10 Pancreas

The Whipple Procedure

The Whipple procedure is, at minimum, a pancreaticoduodenectomy, which may or may not also include pylorus of the stomach and the gallbladder. In the pylorus-preserving Whipple procedure, the simplest version, you receive the segment of duodenum from just past the pylorus to about 20 cm beyond the ampulla of Vater. The head of the pancreas is nestled in the curve of the duodenum near the ampulla; the pancreas is shaped like a J, and the head is the base of the J, with the uncinate process as the hook. The distal common bile duct runs through the pancreas and enters the ampulla, where it is joined by the main pancreatic duct (Figure 10.1). Usually it is only the head of pancreas that comes out; if the tail is also involved, you may get the total pancreas and spleen.

There are five principal margins that are usually sampled on frozen section (see Figure 10.1). The first is the pancreatic margin, or the *pancreatic neck* (where the J is transected). This is usually taken as a shave margin, sampling the entire cross section of pancreas, and cancer anywhere on the slide is a positive margin. There is no neck margin on a total pancreatectomy.

The second margin is the *common bile duct margin*, which is a shave of the bile duct stump. This ensures that cancer is not tracking up the bile duct toward the liver.

The third is the *uncinate margin*. This is the tip of the short end of the J, and it represents the place where the pancreas sits against the major vessels. For the uncinate, you should take one representative perpendicular margin, and the edge of the tissue is inked. Cancer on the slide is okay, as long as it does not touch ink. As this tissue abuts major vessels, the surgeon often cannot resect additional tissue anyway.

The fourth and fifth margins are the *proximal* and *distal duodenal margins*. It is rare for these sections to contain tumor.

Most Whipple procedures are performed for a pancreatic mass seen radiologically. Although it is possible to get a cancer diagnosis by fine-needle aspiration, this is not always performed, and false-negative results are not uncommon. Therefore, often our first look at the tumor is during the Whipple procedure.

The Normal Pancreas

The normal pancreas is a large mixed exocrine and endocrine gland, with acinar cells arranged around ducts in lobular units. The acinar cells secrete digestive enzymes in precursor forms, which travel to the duodenum via the ducts. Normal ducts are low cuboidal epithelium, and the acinar cells are wedge-shaped granular pink and purple cells (Figure 10.2). Scattered among

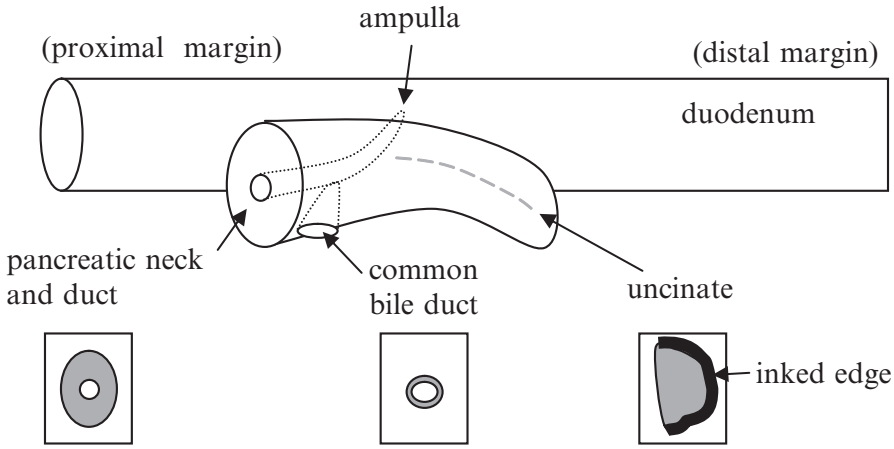

Figure 10.1. Diagram of specimen obtain during a Whipple procedure. The head of the pancreas comes out attached to a segment of duodenum. The main pancreatic duct is visible at the pancreatic neck margin (a surgical margin). The common bile duct enters the pancreas to join the pancreatic duct (also a surgical margin). The uncinate process is the tip of the pancreas, and its edge abuts major vessels (a soft tissue margin).

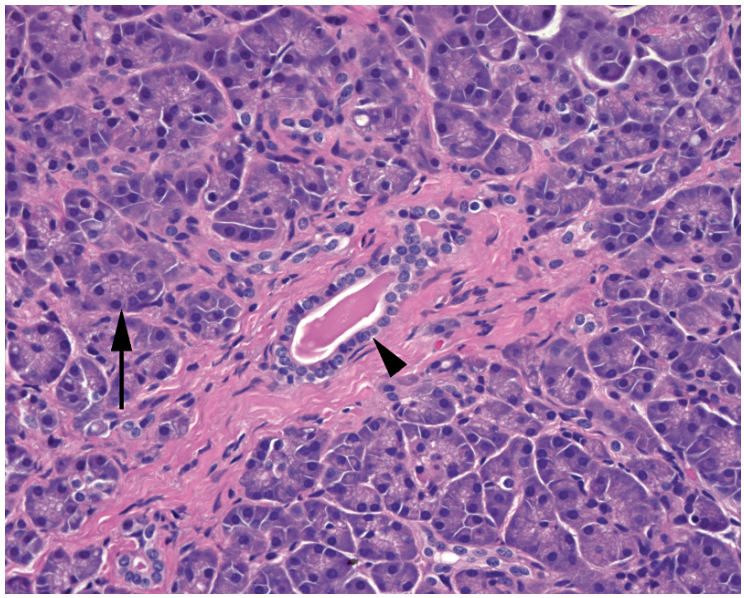

Figure 10.2. Normal pancreatic acinus. The duct is seen at the center (arrowhead), with surrounding acini of secretory cells (arrow).

them are the neuroendocrine islets of Langerhans, which show typical neuroendocrine cytology and are arranged in little nests.

Chronic Pancreatitis Versus Ductal Adenocarcinoma

Chronic pancreatitis is not an uncommon finding in a resected pancreas. The damage done to the pancreas by chronic obstruction, as with a mass, causes diffuse fibrosis, atrophy of the acinar units, reactive changes, and disruption of the normal architecture, all of which can mimic carcinoma. One of the hardest tasks (especially on frozen section) is differentiating reactive

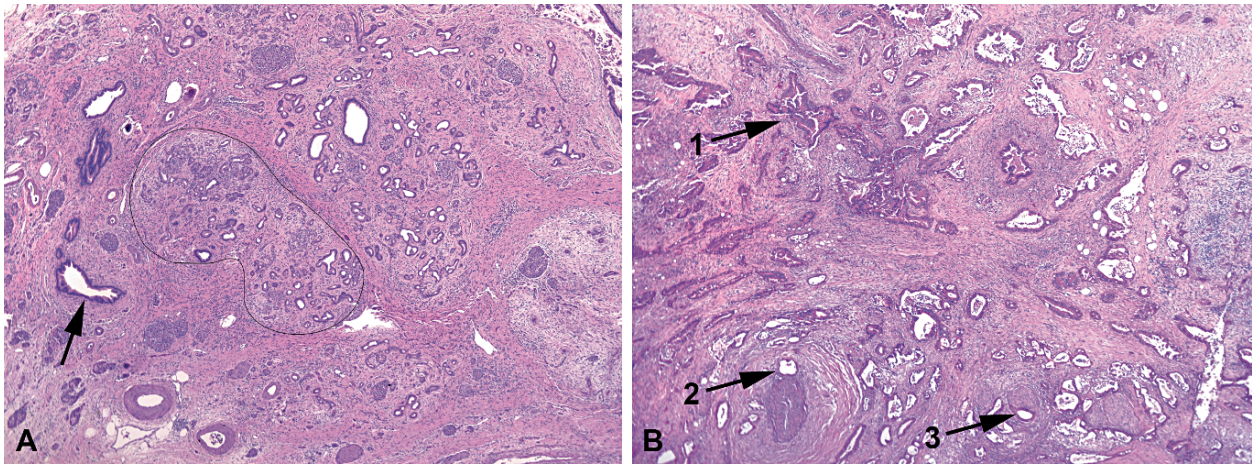

FIGURE 10.3. Chronic pancreatitis versus cancer, low power. **(A)** In chronic pancreatitis, the large ducts may show marked reactive changes, appearing blue and prominent, but they should still be located between lobules of acini (arrow). The acini show marked atrophy and fibrosis such that only the small ducts remain and appear infiltrative; however, the lobules retain a circumscribed outline (black line). **(B)** In adenocarcinoma, large, prominent, irregularly shaped ducts are scattered throughout, without respect to normal architecture (1). Large ducts next to vessels (2) or nerves (3) are diagnostic of cancer.

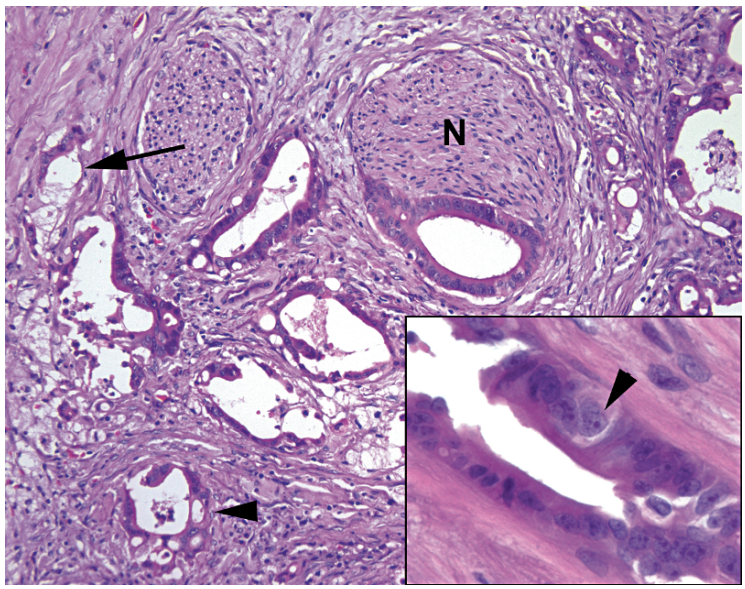

FIGURE 10.4. Adenocarcinoma. On high power, the infiltrative glands show incomplete lumens (arrow), cribriform growth pattern (arrowhead), and perineural invasion (N). **Inset**: Marked variation in nuclear size is diagnostic of cancer. Note the large nucleus with prominent nucleolus (arrowhead) across the gland from nuclei less than one fourth of its size.

pancreatic ducts from well-differentiated infiltrating adenocarcinoma, the most common pancreatic malignancy. Some tips include the following:

- Helpful but subjective
  - On low power, chronic pancreatitis has a lobular architecture, with large central ducts surrounded by smaller peripheral ones. Cancer is haphazard, with random and irregular distribution of glands (Figure 10.3).
  - Incomplete lumina, in which the luminal spaces are not symmetrically surrounded by nuclei, and luminal necrosis both point to a diagnosis of pancreatic cancer (Figure 10.4).

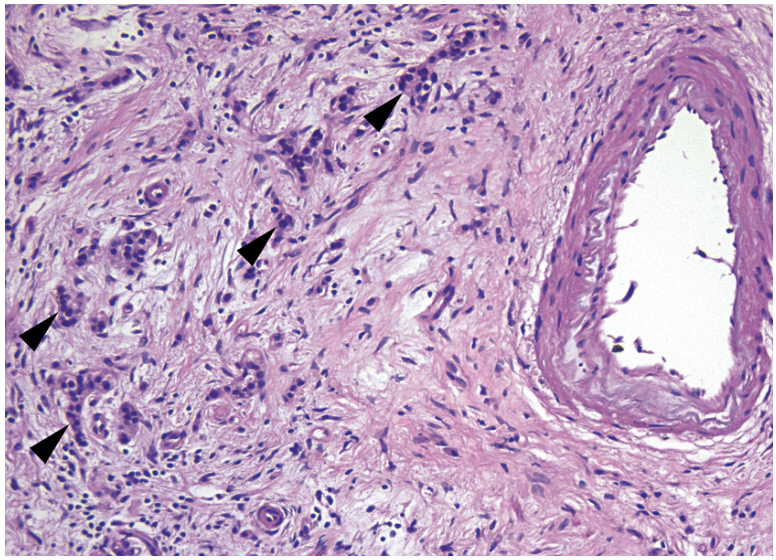

Figure 10.5. Residual islets of Langerhans. Neuroendocrine cells are among the last to go in chronic pancreatitis and appear to infiltrate through the fibrotic stroma (arrowheads). However, their small, round, dense, regular nuclei do not resemble pancreatic adenocarcinoma.

- Note cellular pleomorphism. In general, cancer tends to have hyperchromatic and irregularly shaped nuclei, mitoses, and necrosis (see Figure 10.4). You will hear of the "4:1 rule," which states that if, in one gland, one nucleus is four times the size (area) of another, it is cancer. However, chronic pancreatitis can lead to some more subtle atypia, and it does take some experience to tell the difference between a 4:1 ratio and a 3:1 ratio. Also, you will sometimes see well-differentiated pancreatic carcinoma with uniform nuclei.

- Not helpful
  - The fibrosis of chronic pancreatitis can look much like a desmoplastic stromal response. However, the pale edematous fibrosis can accentuate the lobular architecture of chronic pancreatitis, which is helpful.
  - Every intern dots all the benign islets of Langerhans on a pancreatic neck, usually missing the sneaky invasive stuff. Islets, in chronic pancreatitis, are essentially all that remains of the withered parenchyma, and therefore they look crowded, infiltrative, and haphazard (Figure 10.5). As is true for any endocrine cell, these cells can have some pleomorphism, and in some cases they can involve perineural spaces. Fortunately, the chromatin still looks neuroendocrine, so try to ignore them even though they really do look a little like lobular breast carcinoma.

- Freebies (even the beginner can interpret them)
  - Glands in a nerve, or perineural invasion, always indicate cancer.
  - Large ducts running next to a large muscular vessel almost always indicate cancer (Figure 10.6).
  - Ducts leaving the pancreas to infiltrate the duodenum always indicate cancer.

Dysplasia in the Pancreas

The pancreas is not an organ that can be evaluated with serial biopsies, and thus the natural history and malignant potential of dysplasia are not well understood. However, there are recognized grades of dysplasia within the duct system, called pancreatic intraepithelial neoplasia (PanIN). This ranges from PanIN 1, which may overlap with hyperplastic or reactive changes, to PanIN 3, which is carcinoma in situ. A lesion should always be graded by the highest level of dysplasia seen.

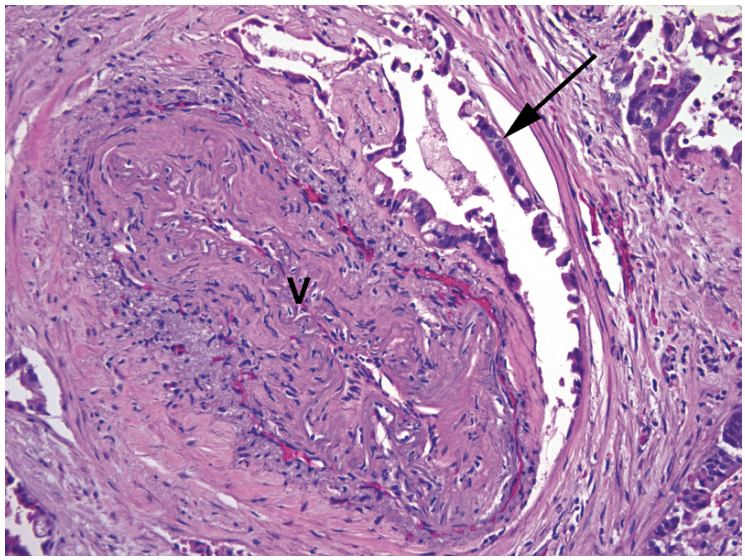

Figure 10.6. Adenocarcinoma next to a vessel. Large duct-like structures (arrow) next to a large-caliber vessel (V) are almost certainly cancer, even if deceptively well differentiated.

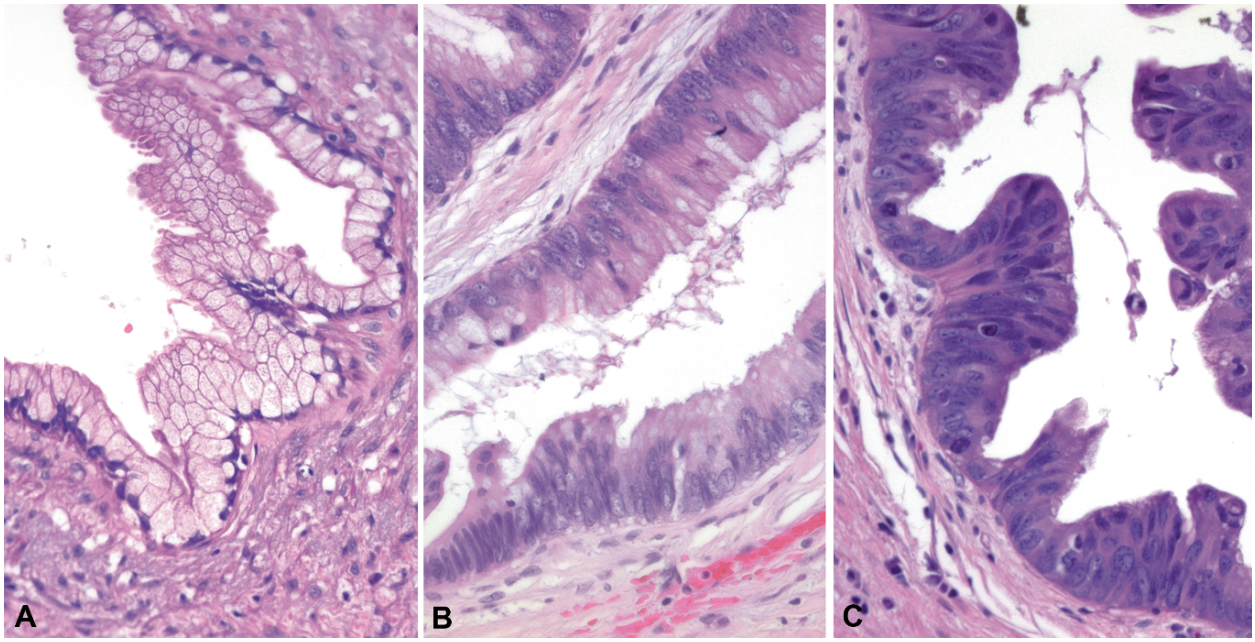

Figure 10.7. The grades of pancreatic intraepithelial neoplasia (PanIN). **(A)** PanIN 1 shows tall mucinous cells resembling endocervix. **(B)** PanIN 2 shows increasing nuclear crowding, enlargement, and atypia, suggestive of a tubular adenoma of colon. **(C)** PanIN 3 shows high-grade nuclei with loss of polarity, frequent mitoses, and loss of mucinous differentiation.

PanIN 1A has a flat layer of tall columnar cells with basal nuclei and apical mucin and no atypia. The cells are similar to normal endocervical glands (Figure 10.7). *PanIN 1B* is the same as PanIN 1A but with a papillary or undulating appearance.

PanIN 2 is flat or papillary but with nuclear abnormalities, including nuclear crowding and enlargement, stratification, hyperchromasia, and sometimes basal mitoses. This epithelium should remind you of a tubular adenoma or what would be called low-grade dysplasia in the gastrointestinal tract (see Figure 10.7).

PanIN 3 is carcinoma in situ. You may see a cribiforming, papillary, or micropapillary architecture or necrosis. Cytologic features include large ugly nuclei with prominent nucleoli, total loss of polarity, atypical mitoses, maloriented goblet cells (upside down)—essentially the same criteria you would use for high-grade dysplasia in other gastrointestinal epithelia (see Figure 10.7).

Invasive carcinoma arising out of PanIN 3 is well documented. However, remember that PanIN is a common incidental finding in a pancreas. It is not visible radiologically, it does not make a mass, and it does not cause obstruction. If you have a clinical mass, you should be thinking instead of an invasive carcinoma or intraductal papillary mucinous neoplasm (IPMN; see next section). Also, do not worry too much about the PanINs. With the exception of PanIN 3, they are of no proven clinical significance; margins with PanIN 1 or PanIN 2 lesions can safely be called negative.

Intraductal Papillary Mucinous Neoplasm

An IPMN is defined as a mucin-producing neoplasm arising in either the main pancreatic duct or a secondary (side-branch) duct. The ducts are usually dilated because they are full of a papillary proliferation and abundant mucin. The main lesion to consider in the differential diagnosis is the mucinous cystic neoplasm (discussed later). If you have a mucin-producing cystic neoplasm in the pancreas, always probe the main duct to see if the cysts are connected to it (an IPMN) or not (a mucinous cystic neoplasm). Essentially it is a gross diagnosis and may even be an endoscopic one; if mucin was seen coming out of the ampulla, the cysts must be connected to the pancreatic ducts and the lesion is more likely to be an IPMN. However, once you have identified an IPMN grossly, you must look microscopically to evaluate the level of atypia and rule out an invasive carcinoma. Intraductal papillary mucinous neoplasms are divided into three categories:

- With low-grade dysplasia: These neoplasms are cytologically bland and have the same criteria as PanIN 1.
- With moderate dysplasia (formerly known as *borderline*): These neoplasms cytologically show increasing nuclear abnormalities and have the same criteria as PanIN 2.
- With high-grade dysplasia: These neoplasms are cytologically malignant (see PanIN 3 criteria, discussed earlier). Any IPMN with high-grade dysplasia must be carefully scrutinized for invasive carcinoma slipping out of the duct.

A common question is, how can I tell PanIN in a largish duct from IPMN in a smallish side-branch duct? Features that favor an IPMN include the following:

- Long papillae, or finger-like projections with fibrovascular cores (Figure 10.8)
- Blue mucin in the lumen of the duct
- Continuity with one of the main pancreatic ducts
- Grossly or radiologically visible

When it comes right down to it, identifying the grade of dysplasia correctly right is much more important than distinguishing between an IPMN and a PanIN.

Invasive Adenocarcinoma (Ductal)

The most common form of infiltrating adenocarcinoma in the pancreas is ductal. It usually arises in the head and often invades adjacent structures before coming to clinical attention. The histologic features of ductal adenocarcinoma have been described earlier. Once you have established carcinoma, look carefully at all sections of duodenum and extrapancreatic bile duct to see if the carcinoma invades those structures (in increase in stage). The bile duct and ampullary region have numerous benign glands branching off of them, but remember that the benign glands will have a lobular and symmetric look at low power. Variants of ductal adeno-

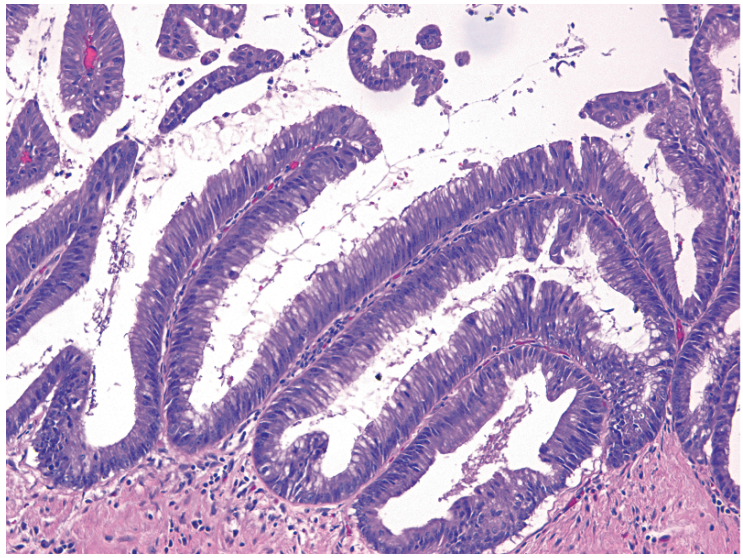

Figure 10.8. Papillary projections, intraductal papillary mucinous neoplasm with moderate dysplasia. These tall papillary fronds are covered with mucinous cells showing moderate dysplasia, similar to PanIN 2.

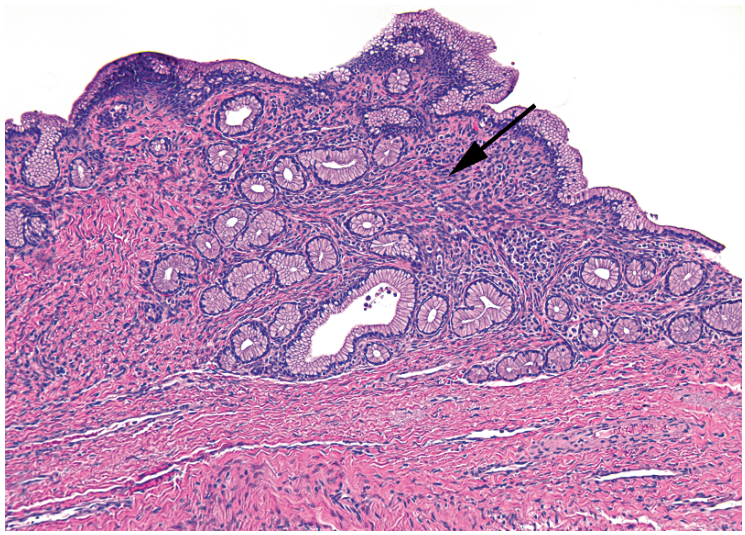

Figure 10.9. Mucinous cystic neoplasm. The cyst lining is composed of mucinous cells, benign in this example, and underlying blue spindly ovarian-type stroma (arrow).

carcinoma include adenosquamous, colloid (mucinous), hepatoid, medullary, signet ring cell, undifferentiated (anaplastic), and undifferentiated carcinoma with osteoclast-like giant cells.

Other Cystic Lesions of the Pancreas

Mucinous Cystic Neoplasm

The mucinous cystic neoplasm occurs almost always in middle-aged women, usually in the tail of the pancreas. This mucinous neoplasm produces multilocular cysts that do not communicate with the main duct system. They have, by definition, a rim of ovarian stroma (Figure 10.9), so think of them as mucinous ovarian tumors heterotopic into the pancreas. As in the ovary, they have three grades, and these grades conveniently parallel the three grades of the IPMN:

- With low-grade dysplasia: no atypia, like PanIN 1
- With moderate dysplasia: increasing nuclear atypia and/or architectural complexity, like PanIN 2
- With high-grade dysplasia: carcinoma in situ, like PanIN 3

Approximately one third of mucinous cystic neoplasms have an associated invasive carcinoma, which would be called *infiltrating moderately differentiated adenocarcinoma arising in association with a mucinous neoplasm with high-grade dysplasia*.

Serous Cystadenoma

Serous cystadenomas of the pancreas, unlike the serous cystadenomas of the ovary, are almost always microcystic. Grossly, they have a central scar and radiating small clear-fluid-filled cysts, like the cross section of a lime. Microscopically, the cysts are lined by cuboidal cells with clear cytoplasm (glycogen) and small, uniform, round nuclei (Figure 10.10). Areas of more solid or trabecular growth may look much like metastatic renal cell carcinoma, which is in fact in the differential. Serous cystadenocarcinomas exist but are extremely rare.

Solid-Pseudopapillary Neoplasm

Solid-pseudopapillary neoplasms are unusual and distinctive tumors in the differential diagnosis of cystic lesions in young women. They are malignant but extremely indolent. The cell of origin is not known, and so the neoplasm is named based on its appearance. These neoplasms start out solid but undergo cystic degeneration and therefore may present as a cyst (despite the name). The cells are characteristically noncohesive, and so the remaining solid areas show a pseudopapillary growth pattern (meaning there is solid growth along fibrovascular septa, with a dropout of the loosely cohesive cells in between septa and a resulting papillary look). The nuclei are small, oval, bland, and grooved (Figure 10.11).

The differential diagnosis for this neoplasm includes well-differentiated pancreatic endocrine neoplasm and acinar cell carcinoma, both of which are discussed later. Immunohistochemical labeling is very helpful, as solid-pseudopapillary neoplasms are CD10 positive and show nuclear labeling for β-catenin.

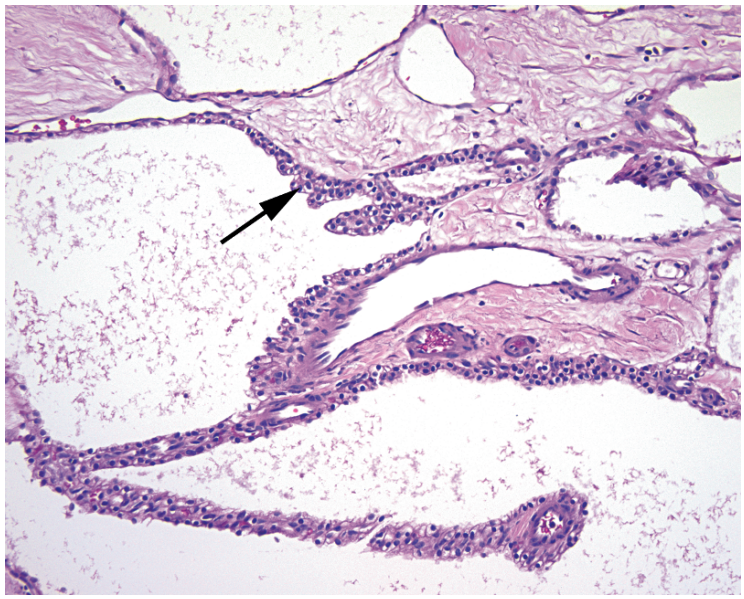

Figure 10.10. Serous cystadenoma, high power. The cells lining the multilocular cyst are small, with dense round nuclei and clear cytoplasm (arrow).

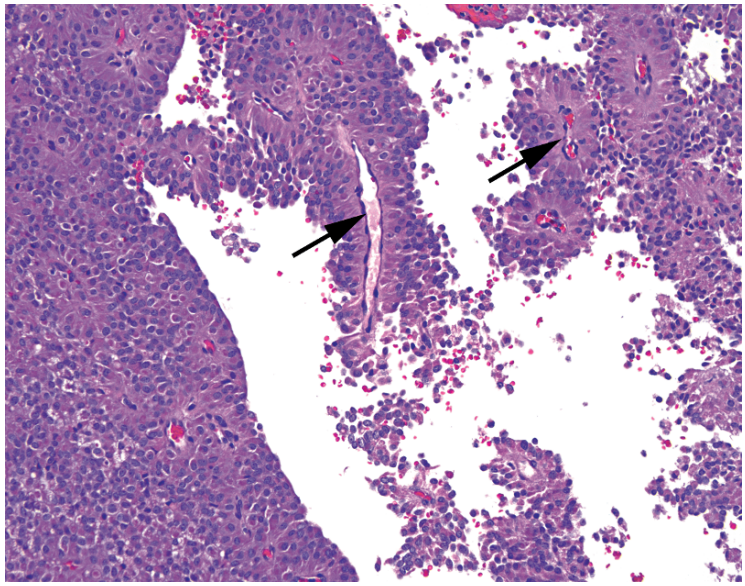

Figure 10.11. Solid pseudopapillary tumor. The small plasmacytoid cells with neuroendocrine-type chromatin could be mistaken for islet cell tumor or acinar cell carcinoma. However, this growth pattern, with rosette-like growth around fibrovascular cores (arrows) and dropout of the intervening cells, is typical of the solid pseudopapillary tumor.

Pseudocyst

The definition of a pseudocyst is "lacking an epithelial lining." This is a walled-off area of fat necrosis and granulation tissue containing high levels of pancreatic enzymes that is not usually mistaken for a malignancy, clinically or microscopically. Remember that most pseudocysts are actually extrapancreatic.

Other Solid Tumors in the Pancreas

There are only two pancreatic cell types not yet discussed (not counting soft tissue elements such as vessels and nerves): the acinar cells (exocrine secretory) and the islet cells (endocrine). Neoplasms composed of these cells are important to remember because they can release enzymes or hormones, causing dramatic clinical presentations. These tumors can also show considerable histologic overlap and may require special stains to distinguish.

Acinar Cell Carcinoma

Acinar cell carcinomas are rare tumors of older adults, usually male. The usual appearance is that of nodules and sheets of densely packed amphophilic (purple) cells with uniform round nuclei. Growth may be trabecular, nested, or acinar (arranged around tiny lumens). Prominent nucleoli are often seen and are a clue to the diagnosis. Like the benign acinar cells, these tumors are usually positive for trypsin.

Well-Differentiated Pancreatic Endocrine Neoplasm

Well-differentiated pancreatic endocrine neoplasms are simply the neuroendocrine tumors of the pancreas, also known as *islet cell tumors*. These tumors are usually well circumscribed and cellular, and the neoplastic cells tend to form nests or trabeculae. The cytology is that of a carcinoid (Figure 10.12). Some are functional and produce clinically significant levels of insulin, glucagon, somatostatin, or other peptides. Cytology is not an indication of behavior,

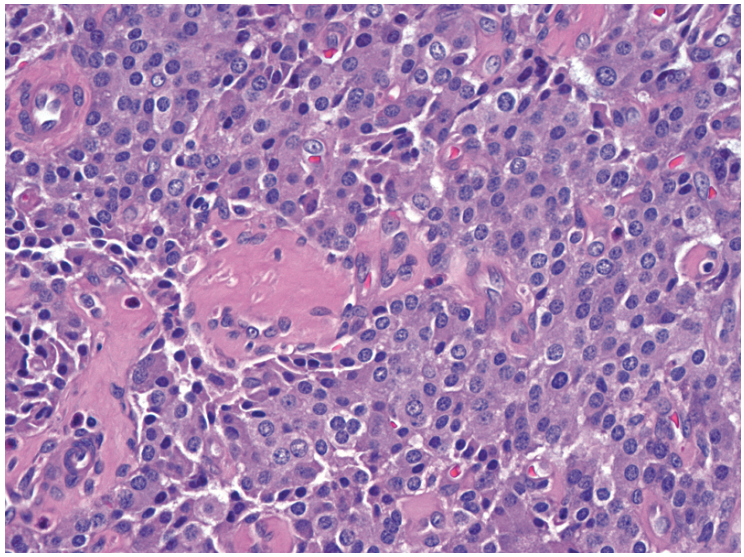

Figure 10.12. Islet cell tumor. This resembles carcinoids in other body sites, with round, well-spaced nuclei and speckled neuroendocrine-type chromatin.

usually, and a bland tumor may look just as bland when you later find it in the liver. High-grade neuroendocrine tumors are rare in the pancreas and when present are usually of the small cell variety. Well-differentiated pancreatic endocrine neoplasms express neuroendocrine markers (SYN, CHR, CD56) as well as any peptides they may be producing.