Acidification of the Gastric Antrum and Inhibition of Gastric Secretion *

MARCEL J. RHEAULT,** M.D., LARS S. SEMB,*** CAND. MED.,
HENRY N. HARKINS,† M.D., PH.D., F.A.C.S.,
LLOYD M. NYHUS,†† M.D., F.A.C.S.

From the Department of Surgery, University of Washington, School of Medicine, Seattle, Washington

UNDER CERTAIN experimental conditions, acidification of the gastric antrum to a pH lower than 2.0 is said to provoke a profound decrease in the acid secretion of a denervated fundic pouch in dogs.[3, 11] Two main hypotheses are proposed to explain this decrease—active inhibition [12, 19] or passive inhibition.[7, 11, 13] The term active inhibition indicates that at a low pH the antrum secretes an inhibitory hormone which will act directly on the parietal cells of the fundus to stop secretion of acid. Passive inhibition indicates that an acid milieu prevents the formation of gastrin by the antrum so the parietal cells are not further stimulated. Opinions regarding each theory are divided.

Three different sets of experiments have been conducted in this laboratory in an attempt to prove or disprove the existence of an antral inhibitory hormone.

In dogs with vagally-denervated antral and fundic pouches, the effect of antral acidification was studied in conjunction with three different stimuli: histamine, exogenous gastrin and acetylcholine. The results of these experiments are reported.

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** Research Associate, R. Samuel McLaughlin Travelling Fellow; on leave from Montreal, Quebec.

*** Research Associate; on leave from Department II, Surgery, Ulleval Hospital, Oslo, Norway.

† Professor and Chairman.

†† Professor.

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Material and Methods

Seven mongrel dogs, weighing 12 to 18 Kg., were prepared with a completely vagally-denervated antrum and a Heidenhain pouch.[6] The cannula draining the fundic pouch was the type described previously.[4] The technical construction of the antral pouch is shown in Figure 1.

One month's convalescence was allowed before the dogs were trained in the "Pavlov-stand." The technic of Heidenhain pouch collection used was that described by Savage *et al.* (1963).[16] Gastric juice was collected in 15-minute samples. The volume was measured in a calibrated test tube, and the acidity by titration using a Fisher Automatic Titrimeter, Model 36, against 0.05 NaOH to an end point of pH 7.0 (titratable acid, T.A.). The acid output per 15-minute sample was calculated by multiplying concentration by the volume.

Effect of Antral Acidification on Histamine-Induced Fundic Secretion

After a 1 to 2-hour collection of resting secretion the fundic pouch was stimulated to secrete hydrochloric acid by a subcutaneous injection of 100 μg. of histamine acid phosphate. During the following 2-hour

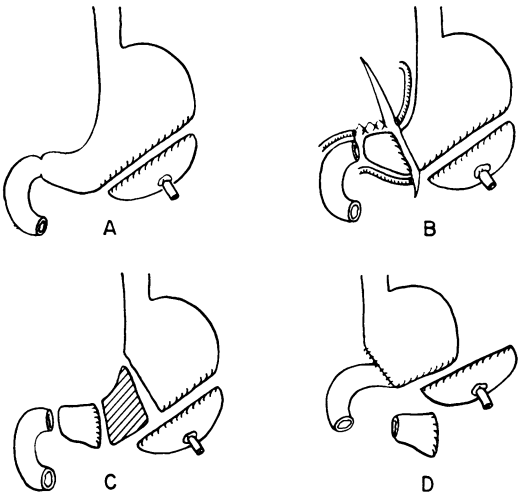

FIG. 1. Operative procedures: A) Heidenhain pouch is prepared in the usual manner. B) A vagally-denervated separated antral pouch is also formed. The lesser curvature of antrum is "cleaned" completely of all tissue, and hepatogastric ligament is sectioned transversely. C) In order to avoid any antral tissue remaining in the gastric remnant, a partial distal gastrectomy is performed, removing nearly all of lesser curvature. D) Gastrointestinal continuity is restored by gastroduodenostomy.

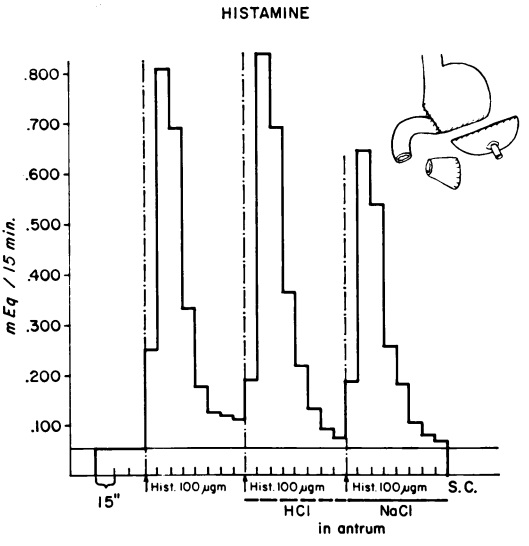

FIG. 2. Failure of pH change in antrum upon secretion of hydrochloric acid from histamine-stimulated Heidenhain pouches in dogs is shown. Abscissa indicates time in 15-minute intervals, and the ordinate average total output of hydrochloric acid in mg./15 min. Arrows indicate subcutaneous injections of 100 mg. of histamine. Dotted line beneath abscissa indicates that the antrum was perfused with 0.1 N HCl; and the solid line, that the perfusate was NaCl.

period, 15-minute samples were collected, constituting the first phase of the experiment. After this 2-hour collection, a second subcutaneous injection of histamine (100 µg.) was given, and at the same time, irrigation of the antrum with hydrochloric acid was started. The technic for irrigation was as described by Shapira and State.[18] The antrum was irrigated with a solution of 0.1 N HCl (pH 1.2) at a rate of 1 to 2 ml./min.; this irrigation was continued for 2 hours. During this period, 15-minute samples of fundic pouch secretion were collected; this constituted the second phase. The third phase of the experiment was identical to the second, except that a solution of NaCl (pH 6.5) was used in place of HCl to irrigate the antrum. This third phase served as a control.

Effect of Antral Acidification on Exogenous Gastrin-Induced Fundic Secretion *

The gastrin used in these experiments is from an alkaline extract of porcine antral mucosa and is considerably purer and more potent than that described in preliminary communications by Fletcher and Anderson.[1, 9, 10]

This experiment was conducted in two phases. In the first phase, a 1-hour base line was established. Irrigation of the antrum was then begun with a solution of 0.1 N HCl (pH 1.2) at a rate of 1 ml./min. Half an hour later, an injection of 5 mg. of gastrin was given subcutaneously. Fifteen-minute samples of secretion were collected from the Heidenhain pouch for the next 3 hours. Titration and volume were determined as described above.

The second phase of the experiment was similar to the first, except that a solution of NaCl (pH 6.5) was substituted for the

* The gastrin used in these studies was provided by Dr. T. Lloyd Fletcher of the Chemistry Research Laboratory of this department.

HCl to irrigate the antral pouch. This phase served as a control.

Effect of Antral Acidification on Acetylcholine-Induced Fundic Secretion

A 1-hour base line was established and irrigation of the antral pouch was started with a solution of acetylcholine bromide (pH 6.8). This irrigation was maintained during the 6 hours of the experiment at a rate of 1 to 2 ml./min., and the fundic juice was collected and titrated every 15 minutes. During the first 2-hour period, the acetylcholine solution alone was bathing the antral mucosa. For the next 2-hour period, this solution was acidified to a pH of 1.5. The last 2-hour period was a repetition of the first 2-hour period, with the perfusate of pH 6.8.

Results

Effect of Antral Acidification on Histamine-Induced Fundic Secretion

Figure 2 shows the results of 100 experiments in six dogs. The average base line of acid secretion for all of these studies was 0.209 mEq. per hour. The results of each of the three test phases are expressed in mEq per 2 hours. The average total acid output for the first phase of the experiment was 2.571 mEq for 2 hours. Antral acidification did not alter acid output. In the second phase the average total acid output was 2.423 mEq per 2 hours. In the control period, of Phase III, there was an average total acid output of 2.045 mEq per 2 hours.

These three series of results have been subjected to the Student's 'T' Test, and there is no statistically significant difference between them.

Effect of Antral Acidification on Gastrin-Induced Fundic Secretion

Figure 3 shows the average results of 50 experiments in five dogs. During antral irrigation with HCl, the average total acid

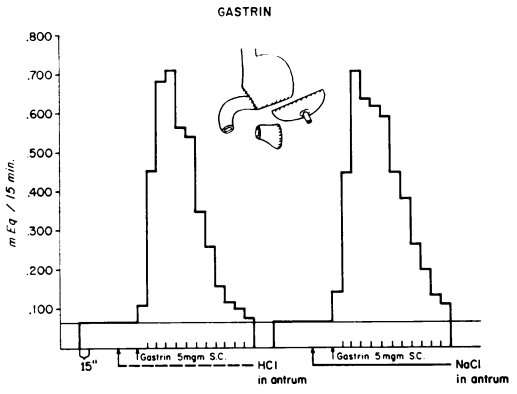

FIG. 3. Failure of pH changes in antrum upon secretion of hydrochloric acid from exogenous gastrin-stimulated Heidenhain pouches in dogs is demonstrated. Arrows indicate subcutaneous injections of 5 mg. of gastrin. Abscissa and ordinate same as in Fig. 2.

output for 3 hours was 4.047 mEq. During the control period with saline irrigation of the antrum, the average total acid output was 4.635 mEq. The Student's 'T' Test shows no significant difference between these two series of results.

Effect of Antral Acidification on Acetylcholine-Induced Fundic Secretion

Figure 4 shows the results of average total acid output from the Heidenhain pouches in five dogs when the antrum is irrigated with acetylcholine with variations in pH. In the first period the pH was 6.8; in the second 1.5 and in the third 6.8. Only the last hour in each of these three phases was studied because it takes at least 45 minutes to reach the appropriate pH. In the first phase of the experiment (pH 6.8) the average total acid output from the fundic pouch was 2.444 mEq. for 1 hour. During the period of antral acidification (pH 1.5) the average total acid output was 0.402 mEq. per hour. In the following period with antral pH 6.8 the average total acid output was 2.060 mEq. per hour. There is a highly significant difference between the average acid outputs in Periods I and II ($P < 0.01$), and also between II and III ($P < 0.001$). There is no statistically sig-

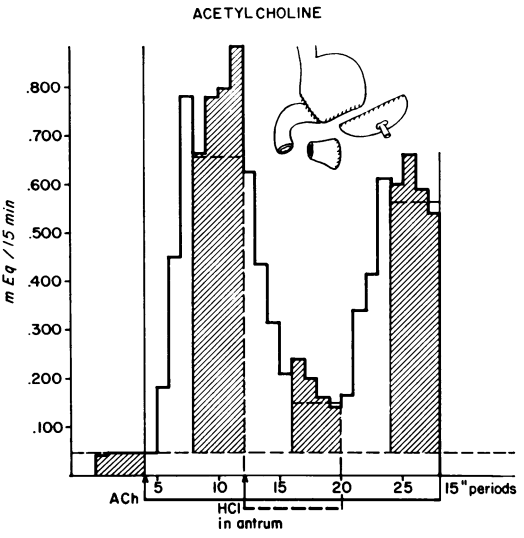

FIG. 4. Inhibitory effect of pH change in acetylcholine-perfused antrum upon the hydrochloric acid secretion from Heidenhain pouches in dogs is shown. Acetylcholine perfusion starts at ACh and is maintained throughout the experiment. At HCl, and as long as the dotted line indicates, the antrum is also perfused with 0.1 N HCl. Cross-hatched areas indicate comparable collections of HCl.

nificant difference between Periods I and III ($P > 0.5$).

Discussion

It has been reported that antral acidification inhibits histamine-induced fundic secretion of acid.[5, 14, 19, 21] Unfortunately the issue has been clouded by contradictory reports.[2, 7, 13, 17, 20] With the experimental design used in the studies presented, antral acidification clearly failed to inhibit histamine-induced acid secretion in the Heidenhain pouch. In addition, this study confirmed the observation of others[11] that fundic acid secretion stimulated by exogenous gastrin is not inhibited by acidification of the antrum.

The negative aspect of these results for both histamine and exogenous gastrin suggests that the endogenous gastrin mechanism and the antral-inhibiting mechanism may have been damaged or destroyed during preparation of the antral pouches. The experiments with acetylcholine serve to prove that these latter mechanisms were functioning in the antral pouches. Thus the same precision of inhibition at the parietal cell level should have been shown clearly with histamine and exogenous gastrin if the inhibition were due to a circulating inhibitory hormone. The complete failure of antral acidification to alter the secretory response to these stimulants of acid secretion in these experiments seems to negate the concept of such a circulating hormone.

These experiments provide further indications that the effect of an acid environment in the gastric antrum is to prevent the release of endogenous gastrin by a local mechanism. It is not possible to support the hypothesis of an antral inhibitory hormone.

Summary

Acidification of the vagally-denervated antrum in our experiments failed to inhibit:

1. histamine-induced fundic secretion,
2. exogenous gastrin-induced fundic secretion, *but inhibited:*
3. acetylcholine-induced fundic secretion at a rate of 83.5%.

These findings suggest that antral acidification acts as a local mechanism to suppress formation or release of gastrin, and not via an inhibitory hormone.

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