Pancreatic Polypeptide-Secreting Islet-Cell Tumors

A Study of Three Cases

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Three cases of pancreatic islet cell tumors, 1 malignant and 2 benign, producing predominantly pancreatic polypeptide (PP) are described. All 3 patients exhibited elevated plasma PP concentrations, either basal or protein-meal–stimulated, during the period of observation. Immunocytochemical study revealed that while PP cells predominated in the tumor, A, B, and D cells were also present. A comparison of the hormone content of the tumor tissue, adjacent pancreatic tissue, and normal pancreas was made by radioimmunoassay of tissue extracts. The PP content of tumors clearly exceeded that of normal pancreas. The insulin, glucagon, and somatostatin (SRIF) content was more variable, but in one case the glucagon content of the tumor was higher than in normal pancreas, and two of the tumors exhibited an elevated SRIF content. Gel filtration of a tumor extract showed that insulin, glucagon, and PP immunoreactivity was of expected molecular dimensions but immunoreactive SRIF in this extract was composed of two species. The PP in gel fractions reacted equally well with antibody directed toward different parts of the PP molecule. (Am J Pathol 1983, 113:134–142)

ALL OF THE MORPHOLOGIC TYPES of endocrine cells in pancreatic islets have now been identified in tumors. Among the orthoendocrine tumors, insulinomas are the most common[1,2]; glucagonomas are much less frequent. A few cases of somatostatin (SRIF)-producing tumors have been reported[3–8]; and like insulinomas and glucagonomas, these cases present a fairly characteristic clinical picture. The most recently recognized islet-cell tumor produces pancreatic polypeptide (PP) and in some cases secretes PP into the blood. Four cases of PPoma have been reported,[9–12] and no clinical findings related to the tumor have been obvious. For this reason, these PPomas have been classified as "nonfunctioning" islet-cell tumors.

In the past 5 years we have encountered 6 patients in whom elevated plasma concentrations of PP have led to detection of pancreatic islet cell tumors containing that peptide; in 3 of these, PP was the predominant peptide present in the tumors. These 3 cases were thoroughly studied with PP radioimmunoassays and immunocytochemical methods. This report describes the findings of these studies.

Materials and Methods

Clinical data on Cases 1 and 2 were presented in more detail earlier[12] and, therefore, are merely summarized here.

Case Summaries

Case 1

C.P. was the oldest of 8 children in a family affected by multiple endocrine adenomatosis (MEA) Type 1. Because of this, he had been followed prospectively since age 26. At age 33, he was found to have markedly elevated fasting and meal-stimulated plasma PP levels (see Table 4). Surgical exploration revealed a large discrete tumor (15 × 13 × 14 cm) in the tail of the pancreas; this tumor was removed by

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distal pancreatectomy. Plasma PP levels gradually decreased following operation but 1 year later were higher than the original preoperative levels. Multiple hepatic metastases were found during laparotomy, and a cannula was placed in the hepatic artery, through which streptozotocin was administered over several months. Plasma PP levels decreased drastically during this time, and the patient had no evidence of tumor recurrence for 3½ years, at which time recurrence of bone metastases led to his death.

Case 2

S.P. was a sibling of Patient 1 who had also been followed systematically for several years without detection of signs of tumor. About 18 months before death, an elevated plasma concentration of PP after a protein meal suggested the development of islet-cell abnormalities. At age 26, she was delivered of a child by cesarean section. Aspiration pneumonia then developed, and she died on the seventh day postpartum. At autopsy, an adenoma (1.5 × 1 × 1 cm) was found in the head of the pancreas in addition to parathyroid hyperplasia involving all four glands.

Case 3

M.T. was a 74-year-old woman also with MEA Type 1, but without a known family history. A subtotal parathyroidectomy had been performed several years prior to admission. On this admission, she underwent hemicolectomy for adenocarcinoma of the descending colon, and biopsy was done on a nodule in the head of the pancreas at that time. After operation, plasma PP levels, both fasting and meal-stimulated, were found to be elevated, and a computerized tomographic (CT) scan 6 months after colectomy confirmed the presence of a small tumor in the head of the pancreas. During the night prior to scheduled operation, the patient died, presumably of a self-administered drug overdose. At autopsy, the head of the pancreas was found to contain an adenoma (1.3 × 1.2 × 1 cm) on the anterior surface. Additional findings were a prolactin-producing adenoma of the pituitary and bilateral adrenocortical hyperplasia.

Tissue Collection

Samples of tumor tissue were collected during operation or at postmortem examination (maximum 5 hours after death). Normal pancreatic tissue was obtained from areas adjacent to the tumor. Samples of pancreatic tissue (approximately 2 g) from subjects with no apparent pancreatic disease were collected at the postmortem examination from the splenic end of the tail and from an area of the head immediately surrounding the common bile duct.[13] Neither of these areas include the uncinate region, where the frequency of PP cells is highest.[14] Immediately after collection, the specimens were either fixed or extracted as described below.

Histology and Immunocytochemistry

Parts of the tumor tissue with attached adjacent normal pancreas were fixed first in Bouin's fluid for 6–8 hours and then fixed in buffered 10% formalin overnight. The tissue was embedded in paraffin, and was cut at 5μ. Deparaffinized sections were processed by an indirect immunocytochemical method[15] for demonstration of pancreatic hormones, using the specific antibodies and procedures described below.

Guinea pig anti-insulin serum was supplied by Dr. P. H. Wright, Indianapolis, Indiana, and was used at a dilution of 1:2000. Rabbit anti-glucagon serum (YY 59) and rabbit antiserum to the COOH-terminal hexapeptide of bovine PP (BPP) was a generous gift from Dr. K. Buchanan, Belfast. The glucagon antiserum was diluted 1:800 for tissue reactions. Rabbit anti-SRIF serum was supplied by Dr. G. Pelletier, of Quebec, and was used at a dilution of 1:500. Rabbit anti-bovine PP and anti-human PP were donated by Dr. R. Chance, Indianapolis, Indiana, and a 1:4000 dilution of anti-bovine PP was applied to tissue sections. All incubations with primary anti-serums were performed for 48 hours, after which second antibody was added and allowed to react for 4–6 hours. Negative controls were prepared by applying antigen-inactivated antiserums. Serial sections were processed for four different hormones with the use of either peroxidase-conjugated swine antirabbit gamma globulin (Accurate Chemical, Westbury, NY), or peroxidase-conjugated goat anti-guinea pig gamma globulin (Cappel Laboratories, Cochransville, Pa).

The frequency of PP cells was estimated by counting specifically stained cells in 20 fields, 15 × 10 cm at ×80 enlargement in head and tail samples of pancreas from tumor cases and in areas immediately adjacent to tumors.

Electron Microscopy and Immunoelectron Microscopy

Small pieces of fresh tissue were fixed immediately with cacodylate-buffered glutaraldehyde, then, for routine transmission electron microscopy, were post-fixed with osmium tetroxide and embedded in Epon 812. For immunoelectron microscopy, the tissue was

embedded in a mixture of Araldite and Epon without postfixation.[16] Thin sections placed on nickel grids were incubated with rabbit anti-bovine PP serum for 30 minutes and then with protein A-gold complex (Pharmacia Fine Chemicals, Uppsala) for 15 minutes.[16,17]

Immunoassays

All tissue utilized for radioimmunoassay was weighed immediately after collection, and peptide hormones were extracted with acid ethanol.[18] Radioimmunoassay for insulin,[19] glucagon,[20] SRIF,[21] and PP[22] was performed on these extracts (diluted 100–26,000 times) using previously reported procedures. The hormone content calculated from mean values of more than two dilutions was expressed as micrograms per gram of wet tissue.

Radioimmunoassay for serum PP was performed essentially as reported previously.[22] Standards (17.75–300 pg/ml) and samples were initially incubated with rabbit anti-human PP serum (1:150,000) for 3 days, then ^{125}I-bovine PP was added and incubated for 1 day. After this, normal rabbit serum (1:100) and goat anti-rabbit serum (1:33, Antibodies Incorporated, Davis, Calif) were added, and the mixtures were incubated for 1 additional day. The standards and the samples were centrifuged at 4C, 1000*g* for 30 minutes. The supernatants were aspirated, and the pellets were counted with a gamma counter. The mean intraassay and interassay errors were 5% and 7%, respectively, at 95% confidence. Seven to 8 healthy volunteers of the same sex, age, and weight were included as controls for each of the 3 patients for comparison of the protein-meal-stimulated PP secretory responses. The protein meal consisted of 35 g of protein, 27 g of fat, and 41 g of carbohydrate.[12]

Gel Chromatography

Acid-ethanol extracts of tumor tissue and adjacent normal pancreas from Case 3 were studied by gel filtration on a 0.9 × 76-cm column of Sephadex G-50SF eluted by upward flow at 5C with 1 M acetic acid. Collected fractions were diluted and assayed for PP with the use of antiserum to intact PP and antiserum to the COOH-terminal hexapeptide of PP.[23] The column was calibrated with bovine serum albumin, bovine insulin, and NaCl.

Results

Characteristics of the Tumors

The tumor from Case 1, a malignant PPoma, exhibited solidly packed cells upon histologic examination. In the tumors from Cases 2 and 3 a trabecular pattern predominated, and these were classified as benign because of the absence of metastases or local invasion.

All three tumors were studied by immunocytochemical methods for the four pancreatic hormones, and these data are summarized in Table 1. PP-containing cells predominated in each tumor, although a few cells containing immunoreactive insulin, glucagon, and SRIF could be found. In general, the majority of the tumor cells positive for PP were stained less intensely than nonneoplastic cells of the adjacent pancreas (Figure 1A and B). In Case 2, PP tumor cells that appeared viable histologically were present primarily at the periphery of the tumor, while in Case 3, PP cells were more uniformly distributed (Figure 2).

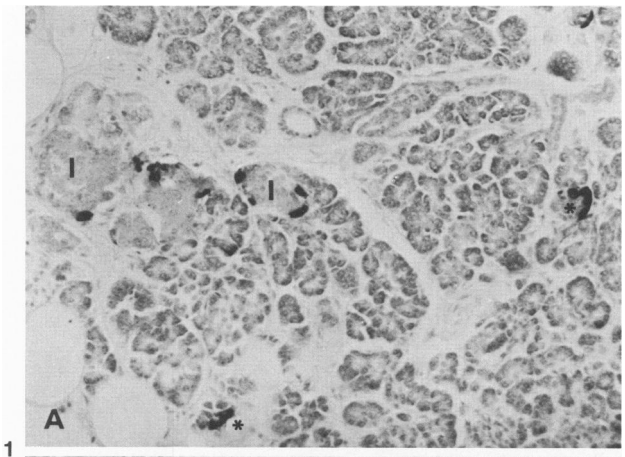
The frequency of PP cells in head and tail samples of normal pancreas and in the adjacent normal pancreas in the tumor cases was estimated, and the results are summarized in Table 2. It should be noted that PP cell frequency in the control tissue appears to be similar in head and tail portions, a finding not necessarily expected,[14] but probably due to the limited sample size taken for sectioning. However, in no case does the PP cell frequency in tissue adjacent to tumor exceed that in control tissue, and on this basis it was concluded that there was no PP cell hyperplasia in normal pancreas surrounding the tumor.

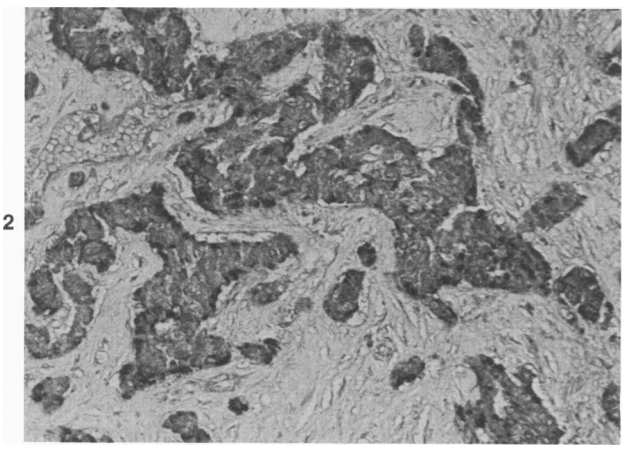
No islet or tumor cells staining specifically for

Table 1—Summary of Immunocytochemical Study

PPoma	Age	Sex	Hormone-containing tumor cells					Histologic diagnosis
			PP	Insulin	Glucagon	SRIF	Gastrin	
1	33	M	+ +*	+	Trace	Trace	–	Malignant PPoma
2	26	F	+ +	+	+	Trace	–	Benign PPoma
3	74	F	+ + +	+ +	+	+	–	Benign PPoma

* Grading system; Trace, fewer stained cells than in adjacent normal tissue; +, number of stained cells approximately equal to those in adjacent normal tissue; + +, most cells positively stained; + + +, practically all cells positively stained.





Figures 1 and 2—Five-micron sections of tissue from the three PP tumors, stained specifically for PP by the immunoperoxidase method. (×80) **Figure 1**—Case 1. **A**—PP cells in the periphery of the normal islets (1) and in exocrine acinar tissue (*). **B**—Tumor cells stained both strongly and weakly for PP. **Figure 2**—Case 3. All of the tumor cells are uniformly positive for PP.

more than one hormone were observed in examination of serial sections.

By electron microscopy, the tumor cells of Case 1 contained variable numbers of round to somewhat elongated secretory granules of moderate electron density, which were tightly encapsulated by a limiting membrane that was separated from the granule by a narrow space (Figure 3). The secretory granules measured 136 ± 21 nm, whereas the morphologically identical PP secretory granules in the adjacent pancreas measured 149 ± 32 nm (Figure 4). Tumor cells from Cases 2 and 3 contained similar secretory granules, although some autolytic changes were evident. The secretory granules in Case 3 tumor cells were positive for PP with protein A-gold complex (Figure 5). A count of gold particles in 0.25-sq cm areas (enlargement = 100,000×, N = 20 fields) yielded a mean of 1.3 ± 0.02 particles in the nucleus, 2.3 ± 0.4 particles in the cytoplasm, and 20.1 ± 0.7 particles in the secretory granules. The difference between secretory granules and other cell areas is significant ($P < 0.001$).

Table 2—PP Cell Frequency in Pancreatic Tissue

Subject	PP cells/150 sq cm*
Control	
Head	7.8 ± 0.8
Tail	6.3 ± 1.2
Case 1†	
Tail	2.7 ± 0.4
Case 2†	
Head	7.2 ± 1.0
Case 3†	
Head	5.2 ± 1.0

* Counted at ×80 enlargement. Data are mean ± SEM.
† Counted in areas adjacent to tumor.

Immunoassayable Hormones in the Tumors

Table 3 gives the results of radioimmunoassay of tumor and pancreatic extracts as well as extracts of normal human pancreas. In the normal cases, the regional distribution of PP and glucagon described by Orci et al[14] is evident.

In two of the tumors the concentration of PP is much higher than in either adjacent normal tissue or control pancreas. The PP concentration in the tumor from Case 2 is probably within the normal range, but it should be noted that a large infarct was present in the tumor itself. There was detectable insulin, glucagon, and SRIF in all three tumors; but, in general, the concentrations were below that observed in the normal pancreas or adjacent tissue. Case 3 is the exception, because the glucagon concentration in the tumor was grossly elevated, even though there did not appear to be a similar increase in the number of A cells (Table 1). We have no explanation for this discrepancy unless it is related to tissue sampling. A larger sample was normally taken for extraction than for histologic studies.

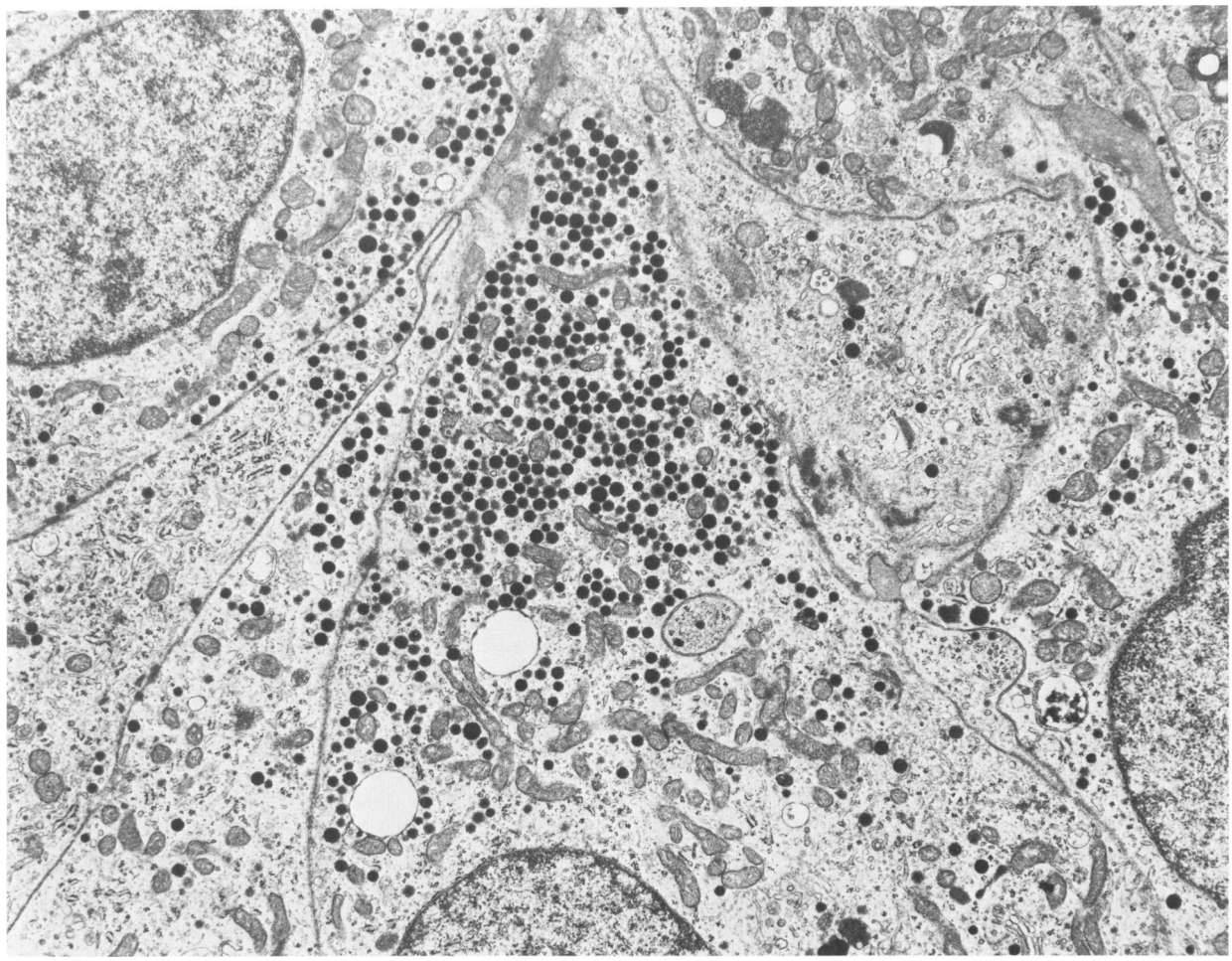


Figure 3—Case 1. Secretory granules in tumor cells. Electron density is moderate, and the granules measure 136 ± 21 nm. (×10,000) (With a photographic reduction of 11%)

Gel Chromatography

Figure 6 shows the elution pattern obtained during gel chromatography of extracts of normal and tumor tissue when fractions were assayed for the four pancreatic hormones. In general, the position of emergence of each hormone is at a volume expected from calibration data on the basis of monomeric molecular weight. There is a suggestion of PP immunoreactivity emerging earlier than PP (Figure 6B), which may correspond to PP precursor.[24,25]

The area under the various peaks is indicative of the amount of each peptide present in the extracts, and the relative abundance of PP in the tumor as compared with normal pancreas is evident. The somatostatin immunoreactivity in the tumor extract is also of interest because of the higher concentration and the presence of higher molecular weight activity, perhaps SRIF-28.[26]

The results obtained when fractions from the gel chromatogram were assayed with antibodies directed toward different parts of the PP molecule are shown in Figure 7. The patterns obtained with the two antibodies are practically superimposable, thus indicating that the PP has a normal conformation and a structurally intact COOH-terminal region, the region generally implicated in biologic activity.[27,28]

Plasma PP Concentrations

In all 3 patients it was possible to study fasting as well as meal-stimulated PP levels in blood plasma.

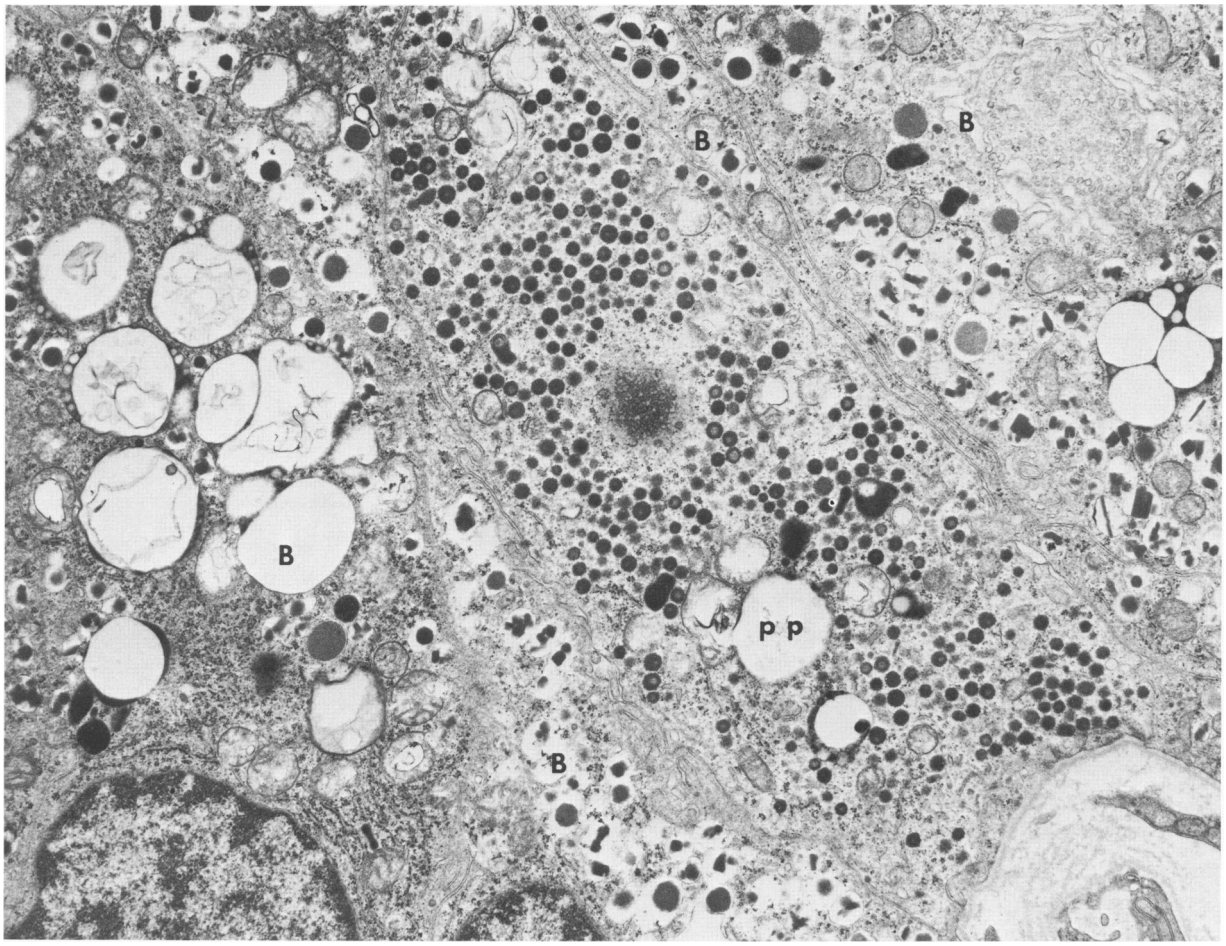


Figure 4—Case 1. One normal PP cell (*PP*) with numerous small granules is surrounded by beta cells (*B*). (×10,000)

The findings are given in Table 4 along with data from normal subjects of comparable age.

Case 1 exhibited grossly abnormal plasma PP concentrations, and this level increased 2–4-fold following a meal. Removal of the tumor had a marked effect on plasma PP, but there was a dramatic increase again when metastases appeared. Intraarterial streptozotocin treatment was effective, and plasma PP levels were still at upper limits of normal 18 months after cessation of treatment.

Cases 2 and 3, also MEA Type 1, showed less dramatic elevations of plasma PP, but Case 2 demonstrated an abnormal response to a meal indicative of the genetic MEA trait and the possible development of PP-cell hyperplasia or PPoma. Case 3 demonstrated abnormalities after the serendipitous discovery of the tumor.

It is noteworthy that no symptoms or physical findings could be attributed to elevated plasma PP concentration in any of the patients.

Discussion

Since the data presented in this study depend heavily upon immunologic reactions, it is important that some information on the specificity of the various antiserums used be presented. The rabbit anti-insulin serum is one widely used for plasma insulin immunoassay in clinical studies. It reacts poorly with proinsulin. The specificity of the anti-glucagon serum and the anti-SRIF has not been documented. Anti-BPP and antiserum to COOH-terminal BPP hexapeptide have been characterized and are highly specific.[29,23] The gel filtration data in Figures 6 and 7 also provide characterization of the substances which are being es-

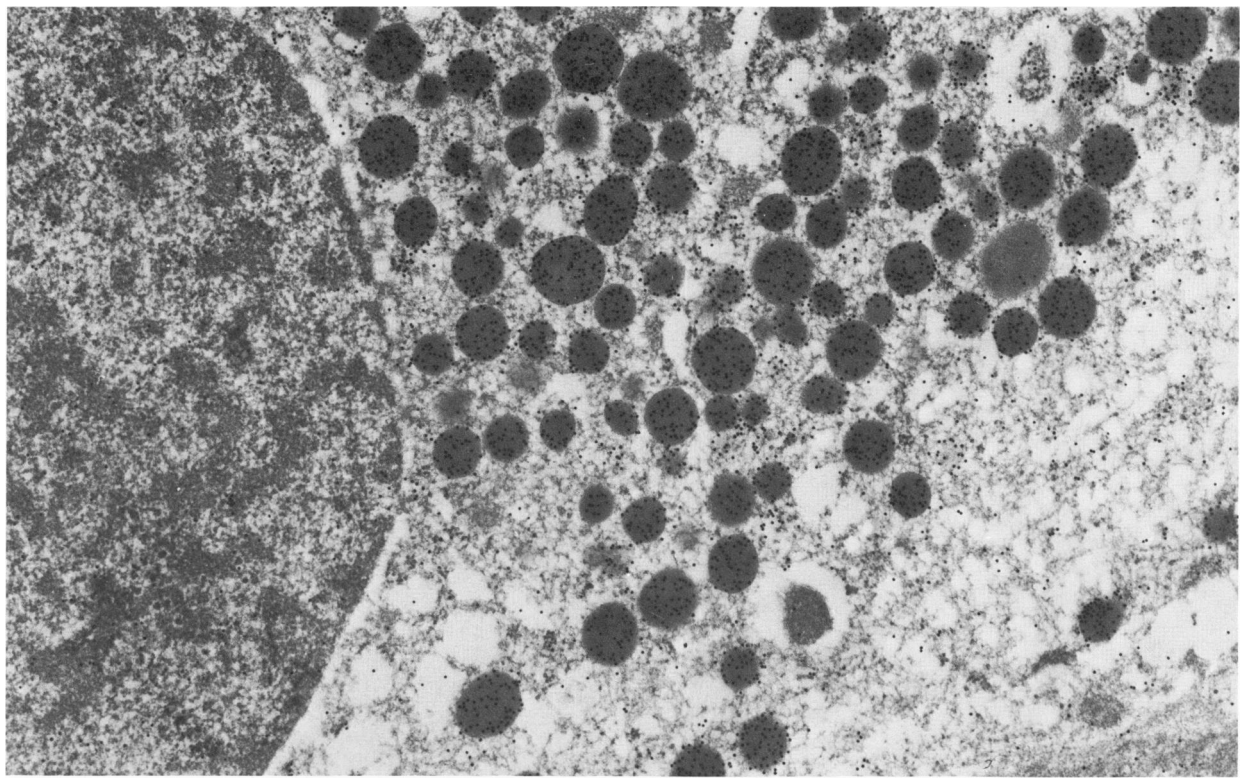


Figure 5—Case 3. Immunoelectron-microscopic study for PP granules. Secretory granules of the tumor cells are positively stained with the protein A-gold complex technique. (×100,000) (With a photographic reduction of 10%)

timated in the extracts as well as specificity data for the antiserums.

The tumor cells in the three cases presented have secretory granules characteristic of PP cells and very similar in dimensions of those described by Bordi et al[9] for PPomas. Although these granules are unique, it should be noted that they may not be differentiated on the basis of morphology alone from those seen in non-B-cell tumors such as gastrinomas and vipomas.[1,2,9] The positive identification of the tumors as PPomas in the cases reported here is based upon immunocytochemical findings and the PP content of the tumor extracts. In all 3 tumors, PP cells predominate; but a few A, B, and D cells are identifiable. This has been the experience of others.[26,30]

The tumor in Case 1 of our group was clearly malignant on the basis of clinical development of metastases and the solid histologic pattern. Cases 2 and 3 would be classified as benign because of the absence of metastases and the trabecular histologic pattern,

Table 3—Hormone Concentration of Tumors and Pancreases (μg/g Wet Tissue)

PPomas	Location in pancreas	Size (cm)	PP	Insulin	Glucagon	SRIF
1. Tumor	Tail	15 × 13 × 14	31.22	3.65	0.73	3.06
(biopsy 1 year after initial surgery)	Tail		2.67	21.91	0.05	1.19
2. Tumor	Head	1.5 × 1 × 1	6.07	3.22	1.89	0.24
	Head		0.62	29.82	9.06	0.69
3. Tumor	Head	1.3 × 1.2 × 1	196.52	32.76	15.36	2.94
	Head		1.42	67.17	5.46	1.99
	Tail		1.26	139.01	8.61	1.20
Controls (n = 8) (Age 35.1 ± 10.2 [17-68])*	Head		3.33 ± 3.44	90.04 ± 50.33	4.48 ± 2.96	2.05 ± 1.66
	Tail		0.86 ± 0.84	103.02 ± 73.82	7.28 ± 6.82	2.28 ± 2.14

* Values are mean ± SEM.

Table 4—Protein Meal-Stimulated PP Secretion (pmol/l)

	0	30 minutes	60 minutes	90 minutes	180 minutes
Case 1: M, 33 at the time of surgery					
1 month before distal pancreatectomy	693.7	1521.3	1642.9	–	1592.5
1 day before surgery	798.2	1451.4	1219.0	–	–
2 months after surgery	144.6	577.3	574.8	714.4	–
12 months after surgical demonstration of liver metastasis	1583.7	3349.3	3644.1	–	3309.2
2 months after streptozotocin treatment	166.4	261.3	261.37	266.7	299.4
18 months after streptozotocin	57.8	125.4	100.9	114.3	98.2
Controls (n = 8) (Age 34.3 ± 1.6 [30–39])*	13.8 ± 5.1	67.6 ± 29.6	58.4 ± 25.6	61.5 ± 32.4	76.4 ± 44.0
Case 2: F, 26 at the time of death					
18 months before death	16.0	103.9	54.6	–	144.2
Controls (n = 7) (Age 27.2 ± 1.5 [22–31])	12.1 ± 5.0	40.9 ± 21.3	44.0 ± 20.6	44.4 ± 27.4	42.5 ± 16.6
Case 3: F, 74 at the time of death					
4 months before death	46.7	102.8	137.0	173.9	170.7
3 days before death	120.2	160.2	164.6	292.4	172.7
Controls (n = 8) (Age 58.4 ± 2.3 [50–70])	30.9 ± 13.2	102.4 ± 42.8	102.3 ± 44.8	112.8 ± 61.1	108.1 ± 42.3

* Values are mean ± SD.

although a minor solid component was present. Of the 4 reported cases of PPoma[9,10,11,12] 1 was benign and 3 were malignant.

Practically all islet tumors, when carefully studied, contain more than one pancreatic hormone[28]; but hypersecretion of one hormone is usually responsible for the clinical manifestations. In the case of PPomas, it has not been possible to associate hypersecretion with any clinical picture[12]; and such is the situation in the tumors reported here, especially in Case 1, where marked hypersecretion of PP was clearly present. If the PP in this patient was inactive

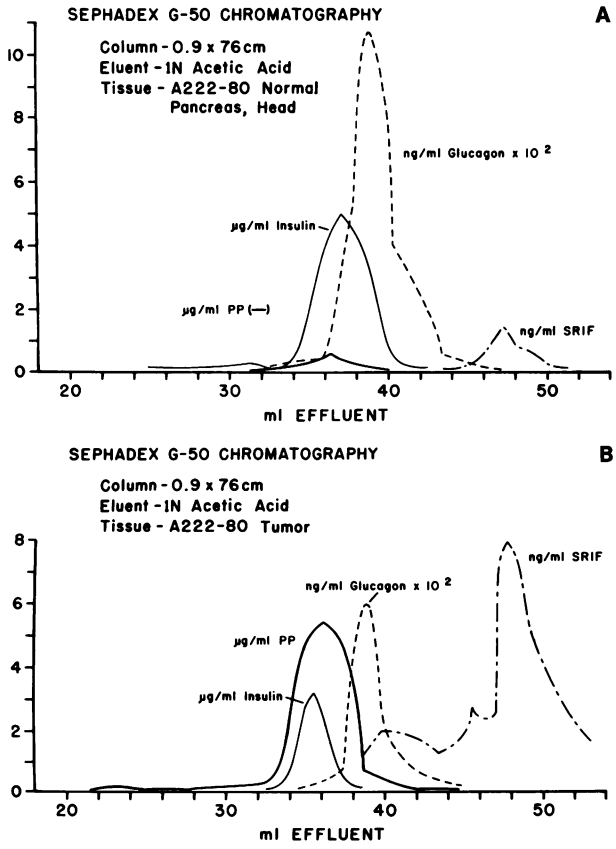


Figure 6A—Gel filtration of 1 ml of an extract of pancreatic tissue adjacent to the tumor in Case 3. The procedure was as described in the text. Appropriate dilutions of effluent fractions were assayed for insulin, glucagon, PP, and SRIF. **B**—Gel filtration of 1 ml of tumor extract from Case 3.

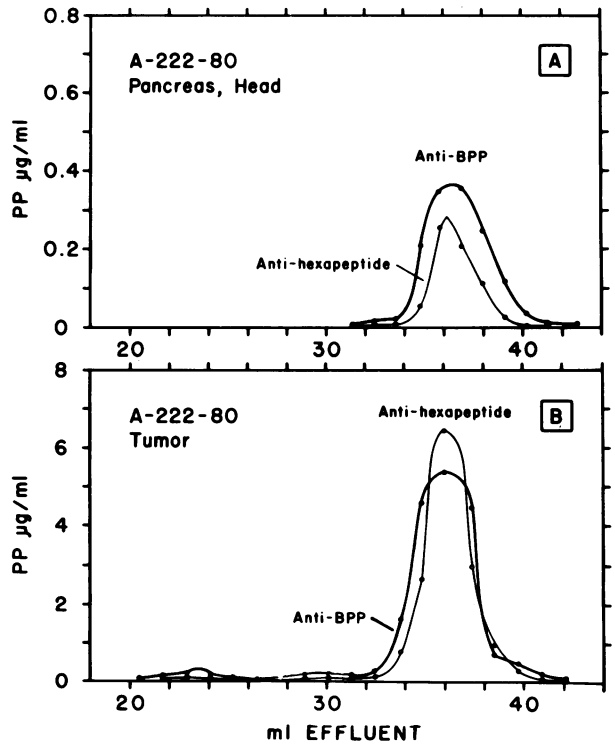


Figure 7—Gel filtration of extracts from Case 3 assayed with anti-BPP and antiserum to the COOH-terminal hexapeptide of BPP. **A**—Pancreatic tissue. **B**—Tumor tissue.

due to some structural abnormality, one might expect no clinical manifestations, but the gel filtration patterns in Figures 6 and 7 suggest that the pancreatic and tumor PP are of the correct molecular dimensions. Furthermore, the equal reaction with antibodies directed toward different parts of the PP molecule provides additional evidence that the tumor PP is intact. Such statements cannot be made about circulating PP, because gel filtration studies were not performed with plasma.

It has not been possible to decide whether PP cells in the tumors are functionally intact, because PP cell hyperplasia in the adjacent pancreas has often been suggested.[4] In the cases described here, the protein-meal-stimulated PP secretory response was roughly proportional to the size of the tumor; therefore, tumor cells may be capable of responding to a protein-meal stimulus. This is further supported by the lack of PP-cell hyperplasia in adjacent tissue.

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