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POTENTIATION OF SECRETIN STIMULATION OF THE PANCREAS

BY J. C. BROWN,* A. A. HARPER AND T. SCRATCHERD

From the Department of Physiology, Medical School, University of Newcastle upon Tyne, Newcastle upon Tyne 1

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SUMMARY

1. In fasted anaesthetized cats which were secreting pancreatic juice at a steady slow rate in response to continuous intravenous infusion of secretin, stimulation of the dorsal vagus trunk increased the rate of secretion, the rate of output of amylase and the concentration of bicarbonate in the juice.

2. The increase in rate of secretion and in concentration of bicarbonate was reduced but not abolished by atropine. It was unaffected by adrenergic blocking agents, but abolished by hexamethonium.

3. No increase in rate of secretion of secretin-stimulated juice was observed on cervical stimulation of vagus nerves in which the efferent fibres had degenerated after supra-nodose section of the nerves. It is concluded that the increase in secretion rate is mediated by 'atropine-resistant' efferent vagal fibres.

4. Pancreozymin, antral extracts and histamine increased the rate of secretion of secretin-stimulated juice. Pancreozymin and antral extracts also increased the rate of amylase output. These effects of pancreozymin and antral extracts were not abolished by atropine or hexamethonium.

5. As vagal stimulation pancreozymin, antral extracts and histamine have little or no effect on the resting pancreas of the anaesthetized cat, it is concluded that they exert a potentiating effect on secretin. It is suggested that the mechanism of this potentiation is an increase in pancreatic blood flow, which facilitates the supply of secretin to the gland.

INTRODUCTION

Recently there has been increasing emphasis on the interrelation between nervous and hormonal regulation of pancreatic secretion during digestion (Blair, Harper & Scratcherd, 1962; Grossman, 1962). Interest has

* During tenure of a Junior Luccock Research Fellowship. Present address: Department of Physiology, University of British Columbia, Vancouver 8, British Columbia, Canada.

been directed chiefly to nervous participation, either locally in the gut wall or by reflexes through the central nervous system, in the release of pancreatic hormonal stimulants from the stomach and small intestine. The pancreatic cells, however, have been thought to show specific responses to nervous and hormonal stimulation, enzymes being released under the influence of vagal or pancreozymin stimulation, and water and electrolytes in response to secretin. The question whether there is an interaction between the nervous and hormonal effects on the pancreatic cells has been asked by a number of investigators, and the contradictory answers obtained seem to depend on the species studied.

In dogs Gayet & Guillaumie (1930*b*) found that vagal stimulation greatly increased the rate of flow of juice produced in response to secretin stimulation, and Thomas (1950) observed that a previous injection of secretin markedly potentiated the response to subsequent vagal stimulation. It was also in dogs that Hermann & Hutet (1943) found that the effect of secretin was potentiated by small doses of eserine which by themselves were ineffective as pancreatic stimulants. In cats on the other hand pilocarpine did not potentiate the response to secretin (Eisler & Ågren, 1936). Nor did stimulation of the vagus, either directly (Harper & Vass, 1941) or reflexly (Harper, Kidd & Scratcherd, 1959), increase the rate of flow of secretin-stimulated juice in cats. Pancreozymin was thought to influence only the enzyme content of pancreatic juice, and any slight stimulant action on the rate of secretion was attributed to residual contamination of the pancreozymin preparations with secretin (Harper & Raper, 1943).

Because of these conflicting results, the effects of nervous, hormonal and pharmacological stimuli on the response of the cat's pancreas to secretin have been re-examined. Preliminary reports of the results have already been published (Brown, Harper & Scratcherd, 1963, 1965).

METHODS

The experiments were performed on unfed cats. Anaesthesia was induced with ether and maintained by intravenous injection of chloralose (80 mg/kg) or chloralose (37·5 mg/kg)-urethane (450 mg/kg). The splanchnic nerves were cut extraperitoneally, and the vagus nerves cut in the neck. The pancreatic duct was cannulated as it passed through the duodenal wall, and the pylorus occluded with a tape ligature. In a number of experiments the stomach was filled with 0·3 M glycine solution, pH 6·4, by a tube inserted through an incision in the cervical part of the oesophagus. In experiments involving stimulation of the abdominal vagus nerves the eighth rib was removed on the left side. Occasionally the ventral or dosal vagus trunks were stimulated, but more often one or other of the two branches from the left vagus nerve to these trunks was identified and cut and the peripheral end placed on electrodes of the type described by Schofield (1952). The chest was closed and respiration maintained by a Starling Ideal pump. Stimulation was applied from a Ritchie–Sneath stimulator.

Secretin and pancreozymin were prepared by the method of Crick, Harper & Raper (1949) and antral extracts by the method of Blair, Harper, Lake, Reed & Scratcherd (1961). The amylase content of pancreatic juice was determined by the modification of Nørby's method described by Lagerlöf (1942), and the results expressed as Nørby units $\times 10$. The bicarbonate concentration of the juice was measured on a Natelson microgasometer by the method of Van Slyke & Neill (1924).

The volume and enzyme content of pancreatic juice were measured in a period, usually 15 or 30 min, from the beginning of the nervous or chemical stimulation. The response to stimulation was expressed as the difference between these measurements and the preceding control periods. The increases are given as means $\pm$ S.E. of the mean of the differences.

In one group of animals, under ether anaesthesia, the left or right vagus nerve was exposed in the neck and cut central to the nodose ganglion. The animals were left for several weeks to allow the preganglionic efferent fibres in the sectioned nerve to degenerate. In the terminal acute experiments the technique was the same as that already described except that the vagus nerves were cut and their peripheral ends stimulated in the neck instead of the thorax.

RESULTS

In most previous studies of the pancreatic response in the cat to vagal stimulation or pancreozymin injections, a background flow of juice was evoked by repeated intravenous injections of secretin, usually at intervals of 15 min, sufficient to produce an average flow of 1·2–1·5 ml. in 15 min, which is considerably less than the maximal response of the gland. If the rate of flow produced by single intravenous injections is estimated by measuring the time interval between drops it is found that the flow, beginning after a latent period of a minute or less, rapidly reaches a maximum which may be maintained for 5–7 min, and thereafter gradually declines to zero by about the 15th min after an injection. Against this varying background it is difficult to demonstrate potentiating effects on flow, particularly if the additional stimulus is applied during the early phase of maximal response to a secretin injection. For this reason the potentiating effects of nervous and chemical stimuli described in this paper have been studied against a steady flow of juice at a slow rate, usually between 0·5 and 1·0 ml./15 min, maintained by a continuous intravenous infusion of secretin.

Effects of stimulation of the vagus nerves. The peripheral ends of the branches from the left vagus nerve passing to the dorsal and ventral vagus trunks were stimulated for periods of 10 or 15 min. Stimulation of the branch to the dorsal vagus trunk produced an increase in the volume, bicarbonate concentration and amylase output of the juice. The volume increase usually occurred only in the sample collected during stimulation, but the increased amylase output frequently continued for an additional 15 or 30 min (Figs. 1, 2). The stimulation frequency was 5/sec, and the strength 15–30 V. In most experiments the pulse width was 1 msec, which was found to be the most effective in producing increase in flow, but re-

sponses were also obtained with 0·1 msec pulses and with faradic shocks from a du Bois–Reymond induction coil. In seventy observations in forty experiments the mean volume of the 15 min sample before stimulation was

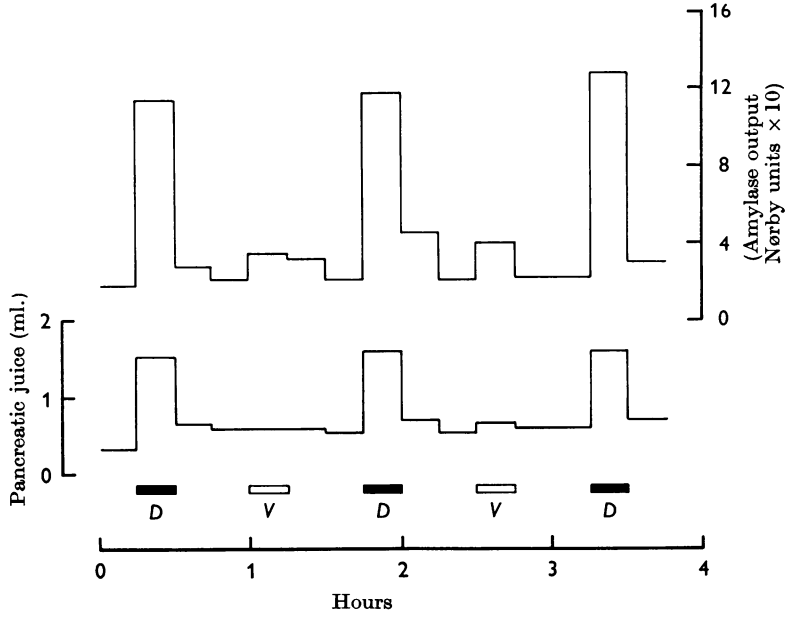

Fig. 1. The effect of stimulation of branches of the dorsal and ventral vagus trunks on the volume and enzyme content of pancreatic juice. In this and subsequent figures a background secretion of juice was maintained by continuous intravenous infusion of secretin. At *D* stimulation of the branch of the left vagus nerve to the dorsal vagus trunk (20 V, 1 msec pulses, 5/sec for 15 min) resulted in increase in the volume of juice and output of enzymes. A similar stimulation of the branch of the left vagus nerve to the ventral vagus trunk at *V* produced little or no change in the volume of juice and only slight increases in enzyme output.

0·80 ml. The mean increase in volume on vagal stimulation was 0·66 ± 0·04 ml. In sixty-one observations in thirty-five experiments there was a mean increase in amylase output of 19·2 ± 2·1 Nørby units × 10 above the mean control secretion of 4·4 Nørby units × 10. In contrast to these results, stimulation of the branch to the ventral vagus trunk in eleven observations on five animals produced little or no change in the volume of the juice. The amylase output was measured in five of these experiments, and the increase was much less than that produced by stimulation of the dorsal vagus trunk (Fig. 1).

The administration of atropine sulphate (1 mg/kg I.V.) occasionally reduced the rate of flow of secretin-stimulated juice, but the mean volumes before and after atropine in eight experiments showed only an insignificant reduction from 0·68 to 0·61 ml./15 min. The potentiating effect on the rate

of secretion of stimulating the dorsal vagus trunk was not prevented by atropine, although the mean increase on stimulation after atropine, $0{\cdot}53 \pm 0{\cdot}11$ ml., was significantly less ($P < 0{\cdot}05$) than that before atropine, $0{\cdot}82 \pm 0{\cdot}13$ ml. The increased bicarbonate concentration on vagal stimulation also persisted after atropine, but the marked increase in amylase

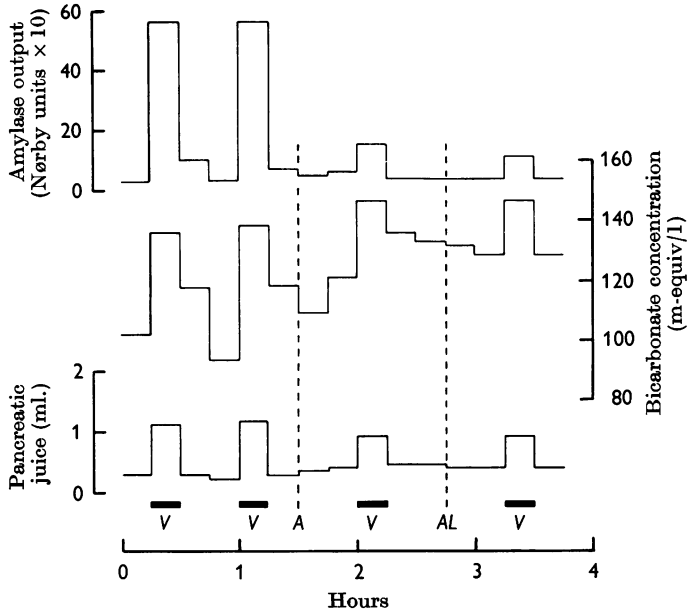

Fig. 2. The effects of atropine sulphate (1 mg/kg) at *A* and Alderlin, 5 mg at *AL* on the changes in volume bicarbonate concentration and enzyme output of pancreatic juice produced by stimulations of the dorsal vagus trunk (15 V, 1 msec pulses, 5/sec for 15 min) at *V*. The increased volume and bicarbonate concentration following vagal stimulation were not blocked by either drug. After atropine the small increases in enzyme output may be accounted for by the 'wash out' effect of the increases in rate of flow.

secretion was abolished. The slight increases in amylase output on stimulation after atropine could be explained as a passive 'washing out' of enzymes by the increase in rate of flow. The adrenergic blocking agents, phenoxybenzamine and pronethalol (Alderlin), also failed to block the effects of vagal stimulation on the volume and bicarbonate concentration of the juice (Fig. 2).

After the injection of hexamethonium bromide (1–10 mg/kg I.V.) stimulation of the dorsal vagus trunk had no effect on the rate of flow or bicarbonate concentration of the juice in ten or eleven observations on seven animals. In one experiment the volume increased by 0·2 ml. In none was there any increase in amylase output (Fig. 3). Hexamethonium may act at ganglionic synapses or at sensory nerve endings (Paton & Vane, 1963). Its

effect in these experiments could therefore have been a ganglionic inhibition of the response of efferent vagal fibres to stimulation. Alternatively it might, by an action on the nerve endings, have blocked the response of afferent vagal fibres to antidromic stimulation.

To decide between these possibilities one or other vagus nerve was cut in a group of animals. The section was made above the nodose ganglion in

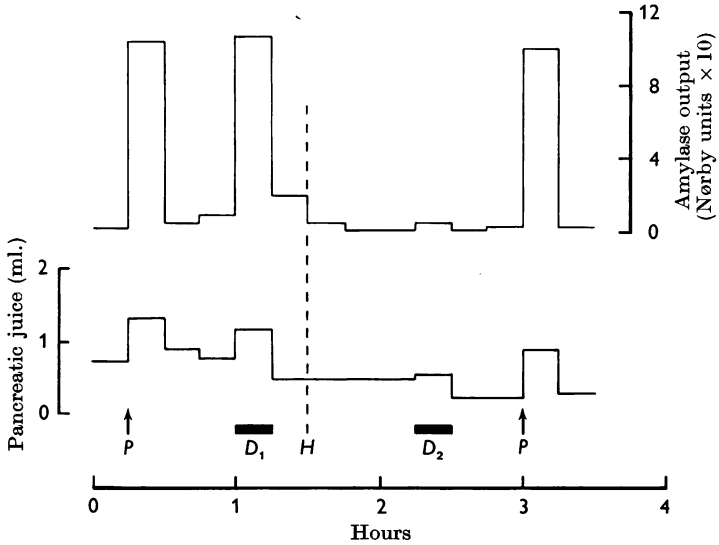

Fig. 3. The effect of hexamethonium bromide (3 mg/kg I.V.) on the pancreatic responses to pancreozymin and vagal stimulation. Injections of pancreozymin (2 mg I.V.) at *P* produced increases in the volume and enzyme output, which were unaffected by hexamethonium. Stimulation of the branch of the left vagus nerve to the dorsal vagus trunk (30 V, 1 msec pulses, 5/sec for 15 min) at D_1 produced the same effect as pancreozymin Hexamethonium at *H* abolished the response to a second stimulation at D_2.

order to preserve those afferent fibres which had their cell bodies in the ganglion. After an interval of several weeks, to allow the preganglionic efferent fibres to degenerate, the animals were anaesthetized and the cardiovascular and pancreatic effects of stimulating the peripheral ends of the vagus nerves in the neck were recorded. Stimulation of the intact vagus nerve produced the expected bradycardia and fall in arterial blood pressure. On the operated side, with only the afferent fibres intact, there was usually a slight increase in blood pressure throughout the period of stimulation. By this criterion a supranodose section of the nerve was achieved in eight animals. In seven of these there was no increase in the volume or amylase content of pancreatic juice on stimulating the nerve on the operated side, but in two of the seven, in which the left vagus nerve had been cut, there was no increased flow on stimulating the right vagus

nerve. In the remaining five animals (four right vagal and one left vagal section) stimulation of the intact vagus nerve increased the volume and amylase content of the juice. The increase in volume persisted after atropine but was abolished by hexamethonium (Fig. 4). There was one anomalous result in an animal in which the left vagus nerve had been cut, and stimulation of the nerve at the terminal operation produced a small increase in the rate of flow of juice, which was not abolished by atropine.

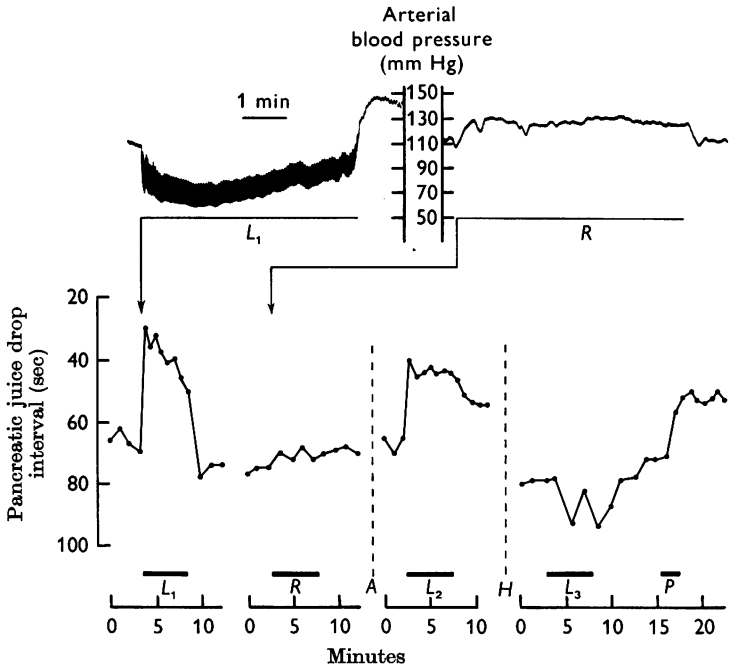

Fig. 4. The effect of stimulating the vagus nerves in the neck (30 V, 1 msec pulses, 10/sec for 5 min), some weeks after supranodose section of the right vagus nerve to produce degeneration of the efferent fibres. Changes in rate of flow of juice are indicated by alterations in the drop interval. Stimulation of the peripheral end of the left vagus nerve(L_1) resulted in a fall in arterial blod pressure and an increase in the rate of flow of pancreatic juice. The latter effect persisted (L_2) after atropine sulphate (1 mg/kg I.V.) at *A*, but was abolished (L_3) by hexamethonium bromide (2 mg/kg I.V.) at *H*, which did not however prevent the increase in rate of flow on injection of 3 mg pancreozymin at *P*. Stimulation of the peripheral end of the right vagus nerve (*R*) was accompanied by a slight increase in the arterial blood pressure, but no change in the rate of flow of juice.

Effects of pancreozymin, antral extracts and histamine. Pancreozymin was injected I.V. in doses of 2–6 mg on thirty occasions in nineteen animals. The expected effect on amylase secretion was observed, the mean increase in output being $13{\cdot}5 \pm 1{\cdot}9$ Nørby units $\times$ 10 over the mean control output of 5·2 Nørby units $\times$ 10. In addition the volume and bicarbonate concen-

tration of the juice increased. The mean volume of the 15 min sample before pancreozymin was 0·81 ml., and the mean increase in volume of the sample collected after pancreozymin was $0·49 \pm 0·08$ ml. Neither atropine nor hexamethonium abolished the effects of pancreozymin on the volume and amylase content of the juice (Figs. 3, 4).

Extracts of the mucosa of the pyloric antrum have a pancreozymin-like action on the pancreas (Blair *et al.* 1961). The effects of injections of antral extracts on the volume and composition of the secretin-stimulated juice were similar to those of pancreozymin, although the increase in volume was less marked. The effects of the antral extracts, like those of pancreozymin, were not abolished by atropine or hexamethonium. In a few observations it was found that intravenous infusion of small amounts of histamine acid phosphate also increased the volume of secretin-stimulated juice.

Effects on the resting pancreas. In the fasted cat, anaesthetized with chloralose or chloralose-urethane, there is usually no flow of pancreatic juice in the absence of secretin stimulation. In these conditions stimulation of the abdominal vagus trunks produces either no secretion or at the most a single drop of juice. Histamine appears to have no secretory effect on the resting pancreas. As there is evidence that the increased enzyme output in response to pancreozymin is accompanied by a slight increase in the rate of secretion (R. M. Case, A. A. Harper and T. Scratcherd, unpublished) and as the impure preparations of pancreozymin used in these experiments may also contain a residual secretin contamination, the effects of pancreozymin on the resting and secretin-stimulated pancreas were compared in a series of experiments. The injection of 5 Crick, Harper & Raper u. of pancreozymin produced a mean secretion of 0·08 ml. from the resting gland. This dose, injected against a background of secretin-stimulated secretion in the same animals, produced a mean increase in flow of 0·29 ml. The mean difference between these volumes, $0·21 \pm 0·03$ ml. (7), was highly significant ($P < 0·001$). When 10 u. of pancreozymin were injected the corresponding figures were 0·19 ml. and 0·48 ml. Again the mean difference, $0·29 \pm 0·05$ ml. (8), was highly significant ($P < 0·001$).

DISCUSSION

In previous studies of the simultaneous application of more than one stimulus to the pancreas, it has not always been clear whether the response was merely the additive effect of these stimuli, or sufficiently exceeded this to indicate a synergistic interaction of the stimuli (see Grossman, 1962). The increases in the volume and bicarbonate content of secretin-stimulated juice described in this paper may be regarded as examples of synergistic action, since the nervous and chemical stimuli which produced

them did not, in the absence of secretin, elicit any comparable flow of water or bicarbonate from the pancreas.

The increase in secretion when vagal excitation is added to secretin stimulation brings the effects on the cat's pancreas into line with those already described in the dog. It seems likely that previous failures to demonstrate this synergism (Harper & Vass, 1941; Harper *et al.* 1959) resulted from the administration of secretin in divided doses, with a consequent variation in flow rate which makes it difficult to demonstrate potentiation. After large doses of atropine, which blocked the ecbolic effect of vagal stimulation, the increase in the volume of juice, although less, was still clearly evident. From the absence of this response on stimulation of vagus nerves in which the efferent fibres had degenerated, it can be concluded that the increased flow was not brought about by antidromic stimulation of afferent fibres which had their cell bodies in the nodose ganglion. This excluded the possibility that hexamethonium inhibited the response by an action on afferent nerve endings, unless the volume response from the intact nerve was entirely mediated by afferent fibres with their cell bodies in the jugular ganglion. It follows that the most likely site of action of hexamethonium was the ganglionic synapses, and that the increased volume of juice resulted from stimulation of efferent preganglionic fibres synapsing with 'atropine-resistant' post-ganglionic fibres. The absence of potentiation of secretion on stimulation of the ventral vagus trunk is in accord with the results of Harper & Vass (1941), who obtained increases in enzyme output only on stimulation of the dorsal vagus trunk. It would, however, be unsafe to conclude that the ventral vagus trunk does not supply fibres to the pancreas. There is evidence in the dog that many vagal fibres reach the pancreas by passing over the pyloric sphincter and along the duodenum. In our experiments such fibres, possibly from the ventral vagus trunk, would have been included in the ligature around the pyloric sphincter.

The most probable explanation of the failure of Harper & Raper (1943) to detect the stimulant effect of pancreozymin on the volume and bicarbonate content of the juice was their use of separate doses of secretin, which provided a background flow of juice varying in rate during each period of collection. The increases in enzyme output and volume of juice in response to pancreozymin and antral extracts were resistant to atropine and to hexamethonium. No physiological significance can be attributed to the increases in volume of juice until these have been elicited by injections of the pure hormones. This has not been done with pancreozymin, but it has been found that pure gastrin II, which does not produce a flow of juice from the resting pancreas of the anaesthetized cat, increases the rate of secretion of the secretin-stimulated gland (H. T. Howat and F. B.

Beswick, personal communication). Our few observations on the potentiation of the effects of secretin by intravenous infusions of histamine confirm the results of an extensive series of experiments by H. T. Howat (personal communication).

To explain the increase in volume of juice produced by such a variety of nervous, hormonal and pharmacological stimuli the simplest hypothesis is that they all augment the blood flow through the gland and thus increase the amount of secretin reaching the pancreatic cells. It is conceivable that an increase in the pancreatic blood flow might, by a passive transudation through the walls of the ducts, increase the volume of water in the secretion. But in these experiments there was also a consistent increase in the concentration and output of bicarbonate in response to stimulation. The statistical significance of the increase has not been determined, as increased rates of flow of secretin-stimulated juice are in any case accompanied by increased bicarbonate concentrations over the range of secretion rates observed in these experiments (Case, Harper & Scratcherd, 1966). The significance of the increased bicarbonate is as an indicator that the increased volumes of juice were the result of the type of active glandular secretion which is specifically evoked by secretin, rather than of passive transudation. The blood flow in the cat's pancreas is increased by histamine (Harper, Sankey & Scratcherd, 1963), pancreozymin and antral extracts (T. E. Barlow, J. R. Greenwell, A. A. Harper & T. Scratcherd, unpublished), and it has been shown in the dog that vagal stimulation increases pancreatic blood flow (Gayet & Guillaumie, 1930*a*).

In a review of previous work on the relation between pancreatic secretion and blood flow Tankel & Hollander (1957) concluded that the dependence of the secretion of the pancreas on its blood supply had not been proved. This conclusion is supported by the observation that although a first injection of purified secretin may increase the blood flow through a resting pancreas, successive injections have less effect or none at all (Maltesos & Watson, 1939; Jones, 1960; Hilton & Jones, 1963; T. E. Barlow, J. R. Greenwell, A. A. Harper & T. Scratcherd, unpublished). Tankel & Hollander (1957) recognize that if a larger amount of stimulant reaches the gland because of an increase in blood flow there will be a corresponding increase in secretion. This was the situation in our experiments in which secretin was being continuously infused into the circulation.

The parasympathetic supply to the submaxillary gland, like that to the pancreas, contains atropine-resistant fibres. The vasodilatation produced in the submaxillary gland by the stimulation of the *chorda tympani* after atropine, has been attributed either to atropine-resistant vasodilator fibres (Bhoola, Morley, Schachter & Smaje, 1965) or to formation of a vasodilator kinin by an enzyme released from the glandular tissue (Hilton

& Lewis, 1955). Either mechanism could explain the vasodilatation and atropine-resistant increase in pancreatic juice in response to vagal stimulation. The increased blood flow produced by pancreozymin may depend on the formation of a kinin, since kinin-forming enzymes have been found in the juice secreted in response to pancreozymin (Lewis, 1959), and detected in the effluent from a perfused pancreas when pancreozymin was added to the perfusing fluid (Hilton & Jones, 1963).

In the cat, unlike other laboratory animals, those nervous hormonal and chemical stimuli which in all species increase pancreatic enzyme output, elicit little or no flow of water and bicarbonate from the quiescent gland. These stimuli were previously considered to be equally ineffective in increasing the volume of juice produced by the secreting gland, but it seems clear from our experiments that this is not so when the pancreas is responding to continuously administered exogenous secretin. In the dog there is a continuous resting flow of pancreatic juice, which may depend in part on the circulation of secretin or of some unknown humoral stimulant. There is good evidence that the pyloric antrum as well as the small intestine is the source of humoral pancreatic stimulants (Blair, Brown, Harper & Scratcherd, 1966), and we do not know of any observations on basal pancreatic secretion in the dog in which the whole hormone-yielding area has been removed. It may be that in the dog also agents such as histamine, which Tankel, Lester, Richman & Hollander (1957) regard as a direct stimulant of pancreatic cells, in fact potentiate pancreatic secretion by a vasodilator action, which increases the supply of a humoral stimulant.

The nervous and hormonal potentiation of the effect of secretin may be of significance in the response of the pancreas during normal digestion. The available evidence suggests that secretin has only a transient stimulant effect on pancreatic blood flow in the initial stages of secretion, when juice containing a high concentration of enzymes is being washed out of the ducts. Although the primary action of the vagus nerves, pancreozymin and the pancreozymin-like stimulant in antral mucosa is to increase the digestive power of the juice, they may by a secondary vasodilator action facilitate the supply of secretin to the gland with a consequent increase in its secretion of water and bicarbonate.

REFERENCES

Bhoola, K. D., Morley, J., Schachter, M. & Smaje, J. H. (1965). Vasodilation in the submaxillary gland of the cat. *J. Physiol.* **179**, 172–184.

Blair, E. L., Brown, J. C., Harper, A. A. & Scratcherd, T. (1966). A gastric phase of pancreatic secretion. *J. Physiol.* **184**, 812–824.

Blair, E. L., Harper, A. A., Lake, H. J., Reed, J. D. & Scratcherd, T. (1961). A simple method of preparing gastrin. *J. Physiol.* **156**, 11*P*.

BLAIR, E. L., HARPER, A. A. & SCRATCHERD, T. (1962). The distribution and physiological properties of pancreozymin. In Ciba Foundation Symposium *The Exocrine Pancreas: Normal and Abnormal Functions*, ed. DE REUCK, A. V. S. & CAMERON, MARGARET P. London: Churchill.

BROWN, J. C., HARPER, A. A. & SCRATCHERD, T. (1963). The effect of the vagus on the rate of flow of secretin-stimulated pancreatic juice in the cat. *J. Physiol.* **166**, 31*P*.

BROWN, J. C., HARPER, A. A. & SCRATCHERD, T. (1965). The effect of the vagus, of pancreozymin and of antral extracts on the rate of flow of secretin-stimulated pancreatic juice in the cat. *Abstracts of Papers. XXIII International Congress of Physiological Sciences*, p. 213.

CASE, R. M., HARPER, A. A. & SCRATCHERD, T. (1966). The relationship between bicarbonate and chloride in pancreatic juice. *J. Physiol.* **182**, 49–50*P*.

CRICK, JOAN, HARPER, A. A. & RAPER, H. S. (1949). On the preparation of secretin and pancreozymin. *J. Physiol.* **110**, 367–376.

EISLER, B. & ÅGREN, G. (1936). Beitrag zur Kenntnis der Pilocarpinwirkung auf das Pancreas. *Klin. Wschr.* **15**, 1686.

GAYET, R. & GUILLAUMIE, MAYLIS (1930*a*). Les relations quantitatives réciproques de la sécrétion du suc pancréatique et du débit sanguin. *C. r. Séanc. Soc. Biol.* **103**, 1216–1219.

GAYET, R. & GUILLAUMIE, MAYLIS (1930*b*). Sur les modifications de l'excrétion pancréatique consécutives à l'hyperglycémie des centres encéphaliques. *C. r. Séanc. Soc. Biol.* **105**, 373–377.

GROSSMAN, M. I. (1962) Nervous and hormonal regulation of pancreatic secretion. In Ciba Foundation Symposium *The Exocrine Pancreas: Normal and Abnormal Functions*, ed. DE REUCK, A. V. S. & CAMERON, MARGARET P. London: Churchill.

HARPER, A. A., KIDD, C. & SCRATCHERD, T. (1959). Vago-vagal reflex effects on gastric and pancreatic secretion and gastrointestinal motility. *J. Physiol.* **148**, 417–436.

HARPER, A. A. & RAPER, H. S. (1943). Pancreozymin, a stimulant of the secretion of pancreatic enzymes in extracts of the small intestine. *J. Physiol.* **102**, 115–125.

HARPER, A. A., SANKEY, ALISON & SCRATCHERD, T. (1963). The effects of adrenaline, noradrenaline and histamine on the electrical conductivity of the pancreas. *J. Physiol.* **170**, 32–33*P*.

HARPER, A. A. & VASS, C. C. N. (1941). The control of the external secretion of the pancreas in cats. *J. Physiol.* **99**, 415–435.

HERMANN, H. & HUTET, G. (1943). Action combinée de la sécrétine de Bayliss et Starling et de l'ésérine sur la sécrétion pancréatique. *C. r. Séanc. Soc. Biol.* **137**, 475–477.

HILTON, S. M. & JONES, MURIEL (1963). Plasma kinin and functional vasodilatation in the pancreas. *J. Physiol.* **165**, 35–36*P*.

HILTON, S. M. & LEWIS, G. P. (1955). The mechanism of the functional hyperaemia in the submandibular salivary gland. *J. Physiol.* **129**, 253–271.

JONES, MURIEL (1960). The effect of secretin on pancreatic blood flow. *J. Physiol.* **151**, 49–50*P*.

LAGERLÖF, H. O. (1942). *Pancreatic Function and Pancreatic Disease Studied by Means of Secretin*. Stockholm: Norstedt and Söner.

LEWIS, G. P. (1959). Plasma-kinin-forming enzymes in body fluids and tissues. *J. Physiol.* **147**, 458–468.

MALTESOS, C. & WATSON, R. H. (1939). Durchblutung und Sekretion des Pankreas bei humoraler Anregung. *Pflügers Arch. ges. Physiol.* **241**, 516–523.

PATON, W. D. M. & VANE, J. R. (1963). An analysis of the responses of the isolated stomach to electrical stimulation and to drugs. *J. Physiol.* **165**, 10–46.

SCHOFIELD, B. M. (1952). The innervation of the cervix and the cornu uteri in the rabbit. *J. Physiol.* **117**, 317–328.

TANKEL, H. I. & HOLLANDER, F. (1957). The relation between pancreatic secretion and local blood flow: a review. *Gastroenterology* **32**, 633–641.

TANKEL, H. I., LESTER, L. J., RICHMAN, A. & HOLLANDER, F. (1957). A study of the pancreatic response to histamine in dogs with total gastrectomies. *Gastroenterology* **32**, 642–650.

THOMAS, J. E. (1950). *The External Secretion of the Pancreas*, p. 109. Springfield: Thomas.

VAN SLYKE, D. D. & NEILL, J. M. (1924). The determination of gases in blood and other solutions by vacuum extraction and manometric measurement. *J. Biol. Chem.* **61**, 523–573.