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THE CONTROL OF THE EXTERNAL SECRETION OF THE PANCREAS IN CATS

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The presence of secretory and trophic fibres to the pancreas in the vagus nerves was first demonstrated by Pavlov [1910] on dogs, and this work has since been confirmed by many observers [Anrep, 1916; Babkin, 1924; Tonkich, 1924; Nakagawa, Kakita & Matsumoto, 1925; Baxter, 1931*b*; Hebb, 1937; Crittenden & Ivy, 1937] on dogs and rabbits.

With the discovery of secretin more emphasis was laid upon the hormonal control of the pancreas, so much so that Bayliss & Starling [1902], who were unable to repeat Pavlov's observations, suggested that 'the nervous process [of pancreatic secretion] is superfluous and therefore improbable'.

These contradictory views seemed to be reconciled by the work of Mellanby [1925], who showed that secretin was responsible for the water and bicarbonate of the pancreatic juice and that the enzyme content of the juice was determined by the vagus nerves. Secretin, according to Mellanby [1926], is carried into the blood stream in association with the bile salts during their passage through the duodenal and jejunal mucous membranes. The importance of bile in this connexion has been denied by Ivy & Lueth [1927], who found that acid in the duodenum was a more potent stimulus to the pancreas. Finally, doubt has recently been cast by Hammarsten, Ågren & Lagerlöf [1937] upon Mellanby's separation of the hormonal and nervous control of pancreatic secretion. These observers claim to have shown in their work on man that secretin stimulates the production of enzymes by the pancreas.

It was in the hope of obtaining a clearer picture of the control of the external secretion of the pancreas that the following experiments were undertaken.

METHODS

All the experiments were performed on cats. The animals were fed a few hours before the experiment. After preliminary anaesthetization with ether the animals were either decerebrated, or the anaesthesia was maintained by the intravenous injection of chloralose (0·07–0·08 g./kg. body weight). Pancreatic juice was collected by a cannula inserted into the pancreatic duct as it passed through the wall of the duodenum. The ligature round the pancreatic duct included also the bile duct, so that thereafter no bile could enter the duodenum. In a number of experiments the pylorus was occluded by a ligature to prevent the passage of acid from the stomach into the small intestine.

A continuous flow of pancreatic juice at a constant rate was maintained by the intravenous injection of secretin. The secretin was prepared by Mellanby's method [Mellanby, 1932], except that the third stage of purification was omitted. The secretin had no vasodepressor action when tested on the cat's arterial blood pressure. The usual dose was an injection of 0·25 mg. of secretin in 1 c.c. of normal saline every 10 or 15 min., which was sufficient to produce a steady flow of juice at rates between 1·0 to 1·5 c.c. in 10 min. Against this background of continuous secretion it was possible to observe the effect of nerve stimulation and section, and of meals on the rate of flow and the enzyme content of the pancreatic juice.

The amylase and trypsinogen contents of successive samples of about 2 c.c. of juice were measured. The amylase was estimated by Wohlgemuth's method [Cole, 1933]. The diastatic power or diastatic index of the juice (D 40/30) is expressed as the number of c.c. of 1% starch solution which would be completely converted to erythrodextrin in 30 min. at 40° C. by 1 c.c. of pancreatic juice. The trypsinogen content of the juice was estimated by allowing 0·25 c.c. of pancreatic juice, activated by the addition of 10 mg. of enterokinase, to digest 5 c.c. of 5% casein solution for 20 min. at 37° C. Formaldehyde was then added and the solution titrated against $N/20$ NaOH with phenolphthalein as indicator. A blank titration was done on a casein sample to which boiled pancreatic juice and boiled enterokinase had been added. To a third casein sample 0·25 c.c. of pancreatic juice and boiled enterokinase were added in order to detect any active trypsin in the juice. The tryptic activity was then converted into amounts of trypsinogen by reference to a graph. The graph was constructed by measuring the tryptic activity of different amounts of a trypsinogen preparation, which was treated in the same way as the pancreatic juice. An arbitrary unit of trypsinogen was taken to be the amount of tryptic activity, measured by the formol titration method, of 0·25 mg. of the trypsinogen preparation, after activation by 10 mg. of enterokinase. The casein solution was prepared as described by Northrop & Kunitz [1932], and the trypsinogen and enterokinase by the methods of Bates & Koch [1935].

The diastatic index and the formol titration give a measure of the concentration of amylase and trypsinogen in the pancreatic juice. More important, however, is the minute output of these enzymes in the various samples of pancreatic juice, and this can be calculated from the diastatic index and the trypsin units by multiplying these by the amount of the sample in c.c. divided by the time of collection of the sample in minutes. In the figures illustrating this paper the terms $D\frac{J}{T}$ and $T\frac{J}{T}$ refer to the minute output of amylase and trypsinogen respectively, calculated in the above manner. The rate of secretion is expressed as the number of c.c. of juice secreted in 10 min.

The experiments fall into two groups, those on the effects of nerve stimulation and nerve section, and those on the effect of foodstuffs.

Results

Stimulation of the vagus nerves

Caudal to the roots of the lungs the right and left vagus nerves form the oesophagal plexus of the vagus round the lower part of the oesophagus. From the oesophageal plexus arise the ventral and the dorsal vagus trunks, which pass through the diaphragm on the ventral and dorsal aspects of the oesophagus respectively, and it is by these two nerve trunks that the vagus nerves reach the abdomen. The ventral vagus trunk is mainly distributed to the stomach, while the major portion of the dorsal vagus trunk passes by its coeliac division to the coeliac ganglia (Fig. 1).

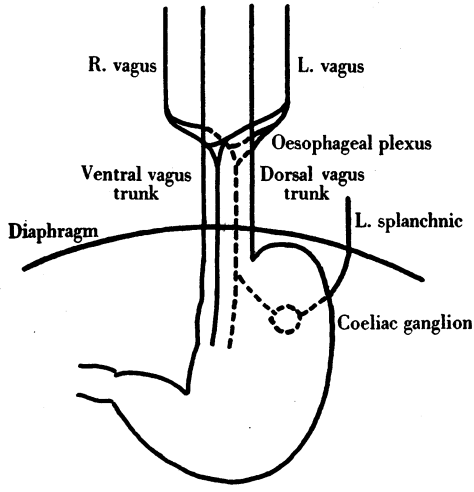

Fig. 1. The abdominal vagus nerves.

One or both of the vagal trunks were sectioned on the lower part of the oesophagus, and the peripheral end of the cut nerve stimulated through bipolar electrodes, by faradic shocks from a du Bois-Reymond induction coil, usually for a period of 5 min.

Stimulation of the dorsal vagus trunk resulted in a well-marked increase in the minute output of enzymes by the pancreas (Fig. 2). The increases in trypsinogen and amylase ran parallel. The increase in enzymes on stimulation of the dorsal vagus trunk was unaffected by occlusion of the pylorus by a ligature, or by previous section of the ventral vagus trunk. After excision of the coeliac ganglia stimulation of the dorsal vagus trunk still brought about an increase in the enzyme content of the

pancreatic juice, from which we conclude that all the 'trophic' fibres to the pancreas do not pass in the major division of the dorsal vagus trunk to the coeliac ganglia. When the splanchnic nerves were cut in the course of experiments, the effect of stimulation of the dorsal vagus trunk on the minute output of enzymes was considerably enhanced compared with the response to stimulation before section of the splanchnic nerves. Large doses of atropine sulphate (1 mg./kg. body weight, intravenously) abolished the response to stimulation of the dorsal vagus trunk.

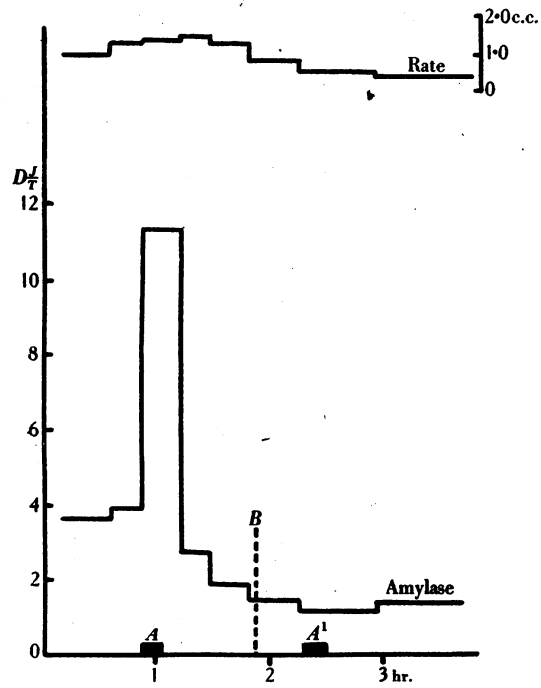

Fig. 2. Stimulation of the peripheral end of the dorsal vagus trunk at *A* resulted in an increase in the minute output of amylase in the pancreatic juice. After the intravenous injection of 5 mg. of atropine sulphate at *B*, repetition of the stimulation at *A'* was without effect.

The effect of dorsal vagus trunk stimulation on the rate of secretion is in sharp contrast to the well-marked increase in the minute output of enzymes. In none of our experiments did we observe any inhibitory effect on the rate of secretion, and in only two out of thirty-one experiments was there any increase in the rate of secretion. In all others the rate was unaltered during stimulation. As an alteration in the position of the cannula occasionally alters the rate of flow of the juice, and as this

cannot always be avoided when stimulating the dorsal vagus trunk in the lower part of the thorax, we feel that such an alteration is the most probable explanation of the two experiments which showed an increase in the rate of flow. In view of the large number of experiments where the rate remained constant while the enzyme output was markedly increased, we conclude that stimulation of the dorsal vagus trunk in the cat does not affect the rate of secretion of pancreatic juice.

Stimulation of the peripheral end of the cut ventral vagus trunk was without effect on either the enzyme output or the rate of secretion by the pancreas.

Section of the vagus nerves

The effect of section of the vagus trunks during the period of collection of pancreatic juice was variable. In some experiments it was followed by a diminution in the minute output of enzymes and rate of secretion. This effect in some cases passed off in ½–1 hr.; in others it persisted for the rest of the experiment. Again, in other experiments section of the vagal trunks did not affect either the enzyme output or the rate of secretion.

In animals in which the splanchnic nerves as well as the vagal trunks had been sectioned before the cannulation of the pancreatic duct, the minute output of enzymes in the pancreatic juice was high, which showed that the integrity of the vagus supply to the pancreas was not necessary for the secretion of a juice rich in enzymes.

Section of the splanchnic nerves

In animals in which the splanchnic nerves were not cut before the abdominal section for the insertion of the pancreatic cannula there was no secretion of pancreatic juice unless secretin was injected intravenously. In experiments in which the splanchnic nerves were sectioned extra-peritoneally before the abdominal section was made, there was a 'spontaneous' secretion of pancreatic juice, without the injection of secretin. The rate of this 'spontaneous' secretion varied in fourteen experiments between 0·6 and 2·0 c.c. The secretion continued in most cases until the experiment was ended 4 or 5 hr. after cannulation of the pancreatic duct, so that in many experiments on splanchnotomized animals it was unnecessary to inject secretin at all. In experiments in which the splanchnic nerves were sectioned during the collection of pancreatic juice the amount of juice secreted in response to secretin was greater after section of the splanchnic nerves than was produced by the injection of the same amount of secretin before section of the splanchnic nerves (Fig. 3).

The enzyme content of the pancreatic juice in splanchnotomized animals was very much higher than in animals with the splanchnic nerves intact. The average minute output of amylase in twenty-one experiments in which the splanchnic nerves were cut was 13·8; in twenty-three experiments in which these nerves were left intact the average minute output was 3·3. The average rate of secretion, 1·2 c.c., was the same in both series of animals.

The 'spontaneous' secretion occurred when the pylorus had been occluded by a ligature. In this case the rate of secretion was slower (0·3 c.c.) and the secretion stopped about 3 hr. after the cannulation of the pancreatic duct. The diastatic index, however, was extremely high, so that the minute output of enzymes during the period of 'spontaneous' secretion was as high as in those experiments where the pylorus was not occluded.

The 'spontaneous' flow of juice with a high enzyme content is obtained in splanchnotomized animals in which the dorsal and ventral vagus trunks have been cut, a result which is not produced by vagal section alone.

We regard the absence of 'spontaneous' secretion when the splanchnic nerves are intact, and its presence when the nerves are cut as presumptive evidence of a splanchnic reflex bringing about directly or indirectly an inhibition of pancreatic secretion in the former case. The efferent pathway for such a reflex is obviously the splanchnic nerves. The afferent pathway might be in the vagus nerves, in the splanchnic nerves, or in somatic nerves, the inhibitory stimuli in the last case arising from the skin wounds made in inserting the tracheal and vein cannulae and in opening the abdomen. These possibilities were investigated in the following experiments.

If the splanchnic nerves are left intact but the vagal trunks are cut above the diaphragm before insertion of the pancreatic cannula, there is no 'spontaneous' flow of juice, and the enzyme level is low. If now the splanchnic nerves are cut the enzyme output rises immediately and there is an increase in the amount of juice secreted in response to injections of secretin (Fig. 3).

Anaesthetization with 1 % novocain of the skin of the neck and leg before insertion of the tracheal cannula and vein cannula, of the skin of the thorax before section of the vagal trunks, and of the abdominal wall before opening the abdomen, did not, in animals with intact splanchnics, result in a 'spontaneous' flow of juice or a high enzyme output. But subsequent section of the splanchnic nerves was followed by a marked increase in the output of enzymes and an increase in the amount of juice secreted in response to injections of secretin.

These experiments eliminate vagal afferent and somatic afferent pathways, and we conclude that in animals in which the splanchnic nerves are intact, there is, as the result of trauma to the duodenum during the insertion of the cannula in the pancreatic duct, a reflex inhibition affecting the external secretion of the pancreas. Both the afferent and efferent pathways for this reflex lie in the splanchnic nerves. Whether this is

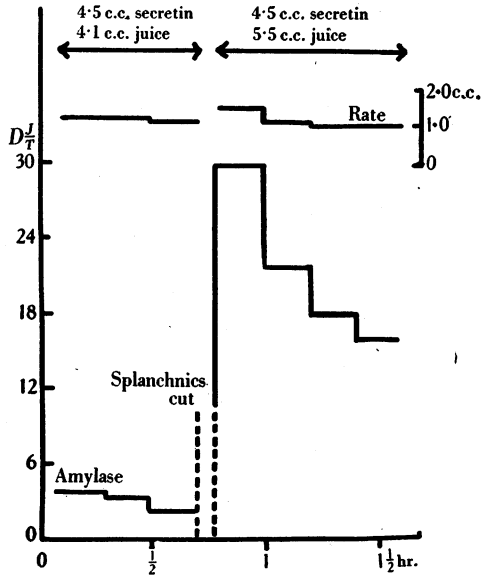

Fig. 3. The vagus nerves were cut before the commencement of collection of pancreatic juice. After section of the splanchnic nerves there was an increase in the amount of juice secreted in response to secretin, and a well-marked increase in the output of amylase.

a direct inhibition of the pancreas through splanchnic fibres supplying the cells or blood vessels of the gland, or whether it is secondary to an inhibition of the absorption of food products from the small intestine will be discussed later.

Stimulation of the splanchnic nerves

When the splanchnic nerves were sectioned in the thorax and the peripheral end of one nerve was stimulated by faradic shocks for a period of 5 min. there was a marked diminution in the minute output of enzymes in the pancreatic juice. During and for some time after the stimulation the rate of secretion was very greatly diminished, a result which may have been secondary to the constrictor effect of the stimulation of the

splanchnic nerve upon the blood vessels of the pancreas. Even, however, when the rate of secretion was kept constant by injections of secretin during and after the stimulation, nevertheless the minute output of enzymes was very much reduced (Fig. 4). From this we conclude that the splanchnic nerves contain fibres which on stimulation diminish the output of enzymes from the pancreas.

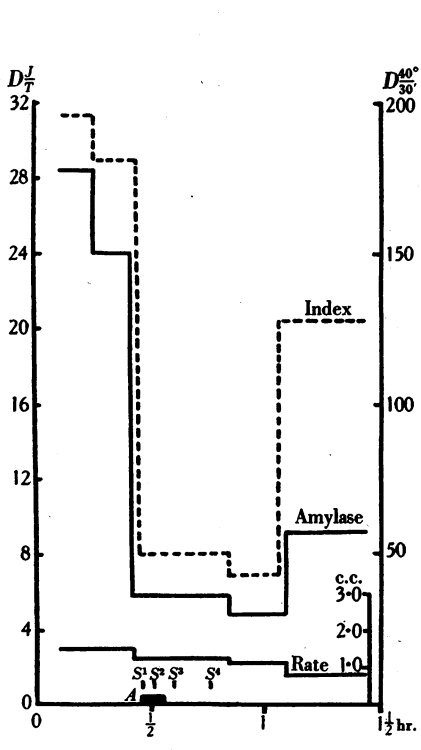

Fig. 4.

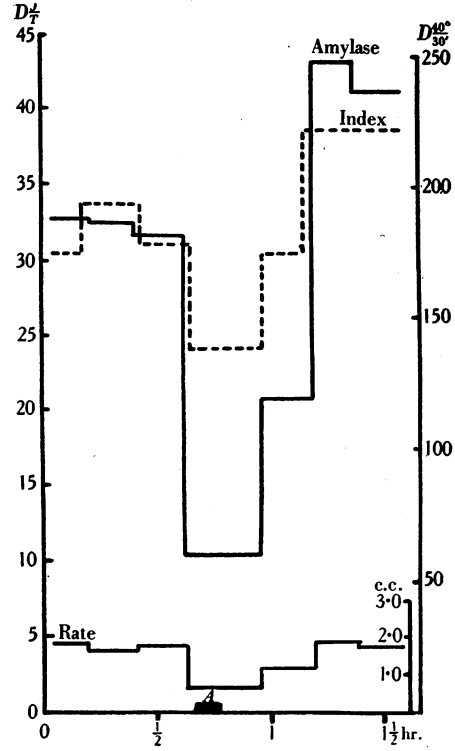

Fig. 5.

Fig. 4. At *A* the peripheral end of the left splanchnic nerve was stimulated in the thorax. At S^1, S^2, S^3 and S^4 injections of 0·25 mg. secretin were given intravenously to keep the rate of secretion of juice constant. For 30 min. following the stimulation the concentration and minute output of amylase in the juice were very much reduced.

Fig. 5. Stimulation of the central end of the left splanchnic nerve in the thorax at *A* was followed by a marked diminution in the rate of secretion, and in the concentration and minute output of amylase.

It has recently been suggested that the splanchnic nerves contain secretory fibres to the pancreas, which, unlike the vasoconstrictor fibres, do not synapse in the coeliac ganglia. In a few experiments we found

that the diminution in enzyme output on stimulation of the splanchnic nerves was much less marked, or even completely abolished after painting the coeliac ganglion on that side with 1 % nicotine. In none, however, did we observe any increase in the enzyme output or rate of secretion on stimulating the splanchnic nerve after painting the coeliac ganglion.

Central stimulation of the vagus and splanchnic nerves

The effect of stimulation by faradic shocks of the central end of the cut ventral vagus trunk on the oesophagus was variable. In some experiments there was no effect, in others some diminution in enzyme output and rate. The strength of stimulation had to be kept weak, as strong stimulation produced a violent vomiting reflex. Stimulation of the central end of one splanchnic nerve was in some experiments ineffective; in others it produced a marked diminution in the output of enzymes and the rate of secretion. An example of the latter type of experiment is shown in Fig. 5. In none of our experiments, even with the dorsal vagus trunk intact, did central stimulation of the ventral vagus trunk or of the splanchnic nerves bring about a reflex increase in the enzyme output or rate of secretion.

The effect of the administration of meals

The effects of various foodstuffs on the enzyme output and rate of secretion by the pancreas was studied by the same technique as in the experiments on the innervation of the pancreas. In these experiments the administration of a meal took the place of the nerve stimulation. Normal saline, distilled water, 5 % inulin solution, and foodstuffs in the form of 5–8 % starch solutions and 5 % casein solutions were injected either into the stomach through a catheter passed down the oesophagus, or into the duodenum. The volume of the stomach meals varied between 60 and 100 c.c., the duodenal meals from 30 to 50 c.c. Before the administration of a stomach meal the stomach was emptied and washed out with warm normal saline. Glass cannulae were tied into the duodenum about 4 in. from the pylorus; either a single cannula directed towards the pylorus to collect the stomach outflow, or directed caudally for the injection of meals into the duodenum; or two cannulae were inserted to allow of simultaneous collection of stomach outflow and the administration of foodstuffs into the duodenum. In a number of experiments where meals were injected into the duodenum the pylorus was occluded by a ligature.

Response to stomach meals

The presence of foodstuffs in the stomach did not increase the enzyme output of the pancreas. As soon, however, as the meal began to pass

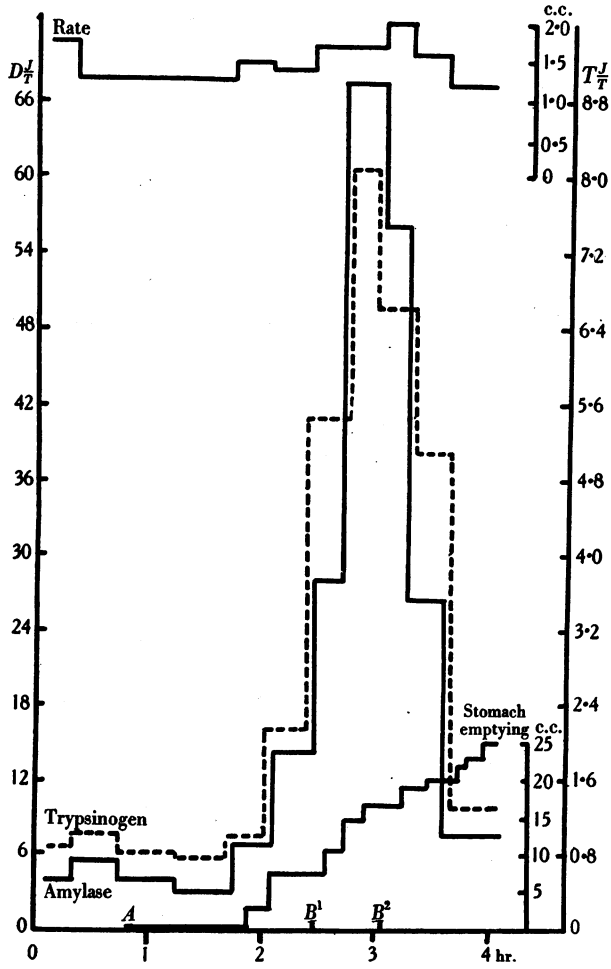

Fig. 6. Besides the usual cannula in the pancreatic duct, two cannulae were inserted into the duodenum, one directed caudally, the other towards the pylorus. At *A* 75 c.c. of an 8% starch solution were run into the stomach. At B^1 and B^2 20 c.c. of a partly digested 8% starch solution were run into the duodenum through the lower cannula. For 1 hr. after the administration of the stomach meal at *A* nothing left the stomach and the enzyme output of pancreatic juice remained low. As soon as food passed through the pylorus there was a marked and parallel increase in the output of amylase and trypsinogen, and an increase in the rate of secretion of pancreatic juice. The enzyme output later fell although the stomach was still emptying.

through the pylorus there was a sharp increase in the minute output of enzymes (Fig. 6). The passage of a casein or of a starch meal from the stomach brought about in each case a parallel increase in the amount of trypsinogen and amylase in the pancreatic juice (Fig. 7). During this

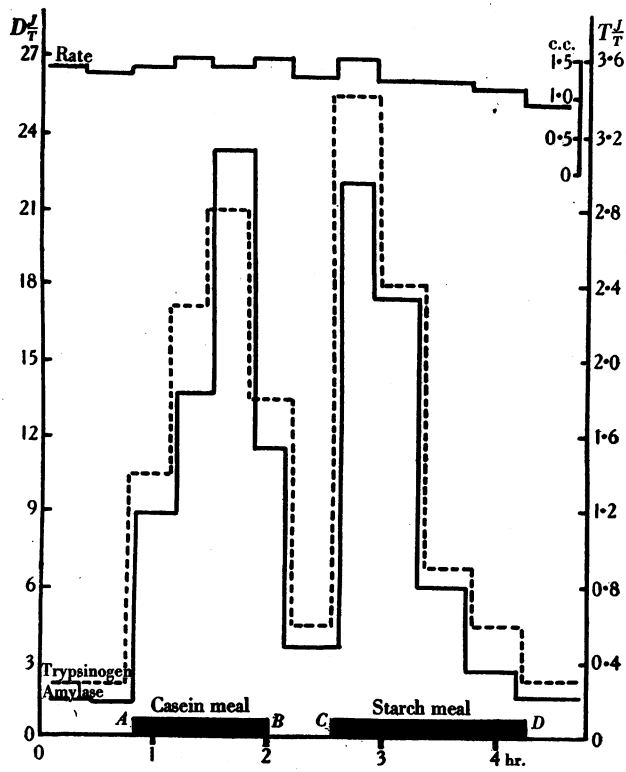

Fig. 7. At *A* 60 c.c. of a 5% casein solution were run into the stomach through a rubber tube passed down the oesophagus. At *B* the stomach was emptied. At *C* a second meal was given, consisting of 60 c.c. of an 8% starch solution. This was removed at *D*. Following the administration of each meal there was a well-marked and parallel increase in the output of trypsinogen and amylase from the pancreas.

period of increased enzyme output there was a measurable amount of active trypsin in the juice. The output of enzymes increased for about 30–40 min. and then declined to resting level over a similar period, even while the stomach was still emptying (Fig. 6). Coincident with the increase in enzyme output by the pancreas there was a definite increase in the rate of secretion of the pancreatic juice, amounting on the average to 50%.

Response to duodenal meals

Results almost the same as those produced by the administration of meals by the stomach were obtained by injecting the meals directly through a cannula into the duodenum. There was a well-marked and parallel increase in the output of trypsinogen and amylase by the pancreas (Fig. 8). In about half the experiments there was an increase in the rate

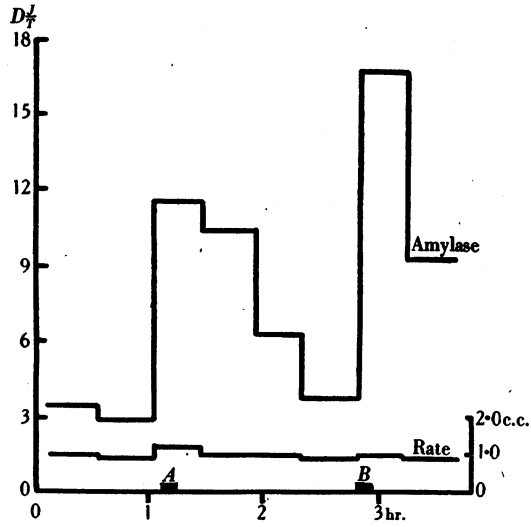

Fig. 8. Effect of duodenal meals. At *A* 30 c.c. of a 5% inulin solution and at *B* 30 c.c. of a 5% starch solution were run into the duodenum through a cannula. Following the administration of each meal there was an increase in the enzyme output by the pancreas.

of flow of the juice coincident with the increase in enzyme output. In all those experiments in which the rate of flow increased the pylorus had been occluded by a ligature.

Increases in the enzyme output by the pancreas were observed after the administration by the stomach or duodenum of starch, casein, inulin, saline or distilled water.

The duodenal meals were run into the bowel slowly and under the minimum head of pressure, but in view of the increased output of digestive enzymes on the administration of saline or water or of a non-utilizable substance like inulin, we decided to examine the possibility that distension might stimulate the pancreas. A balloon, 6 in. in length, was passed through the duodenal cannula into the terminal portion of the duodenum and the first part of the jejunum. Distension of the balloon with air to

pressures of 10, 30 and 50 mm. Hg had no effect either on the enzyme output or on the rate of secretion. As a control the balloon was withdrawn, and 30 c.c. 5% starch injected into the same part of the small intestine had the usual stimulating action on the pancreas (Fig. 9). From this we conclude that distension of the bowel is not an adequate stimulus to the pancreas.

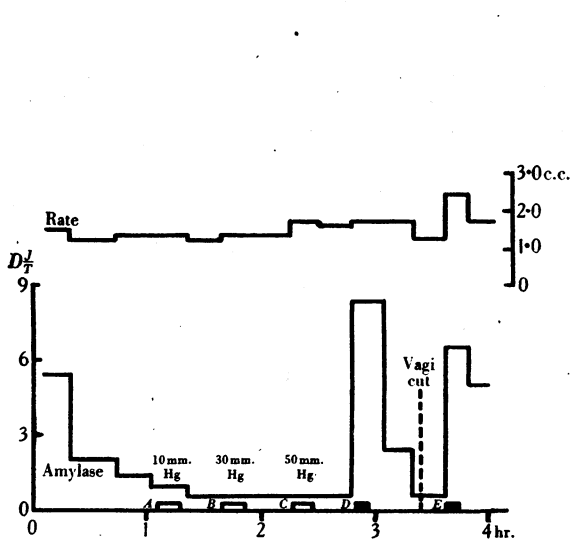

Fig. 9.

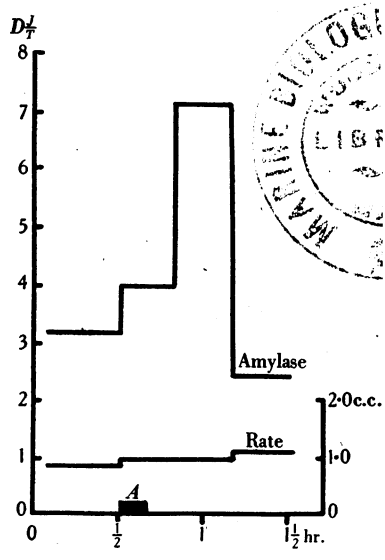

Fig. 10.

Fig. 9. Effect of distension of the duodenum. A balloon, 6 in. in length, was passed into the duodenum. At *A*, *B* and *C* the balloon was distended to pressures of 10, 30 and 50 mm. Hg respectively, without affecting the enzyme output of the pancreas. Control injections of 30 c.c. of a 5% starch solution into the same part of the duodenum at *D* and *E* resulted in an increase in the output of amylase both before and after section of the vagus nerves.

Fig. 10. In this animal both vagus nerves, the splanchnic nerves and the inferior mesenteric nerves were cut, and the pylorus and the common bile duct were occluded. At *A* 50 c.c. of a 5% starch solution were run into the duodenum. Following the administration of the meal there was an increase in the enzyme output by the pancreas.

Effect of nerve sections on the response to meals

The effect of section of the vagal trunks, of the splanchnic nerves, and of the sympathetic fibres from the inferior mesenteric ganglia upon the response of the pancreas to the administration of meals, was studied in a series of animals. The results of these experiments may be summed up in the statement that even when all the extrinsic nerve supply to the small intestine is sectioned (i.e. both vagal trunks cut above the dia-

phragm, the major and minor splanchnic nerves cut extraperitoneally on both sides, and the outflow from the inferior mesenteric ganglia tied off) there is still an increase in the enzyme output by the pancreas on the administration of a meal (Fig. 10).

Effect of secretin upon the output of enzymes by the pancreas

In our search for the mechanism of this stimulation of the enzyme production of the pancreas by meals in an animal with all the extrinsic nervous connexions to the small intestine and pancreas cut, we investigated the possibility that secretin might itself be a stimulant to the

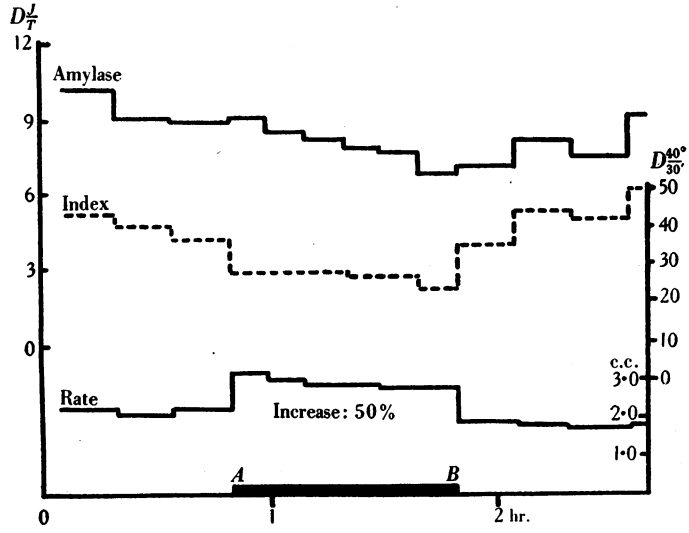

Fig. 11*a*. Effect of secretin injections in a splanchnotomized animal, which showed a 'spontaneous' secretion of pancreatic juice. Between *A* and *B* the 'spontaneous' rate of secretion was increased 50% by intravenous injections of secretin at 10 min. intervals for 1 hr. There was a slight fall in the concentration of enzymes, but almost no alteration in the minute output of amylase.

production of enzymes, as has been suggested by Hammarsten *et al.* These experiments were performed on splanchnotomized animals in which there was a 'spontaneous' flow of juice and a high minute output of enzymes. For a period of 1 hr., at intervals of 10 min., 0·25 mg. of secretin was injected, and a sample of juice collected. The rate and the minute output of amylase were estimated before, during and after the period of secretin stimulation. In an animal in which the spontaneous rate of secretion was high (2 c.c.), and the secretin injection produced only a

moderate increase in rate (50 %) there was a proportionate fall in the diastatic index, so that the minute output of amylase remained practically unaltered throughout the experiment (Fig. 11*a*). Where the 'spontaneous' rate of secretion was lower, and the secretin injections

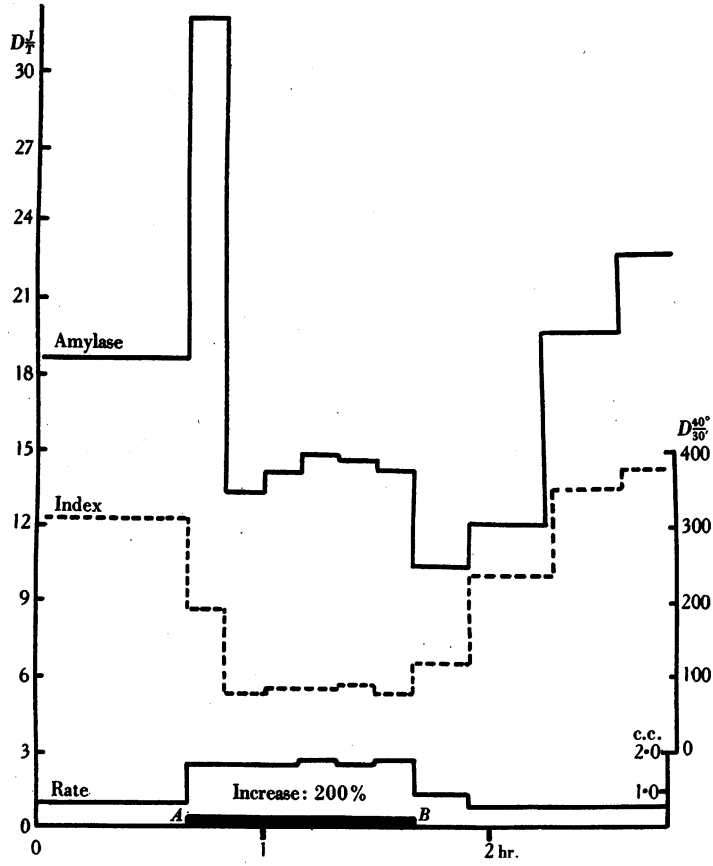

Fig. 11 *b*. Preparation similar to that in Fig. 11 *a*. Injection of secretin at 10 min. intervals between *A* and *B* increased the rate of secretion 200 % above the 'spontaneous' level. The concentration of enzymes fell during this period, and the minute output of amylase increased during the first 10 min. after *A*, and thereafter fell below the level of the control samples.

produced a more marked increase in rate (200 %), the diastatic index again fell during the period of secretin injections. The minute output of amylase rose sharply in the sample collected during the first 10 min. of the secretin period. Thereafter it fell below the level of the samples collected before the injection of secretin, and did not regain that control level

until some 40 min. after the cessation of the secretin stimulation (Fig. 11*b*). These experiments show that during the period of increased secretion brought about by the injection of secretin the minute output of amylase is unaffected if the increase in the rate of secretion is moderate. When the increase in rate is marked, the increase in minute output of amylase during the first 10 min. may be due to a washing out of preformed enzymes in the gland cells. If secretin were a true stimulant of pancreatic enzymes one would expect the minute output of amylase to be increased throughout the whole period of secretin stimulation, whereas the minute output was actually diminished for the rest of the hour, and remained below the control level for some time afterwards. We conclude therefore that the secretin preparation which we were using was not a true stimulant to the production of enzymes by the pancreas. In one experiment we replaced an injection of our secretin preparation by one of 'Pancreotest', the secretin preparation used in Hammarsten's experiments. The sample of juice collected after the injection of 'Pancreotest' showed no increase in the diastatic index or in the minute output of amylase.

Discussion

Almost all workers on the external secretion of the pancreas have experimented on dogs or rabbits, and very few observations have been made on the nervous control of the pancreas in the cat. Apart from a short note by Satake [1923] the only work on the effect of vagal stimulation in this animal is that by Korovitsky [1923] and by Sergeyeva [1938]. The probable explanation is that, as noted by these last two observers, vagal stimulation in the cat produces no 'visible' secretion. We have verified this absence of effect of vagal stimulation upon the rate of pancreatic secretion. We have not found any evidence of an apparent inhibition of secretion due to constriction of the ducts of the pancreas on vagal stimulation, as found by Anrep [1916] on dogs, and as one would have expected from the results of Korovitsky on cats.

All the 'trophic' fibres to the cat's pancreas appear to be contained in the dorsal vagus trunk. It was demonstrated by Savitsch [1909] on dogs that the concentration of amylase, lipase and trypsinogen in the pancreatic juice ran parallel, an observation which has been verified by Anrep, Lush & Palmer [1925] on dogs, and by Baxter [1931*a*, 1935] on rabbits. We have found this parallelism in the concentration of trypsinogen and amylase in the pancreatic juice of cats, under different conditions of stimulation of nerves, by secretin, and by protein and carbohydrate meals.

The difficulty of determining whether the splanchnic nerves contain fibres inhibitory to the pancreatic secretion is that the effects observed upon the rate of secretion and the enzyme content of the juice may be secondary to the constrictor effect of the splanchnic stimulation upon the blood vessels of the pancreas. Edmunds [1909, 1911] came to the conclusion that the inhibitor action of adrenaline and of splanchnic stimulation upon pancreatic secretion was not specific, but secondary to the constrictor action. Babkin [1924] concluded that his experiments gave no support to, but did not disprove, the view that there are special inhibitory fibres in the splanchnic nerves to the acinous cells. The diminution in enzyme output in our experiments during and after stimulation of the splanchnic nerves, even when the rate of secretion is kept constant by increased injections of secretin, seems to point to a true inhibitory action of the splanchnic nerves upon the pancreatic cells, although it may be argued that the cutting down of the blood supply to the pancreas would in itself lead to a diminution in the enzymes of the juice. Taking this piece of evidence, however, in conjunction with the 'spontaneous' secretion and high minute output of enzymes in splanchnotomized animals, and with the enhanced response to vagal stimulation after splanchnotomy we feel justified in concluding that the splanchnic nerves contain fibres which are inhibitory to the acinous cells of the pancreas.

Baxter [1931*b*] showed that in the rabbit the splanchnic nerves contain secretory fibres to the pancreas. Sergeyeva [1938] has brought forward histological evidence, and Babkin, Hebb & Sergeyeva [1939] experimental evidence, that there are secretory and trophic fibres to the pancreas in the splanchnic nerves of the cat, and that these fibres do not synapse in the coeliac ganglia. In some experiments in which we painted the coeliac ganglion on the stimulated side with 1% nicotine, we observed no increase in the rate of the secretion or its enzyme content on subsequent stimulation of the splanchnic nerves. Since we have done only a few experiments of this type, and as in some of these there was still a slight diminution in the rate of secretion on splanchnic stimulation after painting the coeliac ganglion with nicotine (suggesting that the ganglion had not been completely paralysed), and since, moreover, our period of stimulation (5 min.) was very much shorter than the 3–6 hr. of stimulation employed by Sergeyeva, we do not feel justified in drawing any definite conclusion about the existence of secretory fibres in the splanchnic nerves.

It seems clear from our experiments that as the result of trauma to

the duodenum during cannulation of the pancreatic duct an inhibitory reflex is elicited through the splanchnic nerves. The absence of pancreatic secretion in these cases might be due to a direct inhibitory action of the splanchnic fibres on the secretory cells of the pancreas, to a constrictor action on the blood vessels of the gland, or might be secondary to an inhibition of the absorption from the small intestine of digestion products and secretin which would stimulate the pancreas. In favour of the first possibility is the evidence that the splanchnic nerves contain fibres which have a direct inhibitory effect upon the acinous cells of the pancreas. There seems to be little evidence on the effect of the extrinsic nerves upon absorption from the small intestine. Horne, McDougall & Magee [1934] found that either vagotomy or splanchnotomy increased the absorption of glucose from the small intestine in rabbits. In our experiments vagotomy did not prevent the inhibitory effect on pancreatic secretion. On the other hand the shortening of the period of 'spontaneous' secretion of juice when the passage of foodstuffs and acid from the stomach was prevented by occlusion of the pylorus would suggest that the 'spontaneous' secretion depended upon absorption from the small intestine. The evidence is insufficient to allow us to decide upon the mechanism of the inhibition of pancreatic secretion, but the important practical point is that even slight trauma to the duodenum results in an inhibition of the digestive secretion of the pancreas over a period of at least 4 or 5 hr.

The effect of stimulating the central end of vagal and sympathetic nerves was in most cases to produce an inhibition of pancreatic secretion. In none was there any increase in secretion or enzyme output. Our inability to produce a reflex excitation of the trophic fibres in the dorsal vagus trunk raises the question of how a discharge of impulses along these fibres is brought about in the normal animal. The possibilities would seem to be either a reflex brought about by stimulation of afferent fibres in the vagus or splanchnic nerves from the small intestine, an effect which we have been unable to produce by electrical stimulation of these nerves, or a cephalic reflex either from the taste of food or by psychic stimulation. About this latter mechanism there appears to be some doubt. Crittenden & Ivy [1937] state that meat broth produces a psychic stimulation of the pancreas in dogs, but Villaret & Justin-Besançon [1936], reviewing previous work, conclude that any psychic effect on the pancreas is either feeble or non-existent, and they were unable to demonstrate any psychic secretion in a human subject with a pancreatic fistula.

There are two points of interest in the response of the pancreas to the injection of fluids into the small intestine, the increase in rate of flow and the increase in the enzyme output. Well-marked increases in the rate of secretion were observed on giving duodenal meals after the pylorus had been occluded, so that the release of secretin by the passage of acid into the small intestine was prevented. In all experiments the passage of bile into the small intestine was prevented by the ligature of the common bile duct along with the pancreatic duct, so that this mechanism for the release of secretin from the intestinal mucosa was also excluded. The increases in rate were observed after section of the extrinsic nerves to the gut, so that they could not have been brought about reflexly through the central nervous system. These results indicate that there is some other mechanism for the release of secretin than the association with bile salts [Mellanby], or the action of acid [Bayliss & Starling, Ivy & Lueth].

Even more difficult to explain is the increase in enzyme output from the pancreas following the administration of meals to animals in which all the extrinsic nerve supply to the small intestine has been sectioned. This result, coupled with the very high level of enzyme output in vagotomized and splanchnotomized animals would seem to disprove Mellanby's claim that the vagus is responsible for the enzymes of the pancreas. Nor do our experiments on the effect of secretin injections in splanchnotomized animals lend any support to the suggestion by Hammarsten *et al.* that secretin stimulates the production of enzymes by the pancreas. We are left therefore with the possibilities that the increased enzyme output in response to meals in extrinsically denervated animals may be mediated through the intrinsic nerve plexuses of the intestine (though this is difficult to visualize) or by some humoral mechanism, either secretagogue in type, or some hormone other than secretin. These possibilities are now being investigated.

Summary

1. The effect of nervous and alimentary stimuli on the enzyme output and rate of secretion of the cat's pancreas has been investigated.

2. All the 'trophic' fibres to the pancreas are contained in the dorsal vagus trunk.

3. There is a parallel secretion of trypsinogen and amylase in the pancreatic juice during alimentary, nervous or secretin stimulation of the pancreas.

4. Vagal stimulation has no effect upon the rate of secretion of pancreatic juice.

5. The splanchnic nerves contain fibres inhibitory to the acinous cells of the pancreas.

6. Central vagal or sympathetic stimulation is either without effect or brings about an inhibition of pancreatic secretion.

7. Trauma to the duodenum results in a prolonged inhibition of pancreatic secretion by a reflex acting either directly upon the pancreas or indirectly by inhibiting the absorption of pancreatic stimulants from the intestine. The afferent and efferent pathways for this reflex lie in the splanchnic nerves.

8. The presence of foodstuffs in the stomach does not stimulate the pancreas.

9. The passage of foodstuffs, inulin, normal saline or water through the pylorus into the duodenum, or their injection into the duodenum, results in an increase in the enzyme output by the pancreas, and, in most cases, an increase in the rate of secretion. The increase in enzyme output can be observed after section of all extrinsic nerves to the small intestine. The increase in rate of secretion is not prevented by the exclusion of acid and bile from the intestine.

10. Secretin does not increase the production of enzymes by the pancreas.

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