## Studies on the Pancreatic Gland.—By Harry S. Morton, B. A., M. Sc., from the Departments of Physiology and Biochemistry, Dalhousie University, Halifax, N. S.

(Presented 11 April 1927)

The pancreatic gland exists in the body under the interplay of different influences such as:—

1. The influence of the nervous system.
2. The influence of hormones.
3. The blood supply to the gland.
4. The contractile elements in the gland which may influence the process of discharge of the juice.
5. The alterations of the composition of the internal medium of the body, i. e. of the blood and the body fluids.

These various influences may be affected by changes in the following factors:

(*a*) Changes in the acid-base equilibrium of the blood.

(*b*) Changes in the gas content of the blood.

(*c*) Changes in the content of different hormones in the blood.

I have studied some of these conditions during the work of the pancreatic gland. As a stimulus for a steady flow of pancreatic juice, Pilocarpin was used. This acts by stimulating the nerve endings of the vagus.

**Methods.**— The following methods were used:—

Cats were anaesthetized with chloralose administered intravenously, 0.1 gram per kilogram of body weight. Cannulae were inserted in the pancreatic and bile ducts, and the duodenum. The pylorus was tied. After the first few experiments the adrenals were removed for reasons to be discussed later. Finally the vagi in the neck were severed and cannulae were inserted in both carotids, one for blood pressure, and the other for arterial blood samples.

Samples of arterial blood were taken at various intervals and the pH,—hydrogen ion concentration—determined by the Dale-Evans colorimetric method[1]. The alkali reserve was measured by the Van Slyke $CO_2$ method.[2]

**Pilocarpin.**—Pilocarpin acts on the myoneural connections between the nerves and the epithelial cells, the effect being supposed to be identical with that of nerve stimulation. The pancreatic secretion thus obtained may be influenced by several factors; first of all blood pressure.

I. In one of my earlier experiments it was found that a low blood pressure was more favorable to pancreatic secretion than a high blood pressure.

Experiment No. 4, Fig. 1.

| Injection | Secretion | B. P. |
|---|---|---|
| 1 mg. Pilocarpin | 37 | 140 |
| " " | 146 | 45 |

Experiment No. 42, Fig. 2.

| Injection | Secretion | B. P. |
|---|---|---|
| | 21 | 225 |
| 1 mg. Pilocarpin | 21 | 80 |
| " | 113 | 40 |

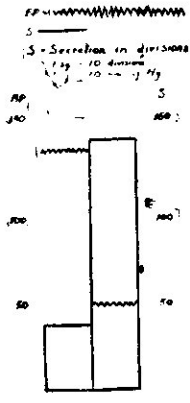


Fig 1

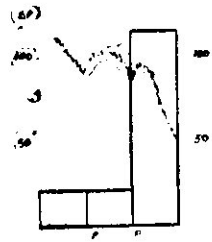


Fig. 2.

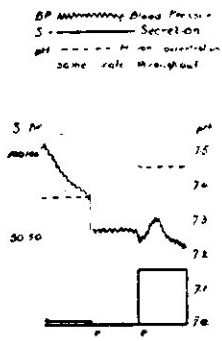


Fig 3.

In the experiments No. 4 and No. 42 the low blood pressure of 45 mm. Hg. is seen to be more favorable than higher values of 80 or more. This may be explained if it is considered that a high blood pressure is due to a constriction of the blood vessels in the splanchnic area. When the vessels in this area are constricted those of the pancreas are particularly affected. This idea has been the outgrowth of work on the antagonism of the pancreas to the adrenal glands. Benedicenti[3] in 1906 described an inhibition of pancreatic secretion following subcutaneous injections of two and three mg. doses of adrenaline. The secretion decreased almost immediately or entirely ceased, this lasted for some time before the rate of secretion returned to normal. Two years later Pemberton and Sweet[4] independently of Benedicenti found the same relation of adrenaline to the pancreas. From the results of their experiments they conclude that the inhibition of the pancreatic secretion is independent of the rise in general blood pressure, but that it is probably specific. Edmunds[5] repeated the work of Pemberton and Sweet and extended it to other drugs on the rate of pancreatic secretion due to continuous injection of secretin. He concluded (1) that the action of adrenaline in inhibiting the pancreatic secretion could not be considered in any sense as specific, and (2) that the inhibition was probably due to anaemia of the organ because practically all drugs and mechanical procedure which increased general blood pressure, by constriction of vessels, also cause inhibition. Mann and McLauchlin[6] confirmed the work of Edmunds and further extended this work from large pressor doses of adrenaline to small doses which would produce a depressor action on the blood pressure. They found using plethysmographic tracings of the pancreas that depressor doses of 6-10 cc. of 1 in 500,000 adrenaline solution caused decrease in pancreatic volume and rate of pancreatic flow. Thus they concluded that adrenaline whether it raises or lowers general blood pressure, (or it may not have enough action to affect blood pressure at all), usually causes local blood vessel constriction, which reduces the amount of blood passing through the pancreatic gland per unit of time. The fact then that the pan-

creatic vessels seem to be more sensitive towards the pressor action of adrenaline than those of any other region in the splanchnic area is clear.

Pavlov[7] observed that inhibition of the heart, or constriction in the splanchnic area from stimulation of the splanchnic nerve, prevented secretion. Gottlieb[8] maintains that the rate of pancreatic secretion depends solely upon the blood supply to the gland. Mett[9] obtained a very small pancreatic flow by splanchnic stimulation so that he supposed this nerve must contain both secretory and vaso-constrictor fibres, which he demonstrated by a slow rate of stimulation. Kudrewetsky[10] and Popielski[11] speak only of secreto-inhibitory fibres. Many using secretin found that stimulation of the splanchnics caused vaso-constriction and a decided slowing in the flow of juice. All are agreed, therefore, that stimulation of the splanchnics, either direct or indirect, will inhibit the secretion of pancreatic juice.

Consequently in all my experiments the splanchnic nerves were cut (a) to remove any inhibitory fibres and (b) to remove the vaso-constrictor fibres and in this way lower the blood pressure to a level favorable for the work of the pancreatic gland. (Expts. No. 4 and No. 42). Again as pilocarpin stimulates the secretion of adrenaline which might affect the blood pressure I found it advantageous to remove the adrenal glands in all experiments with pilocarpin.

II. A second effect on pancreatic secretion from pilocarpine was that of saline. In the earlier esperiments only a very poor or even no secretion was obtained; so Dr. Babkin suggested injecting 25 c. c. of 0.9% saline previously.

Experiment No. 43, Fig. 3.

| Injection | Secretion | pH |
|---|---|---|
| | 2 | 7.37 |
| 1 mg. Pilocarpin | 0 | |
| " | 31 | 7.46 |

In this case only a very small amount of juice was obtained.

Experiment No. 44, Fig. 4.

| Injection | Secretion | pH |
|---|---|---|
| 50 cc. Saline | 5 | 7.40 |
| 1 mg. Pilocarpin | 2659 | 7.31 |

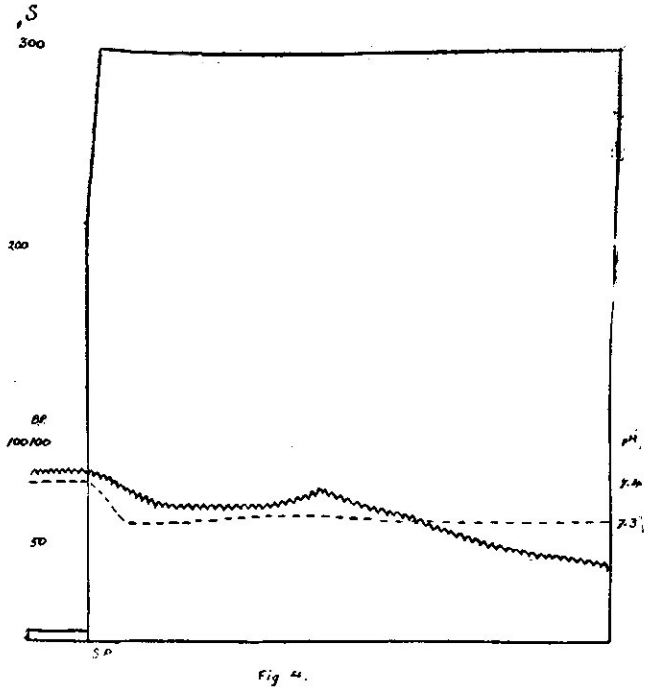



Fig 4.

The beneficial effect of saline on pancreatic secretion is at once evident in experiment No. 44 when contrasted with experiment No. 43. This may be explained: (a) Saline may increase the blood flow through the pancreas as in the case of the salivary glands, or (b) it may increase the permeability of the cells, or (c) it may act by lowering the colloidal osmotic pressure of the blood, as in the kidney, thus allowing water to leave the blood more readily.

The first, must be left for future investigation experiments. The second, will have to be merely a factor until more is known about the influence governing the permeability

of cells. The third, is unquestionably a factor, no matter how slight in amount, which aids the blood flow.

III. In the third place, bicarbonate has a marked influence on the flow of pancreatic juice.

It has been demonstrated by Kestner[12] that during gastric secretion the pH of the arterial blood is higher, i. e. the alkalinity is increased. He observed this in a dog with gastric fistula and further observed that if he replaced the gastric juice into the intestine that the pH fell back to the original level, indicating that either; (1) the gastric juice was absorbed and thus restored the normal reaction of the blood or (2) the acid coming into the intestine produced secretin and this in turn provoked pancreatic secretion which being alkaline would tend to make the blood acid, or (3) in the duodenum the acid from the stomach and the alkali from the pancreas neutralize each other giving NaCl and $H_2O$, the increased alkalinity of the blood due to gastric secretion being counterbalanced by any decrease brought about by pancreatic secretion, so that, both in the blood and in the duodenum equilibrium is restored.

Walther quoted by Babkin, P. 239, noticed in a dog with gastric and pancreatic fistulae a hypersecretion of pancreatic juice preceded by a hypersecretion of gastric juice. Thus one may make a legitimate supposition that the change of the reaction of the blood towards the alkaline side during gastric secretion is favorable for pancreatic secretion.

Furthermore, the various avenues of escape of alkali from the blood must not be forgotten. Thus Carnot et Gruzewska[15] mention an increase of the pH of the bile, i. e. an increase of the alkalinity, as the alkalinity of the blood increases during gastric secretion induced by histamine. They found, however, that under similar conditions the H-ion concentration of the pancreatic juice remained constant, but Cherkess[16] indicates that the total alkalinity of the pancreatic juice is increased after carbonate is injected into the blood. Anrep, Lush and Palmer[17] observed an increase of the titratable alkalinity and the alkali reserve when carbon-

ate was administered intravenously. I have also found this tendency. Thirdly, alkali may be lost through the kidney. Thus we must take into account three different ways for the loss of carbonate from the blood, namely, bile, pancreatic juice and urine.

In my experiments the technique was to obtain a steady flow of pancreatic juice from 1 mg. of Pilocarpin when 3cc. of 3% sodium carbonate were injected intravenously; or to wait until the flow from pilocarpin had ceased, and then inject the same amount of carbonate as above.

Experiment No. 49, Fig. 5.

| Injection | Secretion | PH | B. P. |
|---|---|---|---|
| | | 7.40 | 70 |
| 1 mg. Pilocarpin | 135 | 7.38 | 60 |
| 3 cc. 3% $Na_2CO_3$ | 226 | 7.45 | 60 |
| " | 12 | 7.55 | 40 |

Experiment No. 51. Fig. 6.

| Injection | Secretion | PH | B. P. |
|---|---|---|---|
| 25 cc. Saline | 6 | 7.38 | 85 |
| 1 mg. Pilocarpin | 14 | 7.39 | 80 |
| 3 cc. 3% Na CO | 43 | 7.42 | 50 |
| " | 203 | 7.47 | 25 |
| " | 108 | 7.52 | 20 |

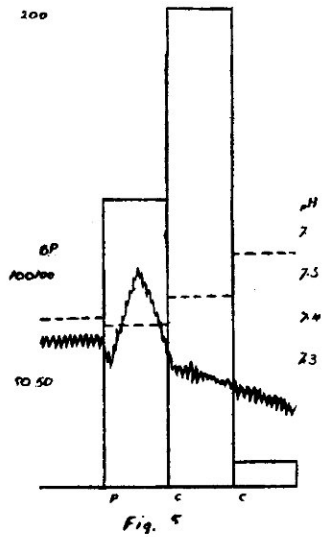


Fig. 5

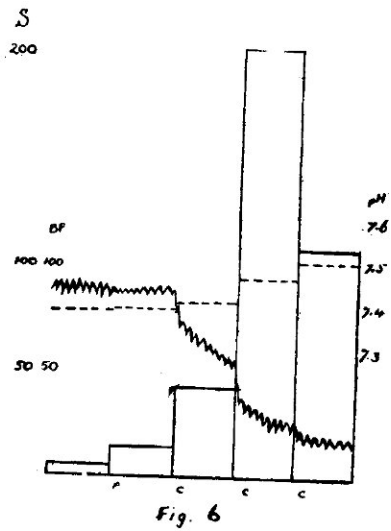


Fig. 6

In experiment No. 49 the first injection of alkali after pilocarpin about doubled the amount of juice, as the pH rose from 7.38 to 7.45. This latter value must have been near the optimum for when pH 7.55 was reached the secretion dropped off to 12 divisions. The falling off of the flow of juice may be partially attributed to a wearing out of the secretory effect of pilocarpin. Expt. No. 51 was slower in reaching its optimum at pH 7.45, thereafter the secretion fell away as the pH increased.

From these experiments it was seen that carbonate often increased the flow of pancreatic juice two and three times or it may give more juice after pilocarpin than pilocarpin alone, yet carbonate alone gave no secretion of pancreatic juice.

This may be due to either or both of two causes. (1) The changed composition of the blood was followed by pH determinations using the Dale-Evans method.

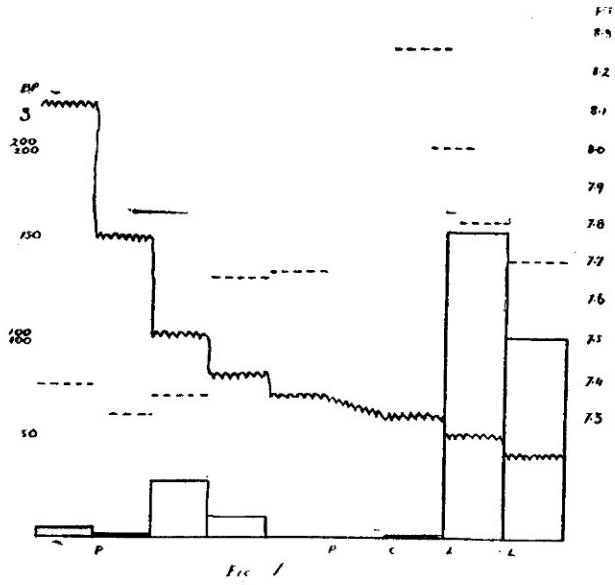
In examining the reaction of the blood no specific range of pH could be found. In each experiment secretion increased parallel to the rise of pH after a while an optimum was reached and then secretion diminished as the pH increased. Further this optimum was found never to be the same in any two experiments, and in two cases was different at different times in the same experiment.

It will be noticed, however, in experiments No. 49 and No. 51, that the pH values run unusually parallel. They increase from pH 7.38 to an optimum at pH 7.45 and pH 7.47 respectively, then one gives 108 divisions of juice at 7.52 while the other yield only 12 at 7.55; thus apparently mapping out a general contour curve, with various points from one experiment nicely filling in the gaps left by the other.

The disillusionment as to the specificity of location of this optimum was effectively furnished by experiments No. 53 and No. 54.

Experiment No. 53. Fig. 7.

| Injection | Secretion | pH | B. P. |
|---|---|---|---|
| | 4 | 7.37 | 220 |
| 1 mg. Pilocarpin | 1 | 7.30 | 150 |
| 3 ccs. 3% Na2 CO3 | 27 | 7.35 | 100 |
| " | 10 | 7.65 | 100 |
| " | 0 | 7.67 | 80 |
| 1 mg. Pilocarpin | 0 | 8.25 | 70 |
| 3 ccs. 3% Na2CO3 | 1 | 8.00 | 60 |
| Lactic acid | 155 | 7.80 | 50 |
| " | 100 | 7.70 | 40 |



Here one sees a very meagre flow of juice from pilocarpin, a fair improvement following carbonate at pH 7.35, complete abolition at pH 7.67, which was not due to a fading out of pilocarpin as more was added with no effect. Then lactic acid was injected into the blood, followed by a copious pancreatic secretion at the extremely high pH of 7.80, the next injection gave 100 divisions at pH 7.70. Here is a case with two

different optima at vastly different levels and quite different from those found in other experiments.

Experiment No. 54. Fig. 8.

| Injection | Secretion | pH | B. P. |
|---|---|---|---|
| | 8 | 7.37 | 100 |
| 1 mg. pilocarpin | 30 | | 60 |
| 3 ccs. 3% $Na_2CO_3$ | 262 | 7.46 | 50–30 |
| " | 38 | 7.47 | 25 |
| " | 24 | | 18 |
| " | 19 | 7.85 | 18 |
| Lactic Acid | 7 | | 12 |
| " | 3 | | 12 |
| " | 7 | | 12 |

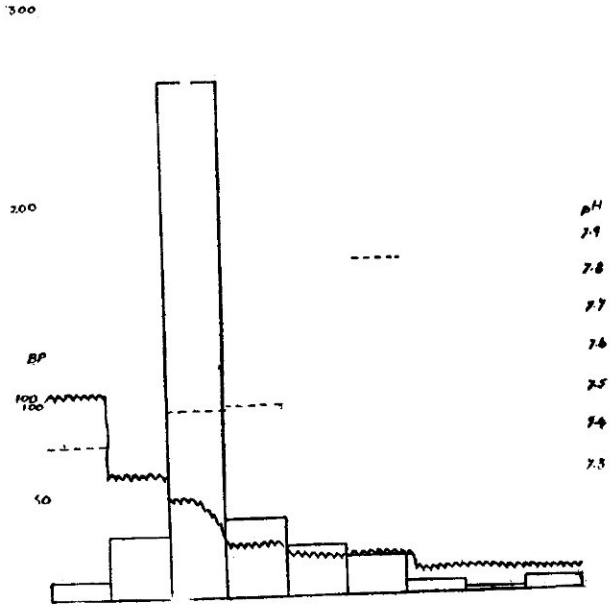



Fig 8

The similarity of this experiment with experiments No. 49 and No. 51 is at once apparent. There is the same level of pH at the beginning and the same optimum point, pH 7.46.

The only difference is the sudden fall at pH 7.47, which afterwards is gradual. Lactic acid did not restore the flow of juice in this case, possibly because the pilocarpin may have been exhausted.

(2) Alkali may increase the blood flow through the gland. This must be examined by blood flow experiments.

Summing up our results it is just possible to suggest an optimum pH for pancreatic secretion somewhere in the neighbourhood of 7.46. This is not to be considered absolute or specific but only in a relative sense.

In conclusion I desire to express my great indebtedness to Dr. Babkin for his advice and criticism, to thank Dr. Young for his supervision, and Miss M. E. MacKay for her assistance during the course of this work.

## SUMMARY.

1. A low blood pressure is more favorable for pancreatic secretion than a high blood pressure.

2. Saline is efficacious in pancreatic secretion following the injection of pilocarpin.

3. The splanchnic nerves have an inhibiting action on the flow of pancreatic juice.

4. Carbonate improves the flow of pancreatic juice provoked by pilocarpin up to an optimum H-ion concentration.

5. Above this point it has an unfavorable influence as far as complete abolition.

6. Lactic acid injected into the blood may restore favorable conditions for a flow of juice.

7. No optimum reaction of the blood for maximal work of the pancreatic gland was found. A relative influence of acid and alkali rather than any optimum or specific range of pH is more in accord with observations made.

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