THE INFLUENCE OF THE BLOOD SUPPLY ON PANCREATIC SECRETION. By B. P. BABKIN.

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The importance of the normal blood supply of a gland for its activity is not of the same degree for all kinds of digestive glands. In the salivary glands the blood supply can be decreased to a certain degree without great damage to their secretory activity (Heidenhain(1), Langley and Fletcher(2), Carlson, Greer and Becht(3), Gesell(4)). The pancreatic gland seems to be extremely sensitive to the changes in the circulation provoked by stimulation of different nerves (Bernstein(5), Pavlov(6), Gottlieb(7), Mett(8), May(9), Edmunds(10), Anrep(11)), or by substances with vasoconstrictor character (Gottlieb(7), Benedicenti(12), Edmunds(10)), or by compression of the aorta above the cœliac artery (Pavlov(6), May(9), Anrep(11)). On the other hand, the pancreatic gland continues to secrete some time after the blood pressure falls to zero (Pavlov(6), May(9)). It must be added that the more copious the pancreatic secretion the more difficult it is to inhibit it.

Thus some points concerning the interrelations of the secretion and blood supply in the pancreatic gland are not quite clear. It seems that not every interference with the circulation influences the secretory work of the gland, but only interference of special kinds. The following observation of Heidenhain and one of the experiments of Gottlieb lead one to accept this supposition. Heidenhain(14) observed in a dog marked periodic variations in the blood-pressure. With the rise in the blood-pressure came a lessening of the pancreatic secretion, with its fall occurred an increase of the secretion. Gottlieb(7) inhibited the spontaneous pancreatic secretion in a rabbit with strychnine. The injection into the blood of chloral hydrate, which relaxed the blood-vessels contracted by strychnine, increased it again. Since chloral hydrate not only paralyses the vaso-constrictor centre, but stimulates the pancreatic secretion also (Wertheimer et Lepage(15)), Gottlieb's interpretation of the phenomenon observed cannot be accepted without further investigations.

All this led me to reinvestigate the question. My task was greatly facilitated because in chloralose I found a narcotic which itself produced

a moderate secretion of the pancreatic juice and did not affect the action of hormones nor of secretory nerves.

Methods. The experiments were performed on dogs. The day before an experiment the dog had his last meal not later than 5 p.m. Water was left during the night. The next morning the stomach as a rule was empty; it contained only alkaline or weakly acid mucous. For a short while the animal was narcotised with chloroform and ether. Chloralose (0·1 g. per kilo weight) was then injected into a vein. A longitudinal incision was made in the pylorus and the stomach was separated from the duodenum by means of circular suture which passed only through the mucous and submucous membrane in the distal part of the pylorus. A cannula was introduced into the main pancreatic duct and was connected with the tubing on a scale each division of which corresponded to ·005 c.c. After establishment of artificial respiration the chest was opened. Both vagi were tied and cut in the neck and below the heart, the right splanchnic nerve also. (If there are not special indications in the description of the experiments it means that the vagi were cut in the neck and below the heart.) A string was put round the left splanchnic nerve in the abdomen. Later by strong quick pulling of the two ends of the string the nerve could be torn in two, without opening the abdomen. In most of the experiments the blood-pressure was registered. (In all experiments quoted below the average blood-pressure is indicated for a given time. If two or more figures appear they represent the consecutive oscillation of the blood-pressure.) At the end of the experiment the contents of the stomach were examined. In no case was accumulation of gastric juice noticed.

Secretory action of chloralose. Chloralose (synonyms = glucochloral, anhydrochloral, α-chloralose) is obtained by means of heating anhydrous chloral hydrate and dry glucose in a closed tube at 100° C. for one hour (16). It retains some of the properties of chloral hydrate and among others the property of stimulating the pancreatic secretion. The following experiment on a dog under chloralose with splanchnic nerves intact shows that the pancreatic secretion lasted 2 hours 15 mins. The oscillations of the secretion and its interruption resulted from the special experimental interventions.

Exp. 1. The secretion is noted in 5 minute intervals.

3, 2, 4, 3, 4, 3, 3, 2, 2, 3, 1½*, 1½, 1, 2, 3, 2, 3, 3, 2½, 3½, 3†, 2, 1, 2, 2, 3.

* Rhythmic stimulation of the peripheral end of the right vagus in the neck during 5 mins. Coil 7 cm.

† Right sympathetic nerve cut in the chest.

The next experiment shows more distinctly the secretory action of chloralose and the action of secretory nerves under it. In this special case the spinal cord in a dog was cut below the medulla and the brain destroyed.

Exp. 2. Spinal dog. 6 kgm. Secretion is noted every 5 mins.

1, 1, 5*, 7, 3, 2, 2 (0·22 chloralose into the vein), 3, 6, 7, 5 (again 0·23 g. chloralose), 5, 14, 9, 6, 4, 3, 4, 10*, 30, 9, 4, 2, 2.

* Stimulation of vagi below the heart during 5 mins., each nerve stimulated 1 min. Coil 7·5 cm.

Like moderate doses of other narcotics (chloroform, ether, morphia) chloralose does not disturb the secretion provoked by the hydrochloric acid or secretin. It is not only not antagonistic to pilocarpine but a summation of the action of these two drugs can be observed.

As to the composition of the pancreatic juice secreted under the influence of chloralose it approaches the composition of the "nervous" juice. Thus the lowest figures obtained were: solids 3·97 p.c.; organic substances 3·20 p.c.; ash 0·77 p.c. 1·25 c.c. of juice were secreted during 1 hour 25 mins.

All this shows that chloralose is a very suitable narcotic for the study of the pancreatic secretion. This anæsthetic gave the opportunity to investigate more closely the interrelations between the secretory process and the blood supply of the pancreatic gland. The pancreatic secretion was provoked not only by secretin, viz. hydrochloric acid, but also by stimulation of the secretory nerves.

The influence of section of the splanchnic nerves on the pancreatic secretion provoked by secretin. The deprivation of the pancreatic gland of sympathetic innervation, which coincides with the fall of the blood-pressure greatly increases the secretion provoked by secretin.

Exp. 3. Dog under chloralose. Steady inflow of secretin (1 cc. in 1 min.) through the jugular vein. Secretion noted every 2 mins.

P.J.	22	25*	22†	38	58	53	55
B.P.	40	44–30	42–25	23	25	24	25

* Right sympathetic torn in two in the chest.

† Left splanchnic torn in two in the abdomen. The rate of the heart's beat increased from 244 per min. to 260.

After the section of the splanchnic nerve, the same dose of secretin provokes nearly a double quantity of pancreatic juice in the same time. This is seen from Exp. 4.

Exp. 4. Both vagi cut in the neck and below the heart and right splanchnic in the chest. Secretion noted every 5 mins.

(A) 4.17 p.m.						
P.J.	0	**62***	55		17	=134 div. in 15 mins.
B.P.	104	51–73–93	100–104		106	
		4.37 p.m. Left splanchnic cut in the abdomen.				
(B) 4.45 p.m.						
P.J.	1	146*	85	21	4	=252 div. in 15 mins.
B.P.	60	34–58–61	64	—	65	
(C) 5.07 p.m.						
P.J.	0	157*	97	29	5	=278 div. in 15 mins.
B.P.	65	43–66–64	67	69	73	

* At the beginning of these 5 minute intervals 1 c.c. of secretin introduced into the jugular vein.

Thus the section of the splanchnic nerves markedly increases the secretion of pancreatic juice provoked by secretin. It coincides with a more or less pronounced fall of the systemic blood-pressure. The same relation has been seen in cases of pancreatic secretion provoked by chloralose.

The most simple explanation of the phenomena observed is that the abdominal viscera, and in particular the pancreatic gland, as a result of elimination of the sympathetic innervation, receive much more blood. And this creates very favourable conditions for the secretory work of the gland. These experiments do not support the view that in the sympathetic nerves there are special inhibitory fibres to the secreting cells of the pancreatic gland. But they by no means deny this. No doubt an assertion that every inhibition of pancreatic secretion is of vasomotor origin is not quite accurate. Anrep(11) and Korovitzky(17) have described the part played by the pancreatic ducts in the inhibition of the secretion. But further proofs are necessary to substantiate the theory that the sympathetics or vagi carry nerve fibres to the pancreatic gland which are capable of making the secretory cells refractory to the nervous or humoral impulses or of blocking the already elaborated secretion in the cells themselves.

Two series of experiments were performed for the more precise determination of the influence of vascular activity of the pancreatic gland: (1) with the temporary lowering of the blood-pressure, and (2) with the rise of it.

Influence of the lowering of the blood-pressure upon the pancreatic secretion. Two methods were employed: (1) rhythmic stimulation of the peripheral ends of the vagi in the neck, the nerves being cut under the heart; (2) compression of the inferior vena cava in the chest. In both

cases the secretion of pancreatic juice was provoked by secretin, hydrochloric acid or chloralose.

The stimulation of the peripheral end of the vagus in the neck, followed by a sharp fall of the blood-pressure and slowing of the heart, does not affect the pancreatic secretion. But if after the stimulation is finished the blood-pressure goes up a marked slowing of the secretion is observed. This can be seen in Exp. 5. The secretion of the pancreatic juice was provoked by means of a steady flow of secretin into the jugular vein (1 c.c. every min.).

Exp. 5. The secretion is noted every 2 mins.

(A)	P.J.	24	23	**25***	11	16	19	19
	B.P.	70	73	**52**	74–100	118–96	86	86
(B)	P.J.	12	12	**12†**	10	14	16	18
	B.P.	89	96	**53**	76–100	86	86	90

* Rhythmic stimulation of vagi in the neck. Coil 7 cm. † Ditto. Coil 6½ cm.

The rise of the blood-pressure following the first stimulation of the vagi (A) was bigger and lasted longer than the second (B). Corresponding with this, the inhibition of the secretion in the first case was more pronounced than in the second. The most striking feature of this experiment is the absence of any inhibition whatever of the activity of the gland during the actual stimulation of the vagi. And this occurred in spite of a notable average fall of blood-pressure and slowing of the pulse rate from 132 or 138 beats per min. to 30 or 36 beats.

In Exp. 6, A shows very distinctly that no changes occur in the secretion if the blood-pressure is not affected after the stimulation of the vagi.

Exp. 6. A. Splanchnics intact. Constant flow of secretin into the jugular vein (0·5 c.c. every min.). Flow of pancreatic juice per 1 min.

P.J.	40	32	36	32	36	**38***	**33***	**39***	37	43	36	38
B.P.	98	103	104	97	84	**48**	**52**	**50**	87	80	81	78

* Rhythmic stimulation of vagi in the neck. Coil 6½ cm.

The same dependence of pancreatic secretion on the rise of a probable constriction of the vessels of the gland, can be seen when other secretory stimuli are employed, *i.e.* hydrochloric acid, chloralose, etc. Thus in Exp. 6, B, the great fall of blood-pressure produced by stimulation of vagi in the neck did not disturb the typical rise of the secretion under hydrochloric acid. But after the stimulation the secretion was inhibited coinciding with the rise of the blood-pressure (Fig. 1).

Exp. 6. B. Both splanchnics intact. 25 c.c. of 0·4 % HCl introduced into the duodenum. Flow of the pancreatic juice every 2 mins.

P.J.	0	9	18	18	**27***	10	13	11	6	6
B.P.	91	102	116	106	**58**	124–150	140–122	112	108	94

* Vagus stimulated in the neck. Coil 6½ cm.

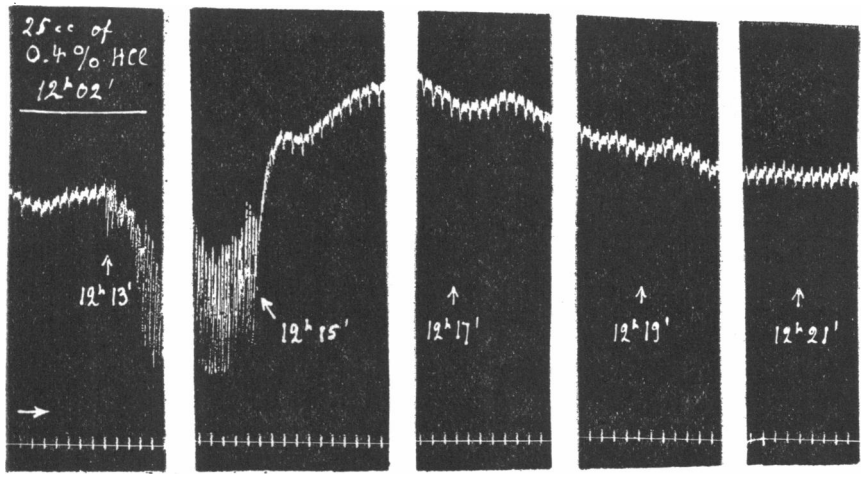

Fig. 1.

It must be added to this that in some cases a certain inhibition of chloralose secretion was already observed during the stimulation of the vagi (cf. Exp. 1). This phenomenon is not peculiar to the chloralose secretion. It can be observed during the action of other stimuli, if only the secretion is slow enough.

The cause of the rise of blood-pressure probably is, as Anrep and Starling (unpublished work) have shown in experiments with crossed circulation, the stimulation of the vaso-motor centre in the brain, provoked by the fall of blood-pressure. And indeed after the section of both splanchnics this rise of the blood-pressure is very small or even absent. Corresponding to this the inhibition following the stimulation of the vagi is insignificant or absent (Exp. 7, Fig. 2).

Exp. 7. Both splanchnics cut. A. First injection of 2 c.c. of secretin into the jugular vein at 4.44 p.m. B. The second injection of 2 c.c. of secretin at 5 p.m. Flow of pancreatic juice recorded every 2 mins.

(A)	P.J.	13	33	14	10	5	3	1	=79 div. in 14 mins.
(B)	P.J.	2	32	**23***	18	4	3	1	=83 div. in 14 mins.
	B.P.	23	24	**16**	23	21	20	18	

* Rhythmic stimulation of vagi during 2 mins. Coil 7 cm.

In order to produce a more considerable congestion of blood in the abdominal viscera periodic closing and opening of the vena cava inferior

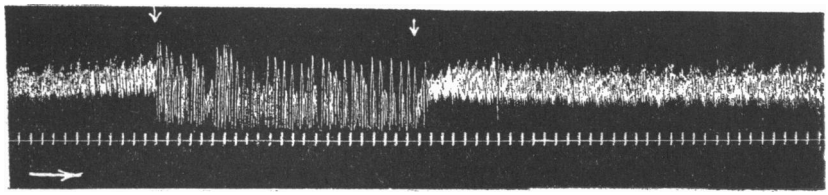

Fig. 2. Vagi stimulated in the neck (between the arrows), coil at 7 cm.

above the diaphragm during 2 mins. was performed. No marked changes in the flow of pancreatic juice could be observed during this procedure. The usual inhibition of the secretion was noted only if a rise of blood-pressure occurred. This can be shown from Exps. 8 and 9 (Fig. 3).

Exp. 8. Both splanchnics cut. 1·2 c.c. secretin introduced into the jugular vein. Flow of pancreatic juice and average blood-pressure noted every minute.

P.J.	2	31	37	**30**	**34**	11	27	20	16	19	13	7	7	3	3
B.P.	65	67	69	v.c. compr.		80	75	74	72	74	72	76	76	81	—

The gradual rise of the blood-pressure towards the end of the observations depends upon the expiration of the action of the secretin.

Exp. 9. Vagi and spl. cut. Continued flow of secretin into the jugular vein per 1 c.c. every min. Two minute intervals for recording the secretion.

P.J.	49	53	48	**48**	41	45	**46**	44	44	45
B.P.	23	23	24 v.c. compr.		32	29 v.c. compr.		31	31	30

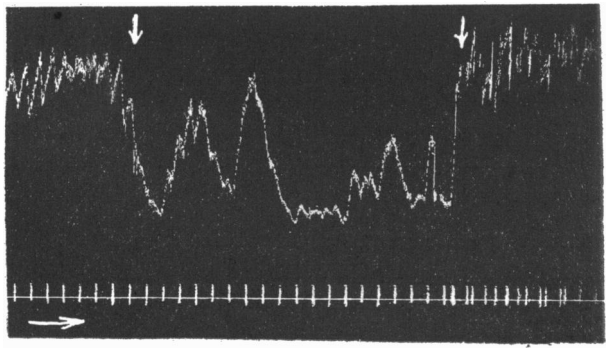

Fig. 3. Vena cava compressed (between the arrows).

The insignificance of the rise of blood-pressure in the experiments depends upon the exclusion from the influence of the vaso-motor centre of a vast vascular district belonging to the abdominal viscera.

The influence of defibrinated blood upon the pancreatic secretion. Although the injection into the circulation of defibrinated blood increases the work of the heart and augments the whole quantity of fluid in the blood vessels it has not a favourable influence upon the pancreatic secretion. The reason is probably that the defibrinated blood has a vaso-constrictor effect. The corresponding Exp. 10 is instructive because it emphasises once more the dependence of the secretory cells of the pancreas upon the condition of the blood vessels.

Exp. 10. Secretion of pancreatic juice provoked by secretion (1 c.c. in 1 min.). A. Before the section of splanchnics. B. After the section of splanchnics. 50 c.c. of defibrinated blood (t. 38° C.) introduced during 1 min. into the femoral vein. Pancreatic secretion recorded every 2 mins.

(A)	P.J.	20	19	**10***	2	4	10	10	11	17
	B.P.	36	35	34–64	52–34–40	40	37	36	36	35
(B)	P.J.	58	59	**55***	37	44	45	58	52	**53***
	B.P.	24	25	25–63	46–34–25	24	30	27	28	26–46
		41	41	47	48	49	53			
		38–29–26	25	24	23	22	23			

* 50 c.c. of defibrinated blood introduced into the femoral vein.

The inhibition in the first case was more pronounced than in the second. That may be due not only to the influence of splanchnic nerve but also to a more scanty secretion which occurred in the first case.

The secretory action of vagi and the blood-pressure. The most striking fact is that the fall of blood-pressure strongly favours the secretory action of the vagi. In Exp. 11 before the section of splanchnic nerves 10 c.c. of a 10 p.c. solution of Na_2CO_3 was introduced into the blood stream (1.05 p.m., 2.10 p.m. and 2.21 p.m.). In spite of this the chloralose secretion of pancreatic juice and the action of the vagi were quite insignificant. But after the section of both splanchnics the spontaneous secretion rose and the stimulation of vagi below the heart greatly influenced the secretion.

Exp. 11. The flow of juice from 2.20 p.m. noted every 5 mins.

1, 3*, 1½, 3*, 1½, 3*, 1. Between 2.55 and 3.10 p.m. both splanchnics cut. The secretion from 3.10 p.m.: 18, 11, 9†, 2½, 12‡, 7, 13‡, 11, 6, 5, 4½, 13, 7, 36‡, 24, 8½.

* The peripheral ends of vagi stimulated below the heart during 5 mins., each nerve stimulated 1 min. Coil 7 cm. † Ditto. Coil 6½ cm. ‡ Ditto. Coil 6 cm.

Since the stimulation of the peripheral ends of the vagi below the heart in no way affects the systemic blood-pressure (see Fig. 4) the secretory action of the vagi cannot be attributed to changes in the latter. The possibility of contraction of the pancreatic ducts under the vagi stimula-

tion and consequent squeezing out of their contents is not excluded, but special experiments are needed for the solution of this question. However, the accumulation in the juice of organic substance in analogous conditions does not substantiate this simplified explanation of the action of vagi.

Exp. 12 is of exceptional interest. As a result of section of both splanchnics and a moderate hæmorrhage during the operation, the blood-pressure was very low. Saline was injected into the circulation repeatedly to maintain the work of the heart. Under such apparently very unfavourable conditions the stimulation of vagi below the heart provoked a very considerable secretion of pancreatic juice.

Exp. 12. Pancreatic secretion recorded every 2 mins. (Fig. 4).

P.J.	½	1	5*	22*	34	7	5	3	3†	3†
B.P.	15	15	14	15	12	11	10	10	—	15

* Stimulation of vagi below the heart during 4 mins., each nerve stimulated 1 min. Coil 6·75 cm. † 25 c.c. of saline injected.

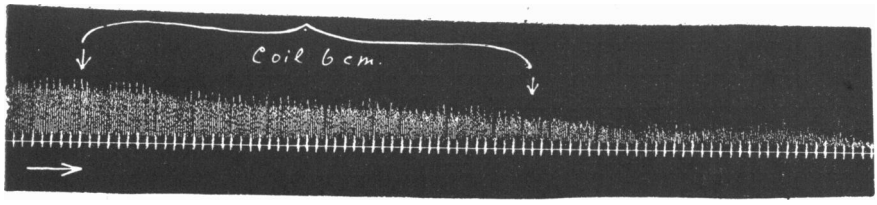

Fig. 4. Vagi stimulated below the heart. 4 mins.

Even a few minutes before death, when the heart was beating slowly (*ca.* 78 in 1 min.) and the blood-pressure gradually fell to zero, the stimulation of the vagi gave some secretory effect (Fig. 5).

Exp. 13. Pancreatic secretion recorded every 2 mins.

P.J.	1	1	4*	4½*	3½	2	0

* Stimulation of vagi below the heart. Coil 6 cm.

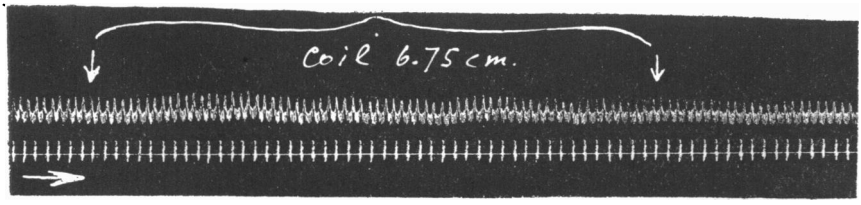

Fig. 5. Vagi stimulated below the heart. 4 mins.

The conditions of the secretion of pancreatic juice in this case resemble very closely the condition in the experiments with the stimulation of the vagi in the neck during chloralose or secretin secretion. The pancreatic juice collected during 1 hour 42 mins. in Exp. 14 was 1·3 c.c. and had the following composition: solids 8·34 p.c.; organic substances 7·47 p.c.; ash 0·86 p.c. Thus it was a typical "nervous" juice.

Discussion.

The above data lead to the conclusion that the pancreatic gland is extremely sensitive to anæmia. Even an insignificant and short contraction of its blood vessels inhibits or in some cases stops the secretion. It is quite possible that in normal conditions the restriction of blood flow in the gland is one of the means by which the secretion is inhibited. On the other hand, the congestion of blood in the abdominal viscera not only does not disturb the pancreatic secretion but to a certain degree assists it. The fall of blood-pressure which is connected with the increased filling of the abdominal vessels is favourable to the humoral as well as to the nervous secretion of pancreatic juice.

The experiments described give the key to understanding the success of the special method of demonstrating the action of pancreatic secretory nerves proposed by Pavlov(6). The most important moment in it is the section of the spinal cord below the medulla. This operation lowers the blood-pressure to two-thirds of its initial level. It prevents or greatly diminishes the possibility of eliciting vaso-constrictor reflexes, which are so noxious for the activity of the pancreatic gland. All this creates very favourable conditions for the action of secretory nerves. If we make use of this knowledge we can obtain action of the secretory nerves in a simply anæsthetised animal, and indeed this is the case with chloralose. The animal under chloralose with both splanchnic nerves cut is a very suitable subject for demonstration of the secretory activity of the vagi. Thus in the pancreatic gland we have an organ whose activity required quite special conditions of the blood flow through its vessels during its work.

Summary.

1. Chloralose provokes a slow continuous flow of pancreatic juice. It is not antagonistic to the secretory action of secretin, vagi and pilocarpine.

2. The section of splanchnic nerves increases the secretion provoked by chloralose, secretin, hydrochloric acid and vagi.

3. The stimulation of the vagi in the neck, the nerves being cut below the heart, practically does not affect the pancreatic secretion. But if a rise of blood-pressure follows the stimulation the secretion is inhibited.

4. The same relations are observed by compressing the vena cava inferior above the diaphragm.

5. The introduction of defibrinated blood into the circulation produces a rise of blood-pressure and inhibition of pancreatic secretion.

6. The stimulation of vagi below the heart provokes the secretion of pancreatic juice under extremely low blood-pressure.

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