CHAPTER 19

Breast

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NORMAL EMBRYOLOGY AND DEVELOPMENT

Mammary glands are modified sweat glands of ectodermal origin that produce milk.[1,2] It is likely that the close embryologic origin of salivary, sweat, and mammary glands relates to the often similar morphologic appearance and immunophenotype of tumors arising in these locations. During embryogenesis, breast tissue develops in both sexes along the paired milk lines, which extend from the axilla to the inguinal region.[3-10] In humans, only one gland normally develops on each side in the pectoral area, but two types of ectopic breast may occur. First, supernumerary breast has been observed in axillary lymph nodes as well as along the milk line that runs from the axilla to the inguinal region. The most common sites are the chest wall and the vulva. Second, aberrant breast tissue is mammary parenchyma found beyond the normal anatomic extent. The mammary gland is not a sharply demarcated organ, and isolated mammary lobules can occur outside the standard anatomic confines of the breast parenchyma, such as in the nipple or in the axilla (axillary tail of Spence). This explains the occurrence of some primary breast carcinomas in the axillary region. Ectopic breast parenchyma is subject to lactational changes as well as the development of both benign and malignant tumors.

Postnatally, in girls, the breasts undergo considerable development at puberty under the influence of prolactin, estrogen, and progesterone.[3-10] Boys may experience mild, transient breast enlargement at puberty, but there is normally little additional development, and the mammary gland remains rudimentary. In women, breast development peaks around age 20 years and is maintained through the reproductive years; atrophic changes begin at about age 40 years and accelerate postmenopausally. Estrogen promotes mammary differentiation of the duct system, whereas progesterone is important in lobular development. Clearly, prolactin is permissive for the action of estrogen and progesterone; however, insulin, growth hormone, human placental lactogen, and thyroxin contribute to normal mammary gland development.[3-10]

ANATOMY

The breast is covered by skin and subcutaneous tissue and lies superficial to the pectoralis muscle, from which it is separated by the pectoralis fascia.[4] It lies within a space of the superficial fascia. Except along its deep surface, the

breast is not precisely defined; microscopic extensions of parenchyma occur beyond these boundaries and, rarely, even into the pectoralis fascia. These extensions explain the rare development of additional breast primary carcinomas in women after simple mastectomy. The major arteries to the breast are the internal thoracic, axillary, and intercostal, with many variations in their individual contributions. The internal thoracic artery is dominant in most cases. The venous and lymphatic drainage is even more variable, but it usually follows the arterial tree.[3-10] Indeed, breast lymphatics "hug" the arterial and venous systems, directing lymphatic flow along the course of the branches of the external thoracic and internal thoracic veins toward the axillary and internal mammary nodes. There is also a subareolar lymphatic plexus that allows lymphatic drainage from skin into the interlobular connective tissue of the breast and subsequently to the general breast parenchymal lymphatic flow. From the breast parenchyma, 75% or more of the lymphatic flow is to the axilla; less than 25% is to the internal mammary nodes. A third and minor flow route is to the posterior intercostal lymph nodes located where the ribs and vertebrae articulate. Obstruction due to lymphatic invasion by tumor may disrupt normal flow patterns, resulting in considerable edema and surface skin changes (peau d'orange); this is considered "inflammatory" breast carcinoma clinically because the changes resemble cellulitis.

The nipple-areolar complex of the breast skin is a disk of increased pigmentation. The centrally disposed nipple has 15 to 25 large collecting ducts (nipple lactiferous ducts) opening individually onto the nipple surface.[3-10] The nipple and areola also contain numerous sebaceous glands that open independently of hair follicles. Eccrine and apocrine sweat glands are present and probably account for the rare skin adnexal tumors that can occur in this area. Intermediate in structure between sweat glands and breast are accessory areolar glands (Montgomery's tubercles).[3-10] These present as areolar protuberances, usually about 20 in number, which become prominent during pregnancy. They are formed by a distinct areolar lactiferous duct associated with a sebaceous gland. These areolar lactiferous ducts are linked to lobular breast parenchyma located deep to the areola, and they rarely become the site of breast disease. Beneath the epidermis lies a dense fibrous stroma admixed with erectile smooth muscle fibers. About 17% of nipples contain normal breast lobules.[3]

During the reproductive years, the basic ductular unit of the breast is the combination of multiple terminal duct lobular units (TDLUs) or lobules and their attached single collecting duct system, which ends at the nipple. The TDLU is formed by the small acini or alveoli within a lobule and the terminal ductule (Figs. 19-1 and 19-2). The TDLU represents the secretory portion of the gland. The terminal ductule connects to the subsegmental duct, which connects to a segmental duct; this in turn connects to a collecting (lactiferous or galactophorous) duct, which empties into the nipple. A fusiform dilation beneath the nipple between the collecting and segmental ducts is called the *lactiferous sinus*. Each breast is composed of 15 to 25 ductular units; each unit defines a functional breast lobe. Unfortunately, there are no gross or microscopic landmarks that allow the definition of individual lobes, which overlap considerably with adjacent lobes. Radiopaque dye injected into an individual lactiferous duct may help define the anatomic extent of a lobe. Excision of the breast lobe in a conical fashion toward the nipple may be a rational surgical approach in the treatment of carcinoma in situ, which theoretically should be limited to the collecting system of one breast lobe duct system ending or emptying at the nipple.

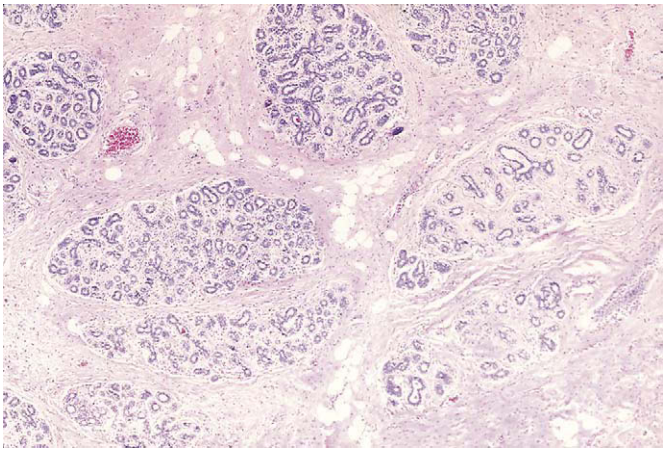

Figure 19-1 ■ Benign breast tissue containing numerous terminal duct lobular units (TDLUs), which are composed of multiple acini clustered together in lobules (proliferative phase during the menstrual cycle). Within lobules, acini are separated by intralobular stroma, and the TDLUs or lobules are separated by interlobular stroma. During the proliferative phase, the TDLUs have a relatively dense cellular intralobular stroma, closed or small acinar lumens, occasional epithelial mitoses, and nonvacuolated myoepithelial cells. The duct luminal and myoepithelial cells are relatively indistinct.

Within a TDLU is an intralobular mantle of specialized stroma, which is variably myxoid and hormone responsive, lacks elastic fibers, and contains many capillaries (see Fig. 19-2).[4] The intralobular stroma is derived from the fetal papillary dermis. The subsegmental and larger ducts have less specialized stroma and are surrounded by a well-developed layer of elastic tissue. These larger ducts lie within the interlobular or extralobular stroma, composed of variable fat and densely collagenized fibrous tissue, which contains the larger blood vessels and lymphatics of the

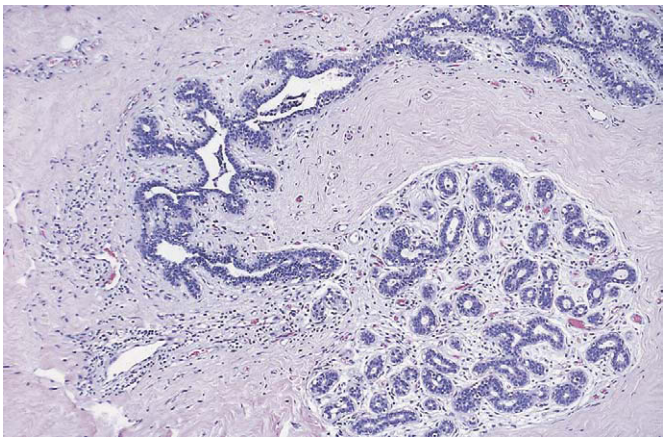

Figure 19-2 ■ Subsegmental duct "feeding" a terminal duct lobular unit (TDLU). Menstrual TDLUs show compact lobular glands, decreased stromal edema, and increased intralobular round cell (i.e., lymphocytic) infiltrate, which is present in this TDLU.

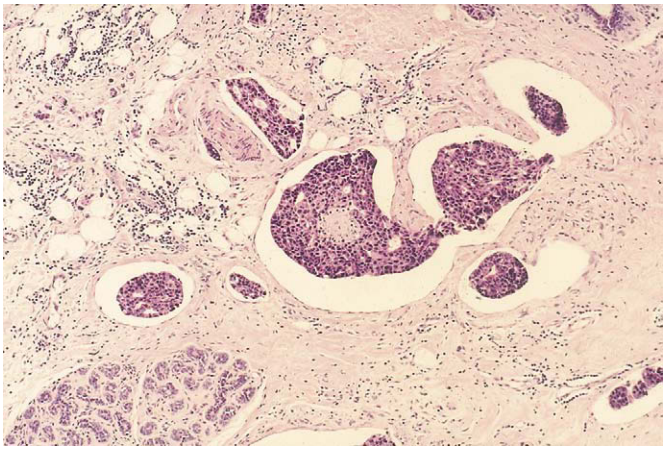

Figure 19-3 ■ Breast lymphatics within the interlobular stroma are situated close to muscle arteries, as shown by tumor emboli within lymphatics. Breast lymphatics "hug" the arterial and venous systems, directing lymphatic flow along the course of the branches of the external thoracic and internal thoracic veins toward the axillary and internal mammary nodes.

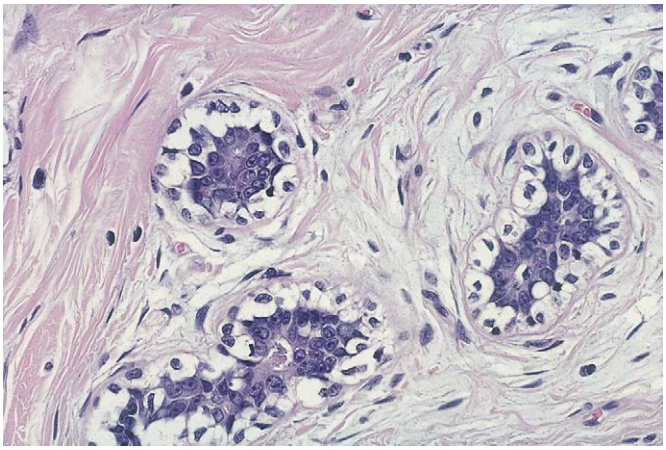

Figure 19-4 ■ Breast acini showing an inner duct luminal layer and an outer myoepithelial layer (secretory phase of the menstrual cycle). During the secretory phase, the intralobular stroma is loose and edematous, and there are varying amounts of secretory material, absence of mitotic figures, and distinct vacuolated myoepithelial cells. Acinar lumens are more open, and there may be cytoplasmic projections from their luminal surfaces.

breast (Fig. 19-3). The extralobular stroma develops from the fetal reticular dermis, and it extends from the breast parenchyma to the skin, forming the suspensory ligaments of Cooper. The duct system of the breast is composed primarily of a two-cell epithelial lining: the inner, secretory, acinar, or duct luminal epithelium and a surrounding or outer myoepithelial cell layer (Fig. 19-4). A much smaller population of endocrine cells as well as intermediate cells (indeterminate or basal clear cells) has been identified.[4,8] These intermediate cells may be multipotential precursor cells.

Ductal or acinar epithelial cells react strongly with antibodies to cytokeratins 18 and 19 as well as with epithelial membrane antigen, human milk fat globule membrane antigen, and α-lactalbumin.[8] Myoepithelial cells are contractile and have both myogenous and epithelial features. They contain bundles of thin filaments with focal densities (i.e., actin filaments) as well as tonofilaments and desmosomes. Myoepithelial cells are calponin, p63, smooth muscle actin, CD10, and cytokeratin 14 positive (Fig. 19-5). Antibodies to S-100 protein react with both ductal and myoepithelial cells, and anti–epithelial membrane antigen preferentially reacts with the apical region of secretory cells.[8] Pan-keratin antibodies react with both epithelial and myoepithelial cells. Outside the myoepithelial cell layers, there is a continuous basement membrane or lamina that contains laminin or collagen type IV.[8]

Breast tissue responds to hormonal and other developmental influences throughout life; thus, the breast displays a wide range of normal appearances.[3-10] At birth, there is often palpable enlargement of the breast buds and secretion of colostrum. This results from exposure of the fetal breast to maternal hormones. These findings typically subside 1 to 2 months post partum. Thereafter and until puberty, the breast is predominantly fibrofatty tissue containing branches of the primary duct system without lobule formation.

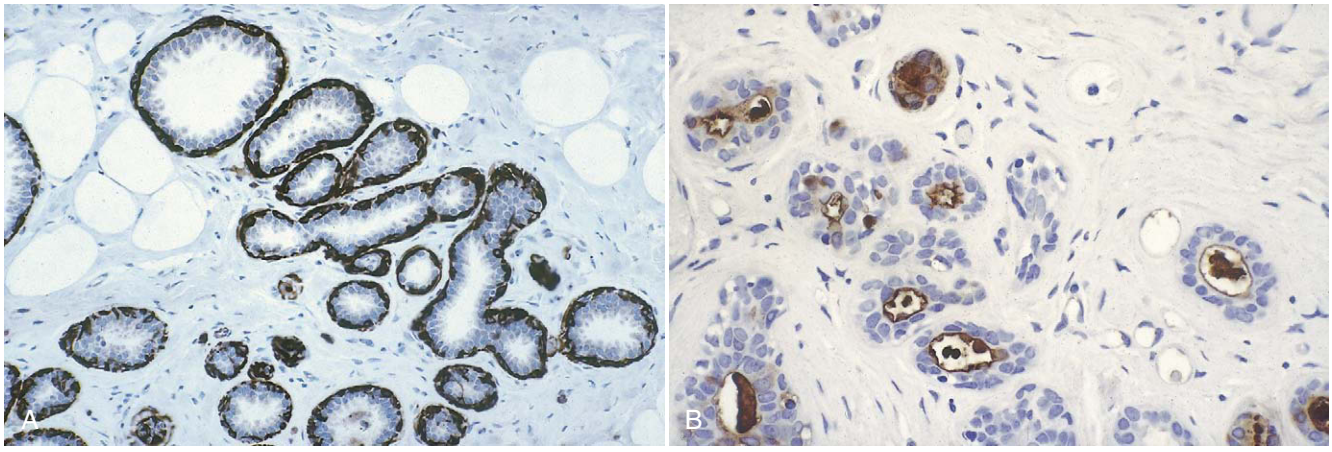

Figure 19-5 ■ **A,** Myoepithelial cells surround the duct luminal cells and contain smooth muscle actin, as shown by immunohistochemical staining. Smooth muscle actin stain can be helpful in distinguishing in situ breast carcinoma from invasive breast carcinoma, which does not have a myoepithelial cell layer. **B,** Antibody to gross cystic disease fluid protein-15 (GCDFP-15), an apocrine marker, reacts with the apices of the duct luminal cells and their secretions. GCDFP-15 is found in approximately 50% of breast carcinomas.

Premature thelarche refers to isolated breast development in the absence of additional signs of sexual maturation, usually before 8 years of age.[7] The clinical presentation is unilateral or bilateral subareolar discoid or nodular thickening. This is a rare occurrence (affecting about 0.02% of white females).[4] The enlargement may measure up to 7 cm, and it resembles gynecomastia microscopically (connective tissue containing increased numbers of ducts, without lobules, with mild epithelial hyperplasia of a solid or micropapillary configuration).[4] The enlargement tends to regress slowly over 6 months to 6 years but in some cases may persist until puberty.[4] Importantly, excision of this tissue results in amastia; thus, great caution must be applied before excision of breast tissue in this age group. Women with premature thelarche do not appear to have an increased risk of breast carcinoma, but they may experience precocious puberty.[4]

At puberty, fibrofatty connective tissues increase and the TDLUs or lobules develop, culminating in a fully formed reproductive breast as already described. Subsequently, the hormonal fluctuations of the menstrual cycle cause mild changes in the breast parenchyma. These changes are uneven within the breast, but some generalizations can be made. Breast volume (i.e., water content and parenchymal growth) increases during the cycle, becoming maximal between days 16 and 28 (secretory phase) and least between days 6 and 15 (latter proliferative phase), which makes the latter part of the proliferative phase the optimal time for breast examination.[4] During the proliferative phase, the TDLUs have a relatively dense cellular intralobular stroma, closed or small acinar lumens, occasional epithelial mitoses, and nonvacuolated myoepithelial cells. The duct luminal and myoepithelial cells are relatively indistinct. In contrast, during the secretory phase, the intralobular stroma is loose and edematous, and there are varying amounts of secretory material, absence of mitotic figures, and distinct vacuolated myoepithelial cells (see Fig. 19-4). Acinar lumens are more open, and there may be cytoplasmic projections from their luminal surfaces. Menstrual TDLUs show compact lobular glands, decreased stromal edema, and increased intralobular round cell (i.e., lymphocytic) infiltrate. With contraceptive therapy, there is often mild and transient breast pain during the first cycles. On microscopic examination, the only definite change caused by the medication is the development of true acini resembling lactating breast.[8]

During pregnancy, the lobular units progressively undergo marked proliferation and enlargement. Eventually, the perilobular stroma diminishes and is displaced by hyperplastic and hypertrophied lobules that are closely apposed. Myoepithelial cells are inconspicuous. Intracytoplasmic secretion droplets (fat rich) accumulate within the duct luminal epithelial cells, and secretion begins to exude into the lumens. During lactation, the epithelial cells show vacuoles and cytoplasmic blebs along the luminal borders (Fig. 19-6). These changes may remain uneven within the breasts for up to 3 months after the cessation of breastfeeding. This postgestational involution shows increased interlobular fibrofatty tissue, decreased numbers of acini, increased intralobular fibrous tissue, and eventual return to a normal reproductive morphologic appearance.

Pregnancy-like changes are sometimes found focally in the breast lobules of women who are neither pregnant nor lactating, in postmenopausal women,[3-10] and even in men treated with estrogens.[4] The incidence is reported to be 1.7% to 3% in surgical pathology and autopsy material,[4] and the cause is unknown. Pregnancy-like change is characterized by acinar epithelial cells showing frayed, vacuolated cytoplasm.[3,4] Pregnancy-like hyperplasia refers to pregnancy-like change occurring in hyperplastic epithelium; this is much less common.[4] Cytoplasm is frayed and vacuolated, but a micropapillary pattern, disorderly cellular arrangement, and sometimes nuclear atypia are also present (Fig. 19-7). The differential diagnosis includes clear cell change, cytoplasmic clearing in apocrine metaplasia, and intraepithelial reactive histiocytes.[4,8] The cause of clear cell change is unknown, and it has no known clinical consequences. It is composed of swollen acinar cells with abundant clear or pale, finely granular cytoplasm and small, round (sometimes centrally disposed) nuclei[4] (Fig. 19-8). Cytoplasmic clearing in apocrine metaplasia is focal and easily recognized when characteristic apocrine metaplasia is adjacent.

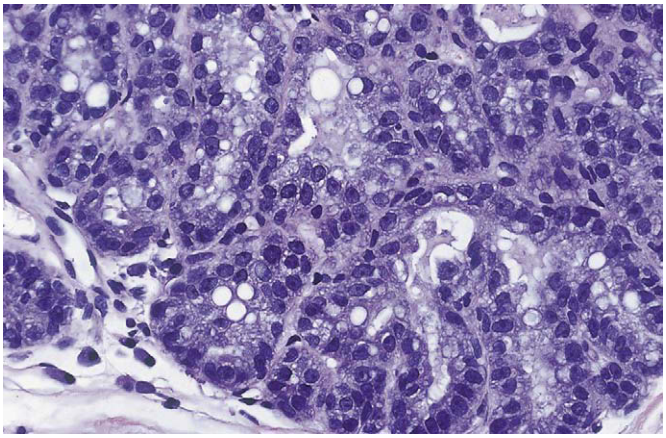

Figure 19-6 ■ Lactational changes in the breast. Vacuolated cytoplasm, vesicular nuclei, and nucleoli are features consistent with milk product synthesis and secretion and should not be confused with malignant atypia.

Small collections of foamy cells are not infrequent within duct lumens or in cohesive masses along duct walls (Fig. 19-9), usually in cases of fibrocystic disease. Duct ectasia is associated with numerous foamy histiocytes, not only within ectatic duct lumens but also in the adjacent fibrous wall, which may not have an epithelial layer (Fig. 19-10). Plasma cells may be numerous in the wall as well (so-called plasma cell mastitis). Histiocytes are CD68 positive and cytokeratin negative; epithelial cells are keratin positive and usually CD68 negative.

After menopause, hormonal support for the breast is markedly reduced, and postmenopausal involution or atrophy occurs. There is a decrease in the cellularity and number of lobules, associated with thickening of lobular basement membranes and collagenization of intralobular stroma. This occurs in a heterogeneous fashion; some lobules are unaffected, whereas adjacent lobules are totally atrophic. There may be some mild duct ectasia and intraluminal microcalcification. This atrophy is attenuated by exogenous estrogen-containing medications.[4]

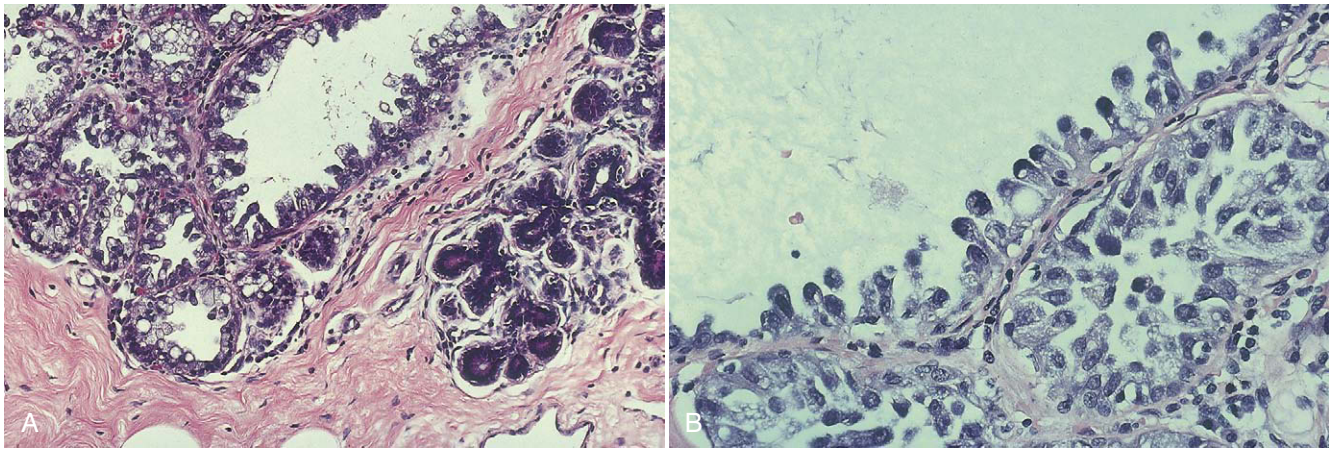

Figure 19-7 ■ **A,** Focal lactational changes in a postmenopausal breast; immediately adjacent acini show no lactational changes. **B,** Focal lactational changes with "hobnail" cells and mild cytologic atypia.

ANOMALIES

In about 2% of women, and more rarely in men, there may be one or more extra breasts (polymastia) or extra nipples (polythelia). Accessory mammary tissue is apparently most common among Asians, especially Japanese, in whom it has been reported to occur in about 5.2% of women and 1.7% of men.[3] These extra breasts or nipples can occur anywhere along the milk lines and can eventually develop various breast diseases. This happens most frequently in the inguinal and axillary regions or just below the normal breasts; when disease develops, the lesions can be mistaken for primary cutaneous adnexal lesions.[3,4] Partial or complete suppression of breast anlagen during embryogenesis results in partial or complete absence of breasts. Complete absence of a breast (amastia) is rare.[4] Underdevelopment (hypoplasia) is usually associated with concomitant hypoplasia of the pectoralis muscle.[3,4] Hypoplasia may be unilateral or bilateral and should not be confused with the much more common and normal minor variations in breast size. Radiation in infancy or childhood, usually for the treatment of hemangiomas, is the most common cause of acquired mammary hypoplasia in women. Surgical removal of the prepubertal breast bud also causes hypoplasia or amastia; thus, the surgeon must take care when making any incision for the drainage of lesions of the nipple-areolar complex or masses within the breast bud to avoid subsequent maldevelopment.

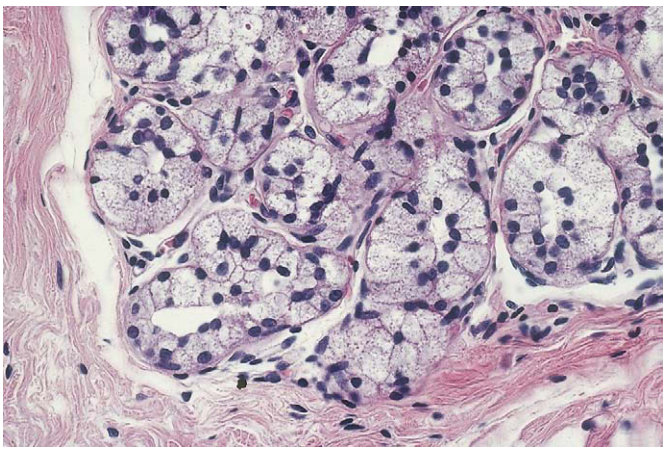

Figure 19-8 ■ Clear cell change or metaplasia. This feature should not be confused with clear cell ductal carcinoma in situ.

Juvenile (adolescent or virginal) hypertrophy or adolescent macromastia is an uncommon condition in which a young girl (usually 11 to 14 years old) experiences a normal puberty but then has continued rapid breast growth and enlargement, even into maturity.[7] There may be a family history of this problem. Most have bilateral symmetrical breast enlargement, although unilateral cases can occur. The breasts do not decrease in size, and reduction mammaplasty is required.[4] Histologic examination shows greatly increased fibrofatty connective tissue, sometimes with increased numbers of ducts resulting in a gynecomastia-like pattern or a pattern resembling pseudoangiomatous stromal hyperplasia.[3,4] Some of these fibrotic breasts may exhibit so-called juvenile units, which are composed of branching ducts without lobules surrounded by a rim of myxomatous, alcian blue–positive stroma. Juvenile units resemble mammary tissue during early breast development. Even more rare is gravid macromastia, which develops rapidly after the onset of pregnancy.[4] The cause is unknown, but once established, it occurs with each subsequent pregnancy. Variable stromal fibrosis, fibroadenoma-like changes, some glandular proliferation or hyperplasia, and pseudoangiomatous stromal hyperplasia have been found on histologic examination.[4]

Gynecomastia, the most common abnormality of the male breast,[4] occurs in 30% to 40% of adolescent and adult men. It produces bilateral or unilateral nodular or diffuse masses, which can be associated with hyperthyroidism, liver cirrhosis, chronic renal failure, chronic pulmonary disease, hypogonadism, exogenous steroid hormones, neoplasia (especially lung carcinoma and germ cell tumors), and drugs (e.g., digitalis, cimetidine, spironolactone, marijuana, tricyclic antidepressants). Florid active gynecomastia presents as prominent periductal stromal edema with epithelial hyperplasia (Fig. 19-11) and is usually of less than 1 year's duration. After 6 months, inactive gynecomastia appears, with reduced periductal stromal edema, collagenized stroma, and minimal epithelial hyperplasia.

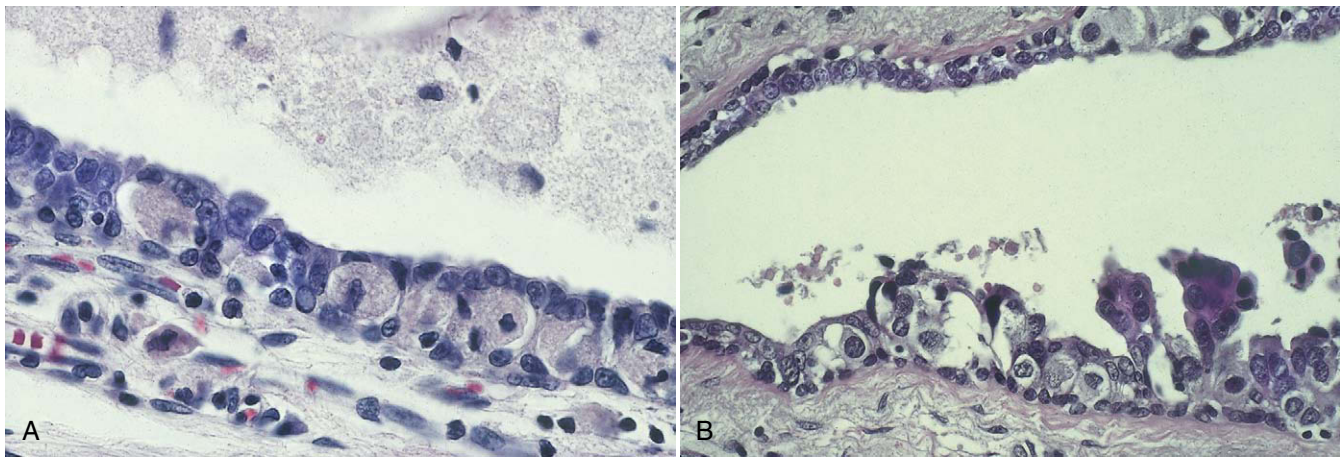

Figure 19-9 ■ **A,** Intraepithelial histiocytes. Also note the intraluminal histiocytes, which is a clue to the histiocytic nature of the intraepithelial cells. **B,** Intraepithelial histiocytes should not be confused with true pagetoid spread of carcinoma cells, shown here. Carcinoma cells show more nuclear atypia, have less distinct foamy cytoplasm, and react with antibodies to cytokeratin.

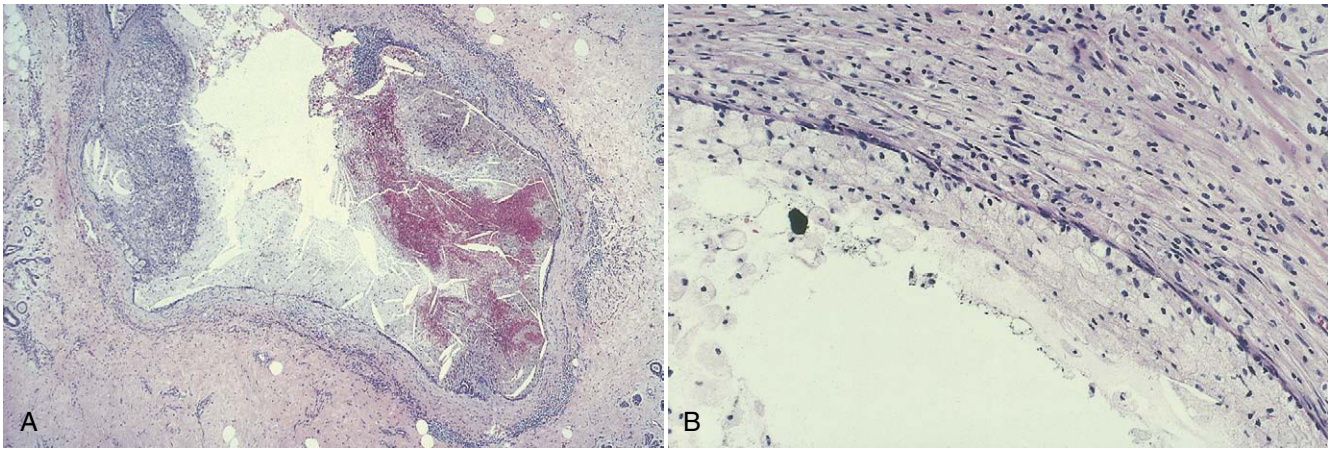

Figure 19-10 ■ Duct ectasia. **A,** Large cavity filled with amorphous debris and blood. **B,** Denuded wall and adherent foamy histiocytes extend into the adjacent fibrous tissues.

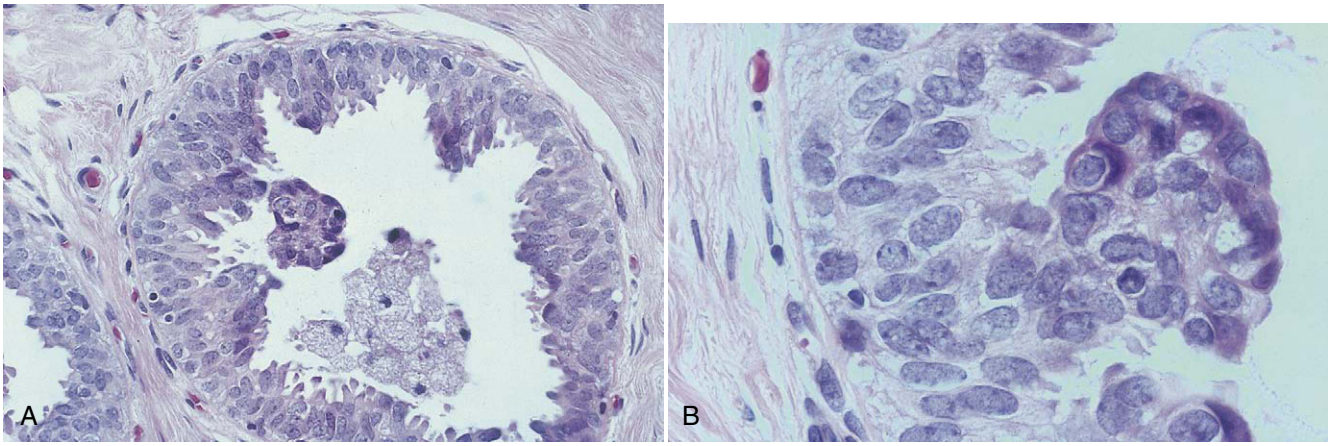

Figure 19-11 ■ Gynecomastia in a man. **A,** Note the absence of terminal duct lobular unit development. **B,** Papillary hyperplasia composed of bland stratified cells. This change (gynecomastoid hyperplasia) may occur rarely within the female breast.