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The Ultrastructure of Focal Islet Cell Adenomatosis in the Newborn with Hypoglycemia and Hyperinsulinism

Contribution to the Classification of Neonatal Insulinomas*

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Summary. In a newborn severe persistent hypoglycemia due to an insulin-producing tumorous proliferation of pancreatic islet cells (insulinoma) was observed. The insulinoma showed the histologic pattern of focal adenomatosis of islet cells. According to the present literature the focal proliferation of islet cell complexes seems to be a frequent and particular feature of insulinomas in the newborn. Differential islet cell staining identified 80%–90% of the proliferated islet cells as B cells. 10%–20% of the cells were found to be A or D cells. Ultrastructurally the majority of the proliferated islet cells were well differentiated B cells. The remaining cells represented either A or D cells or a fourth islet cell type with small spheric granules. Electronmicroscopic evidence of transitions between differentiated islet cells, particularly B cells, and the fourth islet cell type suggests that the fourth islet cell type might represent a precursor cell within the APUD-cell system.

Zusammenfassung. Bei einem Neugeborenen wurde eine schwere persistierende Hypoglykämie als Folge einer Insulin-produzierenden tumorösen Proliferation des Inselzellsystems (Insulinom) beobachtet. Das Insulinom zeigte das histologische Bild einer fokalen Adenomatose der Inselzellen. Nach der vorliegenden Literatur scheint die fokale Proliferation von Inselzellkomplexen ein häufiges und besonderes histologisches Merkmal des neonatalen Insulinoms darzustellen. 80%—90% der proliferierenden Inselzellen konnten mit Hilfe differenzierender Inselzellfärbungen als B-Zellen identifiziert werden, 10%—20% als A- oder D-Zellen. Bei der elektronenmikroskopischen Untersuchung konnte die Mehrzahl der proliferierten Inselzellen als gut differenzierte B-Zellen klassifiziert werden. Die übrigen Zellen repräsentierten entweder A- oder D-Zellen oder einen vierten Inselzelltyp mit kleinen sphärischen Granula. Elektronenmikroskopische Hinweise für Übergangsformen zwischen differenzierten Inselzellen, besonders B-Zellen, und dem vierten Inselzelltyp lassen vermuten, daß der vierte Inselzelltyp eine Vorläuferzelle innerhalb des APUD-Zellsystems darstellt.

The organic hypoglycemic syndrome in the newborn due to hyperinsulinism can be based upon the following structural variations of the pancreatic islets: (1) temporary hyperplasia of the islets, as observed in infants of diabetic mothers and in infants with erythroblastosis fetalis (van Assche and Gepts, 1971), (2) functional secretory defects of the B cells with or without individual cellular hypertrophy (Yakovac *et al.*, 1971), (3) hyperplasia of the islets associated with cellular hypertrophy and ductulo-insular cell proliferation (nesidioblastosis) (Misugi *et al.*, 1970; Brown and Young, 1970; Klöppel *et al.*, 1974), (4) multifocal microadenomatosis (Schwartz and Zwiren, 1971), or (5) focal adenomatosis, respectively circumscribed adenoma (for lit. see Table 1). According to the litera-

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Table 1. Selected morphologic features in reported cases of neonatal insulinomas. d.i. of = description indicative of AD. = Adenomatosis

No. of cases	Author	Sex	Tumour diameter (cm)	Localization	Histology
1.	Sherman (1947)	F	?	tail	d.i. of Focal AD.
2.	Sholten and van der Vegt (1960)	M	?	head	?
3.	Crigler (1962)	?	?	?	?
4.	Crigler (1962)	?	?	?	?
5.	Francois *et al.* (1962)	F	0.5×0.5	head-body	d.i. of Focal AD.
6.	Francois *et al.* (1962)	M	0.2×0.2	head	d.i. of Focal AD.
7.	Perheentupa *et al.* (1967)	F	0.5×0.6	tail	Compact adenoma
8.	Salinas *et al.* (1968)	F	0.4×0.5	body	d.i. of Focal AD.
9.	Garces *et al.* (1968)	M	$0.6 \times 0.6 \times 0.8$	head	Compact adenoma
10.	Grant and Barbor (1970)	F	$0.5 \times 0.5 \times 1$	tail	Compact adenoma
11.	Buist *et al.* (1971)	M	0.4×0.4	body	Compact adenoma
12.	Robinson *et al.* (1971)	M	0.5×0.5	tail	Compact adenoma
13.	Robinson *et al.* (1970)	M	0.5×1	head	Compact adenoma
14.	Schwartz and Zwiren (1971)	M	up to 1×1	body	Multifocal AD.
15.	Todd *et al.* (1972)	M	0.3×0.3	head	d.i. of Focal AD.
16.	Baerentsen (1973)	M	$0.5 \times 0.5 \times 1$	head-body	d.i. of Focal AD.
17.	Presented Case	M	$0.4 \times 0.4 \times 0.5$	head	Eocal AD.

ture islet hyperplasia with cellular hypertrophy and nesidioblastosis seems to be most frequent among the islet alterations associated with neonatal hypoglycemia, whereas islet cell adenomatosis or adenoma are most rare. To our knowledge only 16 cases of islet cell adenomas in the newborn have been reported (for lit. see Table 1). Reports concerning differential islet cell cytology and ultrastructure of those adenomas are lacking. This paper records a further case of a tumorous islet cell alteration in the neonate with particular regard to its histopathologic and ultrastructural details.

Case Report

The clinical data can be summarized as follows. T.S., a male infant was born at term after normal pregnancy. Birth weight was 4080 g. There was neither a family history of diabetes mellitus nor a historical evidence of involvement with familial multiple endocrine adenomatosis (Wermer, 1963). Short time after birth sudden collapse occurred and the newborn turned cyanotic. Subsequent estimations of blood glucose yielded values of 5 to 10 mg%. A variety of laboratory tests for excluding extrainsular endocrine diseases and disorders of carbohydrate metabolism showed no defects. Simultaneous estimations of blood glucose and serum insulin revealed a distinct hyperinsulinism (10 mg%/30 μU/ml). Furthermore, leucine sensitivity was demonstrated. Treatment with diet, corticosteroids and diazoxide was unsuccesful. Because of persistent hypoglycemia associated with clonic convulsions laparotomy was performed at the age of 11 weeks. On operation a small nodule was palpated on the ventrocaudal surface of the head of the pancreas. It was harder than the remaining pancreatic tissue, but was the

same colour. Immediate section of the nodular tissue revealed adenomatous cell proliferations. Subtotal pancreatectomy was carried out[1]. Postoperatively the blood glucose levels stabilized within 3 weeks and have remained normal ever since. Convulsions did not longer occur and the mental development was normal except for occasional opisthotonus positions of the legs.

Material and Methods

For light microscopic examination the resected pancreatic tissue was fixed in Bouin's solution. Serial paraffin-embedded sections were stained with hematoxylin-eosin, period acid Schiff (PAS), phosphotungstic acid hematoxylin (PTAH), Gomori's aldehyde fuchsin and the silver impregnation technique according to Hellerström and Hellman. — For immunohistologic demonstration of insulin or gastrin (Dr. H. Mitschke, Dept. of Pathology, University of Hamburg) Bouin-fixed and paraffin-embedded pancreatic tissue was examined by the indirect technique, using rabbit anti insulin serum or rabbit anti gastrin serum and FITC-labelled anti rabbit γ globulin serum from sheep (Behringwerke, Marburg). — For electron microscopic investigation the pancreatic tissue was immediately fixed following removal by immersion in 3% glutaraldehyde buffered with 0.1 M sodium cacodylate (pH 7.4) for 2 hours. Following brief rinsing in cacodylate buffered osmium tetroxide and after passing propylenoxide embedded in Epon 812. Ultrathin sections were cut on a Reichert ultramicrotome OM U2, double stained with uranyl acetate and lead citrate and examined in a Philips electron microscope EM 300 at 60 kV.

Results

Light Microscopic Examinations

The resected pancreatic tissue[2] exhibited an adenomatous proliferation of islet cells within an area of about 0.4×0.4 cm in diameter. The islet cell clusters showed great variations in size and were of irregular outlines. They were separated and encapsulated by small cords of acinar tissue and distinct fibrous septa (Fig. 1a). On the periphery of the nodular focus islet cell nests extruded into the surrounding exocrine tissue. Since no coherent adenoma was formed by the proliferated islet cell complexes, this finding is described as focal adenomatosis of the islet tissue.

Within the adenomatous nodules the islet cells were arranged in clusters or cords. Ductular structures inbetween the islet cells were frequently present (Fig. 1b). At several points small islet cell clusters appeared to bud off the duct epithelium (Fig. 1b). The islet cells variied considerably in size including an occasional large cell with a prominent round nucleus. Mitotic figures were not seen. Elsewhere the islet tissue appeared hypoplastic.

Differential islet cell staining revealed three different cellular components within the focal adenomatosis. About 80%–90% of the cells, including the hypertrophied cells, were identified as B cells on the basis of positive aldehyde fuchsin stain (Fig. 2a). The B cells were, in general, well granulated, but single degranulated B cells were also observed. The islets outside the tumorous areas contained only small and poorly granulated B cells. About 10%–20% of the proliferated islet cells were A (A_2) or D (A_1) cells, as demonstrated by PTAH

1 Surgery was performed by Priv. Doz. Dr. med Farthmann and his colleagues, Department of Surgery, University of Hamburg.

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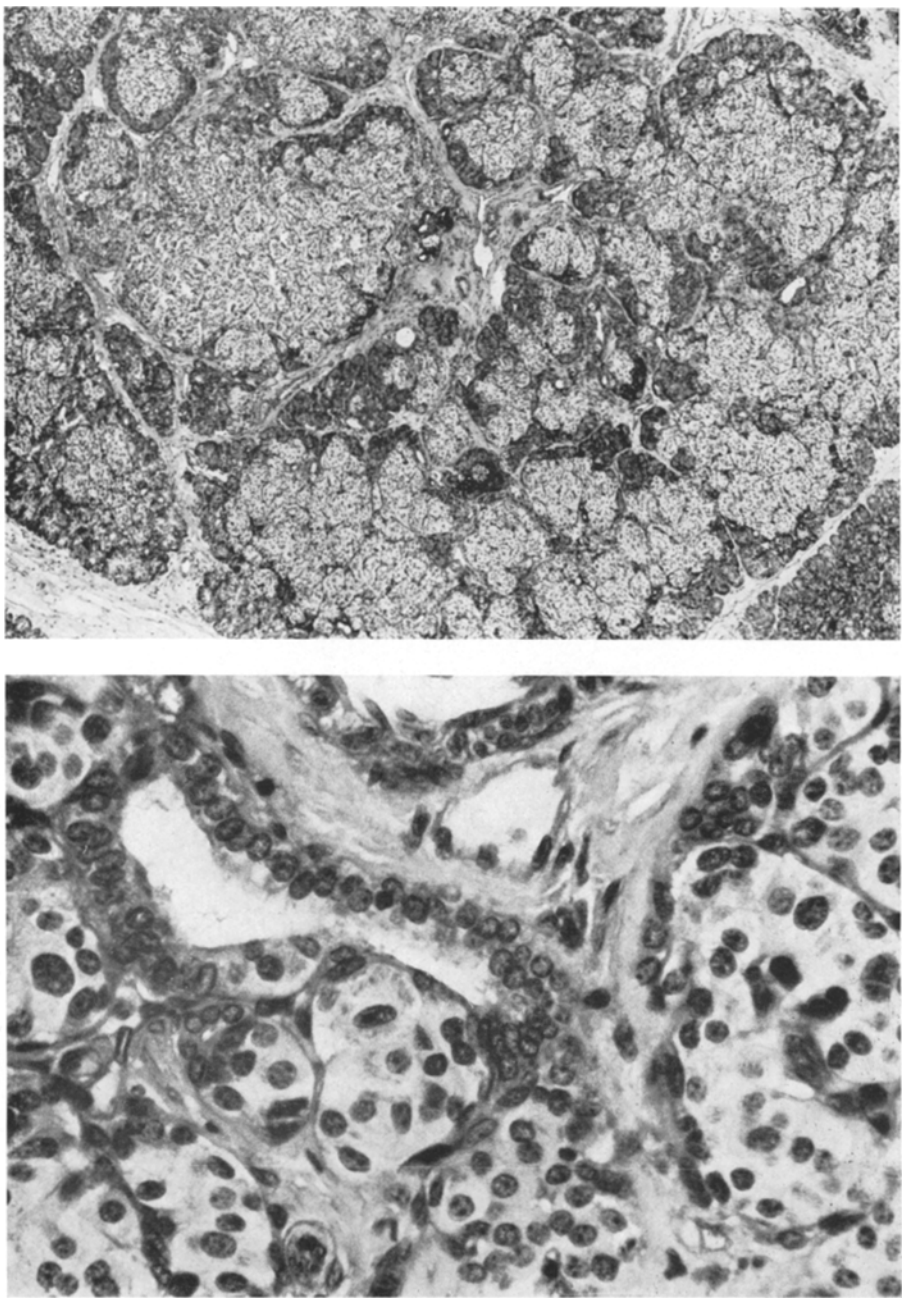

Fig. 1a and b. Insulinoma in a newborn. (a) Part of focal islet cell adenomatosis. The proliferated islet cell clusters are intermingled with and separated by acinar cell cords. PAS ×40. (b) High power view of proliferated islet cell complexes adjacent to a duct. Note the varying size of the islet cells and the interposition of islet cell groups between the duct epithelial cells, suggesting ductulo-insular proliferation (nesidioblastosis). PAS ×500

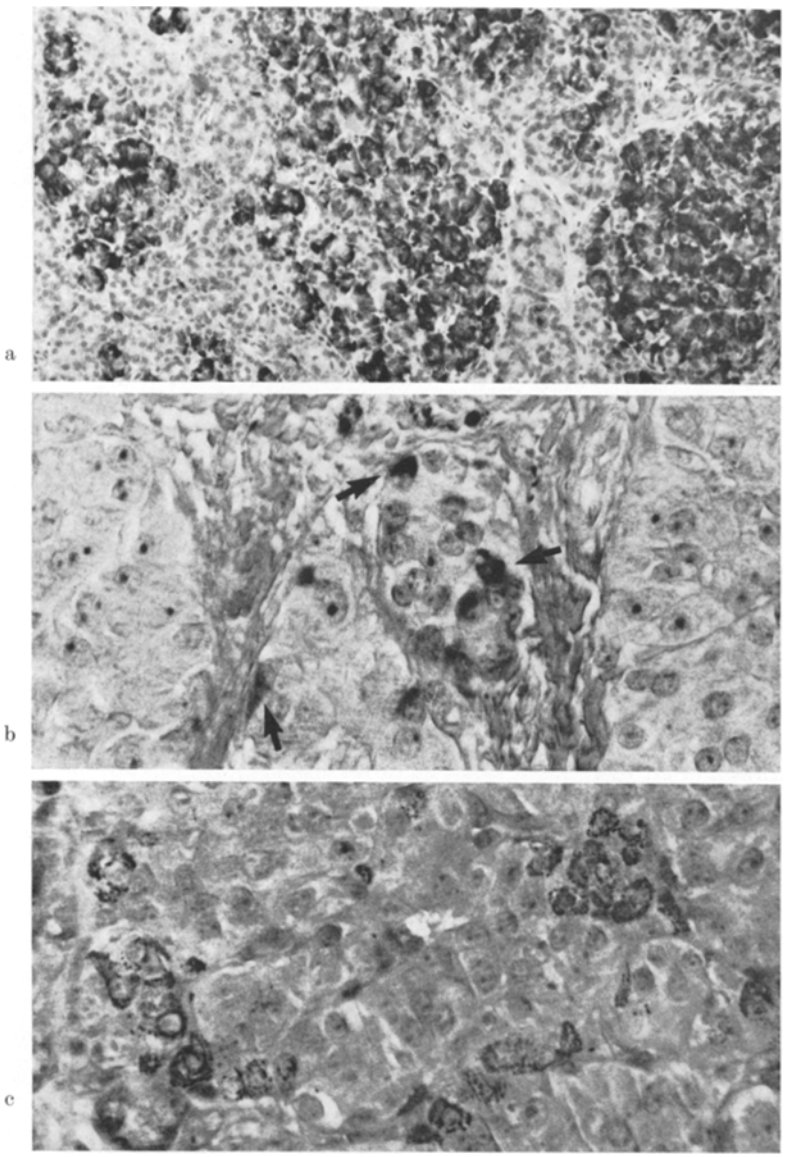

Fig. 2a—c. Differential islet cell stainings in focal islet cell adenomatosis. (a) The majority of the proliferated islet cells represents B cells. Gomori's aldehyde fuchsin ×40. (b) Single A(A_2) cells, mainly located on the periphery of the islet cell clusters (arrow). PAS ×500. (c) Small groups of D(A_1) cells scattered throughout the islet cell proliferations. Silver impregnation according to Hellerström and Hellman ×500

staining or the silver impregnation technique of Hellerström and Hellman (Fig. 2b and c). The A cells were mostly located on the periphery of the adenomatous islet cell clusters, whereas D cells were scattered throughout the hyperplastic areas (Fig. 2b and c).

Immunohistologic Examination

The immunohistologic examination using anti insulin serum revealed a strongly positive reaction in most of the proliferated islet cells. The positive cells correlated well in number with the aldehyde fuchsin positive cells. The B cells outside the hyperplastic areas showed only a weak reaction product for insulin. Gastrin-containing cells could not be demonstrated. Anti glucagon serum for demonstrating glucagon-containing cells was not available.

Ultrastructural Examination

On the basis of the fine structure of the secretory granules A, B and D cells were identified within the proliferated islet cell masses (Fig. 3). In addition a fourth islet cell type and transitional cell types could be demonstrated.

The fine structure of A and D cells (Fig. 3) was in accordance with the structural features of these cell types known from literature (Deconinck *et al.*, 1972). They revealed no signs of functional activity. A and D cells comprised only a small portion of the proliferated islet cells. Concerning the number of D cells it was striking that less D cells could be observed under the electron microscope than were expected from Hellerström-Hellman staining.

The majority of the proliferated islet cells were classified as B cells. They exhibited a varying content of typical secretory granules, showing either a polymorphous core within a wide clear halo or a spheric less electron dense homogenous core surrounded by a narrow halo. The smooth and rough endoplasmic reticulum (ER) was well developed. In many cells focal dilatation of the ER associated with endoplasmic invaginations were present. Prominent Golgi complexes were evident in single cells (Fig. 3) showing numerous microvesicles in their immediate vicinity.

Apart from A, B and D cells with typical secretory granules there were, on the one hand, cells containing a pure population of small spheric granules (150–250 mμ in diameter) (Fig. 4a and b) and, on the other hand, cells with polymorphous β-granules in addition to small spheric granules and some α-granules (Figs. 5 and 6). The spheric granules had a concentrically arranged homogenous core within a narrow halo (Fig. 4b), thus differing from α-granules, which were characterized by their eccentric granule cores. The cells which only contained small secretory granules strongly resembled type IV islet cells according to the islet cell nomenclature of Deconinck *et al.* (1971, 1972). The cells with a mixed population of secretory granules appeared to represent a transitional type between type IV islet cells and B cells (Figs. 5 and 6).

Islet cells of varying differentiation were often seen adjacent to duct cells. Sometimes they were also located between duct cells (Fig. 7).

The fine structure of the islet cells in the remaining pancreatic tissue was normal except for the B cells which exhibited a poor granulation in association with hypoplastic endoplasmic structures. This suggested a suppressed insulin release mechanism for the non-adenomatous B cell population.

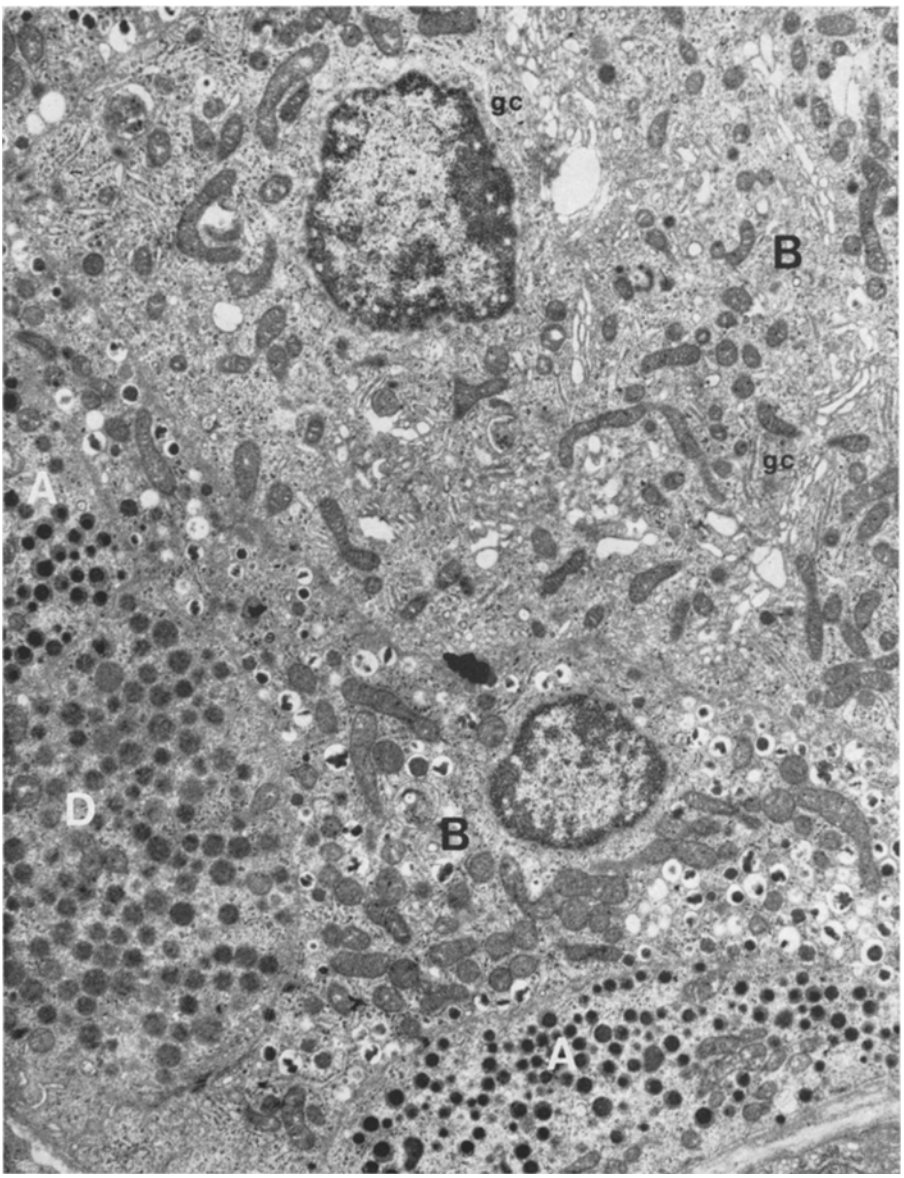

Fig. 3. Electron micrograph of islet cell adenomatosis showing typical A(*A*) and B cells (*B*) and a D cell (*D*). Note the numerous large Golgi complexes and the degranulation of one of the B cells. ×8000

Discussion

In the present case an insulin-producing tumorous alteration of the islet cells (insulinoma) was found to account for hyperinsulinism and severe neonatal hypoglycemia. On gross examination the insulinoma could only be recognized as

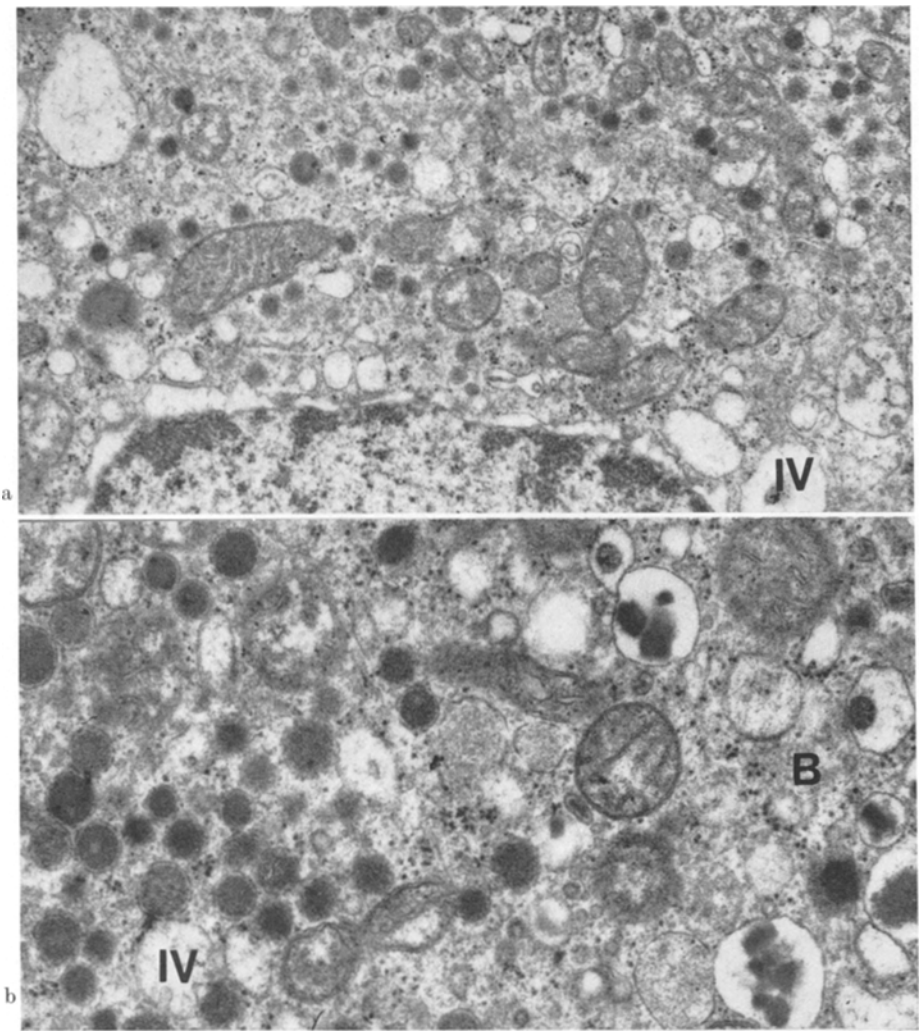

Fig. 4a and b. Islet cell adenomatosis. (a) Part of an islet cell containing small spheric granules with concentric homogenous cores (type IV islet cell) (*IV*). ×19440. (b) Comparison of the secretory granules of a B cell (*B*) and a type IV cell (*IV*). ×31350

a peasized nodule in the head of the pancreas by its consistency. Similar macroscopic statements were also reported for most of the 16 published cases of insulinomas in the newborn (see Table 1). The average size of the tumours was 0.5 cm in diameter. Only in few cases a tumour size up to 1 cm was recorded. The neonatal insulinomas were found scattered through all parts of the pancreas, while ectopic localisations had, at this point, not been observed.

Varying histologic patterns of insulinomas in the newborn have been reported (see Table 1). From the description in literature the following types may be differentiated: (1) encapsulated compact adenoma, (2) focal illdefined adenoma-

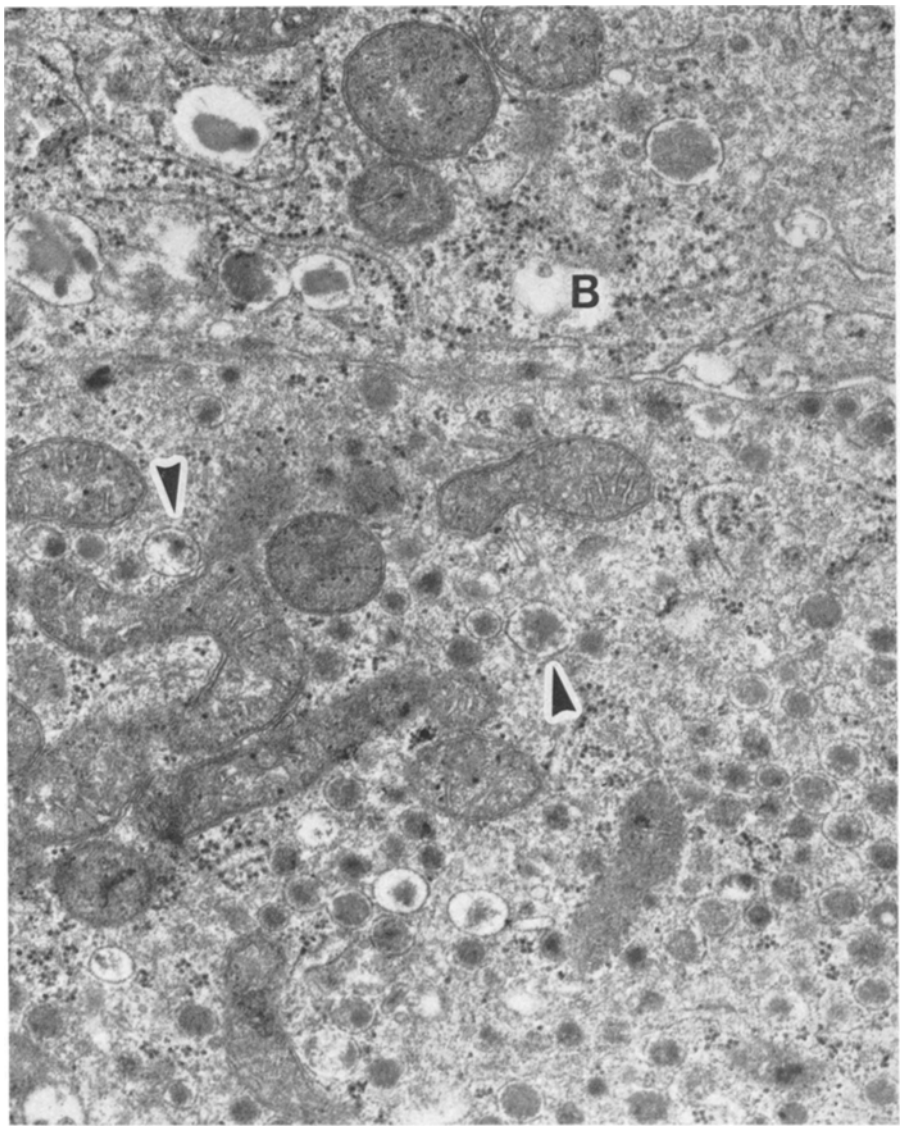

Fig. 5. Islet cell adenomatosis. Transition of type IV cell to B cell. Note the single polymorphous secretory granules (arrow) in addition to numerous small spheric granules. At the top a typical B cell (*B*). ×31350

tosis and (3) multifocal microadenomatosis, that is, tumour-like growths in all or almost all islets. In individual cases multifocal microadenomatosis can be hardly distinguished from diffuse islet hyperplasia with ductulo-insular proliferation (nesidioblastosis) (Brown and Young, 1970; Schwartz and Zwiren, 1971; Fonkalsrud *et al.*, 1974), suggesting that transitions between adenomatosis and islet

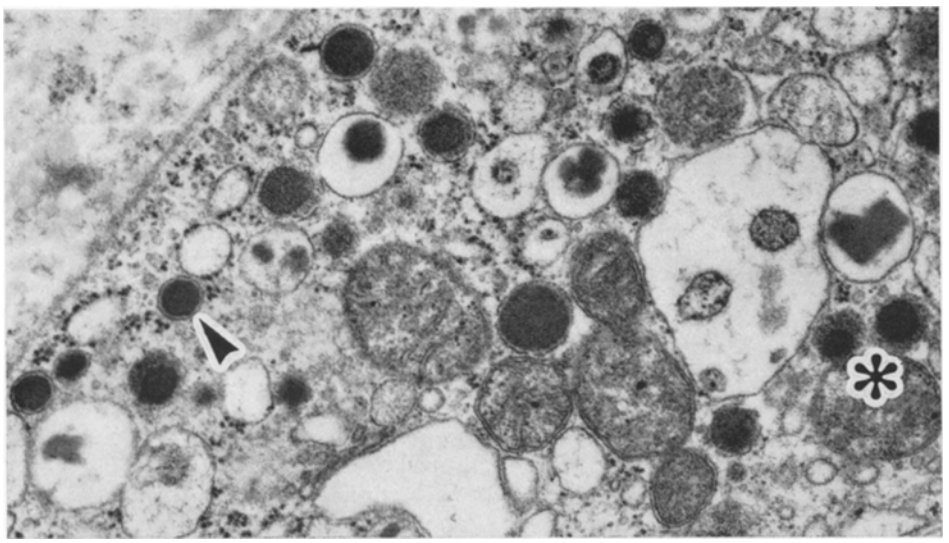

Fig. 6. Islet cell adenomatosis. Part of an islet cell containing a mixed population of secretory granules. Apart from typical β-granules there are spheric granules with concentric cores (arrow), comparable with type IV cell-granules, and granules with α-granule-like eccentric cores (asterix). $\times 31350$

hyperplasia might occur. Apart from compact adenomas focal islet cell adenomatosis, as it was seen in the present case, seems to be a frequent tumorous islet cell alteration in the newborn (see Table 1). The histologic pattern of focal tumour-like proliferation of islet cells intermingeled with and separated by exocrine cell cords has not been noted up to now in insulinomas of adults. Possibly the focal adenomatosis represents a particular pathologic entity of the neonatal islet cell system. Multifocal microadenomatosis, on the contrary, has also been described in adults (Frantz, 1959).

Differential islet cell staining of the neonatal insulinomas, which was only done in a few cases (Grant and Barbor, 1970; Robinson *et al.*, 1971; Schwartz and Zwiren, 1971), revealed B cells to be the major component of the proliferated islet cells. A (A_2) and D (A_1) cells have not yet been demonstrated. In the present case B cells comprised about 80% to 90% of the proliferated islet cells, A cells 5% to 10% and D cells 5% to 10%. The occurrence of A and D cells, confirmed also by electron microscopy, indicates that the proliferation includes, apart from the B cells, also the A and D cell system. Whether the increase in non-B cells had any functional significance, remains unknown, since neither Glucagon nor Gastrin levels in the serum were determined. However, there was no evidence from the clinical picture as well as the ultrastructural examination for a pronounced functional activity of the non-B cells. In adults tumours of the islet cells with multiple hormone production (insulin, glucagon, gastrin, ACTH/MSH, serotonin) have been reported (Aronson *et al.*, 1970; Heitz *et al.*, 1971; Broder and Carter, 1973; Hedinger, 1974; Arnold *et al.*, 1974).

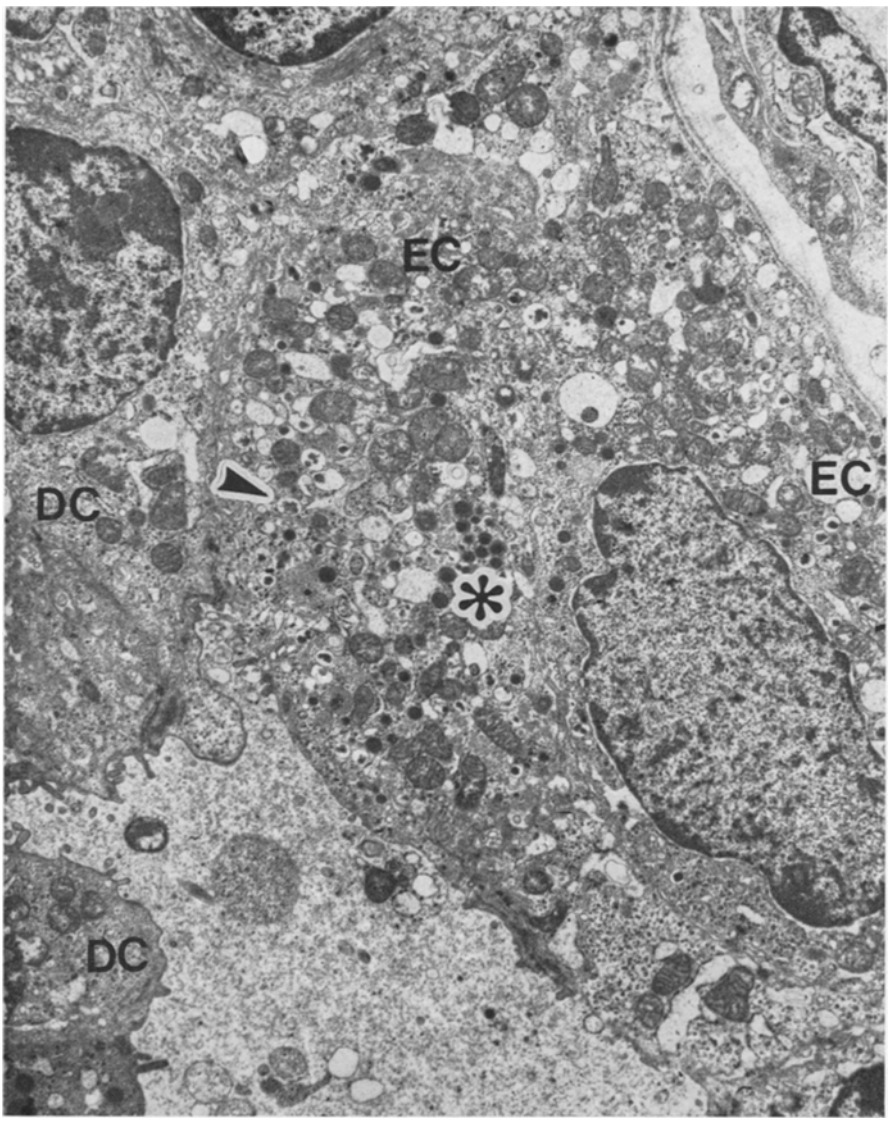

Fig. 7. Islet cell adenomatosis. Interposition of endocrine cells (*EC*) between duct cells (*DC*) showing α-granules (asterix) and β-granules (arrow). ×8000

Ultrastructural examination of neonatal insulinomas are so far not noted in the literature. In the present case electron microscopy revealed the characteristics of mature B cells in the majority of the proliferated islet cells. A small group of islet cells showed the typical fine structure of A or D cells. Evidence for an increased functional activity was only found in some B cells. Different islet cell types were seen adjacent to or inbetween duct cells. This finding might be considered as an argument for a ductular genesis of islet cells in islet cell adenomatosis.

In addition to A, B and D cells islet cells were observed which by their small homogenous spheric granules represented a fourth islet cell type (type IV islet cell according to Deconinck *et al.*, 1971). Some of those islet cells exhibited in addition to the small homogenous granules transitions to polymorphous β-granules. According to the classification of Creutzfeldt and coworkers (1973), distinguishing the insulinomas in adults on the basis of the fine structure of the secretory granules in type I (typical β-granules), type II (typical and atypical β-granules), type III (atypical granules) and type IV (virtually agranular), the present focal adenomatosis of the islet cells would well correspond with a type II insulinoma.

The type IV islet cell was clearly defined from A, B and D cells by Misugi *et al.* (1970), Deconinck *et al.* (1971, 1972) and Munger (1972), although islet cells with similar granules have repeatedly been described in earlier investigations (Björkman *et al.*, 1966; Potet *et al.*, 1966; Shibasaki and Ito, 1969; Greider *et al.*, 1970), but were either classed as A or D cells. Type IV islet cells occur rarely within the islets of adults and newborns (Deconinck *et al.*, 1971, 1972). In cases with neonatal hypoglycemia, hyperinsulinism and islet hyperplasia with ductulo-insular proliferation type IV cells seem to occur in unusual frequency (Misugi *et al.*, 1970; Klöppel *et al.*, 1974). Similar cells were also observed in insulinomas (Creutzfeldt *et al.*, 1973) and non-B cell tumours (Vasallo *et al.*, 1972; Mitschke, 1973; Greider *et al.*, 1974). On the basis of these observations it remains open, whether type IV islet cells represent an independent islet cell type or a precursor cell, not yet fully differentiated as to function and possibly closely connected to an embryonal APUD cell (Pearse, 1969; Pearse *et al.*, 1973). The demonstrated transitions from type IV islet cells to B cells as well as the additional occurrence of single α-granules in those cells might speak in favour of the latter hypothesis.

The clinical appearance of the neonatal insulinoma here described had much in common with the main features of those tumours known from literature. Its main characteristics were hypoglycemia within few hours after birth, elevated serum insulin levels, leucine sensitivity and lack of response to diazoxide. In principle, analogous clinical features are also found in generalized islet hyperplasia of the neonate. Neonatal islet hyperplasia and neonatal insulinoma can, therefore, hardly be differentiated on clinical grounds.

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