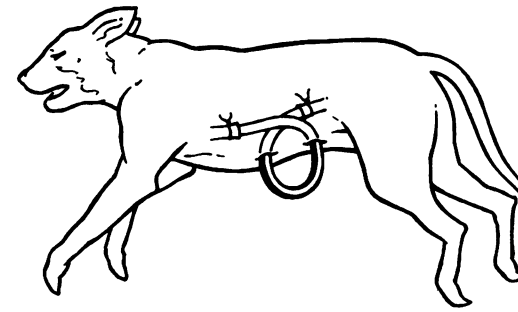

FIG. 2. Schematic representation of a dog prepared for discontinuous cross-circulation. Aorta has been divided and cannulated to itself. The loop made by the cannula projects from the body.

tion with 0.1 N NaOH using Toepher's reagent as indicator. Results were expressed as total milli-equivalents by multiplying the cc. of 0.1 N NaOH required to neutralize 1 cc. of gastric juice by the volume secreted.

Results

Thirty-six dogs were used in this study. Nine pairs served as controls, and in nine pairs inhibition studies were done.

Studies: Nine attempts to influence the gastric secretory response of a stimulated dog, by discontinuous cross-circulation with a dog whose gastric antrum contained 0.1 N HCl, were made. In two, an adequate secretory response to stimulation was not achieved. One additional pair was discarded because of the appearance of hypersecretion, tachycardia and urticaria, presumably due to blood sub-group incompatability. Of the six pairs studied, five demonstrated a considerable depression of the secretory response of the stimulated dog during the period of cross-circulation. The sixth showed no change. A typical response is reproduced in Figure 3. Note that the secretion of the stimulated dog fell from 7.64 to 1.17 Meq HCl/hr. coincident with cross-circulation for one and

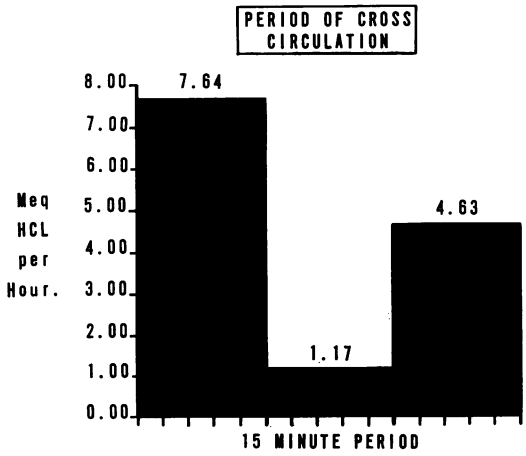

FIG. 3. Secretory response of a dog cross-circulating discontinuously with a dog whose antrum is acidified.

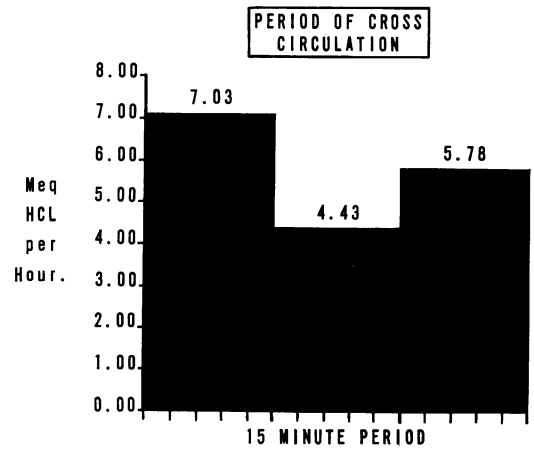

FIG. 4. Secretory response of a dog cross-circulating discontinuously with a dog previously subjected to antrectomy.

one-quarter hours, and returned to 4.63 Meq HCl/hr. for the hour and a quarter after cross-circulation was discontinued.

Controls: Nine control experiments were done in which the antrum of the non-stimulated dog was surgically absent. One was abandoned during the period of cross-circulation when the cannulas clotted; one failed to develop an adequate level of pre-cross-circulation secretion, and one developed a blood incompatability reaction with tachycardia and urticaria. In two of the remaining six, cross-circulation had no effect on the secretory response of the stimulated dog. In the remaining four, however, there was depression of the secretory response of the stimulated dog during the period of cross-circulation. Figure 4 represents one of the more marked responses observed in the latter group. Note that the effect of cross-circulation was to depress the gastric secretory response of the stimulated dog from 7.03 to 4.43 Meq HCl/hr. Following interruption of the cross-circulation, secretion rose only to 5.78 Meq HCl/hr.

Discussion

These results suggest that the experimental artifacts of cross-circulation, noted

earlier,[1] can be effectively countered. In other words, discontinuous cross-circulation has established that the peak secretion of a stimulated dog, which occurs before and after acid perfusion of the antrum of a dog with which it is continuously cross-circulating, cannot be due to cumulative stimulation from both dogs. It is also apparent, although changes in the gastric secretory response may be influenced by a shift of blood volumes during cross-circulation, that these influences can be kept under control.

Meanwhile, discontinuous cross-circulation between dogs, one of which has acid in the antrum of its stomach, produced interference with the secretory response of its stimulated mate. It is tempting to assume that this represents passive transfer of a circulating "inhibitor." However, comparison of this effect with that observed during discontinuous cross-circulation between dogs, one of which has previously been subjected to antrectomy, shows a similar, although less marked, response. Therefore, it would appear that one of the biological effects of cross-circulation itself is to depress gastric secretion. However, the quantitative differences observed suggest that passive transfer of an inhibiting agent may also have been taking place. Further study is currently in progress to define further, these quantitative differences.

Summary

1. A method for the establishment of discontinuous cross-circulation between paired dogs by interconnecting their aortas has been devised.

2. The effect of 0.1 N HCl in the gastric antrum of one member of the cross-circulating pair depresses the gastric secretory response to an inflated antral balloon in the other.

3. Control studies indicate that a similar, but less marked, effect is observed in response to cross-circulation itself.

Bibliography

1. Duval, M. K., Jr. and W. E. Price: The Mechanism of Antral Regulation of Gastric Secretion: Continuous Cross-Circulation. Ann. Surg., **152**:410, 1960.
2. Jordan, P. H. and B. F. Sand: Antral Inhibition of Gastric Secretion. Proc. Soc. Exper. Biol. & Med., **94**:471, 1957.
3. 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. Amer. J. Physiol., **191**:64, 1957.
4. State, D. and L. Morgenstern: The Inhibitory Role of the Pyloric Antrum on the Cephalic Phase of Gastric Acid Secretion in Dogs. Surg., Gynec. & Obst., **106**:545, 1958.
5. Woodward, E. R., E. S. Lyons, J. Landor and L. R. Dragstedt: The Physiology of the Gastric Antrum: Experimental Studies on Isolated Antrum Pouches in Dogs. Gastroenterol., **27**:766, 1954.