

## **Proliferative and Metaplastic Lesions of the Endocrine Pancreas in Rats**

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### **INTRODUCTION**

The proliferative lesions of the endocrine pancreas: hyperplasia, adenoma and carcinoma, are characterized by gradual, rather than abrupt, transitions in cytomorphology and tissue architecture. The normal appearance of the endocrine cells of the Islets of Langerhans are to a large extent retained in hyperplasias and adenomas, and even in many carcinomas. Furthermore, metastasis is an exceedingly rare event in pancreatic islet tumors of the laboratory rat (5).

Most neoplastic lesions of the endocrine pancreas contain only the secretory endocrine cells characteristic of the Islets of Langerhans; however, a small proportion of pancreatic neoplasms, termed "mixed tumors", are populated by neoplastic cellular components exhibiting the features of both endocrine and exocrine pancreatic cells. These tumors, by virtue of their generally small size, regular outline and failure to metastasize, resemble endocrine, rather than exocrine tumors.

A variety of agents exhibiting toxicity towards islet cells, e.g., alloxan, streptozotocin, uric acid and dialuric acid, are recognized as carcinogens of the endocrine pancreas (3). Hyperplasia of islets is induced by agents promoting persistent hyperglycemia, either by physiological means, as in the case of corticosteroids, glucagon and overfeeding, or by the induction of toxicity (6). Included among the latter group are the diabetogenic agents mentioned above as carcinogens, viz., alloxan and streptozotocin (3).

Histochemical studies of the rat pancreas (8,9) have shown insulin to be produced by most islet cell tumors. Other pancreatic polypeptide hormones, including somatostatin and glucagon, may be found in insulin secreting tumors, but cells secreting these hormones are sparse. Hyperplastic islets contain augmented numbers of beta cells, while the cells secreting other pancreatic hormones appear unchanged in number and location.

Tumors of the endocrine pancreas in the rat are small, seldom exceeding 10 mm in diameter. The lesions are generally pale grey to white, but this feature is masked in some tumors by intense vascularity. The texture is also somewhat variable. Fibrous stroma may be abundant, thereby imparting a firm consistency to the lesion, or the stromal component may be minimal.

Hyperplastic islets are frequently visible to the naked eye as pale specks on the surface of the slightly darker exocrine pancreas. When atrophy of the exocrine pancreas has occurred, hyperplastic islets are rendered more readily apparent.

### **MORPHOLOGY**

#### *ISLET CELL HYPERPLASIA (Figure 1)*

Hyperplasia of pancreatic islets is frequently observed in mature rats, especially in males. Hyperplastic islets may reach 500 microns in diameter and are composed of normal to slightly enlarged endocrine cells, having a round to oval nucleus and a prominent rim of pale eosinophilic, finely granular cytoplasm. hyperchromasia is less frequently seen. The cells are arranged in a typical islet pattern. There is no

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evidence of cellular atypia and mitotic activity is not elevated. Hyperplastic islets may contain a few hemosiderin-laden macrophages and mononuclear inflammatory cells; changes more likely to be seen in those islets having an increased fibrovascular stromal component. Hyperplastic islets usually arise individually and retain a regular outline, despite the overall increase in size. Alternatively, irregular foci may develop from the coalescence of two or more smaller islets. Hyperplasia does not affect all islets equally, and a single section may contain one to several hyperplastic islets in company with islets of normal size.

#### *ISLET CELL ADENOMA (Figures 2, 3)*

Adenomas of pancreatic islets are typically discrete and solitary lesions ranging in size from 1-10 mm in diameter. The tumor cells have a well-differentiated and generally uniform appearance. The cytoplasm of adenomatous islet cells usually retains its normal pale eosinophilia or is hypochromatic. Cytoplasmic vacuolation commonly, but not invariably, accompanies hypochromasia. Cytoplasmic hyperchromasia is less frequently seen. Cells vary from larger to smaller than normal. The nucleus usually appears quiescent and mitoses are rare. Occasional cells exhibit karyomegaly. Most tumor cells are polyhedral, but they may acquire a fusiform shape, especially in the subcapsular zone. Tumor cell arrangement often resembles that of normal islet tissue, with small groups of cells being separated by very fine fibrous trabeculae, but larger cell nests, ribbons, having polar nuclear orientation, and cords, are all to be found in islet cell adenomas. Multiple cellular arrangements are often represented in a single tumor.

The fibrous stromal response in islet cell adenomas is highly variable. The majority of adenomas have only scant fibrous trabeculae and minimal encapsulation, however, approximately 20% of tumors have prominent fibrous capsules and are intersected by more substantial fibrous trabeculae. Similar variability is encountered with respect to vascularity: most tumors have a moderate blood supply, but a minority are highly vascularized, ectatic or hemorrhagic. It is very common to observe groups of incarcerated acinar cells, and less frequently ductular remnants, within islet cell adenomas and occasionally within the tumor capsule. The acinar cells appear to be isolated piecemeal from the surrounding normal pancreas. As a result of compression within the tumor, the acini may assume an ellipsoidal shape. Trapped acinar cells occasionally exhibit hypertrophy, possibly due to paracrine stimulation by adjacent tumor cells, but atrophy is a more frequent outcome. Most tumor growth appears to be by expansion, however focal tumor projections may sometimes be seen extending into the normal pancreatic tissue. This excursion probably

occurs in areas of reduced resistance to cell growth and does not appear to signal aggressive tumor behavior.

#### *ISLET CELL CARCINOMA (Figures 4, 5, 6, 7)*

Islet cell carcinomas are differentiated from their benign counterparts on the basis of cellular anaplasia, local invasion and distant metastasis. Carcinomas have macroscopic features similar to adenomas, however a distinct capsule is more often present. Cell growth occurs in nests, sheets, cords or ribbons. The neoplastic cells vary from large, with copious pale eosinophilic cytoplasm and vesicular nuclei, to small, with hyperchromatic round to oval nuclei of varying size and condensed amphophilic cytoplasm. Karyomegalic cells may be numerous in some lesions. Two to four mitotic figures per high power field are usual for more anaplastic lesions. Local invasion is the most common indication of malignancy in islet carcinomas. Tumor infiltration of local areas may be accomplished by insinuating cords of tumor cells, but a more typical finding is expansile growth in which remnants of successively violated fibrous capsules are identifiable within the tumor. Distant metastases are most uncommon, but they have been observed in the liver.

#### *MIXED ACINAR-ISLET CELL TUMORS (Figures 8, 9, 10)*

The presence of neoplastic populations of both endocrine and exocrine pancreatic cells is a prerequisite for pancreatic mixed tumors. Most lesions share the macroscopic and microscopic features of benign islet cell tumors, supplemented by a population of generally well-differentiated exocrine cells. The latter cells must be present in sufficient numbers to indicate replication within the lesion, or they should show a convincing level of mitotic activity. Occasional mixed tumors exhibit histological features of malignancy: moderate cellular anaplasia and local invasiveness.

Endocrine and exocrine elements in mixed tumors are usually separate and clearly recognizable, however, in some of the more aggressive mixed tumors, an intermediate-type cell occurs, which has cytologic features of incompletely differentiated endocrine and exocrine pancreatic cells (4). Intermediate-type cells in mixed tumors may coexist together with differentiated acinar and islet cells.

#### *HEPATOCYTE METAPLASIA (Figure 11)*

A peri-insular zone of acinar cells, one to four cells wide, occasionally undergoes metaplasia to resemble typical hepatocytes.

As an incidental finding in adult rats, the change usually involves one islet in a section. The other islets

are unaffected. Several experimental methods, including treatment with peroxisome proliferating agents, administration of methyl group deficient diets, and a copper depletion-repletion protocol (5) will induce the change in the rat.

### DISCUSSION

Proliferative lesions of the endocrine pancreas have not been associated with clinical changes referable to excess insulin production. This is so despite observations of hyperinsulinemia in mature rats with islet cell hyperplasia (6), and evidence that the majority of islet cell tumors produce detectable insulin. The question is unresolved as to whether insulin produced by rat islet cell tumors possesses biological activity as it does in man, in whom hypoglycemia is commonly observed as a complication of insulinoma (1). If, in fact, rat tumor insulin does prove to be active, the progressive blunting of insulin responsiveness occurring in aged rats (6) may explain the absence of clinical effects.

Comparison of the histological appearance of the various pancreatic islet cell proliferations highlights several features useful for their differentiation. Islet cell hyperplasia most commonly affects multiple, albeit, on occasion widely scattered, islets and exhibits a cellular growth pattern closely resembling that of normal islet tissue. By contrast, adenomas usually occur singly and possess ranges of abnormal growth patterns, stromal proliferation and vascularization which enable them to be differentiated from hyperplasias. Islet cell carcinomas may be separated from adenomas on the basis of any one or more of the following features: cellular anaplasia, marked local invasiveness usually with capsular penetration, and distant metastasis. Mixed acinar-islet cell tumors most closely resemble islet cell adenomas, and possess, in addition, a population of proliferating acinar cells and/or intermediate-type pancreatic cells.

### NOMENCLATURE AND DIAGNOSTIC CRITERIA

#### ISLET CELL HYPERPLASIA

1. Hyperplastic islets may reach 500 microns diameter
2. All islets are not usually affected
3. No compression of surrounding acinar tissue
4. Islets are regularly enlarged
5. Adjacent islets may coalesce
6. Endocrine cells are usually of normal size
7. Endocrine cells possess normal tinctorial properties

#### ISLET CELL ADENOMA

1. Adenomas are usually solitary nodules 1-10 mm diameter
2. Compression of surrounding tissue usually occurs
3. Encapsulation and/or trabeculation may or may not be present
4. Degree of vascularization is highly variable
5. Tumor cells may be larger or smaller than normal
6. Tumor cells may be darker or paler than normal
7. Cellular growth patterns include sheets, nests and ribbons
8. Individual tumors may possess more than one growth pattern
9. Detached acinar cells may be included within the tumor

#### ISLET CELL CARCINOMA

1. Carcinomas share many features with adenomas
2. Usually solitary nodules 5-10 mm diameter
3. Evidence of malignancy includes, cellular anaplasia, local invasion, and rarely, distant metastasis
4. Tumor cells may be larger or smaller than normal
5. Tumor cells may be darker or paler than normal
6. Tumor cells are polyhedral, fusiform or pleomorphic
7. Mitotic activity is moderate
8. Cellular growth patterns include nests, sheets and ribbons

#### MIXED ACINAR-ISLET CELL TUMOR

1. Mixed tumors share many features with islet cell adenomas
2. Evidence of acinar cell proliferation is required
3. Endocrine and exocrine cell types are usually clearly identifiable
4. Intermediate-type cells having features of Islet and acinar cells may be present

#### HEPATOCYTE METAPLASIA

1. Peri-insular cells resembling normal hepatocytes
2. Multiple islets may be affected

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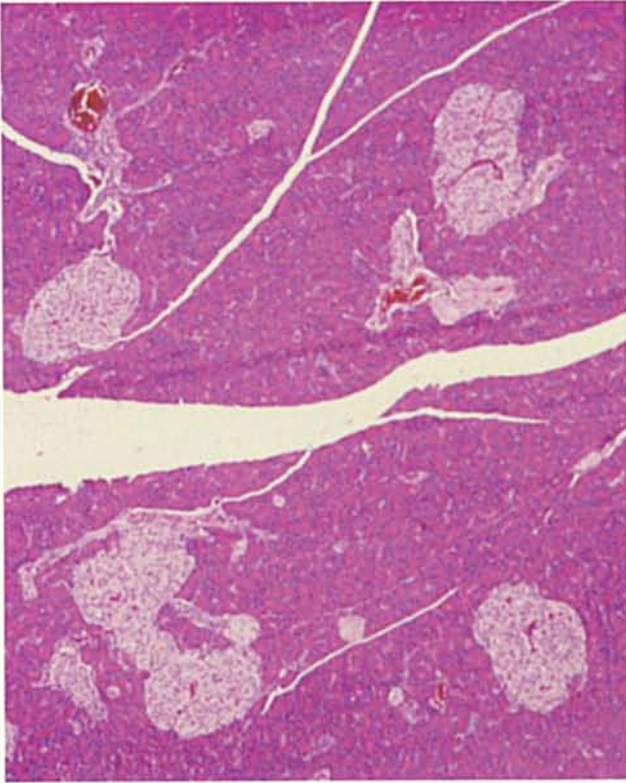


Fig.1 Islet Cell Hyperplasia - Several hyperplastic islets are shown, including two undergoing coalescence. (H&E, 38.4x)

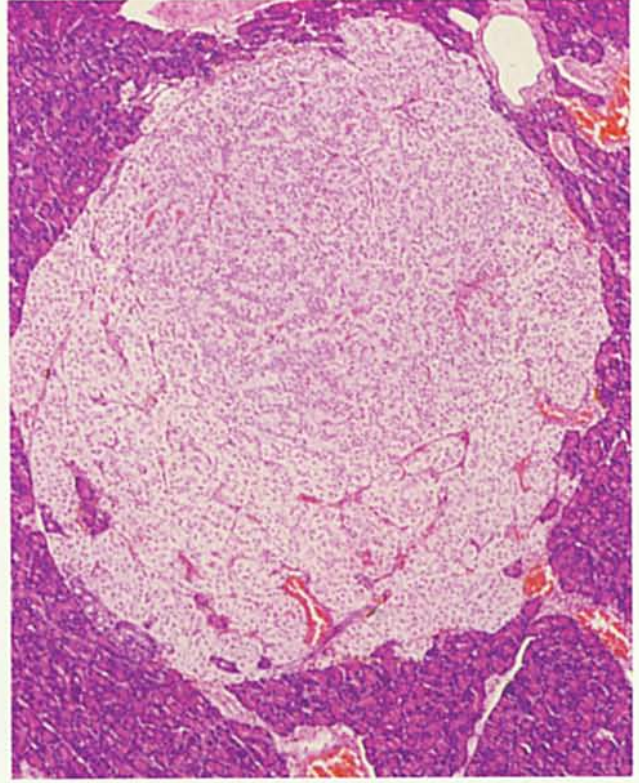


FIG. 2. Islet Cell Adenoma - A discrete unencapsulated nodule containing a small number of entrapped acini. (H&E, 38.4x)

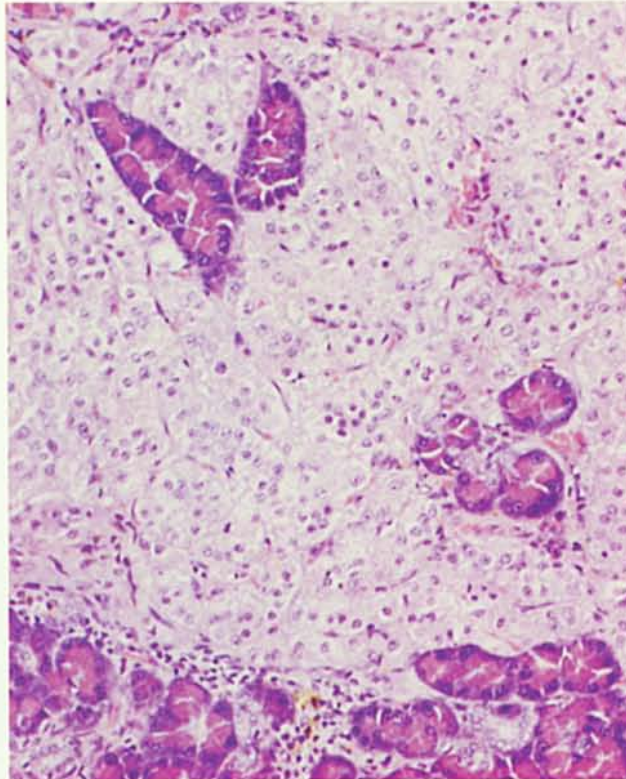


FIG. 3. Islet Cell Adenoma - A higher power view of entrapped acinar cells. (H&E, 120x)

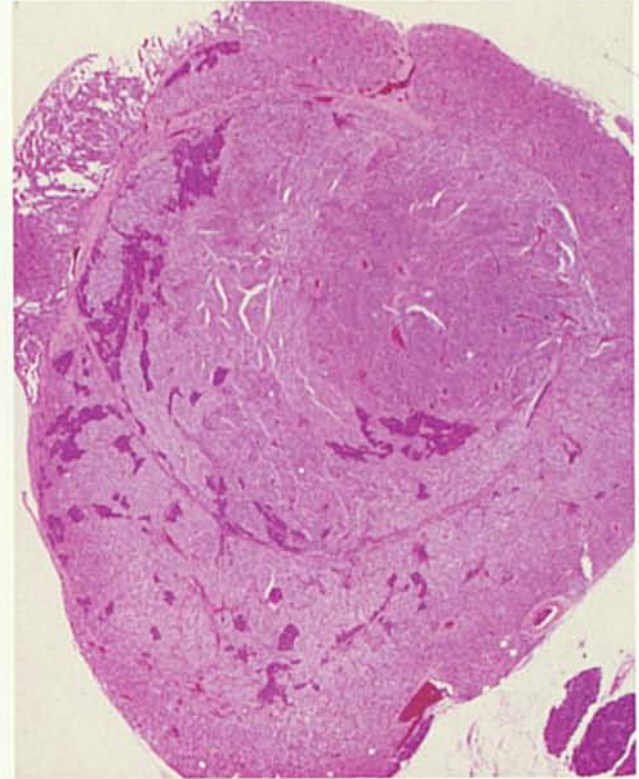


FIG. 4. Islet Cell Carcinoma - A nodular mass with growth extending beyond the primary capsule. (H&E, 12x)

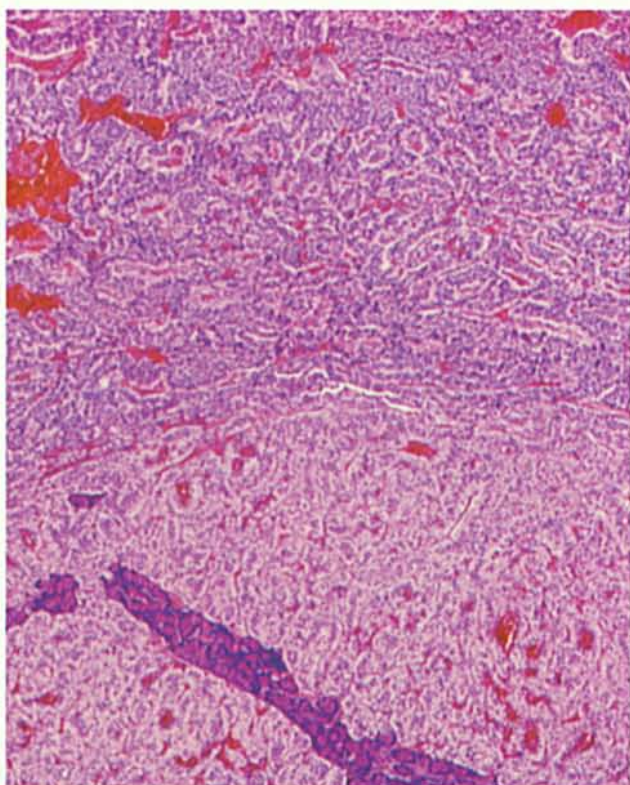


FIG. 5. Islet Cell Carcinoma - Interface of ribbon and nest tumor cell growth patterns. (H&E, 38.4x)

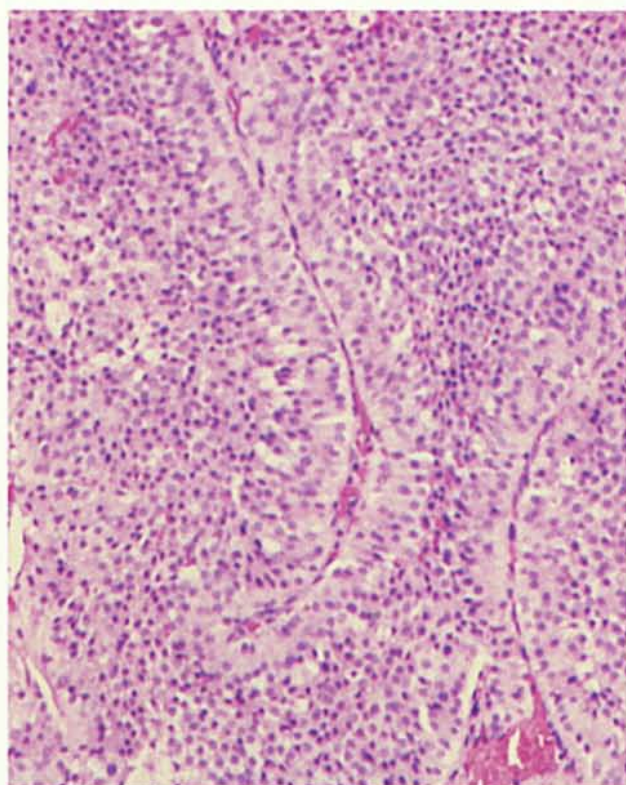


FIG. 6. Islet Cell Carcinoma - Interface of ribbon and sheet tumor cell growth patterns. Polar orientation of endocrine cell nuclei within the ribbon is evident. (H&E, 120x)

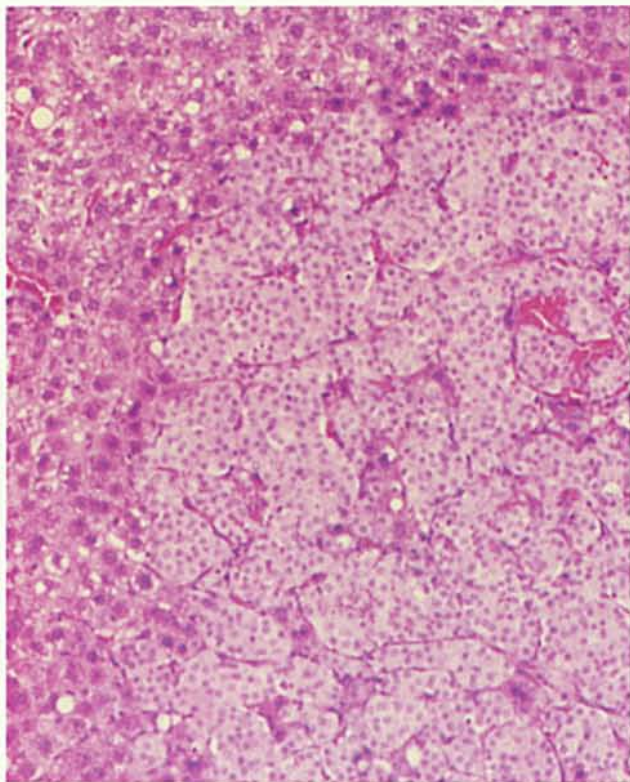


FIG. 7. Islet Cell Carcinoma - Liver metastasis. (H&E, 96x)

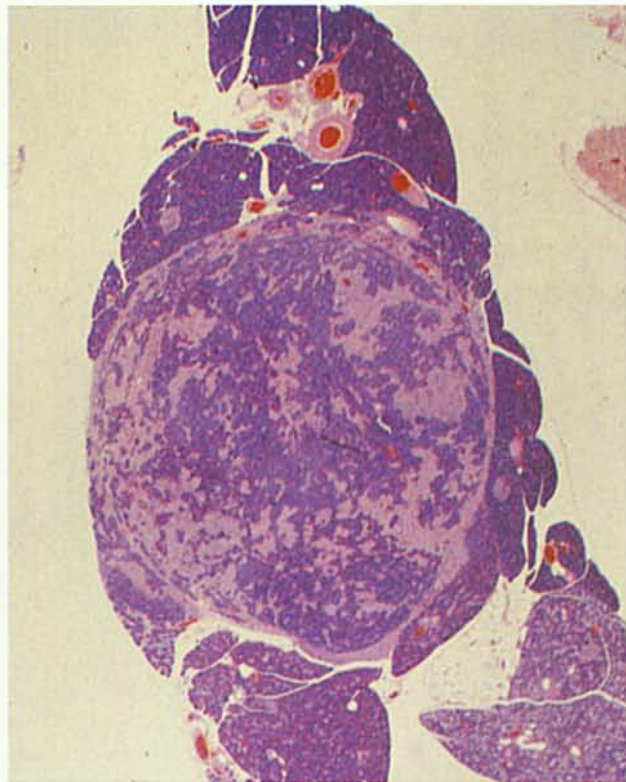


FIG. 8. Mixed Acinar-Islet Cell Tumor - Encapsulated nodule containing islet cells and acini in approximately equal proportions. (H&E, 9.6x)

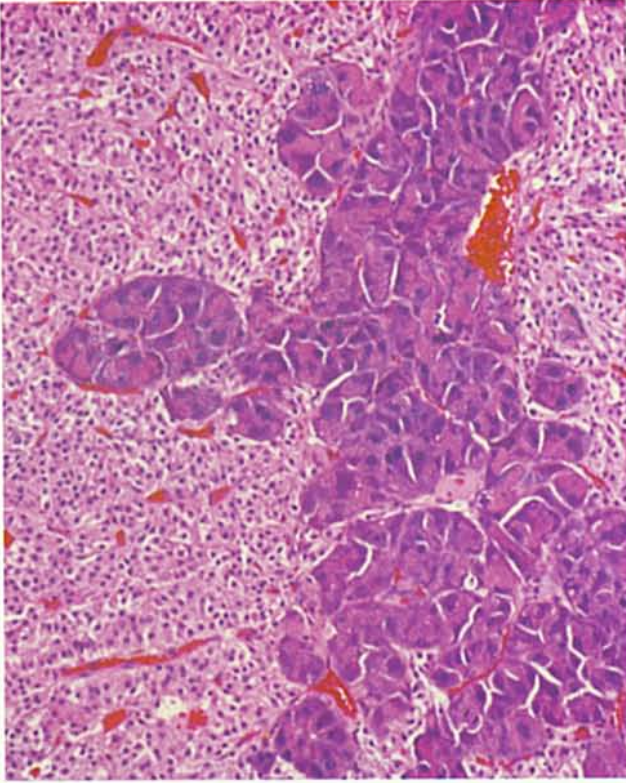


FIG. 9. Mixed Acinar-Islet Cell Tumor - Higher magnification of Figure 8. Acinar cells have reduced zymogen granule complement and are mitotically active. (H&E, 96x)

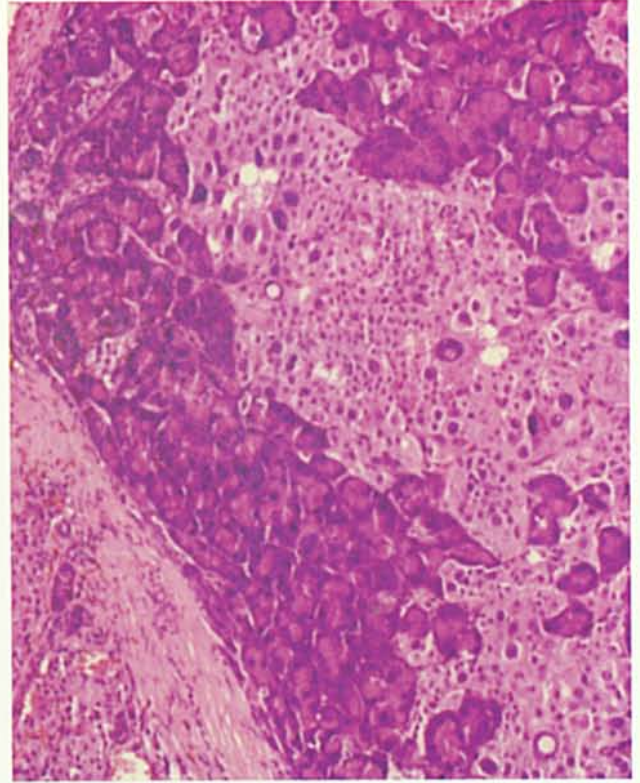


FIG. 10. Mixed Acinar-Islet Cell Tumor - Intermediate-type cells in a locally invasive mixed tumor. (H&E, 79.2x)

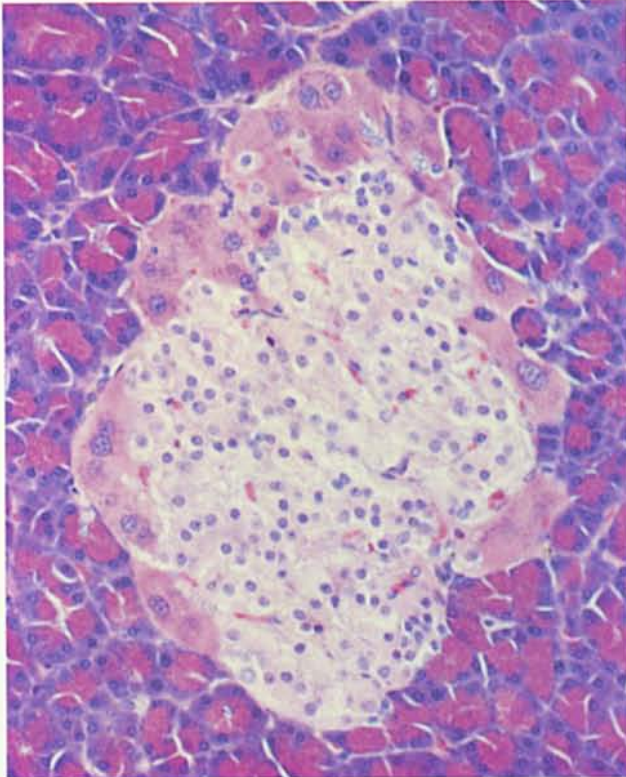


FIG. 11. Hepatocyte Metaplasia. (H&E, 158.4x)