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PROLIFERATIVE AND OTHER SELECTED LESIONS OF THE EXOCRINE PANCREAS IN RATS

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INTRODUCTION

The pancreas is a lobulated gland containing exocrine and endocrine secretory units (1). The exocrine pancreas is divided into rhomboid lobules composed of acinar cells arranged in a tubuloacinar pattern. Acini are irregularly oval to elongated glands containing a single layer of pyramidal cells with the base of the cells resting on the basal lamina and scant stroma (2).

Proliferative lesions of the exocrine pancreas are the subject of the following classification criteria; selected non–proliferative lesions that have the potential to be confused with proliferative lesions are also included. The classification provided here is intended to reflect the biology of the lesions as well as to provide consistency in the classification of neoplasms and non-neoplastic proliferative lesions. Consistency of diagnosis is important in toxicologic pathology so that meaningful historical control data can be compiled and utilized, and so that accurate and meaningful comparisons can be made of histopathologic data from different studies.

MORPHOLOGY

PROLIFERATIVE LESIONS

Focal Acinar Cell Hyperplasia (Figure 1)

Many foci of acinar cell hyperplasia are too small to be detected at necropsy. However, lesions that exceed 1 to 2 mm can be grossly detected as discrete spherical or oval non-encapsulated nodules of otherwise normal pancreatic tissue. As a general rule, as lesions increase in size the probability increases that they will fall within the classification of adenoma, rather than focal hyperplasia (see discussion section for size criteria).

Focal acinar cell hyperplasia is a well-circumscribed spherical or oval lesion with a prominent tubular glandular pattern resulting from enlargement and elongation of the constituent acini. Hyperplastic acinar cells are often more eosinophilic than normal due to an apparent increase in zymogen granules. Nuclei may be slightly enlarged with prominent nucleoli. Mitotic figures and individual cell necrosis (apoptosis) are usually encountered in low numbers. There is often some degree of compression of adjacent parenchyma and some enlargement and rounding distortion of the rhomboid lobular pattern. Islets may be present within hyperplastic foci.

Acinar Cell Adenoma (Figures 2–4)

Adenomas are often single round, oval, or multilobular discrete masses, and may or may not possess a grossly detectable capsule (3). They are usually large enough to be easily seen grossly (see discussion section for size criteria). Their color and texture is usually indistinguishable from normal pancreatic tissue.

Adenomas are discrete round to oval lesions with a prominent tubular glandular pattern resulting from enlargement and elongation of the constituent acini.

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Enlargement of the glandular constituents may result in solid areas of tumor development. Islets are usually not present within adenomas. Adenomatous acinar cells are often more eosinophilic than normal due to an apparent increase in zymogen granules. Nuclei may be slightly enlarged with prominent nucleoli. Mitotic figures and individual cell necrosis (apoptosis) are commonly encountered in low numbers. There is always some degree of compression of adjacent parenchyma. Enlargement and rounding distortion of the rhomboid lobular pattern of the affected lobule is severe. There may be a delicate capsule of compressed stromal elements surrounding the larger adenomas.

Acinar Cell Carcinoma (Figures 5–7)

Carcinomas are variable in size, but often attain a diameter in excess of 1 cm. They may be adhered to adjacent abdominal organs. Areas of necrosis, hemorrhage, or fibrosis may be grossly discernible. Metastasis or direct extension to other organs is not often grossly demonstrable.

Carcinomas have a lobular architecture, often with morphological patterns varying from acinar, tubular, or solid within the same tumor (4). Vascular components and blood filled spaces may be conspicuous in parts of the tumor. The neoplastic acinar cells are frequently, but not always, well-differentiated and contain abundant zymogen granules (5). Tumor cells usually have large irregular vesicular nuclei, abundant basophilic to eosinophilic cytoplasm, and in some areas are arranged in a typical acinar pattern. Varying degrees of anaplasia are common within carcinomas. A partial or complete fibrous capsule and varying degrees of fibroplasia may be present. The tumor should show evidence of anaplasia, invasion, direct extension to adjacent tissues, or metastasis to be classified as a carcinoma.

Well-differentiated pancreatic acinar cell carcinomas are unlikely to be confused with carcinomas of other origins, but must be differentiated from acinar cell adenomas. Morphologic features favoring the diagnosis of acinar cell carcinoma over acinar cell adenoma include a variable growth pattern, well-vascularized areas, fibroplasia, and multiple glandular patterns (4). Invasion, direct extension, or metastasis of the tumor is proof of malignancy. Poorly differentiated acinar carcinomas must be differentiated from islet cell carcinomas and other metastatic carcinomas. Immunohistochemical expression of acinar cell enzymes (a_1-trypsin, a_1-chymotrypsin) and lack of pancreatic hormone expression, as well as electron microscopy, may aid diagnosis (6,7). However, even poorly differentiated acinar cell carcinomas in the rat tend to contain areas of reasonably well-differentiated acinar cells with zymogen granules, which make identification more certain.

NON–PROLIFERATIVE LESIONS

Focal Basophilic Alteration (Figure 8)

Focal basophilic alteration is not observed grossly. This alteration consists of small focal lesions usually involving only part of a lobule. The foci are composed of hypertrophic acinar cells with abundant basophilic cytoplasm (H & E stain) containing fewer zymogen granules than normal cells. The nuclei are enlarged with prominent nucleoli and are basal to parabasal in location. Mitotic figures are occasionally present. However, there is no compression of adjacent pancreatic parenchyma.

Focal Hepatocyte Metaplasia (Figure 9)

Focal hepatocyte metaplasia is not observed grossly. Focal hepatocyte metaplasia is frequently located in the peri-insular parenchyma or occasionally in small isolated focal aggregates. These cells have the morphologic characteristics of well-differentiated hepatocytes by light and electron microscopy (8).

DISCUSSION

While the exocrine pancreas is not a frequent site of toxic effects, necrosis of the parenchyma (whether it is chemically induced or the result of inflammation) is followed by some degree of regeneration. When the extent, distribution, and/or duration of necrosis is sufficient, the pancreatic regeneration may produce nodular lesions with some similarity to the proliferative lesions described above. Regeneration should be distinguished from focal acinar cell hyperplasia or adenoma on the basis of identifying the presence or absence of an underlying destructive process that could reasonably account for the proliferative acinar cell lesions in question.

The diagnoses of acidophilic or eosinophilic foci were specifically omitted within this classification scheme because they are the histological equivalent of small focal hyperplasias (12), and should be considered as synonyms for focal acinar cell hyperplasia.

The criteria used to differentiate between the larger focal acinar hyperplasias and acinar cell adenomas is somewhat arbitrary and not universally applied. For this reason, the reported incidences of pancreatic acinar tumors may vary markedly according to the diagnostic criteria selected (10,13), thus making historical comparisons with published data very difficult and imprecise.

This difficulty is created because there is a histologic continuum between focal acinar hyperplasias and acinar cell adenomas (3,5,9,13,14). While the size of a lesion should not in itself be the criterion for a diagnosis,

it can help add consistency in the application of diagnostic terms. The hallmarks of adenoma include sharp demarcation with compression of adjacent tissue and alteration of the tubuloacinar gland architecture to one that is predominantly tubular. Since larger lesions are more likely to display these characteristics, the size of lesions should be considered in differentiating between hyperplasias and adenomas.

The transplantation potential of acinar cell adenomas measuring 3 to 6 mm has been evaluated (5). In this study, only 3 out of 17 recipients of adenomas still had acinar cell nodules remaining after 3 months, and no acinar cell nodules were found in a second set of recipients after an additional 3 months. The general lack of successful transplantation attempts using these smaller sized proliferative lesions does not support a diagnosis of neoplasia for them. Since the morphologic and biologic continuum progresses with size, only the larger lesions can reasonably be expected to demonstrate biologic activity indicative of neoplasia. Thus, it is suggested that the diagnosis of adenoma be applied to well differentiated proliferative acinar lesions that equal or exceed 5 mm in diameter. This size criteria for the diagnosis of adenoma should be more consistent with the true biologic activity of the lesion than previous recommendations of 3 mm (4,5).

The morphologic continuum of acinar cell hyperplasia, adenoma, and carcinoma likely correlates with a biologic continuum. However, the rate of regression or progression of focal acinar cell hyperplasia or adenoma is unknown in most cases, and may vary with the properties of the inducing chemical or drug or with the mechanism of induction. Genotoxic compounds that are potent pancreatic carcinogens (azaserine, for example) may cause a higher and more rapid rate of progression to carcinoma than compounds that produce proliferative lesions through epigenetic mechanisms. Further, while focal acinar cell hyperplasia or adenoma may have a certain probability of progression, it is not axiomatic that they progress to carcinomas.

A concerted effort to be consistent in the differentiation between focal hyperplasia and adenoma is essential in chronic oncogenicity studies. Since there is no clear morphologic difference between large focal hyperplasias and small adenomas, size may often be the only determinant that will allow reproducible diagnostic results. Without some consideration as to the size of the lesions, comparisons of study data with historical data are almost meaningless. However, the judgment of the pathologist will determine how diagnoses are applied within a study.

The non–proliferative lesions, focal basophilic alteration and focal hepatocyte metaplasia, are included in this nomenclature scheme because they have an architecture that could be confused with a proliferative lesion. Basophilic foci are generally thought not to progress to tumors, and should not be included in the spectrum of proliferative lesions of the acinar pancreas (9,10). Focal hepatocyte metaplasia is thought to represent a differentiation of existing stem cells in the pancreas into hepatocytes, and is not a part of the spectrum of proliferative acinar cell lesions (8,11,12).

Recommended Nomenclature and Diagnostic Criteria for Proliferative and Other Selected Lesions of the Exocrine Pancreas

PROLIFERATIVE LESIONS

Focal Acinar Cell Hyperplasia

1. Spherical or oval alteration of the angular shape of the lobule
2. Small in size (usually less than 5 mm diameter)
3. Comprised of enlarged, elongated tubular glandular units
4. Cells often have increased eosinophilic zymogen granules
5. Occasional mitotic figures and individual cell necrosis (apoptosis)
6. May compress adjacent normal lobules

Acinar Cell Adenoma

1. Spherical or oval alteration of the angular shape of the lobule
2. Moderate to large in size (usually 5 mm or greater in diameter)
3. Comprised of enlarged, elongated tubular glandular units; may have some solid areas in larger adenomas
4. Cells may have increased eosinophilic zymogen granules
5. Occasional mitotic figures and individual cell necrosis (apoptosis)
6. Compresses adjacent lobules

Acinar Cell Carcinoma

1. Mass comprised of acinar, tubular, or solid cell patterns
2. Cell patterns often mixed in the same tumor
3. Variable numbers of cells are recognizable as acinar cells depending on the state of differentiation and zymogen granule content
4. Nuclei are usually large and vesicular
5. Fibroplasia within and around mass not

uncommon
6. Vessels and blood-filled spaces may be conspicuous
7. Invasion, direct extension to adjacent tissues, or metastasis are usually demonstrated

NON–PROLIFERATIVE LESIONS

Focal Basophilic Alteration

1. Usually sublobular in size
2. Comprised of hypertrophic cells with abundant basophilic cytoplasm
3. Nuclei and nucleoli are large and prominent
4. Does not compress adjacent tissue
5. Mitotic figures not common

Focal Hepatocyte Metaplasia

1. Frequently located around islets
2. Closely resembles normal hepatocytes

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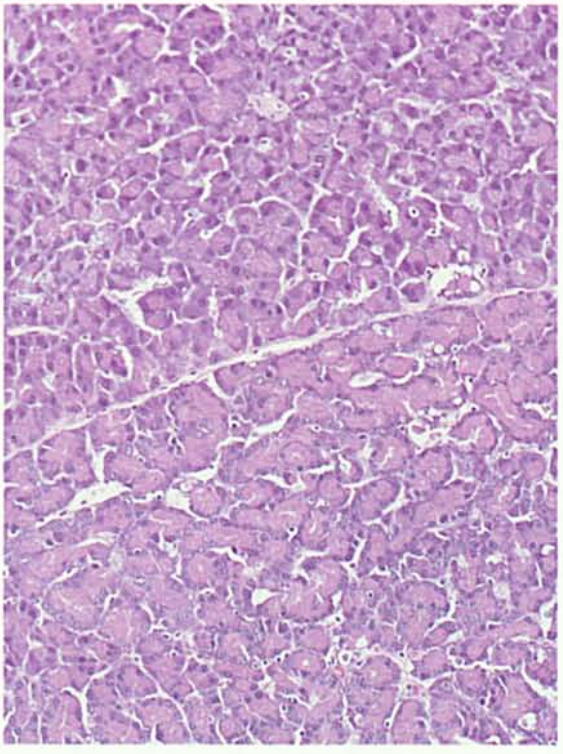

Fig. 1 – *Focal acinar cell hyperplasia. Elongated tubuloglandular units of slightly more eosinophilic cells. There is a distinct boundary between hyperplastic and normal pancreatic parenchyma. (H&E)*

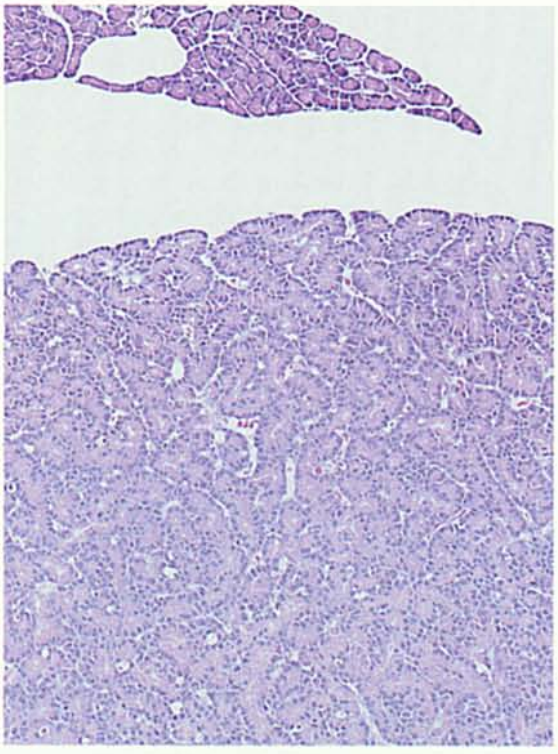

Fig. 2 – *Acinar cell adenoma has a tubuloglandular morphology similar to focal acinar cell hyperplasia in Fig. 1. (H&E)*

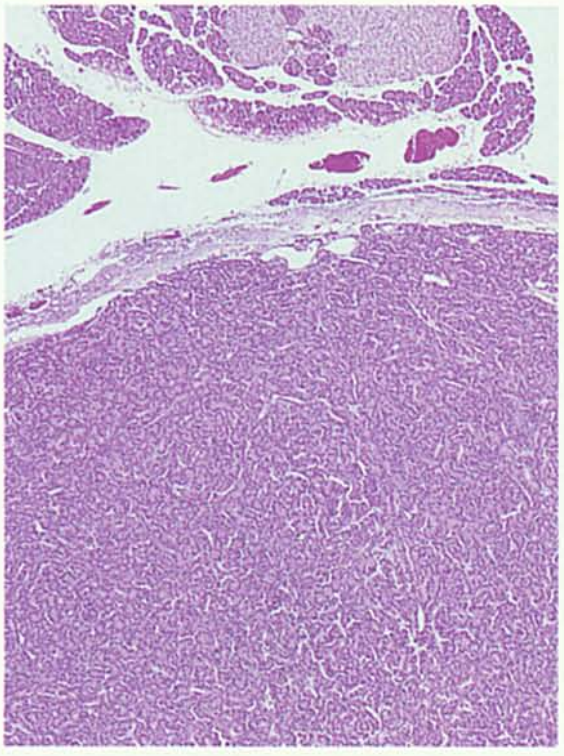

Fig. 3 – *Acinar cell adenoma with a capsule of collapsed stroma and connective tissue. The neoplasm is like other adenomas which lack a capsule. (H&E)*

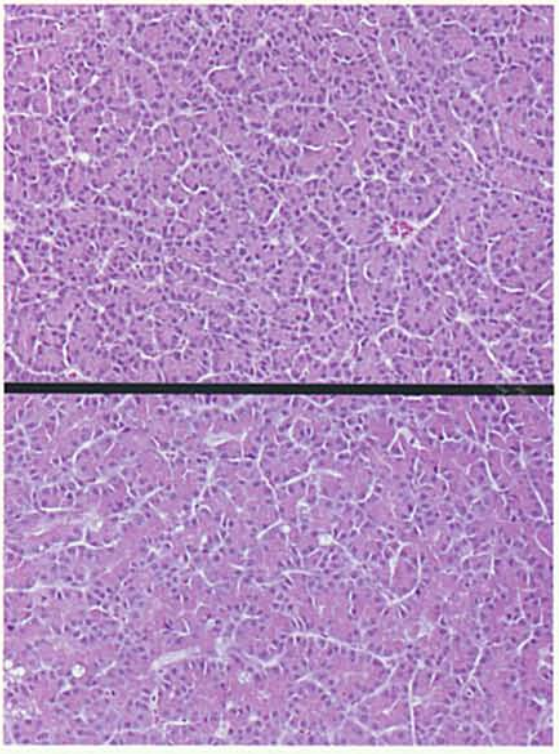

Fig. 4 – *Acinar cell hyperplasia (top) and adenoma (bottom). Note the morphologic similarity; both lesions display a prominent tubuloglandular pattern. (H&E)*

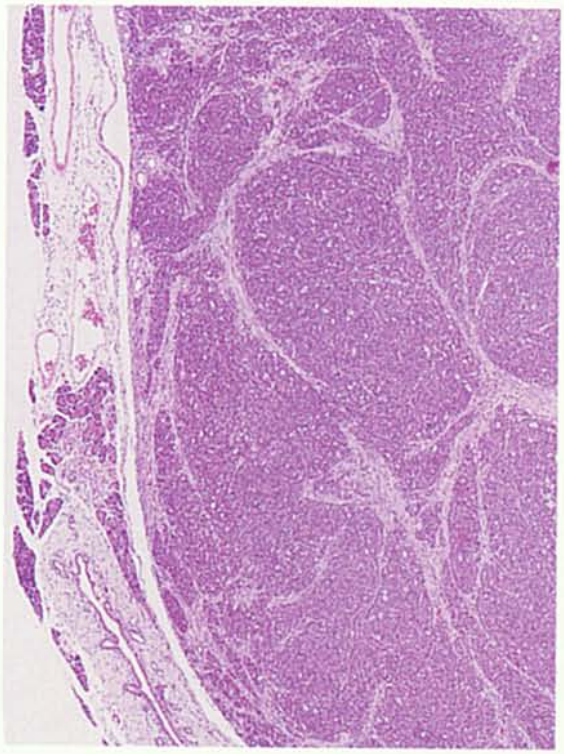

Fig. 5 – *Acinar cell carcinoma. Prominent connective tissue stroma separates solid masses of tumor cells. (H&E)*

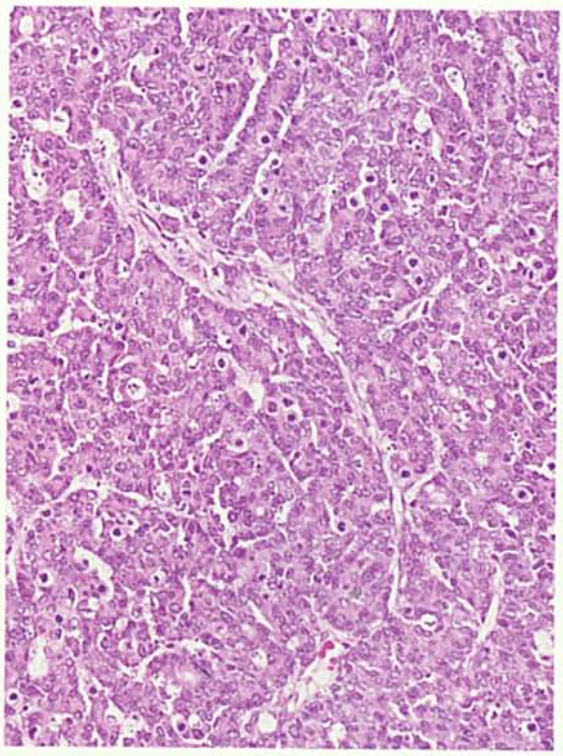

Fig. 6 – *Acinar cell carcinoma. A higher magnification of the tumor in Figure 5 showing a tubuloacinar pattern and many mitotic figures. (H&E)*

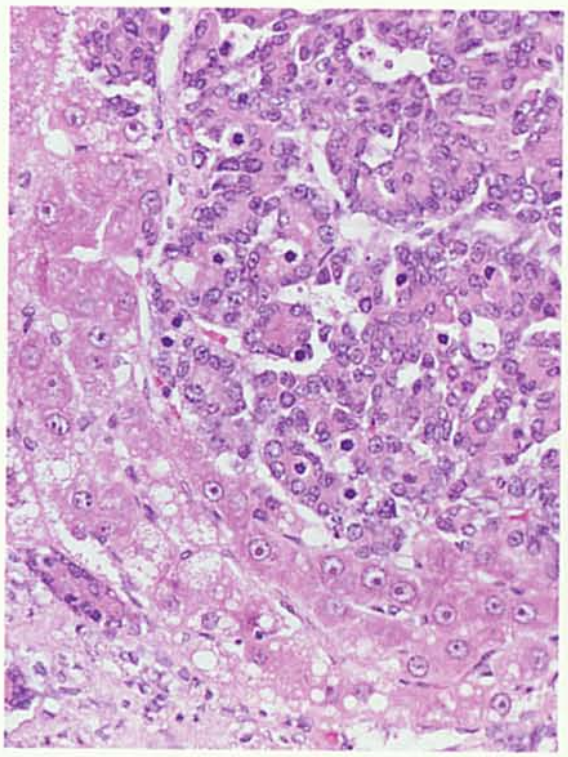

Fig. 7 – *Acinar cell carcinoma. A metastatic focus of acinar cell carcinoma within the liver. The tubulo-glandular pattern and tumor cells containing zymogen granules are apparent. (H&E)*

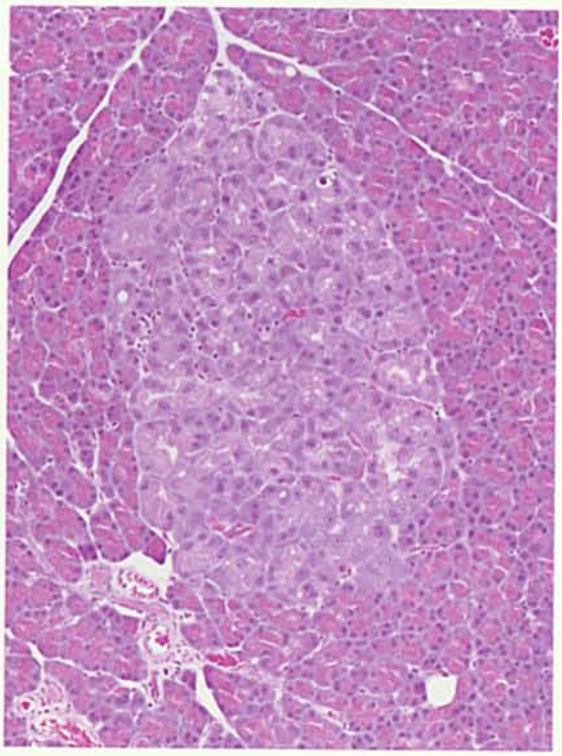

Fig. 8 – *Focal basophilic alteration (non–proliferative). Discrete area composed of hypertrophic acinar cells with abundant basophilic cytoplasm. Nuclei and nucleoli are large and prominent. (H&E)*

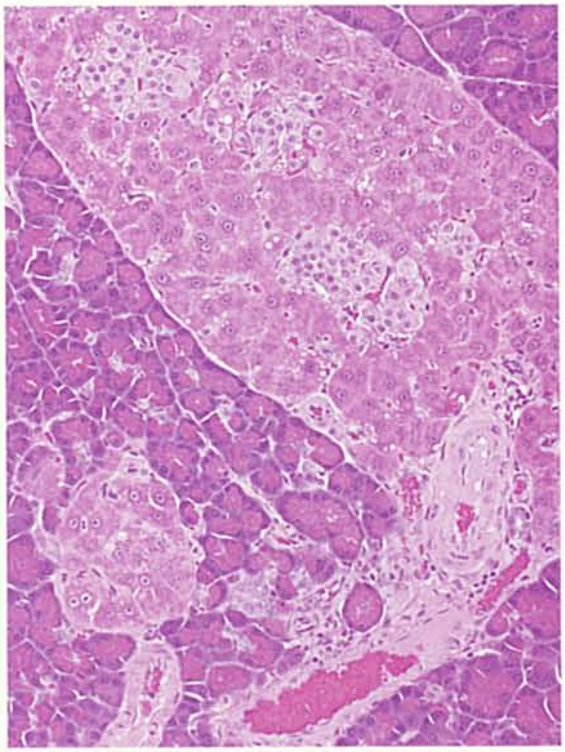

Fig. 9 – *Focal hepatocyte metaplasia (non–proliferative). These peri-insular cells have the morphologic characteristics of well differentiated hepatocytes. (H&E)*