16297

Effect of Vagotomy on Gastric Secretory Response to Histamine.*

HARRY A. OBERHELMAN, JR., AND LESTER R. DRAGSTEDT.
From the Department of Surgery of the University of Chicago.

During the course of routine studies on the gastric physiology of ulcer patients, it was noted that the gastric secretory response to a standard dose of histamine was decidedly less after complete gastric vagotomy than had been secured in the preoperative period. This surprising finding, which suggested that the physiological action of histamine was not solely upon the cellular elements in the gastric mucosa, prompted the present investigation. Early in the work on histamine, it was reported by Popielski[1] and by Keeton, Luckhardt, and Koch[2] that this drug could produce a gastric secretory response after section and subsequent degeneration of the vagus nerves to the stomach. Ivy and Javois[3] found that histamine would stimulate gastric secretion in a denervated gastric pouch prepared after the method of Bickel, and Klein[4] reported that a similar response could be obtained from a transplanted stomach pouch that had been deprived of its muscular layers and the myenteric plexus. These findings indicate that histamine can stimulate the peripheral neuroglandular mechanism of the stomach, or possibly the gland cell itself. Most investigators agree that histamine acts more intensely on acid producing cells than on the cells which elaborate pepsin. It has been suggested that the increased gastric secretion produced by histamine is secondary to the vaso-dilatation and increased blood supply to the mucosa produced by the drug. A central action of histamine is not indicated. The material presented in this paper includes studies both on experimental animals and man.

Experimental Data. The stomach of dogs was isolated from continuity with the alimentary tract by the method described by Dragstedt and Ellis.[5] Great care was taken not to interfere with the vagus nerve supply and blood supply to the isolated stomach. A gold-plated cannula was introduced for the collection of gastric secretions and the continuity of the alimentary tract was restored by anastomosing the lower end of the esophagus to the upper end of the duodenum. Animals prepared in this fashion were found to secrete large volumes of gastric juice daily and they were kept in electrolyte and fluid balance by the injection of large amounts of salt solution intravenously. When they had entirely recovered from the surgical procedure, which usually required approximately two weeks, they were used for the following studies. The isolated stomach preparation of this type permits the quantitative collection of the gastric secretion from the entire stomach for any desirable period of time. After a control collection of the gastric secretion, one milligram of histamine phosphate was injected subcutaneously and the gastric juice secreted in the following 75 minutes examined for volume, free hydrochloric and total acid secretion. Usually a series of 4 such tests were performed on each animal to determine the average secretory response to histamine. A transthoracic section of the vagus nerves to the stomach was then performed under ether anesthesia with a positive pressure apparatus. The completeness of the vagus section was confirmed in each case by a negative response to insulin hypoglycemia. Following recovery from the vagus section, the animals were tested with histamine exactly as before the operation. The results obtained are indicated in Table I. It is apparent that the volume

* This work has been aided by a grant from the Douglas Smith Foundation for Medical Research, University of Chicago.

1 Popielski, L., *Pflug. Arch. f. d. ges. Physiol.*, 1920, **178**, 214.

2 Keeton, R. W., Luckhardt, A. B., and Koch, F. C., *Am. J. Physiol.*, 1920, **51**, 469.

3 Ivy, A. C., and Javois, A. J., *Am. J. Physiol.*, 1924, **71**, 604.

4 Klein, E., *Arch. Surg.*, 1932, **25**, 442.

5 Dragstedt, L. R., and Ellis, J. C., *Am. J. Physiol.*, 1930, **93**, 407.

TABLE I.
Effect of Vagotomy on Gastric Secretory Response to Histamine in Total Pouch Dogs.

	Gastric juice secreted in 75 min. after the subcutaneous injection of 1 mg of histamine phosphate				
	Before vagotomy		After vagotomy		
Dog No.	Vol., cc	Total HCl output m. eq.	Vol., cc	Total HCl output m. eq.	Decrease, %
865	162		81		50
		20.7		7.9	62
875	139		45		67
		17.8		4.1	77
898	78		44		44
		8.72		3.42	60

Note: These data present the average of at least 4 tests on each dog.

TABLE II.
Effect of Atropine on Gastric Secretory Response to Histamine Before and After Vagotomy in Total Pouch Dogs.

		Before vagotomy		After vagotomy	
Dog No.	Stimulus	Vol., cc	HCl output, m. eq.	Vol., cc	HCl output, m. eq.
865	1 mg histamine	162	20.7	81	7.9
	2 mg atropine, 30 min. later 1 mg histamine	20	1.4	17	1.2
875	1 mg histamine	139	17.8	45	4.1
	2 mg atropine, 30 min. later 1 mg histamine	24	2.1	19	1.4

Note: These data present the average of at least 2 tests before and after atropine administration in each dog.

of gastric juice secreted in response to the subcutaneous injection of a standard dose of histamine was decreased by 50, 67, and 44% respectively, by complete division of the vagus nerves to the stomach. The total hydrochloric acid output in the gastric juice in response to histamine was diminished after vagotomy by 62, 77, and 60% respectively, as compared with preoperative values. Similar results were obtained in 2 additional animals prepared in the same way. In 2 of the animals, the effect of atropine on the secretion of gastric juice produced by the subcutaneous injection of histamine was determined both before and after section of the vagus nerves to the stomach. The results are indicated in Table II. One milligram of histamine phosphate was injected subcutaneously and the gastric secretion collected for a period of 75 minutes. Two milligrams of atropine sulphate were then given subcutaneously, and 30 minutes later, a second subcutaneous injection of one milligram of histamine phosphate was made. Following the administration of the atropine, the volume of gastric juice secreted in response to the injection of the standard dose of histamine was reduced in the one case by 88, and in the other by 82%. Likewise, the total acid output decreased 93 and 88% respectively. It is interesting that following vagotomy, atropine exerted as great an inhibition to the gastric secretory response to histamine as before vagus section.

Clinical Studies. The studies on man were carried out on 2 groups of patients. The first comprised 15 patients with peptic ulcer who were treated by transthoracic section of the vagus nerves to the stomach at the Albert Merritt Billings Hospital, while the second group included 18 ulcer patients who underwent transabdominal gastric vagotomy at the Illinois State Penitentiary at Stateville. None of the patients in either group had an associated gastroenterostomy. In the first group, the observations were made as follows: Continuous aspiration of the gastric content was made during the night by means of an indwell-

TABLE III.
Effect of Vagotomy on Gastric Secretory Response to Histamine in Patients with Peptic Ulcer.

	Pre-vagotomy		Post-vagotomy			
Patient	Vol., cc	Total acid output, m. eq.	Vol., cc	Total acid output, m. eq.	Reduction in vol., %	Reduction in acid output, %
No. 24	168	10.1	103	5.9	39	41
68	170	10.9	101	2.0	41	81
73	272	28.9	200	11.2	26	61
71	198	19.0	203	12.8	—3	33
74	338	40.6	151	13.6	56	66
17	292	18.8	95	6.5	67	65
22	164	11.6	84	2.7	49	76
23	194	10.3	109	5.2	44	49
24	168	11.0	186	5.5	—1	50
26	353	39.8	131	5.5	63	86
27	192	21.8	130	12.8	32	41
31	143	4.8	68	2.6	53	46
32	63	2.6	45	.8	30	69
34	243	25.6	43	2.5	82	90
35	81	4.0	52	1.1	36	72
Avg	203	17.3	113	6.1	41	62

Note: One mg of histamine phosphate was given subcutaneously in the fasting state and the gastric content removed by continuous suction for 60 minutes.

TABLE IV.
Effect of Vagotomy on Gastric Secretory Response to Histamine in Male Prisoners with Peptic Ulcer.

	Pre-vagotomy		Post-vagotomy			
Patient	Vol., cc	Total acid output, m. eq.	Vol., cc	Total acid output, m. eq.	Reduction in vol., %	Reduction in acid output, %
No. 10	176	22.2	154	16.8	13	24
4	267	28.8	124	11.9	53	59
11	315	42.5	98	3.7	68	91
8	274	30.7	32	3.0	88	90
9	262	31.4	84	4.7	67	85
5	315	27.1	162	15.1	48	44
14	200	20.6	84	3.1	58	85
13	290	33.3	13	.2	95	99
15	210	26.0	180	17.1	14	34
19	232	24.1	28	.4	88	97
22	350	41.6	88	1.8	75	95
21	286	28.6	80	.2	72	99
25	118	8.1	94	6.3	12	22
28	142	13.4	180	9.7	—21	29
26	210	25.6	40	.7	81	97
24	166	15.8	58	1.2	65	92
30	308	40.9	88	1.9	71	95
23	238	25.9	94	.5	60	97
Avg	242	27.0	94	5.5	56	74

ing gastric tube and the Wangensteen suction apparatus. In the morning, one milligram of histamine phosphate was injected subcutaneously and the gastric content aspirated at 10-minute intervals. Similar tests were made from 7 to 10 days after the gastric vagotomy. The volume of gastric juice secreted during a period of 60 minutes was measured and its free acid concentration determined. From these figures, the total acid output was calculated for each test. In the second group of patients studied at the Illinois State Peniten-

tiary, the tests were performed in a similar manner, except that the gastric content was collected by continuous Wangensteen suction for a period of 60 minutes after the subcutaneous injection of the standard dose of histamine. The postoperative tests were performed from 3 to 6 weeks following the gastric vagotomy when the patients had entirely recovered from the operation. The effect of gastric vagotomy on the secretory response to histamine in the 15 ulcer patients studied at the University of Chicago Clinics is illustrated in Table III. In this series of patients, the vagotomy produced a decrease of 41% in the volume of gastric juice secreted in response to the histamine injection and a decrease of 62% in the total amount of hydrochloric acid produced. The free acid concentration for the 15 tests decreased from an average of 93 clinical units to 67 following the vagus section. Table IV illustrates the results secured in the 18 patients with peptic ulcer studied at the Illinois State Penitentiary. In these patients, the average volume of gastric juice secreted in response to a standard dose of histamine decreased 56%, and the total acid output 74% after the vagotomy. The average free acid concentration of the histamine stimulated gastric juice averaged 110 clinical units before vagotomy and 48 clinical units after the operation.

Conclusions. 1. The gastric secretory response to a standard dose of histamine in dogs with a totally isolated stomach pouch is markedly reduced by bilateral vagotomy.

2. Atropine similarly reduces the gastric secretory response to histamine in these animals.

3. Gastric vagotomy in patients with peptic ulcer also markedly reduces the gastric secretory response to a standard dose of histamine.

16298 P

Effect of Bile Preparations on Fat Absorption in Bile Fistula Dogs.*

J. R. HEERSMA AND J. H. ANNEGERS. (Introduced by J. S. Gray.)

From the Department of Physiology, Northwestern University Medical School, Chicago, Ill.

That bile is concerned in the absorption of dietary fat has been qualitatively established by the observation of steatorrhea in animals[1] and in man[2] when bile fails to reach the intestine. The effectiveness of human whole bile in correcting this absorptive defect has been shown in only 2 patients,[3] and bile acid preparations have not been tested directly in man or experimental animals. Inconclusive and contradictory results from studies of blood fat after a fatty meal,[4] absorption from isolated intestinal loops,[5,6] and *in vitro* diffusion[7] or solubilization[8] constitute the basis for the belief that bile acids are essential for fat absorption, and that

* Supported in part by a grant from G. D. Searle and Company.

1 Coffey, R. J., Mann, F. C., and Bollman, J. L. *Am. J. Dig. Dis.*, 1940, **7**, 143; Sperry, W. M., *J. Biol. Chem.*, 1930, **85**, 455.

2 Hutchinson, H. S., and Fleming, G. B., *Glasgow Med. J.*, 1920, **94**, 65; Thaysen, T. E., *Acta Med. Scand.*, Supplement, 1926, **16**, 384.

3 Shapiro, A., Koster, H., Rittenberg, D., and Shoenheimer, R., *Am. J. Physiol.*, 1936, **117**, 525.

4 Crandall, L. A., and Ivy, H. B., *Am. J. Physiol.*, 1940, **129**, 341.

5 Plant, O. H., *Am. J. Physiol.*, 1908, **23**, 65; Riegel, C., O'Shea, E. K., and Ravdin, I. S., *Am. J. Physiol.*, 1935, **112**, 669; Doubilet, H., and Reiner, M., *Arch. Int. Med.*, 1937, **59**, 857.

6 Virtue, R. W., and Doster-Virtue, *Am. J. Physiol.*, 1942, **135**, 776.

7 Verzar, F., and Kuthy, A., *Biochem. Z.*, 1929, **210**, 265; Breusch, F. L., *Biochem. Z.*, 1937, **293**, 280.

8 McBain, J. W., Merrill, R. C., and Vinograd, J. R., *Am. Chem. Soc. J.*, 1941, **63**, 670; Mellander, O., and Stenhagen, E., *Acta Physiol. Scand.*, 1942, **4**, 349.