

PEPSIN SECRETION, GASTRIC MOTILITY AND MUCOSAL BLOOD FLOW IN THE ANAESTHETIZED CAT

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SUMMARY

1. There is a weak relationship between pepsin output and gastric mucosal blood flow (MBF) during vagal stimulation. When compared with the strong relationship between H^+ output and MBF, this suggests little dependence of pepsin secretion on MBF.

2. Gastric MBF per unit H^+ output was significantly greater during vagal stimulation, when H^+ secretion was accompanied by pepsin secretion, than during pentapeptide stimulation when no pepsin was secreted.

3. Pepsin output was not reduced during splanchnic stimulation whereas MBF and acid output were, when blood pressure was kept constant.

4. Splanchnic stimulation did not produce any pepsin secretion.

5. Gastric motor responses to vagal stimulation and to I.A. injections of acetylcholine were equally reduced by splanchnic stimulation.

INTRODUCTION

In the past 5 years information has accumulated showing a well-defined relationship between acid secretion and gastric mucosal blood flow. Most of this evidence has resulted from the application of the amidopyrine clearance technique, first described by Shore, Brodie & Hogben (1957). As evidence, obtained in various animal preparations and under various secretory conditions has increased, so the amidopyrine technique has gained credence. Other techniques, largely radioisotope clearance techniques and some direct measurements of total blood flow, have not contradicted results so obtained.

However, the relationship of mucosal blood flow with gastric secretion has so far been restricted to investigation of concomitant acid secretion. This study was carried out to investigate the relationship between pepsin secretion and mucosal blood flow.

METHODS

All the cats used were starved for 36 hr before the experiment although allowed water. Anaesthesia was induced with ether, maintained by a single i.v. injection of chloralose (80 mg/kg body wt.), and a glass cannula was inserted into the trachea. An indwelling cannula was placed in the right saphenous vein. A nylon catheter with the tip directed towards the heart was inserted into a carotid artery in the neck to allow monitoring of arterial blood pressure by a mercury manometer and collection of arterial blood samples. Both vagus nerves were sectioned in the neck.

The stomach was exposed through a mid line incision and the pylorus occluded with a tape ligature. A wide-bore rubber catheter (i.d. 8 mm) was inserted through an incision in the cervical portion of the oesophagus, passed into the stomach and secured so that the tip lay in the pyloric antrum.

The eighth rib on the right side was removed in a number of animals and through this incision the dorsal and ventral vagal trunks were dissected free, sectioned and small insulated ring electrodes placed on the distal ends. Respiration in these animals was maintained by a Starling Ideal pump. In all animals the splanchnic nerves were cut extraperitoneally on both sides through incisions in the flanks and ring electrodes placed on the distal ends of the cut nerves.

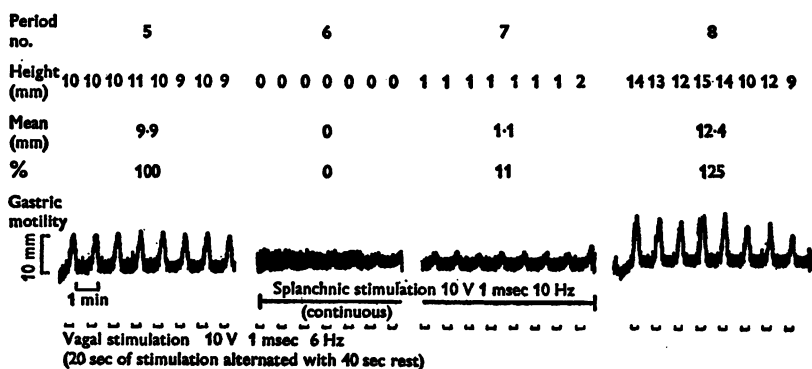


Fig. 1. Gastric motility responses to repeated vagal stimulation and simultaneous vagal and splanchnic stimulation.

An hour was allowed between completion of surgical procedures and the beginning of each experiment. During this time a priming dose of amidopyrine, 30 mg/kg body wt., was given i.v. followed by an infusion of 10 mg/kg.hr thereafter. Routinely 50 ml. of a 1/5 v/v mixture of isosmolar glycine and mannitol, adjusted to pH 3.5 by addition of 0.15 N-HCl, were placed in the stomach at the beginning of each 10 min collection period, drained between 9.5 and 10 min and replaced by a further 50 ml. Acid content was determined by electrometric titration of a 25 ml. sample to pH 7.0 using 0.02 N-NaOH and a pH meter with glass electrode system. Samples of each 10 min mixture of washout fluid and gastric juice were stored for measurement of mucosal blood flow. Arterial blood samples were collected every 20 min throughout experiments, centrifuged, 1 ml. plasma stored for amidopyrine extraction and the R.B.C.s returned to the animal via the indwelling cannula. Gastric mucosal blood flow was measured by the amidopyrine technique described for use in the anaesthetized cat by Harper, Reed & Smy (1968).

The pepsin activity of collected samples was estimated by the method of Hunt (1948) and expressed as Hunt units. Gastric motility was recorded by connecting the oesophageal tube to a volume recorder writing on a kymograph, or a Statham pressure transducer and pen recorder. The responses were calculated as the mean height of the contractions in each period (Fig. 1). In three animals a narrow-bore nylon catheter was inserted into the hepatic artery and passed retrogradely so that its tip lay close to the junction with the coeliac axis. Through this injections of 2 or 5 μg acetylcholine were given.

Gastric activity was stimulated either by electrical stimulation of the vagal trunks (10 V, pulse duration 1 msec, 6 Hz, 20 sec of stimulation being alternated with 40 sec of rest) or by i.v. infusion of pentapeptide (Peptavlon I.C.I. 50123) 1 $\mu\text{g}/10$ min. In the test experiments the splanchnic nerves were continuously stimulated (10 V, pulse duration 1 msec, 10 Hz) for two consecutive 10 min collection periods. A 5 l. air reservoir, with a small compartment containing 5 ml. heparinized saline, was connected to the lower aorta of fifteen animals in which the splanchnic nerves were stimulated. The pressure in the reservoir was adjusted to that recorded in the carotid artery prior to splanchnic stimulation. After stimulation and when blood in the reservoir had returned to the animal, the reservoir was closed to the circulation.

In all experiments three successive collection periods were carried out before stimulation to measure the basal levels of acid and pepsin output and mucosal blood flow. Acid output was measured as H^+ , $\mu\text{-equiv}/10$ min, and expressed as the increase in H^+ output (ΔH^+) above the basal level of H^+ secretion. Similarly mucosal blood flow (MBF) was measured as ml./10 min and expressed as the increase in mucosal blood flow (ΔMBF) above basal MBF. Pepsin was expressed as the increase above basal secretion (Δpepsin).

In the test experiment the splanchnic nerves were stimulated for two consecutive 10 min periods between the 6th and the 11th periods of vagal or pentapeptide stimulation. These experiments were randomly paired with appropriate control experiments. The individual pepsin responses in each experiment were calculated either as % of the observed value in the period before splanchnic stimulation (reference period) or in the case of control experiments as % of the Δpepsin observed in the equivalent stimulation period. The % ΔMBF , % ΔH^+ and % motility responses were calculated similarly.

The ratio $\Delta\text{MBF}/\Delta\text{H}^+$ represents the increase in mucosal blood flow (ml./ $\mu\text{-equiv}$ of increased H^+ output). Data were analysed for correlation (r), slope of regression (m) and significance of difference between means. Results are expressed as the mean ± 1 s.e. (N = number of observations). The mucosal blood flow and acid output results obtained in a number of these experiments during vagal and pentapeptide stimulation, and the effects of splanchnic stimulation on these variables have been published elsewhere (Reed, Sanders & Thorpe, 1971).

RESULTS

Vagal stimulation

In 6 experiments the patterns of pepsin secretion and gastric motility, together with acid secretion and mucosal blood flow, were measured before and during prolonged vagal stimulation for 160 min (Fig. 2). The % Δpepsin , % ΔH^+ , and % ΔMBF responses showed a gradual rise up to the seventh 10 min stimulation period. Thereafter the % ΔMBF and % ΔH^+ responses showed no significant decline or rise, whereas % Δpepsin progressively

decreased to 50 % of that observed during the reference period (Table 1B). In contrast to these patterns, motility responses were greatest during the first 10 min period of stimulation and subsequently declined throughout the experiment at a significant rate of 3.2 % of the mean/10 min ($m = -3.57$, $r = -0.3101$, $P < 0.01$, $N = 96$). The mean absolute values for Δ pepsin, Δ MBF and Δ H⁺ during the reference periods in these experiments were 1434 ± 320 Hunt units, 51.5 ± 12.9 ml. and 261.7 ± 59.4 μ -equiv/10 min respectively.

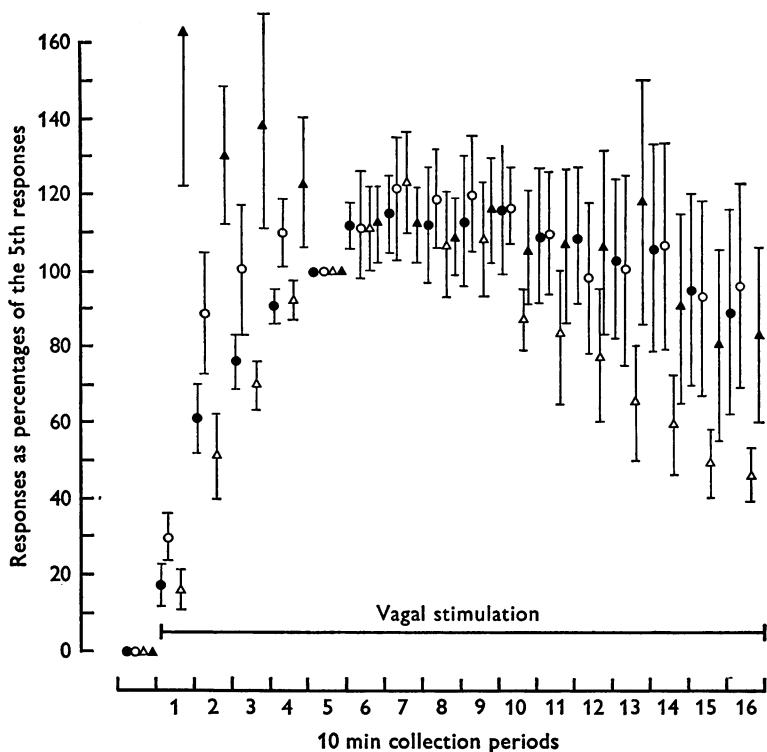


Fig. 2. The increased responses above basal levels of mucosal blood flow (○), H⁺ (●), pepsin (△) and gastric motility (▲) during electrical stimulation of the vagus trunks in the thorax (10 V, 1 msec, 6 Hz, 20 sec stimulation alternated with 40 sec rest). The responses are expressed as % of the appropriate responses occurring during the 5th period of vagal stimulation and shown as means \pm 1 s.e. of observations in six cats.

During the first 70 min of stimulation Δ pepsin, Δ MBF and Δ H⁺ responses and the % responses were all significantly correlated with time ($P < 0.01$ in each case, Table 1A). Between 70 min and 160 min of stimulation Δ MBF and % Δ MBF, and Δ H⁺ and % Δ H⁺, were not significantly correlated with time ($P > 0.1$ in each case) whereas Δ pepsin and % Δ pepsin showed negative correlations with time ($P < 0.001$,

TABLE 1. Relationships between Δ MBF, Δ H⁺ output, Δ pepsin output and time (in 10 min periods) during prolonged vagal stimulation. The responses are calculated as the Δ MBF, ml.; the Δ H⁺, μ -equiv; and Δ pepsin, Hunt units/10 min (the absolute responses) and as the % responses. Data are split into two groups, period 1-7 of vagal stimulation (A) and periods 8-16 (B) of vagal stimulation

	A. Periods 1-7 (0-70 min)		B. Periods 8-16 (70-160 min)	
	Absolute responses	% responses	Absolute responses	% responses
Δ mucosal blood flow (ml.)				
<i>r</i>	0.4387	0.5832	-0.1753	-0.1851
<i>m</i>	5.891	11.49	-1.7911	-3.40
<i>P</i>	< 0.01	< 0.001	> 0.1	> 0.1
Δ H ⁺ output (μ -equiv)				
<i>r</i>	0.7144	0.8494	-0.1723	-0.1558
<i>m</i>	38.89	14.88	-7.4778	-2.872
<i>P</i>	< 0.001	< 0.001	> 0.1	> 0.1
Δ pepsin output (Hunt units)				
<i>r</i>	0.7801	0.8532	-0.7509	-0.5827
<i>m</i>	239.7	16.96	-117.24	-8.31
<i>P</i>	< 0.001	< 0.001	< 0.001	< 0.001
	<i>N</i> = 42	Six cats	<i>N</i> = 54	

TABLE 2. Relationships between Δ MBF and both Δ pepsin and Δ H⁺ outputs, and Δ H⁺ and Δ pepsin during vagal stimulation. The responses are calculated as the Δ MBF, ml.; Δ H⁺, μ -equiv; and the Δ pepsin, Hunt units/10 min (the absolute responses) and as the % responses. Data are split into two groups, period 1-7 of vagal stimulation (A) and periods 8-16 (B) of stimulation

	A. Periods 1-7 (0-70 min)		B. Periods 8-16 (70-160 min)		
	Δ absolute responses	Δ % responses	Δ absolute responses	Δ % responses	
Δ MBF	<i>r</i> ,	0.7396	0.8281	0.3837	0.3419
	<i>m</i> ,	0.0323	0.8210	0.0251	0.4410
	Δ pepsin <i>P</i> ,	< 0.001	< 0.001	< 0.02	< 0.05
Δ MBF	<i>r</i> ,	0.7402	0.8668	0.8322	0.9569
	<i>m</i> ,	0.1826	0.9747	0.1959	0.9544
	Δ H ⁺ <i>P</i> ,	< 0.001	< 0.001	< 0.001	< 0.001
Δ H ⁺	<i>r</i> ,	0.8788	0.9638	0.3665	0.3013
	<i>m</i> ,	0.1557	0.8491	0.1019	0.3892
	Δ pepsin <i>P</i> ,	< 0.001	< 0.001	< 0.02	< 0.05
	<i>N</i> = 42	Six cats	<i>N</i> = 54		

Table 1*B*). The relationships between mucosal blood flow and pepsin; mucosal blood flow and acid secretion; and acid secretion and pepsin have been calculated as both the Δ values and as the % Δ responses. These data have been calculated in two groups, results obtained during the first 70 min of vagal stimulation (group *A*, Table 2) and the results obtained between 70 and 160 min of stimulation (group *B*, Table 2). In group *A* there were significant correlations of MBF with both pepsin and acid secreted (both Δ absolute responses and % Δ responses). In the later part of the experiments, group *B*, mucosal blood flow was weakly correlated with pepsin (Δ MBF/ Δ pepsin, $r = 0.3837$; % Δ MBF/% Δ pepsin, $r = 0.3419$), but strongly correlated with acid secretion (Δ MBF/ Δ H⁺, $r = 0.8322$; % Δ MBF/% Δ H⁺, $r = 0.9569$). Acid secretion was weakly correlated with pepsin secretion (Δ H⁺/ Δ pepsin, $r = 0.3665$; % Δ H⁺/ Δ pepsin, $r = 0.3013$). The Δ MBF/ Δ H⁺ ratio observed in all six experiments during each of the stimulation periods 1–16 have a weak negative correlation with time ($r = 0.4009$, $m = -0.0085$, $P < 0.001$, $N = 96$). The mean ratio was 0.226 ± 0.01 ml./ μ -equiv H⁺, i.e. the ratio significantly decreased by 3.7% of the mean every 10 min.

Pentapeptide stimulation

The dose of pentapeptide used in this study, 0.1 μ g/min i.v., produced neither pepsin secretion nor significant changes in gastric motility (fifty-eight observations in five cats). The mean absolute Δ H⁺ and Δ MBF responses during the reference periods in these experiments were 367.8 ± 82.7 μ -equiv/10 min, and 31.7 ± 10.9 ml./10 min and were not significantly different from those observed during the corresponding reference periods of vagal stimulation (261.7 ± 59.4 μ -equiv and 51.5 ± 12.9 ml./10 min, $P > 0.05$ in each case). Considering all periods studied (0–160 min pentapeptide stimulation) there was a weak negative correlation between the Δ MBF/ Δ H⁺ ratio and time ($r = -0.3452$, $m = -0.0045$, $P = 0.01$, $N = 57$). The mean Δ MBF/ Δ H⁺ ratio was 0.116 ± 0.012 ml./ μ -equiv H⁺, i.e. the ratio significantly decreased by 3.9% of the mean every 10 min.

Splanchnic nerve stimulation

Continuous electrical stimulation of the peripheral ends of both splanchnic nerves (10 V, 1 msec, 10 Hz for two consecutive 10 min periods) did not produce any pepsin secretion in cats secreting acid in response to pentapeptide infusions (ten observations in five cats). This form of splanchnic stimulation has been shown to reduce acid output and mucosal blood flow during vagal and pentapeptide stimulation, as long as the rise in blood pressure associated with splanchnic stimulation is prevented (Reed *et al.* 1971).

In ten animals, secreting acid and pepsin in response to prolonged vagal stimulation, splanchnic stimulation for two consecutive 10 min periods produced no significant reduction in pepsin output when compared to pepsin secreted in control vagal stimulation experiments. Blood pressure

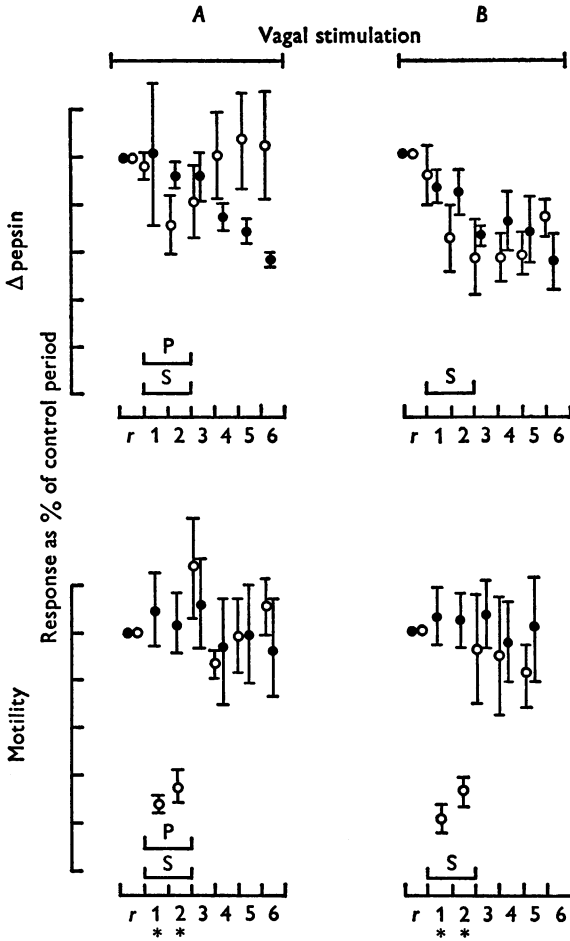


Fig. 3. The effects of splanchnic nerve stimulation on the pepsin and motility responses to electrical stimulation of the vagus nerves. *A.* A comparison of five paired experiments, controls (●) without splanchnic stimulation, test experiments (○) with two consecutive periods of splanchnic stimulation (S) during which time a pressure reservoir was included in the circulation (P). *B.* Five paired experiments, controls (●) had no splanchnic stimulation whereas the test experiments (○) had two periods of splanchnic stimulation (S). All results are shown as mean \pm 1 s.e. of the responses expressed as % of the reference period values (*r*). *Indicates significant difference between means at 5% level.

was allowed to rise during splanchnic stimulation in five of the ten experiments but in the other five experiments the rise in blood pressure was prevented by inclusion of the pressure reservoir in the circulation (Fig. 3A). The mean output of pepsin in the control vagal stimulation experiments during the reference periods was 1434 ± 320 (6) Hunt units. In contrast the mean output of pepsin in the test experiments during the periods before splanchnic stimulation was 1350 ± 363 (5) Hunt units in those experiments without a pressure reservoir, and 1249 ± 409 (5) Hunt units in those experiments with a pressure reservoir.

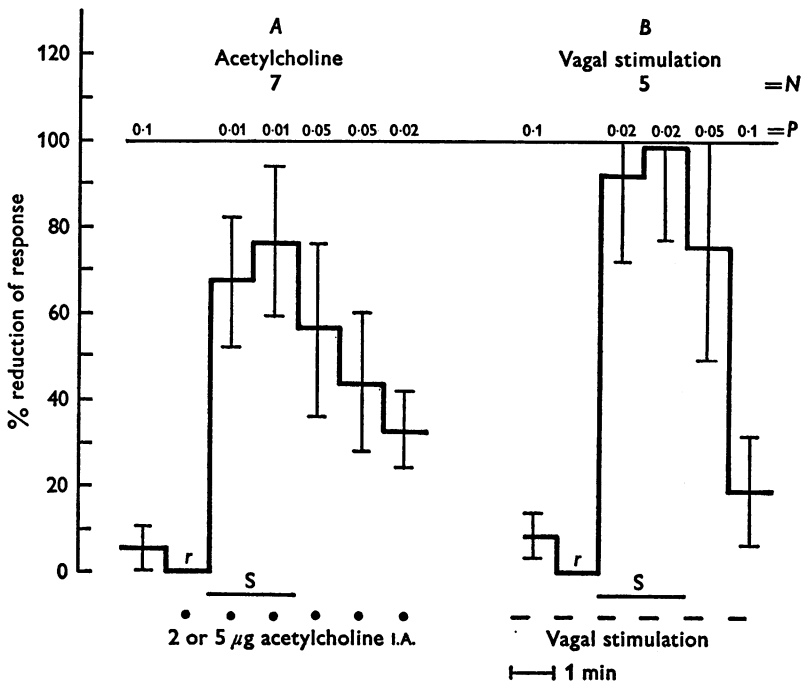


Fig. 4. The inhibitory effect of electrical stimulation of the splanchnic nerve on gastric motor responses to acetylcholine injections (A) and vagal stimulation (B). Motor responses were produced by injection of 2 or 5 μg acetylcholine into the coeliac axis (\bullet , A) in seven experiments or by 20 sec bursts of vagal stimulation (10 V, 1 msec, 6 Hz, —, B) in five experiments. During each experiment the splanchnic nerves were stimulated for 2 min (S). The results were calculated as the mean \pm 1 s.e. of the reduction in responses from the reference periods (r).

Motility spikes produced by the vagal stimulation were markedly inhibited during splanchnic stimulation whether or not the blood pressure rose (Figs. 1 and 3). Comparison was made of the effect of splanchnic nerve stimulation on gastric motility produced by vagal stimulation and

by a series of injections of acetylcholine injected i.a. close to the stomach. Vagal stimulation of 1 msec, 10 V, 6 Hz, during the first 20 sec of each min or injection of 2 or 5 μ g acetylcholine during the same period produced similar motility responses. The responses increased during the first 3–5 min of stimulation and thereafter were constant. When constant responses were evident a 2 min period of splanchnic nerve stimulation was carried out in both groups. Seven observations were made in three cats during acetylcholine stimulation and 5 during vagal stimulation in three cats.

The responses were measured as the height of contraction recorded during each min and expressed as a percentage reduction, relative to the response immediately before splanchnic stimulation. Corresponding responses in each group were averaged and the significance of the mean % inhibition from zero calculated. There were significant reductions during splanchnic stimulation in both groups and for 3 min following in the acetylcholine experiments, and for 1 min following with vagal stimulation. The reduction of motility produced by splanchnic stimulation was the same irrespective of the motility stimulant being either acetylcholine or vagal stimulation ($P > 0.05$ in each case, Fig. 4).

In a previous paper (Reed *et al.* 1971) we reported that in three experiments in which MBF and acid secretion were produced by vagal stimulation and then inhibited by simultaneous splanchnic stimulation, the injection of 3 mg guanethidine produced increases of MBF and acid responses approaching the control vagal stimulation values. In these experiments the splanchnic stimulation reduced motility responses as well as the MBF and acid responses to vagal stimulation. Pepsin output stimulated by the vagal stimulation was not reduced by the splanchnic stimulation. Injection of guanethidine removed the inhibition of motility responses in addition to those of MBF and acid. Furthermore, in two animals with the adrenals removed, splanchnic stimulation for two consecutive 10 min periods during prolonged vagal stimulation produced similar reductions of motility responses to those seen in animals with the adrenals intact (Fig. 3).

DISCUSSION

Many workers have now described a relationship between MBF and acid secretion. The existence of such a relationship has obvious advantages in supplying increased oxygen during acid secretion. Barlow, Greenwell, Harper & Scratcherd (1968) have shown an increased pancreatic blood flow associated mainly with increased enzyme secretion. Secretin produced little increase in pancreatic blood flow whereas pancreozymin markedly increased flow of enzyme and blood. It might therefore be expected that pepsin secretion would increase gastric mucosal blood flow.

In the present study the strong correlations of Δ pepsin, ΔH^+ and Δ MBF with time during early stages of vagal stimulation makes correlation between any two of the measured variables inevitable and meaningless. During the later periods of the experiments, however, Δ MBF and ΔH^+ were not correlated with time whereas Δ pepsin was negatively correlated with time. Δ MBF and ΔH^+ were strongly correlated ($r = 0.9569$) showing the now frequently reported relationship but in this case without the possibility of a spurious correlation caused by time. Δ Pepsin was only weakly correlated with Δ MBF ($r = 0.3419$) (Table 2). This evidence suggests an increase in MBF being closely related to an increase in acid but little influenced by pepsin secretion. The weak correlation between pepsin output and MBF depends upon a significant decline in pepsin at the time when Δ MBF and ΔH^+ are not declining significantly (Table 1B). During vagal stimulation it is not possible to apportion the pepsin secreted from preformed pepsinogens and from more immediate synthesis and release. In the pancreas Webster (1968) has shown that injection of cholinergic agents increases RNA synthesis, and increased incorporation of isotopically labelled amino acids into pigeon pancreatic proteins was evident within 5 min of injection, reaching a maximum within 30 min. Amylase synthesis was increased accordingly.

It is likely that pepsinogens synthesized and secreted by stimulation would require more energy than would secretion of stored, preformed pepsinogens. As yet there is no knowledge of the energy requirement for pepsin synthesis and secretion. Nevertheless, if there exists in gastric juice a mixture of preformed and immediately synthesized pepsinogens and the proportions alter throughout an experiment, a lack of correlation between MBF and pepsin may not be surprising. The decline in pepsin output from the high initial rates (mean 1434 ± 320 Hunt units/10 min in period 5) during the later parts of experiments may indicate depletion of pepsinogen stores and a reduction of secretion towards the rate of synthesis (Fig. 2). Alternatively, the fact that the mean Δ MBF/ ΔH^+ observed during vagal stimulation (0.226 ± 0.010 , $N = 96$) accompanied by high rates of pepsin secretion, was significantly greater than that during pentapeptide stimulation (0.116 ± 0.012 , $N = 57$, $P < 0.01$) with no pepsin secretion, may reflect an influence of pepsin secretion on MBF.

Swan & Jacobson (1967) showed an increase in R

$$= \frac{[\text{gastric juice amidopyrine}]}{[\text{arterial plasma amidopyrine}]}$$

during insulin and 2-deoxyglucose infusion as compared to gastrin, which they take as an indication of increased MBF per unit volume of juice secreted. Although it is difficult to make comparisons between their data

and our own, it appears that the MBF/H⁺ ratio reported by these workers during this form of vagal stimulation is greatly in excess of that reported here.

Splanchnic nerve stimulation produces reduction of gastric acid and MBF when a rise in blood pressure is prevented (Reed *et al.* 1971). However, the pepsin response to vagal stimulation was not reduced by splanchnic stimulation, whether a rise in B.P. occurred or not (Fig. 3), suggesting a different dependence of pepsinogen secretion on mucosal blood flow to that of acid secretion. This observation is consistent with the hypothesis that splanchnic stimulation acts by reducing mucosal blood flow, that reduction of acid is secondary and that the evidence of pepsin secretion not being related to MBF indicates no dependence on blood flow. Presumably this would mean that the blood flow associated with acid secretion supplies sufficient oxygen to satisfy pepsinogen synthesis and secretion.

The fact that splanchnic stimulation did not produce pepsin secretion during pentapeptide stimulation shows that the absence of inhibition of vagal stimulated pepsin output during splanchnic stimulation is not due to an inhibition being masked by a simultaneous splanchnic stimulation of pepsin secretion. Schafer and Kittle (1951) reported a rise in pepsin output following sympathectomy.

Gastric motility responses were unique in this study in being equally and significantly reduced by splanchnic stimulation whether or not a change in arterial B.P. occurred (Fig. 3). The motor response probably corresponds to the low threshold vagal excitatory motor responses referred to by Martinson (1965) and Jansson & Martinson (1966). Veach (1924) has suggested that muscle ischaemia was the cause of splanchnic inhibition of motor activity. Recently, however, Jansson & Martinson (1966) and Jansson & Lisander (1969) have concluded that the primary site of splanchnic action is at the intramural vagal ganglion cells. They showed no effect of reflex activation of efferent sympathetic activity on the motor response to close arterial infusions of acetylcholine. This contrasts with our inhibition of close arterial acetylcholine-stimulated responses by direct stimulation of the splanchnic nerves (Fig. 4). Furthermore it seems unlikely that if the splanchnic response were primarily acting on vagal ganglion cells, the inhibition of vagal and acetylcholine-stimulated motility should be so similar (Fig. 4). Gershon (1967) found no evidence in his studies on *in vitro* preparations that splanchnic stimulation acted via ganglion cells, concluding that the effect was due to the direct action of noradrenaline on the smooth muscle.

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