

Acid Inhibition by the Gastric Antrum: *

Experiments on Antral and Fundic Pouches

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IT IS CLEAR THAT ACID in contact with the antrum mucosa prevents the usual secretory response from antral stimulation. However, the mechanism of this inhibition has not been completely clarified. Apart from the effect of acid on gastrin elaboration is the matter of whether an inhibitory hormone is responsible for acid inhibition. Experiments have been reported both in favor^{3, 6, 13} and against^{1, 8, 11} such a substance. Therefore, the present experiments were undertaken to further study the mechanism of secretory inhibition by acid when in contact with the antrum mucosa. By the control and use of dogs in which vagally innervated or denervated fundic pouches were constructed, a comparison of various stimuli on gastric secretion were analyzed in the same animal as to the significance of antrum exclusion, vagal innervation or denervation, the effects of acid or cocaine, and antrectomy.

Experimental Methods

Twenty-seven healthy mongrel dogs weighing between 10 and 20 kilograms were used. Heidenhain pouches were prepared

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in eight, Pavlov pouches in five, Dragstedt total gastric pouches in eleven, and Lim-Ivy total gastric pouches in three dogs. At a second operation a vagally innervated excluded antrum cutaneous fistula was constructed after the method of Oberhelman.⁹ At a third operation, the animals underwent procedures designed to vagally denervate the antrum mucosa either by antroneurolysis after the method of Jones,⁵ by simple serosal-transection at the level of the previously produced mucosal diaphragm, or by construction of an isolated antrum pouch from the level of the previously produced mucosal diaphragm. At a fourth operation the antro-cutaneous fistula was taken down and the antrum resected (Fig. 1).

The pH of the mucous secretion from the antral pouches was routinely tested and found to range between six and seven. The integrity of the mucosal diaphragm was determined at surgery. If at autopsy antrum mucosa was histologically found on the fundic side of the diaphragm, its effect was presumably constant since the fundus was undisturbed after exclusion.

After a 10-day recovery period from the operative procedures, collections of pouch gastric juice were secured through a stainless steel cannula. Chronic observations were made on the 24-hour output of pouch secretion collected in football bladders. Acute observations were made to various stimuli and collected in small rubber balloons. The bladders and balloons were checked for leaks and if any were found that particular collection was discarded.

Clinical units of free acidity were deter-

mined by taking a sample of gastric juice from either the 24-hour or acute test responses and titrating with N/10 sodium hydroxide using Toepfer's reagent as the indicator. The quantitative output of free hydrochloric acid was then calculated in milliequivalents by multiplying the volume as expressed in liters by the free acid concentration as expressed in clinical units.

Chronic Observations. All 27 animals were fed a standard daily meal of 680 Gm. of a proprietary dog food (Pard), 500 ml. of homogenized milk, with water ad libitum. Five or 10 Gm. of sodium chloride were added to the food daily according to the initial 24-hour level of pouch secretion and then kept constant. Vitamins were given to the total pouch dogs. The animals were fed at the same time daily. If an animal did not eat all the food, the collection of that day was excluded. On the average, 60 24-hour collections were obtained after an operative procedure in each animal.

Acute Observations. Acute experiments

were commenced in 18 animals after each was given three to six weeks to recover from each operation. During this period the presence or absence of pouch vagal innervation was determined by insulin hypoglycemia. The animals were also trained in a Pavlov stand for three to four hours daily.

The animals were tested after 20-24 hours of fasting if after a 15-minute control the pouch volume did not exceed 0.5 milliliters with the free acid less than 20 clinical units. When this criterion for control was not met, the animals were not tested.

1. *The Test Meal:* The secretory response to 100 Gm. of Pard was determined in seven Heidenhain, five Pavlov and two Dragstedt pouch animals. Secretion from the feeding test was collected for four hours. There were 248 feeding tests.

2. *The Insulin Test:* The secretory response to insulin hypoglycemia was performed on five Heidenhain, four Pavlov and five Dragstedt pouch animals. Each

OPERATIVE PROCEDURES:— EXCLUSION OF VAGALLY INNERVATED ANTRA, FOLLOWED BY ANTRAL DENERVATION AND ANTRECTOMY —

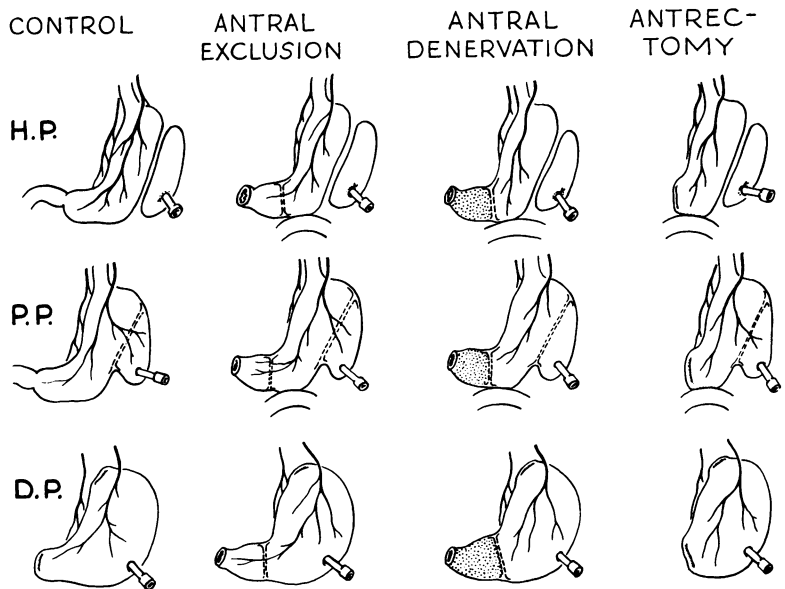


FIG. 1. Operative procedures performed after original pouch preparation. Experiments were performed on eight Heidenhain pouch animals (H.P.), five Pavlov pouch animals (P.P.), and eleven Dragstedt pouch animals (D.P.). Gastroduodenostomy was made in H.P. and P.P. Esophagoduodenostomy was made in D.P.

GASTRIC SECRETION: EXCLUSION OF VAGALLY
INNERVATED ANTRA, FOLLOWED BY ACID AND COCAINE
IRRIGATION, DENERVATION, AND ANTRECTOMY

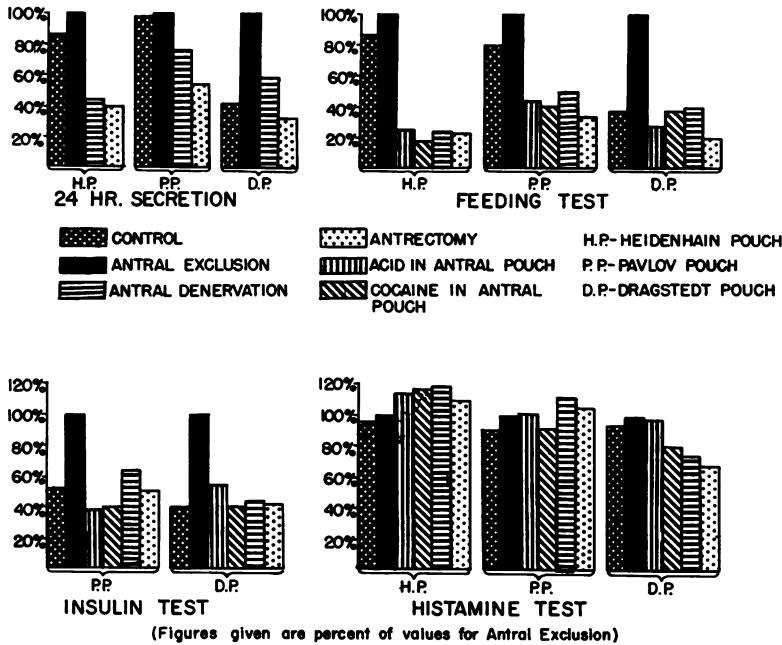


FIG. 2. Effects of exclusion of vagally innervated antra, followed by acid and cocaine irrigation of innervated antra, denervation of antra, and antrectomy on pouch gastric secretion. Mean control secretion in mEq. of HCl from the 24-hour secretion was 27.8 for H.P., 38.0 for P.P., and 39.9 for D.P. From feeding test it was 2.84 for H.P., 6.55 for P.P., and 2.02 for D.P. From insulin test it was 1.12 for P.P., and 4.25 for D.P. From histamine test it was 0.91 for H.P., 1.53 for P.P., and 6.28 for D.P.

animal was given an identical intravenous dose of crystalline zinc insulin (10 or 15 units) during the experiment. Secretion to the insulin test was collected for two hours. The criteria for accepting an insulin test as valid were those recommended by Hollander.⁴ There were 225 insulin tests.

3. *The Histamine Test:* The secretory effect of histamine was determined in five Heidenhain, four Pavlov and four Dragstedt pouch animals. Histamine was given subcutaneously as a single injection of 0.1, or 1.0 mg. dose. Each animal received an identical dose during the experiment. Secretion was collected for 75 minutes. There were 368 histamine tests.

4. *The Effect of Acid or Cocaine Irrigation of the Antrum:* After control tests had been obtained, the antrum of each dog was exteriorized. To evaluate the effect of acid and cocaine on the feeding, insulin and histamine tests, the innervated excluded antrum of each animal was irrigated with N/10 hydrochloric acid or with 2 per cent

cocaine solution. The cocaine solution was adjusted to a pH of seven by sodium bicarbonate. The solutions were immediately administered after the control period and at a rate of not less than 1.0 ml. per minute and not more than 2.0 ml. per minute. The perfusion system was held in place by a colostomy apparatus.

Statistical Methods. Generally recognized statistical methods were used. The mean output of hydrochloric acid in milliequivalents at each stage of experimentation was determined in each animal. The significance between mean milliequivalent differences was determined by *Student's "T" Test*. Per cent change was not used in a test for significance. For convenience the results are expressed in per cent. Per cent changes are expressed as values for antral exclusion and are given in the nearest whole number. Changes expressed as significant are at the five per cent level or less. Unless stated, the changes expressed are significant.

Results

The 24-Hour Gastric Secretion: (Fig. 2). Vagally Denervated Fundic Pouches

The Heidenhain Pouch: After exclusion of the vagally innervated antrum, four animals showed an increase and four did not. Vagal denervation reduced acid secretion an average of 56 per cent. After antrectomy secretion was reduced an average of 61 per cent when compared to exclusion. The difference between vagal denervation and antrectomy was not significant.

The Lim-Ivy Pouch: After exclusion of the vagally denervated antrum, acid secretion was not significantly changed (Fig. 3).

Vagally Innervated Fundic Pouches

The Pavlov Pouch: After exclusion of the vagally innervated antrum, one increased and four showed no significant change. Vagal denervation reduced secretion an average of 24 per cent. After antrectomy acid secretion was further reduced an average of 23 per cent, or reduced an average of 47 per cent when compared to exclusion. The effect of antrectomy was greater than that of vagal denervation.

The Dragstedt Pouch: After exclusion of the vagally innervated antrum secretion was increased an average of 58 per cent. Vagal denervation reduced secretion an average of 42 per cent. Antrectomy further reduced secretion an average of 26 per cent, or 68 per cent when compared to exclusion. The effect of antrectomy was greater than that for denervation, but not significantly different from that of the original controls.

The Test Meal: (Fig. 2).

Vagally Denervated Fundic Pouches

The Heidenhain Pouch: After exclusion of the vagally innervated antrum, one increased and three showed no significant change. Irrigation of the vagally innervated excluded antrum with N/10 hydrochloric acid reduced secretion an average of 75

EFFECT OF ANTRUM EXCLUSION IN THE DENERVATED TOTAL POUCH

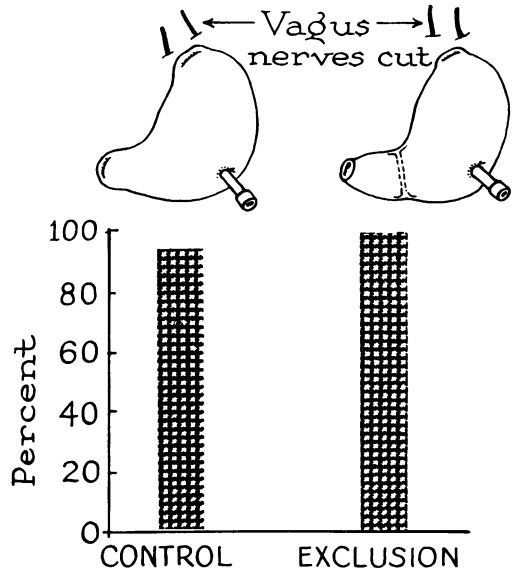


FIG. 3. The effect of exclusion of vagally denervated antra in the denervated total gastric pouch preparation on the 24-hour acid output.

per cent in five dogs. Irrigation with 2 per cent cocaine reduced the response an average of 82 per cent. Vagal denervation reduced the response an average of 75 per cent. Antrectomy when compared to exclusion reduced secretion an average of 77 per cent. The effects of acid, cocaine or vagal denervation were not significantly different from the effect of antrectomy.

Vagally Innervated Fundic Pouches

The Pavlov Pouch: After exclusion of the vagally innervated antrum, one increased and four showed no significant change. Irrigation of the vagally innervated excluded antrum with N/10 hydrochloric acid reduced secretion an average of 56 per cent in five dogs. Irrigation with 2 per cent cocaine reduced the response an average of 60 per cent. Vagal denervation reduced the response an average of 50 per cent. Antrectomy when compared to exclusion reduced secretion an average of 67 per cent. The effects of acid, cocaine or denerv-

ation were not significantly different from the effect of antrectomy.

The Dragstedt Pouch: After exclusion of the innervated antrum, secretion was increased an average of 63 per cent in two animals. Irrigation of the vagally innervated excluded antrum with N/10 hydrochloric acid reduced secretion an average of 74 per cent. Irrigation with 2 per cent cocaine reduced it 63 per cent. Vagal denervation reduced the response an average of 60 per cent. Antrectomy when compared to exclusion reduced secretion an average of 80 per cent. The effect of antrectomy was not significantly different from that of acid irrigation, but was greater than that of denervation.

The Insulin Test: (Fig. 2).

Vagally Denervated Fundic Pouches

The Heidenhain Pouch: After exclusion of the vagally innervated antrum, five showed a positive response as determined by secretory curves. There was a failure to observe a positive secretory curve after irrigation with acid or cocaine, vagal denervation or antrectomy of the excluded antrum.

Vagally Innervated Fundic Pouches

The Pavlov Pouch: After exclusion of the vagally innervated antrum, four showed an average increase of 48 per cent. Irrigation with N/10 hydrochloric acid reduced this response an average of 62 per cent. Irrigation with 2 per cent cocaine reduced it an average of 60 per cent. Vagal denervation reduced secretion an average of 36 per cent. Antrectomy reduced secretion an average of 46 per cent when compared with exclusion. The effects of acid, cocaine or antrectomy were not significantly different from original control values, but were greater than denervation.

The Dragstedt Pouch: After exclusion of the vagally innervated antrum, five showed an average increase of 59 per cent. Irrigation with N/10 hydrochloric acid reduced this response an average of 46 per cent.

Irrigation with 2 per cent cocaine reduced it an average of 59 per cent. Vagal denervation reduced it 54 per cent. Antrectomy reduced it 56 per cent. The effects of acid, cocaine, denervation or antrectomy were not significantly different from the original control values.

The Histamine Test: (Fig. 2).

Vagally Denervated Fundic Pouches

The Heidenhain Pouch: The response to histamine was not significantly altered by exclusion, irrigation with acid or cocaine, vagal denervation or antrectomy.

Vagally Innervated Fundic Pouches

The Pavlov Pouch: The response to histamine was not significantly altered by exclusion, irrigation with acid or cocaine, vagal denervation or antrectomy.

The Dragstedt Pouch: The response to histamine was not significantly altered by exclusion or irrigation with acid. The response to histamine during cocaine irrigation, after vagal denervation of the antrum and after antrectomy was less than during irrigation with acid.

Discussion

Resection of the antrum has been reported to markedly reduce the daily acid output in Heidenhain and Pavlov pouch animals.¹⁵ When the antrum is excluded from contact with the local mechanical and chemical effects of food, it would be expected that acid secretion would fall. However, after exclusion of the vagally innervated antrum in these experiments the 24-hour as well as the test meal secretory response was not reduced. In contrast to the important role of the antrum in the Heidenhain and Pavlov pouch animals, the antrum in the vagally innervated total gastric pouch is considered to be in a state of quiescence.¹⁰ However, after exclusion of the vagally innervated antrum in the Dragstedt pouch animals, the 24-hour acid output and the response to a test meal were significantly increased. The above results

are related to the problem of acid inhibition. In the Heidenhain and Pavlov pouch animals exclusion removed the antrum from the influence of the normal acid gastric content. In the Dragstedt pouch animals exclusion removed the antrum from the influence of pure acid secretion.

The results obtained after exclusion of the vagally innervated antrum could be explained by 1) loss of a local interference by an acid pH on the gastrin mechanism, 2) loss of a potent humoral inhibitory substance which was released by the antrum when in contact with acid, 3) loss of potent acid inhibitory reflexes which were activated when the antrum was in contact with acid, and 4) loss of either an inhibitory substance or reflex as well as the loss of a local controlling effect of an acid pH on the gastrin mechanism.

The finding that the response to histamine was not increased after exclusion of the vagally innervated antrum tends to discount the idea that the results obtained from feeding were due to loss of a potent inhibitory substance or reflexes. Instead, the results of exclusion may be due to increased antrum stimulation. Since vagal innervation was preserved, the vagus nerves may be a source of increased stimulation. Straaten in 1933¹² suggested that vagal stimulation could release gastrin. Uvnas¹⁴ supported this view. In 1951 Lim and Moser⁷ reported that vagal impulses can liberate gastrin. The results of the 24-hour pouch secretion in the present experiments are in accord with results reported by Forrest in 1956² and Oberhelman in 1957⁹ in which they found that if the antrum was excluded and vagally innervated, the output of Heidenhain pouch secretion was not reduced. Oberhelman indicated that vagus nerve impulses produced a release of gastrin.

The increased response from the insulin tests after exclusion of the vagally innervated antrum supports the idea of increased vagal gastrin. If the results of the insulin tests were due to either the loss of acid

inhibitory reflexes or an inhibitory hormone, then the response to both the histamine and insulin tests should have increased.

The importance of vagal integrity in the response after exclusion is shown by the denervated total pouch. After exclusion of the vagally denervated antrum in the Lim-Ivy preparation, the 24-hour acid output from the fundus was not changed. This is in contrast with the Dragstedt pouch preparation. Since vagal innervation was removed at the time of original Lim-Ivy pouch construction, any increase in secretion would suggest the loss of an acid inhibitory substance. The failure to find a significant change after exclusion is interpreted as indicating that the antrum prior to exclusion and when in contact with pure acid secretion of the fundus did not release a potent inhibitory substance.

The data (the 24-hour acid output, the feeding test response, the increased response to insulin hypoglycemia, and lack of change in the histamine tests) after exclusion of the vagally innervated antrum from the Heidenhain, Pavlov, and Dragstedt pouch animals indicate that the results of exclusion are best explained by an increased liberation of vagal gastrin due to the loss of a local antrum controlling effect of an acid pH.

To study this idea, the effects of acid irrigation on controlled secretory tests were observed. If a potent inhibitory substance was lost by exclusion in the Heidenhain animal, then acid irrigation of the excluded antrum should reduce the response to stimuli. If potent acid inhibitory reflexes were lost by exclusion in the Pavlov and Dragstedt animals, then acid irrigation of the excluded antrum should reduce the response to stimuli. If a local interference by acid on the gastrin mechanism was lost by exclusion, the response to histamine should be unaltered by acid irrigation while the response to the test meal and insulin hypoglycemia should be markedly reduced. Since the latter was found, this result sup-

ports the idea that acid locally interfered with the gastrin mechanism.

However, the above interpretation does not completely differentiate the release of an acid inhibitory substance, or activation of inhibitory reflexes from the local interference on the gastrin mechanism by acidification of the antrum. It is recognized that cocaine as well as other local anesthetic agents interfere with the gastrin mechanism.¹⁶ Cocaine should not release an acid inhibitory hormone but could be expected to abolish reflex activity. If an antrum acid inhibitory substance or acid inhibitory reflexes were lost by exclusion in the pouch animals, cocaine should have little or no effect on the various tests. Further, if acid irrigation releases an inhibitory substance or activates reflexes and cocaine irrigation simply interferes with the gastrin mechanism, a significant difference between the results of acid and cocaine irrigation on the vagally innervated excluded antrum should be obtained. However, if a local interference by acid on the gastrin mechanism was lost by exclusion then the results of acid irrigation and those of cocaine irrigation should be quantitatively similar. Acid and cocaine irrigation markedly reduced the response from the four-hour test meals and the two-hour insulin tests in a quantitatively similar manner. No significant effect on the histamine tests were noted.

If it is correct that the results of exclusion of the vagally innervated antrum are due to increased vagal gastrin due to a loss of local acid interference on the gastrin mechanism, vagal denervation should reduce the response to food and insulin hypoglycemia, and have little or no effect on the histamine tests. Such was found.

The results of antrectomy when compared to those of the denervated excluded antrum showed further reduction in 24-hour output in both the Pavlov and Dragstedt pouches regardless of the method of antrum denervation. This was not noted in the denervated Heidenhain pouch, nor

consistently found during acute experiments in the Pavlov and Dragstedt pouches. It is thought that the decrease after antrectomy in 24-hour secretion was due to failure of the operations to completely vagally denervate the antrum mucosa. Apparently the denervated fundic pouches as well as acute experiments fail to readily show subtle differences in vagal gastrin. However, the failure of the operative procedures to produce complete vagal denervation is significant because it implicates the importance of the vagus nerves in producing the effects that were observed after exclusion of the vagally innervated antrum.

The effects of acid or cocaine irrigation of the vagally innervated antrum on the response to a test meal or insulin hypoglycemia were not significantly different from that of antrectomy. If the results of exclusion were due to the loss of a potent inhibitory substance or reflex, a significant difference between the effects of acid and cocaine should have been found. Vagal denervation and antrectomy should not have reduced the response to food or insulin hypoglycemia in the manner observed if an inhibitor, or reflex had been lost since this loss was common to exclusion, denervation and antrectomy. If the results of exclusion of the vagally innervated antrum were due to the loss of a local antrum controlling action of an acid pH on the gastrin mechanism, no significant difference between the effects of acid and cocaine irrigation and antrectomy would be found. Since a significant difference was not found, it is concluded that there was an increased liberation of vagal gastrin from the excluded vagally innervated antrum which was due to the loss of a local antrum controlling effect of an acid pH.

Summary

The problem of acid inhibition by the gastric antrum was studied in 27 dogs with either vagally innervated, or denervated

fundic pouches. The significance of antrum innervation was studied in its relation to humoral and/or reflex changes by comparing the results found before and after vagal denervation with those of acid or cocaine irrigation. After exclusion of the vagally innervated antrum in Heidenhain and Pavlov pouch animals, the 24-hour acid output and the response to a test meal and histamine were not significantly changed. The response to insulin hypoglycemia was increased. After exclusion in Dragstedt pouch animals, the 24-hour acid output and the response to a test meal and insulin hypoglycemia were increased. The histamine test was unchanged. Irrigation of the innervated excluded antrum with acid did not reduce the response to histamine. Acid markedly reduced the response to a test meal and insulin hypoglycemia. Irrigation with cocaine reduced the response to a test meal and insulin hypoglycemia in a manner not significantly different from acid. The results of denervation and antrectomy of the excluded antrum on the above tests did not consistently differ from those found during acid irrigation of the innervated antrum. The results of the vagally innervated excluded antrum-fundic pouch preparation can best be explained by a loss of a local controlling action of an acid pH on the gastrin mechanism, thus allowing for an increased liberation of vagal gastrin.

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