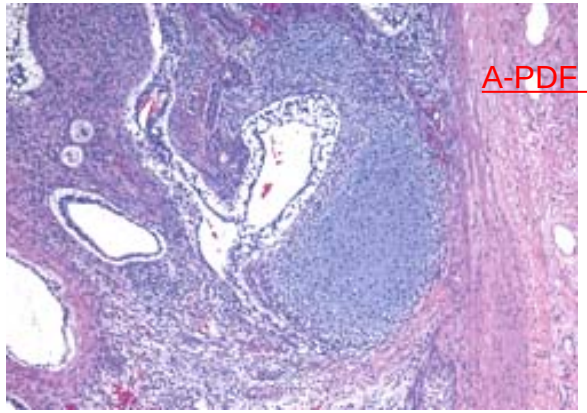


Figure 21-30 Adult prostate. The normal prostate contains several distinct regions, including a central zone (CZ), a peripheral zone (PZ), a transitional zone (TZ), and a periurethral zone. Most carcinomas arise from the peripheral glands of the organ and may be palpable during digital examination of the rectum. Nodular hyperplasia, in contrast, arises from more centrally situated glands and is more likely to produce urinary obstruction early on than is carcinoma.

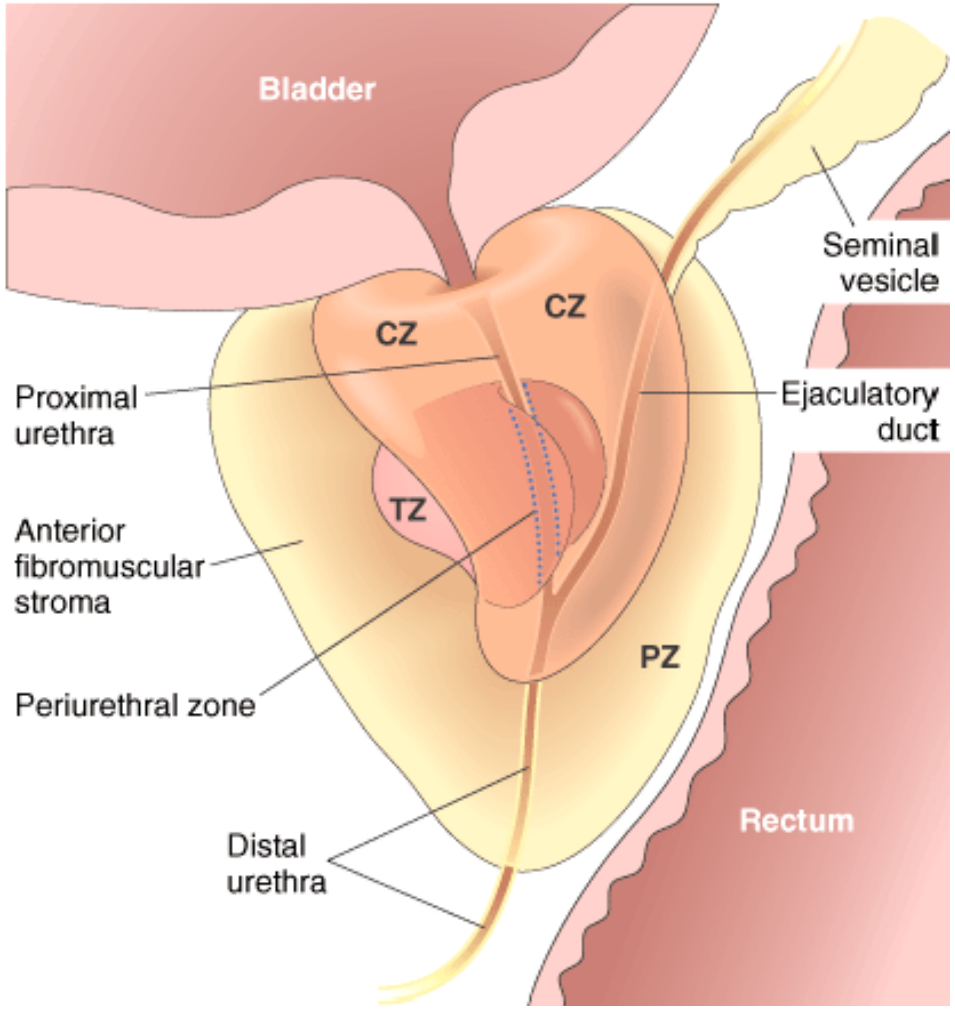


Figure 21-31 Benign prostate gland with basal cell and secretory cell layer.

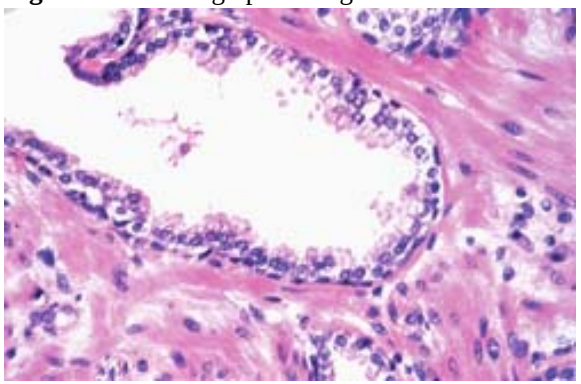


Figure 21-32 Simplified scheme of the pathogenesis of prostatic hyperplasia. The central role of the stromal cells in generating dihydrotestosterone should be noted.

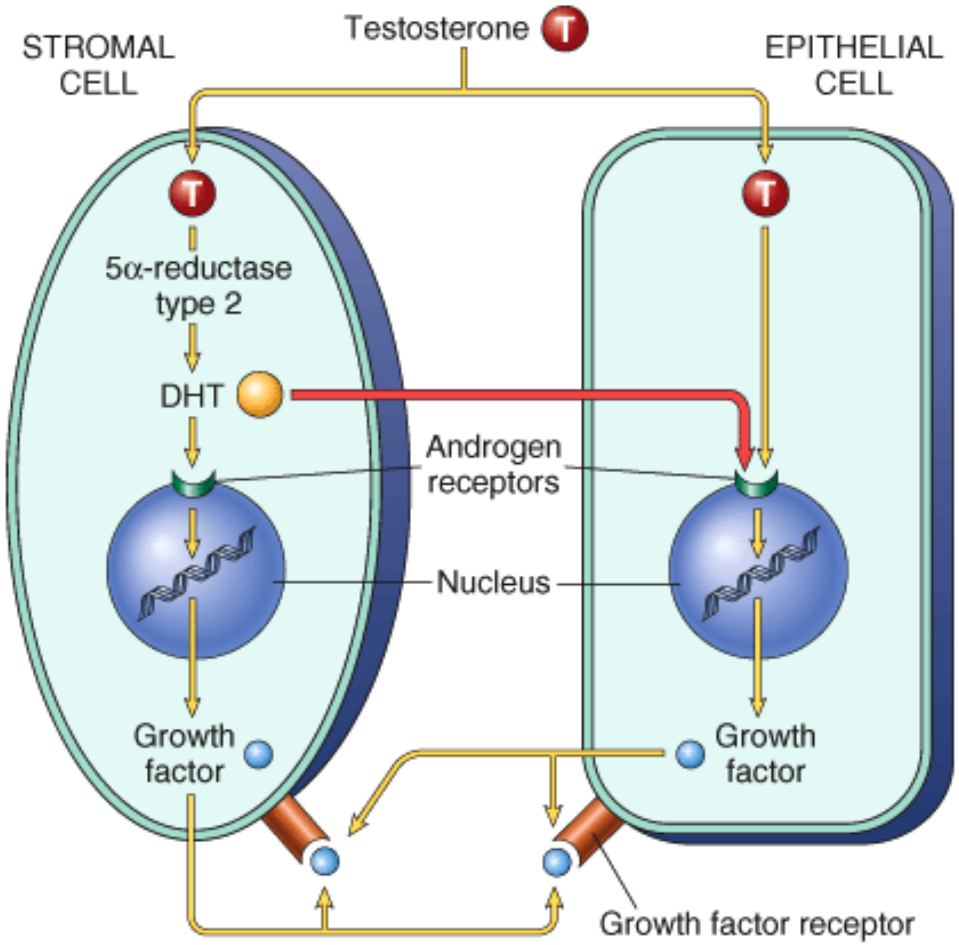


Figure 21-33 Nodular prostatic hyperplasia. *A*, Well-defined nodules of BPH compress the urethra into a slitlike lumen. *B*, A microscopic view of a whole mount of the prostate shows nodules of hyperplastic glands on both sides of the urethra.

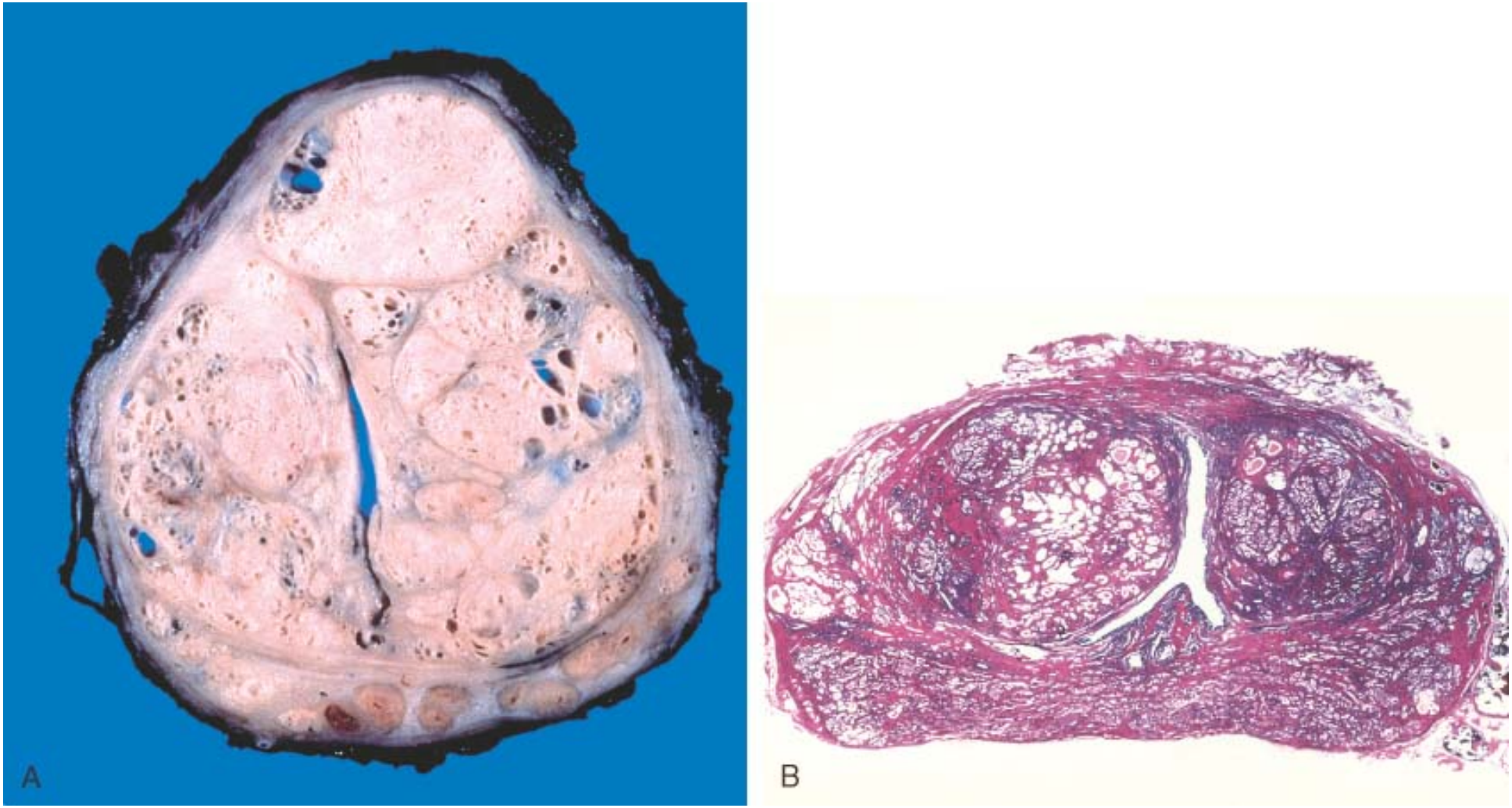


Figure 21-34 Adenocarcinoma of the prostate. Carcinomatous tissue is seen on the posterior aspect (*lower left*). Note the solid whiter tissue of cancer in contrast to the spongy appearance of the benign peripheral zone on the contralateral side.

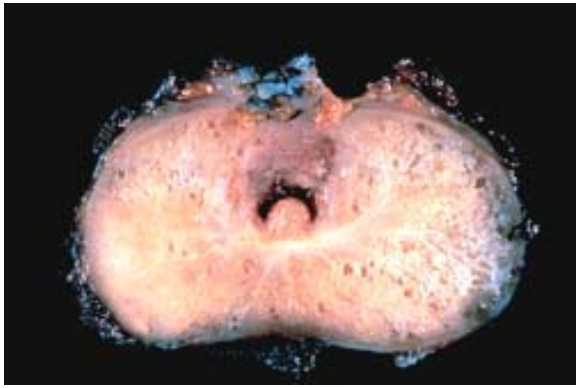


Figure 21-36 *A*, Photomicrograph of a small focus of adenocarcinoma of the prostate demonstrating small glands crowded in between larger benign glands. *B*, Higher magnification shows several small malignant glands with enlarged nuclei, prominent nucleoli, and dark cytoplasm, compared to the larger benign gland (*top*).

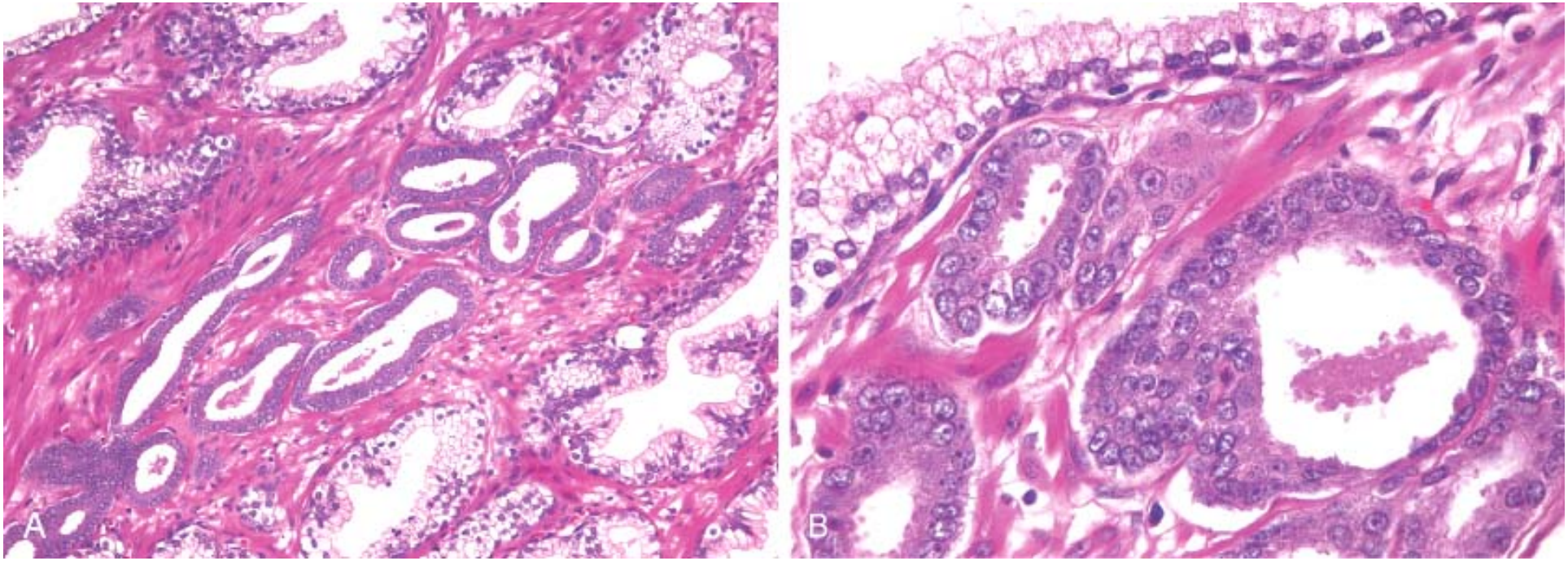


Figure 21-35 Metastatic osteoblastic prostatic carcinoma within vertebral bodies.

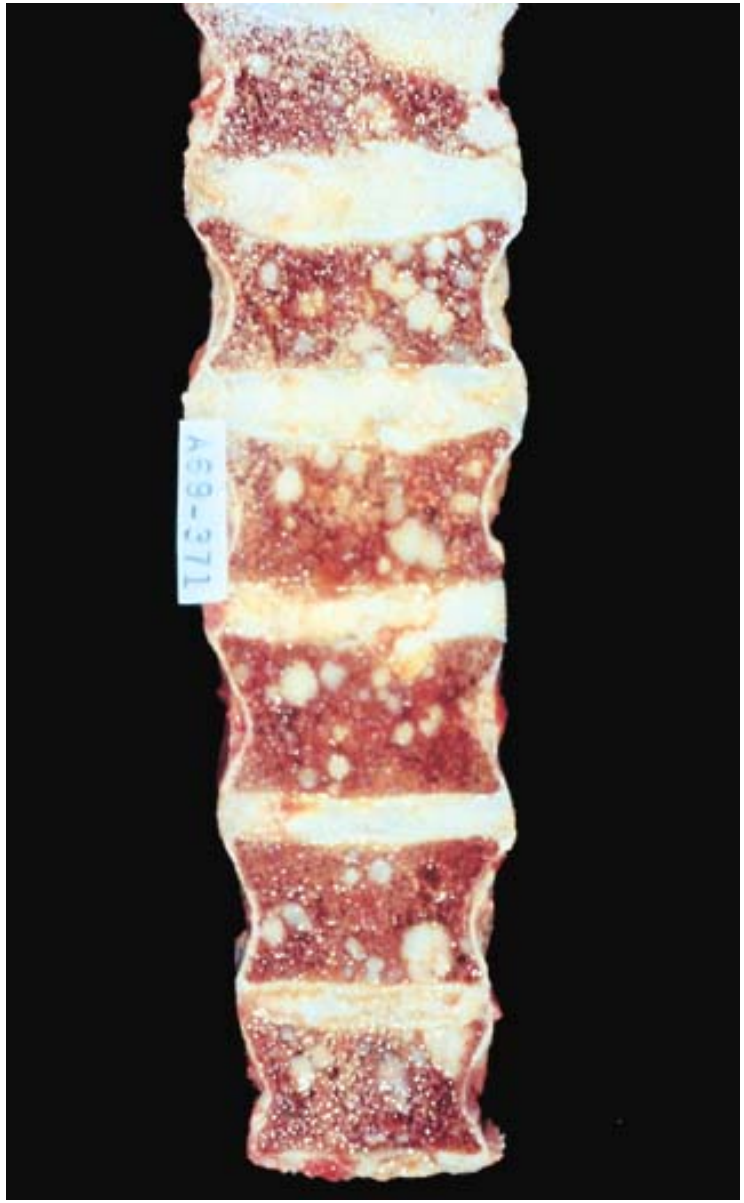


Figure 21-37 Carcinoma of the prostate showing perineural invasion by malignant glands. Compare to a benign gland (*left*).

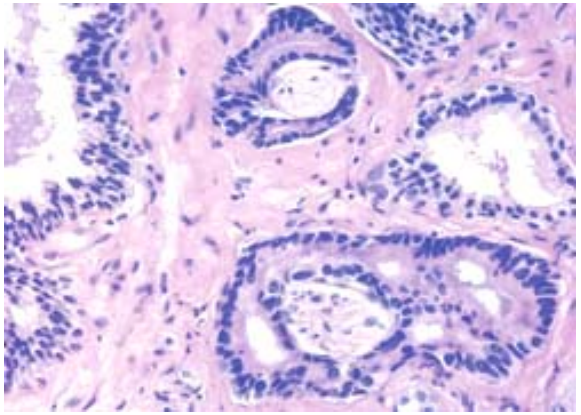
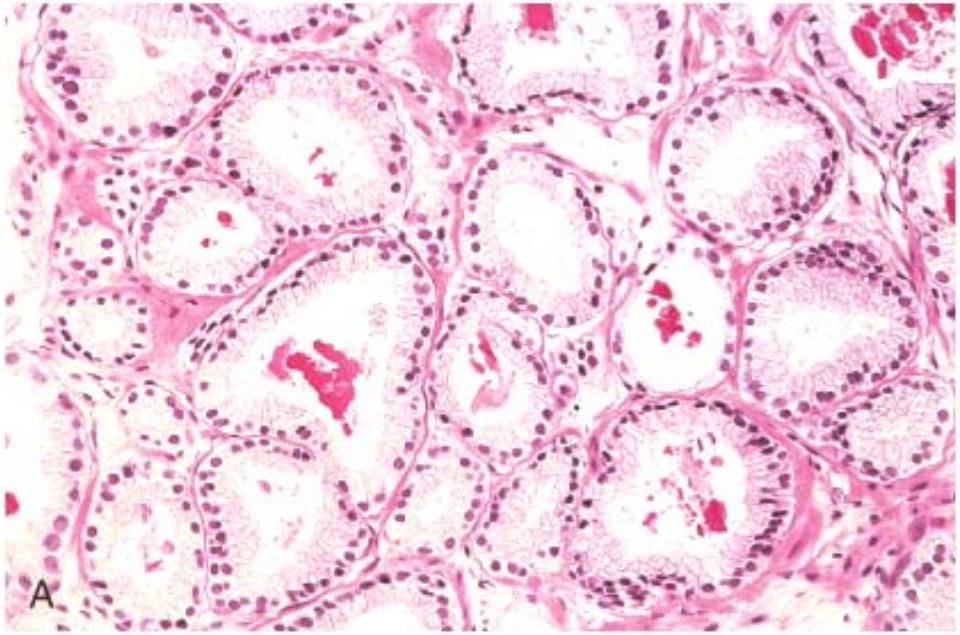
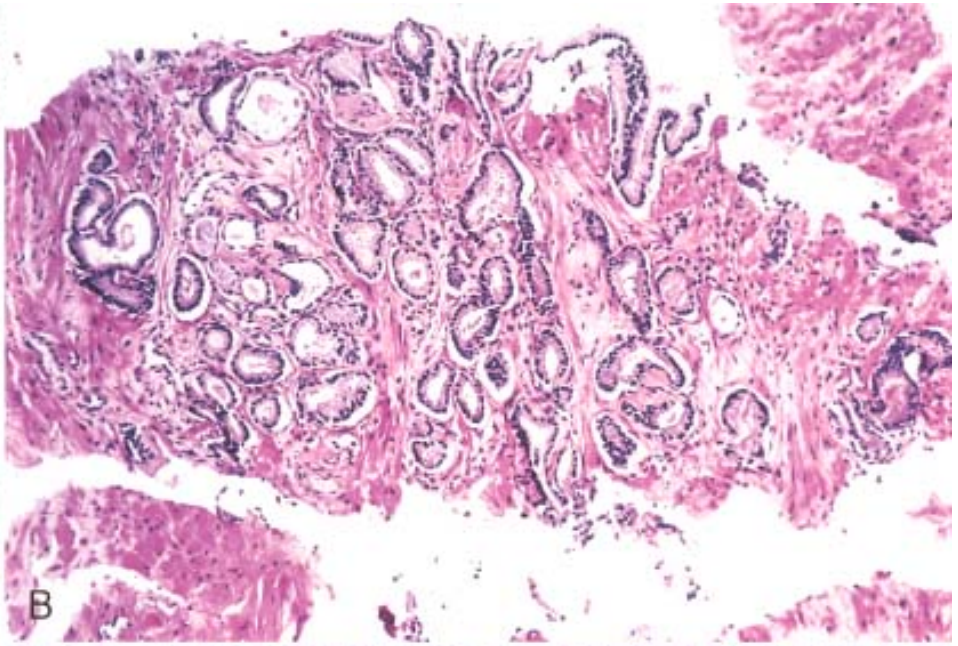
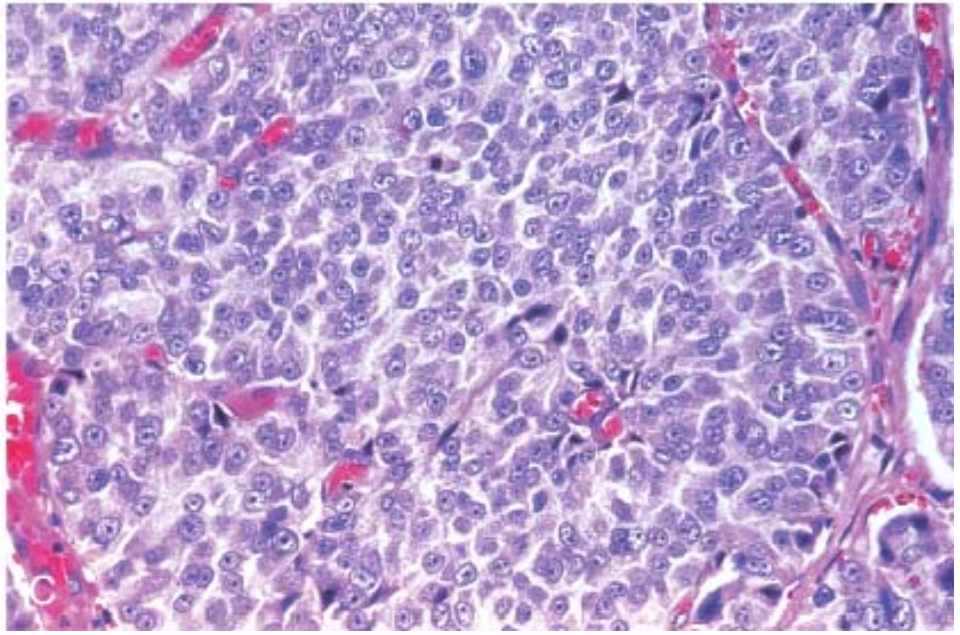


Figure 21-38 *A*, Low-grade (Gleason score 1 + 1 = 2) prostate cancer consisting of back to back, uniformly sized malignant glands. Glands contain eosinophilic intraluminal prostatic crystalloids, a feature that is more commonly seen in cancer than in benign glands and more frequently seen in lower grade than in higher grade prostate cancer. *B*, Needle biopsy of the prostate with variably sized, more widely dispersed glands of moderately differentiated (Gleason score 3 + 3 = 6) adenocarcinoma. *C*, Poorly differentiated Gleason score (5 + 5 = 10) adenocarcinoma composed of sheets of malignant cells.







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Chapter 22 - The Female Genital Tract

Christopher P. Crum MD

Normal

Embryology

The embryology of the female genital tract is relevant to both anomalies in this region and the histogenesis of various tumors. The primordial germ cells arise in the wall of the yolk sac by the fourth week of gestation; by the fifth or sixth week, they migrate into the urogenital ridge. The mesodermal epithelium of the urogenital ridge then proliferates, eventually to produce the epithelium and stroma of the gonad. The dividing germ cells—of endodermal origin—are incorporated into these proliferating epithelial cells to form the ovary.[1] Failure of germ cells to develop may result in either absence of ovaries or premature ovarian failure. Disruption of normal migration may account for extragonadal distribution of germ cell midline structures (retroperitoneum, mediastinum, and even pineal gland) and may rarely lead to tumors in these sites.

A second component of female genital development is the müllerian duct. At about the sixth week, invagination and subsequent fusion of the coelomic lining epithelium form the lateral müllerian (or paramesonephric) ducts. Müllerian ducts progressively grow caudally to enter the pelvis, where they swing medially to fuse with the urogenital sinus at the müllerian tubercle (Fig. 22-1A). Further caudal growth brings these fused ducts into contact with the urogenital sinus, formed when the cloaca is subdivided by the urorectal septum. The urogenital sinus

eventually becomes the vestibule of the external genitalia (Fig. 22-1*B*). Normally, the unfused portions mature into the fallopian tubes, the fused caudal portion developing into the uterus and upper vagina and the urogenital sinus forming the lower vagina and vestibule (Fig. 22-1*C*). Consequently, the entire lining of the uterus and tubes as well as the ovarian surface is ultimately derived from coelomic epithelium (mesothelium). This close embryologic relationship between the mesothelium and müllerian system may be reflected in adult life in the form of benign (endometriosis) and malignant (endometrioid and serous neoplasia) lesions, which may arise in both the surface mesothelium of the ovaries and the peritoneal surfaces.

The epithelium of the vagina, cervix, and urinary tract is formed by induction of basal cells from the underlying stroma, which undergo squamous and urothelial differentiation.[2] A portion of these cells remains uncommitted, forming the reserve cells of the cervix. The latter are capable of both squamous and columnar cell differentiation.[3]

In males, müllerian inhibitory substance[4] from the developing testis causes regression of the müllerian ducts, and the paired wolffian (or mesonephric) ducts form the epididymis and the vas deferens. Normally, the mesonephric duct regresses in the female, but remnants may persist into adult life as epithelial inclusions adjacent to the ovaries, tubes, and uterus. In the cervix and vagina, these rests may be cystic and are termed Gartner duct cysts. Many of the events in the

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Figure 22-1 Embryology and anatomy of the female genital tract. *A,* Early in development the mesonephric (*red*) and müllerian (*blue*) ducts merge at the urogenital sinus to form the müllerian tubercle. *B,* By birth the müllerian ducts have fused to form the fallopian tubes, uterus and endocervix (*blue*) merging with the vaginal squamous mucosa. The mesonephric ducts regress but may be found as a remnant in the ovary, adnexa and cervix (Gartner duct). *(Adapted from Langman J: Medical Embryology. Baltimore, Williams and Wilkins, 1981.) C,* Normal adult genital tract, with cervix, uterus, fallopian tubes, and ovaries. A small paratubal cyst is present on the right.

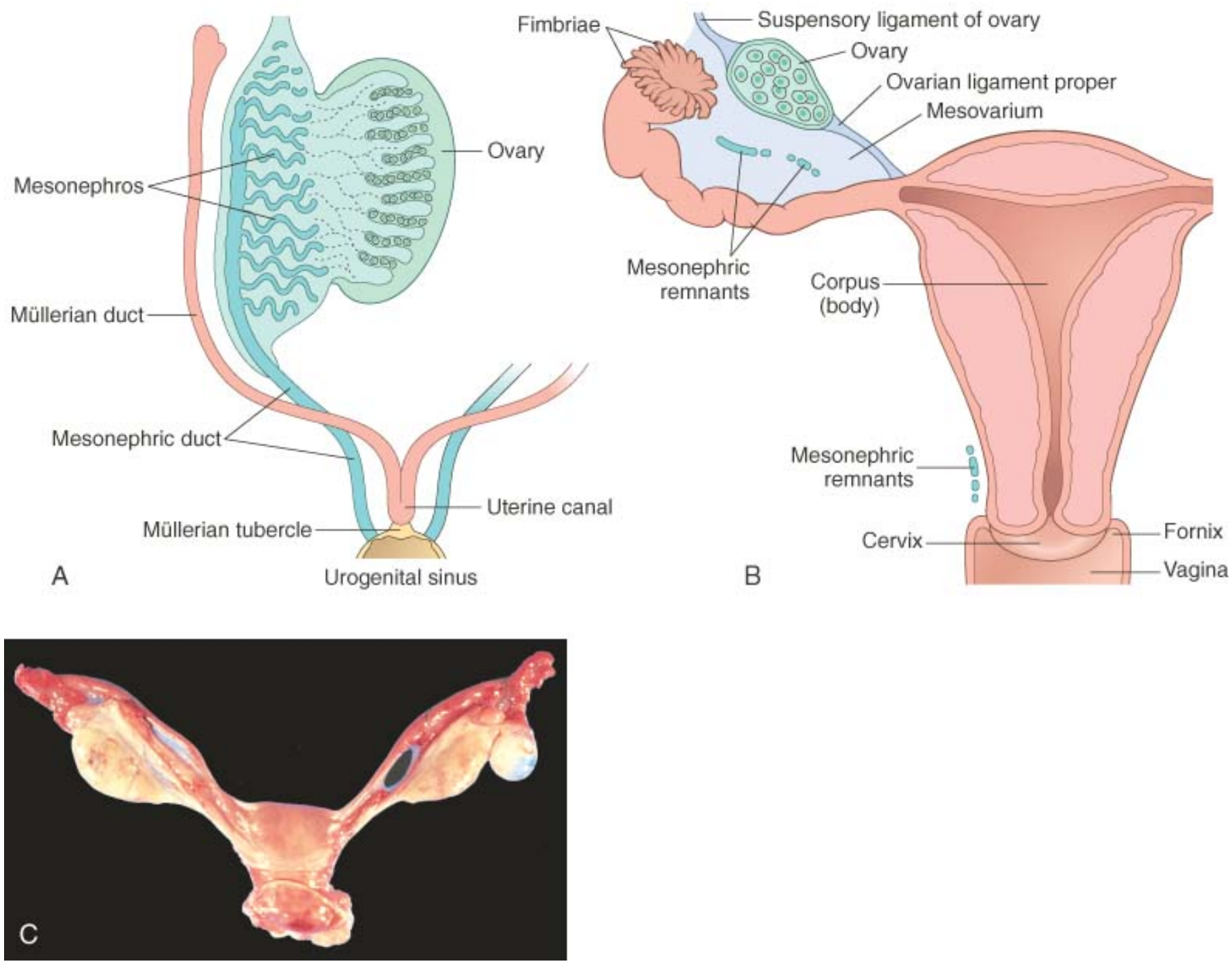
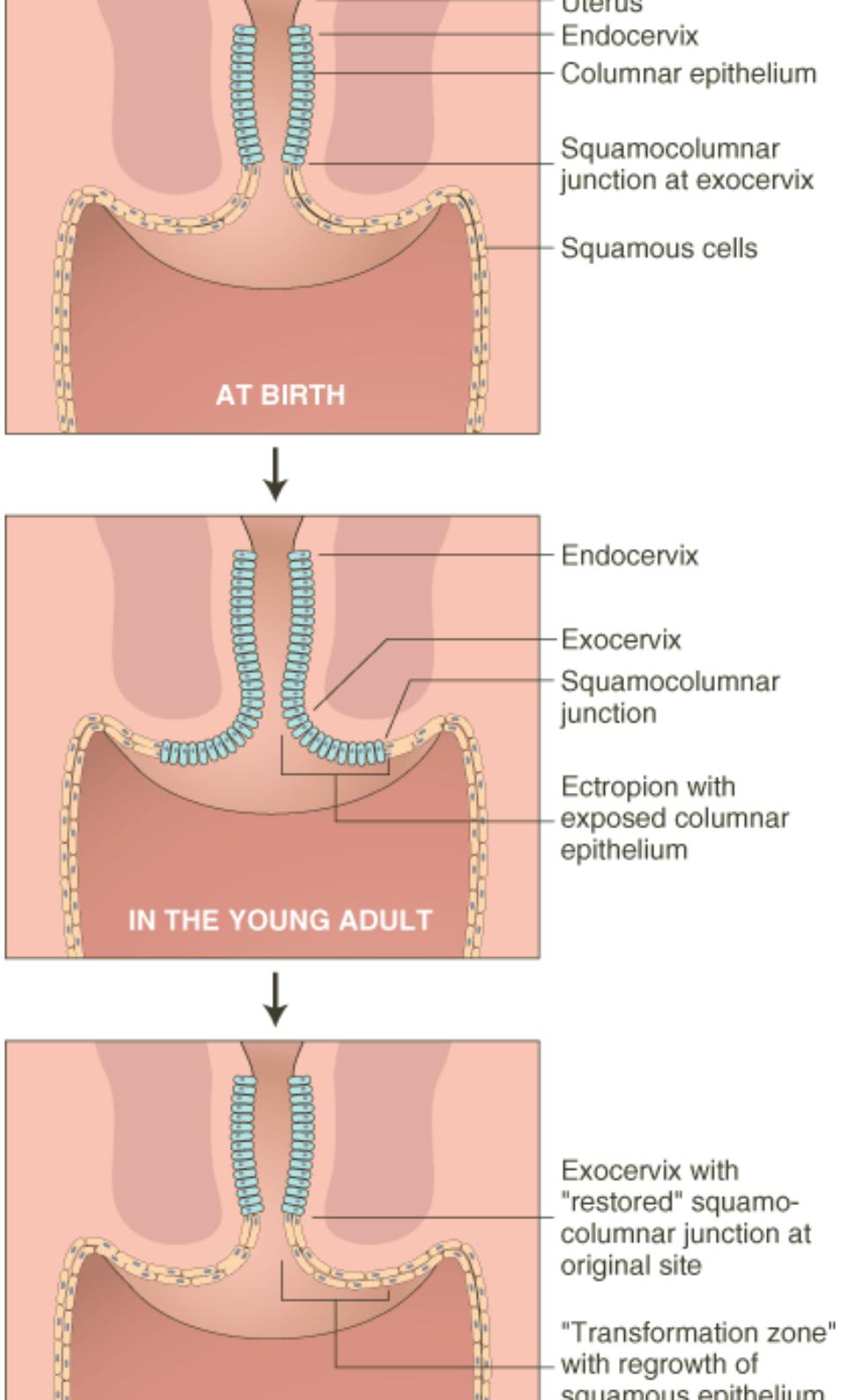


Figure 22-2 Schematic of the development of the cervical transformation zone.


Uterus
Endocervix
Columnar epithelium
Squamocolumnar junction at exocervix
Squamous cells
AT BIRTH
Endocervix
Exocervix
Squamocolumnar junction
Ectropion with exposed columnar epithelium
IN THE YOUNG ADULT
Exocervix with "restored" squamo-columnar junction at original site
"Transformation zone" with regrowth of squamous epithelium

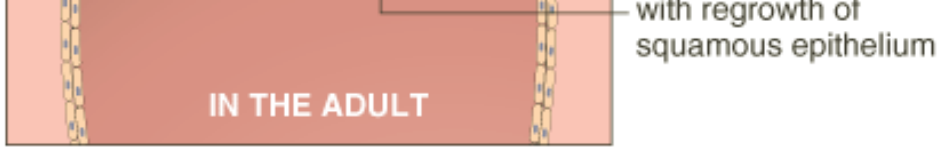


Figure 22-3 *A*, Colposcopic view of the cervix in a reproductive age woman. The portio epithelium (peripheral) merges with (at dotted boundary) and eventually replaces the endocervical columnar epithelium (red and grapelike) to form the transformation zone. The os is in the center. *B*, The postmenopausal cervix. The epithelial surface is smooth and completely covered by squamous epithelium. The squamocolumnar junction is not visible and is inside the endocervical canal. *(A and B, courtesy of Dr. Alex Ferenczy, McGill University, Montreal, Quebec.)*

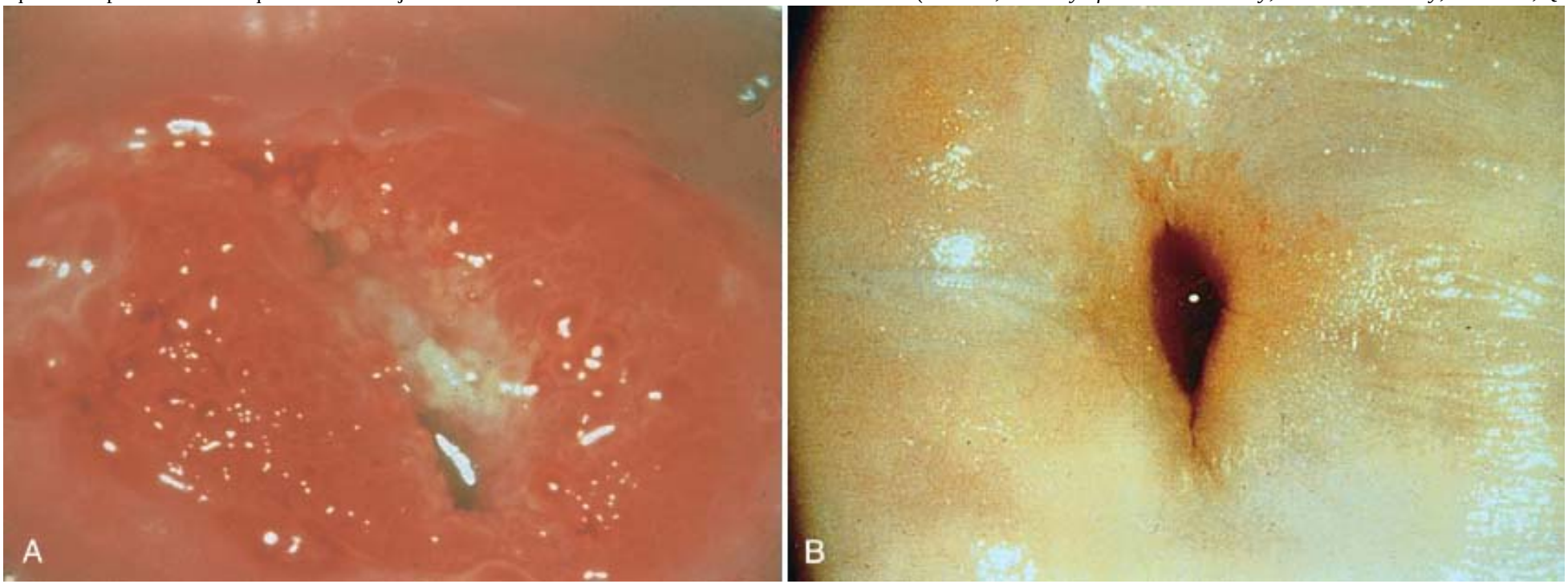


TABLE 22-1 -- Anatomic Distribution of Common Female Genital Infections

		Location and Manifestations of Infection				
Organism	**Source**	***Vulva***	***Vagina***	***Cervix***	***Corpus***	***Adnexa***
Herpesvirus	STD	Herpetic ulcers				
Molluscum contagiosum	STD	Molluscum lesions				
HPV	STD	Genital warts, intrapeithelial neoplasia, invasive carcinoma				
Chlamydia trachomatis	STD		Follicular cervicitis, endometritis, salpingo-oophoritis			
Neisseria gonorrhoeae	STD	Skene gland adenitis	Vaginitis in children	Acute cervicitis	Acute endometritis and salpingitis	
Candida	Endogenous	Vulvovaginitis				

Trichomonas	STD		Cervicovaginitis			

HPV, human papillomavirus; STD, sexually transmitted disease.

risk is highest if the infection is active during delivery and particularly if it is a primary (initial) infection in the mother.[14]

Mycotic and *yeast (Candida) infections* are common; about 10% of women are thought to be carriers of vulvovaginal fungi. Diabetes mellitus, oral contraceptives, and pregnancy may enhance the development of infection, which manifests as small white surface patches similar to monilial lesions elsewhere. It is accompanied by leukorrhea and pruritus. The diagnosis is made by finding the organism in wet mounts of the lesions.

Trichomonas vaginalis is a large, flagellated ovoid protozoan that can be readily identified in wet mounts of vaginal discharge in infected patients (Fig. 22-4). Infections may occur at any age and are seen in about 15% of women in sexually transmitted disease clinics.[15] They are associated with a purulent vaginal discharge and discomfort; the underlying vaginal and cervical mucosa typically has a characteristic fiery red appearance, called strawberry cervix. On histologic examination, the inflammatory reaction is usually limited to the mucosa and immediately subjacent lamina propria.

Figure 22-4 Flagellated trophozoites of *Trichomonas vaginalis*.

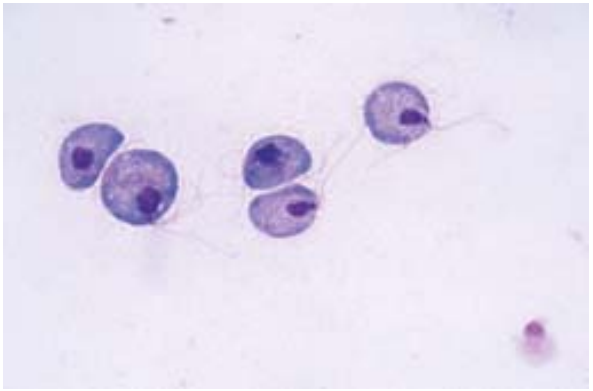


Figure 22-5 *A,* Acute salpingo-oophoritis, with tubo-ovarian abscess. The fallopian tube and ovaries have coalesced into an inflammatory mass adherent to the uterus. (Compare with Figure 22-1 .) *B,* Chronic salpingitis with fusion of the tubal plicae and inflammatory cell infiltrates.

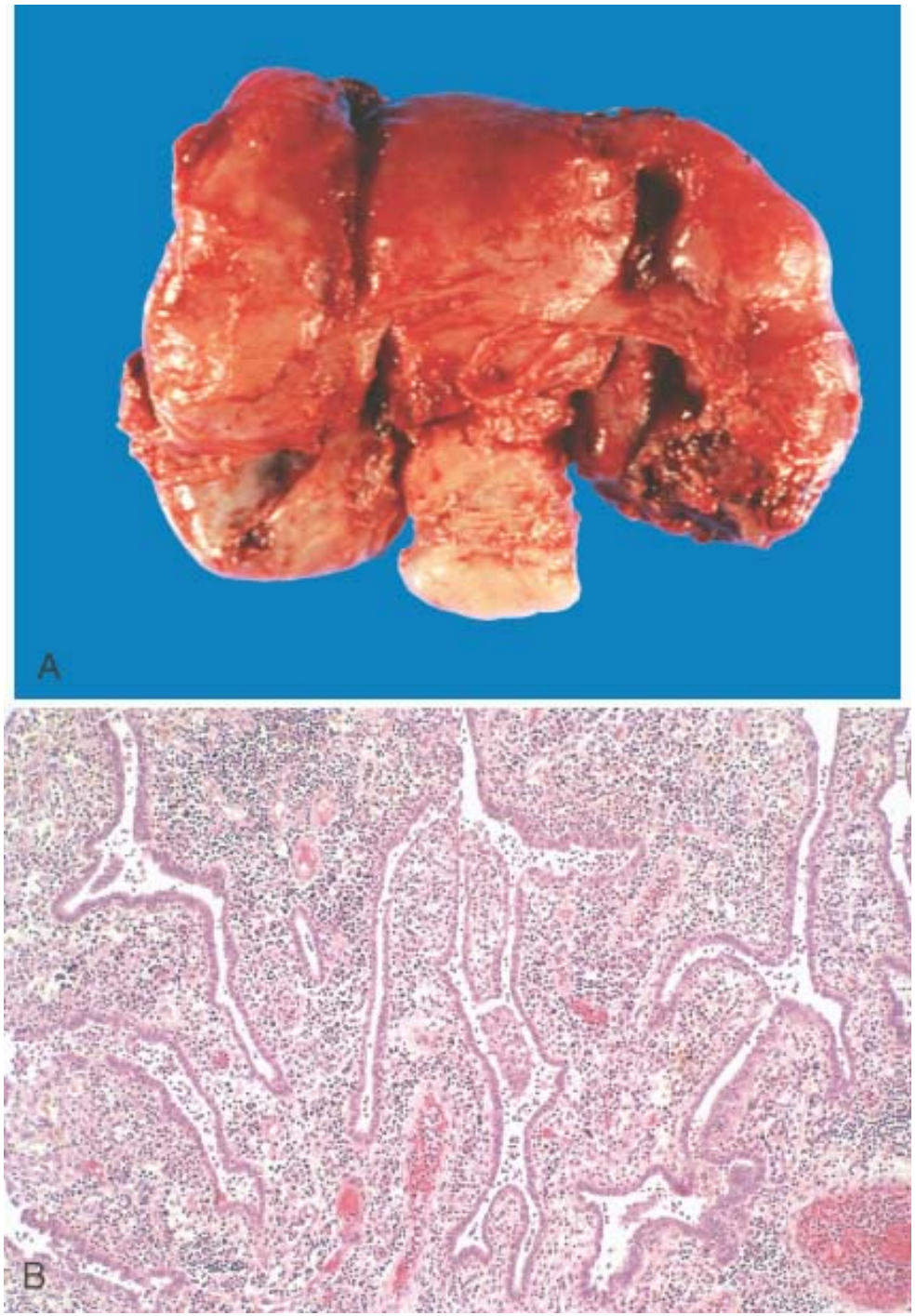


Figure 22-6 Inflammatory vulvar disorders. Lichen sclerosus (*upper panel*). Lichen simplex chronicus (*lower panel*). The main features of the lesions are indicated in the figures.

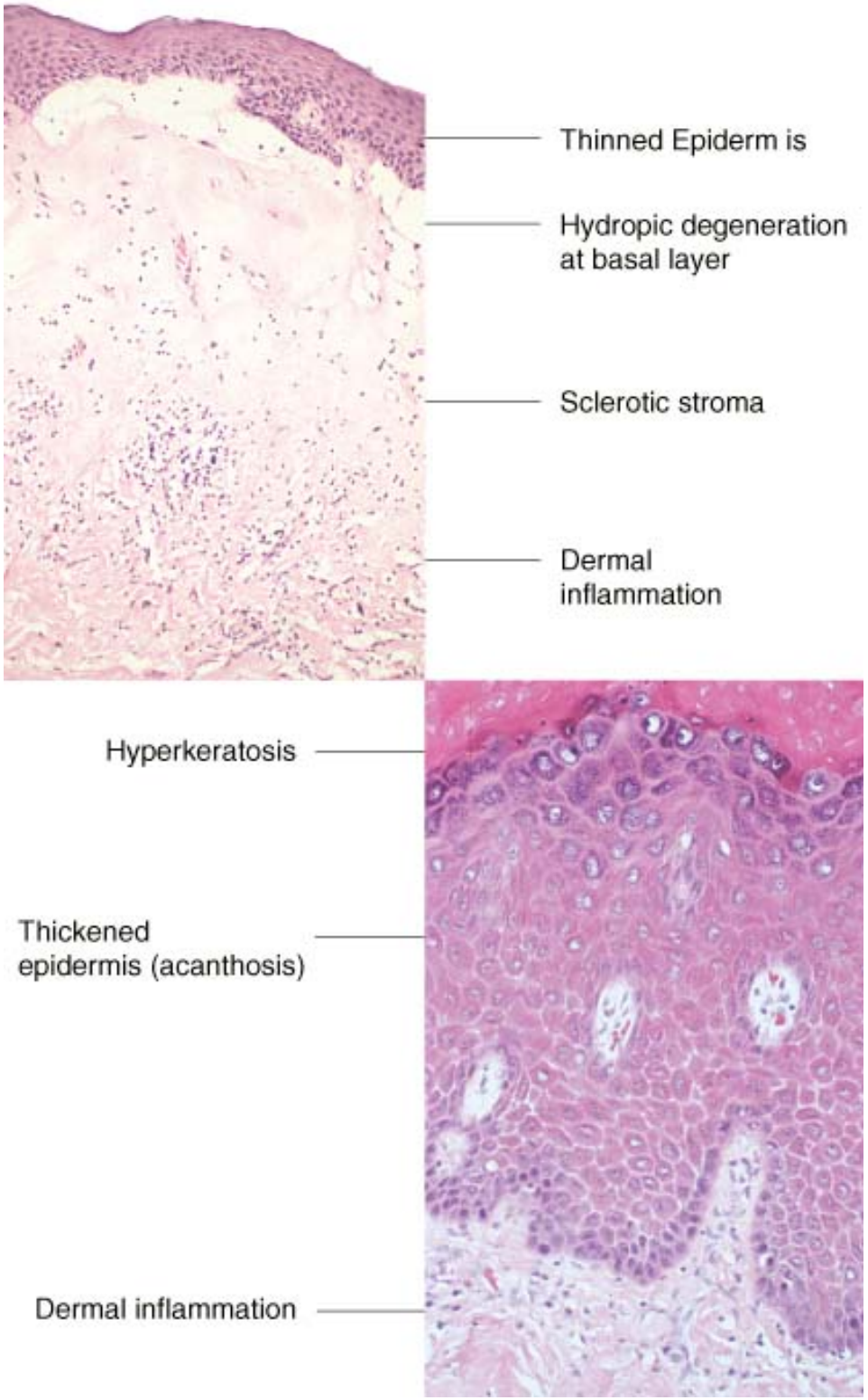

Thinned Epiderm is
Hydropic degeneration at basal layer
Sclerotic stroma
Dermal inflammation
Hyperkeratosis
Thickened epidermis (acanthosis)
Dermal inflammation

Figure 22-7 Lichen sclerosus, exhibiting the white parchment-like patches of the skin of the vulva and labial atrophy.

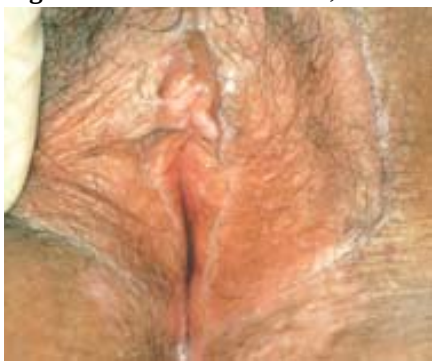


Figure 22-8 *A*, Numerous condylomas of the vulva encircling the introitus. *(Courtesy of Dr. Alex Ferenczy, McGill University, Montreal, Quebec.) B*, Histopathology of condyloma acuminatum showing acanthosis, hyperkeratosis, and cytoplasmic vacuolation (koilocytosis, *center*).

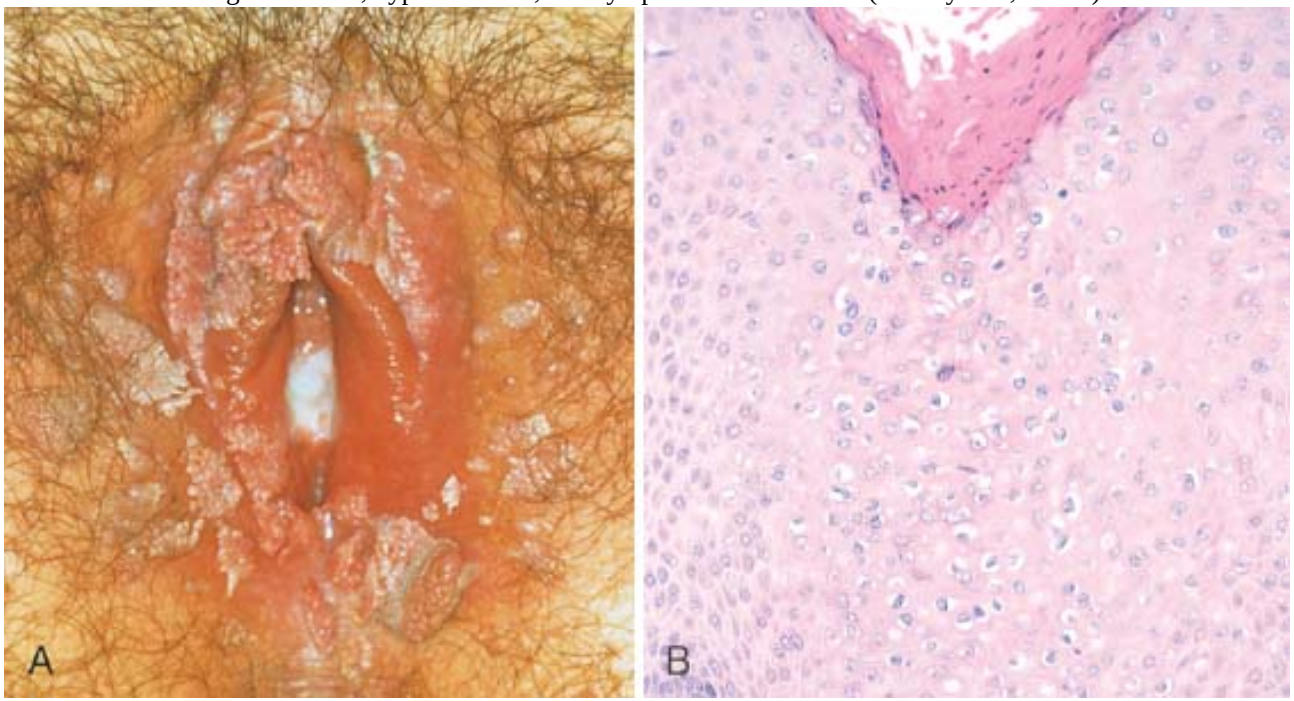


Figure 22-9 *A*, Histopathology of classic (HPV positive) vulvar intraepithelial neoplasia with diffuse cellular atypia, nuclear crowding, and increased mitotic index. *B*, differentiated (HPV negative) VIN, showing maturation, hyperkeratosis and basal cell atypia (*arrow*).

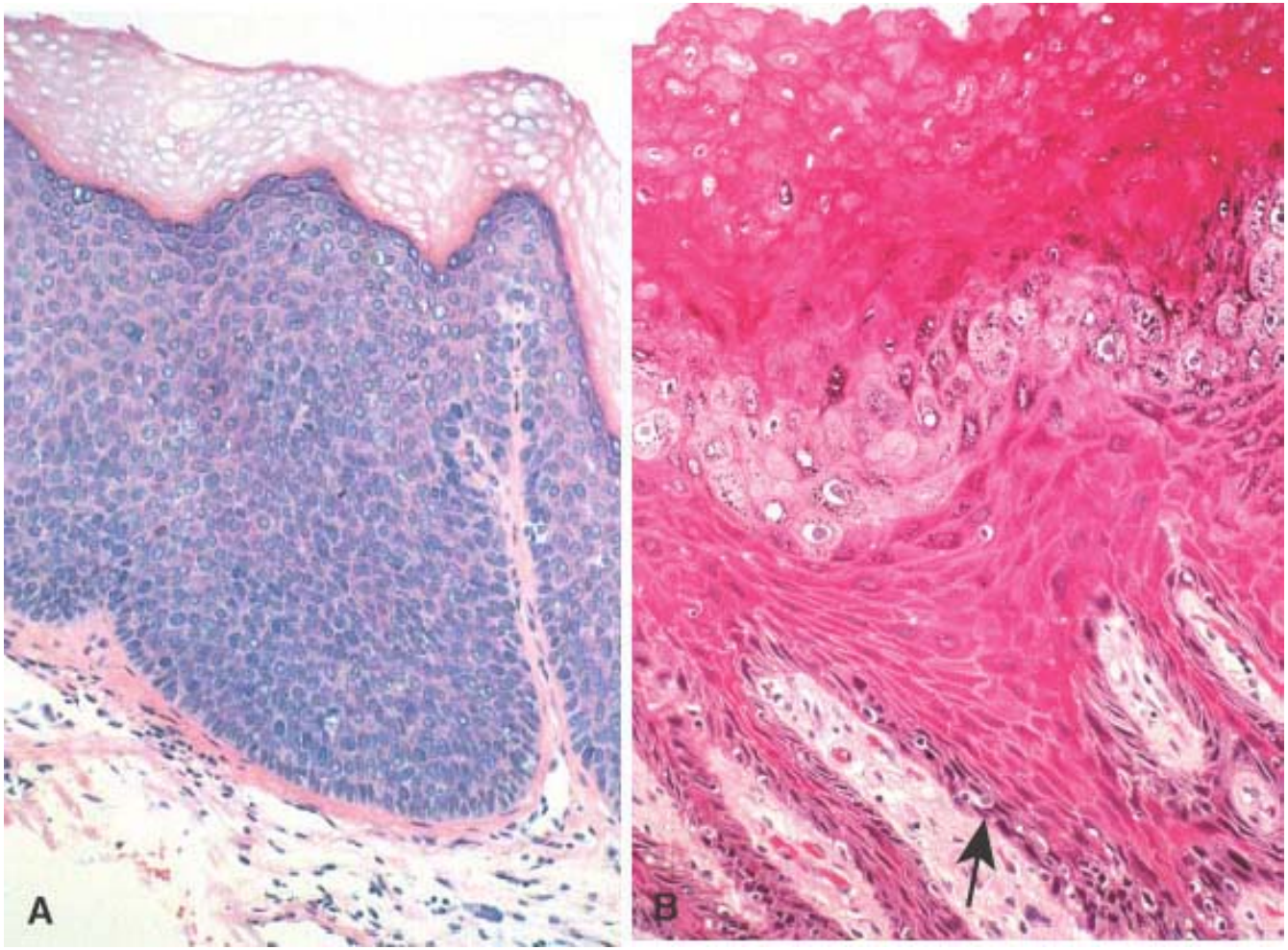


Figure 22-10 *A*, Poorly differentiated vulvar carcinoma associated with human papillomaviruses (HPV). *B*, Well-differentiated keratinizing vulvar carcinoma, typically HPV negative.

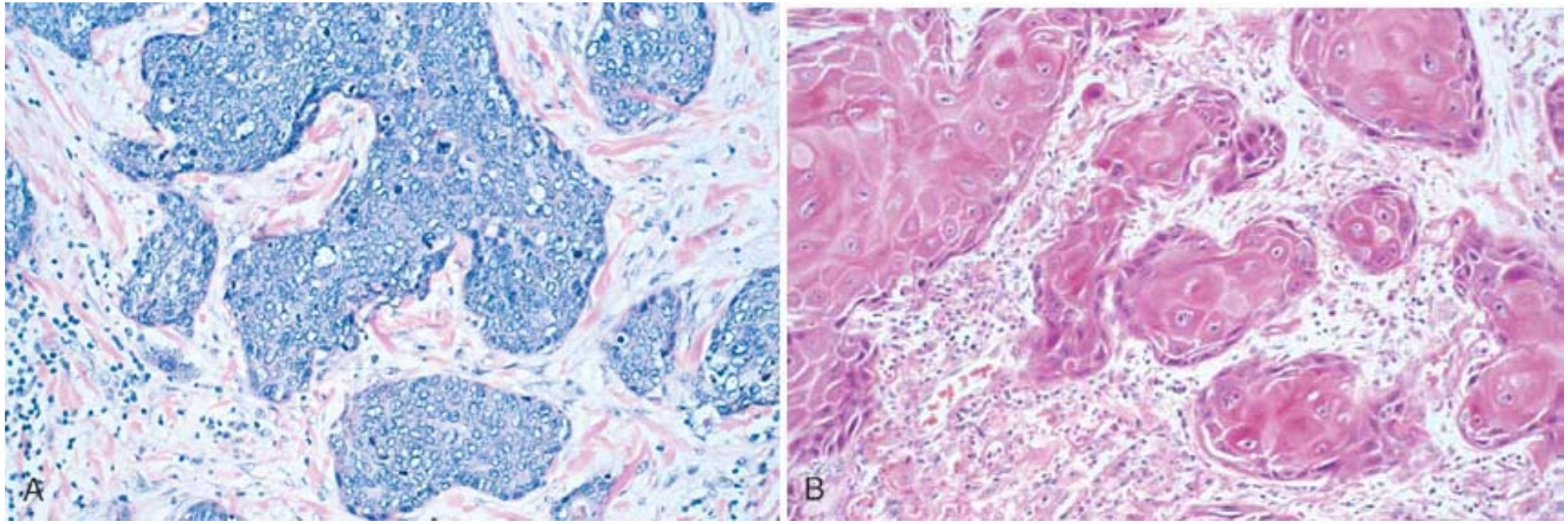


Figure 22-11 *A*, Verrucous carcinoma of the vulva. *B*, Basal cell carcinoma of the vulva.

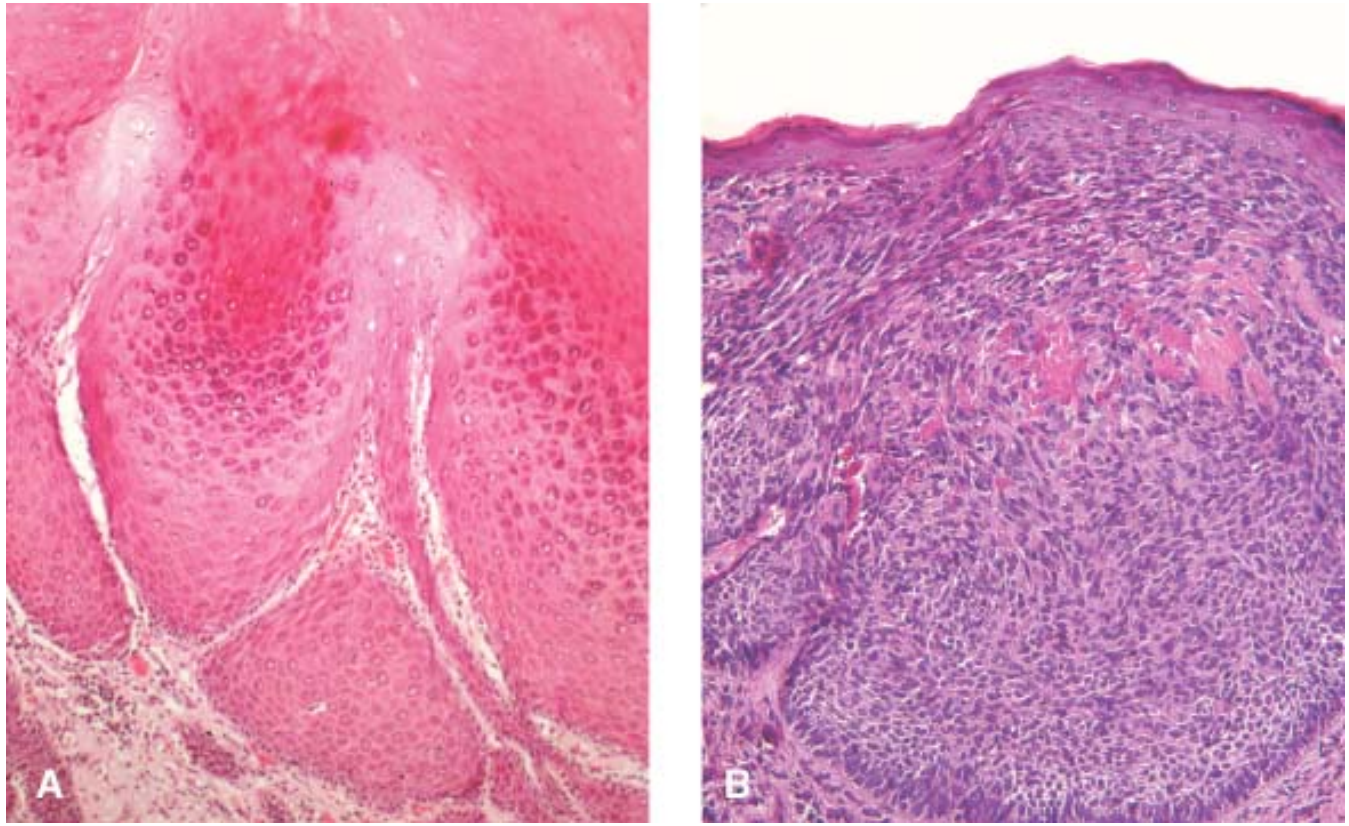


Figure 22-12 Paget disease of the vulva with a cluster of large clear tumor cells within the squamous epithelium.

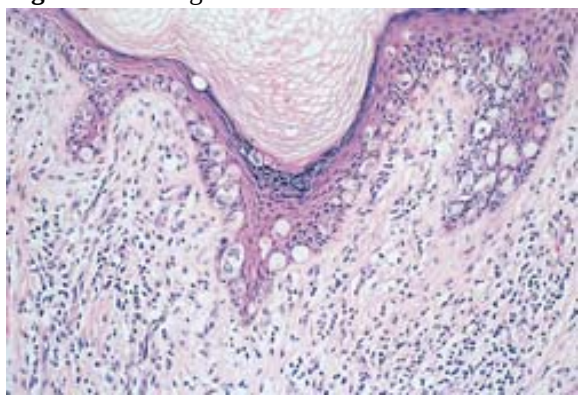


Figure 22-13 *A*, Malignant melanoma involving the vaginal introitus and labia minora. *B*, Histology of invasive melanoma with melanin production (*inset*).

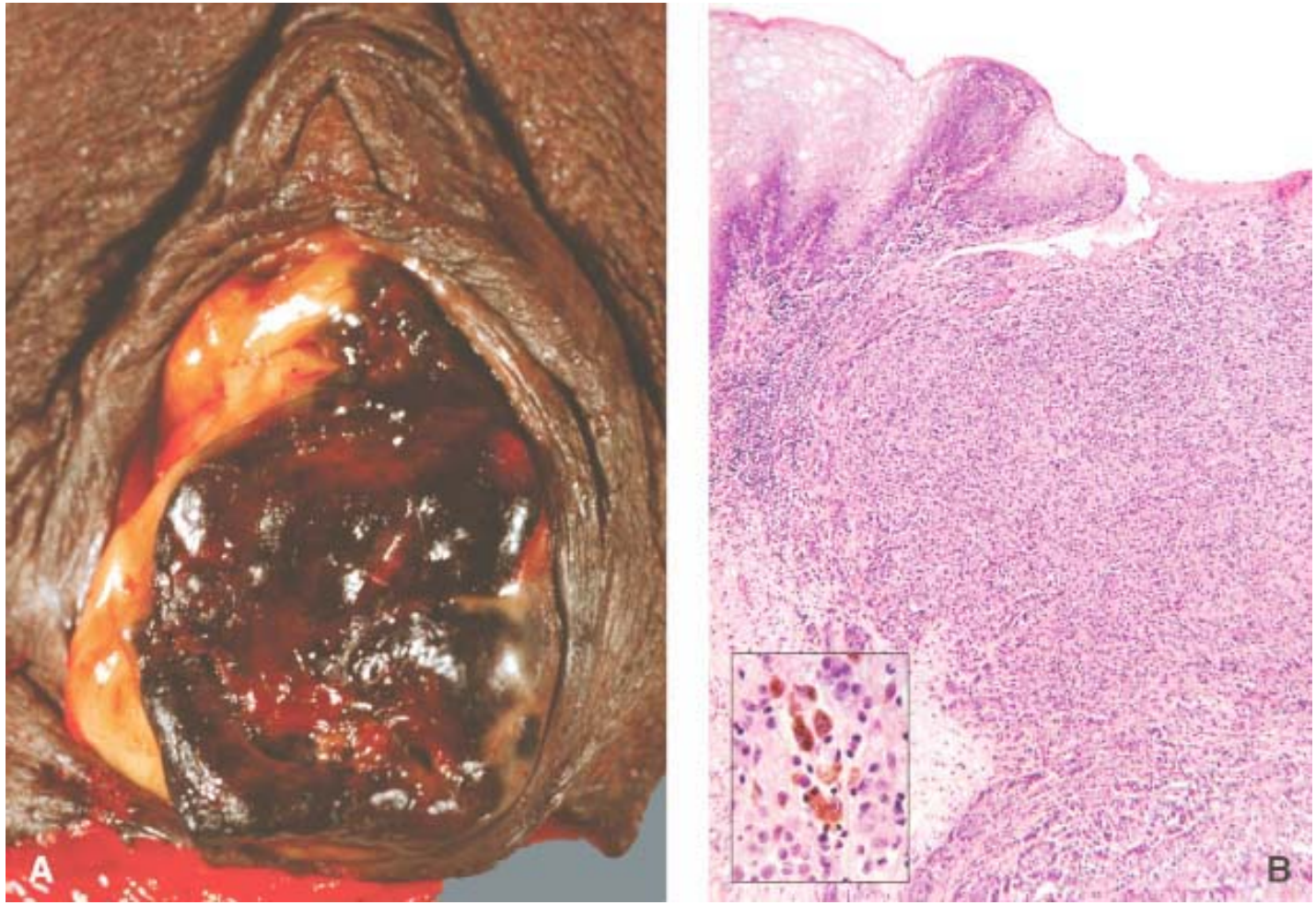


Figure 22-14 Clear cell adenocarcinoma of the vagina showing vacuolated tumor cells in clusters and glandlike structures.

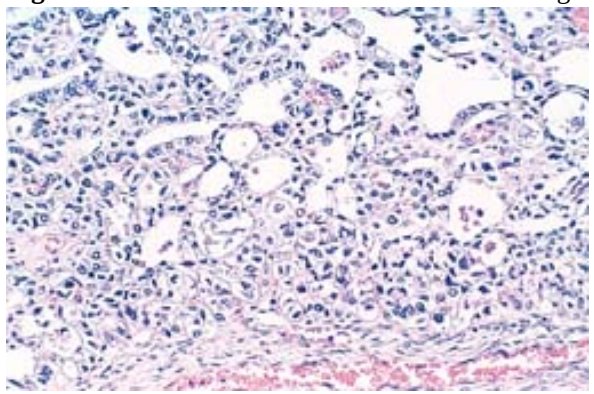


Figure 22-15 Sarcoma botryoides (embryonal rhabdomyosarcoma) of the vagina appearing as a polypoid mass protruding from the vagina. *(Courtesy of Dr. Michael Donovan, Children's*

Hospital, Boston, MA.)

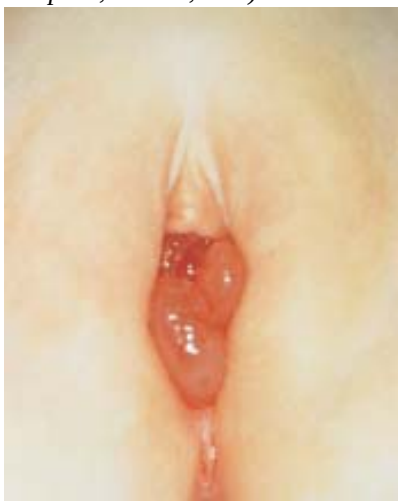


Figure 22-16 In the diagram (*upper*), reserve cells in the transformation zone are continuous with the basal cells of the ectocervix (*right*) and may undergo columnar and squamous differentiation (metaplasia). Photomicrographs at bottom depict (*from left to right*) quiescent subcolumnar reserve cells, reserve cells undergoing columnar differentiation (*second from left*), reserve cells undergoing squamous metaplasia (*second from right*) and ectocervical squamous epithelium (*right*).

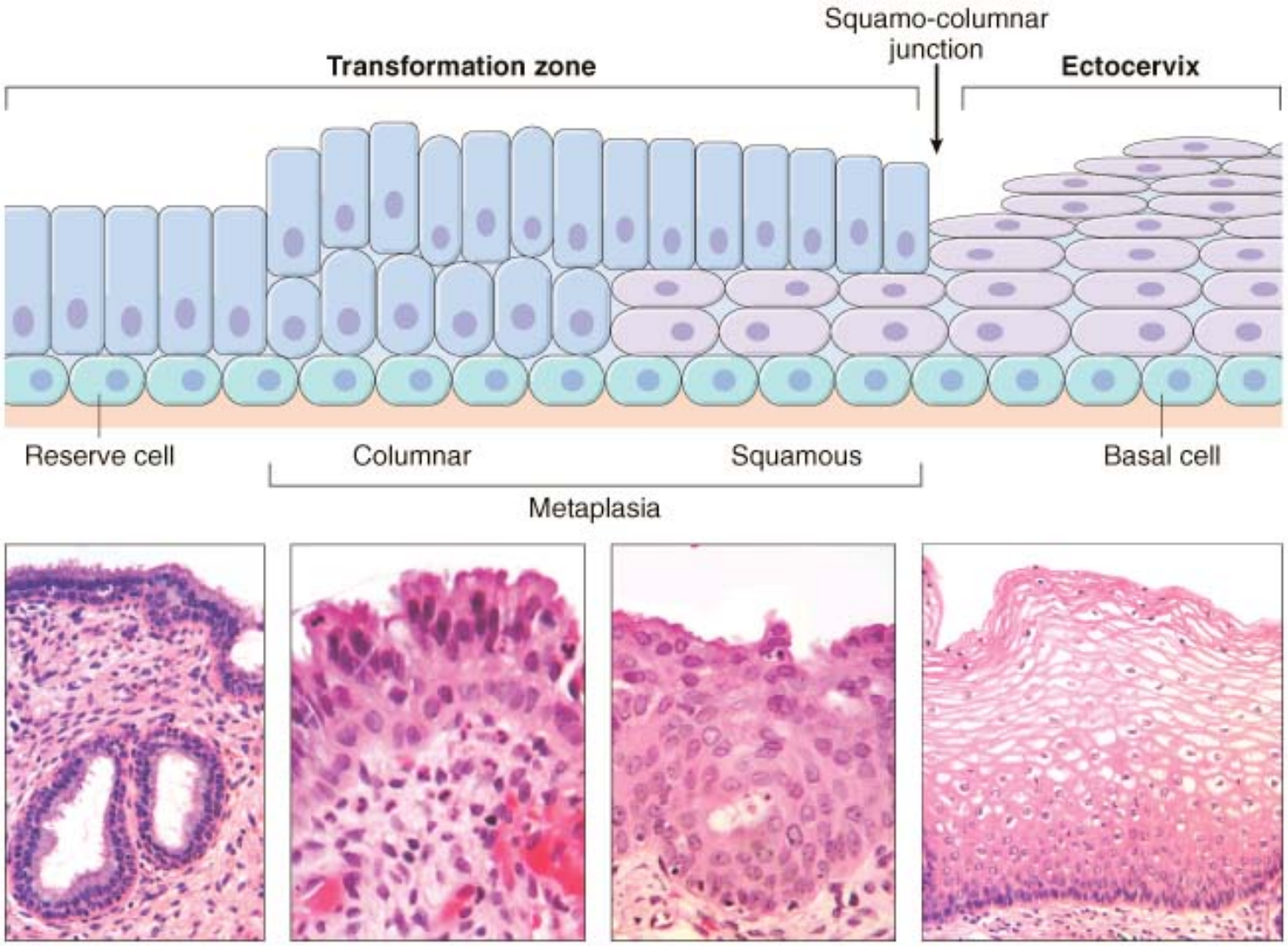


Figure 22-17 Endocervical polyp composed of a dense fibrous stroma covered with endocervical columnar epithelium.

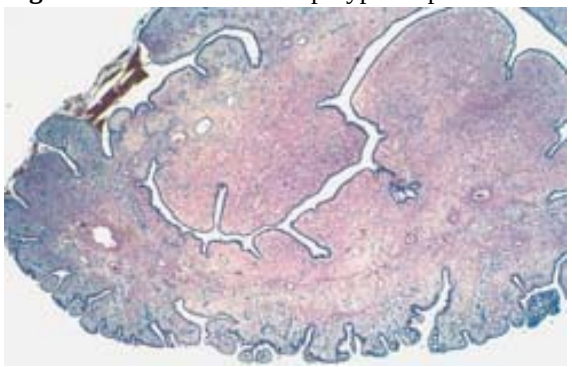


Figure 22-18 *A*, Postulated steps in the pathogenesis of cervical neoplasia. Conditions influencing progression are listed at the lower center of the diagram. *B*, Approximate lifetime risks of acquiring HPV infection (*left*) and dying of cervical cancer (*right*). The intermediate steps include risks of infection with high-risk HPV types, development of advanced cervical intraepithelial neoplasia (CIN), and progression to invasive carcinoma.

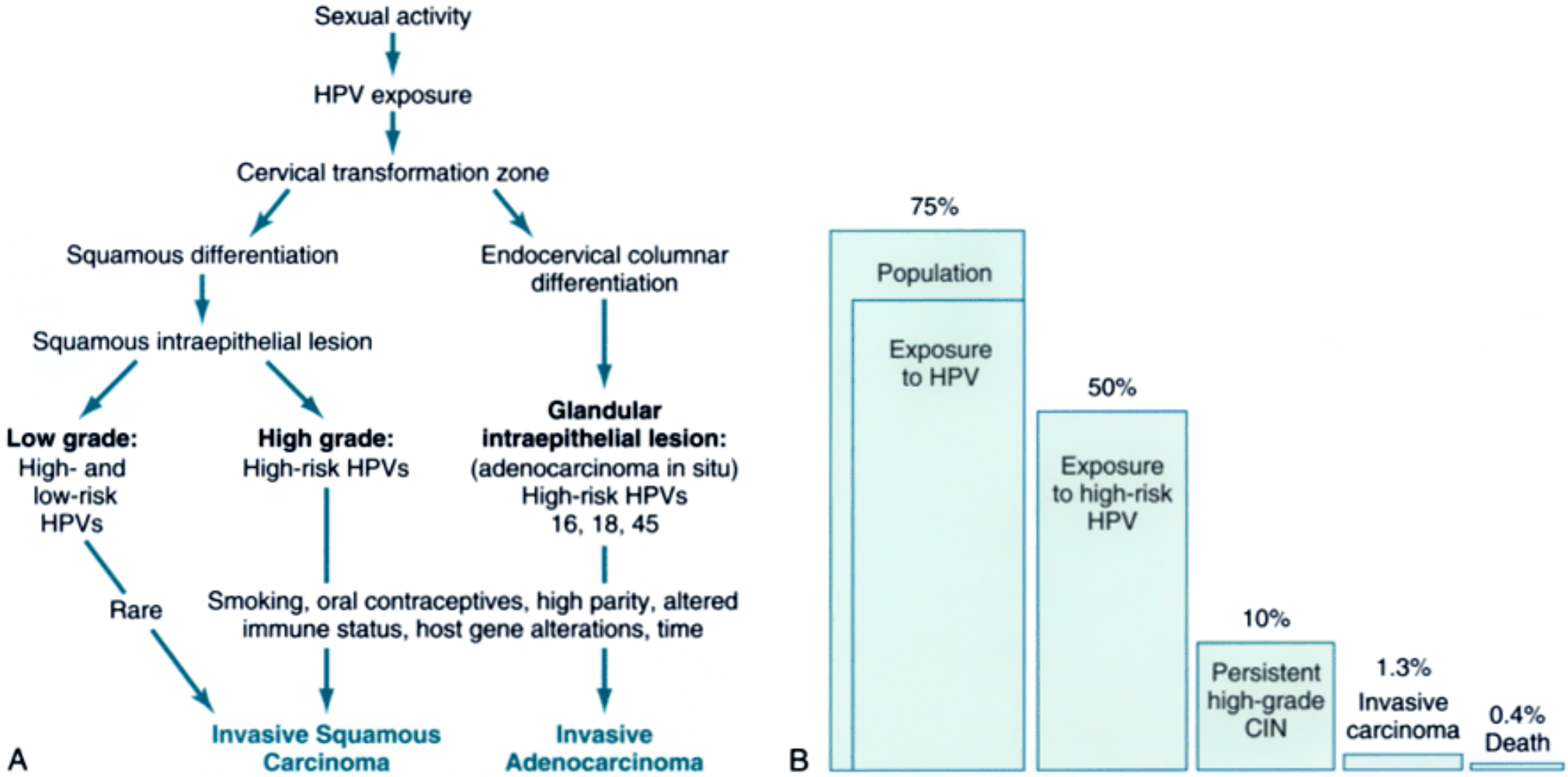


Figure 22-19 Spectrum of cervical intraepithelial neoplasia: normal squamous epithelium for comparison; CIN I with koilocytotic atypia; CIN II with progressive atypia in all layers of the epithelium; CIN III (carcinoma in situ) with diffuse atypia and loss of maturation.

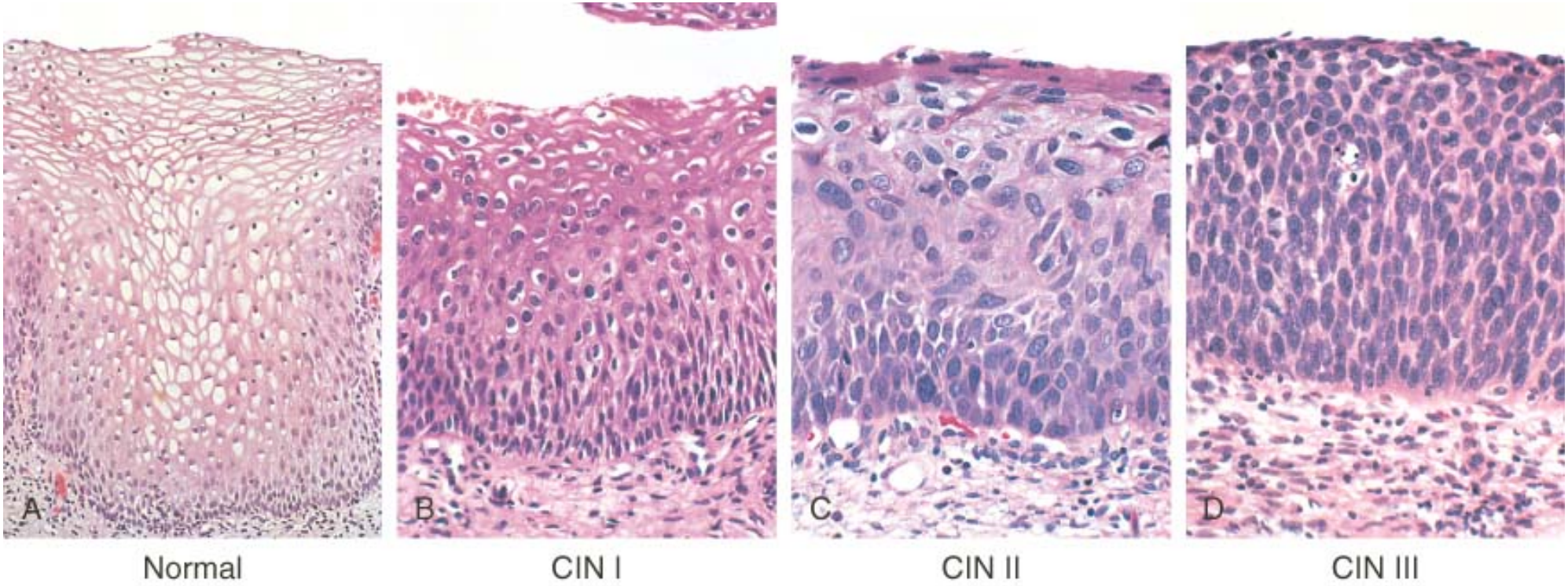


Figure 22-20 *A*, Histology of CIN I (flat condyloma), illustrating the prominent koilocytotic atypia in the upper epithelial cells, as evidenced by the prominent perinuclear halos. *B*, Nucleic acid in situ hybridization of the same lesion for HPV nucleic acids. The blue staining denotes HPV DNA, which is typically most abundant in the koilocytes. *C*, Diffuse immunostaining of CIN II for Ki-67, illustrating widespread deregulation of cell cycle controls. *D*, Up-regulation of p161NK4 (seen as intense immunostaining) characterizes high-risk HPV infections.

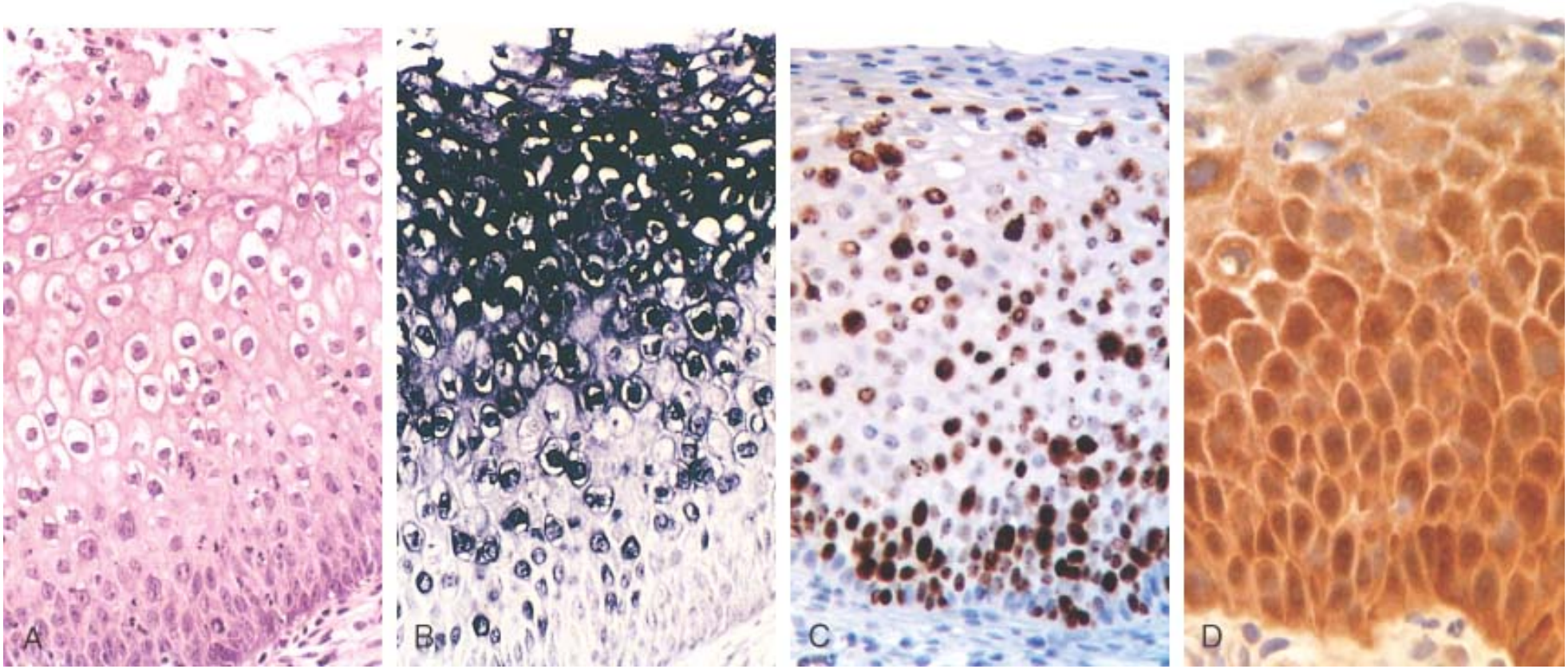
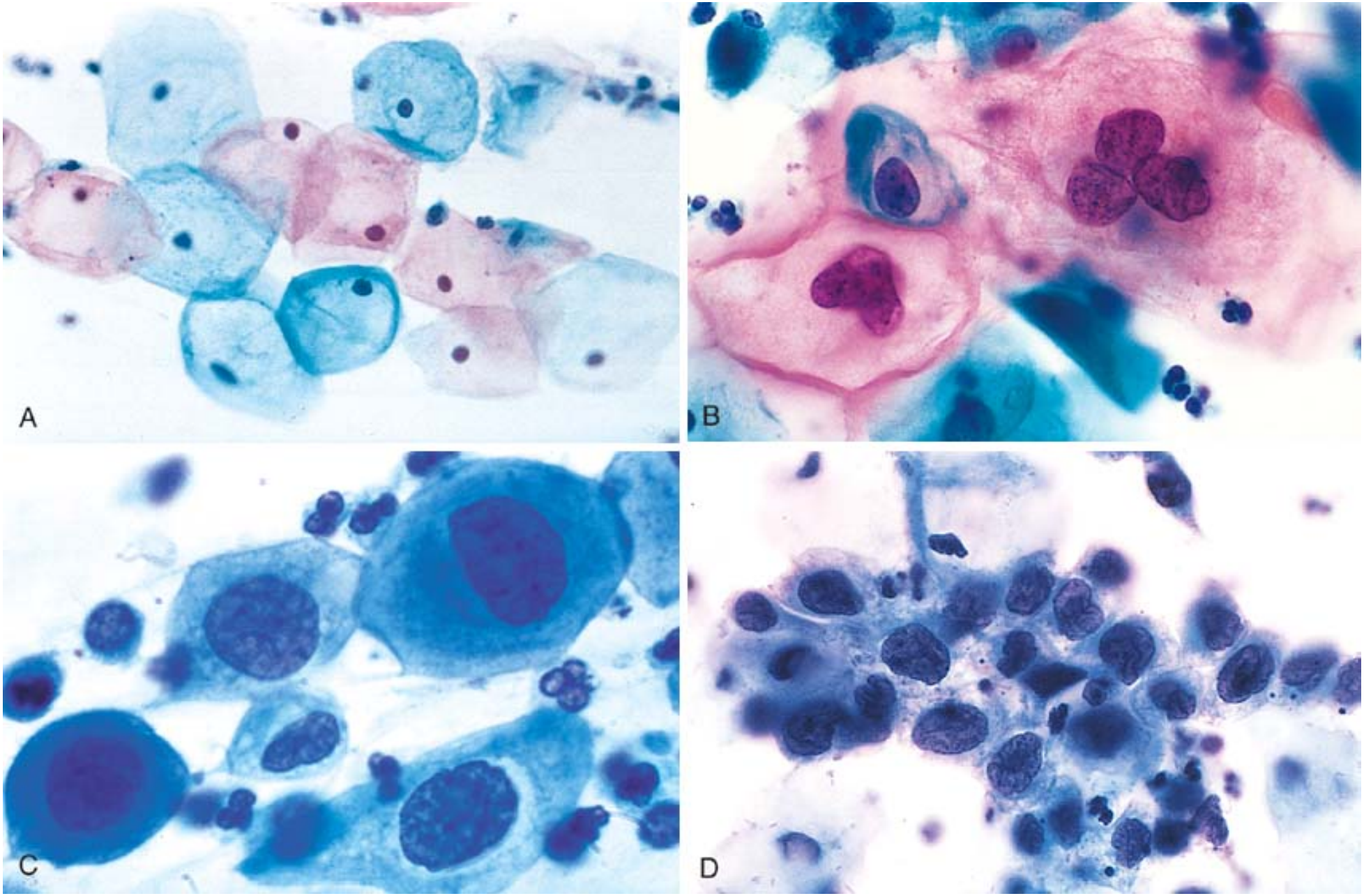


Figure 22-21 The cytology of cervical intraepithelial neoplasia as seen on the Papanicolaou smear. Cytoplasmic staining in superficial cells (*A&B*) may be either red or blue. *A*, Normal exfoliated superficial squamous epithelial cells. *B*, CIN I. *C*, CIN II. *D*, CIN III. Note the reduction in cytoplasm and the increase in the nucleus to cytoplasm ratio, which occurs as the grade of the lesion increases. This reflects the progressive loss of cellular differentiation on the surface of the lesions from which these cells are exfoliated (see Figure 22-19). *(Courtesy of Dr. Edmund S. Cibas, Brigham and Women's Hospital, Boston, MA.)*



Stage I. Carcinoma confined to the cervix

Ia. Preclinical carcinoma, that is, diagnosed only by microscopy

Ia1. Stromal invasion no greater than 3 mm and no wider than 7 mm (so-called **microinvasive carcinoma**) (Fig. 22-22*B*).

Ia2. Maximum depth of invasion of stroma greater than 3 mm and no greater than 5 mm taken from base of epithelium, either surface or glandular, from which it originates; horizontal invasion not more than 7 mm

Ib. Histologically invasive carcinoma confined to the cervix and greater than stage Ia2

Stage II. Carcinoma extends beyond the cervix but not onto the pelvic wall. Carcinoma involves the vagina but not the lower third.

Stage III. Carcinoma has extended onto pelvic wall. On rectal examination, there is no cancer-free space between the tumor and the pelvic wall. The tumor involves the lower third of the vagina.

Stage IV. Carcinoma has extended beyond the true pelvis or has involved the mucosa of the bladder or rectum. This stage obviously includes those with metastatic dissemination.

Ten per cent to 25% of cervical carcinomas are **adenocarcinomas, adenosquamous carcinomas,**

Figure 22-22 The spectrum of invasive cervical cancer. *A*, Carcinoma of the cervix, well advanced. *B*, Early stromal invasion occurring in a cervical intraepithelial neoplasm.

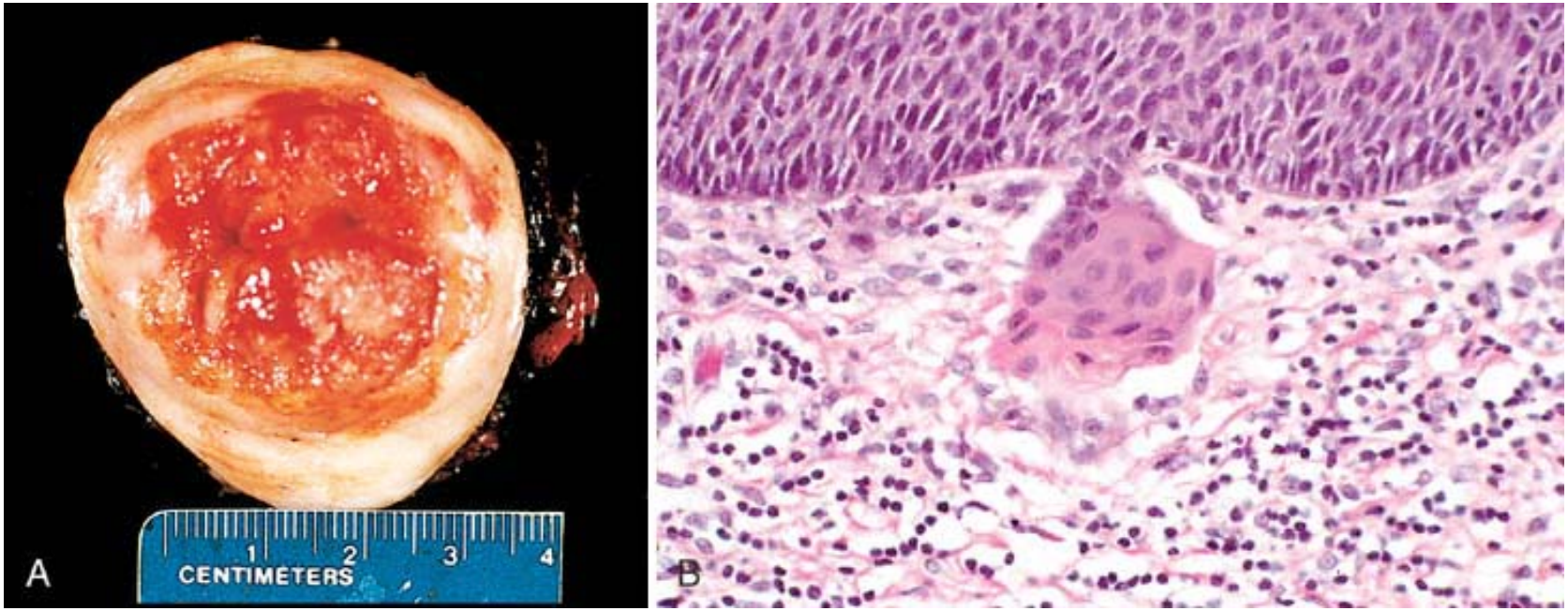


Figure 22-23 Morphology of cervical cancers. *A*, Squamous carcinoma. *B*, Adenocarcinoma in situ (*lower*), associated with CIN 3 (*upper*). *C*, Adenocarcinoma. *D*, Neuroendocrine carcinoma.

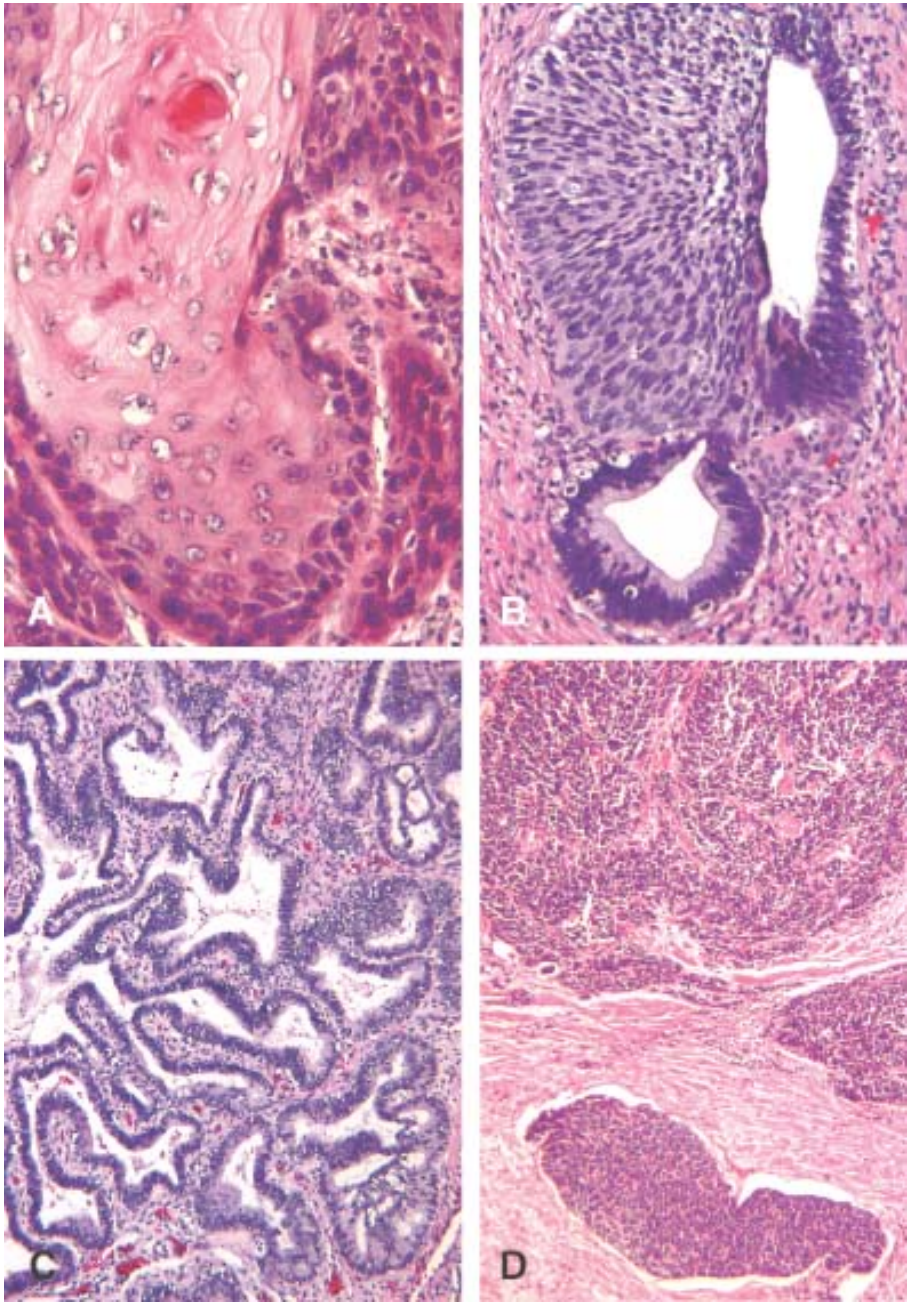


Figure 22-24 Electron micrograph of virus-like papillomavirus particles (VLPs) produced in eukaryotic cells by expression of the late region and used as vaccines. *(Courtesy of lan Frazer, MD, Princess Alexandra Hospital, University of Queensland, Australia.)*

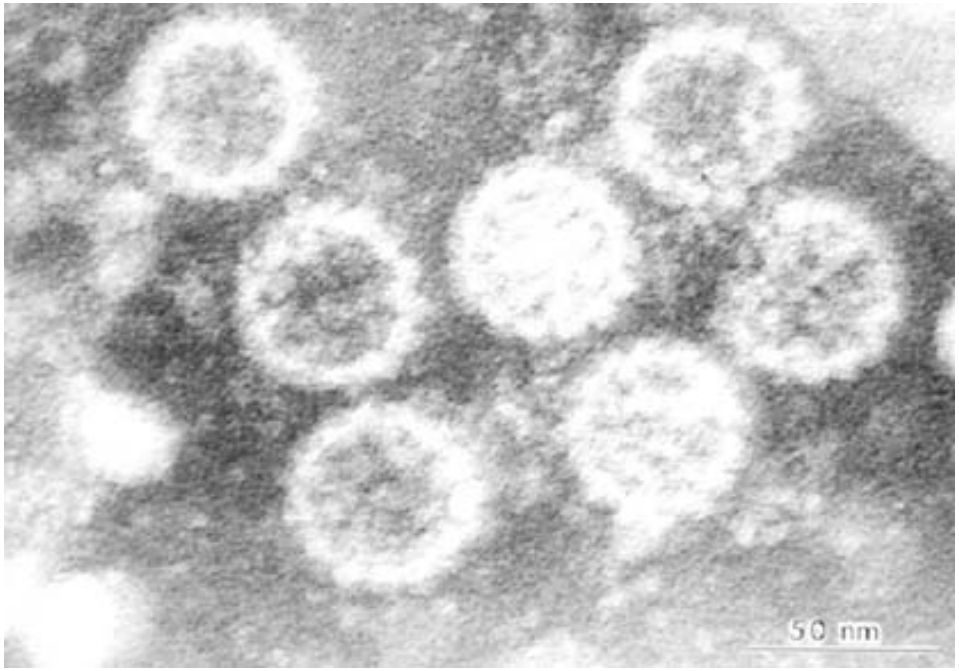
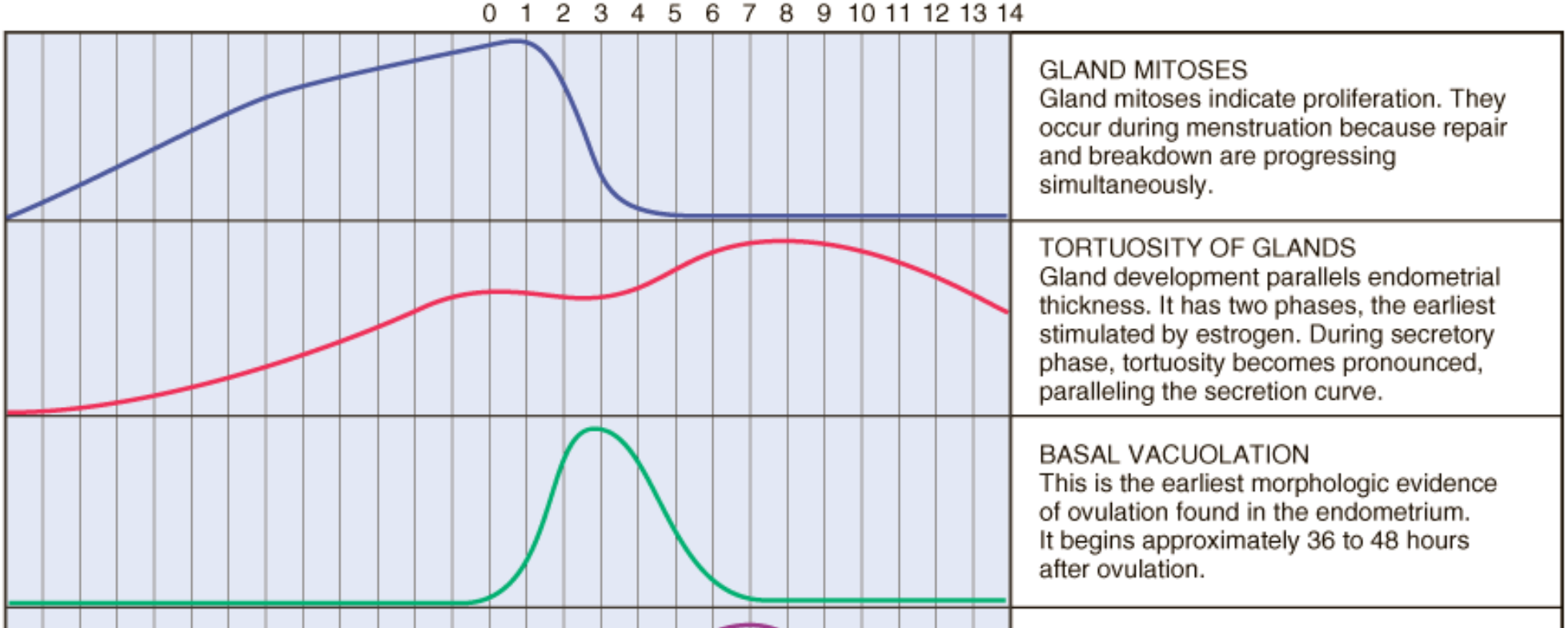


Figure 22-25 Approximate quantitative changes in seven morphologic criteria found to be most useful in dating human endometrium. *(Modified from Noyes RW: Normal phases of the endometrium. In Norris HJ, et al (eds): The Uterus. Baltimore, Williams & Wilkins, 1973.)*



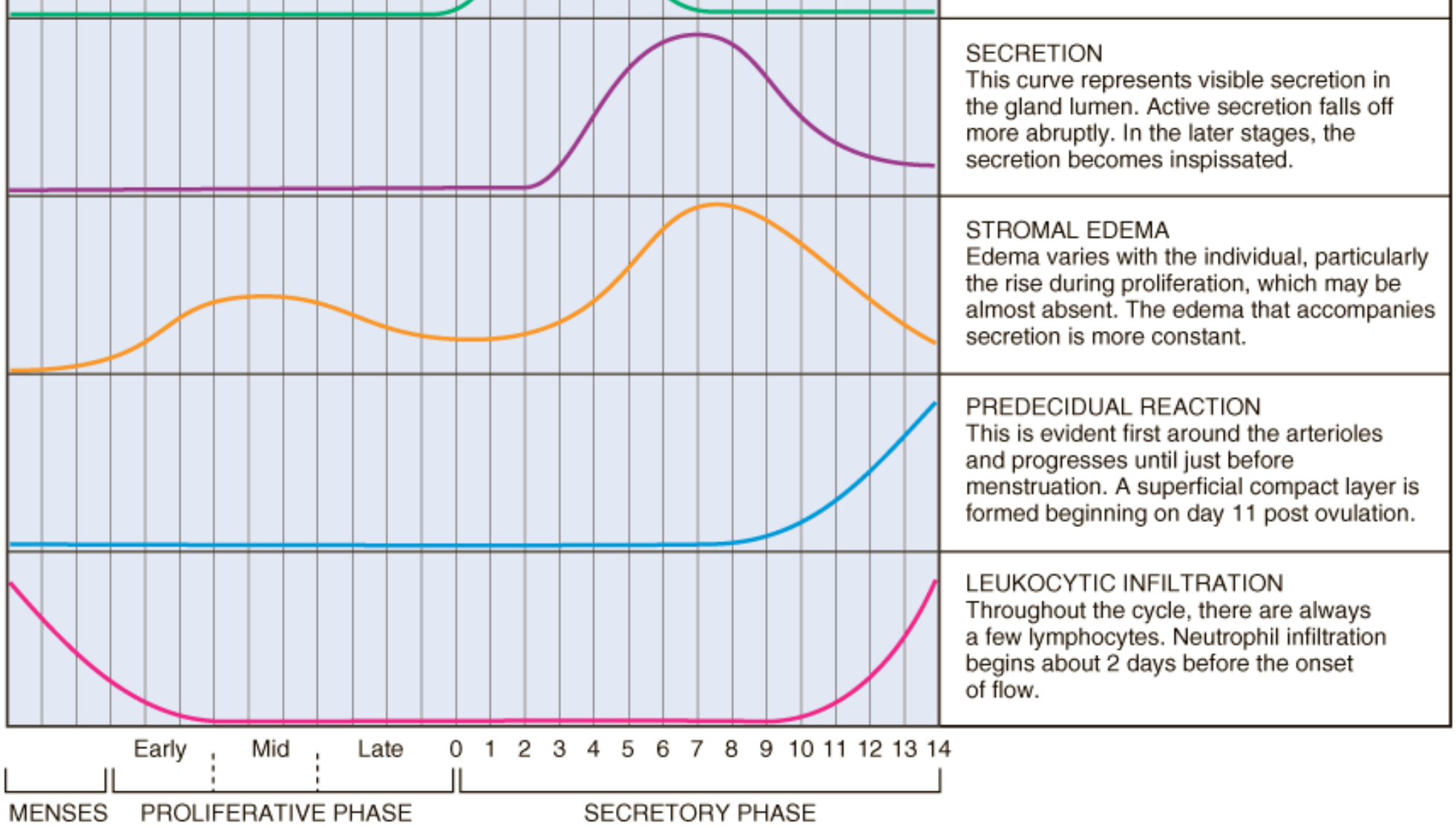


Figure 22-26 Histology of the menstrual cycle, including the proliferative phase with mitoses (*A*), the early secretory phase with subnuclear vacuoles (*B*) followed by secretory exhaustion (*C*), predecidual changes (*D*), stromal granulocytes (*E*), and stromal breakdown at the onset of menses (*F*) (see text).

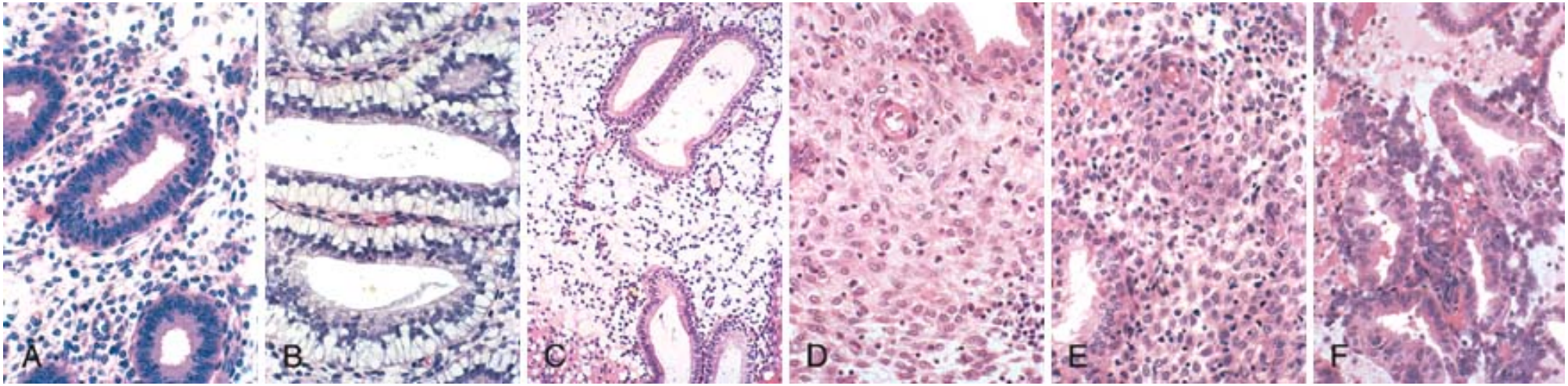


TABLE 22-2 -- Causes of Abnormal Uterine Bleeding by Age Group

Age Group	Causes
Prepuberty	Precocious puberty (hypothalamic, pituitary, or ovarian origin)
Adolescence	Anovulatory cycle, coagulation disorders
Reproductive age	Complications of pregnancy (abortion, trophoblastic disease, ectopic pregnancy)
	Organic lesions (leiomyoma, adenomyosis, polyps, endometrial hyperplasia, carcinoma)
	Anovulatory cycle
	Ovulatory dysfunctional bleeding (e.g., inadequate luteal phase)
Perimenopausal	Anovulatory cycle
	Irregular shedding
	Organic lesions (carcinoma, hyperplasia, polyps)
Postmenopausal	Organic lesions (carcinoma, hyperplasia, polyps)
	Endometrial atrophy

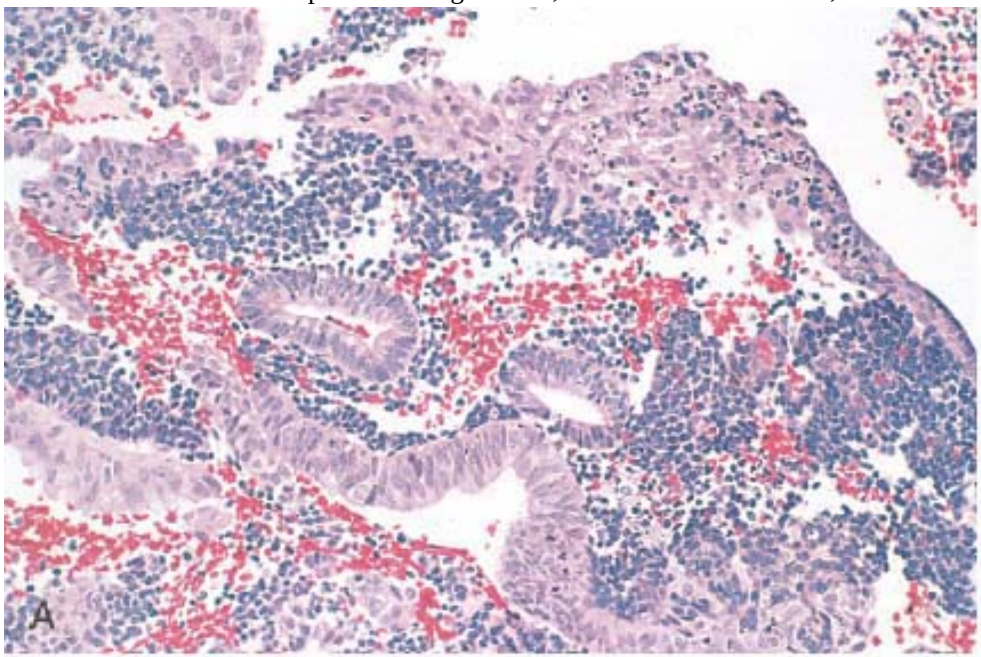
pituitary tumors; (2) a primary lesion of the ovary, such as a functioning ovarian tumor (granulose-theca cell tumors) or polycystic ovaries (see section on ovaries); or (3) a generalized metabolic disturbance, such as marked obesity, severe malnutrition, or any chronic systemic disease. In most patients, however, anovulatory cycles are unexplainable, probably occurring because of subtle hormonal imbalances. Anovulatory cycles are most common at menarche and the perimenopausal period.

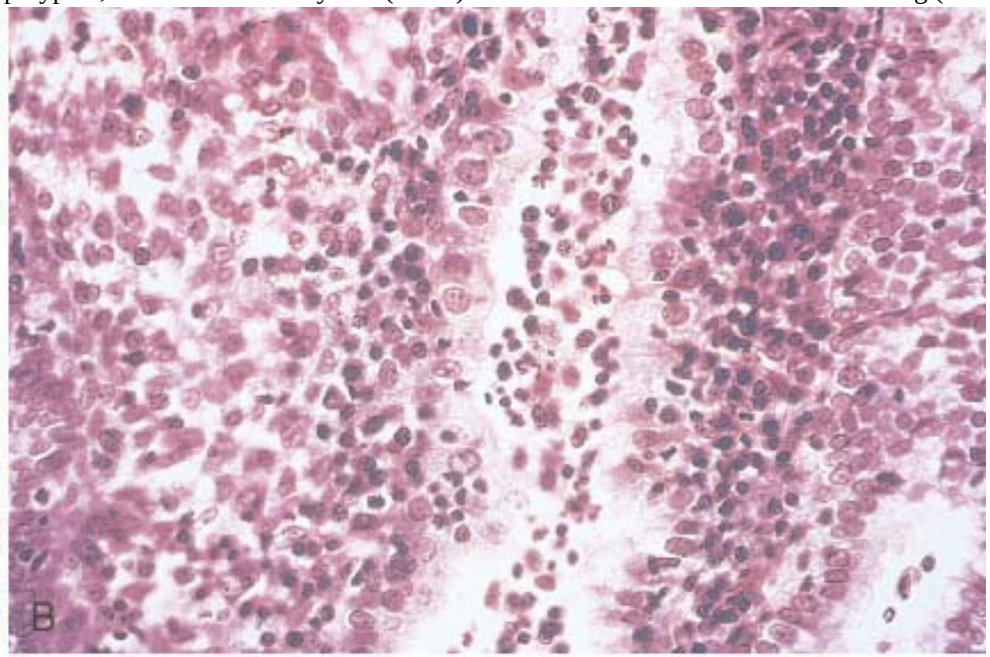
Failure of ovulation results in prolonged, excessive endometrial stimulation by estrogens. Under these circumstances, the endometrial glands undergo mild architectural changes, including cystic dilation (persistent proliferative endometrium). Unscheduled breakdown of the stroma may also occur ("anovulatory menstruation"), with no evidence of endometrial secretory activity (Fig. 22-27*A*). More severe consequences of anovulation are discussed under endometrial hyperplasia.

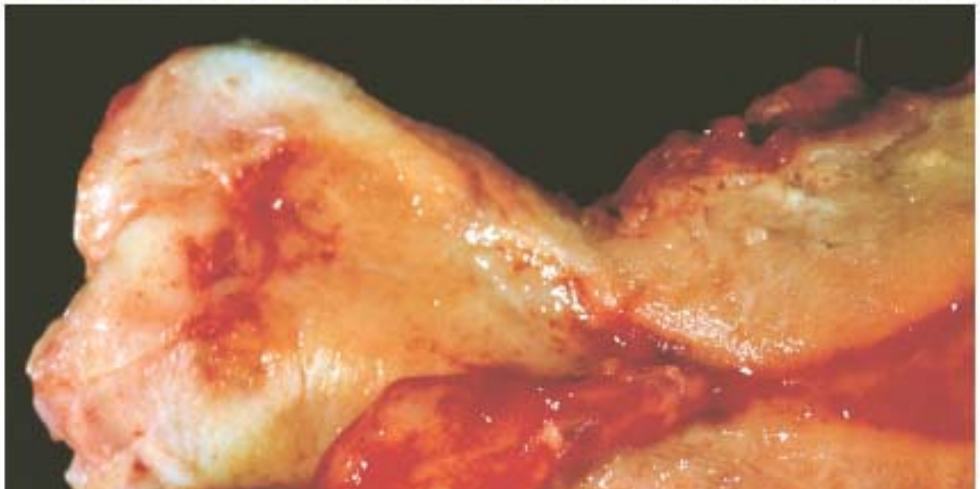
INADEQUATE LUTEAL PHASE

This term refers to the occurrence of inadequate corpus luteum function and low progesterone output, with an irregular ovulatory cycle. The condition often manifests clinically as infertility, with either increased bleeding or amenorrhea. Endometrial

Figure 22-27 Common causes of abnormal uterine bleeding. *A*, The most common is dysfunctional uterine bleeding, seen here as anovulatory endometrium with stromal breakdown. Note breakdown associated with proliferative glands. *B*, Chronic endometritis. *C*, Endometrial polyp. *D*, Submucosal leiomyoma (*lower*) with attenuation of the endometrial lining (*arrow*).







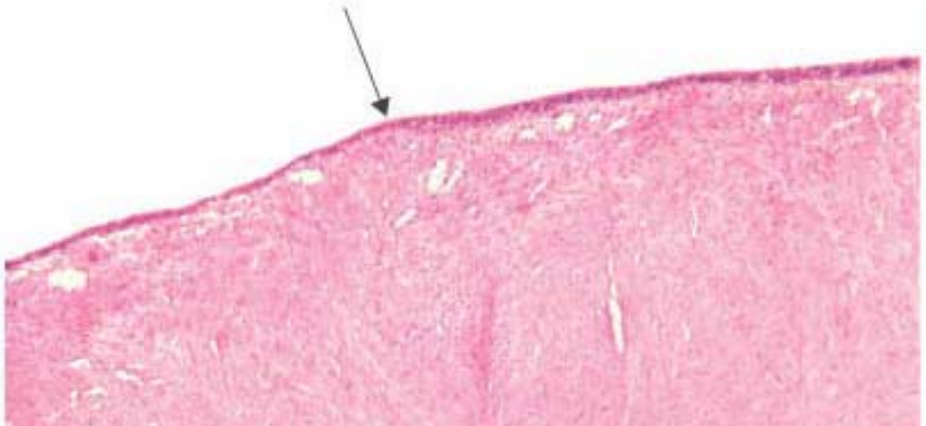


Figure 22-28 Adenomyosis. This disorder is characterized by functional endometrial nests within the myometrium, producing foci of hemorrhagic cysts within the uterine wall.

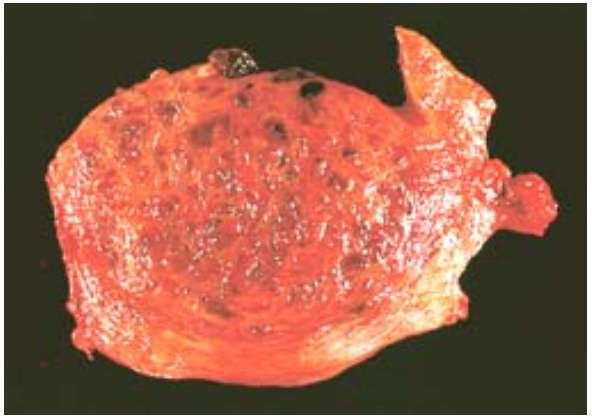


Figure 22-29 The potential origins of endometriosis.

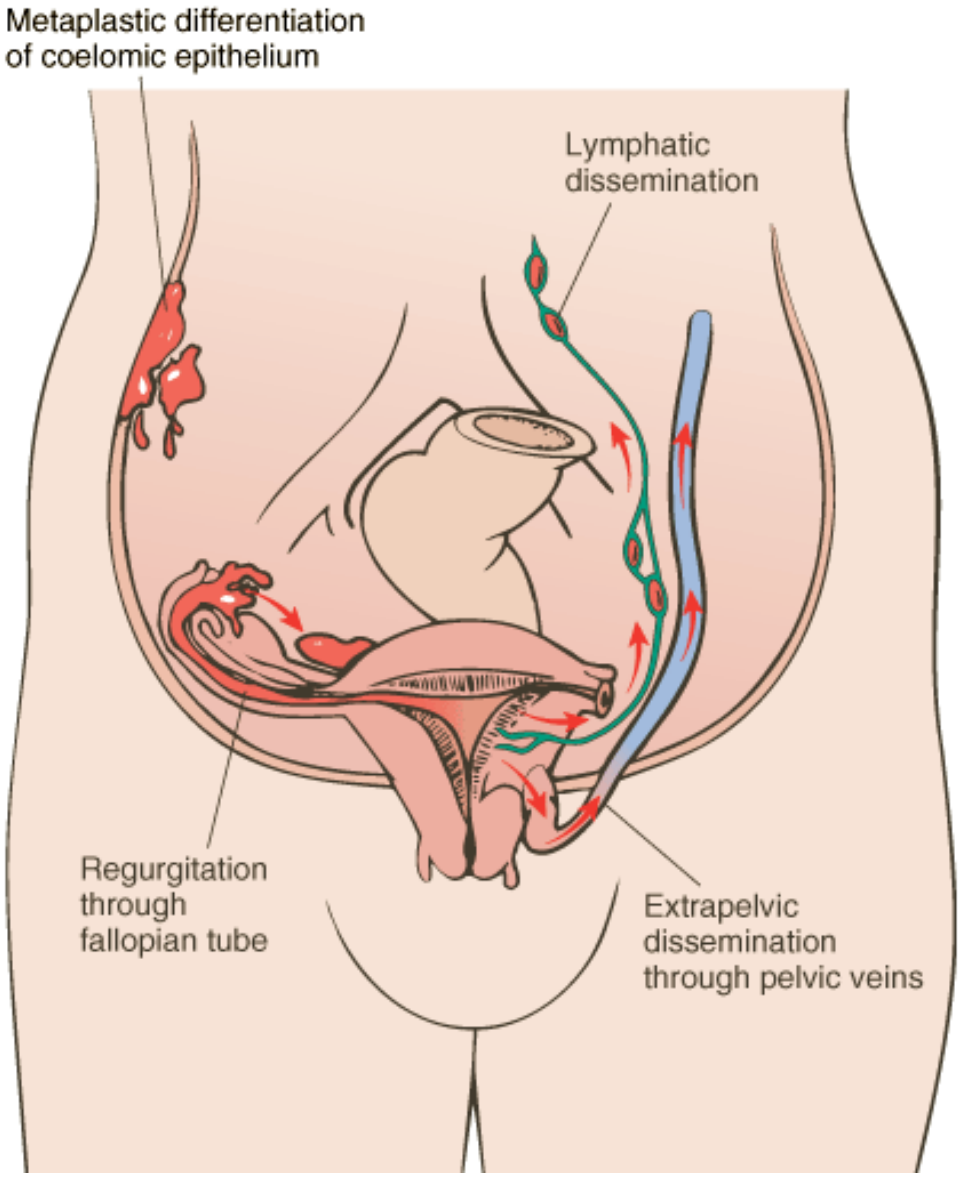


Figure 22-30 Endometriosis. *A*, This ovary has been sectioned to reveal a large endometriotic cyst containing necrotic brown material consisting of degenerated blood (chocolate cyst). *B*, Lining of an endometriotic cyst from a pregnant patient. On the right is an endometrial gland; on the left is endometrial stroma with plump stromal cells characteristic of decidual changes. In the center are numerous macrophages containing hemosiderin.

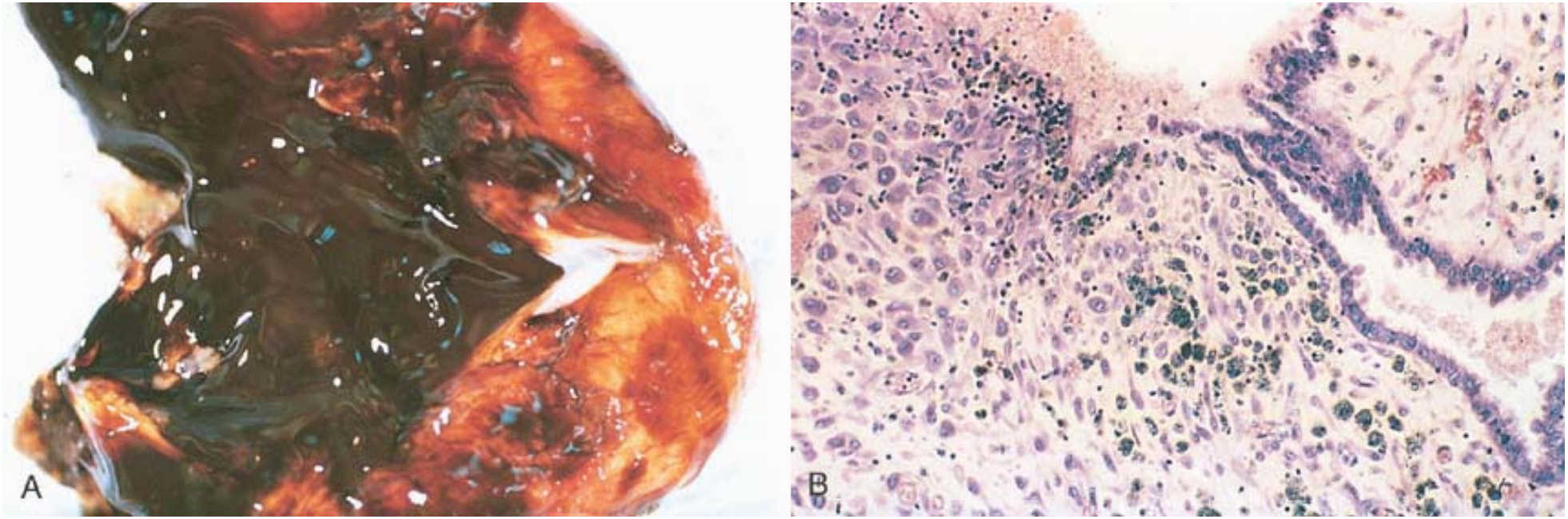


Figure 22-31 *A*, Lower-grade hyperplasias of the endometrium show principally architectural glandular changes with cystic glandular dilatation and are synonymous with anovulatory changes. *B*, Atypical hyperplasias (endometrial intraepithelial neoplasia) exhibit increased gland/stroma ratio (gland crowding) and epithelial stratification (*arrows*). *C*, Loss of *PTEN* gene expression in intraepithelial neoplasia, seen here as absence of staining. Compare to normal glands (*arrows*), which express the gene *(Courtesy of Dr. George L. Mutter, Brigham and Women's Hospital, Boston, MA.) D*, Endometrial hyperplasia with squamous metaplasia.

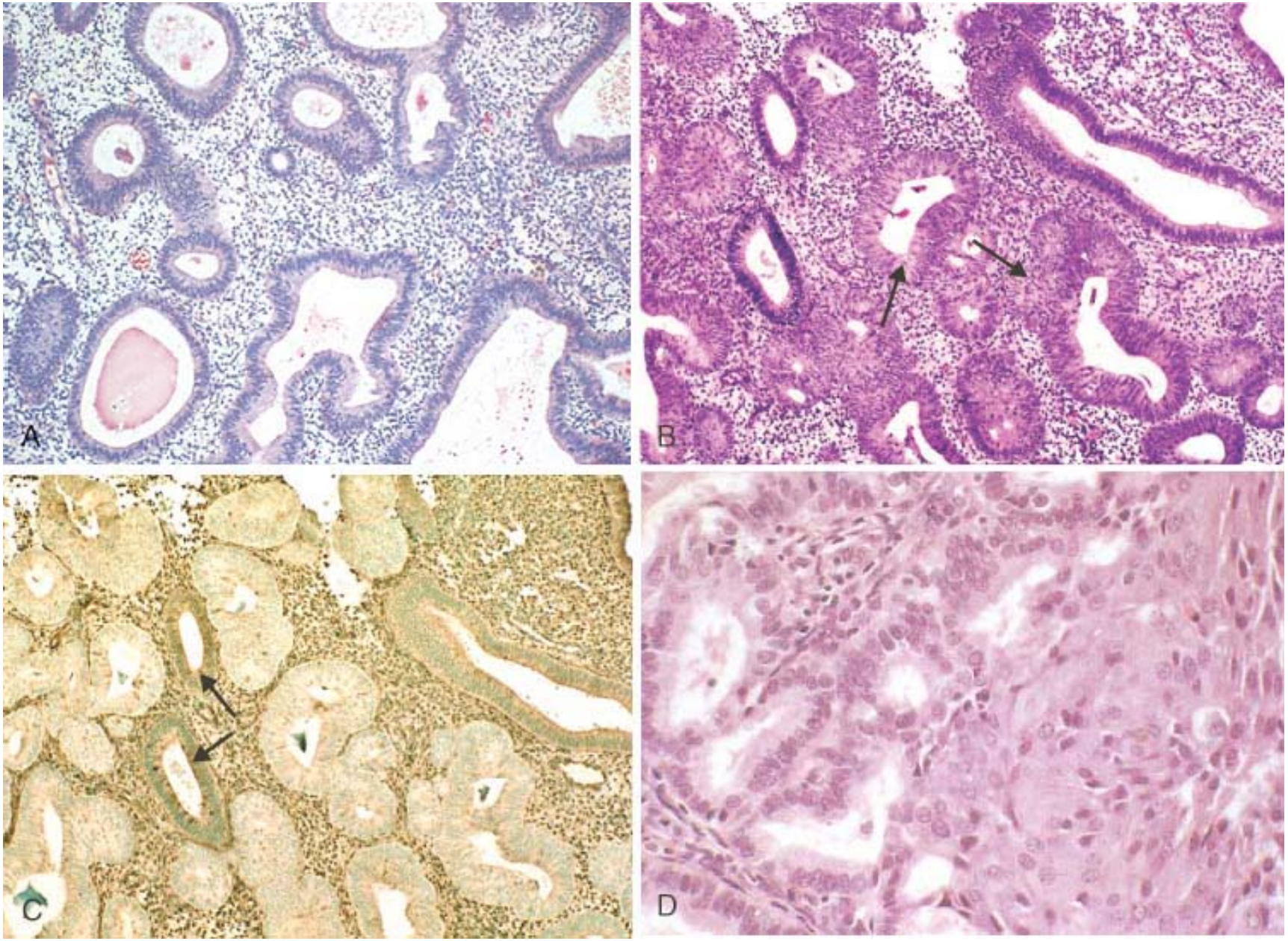
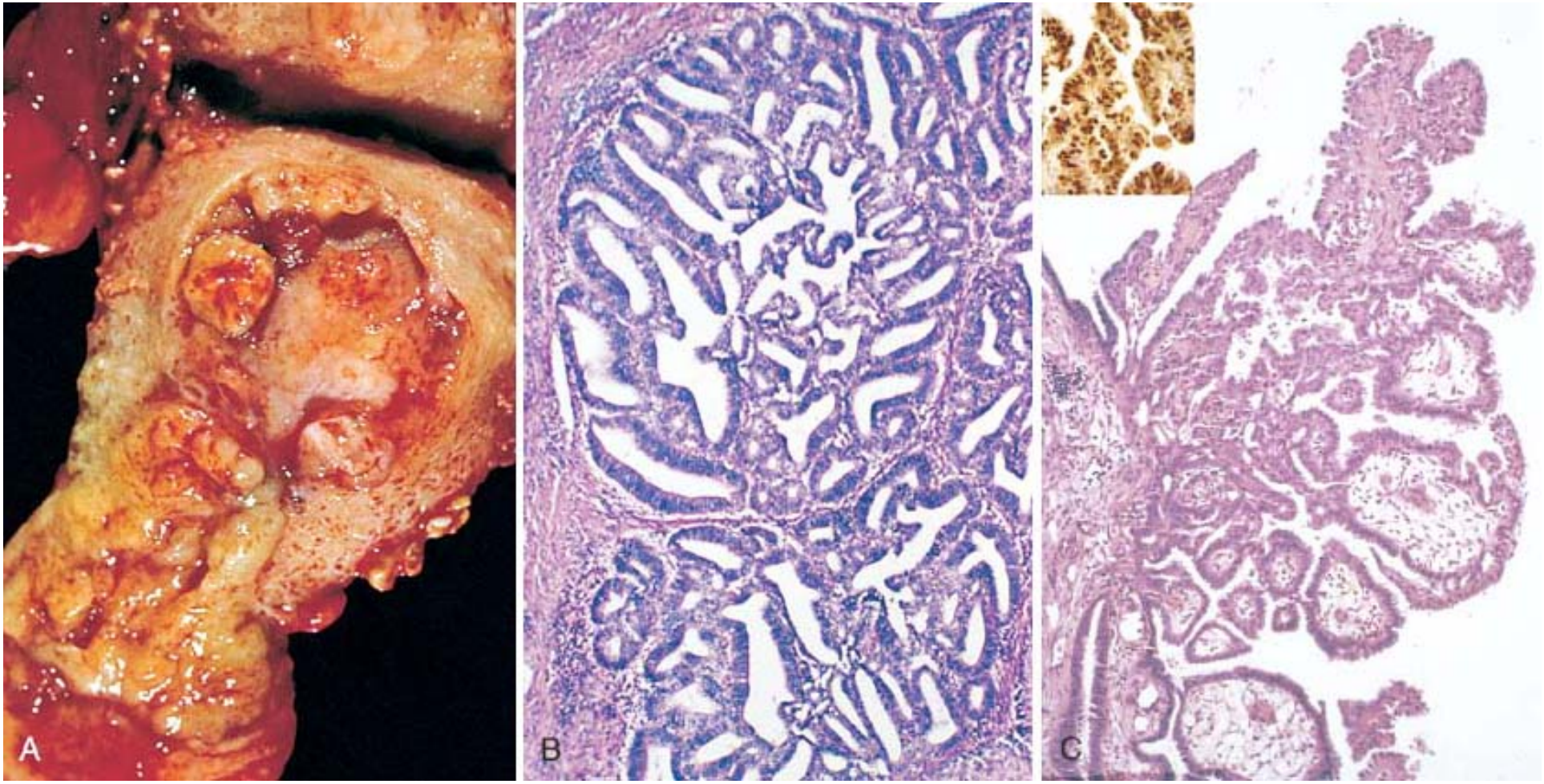


Figure 22-32 *A*, Endometrial adenocarcinoma presenting as a fungating mass in the fundus of the uterus. *B*, Well-differentiated endometrial adenocarcinoma. Glandular architecture is preserved but the tissue is confluent without intervening stroma, which distinguishes carcinoma from hyperplasia. *C*, Papillary serous carcinoma of the endometrium, with accumulation of nuclear p53 protein as seen by immunohistochemistry (*inset upper left*).



Stage II. Carcinoma has involved the corpus and the cervix.

Stage III. Carcinoma has extended outside the uterus but not outside the true pelvis.

Stage IV. Carcinoma has extended outside the true pelvis or has obviously involved the mucosa of the bladder or the rectum.

Cases in various stages can also be subgrouped with reference to the three grades described above:

G1. Well-differentiated adenocarcinoma

G2. Differentiated adenocarcinoma with partly solid (less than 50%) areas

G3. Predominantly solid or entirely undifferentiated carcinoma. Serous and clear cell carcinomas are automatically classified as grade 3.

Clinical Course.

Carcinoma of the endometrium may be asymptomatic for periods of time but usually produces irregular vaginal bleeding with excessive leukorrhea. Uterine enlargement in the early stages may be deceptively absent. Cytologic detection on Papanicolaou smears is variable and most likely associated with serous carcinomas, which produce easily detached clusters of cells that are sampled in pap smears. Exclusion of a cervical adenocarcinoma can usually be based on cervix exam and the fact that older age groups are much more susceptible to primary endometrial (versus cervical) cancer. However, upper genital tract carcinomas (fallopian tube and ovary) may be associated with abnormal cytology. The diagnosis of endometrial cancer must ultimately be established by curettage and histologic examination of the tissue.

As would be anticipated, the prognosis depends heavily on the clinical stage of the disease when it is discovered, and its histologic grade and type. In the United States, most women (about 80%) have stage I disease clinically and have well-differentiated or moderately well-differentiated endometrioid carcinomas. Surgery, alone or in combination with irradiation, gives about 90% 5-year survival in stage I (grade 1 or 2) disease. This rate drops to approximately 75% for grade 3/stage I and to 50% or less for stage II and III endometrial carcinomas.

As mentioned, uterine papillary serous and clear cell carcinomas have a propensity for extrauterine (lymphatic or transtubal) spread, even when confined to the endometrium or its surface epithelium. Overall, fewer than 50% of patients with these tumors are alive 3 years after diagnosis and 35% after 5 years. If peritoneal cytology and adnexal histologic exam are negative, the five year survival of stage I disease is approximately 80% to 85%.[82] The additional advantage of prophylactic radiation or chemotherapy in early-stage disease is unclear.[83] [84]

Tumors of the Endometrium with Stromal Differentiation

A proportion of endometrial adenocarcinomas undergo stromal differentiation and are termed carcinosarcomas. A second group is composed of stromal neoplasias in association with benign glands (adenosarcomas). A third group consists of pure stromal neoplasms, ranging from benign (stromal nodule) to malignant (stromal sarcoma). Together, these tumors comprise less than 5% of endometrial cancers.

CARCINOSARCOMAS

Carcinosarcomas (formerly termed malignant mixed müllerian tumors) consist of endometrial adenocarcinomas in which malignant stromal differentiation takes place.[85] The stroma tends to differentiate into a variety of malignant mesodermal components, including muscle, cartilage, and even osteoid. The epithelial and stromal components are presumably derived from the same cell, a concept supported by the observation that the stromal cells often stain positive for epithelial cell markers. Carcinosarcomas occur in postmenopausal women and manifest, similarly to adenocarcinoma, with postmenopausal bleeding. Many affected patients give a history of previous radiation therapy.

Morphology.

In gross appearance, such tumors are somewhat more fleshy than adenocarcinomas, may be bulky and polypoid, and sometimes protrude through the cervical os. On histology, the tumors consist of adenocarcinoma mixed with the stromal (sarcoma) elements (Fig. 22-33*A*); alternatively, the tumor may contain two distinct and separate epithelial and mesenchymal components. Sarcomatous components may mimic extrauterine tissues (i.e., striated muscle cells, cartilage, adipose tissue, and bone).

Outcome is determined primarily by depth of invasion and stage. As with endometrial carcinomas, the prognosis may be influenced by the grade and type of the adenocarcinoma, being poorest with serous differentiation. It is noteworthy that carcinosarcomas usually metastasize as adenocarcinomas. The tumors are highly malignant, and patients have a 5-year survival rate of 25% to 30%.[85]

Figure 22-33 *A*, Carcinosarcoma, showing both epithelial (*upper right*) and stromal (*arrow*) differentiation. *B*, Endometrial stromal sarcoma infiltrating myometrium. *C*, Fluorescent in situ hybridization using two fluorescently labeled probes (*green and red*) that flank the breakpoint of the gene involved in the chromosomal translocation t(7;17) in endometrial stromal sarcoma. The yellow signal is indicative of the normal copy of chromosome 7. A separate green and red signal indicates that the gene on chromosome 7 has been redistributed. *(Courtesy of Dr. Marisa R. Nucci, Brigham and Women's Hospital, Boston, MA.)*

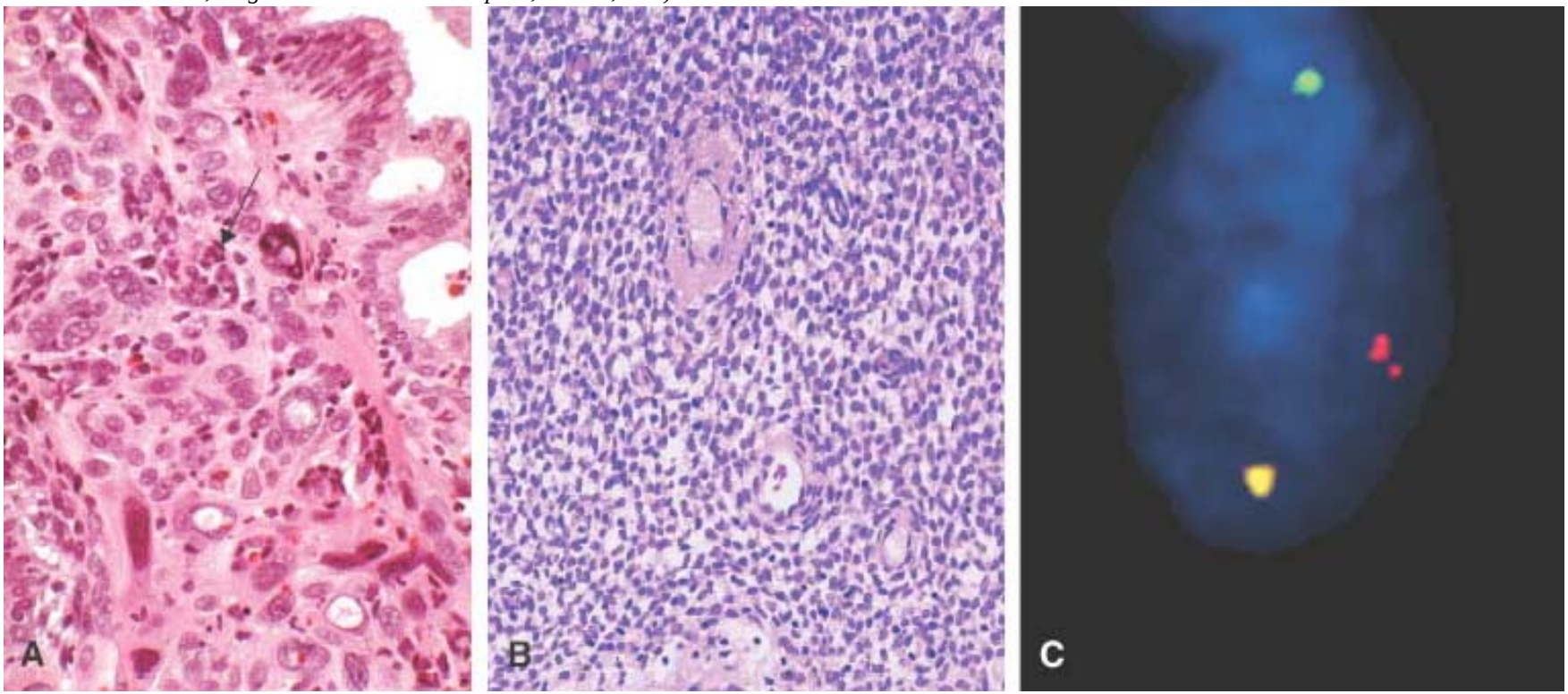


Figure 22-34 *A*, Leiomyomas of the myometrium. The uterus is opened to reveal the tumors bulging into the endometrial cavity and displaying a firm white appearance on sectioning. *B*, Leiomyoma showing well-differentiated, regular, spindle-shaped smooth muscle cells.

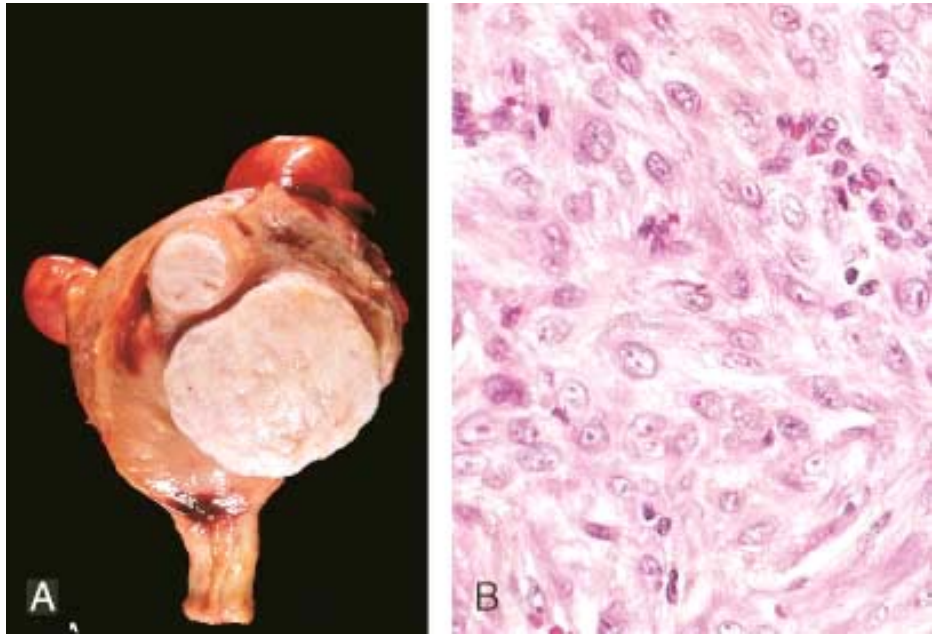
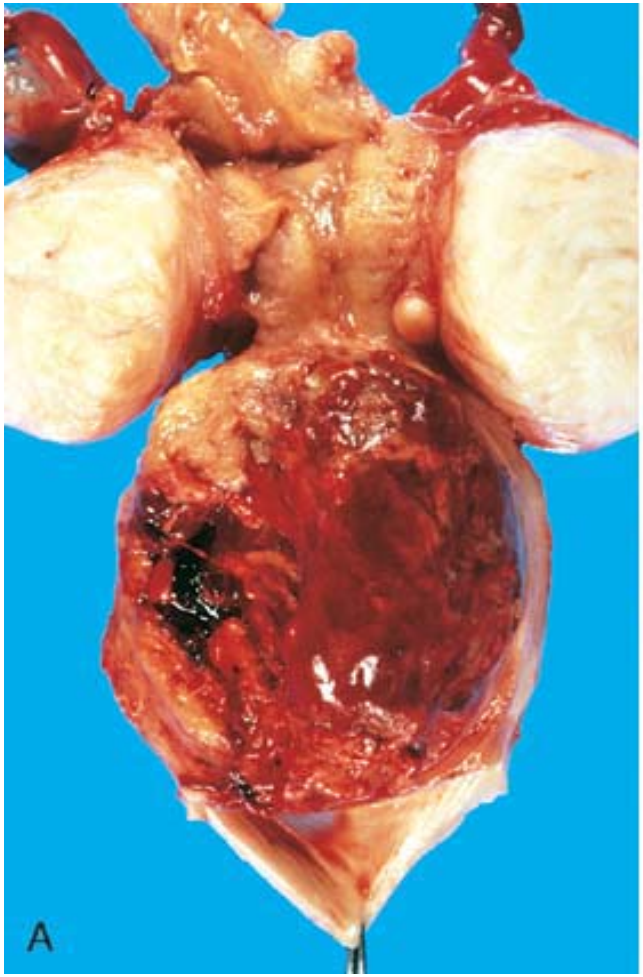


Figure 22-35 Leiomyosarcoma. *A,* A large hemorrhagic tumor mass distends the lower corpus and is flanked by two leiomyomas. *B,* The tumor cells are irregular in size and have hyperchromatic nuclei.



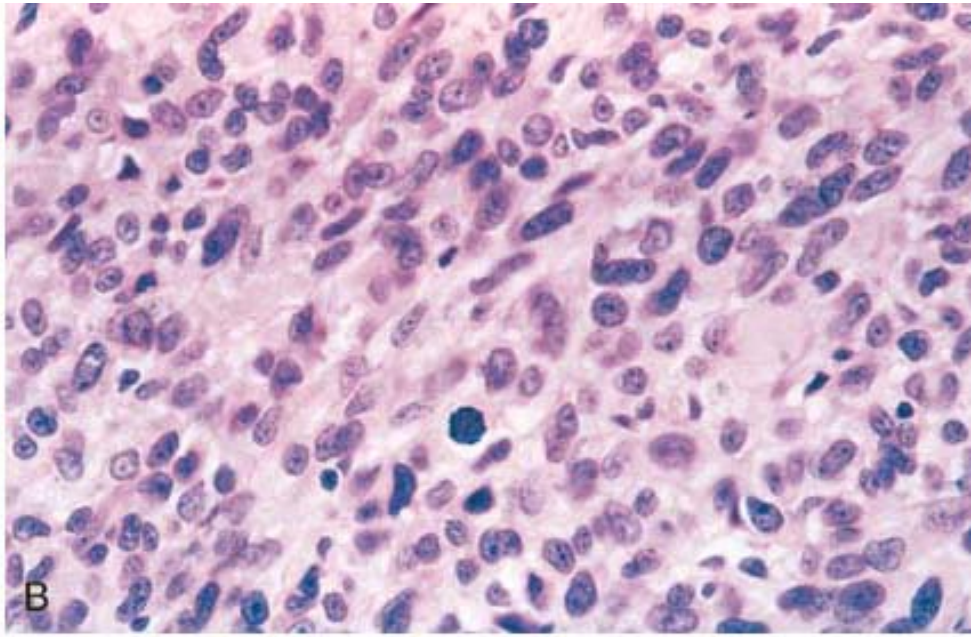


Figure 22-36 Polycystic ovarian disease and cortical stromal hyperplasia. *A,* The ovarian cortex reveals numerous clear cysts. *B,* Sectioning of the cortex reveals several subcortical cystic follicles. *C,* Cystic follicles seen in a low-power microphotograph. *D,* Cortical stromal hyperplasia manifests as diffuse stromal proliferation with symmetrical enlargement of the ovary.

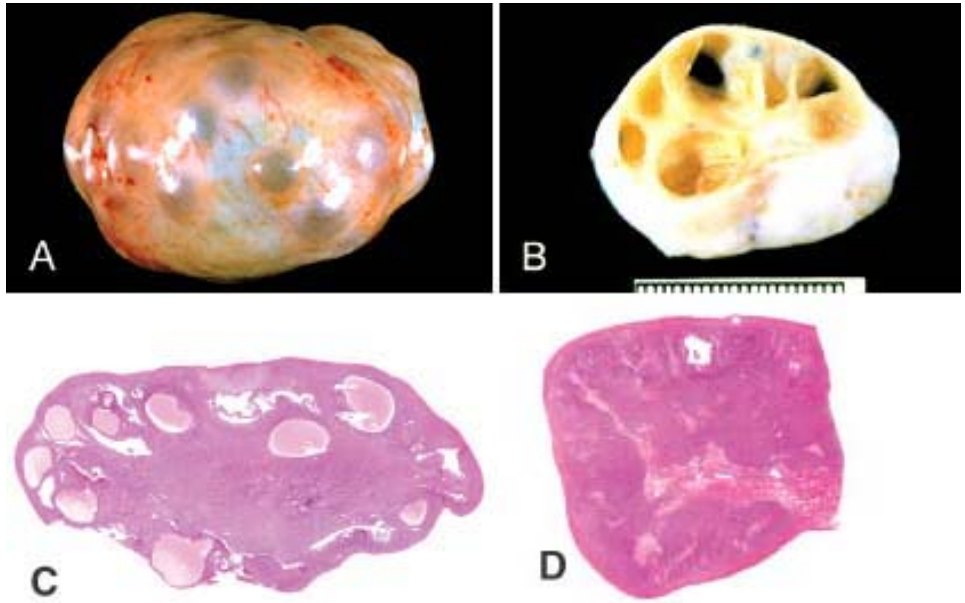


TABLE 22-3 -- Ovarian Neoplasms (1993 WHO Classification)

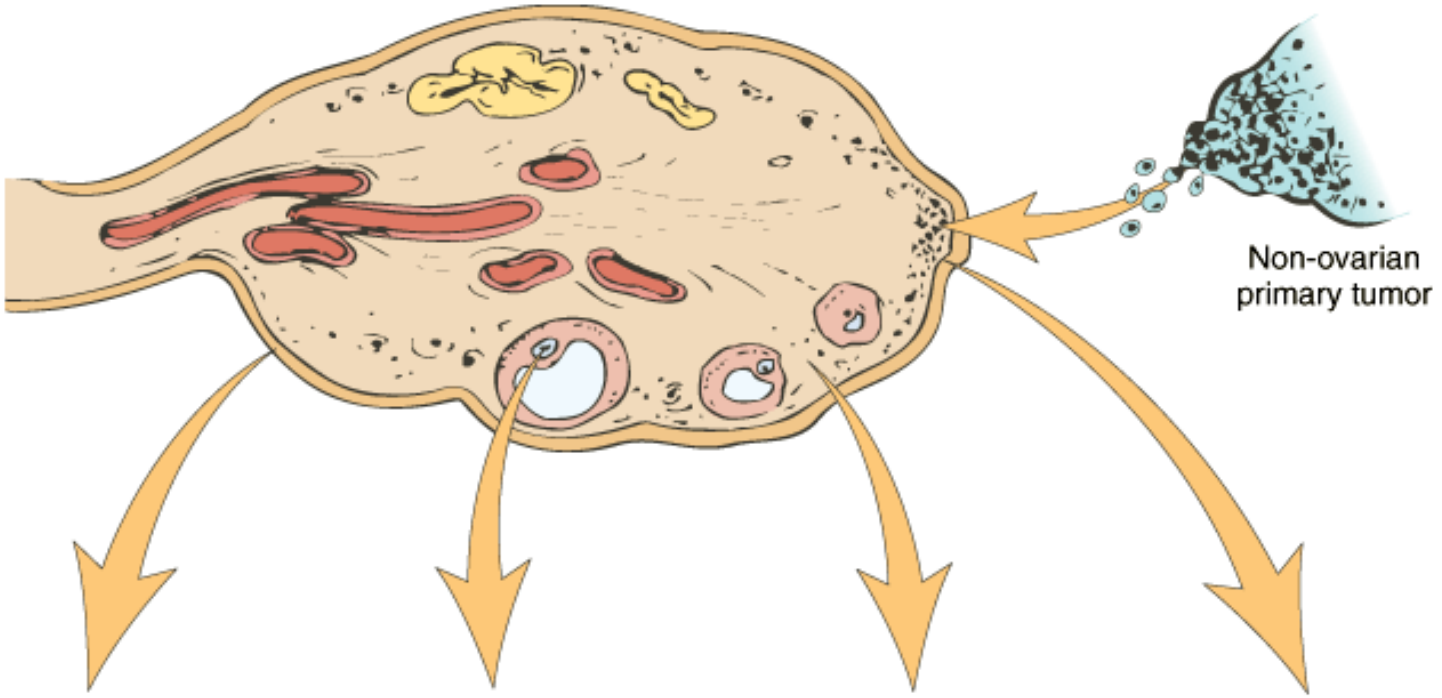
Surface Epithelial-Stromal Tumors
Serous tumors
••Benign (cystadenoma)
••Cystadenoma of borderline malignancy
••Malignant (serous cystadenocarcinoma)
Mucinous tumors, endocervical-like and intestinal type
••Benign
••Of borderline malignancy
••Malignant
Endometrioid tumors
••Benign
••Of borderline malignancy
••Malignant
••Epithelial-stromal
••••Adenosarcoma
••••Mesodermal (müllerian) mixed tumor

••Clear cell tumors
••••Benign
••••Of borderline malignancy
••••Malignant
••Transitional cell tumors
••••Brenner tumor
••••Brenner tumor of borderline malignancy
••••Malignant Brenner tumor
••••Transitional cell carcinoma (non-Brenner type)
Sex Cord-Stromal Tumors
Granulosa-stromal cell tumors
••Granulosa cell tumors
••Tumors of the thecoma-fibroma group
Sertoli-stromal cell tumors; androblastomas
Sex cord tumor with annular tubules
Gynandroblastoma
Steroid (lipid) cell tumors
Germ Cell Tumors
Teratoma
••Immature
••Mature (adult)
••••Solid
••••Cystic (dermoid cyst)
••Monodermal (e.g., struma ovarii, carcinoid)
Dysgerminoma
Yolk sac tumor (endodermal sinus tumor)
Mixed germ cell tumors
Malignant, Not Otherwise Specified
Metastatic Nonovarian Cancer (from Nonovarian Primary)
Data from the WHO Classification. (Courtesy Dr. Robert Scully, Massachusetts General Hospital, Boston, MA.)

being a common site of metastases from a variety of other cancers.

Although some of the specific tumors have distinctive features and are hormonally active, most are nonfunctional and tend to produce relatively mild symptoms until they have reached a large size. Malignant tumors have usually spread outside the ovary by the time a definitive diagnosis is made. Some of these tumors, principally epithelial tumors, tend to be bilateral. Table 22-4 lists these tumors and their subtypes and shows the frequency of bilateral occurrence. Abdominal pain and distention, urinary and gastrointestinal tract symptoms due to compression by tumor or cancer invasion, and abdominal and vaginal bleeding are the most common symptoms. The benign forms may be entirely asymptomatic and occasionally are unexpected findings on abdominal or pelvic examination or during surgery.

Figure 22-37 Derivation of various ovarian neoplasms and some data on their frequency and age distribution.



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 • Mucinous tumor • Endometrioid tumor • Clear cell tumor • Brenner tumor • Cystadenofibroma	• Teratoma • Dysgerminoma • Endodermal sinus tumor • Choriocarcinoma	• Fibroma • Granulosa–theca cell tumor • Sertoli–Leydig cell tumor	

TABLE 22-4 -- Frequency of Major Ovarian Tumors

Type	Percentage of Malignant Ovarian Tumors	Percentage That Are Bilateral

Serous	40	
••Benign (60%)		25
••Borderline (15%)		30
••Malignant (25%)		65
Mucinous	10	
••Benign (80%)		5
••Borderline (10%)		10
••Malignant (10%)		<5
Endometrioid carcinoma	20	40
Undifferentiated carcinoma	10	—
Clear cell carcinoma	6	40
Granulosa cell tumor	5	5
Teratoma		15
••Benign (96%)		
••Malignant (4%)	1	Rare
Metastatic	5	>50
Others	3	—

TUMORS OF MÜLLERIAN EPITHELIUM

Most primary neoplasms in the ovary fall within this category. There are three major types of such tumors: serous, endometrioid and mucinous tumors.[98] These neoplasms range in size and composition. Tumors may be small and grossly imperceptible or massive, filling the pelvis and even the abdominal cavity. Components of the tumors may include cystic areas (cystadenomas), cystic and fibrous areas (cystadenofibromas), and predominantly fibrous areas (adenofibromas). On gross examination, *the risk of malignancy increases as a function of the amount of discernible solid epithelial growth*, including papillary projections of soft tumor, thickened tumor lining the cyst spaces, or solid necrotic friable tissue depicting necrosis.

The most widely accepted theory for the derivation of müllerian epithelial tumors is through the transformation of coelomic mesothelium. This view is based on the embryologic pathway by which the müllerian *ducts are formed and evolve into serous (tubal), endometrioid (endometrium), and mucinous (cervix)* epithelia present in the normal female genital tract (see the section on anatomy). Such tumors occur predominantly in the ovary because coelomic epithelium is incorporated into the ovarian cortex to form mesothelial inclusion cysts. This incorporation occurs by the formation of surface adhesions, atrophy with epithelial infolding, and

repair of ovulation sites. The close association of ovarian carcinomas with either the ovarian surface mesothelium or inclusion cysts may explain the development of extraovarian

carcinomas of similar histology from similar coelomic epithelial rests (so-called endosalpingiosis) in the mesentery.[98] However, this is clearly an oversimplification of the pathogenesis of ovarian cancer. For example, endometrioid carcinomas may be derived from transplanted endometriosis, and some ovarian serous and mucinous (müllerian mucinous) tumors arise in association with endometriosis.[98] The origin of most mucinous tumors is unclear. Some arise within endometriosis; other proposed origins include teratomatous epithelium.

An intriguing question is the origin of the cortical müllerian inclusion cyst (CIC) and its relationship to serous carcinomas (Fig. 22-38). The continuity of pelvic mesothelium with these müllerian cysts suggests that the former gives rise to the latter. However, similarities between some of these cysts and endometrial or tubal epithelium raise the possibility of a uterine or tubal origin for the epithelium. Direct links between CICs and serous carcinoma are not common and studies of ovaries from women with *BRCA* mutations have not disclosed premalignant changes in these cysts.[100] Regardless of their specific origin(s), ovarian epithelial tumors composed of serous, mucinous, and endometrioid cell types are emblematic of the plasticity of müllerian epithelium and range from clearly benign, to tumors of borderline malignancy, to malignant tumors.[98]

Serous Tumors

These common cystic neoplasms are lined by tall, columnar, ciliated epithelial cells and are filled with clear serous fluid. Although the term serous appropriately describes the cyst fluid, it has become synonymous with the tubal-like epithelium in these tumors. Together the benign, borderline, and malignant types account for about 30% of all ovarian tumors. About 75% are benign or of borderline malignancy, and 25% are malignant. Serous cystadenocarcinomas account for approximately 40% of all cancers of the ovary and are the most common malignant ovarian tumors. Benign and borderline tumors are most common between the ages of 20 and 50 years. Cystadenocarcinomas occur later in life on average, although somewhat earlier in familial cases.

Figure 22-38 Cortical inclusion cysts of the ovary. These cysts appear to arise from the overlying mesothelium and are presumed to be the site of origin for many ovarian epithelial neoplasms. Another source of ovarian epithelium neoplasia is endometriosis (see Figure 22-29).

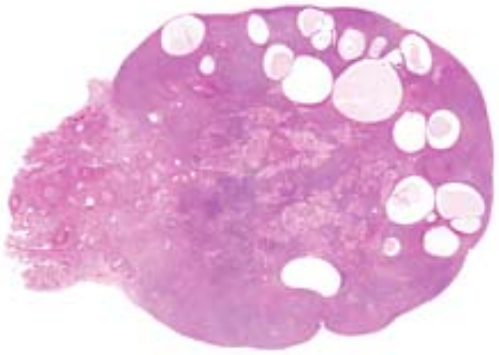


Figure 22-39 *A,* Borderline serous cystadenoma opened to display a cyst cavity lined by delicate papillary tumor growths. *B,* Cystadenocarcinoma. The cyst is opened to reveal a large, bulky tumor mass. *C,* Another borderline tumor growing on the ovarian surface (*lower*).

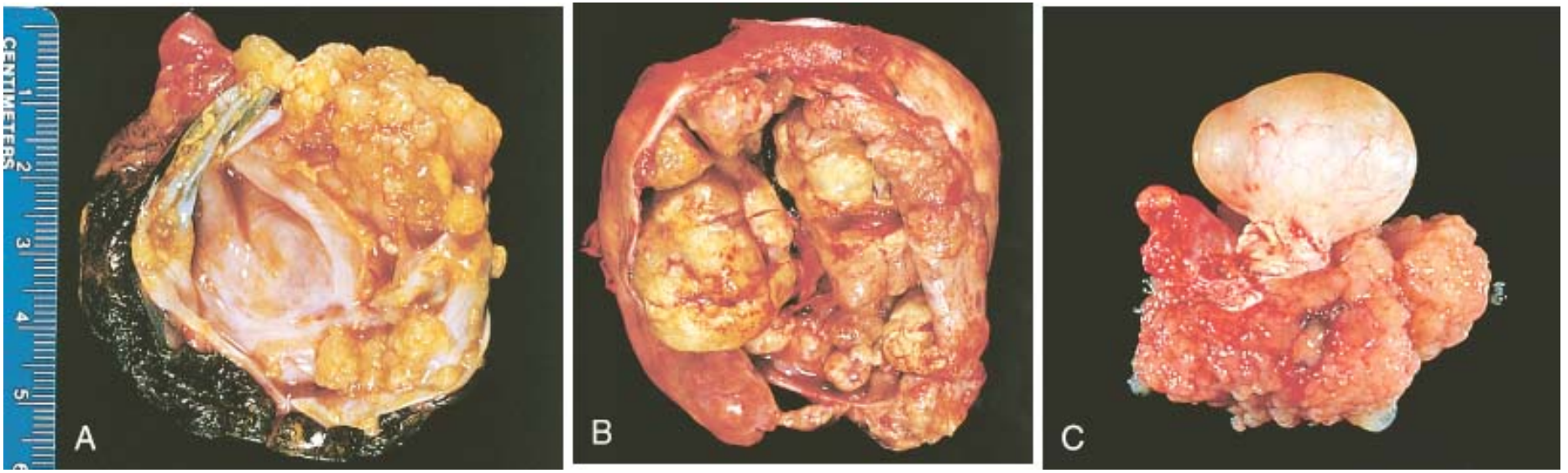


Figure 22-40 Papillary serous cystadenoma revealing stromal papillae with a columnar epithelium.

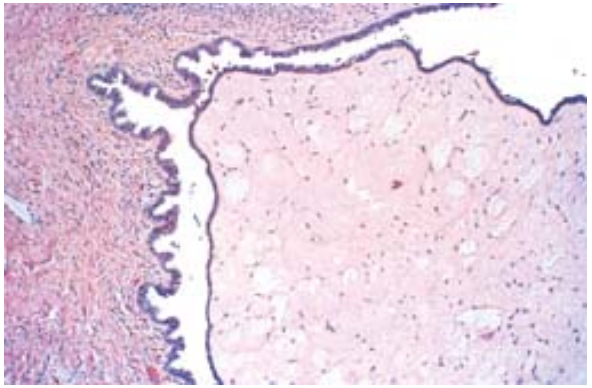


Figure 22-41 Borderline serous cystadenoma exhibiting increased architectural complexity and epithelial cell stratification.

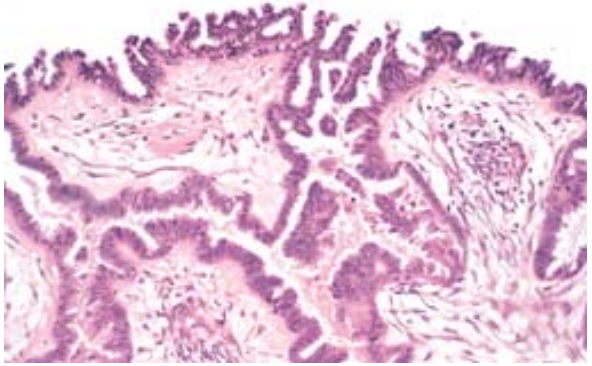


Figure 22-42 Papillary serous cystadenocarcinoma of the ovary with invasion of underlying stroma.

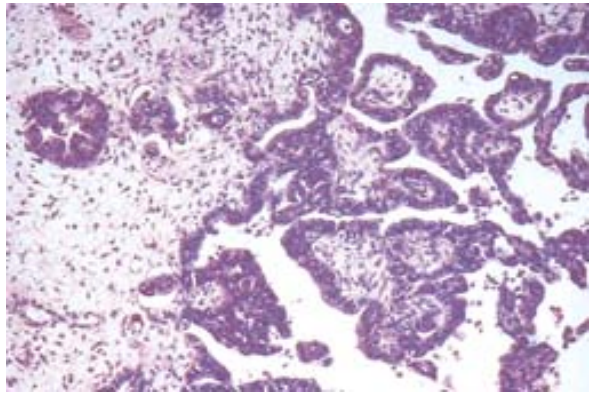


Figure 22-43 Complex micropapillary growth defines a low grade "micropapillary" serous carcinoma.

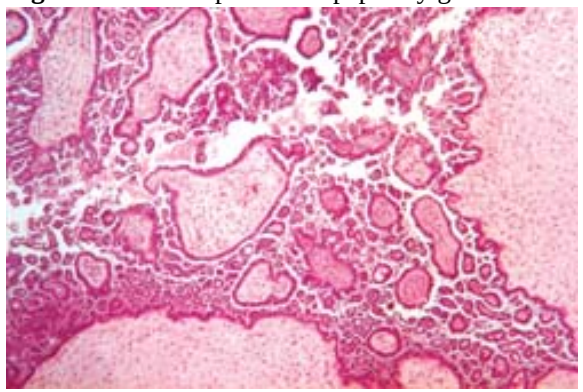


Figure 22-44 *A*, A mucinous cystadenoma with its multicystic appearance and delicate septa. Note the presence of glistening mucin within the cysts. *B*, Columnar cell lining of mucinous cystadenoma.

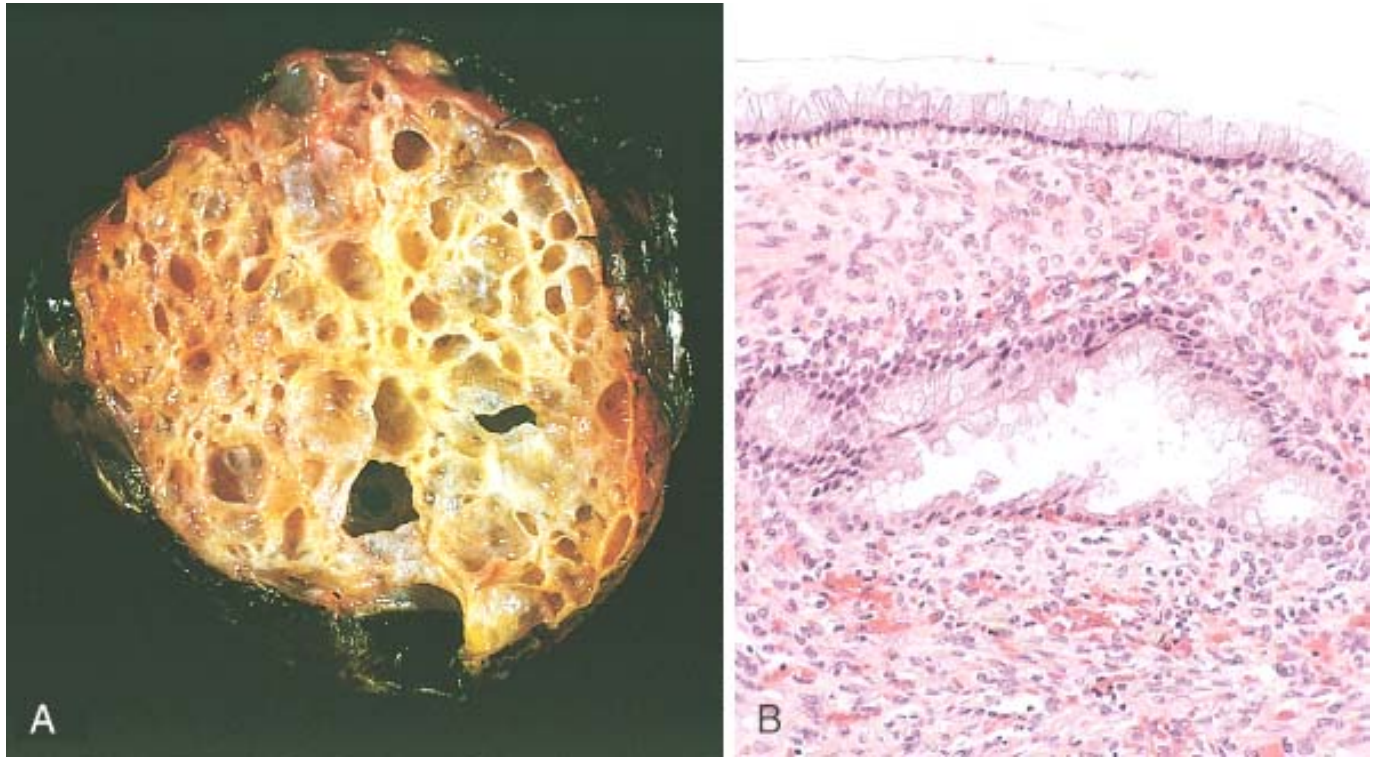


Figure 22-45 *A*, Pseudomyxoma peritonei viewed at laparotomy revealing massive overgrowth of a gelatinous metastatic tumor originating from the appendix. *(Courtesy of Dr. Paul H. Sugarbaker, Washington Hospital Cancer Center, Washington, DC.). B*, Histology of peritoneal implants from an appendiceal tumor, showing mucin-producing epithelium and free mucin (*arrows*).

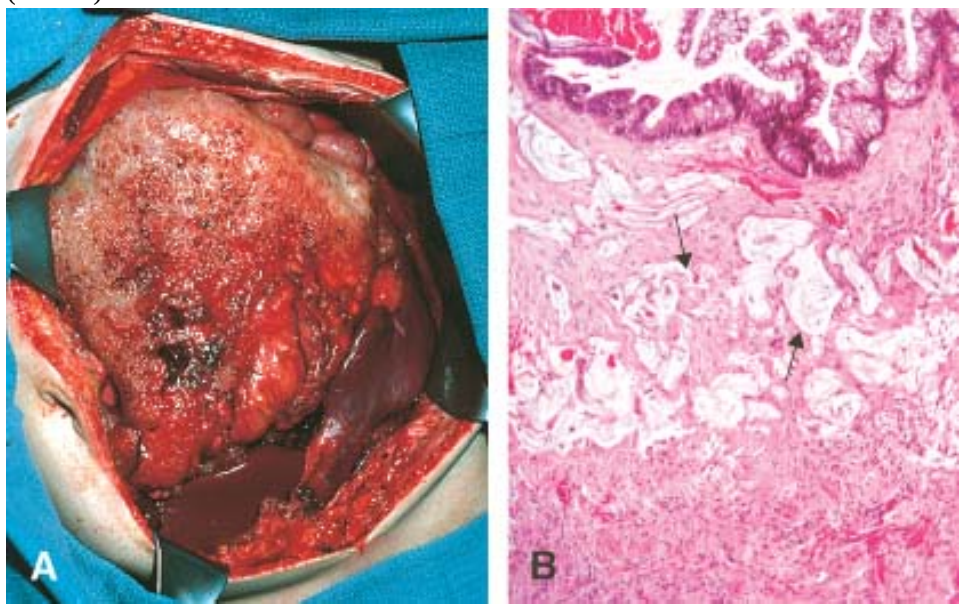
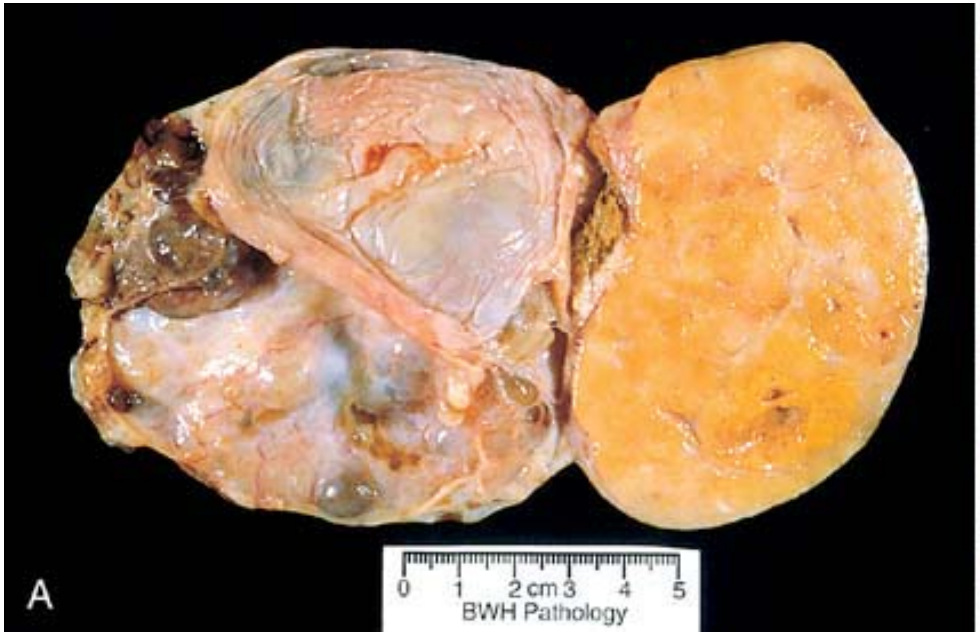


Figure 22-46 *A*, Brenner tumor (*right*) associated with a benign cystic teratoma (*left*). *B*, Histologic detail of characteristic epithelial nests within the ovarian stroma. *(Courtesy of Dr. M. Nucci, Brigham and Women's Hospital, Boston, MA.)*



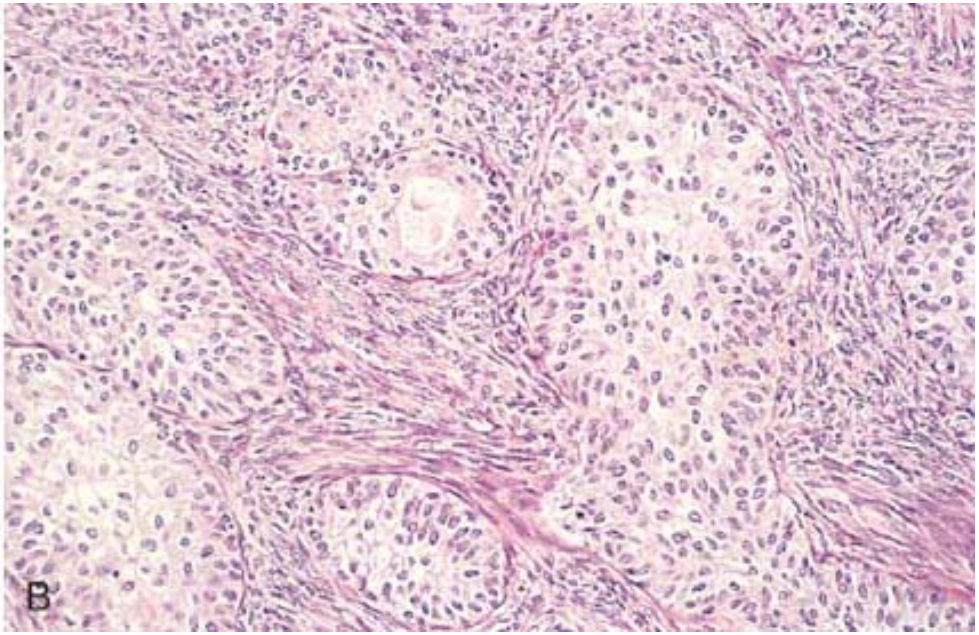


Figure 22-47 Histogenesis and interrelationships of tumors of germ cell origin.

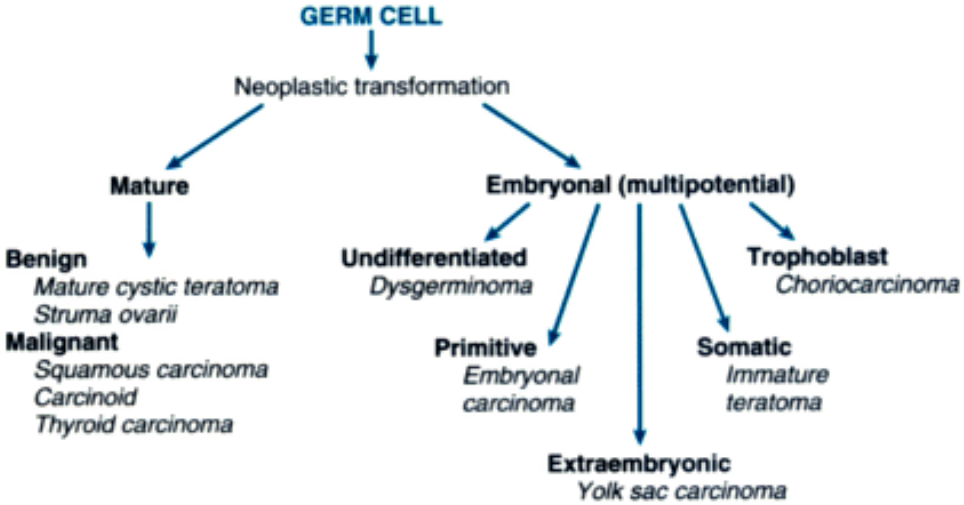


Figure 22-48 Opened mature cystic teratoma (dermoid cyst) of the ovary. Hair (*bottom*) and a mixture of tissues are evident.

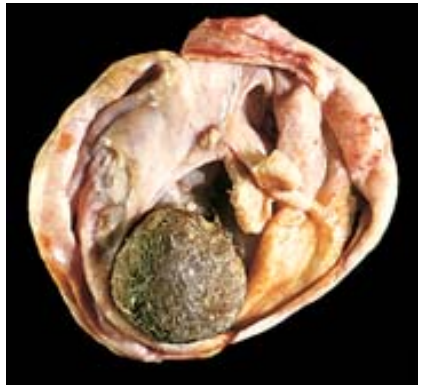


Figure 22-49 Benign cystic teratoma. Low-power view of skin (*top*), beneath which there is brain tissue (*bottom*).

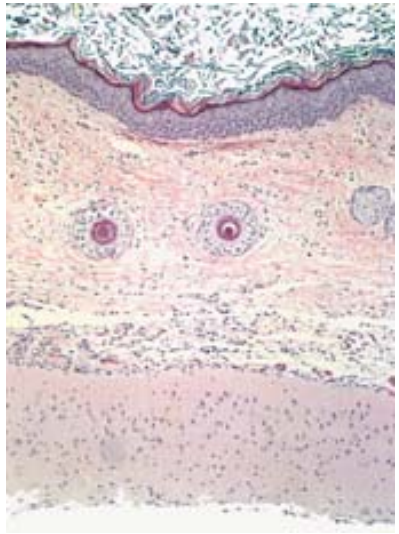


Figure 22-50 Immature teratoma of the ovary illustrating primitive neuroepithelium.

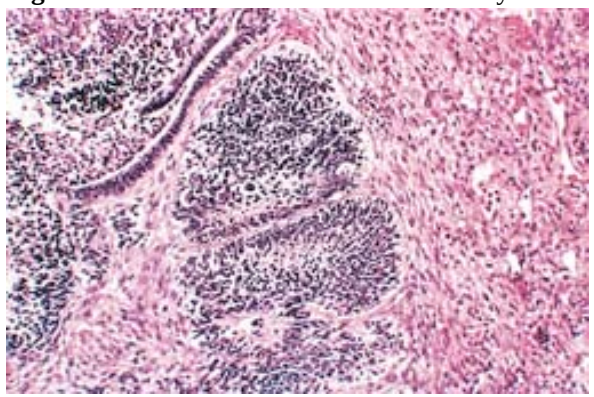


Figure 22-51 Dysgerminoma showing polyhedral tumor cells with round nuclei and adjacent inflammation.

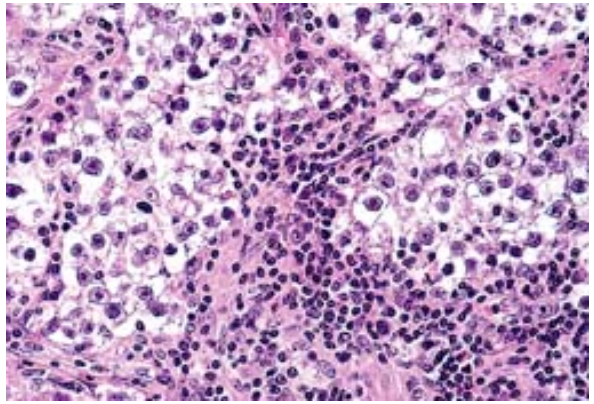


Figure 22-52 A Schiller-Duval body in yolk sac carcinoma.

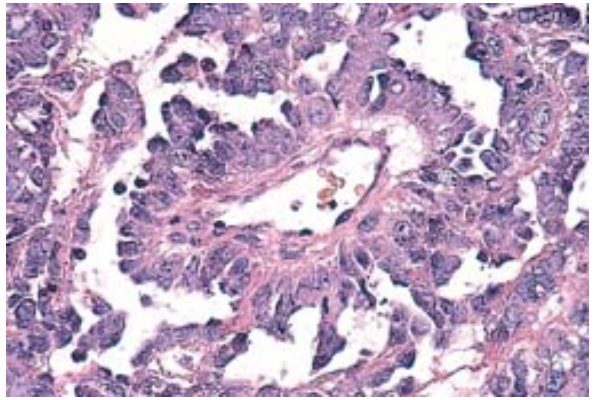


Figure 22-53 Granulosa cell tumor. *A*, The tumor cells are arranged in sheets punctuated by small follicle-like structures (Call-Exner bodies). *B*, Strong immunohistochemical positivity with an antibody to inhibin characterizes these tumors.

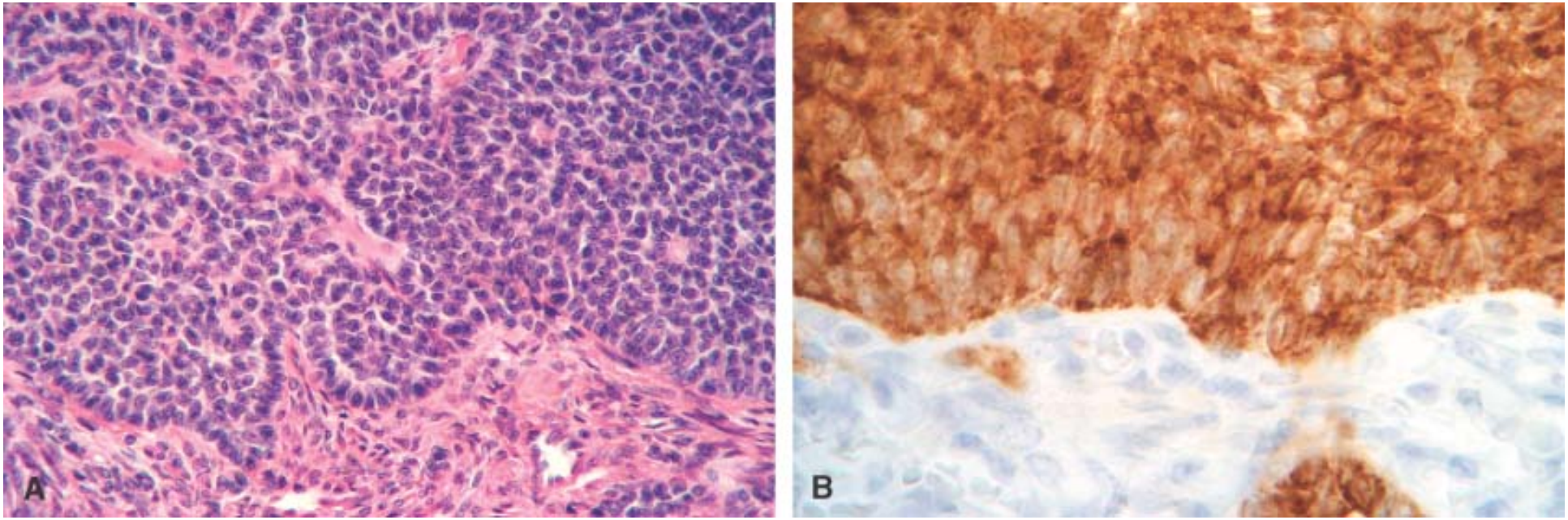


Figure 22-54 *A,* Thecoma-fibroma composed of plump, differentiated stromal cells with thecal appearance. *B,* Large bisected fibroma of the ovary apparent as a white, firm mass (*right*). The fallopian tube is attached.

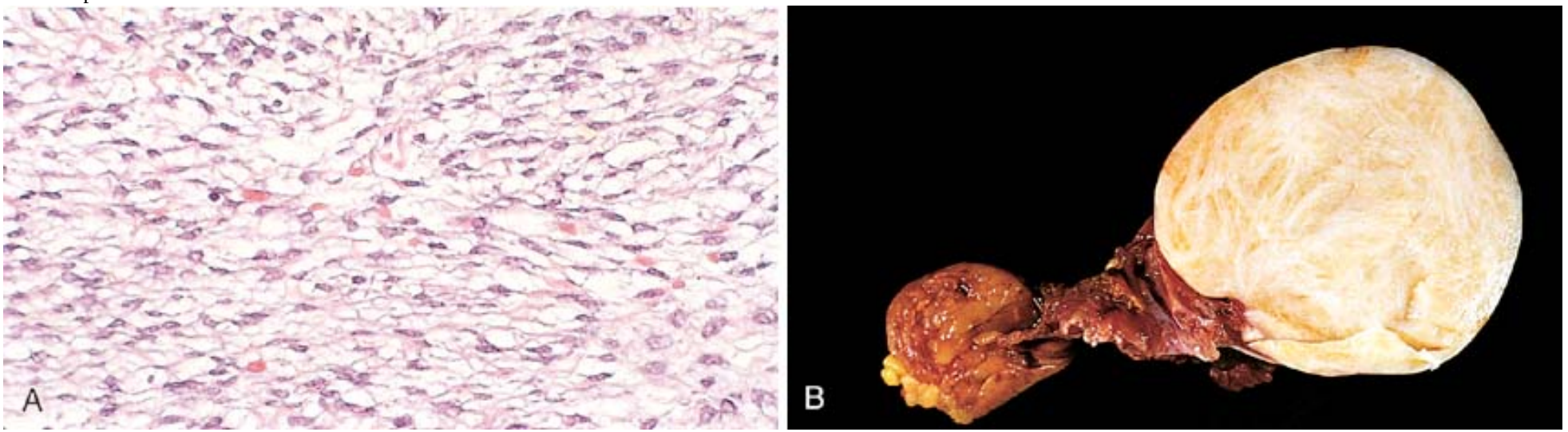


Figure 22-55 Sertoli cell tumor. *A,* Gross photograph illustrating characteristic golden yellow appearance of the tumor. *B,* Photomicrograph showing well-differentiated Sertoli cell tubules. *(Courtesy of Dr. William Welch, Brigham and Women's Hospital, Boston, MA.)*

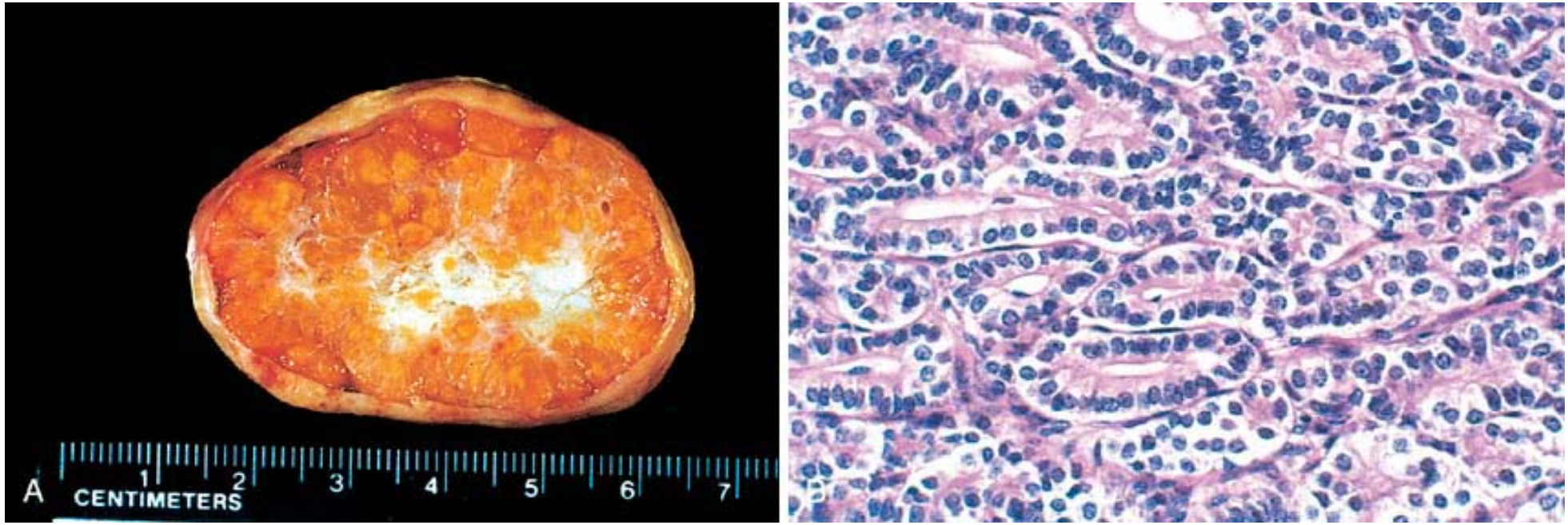


Figure 22-56 Potential sites for ectopic pregnancy, including the fallopian tube, ovary, cornu, and (rarely) abdominal viscera.

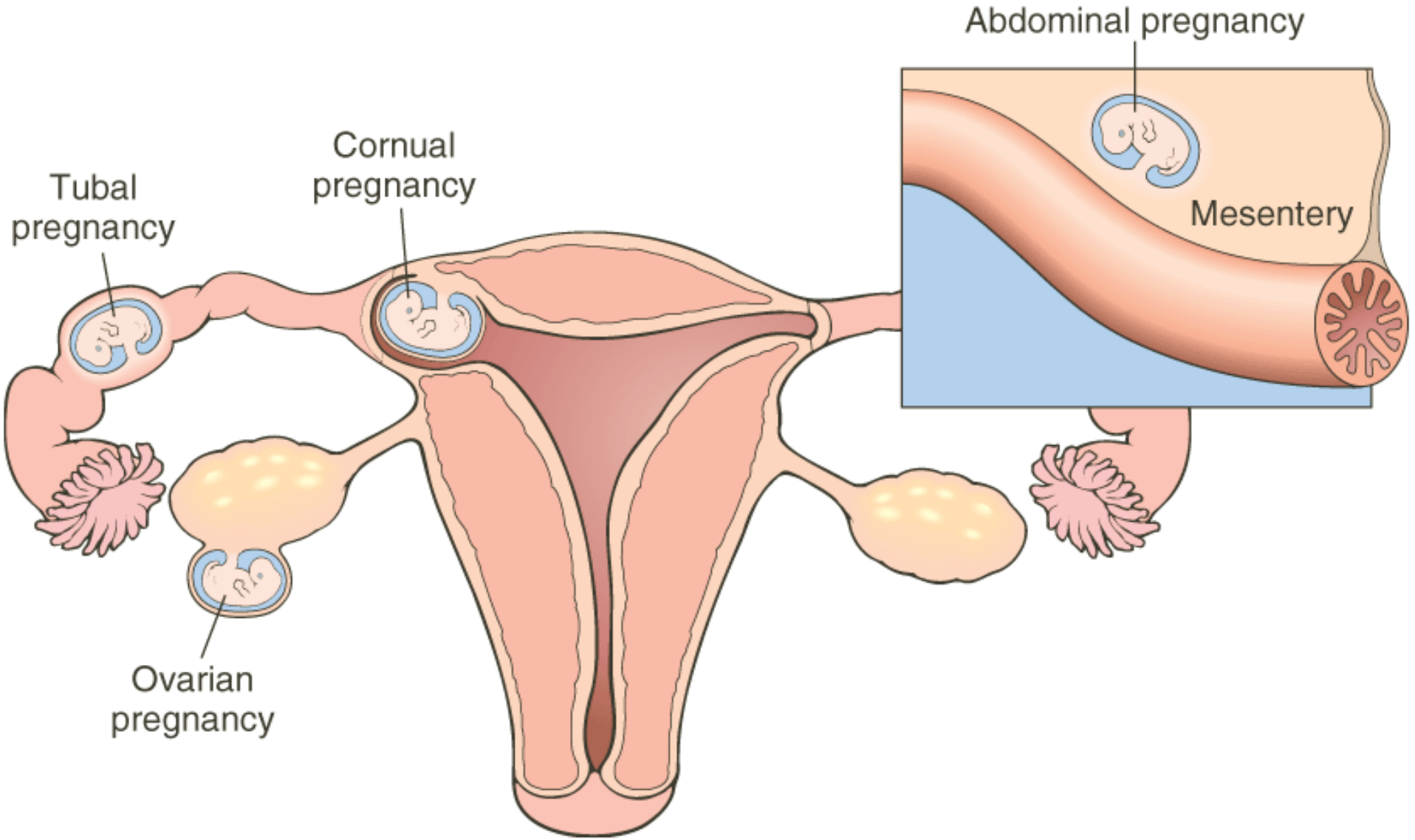
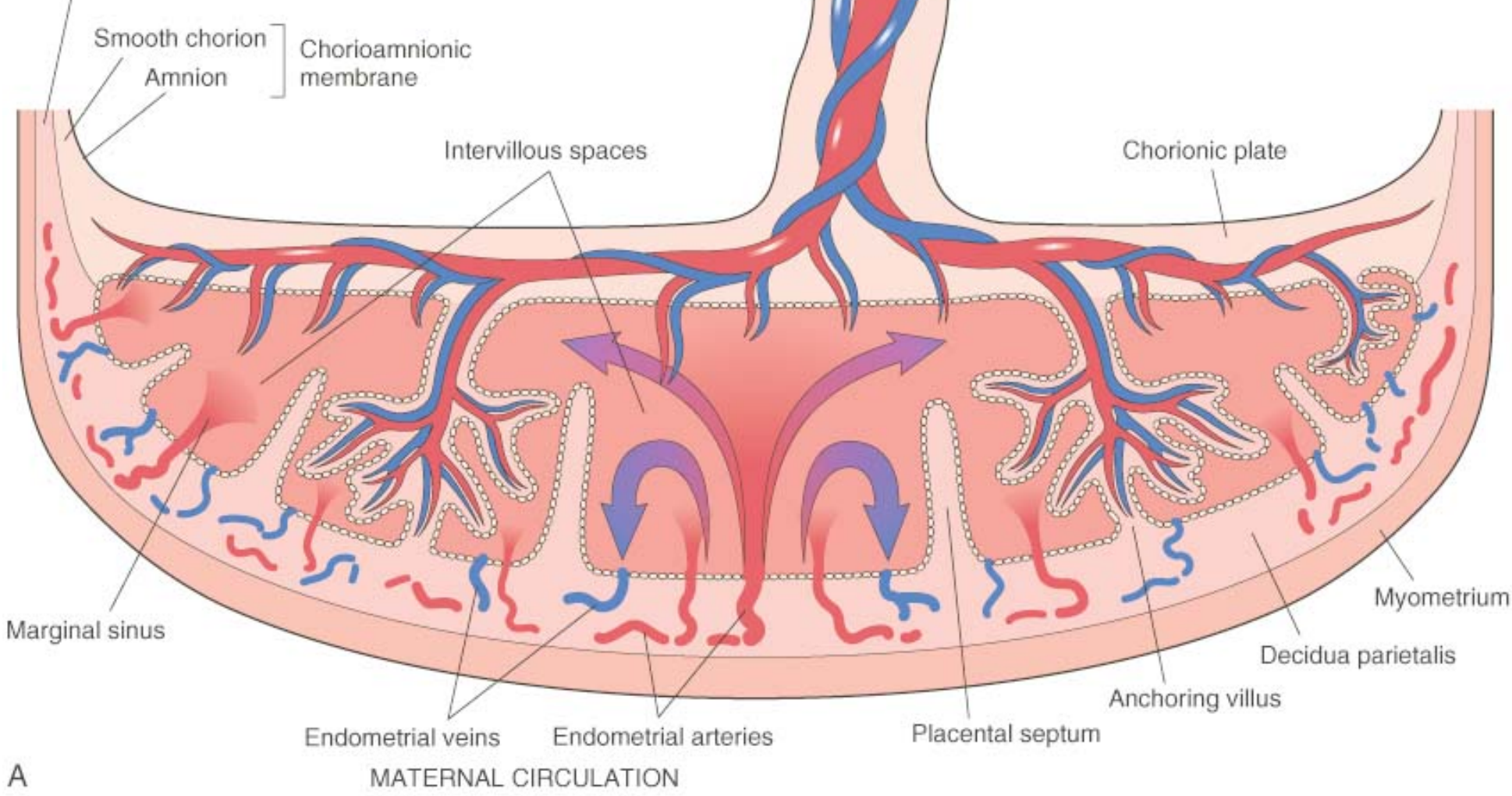
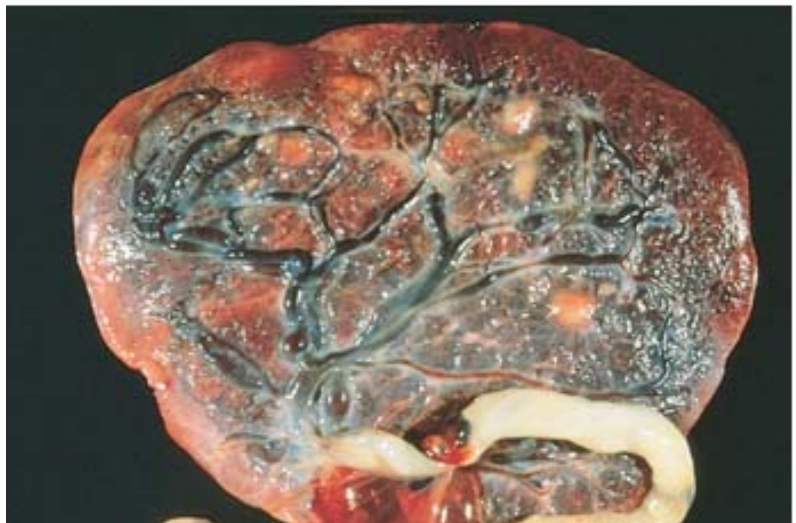


Figure 22-57 *A*, Diagram of placental anatomy. Within the outer boundary of myometrium is a layer of decidua, from which the maternal vessels originate and deliver blood to and from the intervillous spaces. Umbilical vessels branch and terminate in placental villi, where nutrient exchange takes place. *B*, Normal term placenta (fetal surface) with umbilical cord.


Smooth chorion
Amnion
Chorioamnionic membrane
Intervillous spaces
Chorionic plate
Marginal sinus
Myometrium
Decidua parietalis
Anchoring villus
Endometrial veins
Endometrial arteries
Placental septum
MATERNAL CIRCULATION

A



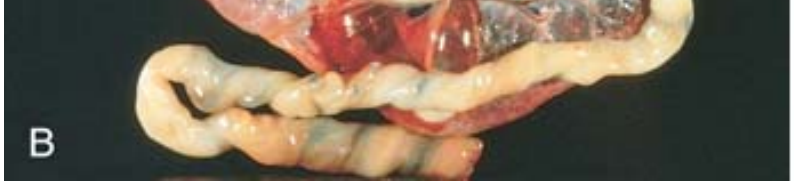


Figure 22-58 Diagrammatic representation of the various types of twin placentation and their membrane relationships. *(Adapted from Gersell D, et al: Diseases of the placenta. In Kurman, R (ed): Blaustein's Pathology of the Female Genital Tract. New York, Springer-Verlag, 1994.)*

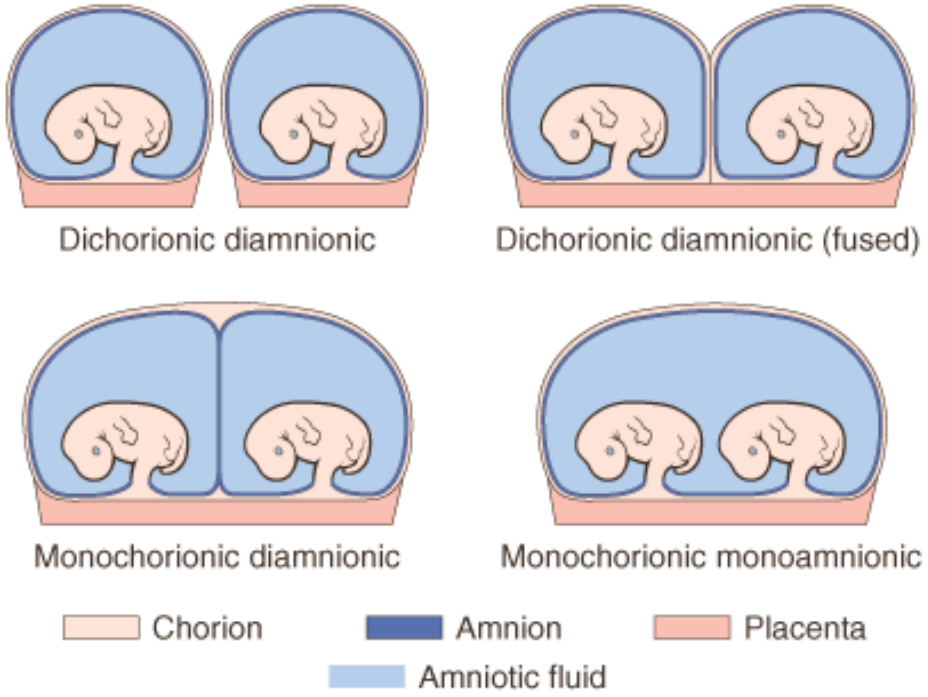


Figure 22-59 Twin-twin transfusion syndrome resulting in the death of both fetuses because of excessive (*left*) or deficient (*right*) blood volume.

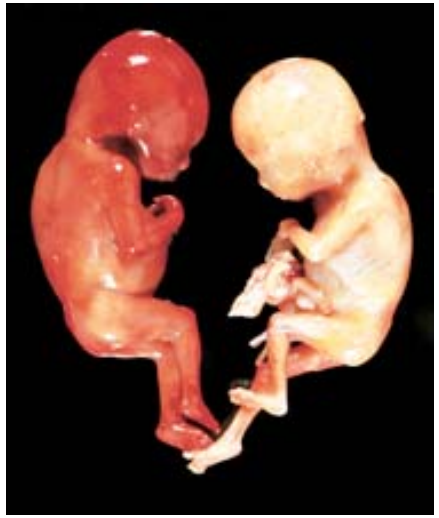
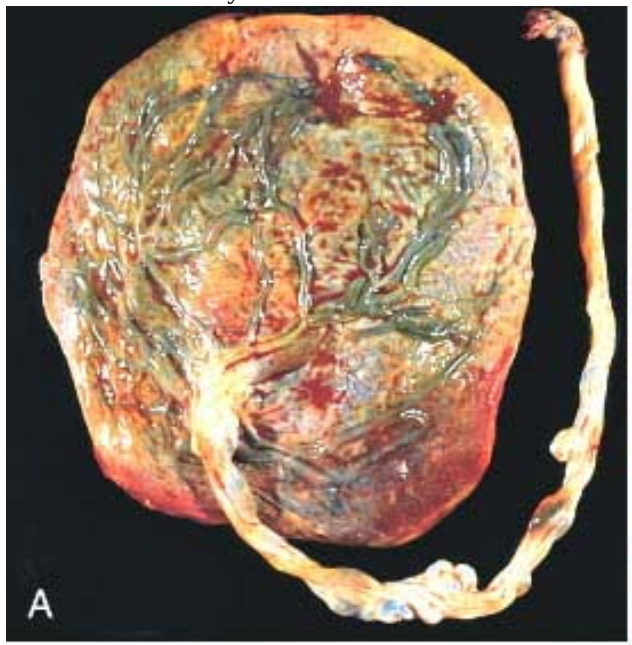
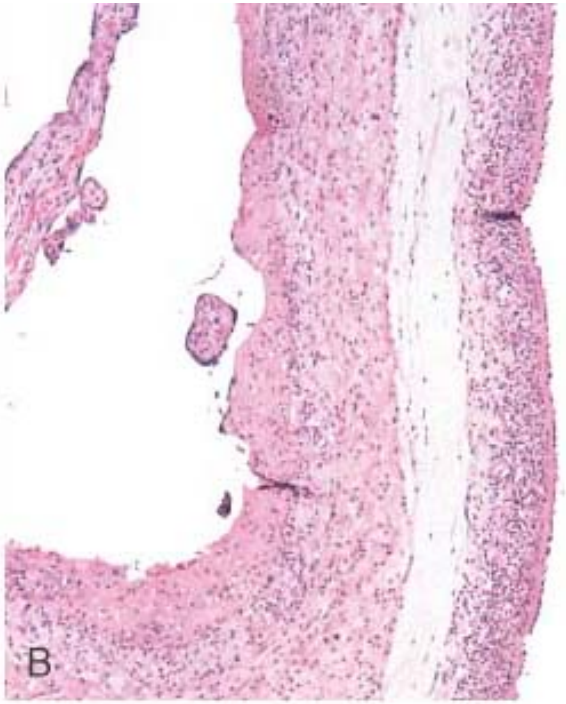


Figure 22-60 Placental infections derived from ascending and blood-borne routes. Acute chorioamnionitis. *A,* On gross examination, the placenta contains greenish opaque membranes. Compare with Figure 22-55*B* . *B,* A photomicrograph illustrates a dense band-like inflammatory exudate on the amniotic surface (*top*). *C,* Acute necrotizing intervillositis, from a fetal-maternal infection by listeria.





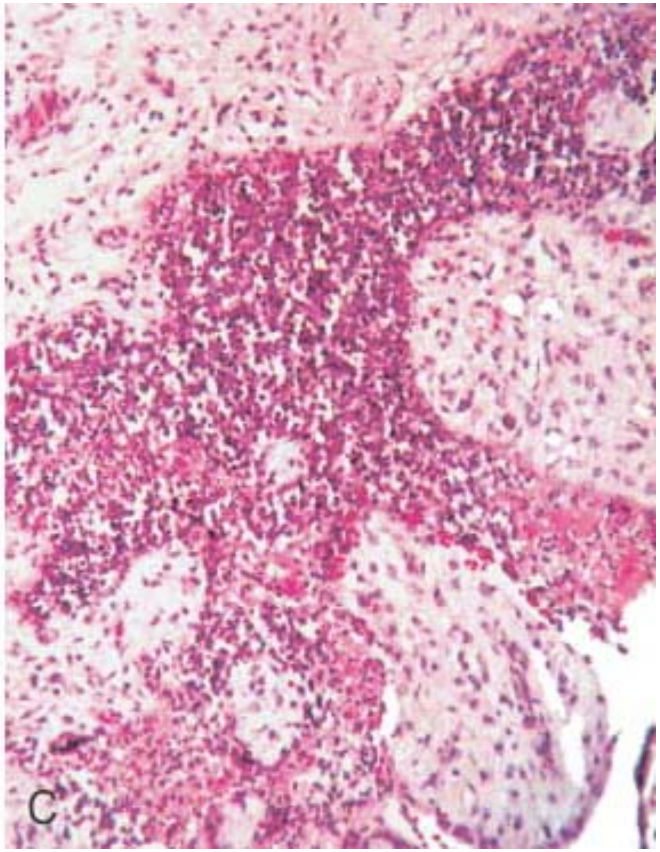


Figure 22-61 Proposed sequence of events in the pathogenesis of toxemia of pregnancy. The main features are (1) decreased uteroplacental perfusion; (2) increased vasoconstrictors and decreased vasodilators, resulting in local and systemic vasoconstriction; and (3) disseminated intravascular coagulation (DIC). *(Adapted from Friedman SA: Pre-eclampsia: a review of the role of prostaglandins. Obstet Gynecol 71:122, 1988. Reprinted by permission of the American College of Obstetricians and Gynecologists; and Khong TY, et al: Inadequate maternal vascular response to placentation in pregnancies complicated by pre-eclampsia and by small for gestational age infants. Br J Obstet Gynecol 93:1049, 1986.)*

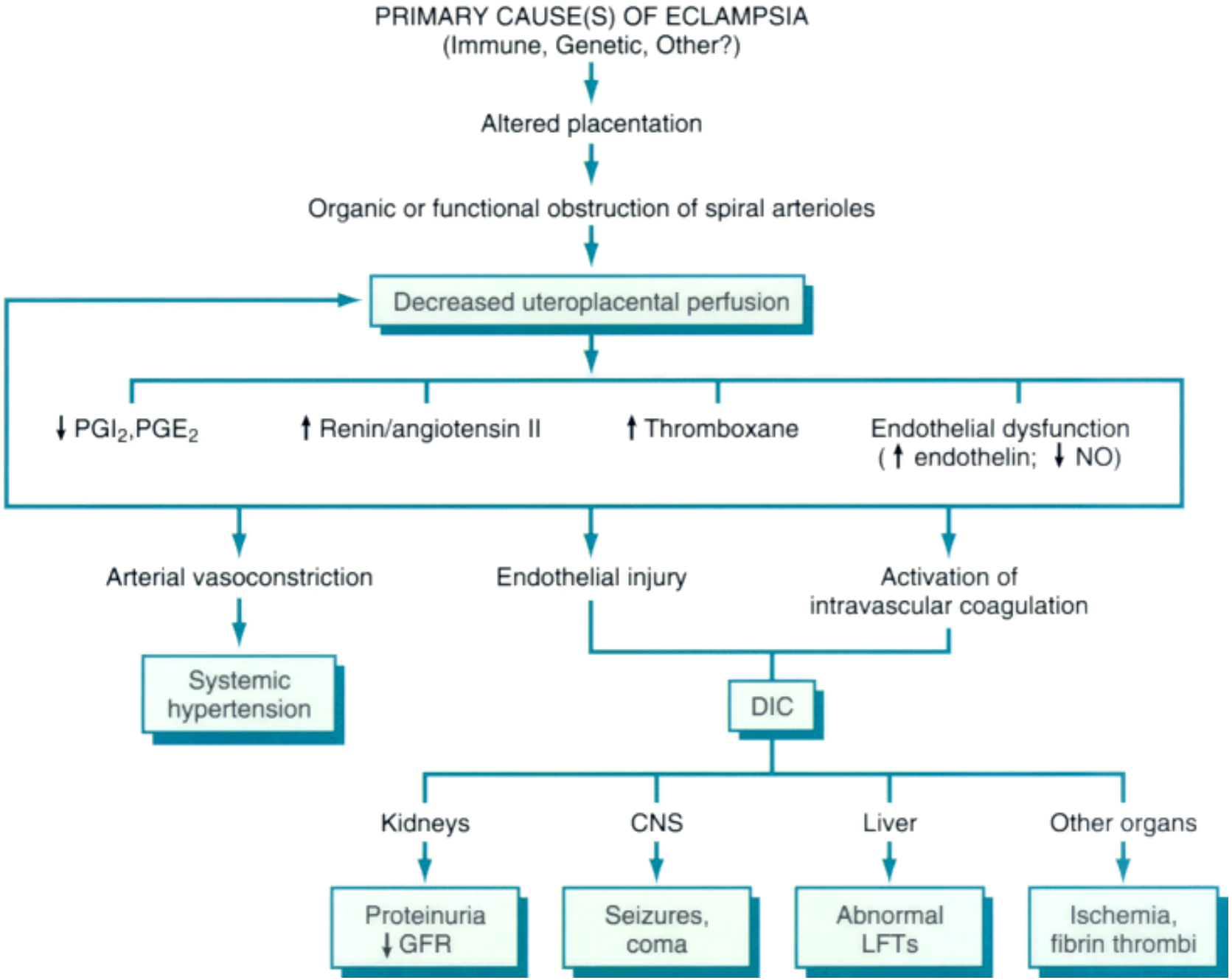


Figure 22-62 Acute atherosis of uterine vessels in eclampsia. Note fibrinoid necrosis of the vessel walls, subendothelial macrophages and perivascular lymphocytic infiltrate. *(Courtesy of Dr. Drucilla J. Roberts, Massachusetts General Hospital, Boston, MA.)*

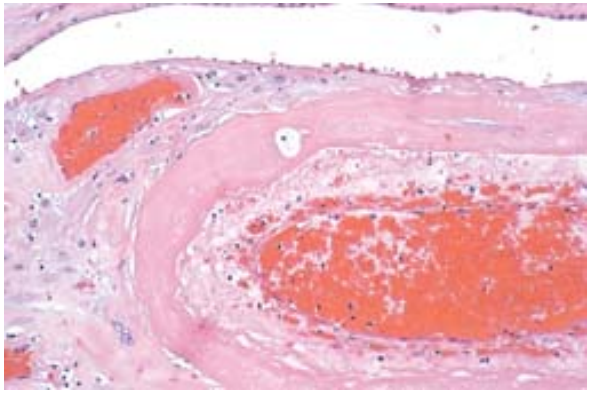


TABLE 22-5 -- Features of Complete Versus Partial Hydatidiform Mole

Feature	Complete Mole	Partial Mole
Karyotype	46,XX (46,XY)	Triploid
Villous edema	All villi	Some villi
Trophoblast proliferation	Diffuse; circumferential	Focal; slight
Atypia	Often present	Absent
Serum hCG	Elevated	Less elevated
HCG in tissue	++++	+
Behavior	2% choriocarcinoma	Rare choriocarcinoma

HCG, human chorionic gonadotropin.

Figure 22-63 Patterns of fertilization to account for chromosomal origin of complete (46,XX) and triploid partial moles (XXY). In a complete mole, one or two sperm fertilize an egg that has lost its chromosomes. Partial moles are due to fertilization of an egg by one diploid, or two haploid sperm, depicted in this example as one 23,X and one 23,Y.

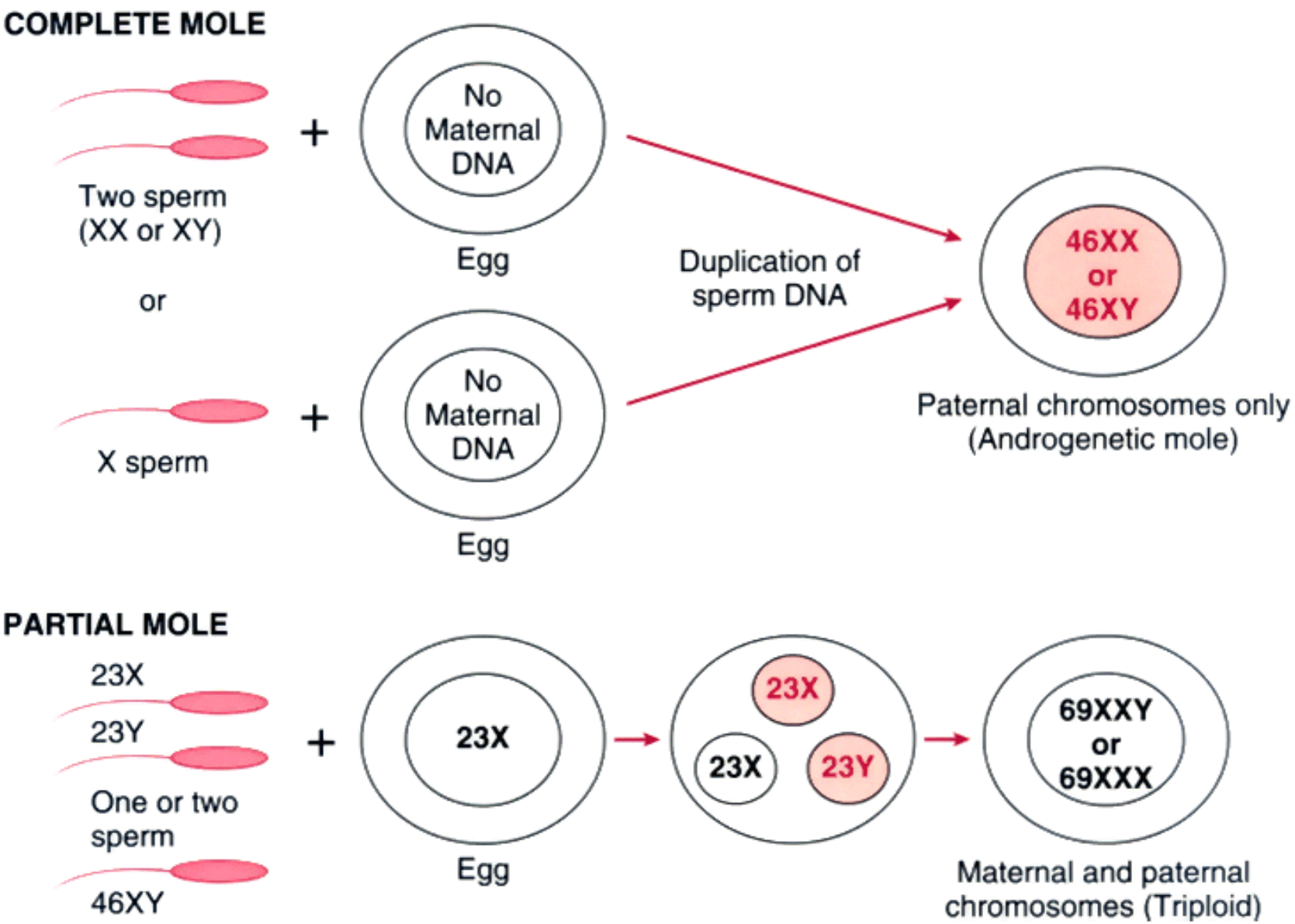


Figure 22-64 Complete hydatidiform mole suspended in saline showing numerous swollen (hydropic) villi.

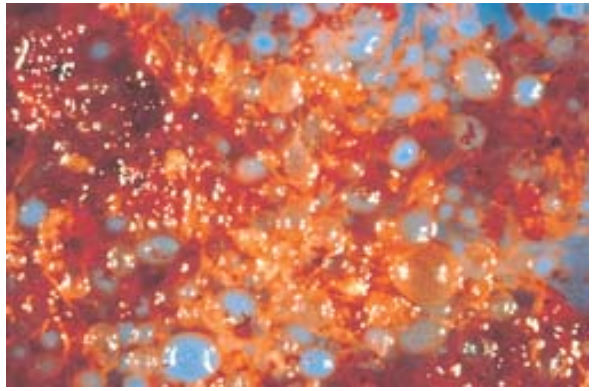


Figure 22-65 *A*, Photomicrograph of partial hydatidiform mole revealing swollen villi and slight hyperplasia of the surface trophoblast. *B*, Complete hydatidiform mole with extensive cytotrophoblastic hyperplasia (*lower field*) *(Courtesy of Dr. David R. Genest, Brigham and Women's Hospital, Boston, MA.). C*, Complete moles lack expression of *p57* in the cytotrophoblast (*arrowheads*) and villous stroma (*arrow*). *D*, Normal placenta immunostained for *p57* exhibits staining in both stromal (*arrows*) and cytotrophoblast (*arrowheads*) nuclei. *(Courtesy of Dr. Diego C. Castrillon, Brigham and Women's Hospital, Boston, MA.)*

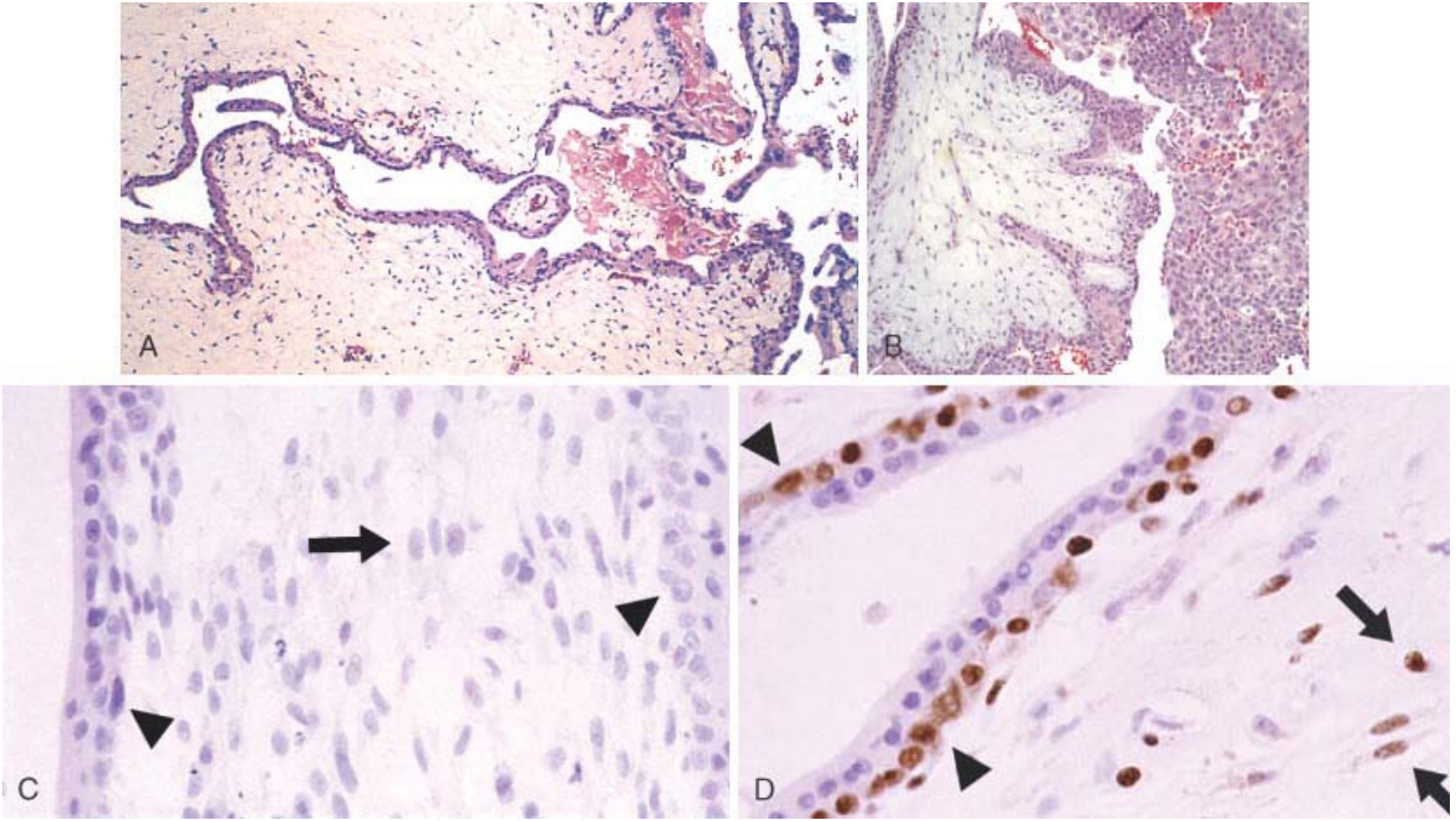


Figure 22-66 *A*, Invasive mole presenting as a hemorrhagic mass adherent to the uterine wall. *B*, On cross-section, the tumor invades into the myometrium. *(Courtesy of Dr. David R. Genest, Brigham and Women's Hospital, Boston, MA.)*

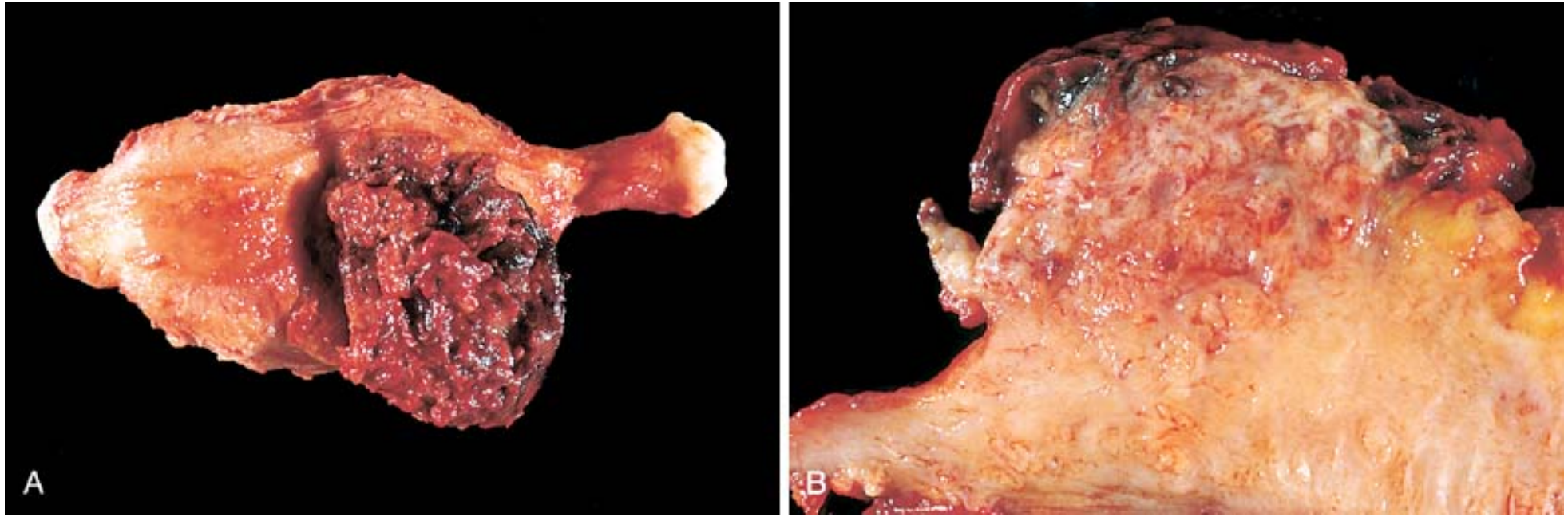


Figure 22-67 *A*, Choriocarcinoma presenting as a bulky hemorrhagic mass invading the uterine wall. *B*, Photomicrograph of choriocarcinoma illustrating both neoplastic cytotrophoblast and syncytiotrophoblast. *(Courtesy of Dr. David R. Genest, Brigham and Women's Hospital, Boston, MA.)*

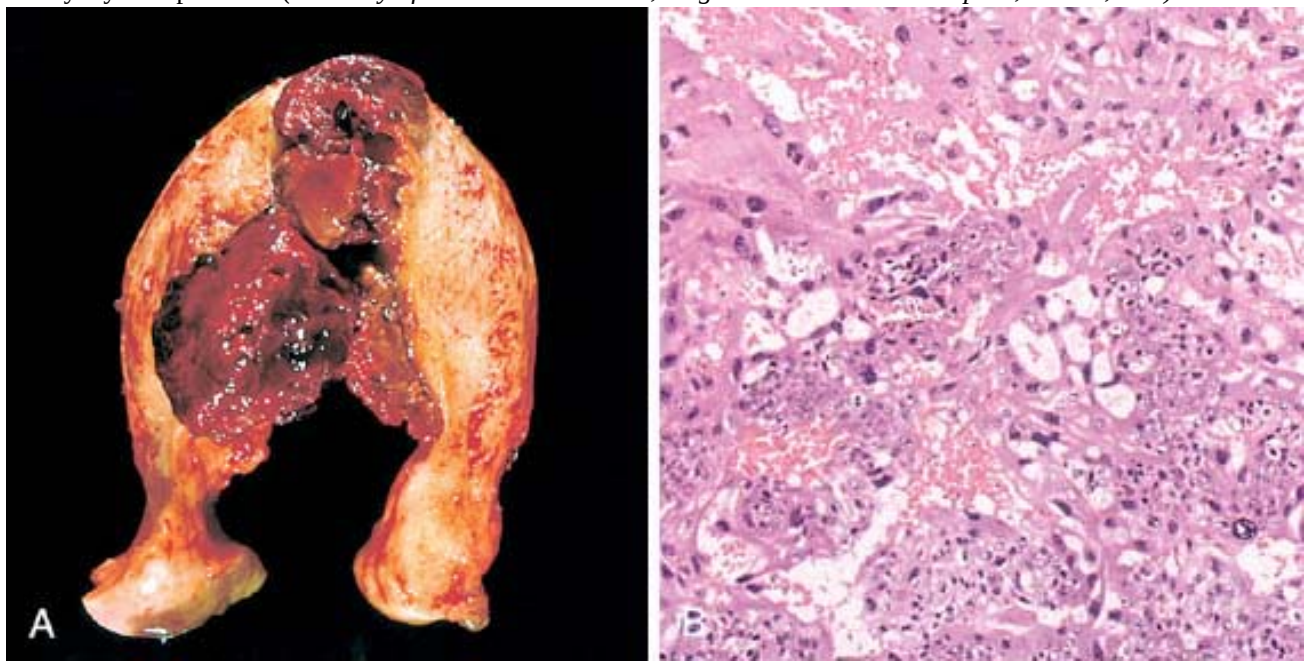
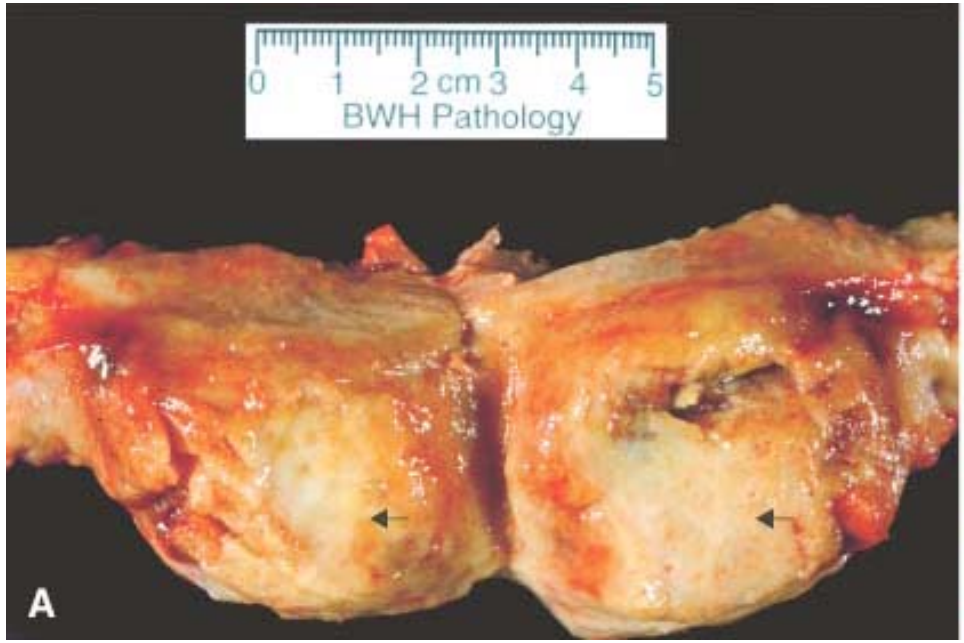
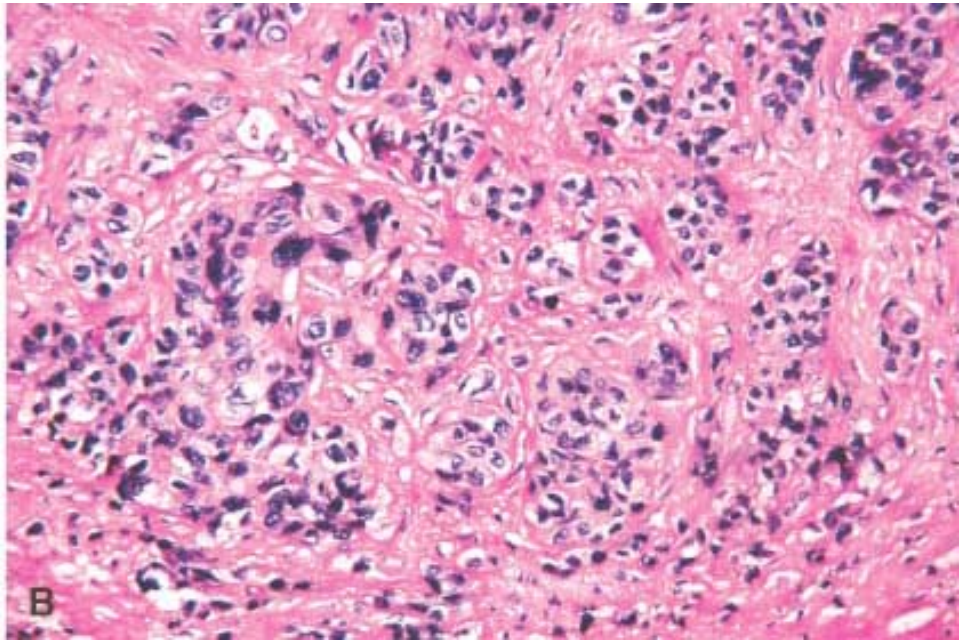


Figure 22-68 *A*, Placental site trophoblastic tumor, presenting as a discrete mass in the myometrium. *B*, Histology of PSTT. *(Courtesy of Dr. Bradley J. Quade, Brigham and Women's Hospital, Boston, MA.)*





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Chapter 23 - The Breast

Susan C. Lester MD, PhD

The Female Breast

Normal

The class Mammalia is remarkable for the evolution of modified skin appendages that provide complete nourishment and immunologic protection for the young. In humans, paired mammary glands rest on the pectoralis muscle on the upper chest wall. The breast is composed of specialized epithelium and stroma that give rise to both benign and malignant lesions specific to the organ (Fig. 23-1).

Six to ten major ductal systems originate at the nipple. The keratinizing squamous epithelium of the overlying skin continues into the ducts and then abruptly changes to a double-layered cuboidal epithelium. A small keratin plug is often found at the duct orifice. The surrounding areolar skin is pigmented and supported by smooth muscle.

Successive branching of the large ducts eventually leads to the terminal duct lobular unit (TDLU). In the adult woman, the terminal duct branches into a grapelike cluster of small acini to form a lobule (Fig. 23-1 and Fig. 23-2*B*). Each ductal system typically occupies over a quarter of the breast, and the systems extensively overlap each other. In some women, ducts extend into the subcutaneous tissue of the chest wall and into the axilla.

Figure 23-1 Normal breast anatomy and anatomical location of common breast lesions.

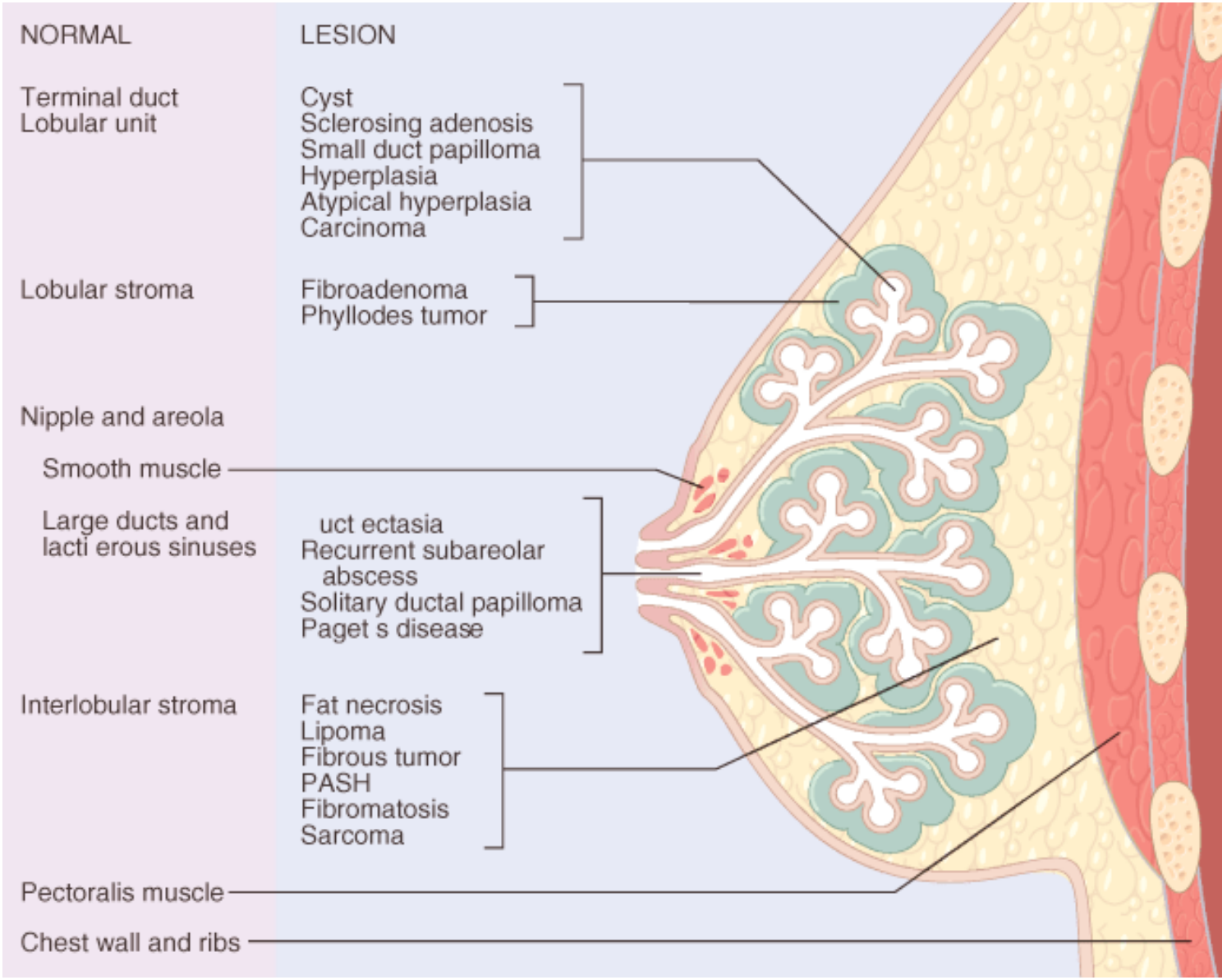

Figure 23-2 Lifecycle changes. *A*, Mammograms in young women are typically "dense" or white in appearance. In this setting, mass-forming lesions or calcifications can be difficult to detect. *(Courtesy of Dr. Darrell Smith, Brigham and Women's Hospital, Boston, MA.) B*, The density of a young woman's breast is due to the predominance of fibrous interlobular stroma and the paucity of adipose tissue (normally radiolucent or black). Prior to pregnancy, the terminal duct lobular units (TDLUs) are small and are invested by loose cellular intralobular stroma. Larger ducts interconnect the TDLUs. *C*, During pregnancy, branching of terminal ducts results in more numerous TDLUs, and the number of acini per TDLU increases. Luminal cells within TDLUs (but not the large duct system) undergo lactational change in preparation for milk production. *D*, With increasing age, the TDLUs decrease in size and number, and the interlobular stroma is replaced by adipose tissue. An older woman's breast typically consists of small ducts and atrophic lobules in adipose tissue. *E*, Mammograms become more radiolucent (darker) with age owing to the increase in adipose tissue. Radio-dense mass-forming lesions, and calcifications become easier to detect. *(Courtesy of Dr. Darrell Smith, Brigham and Women's Hospital, Boston, MA.)*

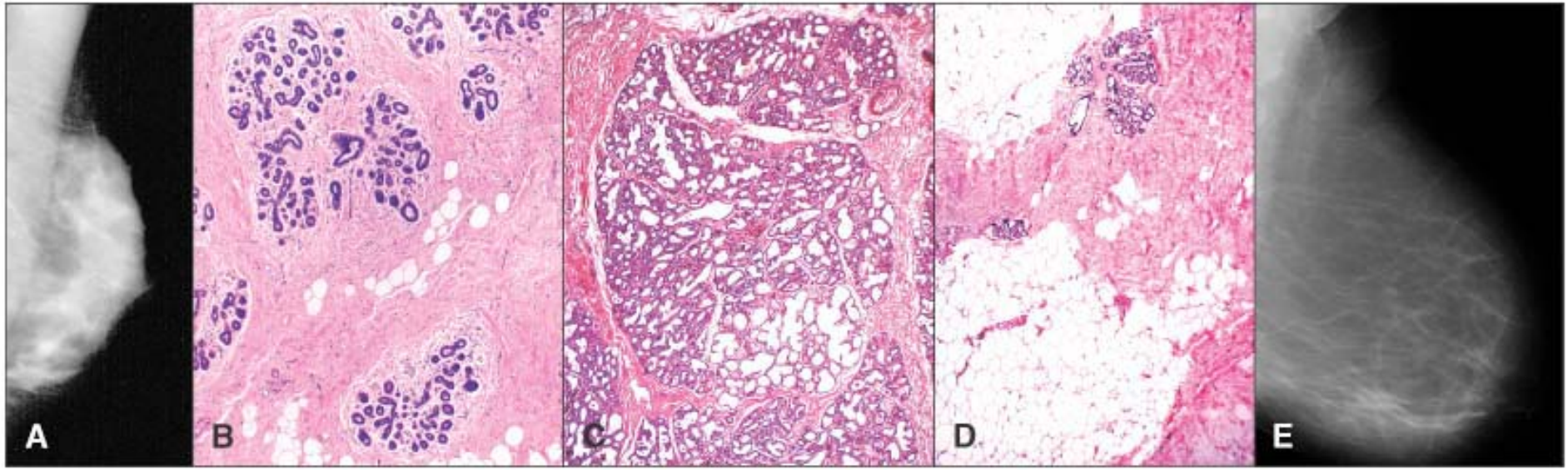

Figure 23-3 Common clinical presentations of breast disease. Over a 10-year period, 372 women over the age of 40 made 539 visits to a health maintenance organization for the listed breast symptoms.[9] Some women had more than one symptom and/or made more than one visit. In 10% of cases, the visit led to the performance of a biopsy.

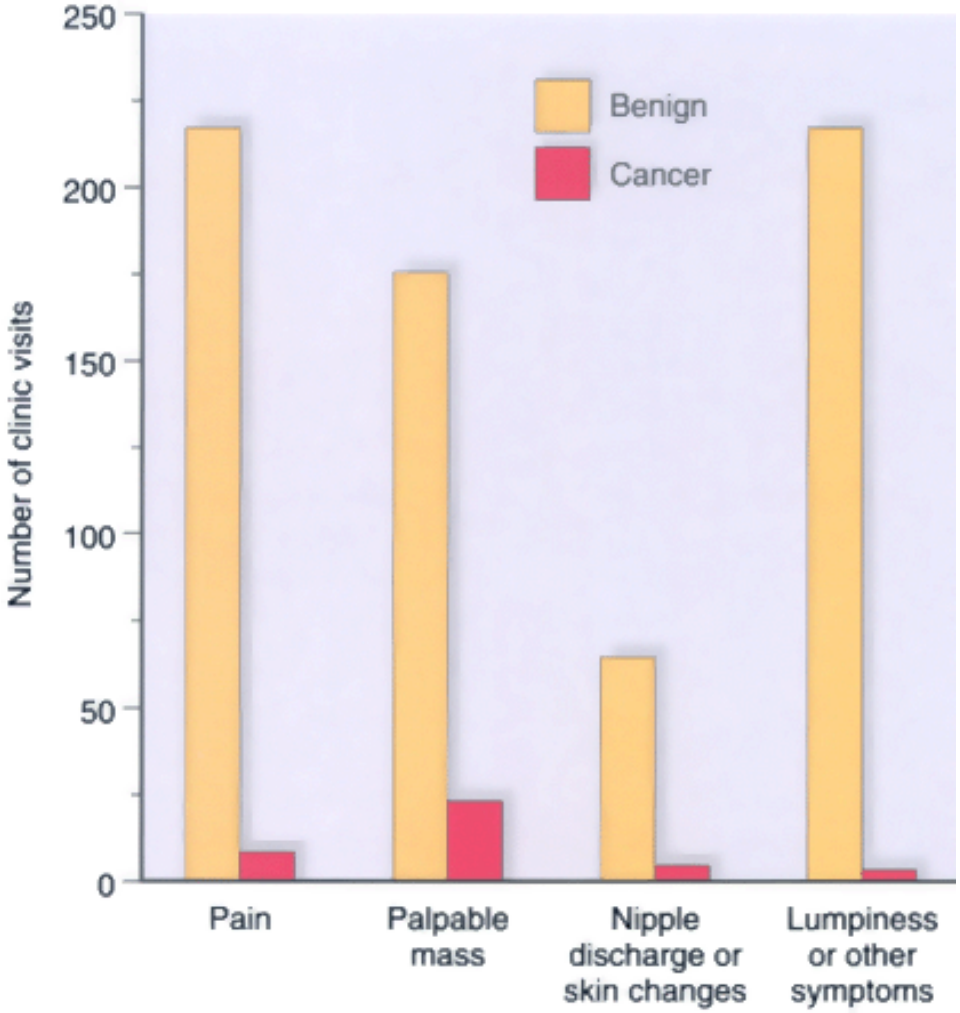

TABLE 23-1 -- Characteristics of Breast Carcinomas by Clinical Presentation

Clinical Presentation	Invasive Carcinoma (% of Carcinomas)	Average Size of Invasive Carcinomas	Carcinomas with Lymph Node Metastases	DCIS (% of Carcinomas)	LCIS (% of Carcinomas)
Palpable mass	94%	2.4 cm	58%	•2%	4%
Mammographic density	94%	1.1 cm	14%	•4%	2%
Mammographic calcifications	26%	0.6 cm	•6%	71%	3%
Based on the results of 235 carcinomas diagnosed in 914 women undergoing diagnostic biopsies at Brigham and Women's Hospital over a 6-month period in 2001.					
Mammographic lesions were nonpalpable.					
DCIS, ductal carcinoma in situ; LCIS, lobular carcinoma in situ.					

compared to 60% of masses in women over age 50 (Fig. 23-4). The most commonly encountered lesions are invasive carcinomas, fibroadenomas, and cysts. Approximately 50% of carcinomas arise in the upper outer quadrant, 10% in each of the remaining quadrants, and about 20% in the central or subareolar region.

Nipple discharge is a less common presenting symptom but is of concern when it is spontaneous and unilateral. A discharge produced by manipulating the breast is normal and unlikely to be associated with a pathologic lesion. A milky discharge (galactorrhea) is associated with increased production of prolactin (e.g., by a pituitary adenoma), hypothyroidism, or endocrine anovulatory syndromes. It can also occur in patients taking oral contraceptives, tricyclic antidepressants, methyldopa, or phenothiazines. Repeated nipple stimulation can also induce lactation (e.g., this method is sometimes used by women who wish to breast-feed adopted infants). Milky discharge has not been associated with malignancy. Bloody or serous discharges are most commonly associated with benign lesions but, rarely, can be due to a malignancy. A normal bloody discharge can also occur during pregnancy, possibly due to the rapid formation of new lobules. The risk of malignancy with discharge increases with age. Discharge is associated with carcinoma in 7% of women younger than 60 years and in 30% of women older than 60 years. The most common etiologies for discharge are a solitary large duct papilloma, cysts, or carcinoma (Fig. 23-4). Carcinomas presenting as nipple discharge not associated with a palpable mass are equally divided between invasive and in situ carcinomas.[10] There is considerable interest in developing the cytologic examination of induced nipple discharge into a screening test for breast cancer.

Mammographic screening was introduced in the 1980s as a means to detect small, nonpalpable breast carcinomas not associated with breast symptoms. The sensitivity and specificity of mammography increase with age. As the dense, fibrous interlobular tissue of the young woman is replaced by the fatty tissue of the older woman, it becomes easier to detect small masses and calcifications. Also, with increasing age, benign lesions become less frequent and malignant lesions become more frequent. Screening is generally recommended to start at age 40. Younger women usually undergo mammography only if they are at high risk for developing carcinoma, owing either to a prior palpable cancer or to a strong family history. Despite the screening of women at high risk of breast cancer, only 12% of mammographic lesions in women

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Figure 23-4 Frequency of benign and malignant breast lesions diagnosed after biopsy by clinical presentation and age. *(Based on 914 women who underwent diagnostic breast surgery at Brigham and Women's Hospital, Boston, from January to June 2001.)*

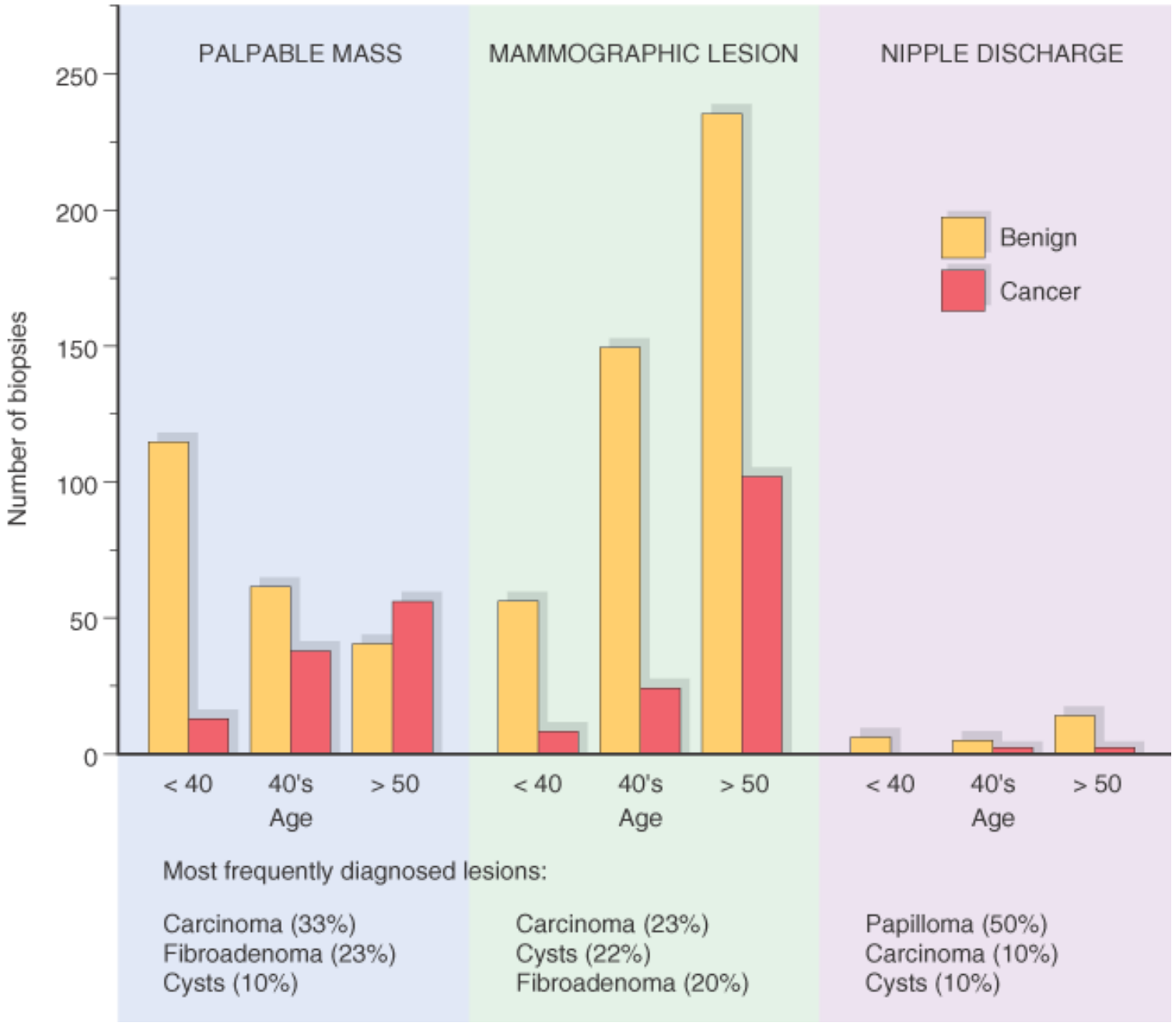

Figure 23-5 Recurrent subareolar abscess. When squamous metaplasia extends deep into a duct, keratin becomes trapped and accumulates. If the duct ruptures, the ensuing intense inflammatory response to keratin results in an erythematous painful mass. A fistula tract may burrow beneath the smooth muscle of the nipple to open at the edge of the areola.

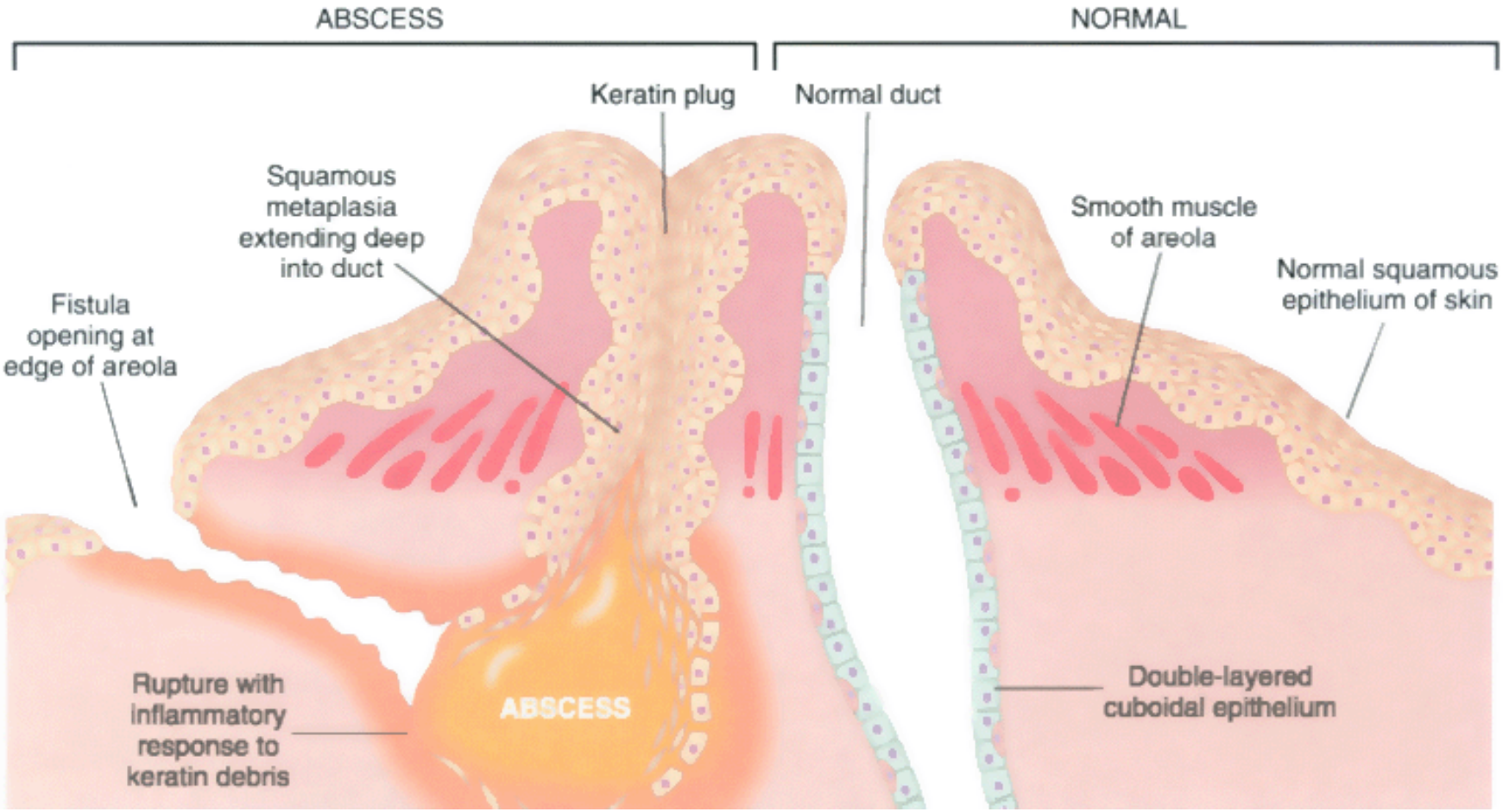

Figure 23-6 Mammary duct ectasia. Chronic inflammation and fibrosis surround an ectatic duct filled with inspissated debris. The fibrotic response can mimic the irregular shape of malignant carcinomas on palpation or mammogram.

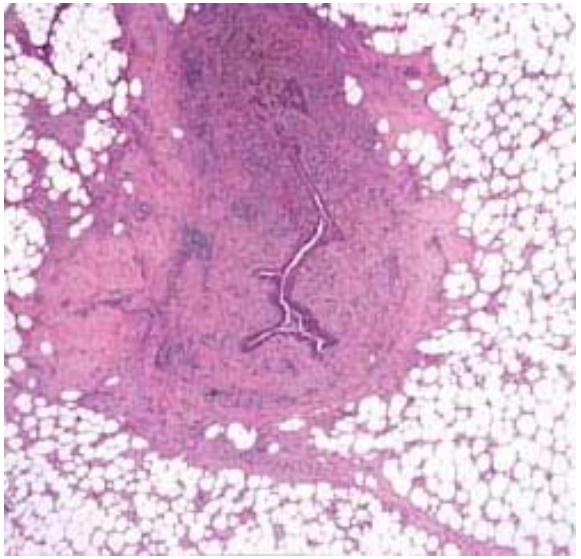

Figure 23-7 Apocrine cysts. Cells with round nuclei and abundant granular eosinophilic cytoplasm, resembling the cells of normal apocrine sweat glands, line the walls of a cluster of small cysts. Secretory debris, frequently with calcifications, is often present. Groups of cysts are common findings associated with clustered mammographic calcifications.

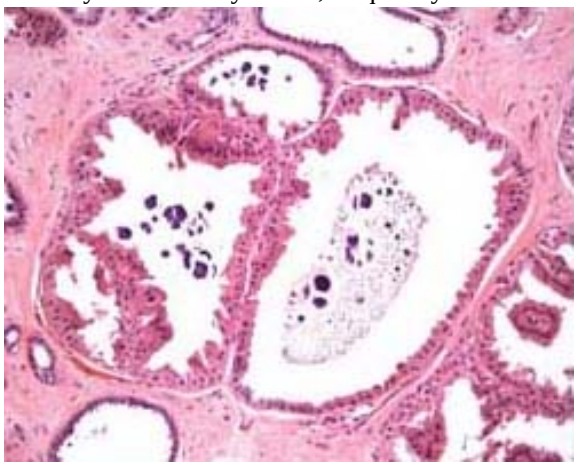

Figure 23-8 *A*, Normal. A normal duct or acinus has a single basally located myoepithelial cell layer (cells with dark, compact nuclei and scant cytoplasm) and a single luminal cell layer (cells with larger open nuclei, small nucleoli, and more abundant cytoplasm). *B*, Epithelial hyperplasia. The lumen is filled with a heterogeneous population of cells of different morphologies, often including both luminal and myoepithelial cell types. Irregular slitlike fenestrations are prominent at the periphary.

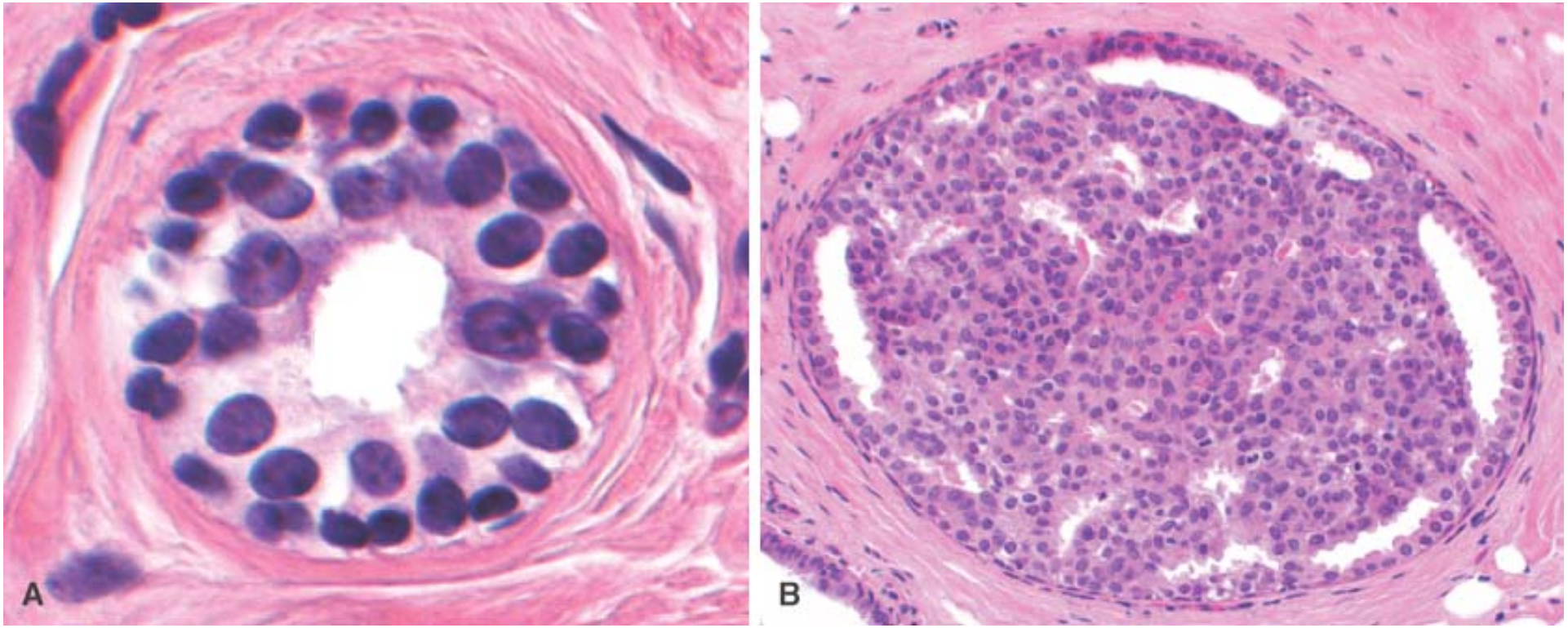

Figure 23-9 Sclerosing adenosis. The involved terminal duct lobular unit is enlarged, and the acini are compressed and distorted by the surrounding dense stroma. Calcifications are often present within the lumens. Although this lesion is frequently mistaken for an invasive carcinoma, unlike carcinomas, the acini are arranged in a swirling pattern, and the outer border is usually well circumscribed.

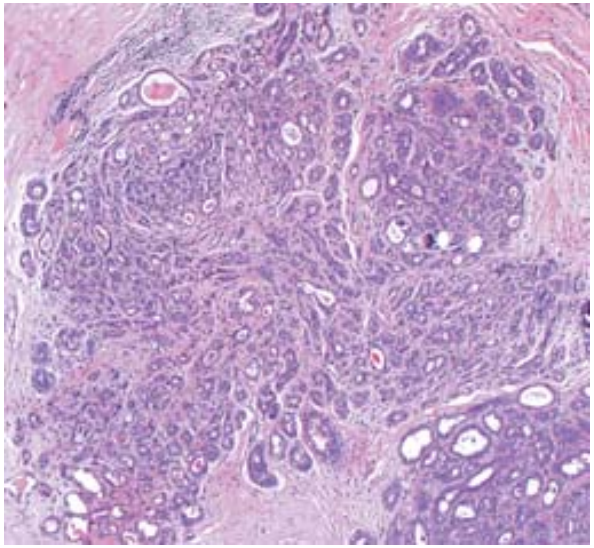

Figure 23-10 Complex sclerosing lesion (radial scar). There is a central nidus consisting of small tubules entrapped in a densely fibrotic stroma surrounded by radiating arms of epithelium

with varying degrees of cyst formation and hyperplasia. These lesions typically present as an irregular mammographic density and closely mimic an invasive carcinoma.

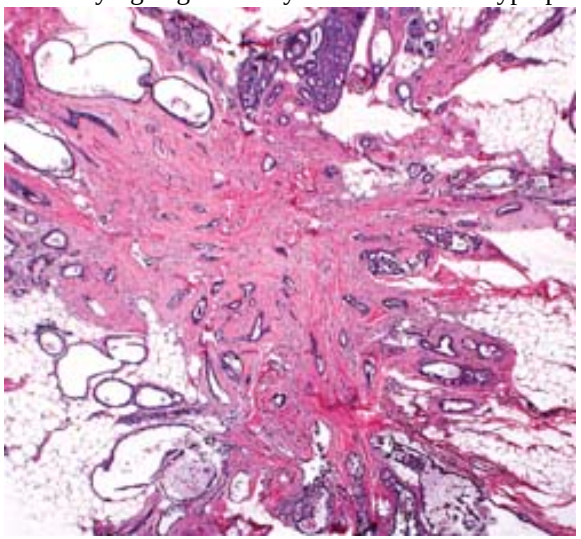

Figure 23-11 Intraductal papilloma. A central fibrovascular core extends from the wall of a duct. The papillae arborize within the lumen and are lined by myoepithelial and luminal cells.

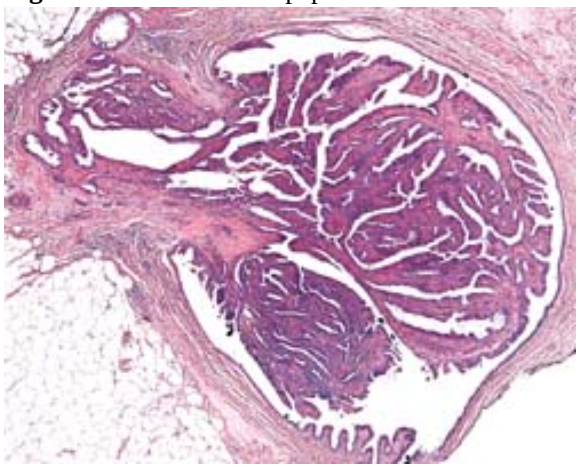

Figure 23-12 *A,* Atypical ductal hyperplasia. A duct is filled with a mixed population of cells consisting of oriented columnar cells at the periphery and more rounded cells within the central portion. Although some of the spaces are round and regular, the peripheral spaces are irregular and slitlike. These features are highly atypical but fall short of a diagnosis of DCIS. *B,* Atypical lobular hyperplasia. A population of monomorphic small, rounded, loosely cohesive cells partially fill a lobule. Some intracellular lumina can be seen. Although the cells are morphologically identical to the cells of LCIS, the extent of involvement is not sufficient for this diagnosis.

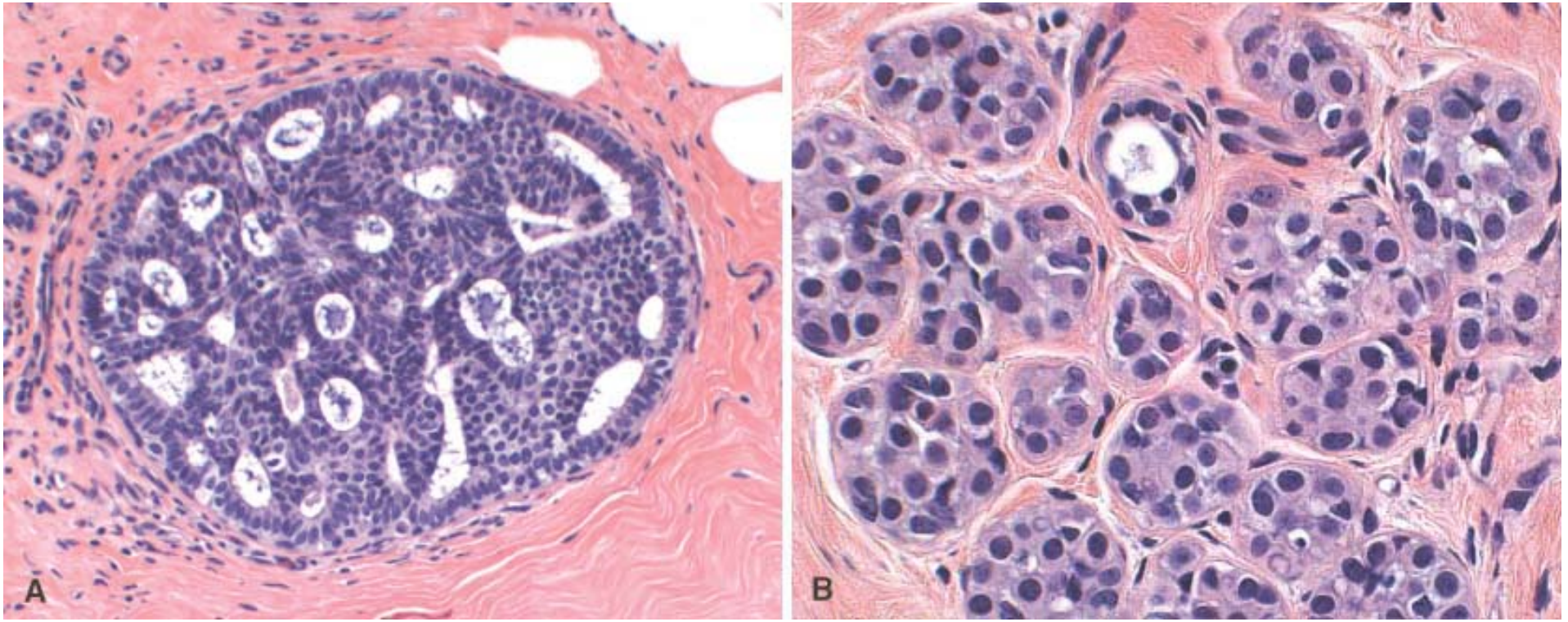

TABLE 23-2 -- Breast Lesions and Relative Risk of Developing Invasive Carcinoma

Pathologic Lesion	Relative Risk of Developing Invasive Carcinoma	Breast at Risk	Modifiers of Risk
Nonproliferative Breast Changes	1.0	Neither	
Duct ectasia			
Cysts			
Apocrine change			
Mild hyperplasia			
Adenosis			
Fibroadenoma without complex features			
Proliferative Disease Without Atypia	1.5–2.0	Both breasts	Increased risk if there is a family history of breast carcinoma
Moderate or florid hyperplasia			Decreased risk 10 years after biopsy
Sclerosing adenosis			
Papilloma			

Complex sclerosing lesion (radial scar)			
Fibroadenoma with complex features			
Proliferative Disease with Atypia	4.0–5.0	Both breasts	Increased risk if there is a family history of breast carcinoma
Atypical ductal hyperplasia			Increased risk if premenopausal
Atypical lobular hyperplasia			Decreased risk 10 years after biopsy for ALH
Carcinoma in Situ	8.0–10.0		
Lobular carcinoma in situ		Both breasts	Treatment (tamoxifen, bilateral mastectomy)
Ductal carcinoma in situ *		Ipsilateral breast	Treatment (tamoxifen, surgery to eradicate the lesion, radiation therapy)

*This risk applies to low-grade DCIS originally misdiagnosed as benign disease and followed without treatment. The risk for progression of high-grade DCIS is presumed to be greater than this.

INCIDENCE AND EPIDEMIOLOGY

After remaining constant for many years (except for a transient rise in 1974 attributed to increased awareness after the publicity surrounding Betty Ford and Happy Rockefeller developing breast cancer), the incidence of breast cancer

Figure 23-13 Breast cancer incidence and mortality rates for women over 50 years of age. Rates are per 100,000 women and are age-adjusted to the 2000 U.S. standard million population. *(SEER Cancer Statistics Review 1973–1999; http://seer.cancer.gov/.)*

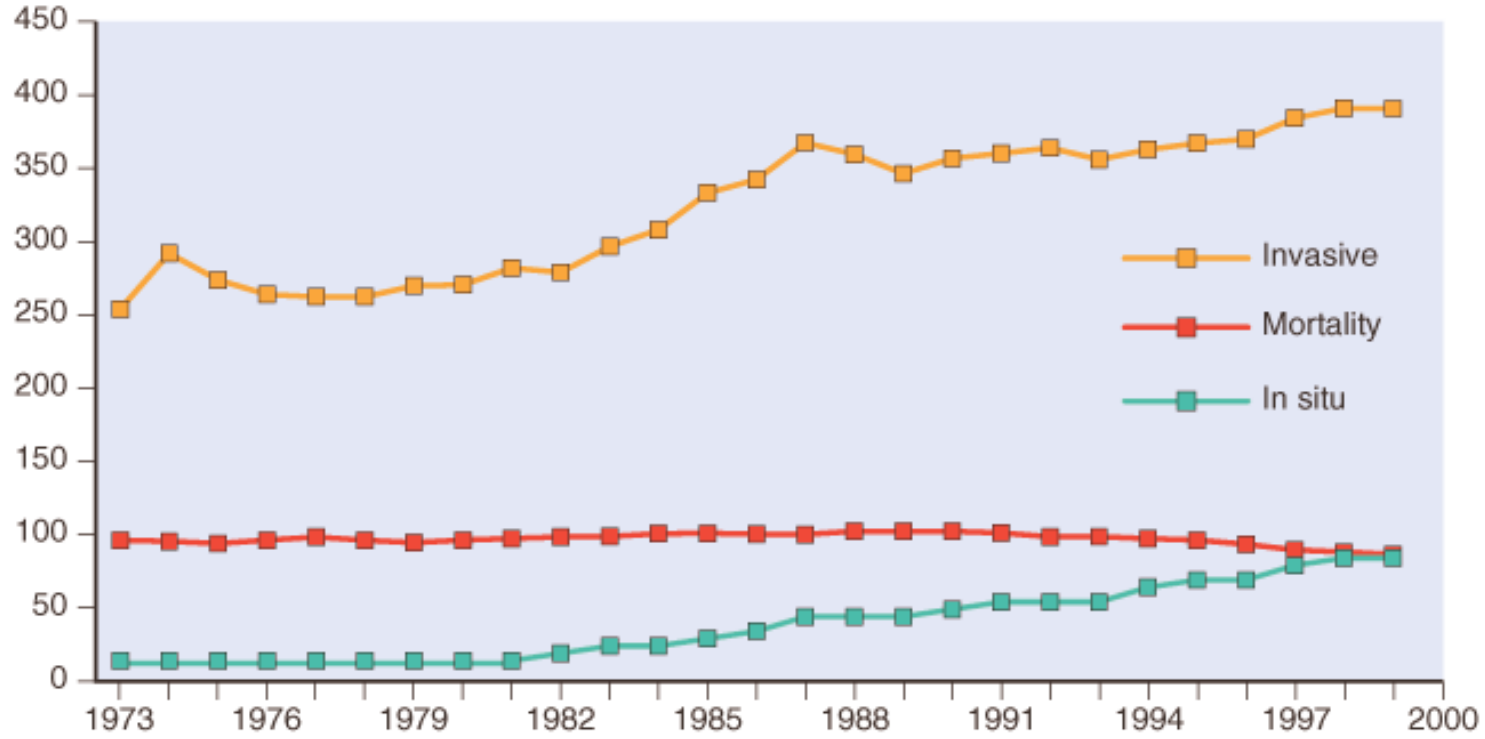

Figure 23-14 Change in stage of breast cancer at presentation from 1983 to 1996. *(SEER Cancer Statistics Review, http://seer.cancer.gov/.)*

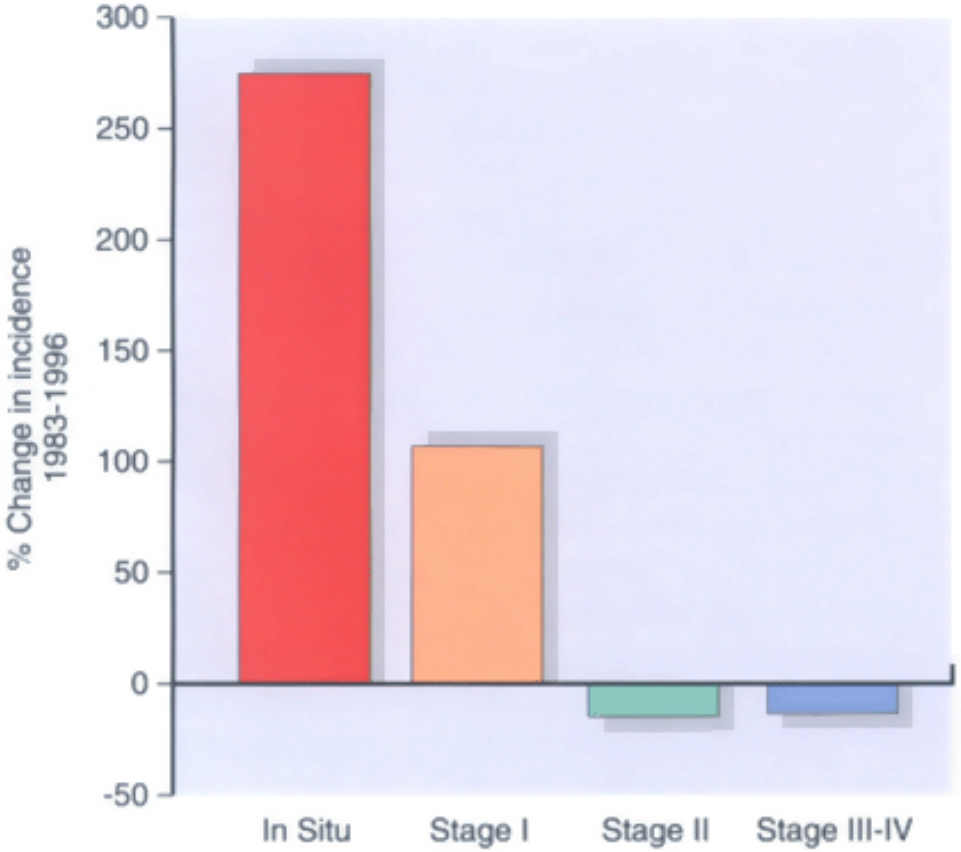

TABLE 23-3 -- *BRCA1* and *BRCA2*

	BRCA1	***BRCA2***
Chromosome	17q21	13q12.3
Gene size	81 kb	84 kb
Protein size	1863 amino acids	3418 amino acids
Function	Tumor suppressor	Tumor suppressor
	Transcriptional regulation	Transcriptional regulation
	Role in DNA repair	Role in DNA repair
Mutations	>500 identified	>300 identified
Mutations in population	about 0.1%	about 0.1%
Risk of breast cancer	60–80%	60–80%
Age at onset	Younger age (40s to 50s)	50 years

Families with breast cancer due to a single gene (%)	52%	32%
Families with breast and ovarian cancer (%)	81% (20–40% risk)	14% (10–20% risk)
Families with male and female breast cancer	<20%	76%
Risk of other tumors (varies with specific mutation)	Prostate, colon, pancreas	Prostate, pancreas, stomach, melanoma, colon
Mutations in sporadic breast cancer	Very rare (<5%)	Very rare (<5%)
Epidemiology	Specific mutations are found in certain ethnic groups	Specific mutations are found in certain ethnic groups
Pathology of breast cancers	Greater incidence of medullary carcinomas (13%), poorly differentiated carcinomas, ER-, PR-, and *Her2/neu*-negative carcinomas, carcinomas with *p53* mutations	Similar to sporadic breast cancers
Additional information about these genes can be found at http://www.ncbi.nlm.nih.gov/.		

cancer, and cataracts. Current clinical trials are attempting to identify other selective estrogen receptor modulators (SERMs) that have the same benefit but fewer side effects.

ETIOLOGY AND PATHOGENESIS

The major risk factors for the development of breast cancer are hormonal and genetic (family history). Breast carcinomas can, therefore, be divided into sporadic cases, possibly related to hormonal exposure, and hereditary cases, associated with family history or germ-line mutations. Hereditary carcinoma has received intense scrutiny in the hopes that the specific genetic mutations can be identified and that these alterations will illuminate the causes of all breast cancer. Recent studies have borne out these hopes. We begin our discussion with hereditary breast cancer and follow with sporadic breast cancer.

Hereditary Breast Cancer

A family history of breast cancer in a first-degree relative is reported in 13% of women with the disease.[21] However, only 1% of women have multiple affected relatives, a history suggestive of a highly penetrant germ-line mutation.

About 25% of familial cancers (or around 3% of all breast cancers) can be attributed to two highly penetrant autosomaldominant genes: BRCA1 and BRCA2 (Table 23-3). The probability of breast cancer associated with a mutation in these genes increases if there are multiple affected first-degree relatives, if individuals are affected before menopause and/or

have multiple cancers, if there is a case of male breast cancer, or if family members also develop ovarian cancer. The general lifetime breast cancer risk for female carriers is 60% to 85%, and the median age at diagnosis is about 20 years earlier compared to women without these mutations. The penetrance (i.e., the number of carriers who actually develop breast cancer) can vary with the specific type of mutation present. Mutated *BRCA1* also markedly increases the risk of developing ovarian carcinoma, which is as high as 20% to 40%. *BRCA2* confers a smaller risk for ovarian carcinoma (10% to 20%) but is associated more frequently with male breast cancer. *BRCA1* and *BRCA2* carriers are also susceptible to other cancers, such as colon, prostate, and pancreas, but to a lesser extent.

Although BRCA1 and BRCA2 do not show sequence homology, they function in similar pathways and interact with the same multiprotein complexes. Both act as tumor suppressors, as it is a loss of function that confers the risk of malignancy. A wide variety of functions have been suggested for these proteins, including transcriptional regulation, cell-cycle control, ubiquitin-mediated protein degradation pathways, and chromatin remodeling. A key function for both appears to be their role in protecting the genome from damage by halting the cell cycle and promoting DNA damage repair in a complex process that is not yet fully understood. BRCA1 is phosphorylated in response to damage and may transduce DNA damage signals from checkpoint kinases to effector proteins. BRCA1 is also bound with BRCA2 and RAD51 in a nuclear dot complex—presumably the site of DNA repair.[33] BRCA2 can bind directly to DNA and functions in homologous recombination for the error-free repair of double-strand DNA breaks.[34] Why loss of these functions specifically affects the breast is unclear. Perhaps the intermittent proliferation of breast epithelium (as opposed to the constitutive proliferation of other epithelia such as colon or skin) makes this organ more susceptible to the accumulation of genetic damage, or possibly, other cell types have additional mechanisms for DNA repair that the breast lacks. BRCA1, but not BRCA2, interacts with the ER and is involved in X chromosome inactivation—two features that may be related to its gender-specific risk.[35] Interestingly, male breast cancers are markedly increased only in families carrying *BRCA2* mutations.

Both genes have a total length of over 80 kb, and hundreds of different mutations distributed throughout the coding region have been reported for each one. The frequency of mutations is only 0.1% to 0.2% in the general population. Some mutations diminish the function of the genes and increase cancer risk, whereas others might be unimportant sequence variants. Genetic testing is difficult and often inconclusive unless several family members are affected or unless the individual belongs to an ethnic group with a known high incidence of specific mutations. [36] For example, people of Ashkenazi Jewish descent have a 2% to 3% risk of three specific mutations. Identification of carriers of clinically significant mutations is important, as prophylactic mastectomy and/or oophorectomy can reduce the risk of cancer mortality. [31] [37] [38]

In hereditary carcinomas, one mutant *BRCA* allele is inherited, and the second allele is inactivated by somatic mutation. Although *BRCA1* and *BRCA2* mutations are rarely found in sporadic tumors, about 50% of such tumors have decreased or absent expression of BRCA1. In most cases, this is accomplished by a combination of loss of heterozygosity (LOH) and methylation of the promoter to inactivate both alleles. [39] Hypermethylation of the promoter is detected in 13% of unselected carcinomas but is more common in medullary carcinomas (67% of tumors) and mucinous carcinomas (55% of tumors)—histologic subtypes that are more commonly found in *BRCA1* carriers. A similar mechanism has not yet been described for *BRCA2*.

BRCA1-associated breast cancers are more commonly poorly differentiated, have a syncytial growth pattern with pushing margins, have a lymphocytic response, and do not express hormone receptors or overexpress HER2/neu (an epidermal growth factor receptor that is commonly overexpressed in breast cancer, to be discussed later), as compared to sporadic breast carcinomas. *BRCA2*-associated breast carcinomas do not have a distinct morphologic appearance. Initial results using gene expression RNA profiling have revealed that *BRCA1*, *BRCA2*, and subtypes of sporadic cancers can be recognized by their gene expression patterns[40] [41] (Box 23-1). Sporadic carcinomas with an mRNA profile similar to *BRCA1* carcinomas have been termed "basal-like" carcinomas owing to the expression of genes that are characteristic of myoepithelial or possible breast progenitor cells. These results demonstrate that a subset of sporadic carcinomas have biologic similarities to hereditary carcinomas.

Genetic susceptibility due to other known genes is much less common, and together this group accounts for fewer than 10% of hereditary breast carcinomas. [42] Only five have been studied sufficiently to be worth noting. Mutations in the cell-cycle checkpoint kinase gene (*CHEK2*), which is an important component of the recognition and repair of DNA damage and which activates *BRCA1*, may account for 5% of familial cases. [43] The risk for a mutation carrier may be as low as 20%. Women with the Li-Fraumeni syndrome (due to a germ-line mutation in the *p53* gene) have an 18-fold higher risk of developing breast cancer before the age of 45. Mutations in *p53* also occur in 19% to 57% of sporadic breast carcinomas. Cowden syndrome ("multiple hamartoma syndrome" due to a mutation of the *PTEN* gene on chromosome 10q) confers a 25% to 50% lifetime risk of breast cancer in affected women. Mutations in the *PTEN* gene are rare in sporadic carcinomas, but LOH is found in 11% to 41%. Further studies will be necessary to determine whether the function of the other allele is altered (e.g., by methylation). Women with Peutz-Jeghers syndrome (caused by truncating mutations in the *LKBI* gene) are at increased risk for breast cancer. There is, as yet, no evidence that this gene plays a role in sporadic carcinoma. The role of the *ATM* gene in breast cancer susceptibility in ataxia telangiectasia carriers has been intensively studied owing to the high frequency of carriers in the population (approximately 7%) and the increased sensitivity to radiation exposure leading to concerns about screening mammography. Studies have had mixed results, some showing an increased risk and others not showing an association. The risk might be dependent on the type of germ-line mutation (e.g., truncating versus missense). Mutations in the *ATM* gene in sporadic carcinomas are rare.

All of these genes considered together still leave at least two-thirds of familial risk unexplained. The search for a putative "*BRCA3*" gene of high penetrance has, as yet, been unsuccessful, and such a gene might not exist.[44] A polygenic model

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in which many weakly penetrant genes (perhaps dozens or hundreds) act in combination to create a spectrum of risk could explain the majority of familial breast cancers, as well as risk in the general population.[45] [46] [47] This model suggests that most breast cancers arise in a minority of women carrying combinations of these susceptibility genes. The identification of these genes might allow better stratification of women into low-risk and high-risk groups, which would help to focus efforts toward prevention and early detection in these women. Yet to be determined are the number of genes that could be involved, the nature of interactions among these genes (e.g., additive or multiplicative), the interaction with environmental factors, and the possible role of protective alleles. Candidates for such genes have been identified by their ability to modify the expression of known genes such as *BRCA1*.

Genome-wide approaches (e.g., microarray technology; Box 23-1) could play an important role in identifying this potentially very large group of susceptibility genes. One current approach classifies hereditary cancers by mRNA profiling in the hopes that cancers arising due to the same germline mutation (or mutations) will have similar patterns, as has been demonstrated with *BRCA1* and *BRCA2*. [48] If true, this would simplify linkage analysis by identifying groups of families likely to carry similar mutations.

Many studies have confirmed that some of the genes involved in hereditary breast cancer (e.g., *BRCA1* and *p53*) are also important in many sporadic cancers. It is hoped that the continued investigation of the wide variety of naturally occurring mutations and combinations of mutations will provide important clues to breast cancer pathogenesis.

Sporadic Breast Cancer

The major risk factors for sporadic breast cancer are related to hormone exposure: gender, age at menarche and menopause, reproductive history, breast-feeding, and exogenous estrogens. The majority of these cancers occur in postmenopausal women and overexpress ER. Estrogen itself has at least two major roles in the development of breast cancer. Metabolites of estrogen can cause mutations or generate DNA-damaging free radicals.[49] Via its hormonal actions, estrogens drive the proliferation of premalignant lesions as well as cancers. However, other mechanisms also undoubtedly play a role, as a significant subset of breast carcinomas are ER-negative or occur in women without increased estrogen exposure.

Mechanisms of Carcinogenesis

The vast array of histologic appearances of proliferative and atypical breast disease, as well as carcinomas, are the outward manifestations of the dozens or hundreds of biologic changes taking place within these lesions and point to the complex and variable pathways to carcinogenesis. Indeed, not one common genetic or functional change can be found in every breast cancer. Most reported changes occur in only a subset of carcinomas and usually in highly variable combinations with other changes.

A general model for carcinogenesis postulates that a normal cell must achieve seven new capabilities, including genetic instability, to become malignant [50] [51] (see Chapter 7) (Fig. 23-15). In hereditary carcinoma, one or more of these alterations is facilitated by the inheritance of germ-line mutations. Each of the new capabilities can be achieved by a change in one of many genes. For example, changes in *ER, EGF-R, RAS,* or *HER2/neu* may result in self-sufficiency in growth signals. On the other hand, one cellular alteration (e.g., a change in a gene such as *p53* that has a central role in controlling the cell cycle, DNA repair, and apoptosis) can affect more than one of these capabilities.

The morphologic changes in the breast associated with the smallest increased risk of cancer are lesions with increased numbers of epithelial cells (proliferative changes). This suggests that these early changes are related to evasion of growth-inhibiting signals, evasion of apoptosis, and self-sufficiency in growth signals. There is evidence that even at this early stage, there is abnormal expression of hormone receptors and abnormal regulation of proliferation in association with hormone receptor positivity. [52]

Genetic instability, in the form of LOH, appears to be a later change, as it is rarely detected in proliferative changes but becomes more frequent in atypical hyperplasias and is almost universally present in carcinoma in situ. Frank aneuploidy, as observed by nuclear enlargement, irregularity, and hyperchromasia, or image analysis to measure DNA content, is seen only in high-grade DCIS and some invasive carcinomas. Limitless replicative potential is suggested by the ability of clonal populations of the cells of DCIS to completely fill a ductal system in the breast. Increased angiogenesis is evident surrounding the basement membrane of some ducts that are involved by some types of DCIS. This might be due to direct stimulation by the malignant cells, secondary stimulatory effects on stromal cells, or the loss of inhibition of angiogenesis by myoepithelial cells.

The morphologic and biologic features of carcinomas are usually established at the in situ stage, as in the majority of cases, the in situ lesion closely resembles the accompanying invasive carcinoma. For example, lobular carcinomas are associated with LCIS, well-differentiated carcinomas with low-grade DCIS, and high-grade carcinomas with high-grade DCIS. Recurrent carcinomas generally have the appearance of the original carcinoma. Breast carcinomas do not generally "dedifferentiate," or become more poorly differentiated over time.

This view of oncogenesis focuses on the malignant epithelial cell and does not take into account the other tissue components. The structure and function of the normal breast require complex interactions between luminal cells, myoepithelial cells, and stromal cells. The same functions that allow for normal formation of new ductal branch points and lobules during puberty and pregnancy—abrogation of the basement membrane, increased proliferation, escape from growth inhibition, angiogenesis, and invasion of stroma—can be co-opted during carcinogenesis by abnormal epithelial cells, stromal cells, or both.[53] While the changes described above are accumulating in the luminal cells (or, less commonly, myoepithelial cells), parallel changes also occur due to mutation or epigenetic changes (e.g., DNA methylation) or via abnormal signaling pathways in these other cell types, resulting in the loss of normal cellular interactions and tissue structure. [54] Loss of these normal functions also occurs with age, and this loss might contribute to the increased risk of breast cancer in older women.

The final step of carcinogenesis, the transition of carcinoma limited by the basement membrane to ducts and lobules (carcinoma

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Box 23-1. GENE EXPRESSION PORTRAITS OF BREAST CARCINOMAS

Until recently, changes occurring in cancer cells were studied one at a time or in small groups in small sets of tumors. New microarray technologies ("gene chips") have enabled investigators to simultaneously detect and quantify the expression of large numbers of genes (potentially all genes) in different tumors (see Box 7-1 , Chapter 7).

A major advantage of gene arrays is the ability to analyze a multitude of changes in cancer cells (i.e., a "molecular portrait") to discern overall patterns that would not be possible to detect by conventional techniques. An example of the type of data that may be generated from such assays is illustrated in a simplified form in the figure on the facing page. The results for 26 breast carcinomas (each corresponding to one column) for 28 genes (represented by each row) are displayed. A relative increased quantity of mRNA (relative to a reference standard) is shown by red, a relative decreased quantity by green, and an average amount by black. Also shown in the figure are the histology of the different tumor types and the expression of selected proteins detected by immunohistochemistry (ER, HER2, e-cadherin, and basal keratin).

Microarray studies, such as this one and others, have identified breast cancer subtypes previously identified by morphology (e.g., lobular carcinomas), by protein expression (e.g., ER-positive and HER2/neu-positive carcinomas), and by germ-line mutations (e.g., *BRCA1* and *BRCA2* carcinomas). In addition, new subtypes that were not previously well defined have been identified (e.g., the basal-like carcinomas). In the figure, results are not shown for many other tumor subtypes, such as tubular, mucinous, and medullary carcinomas, because these are relatively rare and too few cases have been examined to allow firm conclusions.

mRNA levels do not always correspond to changes in protein expression. The quantity of protein within a cell depends not only on the amount and rate of transcription and translation,

but also on protein degradation and the rate of transport out of the cell. Therefore, other assays are necessary to determine actual protein content. Immunohistochemistry (IHC) uses antibodies to detect proteins on tissue sections. Whereas tissue used for mRNA profiling may include both tumor and stromal cells, IHC has the advantage of being able to identify the cell type expressing the protein and the specific cellular location of the protein.

Estrogen Receptor-Positive Carcinomas. Seventy per cent to 80% of breast carcinomas express ER and are thought to arise from intrinsically ER-positive luminal cells. ER-positive ductal carcinomas ("no special type") are usually well to moderately differentiated and often show tubule formation. Most special types of breast cancer (i.e. lobular, tubular, mucinous, and papillary) are also ER-positive. In the microarray data illustrated, the group of ductal carcinomas, in general, show normal or overexpression of the ER-related gene cluster and luminal keratins, and exhibit low levels of mRNAs from the groups of genes characteristic of the other tumor types. In the lower part of the figure, IHC on one representative ductal carcinoma demonstrates that ER is present in the nucleus, e-cadherin on the cell membrane, and that HER2/neu and basal keratins are undetectable.

In contrast to traditional IHC assays that determine the expression of only ER and a single gene under its regulation, PR, mRNA profiling provides information about many other ER-regulated genes. Using this type of assay, it might be possible to identify the cancers that express ER but fail to respond to hormonal treatments due to disruption of the signaling pathway, resulting in low expression of other ER-regulated genes.

Lobular carcinomas can be identified by the distinctive morphologic pattern of infiltration as single cells or loosely cohesive cell clusters. This appearance has been linked to the loss of the normal cell adhesion molecule e-cadherin, which is retained in most other carcinomas within the ER-positive group. By expression profiling, the lobular carcinomas cluster together and are most closely related to the other ER-positive carcinomas. The absence of e-cadherin can be seen by both diminished mRNA and the absence of the protein by IHC.

Estrogen Receptor-Negative Carcinomas. These carcinomas may arise owing to loss of ER expression or from normally ER-negative cells. Expression profiling identifies two major types of ER-negative carcinomas.

HER2-*Positive Carcinomas.* This group of carcinomas was previously identified by overexpression of the HER2/neu protein. In the majority of carcinomas, the mechanism of over-expression is amplification of the gene resulting in increased transcription into mRNA and protein translation. Breast cancers are routinely assayed for *HER2/neu* gene and protein using FISH or IHC (Figs. 23-27*C* and *B* , respectively) in order to predict clinical responses to antibodies targeted to the protein. These carcinomas tend to be poorly differentiated.

The expression profile reveals not only increased copies of *HER2/neu* mRNA, but also increased transcription of other adjacent genes that are amplified within this segment of DNA. These carcinomas do not overexpress the genes that are characteristic of the other subtypes of cancers in this array (e.g. ER and basal keratins), but do express e-cadherin.

Basal-like Carcinomas. This group of carcinomas is distinguished by the expression of keratins that are more typical of myoepithelial cells or potential breast progenitor cells; it has not been previously well characterized. Because the myoepithelial cell is located in the basal area of the lobules and ducts, in the absence of knowing the specific cell of origin, this group of carcinomas was termed *basal-like*. In addition to the expression of specific keratins, they also show expression of other genes in common with myoepithelial cells (e.g., p-cadherin) as well as numerous genes related to cell proliferation. This group of carcinomas does not express ER or ER-related genes or *HER2/neu*, as can be seen by the array data and by IHC.

Carcinomas arising in women with *BRCA1* mutations also cluster with this group. *BRCA1* carcinomas are similar to basal-like carcinomas in being poorly differentiated, lacking ER and HER2/neu expression, and expressing basal-like keratins. However, most women with basal-like carcinomas do not have germ-line *BRCA1* mutations.

Conclusions. mRNA expression profiling is a powerful tool for investigating breast carcinomas. Analogous arrays to analyze DNA and protein expression profiles are under development. In addition to identifying tumor types, as in this example, mRNA arrays have been used for predicting prognosis and response to therapy, examining tumor changes after therapy, and classifying hereditary carcinomas. Although it might not be feasible to perform transcriptional profiling on every clinical case of breast cancer, these studies will generate information that will lead to better diagnostic, prognostic, and therapeutic tests that are applicable to all patients.

Figure 23- Selected data from mRNA expression profiling (26 carcinomas and 28 genes) are shown in the top half of the figure. Each vertical column represents one carcinoma (and shows information acquired from one "gene chip") and each horizontal row represents the data for a gene (identified at the left). Red indicates an increase, green a decrease, and black no change in mRNA relative to a standard. Cluster analysis was used to group carcinomas with similar expression patterns and the groups are identified as basal-like, *HER2* positive, and the ER-positive lobular and ductal carcinomas. The most important gene clusters are identified on the right. These carcinomas have typical morphologic appearances as shown in the middle row of images (H&E). In the lower half of the figure, mRNA expression patterns are correlated with changes in protein expression by using antibodies to detect antigens within tissues. The presence of a protein is indicated by a brown reaction product within the tumor cells and can be localized to a subcellular site (estrogen receptor-nuclear; HER2/neu and e-cadherin-membrane; basal keratin-cytoplasmic). *The array data are courtesy of Dr. Andrea Richardson, Brigham and Women's Hospital, Boston, MA, as modified from Signoretti S, Di Marcotullio L, Richardson A, et al.: Oncogenic role of the ubiquitin ligase subunit Skp2 in human breast cancer, J Clin Invest 110:633–641, 2002.*