BIOLOGY

III. THE EFFECT OF SECRETIN ON THE SECRETION OF THE GLANDS OF THE BODY, PARTICULARLY THE PANCREAS, KIDNEY, LIVER, AND SUB-MAXILLARY GLANDS

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Dolinski (1) pointed out in 1895 that acids brought into contact with the mucous membrane of the duodenum produced promptly a secretion of pancreatic juice. Pawlow (2) believed that the activity of the pancreas is due to the secretory nerves which it receives through the vagus and sympathetic. Popielski (3) Wertheimer and Lepage (4) hoping to reconcile the action of acid in the small intestines with the idea of the nervous control over pancreatic activity, advanced the explanation that the secretion arose from a peripheral reflex through scattered ganglia of the pancreas situated mostly near the duodenum. During the past quarter of century an overgrowing mass of evidence has been accumulated in support of the idea elaborated by Bayliss and Starling (5) to the effect that acid in the duodenum produces a hormone, secretin, which stimulates the cells of the pancreas directly. These workers believe that the acid acted upon a precursor, prosecretin, present in the mucous membrane, thereby permitting its extraction or, in the intact animal, absorption into the blood stream.

The mechanism of bile secretion differs from most other secretory glands as its activity is not directly under control of the nervous system, stimulating the spinal cord or the splanchnic gives a decrease in bile secretion while cutting the splanchnic gives an increase. But the splanchnic carries vaso-motor fibers which control the rise and fall of blood pressure and furthermore pilocarpine and atropine have no effect in any way on the bile secretion.

The secretion of urine is more or less constant but fluctuates under different circumstances. Ordinarily, rise in blood pressure gives increase in urine flow and decrease in blood pressure gives a decrease in the flow, but a rise in blood pressure artificially produced in the kidneys together with a delay or block in the blood stream produces a decrease in urine flow.

Many experiments (6) show that the salivary secretion is usually or partly nervous as sectioning the chorda typmpania nerve abolishes a secretory effect while stimulating the same nerve gives a marked increase and along with this increased flow there occurs a dilation of blood vessels leading to the salivary glands

The present investigation was begun in an attempt to determine what effect secretin has on the secretion of the above named glands.

The animals used in all of our experiments were dogs anesthetized by ether and the secretin used was prepared according to the Bayliss and Startling method (7). (Many dogs were used in each experiment but in each case the same results were obtained as the one reported in this paper.)

From another dog the first two feet of the small intestines are removed and slit lengthwise, and the mucosa washed in running tap water. The gut is now laid on a dry wooden support with the mucous side exposed. With a dull knife the mucous membrane is gently scraped away, rubbed well with sand in a mortar, and then allowed to stand for a brief period under two or three times its volume of 0.4 per cent hydrochloric acid.

Shortly before it is to be used, the mixture is boiled in a porcelain dish, and while boiling made alkaline with a strong caustic soda. Then made slightly acid with acetic acid. The mixture is now strained and pressed through muslin, and the fluid portion filtered through paper. The filtrate contains secretin.

The injection of secretin was made through cannulated femoral vein and the blood pressure was taken by ordinary mercury monometer attached to femoral artery.

In each case the duct of the respective gland was cannulated and a piece of rubber tubing fastened to the cannula leading over a movable tambour. The tube and cannula were filled with normal saline solution.

Since history of secretin starts with its effects on the pancreas, we shall consider it first in this paper.

Bayliss and Starling (5) (6) who gave to the world "the secretin theory" for pancreatic secretion still hold to htis theory and at present it seems to be widely accepted in America, but Popielski (3) and his pupils have attacked it. Heidenbein (8) stimulated the medulla, Pawlow (9) the vagus, and Kudrewetzsky (10) stimulated the splanchnic, each gave an increase in pancreatic flow. But if the spinal cord is sectioned, secretion con-

tinues. After section of nerves proceeding to the pancreas, secretion is set up and increased. This shows that pancreatic secretion is nervous but not wholly.

Table 1.

Shows the effect of injection of 10 c. c. of secretin.

Drop	Time in Seconds	Mean Blood Pressure
16	400	154
17*	415	(158 (68
18	34	130
19	33	134
20	37	138
21	56	146
22	98-	148

In the above table it may be seen that secretin increased the rate of flow of pancreatic juice. Though the rate of secretion of pancreatic juice increased after each injection of secretin, in no place did we have a rise in blood pressure showing quite conclusively that blood pressure played no role in the increased secretion but that it was due to this hormone like substance called secretin (Bayliss and Starling) (5).

The second part of this paper deals with the effect of secretin on the flow of bile. As said before in this paper the mechanism of bile secretion differs from most other secretory glands. Since its activity is not directly under control of the nervous system we may believe then that the quantity of blood through the liver or the composition of the blood that circulates through the liver contains a chemical substance which stimulates the liver cells to action.

These substances are usually termed cholagogues (11) and it is well known that bile is one of the best. The effect is due to bile acids and bile pigments as the bile acids have a haemolytic effect upon red corpuscles and any substance that brings an escape of blood coloring tends to increase secretion of bile.

It is well known that 0.5% hyrdochloric acid injection (20) into the upper duodenum increases the bile flow. It is assumed that the pro-secretin contained in the mucosa is converted by hydrochloric acid to active secretin which is absorbed by the blood and carried to the liver cells stimulating them to action.

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*Time of injection.

Drop	Time in Seconds	Mean Blood Pressure
26	390	142
27*	83	(147 64
28	135	120
29	43	134
30	30	137
31	90	142
32	94	147

From table 2 it may be seen that we get an increase in bile secretion. So we may justly conclude that the injection of secretin gives an increased secretion of bile though not as well marked as pancreatic secretion.

The blood pressure behaves similar to that in the pancreatic secretion so we conclude that there is no relation between the flow of bile and blood pressure.

The third part of this paper deals with the effect of secretin on urine flow. Up to the present time no one definite mechanism by which urine is formed has been accepted by scientists. The two theories advanced are: physiological or Bowmans (12) and mechanical or Ludwigs (23).

The followers of Bowman (12) hold that the uriniferous tubules are the true secretory apparatus while the glomeruli serve to regulate the water content of the blood, while the followers of Ludwig believe if the renal arteries are occluded and then released, secretion is not resumed at once but varies from 10 to 45 minutes. Changes in volume of blood or the lateral pressure at which it circulates in the kidney have no effect on urine secretion, e. g intra venous injection of blood produces no marked increase in the excretion of urine.

Micro-chemical observations show that after injection of fuchsin into lymph sac of a frog, after two hours urine was of a red color; kidney colorless in a cortical region and the tubules were stained red.

Injection of acetone showed alteration in epithelium of convoluted tubules.

The last fact against the mechanical theory is the secretion of hippuric acid which does not pre-exist in the blood, but is formed exclusively by a synthetic process in the kidney, but a reveiw of the mechanical theory cannot entirely be disregarded. As a rule urine increases or decreases with the rise or fall in arterial pressure. The rising of aortic pressure by tying large

arteries as both femoral and carotid gives increase in blood pressure from 127 to 142 mm. and increase in urine flow from7 grams to 21 grams every 30 minutes. Transverse section of lower cord lowers aortic pressure, also suspends urine flow. The efferent vessels of the glomerulus are always much smaller than the afferent vessels.

With an unobstructed urter a normal kidney will secrete more urine if blood flows through it and the factors which affect the amount of blood through the kidney are the general arterial pressure, the degree of contraction of the kidney arteries, and the freedom of venous flow. Digitalis effects are dependent upon (a) improvement in the general circulation through which accumulated tissue fluids pass into the blood to make hydrouric plethora, (b) improvement in kidney circulation. Then digitalis effects are not due to a direct action of the drug upon the kidney cells, consequently the marked diuresis lasts only until the excess of fluid in the body brought about by venous stagnation is removed.

Experiments (14) show that sodium nitrate plus chloral hydrate gives an increase in urine flow, but no increase in blood pressure. Atropine gives same results as sodium nitrate plus chloral hydrate. Morphine diminishes urine flow and gives lowering of blood pressure. These experiments plainly show that urine flow is not entirely dependent upon rise or fall of blood pressure.

The above facts would lead us to believe that the flow of urine is probably controlled through chemical stimuli. Various substances when in excess of a certain concentration are secreted pdesumably on the general theory adopted, because they stimulate or retard in some way the activity of the kidney cells. The general metabolism of the body is constantly adding to the blood substances which manifest some special reaction within the kidney cells in their secretion. But in addition to these stimuli, it is possible that specific hormones may be produced that are adapted to correlate the secretion to conditions elsewhere in the body.

The left ureter was cannulated midway between the kidney and the bladder thus leading the urine direct from the kidney. At starting, the interval of time between drops 5 and 6 was 30 seconds, but the interval between drops lengthened. That just before the injection was 45 seconds, while the blood pressure constantly increased from 103 to 141 mm. of mercury. Immediately following tthe thirty-eighth drop, 20 c. c. of secretin was injected Immediately the blood pressure dropped from 140 to 46 mm. of

mercury while the time interval for drop 40 was 220 seconds but immediately came an increase in secretion as follows: drop 44 in 14 seconds, 45 in 23 seconds, and 46 in 25. It may be seen from table 4 that immediately following an injection of secretin a long interval of time of no secretion follows, and with this comes a great fall in blood pressure. This is followed in each instance by quickened secretion much greater than normal, while the blood pressure returns gradually, so there seems to be no relation between blood pressure and urine secretion after a return of secretion, but the normal period shows a close relation.

Table 4

Shows the effect of injection of 25 c. c. of secretin.

Drop	Time in Seconds	Mean Blood Pressure
38	45	140
39*	115	120½
39¼		46
40	220	126
41	45	128
42	45	129
43	40	134
44	14	133
45	23	129
46	25	128
47	27	140
48	30	148
49	30	148
50	30	148
51	33	150
52	30	151
53	20	160
54	32	153

There is a possibility that the blood pressure plays a part here for in our work we find that secretin does not have an immediate effect and too, if it were secretin causing it we believe that the following secretion would not be increased and too, we find relationship existing between blood pressure and secretion of urine during the normal period.

Sectioning of chorda tympania abolishes the secretory effect, while stimulating the chorda tympania gives a marked increase and along with this increased flow there occurs a dilation of blood vessels leading to the salivary glands. During work the

*Time of injection.

glands use 3-4 times as much oxygen as normal. Bernard (15) showed that puncture of fourth ventricle gave an increase in salivary flow.

There are many substances which when injected into the veins or under the skin promote more or less the secretion of saliva, and it is our purpose to show the effect of secretin on the secretion of saliva. Secretin was made as described in the first part of this paper and Wharton's duct leading from the submaxillary glands, was cannulated and led to tambour as previously described. The total period of running of the experiment may be divided into four divisions including a normal period and three periods at which secretin was injected. The normal period ran for a period of 81 minutes, during this time 146 drops of saliva were registered with very slight variation between drops. The blood pressure was rather constant varying from 140 to 154 mm. of mercury.

The first injection was 10 c. c. secretin. The blood pressure before injection was 154 mm. and after injection it fell to 62 mm. Secretion was 25 drops for a period of 18 minutes. This resulted in a great fall of blood pressure with slow return, (which is a characteristic of secretin injection) and a decrease in secretion of saliva.

The third injection was 10 c. c. given 25 minutes after the second injection. The blood pressure before the injection was 154 mm. after injection it fell to 72 mm. and returned slowly to about normal. The time interval was much longer than the two preceding ones. This interval in addition is divided into four divisions. The first interval was for 21 minutes; drops registered were 15 in number; blood pressure was 152 mm. The second interval was for 21 minutes; during this interval no secretion occurred. Blood pressure registered 156 mm. of mercury. The third interval was 12 minutes, during this time three drops were registered and blood pressure registered 156 mm. The fourth interval was for 10 minutes and nine drops were registered. The blood pressure registered 160 mm.

During each injection of secretin we get a very sudden fall of blood pressure, recovering to normal in about 16 minutes and a decrease of 20 minutes of no secretion with blood pressure resting at 156 and at the time the experiment ended we got a return to almost normal.

What then has brought about the decrease in salivary secretion? Under normal conditions there seems to be a close re

lationship between the blood pressure and the secretion of saliva.

The pancreatic flow was increased more than 1600% above the normal flow. This rapid secretion continued for just a few minutes, followed by a return towards normal.

The bile secretion following an injection of secretin is increased 40%, which continues for a short time and then almost returns to normal. An increase immediately follows of about 36%, which remain constant for a long period.

The flow of urine following an injection of secretin is decreased gradually till it has reached 181% below normal. This period of decrease lasts for about 3 or 4 minutes, then a sudden increase takes place till it reaches 30% above normal, which remains constant for a long period.

The flow of saliva following an injection of secretin is decreased very suddenly to 168% below normal and remains rather constant for a long period, but gradually returns to normal

It seems interesting to note that each of the four glands responded readily following an injection of secretin, decreasing the flow of some and increasing the flow of others.

As pro secretin is inactive and remains so till it is influenced by the presence of the stomach content in the duodenum there seems to be a correlation between the stomach output and the influenced condition of the gland, and in each case the secretion of the secretory glands studied seems to be influenced by specific hormones that are adapted to stimulate the various glands and correlate their activities to conditions elsewhere in the body.

In conclusion we may say that:

1. The addition of secretin into the blood stream always causes an increase in the production of the pancreatic secretion. At no place or time did the blood pressure play any part in the rate of flow of this secretion.

2. The secretion of bile is increased immediately following an injection of secretin into the blood stream but at no time is this increase as great as it is for the pancreas. And like pancreas, there seems to be no relation existing between the rate of increase of flow and the blood pressure.

3. The addition of secretin into the blood stream produces a period of retarded secretion of urine followed by an increase in the rate. There is a possibility that blood pressure does play a part in the secretion of urine for the first part of the period at least, but this relationship seems to disappear after a very short time.

4. The addition of secretin into the blood stream produces a retarded rate of flow of salivary secretion (secretion from the sub-maxillary gland) and unlike the secretion of bile this retardation continues for a very long period. At no time did the rate increase above that of normal. Here again, blood pressure seems to play no role in the change of rate of secretion.

5. It seems that the secretion of each of the four glands (discussed in this paper) responds readily following an injection of secretin, increasing the flow of pancreatic juice and bile and retarding the salivary flow. Secretin first retards the flow of urine, which later is increased and it seems that these glands are influenced and their activity correlated to meet the body demands by "secretin."

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