

# The gastric secretion of pepsin in man

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**EDITORIAL SYNOPSIS** The spontaneous output of pepsin was not found to be significantly reduced in this study of patients who had had a vagotomy.

The control of gastric pepsin secretion continues to excite controversy. The diversity in the results obtained by different investigators may be due, at least in part, to the varying techniques employed to estimate pepsin activity. Thus, edestin (Polland and Bloomfield, 1929), gelatin (Gilman and Cowgill, 1930), egg albumen (Vineberg and Babkin, 1931), beef haemoglobin (Anson and Mirsky, 1932), and human plasma (Hunt, 1948) have each been used as substrates; again, the time of digestion, pH, temperature, and the actual parameters of proteolytic activity have been diverse.

There is widespread acceptance of the view that vagal stimulation evokes the secretion of acid gastric juice rich in pepsin. In dogs with innervated gastric pouches, this has been demonstrated by direct stimulation of the vagus nerves in the neck (Browne and Vineberg, 1932; Vineberg, 1933); in man, insulin-induced hypoglycaemia has been used to effect central excitation of the vagus nerves which in turn stimulated a gastric acid and pepsin secretory response (Ihre, 1938; Chinn, Book, and Beams, 1951; Janowitz and Hollander, 1952; Harrower, Brook, and Cooper, 1956). In contrast to our increasing knowledge of the effect of surgical vagotomy on acid secretion by the stomach little is known of its effect on spontaneous pepsin secretion. The results of such a study are reported in the first part of this paper.

While histamine is known to be a very potent stimulus of acid gastric secretion, debate continues regarding its effect on the secretion of pepsin. In dogs, Gilman and Cowgill (1930), and Vineberg and Babkin (1931) found that histamine failed to stimulate pepsin secretion; by contrast Bucher and Ivy (1941) concluded from their experiments using repeated doses of histamine that pepsin secretion was slightly increased. In man, Toby (1937) and Ihre (1938) using small doses of histamine concluded that the drug was without a stimulant effect on pepsin cells. On the other hand, Ashford, Heller, and

Smart (1949) and Hunt (1960), using slightly larger doses, found histamine to increase pepsin output, Hunt demonstrating a correlation with the acid response.

Most observers, finding an increased output of pepsin following histamine stimulation, have attributed this to a 'wash out' of preformed pepsin by the copious flow of watery acid juice (Polland and Bloomfield, 1929; Toby, 1937; Bucher, Grosman, and Ivy, 1945). In the second part of this paper we report the results of a study in which the output of pepsin has been estimated following the administration of histamine in the dosage known to elicit a maximal acid secretory response.

## METHODS

All patients in this study were men with proven duodenal ulcer who had been admitted to hospital for surgical treatment by vagotomy with gastrojejunostomy. Routine augmented histamine tests (Kay, 1953) were performed before and after operation. In this test total aspirates of gastric secretion are measured every 15 minutes. Four successive 15-minute aspirates are taken to represent one hour's spontaneous secretion, and the maximal acid secretory capacity is based on the sum of the second and third post-histamine 15-minute aspirates. In the present study, in order to compare outputs of similar time intervals, samples from two 15-minute aspirates of basal secretion and from the two specimens constituting the 30-minute period of maximal histamine stimulation were taken for the estimation of pepsin concentration by Hunt's modification of Mirsky's technique (Hunt, 1950). This test measures the amount of proteolytic digestion of human plasma at pH 2.1 effected by the aliquot of gastric juice in a 15-minute period, and thus gives a measure of active pepsin.

## RESULTS

**EFFECT OF VAGOTOMY ON SPONTANEOUS PEPSIN SECRETION** The volumes, HCl, and pepsin outputs before and after surgical division of the vagus nerves

TABLE I  
EFFECT OF VAGOTOMY ON SPONTANEOUS PEPSIN SECRETION

Patient	30-Minute Outputs			30-Minute Outputs		
	Intact Stomach			After Vagotomy		
	Volume (ml.)	HCl (mEq.)	Pepsin (Hunt units)	Volume (ml.)	HCl (mEq.)	Pepsin (Hunt units)
1	63	3.5	700	26	0.5	990
2	37	2.8	152	83	1.4	1,158
3	57	1.4	1,702	94	3.1	3,103
4	35	0.8	3,612	16	0	106
5	29	0.5	2,932	87	1.6	2,873
6	27	1.8	2,581	42	0	98
7	148	2.4	11,250	35	0	0
8	34	1.9	1,738	115	1.2	2,032
9	49	2.5	4,160	185	0	0
10	46	2.5	4,154	50	2.3	2,925
11	44	0.5	3,190	36	0.6	2,059
12	80	4.9	7,320	12	0	368
13	50	1.1	3,790	35	0.3	659
14	40	3.8	2,040	15	0.7	340
15	52	4.5	2,561	65	2.8	5,207
16	67	2.7	2,656	15	0	0
17	44	2.2	3,898	40	0.9	3,321
18	26	1.3	692	40	0.6	580
19	35	1.5	1,655	67	1.8	948
20	48	1.7	1,237	48	2.0	1,279
Means	51	2.2	3,101	55	1.0	1,402

Statistical analyses of differences between means: Volume, N.S.; HCl,  $P = < 0.01$ ; Pepsin,  $P = < 0.05 > 0.02$

are given in detail (Table I). The reduction in pepsin output, from a mean of 3,101 Hunt units to 1,402 Hunt units, is of only borderline significance ( $t = 2.4250$ ;  $P < 0.05 > 0.02$ ) whereas the reduction in HCl output from a mean of 2.2 mEq. to a mean of 1.0 mEq. is significant ( $t = 3.5143$ ;  $P < 0.01$ ). It is noteworthy that there was an increase in the volume of the aspirates after operation, though statistical analysis showed this to be without significance. A similar finding was previously reported in a study of patients having simple gastrojejunostomy and shown to be due to regurgitation of jejunal contents (Tankel, Gillespie, Clark, Kay, and McArthur, 1960).

The enzyme determination used in this study provides a measure of active pepsin alone. Low pepsin concentration will be found in samples of gastric juice with a pH greater than 3.5 (Bucher and Ivy, 1941). Hunt (1960) has suggested that pepsin values in samples of HCl concentration less than 10 mEq./l. are unacceptable. In the present investigation the HCl concentration of all pre-operative specimens was greater than 10 mEq./l.; post-operatively, the HCl concentration was less than this level in seven patients (Nos. 4, 6, 7, 9, 12, 13, and 16). The acceptable results in the remaining 13 patients are given in Table II. The mean pepsin output in this reduced series of 13 is virtually unaffected by vagotomy (2,050 Hunt units before operation, and 2,063 Hunt units after operation).

TABLE II  
EFFECT OF VAGOTOMY ON SPONTANEOUS PEPSIN SECRETION<sup>1</sup>

Patient	Intact Stomach	After Vagotomy
	Pepsin (Hunt units)	Pepsin (Hunt units)
1	700	990
2	152	1,158
3	1,702	3,103
5	2,932	2,873
8	1,738	2,032
10	4,154	2,925
11	3,190	2,059
14	2,040	340
15	2,561	5,207
17	3,898	3,321
18	692	580
19	1,655	948
20	1,237	1,279
Means	2,050	2,063

<sup>1</sup>Patients with HCl concentration  $< 10$  mEq./l. are excluded.

EFFECT OF AUGMENTED HISTAMINE TEST ON PEPSIN SECRETION IN INTACT STOMACH The HCl concentration for both spontaneous and post-histamine specimens was greater than 10 mEq./l. in all cases, and, consequently, the pepsin results for the entire series of 20 patients are acceptable for analysis (Table III). Following the administration of histamine, the mean output of pepsin increased from 3,101 Hunt units to 10,602 Hunt units, and the mean HCl output increased from 2.2 mEq. to 21.2 mEq.

TABLE III  
EFFECT OF AUGMENTED HISTAMINE TEST ON PEPSIN SECRETION IN INTACT STOMACH

Patient	30-minute Outputs			Augmented Histamine Response		
	Spontaneous			Augmented Histamine Response		
	Volume (ml.)	HCl (mEq.)	Pepsin (Hunt units)	Volume (ml.)	HCl (mEq.)	Pepsin (Hunt units)
1	63	3.5	700	180	20.0	1,617
2	37	2.8	152	193	22.1	1,737
3	57	1.4	1,702	146	16.1	4,657
4	35	0.8	3,612	121	12.9	13,855
5	29	0.5	2,932	193	12.7	21,097
6	27	1.8	2,581	150	19.8	14,658
7	148	2.4	11,250	210	10.2	17,784
8	34	1.9	1,738	168	22.5	5,982
9	49	2.5	4,160	158	17.8	10,565
10	46	2.5	4,154	230	20.7	10,143
11	44	0.5	3,190	220	27.6	16,258
12	80	4.0	7,320	280	38.3	19,721
13	50	1.1	3,790	290	34.0	16,256
14	40	3.8	2,040	220	31.1	8,139
15	52	4.5	2,561	170	22.2	8,356
16	67	2.7	2,656	160	12.5	4,829
17	44	2.2	3,898	160	16.1	15,596
18	26	1.3	692	180	20.2	3,600
19	35	1.5	1,655	163	21.1	8,101
20	48	1.7	1,237	258	26.3	9,092
Means	51	2.2	3,101	193	21.2	10,602

Statistical analyses of differences between means: Volume,  $P = <0.01$ ; HCl,  $P = <0.01$ ; Pepsin,  $P = <0.01$

The volume increase, from a mean of 51 ml. to 193 ml., was of the same order as the rise in pepsin output indicating that the pepsin concentration was virtually unaltered. An increase in pepsin output solely due to 'wash out' by acid would have been accompanied by a decrease in pepsin concentration.

EFFECT OF AUGMENTED HISTAMINE TEST ON PEPSIN SECRETION AFTER VAGOTOMY Adopting the same criteria regarding HCl concentration of the post-operative specimens, the data for 13 patients are acceptable for analysis and are given in Table IV. The augmented histamine test resulted in an increase

TABLE IV  
EFFECT OF AUGMENTED HISTAMINE TEST ON PEPSIN SECRETION AFTER VAGOTOMY<sup>1</sup>

Patient	30-minute Outputs			Augmented Histamine Response		
	Spontaneous			Augmented Histamine Response		
	Volume (ml.)	HCl (mEq.)	Pepsin (Hunt units)	Volume (ml.)	HCl (mEq.)	Pepsin (Hunt units)
1	26	0.5	990	144	11.0	9,360
2	83	1.4	1,158	189	12.6	3,135
3	94	3.1	2,103	165	12.5	5,546
5	89	1.6	2,873	165	7.9	7,350
8	115	1.2	2,032	131	11.8	4,294
10	50	2.3	2,925	115	9.4	9,804
11	36	0.6	2,059	147	11.3	9,379
14	15	0.7	340	155	18.0	4,096
15	65	2.8	5,207	102	9.4	9,723
17	40	0.9	3,321	78	11.3	7,596
18	40	0.6	580	148	9.2	3,465
19	67	1.8	948	95	6.0	2,484
20	48	2.0	1,279	139	16.7	6,053
Means	59	1.5	2,063	136	11.4	6,330

Statistical analyses of differences between means: Volume,  $P = <0.01$ ; HCl,  $P = <0.01$ ; Pepsin,  $P = <0.01$

<sup>1</sup>Excluding those with HCl concentration  $< 10$  mEq./litre.

in the mean pepsin output from 2,063 Hunt units to 6,330 Hunt units, and in the mean HCl output from 1.5 mEq. to 11.4 mEq. The volume increase, from a mean of 59 ml. to 136 ml., is less marked than pre-operatively, indicating that the increase in pepsin output was accompanied by an increase in the concentration of pepsin. This finding is again counter to the hypothesis of 'wash out' of preformed pepsin by acid.

#### DISCUSSION

Three features of these results require discussion: first, the apparent failure of vagotomy to reduce the spontaneous secretion of pepsin; secondly, the increase in pepsin output in response to the augmented histamine dosage; thirdly, the finding that, while the outputs of both acid and pepsin to the augmented histamine test are reduced by vagotomy, the percentage by which each exceeds the basal level is unaltered.

Although the present study has not provided clear evidence of any alteration in the mechanism of spontaneous pepsin secretion following vagotomy, it would appear from the overall result in Table I that peptic activity in the stomach is reduced after the operation. Whether brought about by decreased production of the enzyme or simply as a result of intragastric change in pH, the reduced digestive activity is of obvious clinical importance.

It could be argued that vagal section has been less complete in the 13 patients included in Table II than in the seven excluded patients, since the latter group had a greater reduction in acid production. Post-operative insulin tests were not done, but a satisfactory agreement existed between the results of pre-operative 'medical vagotomy' tests and the results of post-operative augmented histamine tests in all 20 patients (Gillespie and Kay, 1961); the 13 patients (Table II) and the seven excluded patients showed similar correlation between the reductions in acid secretion effected by 'medical' and by surgical vagotomy. This indicates that the same completeness of vagotomy had been achieved in the two groups. Thus the 13 patients of Table II would seem to be representative of the entire series of 20.

Our results show that vagotomy did not alter the spontaneous secretion of pepsin in the 13 patients with post-operative HCl concentration sufficiently high to give reliable pepsin recovery. However, as we do not know the change in pepsin production in the remaining seven patients a firm conclusion cannot be drawn. Vagotomy inevitably reduces the production of hydrochloric acid and it would seem that some modification of technique, devised to avoid alkaline inactivation of pepsin, will be required in

order to determine the true secretion of pepsin after vagotomy. Animal experiments involving the use of acid buffer installations into the stomach (Linde, Teorell, and Öbrink, 1947) have been planned.

In the intact stomach, the augmented histamine test produced a three-fold increase in pepsin output from a mean of 3,101 Hunt units spontaneously to 10,602 Hunt units after histamine. It is noteworthy that earlier workers, using small doses of histamine (Toby, 1937; Ihre, 1938), failed to elicit a pepsin response. Our results are in agreement with those of Hirschowitz, London, and Pollard (1957) who, using larger, though submaximal histamine dosage, observed a similar three-fold increase in pepsin output. In the present study this increase in pepsin output in response to the augmented histamine test was accompanied by a ten-fold increase in HCl output from a mean of 2.2 mEq. spontaneously to 21.2 mEq. after histamine, indicating that our histamine stimulation of pepsin secretion was about one third that of HCl secretion. Two possible explanations for this difference are being studied: first, that the dose of histamine employed, while causing the maximal output of HCl, may be submaximal for pepsin; secondly, that peak responses of pepsin and HCl occur at different time intervals after the histamine injection.

Comparison of Tables III and IV shows that the pepsin response to the augmented histamine test was reduced by vagotomy in all but four patients (Nos. 1, 2, 3, and 15). The proportionate reduction from a mean of 10,602 Hunt units (Table III) to a mean of 6,330 Hunt units (Table IV) is only slightly less than the proportionate reduction in HCl output after vagotomy reported in a larger series (Gillespie and Kay, 1961).

For reasons already discussed under 'results', the post-operative results are from a smaller number of patients than the pre-operative ones. Nevertheless, it is apparent that the increase in pepsin output over spontaneous levels produced by histamine in the post-vagotomy tests is again approximately three-fold (from a mean of 2,063 Hunt units to a mean of 6,330 Hunt units). Similarly, after vagotomy the increase in HCl output over spontaneous levels following the histamine injection (from a mean of 1.5 mEq. to a mean of 11.4 mEq.) is of the same order as the pre-operative increase (from a mean of 2.2 mEq. to a mean of 21.2 mEq.). Thus, both before and after vagotomy, the pepsin response to the augmented histamine test appears to be approximately one third that of the HCl response. This similarity of the increments for both pepsin and HCl in response to histamine stimulation in the intact stomach and also after vagotomy suggests that the responsiveness of the chief cells and of the

parietal cells is under vagal control. Recent work by Payne and Kay (1962) provides evidence that after vagotomy acetylcholine restores the HCl response to histamine to pre-operative levels, and it seems likely that this permissive cholinergic mechanism is also required by peptic cells to respond fully to histamine.

We wish to express our thanks to Professor A. W. Kay for much valuable help and advice in the course of this work.

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