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Duodenal and ampullary carcinoid tumors

A report of 12 cases with pathological characteristics, polypeptide content and relation to the MEN I syndrome and von Recklinghausen's disease (neurofibromatosis)

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Summary. Twelve duodenal carcinoid tumours are presented, 4 of them located in the ampulla. Symptoms included the Zollinger-Ellison syndrome (4 patients), the carcinoid syndrome (1 patient), mechanical obstruction (3 patients), bleeding (1 patient) and abdominal pain (1 patient). Two further tumours were detected by chance.

Three patients with the Zollinger-Ellison syndrome had additional endocrine tumours characteristic of the MEN I syndrome. In 2 of them the duodenal carcinoids were of very small size and were multiple. They were observed in close proximity to focal areas of endocrine cell hyperplasia.

Immunohistochemical investigations showed gastrin and somatostatin to be the predominant polypeptide hormones produced by these tumours. No somatostatinoma syndrome was encountered. In half of our cases additional production of insulin, VIP or even calcitonin in smaller amounts was found.

Two of our patients had cutaneous manifestations of von Recklinghausen's disease and in both of them the carcinoid was located in the ampulla. One of these patients also had a pheochromocytoma.

Key words: Duodenal neoplasms – Carcinoid tumor – Neurofibromatosis – MEN I

Introduction

The duodenal mucosa harbors a large number and great variety of cells of the diffuse endocrine system. Using the terminology recommended by the World Health Organisation (Williams et al. 1980) tumours are called carcinoids when they originate from these cells or their precursors.

Even if only representing 1–5% of all carcinoids of the intestinal tract (Hedinger 1973; Godwin 1975) carcinoids of the duodenum are a very inter-

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esting and variable group of endocrine tumours, especially with regard to their polypeptide production which may produce typical clinical syndromes. This sometimes allows a subclassification according to the type of hormone responsible e.g. gastrinoma (or G-cell tumour) for a gastrin secreting carcinoid accompanied by the Zollinger-Ellison syndrome. The use of this nomenclature is, however, limited by the fact that many of the tumours apparently produce one or several immunohistochemically recognizable polypeptides with no clinical manifestations.

The aim of this paper is to review our experience with 12 duodenal and ampullary carcinoids with special regard to their polypeptide content, their relation to the multiple endocrine neoplasia type I (MEN I) syndrome and to von Recklinghausen's disease.

Patients and methods

Eight operative specimens, 1 biopsy and 3 autopsies from patients with duodenal carcinoid tumours have been examined at the Institute of Pathology of the University Hospital of Zürich between 1975 and 1984.

After fixation in formalin or Bouin's solution the specimens were embedded in paraffin and sections stained with haematoxylin and eosin, van Gieson's stain and a combined alcian blue and PAS stain. We used one argentaffin technique (Masson-Hamperl) and two argyrophil techniques (Grimelius, modified after Churukian and Schenk 1979; and Grimelius, only for specimens fixed in Bouin's solution). Immunohistochemical investigations were performed with the immunoperoxydase (PAP) technique. The antisera for insulin, glucagon, somatostatin and neuron specific enolase were purchased from DAKO (DAKO-Kit, Denmark) and for the demonstration of gastrin, vasoactive intestinal polypeptide (VIP) and calcitonin, a histoset from Ortho (Ortho-Histoset, Germany) was used. The demonstration of ACTH was attempted with an antiserum from DAKO (Denmark) with a dilution of 1:200. Positive and negative controls were routinely added to every set of slides.

For electron microscopy some small tissue fragments were fixed in phosphate buffered glutaraldehyde (2%, 0.1 M) overnight, postfixed in s-collidine buffered osmium tetroxide (1%, 0.1 M) for 2 h and embedded in Epon after dehydration through a graded series of ethanols. Ultrathin sections were contrasted with uranyl acetate and lead citrate and examined with a Philips 201 EM.

Results

Table 1 summarizes the main clinical manifestations and shows localization and size of the primary tumour and if metastases could be demonstrated.

Eight patients were men and 4 were women with an age range between 32 and 91 years at the time of diagnosis. The tumours were located exclusively in the first and second part of the duodenum or within the papilla of Vater. Only 1 of the 12 tumours was larger than 1.5 cm (3 cm in patient 2). Three were ulcerated (patients 4, 5 and 12).

The symptoms of patient 2 with a polypoid carcinoid tumour of 3 cm diameter were probably due to mechanical ileus. Acute pancreatitis and jaundice from obstruction of the ampulla led to the diagnosis in patient 1 and 3.

Four patients (patients 6–9) had gastric hyperacidity due to elevated levels of serum gastrin, a typical sign of the Zollinger-Ellison syndrome.

Table 1. Summary of cases

Patient Nr.	sex/ age	Clinical manifestations, surgical proceedings, follow up	Localisation	Size (cm)	Ulcerated	Metastases
1	F/38	Recurrent acute pancreatitis. Transduodenal papillotomy and local excision of tumour. Well after 3 years.	Papilla	1	no	
2	M/56	Cramping abdominal pain for 18 months. Hyperlipidaemia. Billroth II. Well after 5 years.	Duodenal bulb	3	no	
3	F/56	Jaundice. Duodenopancreatectomy. No follow up.	Papilla	0.8	no	Lymph node
4	M/75	Adenocarcinoma of the ampulla. Gallstones. Hyperlipidaemia. Incidental finding of carcinoid tumour in the duodenopancreatectomy specimen. No follow up.	Duodenal bulb	1.2	yes	
5	F/91	Gastrointestinal haemorrhage 1 year prior to death. Gallstones. Diabetes mellitus. Chronic duodenal ulcer. Tumour found at autopsy.	Pars II	1.5	yes	
6	M/59	Zollinger-Ellison syndrome. Polypoid carcinoid tumour removed through the endoscope. Well after 2 years.	duodenal bulb	1	no	
7	M/41	Zollinger-Ellison syndrome. Hyperparathyroidism. Duodenopancreatectomy. Several endocrine pancreatic tumours and seven duodenal carcinoid tumours. Peripancreatic lymph node metastases. No follow up.	Multiple	0.6 0.3 less than 0.1	no	Uncertain if of duodenal or pancreatic origin.
8	M/34	Zollinger-Ellison syndrome. Hyperparathyroidism. Duodenopancreatectomy. Several endocrine pancreatic tumours without gastrin. Microscopical finding of several carcinoid tumours of size less than 0.1 cm in the duodenal submucosa producing gastrin. Periduodenal lymph node metastasis with gastrin. Well after 1 year.	Multiple	less than 0.1	no	Lymph node
9	M/44	Zollinger-Ellison syndrome. Hyperparathyroidism. Pituitary Cushing's syndrome. Glucagon and insulin producing endocrine tumour of pancreatic tail. Cortical nodular hyperplasia of left adrenal; suspected tumour of right adrenal. Gallstones. Endoscopical biopsy of duodenal carcinoid tumor. Alive with chronic duodenal ulcer 3 years later.	Pars II	1	no	
10	M/55	Abdominal pain for 15 years without morphological diagnosis. Finally radiological diagnosis of tiny polypoid duodenal tumour. Transduodenal polypectomy. Died 17 years later with carcinoid syndrome. No other primary tumour at autopsy.	Duodenal bulb	1	no	Liver, peritoneum and lymph nodes at autopsy
11[a]	M/36	Cutaneous neurofibromatosis. Recurrent duodenal ulcers. Vagotomy. Sudden cardiac arrest 4 days later. Autopsy revealed carcinoid tumour and pheochromocytoma in left adrenal.	Papilla	1	?	
12[b]	F/32	Familiar cutaneous neurofibromatosis. Cramping abdominal pain and vomiting. Gallstones. Duodenopancreatectomy. Well after 18 months.	Papilla	1.5	yes	Lymph node

[a] previously published by Zollinger R, Hedinger Chr. (1983) Schweiz Med Wochenschr 113:1086–1092

[b] previously published by Weder W et al. (1983) Schweiz Med Wochenschr 113:885–892

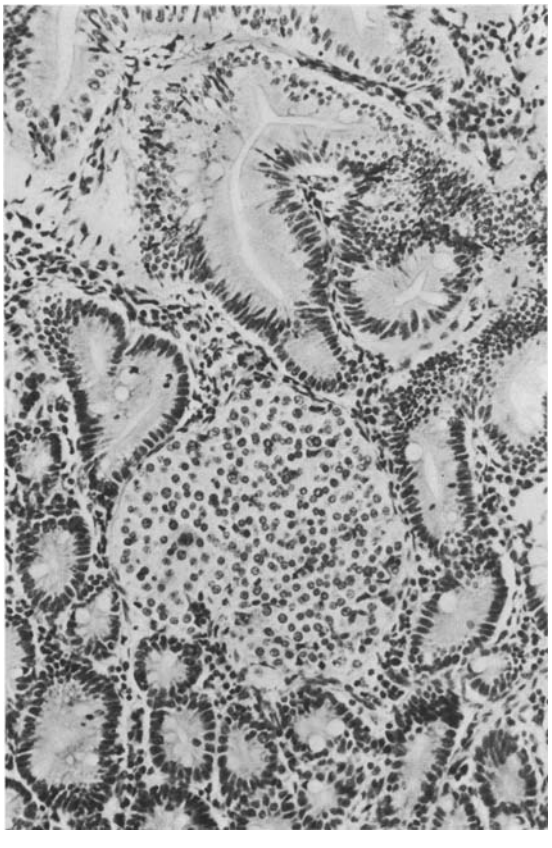


Fig. 1. Microscopic carcinoid tumour in the duodenal mucosa of patient 7. H and E (160×)

Three of them (patients 7–9) has additional endocrine neoplasms and signs characteristic of the MEN 1 syndrome. Among these MEN I syndrome patients two (patient 7 and 8) had multiple small carcinoid tumours in the duodenum (Fig. 1). In patient 7 two of the tumours were grossly visible whereas in patient 8 only multiple microscopic sections led to the diagnosis. Despite their small size they had already metastasised to regional lymph nodes. The silver staining technique showed yet another interesting fact in this patient: some of the microscopic tumours were found in the immediate vicinity of areas of endocrine cell hyperplasia (Fig. 2).

One patient (patient 10) died 17 years after the local excision of a carcinoid tumour measuring only 1 cm in diameter. At the time of his death he suffered from a fully developed carcinoid syndrome. The autopsy revealed metastases in liver, peritoneum and peripancreatic lymph nodes without evidence of another primary tumour. The heart showed typical fibrous plaques superimposed upon the right and left atrial endocardium and upon the tricuspid and pulmonary valves (Isler and Hedinger 1953; Hedinger 1973).

Two of our patients had cutaneous manifestations of von Recklinghau-

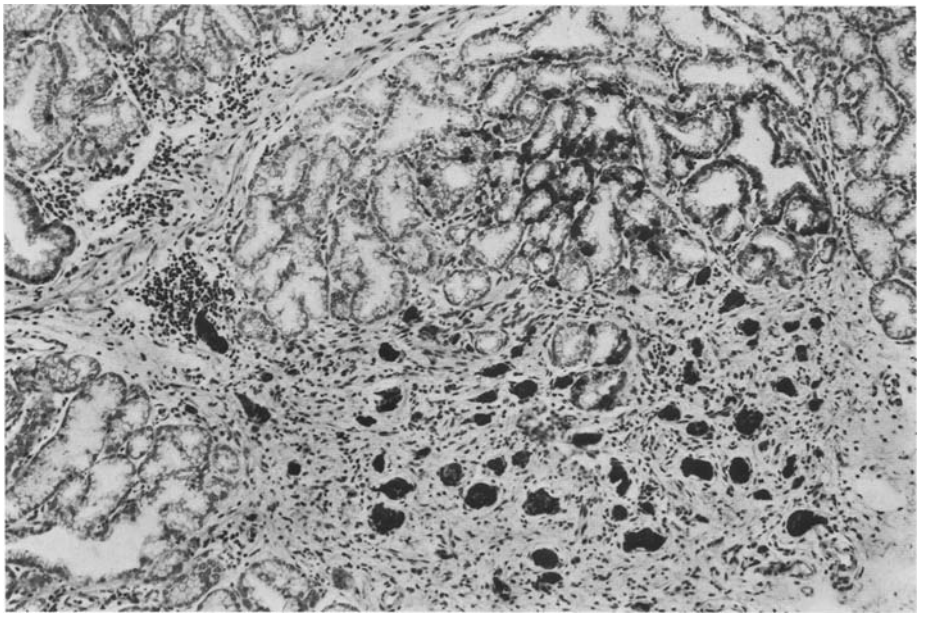


Fig. 2. Area of endocrine cell hyperplasia closely associated with a microscopic carcinoid tumour (patient 8). Masson Hamperl argentaffin technique (80 ×)

sen's disease (patients 11 and 12). Patient 11, a 36 year old man, suffered 16 years of recurrent duodenal ulcers (the carcinoid tumour was negative for gastrin and gastrin had not been searched for in the serum) and underwent vagotomy. Postoperatively he suffered from several episodes of arterial hypertension and died of sudden cardiac arrest. He was not known to have had arterial hypertension prior to this operation. At autopsy an unilateral pheochromocytoma measuring 7 cm in diameter was found in addition to the ampullary carcinoid tumour. Patient 12, a 32 year old woman, indicated that her mother, brother and sister had also café-au-lait spots. The tumour within the papilla of Vater was discovered after several episodes of abdominal cramps and vomiting and a Whipple procedure was performed following a diagnosis of well differentiated adenocarcinoma. The operative specimen revealed metastatic spread to a lymph node of the gastroduodenal ligament.

The tumour was incidentally discovered at autopsy in patient 5 and in a duodenopancreatectomy specimen for adenocarcinoma in patient 4.

Macroscopic examination showed that the bulk of the tumours were usually located in the submucosa. This is an astonishing fact considering that these neoplasms are believed to arise from mucosal endocrine cells. The majority had an infiltrative growth pattern especially when the tumour was extending into the muscle coat and microscopically clear cut borders were exceptional. The histological architecture was variable and none of the known patterns were found to be characteristic. As shown in Fig. 3a–e we saw tumour groth in nests, ribbons, anastomosing trabeculae or tubular

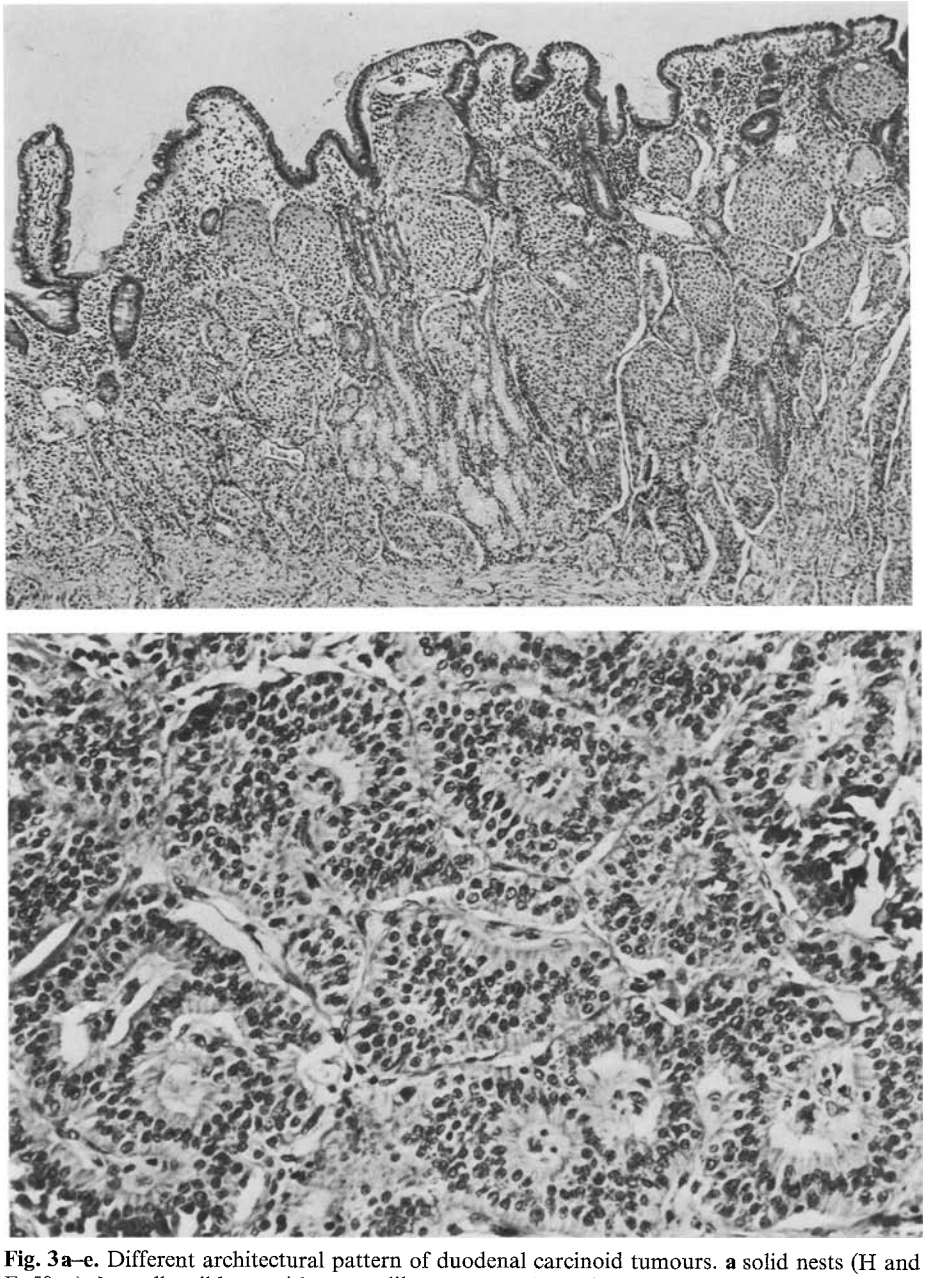
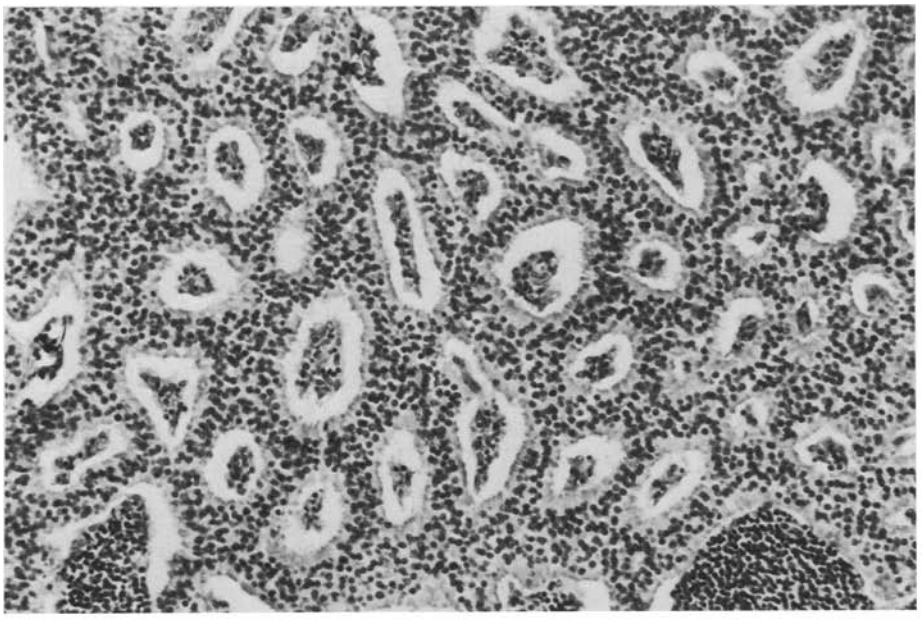


Fig. 3a–e. Different architectural pattern of duodenal carcinoid tumours. **a** solid nests (H and E, 50×); **b** smaller ribbons with rosette like structures (H and E, 200×); **c** broad anastomosing trabeculae (H and E, 125×); **d** smaller anastomosing trabeculae with conspicuous polarisation of nuclei (H and E, 225×); **e** tubular structures infiltrating smooth muscle of papilla (same patient as **a**) (H and E, 250×)



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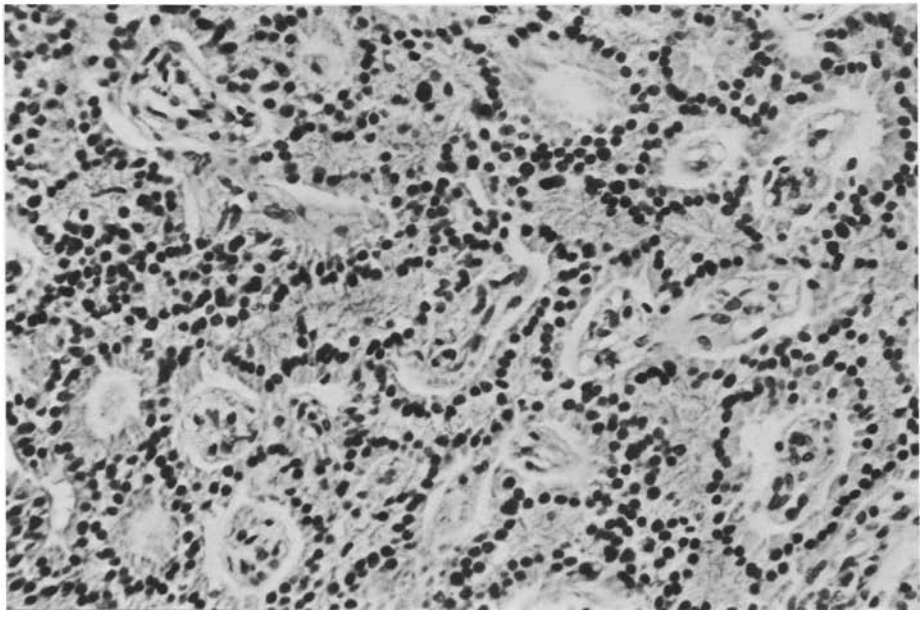


d

structures in descending order of frequency and usually two or more patterns were present within the same tumour. Basaloid or small cell variants, spindle cells or pleomorphic aspects were not encountered.

The tumour cells are usually polygonal with finely granulated, eosinophilic, occasionally vacuolised cytoplasm and sometimes conspicuous polar-

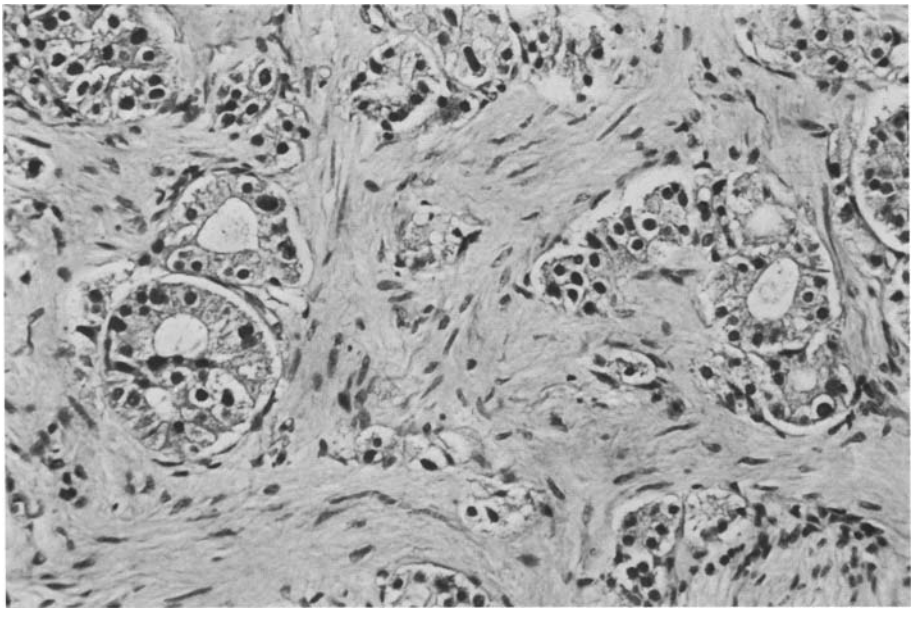


Fig. 3e

isation of nuclei. In most tumours the fibrous stroma is delicate and richly vascularised. Hyalinisation was not observed.

The 3 tumours with proven metastases at the time of operation did not show any distinctive macroscopic or microscopic features.

Table 2 summarizes the results of immunohistochemistry and argentaffine and argyrophil techniques. Somatostatin and gastrin were the 2 polypeptide hormones encountered most frequently and in highest concentrations. The latter was found in patients with and without the Zollinger-Ellison syndrome. Preoperative somatostatin levels in the serum are known only for patient 3 who had normal basic values rising after stimulation with the calcium-pentagastrin test (Somers et al. 1983). Additional single tumour cells producing insulin, VIP or calcitonin were frequently present. Thus many of the tumours proved to be capable not only of producing several different hormones but also hormones that are not normally present in the duodenal mucosa.

Neuron specific enolase was positive in all 12 tumours.

Electron microscopy performed in patients 3, 6, 7 and 12 revealed membrane bound secretory granules in all four cases, similar in size and shape to those of normal G- and D-cells (Fig. 4a–b).

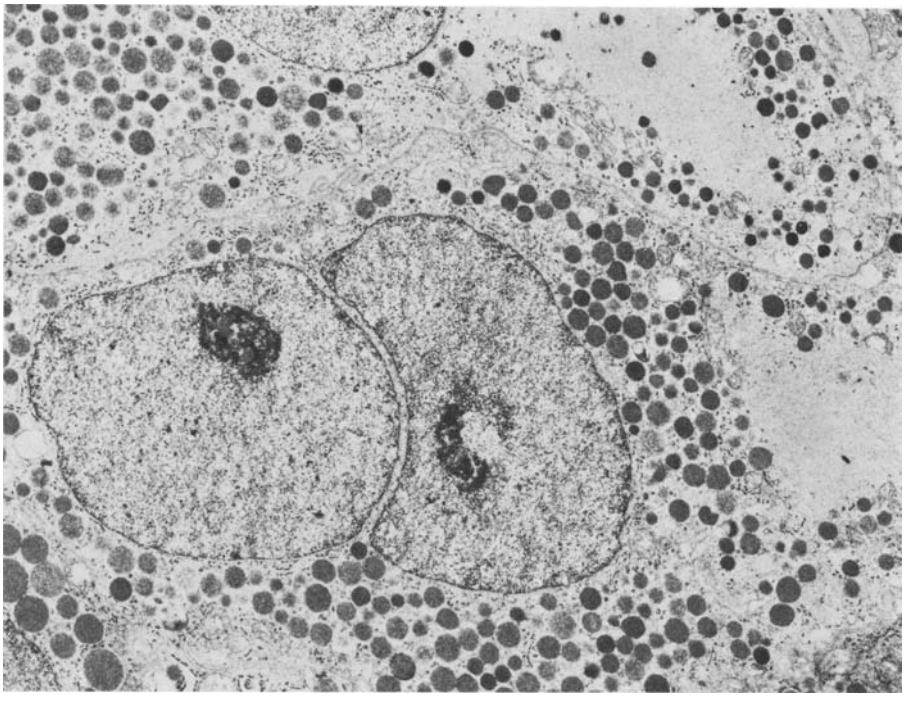
Discussion

We report on 12 patients with duodenal and ampullary carcinoid tumors. Our results parallel the observations of several previous authors (Warren et al. 1964; Weichert et al. 1967 and 1971; Wilander et al. 1979; Williams

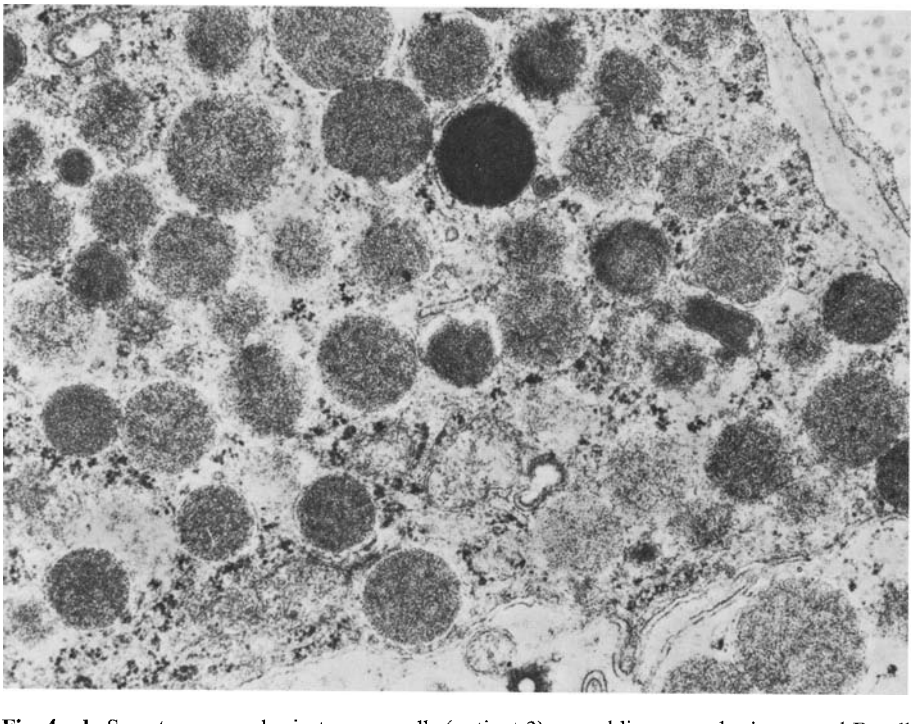
Table 2. Immunohistochemistry and silver staining techniques

Patient	1	2	3	4	5 Autopsy	6	7	8 Micro-scopic-tumours	9 Only biopsy	10 From liver meta-stasis. Autopsy	11 Autopsy	12
Insulin	–	++	–	+	–	–	–	–	–	+	–	–
Glucagon	–	–	–	–	–	–	–	–	–	–	–	–
Somatostatin	++++	–	++++	+	+++	–	++	+	+++	–	+++	++++
Gastrin	–	+++	–	+++	++	+++	++++	+++	++	–	–	–
VIP	–	–	+	–	–	–	+	–	–	–	–	+
Calcitonin	+	–	–	–	–	–	–	–	–	–	–	++
ACTH	–	–	–	–	–	–	–	–	–	–	–	–
Neuron specific enolase	+	++++	+++	++++	+	++++	++++	+	+++	+++	+	+++
Masson-Hamperl	–	–	–	+	–	–	+	+++	–	++	–	–
Grimelius	–	+++	np	np	np	np	np	np	++	–	np	–
Churukian and Schenk	–	+	+	++++	–	+	++++	–	+++	+++	++	–

\+ positive only in rare single tumour cells
++ positive in frequent single tumour cells
+++ positive in groups of tumour cells
++++ positive in the majority of tumour cells
np not performed



a



b

Fig. 4a, b. Secretory granules in tumour cells (patient 3) resembling granules in normal D-cells (EM **a** 8810 × /**b** 28080 ×)

et al. 1980; Klöppel and Heitz 1981; Alumets et al. 1983; Lasson et al. 1983; Besson et al. 1984; Clements and Roche 1984). There seems to be no predilection for sex or age in these tumours. They are usually of small size (below 2 cm diameter) and are located predominantly in the first and second portion of the duodenum including the papilla of Vater, thus arising in the part of the duodenum deriving from the embryonic foregut. They may be multiple (Weichert et al. 1971; Friesen et al. 1974) and they present usually a mixed histological pattern.

In roughly one fourth of these duodenal carcinoids lymph node metastases are demonstrated at the time of diagnosis as happened in 3 of our 12 patients (Weichert et al. 1971; Lasson et al. 1983; Klöppel and Heitz 1981). Malignant behaviour could not be predicted from the histology of the respective carcinoids. None of our 3 examples with lymph node metastases was larger than 1.5 cm and the same was true for the 5 cases reported by Weichert et al. in 1971. He found that 3 of his 5 metastasizing carcinoids were ulcerated and this was the case in only 2 of his other 16 cases. In 3 of our 12 patients the primary tumour was ulcerated and only in one of them were lymph node metastasis demonstrated. If there is a correlation between the kind of hormone or hormones produced and the degree of malignancy, it cannot be derived from our results.

The diagnosis of a carcinoid tumor will therefore not help the surgeon in his choice of the appropriate extent of resection except for the fact that these tumours almost always show very slow progression even if metastases are present (see our patient 10 who died 17 years after the excision of the primary tumor). Clements and Roche (1984) reported a patient who survived more than 30 years with proven hepatic metastases.

Clinically the tumours are manifest either as incidental findings or by mechanical obstruction (more prone to occur in the ampulla than in the duodenal lumen because of the usual small size of these tumors), by bleeding or by the effects of their secretory products. Not all of the clinical manifestations reported in our patients are satisfactorily explained by one of these mechanisms however (long standing abdominal pain in patient 10, duodenal ulcers without proven gastrin production by the tumour in patient 11, abdominal cramps and vomiting in patient 12 and also hyperlipidaemia in patients 2 and 4) and may in part correspond to as yet unknown functional properties of polypeptide hormones.

From our immunohistochemical investigations it appears that these tumours frequently produce more than one polypeptide hormone, but predominantly manufacture somatostatin and gastrin. Similar results have been obtained by previous investigators (Alumets et al. 1983; Lasson et al. 1983, Wilander et al. 1979). The capability to produce more than one of these substances and even hormones not normally present in the duodenum is not a specific property of duodenal carcinoids but seems to be a common finding in carcinoids of foregut and hindgut derivatives and in endocrine tumors of the pancreas (Alumets et al. 1983; Heitz et al. 1982; Dayal et al. 1980). This reveals interesting relationships between hormone producing cells of different organs and shows at the same time the limitations of a nomenclature based on hormone production.

In contrast to the astonishing range of hormones produced, the clinical expression of hormone overproduction by these duodenal carcinoids is limited to the Zollinger-Ellison syndrome with few exceptions. This syndrome was present in 4 of our 12 patients. Three additional patients with gastrin producing tumours had no signs of the syndrome and gastrin had not therefore been searched for in the serum preoperatively. Thus these patients may produce gastrin without secreting it in sufficient amounts or they produce a chemically related substance recognized by our techniques as gastrin but not capable of giving the same biological effects. Duodenal tumours as a cause of a Zollinger-Ellison syndrome are not exceptional. Thirteen percent of 800 patients with this syndrome reported by Hofmann et al. in 1973 had the tumour located in the duodenum, either alone or combined with pancreatic tumours.

Of our 4 patients with the Zollinger-Ellison syndrome 3 had associated endocrine neoplasms and characteristic signs of the MEN I syndrome. Similarly out of 21 carcinoid-islet cell tumours of the dudenum reported by Weichert et al. in 1971, eight were accompanied by the Zollinger-Ellison syndrome and 4 of these 8 patients had or were suspected to have a MEN I syndrome. Two of our patients with the MEN I syndrome had multiple small carcinoids in the duodenum, an observation also reported by Friesen et al. 1974 and by Woodtli et al. 1982. As well demonstrated by our patient 8, these tumours may be so small that only multiple microscopic sections will permit their diagnosis. The close vicinity of some of these microscopic tumours to focal areas of endocrine cell hyperplasia is interesting and suggests that they may be forerunners of carcinoids.

We conclude that in a patient with the Zollinger-Ellison syndrome the possibility of a duodenal carcinoid detectable by endoscopy must be considered and that these tumours may be small and multiple. Whether small size and multiplicity are especially prone to occur in patients with the MEN I syndrome remains to be clarified.

Other clinical syndromes related to polypetide hormone overproduction were not encountered in this series of 12 patients. One patient had a carcinoid syndrome. This seems to be a rare manifestation of duodenal carcinoids as can generally be said for all carcinoid tumors of foregut derivatives.

The most frequently demonstrated polypeptide hormone in the present series of duodenal tumours was somatostatin, a substance normally occurring in the duodenal mucosa. It was present in varying amounts in 9 of the 12 tumours examined. In none of these patients was the somatostatinoma syndrome (Krejs et al. 1979; Pipeleers et al. 1983), including diabetes mellitus, gallstones and maldigestion with dyspepsia and diarrhoea present in a complete form to be helpful in diagnosis. Using the designation somatostatinoma may be somewhat confusing because we are accustomed to relate the designation of gastrinoma to an accompaning clinical state. We know of 7 other somatostatin producing duodenal carcinoids reported in the literature and in none of them has a complete somatostatinoma syndrome been present (Kaneko et al. 1979; Dayal et al. 1983; Marcial et al.

1983; Somers et a. 1983; Jensen et al. 1984). This might be due to the fact that only small amounts of hormone are secreted or to inactivation in the liver. Somers et al. 1983 described a patient who had elevated serum levels of somatostatin only after the appearance of liver metastases. Dayal et al. called in 1983 attention to a peculiar histological type of 3 duodenal somatostatinomas with predominantly tubular structures and numerous psammoma bodies within the tubular lumina. The same observation was also reported by Marcial et al. in 1983 and Griffiths et al. 1984. Kaneko et al. 1979 also observed a tubular architecture in their case reported in 1979. We saw tubular structures but no psammoma bodies as part of the overall mixed histological pattern in patients 1, 3, and 12, which means in the 3 patients with the highest somatostatin content.

The very interesting association of von Recklinghausen's disease and carcinoid tumors of the duodenum has been repeatedly reported in the literature (Lee and Garber 1970; Weichert et al. 1971; Barber 1976; Ross and Dent 1980; Johnson and Weaver 1981; Lee et al. 1982; Cantor et al. 1982; Kapur et al. 1983; Griffiths et al. 1983; Dayal et al. 1983; Zollinger and Hedinger 1983; Weder et al. 1983; Hough et al. 1983 and Dawson et al. 1984). Of these 15 patients 9 were women and 6 were men with an age range of 30–72 years. The carcinoid tumour was always located in the second portion of the duodenum and in 11 patients the papilla of Vater was specially mentioned as the site of the tumour. Somatostatin was found in 6 of 7 tumours examined. Considering that somatostatin seems to be the most frequently found polypeptide apart from gastrin in these duodenal carcinoids this fact may not be of much significance.

Five of the 15 patients had a pheochromocytoma besides von Recklingshausen's disease and duodenal carcinoid tumors and Griffiths et al. proposed in 1983 and 1984 the designation of MEN III a-syndrome for this association.

Another patient's tumour referred recently to us for immunohistochemical investigations is also of interest in this respect[1]. This 62 year old man, known to have cutaneous and intestinal neurofibromatosis, was investigated for early satiety and vomiting and a tumour of 3 cm in diameter located in the head of the pancreas and infiltrating and ulcerating the duodenum in the first and second portion was resected by Whipple's proceedure. The tumour, an endocrine tumour with lymph node metastases, was histologically strongly positive for somatostatin and single tumour cells were shown to produce calcitonin. This latter point is of particular interest because one of our patients (patient 12) with neurofibromatosis and a duodenal carcinoid had also calcitonin producing cells within the tumour.

There is at present no explanation for these associations and especially for the unusual location of the carcinoid. The only common point in these 3 tumours is the supposed embryological origin of their precursor cells from the neuroectoderm.

1 We thank Prof. R. Siebenmann, Stadtspital Triemli, Zürich and Dr. J. Hegglin, Spital Richterswil, for the opportunity to report on this patient

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