J. Physiol. (1975), **252**, *pp.* 791–801
With 4 text-figures
Printed in Great Britain

THE INFLUENCE OF SECRETIN ON THE SECRETION OF PEPSIN IN RESPONSE TO ACID STIMULANTS IN THE ANAESTHETIZED CAT

BY JOAN M. BRAGANZA, A. C. C. GIBBS AND HENRY T. HOWAT

From the University Department of Gastroenterology, Manchester Royal Infirmary and the Department of Social Medicine, University of Manchester

(*Received 23 April 1975*)

SUMMARY

1. Peptic secretion was studied in fasting anaesthetized cats in which the pylorus and common bile duct had been occluded to prevent the release of duodenal hormones which might stimulate or inhibit gastric secretion. Dilute acid was instilled into the stomach at intervals to aid recovery of gastric secretion and to preserve peptic activity.

2. Caerulein, histamine and *N*-methyl histamine did not increase the output of pepsin when given on their own. Desulphated caerulein was a weak peptic stimulant.

3. Two C.H.R. u./kg per hour secretin initiated pancreatic secretion, the volume of which increased progressively as the dose was increased by stages to 32 C.H.R. u./kg per hour.

4. Four C.H.R. u./kg per hour secretin did not increase the output of pepsin. Peptic secretion was stimulated by 8 C.H.R. u./kg per hour. A maximal output of approximately 2000 u. pepsin/15 min was obtained when 16 C.H.R. u./kg per hour was infused.

5. When each acid stimulant was infused along with 4 C.H.R. u./kg per hour secretin the output of pepsin increased significantly. The peak output, which usually occurred between 15 and 30 min after stimulation, did not exceed 1000 u. pepsin/15 min.

6. The proposed explanation for the potentiation of the peptic response when an acid stimulant is infused along with a dose of secretin, in itself below the threshold of peptic stimulation, is that each acid stimulant increases gastric mucosal blood flow, approximately doubling the effective concentration of secretin delivered to the peptic cell.

INTRODUCTION

While studying the effects of caerulein and desulphated caerulein on the stomach and pancreas (Braganza, Beswick, Howat, Kay & Morley, 1969) it became apparent that although caerulein was an effective acid stimulant it produced little pepsin. When a small dose of secretin was infused to facilitate simultaneous observation of the pancreatic responses, caerulein invariably increased peptic secretion. Experiments were therefore designed to elucidate this observation. Histamine and *N*-methyl histamine were also given to stimulate acid secretion.

METHODS

Cats of 3 kg average weight were fasted for 24 hr, anaesthetized with chloralose and prepared according to the technique of Howat & Schofield (1954). In all the experiments the splanchnic nerves were sectioned. A soft rubber tube was introduced into the stomach through an opening in the oesophagus in the neck and secured by a ligature. The pylorus and common bile duct were occluded. At the start of each collection period 25 ml. 5 mN-HCl (125 μequiv), warmed to 37° C, was instilled into the stomach and siphoned off 15 min later. The volume of each specimen was recorded to the nearest 0·5 ml.; free and total acid was titrated with 50 mN-NaOH. Peptic activity was measured by the method of Hunt (1948).

In some experiments the pancreatic duct was cannulated. The volume of pancreatic juice was measured to the nearest 0·05 ml., the concentration of bicarbonate estimated by back titration after treatment with 100 mN-HCl, and lipase activity measured by the pH stat method of Marchis-Mouren, Sarda & Desnuelle (1959).

The doses of the acid stimulants employed are indicated in Table 1. Forty-eight test infusions were given alone; a further thirty-six infusions were given simultaneously with 4 C.H.R. (Crick, Harper, Raper) u./kg per hour secretin (Boots Co. Ltd, Nottingham). All the test substances were made up in a sterile isotonic solution of sodium chloride and delivered by constant infusion into a catheter introduced into the femoral vein. Each infusion lasted 45 min. An interval of 90 min was generally allowed between infusions to permit the stomach and pancreas to return to basal conditions.

For each test substance the total output of pepsin was derived by subtracting twice the sum of the three 15 min outputs preceding the infusion from the sum of peptic outputs of the three 15 min periods of the infusion and three subsequent periods. The significance of the differences in mean post-stimulation outputs and the respective basal outputs of pepsin were computed by a paired t test. The mean post-stimulation outputs of pepsin in response to the four stimulants, both with and without secretin, were compared by applying to each group a t test for uncorrelated means, after it had been ascertained that the variances did not differ significantly. Correlation coefficients were determined to examine the relationship between doses of the stimulants and the outputs of pepsin and the significance of r was tested for each group. A result was considered significant when $P < 0{\cdot}05$.

The hepatic artery was cannulated retrogradely in two experiments according to the technique of Harper, Reed & Smy (1968). Isopropylnoradrenaline (*I.P.N.A.*) was infused into the artery in a dosage 5 μg/min for 45 min to increase gastric mucosal blood flow. Blood pressure was monitored in these experiments.

RESULTS

Peptic responses to four acid stimulants. Caerulein, histamine and *N*-methyl histamine did not stimulate peptic secretion when infused on their own (Table 1). However, 100 ng/kg per minute desulphated caerulein increased peptic output significantly (Table 1).

Peptic responses to secretin. Two C.H.R. u./kg per hour secretin induced a flow of pancreatic juice the volume of which increased as the dose was increased to 32 C.H.R. u./kg per hour (Fig. 1). Eight C.H.R. u./kg per hour secretin initiated peptic secretion. A maximal peptic output of 1935 ± 240 u./15 min (mean $\pm$ S.E. of mean of two experiments) was obtained in response to 16 C.H.R. u./kg per hour (Fig. 1). Acid output increased by 265 ± 85 μequiv/15 min (mean $\pm$ S.E. of mean of two experiments) when the highest doses of secretin were infused. In two experiments atropine did not reduce the peptic response to secretin.

Peptic responses to combinations of the acid stimulants and secretin. The basal output of pepsin did not differ in experiments with or without secretin. When each acid stimulant was infused in the presence of 4 C.H.R. u./kg per hour secretin the concentration of pepsin increased and the total output increased significantly at each dose (Table 1). These peptic responses varied widely, and the correlation and linear regression coefficients relating doses and outputs of pepsin were not significant. The maximal response observed was approximately 1000 u. pepsin/15 min for any combination of stimulants. The mean total peptic outputs in experiments with secretin were all significantly greater than the corresponding mean total outputs of pepsin in experiments without secretin (Table 1). When two identical infusions of an acid stimulant were given during the course of a single experiment peptic secretion occurred only when the stimulant was infused together with secretin (Fig. 2).

The effects of increasing gastric mucosal blood flow on the peptic responses to secretin. In two experiments (Figs. 3 and 4) infusions of isopropylnoradrenaline were given retrogradely into the hepatic artery at 5 μg/min to increase gastric mucosal blood flow (Harper *et al.* 1968). Acid and peptic outputs varied little when the infusions of isopropylnoradrenaline were given on their own; when infused along with 2 or 4 C.H.R. u./kg per hour secretin, however, the output of pepsin increased (Figs. 3 and 4).

DISCUSSION

The difficulties encountered in studying peptic secretion are incomplete recovery of a viscid, enzyme laden juice and escape of acid from the stomach into the duodenum, which may release duodenal hormones

TABLE 1. Mean peptic outputs in response to infusions of four test substances without (*A*) and with (*B*) 4 C.H.R. u./kg per hour secretin

Test substance	Dose ng/kg per minute	(*A*) No secretin Pepsin: No. of expts.	Mean output (units)	S.E. of mean	*P*	(*B*) +4 C.H.R. u. secretin/kg per hour Pepsin: No. of expts.	Mean output (units)	S.E. of mean	*P*	Significance of difference in peptic output between (*A*) and (*B*)
Caerulein	2·5	3	247·5	137·3	$0·3 < P < 0·4$	—	—	—	—	—
	5	3	33·5	17·0	$0·5 < P < 0·6$	3	1443·3	16·3	$< 0·001$	$< 0·001$
	10	3	125·8	57·8	$0·1 < P < 0·2$	3	1199·0	303·7	$0·02 < P < 0·05$	$0·02 < P < 0·05$
	20	6	17·9	36·4	$0·6 < P < 0·7$	3	2043·0	465·6	$0·02 < P < 0·05$	$0·001 < P < 0·005$
Desulphated caerulein	20	3	260·0	102·9	$0·05 < P < 0·1$	3	1640·0	626·0	$0·02 < P < 0·05$	$0·02 < P < 0·05$
	50	3	570·0	287·4	$0·05 < P < 0·1$	3	2105·0	464·8	$0·02 < P < 0·05$	$0·02 < P < 0·05$
	100	4	567·3	141·5	$0·02 < P < 0·05$	3	1898·0	145·5	$0·01 < P < 0·02$	$0·001 < P < 0·005$
Histamine	375	3	40·6	20·5	$0·2 < P < 0·3$	3	110·0	15·2	$0·01 < P < 0·02$	$0·02 < P < 0·05$
	750	3	0			3	621·3	161·9	$0·02 < P < 0·05$	$0·005 < P < 0·01$
	1500	5	58·8	25·2	$0·1 < P < 0·2$	3	1412·0	411·5	$0·02 < P < 0·05$	$0·005 < P < 0·01$
N-methyl histamine	375	3	0	0		3	2000·0	106·2	$P < 0·001$	$P < 0·001$
	750	3	20·3	11·8	$0·4 < P < 0·5$	3	3240·0	1156·3	$0·02 < P < 0·05$	$0·02 < P < 0·05$
	1500	3	38·6	27·3	$0·2 < P < 0·3$	3	1715·0	500·8	$0·02 < P < 0·05$	$0·01 < P < 0·02$
	3000	3	21·3	11·6	$0·4 < P < 0·5$					

Significance of differences of mean outputs over basal levels of pepsin (paired *t* test); and significance of differences in mean peptic outputs in experiments with and without secretin (*t* test, uncorrelated means).

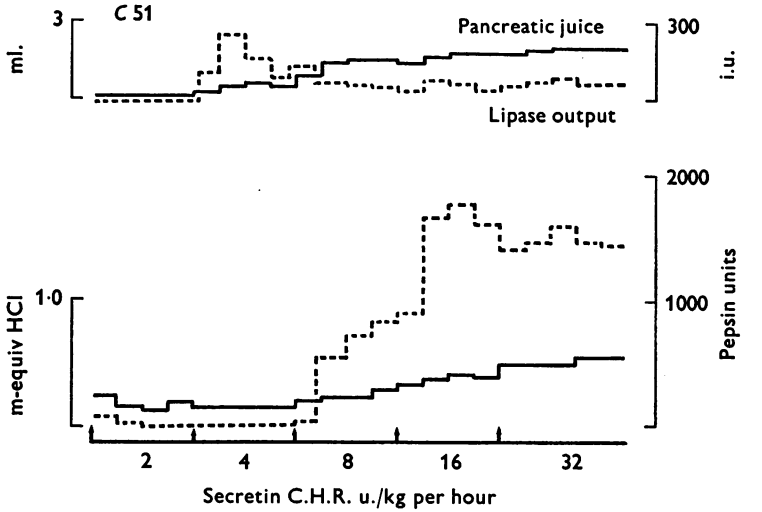

Fig. 1. Gastric and pancreatic responses to a continuous infusion of secretin. The dose of secretin was doubled each hour.

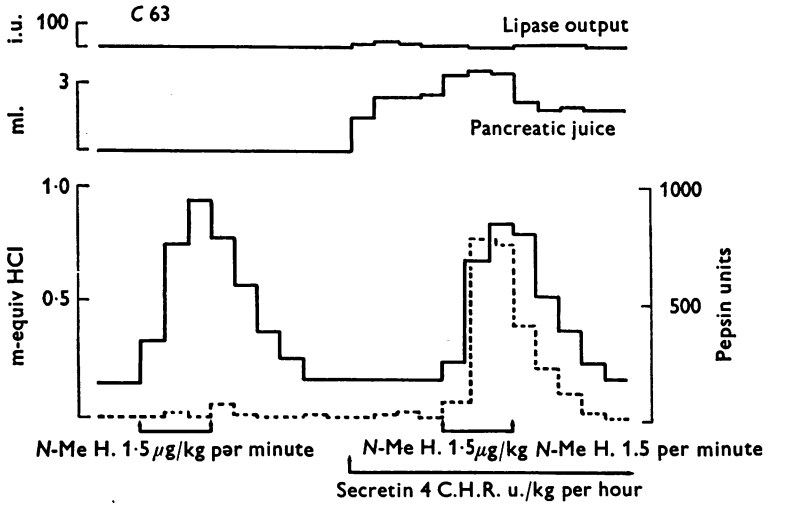

Fig. 2. Gastric and pancreatic secretion in response to two 45 min infusions of *N*-methyl histamine, *N*-MeH. Secretin was infused simultaneously during the second half of the experiment.

which might either stimulate or inhibit peptic secretion. These drawbacks were obviated in our experiments on anaesthetized cats by occluding the pylorus and instilling dilute acid into the stomach each 15 min to aid the collection of gastric secretions and to preserve peptic activity. The common bile duct was occluded to prevent the release of duodenal hormones

by bile salts (Mellanby, 1926*a*, *b*; Forell, Otte, Kohl, Lehnert & Stahlheber, 1971, Forell, 1973). Since single injections of acid stimulants may increase the pepsin content of gastric samples transiently by washing pre-formed

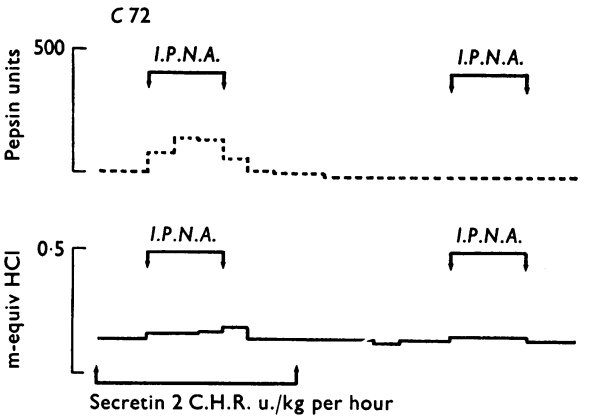

Fig. 3. Gastric acid and peptic responses to two 45 min infusions of isopropylnoradrenaline, *I.P.N.A.* In each experiment 5 μg/min isopropylnoradrenaline was given retrogradely into the hepatic artery. Two C.H.R. u./kg per hour secretin was infused for the first half of the experiment.

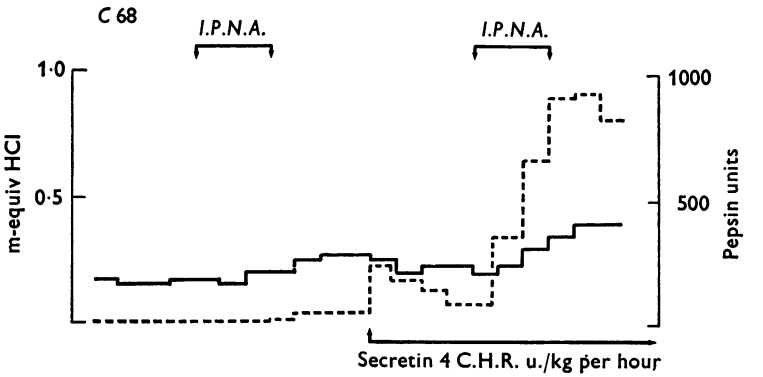

Fig. 4. Gastric acid and peptic responses to two 45 min infusions of isopropylnoradrenaline, *I.P.N.A.* Four C.H.R. u./kg per hour secretin was infused during the second half of the experiment.

pepsin from the glands, continuous infusions of acid stimulants were employed to detect a sustained increase of peptic output which would distinguish stimulation of the peptic cells from a 'wash-out' phenomenon.

Caerulein, histamine and *N*-methyl histamine did not stimulate peptic secretion in the anaesthetized cat, while desulphated caerulein was a weak

peptic stimulant. Previous studies in dogs have indicated that caerulein was a strong peptic stimulant both in the Heidenhain pouch preparation (Bertaccini, Endean, Erspamer & Impicciatore, 1968) and in gastric fistula animals (Stening & Grossman, 1969). Caerulein was twice as potent (Johnson, Stening & Grossman, 1969) and later five times as potent (Johnson, Stening & Grossman, 1970) as desulphated caerulein in stimulating peptic secretion, although Way (1971) concluded that desulphated caerulein was the stronger peptic stimulant.

There has been little agreement on the status of histamine as a peptic stimulant despite the conclusion of Hirschowitz (1967) that this controversy has been settled with the recognition of species differences. In cats our findings agree with those of Linde (1950) and Björkman, Norden & Uvnäs (1943) who used an experimental technique very similar to our own. In dogs most physiologists agree that histamine does not cause a sustained increase in peptic secretion (Babkin, 1930; Linde, 1950; Gilman & Cowgill, 1931) and may indeed inhibit peptic responses (Linde, 1950; Alley, 1935; Hirschowitz, 1966; Hirschowitz & Sachs, 1965). Johnson (1972*b*) believed however that histamine stimulates pepsin in dogs with a vagally denervated pouch.

Since Pratt (1940) showed that intestinal extracts containing secretin increased the output of pepsin in cats, it has been said that secretin itself possesses peptic stimulating activity (Magee & Nakajima, 1968; Berstad, 1969; Brooks, Isenberg & Grossman, 1969; Berstad & Petersen, 1969, 1970). The outputs of pepsin obtained in response to combinations of secretin and gastrin in dogs and cats (Stening, Johnson & Grossman, 1969), secretin and histamine or pentagastrin in dogs (Nakajima, Nakamura & Magee, 1969) and secretin and pentagastrin in man (Berstad & Petersen, 1970) were reported to be significantly greater than the respective outputs of pepsin when the acid stimulants were infused independently. Our data for peptic secretion in response to combinations of acid stimulants and secretin fulfils the definition of potentiation promulgated by Grossman (1967), in that the response to the two agents given together exceeded the response to twice the dose of each agent given singly. The results do not, however, fulfil the additional requirements that the response to the combination must be greater than the observed maximal response to each agent given separately (Gillespie & Grossman, 1964) or that it should exceed the individual calculated maximal responses (Dinbar & Grossman, 1972).

Three possible mechanisms could account for the enhanced peptic responses when an acid stimulant is infused along with a dose of secretin in itself subthreshold for peptic stimulation: (*a*) interaction at the receptor site in the parietal cell; (*b*) an acid sensitive reflex within the gastric mucosa (Johnson, 1972*a*); (*c*) changes in musosal blood flow.

The correlation and regression coefficients relating the doses of each acid stimulant and the peptic responses were not significant, for the individual peptic outputs varied widely. Therefore simple interaction between acid stimulant and secretin at receptor level is an unlikely explanation for our observations.

Johnson (1972*a*) showed that in Heidenhain pouch dogs when the gastric mucosal barrier is broken by instilling 250–300 mN-HCl, fluid with sodium and potassium moves into the lumen and H^+ pass from the lumen of the pouch. He postulated that in traversing the mucosa, the H^+ stimulated a local cholinergic reflex which resulted in a three- or fourfold increase in the output of pepsin from the pouch. A 100 mN-HCl solution increased peptic secretion threefold over basal conditions. A similar level of peptic secretion was attained when 2 c.u./kg per hour GIH* secretin was infused (Johnson, 1972*b*). The combination of secretin and pouch acidification with 50 ml. 100 mN-HCl resulted in a twelvefold increase in the output of pepsin. The maximal acid secreted in 15 min in response to caerulein resulted in an output of 0·8 m-equiv HCl in approximately 30 ml. gastric contents (25 ml. introduced + approx. 5 ml. secreted). This dilution ensured that the gastric mucosa was bathed by a weak solution of 26 mN-HCl. In Johnson's experiments a solution of 25 mN-HCl produced but little pepsin and would not explain the vastly greater peptic responses obtained in our experiments. Moreover, we did not observe any fall off in total acid output when secretin was given such as accompanies disruption of the mucosal barrier.

Each acid stimulant is considered to have increased mucosal blood flow within the stomach and consequently increased the concentration of secretin delivered to the peptic cells. Such a mechanism explains the similarity of the peptic responses to agents so structurally different as caerulein and histamine. Though caerulein has been shown to increase pancreatic blood flow in anaesthetized dogs (Dorigotti & Glasser, 1968) the effects on gastric blood flow have not been studied. Jacobson, Eisenberg & Swan (1966) showed in conscious dogs that histamine increased gastric mucosal blood flow measured by the amidopyrine clearance technique. Harper *et al.* (1968) using the same method in anaesthetized cats also found that histamine and gastrin increased gastric mucosal blood flow with increase in H^+ secretion. When Reed & Smy (1968) injected isopropylnoradrenaline retrogradely into the hepatic artery they found an increase in mucosal blood flow in the stomach. The maximal increase in mucosal blood flow which occurred during the 30–40 min collection period following the infusion of isopropylnoradrenaline was two to four

* GIH = Gastrointestinal Hormone from GIH Research Unit, Karolinska Institute Stockholm.

times greater than the basal level of flow (Reed & Sanders, 1971; Reed, Smy, Venables & Harris, 1973). In the unstimulated stomach, the increase in mucosal blood flow of approx. 30 ml./10 min was associated with a negligible increase in acid of approx. 27 μequiv/10 min (Reed & Sanders 1971). Although actual blood flow measurements were not made in our two experiments in which isopropylnoradrenaline was given the technique employed was exactly as described by these workers, and blood pressure was continuously monitored and maintained constant by appropriate adjustments in the flow rate of isopropylnoradrenaline. In both experiments the blood pressure remained steady after an early tendency to diminish and the flow rate of isopropylnoradrenaline was continued at 5 μg/min at which dose a fourfold increase in mucosal blood flow can be expected (Reed *et al.* 1973). In experiment *C* 72 (Fig. 3) peptic secretion increased when a small dose of secretin of 2 C.H.R. u./kg per hour was infused simultaneously with isopropylnoradrenaline equivalent to a fourfold increase in the concentration of secretin at the peptic cell, for the threshold dose of secretin for peptic stimulation was usually 8 C.H.R. u./kg per hour (Fig. 1). In experiment *C* 68 (Fig. 4) 50 μequiv HCl/15 min was secreted in the control periods. In this cat when gastric mucosal hyperaemia was induced by isopropylnoradrenaline the output of acid increased. We attributed this acid response to an increase in the mucosal delivery of a naturally circulating secretagogue. The early increase in peptic output soon after the start of the secretin infusion may be due to a residual effect of the previous infusion of isopropylnoradrenaline for the acid output was still minimally increased at this time. It has been calculated that the additional 150 μequiv HCl/15 min would be associated with an increase of about 12 ml./15 min blood flow, sufficient to increase the concentration of secretin above threshold amounts (J. R. Smy, personal communication). The alternative explanation that 4 C.H.R. u./kg per hour was above threshold for that cat seems unlikely for the decline in pepsin followed the decline in acid and presumably in blood flow, which supports our surmise that some isopropylnoradrenaline was still present in the circulation an hour after the first infusion. The peak increase in peptic output to approximately 1000 u./15 min (Fig. 4) was similar to the mean peak peptic responses to combinations of 4 C.H.R. u./kg per hour of secretin and the acid stimulants.

We have concluded that in these experiments acid stimulants which produce little or no pepsin enhance the peptic response to a dose of secretin, itself below the threshold of peptic stimulation, by increasing gastric mucosal blood flow and approximately doubling the delivery of secretin to the peptic cell.

We are grateful for generous financial support received for these studies from the Board of Governors of the United Manchester Hospitals. We are indebted to Professor A. A. Harper of Newcastle-upon-Tyne and Dr J. R. Smy of Sunderland Polytechnic with whom we have discussed our results. We also thank Dr R. Ollerenshaw of the Manchester University Department of Medical Illustration for the final preparation of the Figures.

REFERENCES

ALLEY, A. (1935). The inhibitory effect of histamine on gastric secretion. *Am. J. dig. Dis.* **1**, 787–794.

BABKIN, B. P. (1930). Variations in the composition of gastric juice under different conditions. *Trans. R. Soc. Can.* **24**, sect. 5, 201–205.

BERSTAD, A. (1969). Stimulation of gastric secretion of pepsin in man. *Scand. Jnl Gastroenterol.* **4**, 617–622.

BERSTAD, A. & PETERSEN, H. (1969). A comparison between the effects of secretin and histamine on the gastric secretion of pepsin in man. *Scand. Jnl Gastroenterol.* **4**, 511–515.

BERSTAD, A. & PETERSEN, H. (1970). Dose response relationship of the effect of secretin on acid and pepsin in man. *Scand. Jnl Gastroenterol.* **5**, 647–654.

BERTACCINI, G., ENDEAN, R., ERSPAMER, V. & IMPICCIATORE, M. (1968). The actions of caerulein on gastric secretion of the dog and rat. *Br. J. Pharmac. Chemother.* **34**, 311–329.

BJÖRKMAN, G., NORDEN, A. & UVNÄS, B. (1943). Histamine and peptic secretion. *Acta physiol. scand.* **6**, 108–116.

BRAGANZA, J. M., BESWICK, F. B., HOWAT, H. T., KAY, G. & MORLEY, J. S. (1969). A report on the action of caerulein and analogues of caerulein. *4th Symposium European Pancreatic Club*, Goettingen. (Private Publication.)

BROOKS, A. M., ISENBERG, J. & GROSSMAN, M. I. (1969). The effect of secretin, glucagon and duodenal acidification on pepsin secretion in man. *Gastroenterology* **57**, 159–162.

DINBAR, A. & GROSSMAN, M. I. (1972). Interaction of stimulants of acid secretion in the cat. *Gastroenterology* **62**, 242–246.

DORIGOTTI, L. & GLASSER, A. H. (1968). Comparative effects of caerulein, pancreozymin and secretin on pancreatic blood flow. *Experientia* **24**, 806–807.

FORELL, M. M. (1973). Bile salts as stimulants of pancreatic secretion. In *Nobel Symposium XVI, Frontiers in Gastrointestinal Hormone Research.* Stockholm 1970, ed. ANDERSSON, S., Upsala: Almqvist and Wiksell.

FORELL, M. M., OTTE, M., KOHL, H. J., LEHNERT, P. & STAHLHEBER, H. P. (1971). The influence of bile and pure bile salts on pancreatic secretion in man. *Scand. Jnl Gastroenterol.* **6**, 261–266.

GILLESPIE, I. E. & GROSSMAN, M. I. (1964). Potentiation between urecholine and gastrin extract and between urecholine and histamine in the stimulation of Heidenhein pouches. *Gut* **5**, 71–76.

GILMAN, A. & COWGILL, G. R. (1931). The effect of histamine upon the secretion of gastric pepsin. *Am. J. Physiol.* **97**, 124–130.

GROSSMAN, M. I. (1967). In *Handbook of Physiology*, vol. 2, section 6, ed. CODE, C. F., p. 850. Washington: American Physiological Society.

HARPER, A. A., REED, J. D. & SMY, J. R. (1968). Gastric blood flow in anaesthetized cats. *J. Physiol.* **194**, 795–807.

HIRSCHOWITZ, B. I. (1966). Characteristics of gastric electrolyte secretion by insulin. *Am. J. dig. Dis.* **11**, 183–198.

HIRSCHOWITZ, B. I. (1967). Secretion of pepsinogen. In *Handbook of Physiology*, vol. 2, section 6, ed. CODE, C. F., p. 905, Washington D.C.: American Physiological Society.

HIRSCHOWITZ, B. I. & SACHS, G. (1965). Vagal gastric secretory stimulation by 2 deoxy-D-glucose. *Am. J. Physiol.* **209**, 452–460.

HOWAT, H. T. & SCHOFIELD, B. (1954). The effect of urogastrone, enterogastrone and mepyramine maleate on gastric and pancreatic secretion. *J. Physiol.* **123**, 1–15.

HUNT, J. N. (1948). A method of estimating peptic activity in gastric contents. *Biochem. J.* **42**, 104–109.

JACOBSON, E. D., EISENBERG, M. M. & SWAN, K. G. (1966). Effects of histamine on gastric blood flow in conscious dogs. *Gastroenterology* **51**, 466–472.

JOHNSON, L. R. (1972*a*). Pepsin secretion stimulated by topical hydrochloric and acetic acids. *Gastroenterology* **62**, 33–38.

JOHNSON, L. R. (1972*b*). Regulation of pepsin secretion by topical acid in the stomach. *Am. J. Physiol.* **223**, 847–850.

JOHNSON, L. R., STENING, G. F. & GROSSMAN, M. I. (1969). Relative potencies of natural and desulphated caerulein. *Gastroenterology* **56**, 1255.

JOHNSON, L. R., STENING, G. F. & GROSSMAN, M. I. (1970). The effect of sulfation on the gastrointestinal actions of caerulein. *Gastroenterology* **58**, 208–216.

LINDE, S. (1950). Studies on the stimulation mechanism of gastric secretion. *Acta physiol. scand.* suppl. 74, 3–92.

MARCHIS-MOUREN, G., SARDA, L. & DESNUELLE, P. (1959). Purification of hog pancreatic lipase. *Archs Biochem. Biophys.* **83**, 309–317.

MAGEE, D. F. & NAKAJIMA, S. (1968). Stimulatory action of secretin on gastric pepsin secretion. *Experientia* **24**, 689–690.

MELLANBY, J. M. (1926*a*). Mechanism of pancreatic secretion. *Lancet* **211**, 215–218.

MELLANBY, J. M. (1926*b*). The secretion of pancreatic juice. *J. Physiol.* **61**, 419–435.

NAKAJIMA, S., NAKAMURA, M. & MAGEE, D. F. (1969). Effect of secretin on gastric acid and pepsin secretion in response to various stimuli. *Am. J. Physiol.* **216**, 87–91.

PRATT, C. L. G. (1940). The influence of secretin on gastric secretion. *J. Physiol.* **98**, 1–2*P*.

REED, J. D. & SANDERS, D. J. (1971). Splanchnic nerve inhibition of gastric acid secretion and mucosal blood flow in anaesthetised cats. *J. Physiol.* **219**, 555–570.

REED, J. D. & SMY, J. R. (1968). The relationship between gastric acid secretion and mucosal blood flow in response to histamine and gastrin. In *Proc. int. Union Physiol. Sci*, vol. 7; *XXI Int. Congress*, Washington D.C., Abstract 1084. Washington: Fedn Am. Socs exp. Biol.

REED, J, D. SMY, J. R., VENABLES, C. W. & HARRIS, D. W. (1973). The effect of burimamide on gastric acid secretion and mucosal blood flow in the anaesthetised cat. *Int. Symposium on Histamine H_2 Receptor Antagonists*. Smith, Kline & French Laboratories Ltd., London, ed. WOOD, C. J. & SIMKINS, M. A. Welwyn Garden City.

STENING, G. F. & GROSSMAN, M. I. (1969). Gastrin related peptides as stimulants of pancreatic and gastric secretion. *Am. J. Physiol.* **217**, 262–266.

STENING, G. F., JOHNSON, L. R. & GROSSMAN, M. I. (1969). Effect of secretin on acid and pepsin secretion in cat and dog. *Gastroenterology* **56**, 468–475.

WAY, L. W. (1971). Effect of cholecystokinin and caerulein on gastric secretion in cats. *Gastroenterology* **60**, 560–565.