19 Breast

Breast biopsy specimens come in several sizes. There is the initial core biopsy, which is a large-bore needle biopsy, and the excisional biopsy, which is like a small lumpectomy. Some institutions perform cytologic studies (fine-needle aspirations), but their usefulness is limited, as many breast diagnoses are more architectural than cytologic. Biopsies are performed, with few exceptions, to rule out malignancy; there are almost no other disease processes that require tissue monitoring. A biopsy specimen with carcinoma will trigger either a lumpectomy, in which a portion of the breast is removed (a partial mastectomy, breast-conserving therapy), or a mastectomy. The mastectomy itself may include sentinel lymph nodes or, if the sentinel node is positive, an entire axillary dissection. Biopsy and most lumpectomy specimens are entirely submitted, and anything that is oriented is inked with four to six colors so we can identify all of the margins later. Mastectomies have only two margins, deep and superficial, and are representatively sampled by quadrant.

Normal Histology

The breast is sort of a giant specialized sweat gland, and so it has secretory glands (acini or lobules), arranged like grapes, and ducts, like the grape stems. A single bunch of grapes is a terminal duct lobular unit (TDLU; Figure 19.1). The ducts from these TDLUs all converge on the nipple, which has multiple large ducts and smooth muscle for ejecting the milk. The breast of a child or man will have ducts but no lobules. During lactation, the lobules fill up with fatty vacuoles of milk, giving them a very characteristic look usually called *secretory* or *lactational change*.

Each lobule and duct is composed of two cell types, the outer myoepithelial layer and the inner epithelial cells (see Figure 19.1). This is an important feature that can separate an in situ lesion (two cell types) from an invasive one (one cell type). The whole structure is bounded by a basement membrane, which is the boundary between in situ and invasive cancers. While there are unusual myoepithelial tumors, in this chapter we will only cover epithelial lesions.

Approach to the Biopsy Specimen

When signing out a core biopsy, there are certain things that should be included in the diagnosis. For malignant lesions, in situ or invasive, first, it is helpful to give an indication of *how differentiated the tumor is*. Some institutions do not Elston grade (see later) a core, but you should at least note the nuclear grade (for ductal carcinoma in situ [DCIS]) or whether it is

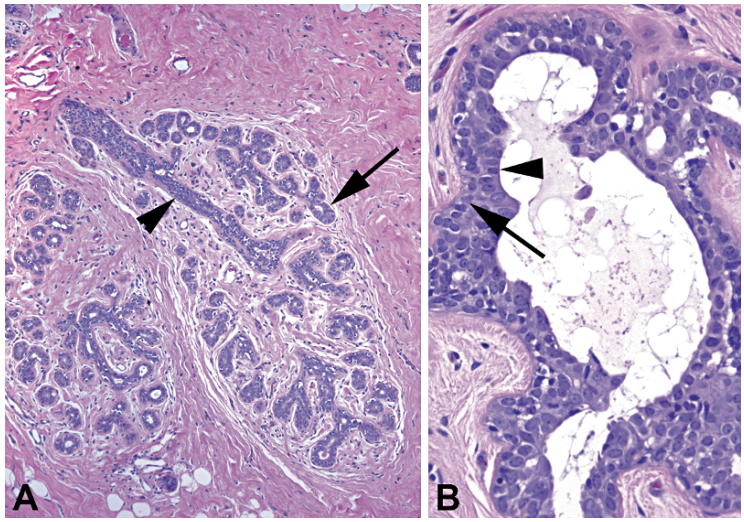

Figure 19.1. Normal breast. **(A)** The terminal duct lobular unit (TDLU) is arranged like a cluster of grapes, with the duct (arrowhead) as the stem and secretory lobules (arrow) as the grapes. The rounded and circumscribed border of the TDLU is a key feature of noninvasive lesions. **(B)** The benign breast always has two cell layers, the outer myoepithelial cells (arrow) and the inner epithelial cells (arrowhead). In situ lesions also have two cell layers.

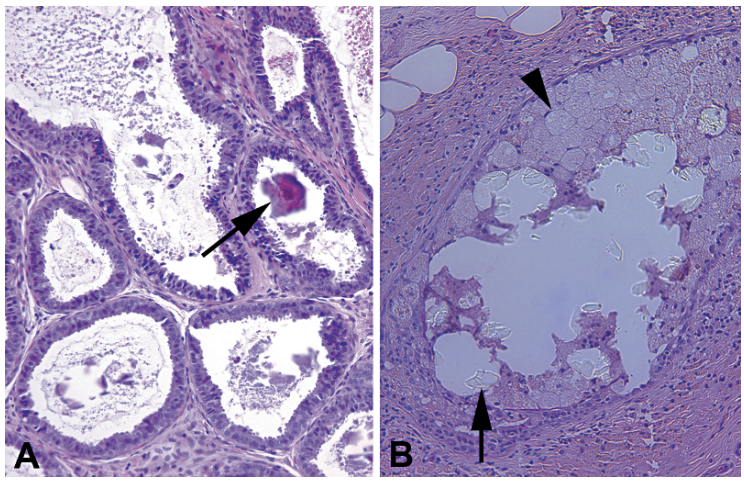

Figure 19.2. Calcifications. **(A)** Microcalcifications in this columnar cell lesion appear as tiny purple rocks (arrow), which may shatter and drag through the tissue, creating telltale scratches in the H&E stain. **(B)** Calcium oxalate does not pick up hematoxylin and therefore is only visible with a polarizer or when the condenser is flipped down, as in this photograph. The oxalate crystals (arrow) are seen in a duct space, surrounded by foamy macrophages (arrowhead).

well/moderate/poorly differentiated (for invasive cancer). These three tiers of differentiation correspond roughly to the three Elston grades.

Second, if microcalcifications were seen on mammography, you must note whether they are present in the specimen and in what context (such as, "in association with usual duct hyperplasia"). Failure to find the microcalcifications leads to x-raying the block, calling the radiologist, and so forth. Microcalcifications usually are gritty and dark purple, like calcification in other tissues, but occasionally take the sneaky form of calcium oxalate, clear refractile crystals best seen with polarized light (or flipping the condenser down; Figure 19.2).

Finally, your goal should be to identify the mass or radiographic abnormality the clinicians have detected. If there is no malignancy, you should be looking for some *explanation for their findings*. Aside from microcalcifications, which do explain a mammographic lesion, you should be looking for anything that could cause a palpable mass, such as fibrosis, cysts or cyst wall, fat necrosis, and benign tumors such as fibroadenomas.

Fibrocystic Changes

Fibrocystic changes are very common in young women, and many palpable lumps turn out to be nothing more than fibrocystic change. These are usually signed out as "Benign breast tissue with fibrocystic changes, including…" and then a list of the features. These features include the following:

- Fibrosis: Fibrosis consists of dense pink collagen among the lobules.
- Cysts: Cysts are often visible grossly, thin walled, and full of clear fluid (Figure 19.3).
- Usual duct hyperplasia: Usual duct hyperplasia is described in detail in a later section.
- Adenosis (too many glands or lobules) or sclerosing adenosis: Adenosis is a big pitfall because the lobules can look very crowded and worrisome. This is especially true of sclerosing adenosis, in which the proliferative lobules are squeezed together by fibrosis, making them look small and infiltrative (Figure 19.4). The reassuring myoepithelial cell layer can be hard to see. However, sclerosing adenosis should have an overall lobular (circumscribed and rounded) architecture, and myoepithelial cells should be visible in some glands.
- Apocrine metaplasia: Breasts are just big sweat glands, remember? Apocrine metaplasia means the epithelial cells lining the ducts look like apocrine glands (Figure 19.5); they acquire a lot of bright pink cytoplasm, can get a hobnail profile protruding into the lumen, and have enlarged nuclei with prominent nucleoli (not unlike Hurthle cell change in the thyroid). It is important to recognize this entity as a metaplastic, not a dysplastic, change.
- Fibroadenomas: A fibroadenoma is a biphasic (two cell types) proliferative lesion. The ducts are proliferating (-adenoma), as is the stroma (fibro-). (A similar lesion in the ovary is called an *adenofibroma*.) This benign tumor has thin, branching ducts set in a sparsely cellular fluffy pink stroma (Figure 19.6). The ducts often have a myxoid pale halo around them, and

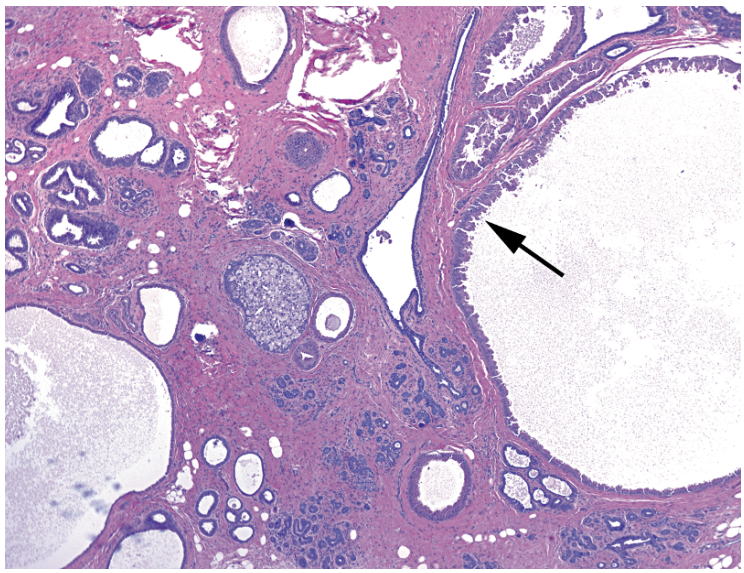

Figure 19.3. Fibrocystic disease. In this example, large dilated duct spaces are visible, some with a lining of apocrine metaplasia (arrow). The stroma is dense and fibrotic (pink).

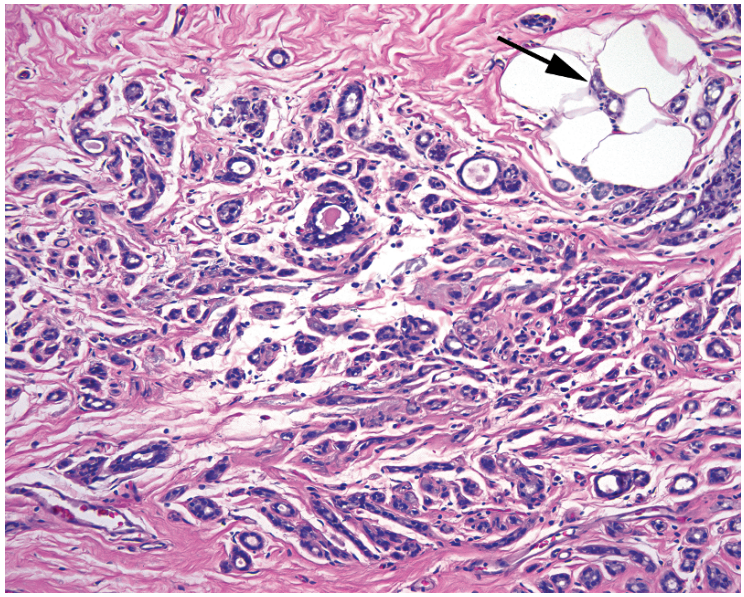

Figure 19.4. Sclerosing adenosis. On high power, this benign lesion looks infiltrative. Tiny tubules are entrapped in a fibrotic stroma, and some tubules are even seen among fat (arrow). Because of the compression, myoepithelial cells are not visible. Clues to the diagnosis include a circumscribed lesion at low power, the lack of desmoplastic (edema and fibrosis) reaction, and an intact myoepithelial cell layer seen on immunostains.

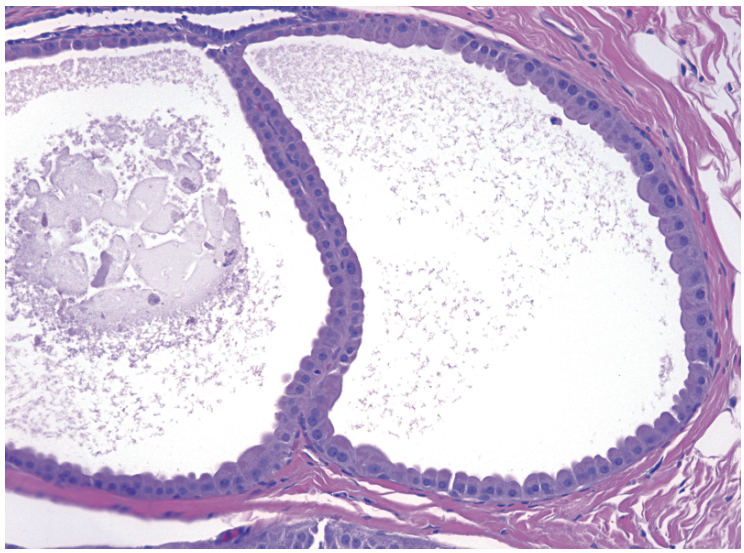

Figure 19.5. Apocrine metaplasia in fibrocystic disease. The epithelial cells lining the dilated duct are large and plump, with abundant dark pink cytoplasm, and round nuclei with prominent nucleoli. Secretions (the granular schmutz in the lumen) are common.

the proliferative stroma compresses the ducts into slits. Old fibroadenomas may become hyalinized and calcified. Fibroadenomas can occur alone or in association with fibrocystic changes.

The *phyllodes tumor* is another biphasic lesion, which has a similar appearance but a much more cellular stroma that a fibroadenoma. The phyllodes (*leaf-like*) tumor is graded based on how aggressive the stromal growth pattern is and ranges from benign to malignant. This

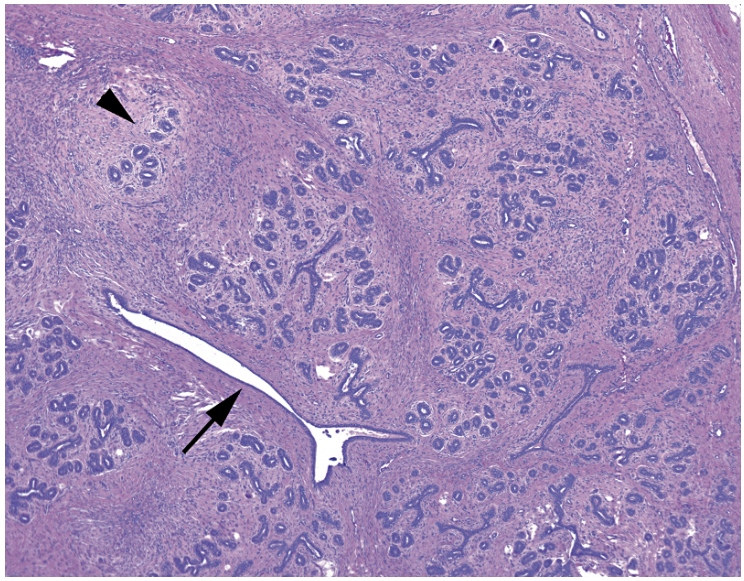

Figure 19.6. Fibroadenoma. At low power, the fibroadenoma is a well-circumscribed nodule. Within the lesion, the secretory lobules stand out in slightly edematous (pale) stroma (arrowhead), and the ducts are compressed into slit-like spaces (arrow) by the proliferative stroma.

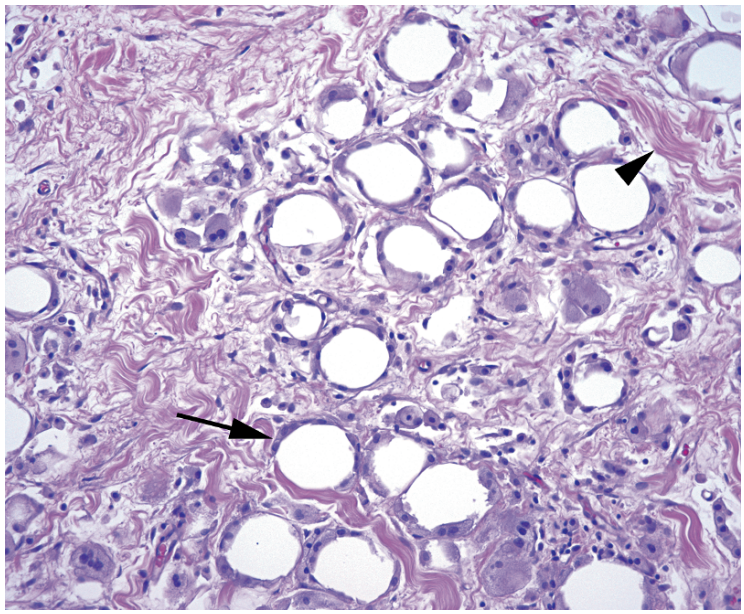

Figure 19.7. Fat necrosis. In an area of fat necrosis, secondary to trauma or surgery, the fat cells die but the globs of lipid remain. Foamy macrophages ring each dead fat cell (arrow), digesting the lipid; the spaces between the fat cells are filled in by fibrosis (arrowhead).

leaf-like pattern is often indicative of biphasic tumors with a very proliferative stroma and is seen in biphasic tumors of other organs.

Fat necrosis is evidence of a prior biopsy or other trauma. It can be hard, painful, calcified, or discolored. By clinical examination it may be very suspicious for malignancy. It is also very distracting in interpreting reexcision biopsies, where the prior surgery has left extensive fat necrosis. The key features (Figure 19.7) are as follows:

- Disrupted and irregular fat cells
- Foamy macrophages and giant cells
- Edema and hemosiderin
- Acute inflammation
- Fibrosis and calcification (in older lesions)

Intraductal Papilloma

The papilloma is composed of proliferative but benign secretory and myoepithelial cells lining a branching arbor of fibrovascular cores (Figure 19.8). The lesion is usually found in the large distal ducts and can become fibrotic (sclerosing papilloma) or calcified with age. Rarely, carcinoma can arise in a papilloma.

Ductal and Lobular Proliferative Lesions

This is the take-home point of the day: *Deciding whether a lesion is ductal or lobular has nothing to do with whether you find it in a duct or a lobule*. Lobular carcinoma in situ (LCIS) can fill a duct, and DCIS can invade a lobule, so there is no need to struggle to identify which structure you are looking at. Instead, *ductal* and *lobular* refer to *distinct morphologic patterns of in situ or invasive carcinoma*. They probably represent cancer pathways arising from a common cell type by two different mechanisms, analogous to the two cancer pathways in colon, but there are plenty of examples of "tweener" lesions (features of both) that are signed out as "mixed mammary carcinoma."

Benign hyperplasia of ductal-type epithelium (usual ductal hyperplasia) is common, whereas benign hyperplasia of lobular-type epithelium is not. However, both cell types can

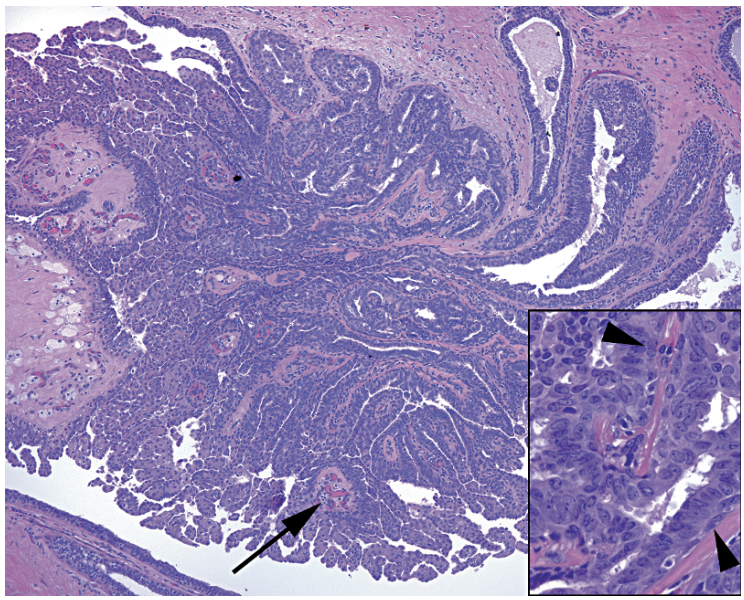

Figure 19.8. Intraductal papilloma. The branching structure fills a subareolar duct; smaller, more distal examples may be called *micropapillomas*. Although there is florid usual ductal hyperplasia, resulting in fusion of multiple branches of the papilloma, distinct fibrovascular cores are still visible (arrow). **Inset**: Along each fibrovascular core, you should still see myoepithelial cells (arrowheads), which differentiates this from a papillary carcinoma.

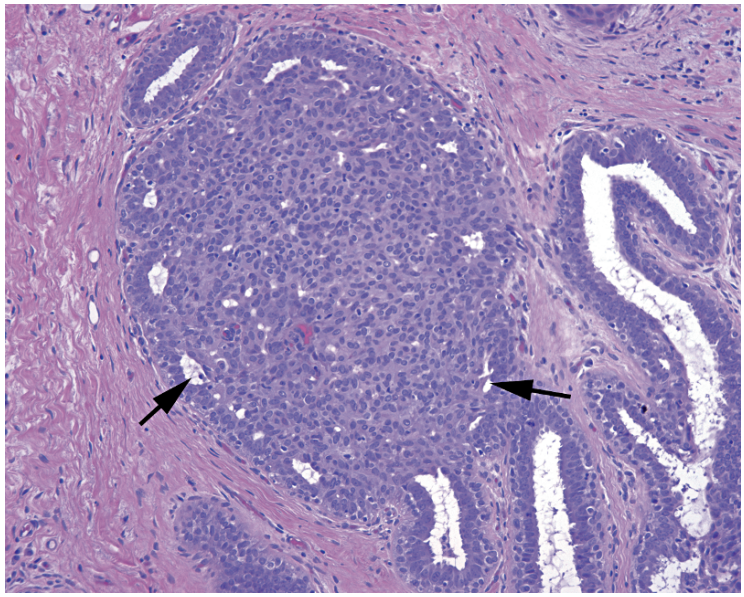

Figure 19.9. Florid usual ductal hyperplasia. The cellular proliferation entirely fills this duct, but the cell population is swirly and heterogeneous, with randomly overlapping nuclei. The peripheral ring of slit-like spaces (arrows), as though this clot of cells floated into the duct and stuck there, is very typical of usual ductal hyperplasia.

occur in an atypical proliferative phase (ADH and ALH), carcinoma in situ (DCIS and LCIS), and invasive carcinoma (IDC and ILC).

Usual ductal hyperplasia refers to a proliferation of cells within the ducts. The usual monolayer of cuboidal cells heaps up into mounds or even fills the ducts. Features of usual ductal hyperplasia include the following:

- The cells have an overall pale look; they are normochromic.
- Cells appear jumbled, overlapping, or streaming and almost syncytial (Figure 19.9).
- Heterogeneity (not to be confused with pleomorphism) is present. The nuclei, all bland with even chromatin and smooth nuclear membranes, range slightly in size and shape as though they were drawn by a sloppy artist.
- Ducts may be filled with cells and may even have a cribriform look at low power, but on higher power the nuclei should be streaming, flowing parallel to the lumens, as opposed to polarizing perpendicularly (radially) around the lumen. Luminal spaces should be slit-like or irregular, not round, and may be "fuzzy" (due to apocrine secretions).

Ductal carcinoma in situ may be low grade, which is a homogeneous population of cells, or high grade, which is a pleomorphic population of cells. In low-grade DCIS, you should get the impression that there is a monotonous, clonal population of cells, with evenly spaced dark nuclei and distinct cell borders. High-grade DCIS, although it loses its monotonous look, should still have discrete nonoverlapping cells; it also may get very pink. Irregular nuclear borders, enlarged nuclei, and nucleoli are common. Patterns of DCIS include the following:

- Cribriform: sharply punched-out round holes in the mass of cells, with cells lined up around the lumens like rosettes (Figure 19.10)
- Solid: a solid sheet of monotonous cells
- Comedo: a rim of malignant, usually high grade, cells with central necrosis (see Figure 19.10)
- Micropapillary: top-heavy lollipop protrusions into the lumen, without true fibrovascular cores; must also have cellular monotony as above.

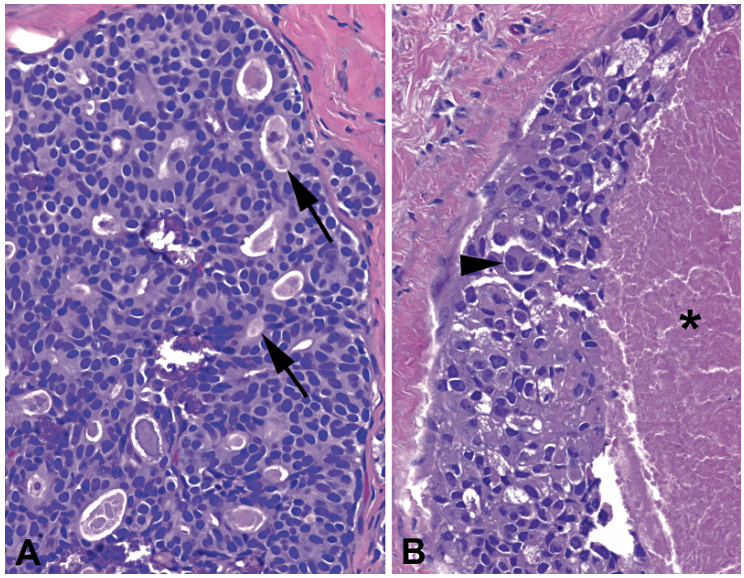

Figure 19.10. Ducal carcinoma in situ (DCIS). **(A)** In low-grade DCIS, the cells are monotonous, uniform, and largely nonoverlapping, and they form cribriform duct spaces with the cells polarized around the tiny lumens (arrows). **(B)** In high-grade DCIS, the cells have lost their monotony and are instead pleomorphic, some with prominent nucleoli (arrowhead). At the center of the dilated duct there is necrosis (asterisk), indicating comedo-type DCIS.

Remember that DCIS by definition has not crossed the basement membrane, and the outer myoepithelial layer remains intact. Ductal carcinoma in situ is treated as a precursor to malignancy, and the treatment goal is total excision. Therefore, on anything but a core biopsy, you must document its distance from each margin (adequate clearance is in the eye of the beholder, but most accept 2 mm).

Do not expect to get comfortable with the diagnosis of *atypical ductal hyperplasia* until you have mastered usual ductal hyperplasia and DCIS. Atypical ductal hyperplasia falls somewhere in between and has no definitive criteria other than "has some but not all of the features of DCIS." This diagnosis is also used in the setting of a single focus of apparent low-grade DCIS (nuclear grade 1 of 3) measuring less than 3 mm. In a core biopsy, atypical ductal hyperplasia is code for "get me more tissue." Features that can push you to DCIS in a tiny focus include high-grade nuclei and/or necrosis.

Invasive ductal carcinoma is invasive carcinoma arising from a DCIS lesion, and therefore the cells of invasive ductal look similar to those you see in DCIS. In its most common form, invasive ductal carcinoma is the cancer formerly known as *scirrhous*, so called because of the dense desmoplastic reaction generated. It is eye-catching even to the untrained eye, as a large cellular lesion with ugly cells, radiating outward in a stellate and decidedly un-TDLU-like shape (Figure 19.11). The cells are large, with large pleomorphic nuclei and substantial pink cytoplasm. Necrosis and mitoses are common. Nests of tumor cells can imitate ducts or tubules in the stroma, or acquire large necrotic centers like comedo-DCIS. For this reason it is sometimes hard to tell invasive carcinoma from DCIS or even benign tubules. Stains for myoepithelial borders are helpful here: invasive cancer does not have any.

Variants of ductal carcinoma include the following (the first five variants have a generally better prognosis than ductal carcinoma NOS):

- Tubular: a very well-differentiated cancer composed entirely of cytologically bland small angular tubules (Figure 19.12)
- Cribriform: similar to tubular, but with cribriform structures instead of tubules

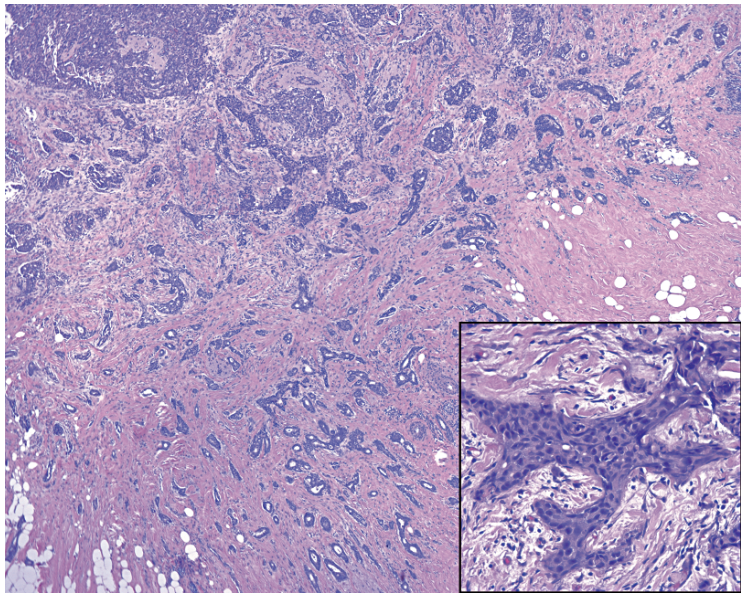

FIGURE 19.11. Infiltrating ductal carcinoma. At low power, the irregular border of the lesion is evident, with small angular tubules radiating outward into the fat. Grossly, this lesion would have a stellate appearance, and the dense stromal reaction would make the lesion very hard. **Inset**: The irregularly shaped nests of tumor cells create a desmoplastic stromal reaction, which is a combination of edema (white space) and fibrosis (pink collagen).

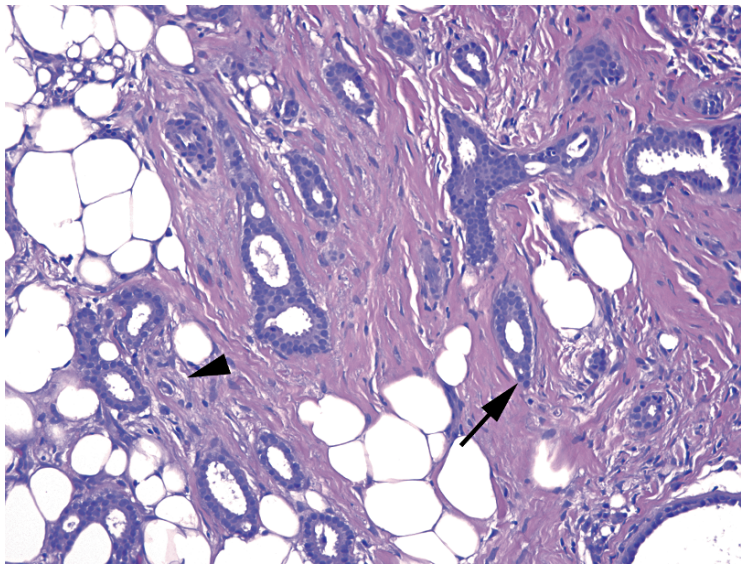

FIGURE 19.12. Tubular carcinoma. Well-formed tubules with pointed ends (arrow) and round, monotonous cells infiltrate through the stroma and fat. The myoepithelial layer is absent, both on H&E stain and by immunostain, and there is a subtle desmoplastic reaction around some of the tubules (arrowhead).

- Mucinous or colloid: characterized by pools of mucin and floating fragments of neoplastic epithelium (Figure 19.13)
- Medullary: a well-circumscribed but paradoxically ugly group of cells, with a dense lymphocytic infiltrate

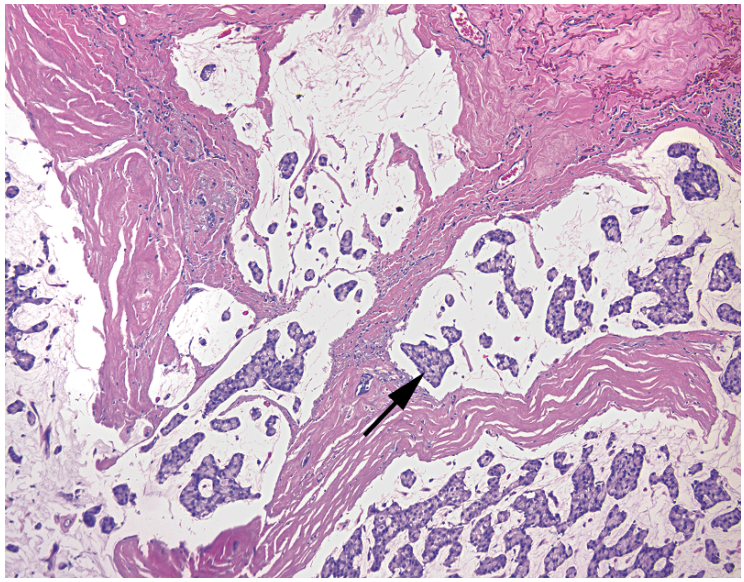

Figure 19.13. Mucinous carcinoma. Pools of extruded mucin dissect into the stroma. Although this can occur in benign mucocele-like lesions, the presence of floating clumps of cells (arrow) is diagnostic of mucinous, or colloid, carcinoma.

- Adenoid cystic carcinoma: a biphasic tumor of epithelial and myoepithelial cells, identical to the salivary gland tumor of the same name
- Metaplastic: a tumor in which there is a mesenchymal or spindle-cell component, such as cartilage, bone, or frank sarcoma, with prognosis depending on grade

In *lobular carcinoma in situ*, lobular cells, when they begin to proliferate, take on a characteristic appearance. They are homogeneous, like DCIS cells, but they have a round fried-egg shape, with a pale cytoplasm, discrete borders, and a central round nucleus (Figure 19.14). Intracytoplasmic vacuoles, even signet-ring cells, are also common. In LCIS, these cells should fill and expand the lobules, appearing at low power like a very circumscribed stippled space (such as the texture of newspaper photos under a magnifying glass). Lobular carcinoma in situ retains its bland cytology right through to invasive carcinoma.

Lobular carcinoma in situ is often multifocal and bilateral, and its progression to cancer is not considered inevitable or predictable. As a result, excision is not the goal of treatment, and so its presence at a margin is not usually noted.

Lobular carcinoma in situ is an incidental finding. It does not form masses or calcify (usually). *Atypical lobular hyperplasia* is generally code for "I'm really worried about LCIS but cannot quite get there." Like atypical ductal hyperplasia, atypical lobular hyperplasia does not have consistently agreed-upon criteria.

E-cadherin is a cell surface molecule that helps cells stick together. Lobular lesions lose expression of E-cadherin and therefore begin to appear very discohesive. You can imagine that this nonsticky surface enables the invasive lobular cells to slip through the stroma as single cells, and that is exactly what they do. Stains for E-cadherin can help to sort out LCIS (negative) from DCIS (positive) in a core biopsy specimen, as low-grade DCIS can resemble LCIS.

The cells of *invasive lobular carcinoma* look similar to those of LCIS. They are small uniform cells with bland round nuclei, pale cytoplasm, and a sometimes plasmacytoid shape with an eccentric mucin vacuole. Because of their normochromic nuclei and lack of malignant cytology, they are identified by the way they slip through the stroma. They line up as single file lines or as concentric rings around ducts and do not cause an appreciable desmoplastic

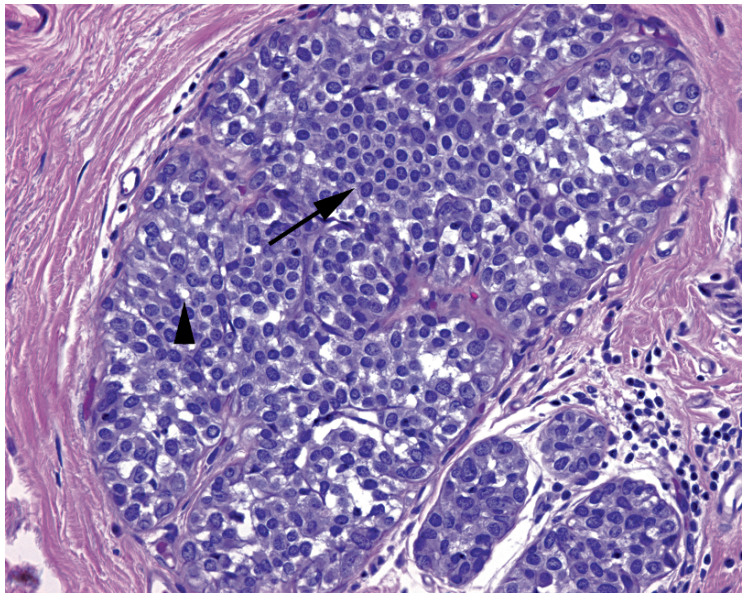

FIGURE 19.14. Lobular carcinoma in situ. The lobule is distended by a population of monotonous cells with distinct cellular borders and small round nuclei (arrow). As the lesion expands, the noncohesive cells will begin to fall apart. Cytoplasmic vacuoles (arrowhead) are typical of lobular carcinoma cells both in situ and invasive.

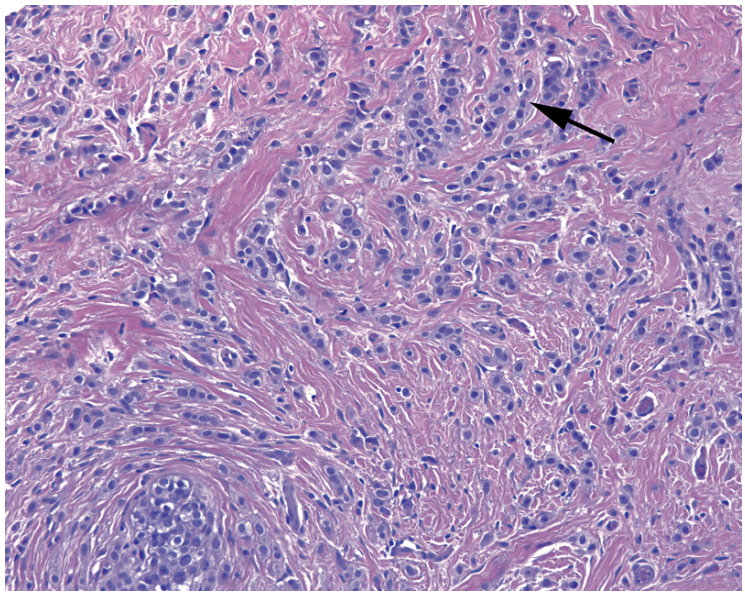

FIGURE 19.15. Invasive lobular carcinoma. The same cells as in Figure 19.14 are seen here invading through the stroma. They often form single file lines (arrow) but may also be seen as single cells or concentric circles around a duct. In some cases there is little to no desmoplastic stromal reaction, making the lesion difficult to palpate or detect.

response (Figure 19.15). They are sneaky and scary, and you have not ruled out lobular until you have looked closely at 10× or 20×. A cytokeratin stain can highlight the individual cells, as everything else in the stroma should be negative.

Invasive epithelial carcinomas must be given an *Elston grade* (A.K.A Nottingham grade, or Elston-Ellis modification of Scarff-Bloom-Richardson) when diagnosed in a lumpectomy or

mastectomy. The Elston grade is the pathologic assessment of the tumor's aggressiveness; the stage is diagnosed separately by features such as size and local extent. The Elston grade takes into account three prognostic factors:

- Tubule formation (the more tubule formation, the lower the score)
- Mitotic rate (the more mitoses, the higher the score)
- Pleomorphism (the more pleomorphic the nuclei, the higher the score)

Each characteristic is scored from 1 to 3, and then all are added, to give you a range of 3 to 9. For details on scoring, see your favorite surgical pathology text; in the beginning, just learn to look for these three features. Pleomorphism, especially, is a fairly subjective criterion that takes some experience to judge.

Papillary Nomenclature

Papillary lesions in the breast represent a confusing area. Here is the nutshell.

A *papilloma* is a benign lesion with papillary architecture. The fibrovascular cores, and the surrounding duct, are lined by myoepithelial cells. Within a papilloma, you can get usual or atypical ductal hyperplasia or DCIS, all of which are diagnosed as "arising in a papilloma." You should still have myoepithelial cells around the perimeter.

Within the DCIS family, there are several architectural types: *micropapillary* (epithelial projections without fibrovascular cores), *papillary* (epithelial projections with fibrovascular cores), and *solid papillary* (a solid ball of cells with residual entombed fibrovascular cores). None of these necessarily has anything to do with a papilloma. All usually have intact myoepithelial cells around the outside. All may be multifocal processes in the breast.

Papillary carcinoma is a specific type of carcinoma with a papillary architecture, homogeneous columnar cells, and a circumscribed profile, as though it once grew in a duct. It should be a single discrete lesion. The fibrovascular cores have no myoepithelial cells. The myoepithelial stains may also be negative around the perimeter, but it is still not really considered a true invasive carcinoma. It may be called *intracystic* or *encysted* papillary carcinoma to get this point across.

The Many Faces of Metaplastic Carcinoma

Numerous morphologies get lumped under the term *metaplastic carcinoma* and hence the struggle to learn to recognize it. You may see this diagnosis applied to the following entities:

- Squamous carcinoma: a ductal carcinoma with prominent squamous differentiation (and technically a form of metaplastic carcinoma)
- Low-grade spindle cell carcinoma: can masquerade as a hypercellular stroma, but the spindle cells should stain for cytokeratins (especially high-molecular-weight cytokeratins such as 34bE12 [CK903])
- High-grade carcinoma with spindle cell features: should also be cytokeratin positive
- Any carcinoma with coexisting sarcoma, such as chondrosarcoma or osteosarcoma (The carcinoma component will be cytokeratin positive, the sarcoma usually will not. In another organ this would be called a carcinosarcoma.)

The differential diagnosis for entities that are spindly and malignant also includes malignant phyllodes tumor and primary or metastatic sarcoma.