

The effect of vagotomy and pyloroplasty on the maximal acid response to histamine

ALVIN M. GELB, IVAN D. BARONOFSKY, AND HENRY D. JANOWITZ

From the Division of Gastroenterology, Departments of Medicine and of Surgery, Mount Sinai Hospital, New York, N.Y.

SYNOPSIS Pyloroplasty alone does not significantly alter the maximal acid response to histamine but it is considerably reduced in those patients who have had a vagotomy.

The role of the vagus in gastric acid secretion has become increasingly complex. A direct stimulating effect on the parietal cells of the body of the stomach and the release of gastrin from the pyloric gland area are facts which are now well established; sensitization of the antrum to local stimuli for the release of gastrin, a less well established function (Maung Pe Thein and Schofield, 1959). A role for the vagus as part of a vago-vagal reflex has recently also been postulated in the acid response of the fundus to local distention (Grossman, 1960).

In addition to these aspects, it has been known for a long time now that the responsiveness of the parietal cell to a wide variety of secretory stimuli is dependent on intactness of vagal innervation. In a considerable number of studies it has been shown that vagotomy reduces the acid response to histamine both in the dog and in man. In the published studies to date the dose of histamine studied has usually been small, and vagotomy in man has almost invariably been performed along with a gastroenterostomy for drainage.

The present study was suggested by the need to evaluate a series of patients with ulcer disease treated by vagotomy and pyloroplasty. This allowed us to study the reactivity of the intact and vagally denervated stomach without the interference of a gastroenterostomy.

To define the responsiveness of the human parietal cells somewhat more accurately, we elected to measure the 'maximal acid output to histamine' using the augmented histamine test of Kay (1953). This investigator has shown that the gastric acid output to four times the standard dose of histamine acid phosphate (0.04 mg./kg. body weight) approximates the maximum response. Card and Marks (1950) have demonstrated that the maximum acid output is a function of the number of parietal cells, although it is clearly recognized that the maximal acid output in

response to histamine does not represent the maximal acid output of which the stomach is capable.

METHOD

Twenty patients with duodenal ulcer who had been subjected to vagotomy and pyloroplasty were studied. The augmented histamine test according to the technique of Kay was performed before surgery, and again one to three weeks following surgery. Six patients were re-studied three months after operation.

Minor modifications were made in the procedure. Pyribenzamine, 100 mg. intramuscularly was used initially as the antihistamine. However, because this produced nausea in some patients, chlortrimeton, 10-20 mg. intramuscularly, was used with better results. Bromphenol blue and phenol red were used as the indicators for titration of free and total acid respectively. All anticholinergic drugs were stopped at least 12 hours before the test. Several studies were performed using a double lumen tube instead of the Levine tube. With one lumen in the duodenum and one in the stomach, we attempted to minimize the amount of gastric secretion lost into the duodenum.

To test the completeness of vagotomy, an insulin test according to the technique of Hollander (1946) was performed post-operatively in 10 patients, seven of whom had had significant reductions, and three with little or no reduction in acid response. In several patients with small reductions, lack of cooperation prevented further testing.

The data were calculated in terms of milliequivalents of free acid and total acid produced during the half-hour period from 15 to 45 minutes after histamine. The volume of parietal and non-parietal component was also calculated, according to the formula of Thompson and Vane (1953), when only acid concentration and volume of secretion are known.

RESULTS

A REPRODUCIBILITY OF AUGMENTED HISTAMINE TEST
Pre-operatively the test was repeated twice in four

patients and three times in two patients. The agreement in free acid production was within 10% except in one patient (Table I). The agreement in total acid was less marked.

II) indicate that the changes observed in the augmented histamine test were of small magnitude. Pyloroplasty and incomplete vagotomy did not affect the augmented histamine response substantially.

TABLE I

Patient No.	Acid	First Test	Second Test	Third Test ^a	Average
1	Free	12.7 ^b	12.6		12.6
	Total	21.6	16.6		19.1
2	Free	9.2	7.0		8.1
	Total	19.6	8.8		14.2
12	Free	13.9	13.6		13.8
	Total	17.0	21.8		19.4
13	Free	12.5	13.0	12.6	12.7
	Total	21.8	16.0	14.9	17.6
14	Free	10.6	11.5		11.0
	Total	20.5	14.6		17.6
20	Free	13.3	13.7	13.4	13.5
	Total	17.6	18.8	16.7	17.7

¹Values expressed as milliequivalents per 0.5 hour.

²Third test performed in tandem to second.

B PATIENTS WITH INCOMPLETE VAGOTOMY Although it was felt at the time of operation that vagotomy had been successfully performed in all patients, postoperatively three patients had a marked rise in acid concentration after the injection of 20u. of insulin intravenously. The results (Table

C PATIENTS WITH VAGOTOMY AND PYLOROPLASTY Seventeen patients are included in this group, although only seven had negative post-operative insulin tests, the proven incomplete vagotomy being reported in section B. One patient was discarded from the study. His pre-operative value of 1.8 mEq. of free acid was so low that it was felt to be due to technical errors. The results in the remaining 16 patients are presented in Table III. There was an average decrease of 7.8 mEq. of free acid produced (an average decrease of 69%). Total acid response decreased by 10.2 mEq. (an average decrease of 61%). If the seven patients in the series with proven complete vagotomy are considered separately, the decrease in free acid averaged 71% and total acid 74%.

D LATE RESULTS (THREE MONTHS) AFTER OPERATION The results in six patients studied three months after operation are given in Table IV. The average decrease in free acid was 12.2 mEq., an average reduction of

TABLE II

CHANGES IN AUGMENTED HISTAMINE TEST IN THREE PATIENTS WITH INCOMPLETE VAGOTOMY

Case No.	Free Acid (mEq./0.5 hr.)			Total Acid (mEq./0.5 hr.)		
	Pre-operatively	Post-operatively	Change	Pre-operatively	Post-operatively	Change
14	11.0	9.7	-1.3 (-12%)	17.6	12.1	-5.5 (-31%)
19	13.1	15.8	+2.7 (+21%)	16.4	19.2	+2.8 (+17%)
20	13.5	13.2	-0.3 (-2%)	17.7	16.2	-1.5 (-8%)
Average			+0.4 (+2.3%)			-1.4 (-7.3%)

TABLE III

CHANGE IN AUGMENTED HISTAMINE TEST IN PATIENTS WITH VAGOTOMY AND PYLOROPLASTY

Case No.	Free Acid (mEq./0.5 hr.)			Total Acid (mEq./0.5 hr.)			Insulin Test
	Pre-operative	Post-operative	Change	Pre-operative	Post-operative	Change	
1	12.6	2.3	-10.3 (-82%)	19.1	6.1	-15.0 (-68%)	Negative
2	8.1	0	-8.1 (-100%)	14.2	0	-14.2 (-100%)	
3	2.7	2.3	-0.4 (-15%)	3.5	5.1	+1.6 (+46%)	
4	7.6	7.0	-0.6 (-8%)	13.0	9.6	-3.4 (-26%)	Negative
6	4.9	0.1	-4.8 (-98%)	8.4	0.2	-8.2 (-97%)	Negative
7	3.8	1.4	-2.4 (-63%)	5.5	4.8	-0.7 (-14%)	
8	19.1	5.9	-13.2 (-69%)	26.0	7.9	-18.1 (-69%)	Negative
9	25.0	0	-25.0 (-100%)	32.2	0.1	-32.1 (-100%)	Negative
10	9.3	7.9	-1.4 (-14%)	12.3	9.7	-2.6 (-21%)	Negative
11	15.3	0.1	-15.2 (-99%)	21.3	0.8	-20.5 (-96%)	
12	13.8	4.8	-9.0 (-65%)	19.4	12.2	-7.2 (-37%)	
13	12.7	4.2	-8.5 (-67%)	17.6	5.5	-12.1 (-69%)	Negative
15	6.4	0.1	-6.3 (-98%)	10.8	0.4	-10.4 (-97%)	
16	9.1	0	-9.1 (-100%)	10.1	0.5	-9.6 (-95%)	
17	9.7	5.8	-3.9 (-40%)	12.3	7.2	-5.1 (-41%)	
18	5.4	0	-5.4 (-100%)	7.1	1.5	-5.6 (-79%)	
Average			-7.8 (-69%)			-10.2 (-61%)	

80%. Total acid decreased 15.3 mEq., an average reduction of 77%.

E RESULTS IN PATIENTS STUDIED WITH DOUBLE LUMEN TUBE In three patients with significant acid reduction (average 61% free and 68% total acid), gastric and duodenal contents were collected simultaneously. Two patients were studied both pre-operatively and post-operatively; one was studied post-operatively (Table V). The volume of secretion collected from the duodenum appeared to be small as compared

with the gastric volume. The pH and concentrations of acid in this collection indicated that a substantial part of this volume was derived from extragastric sources. These data support the idea that the amount of gastric secretion lost into the duodenum after pyloroplasty, although not measured precisely, was not significant.

F PARIETAL AND NON-PARIETAL COMPONENT The volume of parietal and non-parietal component in each test was calculated according to the formula of

TABLE IV

LATE CHANGES (THREE MONTHS) IN AUGMENTED HISTAMINE TEST IN PATIENTS WITH VAGOTOMY AND PYLOROPLASTY

Case No.	Free Acid (mEq./0.5 hr.)			Total Acid (mEq./0.5 hr.)		
	Pre-operative	Three Months Post-operative	Change	Pre-operative	Three Months Post-operative	Change
1	12.6	2.5	-10.1 (-80%)	19.1	4.3	-14.8 (-78%)
4	7.6	2.2	-5.4 (-44%)	13.0	5.3	-7.7 (-59%)
6	4.9	0.8	-4.1 (-83%)	8.4	3.1	-5.3 (-63%)
8	19.1	2.5	-16.6 (-87%)	26.0	3.9	-22.1 (-85%)
9	25.0	2.5	-22.5 (-90%)	32.2	4.9	-27.3 (-85%)
11	15.3	0.8	-14.5 (-95%)	21.3	1.4	-19.9 (-93%)
Average			-12.2 (-80%)			-15.3 (-77%)

TABLE V

VOLUME RECOVERED FROM TESTS USING DOUBLE LUMEN TUBE

Patient No.	Test	Gastric				Duodenal			
		Volume (ml./0.5 hr.)	pH	Acid Concentration (mEq./l.)		Volume (ml./0.5 hr.)	pH	Acid Concentration (mEq./l.)	
				Free	Total			Free	Total
8	Pre-operative	173	1	110	150	21	1	50	110
	Post-operative	77	1	77	102	25	1.5	47	80
10	Post-operative	87	1	90	110	5	5	—	—
11	Pre-operative	133	1	115	160	19	7	—	—
	Post-operative	15	3	5	54	16	7	—	—

TABLE VI

CHANGES IN PARIETAL AND NON-PARIETAL COMPONENT AFTER VAGOTOMY AND PYLOROPLASTY

Patient No.	Parietal Component (ml./0.5 hr.)			Non-parietal Component (ml./0.5 hr.)		
	Pre-operative	Post-operative	Three Months Post-operative	Pre-operative	Post-operative	Three Months Post-operative
1	132	49	32.8	61	47.5	24.2
4	104	79	36.7	81	70.4	20.3
8	153	55.3	32.6	20	21.7	25.4
9	209	28.9	37.3	29	95.1	51.7
11	133	7.2	14.5	7.2	7.8	20.5
12	126	103		0.5	96	
13	115	38.8		17	14.2	
15	81.7	4.2		48.3	5.8	
18	49.1	17.9		22.9	31.1	
2	91.2	0		21.3	9	
3	25.1	36		12.9	15	
6	59.5	2.9	24.6	25.5	5.1	19.4
7	41.4	36.2		26.6	18.8	
10	104.3	65.7		76.7	21.3	
16	66.4	21		16.6	30	
17	91	55.4		49	32.6	
Average	98.8	37.6	29.8	32.2	32.6	26.9

Thompson and Vane (1953) derived from the work of Fisher and Hunt (1950). This formula assumes that the gastric aspirate is a mixture of two components (acid and non-acid) varying in proportion, but each having a fixed composition. In the 16 patients considered to have had a complete vagotomy and pyloroplasty, the parietal secretion decreased on the average from 98.8 ml./0.5 hr. to 37.6 ml./0.5 hr. (average = 62%) (Table VI). The non-parietal component was unchanged, averaging 32.2 ml./0.5 hr. before surgery and 32.6 ml./0.5 hr. after surgery. The three patients with incomplete vagotomy had an average reduction in parietal component of 28%. In the seven patients studied three months post-operatively, parietal cell component averaged 29.8 ml./0.5 hr.

DISCUSSION

That the response of the human stomach to food, alcohol, and small doses of histamine is variable from day to day is well known. In a study of effects produced by a surgical procedure, the augmented histamine test of Kay may improve this situation somewhat. Measuring free acid, Kay reported a 5% variation between tests in intact stomachs. In the present study we found the variation between pre-operative tests done both in tandem and on separate days well within 10% in all but one patient. The reproducibility of the total acid response was not as satisfactory. In some studies using this test, however, the results have been expressed in terms of total acid, which is more variable, at least in our hands. Post-operatively, when the amounts of acid were small, the problem of collection was magnified, and small variations in total amount represented large percentage changes. Hence, the variability between tests was greater. When more than one post-operative study was done, the larger acid response was selected for calculation.

The results of the present study indicate that complete vagotomy reduced markedly the maximal acid response to histamine. This reduction was present on the first post-operative test as early as one to three weeks after vagotomy. When the test was repeated after three months, in most instances the reduction did not differ significantly from the early post-operative results.

Other investigators have been interested in the effect of vagotomy on responsiveness to histamine. Many of the earlier studies used submaximal doses of histamine and were on animals. Most recent studies have used patients with gastroenterostomy. Pyloroplasty is to be preferred because the parietal cell area is not incised. Pylorectomy, in which only a small longitudinal strip of tissue, straddling the

pyloric sphincter, is removed to provide better drainage, is also more suitable, but adds the problem of removal of some pyloric gland area.

In 1946, three reports appeared on this problem in which patients undergoing supradiaphragmatic vagotomy were studied. Moore, Chapman, Schulz, and Jones (1946) found the response to histamine was unchanged. Thornton, Storer, and Dragstedt (1946), using the same procedure with a dosage of histamine dihydrochloride of 0.1 mg./kg. body weight, found similar results. However, in the third report, Grimson, Taylor, Trent, Wilson, and Hill (1946), using 0.4 mg. histamine, found that in general the response after vagotomy was lowered, but results were variable. Stein and Meyer (1948) also reported a decreased responsiveness. Using histamine phosphate (1 mg.), they found a reduction of 72% in patients with vagotomy alone.

Oberhelman and Dragstedt (1948) used isolated dog stomachs. At a dosage of 1 mg. of histamine phosphate, the total acid decreased 62, 77, and 60% in three dogs. They also found that atropine caused a marked decrease in histamine responsiveness both before and after vagotomy. This is supported by many studies, including the work of Janowitz and Hollander (1956), who showed that in dogs receiving large enough doses of atropine, histamine stimulation is virtually completely inhibited. Oberhelman and Dragstedt also found that in man with vagotomy and no drainage procedure, using histamine phosphate 1 mg., the response was markedly reduced.

Antia and Ivy (1949) and Antia, Rosiere, Robertson, and Grossman (1951), using dogs with gastric fistula, found marked reduction with histamine dihydrochloride (0.1 mg./kg.) (average = 57%). Using histamine base (0.06 mg./kg.), the reduction ranged from 24 to 84%. In those animals studied again one year later, the reduction was 82%. They put forward the suggestion that the decreased responsiveness was due to a decrease in production of acetylcholine with loss of sensitizing or potentiating action.

Code (1953), however, could not demonstrate the reduced responsiveness to vagotomy. Using standard and maximum histamine response in dogs with both innervated and denervated pouches, he found vagotomy left 'more or less unchanged the response to histamine'.

Farmer, Howe, Porell, and Smithwick (1951) demonstrated a reduction of 42% using histamine acid phosphate (0.4 mg.) in man after vagotomy and posterior gastroenterostomy. In comparing the response to a variety of stimuli in patients undergoing either oesophagectomy, antral exclusion, both with and without vagotomy, Waddell (1958) also found a decrease in response to histamine; the dosage unfortunately was not mentioned. More

recently, using the augmented histamine test, in patients undergoing vagotomy and gastroenterostomy, Falconer (1959) reported an average reduction of 70.8%, and Gillespie, Clark, Kay, and Tankel (1960), with the same procedure, an average reduction of 79.3%. Our findings of a reduction in free acid of 69.3% and in total acid of 60.7% is consistent with the results of most investigators.

In our study results were also calculated in terms of parietal and non-parietal secretion. This method of calculation derives from the work of Fisher and Hunt (1950). Formulae have been derived on the assumption that gastric juice is of two components. In carefully performed experiments where contamination via oesophagus and duodenum was kept to a minimum, calculated values approximated very closely the observed data. Making the further assumption that both components are produced with a constant fixed composition, Thompson and Vane (1953) derived a formula requiring knowledge of only volume of secretion and concentration of acid. Using this formula, we found that the parietal component was reduced following vagotomy from 98.8 ml./0.5 hr. to 37.6 ml./0.5 hr., a reduction of 62%. Non-parietal component, which was 32.2 ml./0.5 hr. before operation, averaged 32.6 ml./0.5 hr. post-operatively. These results indicate that if histamine has any effect on the production of non-parietal component, it is not altered by vagotomy.

If at the dosage of histamine used in the augmented histamine test, all parietal cells capable of secreting acid are functioning close to the maximum, then individual variation should be related to variation in parietal cell mass. Card and Marks' study, in which they performed cell counts on tissue removed at subtotal gastrectomy and correlated this with changes in response to the augmented histamine test, indicates that this is indeed so. However, it has been shown that without altering the stomach, the response to the augmented histamine test may be changed. Gregory (1958) reported an increased response after portal vein ligation, and Clarke, Neill, and Welbourn (1960) produced an increase by prolonged administration of steroids. Clarke found an increase in the number of parietal cells in this latter study.

In the present study, it is unknown whether the decrease is due to an atrophy of some parietal cells or to a generalized reduction in secretory capacity. The finding of reduction as early as one to three weeks post-operatively suggests the latter, but is by no means conclusive. Whether this reduction is due to an effect directly on the parietal cell or possibly to an alteration in the vascular supply of the tissue is also not known. While the isolated mucosa is capable of responding to histamine *in vitro*, Thomp-

son and Vane (1953) have demonstrated that the secretory response to histamine may be correlated with blood flow in the stomach.

Other than the theoretical importance of the problem investigated in this study, there is significant clinical importance. If the ability of the stomach to respond to stimulation is so markedly reduced, the operation of vagotomy and pyloroplasty seems to offer promise. Two disturbing features, however, are seen in this study. One is that three patients out of 10 had positive insulin tests, and their responses to the augmented histamine test were unchanged from pre-operative values. The other is that not all patients had large reductions, some being much less than average.

SUMMARY

Twenty patients who underwent vagotomy with pyloroplasty were studied by the augmented histamine test pre-operatively and post-operatively. Six were studied again three months after surgery.

Pyloroplasty alone did not significantly alter the response to the augmented histamine test.

In 16 patients with vagotomy, free acid was reduced 7.8 mEq./0.5 hr., a decrease of 69%. The total acid was reduced 10.2 mEq./0.5 hr., a decrease of 61%. After three months, free acid was reduced 12.2 mEq./0.5 hr., an 80% decrease. Total acid was reduced 15.3 mEq./0.5 hr., a 77% decrease.

The parietal component was reduced from 98.8 ml. to 37.6 ml. in the post-operative period and to 29.8 ml. after three months. The non-parietal component was virtually unchanged. Some of the theoretical and clinical implications of the marked reduction in response to the augmented histamine test are discussed.

ADDENDUM

Since the submission of this report, six patients were studied again one year or more after operation. In one of these, in whom an insulin test was positive post-operatively, there was no significant change from the pre-operative values. In the five other patients, there was an average decrease in free acid of 8.4 mEq. (an average reduction of 83%). Total acid was decreased on the average 11.8 mEq. (an average reduction of 76%).

REFERENCES

- Antia, F., and Ivy, A. C. (1949). Effect of vagotomy on gastric secretion and emptying time in the dog. *Fed. Proc.*, 8, 5.
 —, Rosiere, C. E., Robertson, C., and Grossman, M. I. (1951). Effect of vagotomy on gastric secretion and emptying time in dogs. *Amer. J. Physiol.*, 166, 470-479.

- Card, W. I., and Marks, I. N. (1950). The relationship between the acid output of the stomach following 'maximal' histamine stimulation and the parietal cell mass. *Clin. Sci.*, **19**, 147-163.
- Clarke, S. D., Neill, D. W., and Welbourn, R. B. (1960). The effects of corticotrophin and corticoids on secretion from denervated gastric pouches in dogs. *Gut.*, **1**, 36-43.
- Code, C. F. (1953). Do the vagus nerves have an inhibitory influence on gastric secretion? *Fed. Proc.*, **12**, 26.
- Falconer, C. W. A. (1959). Discussion on the surgical management of chronic duodenal ulcer. *Proc. roy. Soc. Med.*, **52**, 840-842.
- Farmer, D. A., Howe, C. W., Porell, W. J., and Smithwick, R. H. (1951). The effect of various surgical procedures upon the acidity of the gastric contents of ulcer patients. *Ann. Surg.*, **134**, 319-331.
- Fisher, R. B., and Hunt, J. N. (1950). The inorganic components of gastric secretion. *J. Physiol. (Lond.)*, **111**, 138-149.
- Gillespie, I. E., Clark, D. H., Kay, A. W., and Tankel, H. I. (1960). Effect of antrectomy, vagotomy and gastrojejunostomy, and antrectomy with vagotomy on the spontaneous and maximal gastric acid output in man. *Gastroenterology*, **38**, 361-367.
- Gregory, R. A. (1958). Gastric secretory responses after portal venous ligation. *J. Physiol. (Lond.)*, **144**, 123-137.
- Grimson, K. S., Taylor, H. M., Trent, J. C., Wilson, D. A., and Hill, H. C. (1946). The effect of transthoracic vagotomy upon the functions of the stomach and upon the early clinical course of patients with peptic ulcer. *Sth. med. J. (Bgham, Ala.)*, **39**, 460-472.
- Grossman, M. I. (1960). Stimulation of acid secretion by distention of the fundic part of the stomach (abstract). *Physiologist*, **3**, 68.
- Hollander, F. (1946). The insulin test for the presence of intact nerve fibers after vagal operations for peptic ulcer. *Gastroenterology*, **7**, 607-614.
- Janowitz, H. D., and Hollander, F. (1956). Effects of atropine on histamine-stimulated gastric secretion in the dog. *Amer. J. Physiol.*, **186**, 373-376.
- Kay, A. W. (1953). Effect of large doses of histamine on gastric secretion of HCl. *Brit. med. J.*, **2**, 77-80.
- Maung Pe Thein, and Schofield, B. (1959). Release of gastrin from the pyloric antrum following vagal stimulation by sham feeding in dogs. *J. Physiol. (Lond.)*, **148**, 291-305.
- Moore, F. D., Chapman, W. P., Schulz, M. D., and Jones, C. M. (1946). Transdiaphragmatic resection of the vagus nerves for peptic ulcer. *New Engl. J. Med.*, **234**, 241-251.
- Oberhelman, H. A., Jr., and Dragstedt, L. R. (1948). Effect of vagotomy on gastric secretory response to histamine. *Proc. Soc. exp. Biol. (N. Y.)*, **67**, 336-339.
- Stein, I. F., Jr., and Meyer, K. A. (1948). Studies on vagotomy in the treatment of peptic ulcer. *Surg. Gynec. Obstet.*, **87**, 188-196.
- Thompson, J. E., and Vane, J. R. (1953). Gastric secretion induced by histamine and its relationship to the rate of blood flow. *J. Physiol. (Lond.)*, **121**, 433-444.
- Thornton, T. F., Jr., Storer, E. H., and Dragstedt, L. R. (1946). Supradiaphragmatic section of the vagus nerves. *J. Amer. med. Ass.*, **130**, 764-771.
- Waddell, W. R. (1958). Secretory function of the stomach after denervating operations. *J. appl. Physiol.*, **12**, 468-472.