STUDIES ON CANINE PANCREATIC SECRETION.

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CONTENTS.

CHAPTER I

INTRODUCTION.

Over the past few years interest has been mounting concerning the part that histamine plays in physiology in general, and in the gastrointestinal tract in particular. Its ability to stimulate gastric secretion is well known, and it is now evident that this action can be inhibited by atropine (Code 1951) and that this inhibition can be complete (Janowitz, 1957). It also induces the flow of salivary secretion from the parotid and submandibular glands, which it does by two mechanisms: first, as a true secretagogue; and second, by causing smooth muscle to contract and so squeezing out retained secretion from the gland (Babkin, 1950). This salivary effect is also inhibited by atropine. There has been a number of reports that histamine also stimulates external pancreatic secretion but there is disagreement as to whether this response is likewise inhibited by atropine. However, the pancreatic response was considered to be of little importance and to depend on the vasodilator effect of histamine more than on a direct secretagogue effect. (Thomas, 1950). Furthermore, the evidence in support of such pancreatic stimulation is marred by two features. First, all except the most recent experiments were done acutely; and secondly, in most of these investigations, no attempt was made to exclude the endogenous secretion mechanism in the course of the experiments. Since 1898, when it was first demonstrated by Pavlov, it has been known that the entry of acid into the

duodenum produces a copious flow of pancreatic juice. This was shown by Bayliss and Starling (1902) to be due to the liberation of secretin, a substance capable of stimulating pancreatic secretion to a marked degree. Consequently, entrance of histamine-induced gastric secretion into the duodenum will ordinarily produce pancreatic secretion by way of this endogenous secretin mechanism. This constitutes an important fallacy in earlier work on the pancreatic response to histamine.

The work reported here was undertaken in an effort to obtain unequivocal evidence in dogs concerning the importance of histamine as a pancreatic secretagogue, and in the hope of resolving the question of the influence of atropine on its action. Two groups of experiments were performed in which the endogenous secretin mechanism was excluded by different methods; (1) by removing the acid bearing area by total gastrectomy and (2) by removing the acid during experiments by means of gastro-:stomy while leaving the acid bearing area intact. The responses to secretin and histamine were studied and compared by each method, and it will be shown that identical results were obtained. The effect of atropine on the histamine response was also studied in these two ways. Next, the effect of vagotomy on the responses to secretin and histamine was studied and evidence will be presented for the presence in the vagus of both secretory and inhibitory fibres to the pancreas. The effect of atropine on the secretin

response was then re-examined and the differences between the effect of atropinisation and of vagotomy discussed. In view of the widespread belief that histamine owes its effect on the pancreas to its vaso-dilator action, a full review of the evidence on the relationship between pancreatic secretion and local blood flow will also be presented.

When Dale and Laidlaw (1910) first reported pancreatic exocrine activity following the injection of histamine, they described a response reaching its maximum in the first five minutes and terminating in about 10 minutes. The response to 1 mgm. beta-iminazolyl-ethylamine was 25 drops in 10 minutes as compared with 135 drops in 16 minutes attained by the injection of a preparation of secretin. The response to histamine was completely inhibited by the injection of 5 mgm. atropine, which left the response to secretin unaltered. Since the response to histamine was something less than one fifth of the response to secretin, they concluded that the histamine response was a different type and of a lower order than that following secretin.

Popielski (1920) reported similar findings except that he could not demonstrate any inhibitory action following atropine.

Molinarri-Tosatti (1928), using dogs with a ligated pylorus, injected 1 mgm. histamine (Bayer) in 20 ml. Ringer's solution intravenously into 15 to 20 Kg. dogs and produced 1 ml. pancreatic juice "in a short time". The response to 2 mgm. histamine was inhibited by the injection of 30 mgm. atropine sulphate a few minutes before. He concluded that "the pancreatic secretion produced by histamine is of small quantity and short duration, and is not comparable to the marked response produced by the physiological secretagogue known as secretin". He was the first to suggest that the response was due to vasodilation.

Mackay (1930) found that 0.25 mgm. of histamine intravenously was sufficient to evoke a fair amount of secretion in a dog of average size, the common bile duct and pylorus both being tied off. The response lasted for several minutes, following a latent period of 40 to 70 seconds, though its volume depended to some extent on the size of the dose. Atropine in doses sufficient to paralyse the vagal nerve endings, as judged by blood pressure changes, did not abolish this histamine effect.

In the rabbit, on the other hand, she reported that histamine produced an inhibitory effect on pancreatic secretion which became evident several minutes after administration, but this was associated with marked toxic manifestations and so reliance cannot be placed on these findings.

MacKay and Baxter (1931) made the interesting observation that in a few dogs repeated instillation of 0,2% HCl into the duodenum appeared to exhaust the pancreatic responses, but if 10 to 30 mgm. of histamine were then added to the HCl the pancreas again responded. They further noted that they were unable to exhaust the pancreatic response to intraduodenal HCl if the animal had had a meat meal on the previous day.

Hallenbeck and Jordan (1952) injected dogs with histamine in beeswax, but since they made no attempt to exclude gastric HCl from the duodenum, it is not surprising that they obtained a profuse flow of pancreatic juice over a period of at least 24 hours. A similar response to histamine was obtained by Routley, Mann,

Bollman & Grindlay (1952) in the course of various experiments on pancreatic secretion without exclusion of gastric HCl.

The only clear failure to obtain such a histamine effect on pancreatic secretion was that reported by Dreiling (1954) for man. The response to 1 mgm. histamine acid phosphate was one third of the response obtained by 1.0 unit/kg. body weight of secretin intravenously, but was no greater than the control response.

As far as the effect of atropine is concerned, it can be seen that while Dale and Laidlaw (1910) and Molinarri-Tosatti (1928) report the inhibition of the histamine response by atropine, Popielski (1920 and MacKay (1930) hold the opposite point of view. Miss MacKay (1930) stated that atropine in doses sufficient to paralyse the vagal nerve endings does not abolish the histamine response. She used doses of 7 to 10 mgm. in 3 experiments with dogs of 11.5 to 19.5 kgs. body weight. In one experiment histamine was given at intervals up to 1 hour 24 minutes after the injection of 2 to 5 mgm. of atropine without any inhibition of response, but unfortunately an initial dose of 0.25 mgm. histamine was compared with a final one of 1 mgm. In the remaining two experiments, the histamine response was slightly diminished after the dose of atropine. In these two experiments the maximum interval between the atropine and subsequent histamine injection was only 13 and 19 minutes respectively. Thus, while such a short interval may be sufficient for paralysis of vagal nerve endings to occur, as

tested by the effect of vagal stimulation on blood pressure, it may be too short an interval for the atropine effect on the pancreas to become significant. Thus the evidence that atropine has no action on the histamine response is somewhat inconclusive, and it was felt worthwhile to reinvestigate this question in addition to a study of the action of histamine.

CHAPTER III

METHODS.

The inaccessibility of the pancreas is responsible for many difficulties in the study of its physiology. While this problem arises mainly in the study of human physiology, it is equally impossible to collect pure pancreatic secretion from the intact animal. The necessity for the use of anaesthesia and operative techniques during the study of pancreatic secretion has, in the past, given rise to many fallacies inherent in the response of the pancreas itself to operative interference, or to the anaesthetic substances used, and so a method is required which will obviate these objections as much as possible. This method should also permit repeated secretion studies on the healthy unanaesthetised animal so as to observe results over a long period and allow their statistical analysis where necessary.

A further difficulty which arises in these experiments is due to the passage of acid gastric juice into the duodenum. Bayliss and Starling (1902) showed that when acid came in contact with duodenal or small bowel mucosa, secretin was elaborated. This endogenous secretin was rapidly absorbed and gave rise to secretion from the pancreas. Thus it is important to exclude this fallacy by preventing the flow of gastric juice across the pylorus. The two methods used to achieve this aim in the course of the present work were either the use of a total gastrectomy which completely removed the acid-bearing area, or secondly the use of a gastrostomy through which the stomach could be kept constantly

empty. (Fig. 1).

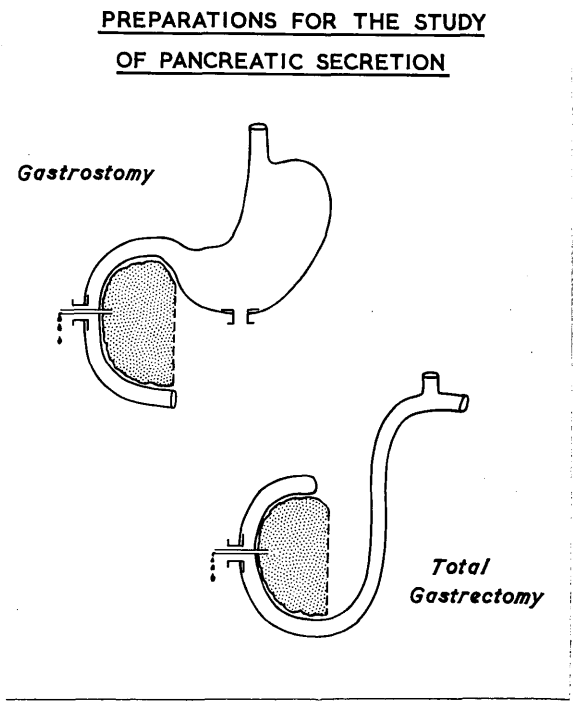


Fig. 1

These methods will be more fully described later when their relative merits will be discussed.

The preparation used for the collection of pancreatic juice in the present experiments was based on a method devised by Thomas (1941) and modified by Scott et al. (1941). The method depends on the use of a plastic and metal cannula (fig. 2) which can be inserted permanently within the duodenum opposite the main pancreatic duct, after ligation and division of the accessory duct, and brought out through the lateral abdominal wall When closed by its cap it prevents leakage of duodenal contents and does not interfere with normal bowel continuity. When open,

it permits cannulation of the main pancreatic duct by means of a special small glass cannula. (Fig. 3). The accessory pancreatic duct is tied at operation so that all the juice must of necessity flow out through the main duct.

Fig. 2.

The Thomas Cannula.

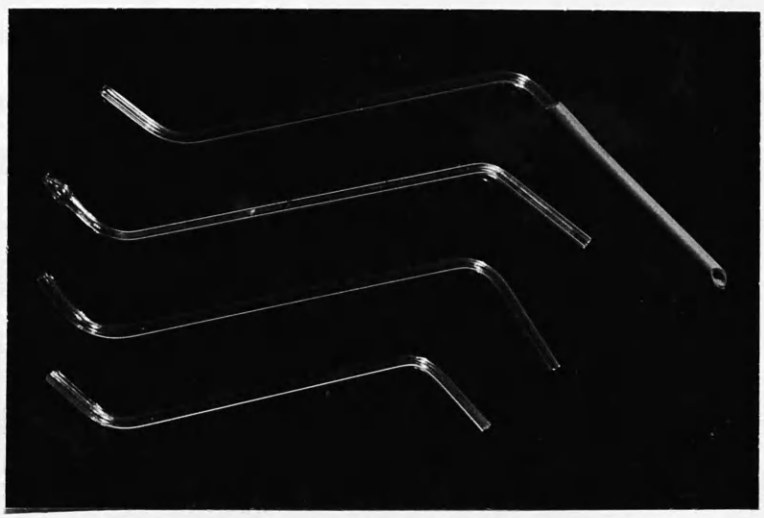


Fig. 3.

Varieties of cannulae for cannulating the main pancreatic duct. One has an olive head.

The method possesses the following advantages:-

1) The pancreatic juice can be collected pure.
2) Operative interference is minimal and the normal blood and nerve supply of the pancreas is preserved.
3) Secretion studies can be performed without anaesthesia and without upset to the animal.
4) Experiments can be performed repeatedly under identical conditions allowing statistical analysis of the results.
5) The animals require no special care and remain in good health indefinitely.

One small disadvantage is that the animal requires close supervision during the course of an experiment.

The Insertion of the Thomas Cannula.

Mongrel bitches weighing 15 to 20 kg. were used. The animal was anaesthetised with intravenous nembutal (veterinary) 30 mgm. / kg. body weight, supplemented by ether if necessary. The abdomen was opened through a midline upper abdominal incision. The accessory pancreatic duct was found in its fairly constant position just distal to the entry of the common bile duct into the duodenum. It was ligated and divided. A search was made for any other accessory ducts, but in the present series no additional ducts were found. The main pancreatic duct was then identified just proximal to the point at which the pancreas sweeps away from the duodenal wall, and a small incision was made in the anti-mesenteric border of the duodenum opposite the duct, the opening

of which was identified from within the duodenum. The plastic flange A was then inserted (see fig. 4) and the plastic cylinder B screwed in place and held by means of a purse string suture. An incision was then made in the right lateral abdominal wall about one inch below the costal margin. The metal cylinder C was inserted through it and screwed on to the plastic cylinder B. The cannula was then closed by means of the screw cap D. Any necessary further preparation was then carried out, and will be described in the appropriate chapter.

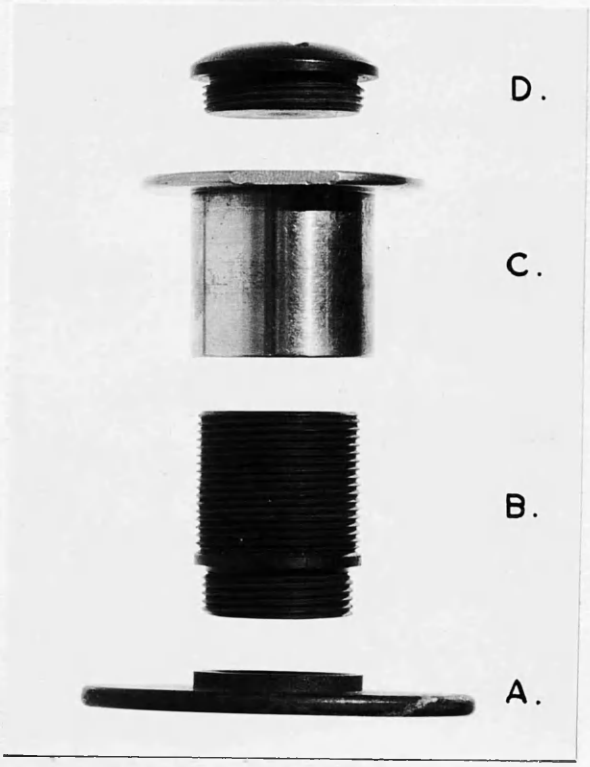


Fig. 4.

The Thomas Cannula in its separate parts.

A - Plastic flange.
B - Plastic cylinder.
C - Metal cylinder.
D - Plastic cap.

CHAPTER 1V

EXPERIMENTS ON DOGS WITH TOTAL GASTRECTOMIES.

A total gastrectomy was carried out on three dogs so as to make acid contamination of the duodenum impossible by ensuring the complete removal of the acid bearing area.

METHODS.

Preparation:- Following the insertion of the Thomas cannula opposite the main pancreatic duct, as just described, the duodenum was divided just distal to the pylorus and enfolded. The stomach was then mobilised and removed it its entirety, continuity being re-established by bringing up a loop of jejunum to the cut end of the oesophagus to form an end-to-side oesophago-jejunostomy. It was recognised that this type of anastomosis provides a more acute nutritional problem in dogs than does a more direct end-to-end oesophago-duodenostomy (McCorkle and Harper, 1954), but its choice was dictated by the necessity for bringing out the Thomas cannula on the lateral abdominal wall - to make cannulation of the main pancreatic duct feasible. Vagal branches in contact with the oesophago-gastric junction were divided when the oesophagus was transected.

Only one of these dogs ate really well, and vomiting was a problem in all three. They were unable to regain any weight lost, and the overnight starvation required before each experiment aggravated this situation progressively. As the abdominal wall became thin, leakage occurred round the Thomas cannula, and a secondary uncontrollable duodenal fistula added its problems of

fluid and electrolyte loss to the picture. As a result none of the dogs lived more than twelve weeks despite attempts at duodenal feeding with high protein jejunostomy-type feeds, which usually resulted in diarrhoea.

Experimental Routine:- Three weeks was considered to be a satisfactory recovery period from the operation of total gastrectomy and insertion of the Thomas cannula. Experiments were then begun with the object, firstly of measuring the response to a standard dose of histamine and comparing it with the response to a standard dose of secretin, and secondly, to measure the effect of a standard dose of atropine sulphate on the response to histamine given after an interval of 30 minutes.

The dogs were starved overnight before each experiment but were allowed water ad lib. They were then weighed, placed in a harness and suspended in a stand. The Thomas cannula was opened and any material in the duodenum allowed to drain. The main pancreatic duct was cannulated with a small glass cannula to which was attached a short length of rubber tubing which was then led into a graduated centrifuge tube. This is well shown in figs. 5, 6 and 7.

Fig. 5.

A dog in its harness showing duodenal and gastric cannulae. In totally gastrectomised dogs no gastric cannula is present.

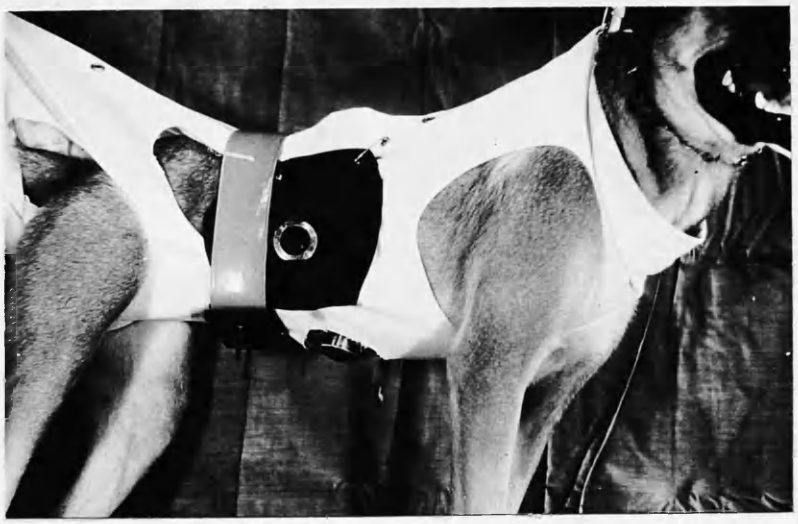


Fig. 6.

A rubber shield has been fitted round the duodenal cannula, and a belt into which a test tube can be fitted is placed round the dog.

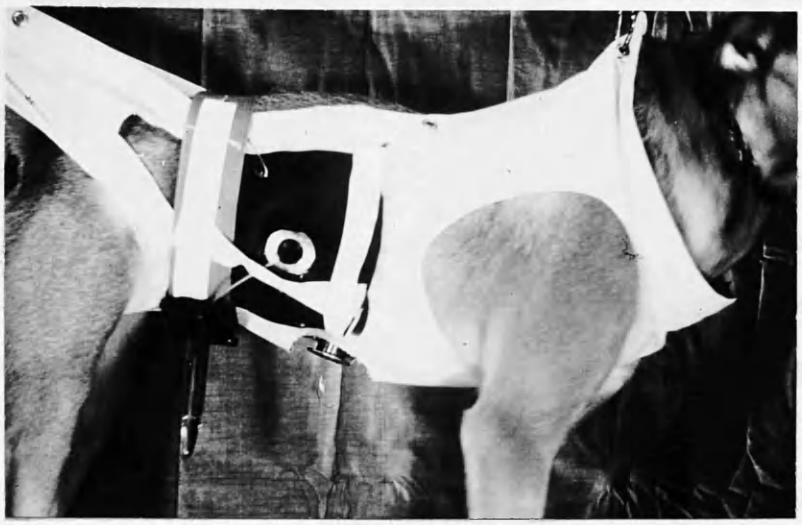


Fig. 7.

The pancreatic duct has been cannulated and the juice is being collected in a graduated centrifuge tube.

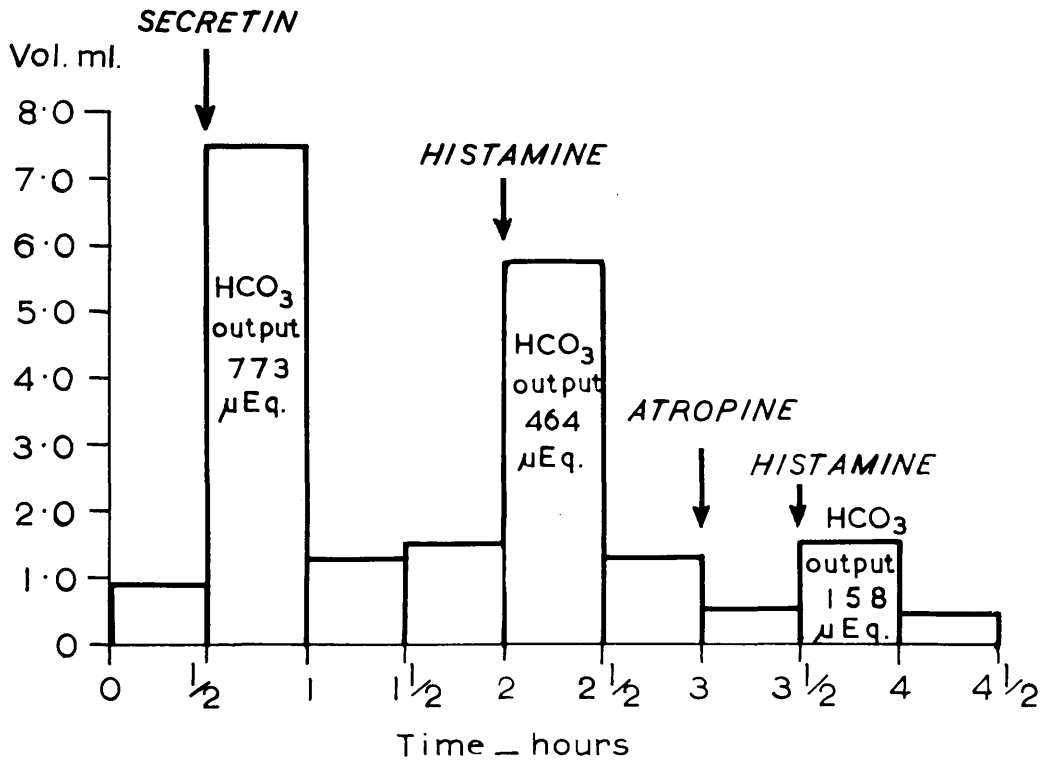
Pancreatic juice was collected in 30-minute periods. At the start of each experiment resting secretion was collected for at least one such period to be sure that the pancreas was secreting at no more than basal unstimulated rates, namely under 2 ml./half hour (Richman, Lester, Hollander and Dreiling, (1954). A secretory stimulus was then injected and secretion collected during the following period. In order that the patterns of response could be more clearly defined, the volume of secretion was noted at one-minute intervals during such a period, although only the total volume for the entire 30-minute period was used in the subsequent analysis. A further one or two periods were then allowed to ensure that secretion had returned to basal levels before a further stimulus was applied. In this way the response

to two or more stimuli in tandem could be compared during the course of the same experiment, thus allowing for possible day to day variation in pancreatic activity. This control device was particularly important in view of the progressive debilitation of these animals and especially their loss of water and electrolytes. The order in which secretin and histamine were given was reversed in alternate experiments to ensure that the order of the injections did not influence the response.

The volume of juice collected per half hour period was measured in ml. The bicarbonate concentration in mEq./l. was estimated in duplicate by the method of Peters and Van Slyke (1932) and the average of the two results used. The total bicarbonate output in micro-equivalents was calculated as the product of the volume in Ml. and the concentration in mEq/l.. The drugs employed in this investigation were secretin (Eli Lilly) 5 μ/Kg. body weight intravenously, histamine diphosphate 0.1 mgm. base/Kg. body weight subcutaneously, and atropine sulphate 0.2 mgm./Kg. body weight subcutaneously. These doses remained standard throughout all the experiments reported in this thesis.

RESULTS.

Fig. 8 shows the results of a typical experiment graphically.



A typical experiment designed to compare the pancreatic responses to secretin, histamine, and to histamine after atropine. (Dog with total gastrectomy. Exp. 310-14)

Fig. 8.

A 30-minute period of basal secretion yielding 0.9 ml. was followed by a secretin injection and a response of 7.5 mg.. Two further half hour periods then gave 1.3 and 1.5 ml. respect-:ively. An injection of histamine was then followed by a response of 5.8 ml. and then a half hour basal response of 1.3 ml.. Atropine was then given and the volume of secretion collected during the next half hour dropped to 0.5 ml., following which a

second injection of histamine was given. This resulted in a half hour yield of only 1.5 ml. which was followed by a final period with a yield of 0.4 ml.. The experiment was then terminated. The bicarbonate outputs in response to stimulation are also shown. It can be seen that this experiment allows for the comparison of the responses to histamine and secretin as well as allowing a comparison to be made between the responses to histamine before and after atropine. In some experiments atropine was not used.

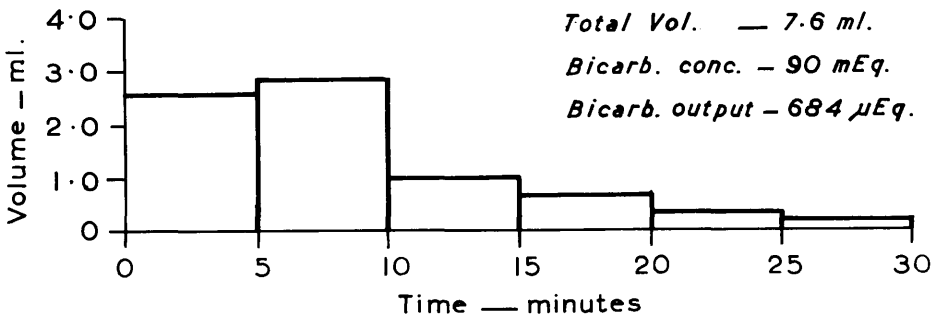
In all, 14 experiments were performed in which the histamine response could be studied relative to the secretin response, and there were 9 experiments in which the effect of atropine on this histamine response could be studied. Before analysing these sets of data the characteristics of the individual responses to the various stimuli will be described.

The Response to Secretin.

Following the intravenous injection of secretin there was usually a latent period of 1 or 2 minutes before pancreatic secretion occurred, though in some cases the response was almost immediate. Usually the maximal volume-rate of secretion was observed during the second 5 minutes, but occasionally it occurred during the first 5 minutes. The response lasted 25 to 30 minutes. A typical response is shown in Fig. 9 where the volumes secreted in successive 5 minute periods are graphed against time.

PANCREATIC RESPONSE TO SECRETIN

Dog with Total Gastrectomy —— Exp. 310-12



The volumes secreted in succeeding 5-minute periods are graphed against time. The response lasted about 25 minutes and was maximal in the second 5-minute period.

Fig. 9.

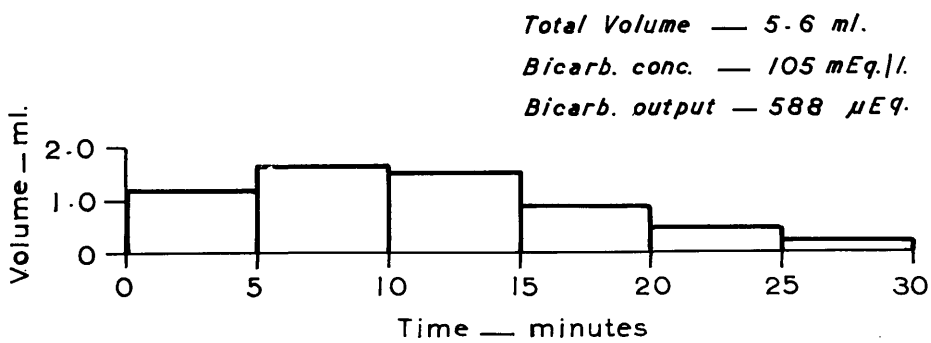
There is a very wide variation in the magnitude of the responses which range from 0.8 to 13.7 ml./half hour (mean 5.6 ml.). Similarly the bicarbonate concentrations range from 30 to 123 meq./l. (mean 85 meq.) and the total bicarbonate outputs range from 24 to 1685 micro-equivalents (mean 569 micro-equivalents). In one dog (No. 310) thick dark bile was discharged 3 - 4 minutes after injection, indicating contraction of the gall bladder. There was also profuse secretion of duodenal juice in all dogs following stimulation.

The Response to Histamine.

Following the subcutaneous injection of histamine there was a latent period of 1 to 3 minutes. The peak of the response occurred during the second five minutes in about half the experiments. In the remainder of the experiments it occurred equally during the first and third five minutes. The response lasted 20 to 30 minutes. Fig. 10 shows a typical response.

PANCREATIC RESPONSE TO HISTAMINE

Dog with Total Gastrectomy — Exp. 310-8



The volumes secreted in succeeding 5-minute periods are graphed against time. The response lasted about 25 minutes and was maximal in the second 5-minute period.

Fig. 10.

The volumes were generally less than those for the related secretin response, being in the range 0.9 to 6.7 ml./

half hour (mean 3.1 ml.). The bicarbonate concentrations ranged from 24 to 109 meq./l. (mean 63 meq.) and the total bicarbonate output from 22 to 534 micro-equivalents (mean 225 micro-equivalents). There was a profuse flow of duodenal juice following injection in all 3 dogs, but gall bladder contraction as indicated by the appearance of dark green bile at the fourth or fifth minute was observed in only one animal (No. 310), the same animal which secreted bile in response to secretin.

Comparison of the Responses to Secretin and Histamine.

The results for all 14 experiments of this kind are tabulated in Table 1.

There is obviously a considerable variation in the volume responses to the same stimulus from dog to dog, and to a lesser extent in the same dog from day to day. The bicarbonate concentrations also vary, but in much less degree. On the other hand, the total bicarbonate output varies to an even greater extent. However, there does not appear to be any definite relationship between these variations and the progressive development of dehydration and emaciation, except perhaps in Exp. 310 - 18 where both histamine and secretin responses are exceedingly low for this animal. This may be the result of the dog's extreme debilitation at the time of observation.

The responses for dog. No. 344 are all markedly lower than those for the other 2 animals. In particular, the bicarbonate concentrations fall below the level which Dreiling and Hollander (1948) considered suggestive of chronic pancreatic insufficiency

in man, namely 47 meq./l. It was interesting to find evidence of pancreatic fibrosis in this dog at autopsy as a confirmation of this suspicion.

COMPARISON OF THE PANCREATIC RESPONSE TO SECRETIN (S) AND HISTAMINE (H)

Dogs with Total Gastrectomies

Dog No.	Exp. No.	Volume Response (Ml./half hour)			Bicarbonate Conc. (mEq./l.)			Bicarbonate Output (micro-Eq.)		
		(S)	(H)	Ratio (H/S)	(S)	(H)	Ratio (H/S)	(S)	(H)	Ratio (H/S)
310	12	7.6	6.7	0.88	90	76	0.84	684	509	0.74
	13	4.5	3.5	0.78	85	70	0.82	383	245	0.64
	14	7.5	5.8	0.77	103	80	0.78	773	464	0.60
	15	8.7	4.6	0.53	97	73	0.75	844	336	0.40
	17	4.5	3.0	0.67	94	77	0.82	423	231	0.55
	18	2.5	1.3	0.52	78	47	0.60	195	61	0.30
Mean		5.9	4.2	0.69	91	71	0.77	550	308	0.54
344	3	0.8	1.8	2.25	30	42	1.40	24	76	3.17
	4	2.9	1.3	0.45	57	46	0.81	165	60	0.36
	5	0.8	1.1	1.38	33	32	0.96	26	35	1.35
	6	2.2	0.9	0.41	52	24	0.46	114	22	0.19
Mean		1.7	1.3	1.12	43	36	0.91	82	48	1.27
345	2	9.4	2.8	0.30	109	65	0.60	1025	182	0.18
	3	13.7	2.3	0.17	123	63	0.51	1685	145	0.09
	7	7.3	4.9	0.67	117	109	0.93	854	534	0.63
	8	6.6	3.0	0.45	116	83	0.72	766	249	0.33
Mean		9.3	3.3	0.40	116	80	0.69	1083	278	0.31
Grand Mean		5.6	3.1	0.73	85	63	0.79	569	225	0.68
S.D.				0.53			0.23			0.77

S.D. - Standard Deviation corrected for small numbers.

Table 1.

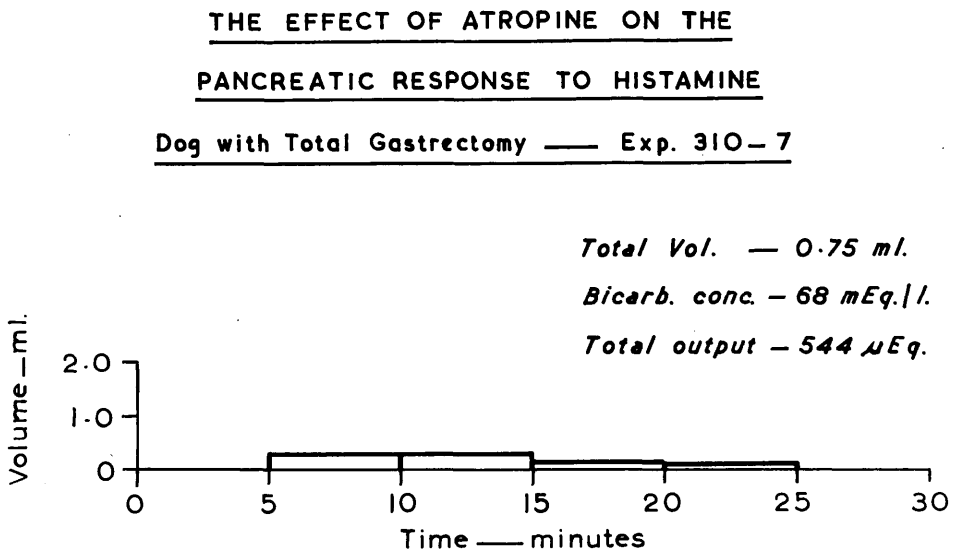
Despite the extensive variations in volume of secretion, the ratios of the volume outputs after histamine to those after secretin show a surprising degree of consistency except in the case of dog No. 344 which exhibited the excessively low volumes. Except for the high values in experiments 344 - 3 and 344 - 5, these ratios are all less than 1, lying in the range 0.17 to 0.88. However, when these two values of 2.25 and 1.36 are included the mean of all 14 observations is 0.73. Hence, on the average, the total volume of pancreatic juice secreted in response to histamine is 73% of that in response to secretin, under the conditions of dosage here employed. In the bicarbonate concentration ratios there is one value greater than 1, (Exp. 344-3), the range being 0.46 to 1.40. The mean for all 14 values is 0.79. The corresponding mean for the total bicarbonate output is 0.68 (range 0.09 to 3.17) which means that in terms of bicarbonate as well as volume the response to histamine is about 70% of the response to secretin.

Experiment 345-3 provides an example of an excessively high volume response. Similarly high readings were occasionally encountered later in these experiments and the validity of explaining them on the basis of an untied accessory duct is discussed. No such duct was found at post mortem in this or any other case.

The Effect of Atropine on the Response to Histamine.

The pattern of the individual responses following atropine

administration, as studied by means of minute-by-minute volume readings, showed little of note. Small volumes were usually accompanied by shortening of the duration, and lowering of the peak of the response as compared with the uninhibited histamine response. This is shown in Fig. 11.



The volumes secreted in succeeding 5-minute periods are graphed against time. Almost complete inhibition of the histamine response is shown in this experiment, the peak and duration both being reduced.

Fig. 11.

Nine experiments in which the responses to histamine before and after atropine could be compared with each other were performed in three dogs. The results are tabulated in Table 11.

COMPARISON OF THE PANCREATIC RESPONSE TO HISTAMINE (H) BEFORE AND AFTER ATROPINE (A)

Dogs with Total Gastrectomies

Dog No.	Exp. No.	Volume Response (Ml./half hour) Before (A)	After (A)	Ratio (A+H/H)	Bicarbonate Conc. (mEq./l.) Before (A)	After (A)	Ratio (A+H/H)	Bicarbonate Output (micro-Eq.) Before (A)	After (A)	Ratio (A+H/H)
510	14	5.8	1.5	0.26	80	105	1.31	464	158	0.34
	15	4.6	3.0	0.65	73	70	0.96	336	210	0.63
Mean		5.2	2.3	0.46	77	86	1.14	400	184	0.49
544	3	1.3	0.8	0.62	67	40	0.67	87	32	0.37
	4	0.8	0.7	0.88	42	21	0.50	34	15	0.44
	5	0.8	0.1	0.13	33	2	0.06	26	0	0.00
	6	0.6	1.1	1.83	20	39	1.95	12	43	3.58
Mean		0.9	0.7	0.87	41	26	0.80	40	23	1.40
545	3	2.3	2.2	0.96	63	80	1.27	145	176	1.21
	7	4.9	5.0	1.02	109	91	0.83	534	455	0.85
	8	3.0	1.6	0.53	83	74	0.89	249	118	0.47
Mean		3.4	2.9	0.84	85	82	1.00	309	250	0.84
Grand Mean		2.7	1.8	0.76	63	58	0.94	210	134	0.88
S.D.				0.50			0.54			1.01

S.D. - Standard Deviation corrected for small numbers.

Table II.

The same variation in response from dog to dog, and from day to day that was noted in Table 1 is evident here also.

Volume:- In only five experiments was there a reasonable inhibition

of the histamine response, the range of the ratios for the volumes being 0.13 to 0.65. In three others the ratios were 0.88, 0.96 and 1.02, and in one experiment (Exp. 344-6) the ratio was as high as 1.83, but this may be erroneous since it differs from the mean of 0.76 by more than twice the standard deviation. If this figure is excluded the mean becomes 0.63. From these numbers the mean degree of inhibition of volume output in these experiments may be taken as 24 per cent at least, and possibly even 37 per cent.

Total Bicarbonate Output:- The total bicarbonate outputs afforded rather better evidence of inhibition. In only 3 of the 9 experiments is the ratio of the response after atropine to the response before it greater than 0.80, in the remaining 6 it varies from 0.00 to 0.63. The mean of all 9 values is 0.88, implying about 12 per cent inhibition by this criterion. However once again the ratio of 3.58 in Exp. 344-6 may be erroneous since it differs from the mean by almost three times the standard deviation. If this figure is excluded, the mean ratio becomes 0.54, which implies an average inhibition of nearly 50 per cent.

Bicarbonate Concentration:- The bicarbonate concentrations show much less evidence of inhibition; in only three of the nine experiments is the ratio of the response after atropine to the response before it less than 0.80. Hence, although these experiments seem to afford some evidence that the pancreatic response to histamine can be inhibited by atropine, the effect as observed here is far from general. The reason for this lack of generality will be discussed later.

ADDITIONAL EXPERIMENTS.

The Effect of Ephedrine and Banthine on the Pancreatic Response to Histamine.

In view of the equivocal results obtained following the injection of atropine it was decided to investigate briefly the effect of two other drugs with a slightly different mode of action. Ephedrine and banthine were used.

Ephedrine is a sympathomimetic drug which Craft (1938) has already shown to have an inhibitory effect on pancreatic secretion. He demonstrated a reduction of 15 to 55 per cent in the secretion of the pancreas in 8 out of 9 experiments on 6 dogs between control days and days on which ephedrine in 10 mgm. doses was given every two hours. This dose was approximately 0.5 mgm./Kg. body weight. He also demonstrated some inhibition in the response to intravenous secretin in 4 acute experiments. It seemed reasonable to try the effect of this drug on the histamine response.

Banthine is an atropine-like drug which not only paralyses parasympathetic nerve endings but also acts at the intermediate ganglia. Annis and Hallenbeck (1950,1951) demonstrated a profound inhibition of the response to a meat meal in dogs following the administration of this substance and again it seemed reasonable to try its effect on the histamine response.

The experimental technique was exactly the same as for atropine; ephedrine 0.5 mgm./Kg. body weight, or banthine 5 mgm./Kg.

body weight, being injected subcutaneously 30 minutes before the second injection of histamine.

The Effect of Ephedrine on the Pancreatic Response to Histamine.

Following the injection of ephedrine there was no difference in the general pattern of the response to histamine. The latent period, the timing of the maximal secretory response, and the duration of the response, all remained unchanged. Fig. 12 shows a typical response.

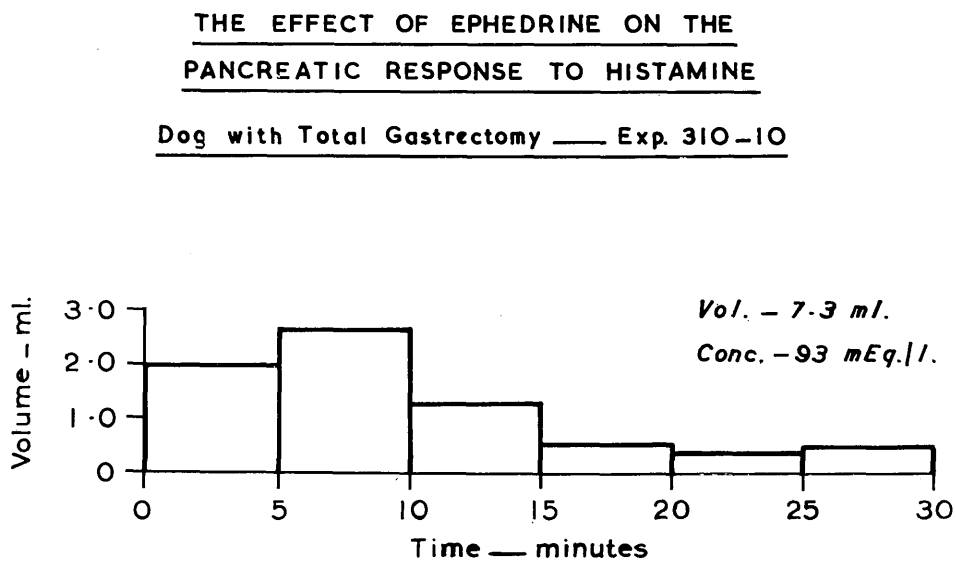


Fig. 12.

Six experiments were performed on three dogs in which the response to histamine before and after ephedrine could be compared. The results are summarised in Table III.

COMPARISON OF THE PANCREATIC RESPONSE TO HISTAMINE (H) BEFORE AND AFTER EPHEDRINE (E)

Dogs with Total Gastrectomies

Dog No.	Exp. No.	Volume Response (Ml./half hour) Before (E)	After (E)	Ratio (E+H/H)	Bicarbonate Conc. (mEq./l.) Before (E)	After (E)	Ratio (E+H/H)	Bicarbonate Output (micro-Eq.) Before (E)	After (E)	Ratio (E+H/H)
510	10	9.9	7.5	0.74	98	93	0.95	970	679	0.70
	16	1.0	2.3	2.30	64	64	1.00	64	147	2.30
544	7	1.1	2.1	1.91	44	48	1.09	49	101	2.08
545	4	1.9[x]	1.9	1.00	67[x]	68	1.01	127	129	1.01
	9	1.4	1.8	1.28	50	54	0.94	70	97	1.39
	10	1.4	1.6	1.14	43	49	1.14	60	78	1.30
Mean		2.8	2.8	1.39	61	63	1.02	223	205	1.46

x - Average of 2 readings.

Table III.

Apart from the comparatively high readings in exp. 310-10, which is in fact within the normal range for that particular dog, the range of the volume responses before ephedrine is 1.0 to 1.9 ml. which is slightly lower than that after ephedrine, namely 1.6 to 2.3 ml.. The bicarbonate concentrations however show little change, being 43 to 67 mEq/l. before ephedrine and 48 to 68 mEq./l. after. The total bicarbonate outputs therefore, are also slightly increased after the administration of ephedrine. However, the means of all six experiments are almost identical as regards volume, bicarbonate

Concentration and total output. There would therefore appear to be no evidence that ephedrine has any effect on the pancreatic response to histamine in these experiments.

The Effect of Banthine on the Pancreatic Response to Histamine.

Experiment 310-9 was the only experiment in which banthine was used. The volume response to histamine was reduced from 5.6 to 1.4 ml. (-75%), the bicarbonate concentration was reduced from 105 to 68 mEq./l. (-35%), and the total bicarbonate output was reduced from 588 to 95 microEq. (-84%). Banthine thus produced considerable inhibition of the response to histamine in this one experiment.

The profile of the response after banthine was similar to that observed after atropine.

POST MORTEM FINDINGS.

One of the dogs died and two were sacrificed because of their emaciated condition. The salient features of the autopsies were as follows:

Dog No. 310. Sacrificed after 12 weeks. The pancreas weighed 18 gm. and appeared normal both macroscopically and microscopically. The liver was not examined.

Dog No. 344. Died after six weeks. The pancreas weighed 13 gm. and appeared to be sclerotic and atrophic. Hist-:ologically there were considerable areas of fibrosis, with atrophy of the pancreatic acini and replacement of fibrous tissue. This may have resulted from interference with the blood supply at operation. Part of the gland appeared fairly normal and capable

of active secretion. These features are well shown in the photomicrograph (fig. 13).

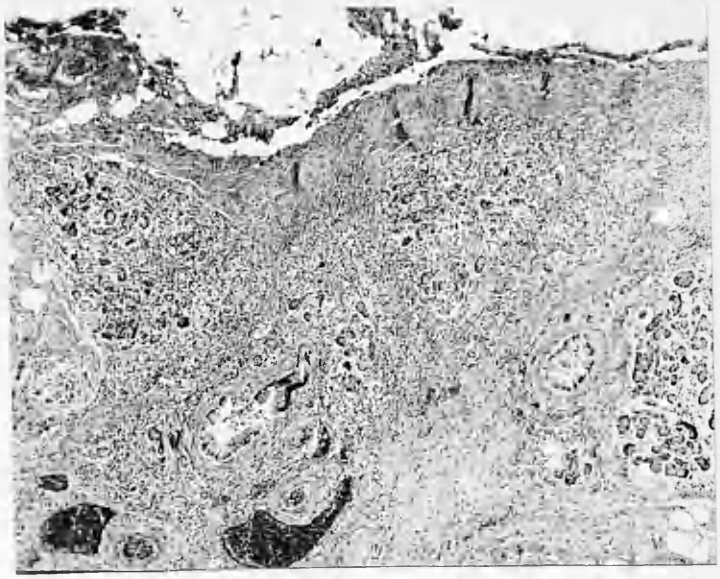


Fig. 13.

Photomicrograph of pancreas from dog 344 (low power). Note the marked replacement of acinar tissue by fibrous tissue.

Dog No. 345. Sacrificed after 10 weeks. The pancreas weighed 15 gm. and was soft. The histological appearances were normal. The liver showed severe fatty infiltration and degener-:ation, as can be seen from the photomicrograph (fig. 14).

In no dog was there any evidence of oesophagitis as a result of anastomosis with the jejunum, nor was there any other abnormality of the gastrointestinal canal. Additional accessory pancreatic ducts were looked for in all the dogs and none were found.

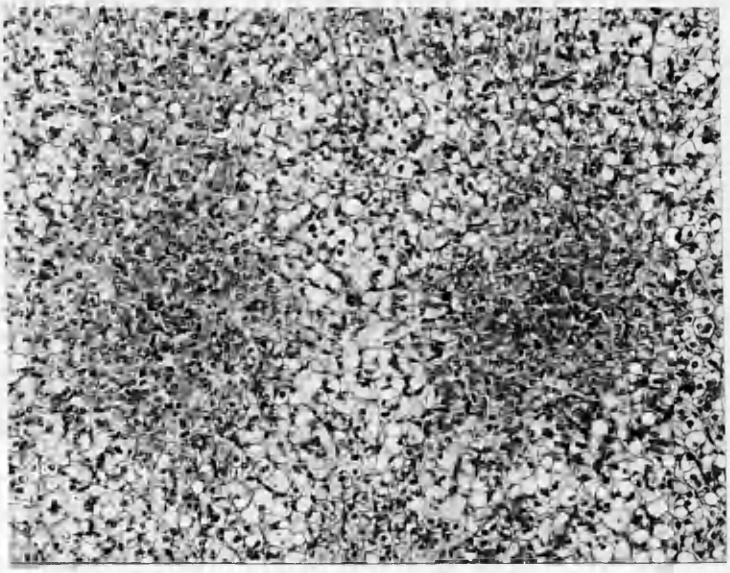


Fig. 14.

Photomicrograph of liver from dog 345 (high power). Note the gross fatty changes, most marked at the periphery of the lobules.

DISCUSSION.

From the data presented so far, it would seem that histamine is a potent stimulator of pancreatic secretion in the absence of any possibility of activation of the HCl endogenous secretin mechanism by entry of acid gastric juice into the duodenum. The mean of the ratios of the volumes in response to histamine and to secretin in this study is 0.73. The corresponding mean ratio for the bicarbonate concentrations is 0.79, and for the total bicarbonate output is 0.68. In other words, histamine evokes a response which is about 70 per cent of that expected in response to secretin as regards both volume and bicarbonate output.

There is a close similarity between the histamine and

secretin responses in regard to the latent period, the time of maximal secretory rate, and the duration of the response. This is particularly interesting in view of the fact that histamine is administered subcutaneously and that secretin is given intravenously. The shortness of the latent period after the administration of histamine is an indication of the rapidity with which it must be absorbed. Probably the fact that the histamine response tends to have its peak a little later than the secretin response and to be a little more prolonged can be explained by differences in the rates of absorption of the two substances.

It was interesting to find evidence of pancreatic fibrosis in the only dog (No. 344) in which both volume and bicarbonate responses were low. The fact that even in this case the ratios of the histamine responses of the secretin responses remained high is further evidence of the potency of histamine as a pancreatic secretagogue. Similar evidence was provided in Exp. 310-18 in which the ratios of the responses remained comparatively constant while the actual volume and electrolyte concentration fell at a time when the dog was severely depleted of fluid and electrolyte. Thus there seems to be a close relationship between the effects of secretin and histamine in the doses given which acts despite the presence of such factors as dehydration, electrolyte loss, or pancreatic pathology having a considerable effect on the actual amount of water and bicarbonate put out. This relationship appears to be of a certain order for each dog.

There is no evidence that the order in which secretin and

histamine were given affected the responses obtained, since the order was reversed in alternate experiments.

Atropine:- While a few experiments using atropine showed a considerable inhibition of the histamine response, the majority showed little change and in a few cases even an increase. The picture is therefore by no means clear cut, and this is in accord-:ance with the conflicting views expressed in the literature. However, we have already pointed out that in some cases the failure to achieve inhibition may have been due to the fact that an insufficient interval was allowed for the atropine to take effect. In order to test out this theory an interval of one hour was allowed in subsequent experiments.

Banthine:- The one experiment in which banthine was used showed a considerable reduction in both the volume and bicarbonate responses to histamine. While it would be quite wrong to argue from a single experiment, as far as it goes, it is in conformity with the profound inhibition of pancreatic activity following a meat meal in dogs reported by Annis and Hallenbeck (1950, 1951), though in the latter case inhibition is probably due to a concomitant reduction in gastric acid secretion, since they made no attempt to exclude the endogenous secretin mechanism.

Ephedrine:- In view of the fact that Craft (1938) reported that 10 mgm. ephedrine in a 20 kg. dog reduced pancreatic secretion by 15 to 55 per cent, it is interesting that we could find no evidence of any reduction in volume or bicarbonate output in response to histamine in our six experiments using a similar dose

of ephedrine (0.5 mgm./kg. body weight). It may be that for some reason ephedrine inhibits the basal pancreatic rate and the response to food and to secretin, but not the response to histamine which we tested.

SUMMARY.

The pancreatic response to histamine has been studied in three dogs in which total gastrectomies had been performed to exclude any fallacy due to activation of the endogenous secretin mechanism.

Histamine is a potent stimulator of pancreatic secretion.

On the average, the response to histamine is about 70 per cent of the response to a control injection of secretin in respect of volume, bicarbonate concentration and total bicarbonate output, in the doses used.

The profile of the responses to histamine and secretin are very similar as regards latent period, duration, and timing of the peak of the response.

The effect of atropine on the histamine response was studied. While some evidence of inhibition was obtained, the effect was by no means general. This may have been due to an insufficient interval of time between the injection of atropine and the subsequent injection of histamine.

In a single experiment banthine profoundly inhibited the volume and bicarbonate responses to histamine.

Ephedrine had no influence on the histamine response.

CHAPTER VI

EXPERIMENTS ON DOGS WITH GASTROSTOMIES.

When discussing the type of preparation to be used in these studies it was pointed out, in the first place, that operative interference must be minimal so as to leave the blood and nerve supply of the pancreas intact, and in the second place, there must be absolute certainty concerning the absence of duodenal contamination with acid gastric juice. These two aims proved to be mutually incompatible. While the insertion of a Thomas cannula on its own did not interfere with the integrity of the pancreas, the addition of a total gastrectomy to exclude the endogenous secretin mechanism may well have interfered with the nerve supply even if it left the blood supply intact. Apart from this, the health of the dogs deteriorated progressively, and so although repeated secretion studies were carried out they were not performed over a long period or under completely identical conditions. Thus the use of a total gastrectomy to provide unequivocal evidence of the action of histamine on the pancreas in the absence of the HCl-endogenous secretin mechanism is not ideal and this is bound to cast some doubt on the value of the findings.

To overcome these objections, a second group of experiments was undertaken in which dogs were provided with a gastrostomy through which the stomach could be kept empty, instead of a gastrectomy. Hence a healthy animal was obtained and the criterion of minimal operative interference adhered to, at the expense of some loss of certainly as to absolute exclusion

of gastric HCl from the duodenum during secretion studies. The question of how far this lack of certainty affected the validity of the experiments is fully discussed later.

METHODS.

Preparation:- A gastrostomy was performed in five dogs immediately after the duodenal Thomas cannula had been inserted. The gastrostomy was placed just proximal to the pylorus and brought out through the abdominal wall so as to be in the most dependent part of the stomach when the animal was standing. In two of the dogs a Thomas cannula was used for this purpose and inserted in the way already described. In the remaining three dogs a Senn gastrostomy was made (Miles & Learmonth, 1950) using large sized rubber catheters (Nos. 20-24). From the experimental point of view both types of gastrostomy proved quite satisfactory in keeping the stomach empty but the dogs with the cannulae were generally easier to handle during experiments and in routine dressings, since the catheters tended to fall out. No problems were encountered in maintaining the weight and health of the dogs. Discharge round the Thomas cannula and the gastrostomy was usually slight and often absent and skin erosion proved no problem.

Experimental Procedure:- A recovery period of two weeks after the operation of gastrostomy and insertion of the duodenal cannula was considered adequate before experiments were begun. The experimental procedure was basically the same as described before. The dogs were starved for 20 to 24 hours before each

experiment but were allowed water ad lib.. After being weighed they were suspended in the stand. The stomach was then emptied by means of the gastrostomy and subsequently kept empty by suction and gravity. The duodenal cannula was then opened and the pancreatic duct cannulated.

Pancreatic juice was again collected in 30-minute periods with the usual precautions to see that secretion was occurring at basal rates before a stimulus was injected, and had returned to basal rates before a subsequent stimulus was applied. During the response to an injection volume readings were made at one minute intervals so that the pattern of the response could be followed. In addition, since it was important to be sure that no HCl entered the duodenum, the pH of the duodenum fluid was measured by pH (pHydrion) paper at least at one minute intervals during the period of response to a stimulus and every few seconds if a fall in pH was detected so that its exact duration could be known. Experiments in which the duodenal pH could not be maintained at satisfactory levels were discarded.

As before, estimations of volume, bicarbonate concentration and total bicarbonate output were made on each 30-minute sample. In addition, in one dog (No. 353), the nitrogen concentration in mMols./l. was measured by a micro-Kjeldhal technique (Hawk, Osler and Summerson, 1954). The total nitrogen output in micro-Mols. was then calculated as the product of the volume in Ml. and the concentration in mMols./l.. Where the available quantity of juice was sufficient, the chlorides in mEq./l. were also estimated by

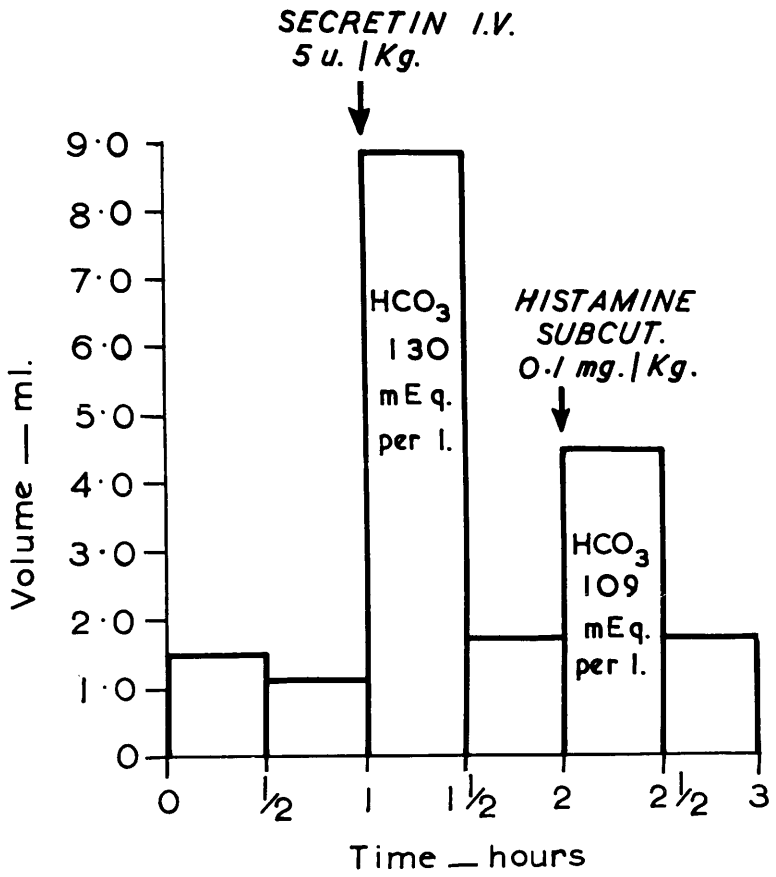
a modified Volhard method (Hawk, Osler and Summerson, 1954). Unfortunately there was insufficient material for the estimation of sodium and potassium.

The same two main groups of experiments were carried out on these animals as in the dogs with total gastrectomies. Firstly, the response to the standard subcutaneous dose of histamine diphosphate was compared with the response to intravenous secretin. Secondly, the effect of atropine sulphate on the histamine response was investigated. However, on this occasion, the atropine was given one hour before the second injection of histamine instead of half an hour before.

A typical experiment of the first group (Exp. 349-3) comprising five 30-minute periods is shown graphically in Fig. 15.

The rate of basal secretion during the first two periods was 1.5 and 1.1 ml./half hour respectively. Secretin was then given and 8.9 ml. of juice collected in the third period. Following this the rate returned to a basal level of 1.7 ml. in the fourth period, whereupon histamine was injected. This was followed by a response of 4.5 ml. in the fifth period and a return to a basal level of 1.7 ml. in the fixth and final period. Seventeen such experiments were performed. Each experiment therefore included its own control in the same dog and on the same day, so that day to day variations in pancreatic activity would not affect the relative magnitude of the responses. Usually the secretin was injected before the histamine as in the above example, so as to minimise the possibility

of disturbance from the secretion of gastric Hcl which continues for a long period after the injection of histamine. In two experiments (Exps. 341-3 and 349-1) however, this order was reversed without any alteration in the pattern of the responses. The character of these responses will now be described.



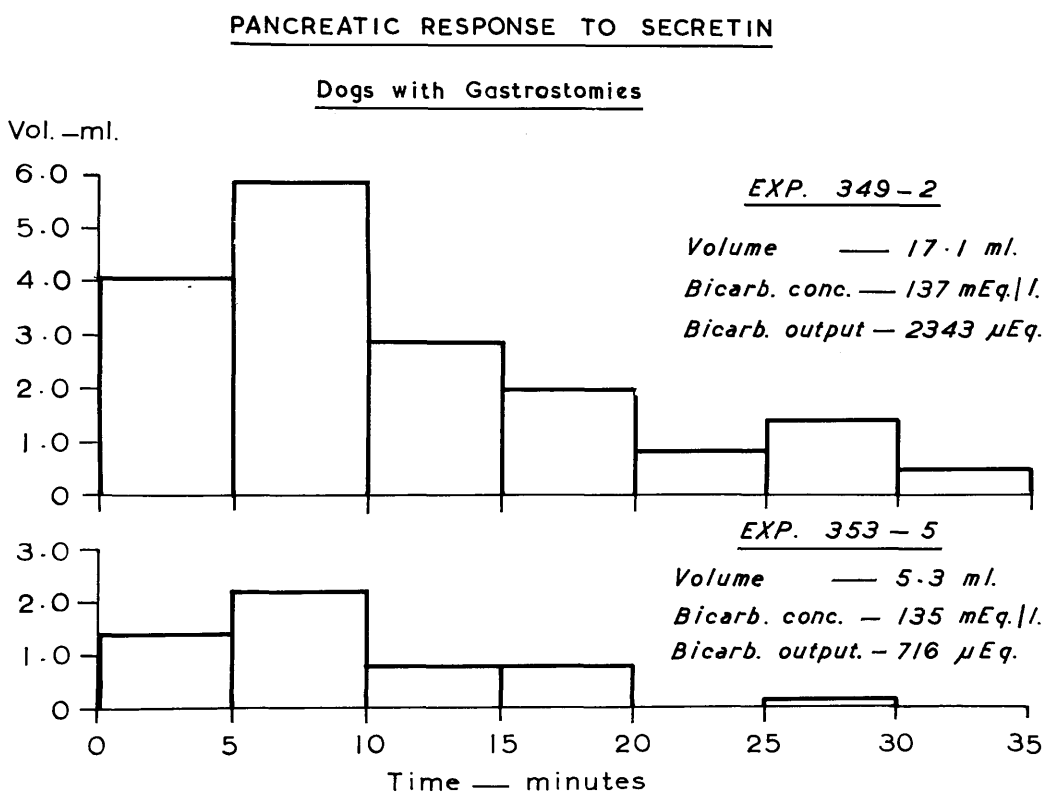
A typical experiment designed to compare the pancreatic responses to secretin and histamine. (Dog with gastrostomy. Exp. 349-3)

Fig. 15.

RESULTS.

The Response to Secretin.

Following the injection of secretin there was a latent period of about one minute which was followed by a rapid rise to a maximum and then a gradual fall. In about one third of seventeen experiments the maximal response was obtained during the first 5 minutes, and in about two-thirds it was obtained in the second five minutes; on one occasion it was delayed till the third five minutes. The response usually lasted 20 - 25 minutes though in three cases it lasted slightly longer. Fig. 16 shows the typical pattern in both high and low responses.



The volumes secreted in succeeding 5-minute periods are graphed against time. A high and low response to secretin are shown. In both cases the maximal response occurs during the second 5 minutes. The larger response is of slightly longer duration than the smaller.

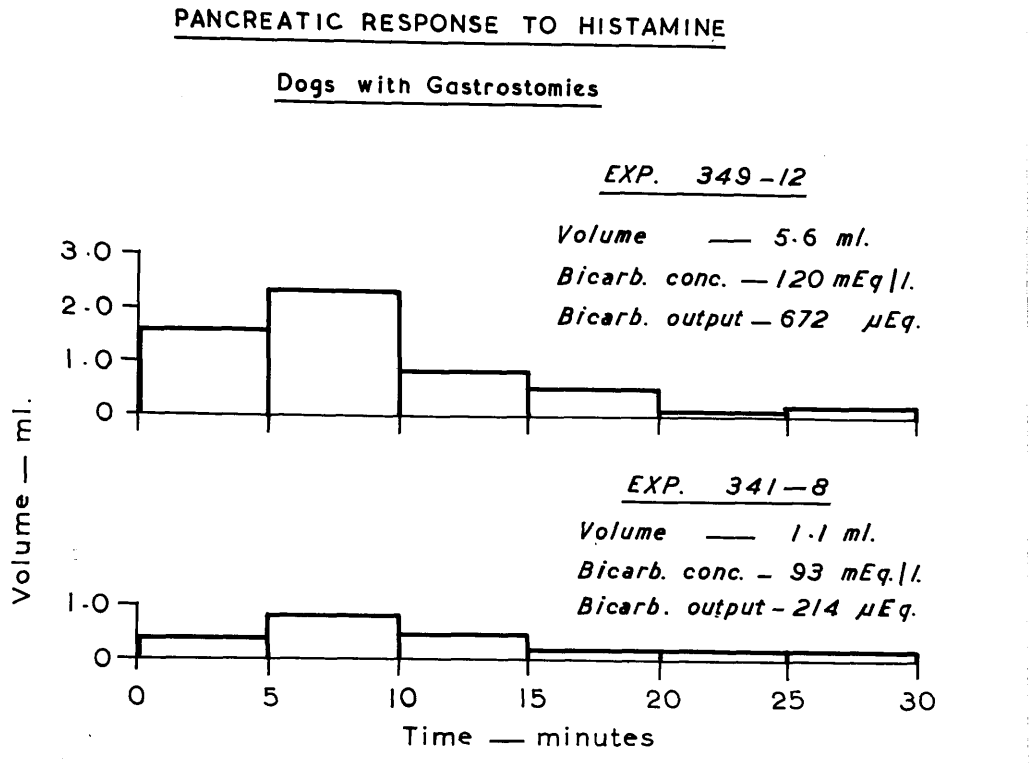
Fig. 16.

The response to secretin was usually associated with a discharge of thick dark bile 3 or 4 minutes after the injection, indicative of gall bladder contraction. A profuse flow of alkaline duodenal juice also started after a few minutes and lasted about 20 minutes. There was no systemic upset.

The Response to Histamine.

The pattern of the response to histamine was generally similar to the response to secretin but started a little slower. Thus the latent period was usually about three minutes, although occasionally secretion occurred as early as the first minute. The maximal rate of secretion occurred during the second five minutes in about two-thirds of the experiments and in the third five minutes in somewhat less than one-third. In the few remaining instances of the 17 experiments the maximum occurred within the first five minutes. The duration of the response was usually about 20 minutes and never greater than 30 minutes. Fig. 17 snows the typical pattern in both high and low responses.

Gastric secretion of acid as indicated by flow through the gastrostomy, began 10 to 15 minutes after the injection of histamine. The gall bladder contracted and clear alkaline duodenal juice was secreted at about the same time as in the secretin response. The animal became flushed and somewhat restless, and on a few occasions it retched after about 20 minutes.



High and low responses to histamine are shown. In both cases the maximal response occurs in the second 5 minutes. The larger response lasts 5 minutes longer than the smaller response.

Fig. 17.

Comparison of the Responses to Secretin and Histamine.

It is obvious from the above descriptions and from a comparison of Figs. 16 and 17 that the profiles of the responses to histamine and secretin are very similar. The results of 17 experiments in which a comparison was made between these responses are summarised in Table IV.

COMPARISON OF THE PANCREATIC RESPONSE TO SECRETIN (S) AND HISTAMINE (H)

Dogs with Gastrostomies

Dog No.	Exp. No.	Volume Response (Ml./half hour) (S)	(H)	Ratio (H/S)	Bicarbonate Conc. (mEq./l.) (S)	(H)	Ratio (H/S)	Bicarbonate Output (micro-Eq.) (S)	(H)	Ratio (H/S)
341	2	1.0	1.1	1.10	79	91	1.20	79	100	1.27
	3	1.1	1.1	1.00	84	78	0.93	92	86	0.93
	4	1.8	2.8	1.55	104	97	0.93	187	272	1.45
Mean		1.3	1.7	1.22	89	89	1.02	119	153	1.22
343	2	9.5	5.0	0.52	118	82	0.69	1121	410	0.37
	4	6.5	2.0	0.30	119	91	0.76	774	182	0.24
	5	8.1	2.5	0.30	122	73	0.60	988	183	0.19
Mean		8.0	3.2	0.37	120	82	0.68	961	258	0.27
348	3	4.8	2.2	0.46	129	87	0.67	619	191	0.31
	4	3.5	5.3	1.51	99	78	0.79	347	413	1.19
	5	6.5	3.0	0.46	114	52	0.47	741	152	0.21
Mean		4.9	3.5	0.81	114	72	0.64	569	252	0.57
349	1	7.9	4.7	0.59	130	96	0.74	1027	451	0.44
	2	17.1	5.7	0.33	137	117	0.85	2343	667	0.28
	3	8.9	4.5	0.51	130	109	0.84	1157	491	0.42
Mean		11.3	5.0	0.48	132	107	0.81	1509	536	0.38
353	1	14.2	5.1	0.36	132	87	0.66	1875	444	0.24
	2	6.5	2.7	0.42	123	84	0.68	800	227	0.28
	3	7.2	2.6	0.36	127	87	0.69	914	226	0.25
	4	10.1	4.8	0.48	133	106	0.80	1343	509	0.38
	5	5.3	1.7	0.32	135	115	0.85	716	196	0.27
Mean		8.7	3.4	0.39	130	96	0.73	1130	320	0.28
Grand Mean		7.0	3.4	0.62	126	92	0.77	890	306	0.51
S.D.				0.41			0.16			0.42

S.D. - Standard Deviation corrected for small numbers.

Table IV.

The individual values vary considerably, but much more so from dog to dog than from day to day.

Volume:- The volume responses to secretin range from 1.0 to 17.1 ml./half hour. The means themselves vary between 1.3 and 11.3 ml./half hour and the grand mean is 7.0 ml.. The histamine responses range from 1.1 to 5.7 ml., the means range from 1.7 to 5.0 ml. with a grand mean of 3.4 ml.. In 13 of these 17 experiments the volume response to histamine is lower than that to secretin; the ratios of these volumes lie between 0.30 and 0.59. In the other four experiments, in which the histamine response is greater than the secretin response, the ratios range from 1.00 to 1.55. Three of these four experiments occur in dog 341, in which the level of the volume responses is unusually low. Occasionally, a very high volume is obtained after secretin for no obvious reason, such as 17.1 ml. in Exp. 349-2, and 14.2 ml. in Exp. 353-1. Such a deviation was pointed out in the previous series of experiments. It is usually accompanied by a high histamine response so that the corresponding ratio is comparatively unaffected. In short, histamine produces a volume response which is usually 1/3 to 2/3 of the secretin response in the doses used, but may on occasion be even greater than it.

Bicarbonate responses:- In spite of the extensive variations in fluid output which were encountered in these experiments, the bicarbonate concentrations frequently exhibited a surprising degree of consistency for any one dog, though not from one dog to another. For instance, in response to secretin, dog No. 353

produces a juice with a bicarbonate concentration with a range of 123 to 135 meq./l. (mean 130 meq.), whereas dog No. 341 provided a range of 79 to 104 mEq./l. (mean 89 mEq./l.). In the response to histamine the level of bicarbonate tended to be somewhat lower and similarly variable, as can be seen from the table.

In all but one of the 17 experiments, the bicarbonate concentrations for histamine and secretin have a ratio of less than 1.00, the mean being 0.77. In the single deviate from this pattern (Exp. 341-2) the ratio is 1.20. It must be remembered however, that bicarbonate concentration varies directly with the rate of secretion (Hart and Thomas, 1945), and so these variations are probably no more than the reflection of this correlation. The total bicarbonate output reflects the variability of the volume response more than the variability of the bicarbonate concentration. The secretin responses range from 79 to 2343 microEq. and the histamine response from 86 to 667 microEq.. The grand mean of the ratios of these responses is 0.51.

Nitrogen responses:- The values for the concentration and total output of nitrogen in dog No. 353 are shown in Table V. These were taken as a convenient indication of total enzyme content of the juice (Thomas and Crider, 1946).

There is the same sort of variation in the individual values as was noted in the previous table. The nitrogen concen-:trations after secretin range from 70 to 165 mMols./l. (mean 113 mMols./l.), and after histamine they range from 166 to 328 mMols./l. (mean 266 mMols./l.). The ratios of these responses are

somewhat more constant and range from 1.99 to 2.97 (mean 2.41), so that on the average, the concentration of nitrogen following the injection of histamine is about 2. times that of the secretin response.

Examination of the total nitrogen output reveals a much larger day to day variation, from 373 to 1495 micro-Nols. (mean 973 micro-Mols.) after secretin, and from 281 to 1592 micro-Mols. (mean 927 micro-Mols.) after histamine. However, despite this, the ratios of these values are remarkably constant with a range of 0.72 to 1.10, and a mean of 0.93 which approaches unity. Thus secretin and histamine appear to evoke a similar total nitrogen response despite the differences in volume and concentration of the juice.

COMPARISON OF THE PANCREATIC RESPONSE TO SECRETIN (S) AND HISTAMINE (H)

Dog with Gastrostomy (No. 353)

Exp. No.	Nitrogen Conc. (mMols./l.)			Nitrogen Output (microMols.)		
	(S)	(H)	Ratio (H/S)	(S)	(H)	Ratio (H/S)
1	105	312	2.97	1495	1592	1.06
2	122	293	2.40	793	791	1.00
3	165	328	1.99	1187	851	0.72
4	101	234	2.32	1016	1122	1.10
5	70	166	2.37	373	281	0.75
Mean	113	266	2.41	973	927	0.93

Table V.

Chloride responses:- Table Vl shows the concentration and total output of chloride in the few experiments in dog No. 353 for which sufficient material was available.

COMPARISON OF THE PANCREATIC RESPONSE TO SECRETIN (S) AND HISTAMINE (H)

Dog with Gastrostomy (No. 353)

Exp. No.	Chloride Conc. (mEq./l.)			Chloride Output (micro-Eq.)		
	(S)	(H)	Ratio (H/S)	(S)	(H)	Ratio (H/S)
1	27	65	2.41	383	352	0.87
2	34	i	-	221	-	-
3	20	63	3.15	144	164	1.14
4	31	55	1.77	313	264	0.84
5	25	i	-	133	-	-
Mean	27	61	2.44	239	253	0.95

i - Insufficient material for chloride estimation.

Table Vl.

The chloride concentration after secretin with its range from 20 to 34 mEq./l. (mean 27 mEq./l.) is invariably less than that after histamine whose range is 55 to 65 mEq./l. (mean 61 mEq./l.). The mean ratio of these responses is 2.44, which is very similar to the ratio of the nitrogen concentrations. The total output of

chloride varies considerably, but once again, as in the nitrogen response the ratios are comparatively constant, being 0.84, 0.87 and 1.14. The mean of these three ratios is 0.95, which again tends towards unity. Thus as with nitrogen, secretin and histamine appear to evoke an equivalent total chloride response, the differences in concentration being balanced by the differences in fluid output.

If the chloride and bicarbonate concentrations in mEq./l. are summated, as in Table Vll, the total concentration varies

RELATIONSHIP OF THE BICARBONATE (B) AND CHLORIDE (C) CONCENTRATIONS IN THE PANCREATIC RESPONSE TO SECRETIN AND HISTAMINE

Dog with Gastrostomy (No. 353) **Conc. in mEq./l.**

Exp. No.	After Secretin			After Histamine		
	(B)	(C)	(B+C)	(B)	(C)	(B+C)
1	132	27	159	87	65	152
2	123	34	157	84	i	-
3	127	20	147	87	63	150
4	133	31	164	106	55	161
5	135	25	160	115	i	-
Mean	130	27	157	96	61	154

i - Insufficient material for chloride estimation.

Table Vll.

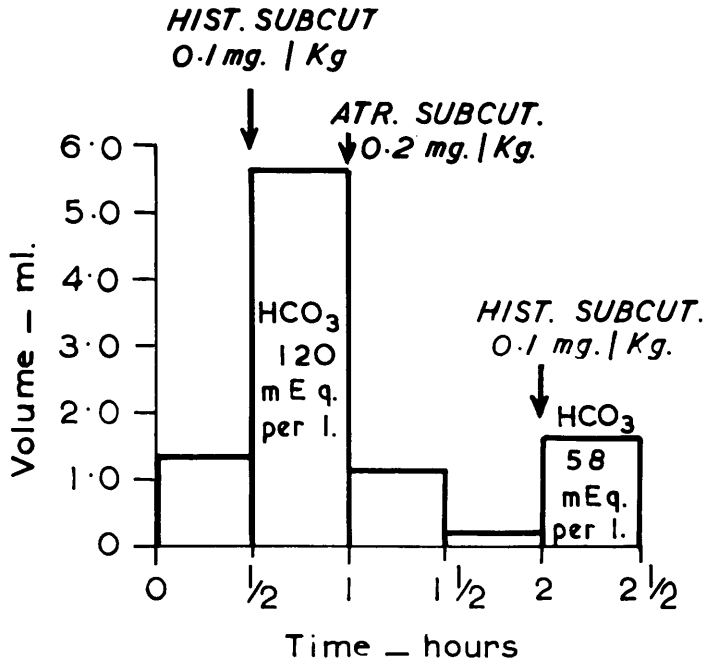
between 147 and 164 mEq./l. (mean 157 mEq./l.) after secretin, and from 150 to 161 mEq./l. (mean 154 mEq./l.) after histamine. The two means are almost identical, showing that the concentrations of bicarbonate and chloride are reciprocally related, as was first noted by Ball (1930) and confirmed by Hart and Thomas (1945).

The Effect of Atropine.

The second main group of experiments on the dogs with gastrostomies was designed to investigate the effect of atropine on the histamine response. As we have already mentioned, it was felt that the somewhat equivocal results obtained on the dogs with total gastrectomies may have been due to the fact that only half an hour was allowed between the injection of atropine and the subsequent injection of histamine. In view of this, in the following experiments a full hour was allowed for the atropine to take effect. The results of a typical experiment employing atropine are shown graphically in Fig. 18.

Histamine was given after a basal period with an output of 1.4 ml., and 5.6 ml. was collected in half an hour. Following this control run, atropine sulphate was administered subcutaneously and this was followed one hour later by a second injection of histamine and collection of 1.6 ml. secretion during a final half hour period. Thus the second histamine response constitutes a test response which can be compared with the first response, as a control on the same dog and day. About 15 minutes after the injection of

atropine secretion of saliva diminished, the tongue became dry, the pupils dilated, and the rate of gastric secretion diminished. The animal also became somewhat restless. Marked restlessness followed by exhaustion occurred in all three experiments in dog No. 341 and also in experiment 349-8.



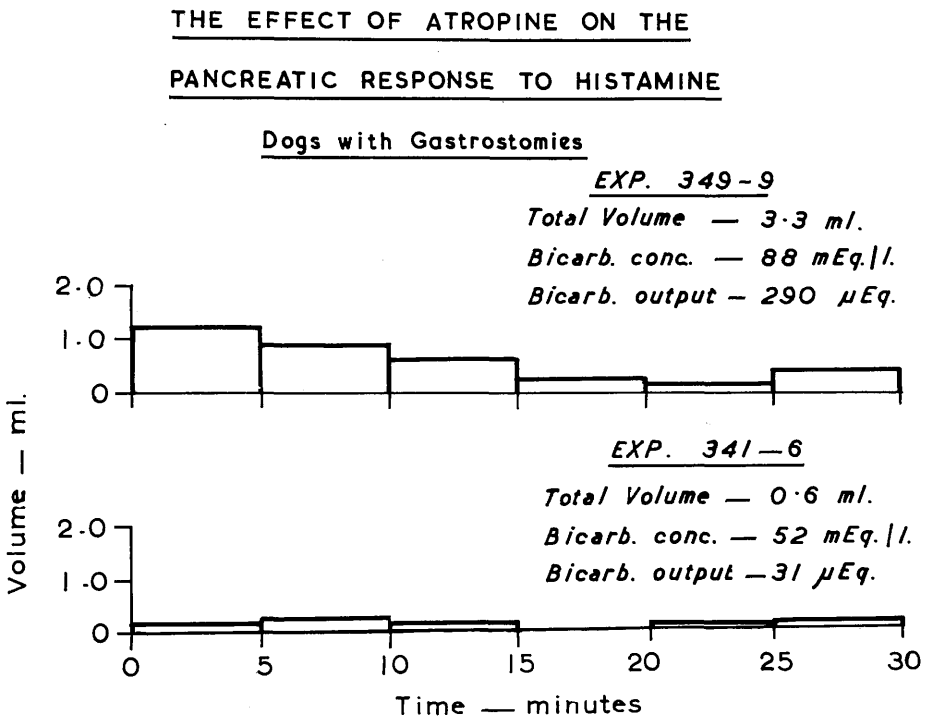
A typical experiment designed to compare the pancreatic responses to histamine before and after atropine. (Dog with gastrostomy. Exp. 349-12)

Fig. 18.

The Pattern of the Response to Histamine in the Atropinised Dog.

The pattern of the histamine response following atropine was also studied by means of minute-by-minute volume readings.

The latent period appeared to be more prolonged than before atropine - never less than 2 minutes and on 6 out of 12 occasions, five minutes or longer. The maximal response occurred indiscriminately in the second, third or fourth 5 minute period, and only once in the first. The response was almost invariably over by the end of 20 minutes. Two examples of this response are shown in Fig. 19.



Examples of moderate and almost complete inhibition of the histamine response by atropine are shown. The duration and peak of the response are both reduced.

Fig. 19.

Comparison of the Responses to Histamine before and after Atropine.

Twelve experiments utilising atropine were performed on four dogs, and the results are tabulated in Table V111.

COMPARISON OF THE PANCREATIC RESPONSE TO HISTAMINE (H) BEFORE AND AFTER ATROPINE (A)

Dogs with Gastrostomies

Dog No.	Exp. No.	Volume Response (Ml./half hour) Before (A)	After (A)	Ratio (A+H/H)	Bicarbonate Conc. (mEq./l.) Before (A)	After (A)	Ratio (A+H/H)	Bicarbonate Output (micro-Eq.) Before (A)	After (A)	Ratio (A+H/H)
341	6	2.3	0.6	0.26	90	52	0.58	207	31	0.15
	7	2.0	0.1	0.05	95	i	-	190	-	-
	8	2.3	0.9	0.39	93	66	0.70	214	59	0.28
Mean		2.2	0.5	0.23	93	59	0.64	203	45	0.22
343	6	1.9	0.2	0.11	50	i	-	95	-	-
	7	2.2	0.0	0.00	69	i	-	152	-	-
	8	2.7	1.0	0.37	70	24	0.34	189	24	0.13
Mean		2.3	0.4	0.16	63	24	0.34	145	24	0.13
348	7	4.7	2.3	0.49	68	56	0.82	320	129	0.40
	8	2.2	1.1	0.50	72	47	0.65	158	52	0.33
	9	3.5	1.5	0.43	72	46	0.64	252	69	0.27
Mean		3.5	1.6	0.47	71	50	0.70	243	83	0.33
349	8	2.5	2.5	1.00	91	71	0.78	228	178	0.78
	9	6.1	3.3	0.54	123	88	0.72	750	290	0.39
	12	5.6	1.6	0.29	120	58	0.48	672	93	0.14
Mean		4.7	2.5	0.61	111	72	0.66	550	187	0.44
Grand Mean		3.2	1.3	0.39	84	56^{x}	0.63^{x}	286	103^{x}	0.31^{x}
S.D.				0.28			0.15			0.20

. - Insufficient material for bicarbonate estimation.

x - Average of the 9 experiments for which data are available.

S.D. - Standard Deviation corrected for small numbers.

Table V111.

The same variability of response that has been noted in all previous tables is evident here also.

Volume Responses:- Atropine lowers the mean volume response to histamine from 3.2 ml. (range 1.9 to 6.1 ml.) to 1.3 ml. (range 0.0 to 3.3 ml.). The only failure to reduce the response was in Exp. 341-7 in which the volume remained unchanged. Apart from this one case, the ratios of the responses after atropine to the responses before it lie between 0.00 and 0.54, and the mean of all 12 experiments is 0.39 which indicates an average inhibition of 61 per cent. In 5 of the 12 experiments the response is reduced to pre-atropine basal levels and in two others it is only slightly greater, as can be seen by a comparison with Table IX which shows the basal secretory rates.

There seems little doubt that atropine inhibits the volume response to histamine under suitable dosage conditions, and that this inhibition can be complete under the experimental conditions and dosage employed in this study. A further examination of Table VIII shows that this also applies to basal secretory rate, the mean of which is reduced from 0.6 to 0.2 ml. (-67%) by atropine.

Bicarbonate Responses:- Similarly, in every case the bicarbonate concentration was lowered following atropine, usually by 30 to 40 mEq./l.. For those experiments in which the post atropine response was large enough to permit a bicarbonate determination, the ratio of the concentration with and without atropine varies

between 0.34 and 0.82 (mean 0.63). This reduction in bicarbonate concentrate may be merely a reflection of the correlation between electrolyte concentration and volume rate of secretion. The total bicarbonate output was also markedly and invariably reduced by atropine, the mean of the response to histamine being reduced from 286 to 103 micro-Eq.. The mean ratio was 0.31 indicating an average reduction of 69 per cent. The range is 0.13 to 0.78.

COMPARISON OF THE UNSTIMULATED PANCREATIC RESPONSE BEFORE AND AFTER ATROPINE (A)

Dogs with Gastrostomies

Dog No.	Exp. No.	Volume Response (Ml./half hour) Before (A)	After (A)	Dog No.	Exp. No.	Volume Response (Ml./half hour) Before (A)	After (A)
341	6	0.1	0.0	343	6	0.3	0.0
	7	0.0	0.0		7	0.2	0.0
	8	0.2	0.1		8	0.7	0.1
Mean		0.1	0.0	Mean		0.4	0.0
348	7	0.6	0.3	349	8	0.9	0.6
	8	0.6	0.2		9	1.5	0.4
	9	1.2	0.7		12	1.4	0.2
Mean		0.8	0.4	Mean		1.3	0.4
Grand Mean x		0.6	0.2				

x - Grand mean of all 4 dogs.

Table 1X.

ADDITIONAL EXPERIMENTS.

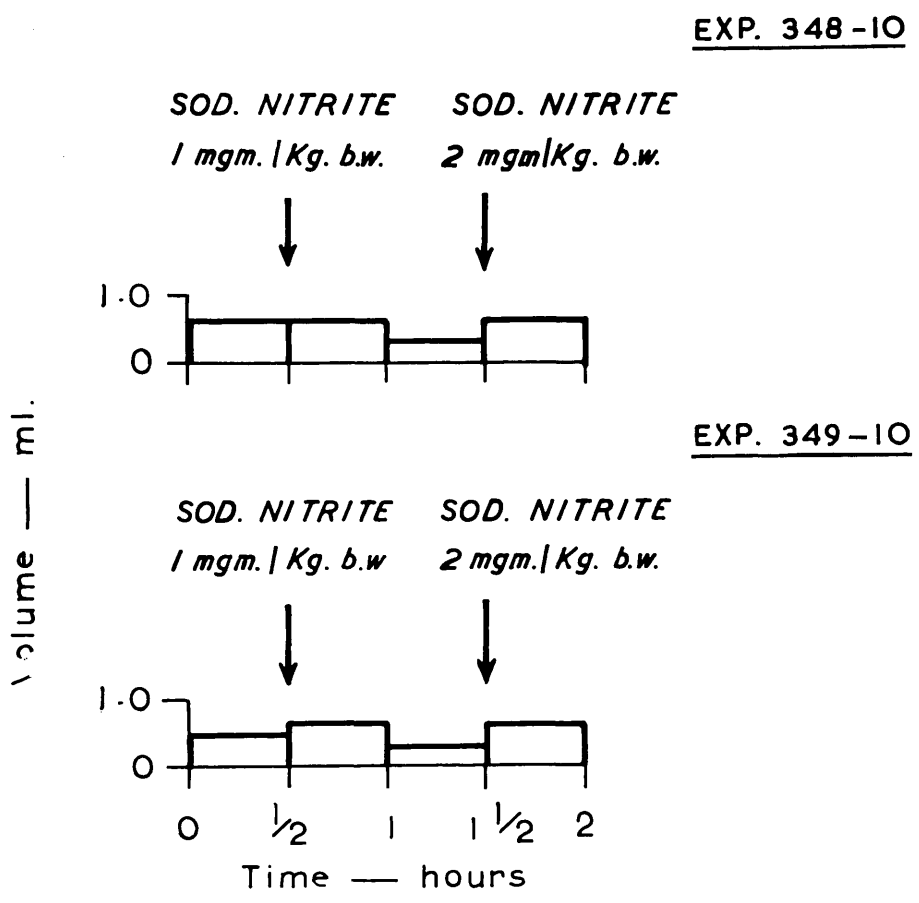
The Effect of Vasodilator Drugs and Histalog on Pancreatic Secretion.

Molinarri-Tosatti (1928) was the first to suggest that the action of histamine on the pancreas might be due to the vascular effects of the drug, though it had been thought for a long time that the pancreas was very sensitive to vascular influences (Gottlieb, 1894; Babkin, 1924). While the whole question of the relationship of pancreatic secretion to local blood flow is fully reviewed in Appendix A, the opportunity was taken to repeat one of the experiments of Barlow (1927b) which is used as evidence for the contention that an increase in blood flow through the pancreas will cause an increase in secretory rate. He injected 15 mgm. of sodium nitrite intravenously into 15 to 20 Kg. dogs under ether and sodium barbitone anaesthesia, having ligated their pylorus. He reported a response similar in profile to that following a control injection of secretin, and thought that this was due to an increase in blood flow produced by the vasodilator effect of sodium nitrite. The following experiments were carried out in the unanaesthetised animal with the usual precautions to prevent the activation of the endogenous secretin mechanism. In addition to sodium nitrite, the effect of glyceryl trinitrate was also investigated.

The Effect of Sodium Nitrite and Glyceryl Trinitrate on Pancreatic Secretion.

Two experiments were performed using sodium nitrite in doses of 1 and 2 mgm./Kg. body weight intravenously. The former

is about the same as the dose used by Barlow. The results are shown in Fig. 20.

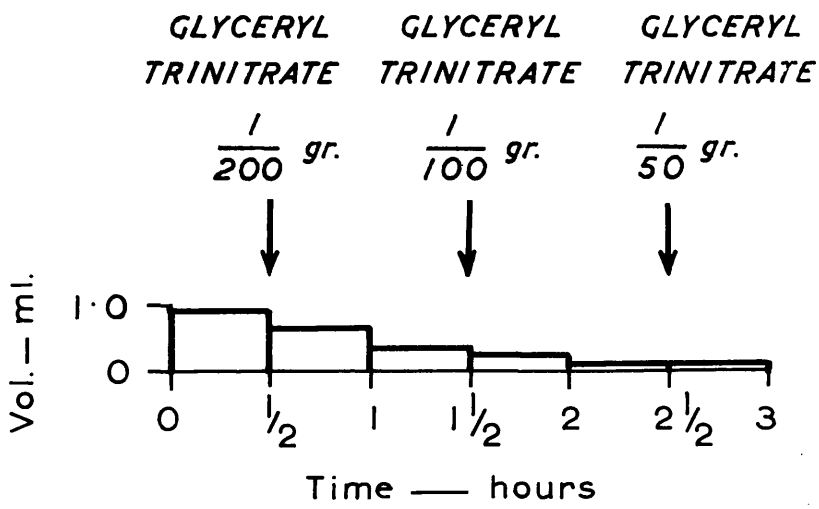


In neither of these experiments is there any response to sodium nitrite, and the variations which occur are well within the normal limits of basal secretory rate.

Fig. 20.

It is obvious that sodium nitrite has no effect on these experiments. A further experiment was therefore performed using glyceryl trinitrate in doses of 1/200, 1/100, and 1/50 grain intravenously. The result is shown in Fig. 21.

THE EFFECT OF GLYCERYL TRINITRATE ON PANCREATIC SECRETION



Glyceryl trinitrate has been given in 3 different doses. There is a steady decrease in secretory rate despite the attempts at stimulation. (Dog with gastrostomy. Exp.348-11)

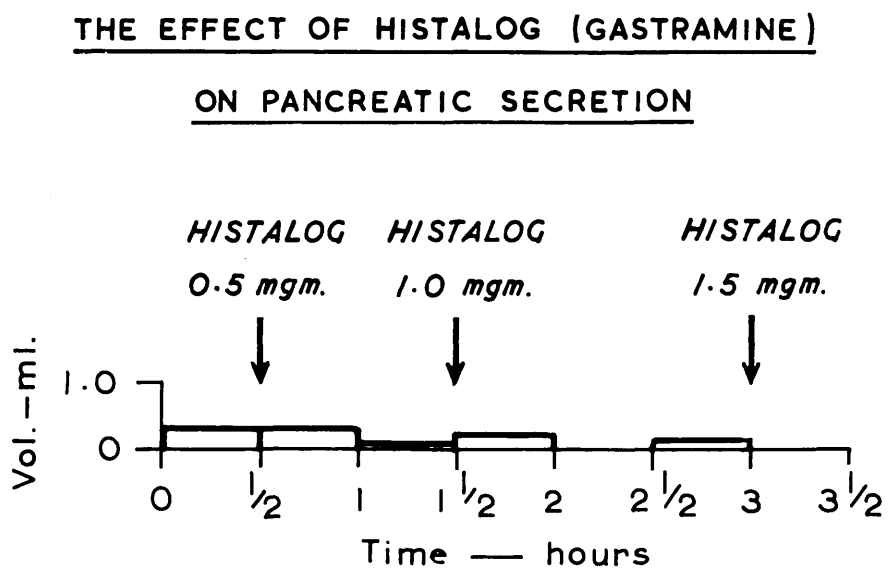
Fig. 21.

Once again it is obvious that there is no response.

The Effect of Histalog (Gastramine) on Pancreatic Secretion.

Rosiere and Grossman (1951) have shown that Histalog or Gastramine (3-beta-aminoethylpyrazole), which is an analog of histamine, has a histamine-like action on gastric secretion without the systemic effects, whether it be given subcutaneously, intramuscularly or intravenously. Dreiling (1954) investigated

the effect of this substance on pancreatic secretion in man and although he detected no response, it was felt worthwhile to investigate its effect on the dog. Histalog (Eli Lilly) was used in doses of 0.5, 1.0, and 1.5 mgm./Kg. body weight subcutaneously. The results of these experiments are shown in Fig. 22.

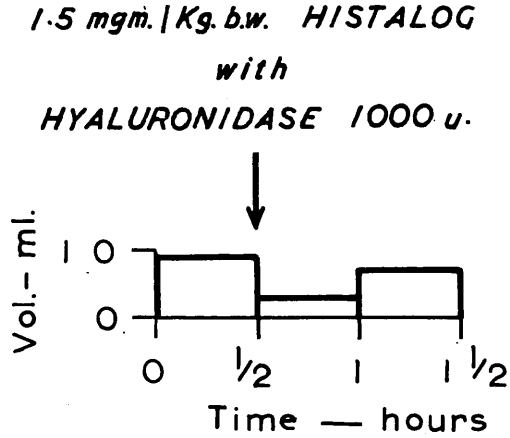


Histalog has been given in 3 different doses. There is no variation in the secretory rate which can be attributed to the injections. (Dog with gastrostomy. Exp. 341-5)

Fig. 22.

It is clearly seen that there is no detectable response. Since it was possible that this might have been due to poor absorption the experiments were repeated using a dose of 1.5 mgm./KG. body weight subcutaneously along with 1 ml. hyaluronidase to aid absorption. Fig. 23 shows that this also failed to produce a response.

THE EFFECT OF HISTALOG (GASTRAMINE) ON PANCREATIC SECRETION



In this experiment Histalog is given along with hyaluronidase in order to increase the rate of absorption. No response is obtained. (Dog with gastrostomy. Exp. 348-7)

Fig. 23.

DISCUSSION.

Before summarising the results and discussing their significance, it is particularly necessary to examine the reliability of the data in view of the experimental method used. It will be remembered that the main object was to obtain pancreatic secretion in such a way that the fallacy due to the activation of the endogenous secretin mechanism was excluded. It was because total gastrectomy did not prove to be an ideal method, in that operative interference was considerable and the dogs steadily deteriorated, that the

experiments were repeated on dogs with gastrostomies. This method, however, reintroduced an old problem, namely the difficulty of being absolutely certain that there was no contamination of the duodenum with gastric juice. Very frequent duodenal pH readings were therefore taken to make sure that the conditions of the experiment remained satisfactory.

Thomas and Crider (1940) have shown that secretin is not elaborated at a pH above 4. Thus the maintenance of a pH above this level ensures the absence of any endogenous secretin effect. This was attained in 55 (91%) out of the 60 experimental periods under discussion involving the use of secretin or histamine. In fact, in 45 (75%) of the 60 experimental periods the pH remained in the region of 7 to 8 throughout the entire half hour. In 10 occasions (16%) the pH fell for a minute or so, but never below 4. However, in the remaining 5 periods (9%) the pH did fall as low as 2; but it never remained at this level for as long as a minute - as a result of the suddenness with which the gastric juice entered the duodenum and the rapidity with which it was expelled through the duodenostomy. It should be pointed out that if a low pH reading was obtained it was checked every few seconds so that its exact duration could be known. Furthermore, this very temporary acidification occurred only in the last 10 minutes of the collection period when the main secretory response was over. Since, even in these 5 experiments, the minute-by-minute volume curve showed no upward deviation in its downward trend - such as would have occurred had an endogenous secretin

effect suddenly been imposed on the experimental situation, the data from these experiments have not been excluded. A few experiments in which these criteria could not be satisfied were discarded. The above data constitute good evidence of the satisfactory nature of the experimental method in excluding the endogenous secretin mechanism.

The Response to Histamine:- Once again we have been able to show that histamine evokes a considerable response from the pancreas in the absence of duodenal contamination. This response was never less than 30 per cent, frequently greater than 50 per cent, and on four occasions greater than 100 per cent of the response to secretin as far as volume was concerned. While the bicarbonate concentration was less than 60 per cent on only one occasion (Exp. 348-5) the total bicarbonate output was sometimes as low as 19 per cent of the secretin response.

The nitrogen concentration after histamine was about $2\frac{1}{2}$ times the concentration after secretin (mean ratio 2.41) but the total nitrogen outputs were almost identical (mean ratio 0.93) suggesting that the differences in the concentrations were due to the differences in fluid output in response to the two stimuli. Another possibility is that this indicates a simple washing out of enzyme without any actual stimulation.

The chloride picture was very similar to the nitrogen picture. The concentration after histamine was also about $2\frac{1}{2}$ times the concentration after secretin (mean ratio 2.44), but

again the total chlorides were almost identical (mean ratio 0.95), again suggesting that the differences in the concentrations might be due to the differences in the corresponding fluid outputs. However, both in the case of chloride and in the case of nitrogen, it would be very dangerous to argue from somewhat inadequate data, and these impressions might be fallacious. In the case of the chloride concentrations this might be due to the fact that there is a reciprocal relationship between it and the bicarbonate concentration (Hart and Thomas, 1945).

In general profile, in the length of the latent period, in the timing of the peak of the peak of the response, and in its duration, the responses to secretin and histamine are very similar. When the results obtained in the dogs with total gastrectomies are compared with those obtained in the dogs with gastrostomies, they are found to be very close. The grand mean of the ratios for the responses in the two groups of experiments are shown in Table X.

There is considerable agreement in the two sets of figures particularly in the bicarbonate concentration. This similarity in the results using two different preparations is further evidence of the significance of the pancreatic response to histamine which is, on the average, between 50 and 80 per cent of the response to secretin and may on occasion be even greater than it. It is also a further measure of the reliability of the results obtained using dogs with gastrostomies.

RATIO (H/S) OF THE PANCREATIC RESPONSES TO HISTAMINE (H) AND SECRETIN (S)

Comparison between dogs with Gastrostomies and Total Gastrectomies.

	Grand Mean Ratio (H/S)	
	Total Gastrectomy	Gastrostomy
Volume Response (Ml./half hour)	0.75 ± 0.55	0.62 ± 0.41
Bicarbonate Conc. (mEq./l.)	0.79 ± 0.25	0.77 ± 0.16
Bicarbonate Output (micro-Eq.)	0.68 ± 0.77	0.51 ± 0.42

Table X.

The Effect of Atropine:- In this group of experiments atropine produces a marked diminution of the histamine response. In only 2 out of 12 experiments did atropine fail to reduce the volume response by more than 50 per cent, and in only 1 experiment did it fail to reduce the total bicarbonate output by more than 50 per cent, and in at least 3 experiments the inhibition was complete.

The increased efficiency of atropine as an inhibitory agent in this second group of experiments is well shown in Table XI where the ratios of the responses to histamine after atropine to the response before it are compared in the two groups of experiments.

RATIO (A+H/H) OF THE PANCREATIC RESPONSE TO HISTAMINE (H) BEFORE AND AFTER ATROPINE (A)

Comparison between dogs with Gastrostomies and Total Gastrectomies.

	Grand Mean Ratio (A+H/H)	
	Total Gastrectomy	Gastrostomy
Volume Response (Ml./half hour)	0.76 ± 0.50	0.39 ± 0.28
Bicarbonate Conc. (mEq./l.)	0.94 ± 0.54	0.63[x] ± 0.15
Bicarbonate Output (micro-Eq.)	0.88 ± 1.01	0.31[x] ± 0.20

x - Excluding 3 samples too small for analysis.

Table XI.

It can be seen that reductions of 0.37 and 0.57 have occurred in the ratios of volume and total bicarbonate output respectively in the dogs with gastrostomies as compared with the dogs with total gastrectomies. In other words, in the second group of experiments the volume and total bicarbonate output were reduced by a further 37 and 57 per cent respectively over the reduction achieved in the first group. On the average, therefore,

the volume response to histamine is reduced by 61 per cent, the bicarbonate concentration by 37 per cent, and the total bicarbonate output by 69 per cent in all, and the inhibition may on occasion be complete. It is felt that these figures are good evidence that atropine inhibits the pancreatic response to histamine.

In our review of the literature we pointed out the possibility that the failure of MacKay (1930) in particular to demonstrate atropine inhibition of the histamine response may have been due to the fact that insufficient time was allowed for the atropine to take effect. It was this criticism which made us extend the interval between the injection of atropine and the subsequent injection of histamine from half an hour in the first group of experiments to one hour in the second group of experiments. The improvement obtained in the inhibitory effect as a result of this change is confirmation of the explanation offered.

The Effect of Vasodilator Drugs:- We have been unable to demonstrate any effect on pancreatic secretion by the use of vasodilator drugs such as sodium nitrite and glyceryl trinitrate in the 3 experiments performed. This contradicts the findings of Barlow (1927b) although the dosage of sodium nitrite used was approximately the same. The explanation for this may be that Barlow's dogs were anaesthetised and there may have been a potentiating effect between sodium nitrite and the anaesthetics used.

However, the question of the influence of the rate of blood flow through the pancreas on the pancreatic secretory rate is a crucial one, since the effect of histamine on pancreatic

secretion has so often been ascribed, in the past, to an increase in blood flow through the gland produced by the vasodilator effects of the drug (Molinarri-Tosatti, 1928; Babkin, 1950; Thomas, 1950). Because of this, a detailed review of the evidence on the relation-:ship between pancreatic secretory rate and local blood flow was made in addition to the above experiments. This review has been placed in Appendix A as it would be cumbersome to introduce at this point in the discussion. The evidence suggests that rate of blood flow has little effect on the rate of secretion, provided that there is a sufficient blood supply for the nutrition of the cells and to provide fluid for secretion.

The Effect of Histalog:- In the experiments with Histalog no pancreatic response was obtained even when hyaluronidase was used to increase the rate of absorption. This occurred despite the fact that the dosage of Histalog was sufficient to evoke a considerable gastric acid response, and is in agreement with the findings of Dreiling (1954) in man. The complete lack of pancreatic response in the presence of a considerable gastric acid response is further evidence of the efficiency with which the endogenous secretin mechanism was excluded by the use of a gastrostomy to keep the stomach empty.

Both in this chapter and in the last the occurrence of an occasional extraordinary increase in the responses to secretin and histamine on a particular day was pointed out. The reason for this is not clear. At first it was thought that an additional accessory pancreatic duct had remained untied at the original operation/

and normally acted as a by-pass. If this by-pass were occasionally blocked then a larger volume than usual would be secreted through the cannulated main duct. However, there was no visual evidence of such a leak by direct inspection of the duodenum through the Thomas cannula and no evidence of any additional untied duct was found at post-mortem. Therefore the possibility remains that some other factor influences the day to day level of the pancreatic secretory output in response to secretin and histamine.

SUMMARY.

The action of histamine on pancreatic secretion has been studied in 5 dogs in which the endogenous secretin mechanism was excluded by the use of a gastrostomy to keep the stomach empty.

The responses to histamine and to control injections of secretin are similar to those obtained in the dogs with total gastrectomies. The profiles of the two responses again exhibit great similarity in respect of latent period, duration and timing of the peak of the response.

The volume response to histamine was about 60 per cent of the response to control injections of secretin. The bicarbonate concentration was about 75 per cent, and the total bicarbonate output was about 50 per cent of the corresponding secretin response.

The chloride and nitrogen concentrations in response to histamine were estimated in one dog and were about 2½ times those in response to secretin, but the total outputs were about equal.

The effect of atropine on the histamine response was

studied in four of the dogs. Atropine inhibits the histamine response to a considerable degree and may even do so completely.

Sodium nitrite, glyceryl trinitrate, and histalog have no effect on canine pancreatic secretion under the conditions and dosage used.

CHAPTER VI

THE EFFECT OF VAGOTOMY ON PANCREATIC SECRETION.

There are two points at which atropine may inhibit the pancreatic response to histamine; it may act on the secretory cell itself, or it may block the vagal nerve endings. In order to localise this action, it seemed logical to investigate the effect of vagotomy on the pancreatic response to histamine. If no inhibition were produced, it would suggest that atropine acted on the secretory cell itself; if inhibition did occur, it would suggest that the vagus played some part in the histamine response and that this was blocked by atropine. At the same time the effect of vagotomy on the secretin response could also be observed as a control.

There is still considerable doubt as to the precise function of the vagus nerves in the control of pancreatic secretion. It is generally believed that the vagus is mainly concerned with the enzyme of the gland in contradistinction to the HCl- secretin mechanism which controls water and bicarbonate output (Mellanby, 1925). However, the matter is not quite so clear cut. There is evidence that the vagus contains both secretory and inhibitory fibres and it has therefore been suggested that the part is plays is that of a tonus mechanism which may augment or inhibit local reflexes (Crider and Thomas, 1944). It was hoped that a study of the effect of vagotomy on the pancreatic response to secretin and histamine would throw some light on these matters as well as on the mode of action of atropine.

LITERATURE.

There have been remarkably few references to the effect

of vagotomy on pancreatic secretion. The earliest study was that of Popielski (1901) who observed no effect on the response to intraduodenal HCl in the anaesthetised dog. Shortly afterwards Buchstab (1904) showed that vagotomy increased the spontaneous secretin in acute experiments on a dog with a duodenal fistula, gastric fistula, gastro-enterostomy and divided pylorus. However, Tonkich (1924), using a similar preparation, found the opposite effect. Crider and Thomas (1944) observed a reduction in the volume and total nitrogen output in response to intraduodenal peptone and HCl, though not to soap, following vagotomy in chronic preparations. Pincus, Thomas and Lachman (1948) observed a similar reduction in the volume and total nitrogen output in response to milk, meat, bread and olive oil in a single dog. On the other hand, Thomas and Crider (1946) reported that degeneration of one vagus cut 10 days prior to experimentation appeared to enhance the response to stimulation of the other. In none of these investigations was the effect of vagotomy on the response to secretin or histamine studied.

Mellanby (1925) in acute experiments in cats, found no change in the volume or bicarbonate outputs in response to secretin, but noted a reduction of 20-50% in the enzymes. In the dog, however, Barlow (1927a) found the volume response to secretin slightly reduced following cervical vagotomy but thought that the change was insignificant in degree and due to a reduction in blood flow through the pancreas. Recently, however, Routley et al. (1952) carried out

a study in unanaesthetised dogs in which no attempt was made to exclude gastric contents from the duodenum. The volume response to secretin was increased by 110 per cent following vagotomy, and although the enzyme concentration was diminished, the total output was also increased. All these results were statistically significant. The volume response to histamine was reduced but, in the type of preparation they used, this may well have been due to a reduction in the gastric acid response to histamine which also follows vagotomy (Oberhelman and Dragstedt, 1948), with a secondary reduction in the HCl endogenous secretin mechanism. However, this possibility, if anything, enhances the validity of the observations on the secretin response. They favoured the hypothesis of Crider and Thomas (1944) that the vagus acted as a tonus mechanism which may augment or inhibit local reflexes.

In a study carried out on human subjects, Shimgleton et al. (1951) could detect no rise above the basal level in the volume or enzyme response to secretin in 7 patients with a transthoracic vagotomy as compared to 13 normal subjects, although the resting volume was increased 5 times. On the other hand, Dreiling et al. (1952) could detect no significant difference in the response to secretin between one group of patients with vagotomy and another group without. This however, was a comparison between a normal group of subjects and agroup who had undergone oesophago-gastrectomy for carcinoma.

METHODS.

Preparation:- Four mongrel bitches weighing 15 to 20 Kg.

with gastrostomies and duodenostomies were used. Sufficient control data were collected on the animals while the vagi were still intact and then a supra-diaphragmatic vagotomy was carried out. Under intravenous nembutal (veterinary) anaesthesia 30 mgm./Kg. body weight with oxygen supplied under positive pressure through a cuffed endotracheal tube, and supplemented by ether if necessary, the chest was opened in the 8th or 9th left interspace. The branches of the vagus were identified, a 2 cm. portion excised and the ends ligated.

In the dog the vagus consists of two branches a short distance above the diaphragm. These two branches lie in contact with the oesophagus and become the anterior and posterior gastric branches, but in most cases a third branch of about equal size was observed which comes off the left vagus one or two inches above the diaphragm and leaves the oesophagus to course down the posterior thoracic and posterior abdominal wall to end in the region of the coeliac plexus. As it seemed likely that this branch might supply fibres to the pancreas which lies in close proximity to the coeliac plexus, particular care was taken to divide this branch and any other additional filaments as well as the two main branches.

Experiments were then repeated so as to compare the results before and after vagotomy.

Experimental Procedure:- The experiments were carried out as already described using secretin and histamine as stimuli. The usual precautions were taken that the pancreas was secreting

at basal rates before an injection was administered and had returned to basal rates before a subsequent stimulus was given. Care was also taken that no HCl entered the duodenum and the duodenum pH was checked at least at one minute intervals throughout every period following stimulation. Out of 110 such periods of observations, in only 6 (5%) did the pH even momentarily fall below 4 - the level above which no secretin is elaborated. This occurred towards the end of the period and was unaccompanied by any increase in the prevailing rate of secretion. Experiments in which these criteria were not satisfied were discarded.

After vagotomy experiments were carried out at frequent intervals from the 6th or 7th day until the 24th or 25th day, so that any transient changes in secretory pattern might be picked up. It was assumed that after this time all divided fibres would have degenerated. Further experiments were then carried out after 7 or 8 weeks and again after about 3½ months in order to establish whether the pattern and order of the response was maintained.

The volume and bicarbonate concentrations of each half hour sample was estimated and the total bicarbonate output calculated from them. In one dog (No. 353) N and Cl were also estimated and the total outputs calculated.

The statistical significance of the effects of vagotomy on all these results was evaluated by means of Student's 't' test corrected for small numbers of samples.

Insulin tests for the completeness of vagotomy were

carried out as described by Hollander (1948) and were all negative. However, this is only evidence that the fibres to the stomach were divided and provides no evidence that all fibres to the pancreas were similarly divided.

RESULTS.

The Basal Secretory Rate.

The results are summarised in Table XII and the detailed data from which this summary was made are shown in Tables XII a, b, c, and d, in Appendix A.

THE EFFECT OF VAGOTOMY ON PANCREATIC BASAL SECRETORY RATE

Rate in Ml./half hour.

Dog No.	Before Vagotomy Mean ± S.D.	After Vagotomy Mean ± S.D.	Increase	Significance Test t	n	p
341	0.31 ± 0.37 (21)[x]	0.35 ± 0.35 (16)	+0.04 (+13%)	0.35	35	0.74
348	0.64 ± 0.45 (25)	1.00 ± 0.58 (16)	+0.36 (+56%)	2.18	39	0.034
349	1.31 ± 0.41 (23)	0.87 ± 0.54 (13)	-0.44 (-34%)	2.70	34	0.012
353	0.93 ± 0.41 (8)	0.55 ± 0.10 (7)	-0.38 (-41%)	1.81	13	0.098

S.D. - Standard Deviation of the distribution.

x - The figures in parentheses indicate the number of observations on which the mean is based.

Table XII

The average volumes vary from 0.31 to 1.31 before vagotomy, and from 0.35 to 1.00 ml. after vagotomy. In two dogs the response was slightly increased and in two the response was slightly decreased

following vagotomy. In no case was the variation in response statistically significant at the 1% level of probability using Student's 't' test corrected for small numbers.

The Response to Secretin.

The volume and bicarbonate data are summarised in Table XIII and the individual results given in Table XIII a, b, c, and d, in Appendix A.

The general pattern of the response after vagotomy was essentially unchanged as regards latent period, duration of response, and timing of the peak of the response, from that already described. There is the usual variation from dog to dog, and to a lesser extent, from day to day in the secretory rate, bicarbonate concentration and total bicarbonate output of the pancreatic juice.

Volume Responses:- In every dog the mean volume of the response is increased by vagotomy. In dogs 341 and 348 the volumes increased 453 and 159 per cent respectively and this increase was statistically significant at the 1% level of probability. In the remaining 2 dogs the increase was not statistically significant.

Bicarbonate Responses:- There is little difference in the bicarbonate concentrations except that in dog No. 341 where the volume changes are greatest there is a statistically significent increase of 35 per cent. This might be expected from the relationship which exists between volume rate of secretion and bicarbonate concentration of the juice. (Hart & Thomas, 1945). The remarkable consistency of the bicarbonate concentration of the juice in the face of marked day

THE EFFECT OF VAGOTOMY ON THE PANCREATIC RESPONSE TO SECRETIN

	Mean Volume Response (Ml./half hour)	Mean Bicarbonate Conc. (mEq./l.)	Mean Bicarbonate Output (micro-Eq.)
	Dog No. 341		
Before Vagotomy (5)[x]	1.3 ± 0.44[y]	89 ± 13.2	119 ± 59.1
After Vagotomy (7)	7.2 ± 1.95	120 ± 10.6	856 ± 219.4
Increase	5.9 (453%)	31 (35%)	737 (619%)
t	4.63	3.46	5.12
n	8	8	8
p	0.0018	0.0082	0.001
	Dog No. 348		
Before Vagotomy (4)	5.1 ± 1.23	116 ± 13.1	596 ± 173.3
After Vagotomy (7)	13.2 ± 3.69	112 ± 7.4	1496 ± 488.7
Increase	8.1 (158%)	-4 (-3%)	900 (151%)
t	3.87	0.69	3.22
n	9	9	9
p	0.0038	0.50	0.011
	Dog No. 349		
Before Vagotomy (5)	11.3 ± 5.05	132 ± 4.2	1509 ± 725.2
After Vagotomy (7)	12.7 ± 2.58	136 ± 1.6	1735 ± 355.5
Increase	1.4 (12%)	4 (3%)	226 (15%)
t	0.53	1.77	0.59
n	8	8	8
p	0.62	0.11	0.57
	Dog No. 353		
Before Vagotomy (5)	8.7 ± 3.57	130 ± 4.9	1129 ± 481.1
After Vagotomy (6)	11.1 ± 2.84	128 ± 5.6	1427 ± 386.3
Increase	2.6 (30%)	-2 (-2%)	298 (26%)
t	1.15	0.64	1.05
n	9	9	9
p	0.27	0.54	0.34

x - The figures in parentheses indicate the number of observations on which the mean is based.
y - Standard Deviation corrected for small numbers.

Table XIII.

to day variation in the volumes in each individual dog which we noted before is of considerable interest.

The total bicarbonate output was also invariably increased by vagotomy but was statistically significant in dogs No. 341 and 348 only.

Nitrogen and Chloride Responses:- The nitrogen and chloride data are summarised in Table XIV, and the individual results are shown in Tables XIVa and XIVb in Appendix A.

THE EFFECT OF VAGOTOMY ON THE PANCREATIC RESPONSE TO SECRETIN

Dog No. 356	Mean Nitrogen Conc. (mMols./l.)	Mean Nitrogen Output (microMols.)
Before Vagotomy (5)[x]	113 ± 34.8[y]	973 ± 422.1
After Vagotomy (6)	87 ± 6.7	951 ± 224.8
Increase	-26 (-23%)	-22 (-2%)
t	1.62	0.10
n	9	9
p	0.14	0.93
	Mean Chloride Conc. (mEq./l.)	Mean Chloride Output (micro-Eq.)
Before Vagotomy (5)	27 ± 5.4	239 ± 108.1
After Vagotomy (6)	33 ± 5.5	463 ± 237.9
Increase	6 (22%)	224 (93%)
t	1.62	1.76
n	9	9
p	0.14	0.12

x - The figures in parentheses indicate the number of observations on which the mean is based.
y - Standard Deviation corrected for small numbers.

Table XIV.

The nitrogen concentration is slightly reduced in the one dog (No. 353) in which this was estimated, but this reduction of 23 per cent is not statistically significant. The total nitrogen outputs are almost identical, vagotomy only producing a reduction of 2 per cent. The increase of 22 per cent in the chloride concentration in this dog was also not statistically significant, nor was the increase of 93 per cent in the total chloride output.

Experiments were carried out from the 6th to the 113th day. Throughout this period of 16 weeks there was no particular systematic trend in the pancreatic responses.

The Response to Histamine.

The volume and bicarbonate data are summarised in Table XV, and the detailed results given in Tables XVa, b, c, and d, in Appendix B.

As in the case of the response to secretin, the general pattern of the response to histamine did not change after vagotomy, and the usual variations occurred from dog to dog and from day to day.

Volume Responses:- The volume response was increased by vagotomy in every dog. The increases of 163 and 131 per cent in dogs

THE EFFECT OF VAGOTOMY ON THE PANCREATIC RESPONSE TO HISTAMINE

	Mean Volume Response (Ml./half hour)	Mean Bicarbonate Conc. (mEq./l.)	Mean Bicarbonate Output (micro-Eq.)
	Dog No. 341		
Before Vagotomy (8)[x]	1.9 ± 0.62[y]	90 ± 6.0	168 ± 64.1
After Vagotomy (7)	5.0 ± 2.22	100 ± 5.6	496 ± 191.5
Increase	3.1 (163%)	10 (11%)	328 (195%)
t	3.62	3.26	4.25
n	13	13	13
p	0.0034	0.006	0.001
	Dog No. 348		
Before Vagotomy (6)	3.5 ± 1.30	72 ± 11.6	248 ± 102.2
After Vagotomy (7)	8.1 ± 1.22	84 ± 12.6	688 ± 173.8
Increase	4.6 (131%)	12 (17%)	440 ± (177%)
t	6.11	1.70	5.00
n	11	11	11
p	0.0001	0.12	0.0004
	Dog No. 349		
Before Vagotomy (6)	4.9 ± 1.30	109 ± 13.3	545 ± 192.5
After Vagotomy (7)	5.4 ± 2.52	107 ± 8.7	584 ± 308.1
Increase	0.5 (10%)	-2 (-2%)	41 (8%)
t	0.44	0.41	0.26
n	11	11	11
p	0.68	0.70	0.80
	Dog No. 353		
Before Vagotomy (5)	3.4 ± 1.49	96 ± 13.9	320 ± 144.9
After Vagotomy (6)	4.5 ± 1.54	85 ± 11.2	384 ± 175.8
Increase	1.1 (32%)	-15 (-14%)	64 (20%)
t	1.07	0.48	0.58
n	9	9	9
p	0.30	0.62	0.57

x - The figures in parentheses indicate the number of observations on which the mean is based.
y - Standard Deviation corrected for small numbers.

Table XV.

Nos. 341 and 348 respectively were statistically significant, but the increases of 10 and 32 per cent in the other two dogs were not significant.

Bicarbonate Responses:- The bicarbonate concentrations are slightly increased in dogs Nos. 341 and 348, and slightly decreased in dogs Nos. 349 and 353. The rise of 11 per cent in dog No. 341 is statistically significant. Once again this is to be expected from the relationship between bicarbonate concentration and secretory rate. The total bicarbonate outputs parallel the volume responses, there being a statistically significant increase in dogs Nos. 341 and 348, and an insignificant increase in the others.

Nitrogen and Chloride Responses:- The nitrogen and chloride data are summarised in Table XVI, and the individual results given in Tables XIVa and XIVb in Appendix B.

Although this time there is a slight rise in the nitrogen concentration (3%), and also in the total nitrogen output (39%) following vagotomy, instead of the fall which characterised the secretin response, there is an equal lack of statistical significance in the results. The increases in the chloride concentration (7%) and total chloride output (21%) are of a similar order and also not statistically significant, but are less than the corresponding increases in the secretin response.

The pancreatic responses to histamine also show no systematic trend during the 16 weeks of experimentation.

THE EFFECT OF VAGOTOMY ON THE PANCREATIC RESPONSE TO HISTAMINE

Dog No. 353	Mean Nitrogen Conc. (mMols./l.)	Mean Nitrogen Output (microMols.)
Before Vagotomy (5)[x]	266 ± 63.8[y]	927 ± 474.8
After Vagotomy (6)	274 ± 82.4	1286 ± 736.8
Increase	8 (3%)	359 (39%)
t	0.16	0.85
n	9	9
p	0.88	0.44
	Mean Chloride Conc. (mEq./l.)	Mean Chloride Output (micro-Eq.)
Before Vagotomy (3)	61 ± 5.3	253 ± 84.5
After Vagotomy (5)	65 ± 5.5	306 ± 81.6
Increase	4 (7%)	53 (21%)
t	0.76	0.79
n	6	6
p	0.48	0.45

x - The figures in parentheses indicate the number of observations on which the mean is based.
y - Standard Deviation corrected for small numbers.

Table XVI.

DISCUSSION.

The occurrence of a momentary fall in duodenal pH below 4 in only 6 (5%) of the 110 experimental periods involving a response to secretin or histamine in this series of experiments, without any

alteration in the prevailing secretory rate, is satisfactory evidence of the reliability with which duodenal contamination by acid was prevented, and the endogenous secretin mechanism excluded. It is a good measure of the acceptability of the data.

The effects of vagotomy in the present study may be summarised as follows:-

1) Vagotomy has no significant effect on the volume rate of basal secretion.

2) The volume response to secretin and histamine are invariably increased, and in the two dogs in which this increase was greater than 100 per cent it was statistically significant.

3) The bicarbonate concentrations remained more or less constant, except for a rise when the volume changes were maximal.

4) The total bicarbonate output increased in line with the increase in the volumes.

5) Apart from a decrease in the nitrogen output and concentration in response to secretin following vagotomy, the chloride and nitrogen responses in response to both secretin and histamine were all increased. None of these variations were significant statistically.

6) The post-vagotomy secretory pattern persisted for at least $3\frac{1}{2}$ months, as long as observations continued.

Basal Secretion:- The conflict in the findings of Buchstab (1904)

and Tonkich (1924), on the effect of vagotomy on basal secretion, fits in with our own observations that both increases and decreases occur, but none of them large enough to be significant at the 1% level of probability. This suggests that the vagus plays little part in the production or regulation of the secretion of water or bicarbonate in the unstimulated gland. However, the observation of Shingleton et al. (1951) in man, that the basal volume is increased 5 times by vagotomy, is at variance with this.

Volume:- The post-vagotomy increase in the volume response to both secretin and histamine is invariable and particularly striking in dogs No. 341 and 348 - the same two dogs which showed an increase in basal secretory activity instead of a decrease, and can be explained in a number of ways. First, the vagus may exert a tonic inhibitory effect on stimulated pancreatic secretion by direct action on the secretory cell, or indirectly, via local reflex arcs. Second, denervation of the pancreas may induce a state of hypersensitivity of the end-organ to the action of certain stimuli, a phenomenon generally recognised in other structures (Cannon & Rosenblueth, 1949).

VAGAL INHIBITION:- The presence of vagal inhibitory fibres to the pancreas has been entertained ever since Claude Bernard (1856) noted that vomiting and inhibition of pancreatic secretion occurred together. Bernstein (1870), and later, Gottlieb (1894) followed up this observation and demonstrated that pancreatic secretion could be inhibited by stimulation of the central end of a single

cut vagus. However, since the spinal cord, the splanchnic nerves and the remaining vagus were all intact, it was impossible to say by which route the inhibitory impulses were being transmitted. Pavlov (1893) thought that the presence of vagal inhibitory fibres might explain certain peculiarities in the response to stimulation of the peripheral end of a divided vagus. Initially there was a long latent period, but this became progressively shorter as stimulation was repeated. This was thought to be because the inhibitory fibres required to be fatigued before the pancreas could respond positively to stimulation. In addition, if the pancreas were already secreting in response to intraduodenal HCl, secretin or vagal stimulation, stimulation of the peripheral vagus would inhibit it (Anrep, 1914).

Popielski (1896) demonstrated that stimulation of the peripheral vagus could inhibit the secretory activity induced by HCl in the intestine. He also reported that certain branches of the vagi were purely inhibitory while others were purely excitatory; a finding which Anrep (1914) could not confirm. This investigator showed that, in a dog with the cord sectioned immediately below the medulla, stimulation of the central end of a divided vagus inhibited pancreatic secretion provided the other vagus was intact, but not if the second vagus was divided. This inhibitory effect was unaffected by atropine. Since the pancreas increased in volume during the periods of inhibition, Anrep (1916) suggested that vagal inhibition might result from duct constriction - a view which was supported later by the

demonstration of Korovitzky (1923) that vagal stimulation caused the ducts to contract. However, in these experiments where there was a cannula into the main pancreatic duct at all times, this view of the mechanism of vagal inhibition - namely, that it is the result of duct constriction - cannot be the explanation for the results, which suggest that true vagal inhibitory fibres have been divided.

HYPERSENSITIVITY:- Concerning the possible development of hypersensitivity following denervation, it is difficult to provide satisfactory evidence either way. On the one hand, hypersensitivity usually takes a few weeks to develop, though not invariably so, while in the present experiments the increase in response was noted in the first week. Secondly, the degree of hypersensitivity does not usually remain constant for as long as 3½ months as in the present case, though of course it may do so. It is therefore felt that hypersensitivity is probably not the explanation of the findings. Further evidence is required to confirm this.

Bicarbonate Responses:- The effect of vagotomy on the bicarbonate concentration is just what may be expected on the basis of present knowledge about the variation of this factor with the volume-rate of secretion. The nearly linear correlation between volume-rate and bicarbonate concentration holds only when the rate is low. With rising rates the curve begins to flatten out, and the bicarbonate concentration tends to become constant (Hart and Thomas, 1945), which is essentially what obtains in the present experiments. Under these circumstances, any rise in the total bicarbonate

output which we observed is merely a reflection of its being calculated as the product of an elevated volume and an almost constant concentration. In view of the general belief that the vagus is predominantly responsible for enzyme output and plays little part in the secretion of water and electrolyte, it is interesting that a considerable and significant increase in water and bicarbonate output can be demonstrated after vagotomy. This suggests that whereas the vagus produces a juice of low water and high enzyme content when stimulated (Babkin and Savich, 1908), it nevertheless exercises a not inconsiderable inhibitory control of water and bicarbonate output.

Nitrogen Responses:- As far as the nitrogen responses are concerned, the reduction in the nitrogen concentration and total output on response to secretin which has been shown following vagotomy is in accordance with the general trend in the literature. Crider and Thomas (1944), Pincus, Thomas and Lachman (1948), in the dog, and Mellanby (1925), in the cat, have all demonstrated a reduction in nitrogen or enzyme output, though not always a large one, following vagotomy in response to a variety of stimuli. Routley et al. (1952) confirmed this for the enzyme concentration in response to secretin but noted that the total enzyme output was increased. This was no doubt due to the fact that the volumes were significantly increased. Dog 353, however, was one of the animals in which there was little change in the volume response following vagotomy, and so a reduction in nitrogen concentration was accompanied by a reduction in total output as well. However, in the face of this, it is rather difficult

to explain why the nitrogen responses to histamine are increased except to say that the increase is very small indeed and probably due to chance.

Chloride Responses:- There is no previous work on the effect of vagotomy on the chloride responses. While the increase in the chloride concentration is very small after histamine, it is somewhat larger than after secretin, and while these results are not statistically significant, it is very interesting that any rise at all could be demonstrated when the bicarbonate concentra-:tions also rose.

Vagotomy and Pancreatic Secretin in Man:- It is difficult to explain why Dreiling et al. (1952) were unable to demonstrate any alteration in the pancreatic response to secretin following vagotomy in the human subject. There may be an inherent difference between the pancreatic response of dogs and humans. On the other hand, their patients may have behaved in the same way as our dogs No. 349 and 353, which likewise failed to show a significant increase after vagotomy. Finally, Dreiling et al. compared normal subjects with patients who had been subjected to oesophago-gastrectomy for carcinoma. These two groups are perhaps hardly a fair comparison. It is even more difficult to explain why Shingleton et al. (1951) could find no response at all to secretin after trans-thoracic vagotomy for peptic ulcer. This is at variance with every other report on the subject, either in man or in dog.

The reason for the difference between the effect of

atropine and the effect of vagotomy will be discussed in the next chapter.

SUMMARY.

The effect of vagotomy on pancreatic secretion has been studied in four dogs with gastrostomies.

Vagotomy has no significant effect on pancreatic basal secretory rate.

The volume and total bicarbonate output in response to both secretin and histamine are invariably increased. The bicarbonate concentration remains almost constant except for a rise when the increase in volume is particularly large.

Apart from a decrease in the output and concentration of nitrogen in response to secretin following vagotomy, the chloride and nitrogen responses to both secretin and histamine were all increased. None of these variations were statistically significant.

The post-vagotomy secretory pattern lasts for at least $3\frac{1}{2}$ months, as long as observations continued.

The vagus exerts a tonic inhibitory influence on the water and bicarbonate output of the pancreas by means of secreto-inhibitory fibres which may act directly on the secretory cell or via local reflex pathways.

While hypersensitivity following denervation cannot be ruled out as an explanation of the effects of vagotomy, it is thought to be unlikely.

CHAPTER VII.

THE EFFECT OF ATROPINE ON THE SECRETIN RESPONSE.

The experiments on vagotomy described in the last chapter were performed in the hope of finding some relationship between the effect of atropine and the effect of vagotomy on the histamine response which would given some information on the mode of action of atropine. However, vagotomy was found to increase the response to histamine, and also to secretin given as a control. It was therefore felt necessary to reinvestigate the effect of atropine on the response to secretin, although previous reports suggest that there is little effect.

The investigations on dog No. 353 were therefore extended to include a study of the effect of atropine on the secretin response.

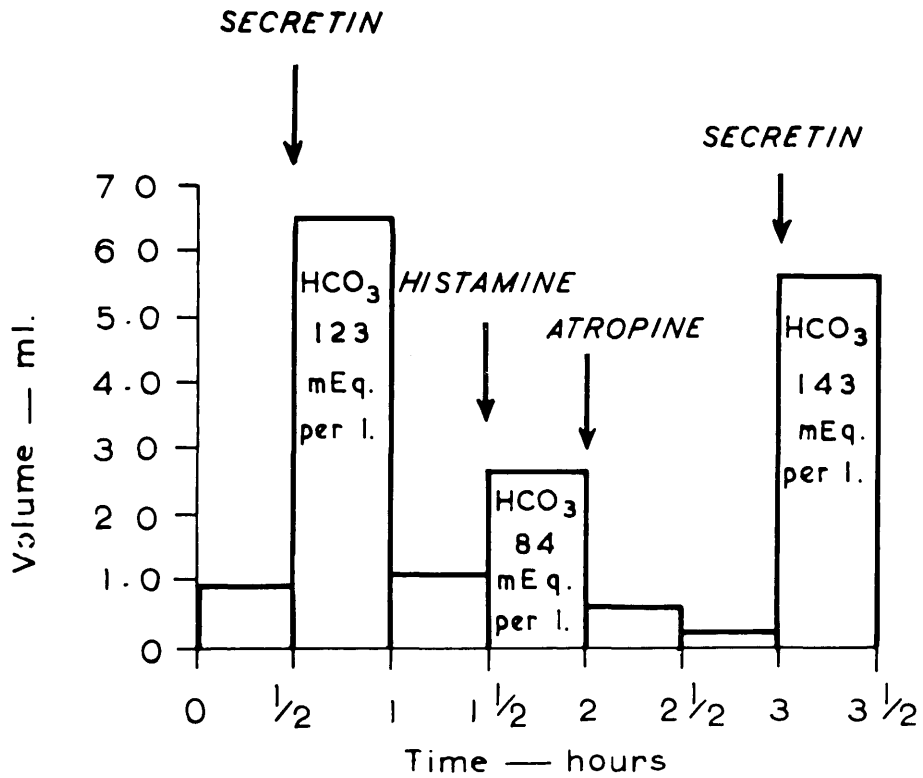
LITERATURE.

Both in the dog (Bayliss and Starling, 1902; Babkin and Sawitch, 1908; Thomas and Crider, 1946) and in the cat (Mellanby, 1925; Eisler and Agren, 1936) atropine produces little change in the volume or bicarbonate output of the gland in response to secretin, although a slight reduction in enzyme and nitrogen output was noted by Mellanby (1925) and by Thomas and Crider (1946) who also noted a reduction in volume of 20 per cent. Barlow (1927a) on the other hand reported a slight rise in the volume response. However, in response to intraduodenal HCl, which can be considered as acting mainly by way of endogenous secretin, all are agreed that there is a diminution in the volume and nitrogen outputs (Babkin and Sawitch, 1908; Bylina, 1911; Ivy, 1927; Thomas and Crider, 1946)

except Farrell and Ivy (1926) who reported no change. In man, Lagerlof (1942) noted a considerable reduction in the volume and bicarbonate output in 2 out of 4 cases, and a reduction of one-third in the enzyme output.

METHOD.

The operative techniques and experimental procedures were exactly the same as have already been described except that atropine was given 1 hour before a second injection of secretin. An example of a typical experiment is shown in Fig. 24 below.



A typical experiment designed to compare the pancreatic responses to secretin, histamine, and to secretin after atropine. The corresponding bicarbonate concentrations are also shown. (Dog with gastrostomy. Exp. 353-2)

Fig. 24.

After a half hour period of basal secretion yielding 0.9 ml. an injection of secretin was given which resulted in 6.5 ml. of juice during the second period. A further basal period yielding 1.1 ml. was followed by a histamine injection which produced 2.7 ml. of juice. Atropine was then given and the next 2 periods yielded 0.6 and 0.2 ml. respectively. The final injection of secretin was then given, resulting in 5.6 ml. secretion. Thus each experiment included its own control and it was possible to compare the responses to secretin and histamine, and to secretin before and after atropine, on the same day. Only the latter comparison is of interest in this discussion. The dosage of secretin and atropine was exactly the same as before. Control data with intact vagi were collected and then the same procedure was carried out after a supradiaphragmatic vagotomy had been performed as already described.

The volume, and the bicarbonate, nitrogen and chloride concentration of each sample was measured by the methods already described and the total outputs calculated.

Since it was important that there should be no contamination of the duodenum with acid gastric juice, the usual care was taken to measure the pH of the duodenal contents at one-minute intervals throughout every period following stimulation. In no case did the pH fall below 7 in this group of experiments. There is thus no possibility of any fallacy due to the endogenous secretin mechanism.

RESULTS.

The Volume Responses.

The results are summarised in Table XVII and the data from which the table was made up are given in Tables XIIId and XVIIa in Appendix B.

EFFECT OF ATROPINE ON THE VOLUME RESPONSE TO SECRETIN BEFORE AND AFTER VAGOTOMY

Mean Volume Response (Ml./half hour)

	Secretin alone.	Secretin after Atropine	Difference	Significance Test t	n	p
Before Vagotomy	8.7 (5)[x]	7.6 (5)	-1.1 (13%)	0.49	8	0.62
After Vagotomy	11.1 (6)	9.8 (5)	-1.3 (12%)	0.71	9	0.50
Difference	2.6 (30%)	2.2 (29%)				
t	1.15	1.28				
n	9	8				
p	0.27	0.22				

x - The figures in parentheses indicate the number of observations on which the mean is based.

Table XVII.

The average half hourly volumes are reduced by atropine from 8.7 to 7.6 ml. (-12.6%) before vagotomy, and from 11.1 to 9.8 ml. (-11.7%) after vagotomy. Neither of these results is statistically significant at the 1% level of probability using Student's "t" test corrected for small numbers.

The Bicarbonate Responses.

The concentrations and total outputs of bicarbonate are summarised in Tables XVIII and XIX. The data from which these tables are taken are given in Tables XIIId and XVIIa in Appendix B.

EFFECT OF ATROPINE ON THE BICARBONATE CONCENTRATION IN RESPONSE TO SECRETIN BEFORE AND AFTER VAGOTOMY

Mean Bicarbonate Concentration (mEq./l.).

	Secretin alone.	Secretin after Atropine	Difference	Significance Test t	n	p
Before Vagotomy	130 (5)x	144 (5)	14 (11%)	3.95	8	0.0044
After Vagotomy	128 (6)	135 (5)	7 (6%)	3.38	9	0.0084
Difference	-2 (2%)	-9 (6%)				
t	0.64	3.42				
n	9	8				
p	0.57	0.0092				

x - The figures in parentheses indicate the number of observations on which the mean is based.

Table XVIII.

Atropine increased the bicarbonate concentrations from 130 to 144 mEq./l. (11%) before vagotomy, and from 128 to 135 mEq./l. (6%) after vagotomy, both these increases being

statistically significant. Vagotomy also produced a reduction of 6 per cent in the response to secretin in the atropinised dog which was also statistically significant.

The bicarbonate concentrations and the volume-rates of secretion vary inversely in all the experiments so that there are only very small and insignificant changes in the total bicarb-:onate output after the giving of atropine.

EFFECT OF ATROPINE ON THE TOTAL BICARBONATE OUTPUT IN RESPONSE TO SECRETIN BEFORE AND AFTER VAGOTOMY.

Mean Bicarbonate Output (micro-Eq.)

	Secretin alone.	Secretin after Atropine	Difference	Significance Test t	n	p
Before Vagotomy	1129 (5)[x]	1093 (5)	-36 (3%)	0.12	8	0.9
After Vagotomy	1427 (6)	1325 (5)	-102 (7%)	0.42	9	0.68
Difference	298 (26%)	252 (21%)				
t	1.05	0.92				
n	9	8				
p	0.54	0.37				

x - The figures in parentheses indicate the number of observations on which the mean is based.

Table XIX.

The Nitrogen Responses.

The results are summarised in Tables XX and XXI and the data from which these tables are taken are given in Table XXa in Appendix B.

EFFECT OF ATROPINE ON THE NITROGEN CONCENTRATION IN RESPONSE TO SECRETIN BEFORE AND AFTER VAGOTOMY.

Mean Nitrogen Concentration (mMols./l.)

	Secretin alone.	Secretin after Atropine	Difference	Significance Test t	n	p
Before Vagotomy	113 (5)[x]	32 (5)	-81 (63%)	4.57	8	0.0018
After Vagotomy	87 (6)	59 (5)	-28 (32%)	3.87	9	0.0039
Difference	-26 (23%)	27 (85%)				
t	1.62	3.40				
n	9	8				
p	0.14	0.0092				

x - The figures in parentheses indicate the number of observations on which the mean is based.

Table XX.

Before vagotomy atropine reduced the concentration of nitrogen from 113 to 32 microMols./l. (-63%), and after vagotomy it reduced the concentration from 87 to 59 microMols./l. (-32%), both these results being statistically significant. The reduction in concentration due to atropine is less after vagotomy

than before it, and this difference in response (85%) is itself statistically significant.

EFFECT OF ATROPINE ON THE TOTAL NITROGEN OUTPUT IN RESPONSE TO SECRETIN BEFORE AND AFTER VAGOTOMY

Mean Nitrogen Output (microMols.)

	Secretin alone.	Secretin after Atropine	Difference	Significance Test t	n	p
Before Vagotomy	975 (5)[x]	232 (5)	-741 (76%)	3.48	8	0.0084
After Vagotomy	951 (6)	574 (5)	-377 (40%)	2.57	9	0.030
Difference	-22 (2%)	342 (148%)				
t	0.10	3.11				
n	9	8				
p	0.93	0.014				

x - The figures in parentheses indicate the number of observations on which the mean is based.

Table XXI.

The pattern of response to the various combinations of atropine and vagotomy shown by the total nitrogen outputs is the same as that shown by the concentrations, decreases and increases occurring in the same way. However, the levels of significance are not quite so great. Thus, while atropine produces a drop in the mean total nitrogen output of 40 per cent

in the vagotomised dog, this was only significant at the 5% level of probability ($p = 0.030$), and while vagotomy increased the response to secretin after atropinisation by 148 per cent, this was only significant at the 2% level of probability ($p = 0.014$).

The Chloride Responses.

The results are summarised in Tables XXII and XXIII and the detailed data are given in Table XXIIa in Appendix B.

EFFECT OF ATROPINE ON THE CHLORIDE CONCENTRATION IN RESPONSE TO SECRETIN BEFORE AND AFTER VAGOTOMY.

Mean Chloride Concentration (mEq./l.)

	Secretin alone.	Secretin after Atropine	Difference	Significance t	n	Test p
Before Vagotomy	27.4 (5)[x]	27.6 (5)	0.2 (1%)	0.05	8	0.99
After Vagotomy	33.3 (6)	28.0 (5)	-5.3 (16%)	1.66	9	0.12
Difference	5.9 (22%)	0.4 (1 %)				
t	1.62	0.07				
n	9	8				
p	0.14	0.95				

x - The figures in parentheses indicate the number of observations on which the mean is based.

Table XXII.

EFFECT OF ATROPINE ON THE TOTAL CHLORIDE OUTPUT IN RESPONSE TO SECRETIN BEFORE AND AFTER VAGOTOMY

Mean Chloride Output (micro-Eq.)

	Secretin alone.	Secretin after Atropine	Difference	Significance Test t	n	p
Before Vagotomy	239 (5)[x]	208 (5)	- 31 (13%)	0.39	8	0.70
After Vagotomy	463 (6)	271 (5)	-192 (41%)	1.58	9	0.15
Difference	224 (93%)	63 (30%)				
t	1.76	0.97				
n	9	8				
p	0.12	0.35				

x - The figures in parentheses indicate the number of observations on which the mean is based.

Table XXIII.

Atropine appears to have little effect on the chloride concentration either before or after vagotomy. In the former case the results are almost identical (+1%), and in the latter case there is a slight fall following atropine (-16%) which is not statistically significant.

Atropine also lowers the total chloride output after secretin from 239 to 208 microMols. (-13%) before vagotomy, and from 463 to 271 microMols. (-41%) after vagotomy, but neither of these reductions were statistically significant. Vagotomy likewise did not produce any statistically significant effect on the response to secretin either before or after atropine.

DISCUSSION.

As already pointed out, the possibility of fallacy by activation of the HCl endogenous secretin mechanism is excluded by duodenal pH readings which never fell below 7 in this series of experiments.

Volume:- Reference has already been made to a number of reports that atropine either does not affect the volume response to secretin or slightly reduces it. The reduction of 12 per cent in volume in this experiment is of a similar order to the average reduction of 20 per cent previously reported by Thomas and Crider (1946). However, although this reduction in volume is small, it is nevertheless important.

Bicarbonate Responses:- Examination of the tables shows that while the total bicarbonate outputs hardly change after atropinisation, the bicarbonate concentrations increase significantly and vary inversely with the volume. Since the total bicarbonate output hardly changes, the fluctuations in concentration must be due mainly to the changes in water output. In other words, a statistically significant rise in bicarbonate concentration is produced by a small but important reduction in water output. This is analogous to the action of atropine on the gastric response to histamine, where a reduction in volume is associated with an increase in the HCl concentration (Gray 1937). The fact that such a change occurs even after vagotomy suggests that atropine acts at a point distal to the vagus and independently of it, probably on the secretory cell itself.

Nitrogen Responses:- Both the concentration and total outputs of

nitrogen were reduced by atropine. This has been reported previously both for intraduodenal HCl and secretin stimulation. The data also confirm that this statistically significant reduction in the nitrogen output occurs after vagotomy as well, and provides further confirmation that atropine acts distal to the vagus and independently of it.

Chloride Responses:- While the changes in the total chloride output are not statistically significant, atropine nevertheless tends to reduce the response and vagotomy tends to increase it. Since generally the chloride concentrations remain almost constant, the changes in output reflect the alterations in the volume of secretion. It is interesting that the chloride concentrations should remain constant in the face of significant alterations in bicarbonate concentration in view of the fact that the sum of the two is usually constant for a particular animal (Hart and Thomas 1945).

Atropine and Vagotomy:- There is a further point of interest. In both the bicarbonate and nitrogen concentrations, and to a lesser extent in the total output of nitrogen, there is a significant difference between the action of atropine before and after vagotomy. This may be explained on the supposition that atropine possesses some action on the vagus as well as distal to it. The evidence that the vagus contains both secretory and inhibitory fibres to the pancreas is reviewed in the previous chapter. Anrep (1914) suggested that atropine had a selective action on the secretory fibres of the vagus, and that it affected

the inhibitory fibres only when given in massive dosage. The observations of Popielski (1896), Wertheimer and Lepage (1901), and Modrakowski (1906), that atropine in massive dosage may even have a secretagogue effect on the pancreas, lends some weight to this suggestion. Thus when the vagi are intact, atropine in the dosage used inhibits the volume and nitrogen output by acting at two points - (a) on the secretory fibres of the vagus, and (b) at some point distal to the vagus, probably on the secretory cell itself. When the vagi are cut, inhibitory fibres as well as secretory fibres are divided with a resultant relative increase in the volume and nitrogen responses to secretin so that these are higher than before vagotomy although still capable of being inhibited by the direct action of atropine on the secretory cell. This also holds good for the bicarbonate and chloride outputs although the changes are small and not statistically significant.

This double action of atropine may also explain its inhibitory effect on the histamine response. Since vagotomy increases the volume and bicarbonate outputs in response to histamine, atropine must either act selectively on the secretory nerve endings of the vagus and not on the inhibitory ones, or it must act on the secretory cell itself, or both. As the effect of vagotomy on the inhibitory effect of atropine on the histamine response has not been studied, there is no proof which of these possibilities in fact occurs. However, it is unlikely that complete inhibition of the histamine response could be achieved simply by inhibition of vagal secretory impulses, and so, as with

secretin, atropine probably produces its effect by acting at both points.

SUMMARY.

1) The effect of atropine on the pancreatic response to secretin has been investigated in one dog.

2) Atropine produces a small but important reduction in the volume output in response to secretin.

3) Atropine produces a significant increase in the bicarbonate concentration but little change in the total bicarbon-:ate output in response to secretin.

4) Both the concentration and total output of nitrogen are significantly decreased by atropine.

5) The concentration and total output of chloride is not significantly affected by atropine.

6) Vagotomy reduces the inhibitory effect of atropine on the concentration and total output of nitrogen, and reduces the increase in the bicarbonate concentration to a significant degree.

7) Atropine acts on the secretory fibres of the vagus as well as on the secretory cell itself. The effects of vagotomy are due to the division of inhibitory fibres to the pancreas.

CHAPTER VIII

THE MODE OF ACTION OF HISTAMINE.

Before discussing the mode of action of histamine the results of the experiments will be recapitulated briefly. The pancreatic response to histamine is similar to the response to secretin in many ways. The general profile, latent period, duration and timing of the peak of the responses are almost identical. However, the volume and bicarbonate concentrations in response to histamine are somewhat lower than the corresponding secretin responses and the chloride and nitrogen concentrations a good deal higher. Both responses are increased by vagotomy. Atropine inhibits the action of histamine but has a much smaller effect on the response to secretin.

How may histamine act in these experiments? The first explanation that comes to mind is that the endogenous secretin mechanism was not completely excluded. However, not only has satisfactory evidence of this exclusion been provided in the dogs whose stomachs were kept empty by way of a gastroscopy, but an equivalent response was obtained in the dogs with total gastrectomies where the fallacy could not occur. This explanation is therefore not tenable.

A second possible explanation for the pancreatic action of histamine is that first suggested by Molinarri-Tosatti (1928), namely, that the secretory effect results from an increase in blood flow to the pancreas which is in turn due to the vascular effects of histamine. Vascular explanations for variations in pancreatic activity have been suggested for nearly a century and the evidence is reviewed in full in Appendix A. Whatever small

amount of evidence there may be that increases in rate of secretion are accompanied by increases in rate of blood flow, there is none to prove that this association is a casual one, i.e. that an increase in blood flow will promptly produce an increase in secretory rate. In this connection our own experiments fail to show any pancreatic response to vasodilator drugs.

Another possible explanation is one which has been invoked secondarily to explain the action of histamine on the salivary glands, namely, that it causes smooth muscle to contract and so squeezes retained secretion out of the gland. However, this interpretation cannot be applied to the pancreatic response to histamine because the volumes are too large to be accounted for in this way, and also because the pancreatic ducts contain no smooth muscle (Maximow and Bloom 1952).

A further possibility is that the presence of bile in the duodenum stimulates pancreatic secretion. Mellanby (1926) was the first to report this phenomenon and thought that it acted by increasing the absorption of secretin from the intestinal mucous membrane. However, subsequent studies in both cats and dogs not only failed to confirm this, but even demonstrated an inhibitory effect (Lueth and Ivy, 1927; Dragstedt and Woodbury, 1934; Florey and Harding, 1935; Thomas and Crider, 1941, 1943). Finally, Thomas and Crider (1943) showed that bile was a stimulus to pancreatic secretion only under conditions of shock, deep anaesthesia or low blood pressure. None of these conditions apply to the present work. Further, in every dog in which bile appeared

in response to histamine, it also appeared in response to secretin, and it did not appear until about the fifth minute by which time the pancreatic responses to both histamine and secretin were well under way.

A fourth possibility is that histamine activates the endogenous secretin mechanism directly, as well as by the intermediation of gastric HCl, an inference which might be made from the observation of MacKay and Baxter (1931) that the addition of histamine to an intraduodenal infusion of HCl will revive the response of a fatigued gland. We have already pointed out that while the profile of the histamine and secretin responses were very similar, there was a distinctive difference in the electrolyte and nitrogen content of the juice. If histamine released secretin, then one would expect to find a juice similar to secretin juice in response to histamine stimulation, as is the case with the response to intraduodenal HCl (Thomas and Crider, 1944). This is not so. Further, if histamine did activate the endogenous secretin mechanism directly it might be expected that the latent period for the pancreatic response to histamine would be appreciably longer than that actually observed - 1 to 3 minutes - because of the time which would be required to bring the concentration of endogenous secretin to an adequate levelbefore pancreatic outflow could start. For a similar reason, the peak of the response would come appreciably later than the 5 to 10 minutes usually observed, and its entire duration would probably be well over the maximum of 30 minutes

encountered in the present experiments. These contradictions are therefore additional evidence against this explanation.

Thomas (1950) considered that histamine may act by lowering the blood pressure or enhancing the response to other stimuli such as secretin. The same objections apply to the acceptance of the latter explanation as applied to the suggestion that histamine activates the secretin mechanism directly. As far as the lowering of blood pressure producing a pancreatic response is concerned, the literature reviewed in Appendix A considers this point and provides no evidence in favour of this hypothesis.

Andfinally, there is the most obvious explanation, that histamine is a true pancreatic secretagogue. Direct evidence for this hypothesis is likewise lacking, but the magnitude of the histamine response relative to the secretin response, the similarity in profile of the two responses, the similarity of their behaviour to vagotomy and the inadequacy of other mechanisms to explain this phenomenon, all lend considerable weight to this interpretation.

It is tempting to suggest that histamine may have some part to play in normal pancreatic secretion. The fact that histamine is a potent pancreatic secretagogue, at least in the dog; that a fatigued response to intraduodenal HCl could be revived by the addition of histamine to the acid (MacKay and Baxter, 1931); and that pancreatic tissue contains appreciable quantities of histamine (Hallenbeck, Dworetzky and Code, 1950) constitute some evidence in favour of this suggestion. However, the demonstration by the latter authors that canine pancreatic juice usually contains no detectable

histamine unless in response to the injection of histamine, and the fact that histamine appears to have no effect on human pancreatic secretion (Dreiling, 1954), is evidence against it.

Dreiling's failure to discover any pancreatic response to histamine in man presents an interesting problem. His method of obtaining pancreatic juice, by aspiration of duodenal content through a double lumen tube, is dependable enough to detect volumes of the order of one third or two thirds of the normal secretin response with considerable reliability. However, the variation in volume of secretion, evoked by a fixed dosage of histamine in different dogs with chronic pancreatic fistulae of the kind used in the present work, is itself very large. So, this observation may mean that the human pancreas, in contrast with that of the dog, is comparatively insensitive to histamine in the dosage ordinarily employed for man.

Since atropine caninhibit the pancreatic response to histamine completely, and vagotomy increases it, it is unlikely that the effect of atropine on the vagus is alone responsible for the inhibition obtained. If the analogy with secretin can be accepted, it seems likely that atropine exerts its effect on the secretory cell itself, as well as by inhibition of the secretory fibres in the vagus.

SUMMARY.

Histamine is a true pancreatic secretagogue. Its action cannot be explained by activation of the endogenous secretin mechanism by gastric HCl, by direct secretin release, or by lowering of the threshold to secretin. It is not due to the concomitant secretion

of bile, to vasodilatation, to lowering of the blood pressure, or to an increase in blood flow through the pancreas.

Atropine probably inhibits the histamine response by a direct action on the secretory cell itself, as well as by inhibition of the vagal secretory nerve endings.

CHAPTER IX

GENERAL SUMMARY.

The Response to Histamine.

The pancreatic response to histamine and to control injections of secretin have been studied in 8 dogs. To exclude any fallacy due to activation of the endogenous secretin mechanism by gastric acid, 3 of the dogs had total gastrectomies carried out, and 5 dogs had gastrostomies through which the stomach could be kept empty.

Histamine is a potent stimulator of pancreatic secretion in the absence of the endogenous secretin mechanism.

The volume, bicarbonate concentration, and total bicarbonate output in response to histamine are on the average about 70 per cent of the response to secretin in the doses used, and on occasion may even be greater than it.

The concentrations of chloride and nitrogen in response to histamine are about $2\frac{1}{2}$ times the corresponding concentrations in response to secretin, but the total outputs are approximately equal.

The profiles of the responses to histamine and secretin are very similar as regards latent period, duration of response, and the timing of the peak of the response.

Histamine is a true pancreatic secretagogue. Its action cannot be explained by activation of the endogenous secretin mechanism by gastric HCl, by direct secretin release, or by lowering of the threshold to secretin. It is not due to the concomitant secretion of bile, to vasodilatation, to lowering of the blood pressure, or to an increase in blood flow through the pancreas.

The Effect of Atropine.

The effect of atropine on the response to histamine has been studied on 3 dogs with total gastrectomies and 4 dogs with gastrostomies.

Atropine inhibits the volume and bicarbonate output in response to histamine and this inhibition may be complete when one hour is allowed to elapse between the injection of atropine and the subsequent injection of histamine. When an interval of only half an hour is allowed, inhibition does not invariably occur.

The effect of atropine on the pancreatic response to secretin has been studied in one dog.

Atropine produces a small but important reduction in the volume response to secretin.

Atropine produces a significant increase in the bicarbonate concentration, but little change in the total bicar-:bonate output in response to secretin.

Both the concentration and total output of nitrogen are significantly decreased by atropine.

The concentration and total output of chloride were not significantly affected by atropine.

Vagotomy reduced the inhibitory effect of atropine on the concentration and total output of nitrogen to a significant degree, and reduced the increase in the bicarbonate concentration.

Atropine appears to act directly on the secretory cell as well as blocking the secretory fibres of the vagus.

The Effect of Vagotomy.

The effect of vagotomy on the pancreatic responses to histamine and secretin was investigated in four dogs with gastrostomies.

Vagotomy does not affect the pancreatic basal secretory rate.

The volume and total bicarbonate outputs in response to both histamine and secretin were invariably increased following vagotomy, and in the two dogs where this increase was greater than 100 per cent it was highly significant statistically.

The bicarbonate concentration in response to both histamine and secretin was increased by vagotomy when the volume changes were large, but otherwise there was no significant difference.

Vagotomy produced a slight fall in the nitrogen concentration and total output in response to secretin and a slight rise in the response to histamine, but none of these variations were statistically significant.

Vagotomy produced a greater rise in the concentration and total output of chloride in response to secretin than in response to histamine, but none of these increases were statistically significant.

The vagus appears to exert a tonic inhibitory effect on water and bicarbonate secretion by the pancreas. This is probably due to presence in the vagus of secreto-inhibitory fibres to the pancreas which act either directly on the secretory cell, or indirectly through local reflex pathways, or both.

The possibility that the increase in the pancreatic response to histamine and secretin following vagotomy is due to the development of hypersensitivity has been considered. While proof is lacking, it is felt that this is probably not the explanation.

The Effect of Blood Flow through the Pancreas.

Sodium nitrite and glyceryl trinitrate have no effect on pancreatic secretion.

Pancreatic secretion is dependent on the blood supply of the gland only to this extent, that a certain minimum flow of blood is required to maintain cellular activity and to provide fluid for secretion.

The Effect of Ephedrine and Histalog.

The effect of ephedrine on the pancreatic response to histamine was studied in 3 dogs with total gastrectomies. There was no significant effect.

The effect of histalog, an analog of histamine, on pancreatic secretion was studied in 2 dogs. No effect was noted.

APPENDIX A

THE RELATION BETWEEN PANCREATIC SECRETION AND LOCAL BLOOD FLOW.

The idea that rate of blood flow is an important factor in glandular activity, and that variations in secretory rate may be ascribed to concomitant variations in the blood supply to the gland has been current for a long time. It has been suggested, and it seems reasonable, that (1) an increase in secretory activity will give rise to anincrease in local blood flow; (2) a reduction in blood flow will reduce glandular activity; and (3) an increase in blood flow through the gland will of itself act as a stimulus to augmented activity. The purpose of this review is to trace the growth of these ideas with reference to the pancreas, and to examine the evidence for and against them. The early evidence will be presented briefly, and then the subject will be discussed from these three individual points of view.

Early Growth of the Idea.

Before the discovery of the importance of vascular activity for salivary secretion, Claude Bernard (1849) pointed out that during digestion the pancreas became congested and red. Then, in 1875, Heidenhain, while making observations on a dog in which there was a pronounced periodic variation in the carotid blood pressure, noticed that when the blood pressure rose the pancreatic secretion diminished, and when it fell the pancreatic secretion increased. He interpreted this as being the result of variations of blood flow through the gland, caused by local vasoconstriction or vasodilatation. Increased glandular activity and vasodilatation appeared to occur simultaneously. Shortly

afterwards, Kuhne and Lea (1882), using the rabbit, confirmed histologically that increased pancreatic flow was associated with marked capillary dilatation, but they noticed similar dilatation occasionally in lobules of the resting gland. Meanwhile, following an observation of Claude Bernard (1856) on the inhibitory effect of retching on pancreatic secretion, Bernstein (1870) stimulated the central end of a single cut vagus in a dog and observed an inhibition of its pancreatic secretion which he thought might be the result of vasoconstriction. Later, Affanassiev and Pavlov (1878) produced a similar effect by stimulation of sensory nerves, including the sciatic.

It was on the basis of this accumulation of evidence that Gottlieb (1894) was able to say that the influence of blood flow on pancreatic secretion had been known for a long time. In addition, he cited his own experiments on curarized dogs in which he found that strychnine inhibited pancreatic secretion, when the blood pressure rose, and that this inhibitory effect could be counteracted by chloral hydrate which relaxed the blood vessels. He also confirmed the effect of stimulating the central end of a divided vagus, and concluded that the flow of pancreatic juice was unquestionably dependent on the supply of blood to the gland.

Underlying all this work there is the tacit presumption that a rise in blood pressure indicates splanchnic vasoconstriction, and a fall, vasodilatation; that such vasoconstriction and vasodilatation is shared by the pancreas with a consequent decrease

or increase in blood flow through this organ; and that this in turn produces a decrease or increase in pancreatic secretion regardless of the original stimulus. The failure of yohimbine to cause the lease vestige of salivary secretion when injected into the arterial stream close to the point of origin of the submixillary artery, in spite of a 10-fold increase in blood flow, constitutes one bit of evidence against this argument - but this was not discovered till later (Barcroft and Muller, 1912).

Does an Increase in Pancreatic Secretion Produce an Increase in Blood Flow?

The need for an accurate method of measuring blood flow was soon realised, and in 1896 Francois-Franck and Hallion enclosed the pancreas in a plethysmograph to observe changes in its volume. Vagal stimulation increased the volume of the gland, and this was interpreted as indicating an increase in blood flow despite the fact that the pancreatic duct had been tied during the experiment. Anrep (1916) therefore repeated the work without constricting the duct. Stimulating the distal end of one cut vagus in a decerebrate dog, he found that the gland increased in volume only during the latent period, but returned to its normal size as soon as a free flow of juice occurred. After repeating the stimulation many times, the latent period became shorter, until it almost disappeared. Under these circumstances there was no measurable increase in the volume of the gland. Anrep also put a cannula in the pancreatic vein and noted no increase in the blood flow through it following vagal stimulation, although there was a reduction following

splanchnic stimulation. He therefore concluded that the increase in gland volume during vagal stimulation was caused by retention of secretion within the duct system, and that there was no evidence of concomitant increase in blood flow. On the other hand, Babkin and Starling (1926) noted that during vascular perfusion experiments the blood flow from the venous side of the pancreas was increased when secretin was added to the perfusing fluid. However, the secretin preparation which they used was rich in vasodilator substances, and so this evidence is unsatisfactory. Barlow (1927a) compared the effects of various secretin preparations and of intraduodenal HCl on pancreatic blood flow and secretion. He decided that an increase in blood flow accompanied secretion even when the systemic blood pressure actually rose. Since the increase in blood flow was inferred from measurements of kidney volume - changes in which were interpreted as an index of volume changes in the pancreas and other splanchnic organs, and so proportional to the blood flow through them - this evidence too was unsatisfactory.

Thus Anrep's work remained virtually undisputed until it was repeated by Gayet and Guillaumie (1930), using a strohmuhr in addition to a plethysmograph so that direct measurements of blood flow could be correlated with changes in the pancreatic volume. These investigators showed that an increase in blood flow accompanied the secretory response to an injection of secretin or to vagal stimulation. Later, (Gayet and Guillaumie, 1933) they noted that occasionally the gland underwent a preliminary reduction in volume following vagal stimulation though this was still accompanied by an increase in blood flow. More usually, however,

there was an increase in glandular volume during vagal stimulation which was coincident with the increase in blood flow, but in general it lasted longer, reached its maximum at the end of vagal stimulation and subsided more slowly. The character of this sequence of volume changes is more suggestive of their having been caused by duct retention than by an increase in blood flow alone, as Gayet and Guillaumie suggest. However, these observers comment that the increases in blood flow which they obtained following humoral stimulation were weak and inconstant. This work was again repeated by Maltesos and Watson (1938), who used a thermostromuhr to measure the blood flow during the response to intraduodenal HCl and to intravenous secretin, free of vasodilatin. The blood flow increased first, then secretion started, and thereafter both curves ran parallel.

The evidence presented by Gayet and Guillaumie, and Maltesos and Watson, for an increase in blood flow to the pancreas following a secretory stimulus, has often been considered conclusive, but already Weaver (1928) had reported that vasodilatin-free secretin could stimulate pancreatic secretion without an increase in blood flow, as measured by bleeding from a cannula placed in the tail vein of the pancreas of a heparinised dog. One possible explanation for this conflicting evidence is provided by Bennett and Still (1933). Using an automatic stromuhr of their own design, in which back pressure was negligible, they collected evidence that an increase in the blood flow of the pancreas occurred only when there was a rise in pressure in the duct or in the

external collecting system, and they explained this in terms of local reflex arc activity. They used a heparinised dog in which both the pylorus and the duodenum below the pancreatic ducts were ligated to exclude intestinal contents; secretion was stimulated by intravenous secretin. Finally, Grossman (1950), in his review of the gastrointestinal hormones, points out that even in the experiments of Gayet and Guillaumie, and of Maltesos and Watson, duct pressure may have been responsible for the increase in blood flow which they noted, and that even in the presence of an apparently free flow of secretion it would be difficult to prove the absence of some increase in pressure within the duct system.

Thus, there exists at the present time no conclusive evidence for the contention that an increase in glandular activity is invariably accompanied by an increase in blood flow. The work of Gayet and Guillaumie (1930, 1933) and of Maltesos and Watson (1933) suggests it; the evidence of Anrep (1916), Weaver (1928), and Bennett and Still (1933) refutes it.

Does a Decrease in Blood Flow Always Induce a Decrease in Pancreatic Secretion?

There are many ways in which the blood flow through the pancreas may be reduced, and methods employing mechanical means, nerve stimulation, and drugs have all been reported many times.

In the course of experiments on dogs which required the frequent taking of blood samples, Bennett and Still (1933) found that pancreatic secretion was reduced progressively as the animal became exsanguinated, but so much else is involved in the general

response to this experimental stiuation that little can be learned from it. Another mechanical method for reducing blood flow was that of aortic compression, when pancreatic secretion had been stimulated vagally (Pavlov, 1893) or by the continuous injection of secretin (Edmunds, 1909; Anrep, 1916). In all cases secretion stopped within 100 seconds of direct external compression of the aorta above the coeliac axis. However, May (1904), using an intra-aortic ballon technique for occlusion, found that pancreatic secretion continued for several minutes before finally ceasing, no doubt because of the time required for the development of cellular anoxia. Extirpation of the heart while the pancreas was secreting yielded similar results. It is interesting that external aortic compression, which can hardly be performed without some pressure on the coeliac plexus, should have produced rapid cessation of secretion whereas the other methods allowed a lag of several minutes. This raises some doubt as to whether diminution in blood supply or splanchnic stimulation is the more important factor in these experiments, but splanchnic stimulation on its own never completely inhibited a rapidly secreting gland (Anrep, 1916).

This brings up the question of sympathetic nerve stimulation in general. Francois-Franck and Hallion (1896), May (1904), and Anrep (1916), in the course of their work with plethysmographs, had shown that splanchnic stimulation was accompanied by shrinkage of the pancreatic gland. That this resulted from a diminution in blood flow was suggested by the observation of Anrep that concomitant bleeding from the tail vein of the pancreas also diminished under

these conditions. However, one must beware of assuming that because a reduction in blood flow is associated with inhibition of secretion that it is a causal association. Any effect that splanchnic stimulation might have on secretory output may still be the result of a true inhibition of secretory activity through inhibitory nerves to the exocrine cells, rather than by the effect of reduced blood supply.

The action of drugs must also be considered. Benedicenti (1906) first noticed that adrenalin inhibited pancreatic secretion, and this was confirmed independently by Pemberton and Sweet (1908). The latter obtained such inhibition regardless of whether the blood pressure was raised in response to the adrenalin, or was actually lowered because of the simultaneous use of a secretin preparation containing vasodilator substances. When old adrenalin was used, the blood pressure was raised without there being any inhibition of pancreatic secretion. From this evidence they inferred that their adrenalin contained two substances, one of which had a specific action on the pancreas which was independent of its blood supply, while the other raised the blood pressure. Direct measurement of gland volume or blood flow were not made.

Edmunds (1909, 1911), reinvestigated the problem and found that the inhibition of secretion produced by adrenalin was associated with a diminution in gland volume. Small doses of nicotine had an adrenalin-like effect, whereas large doses - which presumably paralysed the sympathetic ganglia - had no such effect. Similarly, ergotoxin inhibited secretion as long as it raised the

blood pressure, but after a time, when the vasoconstrictor fibres have become paralysed or no blood pressure rise was being registered, inhibition no longer occurred. Adrenalin given after ergotoxin acted only if it was capable of raising the blood pressure, again suggesting the necessity for intact vasoconstrictor fibres. Similarly, strophanthin, pilocarpine, and barium chloride also inhibited secretion, but only if vasoconstriction was produced. These observations, combined with the fact that splanchnic (sympathetic) stimulation gave inhibition similar to that of these drugs, comprised the evidence put forward by Edmunds (1911) for the argument that inhibition of secretion is caused by vasoconstriction and consequent anaemia of the gland. It must be remembered, however, that these drugs still may act by stimulating true inhibitory fibres and fail to act if these are paralysed; and that because in all these experiments a constant level of pancreatic secretion was produced by means of a continuous intravenous infusion of secretin, the possibil-:ity always remains that if vasoconstriction resulted in inhibition, it did so merely because in some measure it prevented secretin from reaching the gland. This objection also applies to the work of Mann and McLaughlin (1917), who pointed out that doses of adrenalin small enough to lower the systemic pressure while still inhibiting pancreatic secretion can nevertheless reduce the pancreatic volume, indicating the extreme sensitivity of the pancreatic vessels to this pharmacological agent. Babkin (1925) likewise stated that the pancreatic gland was extremely sensitive to anaemia. He found that vagal stimulation or compressing the inferior vena cava above the

diaphragm diminished the pancreatic response to secretin or intraduodenal HCl if a rise in blood pressure occurred, but not if there were no rise. No direct measurements of pancreatic blood flow or volume were made.

Perhaps the best evidence on this question is provided by the work of Gayet and Guillaumie (1930). Under their experimental conditions, secretin gave a greater volume of secretion than did vagal stimulation, but the blood flow following the secretin injection was less than that during the neural stimulation. When a vasodilator secretin was used, the blood flow through the pancreas was reduced but the rate of secretion remained unchanged. This seems to indicate that secretory rate is not proportional to the rate of blood flow through the gland and that a reduction in blood flow per se within physiologic levels has no influence on pancreatic secretion provided the latter has been adequately stimulated.

It appears reasonable to conclude from the foregoing investigations that a massive reduction in blood flow can reduce pancreatic secretion by means of reversible or irreversible changes in the cells, especially by failing to provide the necessary supply of oxygen or water for their activity. But the evidence that a reduction of secretion follows a reduction of blood flow of smaller magnitude than this extreme is very slight. In fact, it seems that hardly more than a very minor, if any, portion of pancreatic exocrine inhibition induced by drugs or nerve stimulation can be ascribed to a reduction in blood flow through the organ.

Does an Increase in Blood Flow Alone Produce an Increase in Pancreatic Secretion?

There is little reliable information on which an answer to this question can be based. Babkin (1924) noted that splanchnic nerve section increased the pancreatic response to secretin and thought that the simplest explanation for this phenomenon "is that the abdominal viscera, and in particular the pancreatic gland, as a result of the elimination of the sympathetic innervation, receives much more blood. And this creates very favourable conditions for the secretory work of the gland". However, he admits that the possibility that the splanchnic nerves carry true secreto-inhibitory fibres to the pancreas is not excluded.

Barlow (1927b) injected solium nitrite intravenously (1 mgm./kg. body weight) in acute experiments in dogs, and found that this induced pancreatic secretion. The latent period and the peak of the response occurred at the same time as in the control experiment with secretin alone, although the duration of the response was longer. From this he concluded that the mechanism which results in pancreatic activity was closely associated with the improved blood supply of the pancreas as a result of the general splanchnic vasodilatation. The pancreatic blood flow was not in itself measured, but was inferred from increases in kidney volume as explained before. However, as stated in Chapter III, this action of sodium nitrite was not confirmed in the unanaesthetised dog, either when double the dose of sodium nitrite was used or with equivalent doses of glyceryl trinitrate.

Osborne and Greengard (1941) reported that the response to a constant intravenous infusion of secretin in dogs was enhanced as much as 7 times by hyperpyrexia induced by short-wave diathermy; furthermore it could be reduced to zero by immersing the animal in cold water. The response to cold may well have been due to general stimulation of the sympathetic nervous system and to adrenaline release, whereas the response to heat may be the result of an increase in general metabolism, rather than to vasodilatation. It is interesting, in this connection to note that hyperpyrexia of suitable magnitude and duration in man has been found to inhibit gastric secretion completely in response to an alcohol test meal (Bandes, Hollander and Bierman, 1948).

The work of Thomson and Vane (1953) on the stomach has often been quoted as evidence in favour of the hypothesis that an increase in blood flow through a gland will increase its secretory rate. They carried out perfusion experiments on the stomachs of cats in such a way that a constant amount of histamine reached the gland in unit time, although the general perfusion rate could be varied. An increase in this general perfusion rate produced a slow increase in gastric secretion which was never noted within the first 10 minutes, and usually required 20 or even 30 to 40 minutes to appear. This type of response and its timing suggests that the changes may have been due to transudation of fluid rather than to a true increase in secretory rate, a possibility which Thomas and Vane themselves admitted. This sort of response is quite different to the rapid increase in secretory rate which follows the injection of

histamine, for example, and for which increased rate of blood flow has received the credit.

The experiments of Barcroft and Muller (1912) on the effect of yohimbin on the submandibular salivary gland have already been quoted as another example of increase in blood flow without any increase in glandular secretion.

Thus there is little direct evidence that an increase in the blood flow to the pancreas will by itself lead to an increase in secretory rate, nor is there any real indirect evidence from the behaviour of the stomach or the salivary glands.

COMMENT.

The unsatisfactory nature of the evidence presented here is inherent in the experimental difficulties of the problem. In plethysmographic work with such a soft and irregularly shaped structure as the pancreas, it would seem impossible that pressure changes produced by changes in pancreatic volume would not be imparted to the lumen of the duct system. If the work or Bennett and Still (1933) on the dependence of an increase of blood flow on a rise in duct pressure is to be accepted, then evidence based on plethysmographic studies must be viewed with caution; only evidence based ondirect measurement of blood flow by stromuhr is reliable. The greatest care would also be required to ensure that the external collecting system for measurement of pancreatic juice outflow is wide and short, to prevent any distension or pressure build-up within the duct system itself.

In any investigation of the effects of changes in blood

flow on pancreatic activity, care must be taken to ensure that the rate at which secretin or any other stimulus reaches the pancreas remains constant, regardless of the amount of blood which the gland receives per unit time, as is the case in the experiments of Thomson and Vane (1953). This is necessary in order to provide a plateau in the curve for rate of secretion. In addition, if a drug were used to increase blood flow, it would be necessary to establish that it is incapable of stimulating the gland directly. If a machanical method were employed, it would have to be of such a nature as not to interfere with the general metabolism of the animal.

SUMMARY.

The evidence at present available does not warrant the conclusion that pancreatic secretion is dependant on the blood supply to the organ, except to this extent, that a certain minimum flow of blood is required to maintain cellular activity and to provide fluid for secretion.

APPENDIX B.

ADDITIONAL TABLES.

THE EFFECT OF VAGOTOMY ON PANCREATIC BASAL SECRETORY RATE

Rate in Ml./half hour. Dog No. 341

Exp. No.	Before Vagotomy	Exp. No.	After Vagotomy
1	1.1 1.1 0.6	9	0.0 0.1
2	0.0 0.0	10	0.0 0.2
3	0.0 0.0	11	0.0 0.4
4	0.3 0.4	12	0.0 0.5
5	0.3 0.3 0.1 0.2 0.0 0.2 0.0 0.9 0.8	13	0.5 0.8
		14	0.0 0.4
6	0.1	15	0.9 0.7 1.0
7	0.0	16	0.2
8	0.2		
Mean	0.31 ± 0.37^{x}	Mean	0.35 ± 0.35^{x}

x - Standard Deviation corrected for small numbers.

Table XIIa.

THE EFFECT OF VAGOTOMY ON PANCREATIC BASAL SECRETORY RATE

Rate in Ml./half hour. Dog No. 348

Exp. No.	Before Vagotomy	Exp. No.	After Vagotomy
1	0.6 1.1	12	0.5
2	1.4	13	1.3 1.4
3	0.5	14	0.6 1.5 1.3
4	0.3 0.2 0.6	15	0.7 0.8 2.0
5	1.9 1.2	17	0.9 2.0 1.4
6	0.3	18	0.1 0.3
7	0.9 0.3 0.7	19	0.5
8	0.6	20	0.7
9	1.2		
10	0.6 0.6 0.3 0.5		
11	0.9 0.7 0.3 0.2 0.1 0.1		
Mean	0.64 ± 0.45^{x}	Mean	1.00 ± 0.58^{x}

x - Standard Deviation corrected for small numbers.

Table XIIb.

THE EFFECT OF VAGOTOMY ON PANCREATIC BASAL SECRETORY RATE

Rate in Ml./half hour. Dog No. 349

Exp. No.	Before Vagotomy	Exp. No.	After Vagotomy
1	1.0 1.4 1.7 0.7 1.2	14	0.4 0.7
2	1.5	15	0.7 1.5
3	1.5 1.1	16	0.8 0.9
4	1.5 1.5 1.5 1.8 1.5	17	0.6 1.0 0.3
8	1.3 1.7 0.2	18	0.2 1.7
9	1.8 1.2	19	1.9
10	0.5 1.5 1.2 1.4	20	0.5
12	1.4		
Mean	1.31 ± 0.41^x	Mean	0.87 ± 0.54^x

Table XIIc.

x - Standard Deviation corrected for small numbers.

THE EFFECT OF VAGOTOMY ON PANCREATIC BASAL SECRETORY RATE

Rate in Ml./half hour. Dog No. 353

Exp. No.	Before Vagotomy	Exp. No.	After Vagotomy
1	0.9 1.4	6	0.6
2	0.9	7	0.2
3	0.2 0.7	8	0.4
4	1.4 1.2	9	0.8
5	0.7	10	0.8 1.0
		11	0.1
Mean	0.93 ± 0.41^x	Mean	0.55 ± 0.10^x

Table XIId.

x - Standard Deviation corrected for small numbers.

THE EFFECT OF VAGOTOMY ON THE PANCREATIC RESPONSE TO SECRETIN

Dog No. 341

Exp. No.	No. of Days After Vagotomy	Volume Response (Ml./half hour)	Bicarbonate Conc. (mEq./l.)	Bicarbonate Output (micro-Eq.)
2	-	1.0	79	79
3	-	1.1	84	92
4	-	1.8	104	187
Pre-Vagotomy Mean ± S.D.		1.3 ± 0.44	89 ± 13.2	119 ± 59.1
9	7	4.3	118	507
11	15	6.3	116	731
12	17	9.8	126	1235
13	21	6.5	129	839
14	23	6.9	125	863
15	50	9.7	98	951
16	100	6.9	125	863
Post-Vagotomy Mean ± S.D.		7.2 ± 1.95	120 ± 10.6	856 ± 219.4

S.D. - Standard Deviation corrected for small numbers.

Table XIIIa.

THE EFFECT OF VAGOTOMY ON THE PANCREATIC RESPONSE TO SECRETIN

Dog No. 548

Exp. No.	No. of Days After Vagotomy	Volume Response (Ml./half hour)	Bicarbonate Conc. (mEq./l.)	Bicarbonate Output (micro-Eq.)
2	-	5.5	123	677
3	-	4.8	129	619
4	-	3.5	99	347
5	-	6.5	114	741
Pre-Vagotomy Mean ± S.D.		5.1 ± 1.25	116 ± 13.1	596 ± 173.3
13	8	10.8	104	1123
14	11	14.0	116	1624
15	15	15.9	118	1876
17	21	10.9	114	1243
18	25	14.8	112	1658
19	54	18.6	118	2195
20	115	7.6	99	752
Post-Vagotomy Mean ± S.D.		13.2 ± 5.69	112 ± 7.4	1496 ± 488.7

S.D. - Standard Deviation corrected for small numbers.

Table XIIIb.

THE EFFECT OF VAGOTOMY ON THE PANCREATIC RESPONSE TO SECRETIN

Dog No. 349

Exp. No.	No. of Days After Vagotomy	Volume Response (Ml./half hour)	Bicarbonate Conc. (mEq./l.)	Bicarbonate Output (micro-Eq.)
1	-	7.9	150	1027
2	-	17.1	137	2343
3	-	8.9	150	1157
Pre-Vagotomy Mean ± S.D.		11.3 ± 5.05	132 ± 4.2	1509 ± 725.2
13	6	16.6	136	2258
14	9	13.3	135	1796
16	19	10.7	137	1466
17	21	8.7	133	1157
18	25	14.4	138	1987
19	49	12.1	137	1658
20	105	15.4	136	1822
Post-Vagotomy Mean ± S.D.		12.7 ± 2.58	136 ± 1.6	1735 ± 355.5

S.D. - Standard Deviation corrected for small numbers.

Table XIIIc.

THE EFFECT OF VAGOTOMY ON THE PANCREATIC RESPONSE TO SECRETIN

Dog No. 353

Exp. No.	No. of Days After Vagotomy	Volume Response (Ml./half hour)	Bicarbonate Conc. (mEq./l.)	Bicarbonate Output (micro-Eq.)
1	-	14.2	132	1874
2	-	6.5	123	800
3	-	7.2	127	914
4	-	10.1	133	1343
5	-	5.3	135	716
Pre-Vagotomy Mean ± S.D.		8.7 ± 3.57	130 ± 4.9	1129 ± 481.1
6	7	9.6	130	1248
7	13	6.2	123	763
8	17	12.4	132	1637
9	20	14.0	131	1834
10	24	11.2	125	1400
11	78	13.1	128	1677
Post-Vagotomy Mean ± S.D.		11.1 ± 2.84	128 ± 3.6	1427 ± 386.3

S.D. - Standard Deviation corrected for small numbers.

Table XIIId.

THE EFFECT OF VAGOTOMY ON THE PANCREATIC RESPONSE TO SECRETIN AND HISTAMINE

Nitrogen (N) Secretion — Dog No. 353

Exp. No.	After Secretin (N) Conc. (mMols./l.)	After Secretin (N) Output (microMols.)	After Histamine (N) Conc. (mMols./l.)	After Histamine (N) Output (microMols.)
1	105	1495	312	1592
2	122	793	293	791
3	165	1187	328	851
4	101	1016	234	1122
5	70	373	166	281
Mean ± S.D. Before Vagotomy	113 ± 34.8	973 ± 422.1	266 ± 63.8	927 ± 474.8
6	93	891	272	869
7	93	574	183	513
8	89	1105	241	844
9	88	1227	246	1598
10	80	894	428	2570
11	77	1013	275	1522
Mean ± S.D. After Vagotomy	87 ± 6.7	951 ± 224.8	274 ± 82.4	1286 ± 736.8

S.D. - Standard Deviation corrected for small numbers.

Table XIVa

THE EFFECT OF VAGOTOMY ON THE PANCREATIC RESPONSE TO SECRETIN AND HISTAMINE

Chloride (C) Secretion — Dog No. 353

Exp. No.	After Secretin		After Histamine	
	(C) Conc. (mEq./l.)	(C) Output (micro-Eq.)	(C) Conc. (mEq./l.)	(C) Output (micro-Eq.)
1	27	383	65	332
2	34	221	i	-
3	20	144	63	164
4	31	313	55	264
5	25	133	i	-
Mean ± S.D. Before Vagotomy	27 ± 5.4	239 ± 108.1	61 ± 5.3	253 ± 84.5
6	34	902	72	230
7	34	211	i	-
8	25	310	62	217
9	34	476	63	410
10	42	470	58	348
11	31	406	68	326
Mean ± S.D. After Vagotomy.	33 ± 5.5	463 ± 237.9	65 ± 5.5	306 ± 81.6

S.D. - Standard deviation corrected for small numbers.

i - Insufficient material for chloride estimation.

Table XIVb.

THE EFFECT OF VAGOTOMY ON THE PANCREATIC RESPONSE TO HISTAMINE

Dog No. 541

Exp. No.	No. of Days After Vagotomy	Volume Response (Ml./half hour)	Bicarbonate Conc. (mEq./l.)	Bicarbonate Output (micro-Eq.)
1	-	1.4	85	119
	-	1.8	88	158
2	-	1.1	91	100
3	-	1.1	78	86
4	-	2.8	97	272
6	-	2.3	90	207
7	-	2.0	95	190
8	-	2.3	93	214
Pre-Vagotomy Mean ± S.D.		1.9 ± 0.62	90 ± 6.0	168 ± 64.1
9	7	2.2	103	227
11	15	5.4	103	556
12	17	4.9	107	524
13	21	4.1	101	414
14	23	4.3	96	413
15	50	9.5	90	855
16	100	4.8	101	485
Post-Vagotomy Mean ± S.D.		5.0 ± 2.22	100 ± 5.6	496 ± 191.5

S.D. - Standard Deviation corrected for small numbers.

Table XVa.

THE EFFECT OF VAGOTOMY ON THE PANCREATIC RESPONSE TO HISTAMINE

Dog No. 348

Exp. No.	No. of Days After Vagotomy	Volume Response (Ml./half hour)	Bicarbonate Conc. (mEq./l.)	Bicarbonate Output (micro-Eq.)
3	-	2.2	87	191
4	-	5.3	78	413
5	-	3.0	52	156
7	-	4.7	68	320
8	-	2.2	72	158
9	-	3.5	72	252
Pre-Vagotomy Mean ± S.D.		3.5 ± 1.30	72 ± 11.6	248 ± 102.2
13	8	9.6	87	835
14	11	6.4	92	589
15	15	8.9	101	899
17	21	9.3	94	874
18	25	7.1	72	511
19	54	8.4	70	588
20	113	7.2	72	518
Post-Vagotomy Mean ± S.D.		8.1 ± 1.22	84 ± 12.6	688 ± 173.8

S.D. - Standard Deviation corrected for small numbers.

Table XVb.

THE EFFECT OF VAGOTOMY ON THE PANCREATIC RESPONSE TO HISTAMINE

Dog No. 349

Exp. No.	No. of Days After Vagotomy	Volume Response (Ml./half hour)	Bicarbonate Conc. (mEq./l.)	Bicarbonate Output (micro-Eq.)
1	-	4.7	96	451
2	-	5.7	117	667
3	-	4.5	109	491
8	-	2.5	91	228
9	-	6.1	123	750
12	-	5.6	120	672
Pre-Vagotomy Mean ± S.D.		4.9 ± 1.30	109 ± 13.3	543 ± 192.5
13	6	6.6	109	719
14	9	9.6	118	1133
16	19	2.7	106	286
17	21	2.7	113	305
18	25	7.0	108	756
19	49	5.2	101	525
20	105	4.0	91	364
Post-Vagotomy Mean ± S.D.		5.4 ± 2.52	107 ± 8.7	584 ± 308.1

S.D. - Standard Deviation corrected for small numbers.

Table XVc.

THE EFFECT OF VAGOTOMY ON THE PANCREATIC RESPONSE TO HISTAMINE

Dog No. 555

Exp. No.	No. of Days After Vagotomy	Volume Response (Ml./half hour)	Bicarbonate Conc. (mEq./l.)	Bicarbonate Output (micro-Eq.)
1	-	5.1	87	444
2	-	2.7	84	227
3	-	2.6	87	226
4	-	4.8	106	509
5	-	1.7	115	196
Pre-Vagotomy Mean ± S.D.		3.4 ± 1.49	96 ± 13.9	320 ± 144.9
6	7	3.2	71	227
7	13	2.8	69	193
8	17	3.5	87	305
9	20	6.5	95	618
10	24	6.0	94	564
11	78	4.8	82	394
Post-Vagotomy Mean ± S.D.		4.5 ± 1.54	83 ± 11.2	384 ± 175.8

S.D. - Standard Deviation corrected for small numbers.

Table XVd.

THE EFFECT OF ATROPINE ON THE PANCREATIC RESPONSE TO SECRETIN BEFORE AND AFTER VAGOTOMY

Secretin after Atropine Dog No. 353

Exp. No.	No. of Days After Vagotomy	Volume Response (Ml./half hour)	Bicarbonate Conc. (mEq./l.)	Bicarbonate Output (micro-Eq.)
1	-	10.8	144	1555
2	-	5.6	143	801
3	-	5.2	136	707
4	-	9.8	146	1431
5	-	6.5	149	969
Pre-Vagotomy Mean ± S.D.		7.6 ± 2.55	144 ± 4.8	1092 ± 379.9
6	7	8.2	136	1115
7	15	6.5	134	871
9	20	12.3	136	1675
10	24	11.8	136	1605
11	78	10.3	132	1360
Post-Vagotomy Mean ± S.D.		9.8 ± 2.40	135 ± 1.8	1525 ± 355.7

S.D. - Standard Deviation corrected for small numbers.

Table XVIIa.

THE EFFECT OF ATROPINE ON THE PANCREATIC RESPONSE TO SECRETIN BEFORE AND AFTER VAGOTOMY

Nitrogen (N) Secretion — Dog No. 355

Exp. No.	Secretin Alone (N) Conc. (mMols./l.)	Secretin Alone (N) Output (microMols.)	Secretin after Atropine (N) Conc. (mMols./l.)	Secretin after Atropine (N) Output (microMols.)
1	105	1495	28	302
2	122	795	38	214
3	165	1187	40	210
4	101	1016	28	277
5	70	373	24	155
Mean ± S.D. Before Vagotomy	113 ± 34.8	973 ± 422.1	32 ± 7.0	232 ± 58.4
6	93	891	68	554
7	93	574	54	350
8	89	1105	-	-
9	88	1227	74	904
10	80	894	57	440
11	77	1015	60	621
Mean ± S.D. After Vagotomy	87 ± 6.7	951 ± 224.8	59 ± 14.5	574 ± 211.9

S.D. - Standard Deviation corrected for small numbers.

Table XXa.

THE EFFECT OF ATROPINE ON THE PANCREATIC RESPONSE TO SECRETIN BEFORE AND AFTER VAGOTOMY

Chloride (C) Secretion — Dog No. 353

Exp. No.	Secretin Alone		Secretin after Atropine	
	(C) Conc. (mEq./l.)	(C) Output (micro-Eq.)	(C) Conc. (mEq./l.)	(C) Output (micro-Eq.)
1	27	383	36	389
2	34	221	34	190
3	20	144	37	192
4	31	313	20	196
5	25	133	11	72
Mean ± S.D. Before Vagotomy	27.4 ± 5.4	239 ± 108.1	27.6 ± 11.5	208 ± 114.0
6	34	902	27	221
7	34	211	32	208
8	25	310	-	-
9	34	476	30	369
10	42	470	22	260
11	31	406	29	299
Mean ± S.D. After Vagotomy	33.3 ± 5.5	463 ± 237.9	28.0 ± 3.8	272 ± 65.1

S.D. - Standard deviation corrected for small numbers.

Table XXIIa.

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