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Secretory response of the human pancreas to continuous intravenous infusion of pancreozymin-cholecystokinin (Cecekin)

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EDITORIAL COMMENT This provides an accurate measurement of maximum enzyme secretory capacity of the pancreas and eliminates errors due to 'wash-out' of amylase.

In a previous study (Banwell, Northam, and Cooke, 1967) the pancreatic secretory response to continuous intravenous infusion of secretin for both volume and bicarbonate output was found to reach a maximum with doses of 4 to 6 units/min. In agreement with earlier work we found pancreatic enzyme output to be independent of the rate of secretin administration (Wang, Grossman, and Ivy, 1948; Preshaw and Grossman, 1965) but directly dependent on pancreozymin administration (Harper, Blair, and Scratcherd, 1962; Lin and Grossman, 1956). During the present study, Cecekin (a pancreozymin-cholecystokinin preparation containing a small amount of secretin[1]) was infused continuously into normal subjects and patients with various gastrointestinal disorders so as to stimulate maximum amylase output in the duodenal fluid. By this continuous infusion procedure 'washout' of amylase from within the pancreatic duct system may be distinguished from pancreozymin-induced release of amylase from acinar cells and a more accurate measurement obtained for the maximum enzyme secretory capacity of the pancreas. The procedure also offers additional information on the emptying response of the gall bladder to cholecystokinin.

MATERIAL

NORMAL SUBJECTS Eight subjects (22 to 65 years of age) without clinical, radiological, or biochemical evidence of pancreatic disease were studied.

PANCREATIC AND BILIARY DISEASE Three patients (H.E., L.M., and H.B.) with clinical features of chronic pancreatitis. All three had abnormal standard secretin-pancreozymin tests (Burton, Evans, Harper, Howat, Oleesky, Scott, and Varley, 1960a). Two (H.E. and L.M.) had steatorrhoea (36 and 60 g. faecal fat/day) and abnormal glucose tolerance tests, and in both of these patients chronic pancreatitis was confirmed at laparotomy by pancreatic biopsy.

One patient (D.C.) was studied three weeks after the onset of acute pancreatitis.

One patient (M.S.) with chronic cholecystitis and cholelithiasis was studied before and another (M.L.) after cholecystectomy. In each of them the pancreas was normal at laparotomy.

MISCELLANEOUS GASTROINTESTINAL DISEASES Four patients (C.G., L.S., B.G., and V.R.) had the classical clinical, radiological, biochemical, haematological, and histological evidence of adult coeliac disease. All patients were studied before the start of treatment.

One patient (P.B.) was studied when in remission after tropical sprue.

Two patients (L.W. and F.T.) had hepatic cirrhosis proven by liver biopsy. In L.W. there had been an excessive alcohol intake. F.T. had had an ileostomy and panproctocolectomy for ulcerative colitis.

One patient (B.S.), with a normal response to the standard secretin-pancreozymin test (Burton *et al.*, 1960a), had diarrhoea of uncertain cause, probably originating from quinidine toxicity.

A diabetic man (C.B.) had steatorrhoea (14 to 16 g. faecal fat/day) attributed to 'diabetic diarrhoea'. The secretin-pancreozymin test (Burton *et al.*, 1960a) was normal.

One patient (G.P.) had diffuse gastrointestinal polyposis and diabetes mellitus (Cronkhite-Canada syndrome).

METHODS

The technique and methods of analysis have been described (Banwell *et al.*, 1967; Northam and Banwell, 1966). In eight of the cases fluoroscopic examination at the end of the test procedure confirmed that the drainage

[1]The composition of each ampoule was reported by the manufacturer to contain 200 Harper units of pancreozymin, 75 Ivy units of cholecystokinin, and 20 to 30 units of secretin.

tubes had not altered position significantly during Cecekin infusion.

Vitrum Cecekin was used throughout the study and infused in a similar manner to secretin at rates ranging from 0·0312 to 0·5 Harper units pancreozymin/kg./min. With higher rates of Cecekin infusion 13 patients had symptoms of malaise, nausea, and abdominal rumbling; intestinal colic developed in four which resulted in irregular drainage of the duodenal fluid. However, in no instance was it necessary to stop the infusion because of these side effects. In 19 of the 24 patients the secretin-pancreozymin test (Burton *et al.*, 1960a) was performed before infusion of Cecekin. An interval of 30 to 40 minutes elapsed between the two procedures to allow amylase output to return to a basal state before the Cecekin stimulation was begun.

RESULTS

BASAL COLLECTIONS IN NORMAL SUBJECTS The amylase output in basal collection ranged from 700 to 2,780 units/min. (Table I). The variation in results is similar to those recorded by Dreiling and Janowitz (1962) and Burton *et al.* (1960a) in man, and by Hansky, Tiscornia, Dreiling, and Janowitz (1964) in the dog. Basal amylase output before the secretin-pancreozymin test (Burton *et al.*, 1960a) was similar in magnitude to the interval output before Cecekin infusion.

CONTINUOUS INTRAVENOUS INFUSION IN NORMAL SUBJECTS The typical response in a normal subject (N.H.) to stepwise increase in the rate of Cecekin infusion is shown in Figure 1. Amylase output showed a steady increase during successive 10-minute collections to attain a maximum level with pancreozymin infusion of 0·125 Harper units/kg./min. Bilirubin output increased markedly after commencement of the infusion due to discharge of gall bladder bile into the duodenum but then fell to a steady constant level with continuation of the infusion. The protein output in the duodenal fluid showed more variable changes which depended on both the amylase output and discharge of bile into the duodenum. The fluid volume and bicarbonate output increased with increasing rates of Cecekin infusion owing to the stimulus of the secretin contained in the Cecekin preparation.

In general, the output was variable in the first 10-minute collection period but good reproducibility was observed in the second and third 10-minute

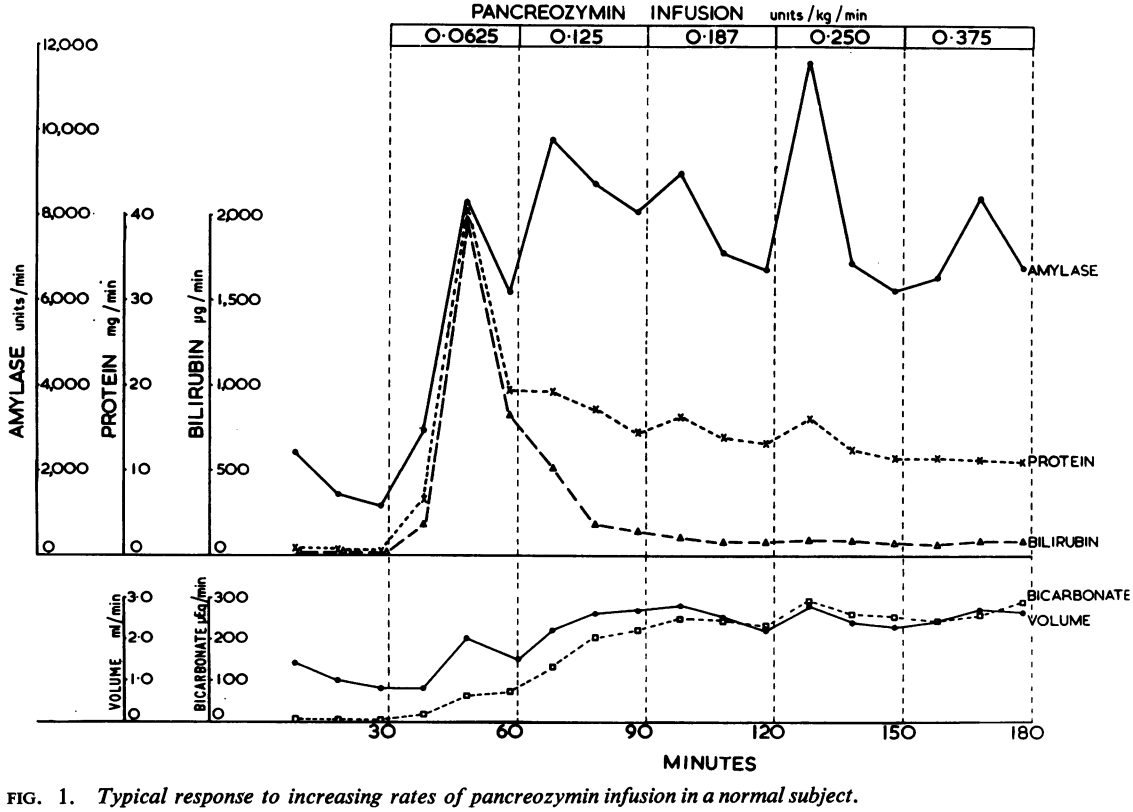

FIG. 1. *Typical response to increasing rates of pancreozymin infusion in a normal subject.*

periods for each infusion. The average value of the second and third 10-minute collections was considered to represent the maximum response at each infusion rate. At the dose of Cecekin which caused a maximum amylase response, there were no appreciable side effects but with supramaximal doses duodenal drainage was irregular and side effects were more prominent.

Figure 2 shows the mean total amylase output with increasing rates of infusion in eight normal subjects. The maximum amylase output ranged from 4,700 to 10,900 units/min. (mean 7,800 units/min. ± S.D. 1,300 units/min.). The maximum response was obtained with pancreozymin doses which varied from 0·125 to 0·375 Harper units/kg./min. (5·1 to 19·7 Harper units/min.). A marked decline from the maximum amylase output occurred in four patients with further increase in the dose of pancreozymin; in each of these, it was associated with intermittent duodenal drainage and symptoms of nausea and malaise. In three subjects a maximum amylase output was not clearly obtained and it may have been that the dosage was submaximal.

The maximum response for fluid volume and bicarbonate (Table I) was at or below the lower limit of the normal range already established for maximum secretin infusion (Banwell *et al.*, 1967). This was to be expected since the calculated dose of secretin infused was also submaximal ranging from 1·6 to 3·2 units/min.

The maximum amylase output in normal subjects and in patients with pancreatic, biliary and miscellaneous disease is shown in Figure 3.

PANCREATIC AND BILIARY DISEASE The patients (H.E., L.M., and H.B.) with chronic pancreatitis had

TABLE I

RESPONSE TO CONTINUOUS PANCREOZYMIN INFUSION IN NORMAL SUBJECTS

Patient, Sex, Diagnosis	*Weight (kg.)*	*Height (in.)*	*Pancreozymin Infusion Rate (units/kg./min.)*	*Volume (ml./min.)*				*Bicarbonate (μEq./min.)*			
				10-Minute Collections			*Mean of 2 and 3*	*10-Minute Collections*			*Mean of 2 and 3*
				1	*2*	*3*		*1*	*2*	*3*	
G.H.	52·5	63	0				0·5[1]				11
Male			0·0625	1·7	2·3	2·1	2·2	163	212	198	205
Psychoneurosis			0·125	0·9	3·6	3·4	3·5	76	327	315	321
			0·375	3·2	4·0	3·6	3·8	323	428	392	410
H.W.	83·2	70	0				0·8[1]				6
Male			0·0625	3·9	4·7	4·3	4·5	274	330	318	324
Psychoneurosis			0·125	4·5	5·2	3·7	4·4	351	426	333	379
			0·187	5·2	4·5	4·0	4·2	489	414	368	391
			0·250	5·8	4·2	3·0	3·6	522	386	288	337
R.G.	49·5		0				0·6[1]				8
Male			0·0312	1·0	2·4	2·5	2·4	88	163	168	165
Fractured tibia			0·0625	2·1	1·0	1·5	1·2	164	68	96	82
			0·125	2·2	1·8	1·8	1·8	139	108	108	108
			0·250	3·2	2·0	2·0	2·0	176	110	110	110
N.H.	41·4	58	0	1·4	1·0	0·8	0·9	1	2	2	2
Female			0·0625	0·8	2·0	1·5	1·7	17	62	70	66
Endogenous depression			0·125	2·2	2·6	2·7	2·6	130	203	219	211
			0·187	2·8	2·5	2·3	2·4	249	238	230	234
			0·250	2·9	2·4	2·5	2·4	293	257	239	248
			0·375	2·4	2·7	2·7	2·7	243	262	286	274
H.D.	69·3	73	0				0·4[1]				8
Male			0·0625	3·6	1·6	1·6	1·6	342	138	109	123
Hypertension			0·125	1·7	0·7	0·7	0·7	119	58	51	54
			0·187	3·3	3·6	5·3	4·4	287	335	514	424
			0·250	3·8	2·2	4·0	3·1	361	207	376	291
E.B.	57·6	67	0		0·5	0·4	0·4		15	12	13
Male			0·0312	2·8	2·8	3·2	3·0	257	263	284	273
Hypertension			0·125	3·3	2·9	3·2	3·0	280	261	281	271
			0·250	3·2	3·1	3·0	3·0	275	264	258	261
E.S.	58·5		0				1·0[1]				14
Male			0·0625	2·3	3·1	2·5	2·8	198	279	208	251
Irritable colon syndrome			0·125	4·2	4·0	2·7	3·3	281	260	214	237
			0·187	3·3	3·2	3·1	3·1	280	295	264	279
			0·250	2·5	2·6	2·4	2·5	220	270	252	261
J.C.	70·6	71	0				0·7[1]				8
Male			0·0625	0·9	2·1	2·2	2·1	16	84	126	105
Epilepsy			0·125	2·4	3·7	3·4	3·5	149	255	245	250
			0·187	4·1	4·6	2·6	3·6	336	395	221	308

[1]Single 10-minute collection of duodenal fluid.

very low maximum amylase outputs (24, 12, and 105 units/min.).

The patient in the post-acute phase of acute pancreatitis (D.C.) had a maximum response in the normal range (5,350 units/min.).

Both M.S. with chronic cholecystitis and M.L., who was studied after cholecystectomy, had normal amylase responses of 9,750 and 6,100 units/min. respectively.

MISCELLANEOUS DISEASES Of the four patients with adult coeliac disease, two had a maximum amylase output within the normal range (L.S. 5,750 units/min., V.R. 7,800 units/min.) and two had significantly reduced levels of amylase output (C.G. 1,650 units/min., B.G., 4,400 units/min.).

The patient (P.B.) with tropical sprue had a low maximum amylase output (3,790 units/min.).

Of the patients with hepatic cirrhosis, one (L.W.) had a low amylase output (4,080 units/min.) and the other (F.T.) had a normal response (6,960 units/min.).

The patient with quinidine-induced diarrhoea (B.S.) had a subnormal response (4,370 units/min.).

C.B. with diabetic diarrhoea had a low amylase output (3,380 units/min.).

G.P. with intestinal polyposis had a normal maximum response (5,800 units/min.).

In patients with a subnormal response the rise in amylase output from the basal value to the maximum output is compared with the normal response in Figure 4. All three patients with chronic pancreatitis showed no significant elevation in amylase output on pancreozymin stimulation.

RELATIONSHIP OF PROTEIN IN DUODENAL FLUID TO AMYLASE SECRETION A close correlation has been

TABLE I—*continued*

RESPONSE TO CONTINUOUS PANCREOZYMIN INFUSION IN NORMAL SUBJECTS

Bilirubin (μg./min.)				*Amylase (units/min.)*				*Protein (mg./min.)*				*Amylase/Protein Ratio (units/mg.)*			
10-Minute Collections				*10-Minute Collections*				*10-Minute Collections*				*10-Minute Collections*			
1	*2*	*3*	*Mean of 2 and 3*	*1*	*2*	*3*	*Mean of 2 and 3*	*1*	*2*	*3*	*Mean of 2 and 3*	*1*	*2*	*3*	*Mean of 2 and 3*
			15				1,260				4·0				315
49	60	67	63	3,760	5,060	5,490	5,275	11·7	13·8	11·6	12·7	322	367	473	419
1	630	374	502	1,120	4,800	5,180	4,990	2·7	24·2	18·7	21·4	415	198	277	233
160	160	72	116	6,230	7,470	7,130	7,300	16·0	18·4	14·4	16·4	389	406	495	445
			15				2,780				4·6				605
976	1,880	1,060	1,470	5,330	6,900	5,820	6,375	22·3	41·0	25·1	33·0	239	169	233	194
675	547	230	388	7,870	9,000	7,740	8,370	22·5	21·8	14·8	18·3	350	413	522	458
203	203	192	197	8,950	9,000	6,400	7,700	18·2	16·7	13·3	15·0	491	539	481	513
302	181	75	128	8,000	7,000	4,800	5,900	18·6	13·0	8·1	10·5	430	538	593	575
			18				1,284				4·0				321
0	546	630	588	880	1,870	2,200	2,035	2·6	14·4	13·9	14·1	339	131	158	144
311	105	117	111	2,460	1,400	3,360	2,380	10·3	5·2	8·2	6·7	239	269	410	355
176	108	90	99	5,270	5,460	4,750	5,105	11·2	10·1	9·6	9·8	470	540	495	522
166	96	90	93	8,390	6,720	5,200	5,960	16·9	10·7	10·1	10·4	497	629	515	573
0	0	0	0	2,440	1,460	1,090	1,275	0·8	0·6	0·4	0·5	305	243	272	255
179	2,000	825	1,412	2,970	8,320	6,200	7,260	6·6	40·1	19·5	29·8	450	208	318	244
517	182	141	161	9,800	8,700	8,100	8,400	19·3	17·2	14·6	15·8	508	506	555	531
101	80	78	79	9,000	7,150	6,750	6,950	16·3	14·0	13·3	13·6	552	510	508	509
90	86	74	80	11,600	6,900	6,250	6,575	16·2	12·5	11·5	12·0	715	552	545	549
67	81	81	81	6,560	8,460	6,800	7,630	11·5	11·3	11·1	11·2	570	748	613	681
			5				2,128				6·2				343
389	112	168	140	6,950	2,740	3,070	2,905	25·6	10·2	11·2	10·7	272	268	274	271
185	59	43	51	5,250	2,730	1,890	2,310	17·2	7·9	6·4	7·1	305	346	295	325
247	180	265	222	10,600	8,300	10,900	9,600	29·3	27·7	34·5	31·2	362	299	316	308
190	101	184	142	7,600	4,000	8,400	6,200	24·7	12·7	28·4	20·5	308	315	296	303
	24	7	15		2,580	1,960	2,270		3·7	3·4	3·5		697	575	636
280	386	272	329	6,880	7,830	7,600	7,715	14·0	14·0	13·8	13·9	491	560	550	555
208	128	131	129	8,500	7,550	8,700	8,125	15·2	12·5	14·4	13·4	560	604	604	604
133	127	120	123	8,380	9,100	8,820	8,965	15·4	14·5	13·8	14·1	545	630	640	635
			100				1,380								
440	1,050	325	687	3,720	7,560	5,350	6,455								
181	100	151	125	7,560	5,360	6,480	5,920								
92	121	90	105	7,000	8,320	7,130	7,725								
97	80	139	109	4,700	6,240	5,660	5,950								
			21				700								
65	776	596	686	1,170	4,030	3,420	3,725								
399	392	258	325	4,610	7,400	4,760	6,080								
230	165	78	121	6,560	7,090	4,360	5,725								

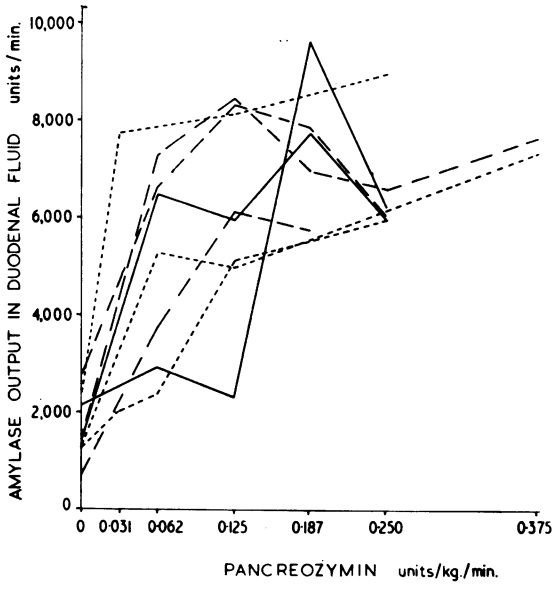

FIG. 2. *Amylase response to pancreozymin infusion in eight normal subjects.*

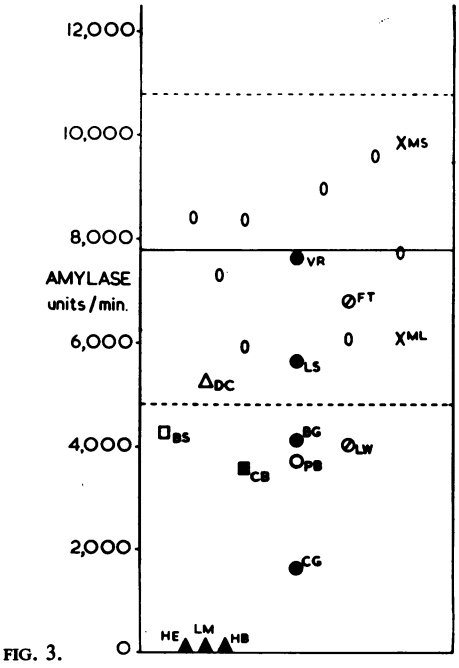

FIG. 3.

0 *Normal subjects*

--- 95% *Confidence limits*

▲ *Chronic pancreatitis*

● *Adult coeliac disease*

○ *Tropical sprue*

⊘ *Hepatic cirrhosis*

× *Gallbladder disease*

△ *Post-acute pancreatitis*

□ *Unexplained diarrhoea*

■ *Diabetic diarrhoea*

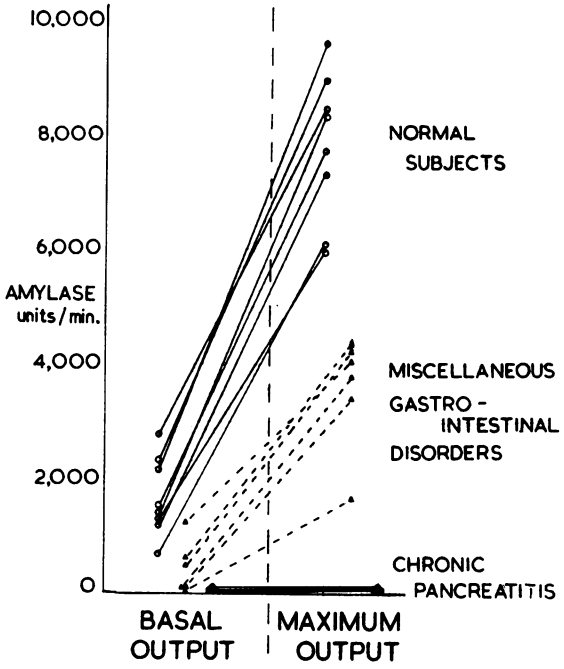

FIG. 4. *Amylase response to maximum pancreozymin infusion showing increase from basal output to maximum output in normal and abnormal subjects. Patients with miscellaneous gastrointestinal disorders giving a normal response are not shown.*

found between the activity of the enzymes of bovine pancreatic fluid obtained by pancreatic duct cannulation and the protein content of the pancreatic fluid (Keller, Cohen, and Neurath, 1958). It has been suggested by Hanscom and Littman (1963) that a similar relationship between enzyme and protein concentration may apply to human duodenal fluid. There is also evidence that the various pancreatic enzymes are produced at any given time in a constant proportion to one another (Grossman, Greengard, and Ivy, 1943). Thus, if the only protein in the duodenal fluid is pancreatic enzyme protein then the ratio of amylase activity to protein concentration would be constant at an optimum *p*H for amylase activity.

In the eight normal subjects the protein content of duodenal fluid usually increased in parallel with amylase activity but with marked increase in biliary flow the amylase to protein ratio was greatly reduced (Table I, Fig. 5). This would be consistent with the presence of a significant amount of non-amylase protein in bile. Hardwicke, Rankin, Baker, and Preisig (1964) found the protein content of pure bile to range from 60 to 230 mg./100 ml. in seven patients. In the present study the protein content of bile

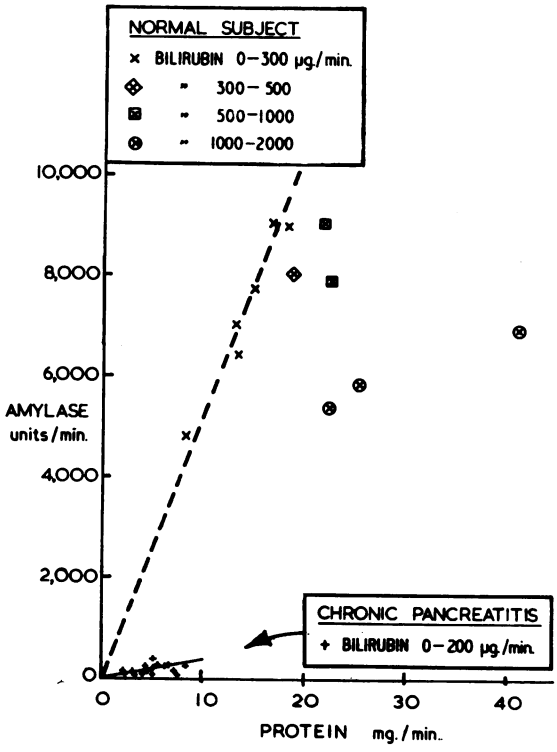

FIG. 5. *Relationship between protein, amylase, and bilirubin in duodenal fluid during pancreozymin infusion.*

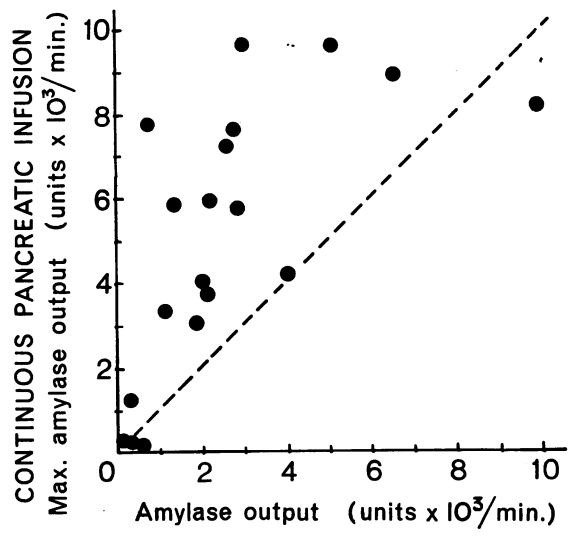

FIG. 6. *Comparison of the amylase output during the secretin-pancreozymin test (Burton* et al., *1960a) with the amylase output obtained by maximum continuous pancreozymin infusion.*

obtained from T-tube drainage of the common bile duct in two patients ranged from 175 to 510 mg./100 ml. Furthermore, in pancreatic disease where the amylase activity was low in the duodenal fluid, even in the absence of bile, the amylase protein ratio was greatly reduced (Fig. 5).

COMPARISON OF THE AMYLASE OUTPUT DURING THE SECRETIN-PANCREOZYMIN TEST WITH THE RESPONSE TO MAXIMUM PANCREOZYMIN INFUSION As shown in Fig. 6, the amylase output with maximum infusion of Cecekin was clearly greater in 14, essentially similar in four (three patients with chronic pancreatitis), and less in only one than the output in the 30-minute post-pancreozymin phase of the secretin-pancreozymin test (Burton *et al.*, 1960a). The peak 10-minute phase of the secretin-pancreozymin test (Burton *et al.*, 1960a) showed greater variability.

DISCUSSION

Pancreozymin probably stimulates the transfer of digestive enzymes across the acinar cell membrane (Hokin and Hokin, 1962) but its exact mode of action is uncertain. At the beginning of pancreozymin administration preformed zymogen granules would be discharged into the duct lumen, whereas with continuation of the infusion amylase output would become dependent on the steady rate of amylase production by the cell. The amylase output during the second and third 10-minute collection periods in this study were thought to represent this steady output state for each pancreozymin dosage, but an exact description of enzyme secretion must await further knowledge of the biochemical effects of pancreozymin on the acinar cell

Constant intravenous infusion of Cecekin was found to cause a maximum secretory response for amylase output in normal subjects with a pancreozymin stimulus of 5·1 to 19·7 Harper units/min. The dose was lower than that used by Hansky *et al.* (1964) to obtain a maximum amylase output in the dog (12·5 to 50 units/min.). Side effects from administration of the drug by continuous infusion were encountered, but at the phase of maximum enzyme output appeared to be less intense than with a maximum rapid injection technique employed by Hartley, Gambill, Engstrom, and Summerskill (1966). A more consistent maximum enzyme response may follow further purification of Cecekin (Jorpes, Mutt, and Toczko, 1964) with less tendency for suppression of enzyme output to occur at high doses from impurities in the material (Hansky *et al.*, 1964).

In contrast to the previously observed relationship between body weight and maximum volume and bicarbonate response to secretin (Banwell *et al.*, 1967), the maximum amylase output on pancreozymin stimulation was independent of body weight. The explanation for this is uncertain. The coefficient of variation for amylase determination is greater than that for volume and bicarbonate, and as only a small number of subjects were studied this may have obscured a correlation. Alternatively, since it is known that bicarbonate and amylase have entirely different functions in the duodenum and jejunum and a probable separate cellular origin within the pancreas (Grossman and Ivy, 1946; Goldberg and Chaikoff, 1951) the different body weight relationships which we have found for bicarbonate and amylase in this study may be a result of their different physiological roles.

All three patients with chronic pancreatitis did not respond to pancreozymin which indicated that they had severe exocrine pancreatic deficiency. Of the six other patients with miscellaneous gastrointestinal disorders who had subnormal responses, one (L.W.) with alcoholic cirrhosis, may have had mild chronic pancreatitis since this condition is associated with hepatic cirrhosis (Pollack and Gerber, 1943) and the low output in C.B., with diabetes mellitus, has also been described in this disease by other workers (Chey, Shay, and Shuman, 1963). The low amylase output in two patients with untreated adult coeliac disease and a patient with tropical sprue in remission are of some interest in view of previous reports of normal pancreatic function in these patients (Frazer, 1952; Dreiling, 1953; Cooke, Peeney, and Hawkins, 1953). However, the pancreatic zymogen content (Gillman and Gillman, 1951) and duodenal amylase concentration in malnourished patients are both reduced (Thompson and Trowell, 1952; Gómez, Galvan, Cravioto, and Frenk, 1954) and this may have been the explanation for the low maximum amylase output in our patients. A dietary factor may also have been involved in this change. Desnuelle, Reboud, and Abdeljlil (1962) have shown that prolonged reduction of the carbohydrate content in the diet will reduce the pancreatic amylase content. Whether the low enzyme output in our patients with adult coeliac disease contributed to their malabsorption state or was restored to normal after treatment of the disorder is not known.

The infusion method of Cecekin administration may be used to test gall bladder function in a similar manner to that used by previous workers (Marks, 1959; Burton, Harper, Howat, Scott, and Varley, 1960b). For example, M.S. with chronic cholecystitis, in this study failed to show a normal rise of bilirubin output with Cecekin infusion owing to the failure of cholecystokinin to cause contraction of the diseased gall bladder.

In our hands measurement of total protein in duodenal juice was an unreliable index of enzyme activity.

SUMMARY

The secretory response of the human pancreas to continuous intravenous infusion of a pancreozymin-cholecystokinin compound (Cecekin) was measured in normal subjects and in patients with various gastrointestinal disorders.

The maximum amylase output was obtained in normal subjects.

The amylase output following pancreozymin injection during the secretin-pancreozymin test (Burton *et al.*, 1960a) was lower than the maximum amylase output with Cecekin infusion.

The maximum amylase output was shown to be subnormal in a variety of gastrointestinal disorders.

The protein content of duodenal fluid was not a satisfactory measure of the total amylase output.

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REFERENCES

Banwell, J. G., Northam, B. E., and Cooke, W. T. (1967). Secretory response of the human pancreas to continuous intravenous infusion of secretin. *Gut*, **8**, 50-57.

Burton, P., Evans, D. G., Harper, A. A., Howat, H. T., Oleesky, S., Scott, J. E., and Varley, H. (1960a). A test of pancreatic function in man based on the analysis of duodenal contents after administration of secretin and pancreozymin. *Gut*, **1**, 111-124.

——, Harper, A. A., Howat, H. T., Scott, J. E., and Varley, H. (1960b) The use of cholecystokinin to test gall bladder function in man. *Gut*, **1**, 193-204.

Chey, W. Y., Shay, H., and Shuman, C. R. (1963). External pancreatic secretion in diabetes mellitus. *Ann. intern. Med.*, **59**, 812-821.

Cooke, W. T., Peeney, A. L. P., and Hawkins, C. F. (1953). Symptoms, signs, and diagnostic features of idiopathic steatorrhoea. *Quart. J. Med.*, **22**, 59-77.

Desnuelle, P., Reboud, J. P., and Abdeljlil, A. Ben (1962). Influence of the composition of the diet on the enzyme content of rat pancreas. In *Ciba Foundation Symposium on the Exocrine Pancreas*, edited by A. V. S. de Reuck and M. P. Cameron, pp. 90-114. Churchill, London.

Dreiling, D. A. (1953). Studies in pancreatic function. V. The use of the secretin test in the diagnosis of pancreatitis and in the demonstration of pancreatic insufficiencies in gastrointestinal disorders. *Gastroenterology*, **24**, 540-555.

——, and Janowitz, H. D. (1962). The measurement of pancreatic secretory function. In *Ciba Foundation Symposium on the Exocrine Pancreas*, edited by A. V. S. de Reuck and M. P. Cameron, pp. 225-258. Churchill, London.

Frazer, A. C. (1952). Studies on the aetiology of the sprue syndrome. *Gastroenterologia (Basel)*, **78**, 357-364.

Gillman, J., and Gillman, T. (1951). *Perspectives in Human Malnutrition*, Grune and Stratton, New York.

Goldberg, R. C., and Chaikoff, I. L. (1951). Selective pancreatic acinar destruction by dl-ethionine. *Arch. Path.*, **52**, 230-238.

Gómez, F., Galvan, R. R., Cravioto, J., and Frenk, S. (1954). Studies on the undernourished child. XI. Enzymatic activity of the duodenal contents in children affected with third degree malnutrition. (Spanish with English translation). *Pediatrics*, **13**, 544-552.

Grossman, M. I., Greengard, H., and Ivy, A. C. (1943). The effect of dietary composition on pancreatic enzymes. *Amer. J. Physiol.*, **138**, 676-682.

——, and Ivy, A. C. (1946). Effect of alloxan upon external secretion of the pancreas. *Proc. Soc. exp. Biol. (N.Y.)*, **63**, 62-63.

Hanscom, D. H., and Littman, A. (1963). Dose-response relationships to pancreozymin in normal subjects and patients with chronic pancreatitis. *Gastroenterology*, **45**, 209-214.

Hansky, J., Tiscornia, O. M., Dreiling, D. A., and Janowitz, H. D. (1964). Maximal secretory capacity of the canine pancreas in response to pancreozymin and secretin. *Amer. J. Physiol.*, **206**, 351-356.

Hardwicke, J., Rankin, J. G., Baker, K. J., and Preisig, R. (1964). The loss of protein in human and canine hepatic bile. *Clin. Sci.*, **26**, 509-517.

Harper, A. A., Blair, E. L., and Scratcherd, T. (1962). The distribution and physiological properties of pancreozymin. In *Ciba Foundation Symposium on the Exocrine Pancreas*, edited by A. V. S. de Reuck and M. P. Cameron, pp. 168-185. Churchill, London.

Hartley, R. C., Gambill, E. E., Engstrom, G. W., and Summerskill, W. H. J. (1966). Pancreatic exocrine function. Comparison of responses to augmented secretin stimulus, augmented pancreozymin stimulus, and test meal in health and disease. *Amer. J. dig. Dis.*, **11**, 27-39.

Hokin, L. E., and Hokin, M. R. (1962). The synthesis and secretion of digestive enzymes by pancreatic tissue *in vitro*. In *Ciba Foundation Symposium on the Exocrine Pancreas*, edited by A. V. S. de Reuck and M. P. Cameron, pp. 186-207. Churchill, London.

Jorpes, E., Mutt, V., and Toczko, K. (1964). Further purification of cholecystokinin and pancreozymin. *Acta chem. scand.*, **18**, 2408-2410.

Keller, P. J., Cohen, E., and Neurath, H. (1958). The proteins of bovine pancreatic juice. *J. biol. Chem.*, **233**, 344-349.

Lin, T. M., and Grossman, M. I. (1956). Dose response relationship of pancreatic enzyme stimulants: pancreozymin and methacholine. *Amer. J. Physiol.*, **186**, 52-56.

Marks, I. N. (1959). Changes in the icteric index of the duodenal aspirate after the injection of secretin and pancreozymin. *Gastroenterology*, **37**, 73-80.

Northam, B. E., and Banwell, J. G. (1966). Automated analysis in the investigation of pancreatic function. In *Technicon European Symposium*, Paris.

Pollack, A. D., and Gerber, I. E. (1943). Abdominal visceral lesions associated with primary disease of the liver. *Arch. Path.*, **36**, 608-611.

Preshaw, R. M., and Grossman, M. I. (1965). Comparison of subcutaneous and intravenous administration of pancreatic stimulants. *Amer. J. Physiol.*, **209**, 803-810.

Thompson, M. D., and Trowell, H. C. (1952). Pancreatic enzyme activity in duodenal contents of children with a type of kwashiorkor. *Lancet*, **1**, 1031-1035.

Wang, C. C., Grossman, M. I., and Ivy, A. C. (1948). Effect of secretin and pancreozymin on amylase and alkaline phosphatase secretion by the pancreas in dogs. *Amer. J. Physiol.*, **154**, 358-368.