Progress report

The control of pancreatic secretion

The control of exocrine pancreatic secretion has been described in the Handbook of Physiology by Preshaw¹ and Harper², and more recently by Grossman³. In the present report emphasis will be placed on publications during the last few years which have amplified or modified accepted concepts of the control of secretion. For descriptive purposes the traditional division of the control into cephalic, gastric, and intestinal is still the most convenient.

Cephalic Phase and Vagal Effect on Pancreatic Secretion

The cephalic phase, which Pavlov considered of little significance, was reinvestigated by sham feeding of dogs by Preshaw, Cooke, and Grossman⁴, and of man by Sarles and his colleagues⁵. The increased protein secretion elicited by sham feeding in dogs was prevented by acidification of an innervated antral pouch. The surgical preparation of the animals had probably interrupted direct vagal pathways to the pancreas, and in these experiments the psychic response depended on a vagal release of gastrin. In human subjects the very brief latent period between stimulation by sight, smell, or taste of food and the onset of pancreatic secretion suggests a direct vagal effect on the pancreas.

As the stimuli for the cephalic phase operate for only a small part of the total time of the pancreatic response to a meal it has been natural to think of this phase as subserving a mobilization of enzyme stores and adjustment of pancreatic blood supply preliminary to the main secretory response produced by acid and digestion products entering the intestine. This concept has been supported by the view that vagal impulses, acting directly on the gland or indirectly by release of gastrin, have little effect on secretion of water and bicarbonate. In fact appreciable amounts of fluid and bicarbonate accompanied the enzyme secretion in Sarles' experiments. In contrast to the small or absent volume response of the canine or feline pancreas, the pancreas of the pig produces large amounts of water, bicarbonate, and enzymes in response to vagal stimulation⁶. As the enzyme secretion was blocked by atropine, it was presumably mediated by cholinergic fibres, but the vagal effect on water and bicarbonate secretion in the pig and the cat^{7,8} is 'atropine-resistant'. Even in the cat, in which vagal stimulation without a secretin background is usually said to be without effect on volume flow, it has been shown that repeated stimulation may produce a secretion, often quite small but on average amounting to 20% of the maximal response to exogenous secretin⁸.

Gastric Phase of Secretion

To Pavlov the main pancreatic response to a meal was based on long reflexes by visceral afferent fibres from the abdomen passing impulses to secretory

centres in the brain stem, which relayed stimulation back by the vagus nerves to the pancreas. With the discovery of secretin and pancreozymin hormonal control of the pancreas was emphasized, but interest in nervous reflex regulation was rekindled when Harper, Kidd, and Scratcherd⁹ demonstrated vago-vagal effects on the stomach intestine and pancreas. This, coupled with the observation that antral extracts had a pancreozymin-like action on the pancreas¹⁰, led to a re-examination of the effects of the stomach on the pancreas. In cats it was shown that distension of the body or antrum increased the output of pancreatic amylase. After vagal section distension of the body had no effect on the pancreas but the response to antral distension persisted¹¹. The gastric phase of pancreatic secretion therefore involved a vago-vagal reflex pathway for the response to stimulation of the body of the stomach. Chemical and mechanical stimulation of the antrum produced a humorally mediated increase in pancreatic enzyme secretion, but a possible nervous reflex element could not be excluded. The effects of atropine and cocaine on the response were consistent with the view that a local cholinergic pathway was involved in the release of the antral stimulant. It has also been shown that there is a gastric phase of pancreatic secretion in dogs^{12,13,14} and man¹⁵.

In all species the gastric phase, like the cephalic phase, produces enzymes rather than a secretion of water and bicarbonate. This is the type of pancreatic response produced by gastrin and gastrin analogues, although there is considerable divergence in the literature about the ratio of gastric and pancreatic activities of the different substances^{16,17,18,19}.

Intestinal Phase of Pancreatic Secretion

The major part of the pancreatic response during digestion is dependent on the passage of acid and the digestion products of protein and fat along the small intestine. In contrast to the neurohumoral basis of the cephalic and gastric phases of secretion the intestinal phase has been regarded as hormonally mediated by secretin and pancreozymin, with a possible local nervous involvement in the release of the hormones. The ability of an extrinsically denervated intestine and pancreas to achieve a satisfactory response to stimulation does not preclude an influence of the central nervous system in the intact animal, and it is of interest that Andrews²⁰ has recently recorded afferent impulses in the mesenteric nerves of rabbits in response to intra-duodenal infusions of acid. Vagotomy, it has been claimed, increases^{21,22}, decreases^{23,24}, or has no effect on²⁵, the responses to secretin. The fact that anticholinergic drugs have less inhibitory effect on the response to injected secretin than on that to stimulants in the intestine supports the concept that the release of the intestinal hormones involves a local cholinergic pathway^{26,27}. Local anaesthetics applied to the intestinal mucosa inhibit or reduce the response of the pancreas to intestinal stimulants^{28,29,30}, and hexamethonium prevents the release of cholecystikinin, possibly by blocking afferent endings in the mucosa³¹. It has been claimed³², and denied³³, that perfusing the small intestine with acetylcholine stimulates the pancreas.

For the last 20 years it has been accepted, from the results of Wang and Grossman³⁴, that a range of substances could stimulate secretion of both secretin and pancreozymin, though the proportions of the hormones released varied for the different stimuli. Hydrochloric acid, for example, was a power-

ful excitant of secretin, but less effective for pancreozymin; with amino acids and fatty acids this situation was reversed. For reasons which will be considered in detail later, Grossman has recently³ stated that the conclusions drawn by Wang and Grossman were based on invalid assumptions.

Intestinal Acid and Pancreatic Secretion

Acidification of the intestine has been the standard technique of achieving secretin release since the time of Bayliss and Starling. There have, however, been doubts about the significance of acid in the response of the pancreas during a meal, because the neutralizing effect of pancreatic juice reduces the acidity of the intestinal contents below the threshold for secretin release except in a short length beyond the pylorus. A valuable analysis of the quantitative relationship between acid infusions into the small intestine and bicarbonate secretion by the pancreas has been made by Grossman and his colleagues^{35,36,37}. They showed that below $pH 3$ bicarbonate secretion was independent of the pH of the acid entering the intestine. Above this level of pH there was a rapid decrease in bicarbonate secretion, with a response threshold about $pH 4.5$. Below this pH threshold, for a segment of fixed length, bicarbonate secretion was a function of the rate of entry of titratable acid into the intestine, the end point of titration being $pH 4.5$. The response was also a function of the length of small intestine acidified. Judged by the response to acidification the gradient of decrease in releasable secretin from the pylorus onwards is less steep than the gradient of extractable secretin.³⁸

Grossman has stated that acid is the only agent which can release secretin³, but has more recently modified this view to the extent that fatty acids may also release small amounts of secretin³⁸. If acid is the only or main releaser of secretin and the pH of intestinal contents during digestion falls below the threshold for secretin release for only some 20 to 30 cm beyond the pylorus, it seems likely that the total amount of secretin released during digestion is small, of the order of 0.5 clinical unit/kg-hr. To account for the large amount of water and bicarbonate secreted by the pancreas during digestion Grossman and his colleagues suggest that pancreozymin, released by amino acids and fatty acids, greatly potentiates the effects of secretin. Gastrin and cholinergic stimuli are also credited with a similar potentiating action.

This concept of interaction of secretin and pancreozymin effects on the pancreas is part of a comprehensive hypothesis about the actions and interactions of gastrointestinal hormones which has been elaborated by Grossman^{39,40}. It is suggested that each of the three fully characterized hormones—gastrin, secretin, and cholecystokinin-pancreozymin—acts on all target organs in the gastrointestinal tract. Some of the effects, eg, of secretin on gallbladder contraction, are produced only by pharmacological doses of the hormone. Pairs of hormones may interact by augmenting or inhibiting, competitively or non-competitively, the primary action of one of the pair. The physiological functions attributed to secretin are a powerful effect on water and bicarbonate secretion and a weak effect on enzyme secretion. Pancreozymin is credited with some stimulant action on the volume and bicarbonate content of the juice in addition to its main action on enzyme output. In addition, both hormones inhibit the acid-stimulating effect of gastrin and may, with the assistance of another unidentified hormone, account for the inhibition of gastric secretion produced by a variety of agents in the small intestine.

Secretin and Pancreozymin Units

Before considering the evidence for this hypothesis it is necessary to deal with the somewhat confused situation about secretin and pancreozymin units. There are two preparations of the hormones currently available. Boots' secretin and pancreozymin are relatively crude preparations, and their potency is defined in Crick-Harper-Raper units⁴¹. Of the highly purified preparations from the GIH laboratory in Stockholm, secretin is issued in clinical units and pancreozymin is standardized on its cholecystokinin activity in terms of Ivy dog units. Jorpes⁴² has stated that 1 Ivy dog unit of cholecystokinin is equivalent to 4 Crick-Harper-Raper units of pancreozymin and this relationship presumably holds for the earlier Swedish preparation, Cecekin. Confusion has arisen over the equivalence of secretin units because, about 1967 or 1968, the potency of the clinical unit was suddenly increased. Previously it had been equivalent to 2 Crick-Harper-Raper secretin units, but in 1968 Stening, Vagne, and Grossman⁴³ reported that 1 clinical unit equalled 8 or 9 Crick-Harper-Raper units. It is difficult in papers published about this time to know whether the authors used the weaker or more powerful secretin preparations. Following the final purification and synthesis of secretin it has been shown that 1 μ g secretin equals 3-4 clinical units⁴⁴.

Several estimates have been made of the dose required to produce a maximal response from the gland. Banwell, Northam, and Cooke found that in man a maximal enzyme secretion was achieved by infusion of 0.125-0.375 Crick-Harper-Raper units of pancreozymin/kg-min. In reports published since the increase in the potency of the clinical unit of secretin it has been claimed that in man a maximal bicarbonate secretion is produced by infusion of highly purified secretion at a rate of 3 clinical units/kg-hr (Rune and Worning⁴⁵) or by 0.9 clinical unit/kg of pure secretin, either by rapid intravenous injection or infusion over an hour (Konturek⁴⁶). In cats the doses required to produce a maximal response are 2.0 units/kg by rapid intravenous injection⁴⁷, and by continuous infusion 3.2⁴⁸ or 4.0⁴⁹ units/kg-hr.

In recent years most investigators have used 'purified' rather than 'pure' hormones, and the 'highly purified' Swedish pancreozymin preparation is in fact 10% pure. In the small minority of papers in which the amount of hormone admixture is stated the degree of contamination is surprisingly high, eg (in Crick-Harper-Raper units), 100 units of Boots' secretin contained 25 units of pancreozymin⁵⁰, and in a purified Swedish preparation of 300 units of pancreozymin there were 50 units of secretin⁵¹.

Release of Secretin and Pancreozymin

With the exception of one claim that intraduodenal acid is a more powerful releasing agent for cholecystokinin than protein or fat digestion products⁵¹, it is generally accepted that the main action of acid is to release secretin, and that only when perfused in larger amounts does it significantly increase enzyme secretion, presumably by releasing pancreozymin⁵⁸. Individual amino acids and mixtures of amino acids have been shown to be effective stimulants of enzyme secretion in man^{51,52}. In dogs Meyer, Spingola, and Grossman⁵³ have claimed that phenylalanine releases only pancreozymin. One of the main pieces of evidence is the similarity between dose response curves for

intraduodenal phenylalanine and exogenous purified pancreatico-zymin. Since this type of pancreatico-zymin preparation is known to contain significant amounts of secretin⁵¹ the logical conclusion would seem to be that phenylalanine releases some secretin as well as larger amounts of pancreatico-zymin, as is now said to be the response produced by micellar preparations of fatty acids³⁸. Grossman's present view is that the range of releasers of secretin or pancreatico-zymin is less and their specificity greater than suggested by Wang and Grossman³⁴, whose conclusions were based on the erroneous assumption that pancreatico-zymin did not excite a secretion of water and bicarbonate by the pancreas.

Mellanby's old hypothesis that bile was concerned with stimulation of pancreatic secretion⁵⁴ has been revived by Forell and his colleagues⁵⁵ and by Wormsley⁵⁶, who have found in man that intraduodenal infusion of bile salts stimulates secretion, particularly of enzymes. It has been claimed that in anaesthetized dogs balloon distension of the proximal jejunum releases pancreatico-zymin⁵⁷, but Sum, Schipper, and Preshaw³³ found that distension of the duodenum in conscious dogs, which increased gastric secretion, had no effect on the pancreas.

Actions and Interactions of Secretin and Pancreo-zymin

In accord with Grossman's hypothesis of the interaction of gastrointestinal hormones secretin should stimulate enzyme secretion and pancreatico-zymin secretion of water and bicarbonate, and each should augment the primary pancreatic action of the other. These effects should be produced by injection of hormones, or their endogenous release by the appropriate intestinal stimuli.

It has been reported by Wormsley⁵⁸ that very large doses of Boots' secretin increased trypsin output in man. In dogs Henriksen⁵⁹ found no clear evidence that synthetic secretin stimulated enzyme output, and Henriksen and Möller⁶⁰ obtained a 50% increase above basal protein output with large doses of pure natural secretin. Douglas and Duthie⁶¹ found that secretin had no effect on protein output in conscious dogs.

Brooks and his coworkers⁵¹ observed increased volume flow and bicarbonate output in human subjects given the maximal tolerated dose of purified pancreatico-zymin by intravenous infusion or intrajejunal infusions of a mixture of amino acids to release endogenous pancreatico-zymin. They considered that the contamination of the pancreatico-zymin preparation by secretin was sufficient to account for the volume and bicarbonate responses to intravenous pancreatico-zymin and that the similar effects produced by the amino acid mixture pointed to a release of secretin by this stimulus. Meyer, Spingola, and Grossman⁵³ used a similar type of pancreatico-zymin preparation in dogs, with intraduodenal phenylalanine, to release endogenous pancreatico-zymin. They also observed increases in bicarbonate output, and, since they maintain that phenylalanine does not release secretin, they concluded that pancreatico-zymin is a weak stimulant of bicarbonate secretion. An alternative explanation, along the lines of that proposed by Brooks, seems possible. In dogs Henriksen⁶² found evidence that pancreatico-zymin affected the secretion of water and bicarbonate, and Douglas and Duthie⁶¹ thought it increased the output of bicarbonate slightly. Case, Harper, and Scratcherd⁶³ found no evidence of stimulation of bicarbonate secretion by pancreatico-zymin in cats.

From experiments on dogs to test whether secretin potentiates the action

of pancreaticozymins it has been concluded that secretin has no effect on pancreaticozymins-stimulated protein output⁶¹, that it has some effect, which may be more apparent than real⁶⁴, and that the protein responses to injected pancreaticozymins or intraduodenal phenylalanine are increased by secretin but the data are inadequate to determine whether the increases indicate a true potentiation⁵³. Csendes, Isenberg, and Grossman⁶⁵ have reported that synthetic secretin increases the protein response to the C-terminal octapeptide of cholecystokinin-pancreaticozymins. There is more general agreement that in cats⁷ and dogs^{50,53,61,62} pancreaticozymins augment the response to secretin. In man supramaximal doses of pancreaticozymins potentiate the bicarbonate response to small amounts of secretin⁶⁶.

It has been suggested that the physiological actions of secretin and pancreaticozymins include not only their pancreatic effects but also inhibition of gastrin-stimulated acid secretion by the stomach. On this basis can be constructed the attractive hypothesis that secretin and pancreaticozymins achieve the optimal intestinal pH and enzyme concentration for digestion not only by stimulating the pancreas but also by restraining the oxyntic cells. The inhibitory effects of secretin and pancreaticozymins have been intensively studied in dogs, and the literature has recently been reviewed by Johnson and Grossman⁶⁷. In this review it is stated (pp 123 and 125) that in dogs secretin and pancreaticozymins are more powerful inhibitors of gastrin-stimulated acid secretion than they are stimulants of pancreatic secretion, which is difficult to reconcile with the observation (p 131) that amino acids in the canine duodenum provoke a typical pancreaticozymins response from the pancreas but do not inhibit gastrin-stimulated acid secretion. In man and the cat the evidence for inhibition of gastric secretion by secretin and pancreaticozymins is much less convincing. Brooks and Grossman⁶⁸ achieved only moderate inhibition of acid secretion by large infusions of pancreaticozymins and supramaximal dosage of secretin. In cats it seems unlikely that this mechanism is of any physiological significance since Emås, Svensson, and Borg⁶⁹ had to administer supramaximal injections of pancreaticozymins or intestinal acid infusions greater than the maximal gastric secretory capacity to achieve inhibition of acid secretion, and Svensson and Emås⁷⁰, from the slight inhibitory effects produced by very large injections of pancreaticozymins, concluded that it was unlikely that pancreaticozymins exert any inhibitory action on acid secretion in physiological conditions.

In assessing the claims for physiological interactions between secretin and pancreaticozymins and for an extension of their individual physiological functions, one must bear in mind that most of the observations have been made with partly purified preparations. Many of the effects attributed to one hormone may be due to contamination with the other. Grossman⁷¹ has suggested as one criterion of a physiological response that it should be produced at a dose level not exceeding that required to produce the maximal 'primary' response of the hormone, eg, secretion of water and bicarbonate by secretin. There seems every justification for applying the more rigorous criterion that the dose should not exceed the amount released during normal digestion. This is difficult to determine accurately but Worning and Henriksen⁷² have estimated that in dogs the mean pancreatic secretion after ingestion of a meal would be produced by 0.6 Crick-Harper-Raper unit/kg of secretin and 0.1 Crick-Harper-Raper unit/kg of pancreaticozymins. These are of course very much less than the amounts required to produce a maximal pancreatic response.

When these stricter criteria are applied to published claims there still remains evidence for an inhibitory action of secretin and pancreozymin on gastric secretion in the dog, but none for any physiological inhibition in cat or man. The species difference may seem surprising, but Wormsley⁷³ has ingeniously suggested that the inhibitory mechanism may be of value in the dog, which has a pancreatic alkaline capacity only one-third of its gastric acid capacity⁷⁴, but an unnecessary luxury in cat and man, who can match gastric acid with pancreatic bicarbonate. Of the pancreatic effects there is no satisfactory evidence that secretin in physiological doses stimulates enzyme output or enhances the action of pancreozymin on enzyme secretion. The evidence that pancreozymin by itself produces significant amounts of water and bicarbonate is not wholly convincing, but there can be no doubt that it potentiates the effects of secretin.

Mechanism of Potentiation of Secretin by Pancreozymin

Pancreozymin may, as suggested by Henriksen and Worning⁵⁰, increase the sensitivity of the bicarbonate-secreting cells to secretin. Alternatively, or in addition, it may, by producing a vasodilatation of the pancreas, increase the supply of circulating secretin to the glandular tissue. Most of the published evidence^{75,76,77} supports the view that the first injection of secretin increases the blood flow of a resting pancreas, but subsequent injections have very little vascular effect although secretion is unimpaired. Vagal stimulation, and injections of pancreozymin and gastrin, all of which potentiate the secretory action of secretin, also increase pancreatic blood flow. Brown, Harper, and Scratcherd⁷ suggested that the basal secretion of water and bicarbonate in the dog might depend in part on an unknown blood-borne stimulant, the effect of which could be potentiated by pancreatic vasodilatation. In accord with this view is the observation by Hermon-Taylor⁷⁸ that in the isolated canine pancreas, perfused with the animal's own blood, there was a basal secretion. This secretion was potentiated by pure gastrin II, which caused a vasodilatation in the gland.

Inhibition of Pancreatic Secretion

There has been little investigation of inhibition of pancreatic secretion. Intestinal infusion of hypertonic glucose solutions inhibits the pancreatic response to secretin in dogs⁷⁹, and oral hypertonic glucose solutions depress pancreatic secretion in man⁸⁰. The mechanism of the inhibition is unknown. Section of the splanchnic nerves⁸¹ or the administration of a beta-blocking agent⁸² increase pancreatic secretion. Harper and Vass⁸¹ suggested that stimulation of the splanchnic nerves might, in addition to its constrictor effect on the pancreatic vessels, directly inhibit the glandular tissues, and it has recently been shown that catechol amines inhibit pancreatic secretion even when their constrictor effect has been abolished by alpha-receptor blockade⁸³. Glucagon has no effect on basal pancreatic secretion in man⁸⁴, but against a background of secretin and pancreozymin stimulation it produces in small doses a well marked depression of flow and enzyme output in dogs⁸⁵ and in man⁸⁶. The physiological significance of these observations is not yet clear.

A. A. HARPER

Department of Physiology, University of Newcastle upon Tyne

References

- ¹Preshaw, R. M. (1967). Integration of nervous and hormonal mechanisms for external pancreatic secretion. In *Handbook of Physiology, Sect. 6, Alimentary Canal*, edited by C. F. Code, vol. II, *Secretion*, pp. 997-1005. American Physiological Society, Washington, D.C.
- ²Harper, A. A. (1967). Hormonal control of pancreatic secretion. In *Handbook of Physiology, Section 6, Alimentary Canal*, edited by C. F. Code, vol. II, *Secretion*, pp. 969-995. American Physiological Society, Washington, D.C.
- ³Grossman, M. I. (1971). Control of pancreatic secretion. In *The Exocrine Pancreas: Proceedings of a Symposium held at Queen's University, Kingston, Ontario, June 1969*, edited by I. T. Beck and D. G. Sinclair, ch. 5, p. 59. Churchill, London.
- ⁴Preshaw, R. M., Cooke, A. R., and Grossman, M. I. (1966). Sham feeding and pancreatic secretion in the dog. *Gastroenterology*, 50, 171-178.
- ⁵Salles, H., Dani, R., Prezelin, G., Souville, C., and Figarella, C. (1968). Cephalic phase of pancreatic secretion in man. *Gut*, 9, 214-221.
- ⁶Hickson, J. C. D. (1970). The secretion of pancreatic juice in response to stimulation of the vagus nerves in the pig. *J. Physiol. (Lond.)*, 206, 275-297.
- ⁷Brown, J. C., Harper, A. A., and Scratcherd, T. (1967). Potentiation of secretin stimulation of the pancreas. *J. Physiol. (Lond.)*, 190, 519-530.
- ⁸Lenninger, S., and Ohlin, P. (1971). The flow of juice from the pancreatic gland of the cat in response to vagal stimulation. *J. Physiol. (Lond.)*, 216, 303-318.
- ⁹Harper, A. A., Kidd, C., and Scratcherd, T. (1959). Vago-vagal reflex effects on gastric and pancreatic secretion and gastro-intestinal motility. *J. Physiol. (Lond.)*, 148, 417-436.
- ¹⁰Blair, E. L., Harper, A. A., Lake, H. J., Reed, J. D., and Scratcherd, T. (1961). A simple method of preparing gastrin. *J. Physiol. (Lond.)*, 156, 11-13P.
- ¹¹Blair, E. L., Brown, J. C., Harper, A. A., and Scratcherd, T. (1966). A gastric phase of pancreatic secretion. *J. Physiol. (Lond.)*, 184, 812-824.
- ¹²Passaro, E., Jr., and Grossman, M. I. (1963). Studies of the gastric phase of pancreatic secretion. *Gastroenterology*, 44, 864-865.
- ¹³Preshaw, R. M., Cooke, A. R., and Grossman, M. I. (1965). Pancreatic secretion induced by stimulation of the pyloric gland area of the stomach. *Science*, 148, 1347-1348.
- ¹⁴White, T. T., Lundh, G., and Magee, D. F. (1960). Evidence for the existence of a gastropancreatic reflex. *Amer. J. Physiol.*, 198, 725-728.
- ¹⁵White, T. T., McAlexander, R. A., and Magee, D. F. (1962). Gastro-pancreatic reflex after various gastric operations. *Surg. Forum*, 13, 286-288.
- ¹⁶Beswick, F. B., Howat, H. T., and Morris, A. I. (1968). The effects of gastrin and peptide analogues related to gastrin on cats. *J. Physiol. (Lond.)*, 197, 71-72P.
- ¹⁷Emås, S., Billings, A., and Grossman, M. I. (1968). Effects of gastrin and pentagastrin on gastric and pancreatic secretion in dogs. *Scand. J. Gastroent.*, 3, 234-240.
- ¹⁸Morris, A. I., Beswick, F. B., Howat, H. T., and Morley, J. S. (1968). Action of gastrin and gastrin analogues on cat stomach and pancreas. *Progress in Pancreatology: Proceedings of the 3rd Symposium of the European Pancreatic Club*, edited by P. Frič, F. Mališ, and R. Ronský, pp. 42-49. Czechoslovak Medical Press, Prague.
- ¹⁹Petersen, H., and Berstad, A. (1971). Effect of pentagastrin on pancreatic secretion in man. In *European Pancreatic Club, 5th Symposium: Abstracts*, 39 bis.
- ²⁰Andrews, C. J. H., and Andrews, W. H. H. (1971). Receptors activated by acid, in the duodenal wall of rabbits. *Quart. J. exp. Physiol.*, 56, 221-230.
- ²¹Moreland, H. J., and Johnson, L. R. (1971). Effect of vagotomy on pancreatic secretion stimulated by endogenous and exogenous secretin. *Gastroenterology*, 60, 425-431.
- ²²Routley, E. F., Mann, F. C., Bollman, J. L., and Grindley, J. H. (1952). Effects of vagotomy on pancreatic secretion in dogs with chronic pancreatic fistula. *Surg. Gynec. Obstet.*, 95, 529-536.
- ²³Magee, D. F., Fragola, L. A., and White, T. T. (1965). Influence of parasympathetic innervation on the volume of pancreatic juice. *Ann. Surg.*, 161, 15-20.
- ²⁴Wormsley, K. G. (1972). The effect of vagotomy on the human pancreatic response to direct and indirect stimulation. *Scand. J. Gastroent.*, 7, 85-91.
- ²⁵Henriksen, F. W. (1969). Effect of vagotomy or atropine on the canine pancreatic response to secretin and pancreozymin. *Scand. J. Gastroent.*, 4, 137-144.
- ²⁶Thomas, J. E. (1964). Mechanism of action of pancreatic stimuli studied by means of atropinelike drugs. *Amer. J. Physiol.*, 206, 124-128.
- ²⁷Thomas, J. E., and Crider, J. O. (1946). The secretion of pancreatic juice in the presence of atropine or hyoscynamine in chronic fistula dogs. *J. Pharmacol. exp. Ther.*, 87, 81-89.
- ²⁸Schapiro, H., and Woodward, E. R. (1962). Inhibition of secretin mechanism with local anaesthetics. *Physiologist*, 5, 208.
- ²⁹Thomas, J. E., and Swena, E. M. (1963). The effect of local anaesthetics applied to the intestinal mucosa on the response of the pancreas to intestinal stimuli. (Abstr.) *Fed. Proc.*, 22, 664.
- ³⁰Slayback, J. B., Swena, E. M., Thomas, J. E., and Smith, L. I. (1967). The pancreatic secretory response to topical anesthetic block of the small bowel. *Surgery*, 61, 591-595.
- ³¹Berry, H., and Flower, R. J. (1971). The assay of endogenous cholecystokinin and factors influencing its release in the dog and cat. *Gastroenterology*, 60, 409-420.
- ³²Brown, J. C. (1964). Physiological studies on the gastrointestinal hormones affecting the pancreas. PhD Thesis, University of Newcastle upon Tyne.
- ³³Sum, P. T., Schipper, H. L., and Preshaw, R. M. (1969). Canine gastric and pancreatic secretion during intestinal distension and intestinal perfusion with choline derivatives. *Canad. J. Physiol. Pharmacol.*, 67, 115-118.
- ³⁴Wang, C. C., and Grossman, M. I. (1951). Physiological determination of the release of secretin and pancreozymin from intestine of dogs with transplanted pancreas. *Amer. J. Physiol.*, 164, 527-545.
- ³⁵Preshaw, R. M., Cooke, A. R., and Grossman, M. I. (1966). Quantitative aspects of response of canine pancreas to duodenal acidification. *Amer. J. Physiol.*, 210, 629-634.
- ³⁶Meyer, J. H., Way, L. W., and Grossman, M. I. (1970). Pancreatic bicarbonate response to various acids in duodenum of the dog. *Amer. J. Physiol.*, 219, 964-970.

- ³⁷Meyer, J. H., Way, L. W., and Grossman, M. I. (1970). Pancreatic response to acidification of various lengths of proximal intestine in the dog. *Amer. J. Physiol.*, 219, 971-977.
- ³⁸Meyer, J. H., and Grossman, M. I. (1971). Release of secretin and cholecystokinin. In *Symposium on Gastrointestinal Hormones*, Erlangen, Germany.
- ³⁹Grossman, M. I. (1970). Effect of gastrin, cholecystokinin and secretin on gastric and pancreatic secretion: a theory of interaction or hormones. In *Origin, Chemistry and Physiology of the Gastrointestinal Hormones*, edited by W. Creutzfeldt, p. 129. Schattauer, Stuttgart.
- ⁴⁰Grossman, M. I. (1971). Interactions of gastrointestinal hormones. In *2nd International Symposium on Protein and Polypeptide Hormones*, Liège.
- ⁴¹Crick, J., Harper, A. A., and Raper, H. S. (1949). On the preparation of secretin and pancreozymin. *J. Physiol. (Lond.)*, 110, 367-376.
- ⁴²Jorpes, J. E. (1968). The isolation and chemistry of secretin and cholecystokinin. *Gastroenterology*, 55, 157-164.
- ⁴³Stening, G. F., Vagne, M., and Grossman, M. I. (1968). Relative potency of commercial secretins. *Gastroenterology*, 55, 687-689.
- ⁴⁴Vagne, M., Stening, G. F., Brooks, F. P., and Grossman, M. I. (1968). Synthetic secretin: comparison with natural secretin for potency and spectrum of physiological actions. *Gastroenterology*, 55, 260-267.
- ⁴⁵Rune, S. J., and Worning, H. (1970). The pancreatic response to instillation of acid into the duodenum and to exogenous secretin in man. *Scand. J. Gastroent.*, 6, 291-296.
- ⁴⁶Konturek, S. J. (1970). Pancreatic dose-response curves to intravenous secretin in man. *Gastroenterology*, 58, 828-832.
- ⁴⁷Stening, G. F., Johnson, L. R., and Grossman, M. I. (1969). Effect of secretin on acid and pepsin secretion in cat and dog. *Gastroenterology*, 56, 468-475.
- ⁴⁸Konturek, S. J., Gabrys, B., and Dubiel, J. (1969). Effect of exogenous and endogenous secretin on gastric and pancreatic secretion in cats. *Amer. J. Physiol.*, 217, 1110-1113.
- ⁴⁹Konturek, S. J., Radecki, T., Mikos, E., and Thor, J. (1971). The effect of exogenous and endogenous secretin and cholecystokinin on pancreatic secretion in cats. *Scand. J. Gastroent.*, 6, 423-428.
- ⁵⁰Henriksen, F. W., and Worning, H. (1967). The interaction of secretin and pancreozymin on the external pancreatic secretion in dogs. *Acta physiol. scand.*, 70, 241-249.
- ⁵¹Ertan, A., Brooks, F. P., Ostrow, J. D., Arvan, D. A., Williams, C. N., and Cerda, J. J. (1971). Effect of jejunal amino acid perfusion and exogenous cholecystokinin on the exocrine pancreatic and biliary secretions in man. *Gastroenterology*, 61, 686-692.
- ⁵²Go, V. L. W., Hofmann, A. F., and Summerskill, W. H. J. (1968). Specificity and potency of amino acids in the release of pancreozymin in man. (Abstr.) *J. Lab. clin. Med.*, 72, 875-876.
- ⁵³Meyer, J. H., Spingola, L. J., and Grossman, M. I. (1971). Endogenous cholecystokinin potentiates exogenous secretin on pancreas of dog. *Amer. J. Physiol.*, 221, 742-747.
- ⁵⁴Mellanby, J. (1926). The secretion of pancreatic juice. *J. Physiol. (Lond.)*, 61, 419-435.
- ⁵⁵Forell, M. M., Otte, M., Kohl, H. J., Lehnert, P., and Stahlheber, H. P. (1971). The influence of bile and pure bile salts on pancreatic secretion in man. *Scand. J. Gastroent.*, 6, 261-265.
- ⁵⁶Wormsley, K. G. (1970). Stimulation of pancreatic secretion by intraduodenal infusion of bile-salts. *Lancet*, 2, 586-588.
- ⁵⁷Chung, R. B. K., Fromm, D., Trencis, L., and Silen, W. (1970). Gastric and pancreatic responses to jejunal distension: effects of extracorporeal mesenteric vascular perfusion. *Gastroenterology*, 59, 387-395.
- ⁵⁸Wormsley, K. G. (1968). The action of secretin on the secretion of enzymes by the human pancreas. *Scand. J. Gastroent.*, 3, 183-188.
- ⁵⁹Henriksen, F. W. (1968). Effect of synthetic secretin on the external pancreatic secretion. In *Progress in Pancreatology: Proceedings of the 3rd Symposium of the European Pancreatic Club*, pp. 207-210. Czechoslovak Medical Press, Prague.
- ⁶⁰Henriksen, F. W., and Möller, S. (1971). Effect of secretin on the pancreatic secretion of protein. *Scand. J. Gastroent.*, Suppl. 9, 181-187.
- ⁶¹Douglas, M., and Duthie, H. L. (1971). Pancreozymin and secretin in the control of pancreatic exocrine secretion. (Abstr.) *Gut*, 12, 862.
- ⁶²Henriksen, F. W. (1968). Effect of pancreozymin on the canine pancreatic secretion of fluid and bicarbonate. *Scand. J. Gastroent.*, 3, 637-640.
- ⁶³Case, R. M., Harper, A. A., and Scratcherd, T. (1969). The secretion of electrolytes and enzymes by the pancreas of the anaesthetized cat. *J. Physiol. (Lond.)*, 201, 335-348.
- ⁶⁴Henriksen, F. W. (1968). The maximal pancreatic secretion in dogs. *Scand. J. Gastroent.*, 3, 140-144.
- ⁶⁵Csendes, A., Isenberg, J. I., and Grossman, M. I. (1971). Pancreatic protein secretion in response to secretin plus C-terminal octapeptide of cholecystokinin. *Gastroenterology*, 60, 770.
- ⁶⁶Wormsley, K. G. (1969). A comparison of the response to secretin, pancreozymin and a combination of these hormones in man. *Scand. J. Gastroent.*, 4, 413-417.
- ⁶⁷Johnson, L. R., and Grossman, M. I. (1971). Intestinal hormones as inhibitors of gastric secretion. *Gastroenterology*, 60, 120-144.
- ⁶⁸Brooks, A. M., and Grossman, M. I. (1970). Effect of secretin and cholecystokinin on pentagastrin-stimulated gastric secretion in man. *Gastroenterology*, 59, 114-119.
- ⁶⁹Emås, S., Svensson, S. O., and Borg, I. (1971). Effect of duodenal acidification or exogenous secretin on gastric acid secretion stimulated by histamine pentagastrin or human gastrin I in conscious cats. *Digestion*, 5, 17-30.
- ⁷⁰Svensson, S.-O., and Emås, S. (1971). Effect of cholecystokinin on histamine- and pentagastrin-stimulated acid secretion in conscious cats. *Scand. J. Gastroent.*, 6, 371-376.
- ⁷¹Grossman, M. I. (1968). Summary of biological actions of secretin. In *Progress in Pancreatology: Proceedings of the 3rd Symposium of the European Pancreatic Club*, pp. 34-35. Czechoslovak Medical Press, Prague.
- ⁷²Worning, H., and Henriksen, F. W. (1968). The external pancreatic response to food and its relation to the maximal secretory capacity in dogs. In *Progress in Pancreatology: Proceedings of the 3rd Symposium of the European Pancreatic Club*, pp. 189-193. Czechoslovak Medical Press, Prague.
- ⁷³Wormsley, K. G. (1972). Inhibition of gastric acid secretion. (Letter.) *Gastroenterology*, 62, 156-157.
- ⁷⁴Perrier, C. V., Baron, J. H., Dreiling, D. A., and Janowitz, H. D. (1967). Relationship between maximum bicarbonate and maximum acid outputs in the dog. *Proc. Soc. exp. Biol. (N.Y.)*, 124, 312-314.
- ⁷⁵Barlow, T. E., Greenwell, J. R., Harper, A. A., and Scratcherd, T. (1968). Factors influencing pancreatic blood flow. In *Blood Flow Through Organs and Tissues: Proceedings of an International Conference*, Glasgow.

- March 1967, edited by W. H. Bain and A. M. Harper, pp. 469-486. Livingstone, Edinburgh.
- ⁷⁴Aune, S., and Semb, L. S. (1969). The effect of secretin and pancreozymin on pancreatic blood flow in the conscious and anesthetised dog. *Acta physiol. scand.*, **76**, 406-414.
- ⁷⁷Hickson, J. C. D. (1970). The secretory and vascular response to nervous and hormonal stimulation in the pancreas of the pig. *J. Physiol. (Lond.)*, **206**, 299-322.
- ⁷⁸Hermon-Taylor, J. (1968). A technique for perfusion of the isolated canine pancreas: responses to secretin and gastrin. *Gastroenterology*, **55**, 488-501.
- ⁷⁹Lawrence, W., Jr., Khentigan, A., Hudock, J., and Vanamee, P. (1961). The effect of intraduodenal administration of hypertonic glucose solution on external pancreatic secretion. *Surgery*, **49**, 666-675.
- ⁸⁰Hong, S. S., Chin, D. S., and Hur, K. B. (1961). Influences of hexamethonium and some dietary factors on human pancreatic and bile secretion. *J. appl. Physiol.*, **16**, 810-814.
- ⁸¹Harper, A. A., and Vass, C. C. N. (1941). The control of the external secretion of the pancreas in cats. *J. Physiol. (Lond.)*, **99**, 415-435.
- ⁸²Suda, Y., Robinson, L. A., and White, T. T. (1969). The effects of adrenergic blocking agents on pancreatic secretion in dogs. *Ann. Surg.*, **169**, 625-630.
- ⁸³Barlow, T. E., Greenwell, J. R., Harper, A. A., and Scratcherd, T. (1971). The effect of adrenaline and noradrenaline on the blood flow, electrical conductance and external secretion of the pancreas. *J. Physiol. (Lond.)*, **217**, 665-678.
- ⁸⁴Dreiling, D. A., Janowitz, H. D., Haemmerli, U. P., and Marshall, D. (1958). The effect of glucagon on the exocrine pancreatic secretion of man. *J. Mt Sinai Hosp.*, **25**, 240-243.
- ⁸⁵Dyck, W. P., Rudick, J., Hoexter, B., and Janowitz, H. D. (1969). Influence of glucagon on pancreatic exocrine secretion. *Gastroenterology*, **56**, 531-537.
- ⁸⁶Dyck, W. P., Texter, E. C., Jr., Lasater, J. M., and Hightower, N. C., Jr. (1970). Influence of glucagon on pancreatic exocrine secretion in man. *Gastroenterology*, **58**, 532-539.