Pancreatic polypeptide

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Pancreatic polypeptide (PP) was discovered fortuitously during the purification of insulin from birds (Kimmel *et al.*, 1968) and later from mammals (Chance *et al.*, 1976). PP has since been extracted and purified from several mammalian species. It contains 36 amino-acid residues and is quite distinct from other known hormonal peptides (Lin and Chance, 1974). The amino-acid sequence of the peptides extracted from man, pig, dog, sheep, and cow differs only in one or two residues in positions 2, 6, or 23 (Lin and Chance, 1974). The biological activity of these mammalian peptides has been found to reside in the C terminal hexapeptide (Lin and Chance, 1978). Rodent PP, however, appears to be somewhat different in that it does not cross-react with the majority of antisera raised to the bovine peptide.

Localisation

PP is localised almost entirely to the pancreas where it is produced by discrete, small, granular endocrine cells (Fig. 1) which are scattered throughout the exocrine parenchyma as well as being found in the periphery of the islets (Adrian *et al.*, 1976; Heitz *et al.*, 1976; Larsson *et al.*, 1976). The PP cells display the ultrastructural features of the D_1-cell of the revised Wiesbaden classification (Solcia *et al.*, 1973). It has been suggested that the cell producing PP should now be given the functional label of the PP cell (Solcia *et al.*, 1978).

Release of PP

PP circulates in plasma and levels rise rapidly after the ingestion of food, particularly protein and fat, and remain raised for several hours (Fig. 2) (Hazelwood *et al.*, 1973; Floyd *et al.*, 1976; Polak *et al.*, 1976; Schwartz *et al.*, 1976). This rise is abolished by total pancreatectomy indicating that the pancreas is the only significant source of this peptide in the circulation (Adrian *et al.*, 1977b). Intravenous infusions of amino-acids, glucose, or lipids do not significantly alter circulating PP levels, so that an entero-PP axis must exist. A substantial increase in plasma PP concentration is also observed during
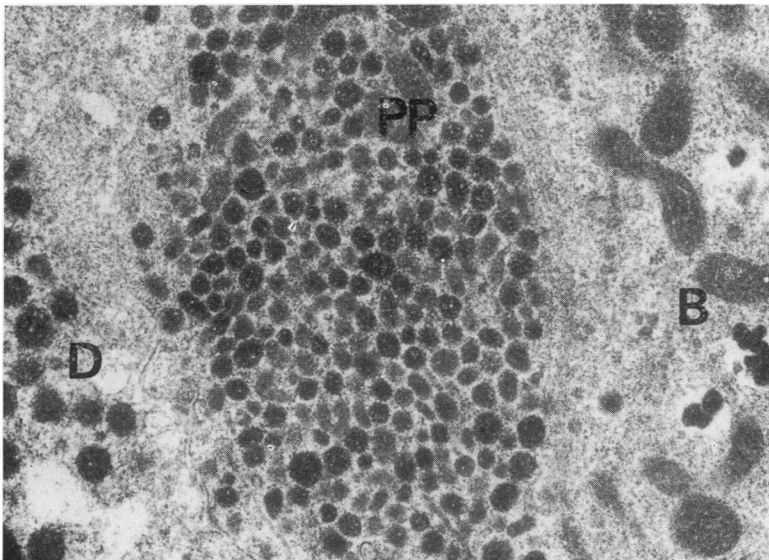

Fig. 1 *Electron micrograph showing a PP cell in an islet of Langerhans and also showing a B-cell (B) and a somatostatin cell (D). (Original magnification × 30 000).*

insulin-induced hypoglycaemia, the peak coinciding with the lowest blood glucose concentrations (Floyd et al., 1976; Adrian et al., 1977b; Schwartz et al., 1978). This effect is, however, blocked by truncal vagotomy, indicating that it is mediated through stimulation of the vagus (Adrian et al., 1977b). Immediately after therapeutic vagotomy the PP response to food is impaired (Schwartz et al., 1976), but several months after vagotomy it is normal (Adrian et al., 1977b; Taylor et al., 1978a). Thus, vagal stimulation is not the only mechanism of PP release. In the isolated perfused canine pancreas caerulein, a cholecystokinin analogue, glucose-dependent insulin-releasing polypeptide (GIP), vaso-active intestinal peptide (VIP), and gastrin, all caused a significant increase in perfusate PP concentration (Adrian et al., 1978b). Acetyl choline also caused a

very marked release in this preparation and may enhance the release evoked by other substances.

Gastrointestinal hormones are potent stimulators of PP release in man (Adrian et al., 1977b). Secretin alone has no effect on PP levels (Adrian et al.,1979b) but an infusion of cholecystokinin and secretin combined increased the plasma PP concentration from 21 $\pm$ 5 pmol/l to 94 $\pm$ 11 pmol/l (Fig. 3). Very low doses of caerulein (123 fmol/kg/min) combined with a very low dose of secretin (137 fmol/kg/min) caused an increase in plasma PP of 117 $\pm$ 26% (P $<$ 0·005) within 90 minutes.

The entero-PP axis, therefore, appears to have two components, the vagus and gastrointestinal hormones. A complex interrelationship between these two components is suggested by the effect of atropine which, in normal subjects, blocks the PP response to gut hormones and also lowers fasting levels of PP (Adrian et al., 1978a). Some degree of cholinergic tone seems to be essential both for maintaining basal secretion of PP and for the response to gut hormones. This may be considered to be analogous to the release of acid from the gastric parietal cell which is dependent on the interaction of acetyl choline, gastrin, and histamine; the removal of any one of these very greatly diminishes acid production after a meal.

Gastric distension, either by water (Adrian et al., 1978a) or a balloon (Schwartz et al., 1979), evokes a significant release of PP in man, perhaps through a local reflex. A local reflex may also be responsible in part for the PP response to hypoglycaemia as, in addition to being abolished by truncal vagotomy, this is also reduced by selective vagotomy (Adrian et al., 1978a). Gastric acid secretion does not seem to be important in the postprandial release of PP which is not affected by the administration of cimetidine (Taylor et al., 1978a), and only slightly so
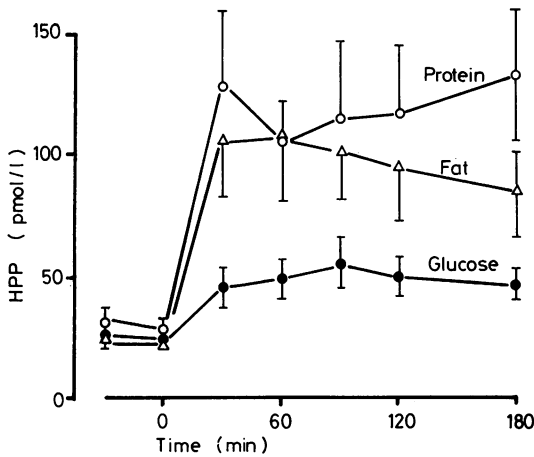

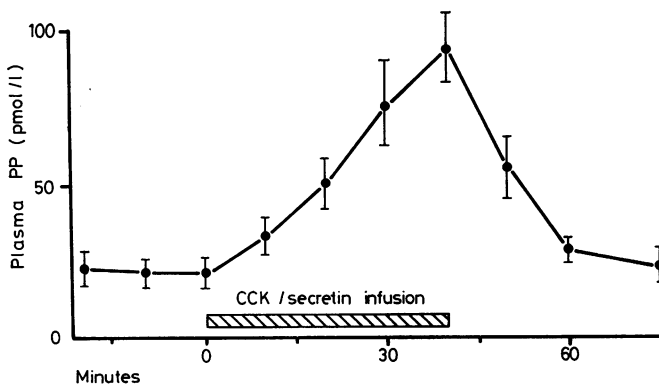Fig. 2 *Effect of individual meal components on plasma PP (HPP) levels in 6 healthy subjects.*

Fig. 3 *Effect of an infusion of cholecystokinin (approx 10% pure CCK 0·5 IDU/kg/h) and secretin (pure natural secretin 137 fmol/kg/min) on plasma PP concentrations in 4 healthy subjects.*

by the instillation of hydrochloric acid into the duodenum (Floyd *et al.*, 1976).

In common with insulin, glucagon, and all of the gastrointestinal hormones so far investigated, the release of PP both in the basal and postprandial state is inhibited by somatostatin (Adrian *et al.*, 1977a; Floyd *et al.*, 1977; Marco *et al.*, 1977).

Actions of PP

Following the isolation and purification of bovine PP, Lin and Chance carried out a systematic study of the biological actions of the peptide on the canine gastrointestinal tract (Lin and Chance, 1974, 1978; Lin *et al.*, 1977). The effects of PP included stimulation of gastric acid secretion, but inhibition of that stimulated by pentagastrin. PP inhibited the secretion of pancreatic juice, and particularly of pancreatic enzymes, both in the basal state and when stimulated by an infusion of cholecystokinin and secretin. The gall bladder was relaxed and the tone of the choledochal sphincter was increased. Gastric emptying and intestinal transit were enhanced in the rat.

Infusion of PP in man

A vital step in establishing that a possible hormone does have a physiological role is to show that a biological response occurs when infusion of the substance produces a circulating concentration similar to that seen after natural stimuli. Therefore, in order to elucidate whether any of the actions of PP mentioned above could be considered to be physiological in man, bovine PP was infused at several doses from 1 to 5 pmol/kg/min in a total of 48 healthy subjects. Plasma levels rose to above those seen postprandially and reached a plateau by 30 minutes. The mean half life was 6·9 minutes (SEM ± 0·3; n = 23), the metabolic clearance rate was 5·1 ± 0·2 ml/kg/min, and the apparent space of distribution was 51 ± 3 ml/kg, which approximates to the plasma volume (Adrian *et al.*, 1978c). The short half life of PP indicates that the sustained rise after eating is the result of active release for several hours after eating.

In the basal state the infused PP significantly reduced the volume of pancreatic juice and the output of trypsin (for both, $P < 0.02$), and also abolished the output of bilirubin into the small intestine (Greenberg *et al.*, 1979). When PP was infused during a low dose infusion of pure secretin, 200 fmol/kg/min, bicarbonate output was reduced by 25 ± 8%, which reflected the change in the volume of duodenal juice ($P < 0.05$), and pancreatic enzyme secretion as measured by duodenal juice protein and tryptic activity was reduced by 67 ± 7% and 59 ±

6%, respectively ($P < 0.001$) (Adrian *et al.*, 1979b) (Fig. 4, 5). The bilirubin output also fell significantly during these experiments ($P < 0.01$). When doses of PP which mimicked the postprandial rise were superimposed on an infusion of small doses of secretin (137 fmol/kg/min) and caerulein (123 fmol/kg/min) there was a 60% reduction of trypsin output and an 80% reduction of bilirubin output (for both, $P < 0.001$) (Greenberg *et al.*, 1978b). In cholecystectomised patients, trypsin output was reduced by this procedure to the same degree as in normal subjects but bilirubin output was unaffected, suggesting that PP had two quite separate effects in man, inhibition of pancreatic enzyme secretion and relaxation of the gall bladder.

Gastric acid and pepsin secretion were unaffected by infusion of PP, both in the basal state and during submaximal stimulation of acid secretion by pentagastrin (Peptavlon 15 pmol/kg/min; Greenberg *et al.*, 1978a). Its effect on gastric emptying was studied in five healthy subjects by infusing PP or saline during the ingestion of a small carbohydrate-rich solid breakfast chosen because it elicited only a small release of endogenous PP. The half-emptying time when PP was infused (66 ± 7 min) was not significantly different from that when saline was infused (71 ± 11 min). In addition, the emptying rate during a higher PP dose, giving levels similar to those seen after a large mixed lunch, was not significantly changed (60 ± 12 min). All infusions
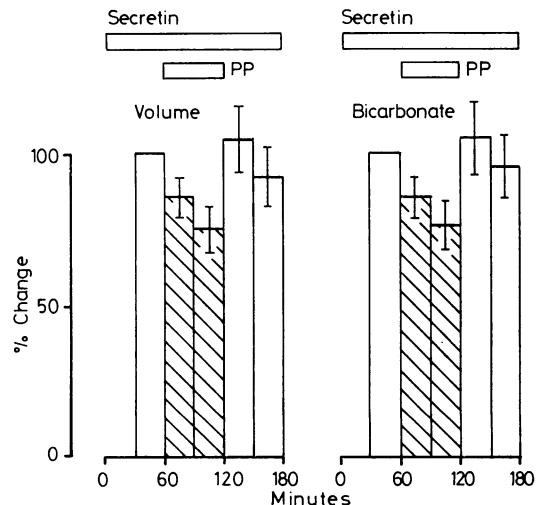

Fig. 4 *The effect of bovine PP (3·3 pmol/kg/min) on duodenal juice volume and bicarbonate output in 5 healthy subjects during stimulation with secretin (pure secretin 200 fmol/kg/min). Values represent % of output during the 30 minute period before PP infusion.*
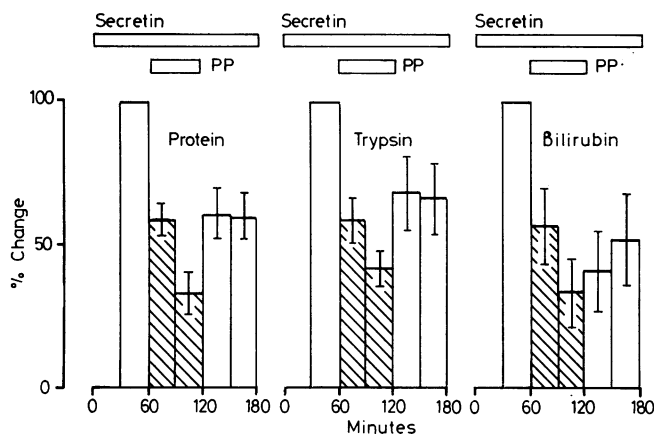
Fig. 5 *The effect of bovine PP (3·3 pmol/kg/min) on duodenal juice enzyme output (measured as tryptic activity and total protein) and bilirubin output in 5 healthy subjects during stimulation with pure secretin (200 fmol/kg/min). Values represent % of output during the 30 minute period immediately before PP infusion,*

in this study were given blind and in random order (Adrian *et al.*, 1979c). Basal and postprandial responses of the hormones insulin, glucagon, gastrin, secretin, enteroglucagon, and glucose-dependent insulin-releasing polypeptide (GIP) were not significantly altered by the infusions. In contrast there was an 80% reduction in fasting concentrations of motilin, a peptide which stimulates gastrointestinal motor activity (P<0·001) (Adrian *et al.*, 1978d). No change in circulating concentrations of glucose or its intermediary metabolites was observed during PP infusion (Adrian *et al.*, 1978e). Thus, PP is unlikely to be a physiological modulator of carbohydrate metabolism, gastric secretion, or gastric emptying rate in man. However, these studies do suggest that PP may have a role in the physiological regulation of gall bladder function and of pancreatic enzyme secretion in man. Similar observations have been reported in the dog (Taylor *et al.*, 1978b).

Pathophysiology of PP

EFFECT OF AGE
The fasting plasma PP concentration increases with age in normal subjects (Floyd *et al.*, 1977; Taylor *et al.*, 1978c). The postprandial rise is also greater in older healthy subjects than in young controls (Fig. 6). It is therefore of great importance when comparing groups of patients with normal subjects that the two groups are matched for age.

DIABETES
Raised plasma PP levels have been reported in both maturity onset and juvenile type diabetes, but the overlap between diabetics and normal subjects is considerable (Floyd *et al.*, 1977). Hyperplasia of PP cells in the pancreatic islets of juvenile diabetics has also been reported (Orci *et al.*, 1976). In a group of

young, well controlled patients on monocomponent insulin we have found PP levels to be identical with those of normal subjects. Because PP is present as a contaminant in most of the available commercial insulin preparations, though not monocomponent insulins, some 60% of conventionally insulin-treated diabetics studied have circulating antibodies which bind to PP. High affinity antibodies are particularly frequent in young insulin-dependent diabetics where both the duration of therapy and the insulin dosage are related to the development of antibodies (Bloom *et al.*, 1979).
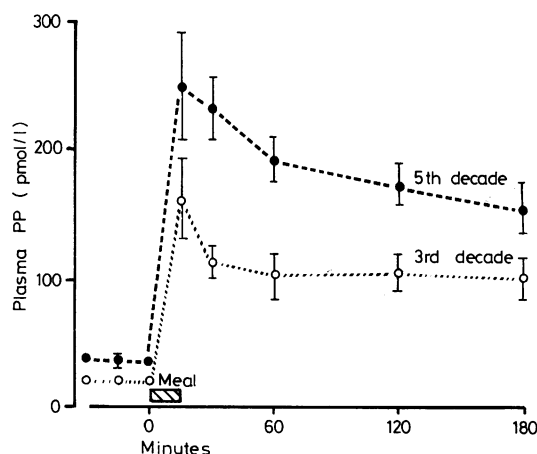
It is to be hoped that this induced autoimmunity

Fig. 6 *Plasma PP concentrations after the ingestion of a standard test breakfast in fasting normal volunteers in their 3rd decade (n = 9) and 5th decade (n = 7). The postprandial response is significantly different at 30 min (P<0·001), 60 min (P<0·005), 120 min (P<0·02), and 180 min (P<0·05).*

will be avoided in the future by the use of highly purified insulins.

OBESITY

The obese hyperglycaemic mouse (ob/ob) is the most intensively studied animal model of human late onset diabetes mellitus. Parabiotic animal experiments where ob/ob animals maintain normal weight when paired with normal but not ob/ob mates have led to the conclusion that the hyperphagia and resulting weight gain is the result of the lack of circulating satiety factor from the gut which in normal animals controls food intake (Coleman, 1978). It has been reported that the administration of PP reverses the hyperphagia and weight gain in these mice, which subsequently become normoglycaemic (Malaisse-Lagae *et al.*, 1977). Studies on the release of PP in the obese mouse are awaited with interest. We have shown (unpublished observations) that the pancreas of the fat mouse contains a normal amount of extractable PP-like immunoreactivity (147 ± 14 pmol/g) compared with that of the lean litter mate (124 ± 10 pmol/g). However, a reduction in the number of PP cells has previously been reported (Orci *et al.*, 1976).

In man, PP release by a standard test breakfast in 19 patients with morbid obesity ($225 \pm 7\%$ ideal weight) was not significantly different from that seen in 16 healthy age- and sex-matched normal controls ($106 \pm 3\%$ ideal weight). In addition the PP response was unaffected by ileojejunal bypass in the obese patients (Besterman *et al.*, 1978c).

PEPTIC ULCER

Because of the observed actions of bovine PP on acid secretion in the dog it was of particular interest to investigate PP release in patients with duodenal ulcer. Both fasting concentrations of PP (n = 40) and the response to food (n = 21) in duodenal ulcer patients were similar to those seen in age-matched controls (Adrian *et al.*, 1977b). It seems unlikely, therefore, that PP is involved in the pathogenesis of this syndrome.

STEATORRHOEA

As PP release appears to be controlled by mechanisms similar to those which control the secretion of pancreatic enzymes, it was clearly of interest to investigate its release in patients with chronic pancreatitis. The PP response to food is grossly impaired in patients with chronic pancreatitis and steatorrhoea (Adrian *et al.*, 1977a; Adrian *et al.*, 1979a); there was a similarly impaired response to the intravenous injection of secretin[1] which normally stimulates PP release. In patients with chronic pancreatitis without

[1] A comparatively impure preparation obtained from Boots.

overt exocrine deficiency the release of PP was not significantly different from normal. In contrast to the findings in pancreatic steatorrhoea, patients with steatorrhoea resulting from active coeliac disease or acute tropical sprue had normal basal and peak levels of PP after the meal. The measurement of PP may thus provide confirmatory evidence that steatorrhoea is of pancreatic origin, but it is unhelpful in assessing chronic pancreatitis without exocrine deficiency, where there is a diagnostic problem.

DIARRHOEA

The infusion of low doses of PP in the dog caused a marked increase in the motility of the gastric antrum, duodenum, ileum, and colon (Lin and Chance, 1978), and the substance was patented as a potential veterinary laxative. We therefore investigated the postprandial PP response in patients with diarrhoea resulting from several different causes. Plasma PP levels after our standard test breakfast were not significantly raised in 12 patients with acute infective diarrhoea, in 14 patients with Crohn's disease, and in 24 patients with ulcerative colitis (Besterman *et al.*, 1978b). Patients with the irritable bowel syndrome had a moderately increased release of PP after the test breakfast. However, this increased response was noted in patients who presented with constipation as well as those with diarrhoea.

GUT RESECTION

PP release appears to be potentiated by an intestinal factor. Its source was investigated by studying plasma PP release after our standard test breakfast in 18 patients with partial ileal resection and nine patients with partial colonic resection for inflammatory bowel disease, neoplasia, radiation, fibrosis, or trauma; the operations had been performed at least one year before the study.

Both basal and postprandial PP levels were surprisingly raised in these two groups of patients (Besterman *et al.*, 1978a). Further work is required to elucidate the cause and effect of this.

PANCREATIC ENDOCRINE TUMOURS

Over half of the endocrine tumours of the pancreas and their metastases so far investigated contain large numbers of PP cells which can be shown by immunofluorescence (Polak *et al.*, 1976). Hepatic and lymph node metastases sometimes contain even higher concentrations of immunoreactive PP than the primary pancreatic tumour, indicating that PP is a product of the tumour. Plasma levels are often grossly raised in these patients, sometimes exceeding 1000 times the normal basal level. The measurement of plasma PP may thus provide additional evidence

of a pancreatic tumour and may help to localise such a tumour by transhepatic portal venous catheterisation (Ingemansson *et al.*, 1971). Plasma PP may also be a useful indicator for assessing the response to treatment, particularly of VIPomas in which PP levels are often far higher than those of VIP, which is in part because of the more rapid clearance of VIP, the half life of which is less than one minute. In contrast to the very high incidence of a raised plasma PP concentration in patients with pancreatic VIPomas (Table), VIP secreting tumours outside the pancreas, for example ganglioneuroblastomas, are associated with normal PP levels. The finding of a raised PP level in the plasma of a patient with raised VIP and watery diarrhoea thus strongly suggests that a pancreatic tumour is responsible for the syndrome.

Plasma PP levels return to normal after resection of the tumour in patients with a benign adenoma. The rate at which the level falls postoperatively is slower than would be expected from the observed half life of PP during infusion experiments (Fig. 7). This is because of the presence of high molecular weight forms of PP in the plasma of these patients (Bryant *et al.*, 1978).

PANCREATIC ADENOCARCINOMA
Fasting plasma PP concentrations in a group of 13 patients with adenocarcinoma of the pancreas were not significantly different from those of patients with adenocarcinoma of the stomach, colon, rectum, bronchus, or breast, or from those of normal subjects of similar age (Bloom *et al.*, 1978).

CARCINOID TUMOURS
Fasting plasma PP concentrations were raised in 10 of 20 patients with carcinoid tumours (Bloom *et al.*, 1978). The presence of high circulating PP concentrations did not appear to be related to the site of the primary tumour, and the incidence of diarrhoea and flushing was similar in the two groups of patients. The degree of weight loss and the urinary excretion of 5HIAA was also similar in the two groups.

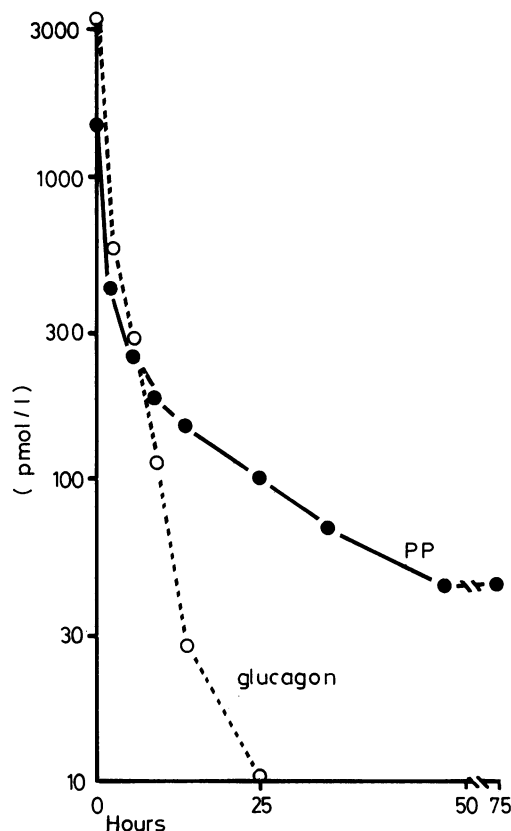Tumour was examined for PP in three of the patients with raised plasma levels, and PP-like

Fig. 7 *Effect of tumour resection on plasma PP and glucagon concentrations in a patient with a benign pancreatic glucagonoma. Both PP and glucagon levels fell to within the normal range postoperatively.*

immunoreactivity was detectable in both primary and metastatic tissue. Only one major peak of PP-like immunoreactivity was detected by Sephadex gel chromatography in each case (Fig. 8).

The future of PP research

Although PP was only discovered a decade ago, considerable progress has been made in establishing this peptide as a gut hormone. Much is now known about the mechanism of PP release after a meal and its physiological role in man, and some interesting observations on its pathophysiology have emerged. There remain some unanswered questions including the nature of the factor or factors from the gut which potentiate PP release after food, whether PP has physiological effects other than on the gall bladder and exocrine pancreas, and whether PP can be used as a clinically useful marker for pancreatic endocrine tumours.

	Total No studied	No fasting PP raised (300 pmol/l)	% positive
Vipoma	49	31	63
Insulinoma	17	4	24
Gastrinoma	60	15	25
PPoma	1	1	100
Glucagonoma	14	7	50
Adenocarcinoma	16	0	0

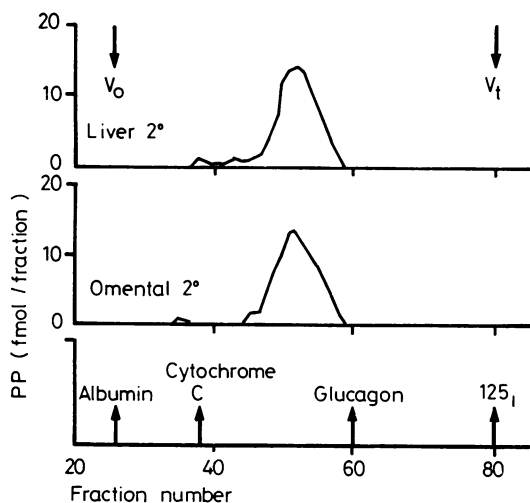Table *Plasma PP in patients with pancreatic tumours*

Fig. 8 *Gel chromatography of PP immunoreactivity in tumour extracts from 2 metastatic carcinoid tumours. One major peak was seen eluting in the same position as pure natural human PP.*

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