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CHAPTER 18

# Female Genital System and Breast

CHAPTER CONTENTS



## VULVA

The *vulva* is the external female genitalia and includes the moist hair-bearing skin and mucosa in that region. Disorders of the vulva most frequently are inflammatory, rendering them more uncomfortable than serious. Malignant tumors of the vulva, although life-threatening, are rare.

### VULVITIS

One of the most common causes of vulvitis is reactive inflammation in response to an exogenous stimulus, whether an irritant (contact irritant dermatitis) or an allergen (contact allergic dermatitis). Scratching-induced trauma secondary to associated intense "itching" (pruritus) often exacerbates the primary condition.

Contact irritant eczymatous dermatitis manifests as well-defined erythematous weeping and crusting papules and plaques (Chapter 23) and may be a reaction to urine, soaps, detergents, antiseptics, deodorants, or alcohol. Allergic dermatitis has a similar clinical appearance and may result from allergy to perfumes; additives in creams, lotions, and soaps; chemical treatments on clothing; and other antigens.

Vulvitis also may be caused by infections, which in this setting often are sexually transmitted (Chapter 17). The most important of these infectious agents in North America are human papillomavirus (HPV), the causative agent of condyloma acuminatum and vulvar intraepithelial neoplasia (VIN) (discussed later); herpes simplex virus (HSV-1 or -2), the agent of genital herpes with its characteristic

*The contributions of Drs. Susan Lester (Diseases of Breast) and Anthony Montag (Diseases of Female Genital System) are gratefully acknowledged.*

vesicular eruption; *N. gonorrhoeae*, a cause of suppurative infection of the vulvovaginal glands; *Treponema pallidum,* the syphilis pathogen, in association with the primary chancre at a vulvar site of inoculation; and *Candida,* also a potential cause of vulvitis.

An important complication of vulvitis is obstruction of the excretory ducts of Bartholin glands. This blockage may result in painful dilation of the glands (a Bartholin cyst) and abscess formation.

## NON-NEOPLASTIC EPITHELIAL DISORDERS

The epithelium of the vulvar mucosa may undergo both atrophic thinning and hyperplastic thickening, often in the form of lichen sclerosus and lichen simplex chronicus, respectively.

### Lichen Sclerosus

Lichen sclerosus is characterized by thinning of the epidermis, disappearance of rete pegs, hydropic degeneration of the basal cells, dermal fibrosis, and a scant perivascular, mononuclear inflammatory cell infiltrate (Fig. 18–1). It appears as smooth, white plaques (termed *leukoplakia*) or papules that in time may extend and coalesce. When the entire vulva is affected, the labia become somewhat atrophic and stiffened, and the vaginal orifice is constricted. Lichen sclerosus occurs in all age groups but most commonly affects postmenopausal women. The pathogenesis is uncertain, but the presence of activated T cells in the subepithelial inflammatory infiltrate and the increased frequency of autoimmune disorders in affected women suggest an autoimmune etiology. Lichen sclerosus is benign; however, a small percentage of women (1% to 5%) with symptomatic lichen sclerosus develop squamous cell carcinoma of the vulva.

### Lichen Simplex Chronicus

Lichen simplex chronicus is marked by epithelial thickening (particularly of the stratum granulosum) and hyperkeratosis. Increased mitotic activity is seen in the basal and suprabasal layers; however, there is no epithelial atypia (Fig. 18–1). Leukocytic infiltration of the dermis is sometimes pronounced. These nonspecific changes are a consequence of chronic irritation, often caused by pruritus related to an underlying inflammatory dermatosis. Lichen simplex chronicus appears as an area of leukoplakia. With isolated lesions, no increased predisposition to cancer has been found, but lichen simplex chronicus often is present at the margins of established vulvar cancer, raising the possibility of an association with neoplastic disease.

Lichen sclerosus and lichen simplex chronicus may coexist in different areas of the body in the same person, and both lesions may take the form of leukoplakia. Similar white patches or plaques also are seen in a variety of other benign dermatoses, such as psoriasis and lichen planus (Chapter 23), as well as in malignant lesions of the vulva, such as squamous cell carcinoma in situ and invasive squamous cell carcinoma. Thus, biopsy and microscopic examination are needed to differentiate these clinically similar-appearing lesions.

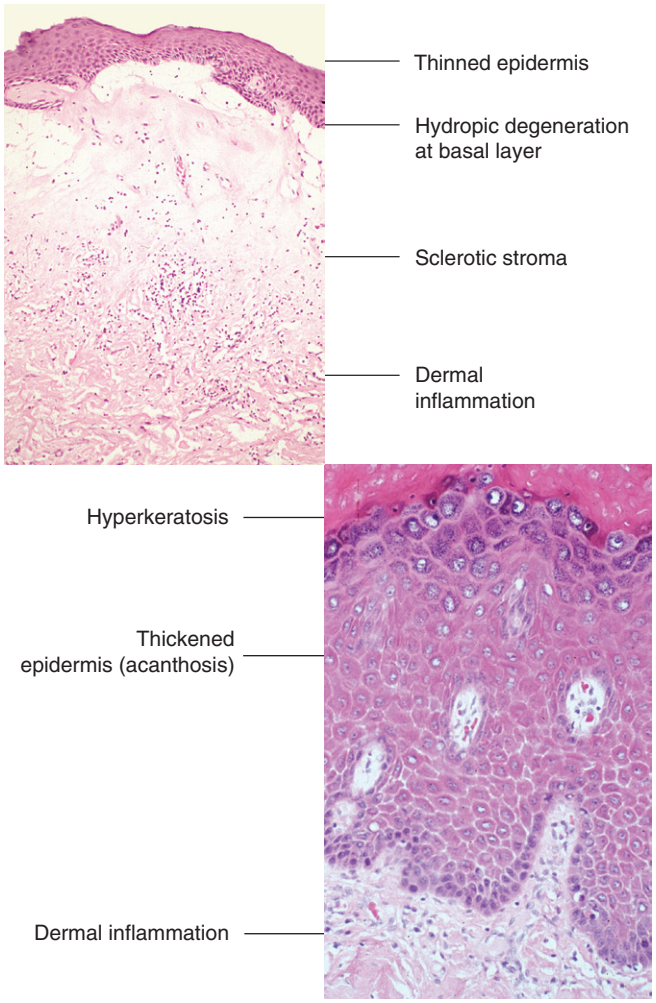



**Figure 18–1** *Upper panel*, Lichen sclerosus. *Lower panel*, Lichen simplex chronicus. The main features of the lesions are labeled.

### SUMMARY

#### Non-neoplastic Epithelial Disorders

- Lichen sclerosus is characterized by atrophic epithelium, usually with dermal fibrosis.
- Lichen sclerosus carries a slightly increased risk for development of squamous cell carcinoma.
- Lichen simplex chronicus is characterized by thickened epithelium (hyperplasia), usually with an inflammatory infiltrate.
- The lesions of lichen sclerosus and lichen simplex chronicus must be biopsied to definitively distinguish them from other causes of leukoplakia, such as squamous cell carcinoma of the vulva.

# TUMORS

## Condylomas

*Condyloma* is the name given to any warty lesion of the vulva. Most such lesions can be assigned to one of two distinctive forms. *Condylomata lata,* not commonly seen today, are flat, moist, minimally elevated lesions that occur in secondary syphilis (Chapter 17). The more common *condylomata acuminata* may be papillary and distinctly elevated or somewhat flat and rugose. They can occur anywhere on the anogenital surface, sometimes as single but more often as multiple lesions. When located on the vulva, they range from a few millimeters to many centimeters in diameter and are red-pink to pink-brown (Fig. 18–2). On histologic examination, the characteristic cellular feature is koilocytosis, a cytopathic change characterized by perinuclear cytoplasmic vacuolization and wrinkled nuclear contours that is a hallmark of HPV infection (Fig. 18–2; see also Chapter 17). Indeed, condylomata acuminata are strongly associated with HPV subtypes 6 and 11. HPV can be transmitted venereally, and identical lesions occur in men on the penis and around the anus. HPV 6 and 11 infections carry a low risk of malignant transformation, and hence, vulvar condylomas do not commonly progress to cancer.

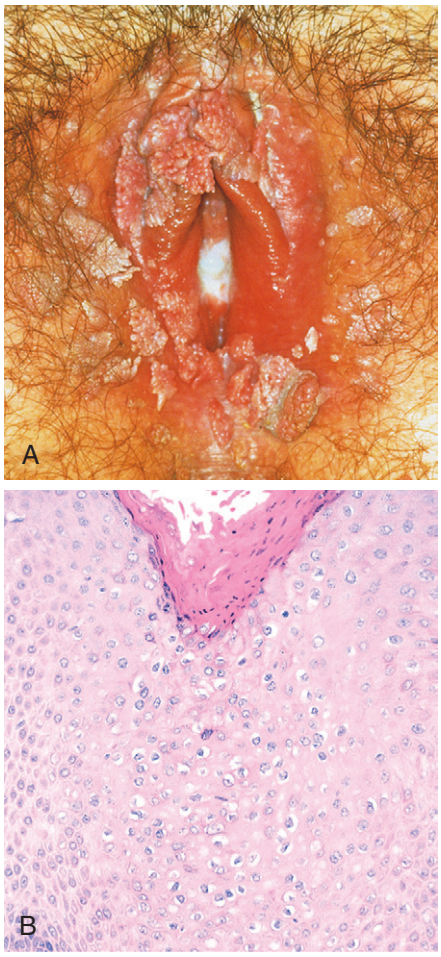



**Figure 18–2 A,** Numerous condylomas of the vulva. **B,** Histopathologic features of condyloma acuminatum include acanthosis, hyperkeratosis, and cytoplasmic vacuolation (koilocytosis, *center*).
*(A, Courtesy of Dr. Alex Ferenczy, McGill University, Montreal, Quebec, Canada.)*

## Carcinoma of the Vulva

Carcinoma of the vulva represents about 3% of all female genital tract cancers, occurring mostly in women older than age 60. Approximately 90% of carcinomas are squamous cell carcinomas; the other tumors are mainly adenocarcinomas or basal cell carcinomas.

There appear to be two distinct forms of vulvar squamous cell carcinoma. The less common form is related to high-risk HPV strains (especially HPV subtypes 16 and 18) and occurs in middle-aged women, particularly cigarette smokers. In this form, the onset of carcinoma often is preceded by precancerous changes in the epithelium termed *vulvar intraepithelial neoplasia* (VIN). VIN progresses in most patients to greater degrees of atypia and eventually undergoes transformation to carcinoma in situ; however, progression to invasive carcinoma is not inevitable and often occurs after many years. Environmental factors such as cigarette smoking and immunodeficiency appear to increase the risk of such progression.

A second form of vulvar carcinoma occurs in older women. It is not associated with HPV but often is preceded by years of reactive epithelial changes, principally lichen sclerosus. The overlying epithelium frequently lacks the typical cytologic changes of VIN, but it may display subtle atypia of the basal layer and basal keratinization. Invasive tumors of this form tend to be well differentiated and highly keratinizing.

### MORPHOLOGY

VIN and early vulvar carcinomas manifest as areas of **leukoplakia** in the form of whitish patches of epithelial thickening. In about one fourth of the cases, the lesions are pigmented owing to the presence of melanin. Over time, these areas are transformed into overt **exophytic** or ulcerative **endophytic tumors.** HPV-positive tumors often are multifocal and warty and tend to be poorly differentiated **squamous cell carcinomas,** whereas HPV-negative tumors usually are unifocal and typically manifest as well-differentiated keratinizing squamous cell carcinomas.

Both forms of vulvar carcinoma tend to remain confined to their site of origin for a few years but ultimately invade and spread, usually first to regional nodes. The risk of metastasis correlates with the size of the tumor and the depth of invasion. Women with tumors less than 2 cm in diameter have about a 90% 5-year survival rate after radical excision, whereas only 20% of those with advanced-stage lesions survive for 10 years.

## Extramammary Paget Disease

Paget disease is an intraepidermal proliferation of malignant epithelial cells that can occur in the skin of the vulva or nipple of the breast. However, unlike in the breast, where Paget disease is virtually always associated with an

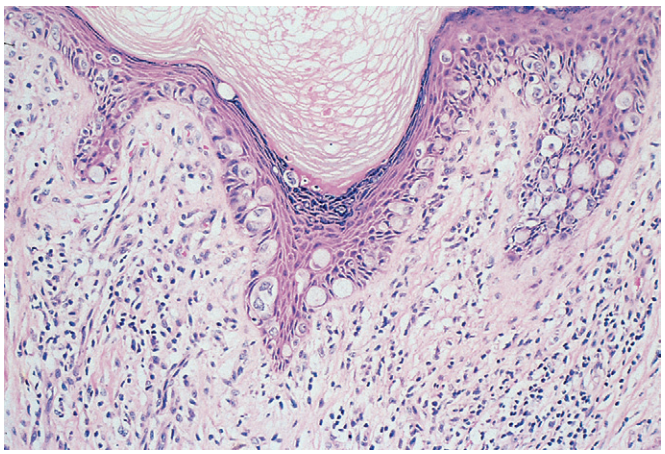


**Figure 18–3** Paget disease of the vulva, with large tumor cells with abundant clear cytoplasm scattered throughout the epidermis.

underlying carcinoma, a majority of cases of vulvar (extramammary) Paget disease have no demonstrable underlying tumor. Instead, vulvar Paget cells most commonly appear to arise from epidermal progenitor cells. Only occasionally, Paget disease in this location is accompanied by a subepithelial or submucosal tumor arising in an adnexal structure, typically sweat glands.

Paget disease manifests as a red, scaly, crusted plaque that may mimic the appearance of an inflammatory dermatitis. On histologic examination, large epithelioid cells with abundant pale, finely granular cytoplasm and occasional cytoplasmic vacuoles infiltrate the epidermis, singly and in groups (Fig. 18–3). The presence of mucin, as detected by periodic acid–Schiff (PAS) staining, is useful in distinguishing Paget disease from vulvar melanoma, which lacks mucin.

Intraepidermal Paget disease may persist for years or even decades without evidence of invasion. However, when there is an associated tumor involving skin appendages, the Paget cells may invade locally, and ultimately metastasize. Once metastasis occurs, the prognosis is poor.

### SUMMARY

#### Squamous Cell Carcinoma of the Vulva

- HPV-related vulvar squamous cell carcinomas usually are poorly differentiated lesions and sometimes are multifocal. They often evolve from vulvar intraepithelial neoplasia (VIN).
- Non–HPV-related vulvar squamous cell carcinomas occur in older women, usually are well differentiated and unifocal, and often are associated with lichen sclerosus or other inflammatory conditions.

#### Paget Disease of the Vulva

- Vulvar Paget disease is characterized by a red, scaly plaque caused by proliferation of malignant epithelial cells within the epidermis; usually, there is no underlying carcinoma, unlike Paget disease of nipple.
- Positive staining for PAS distinguishes Paget disease cells from melanoma.

## VAGINA

In adult fernales, the vagina is seldom a site of primary disease. More often, it is involved secondarily by cancer or infections arising in adjacent organs (e.g., cervix, vulva, bladder, rectum).

Congenital anomalies of the vagina fortunately are uncommon and include entities such as total absence of the vagina, a septate or double vagina (usually associated with a septate cervix and, sometimes, septate uterus), and congenital, lateral Gartner duct cysts arising from persistent wolffian duct rests.

### VAGINITIS

Vaginitis is a relatively common condition that is usually transient and of no clinical consequence. It is associated with production of a vaginal discharge (leukorrhea). A large variety of organisms have been implicated, including bacteria, fungi, and parasites. Many are normal commensals that become pathogenic only in the setting of diabetes, systemic antibiotic therapy (which causes disruption of normal microbial flora), immunodeficiency, pregnancy, or recent abortion. In adults, primary gonorrheal infection of the vagina is uncommon. The only other organisms worthy of mention, because they are frequent offenders, are *Candida albicans* and *Trichomonas vaginalis.* Candidal (monilial) vaginitis is characterized by a curdy white discharge. This organism is part of the normal vaginal flora in about 5% of women, so the appearance of symptomatic infection almost always involves one of the predisposing influences cited above or superinfection by a new, more aggressive strain. *T. vaginalis* produces a watery, copious gray-green discharge in which parasites can be identified by microscopy. *Trichomonas* also can be identified in about 10% of asymptomatic women; thus, active infection usually stems from sexual transmission of a new strain.

### MALIGNANT NEOPLASMS

#### Squamous Cell Carcinoma

Squamous cell carcinoma of the vagina is an extremely uncommon cancer that usually occurs in women older than 60 years of age in the setting of risk factors similar to those associated with carcinoma of the cervix (discussed later). Vaginal intraepithelial neoplasia is a precursor lesion that is nearly always associated with HPV infection. Invasive squamous cell carcinoma of the vagina is associated with the presence of HPV DNA in more than half of the cases, presumably derived from HPV-positive VIN.

### Clear Cell Adenocarcinoma

In 1970, clear cell adenocarcinoma, a very rare tumor, was identified in a cluster of young women whose mothers took diethylstilbestrol during pregnancy to prevent threatened abortion. Follow-up studies determined that the incidence of this tumor in persons exposed to diethylstilbestrol in utero was low (less than 1 per 1000, albeit about 40 times greater than in the unexposed population). However, since this agent was in wide use at the time it appears to be associated with a persistently elevated risk of cancer in those exposed. In about one third of exposed women, small glandular or microcystic inclusions appear in the vaginal mucosa. These benign lesions are seen as red, granular-appearing foci that on histologic examination are lined by mucus-secreting or ciliated columnar cells. This clinical condition is called *vaginal adenosis*, and it is from such precursor lesions that clear cell adenocarcinoma arises.

### Sarcoma Botryoides

Sarcoma botryoides (embryonal rhabdomyosarcoma) is a rare form of primary vaginal cancer that manifests as soft polypoid masses. It usually is encountered in infants and children younger than 5 years of age. It also may occur in other sites, such as the urinary bladder and bile ducts. These lesions are described in further detail in Chapter 20.

## CERVIX

Most cervical lesions are relatively banal inflammations (cervicitis), but the cervix also is the site of one of the most common cancers in women worldwide.

## CERVICITIS

Inflammatory conditions of the cervix are extremely common and are associated with a purulent vaginal discharge. Cervicitis can be subclassified as infectious or noninfectious, although differentiation is difficult owing to the presence of normal vaginal flora including incidental vaginal aerobes and anaerobes, streptococci, staphylococci, enterococci, and *Escherichia coli*.

Much more important are *Chlamydia trachomatis, Ureaplasma urealyticum, T. vaginalis, Candida* spp., *Neisseria gonorrhoeae,* HSV-2 (the agent of herpes genitalis), and certain types of HPV, all of which are often sexually transmitted. *C. trachomatis* is by far the most common of these pathogens, accounting for as many as 40% of cases of cervicitis encountered in sexually transmitted disease (STD) clinics. Although less common, herpetic infections are noteworthy because maternal-infant transmission during childbirth may result in serious, sometimes fatal systemic herpetic infection in the newborn.

### MORPHOLOGY

Nonspecific cervicitis may be either **acute** or **chronic.** The relatively uncommon **acute form** is limited to women in the postpartum period and usually is caused by staphylococci or streptococci. Chronic cervicitis consists of inflammation and epithelial regeneration, some degree of which is common in all women of reproductive age. The cervical epithelium may show hyperplasia and reactive changes in both squamous and columnar mucosae. Eventually, the columnar epithelium undergoes squamous metaplasia.

Cervicitis commonly comes to attention on routine examination or because of leukorrhea. Culture of the discharge must be interpreted cautiously, because (as mentioned previously) commensal organisms are virtually always present. Only the identification of known pathogens is helpful.

## NEOPLASIA OF THE CERVIX

*Most tumors of the cervix are of epithelial origin and are caused by oncogenic strains of human papillomavirus (HPV).* During development, the columnar, mucus-secreting epithelium of the endocervix is joined to the squamous epithelial covering of the exocervix at the cervical os. With the onset of puberty, the squamocolumnar junction undergoes eversion, causing columnar epithelium to become visible on the exocervix. The exposed columnar cells, however, eventually undergo squamous metaplasia, forming a region called the *transformation zone* (Fig. 18–4).

### PATHOGENESIS

HPV, the causative agent of cervical neoplasia, has a tropism for the immature squamous cells of the transformation zone. Most HPV infections are transient and are eliminated within months by an acute and chronic inflammatory response. A subset of infections persists, however, and some of these progress to cervical intraepithelial neoplasia (CIN), a

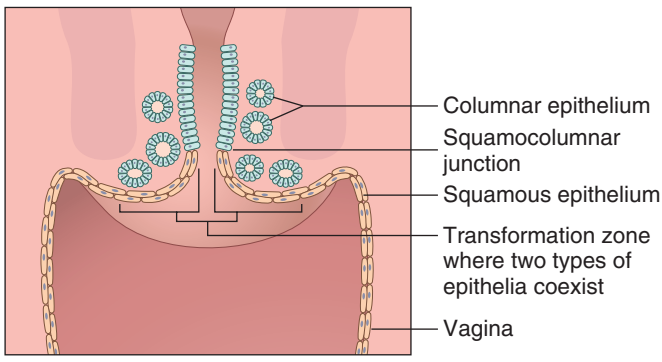



**Figure 18–4** Development of the cervical transformation zone.

precursor lesion from which most invasive cervical carcinomas develop.

HPV is detectable by molecular methods in nearly all cases of CIN and cervical carcinoma. Important risk factors for the development of CIN and invasive carcinoma thus are directly related to HPV exposure and include

- Early age at first intercourse
- Multiple sexual partners
- Male partner with multiple previous sexual partners
- Persistent infection by high-risk strains of papillomavirus

Although HPV infection occurs in the most immature squamous cells of the basal layer, replication of HPV DNA takes place in more differentiated overlying squamous cells. Squamous cells at this stage of maturation do not normally replicate DNA, but HPV-infected squamous cells do, as a consequence of expression of two potent oncoproteins encoded in the HPV genome called E6 and E7. The E6 and E7 proteins bind and inactivate two critical tumor suppressors, p53 and Rb, respectively (Chapter 5), and in doing so promote growth and increased susceptibility to additional mutations that may eventually lead to carcinogenesis.

Recognized serotypes of HPV can be classified as high-risk or low-risk types based on their propensity to induce carcinogenesis. High-risk HPV infection is the most important risk factor for the development of CIN and carcinoma. Two high-risk HPV strains, types 16 and 18, account for approximately 70% of cases of CIN and cervical carcinoma. In general, infections with high-risk HPV serotypes are more likely to persist, which is a risk factor for progression to carcinoma. These HPV subtypes also show a propensity to integrate into the host cell genome, an event that is linked to progression. Low-risk HPV strains (e.g., types 6 and 11), on the other hand, are associated with development of condylomas of the lower genital tract (Fig. 18–5) and do not integrate into the host genome, remaining instead as free episomal viral DNA. Despite the strong association of HPV infection with cancer of the cervix, HPV is not sufficient to drive the neoplastic process. As mentioned below, several HPV-infected high-grade precursor lesions do not progress to invasive cancer. The progression of cervical dysplasias to cervical cancers has been attributed to diverse factors such as immune and hormonal status, or co-infection with other sexually transmitted agents. More recently, somatically acquired mutations in the tumor suppressor gene *LKB1* were identified in more than 20% of cervical cancers. *LKB1* was first identified as the gene mutated in Peutz-Jeghers syndrome, an autosomal dominant condition characterized by hamartomatous polyps of the GI tract (Chapter 14) and a significantly elevated risk of epithelial malignancies at a variety of anatomic sites including the cervix. *LKB1* is also frequently inactivated in lung cancer. The LKB1 protein is a serine-threonine kinase that phosphorylates and activates AMPK, a metabolic sensor. AMPK in turn regulates cell growth through the mTOR complex.

## Cervical Intraepithelial Neoplasia (CIN)

HPV-related carcinogenesis begins with the precancerous epithelial change termed CIN, which usually precedes the development of an overt cancer by many years, sometimes decades. In keeping with this idea, CIN peaks in incidence at about 30 years of age, whereas invasive carcinoma peaks at about 45 years of age.

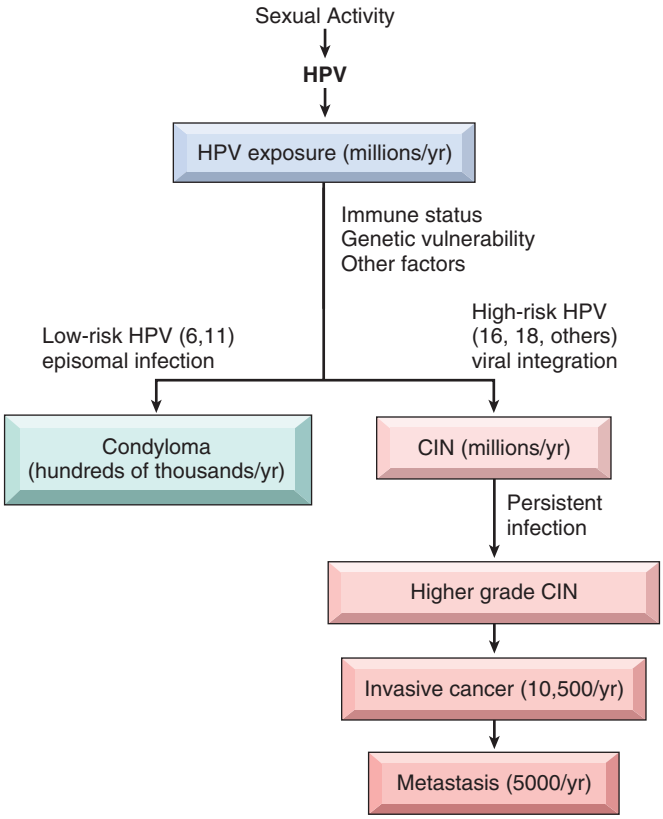



**Figure 18–5** Possible consequences of human papillomavirus (HPV) infection. Progression is associated with integration of virus and acquisition of additional mutations as discussed in the text. CIN, cervical intraepithelial neoplasia.

CIN usually starts as low-grade dysplasia (CIN I) and progresses to moderate (CIN II) and then severe dysplasia (CIN III) over time; exceptions have been reported, however, and some patients already have CIN III when the condition is first diagnosed. Generally speaking, the higher the grade of CIN, the greater the likelihood of progression; of note, however, in many cases, even high-grade lesions fail to progress to cancer and may even regress. Because decisions about patient management are two-tiered (i.e., observation versus surgical treatment), this three-tiered grading system has recently been simplified to a two-tiered system, with CIN I renamed **low-grade squamous intraepithelial lesion** (LSIL) and CIN II and CIN III combined into one category referred to as **high-grade squamous intraepithelial lesion** (HSIL). As shown in Table 18–1, the decision to treat HSIL and to observe LSIL is based on differences in the natural histories of these two groups of lesions.

**Table 18–1** Natural History of Squamous Intraepithelial Lesions (SILs)

| Lesion | Regress | Persist | Progress |
|---|---|---|---|
| LSIL (CIN I) | 60% | 30% | 10% (to HSIL) |
| HSIL (CIN II, III) | 30% | 60% | 10% (to carcinoma)* |

LSIL, low-grade SIL; HSIL, high-grade SIL.
*Progression within 10 years.

Cervical precancerous lesions are associated with abnormalities in cytologic preparations (Pap smears) that can be detected long before any abnormality is visible on gross inspection. Early detection of dysplastic changes is the rationale for the Papanicolaou (Pap) test, in which cells are scraped from the transformation zone and examined microscopically. To date, the Pap smear remains the most successful cancer screening test ever developed. In the United States, Pap screening has dramatically lowered the incidence of invasive cervical tumors to about 12,000 cases annually with a mortality of about 4000 per year; in fact, cervical cancer no longer ranks among the top 10 causes of cancer deaths in U.S. women. Paradoxically, the incidence of CIN has increased to its present level of more than 50,000 cases annually. Increased detection has certainly contributed to this.

The recently introduced quadrivalent HPV vaccine for types 6, 11, 16, and 18 is very effective in preventing HPV infections, which is expected to greatly lower the frequency of genital warts and cervical cancers associated with these HPV serotypes. Despite its efficacy, the vaccine does not supplant the need for routine cervical cancer screening—many at-risk women are already infected, and the vaccine protects against only some of the many oncogenic HPV serotypes.

### MORPHOLOGY

Figure 18–6 illustrates the three stages of CIN. **CIN I** is characterized by dyplastic changes in the lower third of the squamous epithelium and koilocytotic change in the superficial layers of the epithelium. In **CIN II,** dysplasia extends to the middle third of the epithelium and takes the form of delayed keratinocyte maturation. It also is associated with some variation in cell and nuclear size, heterogeneity of nuclear chromatin, and presence of mitoses above the basal layer extending into the middle third of the epithelium. The superficial layer of cells shows some differentiation and occasionally demonstrates the koilocytotic changes described. The next stage, **CIN III,** is marked by almost complete loss of maturation, even greater variation in cell and nuclear size, chromatin heterogeneity, disorderly orientation of the cells, and normal or abnormal mitoses; these changes affect virtually all layers of the epithelium. Koilocytotic change usually is absent. These histologic features correlate with the cytologic appearances shown in Figure 18–7. As mentioned previously, for clinical purposes CIN is divided into LSIL (CIN I) and HSIL (CIN II and CIN III).

CIN is asymptomatic and comes to clinical attention through an abnormal Pap smear result. These cases are followed up by colposcopy, during which acetic acid is used to highlight the location of lesions and the areas to be biopsied. Women with biopsy-documented LSIL are managed conservatively with careful observation, whereas HSILs are treated with surgical excision (cone biopsy). Follow-up smears and clinical examination are mandated for life in patients with HSIL, as these women remain at risk for HPV-associated cervical, vulvar, and vaginal cancers.

## Invasive Carcinoma of the Cervix

The most common cervical carcinomas are squamous cell carcinomas (75%), followed by adenocarcinomas and mixed adenosquamous carcinomas (20%) and small cell neuroendocrine carcinomas (less than 5%). All of these types of carcinomas are caused by HPV. Of interest, the relative proportion of adenocarcinomas has been increasing in recent decades owing to the decreasing incidence of invasive squamous carcinoma and suboptimal detection of glandular lesions by Pap smear.

Squamous cell carcinoma has a peak incidence at the age of about 45 years, some 10 to 15 years after detection of precursor CIN. As already discussed, progression of CIN to invasive carcinoma is variable and unpredictable and requires HPV infection as well as mutations in genes such as *LKB*. Risk factors for progression include cigarette smoking and human immunodeficiency virus

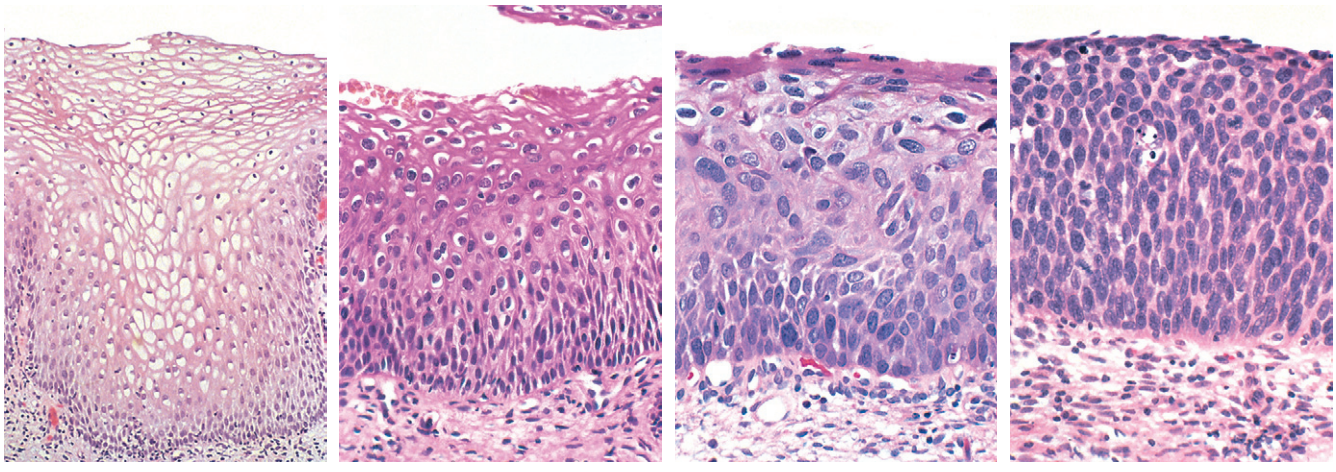



**Figure 18–6** Spectrum of cervical intraepithelial neoplasia (CIN), with normal squamous epithelium for comparison: CIN I with koilocytotic atypia; CIN II with progressive atypia in all layers of the epithelium; and CIN III (carcinoma in situ) with diffuse atypia and loss of maturation.

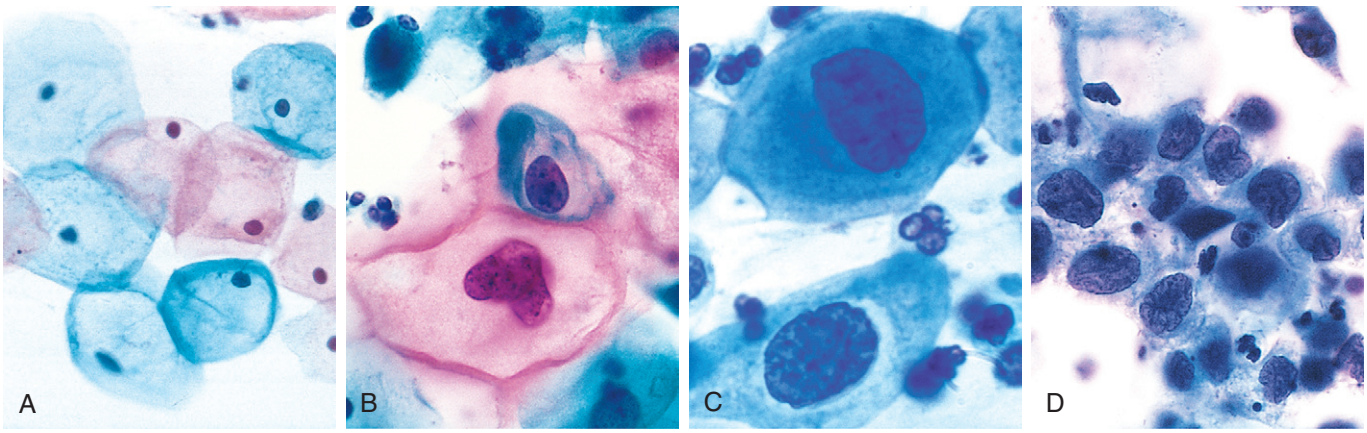



**Figure 18–7** Cytologic features of cervical intraepithelial neoplasia (CIN) in a Papanicolaou smear. Superficial squamous cells may stain either red or blue. **A,** Normal exfoliated superficial squamous epithelial cells. **B,** CIN I—low-grade squamous intraepithelial lesion (LSIL). **C** and **D,** CIN II and CIN III, respectively—both high-grade squamous intraepithelial lesions (HSILs). Note the reduction in cytoplasm and the increase in the nucleus-to-cytoplasm ratio as the grade of the lesion increases. This observation reflects the progressive loss of cellular differentiation on the surface of the cervical lesions from which these cells are exfoliated (Figure 18–6).
*(Courtesy of Dr. Edmund S. Cibas, Brigham and Women's Hospital, Boston, Massachusetts.)*

(HIV) infection, the latter finding suggesting that immune surveillance has a role in holding CIN in check. Although risk factors may help stratify patients who are likely to progress from CIN to carcinoma, the only reliable way to monitor the disease course is with frequent physical examinations coupled with biopsy of suspicious lesions.

## MORPHOLOGY

Invasive carcinomas of the cervix develop in the **transformation zone** and range from microscopic foci of stromal invasion to grossly conspicuous exophytic tumors (Fig. 18–8). Tumors encircling the cervix and penetrating into the underlying stroma produce a **barrel cervix,** which can be identified by direct palpation. Extension into the parametrial soft tissues can affix the uterus to the surrounding pelvic structures. The likelihood of spread to pelvic lymph nodes correlates with the depth of tumor invasion and the presence of tumor cells in vascular spaces. The risk of metastasis increases from less than 1% for tumors under 3 mm in depth to over 10% once invasion exceeds 3 mm. With the exception of unusual tumors exhibiting neuroendocrine differentiation, which are uniformly aggressive in their behavior, cervical carcinomas are graded based on their degree of squamous differentiation.

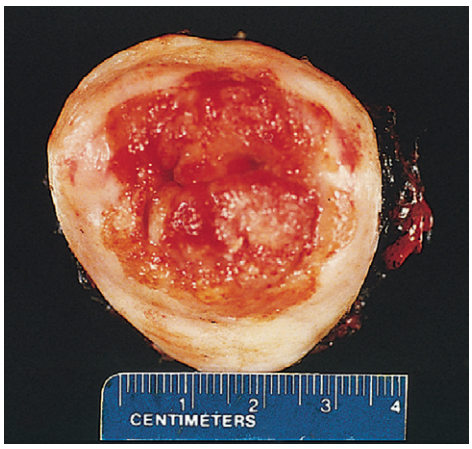



**Figure 18–8** Cervical os with surrounding, invasive, exophytic cervical carcinoma.

### Clinical Course

Invasive cervical cancer most often is seen in women who have never had a Pap smear or who have not been screened for many years. In such cases, cervical cancer often is symptomatic, with patients coming to medical attention for unexpected vaginal bleeding, leukorrhea, painful coitus (dyspareunia), or dysuria. Treatment is surgical by hysterectomy and lymph node dissection; small microinvasive carcinomas may be treated with cone biopsy. Mortality is most strongly related to tumor stage and, in the case of neuroendocrine carcinomas, to cell type. Most patients with advanced disease die as a result of local invasion rather than distant metastasis. In particular, renal failure stemming from obstruction of the urinary bladder and ureters is a common cause of death.

## SUMMARY

### Cervical Neoplasia

- Risk factors for cervical carcinoma are related to HPV exposure, such as early age at first intercourse, multiple sexual partners, and other factors including cigarette smoking and immunodeficiency.
- Nearly all cervical carcinomas are caused by HPV infections, particularly high-risk HPV types 16, 18, 31, and 33; the HPV vaccine is effective in preventing infection due to HPV types 16 and 18.
- HPV expresses E6 and E7 proteins that inactivate the p53 and Rb tumor suppressors, respectively, resulting in increased cell proliferation and suppression of DNA

damage–induced apoptosis. Loss of *LKB1* gene is also involved.
- In high-grade cervical dysplasias (CIN II and III), HPV is incorporated into the genome of the host cell.
- Not all HPV infections progress to CIN III or to invasive carcinoma. The time course from infection to invasive disease is usually 10 years or more. In general, the risk of progression is proportional to the degree of dysplasia.
- The Pap smear is a highly effective screening tool for the detection of cervical dysplasia and carcinoma and has significantly reduced the incidence of cervical carcinoma.

### Endocervical Polyp

Endocervical polyps are benign polypoid masses seen protruding from the endocervical mucosa (sometimes through the exocervix). They can be as large as a few centimeters, are soft and yielding to palpation, and have a smooth, glistening surface with underlying cystically dilated spaces filled with mucinous secretions. The surface epithelium and lining of the underlying cysts are composed of the same mucus-secreting columnar cells that line the endocervical canal. The stroma is edematous and may contain scattered mononuclear cells. Superimposed chronic inflammation may lead to squamous metaplasia of the overlying epithelium and ulcerations. These lesions may bleed, thereby arousing concern, but they have no malignant potential.

## BODY OF UTERUS

The uterine corpus is composed of endometrial mucosa and the underlying smooth muscle myometrium. The more frequent and significant disorders of the uterus are considered here.

## ENDOMETRITIS

Inflammation of the endometrium is classified as acute or chronic depending on whether a neutrophilic or a lymphoplasmacytic response predominates, respectively. The diagnosis of chronic endometritis generally requires the presence of plasma cells, as lymphocytes normally are seen in the endometrium.

Endometritis often is a consequence of pelvic inflammatory disease and is frequently due to *N. gonorrhoeae* or *C. trachomatis.* Histologic examination reveals a neutrophilic infiltrate in the superficial endometrium and glands coexisting with a stromal lymphoplasmacytic infiltrate. Prominent lymphoid follicles are more commonly seen in chlamydial infection. Tuberculosis causes granulomatous endometritis, frequently with associated tuberculous salpingitis and peritonitis. Although seen in the United States mainly in immunocompromised persons, tuberculous endometritis is common in countries where tuberculosis is endemic and should be included in the differential diagnosis for pelvic inflammatory disease in women who have recently emigrated from endemic areas.

Endometritis also may be due to retained products of conception, subsequent to miscarriage or delivery, or to presence of a foreign body such as an intrauterine device. Retained tissue or foreign bodies act as a nidus for ascending infection by vaginal or intestinal tract flora. Removal of the offending tissue or foreign body typically results in resolution.

Clinically, all forms of endometritis may manifest with fever, abdominal pain, and menstrual abnormalities. In addition, there is an increased risk of infertility and ectopic pregnancy as a consequence of damage and scarring of the fallopian tubes.

## ADENOMYOSIS

*Adenomyosis* refers to the growth of the basal layer of the endometrium down into the myometrium. Nests of endometrial stroma, glands, or both, are found deep in the myometrium interposed between the muscle bundles. The aberrant presence of endometrial tissue induces reactive hypertrophy of the myometrium, resulting in an enlarged, globular uterus, often with a thickened uterine wall. Because the glands in adenomyosis derive from the stratum basalis of the endometrium, they do not undergo cyclic bleeding. Nevertheless, marked adenomyosis may produce menorrhagia, dysmenorrhea, and pelvic pain before the onset of menstruation.

## ENDOMETRIOSIS

*Endometriosis* is defined by the presence of endometrial glands and stroma in a location outside the endomyometrium. It occurs in as many as 10% of women in their reproductive years and in nearly half of women with infertility. It frequently is multifocal and often involves pelvic structures (ovaries, pouch of Douglas, uterine ligaments, tubes, and rectovaginal septum). Less frequently, distant areas of the peritoneal cavity or periumbilical tissues are involved. Uncommonly, distant sites such as lymph nodes, lungs, and even heart, skeletal muscle, or bone are affected.

Three hypotheses have been put forth to explain the origin of these dispersed lesions (Fig. 18–9). The *regurgitation theory,* which is currently favored, proposes that menstrual backflow through the fallopian tubes leads to implantation. The *metaplastic theory*, on the other hand, posits endometrial differentiation of coelomic epithelium (from which endometrium originates) as the source. These two theories cannot, however, explain lesions in the lymph nodes, skeletal muscle, or lungs. Hence, the *vascular* or *lymphatic dissemination theory* has been invoked to explain

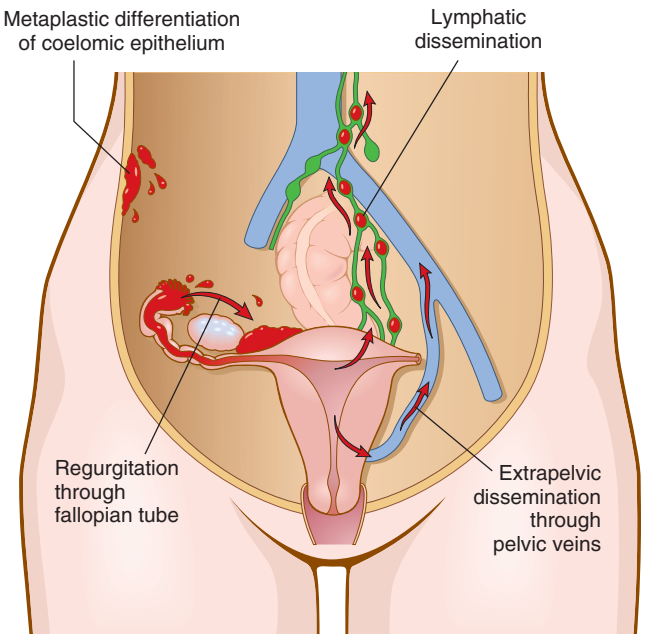



**Figure 18–9** Proposed origins of endometriosis.

extrapelvic or intranodal implants. Conceivably, all pathways could be valid in individual instances.

Recent studies suggest that the *endometriotic tissue is not just misplaced but is also abnormal.* As compared to normal endometrium, endometriotic tissue exhibits increased levels of inflammatory mediators, particularly prostaglandin E2, and increased estrogen production due to high aromatase activity of stromal cells. These changes enhance the survival and persistence of the endometriotic tissue within a foreign location (a key feature in the pathogenesis of endometriosis) and help to explain the beneficial effects of COX-2 inhibitors and aromatase inhibitors in the treatment of endometriosis.

## MORPHOLOGY

In contrast with adenomyosis, **endometriosis** almost always contains **functioning endometrium,** which undergoes cyclic bleeding. Because blood collects in these aberrant foci, they usually appear grossly as red-brown nodules or implants. They range in size from microscopic to 1 to 2 cm in diameter and lie on or just under the affected serosal surface. Often, individual lesions coalesce to form larger masses. When the ovaries are involved, the lesions may form large, blood-filled cysts that turn brown **(chocolate cysts)** as the blood ages (Fig. 18–10). With seepage and organization of the blood, widespread fibrosis occurs, leading to adhesions among pelvic structures, sealing of the tubal fimbriated ends, and distortion of the oviducts and ovaries. The histologic diagnosis at all sites depends on finding two of the following three features within the lesions: endometrial glands, endometrial stroma, and hemosiderin pigment.

### Clinical Features

The clinical manifestations of endometriosis depend on the distribution of the lesions. Extensive scarring of the oviducts and ovaries often produces discomfort in the lower abdominal quadrants and eventual sterility. Rectal wall involvement may produce pain on defecation, while involvement of the uterine or bladder serosa can cause dyspareunia (painful intercourse) and dysuria, respectively. Almost all cases feature severe dysmenorrhea and pelvic pain resulting from intrapelvic bleeding and periuterine adhesions.

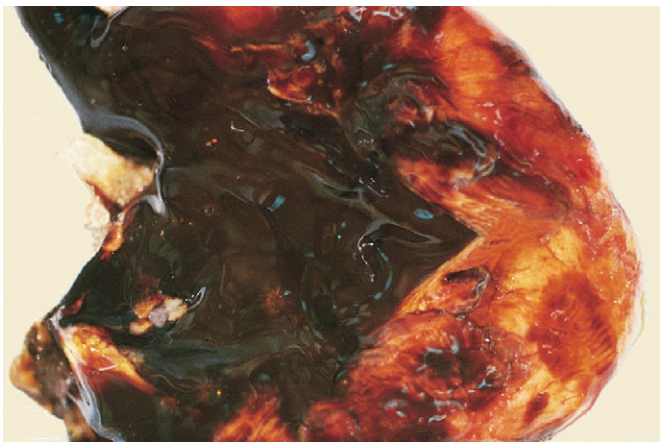


**Figure 18–10** Ovarian endometriosis. Sectioning of ovary reveals a large endometriotic cyst with degenerated blood ("chocolate cyst").

## ABNORMAL UTERINE BLEEDING

Women commonly seek medical attention for some type of abnormal uterine bleeding such as *menorrhagia* (profuse or prolonged bleeding at the time of the period), *metrorrhagia* (irregular bleeding between the periods), or postmenopausal bleeding. Common causes include endometrial polyps, leiomyomas, endometrial hyperplasia, endometrial carcinoma, and endometritis.

The probable cause of uterine bleeding in any given case depends somewhat on the age of the patient (Table 18–2). Abnormal bleeding from the uterus in the absence of an organic uterine lesion is called *dysfunctional uterine bleeding.* The various causes of abnormal uterine bleeding, both dysfunctional and that which is secondary to an organic lesion, can be segregated into four groups:

**Table 18–2** Causes of Abnormal Uterine Bleeding by Age Group

| Age Group | Cause(s) |
|---|---|
| Prepuberty | Precocious puberty (hypothalamic, pituitary, or ovarian origin) |
| Adolescence | Anovulatory cycle |
| Reproductive age | Complications of pregnancy (abortion, trophoblastic disease, ectopic pregnancy)<br>Proliferations (leiomyoma, adenomyosis, polyps, endometrial hyperplasia, carcinoma)<br>Anovulatory cycle<br>Ovulatory dysfunctional bleeding (e.g., inadequate luteal phase) |
| Perimenopause | Anovulatory cycle<br>Irregular shedding<br>Proliferations (carcinoma, hyperplasia, polyps) |
| Postmenopause | Proliferations (carcinoma, hyperplasia, polyps)<br>Endometrial atrophy |

- *Failure of ovulation.* Anovulatory cycles are very common at both ends of reproductive life, due to (1) hypothalamic-pituitary axis, adrenal, or thyroid dysfunction; (2) functional ovarian lesions producing excess estrogen; (3) malnutrition, obesity, or debilitating disease; and (4) severe physical or emotional stress. Regardless of the cause, ovulatory failure results in an excess of estrogen relative to progesterone. Thus, the endometrium goes through a proliferative phase that is not followed by the normal secretory phase. The endometrial glands may develop mild cystic changes or appear disorderly (Fig. 18–11, *A*), while the endometrial stroma, which requires progesterone for growth, may be scarce. This combination of abnormalities makes the endometrium prone to breakdown and abnormal bleeding.
- *Inadequate luteal phase.* The corpus luteum may fail to mature normally or may regress prematurely leading to a relative lack of progesterone. The endometrium under these circumstances fails to show the expected secretory changes.
- *Contraceptive-induced bleeding.* Older oral contraceptives containing synthetic estrogens and progestin induced a variety of endometrial responses, including a lush, decidua-like stroma and inactive, nonsecretory glands. The pills in current use no longer cause these abnormalities.
- *Endomyometrial disorders,* including chronic endometritis, endometrial polyps, and submucosal leiomyomas

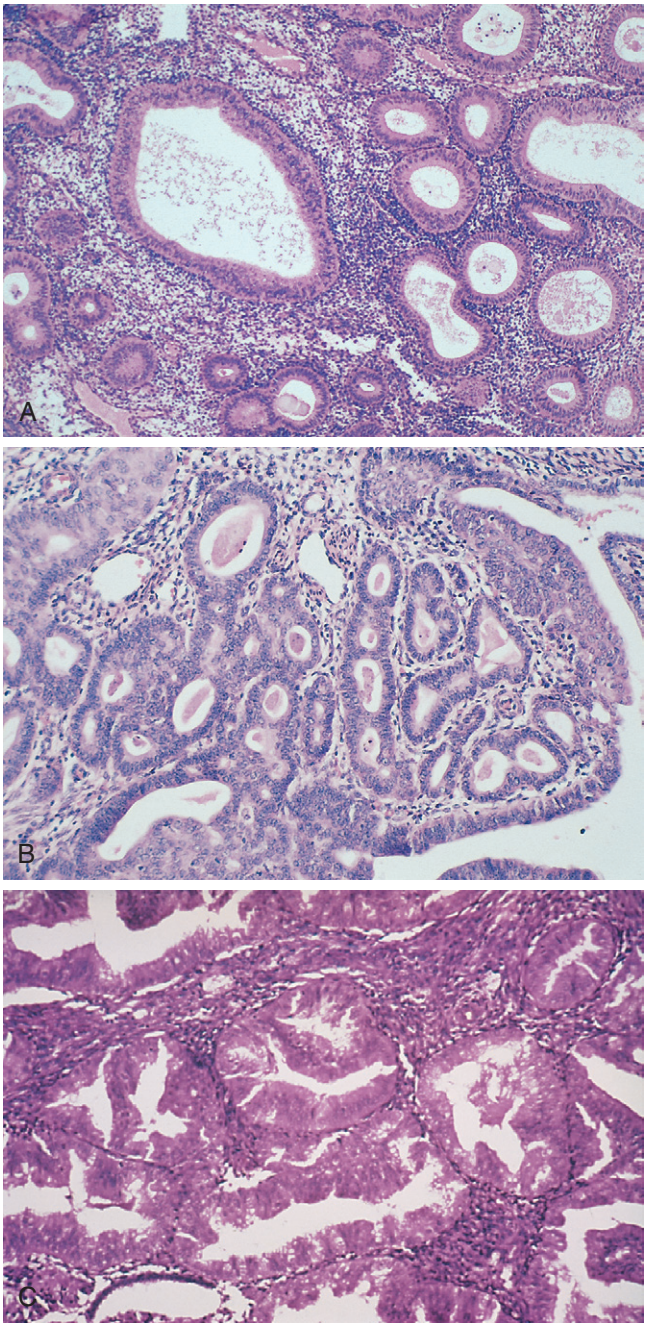



**Figure 18–11** Endometrial hyperplasia. **A,** Anovulatory or "disordered" endometrium containing dilated glands. **B,** Complex hyperplasia without atypia, characterized by nests of closely packed glands. **C,** Complex hyperplasia with atypia, seen as glandular crowding and cellular atypia.

### SUMMARY

#### Non-neoplastic Disorders of Endometrium

- Endometriosis refers to endometrial glands and stroma located outside the uterus and may involve the pelvic or abdominal peritoneum. Rarely, distant sites like the lymph nodes and the lungs also are involved.
- The ectopic endometrium in endometriosis undergoes cyclic bleeding, and the condition is a common cause of dysmenorrhea and pelvic pain.
- Adenomyosis refers to growth of endometrium into the myometrium with uterine enlargement. Unlike with endometriosis, there is no cyclic bleeding.

## PROLIFERATIVE LESIONS OF THE ENDOMETRIUM AND MYOMETRIUM

The most common proliferative lesions of the uterine corpus are endometrial hyperplasia, endometrial carcinomas, endometrial polyps, and smooth muscle tumors. All tend to produce abnormal uterine bleeding as their earliest manifestation.

### Endometrial Hyperplasia

An excess of estrogen relative to progestin, if sufficiently prolonged or marked, can induce exaggerated endometrial proliferation (hyperplasia), which is an important precursor of endometrial carcinoma. Potential causes of estrogen excess include failure of ovulation (such as is seen in perimenopause), prolonged administration of estrogenic steroids without counterbalancing progestin, and estrogen-producing ovarian lesions (such as polycystic ovary disease and granulosa-theca cell tumors of the ovary). A common cause of estrogen excess is obesity, as adipose tissue converts steroid precursors into estrogens.

The severity of hyperplasia is correlated with the level and duration of estrogen excess, and is classified based on architectural crowding (simple versus complex) and the

presence or absence of cytologic atypia (Fig. 18–11, *B* and *C*). The risk of developing carcinoma is related to the presence of cellular atypia. Complex hyperplasia without cellular atypia carries a low risk (less than 5%) for progression to endometrial carcinoma, while complex hyperplasia with cellular atypia is associated with a much higher risk (20% to 50%). When hyperplasia with atypia is discovered, it must be carefully evaluated for the presence of cancer and must be monitored by serial endometrial biopsies.

In time, the hyperplasia may proliferate autonomously, no longer requiring estrogen, and eventually may give rise to carcinoma. In a significant number of cases, the hyperplasia is associated with inactivating mutations in the *PTEN* tumor suppressor gene, an important brake on signaling through the PI-3-kinase/AKT signaling pathway. Acquisition of *PTEN* mutations is believed to be one of several key steps in the transformation of hyperplasias to endometrial carcinomas, which also often harbor *PTEN* mutations.

## Endometrial Carcinoma

In the United States and many other Western countries, endometrial carcinoma is the most frequent cancer occurring in the female genital tract. It generally appears between the ages of 55 and 65 years and is uncommon before age 40. Endometrial carcinomas comprise two distinct kinds of cancer: *endometrioid* and *serous carcinoma of the endometrium*. These two types are histologically and pathogenetically distinct. Endometrioid cancers arise in association with estrogen excess and endometrial hyperplasia in perimenopausal women, whereas serous cancers arise in the setting of endometrial atrophy in older postmenopausal women.

### PATHOGENESIS

The endometrioid type accounts for 80% of cases of endometrial carcinomas. These tumors are designated **endometrioid** because of their histologic similarity to normal endometrial glands. Risk factors for this type of carcinoma include (1) obesity, (2) diabetes, (3) hypertension, (4) infertility, and (5) exposure to unopposed estrogen. Many of these risk factors result in increased estrogenic stimulation of the endometrium and are associated with endometrial hyperplasia. In fact, it is well recognized that prolonged estrogen replacement therapy and estrogen-secreting ovarian tumors increase the risk of endometrioid type of endometrial carcinoma. Additionally, breast carcinoma (which also is estrogen-dependent) occurs in women with endometrial cancer (and vice versa) more frequently than by chance alone. **Mutations in mismatch repair genes and the tumor suppressor gene PTEN are early events in the stepwise development of endometrioid carcinoma.** Women with germline mutations in *PTEN* (Cowden syndrome) are at high risk for this cancer. *TP53* mutations occur but are relatively uncommon and are believed to be late events in the genesis of this tumor type.

The **serous type** of endometrial carcinoma is much less common, accounting for roughly 15% of tumors. Nearly all cases have mutations in the *TP53* tumor suppressor gene, whereas mutations in DNA mismatch repair genes and *PTEN* are rare.

### MORPHOLOGY

**Endometrioid carcinomas** closely resemble normal endometrium and may be exophytic or infiltrative (Fig. 18–12, *A* and *B*). They include a range of histologic types, including those showing mucinous, tubal (ciliated), and squamous (occasionally adenosquamous) differentiation. Tumors originate in the mucosa and may infiltrate the myometrium and enter vascular spaces. They may also metastasize to regional lymph nodes. Endometrioid carcinomas are graded I to III, based on the degree of differentiation. **Serous carcinomas,** on the other hand, form small tufts and papillae, rather than the glands seen in endometrioid carcinoma, and exhibit much greater cytologic atypia. They behave aggressively and thus are by definition high-grade. Immunohistochemistry often reveals high levels of p53 in serous carcinoma (Fig. 18–12, *C* and *D*), a finding that correlates with the presence of *TP53* mutations (mutant p53 accumulates and hence is more easily detected by staining).

### Clinical Course

Endometrial carcinomas usually manifest with leukorrhea and irregular bleeding, often in postmenopausal women. With progression, the uterus enlarges and may become affixed to surrounding structures as the cancer infiltrates surrounding tissues. These tumors usually are slow to metastasize, but if left untreated, eventually disseminate to regional nodes and more distant sites. With therapy, the 5-year survival rate for early-stage carcinoma is 90%, but survival drops precipitously in higher-stage tumors. The prognosis with serous carcinomas is strongly dependent on operative staging and cytologic screening of peritoneal washings; the latter is imperative, because very small or superficial serous tumors may nonetheless spread by way of the fallopian tube to the peritoneal cavity.

### SUMMARY

#### Endometrial Hyperplasia and Endometrial Carcinoma

- Endometrial hyperplasia results from excess endogenous or exogenous estrogen.
- Risk factors for developing endometrial hyperplasia include anovulatory cycles, polycystic ovary syndrome, estrogen-producing ovarian tumor, obesity, and estrogen therapy without counterbalancing progestin.
- The severity of hyperplasia is graded on the basis of architectural (simple versus complex) and cytologic (normal versus atypical) criteria. The risk of developing carcinoma is predominantly related to cytologic atypia.
- On the basis of clinical and molecular data, two major types of endometrial carcinoma are recognized:
  - *Endometrioid carcinoma* is associated with estrogen excess and endometrial hyperplasia. Early molecular changes include inactivation of DNA mismatch repair genes and the *PTEN* gene.
  - *Serous carcinoma* of the endometrium arises in older women and usually is associated with endometrial atrophy. Mutations in the *TP53* gene are an early event.

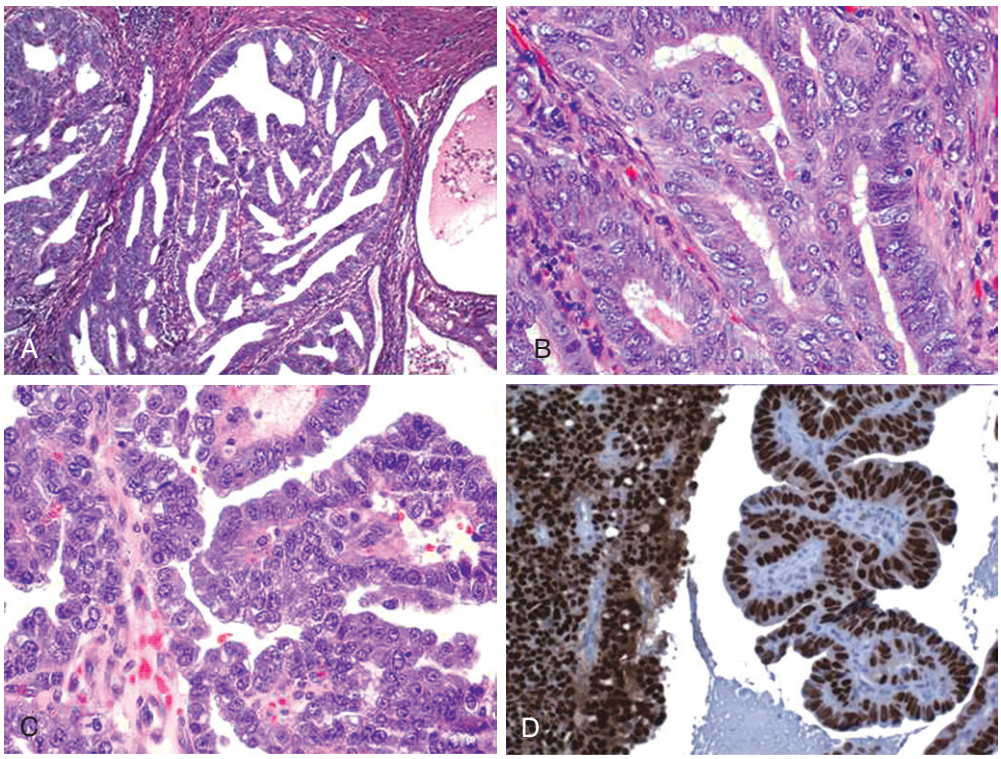



**Figure 18–12** Endometrial carcinoma. **A,** Endometrioid type, infiltrating myometrium and growing in a cribriform pattern. **B,** Higher magnification reveals loss of polarity and nuclear atypia. **C,** Serous carcinoma of the endometrium, with papilla formation and marked cytologic atypia. **D,** Immunohistochemical staining reveals accumulation of p53, a finding associated with *TP53* mutation.

- Stage is the major determinant of survival in both types. Serous tumors tend to manifest more frequently with extrauterine extension and therefore have a worse prognosis than endometrioid carcinomas.

## Endometrial Polyps

These sessile, usually hemispheric lesions range from 0.5 to 3 cm in diameter. Larger polyps may project from the endometrial mucosa into the uterine cavity. On histologic examination, they are composed of endometrium resembling the basalis, frequently with small muscular arteries. Some glands have a normal endometrial architecture, but more often they are cystically dilated. The stromal cells are monoclonal, often with a rearrangement of chromosomal region 6p21, and thus constitute the neoplastic component of the polyp.

Although endometrial polyps may occur at any age, they most commonly are detected around the time of menopause. Their clinical significance lies in abnormal uterine bleeding and, more important, in the risk (however rare) of giving rise to a cancer.

## Leiomyoma

Benign tumors that arise from the smooth muscle cells in the myometrium are properly termed *leiomyomas.* Because of their firmness, however, they often are referred to clinically as *fibroids.* Leiomyomas are the most common benign tumor in females, affecting 30% to 50% of women of reproductive age, and are considerably more frequent in blacks than in whites. These tumors are monoclonal and are associated with several different recurrent chromosomal abnormalities, including rearrangements of chromosomes 6 and 12 that also are found in a variety of other benign neoplasms, such as endometrial polyps and lipomas. Estrogens and possibly oral contraceptives stimulate the growth of leiomyomas; conversely, these tumors shrink postmenopausally.

### MORPHOLOGY

Leiomyomas are typically **sharply circumscribed,** firm gray-white masses with a characteristic **whorled cut surface.** They may occur singly, but more often **multiple tumors** are scattered within the uterus, ranging from small nodules to large tumors (Fig. 18–13) that may dwarf the uterus. Some are embedded within the myometrium (intramural), whereas others may lie directly beneath the endometrium (submucosal) or directly beneath the serosa (subserosal). In the latter location, tumors may extend out on attenuated stalks and even become attached to surrounding organs, from which they may develop a blood supply (**parasitic** leiomyomas). On histologic examination, the tumors are characterized by **bundles of smooth muscle cells** mimicking the appearance of normal myometrium. Foci of fibrosis, calcification, and degenerative softening may be present.

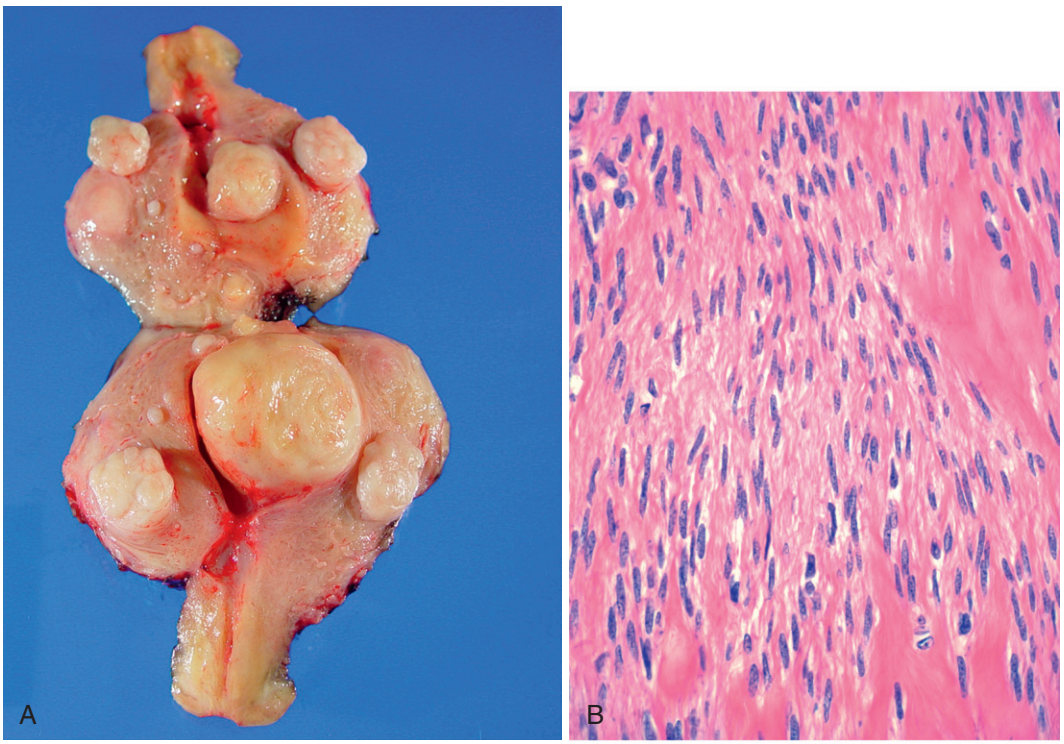



**Figure 18–13** Uterine leiomyomas. **A,** The uterus is opened to reveal multiple submucosal, myometrial, and subserosal gray-white tumors, each with a characteristic whorled appearance on cut section **B.** Microscopic appearance of leiomyoma reveals bundles of normal-looking smooth muscle cells.

*Leiomyomas* of the uterus often are asymptomatic, being discovered incidentally on routine pelvic examination. The most frequent presenting sign is menorrhagia, with or without metrorrhagia. Large leiomyomas may be palpated by the affected woman or may produce a dragging sensation. Leiomyomas almost never transform into sarcomas, and the presence of multiple lesions does not increase the risk of malignancy.

## Leiomyosarcoma

*Leiomyosarcomas* arise de novo from the mesenchymal cells of the myometrium, not from preexisting leiomyomas. They are almost always solitary and most often occur in postmenopausal women, in contradistinction to leiomyomas, which frequently are multiple and usually arise premenopausally.

### MORPHOLOGY

Leiomyosarcomas typically take the form of **soft, hemorrhagic, necrotic masses.** The histologic appearance varies widely, from tumors that closely resemble leiomyoma to wildly anaplastic neoplasms. Those well-differentiated tumors that lie at the interface between leiomyoma and leiomyosarcoma are sometimes designated smooth muscle tumors of uncertain malignant potential; in such cases, only time will tell if the tumor's behavior is benign or malignant. The diagnostic features of overt leiomyosarcoma include **tumor necrosis, cytologic atypia, and mitotic activity.** Since increased mitotic activity is sometimes seen in benign smooth muscle tumors, particularly in young women, an assessment of all three features is necessary to make a diagnosis of malignancy.

Recurrence after removal is common with these cancers, and many metastasize, typically to the lungs, yielding a 5-year survival rate of about 40%. The outlook with anaplastic tumors is less favorable than with well-differentiated tumors.

### SUMMARY

#### Uterine Smooth Muscle Neoplasms

- Benign smooth muscle tumors, called leiomyomas, are common and frequently multiple; they may manifest with menorrhagia or as a pelvic mass or may be detected as a cause of infertility.
- Malignant smooth muscle tumors, called leiomyosarcomas, arise de novo, not from leiomyomas.
- Criteria of malignancy include necrosis, cytologic atypia, and mitotic activity.

# FALLOPIAN TUBES

The most common disorder of the fallopian tubes is inflammation (salpingitis), almost invariably occurring as a component of pelvic inflammatory disease. Less common abnormalities are ectopic (tubal) pregnancy, endometriosis, and, rarely, primary tumors.

*Inflammations of the tube* are almost always microbial in origin. With the declining incidence of gonorrhea, nongonococcal organisms, such as *Chlamydia, Mycoplasma hominis,* coliforms, and (in the postpartum setting) streptococci and staphylococci, are now the major offenders. The morphologic changes produced by gonococci are similar to those in the male genital tract (Chapter 17). Nongonococcal infections can penetrate the wall of the tubes, giving rise to blood-borne infections, with seeding of the meninges, joint spaces, and sometimes even the heart valves. Tuberculous salpingitis is far less common and is almost always encountered in combination with tuberculous endometritis. All forms of salpingitis may produce fever, lower abdominal or pelvic pain, and pelvic masses, which are the result of distention of the tubes with either exudate or inflammatory debris (Fig. 18–14). Adherence of the inflamed tube to the ovary and adjacent ligamentous tissues may result in a *tuboovarian abscess,* referred to as a tuboovarian complex when infection subsides. Even more serious are adhesions of the tubal plicae, which are associated with increased risk of tubal ectopic pregnancy (discussed later). Damage to or obstruction of the tubal lumina may produce permanent sterility.

*Primary adenocarcinomas* of the fallopian tubes may be of serous or endometrioid histologic type. Although less common than ovarian tumors, serous fallopian tube carcinomas seem to be increased in women with *BRCA* mutations. In studies of prophylactic oophorectomies in such women, 10% had occult foci of malignancy, equally divided between the ovary and the fallopian tube, where they usually occurred in the fimbria. This has led to the suggestion that sporadic "ovarian" serous carcinomas (discussed later) may also originate in the fallopian tube, an idea that remains controversial. Because the fallopian tube provides access to the peritoneal cavity, fallopian tube carcinomas frequently involve the omentum and peritoneal cavity at presentation.

## SUMMARY

### Fallopian Tube Disease

- Salpingitis is usually a component of pelvic inflammatory disease; it results in scarring of the fallopian tube lining, increasing the risk of tubal ectopic pregnancy.
- Fallopian tube carcinomas usually manifest at an advanced stage, with involvement of the peritoneal cavity.

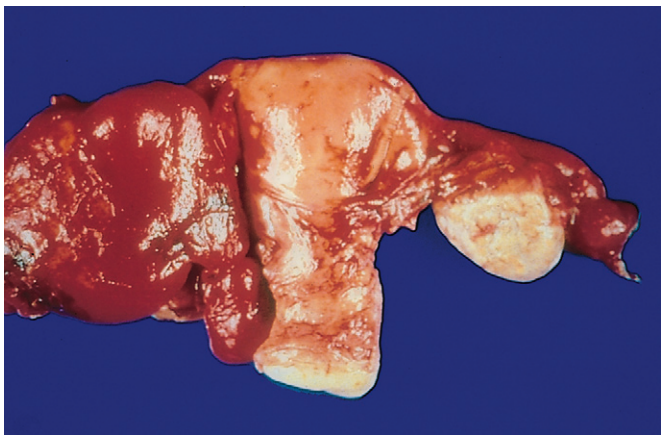


**Figure 18–14** Pelvic inflammatory disease, bilateral and asymmetric. The tube and ovary to the left of the uterus is totally obscured by a hemorrhagic inflammatory mass. The tube is adherent to the adjacent ovary on the other side.

# OVARIES

## FOLLICLE AND LUTEAL CYSTS

Follicle and luteal cysts in the ovaries are so commonplace that they may be considered variants of normal physiology. These innocuous lesions originate from unruptured graafian follicles or from follicles that have ruptured and then become immediately sealed. Such cysts often are multiple and develop subjacent to the serosal covering of the ovary. They typically are small (1 to 1.5 cm in diameter) and are filled with clear serous fluid. Occasionally, they become sufficiently large (4 to 5 cm) to produce palpable masses and pelvic pain. When small, they are lined by granulosa lining cells or luteal cells, but as fluid accumulates, pressure may cause atrophy of these cells. Sometimes these cysts rupture, producing intraperitoneal bleeding and peritoneal symptoms (acute abdomen).

## POLYCYSTIC OVARIAN DISEASE

*Polycystic ovarian disease* (formerly called *Stein-Leventhal syndrome*) is a disorder in which multiple cystic follicles in the ovaries produce excess androgens and estrogens. It usually comes to attention after menarche in teenage girls or young adults who present with oligomenorrhea, hirsutism, infertility, and sometimes obesity.

The ovaries are usually twice the normal size, gray-white with a smooth outer cortex, and studded with subcortical cysts 0.5 to 1.5 cm in diameter. Histologic examination reveals a thickened, fibrotic ovarian capsule overlying innumerable cystic follicles lined by granulosa cells with a hyperplastic luteinized theca interna. There is a conspicuous absence of corpora lutea in the ovary.

In most patients, the principal biochemical abnormalities are excessive production of androgens, high concentrations of luteinizing hormone, and low concentrations of follicle-stimulating hormone. The origins of these changes are poorly understood, but it is proposed that the ovaries elaborate excess androgens, which are converted to estrogenic hormones in peripheral fatty depots, which inhibit the secretion of follicle-stimulating hormone by the pituitary through the hypothalamus.

## TUMORS OF THE OVARY

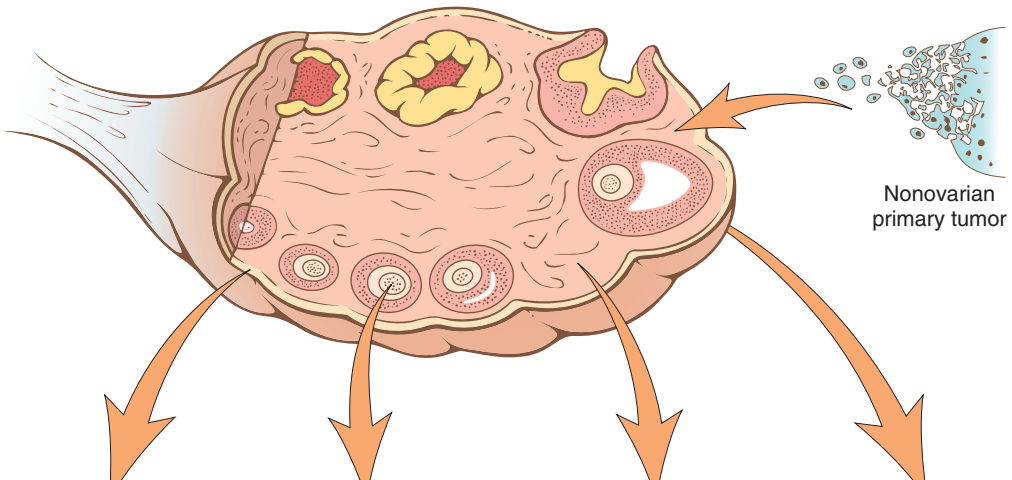
With more than 20,000 new cases diagnosed annually, ovarian cancer is the eighth most common cancer in U.S. women. It also is the fifth leading contributor to cancer mortality in women, with an estimated 14,000 deaths in 2010. Tumors of the ovary are amazingly varied. This diversity is attributable to the presence of three cell types in the normal ovary: the multipotent surface (coelomic) epithelium, the totipotent germ cells, and the sex cord–stromal cells, each of which gives rise to a number of different tumors (Fig. 18–15).

Neoplasms of surface epithelial origin account for the great majority of primary ovarian tumors and, in their malignant forms, account for almost 90% of ovarian cancers. Germ cell and sex cord–stromal cell tumors are much less frequent; although they constitute 20% to 30% of ovarian tumors, they are collectively responsible for less than 10% of malignant tumors of the ovary.

### Surface Epithelial Tumors

The vast majority of ovarian neoplasms is derived from the coelomic epithelium that covers the surface of the ovary. With repeated ovulation and scarring, surface epithelium becomes entrapped in the cortex of the ovary, forming small epithelial cysts. These can become metaplastic or undergo neoplastic transformation to give rise to a number of different epithelial tumors. Benign lesions usually are cystic (cystadenoma) and may have an accompanying stromal component (cystadenofibroma). Malignant tumors may also be cystic (cystadenocarcinoma) or solid (carcinoma). Some ovarian epithelial tumors fall into an intermediate, borderline category currently referred to as *tumors of low malignant potential*. These are best considered low-grade cancers with limited invasive potential and understandably carry a better prognosis than that for overtly malignant ovarian carcinomas.

Important risk factors for ovarian cancer include nulliparity, family history, and germline mutations in certain tumor suppressor genes. There is a higher incidence of carcinoma in unmarried women and married women with low parity. Of interest, prolonged use of oral contraceptives




| ORIGIN | SURFACE EPITHELIAL CELLS (Surface epithelial–stromal cell tumors) | GERM CELL | SEX CORD–STROMA | METASTASIS TO OVARIES |
|---|---|---|---|---|
| Overall frequency | 65%–70% | 15%–20% | 5%–10% | 5% |
| Proportion of malignant ovarian tumors | 90% | 3%–5% | 2%–3% | 5% |
| Age group affected | 20+ years | 0–25+ years | All ages | Variable |
| Types | • Serous tumor<br>• Mucinous tumor<br>• Endometrioid tumor<br>• Clear cell tumor<br>• Brenner tumor<br>• Cystadenofibroma | • Teratoma<br>• Dysgerminoma<br>• Endodermal sinus tumor<br>• Choriocarcinoma | • Fibroma<br>• Granulosa-theca cell tumor<br>• Sertoli-Leydig cell tumor | |

**Figure 18–15** Derivation, frequency, and age distribution for various ovarian neoplasms.

somewhat reduces the risk. Around 5% to 10% of ovarian cancers are familial, and most of these are associated with mutations in *BRCA1* and *BRCA2* tumor suppressor genes. As will be discussed later, mutations in *BRCA1* and *BRCA2* are also associated with hereditary breast cancer. The average lifetime risk for ovarian cancer approximates 30% in *BRCA1* carriers; the risk in *BRCA2* carriers is somewhat lower. In contrast with familial ovarian cancer, mutations in *BRCA1* and *BRCA2* are found in only 8% to 10% of sporadic ovarian cancers, which appear to arise through alternative molecular mechanisms.

## Serous Tumors

Serous tumors are the most common of the ovarian epithelial tumors. About 60% are benign, 15% are of low malignant potential, and 25% are malignant. Benign lesions are usually encountered in patients between 30 and 40 years of age, and malignant serous tumors are more commonly seen between 45 and 65 years of age. Taken together, borderline and malignant serous tumors are the most common ovarian malignancies, accounting for about 60% of all ovarian cancers.

Emerging evidence indicates that there are two types of serous carcinomas: low-grade and high-grade. The former arise from benign or borderline lesions and progress slowly in a stepwise manner to become invasive carcinoma. These low-grade tumors are associated with *KRAS*, *BRAF*, or *ERBB2* mutations. The high-grade serous tumors develop rapidly. As already mentioned, at least some of these high-grade lesions develop from tubal intraepithelial carcinoma, rather than ovarian coelomic epithelium. Recent "deep sequencing" of high-grade serous carcinomas has confirmed that 96% of tumors have mutations in *TP53*. Mutations affecting the Notch signaling pathway and FOXM1, a transcription factor previously implicated in the pathogenesis of ovarian carcinoma, were also detected in a sizable minority of tumors.

### MORPHOLOGY

Most serous tumors are large, spherical to ovoid, cystic structures up to 30 to 40 cm in diameter. **About 25% of the benign tumors are bilateral.** In the benign tumors, the serosal covering is smooth and glistening. By contrast, the surface of the cystadenocarcinoma has nodular irregularities representing areas in which the tumor has penetrated into the serosa. On cut section, small cystic tumors may have a single cavity, but larger ones frequently are divided by multiple septa into multiloculated masses. The cystic spaces usually are filled with a clear serous fluid. Protruding into the cystic cavities are papillary projections, which are more prominent in malignant tumors (Fig. 18–16).

On histologic examination, benign tumors contain a single layer of **tall columnar epithelial cells** that line the cyst or cysts. The cells often are ciliated. **Psammoma bodies** (concentrically laminated calcified concretions) are common in the tips of papillae. When frank carcinoma develops, anaplasia of the lining cells appears, as does invasion of the stroma. In carcinoma, papillary formations are complex and multilayered, and nests or undifferentiated sheets of malignant cells invade the axial fibrous tissue. Between clearly benign and obviously malignant forms lie **tumors of low malignant potential,** which exhibit less cytologic atypia and, typically, little or no stromal invasion. Tumors of low malignant potential may seed the peritoneum, but fortunately the tumor implants usually are "noninvasive." In general, malignant serous tumors spread to regional lymph nodes, including periaortic lymph nodes; distant lymphatic and hematogenous metastases are infrequent.

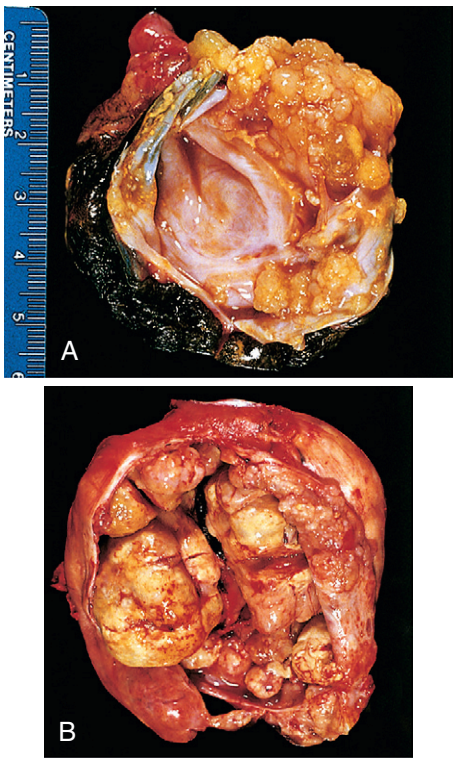



**Figure 18–16** Ovarian serous tumors. **A,** Borderline serous cystadenoma opened to display a cyst cavity lined by delicate papillary tumor growths. **B,** Cystadenocarcinoma. The cyst is opened to reveal a large, bulky tumor mass.
*(Courtesy of Dr. Christopher Crum, Brigham and Women's Hospital, Boston, Massachusetts.)*

The prognosis for patients with invasive serous cystadenocarcinoma is poor, even after surgery, irradiation, and chemotherapy, and depends heavily on the disease stage at diagnosis. If the tumor appears confined to the ovary, frank carcinomas have a 5-year survival rate of about 70%, whereas tumors of low malignant potential are associated with nearly 100% survival. With cancers that have penetrated the capsule, the 10-year survival rate is less than 15%.

## Mucinous Tumors

Mucinous tumors are, in most respects, similar to serous tumors, the essential difference being that the neoplastic epithelium consists of mucin-secreting cells. These tumors occur in women in the same age range as for those with serous tumors but are considerably less likely to be malignant. Overall, only 10% of mucinous tumors are malignant; another 10% are of low malignant potential, and 80% are benign.

### MORPHOLOGY

On gross examination, mucinous tumors produce cystic masses that may be indistinguishable from serous tumors except by the mucinous nature of the cystic contents. However, **they are more likely to be larger and multicystic** (Fig. 18–17, *A*)**. Serosal penetration and solid areas of growth are suggestive of malignancy.** On histologic examination, the cysts are lined by mucin-producing epithelial cells (Fig. 18–17, *B*). Malignant tumors are characterized by the presence of architectural complexity, including solid areas of growth, cellular stratification, cytologic atypia, and stromal invasion.

Compared with serous tumors, mucinous tumors are much less likely to be bilateral. This feature is sometimes useful in differentiating mucinous tumors of the ovary from metastatic mucinous adenocarcinoma from a gastrointestinal tract primary (the so-called **Krukenberg tumor**), which more often produces bilateral ovarian masses.

Ruptured ovarian mucinous tumors may seed the peritoneum; however, these deposits typically are transient and fail to establish long-term growth in the peritoneum. Implantation of mucinous tumor cells in the peritoneum with production of copious amounts of mucin is called **pseudomyxoma peritonei;** in most cases, this disorder is caused by metastasis from the gastrointestinal tract, primarily the appendix (Chapter 14).

The prognosis of mucinous cystadenocarcinoma is somewhat better than with its serous counterpart, although stage rather than histologic type (serous versus mucinous) is the major determinant of outcome.

### Endometrioid Tumors

These tumors may be solid or cystic; they sometimes develop in association with endometriosis. On microscopic examination, they are distinguished by the formation of tubular glands, similar to those of the endometrium, within the lining of cystic spaces. Although benign and borderline forms exist, endometrioid tumors usually are malignant. They are bilateral in about 30% of cases, and 15% to 30% of women with these ovarian tumors have a concomitant endometrial carcinoma. Similar to endometrioid-type carcinoma of the endometrium, endometrioid carcinomas of the ovary have mutations in the *PTEN* tumor suppressor gene.

### Brenner Tumor

The Brenner tumor is an uncommon, solid, usually unilateral ovarian tumor consisting of abundant stroma containing nests of transitional-type epithelium resembling that of the urinary tract. Occasionally, the nests are cystic and are lined by columnar mucus-secreting cells. Brenner tumors generally are smoothly encapsulated and gray-white on cut section, ranging from a few centimeters to 20 cm in diameter. These tumors may arise from the surface epithelium or from urogenital epithelium trapped within the germinal ridge. Although most are benign, both malignant and borderline tumors have been described.

## OTHER OVARIAN TUMORS

Many other types of tumors of germ cell and sex cord–stromal origin also arise in the ovary, but only the teratomas of germ cell origin are sufficiently common to merit description. Table 18–3 presents some salient features of other neoplasms of germ cell and sex cord origin.

### Teratomas

Teratomas constitute 15% to 20% of ovarian tumors. A distressing feature of these germ cell tumors is their predilection to arise in the first 2 decades of life; to make matters worse, the younger the person, the greater the likelihood of malignancy. More than 90% of these germ cell neoplasms, however, are benign mature cystic teratomas; the immature, malignant variant is rare.

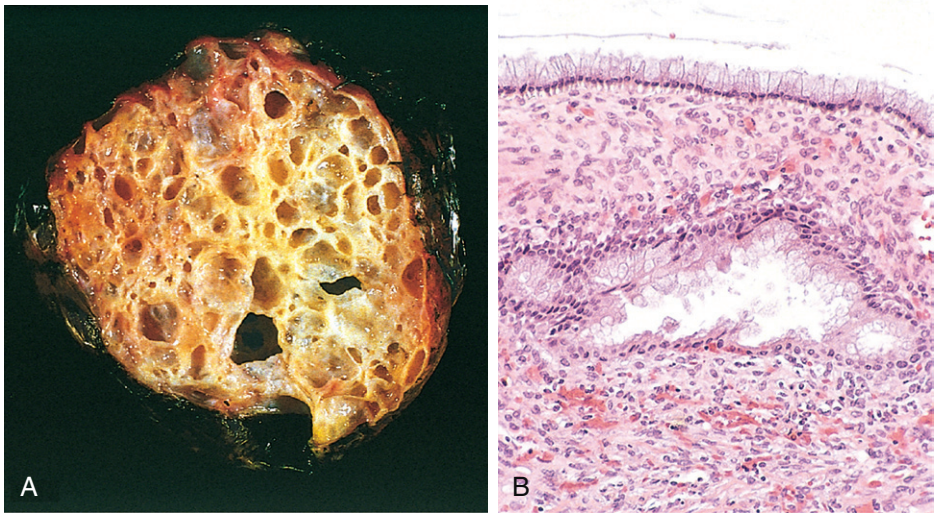



**Figure 18–17** Ovarian mucinous cystadenoma. **A,** Mucinous cystadenoma with multicystic appearance and delicate septa. Note the presence of glistening mucin within the cysts. **B,** Columnar cell lining of mucinous cystadenoma.

**Table 18–3** Salient Features of Ovarian Germ Cell and Sex Cord Neoplasms

| Neoplasm | Peak Incidence | Usual Location | Morphologic Features | Behavior |
|---|---|---|---|---|
| **Germ Cell Origin** | | | | |
| Dysgerminoma | Second to third decade of life<br>Occur with gonadal dysgenesis | Unilateral in 80–90% | Counterpart of testicular seminoma<br>Solid large to small gray masses<br>Sheets or cords of large clear cells separated by scant fibrous strands<br>Stroma may contain lymphocytes and occasional granulomas | All malignant but only one third aggressive and spread; all radiosensitive; 80% cure rate |
| Choriocarcinoma | First 3 decades of life | Unilateral | Identical to placental tumor<br>Often small, hemorrhagic focus with two types of epithelium: cytotrophoblast and syncytiotrophoblast | Metastasizes early and widely.<br>Primary focus may degenerate, leaving only metastases<br>In contrast with gestational tumors, ovarian primaries are resistant to chemotherapy |
| **Sex Cord Tumors** | | | | |
| Granulosa-theca cell | Most postmenopausal, but may occur at any age | Unilateral | May be tiny or large, gray to yellow (with cystic spaces)<br>Composed of mixture of cuboidal granulosa cells in cords, sheets, or strands and spindled or plump lipid-laden theca cells<br>Granulosa elements may recapitulate ovarian follicle as Call-Exner bodies | May elaborate large amounts of estrogen (from thecal elements) and so may promote endometrial or breast carcinoma<br>Granulosa element may be malignant (5% to 25%) |
| Thecoma-fibroma | Any age | Unilateral | Solid gray fibrous cells to yellow (lipid-laden) plump thecal cells | Most hormonally inactive<br>A few elaborate estrogens<br>About 40%, for obscure reasons, produce ascites and hydrothorax (Meigs syndrome)<br>Rarely malignant |
| Sertoli-Leydig cell | All ages | Unilateral | Usually small, gray to yellow-brown, and solid<br>Recapitulates development of testis with tubules or cords and plump pink Sertoli cells | Many masculinizing or defeminizing<br>Rarely malignant |
| **Metastases to Ovary** | | | | |
| | Older ages | Mostly bilateral | Usually solid gray-white masses as large as 20 cm in diameter<br>Anaplastic tumor cells, cords, glands, dispersed through fibrous background<br>Cells may be "signet ring" mucin-secreting | Primaries are gastrointestinal tract (Krukenberg tumors), breast, and lung |

### *Benign (Mature) Cystic Teratomas*

Almost all benign (mature) cystic teratomas are marked by the presence of mature tissues derived from all three germ cell layers: ectoderm, endoderm, and mesoderm. Usually these tumors contain cysts lined by epidermis replete with adnexal appendages—hence the common designation *dermoid cysts*. Most are discovered in young women as ovarian masses or are found incidentally on abdominal radiographs or scans because they contain foci of calcification produced by tooth-like structures contained within the tumor. About 90% are unilateral, with the right side more commonly affected. Rarely do these cystic masses exceed 10 cm in diameter. On cut section, they often are filled with sebaceous secretion and matted hair that, when removed, reveal a hair-bearing epidermal lining (Fig. 18–18). Sometimes there is a nodular projection from which teeth protrude. Occasionally, foci of bone and cartilage, nests of bronchial or gastrointestinal epithelium, and other tissues also are present.

For unknown reasons, these neoplasms sometimes produce infertility and are prone to undergo torsion (in 10% to 15% of cases), which constitutes an acute surgical emergency. A rare, but fascinating, paraneoplastic complication is limbic encephalitis, which may develop in women with teratomas containing mature neural tissue and often remits with tumor resection. In about 1% of cases, malignant transformation, usually to a squamous cell carcinoma, is seen.

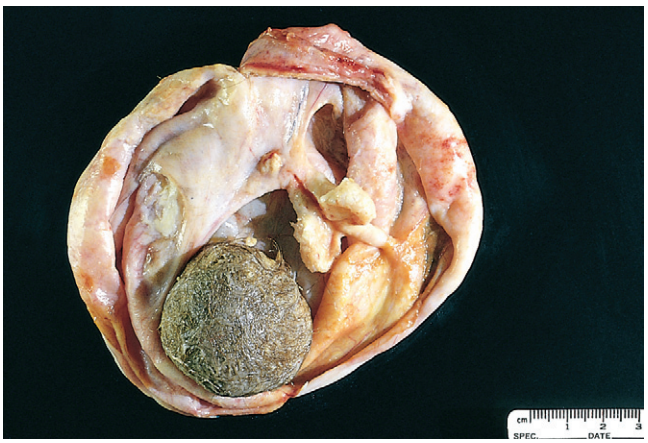


**Figure 18–18** Mature cystic teratoma (dermoid cyst) of the ovary. A ball of hair (*bottom*) and a mixture of tissues are evident.
*(Courtesy of Dr. Christopher Crum, Brigham and Women's Hospital, Boston, Massachusetts.)*

### *Immature Malignant Teratomas*

Malignant (immature) teratomas are found early in life, the mean age at clinical detection being 18 years. They differ strikingly from benign mature teratomas insofar as they often are bulky, predominantly solid on cut section, and punctuated by areas of necrosis; uncommonly, cystic foci are present that contain sebaceous secretion, hair, and other features similar to those of mature teratomas. On microscopic examination, the distinguishing feature is presence of immature elements or minimally differentiated cartilage, bone, muscle, nerve, or other tissues. Particularly ominous are foci of neuroepithelial differentiation, in view of the propensity of such foci to be aggressive and metastasize widely. Immature teratomas are both graded and staged in an effort to predict their behavior. Grade I, stage I tumors often can be cured with appropriate therapy, whereas those of higher grade and stage are associated with a more guarded outlook.

### *Specialized Teratomas*

A rare subtype of teratoma is composed entirely of specialized tissue. The most common example is struma ovarii, which is composed entirely of mature thyroid tissue that may actually produce hyperthyroidism. These tumors appear as small, solid, unilateral brown ovarian masses. Other specialized teratomas may take the form of ovarian carcinoid, which in rare instances produces carcinoid syndrome.

### Clinical Correlations

With all ovarian neoplasms, management poses a formidable clinical challenge, because symptoms or signs usually appear only when tumors are well advanced. The clinical presentation is remarkably similar, except with functioning neoplasms that exert hormonal effects. Ovarian tumors of surface epithelial origin usually are asymptomatic until they become large enough to cause local pressure symptoms (e.g., pain, gastrointestinal complaints, urinary frequency). Indeed, about 30% of all ovarian neoplasms are discovered incidentally on routine gynecologic examination. Larger masses, particularly the common epithelial tumors, may cause an increase in abdominal girth. Smaller masses, particularly dermoid cysts, sometimes twist on their pedicles (torsion), producing severe abdominal pain that mimics an acute abdomen. Metastatic seeding of malignant serous tumors often causes ascites, whereas functioning ovarian tumors often come to attention because of the endocrinopathies they produce.

Unfortunately, treatment of ovarian tumors remains unsatisfactory; only a modest increase in survival has been achieved since the mid-1970s. Screening methods that detect early tumors are badly needed, but those evaluated to date are of limited value. One such marker, the protein CA-125, is elevated in the sera of 75% to 90% of women with epithelial ovarian cancer. However, CA-125 is undetectable in up to 50% of women with cancer limited to the ovary; conversely, it often is elevated in a variety of benign conditions and nonovarian cancers. Hence, its usefulness as a screening test in asymptomatic postmenopausal women is limited. Currently, CA-125 measurements are of greatest value in monitoring response to therapy.

## SUMMARY

### Ovarian Tumors

- Tumors may arise from epithelium, sex cord–stromal cells, or germ cells.
- Epithelial tumors are the most common malignant ovarian tumors and are more common in women older than 40 years of age.
- The major types of epithelial tumors are serous, mucinous, and endometrioid. Each has a benign, malignant, and borderline (low malignant potential) counterpart.
- Sex cord–stromal tumors may display differentiation toward granulosa, Sertoli, Leydig, or ovarian stromal cell type. Depending on differentiation, they may produce estrogens or androgens.
- Germ cell tumors (mostly cystic teratomas) are the most common ovarian tumor in young women; a majority are benign.
- Germ cell tumors may differentiate toward oogonia (dysgerminoma), primitive embryonal tissue (embryonal), yolk sac (endodermal sinus tumor), placental tissue (choriocarcinoma), or multiple fetal tissues (teratoma).

# DISEASES OF PREGNANCY

Diseases of pregnancy and pathologic conditions of the placenta are important contributors to morbidity and mortality for both mother and child. Discussed in this section are a limited number of disorders in which knowledge of the morphologic lesions contributes to an understanding of clinical disease.

## PLACENTAL INFLAMMATIONS AND INFECTIONS

Infections may reach the placenta by either of two paths: (1) ascension through the birth canal or (2) hematogenous (transplacental) spread.

*Ascending infections* are by far the more common; in most instances, they are bacterial and are associated with premature rupture of the fetal membranes. On microscopic examination, the chorioamnion shows neutrophilic infiltration associated with edema and congestion (acute chorioamnionitis). With extension beyond the membranes, the infection may involve the umbilical cord and placental villi, resulting in acute vasculitis of the cord (funisitis). Ascending infections are caused by *Mycoplasma, Candida,* and the numerous bacteria of the vaginal flora.

Uncommonly, placental infections may arise by *hematogenous spread* of bacteria and other organisms; on histologic examination, placental villi are the most frequently affected structures (villitis). Syphilis, tuberculosis, listeriosis, toxoplasmosis, and various viruses (rubella, cytomegalovirus, herpes simplex virus) all can cause placental villitis. Transplacental infections can affect the fetus and give rise to the so-called TORCH (*t*oxoplasmosis, *o*ther infections, *r*ubella, *c*ytomegalovirus infection, *h*erpes) complex (Chapter 6).

## ECTOPIC PREGNANCY

Ectopic pregnancy is defined as implantation of a fertilized ovum in any site other than the uterus. As many as 1% of pregnancies are ectopic. In more than 90% of these cases, implantation occurs in the oviducts (tubal pregnancy); other sites include the ovaries and the abdominal cavity. Any factor that retards passage of the ovum through the oviducts predisposes to ectopic pregnancy. In about half of the cases, slowed passage is attributable to chronic inflammation and scarring in the oviduct; intrauterine tumors and endometriosis may also hamper passage of the ovum. In the other 50% of tubal pregnancies, no anatomic cause is evident. Ovarian pregnancies probably result from rare instances in which the ovum is fertilized just as the follicle ruptures. Gestation within the abdominal cavity occurs when the fertilized egg drops out of the fimbriated end of the oviduct and implants on the peritoneum.

### MORPHOLOGY

In all sites, early development of ectopic pregnancies proceeds normally, with formation of placental tissue, the amniotic sac, and decidual changes. With tubal pregnancies, the invading placenta eventually burrows through the wall of the oviduct, causing **intratubal hematoma (hematosalpinx), intraperitoneal hemorrhage,** or both. The tube is usually distended by freshly clotted blood containing bits of gray placental tissue and fetal parts. The histologic diagnosis depends on visualization of placental villi or, rarely, of the embryo.

Until rupture occurs, an ectopic pregnancy may be indistinguishable from a normal pregnancy, with cessation of menstruation and elevation of serum and urinary placental hormones. Under the influence of these hormones, the endometrium (in approximately 50% of cases) undergoes the characteristic hypersecretory and decidual changes of pregnancy. The absence of elevated gonadotropin levels does not exclude the diagnosis, however, because poor attachment and necrosis of the ectopic placenta are common. Rupture of an ectopic pregnancy may be catastrophic, with the sudden onset of intense abdominal pain and signs of an acute abdomen, often followed by shock. Prompt surgical intervention is necessary.

### SUMMARY

#### Ectopic Pregnancy

- Ectopic pregnancy is defined as implantation of the fertilized ovum outside of the uterine corpus. Approximately 1% of pregnancies implant ectopically; the most common site is the fallopian tube.
- Chronic salpingitis with scarring is a major risk factor for tubal ectopic pregnancy.
- Rupture of an ectopic pregnancy is a medical emergency that, if left untreated, may result in exsanguination and death.

## GESTATIONAL TROPHOBLASTIC DISEASE

Gestational trophoblastic tumors have been divided on histopathologic grounds into three overlapping morphologic categories: *hydatidiform mole, invasive mole,* and *choriocarcinoma.* These demonstrate a range of aggressiveness from benign hydatidiform moles to highly malignant choriocarcinomas. All elaborate human chorionic gonadotropin (hCG), which can be detected in the blood and urine at levels considerably higher than those found during normal pregnancy. In addition to aiding diagnosis, the rise or fall of hormone levels in the blood or urine can be used to monitor treatment efficacy. Clinicians prefer the umbrella term *gestational trophoblastic disease* because the response to therapy, as judged by the hormone levels, is significantly more important than pathologic subtyping of lesions. However, the genetics, pathology, and natural history of these disorders are sufficiently distinct to merit discussion of each.

### Hydatidiform Mole: Complete and Partial

The typical hydatidiform mole is a voluminous mass of swollen, sometimes cystically dilated, chorionic villi, appearing grossly as grapelike structures. The swollen villi are covered by varying amounts of normal to highly atypical chorionic epithelium. There are two distinctive subtypes of hydatidiform moles: *complete* and *partial.* Complete hydatidiform moles are not compatible with embryogenesis and never contain fetal parts. All of the chorionic villi are abnormal, and the chorionic epithelial cells are diploid (46,XX or, uncommonly, 46,XY). The partial hydatidiform mole is compatible with early embryo formation

**Table 18–4** Features of Complete and Partial Hydatidiform Mole

| Feature | Complete Mole | Partial Mole |
|---|---|---|
| Karyotype | 46,XX (46,XY) | Triploid (69,XXY) |
| Villous edema | All villi | Some villi |
| Trophoblast proliferation | Diffuse; circumferential | Focal; slight |
| Serum hCG | Elevated | Less elevated |
| Tissue hCG | ++++ | + |
| Risk of subsequent choriocarcinoma | 2% | Rare |

hCG, human chorionic gonadotropin.

and therefore may contain fetal parts, has some normal chorionic villi, and is almost always triploid (e.g., 69,XXY) (Table 18–4). Both types result from abnormal fertilization. In a complete mole the entire genetic content is supplied by two spermatozoa (or a diploid sperm), yielding diploid cells containing only paternal chromosomes, whereas in a partial mole a normal egg is fertilized by two spermatozoa (or a diploid sperm), resulting in a triploid karyotype with a preponderance of paternal genes.

The incidence of complete hydatidiform mole is about 1 to 1.5 per 2000 pregnancies in the United States and other Western countries. For unknown reasons, the incidence is much higher in Asian countries. Moles are most common before the age of 20 years and after the age of 40, and a history of the condition increases the risk for molar disease in subsequent pregnancies. Although molar disease formerly was discovered at 12 to 14 weeks of pregnancy during investigation for a gestation that was "too large for dates," early monitoring of pregnancies by ultrasound has lowered the gestational age at detection. In both complete and partial moles, elevation of hCG in the maternal blood and absence of fetal heart sounds are typical.

### MORPHOLOGY

The uterus may be of normal size in early moles, but in more advanced cases the uterine cavity is expanded by a delicate, friable mass of thin-walled, translucent cystic structures (Fig. 18–19). Fetal parts are rarely seen in complete moles but are common in partial moles. On microscopic examination, the **complete mole** shows hydropic swelling of poorly vascularized chorionic villi with a loose, myxomatous, edematous stroma. The chorionic epithelium almost always shows some degree of proliferation of both cytotrophoblasts and syncytiotrophoblasts (Fig. 18–20). Histologic grading to predict the clinical outcome of moles has been supplanted by careful monitoring of hCG levels. In **partial moles,** villous edema involves only some of the villi, and the trophoblastic proliferation is focal and slight. The villi of partial moles have a characteristic irregular, scalloped margin. In most cases of partial mole, some fetal cells are present, ranging from fetal red blood cells in placental villi to, in rare cases, a fully formed fetus.

Overall, 80% to 90% of moles do not recur after thorough curettage; 10% of complete moles are invasive. No more than 2% to 3% give rise to choriocarcinoma.

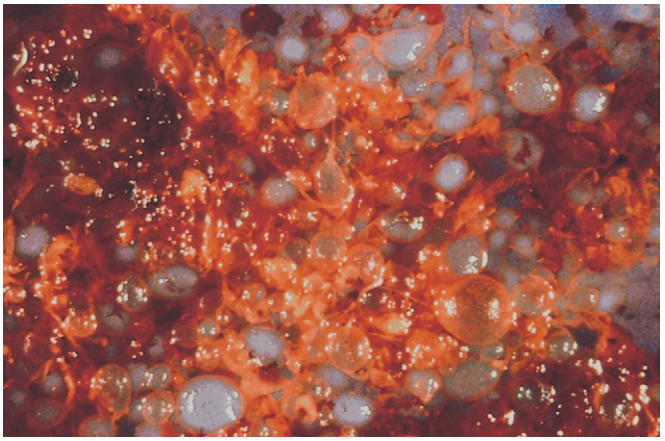


**Figure 18–19** Complete hydatidiform mole, consisting of numerous swollen (hydropic) villi.

## Invasive Mole

Invasive moles are complete moles that are more invasive locally but do not have the aggressive metastatic potential of a choriocarcinoma. An invasive mole retains hydropic villi, which penetrate the uterine wall deeply, possibly causing rupture and sometimes life-threatening hemorrhage. On microscopic examination, the epithelium of the villi shows atypical changes, with proliferation of both trophoblastic and syncytial components.

Although the marked invasiveness of this lesion makes removal technically difficult, metastases do not occur. Hydropic villi may embolize to distant organs, such as lungs or brain, but these emboli do not constitute true metastases and may indeed regress spontaneously. Because of deeper invasion into the myometrium, an invasive mole is difficult to remove completely by curettage, so if serum β-hCG remains elevated, further treatment is

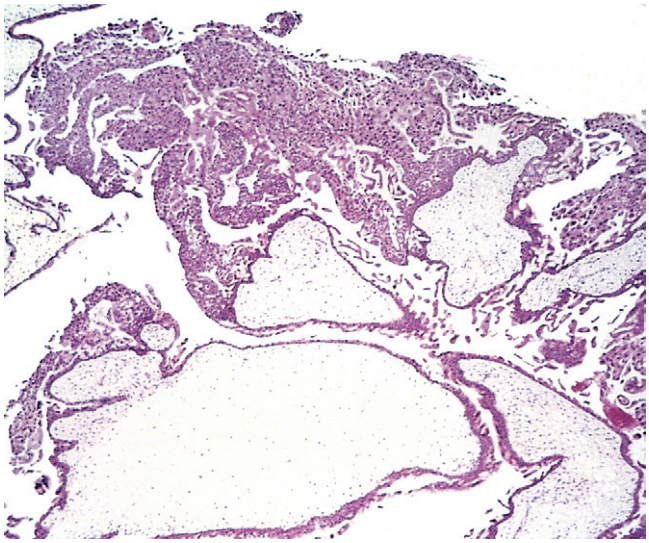


**Figure 18–20** Complete hydatidiform mole. In this microscopic image, distended hydropic villi (*below*) and proliferation of the chorionic epithelium (*above*) are evident.

*(Courtesy of Dr. Kyle Molberg, Department of Pathology, University of Texas Southwestern Medical School, Dallas, Texas.)*

required. Fortunately, in most cases cure is possible with chemotherapy.

## Gestational Choriocarcinoma

Choriocarcinoma, a very aggressive malignant tumor, arises either from gestational chorionic epithelium or, less frequently, from totipotential cells within the gonads (as a germ cell tumor). These tumors are rare in the Western Hemisphere; in the United States, they occur in about 1 per 30,000 pregnancies but are much more common in Asian and African countries, reaching a frequency of 1 in 2000 pregnancies. Approximately 50% of choriocarcinomas arise from complete hydatidiform moles; about 25% arise after an abortion; the remainder manifest after what had been a normal pregnancy. Stated in another way, the more abnormal the conception, the greater the risk of developing gestational choriocarcinoma. In most cases, choriocarcinoma manifests with a bloody, brownish discharge accompanied by a rising titer of β-hCG in blood and urine, in the absence of marked uterine enlargement, such as would be anticipated with a mole. In general, the β-hCG titers are much higher than those associated with a mole.

### MORPHOLOGY

Choriocarcinomas usually appear as hemorrhagic, necrotic uterine masses. Sometimes the necrosis is so extensive that little viable tumor remains. Indeed, the primary lesion may "self-destruct," and only the metastases tell the story. Very early, the tumor insinuates itself into the myometrium and into vessels. **In contrast with hydatidiform moles and invasive moles, chorionic villi are not formed; instead, the tumor is composed of anaplastic cuboidal cytotrophoblasts and syncytiotrophoblasts** (Fig. 18–21).

By the time most choriocarcinomas are discovered, widespread vascular spread usually has occurred to the lungs (50%), vagina (30% to 40%), brain, liver, or kidneys. Lymphatic invasion is uncommon.

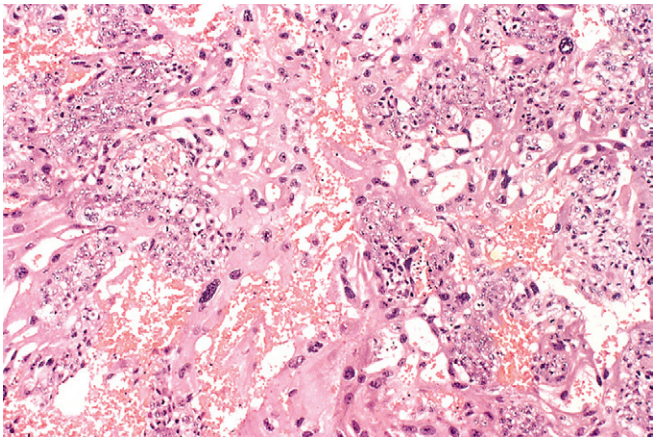


**Figure 18–21** Choriocarcinoma. This field contains both neoplastic cytotrophoblasts and multinucleate syncytiotrophoblasts.
*(Courtesy of Dr. David R. Genest, Brigham and Women's Hospital, Boston, Massachusetts.)*

Despite the extremely aggressive nature of placental choriocarcinoma, these tumors are remarkably sensitive to chemotherapy. Nearly 100% of affected patients are cured, even those with metastases at distant sites such as the lungs. By contrast, response to chemotherapy with choriocarcinomas that arise in the gonads (ovary or testis) is relatively poor. This striking difference in prognosis may be related to the presence of paternal antigens on placental choriocarcinomas that are lacking in gonadal lesions. Conceivably, a maternal immune response against the foreign (paternal) antigens helps clear the tumor by acting as an adjunct to chemotherapy.

## Placental Site Trophoblastic Tumor

Placental site trophoblastic tumors are derived from the placental site or intermediate trophoblast. These uncommon diploid tumors, often XX in karyotype, typically arise a few months after pregnancy. Because intermediate trophoblasts do not produce hCG in large amounts, hCG concentrations are only slightly elevated. More typically, these tumors produce human placental lactogen. An indolent clinical course is typical, with a generally favorable outcome if the tumor is confined to the endomyometrium. Of note, however, placental site trophoblastic tumors are not as sensitive to chemotherapy as are other trophoblastic tumors, and the prognosis is poor when spread has occurred beyond the uterus.

### SUMMARY

#### Gestational Trophoblastic Disease

- Molar disease is due to an abnormal contribution of paternal chromosomes in the gestation.
- Partial moles are triploid and have two sets of paternal chromosomes. They typically are accompanied by fetal tissue. There is a low rate of persistent disease.
- Complete moles are diploid, and all chromosomes are paternal. No embryonic or fetal tissues are associated with complete mole.
- Among complete moles, 10% to 15% are associated with persistent disease that usually takes the form of an invasive mole. Only 2% of complete moles progress to choriocarcinoma.
- Gestational choriocarcinoma is a highly invasive and frequently metastatic tumor that, in contrast with ovarian choriocarcinoma, is responsive to chemotherapy and curable in most cases.
- Placental site trophoblastic tumor is an indolent and usually early-stage tumor of intermediate trophoblast that produces human placental lactogen and does not respond well to chemotherapy.

# PREECLAMPSIA/ECLAMPSIA (TOXEMIA OF PREGNANCY)

The development of hypertension, accompanied by proteinuria and edema in the third trimester of pregnancy, is referred to as *preeclampsia*. This syndrome occurs in 5% to

10% of pregnancies, particularly with first pregnancies in women older than age 35 years. In those severely affected, seizures may occur, and the symptom complex is then termed *eclampsia.* By long-existing precedent, preeclampsia and eclampsia are still sometimes referred to as *toxemia of pregnancy.* No blood-borne toxin has ever been identified, and this historically sanctified term is a misnomer. Recognition and early treatment of preeclampsia have now made eclampsia, particularly fatal eclampsia, rare.

The exact triggering events initiating these syndromes are unknown, but a common feature underlying all cases is *insufficient maternal blood flow to the placenta secondary to inadequate remodeling of the spiral arteries of the uteroplacental vascular bed.* In normal pregnancy, the musculoelastic walls of the spiral arteries are invaded by trophoblasts, permitting them to dilate into wide vascular sinusoids. In preeclampsia and eclampsia, this vascular remodeling is impaired, the musculoelastic walls are retained, and the channels remain narrow. Decreased uteroplacental blood flow appears to result in placental hypoxia, placental dysfunction, and a shift to a systemic antiangiogenic state. Specifically, both increases in the circulating antiangiogenic factors soluble Flt1 (sFlt1) and soluble endoglin (sEng) and reductions in the level of proangiogenic factors, such as VEGF and PIGF, have been noted. These disturbances are hypothesized to result in *endothelial cell dysfunction, vascular hyperreactivity, and end-organ microangiopathy.* While the exact basis of preeclampsia remains to be further defined, several serious consequences have been associated with this condition:

- *Placental infarction,* stemming from the chronic hypoperfusion
- *Hypertension,* due to reduced endothelial production of the vasodilators prostacyclin (i.e., prostaglandin $I_2$) and prostaglandin $E_2$, and to increased production of the vasoconstrictor thromboxane $A_2$
- *Hypercoagulability,* due to endothelial dysfunction and release of tissue factor from the placenta
- *End-organ failure,* most notably of the kidney and the liver, which occurs in patients with full-blown eclampsia. Approximately 10% of the patients with severe preeclampsia develop the so-called HELLP syndrome, characterized by hemolysis, elevated liver enzymes, and low platelets.

### MORPHOLOGY

The morphologic changes of preeclampsia and eclampsia are variable and correlate to some degree with the severity of the disorder. **Placental abnormalities** include:

- **Infarcts,** which can be a feature of normal pregnancy, but are much more numerous with severe preeclampsia or eclampsia
- **Retroplacental hemorrhages**
- **Premature maturation of placental villi** associated with villous edema, hypovascularity, and increased production of syncytial epithelial knots
- **Fibrinoid necrosis** and focal accumulation of lipid-containing macrophages (acute atherosis) of decidual vessels

#### Clinical Features

Preeclampsia presents insidiously during weeks 24 and 25 of gestation, with edema, proteinuria, and rising blood pressure. Should the condition evolve into eclampsia, renal function is impaired, blood pressure rises further, and convulsions may occur. Prompt therapy early in the course aborts the associated organ changes, with all abnormalities resolving promptly after delivery or cesarean section.

### SUMMARY

#### Preeclampsia/Eclampsia

- Preeclampsia is due to abnormalities in maternal and placental blood flow, with resultant placental ischemia and infarction and abnormalities in production of vasodilators.
- Preeclampsia is characterized by edema, proteinuria, and hypertension in the second and third trimesters of pregnancy.
- Eclampsia is characterized, in addition, by seizures. It can be fatal when accompanied by multiorgan damage.

## BREAST

Lesions of the female breast are much more common than lesions of the male breast and usually take the form of palpable, sometimes painful nodules or masses. Fortunately, most are innocent, but as is well known, breast cancer is the most common cancer in women (excluding neoplasia of the skin) and is second only to lung cancer as a cause of cancer-related death. Hence, it is not uncommon for women to seek evaluation of even slightly suspicious *lumps* in the breast (Fig. 18–22).

We start our discussion of diseases of the breast with benign non-neoplastic lesions. Before considering the extremely common fibrocystic changes, several relatively minor lesions warrant brief mention. *Supernumerary nipples or breast tissue* may be found anywhere along the

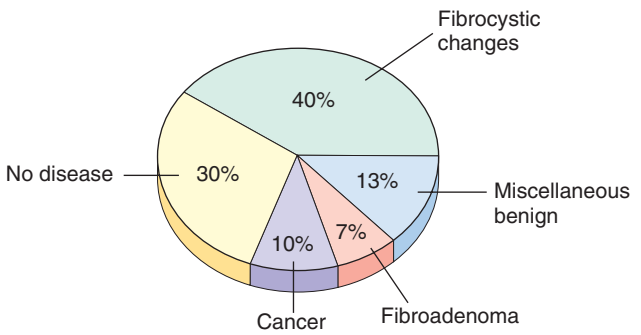



**Figure 18–22** Histopathologic findings in a series of women seeking evaluation of breast "lumps."

embryonic ridge (milk line). Besides being curiosities, these congenital anomalies are subject to the same diseases that affect the normal breast. *Congenital inversion of the nipple* is of clinical significance because similar changes may be produced by an underlying cancer. *Galactocele* arises during lactation from cystic dilation of an obstructed duct. Besides being painful "lumps," these cysts may rupture, inciting a local inflammatory reaction, with production of an indurated focus falsely suggestive of malignancy.

## FIBROCYSTIC CHANGES

The designation *fibrocystic* is applied to a miscellany of changes in the female breast that consist predominantly of cyst formation and fibrosis. In the past, these lesions were called *fibrocystic disease.* However, since most of these changes have little clinical significance beyond the need to distinguish them from cancer, the term *fibrocystic change* is preferred.

Overall, fibrocystic changes are the most common breast abnormality seen in premenopausal women. The changes tend to arise during reproductive age and are most likely a consequence of the *cyclic breast changes that occur normally in the menstrual cycle.* Estrogenic therapy and oral contraceptives do not seem to increase the incidence of these alterations, and oral contraceptives may, in fact, *decrease* the risk.

Fibrocystic changes can be subdivided into nonproliferative and proliferative patterns, as described next.

### Nonproliferative Changes

#### *Cysts and Fibrosis*

Nonproliferative changes are the most common type of fibrocystic lesions, characterized by an increase in fibrous stroma associated with dilation of ducts and formation of variably sized cysts.

#### MORPHOLOGY

A single, large cyst may form within one breast, but changes usually are multifocal and often bilateral. The involved areas appear as ill-defined, diffusely increased densities and discrete nodularities on mammography. The cysts range from less than 1 cm and up to 5 cm in diameter. Unopened, they are brown to blue **(blue dome cysts)** and are filled with watery, turbid fluid (Fig. 18–23). The secretions within the cysts may calcify, producing microcalcifications on mammograms. Histologic examination reveals an epithelial lining that in larger cysts may be flattened or even totally atrophic (Fig. 18–24). Frequently, the lining cells are large and polygonal with abundant granular, eosinophilic cytoplasm and small, round, deeply chromatic nuclei. Such morphology is called **apocrine metaplasia** and virtually always is benign.

The stroma surrounding all types of cysts usually consists of compressed fibrous tissue that has lost the delicate, myxomatous appearance of normal breast stroma. A stromal lymphocytic infiltrate is common in this and all other variants of fibrocystic change.

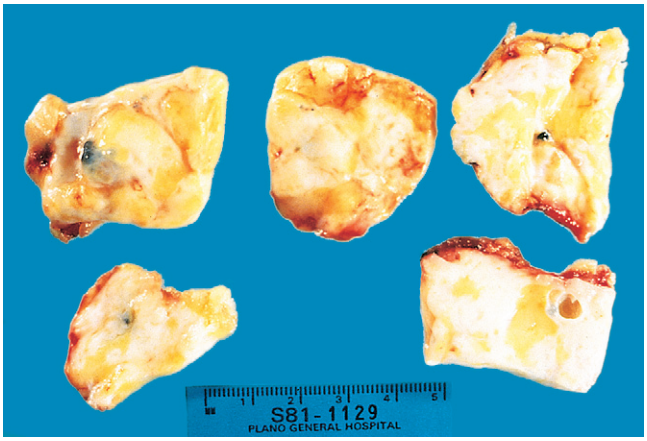



**Figure 18–23** Fibrocystic change seen in breast biopsy specimens. The scattered, poorly demarcated white areas represent foci of fibrosis. In the specimen at the *lower right*, a transected empty cyst is evident; in the two specimens on the *left*, unopened blue dome cysts are seen.
*(Courtesy of Dr. Kyle Molberg, Department of Pathology, University of Texas Southwestern Medical School, Dallas, Texas.)*

### Proliferative Change

#### *Epithelial Hyperplasia*

Normal ducts and lobules of the breast are lined by two layers of cells—a layer of luminal cells overlying a second layer of myoepithelial cells. *Epithelial hyperplasia* is recognized by the presence of more than two cell layers. The spectrum of epithelial hyperplasia ranges from mild and orderly to atypical hyperplasias with features that resemble those of in situ carcinoma.

#### MORPHOLOGY

The gross appearance of epithelial hyperplasia is not distinctive and is dominated by coexisting fibrous or cystic changes. Histologic examination shows an almost infinite spectrum of proliferative alterations. The ducts, ductules, or lobules may be filled with orderly cuboidal cells within which small gland

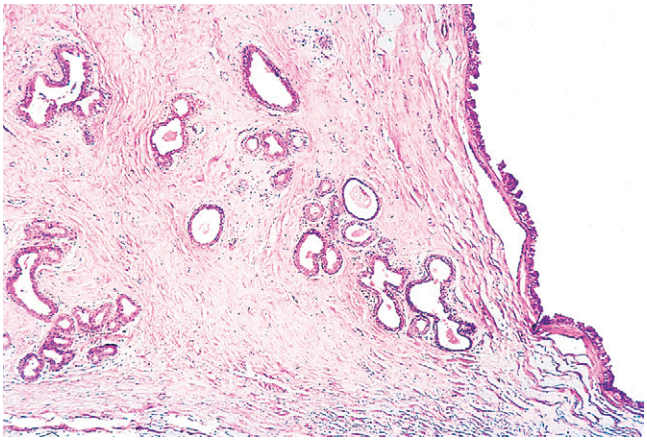


**Figure 18–24** Fibrocystic change of the nonproliferative type in a breast biopsy specimen. Visible in this field are dilated ducts, producing microcysts and, at *right*, the wall of a large cyst lined with epithelial cells.
*(Courtesy of Dr. Kyle Molberg, Department of Pathology, University of Texas Southwestern Medical School, Dallas, Texas.)*

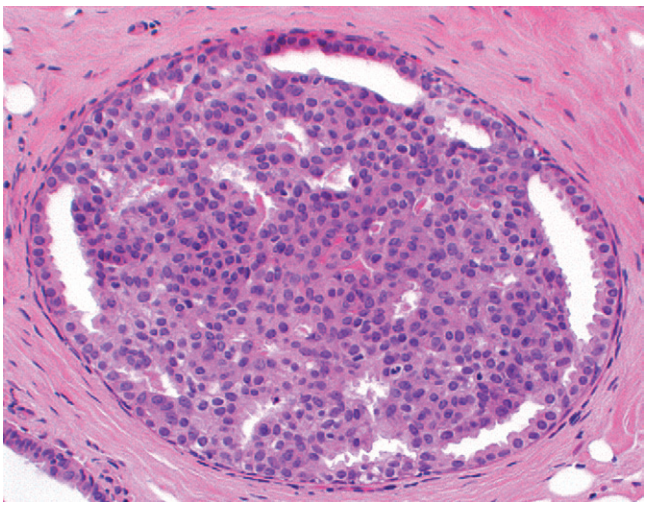


**Figure 18–25** Epithelial hyperplasia in a breast biopsy specimen. The duct lumen is filled with a heterogeneous population of cells of differing morphology. Irregular slitlike fenestrations are prominent at the periphery.

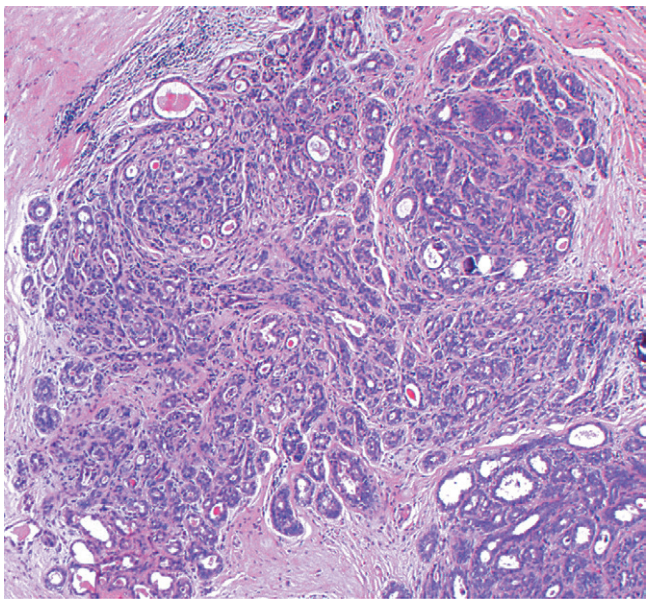


**Figure 18–26** Sclerosing adenosis, breast biopsy. The involved terminal duct lobular unit is enlarged, and the acini are compressed and distorted by surrounding dense stroma. Unlike in breast carcinoma, the acini are arranged in a swirling pattern, and the outer border is well circumscribed.

patterns (called **fenestrations**) can be discerned (Fig. 18–25). Sometimes, the proliferating epithelium projects as multiple small papillary excrescences into the ductal lumen **(ductal papillomatosis).** The degree of hyperplasia, judged in part by the number of layers of intraductal epithelium, can be mild, moderate, or marked. Occasionally, hyperplasia produces microcalcifications on mammography, raising concern for cancer.

In some instances the hyperplastic cells have features bearing some resemblance to ductal carcinoma in situ (described later). Such hyperplasia is called **atypical ductal hyperplasia. Atypical lobular hyperplasia** is used to describe hyperplasias that exhibit changes that approach but do not meet diagnostic criteria for lobular carcinoma in situ. Both atypical ductal and lobular hyperplasia are associated with an increased risk of invasive carcinoma.

### *Sclerosing Adenosis*

The type of fibrocystic change termed *sclerosing adenosis* is less common than cysts and hyperplasia but is significant because its clinical and morphologic features may mimic those of carcinoma. These lesions contain marked intralobular fibrosis and proliferation of small ductules and acini.

#### MORPHOLOGY

Grossly, the lesion has a hard, rubbery consistency, similar to that of breast cancer. Histologic examination shows a characteristic **proliferation of luminal spaces (adenosis) lined by epithelial cells and myoepithelial cells,** yielding masses of small glands within a fibrous stroma (Fig. 18–26). Aggregated glands may be virtually back to back, with single or multiple layers of cells in contact with one another. Marked stromal fibrosis, which may compress and distort the proliferating epithelium, is always associated with the adenosis—hence the designation **sclerosing adenosis.** This overgrowth of fibrous tissue may completely compress the lumina of the acini and ducts, so that they appear as solid cords of cells—a pattern that is difficult to distinguish histologically from invasive ductal carcinoma. The presence of double layers of epithelium and the identification of myoepithelial elements are helpful in arriving at the correct diagnosis.

## Relationship of Fibrocystic Changes to Breast Carcinoma

Certain clinical features of fibrocystic change tend to distinguish it from cancer, but the only certain way of making this distinction is through biopsy and histologic examination. Although fibrocystic changes are benign, some features may confer an increased risk for development of cancer:

- *Minimal or no increased risk of breast carcinoma*: fibrosis, cystic changes, apocrine metaplasia, mild hyperplasia
- *Slightly increased risk* (1.5- to 2-fold): moderate to florid hyperplasia (without atypia), ductal papillomatosis, sclerosing adenosis
- *Significantly increased risk* (5-fold): atypical hyperplasia, whether ductular or lobular

Proliferative fibrocystic changes usually are bilateral and multifocal and are associated with increased risk of subsequent carcinoma in both breasts.

## SUMMARY

### Fibrocystic Changes

- Fibrocystic changes may be classified as nonproliferative (cystic) or proliferative.
- Proliferative lesions include epithelial proliferations of ducts and lobules (with or without features of atypia) and adenosis (proliferation of terminal ducts), sometimes associated with fibrosis (sclerosing adenosis).
- Atypical hyperplasia (whether ductal or lobular) is associated with a five-fold increase in the risk of developing carcinoma.

## INFLAMMATORY PROCESSES

Inflammatory processes involving the breast are uncommon and are usually associated with pain and tenderness in the affected areas. Included in this category are several forms of mastitis and traumatic fat necrosis, none of which increase the risk of cancer.

Acute mastitis develops when bacteria, usually *Staphylococcus aureus,* gain access to the breast tissue through the ducts. The vast majority of cases arise during the early weeks of nursing, when the skin of the nipple is vulnerable to the development of fissures. Clinically, staphylococcal infections induce typical acute inflammatory changes, which can progress to form single or multiple abscesses.

*Mammary duct ectasia (plasma cell mastitis)* is a nonbacterial chronic inflammation of the breast associated with inspissation of breast secretions in the main excretory ducts. Ductal dilation and eventual rupture leads to reactive changes in the surrounding tissue that may present as a poorly defined periareolar mass with nipple retraction, mimicking the changes caused by some cancers. It is an uncommon condition usually encountered in parous women between 40 and 60 years of age.

### MORPHOLOGY

Usually the inflammatory changes are confined to an area drained by one or more of the major excretory ducts of the nipple. On histologic examination, the ducts are filled with granular debris, sometimes containing leukocytes and lipid-laden macrophages. The lining epithelium generally is destroyed. **The most distinguishing features consist of a prominent lymphoplasmacytic infiltrate and occasional granulomas in the periductal stroma.**

*Fat necrosis* is an uncommon, innocuous lesion that is significant only because it often produces a mass. Most women with this condition report some antecedent trauma to the breast.

### MORPHOLOGY

During the early stage of traumatic fat necrosis, the lesion is small, often tender, rarely more than 2 cm in diameter, and sharply localized. It consists of a central focus of necrotic fat cells surrounded by neutrophils and lipid-laden macrophages, sometimes with giant cells. This lesion later becomes enclosed by fibrous tissue and mononuclear leukocytes and eventually is replaced by scar tissue or a cyst consisting of necrotic debris. Calcifications may develop in either the scar or the cyst wall.

## TUMORS OF THE BREAST

Tumors are the most important lesions of the female breast. Although they may arise from connective tissue or epithelial structures, it is the latter that give rise to the common breast neoplasms.

### Fibroadenoma

Fibroadenoma is by far the most common benign neoplasm of the female breast. It is a biphasic tumor composed of fibroblastic stroma and epithelium-lined glands; however, only the stromal cells are clonal and truly neoplastic. Fibroadenomas typically appear in young women with a peak incidence in the third decade of life. They usually manifest as solitary, discrete, mobile masses. An absolute or relative increase in estrogen is thought to contribute to their development. In addition, fibroadenomas may enlarge late in the menstrual cycle and during pregnancy; after menopause, they may regress and calcify.

### MORPHOLOGY

The fibroadenomas form discrete masses, 1 cm to 10 cm in diameter and of firm consistency (Fig. 18–27). A cut section shows a uniform tan-white color, punctuated by softer yellow-pink specks representing the glandular areas. Histologic examination shows a loose fibroblastic stroma containing ductlike, epithelium-lined spaces of various shapes and sizes. As in normal breast tissue, these glandular spaces are lined by luminal and myoepithelial cells with a well-defined, intact basement membrane.

### Phyllodes Tumor

Like fibroadenomas, phyllodes tumors are biphasic, being composed of neoplastic stromal cells and epithelium-lined glands. However, the stromal element of these tumors is more cellular and abundant, often forming epithelium-lined leaflike projections (*phyllodes* is Greek for "leaflike"). These tumors are much less common than fibroadenomas and arise de novo, not from preexisting fibroadenomas. In the past, they had the tongue-tangling name *cystosarcoma phyllodes*—an unfortunate term because these tumors usually are benign. Ominous changes suggesting malignancy include increased stromal cellularity, anaplasia, high mitotic activity, rapid increase in size, and infiltrative margins. Fortunately, most phyllodes tumors remain localized and are cured by excision; malignant lesions may recur, but they also tend to remain localized. Only 15% of all cases are fully malignant, metastasizing to distant sites.

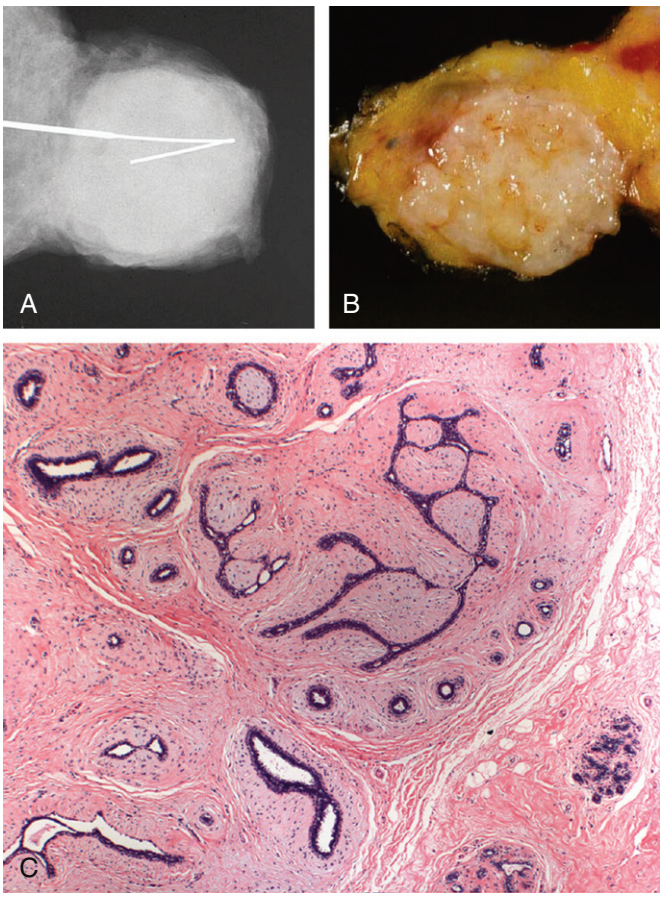



**Figure 18–27** Fibroadenoma. **A,** The radiograph shows a characteristic well-circumscribed mass. **B,** In this gross specimen, a rubbery well-circumscribed mass is clearly demarcated from the surrounding adipose tissue. **C,** In this micrograph, the proliferation of intralobular stroma can be seen to compress the entrapped glands, creating a "pushing" border that is sharply delineated from the surrounding normal tissue.

## Intraductal Papilloma

Intraductal papilloma is a benign neoplastic papillary growth. It is most often seen in premenopausal women. These lesions typically are solitary and found within the principal lactiferous ducts or sinuses. The clinical presentation may include

- Serous or bloody nipple discharge
- The presence of a *small subareolar tumor* a few millimeters in diameter
- *Nipple retraction,* in rare instances

### MORPHOLOGY

The tumors usually are solitary and less than 1 cm in diameter, consisting of delicate, branching growths within a dilated duct. On histologic examination, they are composed of multiple papillae, each having a connective tissue core covered by epithelial cells that are double-layered, with an outer luminal layer overlying a myoepithelial layer. The presence of a double-layered epithelium helps to distinguish intraductal papilloma from intraductal papillary carcinoma, which can present with clinical features similar to benign papilloma.

## Carcinoma

In 2010, more than 200,000 invasive breast cancers were diagnosed in women in the United States, and around 40,000 women died of this disease, making this scourge second only to lung cancer as a cause of cancer-related death in women. The lifetime risk of developing breast cancer is 1 in 8 for women in the United States. During the past 3 decades, the mortality rate among those diagnosed with breast cancer has dropped from 30% to 20%, mostly as a result of improved screening and treatment.

### *Epidemiology and Risk Factors*

A large number of risk factors for breast cancer have been identified. Table 18–5 divides these into well-established and less well-established groups and indicates, when possible, the relative risk posed by each. Some of the more important risk factors are summarized next.

***Age.*** Risk steadily increases throughout life, especially after menopause, peaking at roughly 80 years of age; 75% of women with breast cancer are older than 50 years of age, and only 5% are younger than 40.

***Geographic Variations.*** Surprising differences in the incidence and mortality rates of breast cancer have been reported for various countries. The risk for development of this disease is significantly higher in North America and northern Europe than in Asia and Africa. For example, the incidence and mortality rates are five times higher in the

**Table 18–5** Breast Cancer Risk Factors

| Factor | Relative Risk |
|---|---|
| **Well-Established Factors** | |
| Geography | Varies in different areas |
| Age | Increases after age 30 |
| Family history | |
| First-degree relative with breast cancer | 1.2–3.0 |
| Premenopausal | 3.1 |
| Premenopausal and bilateral | 8.5–9.0 |
| Postmenopausal | 1.5 |
| Postmenopausal and bilateral | 4.0–5.4 |
| Menstrual history | |
| Age at menarche <12 years | 1.3 |
| Age at menopause >55 years | 1.5–2.0 |
| Pregnancy | |
| First live birth from ages 25 to 29 years | 1.5 |
| First live birth after age 30 years | 1.9 |
| First live birth after age 35 years | 2.0–3.0 |
| Nulliparous | 3.0 |
| Benign breast disease | |
| Proliferative disease without atypia | 1.6 |
| Proliferative disease with atypical hyperplasia | >2.0 |
| Lobular carcinoma in situ | 6.9–12.0 |
| **Other Possible Factors** | |
| Exogenous estrogens | |
| Oral contraceptives | |
| Obesity | |
| High-fat diet | |
| Alcohol consumption | |
| Cigarette smoking | |

Data from Bilimoria MM, Morrow M: The women at increased risk for breast cancer: evaluation and management strategies. CA Cancer J Clin 46:263, 1995.

United States than in Japan. These differences seem to be environmental rather than genetic in origin, because migrants from low-incidence to high-incidence areas tend to acquire the rates of their adoptive countries, and vice versa. Diet, reproductive patterns, and nursing habits are thought to be involved.

***Race/Ethnicity.*** The highest rate of breast cancer is in non-Hispanic white women. However, Hispanic and African American women tend to develop cancer at a younger age and are more likely to develop aggressive tumors that present at an advanced stage. Such disparities between ethnicities are an area of intense study and currently are thought to be due to a combination of genetic differences and social factors, such as lifestyle choices and access to health care.

***Other Risk Factors.*** *Prolonged exposure to exogenous estrogens* postmenopausally, as occurs with hormone replacement therapy, has been proved to be useful for the prevention of osteoporosis. However, according to recent studies, relatively short-term use of combined estrogen plus progestin hormone therapy is associated with an increased risk of breast cancer, diagnosis at a more advanced stage of breast cancer, and higher incidence of abnormal mammograms. Because the 2002 Women's Health Initiative report suggested greater harm than benefit of combined estrogen plus a progestin, a precipitous decline has occurred in estrogen and progestin use, along with a serious reevaluation of perimenopausal hormone therapy.

*Oral contraceptives* have not been shown to affect the risk of breast cancer, even in women who have taken the pill for a long time or in women with a family history of breast cancer.

*Ionizing radiation* to the chest increases the risk of breast cancer. The magnitude of the risk depends on the radiation dose, the time since exposure, and age. Only women in whom irradiation occurred before age 30, during breast development, seem to be affected. For example, breast cancer develops in 20% to 30% of women who underwent irradiation for Hodgkin lymphoma in their teens and 20s, but the risk for women treated later in life is not elevated. Of import, the low doses of radiation associated with mammographic screening have no significant effect on the incidence of breast cancer.

*Many other, less well-established risk factors,* such as obesity, alcohol consumption, and a diet high in fat, have been implicated in the development of breast cancer by analysis of population studies. The risk associated with obesity probably is due to exposure of the breast to estrogen produced by adipose tissue.

## PATHOGENESIS

The causes of breast cancer remain incompletely understood. However, three sets of influences seem to be important: (1) genetic changes, (2) hormonal influences, and (3) environmental variables.

**Genetic Changes.** As with all cancers, mutations affecting proto-oncogenes and tumor suppressor genes in breast epithelium underlie oncogenesis. Among the best-characterized is **overexpression of the *HER2/NEU* proto-oncogene,** which undergoes amplification in up to 30% of invasive breast cancers. This gene is a member of the epidermal growth factor receptor family, and its overexpression is associated with a poor prognosis. **Amplification of *RAS* and *MYC* genes also has been reported in some human breast cancers.** Mutations of the well-known tumor suppressor genes *RB* and *TP53* also may be present. A large number of genes including the estrogen receptor gene may be inactivated by promoter hypermethylation. Undoubtedly, the transformation process involves multiple acquired genetic alterations, which can occur in various combinations, thereby giving rise to different subtypes of breast cancer. **Gene expression profiling can separate breast cancer into four molecular subtypes:** (1) luminal A (estrogen receptor–positive, *HER2/NEU*-negative); (2) luminal B (estrogen receptor–positive, *HER2/NEU* overexpressing); (3) *HER2/NEU* positive (*HER2/NEU* over expressing, estrogen receptor–negative); and (4) basal-like (estrogen receptor–negative and *HER2/NEU*-negative). These subtypes are associated with different outcomes and, in some instances, different therapies.

Approximately 10% of breast cancers are related to specific inherited mutations. Women who carry a breast cancer susceptibility gene are more likely to have bilateral cancer, to have other familial forms of cancer (e.g., ovarian cancer), to have a positive family history (i.e., multiple first-degree relatives affected before menopause), to develop breast cancer before menopause, and to belong to certain ethnic groups (e.g., people of Ashkenazi Jewish descent). **Roughly one third of women with hereditary breast cancer have mutations in *BRCA1* (at chromosomal locus 17q21.3) or *BRCA2* (located on chromosomal band 13q12-13).** These genes encode large, complex proteins that do not exhibit close homology to each other or other proteins. Although the molecular basis for their strong association with breast cancer risk is still being elucidated, both BRCA1 and BRCA2 are believed to function in a common DNA repair pathway (Chapter 5).

Genetically, *BRCA1* and *BRCA2* are classic tumor suppressor genes, in that cancer arises only when both alleles are inactivated or defective—the first genetic lesion caused by a germline mutation and the second by a subsequent somatic mutation. Genetic testing is available, but its utility is complicated by the existence of hundreds of different mutant alleles, only some of which confer cancer susceptibility. The degree of penetrance, age at cancer onset, and susceptibility to other types of cancers differ among the specific mutations. Most carriers, however, develop breast cancer by the age of 70 years, as compared with only 7% of women who do not carry a mutation. The role of these genes in nonhereditary sporadic breast cancer is less clear, as mutations affecting *BRCA1* and *BRCA2* are infrequent in sporadic tumors. Less common genetic diseases associated with breast cancer are the Li-Fraumeni syndrome (caused by germline mutations in *TP53*) (Chapter 5), Cowden syndrome (caused by germline mutations in *PTEN*—mentioned earlier under endometrial carcinoma) (see also Chapter 14), and the ataxia-telangiectasia gene carriers (Chapter 5).

**Hormonal Influences.** Endogenous estrogen excess, or more accurately, hormonal imbalance, clearly has a significant role. Many of the risk factors mentioned (long duration of

reproductive life, nulliparity, and late age at birth of first child) involve increased exposure to estrogen unopposed by progesterone (Table 18–5). Functioning ovarian tumors that elaborate estrogens are associated with breast cancer in postmenopausal women. Estrogens stimulate the production of growth factors, such as transforming growth factor-α, platelet-derived growth factor, and fibroblast growth factor and others, which may promote tumor development through paracrine and autocrine mechanisms.

**Environmental Variables.** Environmental influences are suggested by the variable incidence of breast cancer in genetically homogeneous groups and the geographic differences in prevalence, as discussed earlier.

## MORPHOLOGY

The most common location of tumors within the breast is in the upper outer quadrant (50%), followed by the central portion (20%). About 4% of women with breast cancer have bilateral primary tumors or sequential lesions in the same breast.

Breast cancers are classified according to whether they have or have not penetrated the limiting basement membrane: Those that remain within this boundary are termed in situ carcinomas, and those that have spread beyond it are designated invasive or infiltrating carcinomas. In this classification, the main forms of breast carcinoma are as follows:

A. Noninvasive
   1. Ductal carcinoma in situ (DCIS)
   2. Lobular carcinoma in situ (LCIS)
B. Invasive (infiltrating)
   1. Invasive ductal carcinoma ("not otherwise specified"), the most common subtype of invasive carcinoma
   2. Invasive lobular carcinoma
   3. Medullary carcinoma
   4. Colloid carcinoma (mucinous carcinoma)
   5. Tubular carcinoma
   6. Other types

### *Noninvasive (in situ) Carcinoma*

There are two types of noninvasive breast carcinoma: DCIS and LCIS. Morphologic studies have shown that both types usually arise from cells in the terminal duct lobular unit. DCIS tends to fill and distort ductlike spaces. By contrast, LCIS usually expands but does not alter the acini of lobules. Both are confined by a basement membrane and do not invade into stroma or lymphovascular channels.

**DCIS** has a wide variety of histologic appearances. Architectural patterns often are mixed and include solid, comedo, cribriform, papillary, micropapillary, and "clinging" types. Necrosis may be present in any of these types. Nuclear appearance tends to be uniform in a given case and ranges from bland and monotonous (low nuclear grade) to pleomorphic (high nuclear grade). The **comedo** subtype is distinctive and is characterized by cells with high-grade nuclei with extensive central necrosis (Fig. 18–28). The name derives from the toothpaste-like necrotic tissue that extrudes from transected ducts on application of gentle pressure. **Calcifications frequently are associated with DCIS,** originating as either calcified necrotic debris or calcified secretory material. The proportion of breast cancers that are diagnosed at the DCIS stage is only 5% in unscreened populations but up to 40% in screened populations, largely because of the ability of mammography to detect calcifications. DCIS only rarely manifests as a palpable or radiologically detectable mass. The prognosis with DCIS is excellent, with greater than 97% long-term survival after simple mastectomy. In some women, distant metastases develop without local recurrence; these patients usually are found to have extensive high-nuclear-grade DCIS, probably with small, undetected areas of invasion. At least one third of women with small areas of untreated DCIS of low nuclear grade will eventually develop invasive carcinoma. When invasive cancer does develop, it usually is in the same breast and quadrant as the earlier DCIS. Current treatment strategies attempt to eradicate the DCIS by surgery and irradiation. Treatment with antiestrogenic agents such as tamoxifen and aromatase also may decrease the risk of recurrence.

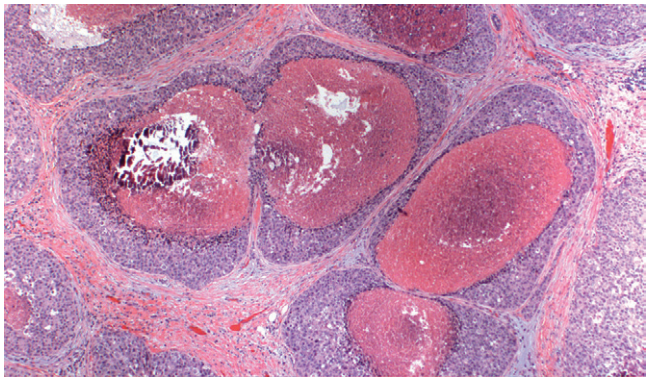


**Figure 18–28** Comedo ductal carcinoma in situ (DCIS). Several adjacent ducts are filled by tumor associated with large central zones of necrosis and calcified debris. This type of DCIS most frequently is detected as radiologic calcifications.

**Paget disease of the nipple** is caused by the extension of DCIS up the lactiferous ducts and into the contiguous skin of the nipple, producing a unilateral crusting exudate over the nipple and areolar skin. In almost all cases, an underlying carcinoma is present, and approximately 50% of the time this carcinoma is invasive. Prognosis is based on the underlying carcinoma and is not affected by the presence of Paget disease.

**LCIS** has a uniform appearance. The cells are monomorphic with bland, round nuclei and occur in loosely cohesive clusters within the lobules (Fig. 18–29). Intracellular mucin vacuoles (sometimes forming signet ring cells) are common. LCIS is virtually always an incidental finding, because unlike DCIS, it is only rarely associated with calcifications. Therefore, the incidence of LCIS has remained unchanged in mammographically screened populations. Approximately one third of women with LCIS will eventually develop invasive carcinoma. Unlike with DCIS, **subsequent invasive carcinomas may arise in either breast.** Most of these cancers are invasive lobular carcinomas; however, invasive ductal carcinomas also arise from LCIS. Thus, **LCIS is both a marker of an increased risk of carcinoma in both breasts and a direct precursor of some cancers.** Current treatment involves either chemoprevention with tamoxifen along with close clinical and radiologic follow-up evaluation or, less commonly, bilateral prophylactic mastectomy.

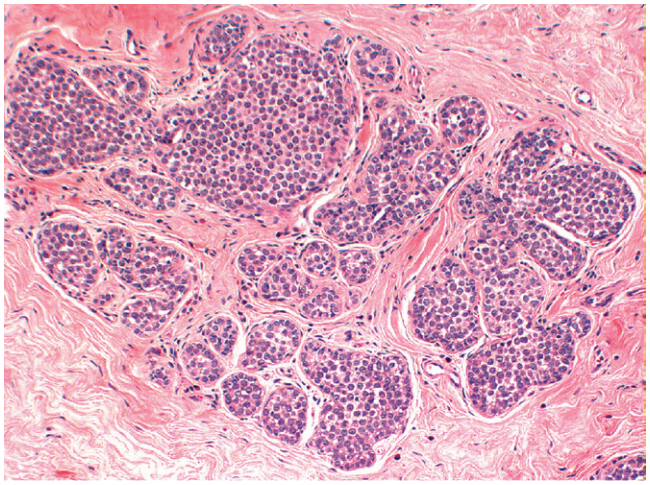


**Figure 18–29** Lobular carcinoma in situ. A monomorphic population of small, rounded, loosely cohesive cells fills and expands the acini of a lobule. The underlying lobular architecture is intact.

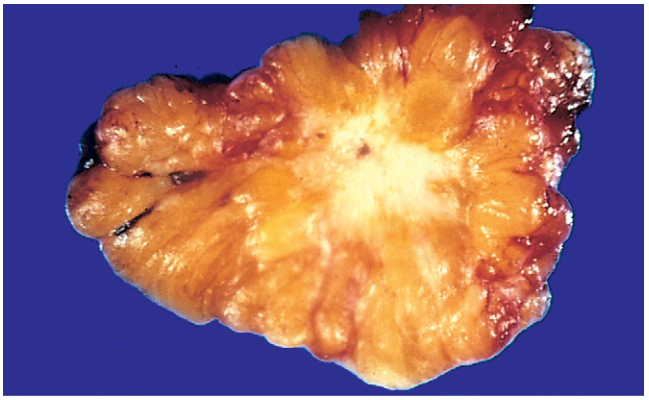


**Figure 18–30** Invasive ductal carcinoma is evident in this breast biopsy specimen. The hard, fibrotic lesion infiltrates the surrounding tissue, causing retraction.

***Invasive (Infiltrating) Carcinoma***

The distinctive histologic patterns of the subtypes of invasive carcinoma are described first, followed by the gross features common to all.

**Invasive ductal carcinoma** is a term used for all carcinomas that cannot be subclassified into one of the specialized types described below**.** A majority (70% to 80%) of cancers fall into this group. This type of cancer usually is associated with DCIS and, rarely, LCIS. Most ductal carcinomas produce a desmoplastic response, which replaces normal breast fat (resulting in a mammographic density) and forms a hard, palpable mass (Fig. 18–30). The microscopic appearance is quite heterogeneous, ranging from tumors with well-developed tubule formation and low-grade nuclei to tumors consisting of sheets of anaplastic cells (Fig. 18–31). The tumor margins typically are irregular. Invasion of lymphovascular spaces may be seen. About two thirds express estrogen or progesterone receptors, and about one third overexpress HER2/NEU.

**Invasive lobular carcinoma** consists of cells morphologically identical to the cells of LCIS. Two thirds of the cases are associated with adjacent LCIS. The cells invade individually into stroma and are often aligned in "single-file" strands or chains. This growth pattern correlates with the presence of mutations that abrogate the function of E-cadherin, a surface protein that contributes to the cohesion of normal breast epithelial cells. Although most manifest as palpable masses or mammographic densities, a significant subgroup may exhibit a diffusely invasive pattern without a desmoplastic response and may be clinically occult. Lobular carcinomas have a unique pattern of metastases among breast cancers;

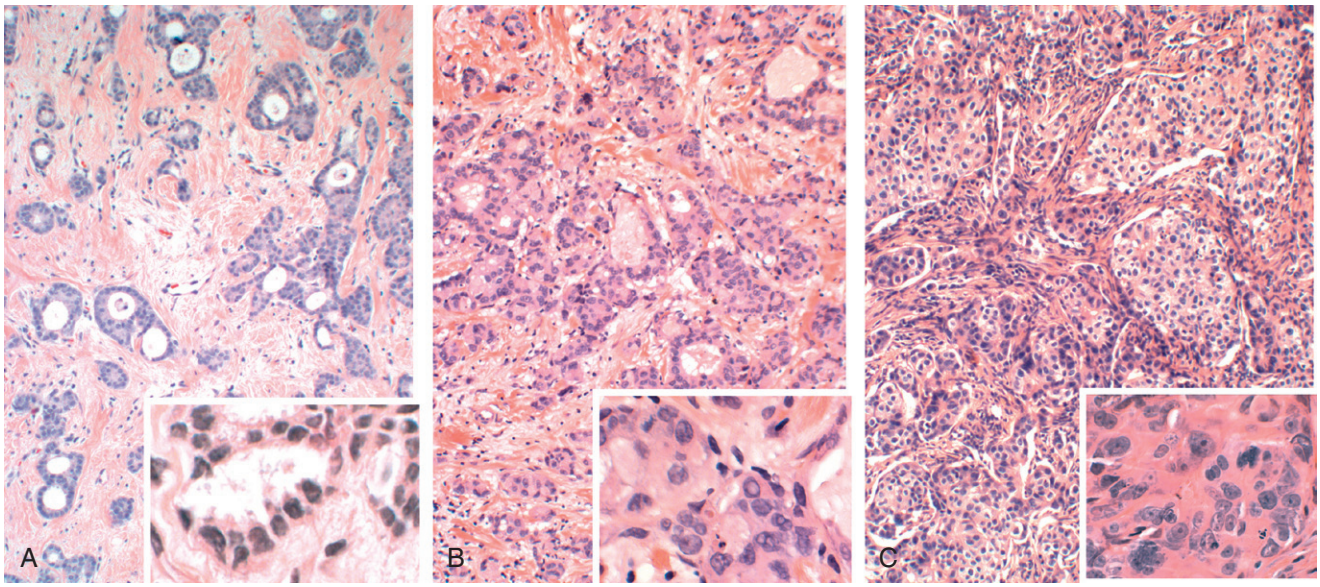



**Figure 18–31** Invasive breast carcinomas of no special type (*insets* show each tumor at higher magnification). **A,** Well-differentiated carcinoma consists of tubular or cribriform glands containing cells with small monomorphic nuclei within a desmoplastic response. **B,** Moderately differentiated carcinoma demonstrates less tubule formation and more solid nests of cells with pleomorphic nuclei. **C,** Poorly differentiated carcinoma infiltrates as ragged sheets of pleomorphic cells containing numerous mitotic figures and areas of tumor necrosis.

they more frequently spread to cerebrospinal fluid, serosal surfaces, gastrointestinal tract, ovary, uterus, and bone marrow. Lobular carcinomas also are more frequently multicentric and bilateral (in 10% to 20% of cases). Almost all of these carcinomas express hormone receptors, whereas HER2/NEU overexpression is rare. These tumors comprise fewer than 20% of all breast carcinomas.

**Inflammatory carcinoma** is defined by the clinical presentation of an enlarged, swollen, erythematous breast, usually without a palpable mass. The underlying carcinoma is generally poorly differentiated and diffusely infiltrative. Characteristically, carcinoma involves dermal lymphatic spaces. The resultant blockage of these channels leads to edema, resulting in the characteristic "inflamed" clinical appearance; true inflammation is minimal to absent. Many of these tumors metastasize to distant sites; the overall 5-year survival is under 50%, and understandably even lower in those with metastatic disease at diagnosis.

**Medullary carcinoma** is a rare subtype of carcinoma, accounting for less than 1% of breast cancers. These cancers consist of sheets of large anaplastic cells with well-circumscribed, "pushing" borders (Fig. 18–32, *A*). Clinically, they can be mistaken for fibroadenomas. There is invariably a pronounced lymphoplasmacytic infiltrate. DCIS usually is absent or minimal. Medullary carcinomas occur with increased frequency in women with *BRCA1* mutations, although most women with medullary carcinoma are not carriers. These carcinomas uniformly lack the estrogen and progesterone receptors and do not overexpress HER2/NEU (a combination that often is referred to as **triple-negative**).

**Colloid (mucinous) carcinoma** also is a rare subtype. The tumor cells produce abundant quantities of extracellular mucin, which dissects into the surrounding stroma (Fig. 18–32, *B*). Like medullary carcinomas, they often present as well-circumscribed masses and can be mistaken for fibroadenomas. On gross evaluation, the tumors usually are soft and gelatinous. Most express hormone receptors but do not overexpress HER2/NEU.

**Tubular carcinomas** rarely present as palpable masses but account for 10% of invasive carcinomas smaller than 1 cm found with mammographic screening. They usually are detected as irregular mammographic densities. On microscopic examination, the carcinomas consist of well-formed tubules with low-grade nuclei. Lymph node metastases are rare, and prognosis is excellent. Virtually all tubular carcinomas express hormone receptors and do not show HER2/NEU overexpression.

#### *Common Features of Invasive Cancers*

In all forms of breast cancer, local disease progression leads to similar physical findings. Invasive cancers tend to become adherent and fixed to the pectoral muscles or deep fascia of the chest wall and the overlying skin, with consequent retraction or dimpling of the skin or nipple. The latter is an important sign because it may be the first indication of malignancy. Involvement of the lymphatic pathways may result in localized lymphedema. In such cases, the skin becomes thickened around exaggerated hair follicles, giving an appearance known as peau d'orange ("orange peel").

### Clinical Course

Breast cancer often is discovered by the patient or her physician as a deceptively discrete, solitary, painless, and movable mass. At the time of clinical detection, the carcinoma typically is 2 to 3 cm in size, and involvement of the regional lymph nodes (most often axillary) is already present in about 50% of patients. With mammographic screening, carcinomas frequently are detected even before they become palpable. The average invasive carcinoma found by mammographic screening is around 1 cm in size, and only 15% of these have produced nodal metastases. In addition, DCIS often is detected before the development of invasive carcinoma during screening. As women age, fibrous breast tissue is replaced by fat, and screening becomes more sensitive as a result of the increased radiolucency of the breast and the increased incidence of malignancy. The current controversy over the best time to begin mammographic screening arises from efforts to balance the benefits of early cancer detection in some women with the

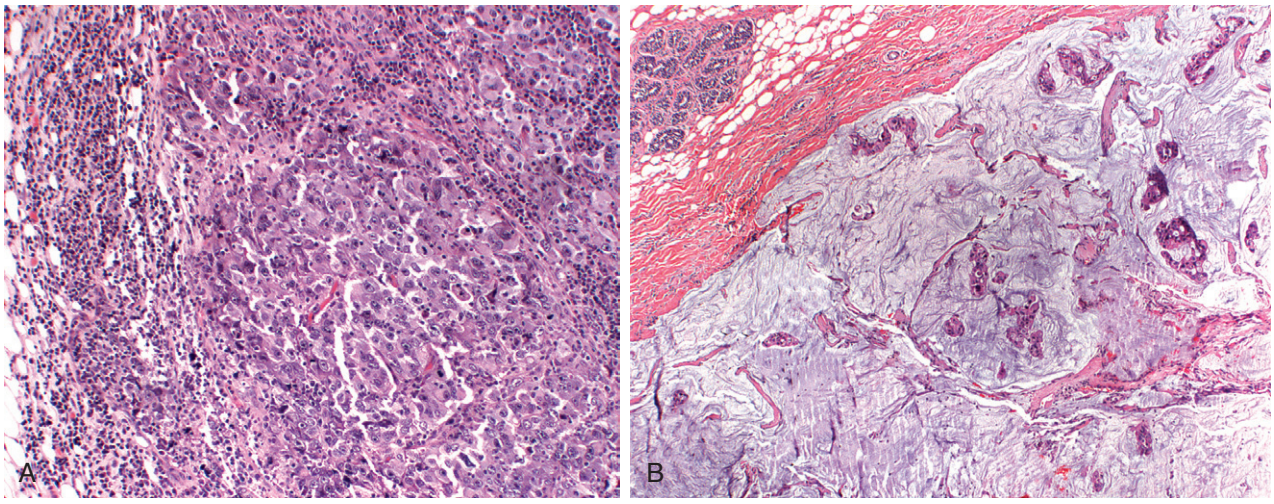



**Figure 18–32** Special types of breast carcinoma. **A,** Medullary carcinoma. The highly pleomorphic tumor cells grow in cohesive sheets and are associated with a prominent reactive infiltrate of lymphocytes and plasma cells. **B,** Mucinous (colloid) carcinoma. The tumor cells are present in small clusters within large pools of mucin. Note the characteristic well-circumscribed border, which mimics the appearance of benign masses.

risks of radiation exposure and the morbidity and expense associated with clinical workup of benign breast lesions (false positives). Magnetic resonance imaging is being studied as an adjunct to mammographic screening in high-risk, young patients with dense breasts that are difficult to image by mammography.

Breast cancer spread occurs through lymphatic and hematogenous channels. Outer quadrant and centrally located lesions typically spread first to the axillary nodes. Those in the medial inner quadrants often travel first to lymph nodes along the internal mammary arteries. More distant dissemination eventually ensues, and can involve virtually any organ or tissue in the body. Favored locations are the lungs, skeleton, liver, adrenals, and (less commonly) brain, but no site is exempt. *Metastases may come to clinical attention many years after apparent therapeutic control of the primary lesion, sometimes as long as 15 years later.* Nevertheless, with each passing year without disease recurrence, the likelihood of cure increases.

Prognosis of breast cancers is influenced by the following variables the first three of which are components of the tumor-node-metastasis (TNM) staging classification:

- *Tumor invasion and size.* In situ carcinomas carry an excellent prognosis (5-year survival rate greater than 90%), as do invasive carcinomas less than 2 cm in size (5-year survival rate of 87%).
- *Extent of lymph node involvement.* With no axillary node involvement, the 5-year survival rate is close to 80%. Survival is inversely related to the number of involved lymph nodes and is less than 50% with 16 or more involved nodes. Sentinel node biopsy is currently the mainstay for staging the axilla. This procedure identifies the primary lymph node(s) that drain the breast parenchyma using dye or a radioactive tracer (or sometimes both). Once identified, sentinel nodes are removed and examined microscopically. A sentinel lymph node that is free from carcinoma (a "negative node") is highly predictive of absence of metastatic carcinoma in the remaining lymph nodes. A "positive node," on the other hand, is an indication for a complete axillary dissection, which is used to stage the patient's disease.
- *Distant metastases.* Patients who develop hematogenous spread are rarely curable, although chemotherapy may prolong survival (the 5-year survival rate is approximately 15%).
- *Histologic grade.* The most common grading system for breast cancer evaluates tubule formation, nuclear grade, and mitotic rate. Well-differentiated carcinomas are associated with a significantly better prognosis than poorly differentiated carcinomas. Moderately differentiated carcinomas initially have a good prognosis, but survival at 20 years approaches that for poorly differentiated carcinomas.
- *The histologic type of carcinoma.* All specialized types of breast carcinoma (tubular, medullary, and mucinous) are associated with a somewhat better prognosis than carcinomas of no special type (*ductal carcinomas*). A major exception is inflammatory carcinoma, which has a poor prognosis.
- *The presence or absence of estrogen or progesterone receptors.* The presence of hormone receptors confers a slightly better prognosis. However, the practical reason for determining their presence is to predict the response to therapy. The highest rate of response (approximately 80%) to antiestrogen therapy (oophorectomy or tamoxifen) is seen in women whose tumor cells express both estrogen and progesterone receptors. Lower rates of response (25% to 45%) are seen if only estrogen receptor is present. If both are absent, very few patients (less than 10%) respond.
- *Overexpression of HER2/NEU.* Overexpression of this membrane-bound protein is almost always caused by gene amplification and can be determined by immunohistochemistry (which assesses protein levels) or by fluorescence in situ hybridization (which assesses the gene copy number). Overexpression is associated with a poorer prognosis. However, the clinical importance of evaluating HER2/NEU lies in predicting response to trastuzumab (Herceptin), a monoclonal antibody that binds and inhibits the function of HER2/NEU. This remains one of the best-characterized examples of an effective therapy directed against a tumor-specific molecular lesion.

Why some cancers recur after postoperative therapy while others do not remains a mystery. As mentioned earlier, gene expression profiling of breast cancers on microarrays (gene chips) (Chapter 5) has defined several molecular classes of breast cancer and also has been used to develop commercial tests that may predict the response of an individual patient's tumor to chemotherapy. At present there is insufficient data on the prognostic value of such tests.

## SUMMARY

### Breast Carcinoma

- The lifetime risk of developing breast cancer for an American woman is 1 in 8.
- A majority (75%) of breast cancers are diagnosed after the age of 50.
- Risk of developing breast cancer is related to estrogen exposure, genetic factors, long duration between menarche and menopause, atypical proliferative lesions, and family history of breast cancer in a first-degree relative, particularly if the disease was multifocal or in a premenopausal woman.
- About 10% of all breast cancers are caused by inherited mutations; *BRCA1* and *BRCA2* genes account for one third of the cases associated with single-gene mutations.
- Ductal carcinoma in situ (DCIS) is a precursor to invasive ductal carcinoma and typically is found on mammographic examination as calcifications. When carcinoma develops in a woman with a previous diagnosis of DCIS, it usually is an invasive ductal carcinoma in the same breast.
- Lobular carcinoma in situ (LCIS) frequently is an incidental finding and usually is not associated with calcifications. When carcinoma develops in a woman with a previous diagnosis of LCIS, it may occur in the affected or unaffected breast and usually is invasive lobular carcinoma but may be invasive ductal carcinoma.

- The natural history of breast carcinoma is long, with metastases sometimes appearing decades after the initial diagnosis.
- Prognosis is most dependent on tumor size, lymph node involvement, distant metastasis at presentation, tumor grade, and histologic type.
- Estrogen and progesterone receptor status and expression of HER2/NEU are used primarily to determine response to treatment. Estrogen receptor–expressing tumors are more likely to respond to tamoxifen. HER2/NEU-overexpressing tumors often are treated with trastuzumab.

## LESIONS OF THE MALE BREAST

The rudimentary male breast is relatively free of pathologic involvement. Only two disorders occur with sufficient frequency to be considered here: *gynecomastia* and *carcinoma.*

### Gynecomastia

As in females, male breasts are subject to hormonal influences, but they are considerably less sensitive in this regard than female breasts. Nonetheless, enlargement of the male breast, or gynecomastia, may occur in response to absolute or relative estrogen excesses. The most important cause of hyperestrinism in the male is cirrhosis and the consequent inability of the liver to metabolize estrogens. Other causes include Klinefelter syndrome, anabolic steroids, and some pharmacologic agents. Physiologic gynecomastia often occurs in puberty and in extreme old age.

The morphologic features of gynecomastia include an increase in connective tissue and epithelial hyperplasia of the ducts; lobule formation is rare. Clinically, a button-like, subareolar swelling develops, usually in both breasts but occasionally in only one.

### Carcinoma

Breast cancer is rare in men, with an incidence less than 1% of that reported for women. It typically is diagnosed in advanced age. Because of the scant amount of breast tissue in men, the tumor rapidly infiltrates the overlying skin and underlying thoracic wall. Both morphologically and biologically, these tumors resemble the invasive carcinomas seen in women. Unfortunately, almost half have spread to regional nodes or more distant sites by the time they are discovered.

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