

## Cephalic phase of pancreatic secretion in man

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The pancreatic secretory response to sham feeding was shown by Pavlov (1902). According to Gregory (1962), in the conscious dog 'sham feeding causes only a scanty flow of (pancreatic) juice rich in enzymes, provided that the gastric juice secreted at the same time is prevented from entering the duodenum and so liberating secretin (Walther, 1897; Krewer, 1899; Tonkich, 1924; Ivy and Crittenden, 1937). Secretion begins a minute or two after the start of feeding and lasts in all about 30 minutes; the volume is small (less than 10 ml) and there is thus no indication that such vagal excitation causes any release of secretin'. For Ivy (1926), 'the cephalic phase [of pancreatic secretion] is so small that it is not important.'

More recently Preshaw, Cooke, and Grossman (1966) have shown that sham feeding causes a marked increase in pancreatic secretion in dogs with permanent pancreatic fistulas. This pancreatic response is inhibited by acidification of an innervated pouch of the pyloric gland area and the authors suggest that it is mediated by the vagal release of secretin. In the rat, sham feeding seems not to have any effect on pancreatic secretion if the animals are provided with a gastric fistula or vagotomized (Alphin and Lin, 1959).

Little is known about the cephalic phase of pancreatic secretion in man. The observations of Kogen (1931) on 17 patients are open to criticism because gastric juice was not prevented from entering the duodenum: the increased pancreatic response after sham feeding may not be a true cephalic phase but secondary to the HCl produced during the cephalic phase of gastric secretion (Alphin and Lin, 1959). In a man with a pancreatic fistula neither Villaret and Justin-Besancon (1936) nor Sinclair (1956) were able to stimulate pancreatic secretion when appetizing food was shown to the patient.

The purpose of our experiments was to investigate whether cephalic stimulation influences pancreatic function in man.

### METHODS

In most of the observations the subjects were volunteers

or convalescent patients without gastrointestinal disease and in a normal nutritional condition. In some experiments we also studied cholecystectomized patients with apparently normal pancreas and patients with chronic calcifying pancreatitis.

Gastric juice was prevented from entering the duodenum by using a modified double-lumen tube. The duodenal portion of the tube measured 25 cm, and had six holes. It contained a metallic chuck, which facilitates passage into the pylorus. The gastric portion of the tube also had six holes. Between the gastric and the duodenal portions the tube was surrounded by a small rubber balloon (9 × 3 cm), which could be inflated by a third tube 2 mm in diameter.

After an overnight fast, an injection of 0.2 g phenobarbital was given and 15 minutes later the tube was inserted as far as the pylorus with the metallic chuck in place. The chuck was then pulled back a distance of 20 cm and the end of the tube pushed inside the duodenum, under fluoroscopic control. The balloon was inflated with 30 ml air. The insertion of the tube usually required about 15 minutes. The patient was then laid down on his left side: this position is essential to ensure occlusion of the pylorus. The efficacy of the balloon in preventing leakage of gastric juice into the duodenum was checked by injecting bromsulphalein (B.S.P.) into the stomach at the beginning of the experiment. When B.S.P. was found in the duodenum the experiment was discarded. About 30 minutes after the phenobarbital injection, suction of gastric and duodenal juice was started, under a steady negative pressure of 20 cm water.

Three types of cephalic stimulation were used. In A a beefsteak was grilled in the same room and in A<sup>1</sup> the more usual French breakfast of rolls and coffee was substituted. In these two types of experiments the patient was allowed to see and smell the food for five minutes, after which it was removed. In B the patient was given a quantity of beefsteak previously grilled in another room and instructed to chew this quickly, then remove it from his mouth, which he rinsed with water. In every case, the patients knew they would have a well prepared meal after the experiment but they were unaware of the purpose or sequence of the experiments. The first stimulus was applied after control collections of gastric and duodenal juice for 60 minutes. Pancreatic and gastric juices were collected in bottles immersed in crushed ice and changed every 15 min except for the 20 min following each stimulation, during which successive two minute fractions were collected.

Bicarbonate was estimated by the Van Slyke method,

amylase by the Lagerlöf method (1942), and lipase estimated as described previously by Sarles, Taulier, and Figarella (1963). Lipase was chosen because its secretion has been shown to be more regular (Sarles, Bauer, and Prezelin, 1965), but in nine patients amylase, chymotrypsin, and trypsin were also measured with specific substrates (Figarella, Taulier, and Sarles, 1965).

To achieve success in this experimental procedure every effort must be made to have the full confidence of the subject under test. Unless the patient is completely relaxed and tranquil the cephalic response may be lost.

## RESULTS

**EFFECT ON THE PANCREATIC RESPONSE OF THE NATURE AND TIMING OF STIMULI** In these experiments the basal secretion before the first stimulation is expressed as the mean output in 30 minutes of water (ml), bicarbonate (m-equiv/l), lipase, trypsin, chymotrypsin (international units = m-equiv of substrate hydrolysed in one minute) and amylase (Lagerlöf-Nörby units). The effect of stimulation is measured by the difference between the 30 minutes' secretion after stimulation and the 30 minutes' basal secretion.

In five patients type A (visual and olfactory stimulation was applied 60 minutes after intubation at approximately 10.30 a.m.) followed by type B

(sham feeding) after a further 60 minutes. Both types of stimulation were followed by an increase in the volume and the bicarbonate and lipase contents of duodenal juice (Table I). In three patients, this increase started after two minutes, and in two patients after four minutes. All patients showed a maximum response after 10 minutes with a decline thereafter, leading to a plateau response which persisted into the subsequent period of sham feeding. The second (type B) stimulus provoked a similar but even greater response than the first. Gastric secretion occurred later than duodenal flow, the delay varying from four to 18 minutes, and in three patients gastric secretion was inhibited for 12 to 15 minutes before the response to the sham feeding began.

To determine whether the time at which sham feeding occurred was important, four patients were given type A at 8.30 a.m., type A again at 10.30 a.m., and then type B at 11.30 a.m. (Table II and Fig. 1). In these experiments the first stimulus caused inhibition of duodenal flow followed by a weak excitation, but the second and third were always followed by a great increase in duodenal juice, after the usual delay of two to four minutes. Gastric flow

TABLE I  
RESULTS OF TYPES A AND B SHAM FEEDING

Case No.	Age (yr)	Basal Secretion			Type of Sham Feeding								
		Lipase (units)	Volume (ml)	CO <sub>2</sub> (m-equiv)	A			B					
					Lipase (units)	Volume (ml)	CO <sub>2</sub> (m-equiv)	Lipase (units)	Volume (ml)	CO <sub>2</sub> (m-equiv)			
144	24	20,917	15	0.50	+ 83,167	+ 47	+ 1.90	+ 114,971	+ 58	+ 3.55			
145	69	40,250	28	0.65	+ 52,214	+ 30	+ 1.05	+ 85,154	+ 43	+ 1.86			
143	25	19,340	30.6	0.86	+ 87,500	+ 35	+ 1.56	+ 170,605	+ 62	+ 3.52			
147	26	37,940	31.5	0.88	+ 66,566	+ 32	+ 1.35	+ 209,326	+ 86	+ 4.97			
146	36	22,800	16	0.55	+ 40,819	+ 25	+ 1.60	+ 76,443	+ 33	+ 2.54			

<sup>1</sup>In all the tables a plus sign indicates an increase over basal values and minus sign a decrease. If stimulation produced inhibition followed by an increased response, two values are given.

TABLE II  
RESULTS OF SHAM FEEDING TYPE A TWICE AND TYPE B ONCE

Case No.	Sex	Age (yr)	Basal Secretion			Type of Sham Feeding											
			Lipase (units)	Volume (ml)	CO <sub>2</sub> (m-equiv)	A at 8.30 a.m.			A at 10.30 a.m.			B					
					Lipase (units)	Volume (ml)	CO <sub>2</sub> (m-equiv)	Lipase (units)	Volume (ml)	CO <sub>2</sub> (m-equiv)	Lipase (units)	Volume (ml)	CO <sub>2</sub> (m-equiv)				
192	♀	43	20,470	21.7	0.05	- 9,520 + 6,270	- 5.2 + 3.2	+ 0.125	+ 70,400	+ 41	+ 2.03	+ 108,700	+ 55	+ 3.46			
193	♀	65	20,590	19.5	0.38	- 5,800 + 2,075	- 3.6 + 1.4	+ 0.09	+ 64,450	+ 49	+ 2.62	+ 90,762	+ 63	+ 4.39			
207	♀	38	22,085	23.7	0.54	- 5,350 + 4,790	- 4.8 + 3.5	+ 0.05	+ 38,040	+ 24	+ 1.45	+ 77,000	+ 45	+ 4.70			
208	♂	30	29,800	30.25	1.24	- 3,200 + 2,900	- 5.5 + 0.5	- 0.16 + 0.07	+ 49,750	+ 23	+ 1.53	+ 82,560	+ 41	+ 3.23			

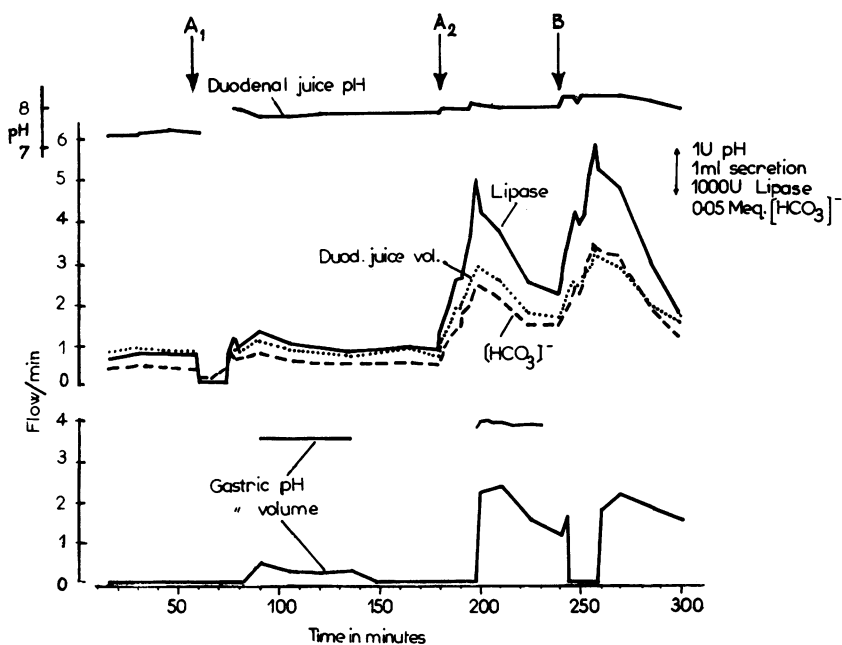


FIG. 1. Response to early and late type A psychic stimulation and of type B sham feeding.

increased 12–15 minutes after the first stimulation whereas pancreatic secretion remained inhibited or weak.

The effect of palatability on psychic stimulation was investigated by substituting type A<sup>1</sup> stimulation for type A at 8.30 a.m., meat being an unusual item for breakfast in France. In five patients, A<sup>1</sup> sham feeding was never followed by an inhibition, but by a small augmentation (Table III and Fig. 2). In one anorectic patient in whom this experiment was performed the repeated stimuli had diminishing effects and produced growing inhibition (case 206, Table III).

**EFFECT OF ANTICHOLINERGIC DRUGS ON THE CEPHALIC RESPONSE** In these experiments type A was followed by type B stimulation, as in the first series,

but an anticholinergic drug was administered 15 minutes before the second stimulus. We measured (a) the duration of the inhibition from the beginning of the decrease of flow to the return to basal secretion, and (b) the duration of the secretory wave following the second stimulus after injection of the drug. For lipase, bicarbonate, and volume we calculated the ratio of the response to the type B stimulation (after the anticholinergic drug) to that following the first type A stimulation (before the anticholinergic drug).

In three patients 1 mg atropine was given intravenously 15 minutes before the type B sham feeding. The results did not differ markedly from those of Table I and atropine was abandoned for a more powerful anticholinergic, because its side effects did not permit the use of such high doses as in

TABLE III  
RESULTS OF SHAM FEEDING TYPES A<sup>1</sup>, A, AND B

Case No.	Age (yr)	Basal Secretion			Type of Sham Feeding								
		Lipase (units)	Volume (ml)	CO <sub>2</sub> (m-equiv)	A <sup>1</sup> at 8.30 a.m.			A at 10.30 a.m.			B		
					Lipase (units)	Volume (ml)	CO <sub>2</sub> (m-equiv)	Lipase (units)	Volume (ml)	CO <sub>2</sub> (m-equiv)	Lipase (units)	Volume (ml)	CO <sub>2</sub> (m-equiv)
195	44	21,945	20	0.49	+ 31,271	+ 16	+ 0.75	+ 75,740	+ 38	+ 1.62	+ 66,300	+ 27	+ 1.49
194	55	26,800	25	0.81	+ 11,560	+ 2	+ 0.30	+ 95,810	+ 45	+ 2.89	+ 132,000	+ 63	+ 4.68
210	22	36,480	31	0.80	+ 18,000	+ 11	+ 0.50	+ 61,280	+ 38	+ 1.86	+ 88,800	+ 47	+ 2.73
211	35	27,130	24	0.94	+ 25,345	+ 17	+ 0.89	+ 62,280	+ 34	+ 1.61	+ 88,000	+ 37	+ 2.71
209	30	31,200	30	1.24	+ 25,000	+ 18	+ 0.95	+ 70,225	+ 37	+ 1.12	+ 89,000	+ 47	+ 3.67
<i>Anorectic patient</i>													
206	53	17,970	22	0.52	+ 21,500	+ 22	+ 0.84	+ 4,326 + 1,883	- 4.16 + 0.76	+ 0.14	- 5,980 + 2,122	- 6.26 + 0.8	+ 0.14

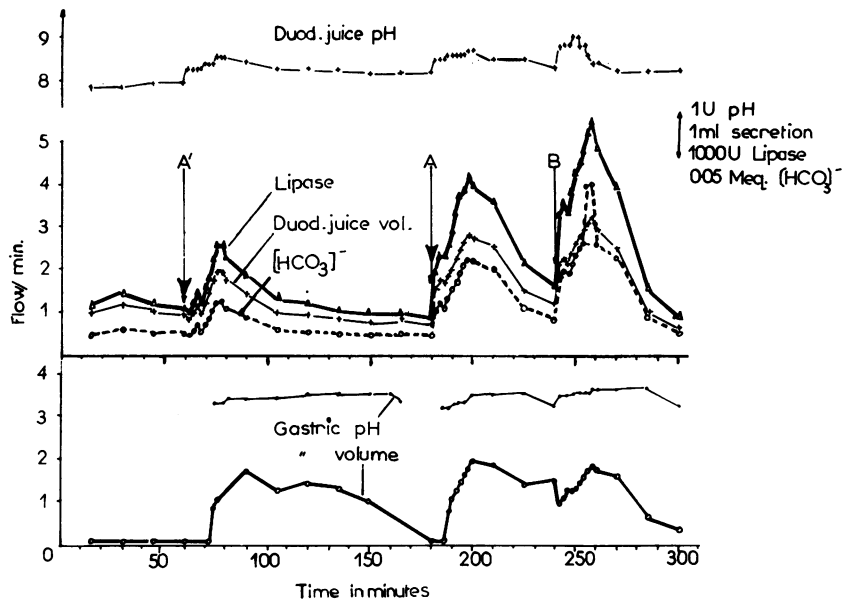


FIG. 2. An experiment similar to that in Figure 1, except that type A<sup>1</sup> replaces type A stimulation at 8.30 a.m.

animals. In four patients, in whom 3 mg Priamide (2-2 diphenyl, 4 diisopropylaminobutyramide methyl iodide) was substituted for atropine, pancreatic and gastric secretion was markedly inhibited and lasted up to 100 minutes. Nevertheless the second stimulus was still able to produce a slight response, lasting 14-21 minutes instead of the usual minimum of one hour (Table IV).

TABLE IV

ACTION OF ANTICHOLINERGIC DRUG PRIAMIDE

Case No.	Sex	Age (yr)	Duration of Inhibition (min)	Duration of Response to B (min)	Maximum Activity		
					Lipase	CO <sub>2</sub> NaH	Volume
156	♀	36	105	20	0.61	0.32	0.57
157	♀	25	115	14	0.60	0.39	0.59
166	♀	56	105	21	0.57	0.43	0.64
167	♀	36	115	20	0.68	0.59	0.70

A COMPARISON OF THE RESPONSE TO PSYCHIC STIMULATION AND TO SECRETIN + PANCREOZYMIN In 32 subjects (16 normal controls, 13 cases of chronic calcifying pancreatitis, and three cholecystomized patients with apparently normal pancreas) a type A stimulus was given at 10.30 a.m. and an intravenous injection of 1 u/kg of secretin (Boots) + 3 u/kg of pancreozymin (Boots) at 11.30, except that in four patients the order of excitation was inverted without any noticeable change in the secretory responses. The duodenal juice was collected in successive 10-minute samples. In assessing the responses we compared the bicarbonate concentration (m-equiv/l) and output of enzymes (u/min) in the most active sample after each stimulation.

In all three groups of patients the secretion of lipase was higher after psychic stimulation than after pancreozymin + secretin (probability calcu-

TABLE V

SECRETION OF LIPASE

	Lipase (units/minute) Basal Secretion	Secretin and Pancreozymin		CO <sub>2</sub> (m-equiv/l) Basal Secretion	Secretin and Pancreozymin	
		After Sham Feeding	Secretin and Pancreozymin		After Sham Feeding	Secretin and Pancreozymin
16 Controls	1,200 (900 - 1500)	8,500 (4,600 - 13,800)	4,800 (3,100 - 6,900)	22 (13 - 28)	43 (22 - 99)	84 (58 - 123)
13 cases of Pancreatitis	1,200 (50 - 600)	1,400 (100 - 2,900)	800 (50 - 1,900)	14 (16 - 25)	19 (7 - 34)	36 (12 - 73)
13 cholecystomized patients	600 (500 - 700)	6,700 (6,300 - 7,200)	5,000 (2,600 - 8,800)	15 (13 - 17)	42 (19 - 88)	88 (79 - 93)

<sup>1</sup>Mean

<sup>2</sup>Range

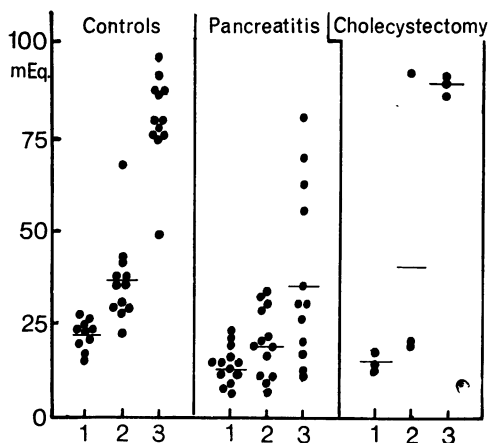


FIG. 3. Maximum concentration of bicarbonate in 15 minutes samples: (1) in basal secretion; (2) after type A sham feeding; (3) after intravenous injection of 1 u/kg of secretin and 1 u/kg of pancreozymin.

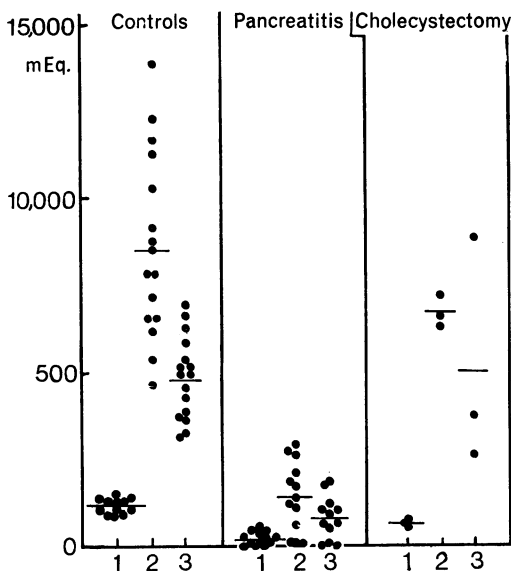


FIG. 4. Maximum output of lipase in one minute in the most active 15-minute sample as in Figure 3.

lated by the Sign test (Siegel, 1956) ( $p < 0.00003$ ). The reverse was the case for the secretion of water and bicarbonate ( $p < 0.00003$ ) (Table IV and Figs. 3 and 4). In seven people (three cholecystectomized patients with normal pancreas and four patients with pancreatic insufficiency), the output of amylase, trypsin, and chymotrypsin was estimated in addition to lipase and bicarbonate (Table VI and Fig. 5). The probabilities for psychic stimulation leading

to a greater output of enzymes than secretin + pancreozymin are 0.016 for amylase, 0.109 for trypsin and chymotrypsin (Sign test). The parallel of the secretion of the four enzymes was almost perfect in the three cholecystectomized patients, and indisputable but imperfect in the others, both after psychic stimulation and after secretin + pancreozymin.

TABLE VI  
OUTPUT OF AMYLASE, TRYPSIN, AND CHYMOTRYPSIN

	Amylase (units/minute)		
	Basal Secretion	After Sham Feeding	After Secretin and Pancreozymin
Pancreatitis	1.4 0.6 0.7 1.3	2.9 0.8 2.3 2.8	1.7 0 0.5 2.5
Cholecystectomized	5.3 0.9	34 1.3	2 11
	Trypsin (units/minute)		
Pancreatitis	1 1 0 12	5 2 3 98	2 0 0 9
Cholecystectomized	31 36	121 100	126 85
	Chymotrypsin (units/minute)		
Pancreatitis	0 1 0 18	2 4 0 70	2 0 2 43
Cholecystectomized	98 32	360 180	150 160

#### DISCUSSION

Our observations support the existence of a cephalic phase of pancreatic secretion in man. Before reaching a definite conclusion certain points require discussion.

The presence of a tube in the duodenum and the stomach may modify the pancreatic secretion, and it has been shown that the collection of juice, without subsequent return to the duodenum, augments the pancreatic secretion of water, bicarbonate, and, to a smaller extent, protein (Annis and Hallenbeck, 1951). Furthermore the distension of the pyloric area by the balloon may cause a gastro-pancreatic reflex (White, Lundh, and Magee, 1960; White, Alexander, and Magee, 1963). However, the balloon used by White *et al.* in man was inflated with 200 to 400 ml of air, compared with the 30 ml used in our experiments.

It is also possible that the tube and the balloon may stimulate a hormonal gastro-pancreatic mechanism (Blair, Clark, Harper, Lake, and Scratcherd, 1961; Preshaw *et al.*, 1966). As the balloon was

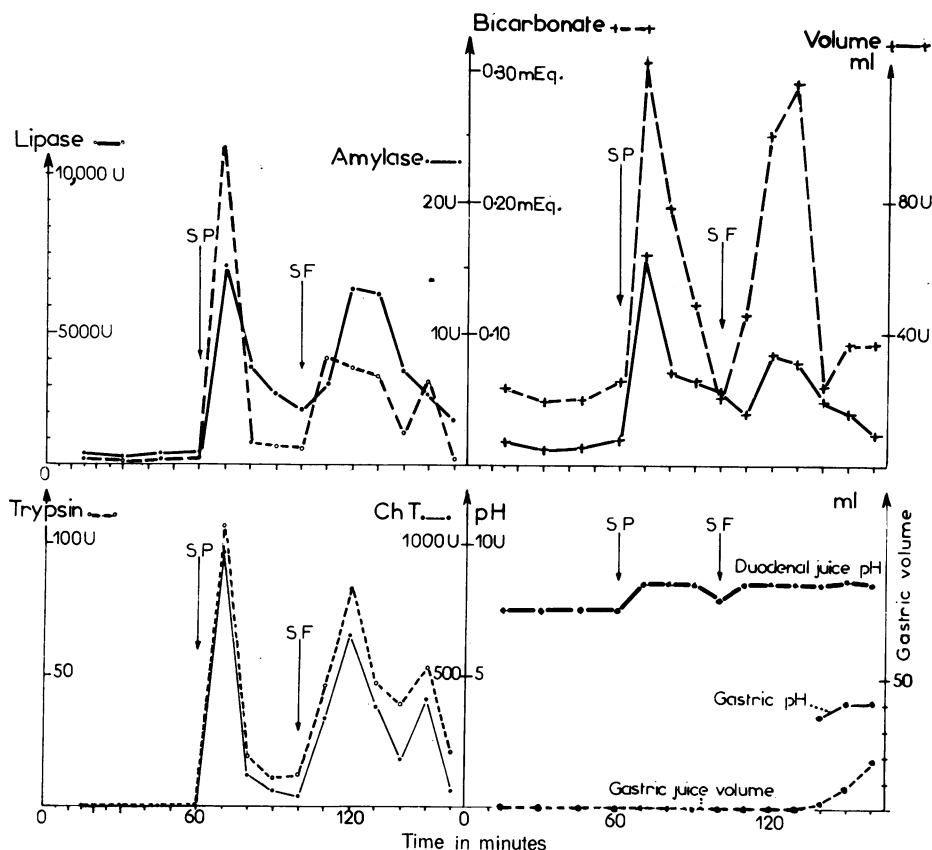


FIG. 5. Output of lipase, amylase, trypsin, and chymotrypsin (units/minute) in 15-minute samples in one of the cholecystectomized patient after sham feeding and pancreozymin.

distended throughout our experiments, this could not explain the results, although it might, by providing a subthreshold background stimulus, have made the pancreas more sensitive to psychic stimulation.

The action of phenobarbital has been described in a previous paper (Sarles *et al.*, 1965). It does not modify significantly the action of cephalic stimulation. In any case, the interval between the phenobarbital injection and the first stimulation was the same in each experiment, except in those in which secretin was infused continuously.

The secretion of pancreatic juice starts within two to four minutes of stimulation. That this secretion is not provoked by gastric juice in the duodenum is shown by (a) the absence of B.S.P from the duodenal aspirate; (b) the absence of any evidence that gastric and pancreatic responses have a parallel course; and (c) the fact that gastric secretion almost always began later than pancreatic flow. This last point was noted by Pavlov (1902, p. 124) in dogs and regarded by him as a very strong argument in favour of the view that the pancreatic response

was a true nervous reflex and not secondary to the passage of gastric acid from the stomach to the intestine: '... But there was another way by which the matter might be decided, viz., the determination of the latent period of sham feeding for the pancreas. The latent period of the gastric secretion in dogs has a sharply marked lower limit, and is never less than four and a half minutes. The pancreatic juice, on the contrary, begins to flow two to three minutes after the application of the exciting agency, for example, an acid. In the experiment of teasing the animal by offering it food, the pancreatic flow also generally begins after two to three minutes. This appears to me to point to a direct psychic influence through the secretory nerves of the pancreas, such as has long been established for the secretory mechanism of the stomach...'

Forell and Strahlheber (1966) consider that in man lipase and trypsin secretions are dependent on the amount of bile present in the duodenum. Kuroyanagi, Chiles, and Necheles (1962) also found that the administration of sodium dehydrocholate to the dog considerably enhanced pancreatic

secretion induced by secretin. It was observed in our experiments that the highest pancreatic output of enzymes, water, and bicarbonate generally coincided with the greatest concentration of bile pigments (judged by the darkness of the duodenal juice). However, the presence of a normal response to psychic stimulation in cholecystectomized patients sufficiently proves that the excretion of gallbladder bile into the duodenum is not the cause of the pancreatic response.

The pancreatic response to psychic stimulation has been compared to the action of 1 u/kg of secretin (Boots) intravenously injected with 3 u/kg of pancreozymin (Boots). The ratio between the means of the output of lipase after psychic stimulation and after secretin + pancreozymin does not differ in controls (1.77) and in patients with pancreatic insufficiency (1.75), the enzymatic response being significantly higher after psychic stimulation. As the dose of 3 u/kg of pancreozymin is quite considerable this difference emphasizes the magnitude in man compared with the dog. The duration of the pancreatic secretion seems to be much longer in man (lasting at least one hour for a stimulus of five minutes) than in the dog. The cephalic phase of pancreatic secretion may therefore play in man a great and sustained part in the pancreatic enzyme response to food.

The action on water and bicarbonate secretion seems to be absent in the dog, and is disputable in man. The increase of water and bicarbonate output after cephalic stimulation could be explained by a secretion of bile which is fairly rich in bicarbonate. Hepatic bile in man contains 20-55 m-equiv/l bicarbonate (Thureborn, 1962), the concentration of gallbladder bile being much lower (Diamond, 1965). In three controls and one cholecystectomized patient in our series the bicarbonate concentration after cephalic stimulation was higher than in a pure bile secretion (respectively 67, 67, 99, and 88 m-equiv/l). It should nevertheless be mentioned that in the cat secretin (Scratcherd, 1965) and in the dog gastrin (Zaterka and Grossman, 1966) increase the bicarbonate concentration of hepatic bile up to 60 to 70 m-equiv/l. The parallel decrease in the responses to psychic stimulation and to secretin in the patients with chronic pancreatitis also favours the view that the bicarbonate secretion after psychic stimulation is at least in part of pancreatic origin. The secretion of water and bicarbonate, if in fact due to a direct action of cephalic stimulation on the pancreas, is nevertheless much less important than the secretion of enzymes, being lower than the secretion following 1 u/kg of secretin.

The mechanism of the cephalic phase of pancreatic secretion in the dog was attributed by Pavlov

(1902) to a direct vagal action and by Preshaw *et al.* (1966) in part to a secretion of gastrin by the antral area. The fact that the pancreatic and the gastric secretions do not have a parallel course does not favour the hypothesis that a prominent part is played by gastrin. The inhibitory effect of priamide, which has a strong anticholinergic action (Van Proosdij-Hartzema, Janssen, and De Jongh, 1955), suggests that in man as in animals the vagus plays an important part. The inefficacy of 1 mg of intravenously injected atropine in decreasing the pancreatic secretion is probably due to the impossibility of using in man as high doses as in animals.

It is well known that appetite influences the response to cephalic stimuli, and this is supported by the poor results in one anorectic patient. One might extend this idea to explain the poor responses to psychic stimulation early in the day, when in fact basal secretion is depressed. Gastric secretion seems less dependent on the time of stimulation, and the early morning stimulus which inhibits pancreatic flow increased gastric secretion. The disparity between the effects of type A and type A<sup>1</sup> stimuli in the early morning is probably related to the dietary habits of the patients studied and underlines the importance of being conditioned to foods. The outputs of amylase, lipase, trypsin, and chymotrypsin after cephalic stimuli follow a parallel course.

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