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SOME PHYSIOLOGICAL OBSERVATIONS ON THE EXOCRINE PANCREAS

THE EFFECTS OF SOME AGENTS ON PANCREATIC SECRETION

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ABSTRACT

Many problems are left unsolved on the exocrine pancreas. Pancreatic secretion is controlled by various factors while maintaining close relations with neighbouring organs. From the view point that the stomach and the pancreas are closely associated by way of gastrointestinal hormones, the factors involved in the mechanism of pancreatic secretion were investigated experimentally and clinically by using a gastrin related substance and serotonin. In the scantiness on the electrolyte changes in the pancreatic secretion, some observations were carried out on the electrolyte metabolism. Experiments with dogs and cats were performed under general anesthesia and pancreatic secretion was maintained by intravenous secretin injection. Clinical observations were carried out following pancreozymin-secretin combined test.

Gastrin appeared to activate pancreatic secretion and serotonin to depress pancreatic juice flow.

Neurogenic factors affecting pancreatic secretion were investigated after the administration of cholinergic and anticholinergic agents. The ecbolic action was activated by the former and the hydrelatic action was inhibited mainly by the latter.

The effects on the pancreatic secretion of two diuretics, acetazolamide and furosemide, were also observed. The depression of pancreatic juice flow with little change of electrolytes was demonstrated.

INTRODUCTION

Pancreatic secretion is regulated by hormonal, neurogenic and vascular factors. Such neighboring organs as the stomach, the duodenum and the biliary system have a close association with the pancreas.

Especially, the reciprocal relationship between the pancreas and the stomach became evident during the past years. The pancreas secretes alkaline juice, the stomach does gastric juice of high acidity. Both fluids contain HCO_3

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and H^+ as the major electrolytes respectively and they are catalized partially by the same enzyme, carbonic anhydrase. Gastric hypersecretion after pancreatic duct ligation[1] and inhibition of the secretion of gastric acid by secretin have been reported[2)3)4)5)6)]. Bayliss and Starling[7] attempted to stimulate pancreatic secretion by using extracts of the mucous area of the pyloric gland for the first time, but failed to find any evidence of secretin-like material in their preparation. Drewyer[8], however, found some secretin-like activity in the extract of antral mucosa and the upper small intestine. Slight stimulation of pancreatic juice flow with gastrin preparation was also reported by Kamarow[9)10)] and Uvnäs[11]. In 1959, Harper[12] observed pancreozymin-like activity in gastrin preparations from hog antral mucosa and then described[13] the effects of antral extracts on the pancreas of anesthetized cat, and he assumed that the extracts contained pancreozymin in addition to gastrin. In 1960, Magee[14] reported that distension of the stomach induced the secretion of fluid and enzymes from the pancreas.

Thus, two mechanisms have been described for stimulation of pancreatic secretion by excitants acting in the stomach: one presumably nervous and acting from the fundic part of the stomach, the other hormonal and acting from the pyloric region.

In 1961[15], Gregory isolated gastrin in a pure form, identified its chemical structure, accomplished total synthesis of the molecule, and showed that the natural and synthetic material had the same physiological properties. He found[16)17)] a slight rise in juice flow and a marked rise in enzyme output from the pancreas after the administration of Gastrin I and II, when a backgronnd of secretin was used.

Recently, Grossman[18] described on the invalidity of the previous concept that a single gastrointestinal hormone had only one target organ and only one major physiological action in the same organ. Preshaw[19)20)] also reported on the stimulation of pancreatic secretion by both endogenous release and exogenous injection of gastrin.

Though the transient stimulatory effect of gastrin on small intestinal motility has been reported as its physiological property, Serotonin, 5-Hydroxytryptamin[21)22)], is a well known agent to take part in the mortor activity of the small intestine, and the pyloric mucosa is very rich in this substance as well as gastrin. The pancreas should be influenced by intestinal motility since the gland has a close neurogenic, and vascular connection with the duodenum. The drop in pancreatic secretion following experimental dumping syndrome[23] might be hemodynamic in origin or related to serotonin release. Drapanas[24] reported a decrease in food-stimulated pancreatic flow by serotonin administration but Hudock[25] observed a suppression of secretin-stimulated pancreatic flow even in the abscence of concomitant change in blood pressure.

Cholinergic stimuli have been shown to potentiate the action of both histamine and gastrin[26], and the action of serotonin[22] on gastrointestinal secretion to be mediated at some point in the parasympathetic or vagal pathway. Concerning neurogenic factors, Grossman[27] summarized clearly the neural mechanisms controlling pancreatic secretion. Magee[28)29)30)31] recently reemphasized the importance of parasympathetic innervation in pancreatic secretion and Thomas[32] observed a significant depression in the volume response to secretin when the anticholinergic drugs were given.

On the other hand, Rawls[33] in 1963, studied the effect of acid-base changes on pancreatic secretion and concluded that about one-half of the bicarbonate output in pancreatic juice is dependent on the carbonic anhydrase-catalyzed reaction. Perks[34] reported that the administration of ADH caused a marked diminution in pancreatic juice flow, whereas sodium, potassium and bicarbonate concentrations in the juice remained constant. An active transport of sodium and potassium was first suggested by Debray[35]. Then Perrier[36] observed the changes of these electrolytes and bicarbonate in pancreatic juice applying renal "stop-flow" techniques. These data on the electrolytes changes of pancreatic juice lead us to the concept that there may be an analogous function between the pancreatic collecting system and the renal tubules.

The purpose of the present study is to investigate the effects of some agents, such as a synthesized tetrapeptide structually related to the active part of Gastrin, Serotonin (5-Hydroxytryptamin), Neostigmine (a cholinegric agent), Hyoscin-N-Butylbromide (an anticholinergic agent), Acetazolamide (a strong inhibitor of carbonic anhydrase), and Furosemide (a new synthesized diuretic) on pancreatic secretion in cats and dogs and, in a part, in human subjects. The study of the microscopic changes was also carried out on the rat pancreas after serotonin administration.

MATERIALS AND METHODS

I) Pancreatic secretion

a) Experimental studies

The experiments were performed on 40 dogs weighing between 6.3 and 11.0 kg and 55 cats weighing between 1.9 and 3.2 kg, under the anesthesia with hexobarbital sodium. The abdomen was entered through a midline incision and the duodenum with its mesentery containning the pancreas was deliverd toward the surface. After occluding the pylorus and ligating the accessory pancreatic duct only in dogs, a polyethylene cathter* was inserted carefully into the main pancreatic duct from the outside of the duodenum by incising its serosa. Two sutures were applied at the incision site to afford fixation of

* Polyethlene tubes: supplied by American Commercial Co., Japan. P. E. 50 in cats and P.E. 100 in dogs, were used.

the catheter to the duodenum. Throughout the experiments, the animals were kept on the supine position with closed abdomen and maintained in the light level of Stage III with subsequent small doses of anesthetics. Steady background flow of pancreatic juice was maintained in dogs by repeated intravenous injection of 5 units of secretin through a superficial venous catheter at intervals of 30 minutes, and in cats by constant secretin infusion through a polyethylene catheter in the femoral vein at the rate of 0.1 unit/minute by means of an autoinjector*. Secretin** was freshly diluted in saline each day. During the period of baseline measurement, relatively constant pancreatic flow was achieved by these methods, and the pancreatic juice was collected at 30 minutes intervals in dogs and at 15 minutes intervals in cats.

In dogs, each of the experimental agents was administered from another vein simultaneously with the fifth injection of secretin after the control period of four successive 30 minute collections of pancreatic juice, and in cats, though different in dosages, the same agents were injected as well after the control period of four successive 15-minute collections of the juice.

b) Clinical studies

Bartelheimer's "dreiläufige Doppelballon Sonde" was used in combined pancreozymin-secretin test. The "Sonde" was passed through the esophagus of the fasted subject under fluoroscopic observation until the top of the "Sonde" reached the distal end of the third portion of the duodenum. After the duodenal juice became clear and alkaline in reaction, duodenal juice was collected in the following way: one for 20 minutes before the stimulation and another for 10 minutes after the pancreozymin administration, then secretin injection (50 units in both) was done, being followed by 10-, 10-, 20-, and 20-minutes fractional collections. After these procedures, some doses of a synthesized tetrapeptides, Hyoscin-N-Butylbromide, and Furosemide were injected, and 15 minutes collections of the juice was repeated for the following 30 or 45 minutes.

All pancreatic juice, obtained experimentally and clinically, were collected in micro-graduated test tubes and volume was accuratelly measured, and aliquots were placed on ice for immediate biochemical analysis. Bicarbonate concentration was determined by a micro-gasanalyser*** and reported as a miliequivalent per liter of pancreatic juice. Amylase activity was determined by the modified Somogyi method, and protein concentration was measured by the absorption at 280 mμ with a spectrophotometer**** and described as mg per dl in amylase concentration and as mg per ml in protein concentration while amylase and protein contents were described as mg per 30 min or per

* K-N type autoinjector; made by Natsume Co., Japan.
** Boots Secretin.
*** E.K.D.S. type: supplied by Kayagaki Co., Japan.
**** No. 101: supplied by Hitachi Co., Japan.

15 min.

Electrolytes, Na, K were measured by using a flame photometer*, and Cl, by Schales and Schales method, and they were described as miliequivalent per liter of pancreatic juice.

II) Pancreatic tissues

a) Experimental studies

5, 10, and 30 mg per kilogram of serotonin creatinine sulfate were injected subcutaneously three or five times a day in 38 rats, and the same volume of distilled water was injected in 7 rats weighing about 200 grams. They were sacrificed 24, 48, and 72 hours after the injection, the gastrointestinal tracts and the pancreas were examined carefully, and histological observations were carried out on the pancreas after fixation and hematoxylin-eosin staining.

RESULTS

I. Standard experiments

A) Basal pancreatic secretion induced by secretin

After four successive collections of pancreatic juice at 15 minutes intervals in 13 cats and at 30 minutes intervals in 13 dogs, the volume, bicarbonate concentration, amylase activity or protein concentration, and electrolytes were measured in the later three successive speciemens as the basal values of pancreatic secretion using the methods previously described. The first specimen was not served for measurement since "wash-out effect" of pancreatic enzyme was evident.

Fig. 1 shows the mean values of pancreatic components in the three successive specimens and their overall mean values in 13 cases of each animal. Each component in the juice appears to be relatively equal in amount among the three collections. But, as shown in Fig. 2, variations are relatively large in the mean values of the components in the three successive collections in 13 individuals of both species, especially in amylase concentration, amylase output, protein concentration and protein amount, varying with a range of 576.0-6924.8 mg/dl (amylase concentration) and 8.8-101.3 mg/15 min (amylase output) in cats and of 1.80-25.13 mg/ml (protein concentration) and 2.80-31.48 mg/30 min (protein output) in dogs. And the same tendency was observed in juice flow in dogs with the range of 0.30-5.54 ml/30 min.

Table 1 shows the geometric means with standard errors calculated from the mean values of the components in the three successive collections as the control pancreatic flow in both species.

B) Relationship among the four components of pancreatic juice and the

* Evans: supplied by Asahitsusho Co., Japan.

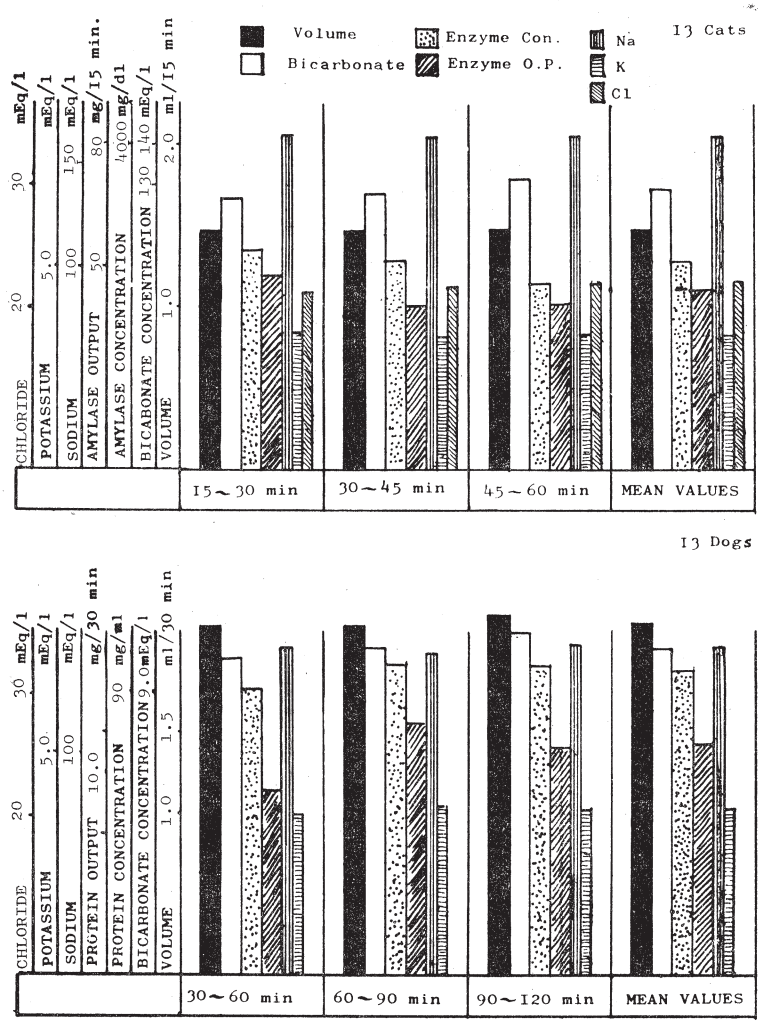

FIG. 1. Mean values of pancreatic components in the three successive specimens of pancreatic juice and their overall mean values.

body weight.

There were a highly significant correlation between protein amount per 30 minutes and the body weight ($r=+0.85$, $p<0.001$), and a relative correlation between protein concentration per 30 minutes and the body weight ($r=+0.63$, $p<0.02$) in the dogs. Other components, on the other hand, were poorly correlated with the body weight in both species, as shown in Fig. 3 and 4.

II. The effects of some agents on the pancreas

As cholinergic activities seem to vary according to animal species and

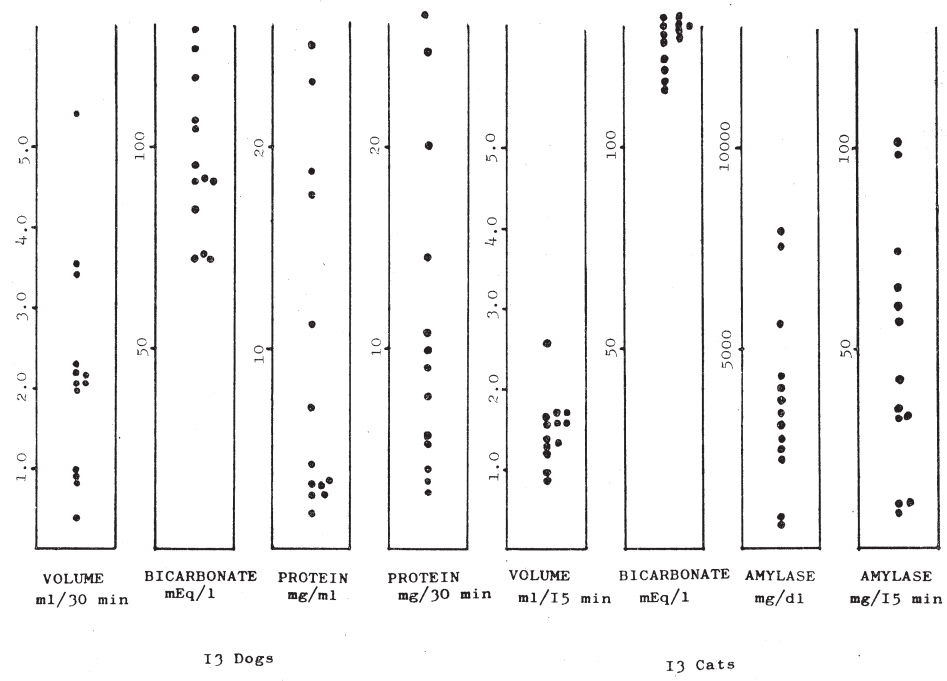

FIG. 2. Variations of mean values of the components in the three successive collections of pancreatic juice of individual animals.

TABLE 1. Basal Pancreatic Secretion Expressed as Geometric Means with Standard Errors

Cats	Volume	Bicarbonate	Amylase		Electrolytes		
			Concentration	Output	Na	K	Cl
G.M.±S.E.	1.42±0.12 ml/15 min	128.3±2.7 mEq/l	2707.2±746.1 mg/dl	31.9±9.13 mg/15 min	163.5±1.3 mEq/l	3.3±0.2 mEq/l	22.6±2.8 mEq/l

Dogs	Volume	Bicarbonate	Protein		Electrolytes	
			Concentration	Output	Na	K
G.M.±S.E.	1.75±0.35 ml/30 min	98.9±0.1 mEq/l	6.25±2.39 mg/ml	8.83±1.68 mg/30 min	160.3±1.3 mEq/l	4.0±0.1 mEq/l

Above; obtained from 13 cats (Background; constant secretin infusion at the rate of 0.1 unit/minute).
Below; obtained from 13 dogs (Background; rapid secretin injection of 5 units in every 30 minutes).

individuals as shown in Fig. 2, calculations were made for the ratios of mean values of each pancreatic component in the three successive collections of the control flow to the values of the corresponding components, measured during

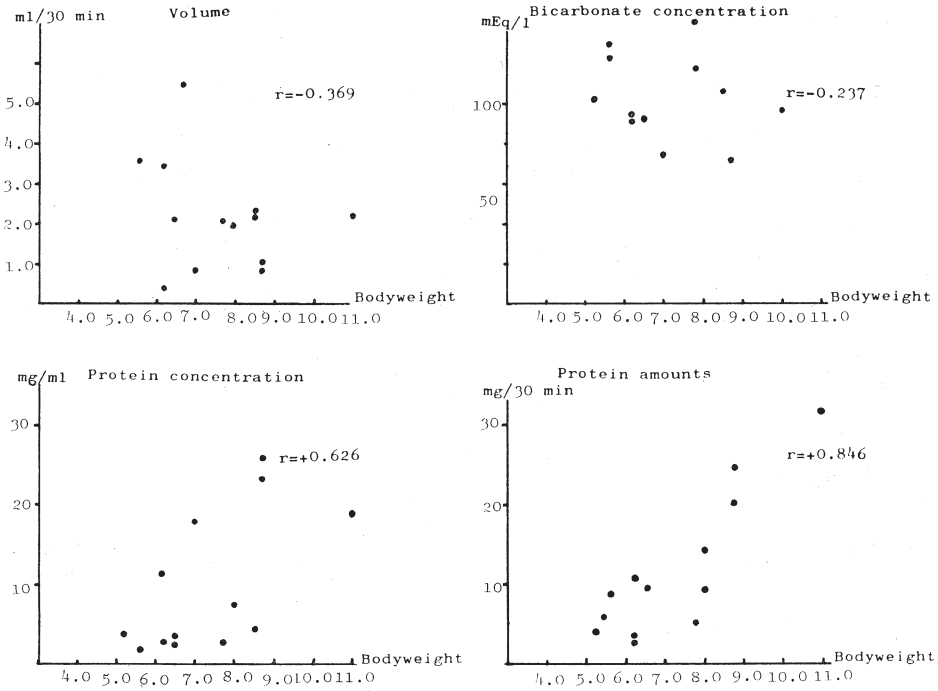

FIG. 3. The relationship between four components of pancreatic juice and the bodyweight in 13 dogs.

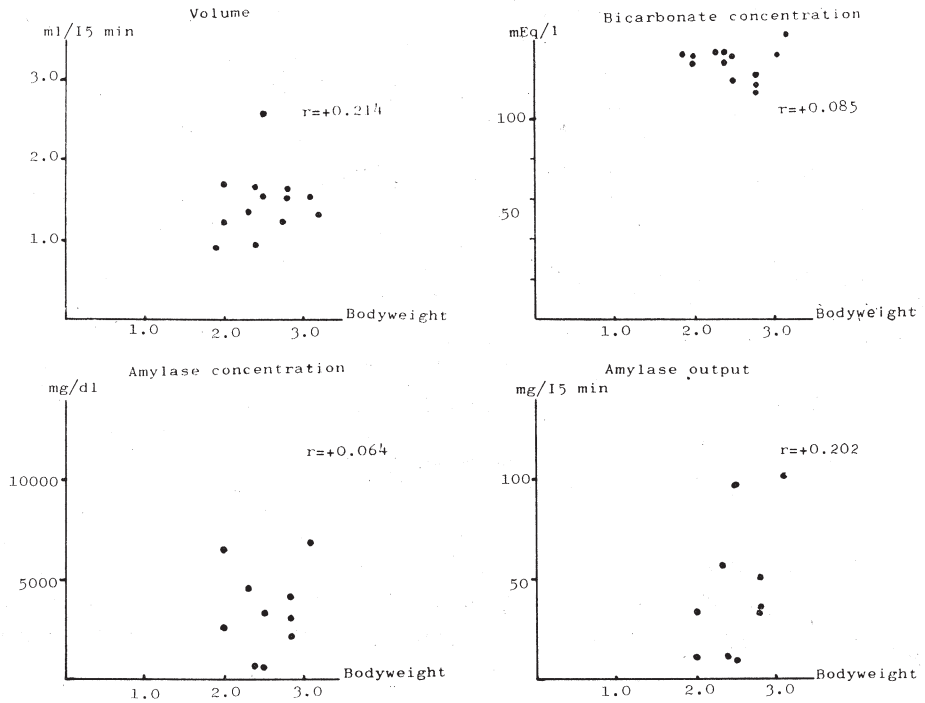

FIG. 4. The relationship between four components of pancreatic juice and the bodyweight in 13 cats.

the 30 minutes and during 30–60 minutes in the dogs, and to the values during the 15 minutes, and to the mean values of those during the 15–30 minutes and during the 30–45 minutes in the cats after the drug administration. Geometric means with standard errors and *t*-values (Student's *t*) were obtained to statistically evaluate the effects of these agents on pancreatic secretion. In a few cases, clinical observations were also made.

A) A synthesized tetrapeptide structually related to an active part of Gastrin (*T*-butoxy carbonyl try. met. asp. phe. NH_2*)

a) Pancreatic secretion

1) Experimental studies

Fig. 5 shows the mean values of the changes in pancreatic components before and after the intravenous administration of this agent in 7 animals of both species. Though the doses were different, as 2 μg perkilogram in the

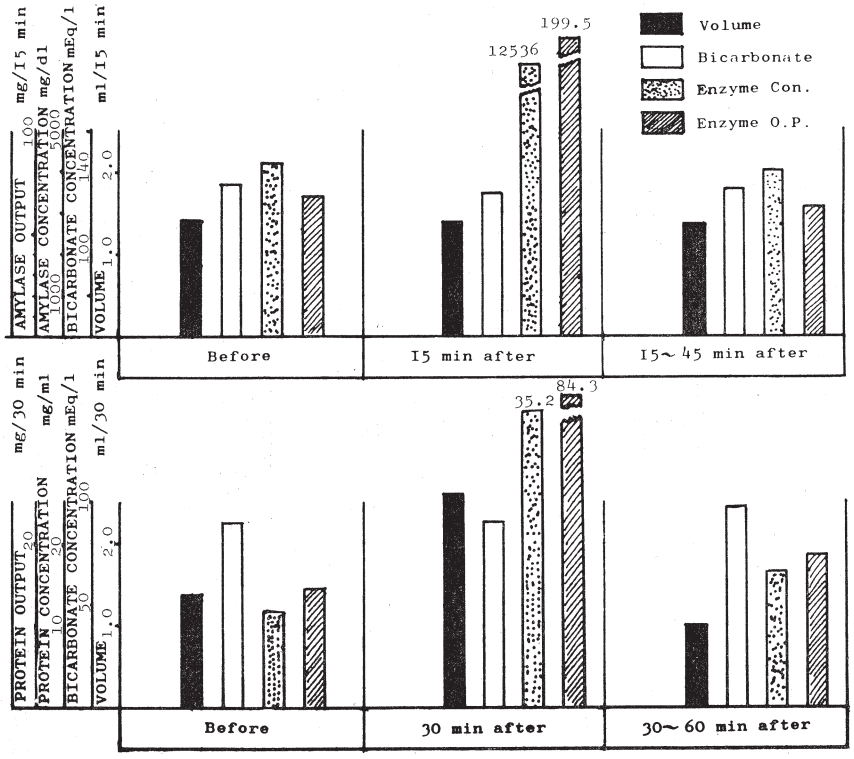

FIG. 5. Effects of gastrin related tetrapeptide on pancreatic secretion.
Four components in the juice illustrated in mean values.
Above; obtained from 7 cats (dosis 2 μg/kg)
Below; obtained from 7 dogs (dosis 50 μg/kg)

* Supplied by Eisai Co., Japan.

cats and 50 μg per kilogram in the dogs, there were observed after the administration in the cats, an extreme increase of amylase concentration with the range of 4,553–39,010 mg/dl (control; 4,180) and amylase output with the range of 90.1–616.4 mg/15 min (control; 68.14) ($p<0.01$ in both).

Similar results were obtained also in the dogs, as represented by protein concentration with the range of 11.54–61.80 mg/ml (control; 11.47) and protein amount with the range of 32.23–153.26 mg/30 min (control: 14.10) 30 minutes after the administration ($p<0.01$ in both). These increases of pancreatic enzymes showed a tendency to return to basal line before the succeeding collection.

Though there were no changes in the pancreatic juice flow in the cats, about two-folds increase of the pancreatic juice flow was observed in the dogs with the range of 1.92–4.45 ml/30 min (control: 1.35) 30 minutes after the administration ($p<0.01$). As regard the other components, no significant changes were observed including electrolytes changes in both species. Table 4 shows the changes of the four components of pancreatic juice after the administration of the tetrapeptide in the experimental animals, as expressed by the geometric mean and the standard error.

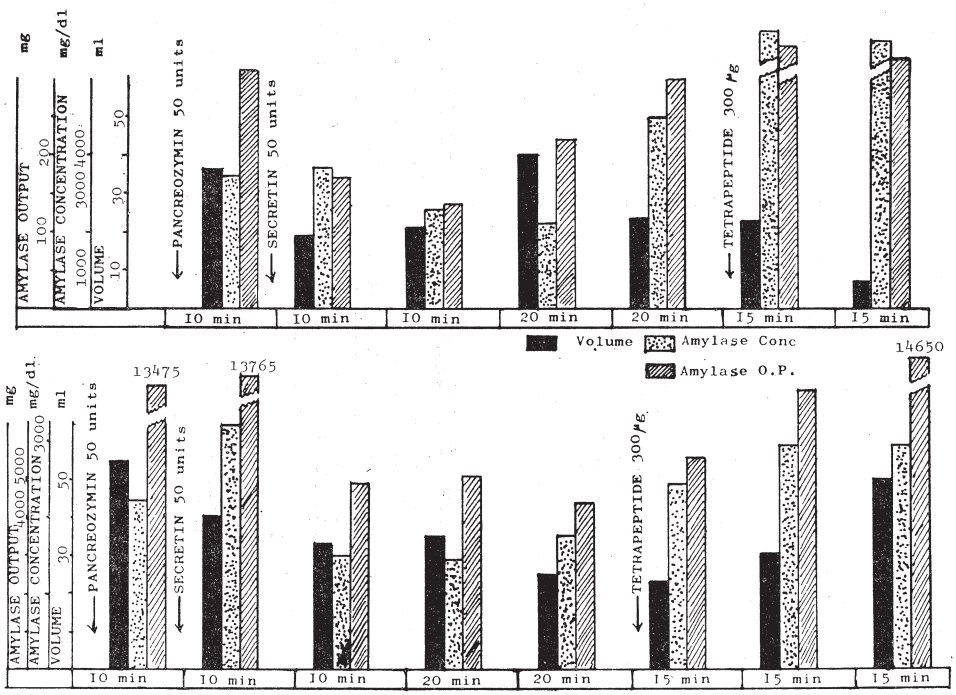

FIG. 6. Effects of gastrin related tetrapeptide on human pancreatic secretion. Two normal subjects.

2) Clinical studies

300 μg of this gastrin related tetrapeptide was administered subcutaneously in the human subjects after the pancreozymin-secretin combined test. Fig. 6 shows the effects of this agent on the pancreatic secretion in two normal subjects. The juice flow and the amylase activity were increased.

B) Serotonin

a) Pancreatic secretion

1) Experimental studies

Serotonin creatinine sulfate were administered by slow injection lasting 5 minutes in the doses of 2, 5, and 10 mg per kilogram to 4, 3, and 4 cases of cats respectively, and 0.25, 0.50 mg per kilogram of the same agents were injected to 8 and 6 cases of dogs in the same way.

Changes of pancreatic components after serotonin administration varied with the doses and animal species used, as shown in Fig. 7 and 8. Depression of the pancreatic juice flow was observed except in one group of the cat receiving 2 mg per kilogram of serotonin.

Fig. 8 shows the depression of the juice flow after the administration of 10 mg per kilogram of the agent in the 4 cats to the range of 0.50–0.70 ml/15

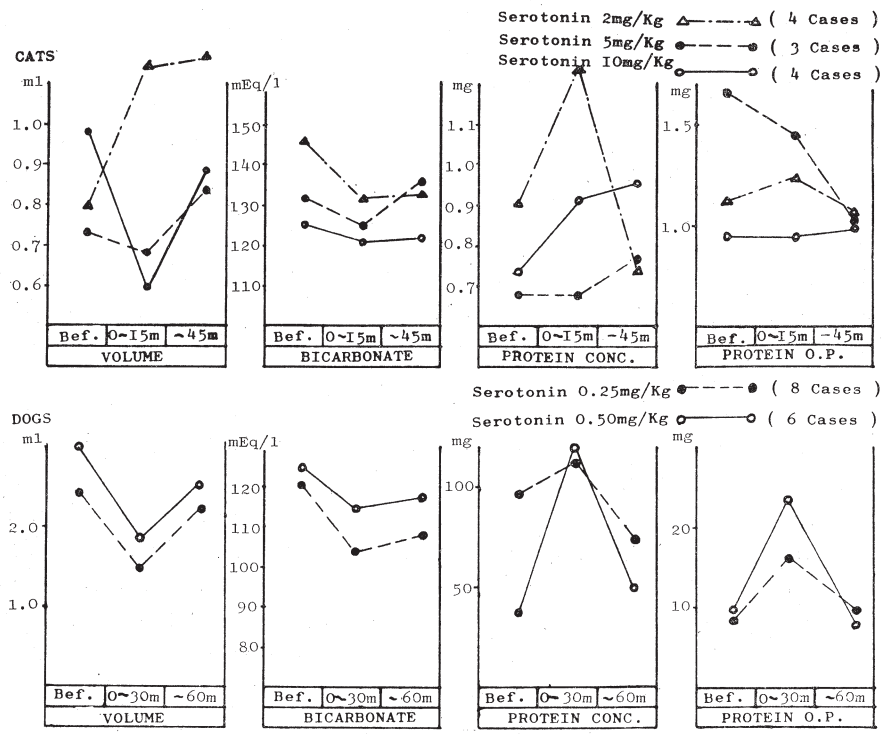

FIG. 7. Changes of four components of pancreatic juice after serotonin administration.

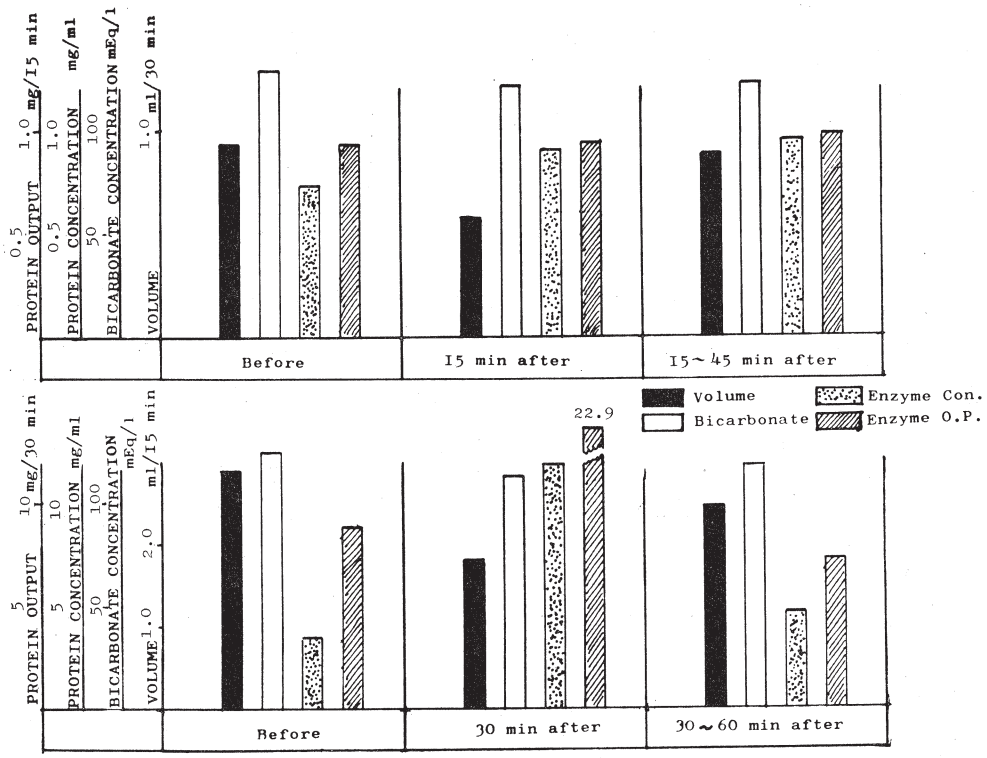

FIG. 8. Effects of serotonin on pancreatic secretion.
Four components in the juice illustrated in mean values.
Above; obtained from 4 cats (dosis 10 mg/kg)
Below; obtained from 6 dogs (dosis 0.50 mg/kg)

min (control: 0.97) 15 minutes after the administration ($0.05<p<0.02$), and also after the administration of 0.50 mg per kilogram of the agent to the 6 dogs to the range of 0.45–2.65 ml/30 min (control: 2.89) 30 minutes after the administration ($p<0.01$).

However, the depression of the juice flow appears to be transient as demonstrated in these figures. A slight depression of bicarbonate concentration was observed in both species.

In the dogs, the protein content (concentration and output) increased immediately after the administration of serotonin as measured in the specimen collected during 0–30 minutes, and the elevation of protein concentration was particularly significant in the 6 dogs to whom 0.50 mg per kilogram of the agent was given, to the extent of 0.74–1.42 mg/ml (control: 0.73) ($p<0.01$), but it showed a tendency to decrease in the subsequent specimen. In the cats, however, protein content was liable to decrease or to be variable as shown in Fig. 7 and 8.

Hyperventilation and increased motility of the duodenum were observed after the administration of serotonin.

In Table 4, there are summarized the changes of the four components of pancreatic juice after the administration of serotonin creatinine sulfate in the experimental animals, as expressed by the geometric mean and the standard error.

b) The pancreas and the stomach

Plate 1 shows the multiple gastric ulcers at the lesser curvature of the stomach of the rats produced by serotonin administration.

The occurrence of gastric ulcer was closely related with the dose of this agent and not with the time when sacrificed. The results of this experiment are shown in Table 2 and 3.

In the pancreas of the rats, careful search for cellular infiltration, hemorrhage, necrosis, intestitital fibrosis and other changes in the islet revealed no significant finding, and the interstitial congestion of the pancreas, which is shown in Plate 2, was the only positive microscopic finding. Yet, this interstitial congestion had no close relation to the dose of serotonin administered, the occurrence of gastric ulcer or the time when sacrificed.

TABLE 2. Effects of Serotonin on Pancreatic Tissues and Stomach of Rats

Group	Exp. No.	Interstitial congestion	Cellular infiltration	Hemorrhage	Necrosis	Interstitial fibrosis	Islet change	Gastric ulcer
A	246	(⊥)	(−)	(−)	(−)	(−)	(−)	(+)
	247	(−)	(−)	(−)	(−)	(−)	(−)	(+)
	248	(±)	(−)	(−)	(−)	(−)	(−)	(−)
	249	(−)	(−)	(−)	(−)	(−)	(−)	(+)
	250	(−)	(−)	(−)	(−)	(−)	(−)	(−)
B	273	(−)	(−)	(−)	(−)	(−)	(−)	(−)
	276	(±)	(−)	(−)	(−)	(−)	(−)	(−)
	277	(−)	(−)	(−)	(−)	(−)	(−)	(−)
	278	(⊥)	(−)	(−)	(−)	(−)	(−)	(−)
C	227	(−)	(−)	(−)	(−)	(−)	(−)	(+)
	229	(−)	(−)	(−)	(−)	(−)	(−)	(+)
	230	(−)	(−)	(−)	(−)	(−)	(−)	(−)
	236	(−)	(−)	(−)	(−)	(−)	(−)	(−)
	237	(−)	(−)	(−)	(−)	(−)	(−)	(−)
	238	(−)	(−)	(−)	(−)	(−)	(−)	(−)
	239	(+)	(−)	(−)	(−)	(−)	(−)	(−)
	240	(−)	(−)	(−)	(−)	(−)	(−)	(−)
	242	(−)	(−)	(−)	(−)	(−)	(−)	(−)

Group A and B; administered with serotonin (5 mg/kg) 5 times in 24 hours and sacrificed 24 hours (A) and 48 hours (B) after the last administration.

Group C; administered with serotonin (10 mg/kg) 3 times in 24 hours and sacrificed 24 hours after the last administration.

Finding order: (−), (±), (⊥), (+), (+)

TABLE 3. Effects of Serotonin on Pancreatic Tissues and Stomach of Rats

Group	Exp. No.	Interstitial congestion	Cellular infiltration	Hemorrhage	Necrosis	Interstitial fibrosis	Islet change	Gastric ulcer
D	257	(±)	(−)	(−)	(−)	(−)	(−)	(+)
	261	(−)	(−)	(−)	(−)	(−)	(−)	(−)
E	283	(⊥)	(−)	(−)	(−)	(−)	(−)	(−)
	284	(−)	(−)	(−)	(−)	(−)	(−)	(−)
	285	(卄)	(−)	(−)	(−)	(−)	(−)	(−)
	286	(±)	(−)	(−)	(−)	(−)	(−)	(−)
	287	(±)	(−)	(−)	(−)	(−)	(−)	(−)
F	302	(−)	(−)	(−)	(−)	(−)	(−)	(+)
	303	(±)	(−)	(−)	(−)	(−)	(−)	(+)
	304	(−)	(−)	(−)	(−)	(−)	(−)	(+)
	305	(⊥)	(−)	(−)	(−)	(−)	(−)	(+)
	306	(±)	(−)	(−)	(−)	(−)	(−)	(−)
	307	(−)	(−)	(−)	(−)	(−)	(−)	(+)
	308	(−)	(−)	(−)	(−)	(−)	(−)	(+)
G	312	(−)	(−)	(−)	(−)	(−)	(−)	(+)
	313	(−)	(−)	(−)	(−)	(−)	(−)	(−)
	315	(−)	(−)	(−)	(−)	(−)	(−)	(+)
H	320	(⊥)	(−)	(−)	(−)	(−)	(−)	(+)
	321	(−)	(−)	(−)	(−)	(−)	(−)	(+)
	324	(−)	(−)	(−)	(−)	(−)	(−)	(+)
Control	243	(−)	(−)	(−)	(−)	(−)	(−)	(−)
	244	(−)	(−)	(−)	(−)	(−)	(−)	(−)
	245	(−)	(−)	(−)	(−)	(−)	(−)	(−)
	253	(−)	(−)	(−)	(−)	(−)	(−)	(−)
	271	(−)	(−)	(−)	(−)	(−)	(−)	(−)
	310	(−)	(−)	(−)	(−)	(−)	(−)	(−)
	319	(−)	(−)	(−)	(−)	(−)	(−)	(−)

Group D and E; administered with serotonin (10 mg/kg) 5 times in 24 hours and sacrificed 24 hours (D) and 48 hours (E) after the last administration.

Group F, G and H; administered with serotonin (30 mg/kg) 3 times in 24 hours and sacrificed 24 hours (F), 48 hours (G) and 72 hours (H) after the last administration.

Finding order: (−), (±), (⊥), (+), (卄).

C) Neostigmine

a) Pancreatic secretion

1) Experimental studies

Neostigmine of 0.1 mg per kilogram was administered intravenously to 6 cats, and 0.5 mg per kilogram to a dog.

Fig. 9 shows the effects of neostigmine on pancreatic secretion. Significant increase of amylase concentration and amylase output was observed 15 minutes and 15–45 minutes after the administration to the extent of 17,506–37,680 mg/dl (control: 5,617) in concentration, and 236.3–376.8 mg/15 min (control: 72.3) in output in the 6 cats ($p<0.01$ in both).

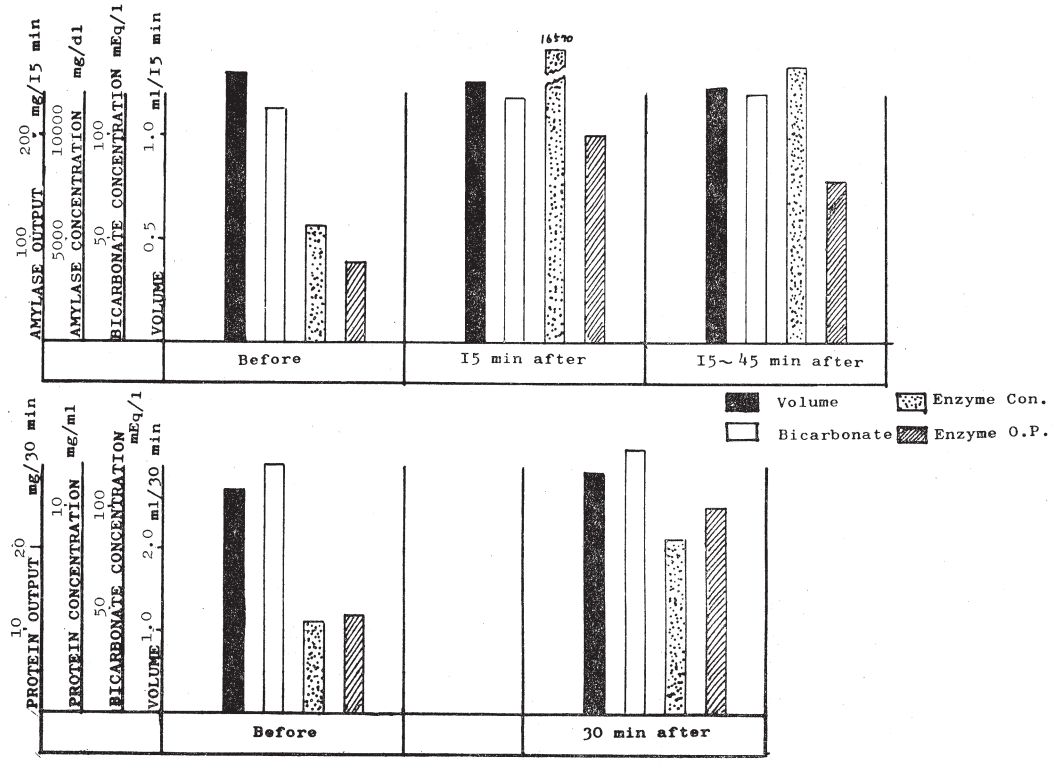

FIG. 9. Effects of neostigmine on pancreatic secretion.
Above; four components in the juice obtained from 6 cats illustrated in mean values (dosis 0.1 mg/kg)
Below; four components obtained from a dog (dosis 0.5 mg/kg)

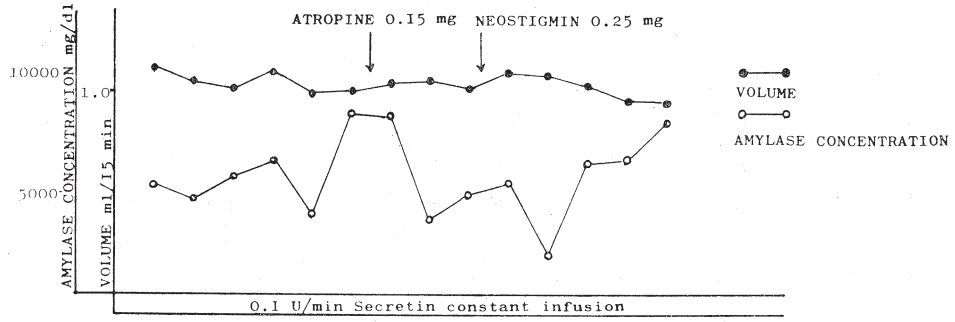

FIG. 10. Effects of neostigmine on pancreatic secretion after atropinization in a cat.

In the dog, a similar result was obtained. Significant changes of juice flow and bicarbonate concentration were not observed following neostigmine administration. The changes of the components of pancreatic juice after the

administration of neostigmine are summarized in Table 5. The blocking effect of atropine sulfate on the increased amylase activity by neostigmine in a cat is illustrated in Fig. 10. Atropine did not affect the pancreatic juice flow but inhibited the enhancement of amylase activity by neostigmine.

D) Hyoscin-N-Butylbromide, a ganglion blocker

a) Pancreatic secretion

1) Experimental studies

The agent of 1 mg per kilogram was administered intravenously to 7 cats and 5 mg per kilogram to two dogs.

In the cats, a significant depression of juice flow was observed 15 minutes after the administration to the extent of 0.28–1.22 ml/15 min (control: 1.47)($p<0.01$), but a tendency was demonstrated to recover to control values before the subsequent collection as illustrated in Fig. 11. Though a slight depression in bicarbonate concentration was observed, amylase concentration had a slight

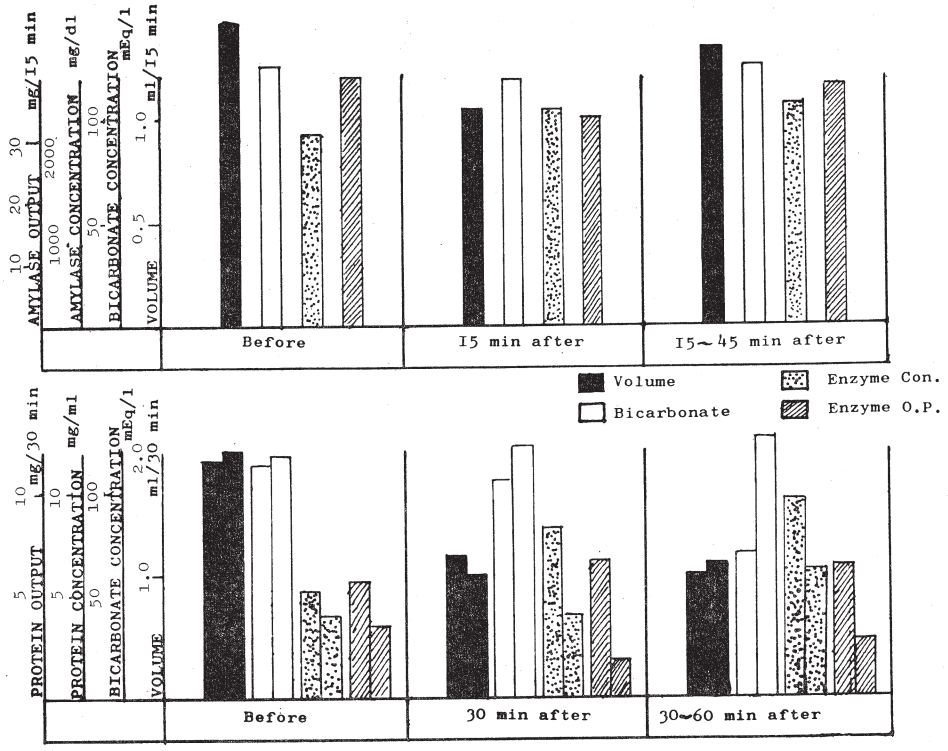

FIG. 11. Effects of hyoscin-N-butylbromide on pancreatic secretion.
Above; four components in the juice obtained from 7 cats illustrated in mean values (dosis 1 mg/kg)
Below; four components obtained from 2 dosis 5 mg/kg)

tendency to increase reciprocally with the depression of juice flow ($0.05<p<0.02$ in 15 min and $p>0.05$ in 15-45 min) but amylase output was depressed in parallel with juice flow ($0.02<p<0.05$ in 15 min).

The results in the cats are summarized in Table 5. In the dogs, the depression of juice flow and the elevation of protein concentration were more evident without any remarkable change in protein amount as illustrated in Fig. 11.

2) Clinical studies

20 mg of this ganglionic blocker was injected intravenously in two human subjects after the pancreozymin-secretin combined test. Fig. 12 shows the effect of this agent on pancreatic secretion of two normal subjects. While a remarkable depression of juice flow with a concomitant decrease of amylase activity was observed in a case, a transient depression of juice flow without any change in the other component was demonstrated in the other.

E) Acetazolamide, an inhibitor of the carbonic anhydrase

1) Experimental studies

30, 20, 10, 5 and 2.5 mg per kilogram of the agent were administered intravenously to 2, 2, 1, 1 and 2 cats respectively. The same agent of 1 mg

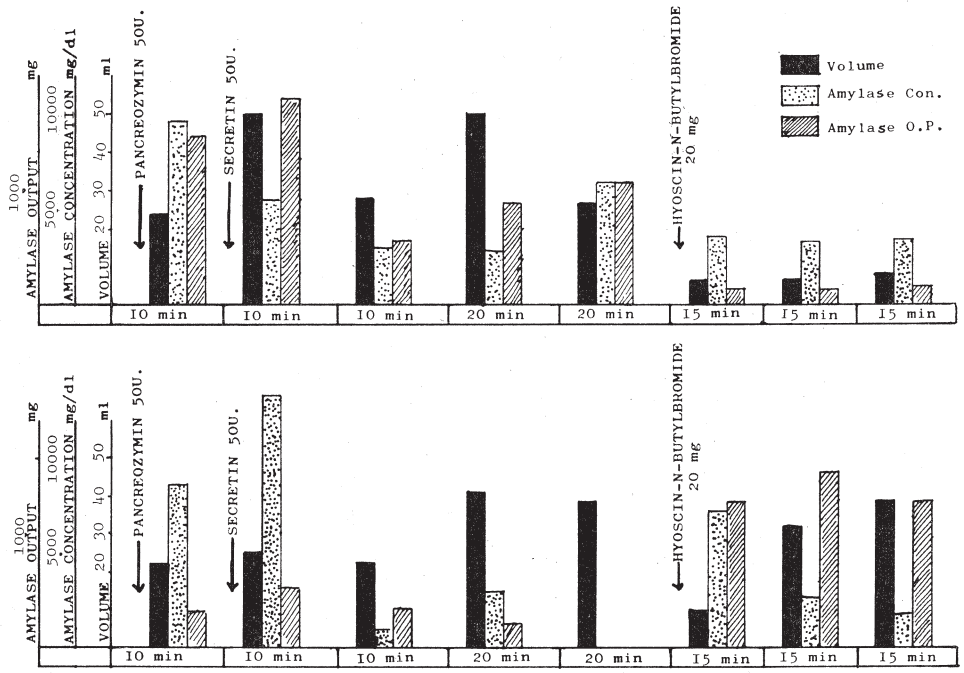

FIG. 12. Effects of hyoscin-N-butylbromide on human pancreatic secretion. Two normal subjects.

per kilogram was given to 7 cats, and 10 mg per kilogram to a dog. The result of this experiment in the cat is summarized in Table 5. No close relation was demonstrated between the depression of the two components, volume and bicarbonate concentration, and the dose of this agent administered. Namely, the degrees of depression in the two components in both groups were minute but the elevation of protein concentration was more eminent in the former group than in the latter, and the decrease of protein amount was seen in the latter. A tendency of K concentration to increase was seen in both groups. Fig. 13 shows the effects of acetazolamide on the four components of pancreatic secretion.

Following the administration of this agent, there was observed a depression of juice flow, with a relatively constant bicarbonate concentration, to the extent of 0.40–0.53 ml/min (control: 0.89) ($p<0.01$ in 15 min, $0.02>p>0.01$ in 15–45 min) in the cats. A moderate elevation of protein concentration was demonstrated, and protein amount, as temporarily depressed ($p>0.05$ in both animals),

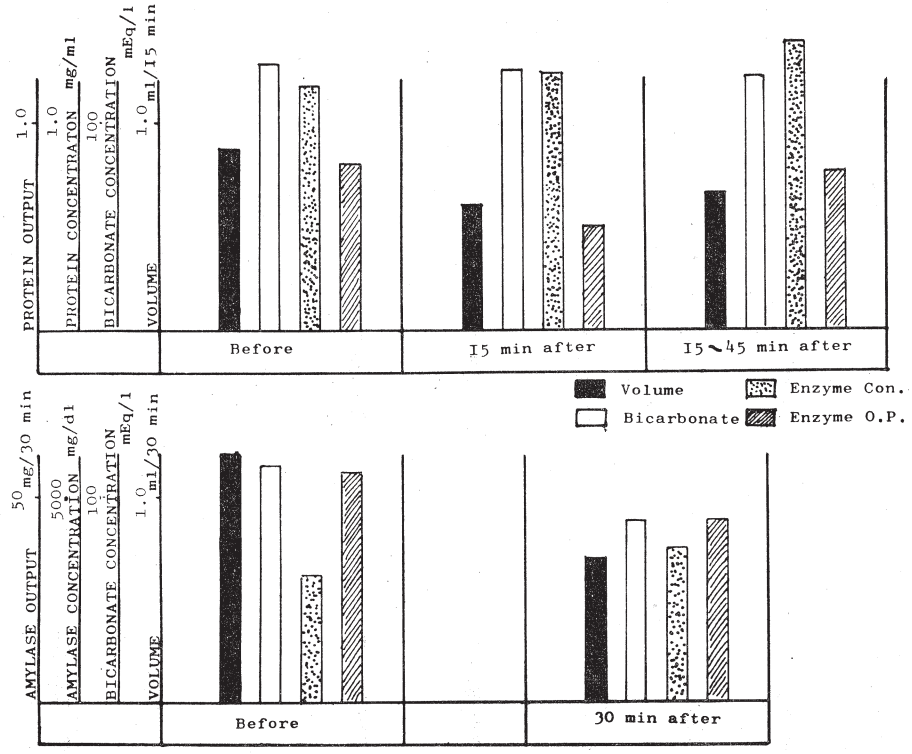

FIG. 13. Effects of acetazolamide on pancreatic secretion.
Above; four component in the juice obtained from 7 cats illustrated in mean values (dosis 1 mg/kg)
Below; four components obtained from a dog (dosis 10 mg/kg)

showed a tendency to recover to the control values by 15–45 minutes after the administration in the 7 cats. Depression in juice flow, bicarbonate concentration and amylase output was observed in a dog.

F) Furosemide, 4 chloro-N-2-furyl methly-5-sulfanyl-anthranilic acid

a) Pancreatic secretion

1) Experimental studies

One mg per kilogram of this agent was administered intravenously to 10 cats, and 10 mg per kilogram to two dogs. As shown in Fig. 14, there was observed a slight depression of juice flow and bicarbonate concentration with a little concomitant elevation of protein concentration in the cats ($0.02<p<0.05$ in juice flow during 15–45 min and $p<0.05$ in others). The results are tabulated in Table 5.

In the dogs, the depression of juice flow and bicarbonate concentration was more evident with a reciprocal elevation of protein concentration. The change of electrolytes was different from the cases of acetazolamide admini-

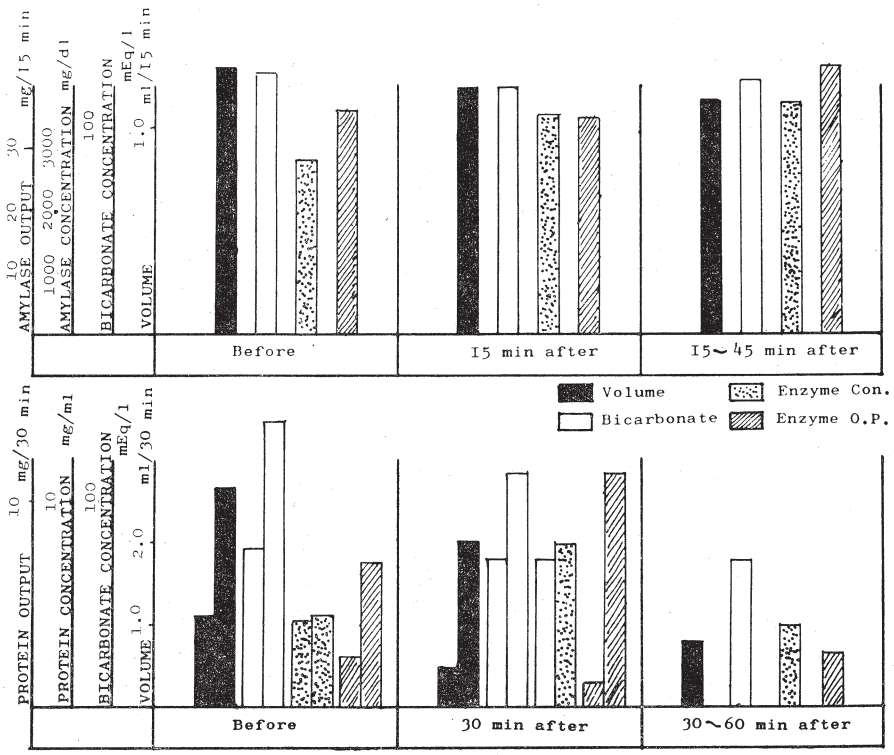

FIG. 14. Effects of furosemide on pancreatic secretion.
Above; four components obtained from 10 cats (dosis 1 mg/kg)
Below; four components obtained from 2 dogs (dosis 10 mg/kg)

stration. Namely, there was a tendency of K concentration to decrease after the administration of this agent as shown in Table 5.

2) Clinical studies

Twenty mg of furosemide was injected intravenously in two subjects following the pancreozymin-secretin combined test. Fig. 15 shows the effect of this agent on pancreatic secretion of normal subject and a patient with chronic pancreatitis. In the normal cases, a normal response was seen in the components of pancreatic juice, as manifested by the depression of juice flow and elevation of amylase concentration. But the elevation of amylase concentration was slight in the patient.

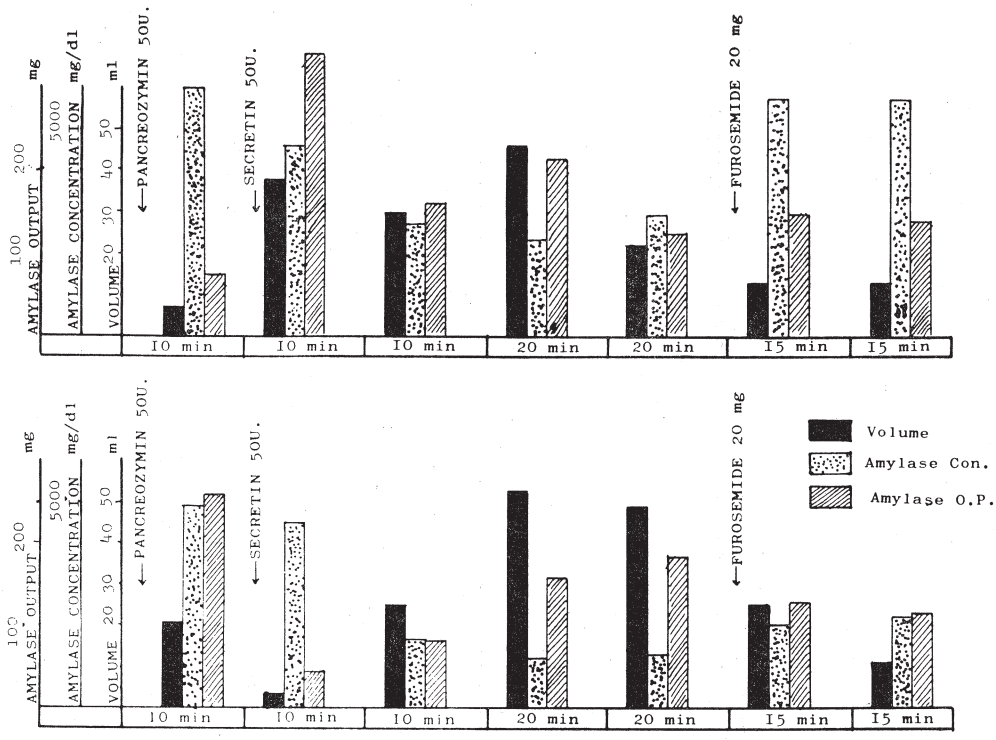

FIG. 15. Effects of furosemide on human pancreatic secretion.
Above; a normal subject
Below; a patient with chronic pancreatitis

TABLE 4. Effects of Some Agents on Pancreatic Secretion Expressed as G.M.±S.E.

Agents	Species	Doses	Observation time (min)	Pancreatic juice			
				Volume	Bicarbonate	Enzyme	
						Concentration	Output
Gastrin related tetrapeptide	7 Cats	2 μmg/kg	0~15	1.01±0.03	0.98±0.03	3.20±0.95	2.24±0.78
			15~45	1.00±0.05	0.98±0.02	0.89±0.20	0.83±0.12
	7 Dogs	50 μmg/kg	0~30	2.05±0.37	0.99±0.23	3.54±0.87	9.22±3.20
			30~60	0.81±0.24	1.03±0.10	1.54±0.69	1.75±0.88
Serotonin creatinine sulfate	4 Cats	2 mg/kg	0~15	1.03±0.42	0.90±0.08	0.91±0.16	1.05±0.22
			15~45	1.18±0.26	0.95±0.07	0.73±0.18	0.85±0.21
	3 Cats	5 mg/kg	0~15	0.89±0.18	0.94±0.08	0.97±0.02	0.90±0.19
			15~45	1.13±0.31	1.04±0.10	1.01±0.06	1.38±0.25
	4 Cats	10 mg/kg	0~15	0.59±0.07	0.94±0.11	1.19±0.11	0.97±0.07
			15~45	0.95±0.04	0.97±0.03	1.25±0.12	1.08±0.02
	8 Dogs	0.25 mg/kg	0~30	0.46±0.15	0.87±0.07	2.17±0.57	1.36±0.43
			30~60	0.85±0.14	0.89±0.06	1.33±0.69	0.93±0.18
	6 Dogs	0.50 mg/kg	0~30	0.53±0.11	0.85±0.04	2.90±0.86	1.55±0.57
			30~60	0.75±0.14	0.93±0.05	1.04±0.30	0.81±0.16

TABLE 5. Effects of Some Agents on Pancreatic Secretion Expressed as G.M.±S.E.

Agents	Species	Doses	Observation time (min)	Pancreatic juice					
				Volume	Bicarbonate	Enzyme		Electrolytes	
						Concentration	Output	Na	K
Neostigmine	6 Cats	0.1 mg/kg	0~15	0.96±0.08	1.01±0.01	2.61±0.47	2.41±0.60		
			15~45	0.96±0.05	1.02±0.01	2.63±0.42	2.32±0.50		
Hyoscin-N-Butylbromide	7 Cats	1.0 mg/kg	0~15	0.65±0.07	0.92±0.03	1.26±0.09	0.66±0.14		
			15~45	0.80±0.12	0.99±0.02	1.16±0.30	0.98±0.24		
Acetazolamide	8 Cats	2.5 mg/kg ~ 30.0 mg/kg	0~15	0.70±0.07	0.93±0.03	1.36±0.38	1.07±0.22	1.01±0.01	1.04±0.02
			15~45	0.64±0.06	0.90±0.03	1.34±0.29	1.05±0.15	0.99±0.01	1.06±0.07
	7 Cats	1.0 mg/kg	0~15	0.70±0.07	0.97±0.03	1.16±0.05	0.76±0.14	1.00±0.01	1.05±0.04
			15~45	0.73±0.16	0.96±0.05	1.46±0.19	0.94±0.08	1.00±0.01	1.05±0.04
Furosemide	10 Cats	1.0 mg/kg	0~15	0.93±0.04	0.94±0.03	1.14±0.42	1.13±0.33	1.02±0.03	0.98±0.05
			15~45	0.89±0.03	0.97±0.02	1.43±0.34	1.27±0.30	0.97±0.01	0.94±0.04

DISCUSSION

The entry of the gastric contents into the duodenum causes the liberation of secretin and pancreozymin, and the consequent secretion of a quantity of alkaline fluid from the pancreas is sufficient to raise the pH of the duodenal contents by neutralization and dilution to a value ineffective for further release of secretin. Self-regulatory mechanism is thus established for neutralization of each portion of gastric chyme entering the duodenum[37].

Secretin, used throughout the present experiment as the background of pancreatic secretion, has been reported to have many actions on various organs, and highly purified secretin is now known to stimulate the volume secretion and bicarbonate output of hepatic bile[38], and to inhibit gastric secretion of acid[2)3)4)5)6)], besides the action on the pancreas of causing a flow of water, salts and alkali from the gland.

The total volume of pancreatic juice secreted is closely related to the dose of secretin injection. The view is well accepted that secretin does not stimulate enzyme secretion at all, and that there is a basal rate of enzyme liberation by the acinar cells which is unaffected by change of the rate of water and alkali secretion. Christodoulopoulos[39] studied the effect of the dose of secretin on the pancreatic response and reported on the linear curve relationship between the logarithm of dose and the 20 minute volume output, the maximal effect of single secretin injection and the prolongation of the duration of response, Baron[40] has demonstrated the maximal output of bicarbonate and amylase in the dog in response to secretin and pancreozymin both by single injection or by continuous intravenous infusion. The low variability of the response was also demonstrated in the repeated experiments using maximal dosages. Hansky *et al.*[41] showed in the dog a highly significant correlation between the pancreatic weight and the maximal bicarbonate output in spite of no correlation between the pancaeatic weight and the amylase output. In their experiments in non-anesthetized dogs with chronic duodenal fistulae, doses of secretin, ranging from 4 to 8 units per kilogram in single intravenous injections, and from 4 to 12 units per minutes in continuous infusion were used to obtain maximal 15-minute output. In the present experiments, however, a close correlation was noted between the protein amount in the pancreatic juice, evoked by repeated injection of secretin, and the body weight of the dogs, without evidence of any close correlation between other components in the juice and the body weight in the dogs and the cats. In the present experiments, only 5 units of secretin was administered to each anesthetized animal. The difference in the dosage of secretin and the presence or absence of anesthesia in the dogs might be the reason for this discrepancy. But further study is required before a more definite relationship is established.

Total protein output was utilized in the present study as an indication of the enzyme production mainly, in the dogs, while amylase activity determined by Somogyi's method was utilized mainly in the cats, because the protein concentration of pancreatic juice has been shown to be related with the amylolytic, lipolytic and proteolytic activities[42], and it had also been reported that the amylolytic content is directly proportional to the total protein content of the juice as measured at 280 mμ[43].

A) Gastric pancreatic relationship

Continuing interest has been focused on the reciprocal relationship between the pancreas and the stomach during recent years[44)45)46)47)48)].

Though Ivy[49)] concluded in 1926 that a "gastric phase" of pancreatic secretion did not exist and the similar conclusion was reached by Hudock and Lawrence[50)]. Blair[51)52)] demonstrated that stimulation of antral pouch caused an increase in pancreatic secretion even when all nervous connections between the pouch and the pancreas had been devided by using the transplantation techniques. The possibility of histamine, evoked by gastrin, to cause pancreatic secretion was denied by their experiments which demonstrated that histamine had a slight effect on juice flow and bicarbinate output of the pancreas and there was little effect on protein output. This coincided with the results obtained by Tankel[53)]. Blair concluded that there existed a humoral mechanism for the control of external pancreatic secretion originating in the pyloric gland area of the stomach, and then he demonstrated that gastric and pancreatic responses were abolished by acidification of the antral pouch. On the other hand, Menguy[54)] observed gastric hypersecretion both by pancreatic duct ligation and biliary diversion to the terminal ileum in Heidenhain dogs. Thus, the interrelationship between the pancreas and the stomach has become more conculsive. Since Harper[55)] wrote in 1959 that gastrin preparations from the hog antrum had a pancreozymin like effect on the pancreas of the anesthetized cat, a number of observations have supported this concept. Magee[14)56)] postulated the existence of gastro-pancreatic distension reflex which could not be explained on a humoral basis, and reported that the distension of the stomach by alkaline solution induced the secretion of both water and protein by the pancreas. He then demonstrated also that[57)] the stimulus to pancreatic secretion produced by gastric distension was not the result of acid liberation which stimulated the endogenous secretin-pancreozymin mechanism. Working with highly purified gastrin, extracted from antral mucosa, Gregory and Tracy[16)] succeeded in separating this hormone into two equally active, yet electrophoretically distinct and homogeneous substances which they named Gastrin I and II. They demonstrated that each of these gastrins equally stimulated both juice flow and enzymatic output in the pancreatic juice of dogs and cats, and that the enzyme response was not due to the "wash-out effect" since these antral hormones significantly increased the enzymatic output from the glands that had already been secreting maximally in response to the continuous secretin infusion. They reported that a slight increase in pancreatic juice-flow was occurred when these gastrins were administered intravenously in the dog. A similar result was obtained by Preshaw[58)] but Gregory and Tracy found that the intravenous injection of these substances produced a much greater rise in juice-flow when the background of secretin was used, hence the hypothesis was put foward that, when the pancreas is secreting in response

to secretin liberated from the intestine during a meal, the simultaneous release of gastrin from the antrum may contribute substantially to the flow of pancreatic juice, and probably also to enzyme output.

Moreover, they have studied the properties of a series of synthetic polypeptides related to gastrin and confirmed that the C-terminal tetrapeptide was the shortest sequence which possessed the entire range of gastrin-like actions, including the stimulation of pancreatic juice and enzyme secretion. The actions of the pure natural peptides were summarised by them as follows: 1) Stimulation and inhibition of gastric acid secretion, 2) Stimulation of pepsin secretion, 3) Stimulation of pancreatic secretion, and 4) Stimulation of gastric tone and motility. Recently, one more action was added by Connell[59] as a possible mechanism for the gastrocolic responses.

In the present experiments, the same results were obtained as Gregory and Preshaw reported. Gastrin related tetrapeptide caused a marked increase of enzymatic output from the pancreas after the venous administration in animals and this result was constant regardless of the presence of pyloric occulusion. The possibility was ruled out that the pancreatic response resulted from a simultaneous stimulation of gastric secretion by the passage of gastric juice into the intestine causing the release of secretin and pancreozymin. Subcutaneous injection of this agent in human subjects showed the same effects. The change of pancreatic juice flow induced by the gastrin-related tetrapeptide was variable.

It seems likely that gastrin acts mainly on the enzyme secreting cells in the pancreas beside the already known action on the stomach.

Here, the existence of gastric phase in pancreatic secretion was identified.

Though the effects of serotonin on the intestinal motility and the gastric secretion[60)61)62)63)] had been reported, the first experimental confirmation regarding the relation of serotonin to the pancreatic secretion was described by Drapanas[24]. He reported on the marked reduction of pancreatic flow rate which occurred following the experimental administration of serotonin, contrary to the clinical report by Warner[64]. Hudock[25] also reported on the suppression of the pancreatic flow after serotonin administration during constant secretin infusion without significant alteration of the blood pressure. He also observed the marked depression of pancreatic flow to occur even after intraduodenal administration of hypertonic glucose solution owing to the release of endogenous serotonin.

Whereas various dosages of serotonin were used in the present experiments, the suppression of secretin-stimulated pancreatic flow was consistently observed except only in one group of cats. The maximal depression of juice flow was present within 15 minutes or 30 minutes in both species and the tendency to return to the control level was observed at the subsequent collec-

tion of the juice. The dosages used in the cats were about 10 to 20 folds as much as in the dogs and the suppression was more intense when 10 mg per kilogram of serotonin was given than when less dosage was given in the cats, but the degree of pancreatic suppression was more evident in the dogs. Bicarbonate concentration of pancreatic juice after the administration of serotonin showed a slight but consistent drop in both species, but this effect seemed to be temporary. Significant elevation of enzyme concentration was observed following serotonin in the dogs.

The great interest shown by various authors in the effects of serotonin is based on the assumption that serotonin may play a role in the physiological functions of the gastrointestinal tract. Serotonin has the multi-faced effects on the cardiovascular system and the response is different at different levels of systemic blood pressure, that is, the response depends upon the neurogenic vasomotor tone[22]. Serotonin has thus both vasodilator and vasoconstrictor effects, depending upon dosage, species, and the experimental situations. Regarding the correlation between this amine and nervous system, it is described that the vagal fibers are stimulated by serotonin in cats and this may explain why this amine is mostly hypotensive in this species, and the initial fall of blood pressure by serotonin in rats is considered as vagal origin because it is inhibited by atropine and by cutting the vagi. It is reported, on the other hand, that serotonin increases the effects of excitation of adrenergic nerves in the cat and facilitates the synaptic transmission in sympathetic ganglia in the rat[22].

The antagonistic action in the arteriole and the synergistic action in the large-artery segment between serotonin and noradrenaline has been reported, and the release of catecholamines from the adrenals has been considered to be one of the mechanisms underlying the pressor responses of serotonin[22]. This release of catecholamines has been observed in the cat but only explains the pressor effects resulting from large doses of serotonin. Another property of serotonin is to alter the body temperature of animals. The hypothermia induced by serotonin in various animal species is still considered to be mainly of peripheral origin and the enhancement of narcosis by serotonin is also reported. The duration of narcosis is said to be prolonged in proportion to the dose of serotonin used. Various hypotheses have been put forward to explain these effects of serotonin, among which are vascular effects, decreased reabsorption of barbiturates, retardation of barbiturate detoxication, decreased heat production and relative brain anoxia.

Thus, serotonin acts on various organs and evokes many responses, including those of nervous system, cardiovascular system, gastrointestinal system and enhancement of narcosis and hypothermia, as a general effect. The effects differ according to its dosage, animal species and the experimental situations. It becomes impractical to elucidate the mechanism of this amine on pancreatic

secretion in a clear-cut way.

The mechanism of the depression of pancreatic juice caused by serotonin is not clear. Drapans postulated the possibility of inhibition of endogenous formation or release of secretin from the duodenum. Hudock also postulated an antagonism or inhibition of secretin and serotonin. These concepts remind us of the two writings regarding serotonin and secretin. In a text book[22], it is described that "serotonin is believed to be linked with the so-called enterochromaffin cell system and the importance of the enterochromaffin cells for the production and storage of serotonin has also been discussed". In another[37], it is described that "it has been suggested that the enterochromaffin cells of the intestinal mucosa may store secretin". This anatomical coincidence as the storage site of both substances suggests some possibility that there may exist close interrelationship between them. On the other hand, a parasympathetic autonomic alteration has been considered by Drapanas, as the possible mechanism and the alteration in the function of pancreatic acini or the alteration in blood flow to the pancreas was suggested by Hudock as the possible explanations of the action of serotonin on the pancreas.

It could better be understood that cardiovascular, respiratory, nervous and gastrointestinal responses elicited by serotonin influenced secondarily on the pancreatic secretion. The wide distribution of this amine in all animals and in some plants suggests some more significant physiologic actions of this amines.

The result in the present study that congestion was the only microscopic finding in the pancreatic tissues of the rat with gastric ulcers after the administration of large doses of serotonin suggests the possibility of the effect of serotonin on pancreatic secretion to be of hemodynamic origin. It has been reported that gastric ulcer produced by serotonin is not associated with the increase of gastric acid and volume, and that the inhibitory effect of serotonin is particularly evident when gastric secretion is artificially stimulated by histamine whereas any antagonistic effect on gastric acidity does not contribute to the production of ulcer. Garattini[22] suggested that the ulcers induced by prolonged administration of corticosteroids could be related to the metaboliam of serotonin in the gastrointestinal tract.

Complete cholinergic activity is the prerequisite for gastrin and serotonin to achieve their full actions, but their effects are antagonistic in a part and synergistic in the other. Gastrin lowers gastric pH by releasing acid secretion but serotonin raises it by mucus secretion under the physiological conditions. While gastrin has a marked pancreozymin-like effect and a slight secretin-like effect on pancreatic secretion, serotonin depresses pancreatic juice flow with the tendency of enhancing enzyme secretion.

The interrelationship between the both agents in the gastrointestinal secretion remained to be elucidated by further studies.

B) Nervous control of pancreatic secretion

Davenport[65] stated in his textbook that preganglionic parasympathetic fibers reach the pancreas from the vagus nerves and they synapse within the pancreas with postganglionic fibers, whose unmyelinated fibers innervate acinar cells, islet cells and smooth muscle cells of the ducts. There is a nervous connection between the pancreatic ganglia and the intrinsic ganglia of the intestinal ganglia. Preganglionic sympathetic fibers synapse with postganglionic cells in the celiac and associated ganglia, and the postganglionic fibers are distributed to the pancreatic blood vessels. In addition, sympathetic secretory fibers which do not synapse in the celiac ganglion, appear in the splanchnic nerves.

Gregory[37] cited many authors, and stated that the effect of the vagus on the pancreas is to cause mobilization and possibly actual discharge of the enzyme, but not to cause a significant flow of water and salts, and suggested that mutual synerigism may exist between the action of the vagus and that of secretin on the pancreas, in which vagal stimulation may increase the response of the effect of secretin on juice flow. Baxter[66] demonstrated the existence of pancreatic secretory fibers in the splanchnic nerve of the rabbit, while Harper[67] was unable to obtain any evidence for the existence of secretory fibers in the splanchnic nerves of the cat. When he stimulated the splanchnic nerves, on the contrary, the output of enzyme was decreased by the injection of more secretin even though the juice flow of secretion was maintained unchanged. He also found that the section of the splanchnic nerves during the sustained response to secretin caused the increase of the juice flow to some extent and the enzyme concentration greatly. It is difficult to detect whether his result was the consequence of vasodilatation caused by splanchnic section or of the removal of the inhibitory influence on the acinar cell. As Gregory[37] suggests, there is no sufficient evidence that the vagi or the sympathetic nerves contain secretion-inhibitory fibers to the pancreatic cells. Though modern Pavlovians emphasized the importance of the sympathetics as the effective pathway of the stimulation of pancreatic secretion, Harper[68] provoked vagovagal stimulation which lead to the increased output of pancreatic enzymes in cats. Lin[69] reported that the parasympathomimetic agents produced a slight increase in volume output only when given with small doses of secretin, the vagal stimulation caused either a decrease or no change in the total volume output, and an adequate stimulus always increased the amylase concentration. Magee[28][29] reported, however, that the vagi influenced the volume as well as the enzyme content of pancreatic juice and that the parasympathetic innervation of the pancreas sensitized the gland to secretin by virture of the liberation of acetylcholine at its endings, and that[30] the total output of amylase and protein decreased in parallel with volume without change in concentration after gastric or truncal vagotomy. Thomas[32] observed a marked depression

of pancreatic juice flow by an anticholinergic drug and stressed on the independence of hormonal and nervous mechanisms in pancreatic secretion. It was also observed that parasympathetic blockade had a greater effect on the response of the pancreas to intravenous secretin, suggesting the local reflex mechanism of the endogenous release of secretin from the duodenum provoked by the acid, and that the enzyme concentration in pancreatic secretion was less liable to be affected by the drugs than was the volume of secretion. Grossman[27] summarized the nervous and hormonal regulation of pancreatic secretion in his conclusive statement and related that there was the convincing evidence of the important participation of the hormones, secretin and pancreozymin, with equally cogent reasons to believe that cholinergic mechanisms co-operate in an essential manner—the profound inhibitory effect of anticholinergic drugs on the volume and the enzyme content of pancreatic juice secreted in response to a meal must, until a satisfactory alternative explanation was given, be taken to mean that cholinergic mechanisms are additional to the hormones, or more probably as co-operative neurohormonal actions.

The data obtained in the present study confirmed the significant elevation of amylase concentration and its output after neostigmine administration without any change in other components. This elevation seemed to be the result of vagal stimulation since the preliminary atropinization blocked this effect, although there is a room left for considering that the increase of pancreatic enzyme is due to a release of gastrin from the stomach as vagal stimulation releases gastrin from the stomach and cholinergic drugs potentiate gastrin-induced acid secretion from the stomach.

Hyoscin-N-Butylbromide caused a significant depression of pancreatic juice flow with minor changes in bicarbonate. The amylase concentration seemed to be less affected, though amylase output decreased except the slight tendency of amylase concentration to increase as was the case with Thomas'[32].

It is presumed on these facts that this ganglion blocker acts mainly on the ductal system and reduces pancreatic juice flow through the inhibition of acetylcholine liberation and the desensitization of the gland to secretin.

C) Water and Electrolytes secretion

Pancreatic juice is a colorless, alkaline fluid which includes the inorganic ions as Na^+, K^+, HCO_3^- and Cl^-. Ca^{++}, Zn^{++}, HPO_3^{--}, and SO_4^{--} are present in lesser concentrations. The concentrations of the major cations, Na^+, K^+ are approximately equal to the concentrations in the blood plasma and the both cations are independent of the flow rate[70][71]. In the dog, the values of the cations obtained from the permanent fistula, according to Solomon[72], are Na^+: 154 ± 7 mM/kgH_2O and K^+: 4.8 ± 0.9 mM/kgH_2O. Dreiling[73] observed that Na^+ varied between 139 and 143 mEq/l and K^+ between 6 and 9 mEq/l in the human pancreatic juice obtained by duodenal intubation. On the other

hand, values obtained from the direct pancreatic catheterization under general anesthesia in the present experiment were Na^+: 160.3±1.3, K^+: 4.0±0.1 mEq/l in the 13 dogs, and Na^+: 163.5±1.3, K^+: 3.3±0.2 mEq/l in the 13 cats. These values are considerably lower compared with those obtained by Solomon, except that of Na^+ which is higher. Bicarbonate and chloride are two principal ions in the anionic composition in pancreatic juice. Bicarbonate concentration varies in direct proportion to the rate of flow, while chloride varies inversely with bicarbonate so that the sum of their concentrations remains constant.

The relationship of the plasma electrolyte concentrations with those in the pancreatic juice has also been reported. Bernier[74] demonstrated, using intravenous radioactive sodium and potassium, that the maximal specific activity appeared more rapidly in the pancreatic juice than in the gastric juice, saliva and the urine, and derived that the volume of the extracellular space and the cell mass was less in the pancreas than in other organs, or the velocity of the metabolic secretory process was greater in the pancreas than in the other organs.

In 1930, Ball[75] reported that the intravenous injection of hypertonic NaCl or KCl solution increased the concentrations of sodium and potassium in the plasma and the juice exactly in the same degree. This report suggested that the major cations, sodium and potassium, were dependent on the same cations in the blood plasma, and the secretion of the both in the pancreatic juice was passive. Rawls[33] reported that metabolic alkalosis, induced by the infusion of $NaHCO_3$, increased the flow rate and the concentration of bicarbonate in the pancreatic juice with no change in the chloride concentration and that the metabolic acidosis, induced by HCl infusion, resulted in a drop of bicarbonate and a rise of chloride in the juice but the respiratory acidosis had only a modest depressing effect on the rate of flow and an insignificant effects on bicarbonate and chloride concentration in the juice. These reports suggest that the changes of anions in the pancreatic juice are mediated by the alterations in plasma bicarbonate concentration and not related purely to pH changes.

Debray[35] recently studied the transport of radioactive sodium and potassium into the pancreatic juice in 4 subjects, comparing the specific activity ratios of the radioactive elements in the pancreatic juice with those in the plasma after intravenous injection, and confirmed the active transport of both ions to the pancreatic juice. Rothman[76] observed the pancreatic secretion of the rabbit *in vitro* in the special enviroments and suggested that the major electrolyte constituents of pancreatic juice were primarily moved transcellularly. The relationship between bicarbonate concentration of the blood and that of the pancreatic juice is thus interesting because the difference is great with much higher concentration in the pancreatic secretion.

The mechanism of production and the site of origin of this highly alkaline secretion have not been completely clarified but the concentrating ability of

bicarbonate has been used as a useful index of the pancreatic function. In 1953, Birnbaum[77] experimentally studied the effect of acetazolamide on the pancreatic secretion. Dreiling[78][79] observed the secretion of electrolytes in the human pancreas and disclosed that the effect of acetazolamide was to markedly reduce the juice flow of pancreatic juice and consequently the output of bicarbonate but that the maximum bicarbonate concentration tended to remain elevated. Sodium and potassium were not affected but chloride concentration varied inversely with the bicarbonate concentration. He proposed that the bicarbonate secreted by the pancreas was exchanged with chloride as the fluids moved down the intercalated ducts, and at the highest rates of secretion, there was the least opportunity for exchange, and the greatest opportunity for exchange was at the lowest rates of secretion. He postulated two actions of acetazolamide: the inhibition of the amount of bicarbonate secreted into the ductular system of the pancreas, and the interference with the bicarbonate-chloride exchange mechanism. He then concluded that the specialized cells of the pancreas secreted bicarbonate in the juice was derived from metabolic CO_2 and from HCO_3 of blood, and the carbonic anhydrase sensitivity was required for the high rate of secretion, and it possibly underwent an exchange with chloride of the interstitial fluid or the blood as bicarbonate solution moved down the collecting system. Thus he proposed the exchange theory to replace the admixture theory, originally postulated by Lin and after then adovocated by Hollander, that the pancreas secreted both a fluid of high bicarbonate content, isotonic with the blood, and another similar in composition to interstitial fluid, namely of low bicarbonate concentration. The effects of acetazolamide in the present study were the marked depression of juice flow and the slight depression of bicarbonate concentration, but the increase of dosage did not always result in the marked depression of juice flow. On the other hand, acetazolamide augmented protein and amylase concentrations. These findings would show that enzyme elaboration and bicarbonate secretion are accomplished by different cells, as reported by many authors and the decrease in total amylase and protein are the result of diminished juice flow.

Recently, Rothman[80] observed the pancreatic secretion *in vitro*, as previously cited, by using a specific technique and reported the results which are incompatible with the direct plasma filtration and the bicarbonate-chloride exchange as the main mechanisms of pancreatic secretion. Then he[81] cast a new light on the changes of chloride in the pancreatic secretion after observing that the chloride content in the secretion increased with time *in vitro*, and suggested that chloride might move into the duct in the process which was not neccessarily dependent on the flow of fluid in the ductal system. He pointed out that acetazolamide produced a profound depression of chloride secretion, and that of chloride output in chronic pancreatitis was considerably more intense, and suggested the possibility of using the bicarbonate: chloride

output ratio for the diagnosis of pancreatic disorders. The basis of this was that acetazolamide produced a decrease in secretion of both chloride and bicarbonate but the ratio of their output did not change greatly, but in the chronic inflamatory dysfunction of the pancreas, bicarbonate output decreased while the output of chloride probably increased.

Perks[34] administered antidiuretic hormone to dogs fitted with the chronic indwelling pancreatic cannula and stimulated pancreatic secretion either with secretin or histamine, and he observed that ADH caused a marked diminution of juice flow, but, sodium, potassium and bicarbonate concentration in the juice remained constant while the total protein and the amylase concentration rose. The same effect was seen when endogenous ADH was stimulated by the infusion of hypertonic saline, suggesting the possibility that ADH influenced the secretory phase of pancreatic exocrine activity. Analogy with the kidney suggested the reabsorption of iso-osmotic electrolytes without passing larger molecules (amylase and protein) out of the fluid. On the other hand, Rothman described that plasma could be filtered into the pancreatic juice in a manner analogous to glomerular filtration of the kidney and that the capillary supply to the pancreas did ramify over the acinar surface and might, in some ways, be linked with the glomerular circulation of the kidney[82].

In the present experiment, Furosemide produced a slight depression in the juice flow and bicarbonate concentration, and the changes in other components were also quite likely as in the case of acetazolamide with the exception that enzyme output tended to increase and potassium concentration to decrease.

The kindney plays a very important role in regulating the electrolyte content of body fluid and thus in maintaining pH of the body. Water is first reabsorbed as the solvent for other reabsorbed substances such as glucose or sodium. As these solutes are removed, the tubular fluid becomes hypotonic to the interstitial fluid of the tubular cells so that more fiuid is lost from the urine as the adjustment to iso osmotic conditions proceeds. This is termed as obligatory reabsorption. The second phase of water reabsorption is termed as facultative reabsorption and this mechanism which operates through pituitary ADH is controlled by the activity of osmoreceptors. Thus, ADH affects the renal tubules and provides for the facultative reabsorption of water. The tubular reaction to ADH is one of the most sensitive of the homeostatic mechanisms of the kidney. Sodium, the principal cation, and chloride and bicarbonate, the principal anions of the extracellular fluid and of the glomerular filtrate, are selectively reabsorbed, mainly in the proximal tubule. In general, chloride reabsorption and excretion roughly parallel that of sodium. Potassium is excreted not only by filtration but also by tubular secretion. The secretion of potassium by the renal tubule is closely associated with hydrogen ion exchange and with acid-base equilibrium. Within the renal tubular cells, the decline in hydrogen concentration permits an increase in secretion of potassium

because of the normal competition for secretion which exists between hydrogen and potassium ions in the distal tubule[83].

The ability of acetazolamide to increase the excretion of potassium into the urine is attributable to its inhibitory effect on the carbonic anhydrase activity, which thus brings about a reduction in hydrogen concentration within the renal tubule cells, and consequent secretion of potassium can be increased. Stop-flow studies[84] suggest that the kaliuresis following furosemide occurs primarily because of the increased distal tubular secretion. Furosemide[85] has little or no carbonic anhydrase inhibiting activity. Sodium plus potassium output exceeds chloride, and potassium and hydrogen excretions are accelerated by the drug as shown by many studies. Primary inhibition of sodium transport in the proximal and distal nephron, interference with passive chloride reabsorption as a consequence of the effects on sodium, and the subsequent inhibitory exchange of some of the rejected sodium for potassium and hydrogen ions would explain the pattern of urinary excretion observed following furosemide administration[86].

The mechanism of active transport of sodium and potassium in the kidney is now well accepted. There is a concomitant movement of sodium and chloride in the reabsorption and excretion and the competitive relationship for secretion between hydrogen and potassium has been shown in the distal tubule, but the information concerning electrolyte changes in the pancreatic secretion is still limited. The possibility of active transport of cations, sodium and potassium, in the pancreatic secretion has been reported by many authors but the metabolism of anions, bicarbonate and chloride, in the juice has not yet been elucidated clearly to provide the full explanation in spite of many hypotheses.

Acetazolamide and furosemide have the indisputable diuretic action with concomitant increase of the electrolytes secretion in the urine. They also depressed pancreatic juice flow without any remarkable changes of electrolytes in the juice. It will be more feasible to understand that the depression of pancreatic juice flow after diuretics administration is the secondary effect induced by the body fluid depletion following diuresis and not the result of its direct action on the pancreatic ductal system, while ADH is reported to have the inhibitory effect on the urine excretion and the pancreatic secretion.

Therfore, it still remains impracticable to fully explain the mechanism of these diuretics and ADH on the pancreatic secretion while the possibility is left that they act on the pancreatic ductal system as on the renal tubule and provoke the changes of tissue fluid and electrolytes metabolism.

It should also be taken into consideration that the results of the present experiment were obtained under the influence of general anesthesia. The influence of anesthesia have been investigated on spontaneous and stimulated pancreatic flow. Friedman[87] reported that general anesthetics reduced the response of the pancreas to the instillation of acid into the duodenum but not

to that of secretin. Shapiro[88] reported on the similar effect of local anesthetics on the duodenal mucosa. Véghelyi[89] also showed in the rat a decrease of pancreatic flow and drastic reduction in enzyme output under general anesthesia.

SUMMARY AND CONCLUSION

After a preliminary study on the basal pancreatic flow, the influence of several agents on pancreatic secretion was observed in dogs and cats under general anesthesia. The change in the aspirated duodenal juice was also observed in a few human subjects after the administration of some agents.

1) There was demonstrated a significant correlation between the protein amount in the basal pancreatic secretion and the body weight in the dog.

2) After the administration of a synthetized tetrapeptide, there were noted an apparent pancreozymin-like effect and a slight secretin-like effect on the pancreatic secretion.

3) Serotonin caused a marked depression of secretin-stimulated pancreatic flow and a slight reduction of bicarbonate concentration with a concomitant increase in enzyme concentrations. The results were variable according to the dose of serotonin and the animal species, especially in the enzyme output, but the possibility was seen that serotonin might have an ecbolic action on the pancreatic secretion. Relatively large doses of serotonin produced gastric ulcers and pancreatic congestion in rats. There was no correlation between the dose and the interstitial congestion of the pancreas.

4) Neostigmine caused a remarkable enzyme secretion without any concomitant changes of the components in the juice and this effect was abolished by preliminary atropinization.

5) Hyoscin-N-Butylbromide produced a marked inhibitory effect on the hydrelatic secretion and a slight inhibitory effect on the ecbolic secretion.

6) Acetazolamide depressed the pancreatic juice flow greatly with a slight depression of bicarbonate concentration and a concomitant increase of enzyme concentration. Sodium concentration was not changed but there was a tendency of potassium concentration to increase.

7) Furosemide produced a minor degree of depression in the pancreatic juice flow and the degree of the increase in enzyme concentrations was more intense than with acetazolamide. Sodium concentration was not changed but there was a tendency of potassium concentration to decrease.

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EXPLANATION OF PLATES

PLATE 1. The multiple gastric ulcers at the lessur curvature of the stomach of the rat produced by serotonin administration (Group F).

PLATE 2. A histological picture of rat pancreas after serotonin administration (Group F).

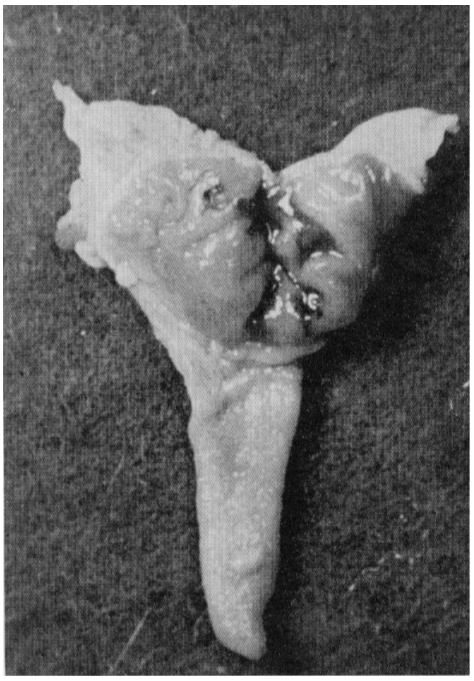

Plate 1

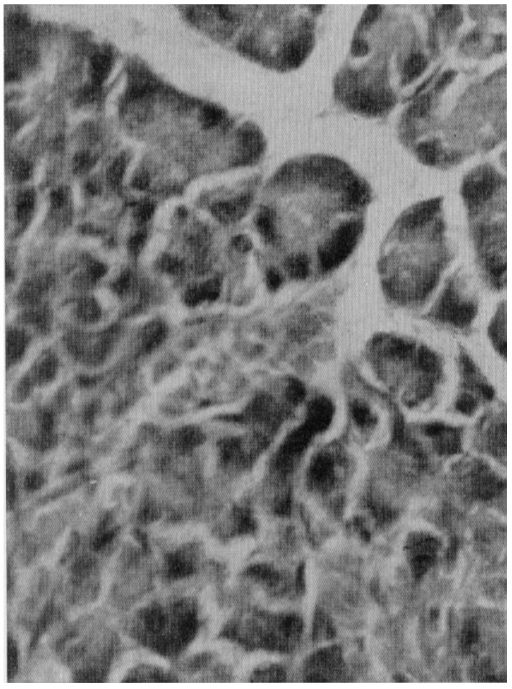

Plate 2