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Cytological Differentiation of Asymptomatic Pancreatic Islet Cell Tumours in Autopsy Material*

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Summary. In eleven cases thirteen pancreatic islet cell adenomas were found in autopsy material from 1366 adult cases. Ten of the adenomas were solitary, while 3 small adenomas were observed in a single case. Another four possible solitary adenomas were observed, but their identity was uncertain owing to marked fibrosis.

All the adenomas contained A_2 (A)[1] cells but no B (B)[1] cells. Nine of them also contained A_1 (D)[1] cells. The majority of cells in the adenomas were A_2 cells or cells which did not stain with any of the techniques used.

The 4 possible adenomas contained islet cells (A_1, A_2, B) in different proportions. With one exception the patients with adenomas and possible adenomas were 65 years of age or older, and in some of these cases adenomas or hyperplasias were also found in other endocrine organs. The frequency of gastroduodenal ulcers or scars in the cases with adenoma or possible adenoma did not differ notably from that found in the cases without pancreatic adenomas.

Among the cases with pancreatic adenoma and possible adenoma there were 3 patients with maturity onset diabetes mellitus, but otherwise no clinical symptoms of endocrine disturbances were noted.

Key words: Islet Cell Tumours — Human Autopsy Material — Non Functional.

Introduction

The symptoms of active endocrine tumours arising from cells of the islets of Langerhans are well known. It is probably rare, therefore, for such a tumour, giving hormonal symptoms, to pass undiscovered. In most cases the diagnosis is followed by excision of the tumour. The number of islet cell tumours to be found in autopsy material will therefore be small. These will consist of tumours that have not been diagnosed, tumours diagnosed but for some reason not removed, and malignant tumours that have recurred after excision. Studies of the frequency of islet cell tumours in autopsy material have been reported by Nicholls (1902), Pappenheimer (see Whipple and Frantz, 1935), Korpássy (1939), Frantz (1959), Warren and Le Compte (1966), Becher (1971). In these reports, however, there has been no classification into different types with regard to cellular composition. The aim of the present investigation was to study both the frequency of such tumours and the different types of cells of which they consisted, in an unselected series of autopsy cases.

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1 According to Wiesbaden/Bologna pancreatic cell terminology.

Material and Methods

The investigation was performed on 1366 adult human autopsy cases (625 females and 741 males). During randomly chosen periods of weeks or months the pancreas from *all* adult autopsy cases was thoroughly examined (see below). The autopsy cases came mainly from a University hospital, but also from a community hospital, two long-stay hospitals and a psychiatric hospital.

The pancreas was excised whole and was cut into sections as thin as possible. The thickness varied with the consistency, from a few mm in the best cases to 5–10 mm in the poorest. All nodules suspected of being tumours were subjected to light-microscopic examination. The other endocrine organs were also examined macroscopically and unclear patho-anatomic changes were investigated microscopically. Where changes were found, only those observed in cases with islet cell adenoma or possible islet cell adenoma are described in this report.

In all 1366 cases a thorough macroscopic examination of the gastric and duodenal mucosa was performed with respect to ulceration or ulcer scars. In cases where the findings were doubtful microscopic examination was carried out.

The tissue specimens were fixed in 10% formalin and the pancreatic tumours were also fixed in Bouin's solution in most cases. The time intervals between death and tissue fixation varied between 8 and 48 hours. (4 hours after death the bodies were stored at $+4°$ to $+6°$ C.) The specimens were dehydrated, embedded in paraffin and sectioned at 5 μ.

The van Gieson stain was used as the routine technique. For demonstrating B cells the Gomori aldehyde stain, as modified by Maske (1955), was mostly used, with ponceau fuchsin as a counterstain (Hultquist, 1962). In some cases the chrome alum-haematoxylin technique (Gomori, 1941), with ponceau fuchsin as a counterstain, and the pseudoisocyanine method (Schiebler and Schiessler, 1959) were also used.

For demonstrating A_1 cells the Davenport alcoholic silver nitrate procedure as modified by Hellerström and Hellman (1960) was used.

As A_2 stains the Bodian silver proteinate methods as modified by Hellweg (1955) and the Grimelius silver nitrate stain (1968) were employed. For demonstration of amyloid the sections were stained with alkaline Congo red (Puchtler *et al.*, 1962) and examined in a polarization microscope.

In one case no sections were available for silver staining. In this case van Gieson stained sections were scraped from the slides with a razor blade and embedded in Epon. Ultrathin sections were then cut with an Ultrotome, contrast-stained with uranyl acetate and lead citrate and examined in an electron microscope (Zeiss EM 9) at 60 kV.

Results

From about 240 autopsy cases greyish white to white pancreatic nodules were taken for microscopic examination. Thirteen of these nodules, from 11 cases, were identified as endocrine adenomas. In a further 4 cases changes which were possibly adenomatous were found. The majority of the remaining pancreatic nodules consisted of scar tissue but occasionally necrotic adipose tissue, angiomas and metastases from extrapancreatic cancer were also observed.

The mean age of the 1351 cases not containing pancreatic adenomas or possible adenomas was 67 years (male 66, female 68).

Adenomas

In 10 cases the adenomas were solitary, while in one case 3 small adenomas occurred (Table 1 A). Six of the solitary adenomas were found in women, with a range of 65 to 85 years and a mean age of 72 years. The male cases ranged between 56–78 years, with a mean age of 66 years.

Five of the solitary adenomas were located in the tail of the pancreas and 2 in the body. In 3 cases the localization was not noted. In the case with 3 adenomas one was located in the body of the pancreas and 2 in the tail.

The adenomas were all approximately spherical and their diameters varied between 3 and 8 mm, apart from one of the solitary adenomas and 2 of the 3 adenomas found in the same case, where the diameter was only about 1 mm.

Microscopic Observations. All the adenomas were well demarcated from the surrounding tissues except one, in which the peripheral, but not the central parts were fibrotic. Apart from this one, the adenomas were completely or almost completely encapsulated. The capsule was usually thin. In one adenoma budding of small tumour cell clusters was seen in the capsule.

The arrangement of the parenchymal cells was predominantly trabecular (Fig. 1). In some of the adenomas clusters of cells or more solid cell areas were observed. Inside 2 adenomas a few tubular formations lined by columnar epithelium were also seen.

In most adenomas the parenchymal cells were moderately rich in cytoplasm, but in the cells in 2 of the solitary adenomas the cytoplasm was more sparse. Some parenchymal cells in a few of the adenomas showed finely vacuolized cytoplasm.

In 2 cases the tumour cell nuclei were hyperchromatic and slightly polymorphic, while in the other cases a monomorphic nuclear pattern was seen. In no adenoma were mitoses observed.

The stroma was sparsely to moderately well developed, with the exception of one adenoma with considerable fibrosis in the periphery. In a few adenomas amyloid substance was seen.

In all 13 adenomas, A_2 cells were found (Fig. 2) but no B cells. In 9 of the adenomas A_1 cells were also observed. In Table 1 A *semiquantitative* evaluation of the frequency of A_1 and A_2 cells is presented. In 4 adenomas the majority of the cells were A_2 cells. The A_1 cells in the tumours were few in number with the exception of one adenoma, where almost half of the tumour cells were of the A_1 type. The majority of tumour cells (Table 2) in most of the adenomas did not stain with any of the staining techniques used.

In the adenomas the A_2 cells were either diffusely scattered or located in the periphery of trabeculae or cell clusters. In one adenoma the central and peripheral zones contained an abundance of A_2 cells, while an intermediate zone contained only a few cells of this type. In most cases the A_1 cells were diffusely scattered or concentrated to certain areas. In the A_2 cells the cytoplasmic silver granules were either diffusely scattered or concentrated to the peripheral part of the cell facing capillaries or stroma.

The cells that formed the above mentioned tubular structures in a few of the adenomas showed a positive reaction to aldehyde fuchsin.

The electron microscopic examination revealed that the tumour cells contained secretion granules of the A_2 type—electron dense granules with a round to oval configuration.

Table 1. Summary of different morphological and clinical data from the 11 cases

	Case No.	Sex	Age	Diam. of adenomas (mm)	Frequency of cell types in the adenomas[a]		
					A_1	A_2	B
A	1	F	75	8	+ (+)	+++	−
	2	M	56	1, 1 and 3 resp. (3 adenomas)	+	++ (+)	−
	3	F	71	6	+	++ (+)	−
	4	F	69	6	−	+++	−
	5	F	65	4	++ (+)	++	−[b]
	6	F	65	5	+ (+)	++ (+)	−
	7	M	78	4	− ?	+[c]	−
	8	M	70	3	(+)	++	−
	9	M	65	6	−	+	−
	10	M	72	1	−	+++	−[b]
	11	F	85	5	+	+++	−
B	12	M	69	4	−	+++	+ (+)
	13	M	67	8	+	+++	+[d]
	14	M	75	4	+	+++	−
	15	M	68	6	+ (+)	+ (+)	+[d]

Abbreviations: M = male, F = female, D = duodenum, S = stomach.

[a] Semiquantitative evaluation: − = no cells, (+) = solitary cells, + = 1 to 5% of tumour cells, + (+) = 6 to 10% of tumour cells, ++ = 11 to 25% of tumour cells, ++ (+) = 26 to 50% of tumour cells, +++ = 51 to 60% of tumour cells.

with clear pancreatic islet cell adenoma (A) and the 4 cases with possible adenoma (B)

Patho-anatomic changes in other endocrine organs	Ulcers	Scars	Diabetes mellitus	Remarks
Bilat. nodular adrenal hyperplasia + non-toxic goitre		S		
Bilat. nodular adrenal hyperplasia + prim. parathyroid hyperplasia (chief cell type)				Chronic pancreatitis
		D		Op. cancer of breast, no metastases, slight pancreatic lipomatosis
			Maturity onset	Slight pancreatic lipomatosis
			Maturity onset	Malignant lymphoma
Two operations for goitre				Pancreatic lipomatosis
				Gastritis last 12 years
				Fairly highly diff. adenocarcinoma in stomach + metastases
Nodular non-toxic goitre				
Solitary thyroid adenoma (foetal type)				Pancreatic lipomatosis. Op. f. renal cell carcinoma 9 years previously
Slight nodular non-toxic colloid goitre + nodular adrenal hyperplasia				
Nodular colloid goitre with adenoma of foetal type + solitary adrenal adenoma + secondary parathyroid hyperplasia	D	S (Multiple)		Renal insufficiency
Slight nodular goitre			Maturity onset	Chronic pancreatitis + amyloid in islet tissue

[b] Occasional tubular structures with aldehyde fuchsin positive cells.
[c] Tumour cells classified by electron microscopy.
[d] Cells located in the periphery of the nodule.

Table 2. Summary of the distribution of cases according to the occurrence of cell types. (Case 7 is excluded because of uncertainty in occurrence of A_1 cells.) "Agranular" cells means that the cells did not stain with any of the staining techniques used

	A_1	A_2	B	"Agranular"	No. of Adenomas	No. of Possible adenomas
I	+	+	−	+	9	3
II	−	+	−	+	3	
III	−	+	+	+		1

Possible Adenomas

In 4 cases solitary fibrous nodules containing cells with an endocrine appearance were seen. These nodules, which had a diameter of 4 to 8 mm, were found in men, whose ages varied between 67 and 75 years (Table 1 B).

Microscopic Observations. The parenchymal cells in the fibrous nodules were moderately rich in cytoplasm and their nuclei were monomorphic; they were arranged in rows and clusters, and also in some places in a trabecular pattern (Figs. 3 and 4). No mitoses were seen.

In all 4 nodules A_2 cells were found, and in 3 cases these constituted the majority of the cells. In the fourth case only a few A_2 cells were observed. In 3 of the cases a few A_1 cells were also found, and in 3 cases a few B cells in addition. With one exception the latter cells were accumulated in clusters and localized to the peripheral zone of the fibrous nodule.

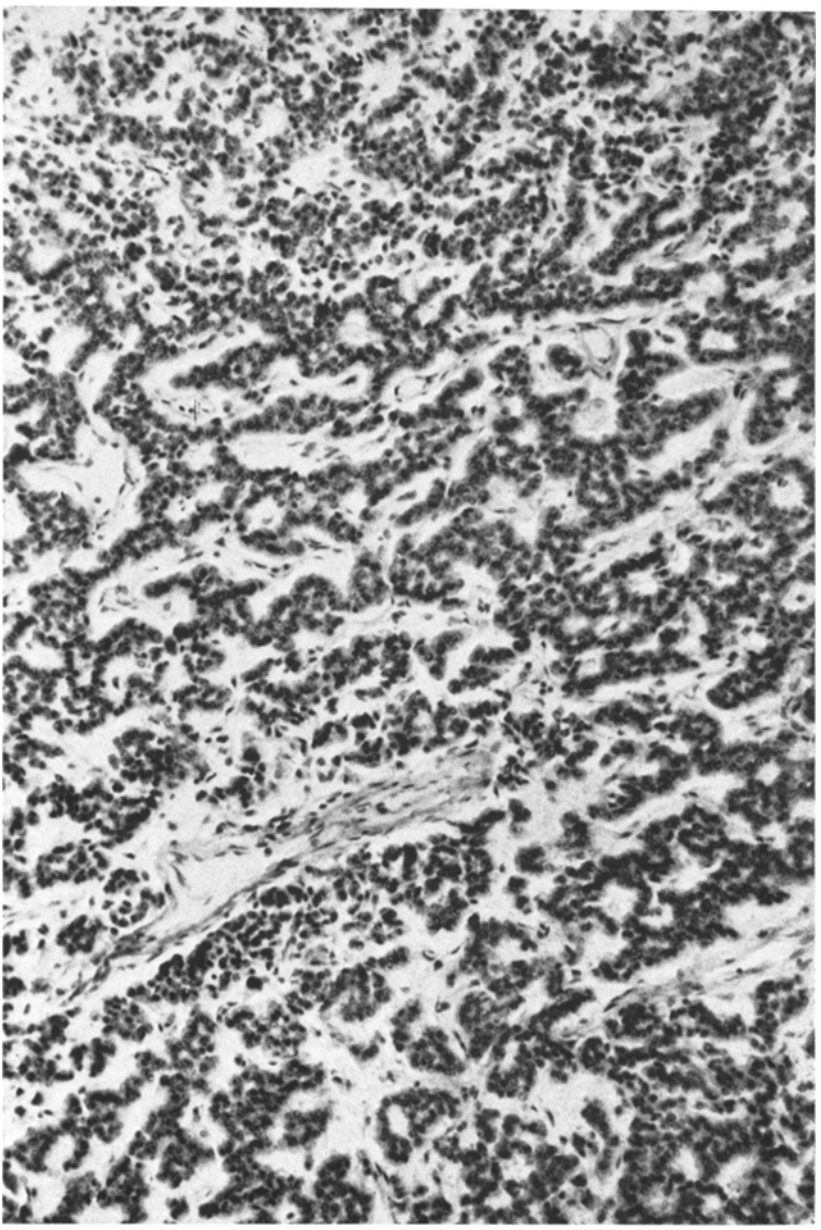
Pancreatic Islet Tissue Outside the Adenomas and the Possible Adenomas

In the majority of cases the islet tissue outside the adenomas and possible adenomas was normal, with respect both to the frequency and size of the islets and to the cell composition and the tinctorial properties of the cells.

In one case a small number of spherical "giant" islets (diameter about $^1/_2$ mm) was observed, but their cell arrangement and the occurrence of different cell types corresponded with those in normal-sized islets. These enlarged islets thus did not show the characteristics of microadenomas. In some of them, as well as in some normal-sized islets, greatly dilated capillaries were seen. Similarly dilated capillaries were found in some of the islets in another case. In this case there were no giant islets but fibrosis was observed in some islets. In these fibrotic islets the frequency of B cells was low and the B cell nuclei were smaller than in the other, non-fibrotic islets. In a third case there was an abundance of small islets, which contained numerous B cells. In the three cases with diabetes mellitus of the maturity onset type the islets showed slight to fairly pronounced hyalinosis.

Exocrine Pancreatic Tissue Outside Adenomas and Possible Adenomas

In 2 of the cases with adenoma pancreatic lipomatosis was observed, and in a further case chronic pancreatitis. In one of the cases with possible adenoma slight pancreatitis was noted.



Figs. 1 and 2 show pancreatic islet cell adenomas from cases 4 and 2

Fig. 1. The cells are arranged mainly in a trabecular pattern. van Gieson stain. ×115

Other Endocrine Organs

Cases with Adenoma. In 2 cases nodular adrenal hyperplasia was found. In one of these there was also primary chief cell hyperplasia of all four parathyroid glands, and in the other case atoxic nodular struma was observed. One further case showed a nodular, enlarged non-toxic thyroid gland. In a fourth case a

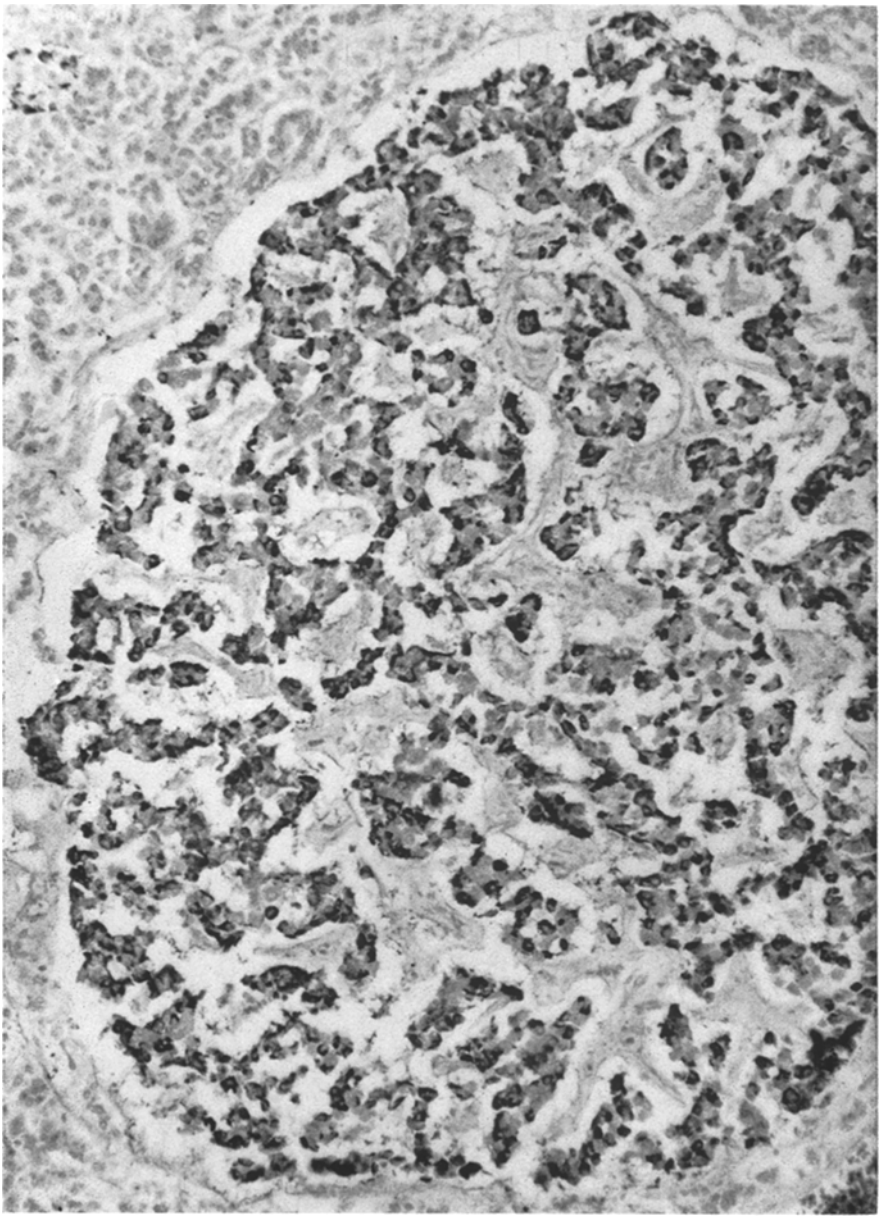


Fig. 2. Argyrophil A_2 cells mainly located in the periphery of trabecules. There is a fairly abundant amount of loose stroma. Grimelius silver nitrate stain. × 115

thyroid adenoma of the foetal type was found and in a fifth case the patient had undergone two operations for goitre.

Cases with Possible Adenoma. In 3 of the 4 cases a nodular goitre was found. In one of the cases a solitary adenoma in the thyroid (foetal type) and adrenal gland were also present, as well as secondary parathyroid hyperplasia. In another

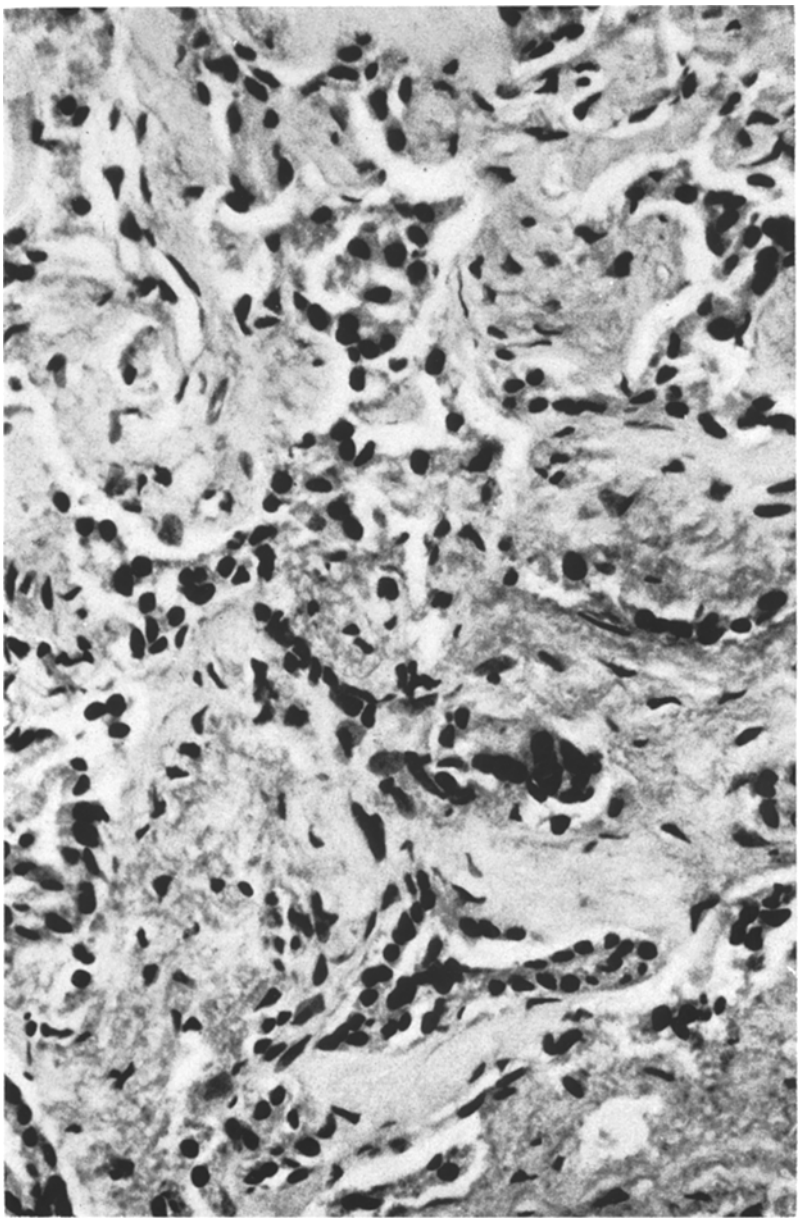


Fig. 3. Rows and clusters of cells in a fibrous stroma. The nuclei are pyknotic. van Gieson stain. ×460

Figs. 3 and 4 show possible adenomas from cases 12 and 15

of the cases nodular adrenal hyperplasia was present in addition to nodular non-toxic goitre.

Frequency of Ulcers/Scars in the Stomach and Duodenum

Cases with Adenoma. In 2 of the cases scars localized to the stomach and duodenum, respectively, were observed. No ulcers were seen.

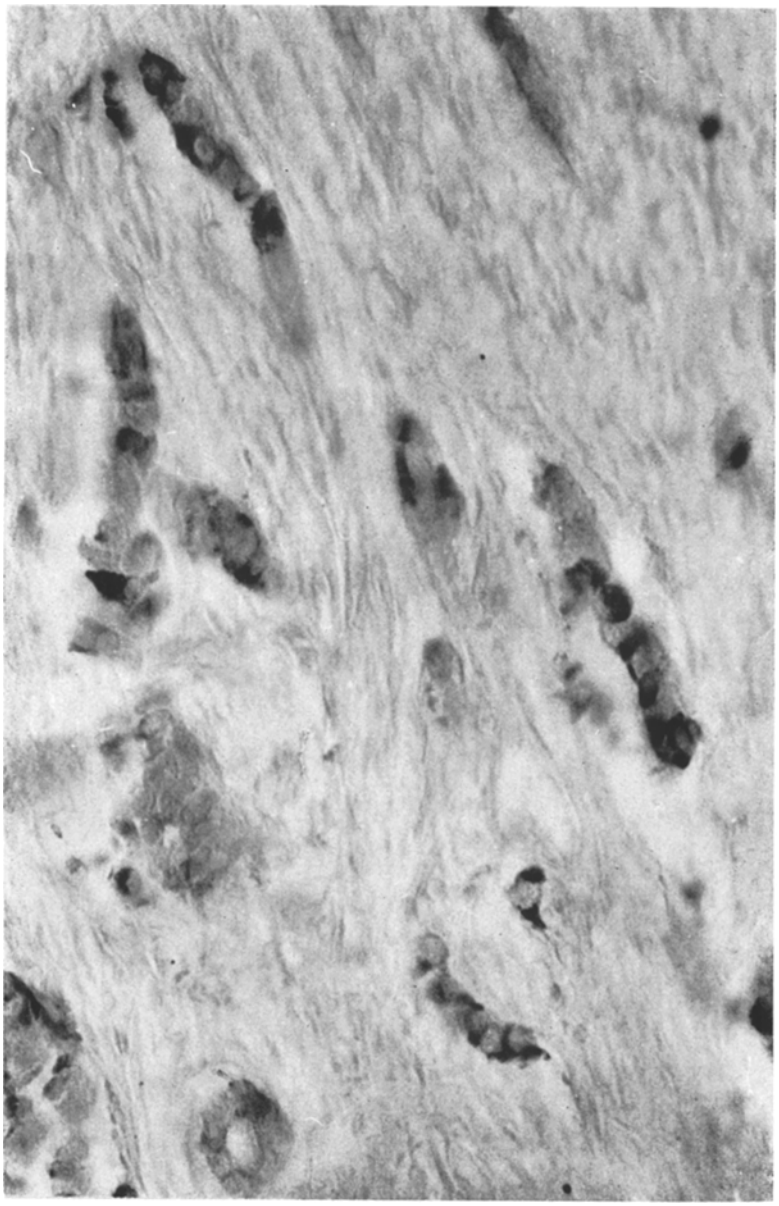


Fig. 4. Rows of cells, some of which are silver positive. Bodian stain. × 460

Cases with Possible Adenoma. In one of the cases multiple small scars were seen in the pyloric canal and also a small ulcer in the proximal part of the duodenum. It was in this case that the above mentioned adenomas of the thyroid and one adrenal gland were found, and secondary parathyroid hyperplasia was also observed.

Cases without Adenoma or Possible Adenoma. Among the 1351 autopsy cases without adenoma or possible adenoma, 94 exhibited ulceration and 103 scar

tissue in the stomach and/or duodenum. In 7 of the cases with ulceration, scars were also seen in the stomach or duodenum. In a further 19 cases gastrectomy had been performed previously for gastric or duodenal ulcer.

Clinical Data

Cases with Adenoma. None of the pancreatic adenomas had been diagnosed or suspected during life. Two of the patients had had manifest maturity onset diabetes, but in one of them this was so mild that the glycosuria disappeared on dietary treatment. (The latter patient's glucose tolerance curve was of the diabetic type). Regarding to the patients with adenomas in their thyroid or adrenal cortex or the patient with primary chief cell hyperplasia of the parathyroid glands no clinical symptoms were evident from their clinical records. One patient had suffered from gastritis during his last 12 years. Three of the other patients had malignant tumours. One of them had a fairly highly differentiated adenocarcinoma of the stomach with metastases, another had cancer of the breast, and the third a malignant lymphoma. These three tumours were examined and compared with the respective pancreatic adenomas. In all three cases the appearance, arrangement and tinctorial properties of the cells of the malignant tumours differed from those of the adenoma. One patient had undergone operation 9 years previously for renal cell cancer, with no recurrence. Otherwise the patient's basic diseases were mainly of a cardiovascular nature. One patient also had concurrent chronic pancreatitis.

Possible Adenoma. One of these patients suffered from maturity onset diabetes, while another had pulmonary fibrosis. The main disease in the 4 patients was of the cardiovascular type, however.

Discussion

When interpreting the nature of the large number of pancreatic nodules found in our series it is clear that in cases 1–11 (Table 1 A) there can be no doubt about the tumorous nature of the nodules. The tumours were classified as *adenomas* as no infiltrative growth or metastases of an endocrine nature were observed in any of the cases. In 4 of the cases, however, malignant tumours of another type had been diagnosed. The appearance, arrangement and tinctorial properties of the cells in these malignant tumours clearly differed, however, from those in the endocrine pancreatic adenomas.

As regards the other group of pancreatic nodules, Nos. 12–15 in Table 1 B, the interpretation was more equivocal. A possible alternative to adenoma is hyperplasia of islet tissue in fibrous pancreatic areas. Supporting a diagnosis of adenoma is the trabecular cell arrangement seen in some places, which corresponds to the picture in the clear adenoma.

As seen in Tables 1 and 2, the cell types in the adenomas were A_1, A_2 and "agranular" cells, but there were no B cells. "Agranular" cells and A_2 cells were present in all of the tumours. A_1 cells were only seen in a small number of the tumours and with one exception were fairly few in number. The presence of more than one hormone in endocrine pancreatic tumours has also been mentioned

previously (Donaldson *et al.*, 1957; Heitz *et al.*, 1971; Vance *et al.*, 1972; Arnold *et al.*, 1974) and lately confirmed by Larsson *et al.* (1974) by the immunofluorescence technique.

In 2 of the possible adenomas B cells were observed in the zone bordering against the pancreas, and we considered that these might represent incorporated islet tissue that had become surrounded by adenoma tissue. The B cells in these nodules were thus probably not tumorous, but arose from secondary changes in islet tissue in the neighbourhood of the tumour. In one further case of possible adenoma B cells which could not be explained by incorporation of surrounding islet tissue were seen.

From the size of these adenomas it would seem fairly unlikely that they would have caused any endocrine disturbances. From their cell composition hyperglucagonaemia and/or Zollinger-Ellison syndrome could be conceivable. No clinical symptom complex of these types was evident from the clinical records, but may of course have been present subclinically or so mildly as to pass unnoticed. To see a relationship between the symptoms of maturity onset diabetes, which had occurred in 3 cases, and the adenomas, would be speculative, and is not supported by the statistics. It is known, however (Frantz, 1959; McGavran *et al.*, 1966; Yoshinaga *et al.*, 1966; Grimelius *et al.*, 1971; Mallinson *et al.*, 1974), that diabetes occurs in patients with adenomas of the A_2 type.

Gastroduodenal ulcers and scar tissue were observed in 3 of 15 cases with adenoma or possible adenoma by thorough examination. In the remaining 1351 cases of the total material 94 showed ulcers and 103 ulcer scars, and in 19 cases gastrectomy had been performed previously for ulcer. The difference in frequency of ulcers/ulcer scars between cases with and those without insuloma is small, and the slightly higher frequency among the adenoma cases cannot at all be regarded as support for a causal genetic relationship.

The frequency of pancreatic adenoma arising from endocrine cells, observed in our investigation, corresponds with some reports in the litterature. Pappenheimer, however, found only 4 non-functioning islet cell adenomas among 4010 consecutive autopsy records. Of these adenomas only two could be observed macroscopically. In a detailed examination of the pancreas for another purpose, Korpássy found 4 islet cell adenomas among 500 autopsies. All of the adenomas could be seen with the naked eye. They contained cell elements of the pancreatic islet type and were delimited by connective tissue. In one of the adenoma cases a perforated duodenal ulcer was found. It was reported that one or two sections were taken from the head, body and tail of the pancreas, but the technique was not described in detail. The examination was focused on findings of metaplasia in the pancreatic ducts.

In autopsy material from 9158 consecutive cases 24 tumours which were designated "benign islet cell neoplasms" were observed (Frantz, 1959). Nicholls reviewed the records of 11500 autopsies in Milan and 1514 in Montreal, and found no such tumours (see Frantz, 1959).

Warren and Le Compte (1966) found 24 island cell tumours, including two carcinomas, in autopsy material from 2708 non-diabetic persons. The corresponding findings among 1854 diabetic persons were 18 tumours, of which 2 were

carcinomas. Recently Becher has reported the finding of 62 islet cell adenomas among 4280 adult autopsy cases.

In the above-mentioned published series of autopsies the frequency of pancreatic endocrine tumours varied between 0 and 1.4%. In our series the tumour frequency was 0.8%. These variations in frequency may depend on the composition of the autopsy material but also on the degree of thoroughness with which the pancreas has been examined. As seen in our material, most of the tumours were small and these could easily have been overlooked if the pancreas had not been cut in thin slices.

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