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CARCINOID-ISLET CELL TUMORS

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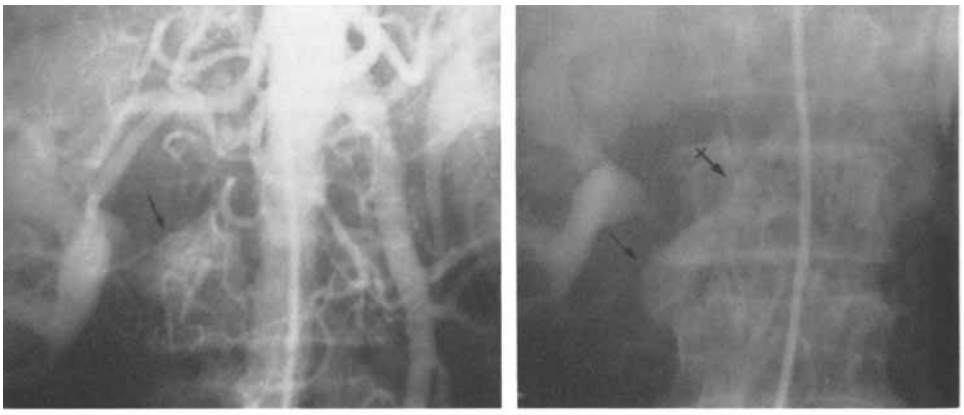
Pathologists have long experienced difficulties in distinguishing between 'carcinoid' and 'islet cell' tumors histologically. Many medical publications have shown a striking overlap in the secretions of these tumors. One of the co-authors of this paper (R. W.) described a series of patients with these tumors (26, 27, 28) in which the overlap in function among them was convincing enough to hypothesize that they are actually variations of the same tumor, should be grouped together as such, and should be referred to as carcinoid-islet cell tumors. The original reports concerned 21 patients. We have added 7 patients to that number and have performed angiography on 6 of these and on 2 patients from the previous series. We shall describe and discuss these findings and how they may be used in the diagnosis and outline of the extensiveness of these tumors. Also, we shall use this information to lend further support to the premise that these are actually variations of the same tumor and should be referred to collectively as carcinoid-islet cell tumors.

Submitted for publication 31 July 1972.



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(Fig. 1. a) Celiac angiography, arterial phase. Large pancreatoduodenal artery with a hypervascularized tumor in its distribution (→). b) Capillary phase. Accumulation of contrast medium (→) persists and is drained by a large, abnormal, early-filling vein crossing the midline (↔).

Case reports

Case 1. Male Negro, aged 67. 1954: Upper gastrointestinal bleeding. Radiography: duodenal ulcer. Gastric laboratory analysis: normal. Blood sugar 66 (normal 80—120). Op.: 80 % gastrectomy. Pathologic examination: 4 duodenal bulb ulcers and a duodenal 'carcinoid' tumor that had been cut through and part of the tumor left in the patient. 1955: Two marginal ulcers, one in the stomach and one in the small bowel. Op.: total gastrectomy. Following surgery, no more peptic ulcer symptoms. Blood sugars 62, 73. 1956: Nephrolithiasis requiring heminephrectomy. Blood sugar 75, elevated serum calcium, lowered serum phosphorus. 1961: Blood sugar 55, elevated serum calcium, lowered serum phosphorus. 1970: Celiac angiography (Fig. 1): accumulation of contrast medium with large early-filling draining vein in distribution of gastroduodenal artery, probably in the duodenal tumor that had been left in the patient. Superior mesenteric angiography normal. 5HIAA (normal). Serum serotonin and gastrin lost in the laboratory. *Summary.* Severe peptic ulcers nonresponsive to partial gastrectomy but responsive to total gastrectomy, multiple decreased blood sugar levels suggesting hyperinsulinism, multiple increased calcium and decreased phosphorus values suggesting a parathyroid adenoma. Pathologic diagnosis: carcinoid tumor of duodenum. Our analysis: Multiple endocrine adenomatoses with a parathyroid adenoma and a carcinoid-islet cell tumor that secreted gastrin and insulin. It is possible that the carcinoid-islet cell tumor secreted parahormone, but probably he had more than one tumor.

Case 2. Male college student, aged 21. 1965: Right upper quadrant abdominal pain and jaundice. Medical management with fair result. 1967: Persistent abdominal pain and jaundice, diarrhea, followed in two months by steatorrhea. BP 134/96. Radiography: duodenal ulcer. Serum amylase 698. Gastric analysis not done. Liver biopsy: minimal inflammation. Laparotomy: common bile duct stricture, small firm nodule in head of pancreas, cystic right kidney. Choledochoduodenostomy. Following operation, disappearance of pain. 1968: Stea-

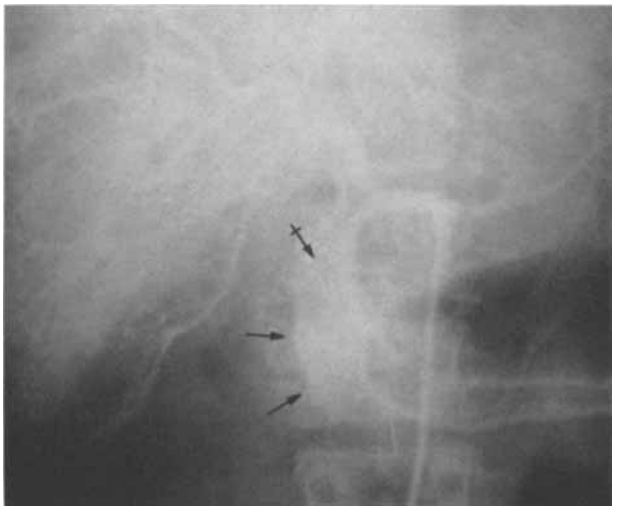

Fig. 2. Celiac angiography. Large superior pancreatoduodenal artery (↔), tumor vascularization in head of pancreas (→).

torrhea persisted, weight loss, recurrence of abdominal pain. BP 192/130. Triolean absorption test, small bowel biopsy, VMA and regitine tests: normal. Aortography: absent right renal artery. Celiac angiography: accumulation of contrast medium in distribution of gastroduodenal artery and enlarged pancreatoduodenal artery (Fig. 2). Superior mesenteric angiography: normal. Course: Deteriorated slowly. One day before death, symtoms of hypoglycemia, blood sugar 60; responded favorably to glucose intravenously. Autopsy: Tumor in head of pancreas with necrotic mestases to liver. Cystic right kidney. *Summary.* Duodenal ulcer, diarrhea, steatorrhea suggesting that this tumor secreted gastrin and produced a variation of the Zollinger-Ellison syndrome. Pathologic diagnosis: malignant islet cell tumor. Our analysis: Carcinoid-islet cell tumor of pancreas that secreted gastrin and probably insulin. It is possible that the episode of hypoglycemia was caused by depleted glycogen stores in the liver because of the extensive metastases.

Case 3. Negro woman, aged 58. 1962: Duodenal ulcer, clinically and radiographically. Medical management without favorable results. 1964: Persistent nausea and vomiting. Gastric analysis: compatible with Zollinger-Ellison syndrome. Op.: hemigastrectomy and vagotomy. Pathology: duodenal ulcer, tumor in wall of duodenum that had been cut through and part of it left in the duodenum. Readmission five months later for consideration of re-operation. She had been asymptomatic in the interval. 5HIAA, blood sugar normal, no operation. 1971: No symptoms for seven years. Celiac angiography: attenuation of gastroduodenal artery and faint accumulation of contrast medium in distribution of this artery that disappeared on later films; uncertain whether the accumulation was in the tumor that had been left or in the wall of the duodenum. Superior mesenteric angiography: normal. *Summary.* Classical Zollinger-Ellison syndrome in a patient with a duodenal tumor. Pathologic diagnosis: carcinoid tumor. Our analysis: Carcinoid-islet cell tumor of duodenum that secreted gastrin and produced the classical Zollinger-Ellison syndrome.

Case 4. White woman, aged 53. 1963: Easily fatigued, postprandial flushing of head and neck for six months. Positive 5HIAA on three separate occasions. Upper gastrointestinal

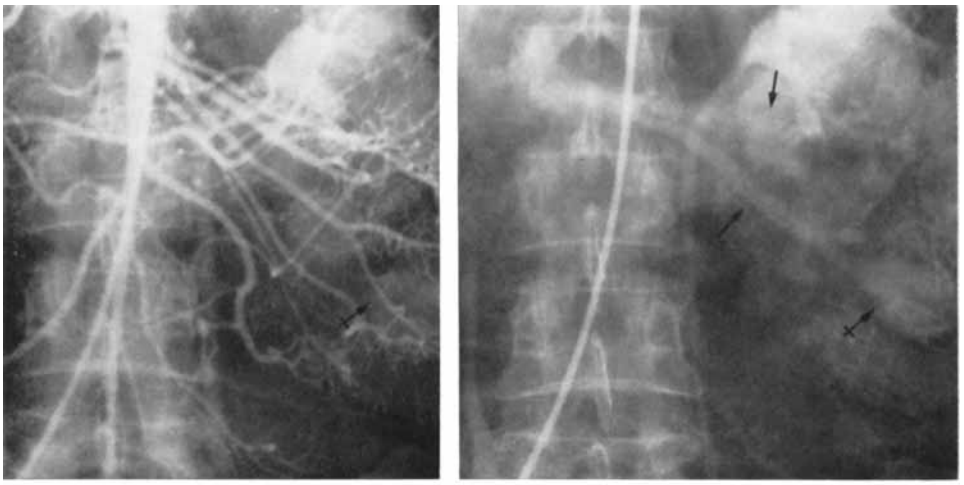

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Fig. 3. a) Superior mesenteric angiography, arterial phase. Tumor vascularization in jejunum (⟷). b) Capillary phase. Accumulation of contrast medium (⟷) persists; large abnormal, early-filling draining veins crossing midline (→).

series and blood sugar were normal. Superior mesenteric angiography (Fig. 3 a): accumulation of contrast medium in jejunum in the arterial phase. Large early-filling draining veins from tumor in the capillary phase (Fig. 3 b). Celiac angiography: metastases in liver. Patient flushed during injections. Op.: resection of jejunal tumor. Pathologic diagnosis: carcinoid tumor. Our analysis: Carcinoid-islet cell tumor of jejunum metastatic to the liver that secreted serotonin.

Case 5. Male Negro, aged 66. 1942: Flushing, tachycardia, headaches, nausea, weakness. A diagnosis of 'peptic ulcer' resulted in his discharge from the Army. 1946: Perforated prepyloric ulcer closed by Graham closure technique. Gastric analysis normal. 1948: Persistent abdominal pain. Op.: subtotal gastrectomy. Pathology: prepyloric ulcer and tumor incidentally found in wall of duodenum. 1954: Slow gastrointestinal bleeding that had persisted for several years. Op.: part of duodenal tumor removed from gastric pouch. 1957: Solitary nodule in lung. 5HIAA positive. Op.: lobectomy of lung, removal of more tumor from gastric pouch. 1959: 5HIAA pos. 1963: 5HIAA neg. 1968: Slow gastrointestinal bleeding continued. Radiography: masses in gastric pouch and head of pancreas (Fig. 4 a). Celiac angiography: accumulation of contrast medium in wall of gastric pouch and head of pancreas (Fig. 4 b) and in liver on later phase films. *Summary.* Severe peptic ulcer disease with clinical and laboratory evidence of serotonin secretion. *Comments.* It seems reasonable to assume that either this tumor originated in the pancreas and spread to the duodenum and stomach and metastasized to the lung, or that the patient had multiple tumors. It is doubtful whether the tumor metastasized to the head of the pancreas. The growth apparently secreted serotonin until 1963, but not later. Pathologic diagnosis: carcinoid tumor in lung and gastrointestinal tract. Our analysis: Carcinoid-islet cell tumors, primary in pancreas and of

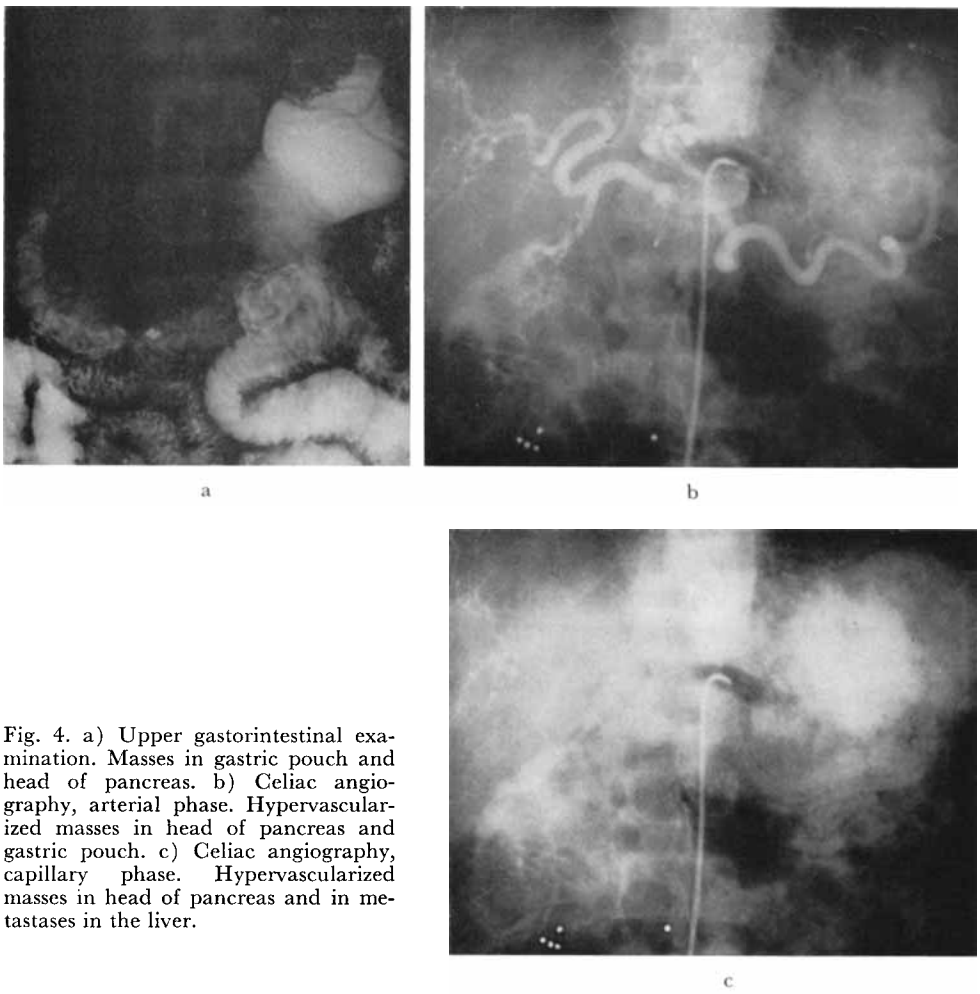

Fig. 4. a) Upper gastorintestinal examination. Masses in gastric pouch and head of pancreas. b) Celiac angiography, arterial phase. Hypervascularized masses in head of pancreas and gastric pouch. c) Celiac angiography, capillary phase. Hypervascularized masses in head of pancreas and in metastases in the liver.

gastrointestinal tract, and lung tumor either primary or metastatic, that secreted serotonin and gastrin or another ulcerogenic substance.

Case 6. White woman, aged 67. 1969: Dizziness, disorientation and shock relieved by intravenous glucose. Blood sugar 50 during one of these attacks. Tolbutamine tolerance test positive for hyperinsulinism. Celiac angiography: arterial phase, hypervascularity of body and tail of pancreas, encasement of splenic artery. Capillary phase: puddling body and tail of pancreas, multiple liver metastases. Upper gastrointestinal series normal. Op.: laparotomy; tumor of pancreas unresectable. Pathologic diagnosis: Islet cell tumor. Our analysis: Carcinoid-islet cell tumor of pancreas metastatic to the liver that secreted insulin. 1971: Patient re-admitted to hospital with unexplainable vomiting and diarrhea. We considered that the

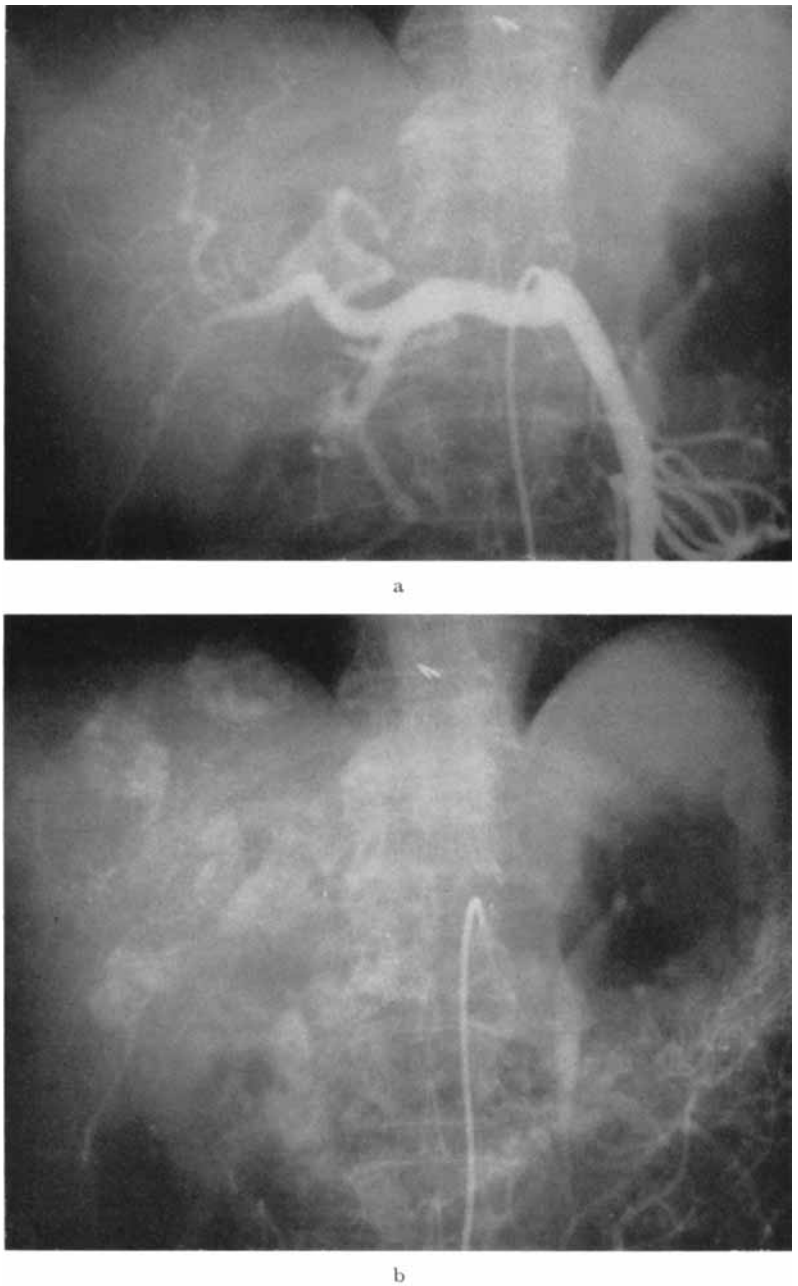

Fig. 5. a) Superior mesenteric angiography, arterial phase. Hepatic artery originates from superior mesenteric artery. b) Superior mesenteric angiography, capillary phase. Hypervascularization in head and body of pancreas and in metastases in liver.

Table

Potential of 28 carcinoid-islet cell tumors to secrete more than one hormone (I) as well as only one (II) or none (III). Twenty-one of these tumors have been previously published by R. W. (27, 28, 29) from the clinical standpoint. No angiographic results from these patients have been published.

I	16 ulcerogenic tumors	
	5 Zollinger-Ellsion syndrome	
	3 Zollinger-Ellison syndrome, multiple endocrine adenomatoses	
	1 Zollinger-Ellison syndrome, insulin	
	3 Peptic ulcer	
	1 Peptic ulcer, multiple endocrine adenomatoses	
	1 Peptic ulcer, insulin, multiple endocrine adenomatoses	
	2 Peptic ulcer, serotonin	
II	2 non ulcerogenic tumors, secretory	
	1 serotonin	
	1 insulin	
III	10 non secretory	

tumor was secreting gastrin at that time but were unable to obtain a serum gastrin level or gastrointestinal series.

Case 7. White male, aged 65. 1969: Abdominal mass discovered during mass health examination. Upper gastrointestinal series normal. Superior mesenteric angiography: accumulation of contrast medium in pancreas with multiple hypervascularized metastases to liver (Fig. 5). Op.: resection of most of tumor, followed by radiation therapy. Pathologic diagnosis: '... argentaffin type neoplasm.' Our analysis: Non-secreting carcinoid-islet cell tumor of pancreas.

Discussion

We have reviewed a total of 28 patients with carcinoid-islet cell tumors, the clinical findings of which are summarized in the Table. The peptic ulcers mentioned were severe peptic ulcers, but we chose to class them as such rather than as Zollinger-Ellison syndromes, since these patients did not have the classical Zollinger-Ellison features. Since published evidence clearly shows that gastrin secreting tumors may produce variations of the Zollinger-Ellison syndrome consisting of diarrhea, steatorrhea, simple peptic ulceration or marginal ulceration, and since 20 per cent of patients with gastrin secreting tumors may not have hyperacidity, we could have as easily classified most of these patients as Zollinger-Ellison syndrome (27). The 28 carcinoid-islet cell tumors were located as follows: 22 in the duodenum or small bowel, 4 in the pancreas and 2 in the pancreas and duodenum. Thirteen of the 16 ulcerogenic tumors were in the duodenum

or small bowel, 1 in the pancreas and 2 in the pancreas and duodenum. Of the 3 serotonin secreting tumors, 2 were located in the small bowel and 1 in the pancreas and duodenum. It is evident that tumors of the pancreas and duodenum overlap significantly in function.

From the Table, it is evident that carcinoid-islet cell tumors may secrete nothing, gastrin or insulin or serotonin or combinations of these hormones. True, we had to assume the secretory functions of some of these tumors from clinical findings since serum gastrin and serum insulin level determinations have only recently become readily available, but the clinical evidence seems reasonably conclusive. For instance, if a patient had the classical Zollinger-Ellison syndrome, as case 3 did, it seems reasonable to assume that the tumor secreted gastrin. If patients had severe peptic ulcers, or other findings that have been intimately linked to gastrin secreting tumors (27), as in cases 1, 2 and 5, it again seems reasonable to assume that these tumors secreted gastrin or at least some ulcerogenic substance. This assumption is further supported by a large autopsy series in which there was a 38 per cent incidence of peptic ulceration associated with 'carcinoid' tumors as opposed to a 5.5 per cent incidence in patients without 'carcinoid' tumors (15). It is to be doubted whether histamines or serotonin are the culprits in ulcer production in these patients, as ZOLLINGER et coll. have shown with fair certainty through laboratory experiments that gastrin will produce the Zollinger-Ellison syndrome whereas histamine and extracts of 'carcinoid tumors' will not. We suppose another ulcerogenic substance could be secreted by these tumors, but this remains to be proven.

Tumors secreting serotonin may either be found in the duodenum, small bowel, or pancreas if we assume that the tumor in the pancreas in case 5 had a part in the secretion of the serotonin.

Nine of the patients with duodenal tumors had the classical Zollinger-Ellison syndrome. This strongly suggests that these tumors secreted gastrin and further confirms the overlap in function between pancreatic and duodenal carcinoid-islet cell tumors. This is a striking observation since most of the gastrin secreting tumors producing the Zollinger-Ellison syndrome have previously been found within the pancreas.

In earlier classifications of 'carcinoid' tumors, they were divided into foregut (lung, stomach, and duodenum), midgut (pancreas, small bowel) and hindgut (appendix, colon) tumors. The foregut and midgut tumors were often secretory but the hindgut tumors were usually not. There were 10 foregut or midgut tumors in this series that apparently secreted no hormones. Perhaps their development was similar to the hindgut tumors. We have no other explanation as to why they were non-secretory.

One patient, previously reported in another publication (29), who had a

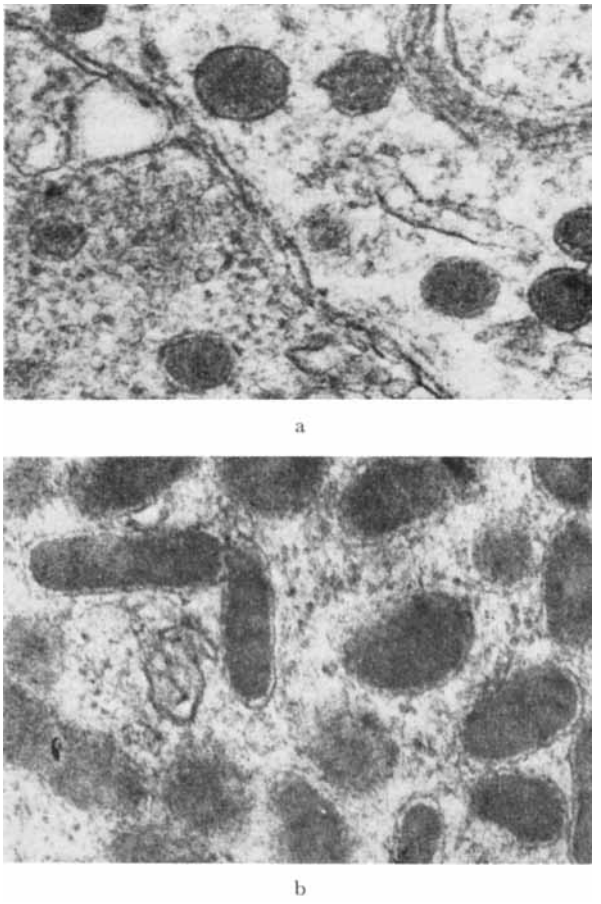

Fig. 6. a) Electron micrograph (multiplied × 31 500) of cytoplasmic granules that have been associated with gastrin secretion and have been found in normal islet cells. These granules were in a duodenal tumor. b) Electron micrograph (multiplied × 31 500) of cytoplasmic granules from an ileal tumor found in same patient as in (a). The granules with halos have been associated with the secretion of serotonin. (Reprinted with the permission of Cancer and J. B. Lippincott Co. and previously published in that journal (29).)

duodenal ulcer non-responsive to medical management over a 10-year period, developed hypersecretions and an acute outlet obstruction of the stomach. No gastric analysis was performed. He was operated on and had a severely scarred duodenal bulb that had produced a total obstruction at the pylorus. A duodenal tumor and eight ileal tumors were found and resected. An electron microscopic examination of the duodenal tumor showed cytoplasmic granules, the so-called delta granules that have been found in normal islet cells and have also been associated with the secretion of gastrin. Granules from an ileal tumor in the same patient contained cytoplasmic granules that have been associated with the secretion of serotonin (29) (Fig. 6).

The angiographic findings associated with 'islet cell' tumors and 'insulinomas'

that have been presented in the literature are quite similar to the findings present in the tumors presented in this paper (3, 8, 10, 14, 16, 18, 24). Only two reports could be found that described angiographic findings associated with 'carcinoid' tumors (REUTER et coll., RÖSCH & STECKEL). The tumors presented in the present report had much more prominent vascularity than the ones reported by REUTER et coll. and were strikingly similar to the findings associated with 'islet cell' tumors. We conclude from these observations that these tumors cannot be separated angiographically. When metastases from these tumors are present in the liver, they are readily demonstrable as they produce an intense accumulation of contrast medium. Necrotic metastases which no longer have a blood supply form an exception.

Since the pathologist cannot separate 'carcinoid' and 'islet-cell' tumors histologically, these tumors cannot be separated as to function because 'carcinoid' tumors may secrete gastrin or insulin in addition to serotonin or histamine (12, 21, 26, 27) and 'islet-cell' tumors may secrete serotonin, insulin or both (1, 2, 4, 6, 7, 9, 11, 13, 17, 25, 26), and since the angiographic findings are the same, it appears that there is no basis upon which to separate them. These two growths should therefore be grouped together, thought of as variations of the same tumor, and referred to collectively as carcinoid-islet cell tumors.

Conclusion

(1) According to histologic, pathologic, functional and angiographic findings, 'carcinoid' and 'islet cell' tumors are actually variations of the same tumor and should be referred to collectively by one term: carcinoid-islet cell tumors.

(2) These tumors are capable of secreting more than one hormone and a patient with a carcinoid-islet cell tumor may have other neuroendocrine tumors (multiple endocrine adenomatoses) and should therefore have a complete clinical and laboratory endocrine analysis (5HIAA, serum gastrin, tolbutamide tolerance test, serum insulin levels, serum calcium, and serum phosphorus, etc.).

(3) Patients with recalcitrant peptic ulcers, marginal ulcers, unexplained diarrhea or steatorrhea may have a carcinoid-islet cell tumor that secretes gastrin or another ulcerogenic hormone and should therefore be considered for an endocrine analysis and visceral angiography.

SUMMARY

The difficulties in distinguishing between carcinoid and islet cell tumors are discussed. According to histologic, pathologic, functional and angiographic findings, these tumors are actually variations of the same tumor and should be referred to as carcinoid-islet cell tumors.

ZUSAMMENFASSUNG

Die Schwierigkeiten, zwischen einem Karzinoid und einem Inselzell-Tumor zu unterscheiden, werden diskutiert. Entsprechend den histologischen, pathologischen, funktionellen und angiographischen Befunden sind diese Tumoren eigentlich Varianten ein und desselben Tumors und sollten als Karzinoid-Inselzell-Tumoren bezeichnet werden.

RÉSUMÉ

Les auteurs examinent les difficultés qu'il y a pour distinguer les tumeurs carcinoïdes des tumeurs à cellules insulaires. D'après les résultats histologiques, fonctionnels et angiographiques, ces tumeurs sont en réalité des variantes de la même tumeur et devraient être appelées tumeurs carcinoïdes à cellules insulaires.

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