THE PART PLAYED BY THE DUCTS IN THE PANCREATIC SECRETION. By L. K. KOROVITSKY.

(*From the Physiological Laboratory, University of Odessa.*)

THE first object of this work was to compare the secretory innervation of the pancreatic gland in the dog with that in the cat, an animal hitherto very little used for experiments on pancreatic secretion. In view of the striking difference between these two animals in respect of the sympathetic secretory fibres of the submaxillary gland, the comparison of the pancreatic innervation seemed to be interesting. Previous observers have shown that the stimulation of the vagus does not cause pancreatic secretion in all animals; in the rabbit for instance the stimulation of the vagus was found to have no effect(1); pilocarpine does not cause a flow of pancreatic juice in the pigeon(2); on the other hand the definite secretory effect of the vagus in the case of the dog is well established. In the cat the innervation of the pancreatic gland has never been studied.

Method. The cats received their last meal 12 hours before the experiment. The animal was anæsthetized with an A.C.E. mixture, both vagi were then cut in the neck, a cannula tied in the trachea, the decerebration performed and artificial respiration started. Cannulæ were also introduced into the duodenum and into the pancreatic duct. A longitudinal incision was made through the pylorus, the mucous membrane of the latter was separated from the muscular coat, a strong ligature passed between the two and tied. In this way the stomach was completely separated from the duodenum, with the least injury to the nerves which run in the muscle coat of the pylorus. The pancreatic cannula was connected with a narrow glass tubing fixed to a millimetre scale. The secretion of the pancreatic juice is given in all experiments in terms of millimetres of this glass tubing per minute.

The action of the vagus nerves on the pancreatic secretion. Pavlov(3) has shown that in the spinal dog the stimulation of the vagi in the neck or below the heart in the chest causes a marked secretion of the pancreatic juice and that this juice is different in properties from the juice obtained with the aid of hydrochloric acid or secretin. The first question raised was whether the vagus has a similar action in the cat.

20 c.c. of 0·4 p.c. HCl were injected in the duodenum of the cat at the beginning of each experiment; this was done in order to verify the correct position of the pancreatic cannula, and the absence of kinks of the duct. When the secretion had completely stopped the vagus was stimulated either in the neck or in the chest above the diaphragm; a faradic current rhythmically broken by a beating metronome was used for the stimulation. Nine experiments were performed and in none was there observed any secretion of the pancreatic juice. Increase in the strength of the stimulus did not alter the fact. It seemed from these experiments that in the cat the secretory fibres are either absent or that their action is entirely different from that in the dog.

Pavlov(3), Popielsky(4), Mett(5) and Koudrevetsky(6) state that in the dog the vagus contains both secretory and inhibitory fibres. According to these observers the pancreatic secretion begins only after a long latent period and can be temporarily stopped by successive stimulation of the vagus. Their explanation of the long latent period is that the inhibitory fibres of the vagus have first to be tired out by a prolonged or repeated stimulation, and that then only can the secretory fibres produce an obvious effect. The absence of the secretion in the cat might have been due to the stronger action of the inhibitory fibres of the vagi over that of the secretory. It was hoped that if this was the real cause of the negative results, a prolonged stimulation of the vagi would tire out the inhibitory fibres and a secretion would be obtained. But stimulations which were continued for over 2–3 hours proved as ineffective as the short ones. Section of the vagus five days before the experiment gave no sign of selective degeneration of inhibitory fibres, for no secretion could be obtained by vagus stimulation.

The action of pilocarpine. The augmented secretion. Intravenous injection of pilocarpine causes in the dog a flow of pancreatic juice, but in the cat it has either only a very small effect or generally none at all. Repeated injections of 1–2 mgms. of pilocarpine were tried in 15 experiments without any definite effect on the pancreatic secretion. One rather curious fact was, however, noticed. As previously stated 20 c.c. or 0·4 p.c. HCl were injected into the duodenum at the beginning of each experiment; the secretion was measured and pilocarpine was injected only after its complete cessation. The absence of secretion after an injection of pilocarpine was unexpected and in order to make sure that this is not due to an occlusion of the duct a further 20 c.c. of the acid were injected into the duodenum. The second injection of the acid caused a pancreatic secretion very much larger than the first. This

experiment was repeated on many animals and it was invariably found that an injection of acid into the duodenum causes a larger and sometimes an enormous secretion after a preliminary intravenous injection of pilocarpine or after a prolonged stimulation of the vagus.

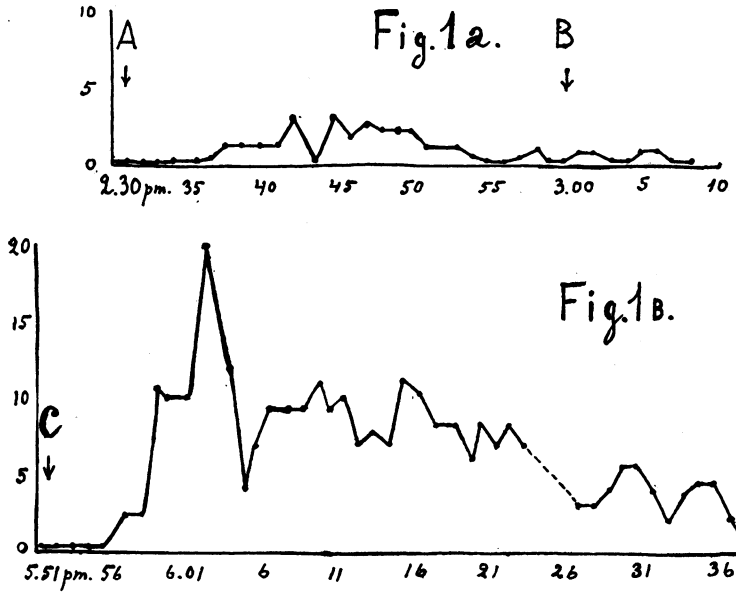

Fig. 1 *a* and *b*. Secretion in millimetres of the glass tubing recorded each two mins. At *A* 20 c.c. of 0·4 p.c. HCl were injected in the duodenum—total secretion 20 mm. From *B* to *C* = 2 hours 40 mins. rhythmic stimulation of the vagus in the neck—no secretion. At *C* a second injection of the same amount of acid in the duodenum—total secretion 278 mm.

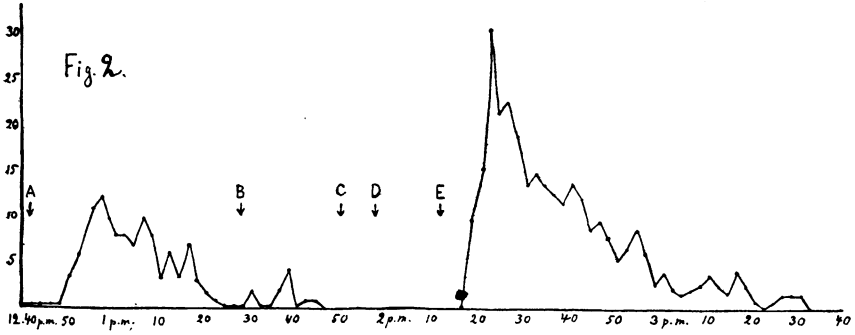

Fig. 2. Secretion recorded every 2 mins. At *A* 20 c.c. of 0·4 p.c. HCl was injected in the duodenum—total secretion 96 mm.; at *B*, *C* and *D*—intravenous injections of 1–2 mgms. of pilocarpine; at *E* a second injection of the acid—total secretion 274 mm.

The two experiments given in Fig. 1 and Fig. 2 are the most striking but on the average the same amount of acid introduced after pilocarpine or vagus stimulation caused a secretion twice as large as the one before the stimulation or injection. Table I presents the mean figures of all the experiments.

TABLE I.

	Mean secretion in mm. of the tubing
First injection of 20 c.c. of 0·4 p.c. HCl ...	31·4
Second injection of the same amount of acid but after pilocarpine	80·7
Second injection of the same amount of acid after prolonged stimulation of the vagus ...	78·9

It has been shown by several authors(7) that repeated injections of acid into the duodenum cause a progressively diminishing secretion of pancreatic juice. I was able to verify this statement in my own experiments and found it to be entirely correct. The augmented action of the acid after pilocarpine or after stimulation of the vagus is evidently a case which needs special consideration. An explanation was at first sought on the lines that pilocarpine as well as the stimulation of the vagus causes a sensitisation of the gland to secretin. This explanation is feasible, but further experiment indicated another cause of the facts described above as being more probable. A few experiments with a continuous slow injection of secretin were performed, the pancreatic secretion was thus maintained at a constant rate. Now every stimulation of the vagus as well as injections of pilocarpine, always caused a marked slowing of the secretion and not an acceleration—evidently the explanation of the augmented action of the acid by a sensitisation of the gland is inadequate.

The character of the pancreatic secretion obtained by the injection of acid into the duodenum before and after the administration of the pilocarpine is different. In the first case the secretion at first accelerates in rate, soon reaches a maximal speed, then gradually slows down and finally stops; the secretion is, however, very uniform in rate, so that the quantities of the juice secreted in any two successive minutes do not differ much. In the second case, the rate of secretion is very irregular, one minute there might be a large secretion, then a small one and so on; the secretion proceeds in a jerky, irregular way, with occasional arrests or even slight backward movements.

In experiments with prolonged stimulation of the vagi or with successive injections of pilocarpine the pancreatic gland is always found to

be swollen up and œdematous and, although no secretion is observed during the experiment, a large amount of juice can be pressed out of the gland by mechanical pressure. Spontaneous movements of the animal as well as general cramps, which are often observed after injections of pilocarpine, also cause some outflow of the juice, due to compression of the gland.

The part played by the ducts of the gland. In 1916 Anrep(8, 9) published his observations on the pancreatic secretion in the dog. He made simultaneous records of the secretion, blood flow and the plethysmographic volume of the gland. Anrep found that the stimulation of the vagus causes the volume of the gland to increase and that this increase continues until the appearance of the secretion. The increase in volume is not due to changes in the blood supply of the gland. On the basis of his experiments Anrep comes to the conclusion that the arrest of the pancreatic secretion as well as the long latent period observed when the vagus is stimulated, is not due to the presence of hypothetic inhibitory fibres but to a constriction of the pancreatic ducts and a retention of the secretory juice. May(10) also made some plethysmographic records of the pancreas secreting under the action of secretin; he observed an increase in the volume of the gland during the whole period of secretion, and ascribed it to vaso-dilation. The experiments of Anrep show that the vagi contain secretory fibres to the pancreas and motor fibres to the pancreatic ducts.

The experiments described in the first part of this communication make it highly probable that in the cat the vagi also contain motor fibres to the ducts and that the juice secreted under the influence of the secretory fibres accumulates within the gland and has no free outflow on account of the strong constriction of the ducts. The capacity of the ducts of the cat's pancreas as determined by injections of suspensions of charcoal was found to be considerable (1·0–1·5 c.c.). From the above point of view, it is probable that the augmented action of the acid when injected after an administration of pilocarpine or after a previous stimulation of the vagi, is due to a washing out of the juice which has been accumulating in the gland. There is therefore a certain excess of juice over that obtained by the action of the acid alone.

Fig. 3 presents an experiment which illustrates all the points mentioned. The first injection of the HCl solution caused the usual secretion, a rhythmic stimulation of the vagus was started when the secretion had stopped. There was a further flow of the juice at the beginning of the stimulation—probably this was due to the constriction of the ducts

and squeezing out of the juice which still remained in the gland. No further secretion was observed during the whole of the stimulation.

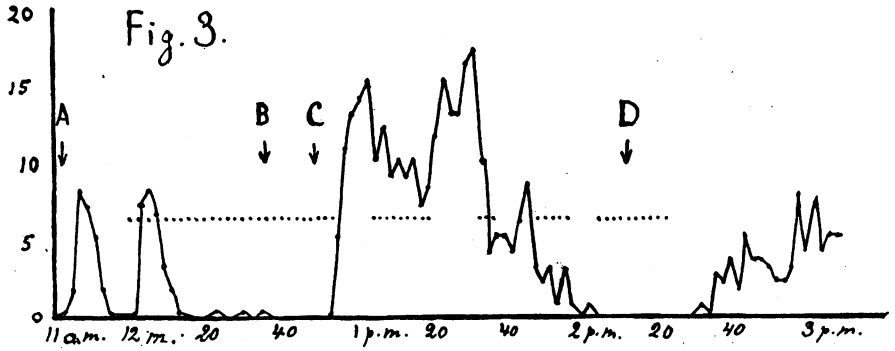

Fig. 3. Secretion recorded each 2 mins. At *A*, *B*, *C* and *D* injections of 20 c.c. of 0·4 p.c. HCl in the duodenum. The dotted line across the figure shows the time when the vagus nerve was stimulated. The nerve was stimulated in the neck, by a rhythmically broken Faradic current (coil 15–11·5 cm.), three minutes on, one minute off.

A second injection of the same amount of acid was made during the stimulation of the vagus; it did not cause a secretion either. Evidently the ducts were constricted to such an extent that the juice had no chance of escaping into the cannula. The stimulation of the vagus was then stopped and a third injection of the acid made. It now caused a free secretion of the juice in a much larger amount than before. Stimulations of the vagus produced each time a diminution of the outflow of the juice. A fourth injection of acid was made during a stimulation of the vagus. It did not cause secretion, but 20 minutes after the injection when the stimulation was stopped, the juice began to flow. Apparently the constriction of the duct had disappeared and the accumulated juice had now a free outflow.

Experiments with perfused pancreatic ducts. The animals were prepared in the same way as described above. Two cannulas were tied in the pancreatic duct instead of one. One cannula was introduced in the usual place near the entry of the duct in the duodenum. The other cannula was introduced near the tail (splenic) end of the gland; a small portion of the duct being dissected with a blunt instrument; in the first experiments the duct was generally injected with Indian ink to make it more visible, this was, however, abandoned in further experiments. The "tail" cannula was then connected with a Marriotte's flask filled with a 0·3 p.c. solution of $NaHCO_3$, with some addition of gum-arabic; a water-manometer was connected by means of a T-piece

to record the pressure; the perfusion fluid was warmed to body temperature. The outflow of the fluid from the pancreatic duct was recorded in the same way as the pancreatic secretion in the previous experiments.

In a dead animal the rate of the perfusion through the duct is very uniform and depends only on the pressure of the perfusion fluid. In an animal which is alive the ducts have a certain changeable tone of their own and the perfusion is not so regular. Stimulations of the vagus, intravenous injections of pilocarpine (1–2 mgs.) or small additions of pilocarpine to the perfusion fluid invariably cause a strong spasmodic constriction of the ducts as judged by the diminution or complete arrest of the outflow. At a pressure of 2–6 cm. of the perfusion fluid the constriction is strong enough to cause an arrest of the flow; at a pressure of 8–10 cm. there is only a more or less definite slowing. On some occasions, however, after repeated injections of pilocarpine the constriction of the ducts is so strong that the pressure has to be raised to 16 cm. to get a flow. Large doses of atropine paralyse the constriction mechanism of the ducts; the ducts dilate and the flow of the perfusion fluid increases. Intravenous injections of large doses of atropine (5–10 mgs.) or addition of atropine to the perfusion fluid abolishes also the constriction effect of pilocarpine (Figs. 4 and 5).

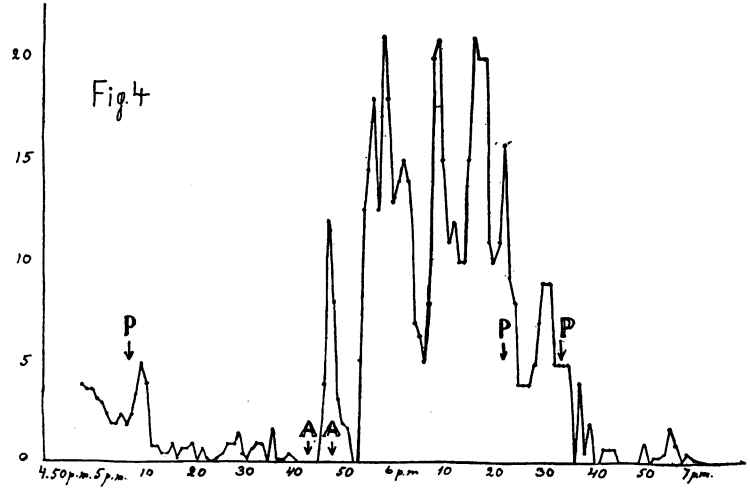

Fig. 4. Perfusion of the pancreatic ducts. The pressure of the perfusion fluid = 6 cm. Outflow records every minute. Intravenous injections of 1 mg. of pilocarpine were made at places marked *P*. Intravenous injections of 10 mgs. of atropine—at places marked *A*.

It is worth mentioning that the irregular, jerky flow which is observed on administration of the HCl after pilocarpine is also observed in the case

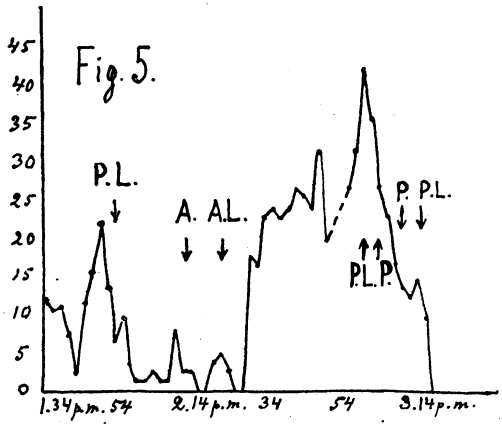

Fig. 5. Perfusion of the pancreatic ducts. The pressure of the perfusion fluid = 4 cm. Intravenous injections of pilocarpine (1 mg.) at *P*; perfusion with pilocarpine (1 c.c. of 1 p.c. solution) added to the perfusion fluid at *PL*; intravenous injections of atropine (10 mgs.) at *A*; perfusion with a solution of atropine in the perfused fluid at *AL* (1 c.c. of 1 p.c. solution).

of the perfused ducts in a pilocarpinised animal or when the vagus nerve is stimulated. These irregularities of the flow are probably due to small periodic contractions and relaxations of the duct. The first effect of pilocarpine is generally an acceleration of the flow which is then replaced by a slowing or arrest. The acceleration is caused by squeezing out of the fluid by the contracting ducts.

The experiments described in this connection show that the pancreatic ducts are not passive conducting tubes, but that they play an active part in the process of the entry of the pancreatic juice in the duodenum. In this respect they act in the same way as the bile ducts which, according to Veselkin(11) take up the rôle of the gall bladder after the latter is removed. Furthermore, Anrep(12) has shown in a recent communication that the ducts of the salivary glands also play a considerable part in the flow of saliva.

Thus in experiments with pancreatic secretion it is imperative to consider two processes: (1) the secretion of the juice by the pancreatic cells and (2) the outflow of the juice from the ducts of the gland into the intestine. In normal conditions the secretory activity of the pancreas is controlled not only by the nervous and humoral secretory mechanism, but also by the motor innervation of the ducts of the gland.

Conclusions.

(1) The ducts of the pancreatic gland have a tone of their own; they are able to constrict and relax.

(2) The motor fibres of the ducts pass along the vagus nerves.

(3) Intravenous injections or local application of pilocarpine has the same effect as the stimulation of the vagi.

(4) The inhibitory effect of the stimulation of the vagus upon the pancreatic secretion is explained by a constriction of the ducts causing a retention of the secretory juice and not by a true inhibitory action.

(5) The vagus in the cat most probably contains secretory fibres to the pancreas as it does in the dog.

(6) Atropine in large doses paralyses the secretory and the motor fibres of the vagus.

(7) The ducts of the pancreas are similar to the bile ducts and the ducts of the salivary glands, not behaving like passive conducting tubes but playing an active rôle in the outflow of the juice.

I have pleasure in recording my thanks to Professor B. P. Babkin for the suggestion of this work and his help and criticism during its performance.

REFERENCES.

(1) Savich. Russian Physiol. Journ. 1. 1918.
(2) Langendorf. Arch. f. (Anat. u.) Physiol. p. 7. 1879.
(3) Pavlov. Clin. Med. Journ. 1888. N. 32 (Russian).
(4) Popielsky. Diss. 1896. (Russian.)
(5) Mett. Diss. 1889. (Russian.)
(6) Koudrevetsky. Diss. 1890. (Russian.)
(7) Bayliss and Starling. Journ. of Physiol. 37, p. 325. 1902.
(8) Anrep. Ibid. 49, p. 67. 1914.
(9) —— Ibid. 50, p. 421. 1916.
(10) May. Ibid. 30, p. 400. 1904.
(11) Veselkin. Collected papers of Lesgaft Inst. 1921. (Russian.)
(12) Anrep. Journ. of Physiol. 56, p. 263. 1922.