FOURTH EDITION

PATHOLOGY IN GYNECOLOGY AND OBSTETRICS

CLAUDE GOMPEL

STEVEN G. SILVERBERG

J. B. LIPPINCOTT COMPANY

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To Marie and Kiyoe

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Preface

As in our three previous editions, the purpose of this edition of *Pathology in Gynecology and Obstetrics* continues to be to provide a concise and practical reference, with thorough bibliographic documentation, of the complex field of gynecologic and obstetric pathology for practitioners and trainees in both pathology and obstetrics and gynecology. We have also found that our previous editions have been useful in the education of those undergraduate medical students who desire more than the very brief introduction to this field provided by most textbooks of general pathology, and we hope that this edition will continue to serve that purpose.

The present edition, like its predecessors, devotes one chapter to each of the organs of the female genital tract, beginning with the embryology, gross anatomy, and normal histology and then progressing to the malformations, inflammatory lesions, hormonal disturbances, and benign and malignant neoplasms that may be responsible for clinical and subclinical variations from the normal state. Because of the close pathophysiologic relations between the genital tract and the breast, and the frequency with which diseases of the breast are encountered in gynecologic practice, we have continued to devote a chapter to the pathology of the breast. This chapter has been greatly expanded in the current edition in order to encompass the dramatic changes that have taken place in breast pathology in recent years, including new biopsy techniques resulting in specimens very different from those seen only a few years ago, an ever-expanding array of therapeutic options for malignant and premalignant lesions, and a vast menu of diagnostic and prognostic tests available to complement standard histopathologic evaluation.

In an attempt to summarize these currently available and emerging techniques as they apply to gynecologic and breast pathology, we have added a new chapter by Drs. Alain Verhest, Hironobu Sasano, Shinji Sato, and Akira Yajima on new technologies in gynecologic pathology. This chapter also further widens the international scope of the book by adding experts from Japan to those from North America and Europe who have already participated in previous editions. Drs. Charles Zaloudek, Hernando Salazar, and Richard J. Stock have revised their chapters, and Dr. Janice Lage has capably taken over the chapter on the placenta and its adnexa. We have continued to expand the integrated coverage of cytologic findings together with clinical, macroscopic and histopathologic ones, and have increased the number of color plates to that end.

Any understanding of obstetric and gynecologic pathology, whether at the level of an individual case or in the writing of a textbook, is always the result of a close collaboration between the clinician and the pathologist. We who practice gynecologic pathology are particularly fortunate in being able to work daily with dedicated clinicians who are especially interested in the pathologic findings in their cases and who are eager to share their clinical knowledge with us. Our clinical colleagues in Brussels and Washington have offered many helpful suggestions in the preparation of this volume.

The late Drs. Fred W. Stewart and Frank W. Foote, Jr., both Chairmen Emeritus of the Pathology Department of Memorial Hospital for Cancer and Allied Diseases of New York, have given both of us the opportunity to study the most varied aspects of gynecologic pathology and to use the vast resources of their histologic collections. We mourn the passing of both of them since the publication of our third edition. We have also been privileged to be able to use the material and expertise of Drs. Saul Kay and

William J. Frable of the Medical College of Virginia in Richmond, Robert H. Fennell of the University of Colorado School of Medicine in Denver, and the late Professor Albert Claude of the Institut Jules Bordet in Brussels. One of us also wants to thank all his colleagues in Chalon-sur-Saône, France, where he acted as consultant pathologist for a few years. The many other excellent clinicians and pathologists with whom we have interacted over the years have provided a constant source of intellectual stimulation and of friendly and helpful advice, as have our residents in pathology at the Institut Jules Bordet and the George Washington University Medical Center.

Some histologic and photographic documents have been communicated obligingly to us by our colleagues whose names appear in the captions beneath the reproductions. The photomicrographs and electron micrographs were produced by Miss Barbara Neuburger, Mrs. M. L. Simonet, Mr. A. Demeire, Mr. Howard Mitchell, Mr. Phil Rutledge, and Mr. Seth Honig. Many of the diagrams and drawings are the work of Mr. Robert Fauconier. Mrs. I. Chorowitz and Mrs. Dorothy Molero contributed their expert services in transcribing the manuscript and aiding us in reviewing it. Our collaboration with J. B. Lippincott Company is now well into its second decade, and Mr. Richard Winters, Ms. Jody Schott and Ms. Elizabeth Durand are the latest of a series of Lippincott professionals who have provided invaluable assistance in the production of these volumes.

Last but certainly not least, none of this would have been possible without the constant encouragement, assistance, and love provided by our wives, Marie and Kiyoe.

Claude Gompel, MD
Steven G. Silverberg, MD

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1 The Vulva

EMBRYOLOGY

The external genital organs originate from three protuberances: the genital tubercle and the genital pads, also known as the labioscrotal swellings, all of ectodermal origin.[1,2] After passing through an undifferentiated stage during the first 2 months of embryonic life, the genital tubercle forms the clitoris, to which is appended a mesodermal fold, the prepuce of the clitoris (Fig. 1-1). The genital pads give rise to the mons pubis, the labia majora, and the posterior commissure. The pads surround the urogenital orifice, whose borders or genital folds are transformed into the labia minora. All these structures form the boundaries of the vestibular orifice, which becomes the vestibule, into which the vagina and the urethra open. The junction of ectoderm and entoderm is at the level of the free border of the labia minora. Bartholin's glands, which originate in the vestibule, probably are of entodermal origin. Frequently, there is a vestigial persistence of the wolffian (mesonephric) ducts, the excretory ducts of the primitive kidneys, in the form of culs-de-sac of variable length opening under the urethral meatus (Gartner's duct; Fig. 1-2). These ducts can give rise to wolffian duct cysts or Gartner's ducts cysts, which are covered with a columnar epithelium.[3–5]

ANATOMY AND HISTOLOGY

The female external genital organs are composed of the labia majora, labia minora, vestibule, hymen, mons pubis, urethral meatus, vulvovaginal glands (notably Skene's glands),[6] and an erectile apparatus comprising the clitoris and vestibular bulbs (Fig. 1-3). The mons pubis is a fatty structure that contains elastic fibers and is covered by a pigmented epidermis overlying hair follicles and sebaceous and sweat glands.

The *labia majora* form a cutaneous fold rich in adipose tissue and sebaceous and sweat glands. They contain some smooth muscle fibers and are covered by a pigmented hair-bearing epidermis (Fig. 1-4). The internal surface is smooth, whereas the external surface contains numerous hair follicles. The two surfaces join anteriorly to form the anterior commissure of the vulva; posteriorly, they continue into the posterior commissure. Their size depends on the amount of fatty tissue. Like the labia minora, they do not develop fully until the onset of genital activity.

The *labia minora* are covered by a pigmented epidermis that lacks hair follicles and rests on a stroma rich in blood vessels, elastic fibers, and sebaceous glands that secrete the vulvar smegma. They are devoid of adipose tissue. Anteriorly, they originate at the prepuce. They fuse posteriorly to form the fourchette.

The *hymen,* which limits the inferior orifice of the vagina, is composed of connective tissue rich in elastic fibers and thin-walled vessels and covered by nonkeratinized squamous mucosa. A depression, the navicular fossa, separates the fourchette from the hymen.

The *clitoris* is an erectile apparatus covered by keratinized squamous mucosa (Fig. 1-5). It is completed by two other erectile structures, the *vestibular*

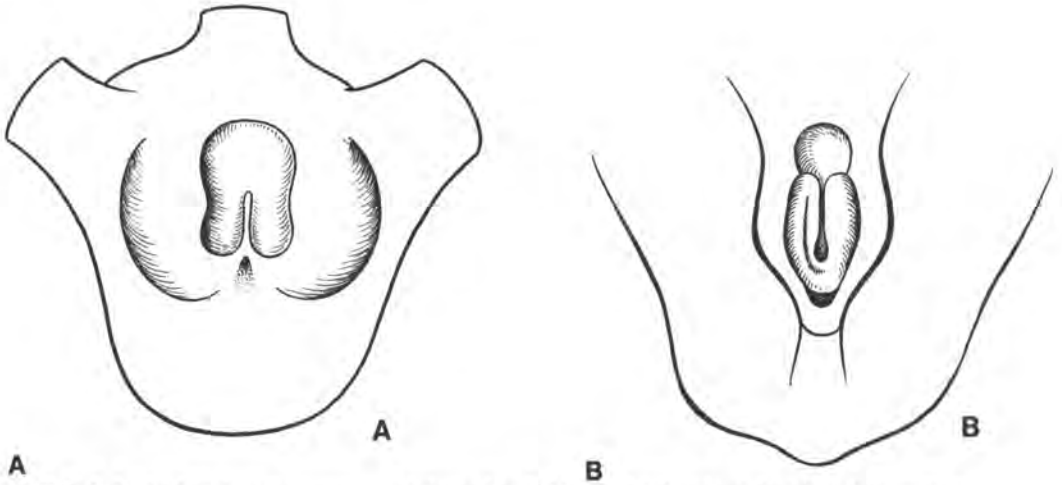


FIGURE 1-1 Embryologic appearance of the vulva. **(A)** Genital tubercle and pads. **(B)** Formation of the clitoris and labia minora.

bulbs, situated on either side of the vulvovaginal orifice. It is half encircled toward the front by the prepuce, formed by the junction of the labia minora. Histologically, it is composed of vascular lacunae separated by connective tissue septa that are rich in collagen and in elastic and smooth muscle fibers. They are lined by an endothelium that is in continuity with that of the blood vessels.

Bartholin's glands, or the *vulvovaginal glands,* are two mucous glands of tubuloalveolar type carpeted with columnar mucus-secreting cells (Fig. 1-6). Their excretory ducts are lined by a noncornified squamous epithelium and are open at the union of the anterior two thirds and posterior third of the groove separating the labia minora from the hymen. The glands produce a clear mucoid secretion.

Skene's glands form a network of glandular canals situated laterally and posteriorly to the urethra. Their number and disposition vary, but the two periurethral ducts described by Skene are always present (Fig. 1-7).[7] These ducts are covered by columnar epithelium containing foci of mucous cells. The glands, on the other hand, possess a pseudostratified columnar epithelium. These structures represent homologues of prostatic glands.

The superficial perineal artery and its branches arise from the internal pudendal artery. The numerous and well-developed veins empty into the internal pudendal and saphenous veins. The lymphatics drain into the superficial and deep inguinal nodes or the external iliac nodes.

The nerves are derived from the perineal branch of the internal pudendal nerve. The sensory innervation is well developed.

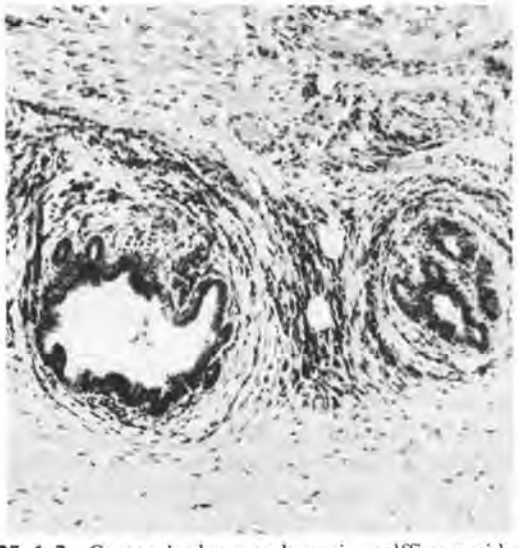


FIGURE 1-2 Gartner's duct: embryonic wolffian residua lined by columnar epithelium and situated in the connective tissue of the clitoral region.

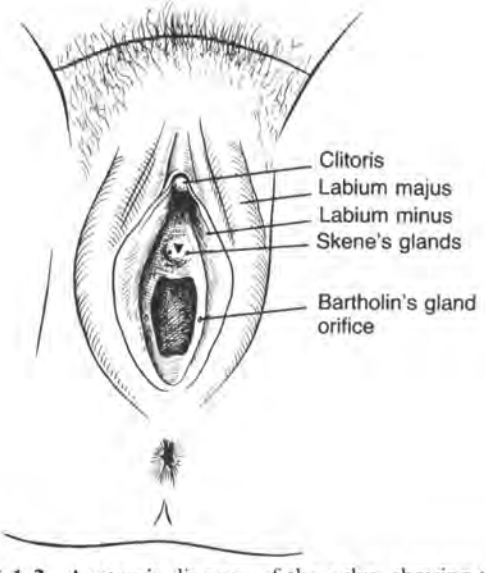


FIGURE 1-3 Anatomic diagram of the vulva, showing the clitoris, labia majora, labia minora, glands of Skene, and orifices of Bartholin's glands.

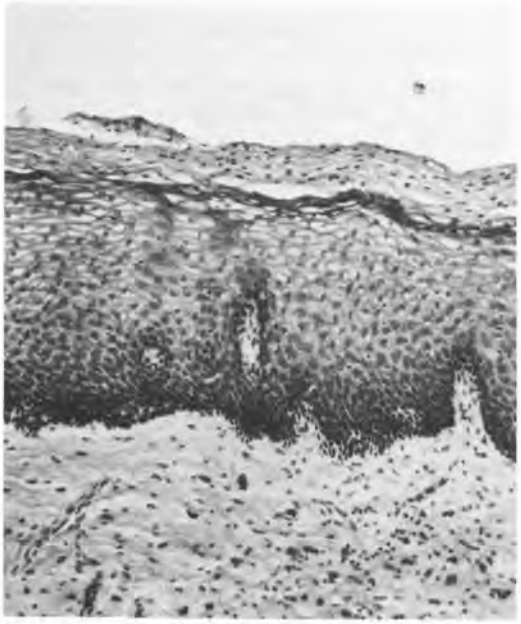


FIGURE 1-4 Squamous epithelium of the labia majora.

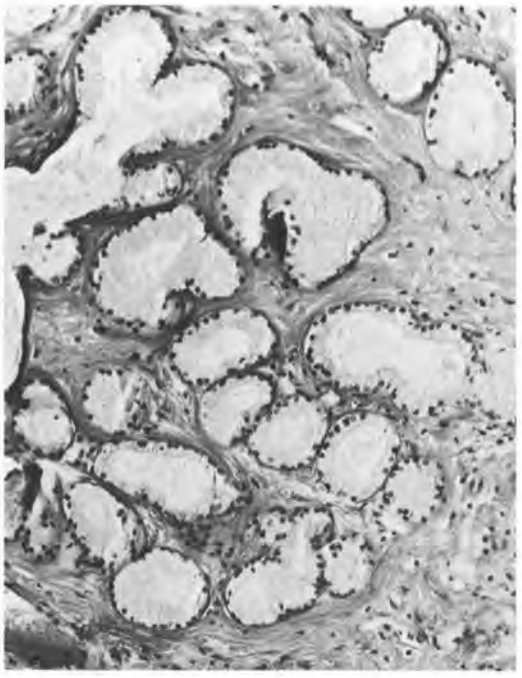


FIGURE 1-6 Bartholin's gland: normal histology.

MALFORMATIONS, HYPOPLASIAS, AND HYPERTROPHIES

Vulvar malformations are not frequent. Total aplasia is extremely rare and is encountered only in certain nonviable fetal monsters and in association with extrophy of the bladder. Hypoplasia is more frequent. When it is pronounced, one finds an infantile vulva with thin and poorly developed labia majora and minora. The clitoris is small, and the mons pubis is almost nonexistent. Any degree of hypoplasia can be encountered, but it is always symmetrical. Duplication of the vulva is a rarity and is accompanied by duplication of the rectum and müllerian structures. Congenital hypertrophy can be partial or total; acquired hypertrophy of the labia minora is encountered in some women who practice masturbation. Total atresia or absence of the vulvar orifice is extremely rare.[8] A partial atresia characterized by stenosis of the vestibular orifice due to partial fusion of the labia is sometimes encountered.[9]

Aplasia of the clitoris is rare.[10] Hypertrophy of the clitoris most often depends on hormonal stimulation. It usually results from prolonged treatment with androgens or progesterone or from a tumoral

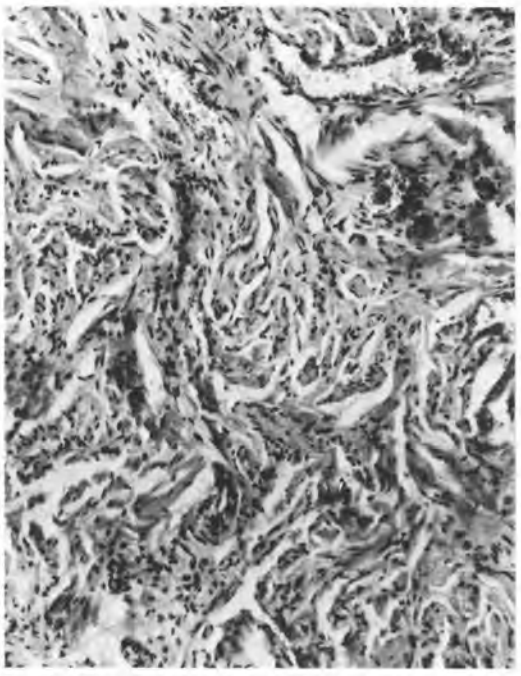


FIGURE 1-5 Clitoris: normal erectile tissue.

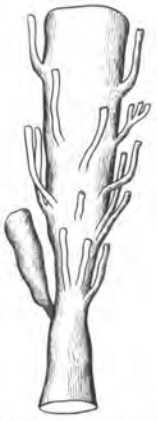


FIGURE 1-7 Anatomic disposition of the paraurethral glands. (Redrawn from Huffman JW: The detailed anatomy of the paraurethral ducts in the adult human female. Am J Obstet Gynecol 55:86–101, 1948)

virilization. Clitoral hypertrophy also is encountered in male pseudohermaphroditism, in which the clitoris may attain a size sufficient to permit penile-like function. Partial removal of the clitoris may correct the anomaly.

Another malformation is anovulvar atresia, which is represented by the opening of the rectum into the vulva due to the absence of the septum of the primitive cloaca. Pseudophimosis occurs when the prepuce, which partially covers the clitoris, hypertrophies and adheres to the clitoris, causing retention of smegma.

Persistence of the peritoneal diverticulum that is found in the elastic sac of the labium majus can give rise to a hydrocele of the canal of Nuck (an inguinal cyst) in the superior part of the labium.[11] The hydrocele is constant or transitory depending on whether it forms a sac that is completely closed or one that is in communication with the peritoneal cavity.

Aplasia of the urethral orifice is extremely rare and is encountered in some nonviable fetal monsters. If it is partial, it results in slight or marked stenosis. Aplasia of Bartholin's glands is very rare.

INFLAMMATORY DISEASES

Bacterial Infections

Many of the inflammatory diseases of the vulva belong to the realm of dermatopathology, but they merit description here as well. They acquire particular characteristics resulting from the symptoms that they cause in the vulvar region, such as abundant perspiration, contamination of adjacent structures, and hormonal influences. Their *histologic appearance* is not always familiar to the pathologist; the tissues are rarely biopsied because their macroscopic appearance usually is sufficient for diagnosis. Bacterial, viral, and parasitic infections may be encountered.[12-14]

Follicular Vulvitis

In follicular vulvitis, the hair follicles and sebaceous glands are invaded by bacterial colonies, most often of staphylococci. Macroscopically, the lesions present as small, red, tumefied, tender papules that transform into pustules. The disease can spread to involve the entire region of the labia majora and mons pubis.

Furuncle

Furuncles are caused by *Staphylococcus,* and the risk for a furuncle is increased by poor hygiene, diabetes, anemia, inoculation from other affected areas of the body, or general debility. It is a pyogenic folliculitis, with edema, vascular congestion, diapedesis of polymorphonuclear leukocytes, and formation of a purulent exudate with necrosis of the hair follicle. Elimination of the hair shaft is usually curative. Several furuncles can fuse to form a carbuncle; they are mostly localized to the labia majora.

Tuberculosis

Vulvar tuberculosis is the rarest localization of genital tuberculosis, representing less than 1% of all genital cases.[15] The lesion is situated at the level of the labia majora or minora. Contamination is effected by the lymphatic system or bloodstream, by direct contact, or rarely by sexual relations secondary to a tuberculous lesion of the male kidney or epididymis.

Macroscopic Appearance. The lesion presents as a nonindurated ulcer with torpid borders that is continuous with a subcutaneous yellow-brown nodule or a lupoid lesion.

Microscopic Appearance. There is an epithelioid cell granuloma containing Langhans' giant cells, surrounded by a peripheral zone of lymphocytes and plasma cells. Caseation necrosis is not common (Fig. 1-8). Other granulomatous lesions with giant cells should not be misinterpreted as tuberculosis. They are more frequent and result from reactions to suture material after surgery or from rupture of an epidermal inclusion cyst.

Gonorrhea

The etiologic agent in gonorrhea is the gonococcus, a Gram-negative encapsulated diplococcus first demonstrated by Neisser in 1879. The transmission is almost entirely by venereal exposure.

The lesion appears as an acute purulent inflammatory reaction at the level of the urethra, Bartholin's or Skene's glands, or the cervical glands. The squamous vulvar and vaginal mucosae are rarely involved. Vulvar localization is more frequent in young children, because the epidermis is thin and nonkeratinized.

The infection may sometimes spread to the endometrium, the fallopian tubes, and the rectum.[16] It can cause articular and cardiac lesions (endocarditis) when spread through the bloodstream.

Macroscopic Appearance. In the acute stage of gonorrhea, the vulvovaginal glands are congested and edematous. The urethra and the excretory ducts of the vulvar glands exude purulent material. If the infection becomes chronic, the sequelae are frequent at the level of Bartholin's glands, with fibrosis, obstruction of the excretory ducts, and cyst formation. The chronic disease can exhibit periods of acute exacerbation, with formation of new abscesses.

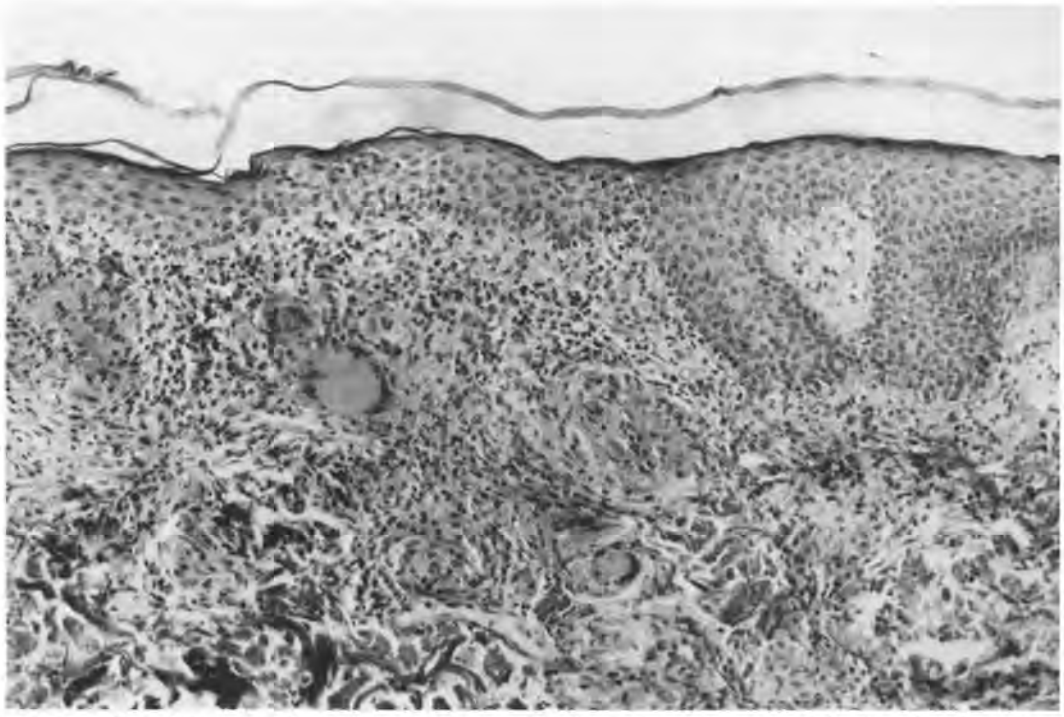


FIGURE 1-8 Vulvar tuberculosis: photomicrograph of a dermal granuloma containing Langhans' giant cells.

Microscopic Appearance. Histologic examination reveals an acute purulent infiltrate with polymorphonuclear leukocytes, the etiology of which can be determined only by culturing the microbe. In chronic gonorrhea, the microscopic structure of Bartholin's glands undergoes pronounced changes: the ductal epithelium is flattened and sometimes reduced to a single layer, and the acini are deformed by the surrounded fibrosis and infiltrated with lymphocytes and plasma cells (Fig. 1-9).

Chancroid

Chancroid is a very rare venereal disease that is more common in men than in women. It is caused by *Haemophilus ducreyi*, the Gram-negative, non-motile, pleomorphic rod discovered by Ducrey in 1889. Chancroid is also known as *soft chancre, soft sore,* and *Ducrey's chancre.*

Clinical Manifestations. After an incubation period of 3 to 10 days, a painful ulcer with a granulomatous purulent surface appears. The pain is often severe and differentiates this disease from syphilitic chancre. It is accompanied by bilateral inguinal lymphadenopathy.

Diagnosis. The diagnosis is made from the appearance of the lesion, from the microscopic demonstration of *Haemophilus ducreyi* in smears of material from scrapings of lesions, from culture, and from serologic identification.

Macroscopic Appearance. The chancre of inoculation is localized on any portion of the external genitalia. It begins as a red macule and is transformed into a pustule. The latter ulcerates and gives rise to multiple purulent granulomatous lesions with sharply defined projecting margins; their nonindurated borders differentiate them from syphilitic lesions. Regional adenopathy develops within 2 weeks after inoculation, becomes voluminous, and ulcerates.

Microscopic Appearance. The lesion is characterized by a granuloma with marked infiltration by lymphocytes and plasma cells. There is edema and superficial ulceration. Acute endarteritis and periarteritis may be present.[17] There may be secondary infection by luetic spirochetes. If disease involves the urethral region, it may provoke a cicatricial stenosis.

Differential Diagnosis. The differential diagnosis must be made with syphilis, lymphogranuloma venereum, and granuloma inguinale.[18]

Granuloma Inguinale

Granuloma inguinale is a rare chronic infection whose etiologic agent is *Calymmatobacterium granulomatosis,* a Gram-negative, non-motile, encapsulated bacillus first mentioned by Donovan in 1904 and demonstrated by Giemsa or Warthin-Starry stains.[19] Synonyms are *granuloma venereum, Donovan's granulomatosis,* and *Donovan's disease.* The diagnosis is made by direct examination of smears, tissue sec-

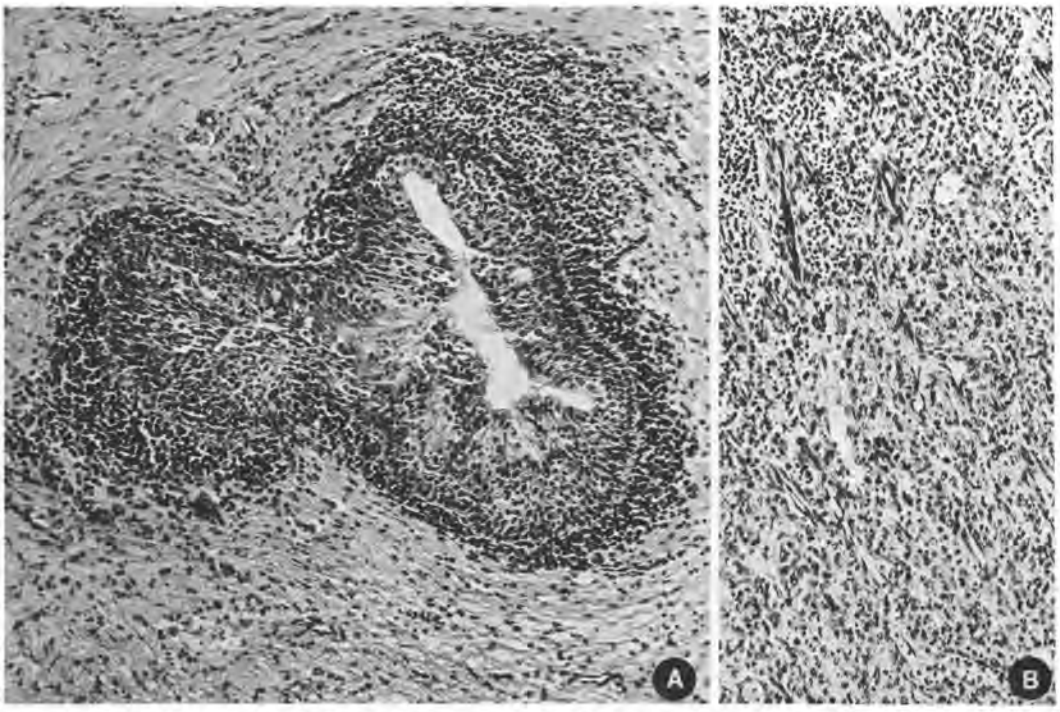


FIGURE 1-9 Gonococcal bartholinitis. **(A)** Periglandular leukocytic infiltrate. **(B)** Inflammatory cells invading the stroma.

tions, culture, or complement fixation test. This granulomatous, ulcerating infection is often associated with venereal diseases.[20,21] It is found more frequently in tropical countries and in the southern states of the United States. Granuloma inguinale is not a venereal disease; the organism is considered to be of fecal origin and may become pathogenic in patients with poor hygiene. There is a risk of developing carcinoma, as in any chronic granulomatous infection.[22]

Macroscopic Appearance. The lesion begins as a nodule or a papule and is localized to the genitalia, the inguinal region, and the anal region. The lower abdominal wall and inner aspects of the thighs may be involved. The original papular lesion ulcerates and forms a dark red, rough-surfaced granulation tissue with well-defined margins, which progressively extends peripherally. Several ulcers may grow separately and become purulent. When the cervix is involved, the process may extend to the endometrium, the ovaries, and the tubes. Uterine lesions are more common in pregnant women, in whom they provoke abortion and are accompanied by a high fetal mortality rate. Lymphatic extension and blockage are frequent and are associated with elephantiasis. Atrophic or sometimes hypertrophic scarring follows.

Microscopic Appearance. The initial papulonodular lesion shows edema of the papillae, epithelial hypertrophy that may progress to the stage of pseudoepitheliomatous hyperplasia, and a neutrophilic infiltrate in the subjacent dermis. The ulcer is covered by a granulation tissue rich in lymphocytes, plasma cells, and histiocytes. Among the latter are large vacuolated macrophages measuring 25 to 90 μm, with nuclei compressed by cellular inclusions known as *Donovan bodies.*[23] They may be detected with methylene blue or in paraffin sections with argentaffine stains.[24] There is proliferation of capillaries and acute endarteritis obliterans. When inguinal nodes are involved, parasite-laden macrophages and polymorphonuclear leukocytes are present.

Differential Diagnosis. The differential diagnosis must be made with the chancre of syphilis.

Syphilis

Syphilis is caused by a spirochete, *Treponema pallidum,* which was discovered by Schaudinn and Hoffman in 1905. The different types of cellular lesions result from combinations of the following elementary alterations:

Lymphoplasmacytic infiltration, with perivascular predominance
Inflammatory vascular and capillary lesions
Necrotic inflammatory granulomata (gumma)
Sclerosis.

None of these microscopic pictures is pathognomonic of syphilis. These cellular modifications are combined and integrated in the three clinical forms

of the disease: the primary period of inoculation, contamination and dissemination; the secondary period of generalization, appearing about 6 weeks later; and the tertiary period of localization, becoming manifest after months or years.[25] In women, the infection can be clinically occult in the primary and secondary stages, becoming obvious only in the tertiary stage.

Primary Period (Chancre of Inoculation)

Macroscopic Appearance. The localizations of the primary chancre are the mucosal surfaces of the vulva and vagina and the external portion of the cervix. After a median incubation period of 3 weeks, a macule appears and is transformed into a painless indurated papule that ranges from several millimeters to 2 cm in diameter. This papule then progresses to a round or oval indurated ulcer with elevated borders, covered by a gray-red exudate and surrounded by a zone of congestion (Color Figure 1-1). During this period, the spirochete disseminates widely in the tissues and lymphatics. The chancre disappears spontaneously in 3 to 8 weeks. The inguinal lymph nodes are enlarged and indurated but not tender.[26] This diagnosis should be considered in the differential diagnosis of ulcerated lesions of the vulva and the vagina.

Microscopic Appearance. The chancre of inoculation is an inflammatory granuloma composed of histiocytes, macrophages, plasma cells, lymphocytes, and vessels showing endothelial proliferation and endarteritis. It is situated in the subcutaneous tissue and surmounted by a zone of ulceration. The inflammatory infiltrate begins around the vessels and extends to form a diffuse mass. The presence of the spirochetes proves the luetic etiology. The organism can be demonstrated by dark-field microscopy in the fresh state or by fluorescence or silver impregnation.[27] Regional adenopathy reveals a follicular hyperplasia, histiocytic infiltration with giant cell formation, and lymphocytic depletion. This depletion can be associated with an impairment of cell-mediated immunity.[25] The evolution is by secondary fibrosis.[28]

Secondary Syphilitic Lesions. Secondary lesions appear 6 to 10 weeks after inoculation. They are disseminated over the entire body and occur in several episodes separated by periods of remission. The lesions contain numerous spirochetes. In the external genital organs, two types of lesions are commonly found: mucous patches and papulohypertrophic syphilids. *Mucous patches* consist of predominantly perivascular lymphoplasmacytic infiltrates, intense neovascularization, and reactive hyperplasia of the surface epithelium (Fig. 1-10). They are disseminated over the entire vulvovaginal mucosa. *Papulohypertrophic syphilids* show marked cutaneous hyperplasia with intercellular edema and leukocytic infiltration. They present in the form of rounded, erosive, slightly elevated brown lesions measuring several centimeters in diameter.

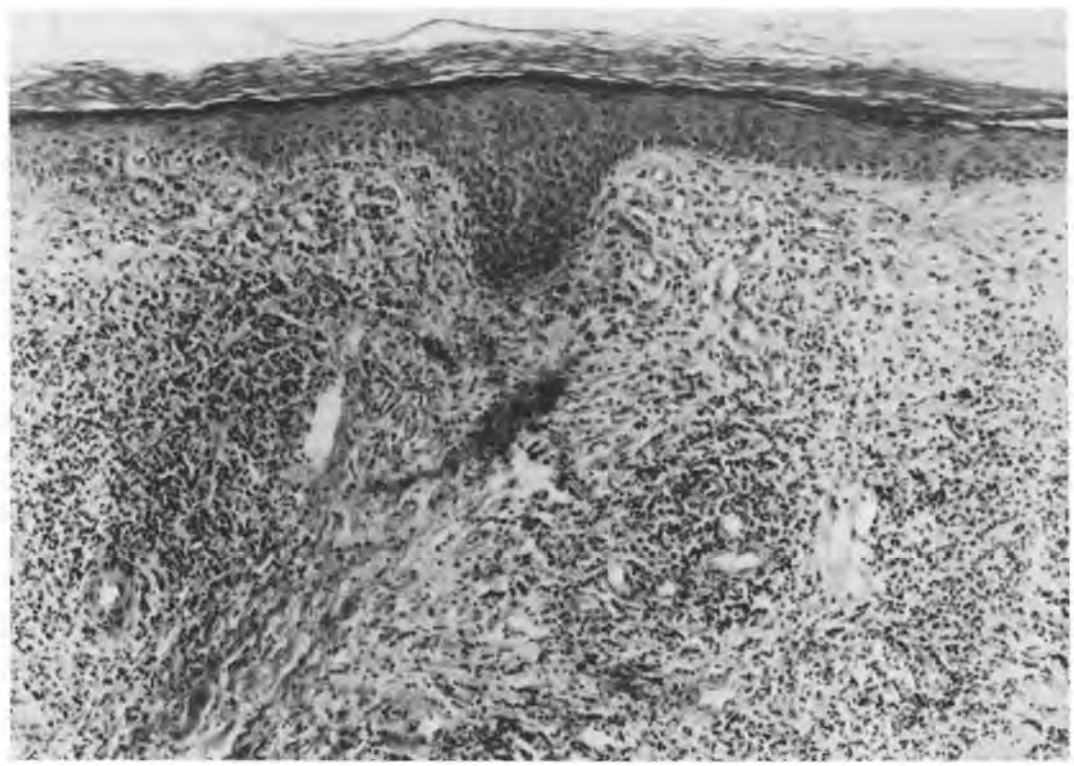


FIGURE 1-10 Late secondary syphilis: lymphoplasmacytic infiltrate principally localized around blood vessels.

Tertiary Syphilitic Lesions. Tertiary lesions become manifest several months or even years after the primary inoculation. Like the other luetic lesions, they are characterized by the presence of lymphocytes, plasma cells, macrophages, and epithelioid cells. The lesions of endarteritis obliterans of arterioles and capillaries are intense and provoke the appearance of zones of necrosis. The *gumma* is a granuloma with a necrotic center surrounded by epithelioid cells, giant cells, lymphocytes, plasma cells, and connective tissue that encloses and limits the lesion. Although the tertiary lesions only rarely involve the genital organs, gumma of the vulva has been described.

Bartholin's Gland Abscess (Bartholinitis)

Bartholin's gland abscess is a frequently occurring lesion. The organisms most frequently responsible are *Neisseria gonorrhoeae, Streptococcus, Staphylococcus, Escherichia coli,* and *Trichomonas vaginalis.*

Macroscopic Appearance. A red, painful tumefaction is found in the inferior portion of the labium majus with or without softening.

Microscopic Appearance. The inflammatory process involves the excretory duct or, less often, the acini. A painful collection of pus is formed and tends to fistulize as a secondary event. The cavity of the abscess may be single or multilocular. The chronic form arises from repeated inflammatory episodes and eventuates in the formation of a cyst. The paraurethral glands (Skene's glands) can be involved by the inflammatory process. Gram-negative diplococci of *Neisseria gonorrhoeae* can be seen in the cytoplasm of neutrophils with a Gram stain. Rare vulvar and vaginal localizations of diphtheria (*Corynebacterium diphtheriae*) have been reported.

Erysipelas

Erysipelas is an acute inflammation caused by β-hemolytic streptococci. It is now a rare infection. Erysipelas is characterized by phlegmonous edema and is seldom localized to the vulva. It begins as a pruritic, erythematous, shiny lesion with an indurated and raised border that may attain a diameter of several centimeters. The microscopic picture shows a diffuse inflammatory lesion extending throughout the epidermis.

Ecthyma

Ecthyma is a pyodermatitis caused by organisms similar to those causing impetigo (*Streptococcus pyogenes*). A debilitated general state or inadequate hygiene often explains the virulence of this infection. Puerperal ulcers are of streptococcal origin. Macroscopically, vesicles or pustules penetrate deeply or spread out on the epidermis. They ulcerate and scar in a few weeks.

The histologic lesion consists of a purulent exudate underlaid by inflammatory granulation tissue rich in neutrophils and newly formed vessels. The vessels often demonstrate endarteritic and phlebitic lesions. Pseudoepitheliomatous hyperplasia sometimes develops in the overlying epidermis.

Chronic Hypertrophic Vulvitis

Chronic hypertrophic vulvitis shows lesions similar to cheilitis granulomatosa (Miescher-Melkersson-Rosenthal syndrome).[29,30] It is characterized by a chronic swelling of the vulva. Microscopic findings include inflammatory infiltrates with epithelioid cell granulomas. The histogenesis is unknown.

Vulvitis Circumscripta Plasmacellularis

Vulvitis circumscripta plasmacellularis is a rare clinicomorphologic entity characterized by a thinned and flattened epithelium accompanied by a dermal inflammatory infiltrate with numerous plasma cells.[31]

Ulcus Vulvae Acutum (Acute Ulcer of Lipschütz)

The labia majora and minora may be sites of chronic and acute ulcers.[32] These ulcers accompany systemic infections such as typhoid fever, amebiasis, brucellosis, and viral pneumonia or are associated with oral ulcers and uveitis (*Behçet's syndrome*).[33,34] In young women, the acute stage of the infection is sometimes confused with a venereal disease. Systemic manifestations such as pneumonitis, gastrointestinal ulcerations, and lesions of the central nervous system have been observed.

Etiology. The etiology of these ulcers is not definitely established. A virus has been suspected, but its existence has not been confirmed. Most likely it is an autoimmune disorder; elevated levels of immune complexes, circulating antibodies against epithelial cells, and deposition of immunoglobulins around vessels are in favor of a humoral mechanism.[35] The *Bacillus crassus* described by Lipschütz is no longer considered the causative agent.

Macroscopic Appearance. These ulcers measure 1 to 3 cm in diameter and have well-defined borders. They are painful, nonindurated, and covered with a gray purulent exudate (Color Figure 1-2). The peripheral skin or mucosa is red and appears edematous. Spontaneous healing is the rule.

Microscopic Appearance. Nonspecific inflammation and small abscesses accompany a vasculitis that is characterized by a lymphocytic infiltrate and marked endothelial swelling. Secondary fibrosis with scarring may occur.[36]

Differential Diagnosis. The differential diagnosis includes syphilitic chancre, chancroid, and herpes.

Viral Infections

Condyloma Acuminatum

Condyloma acuminatum or venereal wart is a contagious viral infection caused by human papillomavirus (HPV), a DNA virus that belongs to the family of *Papovaviridae.*[37,38] The prevalence of condylomata and related intraepithelial lesions has increased significantly in recent decades.[39] The presence of HPV DNA has been demonstrated in the nucleus and cytoplasm of infected cells after passing through the plasma membrane. More than 60 HPV types have been identified by molecular hybridization and restriction enzymes techniques.[40,41] Types 6, 11, 16, 18, 31, and 35 are the types most commonly associated with lesions of the human female genital tract. HPV types 6 and 11 are observed in condyloma and some low-grade dysplasias, whereas types 16, 18, 31, and 35 are found in most intraepithelial neoplasias. HPV infections are frequent in the population and may not always be associated with a neoplastic process. Highly sensitive techniques used to detect HPV, such as the polymerase chain reaction, may be associated with two difficulties: they may detect inadvertent DNA contamination or unrelated latent infection.

Clinical Appearance. Clinically, the lesion presents as multiple hyperkeratotic budding papillomata that have a tendency to agglomerate (Color Figure 1-3). The lesions are situated in the vulva and in the perianal region, urethra, perineum, vagina, and cervix.[40] Transmission occurs mostly with venereal contact. Pregnancy favors the appearance of voluminous lesions, which may be transmitted to the newborn in rare cases. The exophytic condyloma is not the only form of the disease; flat lesions are also described (flat condyloma). They are observed less frequently on the vulva than on the cervix.[37,41] See Chapter 3 for more details on HPV infection and carcinoma.

Microscopic Appearance. Microscopically, the papillomatous formations develop on a fibrovascular stroma, forming a support for the epithelium, which shows papillary acanthosis, hyperkeratosis, parakeratosis, and hyperplasia of the rete pegs. Perinuclear haloes with nuclear atypia and binucleate cells, predominantly in the granular layer, are the morphologic indicators of the presence of HPV. These cells were called *koilocytes* by Koss and Durfee in 1956.[42] The same cellular lesions are found in the flat condyloma and were related to HPV by Meisels and Fortin and by Purola and Savia.[43,44] Table 1-1 summarizes the typical cytologic and histologic features recognized in condyloma.

Ultrastructural or immunohistochemical studies are necessary to demonstrate the intranuclear viral particles. The epithelial changes are accompanied by chronic inflammation and vascular congestion of the underlying dermis. Flat condyloma is characterized by the same cellular anomalies without the formation of exophytic papillary structures.

TABLE 1-1.
Morphologic Features of Condyloma

Koilocytosis
Binucleation
Parakeratosis (incomplete or abnormal keratinization) with nuclear pleomorphism and hyperchromasia
Acanthosis
Papillomatosis

Differential Diagnosis. Differential diagnosis must be made macroscopically with the condyloma latum of secondary syphilis, granuloma inguinale, and verrucous carcinoma. The so-called giant form of condyloma, often associated with HPV-11, is probably a verrucous carcinoma because it can invade adjacent tissues. A similar giant condyloma (condyloma of Buschke-Löwenstein) of the penis has been described.[45]

Microscopically, intraepithelial neoplasms can be differentiated from HPV infection by marked cellular atypia, disorganization of the cellular layers of the epithelium, atypical mitotic figures, and an increased mitotic index. When the histologic anomalies are equivocal for condyloma, analysis for HPV DNA by in situ hybridization may help demonstrate the presence of the virus.[46,47]

Treatment. Treatment of vulvar condylomata ranges from local podophyllin, trichloroacetic acid, and 5-fluorouracil to local excision, cryocautery, electrocautery, and carbon dioxide laser vaporization. When podophyllin is used, one should be careful not to misinterpret podophyllin-induced cellular anomalies as carcinomatous changes. Podophyllin changes regress after 2 weeks. More recently, antiviral agents such as interferon have been used. Cases that do not respond to any type of treatment may eventually progress to (or may already be) vulvar intraepithelial neoplasia (VIN).

Molluscum Contagiosum

Molluscum contagiosum is a contagious viral disease characterized macroscopically by small round elevated papules of several millimeters in diameter. The papules are firm and white-gray, with dark umbilicated centers. They are pruritic and usually are multiple but may be solitary. They appear in the genital region and on the face and arms. The development and multiplication of these lesions take place rapidly. The disease is common in infants, in whom it is often seen in epidemic form. Sexual transmission has been suggested.[48,49] The etiologic agent is a poxvirus containing DNA. The lesions resolve spontaneously.

The histology is that of an acanthotic epithelium extending deeply into the dermis to form the characteristic lobules (Fig. 1-11). In the stratum germinativum, the epithelial cells become strongly eosinophilic and may contain large cytoplasmic viral inclusions

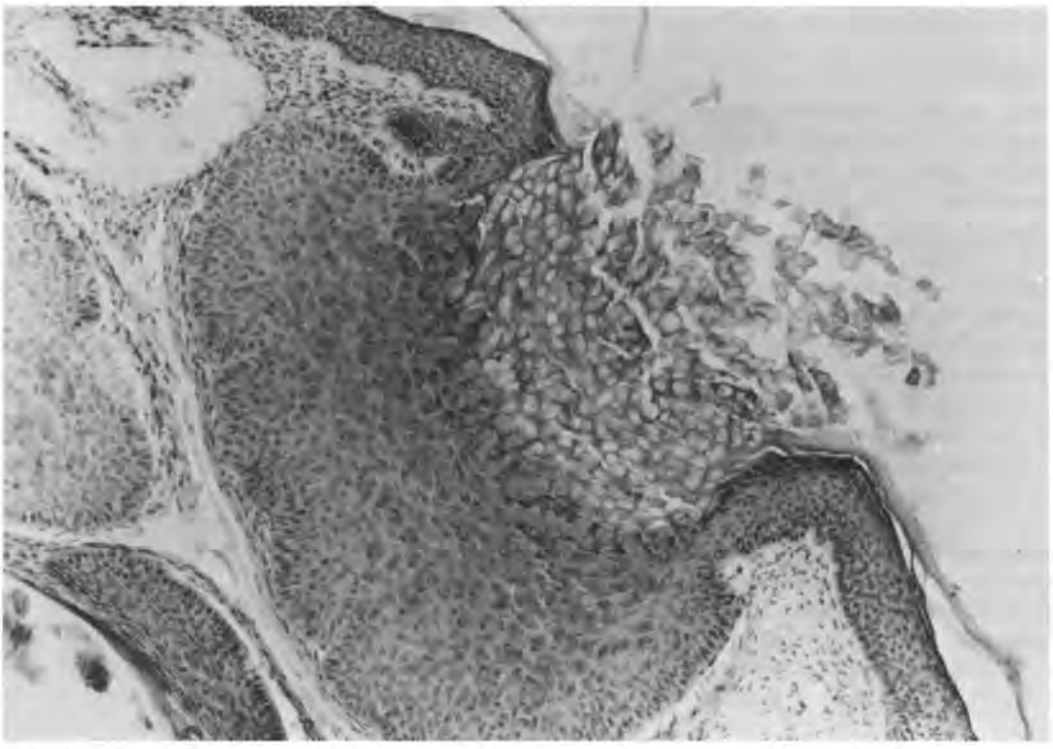


FIGURE 1-11 Molluscum contagiosum: eosinophilic cytoplasmic inclusions agglomerate to constitute a Lipschütz body.

that push aside the nucleus and form eosinophilic masses surrounded by keratohyaline granules (Lipschütz bodies). These masses agglomerate and constitute a molluscum corpuscle, which desquamates on its arrival at the surface of the epithelium. Differential diagnosis must be made with hyperkeratotic verruca, in which the eosinophilic granules found in the stratum granulosum are smaller than those found in molluscum contagiosum.

Contagious pustular dermatitis (ORF) is a rare infection caused by a virus from the same poxvirus group. It occurs in people who are working with sheep. A vulvar localization was diagnosed in a child living in the country.[50]

Herpes Simplex

Herpesvirus hominis infection is caused by two distinct types of DNA virus: herpes simplex virus 1 and 2 (HSV-1 and -2). They can be differentiated by viral culture but cannot be differentiated morphologically. HSV-1 more frequently affects the perioral and ocular regions and upper respiratory tract, and HSV-2 is found predominantly in the genital area (vulva, vagina, and cervix), but both types may be observed at any site.[51–54]

HSV-2 is a common sexually transmitted genital infection and its prevalence is increasing.[55] It is characterized by periods of remission and recurrence. The primary infection is accompanied by constitutional symptoms such as fever, myalgia and headache. The incubation period is 3 to 7 days, and the infection evolves in 2 to 7 days. It causes the appearance of groups of 2- to 5-mm vesicles containing clear fluid that later becomes cloudy. After a few days, one or several painful ulcers appear along the labia majora and minora, which become covered with yellow scabs and finally eventuate in scars.[56] The regional lymph nodes develop inflammatory reactions.

During pregnancy, the transmission of the virus to the newborn may result in a disseminated herpetic infection that can be fatal.[57] HSV infection is, in certain cases, an indication for delivery by cesarean section.[58] Studies show that the prevalence of infection is significantly greater in groups of patients with cervical and vulvar carcinoma, both in situ and invasive.[59] The relation to cervical carcinoma is discussed in more detail in Chapter 3.

The histologic appearance consists of the formation of an intraepithelial vesicle by ballooning degeneration of the epidermal cells, which hypertrophy, degenerate, and desquamate into the vesicular cavity. Intranuclear eosinophilic inclusions are found in variable numbers; they are nonspecific and are seen in herpes zoster and varicella.[60] Lymphocytes and polynuclear leukocytes infiltrate the epidermis and the dermis.

Cytology. Smears should be prepared from the bed of ulceration and not from the serosanguineous content of the vesicle, which usually does not contain ep-

ithelial cells.[61,62] The virus infects squamous, metaplastic, and columnar endocervical cells, and cytologic lesions can be observed in all these cellular types. Alterations of size and shape of cells and nuclei can be seen, with the subsequent appearance of atypical cells with bizarre shapes. Hydropic degeneration with a homogenized appearance of nuclei (ground-glass nuclei) is a common feature. Nucleoli are not significantly increased in size. Internuclear molding and dense cyanophilic staining of cytoplasm are common findings. When present, intranuclear inclusions are often surrounded by a clear zone. Multinucleation is the result of viral replication. These multinucleated cells should not be confused with the foreign-body giant cells and reactive multinucleated cells observed in chronic cervicitis (Color Figure 1-4).

The cytologic changes are not always present. Nevertheless, the cytologic method is almost as sensitive as virus culture and isolation. Treatment is symptomatic. New drugs seem to hasten healing, but recurrence is the rule, because the virus has not been eradicated.

Herpes Zoster

Rarely described in the vulva, herpes zoster is a disease of viral origin that affects the dermatomes located in the territories of peripheral nerves. It appears as erythematous plaques containing masses of vesicles. There are intranuclear inclusion bodies identical in appearance to those of herpes simplex and of varicella. Only the clinical picture establishes the diagnosis. The disease is accompanied by systemic phenomena.[63] The severity of the infection is greatly increased in patients with impaired cellular immunity. The virus has been seen by electron microscopy but has never been cultured.

Lymphogranuloma Venereum

Lymphogranuloma venereum is a venereal disease caused by *Chlamydia trachomatis,* a Gram-negative, intracellular parasite probably derived from Gram-negative bacteria.[64] Once considered to be a virus, chlamydiae have distinctive characteristics that eliminate a viral nature: the simultaneous presence of DNA and RNA and of ribosomes.[65] The intracellular localization of the parasite is the only characteristic it shares with viruses. Lymphogranuloma venereum is also known as *lymphogranulomatosis, lymphogranuloma inguinale, Nicolas-Favre disease, venereal disease of Hellerström,* and *poradenitis inguinale.*

Demonstration of particles in smears is difficult. The Warthin-Starry silver impregnation stain helps to demonstrate the presence of the organism. Isolation of the agent is possible on yolk sac material and by intracerebral injection in mice. A useful diagnostic skin test is the Frei test, which uses a yolk sac emulsion containing chlamydiae. The development of a papule indicates a delayed hypersensitivity reaction to group antigen.[66] More recently, immunologic methods have been developed that yield sensitive and reliable results.[67,68]

Clinical Manifestations. After an inoculation period of 3 to 21 days, the primary lesion develops in the genital region and is followed within 2 to 8 weeks by a unilateral or bilateral ilioinguinal lymphadenitis; this is the primary bubo complex first recognized by Durand, Nicolas, and Favre in 1913.[69] Among the different localizations described are the conjunctivae, the urethra, the fallopian tubes, the vagina, and the cervix uteri. Generalized dissemination may produce fever and systemic symptoms. The disease may be acute or may progress to the chronic form. It is more common in tropical and subtropical regions.

Macroscopic Appearance. The primary lesion involves the mucosa of the vulva and urethra. It is usually a small papular lesion followed by a nonindurated painless ulcer with elevated jagged borders. It usually heals in a few weeks. The combination of edema, fistulas, and ulcers is called *esthiomene.* The major manifestation of the disease is the appearance of a fluctuant, conglomerate, swollen mass of ilioinguinal lymph nodes (ilioinguinal bubo), which may ulcerate and form sinuses.[66] In the chronic stage, fibrosis and edema may produce stricture of the vagina, elephantiasis of the vulva, massive enlargement of the clitoris, and anorectal and urethral strictures.

Microscopic Appearance. The primary lesion is characterized by a chronic inflammatory infiltrate and epithelial hyperplasia. The typical acute lesion in the regional lymph nodes is the stellate abscess: an irregular focus of necrosis infiltrated by neutrophils and surrounded by histiocytes, fibroblasts, epithelioid cells, plasma cells, lymphocytes, and occasional multinucleated giant cells. Purulent discharge follows the spontaneous rupture of the lymph node. Fibrosis and chronic inflammation develop in a later stage. The epithelial hyperplasia may eventually proceed to carcinoma.[70]

The cytologic changes, if present, consist of coccoid bodies surrounded by a clear and well-limited vacuole.[71,72] Studies have shown no correlation between the presence of the typical cytologic images and the positive culture of the microorganism.[73] Therefore, the diagnosis of *Chlamydia trachomatis* must be confirmed by culture. Immunofluorescence methods using a labeled antibody have been developed and give accurate results.[74]

Differential Diagnosis. Differential diagnosis must be made with tuberculous and syphilitic granulomas, with cat-scratch disease, and with pasteurellosis in lymph nodes.

Accidental Vaccinia

Cases of localized accidental vaccinia of the vulva have been reported.[75,76] This condition is uncommon, but the possibility should be considered because most cases have been referred to erroneously as venereal diseases. Usually the lesion shows typical umbilicated vesicles. The diagnosis may be made on clinical grounds and confirmed by laboratory tests (detection of virus and antibodies).

Mycotic Infections

Mycotic infections of the vulva are known as *mycotic vulvovaginitis, aphthous vaginitis, diabetic vulvitis,* and *fungal infection.* The isolation of multiple mycotic strains in the vaginal flora has shown the importance of this etiologic factor in vulvar and vaginal lesions.[77–80]

About 10% of women are considered to be carriers of vulvovaginal fungi: 1% to 2% of non-pregnant women and 5% to 10% of pregnant women present with frank vulvovaginitis. *Candida albicans* (also called *Monilia)* is by far the most frequent etiologic agent. Many factors predisposing women to mycotic infection have been demonstrated. The increased glycogen content of the vaginal mucosa during pregnancy and the elevation of urinary glucose in the diabetic woman explain the increased frequency of mycotic infections in these conditions. Transitory elevations of vaginal glycogen during the progestational phase of the menstrual cycle are responsible for premenstrual exacerbations. The frequency of candidal vaginitis is higher in underprivileged socioeconomic groups, relating the infection to poor hygiene.

Patients with the acquired immune deficiency syndrome (AIDS) develop severe infestation with *Monilia.* Tetracycline and immunosuppressant drugs favor mycotic overgrowth of the normal flora. The dominant symptom is pruritus of the internal surfaces of the labia minora, later extending throughout the vulva. Dyspareunia and, more often, dysuria are found. Abundant creamy white vaginal secretions result in erythema and edema of the vulva. Demonstration of the organism can be accomplished quickly by phase contrast examination of the vaginal secretions, or by Gram stains. The stains of Papanicolaou and of Shorr are useful. Serologic techniques and a culture that will grow typical white colonies are necessary to identify the species.

Macroscopic Appearance. On the mucosae are found multiple white spots with a blue tint, which can be incompletely removed by vigorous scraping (Color Figure 1-5). Ulceration is rare.

Microscopic Appearance. The vulvar epithelium shows leukocytic infiltration, cellular vacuolization, and edema. The small white spots correspond to masses of desquamated squamous cells in varying stages of necrosis. Among these masses are found secondary bacterial flora, especially Döderlein bacilli; the conidia (yeast forms) and the filaments (pseudohyphae) are intimately intertwined (Fig. 1-12). They are mainly localized in the superfical layers of the epithelium. In eroded zones, the fungi penetrate more deeply into the epithelium. Smears stained by the method of Shorr or Papanicolaou show inflammatory alteration of the epithelial cells (eg, eosinophilia, perinuclear haloes, and variations in nuclear size), numerous polymorphonuclear leukocytes and histiocytes, and cellular debris. In the vaginal secretions, the spores and hyphae are dispersed among the squamous cells.

Prognosis, Evolution, and Treatment. When not treated, mycotic infections pass through phases of remission and exacerbation, depending on local or systemic conditions. When infection appears during pregnancy, the mycosis usually regresses spontaneously in the postpartum period, not necessarily reappearing during the course of a subsequent pregnancy. The use of fungicides and antibiotics has led to great progress in the therapy of these infections. The potential of *Candida* infections for more serious infections should be borne in mind: septicemia after ruptured tubo-ovarian mycotic abscess has been reported.

Other Infections

This section briefly mentions the less frequent inflammatory diseases that are encountered in biopsy or cytologic material, except for *Trichomonas vaginalis* infection, which is discussed in Chapter 2.[81]

An *ulcerative vulvitis* may appear after coitus for unknown reasons.[82] *Verruciform xanthoma,* described mostly in the oral cavity, has been mentioned in the vulvar mucosa.[83] *Contact dermatitis* is characterized by eczematous reactions of the vulvar mucosa attributed to substances such as cosmetics, detergents, deodorants, and synthetic fabrics. Recognition of the causal agent helps in treatment of these lesions.

Torulopsis glabrata, a fungus related to *Candida,* has been isolated in vulvar and vaginal infections.[84] *Enterobius vermicularis* migrates from the perianal region and may cause a pruritic vulvovaginitis or be asymptomatic. The worm can be identified in vaginal smears or in cellophane-tape preparations. Vulvar localization of *schistosomiasis* has been reported by Arean.[85] The parasite provokes a papillomatous or ulcerated lesion, sometimes mimicking neoplasia. The recognition of the ova in the biopsy is diagnostic. *Filariasis* has been mentioned as a cause of vulvar elephantiasis. *Entamoeba histolytica* has been identified in rare cases as the cause of ulcerative lesions of the vulvovaginal region. A clitoral localization has been reported.[86] *Arthropodal* inflammatory reactions may last longer than usual and be misinterpreted as lymphomas. Clinical recognition of the mite of *Sarcoptes scabiei* helps eliminate the diagnosis

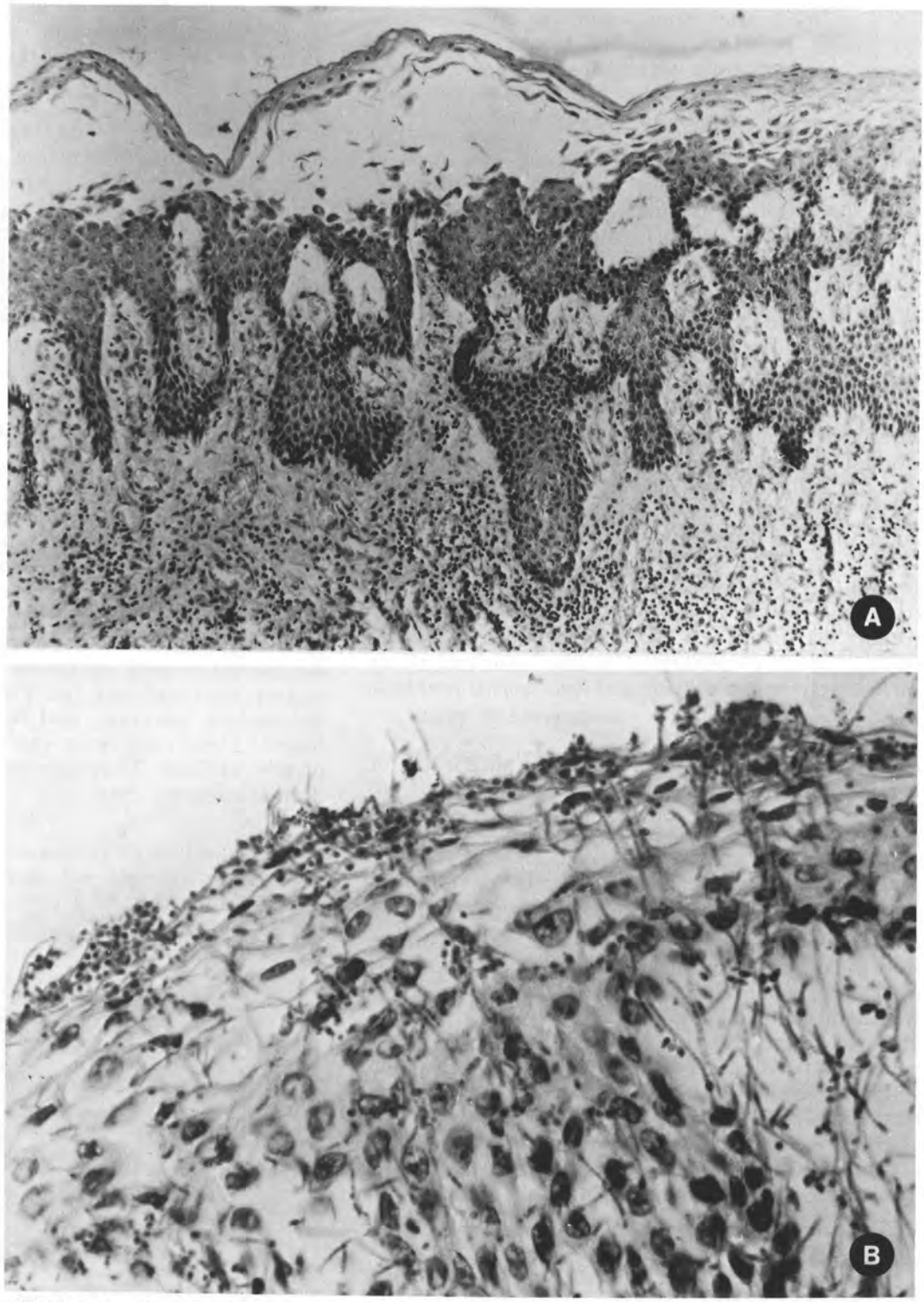


FIGURE 1-12 Mycotic vulvovaginitis showing spores and mycelial filaments.

of a malignant lymphoma. The mite is recovered from the epidermis with a knife blade, mixed with mineral oil, and mounted on a glass slide.[87] *Tinea cruris* and *Tinea versicolor* infections have been noted in the vulva.

Crohn's Disease

Perianal and vulvar lesions such as ulcers, fissures, and enterovaginal fistulas have been described in Crohn's disease.[88,89] In rare instances, they may precede the intestinal manifestations. Microscopically, the lesions consist of inflammatory infiltrates with noncaseating granulomas containing epithelioid and giant cells. Differential diagnosis is made with tuberculosis and foreign body granulomas.

Vulvar Elephantiasis

Vulvar elephantiasis may result from diverse causes. Total or partial obstruction of the lymphatic circulation by inflammatory lesions provokes a subcutaneous proliferation of connective tissue and lymphatics. Chronic infections, particularly lymphogranuloma venereum, tuberculosis, and filariasis, are prominent.[90] Inguinal lymphadenopathy secondary to certain dermatologic conditions of the lower extremity may provoke a homolateral vulvar lymphatic stasis. Vulvar elephantiasis is also referred to as *chronic hypertrophic vulvitis* and *hypertrophic lymphatic stasis.*

Macroscopic Appearance. The appearance is that of hypertrophy and edema of the labia majora and minora. The cutaneous epithelium is thickened, indurated, and hyperkeratotic, explaining the comparison with the skin of an elephant. Ulceration may appear and can be accompanied by pain.

Microscopic Appearance. The most important lesion is lymphatic proliferation and stasis accompanied by chronic inflammatory phenomena. The lymphatic obstruction provokes a secondary proliferation of connective tissue and the development of wide fibrotic zones. The epithelium is hypertrophic with hyperkeratosis and acanthosis; in other foci, the epithelium is thin and ulcerated. One also finds endarteritis, venous thrombi, and perivasculitis. There is a congenital form that is very rarely encountered. Treatment is symptomatic or surgical.

BENIGN TUMORS

Cystic Tumors

Cyst of Bartholin's Gland

Cysts of Bartholin's gland are common and appear at any age before the menopause.[91] The obliteration of the excretory duct of the gland by an acute infection such as gonorrhea later provokes the appearance of cysts measuring up to 5 cm in diameter. The cyst is found in the parenchyma of the inferior third of the labium majus. It presents as a hard, round, slightly tender mass adherent to the surrounding tissues. It is formed by the dilatation of the excretory duct and is therefore lined by squamous epithelium; the compressed glandular tissue is atrophic. The cystic contents are clear or blood-tinged. Clear translucent fluid results from obstruction without inflammatory response. More rarely, dilatations of the glandular acini occur, giving a multicystic appearance.[92] These cysts are lined by a mucus-secreting columnar epithelium. In some cases, the glandular elements are totally replaced by an inflammatory granulation tissue with secondary synechiae of the cystic layers (Fig. 1-13).

Sebaceous Cyst

The sebaceous cyst presents as a small, smooth, subcutaneous nodule associated with the orifice of the pilosebaceous apparatus.[93] The cyst is formed by secondary obliteration and dilatation. It is situated in the labia majora or minora and measures from several millimeters to several centimeters in diameter. The acinar structure of the sebaceous glands disappears because of compression, and the cavity of the cyst is filled with the products of desquamation of the nonkeratinized squamous epithelium of the excretory duct and with fat. The cyst may open onto the surface, ulcerate, and become secondarily infected. These cysts recur easily if they are not completely excised. They are less common than epidermal inclusion cysts.

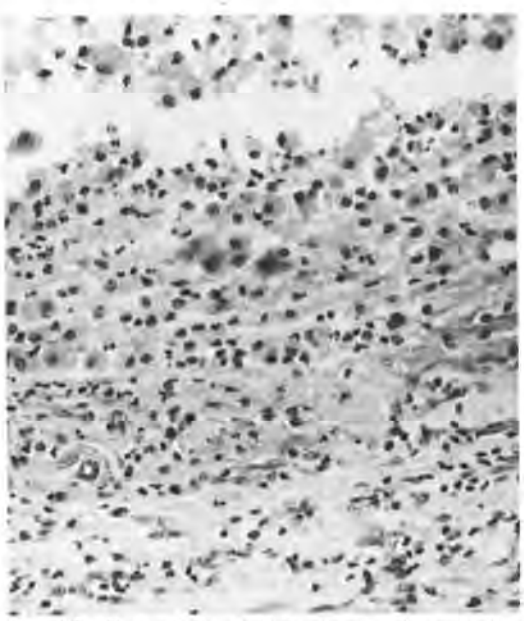


FIGURE 1-13 Cyst of Bartholin's gland: microscopic appearance, showing replacement of epithelial lining by inflammatory cells.

Epidermal Inclusion Cyst

The epidermal inclusion cyst is constituted from fragments of epithelium included in the subcutaneous connective tissue after trauma or surgery (eg, perineorrhaphy, episiotomy). It can also originate from foci of squamous metaplasia in a sebaceous gland.[94] Clinically, it presents the same appearance as the sebaceous cyst and contains a grumous pale yellow substance. It may become inflamed or reach a large volume.

Microscopically, it is lined by a keratinizing squamous epithelium. Fragments of keratin included within the cyst may behave as foreign bodies and provoke a granuloma rich in multinuclear giant cells. These cysts may disrupt or, secondarily, calcify. Rare malignant transformation has been reported. Other postsurgical tumors have been reported, including endometriosis, granulomatous polyps, and fibroepithelial polyps.

Mesonephric Cyst (Cyst of Gartner's Duct)

Cysts of Gartner's duct develop from vestiges of the wolffian duct.[95] They are lined by a columnar or cuboidal, nonmuciparous, and rarely ciliated epithelium. Smooth muscle cells are often identified in the wall.

Cyst of the Canal of Nuck

The persistence of the peritoneal diverticulum of the labium majus gives rise to cysts lined by a flattened mesothelium. They are located near the insertion of the round ligament.[96]

Mucous Cyst

Mucous cysts are predominantly located in the vestibule. Microscopically, they are lined by a mucus-secreting epithelium of cuboidal or columnar cells that stain with Alcian blue and mucicarmine stains. They are probably derived from the urogenital sinus epithelium that forms the vestibule.[97–99]

Cyst of Skene's Glands

Cysts of the paraurethral glands are rare but are occasionally observed in neonates. They are lined by a transitional-type epithelium.[100,101]

Solid Tumors

Squamous Papilloma

The true papilloma is a single verrucous tumor that is slow-growing and appears in elderly women at the level of the labia. It is composed of a connective tissue stroma covered by squamous epithelium showing pronounced hyperkeratosis and papillomatosis. This entity should be differentiated from the fibroepithelial polyp.[102]

Fibroepithelial Polyp

Fibroepithelial polyps of the vulva are common.[103,104] Macroscopically, they are small, papillomatous lesions, large pedunculated tumors, or any intermediate type. The tumors have a soft to rubbery consistency. Microscopically, they consist of loose, edematous connective tissue covered by a hyperkeratotic and acanthotic squamous epithelium (Fig. 1-14). Stromal cells differentiate along two cell lines: fibroblasts and myoblasts. The presence of atypical cells in the stroma should not mislead the pathologist to report the lesion erroneously as sarcoma botryoides.[103] These cells do not invade the overlying epithelium. Immunohistochemical reactivity for vimentin and desmin is present in some cases, supporting the myofibroblastic nature of these polyps.[104] Pigmentation may be abundant, suggesting erroneously the diagnosis of nevus or acanthosis nigricans.

Keratoacanthoma

This rare lesion is a fast-growing proliferation of the squamous epithelium, forming a central mass of keratin that is pushed upward from the surface. Flow-cytometric analysis has shown that this rapidly growing lesion that spontaneously regresses is a true neoplasm and not a reactive hyperplasia.[105,106] Differential diagnosis, as in other more common cutaneous locations, is made with squamous cell carcinoma.

Warty Dyskeratoma

Warty dyskeratoma is a benign tumor occurring as an elevated nodule with a keratotic umbilicated center. It has been reported very rarely in the vulva.[107] Microscopically, it shows an epidermal invagination filled with acantholytic, keratinous material. The bottom of the invagination is covered with elongated dermal papillae lined with a single layer of basal cells. Degenerated cells located in the granular layer (corps ronds), also described in *Darier's disease*, are observed.

Seborrheic Keratosis

The vulvar localization of this flat, pigmented, warty lesion is rare. The microscopic appearance consists of hyperkeratosis, hyperplasia of the parabasal layer, and keratin cysts.

Angiokeratoma

Angiokeratoma looks clinically like a dark red angioma and occurs more frequently on the vulvar mucosa of older patients.[108,109] It is a mixed lesion showing dilated capillaries of the upper dermis associated with hyperkeratosis, papillomatosis, and acanthosis of the overlying squamous epithelium. Some epithelial cords originating from the surface epithelium surround the vascular channels. Erosion of the

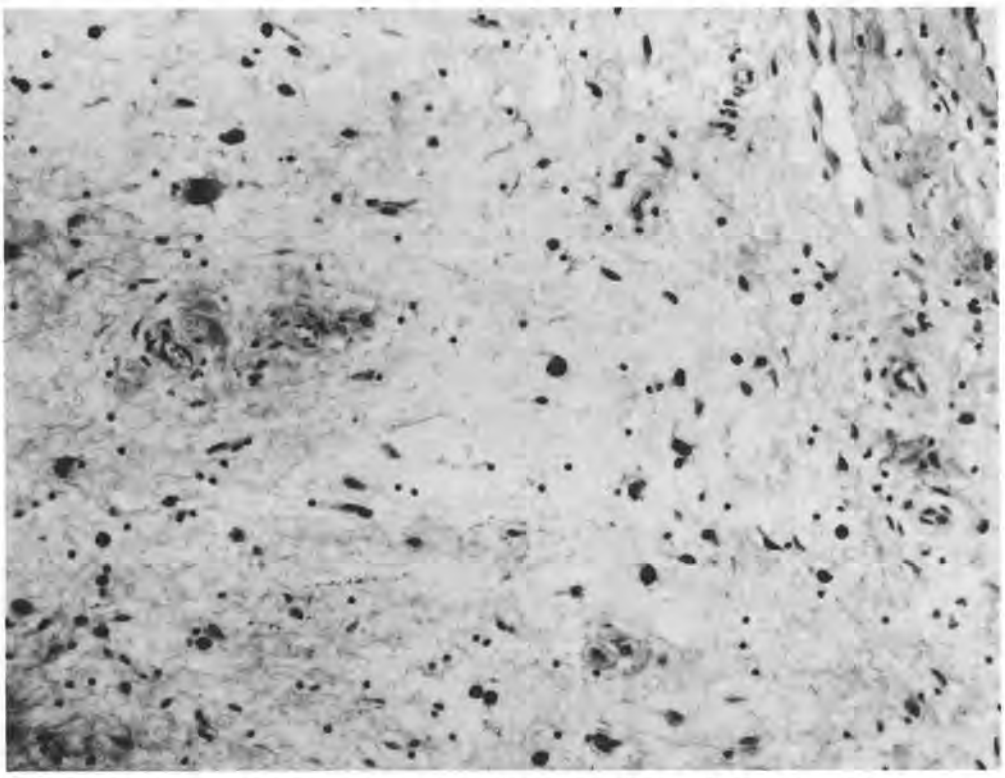


FIGURE 1-14 Stroma of a fibroepithelial polyp of the vulva. The myxoid stroma contains inflammatory cells, variably sized spindle cells, and scattered giant cells with one or more large hyperchromatic nuclei.

superficial mucosa explains the frequent secondary infection. Electron microscopic studies suggest that the lesion is a modified capillary hemangioma.

Urethral Caruncle

The urethral caruncle is a common, nodular, inflammatory rather than neoplastic lesion. It is a single or, rarely, multiple mass, situated at the level of the urethral meatus, in the proximal portion of the urethral wall, or arising from a localized ectropion of the urethral mucosa.[110] It measures several millimeters in diameter and presents as a polypoid or pedunculated mass of bright red color, with a smooth or papillary surface. Microscopically, there is edematous granulation tissue rich in lymphocytes and plasma cells and abundantly vascularized, covered by urethral mucosa (Fig. 1-15). Papillomatous, angiomatous, and granulomatous types are encountered according to the major histologic alterations. The epithelium may ulcerate. This lesion is often asymptomatic or may manifest itself by dysuria or bleeding on contact. Differential diagnosis must be made with carcinoma.

Syringoma

Syringoma is a benign tumor of the eccrine sweat gland duct.[111–113] Clinically, it is constituted by skin-colored or yellow papules situated on both labia majora. Differential diagnosis has to be made with *Fox-Fordyce disease*.[114]

The histology reveals cystic ducts lined by a double layer of epithelial cells of eccrine type with characteristic tail-like strands. The ducts are sometimes filled with keratin. Glycogen accumulation may be observed in tumor cells.

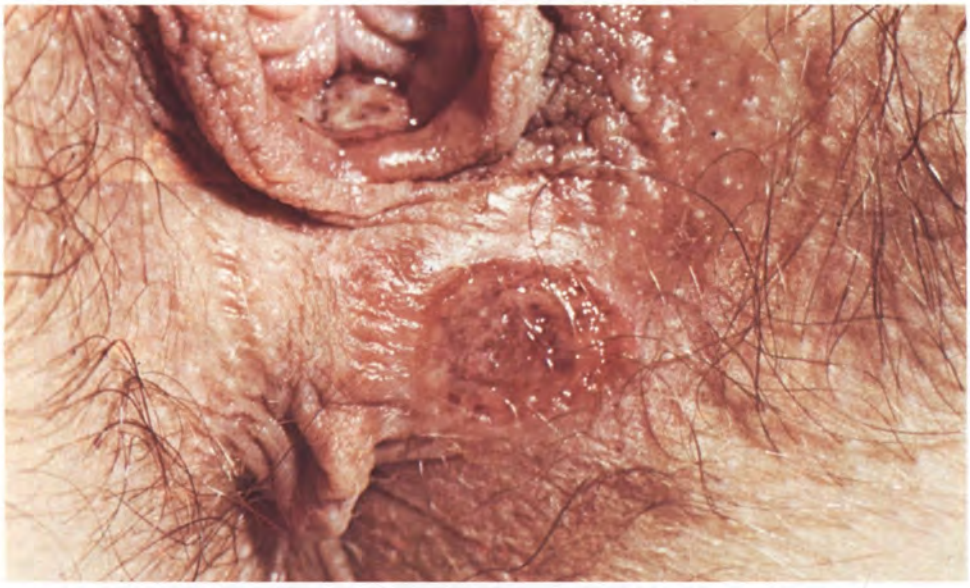
Fibroma and Leiomyoma

Fibroma and leiomyoma are slowly growing, encapsulated benign tumors, situated most frequently at the level of the labia majora or the clitoris. They originate from the connective tissue or from smooth muscle fibers and occur in adults.[115] They are usually small, but in certain exceptional cases may weigh several kilograms.

Microscopic Appearance. The tumor is composed of fusiform connective tissue cells with oval nuclei. In the true fibromyoma, one finds both smooth muscle fibers and collagen fibers. Edema is common. Hyaline or cystic degeneration and calcification may be present. Vascularity varies from one tumor to another. Malignant transformation is extremely rare.

Vascular Tumors

Hemangioma. The hemangioma, or angioma, is seen as a round, wine-red, elevated mass, situated most often in the labia majora. The most common type is cherry hemangioma.



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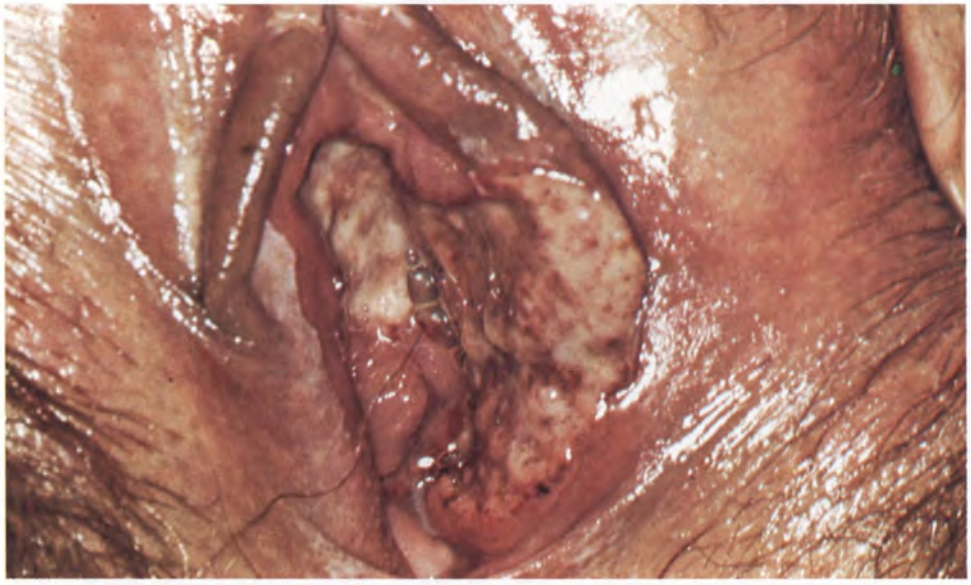
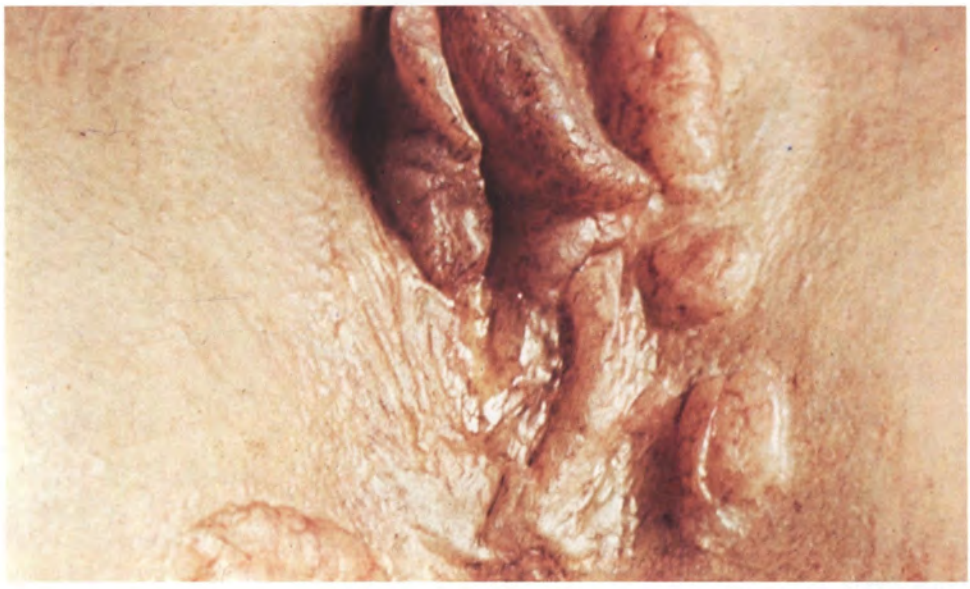


Color Figure 1-2

Color Figure 1-1 Clinical appearance of syphilitic chancre.

Color Figure 1-2 Clinical appearance of ulcus vulvae acutum (Behçet's syndrome).



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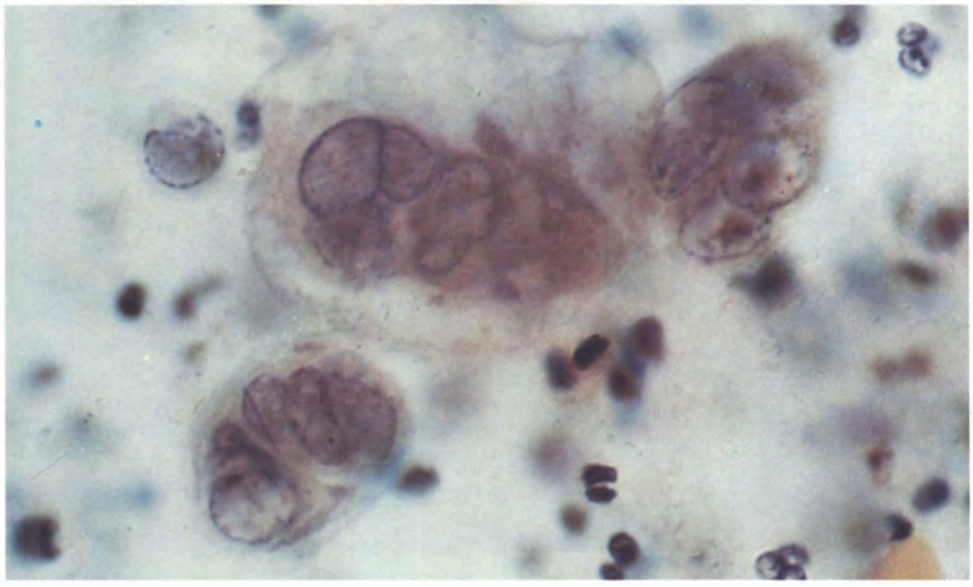
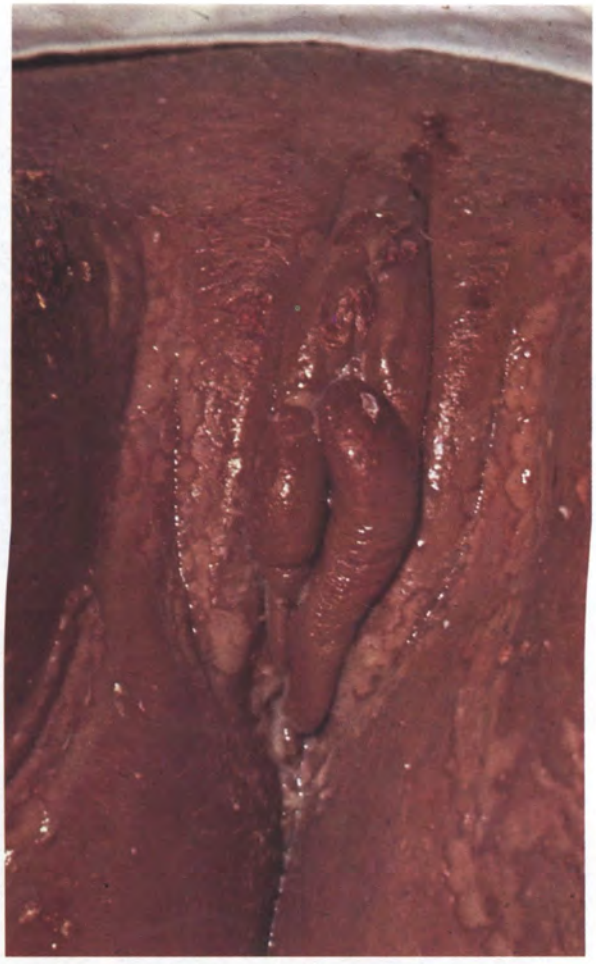


Color Figure 1-4

Color Figure 1-3 Clinical appearance of condyloma acuminatum.

Color Figure 1-4 Vulvovaginal smear showing herpes simplex.



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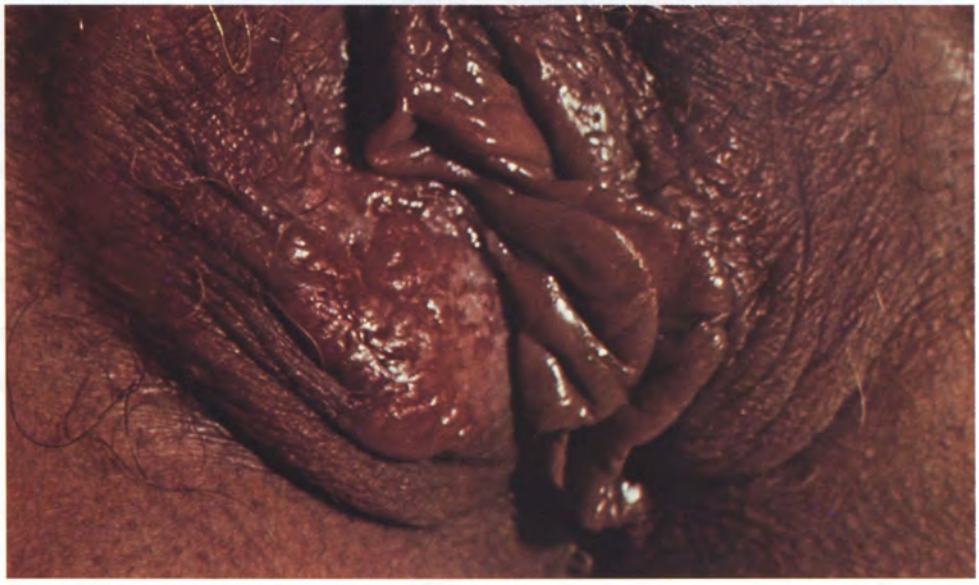
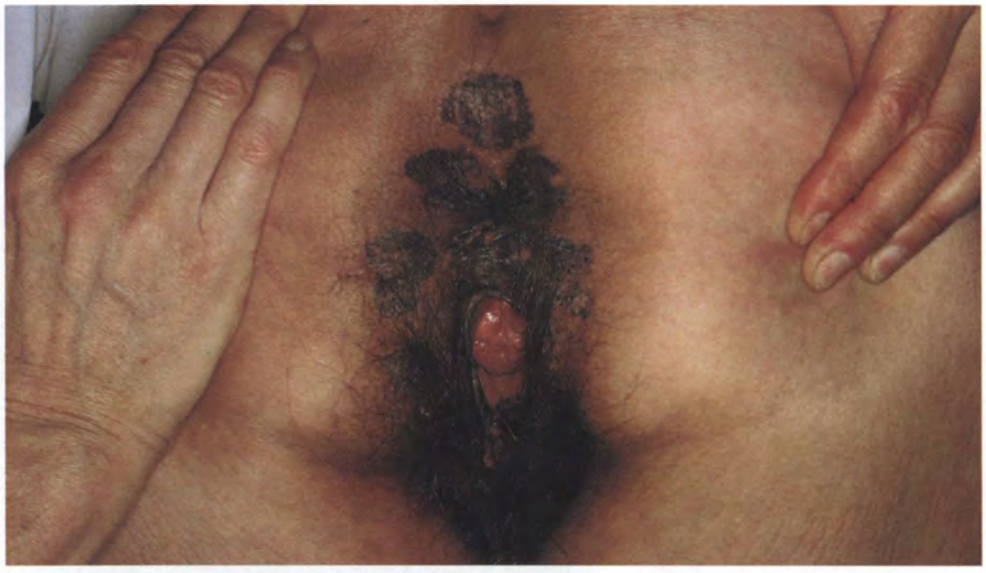


Color Figure 1-6

Color Figure 1-5 Clinical appearance of mycotic vulvovaginitis.

Color Figure 1-6 Clinical appearance of intraepithelial carcinoma.



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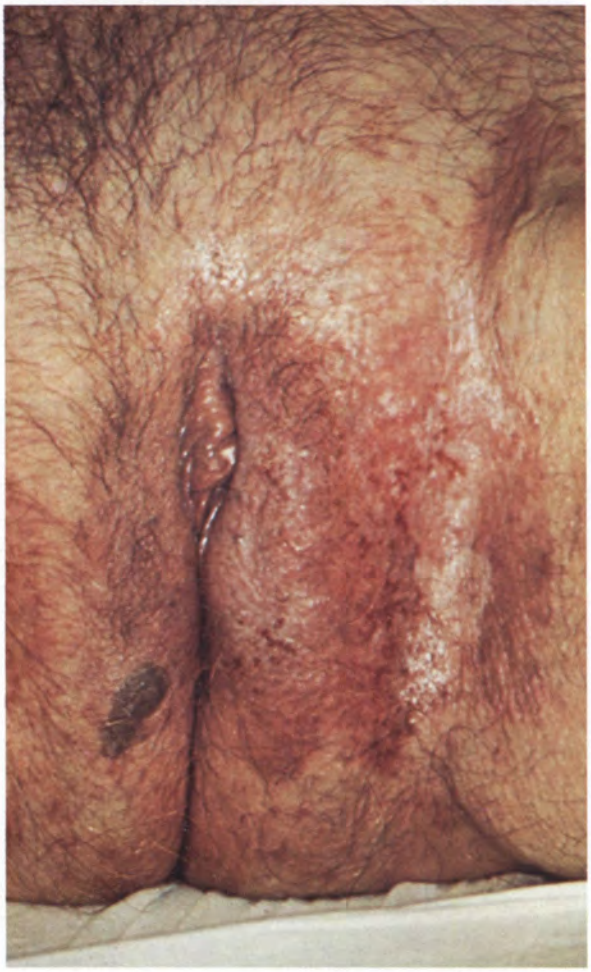
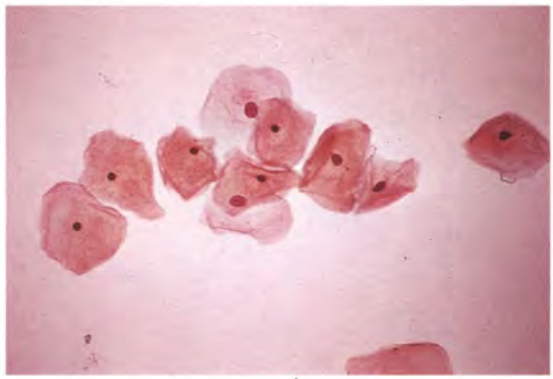


Color Figure 1-8

Color Figure 1-7 Bowenoid papulosis. Multiple pigmented papules of perianal region.

Color Figure 1-8 Clinical appearance of Paget's disease.



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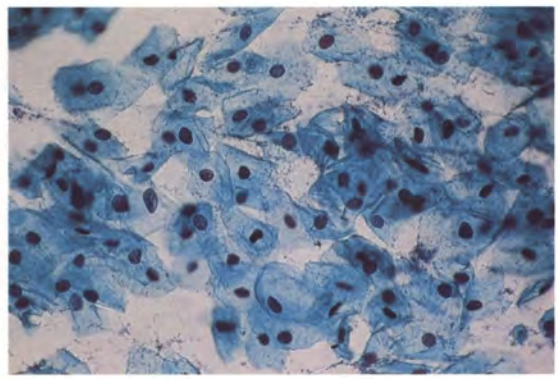

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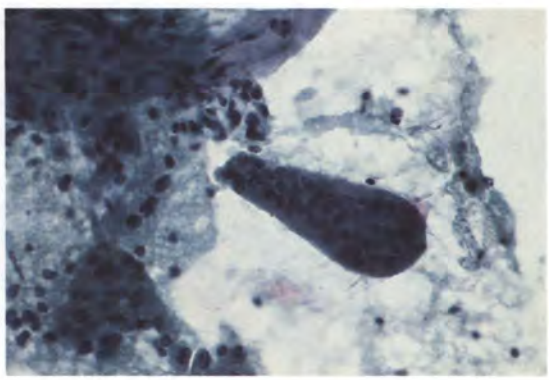

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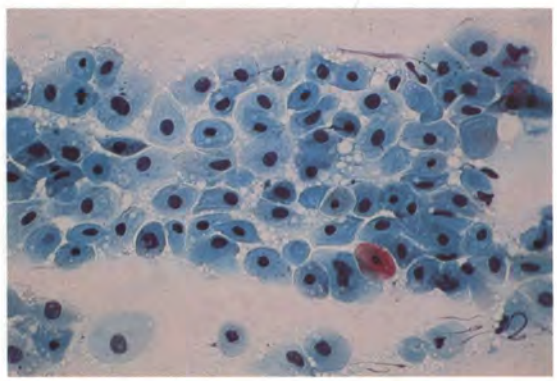


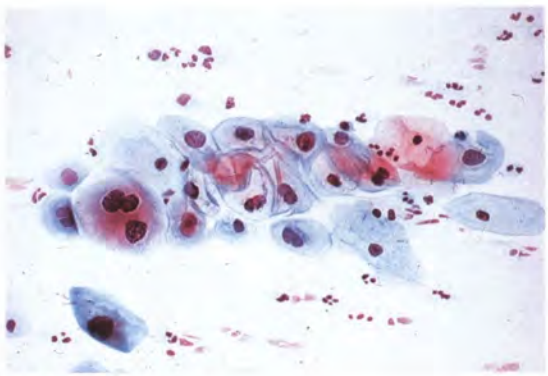
Color Figure 2-4

Color Figure 2-1 Vaginal smear of estrogenic type. Predominantly superficial cells.

Color Figure 2-2 Vaginal smear of luteal type. Mostly intermediate cells.

Color Figure 2-3 Trophoblast in vaginal smear.

Color Figure 2-4 Vaginal smear of atrophic type. Parabasal cells.



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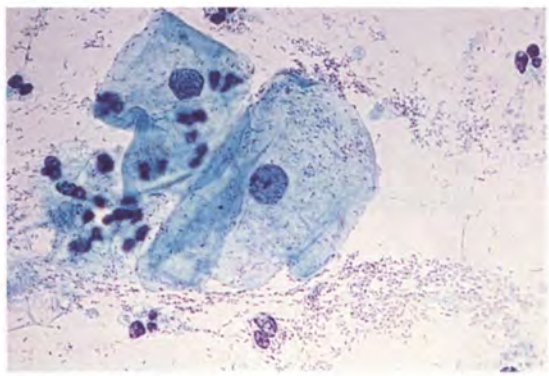

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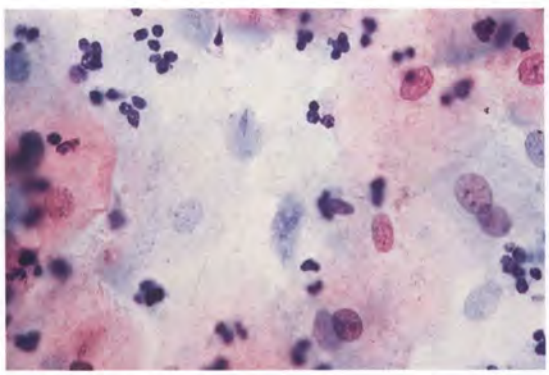

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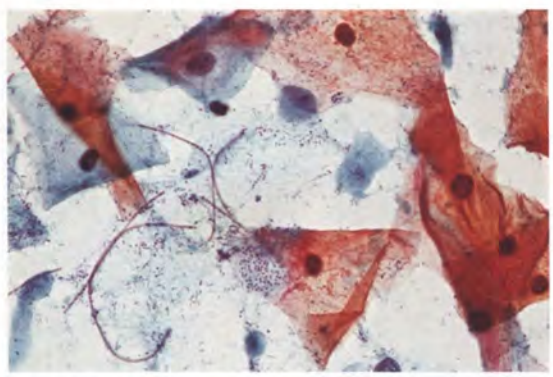


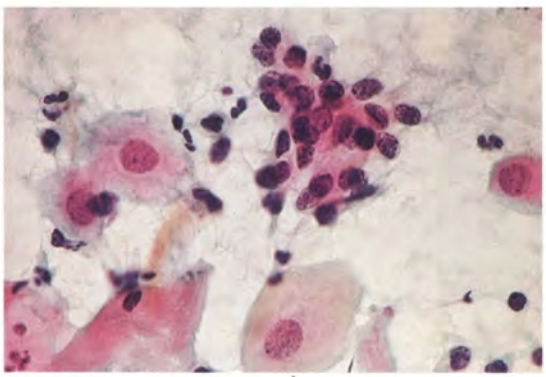
Color Figure 2-8

Color Figure 2-5 Atrophic vaginitis with nuclear atypia. This atypia disappeared after an estrogen injection.

Color Figure 2-6 Clue cells in *Gardnerella* vaginitis: Bacteria partially covering squamous cells.

Color Figure 2-7 *Trichomonas* vaginitis in vaginal smear. Two organisms are seen at center of figure.

Color Figure 2-8 *Leptothrix* organisms in vaginal smear.



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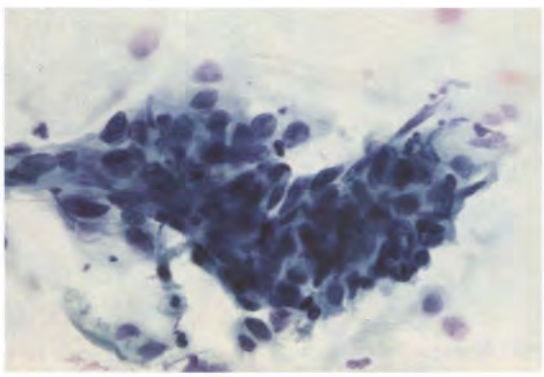

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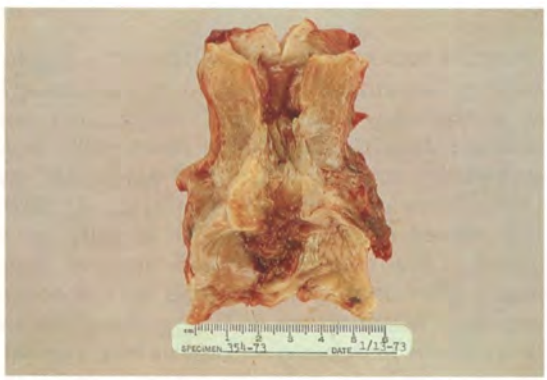

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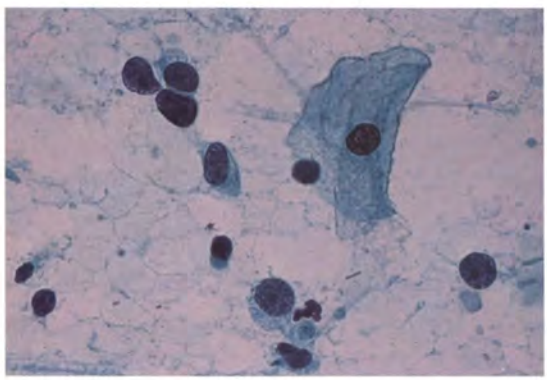

Color Figure 2-12

Color Figure 2-9 Vaginal adenosis. Smear of lateral vaginal wall shows well-preserved endometrial-type cells.

Color Figure 2-10 High grade VAIN in a 54-year-old woman.

Color Figure 2-11 Clear cell adenocarcinoma of vagina and cervix in adolescent girl who was exposed in utero to diethylstilbestrol (DES).

Color Figure 2-12 Clear cell adenocarcinoma of vagina. Malignant glandular cells and one benign squamous cell in vaginal smear from 14-year-old girl who was exposed in utero to DES.

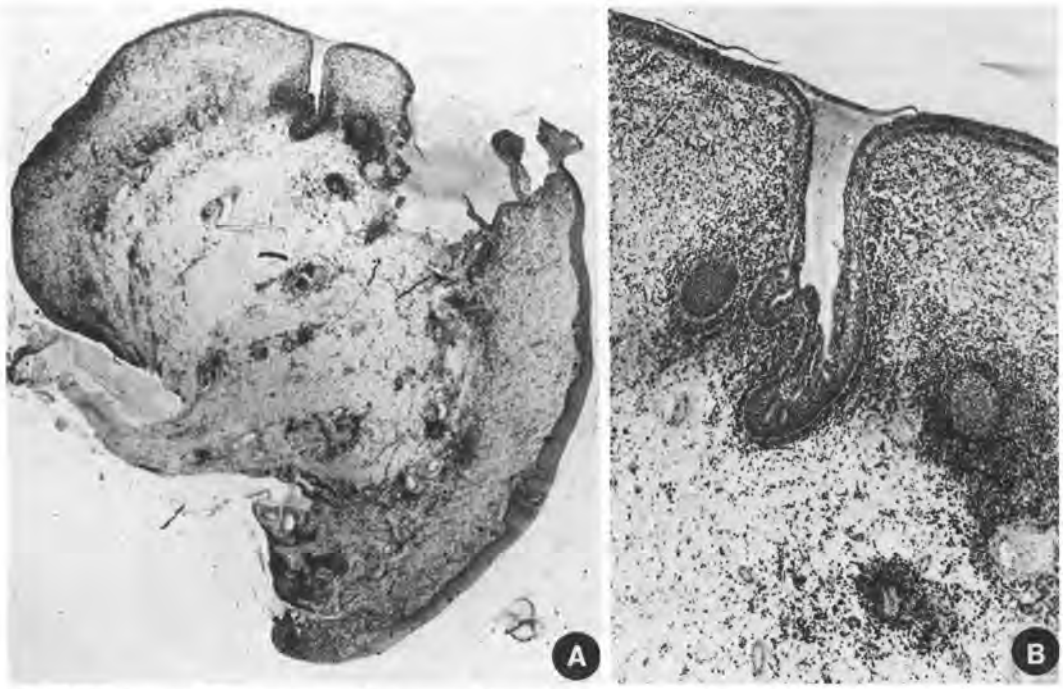

FIGURE 1-15 Urethral caruncle. **(A)** View of the entire lesion. **(B)** Epithelium of urethral type covering an edematous stroma infiltrated by leukocytes.

Histologic examination reveals vascular channels disposed without any order and separated by thin connective tissue septa. The vascular walls are capillary in type. The lesion is not encapsulated. Hemorrhage may take place within the vascular formations and provoke the deposit of hemosiderin within macrophages situated in the stroma. In old lesions, the vessels may become completely sclerosed, leaving only the connective tissue stroma containing these iron-laden macrophages. The evolution of these tumors is benign. *Granuloma pyogenicum,* a lesion composed of lobular arrays of small capillaries in an inflammatory background, may be seen in the vulvar region, most frequently during pregnancy.

Lymphangioma. Lymphangioma, a proliferation of lymphatic vessels, can be encountered but is less common.

Other Vascular Tumors. *Hemangiopericytoma,* a tumor arising from the pericytes, is rarely observed in the vulva. Clinically, it consists of a small mass, easily bleeding and painful. The histology reveals round or spindle-shaped cells proliferating around vascular spaces.[116] Very rare cases of *angiosarcoma* have been cited.[117] A single case of *epithelioid hemangioendothelioma,* a tumor of intermediate malignancy, has been reported.[118]

Lipoma

Lipoma is a benign tumor constituted of adipose tissue. It is soft, encapsulated, and occasionally pedunculated. It is most often found in the labia majora and rarely attains a considerable weight. It is composed of fat cells supported by a more or less abundant connective tissue network.[119,120] When the connective tissue is prominent, it should be called *fibrolipoma.*

Mixed Tumor (Pleomorphic Adenoma)

Mixed tumors are extremely rare. They are histologically similar to their salivary gland counterpart.[121]

Other Benign Soft Tissue Tumors

Among the rare connective tissue tumors are *osteoma, chondroma,* and *myxoma.* The latter is formed by a tissue analogous to the embryonic mesenchyme and is composed of stellate cells anastomosed in a mucoid substance containing collagen fibers. A certain number of fibroepithelial polyps with a loose, edematous stroma have been erroneously labeled *myxomas.*

Glomus tumor has been reported rarely.[122] Single or multiple *neurofibromas* of the vulva are not rare in patients with von Recklinghausen's disease. *Neurilemoma* has been described.[123] Steeper and Rosai described a lesion that they named *aggressive angiomyxoma.*[124] These lesions are usually large, gelatinous, locally infiltrative masses in young women and frequently are related to Bartholin's gland. Histologically, they are characterized by a loose myxoid stroma, prominent thick-walled and often hyalinized blood vessels, and, in some cases, small proliferating

benign-appearing glands that probably are entrapped rather than neoplastic (Fig. 1-16). Local recurrence is common, but distant metastases have not been noted.

Angiomyofibroblastoma is a rare mesenchymal tumor.[125] Clinically, it presents in young women as a superficial, small, soft mass of the vulvar region. Microscopically, it may be similar to an aggressive angiomyxoma. It is a circumscribed nodule of irregularly disposed stromal cells with abundant thin-walled vessels. Immunohistochemically, there is reactivity for vimentin and desmin. This benign neoplasm should not be confused with aggressive angiomyxoma, which is locally infiltrating, generally larger, more myxoid, contains larger and thicker-walled vessels, is desmin negative, and frequently recurs.

Other rare benign mesenchymal tumors that have more or less similar structural patterns should be mentioned. The *myxoid epithelioid leiomyoma* is more cellular but lacks the abundant vascularity of aggressive angiomyxoma and angiomyofibroblastoma. The *myxoid peripheral nerve sheath tumor* shows reactivity for S-100 protein and lacks the vascularity of angiomyoblastoma. *Nodular fasciitis* has been reported in the vulva.[126]

Papillary Hidradenoma

Papillary hidradenoma (hidradenoma papilliferum) is a benign, frequently asymptomatic lesion of the sweat glands first described by Pick in 1904; more than 300 cases have been reported.[127–129] This tumor presents as a round or oval, firm, painless, well-encapsulated nodule measuring 0.5 to 2 cm. There is sometimes central ulceration, with a dark red granular area that bleeds easily (umbilication). Papillary hidradenoma is encountered in patients between 30 and 70 years of age and is found in the labia majora or, more rarely, the labia minora, the interlabial groove, or the posterior commissure. Most cases appear in Caucasian women, and the lesion is rare in black women. It originates in sweat glands that are residua of the embryonic mammary crest. The hypothesis of sudoriferous origin is based on: (1) the histologic similarity of the lesion to sweat glands; (2) localizations corresponding to regions where apocrine glands are found; and (3) histochemical and electron microscopic data. There is a striking resemblance of this lesion to nipple adenoma of the breast, another gland of similar histogenesis.

Histologic Appearance. This tumor is composed of trabecular, tubular, or papillary formations included within a cystic nodule and covered with bistratified epithelium (Fig. 1-17). This epithelium consists of two cell types: (1) large columnar cells with basal nuclei and eosinophilic cytoplasm, showing the picture of apocrine secretion with granules that are periodic acid-Schiff (PAS) positive and diastase-resistant; and (2) external myoepithelial cells, which have the immunohistochemical properties of smooth muscle fibers. These latter cells are themselves bordered by thin connective tissue bundles. Inflammatory reaction of the stroma is minimal.

The hyperplastic, richly papillary appearance and the presence of mitoses have caused this tumor to be confused on occasion with a well-differentiated adenocarcinoma. If the lesion is ulcerated, it must not be confused with a pyogenic granuloma or an epithelioma. Most hidradenomas are cured by local excision. However, one case of hidradenocarcinoma has been reported,[130] and we have seen a metastasizing adenocarcinoma that probably arose in a papillary hidradenoma (Fig. 1-18).

Although not a tumor, *Fox-Fordyce disease,* or "apocrine miliaria" must be mentioned as involving the vulvar apocrine glands.[114] Numerous apocrine

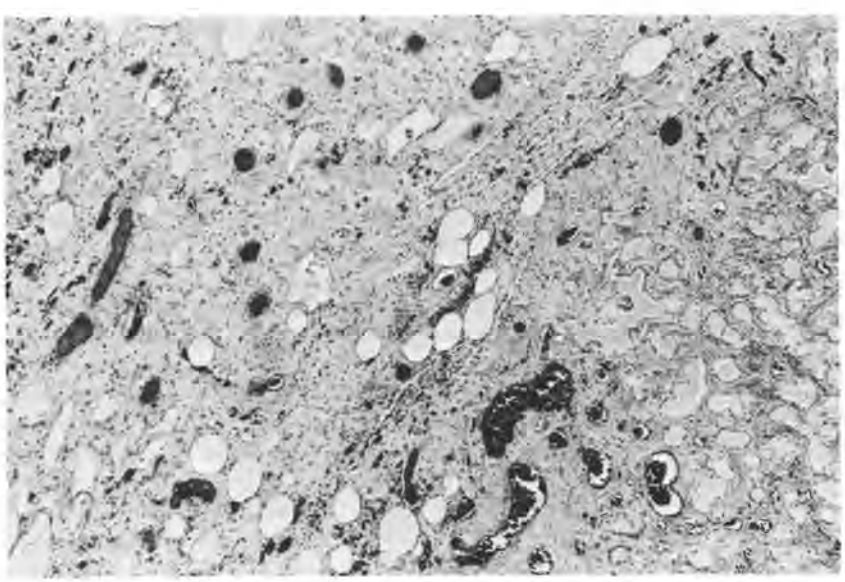

FIGURE 1-16 Aggressive angiomyxoma: myxoid connective tissue containing prominent blood vessels and a cluster of small muciparous glands (*right*) invades pelvic fat in this lesion that recurred clinically at 6 and 9 years after initial local resection.

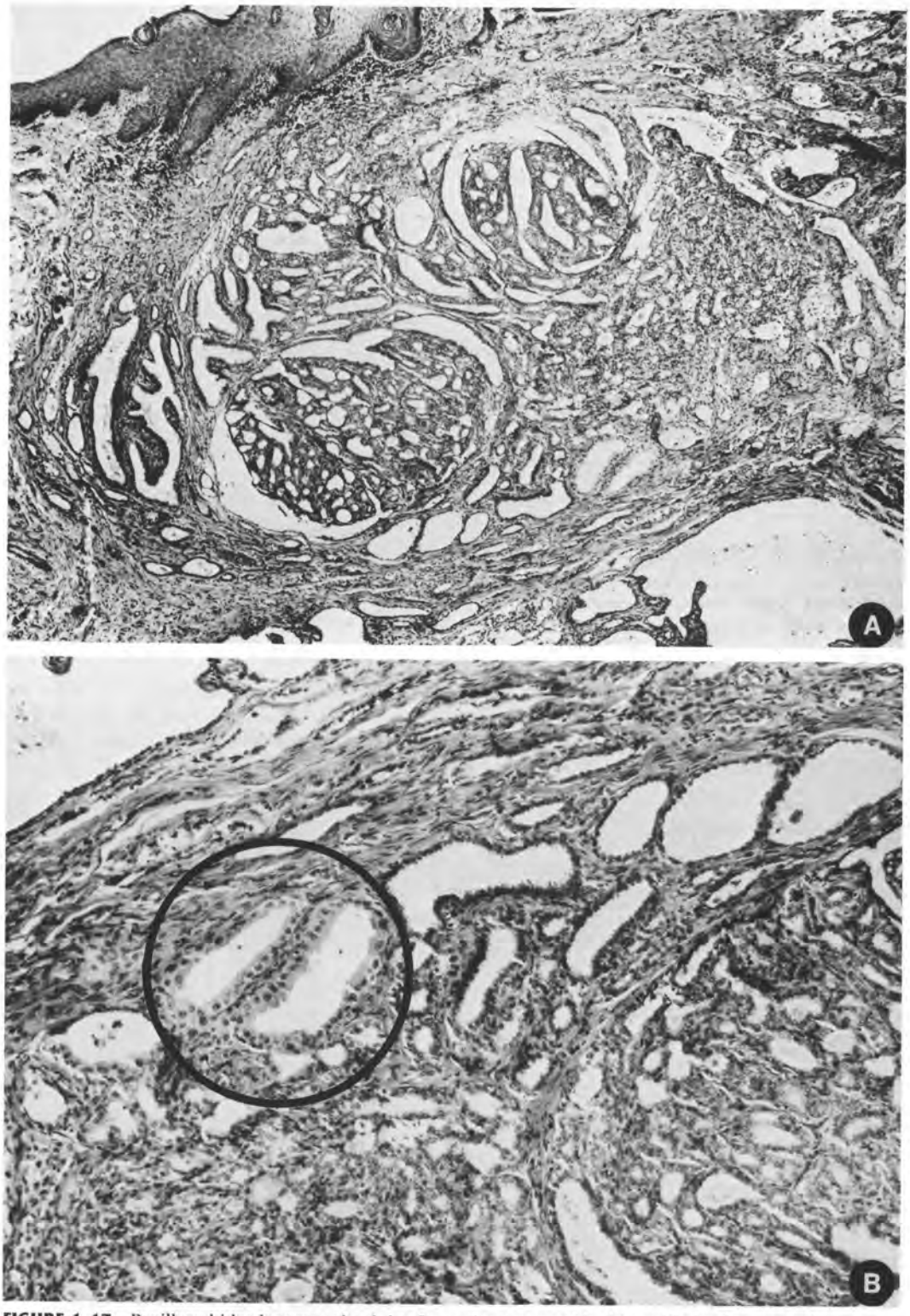

FIGURE 1-17 Papillary hidradenoma: glandular formations covered by bistratified columnar epithelium with foci of apocrine metaplasia.

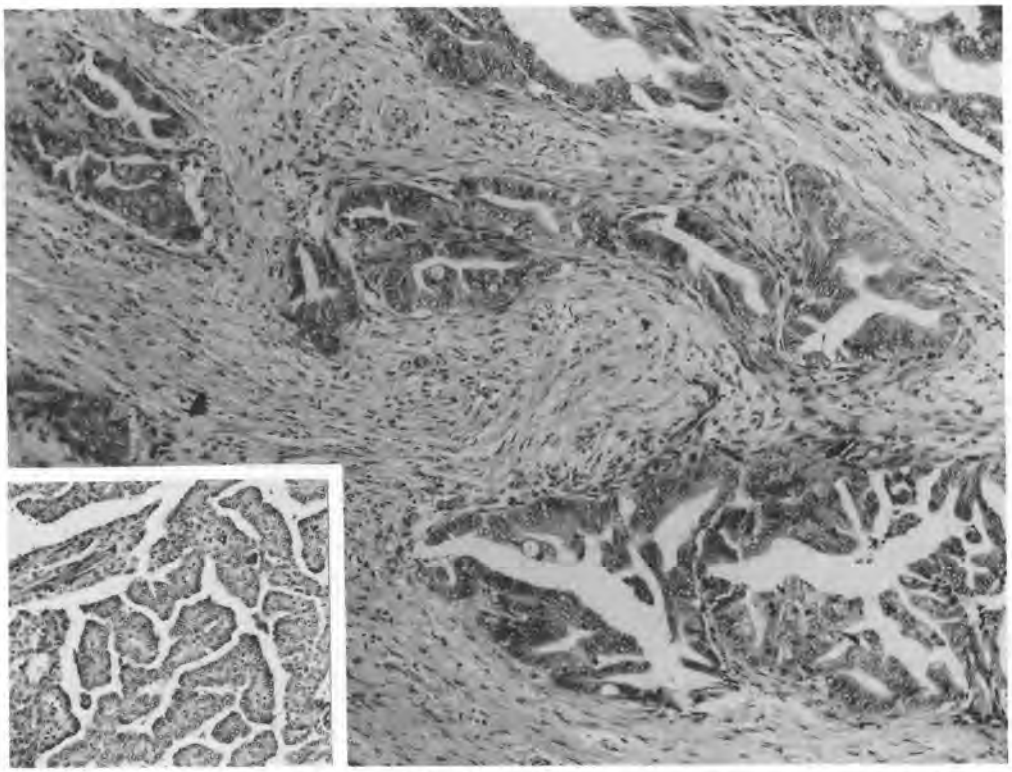

FIGURE 1-18 Invasive adenocarcinoma of vulva in a young woman. This tumor metastasized to the inguinal lymph nodes. Papillary architecture is seen focally in the tumor (*inset*), suggesting possible origin in a papillary hidradenoma or a similar sweat gland tumor.

sweat retention cysts resulting from obstruction of the ducts are seen in this condition; they are accompanied by acanthosis and dermal inflammation, the latter often granulomatous.

Clear Cell Adenoma

Clear cell adenoma is rarely observed in the vulva.[131,132] Presumably derived from eccrine sweat glands, this tumor is composed of solid lobules surrounded by thin collagen bands. Two types of cells are recognized: polygonal cells with small round central nuclei, and round cells with a small dense nucleus surrounded by voluminous clear cytoplasm.

Granular Cell Tumor

Granular cell tumor, a rare tumor described by Abrikosov in 1926, can involve the vulva.[133–135] Rare cases have been reported in prepubertal girls.[134] The tumor is also known as *granular cell myoblastoma* and *Abrikosov's tumor.*

The *histogenesis* of these tumors was subject to debate. According to Abrikosov, they were tumors of muscular origin. A schwannian origin is now widely accepted.[136]

Macroscopic Appearance. The lesion is a firm, well-demarcated, non-tender tumor with smooth surfaces. It measures no more than several centimeters and is situated on the labia majora. In the vulva, the epithelium may be thinned or may show a reactive hyperplasia.[131] Sectioning reveals a yellow color and a fascicular structure.

Microscopic Appearance. Large collagenous bundles are seen separating solid nests of large cells. There are small, round or oval nuclei and abundant, finely granular, PAS-positive cytoplasm (Fig. 1-19). Often a pseudoepitheliomatous hyperplasia of the overlying squamous epithelium is present and raises the differential diagnosis with squamous carcinoma.[135] The presence of the underlying tumor helps to make the diagnosis. Wide excision is necessary to avoid local recurrence. Rare cases with lymph node metastases have been reported.[137] These do not differ histologically from nonmetastasizing tumors.

ECTOPIC TISSUE

The incomplete regression of the mammary crest, which extends from the axilla to the inner thigh, explains the presence of breast tissue in the vulvar region.[138,139] Another source of ectopic breast tissue may be modified sweat glands.

Different forms of breast lesions can be recognized, such as fibroadenoma (Fig. 1-20), fibrocystic change, lactating tissue, adenocarcinoma, and sar-

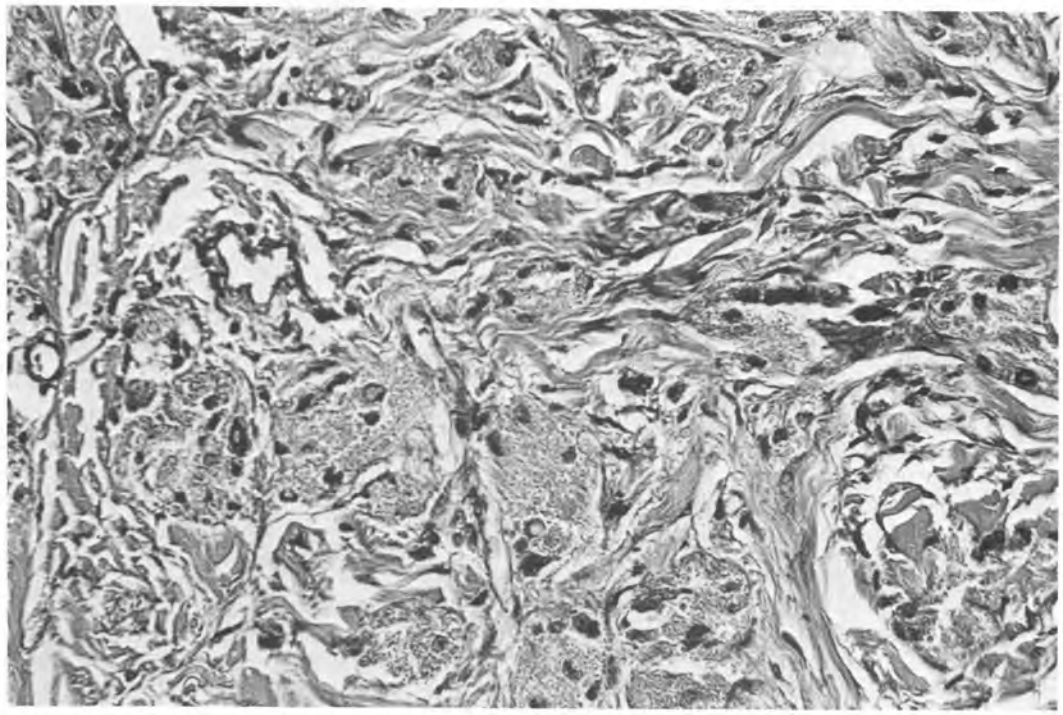

FIGURE 1-19 Granular cell tumor of vulva.

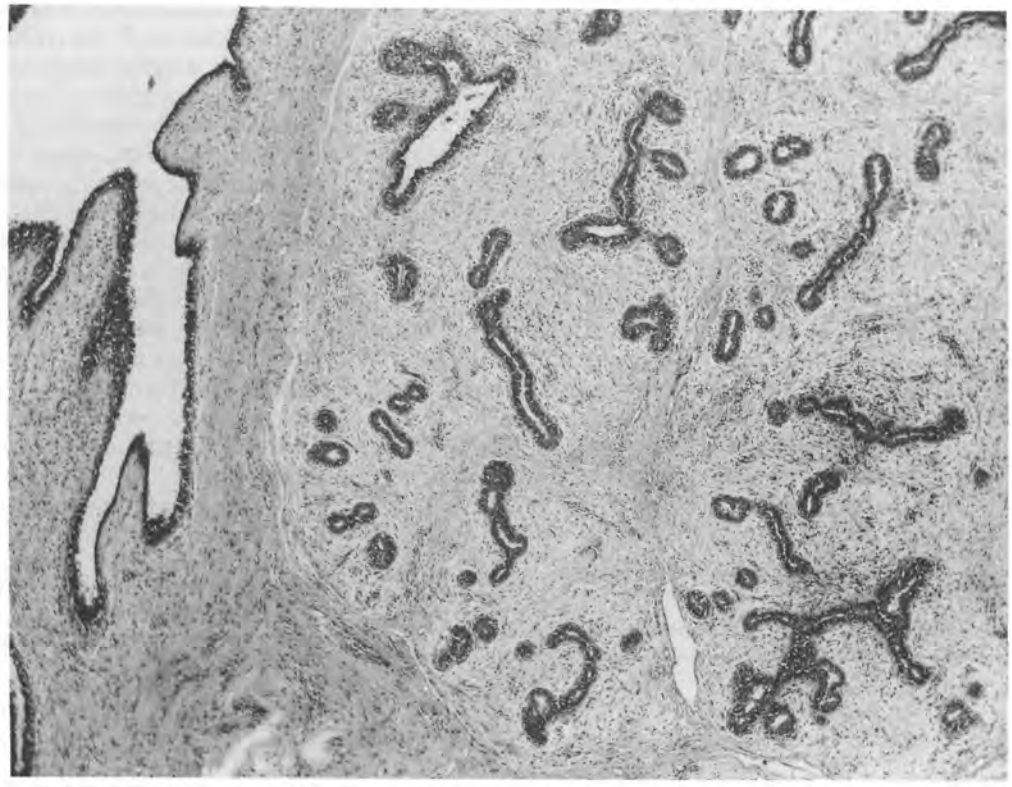

FIGURE 1-20 Fibroadenoma (*right*) arising in vulvar ectopic mammary tissue (*left*).

coma. Some of the benign forms may enlarge with menstruation or pregnancy. Carcinoma arising in vulvar breast tissue has been reported very infrequently.

VULVAR "DYSTROPHIES" OR NONNEOPLASTIC EPITHELIAL DISORDERS AND VULVAR INTRAEPITHELIAL NEOPLASIA (VIN)

Much confusion has arisen in the use of the clinical and histologic definitions that characterize vulvar degenerative and hyperplastic disease. In 1881, Breisky described a progressive atrophy and fibrosis of the vulvar mucosa, which he called *kraurosis vulvae.*[140] This term has since been used to define different atrophic conditions of the vulva, just as the term *leukoplakia* has been popularized by clinicians to characterize white precancerous lesions.

The variety of clinical and morphologic conditions, the different terms used to describe these lesions, the lack of correlations among the findings and opinions of clinicians and pathologists, and the obscure pathogenesis of these conditions partially explain the confusion that has existed in this field. The various terms that have been used for atrophic conditions include *leukoplakia, kraurosis vulvae, white spot disease, sclerotic dermatosis, atrophic* and *hyperplastic vulvitis, neurodermatitis, lichen simplex chronicus,* and *senile atrophy.*

To clarify the situation, the International Society for the Study of Vulvar Disease (ISSVD) proposed the term *dystrophy* in 1976 to qualify atrophic and hyperplastic lesions of the vulvar epidermis and mucosa and the mixed forms resulting from the coexistence of both alterations (Table 1-2).[141] Although this system was preferable to the anarchy that often had prevailed, we found it far from ideal for several reasons:

1. There is little evidence that these lesions are really dystrophic (defective development or degeneration) in the true sense of the word.
2. A term consecrated by long usage and familiar to gynecologists and pathologists alike—*dysplasia*—is available for the most important lesion: so-called hyperplastic dystrophy with atypia. Following the nomenclature adopted for cervical lesions, the term *vulvar intraepithelial neoplasia* (VIN) has been proposed to replace or coexist with dysplasia.[142,143]
3. Although combinations of more than one of these lesions undoubtedly occur, in our experience they are uncommon and probably are the result of coincidence rather than common causality; the use of the term *mixed dystrophy* promotes the misconception that lichen sclerosus is related to dysplasia and thus to carcinoma.[144]

Responding to criticisms such as these, the ISSVD in 1987[143] revised its classification to separate more clearly those epithelial disorders classified as nonneoplastic (Table 1-3) and those considered VIN (Table 1-4).[145] We prefer this classification and use it routinely in our practices. The "intraepithelial neoplasia" terminology as first applied to cervical lesions by Richart and his colleagues (see Chap. 3) was meant to emphasize the concept that the dysplasias and in situ carcinoma form a continuous spectrum of disease. In the cervix, it was pointed out that the likelihood of cure in an individual patient (not a statistical figure in a population) depended more on the location and extent of the lesion than on its histologic severity. Thus, we believe that the use of "IN" terminology in any organ should philosophically commit the user *not* to divide the lesions included into grades of severity. We can therefore accept "VIN" alone as a diagnosis or a concept, but if clinicians wish the lesions diagnosed to be divided into categories by severity, we then use the "dysplasia" and "carcinoma in situ" terminology that is sanctioned in Table 1-4.

TABLE 1-2.
Classification of Vulvar Dystrophies (ISSVD, 1976)[141]

Hyperplastic dystrophy
Without atypia
With atypia
Lichen sclerosus
Mixed dystrophy—lichen sclerosus with foci of epithelial hyperplasia
Without atypia
With atypia

TABLE 1-3.
Nonneoplastic Epithelial Disorders of the Skin and Mucosa (ISSVD, 1987)[143]

Lichen sclerosus (lichen sclerosus et atrophicus)
Squamous cell hyperplasia (formerly hyperplastic dystrophy)
Other dermatoses

TABLE 1-4.
Classification of Vulvar Intraepithelial Neoplasia (ISSVD, 1987)[143]

Grade	*Definition*
VIN I	Mild dysplasia (formerly mild atypia)
VIN II	Moderate dysplasia (formerly moderate atypia)
VIN III	Severe dysplasia (formerly severe atypia)
VIN III	Carcinoma in situ

Nonneoplastic Epithelial Disorders

Squamous Hyperplasia

Squamous hyperplasia is a benign lesion of adult vulvar skin or mucosa. The clinical appearance varies from red to white and can be thickened and indurated or thin and easily excoriated. Pruritus is a frequent symptom. Scratching provokes fissures, ulceration, and secondary inflammation.

Microscopically, the epithelium shows hyperkeratosis, acanthosis, and eventually parakeratosis. The granular layer is sometimes prominent. There is a chronic inflammatory infiltrate of the dermis, with lymphocytes, plasma cells, and macrophages. No cellular atypia is present.

Lichen Sclerosus

Lichen sclerosus is a chronic, progressive lesion that appears at all ages but is more frequent after the age of 50 years and in parous women.[144,145] The labia minora are most commonly affected. Extravulvar localizations may be present, especially on the trunk. The pathogenesis is obscure. The lesion has been reported in children.[146] Stenosis of the vaginal introitus may be observed.

Macroscopic Appearance. The gross appearance consists of ivory-colored, flat, irregular maculopapules or plaques with a characteristic dry, parchment-like appearance. Ulceration and fissures may complicate the lesion. These are seen on the vulva and on the adjacent perineal and perianal skin.

Microscopic Appearance. Microscopy reveals hyperkeratosis with progressive diminution of the total thickness of the epithelium and flattening of the dermoepidermal junction (Fig. 1-21). There is hydropic degeneration of cells of the basal layer; edema and hyalinization of the upper third of the dermis; swelling and splitting of collagen bundles; disappearance of pilosebaceous apparatus, sweat glands, and melanocytes, with absence of melanosomes in the keratinocytes; and lymphocytic and histiocytic infiltrates below the zone of dermal homogenization. No atypia is observed. The number of elastic fibers is decreased. Their destruction could be due to an elastic-type protease present in dermal fibroblasts.[147]

The major complication of lichen sclerosus is lichenification. Transformation to dysplasia and carcinoma is rare, and the lesion should not be considered a premalignant disease.[144,148] The high metabolic activity of the epithelial cells demonstrated by different methods explains why the qualification *atrophicus*, which was formerly included in the definition of the lesion, has been deleted in recent reports.[149]

Differential Diagnosis. Differential diagnosis is made with scleroderma and lichen planus. The former is extremely rare in the vulva, features dense fibrosis rather than the peculiar dermal homogenization of lichen sclerosus, and is part of a systemic disease. In lichen planus, the inflammatory infiltrate abuts immediately against the epidermis rather than being separated from it by a layer of dermal homogenization (Fig. 1-22).

Other Dermatoses

Other dermatoses such as senile atrophy, lichen planus, other noninfectious dermatitides, and nonspecific hyperplasias and hyperkeratoses are seen from time to time.[145] They should be diagnosed using the histopathologic terminology that is best found in texts of dermatopathology. Terms such as *kraurosis* and *leukoplakia* are perfectly acceptable for the clinical description of atrophic and white lesions, respectively, but should be eschewed by the pathologist because of their lack of histologic specificity.

Dysplasia and In Situ Squamous Carcinoma: Vulvar Intraepithelial Neoplasia (VIN)

Recent advances in understanding the development and progression of premalignant epithelial lesions and preinvasive neoplasia have emphasized many similarities between vulvar and cervical lesions. A nomenclature similar to the one originally used for the comparable cervical lesions has been proposed for the vulva. VIN is characterized according to the histologic definition proposed by the ISSVD as "a disorientation of epithelial architecture that extends throughout the full thickness of the epithelium."[141]

Most authors divide VIN into three grades that correspond to the quality and quantity of cellular anomalies and can be compared with the equivalent grades in the cervix.[150–152] We have already stated our objection to this terminology. VIN appears to be increasing in frequency as a proportion of all cases of preinvasive and invasive vulvar cancer. Although common after the menopause, the lesion is now being found more frequently in younger women, and the association with HPV infection is widely reported, although the HPV detection rate is lower than in cervical intraepithelial neoplasia (CIN).[151,153–155] HPV-16 is the most commonly detected type of virus. HPV-positive cases are more frequent in younger women than in older women and are more likely to be of warty (bowenoid, koilocytotic) or basaloid than of simplex (typical) type, suggesting that there are two different types of VIN in terms of pathogenesis on the basis of the presence or absence of HPV.[154–156]

The lesion may precede invasive carcinoma, as suggested by various epidemiologic, clinical, and pathologic studies.[152,157] The mean elapsed period of time (25 years) is considerably longer than that in the cervix.[158] The continuous spectrum of lesions from mild to severe is not so evident as in the cervix, and the high-grade lesions may be divided into dif-

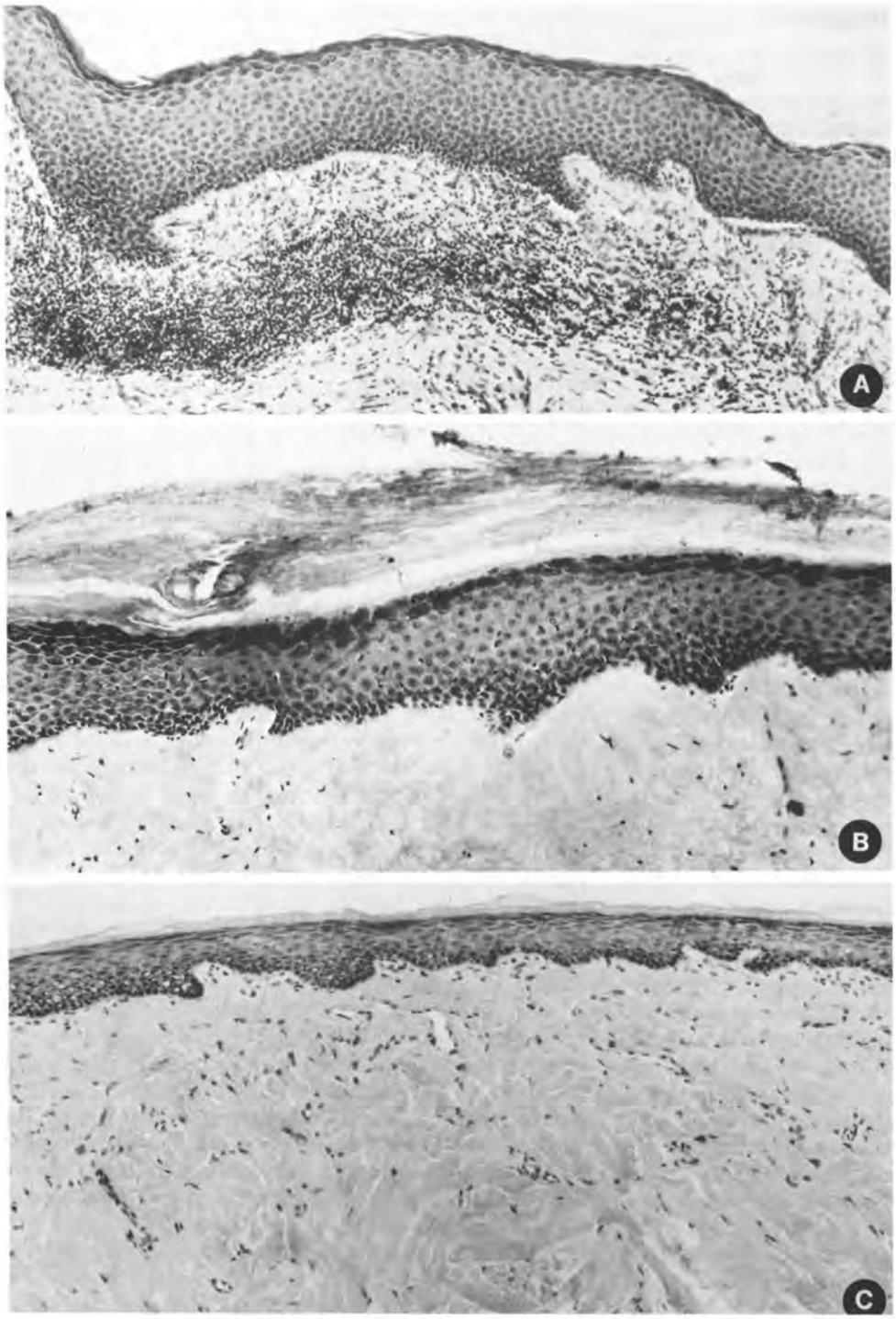

FIGURE 1-21 Lichen sclerosus resulting in kraurosis vulvae. **(A)** Early stage showing moderate hyperkeratosis, edema, and leukocytic infiltration of the stroma. **(B)** Lesion in evolution with distinct hyperkeratosis, alterations in the collagen, and disappearance of the subcutaneous adnexal glands. **(C)** Stage of atrophy.

ferent categories: warty (bowenoid) VIN, basaloid VIN, simplex (typical) VIN, and mixed type. The warty form corresponds to Bowen's disease described in 1912 by that author (Fig. 1-23).[159] The basaloid form resembles the usual carcinoma in situ of the cervix (atypical immature basal cells; Figs. 1-24 and 1-25).[155,158] The simplex type is often confused with squamous hyperplasia without atypia and probably is an uncommon lesion when diagnosed correctly (Fig. 1-26).

Bowenoid papulosis, despite its benign clinical course, should be classified as a carcinoma in situ (see the section on bowenoid papulosis).[160–163]

Vulvar carcinoma in situ is less aggressive than the equivalent cervical lesion. The time between VIN and the development of invasive carcinoma is longer in vulvar lesions than in cervical lesions, and spontaneous regression is more frequent. The presence of VIN in the vicinity of invasive carcinoma is less frequent than the coexistence of CIN and cer-

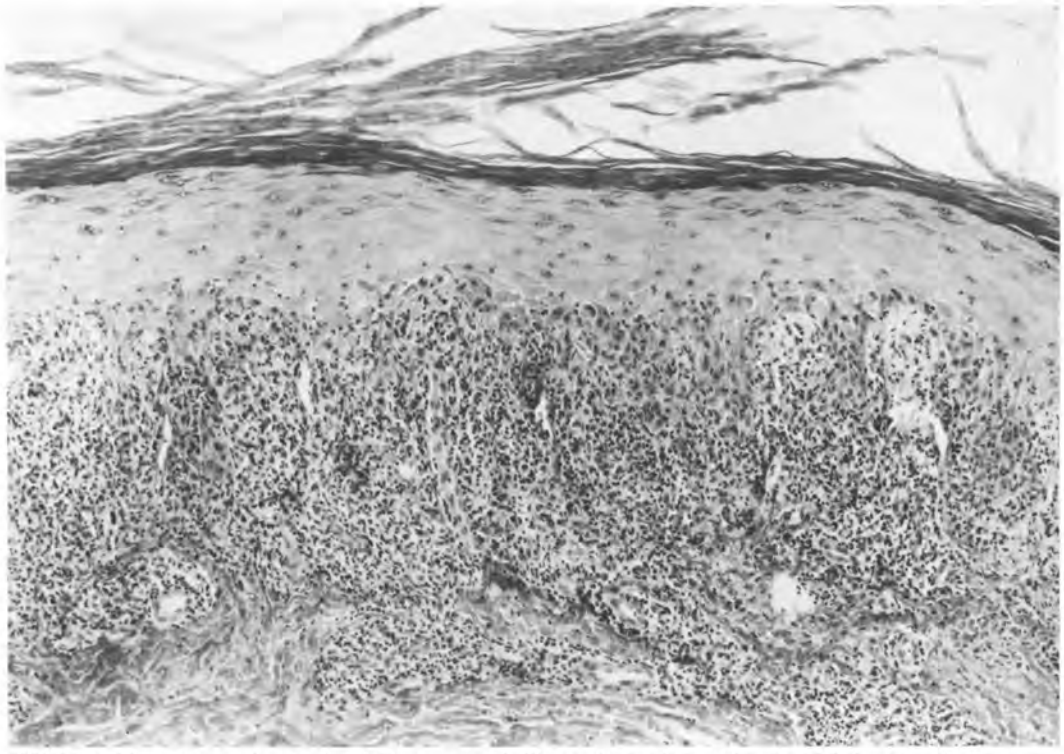

FIGURE 1-22 Lichen planus. An inflammatory infiltrate hugs the epidermis and destroys the basal layer.

vical carcinoma.[158,164,165] The risk of association of VIN with CIN and invasive cervical carcinoma is high (25% in young patients and 15% in older patients)

These differences in behavior between VIN and CIN have not been explained. Normal vulvar epithelium differs from normal cervical epithelium by (among other features) the presence of keratinization, so the threshold for the diagnosis of in situ carcinoma of the vulva is somewhat lower than that in the cervix. In other words, a lesion that might be downgraded to dysplasia in the cervix because of superficial maturation is often acceptable as in situ carcinoma in the vulva. Other factors may intervene,

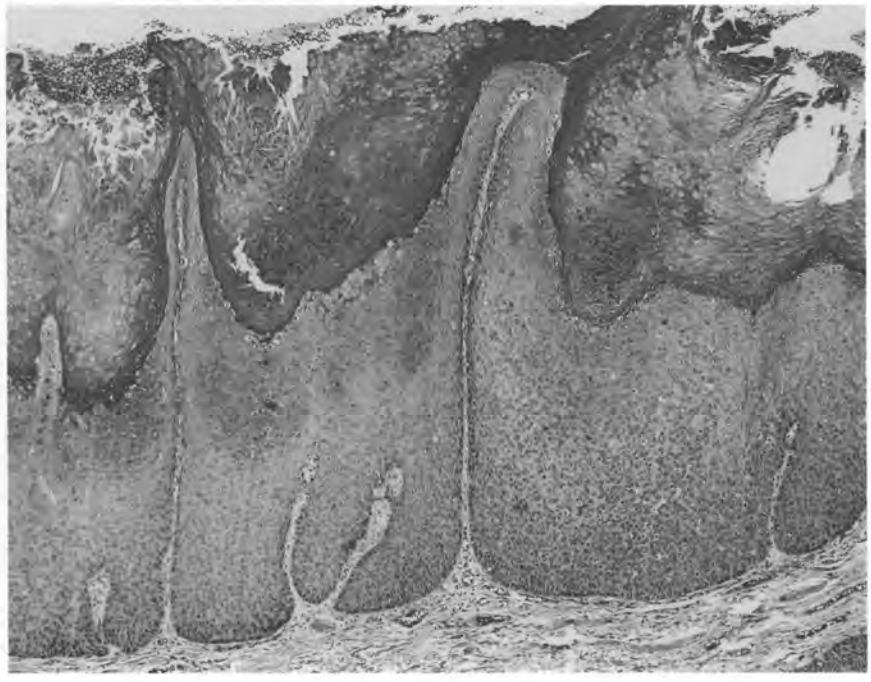

FIGURE 1-23 Warty form of in situ carcinoma of vulva (high-grade vulvar intraepithelial neoplasia). Low-power photomicrograph shows an undulating exophytic surface with extensive keratinization and an overall condyloma-like appearance. High cellularity and increased nuclear–cytoplasmic ratio of proliferating cells are apparent even at low magnification. (Courtesy of Dr. Robert J. Kurman, The Johns Hopkins Hospital, Baltimore, MD).

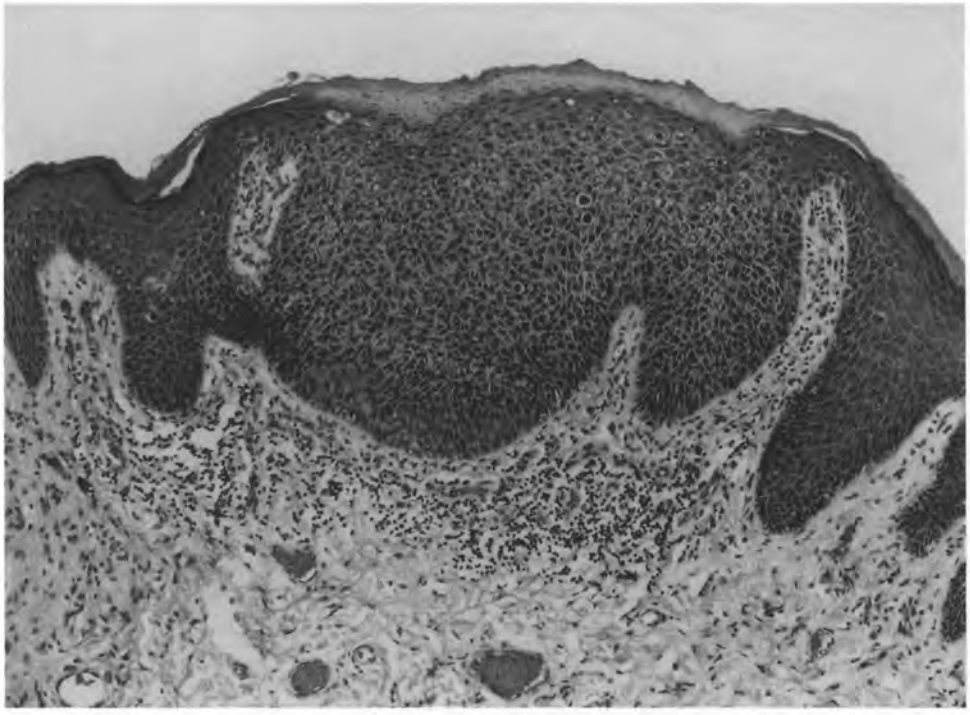

FIGURE 1-24 Basaloid form of in situ carcinoma of vulva (high-grade vulvar intraepithelial neoplasia). The small focus in the center shows a haphazard proliferation of atypical immature basal-type cells extending up to the parakeratotic cells on the flat surface.

such as viral infections, hormonal status, and anatomic localization of the vulvar mucosa.[164]

Macroscopic Appearance. As in the cervix, VIN does not have a diagnostic gross appearance (Color Figure 1-6). Most cases, however, present as *leukoplakia,* or pearly white or ivory, slightly elevated, hyperkeratotic, irregular plaques. Sometimes the lesion exhibits a red-brown surface color. The lesion may be limited to a single focus or may be multicentric. It often involves the perineum, the perianal region, and the vulva. Patients with multifocal disease are found to have a younger age compared with those with unifocal localization. Intra vitam staining

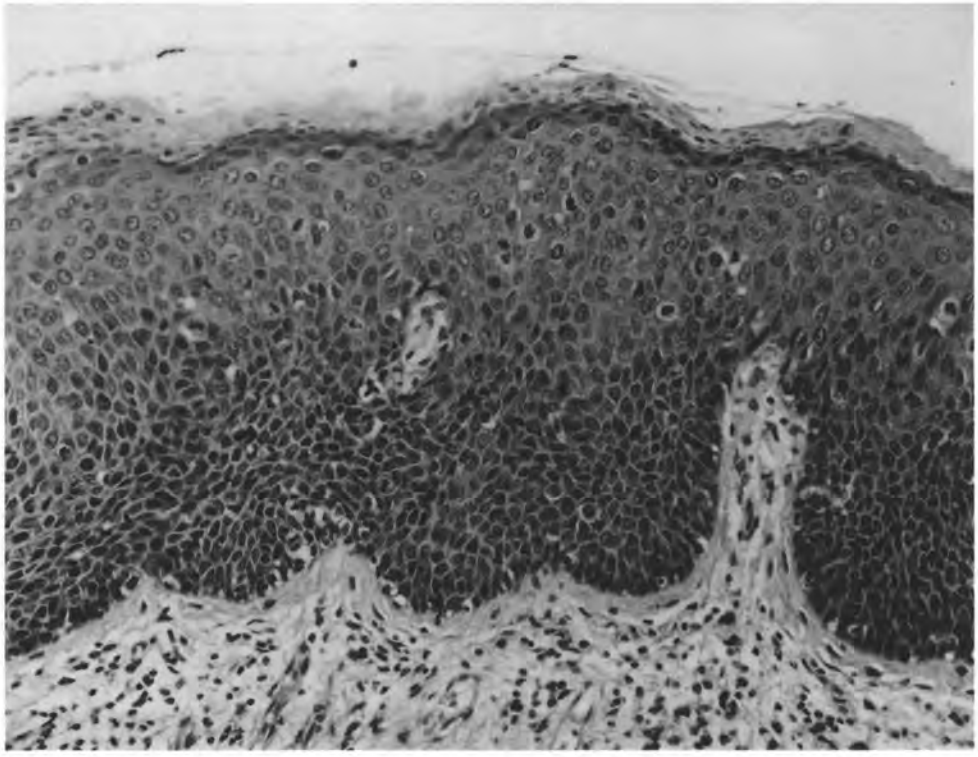

FIGURE 1-25 Basaloid moderate dysplasia of vulva. The atypical immature cells in this lesion proliferate to about the midpoint of the epithelium.

and colposcopic examination may assist in identifying appropriate areas for biopsy or excision.[166]

Microscopic Appearance. The epidermis or mucosa is hyperkeratotic and acanthotic (see Figs. 1-23 through 1-26). A variable degree of atypia (mild, moderate, or severe dysplasia) is present in the deepest epithelial layers, with progression toward the surface but often with some preservation of polarity and maturation in the superficial layers. The atypia consists of the following: disordered polarity of cells; increased nuclear–cytoplasmic ratios; enlarged, irregular, and hyperchromatic nuclei; increased mitotic activity, including abnormal mitoses; and precocious and irregular cellular maturation, with cytoplasmic keratinization and nuclear pyknosis seen focally below the superficial cell layers in which they normally occur. The more diffuse and marked in degree these changes are, and the farther they extend toward the surface, the more severe is the VIN. Sometimes hyperkeratosis is absent. Parakeratosis (with persistence of nuclei in the keratinizing layers) or even focal atrophy may be present, but the sine qua non for the diagnosis is the dyspolarity and cellular atypia. Koilocytes and binucleated cells are generally present in HPV-positive cases. Subjacent stromal inflammation varies from absent to marked, but stromal invasion by neoplastic cells is absent.

Differential Diagnosis. With the increasing experience of pathologists, the diagnostic criteria have become more stringent. If the criteria for dyspolarity and cytologic atypia are adhered to, there should be no confusion with lichen sclerosus, inflammatory dermatoses, or squamous cell hyperplasia with acanthosis and hyperkeratosis. The main problem is the distinction of low-grade VIN lesions from high-grade VIN lesions and of both from bowenoid papulosis (see the section on bowenoid papulosis). Atypias and mitotic figures in the upper third of the epidermis or mucosa usually point toward the diagnosis of in situ carcinoma. Treatment is likely to be similar for dysplasia or carcinoma in situ, so the distinction probably is not of the utmost importance.[166]

Prognosis, Evolution, and Treatment. The evolution is long and may extend over many years with periods of remission. The likelihood of progression to invasive squamous cell carcinoma is small but is far greater in elderly women. The latent period between the appearance of carcinoma in situ and its transformation into invasive cancer is often long, and there is no proof that the former lesion must progress to the latter. Recent studies suggest that the latter, particularly in older women, may not have developed from the former.[158] Patients with multifocal disease are found to have a younger age compared with those with unifocal localization. Occult invasion is more frequently observed in patients of advancing age.[167]

The treatment is predominantly surgical, consisting of wide local excision with careful follow-up. Radical vulvectomy with groin dissection is no longer the only treatment. Conservative techniques (cryotherapy, carbon dioxide laser, skinning vulvectomy with skin grafts) have been developed and should be applied when appropriate.

Bowenoid Papulosis

Bowenoid papulosis occurs in male and female genitalia and microscopically resembles Bowen's disease or squamous carcinoma in situ.[160–163,168,169] Its clinical features and its generally benign behavior have suggested to many that it should be considered a distinct clinicopathologic entity, whereas others regard it as a variant of carcinoma in situ. It was first described in 1970 under the name *multicentric pigmented Bowen's disease,*[170] a term that in retrospect probably has not been improved on subsequently.

Clinical Appearance. The lesion is characterized by multiple (usually 5 to 10) small brown-red to violet papules measuring a few millimeters in diameter each. They are located in the vulvar and perineal areas of young adults; almost all patients are younger than 40 years (Color Figure 1-7). Condylomata acuminata and HSV infection are frequently associated with bowenoid papulosis.

Microscopic Appearance. The lesion may be identical to or only slightly different from true Bowen's disease. The cells with uniformly hyperchromatic nuclei are irregularly arranged in a slightly thickened epithelium with no superficial maturation. Atypical mitoses are present. The rete pegs are enlarged and may coalesce with obliteration of the dermal papillae. There is no invasion of the dermis.

The histologic coexistence of this disease with condyloma acuminatum and less frequently with HSV-2 lesions in the same patient has been demonstrated. Immunohistochemical, ultrastructural, and molecular hybridization techniques have clearly established the HPV-16 genesis of the disease.[161,162,168,169]

Differential Diagnosis. The histologic picture is similar to VIN and often is of no help in the diagnosis, although Ulbright and associates have emphasized cellular uniformity and absence of pilosebaceous involvement as useful indicators of bowenoid papulosis.[160] The age of the patient, the multiplicity and small size of the lesions, the verrucoid aspect, and the tendency toward spontaneous resolution are the main reasons to separate bowenoid papulosis from typical Bowen's disease (in situ carcinoma). Furthermore, the frequent coexistence (20% to 50%) of Bowen's disease and CIN or invasive carcinoma of the cervix is not observed in bowenoid papulosis.

The relation of bowenoid papulosis and Bowen's disease remains to be defined. The fact that Bowen's disease (versus nonbowenoid in situ carcinoma) has

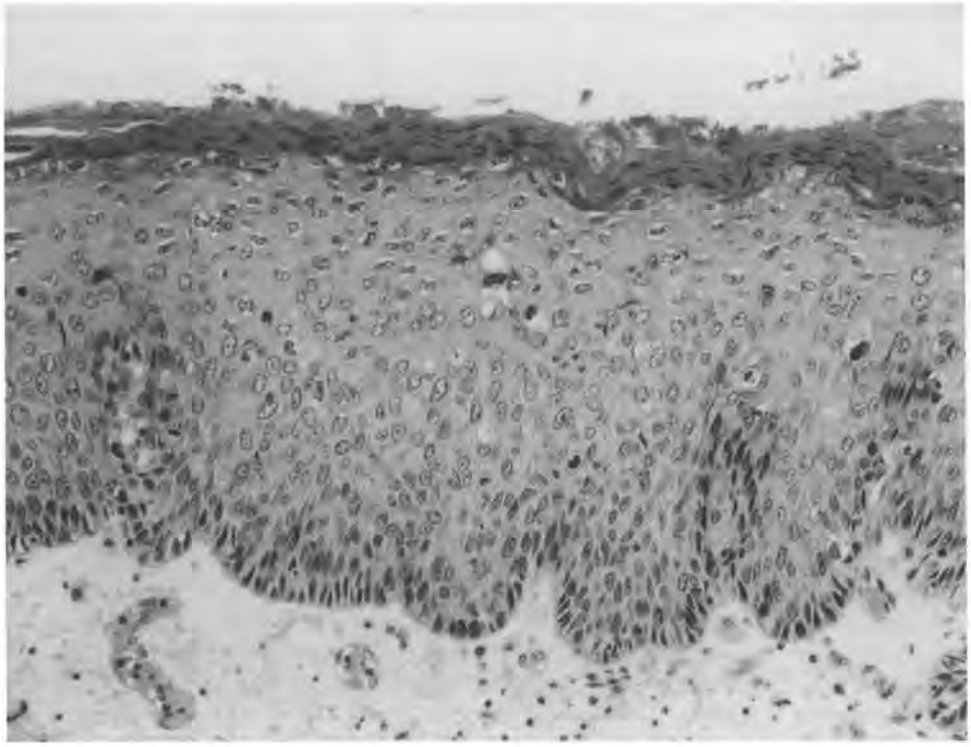

FIGURE 1-26 Simplex (typical) vulvar intraepithelial neoplasia. Large dysplastic cells proliferate toward a parakeratotic but flat surface. Loss of polarity is evident.

been defined in the past as multicentric, occurring in young patients, and less likely to progress to invasive carcinoma suggests that the differences between bowenoid papulosis and "true" Bowen's disease may be more apparent then real. Flow cytometry reveals aneuploid cells with a high DNA content, resulting in a DNA diagnosis of malignancy.[163] Although the typical clinical course is benign, often with spontaneous regression, bowenoid papulosis recurred locally in 20% of cases in one series,[168] and a few reported cases have progressed to or coexisted with invasive carcinoma.[169] Bowenoid papulosis thus should best be considered as a form of carcinoma in situ (VIN) with an unexplained low malignant potential.

VULVAR CYTOLOGY

Techniques of vulvar cytology are direct scraping, imprint of superficial lesions, and fine-needle aspiration of submucosal nodules. The slides should be fixed with 95% ethanol or spray fixative for good preservation. Normal cytology of the vulva is composed of superficial squamous cells and anucleate squames.[171,172]

Vulvar superficial cytology is valuable in the detection of inflammatory diseases and dysplastic or neoplastic lesions of the squamous mucosa and epidermis. The sensitivity of the method to recognize benign, precancerous, and malignant lesions varies according to the severity of the cellular changes. These changes are observed in the cells of the superficial layers obtained by scraping and are characterized by nuclear alterations and modifications of the cell size. Anisonucleosis, hyperchromasia, dyskeratosis, and alterations of the nuclear–cytoplasmic ratio are common features. The anucleate squames present in vulvar imprints are larger in invasive carcinoma than in dysplasia or carcinoma in situ. These diagnoses should always be confirmed histologically.

The classical cytologic manifestation of *condyloma acuminatum* is the presence of koilocytes, sometimes accompanied by parakeratosis in the imprint or scrape smears. *Lichen sclerosus* reveals anucleate squames and parakeratotic cells without cytologic atypia. *Keratinizing carcinoma* is the easiest to recognize: cytoplasmic abnormal keratinization, keratin pearls, apparent intercellular bridges (desmosomes), and nuclear anomalies are evident. *Verrucous carcinoma* imprints or scrapings reveal the presence of hyperkeratotic and parakeratotic cells and slight cellular atypia. Cytology cannot differentiate verrucous carcinoma from pseudoepitheliomatous hyperplasia or condyloma acuminatum in the absence of koilocytes.

Small cell carcinoma shows no sign of keratin maturation, and the cells are small and round with hyperchromatic nuclei. *Paget's disease* exhibits cells with enlarged nuclei and nucleoli and an increased nuclear–cytoplasmic ratio. The nuclei are central or peripheral in location and there is no cytoplasmic keratinization. Mucin vacuoles may be identifiable in the cytoplasm. *Malignant melanoma* and *tumors of Bartholin's gland* can be identified by fine-needle aspiration, as can metastases from vulvar cancers in inguinal lymph nodes. Vulvar cytology is useful in

confirming the nature of some *infectious* processes. Fungal and viral infections (especially herpes genitalis and HPV) are particularly amenable to cytologic diagnosis (see Color Figure 1-4). *Endometriosis* of the vulva is extremely rare, but the diagnosis can be made by fine-needle aspiration.[173]

MALIGNANT TUMORS

Primary Tumors

Invasive Squamous Cell Carcinoma

Squamous cell carcinoma of the vulva is seen predominantly in older women and constitutes 4% of female pelvic cancers.[174–180] The age of predilection is between 60 and 90 years (Fig. 1-27).[180] Carcinoma of the vulva is very rare in young women.[181–185] The gravity of its natural history is explained by the early lymphatic dissemination of the tumor cells by the extensive and diffuse network of vulvar lymphatics.[186] This characteristic differentiates vulvar carcinomas from other cutaneous epitheliomas, which remain localized for longer periods of time.

The clinical symptomatology is often simple: the patient presents because of a visible, slow-growing tumor or, more rarely, because of pruritus, pain, bleeding, vaginal discharge, or a burning sensation on micturition. Frequently, the extent of the tumor at the time of diagnosis does not permit the localization of its point of origin. The labia majora and minora are the most common sites of origin of the tumor, followed by the clitoris.

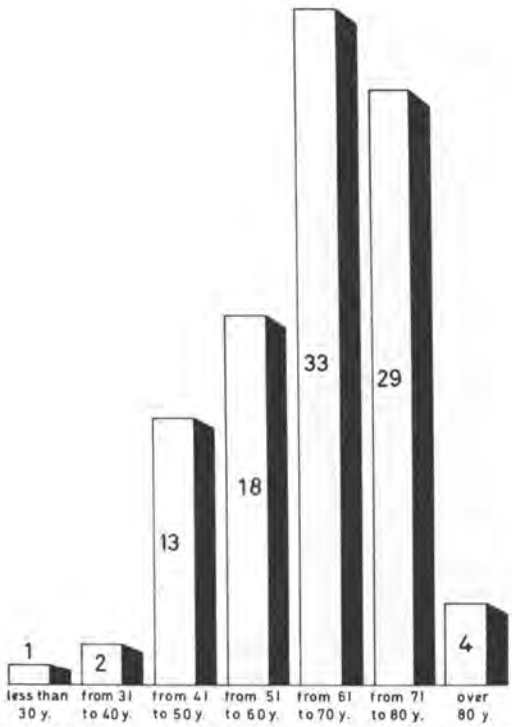

FIGURE 1-27 Frequency (percentage) of carcinoma of the vulva as a function of age (258 cases).

Pathogenesis. The pathogenesis of vulvar carcinoma is not clearly understood. Predisposing conditions are constantly reported: chronic infections such as syphilis and granulomatous venereal diseases are mentioned.[187,188] The occurrence of obesity, diabetes, and hypertension with vulvar carcinoma exceeds the frequency seen in the general population and suggests that some type of endocrinopathy is related to the development of the malignant lesion. Clinical data suggesting a relation between HPV and squamous carcinoma continue to accumulate, although this detection rate is lower than in cervical cancer.[189–191] About 10% of invasive carcinomas show the presence of HPV-16 DNA.[155,192–195] Two groups of tumors can be differentiated according to the presence or absence of HPV (see Microscopic Appearance, below).[155,158,196–198]

Association with other genital cancers, especially cervical lesions, is high (25%).[199] Oncogenic agents such as viruses may operate on different areas of the anogenital epithelium, suggesting a common pathogenetic factor (field response) in the genesis of vulvar, vaginal, and cervical carcinomas and premalignant lesions.

Macroscopic Appearance. The lesion presents as a small, gray, hyperkeratotic, indurated, elevated zone, which has a tendency to become ulcerated and secondarily infected (Fig. 1-28). Alternatively, the tumor may have a papillomatous or multinodular appearance. The labia and clitoris are the most common primary sites. The lesion extends progressively to involve the entire vulva, vagina, and perianal region. In the advanced stages, there is invasion and total destruction of the external genital organs, which are replaced by a large proliferation

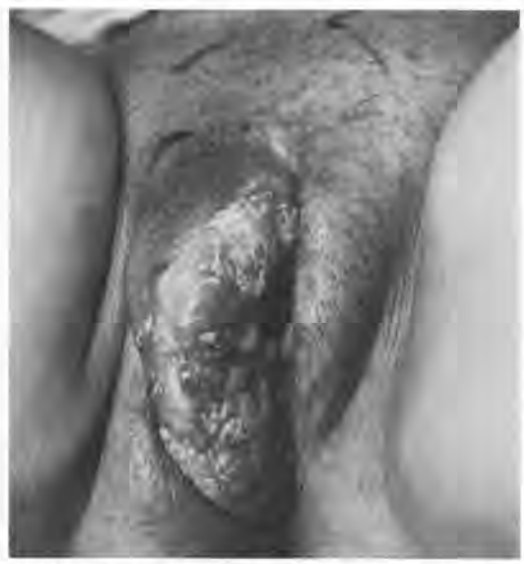

FIGURE 1-28 Squamous cell carcinoma: clinical appearance.

or budding ulceration that is covered with a necrotic fibrinous exudate.

Microscopic Appearance. Vulvar squamous carcinomas are generally better differentiated than those of the cervix and are rich in cornified epithelial pearls (Fig. 1-29). The neoplastic cell cords originate from the basal layers of the epithelium and extend deeply into the dermis and subcutaneous tissue. The squamous cells are large, and their nuclei are irregular, hyperchromatic, and sometimes monstrous. Keratin production is abundant. Mitoses are numerous and atypical (multicentric mitotic figures with aberrant chromosomes). These tumors generally occur in older women, are associated with the "simplex" type of VIN or the lesser grades of dysplasia (or with squamous hyperplasia without atypia), and usually do not contain HPV DNA.[155,158,165,193]

In contrast, squamous carcinomas that contain HPV DNA (usually HPV-16) occur more frequently in younger women and generally are associated with the bowenoid type of VIN (also called *basaloid* by Toki and colleagues), or with warty, condyloma-like lesions, at their periphery.[158] These invasive carcinomas may themselves be of basaloid or warty type. The basaloid type is characterized by large rounded nests or by smaller cords of immature cells with little cytoplasm and little or no keratinization (Fig. 1-30). The warty type has an exophytic condyloma-like appearance at the surface but differs from condyloma or verrucous carcinoma by the presence of a jagged, irregular interface with stroma at the deep invasive border. These two types of invasive carcinoma are associated with the corresponding patterns of VIN (bowenoid or warty) mentioned earlier.[155,158,165,196–198,200]

Other squamous carcinomas may be associated with spindle cell (pseudosarcomatous) metaplasia.[175,201,202] If the entire tumor is of spindle cell type (Fig. 1-31), ultrastructural (desmosomes, tonofilaments) or immunohistochemical (cytokeratin positivity; S-100, HMB-45, desmin and actin negativity) evidence may be required to make the distinction from a spindle cell melanoma or sarcoma.[203]

Grading of vulvar squamous carcinoma is generally performed using a four-grade system, with grade I representing the highly keratinizing tumors with low nuclear–cytoplasmic ratios, little nuclear anaplasia, and few mitotic figures, and grade IV defining the anaplastic spindle cell or small cell tumors.[204] Most of the tumors, regardless of grade, are aneuploid.[205]

Evolution and Prognosis. Early lymphatic dissemination takes place to the inguinal, femoral, and pelvic nodes. Nodal metastases are often bilateral, even if the primary tumor is unilateral. In the absence of inguinal and femoral nodal involvement, deep pelvic nodes are rarely invaded. The necessity of total surgical extirpation of all the nodes is underlined by the fact that an impalpable node is not necessarily a negative node; Way reported that 43% of nonpalpable lymph nodes are microscopically invaded.[202]

The technique of lymphangiography gives some indication of lymph node involvement, as does fine-

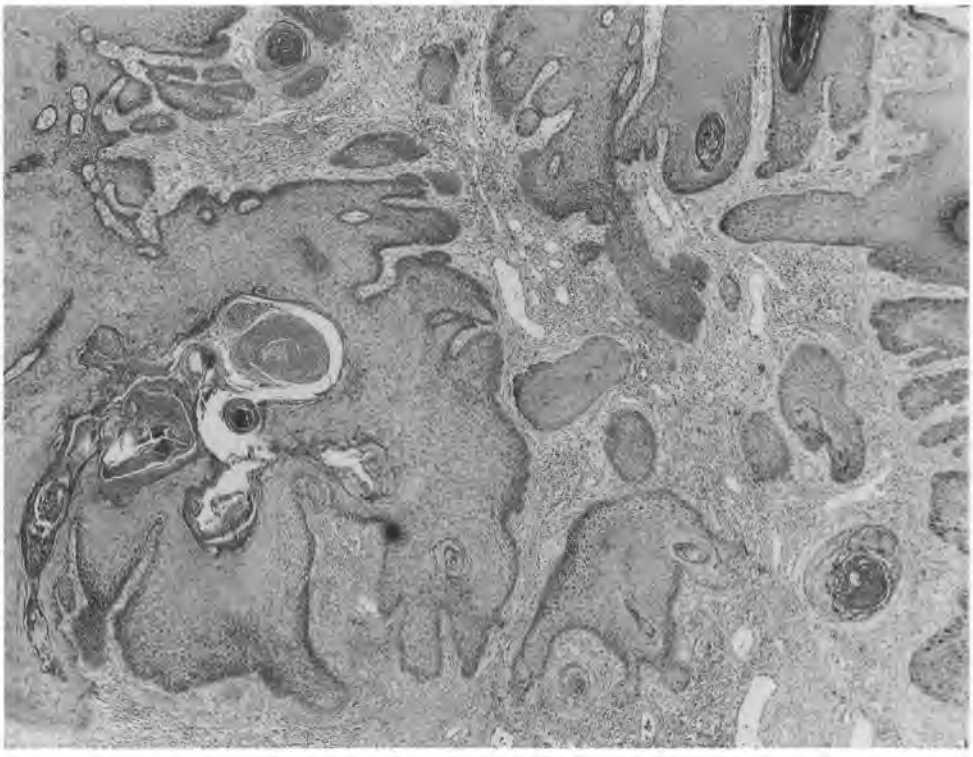

FIGURE 1-29 Squamous cell carcinoma. Microscopic appearance of the typical, highly keratinizing, invasive carcinoma seen predominantly in older women.

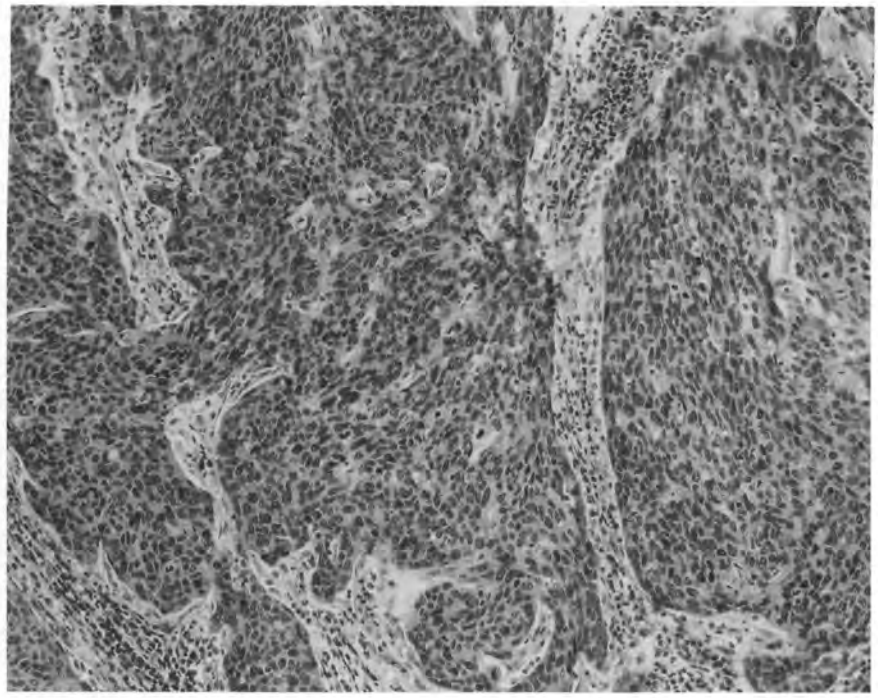

FIGURE 1-30 Squamous cell carcinoma. The basaloid type is characterized by nests of small immature cells showing little clearcut squamous differentiation in this microscopic field. (Courtesy of Dr. Robert J. Kurman)

needle aspiration. Histologic examination of the nodes may reveal not only the presence of a metastasis, but also granulomatous alterations with foreign body multinucleated giant cells, which may be secondary to lymphangiography (in which case fat is seen within the granulomas) or to keratin produced by the tumor cells. Imprint or smear cytology of lymph nodes during surgery may give immediate valuable information to the surgeon, as may fine-needle aspiration cytology before surgery. A relation between the degree of histologic differentiation of the tumor and its clinical malignancy has been proposed by several authors, but this relation is not statistically valid. The prognosis depends much more on the tumor size, the degree of extension of the tumor at the moment of treatment, the integrity of surgical margins,

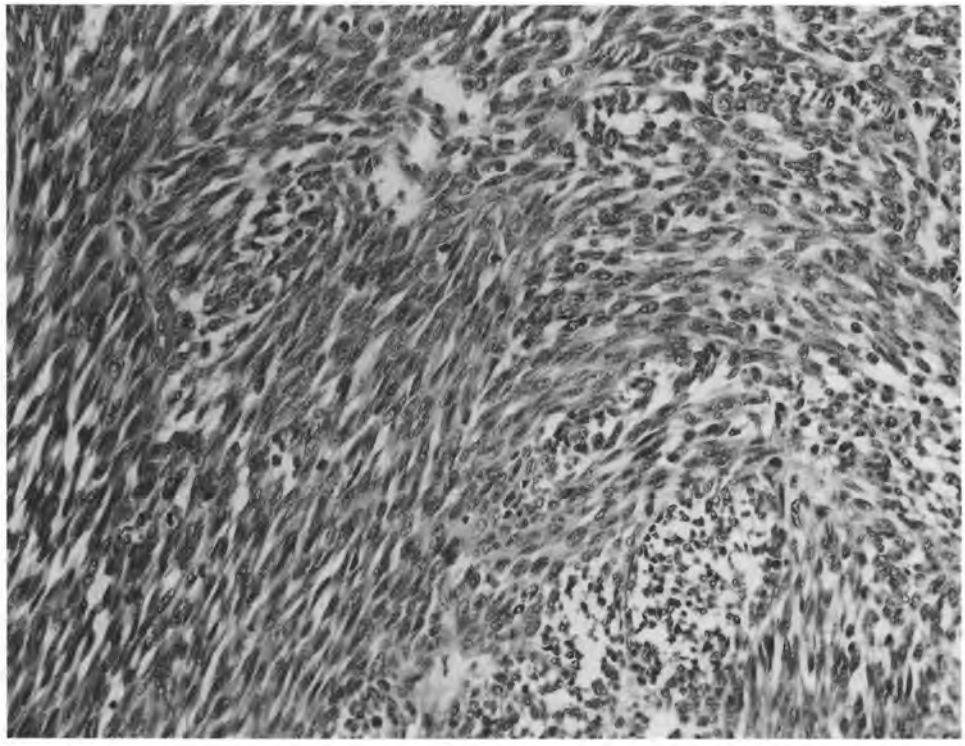

FIGURE 1-31 Spindle cell (pseudosarcomatous) type of squamous cell carcinoma. The tumor cells were immunohistochemically positive for cytokeratins.

and the presence of lymph nodal and distant metastases than on microscopic factors of differentiation.[206-213] The International Federation of Gynecologists and Obstetricians (FIGO) has proposed a classification into four stages that gives a good correlation with 5-year survival (Table 1-5).

The prognosis for cure remains discouraging. The best statistics report from 40% to 60% 5-year survival when there is lymph node invasion, compared with 70% or better in cases with negative nodes.[211] When stromal invasion is limited (less than 1 mm in depth), the prognosis is excellent.[212] Clitoral lesions have a poorer prognosis. Distant metastases occur late to the lungs, liver, and other sites. In summary, long survival depends on early diagnosis, small tumor size, and absence of lymphatic involvement.[213]

Treatment. Vulvectomy with extensive bilateral lymphadenectomy is the usual therapy of choice.[214] The results depend essentially on the precocity of diagnosis and the extent of the surgical resection.[215] The results of radiation therapy do not appear as encouraging, since the classic 5-year survival rates do not surpass 20%, largely because of the difficulty in delivering therapeutic dosages to this highly sensitive region. Newer techniques show more promise, and encouraging results have been reported with chemotherapy using 5-fluorouracil and cisplatin. Chemotherapy acts as a radiosensitizer.[216]

Microinvasive Squamous Cell Carcinoma

Following the observation that squamous carcinomas of the cervix with limited stromal invasion rarely metastasize and are usually cured by conservative therapy, attempts have been made to characterize similar lesions of the vulva.[217,218] As in the cervix, different investigators have used different criteria for the diagnosis of microinvasive carcinoma, with the anticipated different results.[219] Overall, about 12% of patients with tumors characterized as "microinvasive" have had lymph node metastases, and a similar proportion have had clinical recurrence.[220] These results are considerably worse than in most series of cervical microinvasive carcinoma, suggesting that this diagnosis should be made with great caution in a vulvar lesion if it will result in more conservative therapy than for other small invasive vulvar cancers. The ISSVD has recently recommended that the designation of microinvasive carcinoma be abandoned, and that "stage IA" be used to designate solitary lesions less than 2 cm in diameter and 1 mm in depth.[141,221]

TABLE 1-5.
Clinical Staging of Vulvar Carcinoma (FIGO)

Stage	*Definition*
I	Lesion <2 cm and no suspicious groin nodes
II	Lesion >2 cm and no suspicious groin nodes
III	Lesion extends beyond vulva without grossly positive groin nodes, or Lesion confined to vulva with suspicious or positive groin nodes
IV	Lesion extends beyond vulva with grossly positive nodes, or Lesion involves mucosa of rectum, bladder or urethra, or bone, or All cases with distant or palpable deep pelvic nodal metastases

Other Malignant Epithelial Tumors

Basal Cell Carcinoma. Basal cell carcinoma of the vulva is rare, constituting 2% to 3% of all vulvar cancers.[222-224] Its appearance and clinical behavior are analogous to those observed in other cutaneous regions. It presents as a budding, ulcerated, or papillary lesion and shows multiple localizations. There is no known relation between this tumor and VIN or HPV. There is sometimes local recurrence, but metastases are extremely rare.

Adenoid Squamous Carcinoma. Adenoid squamous carcinoma or adenoacanthoma has been reported in the vulva.[225,226] The tumor is a squamous cell carcinoma with pseudoglandular spaces containing acantholytic and dyskeratotic cells. There is no statistical difference in mortality between this type and the usual squamous cell carcinoma.

Verrucous Carcinoma. Verrucous carcinoma is a large, warty, fungating tumor (Fig. 1-32).[227,228] Ulceration may develop as a late event, with secondary infection and regional adenopathy. Local invasion confirms the malignant nature of the lesion, but it rarely metastasizes. More aggressive behavior has been reported after radiation therapy, so the advised treatment is surgical.

The histologic appearance should be clearly recognized to avoid confusion with well-differentiated squamous carcinoma on the one hand and with giant condyloma acuminatum (if such a lesion exists) on the other. The lesion is characterized by a marked but well-circumscribed acanthosis and papillomatosis, parakeratotic hyperkeratosis, keratin cysts in the centers of the acanthotic rete pegs, and a mild stromal inflammatory infiltrate. The tumor may invade deeply, but always with pushing rather than infiltrative borders. Atypia and mitotic activity are absent or minimal.

The lack of prominent cellular atypia and mitotic figures and the lack of invasion of the stroma by isolated cords of keratinized cells emerging from the rete pegs differentiate verrucous carcinoma from well-differentiated squamous carcinoma. The distinction is important, because the latter tumor metastasizes frequently and does respond to radiation therapy.

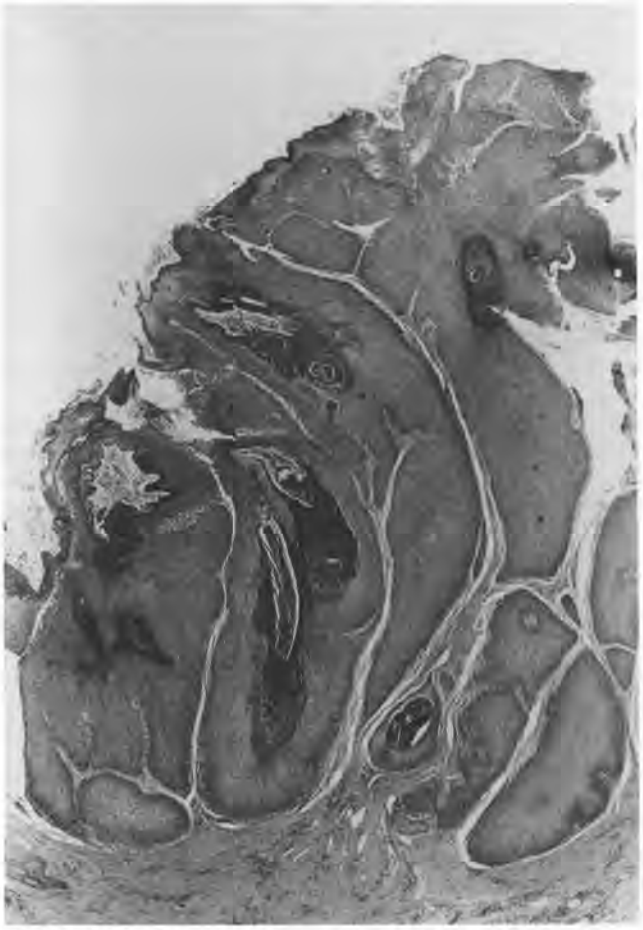

FIGURE 1-32 Verrucous carcinoma. This exophytic papillomatous tumor contains central keratin plugs in its bulbous tumor nests and invades on a broad "pushing" front. Atypia was minimal at higher magnification.

The giant condyloma acuminatum is differentiated by the presence of koilocytotic cells, the existence of fibrovascular cores in the papillae, and the lack of the deep stromal penetration on a broad front that is characteristic of verrucous carcinoma. Many of the lesions initially diagnosed as giant condyloma are found on further study to be verrucous carcinomas. This error may occur if the evaluation is made on a small, superficial biopsy that misses the stromal penetration.

Sarcomatoid or Metaplastic Carcinoma. Sarcomatoid or metaplastic carcinoma was described by Way as a rare type of epithelioma characterized by the presence of giant and spindle cells (see Fig. 1-31).[202] The appearance of this lesion is reminiscent of sarcoma, and it represents an anaplastic form of carcinoma. Each of the five cases that Way studied had an identical evolution: large primary tumor, numerous metastases, and rapidly fatal clinical course. Similar lesions have been described more recently, also with a poor prognosis.[175,229] Ultrastructural findings of desmosomes and tonofilaments in the sarcomatoid cells and immunohistochemical demonstration of keratin are helpful in revealing the true epithelial nature of these cells.

Small Cell Carcinoma. Small cell carcinoma is a rare tumor characterized by trabecular structures of small cells with neuroendocrine differentiation. Electron microscopy reveals the presence of neurosecretory granules. The origin of the cells is still unsettled; they are derived from the Merkel's cell (a skin receptor cell) or from some primitive cell with neuroendocrine differentiation.[214,230]

Sweat Gland Carcinomas. Sweat gland carcinomas are commonly associated with Paget's disease.[231,232] They occur more frequently after the menopause and consist of infiltrating nests of pleomorphic mucicarminophilic cells with inter- or intracellular lumina. Although all these tumors are rare, those showing apocrine differentiation are more common than the eccrine variants.

Paget's Disease. Paget's disease of the vulva is considerably rarer than the corresponding lesion of the breast and is found in elderly women.[233–238]

Histogenesis. The histogenesis of the disease remains debatable. Different suggestions have been proposed: tumor cells from underlying glandular structures (eccrine,[232] apocrine,[231] or sebaceous glands) colonizing the epidermis; transformed keratinocytes; and endodermal cells of the cloacal region.[233] Casein and carcinoembryonic antigen (CEA) have been identified by immunohistochemical techniques.[203]

The diversity of the cellular morphology is understandable if one remembers that the neoplastic cells are derived from the multipotential basal epithelial cell of the epidermis.[239] Melanin imbibed from adjacent melanocytes has been observed in some Paget's tumor cells. This should not suggest wrongly the diagnosis of malignant melanoma. Immunostains for S-100 protein and HMB-45 should be negative.[203] Electron microscopic findings have confirmed the concept of an *in situ* carcinoma: neoplastic keratinocytes or squamous cells and secretory cells of sweat gland type have been described in Paget's disease of the vulva.[240,241]

Compared with the mammary and perianal localizations, vulvar Paget's disease is less frequently related to an underlying carcinoma; the average frequency with which the latter lesion is found is 30%.[238] A careful investigation and histologic examination of all tissue removed by the surgeon is mandatory to exclude the presence of an associated invasive carcinoma.[234,236]

Clinical Appearance. The lesion resembles a chronic dermatitis and is characterized by a well-limited, gray-red zone with white plaques (Color Figure 1-8) that should be differentiated from squamous cell carcinoma in situ.

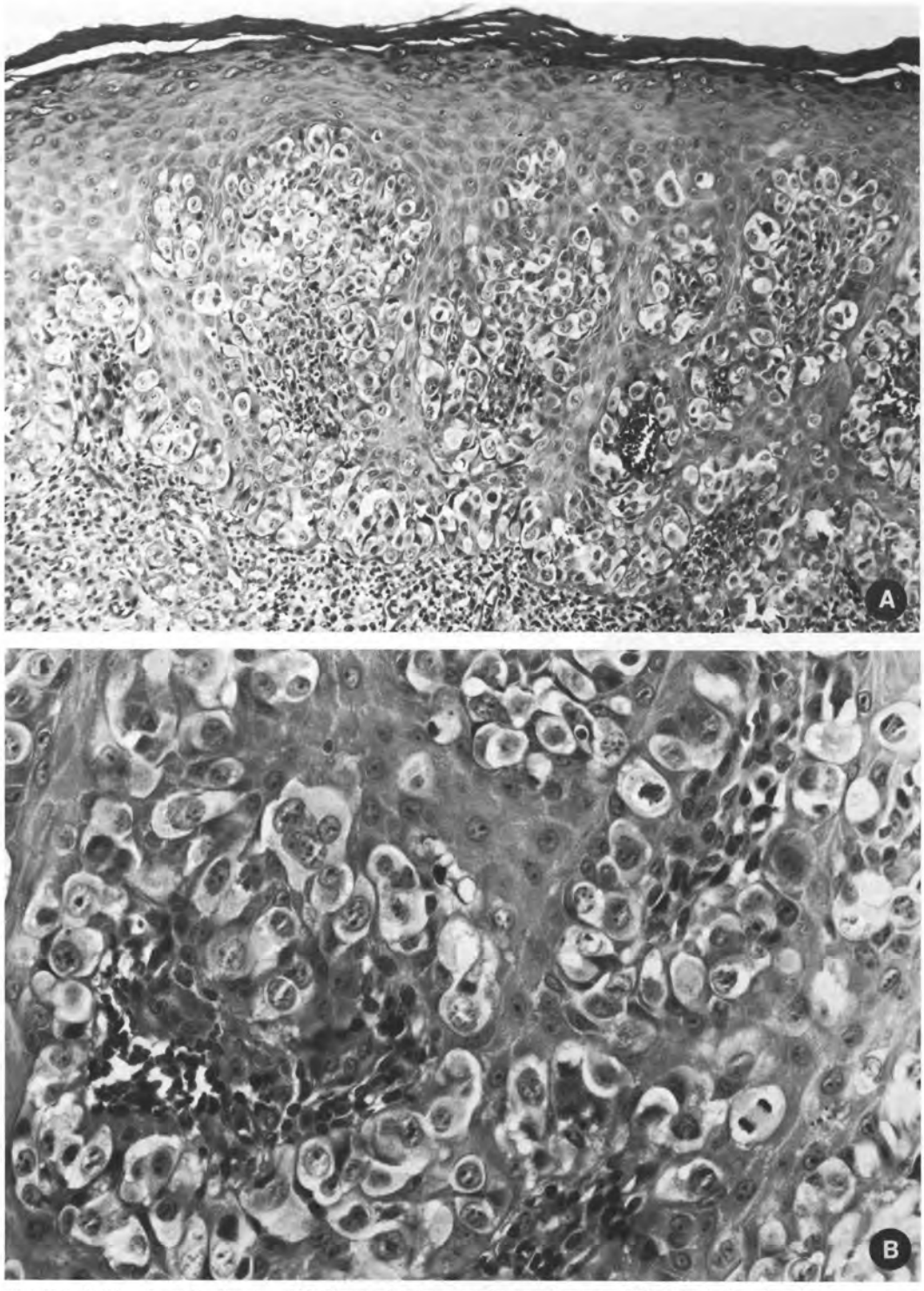

FIGURE 1-33 Paget's disease. **(A)** General microscopic appearance. **(B)** Detail showing large neoplastic cells with clear cytoplasm dispersed throughout the squamous epithelium.

Histologic Appearance. There is a hyperkeratotic and acanthotic epithelium studded with large cells containing clear cytoplasm and voluminous nuclei (Fig. 1-33). They occur singly or in clusters. The tumor cells stain positively with PAS before and after diastase, and most stain with Alcian blue and mucicarmine stains. The subjacent dermis shows a chronic inflammatory infiltrate. Karyotypes from Paget's disease have been reported as normal diploid.[205] Immunohistochemistry is positive for epithelial membrane antigen, CEA, casein, and cytokeratins.[242] Viral investigations have not detected the presence of HPV.[243]

Imprint or abrasive cytology exhibits cells with enlarged nuclei and nucleoli and an increased nuclear–cytoplasmic ratio. The nuclei are central or peripheral, and there is no cytoplasmic keratinization. Binucleation is observed. The cytoplasm has a basophilic stain, and melanin pigment is present in less than 5% of the cells.

Prognosis and Treatment. The type of treatment and the prognosis are determined by the presence of an underlying carcinoma (Fig. 1-34). Lymph node and distant metastases have been reported. Associated extragenital carcinomas (particularly of the breast) are not uncommon.

Adenocarcinoma of Mammary Type. Vulvar mammary tissue (see section on Ectopic Tissue earlier in this chapter) may be the site of malignant lesions.[244,245] These carcinomas are histologically similar to mammary carcinomas arising in the breast.

Carcinoma of Bartholin's Gland. Carcinoma of Bartholin's gland is rare and can be seen at any adult age, with a predilection for elderly women.[246,247] For unknown reasons, the tumor is more frequently localized to the left side. Clinical complaints are nonspecific, and often the first diagnosis is that of an inflammatory lesion or a cyst. Several histologic forms are encountered: adenocarcinoma, squamous cell carcinoma, and, less frequently, adenoid cystic carcinoma, transitional cell carcinoma, mixed and undifferentiated forms. *Adenoid cystic carcinoma* has a distinctive histologic appearance, with epithelial cords scattered through an eosinophilic, often hyalinized, stroma (Fig. 1-35).[248,249] It is identical to the tumor seen in the salivary glands and has a special affinity to invade perineural spaces. *Skene's glands* may be the site of origin of adenocarcinoma in rare cases.[250]

Carcinoma of the Urethra. Although properly belonging to the field of urologic pathology, carcinomas of the urethra are important to this discussion because they usually involve the vulva.[251,252] In the 1952 review by McCrea, 546 authenticated primary urethral malignant tumors were found in the literature: 340 unclassified carcinomas, 116 squamous cell carcinomas, 48 adenocarcinomas, 23 sarcomas, and 19 melanomas.[253] They appear mostly in women older than 50 years of age. The vast majority of these tumors involve the anterior (vulvar) third of the urethra, some involving the entire length of the organ; involvement of the posterior urethra alone is rare. A rare entity is carcinoma arising in a urethral diverticulum.[254,255]

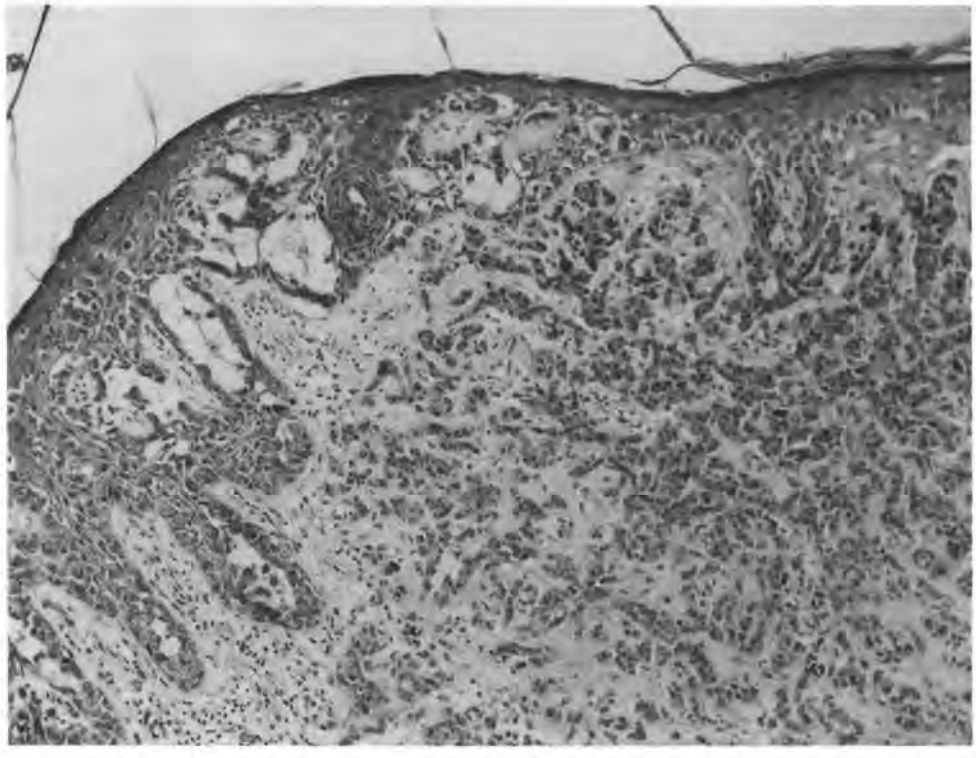

FIGURE 1-34 Invasive Paget's disease. In addition to neoplastic cells in the epidermis, there is a contiguous underlying invasive adenocarcinoma.

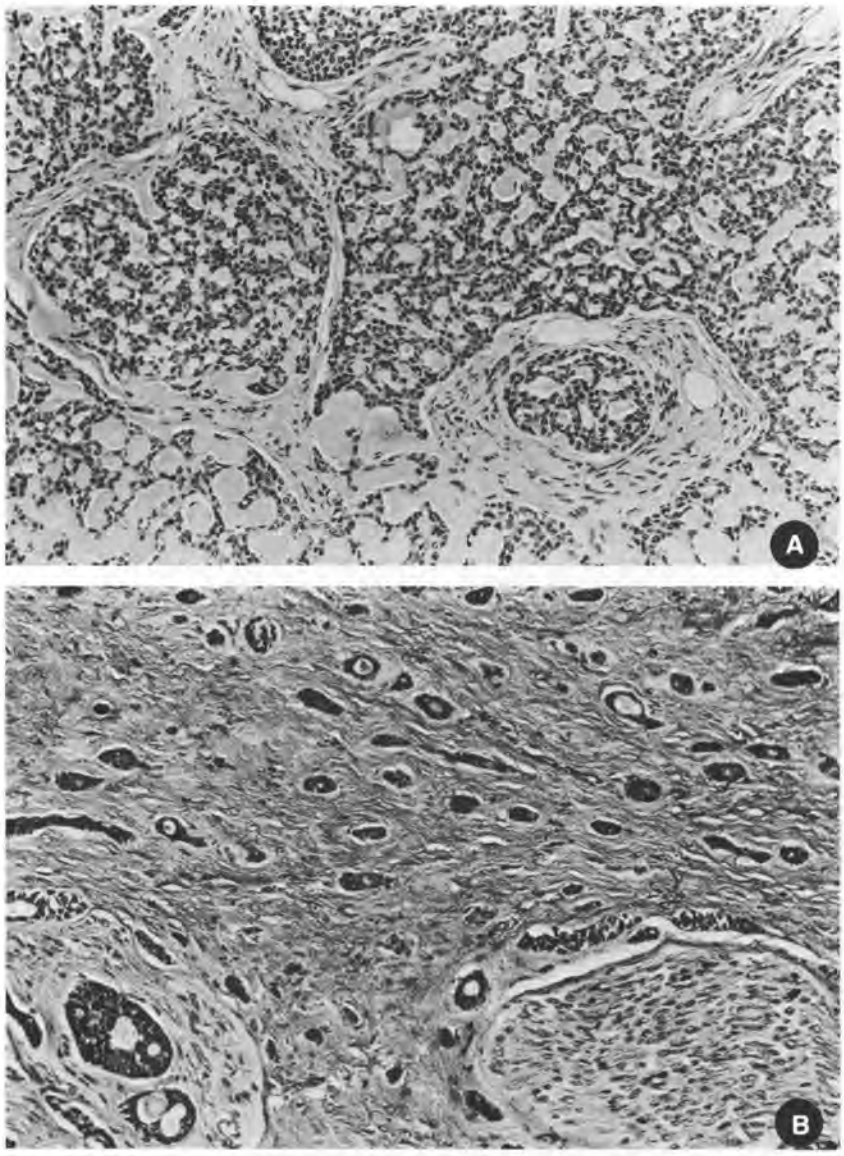

FIGURE 1-35 Adenoid cystic carcinoma of Bartholin's gland. **(A)** Low-power view showing interlacing cribriform glandular formations separated and expanded by hyaline basement membrane-derived material. **(B)** Sclerosing field of tumor with peri- and intraneural invasion.

Macroscopic Appearance. Squamous cell or epidermoid carcinoma begins as a small papillomatous or ulcerated lesion, becoming exophytic when more advanced. Adenocarcinoma, which originates in the paraurethral glands, usually presents as a dark red polypoid mass protruding from the urethral orifice but may be located submucosally.

Microscopic Appearance. The squamous carcinomas are usually well differentiated, resembling other squamous carcinomas of the vulva but with somewhat less keratinization (Fig. 1-36). Spindle cell metaplasia is occasionally present, and inflammatory changes in the stroma are common. The adenocarcinomas are usually composed predominantly of mucin-secreting glands but may contain large cells with clear cytoplasm.[252] Mixed squamous-urothelial (transitional cell) tumors may be observed.

Carcinomas arising in a diverticulum are predominantly adenocarcinomas, followed by transitional and squamous cell tumors. A few cases represent tumors arising from congenital embryonal rests.

Prognosis, Evolution, and Treatment. Small localized tumors have a good prognosis. Pelvic and inguinal lymph node metastases occur predominantly with tumors of the posterior and anterior urethra, respectively. Distant metastases are infrequent, occurring in less than 15% of all cases and possibly more frequently in adenocarcinoma; they have been found in the lungs, brain, liver, and ureters. Squamous cell carcinomas are best treated by surgery or radiation, or both, whereas adenocarcinomas respond poorly to radiation and should therefore be treated primarily by surgery. Five-year survival in most series is in the range of 30%.[256]

The adenocarcinoma type of diverticular origin should be recognized as such, because it appears to

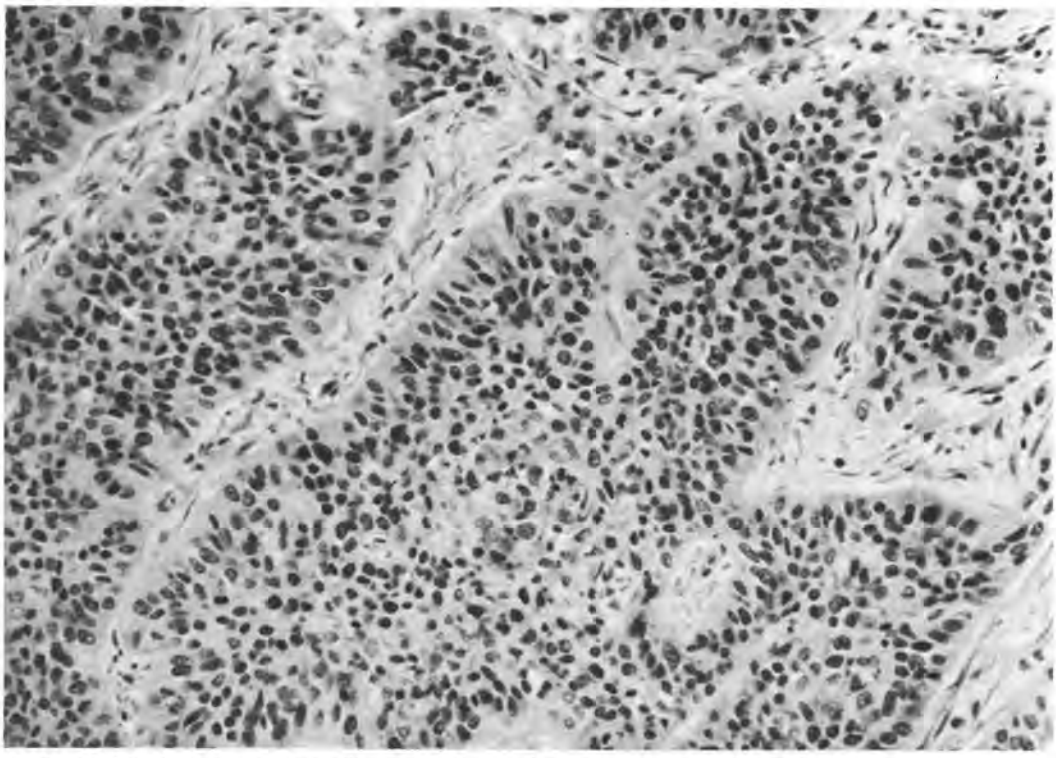

FIGURE 1-36 Squamous cell carcinoma of the urethra.

be less aggressive than the transitional and squamous types.

Malignant Melanoma

Malignant melanoma, a tumor originating from melanin-producing cells, accounts for 2% to 10% of vulvar malignant lesions.[257-261] It affects mainly Caucasians. Lymphatic and bloodstream metastases occur frequently. There is wide hematogenous dissemination to almost all the organs of the body, most notably the lungs, liver, heart, kidneys, and meninges.

Macroscopic Appearance. The macroscopic appearance is that of a black or brown pigmented spot that enlarges and ulcerates (Fig. 1-37*A*). The tumor is most frequently situated at the level of the labia majora.

Histologic Appearance. The histologic appearance is extremely variable and often is not typical (see Fig. 1-37*B*). Nodular and superficial spreading types have been reported with equal frequency. The tumor may resemble squamous cell carcinoma, anaplastic adenocarcinoma, or spindle cell sarcoma. Invasion of the surface epithelium by nests of malignant cells, in a manner similar to that of Paget's disease, is one of the characteristic features of malignant melanoma. In the dermis and the fibroadipose subcutaneous tissue, the cells are disposed in bands or large plaques that are separated by thin fascicles of banal stroma. The nuclei are large, irregular, and hyperchromatic and often contain typical rounded invaginations of cytoplasm (pseudoinclusions). The amount of melanin pigment within the tumor varies from one case to the next, and when it is absent (amelanotic melanoma) the diagnosis is more difficult; in the vulva, this eventuality is rare.

Prognosis. Estimation of the level of invasion of the dermis according to Clark (Table 1-6) and of the thickness of the lesion as suggested by Breslow provides a significant indication of the prognosis. Better 5-year survival rates are correlated with tumors less than 0.75 mm thick and with low levels of Clark classification. Vulvar melanoma is associated with a poor prognosis; the overall survival rate of vulvar melanomas is about 30%.[261] Regional lymph node metastases develop early and rapidly and worsen the prognosis considerably when they are present.

Differential Diagnosis. Differential diagnosis is with Paget's disease for the superficial spreading type and with a metaplastic or sarcomatoid squamous cell carcinoma[229] or sarcoma in the spindle cell nodular type. Immunohistochemistry for S-100 protein (melanoma), carcinoembryonic antigen (Paget's disease), keratin (squamous cell carcinoma), and desmin or vimentin (sarcomas) can be useful, as can special stains for melanin and ultrastructural demonstration of premelanosomes.

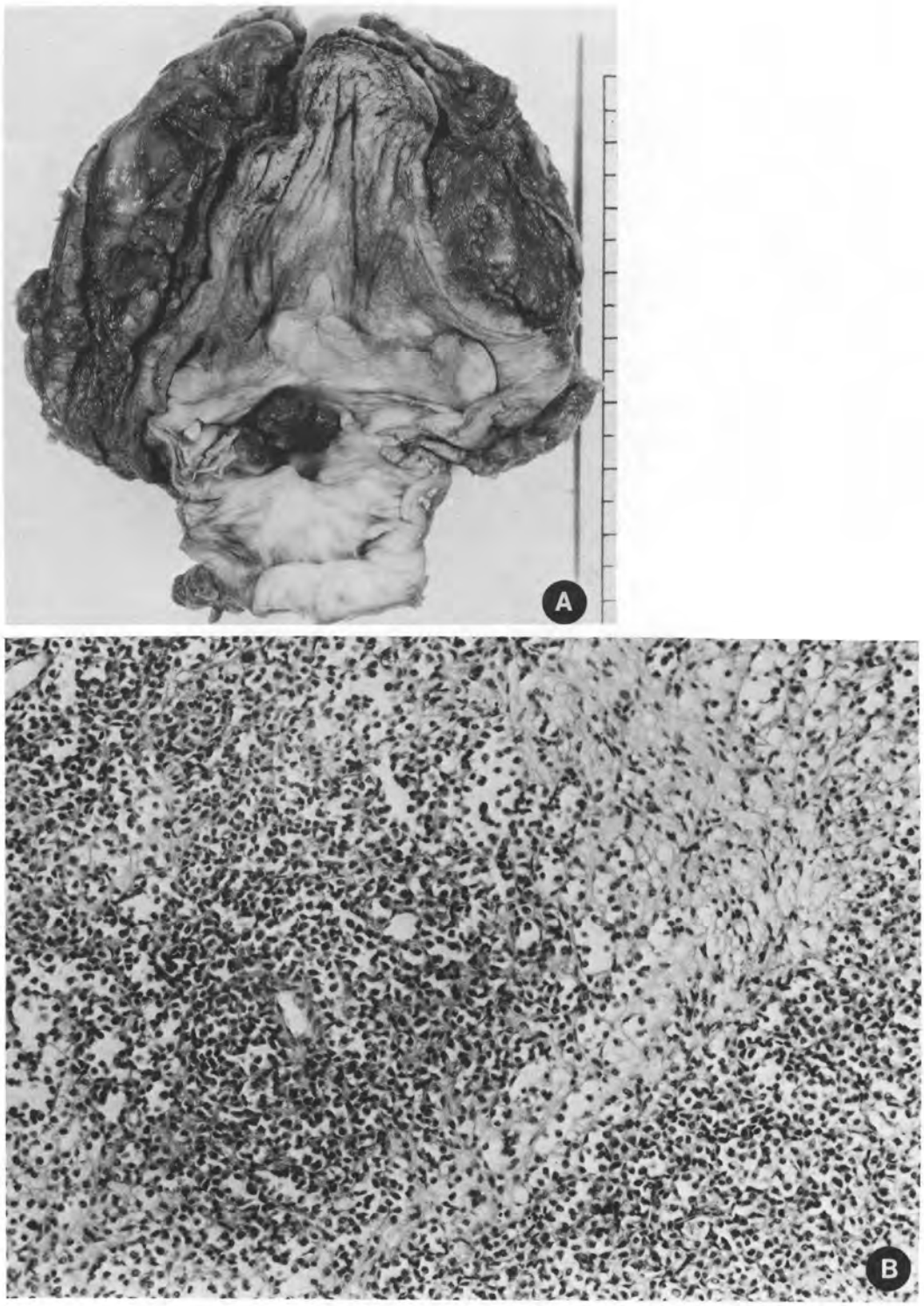

FIGURE 1-37 Malignant melanoma. **(A)** Macroscopic appearance. **(B)** Microscopic appearance.

TABLE 1-6.
Level of Invasion of Malignant Melanoma (Clark Classification)

Level	*Definition*
I	Intraepidermal involvement only
II	Invasion of the papillary dermis
III	Filling of the papillary dermis with abutment on the reticular dermis
IV	Invasion of the reticular dermis
V	Invasion of the subcutaneous tissue

Malignant Nonepithelial Tumors

Vulvar sarcomas are rare tumors observed at any age but are more frequent among tumors in children and young women.[262–264] *Leiomyosarcoma* is the most common histologic type and appears during the third and the fourth decades.[115] It is characterized by a rapidly growing tumor measuring a few centimeters in diameter and located in the labia majora, the clitoris, or the periurethral region. Important criteria of malignancy are an elevated mitotic count (10 or more mitoses per 10 high-power fields) and the presence of abnormal mitoses. Prognosis is poor if the excision is not complete.[265]

Rhabdomyosarcoma occurs rarely in the vulva, and only a few cases have been reported. It appears at any age, but the embryonal (botryoid) and the alveolar types are more frequently seen in infants and young adults, respectively.[262,266,267] In a study from the Armed Forces Institute of Pathology (1970–1979), 5 of 558 rhabdomyosarcomas were located in the vagina or the vulva.[268] The most difficult cases to recognize are the poorly differentiated round or spindle cell tumors. The presence of rhabdomyoblasts with or without cross striations and the use of immunochemistry will facilitate the diagnosis. Desmin, vimentin, and myoglobulin expression are characteristic. Electron microscopy is helpful.

Rare cases of true *fibrosarcoma* have been reported, if malignant fibrous histiocytoma and malignant schwannoma are correctly distinguished.[269,270] Microscopically, the tumor is a proliferation of fibroblasts arranged in fascicles exhibiting a herringbone appearance and surrounded by abundant reticulin-stained collagen fibers. Immunohistochemistry shows that the cells exhibit reactivity for vimentin and type I collagen.

Malignant fibrous histiocytoma is the second most common vulvar sarcoma in adults.[271] Clinically, one observes a large tumor mass. The microscopic appearance is pleomorphic and reveals a wide spectrum of cellular atypia, ranging from small regular fibroblasts to osteoclast-like giant cells to huge irregular cells with atypical and voluminous nuclei (storiform pleomorphic type). These cells may be accompanied by numerous neutrophils (inflammatory type) or by foci of myxoid transformation of the stroma (myxoid type). Immunohistochemical markers of histiocytes and vimentin are expressed.

Dermatofibrosarcoma protuberans has been rarely reported in the literature.[272,273] This low-grade sarcoma occurs in adults and is characterized microscopically by spindle cells arranged in a prominent storiform pattern. Local recurrence has been mentioned, but distant metastases should not take place.

Epithelioid sarcoma occurs in the labia majora of younger women.[274–276] It is characterized by a combination of spindled and epithelioid cells with bland nuclear features; these cells form multiple nodules with central necrosis. It should be differentiated from *malignant rhabdoid tumor,* another aggressive lesion appearing as a mass in young women.[274] Poorly differentiated squamous carcinoma should not be misinterpreted as epithelioid sarcoma.[201,229]

Liposarcoma is exceedingly rare. We have observed a case involving the labium major in a young woman, and another case has been reported by LiVolsi and Brooks.[277] Rare cases of alveolar soft part sarcoma,[278] malignant schwannoma,[262,279] malignant granular cell tumor,[280] angiosarcoma,[117] and Kaposi's sarcoma[277] have been reported.

Carcinosarcoma of the vulva is very rare. It contains both sarcomatous and carcinomatous elements in variable proportions. The natural history varies from one case to another. The case described by Parham and colleagues showed immunohistochemical positivity for vimentin and desmin as well as for the epithelial markers EMA (epithelial membrane antigen) and keratins.[281]

Malignant lymphomas, when present in the vulvar region, are a manifestation of systemic disease.[282,283] The existence of primary *teratomas* of the vulva has been reported; the rarity permits the omission of further comment. A few cases of *sarcomas of Bartholin's gland* have been described.

Metastatic Tumors

Vulvar metastases represent 10% of vulvar malignant lesions. The most frequent are of cervical or corporeal uterine origin; others include metastases of renal carcinoma or malignant melanoma.[284] *Choriocarcinoma* sometimes invades the vulvar region. The cells often have an undifferentiated appearance that may not recall the histology of the primary lesion. In other instances, the metastases closely reproduce the appearance of the primary lesion, for example, well-differentiated adenocarcinoma of the endometrium or squamous cell carcinoma of the cervix. The latter may be difficult to differentiate from primary vulvar squamous carcinoma; demonstration of an epithelial origin, an in situ component, or a bowenoid appearance favors a vulvar primary, whereas metastases tend to be well circumscribed and limited (at least initially) to the dermis or submucosa. Primary invasive or in situ squamous carcinoma of the vulva fre-

quently coexists with synchronous or metachronous primary squamous neoplasms of the cervix and vagina.

Metastatic melanoma may be differentiated from primary melanoma by the presence of epithelial junctional melanocytic activity in early lesions of the latter; in the later stages, differentiation may be impossible. Melanin is not always present in the metastases of melanoma. The prognosis of these generalized tumors is poor.

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2 The Vagina

EMBRYOLOGY

The vagina arises from the fusion of the inferior portion of the müllerian ducts and a portion of the endoderm of the urogenital sinus. A solid plug forms at this junction, and this plug is subsequently recanalized. The part played by the mesonephric epithelium, formerly thought to be involved in this formation, is controversial. After the fusion of the lower portions of the müllerian ducts and the urogenital sinus, the squamous cells from the sinus lining invade the fused müllerian ducts and replace the columnar epithelium up to the external cervical os. This phenomenon is completed after the 20th week of embryonic life.[1–4] Experimental studies in rodents tend to suggest that stromal tissue of the vaginal wall induces the differentiation of the squamous epithelium.[5]

ANATOMY AND HISTOLOGY

The vaginal wall consists of several layers. The *tunica externa* is composed of a loose connective tissue containing venous plexus and nerve branches. The *muscularis* is composed of an external layer of longitudinal smooth muscle fibers and an inner layer of circular ones. The *submucosa* is a connective tissue lamina rich in lymphatics, venous plexus, and elastic fibers. Finally, the *tunica interna* is represented by a pluristratified squamous mucosa comprising three parts: the basal, intermediate, and superficial layers. The relative proportions of these three layers vary according to the hormonal background. The intermediate strata are rich in glycogen (Fig. 2-1). Langerhans cells have been demonstrated in the mucosa.[6] These cells originate from the bone marrow and are involved in the localized immune response. Specific cytoplasmic granules (Birbeck granules) are demonstrated ultrastructurally.[7]

The vascularization of the vagina is richly developed. The *arteries* arise as branches of the uterine artery, inferior vesical artery, middle hemorrhoidal artery, internal pudendal artery, and especially the vaginal artery, a branch of the hypogastric artery. The *veins* form a rich plexus whose branches drain into the internal iliac vein or its tributaries. This vaginal venous plexus is in communication with the uterine, vesical, and hemorrhoidal venous plexus. The *lymphatics* from the upper half of the vagina drain into the internal iliac nodes, notably the obturator, hypogastric, and sometimes the rectal nodes; those of the lower end drain into the inguinal lymphatics and some to the external iliac nodes. Anastomoses exist between the upper and lower halves of the organ and between the left and right sides.[8] The *nerves* issue from the hypogastric and internal pudendal plexus.[9]

MALFORMATIONS

Diverse malformations may be encountered, most of which may be explained by anomalies in fusion of the müllerian ducts.[10] *Absence of the vagina* is rare and oc-

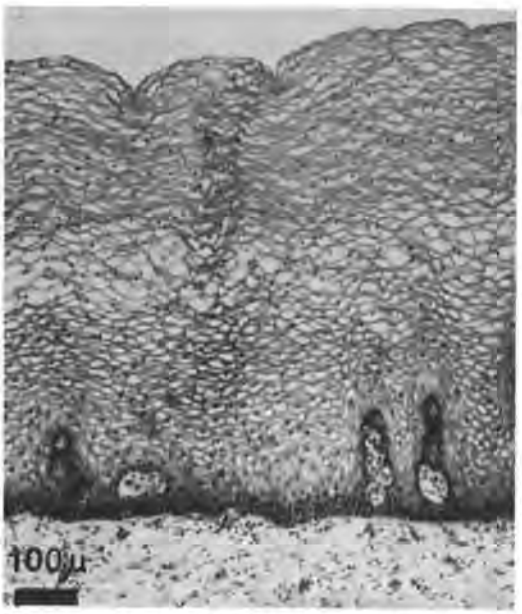

FIGURE 2-1 Functional vaginal epithelium: intermediate cells rich in glycogen.

curs when the müllerian ducts do not come in contact with the urogenital sinus. It is often associated with a rudimentary uterus in otherwise normal females (Rokitansky-Küster-Hauser syndrome).[11] Much rarer is pure vaginal aplasia, commonly associated with hematometra and endometriosis after puberty. Urinary tract anomalies are seen in 15% of cases.[12] Very rare familial cases have been reported.[13]

Solid noncanalized vagina is represented by a massive block of tissue; this malformation is extremely rare. *Transverse* and *diaphragmatic stenoses* are represented by the presence of a transverse septum or regions of stenosis. These may extend over several centimeters. Partial septa or ridges have been noted frequently in young women whose mothers were treated with diethylstilbestrol (DES) during pregnancy.[14]

Double vagina is the presence of a median partition, most often parasagittal, and persistence of internal partitions fused from the müllerian ducts. This septum may occupy the entire vagina or only a portion of its length.[15] One of the normal conduits may be sealed at its inferior end, which will cause hematocolpos at the time of onset of menstruation.

Malformations of the anterior and posterior walls lead to the formation of *diverticula* or urethrovaginal or rectovaginal *fistulas*. Congenital hypertrophy of the mucosal folds (rugae) is rare.

HORMONE-INDUCED VARIATIONS OF THE VAGINAL MUCOSA

Under the influence of estrogen, the vaginal mucosa increases in thickness. The first manifestation is an increase in mitotic activity in the basal layer. Proliferation and growth of cells are stimulated, and the greatest mucosal thickness is noted between days 7 and 14 of a normal cycle. Although it has been thought that mucosal glycogen content increases at this time, quantitative studies disprove this concept.[16]

Thick vaginal epithelia are also seen in the newborn infant (because of the influence of maternal estrogens), in pregnancy (when, under the influence of progesterone, the intermediate layer is most prominent), and in a minority of postmenopausal women (presumably due to residual extragonadal estrogen production). In most postmenopausal women, and between the first few weeks of life and the menarche, when estrogen levels are low, the vaginal mucosa consists of only a few basal and parabasal cell layers, perhaps with a thin cornified layer; this thin epithelium, combined with a neutral to alkaline vaginal fluid at these times, predisposes the vagina to a variety of infections that are discussed later in this chapter.

There are indications that, in addition to epithelial changes, the vaginal vascularization and innervation vary during the menstrual cycle. For several reasons, the most important of which is sampling variation from one part of the vagina to another, biopsy studies often fail to confirm the known cyclic variations of the vaginal mucosa. On the contrary, vaginal smears gather the products of desquamation of large zones of the mucosa and much more effectively reveal the characteristics that vary during the course of a cycle.

Since the historic publication of Pouchet[17] in 1847, and the pioneer work of Papanicolaou[18–20] and Babes,[21] many authors from America and Europe have established the validity of hormonal cytology as an efficient, reliable, rapid and inexpensive method.[22–27] The principle of the method is based on the relation between the degree of cellular maturity and the level of endogenous or exogenous sex steroids present. This relation is mitigated by two factors: (1) the hormonal "climate" is the combination of different specific hormones (estrogens, progestogens and androgens) that have synergic or antagonistic effects, resulting sometimes in nonspecific images; (2) since hormonal cytology depends on accurate clinical data, these must always be correlated with the cytologic image.

Cytosmears for hormonal evaluation should always be prepared from scrapings of the lateral wall of the upper portion of the vagina. If the smears are contaminated with cervical material (indicated by the presence of endocervical cells) or inflammatory infiltrates, a hormonal interpretation should not be attempted.[28]

Hormonal vaginal cytology has lost some of its importance because more accurate methods of measurement of serum or urine hormone concentrations have been introduced (eg, radioimmunochemical assays). Vaginal cytology, however, remains an easy and inexpensive preliminary method of evaluation in

daily practice. To obtain better results, four smears should be prepared at different phases of the cycle: two during the proliferative phase governed by estrogen, and two after ovulation during the secretory phase governed by progesterone.

Smears of Estrogenic Type

Estrogens provoke the proliferation and maturation of the squamous cells. A typical appearance, composed of differentiated superficial cells, results; the cells are large, flat, and polyhedral, with eosinophilic cytoplasm and pyknotic nuclei (Fig. 2-2 and Color Figure 2-1). The numerical evaluation of the number of eosinophilic cells with pyknotic nuclei compared with the numbers of other cell types permits an estimation of estrogenic activity. The *karyopyknotic index* is the percentage of superficial eosinophilic and cyanophilic cells with a nucleus whose diameter is less than 6 µm.[25] The *eosinophilic index* is the percentage of eosinophilic superficial cells in the general cell population. Another method of expressing the hormonal activity is calculation of the *maturation index*.[29] This is the count of the different cell types and their expression as percentages based on the evaluation of at least 200 cells (eg, 25% parabasal cells, 35% intermediate cells, and 40% superficial cells). This information must be correlated with the clinical data to have any value in the interpretation of steroid hormonal activity.

Smears of Luteal Type

There is no specific picture reflecting activity of the corpus luteum. The only criteria of luteal stimulation are folding of the superficial and intermediate cells and increased glycogen content of the intermediate cells (navicular cells). Progestational activity in effect favors the proliferation and desquamation of cells before they have arrived at the eosinophilic and pyknotic stage of maturation.[30] This appearance, as we have stated, is not specific: it is seen after suppression of estrogenic activity (by surgical or physiologic menopause) and after stimulation of an atrophic epithelium by estrogens or androgens (Fig. 2-3 and Color Figure 2-2). To be precise and complete, the evaluation of progestational activity should include endometrial biopsy, study of the thermal curve, and a biochemical hormonal study.

Lactobacilli are normally present in abundance in the luteal phase and are observed in more than 50% of healthy women. These Gram-positive, immobile, anaerobic bacilli provoke a cytolysis of the glycogen-rich intermediate cells.

Smears of Gravid Type

The cytologic picture of pregnancy is characterized by the presence of intermediate cells rich in glycogen (navicular cells) and desquamating in plaques.[31-33] Lactobacilli occur in abundance with secondary cytolysis. Endocervical cells are numerous, with an enlarged cytoplasm rich in mucin; rarely, trophoblastic cells are seen and are represented by large, multinucleated cells with an eosinophilic or basophilic cytoplasm (Color Figure 2-3).[34] Decidual cells may be observed when decidual changes occur in the uterine cervix.[35,36] These stromal cells have an abundant, homogeneous, often eosinophilic cytoplasm and a round, centrally located nucleus.

This typical picture does not develop until the end of the third month of pregnancy; before that

FIGURE 2-2 Vaginal smear of estrogenic type: superficial cells.

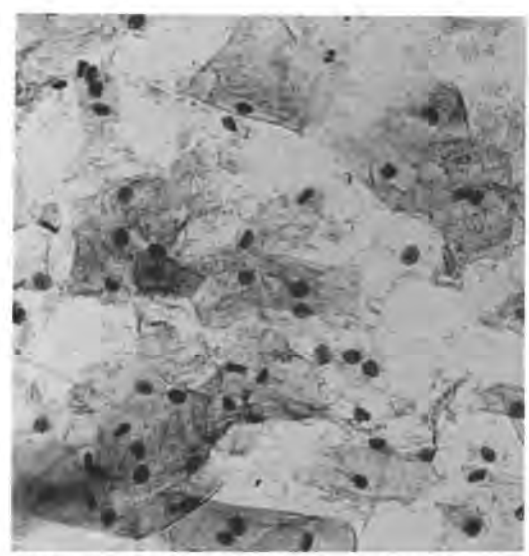

FIGURE 2-3 Vaginal smear of luteal type: folded superficial and intermediate (navicular) cells.

time, the smear is of the menstrual, luteal, or even estrogenic type. The vaginal smear is therefore not a method of diagnosis of pregnancy, but it does permit suspicion of certain anomalies of hormonal equilibrium during pregnancy, notably deficiencies of the corpus luteum. Changes in the smear pattern during the course of a pregnancy are more important than a single abnormal smear.

Smears of Postpartum Type

Immediate postpartum smears show an atrophic pattern, more pronounced in women who are lactating. It is followed by an increase in estrogenic activity after a few weeks postpartum or after cessation of lactation.[37,38]

Smears of Androgenic Type

Androgenic hormones stimulate the proliferation of the basal and intermediate cell layers of the epithelium and provoke the disappearance of the superficial cells. This antiestrogenic effect is clearly visible during the period of hormonal activity. In an atrophic vaginal mucosa, androgens cause the appearance of intermediate and parabasal cells, among which are found cells of a particular type with voluminous nuclei containing scant finely dispersed chromatin (so-called androgenic cells).[39]

Smears of Nonspecific Proliferation

Sex steroid hormones of endogenous or exogenous origin first stimulate the proliferation of the vaginal epithelium. The parabasal cells multiply, and the number of intermediate cells is notably augmented. This cytologic appearance represents a picture of nonspecific epithelial proliferation, composed of plaques of intermediate cells, less numerous parabasal cells, and some superficial cells (Fig. 2-4). If the hormonal activity persists, cytologic changes that are more specific for the hormone administered appear secondarily.[40] This same appearance is found physiologically in women presenting only a modest hormonal activity, such as in the first years of menopause.

Smears of Atrophic Type

Suppression of all hormonal activity produces a progressive atrophy of the epithelium, which then consists of cells of parabasal type (Fig. 2-5 and Color Figure 2-4).[41] In an atrophic epithelium, there are often secondary inflammatory lesions, manifested by nuclear and cytoplasmic alterations and the presence of polymorphonuclear leukocytes and a varied bacterial flora. The picture of atrophy is not always present after menopause; a nonspecific hormonal stimulation of ovarian or extraovarian (notably adrenal) origin often persists for a long time.[42] The atrophic picture supervenes more rapidly after surgical castration. Atrophic smears with degenerative cellular anomalies and cellular necrosis may represent problems of differential diagnosis with dysplasia or even carcinoma (Color Figure 2-5). The administration of estrogens for a short period (*estrogen test*) eliminates anomalies of atrophic origin and facilitates the recognition of true neoplasia.[42]

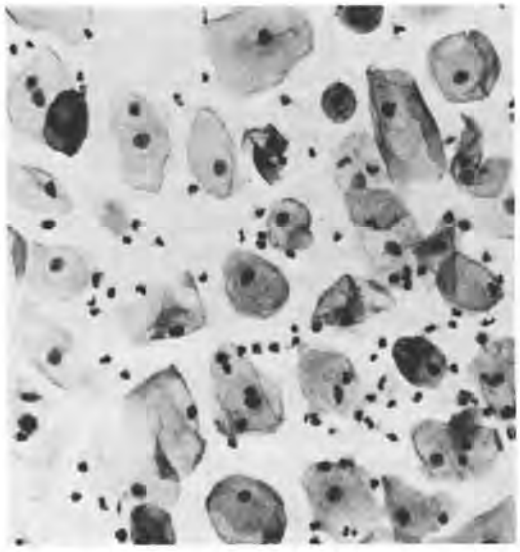

FIGURE 2-4 Vaginal smear of nonspecific proliferation.

Cell Types Accompanying the Vaginal Cells

A variety of cells may be present in the vaginal smears, which will modify the normal cytologic pat-

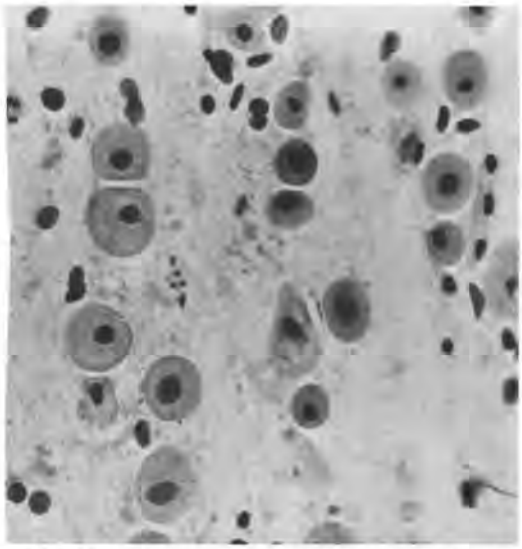

FIGURE 2-5 Vaginal smear of atrophic type: parabasal and inflammatory cells.

tern. Glandular cells of cervical or endometrial origin can be observed. Endometrial cells normally disappear after the 12th day of the cycle. Endocervical and metaplastic cells are more abundant in inflammatory conditions with or without ectropion. Histiocytes, polymorphonuclear leukocytes, and lymphocytes indicate inflammatory reactive changes. Anucleate squamous cells normally are not present; they originate (1) from the lower third of the vaginal mucosa, where they represent, as in the skin, the final step of squamous differentiation; (2) from inflammatory foci of the mucosa (clinical leukoplakia); and (3) from the epidermis of the infant, in pregnant women with ruptured fetal membranes.

INFLAMMATORY DISEASES

A number of inflammatory lesions simultaneously involving the vulva and the vagina are described in detail in Chapter 1. These lesions include those of human papillomavirus (HPV) infection, gonorrhea, diphtheria, chancroid, granuloma inguinale, tuberculosis, syphilis, and mycotic infection. Organisms commonly encountered in association with vaginal lesions include *Trichomonas vaginalis, Herpesvirus hominis, Gardnerella vaginalis,* and *Enterobius vermicularis.* Among etiologies rarely encountered in temperate climates are amebiasis and schistosomiasis. Some of these organisms may be present without manifestations of clinical symptoms.

In healthy women, the vaginal milieu includes a variety of aerobic as well as obligate and facultative anaerobic organisms that do not necessarily equate with inflammation.[43–45] Predisposing conditions and a trigger mechanism that often is not clearly understood are necessary to modify the saprophytic status of these organisms into that of pathogens. Among the predisposing conditions are variations of the vaginal pH, mucosal injuries during pregnancy and delivery, and absence of the protective squamous maturation in prepubertal girls and postmenopausal women.

Bacterial or Nonspecific Vaginosis

Facultative and anaerobic flora may cause a specific condition called *nonspecific vaginosis*[46] or *bacterial vaginosis.*[47] It is a polymicrobial vaginitis resulting from synergism between these anaerobic bacteria and coccobacilli.[48–51] Cervicovaginal smears reveal the presence of squamous cells covered with bacilli as well as cocci and bacilli diffusely scattered or occurring in clumps. Their identification can be obtained by microbiologic isolation but is not required for the clinical management of this frequent disease. It is common in adolescent girls and may be hormonally dependent.[52]

Gardnerella Vaginitis

This type of vaginitis is characterized by the presence of *Gardnerella vaginalis,* previously classified as *Haemophilus vaginalis.* It was described by Gardner and Dukes[53] and classified by Greenwood and Pickett.[54] The organism is Gram-negative or Gram-variable, catalase-positive, believed to be sexually transmissible, and frequently found in asymptomatic women. It is assumed that it may be responsible for the development of an infection without the interaction of other bacteria. The infection becomes symptomatic when the vaginal pH rises to more than 4.5; other aerobic and anaerobic bacteria may be present. The results should be interpreted with caution because the isolated bacterial agent is not always the etiologic factor responsible for the clinical disease. The vaginal flora identified may vary according to factors such as differences in collecting, transporting, or handling the material and the presence of chemical agents such as contraceptives. The disease is associated with a characteristic vaginal discharge with a fishy odor.

Microscopically, numerous organisms cover over the squamous cells or stick to the cellular edges; these so-called clue cells are observed in stained Papanicolaou smears or under phase contrast (Color Figure 2-6). Some authors believe that in smears the organisms should cover the epithelial cells and spread beyond the cellular margins to avoid overdiagnosis.[55] Culture should confirm the diagnosis. Histologic examination does not reveal any significant alteration, the organism being localized at the surface of the epithelium.

Lactobacillus "Vaginitis"

Lactobacilli are aerobic, Gram-positive organisms that are present in the vaginal flora of most women. They are common in the luteal phase and in pregnancy when glycogen is abundant. Their presence corresponds to a low acid vaginal pH (around 5). The glycogen contained in the cytoplasm of intermediate cells is metabolized and generates lactic acid. The destruction of the cytoplasm explains the presence of naked nuclei. It is still a matter of debate whether lactobacilli can acquire a pathogenic significance.

Atrophic Vaginitis

Atrophic vaginitis is encountered in certain women at the time of cessation of ovarian activity, whether physiologic (menopause) or therapeutic (surgery or radiation). It is accompanied by clinical symptoms: burning sensations, at times painful, purulent leukorrhea, and hemorrhages. The atrophic mucosa becomes ulcerated, often effacing the posterior cul-de-

sac and stenosing the bottom of the vaginal canal. Later developments include the formation of adhesions, synechiae, and other cicatricial processes.

Macroscopic Appearance. The mucosa is thin, pale, and smooth; it is the site of small congestive foci, with subsequent ulceration. When the vaginitis is acute, the mucosa is bright red and shiny.

Microscopic Appearance. The epithelium is reduced to a few layers of parabasal and basal cells; it is the site of polymorphonuclear leukocytic infiltration, which is sometimes massive.

The *cytologic pattern* is characterized by the presence of parabasal cells altered by the dryness of the mucosa. The cells are enlarged and the nuclei are discolored, losing their affinity for hematoxylin. A marked eosinophilia of the cytoplasm accompanied by nuclear pyknosis and karyorrhexis characterizes some parabasal cells. When these anomalies are pronounced, they can raise problems of differential diagnosis with dysplasia or carcinoma (see Color Figure 2-5).

The atrophic epithelium shows poor resistance to secondary infection. Local or systemic administration of estrogens brings about a regeneration of the mucosa favorable to cure and "cures" the cytologic abnormalities.

Postpartum Atrophic Vaginitis

Rarely during the period of nursing, one finds a vaginitis that presents the same gross appearance as atrophic vaginitis: bright red congested mucosa covered with ulcers and accompanied by purulent discharge.

Microscopically, there is a thinned vaginal epithelium, reduced to the basal layers and several rows of superficial cells infiltrated with neutrophils. This appearance is comparable to that of an atrophic epithelium, and it is classically considered to be an atrophy of hormonal origin.

The cytologic pattern is similar to the one described in atrophic vaginitis. The administration of estrogens remains efficacious in provoking proliferation of the superficial keratinized layers that protect the epithelium against the bacterial flora.

Fungal Infections

Vaginal Candidiasis

Candida albicans may involve the vaginal mucosa and is the most frequent fungal agent observed in the female genital tract. Vaginal candidiasis is also called *vaginal moniliasis, mycotic* or *yeast vaginitis,* and *vaginal thrush.*

Different candidal types exist; the most common is *C. albicans* followed by *C. glabrata.*[56–60] Some doubts persist about the pathogenic character of the yeast. Clinically, the fungus may not be associated with vaginitis or may produce a white, creamy vaginal discharge with itching. Pregnancy, diabetes, antibiotic agents, corticoids, and immunosuppressive drugs may be related to the presence of the fungus, and it is very common in patients with acquired immunodeficiency syndrome (AIDS). Little is known about the mechanism that provokes the transition from asymptomatic yeast presence to vaginitis. Some strains are refractory to available therapeutic agents, explaining the difficulty of eradicating the causal organism.

Microscopically, the vaginal epithelium is superficially colonized by *Candida,* and it has been suggested that it may penetrate the cells.[61] Acanthosis, intracellular edema, and an inflammatory infiltrate located in the epithelium or in the stroma may be present. Vaginal smears reveal the presence of filamentous structures (hyphae) and/or conidia, which appear as small, oval, encapsulated organisms. Minor epithelial inflammatory changes accompany the fungus, which can be localized in the cytoplasm of squamous cells.[62]

Other Fungi

Vaginal coccidioidomycosis,[63] toxoplasmosis,[64] and blastomycosis[65] have been reported. The organisms can be recognized in vaginal smears but their identification requires cultural characterization.

Parasitic Infections

Trichomonas *Infection and Infestation*

Infection due to *Trichomonas* has been known since Donné, in 1836, published a complete description of these lesions.[66] *Trichomonas vaginalis,* a protozoan, is very common, and 20% to 25% of women undergoing routine gynecologic examinations are revealed to be carriers of the parasite.[67] The practice of exfoliative cytology on a large scale has confirmed the high frequency of this infestation. The parasite is transmitted by sexual contact and can be carried by the male partner.[68] The infection is most frequent during the reproductive years and in pregnancy,[69] is infrequent after menopause, and is rare before puberty.

The trichomonad is a mobile flagellate with four cilia that is refringent on direct examination. The parasites are of various sizes, measuring 10 to 20 μm; giant forms are rarely encountered. Their presence in vaginal secretions is not accompanied by an inflammatory reaction in most cases (infestation).

Clinical Manifestations. The infection is characterized by leukorrhea accompanied by burning sensations and pruritus, dyspareunia, dysuria, and irritation of the adjacent epithelia. The incubation period is between 5 and 28 days. This leukorrhea, pathog-

nomonic of the infection, is yellow-gray and of a foamy or creamy consistency, and it occurs in about 25% of patients. It is very irritating to the tissues. When a bacterial flora coexists, the discharge may be frankly purulent. The vaginal pH is lowered to around 5.0 after the destruction of carbohydrates and liberation of acid radicals. Lower urinary tract infection with dysuria and urethral discharge may be observed.

Laboratory Diagnosis. Laboratory diagnosis relies on the demonstration of the protozoan in the vaginal discharge, which is diluted with isotonic saline solution and examined under the microscope as a wet preparation or is fixed in 50% alcohol and stained with the Papanicolaou technique. The number of trichomonads varies, and a careful examination of the slide is needed before it is recognized. Bare epithelial nuclei should not be misinterpreted as trichomonads.

Macroscopic Appearance. In acute vaginitis due to *Trichomonas,* the mucosa is red, congested, edematous, and granular (so-called strawberry vagina). Small hemorrhagic zones are present, and there may be occasional small superficial ulcers. These alterations involve the vaginal, vulvar, and ectocervical mucosae. Colposcopy reveals a characteristic vascular pattern.[70]

Microscopic Appearance. The vaginal mucosa shows acute or chronic inflammatory lesions, depending on the state of evolution of the infection. Biopsy of the vaginal mucosa (which is seldom done) reveals a neutrophilic, lymphocytic, and plasmacytic infiltrate, vascular congestion, and stromal edema, as well as disseminated foci of cellular atypia throughout the epithelium. Reserve cell hyperplasia and squamous metaplasia may be present. One finds the organisms on the surface of the squamous epithelial cells or rarely in the epithelium, especially in the superficial cell layers. The parasite shows a pale, cyanophilic cytoplasm and a small, faint, vesicular, eccentric nucleus.

The modifications of the epithelial cells are easily visible in vaginal smears and are manifested by increased eosinophilia and the presence of characteristic perinuclear haloes (Fig. 2-6 and Color Figure 2-7). The nuclei show variation in size, with a general increase in volume, binucleation, karyorrhexis and pyknosis. These cytologic alterations are sometimes so accentuated that they approach cellular abnormalities of neoplastic type. The absence of hyperchromatism and of bizarre nuclei and the presence of the parasite orient the pathologist toward the diagnosis of *Trichomonas* infection. Aggregates of leukocytes called "cannonballs" covering the surface of squamous cells are sometimes recognized and represent *T. vaginalis* located on squamous cells and secondarily phagocytized by leukocytes and macrophages. *Leptothrix* organisms are frequently seen in association with Trichomoniasis, and may be the first clue to the presence of *T. vaginalis* (Color Figure 2-8).

Prognosis, Evolution, and Treatment. *Trichomonas* infection was once considered to be favorable to the

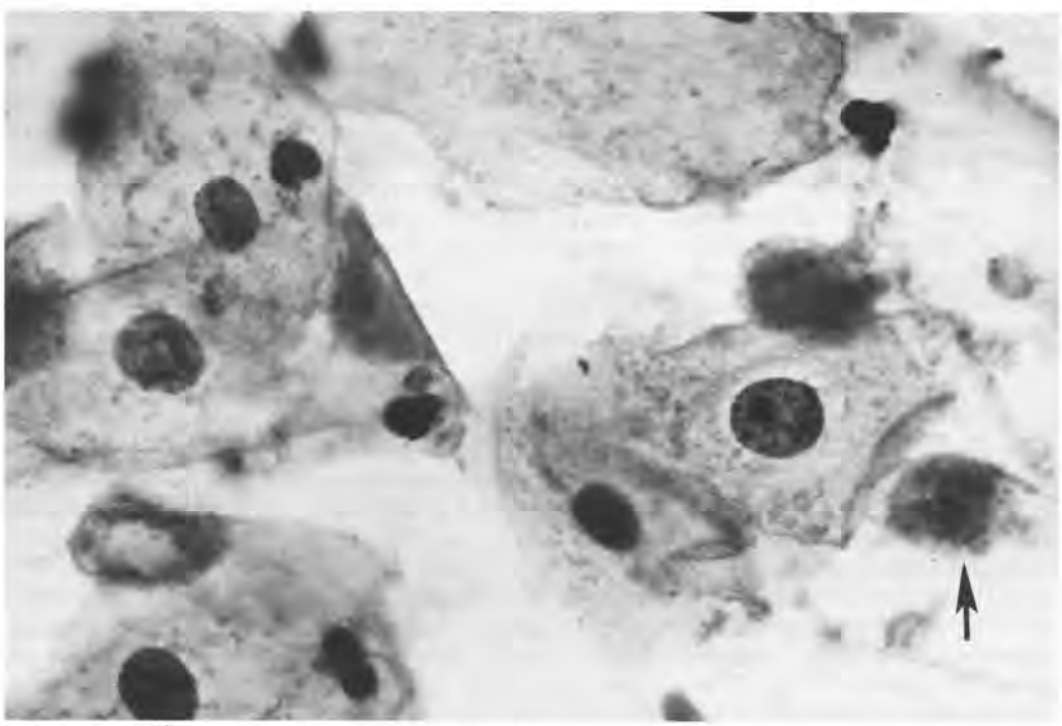

FIGURE 2-6 *Trichomonas* vaginitis: cytologic appearance.

development of cervix cancer. This hypothesis is now discarded, even though a higher incidence of *Trichomonas* infestation is noted in patients with cervical cancer.[71] The essential principles in therapy are the use of local germicides and disinfectants and of local or systemic estrogens over a prolonged period, identification and oral treatment of urinary localizations (urethra, bladder, and Skene's glands), careful search for the parasite in the urogenital tract of the sexual partner, and prophylactic hygiene. Despite apparent cure, even of long duration, the infection often reappears.

Other Parasitic Infections

Enterobius vermicularis, Ascaris lumbricoides, Filaria (nematodes), *Entamoeba histolytica* (protozoan), *Cysticercus, Toxoplasma,* schistosomes, and arthropods have been described as occasional contaminants of the vagina.[72–76]

Desquamative Inflammatory Vaginitis

This entity consists of an atrophic vaginitis, usually limited to the upper half of the vagina, in which desquamation of parabasal cells and neutrophils is prominent despite normal ovarian function. The etiology is unknown, and corticosteroids are the only therapeutic agents that afford relief.[77]

Emphysematous Vaginitis

Emphysematous vaginitis is a rare disease, first described by Huguier, that has been reported most often in association with pregnancy or cardiopulmonary disease.[78] In 1964, Gardner and Fernet found 145 cases in the literature, to which they added 10 of their own.[79] The disease involves the superior portion of the vagina and the ectocervix. Clinically, one observes a red, sometimes superficially ulcerated mucosa. Synonyms are cystic vaginitis, gaseous cysts of the vagina, and emphysematous colpitis.

Macroscopic Appearance. This lesion is characterized by the presence of small liquid- or gas-containing cysts in the mucosa. These cysts may rupture and give rise to ulcers.

Microscopic Appearance. There are cystic cavities with thin walls. They are bordered by giant cells or by an epithelium or endothelium containing multinuclear cells that are surrounded by fibrous cords rich in elastic fibers. This appearance has suggested obliterated and distended lymphatics. The gaseous content of the cysts is probably produced by anaerobic bacteria, but a theory of its production by migrating epithelial cells has been advanced. These hypotheses still demand confirmation, because the inoculation of the cystic contents into the guinea pig has never been able to reproduce the clinical picture of the disease.[80]

Treatment. There is no specific treatment, but treatment of the accompanying or underlying bacterial infection may be efficacious.

Vaginitis Caused by Physical or Chemical Agents

A variety of physical and chemical phenomena produce acute or chronic inflammatory lesions of the vaginal mucosa. Some examples are pessaries, foreign bodies, contraceptive devices, irradiation, injected products having potassium permanganate as a base, zinc sulfate, and other antiseptics. A local granulation tissue reaction in the vault may be seen after hysterectomy.[81]

Special mention should be made of the mucosal alteration associated with the use of superabsorbent tampons. The lesions include mucosal drying, epithelial layering, and microulcerations. These microscopic lesions may lead to clinically evident mucosal ulcers accompanied by bleeding and discharge.[82,83] The etiology can be explained by cell membrane alterations followed by extracellular fluid transfer and secondarily widened intercellular spaces. Vaginal ulcers represent a portal of entry for *Staphylococcus aureus,* and the relation of this local lesion to the *toxic shock syndrome* has been considered.[84] The syndrome is caused by the release of the staphylococcal toxin into the circulation.[85,86] The syndrome, initially associated with tampon use, is now described with any staphylococcal infection (see Chap. 12).

Macroscopic Appearance. The mucosa is red, congested, and edematous. The surface is often granular.

Microscopic Appearance. There is leukohistiocytic infiltration of the mucosa accompanied by edema or vascular congestion of the subjacent stroma. In places, the mucosa may be ulcerated and replaced by granulation tissue. Nuclear and cytoplasmic anomalies may be found: anisocytosis, anisonucleosis, cytoplasmic vacuolization, and cellular necrosis.

Langerhans Cell Histiocytosis

Langerhans cell histiocytosis is a rare disease that may affect the female genital tract and notably the vagina. Of unknown etiology, it may represent the manifestation of an undefined immunologic disorder. Macroscopically, it is characterized by papular, erythematous, pruritic lesions that sometimes ulcerate. Microscopically, it is a chronic, necrotizing inflammatory lesion with the presence of Langerhans cells with a typical grooved and folded vesicular nucleus. The differential diagnosis is with various inflammatory conditions.[87]

BENIGN TUMORS

Cystic Tumors

Gartner's Duct Cyst

Gartner's duct (mesonephric) cysts are rare; they originate from vestiges of the mesonephric ducts and are found in the lateral vaginal walls. They may attain 2 cm in diameter and may cause dyspareunia.[88]

Histologic Appearance. The cyst wall is lined by a nonciliated, nonmuciparous, columnar or cuboidal epithelium with large pale nuclei (Fig. 2-7). Tension caused by the intracystic liquid may cause flattening or disappearance of the epithelium, making identification difficult. There may be foci of squamous metaplasia. Smooth muscle fibers may be present in the wall. A case of mesonephric carcinoma has been reported.[89]

Cyst of Müllerian Origin

Müllerian or paramesonephric cysts are identical in gross appearance to cysts of Gartner's duct.[88,90,91] Cysts of the inferior third of the vagina are the most frequent, and they may exteriorize at the vulvar orifice. *Histologically,* they are usually lined by muciparous endocervical-type epithelium, but tubal or endometrial features are present in a minority of cases. In the latter instance, the lesion must be differentiated from true *endometriosis,* in which endometrial stroma is present as well as epithelium. If the epithelium is tubal in type, with ciliated cells, a *prolapsed fallopian tube* (see below) presents the major diagnostic confusion.

Epithelial Inclusion Cyst

Epithelial inclusion cysts are the most common vaginal cysts.[88,90] They are frequent at the level of the culs-de-sac. They originate from inclusions of fragments of squamous epithelium in the mucosa, often by obstetric or surgical trauma. Of variable size, but never more than a few centimeters, these cysts are lined by squamous epithelium and contain a grumous pale yellow substance that represents products of desquamation (Fig. 2-8). Immunohistochemically, they stain for keratin but not carcinoembryonic antigen.

Urothelial Cyst

Urothelial cysts are rare and usually measure less than 1 cm in diameter. Most of them are localized beneath the mucosa of the vulvar vestibule. They are lined by transitional or stratified columnar epithelium, or by both, confirming the urothelial origin.[92] They may represent remnants of the urogenital sinus or may originate from the mucinous Skene's glands; in this case they are lined by a mucinous epithelium.

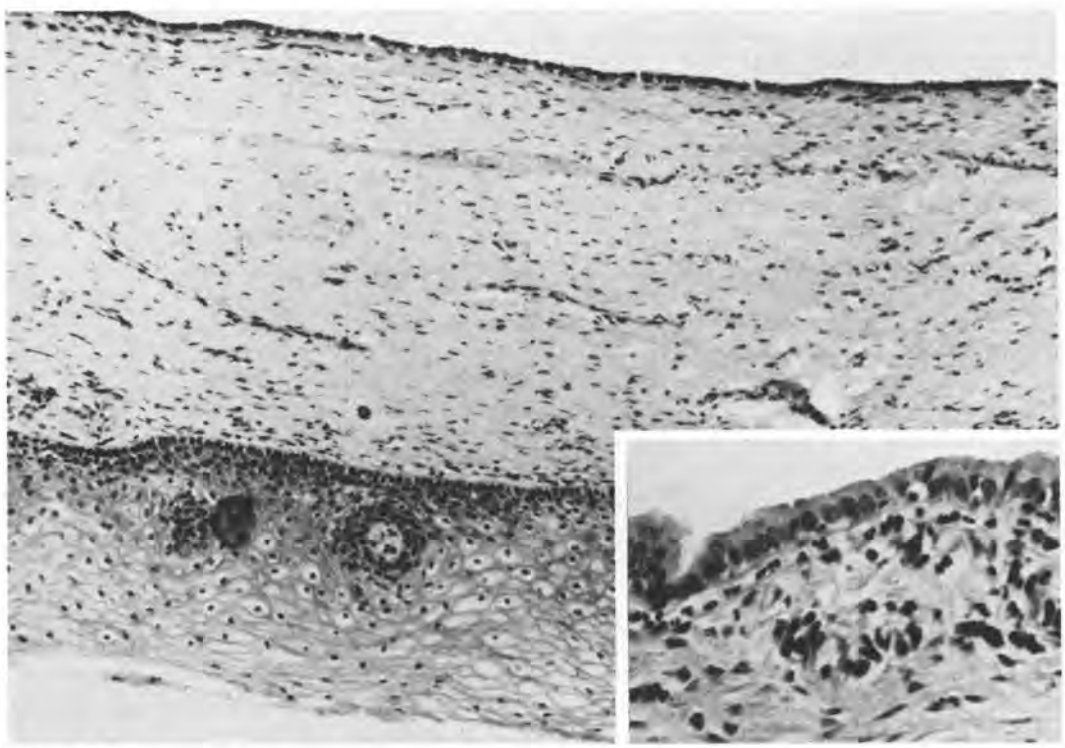

FIGURE 2-7 Gartner's duct cyst lined by nonciliated and nonmuciparous cuboidal epithelium underlain by smooth muscle fibers.

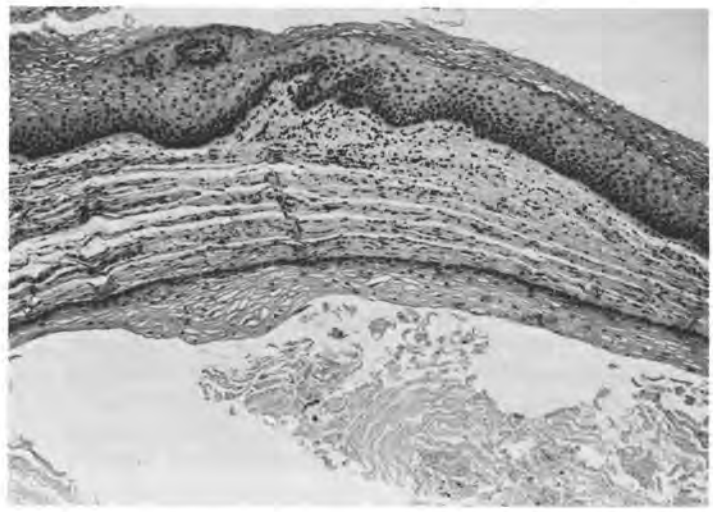

FIGURE 2-8 Epithelial inclusion cyst of vagina.

Solid Tumors

Leiomyoma and Fibroma

Leiomyoma and fibroma are rare tumors.[93,94] They are manifested clinically by the appearance in an adult woman of a mass that produces signs of compression, dyspareunia, and urinary difficulties.

Macroscopic Appearance. There is an ovoid submucosal mass, usually 1 to 5 cm in diameter, which is encapsulated and of firm elastic consistency; the tumor is single or rarely may be multiple. It may on occasion herniate at the vulvar orifice. Rarely, it may attain an enormous volume. Sessile and pedunculated forms exist. When the tumor is large, the overlying vaginal mucosa has a tendency to ulcerate.

Microscopic Appearance. The tumors are composed of connective tissue, smooth muscle fibers, or both. Either of these two elements may dominate. Hyaline degeneration is much rarer than in uterine myomata.

Fibroepithelial Polyp

Vaginal polyps have been described under various names, including *fibroepithelial polyp, sarcoma botryoides-like lesion, pseudosarcoma botryoides,* and *myofibroblastoma.* This benign lesion occurs infrequently in late reproductive life or more rarely during pregnancy.[95–98]

Clinically, it is discovered as a vaginal nodule by the patient, is associated with postcoital bleeding or may be asymptomatic. A history of previous vaginal surgery is mentioned in a significant number of cases.

Macroscopically, it consists of a polypoid nodule usually measuring less than 3 cm in diameter. *Microscopically,* it is covered by a squamous epithelium with foci of hyperkeratosis and parakeratosis. The underlying loose fibrillary stroma is rich in stellate-shaped cells and benign-appearing multinucleated giant cells (Fig. 2-9). The nature of these atypical stromal cells remains obscure. They express vimentin, desmin and receptors for estrogen and proges-

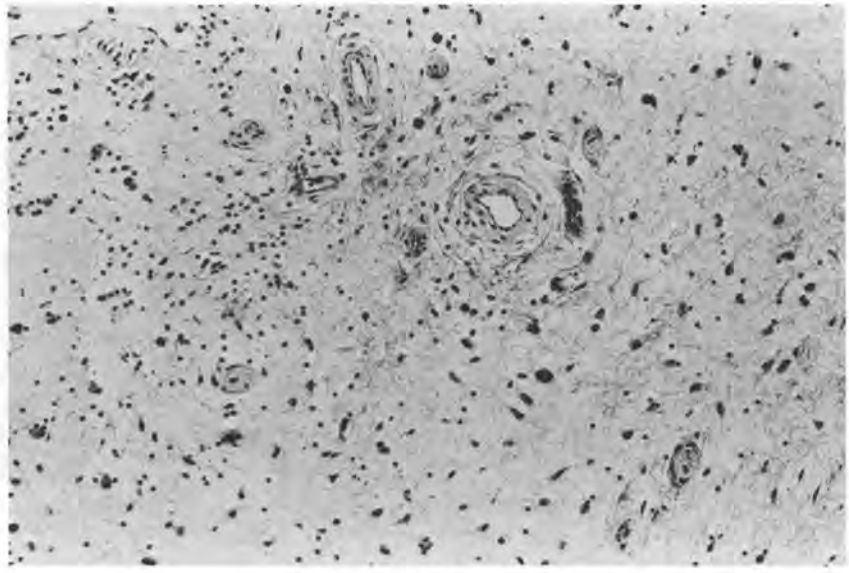

FIGURE 2-9 Vaginal polyp: loose fibrovascular stroma containing scattered cells with large hyperchromatic nuclei. There are no mitotic figures, rhabdomyoblasts, or "cambium layer."

terone, suggesting that they represent stromal cells with a myoid component.[99,100] Numerous capillaries are dispersed in the stroma and numerous mast cells and lymphocytes are present. An alarming degree of atypia may be present in the fibroblastic elements, particularly in association with pregnancy. The absence of a "cambium layer" and the age of the patient should preclude a false diagnosis of sarcoma botryoides, which occurs almost exclusively in infants.

These polyps may represent a localized hyperplasia of the subepithelial zone of the stroma as a result of a granulation tissue reaction after local injury of the mucosa. Physical irritation and hormonal imbalance have been suggested as etiologic factors.[101,102] A few cases with high cellularity, atypical nuclei, and a high mitotic count with abnormal mitotic figures may represent difficulties of interpretation and should be managed carefully.

Vaginal polyps must be differentiated from aggressive angiomyxoma, myxoid neurofibroma, and sarcoma botryoides. Table 2-1 summarizes some characteristics of these different lesions. Local resection is the treatment.

ENDOMETRIOSIS

Endometriosis is the consequence of implantation of endometrial mucosal debris during menstruation or a surgical procedure at the vaginal site. This rare localization appears as a submucosal solid or cystic nodule with a red or blue color. Endometriosis can be localized in the rectovaginal septum; subsequent malignant transformation may occur.[103] Histologic examination reveals characteristic endometrial glands and stroma with secondary hemorrhage or fibrosis.

TABLE 2-1.
Differential Diagnosis of Atypical Stromal Lesions of the Vagina

	Vaginal Polyp	*Aggressive Angiomyxoma*	*Sarcoma Botryoides*
Age	Adult	20–30 y	Under 5 y
Size	< 3 cm	Large, ill-defined	Polypoid mass, often large
Localization	Vagina, vulva	Vagina, vulva, pelvis	Anterior wall of vagina
Histology	Loose stroma with stellate and spindle-shaped cells	Hypocellular myxoid stroma with numerous vessels	Myxoid stroma and undifferentiated rhabdomyoblastic cells
Evolution	Benign	Local recurrence	Malignant

POSTOPERATIVE CONDITIONS

Tubal prolapse into the vaginal vault after vaginal hysterectomy has been reported.[104,105] Macroscopically, it is characterized by a granulomatous nodule appearing a few weeks to many years after the operation. Microscopically, the biopsy shows glandular, villous structures covered with a columnar epithelium suggesting a tubal origin (Fig. 2-10); the presence of smooth muscle confirms this impression. An inflammatory infiltrate is common. These glandular structures infiltrated by an inflammatory and granulomatous stroma should not be erroneously interpreted as adenocarcinoma. The presence of smooth muscle and of ciliated epithelium helps to make the distinction. Muscle and the inflammation differentiate tubal prolapse from a benign müllerian cyst.

Postoperative spindle cell nodule, a lesion simulating a sarcoma, has been reported occasionally in the genitourinary tract after surgery. Some cases have been described in the vagina. Macroscopically, it consists of polypoid, hemorrhagic nodules measuring several centimeters in diameter. Microscopically, it is represented by a highly vascularized proliferation rich in spindle cells that have been identified as myofibroblasts. Absence of severe cellular atypia and abnormal mitoses rules out the differential diagnosis of leiomyosarcoma.[106,107]

ADENOSIS

This condition is characterized by the presence of glandular structures in the vaginal mucosa or the lamina propria. The simultaneous involvement of the epithelium and the underlying stroma is present in most cases. Adenosis is caused by a failure of squamous epithelium to replace the original müllerian epithelium that covers the vaginal wall and the ectocervix during fetal life. Adenosis is observed in late fetal life and in infants, children, and adults.

The prevalence of adenosis differs in various published reports.[108,109] Sandberg noted the pres-

FIGURE 2-10 Prolapsed fallopian tube in vaginal vault: detail of tubal epithelium and inflammatory reaction.

ence of adenosis in 41% of 22 postpubertal vaginas examined by step sections at autopsy, although the lesion was not identified in any of 13 vaginas from prepubertal girls.[110]

More attention has been devoted to this lesion because it was observed with high frequency in young women whose mothers were treated with DES during at-risk pregnancy. The exact prevalence is not known, but Herbst and coworkers[111] have quoted a figure of 38% in routine clinical examination, whereas other authors using colposcopy have suggested that the incidence approaches 100%.[112] About one fifth of the women exposed in utero to DES demonstrate gross structural changes of the vagina and the cervix,[113] and one half exhibit microscopic changes in the vaginal mucosa, consisting of glandular structures and foci of squamous metaplasia.[114–116]

Macroscopic Appearance. The vaginal epithelial changes consist of flat or papillary, iodine-negative, red granular spots detected clinically, on the basis of iodine staining, or by colposcopy. As squamous epithelium replaces the glandular formations, the translucent appearance becomes white and opaque. More rarely, the lesion is confined to the lamina propria and is characterized by a submucosal nodule.

Microscopic Appearance. Glandular formations are lined by mucinous, endocervical-type columnar cells (Fig. 2-11) and more rarely by an endometrial or tubal-type epithelium.[117,118] Squamous metaplasia is frequent and represents the delayed (from fetal life) process of regression and healing of the glandular proliferation.[119–122] The glandular structures originate from the reserve cells of the müllerian epithelium. They progress to immature and mature squamous metaplasia, which finally replaces the columnar cells. Vestiges of the columnar cells are often represented by intracellular droplets of mucin.[118] Increased vascularity and inflammatory infiltrates around the glandular structures in the lamina propria are commonly present. Immunohistochemically, the columnar cells react positively for carcinoembryonic antigen, notably the cytoplasmic membrane of the luminal cell border. Retained glands may eventually be the origin of neoplastic changes (see the discussion below and in the section on adenocarcinoma).

Cytologic examination contributes to the diagnosis of adenosis under certain conditions: the lesion must be located on the vaginal wall; the mucosa should be involved; and the age of the patient should correspond to the period when adenosis is appearing.[123–127] Direct scraping of the macroscopic lesion avoids cervical contamination. The smears reveal the presence of columnar endocervical-type cells accompanied by squamous metaplastic cells in variable number. The columnar cells have eccentric, basally located nuclei with a finely dispersed chromatin. The cyanophilic cytoplasm may contain numerous small vacuoles or a large single one. Occasionally the glandular cells may be of endometrial or tubal type (Color Figure 2-9). Absence of cellular atypia may help to rule out a malignant lesion, but one has to know that well-differentiated adenocarcinoma may desquamate clumps of regular, small columnar cells with round normochromatic nuclei. One of our cases of clear cell adenocarcinoma revealed the presence of small, very regular columnar cells with dense, round nuclei without atypia.

Squamous metaplasia is represented by parabasal cells with a central, round, bland nucleus and dense cyanophilic cytoplasm with elongated cell extremities.

The cytologic follow-up of adenosis by direct scraping of the lesion shows a decrease or a loss of columnar cells with the presence of an increasing number of metaplastic cells. This reflects the regression of the lesion. False-negative results represent about 25% of the cases and are encountered when the conditions mentioned above are not fulfilled. Cytology is therefore not a screening tool for the diagnosis of adenosis and is not recommended as the sole

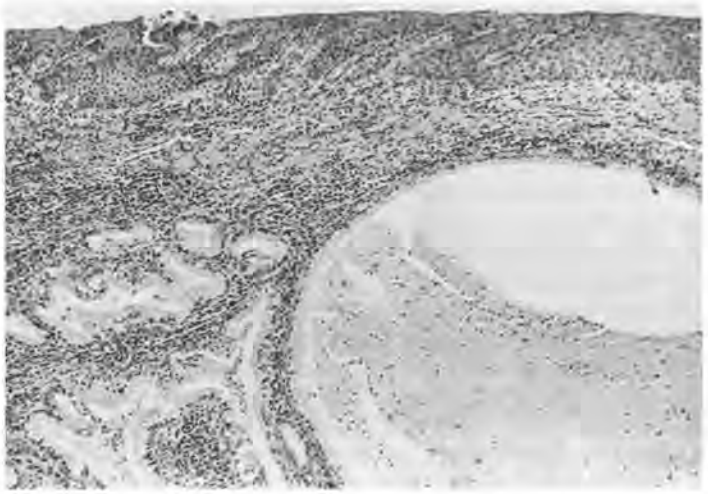

FIGURE 2-11 Vaginal adenosis: submucosal glands lined by endocervical-type epithelium.

tool in monitoring for the possible development of carcinoma.

The *etiology* of adenosis is poorly understood.[128,129] Forsberg has described a probable animal model.[130] Because neonatal estradiol and DES injections in mice induce similar lesions, he postulated an inhibition of mitotic activity in the vaginal columnar epithelium, thereby preventing its transformation to squamous epithelium. Prevention of this change by castration indicates that ovarian hormones are required, which correlates well with the reported absence of adenosis in prepubertal girls.[131] Herbst and associates, however, have reported adenosis in 6 of 73 prepubertal girls at autopsy.[132] More recent studies suggest an important inductive role of the cervicovaginal submucosal stroma. When adenosis is not associated with DES, it has been reported in conjunction with disorders of müllerian development, or after mucosal injury.[133]

The main clinical significance of vaginal adenosis lies in its association with vaginal clear cell carcinomas. A case of vaginal adenosis followed by clear cell adenocarcinoma has been reported after 5-fluorouracil treatment for condyloma.[134] The causal role of viruses or chemotherapy in the development of the lesion remains debatable.

DES and Cervical Intraepithelial Neoplasia

Considering that adenosis shows widened zones of squamous transformation, Stafl and colleagues predicted an increase in cervical intraepithelial neoplasia (CIN) among DES-exposed women.[114] Some further investigations confirmed this contention,[119,135] whereas others did not support it.[120,136] The epidemic of squamous carcinoma predicted by some has not appeared, although DES-exposed progeny are certainly no less likely than other sexually active young women to manifest papillomavirus and other cervicovaginal infections. Different factors can be mentioned to explain the discrepancies: subjectivity in interpretation and grading of dysplastic and metaplastic lesions, absence of evaluation of factors that contribute to the appearance of dysplasia (eg, age of onset of coitus and number of sexual partners and chronic inflammatory lesions), and more biopsy controls in patients who are self- or physician-referred than in patients screened by record review.[137,138] The DESAD project in 1984 provided further data supporting the finding of an increased incidence of CIN in DES-exposed patients.[135]

Squamous carcinomas may eventually prove to be more of a threat than adenocarcinomas, because adenosis heals by squamous metaplasia. Evidence of immune alterations have been demonstrated experimentally, and autoimmune conditions are increased in DES-exposed women, resulting in alterations of development of squamous cell lesions.[139,140]

Microglandular Hyperplasia in Adenosis

Microglandular hyperplasia is more frequently found in the cervix but may appear in the vagina in adenosis lesions. It is most commonly seen after long-term use of oral contraceptives or during pregnancy.[141] *Macroscopically,* there is an elevated, sometimes polypoid, soft, tan-yellow nodule arising on the mucosa. *Microscopically,* there is a proliferation of small mucinous glands with extensive foci of squamous metaplasia. The lesion should not be confused with adenocarcinoma (see Chap. 3 for differential diagnosis).

OTHER BENIGN LESIONS

Other soft tissue tumors such as *hemangioma,*[142] *rhabdomyoma,*[143] *neurofibroma*[144] and *paraganglioma*[145] are occasionally encountered in the vagina. Rhabdomyoma, which is a rare tumor occurring in adults, must be differentiated from embryonal rhabdomyosarcoma (sarcoma botryoides), which occurs in young children (see below). Benign primary vaginal *teratoma* has been reported.[146] Much more common are *squamous papilloma* and *condyloma acuminatum,* the pathologic features of which are described in Chapter 1, because these lesions more frequently occur in the vulva. Benign *nevus* and *blue nevus* are rarely reported.[147] Chen described a polypoid vaginal tumor suggesting the structure of a *Brenner tumor.*[148]

Rare benign *mixed tumors* of müllerian origin have been reported.[149,150] They exhibit epithelial and stromal proliferations reminiscent of ectopic müllerian tissue. A case with local recurrence 8 years after local excision is mentioned in the literature.[151]

MALIGNANT TUMORS

Primary Tumors

Malignant tumors of the vagina are rare. They represent about 1% to 2% of all gynecologic cancers.[152] They are most often squamous carcinomas, more rarely adenocarcinomas or sarcomas. It is important to eliminate the possibility of a squamous cervical carcinoma with vaginal extension before making the diagnosis of a primary vaginal tumor; this applies equally to intraepithelial carcinoma. Similarly, vaginal adenocarcinoma is more frequently metastatic (usually from endometrium) than primary.

Vaginal Intraepithelial Neoplasia

The prevalence of primary vaginal intraepithelial neoplasia (VaIN) is lower than that of similar cervical lesions (CIN).[153–155] A few hundred cases have been

reported in the literature.[156] Risk factors include a history of HPV infection (particularly types 16 and 18) and a low socioeconomic status.[157] Coexistence with the human immunodeficiency virus is being increasingly reported.[158] A large number of these lesions are multifocal and are associated with concomitant vulvar or cervical equivalent lesions. Multicentric primaries invoke a "field" concept of carcinogenesis in the lower genital tract. Therefore, it seems coherent to adopt the same classification as the one proposed earlier for cervical lesions and combine under one denomination the different dysplasias (mild, moderate, and severe) and carcinoma in situ (CIS). Now that the new Bethesda nomenclature is becoming widely recognized, it could be extended to the vaginal lesions, which can be divided into low-grade (VaIN I) and high-grade (VaIN II) lesions. Table 2-2 summarizes the different classifications. In practice, one of us (CG) uses the VaIN classification and the other (SGS) the dysplasia/CIS terminology. Whichever system is chosen, its implications should be understood clearly by all pathologists and clinicians in an institution.

Clinically, VaIN is usually asymptomatic and is discovered by routine cytology.[159–162] These lesions appear at a later age than cervical neoplasia, suggesting a different pathogenesis or a longer latency period. HPV DNA is frequently detected and, as in the cervix, high-grade lesions tend to be associated with type 16.[163,164] A case has been reported after immunosuppressive therapy.[165] Colposcopic examination may help to localize the lesion or lesions.

Macroscopic Appearance. When the lesion is single, it consists of a white or pink, slightly elevated, well-limited area. Almost half the lesions are multifocal and localized in the upper third of the organ.

Microscopic Appearance. The lesions are similar to those described in the cervix. According to the severity of the lesion, one observes loss of cell maturation, disorganized stratification of the epithelium with loss of nuclear polarity, hyperchromatic nuclei, increased mitotic activity with or without atypical mitoses, and abnormal keratinization. In mild dysplasia, superficial hyperkeratosis may be present. The notion of the existence of a microinvasive stage has been introduced,[166] and lesions that penetrate less than 2.5 mm from the vaginal mucosa may have the same chance of survival as noninvasive lesions. This evaluation may be difficult to realize on biopsy material, and the criteria therefore remain controversial.[167] Very few cases with adequate follow-up have been reported.

In *smears,* the cytologic changes can be compared with those observed in cervical scrapings.[168] Koilocytosis is observed in low-grade and, less frequently, in high-grade lesions. Vaginal origin of the atypical cells is suspected if clinical and colposcopic examination of the cervix reveal no lesion. Direct scraping of the vaginal mucosa orients the diagnosis (Color Figure 2-10). If the lesions are located in the lower part of the vagina, the cellular changes have more similarities with vulvar cytologic alterations (marked hyperkeratosis).

Evolution and Treatment. Most cases persist or regress, and some progress to invasive carcinoma. In a series of 23 untreated patients followed for at least 3 years, vaginal carcinoma occurred in 2 cases.[169] Spontaneous regression is more common in low-grade VaIN than in more advanced lesions. The treatment depends on the size, number, and location of the lesions and on the age of the patient. Local excision, cryosurgery, laser therapy, or more extended surgery are the common treatments.

Postirradiation VaIN. Postirradiation VaIN is observed after radiation therapy for invasive carcinoma of the vagina or the cervix. It should be differentiated from postirradiation lesions of benign squamous cells, which can persist in the atrophic mucosa many years after treatment. Postirradiation VaIN is characterized by hyperchromatic, often binucleated nuclei surrounded by a vacuolated cytoplasm. The nucleocytoplasmic ratio is increased, and the presence of very large and atypical cells suggests a postirradiation origin.[170,171] HPV infection facilitated by postirradiation immunodepression may represent an etiologic factor.[172] Postirradiation VaIN may precede a recurrence of invasive carcinoma. The existence of an aneuploid cellular DNA content is associated with a poor clinical prognosis.[173]

TABLE 2-2.
Classifications of Vaginal Intraepithelial Neoplasia (VaIN)

Mild dysplasia	Moderate dysplasia	Severe dysplasia	Carcinoma in situ
VaIN I	VaIN II	VaIN III	
Low-grade intraepithelial lesion	High-grade intraepithelial lesion		

Invasive Squamous Cell (Epidermoid) Carcinoma

Primary invasive squamous cell carcinoma of the vagina is rare and represents 2% of all gynecologic invasive cancers.[174–178] It occurs most frequently after the age of 45 (Fig. 2-12). It is a much less common lesion than squamous cell carcinoma of the cervix or vulva.[179] Before this diagnosis is accepted, an extension from one of the latter sites must be ruled out. In addition, multicentric synchronous or metachronous primaries are often present. This pattern is as true of in situ as of advanced invasive tumors.[180,181]

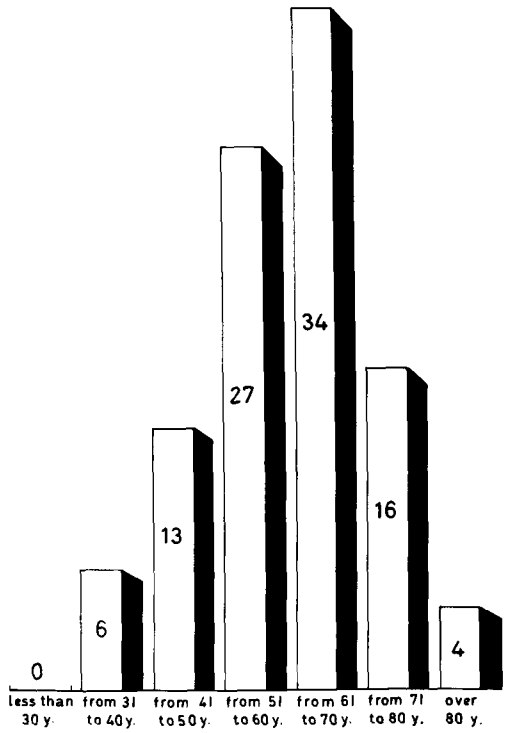

FIGURE 2-12 Incidence of vaginal squamous cell carcinoma (percentage) as a function of age. (Institute J. Bordet, 1925–1960 [118 cases])

Most vaginal cases occur in the upper third of the vagina, usually in the vault, and are more often posterior than anterior or lateral. When cervical cancer is present concurrently, the lesions are usually contiguous and the vaginal focus is then considered to represent secondary extension. In many instances, when only small biopsies are available, the question of second primary versus extension cannot be answered definitively; this is particularly true when the vaginal lesion is detected years after treatment of the cervical cancer. Colposcopy may be helpful in these cases.

HPV DNA, most frequently type 16, is present in a great number of lesions, suggesting, as in the cervix, the role of HPV in oncogenesis.[163,164,182] A case has been reported in a DES-exposed woman.[183]

Clinically, the lesion is asymptomatic or may manifest vaginal bleeding or discharge. A palpable mass may be the first manifestation of the tumor.

Macroscopic Appearance. Invasive squamous cell carcinoma presents as an infiltrative, ulcerated, exophytic, or papillomatous lesion measuring a few centimeters in diameter. The International Federation of Gynecologists and Obstetricians (FIGO) adopted in 1961 the following clinical staging system:

Stage I. Carcinoma limited to the vaginal wall
Stage II. Involvement of subvaginal tissues, without extension to the pelvic side walls
Stage III. Extension to one or both pelvic side walls or the pubic symphysis
Stage IV. Involvement of vesical or rectal mucosa or extension beyond the true pelvis

If a tumor involves the vagina and cervix, it is classified as primary in the cervix even if the bulk of the tumor is in the vagina.

Microscopic Appearance. The tumor is composed of neoplastic squamous cell cords originating in the vaginal epithelium. They invade the underlying submucosa and extend under the uninvolved epithelium. These cords are formed of undifferentiated basal-type cells or of differentiated keratinized cells forming cornified pearls (Fig. 2-13). Undifferentiated tumors exhibit atypical spindle cell features that may mimic mesenchymal tumors. The degree of histologic differentiation, based on the amount of keratinization and the number of squamous pearls, does not form a sound basis for estimating the prognosis, the clinical evaluation, or the efficacy of the treatment. Between the differentiated and undifferentiated types, all the intermediate appearances are encountered. The tumor is accompanied by a stromal chronic inflammatory infiltrate, and on occasion one may note the presence of carcinoma in situ at the periphery of the invasive lesion.

Prognosis, Evolution, and Treatment. Extension of the tumor is more often toward the cervix than toward the vulva. It extends even more often outward to the paravaginal and parametrial soft tissues. Direct extension to the rectum, bladder, and urethra takes place. Lymphatic metastases of tumors of the superior portion of the vagina lodge in the iliac, hypogastric, obturator, and sacral nodes; those from the inferior portion go to the pararectal, inguinal, and external iliac nodes.[8] The prognosis is based mainly on the clinical stage of the disease at the time of treatment. Long-term survival depends on early diagnosis, small size of the primary tumor, and absence of lymphatic involvement.[178] The 5-year survival rate is about 20% to 30%, with carcinomas of the upper third of the vagina having a somewhat better prognosis. Treatment may be by surgery, irradiation, or chemotherapy.[184]

Verrucous Carcinoma

Verrucous carcinoma is a distinctive entity that occurs infrequently in the vaginal mucosa (in less than 1% of vaginal carcinomas).[185,186] The same characteristics present in the vulva are encountered in the vagina: a slowly growing fungating mass with a benign histologic appearance and invasion on a broad front. There is frequent secondary ulceration. Microscopically, the lesion is characterized by a warty proliferation of large hyperkeratotic cellular nests extending into the underlying stroma in a pushing fashion (Fig. 2-14). Cellular atypia is very discrete, and the cellular polarity is preserved. It is important that the base of the lesion should be included in the

FIGURE 2-13 Squamous cell carcinoma of vagina: microscopic appearance.

biopsy to evaluate the rete pegs extending into the superficial stroma.

Verrucous carcinoma must be differentiated from condyloma acuminatum, pseudoepitheliomatous hyperplasia, and well-differentiated squamous carcinoma. The invasion on a broad front is most important, because invasion is absent in condyloma and infiltrative (with greater atypia as well) in squamous cell carcinoma.

Direct scraping of the lesion shows minimal cellular atypia; hyperkeratotic cells with minimal nuclear changes are abundant. This method is unreliable for diagnosis of this tumor.

Verrucous carcinoma should be properly recognized because it is locally aggressive but rarely metastasizes. Adequate local excision is the treatment of choice. Radiation therapy may result in recurrence of a more aggressive and less differentiated tumor.

Adenocarcinoma

Primary vaginal adenocarcinoma has been recognized since early in this century, predominantly in postmenopausal women and unrelated to exogenous hormonal influence.[132,187–189] It is a rare tumor and is now usually related to adenosis (see above) or orig-

FIGURE 2-14 Verrucous carcinoma. The deep border of this bulky lesion shows the classical pattern of invasion on a broad front. See Figure 1-32 for the exophytic surface of another verrucous carcinoma.

inates from mesonephric duct or Gartner's duct rests.[190,191] A remarkable rise in incidence was first documented by Herbst and associates[192,193] and is attributed to the widespread use from the late 1940s to the 1970s of DES during early pregnancy in cases of habitual or threatened abortion. DES, the nonsteroidal estrogen diethylstilbestrol, was first synthesized in 1938 by the British biochemist Charles Dodds. An estimated 3 to 7 million women had taken the drug by 1971, when the very rare development of clear cell adenocarcinoma of the vagina and the cervix in young female offspring was linked to in utero exposure to the drug.[193–195] More than 500 cases have been recorded, and it is probable that this number is underestimated.[196]

Most recent patients with vaginal adenocarcinoma have been products of DES-treated pregnancies, so that these cases have occurred in young women between the ages of 7 and 33 years, with most cases appearing between the ages of 17 and 21.[196–198]

The risk is higher if the administration of DES was started before 12 weeks of pregnancy. About 60% of the cases originate in the vagina, and the others involve the vagina and cervix or the cervix alone. Most vaginal tumors arise from foci of adenosis on the upper third of the vaginal wall. Adenosis with atypia is often seen adjacent to the tumor and may represent an intermediate lesion (see below). Although we accept that a link between in utero DES exposure and adenocarcinoma is established, it is important to mention that the published series of cases are gathered from retrospective case-control and tumor registry reports that may introduce selection bias affecting the published results. About 25% of the cases have no history of maternal medication,[198,199] and a prospective study revealed no case of invasive genitourinary cancer in the group exposed to DES.[200] These data suggest that DES is not a complete carcinogen and that other factors, some associated with the onset of puberty, may be involved in the development of the tumor.[201]

Macroscopic Appearance. The tumor is usually superficial, often polypoid, and presents in most cases on the anterior wall of the upper vagina (Color Figure 2-11). Some cases may appear as firm nodules more deeply located in the vaginal wall. Ulceration may occur. Lymph node metastases may be present even when the primary tumor is of limited extent.

Microscopic Appearance. The tumor is an adenocarcinoma that grows in one of three patterns: *tubulocystic, papillary,* or *solid* (Fig. 2-15).

The *tubulocystic* pattern is seen more often in patients older than 15 years and is associated with a better 5-year survival rate. *Papillary, solid,* and *combined* patterns are more often seen in the group of patients younger than 15 years. At high-power magnification, the tumor is seen to be composed of variable proportions of clear and hobnail cells, the former characterized by voluminous clear cytoplasm filled with glycogen and the latter by single-cell apical projections into the central lumina of the epithelial structures.[202,203] Mitoses usually are not abundant. The tumor is histologically, histochemically, and ultrastructurally identical to other clear cell carcinomas of the female genital tract, notably those of the ovary and endometrium.[204–206] Cytoplasmic mucin stains are negative, but mucin is often present at apical cell borders and in lumina. Expression of carcinoembryonic antigen is inconstant. Spectrophotometric DNA analysis of one case has shown an aneuploid chromosomal pattern.[207] Adenocarcinoma in situ is exceedingly rare and may represent an extension of a cervical lesion.[208]

Etiology. The origin of the tumor appears to be müllerian, although tumors of this type were formerly thought to be of mesonephric nature. The

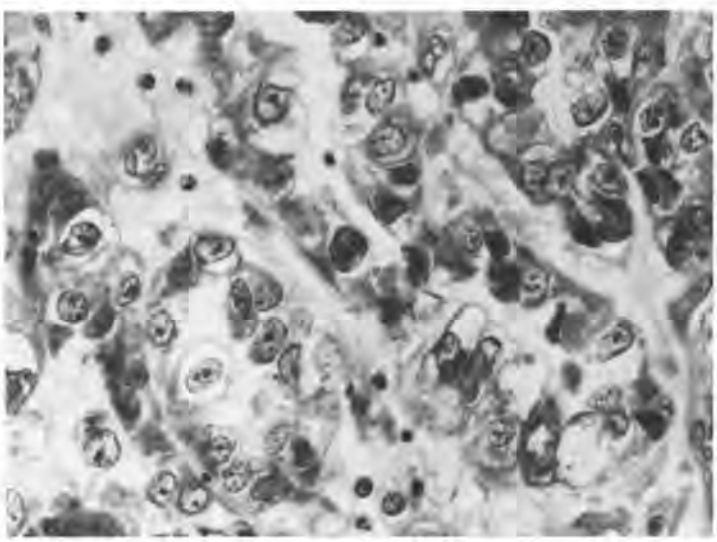

FIGURE 2-15 Clear cell adenocarcinoma of vagina in 17-year-old girl. Tubules are lined by clear and hobnail cells.

müllerian origin is supported by electron microscopic studies.[204–206] The etiology of the cases without any hormonal exposure remains unsettled; the presence of adenosis has been described and may be the origin of the tumor.[110] The precise method by which DES influences the fetal lower genital epithelium is not known, but ultrastructural studies suggest that DES acts on the stroma of the vaginal wall, affecting secondarily the epithelial cells.[209] Most adenocarcinomas arise from foci of adenosis,[203,210] and different morphologic arguments tend to implicate the endometrial-tubal type cell and not the endocervical-type cell as the precursor of the malignant elements. Morphologic similitudes exist between clear cell adenocarcinoma and endometrial carcinoma, and foci of adenosis adjacent to the tumor are composed of endometrial-tubal cells.[211,212] Occasional examples of transitional microscopic images (*atypical adenosis*)[213] have been encountered (Fig. 2-16), some of which have eventuated in carcinoma of clear cell or endometrioid type. The columnar cells of atypical adenosis have hyperchromatic nuclei, large nucleoli, and irregular cytoplasm. An aneuploid chromosomal pattern, a common finding in adenocarcinoma, has been demonstrated by spectrophotometric DNA analysis.[214]

Diagnostic procedures include frequent and thorough clinical examination of DES-exposed patients with cytologic sampling (Color Figure 2-12) and colposcopy with iodine staining. The smears of clear cell adenocarcinoma show isolated elements or aggregates of regular columnar cells with hyperchromatic nuclei and macronucleoli.[215] Very atypical cells may be observed in the solid type of tumor and may be wrongly interpreted as squamous or sarcomatous. The vaginal origin of the cells must be established to suggest the diagnosis. Cytology detects only a fraction of the cases; the Netherlands Registry notes that only 33% of the vaginal tumors were identified in smears.[216] Absence of routine vaginal sampling, squamous metaplasia covering the tumor, or localization of the lesion under the mucosal surface are tentative explanations of this poor result.[216] Biopsy remains the mandatory procedure in any suspicious area.

The *prognosis* of clear cell carcinoma is relatively favorable, with a 5-year survival rate among cases with adequate follow-up data in the range of 75% to 80%, and about 90% among stage I cases.[197] Poor prognostic factors, in addition to extravaginal extension, include high mitotic activity and lymphatic invasion at the primary site. When recurrence takes place, it tends to be pelvic or intrathoracic, or both. Most cases have been treated surgically, but radiation therapy has also been proved effective.[205]

The *differential diagnosis* comprises other adenocarcinomas of the vagina, the most common of which are metastatic (see below). Carcinomas other than clear cell type, including *endometrioid, intestinal,* and *small cell* types, have been reported as arising on a background of vaginal adenosis.[189,217,218] Adenosis undergoing *microglandular hyperplasia* (see Chap. 3) in women who are pregnant or taking exogenous hormones should not be confused with adenocarcinoma. Rare cases of adenocarcinomas arising in endometriosis of the rectovaginal septum have been reported.[219,220] Another rare lesion is the *endodermal sinus tumor* (yolk sac carcinoma, carcinoma of infant vagina).[221–224] Originally also thought to be a "mesonephroma," this highly malignant tumor of infancy is currently considered to be a germ cell tumor, identical to its more frequent counterparts in ovary and testis. Characteristic histologic features include tubules growing in a loose reticular stroma, papillae with vascular cores projecting into tubules (the so-called glomeruloid bodies of Schiller or endodermal sinuses of Duval), prominent clear cell foci, and intra- and extracellular hyaline globules that are

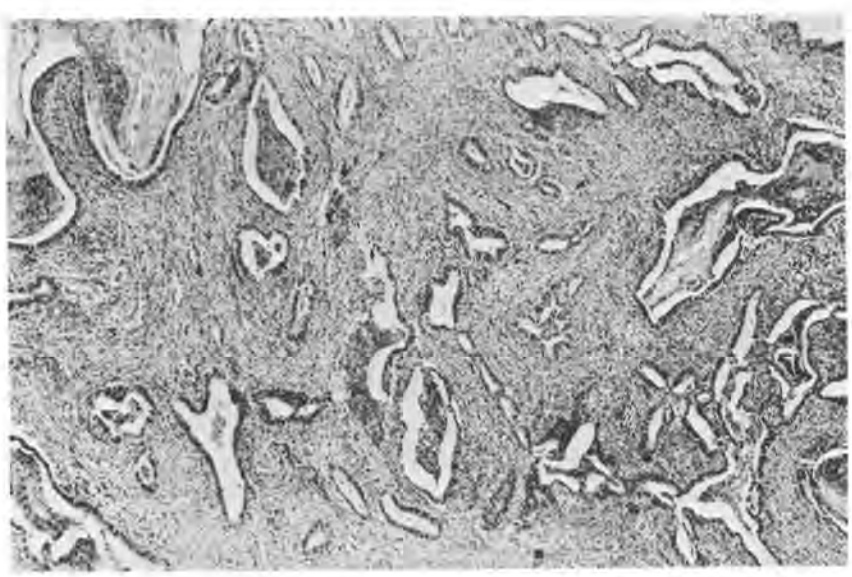

FIGURE 2-16 Atypical adenosis: endometrial-type glands proliferating in anarchic appearance reminiscent of adenomatous hyperplasia of endometrium. This patient (a young woman exposed in utero to diethylstilbestrol) subsequently developed adenocarcinoma at the vaginal site from which this biopsy was obtained.

positive for periodic acid-Schiff (PAS) stain and contain α-fetoprotein (Fig. 2-17). Finally, a prolapsed fallopian tube after hysterectomy (see above) may also enter the differential diagnosis.

Sarcoma

Sarcomas of the vagina are extremely rare and merit only brief commentary. *Leiomyosarcomas*[225–228] are the most common in adults, but variably documented cases of fibrosarcoma,[228] angiosarcoma,[229,230] alveolar soft part sarcoma,[231] synovial sarcoma-like tumor,[232] and various endometrioid sarcomas (Fig. 2-18) also have been reported. They are usually submucosal in origin and ulcerate only as a late event. In children and more rarely in adults, there exists a particular type of sarcoma that merits a more complete description: the *sarcoma botryoides.*

Sarcoma Botryoides (Embryonal Rhabdomyosarcoma). Sarcoma botryoides presents as a pale red, edematous, polypoid "bunch of grapes" appended to the vaginal wall.[233–236] Two theories have been proposed to explain its nature. It may rise from embryonic rests composed of the mesenchyme surrounding the müllerian ducts, which has retained the ability to differentiate into varied mesodermal tissues, or from tumor cells that secondarily take on an embryonal character. The first hypothesis enjoys the most support. Ninety percent of cases are seen in children under 5 years of age.

Macroscopic Appearance. The tumor exhibits the form of a polypoid mass that owes its red or white color to its richness in myxomatous tissue. It is friable, hemorrhagic, and soft. Cut sections reveal a pale yellow-white, uniform tissue. When it is voluminous, it may be present at the vaginal orifice in the form of nodular clusters of variable size. Some tumors remain localized under the mucosa, eventually herniating into the vaginal cavity and ulcerating.

Microscopic Appearance. The great majority of tumors grow as pure embryonal rhabdomyosarcoma (Fig. 2-19). Beneath the mucosa is a condensed "cambium layer" of small round cells with brightly eosinophilic cytoplasm, in which cross-striations can occasionally be demonstrated; the deeper tissues are edematous and contain fewer tumor cells.

Other histologic patterns may be present: large cells with central nuclei and a clear, abundant cytoplasm containing PAS-positive diastase-soluble material, or small cells with dense nuclei and an elongated eosinophilic cytoplasm. The loosely arranged cells are dispersed in an edematous stroma. Mitoses are numerous. Immunohistochemically, most cases express myoglobin[237] and desmin.[238]

The *clinical prognosis* is poor, with 5-year survival approximating 15%. The evolution is one of local recurrences and extension to adjacent organs, as well as metastases to lymph nodes and lungs. A better prognosis can be expected if the tumor is strictly localized.[235]

Differential diagnosis must be made with the *fibroepithelial polyp*,[95–100] which exhibits the same myxoid stroma but does not have a dense cellular subepithelial layer and reveals no muscular differentiation. This lesion occurs almost exclusively in adults, as does the *fetal rhabdomyoma*,[143,239,240] a rare benign tumor with a myxoid stroma containing strap cells with cross-striations but no cambium layer and no mitotic figures.

Other Malignant Tumors

About 150 cases of primary vaginal *malignant melanoma* have been reported, most often in elderly women.[241–245] They account for less than 3% of all

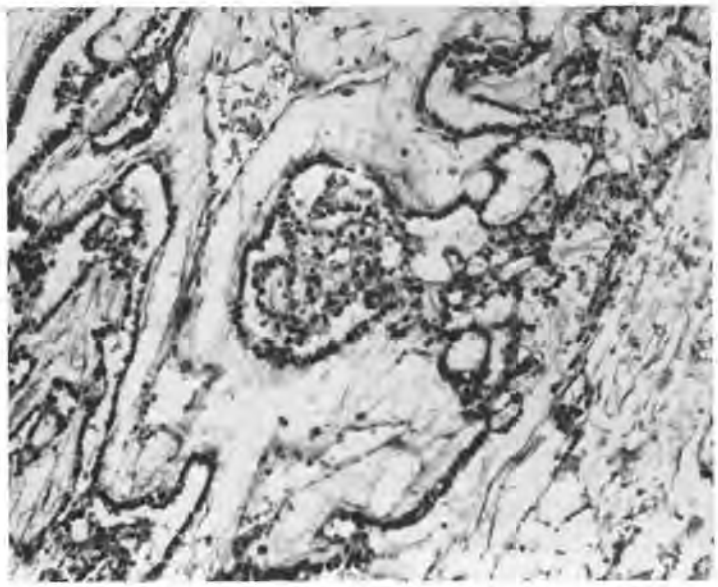

FIGURE 2-17 Endodermal sinus tumor of infant vagina. A Schiller–Duval body is present in the center.

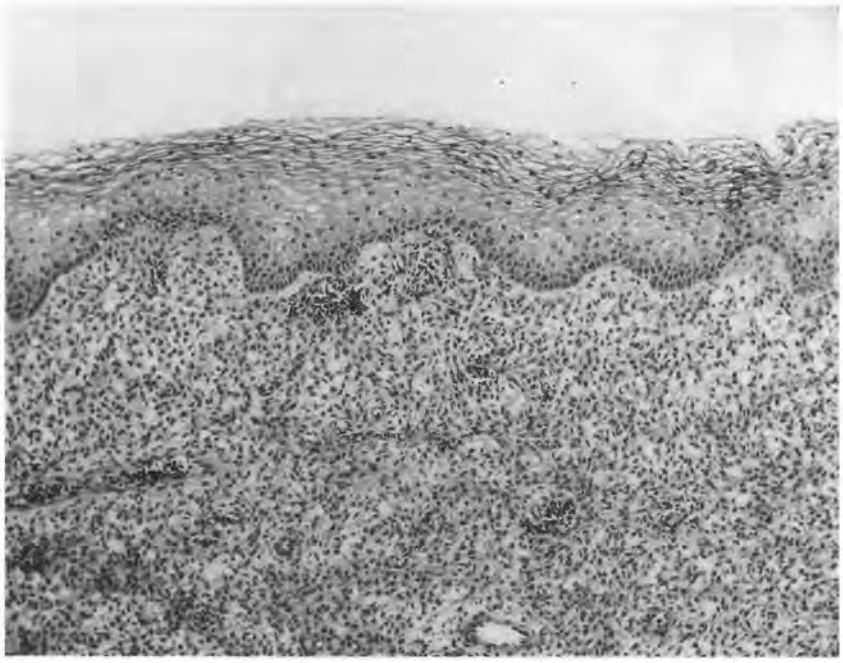

FIGURE 2-18 Low-grade endometrioid stromal sarcoma. The tumor is covered by unremarkable vaginal mucosa.

malignant tumors of the vagina. They appear as blue or black, frequently ulcerated nodules. Histologically, they resemble melanomas in other sites. The depth of invasion (Clark level)[243] and the thickness of the tumor (Breslow method)[246] should be measured, because they represent valuable prognostic factors. The prognosis is poor.

Neuroepithelial small cell carcinoma has been rarely reported in the vagina.[247,248] It is characterized by dense cords of small cells with hyperchromatic nuclei and cytoplasmic argyrophilic granules. The granules are well demonstrated by electron microscopy or immunohistochemistry (chromogranin, neuron-specific enolase). These tumors should be recognized because they have an aggressive nature with rapid recurrences and distant metastases. A case associated with adenosis has been reported.[217]

Among the rarer tumors are *plasmacytoma,*[249,250] *malignant lymphoma,*[251] *basal cell carcinoma,*[252] and *malignant mixed tumor.*[150,253] Seven cases of primary *carcinosarcoma* (malignant mixed mesodermal tumor) have been reported.[228]

Metastatic Tumors

Vaginal metastases are more frequent than primary tumors in this site. They are occasionally the first clinical manifestations of an occult neoplasm elsewhere. They arise most frequently from carcinomas of the vulva, cervix,[180,181] endometrium[254] (Fig. 2-20), or ovary.[255] They are usually found on the posterior vaginal wall. Also encountered are metastases from tumors of the kidney,[256] breast,[257] pancre-

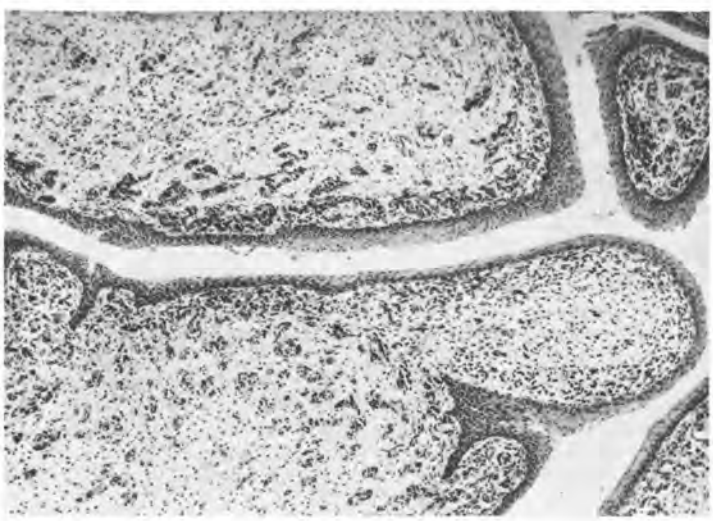

FIGURE 2-19 Sarcoma botryoides: polyps with submucosal "cambium layer" of tumor cells.

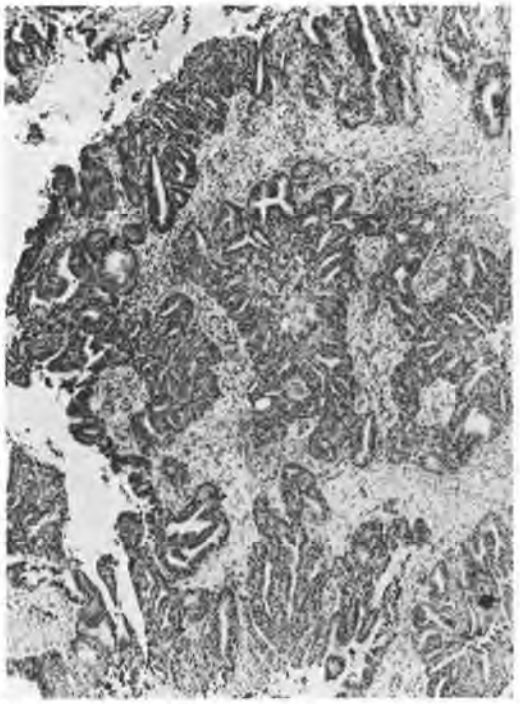

FIGURE 2-20 Metastatic adenocarcinoma of the endometrium in the vagina.

as,[258] and colon and rectum.[259] Metastases of renal clear cell carcinoma may be confused with primary vaginal clear cell carcinoma; the clinical history, tumor location, and ultrastructure are all useful distinguishing features. The metastasis may clinically precede the manifestation of the primary renal lesion.[256,260] Choriocarcinoma not frequently gives rise to blue, very hemorrhagic nodules, the growth of which may be extremely rapid. Uterine sarcomas, like endometrial carcinomas, have a high propensity for vaginal metastases. The prognosis is very poor in these disseminated lesions.

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3 The Cervix

The frequent morphologic alterations of inflammatory, hormonal, or tumorous origin in the uterine cervix constitute a vast field of clinicopathologic investigation that has been greatly exploited since the beginning of this century. These studies are of value to us notably with respect to the early diagnosis of cancer, knowledge of the extremely varied pictures of cervical infections, and discovery of new histologic and clinical concepts such as the entities of dysplasia and in situ carcinoma. The study of the uterine cervix has been of general interest and has led, for example, to the investigation of intraepithelial cancers of other organs, such as the bronchus, the larynx, and the stomach. The role of viruses in the early stages of carcinogenesis of solid tumors has been studied in greatest detail in the cervix. These few remarks serve to illuminate the important position of the cervix in pathologic anatomy.

EMBRYOLOGY

The uterine cervix is of mesodermal origin. It arises from the fusion of the middle portions of the müllerian ducts; the adjacent mesenchyme gives rise to the connective tissue stroma and muscle fibers. The stratified squamous epithelium of the ectocervix originates from the epithelium of the primitive uterine canal derived from the urogenital sinus.[1] The glandular epithelium becomes mucus-producing by metaplasia from the primitive cuboidal epithelium derived from the müllerian ducts. During the late fetal and neonatal period, the junction between the two epithelia is located on the ectocervix; this ectropion may be the result of maternal hormonal stimulation.[2] The cervical stroma is invaded by straight glands issuing from the surface epithelium; these glands ramify secondarily.

ANATOMY

The cervix has a more or less cylindrical shape and forms the inferior third of the uterus. Its lowest part, known as the *portio vaginalis*, projects into the vagina. The external os represents the junction between the portio and the endocervical canal, which itself communicates with the endometrial cavity at the internal os.[3] The average length of the cervix is about 3 cm, its diameter at the base is 3 cm, and its inferior diameter is from 2.5 to 3 cm. It represents a fibromuscular structure covered by a mucosa. The internal surface is covered by rugae directed obliquely toward the upper portion, originating from an anterior and a posterior longitudinal fold. The vascularization issues from branches of the uterovaginal artery and the vaginal artery (a branch of the hypogastric artery).[4] The cervix is innervated by the uterine plexus and contains sensory fibers.[5] The lymphatics from the superficial and deep stroma collect into different channels, which run to the iliac, hypogastric, obturator, and sacral nodes.

HISTOLOGY

The cervix comprises two distinct parts. The *ectocervix* is covered by a stratified squamous epithelium that overlies a dense fibrous stroma.[6–9] The *endocervix* is covered by an unistratified columnar mucosa resting on a stroma rich in mucus-secreting glands. Fluhmann[10] has demonstrated that these glands are actually clefts issuing from the surface mucosa.

The *squamous ectocervical epithelium* is composed of basal, intermediate, and superficial cell layers identical to those of the vaginal mucosa. Five layers are recognizable (Fig. 3-1).

The *basal layer (C1)* is in contact with the basement membrane; this is the reserve cell layer. The cells are oriented perpendicular to the basal lamina and normally exhibit mitotic figures because they constitute the reproductive cells of the epithelium. The enzymes phosphorylase and amylo-1,6-glucosidase, required for glycogen synthesis, are localized in these cells.

Layer C2 consists of two or three rows of parabasal cells; this is the most rapidly proliferative layer. *Layer C3* is characterized by the presence of glycogen[11] (manifested by clear cytoplasm) and the development of intercellular bridges (desmosomes). *Layer C4* is rich in glycogen, and the intercellular bridges begin to disappear; it does not contain eleidin granules like its cutaneous equivalent.

The *superficial layer (C5)* contains large cells with pyknotic nuclei. Eosinophilia of the cytoplasm is related to the presence of keratin microfilaments.[12] Immunohistochemistry reveals the existence of 19 different cytokeratins.[13,14]

The *endocervical muciparous columnar epithelium* is composed of tall cells with elongated basal nuclei and occasional ciliated cells (Figs. 3-2 and 3-3 and Color Fig. 3-1). This mucosa penetrates into the stroma, where it gives rise to glands lined by columnar cells with abundant clear cytoplasm and basal nuclei.[15]

The cervical stroma is dense and comprises fascicles of fusiform connective tissue cells, collagenous and elastic fibers, and scattered smooth muscle fibers. The latter are more numerous in the superior part of the cervix, where they constitute about 15% of the stromal elements. A narrow subepithelial myxoid zone may be present. The stroma does not undergo cyclic histologic modifications such as those of the endometrial stroma.

The junction of the two epithelia occurs normally at the level of the external os by direct contact or more frequently by a transformation zone of metaplastic squamous epithelium (squamocolumnar junction or transformation zone).[16]

The schema adapted from Ober[17] indicates the different modes of junction encountered (Fig. 3-4). During the period of genital activity, the endocervical mucosa tends to extend toward the external cervical orifice (ectopy or ectropion). Before puberty and after ovarian activity ceases, the glandular epithelium is pushed back into the endocervical canal by the squamous ectocervical epithelium (entropion,

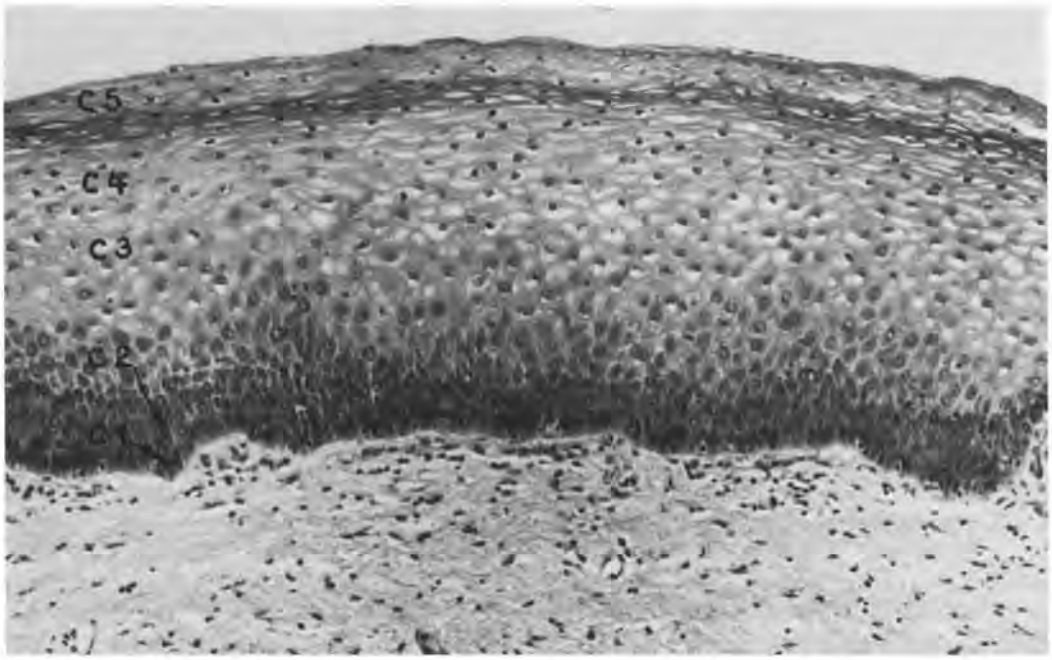


FIGURE 3-1 Normal squamous mucosa of ectocervix: C1, deep layer in contact with basement membrane; C2, parabasal layer constituted by two or three rows of cells; C3, intermediate layer rich in glycogen; C4, layer rich in glycogen and showing beginning disappearance of intercellular bridges; and C5, superficial layer with pyknotic nuclei.

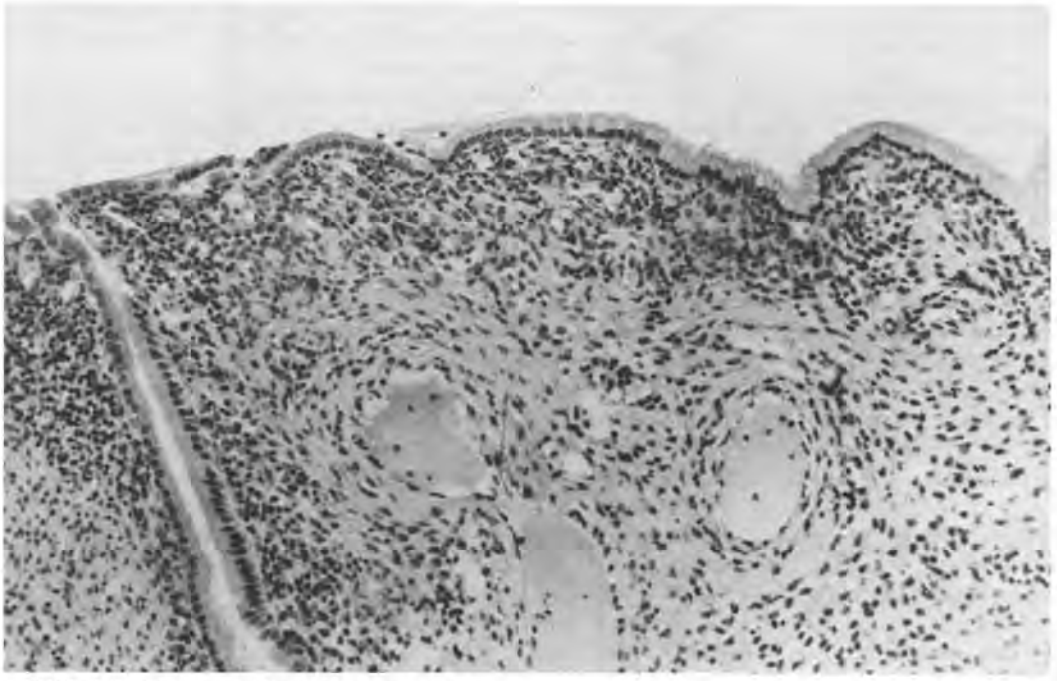


FIGURE 3-2 Endocervical columnar mucosa.

Fig. 3-5).[18,19] The clinical significance is that in postmenopausal women, intraepithelial and invasive squamous carcinomas are seen in the endocervical canal.

The squamous mucosa presents the same hormonal modifications as the vaginal mucosa and undergoes cyclic keratinization in relation to estrogenic activity. It contains glycogen, particularly in the intermediate cell layers (navicular cells). The maturation cycle of the squamous cell takes about 4 days.

With regard to the endocervical glandular mucosa, cyclic modifications are discrete. Wollner[20] has described in the estrogenic phase of the cycle an augmentation of cellular proliferation and of the number of papillary projections of the mucosa. It must be admitted that the endocervical mucosa, although of müllerian origin like the vaginal and endometrial mucosae, reacts only discretely to genital hormonal stimulation. On the contrary, the secretion of glandular cells constitutes the cervical mucous gel and exhibits cyclic variations. The secretion is abundant and alkaline, and it facilitates the penetration of spermatozoa during the estrogenic phase; it is scant, acid, and thick after ovulation, thus hindering sperm migration. Biochemical and electron microscopic studies have revealed the complex structure of the mucous gel.[8] It is composed of a micellar network of glycoproteins in which the intermicellar spaces are occupied by cervical plasma. Crystallization of the mucus is favored by the presence of potassium and sodium chloride ions. The parallel orientation of the glycoprotein micelles during the estrogenic phase favors sperm migration. This orientation disappears during the progestational phase.

Electron microscopy shows that the endocervical cell cytoplasm contains numerous clear vacuoles related to mucous secretion, as well as filamentous structures of still unknown function (see Fig. 3-3).

The squamocolumnar junction or transformation zone shows the presence of Langerhans cells dispersed among the squamous cells.[21–23] These cells have a vesicular nucleus surrounded by a clear cytoplasm. Their presence can be demonstrated immunohistochemically by the use of monoclonal antibodies to S-100 protein. Langerhans cells are of bone marrow origin and are involved in local immune mechanisms.[24] They form part of the system of mucosal-associated lymphoid tissue similar to that found in other mucosae exposed to the external environment. Their activity is influenced by clinical circumstances such as the presence of human papillomavirus or the existence of cervical intraepithelial neoplasia.[25]

Atypical Ectodermal and Mesodermal Structures

On rare occasions, ectodermal and mesodermal structures have been described in the cervix. Ectodermal structures include hair follicles, sweat glands, and sebaceous glands. Two explanations are proposed: (1) under appropriate stimuli, adult mesodermal tissue is able to form epidermis and epidermal appendages, or (2) misplaced ectodermal embryonal precursors after an abnormal cephalic

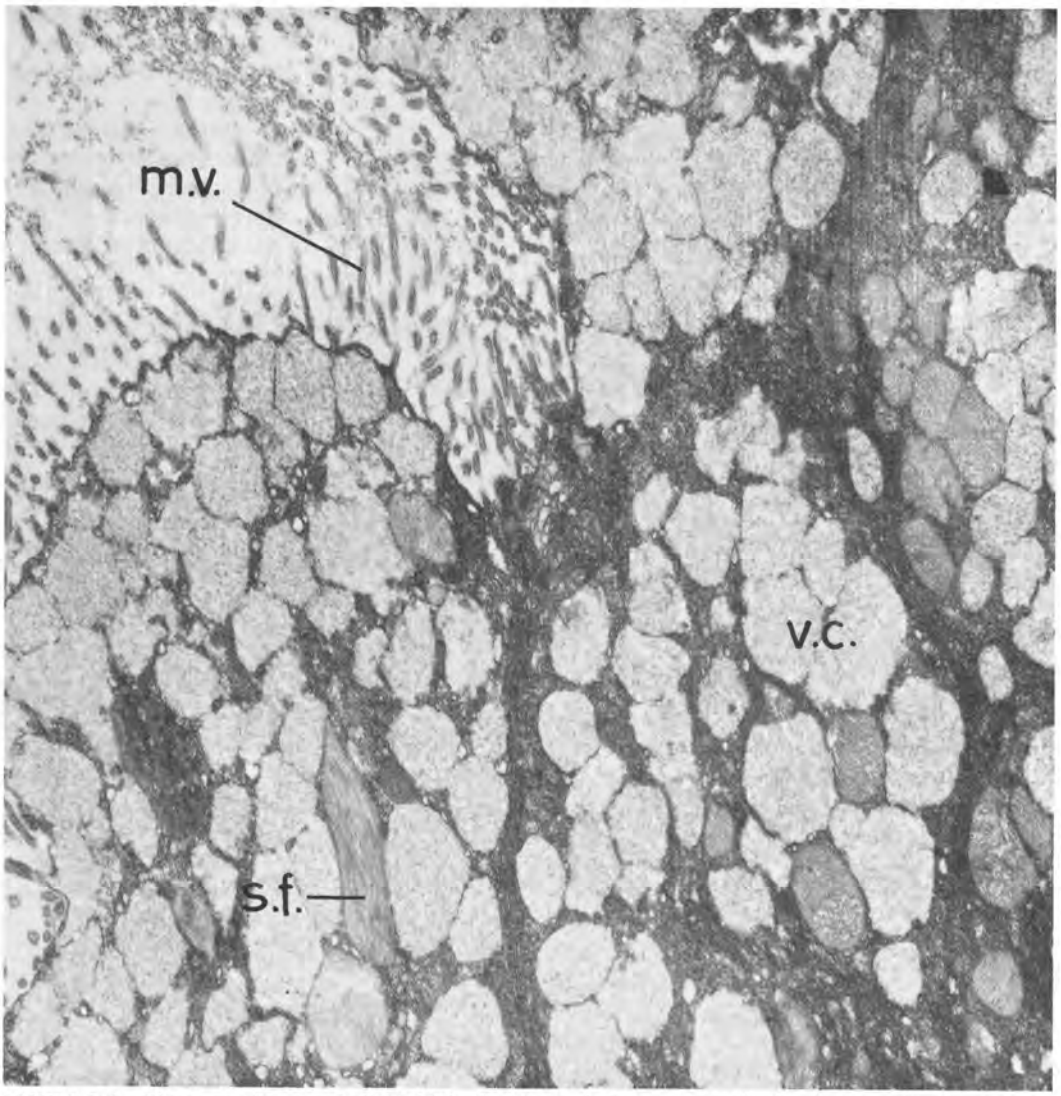


FIGURE 3-3 Electron micrograph (×22,050) of endocervical mucosal cells showing cytoplasmic clear vacuoles of mucin secretion (*v.c.*) and filamentous structures (*s.f.*), with microvilli bordering the apical poles of the cells (*m.v.*).

migration remain in the cervical region. The former theory seems more probable and may represent a metaplastic phenomenon.[26] Atypical localization of mesodermal tissue such as cartilage has been reported in the cervix.[27] This has no clinical significance.

Mesonephric Remnants

Mesonephric remnants representing the distal end of the mesonephric ducts are present in about 1% of cervices.[28] They consist of small tubules or cysts lined by a cuboidal or flattened nonciliated epithe-

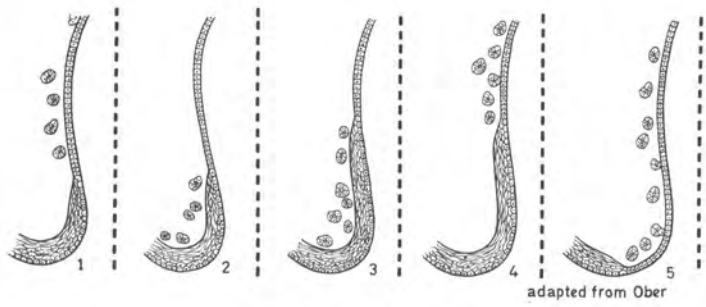


FIGURE 3-4 Schematic drawing of the different modes of junction between the squamous and columnar epithelia of the cervix. (Adapted from Ober KG: Les variations morphologiques du col durant la vie de la femme. Bull Soc Belge Gynécol Obstét 28:203–213, 1958).

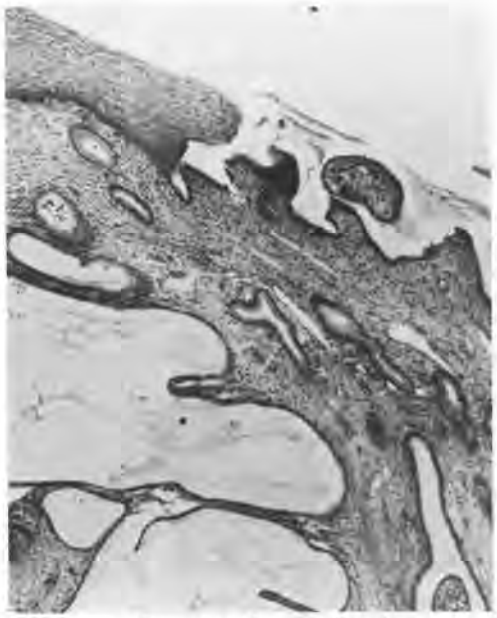


FIGURE 3-5 Zone of squamocolumnar junction and nabothian cysts.

lium and are located in the lateral cervical walls.[28–30] The absence of mucin or glycogen is characteristic of the mesonephric epithelium. Rare cases of adenocarcinoma arising in the lateral wall and consisting of nonmucinous structures have been considered to be related to a mesonephric origin.[28,31]

Histologic Appearance During Pregnancy

The histologic appearance of the cervix is modified during pregnancy.[32,33] The squamous epithelium shows an increase in thickness and hyperactivity of the basal cells manifested by the appearance of supplementary basal cell layers. This hyperplasia only partially involves the epithelium, leaving intact rows of differentiated cells at the surface. When dyspolarity, cellular atypia, and full-thickness epithelial immaturity are seen, these changes should not be attributed to pregnancy but rather to a dysplastic or neoplastic condition.

The endocervical glands also manifest hyperplastic phenomena, accompanied sometimes by squamous metaplasia (Fig. 3-6*A*). According to Fluhmann,[10] these glands, which actually represent infoldings of endocervical mucosa, will present new and more pronounced invaginations in the course of pregnancy (tunnel clusters). Secretory activity of the cells is augmented, and the apical pole, filled with mucin, presents a bulging appearance. This important proliferation of endocervical mucin-secreting cells results in eversion of the endocervical mucosa into the exocervix, pushing the squamous epithelium away from the external os. This ectropion is a common feature in the primigravida, with eventual secondary erosion of the fragile epithelium. Healing by replacement with squamous epithelium is the rule after pregnancy. Positive immunoreactivity with S-100 protein has been found in cervical glands during pregnancy.[34]

More marked *microglandular* endocervical hyperplasia (see below) may also occur. It is also observed in patients using oral contraceptives[35] and rarely after menopause.[36] Correlation with a high level of progesterone activity is postulated.

Decidual Change

In pregnancy, there may be a decidual transformation of the cervical stroma (Fig. 3-6*B*).[37,38] With the extended use of colposcopy, it is more frequently seen both in the endocervix and the ectocervix.[39,40] *Macroscopically*, one observes a small structure that is raised, nodular, and highly vascularized. *Microscopically*, the decidual cells are large, with round nuclei containing conspicuous nucleoli, surrounded by abundant glycogen-rich cytoplasm. If degenerative changes occur, these cells may be irregular with hyperchromatic nuclei. They should not be mistaken for neoplastic cells. Very marked decidual reaction may present as a submucosal tumor or an endocervical polyp composed largely of decidual cells. Regression is observed after the pregnancy.

Arias-Stella Reaction

Gestational Arias-Stella reaction may be observed in endocervical glands (Fig. 3-7).[41] These cellular atypias should not be confused with adenocarcinoma.

MALFORMATIONS

Congenital malformations of the cervix generally accompany those of the corpus uteri. In this form, bicervical uterus, coupled and partitioned cervices, and cervical hypoplasia and aplasia may be encountered.[42] Cervical hoods and "cockscomb" malformations are seen in young women who were exposed in utero to diethylstilbestrol (DES), and they may be associated with infertility or habitual abortion.[43]

INFLAMMATORY DISEASES

Acute Cervicitis

Inflammatory diseases are discussed at length in Chapter 2. The same causal agents may involve the cervix and cause acute and chronic lesions. The infection may be the result of direct invasion of the cervix, spread of an infection from other parts of the genital tract and adjoining organs, or blood-borne contamination. Routine bacteriologic studies often

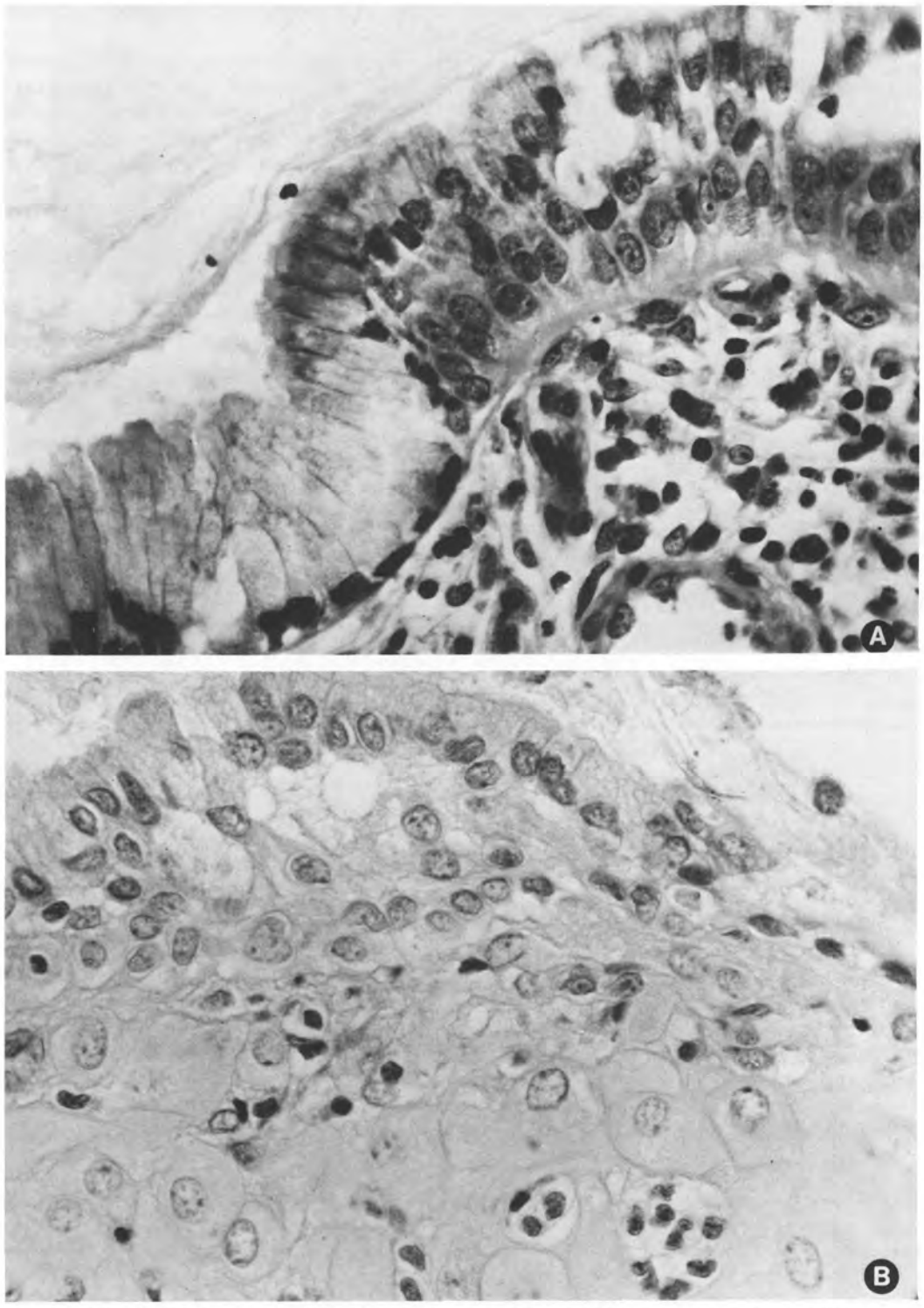


FIGURE 3-6 Photomicrograph of cervix uteri during pregnancy. **(A)** Hyperplasia of glandular epithelium. **(B)** Decidual reaction of stroma.

demonstrate the presence of pathogenic organisms not accompanied by clinical symptoms.

Acute cervicitis may result from primary infection by different organisms such as bacteria, fungi, parasites, or viruses. Table 3-1 indicates the various agents that can cause cervicitis.

Clinically, acute infection is manifested by a purulent, leukorrheal, malodorous discharge. *Macroscopically*, the cervix is edematous, congested, and exhibits an intense red color; the causative organism may be identified in the purulent leukorrheal discharge. The *histologic appearance* is that of a predom-

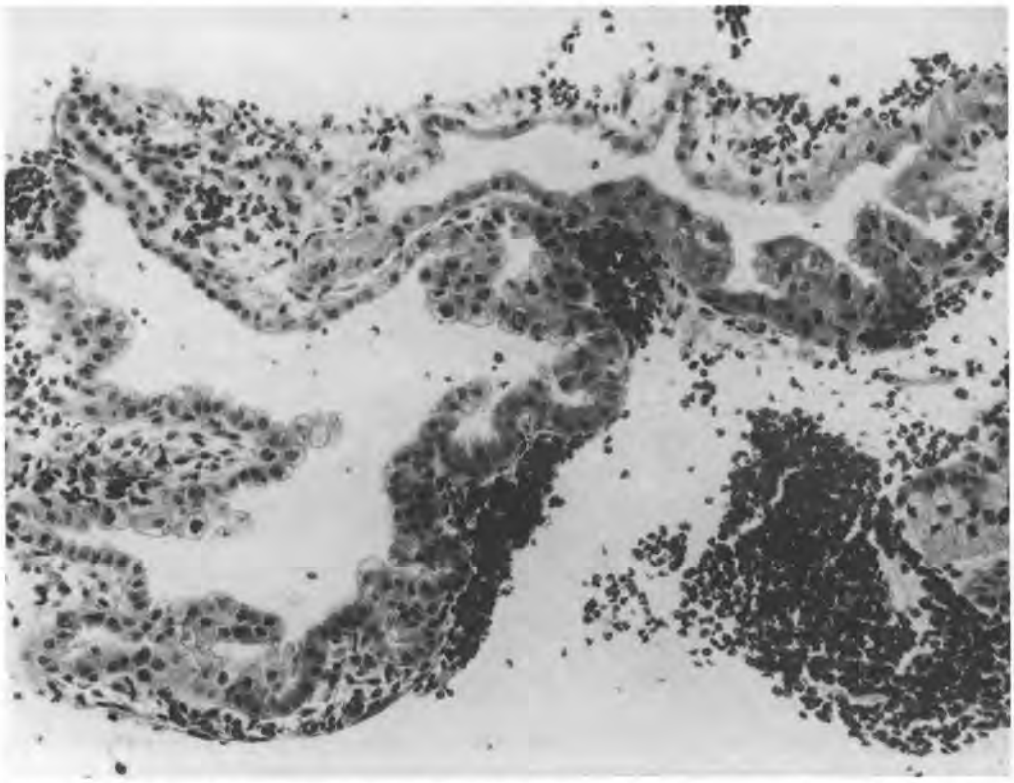


FIGURE 3-7 Arias-Stella reaction of endocervical glands seen in curettage specimen. The angular, hyperchromatic but uniformly dense nuclei are typical.

inantly polymorphonuclear leukocytic inflammatory infiltrate, with marked vascularization and edema of the submucosa (Fig. 3-8). When the squamous epithelium is infiltrated by neutrophils, it may exhibit spongiosis, acanthosis, and nuclear and cytoplasmic vacuolization.

Vaginal smears show an abundant inflammatory exudate rich in neutrophils, histiocytes, and mucus, with the squamous cells presenting diverse nuclear (anisonucleosis, pyknosis, karyorrhexis) and cytoplasmic changes (precocious eosinophilia, vacuolization, and alteration of the cell membrane with cytolysis; Color Fig. 3-2). The intensity of these cytologic alterations is a function of the gravity of the cervical lesions and permits the observer to follow the evolution of the disease. Columnar endocervical cells may also reveal morphologic alterations such as hypertrophic nuclei and vacuolated cytoplasm.

Repair phenomena appear if the inflammation subsides. Granulation tissue is replaced by regenerating epithelial cells, which exhibit large, hyperchromatic nuclei with frequent mitoses. In smears, these regenerating cells should not be misinterpreted as dysplastic or neoplastic. The absence of definite criteria of malignancy, the recognition of the inflammatory event, and amelioration after treatment of the inflammation may help to solve the problem. These alterations are particularly difficult to interpret when they occur in endocervical columnar cells.[44]

TABLE 3-1.
Causal Agents of Cervicitis

Bacterial agents: Various cocci (streptococci, staphylococci, enterococci), lactobacilli (?), *Gardnerella, Corynebacterium diphtheriae, Neisseria gonorrhoeae, Chlamydia trachomatis, Treponema, Mycobacterium tuberculosis, Leptothrix*
Fungal agents: *Candida albicans, Torulopsis glabrata, Coccidioides immitis, Aspergillus, Toxoplasma, Blastomyces*
Parasitic agents: *Trichomonas vaginalis*
Viral agents: Herpes genitalis, cytomegalovirus, human papillomavirus
Protozoal agents: *Entamoeba histolytica, Balantidium coli, Vorticella*
Helminthic agents: *Schistosoma haematobium/mansoni/japonicum*

Chronic Cervicitis

The existence of chronic infection of the uterine cervix has been recognized for about a century. Before then, the clinical signs of cervicitis such as leukorrhea were attributed to "chronic inflammation of the matrix," the etiology of which was poorly defined. Chronic cervicitis is the most common gynecologic disease and the most common cause of leukorrhea, being discovered in about one third of women examined by gynecologists. Several factors explain its frequency:

1. The cervix is exposed to diverse traumata of genital life.
2. The multiple folds of the cervical mucosa favor microbial pollution.
3. The constant presence of cervical and endometrial secretions constitutes an environment favorable to the development of pathogenic organisms.
4. The rich lymphatic drainage in the region facilitates the dissemination of infections, originating most commonly in the urinary tract.
5. Modifications of the hormonal milieu create morphologic alterations in the mucosa.

The causal organisms are the same as for acute cervicitis (see Table 3-1). The gonococcus, one of the most common, has decreased in frequency since the beginning of the antibiotic era. *Mycoplasma, Chlamydia,* and *Gardnerella vaginalis* have been recognized recently as playing a frequent role.

Macroscopic Appearance. The macroscopic pictures seen in chronic cervicitis are varied. The ectocervix may appear normal, the infection being localized to the endocervical canal, or it may display profound alterations. In the latter case, it is deformed, budding, granular, congested, and edematous, or it may contain more or less extensive zones

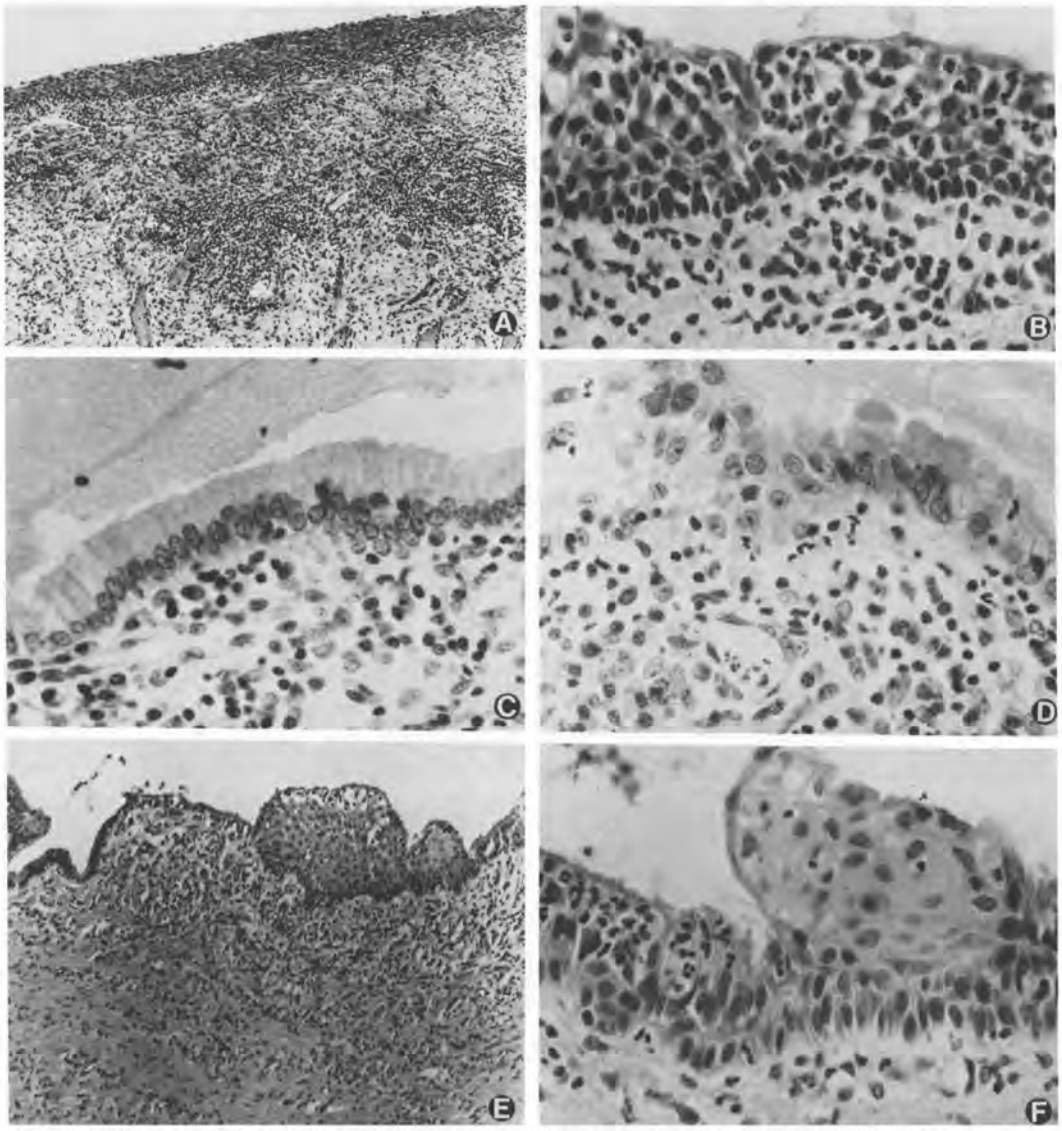


FIGURE 3-8 Acute and chronic cervicitis: microscopic appearances. **(A)** Leukocytic infiltration of epithelium and subjacent stroma, vascular congestion. **(B)** Acute inflammatory infiltrate rich in polymorphonuclear leukocytes invading epithelium and stroma. **(C)** The stroma shows a discrete chronic inflammatory infiltrate rich in lymphocytes and plasma cells, with no alteration of the glandular epithelium. **(D)** Polymorphonuclear leukocytic stromal infiltrate and alterations of the glandular epithelium. **(E)** Focus of squamous metaplasia and leukocytic infiltration. **(F)** Detail of the focus of squamous metaplasia seen in **E**.

of red granular surface erosion. Glandular cysts project under the mucosa, and lacerations are sometimes visible. The extent and severity of these lesions determine the macroscopic appearance and the clinical manifestations. With time, progressive fibrosis takes place occasionally resulting in a cicatricial stenosis of the cervical canal.

Colposcopic examination facilitates the identification of these lesions.[45,46] The best known findings by this technique are (1) true erosion of the mucosa, (2) leukoplakic foci due to mucosal hyperkeratosis, (3) hyperemia and infiltration of the submucosa in the zones of erosion, and (4) ectropion, or the presence of glandular epithelium covering the ectocervix.

Certain chronic infections cause specific anatomic modifications. The most notable of these are condylomata acuminata and the mucous plaques of secondary syphilis.

Microscopic Appearance. The histologic lesions provoked by chronic inflammatory phenomena are varied, and their intensity depends on local and systemic factors (Figs. 3-8 and 3-9). The most discrete consist of lymphoplasmacytic infiltration and vascular congestion of the submucosa without alteration of the squamous or glandular mucosa. This type of lesion is extremely frequent and often is of little clinical significance. When the inflammatory infiltrate is more extensive, it reaches the basal layers of the epi-

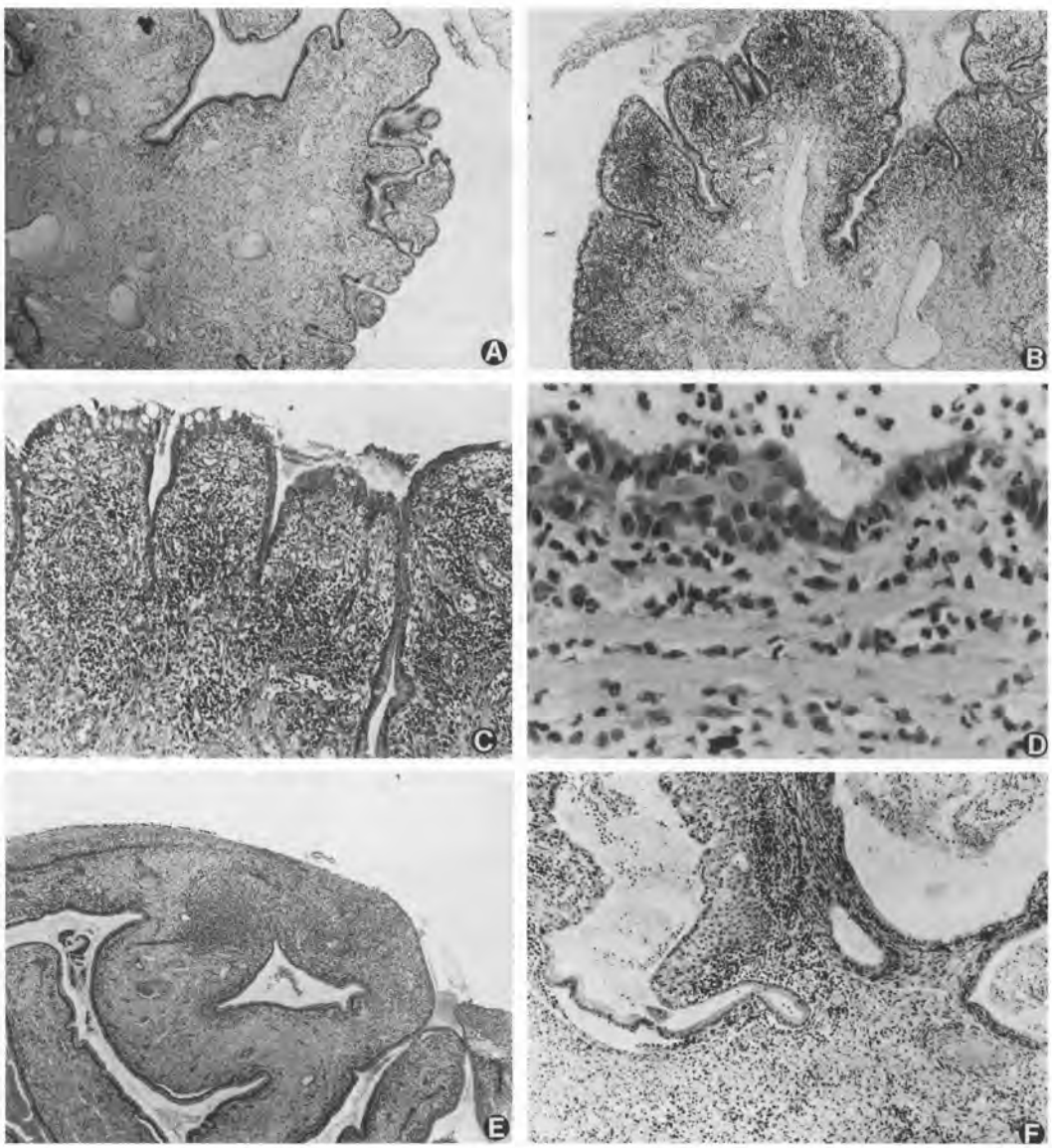
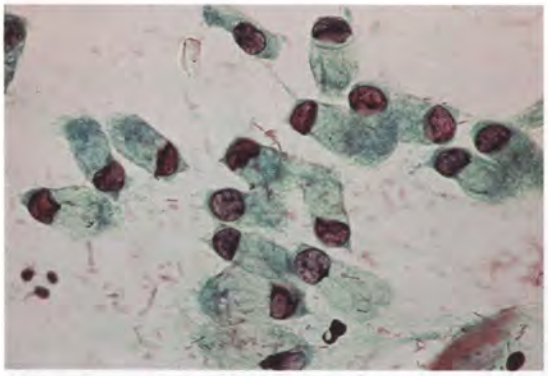
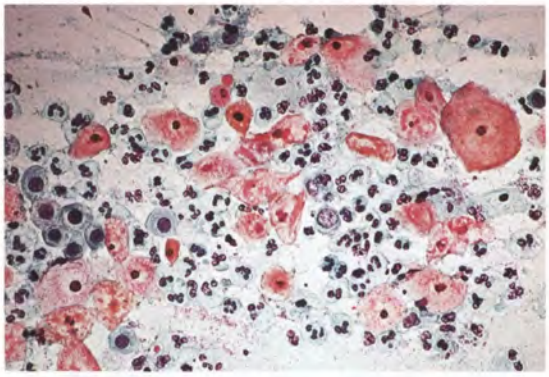


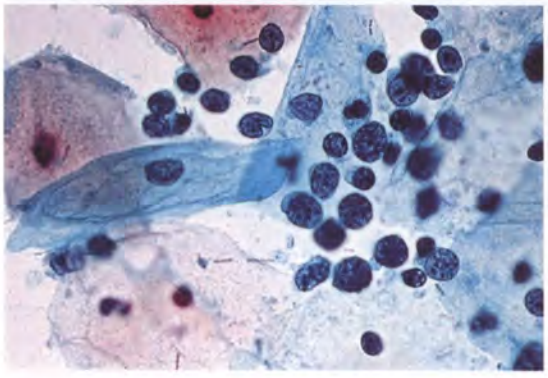
FIGURE 3-9 Chronic cerviticis: microscopic appearances. **(A,B)** Papillary structure of the endocervical mucosa with leukocytic infiltration. **(C)** Degenerative alterations of surface epithelium. **(D)** Leukocytic inflammatory infiltrate and discrete squamous metaplasia at left. **(E)** Papillary structure of endocervical mucosa, leukocytic stromal infiltrate. **(F)** Focus of squamous metaplasia.



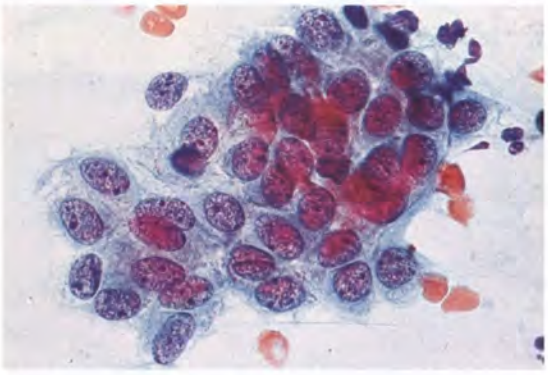
Color Figure 3-1



Color Figure 3-2



Color Figure 3-3



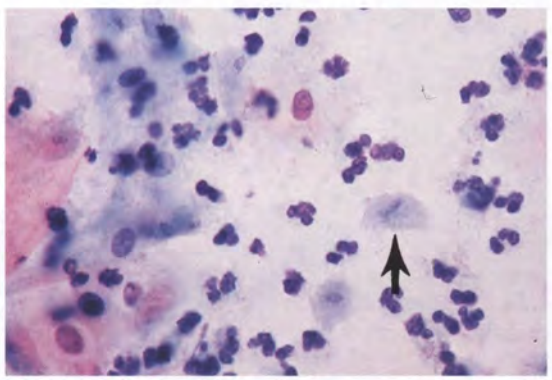
Color Figure 3-4

Color Figure 3-1 Cervical smear: normal endocervical cells. The presence of endocervical cells such as these or of metaplastic cells (see Color Figs. 3-7 and 3-8) should be noted as an indication that the smear has attained the squamous–columnar junction.

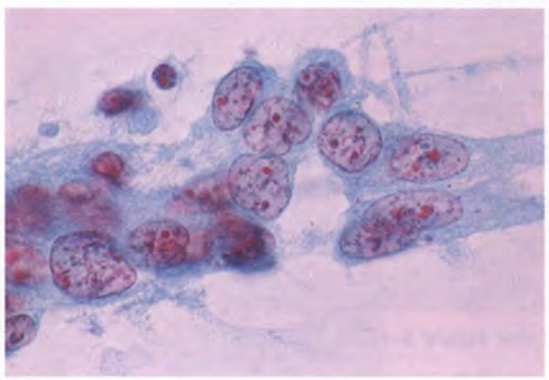
Color Figure 3-2 Cervical smear: atypia due to *Trichomonas vaginalis* infection. Note anisonucleosis, nuclear hyperchromasia, and perinuclear haloes. The inflammatory background and the presence of the parasite (see Color Fig. 3-5) aid in the distinction from condyloma (Color Figs. 3-10 through 3-12) and dysplasia (Color Figs. 3-22 through 3-25).

Color Figure 3-3 Cervical smear: follicular cervicitis. Numerous benign lymphocytes must not be mistaken for endometrial cells or cells exfoliated from a small cell carcinoma or malignant lymphoma.

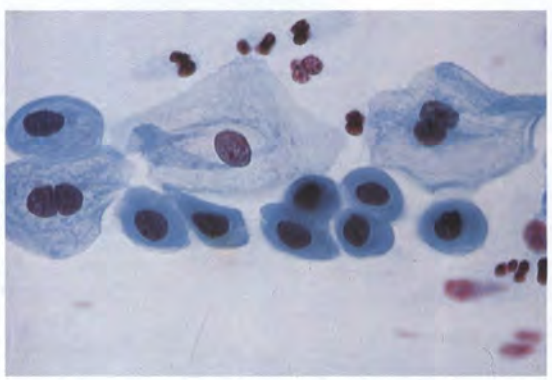
Color Figure 3-4 Cervical smear: endocervical cells showing hyperplasia with nuclear atypia in biopsy-proven severe acute and chronic endocervicitis with microglandular hyperplasia. (Compare with Color Figs. 3-6, 3-31, and 3-32.)



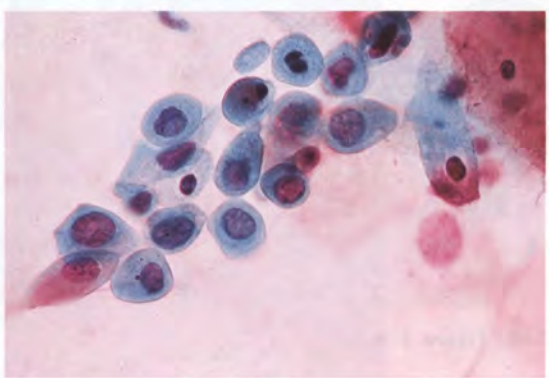
Color Figure 3-5



Color Figure 3-6



Color Figure 3-7



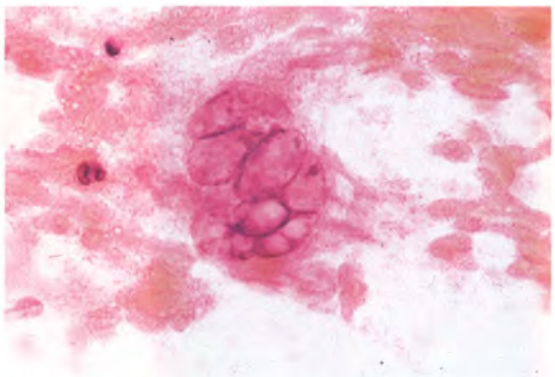
Color Figure 3-8

Color Figure 3-5 Cervical smear: trichomoniasis. Several organisms with distinct nuclei are present in an inflammatory background *(arrow)*.

Color Figure 3-6 Cervical smear: atypia due to endocervical repair phenomenon. Note variability in cell size and enlarged nuclei with prominent nucleoli and granular chromatin. (Compare with Color Figs. 3-4, 3-31, and 3-32.)

Color Figure 3-7 Cervical smear: squamous metaplasia. Group of parabasal-type cells in a row with cytoplasmic molding and flattening at one surface.

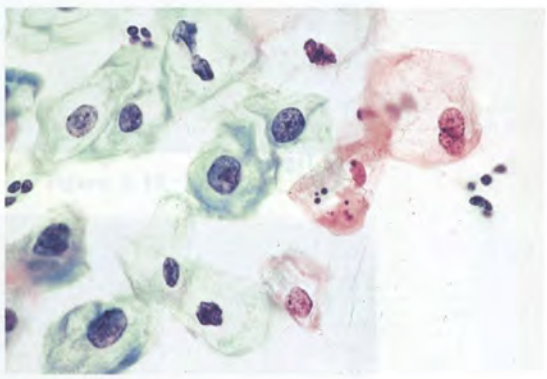
Color Figure 3-8 Cervical smear: atypical metaplasia. Small cells similar in shape and orientation to those seen in Color Figure 3-7 but with moderate nuclear atypia. Abnormal chromatin clumping of dysplasia in parabasal or metaplastic cells is absent. (Compare with Color Figs. 3-23 through 3-25.)



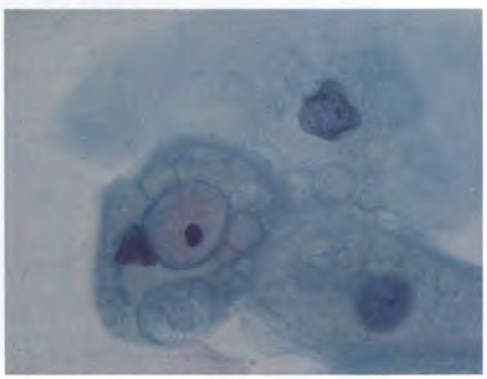
Color Figure 3-9

Color Figure 3-10

Color Figure 3-11



Color Figure 3-12



Color Figure 3-13

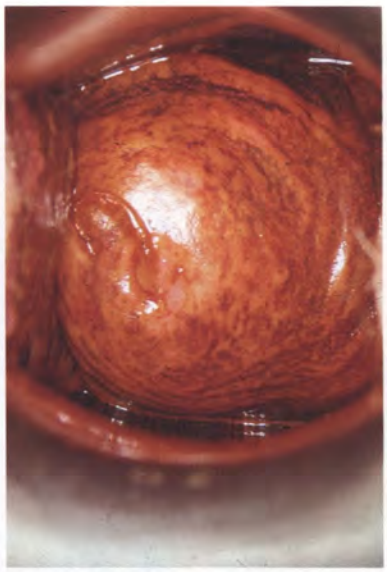
Color Figure 3-9 Cervical smear: *Herpesvirus hominis* type 2 infection. Multinucleated cells with "ground-glass" nuclei can be seen.

Color Figure 3-10 Cervical smear: flat condyloma or wart virus infection. Typical cytoplasmic haloes and peripheral cytoplasmic thickening of squamous cells with orangeophilic or fuchsia red staining. Nuclei are small, dense, and irregular.

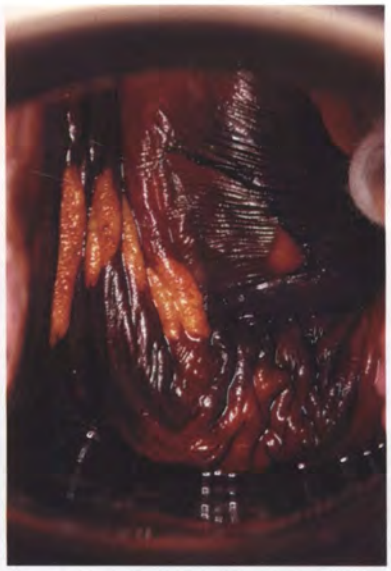
Color Figure 3-11 Cervical smear: flat condyloma or wart virus infection. Koilocytotic cells with cytoplasmic haloes, peripherally dense cytoplasm, and "raisinoid" nuclei.

Color Figure 3-12 Cervical smear: flat condyloma or wart virus infection. Pronounced cytoplasmic vacuolation and moderate nuclear atypia including binucleation. This should be reported as "mild dysplasia of probable viral origin."

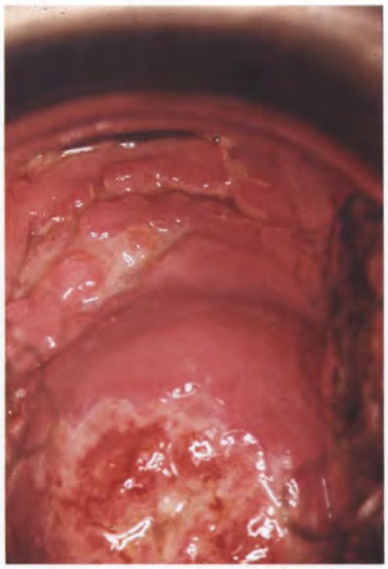
Color Figure 3-13 Cervical smear: chlamydial cervicitis. Cell with typical cytoplasmic inclusion with distinct borders.



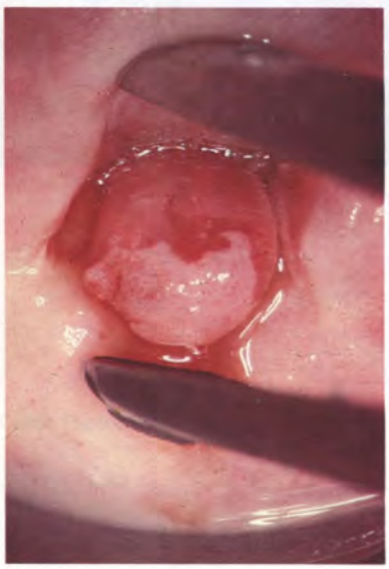
Color Figure 3-14



Color Figure 3-15



Color Figure 3-16



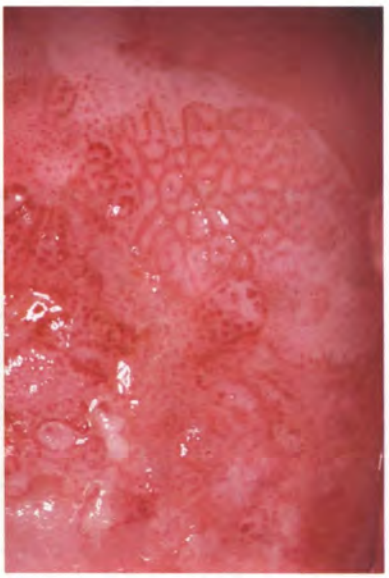
Color Figure 3-17

Color Figure 3-14 Positive Schiller test in extensive cervicitis. Squamous epithelium is only slightly stained by iodine. No dysplasia was present (Courtesy of Dr. R. Cartier)

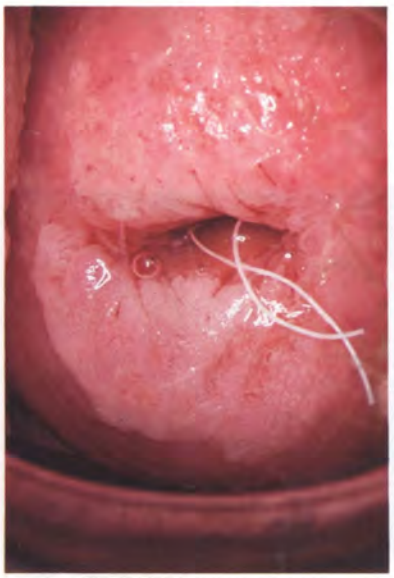
Color Figure 3-15 Positive Schiller test in vaginal condyloma. Cervix is normal and is deeply stained by iodine. (Courtesy of Dr. R. Cartier)

Color Figure 3-16 Colposcopic view of herpetic ulcers of anterior vaginal fornix and cervix. (Courtesy of Dr. R. Cartier)

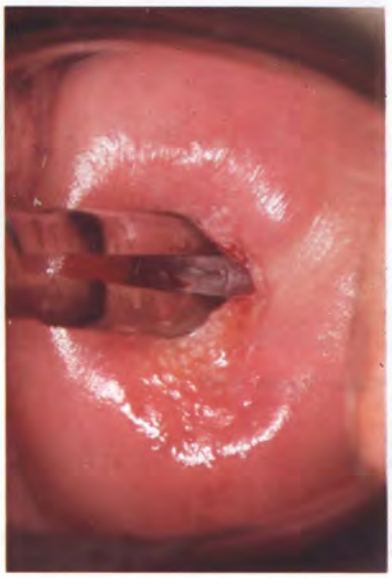
Color Figure 3-17 Colposcopic picture of endocervical polyp. The polyp protrudes through the external os and shows squamous metaplasia (white) on its surface. (Courtesy of Dr. R. Cartier)



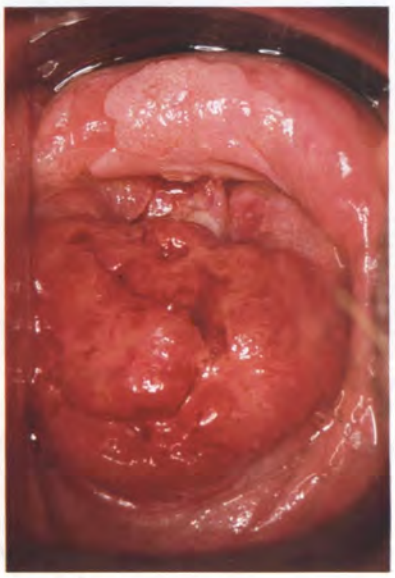
Color Figure 3-18



Color Figure 3-19



Color Figure 3-20



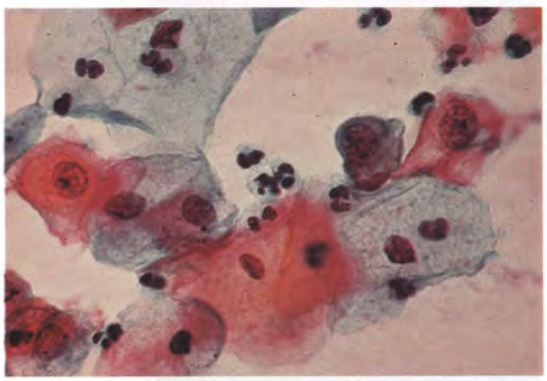
Color Figure 3-21

Color Figure 3-18 Colposcopic picture of severe dysplasia (CIN III). After application of acetic acid, the cervix shows a polymorphous appearance, with mosaic punctation, marked congestion, and a white cuffed gland opening at the lower left of the figure. (Courtesy of Dr. R. Cartier)

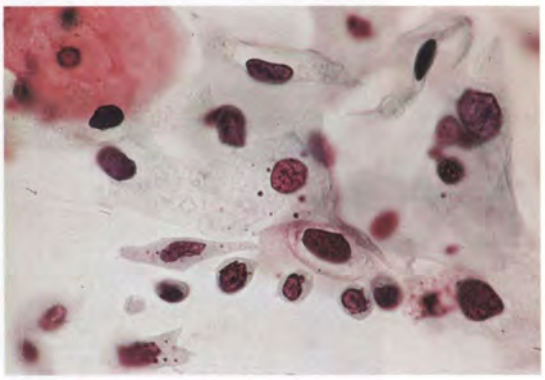
Color Figure 3-19 Colposcopic picture of severe dysplasia (CIN III). Acetowhite epithelium indicates a large ectocervical lesion. The squamocolumnar junction is visible at the external os. An IUD string protrudes from the endocervical canal. (Courtesy of Dr. R. Cartier)

Color Figure 3-20 Colposcopic picture of severe dysplasia (CIN III). Examination using a Palmer polyp forceps as endocervical speculum demonstrates that the endocervical mucosa is white and smooth, with no squamocolumnar junction visible (compare with Color Fig. 3-19). (Courtesy of Dr. R. Cartier)

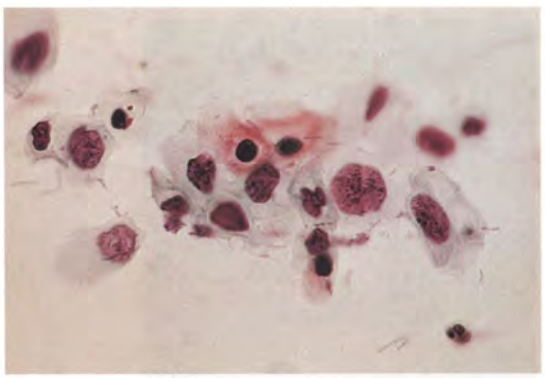
Color Figure 3-21 Colposcopic picture of invasive squamous cell carcinoma. This large fungating tumor extends to the posterior vaginal wall. Note atypical pattern of surface blood vessels. (Courtesy of Dr. R. Cartier)



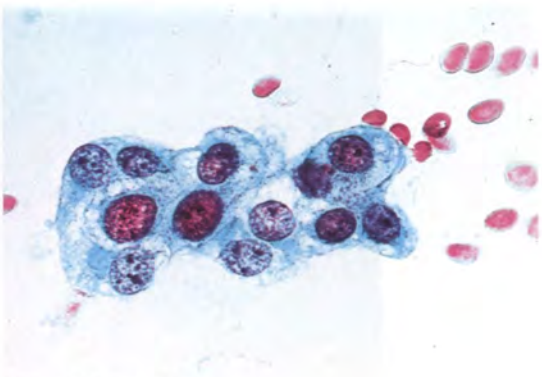
Color Figure 3-22



Color Figure 3-23



Color Figure 3-24



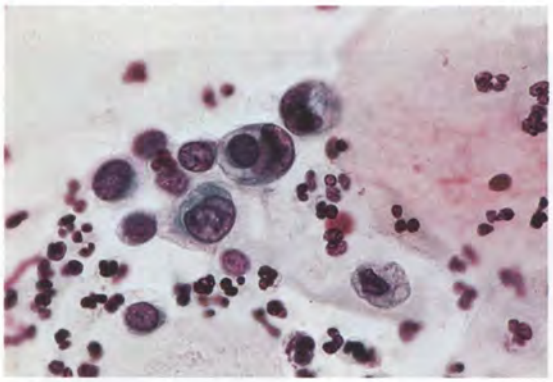
Color Figure 3-25

Color Figure 3-22 Cervical smear: mild dysplasia (CIN I). Dyskaryosis and slight nuclear atypia of superficial and intermediate squamous cells.

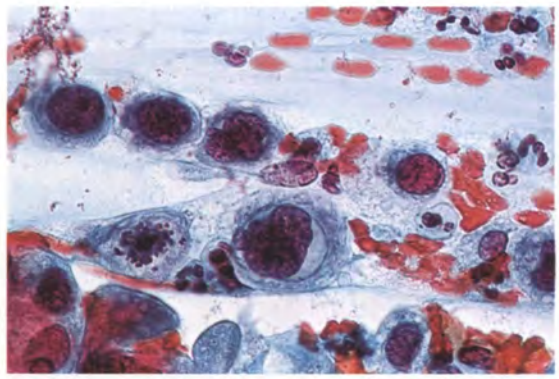
Color Figure 3-23 Cervical smear: moderate dysplasia (CIN II). Intermediate and parabasal squamous cells show anisonucleosis, nuclear hyperchromasia, and fine chromatin clumping.

Color Figure 3-24 Cervical smear: moderate dysplasia (CIN II). Intermediate and parabasal squamous cells show anisonucleosis, nuclear hyperchromasia, and fine chromatin clumping.

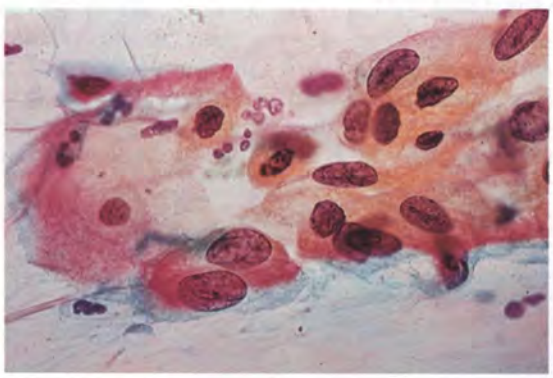
Color Figure 3-25 Cervical smear: severe dysplasia (CIN III). Parabasal dyskaryosis of small squamous cells with basophilic cytoplasm and marked nuclear atypia.



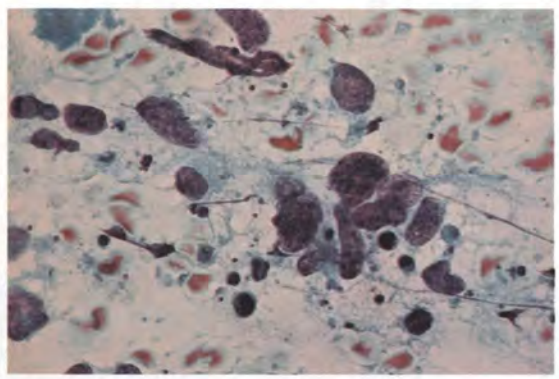
Color Figure 3-26



Color Figure 3-27



Color Figure 3-28



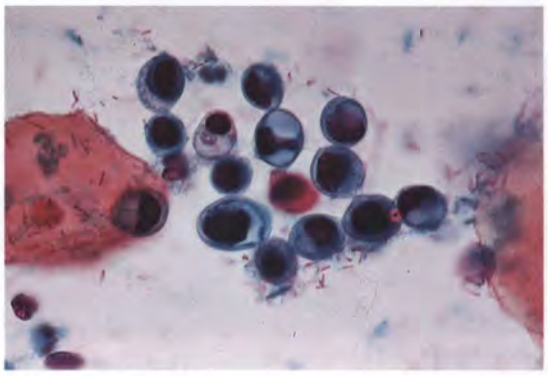
Color Figure 3-29

Color Figure 3-26 Cervical smear: squamous carcinoma in situ (CIN III or CIS). Findings are similar to those in Color Figure 3-25, but less cytoplasm is present. The similarity of these two cases argues in favor of the CIN classification.

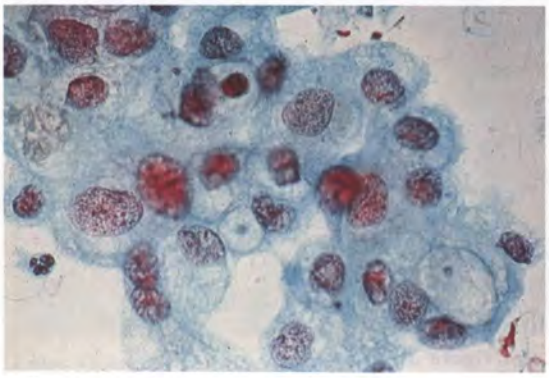
Color Figure 3-27 Cervical smear: squamous carcinoma in situ (CIN III or CIS), large cell type. This smear is similar to that depicted in Color Figure 3-26, but the neoplastic cells are considerably larger (figures taken at same magnification). The uniformity of the neoplastic cells and the absence of a "tumor diathesis" are factors against the diagnosis of invasive large cell carcinoma (compare with Color Fig. 3-29).

Color Figure 3-28 Cervical smear: invasive keratinizing squamous cell carcinoma. Cells with malignant nuclei and voluminous cytoplasm showing keratinization.

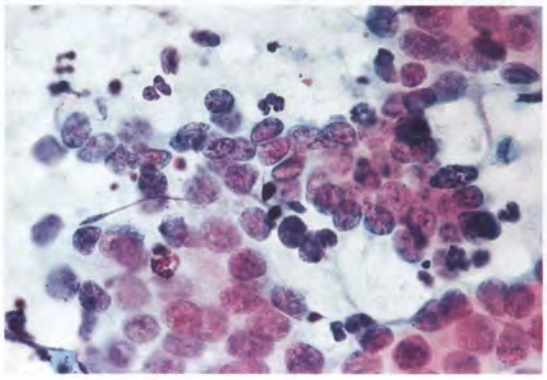
Color Figure 3-29 Cervical smear: invasive squamous cell carcinoma, large cell nonkeratinizing type. In addition to nuclear criteria of malignancy, cells are pleomorphic and there is a necrotic background ("tumor diathesis"). (Compare with Color Fig. 3-27).



Color Figure 3-30



Color Figure 3-31



Color Figure 3-32

Color Figure 3-30 Cervical smear: invasive small cell carcinoma. Cells are small, round, and fairly uniform. "Tumor diathesis" was present elsewhere in the smear.

Color Figure 3-31 Cervical smear: adenocarcinoma of endocervix. The neoplastic cells are in a papillary cluster and show the usual nuclear criteria of malignancy. Compared with adenocarcinoma of the endometrium (Color Figs. 3-32 and 4-6), the cells of endocervical adenocarcinoma are larger and have large cytoplasmic vacuoles; they are also more likely to contain macronucleoli (not seen in this figure). Also compare with benign endocervical atypias in Color Figures 3-4, 3-6, and 3-8.

Color Figure 3-32 Cervical smear: adenocarcinoma of endometrium extending to cervix (direct scrape and smear of tumor). Compare with Color Figure 3-31.

thelium, spreads within the stroma, and surrounds the endocervical glands. This infiltrate is composed of lymphocytes, neutrophils, plasma cells, and histiocytes. If lymphoid follicles are prominent, the designation *follicular cervicitis* is applied (Fig. 3-10 and Color Fig. 3-3). *Cervical smears* may reveal the presence of a characteristic rich pleomorphic infiltrate composed of lymphoid cells and macrophages. *Follicular cervicitis* is frequently associated with chlamydial infection.[47] It is more frequent in postmenopausal women and should not be confused microscopically with a leukemic or lymphomatous lesion.[48] The endocervical mucosa reacts by proliferating and developing superficial papillary formations that may project at the external orifice of the cervix (ectropion). The endocervical mucosa, congestive and proliferating, forms a visible collar around the cervical os.

The squamous epithelium is more resistant, and the lesions are limited at this stage to the basal cell layers. These cells show discrete nuclear and cytoplasmic atypias, and leukocytes infiltrate the epithelium.

In more severe cervicitis, all the histologic structures are altered or destroyed by the inflammatory infiltrate. Either the epithelia are replaced by inflammatory infiltrates or they present cytologic alterations of reactive type (Fig. 3-11). The squamous epithelium shows hyperkeratosis, acanthosis, and anomalies of size and shape of cells and of nuclei. Intracellular glycogen is diminished or absent. This disappearance of glycogen is demonstrated clinically by the Schiller test (the cervical mucosa is stained brown by iodine except in areas in which glycogen is deficient). These cellular anomalies should not be confused with cervical intraepithelial neoplasia (CIN). The stroma is congested, edematous, and contains numerous leukocytes and histiocytes concentrated around blood vessels. The glands are dilated, cystic (*nabothian cysts*; Fig. 3-12), or destroyed by the inflammation. Nabothian cysts result from blockage of the endocervical gland necks by inflammation or subsequent squamous metaplasia. Vascular congestion favors the appearance of hemorrhages, especially during pregnancy.

Repair phenomena appearing in longstanding cervicitis are characterized by considerable cellular alterations of squamous and columnar cells which should not be confused with CIN.[49] They correspond to an epithelial proliferation replacing the destroyed epithelium. The presence of enlarged nucleoli is the expression of active repair protein synthesis (cell regeneration). The nuclei, though enlarged, irregular, and hyperchromatic, lack the very marked anomalies of neoplastic cells. The columnar cells have large clear, hypochromatic nuclei, conspicuous nucleoli, and dense eosinophilic cytoplasm. Mitoses are normal. The nuclear–cytoplasmic ratio is within normal limits. These repair anomalies are well illustrated in postconization smears and biopsies and after radiation therapy.

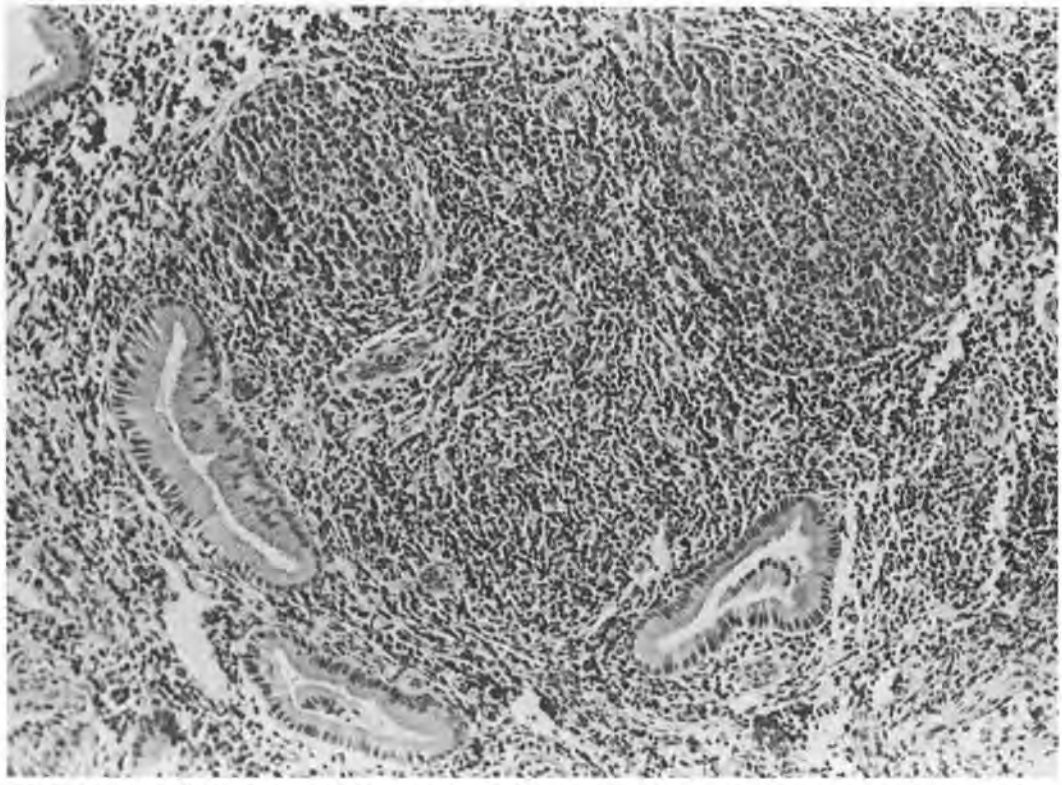


FIGURE 3-10 Follicular cervicitis: lymphoid tissue with germinal centers in endocervix.

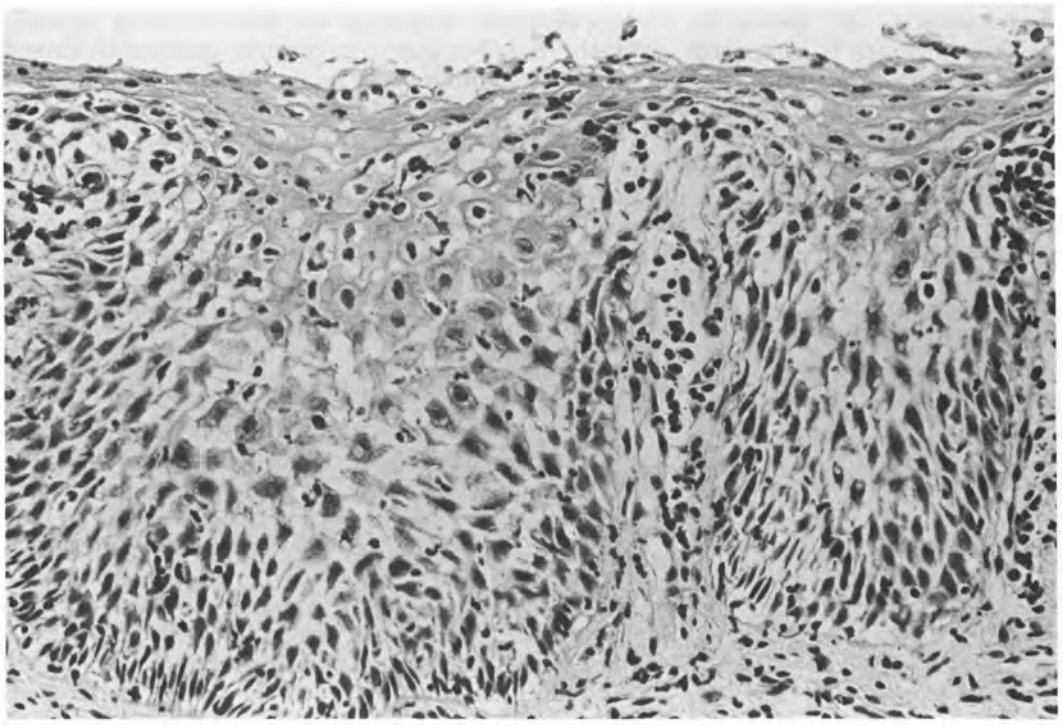


FIGURE 3-11 Cervicitis with mild reactive atypia of squamous mucosa.

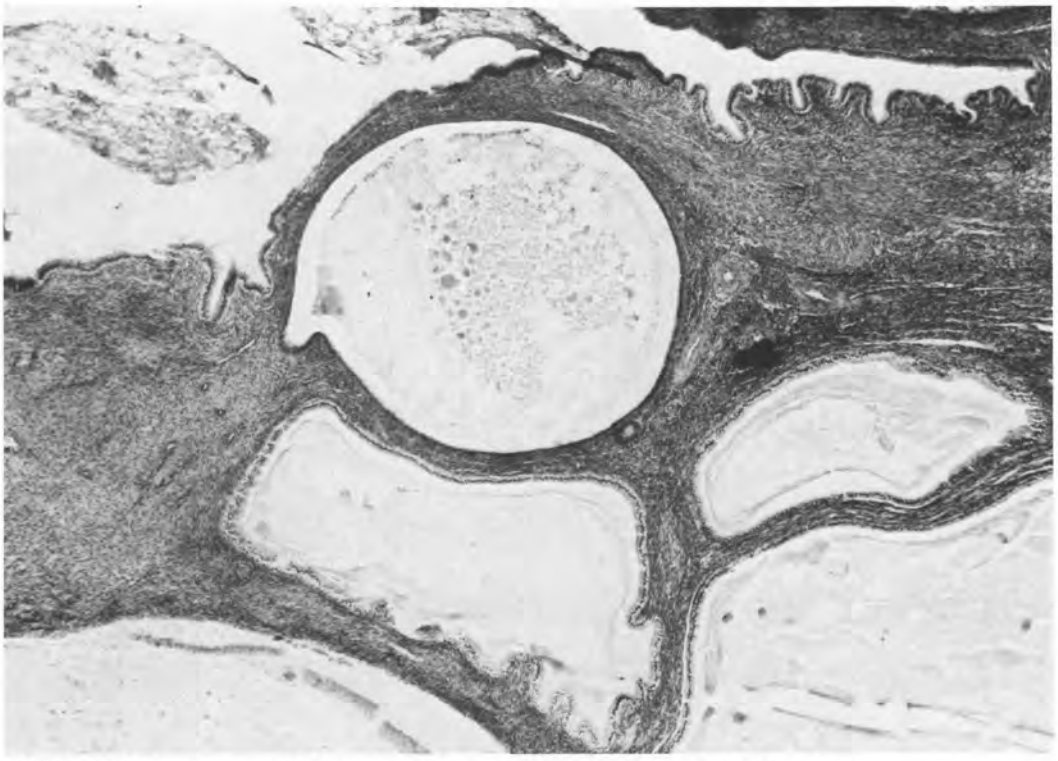


FIGURE 3-12 Chronic cervicitis: cystic dilatation of cervical glands (nabothian cysts).

Erosion and Squamous Metaplasia

The term *erosion* has been used in several different senses, but because the early description by Meyer[50] emphasized its relation to inflammatory processes, it will be considered at this point. Most important is that the common usage of the term does not denote an erosion in the histopathologic sense (ie, mucosal denudation or ulceration), but rather an outgrowth of endocervical columnar epithelium onto the portio (ectropion), where, because the thinner mucosa is relatively transparent, the underlying blood vessels give the area involved (often a ring-like zone around the external os) a red or eroded appearance. To understand its development, it is necessary to recall that the external os of the cervix represents the normal boundary between mucus-secreting glandular epithelium and stratified squamous epithelium (transformation zone).

Modifications in pH, under the influence of bacterial or hormonal factors, bring about disturbances in the equilibrium between the two epithelia. In the first stage, the glandular epithelium proliferates onto the squamous territory by the following mechanism: an elevation of pH provokes maceration of the squamous epithelium, which becomes infiltrated by polymorphonuclear leukocytes, degenerates, disappears, and is replaced by glandular epithelium. When the pH is lowered, the glandular epithelium this time recedes before the squamous lining. The latter creeps under the columnar cells, pushes them back, invades the necks of the glands, and produces the picture of *squamous metaplasia* (Figs. 3-13 through 3-16). Thus, the localization of the borderline or transformation zone varies according to the factors mentioned previously and is better visualized with the use of the colposcope, which can also determine the location and extent of cervical lesions. These lesions are so common that they can be considered as physiologic changes expressing the search for a constant equilibrium between the two epithelia.

Although the inflammatory etiology of cervical erosion represents the classic theory, many authors agree with Fluhmann[51] that the lesion is more often either congenital or acquired from an ectropion secondary to trauma. Biopsies often show papillary projections of columnar epithelium overlying a stroma devoid of inflammatory cells. The classic explanation of squamous metaplasia is also not accepted by all authors. According to the historic work of Meyer,[50] the image of metaplasia is produced when the squamous epithelium becomes dominant and insinuates itself under the glandular epithelium; it therefore becomes evident that the term *metaplasia* is inexact because it is not a case of epithelial transformation but rather of squamous epithelialization. The term *epidermization* has been used for this phenomenon—although incorrectly, because true epidermis does

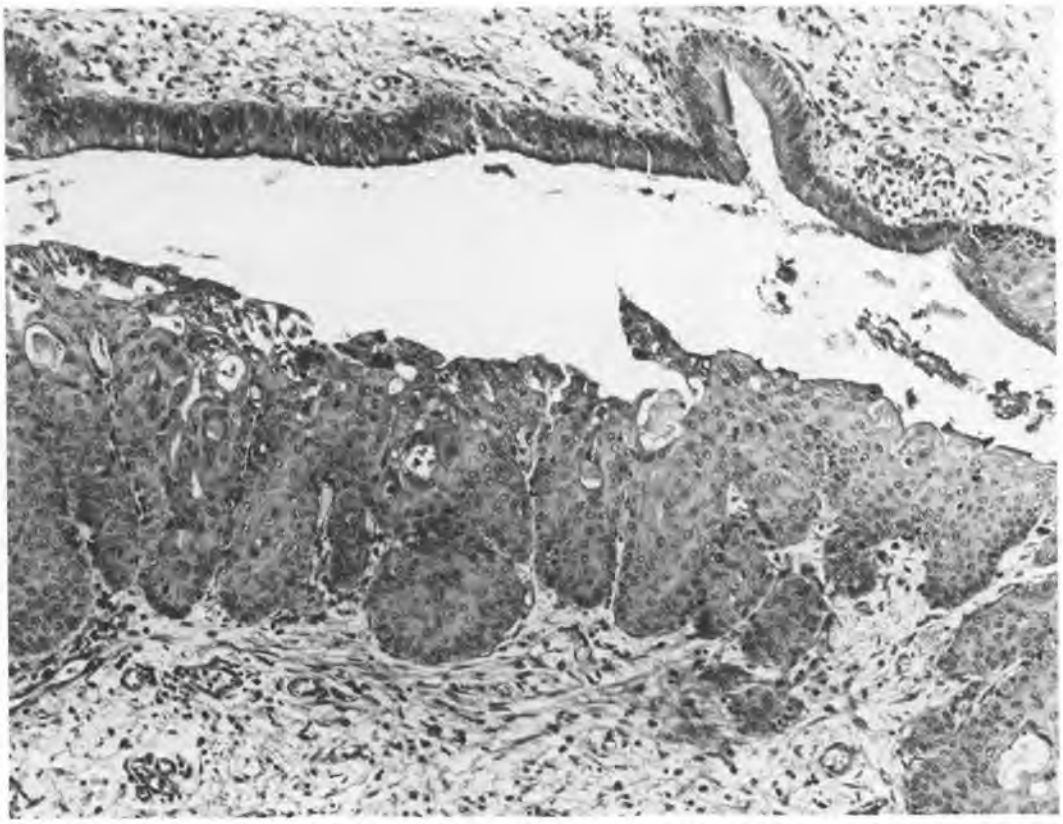


FIGURE 3-13 Squamous metaplasia at the level of a cervical gland neck.

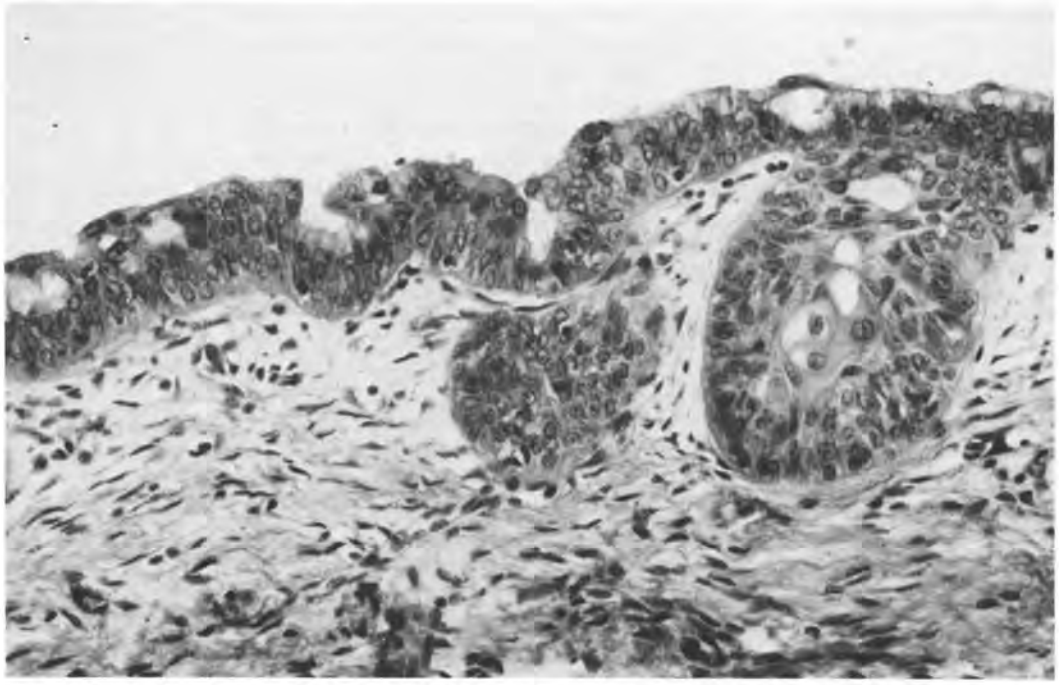


FIGURE 3-14 Squamous metaplasia (*right*), arising in reserve cell hyperplasia (*left*).

not participate. Usage and numerous works, however, have consecrated these terms.

The second hypothesis postulates the existence of a true metaplasia (squamous prosoplasia of Fluhmann) arising from the pluripotential subcolumnar reserve cell (Fig. 3-17). These cells, also called *basal cells,* are capable of undergoing, under the influence of diverse stimuli, various transformations such as simple proliferation, hyperplasia, metaplasia, and anaplasia. Numerous authors have shown convincing pictures in favor of the hypothesis.[49,52–55] According to them, these cells have a potential for differentiation into either muciparous glandular epithelium or squamous epithelium. The presence of mucus in squamous cell plaques illustrates this double potential.

The immature squamous metaplasia resulting from the proliferation of reserve cells pushes the overlying endocervical epithelium toward the surface (see Figs. 3-15 and 3-16). The immature metaplastic cells are rather small, contain no abundant glycogen, and often have an eosinophilic cytoplasm. When these cells differentiate, they become similar to normal squamous cells constituting a mature squamous epithelium.

Supporters of the true metaplasia theory reject the idea of epithelial migration because of pictures in which the border between the normal and the atypical metaplastic zones is sharp. Another argument in favor of the metaplasia hypothesis is the existence of foci of metaplasia distant and isolated from the squamocolumnar junction. Our own experience indicates

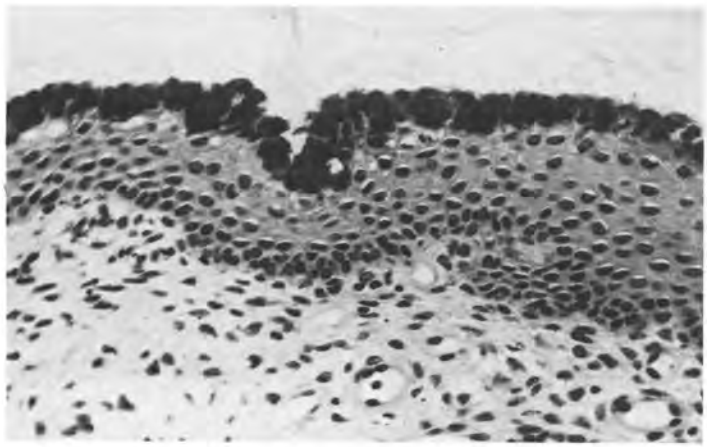


FIGURE 3-15 Squamous metaplasia: mucin stain demonstrating the columnar superficial layer.

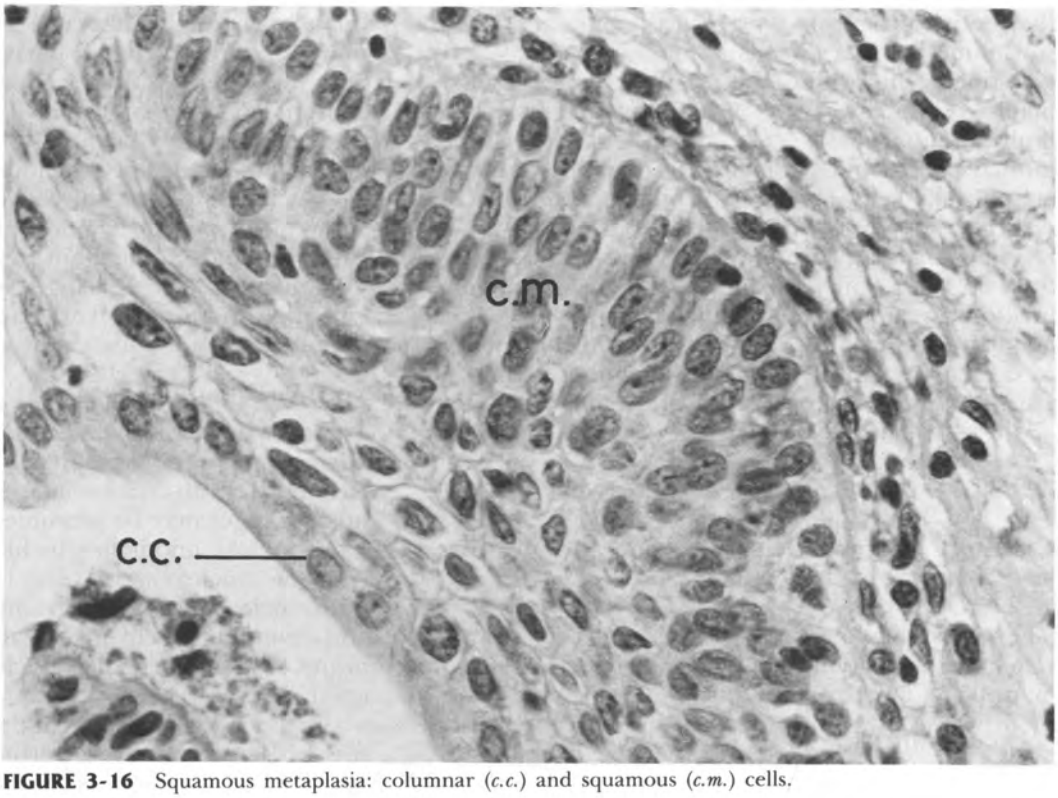


FIGURE 3-16 Squamous metaplasia: columnar (*c.c.*) and squamous (*c.m.*) cells.

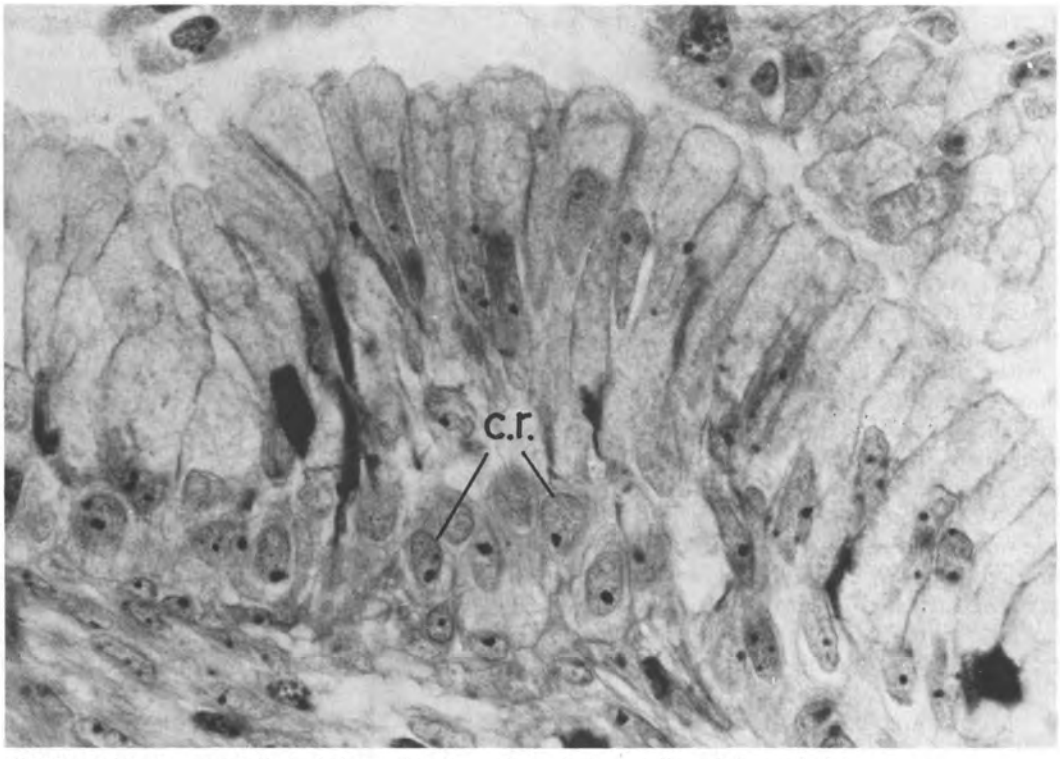


FIGURE 3-17 Reserve cells (*c.r.*) situated between the columnar cells and the underlying stroma.

that both mechanisms exist, but the one mediated by subcolumnar reserve cells is far more common. Interestingly, the origin of these reserve cells itself remains a mystery.[53,56–58] They may originate from multipotential basal cells, from endocervical columnar cells, from stromal cells, or from embryonic endodermal cells. Hormonal stimuli and local factors may play a role in this proliferation.

It is important to know these histologic pictures to avoid confusion with cancer, because of the immaturity of metaplastic epithelium. The absence of cellular atypia and of bizarre mitoses and the presence of normal stratification of the squamous epithelium are morphologic supports for the benign character of these lesions.

Cytology in Cervicitis and Squamous Metaplasia

The great majority of abnormal cervicovaginal smears exhibit atypia on the basis of cervical inflammation or metaplasia. These pictures, although themselves not of great clinical significance, are important to recognize to avoid the false diagnosis of a dysplastic or neoplastic process. Although the changes of inflammatory and metaplastic lesions will be described separately, in most cases they occur together and are frequent.[59] Normal and abnormal cervical cells are illustrated in Figure 3-18.

Cervicitis

In chronic cervicitis, the background of the smear is generally normal, although in rare cases of follicular cervicitis (see above), numerous lymphocytes and larger germinal center cells may be exfoliated, raising the differential diagnosis with a malignant lymphoma (see Color Fig. 3-3). In acute cervicitis, the smears are usually rich in neutrophils, with many large clumps of necrotic debris. The neutrophils may cluster around epithelial cells, and in endocervicitis may be found within the cytoplasm of large, often markedly atypical endocervical cells. The offending organisms, particularly *Trichomonas vaginalis,* may be identified in the smears as well (Color Figs. 3-2, 3-4, and 3-5). Reserve cells, easily observed in biopsies, are not frequently identifiable in the smears. Only in marked reserve cell hyperplasia may one notice the presence of small, round, regular cells with round normochromatic nuclei surrounded by a slim rim of cyanophilic cytoplasm. They desquamate in syncytial aggregates.

More important is the cellular atypia that may be encountered in these smears (see Color Fig. 3-2). These are seen predominantly in acute cervicitis, and chronic cervicitis exhibits few cytologic changes. Parabasal cells are often increased in number and show degenerative phenomena such as karyorrhexis, nuclear pyknosis, and cytoplasmic vacuolization. Some variation in size and shape of epithelial cells may be seen, and nuclei may be slightly to moderately enlarged, with a uniform "ground glass" appearance. Endocervical cells (see Color Fig. 3-4) and their nuclei may be markedly enlarged, and the nuclei may contain one or more large, prominent nucleoli. The endocervical cells may be multinucleate, show mitotic figures, and contain intracytoplasmic vacuoles and neutrophils. Naked nuclei are frequently seen. These changes may be extremely difficult to differentiate from those of endocervical or endometrial adenocarcinoma (see text below and Color Figs. 3-31 and 3-32).

Some additional changes resulting from specific organisms may also be encountered. The pictures in herpesvirus and papillomavirus infections are discussed later. In *Trichomonas* infection, atypical cellular changes may be prominent (see Color Fig. 3-2). The nuclear anomalies include enlargement, blurring of nuclear structure, irregularity of form, multinucleation, finely granular hyperchromatism, and clumping of chromatin along the nuclear membrane. These worrisome nuclear atypias are usually combined with characteristic cytoplasmic findings, which aid in the differential diagnosis from dysplasia: the presence of clear perinuclear haloes and of marked cytoplasmic eosinophilia. The organisms usually can be identified as well. However, there is no reason that trichomoniasis and dysplasia or even cancer cannot coexist, and therefore if the diagnosis of atypia secondary to *Trichomonas* infection is made, a repeat smear should always be obtained after treatment of the infection to be sure that the cellular anomalies do not persist.

Marked inflammatory changes affecting both squamous and glandular cells may be attributed to the presence of an intrauterine device (IUD). The cellular atypias (see Chapter 4) are accompanied by a severe inflammatory reaction. The age of the patient and the presence of an IUD may help to make the correct diagnosis.[60–62]

Immunodeficiencies or immunodepressive drugs can favor the development of infections, particularly herpes simplex and human papillomavirus.[63]

Repair and Regeneration

Although not related to typical cervicitis, the cytologic changes encountered in repair and regeneration (Color Fig. 3-6) should be mentioned here. These changes are similar to those described earlier as typical of inflammatory changes in endocervical cells, and similarly may be difficult to differentiate from carcinoma. These cells vary in size, and their enlarged, irregular, slightly hyperchromatic nuclei reveal nucleolar hypertrophy. The vacuolated cytoplasm may be infiltrated with polymorphonuclear leukocytes. The absence of marked hyperchromatism and the persistence of cohesiveness between cells are in favor of the benign and metaplastic origin of the lesion. The etiology is a recent surgical proce-

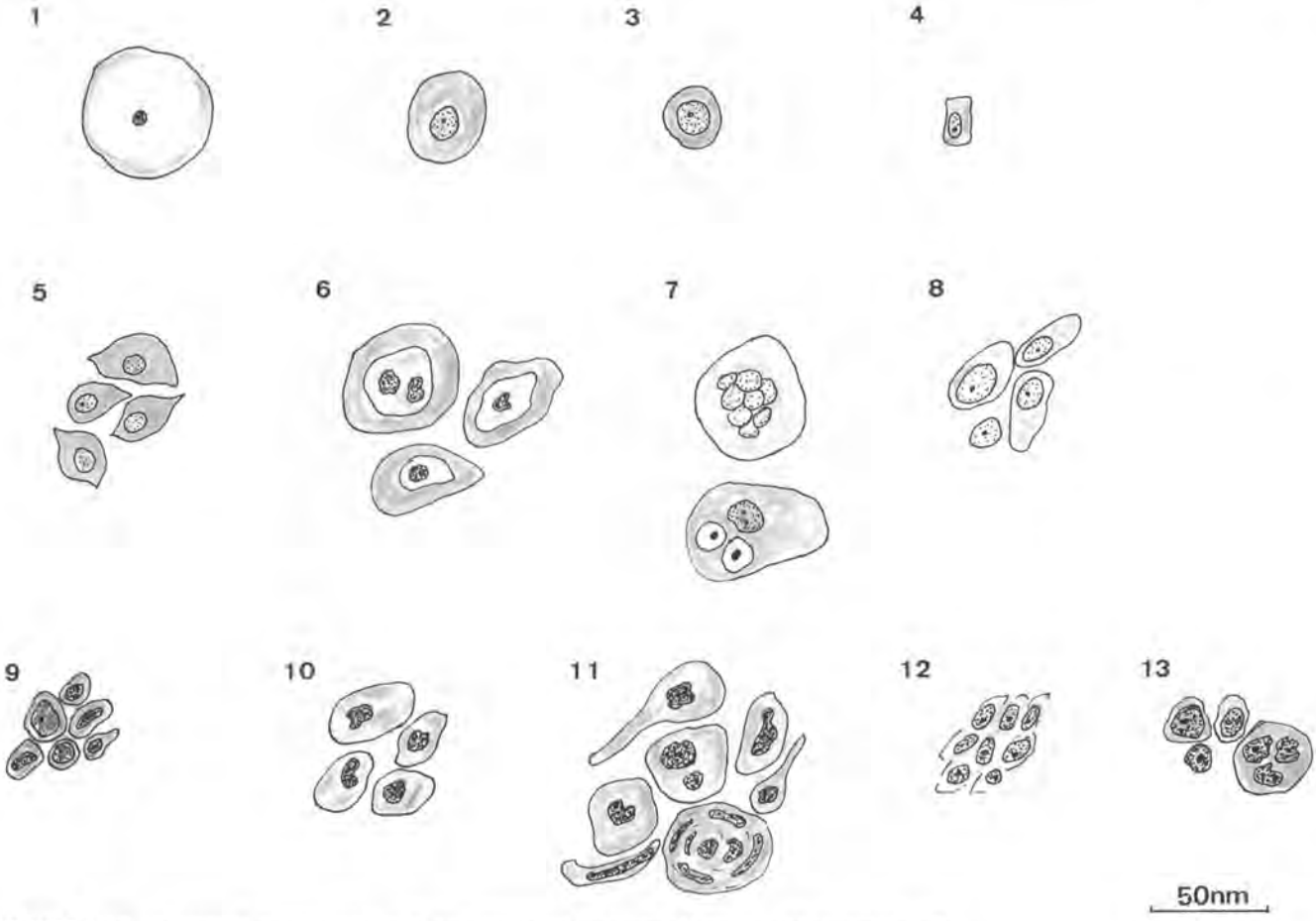


FIGURE 3-18 Schematic representation of cervicovaginal cytology: (1) superficial squamous cell; (2) intermediate squamous cell; (3) parabasal squamous cell; (4) columnar endocervical cell; (5) mature squamous metaplasia; (6) cytologic alterations compatible with human papillomavirus (koilocytes); (7) cytologic alterations compatible with *Herpesvirus* (multinucleate cell) and *Chlamydia* infection (cytoplasmic inclusions); (8) inflammatory benign changes of columnar endocervical cells; (9) CIN, small cell type; (10) CIN, intermediate cell type; (11) CIN, differentiated superficial type; (12) differentiated adenocarcinoma of endocervix; and (13) undifferentiated adenocarcinoma of endocervix.

dure rather than infection, although cautery, cryocoagulation diathermy, radiation therapy, and past infection may represent causal agents. Because of the diagnostic problems that these changes may pose, the history of prior surgery or irradiation should always be supplied by the clinician submitting a smear in such a case.

Squamous Metaplasia

In *squamous metaplasia*, parabasal-type cells are numerous in the smear. Many of these form clusters that are contiguous with endocervical cells, mimicking the close relation between these two cell types encountered in biopsy specimens. The metaplastic cells (Color Fig. 3-7) are larger than adjacent endocervical cells and have slightly enlarged nuclei and, frequently, well-developed intercellular bridges. One surface of the cluster of metaplastic cells is frequently flattened, suggesting that it arose in the endocervical canal. The cytoplasm may contain fine mucin vacuoles. Clusters of altered endocervical cells with marked vacuolated cytoplasm overlie the metaplastic zones, which contributes to their desquamation. The metaplastic cells occasionally show nuclear atypia that may range in degree from mild to severe (Fig. 3-19 and Color Fig. 3-8). The hyperchromatism, chromatin clumping, and nuclear irregularity of dysplasia are not present, however. If they are, and if the atypical metaplasia is severe, the diagnosis of a dysplasia arising in metaplastic epithelium should be suggested. Clusters of altered endocervical cells are often present; they have a vacuolated cytoplasm that pushes the nucleus to the periphery. The nuclei are regular, normochromatic, and moderately enlarged. Leukocytes infiltrate the cytoplasm and contribute to the existence of lytic phenomena. To summarize, all these cytologic anomalies can be classified into three main categories: immature, mature, and atypical metaplasia.

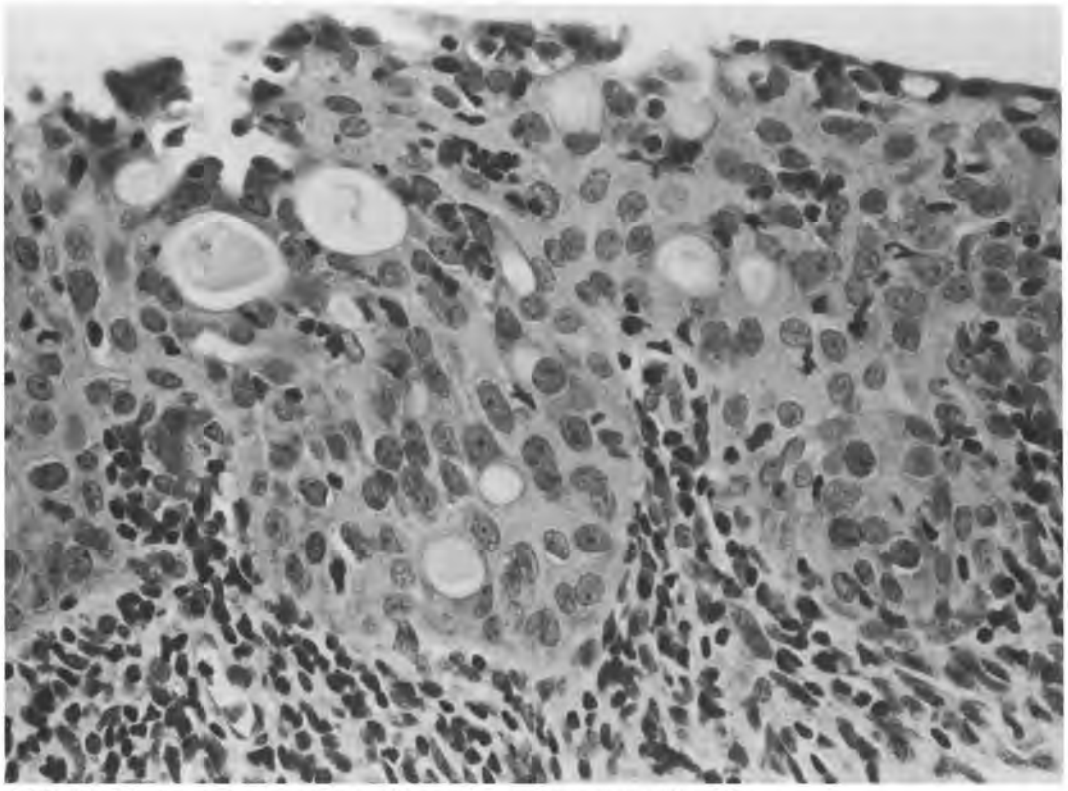


FIGURE 3-19 Squamous metaplasia with nuclear enlargement and moderate atypia.

Immature squamous metaplasia is characterized by the presence of elongated streaks of round, oval, or elongated cells with large, regular nuclei and a dense, predominantly cyanophilic cytoplasm. Nucleoli may be prominent. They have the size of parabasal or intermediate cells.

Mature squamous metaplasia is represented by larger cells, usually isolated, round, or elongated, with a lower nuclear–cytoplasmic ratio than that observed in immature metaplasia. The nuclei have a finely dispersed chromatin. The density of the cytoplasm is usually higher than in normal squamous cells and varies from one cell to another and in different areas of the same cell. One may note the presence of bipolar cells with a finely elongated cytoplasm at both ends of the cell.

Atypical metaplasia is characterized by the appearance of moderate cellular anomalies such as binucleation, nuclear enlargement, moderate hyperchromatism, and prominent nucleoli. Some disorder in the cellular arrangement is observable when large clusters are present.[64]

Specific Infections

Herpes Genitalis

This common viral infection is due to a DNA-containing poxvirus with a diameter of 150 nm, which is surrounded by a protein capsid. Viruses are located in the host cell nucleus and modify the cellular metabolism by inducing the synthesis of proteins necessary for the replication of viral DNA. Two types, herpes simplex viruses 1 and 2 (HSV-1 and HSV-2), are described; the distinction is based on serologic studies because they are morphologically identical. HSV-1 is responsible for lesions appearing in infancy and adolescence, and HSV-2 occurs predominantly after puberty. In pregnant women, the risk of transmitting the virus to the fetus is great, resulting in major fetal abnormalities and specific infections such as conjunctivitis.[65] It is also responsible for fetal mortality and abortion.

Cervicitis due to infection with herpes genitalis has acquired added importance because of the suggestion by different authors that this virus may play a role in the development of cervical carcinoma.[66–68]

Seroepidemiologic studies have demonstrated that patients with cervical cancer have a significantly higher incidence of neutralizing antibodies against HSV-2 and that patients with antibodies to HSV-2 are more susceptible to invasive cancer than women without such antibodies.[69,70] Prospective studies have confirmed these data; in patients with herpes genitalis, dysplasia is statistically more frequent than in control groups of patients.[71] These studies suggest that the viral infection precedes the development of dysplasia and carcinoma. In addition, cervical cancers have been induced in mice by local application of inactivated herpesvirus,[72] and the virus has been observed by electron microscopy in cervical carcinoma cells in tissue culture.[73] These data were chal-

lenged by other studies; Adam and colleagues[69] did not demonstrate an increase of HSV-2 antibody titers in cervical cancer patients. Vonka and associates[74] showed that the incidence of antibodies correlates with sexual behavior and socioeconomic status of patients rather than with the existence of neoplasia. Furthermore, in several studies cervical atypias preceded the herpetic infection more often than they followed it.[75,76] Thus, the data supporting the role of HSV-2 as a cervical carcinogen or cocarcinogen are intriguing but by no means conclusive.

Diagnosis. The diagnosis relies on cervical cultures, antibody serology, and clinical cytology. Herpetic cervicitis may be seen clinically as multiple, superficial, painful ulcers of the mucosa resulting from the transformation of papules and vesicles. The clinical lesions usually are more severe in the primary manifestation of the disease. In recurrent, even clinically silent, episodes, cellular alterations are observed in the biopsy or smear. The virus isolation is difficult and has to be done during the acute phase of the disease. After the first infection, the virus remains dormant in the sacral root ganglia of the spinal cord. *Histologically,* it is an ulcerative lesion with typical epithelial cell alterations. If a biopsy is obtained during the vesiculopapular phase, one may observe suprabasal intraepithelial vesicles. Some cells present in the vesicles exhibit intranuclear eosinophilic inclusions. The morphologic alterations caused by the virus are observed in squamous, endocervical columnar, and metaplastic cells.

Cytology. More frequently the disease is recognized by these same alterations in cytologic material if the smears are taken during the acute stage of the disease (2 to 3 weeks). The smears should be taken from the edge and bed of ulceration because the vesicular content is inflammatory and does not reveal typical cells. The cellular changes include (1) enlarged nuclei with homogenized, opaque, basophilic content ("ground glass" nuclei) corresponding to the massive presence of the virus; (2) large multinucleated cells characterized by internuclear molding and the existence of intranuclear eosinophilic inclusions surrounded by a clear halo; and (3) late degenerative phenomena expressed by hyperchromatic, large nuclear debris. The cytoplasm is dense, and degenerative vacuoles are often present.[49] Nucleoli are conspicuous and moderately enlarged. Ng and associates[77] have emphasized that the classic large eosinophilic nuclear viral inclusions are seen predominantly in recurrent infections, whereas primary infections are characterized by "ground glass" nuclei with unusually clear nucleoplasm (Fig. 3-20 and Color Fig. 3-9). These data were not confirmed by Vesterinen and colleagues.[78]

Multinucleation is not a specific image of HSV; it is also encountered in trophoblastic cells, in nonspecific giant cells observed in postmenopausal smears or in cervicitis, and in postsurgical foreign-body multinucleated giant cells. A case of measles cervicitis in a 20-year-old pregnant woman revealed in the Papanicolaou smear the presence of innumerable multinucleate superficial and intermediate cells and metaplastic elements.[79]

Human Papillomavirus

Molecular biology techniques have established that human papillomaviruses (HPV) are associated with a spectrum of genital lesions including condyloma acuminatum, flat condyloma, CIN, and invasive carcinoma.[80–84]

HPV is a heterogeneous group of DNA viruses, and at least 68 different types have been isolated using molecular hybridization and restriction enzymes analyses.[85,86] Among these, about 30 types have been identified in the lower female genital tract.[87,89]

Different data favor the role of HPV in the etiology of cervical neoplasia, but many aspects of this re-

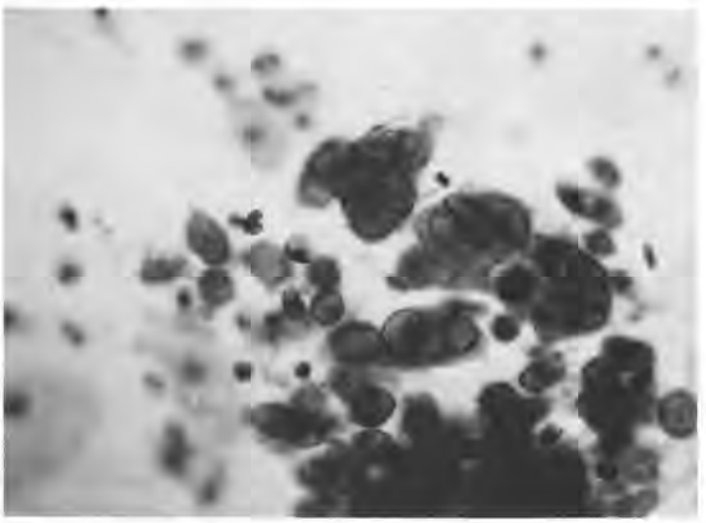


FIGURE 3-20 Herpetic cervicitis: appearance of cervical smear in primary infection, showing multinucleated cells with "ground glass" nuclei.

lation remain to be clarified. HPV antigens have been identified in tissue sections of CIN,[90–92] and HPV particles have been observed ultrastructurally in koilocytotic cells (Fig. 3-21).[92]

Human cervical cancer lines such as HeLa cells may contain HPV DNA.[93] Metastatic cervical cancer and the primary tumor may harbor the same HPV type.[94] HPV DNA can be integrated in the cell nuclear DNA in high-grade dysplasia and carcinoma. It is also frequently reported in immunodeficient patients (eg, patients with lymphomas, AIDS, or immunosuppressed organ transplants).

Condylomatous lesions seem to be a frequent disease of the cervix and may be detected frequently in adult women screened by cytology. Meisels and coworkers[95] estimate in retrospect that about 70% of their cervical dysplasias are related to condylomatous lesions, and condylomas may progress to dysplasia and carcinoma in situ. Different authors[85,96–100] have shown that high-grade intraepithelial neoplasms and invasive carcinoma of the cervix are mostly related to papillomavirus types 16, 18, 31, 33 and 35, whereas types 6 and 11 are associated with flat condyloma and low-grade intraepithelial neoplasia. This correlation is not constant, because high-risk types of viruses do not necessarily correspond to high-grade lesions and, on the contrary, lesions with HPV-6 and -11 occasionally may progress to carcinoma. This finding confirms the existence of at least two biologic subsets, one with a greater risk of progression to more severe forms of intraepithelial neoplasia and invasive carcinoma.[101,102]

Different findings should be mentioned to emphasize the need for additional studies before reaching a definite conclusion on the role of HPV in lower female genital tract oncogenesis.

1. About 10% of the female population harbors HPV, and more than 60% of this population has a normal Pap spear and no clinical lesion. The wide distribution of the HPV does not militate against its role in cervical oncogenesis, but it must be confirmed by more prospective epidemiologic studies.[103,104]
2. The correlation between the type of cervical lesion and the type of HPV present is not always as expected (see above).
3. The unpredictable evolution of CIN may be linked with the diversity of genital HPV types associated with the lesion.[84]
4. In a small percentage of case, HPV may have no role in the development of CIN.[105]
5. The correlation between the morphologic image and the presence of HPV is not constant; typical CIN images are not accompanied by HPV and vice versa.
6. Strict cytologic and histologic criteria should be used for the diagnosis of HPV infection to avoid overdiagnosis and subsequent overtreatment.

Colposcopy. The colposcope identifies four types of condylomatous lesions[45,46]:

1. The florid condyloma acuminatum is charac-

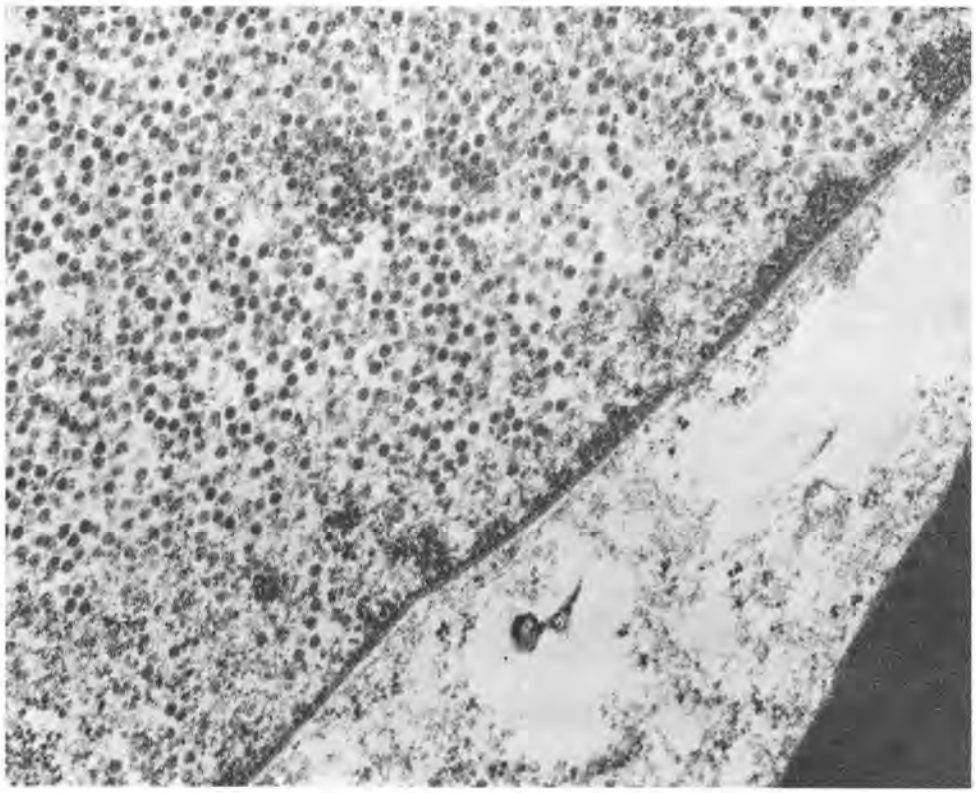


FIGURE 3-21 Electron micrograph of intranuclear papillomavirus particles in condyloma. (Courtesy of Drs. Bennett A. Jenson and Robert J. Kurman, Georgetown University Medical Center, Washington, DC)

terized by a white thickened epithelium with finger-like projections.
2. The spiked condyloma shows a white area with roughened peaks.
3. The flat condyloma reveals a flat, white lesion with a mosaic pattern, in which vessels are not apparent.
4. Condylomatous cervicitis or vaginitis shows a red epithelium with raised white dots and can be found alone or in association with flat condyloma.

Histopathology. Histologically, condyloma presents three main structural variations:

1. A papillary growth (*condyloma acuminatum*) is characterized by a papillomatous exophytic proliferation (Fig. 3-22). This type is more commonly seen on the external genitalia. The epithelium shows acanthosis, hyperkeratosis, parakeratosis, and cellular atypia.
2. A rare type, the *inverted condyloma,* shows a downward proliferation into the stroma (involving endocervical glands) and has often been confused with carcinoma (Fig. 3-23).
3. The most common type is the *flat condyloma,* which exhibits the same cellular atypias but lacks the papillomatous or inverting proliferation (Figs. 3-24 and 3-25). The terminology is actually contradictory, because condyloma means a focal raised lesion and not a flat structure. The term *noncondylomatous cervical HPV infection* is more correct, but it is difficult to change a denomination consecrated by daily usage.

The characteristic *cellular changes* present in all types of condyloma (see Figs. 3-24 and 3-25) are the existence of superficial and intermediate cells with (1) voluminous clear, glycogen-poor cytoplasm and (2) an irregular, hyperchromatic or pyknotic nucleus. The localization of the cytoplasmic organelles at the periphery of the cell creates the impression of a thickened cell membrane surrounding a perinuclear halo (*koilocytosis*). Ireland* has referred to the nuclei as "raisinoid," emphasizing their irregularly wrinkled appearance. Binucleate cells are common.[106] Parakeratosis is constant, and small peaks of superficial epithelium (perhaps abortive papillae) are seen even in the flat lesions.

The presence of HPV alterations in the intermediate and superficial cells and not in the parabasal layers can be explained by the fact that viral structural antigens are not synthesized in proliferating basal cells but occur in the differentiated cells, which are permissive for the synthesis of the structural proteins of the virus.

The simultaneous presence of condylomatous lesions in the superficial layers of the epithelium and dysplasia in the basal layers may shed some light on the development of *intraepithelial neoplasia* (see Figs. 3-48, 3-49 and 3-50). Hyperplasia of parabasal cells occurs beneath the areas of virus-induced atypias; this induced proliferation of the parabasal layers is susceptible to neoplastic transformation through the potentiating action of the viral agent. The morphologic manifestation of the viral infestation is not apparent in the parabasal cells that contain the viral genome; on the contrary, when the cells differentiate, they become permissive for synthesis of the viral structural proteins and their manifestations become apparent.

The failure to detect HPV antigens in more severe forms of dysplasia and carcinoma in situ can be interpreted as a disturbance in virus production when the neoplastic transformation has taken place or as a suppression of virus protein synthesis in cells that already show evidence of HPV infestation.[96]

Cytology. Cytologic examination is the routine technique for the detection of HPV infection in the genital tract: it is economical, convenient and rapid (Color Figs. 3-10 through 3-12).[106,107] Papanicolaou-stained smears reveal the presence of koilocytes. These elements are intermediate or superficial squamous cells and metaplastic-type cells from the transformation zone. Their nuclei are eccentrically located, hyperchromatic, enlarged, irregular, and wrinkled, or small and dense, and surrounded by a clear cytoplasmic halo, which is itself surrounded by peripheral dense blue-green or fuchsia-red cytoplasm. This staining is very different from the normal orangeophilia. This zone corresponds to cytoplasmic necrosis. Binucleation or multinucleation is common. The degree of nuclear abnormality varies from mild to marked. Phagocytosed material may be present in the clear space. These cells constitute small aggregates or are isolated. In early stages of the viral infection, one may observe clumps of rounded and blunt cells with dense and opaque cytoplasm representing the first morphologic alterations. Dyskaryotic cells are present and characterized by a yellow or orangeophilic cytoplasm and a small, dense nucleus without prominent nucleoli. Metaplastic-type immature cells from the transformation zone reveal the same alteration: nuclear enlargement, moderate hyperchromatism, bi- or multinucleation, and peripherally condensed cyanophilic cytoplasm. Columnar endocervical cells do not reveal specific changes. According to these descriptions, the koilocyte is a dyskaryotic cell with a very typical perinuclear halo. These various cellular alterations, described by Koss and Durfee[108] under the term *koilocytosis,* had been called *nearo-carcinoma* by Ayre[109] and *balloon cells* by Meisels and Fortin.[106] These authors had guessed the viral origin of the cellular alterations.

Natural History and Prognosis. The natural history and prognosis of cervical HPV infection are still

(*Text continued on page 94.*)

*Ireland: Personal communication.

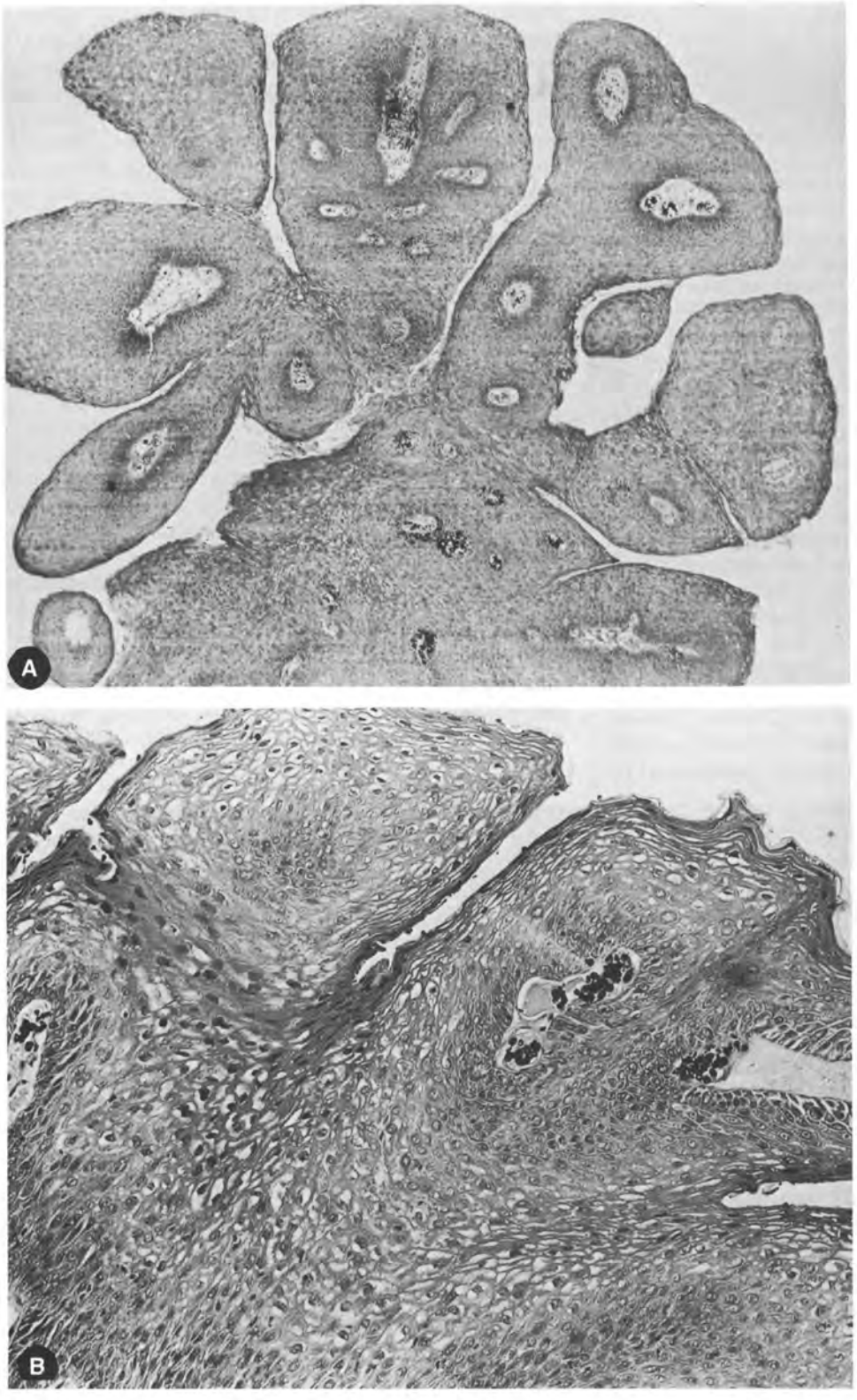


FIGURE 3-22 Condyloma acuminatum of cervix. **(A)** Low-power view of papillary growth pattern. **(B)** Detail showing koilocytotic atypia.

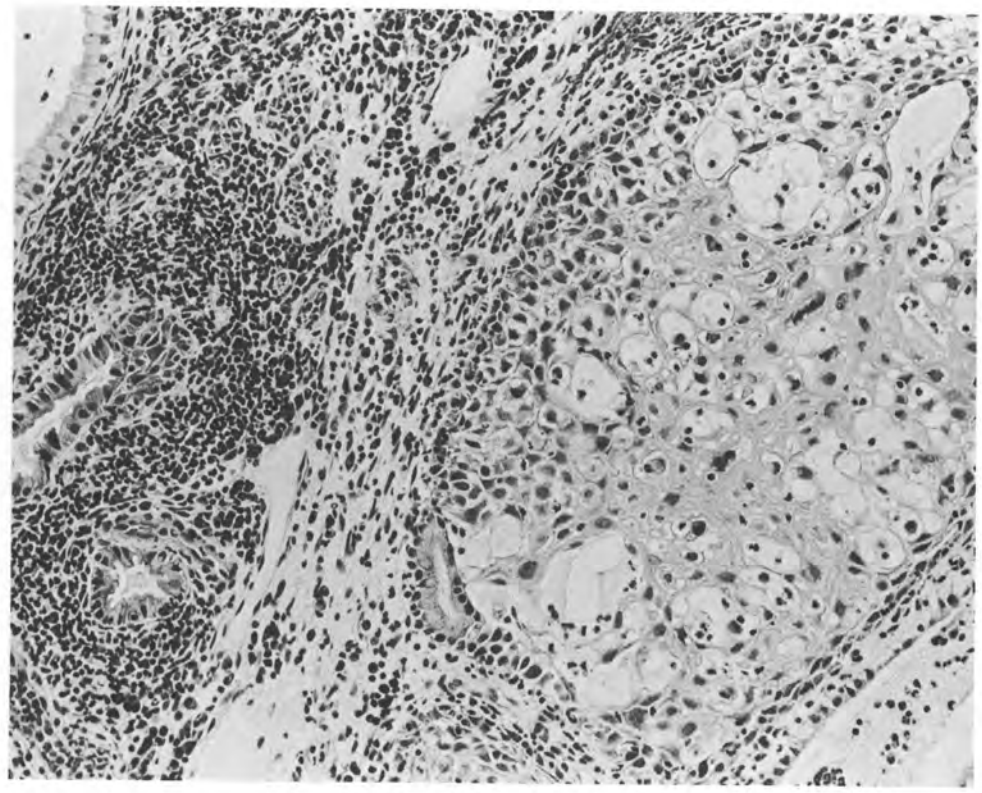


FIGURE 3-23 Inverted condyloma involving endocervical gland.

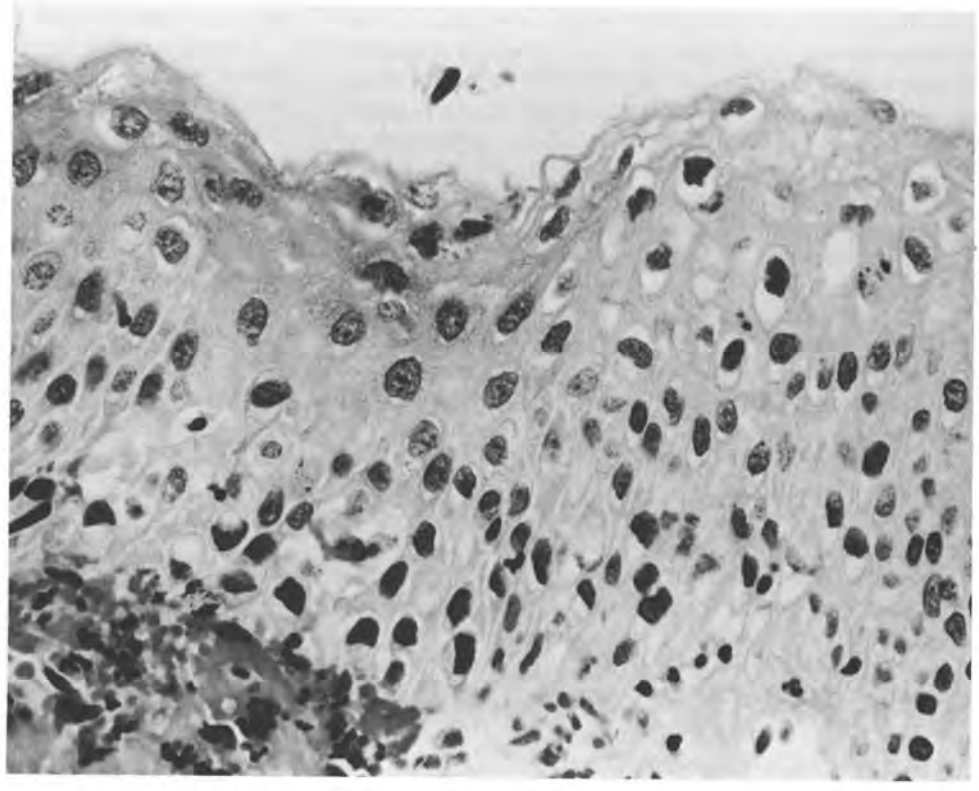


FIGURE 3-24 Flat condyloma showing peaks of surface epithelium and typical cellular manifestations.

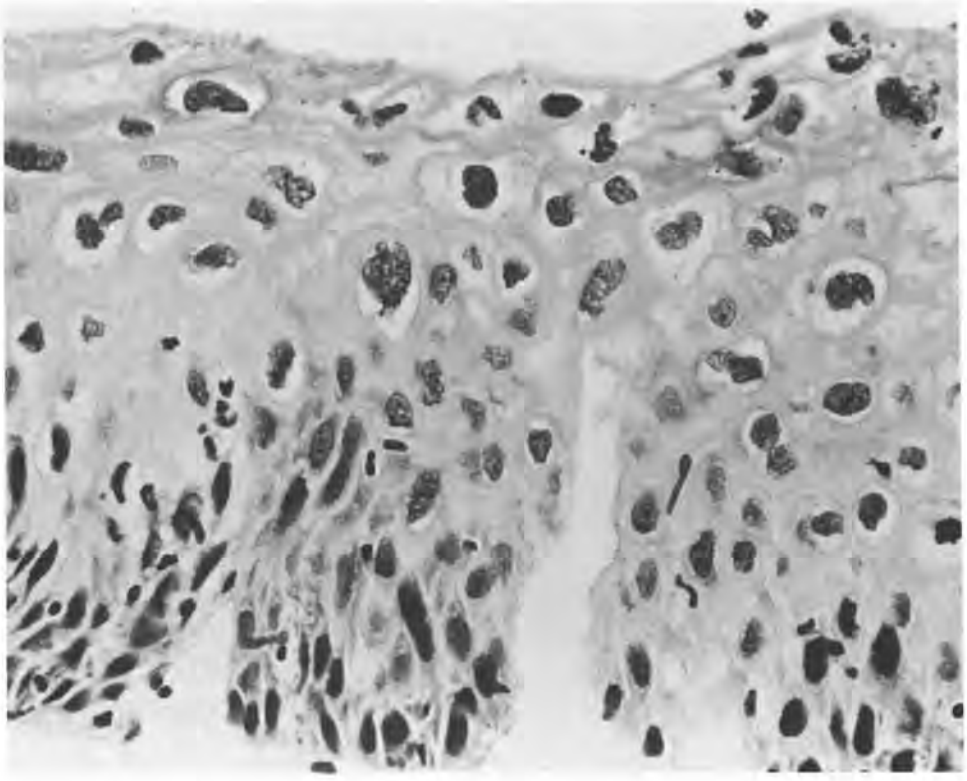


FIGURE 3-25 Flat condyloma demonstrating "raisinoid" nuclei and perinuclear haloes.

poorly understood. One would expect condylomatous lesions unassociated with classic dysplasia or carcinoma in situ to be less likely to progress to cancer if untreated, but this has not been demonstrated adequately. The specific antigenic type of HPV (particularly types 16 and 18) and the presence of aneuploid cells may portend progression, but most laboratories cannot routinely perform the studies necessary to yield these data. Dysplasia may be seen directly beneath the superficial layers showing condylomatous manifestations, immediately adjacent to the condylomatous lesion, or at some distance from it in the same or a different biopsy specimen. Because the clinical significance of these different patterns is not clearly understood, it is recommended that the treatment and follow-up of the "pure" cervical condyloma be the same as for cervical dysplasia at the present time.[110,111]

This story is not at all complete, and more correlative histologic and virologic analysis, further characterization of HPV types, and prospective studies of low-grade CIN lesions are needed before the exact role of HPV will be determined. At present, cytology is the most practical method to detect virus-associated cellular abnormalities.

Trichomonas Cervicitis

It has been estimated that as many as 20% to 25% of adult women harbor the parasite *Trichomonas vaginalis* in the lower genital tract, although many of these women are asymptomatic. Inflammatory reactions due to *Trichomonas* are characteristically intermittent and difficult to treat.

Histologically, cervical vascular congestion is followed by edema, cellular inflammatory infiltrates, and ulceration of the squamous mucosa (Fig. 3-26). This picture is nonspecific unless the parasite is identified, usually in cervicovaginal smears (see discussion above and in Chap. 2). When the infection is severe, one may observe reserve cell hyperplasia, squamous metaplasia, and superficial papillomatosis of columnar cells. Patients with *Trichomonas* infections often have notable epithelial atypia in cytologic material, which should regress after treatment of the infection (see Chap. 2). Cervical cancer and precancerous states are also more frequent in women with trichomoniasis, probably coincidentally rather than causally.[112–115]

Chlamydial Cervicitis

Chlamydial cervicitis is a common sexually transmitted disease often restricted to the cervix and the urethra.[116–118] The organism may be responsible for other infections such as endometritis, salpingitis, trachoma, and lymphogranuloma venereum. Contamination of the neonate during delivery may cause conjunctivitis and pneumonia.

The cervical infection is asymptomatic or clinically associated with a mucopurulent endocervical discharge.[119] It has been reported that *Chlamydia trachomatis* infection may produce follicular cervicitis.[47,120]

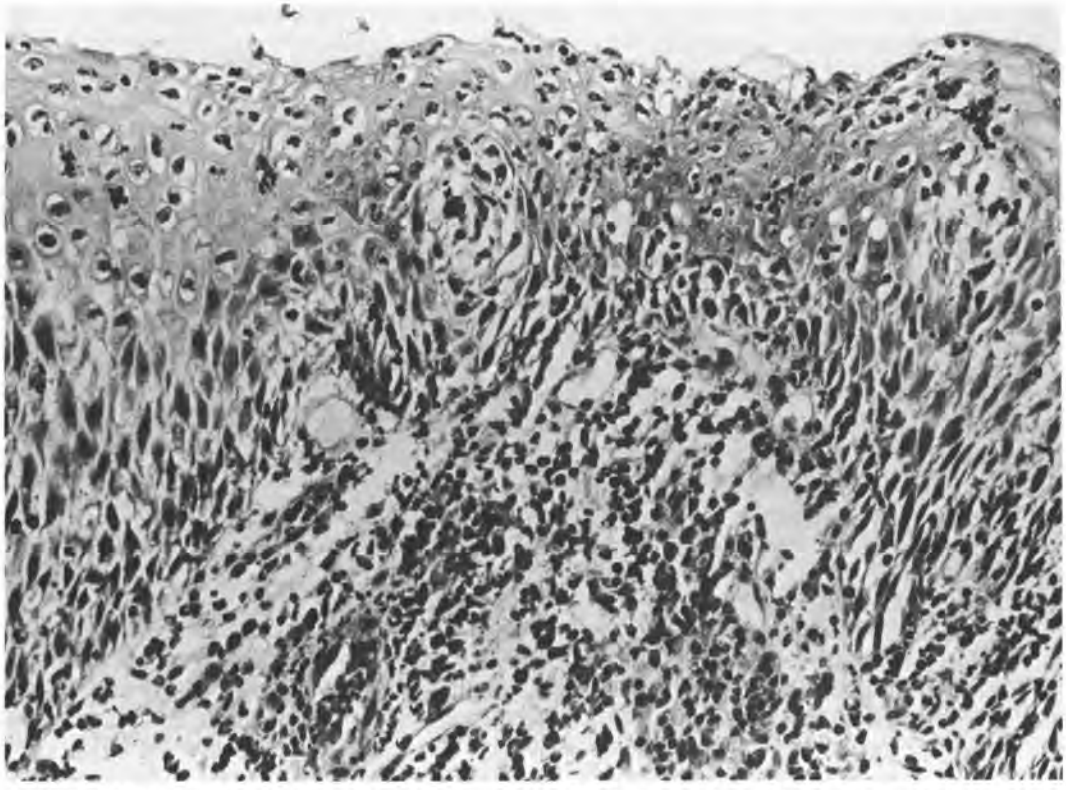


FIGURE 3-26 *Trichomonas* cervicitis, with acute and chronic inflammation and reactive atypia of squamous mucosa.

The organisms, which measure about 300 nm, enter squamous metaplastic and endocervical columnar cells, multiply, and constitute intracytoplasmic inclusions. After lysis of the cell, the elementary bodies are free and enter new cells.

Electron microscopy has confirmed that the cytoplasmic vesicles contain several morphologic forms (elementary bodies, reticulate bodies, and intermediate forms) typical of *Chlamydia*.[121] These obligate intracellular organisms are classified as bacteria. *Histologically*, chlamydial cervicitis consists of a chronic inflammatory infiltrate with macrophages, plasma cells, lymphocytes, neutrophils, and eosinophils.

Cytology. The elementary bodies cannot be identified in Papanicolaou-stained smears, but the presence of intracytoplasmic aggregates of elementary bodies produces cellular changes that can be observed microscopically.[122–128] First, numerous, small vacuolated structures are present in the cytoplasm, suggesting a "moth-eaten" appearance. Dot-like structures occupy these vacuoles. Later, these aggregates condense and develop the distinct intracytoplasmic inclusion underlined by a well-defined wall (Color Fig. 3-13). Multinucleation is common. The typical cytoplasmic inclusions are not always present, and therefore the diagnosis is based on tissue culture and immunodiagnosis.[129]

Cervical Tuberculosis

Cervical tuberculosis represents only 1% of cases of genital tuberculosis and is secondary to tuberculous endometritis and salpingitis. Several observations have revealed the simultaneous presence of cervical tuberculosis and epidermoid carcinoma, although no etiologic relation has been established.[130–132]

Macroscopic Appearance. The cervix is proliferative, irregular, and sometimes ulcerated, and suggests the existence of a malignant tumor. Examination of the biopsy makes the diagnosis, but it should be confirmed by culture of *Mycobacterium tuberculosis.*

Histology. The lesion is a typical tuberculous granuloma; epithelioid cells and Langhans' giant cells surrounded by lymphocytes, with little or much central caseation.

Cytology. Cytology of tuberculosis includes the presence of clusters of epithelioid cells, lymphocytes, and huge multinucleated giant cells. If all these components are present, the diagnosis of tuberculosis can be suspected. This eventuality is rare, especially in the regions of the world where tuberculosis has been treated effectively. The epithelioid cells form aggregates of large, pale, cyanophilic, irregular cells

with oval, vesicular nuclei. The multinucleated giant cells have numerous, peripherally located small nuclei.[133–135]

Other Granulomatous Lesions

Other granulomatous lesions that can involve the cervix are the *foreign body giant cell granuloma* secondary to a previous surgical procedure and *schistosomiasis* (bilharziasis). Schistosomiasis is characterized microscopically by multinucleate giant cell granulomas surrounding the eggs with their characteristic spines.[136,137]

A case of *ceroid granuloma* been described in the cervix.[138] The cervical biopsy revealed an ulcerated granulomatous lesion of the epithelium with macrophages containing ceroid pigment. A tampon-related etiology has been suggested. Protozoa uncommonly observed in cervical smears are *Entamoeba histolytica* and *Vorticella.*[139,140]

Langerhans cell histiocytosis of the lower genital tract is a rare disease thought to represent a disorder of immune regulation; a few cases have been described involving the cervix.[141] Microscopy reveals a cellular granulomatous infiltrate composed almost exclusively of proliferating Langerhans cells with associated inflammatory cells. Immunohistochemically, these cells express S-100 protein. Elongated Birbeck granules are visible at the electron microscopic level.

Cervical Syphilis

Next to vulvar chancre, cervical chancre is most frequent in the female genital tract.[142] The lesion may be confused with a simple cervical erosion. In the great majority of cases, it is situated at the circumference of the external os. The chancre presents in one of two forms: (1) an ulcer with indurated base and elevated borders, surrounded by a zone of edema, or (2) a simple nonindurated erosion covered by a gray membranous exudate. Search for the treponeme is mandatory in all doubtful lesions; its demonstration permits the differential diagnosis from granuloma inguinale, acute gonorrhea, chancroid, and carcinoma.

Secondary papular lesions of the cervix have been described rarely, and tertiary lesions are very rare. Chapter 1 provides a microscopic description of these lesions.

Other Specific Infections

Other rare specific infections are occasionally seen. *Cytomegalovirus,*[143–146] which belongs to the herpesvirus group, is serologically common, but clinical manifestations are rare. It may be associated with herpesvirus and HPV. In cervical smears, columnar cells are more frequently affected and contain round, large intranuclear inclusions surrounded by a clear halo (Fig. 3-27). Cervical *actinomycosis* has been

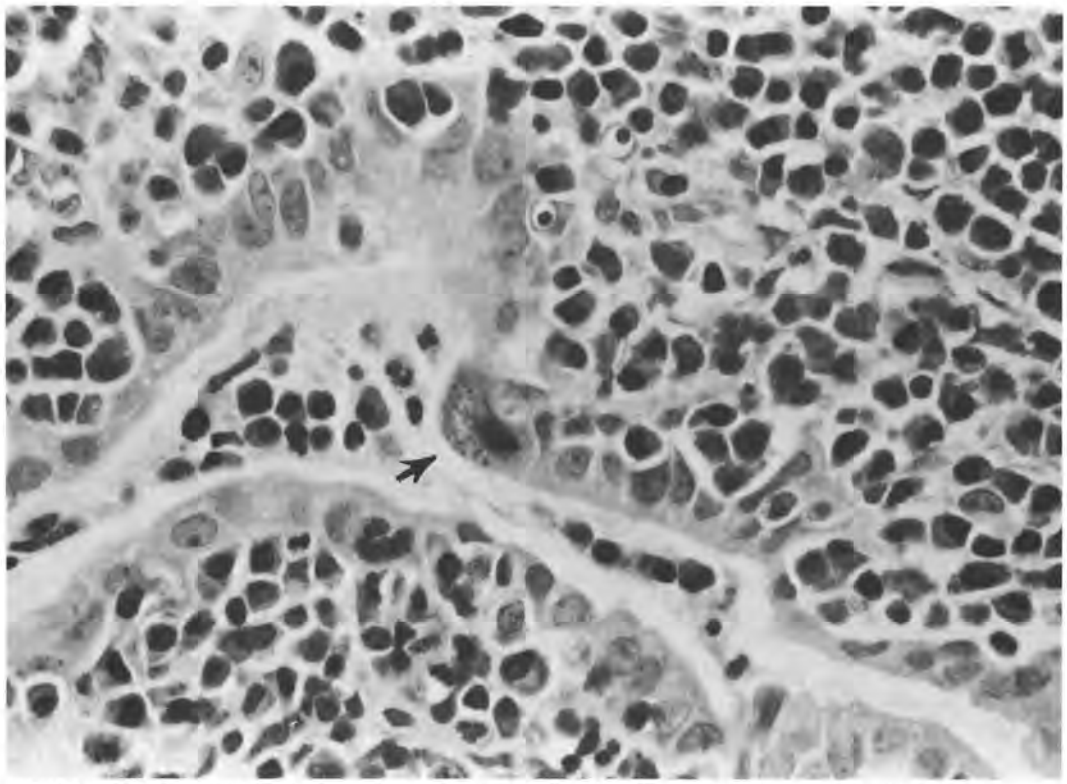


FIGURE 3-27 Cytomegalovirus cervicitis: endocervical cell with nuclear and cytoplasmic inclusions (*arrow*).

reported.[147] The typical filaments and peripheral palisading clubs are easily recognized. Some cases have been associated with use of intrauterine contraceptive devices.[148,149] Rare cases of *giant cell arteritis* limited to the cervix have been described.[150–152] These seem to be incidental findings of no clinical importance. The nematode *Ascaris lumbricoides* has been mentioned in cervicovaginal smears,[139,153] as have microfilariae.[154]

BENIGN TUMORS AND TUMOR-LIKE LESIONS

Endocervical Polyp

The cervical polyp is a pedunculated tumorous formation developing at the surface of the cervix. It is considered a hyperplastic phenomenon of the epithelium and stroma rather than a true neoplasm. It is sometimes accompanied by small hemorrhages, either spontaneous or on contact, and by leukorrhea, but most often it is asymptomatic. It is more common in middle-aged women and multigravidas.

Macroscopic Appearance. The cervical polyp presents as a single small spherical mass that herniates at the level of the cervical orifice and usually measures several millimeters in diameter. It is usually attached to the cervical wall by a short stalk but is occasionally sessile. The surface is smooth, shiny, and pale pink, or granular, lobulated, and dark red (Fig. 3-28). Signs of secondary infection are frequent. More rarely, the lesion actually may be an endometrial polyp attached by a long stalk to the isthmus or to the corporeal mucosa and exteriorized at the cervical orifice.

Microscopic Appearance. The cervical polyp is covered by a glandular epithelium showing frequent foci of squamous metaplasia (Fig. 3-29). It contains a loose, edematous, richly vascularized connective tissue stroma, infiltrated by inflammatory cells of predominantly lymphoplasmacytic type. This inflammatory infiltrate is found in 80% of cases; it is more marked in the presence of ulceration of the surface epithelium. Highly vascularized polyps are occasionally encountered. The development of dysplasia and in situ or invasive carcinoma in a polyp occurs in less than 1% of cases.[155] In a case with malignant change, it is important to verify the integrity of the base of the stalk at the implantation site. Another possibility is the secondary invasion of the polyp by an adjacent carcinoma. A small number of polyps contain in their stroma large, clear cells with foamy cytoplasm containing lipids; their significance is not known.[156] Bizarre stromal cells with hyperchromatic nuclei may be encountered rarely in pseudosarcomatous

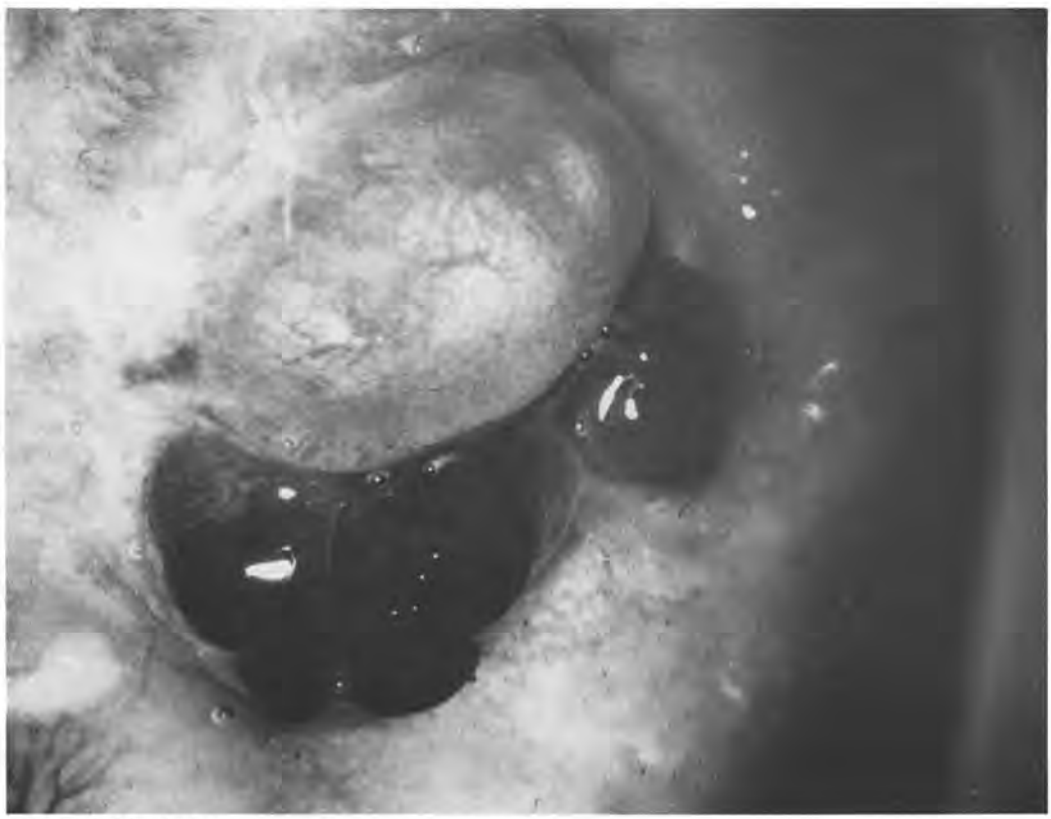


FIGURE 3-28 Endocervical polyp: clinical appearance.

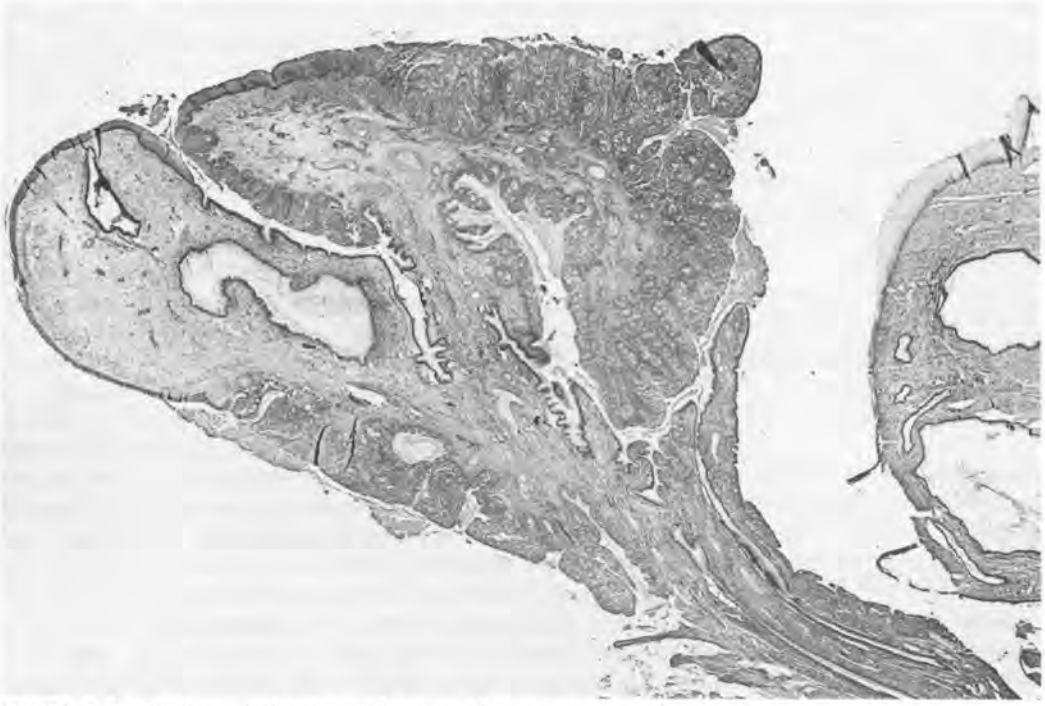


FIGURE 3-29 Endocervical polyp with zones of squamous metaplasia.

botryoid polyp of the cervix. Decidual reaction is encountered in some pregnancies (decidual polyp).[37–40,157]

Cytology. The cervical smear may reveal inflammatory or dysplastic lesions of the epithelium lining the polyp. Eroded areas are the origin of repair changes (see above). Abundant aggregates of columnar cells are present when a direct scraping of the polyp is obtained. Numerous endocervical columnar cells showing no cellular atypia and accompanied by abundant inflammatory cells may suggest the existence of a polyp.

Squamous Papilloma

The squamous papilloma is a polypoid formation covered by a papillomatous squamous epithelium beneath which is a richly vascularized stroma.[158,159] It is a rare tumor, usually encountered during pregnancy, which represents less than 1% of the benign tumors of the cervix. Chronic inflammatory conditions such as gonorrhea, tuberculosis, and viral infections are said to favor its appearance, but this notion demands confirmation. The evolution of these lesions is benign, and excision is curative.

Macroscopic Appearance. The tumor has the form of an ectocervical polyp and is several millimeters in diameter.

Microscopic Appearance. The covering squamous epithelium shows papillomatosis, hyperkeratosis, acanthosis, and parakeratosis. Mitoses are infrequent. The stroma is richly vascularized and contains a chronic inflammatory infiltrate. Benign epithelial atypia or (rarely) in situ or invasive carcinoma may develop in the epithelium.[160,161] *Condyloma acuminatum* is a particular, usually multiple, very exuberant type of squamous papilloma. This and other papillomavirus-induced lesions are discussed earlier in the chapter.

Leiomyoma

The leiomyoma is a single spherical or nodular tumor consisting of smooth muscle fibers and fibrous connective tissue (Fig. 3-30). It is a relatively infrequent tumor in the cervix and represents less than 10% of all uterine myomas.[162] It may be immense and either encapsulated or diffuse. It is often associated with leiomyomata of the corpus uteri and resembles them histologically. Different forms of degeneration identical to those observed in leiomyomas of the corpus may occur. Malignant transformation is rare.[51] The vascular leiomyoma is an association of a leiomyomatous growth with abundant, disseminated, thick-walled vessels.

Glandular Hyperplasias and Metaplasias

A number of benign endocervical glandular proliferative lesions lacking cytologic atypia or premalignant significance have been described. Their main clinical

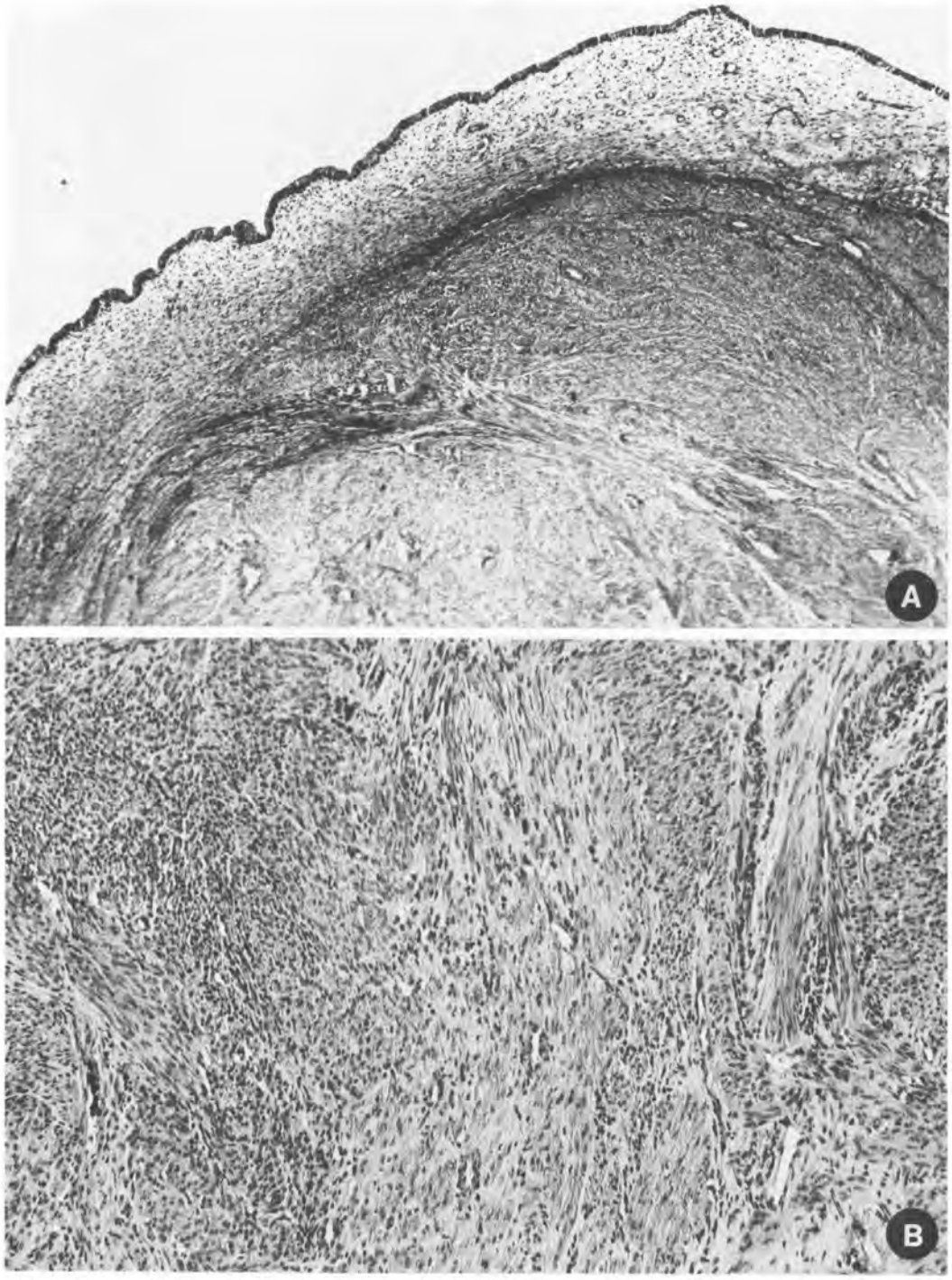


FIGURE 3-30 Submucosal leiomyoma of cervix. **(A)** General appearance. **(B)** Detail.

importance lies in the occasional tendency of the inexperienced pathologist to misinterpret them as adenocarcinoma.

Tunnel Clusters

Tunnel clusters,[51,163] sometimes referred to as *adenomatous hyperplasia*,[163,164] are characterized by the presence of groups of endocervical glands, often cystic, with columnar, cuboidal, or flattened epithelium (Fig. 3-31). These glands contain mucus and are surrounded by a fibrous stroma disposed in concentric layers. The lesions are situated in the endocervix and may extend the entire length of this portion but rarely involve the ectocervix. They lack glandular angularity and a surrounding inflammatory stromal response, differentiating them from minimal deviation adenocarcinoma.

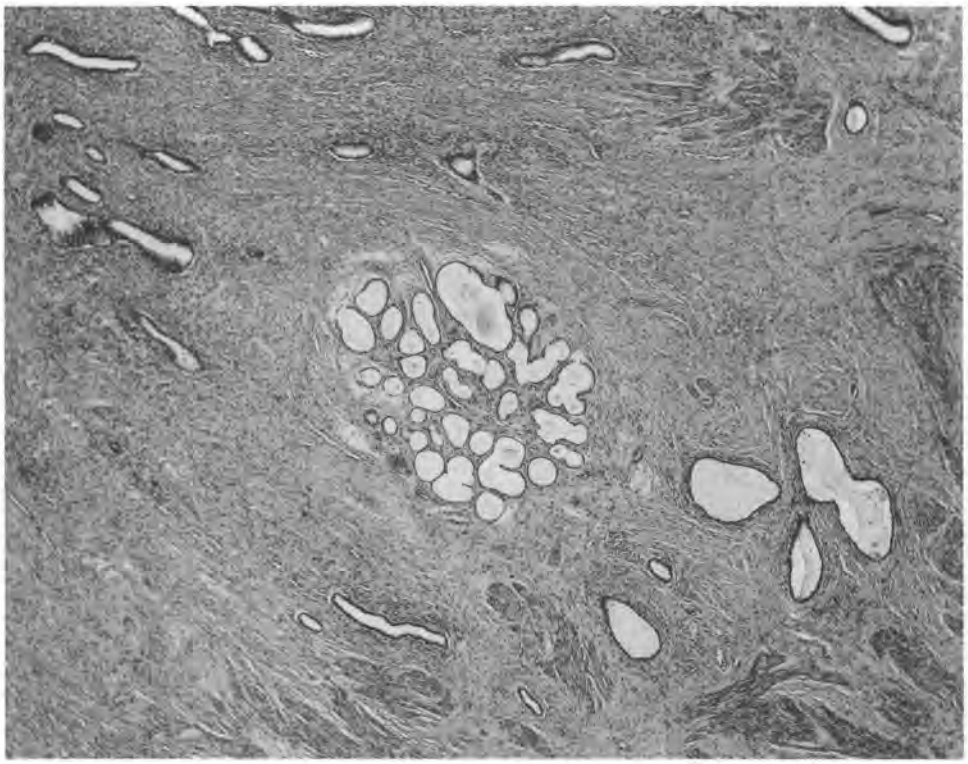


FIGURE 3-31 Tunnel cluster of endocervix.

Microglandular Hyperplasia

Frequently seen in women taking oral progestational agents for contraception and in pregnant and postpartum women is a lesion known as *microglandular hyperplasia* (MGH; Fig. 3-32).[165–167] *Clinically,* it may simulate an endocervical polyp or occur in the endocervical clefts and present no evident macroscopic lesion.

Microscopically, MGH shows numerous irregular glandular structures disposed in a dense or reticulated pattern and lined by hyperplastic cuboidal cells. Small glands containing intraluminal mucin and neutrophils fuse to form larger cystic spaces. The glands often appear continuous with the surrounding stroma, and two or more adjacent glands share "party walls," being lined by the same single layer of cells. The presence of subcolumnar reserve cells and squamous metaplasia is often observed. Mitoses are very rare. The stroma is loose and edematous and shows vascular congestion, multiplication of vessels, and leukocytic infiltration that is predominantly lymphoplasmacytic.

The benign character of the lesion is emphasized by the uniformity of the cells (which often contain subnuclear vacuoles), the absence of stromal invasion, the generally absent mitotic activity, and the clinical history. Immunohistochemically, there is no reaction for carcinoembryonic antigen (CEA), which helps in the differential diagnosis with adenocarcinoma.[168,169] Leslie and Silverberg[166] have emphasized that rare atypical cases may be encountered, by virtue of cytologic atypia (Fig. 3-33) or an unusual clinical presentation (eg, in a postmenopausal woman or in the endometrium). Their schema for differential diagnosis from adenocarcinoma of endocervix and endometrium is reproduced in Table 3-2. Rare cases of endometrial or endocervical adenocarcinoma may present with an MGH-like picture in a curettage or biopsy specimen.[166,170] Thus, the differential diagnosis may be confusing in both directions.

Deep Nabothian Cysts

Nabothian cysts (see Fig. 3-12) have been described above as part of the picture of chronic cervicitis. These generally are located immediately beneath the endocervical or metaplastic surface epithelium, but occasionally they can be found deep in the cervical wall, where they may be confused with a type of adenocarcinoma known as *minimal deviation adenocarcinoma.*[171] The uniform round contours and cystic dilatation of the nabothian cysts and the absence of a stromal reaction around them should prevent this error.

Diffuse Laminar Endocervical Glandular Hyperplasia

Jones and colleagues[172] have described this lesion as an incidental finding in specimens from hysterectomies performed for other indications. It consists of a glandular proliferation confined to the inner third of the cervical wall and sharply demarcated from the underlying stroma. The glands are of moderate size, evenly and closely spaced, and highly differentiated.

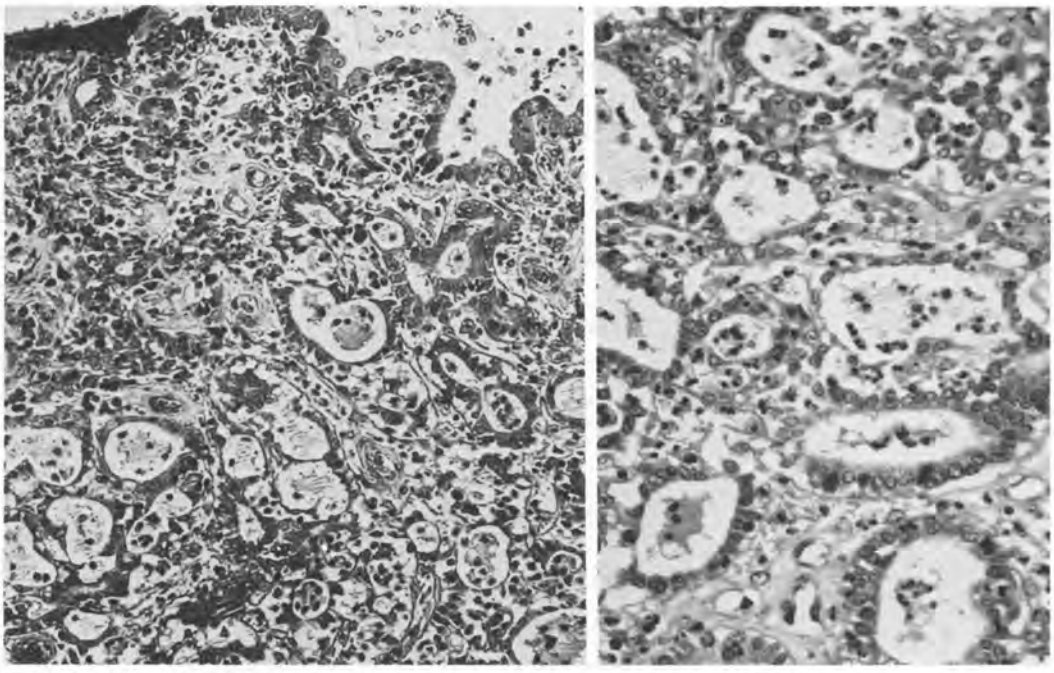


FIGURE 3-32 Microglandular hyperplasia in woman receiving oral contraceptives: general appearance (*left*) and detail (*right*).

Marked inflammation and reactive atypia may be present. The absence of irregular and deep stromal infiltration and of a desmoplastic stromal response help in the differential diagnosis from minimal deviation adenocarcinoma.

Glandular Metaplasias

In addition to the ubiquitous squamous metaplasia, endocervical glands can also undergo *intestinal, endometrial*, and *tubal metaplasia*. Intestinal metaplasia is predominantly encountered in neoplastic (in situ or invasive) glandular epithelia. Endometrial metaplasia is uncommon, and by definition must be located distal to the endometrial-endocervical junction and be unassociated with endometrial stroma (endometriosis). Tubal metaplasia[173,174] is the most common of these conditions, occurring in 31% of hysterectomy specimens in one recent series, and even more frequently in cases from which many tissue blocks were submitted for microscopic examination.[174] In this lesion, the surface epithelium, glands, or both are lined focally by a pseudostratified epithelium containing all three cell types (ciliated, secretory, and in-

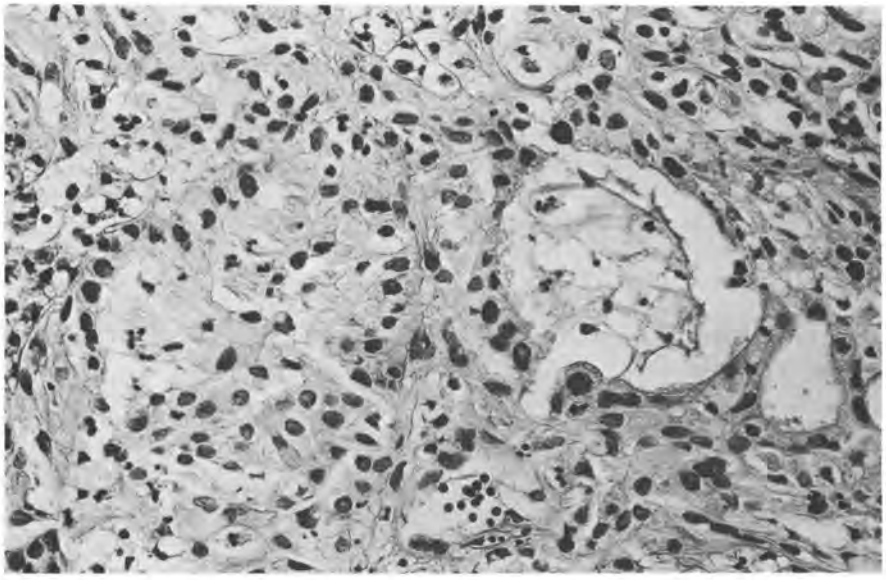


FIGURE 3-33 Microglandular hyperplasia of cervix with focal nuclear atypia. (Leslie KO, Silverberg SG: Microglandular hyperplasia of the cervix: Unusual clinical and pathological presentations and their differential diagnosis. Prog Surg Pathol 5:95–114, 1984)

TABLE 3-2.
Differential Diagnosis of Microglandular Hyperplasia from Endocervical and Endometrial Adenocarcinoma

	Microglandular Hyperplasia	***Endocervical Adenocarcinoma***	***Endometrial Adenocarcinoma***
Age	Predominantly young	Usually over 40	Usually over 40
Menstrual status	Predominantly premenopausal, frequently pregnant	40% premenopausal	Predominantly postmenopausal
Constitution	No special characteristics	No special characteristics	Obese, hypertensive, diabetic, nulliparous
Hormone usage	Oral contraceptive therapy (predominantly progestational effect)	Oral contraceptive therapy?	Estrogen effect
Atypia	Rare (inflammatory)	Characteristically present	Characteristically present
Mitoses	Extremely rare	Characteristically present	Characteristically present (numerous)
Architecture	Central core of glands with peripheral stromal pseudoinfiltration. Glands share "party walls." No true cribriform areas	Usually little cribriform pattern. Glands separated by scirrhous or edematous stroma	Diffuse stromal infiltration by glands. Solid sheets of cells may be central (morules), peripheral, or both. Glands "independent" except in cribriform areas
Inflammatory cells	Always present; within glands, glandular epithelium, and stroma	May be absent or inconspicuous without necrosis	May be absent or inconspicuous without necrosis
Mucin	Present in gland lumina, not in cells or stroma	Voluminous mucin in cells and gland lumina	Generally not prominent; when present, mainly apical and intraluminal
Squamous metaplasia	Characteristically present	Uncommon	Present in up to 50% of cases—squamous element frequently histologically malignant
Tissue CEA	Uniformly negative	Usually positive	Usually negative

Leslie KO, Silverberg SG: Microglandular hyperplasia of the cervix: Unusual clinical and pathological presentations and their differential diagnosis. Prog Surg Pathol 5:95–114, 1984

tercalated) seen in the normal fallopian tube. The main significance of this lesion is its potential confusion with adenocarcinoma in situ histologically or with any glandular neoplasia cytologically. The observation of ciliated cells should lead to the correct diagnosis. Tubal metaplasia is illustrated in this chapter in the section on adenocarcinoma in situ (see Fig. 3-80).

Mesonephric Remnants, Cysts, and Hyperplasias

Mesonephric remnants or rests in the cervix are a common incidental finding.[175] They are situated deep in the substance of the lateral walls of the endocervix and are lined by cuboidal epithelium. There is no secretion of mucus or glycogen and no ciliation. The histologic distinction between deep endocervical glands, especially malignant ones, and mesonephric rests is important to make.[28,176] Most important is the nonciliated and nonmuciparous nature of the mesonephric epithelium and the usual presence of a central slit-like duct from which the small glands radiate (Fig. 3-34). Dense eosinophilic material in the gland lumina is also characteristic. Ferry and Scully[28] have proposed a classification and a definition of the mesonephric lesions that should avert misdiagnosis (Table 3-3). These lesions, with the exception of mesonephric remnants, are rare, with mesonephric carcinoma being the rarest.

Papillary Adenofibroma

Papillary adenofibroma is a rare lesion. First delineated by Abell,[177] it is characterized by a lobulated and papillary configuration, with flattened endocervical epithelium covering a compact or loose solid growth of small, uniform fibroblasts (Fig. 3-35). No

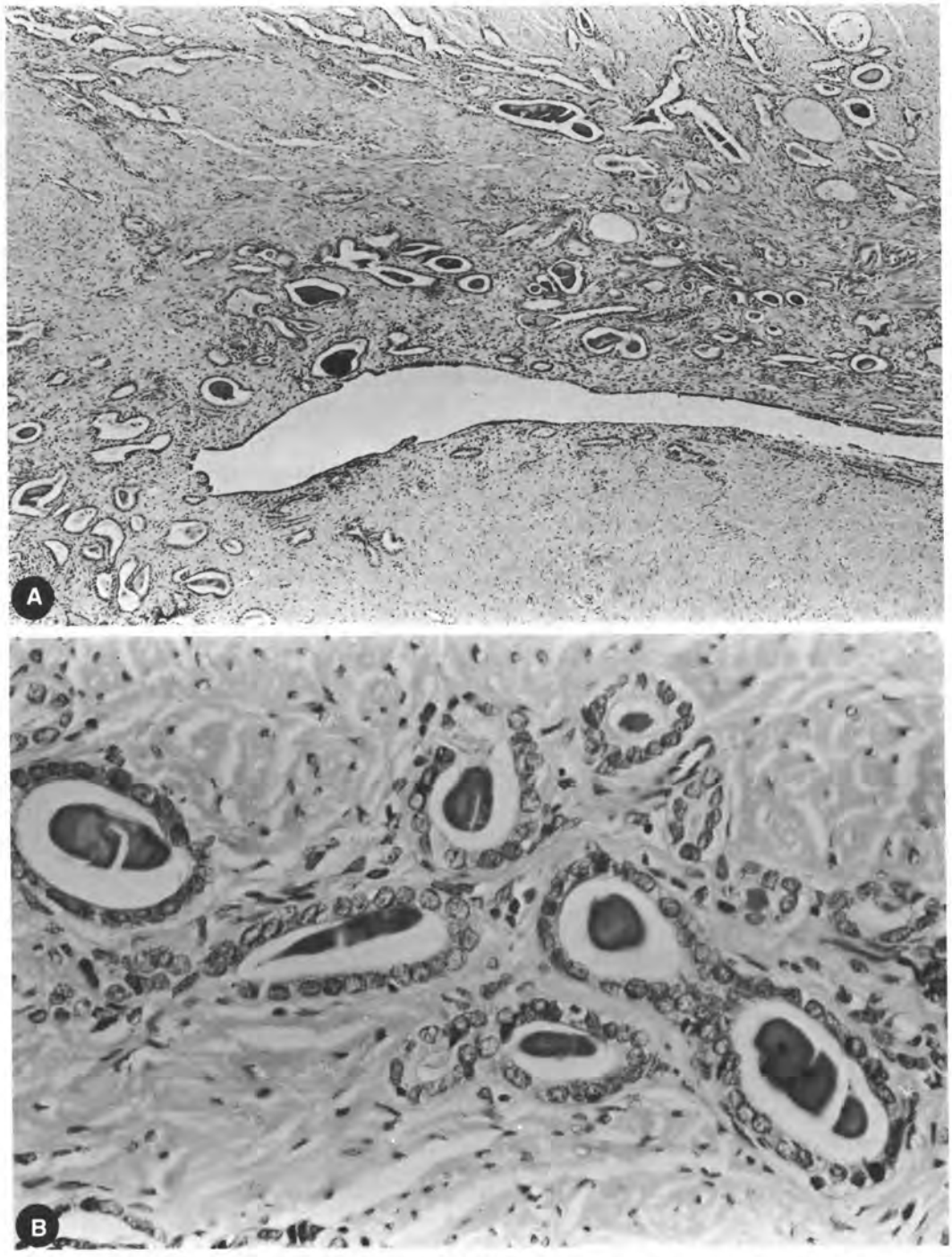


FIGURE 3-34 Hyperplastic mesonephric rests. **(A)** Slit-like duct with radiating tubules. **(B)** Detail of tubules lined by nonciliated, nonmuciparous cuboidal cells, with dense eosinophilic material in lumina.

smooth muscle cells and no mitoses are observed. Microscopically, it resembles adenofibromas arising in the ovary and the endometrium.[178] Most of the cases are described in postmenopausal women. The evolution is benign, but the lesion must be differentiated from the closely related müllerian adenosarcoma (see Chap. 4).

Rare Benign Tumors

Let us also note briefly a few rare cases of *hemangioma,*[179] *blue nevus,*[180] *traumatic neuroma,*[181] *ganglioneuroma,*[182] *neurilemmoma,*[183] and *granular cell tumor.*[184] *Glial polyps* of the cervix are probably sequelae of a previous occult abortion.[185] A few authors have

TABLE 3-3.
Mesonephric Lesions of the Cervix

Mesonephric remnants
Mesonephric cysts
Lobular mesonephric hyperplasia
Diffuse mesonephric hyperplasia
Mesonephric ductal hyperplasia
Mesonephric carcinoma

Adapted from Ferry JA, Scully RE: Mesonephric remnants, hyperplasia, and neoplasia in the uterine cervix: A study of 49 cases. Am J Surg Pathol 14:1100–1111, 1990.

noted the presence in the cervix of *sebaceous glands,* which are products of metaplastic phenomena from squamous epithelium or represent misplaced embryonic tissue.[186–188]

The *müllerian papilloma* (previously called *mesonephric papilloma*) is a rare cervical or vaginal benign tumor of infancy.[189–191] It is characterized by papillary structures lined by a cuboidal epithelium and underlain by a loose fibrovascular stroma. The presence of mucin-filled cells and the ultrastructural appearance have confirmed the müllerian origin.[192]

Cervical Endometriosis

More than 100 cases of cervical endometriosis have been published,[193–195] but our experience suggests that the lesion is far more common. The most reasonable pathogenic mechanism is post-traumatic implantation of fragments of endometrium.[196] The clinical history frequently reveals the existence of prior gynecologic trauma during a delivery or a curettage. Why is this implantation rare, considering the frequency of passage of endometrial debris into and through the cervix with each menstrual period? One may explain this rarity by the resistance of the untraumatized intact squamous epithelium to the implantation of endometrial fragments. Thus, the lesion is seen most frequently after combined cervical conization and endometrial curettage.

The lesion is asymptomatic or may cause premenstrual hemorrhages. More rarely, they are inter- or postmenstrual. It develops in the adult women between 20 and 50 years of age.

Macroscopic Appearance. Cervical endometriosis does not always present a typical appearance. The presence of a slightly elevated, dark red or brown cystic structure suggests a focus of endometriosis. Endometriosis may also present as a zone of erosion, a granular-surfaced nodule, or a proliferating lesion; these may arouse suspicion of malignancy, and only microscopic examination permits the assessment of their true nature.

Histologic examination shows endometrial glands (proliferative or secretory) surrounded by endometrial stroma. To be labeled *endometriosis*, this lesion should have no connection with the adjacent endometrium. Stromal endometriosis that emphasizes the stromal proliferation has been described.[197] A case

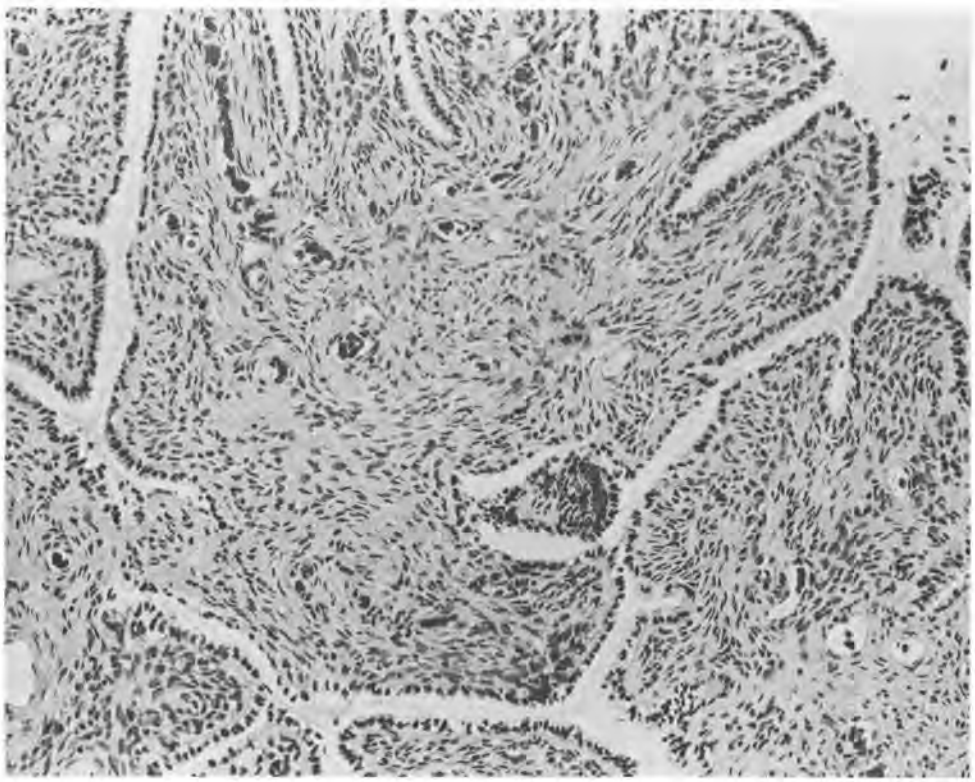


FIGURE 3-35 Papillary adenofibroma of cervix.

of adenocarcinoma has been reported within a focus of cervical endometriosis.[198]

Cytology may reveal the presence of well-preserved endometrial cells of epithelial and stromal origin. The visual or colposcopic observation of a cervical lesion must be correlated with the abundance of endometrial cells and suggests the diagnosis.[199]

CERVICAL INTRAEPITHELIAL NEOPLASIA (DYSPLASIA AND IN SITU CARCINOMA, LOW- AND HIGH-GRADE SQUAMOUS INTRAEPITHELIAL LESIONS)

Although many descriptions of the precancerous lesions are found in the literature of the late 19th century and early 20th century (Cullen[200] illustrated changes of carcinoma in situ as early as 1900), the first attempt to classify the precancerous lesions can be attributed to Broders[201] in 1932. The term *cervical dysplasia* was mentioned by Papanicolaou[202] in 1949, and Reagan[203] in 1953 defined the lesion as an atypical hyperplasia of the cervical squamous epithelium. The important contribution of Reagan pointed out that the clinical prognosis cannot be determined from the morphologic appearance of the lesion, and he introduced the notion that two categories of lesions are present in the cervical epithelium : an ill-defined category that includes various benign alterations (dysplasia), and carcinoma in situ, which represents the precursor of invasive carcinoma. Because dysplasia is considered to comprise epithelial atypical changes below the level of carcinoma in situ, the crucial definition is that of the latter lesion.

The definition established in 1961 by the International Committee for Histological Definitions[204] was strictly histologic:

> Only those cases should be classified as carcinoma in situ which, in the absence of invasion, show a surface epithelium in which, throughout its whole thickness, no differentiation takes place. The process may involve the lining of the cervical glands without thereby creating a new group. It is recognized that the cells of the uppermost layers may show some slight flattening. The very rare case of an otherwise characteristic carcinoma in situ which shows a greater degree of differentiation belongs to the exceptions for which no classification can provide.

Koss[205,206] has suggested a broader functional definition of carcinoma in situ as "a lesion confined to the epithelium of the uterine cervix, morphologically resembling invasive cancer."

The disadvantage of this dual terminology was to tend to represent dysplasia and carcinoma in situ as two different diseases. We know that the epithelial changes of the cervix form a continuous spectrum of the same disease. To meet this major objection, the term *cervical intraepithelial neoplasia (CIN)* was proposed by Richart[207–210] to indicate the spectrum of epithelial changes constituting various forms of dysplasia and in situ squamous cell carcinoma. This nomenclature recognizes the concept of a single disease, considers dysplasia as a neoplastic entity, and correlates histologic images with adequate treatment. When the CIN terminology is used, we prefer that the lesions not be subclassified as CIN I, II, and III, although most systems now do this; the reason is that the entire philosophic basis of CIN terminology is to emphasize the continuous spectrum of these lesions.

More recently, a new classification for cytologic diagnosis has been proposed by a committee convened under the auspices of the National Cancer Institute in Bethesda in 1988,[211] with further modification in 1991.[212] This Bethesda system suggests the use of only two grades to qualify these morphologic anomalies: *low-grade* and *high-grade squamous intraepithelial lesions.* Richart has proposed to modify the CIN classification accordingly into two groups,[213] although some arguments exist to maintain the subdivision of CIN into three grades.[214] Table 3-4 summarizes the three current classifications and their relation to one another.

Difficulties in Studying Cervical Intraepithelial Neoplasia

The difficulties involved in attempting to study the natural history of cervical dysplasia and in situ carcinoma result largely from the following almost insurmountable obstacles.

Lack of Universally Accepted Definitions

We have just mentioned the different classifications proposed in the last decades. Unanimity has not been reached, although the tendency is to adopt a uniform simple terminology that would communicate the necessary information to the physician. More biologic, epidemiologic, and pathologic infor-

TABLE 3-4.
Classifications of Cervical Intraepithelial Neoplasia

CIN	*Classical*	*Bethesda*
CIN I	Mild dysplasia	Low-grade SIL*
CIN II	Moderate dysplasia	
CIN III	Severe dysplasia	High-grade SIL
	Carcinoma in situ	

SIL, squamous intraepithelial lesion

*Low-grade SIL also encompasses HPV-related cellular changes (condyloma, koilocytotic atypia). This is designed as a cytopathologic reporting system, whereas the other two are histopathologic.

mation is needed to clarify the pathogenesis of the different steps of cervical cancerization, for example, to be able to separate benign and potentially malignant lesions that reveal similar cytohistologic images.

Observer Disagreement in Histopathologic Diagnosis

Numerous authors[215-218] have demonstrated a remarkable variability in the interpretation of identical lesions by different pathologists (or even by the same pathologist on different days). Although these different interpretations usually vary only slightly (eg, mild versus moderate dysplasia, *not* moderate dysplasia versus invasive cancer), they indicate that any population study based on biopsy diagnosis is subject to considerable observer bias.

Possible Differences in Natural History Based on Etiologic Agents

The demonstration that most lesions classified as CIN are related to HPV infection[80-84,87-89,99,102,110,219-222] has raised a new caveat in the study of these atypias. We now need to differentiate "pure" condyloma, dysplasia or carcinoma in situ without evidence of condyloma, and various patterns of coexistence of the two processes, before we can attempt follow-up studies. The suggestion that particular viral subtypes may be more likely to be associated with lesions that progress indicates that morphologic interpretations alone may be inadequate in the study of these lesions.[82,84,85,87,89,99,100,223-226] It is generally accepted that types 16 and 18 belong in this "high-risk" group; some investigators also include types 31, 33, 45, and 56, whereas others assign these types (as well as 30, 34, 40, and 47) to an intermediate risk category; types 6, 11, and 42 are universally considered low risk.[222-226] Finally, because none of these distinctions was made in the classic studies of earlier years, all their conclusions must be reexamined.

Effect of the Investigative Procedure on the Process Being Studied

Several investigators[206,208] have shown that even small punch biopsies that do not remove all of the abnormal epithelium can induce subsequent replacement of dysplastic or in situ carcinomatous epithelium by benign mucosa. Because the interpretation of colposcopic and cytologic observations is even more variable than that of biopsy material, we must conclude that no method of study will give us a definitive, quantitative picture of the natural history of CIN. Similarly, although we will continue to use the terms *dysplasia* and *carcinoma in situ* in the classic sense to delineate certain cytologic and histopathologic pictures, we must remember that no studies—whether cytogenetic,[223,227] electron microscopic,[228] chromosomal,[229,230] immunohistochemical,[231,232] or tissue cultural[210,233]—have succeeded in delineating the exact stage at which dysplastic changes become irreversible and malignant.

Possible Progression to Invasive Cancer

Nevertheless, an impressive body of evidence has been assembled to support the concept of an origin of invasive cancer from these lesions:

1. These lesions occur in the same population groups, and groups with low prevalence rates for one lesion have low prevalence rates for all.[234]
2. The prevalences of dysplasia, in situ carcinoma, and invasive carcinoma are similar in women examined for the first time.[49,235,236]
3. Studies of untreated women with dysplasia and carcinoma in situ have shown subsequent development of invasive carcinoma.[237-239]
4. Women with invasive carcinoma have been found, on review of previous biopsy specimens, to have had prior dysplasia, in situ carcinoma, or both.[240]
5. Coexistence of these lesions frequently can be demonstrated by serial sections of cervices.[237,241]
6. There is a constant spatial relationship, in that all of these lesions arise most frequently in the region of the squamocolumnar junction or the transformation zone; when lesions of varying severity (eg, dysplasia and in situ carcinoma) coexist, the least severe pattern is usually seen in the most exterior site. Similar histologic patterns are seen in similar sites (eg, keratinizing dysplasia and keratinizing invasive carcinoma both involve the portio with greater frequency).[49,237,242]
7. There is a constant temporal relationship; the median age for dysplasia is 5 to 10 years younger than that for invasive carcinoma—the actual ages vary with the population studied, but this progression always applies.[49,206,235,243]
8. Studies of populations previously screened by cytologic examination have demonstrated up to 1200 times higher incidence of in situ carcinoma, and 100 times higher incidence of invasive carcinoma, in women initially found to have dysplasia.[235]
9. Incidence rates of, and death rates from, invasive cervical carcinoma have been lowered substantially in populations of women subjected to mass cytologic screening in whom dysplasia and in situ carcinoma were efficiently detected and treated.[244-250]

The exact rates of progression to invasive cancer of dysplasia and carcinoma in situ are not known, for reasons previously explained, but most authors believe that mild dysplasias are more likely to regress than progress, in situ carcinomas are much more

likely to become invasive if untreated, and moderate and severe dysplasias fall somewhere in between. In a series of 49 cases of severe dysplasia reported by Westergaard and Norgaard,[251] 57.1 % progressed to in situ and microinvasive carcinoma. Similar data, accumulated from many studies predominantly in the Anglo-American and European literature, have been summarized by various authors.[203,206,236,238,252,253]

Methods of Identification and Diagnosis

Macroscopic Appearance. CIN does not have a characteristic macroscopic appearance. The cervix often appears entirely normal, and occasionally shows nonspecific pictures of leukoplakia, erosion, or cervicitis. The most suspicious of these is a zone of *leukoplakia* (by definition, a white plaque), but one study demonstrated that only 10% of patients with clinical leukoplakia had dysplasia or in situ carcinoma.[254]

Schiller Test. As a supplement to clinical inspection of the cervix, Lugol's solution may be applied to its surface. A positive stain is given when the iodine reacts with glycogen-rich normal squamous epithelium (Color Figs. 3-14 and 3-15). When glycogen is depleted, as in absence (erosion, inflammatory ulcer) or abnormality (metaplasia, dysplasia, carcinoma in situ) of the squamous epithelium, the stain will be negative (interestingly, this is considered a positive test). Thus, the test can locate abnormalities to be biopsied but cannot define the type of lesion present.

Colposcopy. It was in 1923 that Hinselmann,[255] aware of the imperfection of then extant methods for the diagnosis of cervical cancer, devised a system of a stereoscopic microscope with direct lighting of the cervix for improvement of the quality of visual examination. The colposcope was born, enabling the observer to describe with great precision the physiologic and pathologic variations in the cervical mucosa and to establish the relationship between these macroscopic modifications and the corresponding histologic pictures (Color Figs. 3-16 through 3-21). The usual magnification factor is 16, and the main features examined are the vascular patterns, surface patterns, interpapillary distances, and color relationships. Particularly important are zones of white epithelium, foci showing a punctate vascular pattern, and zones of mosaicism (polygonal areas of white epithelium separated by red borders of highly vascularized connective tissue papillae). These elementary solitary or multiple lesions at times represent inflammatory conditions, at times benign atypias, and at times lesions of CIN.

The advantages of colposcopy may be summarized as follows: it precludes the necessity of conization biopsy for visible benign lesions and localizes the best biopsy site when biopsy is deemed necessary.[256-261] As far as invasive carcinoma is concerned, visual examination alone is most often sufficient to suspect the diagnosis, whereas colposcopy facilitates the diagnosis of minuscule lesions. The method does not permit the visualization of subepithelial lesions or of lesions within the endocervical canal.

Cytology. Cytologic examination has contributed greatly to the early diagnosis of dysplasia and in situ carcinoma, and it possesses the advantage over the Schiller test and colposcopy of demonstrating lesions originating in the endocervical canal. This technique has been shown to be of great value as a mass population screening device, and some authors have predicted that widespread use of exfoliative cytology could completely eradicate invasive cervical carcinoma within a population, by detecting epithelial atypias at an earlier, curable stage (CIN, dysplasia, or in situ carcinoma).[244,245,248,262-265]

The other major advantage of this method is that it can be practiced by the gynecologist and by the physician untrained in this specialty, with a cytotechnologist and a cytopathologist being required at a later time to interpret the smears obtained. If the cervical scraping includes a good sampling of the endocervical canal, the chances of missing an intraepithelial lesion are slight. However, the true *false-negative* rate of cytology is not negligible and may represent 10% of cases.[266,267] These cases are by definition identified retrospectively; if the clinical examination and the cytology report are both negative, there is no adequate prospective clinical follow-up. False-negative reports are engendered both by the absence of suspicious cells in the smears (which may be otherwise adequate or inadequate) and by a wrong interpretation of the cellular atypias present. Different endocervical sampling instruments have been introduced to increase the chance of obtaining a smear from the squamocolumnar junction (transformation zone). Although some authors[268,269] are enthusiastic, others are reluctant to use them[206] because of the poor quality of the smears. In addition, it has been recommended that the false-negative rate could be reduced substantially by taking two smears rather than one at the time of pelvic examination.[249] Vaginal pool aspiration increases the chances of detecting endometrial lesions as well.

Is the presence of endocervical columnar cells necessary to consider a smear adequate? This rule should not be strictly applied in our experience. If the smears are richly provided with well-preserved and fixed cells, and if endocervical mucus is present with inflammatory and metaplastic cells trapped in it, one should consider these smears technically adequate. Mitchell and Medley[270] have suggested that the endocervical component of the cervical smear be defined on the basis of metaplastic cells alone or in combination with columnar cells. Their study tends to show that metaplastic cells are a more important marker than columnar cells.

The optimal interim period between screening examinations has been debated recently, and this pe-

riod can influence the clinical impact of a false-negative report. We agree with the guideline proposed by the American Cancer Society[271] that "all women who are or have been sexually active, or have reached age 18 years, have an annual Pap test and pelvic examination. After a woman has had three or more consecutive satisfactory normal annual examinations, the Pap test may be performed less frequently at the discretion of her physician." This opinion is not shared by all authors in view of the medical cost of yearly tests. With the exception of women with positive herpes II antibodies or with previously diagnosed HPV infection or CIN, triennial screening can be proposed.[246,249] Some investigators still think that periods longer than 1 year will demotivate the women.

The cytologic picture of in situ carcinoma differs only in degree from that of invasive carcinoma on the one hand and severe dysplasia on the other. Although many authors claim a high degree of accuracy in differentiating these lesions cytologically, we believe that tissue examination (biopsy or conization) is required for a definitive diagnosis. Cytologic interpretations should always be expressed in histologic terminology so that the cytologic and biopsy diagnoses are comparable. The Bethesda system[212] is summarized in Table 3-5 as an advisable terminology.

Histology. The final diagnosis of any malignant or suspicious cervical lesion should be made by biopsy. Much has been written arguing the relative merits of multiple punch biopsies and conization biopsy, the latter being the technique that samples the entire circumference of the squamocolumnar junction. There is no doubt that the conization specimen, when totally sectioned, embedded, and examined in detail by the pathologist by a technique such as that of Foote and Stewart,[272,273] will reveal lesions that may not have been sampled by prior punch biopsies;[266] but many have questioned whether the additional information is often of enough significance to justify the occasional morbidity of the procedure. Colposcopically directed biopsies combined with endocervical curettage can provide the same information with less morbidity.[259,260,274,275] Conization (by cold knife, laser, or loop excision) is advised when the entire lesion cannot be located or visualized by colposcopy (positive or inadequate endocervical curettage specimen). Some workers also recommend conization for in situ carcinoma.[276]

The pathologist working with conization specimens must be sure to section and examine the entire specimen. Usually 15 to 25 tissue pieces are submitted for histologic preparation if the specimen permits, and at least three or four levels of each should be examined. Some authors have recommended routine serial step sectioning of all tissue blocks,[277] but we believe that the imposition of this task on a busy laboratory is simply not practical; certainly, any block with a suspicious lesion should be subjected to step sectioning. Another question that is often raised is that of performing frozen section on conization specimens; again, we believe that the advantages are offset by the difficulty of the procedure, the lack of immediately important therapeutic information to be gained (most microinvasive carcinomas will not be treated differently from CIN), and the inherent risk of error involved (an average of 12.6% incorrect diagnoses in one literature review[278]). In reporting the final results of a conization biopsy for carcinoma in

TABLE 3-5.
The 1991 Bethesda System

- Adequacy of the specimen
  - Satisfactory for evaluation
  - Satisfactory for evaluation but limited by . . . (specify reason)
  - Unsatisfactory for evaluation . . . (specify reason)
- General categorization (optional)
  - Within normal limits
  - Benign cellular changes: See descriptive diagnosis
  - Epithelial cell abnormality: See descriptive diagnosis
- Descriptive diagnoses
  - Benign cellular changes
    - Infection
      - *Trichomonas vaginalis*
      - Fungal organisms morphologically consistent with *Candida* spp
      - Predominance of coccobacilli consistent with shift in vaginal flora
      - Bacteria morphologically consistent with *Actinomyces* spp
      - Cellular changes associated with herpes simplex virus
      - Other
    - Reactive changes
      - Reactive cellular changes associated with
        - Inflammation (includes typical repair)
        - Atrophy with inflammation ("atrophic vaginitis")
        - Radiation
        - Intrauterine contraceptive device (IUD)
        - Other
  - Epithelial cell abnormalities
    - Squamous cell
      - Atypical squamous cells of undetermined significance: Qualify*
      - Low-grade squamous intraepithelial lesion encompassing: HPV,** mild dysplasia/CIN I
      - High-grade squamous intraepithelial lesion encompassing: Moderate and severe dysplasia/CIS, CIN II and CIN III
      - Squamous cell carcinoma
    - Glandular cell
      - Endometrial cells, cytologically benign, in a postmenopausal woman
      - Atypical glandular cells of undetermined significance: Qualify*
      - Endocervical adenocarcinoma
      - Endometrial adenocarcinoma
      - Extrauterine adenocarcinoma
      - Adenocarcinoma: not otherwise specified
  - Other malignant neoplasms: Specify
  - Hormonal evaluation (applies to vaginal smears only)
    - Hormonal pattern compatible with age and history
    - Hormonal pattern incompatible with age and history: Specify
    - Hormonal evaluation not possible due to: Specify

*Atypical squamous or glandular cells of undetermined significance should be further qualified as to whether a reactive or a premalignant/malignant process is favored.

**Cellular changes of human papillomavirus (HPV)—previously termed koilocytosis, koilocytotic atypia, or condylomatous atypia—are included in the category of low-grade squamous intraepithelial lesion.

situ, the pathologist should always mention the adequacy of the upper and lower resection margins, particularly if the uterus may be retained. A recent study showed a 12% incidence of residual tumor in postconization uteri with adequate margins, compared with 82% when margins were inadequate. Margin involvement was a better predictor of residual disease at repeat surgery than was abnormal follow-up cytology.[279]

Diagnosis of Cervical Intraepithelial Neoplasia (Dysplasia and Carcinoma In Situ, Low-Grade and High-Grade Squamous Intraepithelial Lesions)

Histologic Appearance

The great majority of intraepithelial lesions originate at the squamocolumnar junction or transformation zone and may involve the epithelium of the adjacent endocervical gland necks. Reserve cells differentiate into squamous epithelium through the steps of squamous metaplasia. We are all familiar with the common picture of biopsies from the junction: the coexistence of areas of normal squamous epithelium, columnar glands and foci of basal hyperplasia, and squamous metaplasia combined with inflammatory infiltrates.

CIN is characterized by the combination of the following elementary lesions (Figs. 3-36 through 3-47):

(*Text continued on page 113.*)

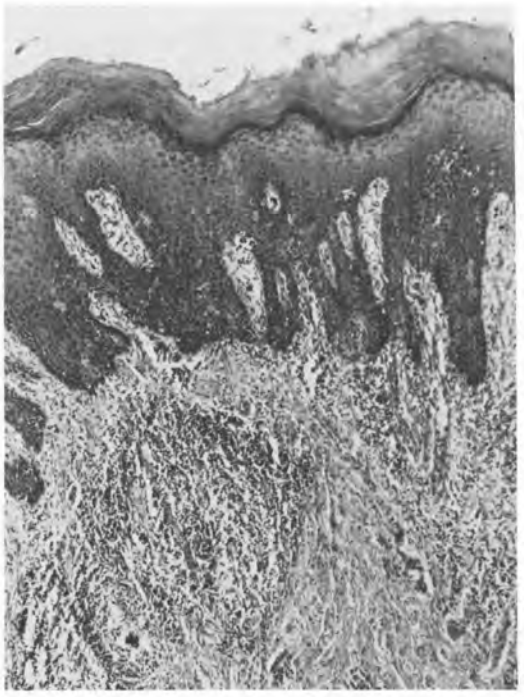


FIGURE 3-36 Mild cervical dysplasia with hyperkeratosis (leukoplakia).

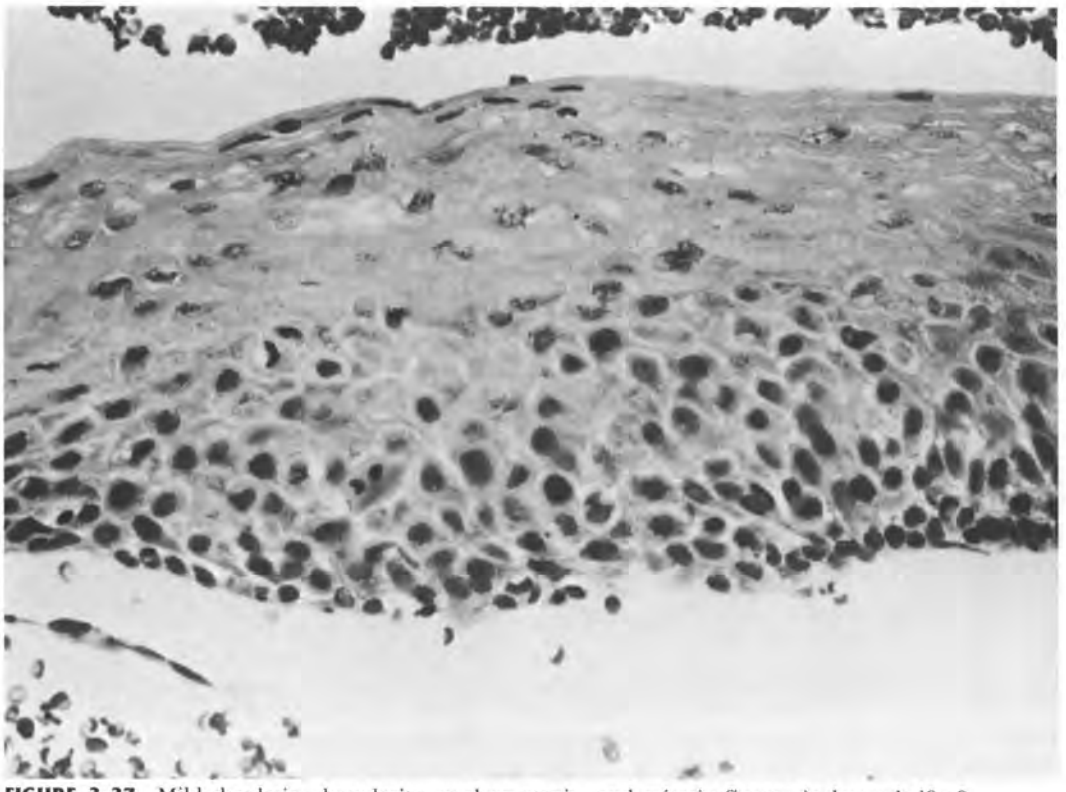


FIGURE 3-37 Mild dysplasia: dyspolarity, nuclear atypia, and mitotic figures in lower half of mucosa only.

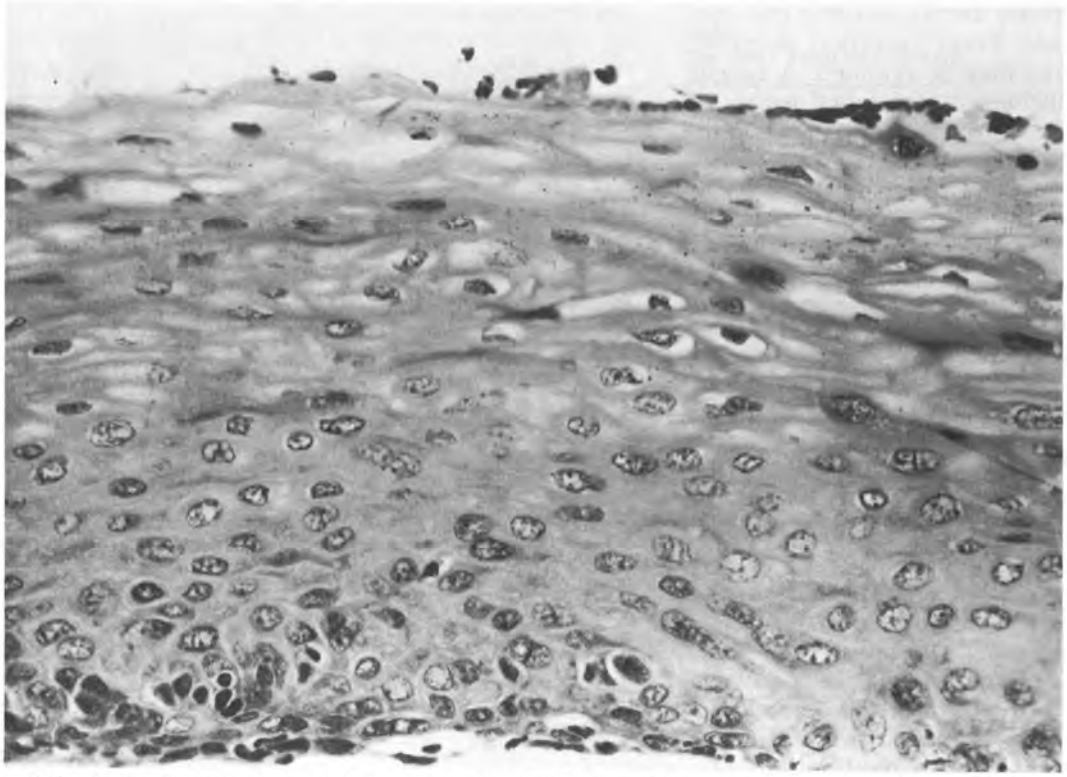


FIGURE 3-38 Mild dysplasia: slightly more atypia but fewer mitoses than in Figure 3-37.

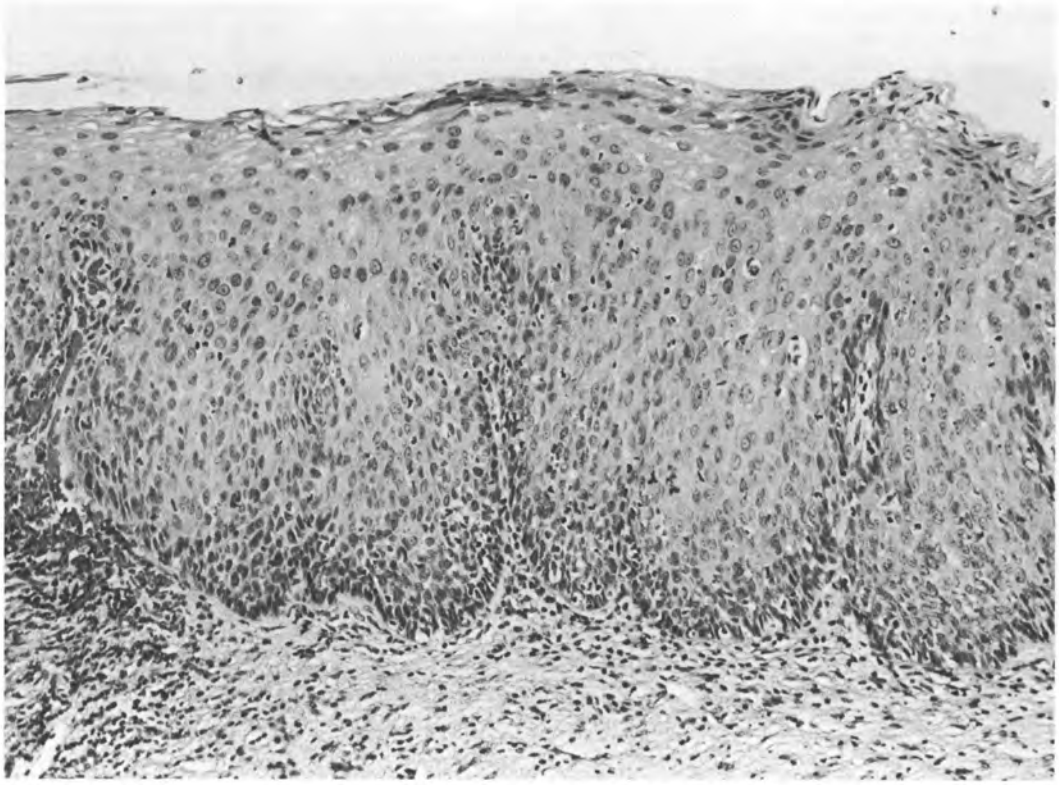


FIGURE 3-39 Moderate dysplasia: focal parakeratosis and epithelial peaking suggest origin in flat condyloma.

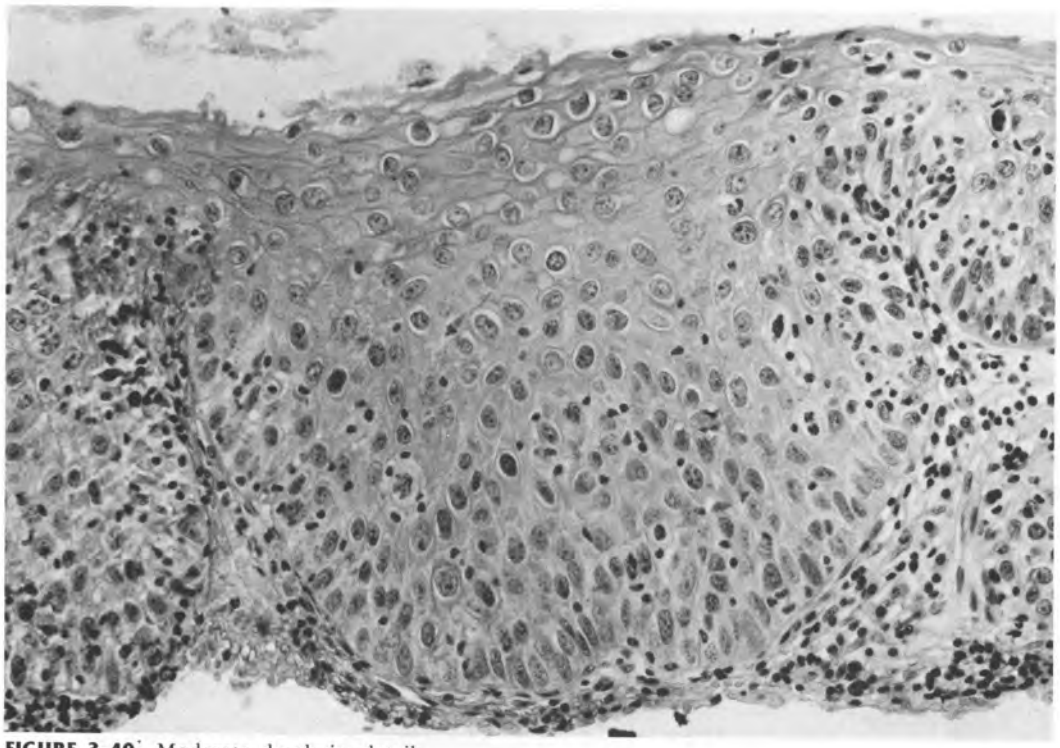


FIGURE 3-40 Moderate dysplasia: detail.

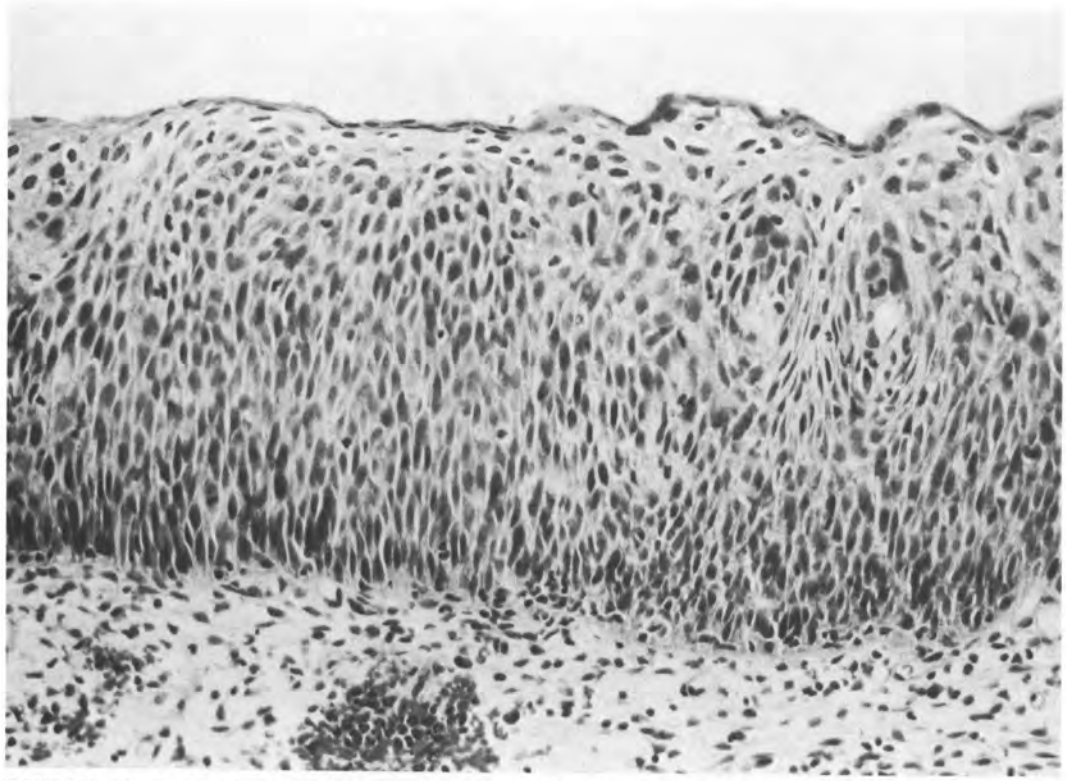


FIGURE 3-41 Severe dysplasia: flattening and maturation limited to upper fifth of mucosa.

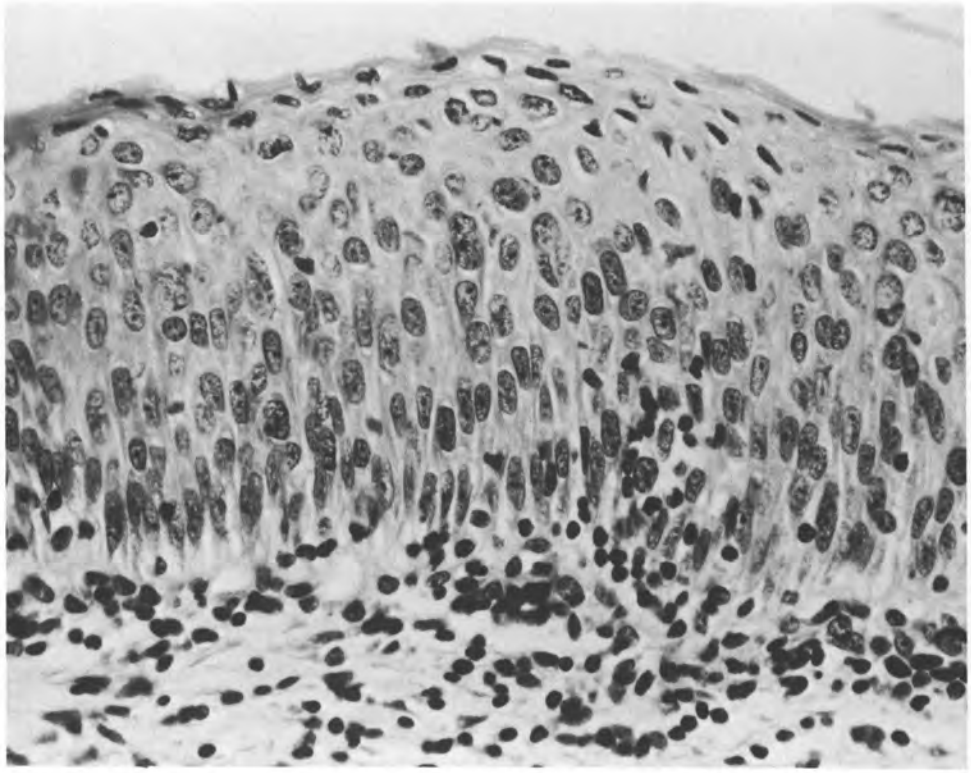


FIGURE 3-42 Severe dysplasia.

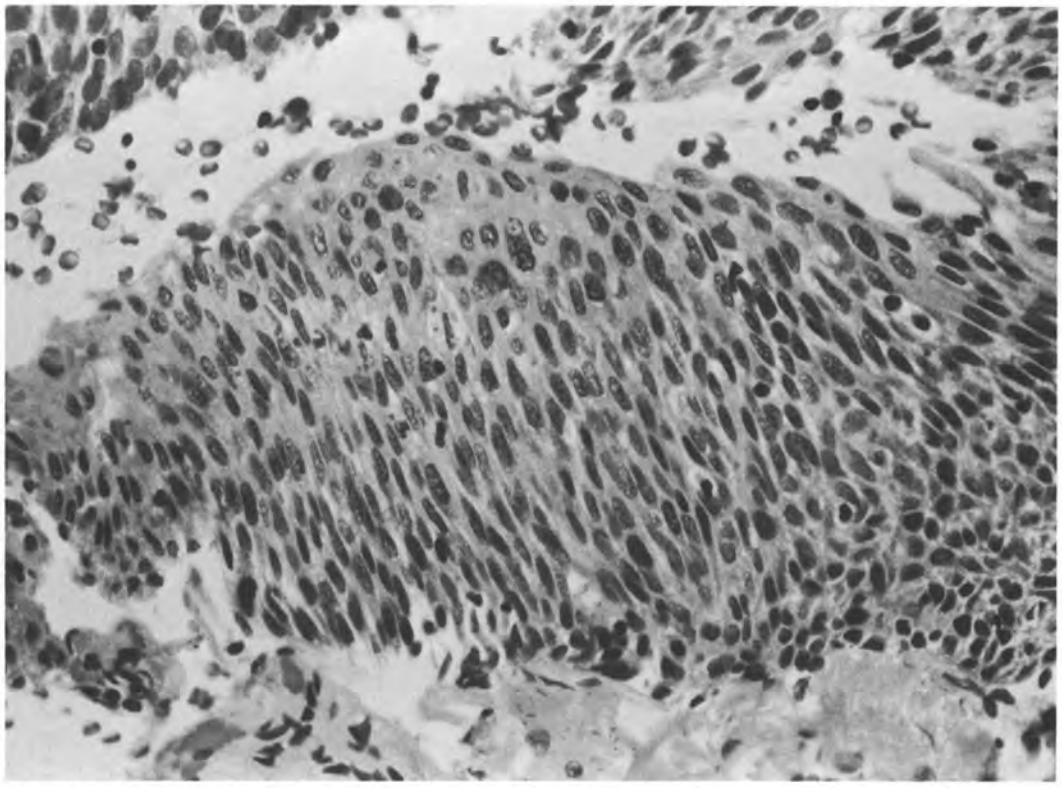


FIGURE 3-43 Borderline lesion of high-grade CIN. Iatrogenic loss of some surface epithelium in this endocervical curettage specimen makes it difficult to distinguish between severe dysplasia and in situ carcinoma.

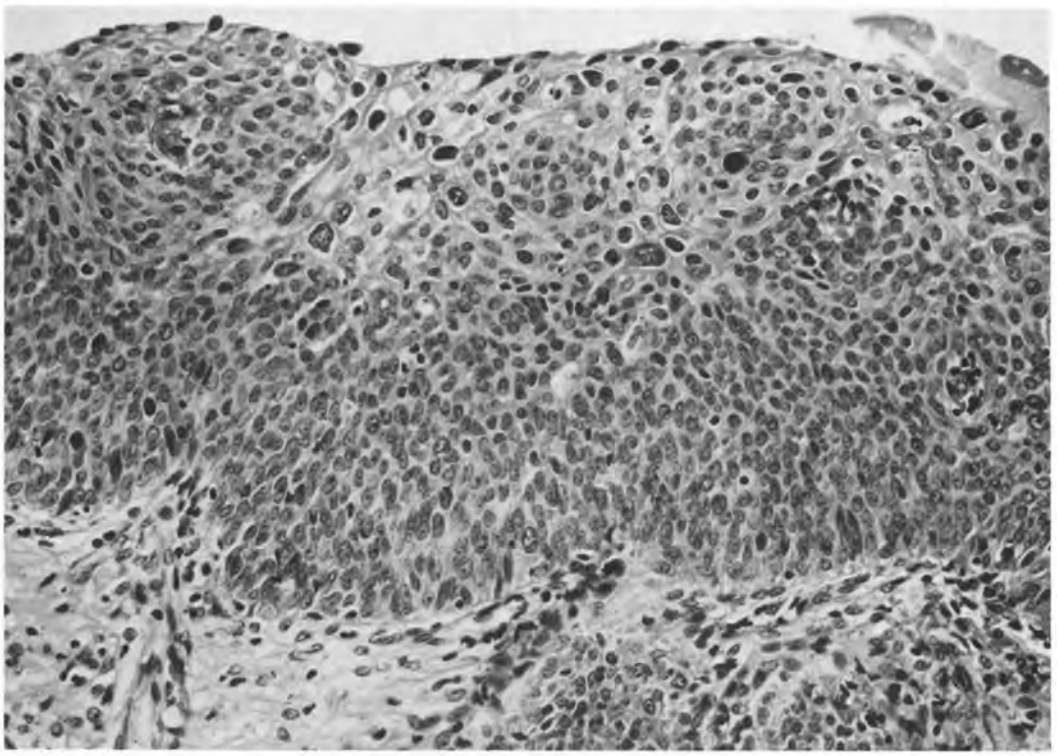


FIGURE 3-44 In situ carcinoma: microscopic appearance.

Hyperplasia of the basal cell layers, particularly layers C1 and C2, occurs with or without cellular anomalies. The basal layer is augmented in thickness and encroaches on the intermediate layers. The basal cells are normal in appearance or may show discrete cytologic modifications (increase in size of cells or of nuclei, irregularities of shape). In high-grade CIN (carcinoma in situ) there is a total lack of maturation toward the surface with uniform proliferation of immature cells. Minor degrees of flattening may be seen but the cells at the surface are as immature as those at the base, and do not show such features of

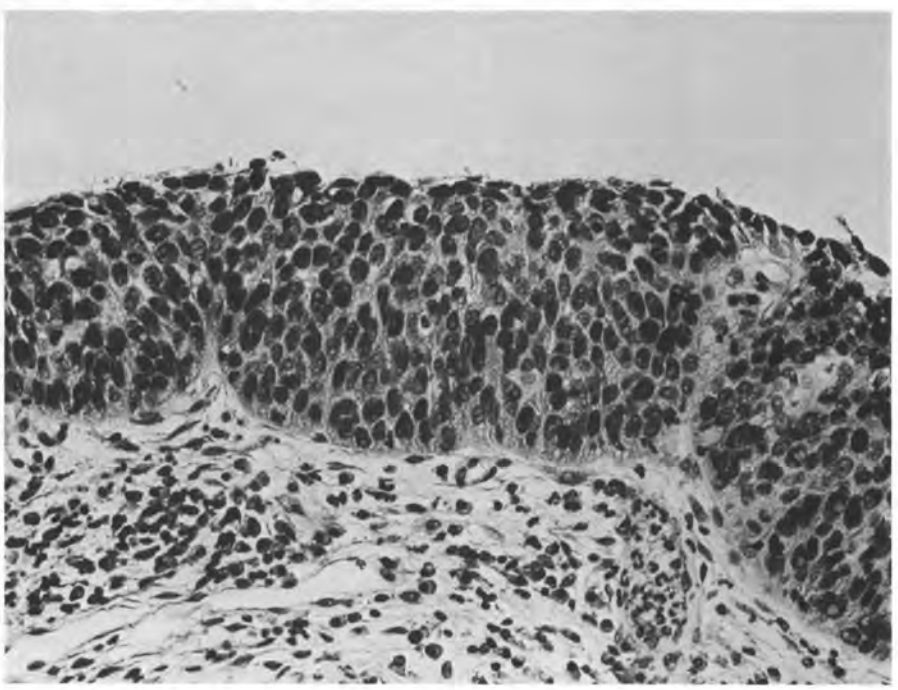


FIGURE 3-45 In situ carcinoma composed of basal-type cells. (Silverberg SG: Surgical pathology of the uterus. New York, John Wiley & Sons, 1977)

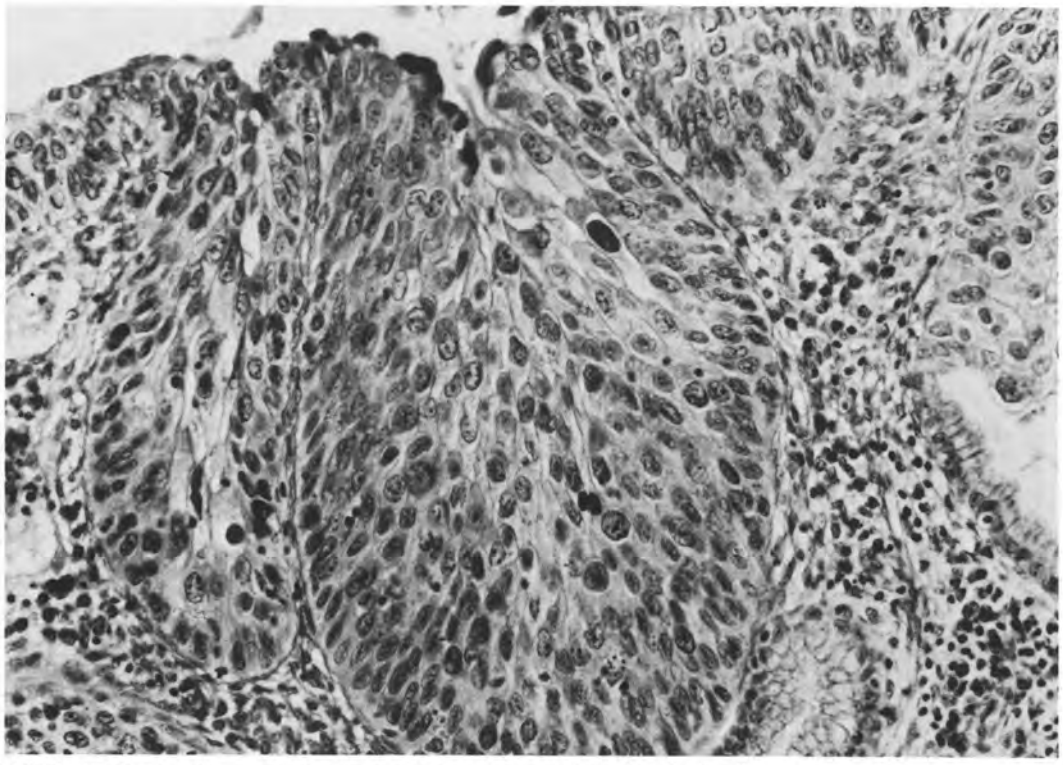


FIGURE 3-46 Carcinoma in situ with gland neck extension: detail of cells.

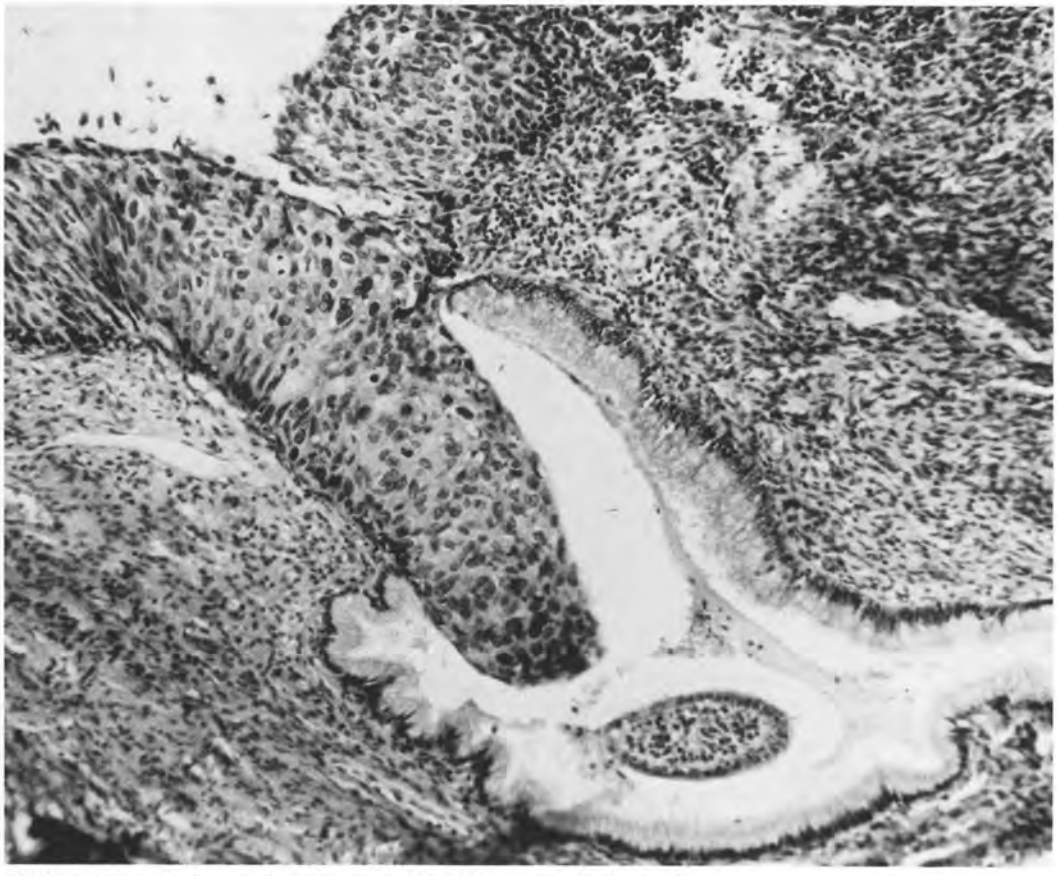


FIGURE 3-47 In situ carcinoma: extension into endocervical glands.

squamous differentiation as increased cytoplasm, cytoplasmic glycogen, and sharp intercellular borders.

Anomalies of size and shape are found in cells and nuclei, principally in the intermediate and deep epithelial layers. Premature keratinization may be present. *Nuclear hyperchromatism* is present, often with relatively normal cytoplasm. *Quantitative and qualitative abnormalities of mitoses* include increased mitotic rate, with abnormal mitoses usually confined to the lower half of the epithelium in low-grade CIN (mild and moderate dysplasia) and distributed in all levels in severe dysplasia and carcinoma in situ. The presence of three-part mitoses or three-group metaphase multipolar spindles and multinucleate cells is a good indicator of the severity of the lesion.[281-284] DNA ploidy is another expression of these anomalies.[285]

The *nuclear–cytoplasmic ratio* (expression of nuclear area to cytoplasmic area) increases with the severity of the lesion. *Acanthosis* occurs with accentuation of the papillary structure. *Dyspolarity* is present, with disturbance of the normal orderly maturation toward the surface. *Leukocytic and histiocytic infiltration* of the subjacent stroma is accompanied by anarchic angiogenesis.

Decrease of surface maturation is a variable criterion, largely based on the epithelium of origin. Thus, dysplasias arising in native squamous epithelium (ie, distally) tend to show extensive surface maturation, frequent isolated cell keratinizations, and prominent parakeratosis, and tend to be considered mild or moderate (keratinizing dysplasia). On the other hand, dysplasias arising in metaplastic epithelium possess few of these characteristics, appear immature, and often are labeled *severe dysplasia.* Severe dysplasia may be difficult to differentiate from carcinoma in situ and both are encompassed by the term *CIN III.*

There is *extension of the abnormal epithelium* into underlying cervical gland necks, generally more extensive in CIN III (see Figs. 3-46 and 3-47). Fluhmann clearly showed many years ago that this histologic picture does not indicate invasion[51] because the deep-seated nests of tumors are rounded, with intact basement membranes and no surrounding stromal response. Residual glandular epithelium often facilitates the diagnosis.

Different combinations of these elementary lesions will explain the highly various aspects of CIN.

Mild Dysplasia (CIN I). The morphologic alterations are limited to the basal and parabasal layers of the native squamous epithelium or to the area of squamous metaplasia. Nuclear anomalies are minimal, with mild hyperchromasia and anisonucleosis. Dyspolarity is moderate. The nuclear–cytoplasmic ratio can be slightly increased. Stratification and differentiation of intermediate and superficial squamous layers are preserved. Few mitoses are observed.

Moderate Dysplasia (CIN II). The cell polarity is disturbed in the lower two thirds of the epithelium, and stratification is maintained in the upper third. Cellular atypia is present throughout the epithelium but is less evident in superficial cells. The nuclear–cytoplasmic ratio is increased. Surface maturation persists even if some abnormal nuclei are observed. Mitoses, some abnormal, are present.

Severe Dysplasia and In Situ Carcinoma (CIN III). Dyspolarity is present in all layers of the epithelium. Nuclear atypias are severe and abundant. Anomalies of cellular size and shape are constant. Nuclear hyperchromasia is pronounced, and the nuclear–cytoplasmic ratio is notably increased, particularly in parabasal and intermediate cells. Superficial maturation is absent or minimal. Stratification may persist superficially or may be absent in CIN III of metaplastic type. Mitoses are present in all layers, and abnormal figures are evident. The more severe lesions correspond to carcinoma in situ. Then maturation is totally absent, but parallel arrangement of the most superficial cells may persist, probably for mechanical reasons. Extension into the cervical gland necks is frequent.

Study of the different cytokeratins elaborated by cervical cells and revealed by immunocytochemistry allows the distinction between normal ecto- and endocervical cells, reserve cells, squamous metaplasia, and CIN.[231,232] These determinations probably add little to routine histopathology for diagnostic purposes.

Different classifications of CIN III have been proposed, which recognize three major types based on the predominant pattern:

1. *The small cell type* (poorly differentiated or anaplastic carcinoma), composed of small cells with sometimes elongated nuclei and no sign of keratinization, suggesting the structure of basal cells
2. *The large cell type,* also referred to as *nonkeratinizing* or *moderately well differentiated*
3. *The keratinizing type,* which reveals differentiation and keratin formation. Surface keratinization is prominent and nuclear abnormalities are present even in these keratinized cells. As mentioned earlier, in some classification systems these keratinizing lesions are all considered dysplasias.

The differential diagnosis of dysplasia from *condyloma* (HPV infection-related atypia) is based on the observation that routinely visible condylomatous atypias involve predominantly the superficial and intermediate cell layers of the mucosa, whereas dysplasias begin in the basal and parabasal cell layers and grow toward the surface with increasing severity. Findings such as peaking of the surface epithelium, koilocytotic perinuclear haloes, and irregularly wrinkled, "raisinoid," often bizarre nuclei are characteristic of condyloma, whereas dysplastic cells are usually more uniform, contain hyperchromatic but not wrinkled or pyknotic nuclei, and demonstrate

more frequent mitotic figures. Abnormal mitoses should not be seen in condyloma without coexisting dysplasia. Classic dysplasia may coexist with condyloma (Figs. 3-48 through 3-50) in one or more of three fashions: (1) involving the basal and parabasal cell layers beneath a superficial condylomatous atypia; (2) immediately adjacent to a condylomatous lesion; or (3) synchronous with but spatially distant from a condyloma.

Dysplasia may also be difficult to differentiate from *atypical squamous metaplasia* or *reactive (repair) atypia* of the squamous mucosa secondary to inflammation. The disorderly dyspolarity of dysplasia is absent in both of these situations, mitotic figures are rare, and nuclei, although they may be large, are generally normochromatic or less hyperchromatic than in dysplasia. In inflammatory atypias, the inflammatory cells usually extend into the altered epithelium, whereas the inflammation associated with dysplasia is generally limited to the stroma. Immunoperoxidase staining for involucrin is said to be negative in most dysplasias and positive in 95% of normal, metaplastic, and condylomatous epithelia.[286] At the other end of the spectrum, the distinction of severe dysplasia from in situ carcinoma may pose problems, as discussed above. The inclusion of both severe dysplasia and in situ carcinoma in the CIN III grouping, however, indicates that the treatment and prognosis of these lesions depend more on their distribution (eradicable or not by conservative therapy) than on their exact histologic pattern.

Cytologic Appearance

The number of exfoliated cells depends on the method of collection, the skill of the sample taker, the extension and the location of the lesion, and the severity of atypia (Figs. 3-51 and 3-52 and Color Figs. 3-22 through 3-25).

Low-Grade Squamous Intraepithelial Lesion (Mild Dysplasia, CIN I). Superficial and intermediate squamous cells or metaplastic cells reveal mild atypia characterized by enlarged and irregular nuclei with a finely granular chromatin. Hyperchromasia is discrete. Anisonucleosis is not prominent. Nucleoli are inconspicuous. The nuclear–cytoplasmic ratio is slightly increased.

High-Grade Squamous Intraepithelial Lesion. This classification in the Bethesda system includes both moderate dysplasia (CIN II) and severe dysplasia and carcinoma in situ (CIN III). Because there are usually cytologic differences between these lesions, we will discuss them here separately. In *moderate dysplasia (CIN II),* squamous cells of all cellular layers (parabasal, intermediate, and superficial) or metaplastic cells reveal moderate nuclear abnormalities. One observes anisonucleosis, nuclear enlargement, and folding of the nuclear membrane. Nucleoli are inconspicuous. The nuclear–cytoplasmic ratio is increased by enlargement of the nucleus or decrease in size of the cytoplasm. Cytoplasmic staining is cyano-

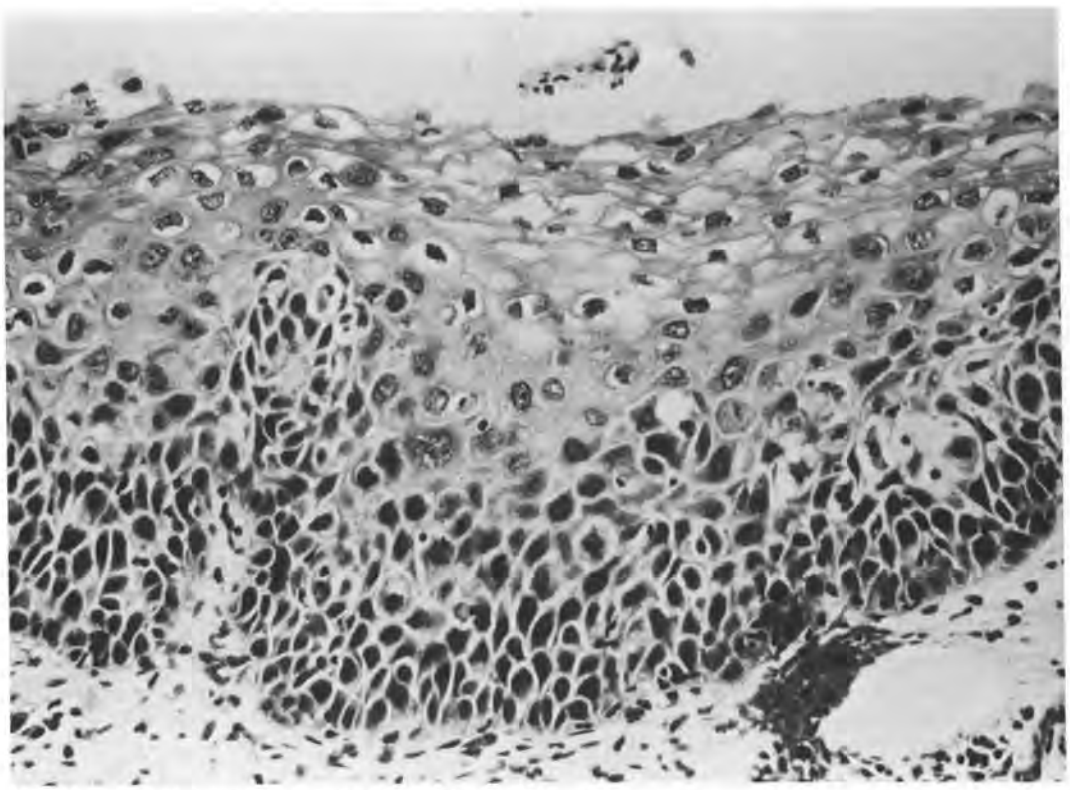


FIGURE 3-48 Flat condyloma with underlying mild dysplasia.

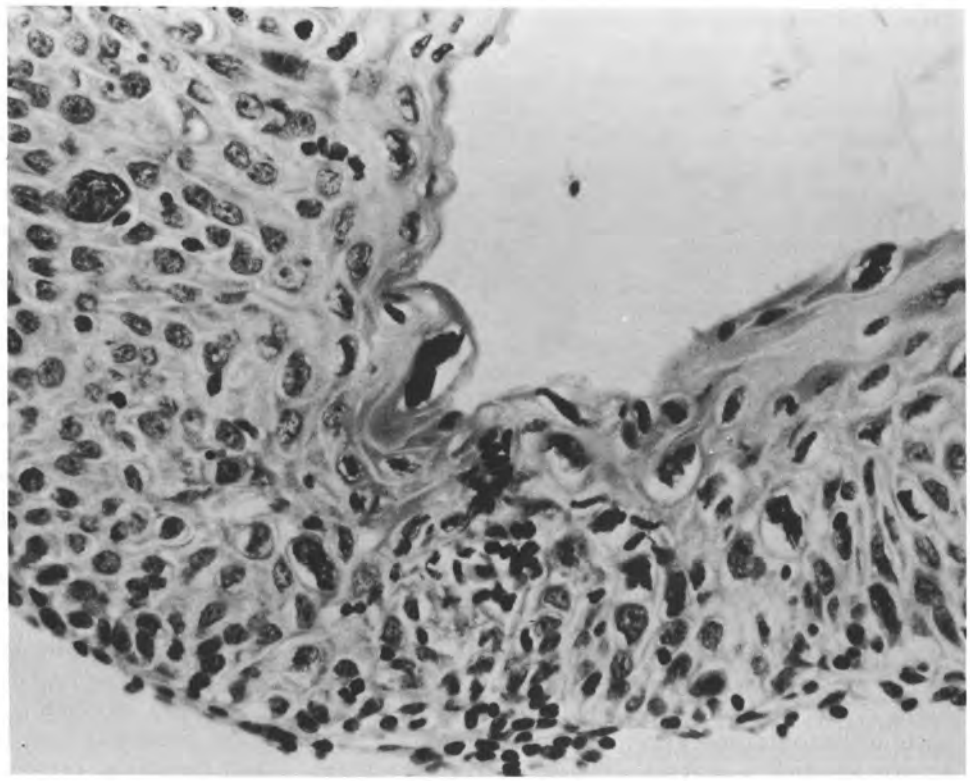


FIGURE 3-49 Flat condyloma with underlying mild to moderate dysplasia.

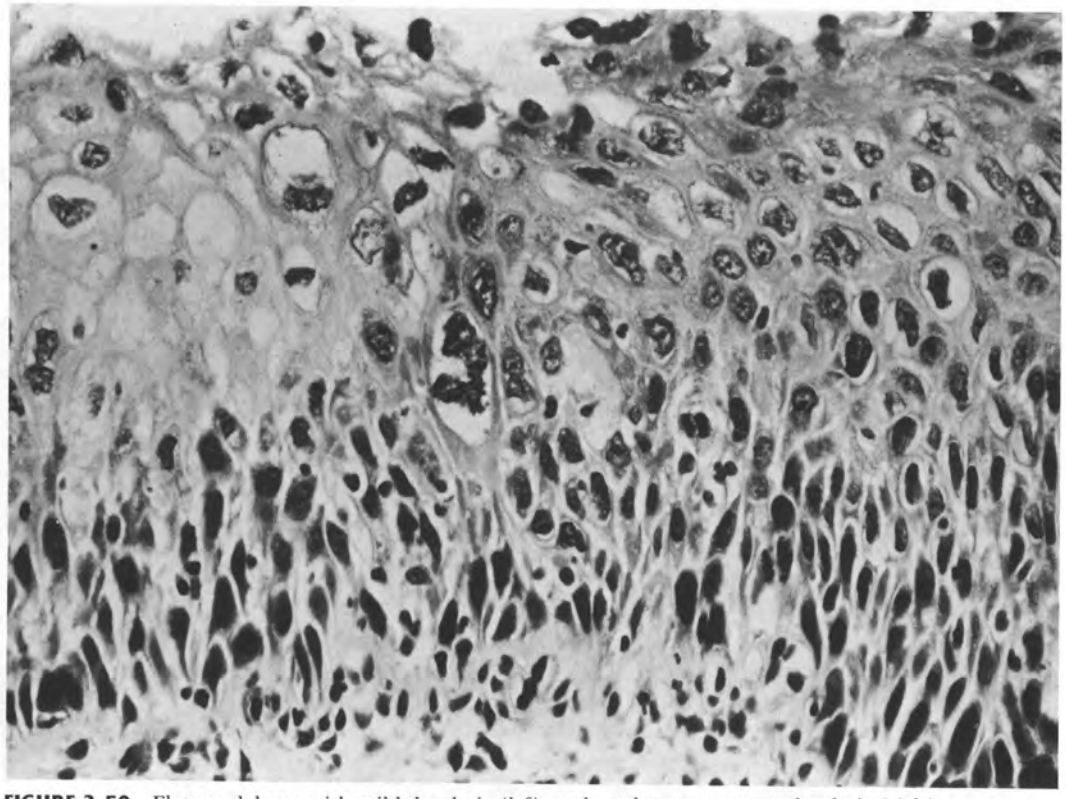


FIGURE 3-50 Flat condyloma with mild dysplasia (*left*), and moderate to severe dysplasia (*right*).

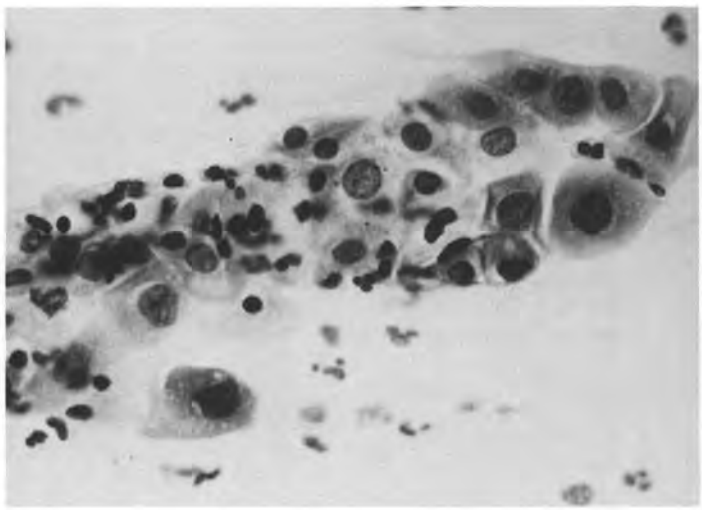


FIGURE 3-51 Moderate dysplasia: appearance of cervical smear.

philic or eosinophilic when cellular maturation is precocious.

Severe dysplasia/carcinoma in situ (CIN III) exhibits the most atypical lesions. Depending on the histologic type, the cells are small or large with or without cytoplasmic keratotic differentiation. The smears are rich in atypical cells and form aggregates of disorderly arranged elements. Nuclei are large, irregular, and hyperchromatic with scanty surrounding cytoplasm. Enlarged eosinophilic nucleoli are visible in the dense coarse chromatin. Bizarre-shaped cells may be present. The nuclear–cytoplasmic ratio is significantly increased, particularly in undifferentiated cells. Indistinct cell borders create pseudosyncytial structures.

The three histologic types of carcinoma in situ can be differentiated cytologically (Color Figs. 3-26 and 3-27). According to the cell type, the smears will show predominantly (1) small cells with large nuclei and basophilic cytoplasm occurring singly or in clusters; (2) large cells with basophilic or, less often, acidophilic orange cytoplasm; or (3) keratinized cells with abundant homogeneous eosinophilic cytoplasm and dark, often dense, irregular or pyknotic nuclei; the tadpole cell is commonly present in this type. A clear-cut distinction between the different types is

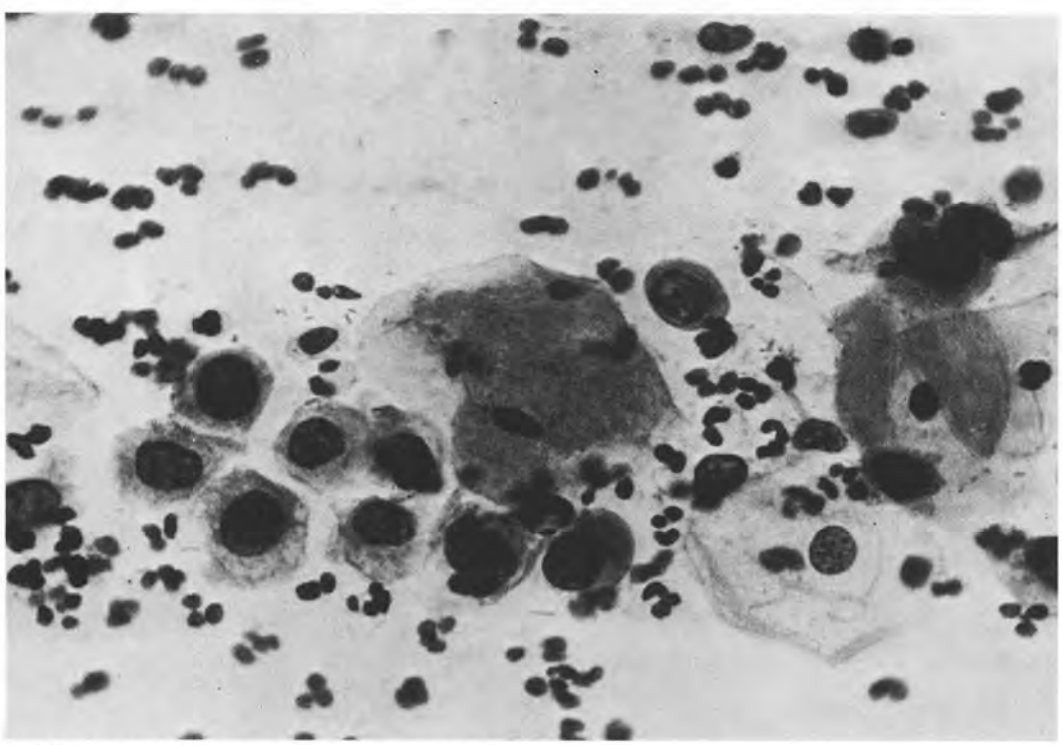


FIGURE 3-52 In situ carcinoma: appearance of cervical smear.

not always possible and mixed forms occur. Cells exfoliated from in situ carcinoma are usually more numerous, more uniform, and smaller than those seen in dysplasia, often grow in syncytia, and are round, with little cytoplasm surrounding their large, hyperchromatic, coarsely granular nuclei (see Fig. 3-52). The general background, as in dysplasia, is usually "clean" (lacking cell debris), but an inflammatory diathesis can be present, although this characteristic is classically attributed to invasive carcinoma.

The cytologic *differential diagnosis* with inflammatory, regenerative and metaplastic atypias has been discussed previously, and that with invasive squamous cell carcinoma will be discussed below.

INVASIVE MALIGNANT TUMORS

Cervical cancer represents about 10% of all cancers in women and 25% to 45% of female genital cancers. It was estimated that in the United States in 1991, 13,000 women would develop invasive cervical cancer and 7,000 women would die of the disease. It is found with the same frequency among almost all populations except Jews and certain other people such as the Fiji Islanders and with higher frequency among populations in which routine cytologic screening has not been adopted. Low socioeconomic status and poor sexual hygiene represent important factors in the increase of carcinoma in certain populations.

Invasive malignant cervical tumors consist of about 85% squamous carcinomas, 15% adenocarcinomas and adenosquamous carcinomas, and rare cases of sarcomas and metastatic tumors. Table 3-6 summarizes the International Society of Gynecological Pathologists (ISGP) classification of invasive cervical squamous carcinomas.[226]

Carcinoma of the cervix is a rapidly fatal disease; 95% of untreated patients are dead at the end of the fifth year after diagnosis. We should emphasize, at the beginning of the discussion, the social importance of cancer of the cervix uteri, which strikes about 2% of all women who attain the age of 80 years. More than 50% of the patients whose tumors are detected and treated early may hope for a survival of 5 or more years. This figure approaches 100% when the diagnosis of cancer is made in the noninvasive stage. These figures show the importance of diagnosing this disease in its early stages and, toward that end, of persuading the female population to have regular gynecologic examinations, which should always include cytologic smears.

Clinically, the easy access to the lesion, the slow growth of the tumor, and the efficacy of therapeutic modalities should increase the frequency of cure. If they are neglected by the patient, the first symptoms may escape a cursory examination, and too often the tumor evolves to a stage in which therapy is hazardous and palliative.

TABLE 3-6.
International Society of Gynecological Pathologists Classification of Invasive Squamous Cell Carcinomas

Keratinizing
Nonkeratinizing
Verrucous
Warty (condylomatous)
Papillary (transitional)
Lymphoepithelioma-like

Squamous Cell Carcinoma

Epidemiology and Etiology. The etiology of cervical squamous cancer is unknown, but certain factors influence the frequency of its appearance. The rarity of this lesion among Jewish women has led some workers to suppose a genetic factor, but a more widely held notion is that of a protective role of male circumcision. This latter hypothesis is confirmed by some studies that found that, among those natives of the Fiji islands who practice circumcision, the cervical cancer incidence was only one eighth as high as among those who abstain from this practice. Similar data have been obtained from the Moslem and Hindu populations of India, the former of whom practice circumcision, whereas the latter do not. The definite role of circumcision is not settled, even if its protective effect has been confirmed in different epidemiologic studies. Smegma appears to be a causal factor. The carcinogenic properties of smegma may be due to the transformation of its cholesterol by a bacterium (*Mycobacterium smegmatis*) into a unknown carcinogen. Another hypothesis has been proposed by Reid,[287] who emphasized the carcinogenic role of the nuclear DNA of spermatozoa, which could act in the same way as DNA of carcinogenic viruses when penetrating into the nuclei of host cells of the epithelium. As no objective evidence has been offered, these theories still need confirmation.[288]

Some studies support the concept that smoking may represent a risk factor. Nicotine may lower the immunologic defense of the cervix or make it more susceptible to viral infection.[289] A significant decrease in the Langerhans cell population, producing local immunodepression, has been observed in both normal cervical epithelium and CIN among cigarette smokers.[290]

The influence of the type of sexual life appears equally evident. Cervical cancer is statistically more frequent in the multiparous women than in the nulliparous; this frequency does not seem rigorously proportional to the number of pregnancies. It is equally more frequent in the group of married women without children than among virgins, and women with cervical cancer also seem to have begun

to have sexual relations at an earlier age than women in a control population. The works of Gagnon[291] and of Schömig[292] have noted the relative frequency of cancer of the cervix among Danish prostitutes, and attribute this in part to sexual hyperactivity. The anatomic modifications, traumata, and inflammatory lesions that are the result of genital activity and multiparity provoke important histologic alterations, but we must also remember the infections (particularly viral) and hormonal stimuli to which these women are exposed (the roles of herpesvirus and HPV have been discussed in detail earlier). Age also appears to play a role, because the condition is found with greatest frequency in women between 45 and 55 years of age. The frequency curve, very low below 20 years, rises slowly between 20 and 30 years, and then rapidly until age 50, and finally descends progressively beyond 55 years of age. At the Institut Bordet, 11% of the patients with cervical cancer were under 40 years of age (Fig. 3-53). With more precocious sexual habits, these lesions appear at an earlier age, and it is now common to detect dysplasias in patients as young as 15 years. Consequently, cytologic screening should be recommended with the beginning of sexual intercourse. It is interesting to note that the most frequent age of appearance of carcinoma in situ is between 30 and 40 years, that is, about 10 years earlier than invasive carcinoma. The role played by estrogens in the genesis of these tumors is not established with certitude. Although cervical cancers have been produced in mice by administering high doses of estrogens, there is no clinical evidence that the situation is the same in the human female.

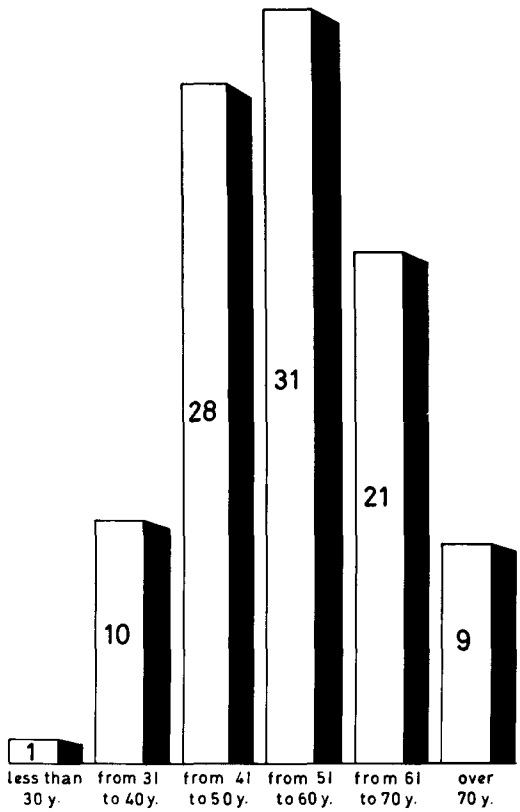


FIGURE 3-53 Percentage of incidence of cervical carcinoma as a function of age (4147 cases).

Jones and colleagues,[293] in a intensive study of the epidemiologic factors that we have just cited briefly, have cast doubt on the validity of these as isolated factors. They think that precocious sexual maturity, a reflection of varied socioeconomic factors, constitutes a background favoring the appearance of cancer.

Finally, in recent years, the evidence for induction or promotion of cervical neoplasia by different transmissible agents has become more persuasive. Among these agents are HPV[80–105,294,295] and, with considerably weaker evidence, HSV-2,[66–74] cytomegalovirus,[296] and chlamydia.[47] *Trichomonas vaginalis,* once regarded as a potential promoting agent, is no longer considered as such.[113–115,117]

Extensive recent studies tend to show that the development of intraepithelial and invasive cervical neoplasia may be favored by sexually transmitted agents. These findings suggest that there may be different forms of dysplasia due to different causes and with subsequently different natural histories. Although the natural history of the various forms of CIN (dysplasia and carcinoma in situ) cannot be predicted on morphologic grounds alone, it is important that these lesions continue to be reported according to the degree of morphologic abnormality.[110]

The mention of the virus-associated alterations should not modify the clinical and therapeutic approach to the lesion until more information is available on the differing relations (if any) of the transmissible agents to the natural history of the disease.

Development and Detection. The advanced stages of squamous cell carcinoma are comparatively more frequent in elderly women, in whom stage 0 (carcinoma in situ) represents only a small fraction of the total number of cases. After an intensive cytologic screening program in a community, these figures in all women will change to indicate a considerably higher frequency of stage 0 and I cases and, a few years later, a much lower frequency of stage III and IV cases, suggesting that many potential advanced cases have been detected at an earlier stage by this method.[244–248,297] An important conclusion should be drawn from these statements: *the absolute necessity of early detection.* For this reason, better education of the public and of the practicing physician and the organization of this detection survey on a population-wide level should be actively encouraged.

The tumor develops most frequently at the level of the squamocolumnar epithelial junction. The localization of the tumor therefore depends on the location of this junction in the cervix. This explains why about 20% of cases originate within the cervical

canal, a location in which clinical detection is more difficult.

At first invisible to the naked eye, the early structural changes are limited to a small region and consist of lesions of intraepithelial or early invasive type. The Schiller test visualizes them as pale iodonegative plaques. It is at this submacroscopic stage that methods of detection (cytology and colposcopy) have their major value. The method of transformation of a normal cell into a cancer cell is unknown, but several facts define the manner of appearance of early cancer:

1. The tumor passes through a first intraepithelial or noninvasive stage, and in the course of a second stage invades the underlying tissues. The first stage may be prolonged for months or years or, on the contrary, may represent only a first brief step in the development of the tumor.
2. Certain carcinomas appear to invade the stroma from their onset, without an earlier intraepithelial stage.
3. The tumor may originate in a single focus or as multicentric cancerous zones. It is not rare to find separate foci of in situ carcinoma separated by intervening normal mucosa. The multicentric character demonstrates that the etiologic agent acts at several foci in the cervix.
4. The transformation of benign into malignant cells should take place in young immature cells, that is, among the basal cells of the squamous epithelium or the reserve cells of the columnar epithelium.

Macroscopic Appearance. The tumor grows progressively and becomes visible to the naked eye. It presents as an elevated granular zone, darker red than the normal mucosa, which bleeds easily on contact. Two macroscopic forms are encountered:

1. The proliferative, papillary, or exophytic form. The tumor projects from the surface and forms multiple budding masses that are hemorrhagic and very friable, often with surface necrosis.
2. The infiltrating or endophytic form burrows into the cervical canal and forms a hard submucosal mass that causes augmentation of the volume of the cervix while, in the early stages, leaving the surface intact. At a later stage than in the proliferative form, the mucosa shows necrotic ulcers.

These two forms are distinguishable when the tumor is small. At a more advanced stage, the tumor involves the entire cervix and the adjacent vaginal wall and presents as a large necrotic ulcer crater (Fig. 3-54).

The international classification adopted in 1950 and modified in 1974 and 1985 subdivides cervical cancer into five macroscopic stages (Table 3-7).[226,298] The classification of a tumor should be made as a result of clinical examination before the institution of therapy. In the case of hesitation between two stages, the less advanced must be chosen.

FIGURE 3-54 Squamous cell carcinoma: macroscopic appearance.

The use of this classification permits comparison of therapeutic results from any medical institutions in the world. This staging is done on the basis of clinical examination; pathologic examination of a re-

TABLE 3-7.
Clinical Staging of Invasive Squamous Carcinoma (FIGO)

Stage 0. Intraepithelial (in situ) carcinoma
Stage I. Invasive carcinoma strictly limited to the cervix
- **Stage Ia.** Preclinical carcinoma—can only be diagnosed microscopically
  - **Stage Ia1.** Minimal microscopic invasion
  - **Stage Ia2.** Microscopic stromal invasion not exceeding 7 mm horizontally and 5 mm vertically, as measured from the base of the epithelium, either surface or glandular, from which the lesion originates
- **Stage Ib.** The lesion is larger than in stage Ia2, whether clinically apparent or not

Stage II. Carcinoma extending beyond the cervix proper but not reaching the pelvic wall: cancer involving the vagina, but not its lower third
- **Stage IIa.** No obvious involvement of the parametrium (involvement of upper two thirds of vagina only)
- **Stage IIb.** Obvious involvement of parametrium

Stage III. Cancer extending to the pelvic wall and/or involving the inferior third of the vagina and/or causing hydronephrosis or nonfunctioning kidney
- **Stage IIIa.** No extension to the pelvic wall
- **Stage IIIb.** Extension to the pelvic wall or hydronephrosis or renal nonfunction

Stage IV: Cancer extends beyond the true pelvis or involves the mucosa of the bladder or rectum
- **Stage IVa.** Spread to adjacent organs
- **Stage IVb.** Spread to distant organs

sected, biopsied, or postmortem specimen often changes the stage of a tumor, but for the sake of comparison of therapeutic modalities only the clinical staging should be used.[299,300] This point of view is open to criticism, because it enables the staging to be based on nonobjective criteria. However, although a classification based on gross and microscopic pathologic data would be more objective and precise, in practice this would eliminate most cases of advanced disease from analysis, because surgery is seldom performed in these instances. Therefore, this method unjustly weighs all reports with an unbalanced number of stage 0 and I cases.

Histologic Classification. Squamous carcinomas of the cervix have been the object of numerous histologic classifications elaborated with the intent of finding a relationship between the histologic type, the clinical prognosis, and the efficacy of surgical and radiotherapeutic modalities.

Martzloff[301] divided these tumors into three groups according to the dominant cell type: superficial keratinized, intermediate, and basal types. This classification has the merit of being simple and easily reproducible. A slightly modified approach simply distinguishes differentiated or spinocellular and undifferentiated or basocellular epitheliomas.

Broders[302] proposed four groups of epidermoid carcinomas, depending on the percentage of undifferentiated cells: group I is the most highly differentiated, containing only 0 to 25% undifferentiated cells, whereas group IV is the undifferentiated form (75% to 100%), with groups II and III in intermediate positions. Pendl[303] used no fewer than 5 groups and 16 subgroups to classify the cervical epithelial tumors, although this long classification does include the adenocarcinomas. It is, in our opinion, too involved and subjective.

Recent workers have used three groupings originally suggested by Wentz and Reagan[304] and revised in 1973 by Reagan and Ng:[305]

Group I: keratinizing type
Group II: large cell nonkeratinizing type
Group III: small cell type (small cell nonkeratinizing type)

This classification has two advantages. First, it conforms to modern theories of histogenesis, in which keratinizing cancers arise from ectocervical mucosa by way of dysplasia, large cell nonkeratinizing cancer arises from endocervical squamous metaplasia by way of dysplasia and large cell in situ carcinoma, and small cell carcinoma arises from endocervical reserve cell hyperplasia by way of small cell carcinoma in situ. Second, it appears to convey useful prognostic information (group II tumors showing the best survival and group III the worst in many series, particularly in cases treated by radiation therapy).[304-308] However, equal numbers of more recent studies have failed to confirm the histogenetic relation,[309-312] and some of these same studies have failed to confirm the prognostic utility of tumor grading.

In addition, the utility of the Wentz and Reagan classification is compromised by the fact that it is now known that most small cell carcinomas of the cervix are not of squamous type but actually represent neuroendocrine carcinomas.[313-316] The ISGP classification[226] (see Table 3-6) does not include a small cell variant of squamous cell carcinoma, and classifies small cell carcinomas separately on the assumption that they are all neuroendocrine. This classification also adds to the classical keratinizing and nonkeratinizing types four other patterns: verrucous, warty or condylomatous, papillary or transitional, and lymphoepithelioma-like. We recommend including the warty type (more common in the vulva—see Chapter 1) with the keratinizing group and classifying the three others—all rare in the cervix—separately from squamous carcinoma.

In addition to the classifications discussed so far, the prognostic significance of which is questionable, other authors have favored a "malignancy grading system" that evaluates eight different factors: structure, cell type, nuclear atypia, mitotic activity, pattern of invasion, type of tumor margin, vascular invasion, and host inflammatory response.[317,318] Although these investigators have found this system useful in providing prognostic information, it is complex and is not widely used.

Another observation that has provided useful information in several reports is the presence of stainable mucin within tumor cells in tumors diagnosed without special stains as squamous cell carcinomas.[319-323] Most studies have demonstrated either a greater likelihood of lymph node metastases or a poorer prognosis or both in these *squamous carcinomas with mucin secretion,*[320,323] which Thelmo and colleagues referred to as *mucoepidermoid carcinoma.*[322]

The histologic appearance represents only one prognostic element. Other factors are significant, most notably the degree of extension of the tumor at the time of diagnosis (see Table 3-7). For example, a clinical stage III cervical carcinoma has a poorer prognosis for long survival than a stage I or II lesion, regardless of the histologic appearances of the two tumors being compared. A small biopsy may reveal a local histologic appearance different from that which predominates in the entire tumor.

Microscopic Appearance. Squamous cell carcinoma is composed of epithelial cell cords and nests, the size and shape of which vary greatly from one case to the next. The point of origin of the tumor from the epithelium may be definite and easily seen when the tumor is small, if the biopsy happens by chance to include this region. More often, a large tumor shows surface ulceration and necrosis, with no evidence of its exact point of origin. The cell cords are disposed in random fashion and form multiple arborescences of all sizes.

In the *keratinizing type*, the cells are large, well differentiated, and show foci of keratinization with cornified pearls. A few mitotic figures are present. The cell cords are arranged in an infiltrative pattern (Fig. 3-55). By convention, a single pearl characterizes a squamous carcinoma as keratinizing, but even multiple single keratinized cells do not. If the tumor surface is papillary and hyperkeratotic, the term *warty carcinoma* can be used.

The *large cell nonkeratinizing type* is characterized by large and moderately differentiated cells, with a large, round nucleus, prominent nucleolus, and voluminous cytoplasm but no cornified pearls. Typically the tumor-stromal border is well demarcated (Figs. 3-56 and 3-57). In a few of these tumors, the cells are smaller and may be spindled, resembling the basaloid type of carcinoma described more fully in Chapter 1.

From the cytologic point of view, the cells are of variable size and irregular in shape; these variations are often independent of the cell type, because the presence of even one cornified pearl classifies an otherwise poorly differentiated tumor as a keratinizing (group I) carcinoma. The cytoplasm is basophilic (except in foci of keratinization) and its glycogen content is slight or none. The nuclei are enlarged, with an increased ratio of nucleus to cytoplasm. They present diverse anomalies of form (anisonucleosis) and size, the chromatin is abundant and irregularly disposed, and multinucleation is frequent.

The nucleolus is also enlarged, and multiple nucleoli are encountered in a single nucleus. The presence of these nucleolar anomalies is one of the most certain cytologic indications of the neoplastic nature of the cells. Staining with methylpyronine and microspectrophotometry permit study of the DNA content of the nuclei and evaluation of the volumetric variations of the nucleoli. Mitoses are more abundant than in benign lesions, and they show quantitative alterations such as pluripolar mitoses and disorderly distribution of chromosomes.

Several histochemical methods have been applied to the study of the uterine cervix, but none has established absolute criteria of malignancy.[324,325] Immunohistochemistry brings some valuable information but also no specific diagnostic data. CEA and cytokeratins are expressed in most squamous carcinomas. The blood group isoantigens A, B and H, normally present in the cervical epithelium, have not been detected in squamous carcinomas.[326,327]

Results of *electron microscopic* study of invasive squamous carcinomas have not disclosed specific characteristics of malignancy.[328] We know, however, that even in very anaplastic tumors, ultrastructural evidence of squamous differentiation is usually present.[329]

Cytologic Appearance. Invasive squamous cell carcinomas differ from their in situ counterparts primarily by greater pleomorphism and the presence of a "tumor diathesis" (an amorphous precipitate composed of debris from breakdown of tumor cells and erythrocytes). Most of the tumor cells are smaller than normal squamous cells, and the nuclear–cytoplasmic ratio is increased. The usual nuclear features of malignancy are present, and the size, shape, and cytoplasmic appearance of the tumor cells vary with

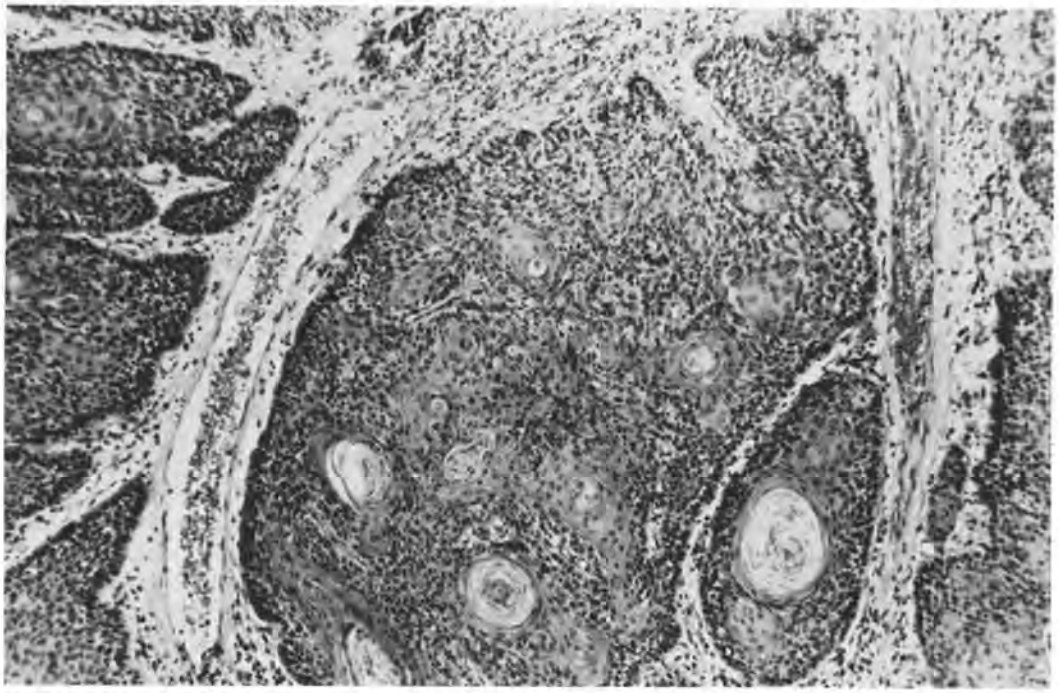


FIGURE 3-55 Keratinizing squamous cell carcinoma: microscopic appearance.

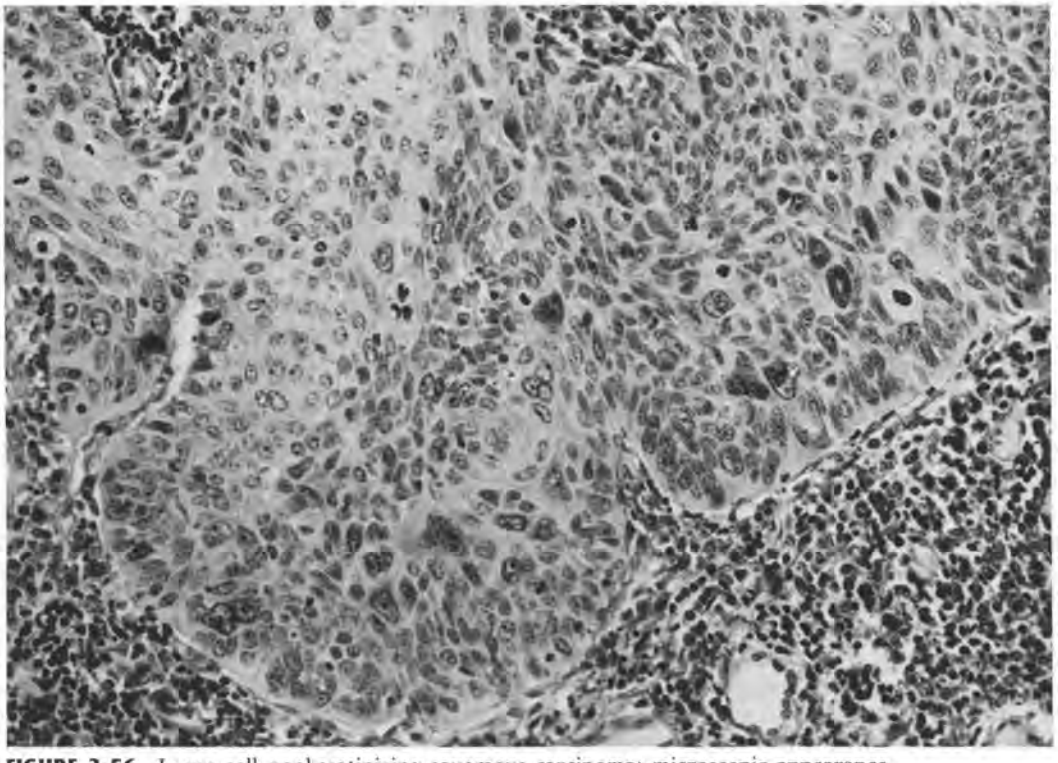


FIGURE 3-56 Large cell nonkeratinizing squamous carcinoma: microscopic appearance.

the histologic type of the tumor. Keratinizing tumors generally exfoliate the fewest, the largest, and the most pleomorphic cells, whereas large cell nonkeratinizing cancers exfoliate greater numbers of more uniform cells with less cytoplasm, no keratinization, and prominent nucleoli (Figs. 3-58 and 3-59 and Color Figs. 3-28 and 3-29). Small cell carcinoma (Color Fig. 3-30) differs from the large cell nonkeratinizing type predominantly in size.

Invasive carcinomas are more frequently missed cytologically than are in situ cancers, because the former are often covered by a surface layer of inflammatory and necrotic debris that may mask the underlying cancer; therefore, *grossly visible cervical lesions should always be biopsied.* Punch biopsy of an invasive carcinoma eliminates the necessity for conization, the main purpose of which is to *rule out* the presence of invasive carcinoma.

Evolution, Metastatic Dissemination, Prognosis, and Treatment. After extending along the surface and into the wall of the cervix, the tumor surpasses the anatomic limits of the cervix and invades the paracervical regions and, more rarely, the corpus uteri. Extension to the corpus does not change the clinical stage.

The parametria are invaded rather early, with an apparent predilection for the left parametrium. Lymphography of the normal genital system shows that the lymph flow is more rapid on the right than on the left for reasons of anatomic disposition. The relative torpor of the left-sided lymphatic circulation favors the implantation of neoplastic cells.

The lymphatic dissemination of cancer cells is generally early, and lymphatic metastases may be present when the primary tumor is still small,[330] although in one series[331] the parametrium, or at least the parametrial border of the cervix, was always involved in cases in which lymph node metastases were present. The percentage of lymph node metastases in lesions of all clinical stages combined ranges from 20% to 50% in various series.[332–334] There appears to be a definite increase in the proportion of cases with positive lymph nodes as the clinical stage advances and the tumor size increases. There may be a difference in frequency of lymph node involvement that depends on the histologic type of the primary tumor; Nogales and Botella-Llusia[335] have reported only 8% involvement in "basal cell" squamous cancers, as compared with 51.8% in "spindle cell" squamous and 84.8% in adenocarcinomas. Chung and coworkers[336] claim that, regardless of clinical stage, poorly differentiated tumors are more likely than well-differentiated ones to metastasize to pelvic or paraortic lymph nodes, and Boyce and associates[337] note more lymph node metastases in cases with primary tumors exceeding 10 mm in depth. Stendahl and coworkers[318] have developed a multiparameter grading system that they also claim exceeds clinical staging alone in prognostic value. The prognostic significance of vascular or lymphatic invasion is debatable; different studies have claimed that this histologic finding is[338] and is not[339] associated with a poorer survival rate. The depth of invasion of the tumor is a significant prognostic factor; tumor invasion exceeding 10 mm in depth is a poor prognostic

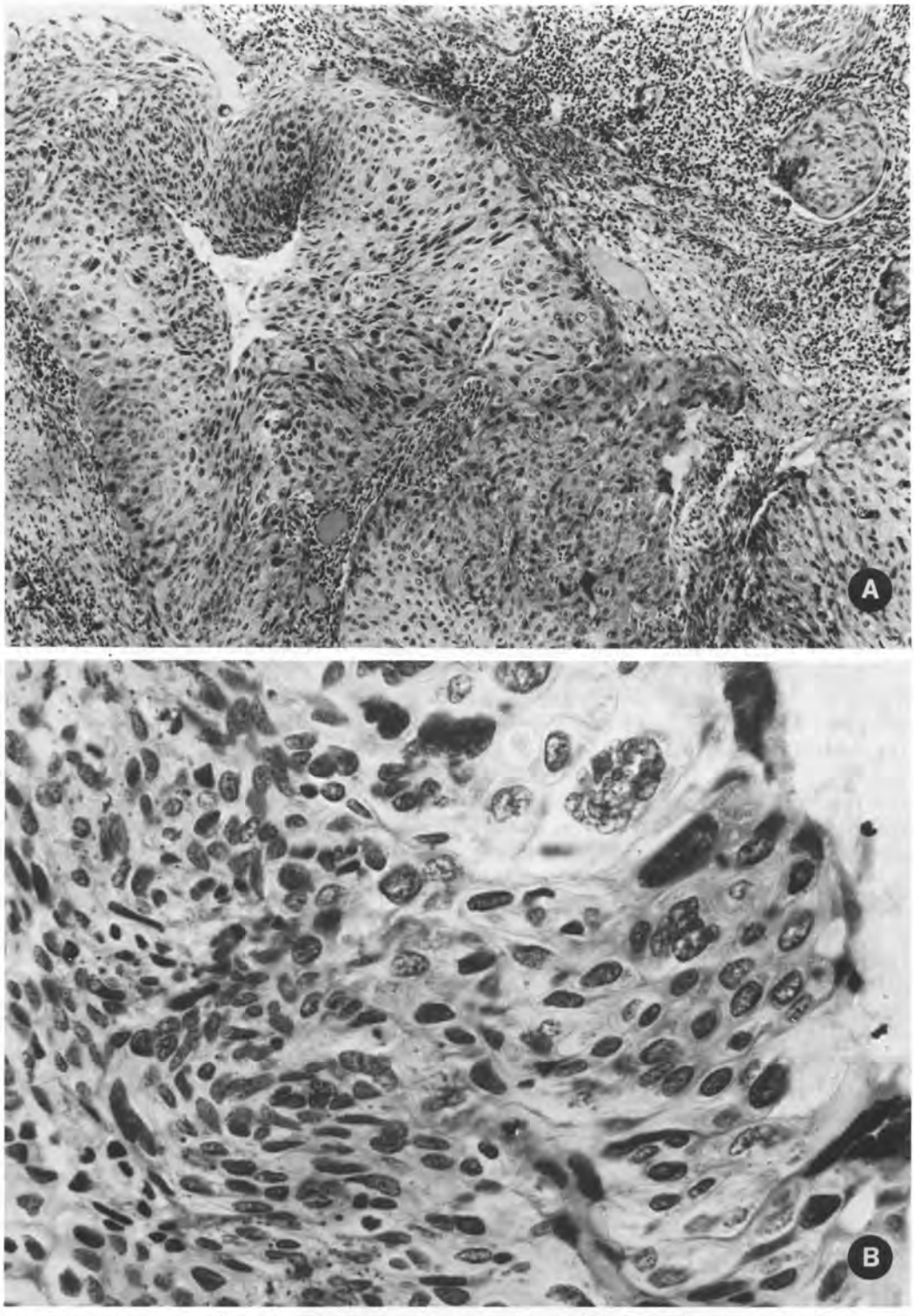


FIGURE 3-57 Large cell nonkeratinizing squamous carcinoma. **(A)** General appearance. **(B)** Detail.

factor and is associated with increased incidence of pelvic node metastases and local extension.[337]

Metastatic lymphadenopathy develops in the following manner (Fig. 3-60). A first nodal group is involved, comprising the highest external iliac and the hypogastric nodes. Among these, the middle node of the internal chain of the external ilial group, named the *obturator node,* appears to be most frequently invaded. A second group is subsequently reached, comprising the common ilial, sacral, and aortic nodes. However, a more distant node may be involved when the first order nodes are intact; for ex-

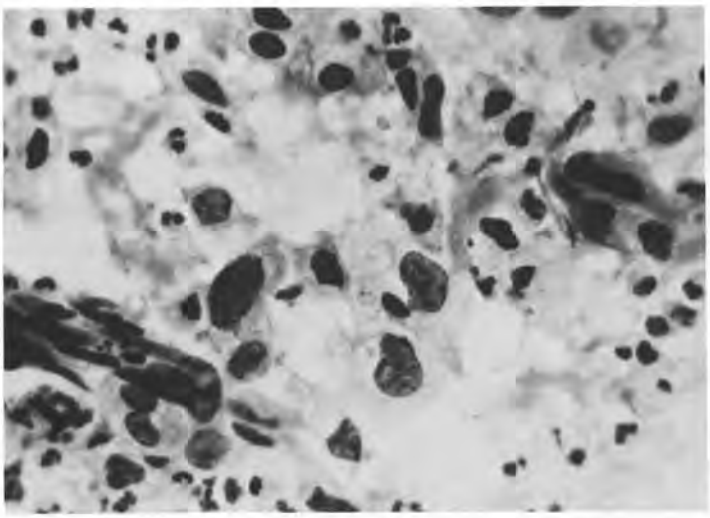


FIGURE 3-58 Keratinizing squamous cell carcinoma: cytologic appearance. Note pleomorphism and "tumor diathesis."

ample, it is not rare to see a supraclavicular node invaded as the first indication of a disseminated tumor.[340] The commonly involved nodes, in descending order of frequency, have been stated to be parametrial, common ilial, paracervical, hypogastric, obturator, external iliac, aortic, sacral, and inguinal.

When the tumor continues its evolution, it involves the vesicovaginal and rectovaginal regions, the bladder, the rectum, and the low ureteral region (Fig. 3-61). In the bladder, the serosa and muscular layers are invaded, but rarely the mucosa. Similarly, the rectal wall is invaded in its submucosal layers by the lymphatic route. The ureters are frequently obstructed (about 80% of autopsied cases), sometimes by external compression, sometimes by radiation fibrosis in the absence of residual tumor (this last event may occur many years after primary therapy). The sequelae of this ureteral involvement consist of alterations of the upper urinary tract (hydronephrosis, pyelographic abnormalities, pyelonephritis, and disorders of renal function). Uremia and sepsis intervene frequently and are the most common causes of death. Distant metastases may involve any of the viscera; the liver, lungs, bones, adrenals, ovaries, and brain are among the most frequently involved (Fig. 3-62).

Studies of prognostic criteria have often been contradictory, but it is universally accepted that *clinical stage* (see Table 3-7) is the most important prognostic indicator. In most series, clinical stage 0 (in situ) cancers are associated with 5-year survival rates of close to 100%. This figure drops to 75% to 80% in stage I, 50% to 60% in stage II, about 30% in stage III, and 10% in stage IV. Extension to the corpus does not advance the stage but may worsen the prognosis.[341] Within the group of stage I tumors, tumor size and depth of invasion correlate well with survival.[342,343] Five-year survival rates are good indications of the therapeutic results, because more than 90% of deaths caused by cervical cancer occur within the first 5 years after treatment.[317,344]

The prognostic significance of most other indicators remains debatable. We have already discussed such factors as tumor type and grade, presence of

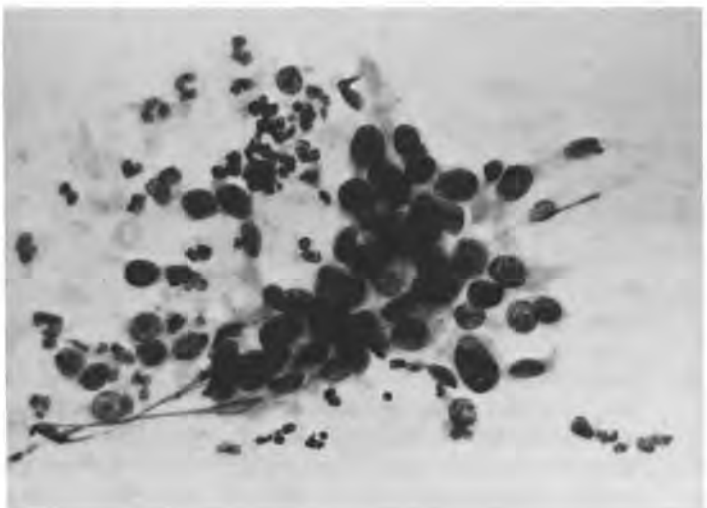


FIGURE 3-59 Large cell nonkeratinizing squamous cell carcinoma: cytologic appearance.

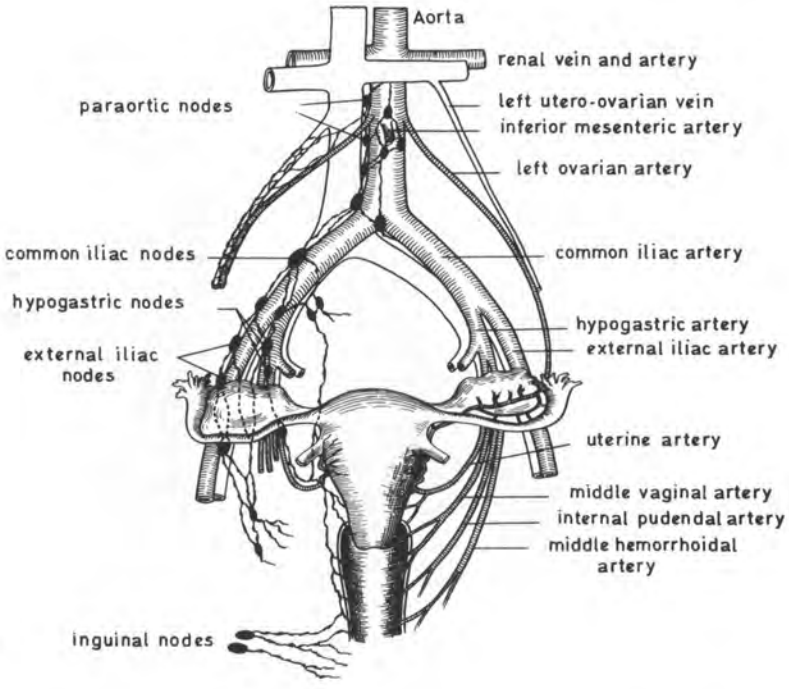


FIGURE 3-60 Lymphatic system of the genital organs.

stainable mucin, and lymphatic or vascular space invasion in the section on classification. Other investigators have been more interested in the host immune response. Both host cellular immunity and tumor-associated antigens have been demonstrated in cervical carcinoma, and this field deserves further exploration. Squamous cell carcinoma antigen (SCC-A) and CA-125 are said to predict and to detect recurrent disease.[345,346] In another series, invasive squamous carcinomas infected with HPV-16 spread to the parametria and pelvic nodes significantly more often than did HPV-16-negative tumors,[347] whereas HPV-18[348,349] or absence of HPV[350] suggested a worse prognosis to other investigators.

Lymphoplasmacytic infiltration of the tumor

FIGURE 3-61 Squamous cell carcinoma of the cervix: bladder with metastases invading submucosally.

FIGURE 3-62 Squamous cell carcinoma of cervix: hepatic (*left*) and pulmonary (*right*) metastases.

may have a significant value in the prognostic evaluation.[338,351,352] Age 60 or older can be considered a prognostic factor; prognosis of patients in this age category is significantly better than that of patients in younger age groups in some series.[353] A report of Sorensen and colleagues[354] has shown that the nuclear volume is of prognostic value for objective malignancy grading. Such factors as AgNOR counts,[352] flow cytometry,[355] and oncogene overexpression[356,357] have been assigned prognostic significance in recent studies. In summary, the ideal prognostic factors still remain to be defined in this disease.

Studies have shown that therapeutic results—particularly in advanced stages—are improved when patients are treated in large centers by specialists skilled in the treatment of this disease.[358] The longstanding battle between advocates of surgery (Wertheim hysterectomy in stage I or II and exenteration for more advanced cases) and radiation therapy largely has been abandoned, because the therapeutic results are about equal.[359,360] The advent of high-voltage radiation therapy has greatly lowered the incidence of complications of treatment, and most institutions are treating most patients by this modality. Combination chemotherapy in advanced stages is being tested, and induction chemotherapy may potentiate surgery or radiation therapy in earlier stages.[361] An interdepartmental tumor conference or consultation system involving gynecologic and radiation oncologists and pathologists usually guarantees optimal and individualized treatment for each patient.

Microinvasive Squamous Carcinoma

The term *microinvasive squamous carcinoma* has been used to define an early stage of invasive squamous carcinoma in which no lesion is visible clinically and the diagnosis is first made histologically.[362–372,374–378] Criteria for diagnosis have varied markedly over the past 30 years, creating some confusion in the definition and treatment of the lesion. The depth of invasion, the configuration of the invasive tongues of neoplastic epithelium, and the evaluation of vascular and lymphatic permeation are among the subjects of contention. According to different proposed classifications, the maximal stromal invasion varies from 1 mm[364] to 9 mm,[365] and some authors include three-dimensional measurements in the definition.[366,368] The ultimate goal is to describe a lesion that can be treated safely by more conservative means than other squamous cancers.

In the clinical staging system of the International Federation of Gynecology and Obstetrics (FIGO; Tables 3-7 and 3-8), microinvasive carcinoma is considered stage Ia, which can be divided into Ia1 (invasive foci confined to a few tongue-like processes) and Ia2 (measurable tumor limited to a depth of less than 5 mm with a horizontal dimension of less than 7 mm).[367,378]

TABLE 3-8.
Criteria for Diagnosis of Microinvasive Squamous Carcinoma of the Cervix

Criteria	*International Federation of Gynecology and Obstetrics (FIGO)*	*Society of Gynecologic Oncologists*	*Japanese Joint Study Committee*
Size	Ia1: tongue-like processes only Ia2: up to 5 mm deep,* 7 mm wide	Up to 3 mm deep*	Up to 3 mm deep*
Lymphatic/vascular space involvement	May be present	No	No
Confluent growth pattern	May be present	May be present	No

*Measured from base of overlying epithelium.

Other studies[368,369,377] have indicated that lesions with a maximal stromal penetration of 3 mm and no lymphatic/vascular space invasion (LVSI) have an excellent prognosis, with virtually no potential for recurrence or metastasis. The definition of the Society of Gynecologic Oncologists (SGO) meets these criteria.[377] It states that "neoplastic epithelium invades the stroma in one or more places to a depth of 3 millimeters or less below the epithelium and lymphatic or vascular involvement is not demonstrated." It is not stated, however, how many serial step sections are needed to rule out deeper invasion or lymphatic or vascular permeation. Finally, the definition of the Japanese Joint Study Committee on Stage Ia Cancer of the Uterine Cervix[376] accepts a depth of 3 mm or less but excludes cases with either LVSI or confluent invasion. We tend to favor this lattermost definition.

Histology. The very early manifestation of microinvasion is the presence of a nidus of well-differentiated cells originating from the basal layers of the epithelium and disrupting the basement membrane. Downward tongue-like processes develop from this initial invasion and expand into the stroma vertically and horizontally. Multiple foci may develop. Confluent growth is characterized by anastomosing tongues of tumor cells with pushing borders.[370] The most common cellular growth patterns are finger-like cords, networks of confluent strands, or small clusters. The histologic types are, with decreasing frequency, large cell nonkeratinizing, keratinizing, and small cell types.[371]

Capillary/lymphatic space invasion should be diagnosed with care. The presence of endothelial cells is mandatory to affirm this invasion. Clear spaces around tumor cells may represent fixation artifacts. Roche and Norris[372] demonstrated that the finding of LVSI is directly proportional to the number of levels examined, and many more cases would be excluded by the SGO and Japanese criteria if dozens of levels were examined routinely.

It is important not to diagnose microinvasion when only endocervical gland extension is present. In true microinvasion, the invasive tongues of cancer have angular rather than round and smooth contours, lack a surrounding "basement membrane" (as seen with the light microscope), and almost invariably show evidence of increased differentiation (eg, increased volume of eosinophilic cytoplasm, and intercellular bridges) compared with overlying epithelium, which has the appearance of in situ carcinoma or (less frequently) dysplasia (Figs. 3-63 through 3-65 and Table 3-9).

Microinvasive carcinoma can be diagnosed only in an adequate specimen, defined as a cone biopsy or hysterectomy specimen. In punch biopsies, the diagnosis may occasionally be suggested, but conization or hysterectomy remains mandatory for confirmation.

Cytology. The picture is usually that of coexisting in situ and invasive carcinoma. Some authors claim great accuracy in the exact cytologic diagnosis of the lesion, whereas others, like us, experience considerable difficulty. The most frequently reported criteria are (1) the presence of inflammation and necrosis ("tumor diathesis"); (2) abnormal cells in syncytial groupings; (3) abnormal cells whose nuclei have irregular chromatin distribution; and (4) abnormal cells with prominent nucleoli.[373]

Clinical Features. The incidence of microinvasive carcinoma as a proportion of in situ carcinomas has varied from 3% to 50% of in situ carcinoma in reported series,[374] pointing out the need for an adequate definition. The true incidence is probably around 5% to 10%. The *clinical significance* of the lesion is that, despite its invasive nature, it can be treated conservatively (like in situ carcinoma) with great success. We believe that for this statement to be true, all cases with lymphatic or blood vessel invasion and all cases with confluent tumor nests in the stroma must be eliminated from the microinvasive group and treated more vigorously. As discussed above, this concept is still controversial, with some authors (and the FIGO definition) stating that the depth of invasion should be the only significant fac-

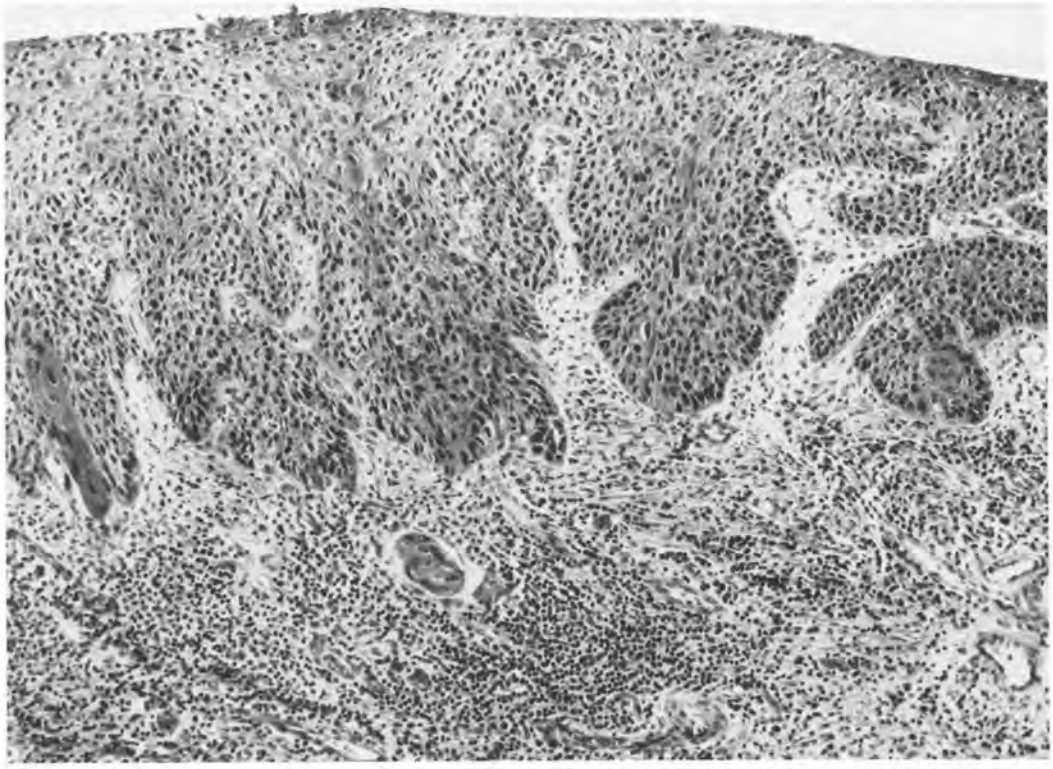


FIGURE 3-63 Microinvasive carcinoma: invasive tongues and one discontinuous nest of differentiated malignant cells.

tor. Boyes and colleagues[375] have suggested the separate term *occult invasive carcinoma* for the confluent tumors and have shown an appreciable incidence of recurrence, metastasis, or both, when this group is treated conservatively. Yamabe[376] has discussed the importance of separating local (eg, vaginal stump) recurrences from true metastases, because it is the latter which should be used to define the group of cases requiring more aggressive treatment.

Carcinoma of the Cervical Stump

The appearance of a cancer in a cervical stump (ie, that portion remaining after supracervical hysterec-

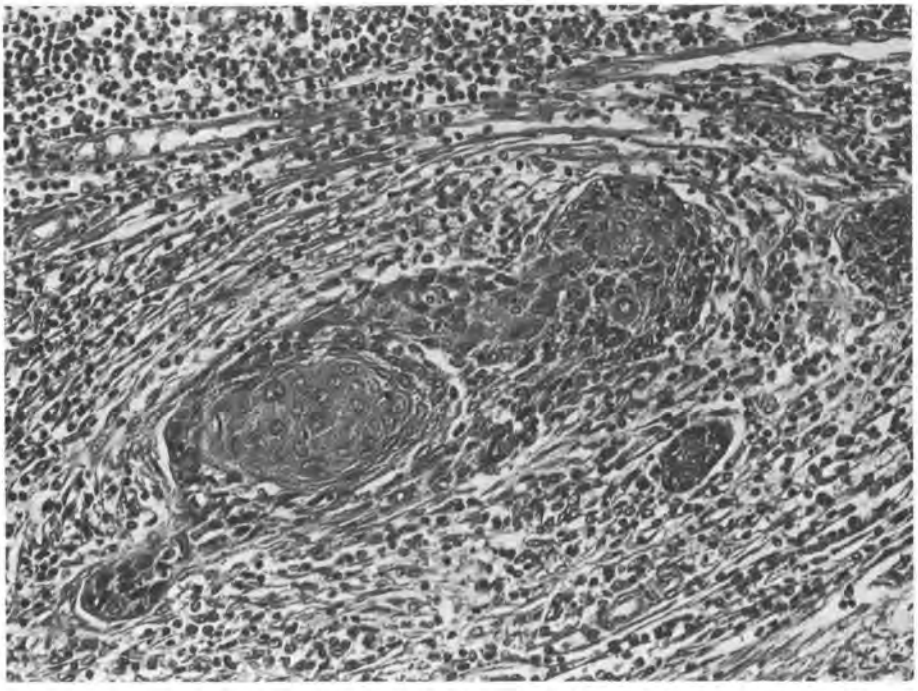


FIGURE 3-64 Microinvasive carcinoma: detail of a nest of tumor cells showing central squamous differentiation, lack of basement membrane, and surrounding stromal reaction.

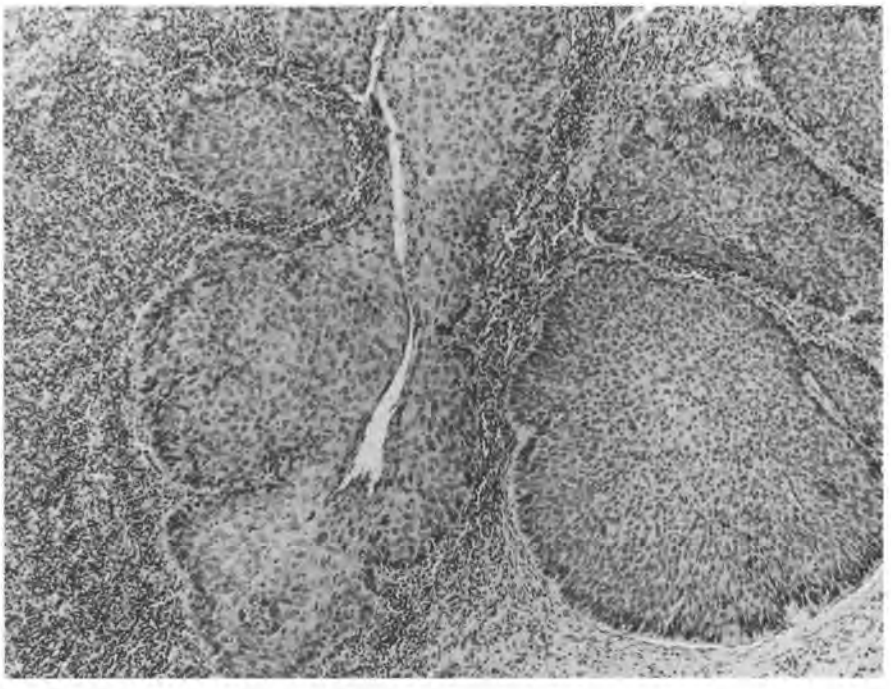


FIGURE 3-65 High-grade CIN extending into and completely replacing endocervical glands. Note roundness of the tumor nests, good circumscription from surrounding stroma, and lack of squamous differentiation.

tomy) poses important clinical problems.[379–381] It represents 4% to 8% of cervical cancers. Of the 183 cases cited by Creadick,[380] 14 were intraepithelial. Among the invasive cancers, the various histologic subtypes are found in about the same proportions as in the intact cervix, and even sarcomas have been reported.[382] Their macroscopic and microscopic appearance do not differ from those of cervical cancers in the intact uterus: only the therapeutic problems are different. It is more difficult, technically speaking, to irradiate or to operate on a cervical stump.

This is why, after a subtotal hysterectomy, it is necessary to verify the state of the cervix and to eliminate the presence of a neoplastic lesion. The complete avoidance of supracervical hysterectomy eliminates the problem entirely. If the tumor is detected less than 2 years after subtotal hysterectomy, it was probably already present at the time of initial surgery.[381]

Verrucous Carcinoma

This rare form of very well-differentiated squamous cell carcinoma may develop in the cervix,[383] but it is more common in the vulva and vagina and has been

TABLE 3-9.
Differential Diagnosis of Cervical Microinvasive Carcinoma Versus CIN With Gland Extension

Criteria	*Microinvasion*	*CIN With Gland Extension*
Size of tumor nests	Variable	Uniform
Shape of tumor nests	Angular	Rounded
Basement membrane	Absent	Present
Stromal inflammation	Present	Often absent
Squamous differentiation (eosinophilic cytoplasm) in tumor nests	Present	Absent (tumor cell differentiation $\leqq$ surface epithelium)
Adjacent glands	Variable	Usually present, often focally involved by CIN
Lymphatic/vascular space invasion	Sometimes*	Never
Confluence of tumor nests	Sometimes*	Never

*May be excluded by definition of microinvasion.

discussed in Chapters 1 and 2. Microscopically, it is characterized by marked papillomatosis, normal squamous maturation, and the absence of cellular atypia. The tumor expands into the underlying stroma by pushing, bulky rete pegs with smooth margins. This lesion requires a full-thickness excisional biopsy to be recognized. The differential diagnosis comprises condyloma acuminatum and well-differentiated squamous carcinoma. If treated by adequate local excision, metastases should not occur.

Papillary Squamous Cell Carcinoma

This rare form of carcinoma, reported by Randall and associates,[384] reveals a papillary, wart-like macroscopic appearance corresponding microscopically to fibrovascular cores covered with a dysplastic epithelium showing moderate to severe cellular atypia. The lesion can be in situ or invasive, and a cone biopsy or hysterectomy specimen is necessary to rule out stromal invasion. The ISGP classification (see Table 3-6) uses *papillary transitional cell carcinoma* as a synonym for this lesion because of its resemblance to bladder carcinoma. The cytologic atypia distinguishes it from verrucous carcinoma or benign papilloma. If invasive, the tumor can metastasize, sometimes as a late event.[384]

Lymphoepithelioma-Like Carcinoma

Lymphoepithelioma-like carcinoma is another tumor included in the ISGP classification as a variant of squamous cell carcinoma.[226] It is a rare lesion, usually well circumscribed, consisting of solid nests of undifferentiated cells with indistinct cell borders and an interspersed marked inflammatory infiltrate of lymphocytes, plasma cells, and eosinophils.[385,386] Similar tumors in the nasopharynx and salivary glands have been referred to as *lymphoepitheliomas*, and in the breast as *medullary carcinomas*. The behavior of this lesion in the cervix remains to be defined, but one report has suggested a relatively favorable prognosis.[385] The differential diagnosis includes inflamed squamous cell carcinoma, glassy cell carcinoma, and malignant lymphoma. The first two have larger cells with distinct cell borders; the last may require immunohistochemical evaluation for definitive diagnosis.

Small Cell Neuroendocrine Carcinoma

Small cell neuroendocrine carcinomas[313–316,387–389] exhibit small or intermediate-type cells that arise from argyrophilic cells present in the ectocervical or endocervical epithelium[390,391] or from undifferentiated stem cells. The neoplastic cells are arranged in nests or sheets or are disposed in single files. They have hyperchromatic nuclei with finely dispersed chromatin and an elevated nuclear–cytoplasmic ratio (Fig. 3-66). Molding, crushing and overlapping modify the disposition of the nuclei. Intermediate-type cells are larger and exhibit a pale, eosinophilic cytoplasm with ill-defined borders. Their nuclei are oval and uniform. In both types mitoses are numerous. Nucleoli are inconspicuous. Necrosis is common, particularly in tumors growing in large nests or sheets. Foci of squamous or glandular differentiation are not rare.[313] A high prevalence of HPV types 16 and particularly 18 has been reported in neuroendocrine carcinomas.[388]

The differential diagnosis includes squamous cell and adenocarcinoma, carcinoid tumor, stromal sarcoma, and malignant lymphoma. Immunohistochemical and ultrastructural studies can establish the diagnosis in problem cases. Argyrophilic granules vary in quantity from one case to another and may require prolonged search at the light microscopic and ultrastructural levels. Positive immunoreaction is observed for cytokeratins, CEA, chromogranin, neuron-specific enolase, synaptophysin, and a variety of polypeptides such as ACTH, serotonin, calcitonin, gastrin, and somatostatin.[315,389,391]

Few cytologic reports are available, and rarely the tumor has been discovered by cytology.[315,316] The aggressive, often voluminous tumor generally is clinically evident. Smears reveal small cells with round or oval hyperchromatic nuclei and scant basophilic cytoplasm. Nucleoli are small and inconspicuous. In some cases, glandular structures coexist with the neuroendocrine cells.[387,392]

The prognosis is poor, and distant metastases are often present at the time of initial diagnosis or soon thereafter. Liver and bones are frequently involved, as in small cell carcinoma of the lung. Chemotherapy may produce a response but rarely a cure.

Carcinoid Tumor

It is not clear whether a better differentiated neuroendocrine tumor that may be classified as pure carcinoid tumor occurs in the uterine cervix. This tumor appears in the ISGP classification as a synonym for

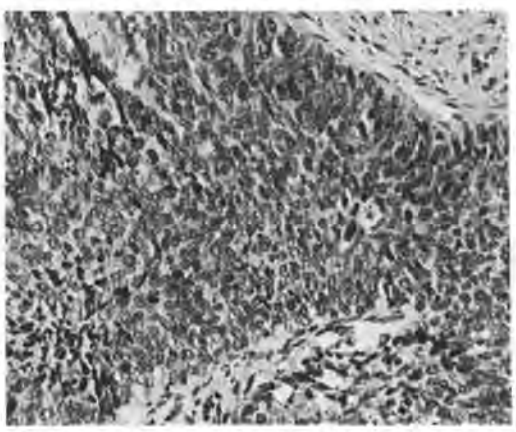


FIGURE 3-66 Small cell carcinoma: microscopic appearance.

adenocarcinoma with features of carcinoid tumor, and Kurman and colleagues question whether a pure carcinoid of the cervix exists.[226] We have seen rare cases (Fig. 3-67) that appear to represent pure carcinoids, usually found as incidental microscopic lesions in cervices removed or biopsied for other indications. More commonly, the typical carcinoid pattern is seen focally in otherwise typical small cell carcinomas or adenocarcinomas.

Adenocarcinoma

Thirty or forty years ago, 95% of all cancers of the uterine cervix were of squamous origin, and adenocarcinomas and their precursor lesions were considered rarities. In subsequent years, the cytologic detection and early treatment of precursors of squamous carcinoma have reduced the frequency of that lesion in many parts of the world, and the proportion of cervical cancers that have an adenocarcinomatous component has increased to 15% or greater in recent reports. Some of these reports have suggested that the absolute as well as the relative incidences of adenocarcinoma may be rising.[393,394]

As these glandular lesions become more common, we are learning more about their clinical and pathologic manifestations, including the recognition of new variants of invasive adenocarcinoma, of precursor lesions, and of benign neoplastic and nonneoplastic lesions that may enter into their differential diagnosis.[395–399] The new ISGP classification of cervical glandular tumors, other nonsquamous epithelial tumors, and glandular tumor-like lesions is presented in Table 3-10.

Adenocarcinoma does not display the same relationship to sexual activity that has been described previously for squamous cell carcinoma, which suggests that different etiologic factors are involved.[400] Nevertheless, the two tumors or their preinvasive variants frequently coexist in the same patient,[401,402] and adenocarcinomas have been associated with HPV, particularly type 18.[82,83,89,402–404] Dallenbach-Hellweg[405] has suggested a link between oral contraceptive usage and the development of cervical adenocarcinomas in young women, but these data have not been confirmed in other series.[406]

Invasive Mucinous Adenocarcinoma

The prototype for adenocarcinoma of the cervix is the mucinous type, particularly its endocervical variant. This is a tumor largely limited to adult women, whose average age is about 50 years. From 80% to 90% of the patients present with abnormal uterine bleeding, although other complaints occur and up to 20% of patients may be asymptomatic. Some of these latter cases are detected by an abnormal Papanicolaou smear, but in most series 50% or more of women with adenocarcinoma of the cervix have a normal smear.[407]

The *gross appearance* of adenocarcinoma of the cervix is variable, some of the tumors presenting as exophytic, polypoid, or papillary processes (Fig. 3-68), whereas others have a grossly normal surface and grow entirely endophytically. In some cases,

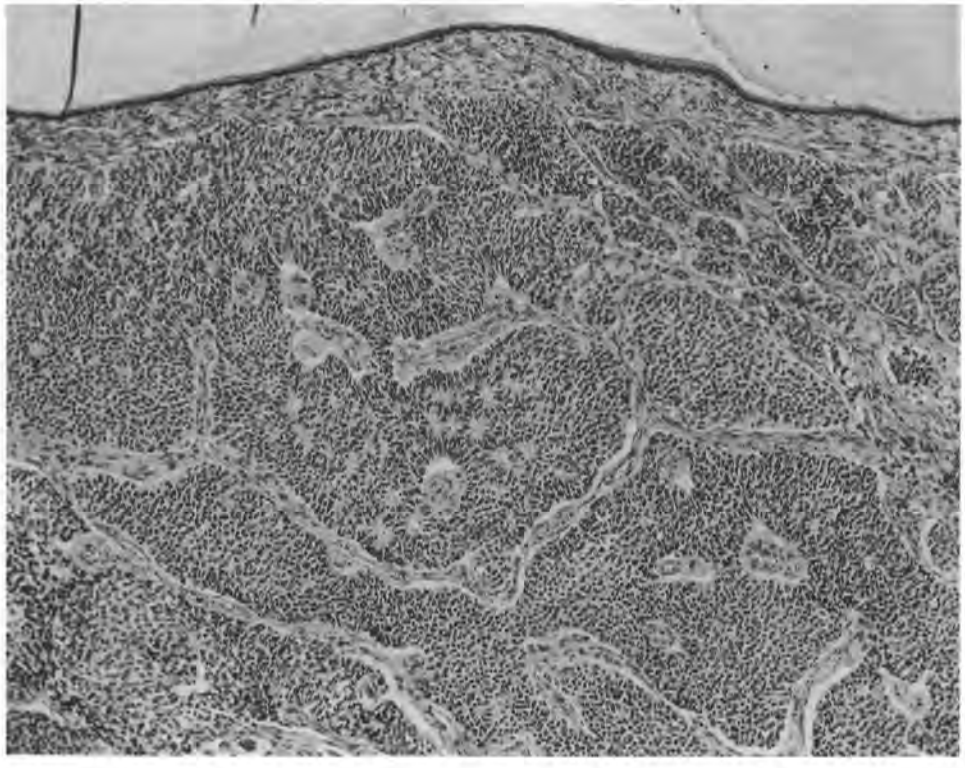


FIGURE 3-67 Carcinoid tumor of the cervix. This tumor was an incidental microscopic finding.

TABLE 3-10.
International Society of Gynecological Pathologists Classification of Cervical Glandular Tumors and Tumor-Like Lesions (1991)

Glandular Lesions
Endocervical polyp
Müllerian papilloma
Glandular atypia
Atypical hyperplasia (glandular dysplasia)
Adenocarcinoma in situ
Adenocarcinoma
Mucinous (endocervical, intestinal, and signet-ring types)
Endometrioid
Clear cell
Minimal deviation (adenoma malignum)
Papillary villoglandular
Serous
Mesonephric
Glandular Tumor-Like Lesions
Microglandular hyperplasia
Mesonephric remnants
Mesonephric hyperplasia
Arias-Stella reaction
Endometriosis
Cysts
Intestinal metaplasia
Tubal metaplasia
Tunnel clusters
Other Epithelial Tumors
Adenosquamous carcinoma
Glassy cell carcinoma
Adenoid cystic carcinoma
Adenoid basal carcinoma
Carcinoid tumor (adenocarcinoma with features of carcinoid tumor)
Small cell carcinoma
Undifferentiated carcinoma

gross examination of the cervix may even reveal only benign changes.

Microscopically, as mentioned above, the most common type is adenocarcinoma of endocervical type, which is said to account for about 70% of all cervical adenocarcinomas.[395] By definition, these tumors must contain at least some cells in which cytoplasmic mucin can be demonstrated. In most of these tumors, glands of variable size and shape infiltrate through the wall of the cervix, with a variable amount of stromal reaction around them. There is at least some cellular stratification, loss of mucin, nuclear enlargement, hyperchromasia, and mitotic activity, and the severity of these changes varies with the differentiation of the tumor (Figs. 3-69 through 3-72).

Unlike *endometrioid adenocarcinomas*—whether of endocervical or endometrial origin—the glands generally do not grow together in a cribriform pattern and usually are unassociated with a prominent squamous component. Mucin can be demonstrated in the cytoplasm of at least some of the cells of endocervical-type adenocarcinomas, whereas mucin usually is present only at the apical borders of the tumor cells and in tumor lumina in endometrioid adenocarcinomas. This difference is reflected in differences in immunohistochemical reactivity. For example, CEA is said by some authors to be much more common in endocervical than in endometrial adenocarcinoma,[408,409] although others deny this difference.[410] Some authors claim that vimentin immunoreactivity is much more common in endometrial than in endocervical adenocarcinoma, and 1C-5, a

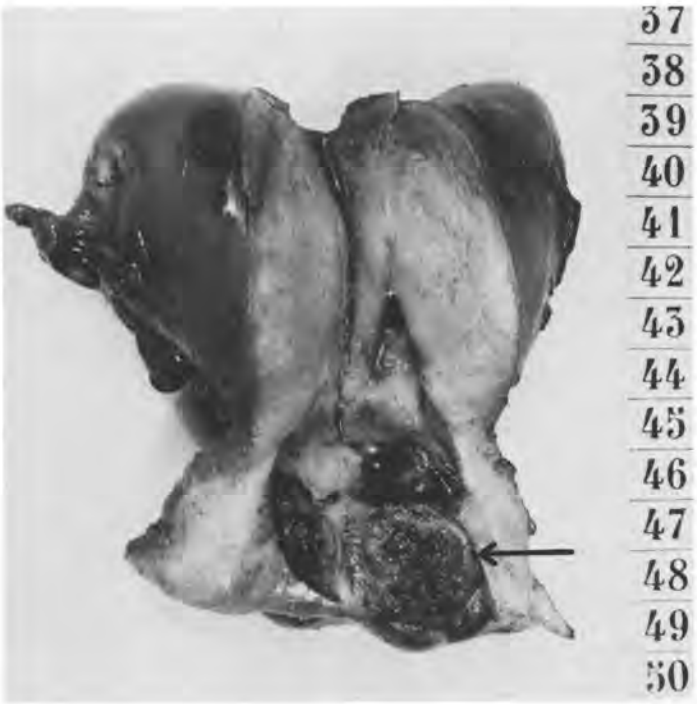


FIGURE 3-68 Adenocarcinoma of the cervix: macroscopic appearance.

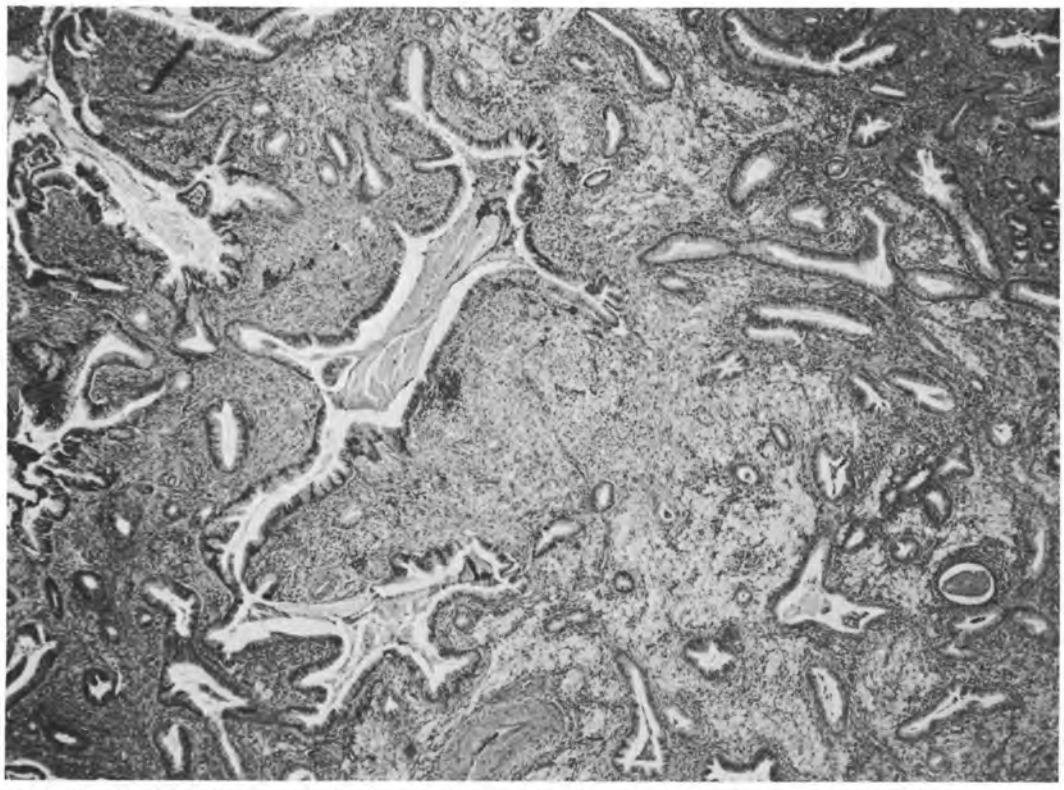


FIGURE 3-69 Well-differentiated adenocarcinoma of endocervical type: low-power photomicrograph of angular glands infiltrating stroma.

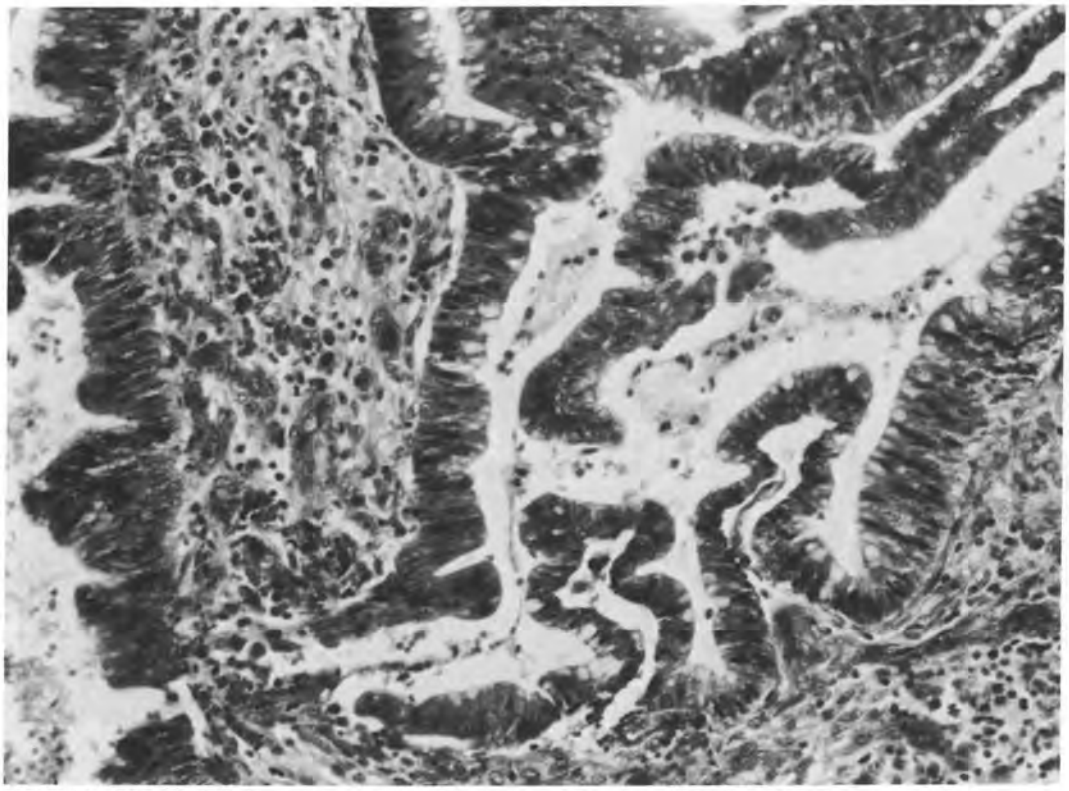


FIGURE 3-70 Well-differentiated endocervical adenocarcinoma: detail of invasive malignant glands.

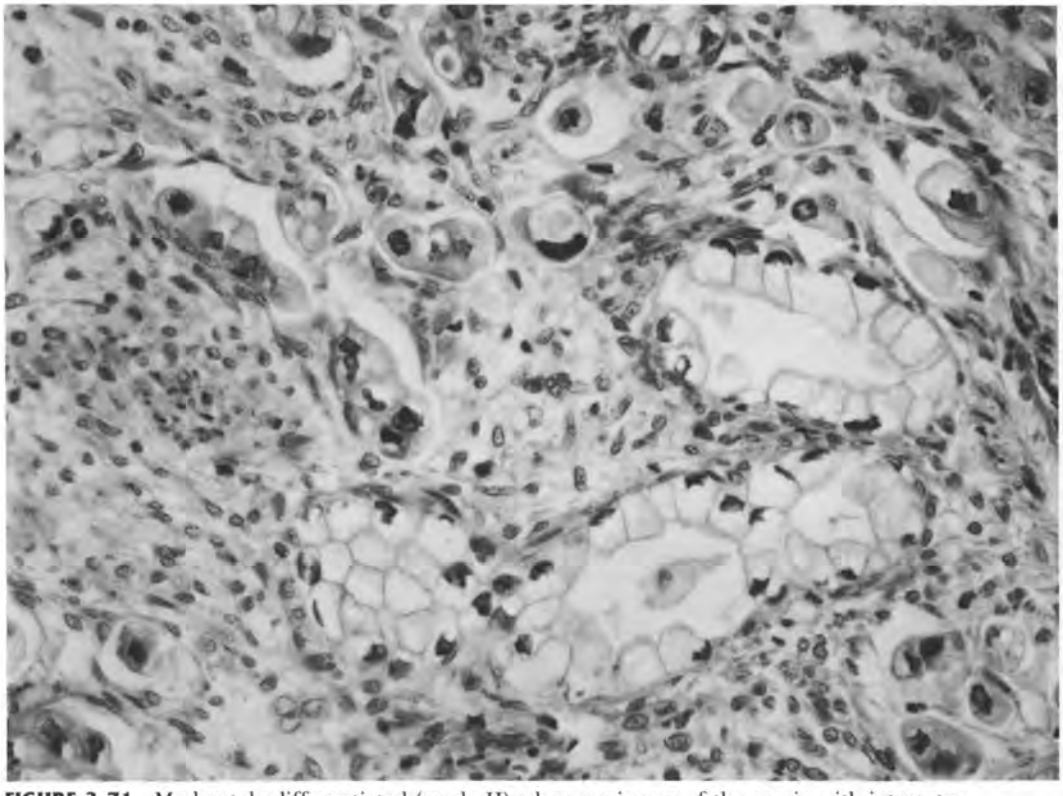


FIGURE 3-71 Moderately differentiated (grade II) adenocarcinoma of the cervix with intracytoplasmic mucin globules within malignant glands and in single signet-ring cells.

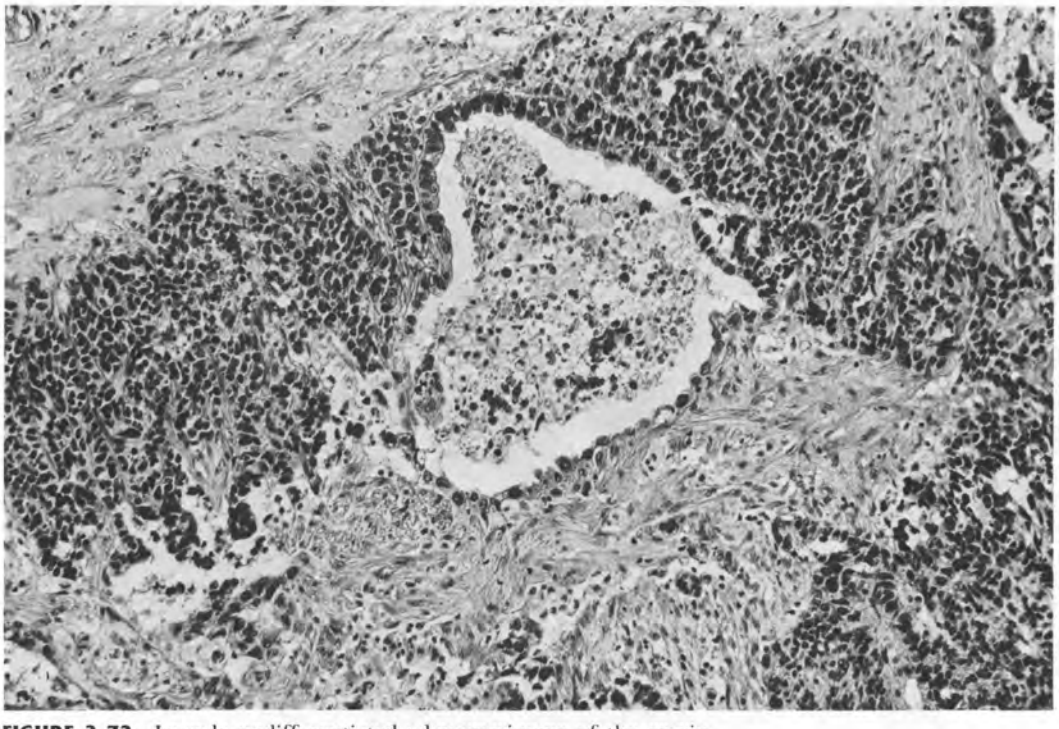


FIGURE 3-72 Largely undifferentiated adenocarcinoma of the cervix.

new monoclonal antibody, has also proved useful in one published report.[411] These stains and histologic appearances differentiate between adenocarcinomas of endometrioid and endocervicoid *types,* rather than of endometrial and endocervical *origin.*[412] Because as many as 15% to 20% of primary adenocarcinomas of the endocervix are of endometrioid type, and about 5% of adenocarcinomas of the endometrium are of mucinous (generally endocervicoid) type, the site of origin of these tumors will always be stated incorrectly by any test relying on histologic appearance or markers of differentiation. The presence of a typical endometrial or endocervical stroma identifies the involved tissue site but may not indicate tumor origin, because carcinoma of the endometrium may extend downward to involve the endocervix and vice versa. The differential diagnosis of endocervical versus endometrial adenocarcinoma is summarized in Table 3-2.

As endocervical adenocarcinomas become more undifferentiated, they may contain solid areas that cannot be differentiated from poorly differentiated squamous carcinoma or even small cell carcinoma (see Fig. 3-72). Even the presence of cervical squamous dysplasia or in situ carcinoma does not resolve the differential diagnosis between poorly differentiated adenocarcinoma and poorly differentiated squamous carcinoma, because these lesions accompany about 40% of cases of well-documented cervical adenocarcinoma.[401,413]

The level of differentiation of cervical adenocarcinoma is important, because it has been shown in numerous studies to be associated with prognosis, well-differentiated tumors having better survival rates than poorly differentiated ones.[407,414,415] Poorly differentiated tumors also tend to present in higher clinical stages, and sometimes it is difficult to separate the prognostic effects of grade and stage. This is also a problem when comparing the outcomes of adenocarcinomas and squamous carcinomas of the cervix. Most studies have suggested that adenocarcinoma is associated with a poorer prognosis, but this is not always true when tumors of the same clinical stage are compared.[393,416,417] The routes of local and distant metastatic spread are the same as for squamous cell carcinoma.

Cytologic Findings. Although the cytologic characteristics of endocervical adenocarcinoma are well established, as many as half of the cases in some series have been missed by cytologic examination.[407,418] The reason for this high false-negative rate is that adenocarcinomas frequently arise high in the endocervical canal and beneath an intact surface mucosa, so that the cells may easily be missed unless vigorous direct endocervical sampling is performed. In endocervical adenocarcinoma, the tumor cells in cytologic material occur most frequently in clusters, often with a papillary arrangement (Color Fig. 3-31). The papillary or glandular arrangement is less apparent in more poorly differentiated tumors.

The cells are generally elongated, with an apparent apical pole and peripheral nucleus; this polarity is a useful distinguishing feature from the more common cervical squamous cell cancers. The cytoplasm is often vacuolated and lacks evidence of keratinization. The nucleus is round to oval and shows considerable enlargement and variation in size and shape from one cell to the next. There is prominent clumping of chromatin within the nuclear substance and along the nuclear membrane, and one or more large prominent nucleoli. The background often shows the same necrotic debris or "tumor diathesis" seen in squamous cell carcinoma.

The cytologic differential diagnosis is with benign reactive endocervical and metaplastic conditions (see Color Figs. 3-4 through 3-8), with large cell nonkeratinizing squamous cell carcinoma of the cervix (see Color Fig. 3-29), and with adenocarcinoma of the endometrium (Color Fig. 3-32). This last distinction is the most difficult; even histologically it may be a problem to differentiate these two entities (see above). The cells of an endocervical adenocarcinoma are generally larger, with larger nuclei and nucleoli and greater cytoplasmic vacuolization, than those of endometrial cancer (compare Color Figs. 3-31 and 3-32). Adenocarcinoma cells arising from the ovary, the fallopian tube, or an extragenital primary cancer metastatic to the genital tract are usually unaccompanied by a tumor diathesis.

Other Types of Invasive Adenocarcinomas

In addition to the most common mucinous tumor of endocervical type, rarer invasive mucinous tumors may show intestinal or signet-ring differentiation.[407,419,420] Any of the other types of differentiation seen elsewhere in the female genital tract may be encountered, including endometrioid (as discussed above), clear cell, and serous adenocarcinomas. *Endometrioid adenocarcinoma* is the most common of these, comprising 15% to 20% of endocervical adenocarcinomas in most reports.[395] As mentioned above, this tumor needs to be differentiated both from the endocervical type of tumor and from adenocarcinoma arising in the endometrium.

Clear Cell Adenocarcinoma. Clear cell adenocarcinoma is seen most frequently in young women who have been exposed to DES in utero, but it is also encountered in all age groups in DES-unexposed patients.[421,422] The DES-related tumors invariably involve the ectocervix, often extending upward into the endocervix or downward into the vagina; indeed, many of these may have originated in the vagina and extended upward to involve the cervix. Microscopically, the tumors grow in varying mixtures of

tubulocystic, solid, and papillary patterns, and are characteristically composed of clear or hobnail cells, with some tumors containing many flattened cells as well. The clear cells are characteristically rich in glycogen and poor in mucin. The appearance of these tumors is illustrated in Chapters 2 and 4. The differential diagnosis of these tumors includes other types of adenocarcinoma, as well as the Arias-Stella reaction (see Fig. 3-7) and yolk sac carcinoma—the former seen predominantly in pregnancy and the latter almost exclusively in infancy.

Serous Adenocarcinoma. Also important in the differential diagnosis of clear cell adenocarcinoma is primary serous adenocarcinoma of the cervix. This is an extremely rare tumor, only a few cases of which are described in the literature.[423] Its histologic appearance is similar to that of serous carcinomas in more common sites, such as the ovary, fallopian tube, and endometrium.

Minimal Deviation Adenocarcinoma. Another uncommon type of cervical adenocarcinoma is minimal deviation adenocarcinoma, also known as *adenoma malignum.*[424-431] The controversy over this lesion extends to its classification; Young and Scully[395] characterize it as a variant of endocervical-type adenocarcinoma, whereas the ISGP classification (see Table 3-10) lists it as a separate and independent variant. This is because Kaminski and Norris[426] included an endometrioid type in their report, whereas most others have limited the diagnosis of minimal deviation adenocarcinoma to tumors of endocervical type. In any event, the defining feature is that the glands comprising the tumor lack significant nuclear stratification, pleomorphism, or mitotic activity, although the glands are usually of bizarre shape, with numerous angular outpouchings, and deeply infiltrate the cervical wall (Figs. 3-73 and 3-74). These tumors can be confused with usual endocervical adenocarcinomas but are even more likely to be confused with benign lesions, such as tunnel clusters[51,164] (see Fig. 3-31), deep nabothian cysts,[171] and mesonephric hyperplasias (see Fig. 3-34).[28,175,176] Among the distinctive features of minimal deviation adenocarcinoma are the irregular and angular appearance of the glands, the presence of a stromal reaction around at least some of them as they infiltrate the cervical wall, the presence of large amounts of mucin in the cytoplasm of the neoplastic cells (a distinction from mesonephric hyperplasia), and the presence of CEA demonstrated immunohistochemically in the tumor cells (not seen in benign glandular lesions of the cervix, although certainly it is present in many adenocarcinomas).[428,429,432] The tumors are often large and clinically apparent, but small biopsies may yield a false-negative diagnosis. The tumor is seen in some women in association with the Peutz-Jeghers syndrome.[399,427,430]

Cytologic diagnosis is difficult. The exfoliated cells resemble normal columnar endocervical cells, and cellular atypias are scarce. Only the crowding of the columnar elements may suggest the existence of some cervical pathology.[431]

Controversy surrounds the *prognosis* of minimal deviation adenocarcinoma. The tumor initially was thought to have an extremely poor prognosis, but Silverberg and Hurt[424] subsequently suggested that this might be related to misdiagnosis and consequent delayed treatment. Kaminski and Norris[426] also re-

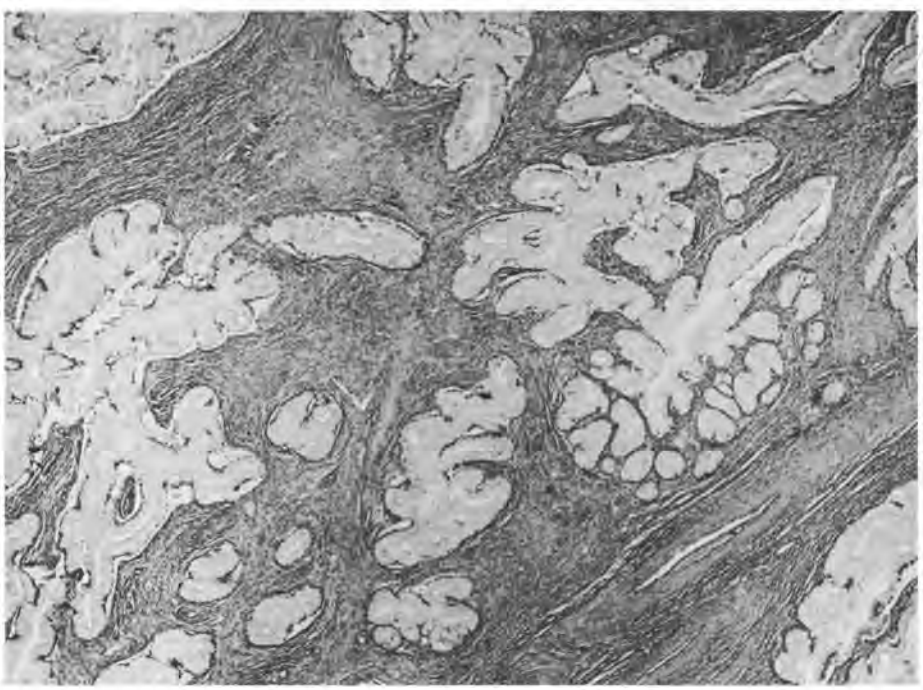


FIGURE 3-73 Minimal deviation adenocarcinoma of cervix: infiltrating glands with angular pointed contours. (Silverberg SG: Surgical pathology of the uterus. New York, John Wiley & Sons, 1977)

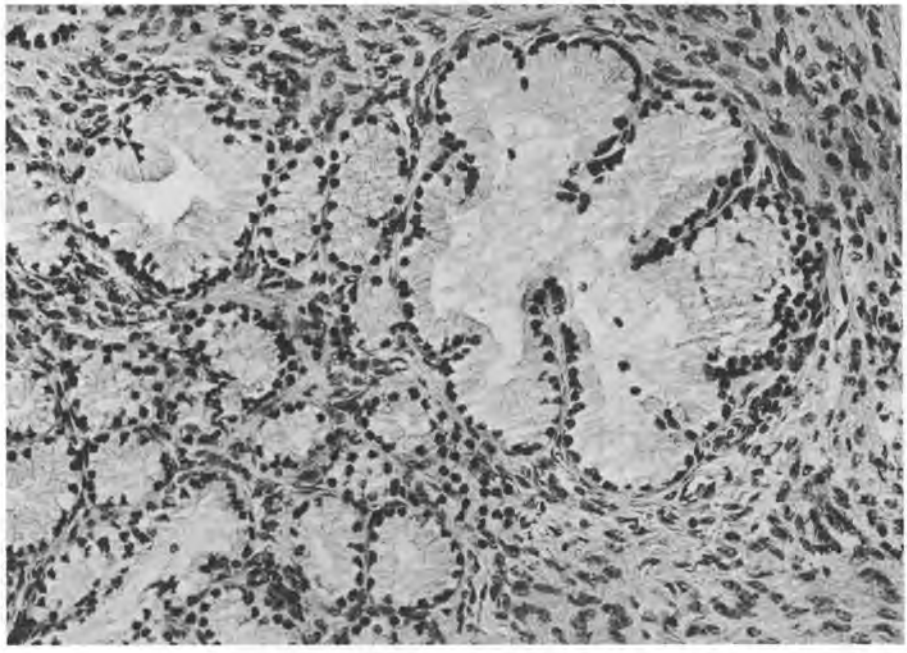


FIGURE 3-74 Minimal deviation adenocarcinoma of the cervix: detail showing lack of cellular atypia.

ported a relatively favorable prognosis, but both Kaku and Enjoji[425] and Gilks and colleagues[427] have noted unfavorable results even in patients who appeared to be adequately treated. Larger series need to be analyzed, but it appears that the tumor has a poor prognosis and needs to be treated vigorously.

Well-Differentiated Villoglandular Adenocarcinoma. Another type of tumor whose pathology and natural history are still being characterized is well-differentiated villoglandular adenocarcinoma.[433,434] The results of two published series of 13 and 24 cases, respectively, suggest that this tumor occurs preferentially in young women (average age in the lower thirties) and has an extremely favorable prognosis. The tumor grows predominantly exophytically, with a prominent papillary component. The papillae typically have a fibrous stroma and are lined by stratified cells showing only modest cytologic atypia (Figs. 3-75 and 3-76). The tumor may show endocervical, endometrial, or intestinal differentiation, and frequently has an admixture of these types. Superficial invasion into the cervical wall is usually seen, but deep invasion is uncommon and distant metastases

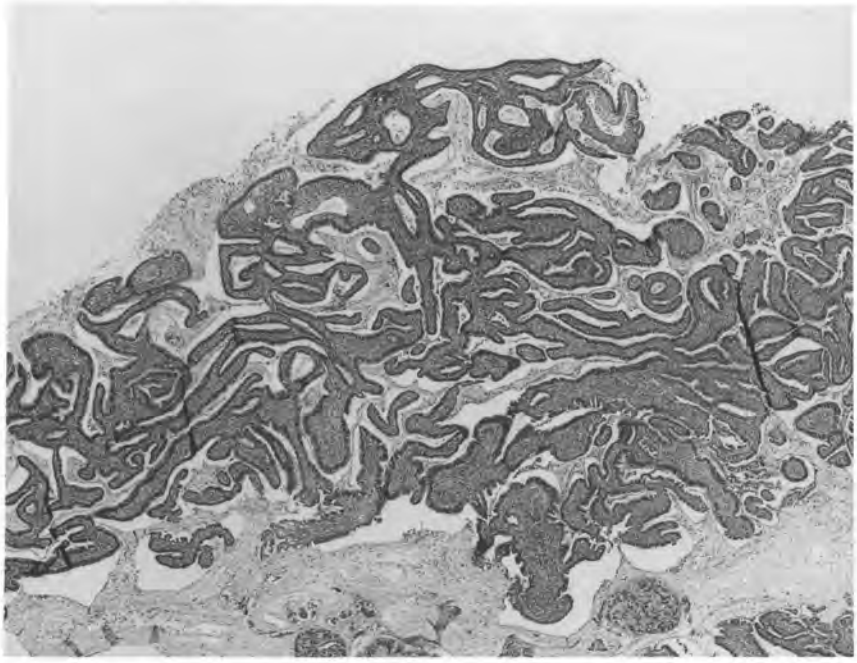


FIGURE 3-75 Well-differentiated villoglandular adenocarcinoma: typical architectural picture at low magnification. (Courtesy of Dr. Mirka Jones, Washington, DC)

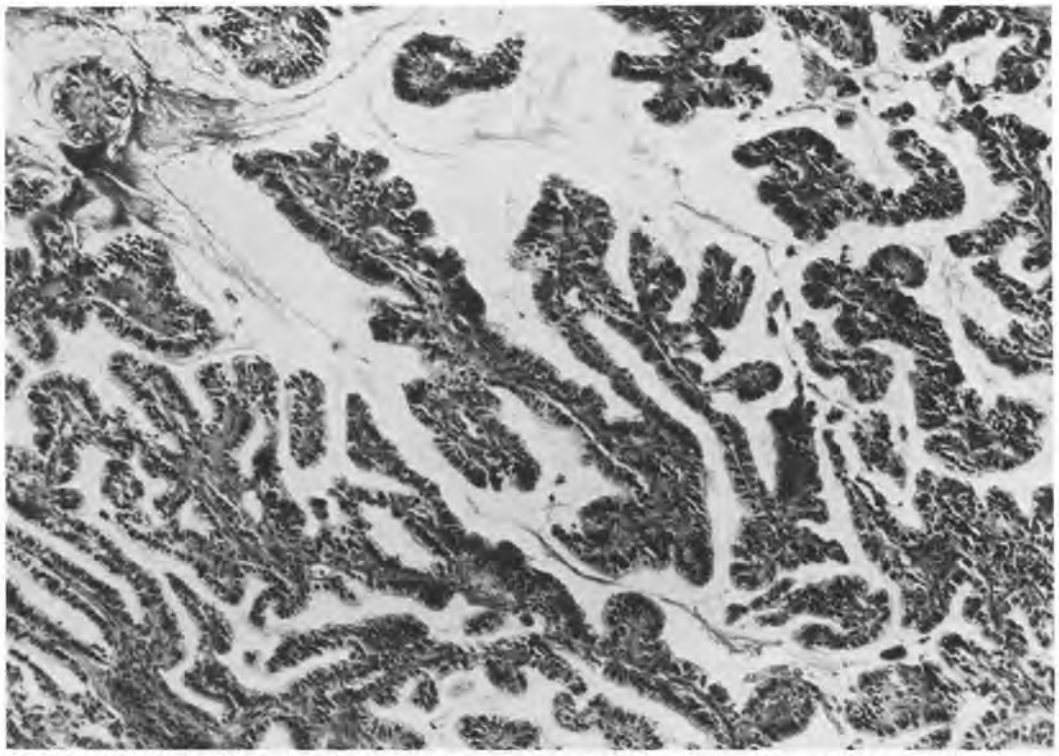


FIGURE 3-76 Well-differentiated villoglandular adenocarcinoma: villoglandular architecture and low cytologic grade are characteristic of the invasive component of this tumor.

have not been seen in any of the 37 cases reported. A few patients treated by less than hysterectomy (predominantly cone biopsy) have shown long-term survival, as have all of the other patients with adequate follow-up. These data seem to suggest that radical surgery and adjuvant therapy are not necessary for the successful treatment of the great majority of these tumors. In our case material, a relation to the use of oral contraceptives was suggested, although the data are not conclusive.[434] The cytologic appearance of these tumors has not been characterized.

Mesonephric Adenocarcinoma. The final subtype of invasive adenocarcinoma listed in the ISGP classification is mesonephric adenocarcinoma. This is probably the rarest subtype, with only 7 well-documented cases in the literature, including 4 in one recent report.[28] Despite early reports equating mesonephric origin with clear cell carcinoma (see above), it is now recognized that clear cell carcinomas are of müllerian type. True mesonephric carcinomas are best recognized by their location deep in the cervical wall, their tubular pattern (reminiscent of benign mesonephric remnants but more atypical and more haphazardly arranged), and the lack of involvement of endocervical mucosa.[28,226,399]

In Situ Adenocarcinoma

With the recent increase in the relative—if not the absolute—frequency of invasive adenocarcinoma of the cervix, it is not surprising that adenocarcinoma in situ (AIS) has been encountered more frequently as well, leading to a better understanding of its pathologic appearance and natural history. This term was first introduced in 1953,[435] and the true population-based frequency is still not known, in part because AIS is thought to be frequently underdiagnosed.[396,436–439] It is diagnosed far less frequently than the corresponding squamous CIN, but 50% or more of cases of AIS show coexisting squamous CIN.[440,441]

As with well-differentiated villoglandular adenocarcinomas, AIS lesions are generally divided into endocervical, endometrioid, and intestinal types. Both in the literature[396,440] and in our own experience, the vast majority of cases have been predominantly of endocervical type, although occasional glands showing endometrioid or intestinal differentiation may be encountered. We prefer to consider this lesion as the exact opposite of minimal deviation adenocarcinoma of the cervix; whereas minimal deviation adenocarcinoma is characterized by glands that are architecturally malignant and cytologically benign, AIS consists of architecturally unremarkable glands showing cytologic evidence of malignancy.

Thus, the glands are normally situated in the cervix and are of normal size and shape, but they reveal cellular stratification, loss of polarity, increased nuclear size, hyperchromasia, loss of cytoplasmic mucin, and mitotic activity (Figs. 3-77 and 3-78). A cribriform glandular pattern has been reported by some authors in AIS, but others might consider this

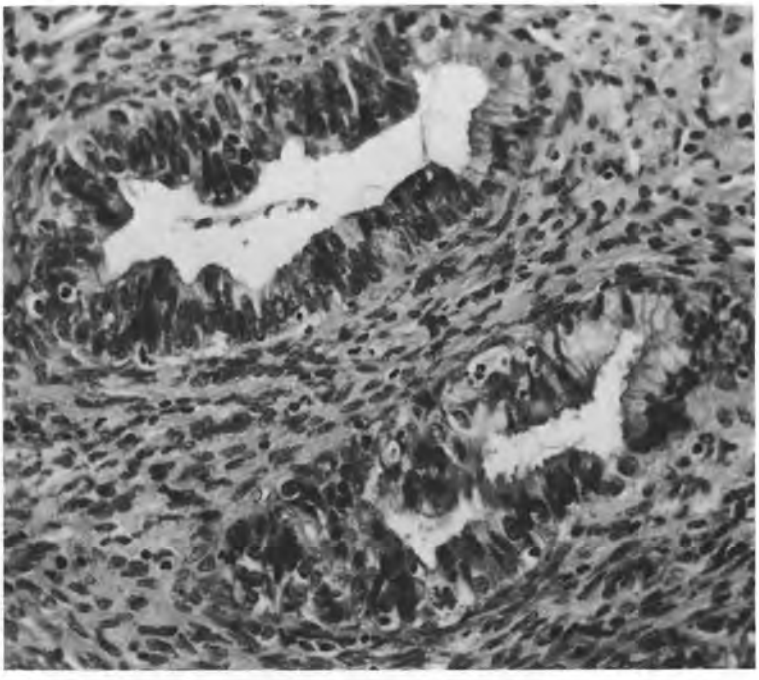


FIGURE 3-77 Adenocarcinoma in situ of the cervix. These two glands are only partially filled by malignant epithelium, are of normal size and shape, and show no stromal reaction around them.

a manifestation of microinvasion (Fig. 3-79). AIS is seen most frequently in the region of the transformation zone of the cervix, and most cases involve both glandular and surface epithelium. It is not completely understood whether the lesion is invariably unicentric or frequently multicentric.

Several studies[402,403] have indicated that HPV is frequently associated with AIS (as it is with invasive cervical adenocarcinoma), and that the type most frequently seen is HPV-18. Ploidy studies are only beginning to be reported, and their diagnostic or prognostic significance remains to be determined.[442] Immunohistochemistry is not diagnostically useful.[443]

The *differential diagnosis* of AIS is predominately with tubal metaplasia, glandular atypias—both reactive and preneoplastic—of lesser degree, and microinvasive adenocarcinoma. Microglandular hyperplasia, cervical endometriosis, and Arias-Stella reaction

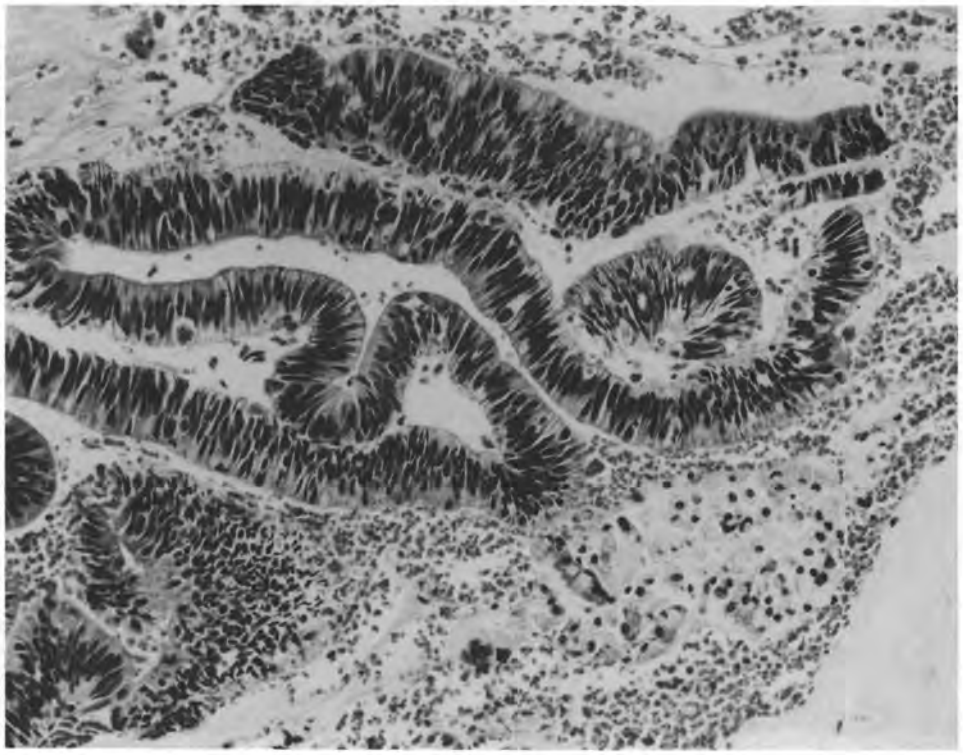


FIGURE 3-78 Adenocarcinoma in situ in curettage specimen. Conization is necessary to rule out stromal invasion.

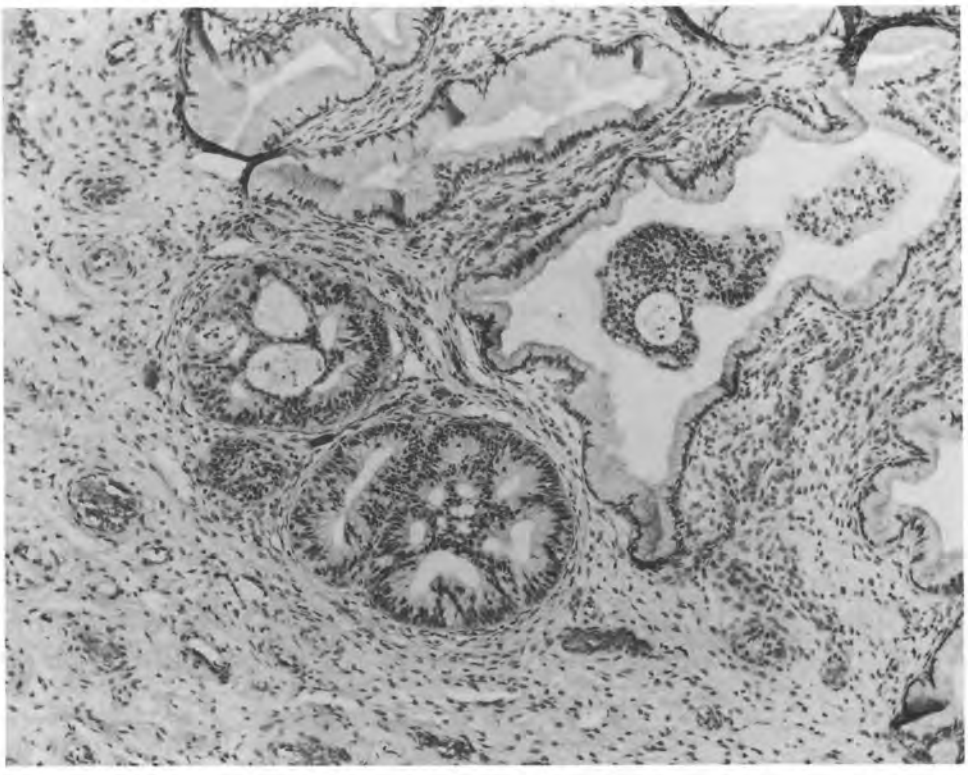


FIGURE 3-79 Adenocarcinoma in situ versus microinvasive adenocarcinoma. The cribriform pattern probably signifies early stromal invasion.

have been mentioned.[396] In cases that we see in consultation, the most frequent misdiagnosis is that of tubal metaplasia.[173,174] The absence of nuclear atypia and mitotic activity and the presence of ciliated cells in this lesion should serve to differentiate it from AIS (Fig. 3-80).

Cytologically, AIS resembles invasive adenocarcinoma but usually lacks a tumor diathesis.[444–446] The definitive diagnosis, in which stromal invasion is ruled out, must be made in a conization or hysterectomy specimen. If the conization resection margins are negative, this procedure is usually therapeutic as well. In one recent study, only 1 of 7 patients reported and only 1 of 25 reviewed in the literature had residual

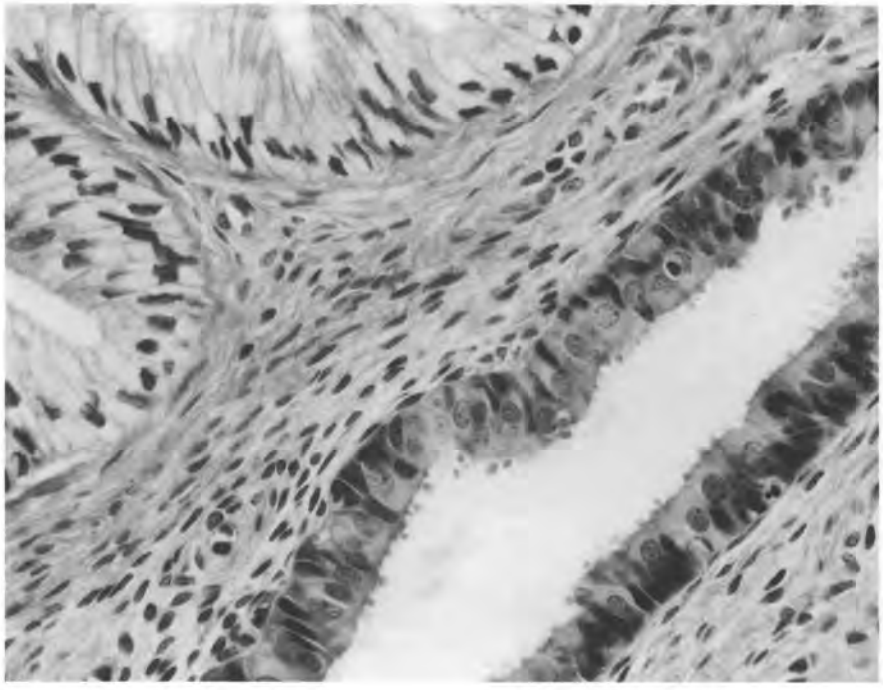


FIGURE 3-80 Tubal metaplasia of endocervical gland (*lower right*). Compare with normal glands at upper left and with adenocarcinoma in situ in Figures 3-77 and 3-78.

disease at hysterectomy when the cone biopsy margins were uninvolved.[447] Evaluation of an endocervical curettage performed after the cone biopsy may be useful. Although the lesion is inferred to have the potential to progress to invasive adenocarcinoma if inadequately treated, only rare cases have been reported as showing such progression.[439,448]

Endocervical Glandular Dysplasia

Much more difficult differential diagnostic problems involve the distinction of AIS from endocervical glandular dysplasia (EGD) at the lower end of the spectrum and microinvasive adenocarcinoma at the upper end. We believe that the diagnostic criteria for both of these lesions have been poorly defined in the literature, and it is not clear that the natural history of either of them differs significantly from that of AIS. The natural history of AIS itself is very poorly established despite the large number of reported cases. The best attempts at definitions of EGD have been made by Jaworski[396] and Brown and Wells,[449] but they are still difficult to understand. Jaworski states that "it should be realized that EGD and AIS form a spectrum and that a sharp division between the two is not possible." When one adds to this confusion the problem of distinguishing glandular dysplasia from reactive glandular atypia secondary to inflammatory lesions, we find that we rarely make the diagnosis of glandular dysplasia in our own practice. When we do, it defines a lesion in which glands in an uninflamed region of the cervix (to rule out reactive atypias) are architecturally unremarkable but display moderate nuclear enlargement, hyperchromatism, and atypia, with less stratification, mitotic activity, and severe atypia than seen in AIS (Fig. 3-81).

The *cytologic appearance* is characterized by strips of columnar cells showing nuclear pseudostratification and different degrees of atypia.[446] Rosettes indicate the glandular origin of the lesion. Numerous tightly crowded clumps of atypical cells confirm without doubt the existence of an endocervical lesion that requires further investigation. Isolated cells are of little diagnostic value because inflammatory changes may mimic dysplastic anomalies. Differential diagnostic difficulties are posed by inflammatory and repair changes. For example, postconization smears may reveal numerous densely cellular clumps with pseudostratified nuclei that puzzle the cytopathologist.

Microinvasive Adenocarcinoma

Equally confusing as the distinction between AIS and EGD is that between AIS and microinvasive adenocarcinoma. Some investigators have defined microinvasive or "early invasive" adenocarcinoma as a tumor that invades into the underlying cervical stroma to a depth of less than 5 mm as measured from the mucosal surface of the endocervical canal.[436,450] Others use different measurements, whereas yet others (including ourselves) do not measure at all, but merely try to distinguish lesions characterized by invasion of only a few cells or a few glands. Still other authors recommend against using the diagnosis of microinva-

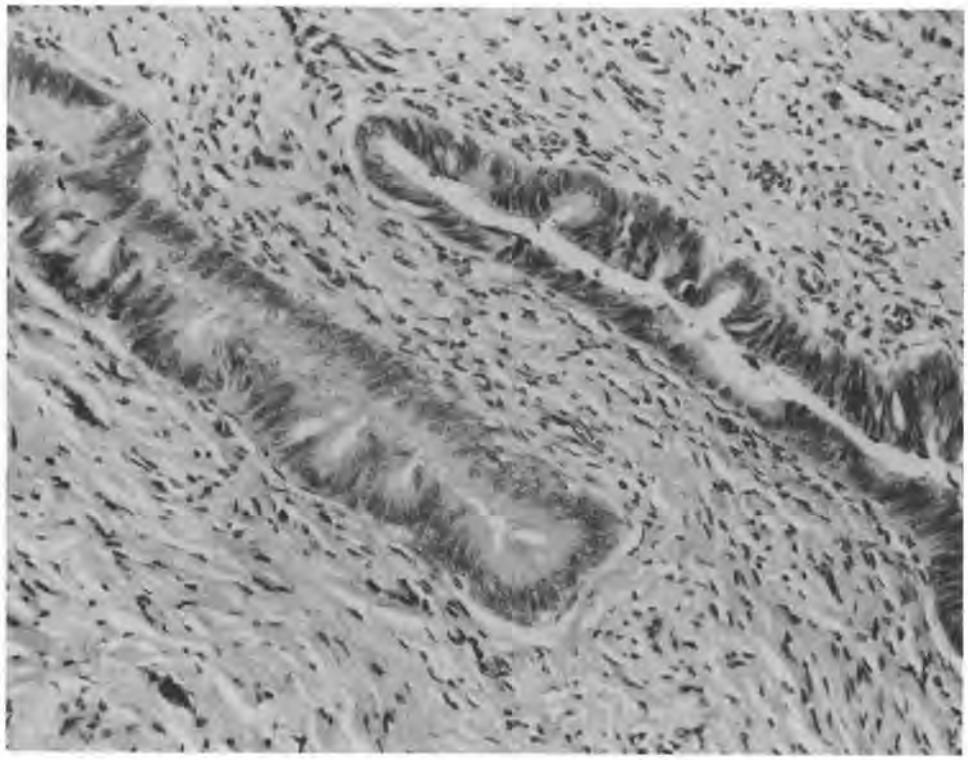


FIGURE 3-81 Endocervical glandular dysplasia. The atypia seen is less than that encountered in adenocarcinoma in situ. The lack of inflammation in adjacent stroma rules out a reactive atypia.

sive adenocarcinoma at all, and Jaworski[396] summarizes the confusion by stating that "the existence of microinvasive adenocarcinoma as an entity remains in dispute."

Given this confusion, it hardly seems appropriate to pontificate at length on the diagnostic criteria for this questionable lesion, but we have made the diagnosis in our laboratories when we encounter a lesion reminiscent of AIS but showing: (1) individual cells, often of apparent squamous type, dropping off into the stroma; (2) a higher concentration of cytologically malignant glands, often with small sizes and variable shapes, than would be expected in normal endocervix or endocervix involved by AIS; (3) glands that have grown together in a confluent pattern (see Fig. 3-79); or (4) glands that are irregular in orientation and have elicited a stromal response (Fig. 3-82). In our experience, this has always been an extremely focal change, and we have not found it necessary to measure these lesions. Invasive adenocarcinomas that are measurable—even if only 2 or 3 mm in greatest dimension—should be diagnosed as invasive adenocarcinoma, although the pathologist may wish to specify their dimensions.

As mentioned above, the *natural history* of all these lesions (EGD, AIS, and microinvasive adenocarcinoma) is poorly understood. It appears that many patients can be managed by cone biopsy alone, but that it is important for the pathologist to check and report the adequacy of the cone biopsy margins. We believe that—until extensive data to the contrary are available—measurable small invasive adenocarcinomas should be treated more aggressively.

Adenosquamous Carcinoma

Adenosquamous carcinoma of the cervix is a difficult lesion to define, because there are several candidates for this designation. First, it has become increasingly apparent over the past few years that the presence of stainable mucin in otherwise typical squamous carcinomas of the cervix portends a poorer prognosis; different authors have used the terms *adenosquamous carcinoma, mucoepidermoid carcinoma,* and *mixed carcinoma* to define tumors identified by positive mucin staining.[319–323] Some authors have also used the term *adenosquamous carcinoma* to characterize "collision" tumors, in which two different tumors—a squamous cell carcinoma and an adenocarcinoma—coexist in the same cervix. Third, certain endometrioid carcinomas of the cervix with squamous differentiation (Fig. 3-83) may logically be referred to as *adenosquamous carcinomas.* In our opinion, only the fourth type—a single carcinoma of endocervical type in which both squamous and glandular differentiation are identifiable without special stains—should be designated as adenosquamous carcinoma (Figs. 3-84 and 3-85).

Defined in this manner, adenosquamous carcinoma is a relatively uncommon tumor, although there is a possibility that it is increasing in frequency, and the question of a relation to oral contraception and to pregnancy has been raised. Most epidemiologic features are closer to those of squamous cell carcinoma than those of adenocarcinoma.[451] Adenosquamous carcinoma has been said by some authors to have a particularly unfavorable prognosis,

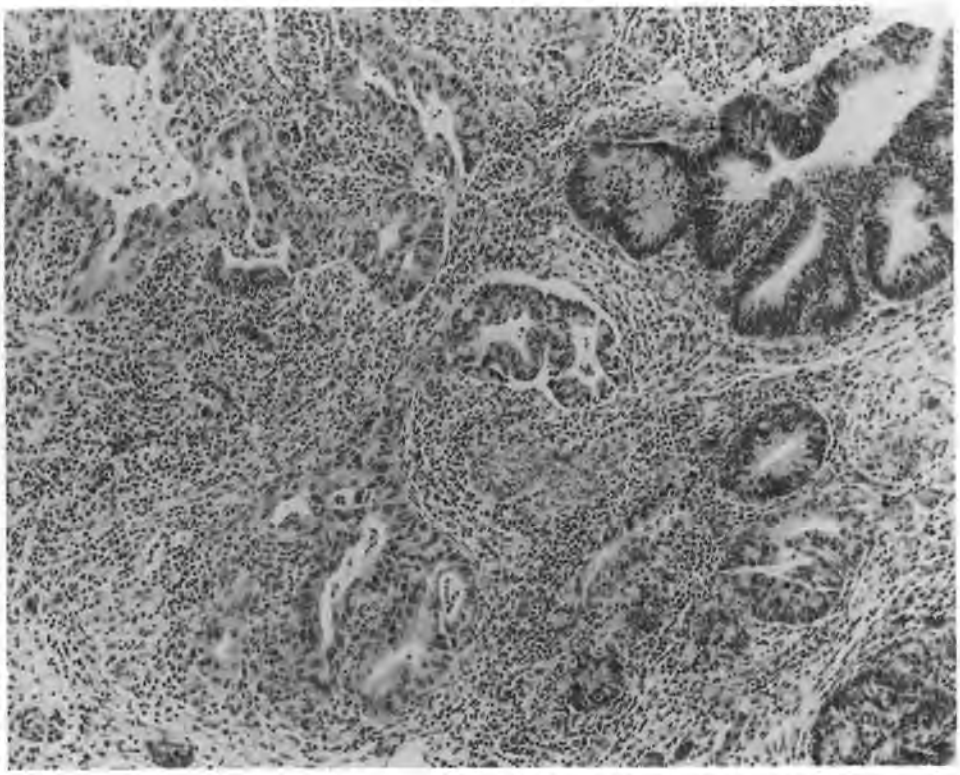


FIGURE 3-82 Microinvasive adenocarcinoma. Glands with in situ adenocarcinoma are seen on the right. The focus of invasion is seen almost in its entirety in this photomicrograph.

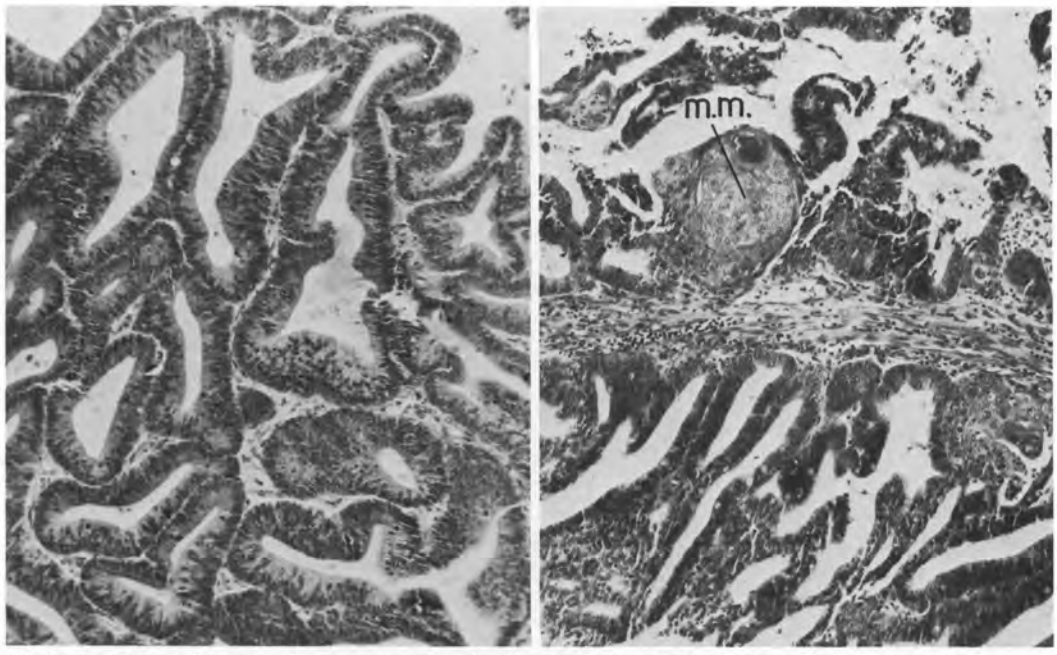


FIGURE 3-83 Adenoacanthoma type of mixed carcinoma of the cervix. *m.m*, squamous metaplasia.

but it is not always clear which of the definitions referred to above is being quoted in this situation.[416,452] Other studies have suggested that the prognosis is no worse than that for comparably staged squamous cell carcinoma.[453,454] The cytologic diagnosis is unreliable.

Glassy Cell Carcinoma

Controversy surrounds the diagnosis and clinical significance of glassy cell carcinoma, which is considered by most authors to be a variant of adenosquamous carcinoma. The tumor is generally easy to

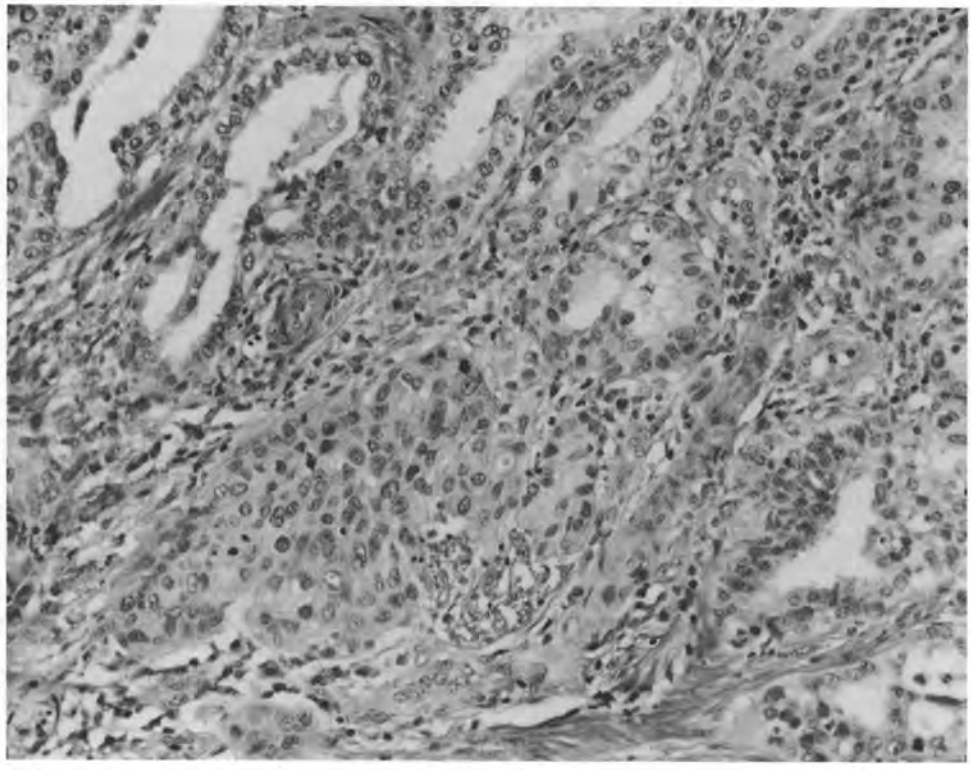


FIGURE 3-84 Adenosquamous carcinoma. This invasive cancer shows both glandular and squamous differentiation.

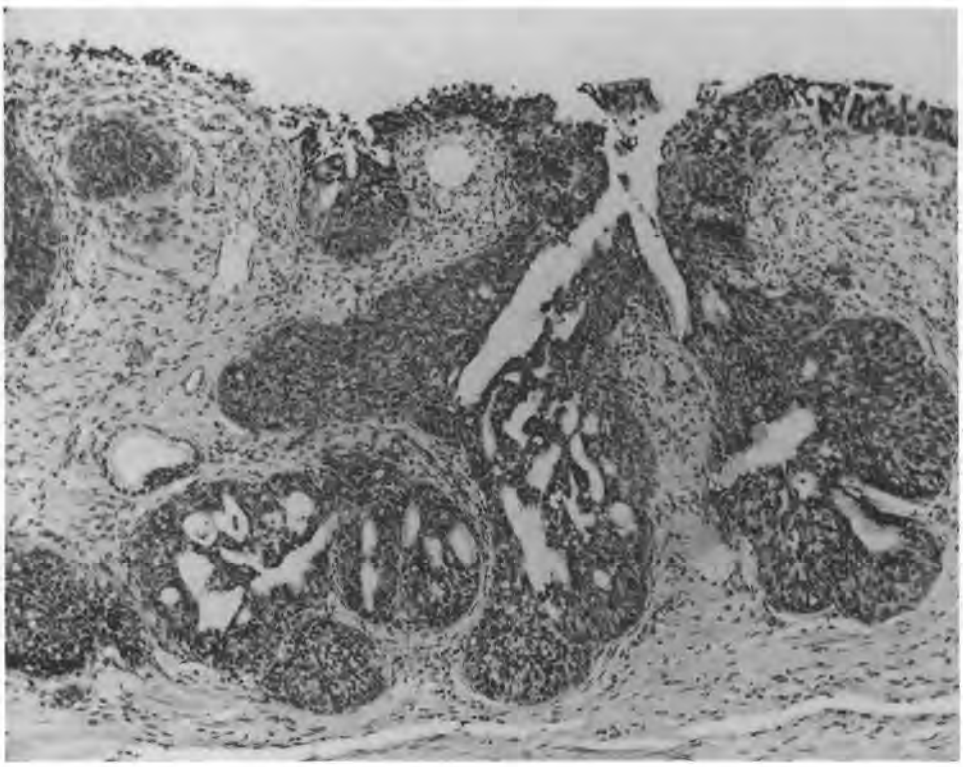


FIGURE 3-85 Adenosquamous carcinoma in situ. Biphasic differentiation in a noninvasive tumor.

diagnose microscopically, because it is composed of characteristic sheets of large cells with abundant eosinophilic or amphophilic, ground-glass or finely granular cytoplasm, prominent cell borders, large nuclei with prominent solitary nucleoli, and a notable stromal inflammatory infiltrate of eosinophils and plasma cells, which divides the tumor into neoplastic cell islands (Fig. 3-86). By the usual definition, an easily recognizable component of classical squamous cell or adenocarcinoma should not be present. Although this tumor is said by some authors to be associated with a typical clinical history, including an appearance in younger, often pregnant patients, and a particularly poor prognosis,[455] other authors who have studied the same subject have denied that it is a distinct entity and believe that the glassy cell morphologic pattern occurs focally in other types of cervical carcinoma.[456,457] Thus, although the diagnosis can usually be made easily, it remains questionable whether it should be made.

Adenoid Basal Carcinoma and Adenoid Cystic Carcinoma

Adenoid basal carcinoma and adenoid cystic carcinoma were once regarded as a single entity, but further studies have shown that they are clinically and pathologically distinct. Adenoid basal carcinoma has an excellent prognosis, whereas adenoid cystic carcinoma is frequently fatal. Different features suggest that these tumors are closely related: (1) they both contain basaloid, squamous, and glandular elements; (2) adenoid cystic carcinoma may reveal the presence of basaloid nests of cells or exhibit foci of squamous differentiation; and (3) they both appear preferentially in elderly women.

Adenoid basal carcinoma usually does not reveal any palpable mass. An abnormal smear (usually indicative of an overlying CIN) is the most common clinical finding. *Microscopically,* one observes small, regular, round or oval nests of cells suggesting those of basal cell carcinoma (Fig. 3-87).[458–460] These cells are small, with oval, hyperchromatic nuclei surrounded by a thin rim of cytoplasm. Mitoses are rare. The cells nests may contain small lumina. Foci of squamous differentiation are commonly observed, and association with squamous dysplasia, carcinoma in situ or early invasive squamous cell carcinoma has been reported. The tumor cells are immunoreactive for cytokeratins but not for CEA, epithelial membrane antigen, or S-100 protein.[460] The prognosis is good.

Adenoid cystic carcinoma presents as a polypoid or infiltrating cervical mass often accompanied by bleeding. Some of the patients have synchronous mucinous or other epithelial ovarian tumors.

Microscopically, small basal cells form cords, sheets and cellular nests which infiltrate a stroma modified by fibroblastic proliferation, hyalinization and myxoid change (Fig. 3-88). Mitoses are frequent. Cylindromatous structures and palisading arrangements of cells are similar to those observed in the more common salivary gland location of adenoid

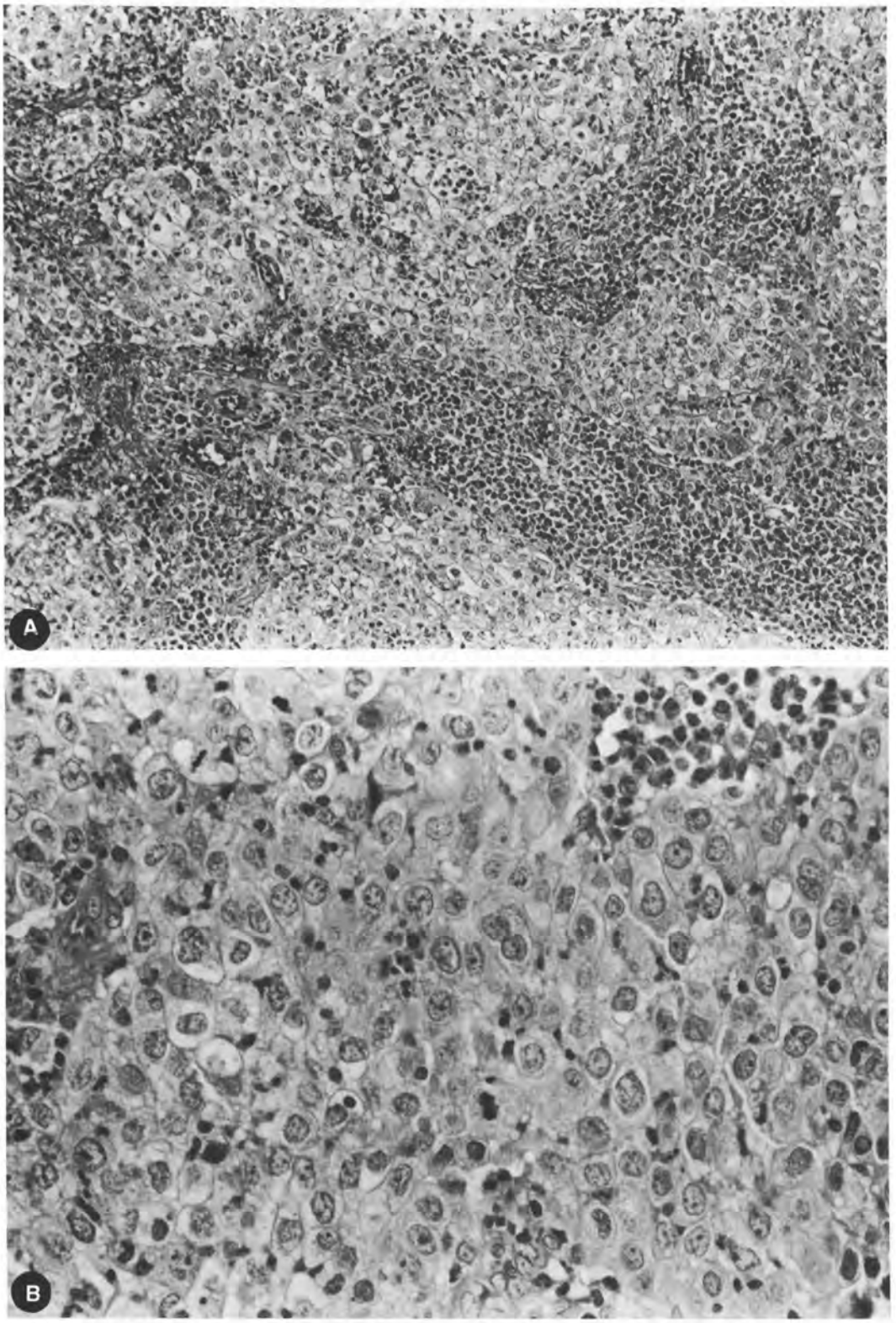


FIGURE 3-86 Glassy cell carcinoma. **(A)** Low-power photomicrograph showing prominent inflammatory reaction. **(B)** Detail of malignant cells.

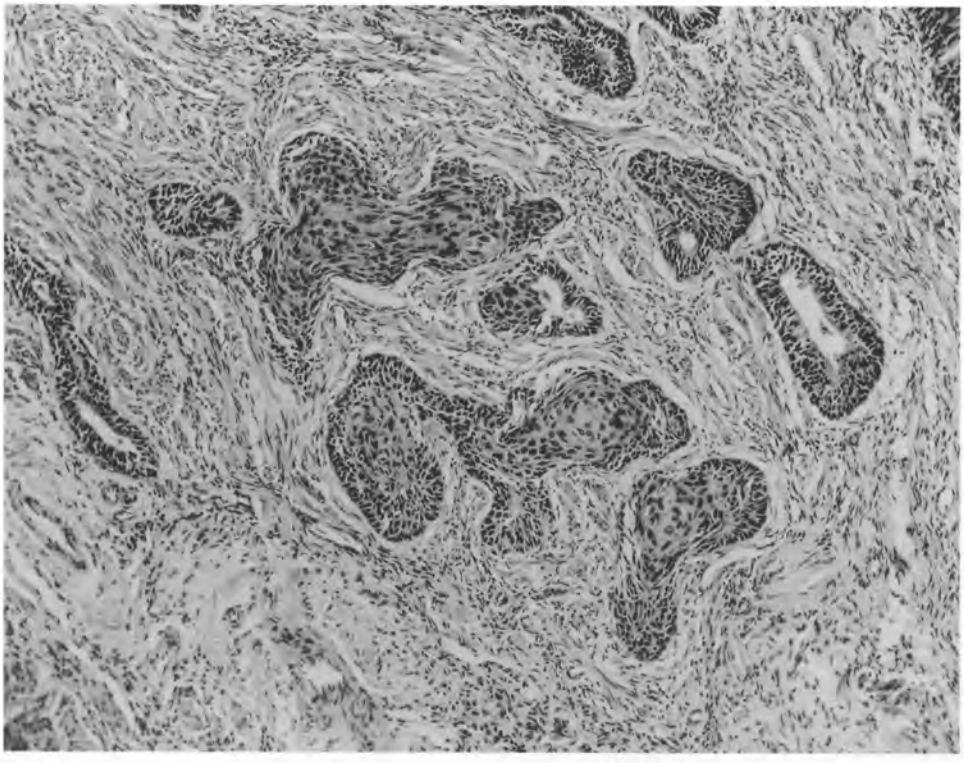


FIGURE 3-87 Adenoid basal cell carcinoma.

cystic carcinoma. Immunohistochemically, the tumor cells express cytokeratins, CEA and epithelial membrane antigen, and, less frequently, S-100 protein.[461] Myoepithelial differentiation is rare in the cervical tumor, although it is expressed in almost all the similar salivary gland tumors. The clinical prognosis is very poor.[459–461]

Invasive Carcinoma of the Cervix and Pregnancy

The appearance of an invasive cervical carcinoma during pregnancy is an uncommon event (0.05% of pregnancies).[462] However, this combination represented 3.6% and 4.5% of all cervical carcinomas in

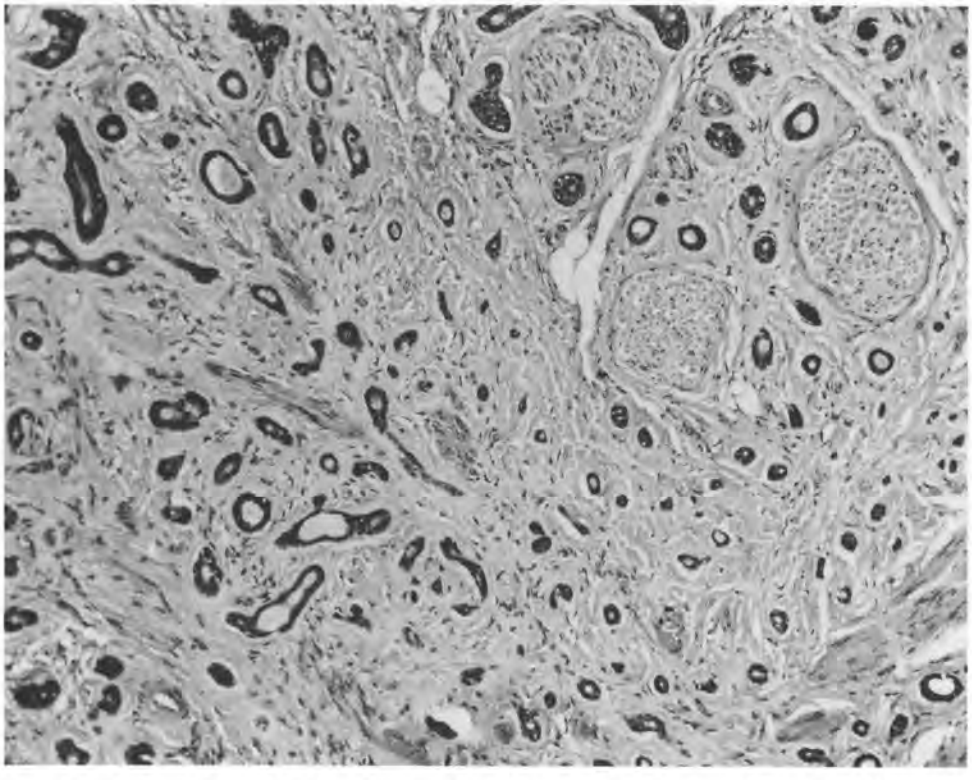


FIGURE 3-88 Adenoid cystic carcinoma.

two series.[463,464] Does pregnancy exert an influence on the evolution of the tumor? Contrary to widespread belief, there is no significant evidence that CIN and invasive carcinoma behave differently during pregnancy; the former should be managed conservatively[465,466] and the latter managed as in the non-pregnant patient.[464,467,468]

In the great majority of cases, these tumors are in situ or invasive squamous cell carcinomas. Some adenocarcinomas and mixed adenosquamous carcinomas have been described. Glücksmann[469] reported that mixed carcinomas are proportionately more frequent in pregnant than non-pregnant women. This finding has not been confirmed by all authors.[467]

Cancer of the Cervix and Radiation Therapy

The question of radiation therapy and cervical cancer may be considered from two different viewpoints: that of the action of radiation on the tumor cells, and that of the clinicopathologic sequelae of irradiation.

Radiation therapy (x-rays and interstitial radium or cesium) acts on tumors and their beds by three mechanisms:

1. Destruction of cancer cells by arrest of cellular divisions, alterations of mitoses, cytolysis, and pyknosis; development of bizarre cells from among the cells injured but not killed by radiation (Fig. 3-89)
2. Appearance of endarteritis with destruction of the vascular architecture, and tissue necrosis with inflammatory granulomata containing foreign body giant cells
3. Tissue fibrosis (often showing many atypical and even bizarre fibroblastic cells).

The sequelae of radiation therapy may be found in the tumor or in the adjacent organs (Fig. 3-90). The injured organs show endarteritis, telangiectasis, cellular necrosis, leukohistiocytic infiltrates, secondary fibrosis, and swelling and degeneration of collagen fibers. These lesions may appear many years after the cessation of radiation therapy. Rarely, new tumors may be induced by radiation.[470,471] The cytologic or histologic diagnosis of cervical dysplasia after radiation therapy (usually within 3 years) is often a sign of subsequent recurrence of cervical cancer with poor survival.[472]

Attempts have been made, with variable degrees of success, to predict the success or failure of radiation therapy in an individual case by biopsy or cytologic evaluation. The biopsy method[473,474] consists of pre- and post-treatment tumor biopsies to evaluate the degree of alteration in the tumor cells brought about by the course of irradiation. The cytologic technique,[475–478] on the other hand, calls for the evaluation of radiation-induced changes in *benign* cells. Each of these methods has been claimed by its proponents to have a high degree of accuracy in predicting within a short while (usually 1 week) after the beginning of treatment which patients are likely to survive 5 years if treated by irradiation alone (radiation responsive) and which are likely to succumb to their disease unless surgical therapy is added (radiation resistant). However, the values of these methods have been much disputed by other workers in the field. The biopsy method, in particular, is often impractical because of the difficulties encountered in biopsying a necrotic, friable, hemorrhagic tissue. Some types of cancer, such as keratinizing squamous carcinoma, have been said to be usually radioresistant,[304–306] but newer studies do not confirm this finding.[311,312]

Sarcomas and Other Rare Tumors

Primary sarcomas of the cervix are rare. *Sarcoma botryoides* or *embryonal rhabdomyosarcoma* is encountered at a later age in the cervix (mean age about 18 years) than in the vagina.[479,480] *Macroscopically,* the tumor has the form of a polypoid mass with a smooth irregular surface protruding through the external os and measuring a few centimeters in diameter. *Microscopically,* it is characterized by a loose and vascular stroma containing large elongated and small round undifferentiated cells. The rhabdomyoblasts have a dense eosinophilic cytoplasm in which cross striations may be observed. These cells are immunoreactive for myoglobulin or desmin. A condensed zone of small round cells with hyperchromatic nuclei is often present under the columnar mucosa (cambium layer). The mitotic rate can be moderately elevated (up to about 10 mitotic figures per 10 high-power fields). Foci of heterologous tissue such as cartilage may be present. This tumor should be distinguished from adenosarcoma, which usually contains more glandular structures, and from endocervical stromal sarcoma, which occurs at a later age, does not reveal a typical cambium layer, and does not exhibit rhabdomyoblasts. Cervical embryonal rhabdomyosarcomas have a better prognosis than the vaginal tumors.[480,481]

Stromal sarcoma, described by Abell and Ramirez,[482] has been reported rarely in the cervix (endocervical stromal sarcoma).[483,484] It appears late in the reproductive period or after menopause. This rare tumor is analogous with endometrial stromal sarcoma. *Macroscopically,* it consists of a polypoid or an infiltrating mass arising in the cervix. *Microscopically,* ovoid, spindled, or stellate cells with enlarged, hyperchromatic nuclei are arranged in a fascicular pattern infiltrating the stroma, with persisting normal endocervical glands (Fig. 3-91). Mitoses are abundant, and foci of edema, necrosis, and hemorrhage with inflammatory infiltrates are observed. This tumor must be differentiated from a *spindle cell* or *sarcomatoid carcinoma,* often only with the aid of ultrastructural or immunohistochemical (intermediate filaments) studies, and from an endometrial

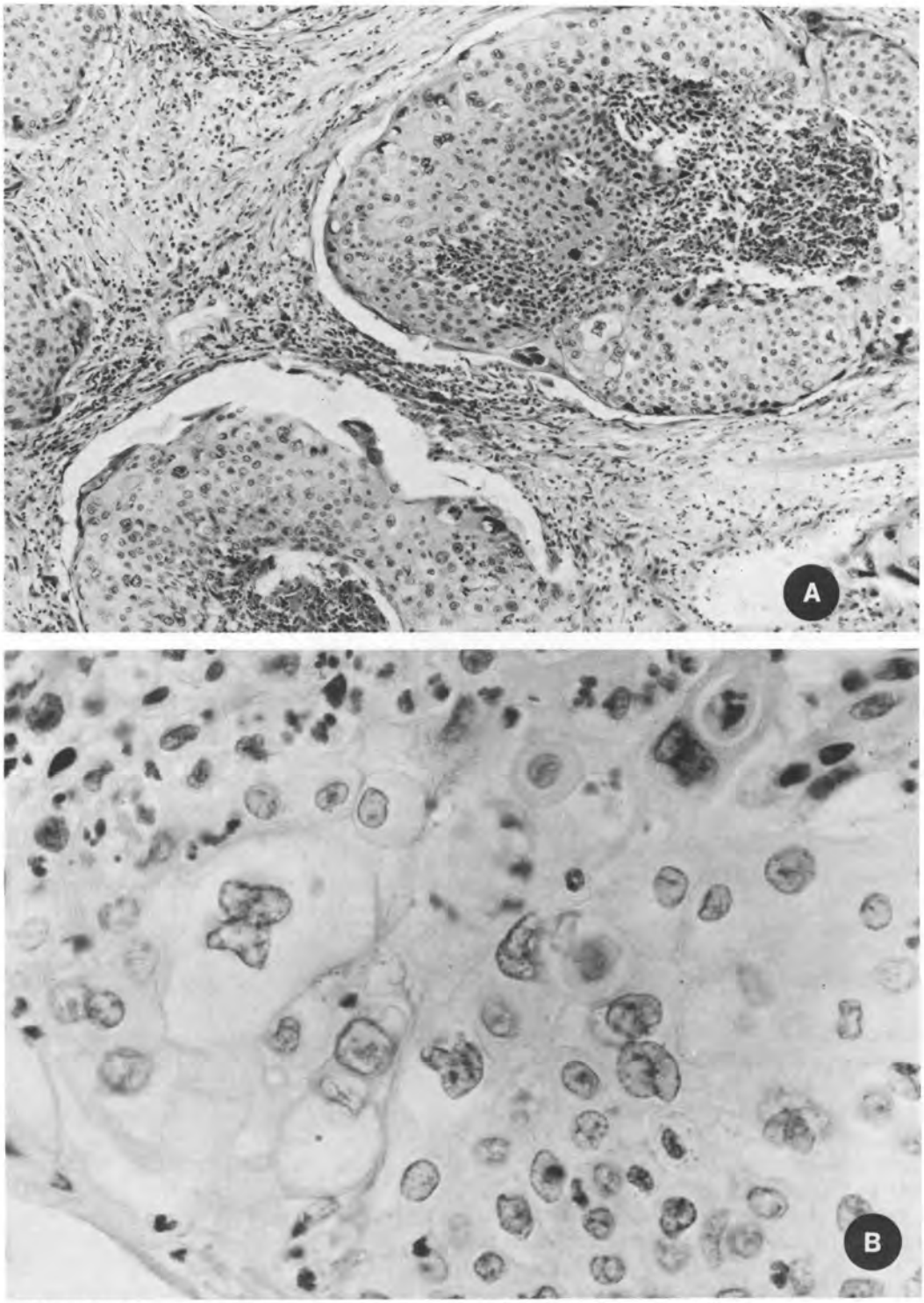


FIGURE 3-89 Squamous cell carcinoma: action of irradiation on the tumor cells.

stromal sarcoma extending to the cervix. Also reported are rare cases of *leiomyosarcoma,*[485] *Wilms' tumor,*[486] *osteosarcoma,*[487] *fibroxanthosarcoma,*[488] *liposarcoma,*[489] *malignant schwannoma,*[490] *germ cell tumor,*[491] *choriocarcinoma,*[492,493] and *malignant melanoma.*[494–496] *Carcinosarcomas*[382,497] and *adenosarcomas* similar in appearance to those seen more frequently in the endometrium are occasionally primary tumors of the cervix, but more often represent extensions from an endometrial primary source.

Lymphomas

Although lymphomas frequently infiltrate the cervix in cases of advanced disease, primary localizations

FIGURE 3-90 Sequela of an overdose of radiation: tissue necrosis in the colon.

are rarely reported (Fig. 3-92).[498–503] The main clinical symptom is vaginal bleeding.

Macroscopically, the cervix is diffusely enlarged and may present nodular polypoid deformations. Tissue sections show the typical aspect of malignant lymphoma: a diffuse or nodular, white to tan, homogeneous, granular dense structure. The vagina and uterine corpus may be involved.

Microscopically, the cervical stroma is infiltrated by nodules of different size. The overlying epithelium is rarely infiltrated. The various histologic types of non-Hodgkin's malignant lymphoma have been described. Diffuse "histiocytic" lymphoma was diagnosed more frequently in the series of Harris and Scully.[503] Hodgkin's disease and Burkitt's lymphoma have been mentioned in rare cases.[504,505]

If there is no evidence of dissemination beyond the uterus, cervix, or vagina, the prognosis is excellent, in contradiction to primary ovarian lymphoma, which is almost always a manifestation of known or occult disease outside the genital tract.[503]

Granulocytic sarcoma of the cervix is a mass of granulocytic leukemic cells. The patient may or may not be known to have leukemia when the cervical mass develops;[503,506] if the leukemia is not already manifest clinically, the diagnosis can easily be missed unless the possibility is kept in mind and a chloracetate esterase stain and immunochemical stain for lysozyme are performed. Prognosis is poor, because most patients develop acute leukemia.[507] Decidualized stroma should not be confused with lymphoma.[508]

METASTATIC TUMORS

Metastases to the cervix uteri are very rare; only the fallopian tube is a less frequent site of metastatic disease in the female genital tract.[509] Wallach and Edberg[510] attempt to explain this rarity by invoking the small volume of the cervix, its poor supply of vessels and lymphatics, and the absence of studies involving careful searches for metastases to this organ. These metastases arise, in most reported cases, from ovarian and endometrial primaries (the latter often by direct extension). Of extragenital primary sites, the most common are mammary,[511] gastric,[512,513] pulmonary,[514] and intestinal.[515] A few cases of secondary cervical involvement by tumors of the liver, pancreas, kidney, and gallbladder have been reported. Because almost all these tumors are adenocarcinomas, the differential diagnosis from primary cervical adenocarcinoma must be kept in mind.[516,517] The problem of the distinction between endometrial and endocervical primary adenocarcinomas is discussed earlier in this chapter and in Chapter 4. Metastatic malignant melanoma, usually from a primary tumor of the vulva, has been reported. It is best differentiated from primary cervical melanoma by the absence of junctional activity.[494–496]

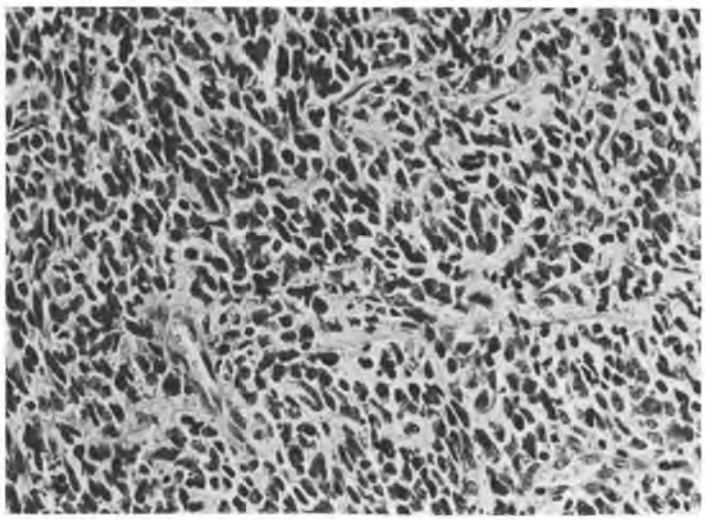


FIGURE 3-91 Endocervical stromal sarcoma: microscopic appearance.

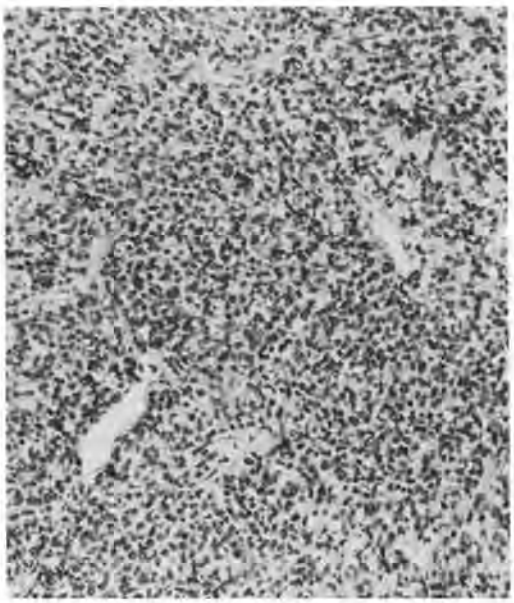


FIGURE 3-92 Maligant lymphoma of the cervix.

The cytologic diagnosis of metastatic cancer to the cervix is a rare eventuality. The presence in the cervical smear of malignant cells that do not resemble the usual patterns of genital cancer and lack a tumor diathesis of necrotic debris may orient the diagnosis to a metastatic tumor. We have observed in cervicovaginal smears malignant cells originating from the breast, the gastrointestinal tract, and the skin (malignant melanoma).

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4 The Corpus Uteri

EMBRYOLOGY

The corpus uteri arises as a result of the fusion of the caudal portions of the müllerian ducts, which themselves arise as invaginations of coelomic epithelium. From the beginning of its formation, the lumen of this canal is lined by a columnar epithelium, from which the endometrial glands later proliferate.[1] Whether these glands induce the formation of endometrial stroma or vice versa is still being debated, but certainly these two structures—as well as the smooth muscle fibers, which arise during the fourth month of fetal life—are intimately related during the course of their development. This intimate relationship is reproduced pathologically in the development of endometriosis and of certain tumors, in each of which two or three of these elements may coexist.[2,3] All three are ultimately of coelomic, and thus of mesodermal, origin. The corpus is well formed by the 21st week of gestation; its subsequent development is limited to an increase in size, although it remains smaller than the cervix well into childhood.[4]

ANATOMY

The corpus uteri has the form of a pyramid, the apex of which is bent toward the base. It presents two surfaces and three borders and measures, in the adult, 45 to 50 mm in height, 50 mm in width, and 25 mm in thickness. The weight under normal conditions ranges from 40 to 70 g, the higher weights prevailing in the multipara and the lower weights after the menopause.[5] Uterine size measured in vivo by new radiographic techniques probably reflects physiologic conditions better than the classic autopsy studies.[6,7] Considerable symmetrical enlargement may occur in the absence of demonstrable pathology; the mechanism of this change is unknown because it may occur in nulliparous and parous women.[8]

MALFORMATIONS

When the development and fusion of the müllerian ducts and the disappearance of the septum do not take place normally, a series of malformations that depends on several mechanisms ensues (Fig. 4-1).[9–11] The most reduced malformation is the *uterus arcuatus,* which presents a heart-shaped appearance and often an outline of a median partition at the base. These anomalies are frequently associated with vaginal, tubal, or urinary tract (single kidney, double ureter, pelvic kidney) anomalies.

Recently, a series of anomalies has been described in women who were exposed in utero to diethylstilbestrol (DES), including hypoplasia, a

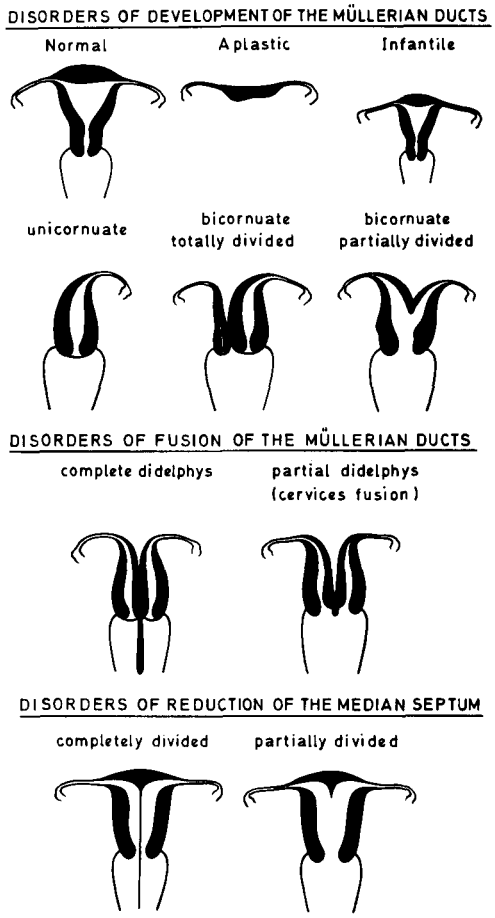


FIGURE 4-1 Congenital malformations of the uterus.

T-shaped uterus, and constriction bands in the endometrial cavity;[12,13] more is known of their hysterographic than of their morphologic appearances. These and other anomalies in these women may result in fertility disorders.

A rare malformation not related to müllerian maldevelopment is uterine arteriovenous fistula.[14] This lesion is more commonly acquired than congenital.

HISTOLOGY

From the histologic point of view, the uterus consists of three layers: the serosa, myometrium, and endometrium. The *serosa* or *visceral peritoneum* is composed of mesothelial cells.

The *muscular layer* or *myometrium* is composed of smooth muscle fibers separated by collagen and elastic fibers; this muscular layer is divided into an external zone of longitudinal fibers, a middle zone of interdigitating fibers coursing in all directions, and an internal zone of circular fibers.[1,15] The internal zone is particularly well developed in the inferior portion of the uterine corpus (isthmic zone). A lateral muscle bundle has been described as extending from the cornua to the cervix;[16] this has been designated the *fasciculus cervicoangularis* and may play a role in conduction.

The role of the *mucosa* or *endometrium* is to provide a site of implantation and nutrition for the fertilized egg. The endometrial surface is covered by a columnar epithelium, into which the glands open. The glands are distributed in a stroma formed of round to ovoid cells. Around the glands is a fibrillar network and a characteristic vascular apparatus. Three successive layers in the endometrium can be distinguished.[1,17] The *deep layer* or *basalis* comprises the depths of the glandular cul-de-sacs, which during the menstrual cycle respond only feebly to estrogenic stimulation and never to progesteronal stimulation. Some of these cul-de-sacs have a tendency to penetrate into the adjacent myometrium. When this phenomenon is pronounced, it is interpreted as adenomyosis. The stroma of the deep layer is dense and composed of small rounded cells with little cytoplasm. Some authors have denied the existence of a functionally distinct basalis.[18]

The *middle layer* or *spongiosa* occupies the greatest part of the thickness of the endometrium and reacts intensely to hormonal stimulation. The vascular apparatus is well developed.

The *superficial layer* or *compacta* includes the necks of the glands and the surface epithelium. During the luteal phase, the glandular convolutions in this layer are less accentuated than in the spongiosa. The surface epithelium does not show the same cyclical variations as the rest of the mucosa.

Endometrial *vascularization* involves a distribution that is unique to this organ.[19-21] Two types of arteries, basal and spiral, arise from the myometrial arteries to supply the endometrium.

The *basal arteries*, whose territory is confined to the deep part of the endometrium, do not vary in structure during the course of the menstrual cycle. Their independence of the ovarian hormones is confirmed experimentally by the fact that, in the rhesus monkey, they are not involved by the hyalinization that is found in the spiral and myometrial arteries.

The spiral arteries penetrate to the surface of the mucosa and undergo evident cyclical modifications (Figs. 4-2 and 4-3). During the proliferative phase, they are less numerous, moderately spiral, and localized to the deep part of the functional zone. Progressively during the course of the secretory phase, their digitations increase and their spiral structure becomes more accentuated. They reach the superficial part of the functional zone and attain their maximum growth at the premenstrual period. They feed into the capillary and venous lakes situated under the endometrial surface. At the end of the cycle, their walls show lesions consisting of hyalinization and alterations of the elastic fibers.

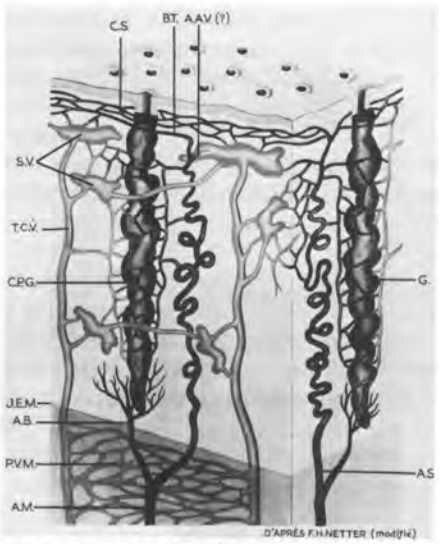


FIGURE 4-2 Schematic representation of the spiral arteries. *A.M.*, myometrial artery; *A.S.*, spiral artery; *A,B.*, basal artery; *A.A.V.*, arteriovenous anastomosis.

Cellular Components of the Endometrium

The Epithelium of the Glandular System

The *glandular cell* is a columnar element whose height varies from 6 to 20 μm according to the phase of the cycle. The nucleus is elongated but becomes round and vesicular during the secretory phase. The cytoplasm is the site of synthesis of RNA, proteins, mucopolysaccharides, glycogen, lipids, and various enzymes. The massive production of glycogen after ovulation justifies the term *secretory phase*.

The ultrastructure of the glandular cells reveals the typical organelles of epithelial cells.[22] The chromatin structure is finely distributed and bordered by the double-layered nuclear envelope; the nucleolus is rich in RNA and has a maximal volume at the time of ovulation. The endoplasmic reticulum, a ramified system of tubules and cisternae, is covered with numerous small granules rich in RNA (ribosomes). Some of the ribosomes are free in the cytoplasmic matrix. The Golgi apparatus or zone is a group of vacuoles and cisternae situated in the juxtanuclear region; it is concerned with synthesis and concentration of secretory products. Lysosomes are more abundant during the late secretory phase.

Mitochondria are numerous and are bordered by a double membrane that sends numerous digitations or cristae through the thickness of the matrix. The mitochondria play an essential role in the cellular mechanisms of oxidation because of their richness in enzymes.

Intensely osmiophilic lipid inclusions are found disseminated in the cytoplasm. The significance of their variations in size and shape is not precisely defined. Rounded granular formations of the size of a mitochondrion may be connected with the lysosomes; these are known as *microbodies*.

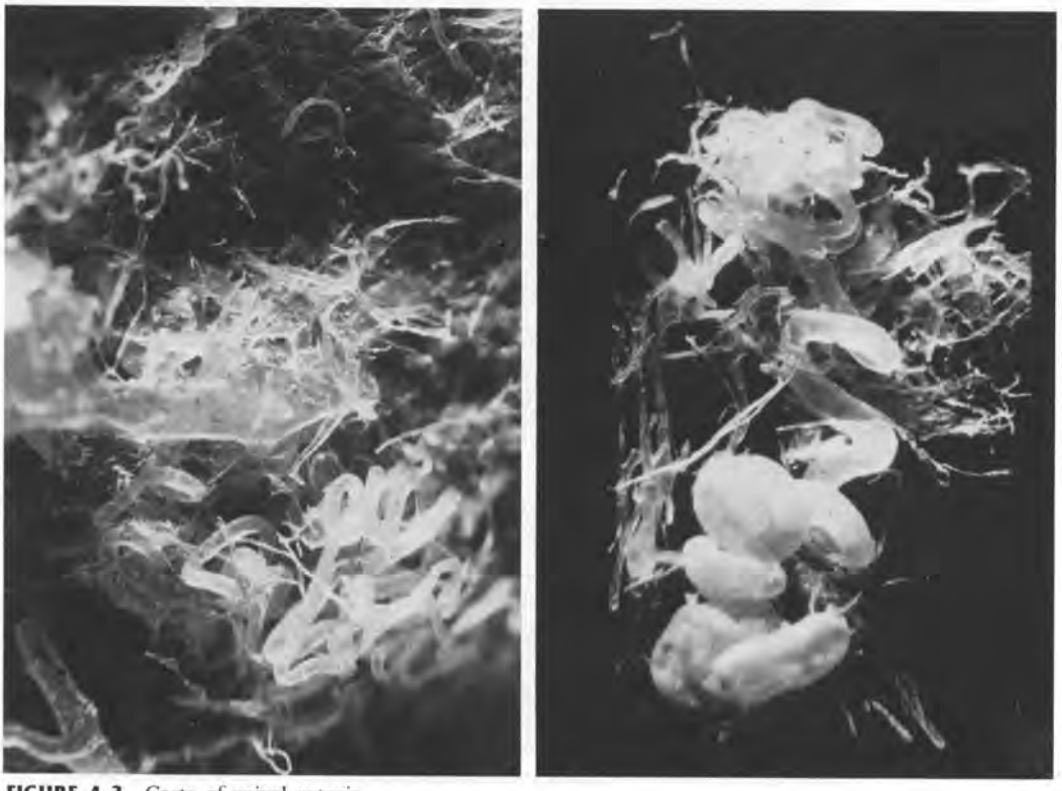


FIGURE 4-3 Casts of spiral arteris.

The ciliated cell appears as a clear cell dispersed among the glandular cells; the former are most numerous during the late proliferative phase and in endometrial hyperplasia, suggesting an estrogen-dependent mechanism. The cilia possess a complex structure consisting of nine double filaments grouped around an axial double filament (Fig. 4-4). The whole structure is surrounded by a thin casing of cytoplasm.

The other (nonciliated) cells show an apical pole covered with simple cytoplasmic prolongations (microvilli) that give a hairy appearance to the cells (Fig. 4-5). Other cells are found at the bases of the glands and have central small round nuclei and clear cytoplasm. These ciliated cells have not yet reached the luminal surface, where they can extrude their cilia.

The Superficial Epithelium

The superficial epithelium is composed of a layer of columnar cells that are rich in RNA and glycogen (Fig. 4-6).

Endometrial Stroma

Stromal cells arise from pluripotential mesenchymal cells. They are elongated elements with irregular nuclei that will become predecidual cells during the

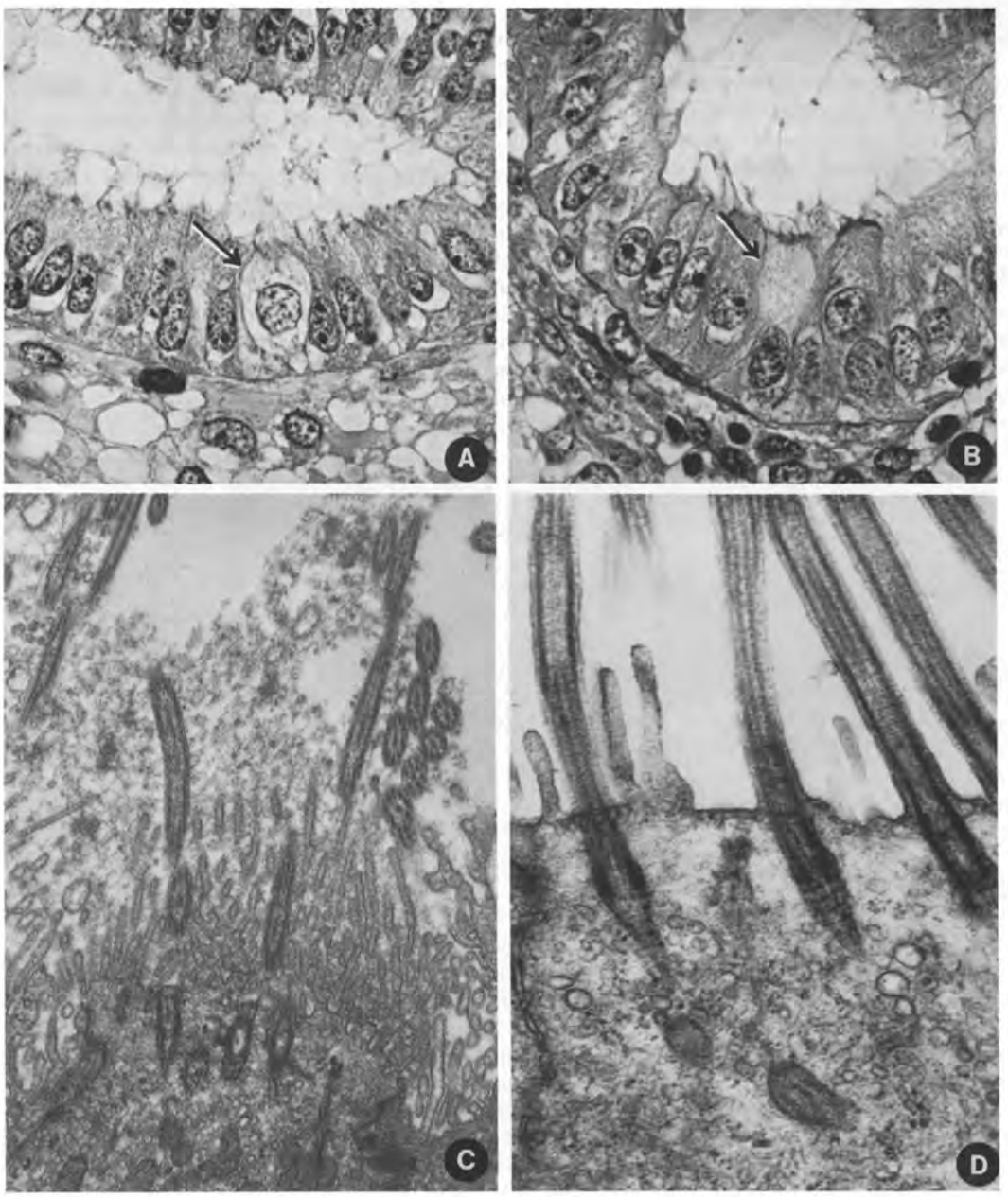


FIGURE 4-4 Ciliated cells of the endometrium. **(A,B)** Optical microscopy. **(C,D)** Electron micrographs (×23,400 and ×34,500).

late secretory phase. Glycogen and lipids are found in the abundant cytoplasm of predecidual cells. Other stromal cells have been thought to transform to endometrial granulocytes, the cytoplasmic phloxinophilic granules of which contain relaxin, which dissolves the reticulin fibers surrounding individual stromal cells immediately before menstruation.[23] More recent studies have identified these cells as lymphoid in nature.[24–26]

The *basal lamina* underlies the epithelial elements and separates them from the subjacent stroma (Fig. 4-7). Its structure varies depending on whether it is examined by optical or electron microscopy. Under the electron microscope, it appears as a dark band, about 250 nm thick, rich in reticulin fibers that run parallel to the cellular membranes of the glandular cells. It is separated from this cell membrane by a clearer zone of the same thickness. The deep surface of the membrane is in direct contact with the stromal cells and collagen fibers.

Examined with the optical microscope after silver impregnation, it appears thicker and measures about 2500 nm. This indicates that in addition to the structures that we have just described, ordinary histologic methods also stain fibrillar elements that make up part of the underlying stroma. The periodic acid-Schiff (PAS) stain is positive and reveals the presence of mucopolysaccharides.

MECHANISM OF HORMONAL INFLUENCES ON THE ENDOMETRIUM

Different portions of the endometrium respond differently to hormonal stimuli. It has been shown that estrogen- and progesterone-binding proteins (receptors) are present in normal human endometrium and mediate the effects of these hormones on the endometrial cycle.[27–30] These receptors appear to be

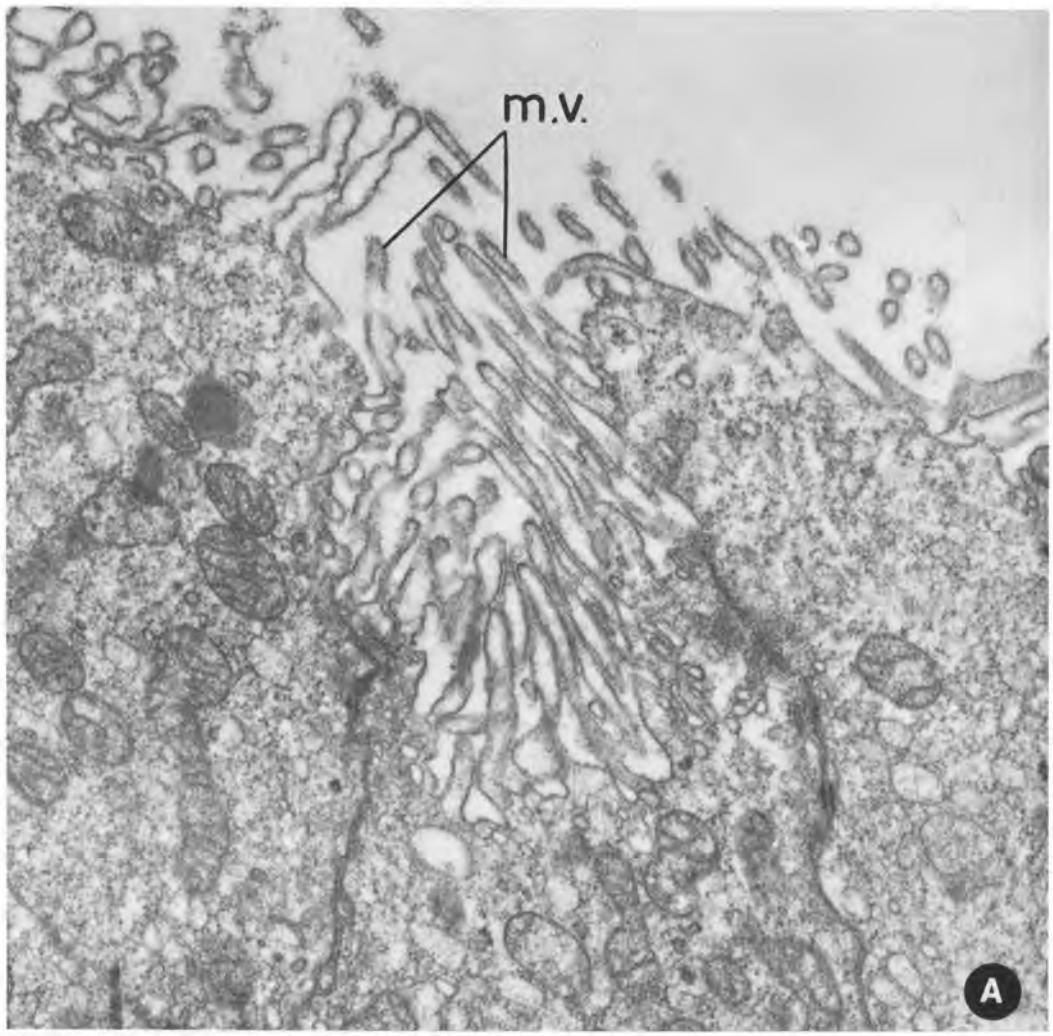


FIGURE 4-5 **(A)** Early proliferative phase (electron micrograph): cytoplasmic microvilli (*m.v.*) bordering the apical pole (×27,300). **(B)** Early proliferative phase (electron micrograph): endometrial stromal cells: nuclei (*n.*) and collagen fibers (*f.c.;* ×10,800).

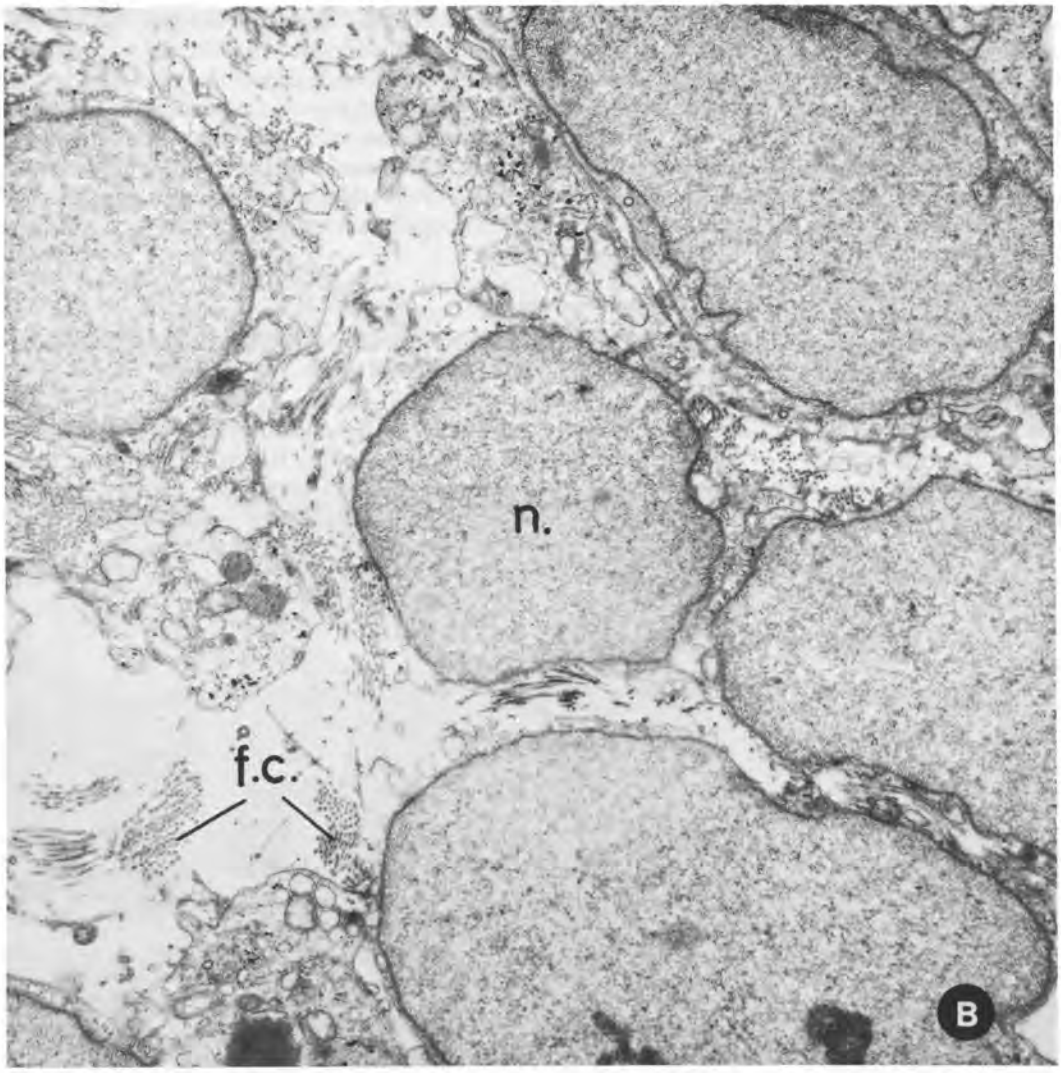


FIGURE 4-5(B) *(continued)*

more numerous in glandular than in stromal cells and in endometrium of the fundus than of the isthmus or lower uterine segment. Estrogen increases the concentration of these receptors, whereas progesterone decreases them.[31] Steroid hormone molecules combine with their cytoplasmic receptors, and the complex moves to the nucleus, where it affects DNA-dependent RNA transcription and, ultimately, the appearance of the endometrium.

The production of different enzymes within the endometrium is influenced by the ovarian hormones that act on these receptors. For example, alkaline phosphatase is found in greatest concentration in glandular epithelial cells during the estrogenic phase, whereas estradiol dehydrogenase (which converts estradiol to estrone) is increased by progesterone and thus is found mostly in the luteal phase.[32,33] The endometrium can also produce hormones, such as prostaglandins and prolactin.[34,35]

CYTOLOGY OF NORMAL ENDOMETRIUM

The cytologic appearance of normal endometrial cells depends on their source. Endometrial glandular cells generally are seen in vaginal pool smears during the first 10 days of each menstrual cycle, in which situation they present as compact balls of uniform small cells with dark nuclei showing varying degrees of degeneration and very little preserved cytoplasm (Color Fig. 4-1). In vaginal material, the presence of endometrial cells after the tenth day of a cycle or in a postmenopausal woman who is not cycling because of exogenous hormones should suggest the possible presence of an endometrial hyperplasia or (particularly if the cells are atypical) carcinoma.

In material obtained by direct aspiration of the endometrial cavity, on the other hand, endometrial cells should be seen at all times, even in the absence

of pathology, and should be better preserved. The glandular columnar cells are smaller than those of the endocervix and may appear as clusters with well-defined borders ("honeycomb" pattern; Color Fig. 4-2), as an elongated palisade, or as single cells. The nuclei are rounded or ovoid and exhibit finely granular chromatin and a nucleolus that may be prominent. In the luteal phase, the nuclei are rounder and paler and the cytoplasm more abundant and frequently vacuolated. Occasional ciliated cells may be encountered; if they are numerous, a hyperestrogenic state is suggested.

Endometrial stromal cells are also seen, and they are particularly numerous at the end of the menstrual phase. These cells resemble the glandular cells but may have less well-defined cell borders (Color Fig. 4-3). Like glandular epithelial cells, they become loaded with glycogen during the luteal phase.

PHYSIOLOGIC MECHANISMS OF MENSTRUATION

The intimate mechanisms of menstruation still are not entirely elucidated. One may appreciate the long road followed since the earliest studies by reading the first chapter of the "Traité des maladies des femmes," written in Paris in 1761 by J. Astruc,[36] Royal Professor of Medicine and consultant physician to King Louis XV. We have extracted and translated the following passage:

> The understanding of the structure of the matrix and of the distribution of its vessels is sufficient to state that it is from the venous appendages that this blood must flow. These are all venous ramifications; those which advance the farthest in the cavity of the matrix are the only ones which pene-

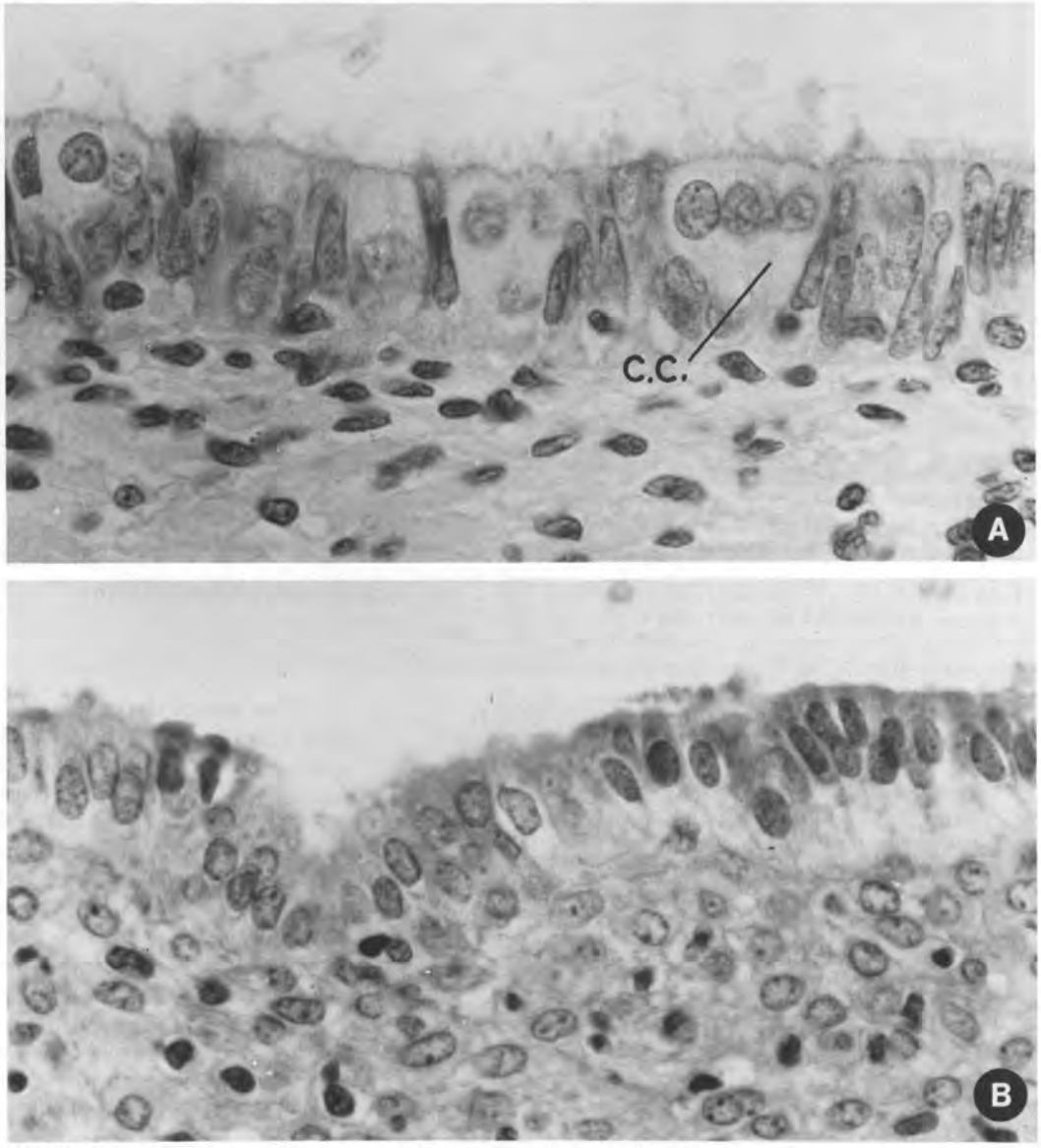


FIGURE 4-6 Covering epithelium of endometrium; ciliated cells (*c.c.*).

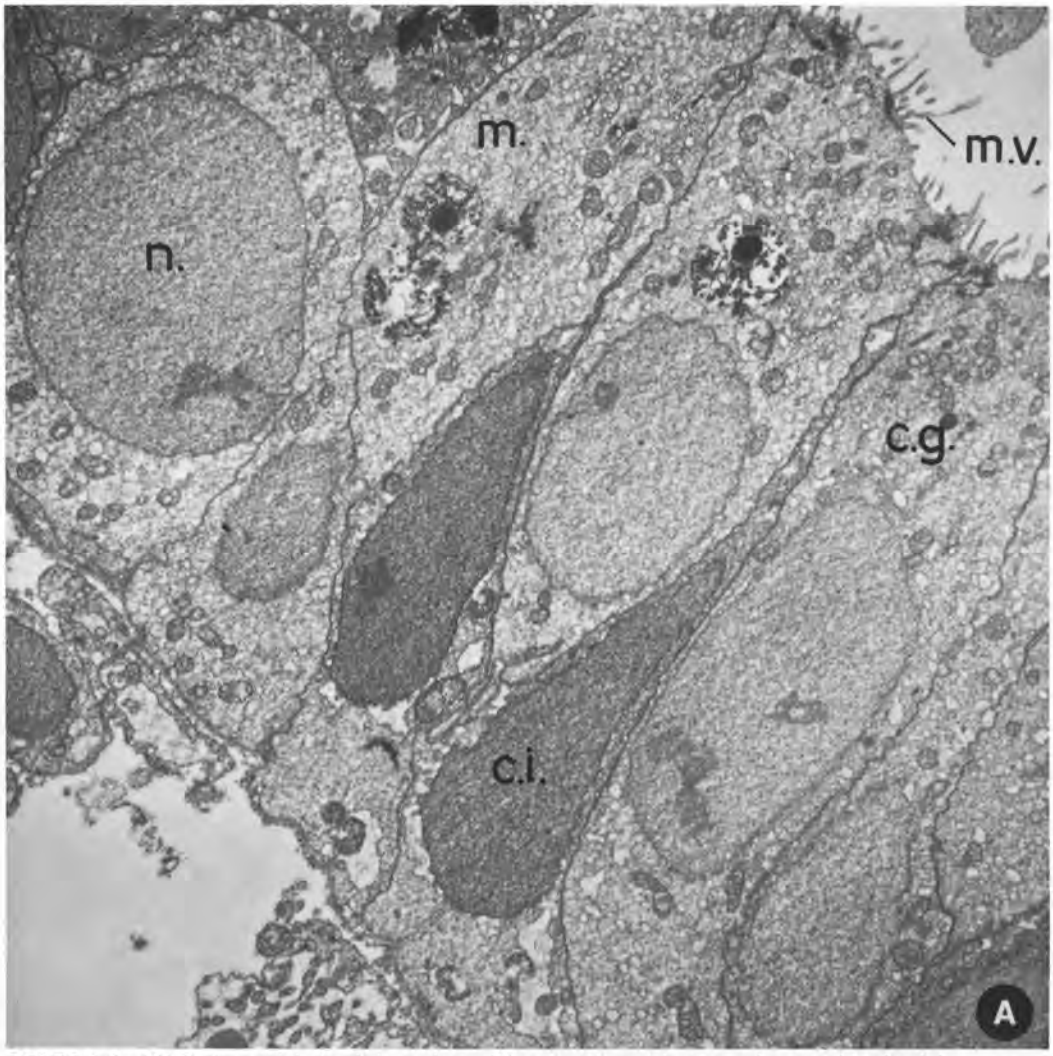


FIGURE 4-7 **(A)** Endometrial glands in early proliferative phase (electron micrograph): glandular cells (*c.g.*): intercalated cells (*c.i.*); nuclei (*n.*); mitochondria (*m.*); microvilli (*m.v.;* ×7500). **(B)** Early proliferative phase (electron micrograph); mitochondrion (*m.*); basement membrane (*m.b.*); collagen fibers (*f.c.*). The structure of the basement membrane is easily visible here. It is constituted, from top to bottom, by the basal membrane of the cell, a clear space, and a dark band. The entire structure is about 250 nm thick and rich in reticulin.

> trate the full thickness of the tunica interior. These are kinds of venous endings which should be destined for some usage in the design of nature, but, however, have none in the ordinary order of the circulation. Finally, these are vein endings simply wrinkled at their extremities and therefore capable of extending, folding, opening without tearing. All these facts form so many presumptions that should make one conjecture that it is from these appendages that bleeding takes place into the cavity of the matrix during menstruation.

The theory proposed in 1761 by Astruc (Fig. 4-8), based essentially on visual observation and good sense, as the author himself said, permitted the prediction with remarkable prescience of the existence of the spiral arteries and of their mechanism of action in the process of menstruation.

The endometrial vessels were described for the first time in 1754 by Hunter, who compared their convolutions to the undulations of a snake.[21] It was not until 1847 that the existence of a true mucosa was recognized by Coste. It was described histologically for the first time in 1873 by Kundrat and Engelmann; in 1877, Leopold described the spiral arteries; and in 1908, Hitschmann and Adler[37] recognized the cyclical nature of the histologic modifications of the endometrium. Schröder[38,39] was the first to synthesize these diverse observations; he recognized the relationship existing between maturation of the ovarian follicle and the proliferative phase of the endometrium and between the corpus luteum and the secretory phase.

Subsequent studies over the next three quarters of a century have served to increase our knowledge

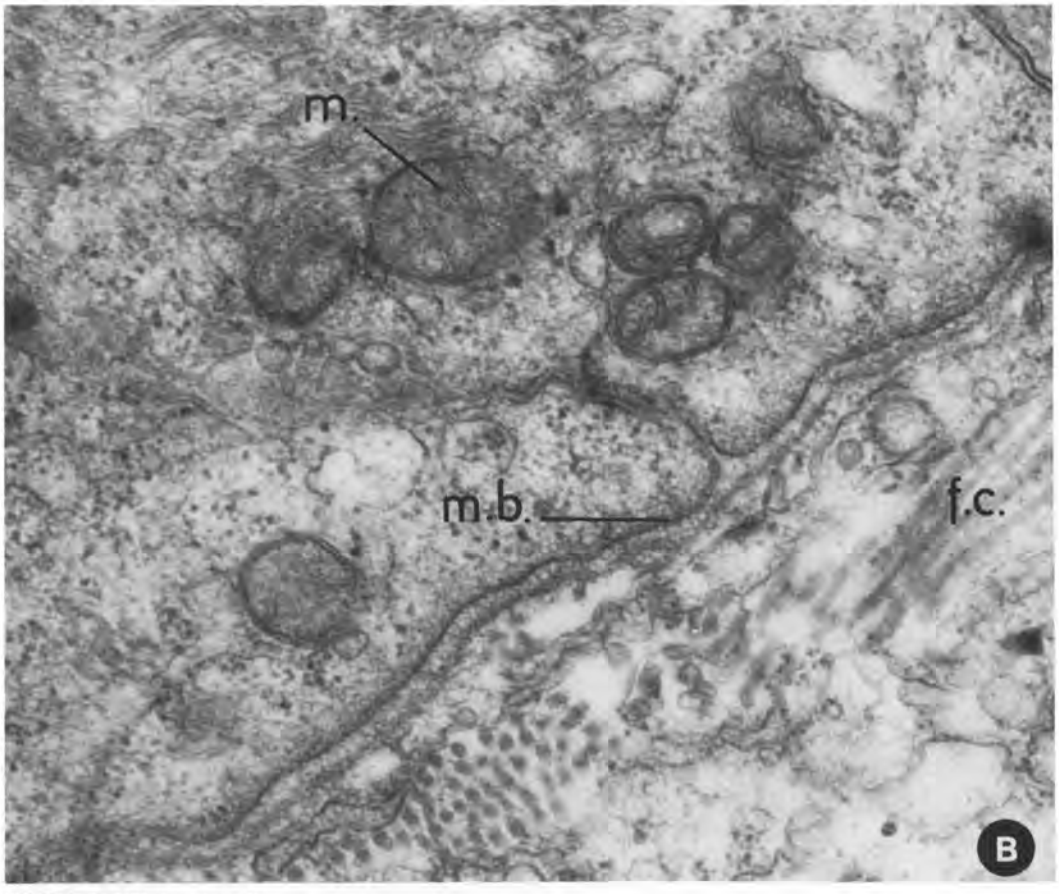


FIGURE 4-7(B) *(continued)*

greatly but still have not provided a universal explanation for the phenomenon of menstruation. For the purposes of the diagnostic pathologist who is seeking to correlate structure with function, much has been learned about the normal cyclical variations of the endometrium. The information provided by these studies is summarized in the following section.

CYCLICAL VARIATIONS OF THE ENDOMETRIUM

Histologic Modifications of the Endometrium

An essential role of the histologic modifications of the endometrium under the influence of ovarian hormonal stimulations is the preparation of the mucosa for the implantation of the fertilized ovum. The morphologic conditions necessary for this implantation are reproduced with a remarkable regularity and constancy in the absence of fertilization.

These modifications are under the influence of the estrogenic hormones during the first half of the cycle and of progesterone and estrogens during the second half. The combination of these two hormonal activities conditions the appearance of the endometrium. Their production is under the influence of the anterior pituitary through the mediation of the hormones of follicular maturation or stimulation (follicle-stimulating hormone [FSH]) and of luteinization (luteinizing hormone [LH]). The anterior pituitary is itself under the influence of the central nervous system through the hypothalamus.

The aspects of the uterine mucosa are classified schematically in eight phases. If we consider the duration of the "normal" (ie, average) cycle to be 28 days, the phases are as follows:

1. The early proliferative (estrogenic) phase (days 4–9)
2. The late proliferative (estrogenic) phase (days 10–14)
3. The phase of ovulation (interval phase) (days 14 and 15)
4. The early secretory (luteal, progestational) phase (days 16–18)
5. The mid-secretory (luteal, progestational) phase (days 19 and 20)
6. The late secretory (luteal, progestational) phase (days 21–25)
7. The immediately premenstrual phase (days 26–28)
8. The menstrual phase (days 1–3).

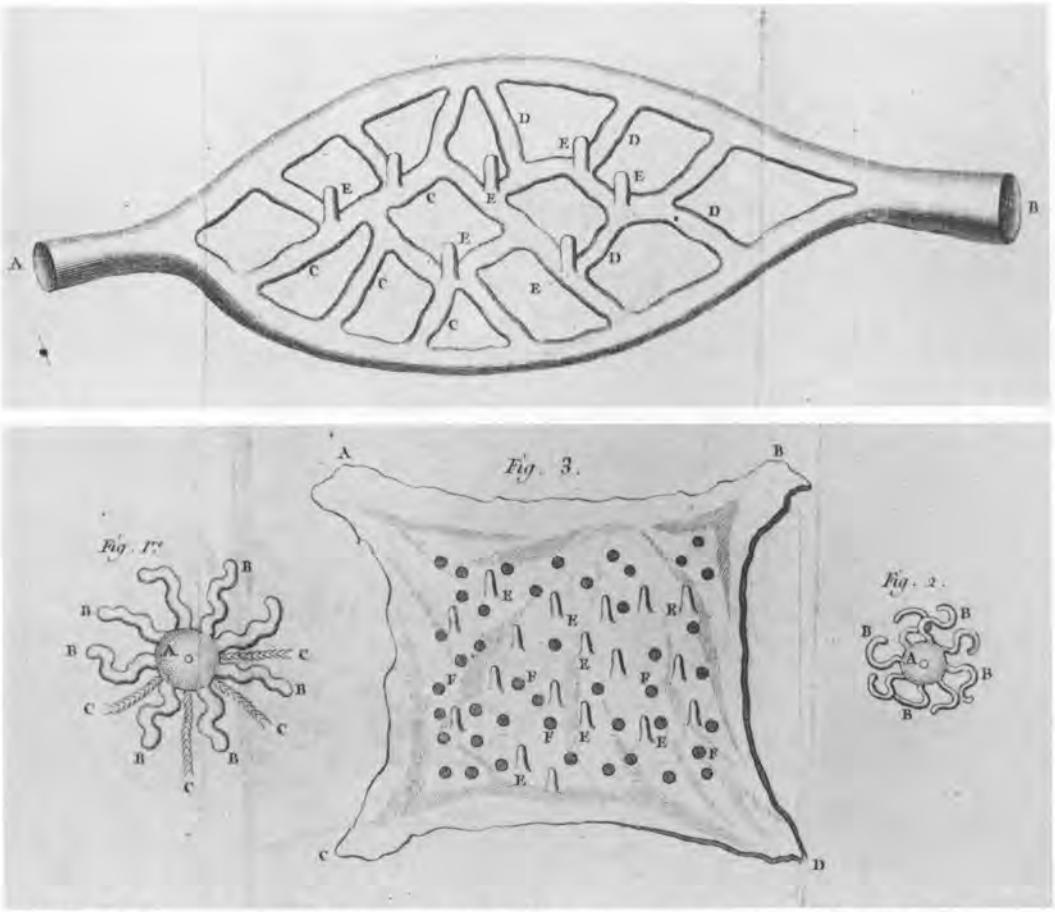


FIGURE 4-8 Representation of the vascularization of the endometrium (Astruc J: Traité des maladies des femmes. Paris, PG Cavelier, 1761).

This system is useful diagnostically as well as descriptively, because it has been shown that about 75% to 80% of endometrial biopsies can be dated histologically within 2 days in either direction.[40–42] Exact dating with reference to circulating hormone levels or the onset of the next menses is much less accurate. Because it is easier to demonstrate day-to-day variations in postovulatory endometria, it has been suggested that the designation of day 1 should be assigned to the first day after ovulation (day 15 in the schema presented here), rather than the first day of menstrual bleeding.[41] We have no objection to this system but emphasize that all clinicians and pathologists within a given institution should use and understand the same system.

Although the lengths of the proliferative and secretory portions of the cycle both average 14 days, the former may vary in presumably "normal" women from 9 to 21 days and the latter from 9 to 17 days,[40] thus pointing out again the imprecision of the comments presented below.

Because of these variations, particularly in the secretory phase, correlation between histologic dating and chronologic dating is considerably better if the LH peak rather than the date of the next menstrual period is used as the chronologic standard.[43,44] Endometrial morphology also has been shown to correlate well with corpus luteum morphology[44] and the date of ovulation determined by ultrasonography.[45] Morphometric analysis of the endometrium may be even more reliable than standard histopathology,[46,47] but it is considerably more time and labor intensive.

Early Proliferative Phase (Days 4–9)

General Appearance of the Mucosa. The thickness of the endometrium at the beginning of the cycle is about 1 to 2 mm. The glands have regular contours, are of small diameter, and are dispersed in a relatively dense stroma (Fig. 4-9). The middle part of the endometrium may contain a few clumps of lymphocytes, which have no pathologic significance (Fig. 4-10). This appearance characterizes the mucosa, which, after having reconstituted its anatomic integrity, undergoes a phase of growth of its glands, stroma, and vessels. The covering superficial epithelium, now completely regenerated, is cylindrical and contains ATPase and alkaline phosphatase. It is rich in ciliated and mucus-secreting cells.

Glandular Epithelium. The glandular columnar cell shows a basal elongated nucleus and abundant

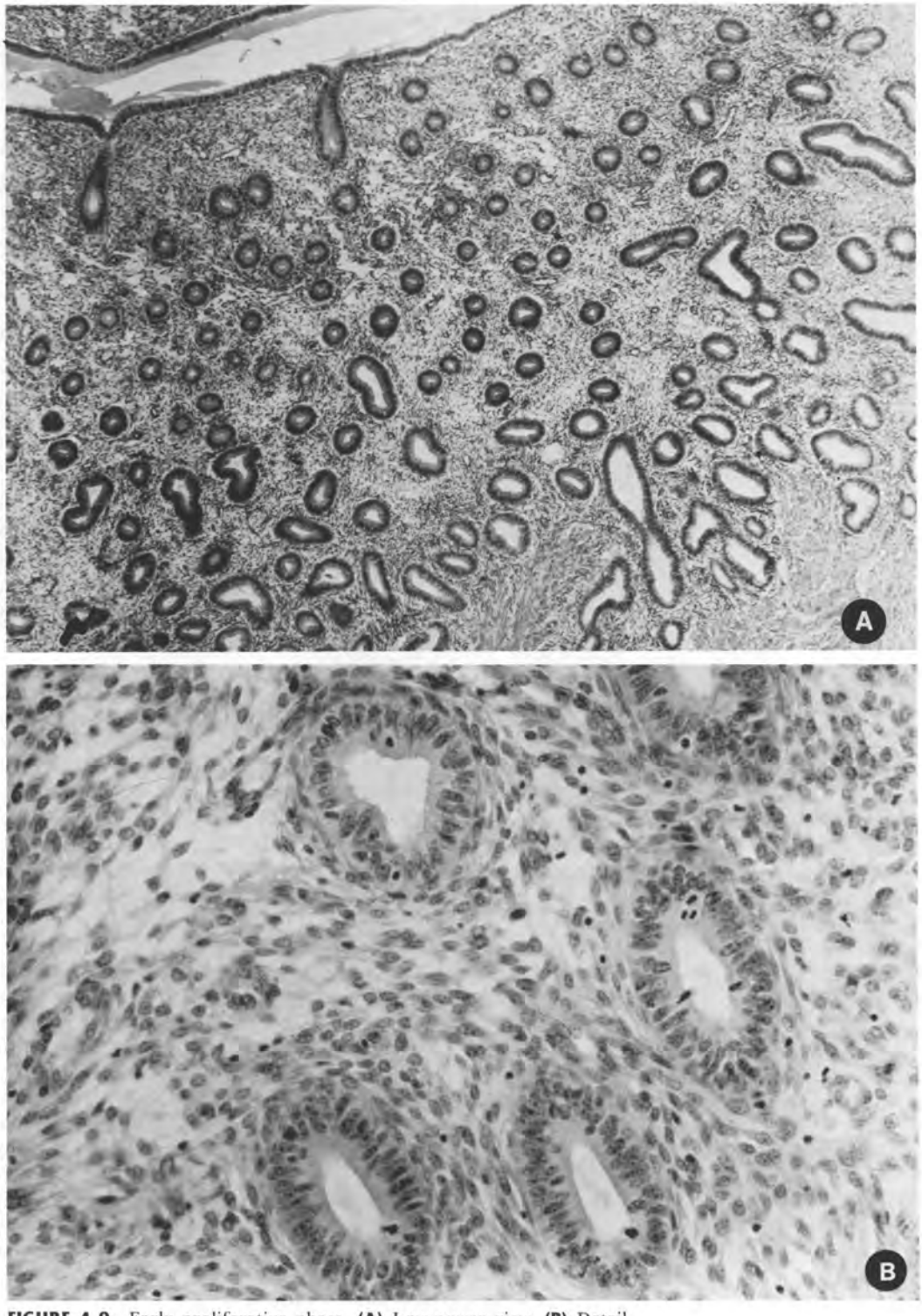


FIGURE 4-9 Early proliferative phase. **(A)** Low-power view. **(B)** Detail.

apical cytoplasm bordered by microvilli (see Fig. 4-5*A*). The nuclei are not all situated at the same level, and this variation creates a pseudostratified appearance that must not be confused with the picture of hyperplasia. Mitoses are frequent; they are found at the apical pole of the cell and in the middle if the gland is sectioned transversely. The cytoplasm of the glandular cells contains small elongated mitochondria. RNA synthesis is very active, as indicated by the abundance of free ribosomes and granular endoplasmic reticulum. Ciliated cells are dispersed in the glandular epithelium (see Figs. 4-4 and 4-6).

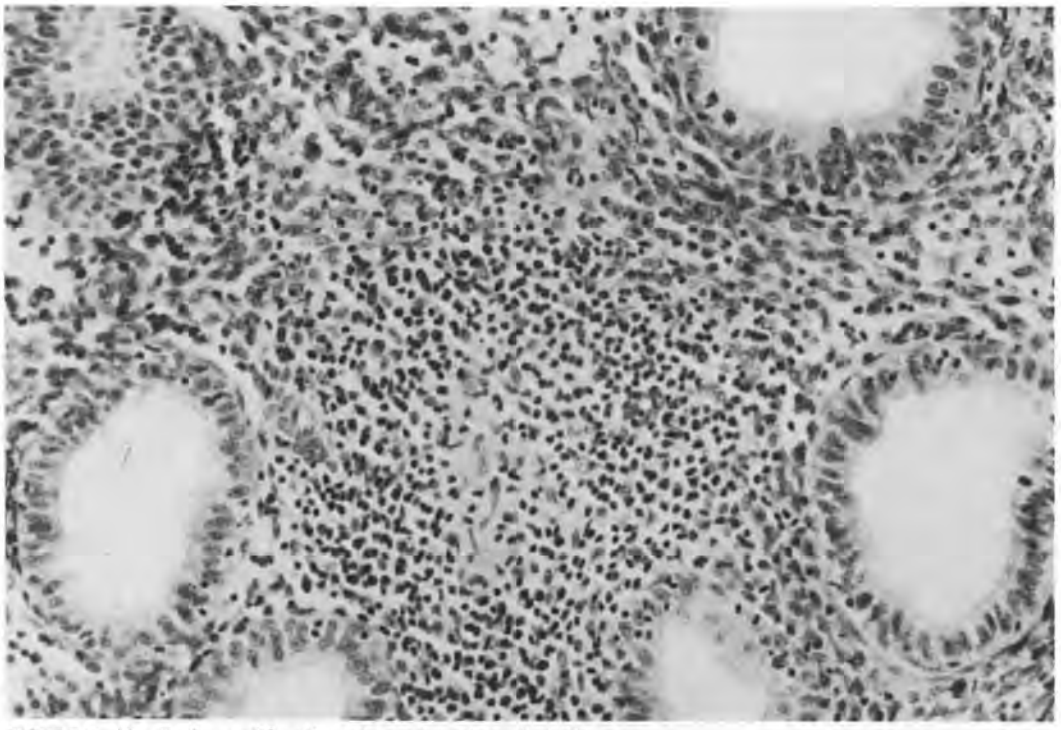


FIGURE 4-10 Early proliferative phase: lymphocytic infiltrate.

Stroma. The stroma is dense and richly populated with small cells containing rounded or elongated nuclei (see Fig. 4-9*B*). Ultrastructurally, they resemble fibroblasts and produce numerous collagen fibers (see Fig. 4-5*B*). Mitoses are present. Between the cells, there is a well-developed collagenous network formed of bundles of fibers anastomosing in all directions. Here and there, one may find rare leukocytes in the concentration of about one per square millimeter of endometrium. Thin-walled spiral arteries are situated in the deep layers; they give rise to a few collaterals that irrigate the periglandular capillary plexus. The moderately dilated venous networks empty into the venous plexus, which form lakes in regions of anastomoses of venous trunks. These reassemble into collecting trunks that enter the myometrium.

Late Proliferative Phase (Days 10–14)

General Appearance of the Mucosa. The thickness of the endometrium increases to about 2 to 3 mm. The gland contours become more sinuous, and their diameters increase as well. At this time, numerous glands have convoluted contours, and the surface epithelium forms large undulations (Fig. 4-11). The stroma is abundant. Edema appears between the cells at the onset of this phase and tends to regress before ovulation. The spiral arteries continue their development and reach the superficial part of the endometrium. The arteriolar walls thicken and become enriched in elastic fibers. The capillaries, lymphatics, and veins grow and dilate. Sometimes in the deep layers there exist a few small lymphoid follicles, the presence of which has no pathologic significance.

Glandular Epithelium. Proliferation of the glandular cells is evidenced by the number of mitoses present. Their nuclei are elongated and enlarged and are always found at the base of the cell (see Fig. 4-11). Ultrastructurally, RNA synthesis is still very active. The Golgi apparatus is well developed, and lipid droplets are present in the apical part of the cytoplasm. The number of ciliated cells increases proportionately, but they remain in the minority. Clear cells appear as isolated and dispersed elements at the base of the glandular epithelium.[48] Their abundant clear cytoplasm stands out against the darker appearance of the neighboring cells. These cells appear to be precursors of fully ciliated cells and are useful markers of estrogenic activity because they are rarely seen in inactive or atrophic endometria.

Toward the 14th day of the cycle, fine glycogen inclusions appear ultrastructurally at the basal pole of the glandular cell. They accompany the presence of voluminous mitochondria in intimate relation with the endoplasmic reticulum. This morphologic connection suggests that these two organelles play collaborative roles in the synthesis of glycogen. A microtubular system distinct from the endoplasmic reticulum has been described by Cavazos;[49] these structures are said to be spatially and temporally related to glycogen. Clyman[50] has more recently denied their existence and believes that they are tonofilaments. The cytoplasm of the glandular cells shows three distinct zones when examined by electron microscopy: the basal zone, in which the glycogen appears (Fig. 4-12*A*), the juxtanuclear zone, in which the mitochondria are elongated and less numerous, and the apical zone. The apical zone con-

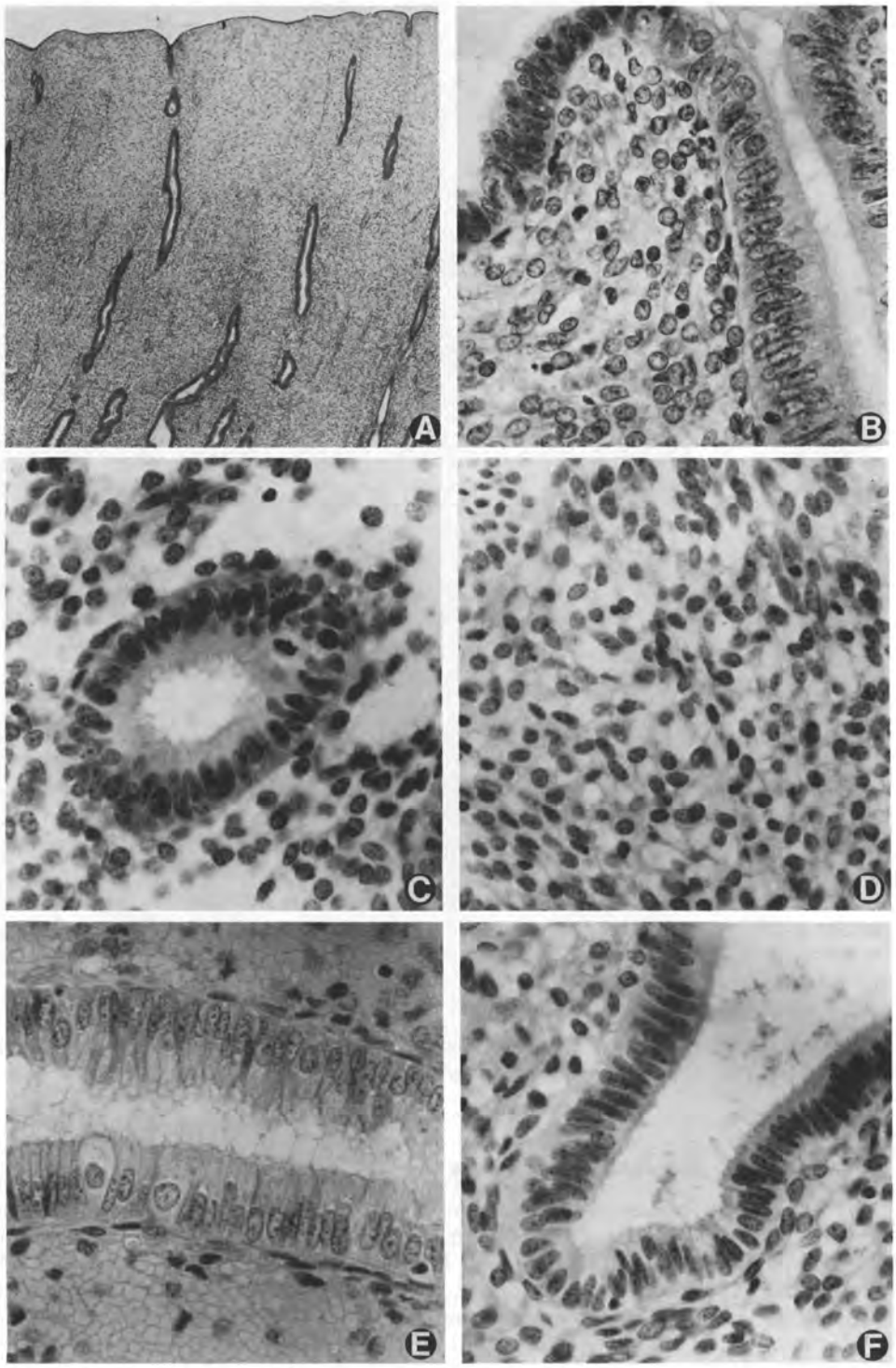


FIGURE 4-11 Late proliferative phase. **(A)** General appearance. **(B)** Surface epithelium and gland neck. **(C)** Mitosis in gland. **(D)** Stroma. **(E)** Gland showing a ciliated cell and a small clear cell (*at right*). **(F)** Proliferative gland showing a clear cell toward the bottom.

tains numerous mitochondria, well-developed endoplasmic reticulum, lipid inclusions, and vacuoles that are either simple or filled with microvesicles. The Golgi apparatus, situated immediately above the nucleus, comprises a series of longitudinal fissures and rounded vacuoles. These submicroscopic modifications are connected with the secretory activities of the cell.[51]

The basement membrane loses its rectilinear disposition and presents more and more numerous and accentuated invaginations toward the glandular epithelium; these are the precursors of the connective tissue spines of the secretory phase.

Stroma. The stroma increases in volume and is composed of stellate cells anastomosed to one another (see Fig. 4-11). It forms a loose network containing more or less abundant edema fluid, which

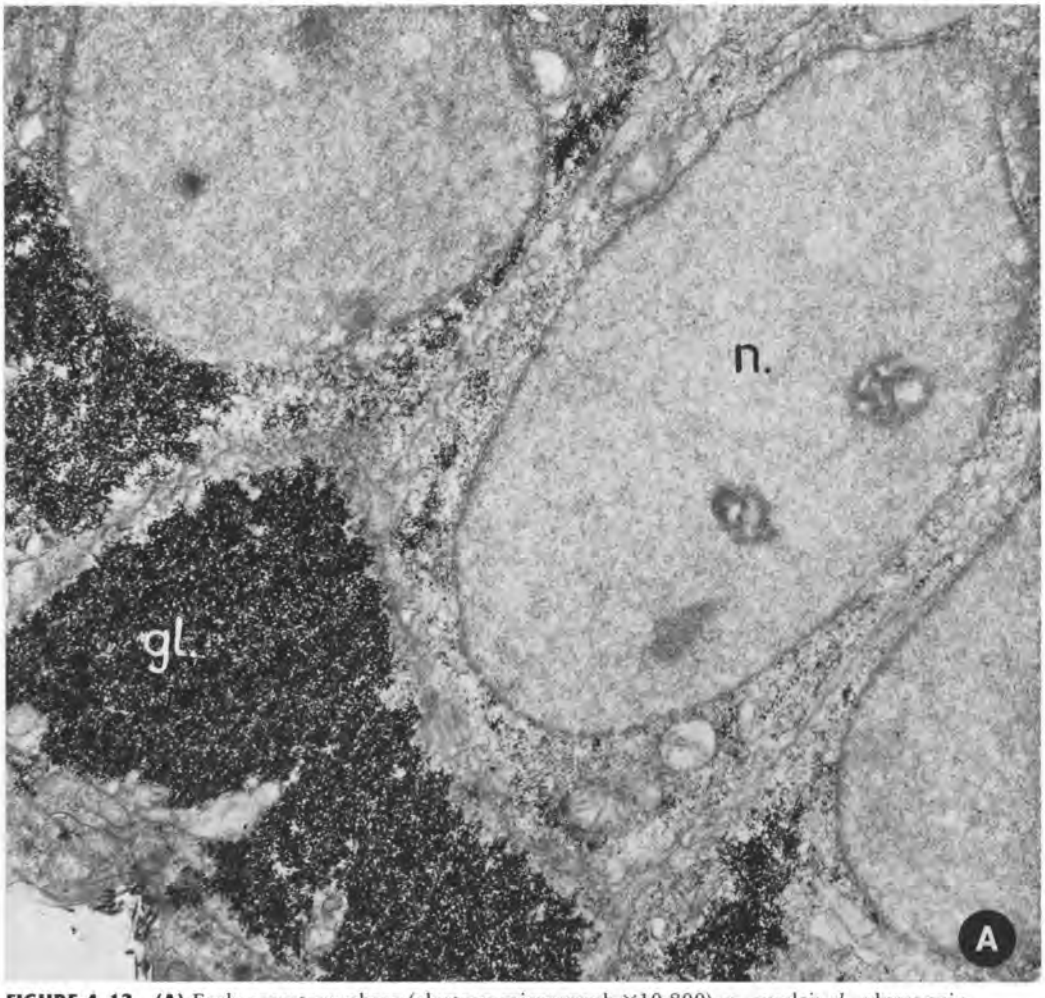


FIGURE 4-12 **(A)** Early secretory phase (electron micrograph ×10,800). *n.*, nuclei; *gl.*, glycogenic vacuoles. **(B)** Intranuclear tubular structures.

tends to diminish immediately after ovulation. A few leukocytes are found here and there. Mitoses are numerous.

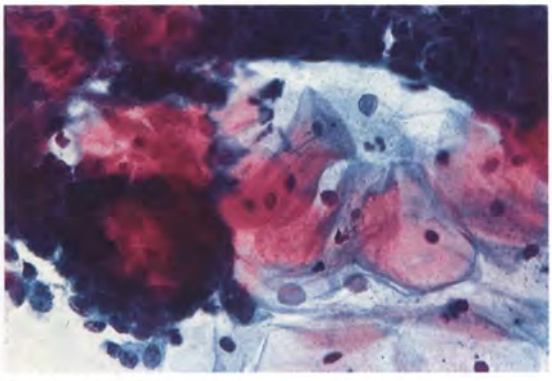
Ovulatory (Interval) Phase (Days 14–15)

The combined influence of estrogens and progesterone characterizes the ovulatory phase. Edema of the compact layer begins to develop. Transient focal hemorrhagic phenomena may appear, limited to the superficial portion of the endometrium (Fig. 4-13); this is manifested clinically by a small loss of blood in about 5% of women. Microscopic examination shows tiny hemorrhagic foci situated below the surface epithelium.

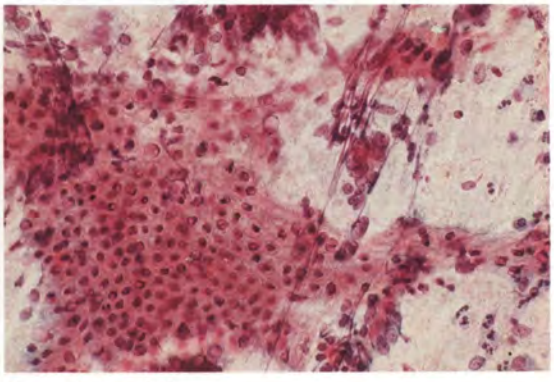
Early and Mid-Secretory Phases (Days 16–20)

General Appearance of the Mucosa. The thickness of the endometrium is at its maximum (3 to 5 mm). The glands are numerous, and their caliber has increased in comparison with the preceding phase. The "sawtooth" appearance of their contours is caused by invaginations of the membrane and of the adjacent stroma, which form small connective tissue axes on which are implanted the glandular cells. However, their presence is not indispensable for the diagnosis of a secretory endometrium. Their number and height increase during the course of this phase. The surface epithelium is markedly convoluted. The stroma is abundant and of loose consistency. The vessels continue their growth, the walls of the spiral arteries thicken and their spiralization increases, and the foci of edema in the spongiosa (which tend to regress somewhat between days 12 and 18) again become more numerous. The basal endometrium continues to show a discrete proliferative appearance and is not affected by the postovulatory modifications.

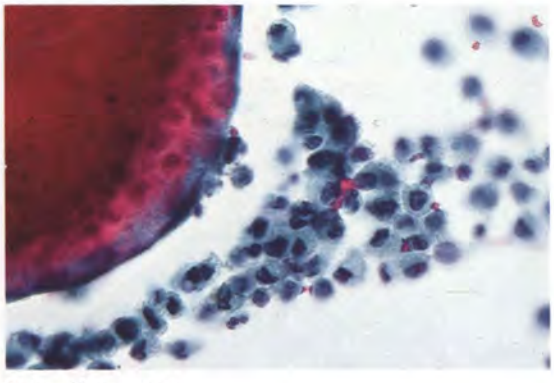
Glandular Epithelium. About 24 to 72 hours after ovulation, basal vacuoles appear in the secretory glandular cells;[41,52] they represent the massive glycogen content of the cytoplasm and correspond to the beginning of progestational activity (Figs. 4-14 and 4-15; see Fig. 4-12).



Color Figure 4-1



Color Figure 4-2



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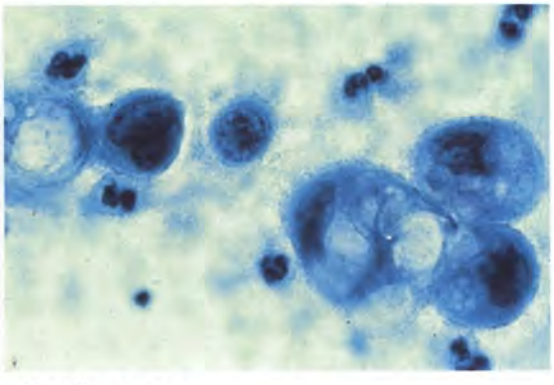


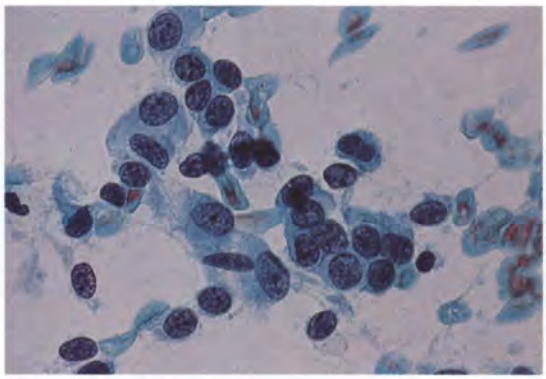
Color Figure 4-4

Color Figure 4-1 Poorly preserved benign endometrial glandular cells in vaginal smear.

Color Figure 4-2 Endometrial glandular cells in "honeycomb" pattern in endometrial aspirate.

Color Figure 4-3 Endometrial stromal cells (*right*) in vaginal smear taken during menses. The large ball of glandular cells (*left*) is markedly degenerated.

Color Figure 4-4 Vaginal smear from an IUD wearer, showing both atypical columnar cells (*right*) and "IUD cells" with a high nuclear–cytoplasmic ratio (*left*). (Courtesy of Dr. Prabodh K. Gupta, Hospital of the University of Pennsylvania, Philadelphia)



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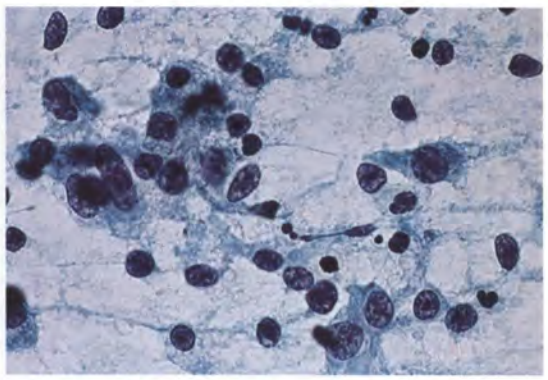

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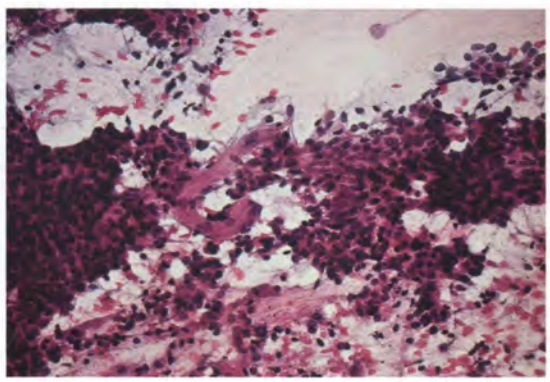

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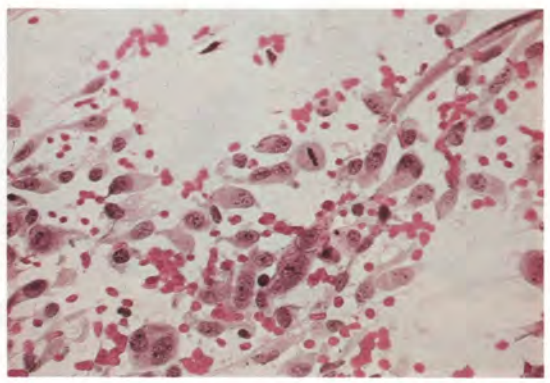


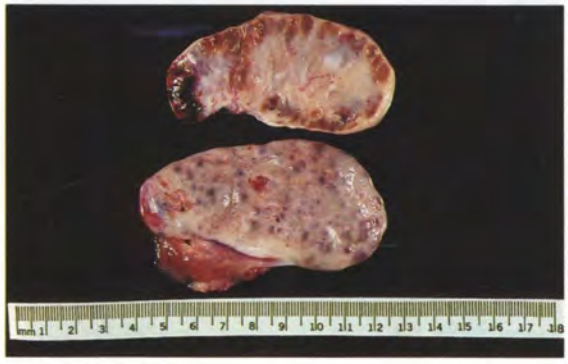
Color Figure 4-8

Color Figure 4-5 Complex hyperplasia (endometrial aspirate).

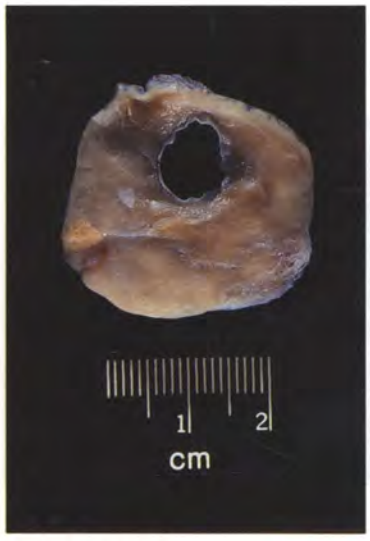
Color Figure 4-6 Well-differentiated adenocarcinoma (endometrial aspirate). Atypia is increased only slightly from Color Figure 4-5.

Color Figure 4-7 Aspirate of adenoacanthoma: squamous cells in center surrounded by well-differentiated adenocarcinoma cells.

Color Figure 4-8 Leiomyosarcoma: cytologic picture featuring marked pleomorphism, spindled tumor cells, and mitotic figures.



Color Figure 6-1



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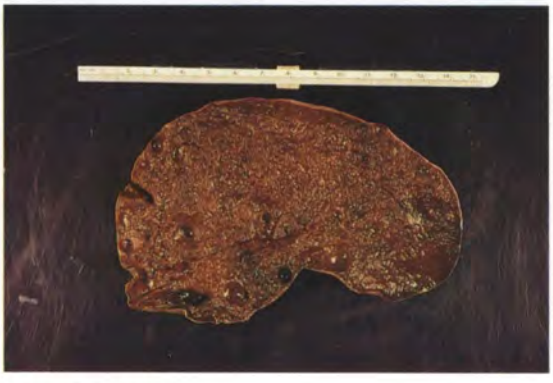
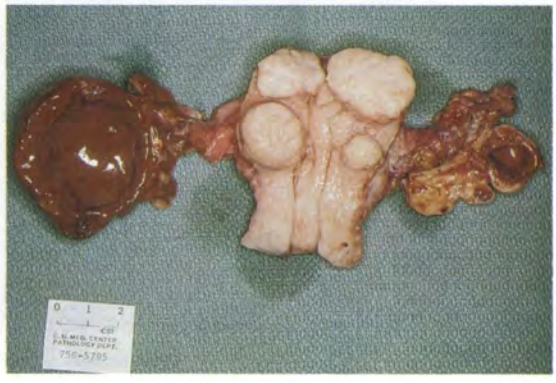


Color Figure 6-3



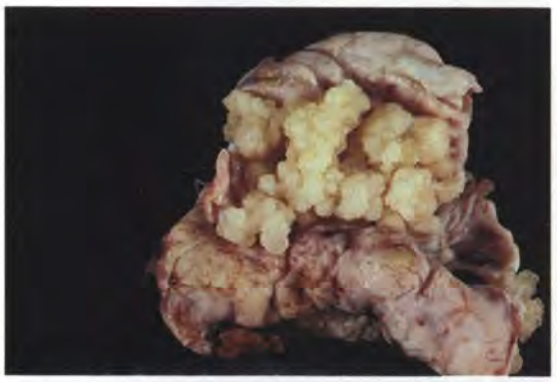
Color Figure 6-4

Color Figure 6-1 Hyperreactio luteinalis. Cortical and cut surfaces of one of two enlarged ovaries in a woman with a twin pregnancy.

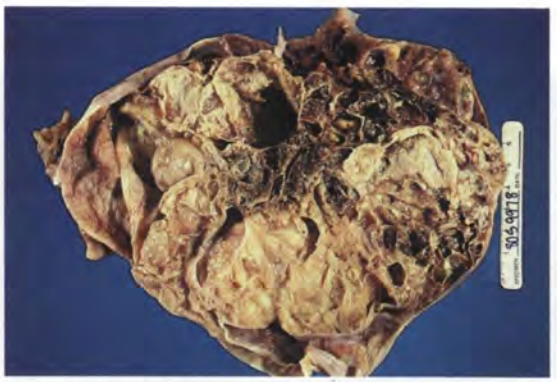
Color Figure 6-2 Ovary with hyperthecosis. Tan cortical stromal nodules are present. The benign cyst and the corpus luteum are incidental.

Color Figure 6-3 Massive edema of the ovary. The ovary is enlarged, and clear fluid exudes from the cut surface.

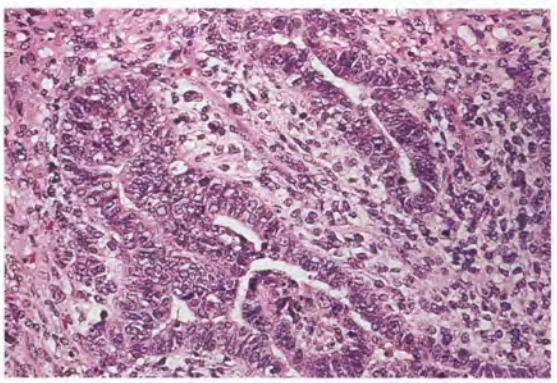
Color Figure 6-4 Endometriosis of the ovary. The bilateral "chocolate cysts" are associated with uterine leiomyomata.



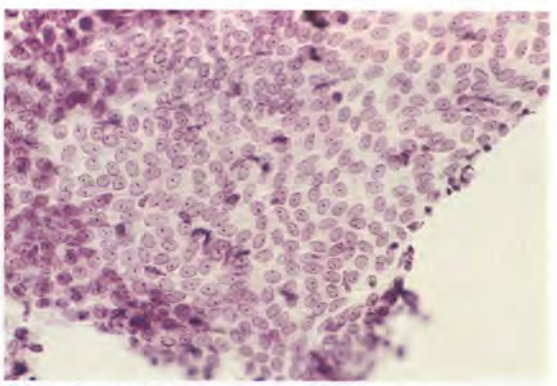
Color Figure 6-5



Color Figure 6-6



Color Figure 6-7



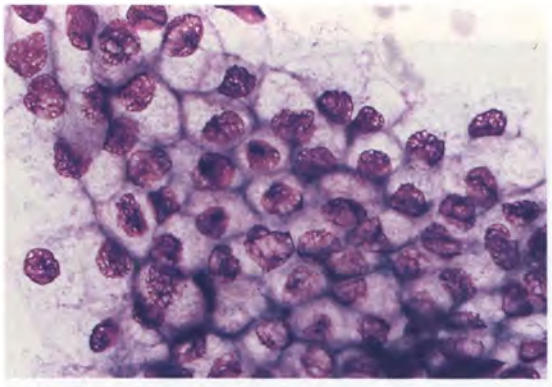
Color Figure 6-8

Color Figure 6-5 Serous tumor of low malignant potential. Coarse polypoid processes project into the cyst lumen.

Color Figure 6-6 Mucinous tumor of low malignant potential. These are generally large, multiloculated cystic neoplasms.

Color Figure 6-7 Carcinosarcoma. The tumor is composed of malignant epithelial and mesenchymal elements.

Color Figure 6-8 Smear from serous cystadenoma showing a broad flat sheet of uniform cohesive cells with small regular nuclei.



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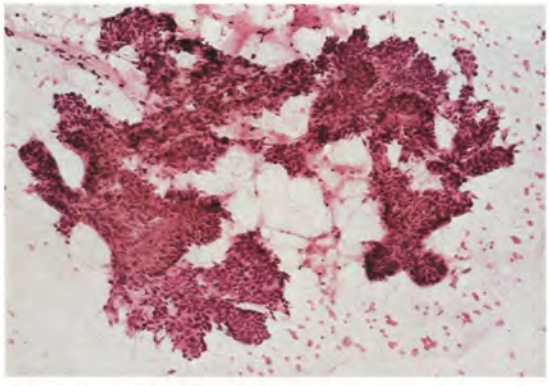

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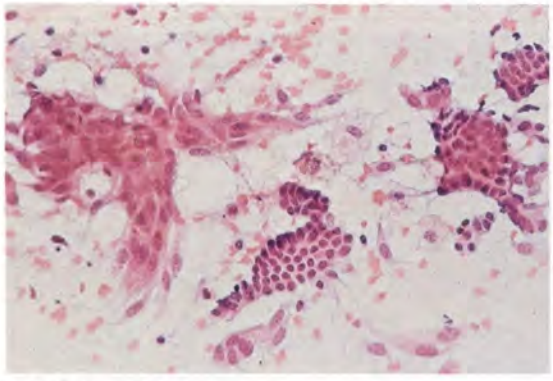
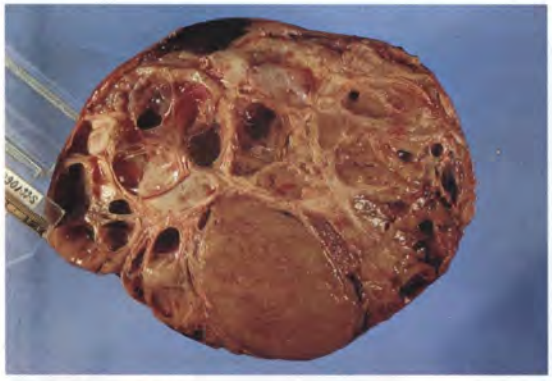


Color Figure 6-11



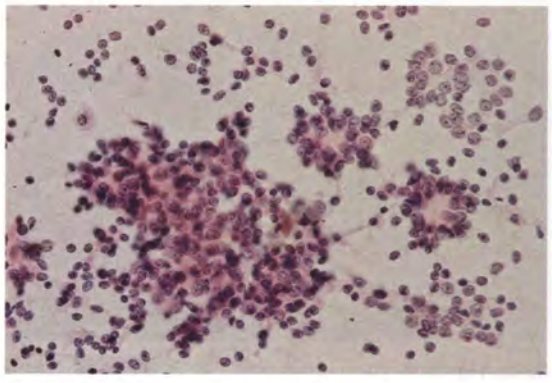
Color Figure 6-12

Color Figure 6-9 Smear from mucinous cystadenoma. Uniform cohesive cells in a honeycomb arrangement.

Color Figure 6-10 Fine needle aspirate of serous cystadenocarcinoma of the ovary. Papillary clusters have frequent branches composed of small, tightly packed cells with high nuclear–cytoplasmic ratio and nuclear hyperchromasia. (Courtesy of M. Nadji, MD, University of Miami, Miami, FL).

Color Figure 6-11 Transabdominal needle aspirate of an endometrioid tumor of low malignant potential. Glandular elements (*right*) contrast with the squamous component (*left*). (Courtesy of M. Nadji, MD, University of Miami, Miami, FL).

Color Figure 6-12 Granulosa cell tumor. Granulosa cell tumors typically are partially cystic. The intervening solid areas are soft and tan or yellow.



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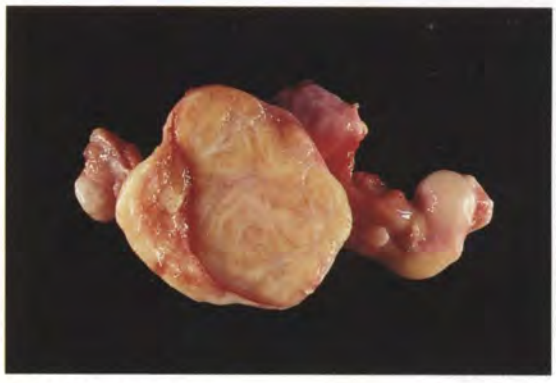

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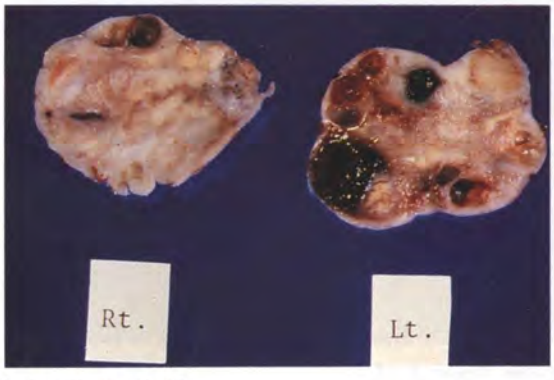
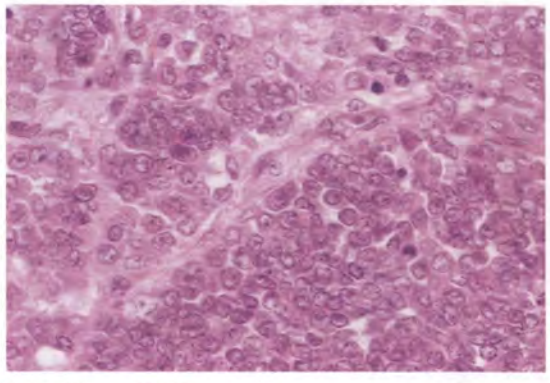


Color Figure 6-15



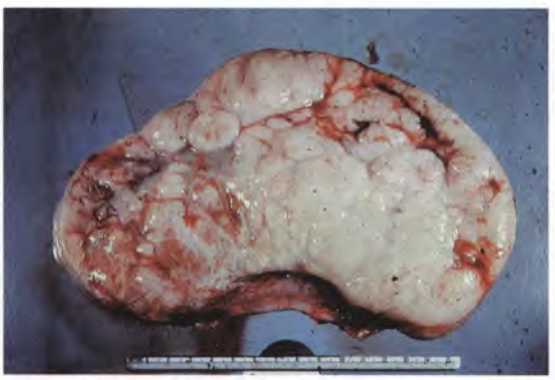
Color Figure 6-16

Color Figure 6-13 Fine-needle aspirate of granulosa cell tumor. Groups of cells with uniform oval nuclei, indistinct cytoplasmic borders, and structures resembling Call-Exner bodies. (Courtesy of M. Nadji, MD, University of Miami, Miami, FL)

Color Figure 6-14 Thecoma. Firm solid tumor with a whorled, yellow and white cut surface.

Color Figure 6-15 Sex cord tumor with annular tubules. Multiple yellow tumor nodules were found in both ovaries in a patient with Peutz-Jeghers syndrome.

Color Figure 6-16 Small cell carcinoma. Small cells with scanty cytoplasm are adjacent to larger cells with more abundant eosinophilic cytoplasm.



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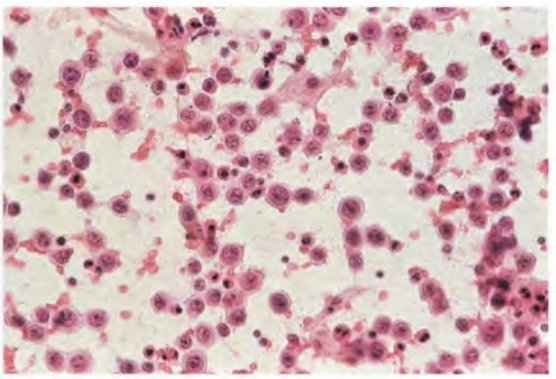

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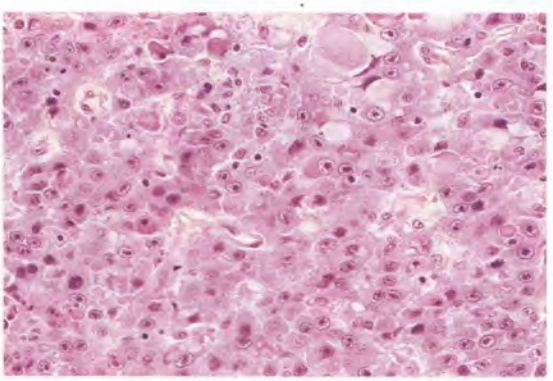
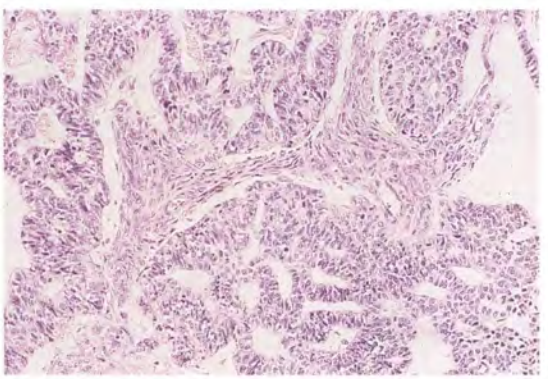


Color Figure 6-19



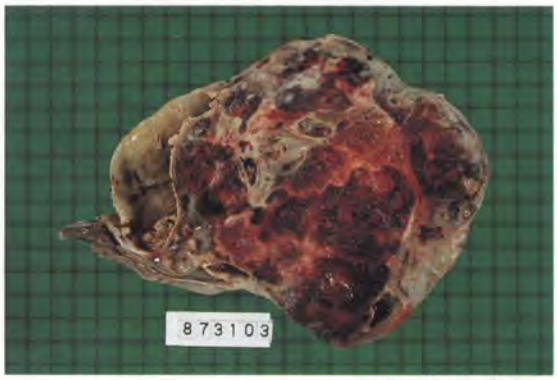
Color Figure 6-20

Color Figure 6-17 Dysgerminoma. The dysgerminoma is a solid neoplasm with a fleshy, white or tan cut surface.

Color Figure 6-18 Dysgerminoma of the ovary. Transvaginal aspirate showing isolated or loosely bound cells with large nuclei and prominent nucleoli. Lymphocytes are intimately associated with tumor cells. (Courtesy of M. Nadji, MD, University of Miami, Miami, FL).

Color Figure 6-19 Hepatoid yolk sac tumor. Other yolk sac patterns were seen elsewhere in this tumor.

Color Figure 6-20 Glandular endometrioid yolk sac tumor resembling endometrioid carcinoma. Other yolk sac patterns were found elsewhere in this tumor.



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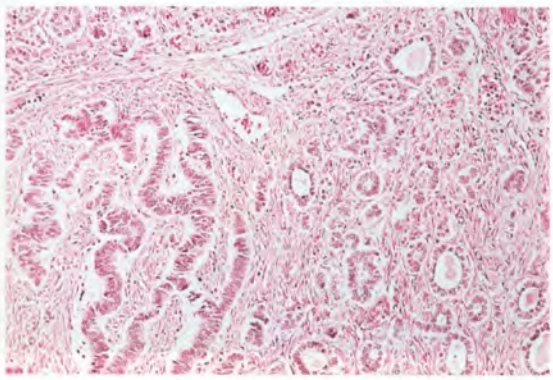

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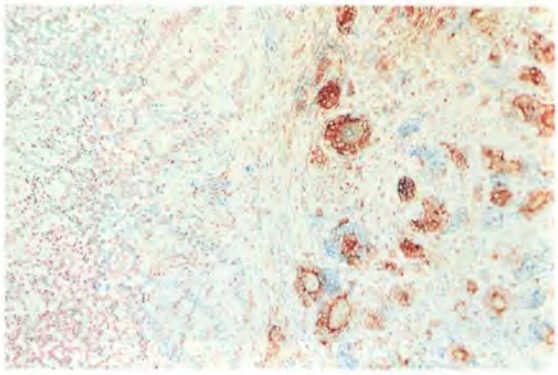

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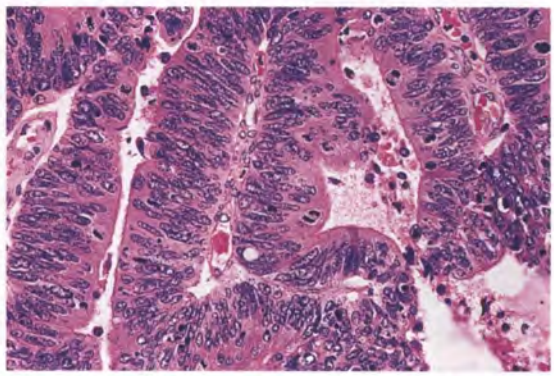

Color Figure 6-24

Color Figure 6-21 Mature (benign) cystic teratoma with extensive infarction following torsion.

Color Figure 6-22 Strumal carcinoid. The neoplasm contains trabecular arrangements of cells typical of carcinoid (*left*) and follicles resembling thyroid tissue (*right*).

Color Figure 6-23 Strumal carcinoid. Immunoperoxidase stain of the tissue block seen in Color Figure 6-22. Thyroglobulin is present in the cells lining the follicles but not within the cells in the trabeculae.

Color Figure 6-24 Metastatic adenocarcinoma from the large intestine.

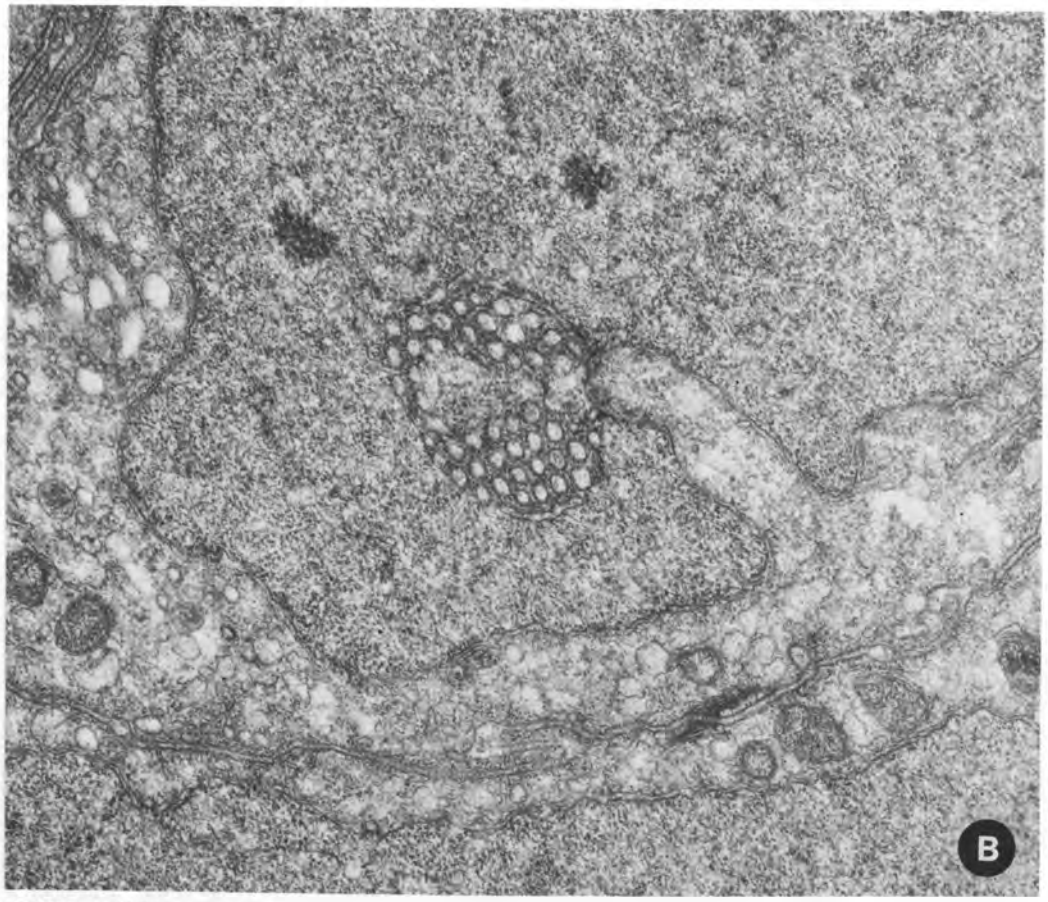

FIGURE 4-12(B) *(continued)*

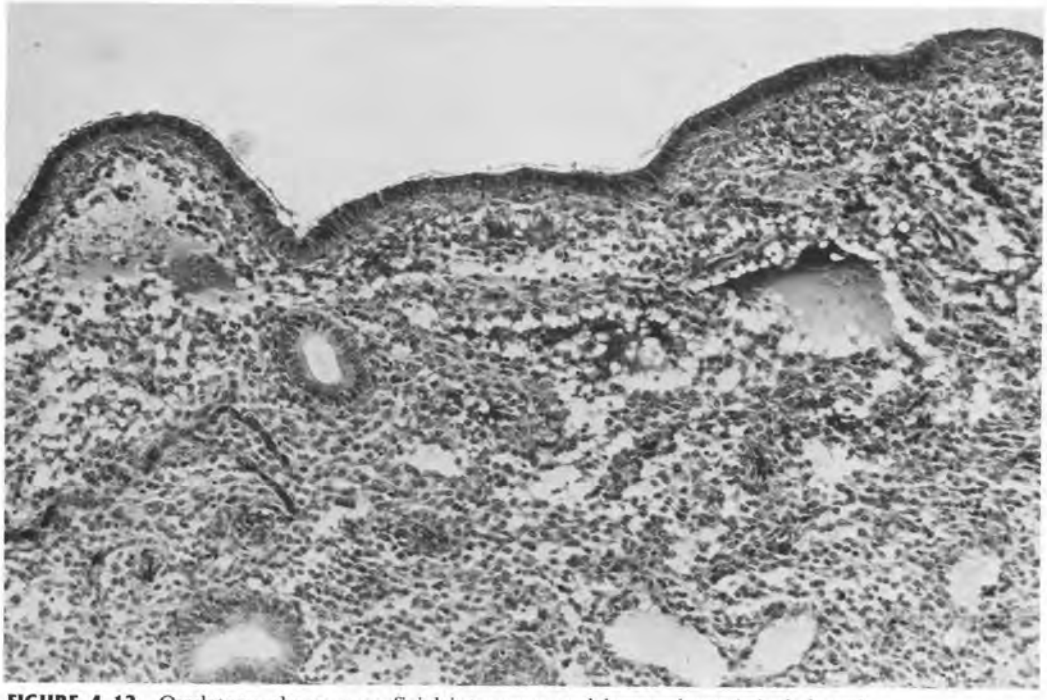

FIGURE 4-13 Ovulatory phase: superficial intermenstrual hemorrhage (*mittelschmerz*).

Glycogen may appear in the endometrial glands under the action of estrogens alone. It is present in small quantities during anovulatory cycles and may be explained by deficient luteinization of a persistent follicle. However, a combination of estrogenic and progestational activity is necessary for its presence in significant quantities. Therefore, we may consider the presence of basal vacuoles in significant numbers as a sign of the beginning of activity of the corpus luteum. These vacuoles are seen at first in a few cells, and then progressively in all the glands of the functional strata. By day 18, they move into an apical po-

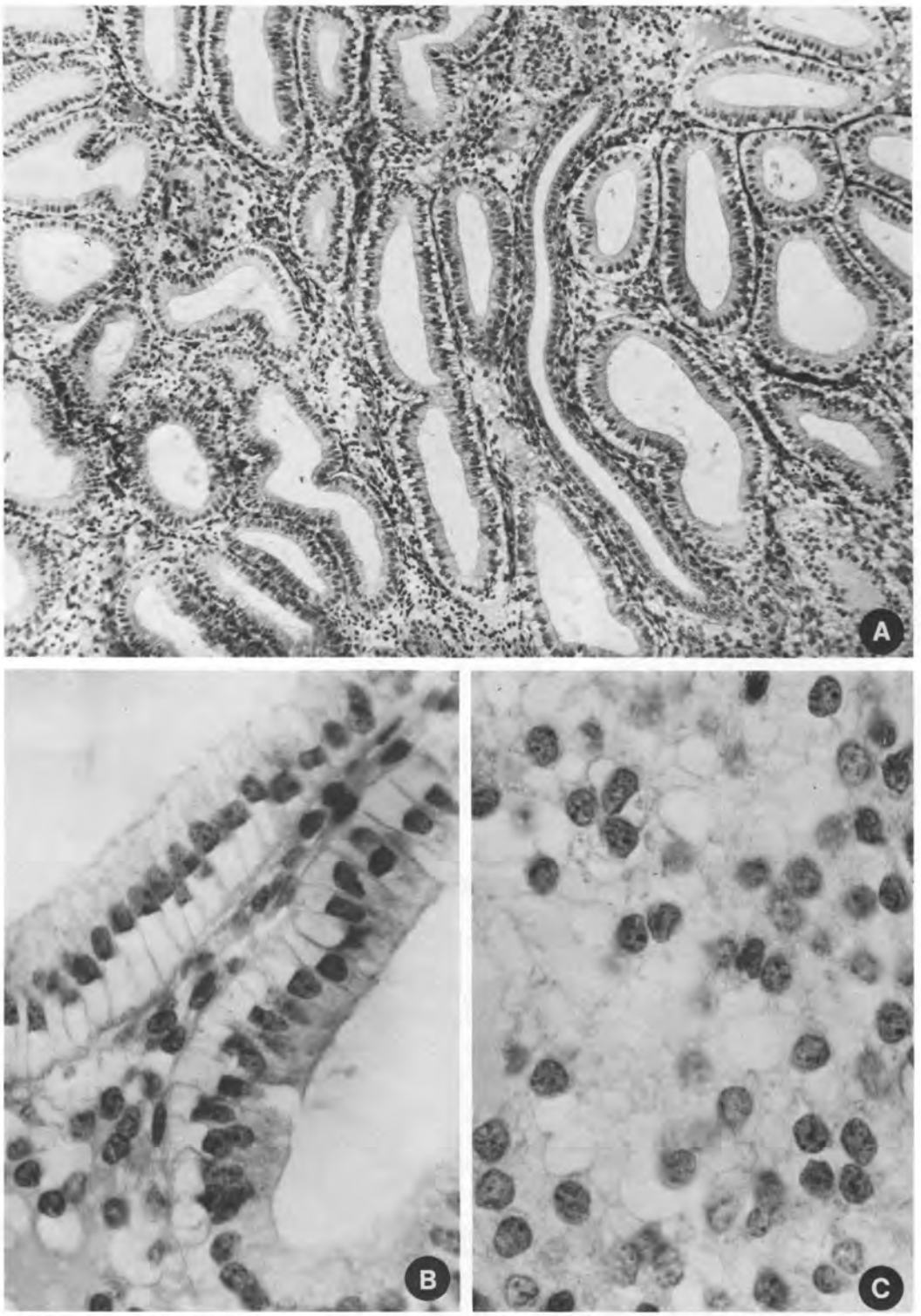

FIGURE 4-14 Early secretory phase: basal vacuoles containing glycogen. **(A)** General appearance. **(B,C)** Details of vacuoles and stroma.

sition (this may be called the *mid-secretory phase*), and by day 20 discrete vacuoles disappear, with glycogen expanding throughout the entire cell (Fig. 4-16).

Toward the end of this stage, an amorphous substance is found in the gland lumina. This substance is stainable with eosin and contains products of secretion and cellular debris in the process of necrosis.

With the electron microscope, intranuclear tubular structures (see Fig. 4-12*B*), formed by tubules or canaliculi in parallel or concentric distribution, have been demonstrated in the secretory phase, apparently related to a strong balanced progesterone effect.[53] In hyperestrogenic states, cytoplasmic annulate lamellae have been seen at this time. These small clusters of paired parallel membranes converge at regular intervals and are found in supranuclear loca-

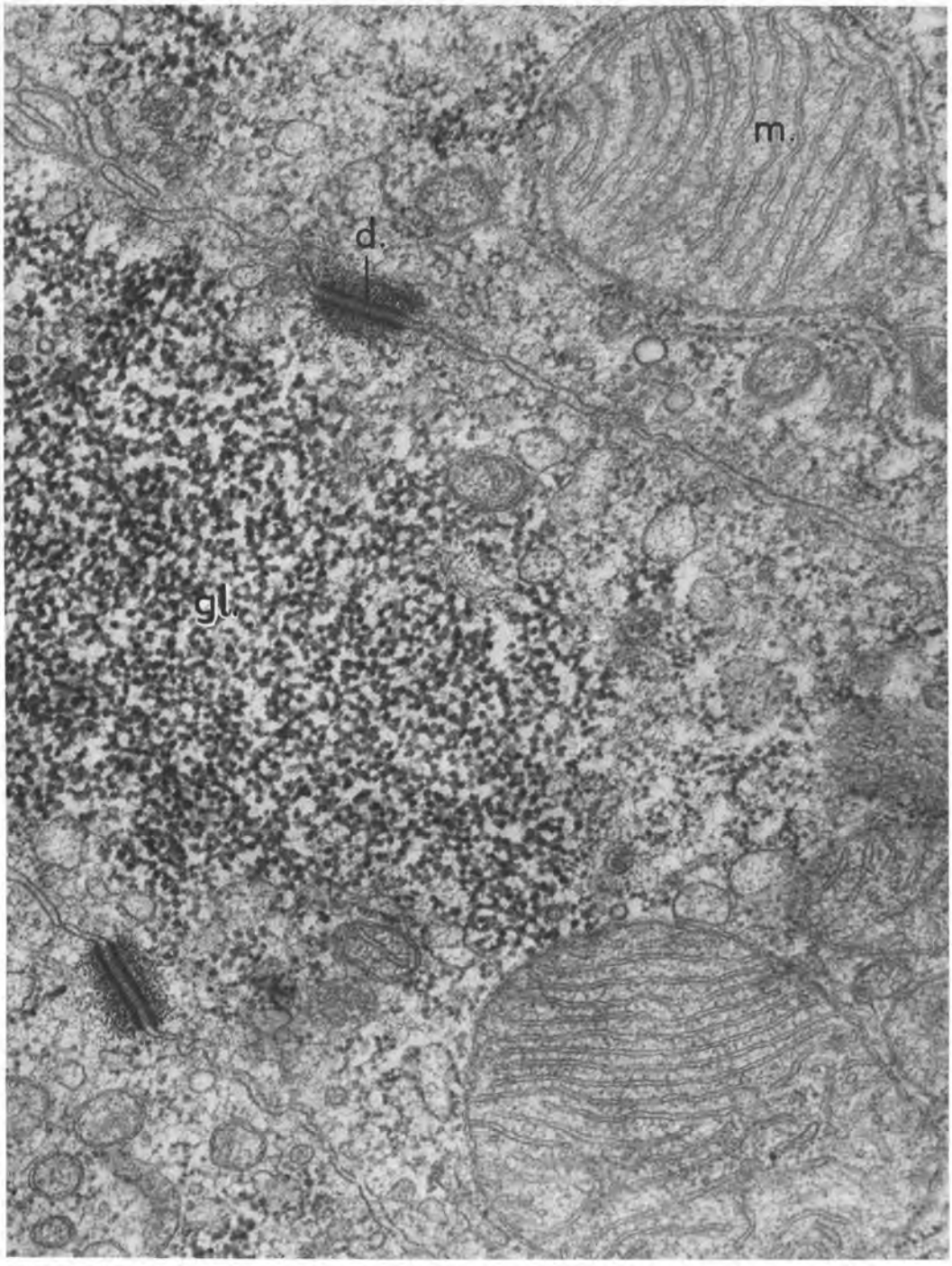

FIGURE 4-15 Early secretory phase (electron micrograph, ×84,000). The glycogen, stained with ferric hydroxide, is seen as round granules grouped in large masses. A large mitochondrion is present in each of the cells. The desmosomes binding two cellular membranes are easily seen. *gl.*, glycogen; *m.*, mitochondria; *d.*, desmosomes.

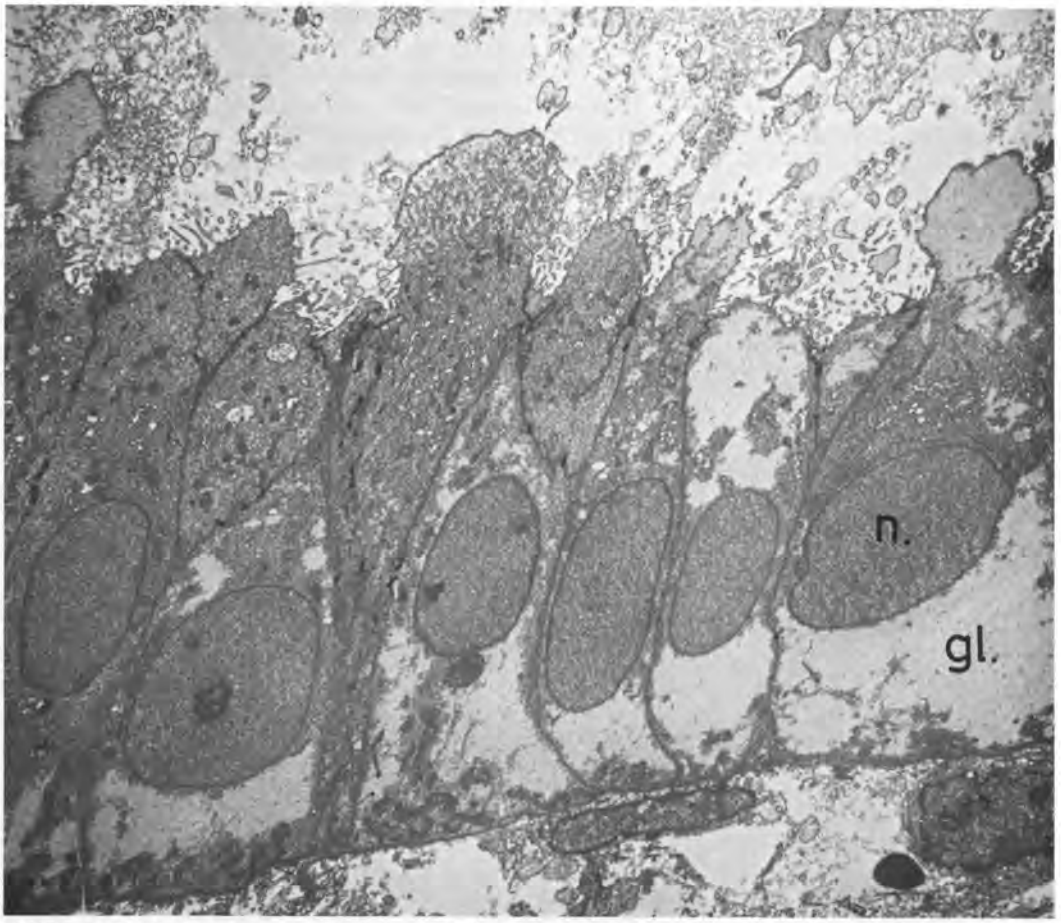

FIGURE 4-16 Endometrium at 22nd day of cycle (electron micrograph, ×4200) showing the distribution of glycogen throughout the cytoplasm.

tions when estrogenic stimulation is marked and in the subnuclear zone when luteal changes are also seen.[54] Their origin may be from the nuclear membrane or from the Golgi apparatus. Their significance is unknown.

Stroma. The stroma presents a looser appearance; edema reappears and attains its maximum intensity around the 22nd day (Fig. 4-17). The cells are always separated and of stellate shape. The rounded or elongated nuclei are only rarely in mitosis.

Late Secretory Phase (Days 21–25)

General Appearance of the Mucosa. The mucosa is edematous and succulent but by the end of this phase begins to show regressive changes. It contains numerous glands with marked sawtooth configurations (Figs. 4-18 and 4-19). The glandular convolutions attain their maximal intensity and may be so well developed that the glands assume a papillary aspect. These modifications involve the strata spongiosa and compacta and leave the basalis intact. The stroma is abundant, loose, and edematous. The predecidual reaction begins around the vessels toward the 24th day and extends to the entire superficial part of the stroma. The spiral arterioles (Fig. 4-20) attain their full development, and their most superficial appendages are situated immediately beneath the surface epithelium. Occasionally they run parallel to this epithelium for as long a distance as 1 mm. They become prominent around day 23.

Glandular Epithelium. The secretory glandular cells contain voluminous round basal nuclei.[52] The chromatin is finely dispersed, and the nucleolus can be seen easily. The cytoplasm bulges and herniates into the gland lumen. It contains pools of glycogen; other cells have lost their glycogen and are evolving toward a resting state. This bulging appearance of the superior pole brings to mind secretion of apocrine type, but electron microscopic observations point toward the diffusion of the glycogen into the glandular lumen. Some of the microvilli contain plaques of glycogen and have the appearance of a club (Fig. 4-21). The mitochondria are small and numerous and are localized principally in the supranuclear region. The rough endoplasmic reticulum is well developed. The Golgi apparatus is voluminous and presents dilated vacuoles and cisterns. Lipid inclusions and vesicles persist in the supranuclear region. The lateral cell membranes show numerous

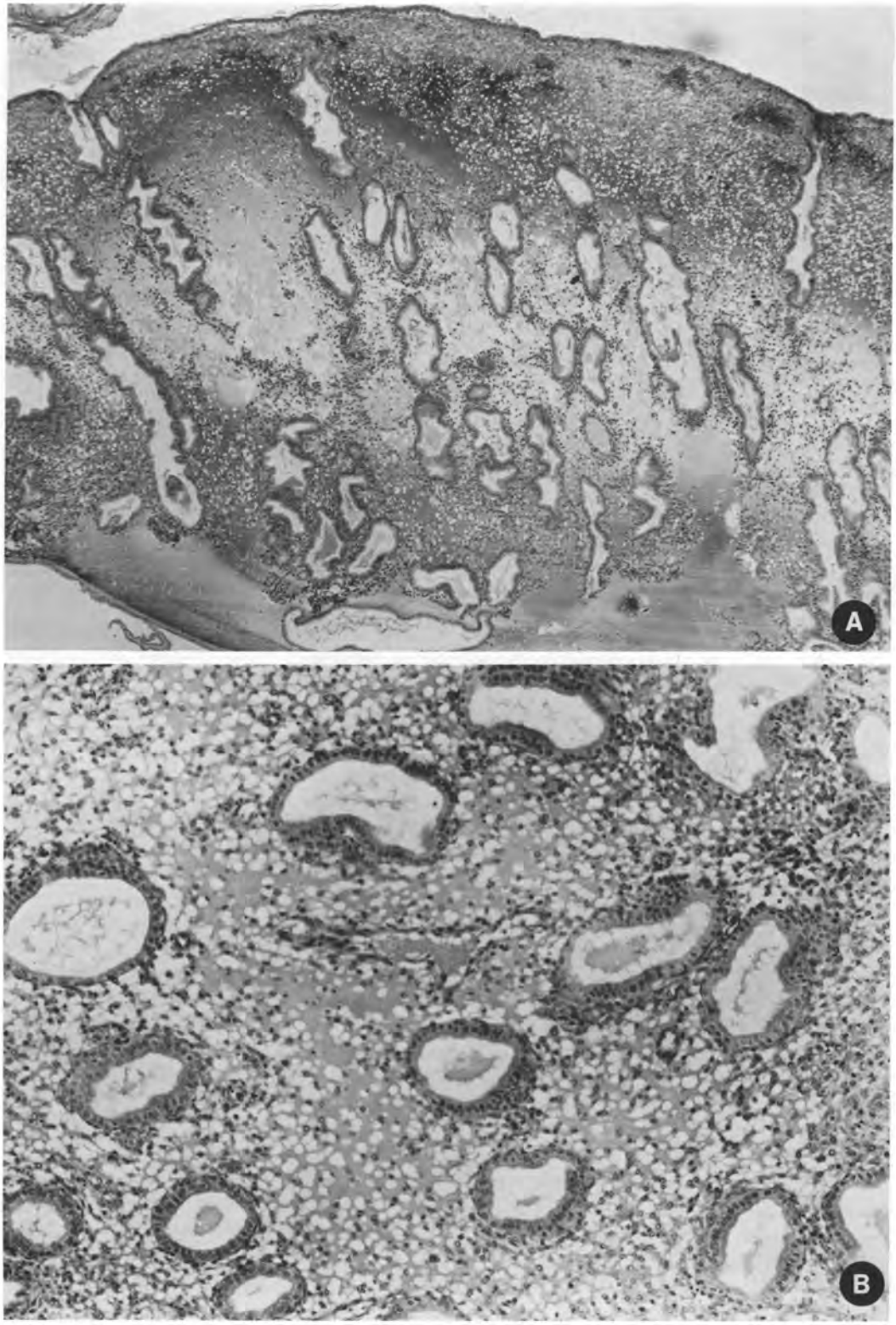

FIGURE 4-17 Endometrium at 21st day of cycle. **(A)** General appearance. **(B)** Detail.

convolutions. The basement membrane forms invaginations that constitute the axes of connective tissue spines (Fig. 4-22). The formation of these spines constitutes one of the criteria of progestational activity. They appear more rapidly than the predecidualization of the stroma but require higher doses of progesterone. Here and there, between the secretory cells, are found intercalated cells with dark, dense cytoplasm and ovoid nuclei, stretched out between two adjacent cells. There are fewer ciliated cells than during the proliferative phase. Small clear cells are also rare.

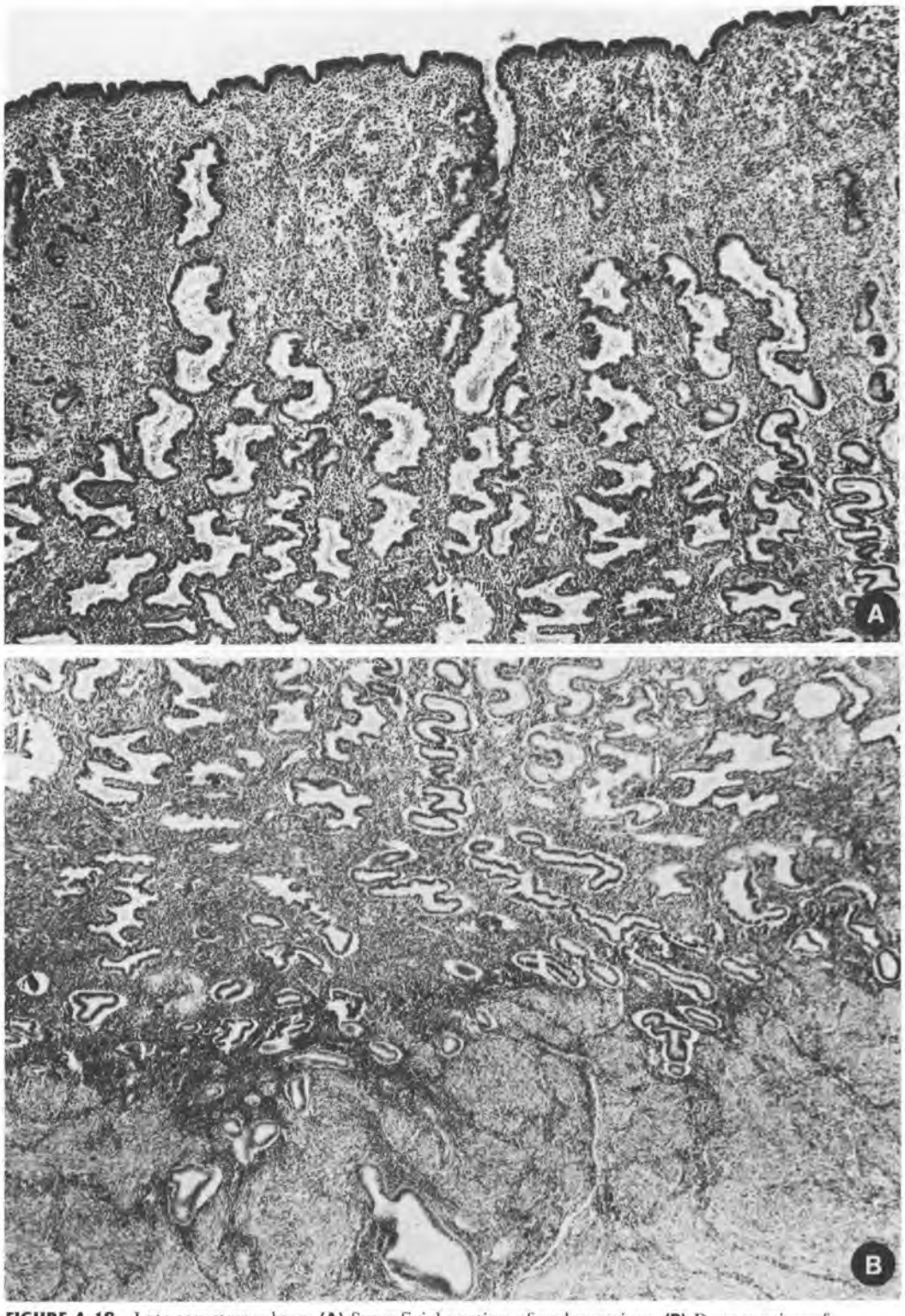

FIGURE 4-18 Late secretory phase. **(A)** Superficial portion of endometrium. **(B)** Deep portion of endometrium.

This characteristic appearance of the secretory gland persists until 3 days before menstruation. Then, the first signs of mucosal involution appear, following the fall of estrogen and progesterone levels.

In some endometria in which histologic examination reveals a very recent implantation of the ovum, typical progestational hyperplasia may be seen. This is manifested at first by more marked edema and congestion of the capillary network of the compact layer. Subsequently, the normal manifestations of luteal impregnation are more accentuated, notably de-

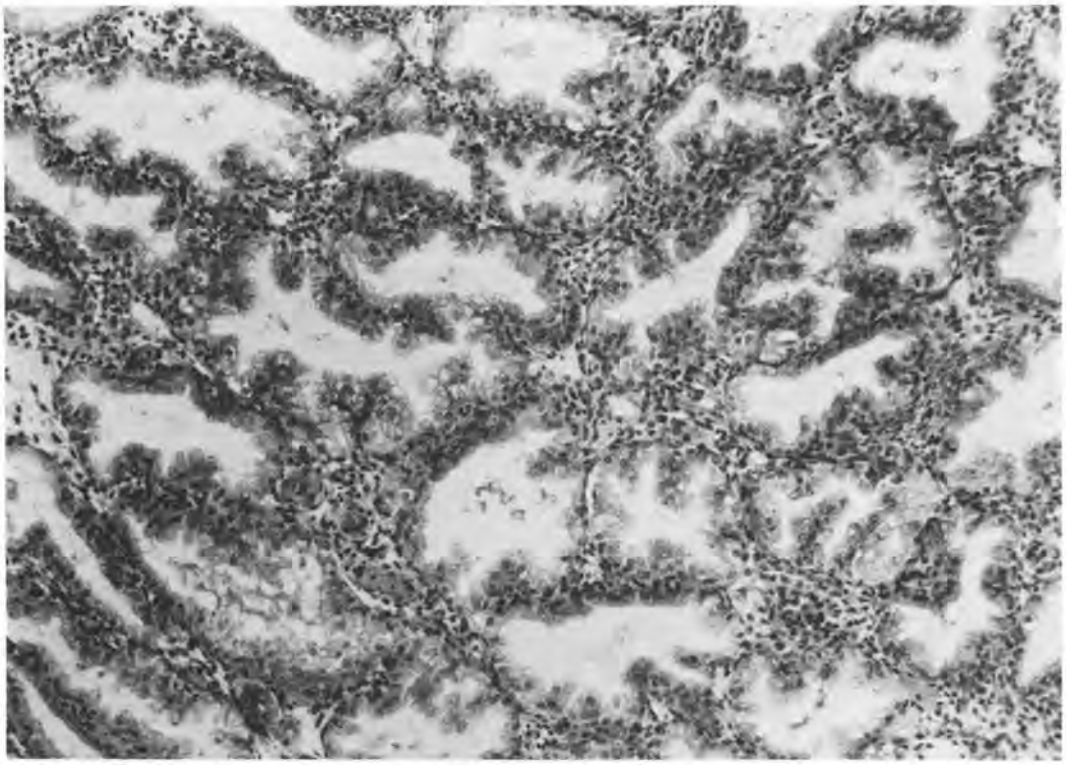

FIGURE 4-19 Late secretory phase: gland with sawtooth contours.

cidual change, edema, glandular secretion, and development of the spiral arteries.

Stroma. Stromal edema is accentuated and the connective tissue network becomes more and more loose. The stroma of the functional layers undergoes predecidual change (Fig. 4-23*A*), manifested by a major increase in cytoplasmic glycogen. Appearing at first around spiral arterioles (decidual cuffs) around day 24, these cells eventually form large plaques; they are easily recognizable by their size and their clear cytoplasm. Their number decreases in the deeper functional layers.

A particular cell type makes its appearance at this phase (Fig. 4-23*B*): the granulocyte or metrial cell, characterized by an indented nucleus and by round eosinophilic cytoplasmic granules whose chemical structure differs from that of the granules of eosinophilic polymorphonuclear leukocytes. The granules are stained by the method of Lendrum with tartrazine phloxine and by that of Weigert with methyl violet. Immunohistologic studies have been reported to demonstrate that this polypeptide molecule represents relaxin.[23] These cells are localized with predilection in the compact zone and around blood vessels. They are found only during the secretory phase and in the first 3 months of pregnancy. They were thought for many years to be derived from endometrial stromal cells and to be involved in menstruation and implantation, but more recent studies have indicated that they are either T lymphocytes or macrophages.[24–26]

True polymorphonuclear leukocytes are also found in the stroma, almost exclusively from day 26 on, and reflect the approach of the menses.[55] Ultrastructurally, stromal cell cytoplasmic organelles increase in number and size, and collagen precursors are secreted into the extracellular space, where polymerization occurs.

Premenstrual Phase (Days 26–28)

This brief phase is essentially an accentuation of the late secretory phase. The predecidual stromal reaction has spread to involve the entire compacta, whereas the underlying spongiosa is comprised largely of "sawtooth" glands that show profound shrinkage and diminished secretions. Dilated thin-walled capillaries are prominent near the endometrial surface. Stromal leukocytic infiltrates are marked, and discrete glandular and stromal hemorrhages are present.

Menstrual Phase (Days 1–3)

The mucosa becomes fragmented and desquamates as large or small fragments of debris (Fig. 4-24). The stroma retracts and shows dense foci of cells compressed against each other (Fig. 4-25), adjacent to still edematous or superficial hemorrhagic zones. At this time, the mucosa undergoes marked dehydration. The leukocytic infiltrate reaches its maximal intensity. The glandular cells, some of which are still secretory, whereas others are already in an ex-

hausted state, become necrotic and lose their tinctorial affinity. Desquamation usually involves small fragments but may in the case of *membranous dysmenorrhea* consist of large scraps of mucosa. The spiral arteries are dilated and show gaping apertures. Their walls present signs of degeneration: confluence of endothelial cells, hyalinization of muscular fibers, and disappearance of elastic fibers. The capillaries and venous plexus are also dilated. The absence of thrombi in the vessels broken off by desquamation suggests the existence of a mechanism of control of vasoconstriction in the arteries remaining in place. Fibrils of fibrin are present in small amounts in the capillaries and stroma during the

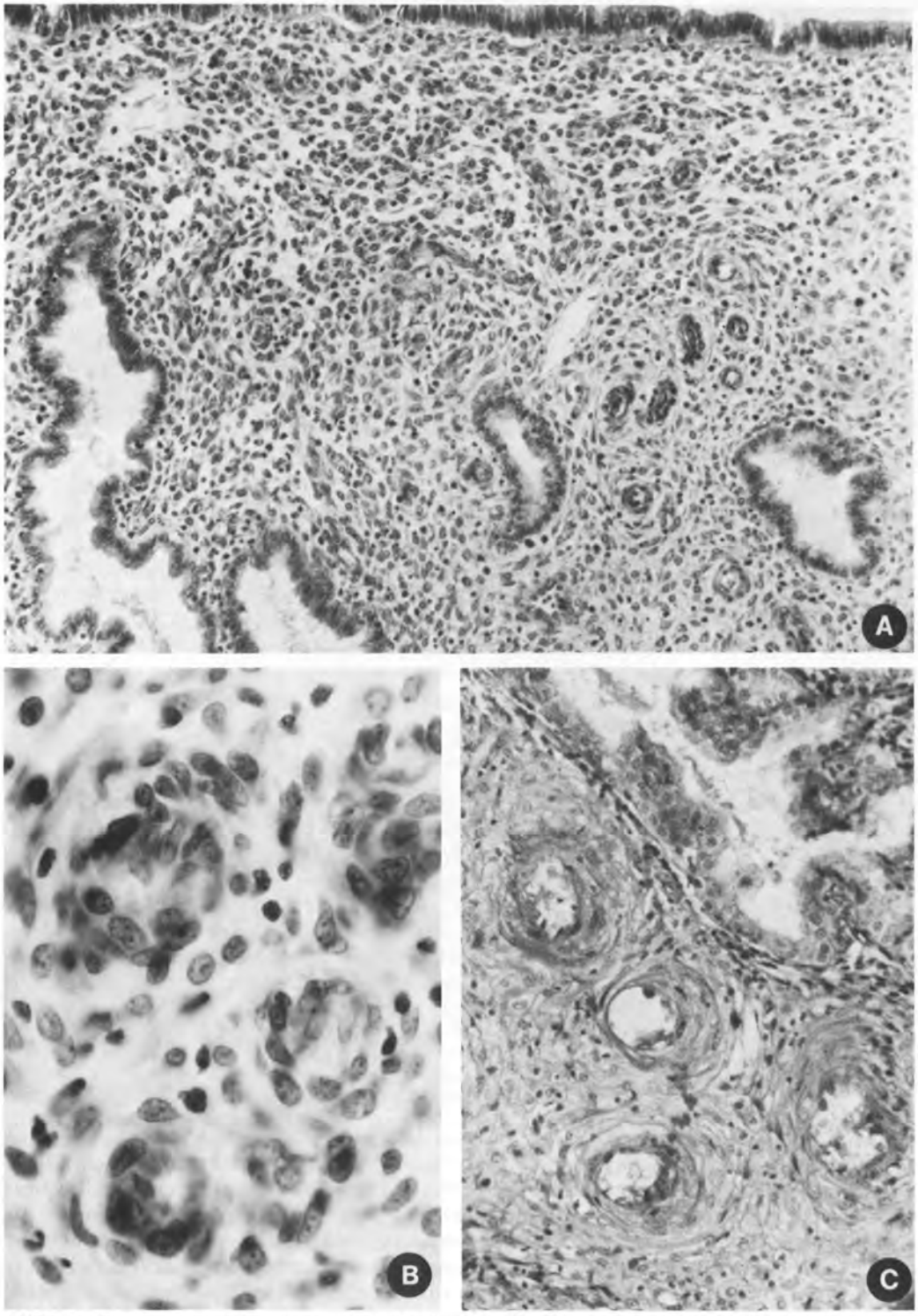

FIGURE 4-20 Late secretory phase: spiral arteries. **(A)** General appearance. **(B,C)** Details.

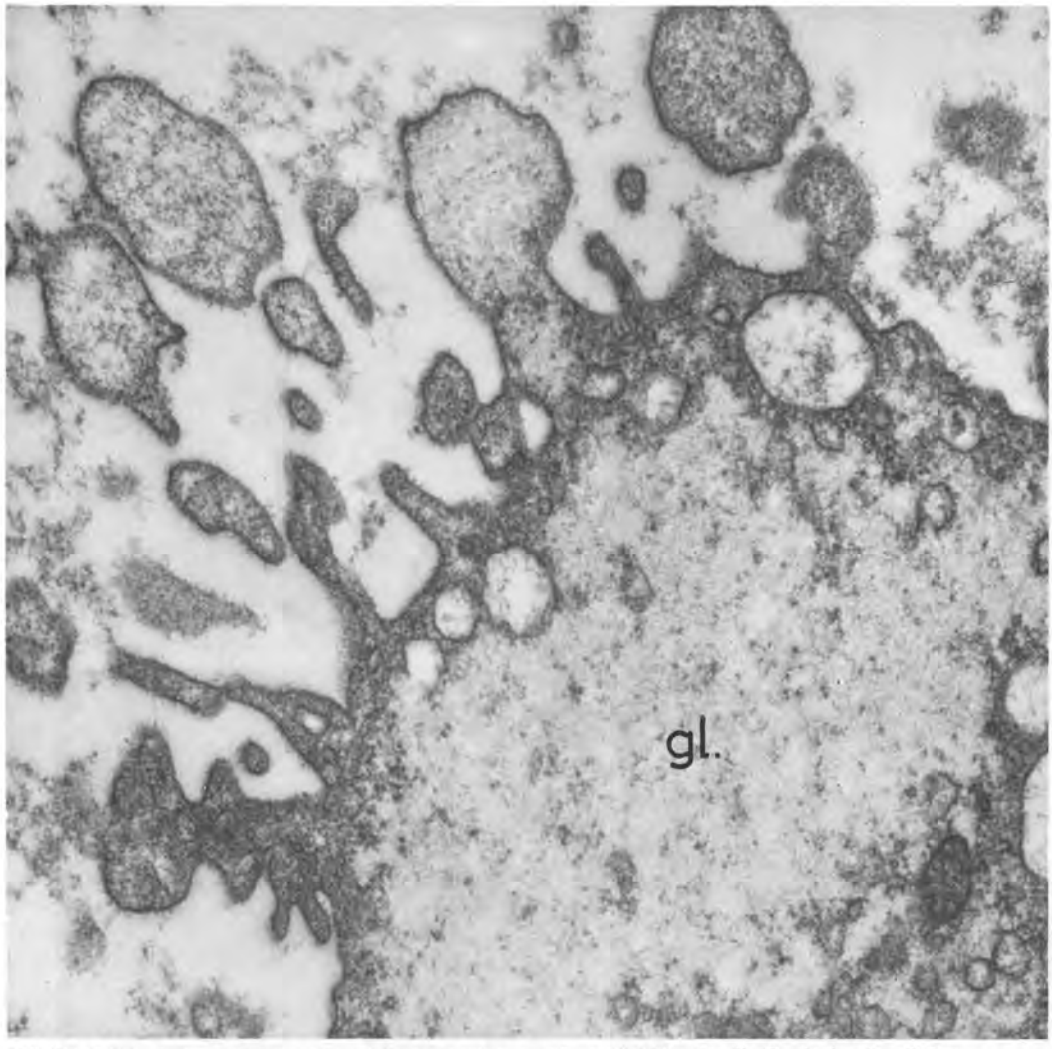

FIGURE 4-21 Late secretory phase (electron micrograph, ×43,350); detail of apical pole of glandular cell showing the presence of glycogen in the microvilli.

premenstrual phase. Subsequent fibrinolytic activity with dissolution of the clots explains the fluidity of the menstrual blood. Desquamation involves the compacta and at least part of the spongiosa; how much spongiosa remains above the basalis is still debated.[18,56] Menstrual shedding generally lasts about 72 hours.

Subsequently, the regenerative phase begins and is accomplished very rapidly, because at the end of menstruation the surface epithelium is already practically reconstituted.[57,58] Reorganization of the stromal components is evident by the fifth day.

Histologic Appearances of the Endometrium Encountered Outside the Menstrual Cycle, and Pathologic Appearances

Modifications in histologic appearance of the endometrium due to physiologic states encountered outside the menstrual cycle and to pathologic states may be separated schematically into three groups:

1. Physiologic states outside the period of functional activity
2. Normal histologic pictures whose moment of appearance is pathologic
3. Histologic pictures invariably of pathologic nature.

This classification points out the importance of clinical data in the interpretation of an endometrial biopsy or curettage. A picture that may be entirely normal at one period during the cycle becomes pathologic at another moment. It is therefore essential that the pathologist be in possession of the pertinent clinical information to interpret the pictures observed.

Physiologic States of the Mucosa Outside the Functional Period

Fetal Endometrium. Differentiation of the uterine mucosa is terminated around 4½ months of fetal life.[1,17] It consists at this time of a cuboidal epithe-

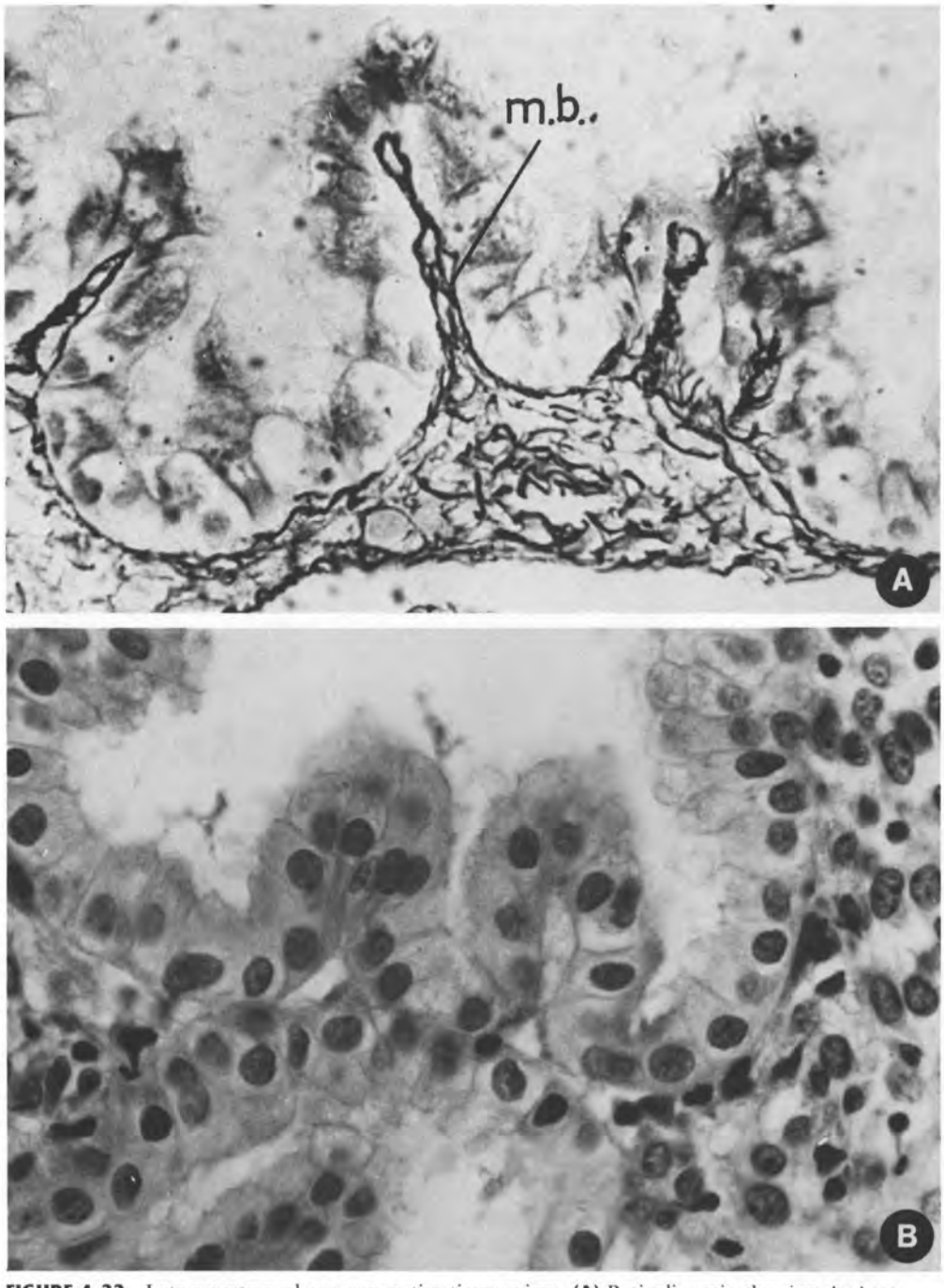

FIGURE 4-22 Late secretory phase: connective tissue spines. **(A)** Reticulin stain showing the basement membrane (*m.b.*). **(B)** Hematoxylin and eosin stain.

lium covering a dense stroma and containing small cells; the glands are practically nonexistent, and the surface epithelium presents a few large undulations (Fig. 4-26). Around the fifth month, estrogenic stimulation begins, and this is prolonged until about 7½ months. A few glands appear, lined by columnar epithelium with elongated nuclei, and the stroma shows an outline of vascularization in its deep layer. Toward the eighth month, the glands develop and are lined by epithelium showing secretory activity, proved by the presence of glycogen in the glandular cells; the stroma is loose and edematous. This secretory activity persists until birth and then regresses and is succeeded by a state of atrophy about 1 month after delivery. The histologic pictures of the fetal uterus are due to fetal and maternal hormonal stimuli, predominantly estrogens. The fetal hormones are of extraovarian, notably adrenal cortical, origin.

Infantile Endometrium. Infantile endometrium is of atrophic type. The glands are few in number, of

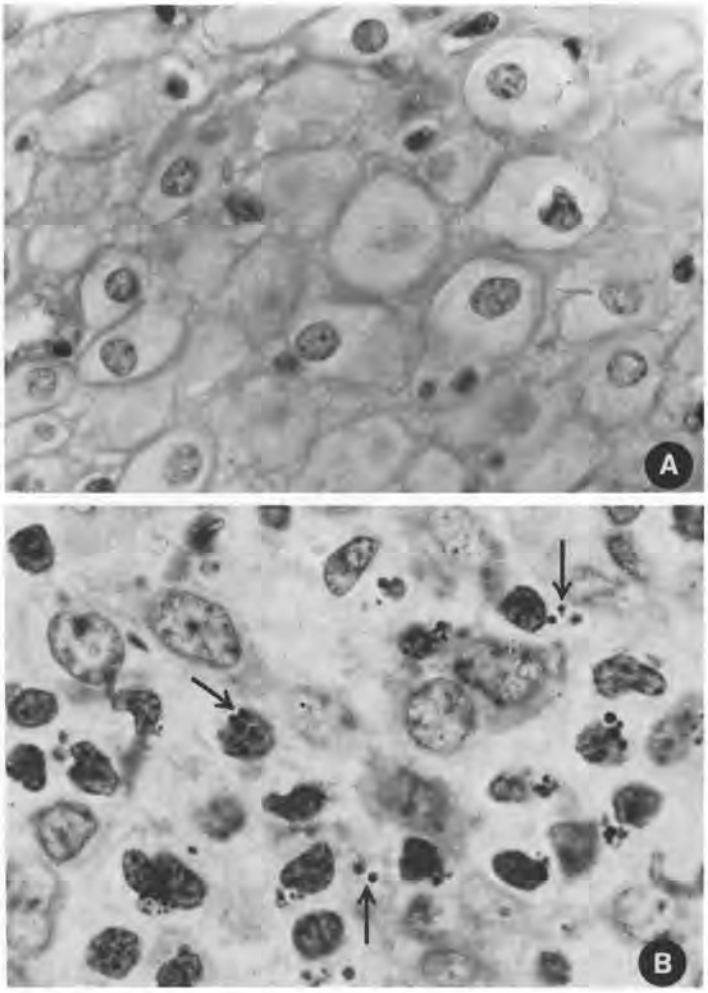

FIGURE 4-23 Late secretory phase. **(A)** Predecidual reaction of the stroma. **(B)** Granular or lymphoreticular cells of the stroma.

small caliber, and lined by columnar or cuboidal epithelium. Mitoses are absent. The stroma is composed of small cells compressed one against the others. The vascularization is rudimentary.

Pubertal Endometrium. At the moment of puberty, the first signs of estrogenic stimulation appear and are soon followed by the first menstrual cycles, of which most are anovulatory.[4]

Postpartum Endometrium. Postpartum regeneration of the endometrium generally is complete within 3 weeks. In women who are not breast-feeding, the first ovulation usually takes place during the seventh postpartum week. During the preceding menstrual period, the endometrium often reveals venous thrombi and hyalinization of arterial walls. In the weeks following delivery, during the first postpartum cycle, there is most frequently moderate or diminished estrogenic stimulation and more rarely signs of secretory activity. The most frequent complication seen in the postpartum endometrium is the presence of retained placental cotyledons or an exaggerated placental site (exuberant proliferated intermediate trophoblast) with secondary inflammatory changes (endometritis). Thrombosed and secondarily hyalinized vessels may be responsible for the existence of small hyalin masses (hyalin bodies) that may be the cause of hemorrhages. Curettage usually suppresses this type of complication.

Postmenopausal Endometrium. *Atrophy* of the endometrium proceeds progressively after the menopause, and in some cases this transformation may take years.[1,17,31,59,60] This is why it is not rare to find after the menopause signs of proliferative or, more rarely, secretory activity. The existence of extraovarian sources of genital hormones, notably the adrenal cortices, and to a lesser extent persistent ovarian activity, explains the persistence of hormonal response long after menopause. MacBride[61] reported in 1521 cases of curettage in menopausal women that the endometrium was of atrophic type in 31.5% and of cystic atrophic type in 42.7%. Hyperplasia was seen in 12.6% of women, who were usually only a few years postmenopausal. This series is of more than historic interest, because it serves as a baseline before the era of menopausal hormone replacement.

The *macroscopic appearance* of the atrophic mucosa is pale, thin, and smooth. It measures about 0.4

mm in thickness. The *histologic picture* is characterized by the presence of scanty glands of regular contours and small caliber, lined by a single layer of small cylindrical cells (Fig. 4-27). The stroma is dense and composed of small round cells. The vascularization is poorly developed. Arteriosclerotic lesions may be found (Fig. 4-28). When atrophy has been present for a long time (ie, in women older than 65 years), it is often of cystic type (Fig. 4-29). The formation of cysts is apparently due to obstruction of the gland necks with secondary subjacent dilatation. This picture of cystic atrophy should not be

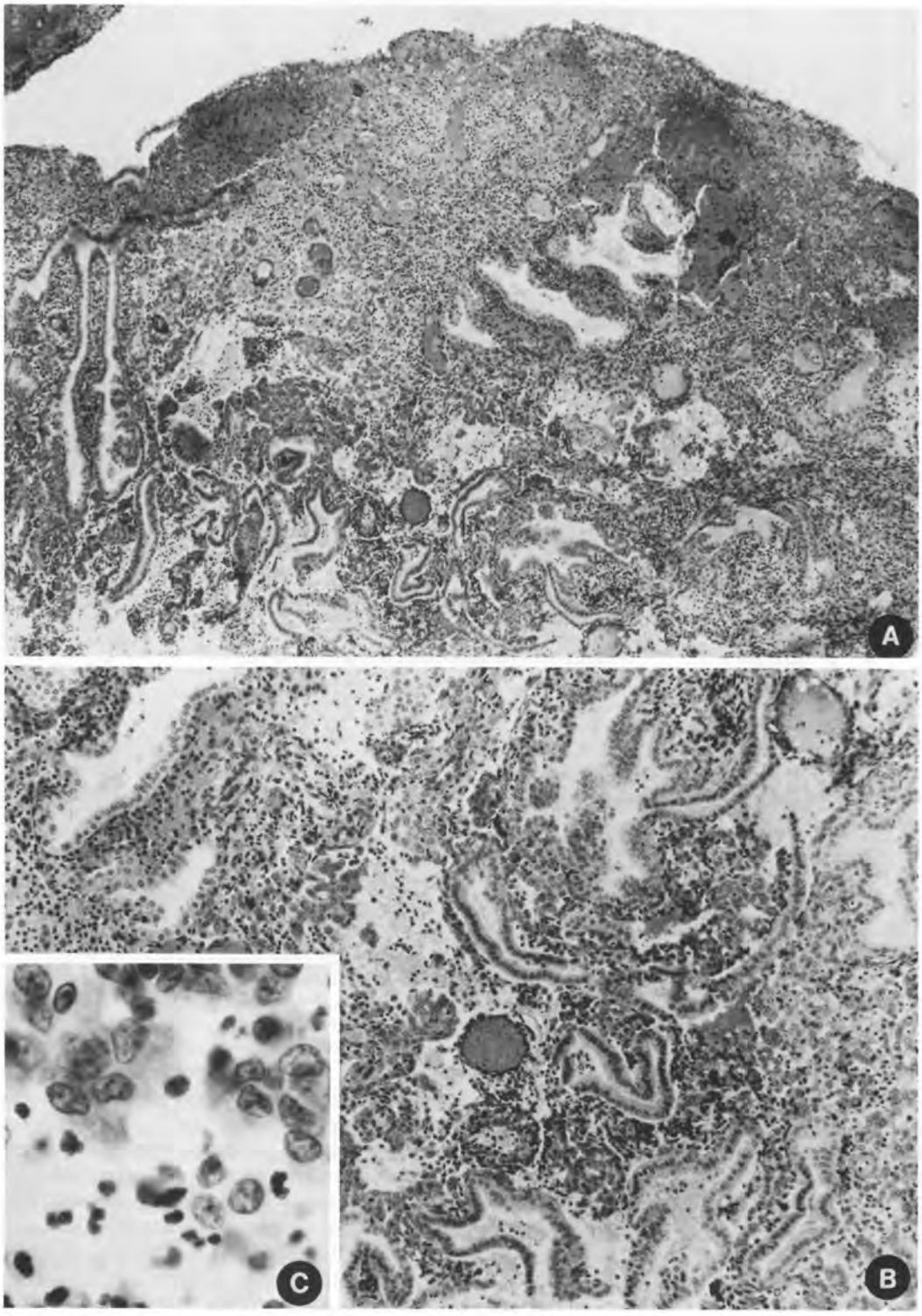

FIGURE 4-24 Menstrual phase. **(A)** General appearance. **(B,C)** Details showing stromal disintegration and leukocytic infiltration.

confused with that of cystic hyperplasia, in which the gland epithelium is stratified and mitotically active. In some atrophic endometria, the small elongated glands take an orientation parallel to the mucosal surface. The reason for this flattening is not understood.

Postmenopausal bleeding in an atrophic endometrium can be explained by myometrial arteriosclerosis, venous congestion in uterine prolapse, and venous bleeding accompanying rupture of atrophic endometrial cysts.

The same pictures of atrophy are encountered after surgical or radiotherapeutic[62] castration, in total ovarian functional insufficiency,[63,64] in certain disease states such as Sheehan's and Schmidt's syndromes, and occasionally after prolonged oral contraception.[65]

Normal Histologic Pictures Whose Moment of Appearance Is Pathologic

Persistent Estrogenic Endometrium (Anovulatory Cycle). Anovulatory cycles are more frequent than previously thought. Many postmenarchal and premenopausal cycles are anovulatory, and during the reproductive years anovulatory cycles are of a sporadic character in some women. Their frequency has been evaluated by Levan and Szanto[66] in a study of 261 biopsies performed in 103 patients: they found 9 patients who presented 14 anovulatory cycles. These were more frequent in women older than 40 years. Since the study was reported in 1944, it did not include any women who had received exogenous hormones.

The anovulatory cycle, defined as a cycle terminating in a menstrual period in the absence of ovulation, is a frequent cause of sterility. Irregular and heavy menstrual periods may also be seen. The intensity and duration of estrogenic activity vary according to the mode of regression of the persistent follicle with subsequent modification of the duration of the cycle. The estrogenic secretion of the persistent follicle may last only a few days or remain at a low level during the entire cycle. Sometimes there is a moderate follicular luteinization due to abnormal gonadotropin activity.

Microscopic examination of the endometrium shows an absence of secretory changes in the second part of the cycle and a pronounced proliferative activity (Fig. 4-30). Glycogen may be present in small amounts when there is follicular luteinization or abnormal hypophyseal activity. Erythrocytes may be seen in the stroma and fibrin thrombi in dilated capillaries.

Ovulation, with the appearance of normal postovulatory endometrial maturation, can be induced by clomiphene citrate, a weak estrogen. The feedback effect of this drug increases the release of gonadotropins with subsequent ovulation.

The differential diagnosis must be made between anovulatory cycle and late ovulation, which can take place during the third week of the cycle. A biopsy to confirm the former condition should be taken during the fourth week.[67,68]

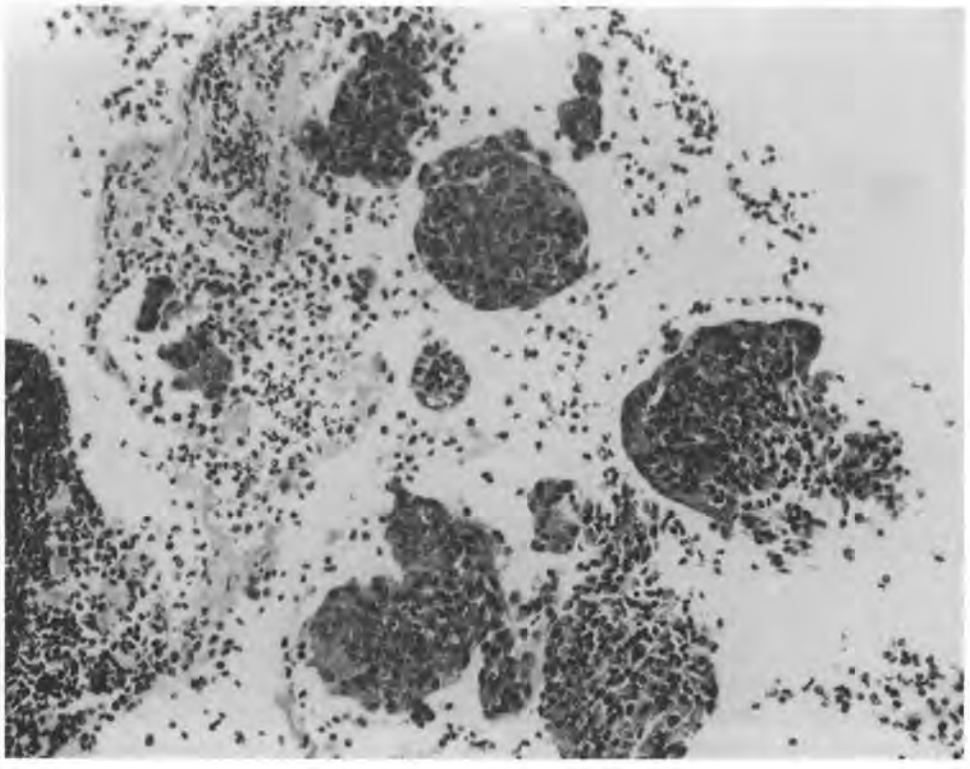

FIGURE 4-25 Menstrual endometrium showing compact aggregates of endometrial stroma.

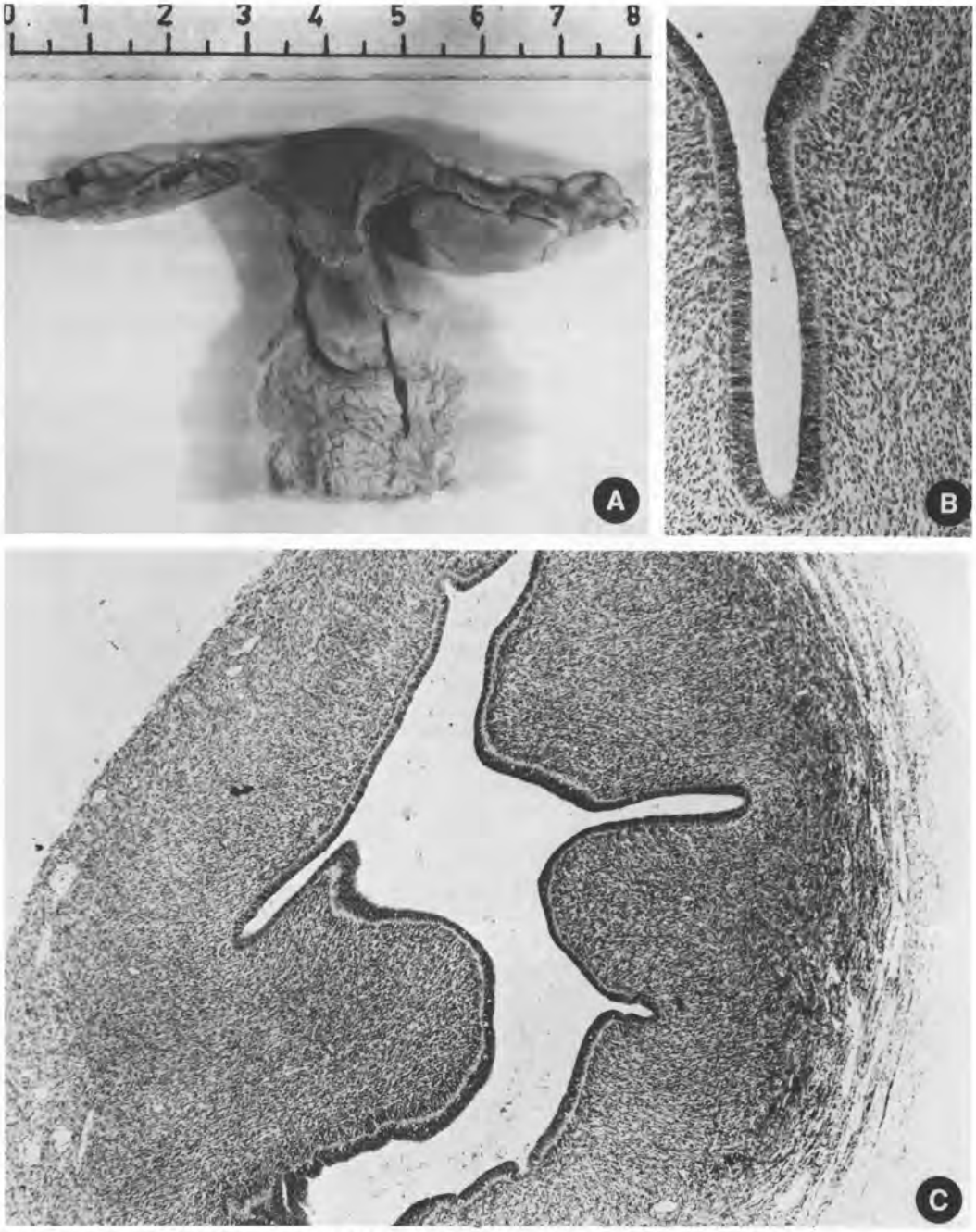

FIGURE 4-26 Fetal endometrium. **(A)** General appearance of the uterus, vagina, tubes, and ovaries. **(B)** Superficial epithelium and precursor of gland. **(C)** General appearance of the endometrium.

Luteal Phase Dysfunction. Luteal phase defects are demonstrable in up to 3% or 5% of infertile women and up to 35% of habitual aborters.[69–74] However, they are also encountered in women with a completely normal reproductive history.[75] These defects may be divided into the short luteal phase,[76] in which the interval between ovulation and menstruation is 10 days or less, and the inadequate luteal phase, in which the interval is normal but progesterone output is low. Hyperprolactinemia may be demonstrated in both disorders, whereas low FSH levels are seen only in the short luteal phase.[77] In the latter circumstance, the usual etiology is a defect in the pituitary–hypophyseal axis, and treatment consists of clomiphene or gonadotropin. The inadequate luteal phase may be due to corpus luteum deficiency, relative estrogenic hypersecretion, or local disturbances of the receptivity of the endometrium to progestational hormones.

In either situation, endometrial biopsy shows evidence of ovulation, but the histologic appearance is inappropriate for the date at which the biopsy was

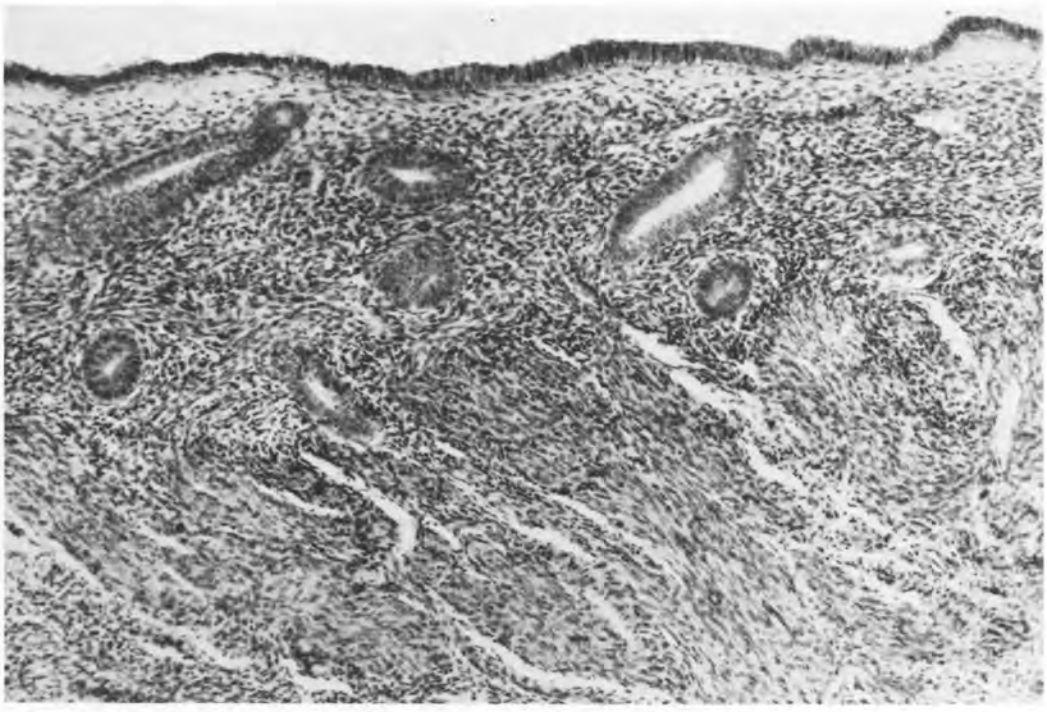

FIGURE 4-27 Atrophic endometrium.

taken. A discrepancy of 3 days or more must be seen (Fig. 4-31), because 2 days is within the normal range of error of endometrial biopsy interpretation. The picture may be entirely normal except for the retardation (coordinated pattern), or there may be an intrinsic abnormality (dissociated pattern). In the latter type, which is seen with increased estrogenic activity or decreased responsiveness to progesterone, proliferative and secretory endometrium may coexist or there may be glandular-stromal dissociation, with one of these elements appearing more advanced in the cycle than the other.

For the diagnosis of this dissociated pattern (which also has been called *irregular maturation*), the

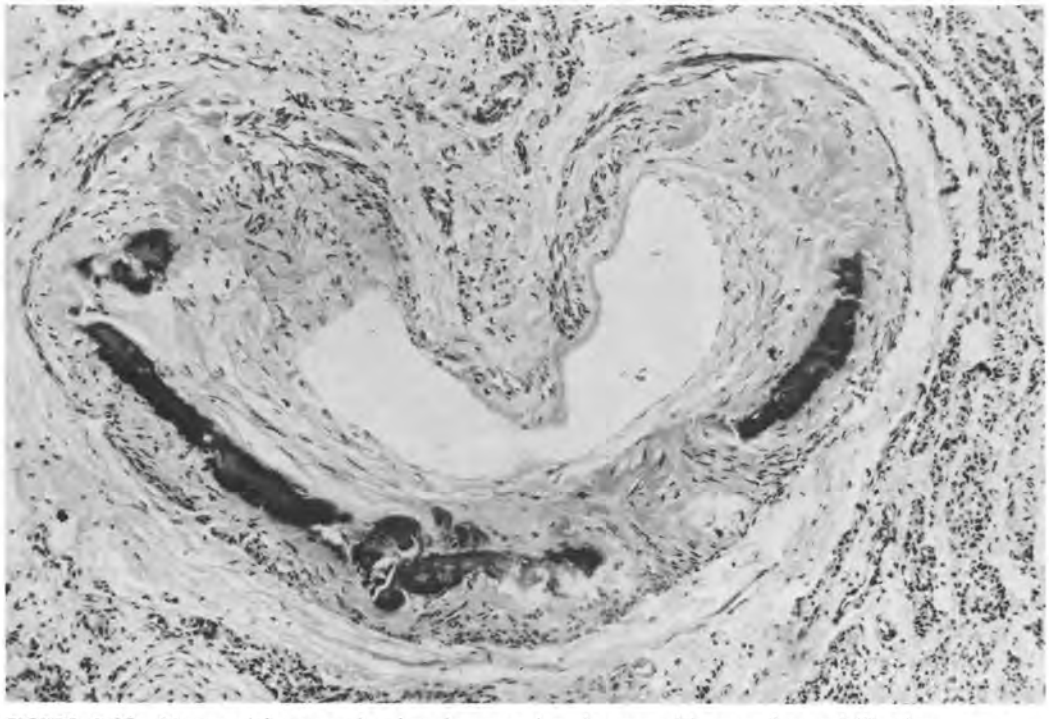

FIGURE 4-28 Myometrial artery showing degenerative changes with secondary calcification.

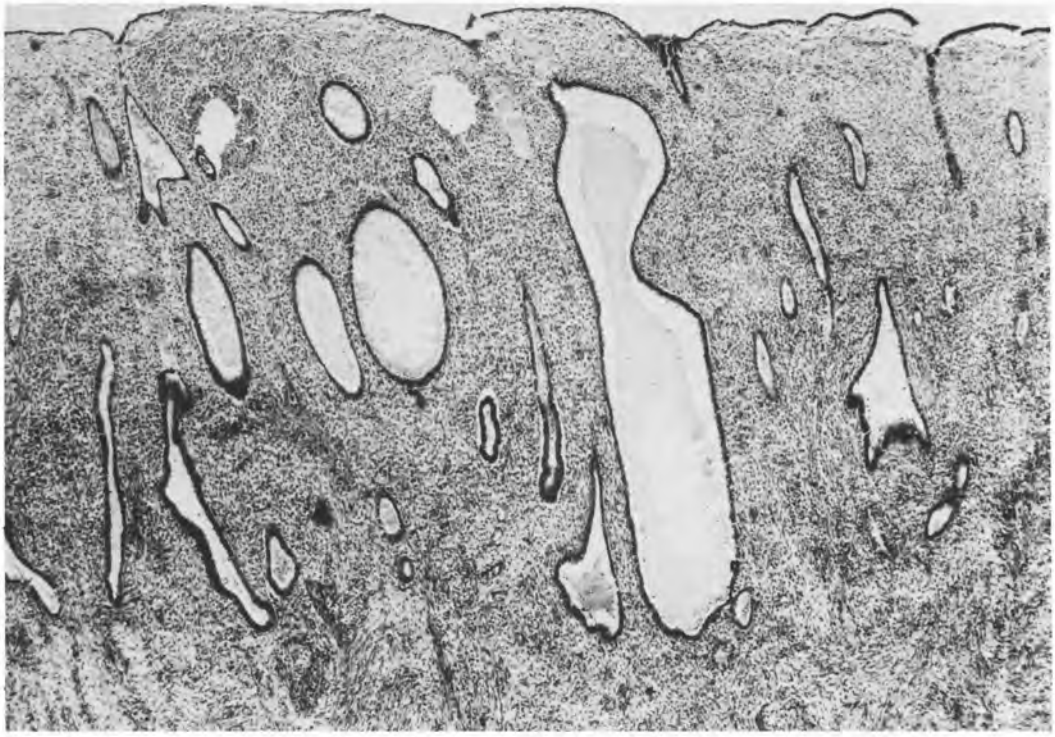

FIGURE 4-29 Cystic atrophic endometrium.

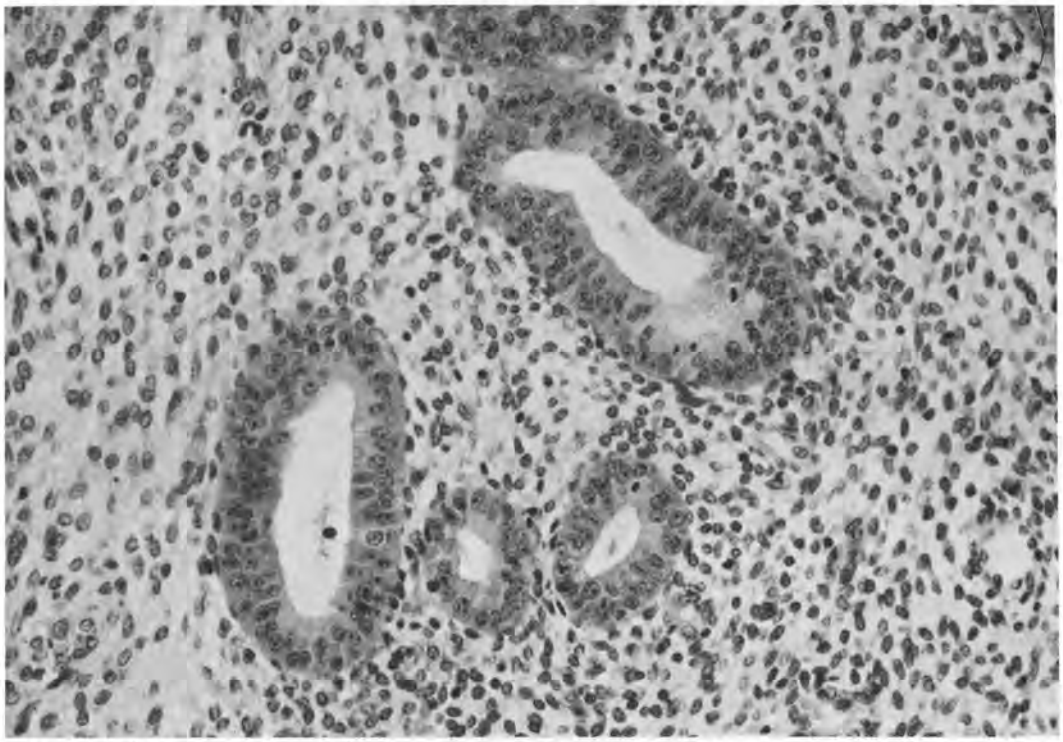

FIGURE 4-30 Endometrium at 22nd day of cycle; anovulatory cycle with relative hyperestrogenism.

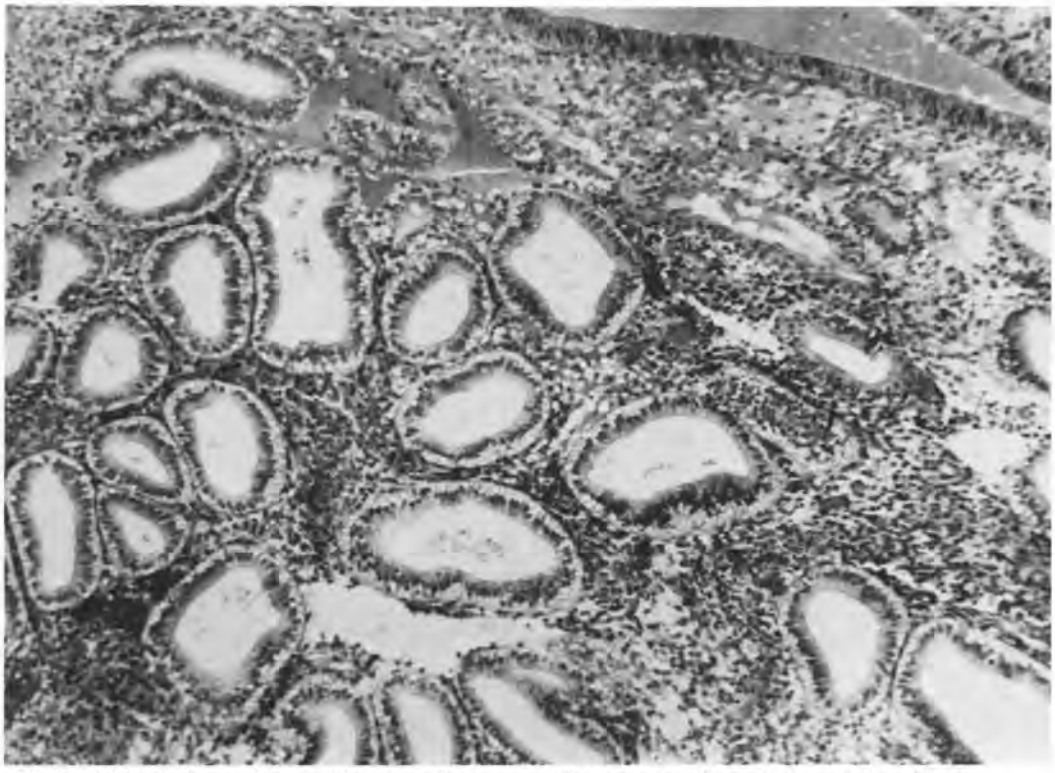

FIGURE 4-31 Endometrium at 26th day of cycle: coordinated type of luteal phase defect (basal vacuoles).

contrasting pictures must be found totally within the functional layer of the endometrium (Fig. 4-32). The presence of an endometrial polyp must be excluded, because in this latter lesion it is common to find endometrium that is totally or partially nonreactive to hormonal stimuli. It is also essential to ensure that the biopsy does not come from the isthmic region (lower uterine segment), which does not manifest distinct cyclic modifications. Endometritis must also be excluded, as should treatment with exogenous hormones (Fig. 4-33).

Although luteal phase deficiency is thought by many to be an important cause of infertility, this has been questioned by a recent study in which this was never the only factor in an infertile patient and in which clomiphene citrate therapy was equally effective in inducing pregnancy in the presence or absence of luteal phase defects.[78] Clement has summarized some of the controversy over this entity in a recent symposium.[79]

Histologic Pictures of Pathologic Nature

Endometrial Hypoplasia. Endometrial hypoplasia (inactive endometrium) secondary to ovarian hypofunction is characterized by a thin mucosa containing resting glands of regular contours and small caliber (Fig. 4-34).

The epithelium is constituted by cuboidal cells with flattened or ovoid nuclei situated in the basal part of the cytoplasm. Ciliated cells are rare. Mitoses are not seen. The stromal cells are small and take a fibroblastic appearance. The vascular apparatus is poorly developed.

Ovarian hypofunction, often resulting from hypophyseal gonadotropic insufficiency or autoimmune oophoritis, is ordinarily encountered in young girls or in women around the age of 40 (precocious menopause).[63,64,79] Hypomenorrhea or amenorrhea is the rule. Hypoplastic endometrium can rarely be seen in the presence of histologically normal ovaries containing follicles and corpora lutea. The defect has been characterized as a deficient ovarian aromatizing enzyme system.

Endometrial Hyperplasia. The clinical and pathologic significance of endometrial hyperplasia is in many respects analogous to that of dysplasia of the cervix uteri. As in this latter lesion, the pictures of endometrial hyperplasia vary from an image only slightly distorted from normal to a picture indistinguishable from that of a lesion that has been designated carcinoma in situ. Also, as in the case of cervical dysplasia, it appears that the changes seen in endometrial hyperplasia may be reversible (either spontaneously or with treatment), may persist unchanged for many years, or may follow a relentless progression over a period of time, perhaps through an in situ phase, into clinically apparent invasive carcinoma. The final analogy that we may draw be-

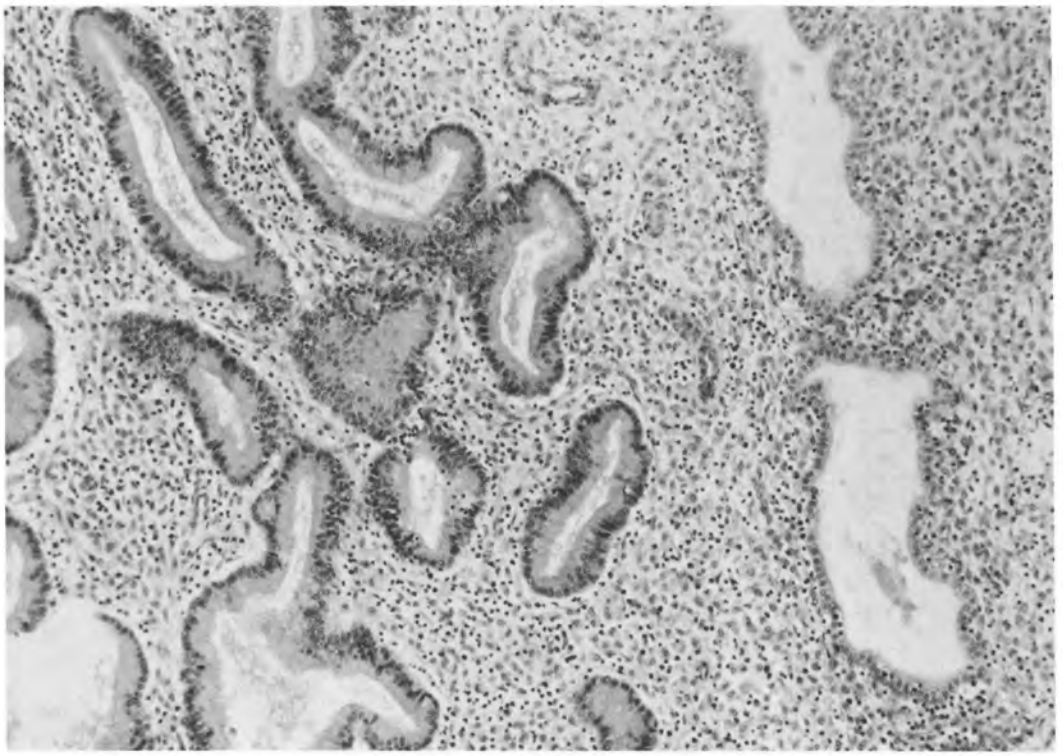

FIGURE 4-32 Irregular maturation (dissociated pattern of luteal phase defect) of endometrium: simultaneous presence of secretory and proliferative glands.

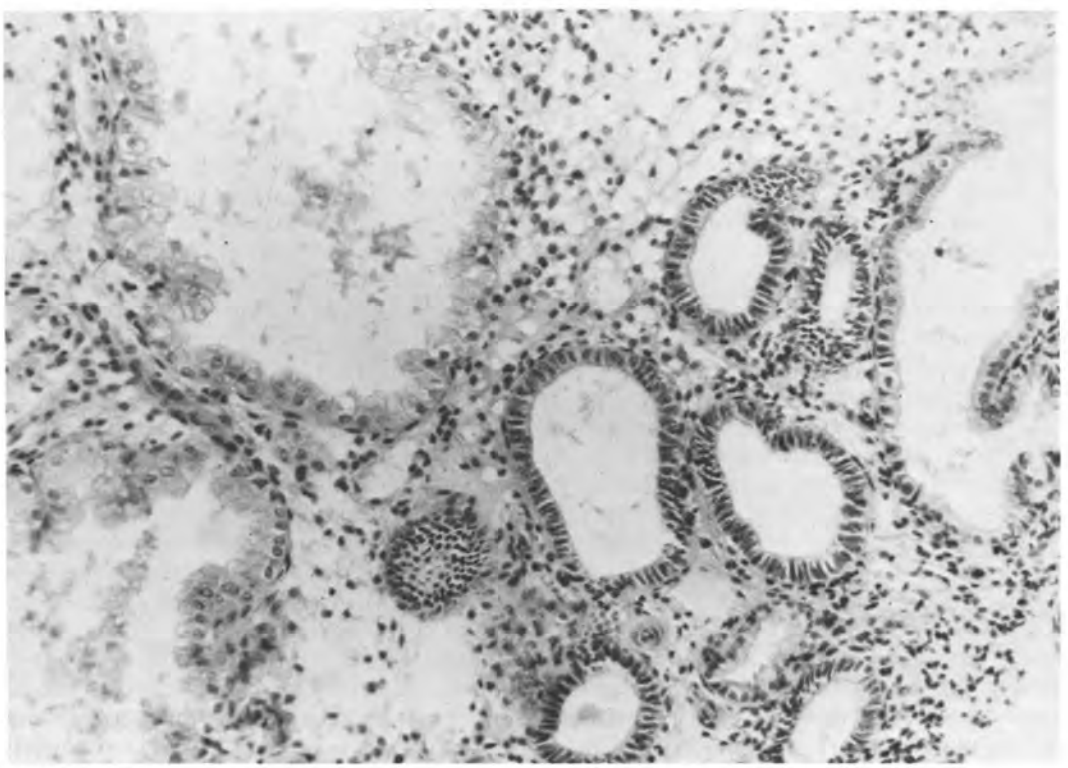

FIGURE 4-33 Complex hyperplasia treated by progestogens (irregular maturation).

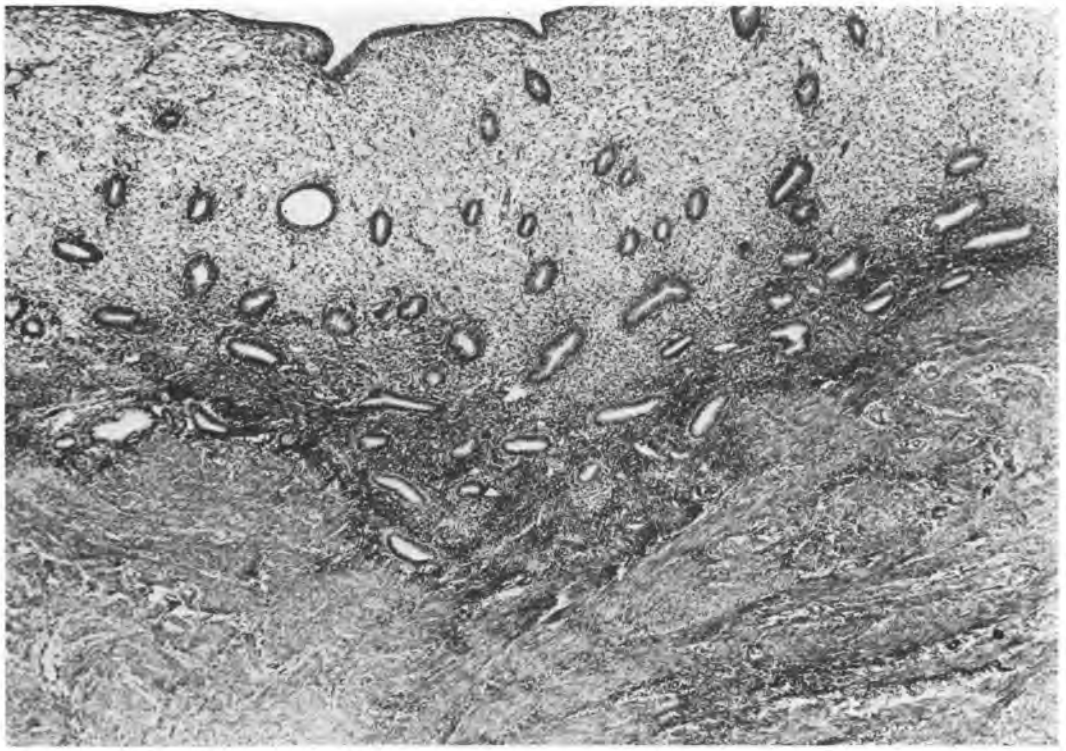

FIGURE 4-34 Hypoplastic endometrium.

tween these two lesions is that the diagnosis of both, and of the early malignant changes associated with them, is clouded by the profusion of different terminologies that have been proposed in the past and by the often highly subjective factors in distinguishing histopathologic pictures.

Because of the premalignant significance of this lesion, it will be discussed in greater detail in the section on endometrial carcinoma.

Endometrium of Irregular Shedding. Synonyms are *irregular desquamation* and *endometrium of prolonged luteal activity.* Examination of the endometrium in certain cases of profuse and prolonged menstruation shows glands in all stages of involution intimately associated with other glands of secretory type; the stroma is retracted and abundant[80] (Figs. 4-35 and 4-36). This picture becomes pathologic when it is found 5 days or more after the onset of the men-

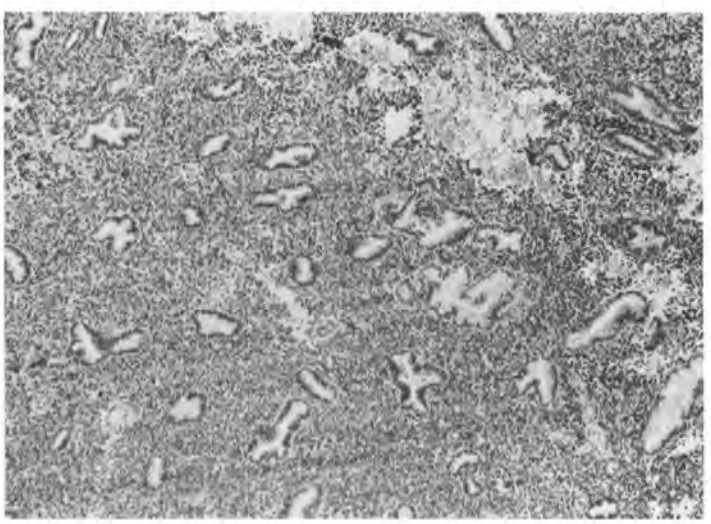

FIGURE 4-35 Irregular shedding: shrunken star-shaped glands in compact stroma.

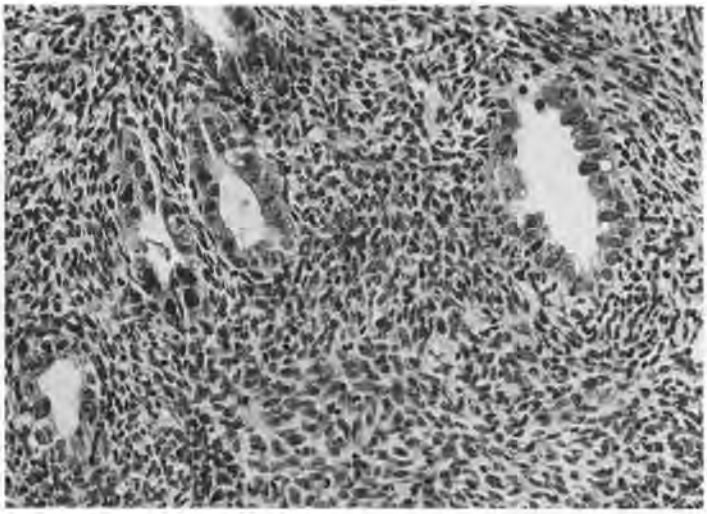

FIGURE 4-36 Irregular shedding (detail). Contracted glands show focal secretory activity and Arias-Stella changes (case of tubal ectopic pregnancy).

strual period. A small biopsy will not suffice; only a complete curettage of the mucosa can furnish the pathologist with the necessary elements for diagnosis. The existence of an organic disease should be eliminated before the diagnosis is made, because anomalies of desquamation and regeneration may be provoked by an endometrial polyp, uterine leiomyoma, or placental retention.

The retraction of the endometrium by resorption of the stromal edema, the fragmentation and separation of the mucosal debris, and the subsequent regeneration of the endometrium—phenomena that take place normally in the course of 36 to 72 hours—have their evolution prolonged beyond this time. The histologic picture is a consequence of slowing of the menstruation process. Retraction of the stroma by loss of extra- and intracellular fluid following the fall of progesterone levels does not take place completely. This causes retention of functional endometrium and of fragments of secretory mucosa adjacent to mucosa in involution. The arteries have thick hyalinized walls and are increased in diameter.

Endometrial Pattern With Oral Contraceptive Agents. The use of certain progestational agents as inhibitors of ovulation produces an increasingly more common histologic appearance of the endometrium, which we may conveniently classify among the prolonged luteal activities. These changes have been described frequently in the literature.

The administration of synthetic progestational agents (19 nor-testosterone and 17 α-hydroxyprogesterone derivatives) in association with ethinyl estradiol or mestranol from the 5th to the 24th day of the cycle provokes the appearance of precocious signs of luteinization around days 12 to 14. The histologic picture varies according to the drug dosage, the number of cycles of therapy, and other individual factors.[23,81,82] It is characterized by diminution of glandular proliferation and minimal secretion, stromal decidualization, and the absence of mitoses (Fig. 4-37). At the 24th day, we find an atypical secretory state in which are seen glands of small caliber that are inactive and without mitoses or connective tissue spines. The stroma is very congested and shows venous lacunae and decidualization. Another characteristic finding is suppression of the spiral arterioles with development of thin-walled sinusoids.

After a few cycles, the glands are small, secretion is minimal or absent, and the epithelium is devoid of mitoses. Large doses produce earlier and more intense changes. A rare complication after many cycles is amenorrhea with persistent and irremediable endometrial atrophy.[65,83] Decidual necrosis and Arias-Stella changes have been described in rare cases.

The regimen described here is the one most commonly prescribed for oral contraception and is known as *combined therapy.* Other agents are known as *sequentials* and are characterized by an estrogen given alone from the 5th to the 19th day of the cycle, followed by 5 days of estrogen combined with a progestogen. Cycles with these agents are characterized histologically by prolonged proliferative activity preceding a shortened and less intense secretory phase.[84] Cases of endometrial hyperplasia and carcinoma have been reported after prolonged sequential therapy (Fig. 4-38). The vast majority of these cases occurred after the administration of a sequential agent (Oracon) that combined a strong estrogen with a particularly weak progestin.[85] It was subsequently shown that Oracon was the only oral contraceptive associated with an increased risk of endometrial carcinoma and that other oral contraceptives appear to be associated with a decreased risk.[86,87] In any event, all sequential agents were removed from the American and Canadian markets in 1976.

Intramuscular Administration of Long-Acting Progestogens. Long-acting progestogens (eg, Provera) administered intramuscularly produce characteristic endometrial changes that may persist for several

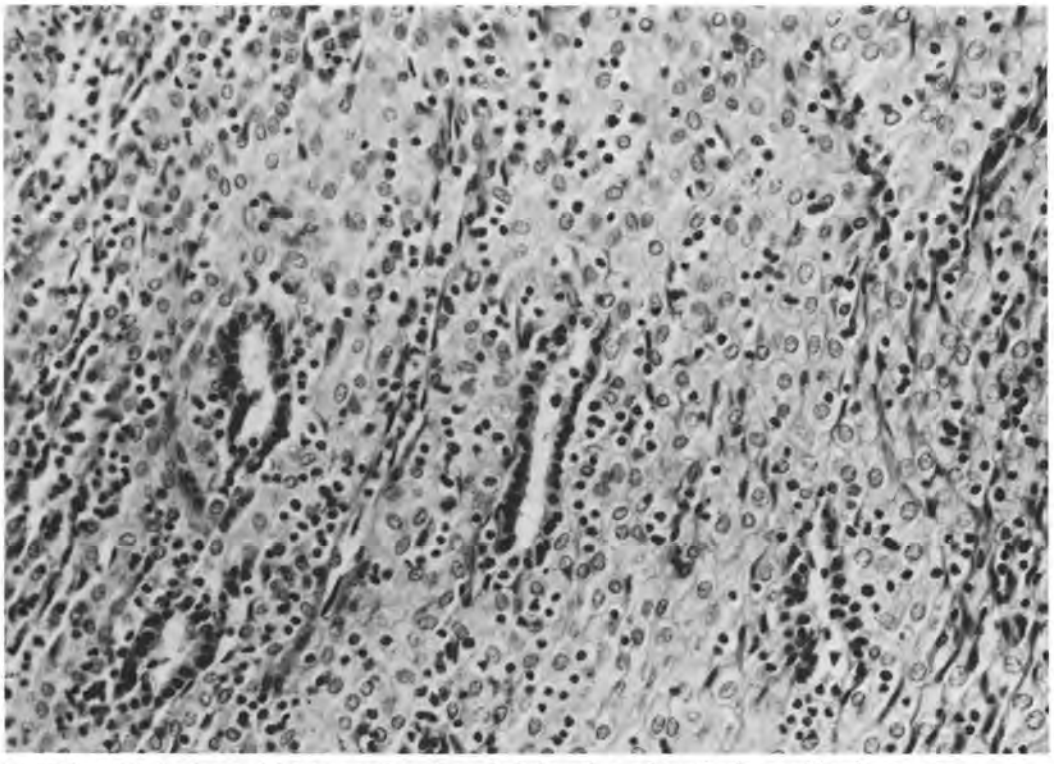

FIGURE 4-37 Endometrial biopsy after the administration of synthetic combined-type progestational agents.

months. These changes consist of decidualization of the compacta and a functional layer composed of small inactive glands, spindle cell stroma, and widely dilated venules (Fig. 4-39). Other changes reported with pure progestogens include discrete stromal cell atypias and scanning electron microscopic findings of defective cilioneogenesis.[88]

Other Progestins and the Endometrium. Progestins, alone or in combination with estrogenic agents, are administered in other situations and dosages. One of the most common patterns of administration is in the form of combined or sequential estrogen/progestin therapy in postmenopausal women, for the main purpose of decreasing the severity of osteoporosis and cardiovascular disease without the increased risk of endometrial carcinoma noted in women who receive estrogen alone.[86,87] The sequential regimens are generally associated with endometrial histologic appearances similar to those seen in

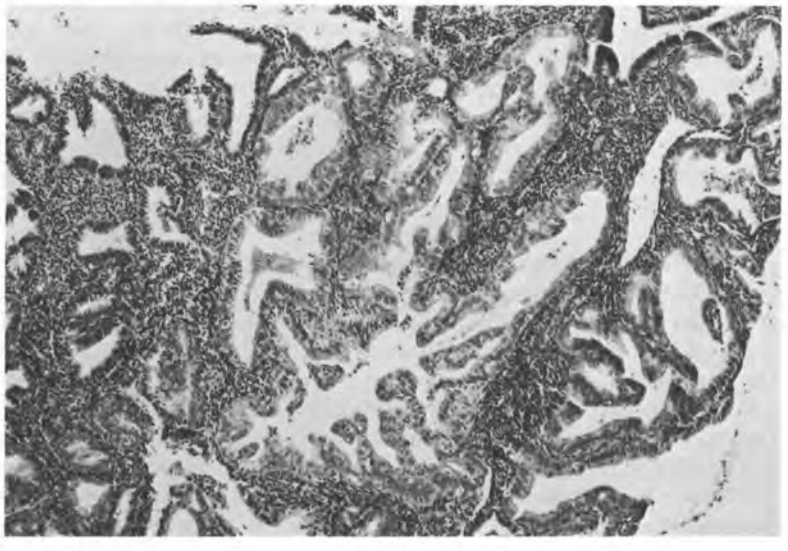

FIGURE 4-38 Focus of early adenocarcinoma of endometrium in a 34-year-old woman after 4 years of sequential oral contraceptive medication. No residual tumor was found at hysterectomy.

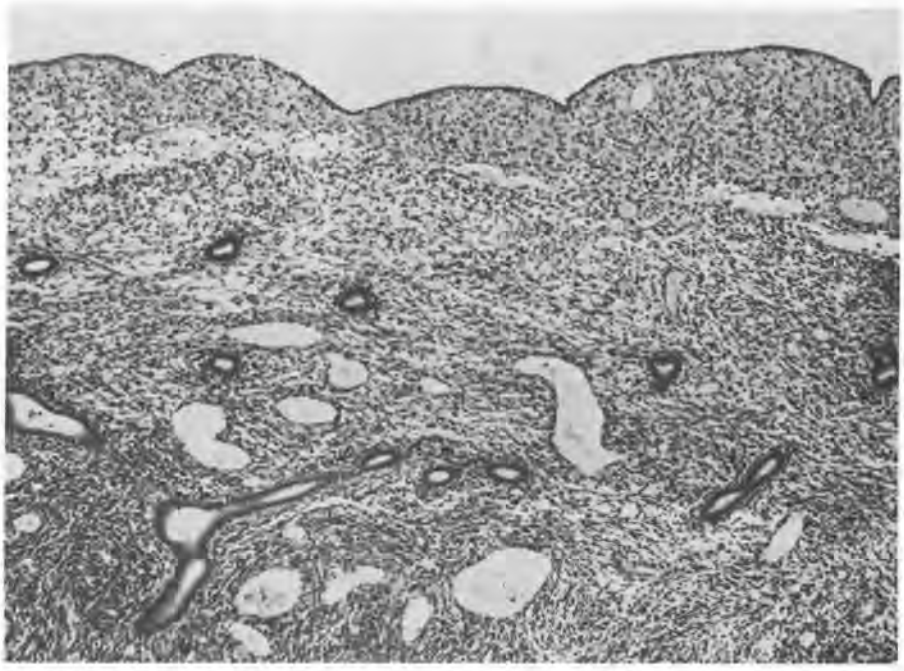

FIGURE 4-39 Endometrium at hysterectomy in a woman who received intramuscular progestogen (Provera) 1 month previously.

cycling premenopausal women, depending on when in the artificial cycle the biopsy is performed, and varying with the relative doses of estrogen and progestin. The combined continuous regimens, which are preferred by many women because of the absence of monthly withdrawal bleeding, are associated with an unpredictable endometrial response for the first 3 to 6 months, followed by an inactive or atrophic endometrium.[89,90] Patients who experience breakthrough bleeding after achieving amenorrhea for some time have in some instances been found to have polyps or carcinomas.[89]

Progestational agents can also be administered for contraceptive purposes in other than oral forms. Among the pathways of administration encountered in experimental or—in some parts of the world—clinical situations are progestin-releasing intrauterine or intracervical devices, subcutaneous implants, nasal sprays, and others. These seem to share a final common pathway of effect on the endometrium similar to those discussed above for oral or intramuscular progestogens.[91] The progestin-releasing devices may lead to endometrial stromal calcification, small polyps, and thick-walled fibrotic blood vessels after several years.[91,92]

Endometrial Pattern With Intrauterine Contraceptive Devices. Intrauterine contraceptive devices (IUDs) consist of diverse metal and plastic loops, bows, and other structures that are retained within the uterus and exert a contraceptive effect by a mechanism that is not clearly established. One of the two most widely accepted hypotheses assumes that the ovum arrives in the uterus when the endometrium is out of phase for implantation (endometrial asynchronism), whereas the other favors a primary retardation of the biochemical maturation of the endometrium.[93]

Several studies have investigated endometrial histology after prolonged retention of the IUD. However, both IUDs and studies related to them have become less popular in the Western world in recent years. Although Rozin and his colleagues[94] noted no significant histologic abnormality except for chronic endometritis in 17% of cases, other workers have described minor but consistent focal changes.[93,95,96] The most common of these is superficial stromal edema beneath the IUD, often with some fibrosis and increased superficial vascularity consisting of large thin-walled vascular channels. A precocious decidual reaction around the vessels, sometimes accompanied by discrete hyalinization, also has been noted. Endometrial dating is often, but by no means always, behind the expected pattern. Significant changes in the glands have not been described. True endometritis can be diagnosed only by finding inflammation away from the immediate vicinity of the IUD. Copper-containing IUDs may influence various biochemical mechanisms and have a spermotoxic effect. The findings associated with progestin-impregnated devices have been discussed above.[91] A rare complication of the shield-type IUD has been fatal sepsis during pregnancy.[97]

The *cytologic findings* in IUD wearers have been reviewed by Risse and associates[98] and by Gupta.[99] Prominent among these is the finding of *Actinomyces* organisms (see Fig. 4-57) in the cervicovaginal smears of about 10% of women with an IUD in place and in about 25% of IUD wearers with symptoms of infection (eg, brown, foul-smelling vaginal discharge).[99,100] Some of these women may develop clinically significant, often unilateral, salpingitis and

tubo-ovarian abscesses due to these organisms. See Chapter 5 for a more complete discussion of this problem.

Another worrisome cytologic complication of the IUD is the appearance of atypical cells in Pap smears. The most commonly encountered atypias are represented by vacuolated columnar cells (Fig. 4-40*A* and Color Fig. 4-4), which probably are derived from atypical endocervical hyperplasia, endometrial tubal metaplasia, or both, and by *IUD cells* of indeterminate type with a high nuclear–cytoplasmic ratio (Fig. 4-40*B* and Color Fig. 4-4), which are thought to be of histiocytic or endometrial origin. The differential diagnosis of the former cell type must include various adenocarcinomas, but the age of the patient, small number of atypical cells, and absence of a "tumor diathesis" all militate against a malignant diagnosis, as does the prompt disappearance of these cells after removal of the IUD. The IUD cells bear a strong resemblance to the "third-type

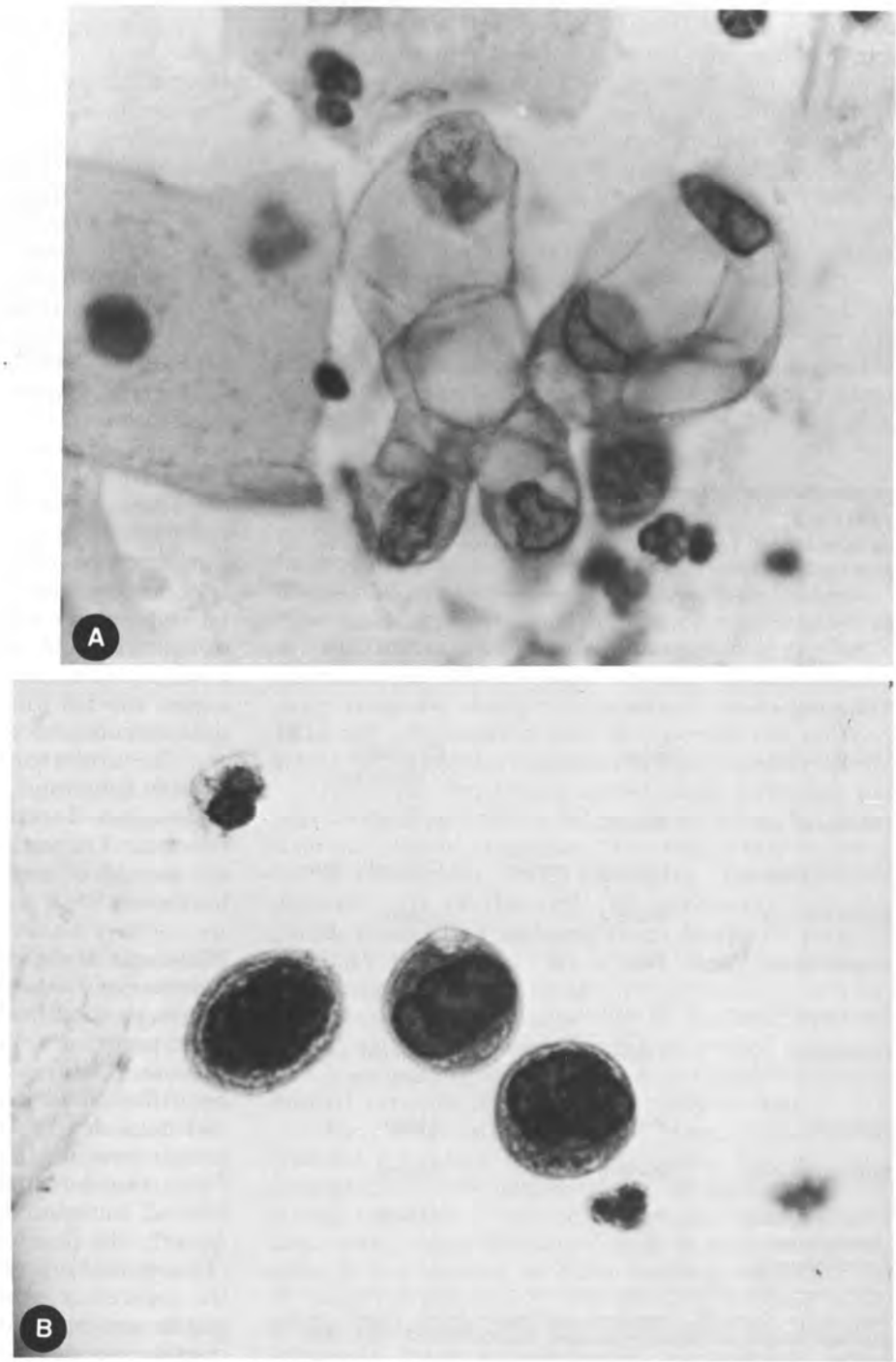

FIGURE 4-40 Atypical cells seen in cervicovaginal Papanicolaou smears of IUD wearers. **(A)** Vacuolated columnar cells. **(B)** Cells of probable histiocytic or endometrial origin resembling "third-type" cells of cervical in situ squamous carcinoma. (Gupta PK: Intrauterine contraceptive devices: Vaginal cytology, pathologic changes and clinical implications. Acta Cytol 26:571–613, 1982)

cells" of squamous cell carcinoma in situ, and this differential diagnosis is summarized in Table 4-1. The most helpful single feature is the absence of dysplastic cells of a lesser degree of atypia in smears with IUD cells. Dysplasias and carcinomas can, of course, occur in IUD wearers, but there is no good evidence to suggest an increased frequency of these lesions in this population.

Other Iatrogenic Stimuli. Premenopausal infertile women in whom some form of in vitro fertilization is being considered may be subjected to *mock cycles*, in which their endogenous menstrual cycle is suppressed with an agent such as leuprolide (Lupron) and an exogenous cycle stimulated with estrogen and progesterone. Biopsies are performed during these cycles to determine how closely the iatrogenic cycle simulates a natural one; thus, a biopsy performed on day 18 or day 26 should be evaluated to determine whether it conforms to the corresponding date of a natural idealized 28-day cycle or one with a shortened or lengthened proliferative phase.[101]

Clomiphene citrate is an agent that is thought to bind estrogen receptors in the hypothalamus (antiestrogenic effect), promoting secretion of FSH with subsequent increased estrogen production followed by an LH surge. Clomiphene is used as an inducer of ovulation in certain infertile women and has been shown to have estrogenic and antiestrogenic effects in various organs. In a recent study, Benda noted that secretory-phase endometrial biopsies from infertility patients receiving clomiphene showed a characteristic hypoestrogenic effect (less tortuous glands than normal, scant secretions, inspissated luminal secretions, low cuboidal late secretory glandular epithelium, and sometimes smaller than normal decidualized stromal cells).[102]

Postcoital contraception (also known as *morning after pills*) is available in many parts of the world.[103] Several different types of agents are used, and their effects on the endometrium are variable and in some instances poorly described. RU 486, an antiprogesteronal steroid, has been noted to cause degenerative changes in endometrial stroma and endothelial cells.[103]

Endometrium of Traumatic Amenorrhea (Asherman's Syndrome). Another iatrogenic condition is the rare Asherman's syndrome, which is characterized clinically by secondary amenorrhea or hypomenorrhea and pathologically by destruction of the endometrium with subsequent synechial (and rarely calcific) obliteration of the uterine cavity.[104,105] More than 25% of all the cases in the literature have been reported from Israel, the site of the first description of the entity. The etiology generally involves a vulnerable endometrium affected by inflammation and trauma. The great majority of all cases follow curettage related to pregnancy, usually postpartum or postabortal. Other operative procedures may also be represented, and a small proportion of cases are unrelated to surgical trauma; these latter cases are usually the result of tuberculous endometritis.[104] A new cause is laser ablation of the endometrium, which is performed under hysteroscopic control for the conservative management of dysfunctional uterine bleeding.[106,107]

The underlying endometrium in this condition is often functional, and the presence of adenomyosis is common. Treatment (if desired) is by repeat dilatation and curettage, usually followed by insertion of an IUD and administration of estrogenic hormones.[104,108]

Histologic Modifications of the Endometrium in the Presence of Trophoblast. Characteristic endometrial histologic modifications occur in the presence of ectopic pregnancy, hydatidiform mole, and choriocarcinoma. Pictures of endometrial regression have been described in cases of extrauterine pregnancy with fetal death. According to Baniecki,[109] these histologic modifications are divided into three stages. First, the decidual reaction regresses but persists around convoluted and hyalinized arterioles. Subsequently, the decidual reaction disappears, the stroma retracts, and arteriolar hyalinization is aggravated. In the third stage, stromal retraction continues, and the glands are small and round and still show signs of discrete secretory activity (Fig. 4-41; see Fig. 4-36).

TABLE 4-1.
Differentiating Features of IUD Cells versus Carcinoma In Situ Cells

	IUD cells	*Carcinoma In Situ Cells*
Tissue fragments	Present	Absent
Cell quantity	Scant	Generally abundant
Dysplastic cells	Absent	Present
Inflammation	Generally present	Generally absent
Bizarre forms	Present	Absent
Preservation	Poor	Good
Nuclear envelope	Wrinkled	Wavy
Chromatin	Clumped and fuzzy	Granular and uniform
Nucleoli	Present	Absent
Multinucleation	Present	Absent
Crisp cytoplasm (squamoid, metaplastic)	Present	Absent

Adapted from Gupta PK: Intrauterine contraceptive devices. Vaginal cytology, pathologic changes, and clinical implications. Acta Cytol 26:571–613, 1982.

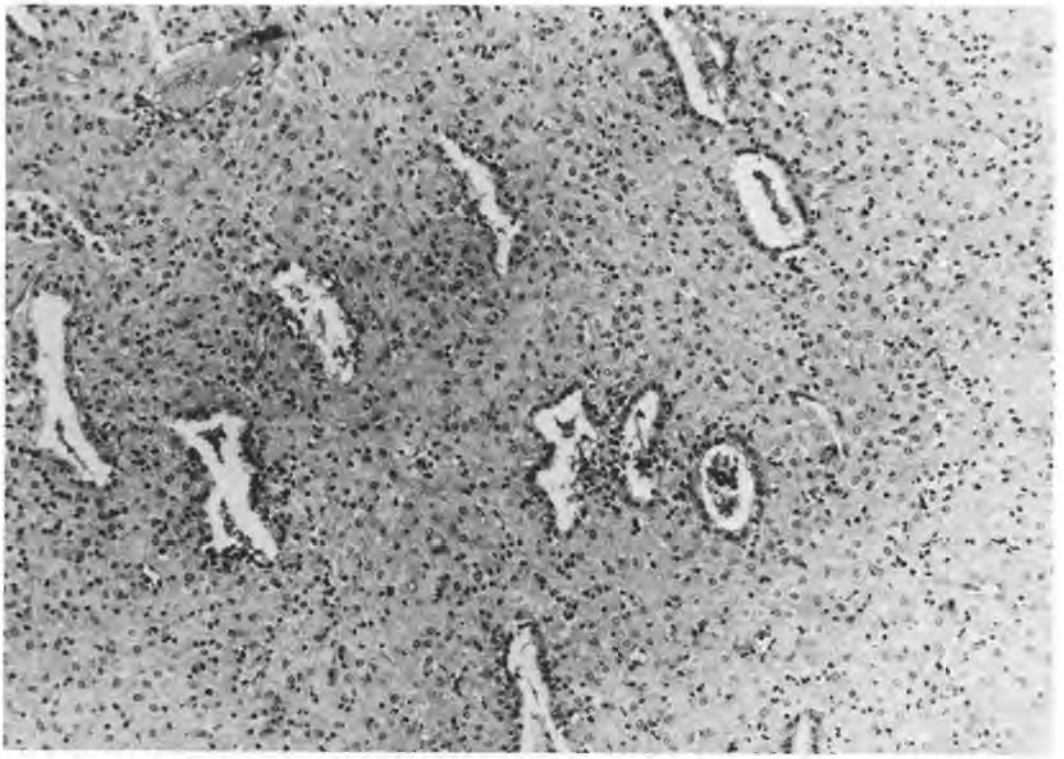

FIGURE 4-41 Regressive transformation of endometrium in the presence of an extrauterine pregnancy.

This regressive transformation of the endometrium permits suspicion of the existence of an extrauterine pregnancy in the process of degeneration. This picture is not specific and is found in irregular shedding, in certain intrauterine abortions, during oral contraceptive administration, and even in the normal mucosa in its resting phase.

Arias-Stella[110,111] studied specifically the endometrial glands in curettings from women carrying ectopic pregnancies and found the characteristic nuclear and cytoplasmic atypical changes (Fig. 4-42*A*) that have come to bear his name (*Arias-Stella phenomenon*). He attributes these cellular alterations to the presence of chorionic tissue. The mechanism of appearance of these changes has not been definitely elucidated, although they appear in most instances to represent a response to elevated levels of chorionic gonadotropin. Although some authors have considered them to be regressive changes,[112] Silverberg[113] has shown that they are present with presumably normal intrauterine gestations, and Wagner and Richart[114] have demonstrated that the constituent glandular cells are polyploid. These two observations and others like them suggest that the phenomenon is proliferative and secretory rather than regressive.

These changes are encountered in all of the following conditions: normal pregnancy, postabortal and postpartum metropathies, ectopic pregnancy, and chorionic tumors. We have seen them on rare occasions in the absence of any known source of gonadotropic hormonal stimulation. Although Arias-Stella himself emphasized their significance in the diagnosis of ectopic pregnancy (particularly when neither decidua nor chorionic villi are seen in an endometrial curettage specimen), Kjer and Eldon[115] have noted that ectopic pregnancy was present in only 16% of cases in which endometrial Arias-Stella phenomenon was observed. In cases of intrauterine pregnancy, the changes may be seen as early as the 12th day of gestation and may persist for up to 8 weeks following the expulsion of the placental tissue.

Histologic examination shows large, irregular, hyperchromatic glandular nuclei surrounded by abundant vacuolated cytoplasm. The nuclei are disposed in all directions, not necessarily following the greatest axis of the cell. The epithelium of the glands is stratified and sometimes assumes a pseudopapillary disposition. In some cases, particularly when associated with an abnormal gestation or a tumor, secretory vacuolation may be minimal. Hobnail and clear cell epithelial changes, described predominantly in gestational endometria, probably represent limited variants of Arias-Stella phenomenon.

The diagnostic value of these endometrial changes is relative, as seen previously, because they lack specificity. Nonetheless, they at least permit the strong suspicion of an ectopic pregnancy or a chorionic tumor when they are found on endometrial biopsy in the absence of other findings diagnostic of intrauterine pregnancy. Ultrastructural studies have shown that these cells have high metabolic activity, expressed by a well-developed endoplasmic retic-

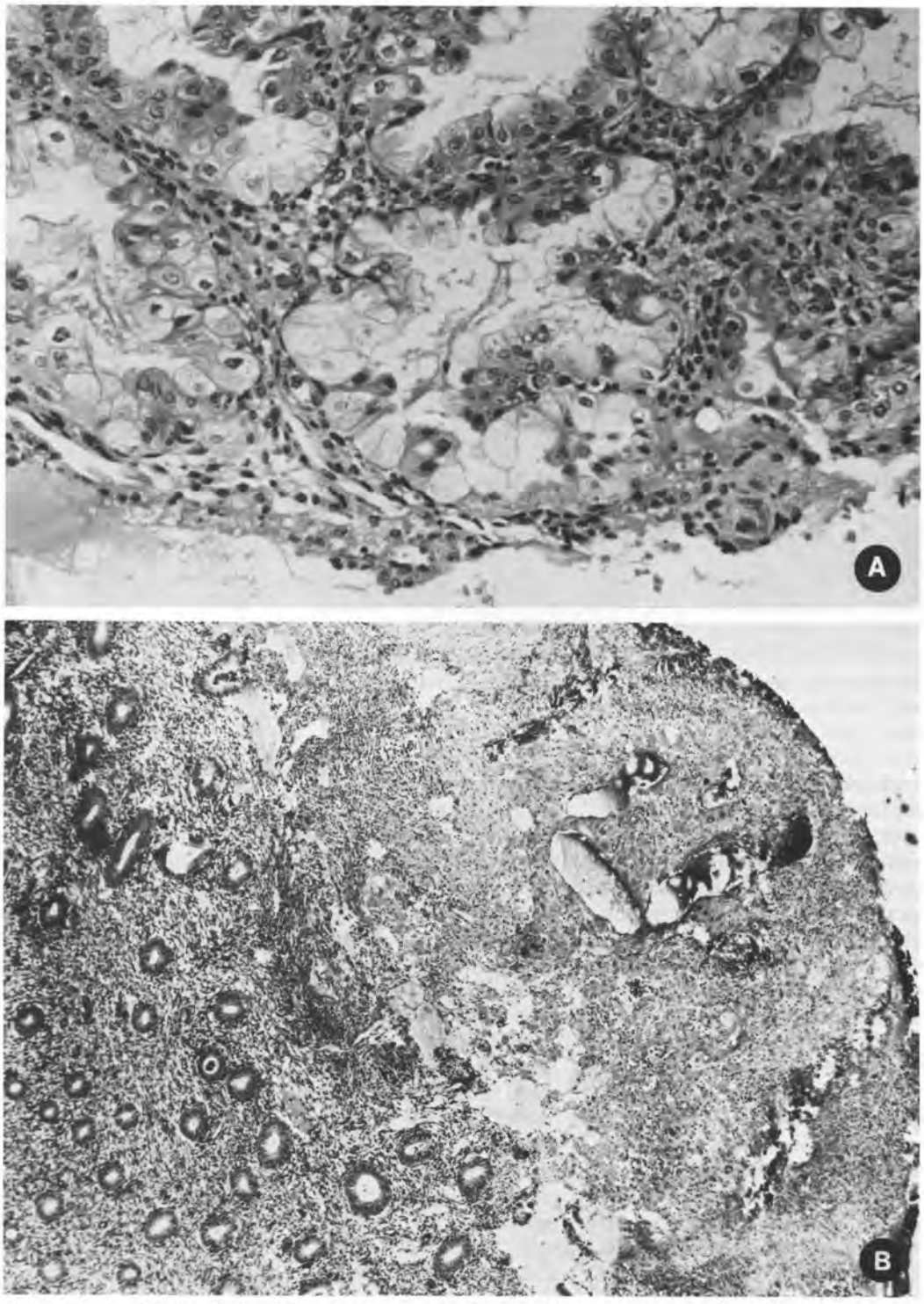

FIGURE 4-42 **(A)** Atypical cellular changes in association with pregnancy described by Arias-Stella. **(B)** Superficial retained placental tissue in the process of necrosis.

ulum and the presence of numerous glycogen granules.[116]

Differential Diagnosis. Differential diagnosis of these alterations must be made with clear cell carcinoma of the endometrium. In the latter condition, although the cytology is similar, the architectural features of stromal invasion are present. The Arias-Stella phenomenon may be seen in intrauterine endometrial glands, in foci of endometriosis, in endocervical glands, in the glands of vaginal adenosis, and in the mucosa of the fallopian tube. Finally, nuclear pseudoinclusions occasionally seen within the glandular cells should not lead to confusion with a herpetic or cytomegaloviral endometritis.[117]

Postabortal Endometrium. Surface re-epithelialization is completed by 1 week postabortion, and signs of active proliferation are present around 10 days postabortion. Ovulation, which occurs around day 44 after a normal delivery, appears earlier after abortion. Decidual fragments have been found during the first 3 weeks postabortum (Fig. 4-42*B*). The inflammatory reaction that is often present (polymorphonuclear leukocytes and plasma cells) is not accompanied by clinical signs of endometritis. This foreign body reaction follows the necrosis of degenerating decidua and trophoblast.

Mucus- or Lipid-Laden Macrophages in the Endometrial Stroma. Large macrophages with abundant foamy cytoplasm (Fig. 4-43) are occasionally encoun-

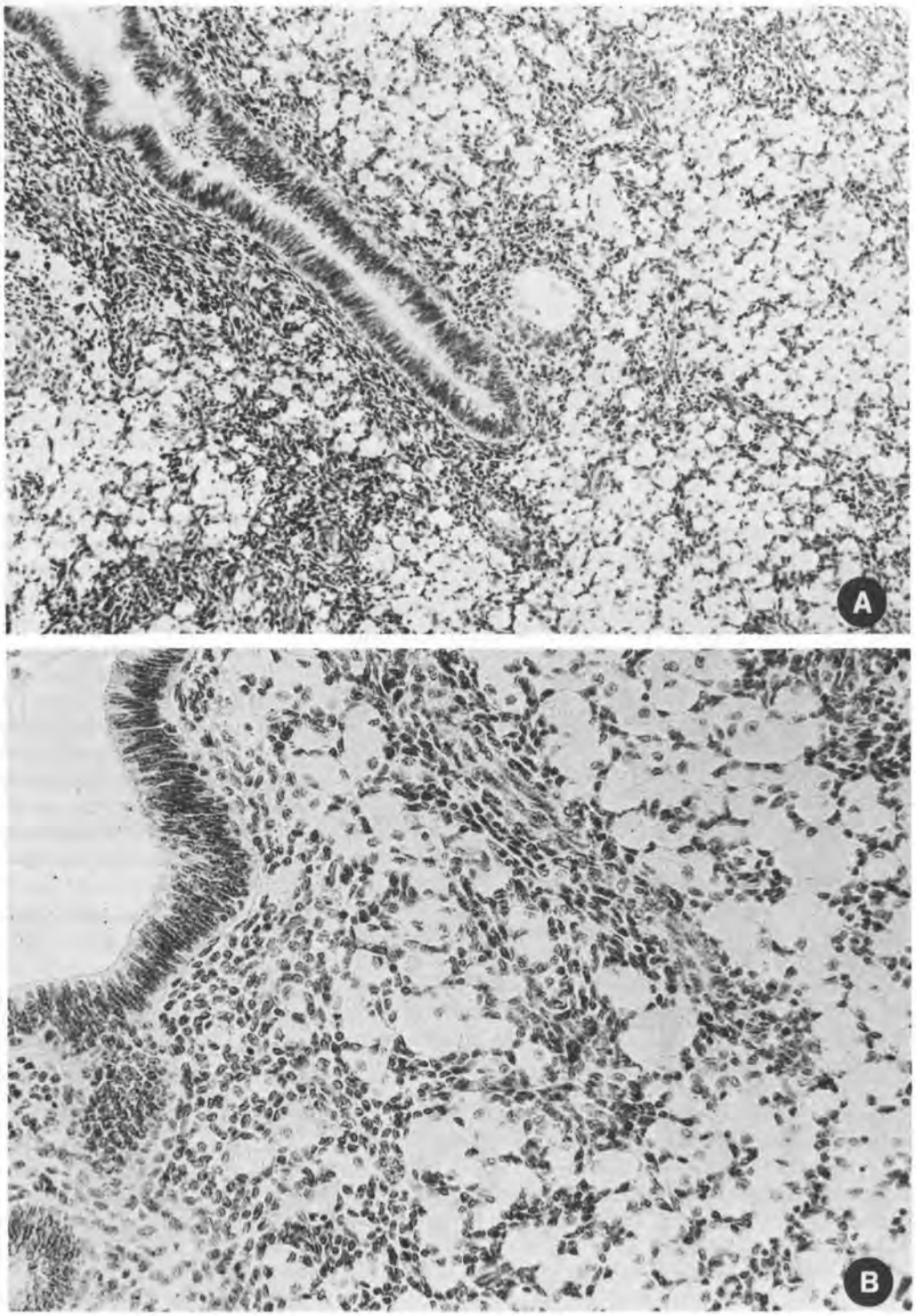

FIGURE 4-43 Fatty degeneration of stromal cells. **(A)** General appearance. **(B)** Detail. (Courtesy of Dr. R. Cordier)

tered in banal mucosae, polyps, hyperplasias, and carcinomas and low-grade stromal tumors of the endometrium. Their pathologic significance is not clear. Macrophages containing mucicarminophilic and PAS-positive substances probably represent phagocytosis of material coming from the glands. Cells rich in lipids (neutral fats) are seen with greater frequency in cases of carcinoma and may arouse a suspicion of malignancy even when seen in an otherwise benign curettage; however, in a late secretory endometrium, these probably represent merely a regressive phenomenon.[118] The mechanism of appearance of these cells is unknown. Ultrastructural studies have shown them to be of stromal origin.[119] When seen in association with carcinoma, they are of no prognostic or other clinical significance.[120] This picture is different from that observed after the injection of contrast media, in which case a true foreign-body granulomatous reaction is seen.

Glandular Invaginations or Double Contours. Invaginations of the glandular epithelium sometimes appear in endometrial glands. On occasion, the base of invagination is visible and forms a papillary digitation. More often, the plane of section does not pass through the region of implantation, and the image formed is that of several concentric epithelial walls or glands within glands (Fig. 4-44). This image does not necessarily result from poor fixation or the trauma of the biopsy technique, because it is also found in hysterectomy specimens fixed in toto with no manipulation of the endometrium before fixation. Plastic reconstitutions have been carried out by Hampson and Gerlis,[121] who attribute the origin of these invaginations to the disposition of the endometrial vessels. They appear especially in the deep parts of the glands, which are irrigated by the basal arteries. This vascularization, more abundant than that of the spiral arteries, causes a difference in the development of the gland and the appearance of these epithelial invaginations.

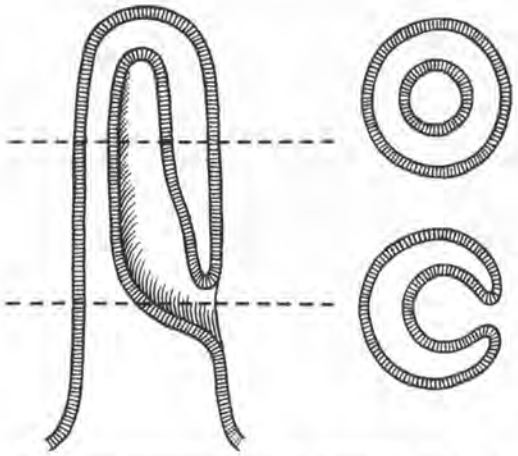

FIGURE 4-44 Endometrium: double glandular contours.

"Cracking" Artifact of the Glands. The glands are separated from the stroma by an empty space (Fig. 4-45). This artifact is caused by tardy fixation.

Hemorrhage. Diffuse recent hemorrhages may be due to the manipulations of the biopsy procedure. A method of eliminating them is to wash the curettings rapidly in physiologic liquid (normal saline) before placing them in the fixative.

Postradiotherapeutic and Postcurettage Lesions. Irradiation of the normal uterine mucosa,[122] as in the course of radiation therapy of cervical cancer, produces atrophy of the mucosa with bizarre glandular cells, nuclear pyknosis, and loss of the tinctorial affinities of the cells (Fig. 4-46). Similar pictures may occur as *regenerative atypias* after previous curettage. Flattened surface epithelial cells may be present within 3 days after curettage, but it takes 7 to 9 days or more for complete restoration of the endometrium; regeneration is even slower if the curettage was performed in the secretory phase[123] and may take 3 months or more after total endometrial ablation by laser.[106]

If the curettage or radiation therapy was administered for endometrial carcinoma, it is important not to misinterpret these reactive glandular changes as residual carcinoma. A false impression of myometrial invasion by carcinoma may be given, particularly if these changes are seen in glands participating in adenomyosis. As in the differential diagnosis of the Arias-Stella phenomenon (see above), the absence of architectural features of stromal invasion is of primary importance.

After radiation therapy, the stroma shows cytologic alterations of atypical nature and is infiltrated with leukocytes. If the dose of radiation is very high, phenomena of necrosis dominate. Depending on the modalities of irradiation, the atrophy may be complete or followed by partial regeneration. Appearance of malignant endometrial tumors several years after pelvic irradiation has been reported.[124]

Foci of Dense Stromal Cellularity. The appearance of nodular aggregates of closely packed but otherwise cytologically normal stromal cells was noted by Picoff and Luginbuhl[125] in 10.7% of the endometria that they examined. This finding was almost always associated with bleeding for 24 hours or longer, either physiologic (menstruation) or pathologic, and was not specific for any one diagnostic entity. The researchers ascribed the origin of these foci to compaction of stromal cells rather than to hyperplasia. We have seen these "stromal balls" misinterpreted as carcinoma, but they are totally lacking in cytologic atypia (see Fig. 4-25).

Fibrin in the Endometrial Stroma. Clumps of material identifiable as fibrin are not infrequently seen in

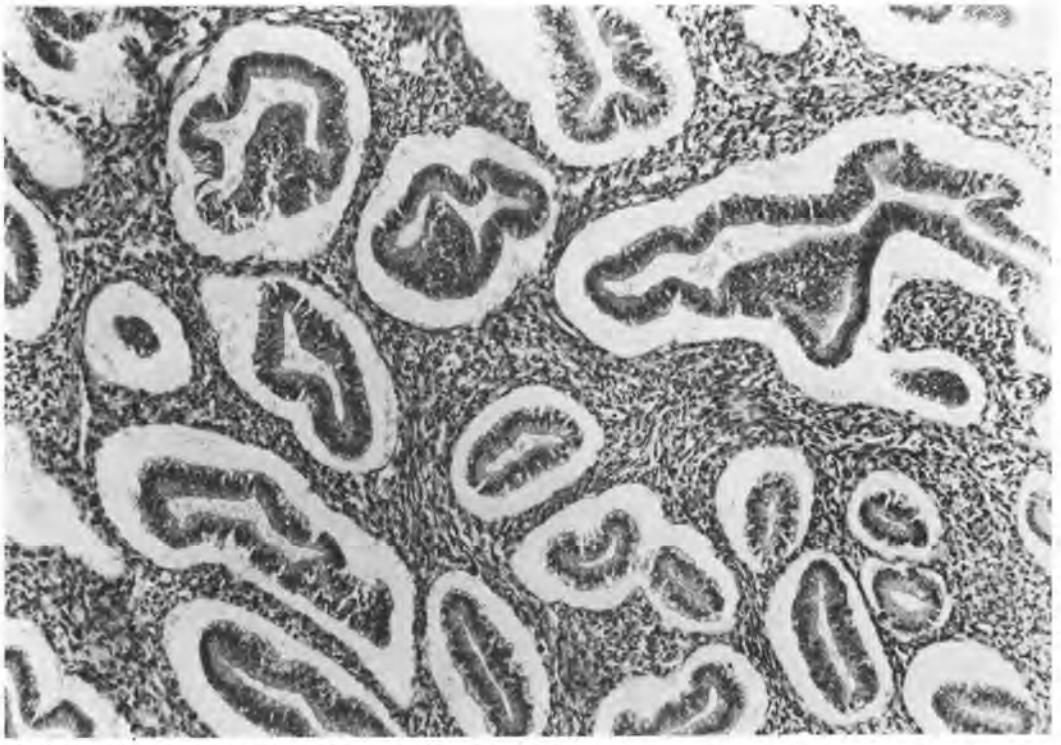

FIGURE 4-45 Glandular retraction with "cracking" artifact.

curetted endometria and seem to be associated with the presence of abnormal bleeding. Picoff and Luginbuhl[126] have proposed that these fibrin clumps may be the histologic evidence of an underlying defect in the fibrinolytic mechanism in these states.

ENDOMETRIAL METAPLASIAS

A great number of metaplastic phenomena can occur in the endometrium, some appearing after known etiologic stimuli and others occurring without known antecedents. The metaplasias can be grouped into epithelial and stromal types and will be discussed in that order. Hendrickson and Kempson[127] have classified the epithelial metaplasias into seven categories:

1. morules and squamous metaplasia
2. papillary metaplasia
3. ciliated cell or tubal metaplasia
4. eosinophilic metaplasia
5. mucinous metaplasia
6. hobnail metaplasia
7. clear cell metaplasia.

The newer classification of the International Society of Gynecological Pathologists (ISGP; Table 4-2) expands these seven to nine, notes that most of them are not truly metaplastic phenomena, and includes nonepithelial metaplastic and related changes.[128]

Squamous Metaplasia

Squamous metaplasia of slight or considerable proportion is seen in endometria under a large variety of circumstances (Fig. 4-47). Among these are excessive hormonal stimulation, intrauterine administration of chemicals, presence of an IUD, vitamin A deficiency, senility, polyps, tumors, chronic inversion, chronic endometritis (including tuberculous and luetic endometritis), and pyometra.[129] Very extensive squamous metaplasia is sometimes designated as *ichthyosis uteri*, especially if it largely covers the surface of the endometrium. Foci that are epidermoid in appearance but lack intercellular bridges are known as *morules* (Fig. 4-48).[130]

The main significance of these proliferations is that, like many of the other epithelial metaplasias, they are frequently confused with cancer. It is important to remember that carcinoma of the endometrium is diagnosed primarily from the glandular component. If the glands appear benign and do not invade their own stroma, and if the squamous or morular elements are also histologically benign, it is safe to assume that the overall lesion is benign.[131] If the glands show malignant characteristics, the diagnosis is adenocarcinoma with squamous differentiation (see below).

It has been hypothesized that squamous metaplasia may be a precursor of squamous cell carcinoma of the endometrium, but this malignant transformation, if it occurs at all, is extremely rare, because only about 30 cases of pure squamous cell carcinoma of the endometrium have been reported.

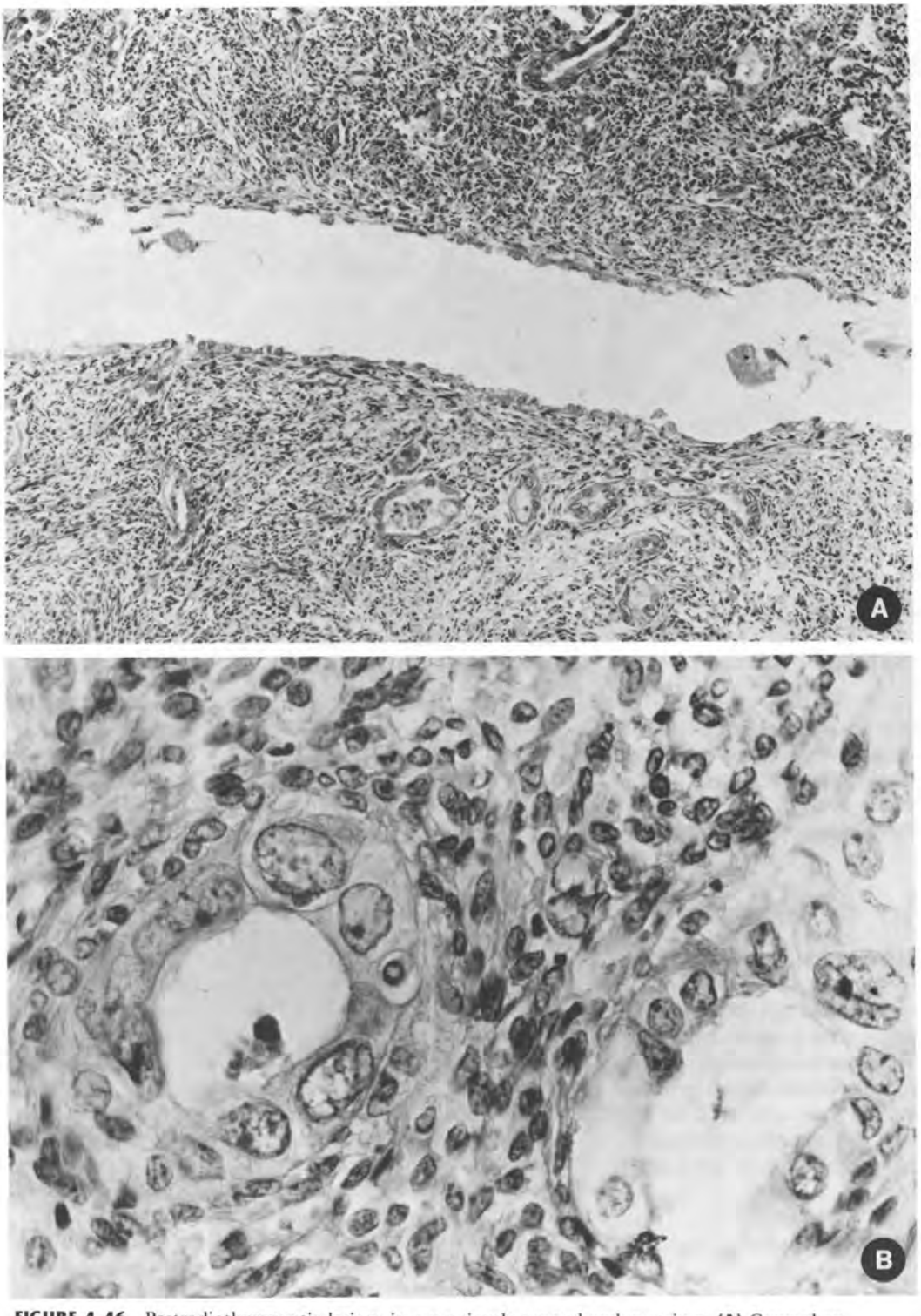

FIGURE 4-46 Postradiotherapeutic lesions in a previously normal endometrium. **(A)** General appearance. **(B)** Detail.

Papillary Proliferation and Surface Syncytial Change

It is often difficult to differentiate papillary proliferation from surface syncytial change. They tend to occur together, although the latter is more common. Both usually are found at or near the endometrial surface. Surface syncytial change is characterized by cells that appear to form a syncytium (Fig. 4-49) but may contain papillary projections as well (Fig. 4-50). When the papillae contain fibrovascular stromal cores, the designation of papillary proliferation is

TABLE 4-2.
Endometrial Metaplasias and Related Changes

Epithelial metaplastic and related changes
- Squamous metaplasia and morules
- Mucinous metaplasia (including intestinal)
- Ciliary change
- Hobnail change
- Clear cell change
- Eosinophilic cell change (including oncocytic)
- Surface syncytial change
- Papillary proliferation
- Arias-Stella change

Nonepithelial metaplastic and related changes
- Smooth muscle metaplasia
- Osseous metaplasia
- Cartilaginous metaplasia
- Fatty change
- Glial tissue
- Foam cell change
- Retained fetal products

Silverberg SG, Kurman RJ: Tumors of the uterine corpus and gestational trophoblastic disease. In Atlas of tumor pathology, 3rd series, fascicle 3. Washington, DC, Armed Forces Institute of Pathology, 1992

preferable. The overall appearance is often reminiscent of microglandular hyperplasia of the endocervix, but this endometrial lesion is usually seen in patients under estrogenic stimulation rather than progestational stimulation. The surface location of the lesion, the cytologically bland nuclei, the indistinct cytoplasmic margins, and the frequent penetration of the lesion by neutrophils all help make the differential diagnosis from papillary serous or endometrioid adenocarcinoma. Although surface syncytial change appears to be benign, we have now seen several cases in which it was associated with an underlying carcinoma, so this possibility should always be kept in mind.

Ciliary Change

Ciliary change is commonly known as *tubal metaplasia*, but it may or may not include the full spectrum of cell types seen in adult fallopian tubal mucosa. The characteristic feature is the presence of glands lined by cells with bland nuclei, brightly eosinophilic cytoplasm, and numerous cilia (Fig. 4-51). In some instances, intercalated and muciparous cells may also be present, intensifying the resemblance to tubal epithelium. This change also seems to be more common in endometria in hyperestrogenic states.[132]

As in most of the epithelial metaplasias, the main significance of this lesion lies in its frequent confusion with more worrisome lesions, particularly atypical hyperplasia, which is also often recognized at low power by the presence of cytoplasmic eosinophilia. The main distinction is the presence of ciliated cells and the absence of nuclear stratification and atypia in ciliary change. However, carcinomas containing many ciliated cells do occur in the endometrium, and these are best diagnosed by architectural evidence of stromal invasion.[133]

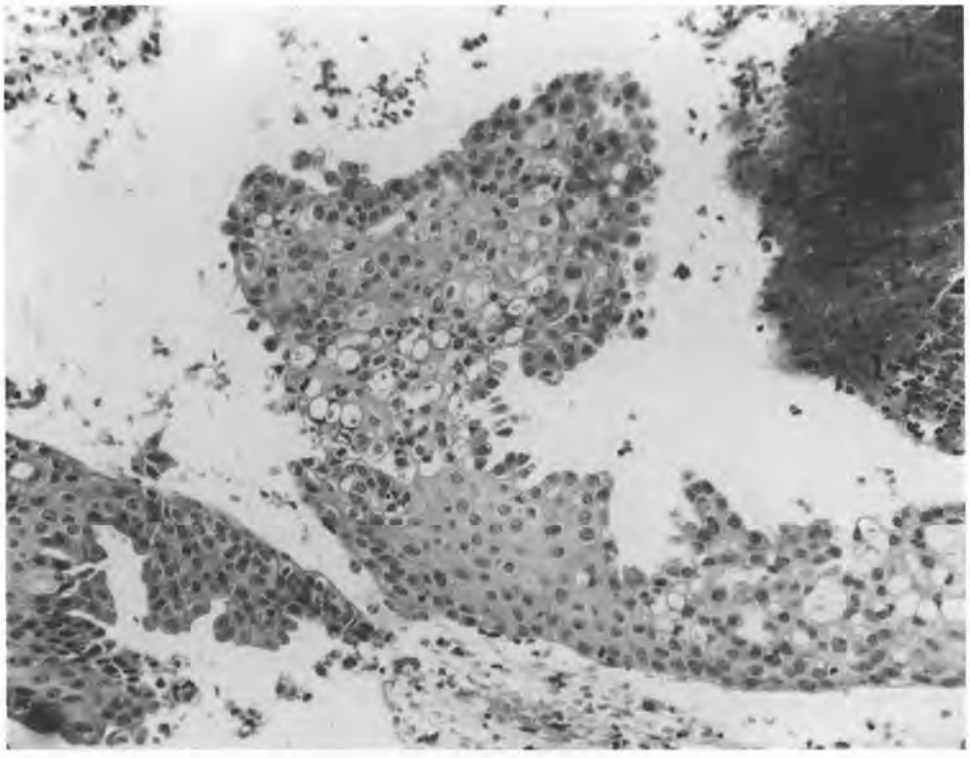

FIGURE 4-47 Squamous metaplasia in endometrial curettage specimen.

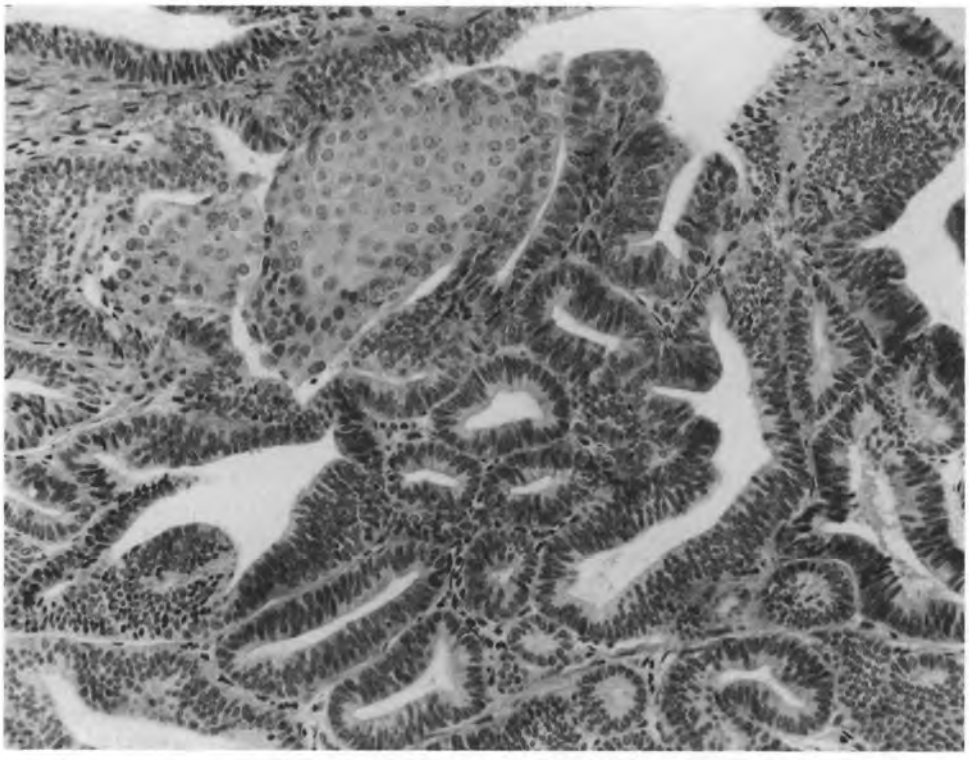

FIGURE 4-48 Morular metaplasia in hyperplastic endometrium.

Eosinophilic Cell Change

Eosinophilic cell change includes cells with the brightly eosinophilic cytoplasm of ciliary change but without the cilia (see Fig. 4-49). Occasionally these cells may demonstrate the typical features of oncocytes, in which case some nuclear atypia may also be present.[134] In most instances, however, the absence of atypia helps in the differential diagnosis from atypical hyperplasia.

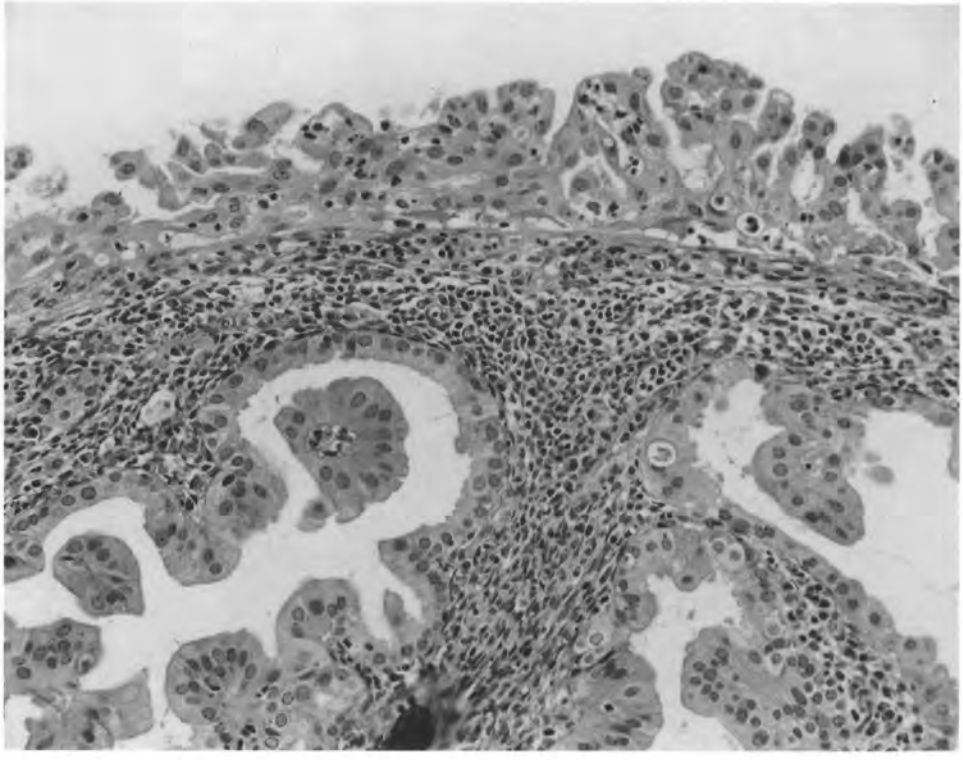

FIGURE 4-49 Surface syncytial change and underlying eosinophilic cell change with focal papillary proliferation.

FIGURE 4-50 Surface syncytial change with papillary features.

Mucinous Metaplasia

Mucinous metaplasia is usually a true endocervical metaplasia because, as in the case of full tubal metaplasia, the lesion seems to represent an example of cells in the endometrium differentiating along another müllerian pathway. Demopoulos and Greco[135] have shown that the endometrial epithelial cells in mucinous metaplasia are identical to endocervical epithelial cells both ultrastructurally and histochemically. Occasionally, an intestinal type of mucinous metaplasia is encountered.

Although the usual appearance of this uncommon metaplasia consists of glands lined by tall columnar mucin-secreting cells (Fig. 4-52), we have seen examples in which this metaplastic endocervical-type epithelium developed a secondary microglandular hyperplasia (Fig. 4-53).

As with the other types of metaplasia, the main significance of this lesion is its distinction from the uncommon endocervical-type mucinous carcinoma arising in the endometrium.[136,137] When mucinous metaplasia is seen in a curettage or biopsy specimen, it may be difficult to appreciate that the source of

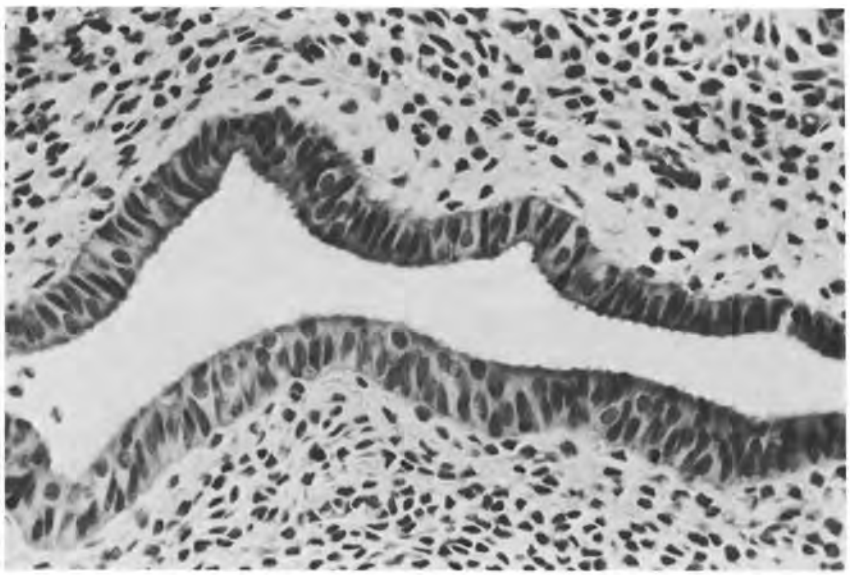

FIGURE 4-51 Tubal metaplasia. Ciliated and intercalated cells are present.

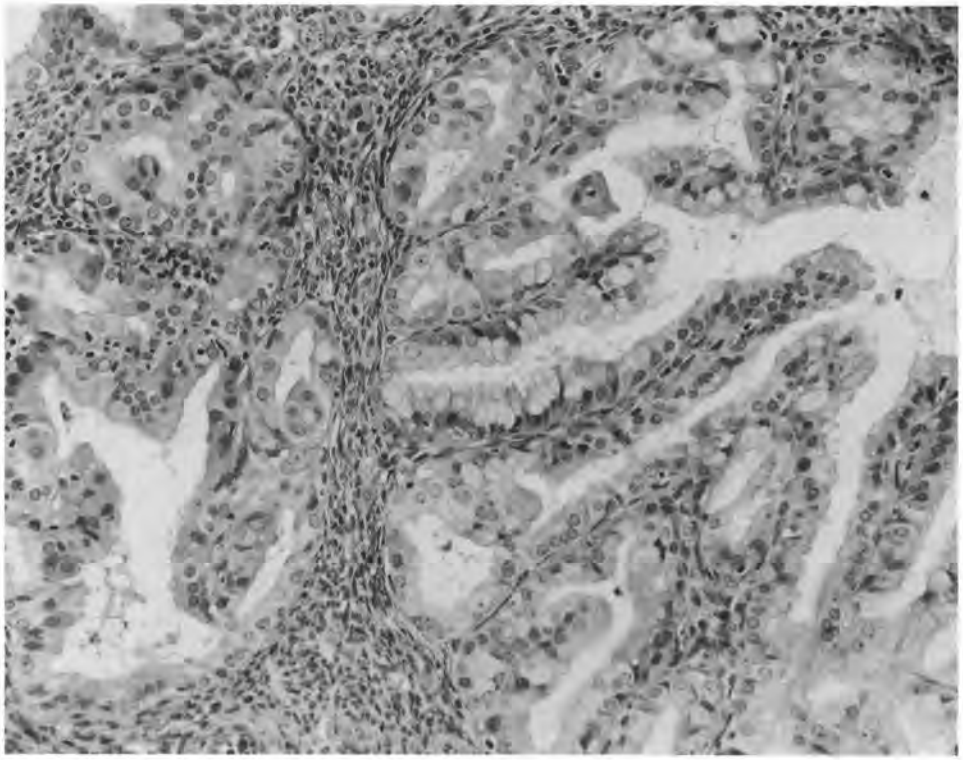

FIGURE 4-52 Mucinous metaplasia of endometrium. Although the cells are mostly of endocervical type, a few goblet cells (intestinal-type mucinous metaplasia) are present.

the specimen was indeed the endometrium rather than the endocervix.

Hobnail and Clear Cell Changes

Two other epithelial changes described by Hendrickson and Kempson[127] are the hobnail and clear cell types. These are both rare and, as would be expected, their differential diagnosis lies mainly with clear cell carcinoma and Arias-Stella phenomenon. Like the latter, they are both encountered mainly in gestational endometria. We have observed hobnail cells in the endometrium not infrequently as a response to trauma.

Frequency of Epithelial Metaplastic and Related Changes

Careful searches for these lesions have not been performed in large series of consecutive otherwise

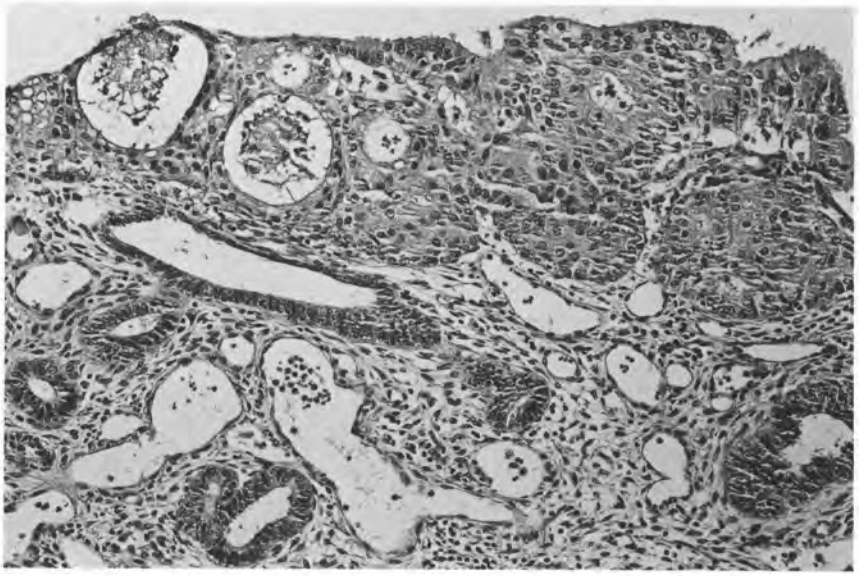

FIGURE 4-53 Microglandular hyperplasia with squamous metaplasia in endocervical-type surface epithelium overlying endometrial basalis. Section is from high in the uterine corpus and is not contiguous with mucosa of endocervical canal.

normal endometrial specimens, so we do not know their population-based prevalences. Many of them, as mentioned above, seem to be related to specific hormonal stimuli (including Arias-Stella change, which is discussed earlier in this chapter). In our own anecdotal experience, the most commonly seen forms other than Arias-Stella change have been (in descending order of frequency) ciliary change, surface syncytial change, and squamous metaplasia and morules. Because these pictures often occur together, it is not unusual to see two or three of them in the same specimen (see Fig. 4-49). There are no known clinical signs or symptoms associated with these lesions, so that they are basically incidental findings in endometrial specimens seen by the pathologist for other reasons.

One of these reasons may be endometrial hyperplasia or carcinoma, and one or more of the metaplastic and related changes may be noted either within the hyperplastic or neoplastic epithelium or in the nonlesional endometrium accompanying it.[138–140] This phenomenon seems to be more common in the United States than in Japan, and in well-differentiated than in poorly differentiated carcinomas, and is probably a favorable prognostic marker when seen in association with carcinoma.

Mesenchymal Metaplasias and Related Changes

In addition to epithelial changes, certain rare types of metaplastic and related changes occur in the endometrial stroma (see Table 4-2). These involve the formation of islands of benign cartilage, bone, smooth muscle, and adipose and perhaps glial tissue. Also encountered are foam cell change (discussed above) and retained fetal products (listed in this classification because they enter into the differential diagnosis of most of the other changes).

Smooth muscle metaplasia is the most common of these mesenchymal metaplasias, as would be expected from the well-known ability of endometrial stroma to differentiate into smooth muscle.[141] These are usually small foci of typical benign smooth muscle, which have sometimes been referred to as *intraendometrial leiomyomas*. Smooth muscle, apart from blood vessel walls, is also seen in about 1% of endometrial polyps (adenomyomatous polyps). Its main differential diagnosis is with epithelial morules.

Foci of *osseous*[142] and *cartilaginous*[143] *metaplasia* are encountered rarely in the endometrium, usually in the postabortal state. These lesions occasionally may represent fetal parts from a previous abortion, but more often they represent a true metaplasia, because their origin from endometrial stromal cells may be demonstrable. These benign metaplasias occasionally can be seen within the stroma of an endometrial carcinoma or sarcoma and should not lead to the erroneous diagnosis of a carcinosarcoma (malignant mixed mesodermal tumor), in which the heterologous stromal elements are histologically malignant.[144]

Glial tissues in the uterus represent the most controversial of these lesions,[145–147] because only mesodermal-derived tissues would be expected to be within the metaplastic capabilities of the endometrial stroma. Most observers of these lesions have postulated an origin from a previous abortion. Although the glial tissues may present in the endometrium per se, they are most frequently found in a cervical polyp. They may be associated with foci of cartilage, bone, and squamous epithelium. Occasionally they may resemble a true glioma.[147]

INFLAMMATORY DISEASES OF THE ENDOMETRIUM

Discussion of the inflammatory pathology of the endometrium formerly occupied a major position in tracts of anatomic pathology. Its importance has been reduced considerably since the discovery of the genital hormones, because most of these histologic alterations are in reality due to modifications of the hormonal equilibrium. Furthermore, the use of antibiotics has reduced the frequency of infections.

Endometritis is encountered in acute or chronic form. In the past it was most often of bacterial origin, and in most cases the causative organism was a streptococcus, staphylococcus, colibacillus, enterococcus (principally in puerperal infection), gonococcus, or tubercle bacillus.

More recent reports[148–151] have stressed the importance of anaerobic infections of the endometrium and of using appropriate culture techniques to identify these infections. Specific organisms that have been identified with increasing frequency include *Chlamydia trachomatis*,[148,151,152] which is sometimes identified in the endometrium of salpingitis patients with irregular bleeding; *Ureaplasma urealyticum*,[153] which has been mentioned as a possible cause of infertility; *Mycoplasma* organisms,[154] which have been mentioned as a cause of infertility; *Toxoplasma gondii*,[155] which has been associated with repeated spontaneous abortions; and *Actinomyces* species,[99,100] which have been seen notably in women using IUDs.

Acute Endometritis

Acute Puerperal Infection

Postpartum endometritis, the frequency and severity of which have diminished considerably since the discovery of antibiotics, represented a major scourge in maternities a half century ago. The pathologic anatomy of this infection was the object of a very complete study by Halban and Koehler,[156] based on 163 autopsied cases. The bacteria isolated include group A hemolytic streptococci, hemolytic *Staphylococcus aureus*, and various anaerobes. Mixed infections are

common, and *Chlamydia* are seen frequently in late infections.[148,151]

The *etiology* should be looked for in surgical interventions, minor daily traumata to the genital organs, perineal and cervical lacerations, or curettages. The internal surface of the uterus is edematous and congested, dark in color, covered with petechiae, and involved by ulcers of diverse sizes. When the infection is aggravated, there is necrosis of the decidua with gray shreds of tissue eliminated spontaneously, among which are found vestiges of chorionic villi. Necrotic decidua can be seen, however, in the absence of significant endometritis. The ulcerated surfaces are covered with a purulent necrotic exudate. The infection extends to the myometrium, which is soft and edematous and may, in certain cases, undergo partial or even total necrosis. In these most severe but fortunately rare cases, greatly feared complications include uterine necrosis, propagation of the infection into the fallopian tubes, and extension into lymphatics and veins. Notable sequelae include thrombophlebitis with pulmonary emboli, parietal or intraligamentous abscesses, peritonitis, and episodes of septicemia.

Microscopically, the endometrial mucosa is invaded or even replaced by an acute inflammatory infiltrate that extends into the myometrium. Zones of tissue necrosis and microabscesses are more or less extensive and bacterial colonies are found in them. Thrombi with periarterial inflammatory infiltrates are also seen.

Gonococcal Endometritis

Contamination of the endometrium takes place by the ascending route. The endometrium presents the classic signs of an acute infection: stromal and intraglandular infiltration with neutrophils, marked vascular congestion, edema, and necrotic alteration of the glands and stroma by the inflammatory process.

Uteroadnexal Infarction

The uteroadnexal infarct is a rare and ominous lesion. It consists of gangrenous phenomena of toxic origin appearing at the beginning or end of pregnancy. At the beginning of pregnancy, the infarct is in general a complication of abortion; at the end of pregnancy, it is related to toxemia.[157]

The *etiology* may be of autonomic neural reflex origin (vascular spasm) or may involve bacterial toxicity when there is a secondary infection. The organisms responsible are predominantly anaerobes (*Clostridium perfringens*) and streptococci. *Clinical manifestations* are a state of shock, signs of septicemia, and an acute painful abdominal syndrome, with eventual complications of oliguria or anuria, myocarditis, and hypofibrinogenemia.

Macroscopically, the uterus is dark red with black or gray zones corresponding to hemorrhagic or necrotic foci. The vessels are all thrombosed. Sections reveal a largely necrotic myometrium. Perforation is occasionally seen. Infarction may extend to the adnexa and the parametria, which also appear dark red or black.

Histologically, there is infarction with massive hemorrhage and secondary necrosis, the cause of which is found more often in reflex arterial spasm than in venous thrombosis.

The evolution is always grave and necessitates rapid intervention with resection of the involved structures. Infarction of the uterus may also occur rarely as a complication of arteriosclerosis, thromboembolism, or dissecting aneurysm.

Chronic Endometritis

Bacterial Endometritis

The origin of a chronic endometritis should be searched for in inflammatory lesions of other portions of the genital system, particularly the fallopian tubes, which secondarily involve the endometrium.[151] These lesions are often secondary to minor traumata of the cervix, vagina, and perineum during delivery. The periodic desquamation of the endometrium explains why these lesions rarely attain the intensity and chronicity of those of the cervix. They are characterized by lymphoplasmacytic infiltrates of the stroma and glands. Because lymphocytes and even lymphoid follicles may be found in normal endometria,[1,24–26] most authors require the presence of plasma cells for the diagnosis of chronic endometritis.[158,159] Although these may be difficult to find, their presence (and that of endometritis) is suggested when an endometrium shows a phase discrepancy in the absence of another cause or shows pronounced spindle cell alteration of the stroma (Fig. 4-54).

Cases of chronic endometritis frequently show proliferative responses of the endometrial glands that may be characterized by architectural (Fig. 4-55) or, less frequently, cytologic atypia (see Fig. 4-54*B*). Pathologists should realize that this proliferative response precludes dating the endometrium, and they should not fall into the trap of overdiagnosing a chronic endometritis as an endometrial hyperplasia.

A frequent cause of chronic endometritis is placental retention (see Fig. 4-42*B*). This etiology is easily recognized by the presence of placental villi that may be well preserved, in the process of hyalinization, or reduced to hyaline and fibrous masses. In other cases, islands of decidual cells surrounded by leukocytic and histiocytic infiltrates persist in the depths of the endometrium and maintain chronic inflammatory foci. These cells should not be confused with the groups of stromal foam cells found in zones of tumor necrosis.

Endometrial Tuberculosis

The development of endometrial tuberculosis is related to that of pulmonary tuberculosis. Dissemina-

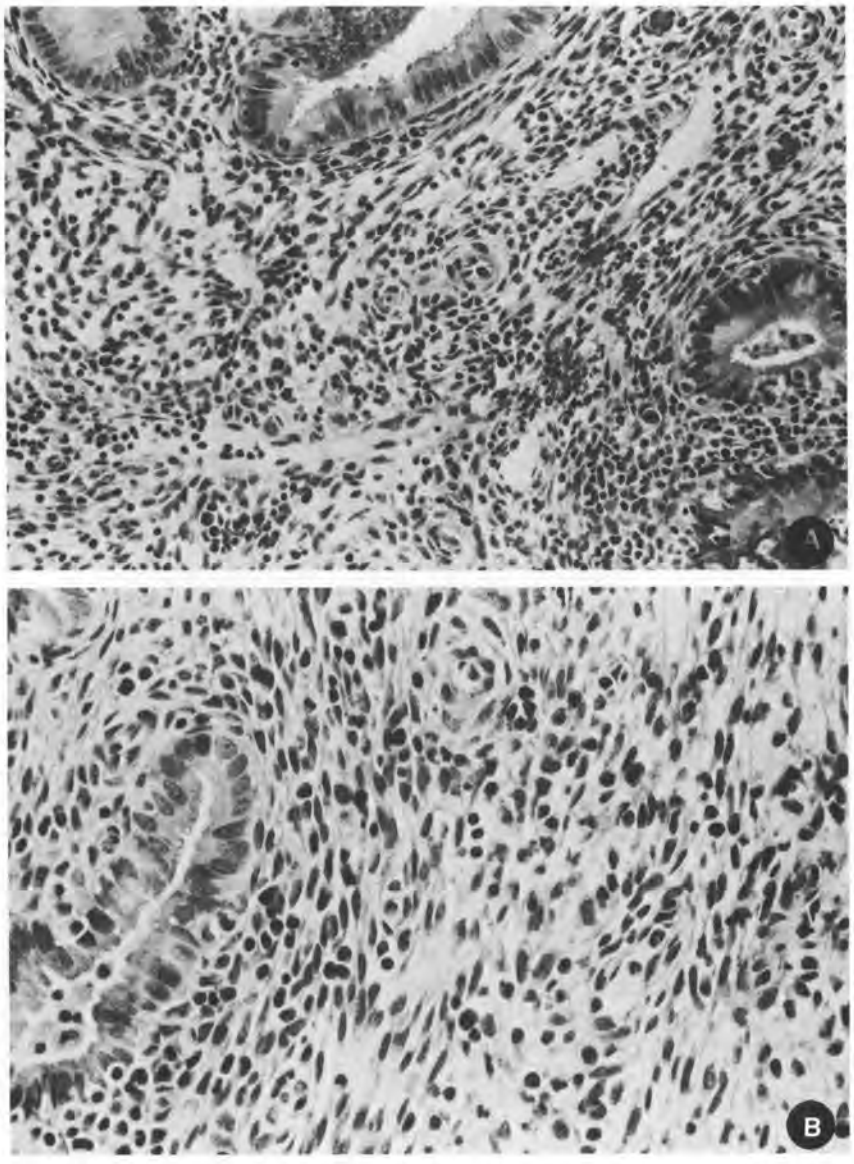

FIGURE 4-54 Chronic endometritis. **A** and **B** are from different cases, but both show spindled and edematous stroma infiltrated by lymphocytes and plasma cells. **B** also shows some reactive atypia of an endometrial gland.

tion takes place by the hematogenous route. Endometrial localization is, in the great majority of cases, secondary to a tubal lesion and represents the second most frequent genital site of this infection. It is found most commonly in young women between 15 and 40 years of age and is very rare after the menopause.[160]

Endometrial tuberculosis is often asymptomatic and may be discovered in the course of a routine gynecologic examination, often performed because of sterility.

Sharman[161] detected 216 cases of endometrial tuberculosis among 3804 cases of sterility, an incidence of 5.6%. Sutherland[162] found the incidence of tuberculosis to be 1.1% among 5521 curettages and 1.4% among 864 hysterectomy specimens. However, the incidence is considerably lower today in most Western countries.

The most readily observed *symptoms* are amenorrhea, menorrhagia, and rarely metrorrhagia. Sterility is the rule, with only rare exceptions. Peritoneal dissemination should be searched for, because this is a possible complication.

The *macroscopic appearance* of the mucosa is not always typical and may not be particularly suspicious. Occasionally, small yellow miliary granulomata are visible grossly on the mucosal surface. At an advanced stage of the disease, caseous abscesses may be seen in the mucosa and the myometrium.

The *microscopic appearance* is characterized by the presence of a granuloma rich in epithelioid cells surrounded by lymphocytes and containing Langhans-type giant cells in variable number (Fig. 4-56). Caseation is rare. These tubercles are found throughout the mucosa. In many cases, all the classic elements of the granuloma may not be present; there may be epithelioid cells without giant cells or without the surrounding crown of lymphocytes, or per-

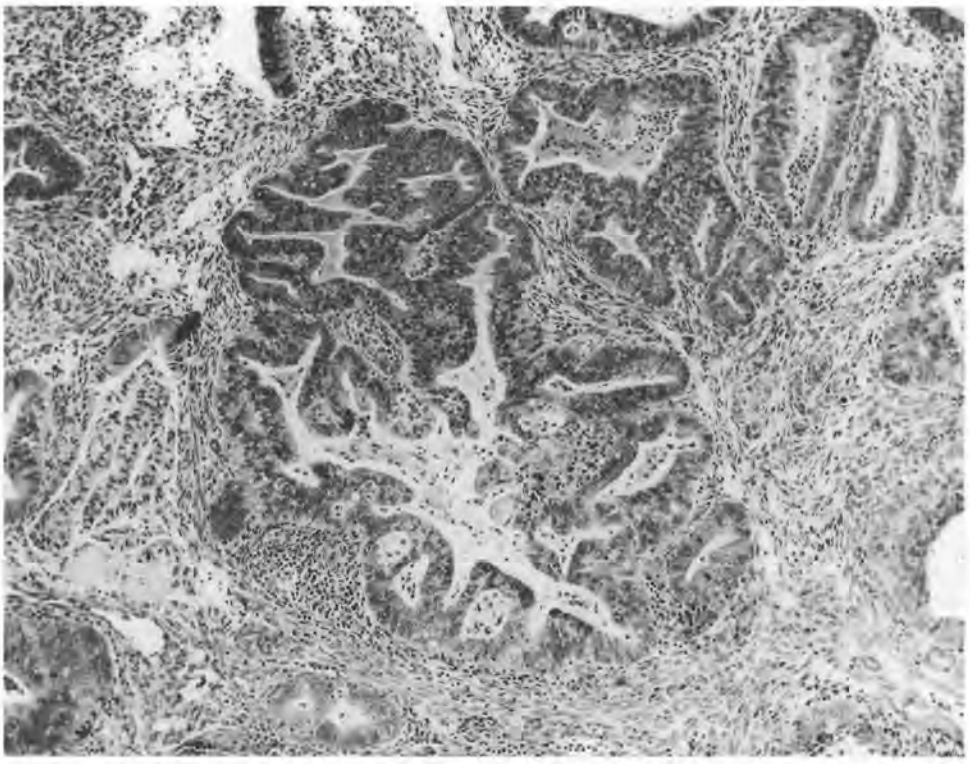

FIGURE 4-55 Chronic endometritis with marked reactive architectural atypia of endometrial glands.

haps even just diffuse lymphoplasmacytic infiltrates in the stroma and in dilated gland lumina.[163,164] In cases of sterility, these latter lesions should incite a careful search for typical granulomata, either in new sections of the original pathologic material or in a repeat biopsy. The demonstration of acid-fast bacilli by histologic means is usually impossible, and culture of the endometrium and its inoculation into the guinea pig remain indispensable for confirmation of the tuberculous nature of the lesion. Accordingly, when this diagnosis is a likely possibility, a portion of the curettings should be sent for these cultural studies rather than fixed in toto in formalin or similar material for microscopic study. Because the granulomata take up to 2 weeks to develop and are most frequently seen in the spongiosa and compacta, which are shed every 4 weeks, curettage should be performed during the premenstrual or menstrual phase.[164]

In any case of endometritis, but particularly those of tuberculous etiology, marked atypical proliferation of endometrial glands may be present. This should not be confused with a true hyperplasia or even carcinoma of the endometrium.

Viral Endometritis

Rare cases of intranuclear inclusions associated with chronic or acute endometritis have been reported in cases of herpes simplex[165] and cytomegalovirus.[166] These may be important as causes of abortion or perinatal infection. Dardi and colleagues[117] have pointed out that nuclear pseudoinclusions similar to viral inclusions may be seen in some cases of Arias-Stella phenomenon and should not lead to confusion with viral endometritis.

Endometritis Associated with Intrauterine Contraceptive Devices

IUDs may induce a focal acute or chronic inflammatory response, which may be diffuse or limited to the endometrium immediately beneath the device. Of considerably more importance is pelvic infection in some IUD users by *Actinomyces* species, particularly *Actinomyces israelii*.[99,100] The organisms typically present as isolated, irregular, spidery, dark brown to black bodies (Fig. 4-57). Also encountered are filamentous forms and "sulfur granules" consisting of a dense central mass of tangled hyphae surrounded by peripheral, radiating, club-shaped filaments. Because other organisms and even debris from the IUD surface may simulate this morphology, Gupta[99] has recommended that the diagnosis be confirmed by a fluorescent antibody technique.

In about 10% of IUD users, *Actinomyces* organisms are seen on vaginal smears.[99] Some of these women develop significant pelvic infections, particularly salpingitis, which is often unilateral. This complication is discussed in more detail in Chapter 5.

Other Causes of Endometritis

Virtually every organism has at one time or another been reported as a cause of at least a single case of endometritis. In addition to the organisms already

mentioned, these include *parasites*,[155,167,168] the most important of which worldwide are schistosomal, and various *fungi*,[169] the endometrial localization of which is generally an incidental finding in a case of widely disseminated infection. These organisms all produce granulomatous endometritis, as does *sarcoidosis*.[170] Granulomatous endometritis may also be caused by foreign bodies, particularly talc.

Malacoplakia[171] has been reported in the endometrium, although it is more frequently seen in the urinary or intestinal tract. It presents as a xanthogranulomatous inflammatory process, in which Michaelis-Gutmann bodies (intracellular and extracellular calcific spherules) are found. The etiology is thought to be bacterial. Cases of xanthogranulomatous or histiocytic endometritis without

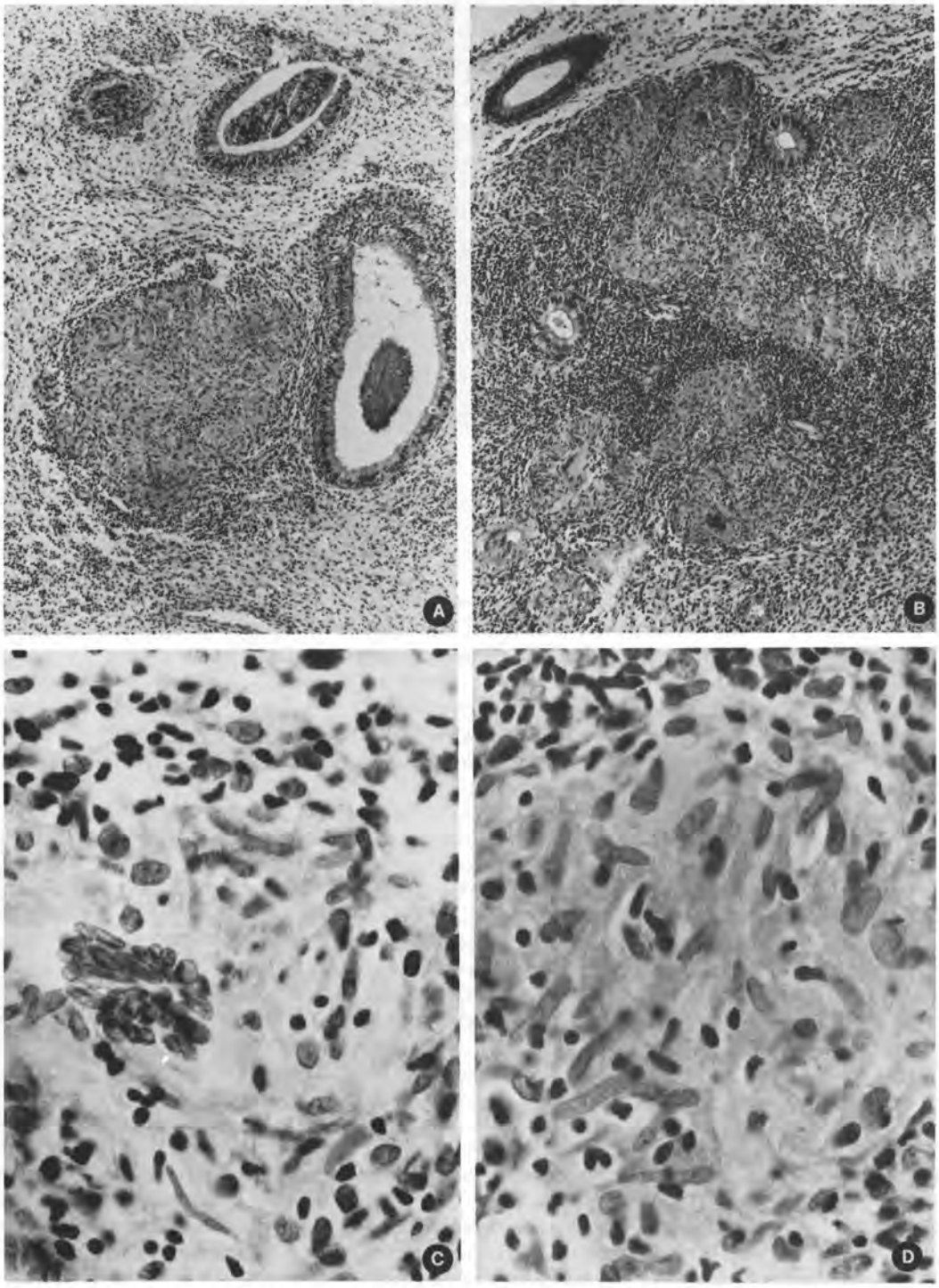

FIGURE 4-56 Endometrial tuberculosis. **(A,B)** Noncaseating giant cell granulomata. **(C,D)** Detail of epithelioid cells and giant cells.

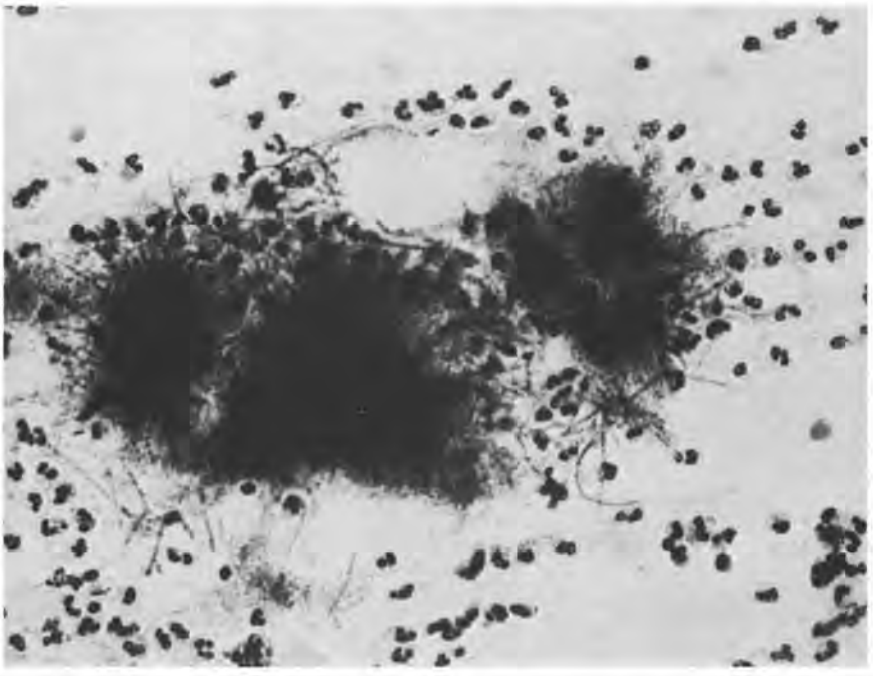

FIGURE 4-57 *Actinomyces* organisms in Papanicolaou-stained cervicovaginal smear from an IUD wearer. These dense "spidery" bodies are the most common pattern in which the organisms are encountered. (Gupta PK: Intrauterine contraceptive devices: Vaginal cytology, pathologic changes and clinical implications. Acta Cytol 26:571–613, 1982)

Michaelis-Gutmann bodies are probably of similar origin.[172]

Vasculitis

A rare inflammatory lesion of the uterus, as well as other portions of the female genital tract, is arteritis, which is usually diagnosed incidentally in specimens received for other clinical indications.[173,174] These lesions may represent an isolated finding of no clinical significance or be part of a generalized vasculitis, which is often previously undiagnosed. Based on a literature review of 35 cases in addition to their 2 cases, Bruch and colleagues[174] suggest that granulomatous arteritis is usually a systemic disease requiring corticosteroid therapy, whereas necrotizing arteritis of polyarteritis type (Fig. 4-58) is most often an isolated finding requiring no treatment. Bell and colleagues, however, report 3 cases of extensive giant cell arteritis of the female genital tract, of which one required systemic treatment and one was asymptomatic for 17 years after surgery without any intervening treatment.[173]

ADENOMYOSIS

Adenomyosis consists of endometrial glands and stroma within the myometrium. It is frequently called *endometriosis interna* to differentiate it from endometriosis externa, which is characterized by the presence of extrauterine localizations of similar benign endometrial glands and stroma. Because the latter is an extrauterine disease, the most frequent localizations of which are related to peritoneal mesothelium, it is discussed in Chapter 7 on the female peritoneum. However, the uterine serosa and immediately subserosal myometrium may be involved by endometriosis externa, so not every case of deeply situated endometrium in the uterine corpus represents adenomyosis.

Definition

Because the junction of endometrium and myometrium in a normal uterus is often irregular, multiple sections of most uteri show endometrial glands and stroma penetrating at least superficially into the myometrium. Therefore, the definition of adenomyosis is arbitrary, and the depth of penetration required for the diagnosis determines such factors as the frequency of the condition and its clinical significance. We generally use the dividing line of one medium-power (× 100) microscopic field below the endometrial–myometrial junction as the distinction between "physiologic" penetration of endometrium into the myometrium and the "disease" of adenomyosis. Others have accepted either shallower or deeper penetration. In the former case, adenomyosis is seen in most hysterectomy specimens and is of little clinical significance, whereas in the latter it is a relatively rare diagnosis usually associated with characteristic clinical findings and gross uterine enlargement.[175–180]

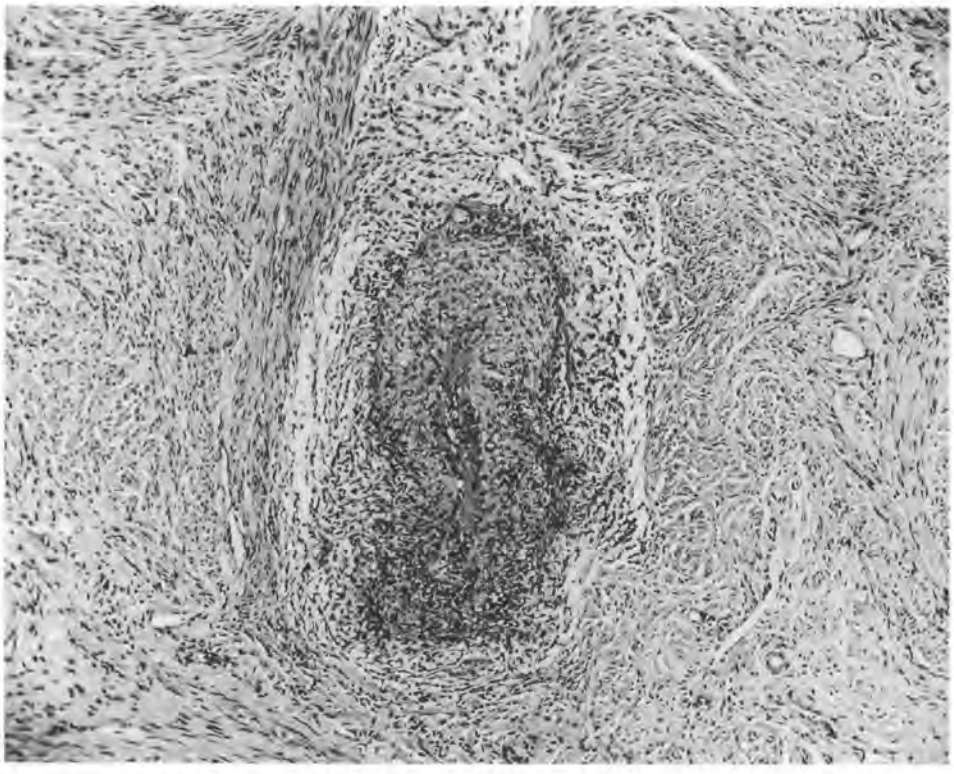

FIGURE 4-58 Isolated necrotizing angiitis in myometrium.

Frequency and Clinical Presentation

Reported frequencies of adenomyosis in hysterectomy specimens vary from less than 10% to greater than 50%. In our own material, because of the diagnostic criteria that we apply, the figure is probably closer to but slightly above the lowest reported.

If one accepts such a low prevalence figure, adenomyosis will frequently be a symptomatic disease. It occurs primarily in women in the reproductive years, and it is most commonly associated with abnormal menstrual bleeding, dysmenorrhea, uterine enlargement, and occasionally infertility. However, because adenomyosis is associated with endometriosis externa in about 15% of cases, and with uterine myomata in more than 50%,[179] it is often difficult to know to which lesion to ascribe the symptoms. Because of the nonspecificity of these symptoms, and because many women with adenomyosis have no symptoms whatsoever, the diagnosis usually is not made preoperatively.[178]

Pathogenesis

In most instances, adenomyosis appears to represent a diverticulosis of endometrium into the myometrium. Thus, serial sections of the uterus frequently show that the islands of endometrium that appear to be isolated deep in the myometrium are actually in contact with the overlying endometrium. Some cases, however, may arise by metaplasia from multipotential mesenchymal cells located around blood vessels within the myometrium.

Macroscopic Appearance

The uterus is of normal size in 20% to 25% of cases, and in many of the others the enlargement is at least partly due to associated myomata. However, some cases may show massive enlargement without any other disease. In these instances, the enlargement is symmetrical and occurs primarily as a result of smooth muscle hypertrophy around the deep-seated islands of endometrium.

In some cases, the lesions may be grossly visible as small pink or gray-white zones that are less dense and less firm than the surrounding myometrium. In rare cases, these foci are dark red as a result of hemorrhage. Small cysts are occasionally seen. If the lesion is solitary and focal, it is sometimes called an *adenomyoma*.

Microscopic Appearance

The endometrium seen within the myometrium is generally inactive or proliferative and only rarely shows functional changes consonant with the ovarian hormonal cycle and with the appearance of the over-

lying normal endometrium. This histologic appearance correlates with the observation by Tamaya and associates that estrogen receptors are always present in foci of adenomyosis but progesterone receptor levels are low or absent.[181] In pregnancy, foci of adenomyosis may show glandular secretions and decidual stroma.[182]

Because of the lack of hormonal response, neither fresh hemorrhage nor deposits of hemosiderin pigment are generally seen in adenomyosis, as they usually are in endometriosis externa. Hyperplastic smooth muscle fibers are usually seen around the ectopic endometrial glands and stroma. The ultrastructural appearance of adenomyotic glandular epithelium is said to be less differentiated than that of normal proliferative endometrium.[183]

Malignant Transformation

Ectopic endometrium, whether in adenomyosis or endometriosis externa, shares with normally situated endometrium the ability to undergo hyperplastic or malignant change. To accept a carcinoma as having arisen within adenomyosis, the overlying endometrium must be thoroughly sampled to prove that it is not involved, and such cases are rare.[184]

Much more frequent is the extension of a carcinoma arising in the overlying endometrium into the islands of adenomyosis. In these instances, the nests of carcinoma within the myometrium have rounded rather than irregular contours, and residual benign endometrial stroma may be seen at their periphery. The poor prognosis generally associated with true deep myometrial invasion is not present.[184,185]

The term *stromal endometriosis* has been used in the past to describe intramyometrial lesions composed of benign-appearing endometrial stromal cells without glands. Although it was once assumed that these represented a variant of adenomyosis that might demonstrate malignant behavior, it is now generally accepted that these lesions represent low-grade endometrial stromal sarcoma, which is discussed later in this chapter.

BENIGN TUMORS

Leiomyoma

The leiomyoma is a very common benign uterine tumor found in about 40% of women after the age of 35 years.[186] Synonyms are *fibroma, myoma,* and *fibroid.* This tumor is often called *fibroma,* and usage has consecrated this false term. In reality, the tumor takes its origin in the smooth muscle fibers of the myometrium.

The *pathogenesis* is not clear. There does not seem to be any hereditary factor, but its demonstration would be difficult because of the great frequency of the tumor.[187] Certain clinical facts suggest the existence of a hormonal factor: the tumor appears during the period of genital activity and stabilizes or regresses after the menopause. It sometimes increases in size and demonstrates atypias during pregnancy or administration of oral contraceptives.[188,189] Serum growth hormone and estradiol levels are elevated in women with myomata,[190] and estrogen and progesterone receptors have been demonstrated in the tumors.[191,192] Attempts to reproduce the tumor experimentally using hormones have met with partial failure. The appearance of disseminated fibromatous tumors in the abdominal cavity of the guinea pig and the rabbit has been provoked by the administration of estrogens.[193] However, these experimental tumors have not been morphologically identical to human uterine leiomyomata; they are fibromas rather than myomas. The regression of the tumor after the menopause and after the administration of a gonadotropin-releasing hormone agonist (Lupron)[194,195] may not be a hormonal phenomenon but rather may be explicable by vascular involution; the shrinkage of leiomyomas after radiation therapy is at least in part the result of the same mechanism. Additional evidence of at least partial hormone dependence of these tumors is provided by studies showing increased mitotic activity during the secretory phase of the menstrual cycle[196,197] and ultrastructural evidence of increased differentiation (myofilaments, dense bodies) in leiomyoma cells cultured with estrogen and progesterone added to the media.[198] To conclude, we may say that sex steroid hormones influence the growth of the leiomyoma but that we can not conclusively affirm that they bring about its original appearance.

Other substances such as growth factors have been suggested to play a role in tumorigenesis.[187] Cytogenetic studies have demonstrated clonal chromosomal abnormalities in one-third to one-half of leiomyomas, but numerous different abnormalities are found.[199,200] The demonstration that uterine leiomyomas are less commonly found in the cervix and more commonly in the fundus than would be expected based on the intrauterine distribution of normal smooth muscle has been presented as a possible clue to histogenesis.[192] Nevertheless, the origin of this common tumor is still in doubt.

Clinical Signs. Many asymptomatic myomata are discovered during a routine gynecologic examination. Others are manifested by the following symptoms: pain, menorrhagia or metrorrhagia, dysmenorrhea, urinary disturbances, and constipation. The most frequent complications are compression of neighboring organs, torsion, and necrosis. Fetal death as a result of compression has been described (Fig. 4-59). Spontaneous abortion and infertility are frequent associations,[186] and abruptio placentae, intrapartum increased pain, and premature labor have been reported as clinically significant complications during pregnancy.[201]

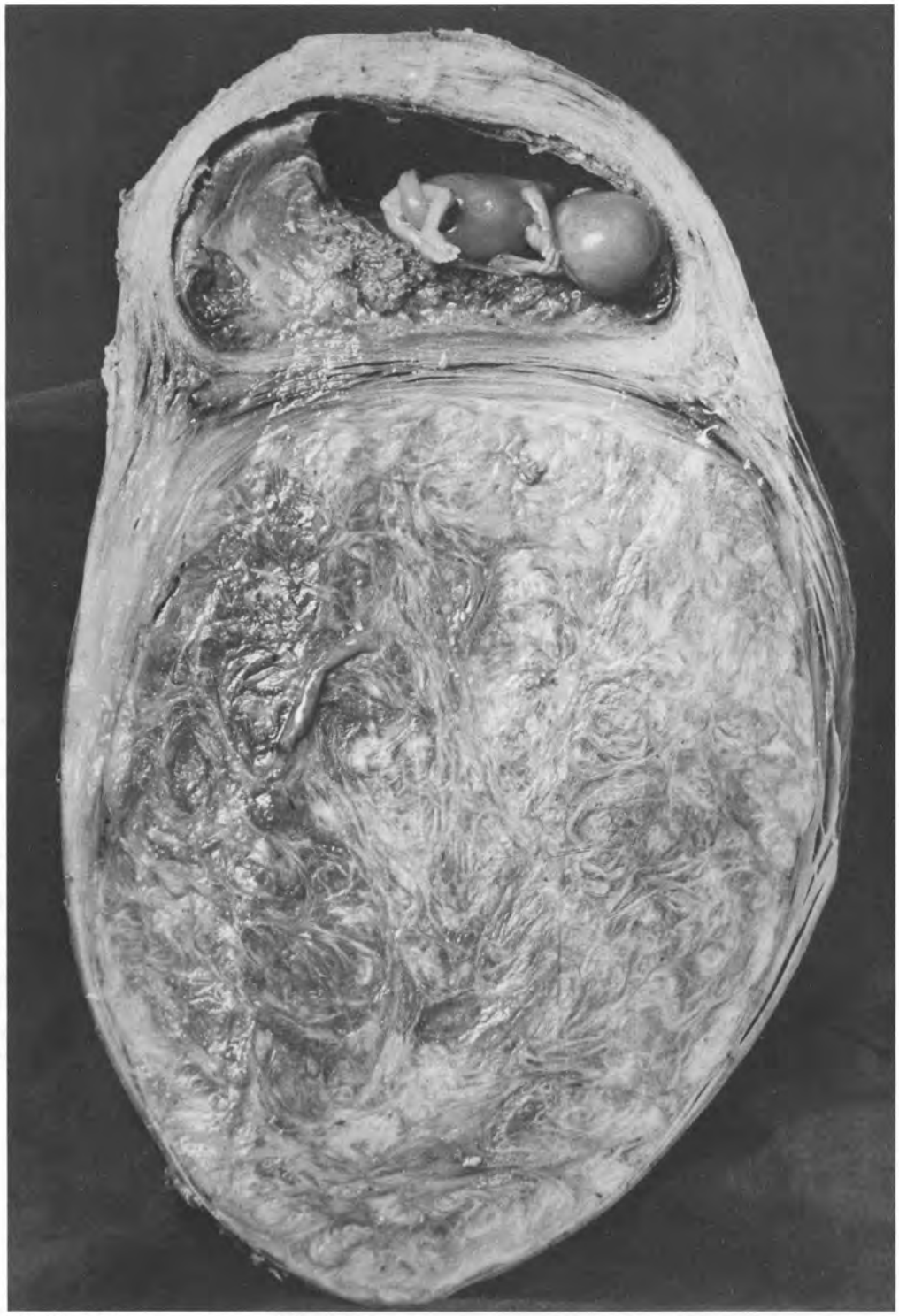

FIGURE 4-59 Leiomyoma and dead fetus.

Macroscopic Appearance. The uterine myoma is spherical, firm and elastic in consistency, and white. Sections through it show pearly tissue, with the typical appearance of whorled bundles of smooth muscle fibers (Fig. 4-60). These are separated by a connective tissue stroma that varies in quantity. Hemorrhagic and necrotic foci are identified by their dark red or yellow color and their softer consistency. Hyalinized or calcified nodules are frequently seen; their number and size vary greatly from one case to another. Myomata sometimes attain a size of 20 cm or more in diameter. They are usually multiple but may be solitary.

Submucous leiomyomata are the least frequent.

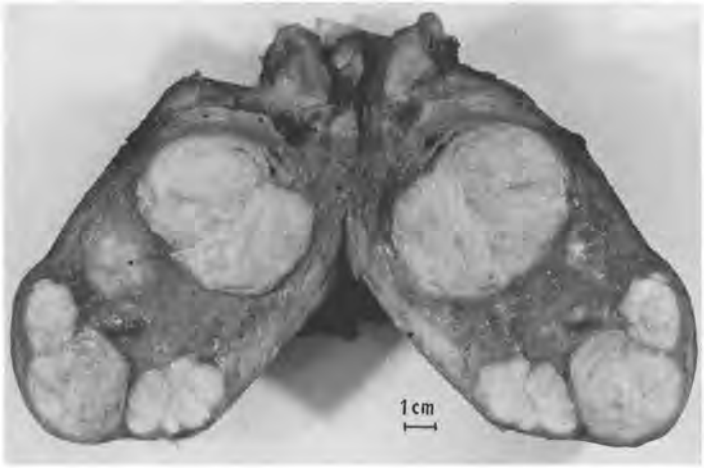

FIGURE 4-60 Intramural leiomyomata.

They often cause significant uterine hemorrhages. They are occasionally pedunculated and may prolapse into the cervical orifice of the vagina. Their mass causes phenomena of compression, and they often become superficially ulcerated, necrotic, and inflamed.

Intramural myomata are not detected when they are small; when large, they bulge under the mucosa or the serosa. They are the most frequent leiomyomata (see Fig. 4-60).

Subserous myomata herniate beneath the peritoneal serosa and are frequently pedunculated. If the pedicle is long, the tumor floats in the peritoneal cavity. It may undergo torsion or rupture, and in the latter case the tumor becomes migratory or aberrant and may adhere to other intra-abdominal organs, from which it receives a new vascular supply (*parasitic myoma*). Also seen are leiomyomas of the broad ligament, which are difficult to distinguish clinically from an ovarian mass (Fig. 4-61).

Microscopic Appearance. The leiomyoma consists of anastomosed and whorled fascicles of fusiform cells of uniform size. The nuclei are elongated and their extremities rounded (Figs. 4-62 and 4-63). Mitoses are not frequent. Blood vessels are small and not numerous. Between the bundles of smooth muscle fibers are found variable amounts of fibrous connective tissue. When the tumor is richly cellular, it must not be confused with leiomyosarcoma; the absence of bizarre cellular atypia, infiltrative borders, and numerous mitoses facilitates the identification of the lesion as benign.

Leiomyomas may present several types of degenerative histologic transformation: hemorrhage, necrosis, hyalinization, fibrosis, and calcification. Hyaline degeneration appears grossly as a smooth, homogeneous, translucent zone; if it is located interstitially, it is difficult to recognize grossly. Histologically, it consists of eosinophilic bands infiltrating the muscle bundles or of homogeneous plaques in which all cellular structure has disappeared. When the hyalinized zones present liquefaction and edema, there appear gelatinous and myxoid plaques or even cystic cavities measuring up to several millimeters in diameter. Calcification is particularly frequent after liquefaction, hemorrhage, or necrosis.

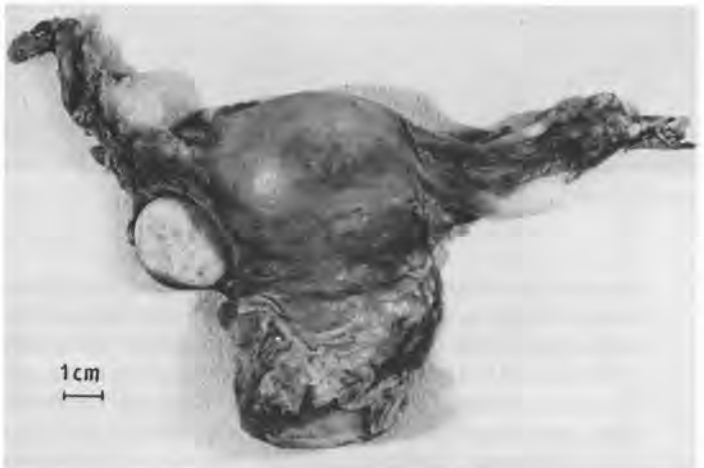

FIGURE 4-61 Leiomyoma of broad ligament.

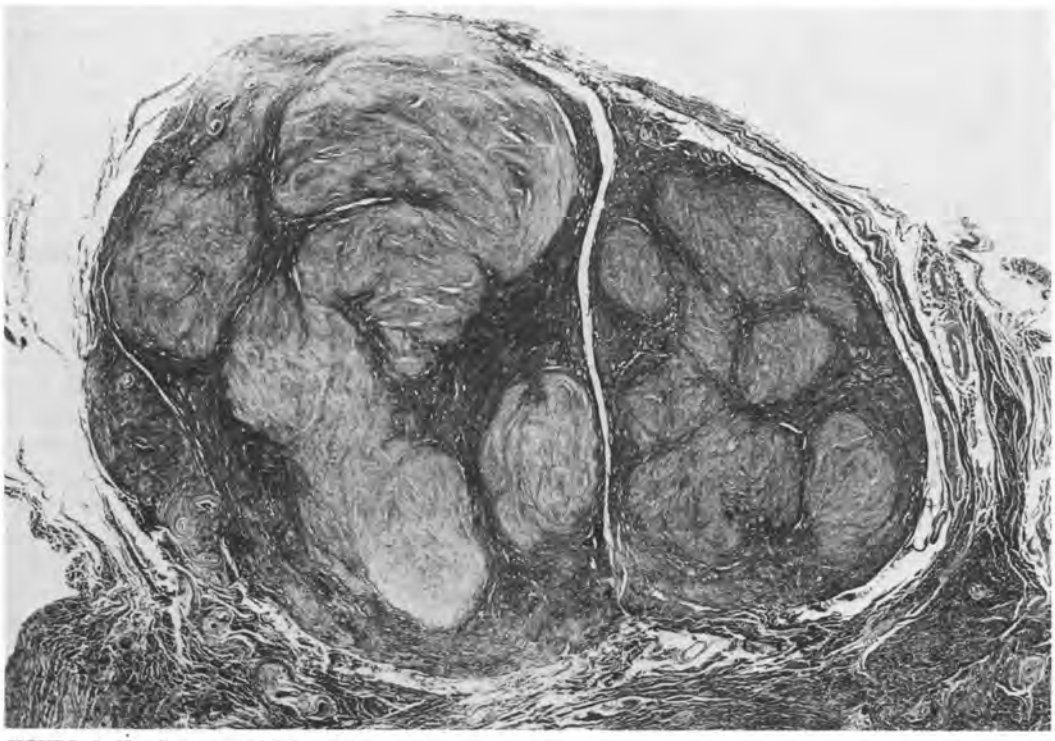

FIGURE 4-62 Intramural leiomyoma.

Often seen in association with these degenerative changes are symplastic giant cells (*bizarre, symplastic,* or *pleomorphic leiomyoma*; Fig. 4-64). These may be mono- or multinucleate and are characterized by large, often monstrous, hyperchromatic nuclei that appear degenerative rather than malignant. The invariable absence or paucity of mitotic figures, the absence of tumor necrosis, the usual youth of the patient, and the frequent history of pregnancy or oral contraceptive usage all help in the differential diagnosis from leiomyosarcoma.

Certain other histologic changes occasionally seen in leiomyomata may represent manifestations of the metaplastic capabilities of the cell of origin. These include foci that, at the light microscopic level, resemble neurilemoma[202] or hemangiopericytoma.[203] Also seen are smooth muscle tumors containing foci of adipose tissue (*lipoleiomyoma*)[204–206] of endometrial stroma, or of tubular or cord-like structures that may be reminiscent of ovarian sex cord elements (Fig. 4-65).[207,208] Sex cord–like structures may also be seen in endometrial stromal tumors or may form tumors with no obvious muscular or stromal differentiation, so a classic leiomyomatous component must be observed for the diagnosis of leiomyoma with sex cord–like foci. Devaney and

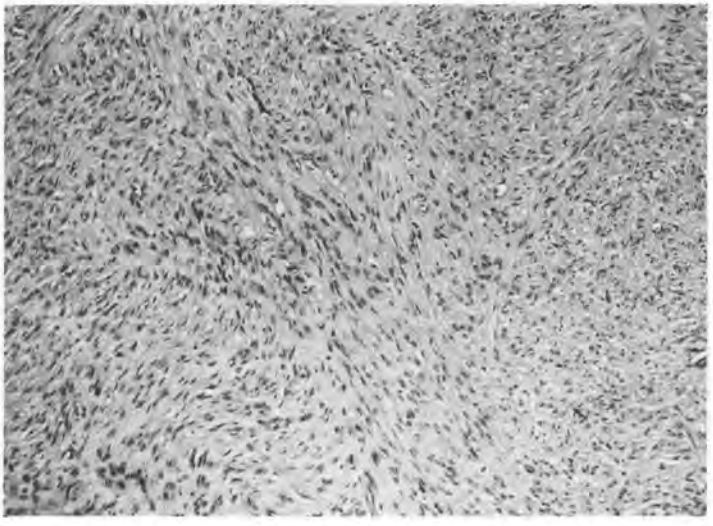

FIGURE 4-63 Leiomyoma: detail of histologic structure.

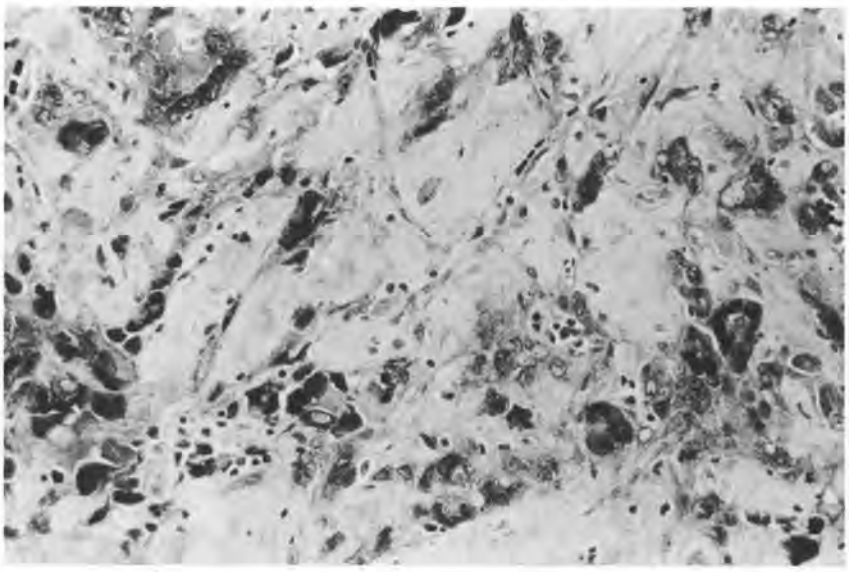

FIGURE 4-64 Symplastic giant cells in leiomyoma with edema and hyalinization.

Tavassoli[209] have claimed on the basis of immunohistochemical studies that all sex cord–like tumors are combined smooth muscle and endometrial stromal tumors.

Endometrial Changes in the Presence of a Leiomyoma. The mechanical compression exerted by a submucous leiomyoma causes atrophy of the overlying endometrium. The glands are flattened and lined by cuboidal and flat epithelium. There is no secretory activity. The stroma is dense and formed of small round cells. Dilated venous spaces are present throughout the endometrium. The picture of irregular shedding (see above) has been described in these cases.

Evolution and Treatment. Sarcomatous transformation is rare but should be systematically searched for in any smooth muscle tumor that increases rapidly in volume, particularly after the menopause, or that grossly shows softening, hemorrhage, or cystic degeneration. Liebsohn and colleagues found unsuspected leiomyosarcoma in 1% of a series of hysterectomies performed for presumed leiomyomas.[210] Symptomatic leiomyomata are classically treated by myomectomy (if uterine preservation is desired)[211] or

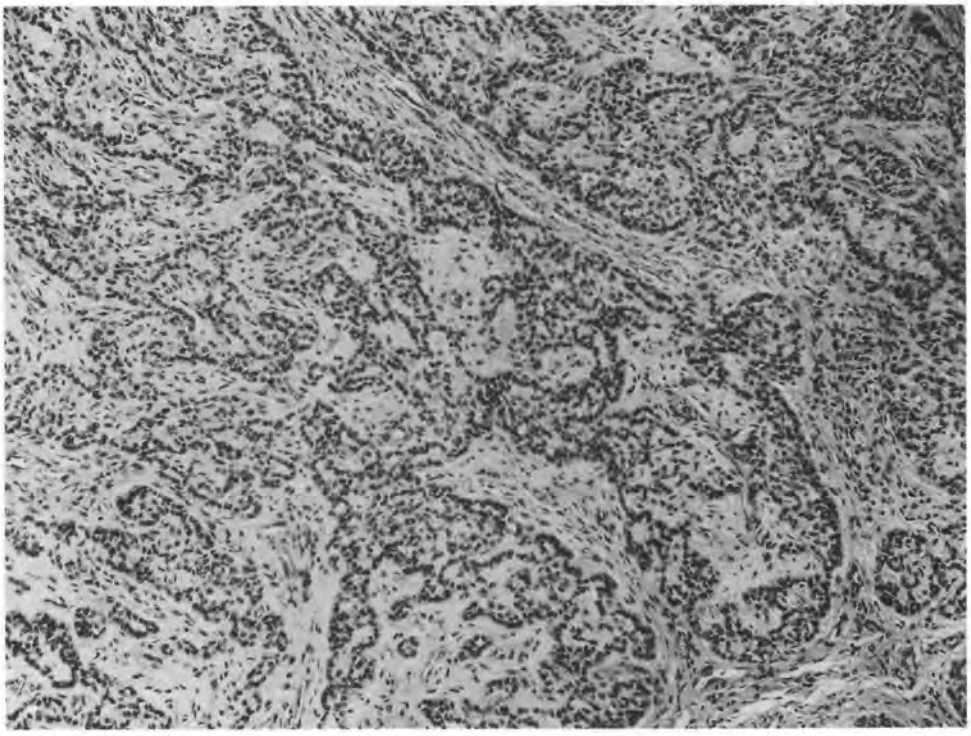

FIGURE 4-65 Uterine leiomyoma with sex cord–like differentiation.

hysterectomy, but recent therapeutic alternatives include medical treatment with a gonadotropin-releasing hormone agonist (Lupron),[194,195] hysteroscopic resection,[212] and Lupron followed by hysteroscopic laser devascularization of the tumor.[213] Recurrences have been reported in 15% of cases treated by myomectomy.[214]

Variants of Leiomyoma

The ISGP classification of uterine smooth muscle tumors (Table 4-3) includes several histologic variants (lipoleiomyoma and cellular, epithelioid, and bizarre leiomyomas) and variants characterized by an unusual growth pattern (metastasizing leiomyoma, intravenous leiomyomatosis, and diffuse leiomyomatosis).[215,216] *Lipoleiomyoma* and *bizarre (symplastic) leiomyoma* have been discussed above. *Cellular leiomyoma* is defined as a benign smooth muscle tumor that is significantly more cellular than the surrounding myometrium. Because the interpretation of "significantly" varies from one pathologist to another, the relative frequency of these tumors varies. The important fact to remember is that these tumors are differentiated from leiomyosarcoma by their bland nuclear appearance and lack of notable mitotic activity. The remaining variants will be discussed in the following paragraphs.

Epithelioid Leiomyoma. Muscle fibers may undergo modifications that cause them to resemble epithelial elements,[217] sometimes during pregnancy. In the *leiomyoblastoma* variant, the cells may be nested in a hyalinized stroma, the nuclei are voluminous and round, and the cytoplasm becomes strongly eosinophilic and homogeneous (Fig. 4-66).[218,219] A *clear cell* type is characterized by cells with voluminous clear cytoplasm (Fig. 4-67).[217,220]

These epithelioid leiomyomas are probably analogous to similar tumors described originally in the stomach and, like their gastric counterparts, may occasionally behave malignantly.[216,217] Because the tumors by definition are virtually all markedly atypical histologically, it is difficult to predict which will metastasize; however, frequent mitotic figures and evidence of local aggressiveness are helpful features. The origin of the clear vacuoles seen in the cytoplasm of the clear cell leiomyomas is controversial, but one ultrastructural study has suggested that they are derived from swollen mitochondria.[219]

The third category of epithelioid leiomyoma is the plexiform type, usually called *plexiform tumorlet.* These small lesions, usually incidental findings in uteri removed for other reasons, were first reported by Borghard-Erdle and Hirsch[221] and were subsequently reported under a variety of names, reflecting the lack of unanimity on their histogenesis. Ultrastructural studies have subsequently shown them to be of smooth muscle origin,[222] and indeed plexiform foci may be found within otherwise typical smooth muscle tumors of the uterus. When they occur as separate lesions, they are small, usually solitary but occasionally multiple, well localized but unencapsulated, and usually found in the myometrium near its junction with the endometrium. Histologically, they are composed of randomly oriented rows or plexiform masses of uniform small cells with clear vesicular nuclei, separated by abundant connective tissue stroma (Fig. 4-68). All plexiform tumorlets reported have been benign.[215,223]

Intravenous Leiomyomatosis. Intravenous leiomyomatosis has as a typical feature worm-like masses within the veins of the uterus and broad ligaments.[224–226] This gross picture resembles that of low-grade endometrial stromal sarcoma. However, these masses are not composed of endometrial stromal tissue but rather of intermingled smooth muscle and fibrous tissue containing very prominent small blood vessels. The masses are often lobulated by the presence of small clefts and show none of the whorled pattern that is so common in the "usual" leiomyoma. No significant cellular atypia is seen in the usual case, and mitoses are rare. The cases reported have almost all been associated with "typical" myomas, but controversy rages over whether the intravenous myomatous tissue arises from invasive uterine myomas or from the vein walls themselves. Only 25% of the cases have shown extension beyond the broad ligaments, and only rare deaths have been reported, resulting from direct extension of tumor into the inferior vena cava and the right atrium. Metastases do not occur, and even when resection has been incomplete, patients usually have shown no further evidence of disease. Any of the leiomyoma variants (eg, cellular, epithelioid, bizarre) may show this intravascular growth pattern.[226,227] If mitoses are

TABLE 4-3.
Uterine Smooth Muscle Tumors

Leiomyoma
Variants:
Cellular
Epithelioid
Bizarre (symplastic, pleomorphic)
Lipoleoimyoma
Smooth muscle tumor of uncertain malignant potential
Leiomyosarcoma
Variants
Epithelioid
Myxoid
Other smooth muscle tumors
Metastasizing leiomyoma
Intravenous leiomyomatosis
Diffuse leiomyomatosis
Mixed endometrial stromal and smooth muscle tumors

Silverberg SG, Kurman RJ: Tumors of the uterine corpus and gestational trophoblastic disease. In Atlas of tumor pathology, 3rd series, fascicle 3. Washington, DC, Armed Forces Institute of Pathology, 1992

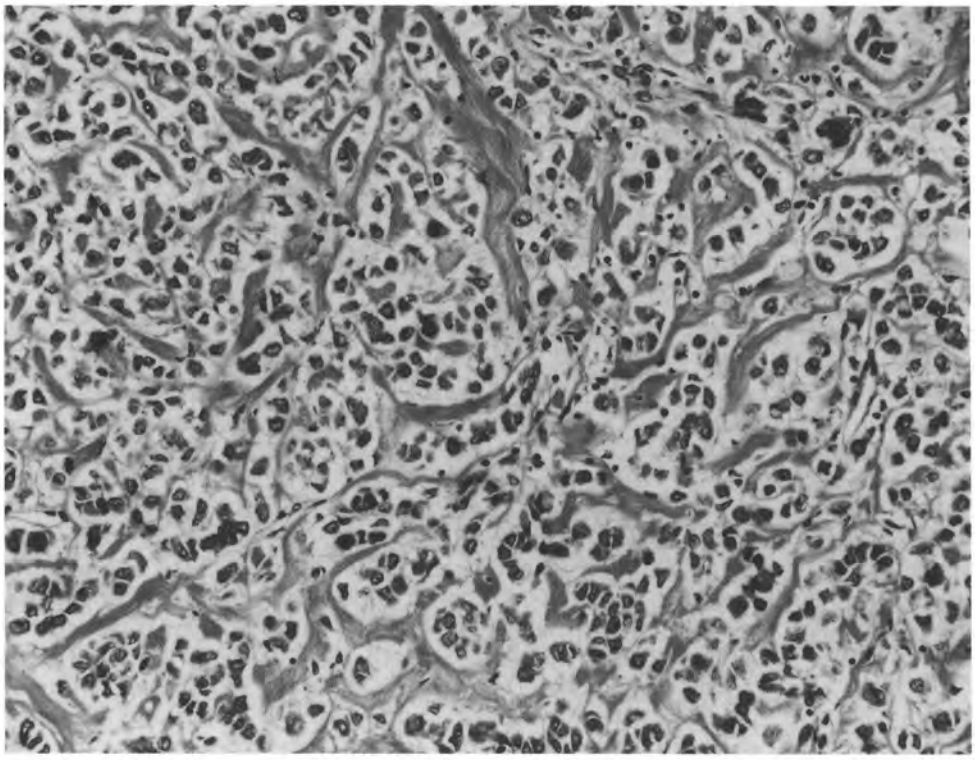

FIGURE 4-66 Epithelioid leiomyoma, leiomyoblastoma type.

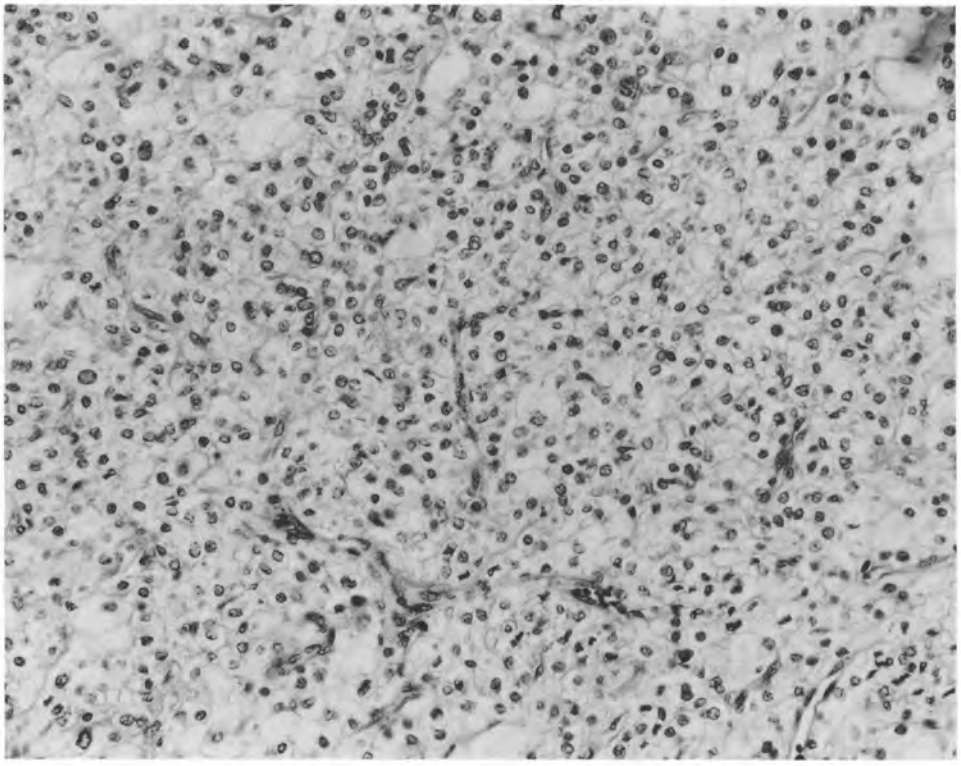

FIGURE 4-67 Epithelioid leiomyoma, clear cell type.

sparse and myometrial (rather than vascular) invasion is absent, leiomyosarcoma usually can be ruled out.

Metastasizing Leiomyoma. Metastasizing leiomyoma is equally rare, with only about two dozen cases documented.[228–230] The usual clinical history in these cases has been the appearance of pulmonary metastases several years after hysterectomy for "benign" leiomyomata. Histologic examination of both the pulmonary and uterine tumors has in each case (when both were available) demonstrated the typical cellular pattern of benign leiomyoma. The burden of proof in these cases is on the author making the assertion, and we believe that in the absence of serial sections of the entire uterus, it cannot be definitively stated that a leiomyosarcoma was not originally present; nevertheless, the published photomicrographs of the pulmonary tumors do indeed look benign, as do our cases. An alternative explanation is that the pulmonary lesions may be primary pulmonary leiomyomas. However, lymph node metastases have been reported.[228] Finally, the almost invariable history of surgery suggests iatrogenic dissemination of biologically benign tumors.

Endometrial Polyp

The endometrial polyp consists of a mass of endometrial tissue appended to the mucosa by a pedicle. Polyps are of diverse sizes, may be single or multiple, and are located in all parts of the uterine cavity. Usually they measure from 0.5 to 3 cm in diameter. They may appear long after the menopause or during active genital life.

Clinical Manifestations. Frequently, the polyp is asymptomatic and represents a fortuitous discovery during the course of a clinical examination or in the dissection of a surgical specimen. In some cases, its presence is manifested by hemorrhages. When voluminous, it may herniate at the cervical orifice, and in some cases it becomes ulcerated. Large polyps have been reported to develop in postmenopausal breast cancer patients receiving tamoxifen.[231,232]

Macroscopic Appearance. The polyp presents as a small, gray or pink, smooth-surfaced, firm mass (Fig. 4-69). It is attached to the mucosa by a stalk of variable length or may be sessile. In some cases, polyps are numerous and disseminated throughout the entire endometrial cavity.

Microscopic Appearance. The polyp is covered by a cuboidal or flattened epithelium, which is sometimes eroded. The endometrial tissue may undergo cyclic modifications, but more commonly it shows a nonfunctional appearance of discrete proliferative or atrophic type.[233,234]

Hyperplasia may be present. About 1% of polyps contain smooth muscle (*adenomyomatous polyp*). The presence of cystic glands is common, dilated thick-walled vessels are prominent, and the stroma is fibrotic, permitting the diagnosis of a polyp in material obtained by curettage, in which the stalk is not

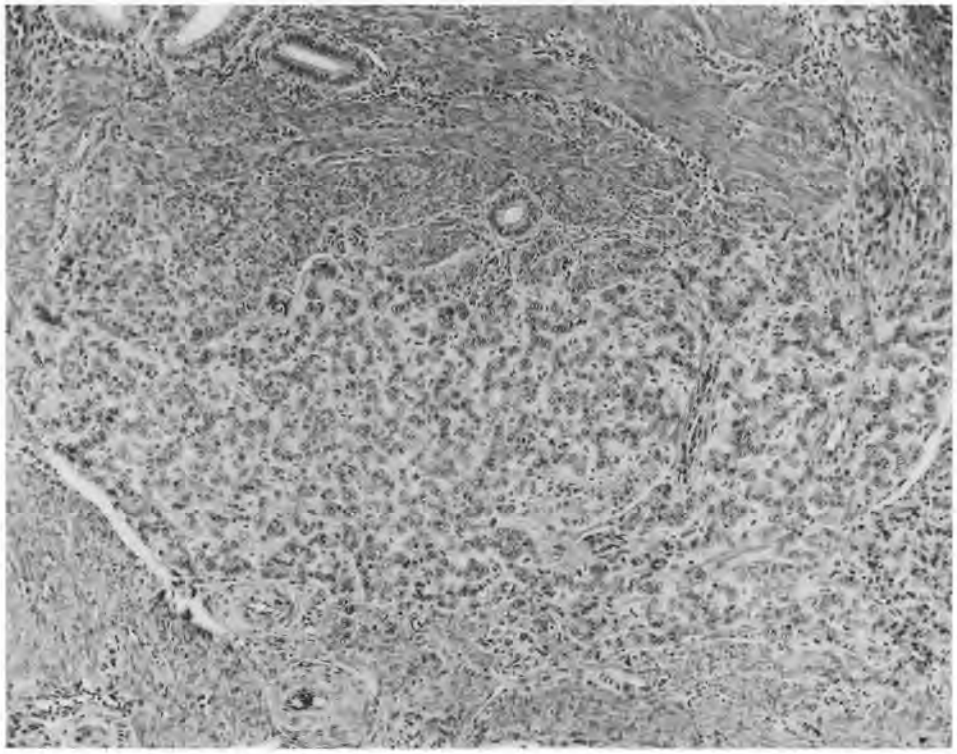

FIGURE 4-68 Epithelioid leiomyoma, plexiform tumorlet type.

visible (Figs. 4-70 and 4-71). Similar changes may be seen in a nonpolypoid configuration within the endometrium, often related to the basalis, suggesting that polyps arise as localized proliferations or hyperplasias of basalis-type endometrium. Indeed, Dallenbach-Hellweg[23] includes polyps in her discussion of endometrial hyperplasia, although many polyps, particularly in postmenopausal women, are composed of atrophic endometrium.

Prognosis, Evolution, and Treatment. The great majority of endometrial polyps are benign. Their evolution may be asymptomatic or accompanied by hemorrhagic manifestations. Focal (Fig. 4-72) or diffuse hyperplasia within the polyp is not uncommon. A small number show malignant transformation, which may or may not be limited to the polypoid mass itself. In these cases, it is difficult to determine whether one is dealing with a carcinoma that has

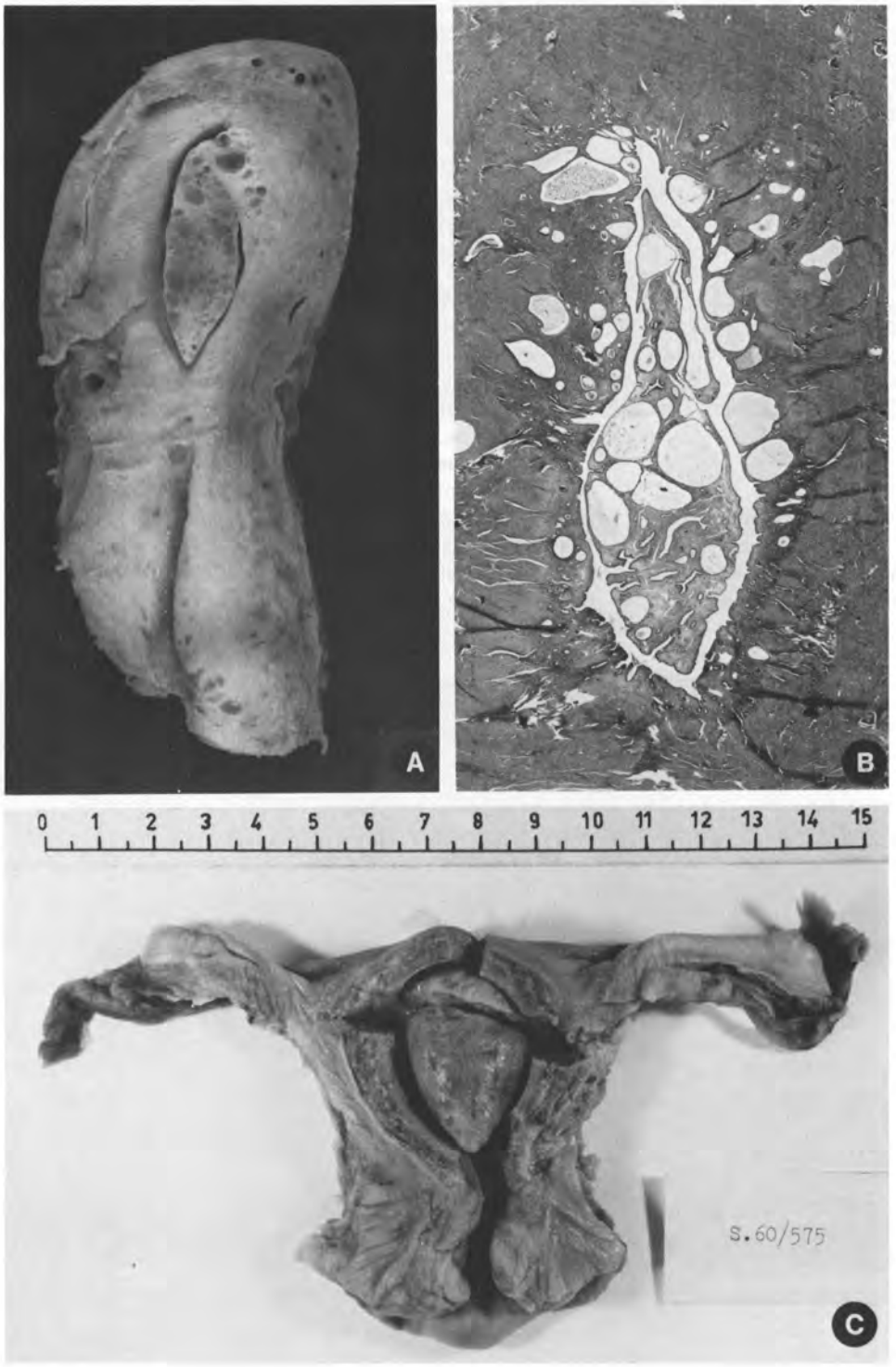

FIGURE 4-69 Endometrial polyp. **(A)** Macroscopic appearance. **(B)** Microscopic appearance of same polyp. **(C)** Macroscopic appearance in another case.

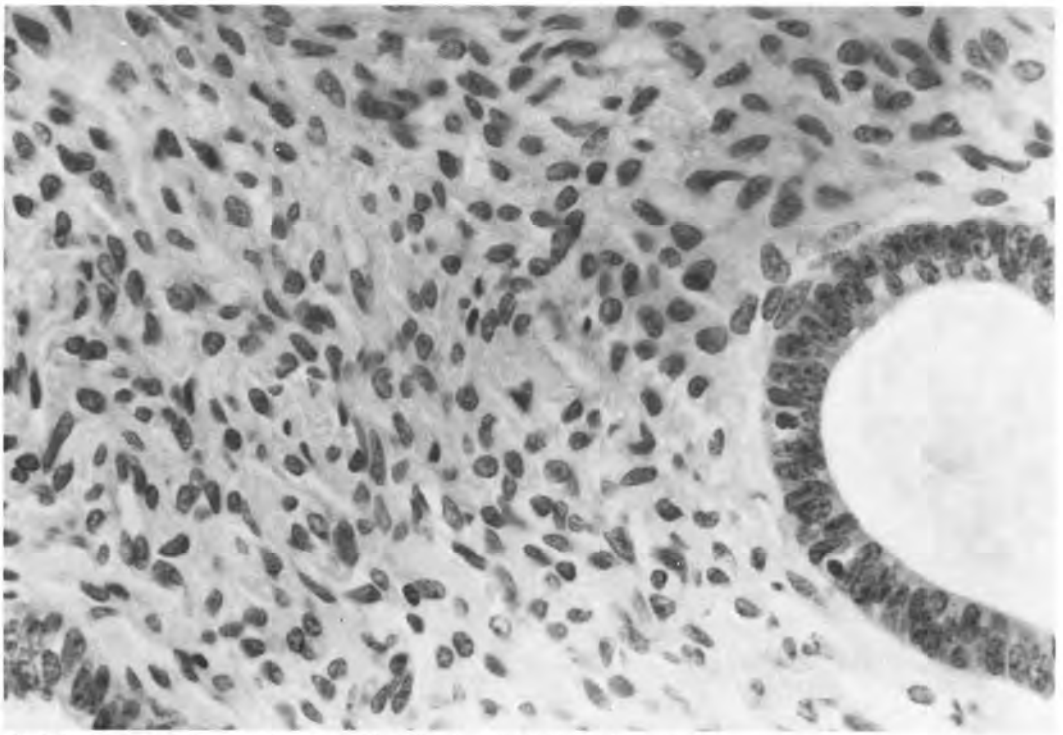

FIGURE 4-70 Endometrial polyp: fibroblastic appearance of stroma.

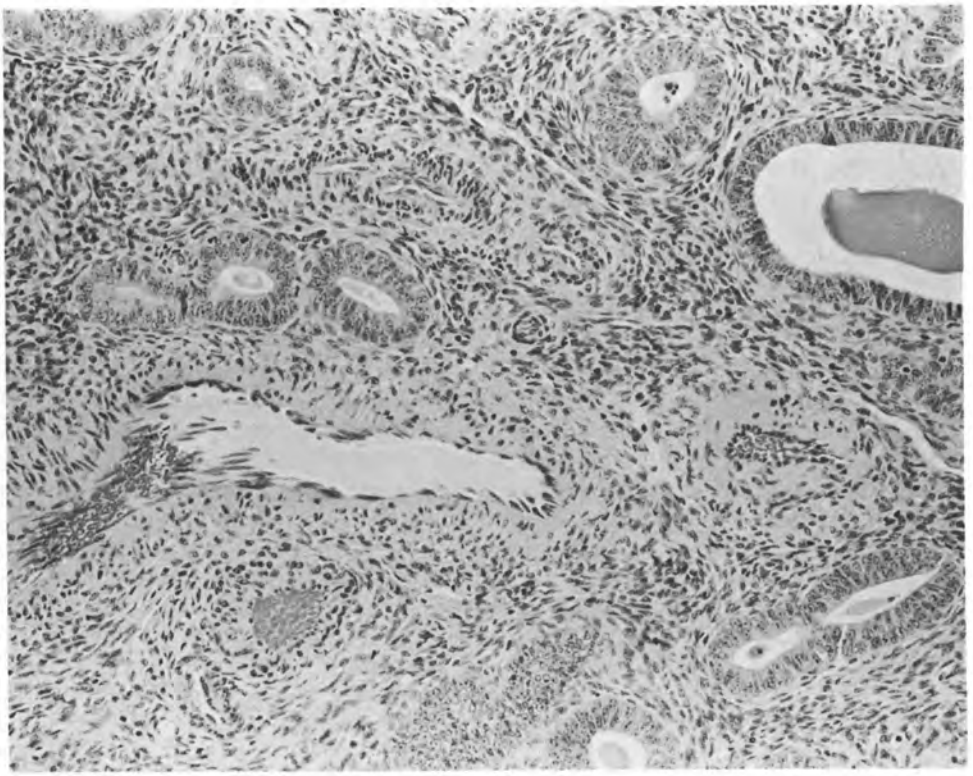

FIGURE 4-71 Endometrial polyp: detail showing thick-walled blood vessels, fibrotic stroma, and glands of proliferative phase type.

FIGURE 4-72 Complex hyperplasia (*left*) in an endometrial polyp.

arisen within a benign polyp or with a carcinoma, malignant from its onset, of polypoid type. When the carcinoma is limited to the polyp and is of endometrioid type, the prognosis is excellent; however, serous and clear cell adenocarcinomas[235,236] and carcinosarcomas[237] can disseminate even when confined to a polyp. Surgical excision with adequate pathologic examination is the treatment of choice for all polyps.

Vascular Tumors

The benign vascular tumors comprise *hemangiomas* and *lymphangiomas*. In 1955, Pedowitz and coworkers[238] found 128 published cases in the literature, to which they added 10 personal cases, but some of these were probably cases of low-grade endometrial stromal sarcoma. They are congenital but are discovered most frequently between the ages of 40 and 60 years, usually producing menstrual disturbances or some other form of hemorrhage.[239] They rarely attain sufficient size to be palpable. In a few cases, observation of the pulsatile character of the tumor during laparotomy has led to the correct diagnosis.

Hemangiomas may be subserous and pedunculated or intramural. They are less commonly found within the endometrium. They vary in size from a few millimeters to several centimeters (Fig. 4-73). *Histologically*, they are composed of small interwoven capillaries (capillary hemangioma), large dilated capillaries (cavernous hemangioma), or vessels surrounded by cuffs of smooth muscle fibers (angiomyoma). Cavernous hemangioma of the uterus may be associated with angiomatous lesions of other sites.

Lymphangiomas are rare. They are composed of lymphatic vessels, recognizable by the absence of erythrocytes in their lumina. Their differential diagnosis is with the adenomatoid tumor (see below).

The treatment of choice for these tumors is surgical excision. Radiation therapy appears to bring about regressions that are temporary at best.

Lipoma

More than 100 cases of lipomatous tumors of the uterus have been reported.[206,240,241] Most of these have been associated with vascular and leiomyomatous elements and have been designated *lipoleiomyomas, angiomyolipomas,* or *benign mixed mesodermal tumors.*[242] Although related to myomata, 90% of uterine lipomatous tumors have occurred in women older than 40 years. The origin of these tumors may be from multipotential mesenchymal tissue or from the adipose tissue in the adventitia of uterine blood vessels.

Adenomatoid Tumor

Of the 76 reported cases of adenomatoid tumors in women found in a review of the literature by Teel,[243] 35 were situated in the uterus, 33 in the fallopian tube, 5 in the ovary, 1 in the broad ligament, and 1 in parovarian connective tissue. Regardless of the lo-

cation, they are usually asymptomatic, classically discovered during an operation for an unrelated condition. In the uterus, they are usually found in a subserosal location, reflecting their now generally accepted mesothelial histogenesis.[244–247] Multiple sections of routine hysterectomy specimens reveal adenomatoid tumors in 0.6% to 1.2% of cases.[244,246]

Macroscopic Appearance. The lesions generally are small and usually are located at or near the serosal surface. They may resemble leiomyomata. However, they are generally softer and may have infiltrating borders. Occasional tumors that are large and extend to the endometrium have been reported.[248]

Microscopic Appearance. The most common pattern is the adenoid[245] or tubular one, consisting of anastomosing tubules lined by flattened to cuboidal cells (Fig. 4-74). In many instances, these tubules may assume an angiomatoid configuration; for this reason, these tumors were frequently confused with lymphangiomas in the past. Less common are solid and cystic growth patterns.[245,247]

Infiltration of the myometrium is frequently seen, and cases submitted to us in consultation are often thought to represent adenocarcinomas. Important distinguishing features include the subserosal location of the adenomatoid tumor, its lack of cellular atypia and mitotic activity, and the absence of myometrial destruction or a stromal response suggestive of invasion by a malignant tumor. The differential diagnosis with lymphangioma is aided by the presence of immunohistochemically detected epithelial antigens in the adenomatoid tumor. The *evolution* of the uterine adenomatoid tumor is benign.

Other Benign Tumors

Rare cases of *nonchromaffin paraganglioma* have been referred to briefly in the literature.[249] Somewhat less rare are *papillary adenofibroma, atypical polypoid adenomyoma,* and *adenomyomatosis.* Because these three benign lesions seem to be part of a spectrum including the low-grade malignant tumor known as *müllerian adenosarcoma,* they will be discussed in the later section on malignant neoplasms. *Stromal nodule* is also discussed later with endometrial stromal sarcomas. Such rare uterine benign lesions as *neurofibroma,*[209] *melanotic schwannoma,*[209] *fetal rhabdomyoma,*[250] *postoperative spindle cell nodule,*[251] and *inflammatory pseudotumor*[252] have been reported.

ENDOMETRIAL HYPERPLASIA

Endometrial hyperplasia embraces a spectrum of histologic appearances that have been compared with those of cervical dysplasia. As in the latter, the milder forms of endometrial hyperplasia tend to occur in younger patients and in the great majority of cases to regress, either spontaneously or after treatment. The more severe forms, occurring pre-

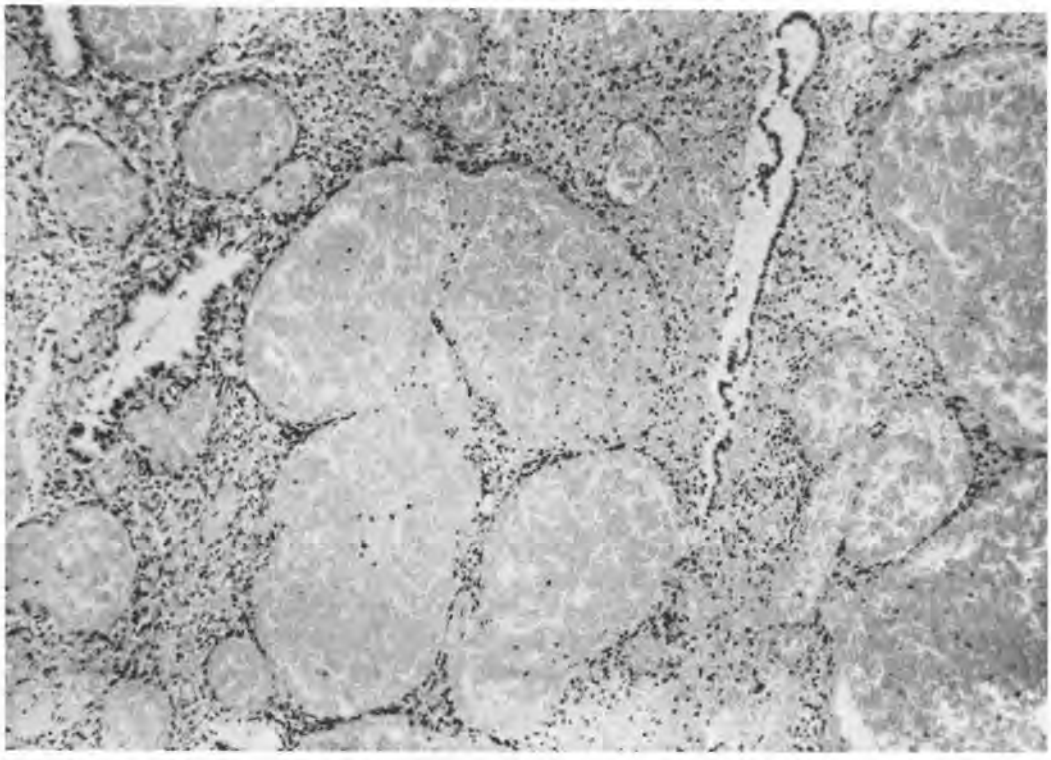

FIGURE 4-73 Endometrial hemangioma.

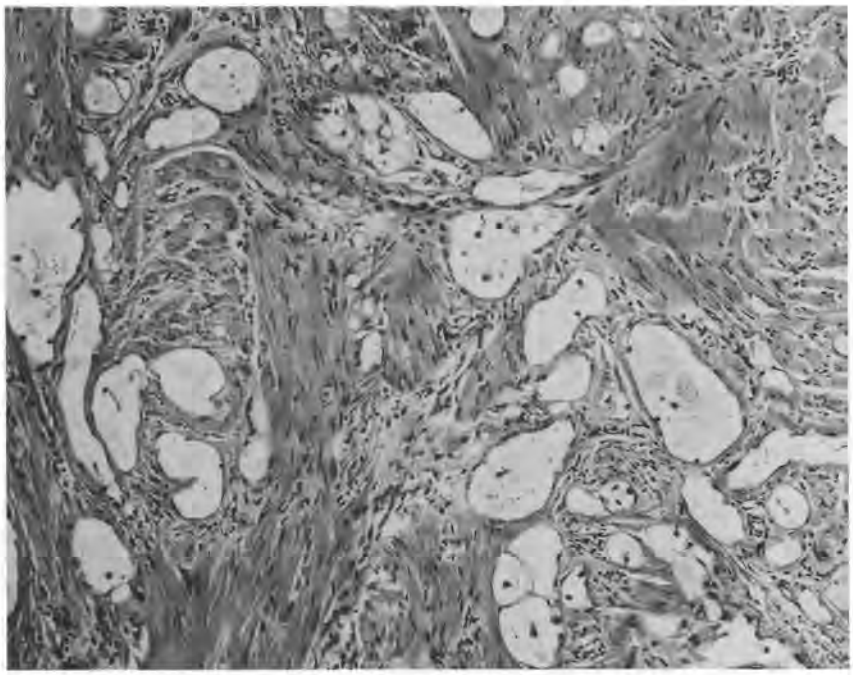

FIGURE 4-74 Adenomatoid tumor infiltrating the myometrium. (Silverberg SG, Kurman RJ: Tumors of the uterine corpus and gestational trophoblastic disease. Atlas of tumor pathology, 3rd series, fascicle 3. Washington, D.C., Armed Forces Institute of Pathology, 1992)

dominantly in peri- and postmenopausal women, appear to have a significant premalignant potential, the evidence for which will be discussed below.

Clinically, the hyperplasia is manifested principally by abnormal uterine bleeding, whose severity is not necessarily proportional to that of the histologic changes.[253] Endometrial hyperplasias are uncommon in asymptomatic women, with a reported prevalence of slightly more than 8 cases per 1000 screened postmenopausal women.[254] There is an association with obesity (and a Western diet), nulliparity, diabetes mellitus, hypertension, and endogenous and exogenous hyperestrinism.[253–255]

Macroscopic Appearance. The *macroscopic appearance* of endometrial hyperplasia may not vary significantly from the normal, or it may show considerable thickening of either the entire mucosa or focal regions. When focal thickening occurs, the lesion may acquire a polypoid aspect. The consistency is usually soft and the color pale pink. Curettage usually yields increased amounts of tissue.

Microscopic Appearance. The *microscopic appearance* depends on the degree of hyperplasia. Lesions of different degrees of severity have been given diverse names by different authors. The current ISGP nomenclature[128] uses the terms *hyperplasia* and *atypical hyperplasia* to refer to processes without and with cytologic (nuclear) atypia respectively, and each of these is divided into a *simple* and a *complex* (adenomatous) type, reflecting the degree of architectural complexity.[256–261] In all patterns, by definition the volume of endometrium is increased, although this may not be apparent in a small biopsy specimen.

Simple Hyperplasia

Simple hyperplasia is the least distressing form histologically. In this form, there is an increase in both the glandular and stromal compartments, and although the ratio of glands to stroma is somewhat increased, the glands are not markedly crowded (Figs. 4-75 and 4-76). The numerous glands usually include many that are dilated or cystic, the height of the epithelium varying inversely with the degree of dilatation. The slightly dilated glands are lined by stratified proliferative type epithelium, whereas the markedly dilated ones may show stratified, cuboidal, or, rarely, flattened epithelium (see Fig. 4-75). Rarely, in this or one of the other types of hyperplasia, some or all of the glands show secretory changes (*secretory hyperplasia*). The general appearance of the endometrium has been likened to the small and large holes of Swiss cheese, and this pattern is often referred to as "Swiss cheese hyperplasia." It is frequently polypoid. Ciliated cells are numerous; mitoses are present but are not numerous, and no atypical mitoses are seen. No dyspolarity or nuclear atypia is present. The gland lumina may contain cellular debris. The stromal cells are densely packed and have small nuclei and scanty cytoplasm; mitoses are present.[262] The spiral arteries are poorly developed, but the superficial capillaries are numerous and uniformly distributed. Hyaline deposits in the stroma are frequent and may represent residual products of incomplete fibrinolysis caused by local enzymatic deficiencies. This lesion should not be confused with the pattern of cystic atrophy seen predominantly in postmenopausal women, in which the epithelium of all the glands is flattened and inactive. Similarly, the presence of a few cysts is common in

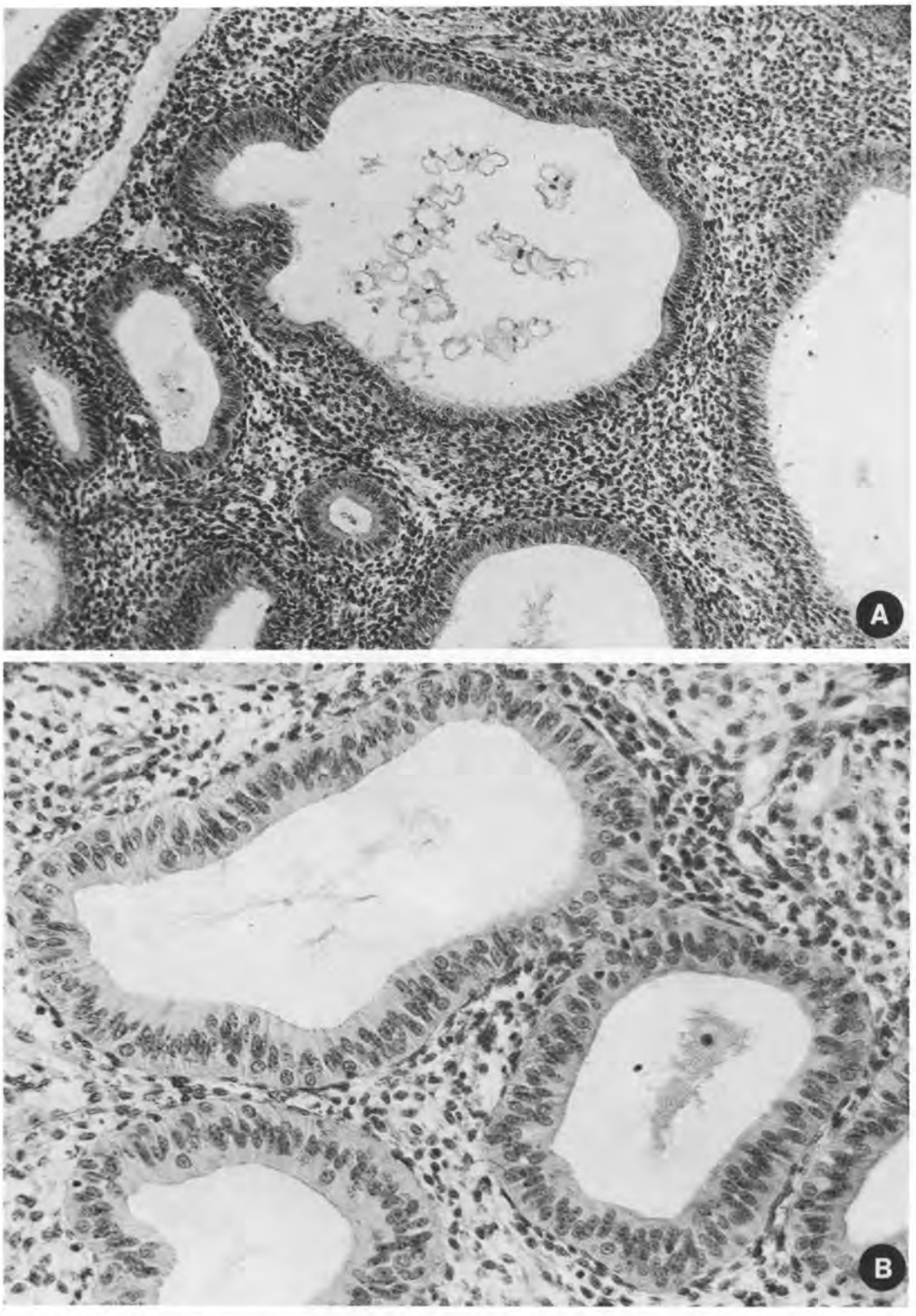

FIGURE 4-75 Simple hyperplasia. **(A)** General appearance. **(B)** Detail.

endometritis, in endometria overlying submucous myomata, and even in normal endometria. Therefore, the mere presence of dilated glands or cysts does not establish the diagnosis of simple hyperplasia. Opinions concerning the premalignant potentialities of this lesion are unanimous in assigning it a very low risk of progression to cancer (probably in the range of 1% to 5%).[256,257,259,260,263]

Complex Hyperplasia

Complex hyperplasia (Figs. 4-77 and 4-78; see Fig. 4-76*B*) may involve the entire endometrium or may be found in foci intermingled with normal or simple hyperplastic endometrium . The glands are closely packed and distributed irregularly in a cellular compact stroma. The glandular to stromal ratio is mark-

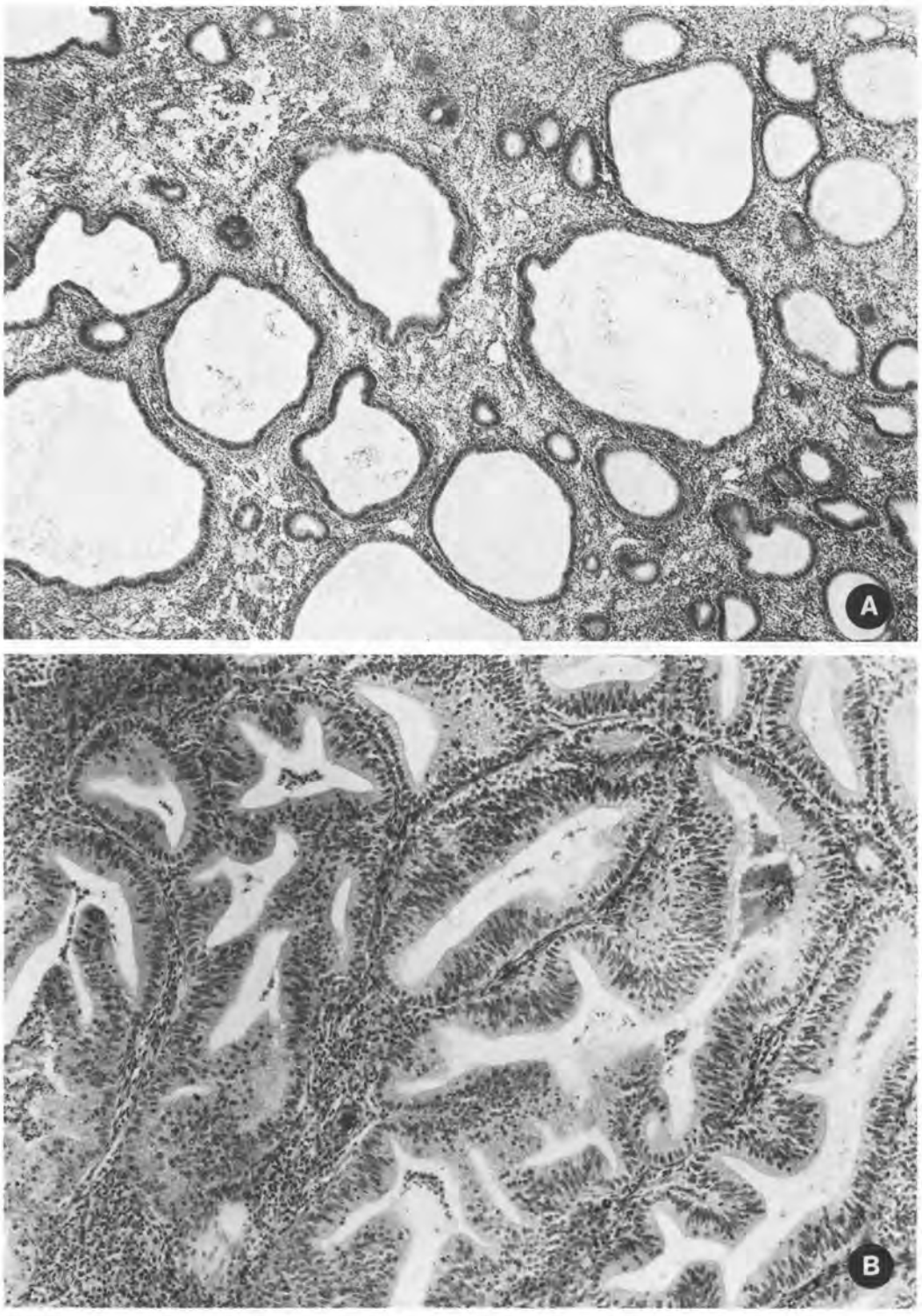

FIGURE 4-76 Endometrial hyperplasia. **(A)** Simple. **(B)** Complex.

edly increased. The glands are often irregular in size and shape. Outpouching or branching of these glands is a common feature (see Fig. 4-78); small bud-like projections may be pinched off to form small nests of closely packed glands in a microfollicular pattern. The epithelium is usually stratified and proliferative in appearance; mitoses are frequent. Cellular atypia is not present. Lipid-laden stromal cells (foam cells) may be noted.

The overall frequency of transformation of this lesion to carcinoma is not entirely clear. It is around 25% according to Sherman and Brown[264] and

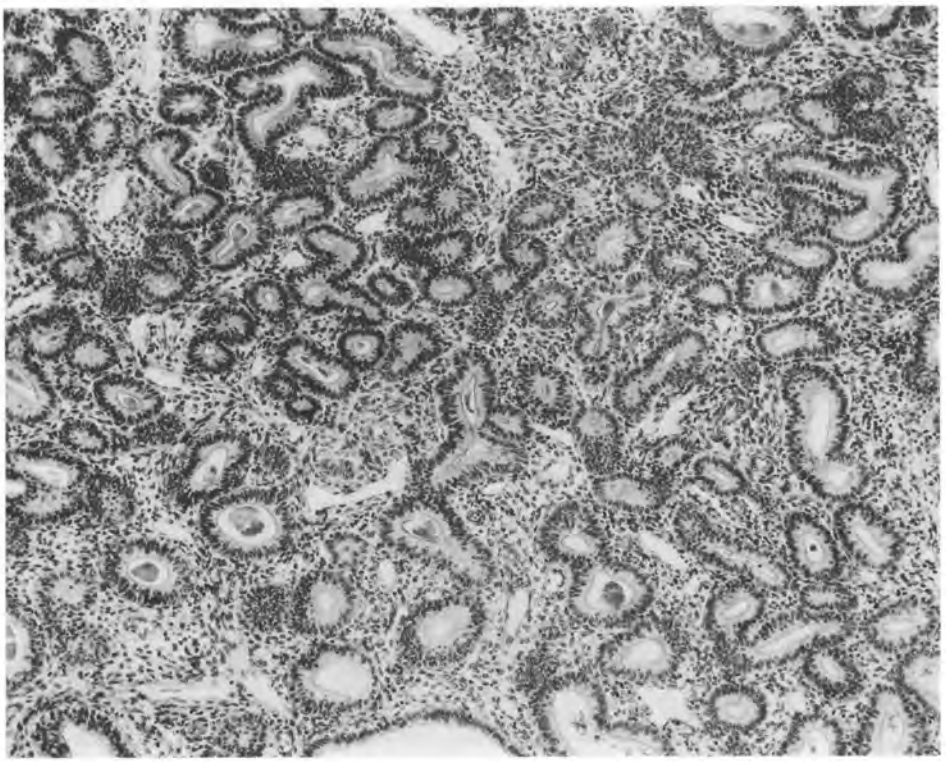

FIGURE 4-77 Complex hyperplasia. Glands are crowded and show some architectural atypia but no nuclear atypia.

Wentz[265] and less than 10% for most other investigators.[256,257,261,263,266] Curettage of this lesion usually yields more voluminous material than in the case of simple hyperplasia, and the patients tend to be somewhat older.

Atypical Hyperplasia

Atypical hyperplasia appears to be the same lesion that is alternately called *marked adenomatous hyperplasia,*[267] *anaplasia,*[268] or *carcinoma in situ*[269–271] in

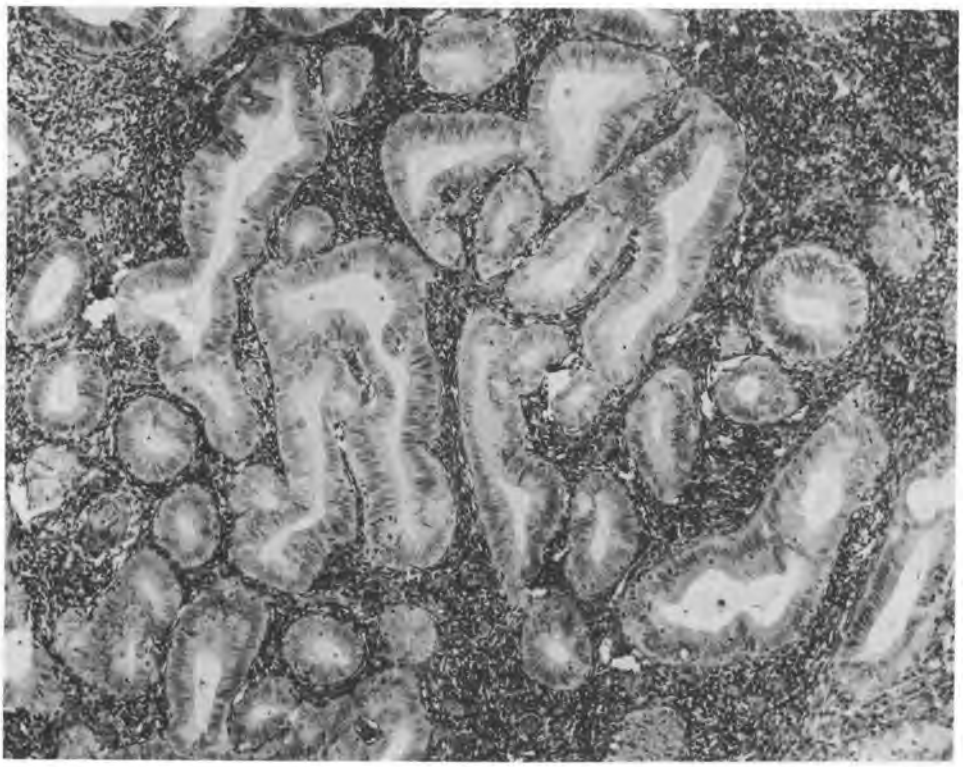

FIGURE 4-78 Complex hyperplasia. Nuclear atypia is absent.

the older literature. This lesion is usually focal and may be of simple or (more commonly) complex architectural type, but in addition the glandular epithelium demonstrates cellular atypia. Cellular disorientation, anisocytosis, and stratification are common (Figs. 4-79 through 4-81). Papillary projections and syncytial formations are often seen projecting into gland lumina (see Fig. 4-81). Mitoses are present but are no different in number or appearance from those in other hyperplastic lesions. Nuclear hyperchromatism, clumping of chromatin, and enlarged nucleoli are present. The nuclei tend to be round rather than columnar. Some cases are also characterized by marked cytoplasmic eosinophilia (see Figs. 4-80 and 4-81); these have been designated carcinoma in situ by some authors, but there is little evidence that this is a more advanced lesion than the more common noneosinophilic variant. Whatever term is chosen by the individual pathologist, the clinical significance of the lesion should be fully understood by both the clinician and the pathologist. If untreated, a large proportion of these lesions will probably progress to cancer,[256,257,261,263–266] although the exact figure in different reports ranges from 25% to 80%. In some of these studies, the complex type has had a higher progression rate than the simple type.

Premalignant Potential

What is the evidence for considering endometrial hyperplasia as a lesion with a significant premalignant potential? As in cervical lesions of this nature, the major studies along these lines may be divided into those of prospective, retrospective, and concurrent nature.

The earliest observation of the concurrent existence of endometrial hyperplasia in uteri examined because of the known presence of endometrial adenocarcinoma was that of Cullen[272] in 1900; he believed that this atypical change was not pathognomonic of carcinoma but rather an early change suggestive of a nearby cancer. Subsequently, many case reports and systematized studies have accumulated that show the simultaneous presence of endometrial hyperplasia and carcinoma; these studies are summarized in the review of Scully.[273]

Retrospective studies of previous biopsies in patients seen with endometrial carcinoma have suggested a significant relationship between these two lesions. These studies have been summarized by Foster and Montgomery,[268] who state that in 88 case reports of endometrial carcinoma extracted from the literature in which prior material was also reviewed, 61 of the 88 previous biopsies were reported as abnormal, most having shown varying degrees of hyperplasia. In the series in which this information is available, the degree of these changes seems to vary inversely with the amount of time that elapsed between the early biopsy and the subsequent demonstration of carcinoma.[265,274]

The other main avenue of approach to the natural history of endometrial hyperplasia has been the prospective follow-up of patients demonstrated to have this lesion on endometrial biopsy who are sub-

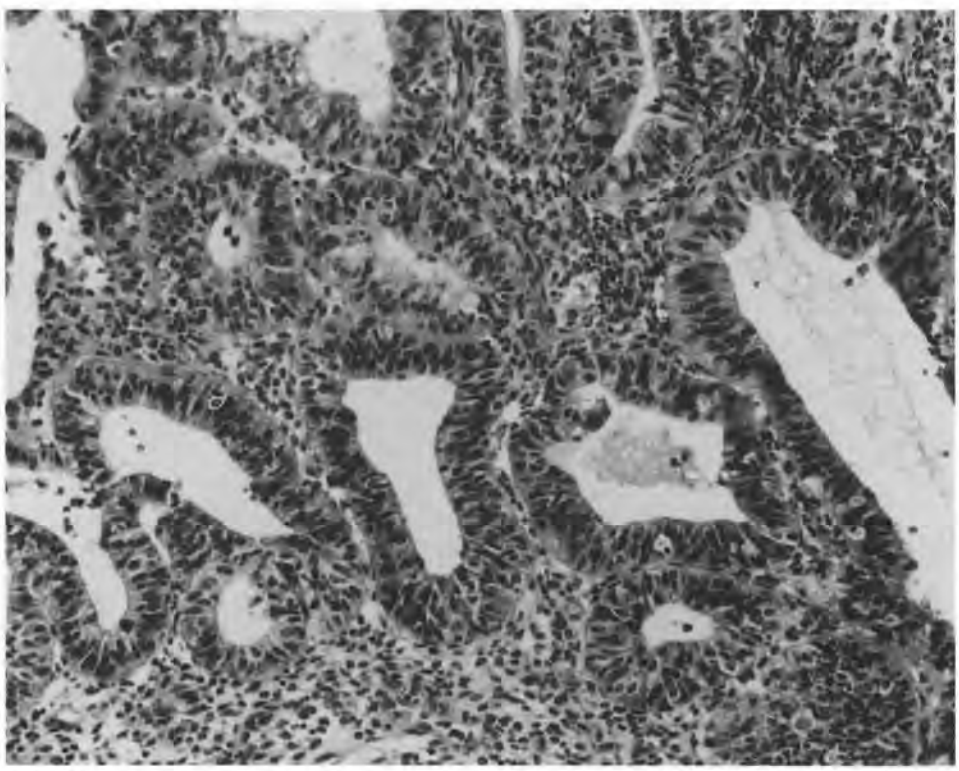

FIGURE 4-79 Atypical hyperplasia (complex). Note the irregular stratification and the roundness of nuclei. Debris in the gland lumina is a common feature.

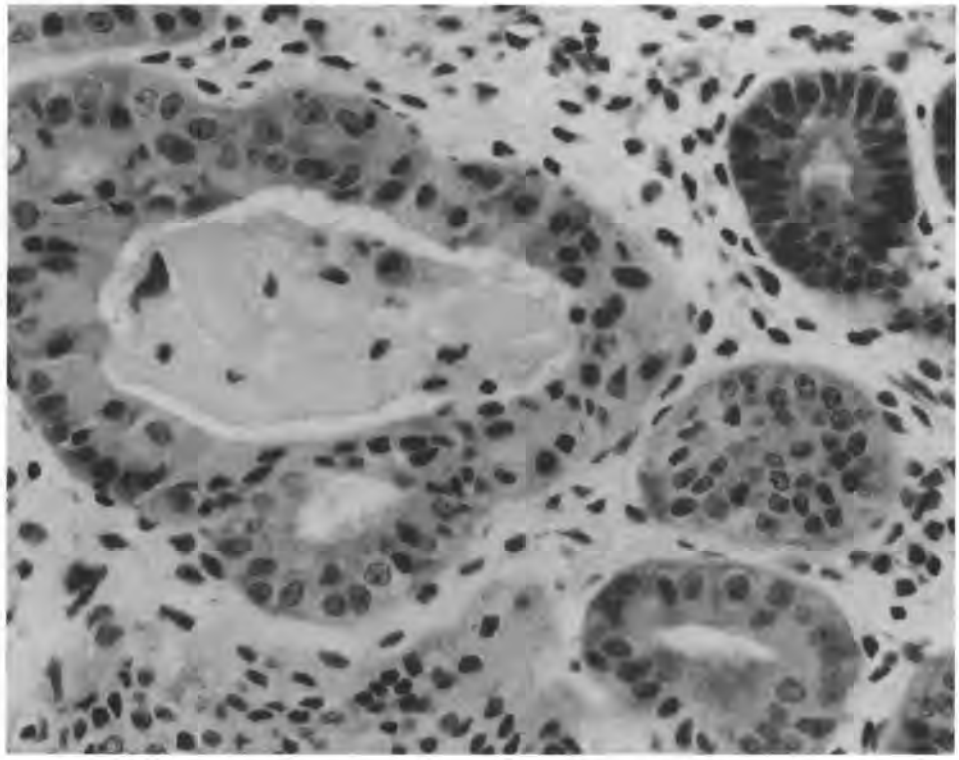

FIGURE 4-80 Atypical hyperplasia. These atypical glands have eosinophilic cytoplasm, dyspolaric cell stratification, and nuclear atypia.

sequently either treated conservatively or untreated and observed clinically and biopsied at intervals thereafter. Of 23 patients with atypical hyperplasia followed pathologically by Copenhaver,[275] 8 subsequently developed invasive carcinoma. TeLinde and colleagues[276] report the same progression in all of their 14 patients who had a second curettage from 10 months to 23 years later. Gusberg and Kaplan[267] report 191 patients with a pathologic diagnosis of "adenomatous hyperplasia" of variable severity (probably including all types in the current nomenclature). Of the 90 treated by immediate hysterectomy, 20% had coexistent carcinoma; of those untreated in this fashion, 68 patients were followed for 1 year or more, and 8 developed carcinoma from 1½ to 9 years later.

In more recent studies, Wentz[265] reported subsequent carcinoma within 2 to 8 years in 27% of women with adenomatous (here probably meaning complex) hyperplasia, 82% with atypical hyperplasia, and 100% with "adenocarcinoma in situ." Sherman and Brown[264] found carcinoma developing within 2 to 18 years in 22% of women with adenomatous (also comparable to complex) hyperplasia, 57% with atypical hyperplasia, and an almost identical 59% with adenocarcinoma in situ. In contrast to this latter series, in which all the patients were older than 50 years, Chamlian and Taylor[277] reported the development of adenocarcinoma in only 14% of women 35 years or younger with adenomatous or atypical hyperplasia who were followed for 1 to 14 years. Thus, the age of the patient seems to influence the risk of progression to carcinoma, and we would anticipate that the mediation of exogenous estrogens would do so as well (hyperplasias developing in the estrogen-treated women should be more likely to regress and less likely to progress if the source of exogenous hormone is withdrawn). Few studies have critically analyzed the relation of exogenous estrogens to endometrial hyperplasias,[255] although the magnitude of this problem in recent years is demonstrated by the fact that, of 48 consecutive patients who underwent hysterectomy for atypical hyperplasia in the series of Tavassoli and Kraus,[278] 39 had previously received exogenous hormones. In this series, in which hysterectomy was performed more or less immediately after the diagnosis of atypical hyperplasia, 25% of the uteri contained at least a single focus of well-differentiated carcinoma, but another 15% had neither hyperplasia nor carcinoma despite the absence of intervening treatment with progestational agents.

More recent studies have tended to use more modern terminology for the lesions analyzed, but they still have involved relatively limited numbers of cases with varying follow-up periods and intervening treatment. Kurman and colleagues[263] found progression rates to carcinoma of 1% in cases of simple hyperplasia, 3% in complex hyperplasia, and 23% in atypical hyperplasia (8% of those with the simple architectural pattern and 29% of those with complex atypical hyperplasia). The follow-up ranged from 1 to 26.7 years after the diagnosis of hyperplasia. Many of the patients received hormones in the intervening period, but this treatment had little influence on the progression rate. In addition to those cases

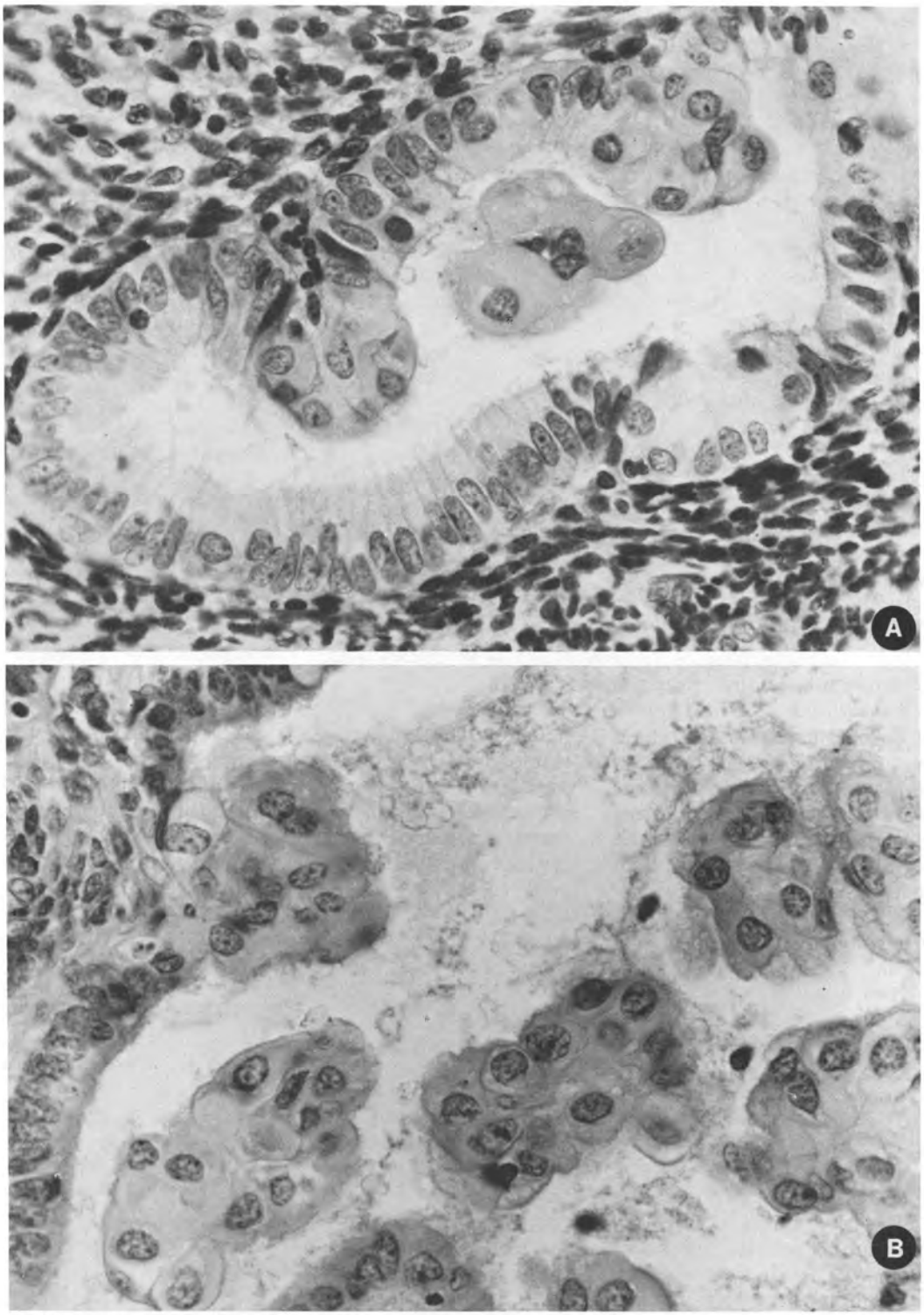

FIGURE 4-81 Atypical hyperplasia showing large eosinophilic cells and papillary epithelial infoldings.

that progressed to carcinoma, another 19% of both atypical and typical hyperplasias persisted.

Huang and associates[257] studied a somewhat smaller group of patients with hyperplasia, who had a subsequent endometrial specimen from 1 to 13 years later. Some patients received hormones and some were untreated. Twenty-four percent of patients with hyperplasia with nuclear atypia showed progression to carcinoma, versus 2.9% of hyperplasias without atypia. This study also included 38 patients originally diagnosed with hyperplasia whose specimens were interpreted on review as persistent

proliferative endometrium; none of these progressed to either atypical hyperplasia or carcinoma. Schwartz and colleagues[288] reviewed a subset of the same cases reported by Huang and colleagues and confirmed their findings. Immunohistochemical staining of the original blocks with monoclonal antibodies B72.3 and MSN-1 proved that neither was better than cytologic atypia in predicting the behavior of endometrial hyperplasia, although MSN-1 showed some promise.

Ferenczy and Gelfand,[261] in the latest of a series of reports, studied 85 peri- and postmenopausal women with endometrial hyperplasia without (65 patients) and with (20 patients) cytologic atypia. In this prospective study, all women were treated with a uniform regimen of medroxyprogesterone acetate and followed from 2 to 12 years (mean 7 years). In the group without atypia, 20% had persistence or recurrence of hyperplasia and none developed carcinoma. Of the 20 patients with atypical hyperplasia, 15 (75%) had persistence or recurrence and 5 (25%) developed adenocarcinoma at 2 to 7 years (mean 5.5 years).

Baak and associates[279] compared morphometric analysis with standard morphologic criteria in a series of 39 patients. They estimated that in their population the ratio of hyperplasia to carcinoma was about 4.5 to 1, and about 2% of all hyperplasias were atypical. On follow-up, none of 8 patients with simple hyperplasia developed carcinoma, versus 2 of 20 (10%) with either complex hyperplasia or atypical simple hyperplasia and 5 of 11 (45%) with atypical complex hyperplasia. The specificity of prediction was better with these criteria, but the sensitivity was higher with morphometry.

To summarize these and other studies in this complex field, we can say, first, that the perfect study still has probably not been done. For one thing, the different terminologies that have been used for this group of lesions make different studies in the literature extremely difficult to compare. For another, the diagnosis of hyperplasia made on a biopsy or a curettage specimen usually has provoked hormonal, radiotherapeutic, or definitive surgical (hysterectomy) treatment and will no doubt continue to do so in the future, making it virtually impossible to obtain follow-up on a large series of untreated patients. Despite formal data, it seems prudent to accept the thesis that atypical hyperplasia, as previously defined, carries a significant risk of progression to carcinoma, particularly in the postmenopausal woman. Additional evidence for the separation of atypical hyperplasia comes from cytologic,[280] microspectrophotometric,[281,282] flow cytometric,[283] immunohistochemical,[284–288] morphometric,[279,289,290] and chromosomal[291] studies that all show a close relation of this form of hyperplasia to adenocarcinoma. Some studies of proliferation markers have shown a wider separation between all the hyperplasias and adenocarcinomas (Sasano H, personal communication).[292] Ultrastructural studies are somewhat contradictory; in some studies, atypical hyperplasias look more like milder hyperplasias, whereas in others they more closely resemble carcinomas.[293,294] Of the hyperplasias without atypia, simple hyperplasia clearly has no significant premalignant potential, whereas that of complex hyperplasia is probably small but possibly real.

Differential Diagnosis. The *differential diagnosis* of these hyperplastic lesions depends on the type of hyperplasia being considered (Table 4-4). Simple hyperplasia has its differential diagnosis primarily with cystic atrophy and with polyps containing cystically dilated glands.[295] Because simple hyperplasia is frequently polypoid, this latter distinction may be more apparent than real. The main features to look for in simple hyperplasia are the proliferative rather than atrophic appearance of all or nearly all the glands and the participation of the stroma in the hyperplastic process. Polyps are identifiable by their fibrotic stroma and thick-walled blood vessels. Complex hyperplasia may be difficult to distinguish from a normal endometrium in late proliferative phase, a polyp or polyps, a chronic endometritis, or a *disordered proliferative endometrium* (Fig. 4-82). The latter appearance may be associated with anovulatory cycles and has irregularly distributed, sometimes architecturally abnormal glands. However, the volume of endometrium is not increased, and the stromal compartment is neither increased (as in simple hyperplasia) nor decreased (as in complex hyperplasia), thus leaving the glandular–stromal ratio normal for a proliferative-phase endometrium. In normal prolifer-

TABLE 4-4.
Differential Diagnosis of Endometrial Hyperplasia

Simple
Cystic atrophy
Polyp(s)
Disordered proliferative phase
Normal cycling endometrium with compression artifact
Complex
Polyp(s)
Chronic endometritis
Disordered proliferative phase
Normal cycling endometrium with compression artifact
Atypical polypoid adenomyoma
Simple hyperplasia
Complex atypical hyperplasia
Adenocarcinoma (rarely)
Atypical
Ciliary change
Surface syncytial change
Papillary proliferation
Eosinophilic cell change
Arias-Stella change
Chronic endometritis (rarely)
Other hyperplasias
Adenocarcinoma

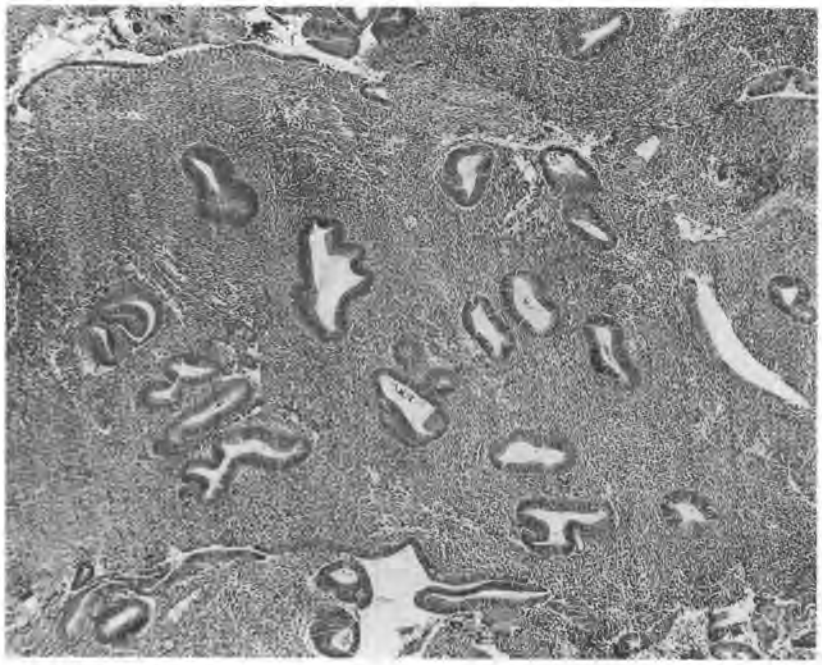

FIGURE 4-82 Disordered proliferative endometrium. The glands are irregularly distributed and somewhat irregular in shape, but the gland-to-stromal ratio is unchanged.

ative endometrium, the regularity of the glandular distribution should prevent confusion. In chronic endometritis, it is important to identify the inflammatory infiltrate; stromal edema, spindle cells, or both are commonly seen as well.

Finally, atypical hyperplasia must be distinguished from ciliary, eosinophilic, papillary and surface syncytial changes on the one hand, and focal adenocarcinoma on the other. The former distinction is based largely on the absence of cytologic and nuclear atypias in the metaplasias and related changes (see above), whereas we believe that the distinction from carcinoma is best made on the basis of the presence or absence of stromal invasion (see below).[128,260,296] Other authors who have dealt with the problem of the differentiation between atypical hyperplasia and well-differentiated carcinoma have proposed criteria that seem markedly different on first reading,[258,278,279,296–299] but in fact will yield similar results if applied to a series of practical rather than theoretical cases. Metaplastic changes, particularly squamous metaplasia or morules, in a complex hyperplasia (Fig. 4-83) should not lead to a diagnosis of adenocarcinoma unless the glands show the appropriate features.

Computer-aided diagnosis may prove to be of value in the future,[289,290,300,301] or we may fall back on the concept of endometrial intraepithelial neoplasia (EIN)[264,266] for those focal lesions in which treatment should be the same regardless of whether the lesion is called *severe atypical hyperplasia* or *focal well-differentiated adenocarcinoma.*

Additional differential diagnoses of all of the hyperplasias are with each other. Clues to avoid pitfalls in this area have been presented in the earlier section on microscopic appearance.

Cytologic Detection and Diagnosis. Cytologic detection and diagnosis of endometrial hyperplasias are still controversial; some authors claim excellent results for purely cytologic techniques,[280,302,303] whereas most[304–309] find histologic specimens far better than cytologic specimens for making the diagnosis. Our experience supports the latter viewpoint, although we certainly have been able to suggest the diagnosis of hyperplasia in some situations. With vaginal or cervical material, the only way that the suspicion of hyperplasia can be raised is by finding endometrial cells at an abnormal time (after the tenth day of a menstrual cycle or after the menopause), often in association with an abnormal hormonal background (numerous superficial cells in a scrape from the lateral vaginal wall suggesting estrogenic stimulation in a postmenopausal woman). In material obtained directly from the endometrial cavity, and less frequently in an endocervical aspirate, the presence of endometrial hyperplasia is suggested by abundant cellular material in which cell clusters show increased cell volume, anisonucleosis, and stratification or piling up of cells, without the more severe abnormalities seen in adenocarcinoma (Color Fig. 4-5). In Vuopala's literature survey,[309] however, even direct endometrial aspiration was able to detect only 20% to 70% of hyperplasias in various series, and false-positive diagnoses of carcinoma were not infrequent. We agree with Vuopala, Bibbo and coworkers,[304] Gusberg and Milano,[306] and others that sampling techniques that obtain material suitable for histologic study are preferable for the detection and diagnosis of these hyperplastic lesions.

Treatment. The *treatment* of these lesions is of interest both to the clinician and the pathologist. In

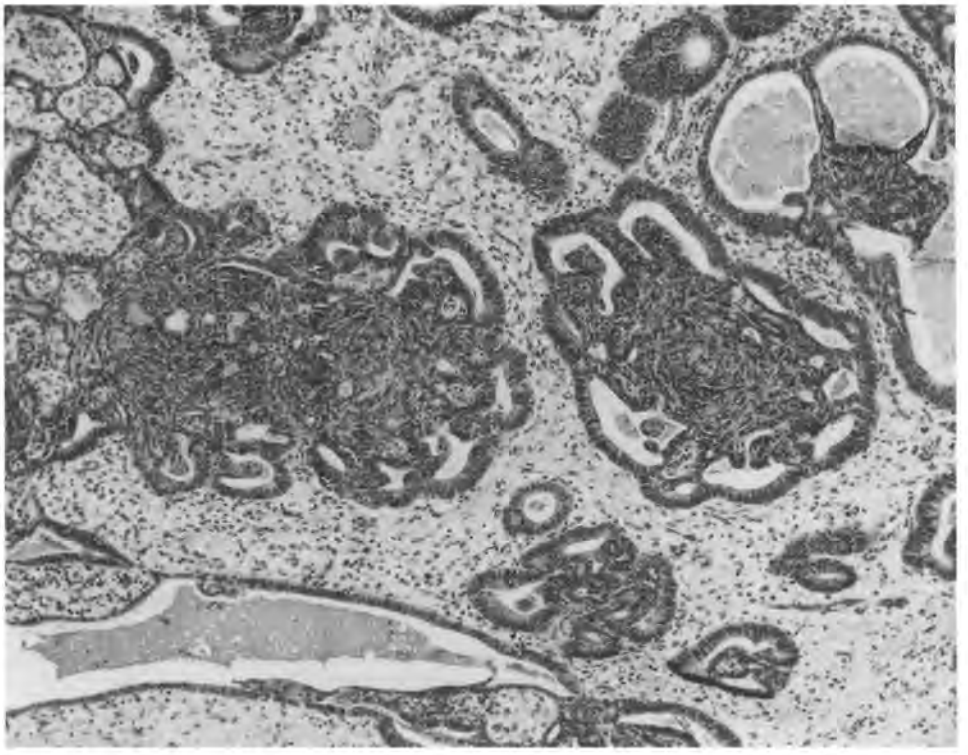

FIGURE 4-83 Complex hyperplasia with morular metaplasia. The glands do not satisfy the criteria for the diagnosis of adenocarcinoma.

postmenopausal women, the wisest course to follow is probably hysterectomy, which will be permanently curative for all noninvasive lesions. In younger women, therapy may profitably be directed along endocrine lines. Any underlying source of abnormal estrogenic stimuli (eg, polycystic ovarian syndrome, ovarian cyst or tumor, hyperthecosis, exogenous estrogen administration) should be uncovered and treated. Specific therapy for the endometrial lesion consists of the administration of progestational agents; in most cases of hyperplasia without atypia, the hyperplastic changes regress considerably, and usually completely, and progression to invasive carcinoma after this treatment is rare.[261,265,310] The endometrium after treatment may take on a completely normal histologic appearance, show glandular atrophy with stromal decidual reaction, or show persistent hyperplasia of lesser severity than in the pretreatment biopsy. Atypical hyperplasias, on the other hand, frequently persist or progress despite treatment and must be monitored carefully. A new alternative to progestin treatment is the oral administration of danazol; more studies on this agent must be reported.[311]

MALIGNANT TUMORS

Malignant tumors of the uterus can be classified as epithelial (carcinomas, the most common), nonepithelial, and mixed epithelial-nonepithelial (Table 4-5). There are also a few other rare tumors such as sex cord–like tumors, tumors of germ cell type, neuroectodermal tumors, and malignant lymphomas. In addition to these primary tumors, there are metastatic tumors, more commonly epithelial than sarcomatous. Cancers of the corpus uteri represent about 10% to 15% of the malignant tumors seen in women. They appear with greatest frequency between 50 and 70 years of age.

Primary Tumors

Carcinoma

Carcinoma of the endometrium accounts for about 90% of malignant tumors of the uterine corpus. It is the fourth most common cancer in Western women and the most frequent invasive gynecologic cancer. Its frequency tends to increase with the increased longevity of the population, because 75% of cases appear after the age of 50 years (Fig. 4-84). This increasing frequency, combined with the decreasing incidence of invasive cervical cancer, has greatly modified the formerly quoted proportion of 10 cervical cancers to 1 endometrial cancer in favor of the latter. The most recent epidemiologic surveys, however, have noted a decline in endometrial cancer incidence in the United States since 1975, generally attributed to decreasing estrogen usage.[312,313] Endometrial carcinoma is rare before the age of 40 years.[85,314,315] Classically, 95% of endometrial carcinomas have been adenocarcinomas, and 95% have occurred after the menopause. In more recent series, as many as 50% of the tumors have contained

TABLE 4-5.
Malignant Tumors of the Uterine Corpus

Epithelial
Endometrial carcinoma
  Endometrioid
    Adenocarcinoma
      Variants:
      Secretory
      Ciliated cell
    Adenocarcinoma with squamous differentiation
      Adenocarcinoma with squamous metaplasia (adenoacanthoma)
      Adenosquamous carcinoma
  Serous adenocarcinoma
  Clear cell adenocarcinoma
  Mucinous adenocarcinoma
  Squamous cell carcinoma
  Mixed carcinoma
  Undifferentiated carcinoma

Nonepithelial
Endometrial stromal tumors
  Low-grade stromal sarcoma
  High-grade stromal sarcoma
Leiomyosarcoma (see Table 4-3)
Other soft-tissue tumors
  Homologous
  Heterologous

Mixed Epithelial-Nonepithelial
Adenosarcoma
  Homologous
  Heterologous
Carcinosarcoma (malignant mixed mesodermal tumor; malignant mixed müllerian tumor)
  Homologous
  Heterologous

Silverberg SG, Kurman RJ: Tumors of the uterine corpus and gestational trophoblastic disease. Atlas of tumor pathology, 3rd series, fascicle 3. Washington, DC, Armed Forces Institute of Pathology, 1992

squamous elements, and many tumors have affected premenopausal women.[316,317]

Etiology. The etiology is not known, but several favorable factors have been demonstrated. In general, these are the same as for endometrial hyperplasia, reinforcing the concept of the premalignant potential of this lesion. Many of these factors have been related to prolonged or exaggerated estrogenic stimulation,[318-320] including nulliparity, failure of ovulation (eg, polycystic ovary syndrome),[321] late menopause, obesity (adipose tissue increases estrone formation),[322] feminizing mesenchymal ovarian tumors,[323] ovarian stromal hyperplasia and hyperthecosis,[324] and exogenous estrogen (including tamoxifen) administration.[325-328]

Factors that have not been related to the estrogen hypothesis of carcinogenesis include diabetes, hypertension, prior pelvic irradiation,[124] and familial predisposition.[329,330] Animal experiments have produced conflicting data on estrogen carcinogenicity; a neoplastic response has been demonstrated in animals such as rats, mice, and rabbits but not in subhuman primates. Numerous studies have indicated that estrone is the most important estrogen in endometrial carcinogenesis and that this hormone is produced primarily by extraglandular aromatization of plasma androstenedione.[320,331,332] Estrogen receptors have been demonstrated in normal and neoplastic endometrium,[332-336] adding to the evidence for specific responsiveness of this tissue. Some authors[336-339] have postulated that endometrial carcinomas that develop in this hormonal milieu have a more favorable prognosis than those that do not. Finally, the role of oncogene alterations in the development and natural history of endometrial hyperplasia is just beginning to be defined.[340,341]

Clinical Signs. The dominant clinical sign of carcinoma is painless vaginal bleeding, at first slight and at intervals, later continuous and profuse. Pain appears only late in the course of the disease. Postmenopausal bleeding should be emphasized as an important sign. In one study, endometrial carcinoma was found in 107 (13.7%) of 782 patients with this complaint.[342]

Diagnosis. The methods of diagnosis of endometrial carcinoma include study of the clinical signs (metrorrhagia, white blood-tinged discharge, pain), hysterography,[343] hysteroscopy,[344] sonoangiogra-

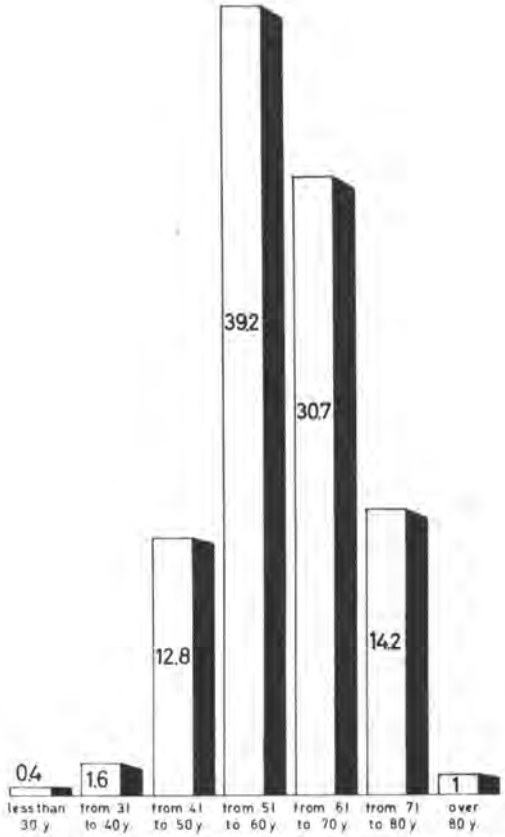

FIGURE 4-84 Adenocarcinoma of endometrium: frequency (percentage) of appearance as a function of age (879 cases).

phy,[345] ultrasonography,[346] exfoliative cytology, and (ultimately) histologic examination. Early diagnosis is often the result of the practice of exfoliative cytology;[254,306,307,347,348] the finding of neoplastic cells in vaginal, cervical, or endometrial secretions brings about the discovery of some asymptomatic cases. Endometrial aspiration is the technique of choice,[304,306,309,349] because it produces fewer false-negative results than cervical scrapings (the poorest technique) or vaginal pool or endocervical aspiration (intermediate in value). Despite these technical precautions, the percentage of false-negative reports remains in the range of 10% or greater, pointing out the need for adequate endometrial biopsy in clinically worrisome cases.[304,309,347,348]

In recent years, new instruments and techniques have permitted direct histologic sampling of the endometrium as an outpatient procedure.[304–306,309] Although dilatation and curettage under anesthesia is generally considered the most reliable procedure, it does not sample the entire endometrium in most cases,[350] and it is far more expensive and prone to complications than the outpatient procedures.[351]

Macroscopic Appearance. With the exception of a few tumors that arise in deep-seated foci of adenomyosis, endometrial carcinoma begins on the surface of the uterus, most frequently on the posterior wall. It develops slowly and presents in one of two macroscopic forms: localized or diffuse.

Localized carcinoma consists of a round, polypoid, or exophytic mass that is friable and often shows surface ulceration. The uterine cavity is progressively encroached on by soft, easily detachable neoplastic masses, which are embedded superficially in the myometrium (Fig. 4-85).

Diffuse carcinoma extensively infiltrates the thickened and indurated mucosa (Fig. 4-86). The volume of the uterus is increased but rarely surpasses that of a 3-month pregnancy. In advanced cases, the uterine cavity is filled with tumor, which may block the cervical canal and cause hematometra or pyometra.

Microscopic Appearance and Histologic Grading of Endometrioid Adenocarcinoma. Endometrioid adenocarcinoma is the most common type of carcinoma seen in the endometrium (see Table 4-5). It is characterized by numerous rounded glands of generally small and uniform size disposed in random fashion. They are lined by stratified epithelium, the cells of which show nuclear atypia and mitoses, the number and character of which vary according to the degree of differentiation of the tumor. The cells usually are oriented with their axes perpendicular to the basement membrane. In many cases, the degree of differentiation varies from one region to another.

The abundance of the connective tissue stroma also varies. It is in general well vascularized and contains prominent leukocytic and histiocytic infiltrates. Stromal foam cells are often seen.[120] Reactive fibrosis may be prominent. Foci of benign cartilaginous or osseous metaplasia are rarely present, but they must be differentiated from their malignant counterparts in mixed mesodermal tumors.[144]

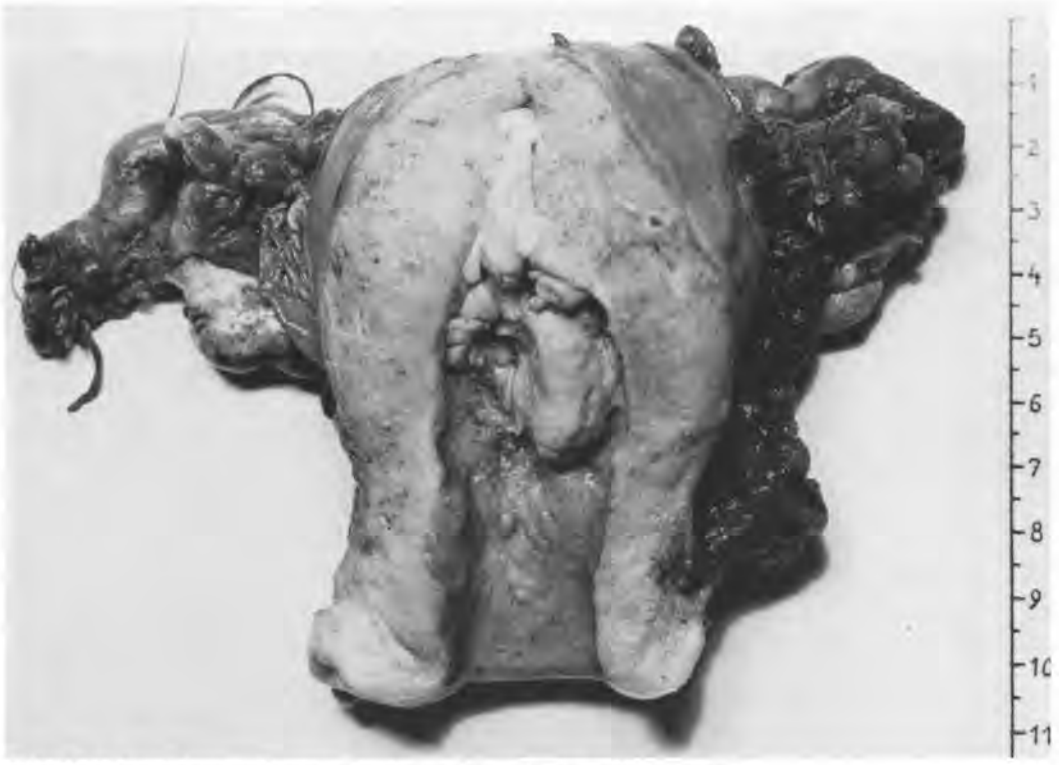

FIGURE 4-85 Adenocarcinoma of endometrium: macroscopic appearance.

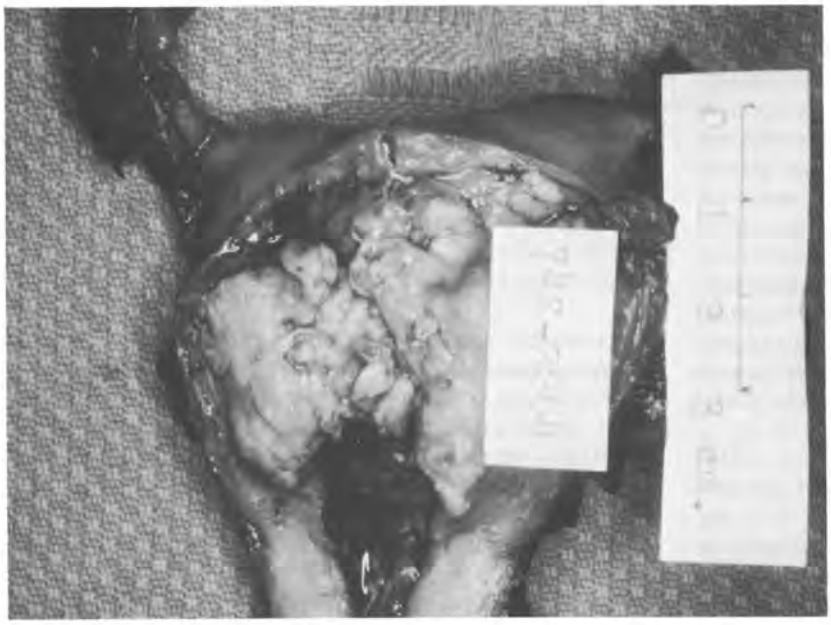

FIGURE 4-86 Diffuse macroscopic pattern of endometrial carcinoma with deep myometrial invasion despite small size of uterus (compare with Fig. 4-85, in which a much larger uterus shows a more limited tumor).

The International Federation of Gynecology and Obstetrics (FIGO) and ISGP grading system for endometrioid adenocarcinoma is based primarily on the concept that these tumors become less differentiated by deviating from a glandular or papillary pattern to form solid sheets.[128,352]

Well-differentiated (grade I) adenocarcinoma is characterized by 5% or less of a nonsquamous and nonmorular solid growth pattern. The glands are of regular contour and little cellular atypia. The only histologic finding suggesting malignancy is the overabundance of glands, which are crowded against each other with either no stroma separating them or separated by a reactive fibrous stroma or necrotic debris (Figs. 4-87 through 4-90). Pluristratification is present in most of the glands (Fig. 4-91). Mitoses may be numerous. The nuclei are larger than in normal cells, and their contours are indented. The nucleoli are enlarged, and the nuclear–cytoplasmic ratio is moderately augmented. If marked nuclear

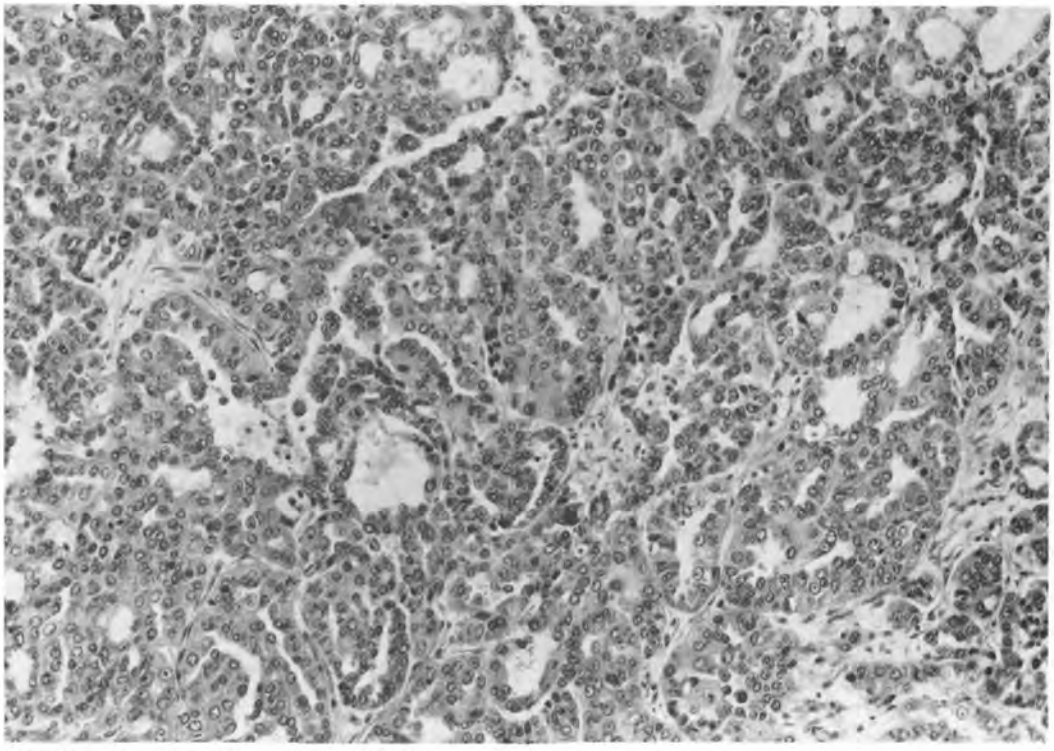

FIGURE 4-87 Well-differentiated (FIGO grade I) adenocarcinoma.

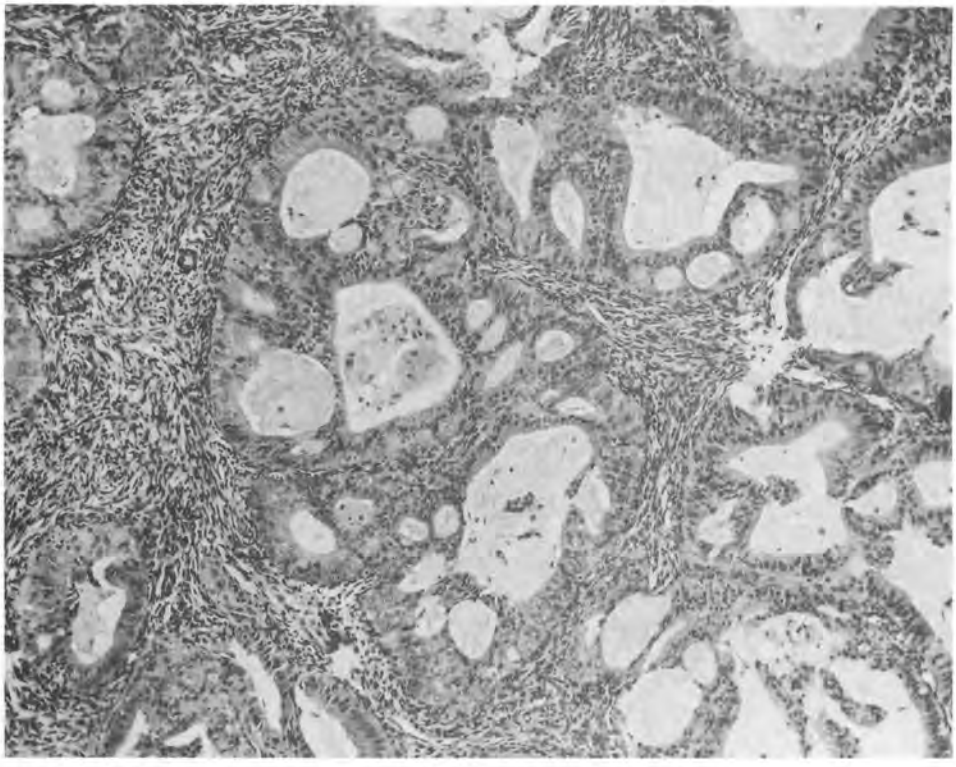

FIGURE 4-88 Focal well-differentiated (FIGO grade I) endometrioid adenocarcinoma in atypical hyperplasia. Note cribriform (confluent) pattern of glands.

atypia is present, the FIGO grade is elevated to grade II.

Papillary structures may be prominent in some tumors (*papillary* or *villoglandular endometrioid adenocarcinomas*). These tumors must be distinguished from papillary clear cell or serous carcinomas (see below). The main diagnostic feature is that the cells are similar to those of the classic glandular endometrioid pattern (Figs. 4-92 and 4-93).[353]

Electron micrographs have not demonstrated morphologic characteristics specific for the cancer cell. The modifications of fine structure of the malignant

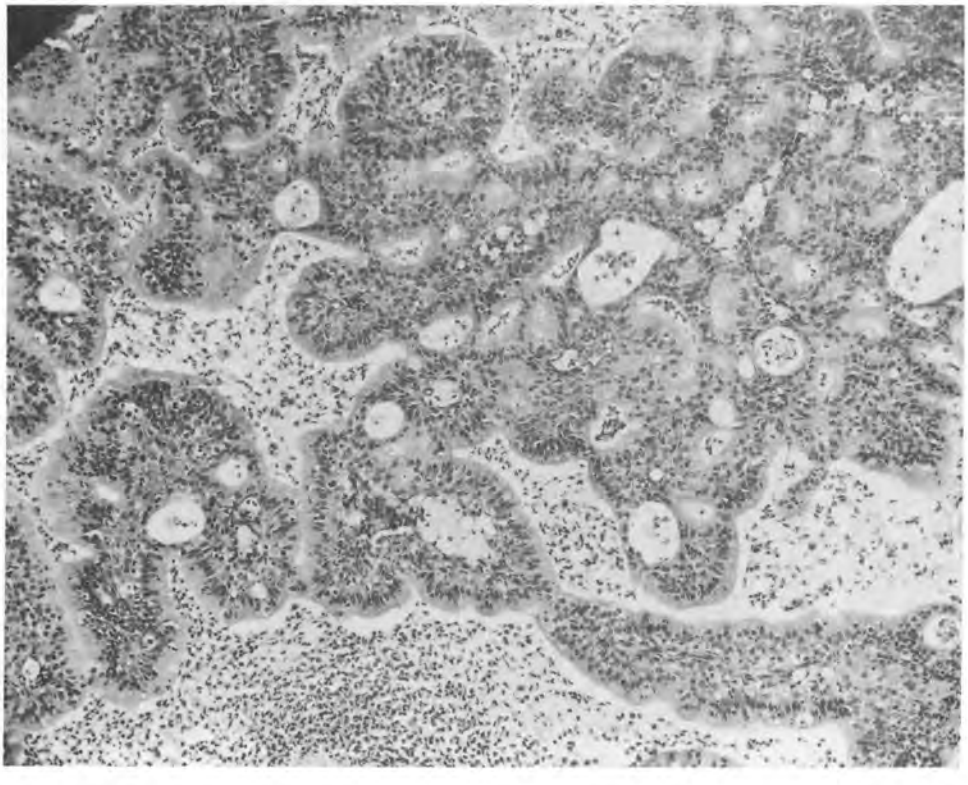

FIGURE 4-89 Well-differentiated (FIGO grade I) endometrioid adenocarcinoma showing necrosis of stroma between glands, identified by replacement of stromal cells by neutrophils.

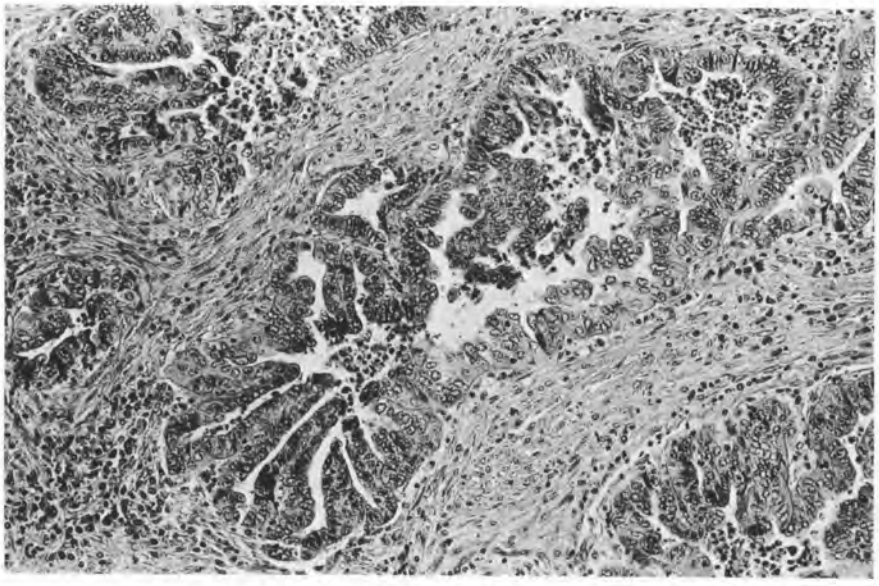

FIGURE 4-90 Adenocarcinoma of endometrium with stromal fibrosis.

cell are more of a quantitative than a qualitative nature.[293,294,354,355]

The nuclei are multilobate and show more or less deep invaginations of the membranes. They have a dense homogeneous structure, in which is found a voluminous nucleolus (Fig. 4-94). Enlargements of about 50,000 times permit recognition of the filamentous and granular structure of this organelle, as has been described in phase-contrast microscopy. Its contours are poorly defined, but its components appear in parallel rows of round particles measuring about 15 nm in diameter each. The nucleolus contains principally RNA (Feulgen-negative and ribonuclease-positive).

The cytoplasm contains numerous mitochondria of similar size and appearance as those in normal endometrial cells. The lysosomes or dense bodies are found in greater number than in normal cells and their size is variable; most, however, are of the same size as mitochondria. They contain catabolic enzymes such as urease, phosphatases, and desoxyribonucleases.

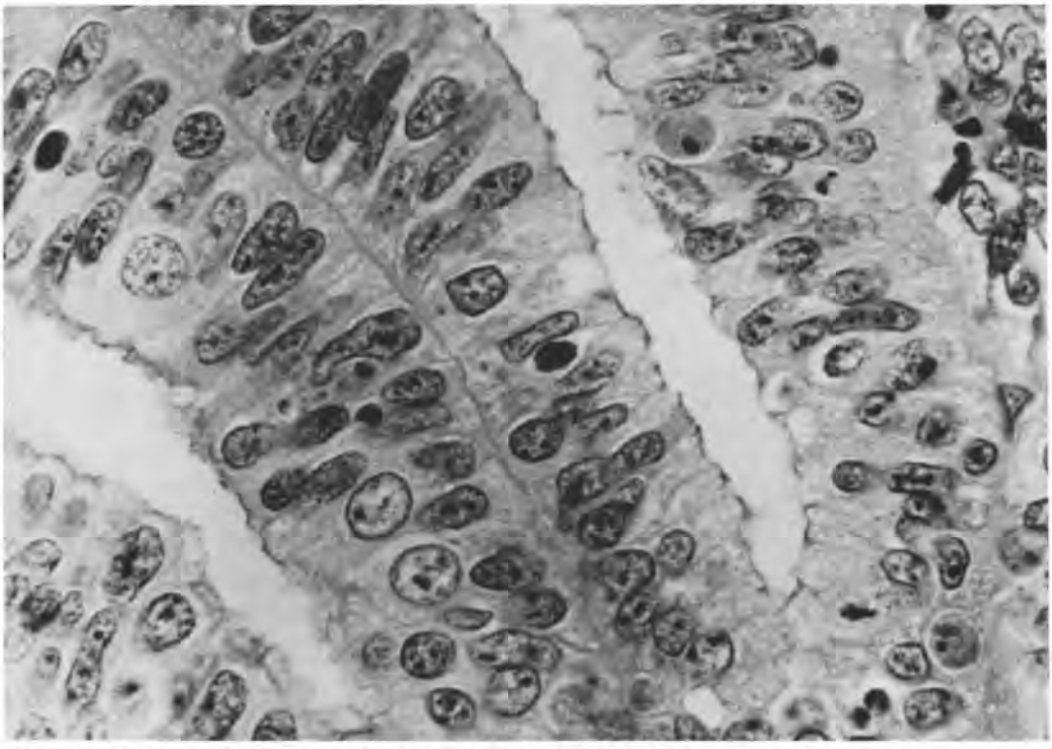

FIGURE 4-91 Well-differentiated adenocarcinoma: detail of a gland.

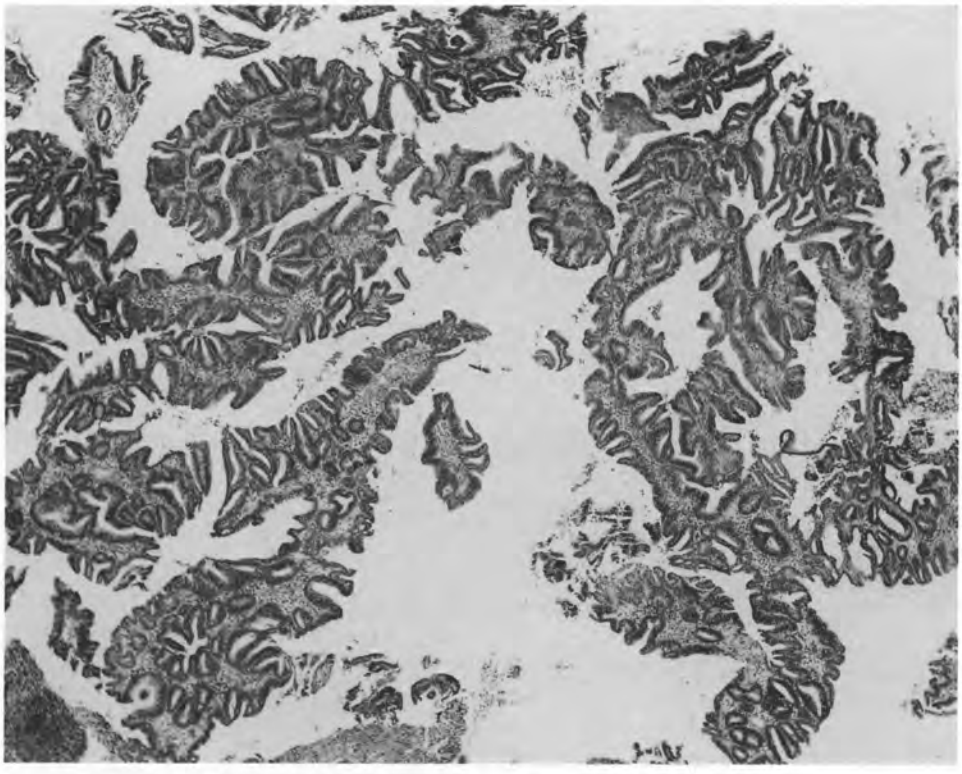

FIGURE 4-92 Well-differentiated (FIGO grade I) endometrioid adenocarcinoma of papillary (villoglandular) type.

The Golgi apparatus is well developed and sometimes shows dilatation of its vacuolar structures (Fig. 4-95). The appearance of the endoplasmic reticulum does not differ significantly from that of the normal cell; rarely, the membranes separate to form vacuoles of varied shapes.

Pools of lipid with irregular contours are found disseminated in the cytoplasm, and many cells contain variable amounts of glycogen (see Fig. 4-95). The cell membranes are sinuous and here and there reveal desmosomes. Bundles of fine filaments of about 10 nm in diameter, frequently related to des-

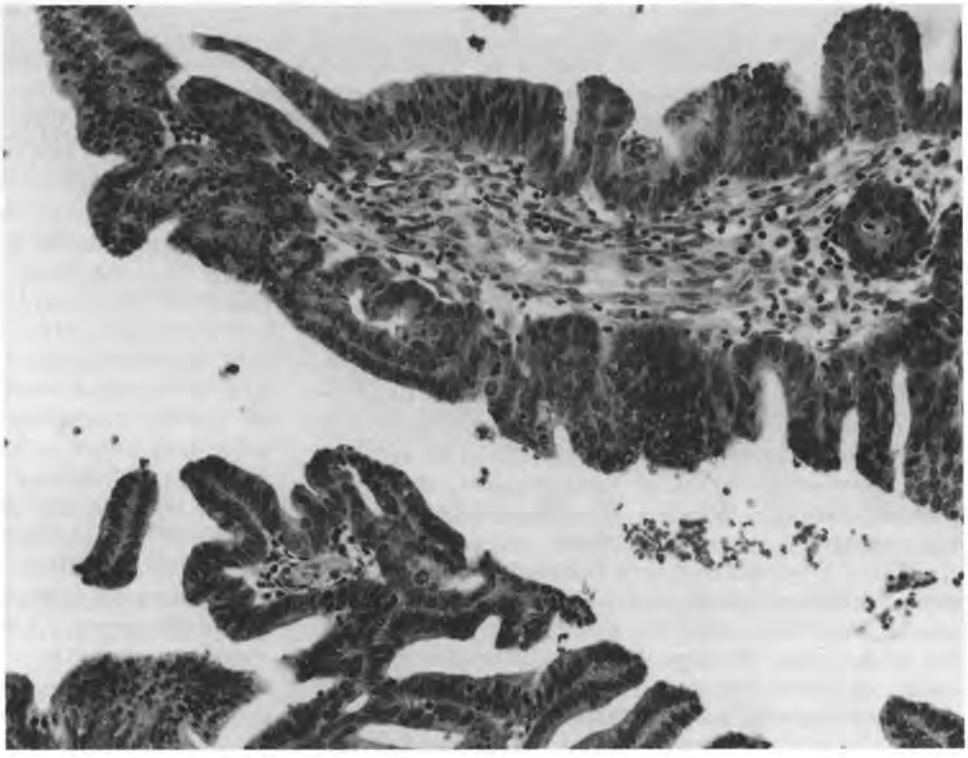

FIGURE 4-93 Well-differentiated (FIGO grade I) endometrioid adenocarcinoma of papillary (villoglandular) type. Note the low-grade cytologic features (compare with Fig. 4-103).

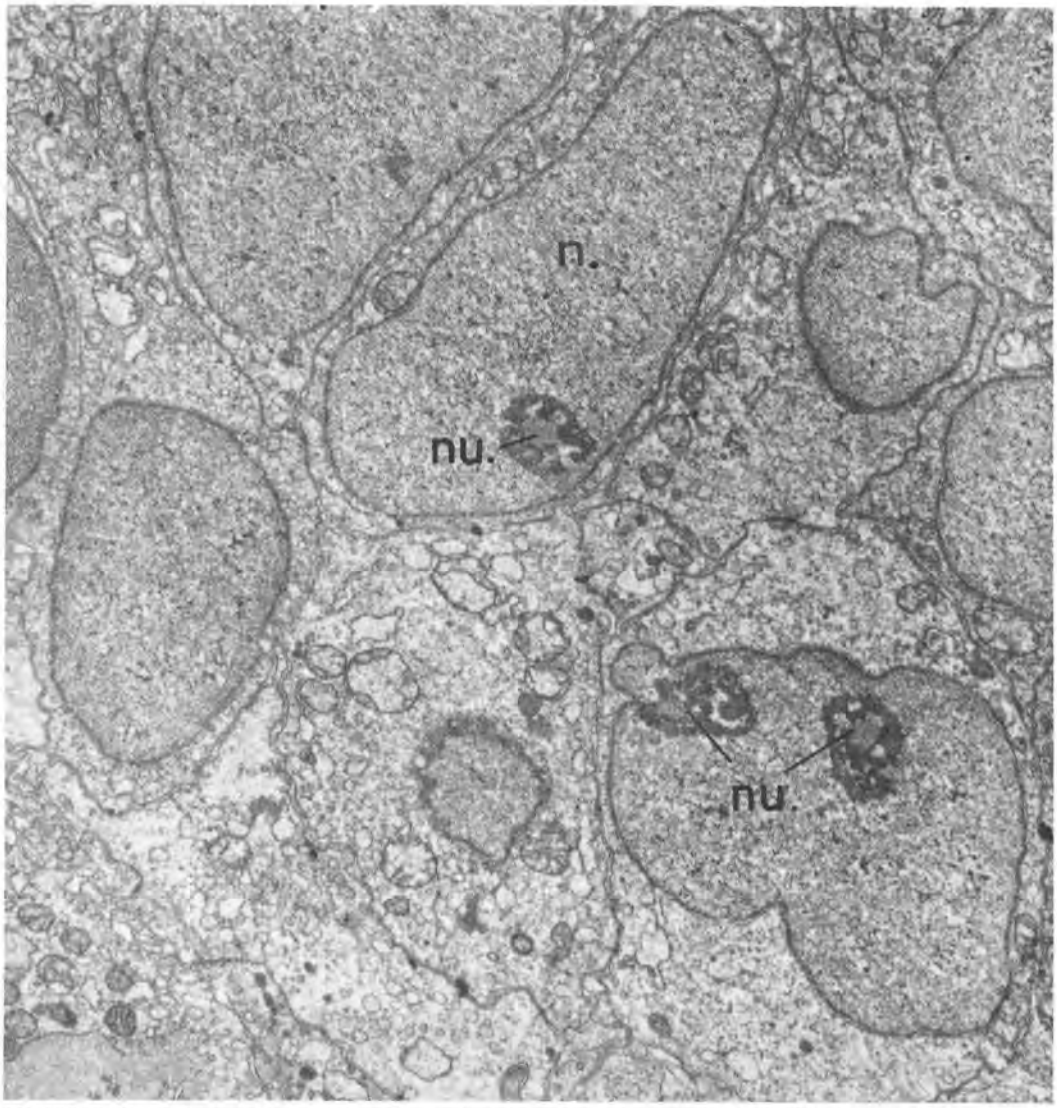

FIGURE 4-94 Adenocarcinoma of endometrium (electron micrograph, ×12,000): indented nuclei (*n.*), voluminous nucleoli (*nu.*), and convoluted cell membranes. The irregular nuclear contours, the volume of the nucleoli, and the anarchic distribution of the cells characterize the neoplastic nature of the cells.

mosomes, are more numerous than in normal endometrial cells. Basement membranes such as we have described in the normal endometrium are found around the neoplastic cell masses and constitute the junction between the epithelial elements and the stroma. This fact casts doubt on the classic description of rupture of the basement membrane as one of the cardinal manifestations of cancer. The stromal cells show irregularity of their nuclear and cytoplasmic contours. Bundles of collagen fibers insinuate among them in all directions.

The *differential diagnosis* between well-differentiated adenocarcinoma and certain atypical hyperplasias is difficult, and the pathologist must call on his or her fund of experience in distinguishing between the two lesions.[128,258,260,295–299] Haphazardly arranged glands, polystratification, and moderate nuclear atypia are typically found in cancer but are seen in some cases of hyperplasia as well. The absence of myometrial invasion cannot be considered proof of benignity, because many carcinomas become invasive only as a late event. The most important single criterion of carcinoma is the presence of stromal invasion, which may present as diminution or loss of stroma between glands (see Figs. 4-87, 4-88, and 4-96), as stromal necrosis (see Fig. 4-89), or as stromal fibrosis (see Fig. 4-90). The absence of this criterion is also important for distinguishing benign postradiotherapy atypias in hysterectomy specimens from persistent tumor.[356]

Moderately differentiated (grade II) adenocarcinoma is a predominantly glandular lesion, but it contains a significant minority (6% to 50%) of solid cell nests, often composed of anaplastic cells (Fig. 4-97). Even the glandular component usually shows more atypia than is seen in grade I adenocarcinomas.

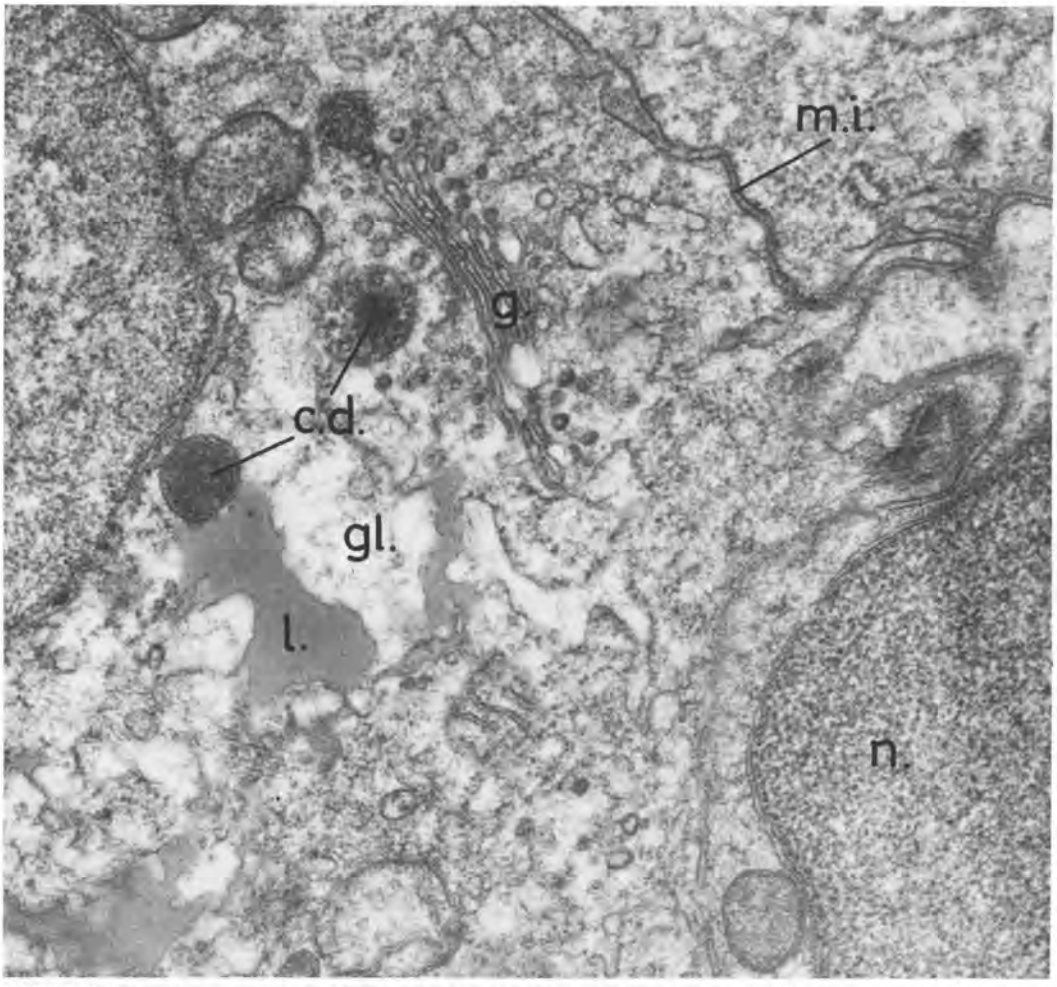

FIGURE 4-95 Adenocarcinoma of endometrium (electron micrograph, ×42,000), *n.*, nucleus; *g.*, Golgi apparatus; *c.d.*, lysosomes or dense bodies; *gl.*, glycogen; *l.*, lipids; *m.i.*, cell membranes.

Poorly differentiated (grade III) adenocarcinoma consists predominantly of solid cell nests (Fig. 4-98), with glandular elements seen in less than 50% of the tumor or perhaps not at all. Differential diagnosis of this lesion from a carcinosarcoma (if malignant glands are present) or endometrial stromal sarcoma (if no glands are seen) may be extremely difficult. In some instances, a residual nesting of epithelial type may be seen (see Fig. 4-98) and may be accentuated with a reticulin stain. In others, electron microscopic evidence of epithelial differentiation or immunohistochemical demonstration of keratin filaments[357] may be the only evidence that the tumor is, indeed, a pure carcinoma. As we shall see, these markers of epithelial differentiation may also be present in tumors that are classically considered to be of stromal origin.

Adenocarcinoma in situ. Adenocarcinoma in situ is a term that has been used in different ways by different observers. Some researchers[269–271] have used it to describe the lesion that we call atypical hyperplasia (see above), associated with a particular cytoplasmic eosinophilia, whereas others[299] have suggested that it be used to describe a particularly small focus of what we would designate as invasive adenocarcinoma. Because the endometrium is the epithelium of the uterine corpus, this term could also be used to describe any adenocarcinoma that has not yet invaded the myometrium. With this wide discrepancy in its definition, we agree with such authors as Tavassoli and Kraus[278] and Fox and Buckley[266] that it is best not to use this term at all. Certainly, if only a small focus of adenocarcinoma invading its own stroma is seen in a curettage or a hysterectomy specimen, it should be so described and treatment should be discussed with the clinician.

Secretory Carcinoma. A variant of endometrioid adenocarcinoma has been designated secretory carcinoma; it consists of very well-differentiated cells forming glands that differ slightly if at all from those of normal secretory endometrium (Fig. 4-99). These tumors are rare in pure form but occur more frequently as foci within other endometrioid carcinomas.[358] They appear to be associated with a favorable prognosis.

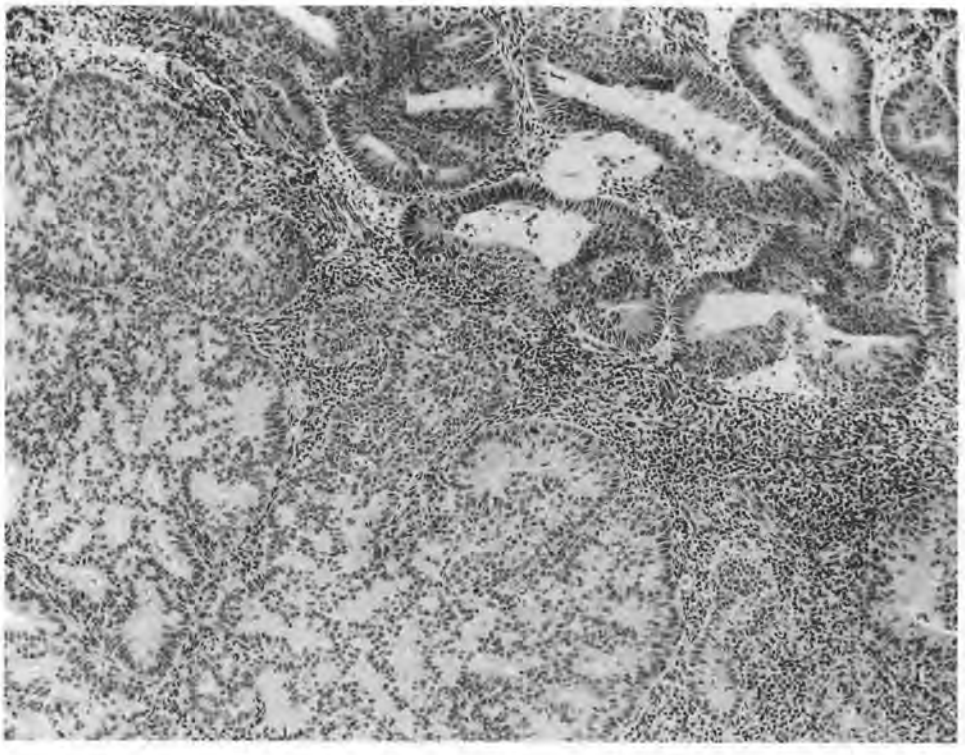

FIGURE 4-96 Well-differentiated adenocarcinoma (*bottom left*) and complex hyperplasia (*top right*).

Ciliated cell adenocarcinoma. *Ciliated cell adenocarcinoma* is another uncommon variant of endometrioid adenocarcinoma. In this form, the neoplastic glands are composed predominantly or exclusively of ciliated cells.[359] The outcome of the few cases reported has been relatively favorable. The differential diagnosis is with the much more common benign ciliary change, in which stromal invasion is obviously not present.

Adenocarcinoma with Squamous Differentiation (Adenoacanthoma [Adenocarcinoma with Squamous Metaplasia] and Adenosquamous Carcinoma). In the past decades, concepts of these tumors have changed considerably. They originally were thought to be rare tumors, characterized by foci of benign squamous metaplasia within an adenocarcinoma, and carrying a better prognosis than that of adenocarcinoma without this additional finding.[360] In the past quarter century,[316,317,361–365] these tumors became recognized as fairly common (up to 50% of endometrial carcinomas in some series). Although it was originally thought that this reflected a true increase in incidence in recent years,[361] most subsequent studies have not revealed such an increase.[316,363,366] The separation of adenocarcinomas with squamous elements into adenoacanthomas and mixed adenosquamous carcinomas resulted from the work of Ng and colleagues.[361] The former lesion is characterized by squamous or morular elements that appear histologically benign and generally grow either on the surface of the endometrial tumor or within gland lumina (Figs. 4-100 and 4-101). The glandular elements are almost always of histologic grade I; the prognosis is at least as favorable as for similar-grade adenocarcinomas and in our hands is probably even more favorable. On the other hand, in adenosquamous carcinomas, the squamous elements possess cellular characteristics of malignancy and usually invade the stroma (Fig. 4-102). The glandular elements are usually moderately or poorly differentiated, and indeed sometimes it is difficult to distinguish the undifferentiated portion of a grade II or III adenocarcinoma from poorly differentiated squamous elements. In such a case, unless squamous differentiation can be demonstrated clearly, the diagnosis of adenosquamous carcinoma should not be made. The criteria for squamous differentiation adopted by ISGP[128] are as follows:

1. keratinization demonstrated with standard staining techniques
2. intercellular bridges
3. three or more of the following four criteria:
   sheet-like growth without gland formation or palisading
   sharp cell margins
   eosinophilic and thick or glassy cytoplasm
   a decreased nuclear–cytoplasmic ratio (compared with foci elsewhere in the same tumor).

Although the criteria discussed above for benignity versus malignancy of the squamous elements can then be applied, the ISGP and several recent reports[317,364,365] have recommended the use of the more inclusive term *adenocarcinoma with squamous*

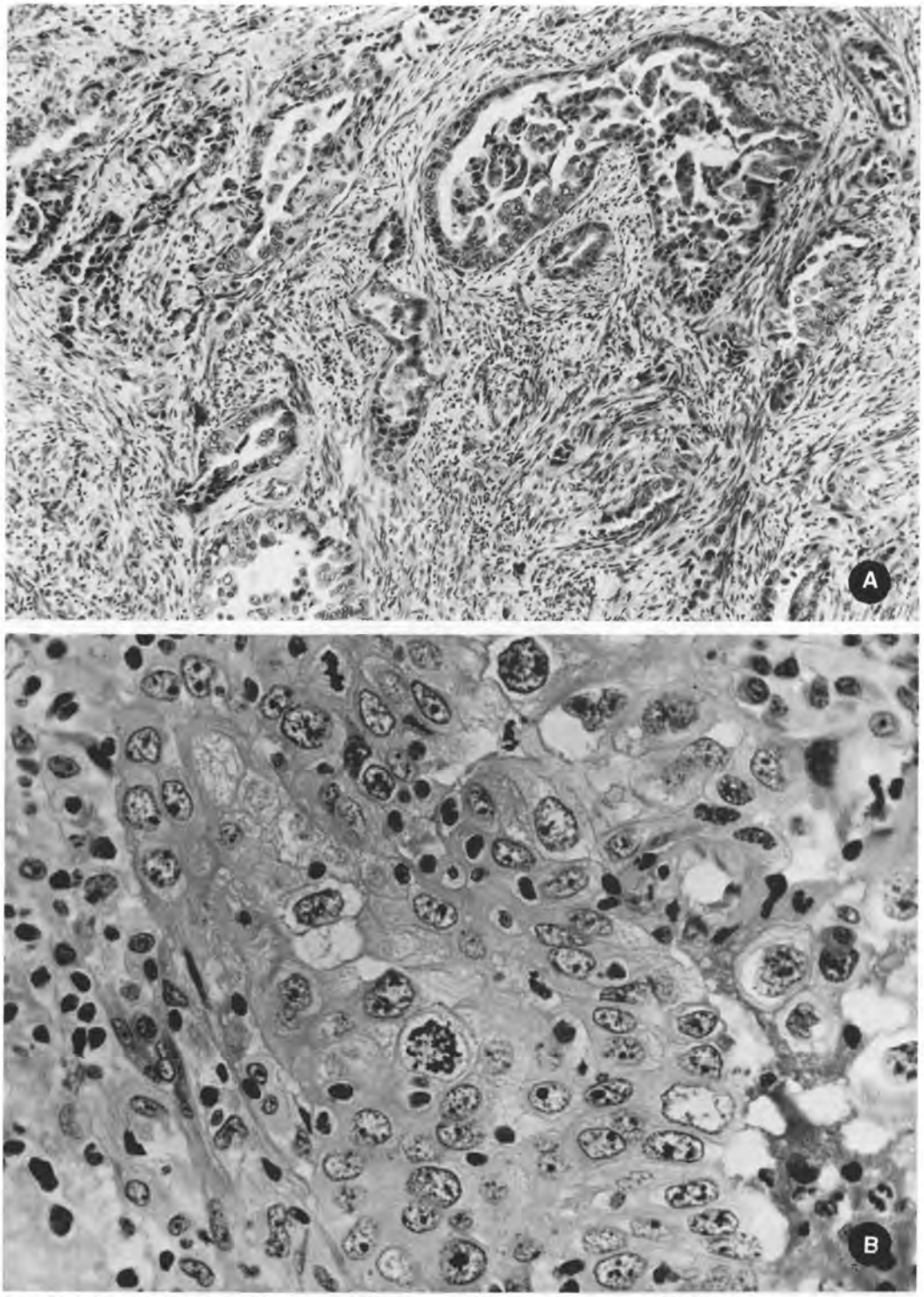

FIGURE 4-97 Moderately differentiated (FIGO grade II) adenocarcinoma. **(A)** Glandular components. **(B)** Detail of solid component.

differentiation for both adenoacanthoma and adenosquamous carcinoma, on the basis of the demonstration that the grade of the glandular component rather than the appearance of the squamous elements is most important prognostically.

The differential diagnosis of adenoacanthoma is with extensive squamous or morular metaplasia (see above) associated with benign glandular elements, frequently in the form of endometrial hyperplasia (see Figs. 4-48 and 4-83). The diagnosis of this type of carcinoma is made from the glandular elements, which must show the features previously described for grade I or II adenocarcinoma. In adenoacanthoma, the glandular elements almost always domi-

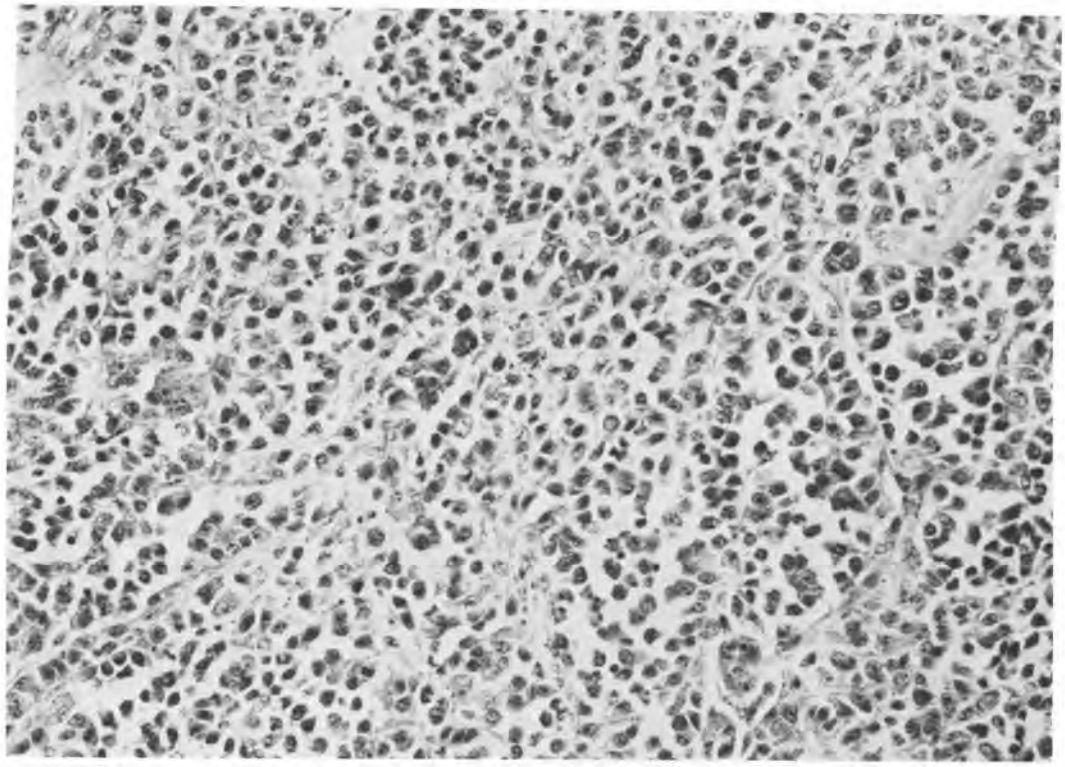

FIGURE 4-98 Poorly differentiated (FIGO grade III) adenocarcinoma.

nate the squamous or morular ones. In adenosquamous carcinoma, although the glandular elements most often dominate, the squamous component may be equally prominent or even dominate the picture. Indeed, we have seen adenosquamous carcinomas that we thought were pure squamous cell carcinomas of the endometrium until multiple sections were taken. Similarly, adenosquamous carcinoma may metastasize as an adenocarcinoma, a pure squamous cell carcinoma, or in a mixed pattern. As mentioned above, the usual poor survival figures reported for adenosquamous carcinoma are thought to be due largely to the generally poor differentiation of the glandular elements. The squamous elements in this tumor are said to be aneuploid, as opposed to those in adenoacanthoma.[366]

Squamous Cell Carcinoma or Epidermoid Carcinoma. Squamous cell carcinoma or epidermoid carcinoma of the endometrium is rare, with about 30 cases reported.[367] It originates in a focus of benign

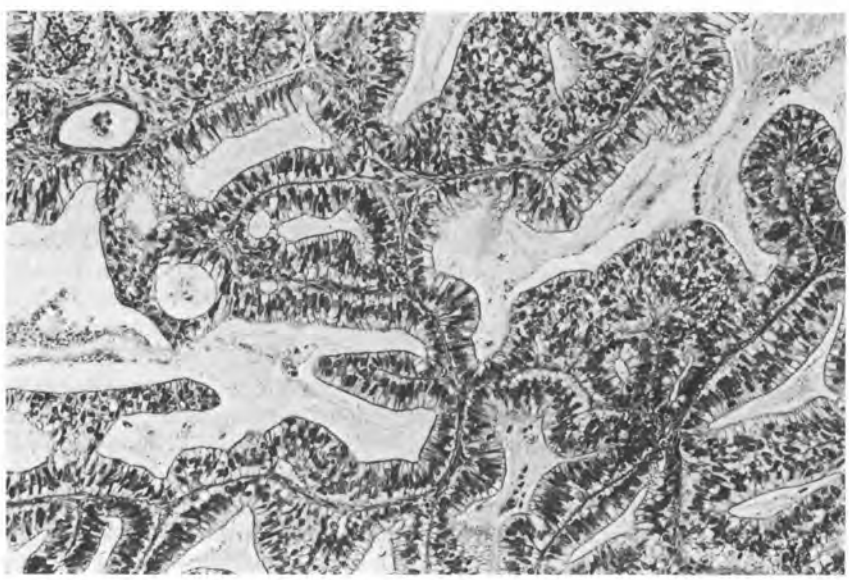

FIGURE 4-99 Secretory carcinoma: back-to-back glands cytologically resembling normal early secretory endometrium.

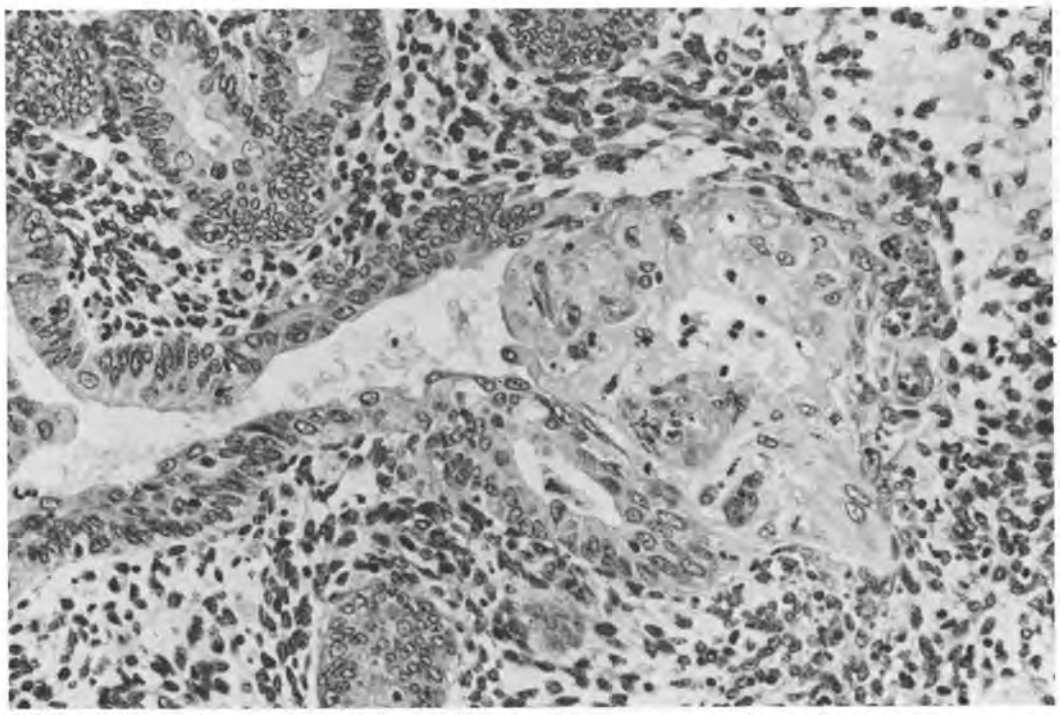

FIGURE 4-100 Adenoacanthoma (adenocarcinoma with squamous metaplasia) of endometrium: histologically benign squamous epithelium within gland lumen.

squamous metaplasia or as an overgrowth of an adenosquamous carcinoma. To establish a corporeal epidermoid carcinoma as definitely of endometrial origin, one must prove the absence of foci of adenocarcinoma in the endometrium, of coexistent invasive epidermoid carcinoma of the cervix, and of any continuity between the tumor and the cervical squamous mucosa.[368,369] These rare cases are composed of cords and nests of poorly differentiated squamous cells, among which are outlines of pearls and other foci of keratinization. Nuclear anomalies and mitoses are of variable prominence.

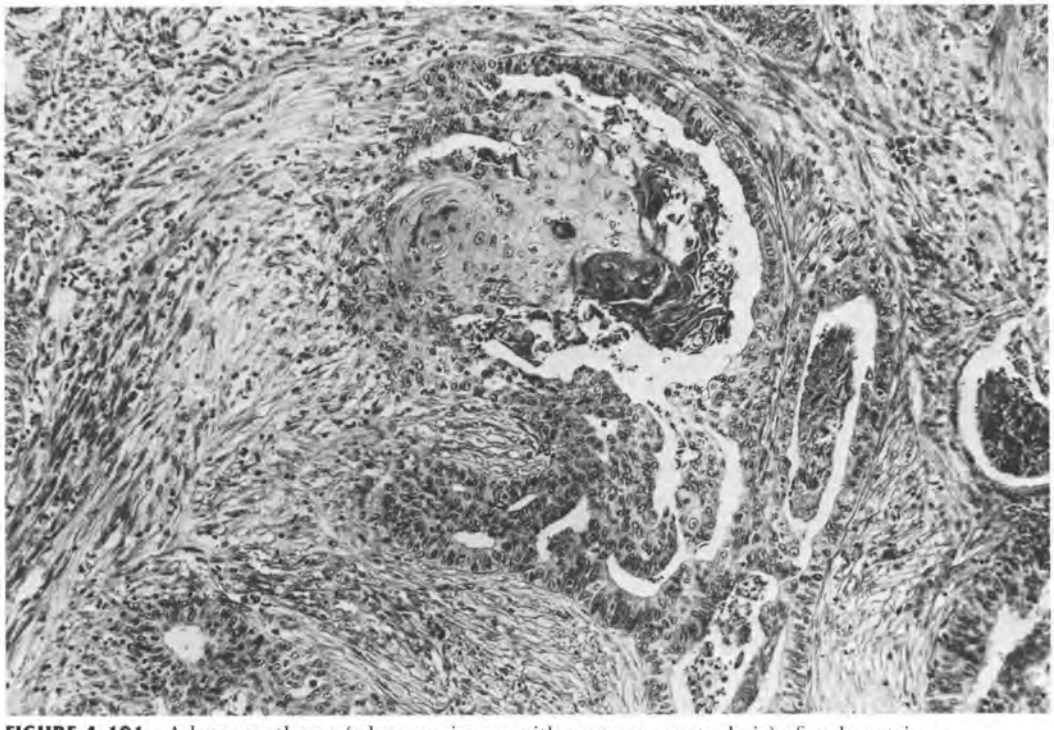

FIGURE 4-101 Adenoacanthoma (adenocarcinoma with squamous metaplasia) of endometrium.

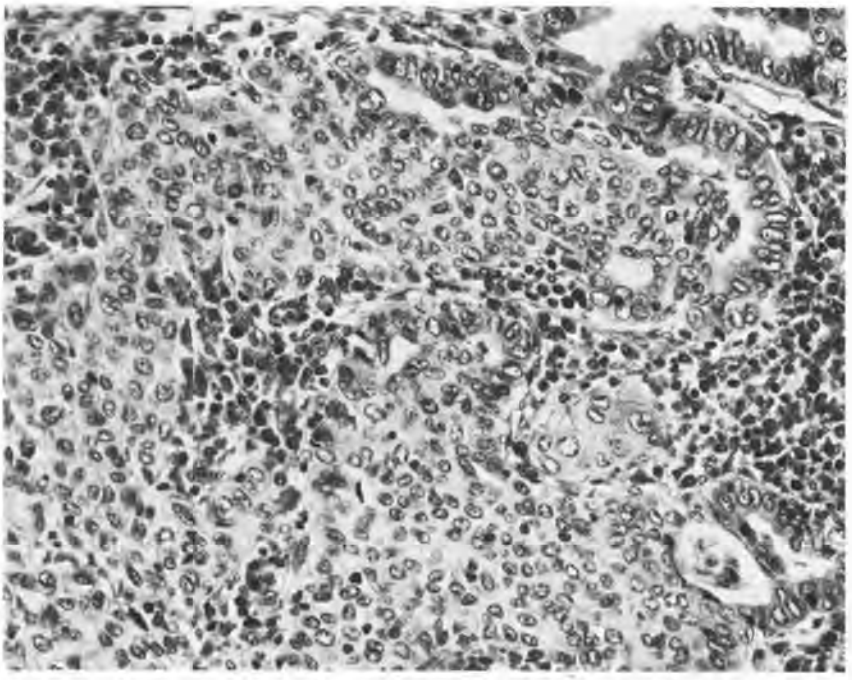

FIGURE 4-102 Adenosquamous carcinoma: detail of neoplastic glands and invasive, histologically malignant, squamous elements.

Serous Carcinoma. *Serous carcinoma* is probably the most important of the nonendometrioid adenocarcinomas, both because of its frequency (5% to 10% of all endometrial carcinomas) and its distinctive natural history. It is defined as a primary carcinoma of the endometrium that is histologically identical to its more common counterpart seen in the ovary.[235,236,370–376] This type of tumor is generally seen in older women and is usually moderately to poorly differentiated (Fig. 4-103). Characteristic histologic findings include broad papillae with fibrovascular cores, lined by secondary papillae with tufting and exfoliation of small clusters of cells. Psammoma bodies are a frequent but not universal finding. The cells and their nuclei are generally smaller and rounder than those of most endometrioid adenocarcinomas. The differential diagnosis includes papillary variants of both classic endometrioid and clear cell carcinoma, as well as the papillary metaplasia usually seen at or near the endometrial surface (see above). Although they frequently occur in small uteri, serous carcinomas generally extensively invade the myometrium within lymphatics or blood vessels (Fig. 4-104), are usually disseminated beyond the uterus at the time of diagnosis, and have a very poor prognosis. It has recently been shown that dissemination (perhaps really multifocal peritoneal neoplasia) is a major threat even when serous carcinoma in the uterus is limited to the endometrium or an endometrial polyp.[235,236,375,376]

Clear Cell Adenocarcinoma. This tumor, like serous carcinoma, is associated with a poor prognosis even when apparently confined to the uterine corpus or to the endometrium itself.[236] It comprises about 4% of endometrial carcinomas.[373,377–380] It occurs predominantly in postmenopausal women and is often in an advanced stage when first detected. Microscopically, the characteristic feature is the presence of large tumor cells with voluminous clear cytoplasm containing glycogen. A second population of cells projecting individually into lumina (hobnail cells) may be as numerous or even more so than the clear cells. Mucin may be present in lumina but rarely in tumor cell cytoplasm. The stroma is often focally hyalinized. The tumor cells grow in tubular (Fig. 4-105), papillary (Fig. 4-106), solid (Fig. 4-107), or mixed architectural patterns. The nuclei are usually pleomorphic and, if these tumors are to be graded at all, nuclear grading should be used exclusively. The differential diagnosis is with benign clear cell, hobnail cell, and Arias-Stella changes, and with serous carcinoma. The latter may frequently coexist with clear cell carcinoma.[376]

Mucinous Adenocarcinoma. *Mucinous adenocarcinoma* comprised 9% of all stage I endometrial carcinomas in one series[381] but is much less common in our experience. It is defined as an adenocarcinoma in which most of the tumor cells contain prominent intracytoplasmic mucin (Fig. 4-108). The tumor is usually well differentiated and the prognosis is favorable.[381,382] The differential diagnosis includes mucinous metaplasia (distinguishable on architectural features), primary endocervical adenocarcinoma, and otherwise typical endometrioid endometrial adenocarcinomas with minor foci of mucinous differentiation or abundant luminal rather than intracytoplasmic mucin.

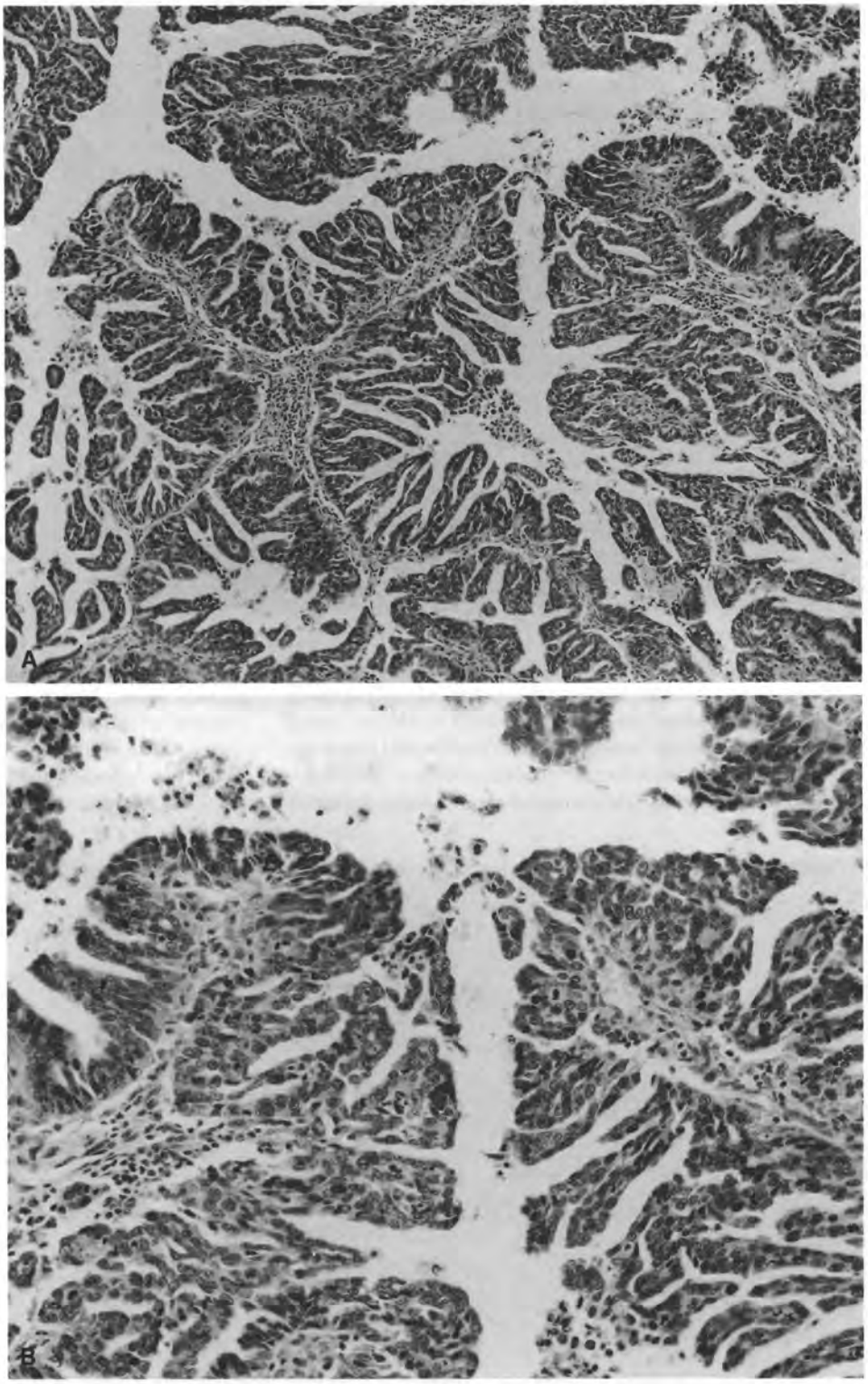

FIGURE 4-103 Serous adenocarcinoma. **(A)** Low-power photomicrograph showing complex papillary architecture. **(B)** Detail of small cells with round nuclei and frequent mitotic figures; tumor cells and necrotic debris are exfoliated into lumina. Compare with Figures 4-92 and 4-93.

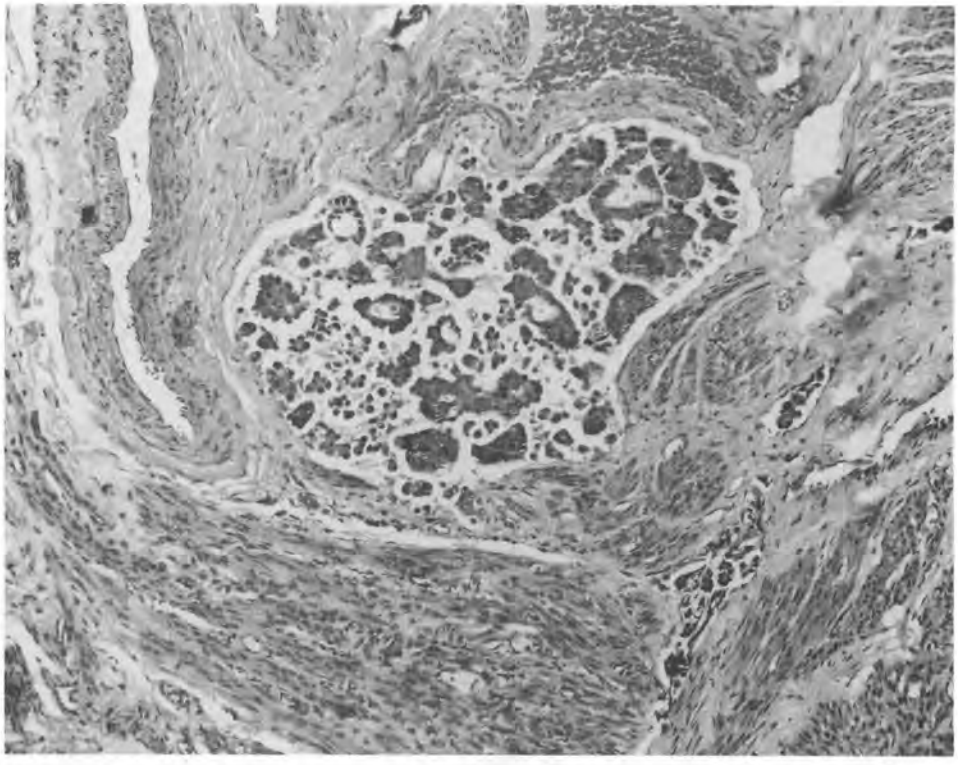

FIGURE 4-104 Serous adenocarcinoma of endometrium invading myometrial lymphatics.

Other Forms of Carcinoma. In addition to these histologic types of carcinoma, certain other patterns have been reported in the endometrium. Some cases of adenocarcinoma indistinguishable from the more common types described here may be shown, with appropriate stains, to contain argyrophil cells.[383] This demonstration is probably not of prognostic significance. Much more rare is a true *small cell carcinoma* of the endometrium resembling similar tumors seen in the bronchial tree.[384,385] These and other *undifferentiated carcinomas*[385] have a very poor prognosis.

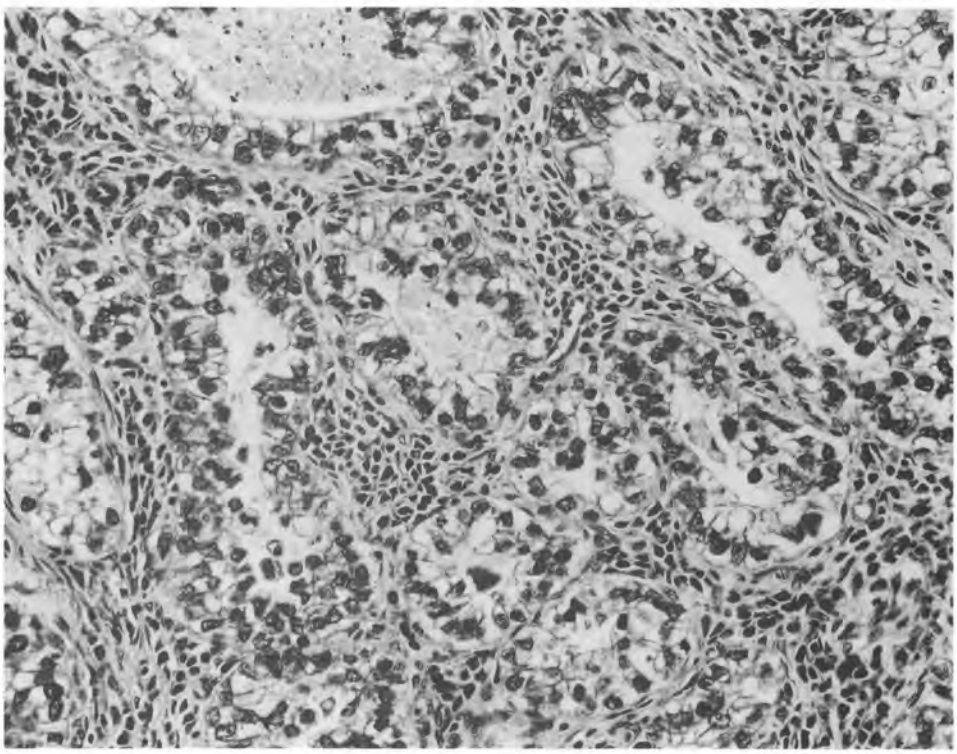

FIGURE 4-105 Clear cell adenocarcinoma, tubular pattern.

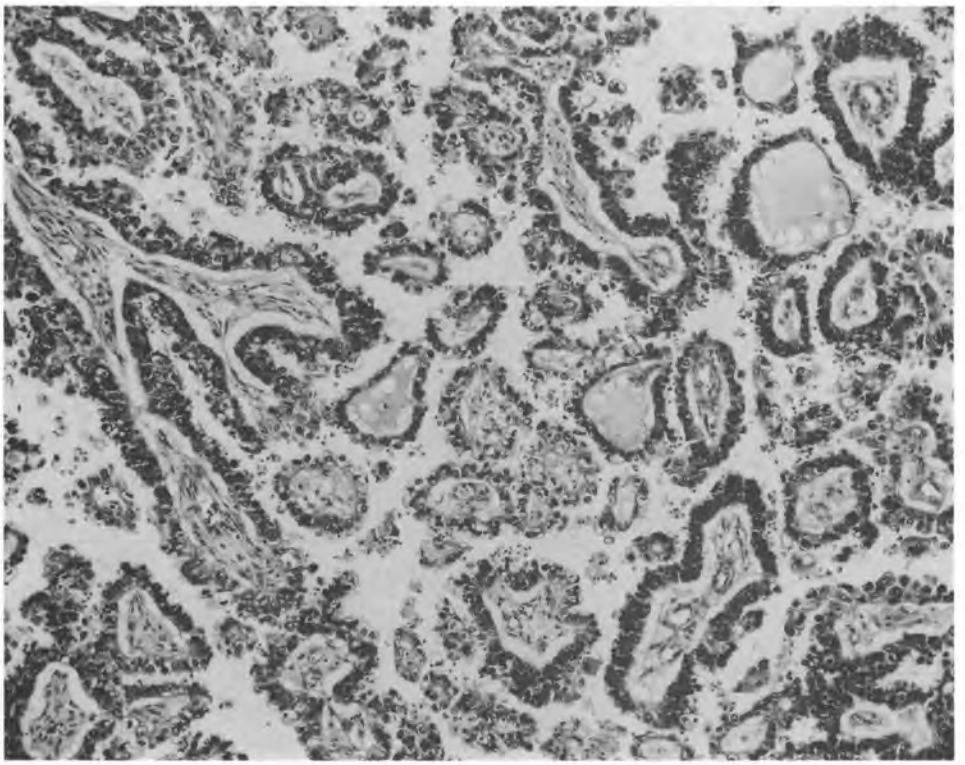

FIGURE 4-106 Clear cell adenocarcinoma, papillary pattern.

Other tumor types that occur more frequently in the cervix, but have been reported in the endometrium, include *glassy cell carcinoma*,[386] *verrucous carcinoma*,[387] and adenocarcinomas with *giant cell carcinoma*[388] and with *trophoblastic differentiation*.[389]

Mixed Carcinomas. *Mixed carcinoma of the endometrium* is a carcinoma containing more than one of the cell types described above. For the tumor to be characterized as mixed, the second type must comprise at least 10% of the total volume of the tumor,

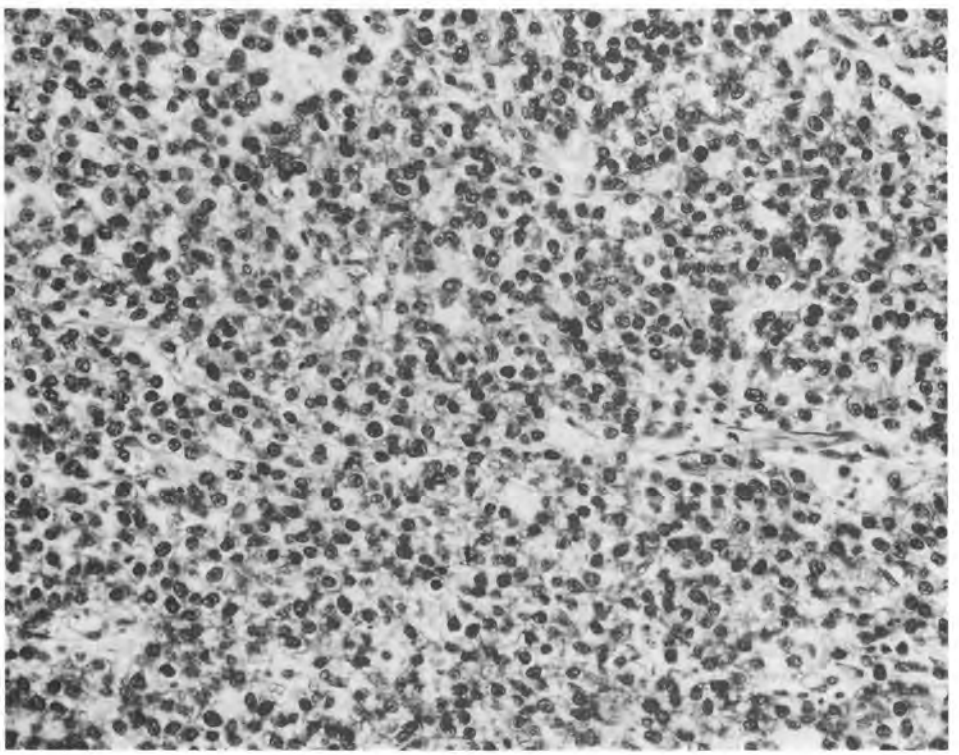

FIGURE 4-107 Clear cell adenocarcinoma, solid pattern. Figures 4-105 through 4-107 represent different fields within the same tumor.

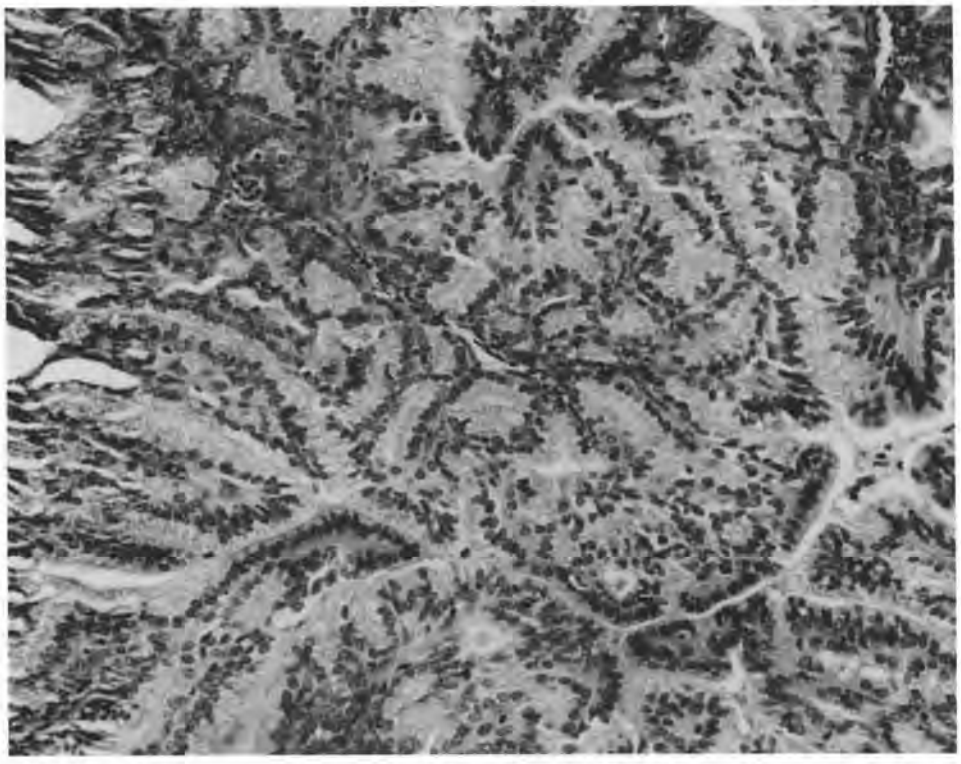

FIGURE 4-108 Mucinous adenocarcinoma of endometrium.

as estimated from the examination of multiple sections. The types of tumor encountered and their relative proportions should be specified in the pathology report. The prognostic implications of mixed carcinomas in which the subordinate type is less favorable have been poorly characterized, but Sherman and colleagues have suggested that tumors with 25% or more of a serous pattern display the unfavorable prognostic characteristics of pure serous carcinoma.[376]

Cytology. We prefer techniques that provide histologic rather than cytologic material for the definitive diagnosis of endometrial carcinoma, and techniques are available that provide such material on an outpatient basis in most cases. In a summary of the literature, Vuopala[309] noted an accuracy rate of 97% in the diagnosis of endometrial carcinoma with the Vabra aspiration technique, as compared with 42% to 70% in techniques relying predominantly on cytologic interpretation of vaginal or cervical material, 73% for endocervical aspiration, and 75% to 88% for techniques using cytologic interpretation of material obtained directly from the endometrial cavity. The criteria for diagnosis of endometrial carcinoma from vaginal or cervical material are similar to those described for endometrial hyperplasia and often merely involve finding endometrial cells at the wrong time (late in the menstrual cycle or in a postmenopausal woman). In the case of carcinoma, these cells usually show greater cytologic atypia than is encountered in most hyperplasias.

Although poorly differentiated endometrial carcinomas usually do not pose any problems in cytologic diagnosis, a well-differentiated or grade I lesion may be difficult to distinguish from hyperplasia or even normal endometrium. The major distinguishing characteristic is cell size, which is generally larger than that of any benign endometrial cell, although smaller than the malignant endocervical cell. The cell size in endometrial carcinoma increases as the differentiation decreases. In addition to size, the nuclear chromatin is irregularly distributed and varying degrees of hyperchromasia are present (Color Fig. 4-6). The nucleus is generally round to oval, as is the cell itself. Although isolated cells may be seen, small groups are the rule. Enlarged solitary nucleoli are the general rule, although occasionally multiple nucleoli may be seen in a single nucleus. The cytoplasmic borders are usually indistinct, and one, several, or many vacuoles may be present in the cytoplasm. The cells often contain leukocytes or cellular debris. Relatively few tumor cells may be seen, particularly in material obtained distant from the endometrial cavity itself and in well-differentiated carcinomas. In these cases, an inflammatory diathesis consisting of cellular debris, leukocytes, erythrocytes, histiocytes, and fibrin may provide the first clue to the diagnosis of a carcinoma.

Although this discussion is largely relevant to adenocarcinoma of the endometrioid type, other histologic types may be diagnosed by finding the appropriate cells in cytologic material: benign squamous cells coexisting with malignant glandular ones in ade-

noacanthoma (Color Fig. 4-7), malignant glandular and squamous cells in adenosquamous carcinoma, abundant well-preserved cytoplasm (occasionally optically clear) in clear cell carcinoma, and papillary structures with occasional psammoma bodies in serous carcinoma.

Staging of Endometrial Carcinoma. The FIGO clinical staging system in use for many years was superseded in 1988 by a surgical staging system (Table 4-6).[352] Clinical staging is now supposed to be used only for patients who are not candidates for staging by laparotomy, usually for medical reasons (eg, marked obesity and severe diabetes). The extent of surgical staging in an individual patient—for example, whether lymph node dissection will be performed—is often based on an estimate of risk versus benefit, which in turn is based on an assessment of tumor type and grade, extension to involve the cervix, and depth of myometrial invasion. Most studies have shown the intraoperative evaluation of these factors to be more reliable by frozen section than by gross evaluation only of the hysterectomy specimen.[390-392]

One effect of surgical staging is to eliminate the confusion formerly caused by the use of fractional (endometrial and endocervical) curettage to identify carcinomas that have extended to the cervix (stage II). If such a procedure is performed, the pathologist should remember that the presence of carcinoma in the specimen submitted as "endocervix" does not confirm stage II disease unless cancerous invasion of endocervical stroma can be demonstrated histologically.[390,393,394] The value of separating new surgical stages IIA and IIB has been confirmed in one recent report in which the recurrence rates in these two stages were 0 and 63% respectively.[395]

Another problem encountered in staging endometrial carcinomas involves the best definition of stage III disease. It has been shown in several series[396-399] that some patients with carcinoma involving the endometrium and one or both ovaries probably have separate primaries rather than metastatic disease. In these cases, the patients are usually young, the tumors well-differentiated, and the prognosis excellent, in contrast to other patients with true stage III disease.

Despite these problems, several studies have already confirmed the value of surgical staging of endometrial carcinoma.[395,400,401] Because grading is included in the new staging system, the advisability of raising the architectural grade for "inappropriate" nuclear atypia has been questioned by some investigators.[402,403]

Evolution, Prognosis, and Treatment. The degree of differentiation in adenocarcinoma shows good correlation with the clinical prognosis. As a general rule, the better differentiated the tumor, the longer the median survival (all other factors, such as size, myometrial invasion, clinical stage, patient age, and adequacy of initial therapy, being equal).[390,400,401,404-406] Only endometrioid adenocarcinoma and its variants can be graded reproducibly and meaningfully by the usual criteria.

Adenocarcinoma of the endometrium remains localized for a long time and, for this reason, has a more favorable evolution than carcinoma of the cervix. Metastatic dissemination by the lymphatic route involves the hypogastric, iliac, aortic, and lumbar nodes, but rarely occurs in the absence of myometrial or cervical invasion.[400,407,408] It is common to find intralymphatic tumor infiltrates beneath the vaginal mucosa as the first sign of recurrence after surgical or radiation therapy;[409] modifications of the lymphatic circulation brought about by postradiotherapeutic secondary fibrosis may be invoked to explain these retrograde localizations. The occurrence of ovarian and pelvic peritoneal metastases by means of the intratubal route,[410] by a mechanism identical to that advanced to explain these localizations of endometriosis, may not be of great importance.[411] Peritoneal dissemination in cases of serous carcinoma may represent multifocal carcinomatosis.[235,236,375,376] Hematogenous metastases generally appear late in the course of the disease and localize with greatest frequency in the lungs, liver, and bones. In extensive cases, the tumor breaks through the uterine serosal surface and involves the peritoneum. Considering all clinical and histologic groupings together, endometrial adenocarcinoma shows a 5-year survival rate in the range of 70%, somewhat more favorable than that of cervical carcinoma.[412] By clinical stage, the 5-year survival rate is about 75% to 80% in stage I, 50% to 60% in stage II, 30% in stage III (but better if the only extrauterine tumor is in the ovaries),[396-399] and 10% in stage IV. These survival rates are better in the corresponding surgical stages.[412] They are generally worse for serous, clear cell, pure squamous cell, and undifferentiated carcinomas.

TABLE 4-6.
The 1988 FIGO Surgical Staging System for Uterine Corpus Carcinoma

Stage I: Confined to the uterine corpus
- IA Tumor limited to endometrium
- IB Invasion of less than half of the myometrium
- IC Invasion of more than half of the myometrium

Stage II: Uterine cervix involved
- IIA Endocervical glandular involvement only
- IIB Cervical stromal invasion

Stage III: Pelvic extension
- IIIA Tumor invades serosa and/or adnexa and/or positive peritoneal cytology
- IIIB Vaginal metastasis
- IIIC Metastases to pelvic and/or paraaortic lymph nodes

Stage IV: Extrapelvic extension
- IVA Tumor invasion of bladder and/or bowel mucosa
- IVB Distant metastases including intra-abdominal and/or inguinal lymph nodes

Regardless of the histologic type, the presence and extent of myometrial invasion are important prognostic features. Most important is the observation that endometrioid tumors without any myometrial invasion have a negligible risk of metastasis.[390,400,401] The extent of myometrial invasion, when present, definitely relates to the likelihood of metastasis and death. Different authors have proposed different ways of measuring the extent of myometrial involvement,[413,414] although the classic expression of invasion into the inner, middle, or outer third of the myometrium is the system that we have usually used, and the inner or outer half is now mandated by FIGO. It is important not to overinterpret as myometrial invasion the extension of carcinoma into "tongues" of endometrium penetrating shallowly into the myometrium or extension into foci of adenomyosis.[184,185] Rounded rather than angular tumor borders, as well as residual nests of benign endometrial stromal cells, are helpful in both of these circumstances.

In addition to these tumor-related factors, host-related factors are of prognostic importance. The favorable prognosis of endometrial carcinoma in young women, particularly in association with the Stein-Leventhal syndrome, has long been noted, and observations have indicated that elderly patients with endometrial carcinoma have a particularly poor prognosis.[415] The significance of a host immunologic response is probably also considerable.[338]

Other factors of unfavorable prognostic significance include the presence of myometrial lymphatic/vascular space invasion,[416–419] involvement of the lower uterine segment by cancers limited to the corpus,[420,421] and positive peritoneal cytology.[422–424] It is hotly debated whether the latter finding is an independent indicator of poor prognosis, with most studies claiming that it is not independent of other factors such as stage and grade. The last major histologic factor associated with prognosis is the presence in nonneoplastic endometrium accompanying the tumor of hyperplastic[425,426] or metaplastic changes,[139,140] which appears to convey a more favorable prognosis. This goes along with the observation that carcinomas developing in a background of endogenous or exogenous hyperestrinism tend to be of a more favorable type.[326,337,339,427]

Other nonmorphologic factors may also be important in prognosis. These include the presence of estrogen and progesterone receptors in the tumor[333,334,336] (although a primary carcinoma and its metastases may not show the same pattern[428]), the finding of specific oncogene alterations,[340,341] and quantitative features including those analyzed by flow cytometry.[429–431]

Treatment is determined in large measure by the surgical staging findings and usually is limited to surgery in favorable cases. Vaginal or external irradiation may be added (formerly often before surgery, now usually postoperatively).[432–434] Some medically inoperable patients may be treated by radiation therapy alone.[435] Chemotherapy[436] or hormonal therapy[437] can be used for advanced or recurrent disease. The presence of hormone receptors in the tumor augurs a favorable response to treatment with progestins.[437] Recurrences in endometrial carcinoma are detectable within 2 years in 70% of the cases destined to recur.[438]

Uterine Sarcomas and Mixed Epithelial-Nonepithelial Tumors

Malignant connective tissue and mixed tumors are more common in the corpus than in the cervix uteri and characteristically appear in mature women. They represent 5% or fewer of malignant uterine corporeal tumors, although they constitute a higher percentage in black women. Their clinical presentation is essentially identical to that of endometrial carcinoma: serosanguineous or frankly hemorrhagic discharge; presence of a palpable mass; pain when the tumor is extensive; cachexia, anemia, and metastatic generalization at the terminal stage. The background of hyperestrogenism and the clinical triad of obesity, hypertension, and diabetes often seen in women with endometrial carcinoma are of less significance in relation to sarcomas. Epidemiologic factors are difficult to analyze in this heterogeneous group of tumors, because factors favoring the development of, for example, leiomyosarcoma may be entirely different from those related to carcinosarcoma. Unfortunately, most studies tend to consider all of these tumors as a single group.[439] We do know that pelvic irradiation seems to play a role in the development of carcinosarcomas but probably not of the other tumors in this group.[440] Hyperestrinism may also contribute to the development of carcinosarcomas.[441]

The classification of uterine sarcomas and mixed tumors is presented in Table 4-5, with the exception of the malignant smooth muscle tumors (leiomyosarcomas), which are included in Table 4-3. The discussion here will focus first on pure endometrial stromal tumors, then the mixed tumors (including some benign variants) of endometrial origin, and finally on leiomyosarcoma and rare malignant tumors of the uterine corpus.

Any classification, no matter how complete, must still leave room for an occasional undifferentiated or unclassifiable sarcoma, as well as for malignant tumors the epithelial or nonepithelial nature of which is not apparent. We hope that future studies will resolve continuing problems about the nature, treatment, and natural history of such lesions.

Endometrial Stromal Tumors. Although the uterine tumors of pure endometrial stromal type were first described in 1908,[442] they were not well characterized until the classic study of Norris and Taylor in 1966.[443] This latter publication divided the endometrial stromal tumors into three types with very different clinical implications:

1. Stromal nodule, a benign tumor
2. Low-grade endometrial stromal sarcoma, formerly known as *endolymphatic stromal myosis,* a malignant tumor of generally indolent aggressive behavior
3. High-grade endometrial stromal sarcoma, a fully malignant tumor with a generally unfavorable prognosis.

The pathologic criteria for distinguishing these three lesions have become somewhat controversial in recent years, with the proposed addition of a fourth diagnostic entity—poorly differentiated endometrial sarcoma.[444]

Despite the controversy at the higher end of the spectrum of malignancy in this group of neoplasms, the criteria for the diagnosis of the benign *stromal nodule* have remained constant. This lesion is defined as a well-circumscribed tumoral proliferation of uniform cells resembling the stromal cells of normal proliferative-phase endometrium. The key term in this definition is *well-circumscribed,* because the pushing margins of this lesion are essentially the only feature by which it may be distinguished from low-grade endometrial stromal sarcoma. *Nodule* is probably a misleading term, because these lesions can measure up to 15 cm in diameter, with median diameters of 4.0 cm[445] and 5.7 cm[446] in the two largest series reported. In any event, there is complete agreement that stromal nodules—regardless of their size—are completely benign, with no known recurrences or deaths in any published series.

As indicated above, *low-grade endometrial stromal sarcoma* is composed of cells that are essentially identical to those of the benign stromal nodule, the only difference between the tumors being the infiltrative margins of low-grade stromal sarcoma, compared with the virtually total circumscription of the stromal nodule. Low-grade stromal sarcomas may appear grossly well circumscribed, but at least half of these tumors are described as demonstrating diffuse myometrial permeation by worm-like masses or multiple nodules, with gross extrauterine extension in as many as one-third of cases.[444–447] At the microscopic level, these tumors are by definition infiltrating. They are always seen in the myometrium and frequently involve the endometrium as well. Plugs of tumor are commonly identified within lymphatic or venous channels, leading to the frequent designation of this tumor in the older literature as *endolymphatic stromal myosis.* Despite this extensive invasion, these tumors are cytologically no more malignant in appearance than the stromal nodule. The component cells are small and uniform in size and shape, with minimal cytologic atypia and generally few mitotic figures (Figs. 4-109 and 4-110). More than 10 mitotic figures per 10 high-power microscopic fields are occasionally seen, but increased mitotic activity alone, in the absence of other criteria of high-grade malignancy, does not appear to influence the behavior of the tumor. Atypical mitoses are not seen in the low-grade tumors, and large foci of necrosis are usually absent.

A characteristic feature is the vascular pattern, with many of the numerous vessels in the tumor resembling the spiral arterioles of normal endometrium, with tumor cells arranged in a whorling pattern around them. Additional features occasionally encountered focally or diffusely include epithelioid differentiation, characterized by a glandular or sex cord–like pattern,[446–448] and foci of smooth (and rarely skeletal) muscle differentiation.[449]

Immunohistochemical studies have shown a highly variable pattern, with virtually all tumors positive for vimentin, many for both desmin and smooth muscle actin, and some for epithelial markers.[450,451] Flow cytometric analysis reveals a diploid or near diploid pattern.[452,453] The tumors usually contain estrogen and progesterone receptors and are responsive to progestin therapy.[452,454–456]

Low-grade stromal sarcoma is a malignant tumor, but the initial local recurrence or distant metastasis may take place many years after the initial surgery was performed, especially in the case of tumors that were initially limited to the uterine corpus. It is not at all unusual in our experience to see a patient who presents with a pelvic, abdominal, or even pulmonary tumor with the histologic features of low-grade endometrial stromal sarcoma and a history of hysterectomy for supposed leiomyomata or adenomyosis 10 or 15 years earlier. On histologic review of the hysterectomy specimen, the primary sarcoma generally is identified. These tumors may also be primary in the ovary or in extrauterine and extraovarian foci of endometriosis—a fact that is also true for the other sarcomas and mixed tumors and (as is well known) for endometrioid carcinoma as well.

The differential diagnosis between endometrial sarcomas of low and high grade has become somewhat controversial within the past decade. In the classic article of Norris and Taylor,[443] the distinction between low-grade and high-grade sarcomas of endometrial stromal type was made solely on the basis of mitotic counting, with more than 10 mitotic figures per 10 high-power fields considered diagnostic of the high-grade tumor. More recent studies have suggested that increased mitotic activity alone does not alter the behavior of a low-grade sarcoma, and more than 10 mitoses per 10 high-power fields are even reported in occasional stromal nodules, which still behave benignly if otherwise well differentiated and well circumscribed.[445,446] In 1982, Evans[444] suggested that there were really two fundamental types of sarcoma derived from the endometrial stroma: a tumor for which he retained the name *endometrial stromal sarcoma,* which could be more or less mitotically active but still resembled endometrial stroma histologically, and a tumor that he designated *poorly differentiated endometrial sarcoma,* characterized by its anaplastic appearance, lack of resemblance to normal endometrial stroma, and frequent resemblance to the stromal component of carcinosar-

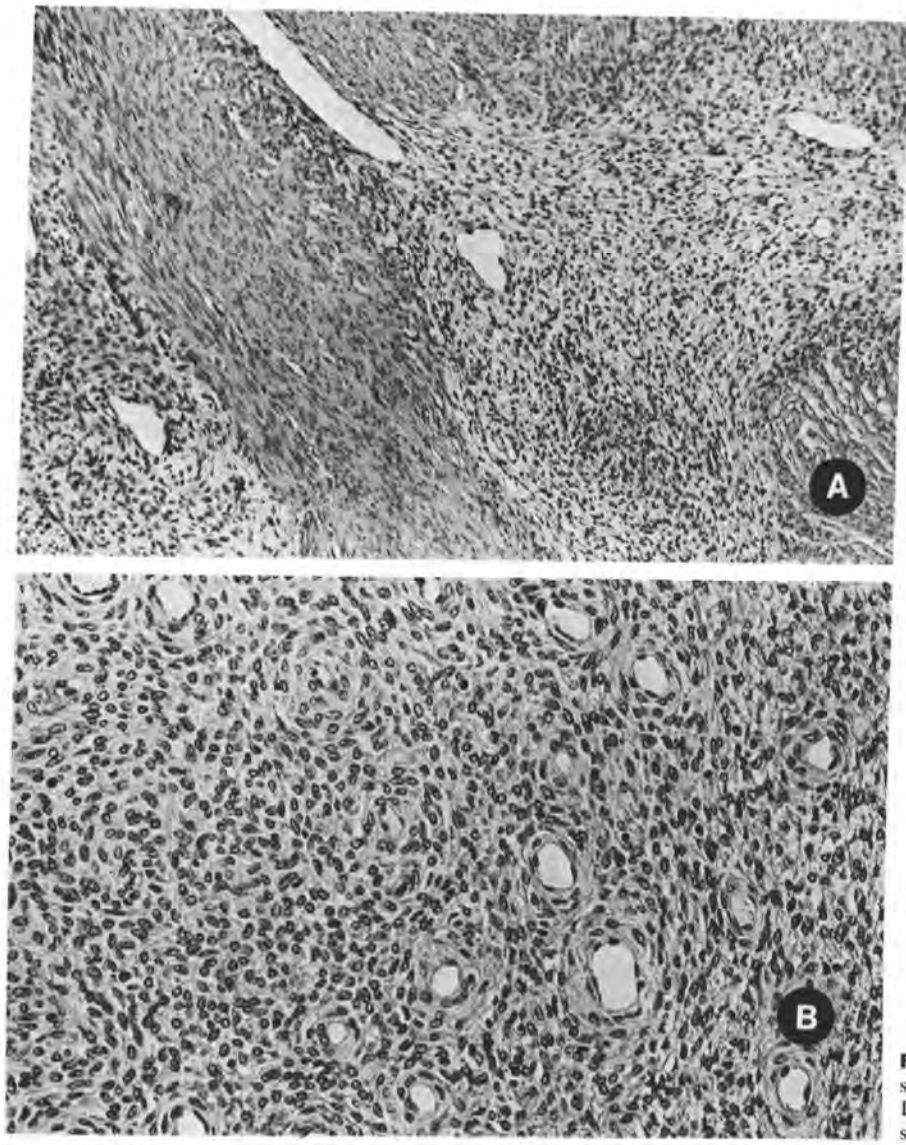

FIGURE 4-109 Low-grade endometrial stromal sarcoma. **(A)** Low-power view. **(B)** Detail. Note prominent vascularity and absence of atypia.

comas. Chang and colleagues[447] have recently endorsed this view. In their large series, neither mitotic activity nor cytologic atypia was predictive of tumor recurrence for patients with stage I sarcomas showing typical endometrial stromal differentiation.

The main question that remains to be answered is whether the complete body of endometrial stromal sarcomas should be divided into two groups with the nomenclature suggested by Norris and Taylor, two groups as defined by Evans, or three groups, as we would prefer—*low-grade stromal sarcoma, high-grade stromal sarcoma,* and *undifferentiated sarcoma.* In an unpublished study of Gynecologic Oncology Group (GOG) cases, we recently used this tripartite classification, accepting as high-grade endometrial stromal sarcomas those tumors that still showed to some extent the vascular pattern and cytologic features of endometrial stromal differentiation, but with considerably more cellular pleomorphism, often accompanied by necrosis, increased mitotic activity, and atypical mitotic figures as well (Fig. 4-111). Undifferentiated sarcoma was defined as a nonepithelial malignant neoplasm originating in the endometrium but showing no histologic features suggestive of endometrial stromal differentiation, and no features of any of the other common sarcomas (eg, leiomyosarcoma or rhabdomyosarcoma). Using these definitions, both of these tumor types were associated with a high probability of both initial extrauterine spread and subsequent recurrence, with a mortality rate in the range of 50% at a mean 2½-year follow-up. There were no deaths among the patients with low-grade stromal sarcomas in this series, although a few patients had already demonstrated local or distant recurrences. We anticipate that some of the low-grade tumors will prove to be lethal in the future, but probably for the most part more than 5 years after initial treatment.

The highly aggressive behavior of the high-grade and undifferentiated sarcomas is in agreement with

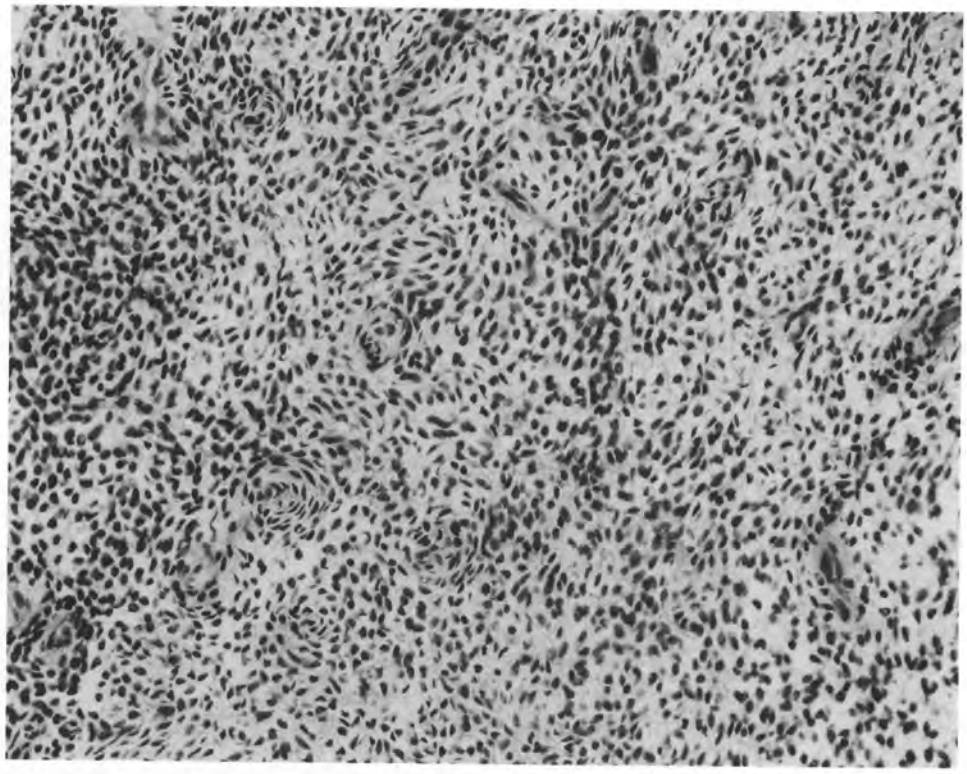

FIGURE 4-110 Low-grade endometrial stromal sarcoma: detail of bland cells and uniform vascular pattern.

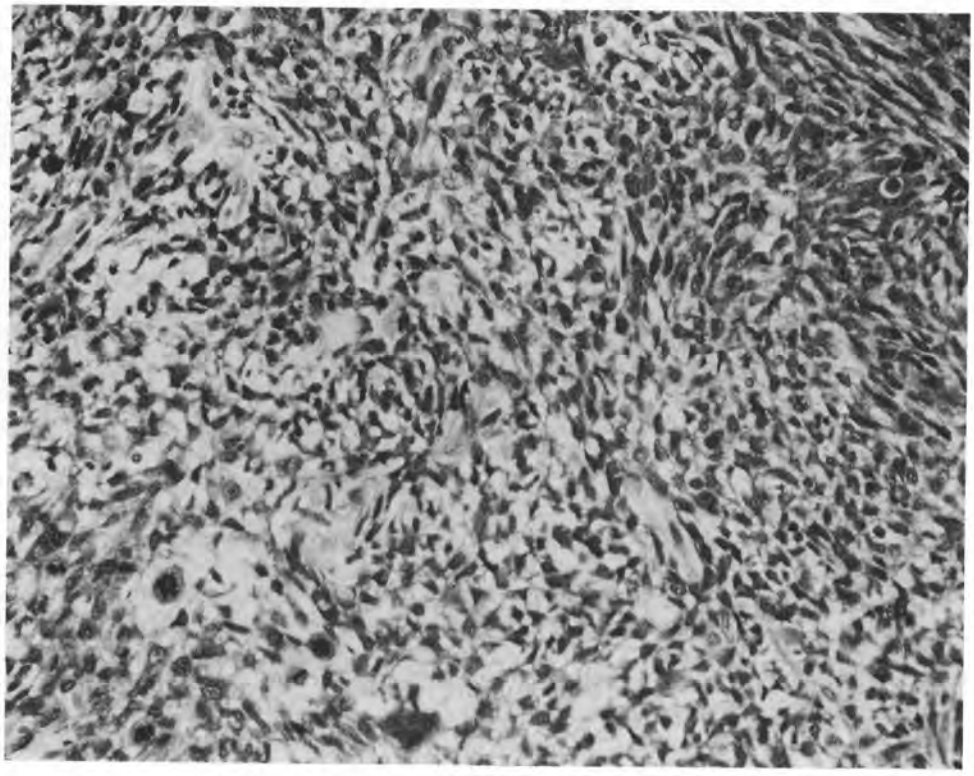

FIGURE 4-111 High-grade endometrial stromal sarcoma. General stromal pattern is retained, but the tumor cells are pleomorphic (compare with Fig. 4-110 at the same magnification). Note the atypical mitotic figure at lower left.

the studies reported in the literature.[444,446,456,457] However, the reported experience with these tumors is limited and perhaps not reliable, in part because they are considerably less common than the low-grade stromal sarcomas, and in part because diagnostic criteria and nomenclature have varied so widely, as discussed above. High-grade stromal sarcomas, in contrast to the low-grade type, tend to be receptor-negative and may be aneuploid.[458,459] Ploidy studies do not predict behavior better than classic histologic analysis.[459]

The primary *differential diagnosis* of the three tumors in this group is with each other. Low-grade stromal tumors must also be distinguished from intravenous leiomyomatosis and the extremely rare uterine *hemangiopericytoma*, which has a similar vascular pattern.[460] The high-grade and undifferentiated sarcomas have their differential diagnosis with poorly differentiated and undifferentiated endometrial carcinomas and other high-grade sarcomas of specific types (eg, malignant fibrous histiocytoma and leiomyosarcoma).

Mixed Epithelial-Nonepithelial Tumors. This group of tumors is one in which both an epithelial and a stromal component contribute to the architecture of the tumor. Because of the unusual composition of this group of tumors, they have always raised questions concerning their histogenesis and pathways of differentiation, as well as the relative contributions of the different elements in determining the natural history, prognosis, and treatment of each tumor in the group.

The nomenclature for the group of tumors presented in Table 4-5 provides a prefix (*adeno-* or *carcino-*) that conveys the benign or malignant appearance of the epithelial component, and a suffix (*-fibroma, -myoma,* or *-sarcoma*) that indicates the benign or malignant appearance of the nonepithelial component. Therefore, of the common mixed tumors of malignant type, carcinosarcoma contains both epithelial and nonepithelial elements that are histologically malignant, whereas adenosarcoma is characterized by a benign epithelial component and a malignant stroma.

In the current classification, carcinosarcoma is synonymous with the terms *malignant mixed mesodermal tumor* and *malignant mixed müllerian tumor.* Although we and others have sometimes used the term *carcinosarcoma* to denote a homologous tumor and *malignant mixed mesodermal tumor* to indicate one with heterologous elements, the current terminology uses a single term for both and then specifies whether the tumor is homologous or heterologous.

By definition, any lesion placed in the mixed tumor category must contain separate epithelial and nonepithelial components, both of which are integral parts of the lesion. Therefore, among the lesions that are excluded from this category but may be confused with it are pure endometrial stromal tumors (usually of low grade) in which the stromal cells differentiate focally into tubular, gland-like, or sex cord–like structures, and endometrial carcinomas with spindle cell (sarcomatoid) metaplasia which are identifiable as such with routine histologic staining.

Carcinosarcoma. Carcinosarcoma is the most common of the neoplasms in the uterine mixed tumor group, and the most common endometrial cancer after carcinoma. Many clinical and epidemiologic discussions of "uterine sarcomas" in the literature refer primarily to this tumor. Although common within this group, carcinosarcoma is still a rare tumor, comprising only 2% to 3% of all uterine cancers.[461]

Carcinosarcoma is predominantly a tumor of elderly women, but well-documented cases have occurred in younger patients. They are generally large, bulky, solitary, polypoid masses. The tumors present clinically with abnormal vaginal bleeding, often fill the uterine cavity, and may protrude through the external cervical os. The diagnosis is usually made by endometrial curettage, but sometimes only the epithelial or the stromal component is recognized in the initial specimen. Cervicovaginal smears are often also initially interpreted as adenocarcinoma.[462,463]

The cut surface of a carcinosarcoma of the endometrium is generally fleshy and variegated, with grossly recognizable areas of hemorrhage and necrosis (Fig. 4-112). The tumor usually invades into the myometrium and often has spread beyond the uterine corpus at the time of initial surgery.

Microscopically, carcinosarcomas are characterized by an intimate admixture of malignant epithelial and nonepithelial elements (Figs. 4-112, 4-113 and 4-114). The epithelial component is generally an adenocarcinoma showing one or more of the patterns of differentiation (eg, endometrioid, serous, clear cell) usually encountered in pure endometrial carcinoma. A squamous component is frequently present. There is a tendency for the carcinomatous component to be moderately to poorly differentiated.[464]

The stromal component is usually a high-grade sarcoma of indeterminate type, but may occasionally be well differentiated and may be recognizable as endometrial stromal sarcoma, fibrosarcoma, or leiomyosarcoma. In about half of the cases, there is a heterologous stromal component, meaning that the tumor contains foci of sarcoma differentiating toward elements not normally found in the uterine corpus. The most common type is rhabdomyosarcoma, characterized by a malignant striated muscle component (see Fig. 4-112). Less common elements, in decreasing order of frequency, are chondrosarcoma (see Fig. 4-113), osteosarcoma, and liposarcoma. More than one heterologous element may be present.

The *pathogenesis* and pathway of differentiation of these tumors have been of interest to many investigators. Speculation has centered on whether they represent collision tumors (a mixture of two histogenetically distinct malignant cell populations), com-

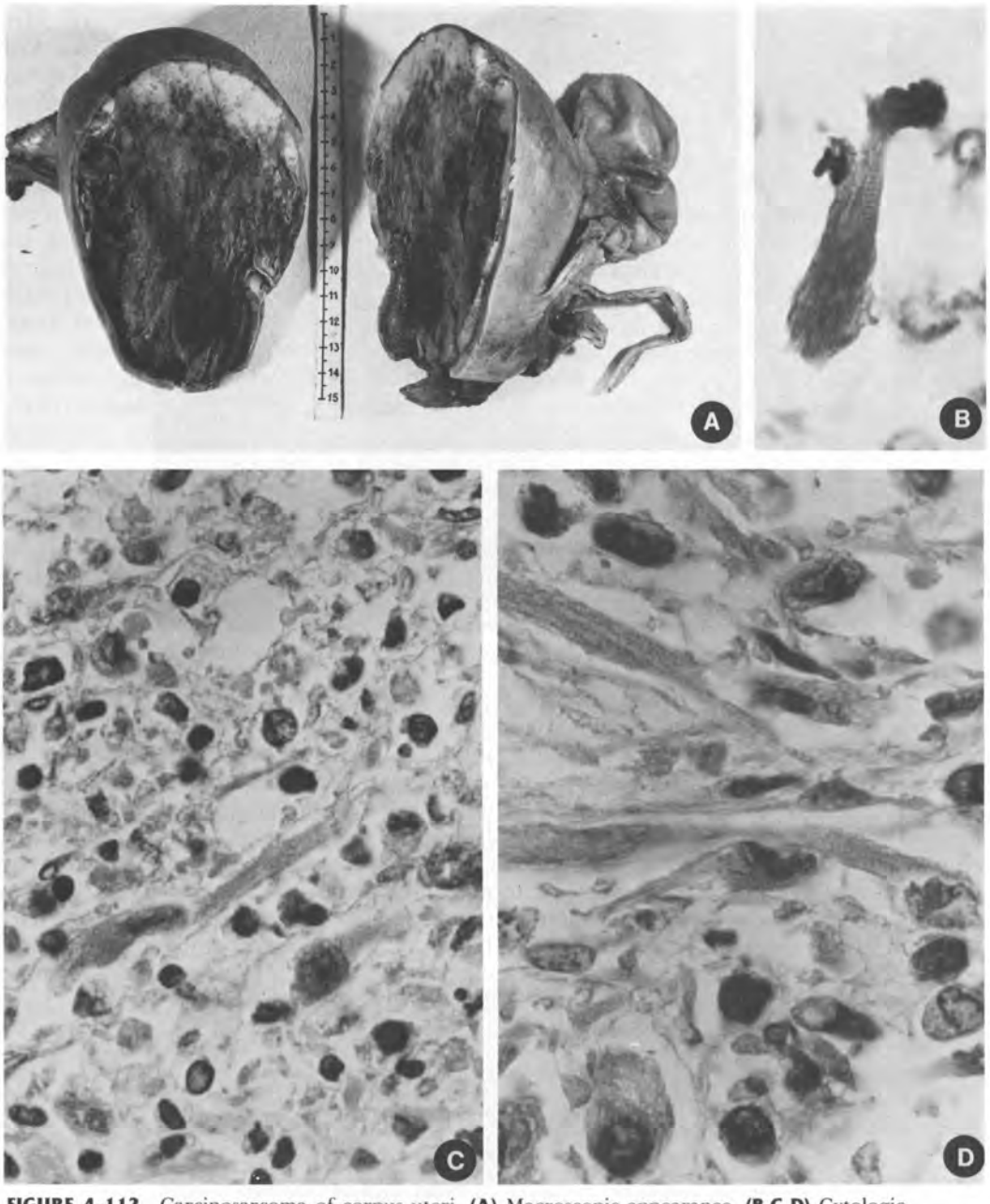

FIGURE 4-112 Carcinosarcoma of corpus uteri. **(A)** Macroscopic appearance. **(B,C,D)** Cytologic and histologic appearances, showing the presence of striated muscle cells.

bination tumors (representing an origin of both elements from a common stem cell), or composition tumors (pure carcinomas with reactive, atypical, but benign stromal elements). These possibilities have been investigated by numerous studies using electron microscopy, tissue culture, heterotransplantation, and immunohistochemistry. Most of the recent studies have been interpreted as supporting the "combination tumor" theory.[464] Of particular interest are immunohistochemical studies[465–467] that have confirmed that epithelial markers such as cytokeratins and epithelial membrane antigen are frequently displayed by the sarcomatous-appearing cells.

Additional evidence in favor of the combination tumor theory comes from observations that the initial metastases of uterine carcinosarcomas are usually of pure carcinomatous type, less frequently mixed and only rarely of pure sarcomatous appearance.[464,466] Silverberg and colleagues,[464] in a GOG series of 203 cases, noted that metastases to lymph nodes occurred with about the same frequency as in poorly differentiated endometrial carcinomas, and that the presence or absence of metastases at initial

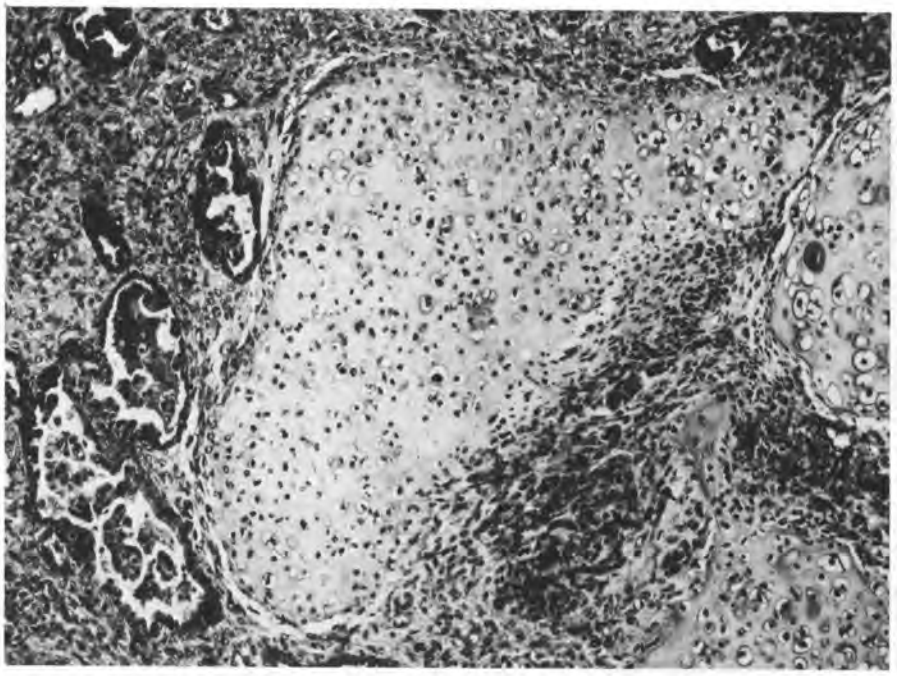

FIGURE 4-113 Carcinosarcoma: adenocarcinoma, stromal sarcoma, and chondrosarcoma.

exploratory laparotomy correlated more closely with the appearance of the epithelial component than that of the stromal component of the primary tumor. All these observations suggest that (1) both the epithelial and nonepithelial elements within these tumors are derived from a single precursor cell type; (2) the carcinomatous component ultimately drives the behavior of the tumor; and (3) perhaps most of the carcinosarcomas are truly metaplastic carcinomas, as encountered in most other organs of the body.

Because of the complex histologic appearance of these tumors, the relationship of the different elements within them to *prognosis* has been investigated in numerous studies over the years, often with variable results. The surgical stage and depth of myometrial invasion have been shown to be important prognostic indicators in almost every large published series, although other pathologic factors have been more controversial.[464] Although early studies suggested that heterologous tumors—particularly those containing rhabdomyosarcoma—had a poorer prognosis than homologous ones, more recent studies generally have not confirmed this observation.[464,468–470]

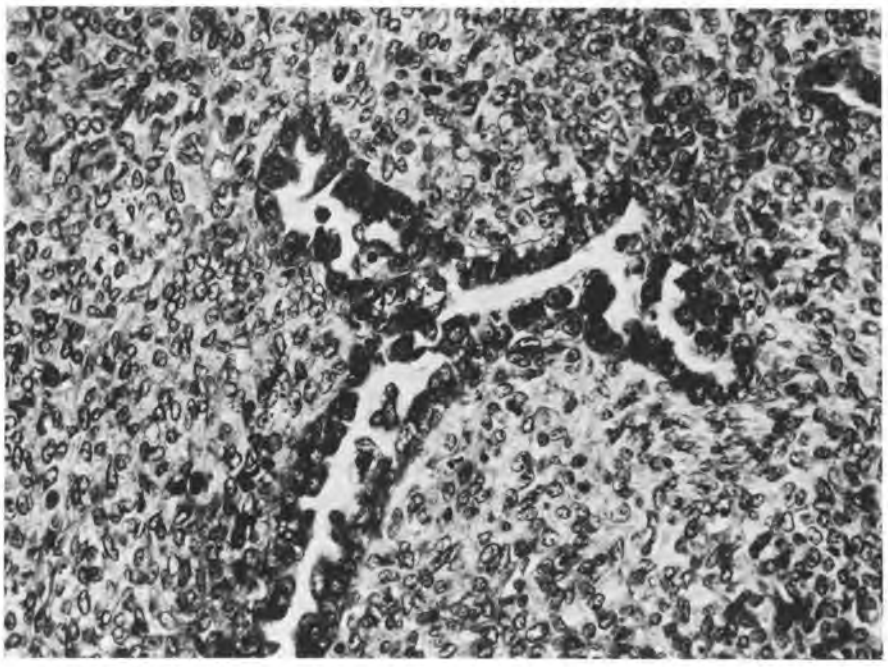

FIGURE 4-114 Carcinosarcoma of endometrium: malignant gland and stroma.

Features related to the frequency of metastases detected at staging laparotomy in the large series of Silverberg and colleagues[464] included the following: a carcinomatous component that was high-grade endometrioid, serous, or clear cell; deep myometrial invasion; lymphatic or vascular space invasion; and involvement of the isthmus or cervix. On the other hand, most features of the stromal component of the primary tumor, including grade, mitotic index, and the presence or absence and types of heterologous elements, showed no relation to the presence of metastases at operation. Longer follow-up is required to determine whether these factors may eventually prove to be of some prognostic significance. Other factors that have not been investigated adequately include the relative proportions of epithelial and nonepithelial elements and the immunophenotype of the tumor (ie, whether or not the stromal component is immunohistochemically positive for epithelial markers).

Initial metastases of these tumors appear to be predominantly of the epithelial component. Thus, metastatic endometrioid, serous, or clear cell carcinoma is typical of early spread from an endometrial carcinosarcoma. Deligdisch and colleagues[471] have noted that subsequent recurrences, on the other hand, were composed largely of sarcomatous elements.

Adenosarcoma. Unlike carcinosarcoma, which has been recognized for many decades, adenosarcoma was first described in 1974.[472] Thus, there are still large gaps in our knowledge of the epidemiology, histogenesis, and clinical and pathologic features of this tumor. Several hundred cases have, however, been reported, with the largest series comprising 100,[473] 31,[474] and 25[475] cases.

Adenosarcoma is defined as a tumor composed of a benign epithelial and a malignant nonepithelial component. It fills the gap between the completely benign (adenofibroma, adenomyoma) and high-grade malignant (carcinosarcoma) neoplasms in the endometrial mixed tumor group.

Adenosarcomas are usually diagnosed in a somewhat younger population than that which is characteristic of carcinosarcoma. The mean age in most series has been between 55 and 60 years, but cases have been seen in younger women and even in children. Like other endometrial malignant tumors, adenosarcomas usually present with abnormal vaginal bleeding. They are usually solitary lesions arising in the uterine fundus and projecting into the endometrial cavity, and average about 5 cm in diameter. They are occasionally associated with prior pelvic radiation or with exogenous or endogenous hyperestrinism.[473]

Microscopically, adenosarcoma is characterized by benign epithelial elements intimately admixed with a malignant stromal component (Fig. 4-115). Many histologic features of the tumor are reminiscent of those of cystosarcoma phyllodes of the breast.[476] Broad, leaf-like, papillary processes are usually present on the surface, and the deeper epithelial component is almost always cuffed by bands of hypercellular stroma. The tumor is usually limited to the endometrium, with a generally sharp

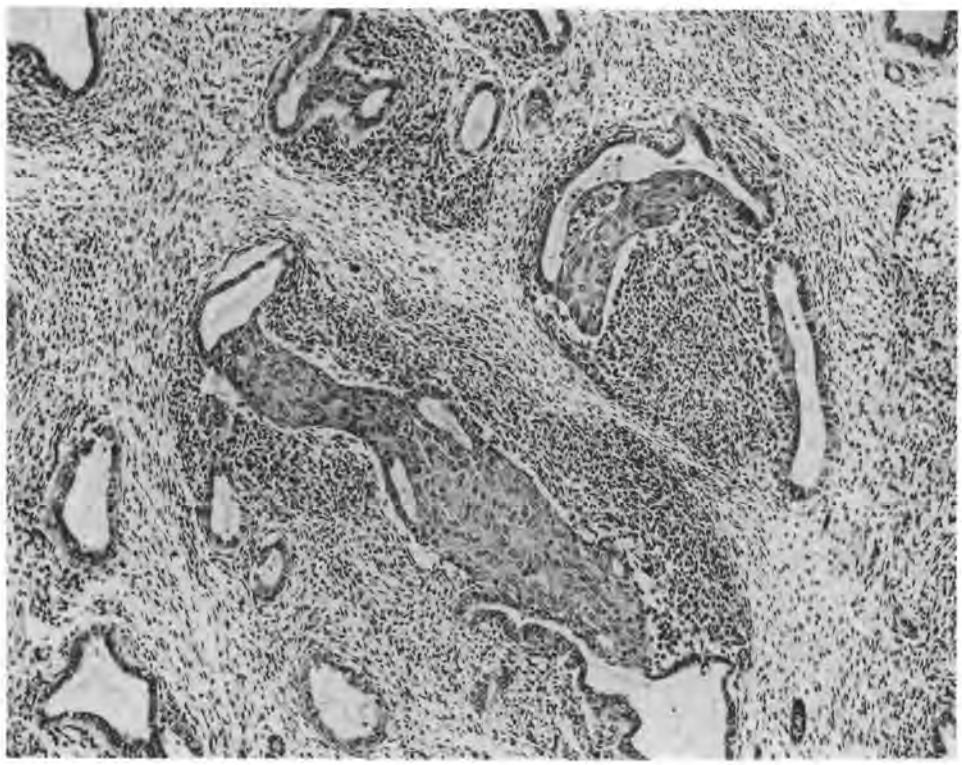

FIGURE 4-115 Adenosarcoma. Benign-appearing glands show squamous metaplasia and are cuffed by hypercellular malignant stroma.

junction between its base and the underlying myometrium. In a proportion of cases that varies from one series to the next, myometrial invasion is present. The myometrial invasion may be deep and may include involvement of vascular and lymphatic spaces. Extrauterine spread was present in the GOG series of Kaku and colleagues in 6 of 31 cases subjected to hysterectomy and staging laparotomy.[474]

The benign epithelial component of the tumor is generally characterized by papillary processes, cystically dilated glands, and compressed slit-like glands. Metaplastic changes and some degree of glandular atypia may be present, but by definition malignant change is absent. If even focal carcinomatous elements are encountered, the diagnosis becomes carcinosarcoma.

The stromal component by definition is cytologically malignant, but it is usually of lower grade than that which is characteristically seen in carcinosarcoma. In most adenosarcomas, the stroma is of homologous type and is composed of spindled or round cells resembling fibroblasts, endometrial stromal cells, or both. Focally dense cuffs of hypercellular stroma surrounding glands are almost always seen. Stromal mitoses are present but, as in the case of atypia, usually do not reach the levels seen in carcinosarcoma. They generally range in number between 3 and 20 mitotic figures per 10 high-power fields. Tumors with fewer than this number of mitoses are generally found to be adenofibromas, which behave in a completely benign manner.

Foci of hemorrhage, necrosis, foam cells, smooth muscle cells, stromal fibrosis, and stromal hyalinization may be present in varying proportions. A heterologous stromal component—usually rhabdomyosarcoma or chondrosarcoma—may be present. As with carcinosarcoma, it is debatable whether the presence of a heterologous component alters tumor behavior. Sex cord–like elements, consisting of solid nests, trabeculae, and solid or hollow tubules composed of benign-appearing epithelial-type cells, may occasionally be present in the stromal component of the tumor and do not appear to alter its behavior.[477]

The most important histopathologic variant of adenosarcoma is the pattern that has been designated *adenosarcoma with sarcomatous overgrowth*.[474,478] This is defined by the presence of a pure sarcoma—usually of a higher grade and mitotic index than encountered elsewhere in the tumor—that overgrows the typical adenosarcoma to account for at least 25% of total tumor volume (Fig. 4-116). The true frequency of this phenomenon is not known, because it represented 10 of 125 cases of adenosarcoma in one series[478] and 17 of 31 in another.[474] Because the former series was composed largely of consultation cases, and the latter of GOG cases subjected to staging laparotomy, we suspect that the true prevalence of this tumor type is probably intermediate between the two extremes reported.

In both series, nevertheless, sarcomatous overgrowth was an ominous *prognostic* feature, with tumor recurrences developing in 44% to 70% of cases, compared with 14% to 25% of those without sarcomatous overgrowth. Thus, adenosarcoma can in general be considered a relatively favorable malignant tumor unless stromal overgrowth is present.

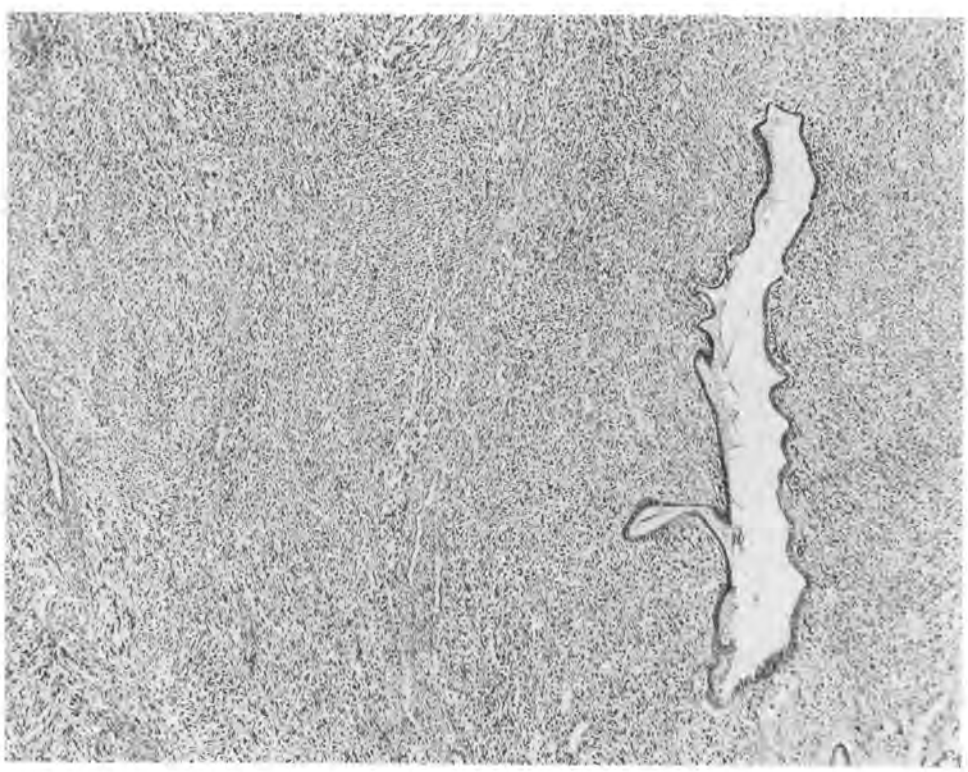

FIGURE 4-116 Adenosarcoma with sarcomatous overgrowth. Pure high-grade sarcoma occupies most of this field and accounts for more than 25% of the tumor sampled for microscopic examination.

Initial recurrences are usually vaginal, pelvic, or abdominal, and often appear at an interval of 5 years or more after hysterectomy. Vaginal recurrences may resemble the primary tumor or be composed of pure sarcoma, whereas distant metastases are almost always composed of the sarcomatous component alone.

As emphasized above, this relatively favorable prognosis is altered dramatically by the presence of sarcomatous overgrowth. An increased risk of recurrence is also noted with myometrial invasion. Other features that have been reported in some series as unfavorable prognostic factors include the presence of extrauterine spread at the time of diagnosis, necrosis in the primary tumor, the presence of heterologous elements (particularly rhabdomyosarcoma), high sarcoma grade, and high mitotic index of the stromal component.[473–476] In the GOG series of Kaku and colleagues,[474] the triad of stromal overgrowth, rhabdomyosarcoma, and lymphatic/vascular space invasion predicted both of the two cases (of a total of 31) in which lymph node metastases were present at the time of exploratory laparotomy. Because these two cases were the only ones in the series with these three findings in the hysterectomy specimen itself, it was suggested that lymphadenectomy might be reserved in the future for similar cases.

Atypical Polypoid Adenomyoma and Papillary Adenofibroma. These two uncommon lesions are grouped together here because they seem to form a continuous clinical and pathologic spectrum with the malignant mixed tumors discussed above and because they are a major part of the differential diagnosis with these tumors. Both lesions have been characterized within the past two decades, although there is some question whether this represents a real increase in frequency. The lesions resemble carcinosarcomas and adenosarcomas in that they consist of both epithelial and stromal elements; they differ, however, in that the epithelial and stromal components are always histologically benign and the lesions are benign in their clinical behavior.[479,480]

Clinically, adenofibromas usually occur in middle-aged to elderly women and atypical polypoid adenomyomas in premenopausal women. They both present most frequently with abnormal vaginal bleeding.

Macroscopically, they present as endometrial polyps of variable size, sometimes large and occasionally occupying the entire endometrial cavity and prolapsing down into the cervix, with atypical polypoid adenomyoma frequently originating in the lower uterine segment. There is a strong tendency for these polyps to be sessile. Foci of hemorrhage and necrosis are generally absent.

Microscopically, the lesions consist of intimate admixtures of epithelial and stromal elements. In the *papillary adenofibroma*,[475,476,481] the basic architecture is papillary, both the epithelial and stromal elements appear benign, and the latter is predominantly fibroblastic (Fig. 4-117). The benign histologic appearance correlates well with the clinical behavior, although adenofibromas can invade the myometrium and pelvic veins[482] and recur locally[483] on rare occasions.

Atypical polypoid adenomyoma is characterized by an intimate admixture of benign endometrial glands and a stroma consisting predominantly or exclusively of equally benign-appearing smooth muscle (Fig.

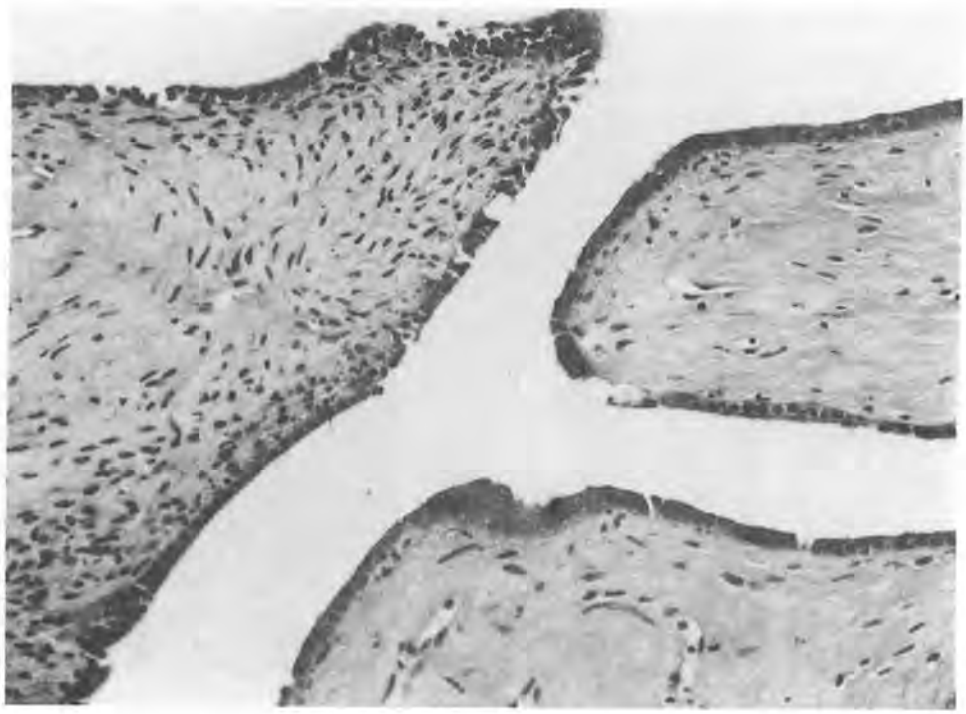

FIGURE 4-117 Papillary adenofibroma. In contrast to adenosarcoma (see Fig. 4-115), the stroma is histologically benign.

4-118). The glands invariably exhibit architectural atypia and may show cytologic atypia (usually slight but occasionally marked) as well. Squamous or morular metaplasia is found in most cases and is often extensive. Although central necrosis may be present in these large metaplastic foci, their cytologic appearance is benign. The stromal component consists of swirling and interlacing fascicles of smooth muscle cells that appear cytologically benign. Mitotic activity in this compartment is usually less than 2 mitotic figures per 10 high-power fields.

Adenocarcinoma has been noted within and associated with this tumor.[484,485] The most important differential diagnosis of atypical polypoid adenomyoma, particularly in a curettage specimen, is with endometrial carcinoma invading the myometrium. It is unusual for myometrial invasion to be demonstrated in a curettage specimen; the glands of atypical polypoid adenomyoma lack cytologic and architectural features of malignancy, and the smooth muscle component exhibits a cellularity and fascicular pattern that would be unusual for myometrium invaded by carcinoma and lacks the usual stromal response to invasive cancer.

Leiomyosarcoma. Leiomyosarcoma represents the most frequent type of pure uterine sarcoma. It may arise in a previously existing benign leiomyoma or de novo from the smooth muscle fibers of the myometrium. Different authors report various frequencies of each of these modes of origin. Stearns and Sneeden[486] believed that 49 of 54 leiomyosarcomas in their series arose in benign myomas, whereas Aaro and colleagues[487] demonstrated this origin in only 22 of their 105 cases, and Taylor and Norris[488] denied it completely. Feulgen microspectrophotometric observations by Herbold and associates[489] seem to confirm that such transitions can take place, although their frequency is still unknown. The 105 leiomyosarcomas in Aaro's series were found in a total of 177 uterine sarcomas and malignant mixed tumors; most other series have also indicated that leiomyosarcomas comprise half or slightly more of all uterine nonepithelial malignant tumors, with most of the others being carcinosarcomas.[490–492] They are predominantly tumors of older women, but cases have been described in young patients. Rapid increase in the size of an apparent leiomyoma after the menopause should arouse suspicion of sarcoma. However, the diagnosis is often first suspected by the pathologist during the examination of a uterus removed for supposedly benign myomata.[210]

Macroscopically, the tumor is found within a leiomyomatous nodule or forms an isolated intramural mass (Fig. 4-119). It presents as a soft or fleshy zone of gray-yellow or pink color, with poorly defined borders. This appearance contrasts with that of benign leiomyomatous tissue, which is firm, white, and shows a prominent whorled pattern on section. Zones of necrosis and hemorrhage are frequent (in one series,[488] necrosis was seen grossly in 74% of leiomyosarcomas versus only 12% of benign cellular myomas). The tumor may be solitary or associated

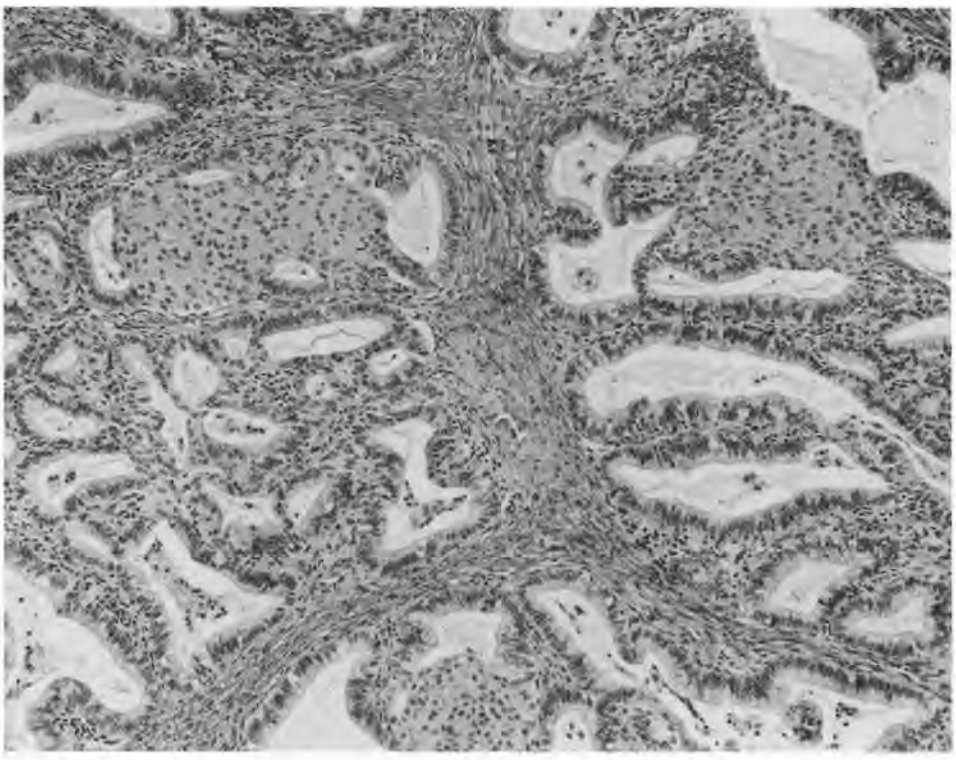

FIGURE 4-118 Atypical polypoid adenomyoma. Architecturally irregular and crowded glands with morular metaplasia are separated by interlacing fascicles of smooth muscle.

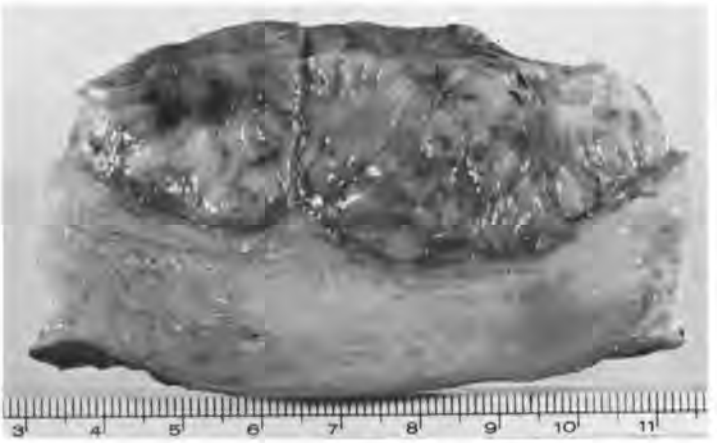

FIGURE 4-119 Leiomyosarcoma: macroscopic appearance of cut surface.

with multiple benign myomata, with different authors disagreeing about which pattern is more frequent.

Occasionally, the tumor grows out of the confines of the uterine wall and forms a nodular, budding, or grape-like mass within the uterine cavity. In advanced stages, the tumor grows inward to involve the endometrial cavity or outward to the peritoneal serosa, at times with distant peritoneal spread.

Microscopically, the tumor is composed of whorled and interwoven bundles of fusiform cells with elongated hyperchromatic nuclei, which may be enormous and bizarre (Fig. 4-120). Mitoses are usually numerous. Some authors have attached a major prognostic significance to the number of mitoses present,[488,491,493] whereas others believe that the macroscopic extent of the tumor and its overall differentiation are equally valuable in this respect.[486,494–497] When the tumor attains a certain volume, it is common to find zones of necrosis, hemorrhage, and edema.

There is considerable confusion in the literature between the diagnosis of leiomyosarcoma and that of cellular or bizarre but benign leiomyoma (Table 4-7 summarizes our criteria). Certain authors believe that a quantitative estimation of mitotic activity will always solve this problem, the figure of 5 mitoses per 10 high-power fields being most often quoted as the dividing line. However, we believe that individual variations, both in tumors and in observers, make this approach untenable.[498–500] The entity of *mitotically active leiomyoma*, a benign tumor generally occurring in young women, in which many normal mitotic figures but no atypia or tumor necrosis is seen, also demonstrates the inutility of using mitotic activity as the single criterion to separate benign from malignant.[501–503] The absence of bizarre nuclei and of atypical mitoses points to a benign tumor; a few giant cells, however, may be found in benign leiomyomas of "symplastic" type (see above). Tumor necrosis is an important additional criterion of leiomyosarcoma, as is obvious invasion of the myometrium.[504,505] The problem of the "benign metastasizing leiomyoma" has already been discussed; these cases are so rare that they seldom pose a significant problem. Myxoid smooth muscle tumors must be viewed with alarm even in the absence of prominent mitotic activity,[506] because they have been stated to have a high malignant potential. Other lesions to be considered in the differential diagnosis include intravenous leiomyomatosis, spindle cell carcinoma, endometrial stromal sarcoma, rare rhabdomyosarcomas, and other soft-tissue sarcomas.

In recent years, a category of *smooth muscle tumor of uncertain malignant potential* has been added to the classification of smooth muscle tumors (see Table 4-3), to encompass "borderline" lesions with some criteria of malignancy. This is a valuable addition, because it recognizes that we do not know with certainty the true clinical potential of every tumor encountered. This is especially true of some of the variants (such as epithelioid smooth muscle tumors) of which too few cases have been reported. Nevertheless, the prudent pathologist must be wary of overuse of this diagnosis to avoid being labeled by clinical colleagues as a "pathologist of uncertain malignant potential."

Several clinical and pathologic features should be considered in evaluating the *prognosis* of leiomyosarcoma. Poor prognostic factors are marked anaplasia of the tumor cells, high mitotic rate, evidence of blood vessel invasion, obvious malignant tumor on gross inspection, and (perhaps most ominous of all) the postmenopausal state of the patient.[495,497] Published 5-year survival rates have been as variable as the diagnostic criteria, but they probably average 40% or less. The *treatment* of choice is surgical. Irradiation seems to be of little value, but chemotherapy is beginning to show some promise.[507] When metastases occur, they most frequently involve intrapelvic structures, the lungs, and the liver.

Cytologic Appearance of Uterine Sarcomas. Because of the rarity of uterine sarcomas, coupled with the fact that they are almost always symptomatic and

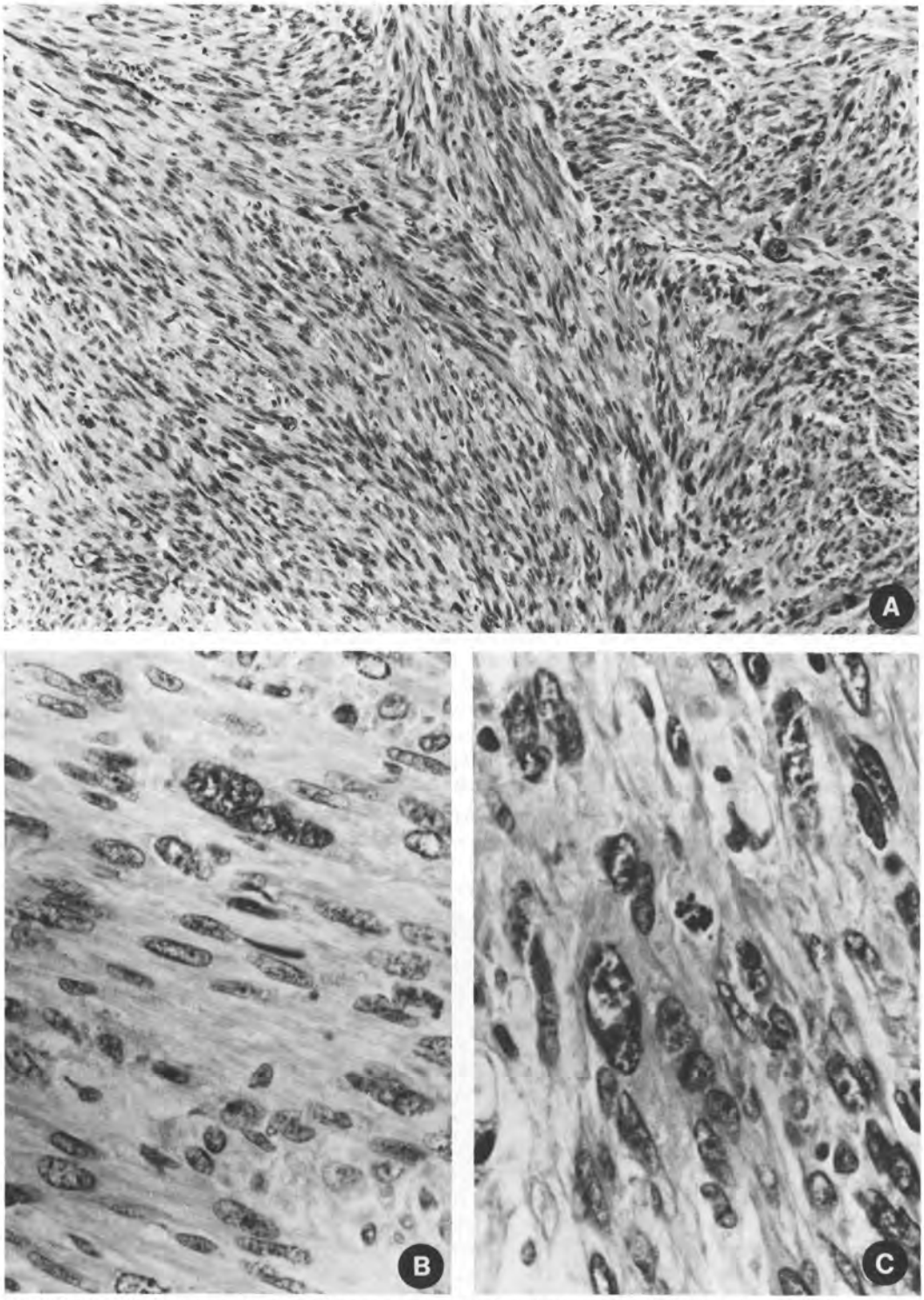

FIGURE 4-120 Leiomyosarcoma of uterus: microscopic appearance. **(A)** General view. **(B,C)** Cytologic details.

therefore not detected by screening procedures, the cytologic appearance of most of these tumors is poorly characterized. In general terms, most of the sarcomas exfoliate highly disorganized clusters of huge polymorphous cells, which lack the grouping into rounded cell balls or papillary structures frequently seen in endometrial carcinoma. Leiomyosarcomas exfoliate the most characteristic cells, with a spindled shape and large markedly irregular nuclei (Color Fig. 4-8). However, because these tumors frequently occur beneath an intact endometrium, malignant cells may not be seen, even with direct

TABLE 4-7.
Differential Diagnosis of Uterine Smooth Muscle Tumors

Hypercellularity	−	+	+	−	−	+	+	−
Atypia	−	+	−	+	−	+	−	+
Prominent mitotic activity	−	+	−	−	+	−	+	+
Diagnosis	M	S	CM	AM	AM	S	S	T

M, benign myoma; *CM*, cellular myoma; *AM*, atypical myoma; *S*, sarcoma; *T*, theoretical combination only.

sampling of the endometrial cavity. Equally distinctive cytologically are the malignant heterologous elements seen in some carcinosarcomas—particularly rhabdomyoblasts with prominent cross-striations (see Fig. 4-112)—but these are even more rarely encountered in cytologic material, because even histologic examination frequently reveals only very small foci of these cells in otherwise homologous tumors.

Other Malignant Tumors of the Corpus Uteri

Among the malignant tumors that have been reported to show rare uterine primary localizations are rhabdomyosarcoma,[508,509] osteogenic sarcoma,[510] chondrosarcoma,[511] liposarcoma,[512] malignant fibrous histiocytoma,[513] angiosarcoma,[514,515] alveolar soft part sarcoma,[516] endodermal sinus tumor,[517,518] primitive neuroectodermal tumor,[519] immature teratoma,[520] malignant rhabdoid tumor,[521] and Wilms' tumor.[522] Malignant lymphomas[523] are usually a manifestation of disseminated disease. They should not be confused with lymphoma-like benign lesions, including leiomyomas with marked lymphoid infiltration.[524,525]

METASTATIC TUMORS OF THE CORPUS UTERI

The corpus uteri may be involved by distant metastases from primary tumors of diverse organs or by local extensions of tumors of other parts of the female genital tract or other pelvic organs. Most frequently, metastases are from ovarian cancers, and it is sometimes difficult to determine whether the primary tumor is ovarian or uterine (or, as is frequently the case, both).[396–399] Of extrapelvic tumors metastasizing to the uterus, by far the most frequent are mammary and gastrointestinal carcinomas (Fig. 4-121).[526,527] Carcinomas of other organs, leukemias and lymphomas, and carcinoid tumors have been reported as rare sources of uterine metastases. Carcinomas of the cervix,[528] ovary, sigmoid, and urinary bladder extend to the corpus uteri directly or by the lymphatic route (Fig. 4-122).

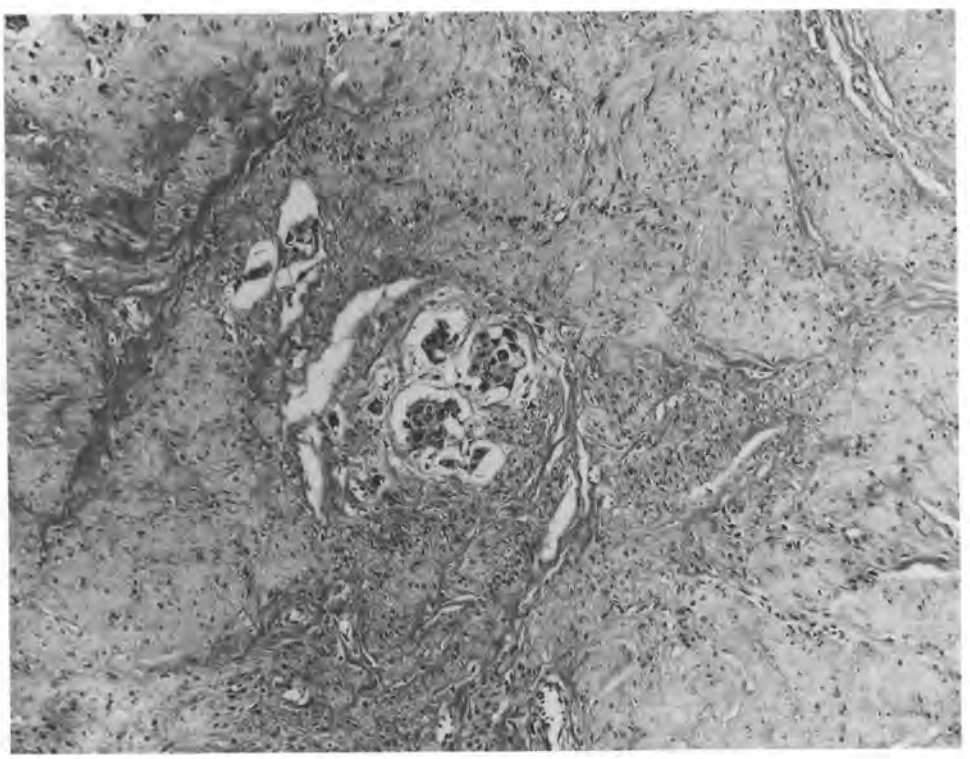

FIGURE 4-121 Metastatic mammary carcinoma in uterine leiomyoma.

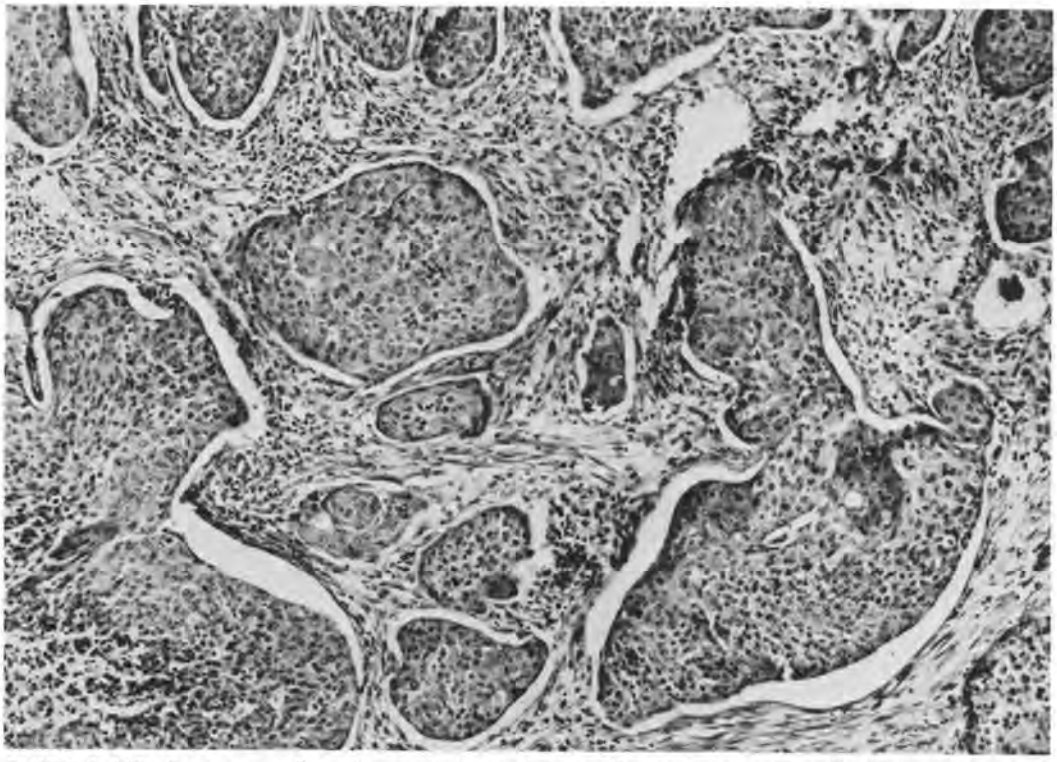

FIGURE 4-122 Squamous cell carcinoma of the cervix extending to the corpus uteri: microscopic appearance.

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5 The Fallopian Tube

EMBRYOLOGY

The fallopian tubes arise from the superior portions of the müllerian ducts. This differentiation takes place in the embryo at the 55-mm stage of development.[1,2] The tubes are in vertical position at first, and then accompany the ovaries in their migration, assuming a nearly horizontal position.

ANATOMY

The fallopian tube or oviduct is a musculomembranous tube situated in the superior wing of the broad ligament.[2,3] Its average length measures 10 to 12 cm, and its diameter ranges from 0.4 to 0.9 cm. The tube consists of four segments (Fig. 5-1),which are, from center to periphery:

1. The *interstitial portion,* situated within the uterine wall
2. The *isthmus, or horizontal portion*
3. The *ampulla,* which embraces the ovary in its concavity and is the site of fertilization
4. The *infundibulum* or fimbriated portion.

The ampulla presents sinuosities that are progressively effaced with age. These sinuosities may constitute an obstacle to the flow of secretions and favor the appearance of partial or complete obstructions.

The tubal wall presents longitudinal folds (mucosal rugae) whose number and dimensions increase from the internal orifice to the infundibulum. The tubal canal opens into the superoexternal angle of the uterine cavity by an orifice (ostium uterinum) of about 0.1 cm in diameter;[4] it terminates in the peritoneal cavity through an orifice (peritoneal ostium) measuring 0.2 to 0.3 cm in diameter. The wall consists of a serosa, a muscularis, and a mucosa in continuity with the uterine mucosa.

The tubal arteries arise from the arcade constituted by the internal tubal artery (a branch of the uterine artery) and the external tubal artery (a branch of the ovarian artery).[5] Spiral arterioles in the tubal mucosa react in the same fashion as those of the endometrium during the menstrual cycle.[6] The veins flow into the uterine and ovarian veins. The lymphatics, richly anastomosed with those of the adjacent organs, drain into the ovarian lymphatics and the paraortic lumbar lymph nodes. These lymphatics course along the folds of the tubal mucosa, where they form a network of intercommunicating lymphatic sinusoids. The nerves innervating the tube come from the intermesenteric and hypogastric plexus. Adrenergic fibers predominate over cholinergic fibers.[7]

HISTOLOGY

The tubal wall consists of the following layers: the serosa, subserosa, muscularis, submucosa, and mucosa.

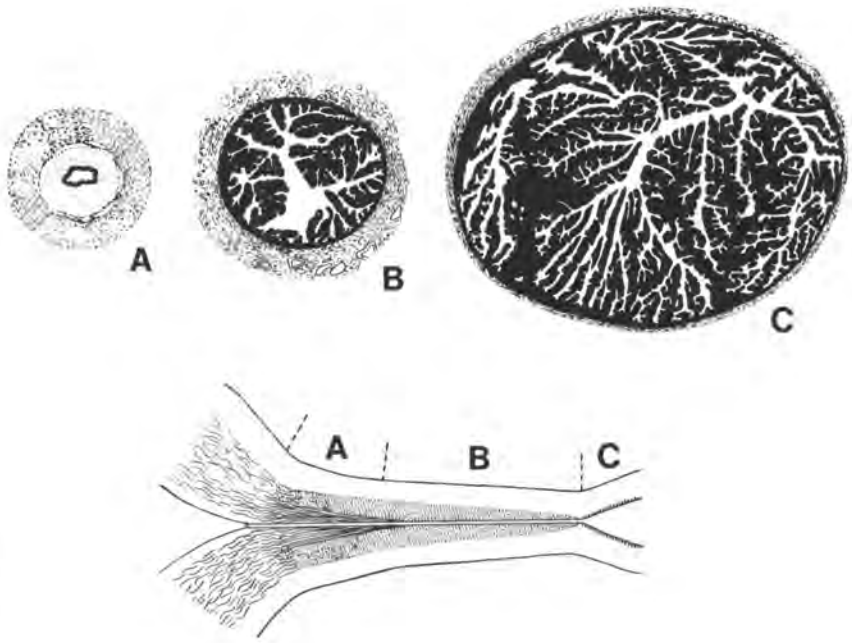

FIGURE 5-1 Normal fallopian tube. Schematic representation of longitudinal and cross sections of the wall. **(A)** Interstitial portion. **(B)** Isthmic portion. **(C)** Ampullary portion. (Adapted from Dubreuil.)

The serosa is the external layer, a peritoneal layer consisting of a mesothelial lining and well-vascularized connective tissue. Cystic or solid (Walthard's cell rests) proliferations of mesothelial cells are often present (see Chap. 6). The subserosa is a loose connective tissue network.

The muscularis is formed by an external plexiform layer thickest at the isthmus; a circular layer, thin in the ampulla and thickening toward the isthmus; and an internal longitudinal layer present in the internal third of the isthmus.

The submucosa is a loose vascularized connective tissue; the mucosa is composed of a cuboidal to columnar unistratified lining. Several cell types are found in the tubal mucosa: secretory, ciliated, interstitial (intercalary or "peg"), and wandering cells (Fig. 5-2). Cyclical changes in the tubal mucosa are not as evident as those of the endometrium. They are manifested by an increase in cell size during the first half of the cycle and by the presence of cytoplasmic glycogen and lipids, especially marked around the 22nd day. Alkaline phosphatase is found in greatest concentration in the apical cytoplasm during the ovulatory phase.

The *secretory cells* are characterized by the presence of an apical border of cytoplasmic microvilli demonstrable by electron microscopy (Fig. 5-3). They have more basophilic cytoplasm than the ciliated cells and possess elongated nuclei with dense chromatin. These elements undergo cyclical modifications.[8–10] They are nearly cuboidal during the early estrogenic phase, become elongated at the time of ovulation, and retain a columnar form until the menstrual phase, at which time they again diminish in height. During the luteal phase, the apical pole herniates into the tubal lumen, and the nucleus comes level with the cell surface, occasionally giving the impression of having been expelled from the epithelium. The increased volume of the cell at this time is responsible for this appearance. These cells possess secretory activity, which is confirmed by the presence of lipids and glycogen in the cytoplasm. Under the electron microscope during the secretory phase, secretory droplets are seen to swell up between the microvilli, which decrease in number and height; the endoplasmic reticulum expands and lysosomes appear during the late portion of this period.

Estradiol and progesterone receptor concentrations can be shown to vary in tubal mucosa during the menstrual cycle.[11] During pregnancy, the secretory cells become filled with glycogen, but the level of lipids is unchanged. They are low and regularly disposed. Increased ergastoplasm, swollen mitochondria, and the presence of secretory granules are seen with the electron microscope. Some tubal mucosae show a true decidual transformation during pregnancy (Fig. 5-4). No specific changes are seen during the postpartum period. *Atrophy* of the tubal mucosa after the menopause takes place slowly, and the functional appearance persists for many years after the cessation of ovarian activity.[12]

The *ciliated cells* are columnar elements of 30 to 35 μm, with clear cytoplasm and a round or oval nucleus situated in the basal part of the cytoplasm. They contrast sharply, by virtue of their pale appearance, with the surrounding secretory cells. The chromatin is gathered in easily visible clumps, and the nucleolus is large. The ciliated cells are often found in groups. They decrease in frequency from the fimbriated end of the tube to its interstitial portion.[3,12,13] They attain their maximal size at the time of ovulation, and thereafter decrease in height until the early estrogenic

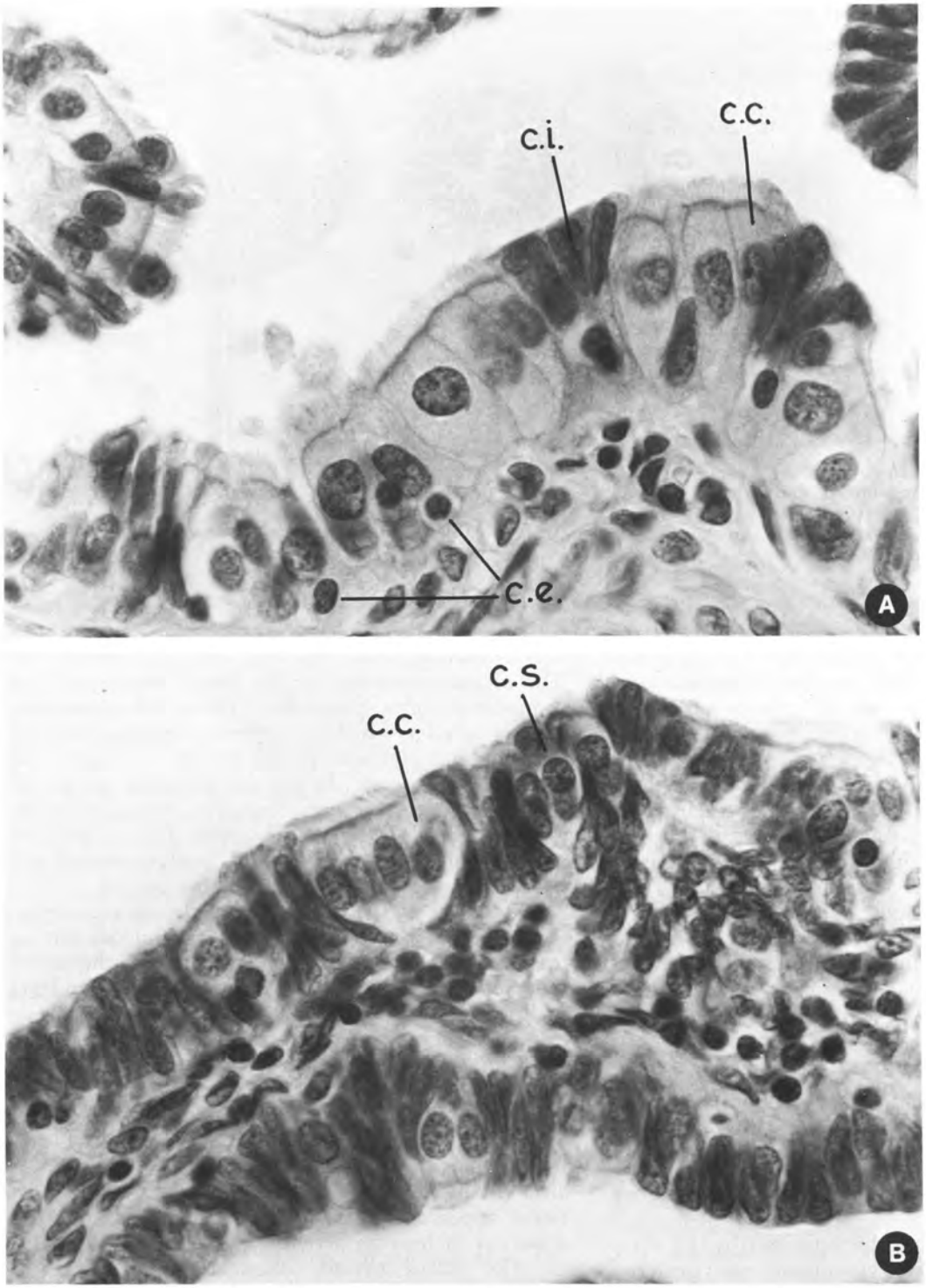

FIGURE 5-2 Fallopian tube: normal histologic appearance showing ciliated cells (*c.c.*), secretory cells (*c.s.*), intercalated cells (*c.i.*), and wandering cells (*c.e.*).

phase. The apical pole is covered with cilia of about 8 μm in length, which reveal the typical structure: nine double filaments disposed around two central filaments, with axes on a parabasal apparatus (see Fig. 5-3). This pattern may be altered in Kartagener's syndrome[14] or after use of an intrauterine contraceptive device (IUD).[15] Cell size increases during the estrogenic phase. Except for these changes, the ciliated cells show no major cyclical variation, although some authors state that about 10% of these cells lose and regenerate their cilia in each menstrual cycle.[10]

The *intercalated cells* or *peg cells,* long and

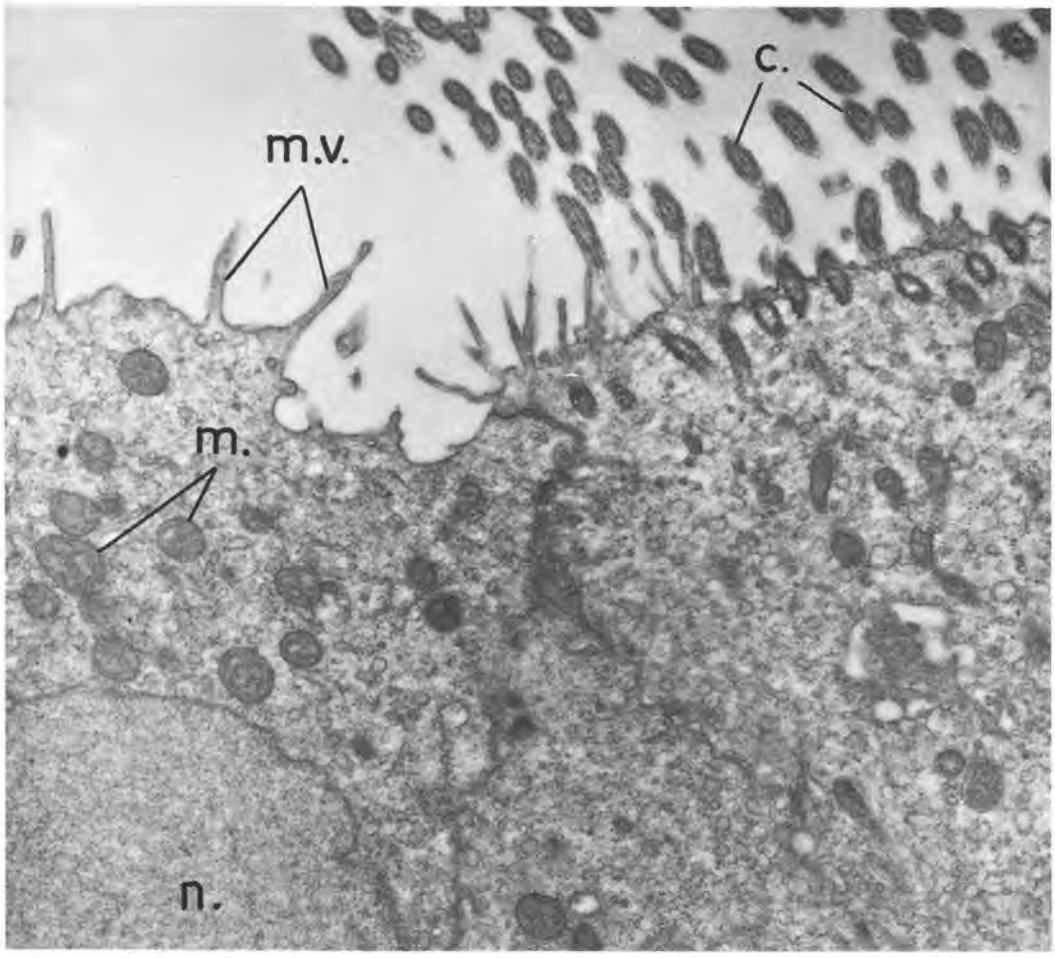

FIGURE 5-3 Electron micrograph of tubal epithelial surface showing microvilli (*m.v.*) and cilia (*c*) in secretory and ciliated cell, respectively. *m.*, mitochondria, *n.*, nucleus.

straight elements, appear crushed between the neighboring elements (see Fig. 5-2). The nucleus, thin and drawn out, is surrounded by a thin, dense, deeply staining rim of cytoplasm. The apical border is composed of cytoplasmic microvilli. This appearance recalls that of an altered secretory cell. Similar elements are encountered in the endometrium during the secretory phase.

The *wandering cells* or *dark cells* described by Andrews are small round cells with a central nucleus and clear cytoplasm situated in the deep part of the epithelium (see Fig. 5-2).[16] They have been shown to be lymphocytes that migrate among the epithelial cells from the subjacent stroma (mucosa-associated lymphoid tissue, or MALT).[17]

MALFORMATIONS

Aplasia of the tube is encountered in unicornuate uterus. Bilateral aplasia is rare. Diverse degrees of *hypoplasia* may be seen, but marked hypoplasia is rare. *Atresia* is generally combined with atresia of a uterine cornu but may be segmental and isolated.[18,19] The presence of two tubes on one side may be noted, and the existence of multiple external orifices and of diverticula.

Changes have been reported in the tubes of women who had been exposed in utero to diethylstilbestrol (DES). These consist of foreshortened, convoluted tubes with "withered" fimbriae and a pinpoint os, and they seem to be associated with increased frequencies of infertility and ectopic pregnancy.[20] Their prevalence in the DES-exposed population remains unknown.

Although not strictly a malformation, tubal *heterotopia* can follow various forms of pelvic surgery.[21] The most common situation is that of a tube prolapsed into the vaginal vault after vaginal hysterectomy.[22] In this setting, recognition of tubal mucosa and wall (including smooth muscle) avoids confusion with other types of vaginal cysts and tumors (see Chap. 2).

TORSION

Torsion of the fallopian tube usually presents as a painful surgical emergency during the period of ac-

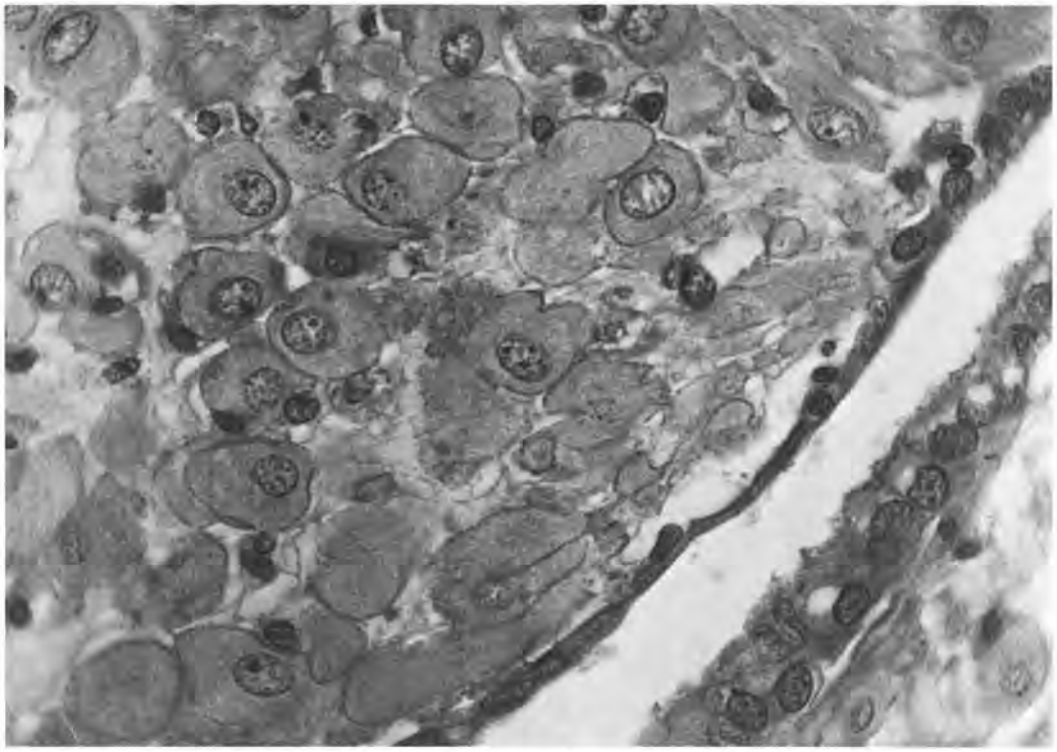

FIGURE 5-4 Tubal mucosa: decidual transformation of stroma.

tive genital life. It is almost always unilateral, but bilateral cases have been reported. Youssef and colleagues divide the etiologic factors into intrinsic and extrinsic conditions.[23] Factors intrinsic to the tube include congenital anomalies, acquired structural defects (hydrosalpinx, tumors, previous surgery), and abnormal peristalsis due to autonomic dysfunction. The extrinsic causes comprise changes in adjacent organs (adhesions, tumors, pregnancy), mechanical factors (trauma, sudden movements), and pelvic congestion. Torsion of an apparently previously normal tube is not rare and has been described on occasion in children and in pregnant women.[24] Isolated torsion of the fimbriated end of the tube is much rarer.[25]

Macroscopic Appearance. The twisted tube may be normal or swollen, and it often contains serous or frankly bloody fluid. Depending on the amount of torsion, which may vary from one half to several twists, severe gangrene may be present. The ovary is involved in the process in about 50% of cases.

Microscopic Appearance. The microscopic appearance is often primarily that of the underlying disease (hydrosalpinx, tumor, or other). The wall of the tube usually shows inflammation, congestion, and edema, and may be completely gangrenous. The prognosis is grave unless surgical measures are instituted rapidly.

INFLAMMATORY DISEASES

Inflammatory disease of the tube, or *salpingitis,* constitutes an important chapter in gynecologic pathology. Although antibiotics have considerably modified the clinical and pathologic aspects of this condition, salpingitis nevertheless remains a severe and relatively common process. It remains responsible for a significant percentage of cases of secondary sterility by occlusion or stenosis. Its frequency varies with the social milieu, and improved hygiene diminishes its incidence.

The most frequently encountered causative organisms in classic studies have been staphylococci, streptococci, *Escherichia coli,* pneumococci, *Proteus, Mycobacterium tuberculosis,* and gonococci. Streptococci and staphylococci that are resistant to antibiotics are common. Gonococcal infection does not account for more than 10% of all cases, although formerly it was far more common. Tubal syphilis has become a great rarity in Europe and North America. A few cases caused by *Enterobius vermicularis* and other parasites have been reported.[26,27]

Recent reports have suggested a possible significance for such organisms as *Chlamydia trachomatis, Mycoplasma hominis, Ureaplasma urealyticum,* and *Bacteroides* and other aerobic species.[28–32] Better documented is the relation between pelvic inflammatory disease (PID), often unilateral, and the IUD. Al-

though certain forms of IUD are frequently associated with minor tubal mucosal structural changes[33] and sterile salpingitis,[34,35] more important statistics are that one third[36] to one half[37] of PID patients in some series have been IUD wearers and that in as many as 87% of patients with PID, *Actinomyces* organisms could be incriminated.[38,39] The presence of the typical "sulfur granules" of *Actinomyces* (see Figs. 5-17 and 4-57) in the vaginal smear of an IUD wearer should raise concern, particularly if signs or symptoms of PID develop. The Dalkon shield IUD has figured most prominently in reports of PID in IUD wearers, and Gram-negative and anaerobic bacteria also have been identified in this situation.[37]

Lukasik compared the flora of the tube and of the cervix in cases of salpingitis and found that these were usually identical when the salpingitis was chronic but that in acute cases they bore no relation to one another.[40] Because the cervix can be easily cultured, this procedure often gives valuable information in cases of chronic salpingitis. More recently, Kiviat and colleagues demonstrated that an endometrial biopsy showing the simultaneous presence of five or more neutrophils per 400× field in surface endometrial epithelium and one or more plasma cell per 120× field in endometrial stroma was highly predictive of the presence of acute salpingitis.[41]

Salpingitis is usually a postpartal or postabortal complication or a tubal extension of a cervicouterine or peritoneal infection. Ascending infections (often chlamydial, less frequently gonococcal) lead to mucosal involvement (*endosalpingitis*) in the earliest stage, whereas postpartal and postabortal infections (usually staphylococcal, streptococcal, and anaerobic) classically spread by means of uterine lymphatics and blood vessels to produce a *perisalpingitis*, with a relative sparing of the tubal lumina.

More rarely, salpingitis may be a complication of a generalized infectious process: typhoid fever, variola, acute colitis with sepsis, or a distant abscess (eg, mastoid, tonsil). The lesions are often bilateral and extend to adjacent organs, principally to the ovaries, pelvic peritoneum, and other pelvic organs. Antibiotic therapy has diminished the frequency and the severity of these extensions. Acute salpingitis may rarely be a complication of tubal ligation.[42]

Acute Salpingitis

The acute pyogenic salpingitides are manifested clinically by fever, pains in the pelvis and iliac fossae, nausea and vomiting, menstrual abnormalities, and pelvic peritonitis. When the infection is not treated correctly, it may pass into a chronic phase, with all the complications discussed below.

Macroscopic Appearance. The tube is enlarged, congested, dark red, and flabby in consistency (Fig. 5-5). The peritoneum is opacified, and there are loose fibrinous adhesions between the tube and neighboring structures. Section reveals a thick edematous wall with congested mucosal plicae. The lumen contains serous or frankly purulent fluid. The plicae of the infundibulum are thick, turgid, and engorged with blood. The increase in tubal size due to thickening of the wall is much more marked in other pyogenic salpingitides than in gonococcal infection. The increased volume causes accentuation of the tubal angles and favors a superimposed acute obstruction or stenosis.

FIGURE 5-5 Acute salpingitis: macroscopic appearance.

If obstruction occurs, hydrosalpinx or pyosalpinx ensues, depending on the quality of the exudate. The wall is thick and fibrous, or it may be thin. A possible complication is rupture of the tube.

Microscopic Appearance. When inflammation is discrete, the microscopic lesions may be localized to the mucosa and manifested by stromal edema and infiltration by polymorphonuclear leukocytes and a few plasma cells and lymphocytes. At this stage, the epithelium is not involved. Such infiltration accompanied by vascular congestion may be seen in the normal menstrual cycle during the menstrual phase, and in this circumstance should not be considered to represent an infection. In more severe cases of salpingitis, the epithelium is altered, showing cellular atypia (anisocytosis, anisonucleosis, cytoplasmic vacuolization) and polymorphonuclear leukocytic infiltration (Fig. 5-6). The mucosal rugae are thickened, fill the tubal lumen, and adhere one to another. The surface epithelium may desquamate or become necrotic, leaving a naked submucosa, and microabscesses appear. The vessels are congested, and interstitial hemorrhages take place. Finally, the inflammatory process overflows the mucosa and invades the muscularis, the fibers of which are separated by the leukocytic infiltrates.

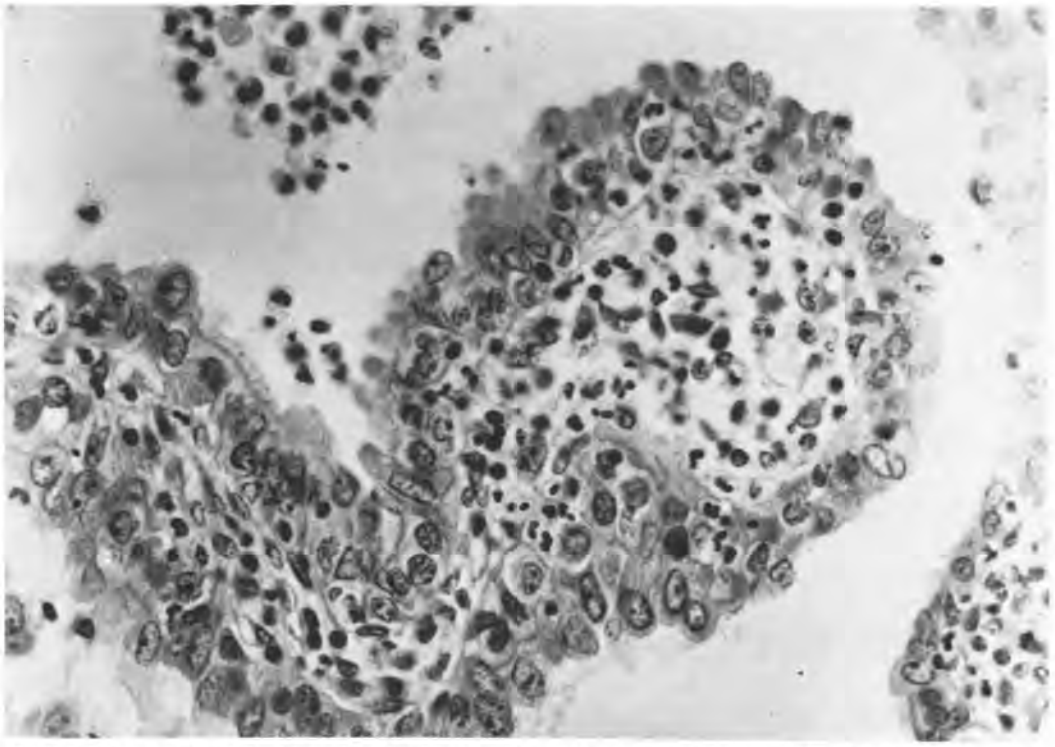

FIGURE 5-6 Acute salpingitis: microscopic appearance, showing neutrophilic infiltrate and mucosal atypia.

When phenomena of necrosis are marked, an abscess is formed that may overflow the tubal wall and invade the ovary (*tubo-ovarian abscess*).[43] The inflammation eventually regresses after one or several acute episodes and is replaced by fibrotic lesions that determine the final anatomic and functional state of the tube. The etiologic microbial agent may be demonstrated by direct microscopic examination or by culture of the secretions or of a tissue fragment.

Several authors have developed clinical staging systems for acute salpingitis.[44,45] These systems may be based on routine clinical examination alone or may be combined with laparoscopic inspection, and they seem to correlate with the eventual clinical outcome. The diagnostic criteria and therapeutic goals in Monif's staging system are summarized in Table 5-1.

Chronic Salpingitis

Salpingitis may be chronic at its onset or it may be a sequel of acute salpingitis. Clinically, it is manifested by pains and menstrual, urinary, and gastrointestinal disturbances. Clinical examination reveals the presence of a tender mass in the vaginal cul-de-sac.

Macroscopic Appearance. Chronic inflammatory lesions of the tube present in two principal forms: hypertrophic or atrophic. In the *hypertrophic form*, the tube is increased in volume and shows accentuated angles connected by fibrous adhesions (Fig. 5-7). The peritoneal serosa is opacified and gray-yellow, deep red, or brown. There are adhesions to adjacent structures, particularly the ovary, which often participates in the chronic tubal inflammatory processes. Section shows fibrotic thickening of the submucosa and muscularis. The mucosal rugae lose their normal structure and are replaced by thickened mucosal folds that adhere to one another, sometimes forming partitioned cavities of variable size (*follicular salpingitis*). The epithelium is focally ulcerated and necrotic.

TABLE 5-1.
Clinical Staging of Acute Bacterial Salpingitis

Stage	*Diagnostic Criteria*	*Therapeutic Goal*
I	Acute endometritis/ salpingitis without peritonitis	Eradication of symptoms and infectivity
II	Salpingitis with peritonitis	Preservation of tubal structure and function
III	Salpingitis with superimposed tubal occlusion or tubo-ovarian complex	Preservation of ovarian function
IV	Ruptured tubo-ovarian abscess	Preservation of life

Monif GRG: Clinical staging of acute bacterial salpingitis and its therapeutic ramifications. Am J Obstet Gynecol 143:489–495, 1982

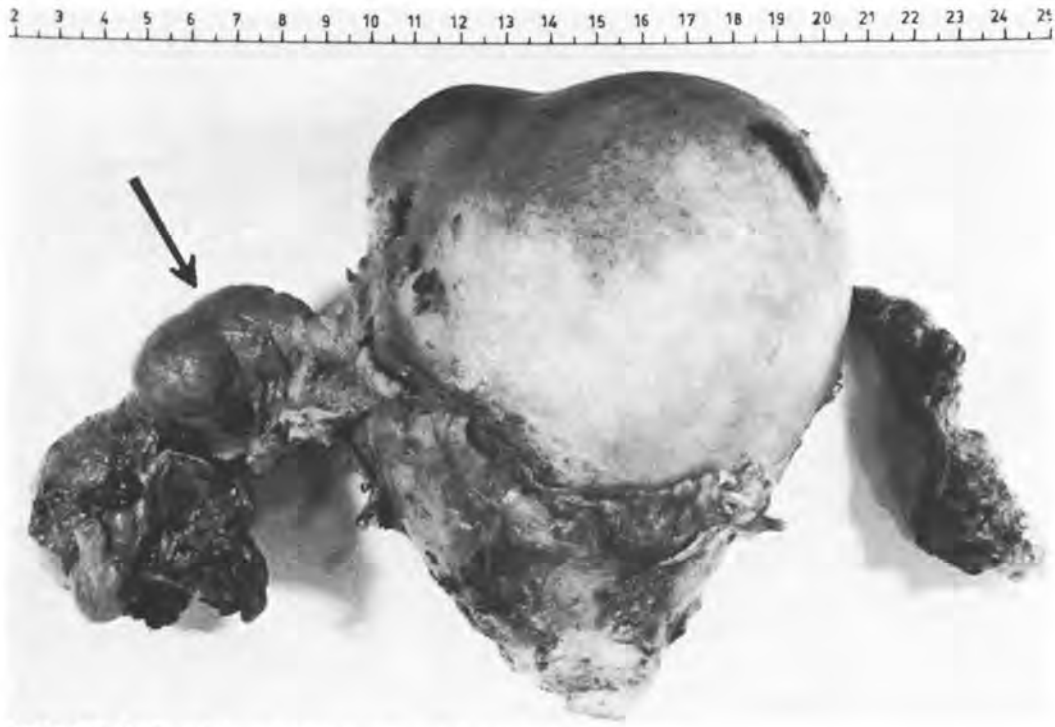

FIGURE 5-7 · Pyosalpinx: macroscopic appearance.

In the *atrophic form*, the tube is reduced to a thin, firm cord. Section shows a fibrotic wall with marked diminution of the mucosal rugae.

When the infundibulum and the uterine orifice are obliterated by rugal adhesions, edema, or deformity, a cystic pocket is formed, the contents of which may be purulent (pyosalpinx), serous (hydrosalpinx), or, more rarely, hemorrhagic (hematosalpinx). Chronic *pyosalpinx* shows a thick fibrotic wall, with the internal mucosal surface gray and granular or smooth and shiny. The mucosal folds are atrophic or have disappeared completely. *Hydrosalpinx* forms most frequently by resorption of purulent contents, leaving residual serous or seromucous fluid. This fluid may continue to accumulate as a mucosal secretion or (more important) as a transudate from injured blood vessels.[46,47] The cystic pocket may attain great volume and adhere to adjacent organs. The wall is thin, smooth, and translucent. Section reveals a unilocular or multilocular cavity lined by a flat epithelium and a thin fibrotic muscularis. The multilocular appearance is explained by rugal adhesions with persistent small cavities between them; these cavities later become dilated and filled with fluid. Winston has commented on estrogen and progestin receptor deficiency in the tubal mucosa in hydrosalpinx.[48]

Pyosalpinx and hydrosalpinx may be complicated by hemorrhages that appear in the edematous and congested stroma of the mucosal rugae; this complication is known as *hematosalpinx* (Fig. 5-8). This stroma forms fleshy buds in the zones of epithelial erosion. Hematosalpinx may be confused with an ectopic tubal pregnancy; the absence of fetoplacental debris orients the differential diagnosis toward the inflammatory etiology.

Boer-Meisel and colleagues have suggested that the likelihood of subsequent conception in patients treated for hydrosalpinx could be predicated by a macroscopic analysis of the nature and extent of adhesions, the appearance of the endosalpinx, the thickness of the tubal wall, and the maximal tubal diameter.[49] They were able to combine these observations into scores that resulted in three groups with 77%, 21%, and 3% probabilities of subsequent uterine pregnancy.

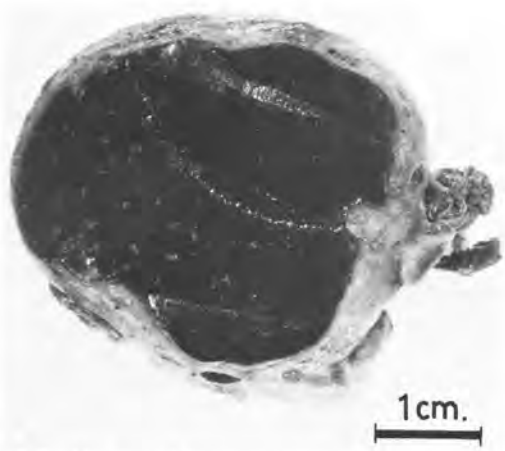

FIGURE 5-8 Hematosalpinx: macroscopic appearance.

Microscopic Appearance. The *hypertrophic form* shows multiplication and enlargement of the mucosal rugae, which become adherent and constitute cystic cavities of variable sizes (Fig. 5-9).The mucosal stroma is edematous, congested, and infiltrated by lymphocytes and plasma cells (Figs. 5-10 and 5-11). There may be small granulomata or microabscesses that destroy the mucosa. The epithelium is atrophic and flattened, and ciliated cells have become rare. In certain cases, mucosal hyperplasia is so pronounced that it is confused with adenocarcinoma. The absence of malignant cytologic abnormalities and the presence of pronounced chronic inflammation permit the recognition of this process as hypertrophic salpingitis. The submucosa and muscularis show lymphoplasmacytic infiltrates and fibrosis. The rugal adhesions with partial or complete tubal obstruction do not prevent the transit of spermatozoa, but they cause abnormal implantations of the egg in the tube.

The *atrophic form* shows effacement of the mucosal folds and marked atrophy of all the layers of the tubal wall. The epithelium is cuboidal or flattened; ciliated cells are as rare as in the hypertrophic form. The inflammatory infiltrates are of the lymphoplasmacytic type. Transit of the egg is disturbed by the slowing of the serous current normally present in the tube.

The microscopic appearance of chronic *pyosalpinx* reveals the tubal wall infiltrated by plasma cells, lymphocytes, neutrophils, and histiocytes. Adhesions between mucosal folds cause the appearance of cystic cavities lined by columnar epithelium or epithelium flattened by the inflammatory process. The serosa frequently shows fibrous adhesions. The cavity contains a purulent exudate. It is not rare to see foci of acute inflammation complicating a chronic pyosalpinx.

Hydrosalpinx is lined by an atrophic flat epithelium, in which a few mucosal rugae may persist (Fig. 5-12). In the multilocular form, the cystic spaces are lined by an atrophic epithelium overlying a greatly thinned and fibrotic wall. Microscopic evidence of inflammation may be absent but usually is present.

Hematosalpinx reveals stromal hemorrhagic foci and hemorrhages in the mucosal rugae, with rupture of the epithelium and hemorrhagic inundation of the tubal lumen. The mucosa becomes atrophic under the pressure of the hemorrhagic exudate, and it is limited to a single layer of flattened cells. In an ancient hematosalpinx, the wall is reduced to a dense fibrotic layer.

Salpingitis Isthmica Nodosa

Salpingitis isthmica nodosa is a common, usually asymptomatic, lesion. It was described for the first time by Chiari in 1887.[50] It is characterized by muscular hyperplasia with invasion of the muscularis by glandular islands that have usually lost contact with the overlying mucosa. The pathogenesis is still disputed. According to some authors, it is basically a dystrophic lesion of the glandular mucosa accompanied by hyperplasia of smooth muscle fibers (tubal adenomyosis). Because contact with the mucosa can sometimes be demonstrated (Fig. 5-13), other authors prefer the term *diverticulosis.* According to oth-

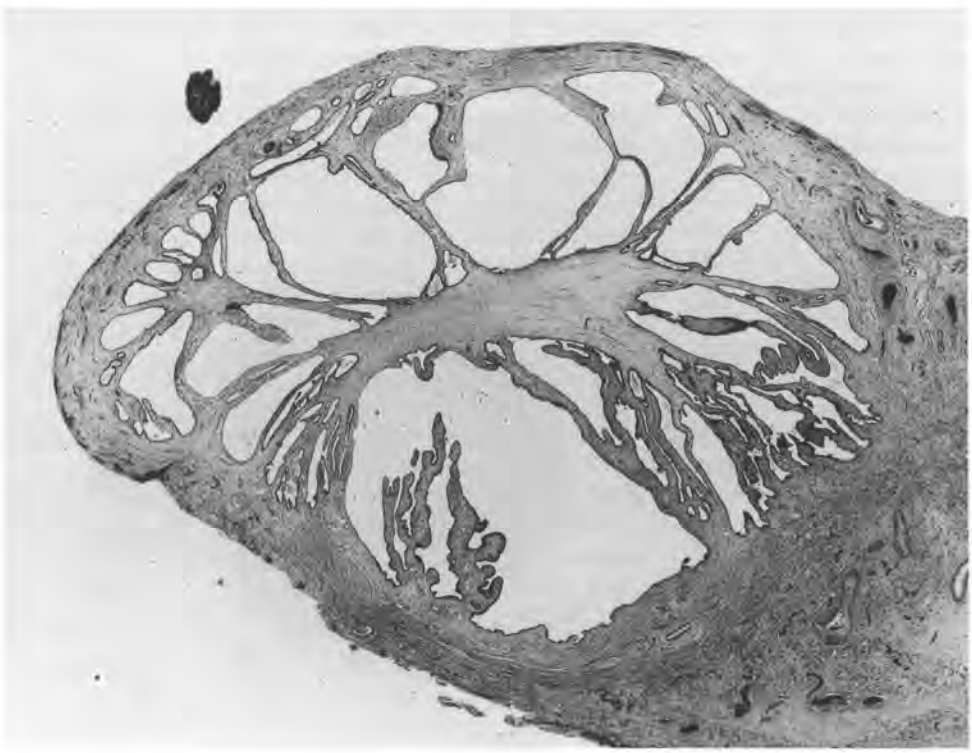

FIGURE 5-9 Follicular salpingitis. Mucosal rugae are adherent and form a network of cystic cavities.

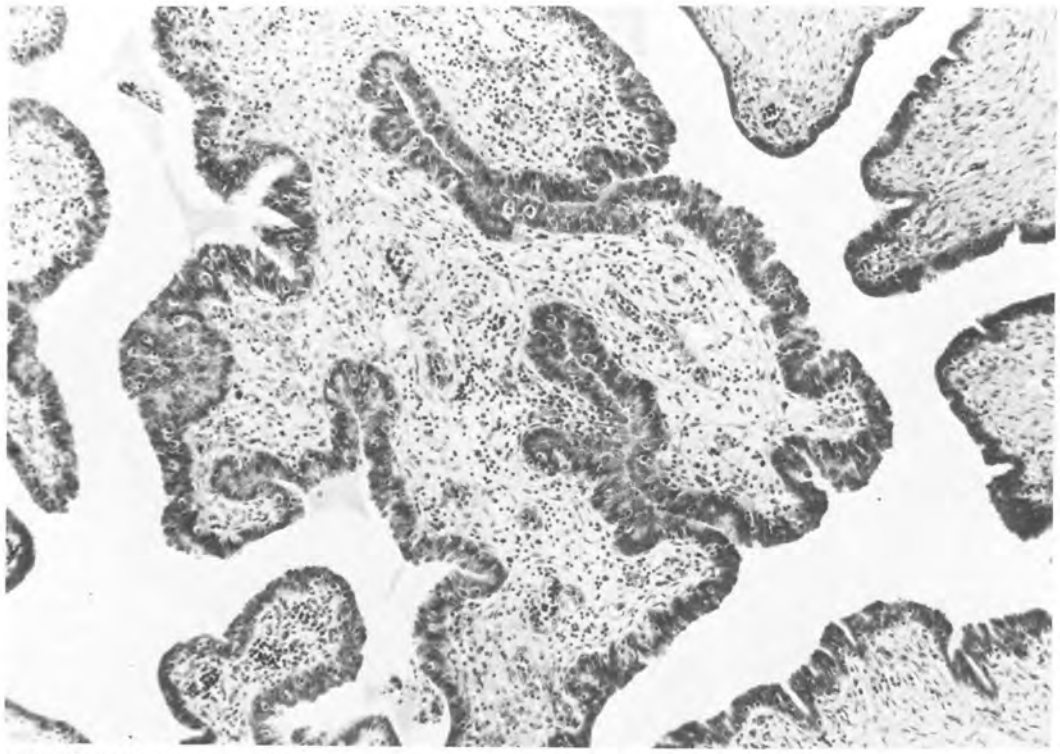

FIGURE 5-10 Chronic salpingitis: microscopic appearance.

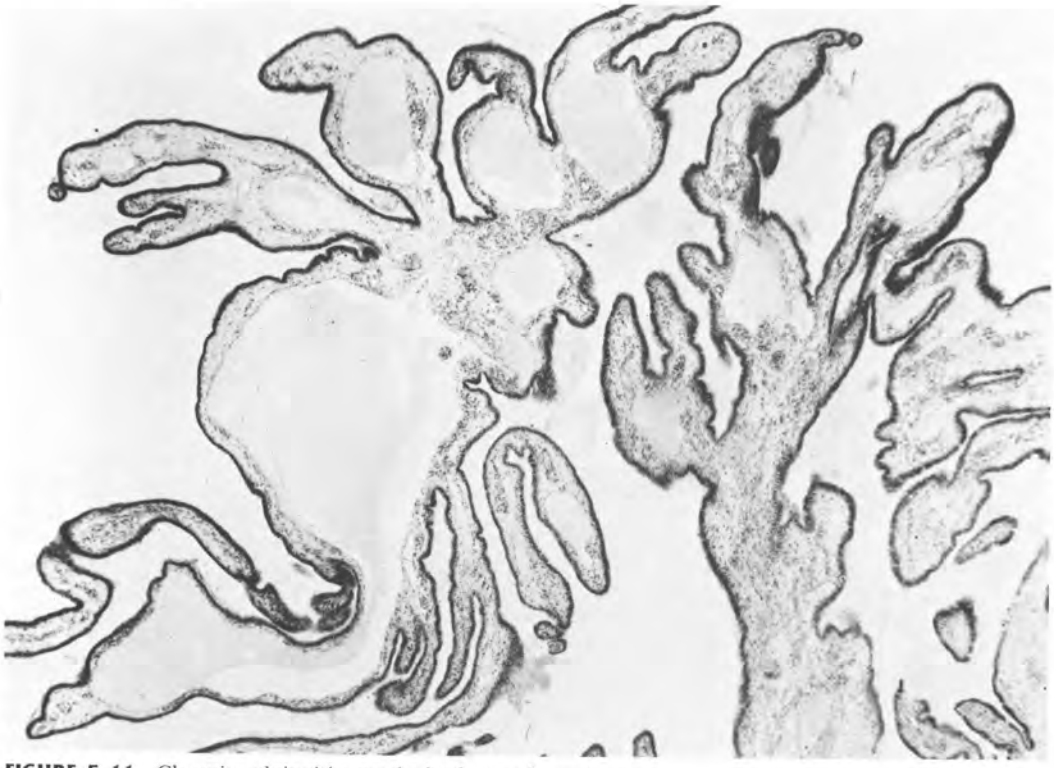

FIGURE 5-11 Chronic salpingitis: marked edema of rugae.

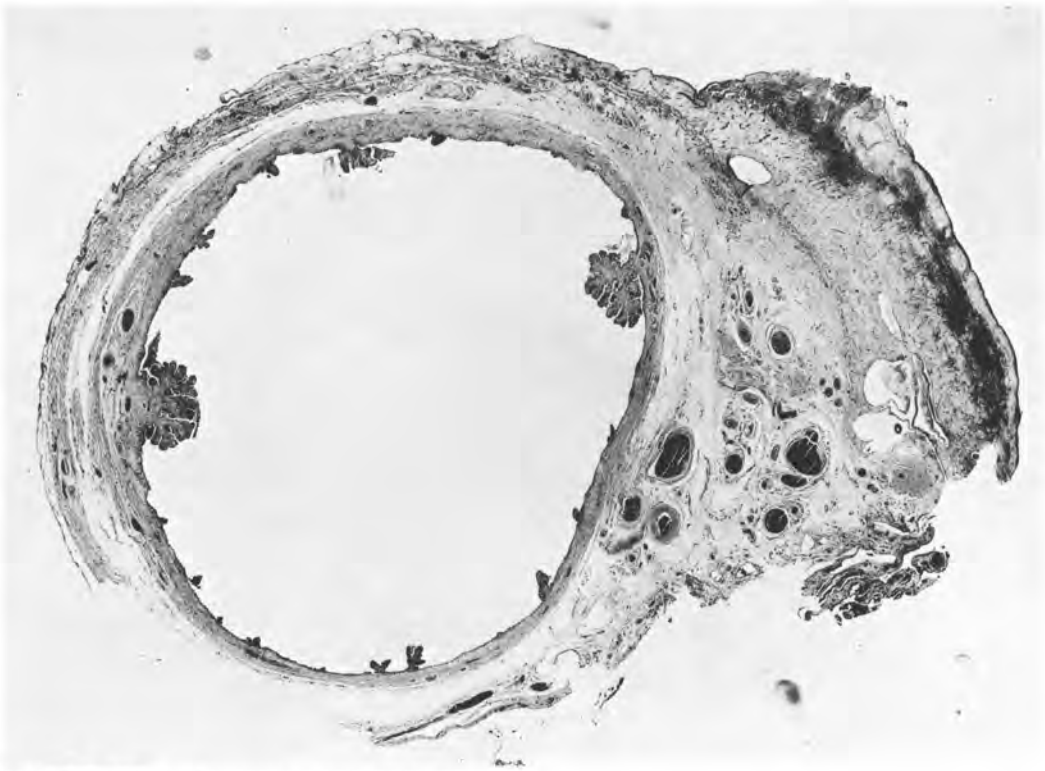

FIGURE 5-12 Hydrosalpinx: microscopic appearance.

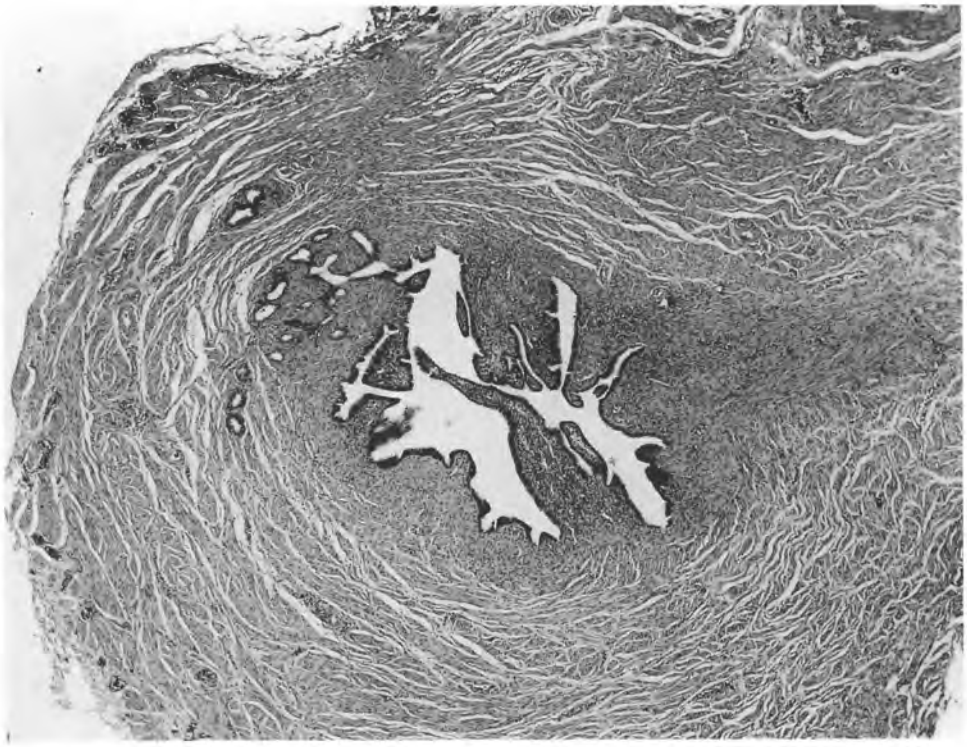

FIGURE 5-13 Salpingitis isthmica nodosa. Early lesion with diverticula extending from the mucosa into the tubal muscular wall.

ers, it is a sequel of chronic salpingitis.[51] It is sometimes considered to be a congenital malformation, although its absence before the menarche militates against this theory. Cioltei and associates have commented on hyperandrogenism in nearly half of their cases of "nodular salpingitis," but the significance of this observation is blunted by their apparent inclusion of salpingitis isthmica nodosa and follicular hydrosalpinx in this grouping.[52]

Macroscopic Appearance. The tubes, principally the isthmic regions, reveal thickened walls in which are noted one or several firm yellow or brown nodules of 1 to 2 cm in diameter.

Microscopic Appearance. In the hypertrophic muscularis, glandular formations not in continuity with the surface epithelium are found, lined by tubal-type epithelium (Fig. 5-14). The smooth muscle fibers surrounding the glands are hyperplastic and hypertrophic. A few discrete lymphoplasmacytic infiltrates are often seen. This lesion should not be confused with true tubal adenomyosis, which consists of invasion of the tubal wall by foci of adenomyosis (endometrial glands and stroma) arising in the uterine cornua.[53]

Tuberculous Salpingitis

About 10% of cases of chronic salpingitis are of tuberculous origin. Its clinical and social importance is great, because about 25% of cases of primary sterility were formerly due to genital tuberculosis. It has recently become a much less common disease, especially in Western countries.[32] Adnexal tuberculosis arises most frequently during adolescence and is accompanied by other manifestations of tuberculosis, notably pleural, peritoneal, pulmonary, nodal, and osseous manifestations. Genital tuberculosis may remain latent for long periods or may manifest itself by discrete clinical signs. Endometrial biopsy undertaken to investigate a case of sterility sometimes uncovers a previously unsuspected gynecologic tuberculous infection.[54]

Tubal contamination takes place by the hematogenous route from the primary pulmonary focus, by lymphatic dissemination after peritoneal or mesenteric lymph nodal involvement, or more rarely by the ascending route from a vaginal infection.

Macroscopic Appearance. The macroscopic appearance of tuberculous salpingitis includes several forms. The least specific form is similar in appearance to any other chronic salpingitis. The *ulcerocaseous* form shows a pale yellow, granular, caseous mass involving a large segment of the tube. The *chronic* form is grossly identical to salpingitis isthmica nodosa. The *miliary* form is characterized by multiple tiny granulomata disseminated on the tubal surface and in the wall. The tube is congested, edematous, and fixed to neighboring organs by numerous adhesions. This miliary form is commonly accompanied by abundant ascitic fluid. These tuberculous granulomata must not be confused with small epithelial inclusion cysts, Walthard's cell rests, or foci of endosalpingiosis. An important characteristic of tuberculous salpingitis is that the infundibulum remains patent, with its fimbriae everted, in about 50% of cases, whereas in gonococcal salpingitis it is almost always obstructed.

Microscopic Appearance. When a caseating granuloma is found, the diagnosis poses no problem: abundant giant cells are seen in the granulomata (Fig. 5-15). In other cases, granulomatous lesions are rare, and serial sections of one or more biopsies are necessary to demonstrate them. The presence of a hyperplastic and adenomatous mucosa, even in the absence of granulomata, should cause suspicion of a tuberculous origin. This hyperplasia should not be confused with adenocarcinoma of the tube, although the latter may coexist with tuberculous salpingitis.

Granulomatous Salpingitis

There are other granulomatous salpingitides besides that of tuberculosis. Their symptomatology is the same as for chronic salpingitis; there may be signs of lesions in other sites. The most frequent complications of these tubal lesions are tubal pregnancy and secondary sterility.

Foreign-Body Granuloma. The causal foreign body often is contrast medium (Lipiodol) introduced during hysterosalpingography (Fig. 5-16). Other foreign bodies are materials deposited during a surgical procedure (eg, talc), silk sutures used for tubal ligation, and lipid or keratin debris from a dermoid cyst. Granulomata rich in epithelioid cells and multinucleated giant cells are found around the foreign material.

Mycotic Inflammatory Granuloma (Actinomycosis). The markedly increased frequency of actinomycotic infection of the tubes in recent years, its often unilateral localization, and its usual relation to the intrauterine device have been commented on earlier.[30] The inflammatory response in these cases is often purulent and granulomatous, although one or the other condition may predominate. Careful search (multiple sections of multiple blocks) may be necessary to demonstrate the typical "sulfur granules" of Gram-positive organisms (Fig. 5-17).

Sarcoidosis

Macroscopic Appearance. The macroscopic appearance, consisting of disseminated miliary nodules, causes the observer to think of tuberculosis.

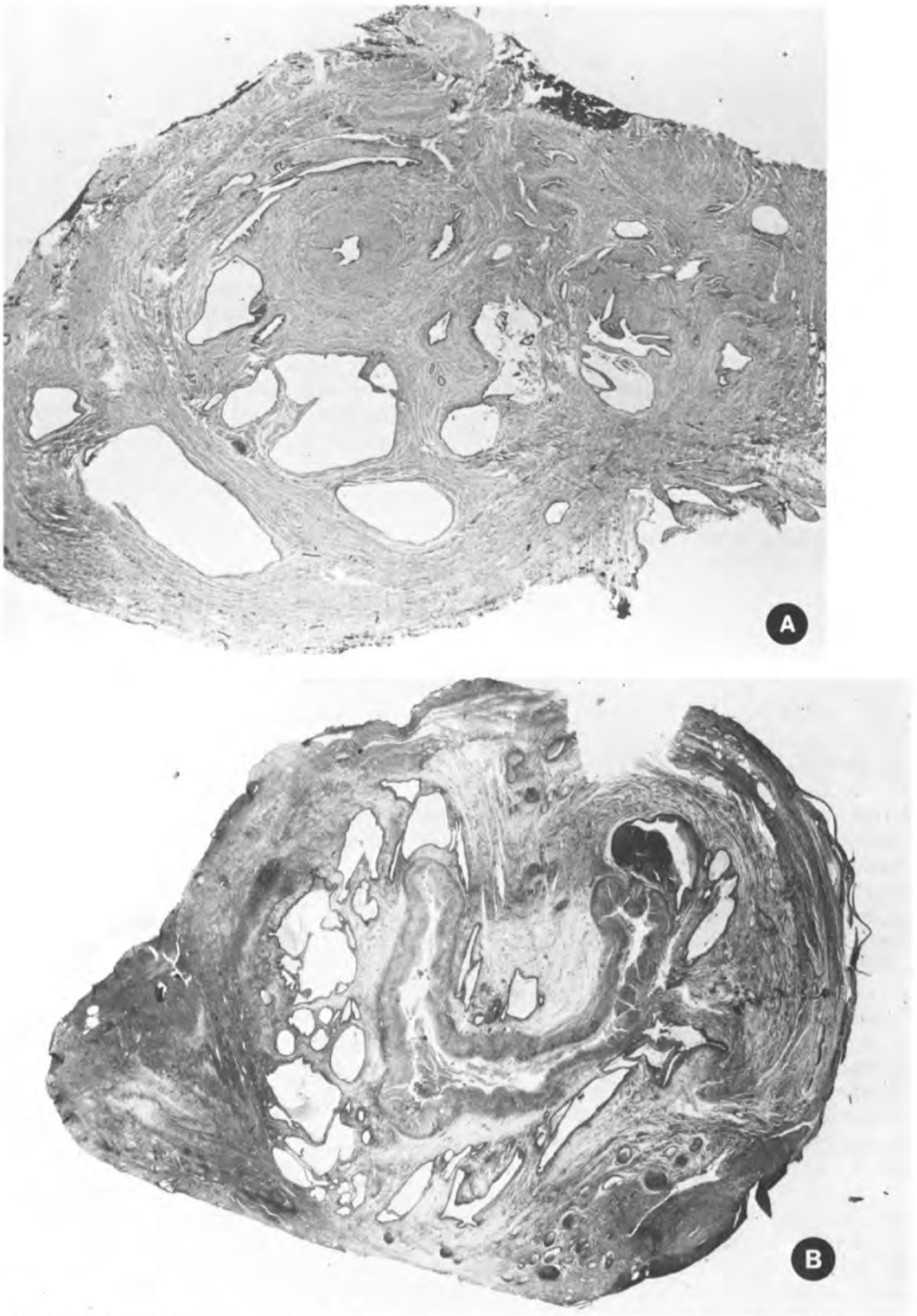

FIGURE 5-14 (A,B) Two cases of salpingitis isthmica nodosa. Both are more advanced than the case shown in Fig. 5-13. (**A** courtesy of Dr. Henry J. Norris and the Armed Forces Institute of Pathology, Washington, DC)

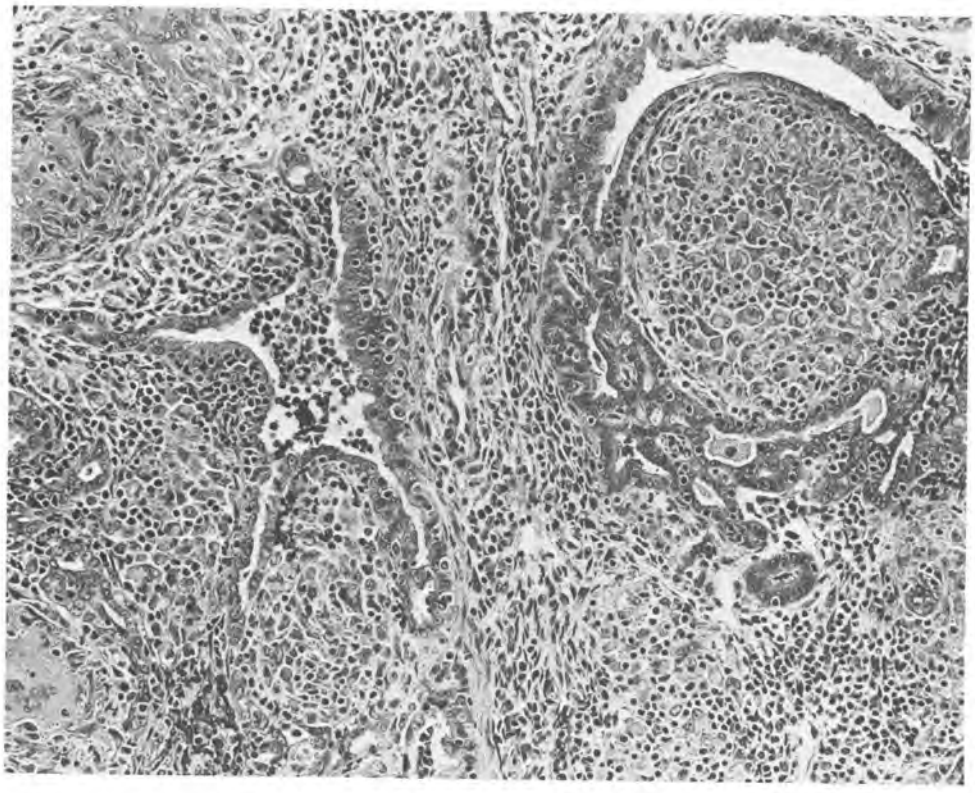

FIGURE 5-15 Tuberculous salpingitis: epithelioid and giant cell granulomata with reactive mucosal hyperplasia.

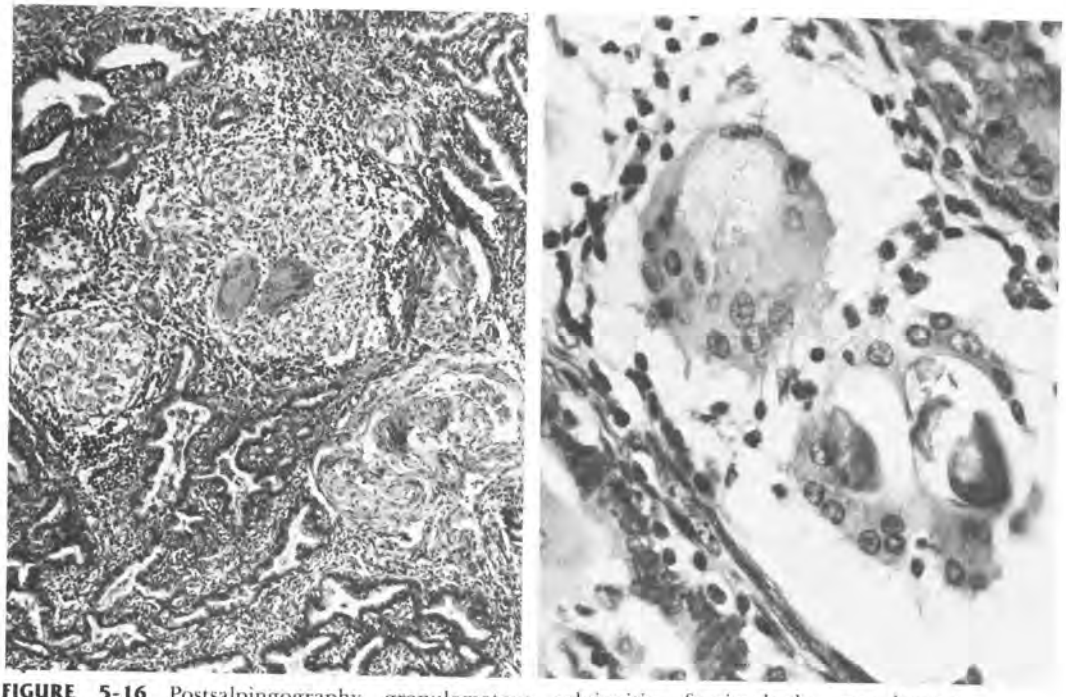

FIGURE 5-16 Postsalpingography granulomatous salpingitis: foreign-body granulomata (Lipiodol).

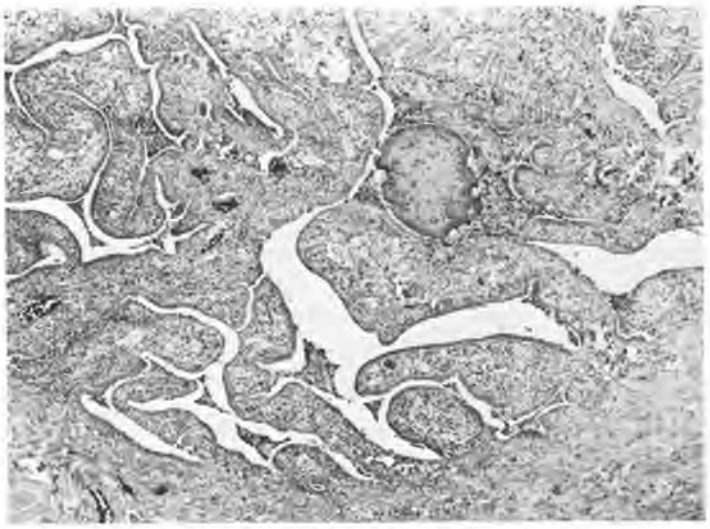

FIGURE 5-17 Actinomycotic salpingitis in an IUD wearer: mixed inflammatory infiltrate, reactive mucosal hyperplasia, and a single "sulfur granule."

Microscopic Appearance. The microscopic picture is that of a giant cell granulomatous process similar to tuberculosis, but without caseation and without tubercle bacilli.

Other Granulomatous Salpingitides. Other conditions associated with granulomatous salpingitis include *parasitic disease* (schistosomiasis, oxyuriasis) and *Crohn's disease* (regional enterocolitis).

Xanthogranulomatous Salpingitis

Xanthogranulomatous salpingitis is a rare lesion that is easily confused with tuberculous salpingitis. It is characterized by the presence of deposits of lipid in the mucosa and submucosa.[55]

Macroscopic Appearance. The macroscopic appearance is that of a chronic salpingitis with pyosalpinx. The mucosa presents a unique appearance of multiple small yellow-white nodules disseminated on the surface (Fig. 5-18*A*), resembling the surface of a strawberry. This same gross appearance is seen in the gallbladder in cholesterosis (so-called strawberry gallbladder).

Microscopic Appearance. Microscopic examination reveals that these nodules are thickened mucosal rugae filled with numerous lipid-laden macrophages in the stroma (see Fig. 5-18*B*). This accumulation of macrophages represents a sequel of tissue degeneration or necrosis. In the gallbladder, it is usually explained as a local disturbance in cholesterol metabolism (defect in mucosal resorption or elimination). The reason for this accumulation of lipids in the fallopian tube is not clear. The lesion needs to be differentiated from the collections of histiocytes seen in malacoplakia,[56] in association with endometriosis,[57] and after radiation therapy.[58] The histiocytes contain calcium and iron in the first of the conditions and lipofuscin in the other two.

ENDOMETRIOSIS

Tubal endometriosis develops in the muscularis or beneath the serosa. It is most common in the intramural portion of the tube, but it is occasionally found in the isthmic portion. It may project in polypoid fashion into the tubal lumen and may be associated with infertility.[59] Endometriosis is said to be seen frequently in the proximal tubal segment after partial salpingectomy for sterilization.[60] For a discussion of the pathogenesis of endometriosis, see Chapter 7.[61]

Macroscopic Appearance. Endometriosis presents as small dark blue or black nodules, from a few millimeters to 1 or 2 cm in diameter. These nodules may compress the mucosa and narrow the tubal lumen.

Microscopic Appearance. Microscopically, endometrial glands are surrounded by more or less abundant endometrial stroma, which may undergo decidual transformation during pregnancy or treatment with progestational agents (Fig. 5-19). Endometriosis must not be confused with a well-differentiated adenocarcinoma or an adenofibroma or adenosarcoma.

TUBAL SURGERY IN FERTILITY CONTROL AND STERILITY

The surgical pathologist sees many more normal than abnormal fallopian tubes because of the popularity of tubal surgery as a means of fertility control. Classic abdominal tubal ligation (often at delivery, postpartum, or postabortal) has been supplanted in some institutions by vaginal tubal ligation, laparoscopic tubal electrocoagulation, culdoscopic tubal clipping, or hysteroscopic tubal plugging. Because failure rates of close to 1% have been reported with

most of these procedures,[62] the pathologist should be sure that the specimen received represents a complete transection of each tube. Occasionally, multiple sections are necessary to demonstrate the mucosa and lumen. The incidence of histologic salpingitis in puerperal tubal ligation specimens has been quoted as ranging from 7% to 38%, and positive tubal cultures have been obtained in from 0% to 50% of these cases; however, most authors agree that these "infections" are of no clinical significance.[63,64] Stromal decidual change is seen in 3% or more of puerperal tubes and is clinically unimportant.[65]

The reasons for the occasional failure of tubal sterilization procedures are still debated. The type of procedure must play a role, because about half of the pregnancies after failed laparoscopic tubal coagulation are ectopic, whereas almost 90% after failure of other tubal sterilization procedures are intrauterine.[62] Some authors have championed the role of "endosalpingiosis" or "endosalpingoblastosis" (probably in reality salpingitis isthmica nodosa) as evidence of the ability of tubal mucosa to invade and recolonize the poststerilization tubal defect,[62] whereas others have downplayed the significance or even existence of this lesion.[60] Endometriosis and tuboperitoneal fistula are said by others to be common poststerilization tubal lesions. Their clinical significance may be minimal, however, because Rock and coworkers noted no difference in pregnancy rates after tubal reanastomosis in women whose tubes did or did not show these or other less common lesions.[60,66]

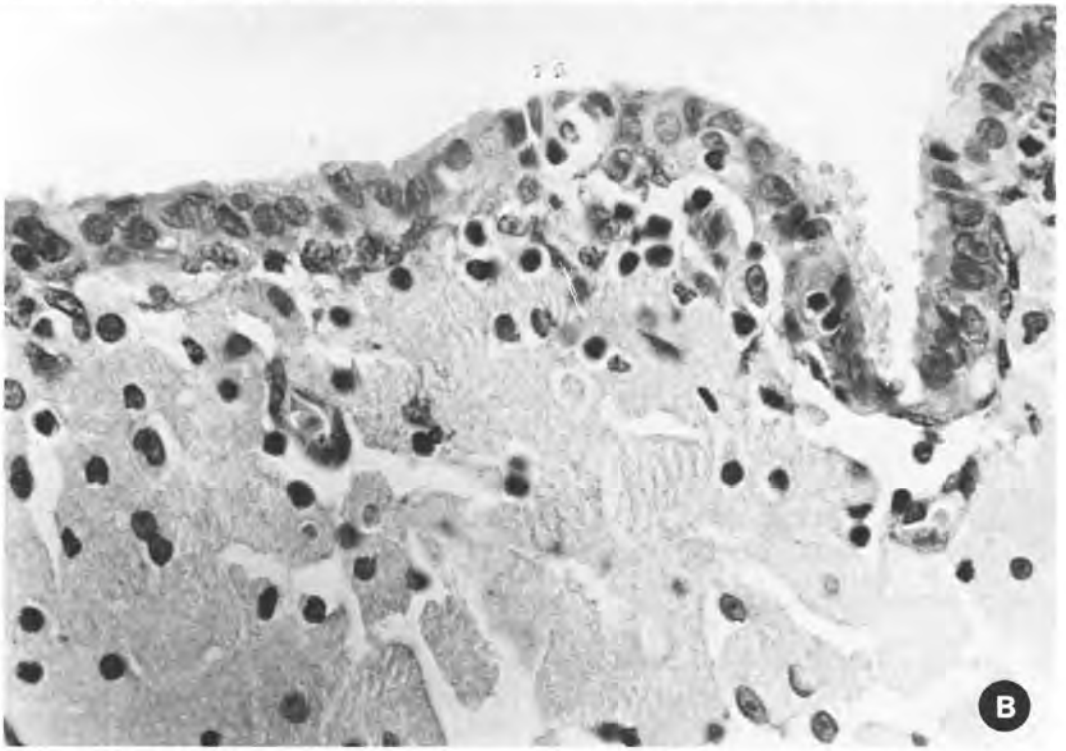

FIGURE 5-18 Xanthogranulomatous salpingitis. **(A)** Macroscopic appearance. **(B)** Microscopic appearance.

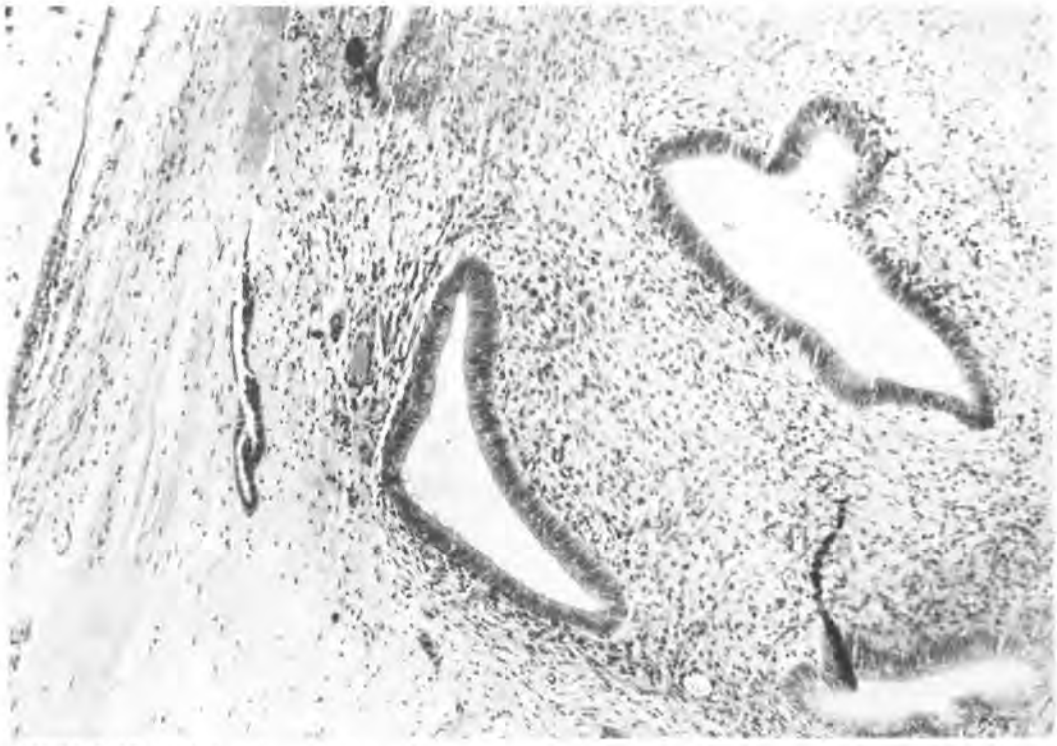

FIGURE 5-19 Tubal endometriosis.

Vasquez and associates have commented on deciliation, polyposis, and loss of mucosal folds as seen by scanning electron microscopy in the tubal isthmus after sterilization.[67] They believe that these lesions increase in severity with time and militate against successful operative reversal of sterilization. Inadequate initial procedures may be blamed for some poststerilization pregnancies, as may spontaneous reanastomosis without initiating pathology, although the latter would seem to be rare.

The pathologist who receives for examination a tube that was ligated at mid-tube years earlier generally encounters some degree of hydrosalpinx in the proximal (uterine) segment and an unremarkable distal (ovarian) segment, each of which ends blindly at a gap measuring 0.5 cm to several centimeters.[68] Mucosal endometriosis may be present at the proximal stump and is thought to result from menstrual reflux followed by implantation in damaged tissues.[60] Polyps projecting into the lumen and a picture resembling salpingitis isthmica nodosa in the wall may be present.[69]

The opposite aspect of tubal surgery consists of operations performed in infertile women in whom tubal pathology is suspected as the cause of the inability to conceive or for reversal of previous tubal sterilization procedures. Microsurgery has been used in these situations since 1959 and is considered by many authors to be the technique of choice.[70–72]

As many as 30% to 40% of cases of female infertility are related to tubal factors.[73] In infertility surgery for tubal disease, one of the most common lesions encountered is a blocked cornu, usually due to postpartal or postabortal inflammation, but also often associated with salpingitis isthmica nodosa, tuberculous salpingitis, tubo-ovarian abscess, polyps, casts of amorphous debris, adenomyosis, or leiomyomata.[48,72–75] After microsurgical treatment of a blocked cornu, 25% to 50% of patients are able to give birth.[72,76] De Brux has determined that the prognosis varies inversely with the severity of disease, and others have confirmed this observation.[72,77,78]

Some idea of the pathology of a blocked tube may be obtained preoperatively or intraoperatively by salpingoscopy.[79] Severe disease is generally evaluated correctly by this method, but histologically proved moderate epithelial or stromal pathology is frequently missed. Ultrastructural examination is even more sensitive for the demonstration of mucosal abnormalities, revealing degenerative changes in ciliated and secretory cells.[79,80]

The other major indication for tubal surgery in infertility occurs when the infertility is iatrogenic, subsequent to one of the tubal sterilization procedures discussed previously.[66,67,76,81] Results in different series are still variable, but Winston reports a 70% to 80% success rate.[76] Vasquez and associates state that results are poorer when the interval after sterilization surgery exceeds 5 years.[67] Siegler, on the other hand, reports that the success rate is independent of this interval, but is poorest with ampullary-isthmic anastomoses and tubes less than 4 cm in length.[81] The tubal specimens from these procedures frequently show pathologic changes, although the prognostic significance of these changes may be minimal (see above). Rock and colleagues report that

after unipolar cautery 40% of tubes show endometriosis, 21% show fistulas, and smaller proportions show chronic salpingitis, inclusion cysts, adhesions, or proximal hydrosalpinx.[66] An interesting approach to infertility surgery is the so-called paradoxical oophorectomy, or removal of the normal ovary on the same side as a unilateral diseased tube.[81,82] The rationale here has been described as "putting all the eggs in one (healthy) basket."

BENIGN TUMORS

Leiomyoma

Leiomyoma is also called *fibromyoma or fibroid.* The leiomyoma is a rare tumor in the fallopian tube. It may be solitary or multiple and usually measures from a few millimeters to several centimeters in diameter, although large, clinically significant tumors do occur. It presents macroscopically as a spherical mass protruding under the peritoneal serosa. Microscopically, it appears identical to the uterine leiomyoma: whorled smooth muscle fibers separated by narrow connective tissue bundles.[83,84]

Adenomatoid Tumor

The adenomatoid tumor or mesothelioma is a small, well-demarcated, benign tumor situated in the tubal muscularis or subserosa. It is composed of pseudoglandular formations surrounded by a fibromuscular stroma.[85] Different theories have claimed that the lining cells of these pseudoglandular structures are mesothelial, endothelial, vascular, or epithelial, but ultrastructural and immunohistochemical evidence has established the mesothelial (peritoneal) origin.[86,87] These tumors are rare and are asymptomatic, usually being discovered fortuitously during examination of a surgical or postmortem specimen. They are found during the period of genital activity and are histologically identical to similar tumors of the corpus uteri and the male epididymis.

Macroscopic Appearance. Macroscopic examination reveals a small, well-limited mass visible beneath the peritoneal serosa. Section shows firm, pink-white, homogeneous tissue. Small foci of calcification may be present.

Microscopic Appearance. The microscopic appearance consists of spaces lined by flat or cuboidal cells, surrounded by a stroma rich in collagen fibers and smooth muscle fibers. No cellular atypia or mitotic activity is noted (Fig. 5-20). The flattening of the lining cells, very marked in some cases, has wrongly suggested to some observers a lymphangiomatous origin. In other tumors, the cell nests are massive and contain small cystic spaces. In a few cases, continuity with the peritoneal surface lining has been demonstrated.

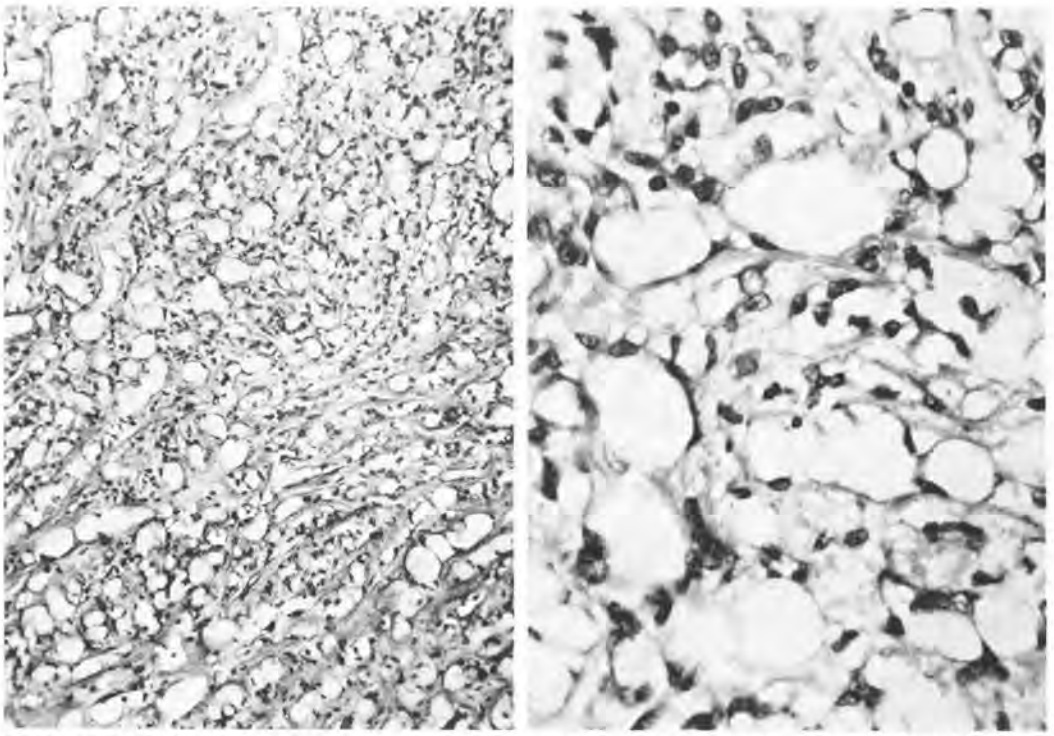

FIGURE 5-20 Adenomatoid tumor of tube. (Hinerman DL, Gould SE: What is your diagnosis? Am J Clin Pathol 37:204, 1962)

Endometrial Polyp and Adenofibroma

These lesions are benign proliferations of epithelium and stroma, which can present as intraluminal masses. The endometrial polyp is common, occurs in the intramural portion of the tube, and is histologically identical to the polyp described in Chapter 4.[59,88] The adenofibroma is rare and consists of tubal epithelium supported by fibrous stroma.[89,90] It also resembles its more common uterine counterpart.

Papillary Tumors

Benign papillomas have been reported rarely in the tube, presenting with hydrosalpinx or with sterility related to tubal occlusion.[91,92] Pathologically, they are composed of papillary processes lined by epithelium resembling normal tubal mucosa, with little stratification, few mitoses, and no atypia.

A lesion that appears to be unique to the fallopian tube and has been reported only in pregnant or postpartum women is the *metaplastic papillary tumor* (Fig. 5-21).[93,94] It was an incidental microscopic finding in all reported cases. The papillae are lined by mucin-secreting cells and cells with eosinophilic cytoplasm, which have been interpreted by some authors as oncocytes,[93] although ultrastructural study of one case[94] did not show the packed mitochondria expected in oncocytes. Mitotic figures are rare, and the tumor does not invade into the wall of the tube. Follow-up findings have been benign in the few cases reported, and it is not known whether the lesion is a hormonally-induced hyperplasia and metaplasia or a true neoplasm.

Teratoma

The fallopian tube is the second most common site (after the ovary) of female genital tract teratoma, with about 50 cases reported.[95] Six of these have been associated with an ectopic pregnancy,[95] and 3 have been malignant (immature).[96] They no doubt arise from germ cells arrested in their maturation toward the genital crest. Their pathologic features are similar to those encountered in the ovary (see Chap. 6).

Other Benign Tumors

Within the tube, rare cases of *hemangioma,*[97] *lipoma,*[98] *fibroma,*[99] *neurilemoma,*[100] and *sex cord tumor with annular tubules*[101] have been reported.

MALIGNANT TUMORS

Primary Tumors

Adenocarcinoma

Adenocarcinoma of the tube arises from the mucosal epithelium. It is an uncommon tumor, but well over 1000 cases have been reported in the literature. It represents about 0.5% of all malignant tumors of the female genital tract,[102] and its incidence in the United States is 3.6 per million women per year, with no recent change in this figure noted.[103] Like epithelial cancers of the ovary and endometrium, tubal carcinoma seems to be less common in Japan.[104] It is encountered in women between 40 and 60 years of age, although patients as young as 18 years have been observed.[105] A high incidence of chronic inflammatory lesions has been noted,[106] but a causal relation has not been established; tuberculosis of the tube is thought by some authors to be frequently associated with carcinoma, but others[107] think that other forms of salpingitis are much more commonly involved. In any event, we must remember that inflammatory lesions of the tube are frequent and that carcinoma is equally rare, and that salpingitis (particularly of tuberculous etiology) may be associated with a hyperplastic mucosal reaction that can be and has been misdiagnosed as carcinoma (see Fig. 5-15). Adenomyosis has been noted in a high percentage of cases by some authors, but again, this is a common lesion.[106]

Other lesions that appear to have a premalignant potential in other portions of the female genital tract have been demonstrated far less frequently in the tube. *Adenomatous hyperplasia* has been discussed in detail by Dougherty and Cotton but has not been shown to be significantly related to carcinoma in the fallopian tube (Fig. 5-22).[108] These authors state that this lesion is often found in conjunction with chronic salpingitis and with estrogen-producing ovarian tumors. Dallenbach-Hellweg found it most commonly associated with endometrial hyperplasia and carcinoma,[109] Stern and coworkers noted it in association with epithelial ovarian tumors and in women receiving exogenous estrogens,[110] and Robey and Silva have commented on a particular association with serous borderline tumors of the ovary.[111] Our experience is similar, but Moore and Enterline doubt the clinical significance of the lesion and believe that careful searching will prove its common occurrence in tubes removed from women with no other disease.[112] In the earliest form, the only abnormalities seen are increased height of the tubal epithelial cells, with crowding and epithelial tufting into the lumen. This is followed by the creation of small glandular spaces within the epithelium. In the most advanced instances, there are numerous small and medium-sized glands crowded together in a greatly thickened epithelium. The cells show hyperchromatism, pseu-

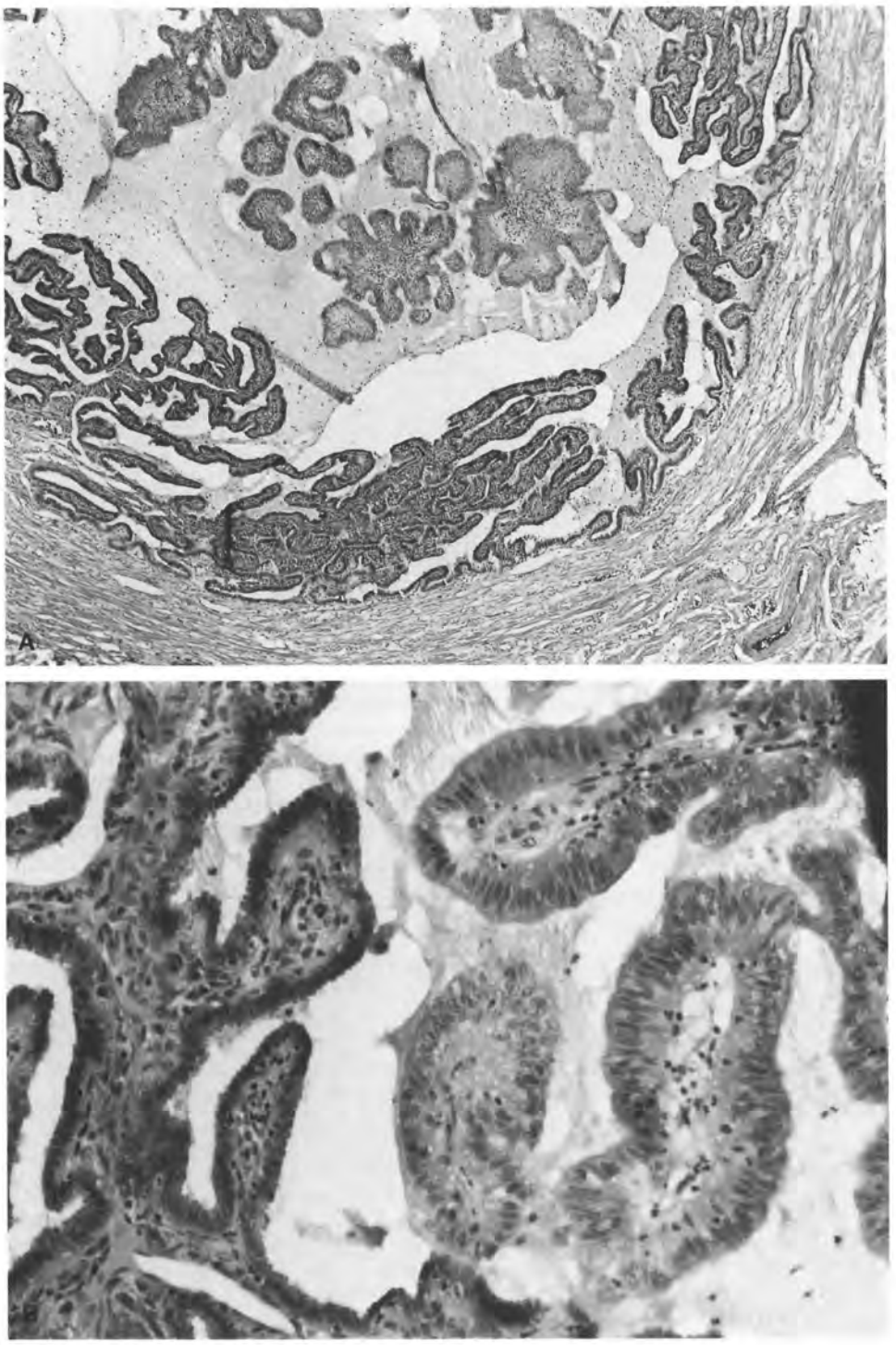

FIGURE 5-21 Metaplastic papillary tumor. **(A)** Low-power view. **(B)** Detail. Compare the normal tubal epithelium (*left*) with the tall columnar cells containing cytoplasm that was eosinophilic in sections stained with hematoxylin-eosin (*right*). Courtesy of Dr. Mirka Jones, Armed Forces Institute of Pathology, Washington, DC)

dostratification, and true stratification; but in contradistinction to carcinoma few mitoses are seen and large abnormal nucleoli are not present. The presence of any mitoses is important, because they are not seen in normal tubal mucosa.

Adenocarcinoma in situ is difficult to differentiate from adenomatous hyperplasia and probably is a more advanced stage of the latter lesion (Fig. 5-23).[110] Bannatyne and Russell stress as important features of in situ carcinoma its focal rather than widespread distribution, frequent and sometimes abnormal mitotic figures, loss of multiple cell types, and marked nu-

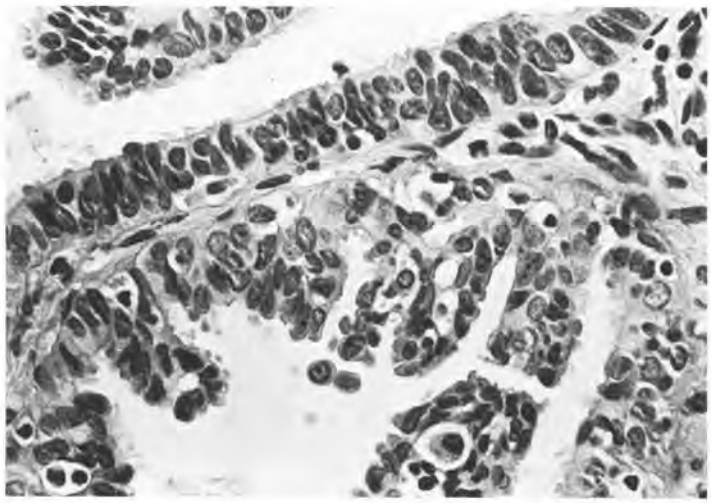

FIGURE 5-22 Adenomatous hyperplasia of tube in a case of ovarian carcinoma. Compare the hyperplastic epithelium (*below*) with the normal tubal mucosa (*above*).

clear pleomorphism with multiple large nucleoli.[113] Because in situ carcinoma is diagnosed after resection, progression to invasive carcinoma can rarely, if ever, be demonstrated. The in situ tubal lesion is usually associated with ovarian or endometrial carcinoma, particularly serous carcinoma of the ovary.[113] *Borderline mucinous and serous tumors* might be considered in situ carcinomas of the tube; two such mucinous lesions, both associated with pseudomyxoma peritonei, have been reported,[114,115] and we have seen a third case that coexisted with an ovarian borderline mucinous tumor (Fig. 5-24).

We must wonder why tubal cancer is so rare, considering that it arises in müllerian-derived epithelium such as that of cervical and endometrial carcinomas, both of which are common lesions, and histologically usually resembles serous carcinoma of the ovary, also a common tumor.[116] This question is one that we are unable to answer at the present time.

Clinical Signs. Clinical signs of invasive carcinoma are not characteristic. They include pain, the presence of an adnexal mass, and serous, purulent, or bloody vaginal discharge. Any of these findings may be absent; the complete triad is seen only rarely. Vaginal discharge is present in about half of the

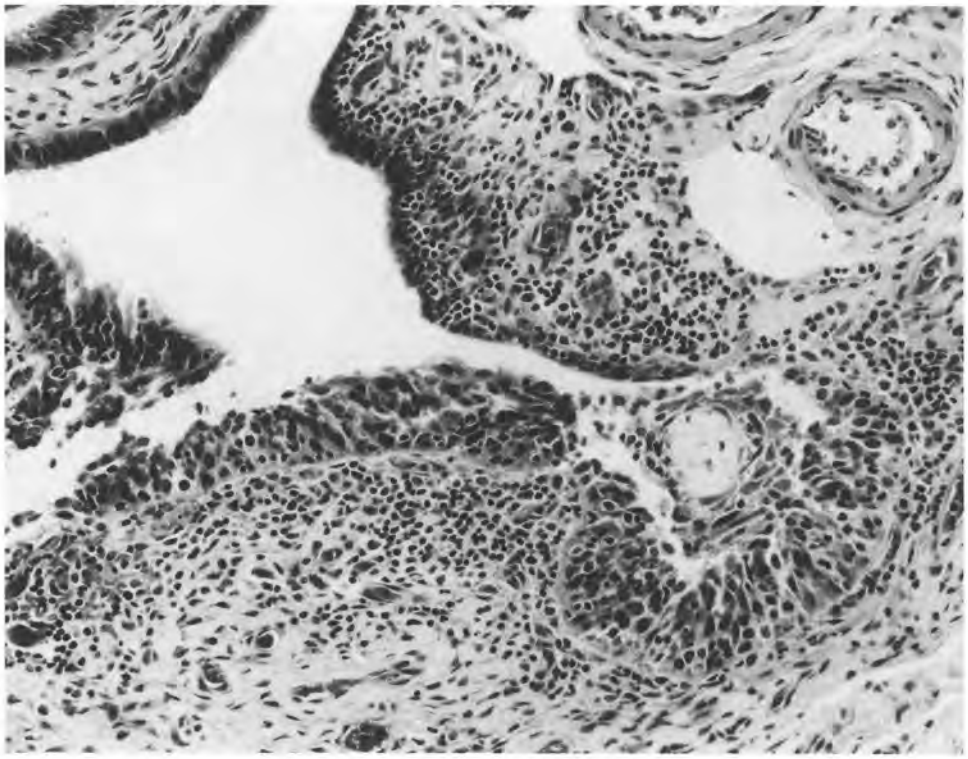

FIGURE 5-23 In situ adenocarcinoma of fallopian tube. Although lymphoid inflammation is present, the mucosal atypia is out of proportion to the infiltrate, and invasive carcinoma was situated nearby.

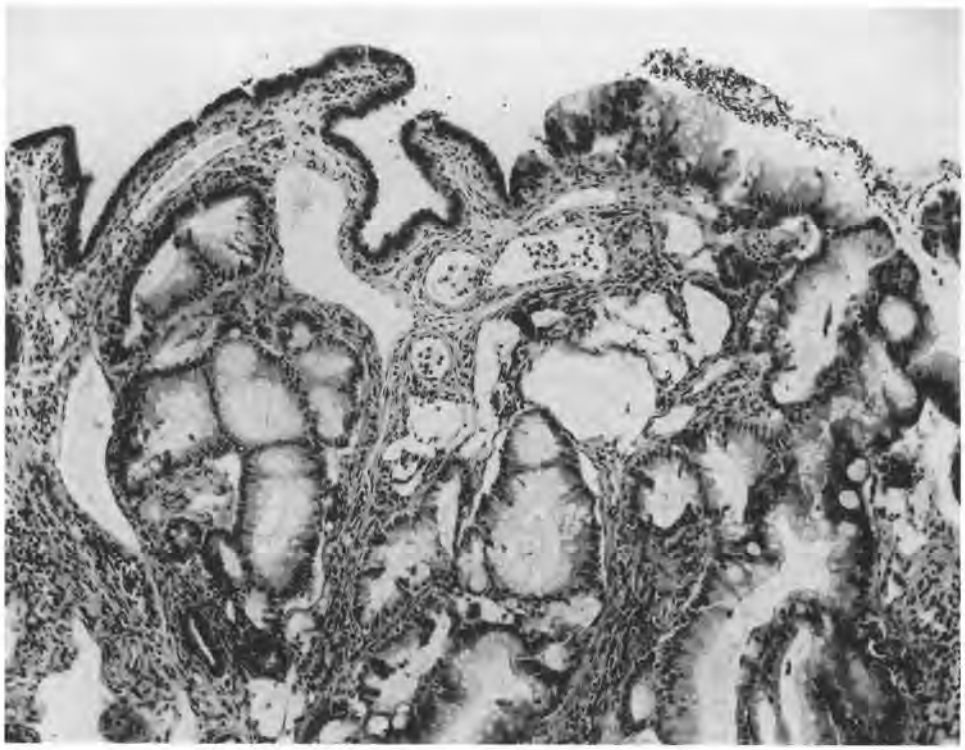

FIGURE 5-24 Borderline mucinous tumor (tumor of low malignant potential) of tubal mucosa. This tumor was an incidental microscopic finding in a patient who also had a borderline mucinous (intestinal-type) tumor of the ipsilateral ovary. Origin of this lesion in the tubal mucosa is seen at top right.

cases. More rarely, intestinal obstruction represents the first sign of the tumor. The diagnosis is made in less than 5% of cases before exploratory laparotomy.[102,107] Clues to the correct diagnosis are furnished by the clinical signs, hysterosalpingography, and vaginal exfoliative cytology. It has been stated that vaginal cytology reveals malignant cells in 60% of cases,[107] but other authors find that this procedure is much more often unrewarding.[105] Endometrial aspiration is probably a more effective cytologic procedure.[117] Carcinomatous cells have been recognized in cul-de-sac washes at the time of vaginal hysterectomy for other indications.[118] Occasionally, the exfoliated malignant cells may be recognized as being of tubal origin, but this is unusual. The cytologic appearance is usually similar to that of serous carcinoma of the endometrium or ovary. Hysterosalpingography is probably the best technique available for making the diagnosis before laparotomy, and ultrasonography is useful.[118]

Even after surgery, definitive diagnosis may be difficult, because tubal origin is difficult to prove in the presence of involvement of the ovary or endometrium, or both. In these situations, the tumor in the tube should look tubal histologically, show a transition from benign epithelium, and perhaps even represent the most bulky tumor mass before a tubal primary is diagnosed with confidence.[119]

Macroscopic Appearance. The tumor may be small or may attain a diameter of several centimeters. In a great number of cases, it is localized to the ampullary portion of the tube and forms an elongated bulge suggestive of chronic salpingitis. When the serosa is not involved, it is smooth and stretched; often fibrous adhesions are present. The tumor involves the right and left tubes with about equal frequency and is bilateral in about 20% of all cases. Coexistent chronic salpingitis is frequently present. On opening the tube, a soft, sometimes encephaloid, tumor mass is seen. It is red or gray and often necrotic, and close inspection often reveals papillary formations (Fig. 5-25). In more advanced cases, the tumor invades completely through the tubal wall and forms papillary nodules on the peritoneal serosal surface; this is usually a late occurrence. The tube frequently becomes obstructed, with the development of a pyosalpinx or hematosalpinx. Isthmic localizations are less frequent, but they show a much more malignant and rapid evolution.

Microscopic Appearance. The most common histologic type is serous papillary adenocarcinoma resembling that more commonly seen in the ovary (Figs. 5-26 and 5-27).[116] In the well-differentiated (grade I) pattern, columnar cells line the connective tissue axes of the papillae and recall the cytologic structure of normal tubal epithelium. Marked cellular atypia is uncommon, but mitoses are frequently seen. Nucleoli are prominent and often multiple.

In the less differentiated tumors, bizarre cellular atypias are numerous and marked; the cells are found in dense nests and sheets, without any morphologic similarity to tubal mucosa. It is not rare to

FIGURE 5-25 Well-differentiated adenocarcinoma of tube: macroscopic appearance.

see cystic structures and intracystic papillary formations. Mitoses are numerous.

As elsewhere in the female genital system, other types of carcinoma may be encountered. After serous carcinoma, the most frequent type is *endometrioid carcinoma,* but only a handful of such cases have been documented.[120,121] A type that may pose a particularly difficult differential diagnostic problem resembles the adnexal tumor of probable wolffian origin (juxta-ovarian tumor).[122] Scattered cases of

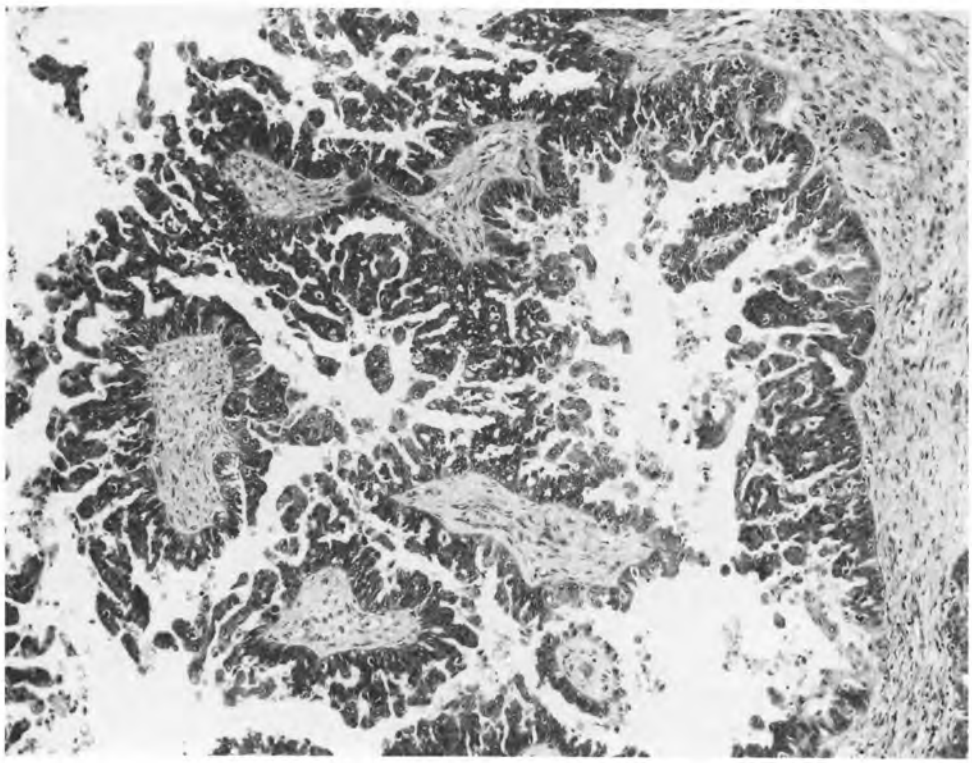

FIGURE 5-26 Well-differentiated serous carcinoma of fallopian tube. Broad papillae are lined by relatively uniform cells with stratification, tufting, and cell exfoliation.

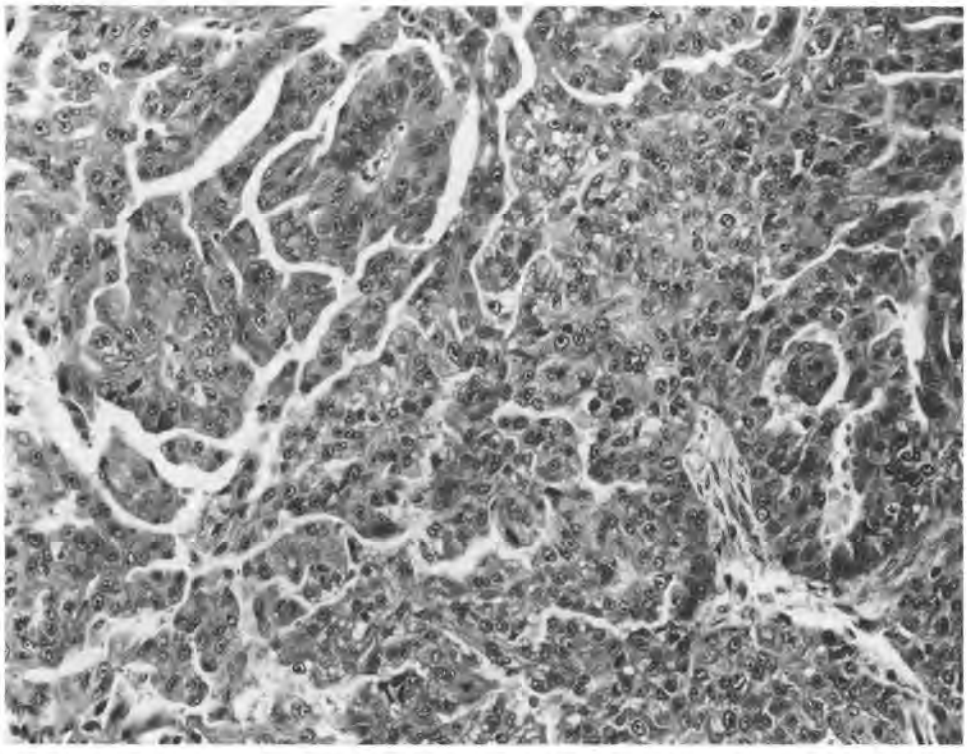

FIGURE 5-27 Poorly differentiated serous carcinoma of fallopian tube. Poorly formed papillae coexist with solid sheets of tumor cells.

clear cell adenocarcinoma,[123] *transitional cell carcinoma,*[124] *glassy cell carcinoma,*[125] and *squamous cell carcinoma*[126] have been reported, as has *mucinous carcinoma of low malignant potential.*[114,115] Endometrial and cervical carcinomas, including *in situ squamous carcinoma of the cervix,* can involve the tubal mucosa by direct extension, but should not be considered primary tubal carcinomas. Primary tubal carcinoma can coexist with primary carcinomas elsewhere in the genital tract, as in the case reported of synchronous papillary mucinous adenocarcinomas of the endocervix and both fallopian tubes.[127]

Prognosis, Evolution, and Treatment. The prognosis of tubal carcinoma is poor, the most favorable results showing only about 40% to 50% 5-year survival.[102,104,128–130] The tumor spreads directly through the fimbriated end of the tube or by penetration through the wall. Lymphatic invasion takes place early and involves the iliac, aortic, and lumbar nodes, the ovaries, the pelvic and abdominal peritoneum, the uterus, the intestine, and the urinary bladder.[127,131,132] Vaginal, ureteral, renal, hepatic, adrenal, pulmonary, splenic, and cutaneous metastases are frequently seen. Survival is better correlated with the gross extent of the tumor at the time of treatment than with histologic differentiation. Most authors[102,128] have advocated the same clinicopathologic staging system as in ovarian cancer, but we prefer a modification of the Dukes system for rectal cancer (Table 5-2).[133] The treatment is primarily surgical; radiation therapy has been used in conjunction with surgery but has not been demonstrated to improve the therapeutic results. Cisplatin-based combination chemotherapy is promising in localized and advanced-stage cases.[134,135]

Primary Sarcomas

Primary sarcomas of the tube are rare, with only a few dozen cases having been reported. They are predominantly fibrosarcomas and leiomyosarcomas, with even rarer malignant fibrous histiocytomas reported.[136] The clinical evolution is almost always fatal.

TABLE 5-2.
Pathologic Staging of Carcinoma of the Fallopian Tube*

Stage 0	Carcinoma in situ (limited to the tubal mucosa)
Stage 1	Tumor extending into the submucosa and/or muscularis but not penetrating to the serosal surface of the fallopian tube
Stage 2	Tumor extending to the serosa of the fallopian tube
Stage 3	Direct extension of the tumor to the ovary and/or endometrium
Stage 4	Extension of tumor beyond the reproductive organs (eg, other pelvic organs, pelvic soft tissues, peritoneal implants, abdominal viscera)

*The staging of tumor in stages 0, 1, and 2 is not altered by bilateral tubal cancer per se, but the most extensive focus of disease in either tube determines the stage.

Adapted from Schiller HM, Silverberg SG: Staging and prognosis in primary carcinoma of the fallopian tube. Cancer 28:389–395, 1971

Carcinosarcoma

About 40 cases of carcinosarcoma (homologous and heterologous) arising in the fallopian tube have been reported.[137–139] This corresponds to 4% of all such tumors of the female genital tract, the more common localizations being corporeal, ovarian, vaginal, and cervical (in descending order of frequency). These tumors occur predominantly in postmenopausal women, are histologically similar to endometrial carcinosarcomas (see Chap. 4), and share the poor prognosis of uterine carcinosarcoma. A single reported tubal case was bilateral.[139] Anecdotal responses to radiation therapy and chemotherapy have been reported, but the primary treatment is surgical.

Choriocarcinoma

Primary choriocarcinoma of the fallopian tube is a rare lesion; a comprehensive review in 1981 accepted only 76 reported cases.[140] The tubal tumors are gestational in origin and must be differentiated from extensions from the more common intrauterine gestational choriocarcinomas and from choriocarcinomatous components of malignant ovarian germ cell tumors. Symptoms mimic those of a tubal ectopic pregnancy or an ovarian tumor, and the tumor may coexist with an ectopic pregnancy.[141] The gross and microscopic appearance, metastatic pathways, and responsiveness to chemotherapy are similar to those of intrauterine gestational choriocarcinoma.

Metastatic Tumors

Metastatic tumors of the fallopian tube are more frequent than primary tumors and most often represent extensions from ovarian, endometrial, or cervical adenocarcinomas. In one large series, 36% of ovarian and 11% of endometrial carcinomas were associated with tubal "metastases," although many of these may have represented multicentric primary cancers (Fig. 5-28).[142] Bannatyne and Russell have clearly shown in patients with ovarian carcinoma that small foci of primary carcinoma can arise in the tubal mucosa and even in the tubal serosa.[113] The same dilemma applies to bilateral tubal carcinomas.

Extragenital primary cancers with tubal metastases are much rarer and usually are mammary or gastrointestinal. The submucosal lymphatics are invaded by neoplastic cell nests that compress the mucosal plicae and replace the tubal epithelial cells (Fig. 5-29). Neoplastic cells desquamate secondarily into the tubal lumen and are subsequently carried to the peritoneal cavity, the surface of the ovary, and the uterine cavity. Direct implantation of tumor cells in the tubal mucosa or serosa is encountered, but lymphatic spread remains considerably more common. The tumor cells are disposed in cords or irregular masses, and they present the usual criteria of malignancy: nuclear hyperchromatism, anisonucleosis, and pathologic mitoses.

In situ squamous carcinoma of the endometrium and endosalpinx has been reported as an extension of invasive squamous carcinoma of the cervix.[143]

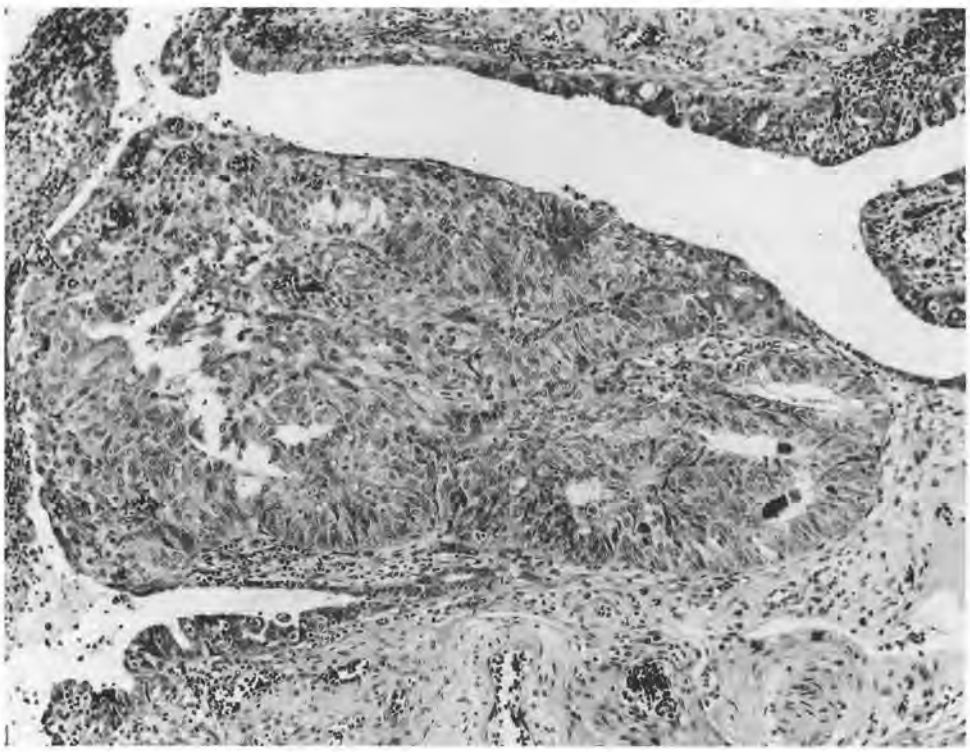

FIGURE 5-28 Endometrioid carcinoma of the fallopian tube in a patient with carcinosarcoma of the endometrium. It is uncertain whether this is a metastasis (the tumor grows predominantly beneath the mucosal surface) or an incidental separate primary tumor (note the mucosal atypical hyperplasia [*top*].)

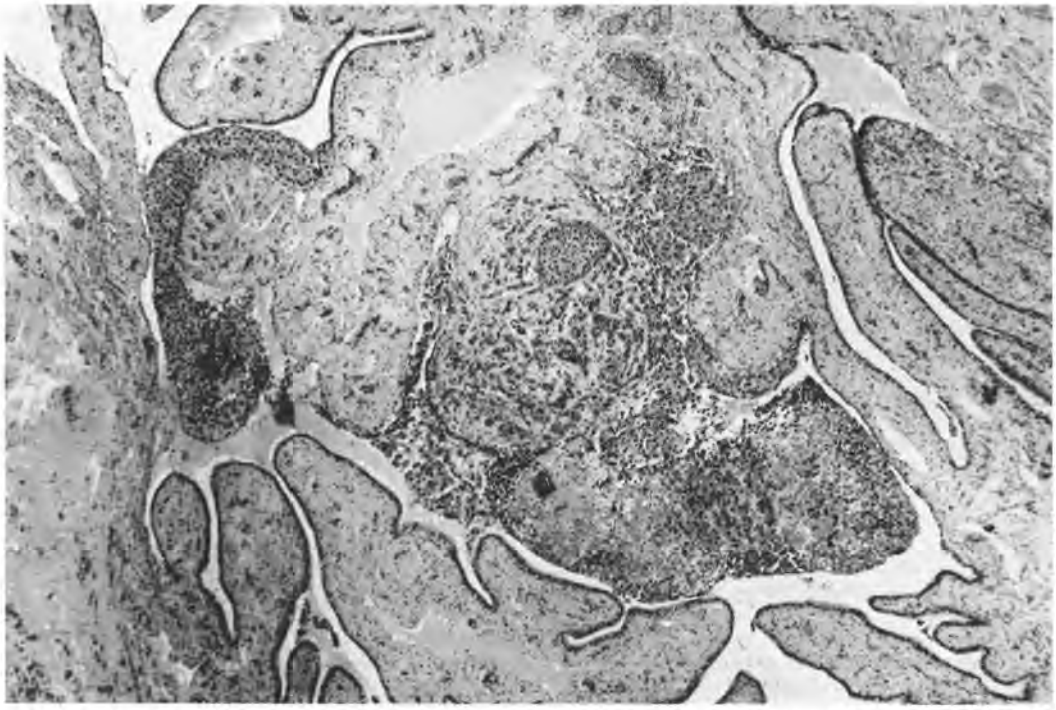

FIGURE 5-29 Tubal metastasis from adenocarcinoma of the breast. There is submucosal and lymphatic invasion and partial replacement of mucosa (*left*) by tumor cells.

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6 The Ovary

Charles Zaloudek

EMBRYOLOGY

The embryonic development of the ovary begins in an undifferentiated stage that is similar for the male and female genitalia. The undifferentiated gonad consists of an accumulation of mesenchymal cells covered by coelomic (germinal) epithelium. It forms an elongated bulge on the ventral surface of the mesonephros. Early in embryonic life, around the 32nd day, the primordial germ cells migrate from the yolk sac entoderm into the mesenchyme of the genital crest, passing through the root of the mesentery (Fig. 6-1). The primitive gonad begins to differentiate along ovarian lines in the seventh week. According to the most accepted embryologic theory, the migration of the primordial germ cells is accompanied by the growth of groups of cells (sex cords) from the germinal epithelium into the underlying mesenchyme (Fig. 6-2). Some of the epithelial cells invest the germ cells and differentiate into granulosa cells. The rest degenerate, except for remnants in the ovarian medulla (the rete ovarii). There may be limited downgrowth of epithelial cells from the germinal epithelium throughout embryonic life. An alternative embryologic view is that the coelomic epithelium does not contribute to the formation of the sex cords. Instead, the primordial germ cells, after migrating into the gonadal mesenchyme, play the role of organizer and induce the differentiation of the granulosa cells. This theory holds that the entire ovary, except for the germinal epithelium, is of mesenchymal origin.

Whatever their derivation, the granulosa cells become organized around the oocytes during the third trimester to form the follicles. The perifollicular stroma is derived from the gonadal mesenchyme. It is disposed around the follicles in concentric layers and constitutes the richly vascularized theca interna and the fibrous theca externa. The theca appears to represent a transformation of stromal cells that is induced by adjacent granulosa cells.

ANATOMY

The ovary has an ovoid shape and a bosselated surface. It is firm and pink or tan. During the period of gonadal activity, the ovary weighs 5 to 8 g. It increases in volume at the time of ovulation and during pregnancy. The presence of follicles of different sizes occasionally conveys a false impression that cysts are present. A diminution in size begins around age 30. The ovary atrophies after menopause and becomes small, firm, and pearly gray-white.

The ovary is situated in the retrouterine space behind and above the fallopian tube, behind the broad ligament, and in front of the rectum. It is fixed to the broad ligament at its anterior border and to the fibrous connective tissue of the mesovarium. It is attached to the uterine cornu by the utero-ovarian ligament, to the tube by the tubo-ovarian ligament, and to the lateral pelvic wall by the infundibulopelvic ligament.

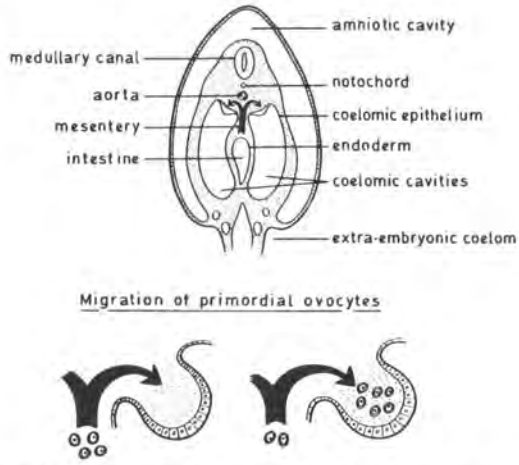


FIGURE 6-1 Migration of primordial oocytes from the roof of the mesentery to the genital crest.

The ovarian artery, a branch of the abdominal aorta, runs along the anterior border of the ovary and anastomoses with the ovarian branch of the uterine artery. About 10 arterial branches arise from this arcade and penetrate the ovary. The veins meet at the hilus, where they form a rich plexus that drains into the right and left utero-ovarian veins. The lymphatics follow the course of the veins and drain into the lumbar nodes. Nerves arise from the lumboaortic and renal plexi and enter the ovary from the ovarian plexus.

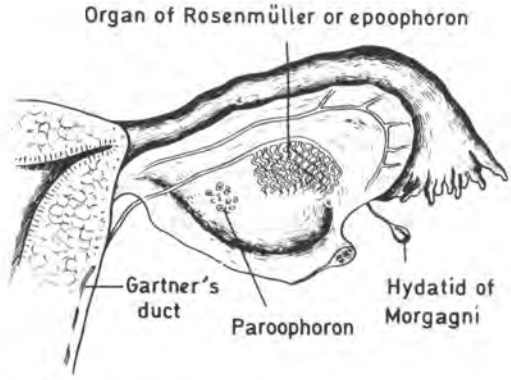


FIGURE 6-3 Parovarian organs.

Several parovarian structures are important to the pathologist (Fig. 6-3). The *epoöphoron* is a mesonephric remnant composed of a series of parallel tubules opening into a duct that courses along the fallopian tube in the mesovarium. The epoöphoron is lined by a simple cylindrical epithelium and is surrounded by a connective tissue network containing smooth muscle fibers. The *paroöphoron,* situated in the broad ligament adjacent to the epoöphoron, is most prominent in the fetus or infant and is composed of a few tubules that are histologically similar to the epoöphoron. In contrast to the two previous structures, the *hydatid of Morgagni* is of müllerian origin. It is a small, smooth-walled cyst attached to the tubal fimbria. Its epithelium resembles that of the

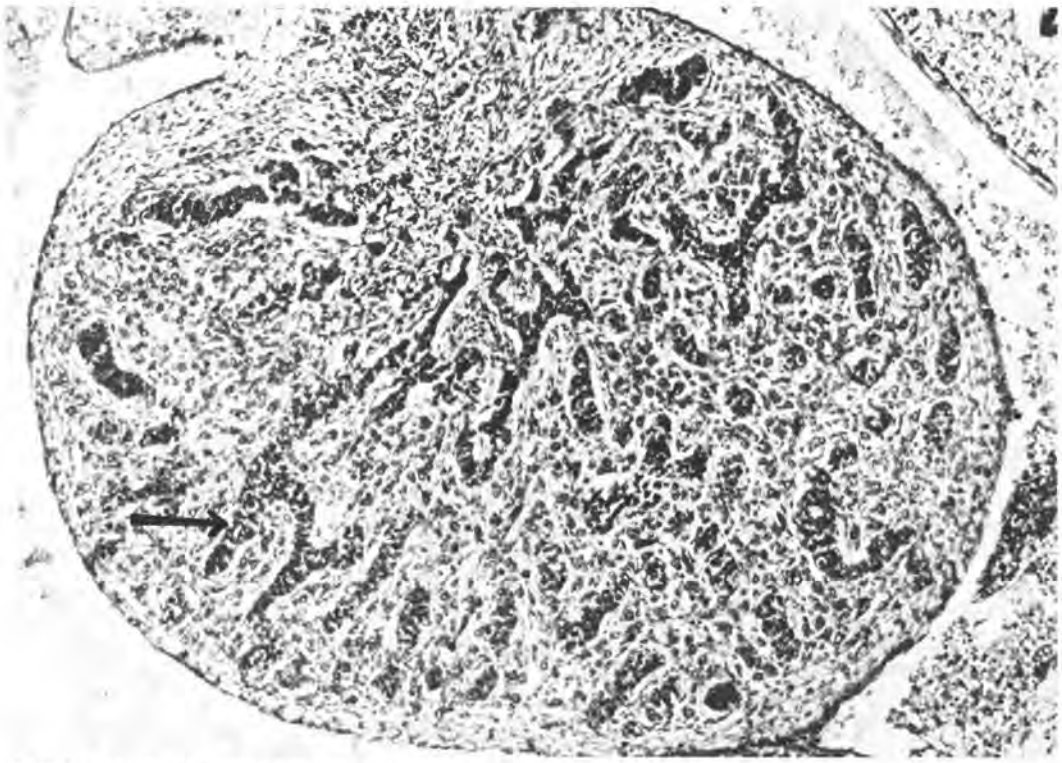


FIGURE 6-2 Fetal ovary showing sex cords.

fallopian tube and responds to hormonal stimuli in a similar manner. It may become greatly distended with clear fluid.

HISTOLOGY

The ovary consists of a stromal mass containing the follicles, vessels, and nerves. The coelomic surface epithelium is conspicuous in the infant but often is flattened and difficult to identify in the postmenopausal ovary (Fig. 6-4).

The external, or cortical, zone is composed of a stroma of fusiform connective tissue cells between which are bundles of collagen fibers. The cortex contains follicles in different stages of maturation. These follicles are numerous in infants and young adults, but their number decreases progressively with age and they disappear by menopause. The primordial follicle consists of an oocyte surrounded by a layer of cuboidal granulosa cells (Fig. 6-5). In the course of follicular maturation, the granulosa cells multiply and the granulosa cell layer becomes thickened (Fig. 6-6). It consists of round cells with regular, dark nuclei that are compressed one against the other. The oocyte becomes localized at one pole, where the granulosa proliferates to form the cumulus oophorus. When the follicle becomes mature, small spaces called *Call-Exner bodies* appear among the granulosa cells (Fig. 6-7). At the same time, a central cavity containing estrogen-rich follicular fluid develops. The stromal cells surrounding the follicle differentiate into the theca interna (Fig. 6-8). These cells sometimes assume an epithelioid appearance. They contain lipid granules when the follicle is mature, and they are surrounded by numerous capillaries that insinuate themselves between the cell cords. Mature follicles are known as *graafian follicles.*

At ovulation, the mature follicle opens at the surface of the ovary and releases its oocyte. When the oocyte leaves the follicle, the opening through which it is extruded is closed by a fibrin plug, producing the follicular stigma. The empty follicle forms a festooned vesicle, which is the beginning of the corpus luteum. After the oocyte is expelled, the granulosa becomes vascularized by capillaries from the theca interna. This vascularization may give rise to hemorrhage, which collects in the lumen of the developing corpus luteum. As the corpus luteum develops, the granulosa cells become luteinized. They have abundant pale eosinophilic cytoplasm that contains small lipid droplets (Fig. 6-9*A*).

Ultrastructurally, the luteinized granulosa cells have abundant smooth and rough endoplasmic reticulum arranged in whorls or in parallel arrays (Fig. 6-9*B*). Mitochondria are numerous and have tubular cristae. The Golgi complex is well developed and there are numerous lipid droplets. The theca cells are enlarged and luteinized, but they are smaller than luteinized granulosa cells (Fig. 6-10). The luteinized theca cells often have an epithelioid appearance and may be referred to as *theca lutein cells.*

The mature corpus luteum forms a mass of up to 1.5 cm in diameter. It appears macroscopically as a large yellow structure with a central fibrous or cystic focus (Fig. 6-11). If pregnancy does not occur, the corpus luteum involutes, with degeneration of the luteinized cells and fibrosis, ultimately resulting in a convoluted, hyalinized scar known as a *corpus albicans.*

If pregnancy occurs, a corpus luteum of preg-

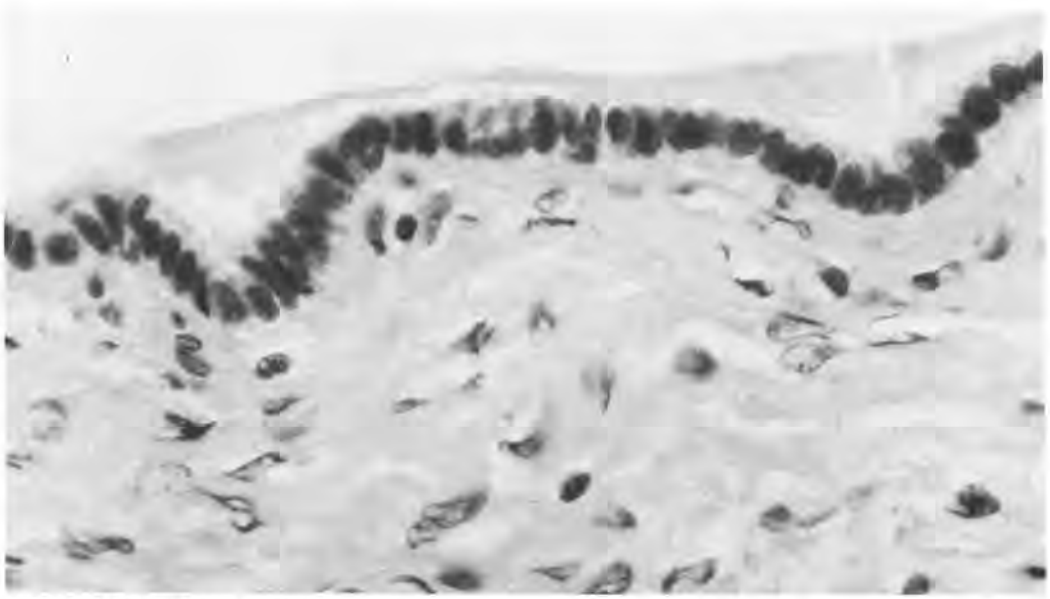


FIGURE 6-4 Surface epithelium of the ovary.

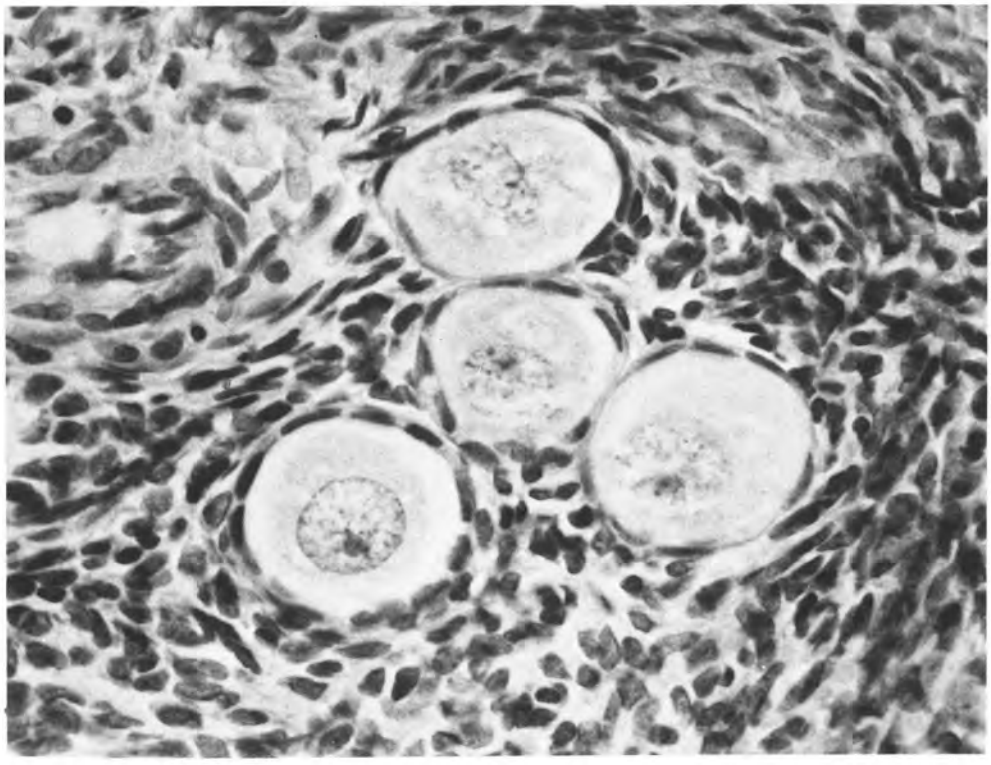


FIGURE 6-5 Primordial follicles. Oocytes are surrounded by a single layer of granulosa cells.

nancy evolves. It occupies almost half the ovary and is golden-yellow with a fibrinohemorrhagic or cystic center. The luteinized cells contain eosinophilic hyaline inclusions and lipid droplets. Regression of the corpus luteum begins after the third month of pregnancy. At the eighth month, the corpus luteum of pregnancy is only 1 or 2 cm in diameter and it subsequently undergoes total regression and fibrosis. Clusters of decidual cells are frequently present in the subcoelomic stroma in pregnant women. These

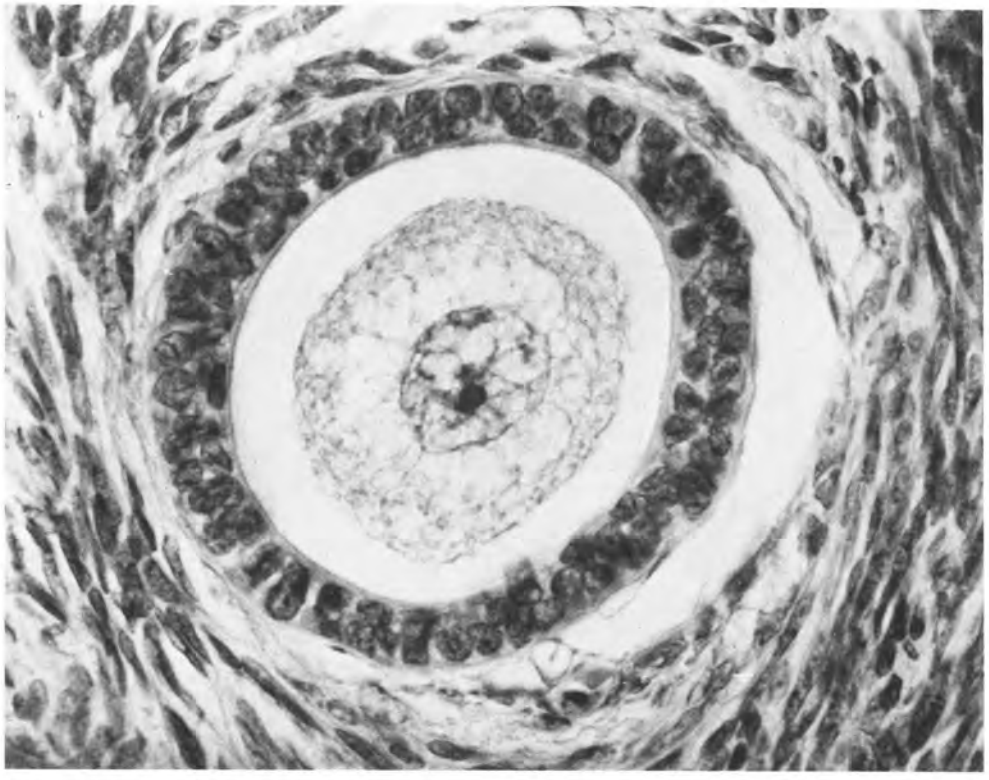


FIGURE 6-6 Oocyte surrounded by several layers of granulosa cells in primary follicle.

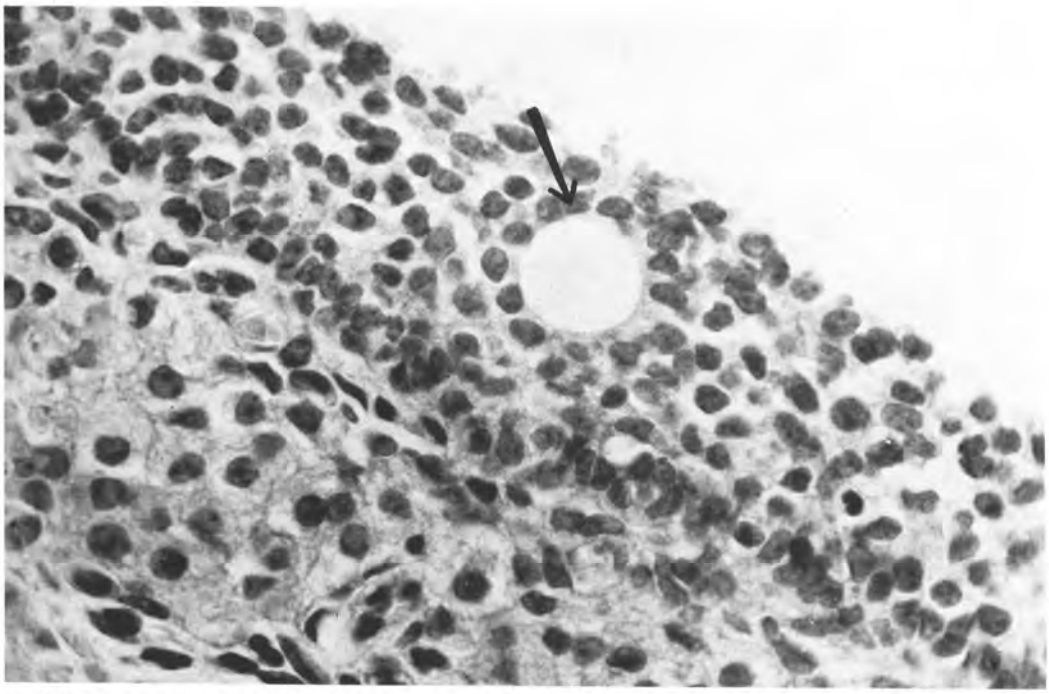


FIGURE 6-7 Graafian follicle with a Call-Exner body (*arrow*).

decidualized stromal cells have regular round nuclei and abundant eosinophilic cytoplasm.

Most of the 400,000 follicles present at birth degenerate rather than mature. Death of the ovum precedes degeneration of the follicle, which is manifested by nuclear or cytoplasmic vacuolization, condensation of the chromatin, and thickening and hyalinization of the follicular basement membrane. The resulting structure is called an *atretic follicle.* The wall of the atretic follicle consists of granulosa cells or, when these have disappeared, of theca interna cells. As degeneration of the follicle continues, it becomes fibrotic, and the structure finally remaining is the corpus atreticum, composed of hyalinized connective tissue.

(*Text continued on page 320.*)

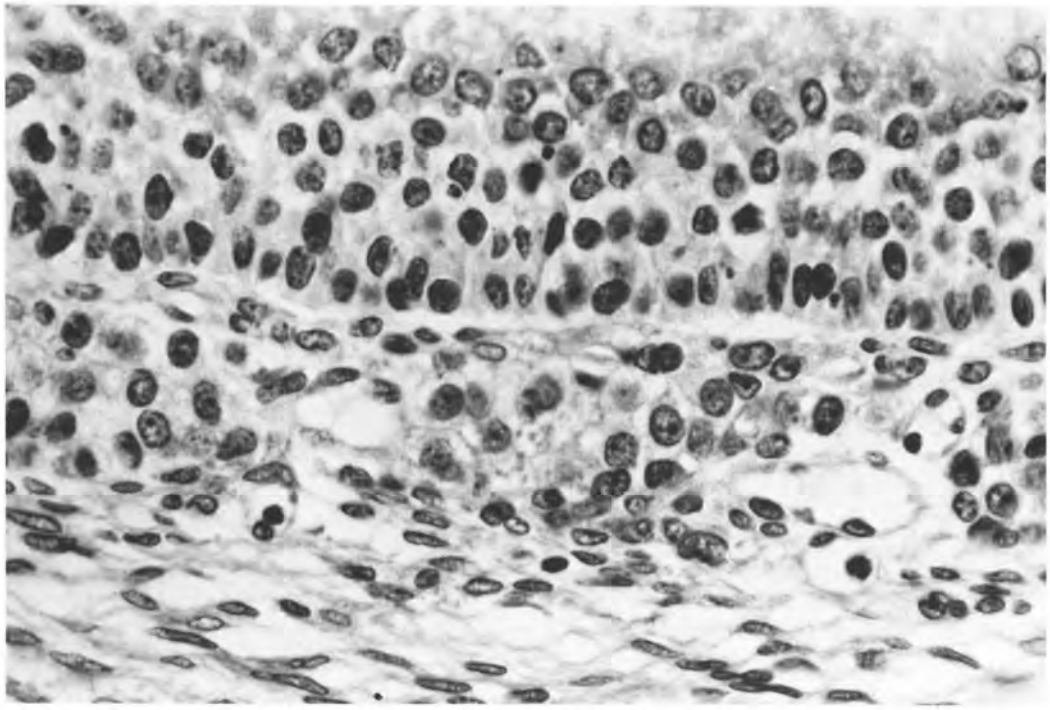


FIGURE 6-8 Graafian follicle: granulosa and theca interna and externa.

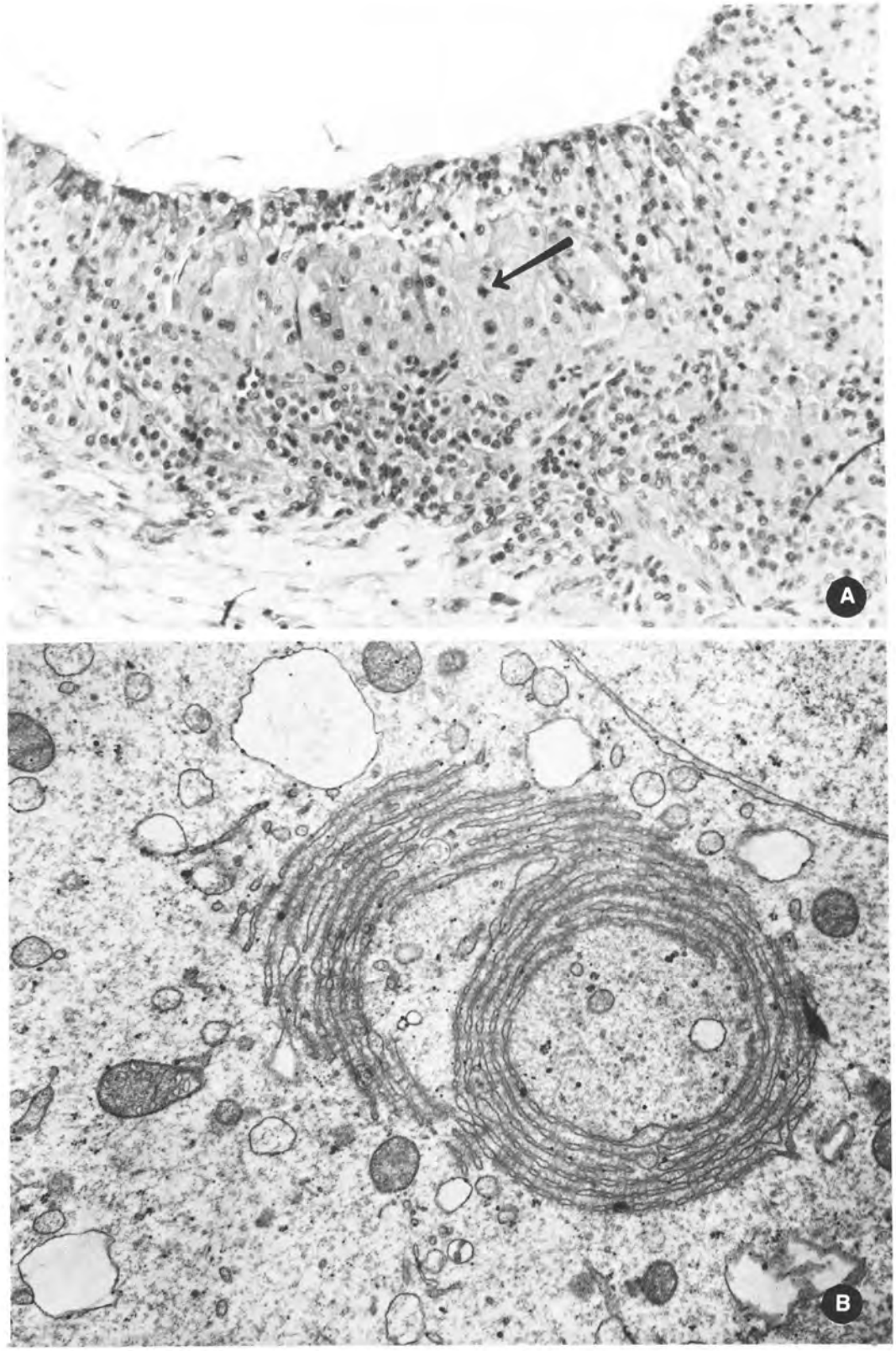


FIGURE 6-9 **(A)** Luteinized granulosa cells (*arrow*). **(B)** Whorled arrangement of annulate lamellae in luteinized granulosa cells (**B**×17,500).

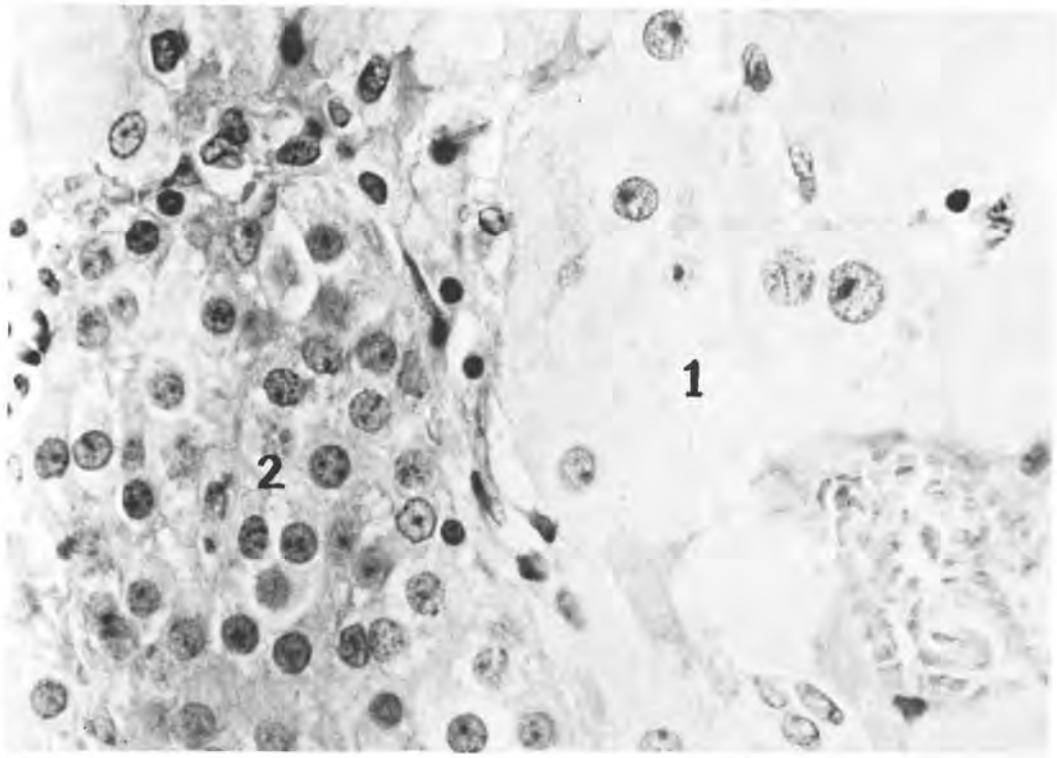


FIGURE 6-10 Wall of corpus luteum: luteinized granulosa cells (*1*) and theca cells (*2*).

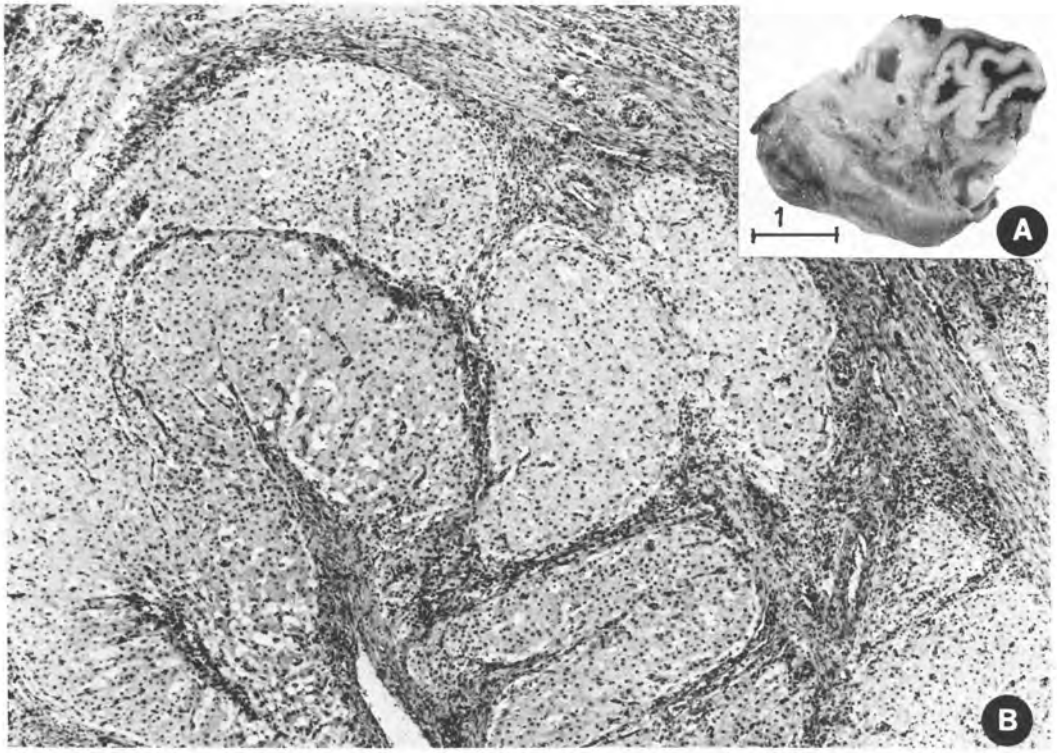


FIGURE 6-11 Mature corpus luteum. **(A)** Macroscopic appearance. **(B)** Microscopic appearance.

The medulla of the ovary is composed of stromal cells, blood vessels, lymphatics, and nerves. The hilum contains hilus cells and embryonic residua. Hilus cells are found adjacent to nonmyelinated nerves in the hilum in more than 80% of ovaries. They are round or oval cells with granular eosinophilic cytoplasm and a central round nucleus. The cytoplasm contains small brown lipochrome granules, small eosinophilic hyaline spheres, and crystals of Reinke (Fig. 6-12). The latter are eosinophilic proteinaceous rods 10 to 30 μm in length. Electron microscopy reveals that Reinke crystals have a hexagonal internal pattern.[1] Elementary tubular inclusions may be precursors of the crystals; they correspond to the eosinophilic, hyaline bodies observed by light microscopy. In addition to the crystals, the cytoplasm contains prominent smooth endoplasmic reticulum and mitochondria with tubular cristae.

The *rete ovarii,* which is the ovarian homologue of the rete testis, is an embryonic remnant with no known function. It is found in the hilum of the ovary and consists of slit-like tubules lined by cuboidal epithelial cells (Fig. 6-13). The rete tubules are surrounded by spindle-shaped stromal cells. Cysts of the rete ovarii are an occasional cause of ovarian enlargement.[2]

MALFORMATIONS AND ATROPHY

The *congenital absence* of one or both ovaries is rare. The chromosomal pattern in such cases is of female type, and the secondary sexual characteristics are typically female as well. The absence of one ovary is usually clinically inapparent because the single ovary present is capable of adequately performing the functions of both. *Ovarian agenesis* differs from the congenital absence of both ovaries in that the gonads are present but rudimentary, and there are various associated somatic malformations such as pyloric stenosis, coarctation of the aorta, cataracts, and osteoporosis.

Ovarian atrophy may be seen during the reproductive years as a morphologic manifestation of the clinical syndrome of ovarian failure. Some cases are associated with antiovarian antibodies[3–7] and may be accompanied by diabetes mellitus, hypothyroidism, adrenal cortical hypofunction, or several of these conditions, all apparently on the basis of autoimmune disease. The etiology of other cases of ovarian failure (eg, primary amenorrhea, secondary amenorrhea, or premature menopause) is unknown. The triad of endogenous hypergonadotropinemia, hyporeceptivity of the ovaries to stimulation with exogenous gonadotropins, and a histologic picture showing noncystic, unstimulated follicles has been called the *gonadotropin-resistant ovary syndrome.*[8] Hypogonadotropic ovarian failure is caused by an abnormality of the pituitary or hypothalamus that prevents normal production of gonadotropins. The ovary contains many primordial follicles, but developing follicles are not present. As many as 30% to 40% of patients with primary ovarian failure have abnormal sex chromosomes, dysgenetic gonads, or both. Finally, iatrogenic factors such as radiation therapy, chemotherapy, or surgery affecting the ovarian blood vessels can result in ovarian atrophy.

Supernumerary ovaries arise as a result of reduplication of the primitive gonadal precursors.[9–13] They are extremely rare. *Accessory ovaries* are a more frequent finding, consisting of islands of ovarian tissue attached or adjacent to the normal ovary.[14,15] So-called ectopic ovarian tissue is a characteristic of the *ovarian remnant syndrome,* in which ovarian tissue is unintentionally left in the pelvis during a technically difficult oophorectomy.[16–19] Cysts or neoplasms may develop in aberrant ovarian parenchyma, whatever its origin.

INFLAMMATORY DISEASES

Inflammatory diseases of the ovary are much rarer than salpingitis, and in most cases they are part of the clinicopathologic picture of pelvic inflammatory disease. The etiologic agents are the same as those commonly encountered in salpingitis. More rarely, ovarian infections result from the hematogenous dissemination of organisms from a distant site.

Acute Oophoritis

Acute oophoritis occasionally accompanies acute salpingitis. When the ovary is involved by an inflammatory process, it is enlarged and hyperemic, and the inflammatory exudate is accompanied by adhesions among the ovary, the tube, and the adjacent peritoneum. Occasionally, an abscess develops, although abscesses confined to the ovary are considerably rarer than tubo-ovarian abscesses.[20,21] Most ovarian abscesses develop following a surgical procedure or an abortion. An abscess consists of polymorphonuclear leukocytes, lymphocytes, plasma cells, histiocytes, and necrotic cellular debris within a richly vascularized and congested connective tissue framework. Although an abscess may rupture into the pelvis and cause peritonitis, it usually undergoes resorption and fibrosis.

Chronic Oophoritis

In chronic oophoritis, the ovary is small and fibrotic and usually adheres to adjacent tissues. Sterility is a common clinical complication. Macroscopically, the ovary is often involved in a mass of adhesions, which

may form a fibrotic bloc that involves the tube. *Tuberculosis* of the ovary is characterized by the presence of epithelioid granulomas with giant cells in the ovarian parenchyma (Fig. 6-14). Tuberculous oophoritis is part of the spectrum of adnexal tuberculosis, but the ovary is less frequently involved than the tube or the endometrium. Ovarian *actinomycosis* presents as a gray abscess containing purulent granular tissue surrounded by a fibrous wall.[22] Microscopic examination reveals a granuloma, the center of which is occupied by mycelial filaments and the periphery by epithelioid cells, a few giant cells, plasma cells, and lymphocytes. The tube is often involved. The infection is generally secondary to uterine acti-

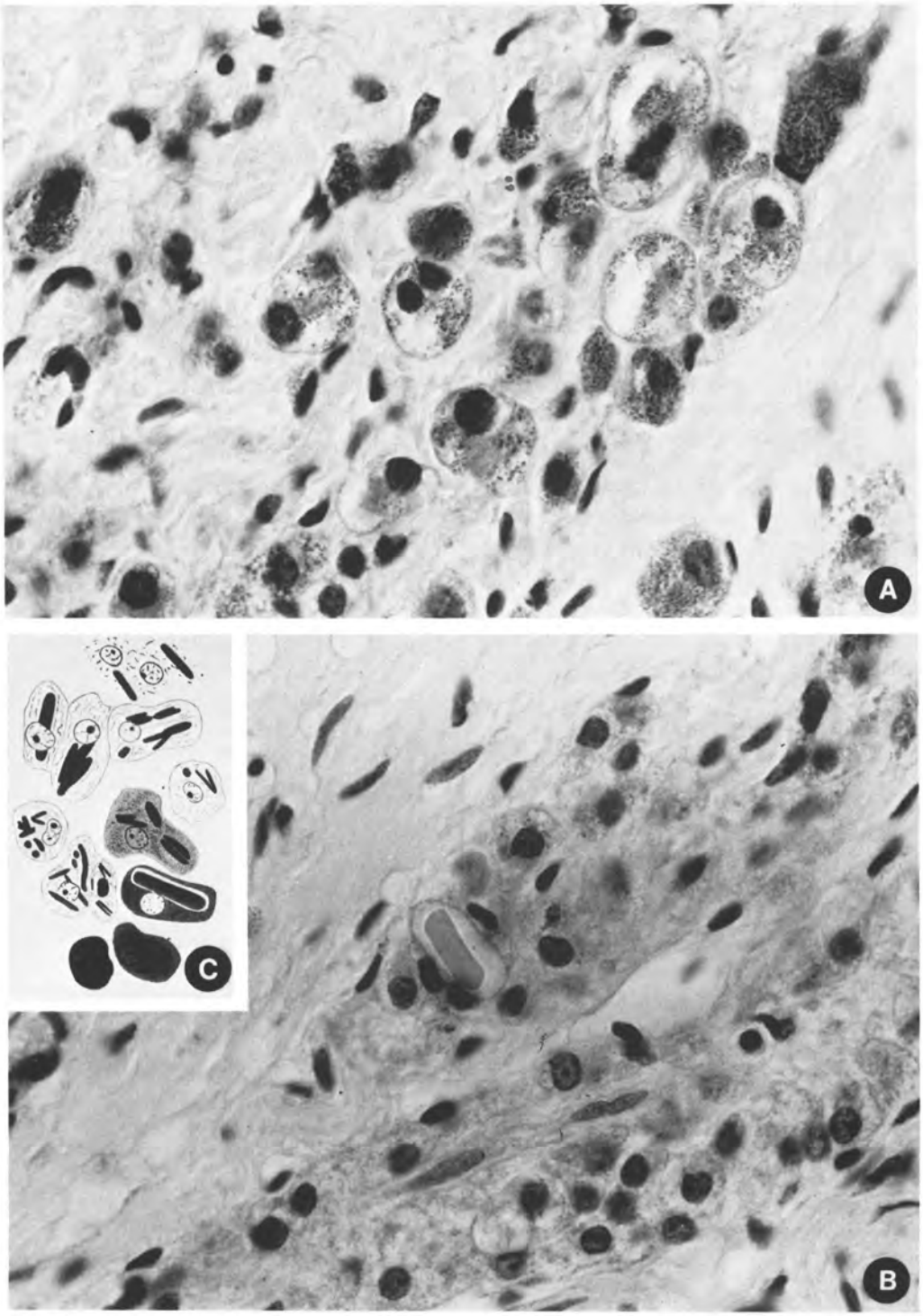


FIGURE 6-12 Ovarian hilar cells. **(A,B)** Two different views of the same cells show detail of cells and Reinke crystals. **(C)** Detail of original plate published by Reinke.

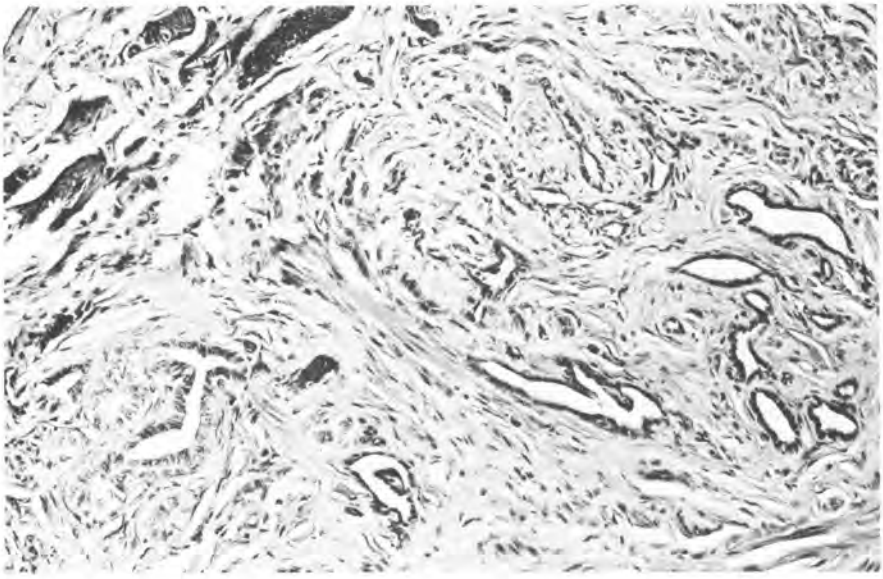


FIGURE 6-13 The rete ovarii is composed of tubules that are lined by cuboidal cells and surrounded by stromal cells.

nomycosis, which occurs after abortive procedures or in patients with an intrauterine device (IUD). *Luetic* oophoritis, or ovarian gumma, is extremely rare. Ovarian *schistosomiasis* is encountered in those parts of the world where this infection is endemic.[23,24] The schistosome ova are found within the epithelioid granulomata. Ovarian *xanthogranulomatous* reactions are rare and their etiology is unknown.[25]

NONNEOPLASTIC CYSTS AND TUMORS

Germinal Inclusion Cyst

Invaginations of the surface epithelium may be incorporated into the cortex of the ovary. Such inclusions are most numerous in conditions that cause an

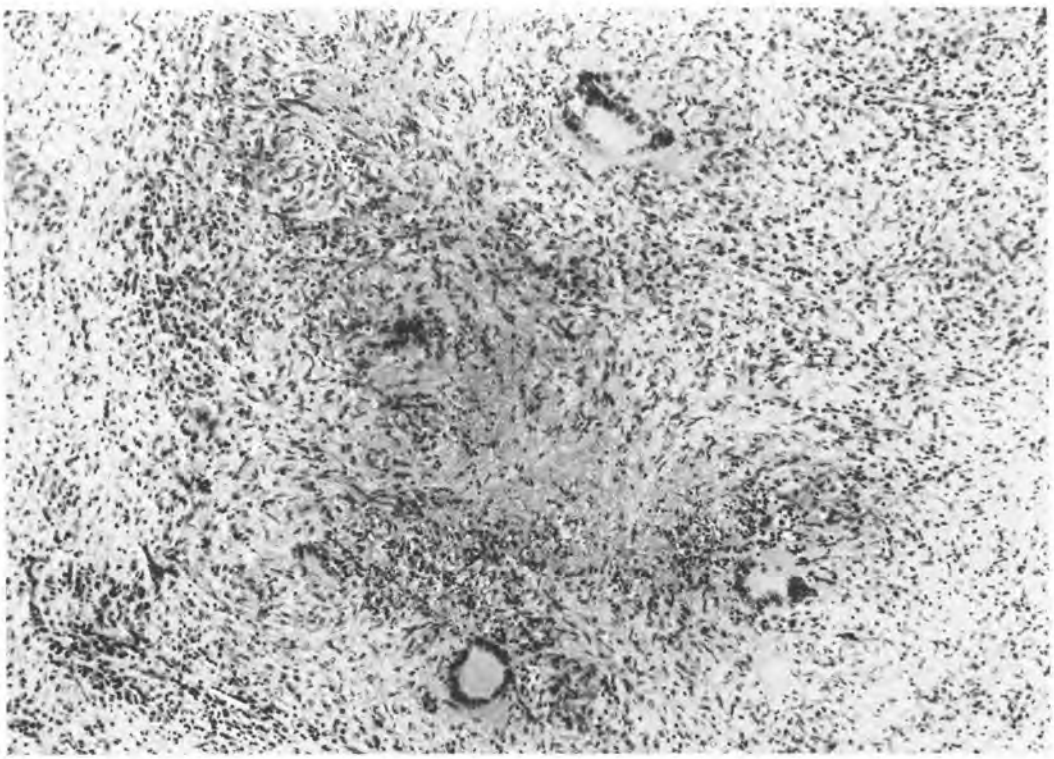


FIGURE 6-14 Ovarian tuberculosis: necrotizing granuloma with giant cells.

inflammatory or fibrotic reaction in the ovary, such as pelvic inflammatory disease or endometriosis. When epithelial inclusions lose their connection with the surface and fluid accumulates within them, a germinal inclusion cyst is formed (Fig. 6-15). Germinal inclusion cysts are common, generally small and multiple, and usually have no clinical significance. Degenerative changes, such as atrophy of the epithelial lining secondary to intracystic fluid pressure and calcification with psammoma body formation, are often seen. Tubal metaplasia of the epithelial lining is frequent. Other types of metaplasia occur, including transitional and squamous metaplasia. *Epidermoid cysts* are lined by stratified squamous epithelium. In contrast to the dermoid cyst, or benign cystic teratoma, no skin appendages are present. Some consider epidermoid cysts to be of teratomatous origin, but such cysts may arise by squamous metaplasia in germinal inclusions.[26,27]

Follicular Cyst

The most common type of ovarian cyst is the follicular cyst. These cysts develop in the ovarian cortex and may be seen beneath the surface of the ovary as translucent nodules. Clinically significant follicular cysts range from 3 to 10 cm in diameter. They have a smooth white lining and contain clear yellow or hemorrhagic fluid. Most follicular cysts develop in adults, but they also occur in neonatal and premenarchal children, in whom they account for 30% to 50% of cases of ovarian enlargement. Microscopically, the lining of a follicular cyst is composed of granulosa and theca cells separated by a basal lamina, as in a normal follicle. The granulosa cells may be proliferative and exhibit mitotic figures. Cytologic evaluation of the cyst fluid may be confusing when the lining exhibits marked proliferative activity.[28,29] The cyst lining may atrophy or even disappear due to the pressure exerted by the intracystic fluid. When the lining is atrophied or reduced to a single cell layer, the follicular origin of the cyst is difficult to prove, and the lesion should be classified as a simple cyst. Follicular cysts in which the granulosa cells are luteinized are called *granulosa lutein cysts. Theca lutein cysts* exhibit luteinization predominantly in the theca cell layer of the follicle. Multiple theca lutein cysts are discussed below. Exceptionally large follicular cysts are occasionally discovered during pregnancy or in the puerperium.[30] Such cysts are hormonally inactive. They are distinctive because of their size and because the cells lining them are atypical and luteinized, without clear distinction between the granulosa and theca cell layers.

Hyperreactio Luteinalis (Multiple Bilateral Theca Lutein Cysts)

Massive bilateral ovarian enlargement secondary to multiple theca lutein cysts usually is observed in women with gestational trophoblastic disease; it develops in about 25% of such patients.[31] It occurs in other conditions associated with an increased level of human chorionic gonadotropin, such as fetal hydrops and multiple gestations, and it is rarely seen in singleton gestations.[32] The *ovarian hyperstimulation syndrome,* which occurs in women undergoing ovulation induction for infertility, has similar ovarian pathology.[33]

The ovarian enlargement is usually asymptomatic. Hemorrhage into the cysts may cause pain, and torsion or rupture causes acute abdominal symp-

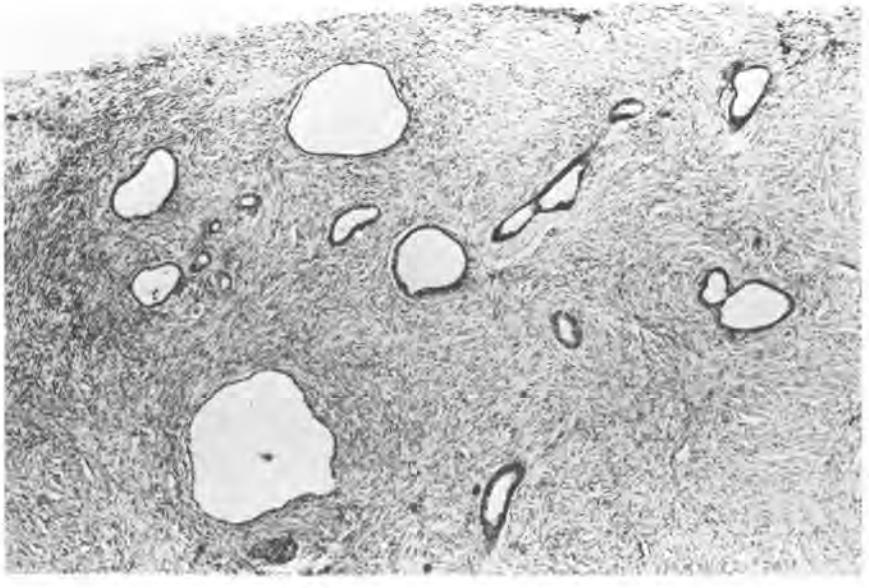


FIGURE 6-15 Multiple epithelial inclusions in cortical stroma.

toms. Signs of virilization are observed in about 25% of cases not associated with gestational trophoblastic disease. The ovaries are large, edematous, and congested (Color Figure 6-1). They contain numerous cysts measuring up to 3 to 4 cm in diameter. A corpus luteum is identified in some cases. Microscopically, the theca cell layer of the cysts is luteinized (Fig. 6-16). The granulosa cell layer shows a variable degree of luteinization, and the stroma is edematous. The ovarian cysts regress after delivery, so treatment is conservative once the diagnosis is established. Accurate diagnosis of hyperreactio luteinalis, particularly in those cases not associated with trophoblastic disease, is important if excessive surgery is to be avoided.[32]

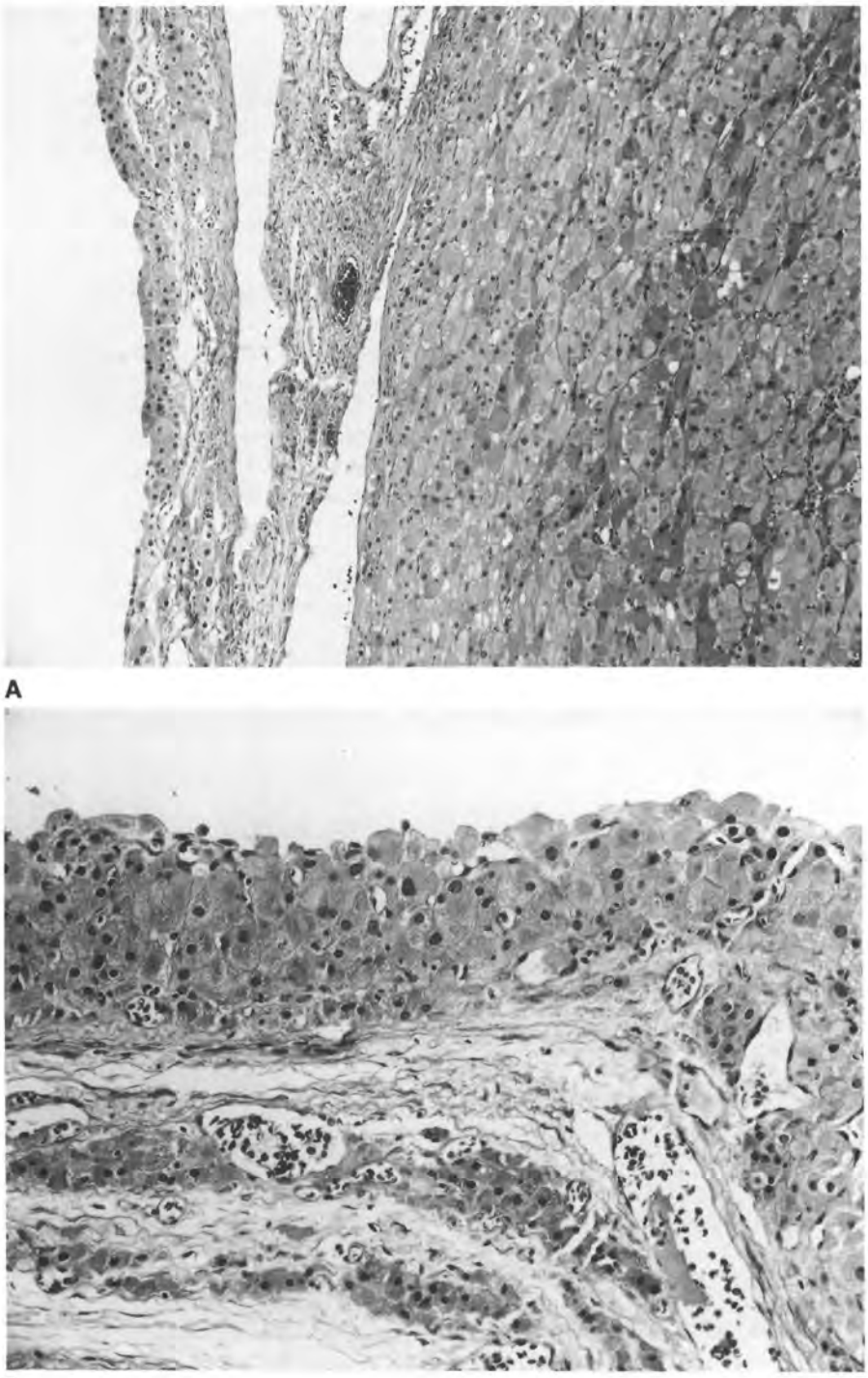


FIGURE 6-16 Hyperreactio luteinalis. **(A)** Low-magnification view showing thin-walled cyst and solid nodule. **(B)** Detail of cyst wall showing luteinization of lining and wall of follicle.

FIGURE 6-17 Hemorrhagic corpus luteum cyst.

Cysts of the Corpus Luteum

A *cystic corpus luteum* is the result of the accumulation of fluid and fibrin in the center of a corpus luteum. The central cavity may be large enough to be interpreted as a true cyst. The lining exhibits the typical microscopic features of a corpus luteum.

A *corpus luteum cyst* is formed when there is hemorrhage into the center of a corpus luteum. Early on, the cyst contains an organizing hematoma (Fig. 6-17). The lumen is surrounded by fibrin and luteinized granulosa and theca cells (Fig. 6-18). Over time, the blood is resorbed and the cyst fluid becomes clear or yellow. The cyst wall is then composed of fibrous tissue and involuting luteinized cells. If a central cavity remains after a corpus luteum cyst involutes and becomes fibrotic, it is designated as a *corpus albicans cyst.*

Cysts derived from the corpus luteum are usually asymptomatic. Occasionally, such cysts must be excised because they rupture and cause peritoneal hemorrhage.

Luteoma of Pregnancy

The luteoma of pregnancy is not a true neoplasm; it is a nodular hyperplastic reaction that becomes apparent during the last trimester of pregnancy and regresses spontaneously after delivery.[31,34,35] Its development depends on human chorionic gonadotropin. The paucity of cases reported in the literature is probably not representative of the true incidence of this lesion.

Clinical Findings

Luteoma occurs in pregnant women 19 to 41 years of age. Most patients have had more than one previous pregnancy, and the average age is 27 to 28 years. Most patients are black. Maternal virilization develops in the third trimester in 30% of women with luteoma of pregnancy.[34] Androgen levels, when measured in such patients, are elevated. Sixty-five percent of the female infants born to virilized mothers are masculinized.[34] Male infants are unaffected. Most luteomas are nonpalpable and are discovered unexpectedly during the course of a cesarean section or tubal ligation.

Macroscopic Appearance

Luteoma of pregnancy produces unilateral (two thirds of cases) or bilateral nodular ovarian enlargement. On cross section, one or more soft nodules are noted within the cortex or medulla of the ovary (Fig. 6-19*A*). The nodules are solid and measure 1 to 20 cm in diameter; most measure 6 to 10 cm. They are gray, tan, brown, or yellow and may contain small areas of hemorrhage or necrosis.

Microscopic Appearance

The luteoma of pregnancy is composed of sheets and nests of uniform polyhedral cells with granular eosinophilic cytoplasm and central small round vesicular nuclei (see Fig. 6-19*B*). There is minimal nuclear atypia, but mitotic figures (1 to 2 per 10 high-power fields) are readily identified. The luteoma of preg-

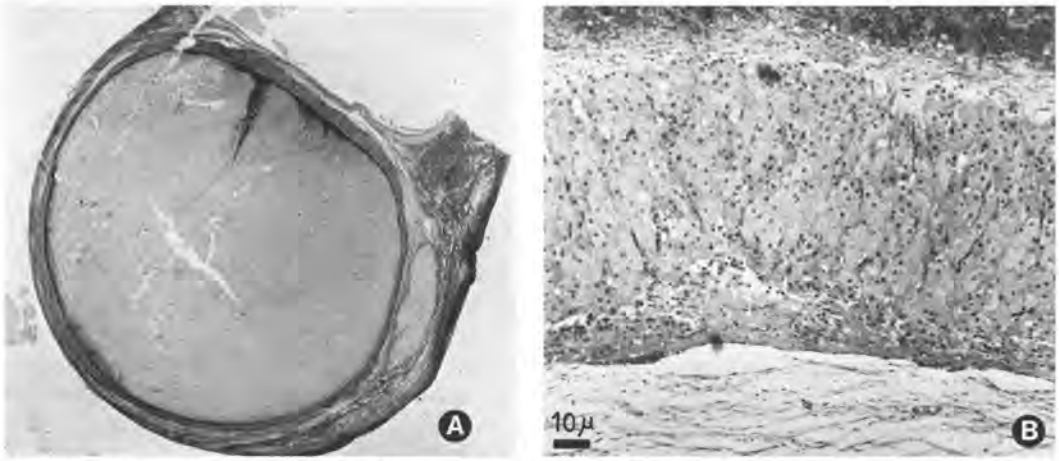


FIGURE 6-18 Corpus luteum cyst. **(A)** General appearance. **(B)** Microscopic appearance of the wall.

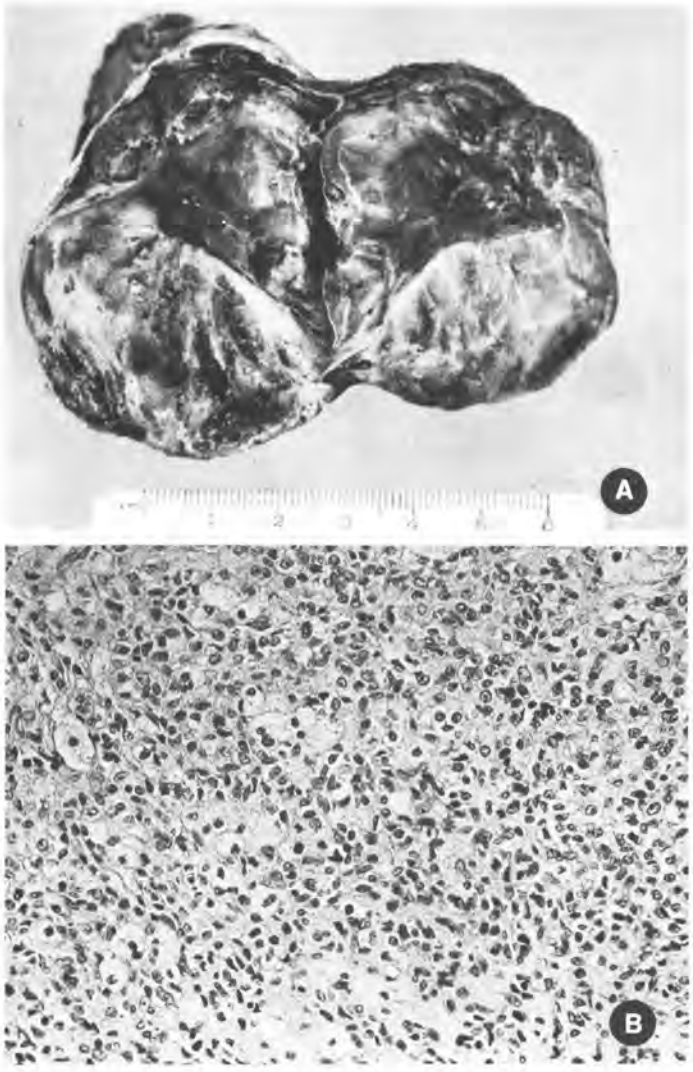


FIGURE 6-19 Luteoma of pregnancy. **(A)** Macroscopic appearance. **(B)** Microscopic appearance. (**A** courtesy of the late Dr. J. Holyoke, St. Joseph Hospital, Denver, CO).

nancy may be formed by nodular proliferation of luteinized stromal cells or by nodular hyperplastic proliferation of luteinized theca cells in cystic and atretic follicles.

Differential Diagnosis

The main differential diagnostic consideration is a Leydig cell tumor of hilar or non-hilar type.[36–38] The clinical setting and the presence of multiple and often bilateral nodules points to the correct diagnosis. Leydig cell tumors are unilateral and unifocal. Intracytoplasmic crystals of Reinke must be identified for the diagnosis of a non-hilar Leydig cell tumor. Hilar Leydig cell tumors are found in a different part of the ovary than the luteoma of pregnancy, which is located in the cortex or medulla. A luteinized thecoma has a fibromatous or thecomatous background stroma, which is not seen in association with a luteoma.[39,40] Hyperreactio luteinalis occurs in a different gestational setting from pregnancy luteoma (as discussed earlier) and is cystic and always bilateral.

Clinical Behavior and Treatment

The development and maintenance of a luteoma of pregnancy depends on the presence of human chorionic gonadotropin. The lesion involutes in the immediate postpartum period, when levels of this hormone drop. Degenerative changes occur as early as 5 days after delivery.[35] Most luteomas reported in the literature have been treated by unilateral salpingo-oophorectomy.[34,35,41] This is excessive treatment, considering the natural history of spontaneous involution. A nodule should be biopsied; if the pathologist is able to make an intraoperative diagnosis of luteoma of pregnancy, further surgery is unnecessary.

Polycystic Ovary Syndrome (Stein-Leventhal Syndrome)

In 1935, Stein and Leventhal described a syndrome consisting of bilateral polycystic ovaries and "menstrual irregularity featuring amenorrhea, a history of

sterility, masculine type hirsutism, and, less consistently, retarded breast development and obesity."[42] The polycystic ovary syndrome accounts for 1% to 3% of female infertility.[43–49] The most popular theories consider the etiology to be disordered steroidogenesis and alterations in hypothalamic-pituitary-ovarian relations. Insulin resistance plays a role in some cases.[50] It is not certain whether the ovarian morphology is primary or secondary to the hormonal disturbances. It is generally agreed that the ovary is the site of increased androgen synthesis and inefficient estrogen synthesis. Hormonal studies show increased levels of androstenedione, testosterone, and other androgens. Levels of luteinizing hormone and pregnanetriol are also increased, and estrogen levels are normal or slightly increased with an increased proportion of estrone. Levels of follicle-stimulating hormone and progesterone are decreased.

Cystic ovaries may be associated with normal or abnormal ovarian function (Fig. 6-20). The Stein-Leventhal syndrome is only part of a larger spectrum of clinical conditions associated with cystic ovaries. There is no constant relation between the appearance of the ovaries and the clinical setting.

Macroscopic Appearance

Both ovaries are enlarged and may even be larger than the uterus. They are oval and have a thick, pearly white tunica. Cysts may be visible beneath the surface, but they often are not. Sectioning reveals a dense white tunica and many small cortical cysts measuring about 1 cm in diameter. Corpora lutea are absent.

Microscopic Appearance

There is marked subcapsular fibrosis. Primordial follicles are present in normal numbers, but primary and small antral follicles are absent or decreased. There is prominent hyperplasia of the cortical and medullary stroma. Cystic follicles with a luteinized theca interna are numerous (Fig. 6-21). Evidence of ovulation, such as a corpus luteum, is absent in classic cases.

Treatment

Treatment depends on whether the goal is to ameliorate hirsutism or induce ovulation.[44,45] Hirsutism is treated by ovarian suppression with oral contraceptives or by administration of corticosteroids. Weight loss may be helpful. Methods of ovulation induction include administration of corticosteroids, clomiphene citrate, bromocriptine, or gonadotropins with or without gonadotropin-releasing hormone agonists. Wedge resection of the ovaries or laparoscopic treatments may be used if medical management is ineffective.

Stromal Hyperplasia and Hyperthecosis

Ovarian stromal hyperplasia and hyperthecosis are found in some women with metabolic or endocrine disorders, such as obesity, hypertension, insulin resistance, and virilization.[51,52] The same ovarian morphology is observed as an incidental finding in women with no clinical abnormalities.[53] Ovaries that exhibit *stromal hyperplasia* are moderately enlarged and nodular. The cut surface is homogeneous and tan or brown, and the corticomedullary junction is ill-defined (Color Figure 6-2). Microscopically, there is hyperplasia of the stromal cells, which often form nodular aggregates (Fig. 6-22). *Hyperthecosis* is characterized by the presence of small clusters of luteinized stromal cells among the hyperplastic stromal cells. These cells have round or ovoid nuclei and abundant eosinophilic cytoplasm (Fig. 6-23). No crystals of Reinke are identified. There is immunoreactivity for enzymes that catalyze 17α-hydroxylation but not aromatization in the luteinized stromal cells of hyperthecosis.[51] No such immunoreactivity is observed in the nonluteinized stromal cells in hyperthecosis or stromal hyperplasia. These observations support the concept that the luteinized stromal cells produce the androstenedione that is found in increased amounts in some women with hyperthecosis. The excess androgen is converted to estrogen in the periphery, increasing the risk of hyperplasia and carcinoma of the endometrium.[51]

Massive Edema

Massive ovarian edema is a rare condition that occurs in young women.[54–57] It is characterized clinically by acute abdominal symptoms and the presence of a solid pelvic mass. The ovary is enlarged, with an average diameter of 11.5 cm, and has a smooth, glistening pink-yellow cut surface (Color Figure 6-3).[57] Microscopically, there is marked diffuse edema and the blood vessels are congested and dilated. Luteinization of the stroma is attributed to edema and can cause virilization. The most likely cause of massive ovarian edema is partial torsion of the mesovarium with vascular compression. *Ovarian fibromatosis* is a related condition in which the ovary is enlarged by a proliferation of small fibroblastic cells.[57] These cells surround normal ovarian structures and are associated with variable collagen deposition and edema.

Endometriosis

Endometriosis is a common condition, estimated to occur in 15% of the female population. The main clinical symptoms are pelvic pain, dysmenorrhea, dyspareunia, and infertility. The ovaries are involved in about 50% of women with endometriosis. Macroscopically, endometriosis of the ovary presents as small white or red plaques on the ovarian surface, as

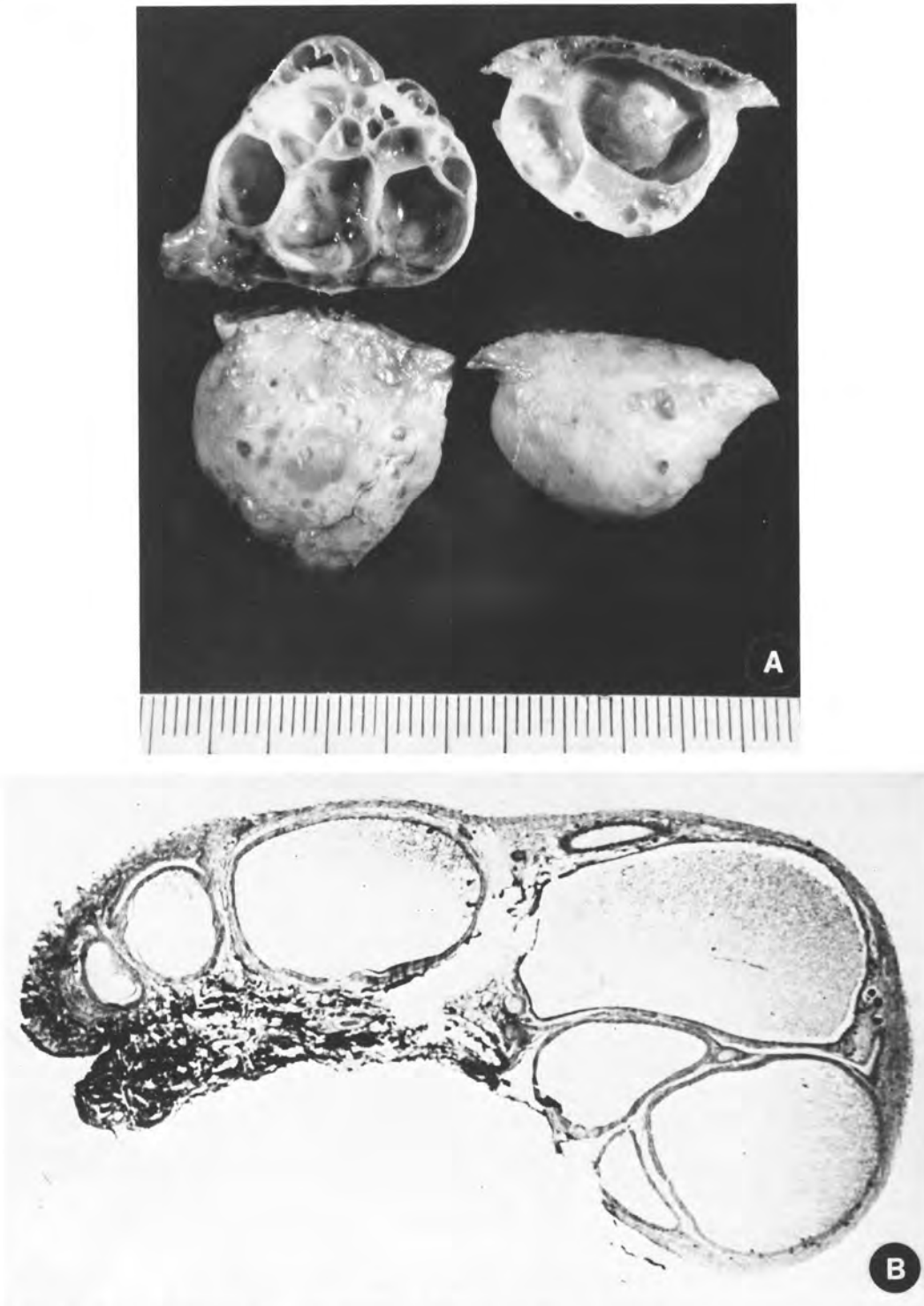


FIGURE 6-20 **(A)** Senile polycystic ovaries. **(B)** Polycystic ovary of newborn infant.

hemorrhagic foci within the ovarian parenchyma, or as cysts. The cysts have a red granular lining and are filled with a red-brown fluid that gives them the name *chocolate cysts* (Color Figure 6-4). The wall is thick, gray-white, and fibrous. Adhesions between the ovaries and adjacent structures, especially the fallopian tubes, are common. Microscopically, endometriosis is characterized by the presence of endometrial glands and stroma within the ovarian parenchyma or serosa. Hemorrhage and hemosiderin or hemofuscin often are present, and fibrosis, histiocytic reaction, and chronic inflammation commonly occur. The morphology may be obscured by degenerative or reparative changes. The lining of endome-

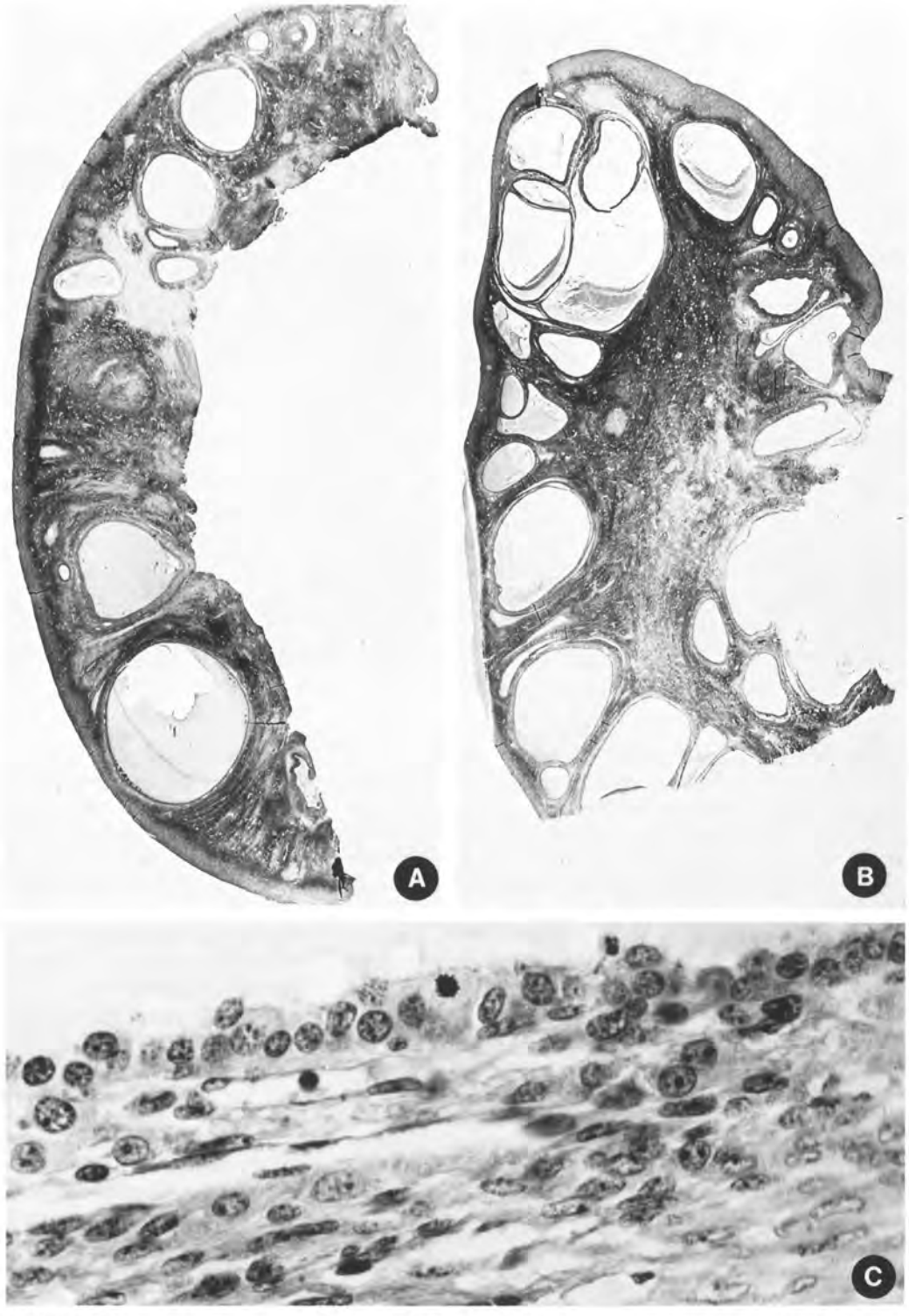


FIGURE 6-21 Polycystic ovary syndrome. **(A,B)** General appearance of polycystic ovaries. **(C)** Wall of a cyst showing mitotic figures in granulosa cells and luteinization of the theca interna.

trioid cysts is often partly or completely denuded and replaced by granulation tissue, fibroblastic proliferation, or histiocytes. Such areas can be designated as "consistent with endometriosis" even though the endometrial glands and stroma have been obliterated, provided that the clinical setting is appropriate. The formation of pseudoxanthomatous nodules with central necrosis is an unusual manifestation of advanced degeneration in endometriosis.[58]

Endometriosis is a frequent finding in the ovaries or pelvis in women with clear cell or endometrioid carcinoma. Less often, a neoplasm arises di-

FIGURE 6-22 Ovarian cortical stromal hyperplasia.

rectly from endometriosis; this occurs in less than 1% of women with endometriosis.[59] The tumors most likely to originate in endometriosis are endometrioid carcinoma, clear cell carcinoma, and carcinosarcoma.[60] Cytoplasmic eosinophilia and nuclear enlargement and pleomorphism are common in endometriosis. These changes generally occur in areas of inflammation, degeneration, and regeneration and represent a reactive change. There is marked atypia in 3% to 4% of cases of ovarian endometriosis.[61] Most examples of markedly atypical endometriosis are due to an extreme reactive change, but some may be preneoplastic. If there is marked atypia in the absence of inflammation, the endometriosis should be excised completely and the patient followed carefully.[62] Malignant neoplasms such as clear cell carcinoma and endometrioid carcinoma may arise in atypical endometriosis.[62,63]

OVARIAN NEOPLASMS

Most primary ovarian neoplasms are derived from one of the following three sources:

1. The coelomic surface epithelium covering the ovary
2. The ovarian stroma, the sex cords, or both
3. The germ cells.[64]

A few rare ovarian tumors cannot be categorized easily. The gonadoblastoma, for example, contains germ cells and sex cord stromal elements. Many tumors that are not specific for the ovary, such as soft-tissue tumors and lymphomas, may arise there, and a significant proportion of ovarian neoplasms are metastatic from some other site.

Epithelial Tumors

Tumors of surface epithelial origin comprise 60% of all ovarian neoplasms and an even greater proportion of ovarian malignant neoplasms (Table 6-1). They occur predominantly in adults, with the malignant forms generally appearing later in life (Fig. 6-24). They are more likely to be bilateral than tumors in the other major groups. Epithelial tumors are classified according to the predominant pattern of differentiation of the neoplastic cells (Table 6-2).[64] *Serous tumors* are the most common epithelial tumors. Their epithelium resembles that of the fallopian tube, with an admixture of ciliated, muciparous, and intercalated cells. The tumor is *mucinous* if the epithelium is endocervical in type, is composed of tall columnar mucinous cells, or contains intestinal-type epithelium with goblet cells. *Endometrioid tumors* are composed of tall columnar cells similar to those seen in proliferative-phase endometrium or endometrial carcinoma. *Clear cell tumors,* formerly misclassified as of mesonephric origin, are closely related to the endometrioid group, as are the rare stromal sarcomas and mixed mesodermal tumors. Tumors whose epithelial elements are urothelial in appearance, resembling the transitional cell lining of

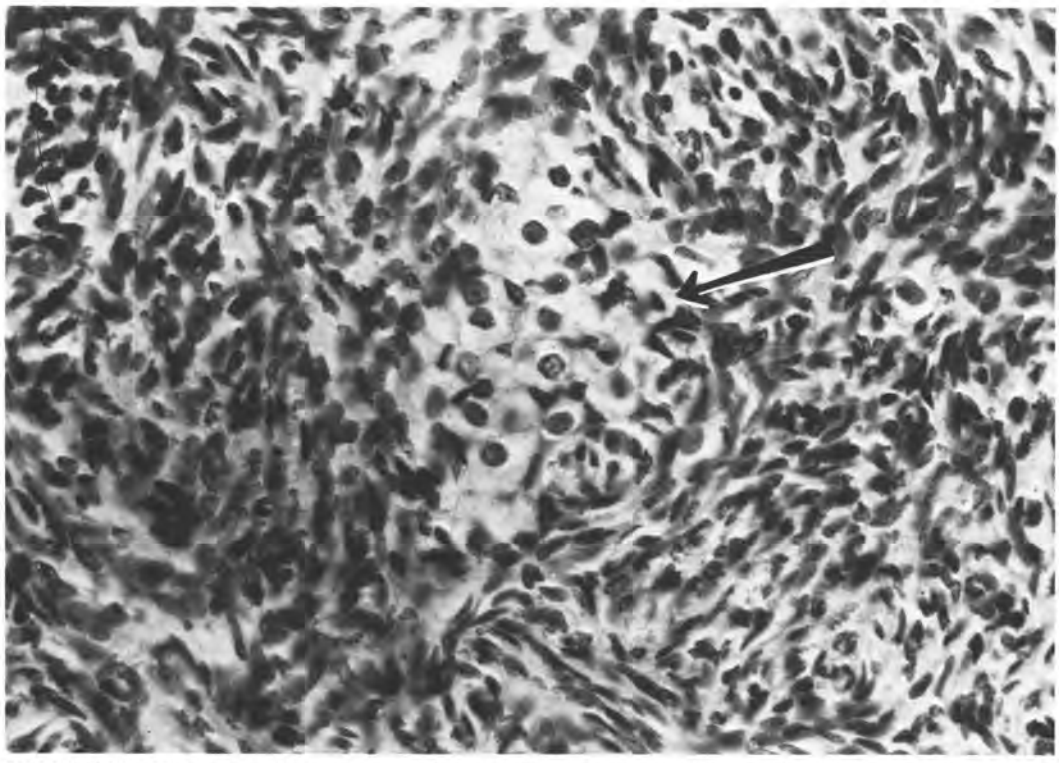


FIGURE 6-23 Hyperthecosis: ovarian cortical stromal hyperplasia with luteinized cells (*arrow*).

the urinary bladder, are known as *Brenner tumors*, or, if no benign Brenner elements are present, as *transitional cell carcinoma*. Tumors that contain two or more prominent patterns of differentiation are termed *mixed epithelial tumors*. A significant proportion of malignant epithelial tumors are so undifferentiated that they cannot, and for prognostic purposes should not, be included in the above groups. They are designated as *undifferentiated carcinoma*.

Except for undifferentiated carcinoma, each of the tumor types is subdivided into *benign, low malignant potential (LMP)*, and *malignant (carcinoma)* categories (Table 6-3). In practice, serous and mucinous tumors are the only ones in which examples in all three categories are common. Most Brenner tumors

TABLE 6-1
Malignant Tumors of the Ovary: Approximate Prevalence, Bilaterality, and Survival (Literature Review)

Type of Tumor	*Prevalence*	*Bilaterality (%)*	*5-Year Survival (%)*
Serous LMP	10–15	60	95
Serous carcinoma	25–35	60	20
Mucinous LMP	5–10	20	95
Mucinous carcinoma	5–10	20	45
Endometrioid carcinoma	15–30	30	50
Clear cell carcinoma	4–6	10–30	40
Undifferentiated carcinoma	5–10	55	10
Dysgerminoma	1–2	10–20	90
Yolk sac tumor	<1	<5	>50
Immature teratoma	<1	<5	>50
Secondary malignant teratoma	<1	0	15
Granulosa cell tumor	2–3	5	90
Sertoli-Leydig cell tumor	<1	5	90

LMP, low malignant potential.

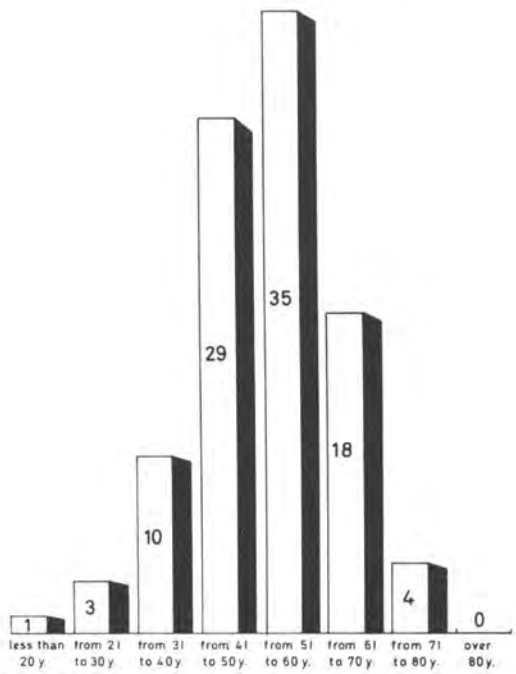


FIGURE 6-24 Primary ovarian carcinoma. The frequency (percentage) is shown as a function of age.

TABLE 6-2
Epithelial Tumors of the Ovary

Serous tumors
Mucinous tumors
Endocervical-like
Intestinal-type
Endometrioid tumors
Adenofibroma
Adenosarcoma
Carcinoma and LMP
Carcinosarcoma
Endometrial stromal sarcoma
Clear cell tumors
Transitional cell tumors
Brenner tumors
Transitional cell carcinoma
Squamous cell tumors
Mixed epithelial tumors
Undifferentiated carcinoma
Unclassified

are benign, and most endometrioid and clear cell tumors are malignant.

Clinical Findings

Epithelial tumors of the ovary cause such protean symptoms that even the malignant variants are often not detected until late in their evolution. Menstrual abnormalities are frequent, and, as the neoplasm enlarges, compression of adjacent structures causes pelvic discomfort, pain, pressure, or urinary frequency. Torsion or rupture may precipitate acute abdominal symptoms. Neoplasms that are larger than 15 cm in diameter distend the abdomen, may be palpated by the patient, and may cause gastrointestinal symptoms. Ascites may occur in women with benign tumors but is more often observed in women whose tumors are malignant. Ascites produces progressive abdominal distention with disturbances of gastrointestinal function and nausea and vomiting. Only a minority of epithelial tumors are detected during routine examination of an asymptomatic patient. Ovarian enlargement of any degree in women older than 45 years prompts consideration of ovarian cancer and calls for further evaluation. Functional cysts (eg, follicular and luteal cysts) may enlarge the ovary in women of reproductive age. Functional cysts rarely exceed 5 to 7 cm in diameter, and they generally resolve within 4 to 6 weeks. A large mass that does not involute or that exhibits sonographic features suggestive of a neoplasm must be further evaluated. The CA-125 monoclonal antibody test is useful in the evaluation of women with epithelial tumors.[65] This test detects an antigenic determinant on a high-molecular-weight glycoprotein. Increased levels of CA-125 are typically observed in women with malignant epithelial tumors. The test is not specific, however, because elevated levels of CA-125 are also detected in pregnancy and in women with endometriosis, lupus, and other benign conditions.

Clinical Behavior and Treatment

Benign tumors are treated conservatively by cystectomy or unilateral salpingo-oophorectomy. They do not recur or metastasize.

Women with *epithelial tumors of LMP* have a favorable prognosis. Total abdominal hysterectomy and bilateral salpingo-oophorectomy is the standard surgical treatment. Extraovarian tumor is resected if possible, but aggressive cytoreduction is not indicated.[66] Women with tumors of LMP typically are in

TABLE 6-3
Histogenesis and Nomenclature of Differentiated Surface Epithelial Tumors

Pathway of Differentiation	*Benign Tumor*	*Tumor of LMP*	*Malignant Tumor*
Tubal	Serous Cystadenoma Adenofibroma Surface papilloma	Serous tumor of LMP	Serous carcinoma Serous surface papillary carcinoma
Endocervical or intestinal	Mucinous Cystadenoma Adenofibroma	Mucinous tumor of LMP Intestinal-type Müllerian-type	Mucinous carcinoma
Endometrial	Endometrioid adenofibroma	Endometrioid tumor of LMP	Endometrioid carcinoma Adenosarcoma Carcinosarcoma Stromal sarcoma
Clear cell	Clear cell adenofibroma	Clear cell tumor of LMP	Clear cell carcinoma
Transitional	Brenner tumor	Intermediate Brenner tumor Proliferating LMP	Malignant Brenner tumor Transitional cell carcinoma

LMP, low malignant potential.

their early 40s. Many women with these neoplasms are of reproductive age, and conservation of fertility often is an issue. Unilateral salpingo-oophorectomy, or, in some circumstances, cystectomy, is a valid treatment alternative in young women with localized (stage IA) disease.[67,68]

The *serous tumor of LMP* is the most common tumor of LMP in most[68–73] but not all[74–76] studies. Survival approaches 100% in women with localized tumors (stage I and IIA), and adjuvant therapy is not indicated.[77,78] Those with more extensive tumors have a significant risk of recurrence, and as many as 20% die of tumor.[77] Tumor progression is indolent, and most deaths occur more than 5 years after initial diagnosis.[79] The role of chemotherapy and radiation therapy in the treatment of tumors of LMP is controversial. There are some reports that extraovarian tumor deposits respond to chemotherapy, but neither chemotherapy nor radiation therapy has been shown to increase the likelihood of survival in women with advanced stage serous tumors of LMP.[77,80,81] Surgical resection of extraovarian tumor appears to be the most effective treatment for symptomatic women with progressive or recurrent tumor.

Mucinous tumor of LMP has a favorable prognosis. Most mucinous tumors of LMP are confined to one ovary at diagnosis (stage IA), and 5-year survival rates exceed 95%.[70,82,83] Most deaths from mucinous tumors of LMP occur in women who have pseudomyxoma peritonei.[75,84,85] There is no effective treatment for this condition, and most patients have slowly progressive disease that results in death after many years.[86]

Clinical studies of other types of epithelial tumors of LMP, such as *endometrioid*,[87,88] *clear cell*,[89] and *Brenner* types,[90–93] are limited. Most of these tumors are confined to one ovary at diagnosis, and tumor-associated deaths are rare.

Invasive carcinoma of the ovary spreads by direct invasion to adjacent organs such as the large and small intestines, the uterus and fallopian tubes, and the urinary bladder. Dissemination by way of the peritoneal fluid to (or multifocal tumor development in) the omentum (Fig. 6-25), the peritoneum, the serosal surfaces of the abdominal viscera, and the diaphragm is one of the most characteristic features of carcinoma of the ovary, and it explains why most ovarian cancers are in a high clinical stage when they are first detected. Lymph node metastases involve the abdominal (ie, hypogastric, iliac, and aortic) and thoracic chains. Distant metastases are observed most often in the lungs, pleura, and pericardium. Supraclavicular lymph node involvement may be the first sign of distant spread. The pathologic stage at operation is the single most important prognostic factor (Table 6-4).

The treatment of carcinoma of the ovary is primarily surgical. The standard operation is hysterectomy with bilateral salpingo-oophorectomy and, usually, omentectomy. If disseminated carcinoma is present, the surgeon should remove as much tumor as possible to facilitate subsequent chemotherapy or radiation therapy. Conservative surgery can be considered for young women who require conservation of fertility. Such patients can be treated by unilateral salpingo-oophorectomy if their carcinoma is stage IA and well differentiated. Systemic platinum-based combination chemotherapy is used to treat women with high-grade stage IA carcinoma and women who have advanced carcinoma.[94–96] Such therapy results in a complete clinical remission in about 50% of women with advanced cancer, but only about 30% of such patients have a pathologic complete remission documented by second-look laparotomy with multiple biopsies.[94,97–100] Women whose tumors contain a predominant (>50%) transitional cell component may be more likely to respond favorably to chemotherapy.[101] Other forms of treatment that are used in women with ovarian cancer include intraperitoneal chemotherapy,[102–104] intraperitoneal therapy with radiocolloids,[105–107] and external-beam radiation therapy.[108–111]

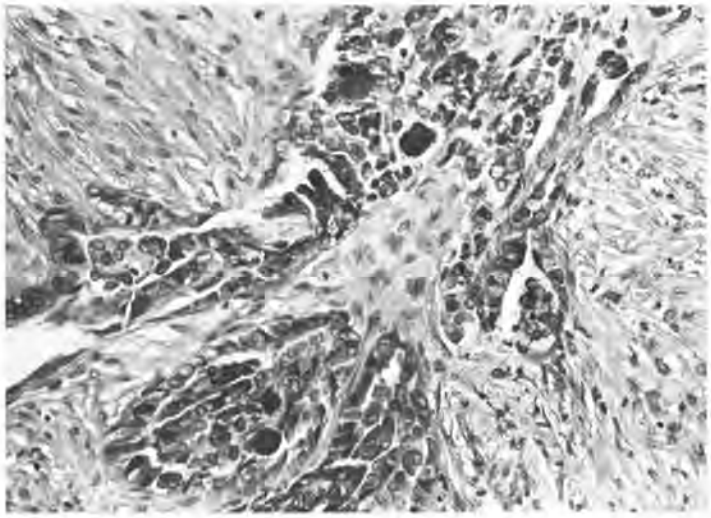


FIGURE 6-25 Omental metastasis of serous carcinoma with psammoma bodies.

TABLE 6-4
FIGO Staging of Carcinoma of the Ovary

Stage I	Growth limited to the ovaries
IA.	Growth limited to one ovary; no ascites; no tumor on the external surface; capsule intact
IB.	Growth limited to both ovaries; no ascites; no tumor on the external surface; capsule intact
IC.	Growth involving one or both ovaries but with tumor on the surface, or with capsule ruptured, or with ascites containing malignant cells, or with positive peritoneal washings
Stage II	Growth involving one or both ovaries with pelvic extension
IIA.	Extension and/or metastasis to the uterus and/or tubes only
IIB.	Extension to other pelvic tissues
IIC.	Stage IIA or IIB plus tumor on the surface, or ruptured capsule, or ascites with malignant cells, or positive peritoneal washings
Stage III	Growth involving one or both ovaries with peritoneal implants outside the pelvis and/or positive retroperitoneal or inguinal nodes; superficial liver metastasis; limited to the true pelvis but with extension to small bowel or omentum
IIIA.	Limited to true pelvis with negative nodes, but with microscopic seeding of abdominal peritoneal surfaces
IIIB.	Implants on abdominal peritoneal surfaces not exceeding 2 cm in diameter, negative nodes
IIIC.	Abdominal implants > 2 cm in diameter and/or positive retroperitoneal or inguinal lymph nodes
Stage IV	Growth involving one or both ovaries with distant metastasis outside the peritoneal cavity

Pathologic Examination

The treatment and prognosis of ovarian neoplasms is based on accurate surgical staging and a thorough pathologic evaluation. Careful gross examination is the first step in the pathologic examination. The tumor is weighed and measured, and its exterior is examined. The appearance of the tumor capsule is particularly important because capsular rupture or tumor growth on the surface of the ovary affects the stage (see Table 6-4). Next, the tumor is sectioned at 1-cm intervals, and the cut surfaces are examined and described. Tissue for microscopic examination is taken from cyst walls, solid and papillary areas, and any unusual areas (eg, zones of hemorrhage or calcification). Representative sampling is generally ensured if a block is taken for each centimeter of tumor diameter. Most immunohistochemical stains useful in the diagnosis of ovarian neoplasms are performed on fixed tissue. Tissue need not be frozen for immunohistochemistry unless a lymphoma is suspected. Tissue can be fixed in glutaraldehyde for electron microscopic study if the gross or frozen-section examination suggests a diagnostic problem that might be resolved by ultrastructural study. DNA ploidy and cell cycle measurements appear to have prognostic value in epithelial tumors, so the tissue submitted for analysis should be fresh (see Chap. 12).[112–121] Neither the measurement of estrogen and progesterone levels nor the study of oncogenes is routine in the evaluation of ovarian tumors, and tissue need not be submitted for such tests unless required by a protocol.[122] The clinical significance of histopathologic grading of invasive carcinomas is poorly understood, in part because different series use different grading systems (eg, architectural, cytologic, or combined). In general, the differences in survival between well- and poorly differentiated cancers seen in older reports disappear in series of cases treated with modern chemotherapeutic regimens.[122]

Serous Tumors

Serous neoplasms constitute about 25% of all benign and malignant ovarian neoplasms, making them the most common of the ovarian neoplasms. They represent 20% of benign and 40% of malignant primary tumors of the ovary. Of all serous tumors, 50% are benign, 15% are of LMP, and 35% are invasive carcinomas.[123,124] Benign serous tumors and serous tumors of LMP arise most often in premenopausal women. Serous carcinoma occurs predominantly in older women. Epithelial tumors in general are uncommon in children.[125–127] The incidence of bilaterality is high; it is about 20% in benign serous tumors and 40% to 60% in borderline and malignant serous tumors.

Macroscopic Appearance. *Serous cystadenoma* varies in appearance. It may be a unilocular cyst with a smooth shiny surface that is stretched by the tension of the intracystic fluid (Fig. 6-26). Other cases are multilocular and composed of pale yellow or gray-white cysts of variable size (Fig. 6-27). The cut surface reveals fascicles of homogeneous white fibrous tissue between the cysts. Small coarse papillae may be present on the interior surface of the cyst walls (Fig. 6-28). An *adenofibroma* is a predominantly solid fibrous tumor that has a convoluted, clefted surface and multiple small cysts within its fibrous stroma. A *cystadenofibroma* is similar, except that the cystic component occupies a significant proportion of the neoplasm. The *surface papilloma* is an uncommon serous neoplasm that grows predominantly on the surface of the ovary and lacks a cystic component. It is composed of finger-like papillary projections. Large, fleshy papillae, invasion through the cyst wall with proliferation of papillae on the external surface, and solid areas are signs of probable malignancy. Solid and papillary areas should always be sampled carefully for microscopic examination.

Serous tumor of LMP resembles serous carcinoma in many respects. It is frequently large and bilateral, with areas of cystic and papillary growth (Color Figure 6-5). Tumor is present on the external surface of the ovary in about 40% of cases. Unlike carcinoma, an LMP tumor rarely has solid areas or foci of hemorrhage and necrosis. Microscopic analysis is the only certain way to determine whether a serous tumor is an LMP neoplasm or a carcinoma.

Serous carcinoma is usually large and is often bi-

FIGURE 6-26 Serous cystadenoma (scale shown here and throughout chapter is in cm).

lateral. It exhibits a mixture of cystic, papillary, and solid growth patterns (Figs. 6-29 and 6-30). The carcinoma often invades through the ovarian capsule and grows on the surface of the ovary. The *serous surface papillary carcinoma* grows predominantly on the surface of the ovary and lacks an intracystic component.[128–131] Foci of necrosis and hemorrhage are common in serous carcinoma.

Microscopic Appearance. The epithelial lining of a *serous cystadenoma* may resemble the germinal epithelium, but it always contains at least a few foci of tubal-type epithelium, illustrating its metaplastic potential. In a typical serous cystadenoma, tubal-type epithelium predominates; the lining is composed of tall ciliated and non-ciliated columnar cells with elongated nuclei (Fig. 6-31). The numbers of intercalated and clear cells are fewer. If the cyst is under tension, the epithelium becomes flattened, and the various cell types are no longer recognizable. The epithelium is surrounded by a variable amount of fibrous ovarian stroma. The stroma is the dominant component of the neoplasm in a *serous adenofibroma.* The epithelium lines glands and cysts within the stroma and covers the surface of the neoplasm. A *serous cystadenofibroma* is similar, except that cystic spaces comprise a dominant portion of the neoplasm (Fig. 6-32).

FIGURE 6-27 Serous cystadenoma. There are multiple cysts with a smooth lining.

FIGURE 6-28 Cut surfaces of serous cystadenomas, showing blunt papillary structures (*right*) and a smooth-walled unilocular cyst (*left*).

Psammoma bodies are small, whorled, calcified structures. They are numerous in some serous tumors and may be found in cellular and acellular areas. They probably arise as products of cellular degeneration. Ultrastructural and x-ray diffraction studies indicate that psammoma bodies are composed of calcium apatite and that the initial site of calcium deposition is the lipid-rich vesicles in tumor cells and histiocytes.[132] The presence of psammoma bodies in a tumor strongly suggests a serous neoplasm, but it does not differentiate a benign tumor from a malignant tumor. Psammoma bodies are fre-

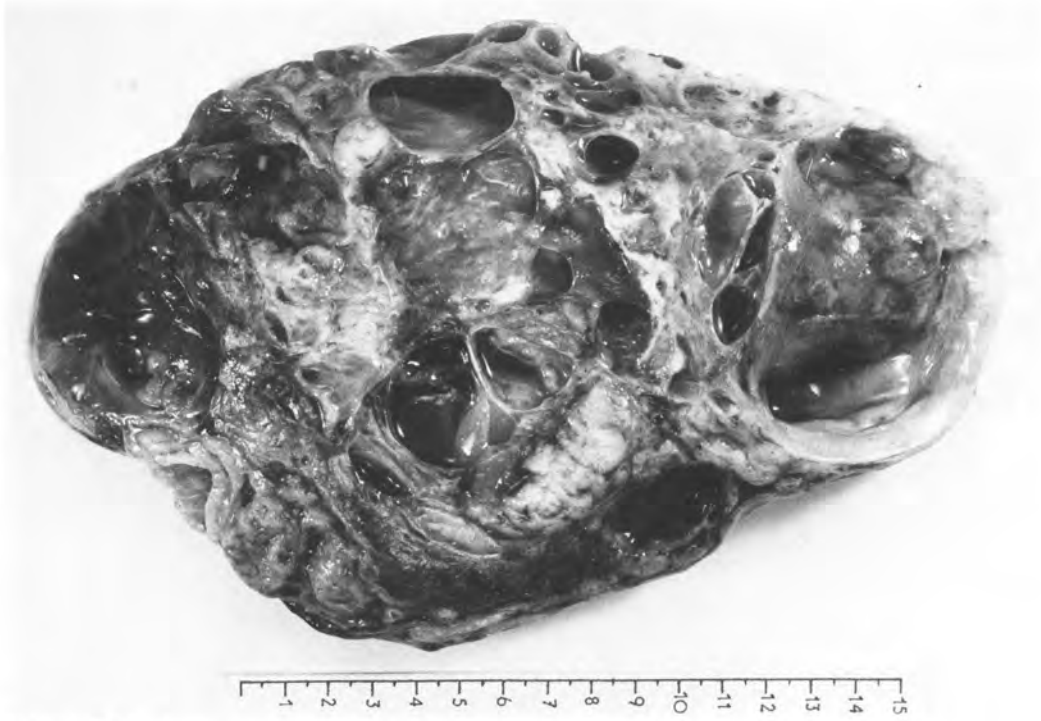


FIGURE 6-29 Serous carcinoma. Solid, fleshy areas alternate with cysts.

FIGURE 6-30 Serous carcinoma involving both ovaries. Note the surface papillary tumor growth.

quently encountered in nonneoplastic lesions, such as germinal inclusion cysts.

A *serous tumor of LMP* is composed of the same cell types as a benign serous tumor, but with fewer ciliated cells and some evidence of proliferative activity.[70,73,79,133] The cells are stratified into several layers, forming tufts from which clusters of cells are detached into the cystic lumina (Fig. 6-33). Complex papillary and glandular patterns of growth are typical (Fig. 6-34), and the formation of secondary cysts is a characteristic feature. The tumor cells are cytologically atypical, and mitotic figures are present, but neither of these features is as pronounced as in serous carcinoma. Most significantly, true stromal invasion is not identified. Glands encountered within the stroma are the result of tangential cutting of complicated infoldings; they do not have an infiltrative appearance, and they are separated from each other by bands of stroma that show no evidence of reaction to the tumor. Some borderline serous tumors have sufficient stroma to be regarded as cystadenofibromas.[134]

Microscopic stromal invasion is an infrequent finding in a serous tumor of LMP.[135,136] When it occurs, nests and cords of cells with eosinophilic cytoplasm, round vesicular nuclei, and prominent nucleoli in-

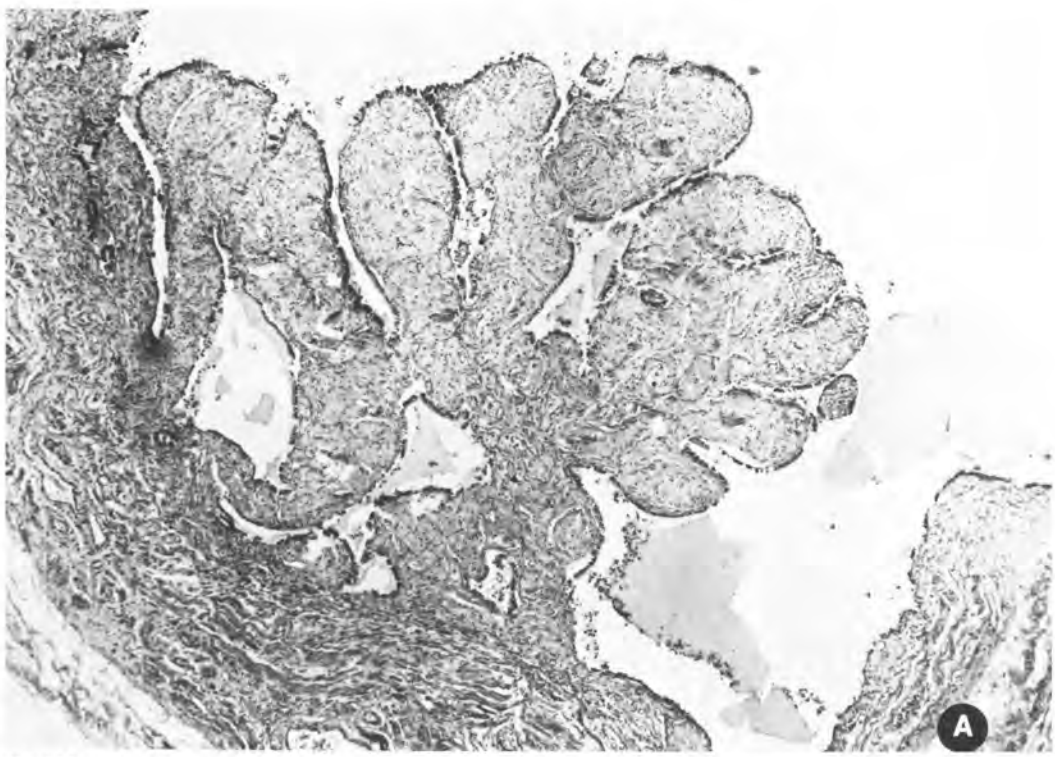


FIGURE 6-31 Serous cystadenoma. **(A)** General appearance, illustrating blunt papillae covered by a single layer of epithelial cells. **(B)** Detail of epithelium.

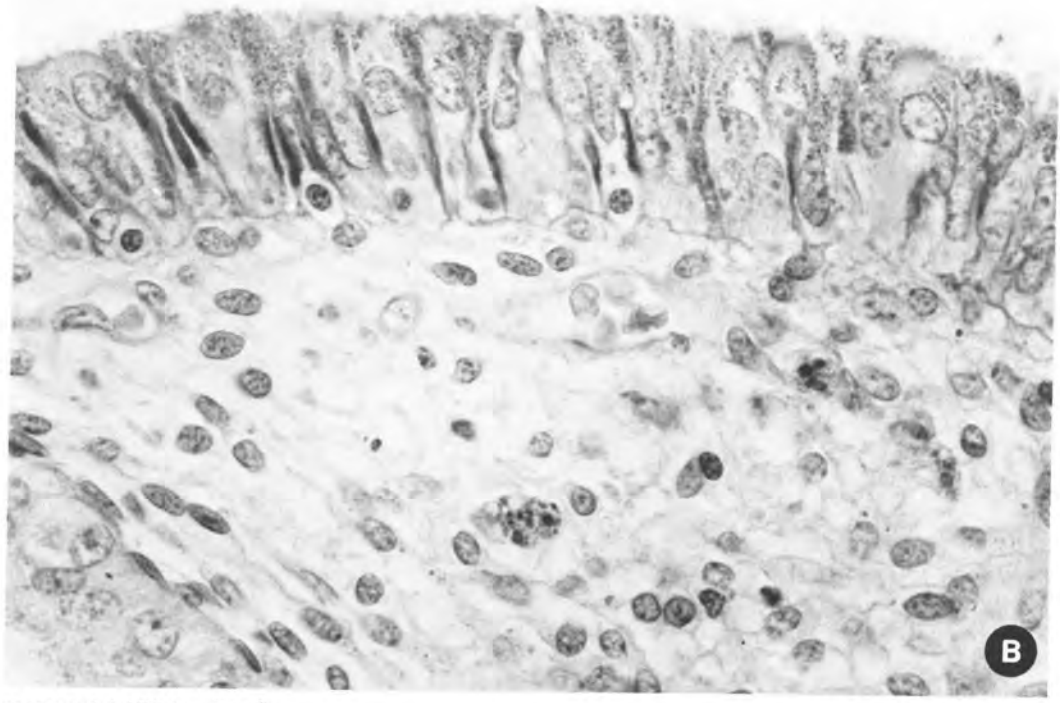


FIGURE 6-31(B) *(continued)*

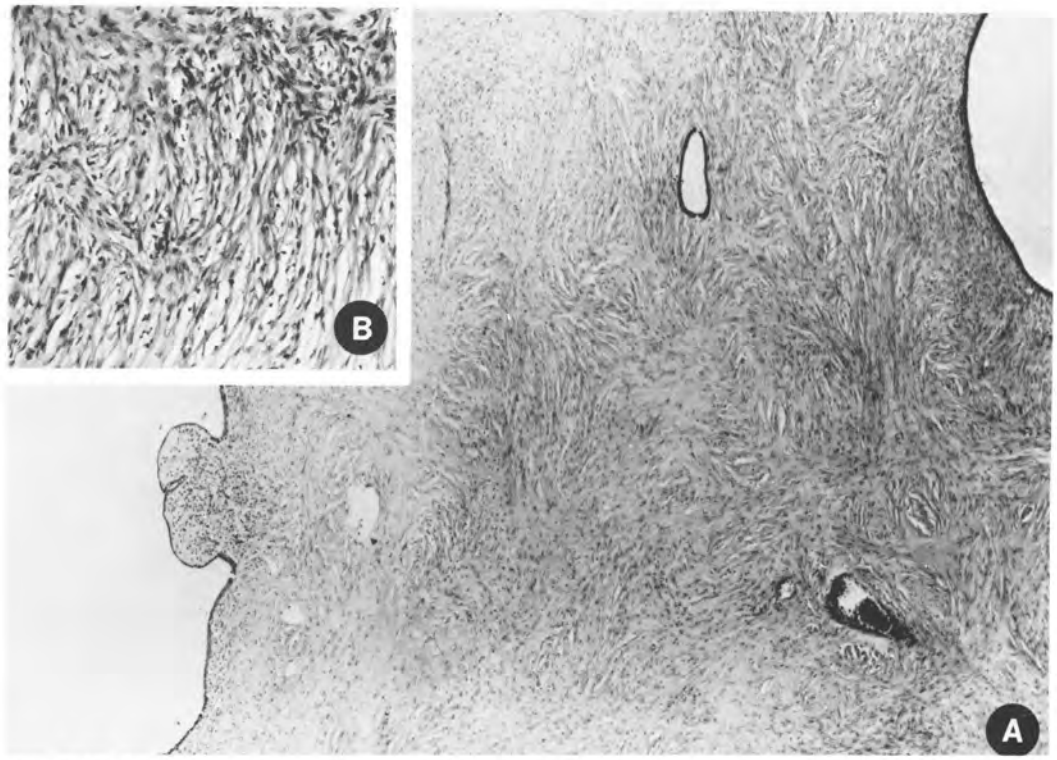


FIGURE 6-32 Serous cystadenofibroma. **(A)** Low-magnification view illustrating cystic spaces and abundant stroma. **(B)** Detail of stroma.

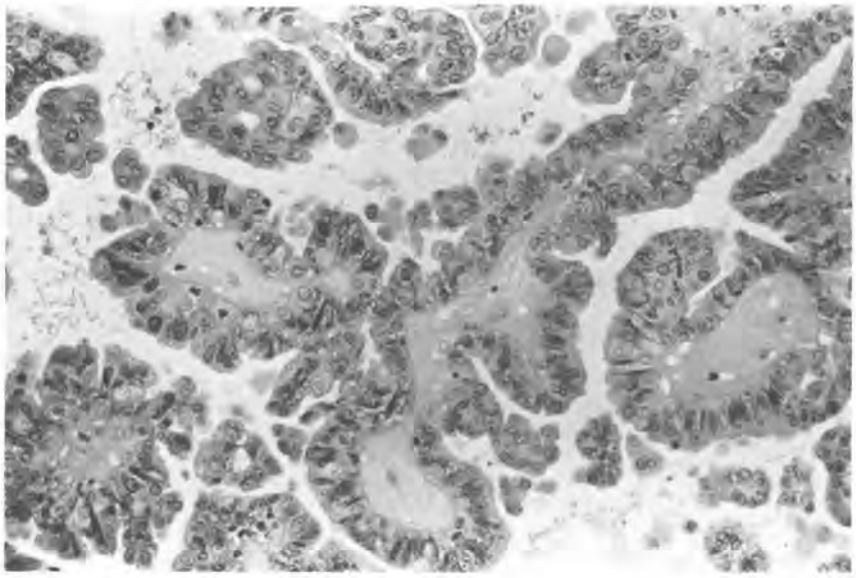


FIGURE 6-33 Serous tumor of low malignant potential, illustrating mild atypia, stratification, and detachment of cells into lumen.

vade the fibrous stroma between cysts lined by noninvasive serous LMP (Fig. 6-35). The areas of invasion are microscopic (smaller than 3 mm), and there is no stromal reaction. The clinical outcome is comparable to that observed in noninvasive serous tumors of LMP of the same clinical stage.[79,135,136]

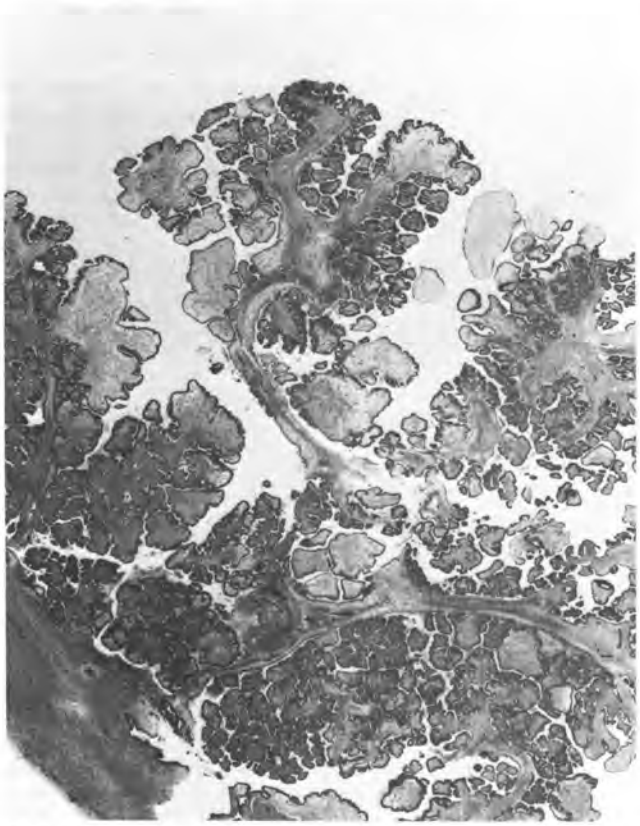


FIGURE 6-34 Serous tumor of low malignant potential with a complex papillary pattern.

Peritoneal tumor deposits are common in women with serous tumors of LMP. It is uncertain whether they represent implants from the ovarian tumor or sites of synchronous peritoneal neoplasia. Three types of deposits are described by Bell and colleagues: noninvasive epithelial, noninvasive desmoplastic, and invasive.[137]

Noninvasive epithelial implants contain a papillary epithelial proliferation of LMP on the peritoneal surface or in a circumscribed subsurface cyst. Desmoplastic implants contain papillae and glands trapped and compressed by fibrous tissue. Such implants are superficial and sharply circumscribed from the surrounding tissues. Invasive implants, which are better thought of as invasive serous carcinoma, contain irregular nests of epithelium that infiltrate underlying tissues. Marked nuclear atypia is often noted in invasive implants. Women with invasive implants also have noninvasive implants, so extensive sampling is necessary to detect them. Some researchers have observed a correlation between the histology of the peritoneal deposits and the clinical course,[137] but others have not.[138,139] The morphology of the peritoneal deposits should be evaluated carefully for invasion, although its significance is uncertain. Peritoneal deposits from a serous tumor of LMP must be differentiated from endosalpingiosis, a benign condition that is most commonly observed in the peritoneum and ovary. It is characterized by small cysts and simple papillae that are lined by cytologically bland ciliated columnar epithelial cells of tubal type. Psammoma bodies may be present, and fibrosis and chronic inflammation often surround the nests of epithelium. In contrast to a serous tumor of LMP, the cells are not stratified, there is no proliferative activity, and there is no cytologic atypia. Endosalpingiosis is discussed in more detail in Chapter 7.

Serous carcinoma is composed in part of papillae

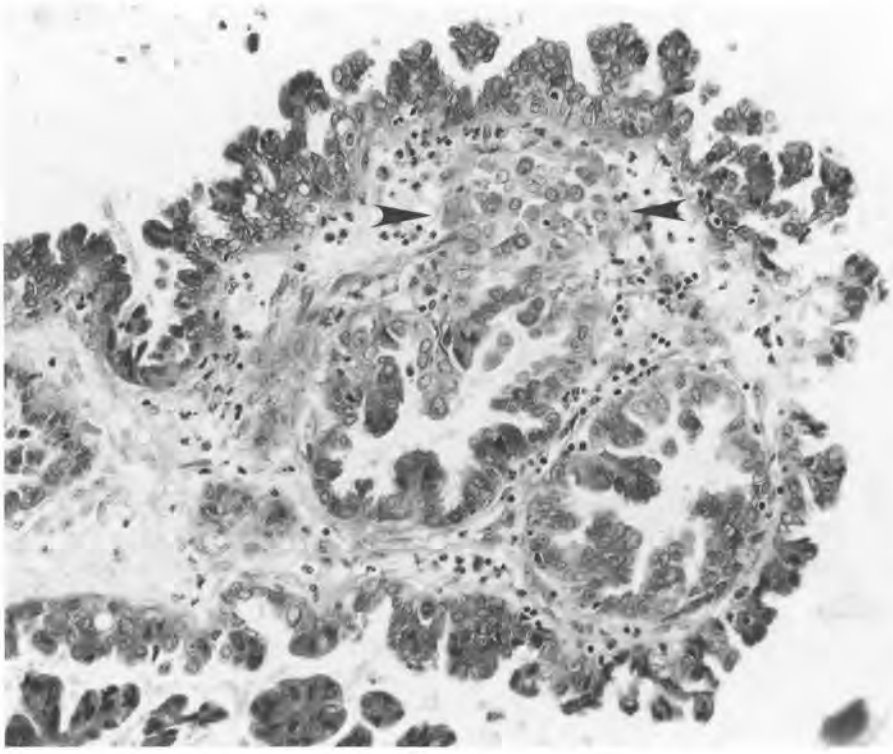


FIGURE 6-35 Serous tumor of low malignant potential with microscopic stromal invasion (*top center*). The invasive cells have large vesicular nuclei and abundant eosinophilic cytoplasm.

lined by stratified cells of serous type (Figs. 6-36 through 6-38). Ciliated cells are rare, and the degree of cytologic atypia and mitotic activity varies. In addition to papillae, the tumor may contain glands, solid cell cords, or sheets of cells, with the prominence of these patterns increasing as differentiation decreases (Figs. 6-39 and 6-40). The epithelium diffusely infiltrates a fibrotic stroma. Squamous differentiation is occasionally observed in serous carcinoma.[140] In rare cases, a serous carcinoma contains so many psammoma bodies that they dominate the histologic picture.[141]

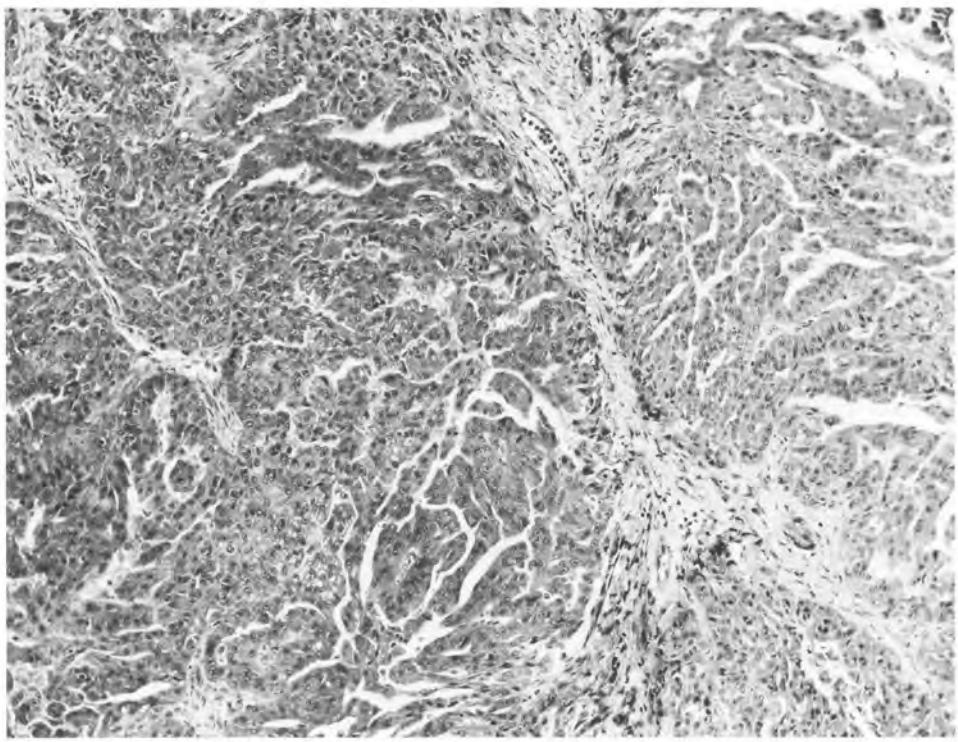


FIGURE 6-36 Serous carcinoma. Large masses of tumor cells with irregular slit-like spaces representing remnants of papillae. Compare with the more regular villoglandular architecture seen in Figure 6-50*A* (same magnification).

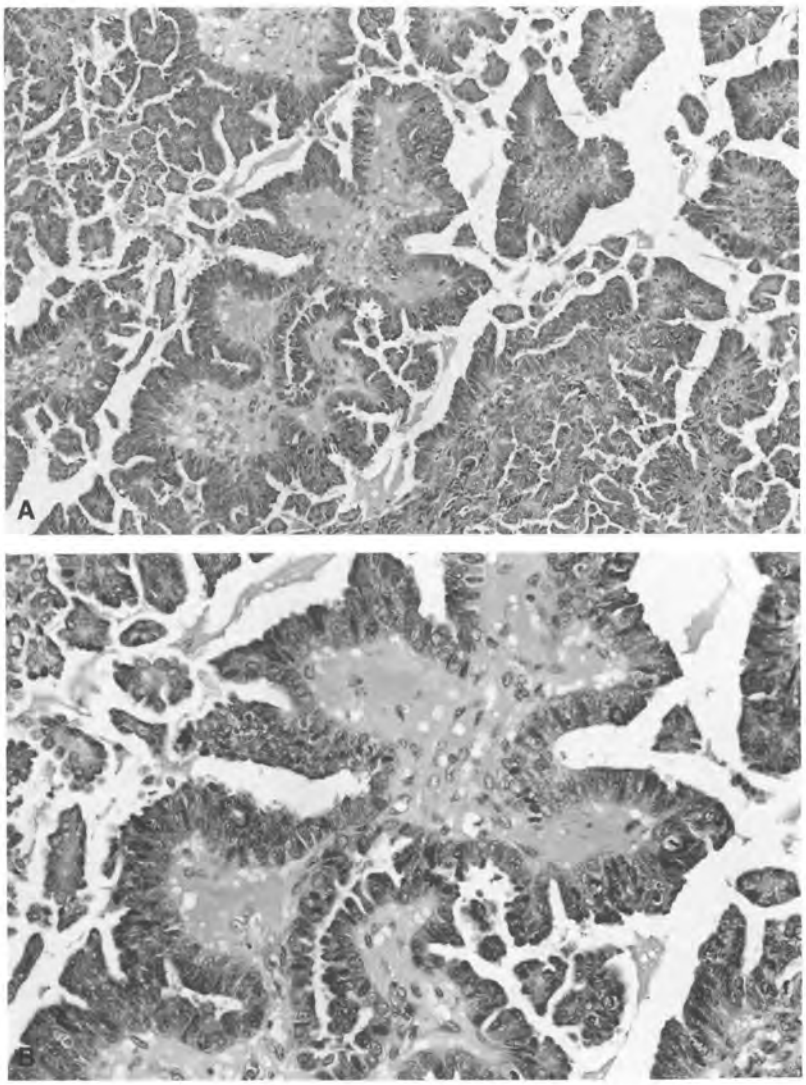


FIGURE 6-37 Moderately differentiated serous carcinoma. **(A)** Complex papillary structures. **(B)** Papillae lined by stratified, atypical cells.

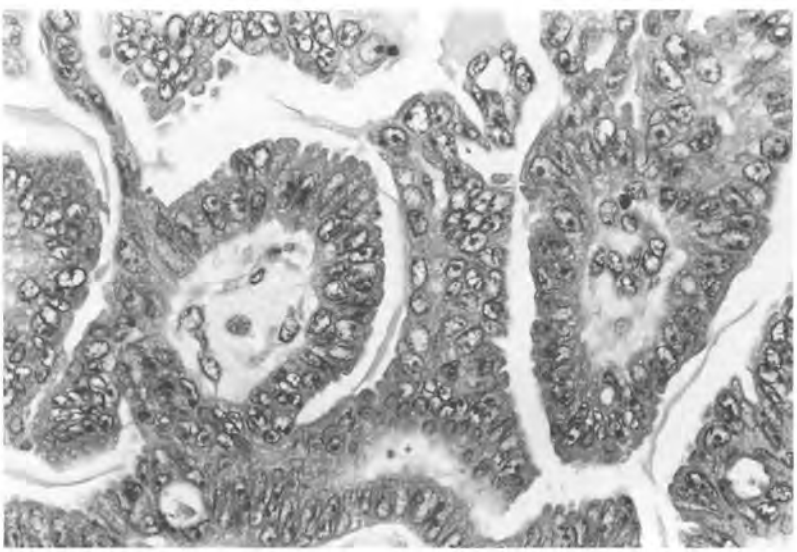


FIGURE 6-38 Moderately differentiated serous carcinoma with typical nuclear morphology. The vesicular nuclei contain prominent nucleoli.

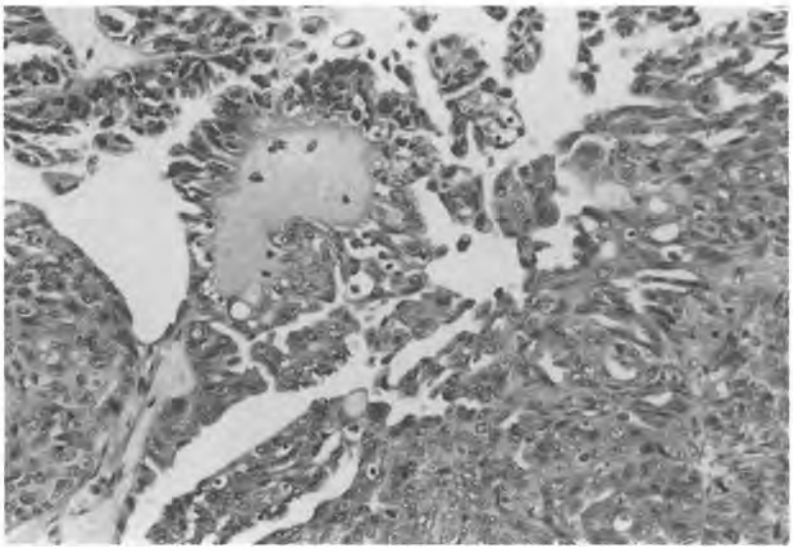


FIGURE 6-39 Serous carcinoma. Papillae are present in this poorly differentiated carcinoma (*center*), but areas of solid growth are prominent (*left* and *right*).

Ultrastructural study confirms the resemblance between a serous tumor and tubal epithelium. The papillae are lined by ciliated columnar cells, non-ciliated cells with apical microvilli, and cuboidal basal cells (Fig. 6-41).[129,142–144] As expected, cytoplasmic and nuclear anomalies become more pronounced with the progression from benign tumor to tumor of LMP to carcinoma, and specific cell structures, such as cilia, are observed with decreasing frequency.

Differential Diagnosis. The differential diagnosis of serous tumor of LMP includes müllerian mucinous tumor of LMP and Sertoli-Leydig cell tumor with prominent retiform differentiation. *Müllerian mucinous tumors of LMP* comprise 10% to 15% of all mucinous tumors of LMP.[145] Like serous tumors of LMP, they are frequently bilateral, grow in a complex papillary pattern with epithelial budding, contain indifferent cells with eosinophilic cytoplasm, and

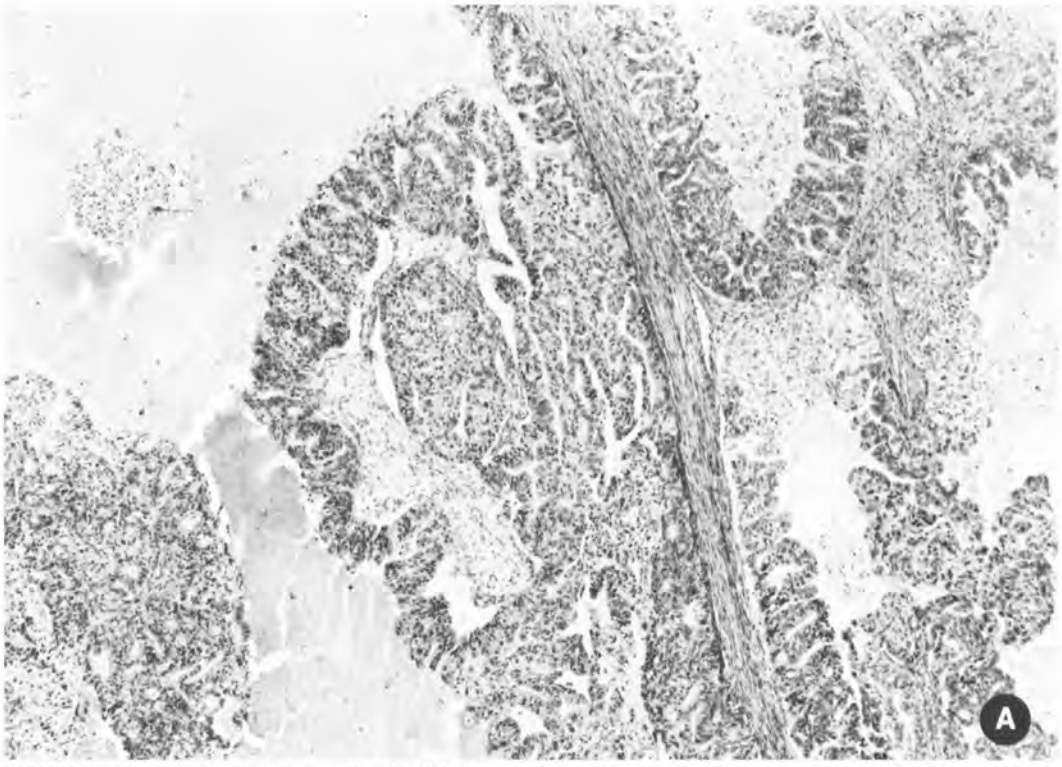


FIGURE 6-40 Serous carcinoma. Poorly differentiated carcinoma in which the cysts are lined by irregular micropapillae, glands, and solid sheets of cells.

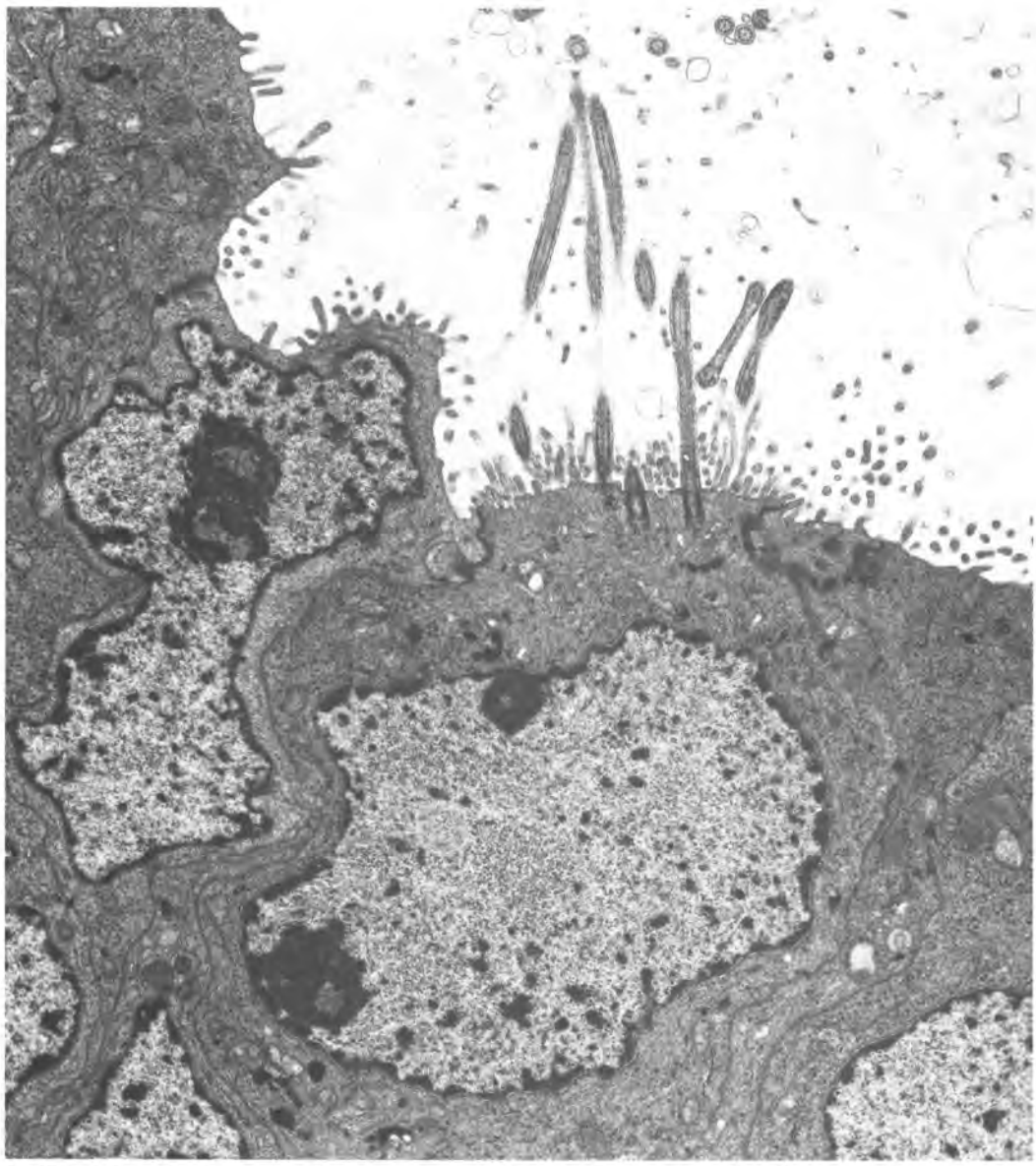


FIGURE 6-41 Ultrastructure of a serous tumor of low malignant potential. Tumor cells have cilia, microvilli, irregular nuclei with marginated chromatin, and prominent nucleoli (×10,000). (Courtesy of Dr. J. M. Orenstein, George Washington University, Washington, DC).

may be associated with peritoneal implants. Unlike serous tumor of LMP, the predominant tumor cell is a columnar mucinous cell of endocervical type. A *Sertoli-Leydig cell tumor* may be confused with a serous tumor if it exhibits exceptionally prominent retiform differentiation.[146] Patients with Sertoli-Leydig cell tumors tend to be younger than patients with serous tumors. In addition to retiform tubules, Sertoli-Leydig cell tumors contain, at least focally, typical Sertoli tubules, primitive stromal cells, and Leydig cells.

The main diagnostic problem in serous carcinoma is to differentiate it from other types of surface epithelial carcinoma. Interobserver agreement in the classification of serous carcinoma is only about 70%.[147] The classification of surface epithelial carcinomas of the ovary, particularly of poorly differentiated examples, is imprecise because their morphologic features overlap. Serous carcinoma most often is confused with endometrioid carcinoma and undifferentiated carcinoma. *Endometrioid carcinoma* is more likely to be unilateral, confined to the pelvis, and associated with a synchronous endometrial carcinoma. It is composed of columnar cells that grow in glands and trabeculae, and it frequently contains areas of squamous differentiation. Prominent nucleoli, which are characteristic of serous carcinoma, are not a usual feature of endometrioid carcinoma. Poorly differentiated carcinomas that grow as sheets of malignant cells are best classified as *undifferentiated carcinoma.*[122]

Mucinous Tumors

Mucinous cystadenoma is one of the most common ovarian neoplasms. It is about as prevalent as serous cystadenoma and comprises about 20% of all benign ovarian tumors. Malignant mucinous tumors are considerably less numerous than their serous counterparts. Mucinous carcinoma constitutes 5% to 15% of primary malignant ovarian tumors, and the mucinous tumor of LMP is equally common.

Macroscopic Appearance. *Mucinous cystadenoma* is a cystic neoplasm with a smooth, blue-white or gray external surface that is covered by numerous blood vessels. Most examples are smaller than 10 cm in diameter, but huge tumors with weights of up to 100 kg have been reported. The tumor may be firm, rubbery, or soft, depending on the amount of mucin within the cysts and the abundance of stroma. The cut surface features smooth, thin-walled cysts ranging from a few millimeters to several centimeters in diameter (Fig. 6-42). An occasional tumor is a single large unilocular cyst. The mucoid material within the cysts may be clear, yellow and turbid, or, if there has been hemorrhage into the cyst, red-brown. *Mucinous cystadenofibroma* is a solid neoplasm that contains mucin-filled cystic spaces. Benign mucinous tumors are usually unilateral; only about 5% are bilateral.

Mucinous intestinal tumors of LMP average 15 cm in diameter, and less than 10% are bilateral. They are multilocular cystic neoplasms (Color Figure 6-6), about half of which contain solid areas. The cysts contain mucoid material and generally have a smooth lining (Fig. 6-43). Intracystic papillary projections are present in only a minority of tumors. The less common mucinous LMP tumor, the *mucinous müllerian tumor of LMP,* tends to be smaller than the mucinous intestinal LMP tumor. It is more frequently bilateral and is often paucilocular, with grossly apparent intracystic papillae. *Mucinous carcinoma* is a multilocular cystic neoplasm that averages 15 to 20 cm in diameter. Firm, solid areas are slightly more common in mucinous carcinoma than in mucinous tumor of LMP, and the carcinoma is more likely to contain foci of hemorrhage and necrosis. The tumor extends to the ovarian surface in less than 10% of cases, and about 10% of cases are bilateral.

Microscopic Appearance. *Mucinous cystadenoma* typically is lined by a single layer of columnar mucinous cells of endocervical type. The cells have clear cytoplasm and a small, oval, basal nucleus (Fig. 6-44). Small papillae with a well-defined fibrovascular core are present in some neoplasms. The cytoplasmic mucin stains to a variable degree with periodic acid-Schiff stain, alcian blue stain, and mucicarmine stain. With increasing intracystic pressure, the lining cells become cuboidal or flattened and may disappear completely. Intestinal-type epithelium with goblet and endocrine cells is found in many mucinous cystadenomas.[148,149] The stroma is moderately cellular and focally edematous. The amount of stroma occasionally is sufficient to warrant designating a neoplasm as a *mucinous adenofibroma* or

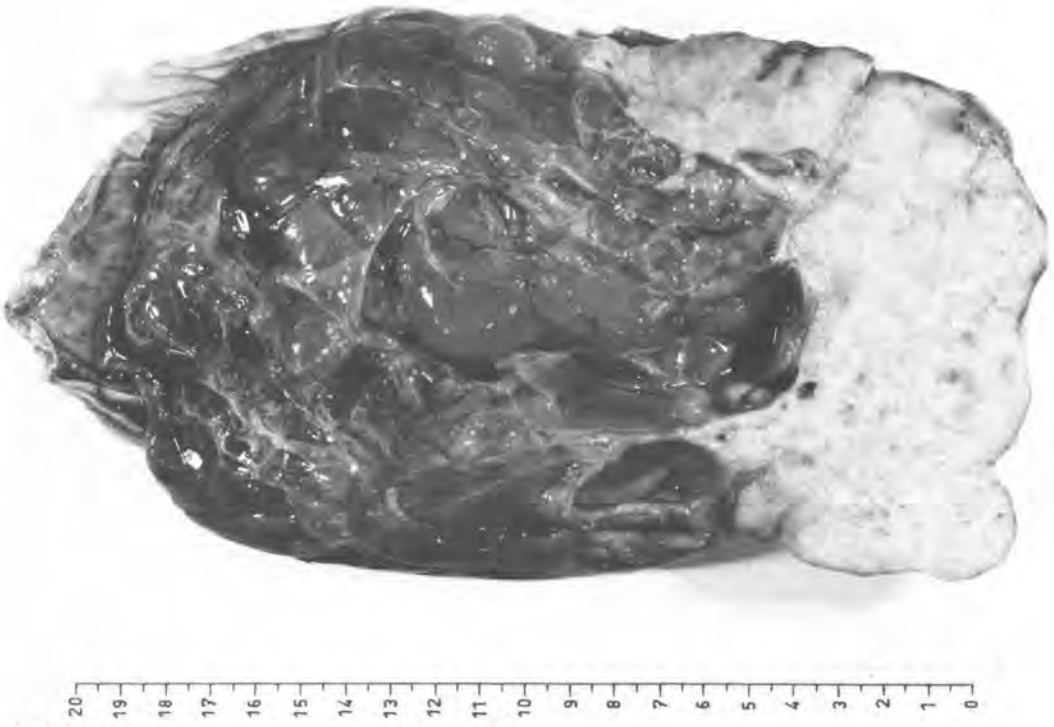


FIGURE 6-42 Mucinous cystadenoma. Thin-walled cysts contain viscous mucin.

FIGURE 6-43 Mucinous tumor of low malignant potential. The cut surface shows translucent grape-like cysts filled with mucin.

cystadenofibroma.[150,151] Luteinized stromal cells are a common finding in mucinous tumors.

There are two types of *mucinous tumor of LMP* (see earlier discussion). The more common type is composed of proliferating mucinous epithelium in which *intestinal* differentiation predominates.[82,83] The epithelium lines secondary cysts and papillary infoldings supported by fine, connective tissue cores. The mucinous epithelium contains goblet cells, endocrine cells, and, rarely, Paneth's cells.[148,152–157] The epithelial cells are immunoreactive for carcinoembryonic antigen, exhibit slight to moderate atypia, have occasional mitotic figures, and are stratified into two or three (and occasionally more) layers (Fig. 6-45). A second type of mucinous tumor of LMP, the *müllerian mucinous tumor of LMP,* makes up 15% of mucinous tumors of LMP.[145] It exhibits a papillary growth pattern similar to that seen in the serous

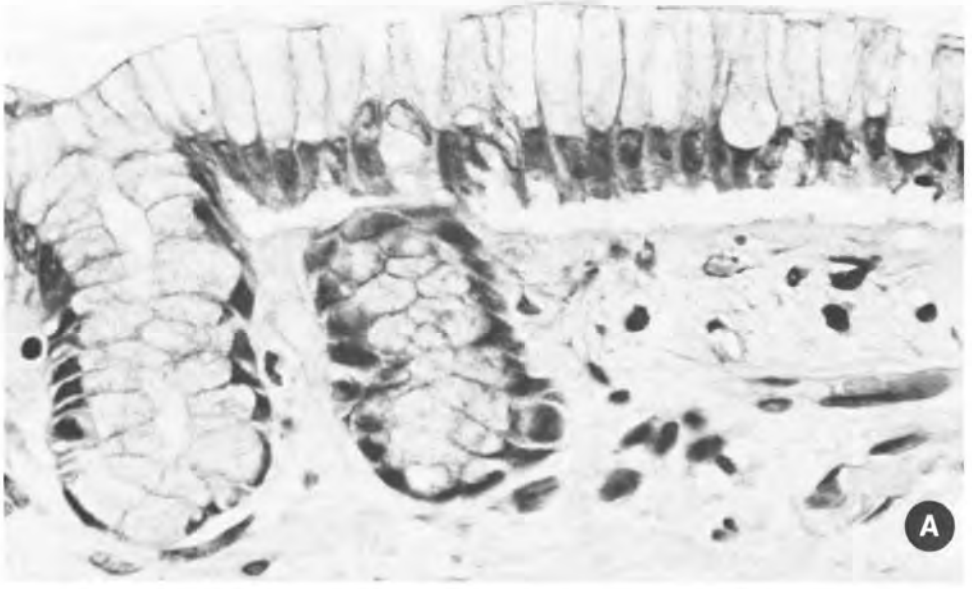


FIGURE 6-44 Mucinous cystadenoma. The epithelium is composed of endocervical-type columnar cells.

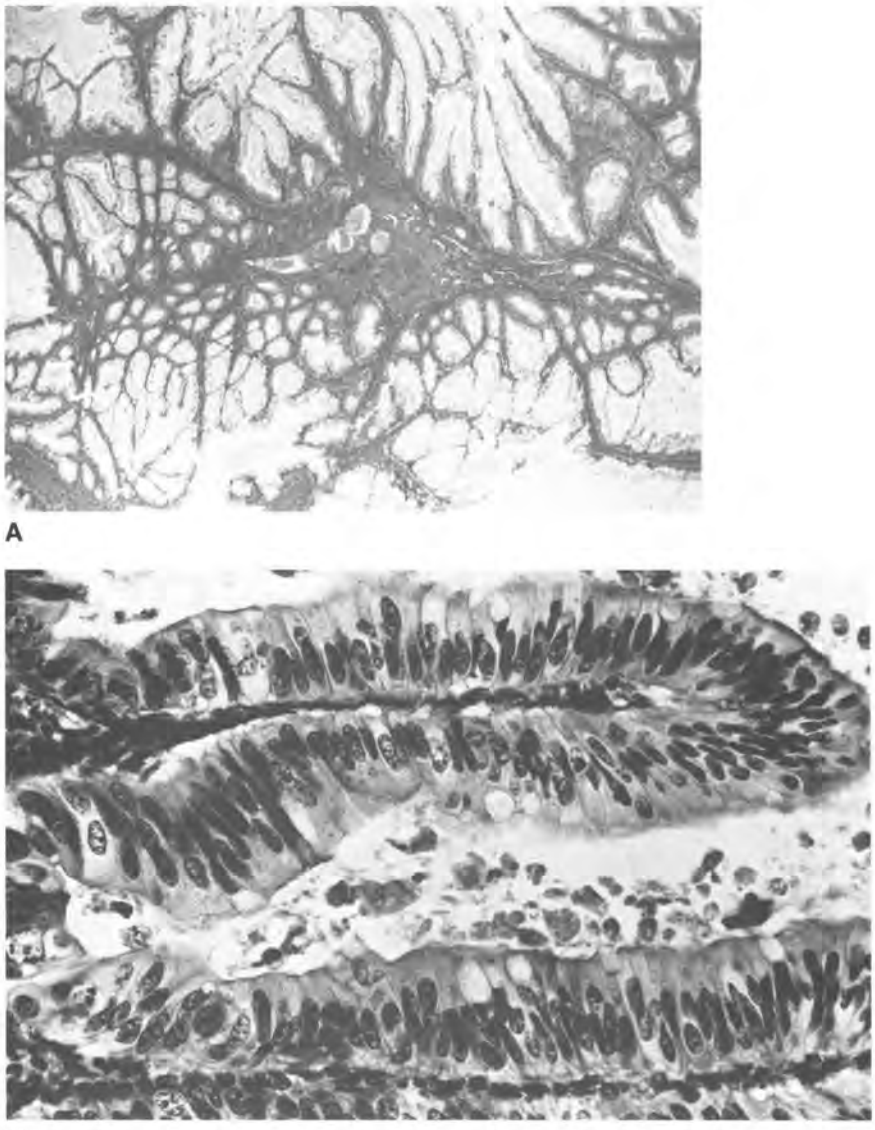


FIGURE 6-45 Mucinous intestinal tumor of low malignant potential. **(A)** Low-magnification view showing general architecture, with formation of complex papillae and cysts and absence of stromal invasion. **(B)** The cells have hyperchromatic, mildly atypical nuclei and are stratified into two or three layers. Note the goblet cells.

tumor of LMP (Fig. 6-46). The papillae are lined by columnar mucinous cells of endocervical type. The incidence of bilaterality is greater in this type of mucinous LMP tumor, and peritoneal implants are detected in about one third of cases. The prognosis is favorable, even for patients with extraovarian tumor deposits. Stromal invasion is not present in either type of mucinous tumor of LMP. Pseudocribriform patterns and secondary cyst formation may simulate invasion and should not be misinterpreted.

Mucinous carcinoma is composed of irregular cysts and glands lined by an atypical epithelium, which often is stratified into four or more cell layers (Fig. 6-47). The tumor cells have enlarged, hyperchromatic nuclei, prominent nucleoli, and frequent mitoses. There is less intracytoplasmic mucin than in a mucinous tumor of LMP. The main criterion of invasive carcinoma is the presence of stromal invasion by irregular epithelial cords and nests. Many authors accept the presence of marked cytologic atypia or of atypical epithelial cells stratified into four or more cell layers, even in the absence of demonstrable stromal invasion.[82,83,158,159] The presence of a true cribriform pattern with intraglandular bridging or of areas in which glands are arranged back-to-back without intervening stroma indicates invasion.

Rare mucinous tumors contain solid *mural nodules* composed of sarcoma-like connective tissue,[160] sarcoma,[161,162] or anaplastic carcinoma.[163–166] Tumors with sarcoma-like nodules have a benign clinical evolution and are interpreted as representing a reactive process, whereas mural nodules composed of sarcoma or anaplastic carcinoma are cytologically malignant, invasive, and capable of metastasis. Immunoreactivity with antibodies against cytokeratin and other markers of epithelial differentiation is helpful in recognizing anaplastic carcinoma.

Electron microscopy reveals a variety of cell types in mucinous tumors of the ovary.[143,167] Most mucinous cystadenomas are lined by endocervical-type cells. The supranuclear cytoplasm of these cells contains numerous uniform mucin droplets and mem-

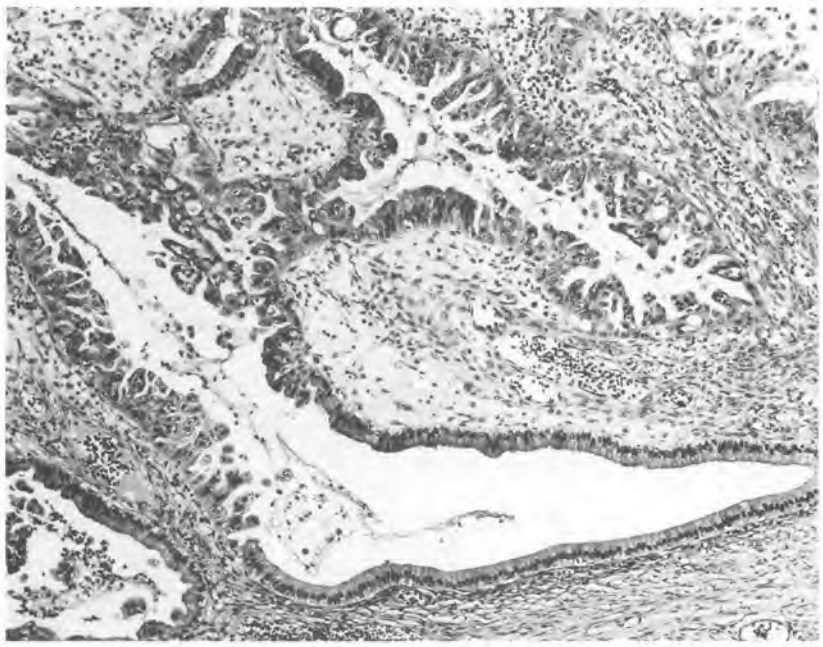


FIGURE 6-46 Mucinous müllerian tumor of low malignant potential. Endocervical-type mucinous epithelium shows focal stratification, tufting, and mild nuclear atypia. Mucin and neutrophils are present in the lumina, and neutrophils are present in the stroma.

brane-bound structures containing fibrillar material, and their apical surface is covered by microvilli. Intestinal types of epithelial cells are seen in many mucinous cystadenomas. Four types of intestinal cells are present:

- Goblet cells, which contain irregular mucin droplets that sometimes coalesce into a supranuclear or apical globule
- Absorptive cells, which are covered by microvilli having prominent core rootlets
- Cells that are intermediate between goblet and absorptive cells
- Endocrine cells.

Endocrine cells are situated adjacent to the basal lamina and contain distinctive electron-dense cytoplasmic granules. A mixture of intestinal and endocervical-type cells invariably is present in mucinous intestinal tumors of LMP (Fig. 6-48), but goblet cells and argentaffin cells are absent by light microscopy in the mucinous müllerian LMP tumor.[145] Intestinal-type cells predominate in mucinous carcinoma, with endocervical-type cells being found only focally and only in well-differentiated carcinoma. Ultrastructural studies confirm the light microscopic finding of increased anaplasia in the progression from benign to high-grade malignant mucinous tumors.

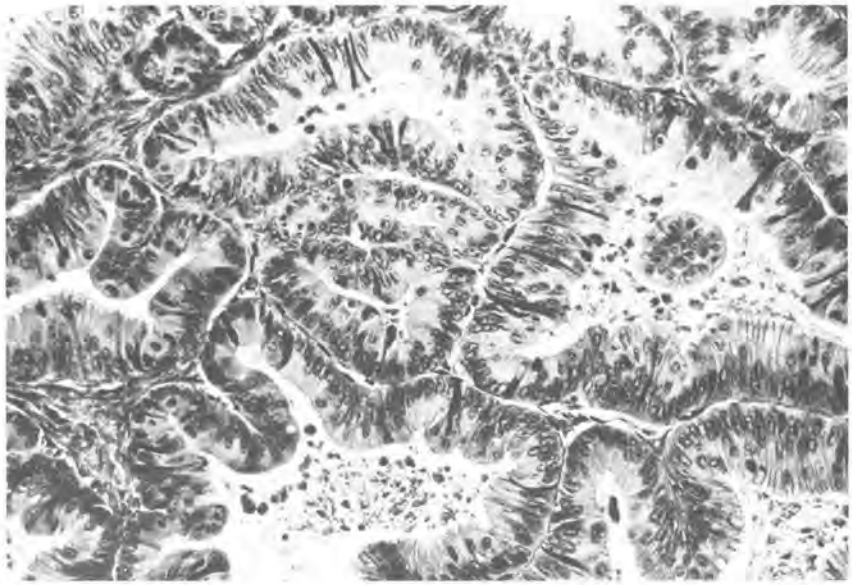


FIGURE 6-47 Mucinous carcinoma.

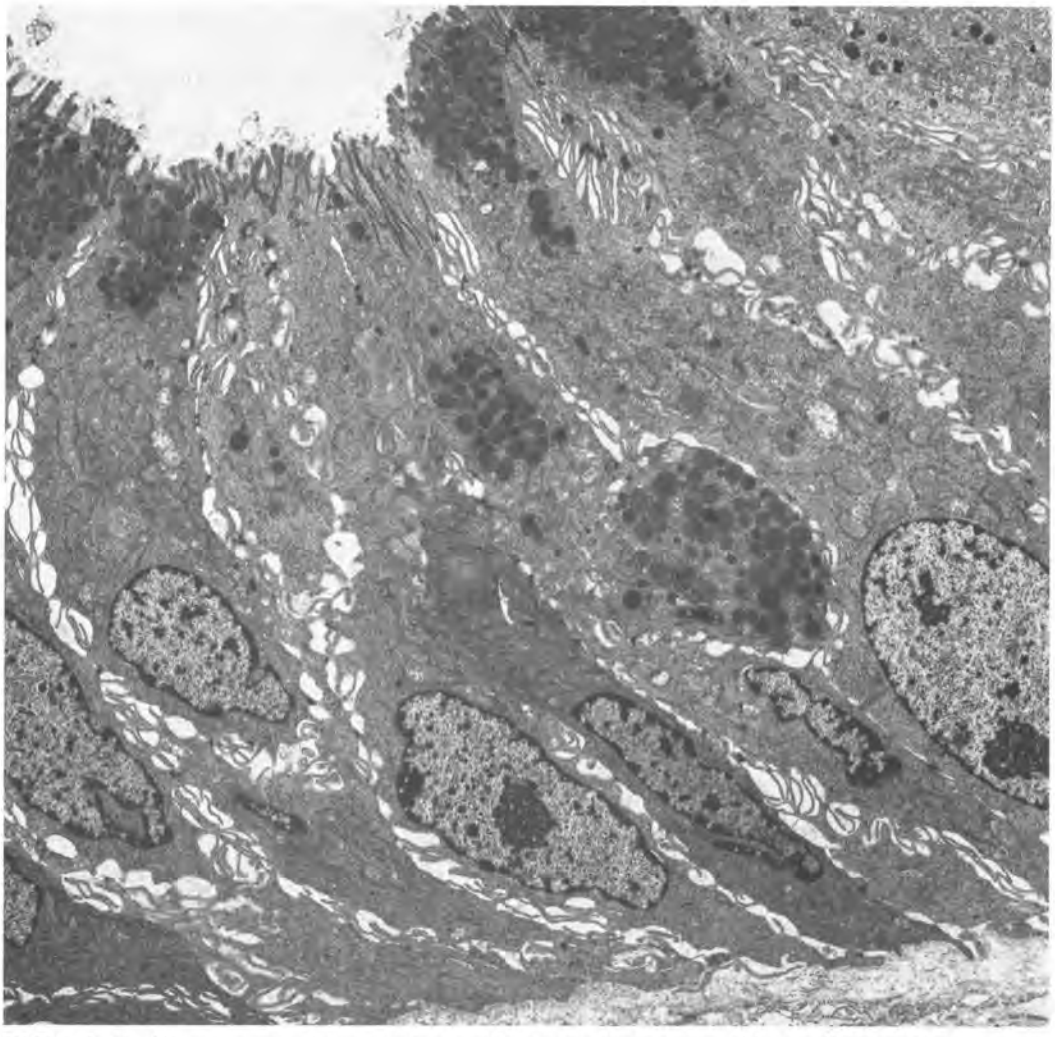


FIGURE 6-48 Ultrastructure of intestinal-type cells in a mucinous tumor of low malignant potential. The cells have microvilli with prominent core rootlets, and they contain electron-dense mucin vacuoles (×5200). (Courtesy of Dr. J. M. Orenstein, George Washington University, Washington, DC)

Pseudomyxoma Peritonei as a Complication of Mucinous Tumors. When the wall of a mucinous tumor perforates, mucin and tumor cells escape. Extracystic collections of mucin within the substance of the ovary are designated as *pseudomyxoma of the ovary*.[85] *Pseudomyxoma peritonei* is an infrequent condition characterized by accumulation of mucus and small numbers of tumor cells within the peritoneal cavity.[84,85,168,169] It is usually produced by slow leakage of mucus from a mucinous tumor of LMP or a well-differentiated mucinous carcinoma. In some cases, tumor cells escape the ovary and become implanted in the peritoneal cavity, where they grow independently. An alternative histogenetic theory is that multiple foci of mesothelial mucinous metaplasia occur in these patients, along with intraperitoneal mucin secretion.[169] Pseudomyxoma often develops early in the natural history of the ovarian tumor; in most reports, intraoperative rupture of a mucinous tumor is not followed by development of pseudomyxoma peritonei. Because this condition may be a complication of a ruptured mucinous tumor of the appendix, the appendicular region must be examined in patients with pseudomyxoma peritonei whether or not they have ovarian lesions. When both appendiceal and ovarian tumors are present, the appendix may be the primary site.[170] A huge volume of mucoid material may fill the peritoneal cavity in women with pseudomyxoma peritonei of ovarian or appendiceal etiology. Treatment usually fails to prevent multiple recurrences, and patients have a prolonged but uncomfortable survival.[84,86]

Differential Diagnosis. It is difficult to differentiate mucinous carcinoma from metastatic intestinal adenocarcinoma.[171,172] Bilaterality and multinodularity suggest metastatic adenocarcinoma. Unfortunately, metastatic intestinal adenocarcinoma often is unilateral and at least partly cystic, simulating primary mucinous carcinoma. The presence of mucinous cells of

endocervical type in the tumor is evidence that the neoplasm is primary in the ovary. Glands and cysts lined by intestinal-type cells that resemble those in a mucinous tumor of LMP or even a benign mucinous cystadenoma are not conclusive evidence of a primary ovarian neoplasm, because such areas occur in metastatic intestinal adenocarcinoma. Special stains for mucin and carcinoembryonic antigen are not helpful in the differential diagnosis, because they are positive in both primary and metastatic mucinous tumors. It may be impossible to arrive at the correct diagnosis without knowledge of the clinical history and operative findings. Parenchymal liver metastases are uncommon in women with mucinous carcinoma of the ovary, and their discovery suggests a primary tumor of the intestine, pancreas, or biliary tract.

Endometrioid Tumors

Benign and borderline endometrioid tumors are rare. In contrast to serous and mucinous tumors, most endometrioid neoplasms are invasive carcinomas.[124] Endometrioid carcinoma, a neoplasm that histologically resembles the usual adenocarcinoma of the endometrium, is the second most frequent type of ovarian carcinoma, comprising 12% to 30% of all malignant epithelial tumors of the ovary.[173] Endometriosis, in the ovary or elsewhere in the pelvis, is common in women with endometrioid tumors.[174] Some endometrioid tumors arise in endometriosis, but most are of surface epithelial origin.

Macroscopic Appearance. *Benign and LMP endometrioid tumors* usually have a fibrous stromal component that dominates their appearance.[87,88,134,151,175] They average 8 to 10 cm in diameter and are firm, tan, solid neoplasms, many of which contain cysts of variable size. *Endometrioid carcinoma* is typically a cystic neoplasm 10 to 20 cm in diameter.[174,176–179] It contains soft or firm, tan, solid nodular regions. Some examples are predominantly solid. As many as 30% are bilateral.

Microscopic Appearance. *Benign endometrioid tumors* are virtually all adenofibromas.[151,175] They are composed of fibrous stroma within which there are glands lined by a single layer of endometrial-type cells. These are columnar cells, with basophilic or amphophilic cytoplasm and fusiform nuclei. The nuclei may be pseudostratified, as in proliferative endometrium, but mitotic figures are not seen.

The epithelial component of an *endometrioid tumor of LMP* resembles hyperplastic endometrium, with the degree of glandular crowding and cytologic atypia usually approximating that observed in atypical hyperplasia (Fig. 6-49).[87,88,134,175] Squamous metaplasia is a common finding. Most endometrioid tumors of LMP have a prominent fibrous stromal component and are appropriately classified as adenofibroma or cystadenofibroma of LMP. A significant minority are partly or exclusively papillary, with intracystic growth. Nuclear atypia and frequent mitotic figures may be noted, but there is no stromal invasion.

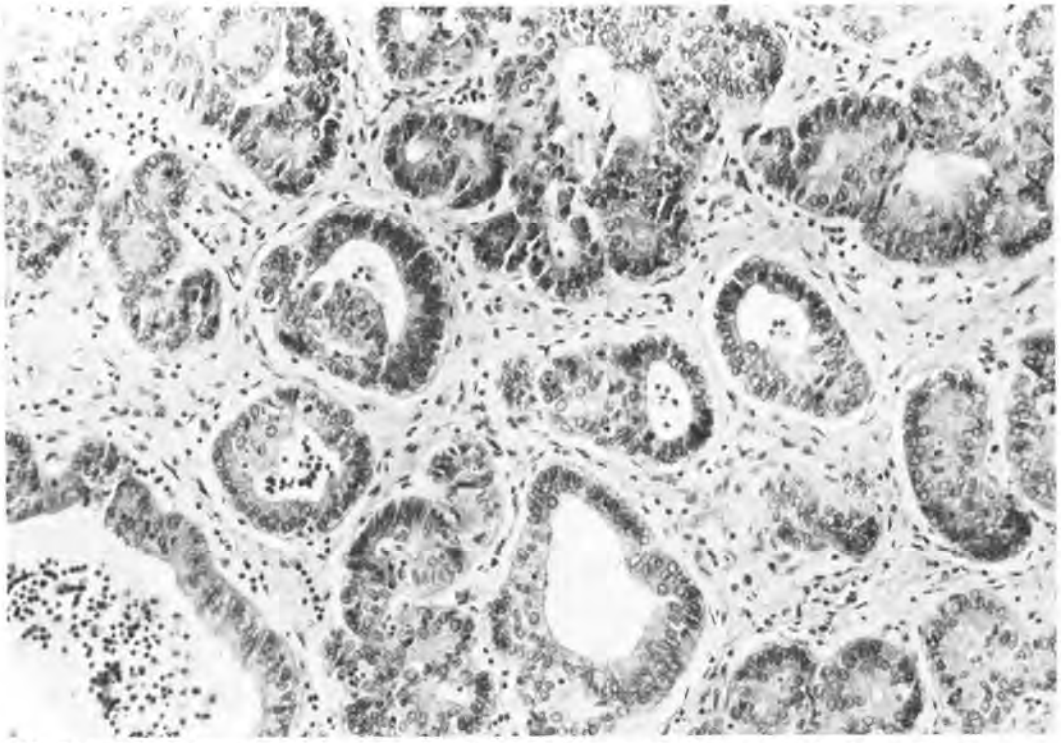


FIGURE 6-49 Endometrioid tumor of low malignant potential. The glands resemble hyperplastic endometrium and are surrounded by fibrous stroma.

Endometrioid carcinoma is a glandular neoplasm that resembles adenocarcinoma of the endometrium.[174,176-178,180] The glands generally are small and round, and they are lined by columnar cells with large atypical oval nuclei and basophilic cytoplasm (Fig. 6-50). The cells grow in single or multiple layers. Papillae, when present, are blunter and lined by less stratified cells than those observed in serous carcinoma. These cells are taller and more uniform, and they rarely exfoliate. Foci of squamous differentiation are present in 25% to 50% of endometrioid carcinomas.[176,181]

Differential Diagnosis. The differential diagnosis includes metastatic endometrial adenocarcinoma, metastatic adenocarcinoma from the large intestine, yolk sac tumor, and, particularly when luteinized stromal cells are present, a Sertoli-Leydig cell tumor. *Metastatic endometrial adenocarcinoma* must be excluded before a diagnosis of endometrioid carcinoma is made. This can pose difficulties, because simultaneous primary carcinomas in the endometrium and ovary are not infrequent.[182] If the carcinoma in the endometrium is small and superficial, both tumors generally are regarded as primary. On the other hand, if the endometrial tumor is of high grade and invades the myometrium, it is likely that the ovarian tumor is metastatic. *Metastatic colorectal carcinoma* is typically bilateral, exhibits extensive necrosis, and lacks squamous metaplasia.[171] The *endometrioid variant of yolk sac tumor* occurs in young women and children, is generally mixed with other more typical patterns of yolk sac tumor, and exhibits positive immunoreactivity for α-fetoprotein.[183] In contrast to a Sertoli-Leydig cell tumor, the sertoliform variant of endometrioid carcinoma arises in postmenopausal women and does not cause hormonal symptoms.[184-186] Characteristic areas of endometrioid carcinoma with squamous metaplasia or an adenofibromatous pattern generally are present. *Serous and mucinous carcinomas* of the ovary must be excluded, particularly if papillary foci are present; mixed patterns are common.

Clear Cell Tumors

Nearly all clear cell tumors are invasive carcinomas. Clear cell carcinomas comprise 5% to 10% of all ovarian cancers.[176,178,187-191] Benign and borderline variants occur but are rare.[89,134,151,192] Initially described as tumors of mesonephric origin, clear cell tumors are now known to be surface epithelial neoplasms closely related to the endometrioid tumors.[193] Evidence for the surface epithelial origin of clear cell tumors includes the frequent coexistence of clear cell carcinoma and other types of surface epithelial carcinoma, the frequent presence of pelvic endometriosis in women with ovarian clear cell carcinoma, and the light and electron microscopic similarity between clear cell carcinoma of the ovary and clear cell carcinoma in other sites (eg, endometrium, cervix, and vagina) where the tumor is clearly of müllerian rather than mesonephric derivation.

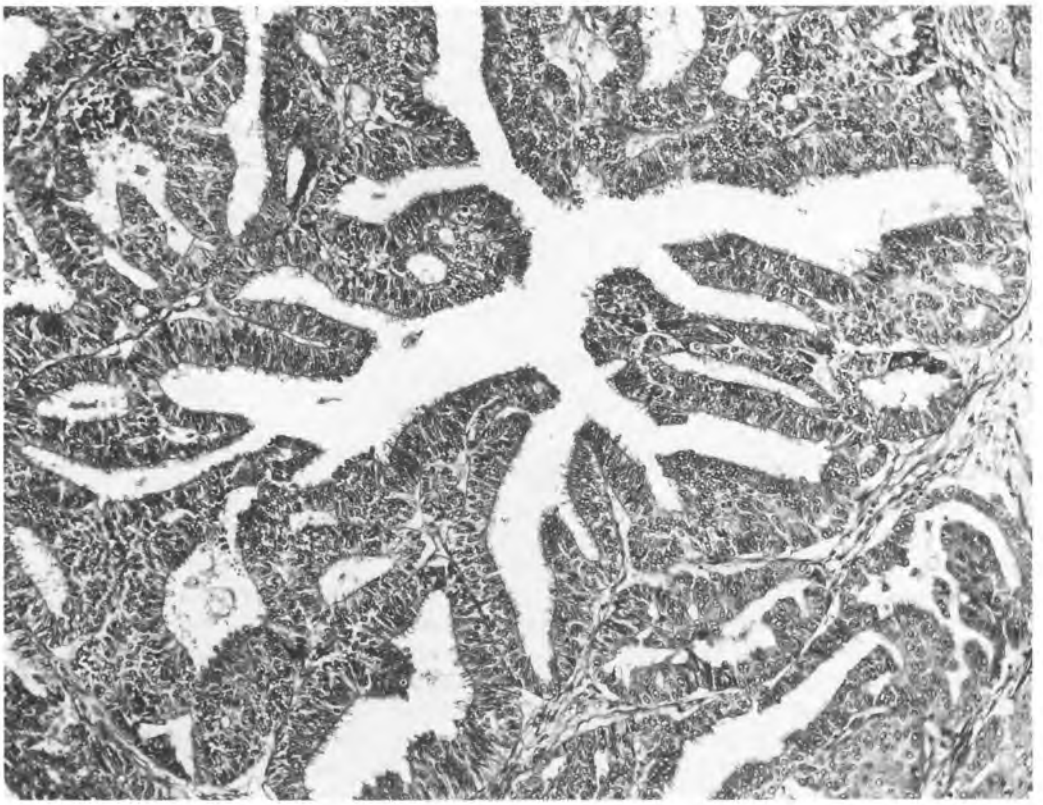
Macroscopic Appearance. Most *benign clear cell tumors* are unilateral. They are 3 to 15 cm in diameter and have solid white or tan cut surfaces that contain tiny cysts filled with clear fluid. *Clear cell tumors of LMP* are similar in appearance. They measure 7 to 32 cm, with an average diameter of 14 to 15 cm. The cut surface is predominantly solid, but it contains cysts of small to medium size. Most tumors are unilateral.

The macroscopic appearance of *clear cell carcinoma* is not specific. Most are cystic tumors with solid gray-tan nodules in their walls, or they are entirely solid. Bilaterality is uncommon in neoplasms that are confined to the ovaries (stage I), but it is seen in as many as 30% of cases when tumors of all stages are considered.

Microscopic Appearance. The diagnosis of a benign or LMP clear cell tumor should be made only after thorough histologic study, because clear cell carcinoma may contain bland areas. All *benign clear cell tumors* are adenofibromas. Small cysts or tubules lined by clear or hobnail cells are uniformly distributed within a fibrous stroma. Neither cytologic atypia nor mitotic activity is present.[89,151,192] The *clear cell tumor of LMP* is an adenofibromatous neoplasm.[73,89,134,192] It is composed of tubules that are distributed irregularly in a fibrous stroma. The tubules are lined by a multilayered or tufted epithelium, or there is modest mitotic activity and mild or moderate nuclear atypia. Areas of benign clear cell adenofibroma frequently are admixed.[89] There is no evidence of stromal invasion. Clear cell tumors that exhibit marked nuclear atypia or contain many mitotic figures are best classified as clear cell carcinoma, even if stromal invasion is not recognized.

Clear cell carcinoma contains clear cells and hobnail cells (Figs. 6-51 and 6-52).[176,187-189,191,193-195] One or the other may predominate, or both cell types may be prominent. The clear cells are polygonal, with abundant clear cytoplasm and central vesicular nuclei. Hobnail cells are columnar cells with granular eosinophilic or clear cytoplasm and apical nuclei that project into the lumina (see Fig. 6-51). Rare clear cell carcinomas are composed predominantly of polygonal cells with abundant eosinophilic (so-called oxyphilic) cytoplasm.[196] The growth pattern may be tubular, papillary, solid, or, frequently, mixed (see Fig. 6-52). The clear cells contain abundant glycogen, which is recognizable with special staining procedures (diastase-labile periodic acid-Schiff stain positivity).

Ultrastructurally, the cells have irregular short microvilli that contain filaments. The cells are joined by desmosomes. The dominant electron microscopic feature is the presence of abundant cytoplasmic gly-



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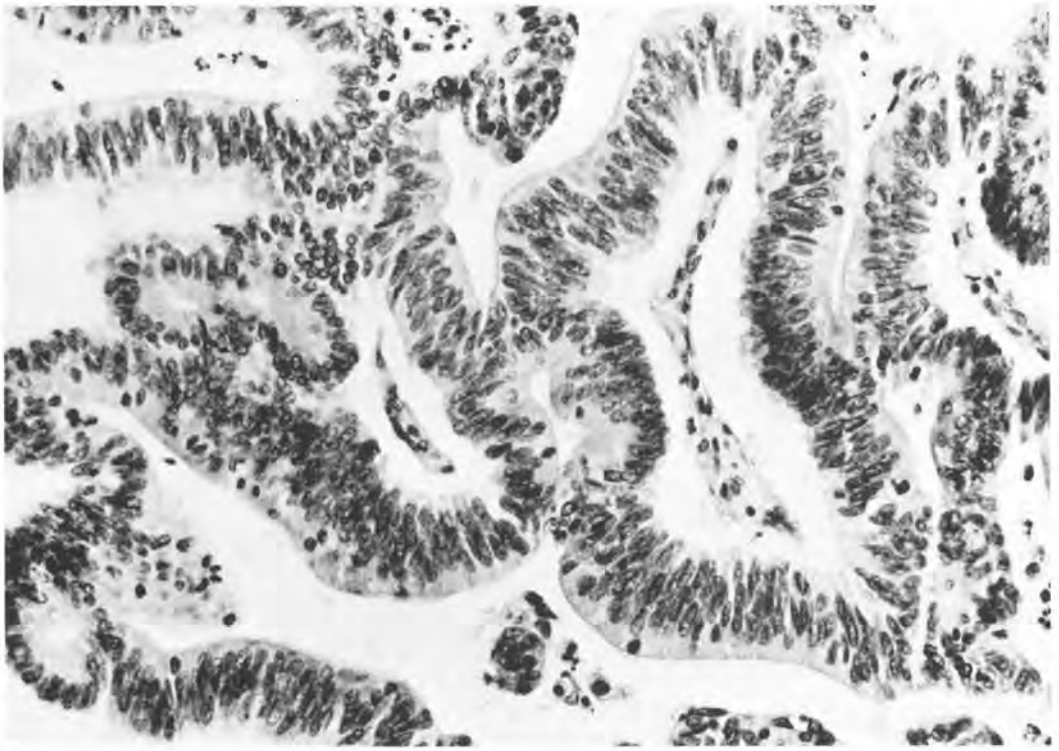

B

FIGURE 6-50 Endometrioid carcinoma of ovary. **(A)** Villoglandular pattern (compare with Fig. 6-36). **(B)** Detail showing orientation of cells perpendicular to basement membrane.

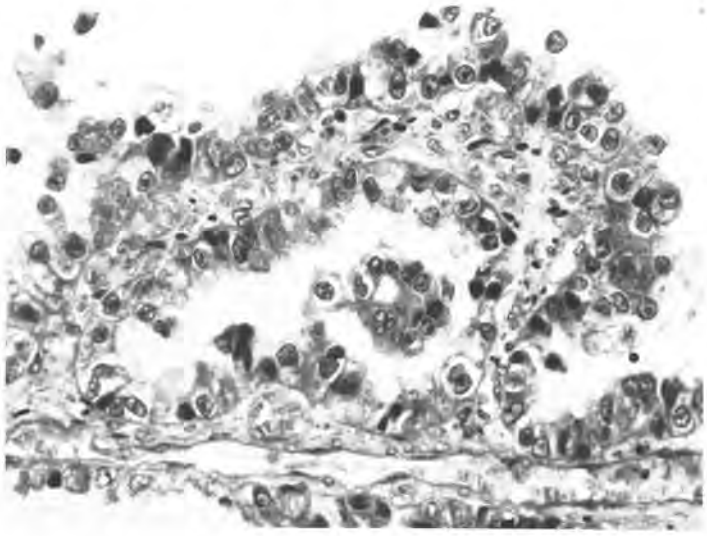

FIGURE 6-51 Clear cell carcinoma, showing clear and hobnail cells.

cogen.[197–199] The cytoplasm also contains a modest amount of rough endoplasmic reticulum, which may be stacked, and ribosomes and polyribosomes are readily identified. The Golgi is well developed, and the cytoplasm contains small mitochondria and, occasionally, bundles of microfilaments. The nuclei are irregular and round or oval. The nucleoli are prominent and homogeneous.

Differential Diagnosis. Clear cell carcinoma was confused with yolk sac tumor for many years. This differential diagnosis is crucial, however, because the treatments are different. *Yolk sac tumor* typically occurs in women younger than 30 years, whereas clear cell carcinoma occurs in women with an average age of 50 to 55 years. Serum levels of α-fetoprotein are elevated in patients with yolk sac tumor, but not in those with clear cell carcinoma. There typically is greater cytologic atypia and mitotic activity in a yolk sac tumor, which often contains areas of embryonal stroma. Immunohistochemical staining, particularly for α-fetoprotein and α_1-antitrypsin, is helpful.[200] *Renal cell carcinoma,* which typically has a clear cell appearance, rarely metastasizes to the ovary and is not a practical diagnostic consideration.[201]

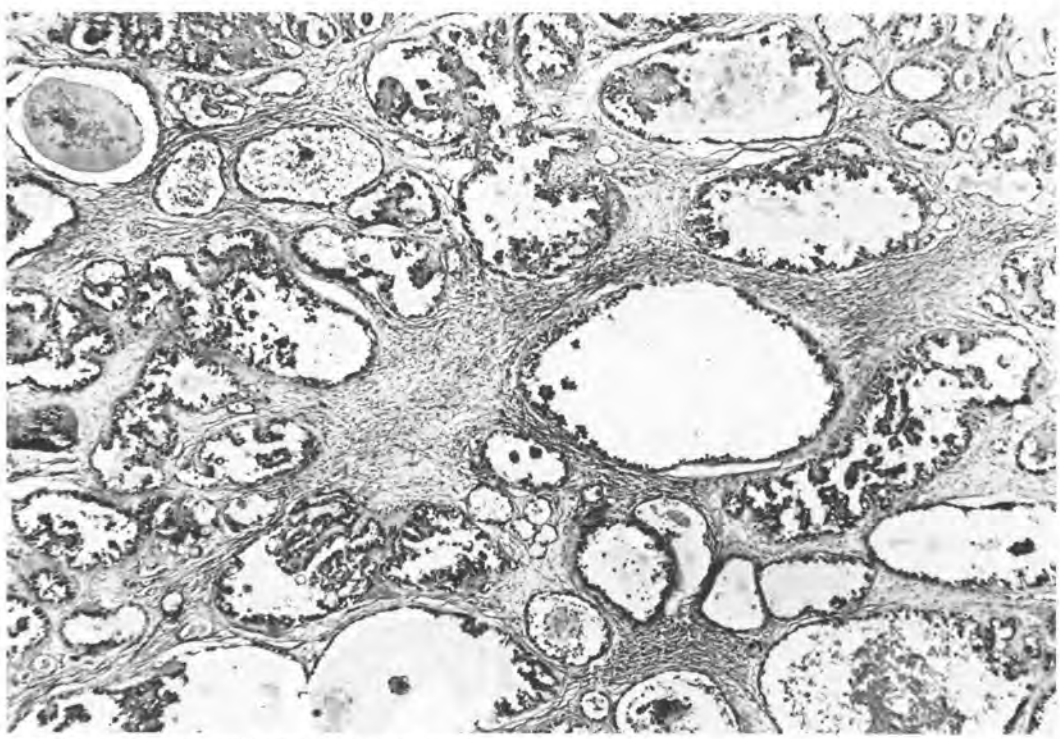

FIGURE 6-52 Clear cell carcinoma growing in a tubulocystic pattern.

Brenner Tumor and Transitional Cell Carcinoma

The Brenner tumor is a solid or partially cystic fibroepithelial tumor composed of nests of transitional epithelial cells in a connective tissue stroma.[202–208] It is an uncommon but not rare tumor, comprising about 2% of all ovarian tumors. Many Brenner tumors are found during surgery for another gynecologic problem or at autopsy. About 20% are associated with a mucinous cystadenoma or other epithelial tumor. Most Brenner tumors are benign, but intermediate (eg, proliferating or LMP) and malignant Brenner tumors can occur.[90–93,209–212] A malignant tumor composed of transitional epithelium within which no residual benign Brenner tumor can be identified is termed a *transitional cell carcinoma of the ovary*.[213]

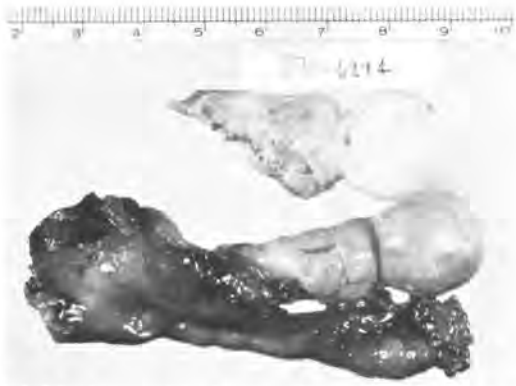

FIGURE 6-53 External and cut surface of a Brenner tumor.

Macroscopic Appearance. The typical *benign Brenner tumor* is a unilateral, firm, fibrous tumor that is pale yellow or light gray; it resembles a fibroma (Fig. 6-53). Occasionally, the tumor is cystic, and about 5% of Brenner tumors are bilateral.[214] Most of these tumors are 1 to 2 cm in diameter, but they can measure more than 10 cm. The Brenner tumor is usually found alone in the ovarian parenchyma but may occur in the wall of a mucinous cystadenoma or in association with a benign cystic teratoma.

Intermediate Brenner tumors are 8 to 28 cm in diameter, with an average size of 14 cm. Some are entirely solid, but most are partly or mainly cystic, with white or tan solid areas in their walls and polypoid or papillary masses projecting into the cyst lumens. The *malignant Brenner tumor* ranges from 5 to 22 cm in diameter, with an average diameter of 15 cm. Most are partly cystic. The solid areas are gray, yellow, or tan and often contain calcifications.

Microscopic Appearance. The *benign Brenner tumor* contains nests and cords of large polyhedral epithelial cells that resemble urothelial cells (Fig. 6-54). Some cells have clear cytoplasm and elongated, grooved nuclei, whereas others have a squamoid appearance, with a suggestion of cytoplasmic keratinization. Occasionally, the transitional cell nests are cystic, and some are lined by metaplastic columnar mucinous cells (Fig. 6-55). The epithelial cells in the Brenner tumor are similar to those seen in the Walthard's cell rest, which is a coelomic inclusion

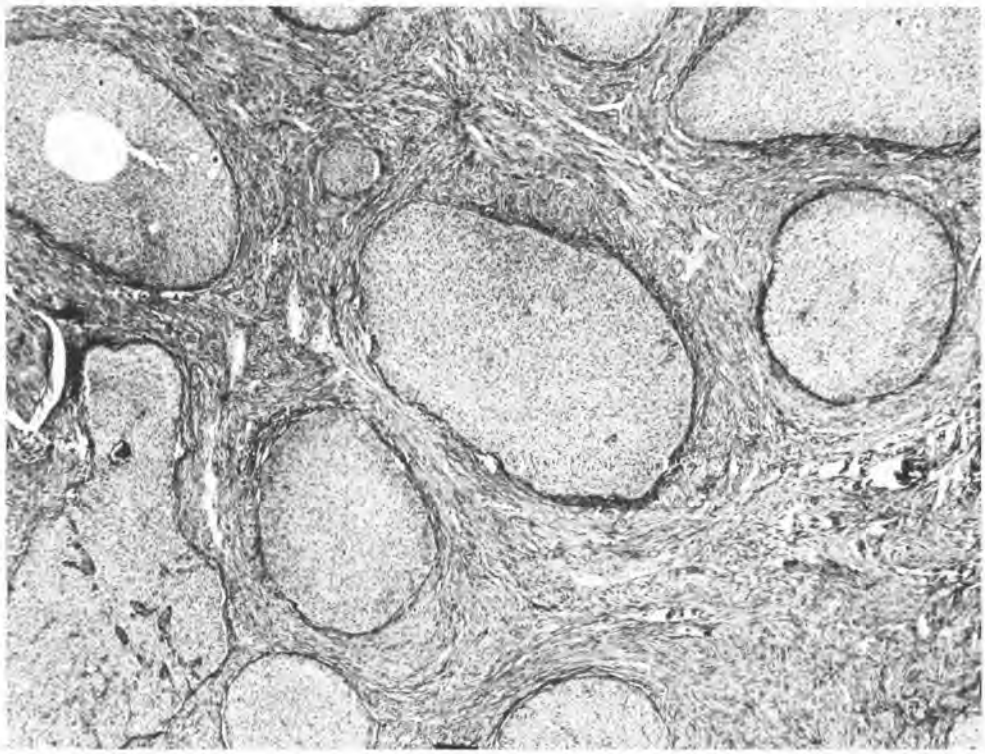

FIGURE 6-54 Brenner tumor. Nests of transitional epithelium are surrounded by fibrous stroma.

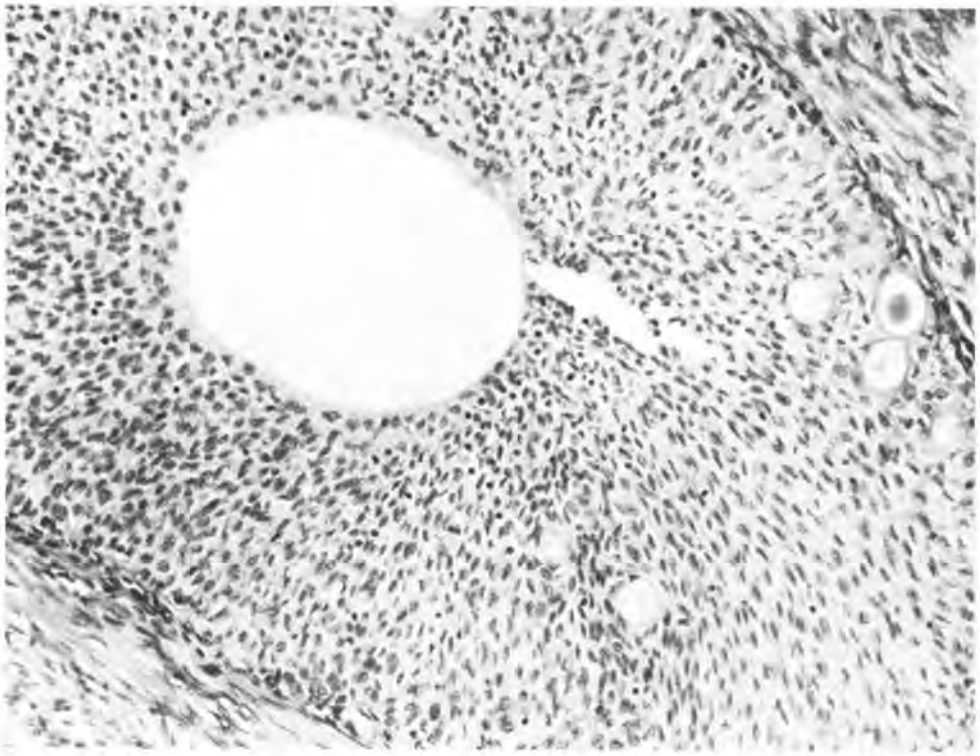

FIGURE 6-55 Brenner tumor. Nest of transitional epithelium with a central cystic space lined by columnar cells.

found uncommonly beneath the surface epithelium of the ovary and more frequently in the fallopian tube or the broad ligament (Fig. 6-56).[215,216] The nests of epithelial cells are dispersed in a fibrous stroma that contains fascicles of collagen fibers and, occasionally, luteinized stromal cells.

Intermediate Brenner tumors exhibit proliferative activity and resemble noninvasive papillary transitional cell carcinoma of the urinary bladder. The *proliferating Brenner tumor* resembles a low-grade papillary transitional cell carcinoma of the urinary bladder.[90–93] The papillary stalks are composed of delicate fibrovascular cores covered by stratified polygonal cells with uniform, slightly atypical nuclei. Mitotic figures are present but usually are not numerous. There may be marked epithelial proliferation, but it is entirely circumscribed or intracystic, and stromal invasion is not present (Fig. 6-57). Benign Brenner tumor is identified adjacent to or admixed with most proliferating Brenner tumors. Some researchers suggest that a *Brenner tumor of LMP* should be differentiated from the proliferating Brenner tumor on the basis of greater cytologic atypia in the former.[93] There are no significant clinical or macroscopic differences between these types of intermediate Brenner tumor, and the validity of the subdivision is unproved.

Malignant Brenner tumor resembles a high-grade transitional cell carcinoma of the bladder.[91,210–212,217] The tumor cells have pleomorphic, atypical nuclei, and the malignant transitional epithelium infiltrates the stroma (Fig. 6-58). Squamous and glandular differentiation is common in malignant Brenner tumor, and calcifications are noted in most. Benign or proliferating Brenner tumor must be identified in or adjacent to these carcinomas for a diagnosis of malignant Brenner tumor. *Transitional cell carcinoma* of the ovary is indistinguishable in appearance from malignant Brenner tumor, except that benign or proliferating Brenner tumor is not present.[210] The distinction between malignant Brenner tumor and transitional cell carcinoma has clinical significance. Transitional cell carcinoma exhibits more aggressive biologic behavior but is more likely to respond to chemotherapy.[213] The microscopic appearance of the metastases is important in transitional cell carcinoma because the presence of nontransitional cell types of carcinoma, such as serous carcinoma, is associated with an unfavorable outcome.[213]

Undifferentiated Carcinoma

These predominantly solid tumors constitute 5% to 10% of ovarian cancers.[218] They are characterized by the growth of poorly differentiated glands, large nests or sheets of pleomorphic epithelial cells (Fig. 6-59), or small nests, cords, or single files of malignant cells disseminated in an abundant fibrous stroma. Marked cellular atypia, bizarre giant cells, and atypical mitoses are frequent. The carcinoma is too poorly differentiated to be recognized as one of the specific types described above. Undifferentiated carcinoma grows rapidly, and there is usually extraovarian spread at the time of diagnosis. These neoplasms have the poorest prognosis of any surface epithelial carcinoma of the ovary (5-year survival is 10% or less).

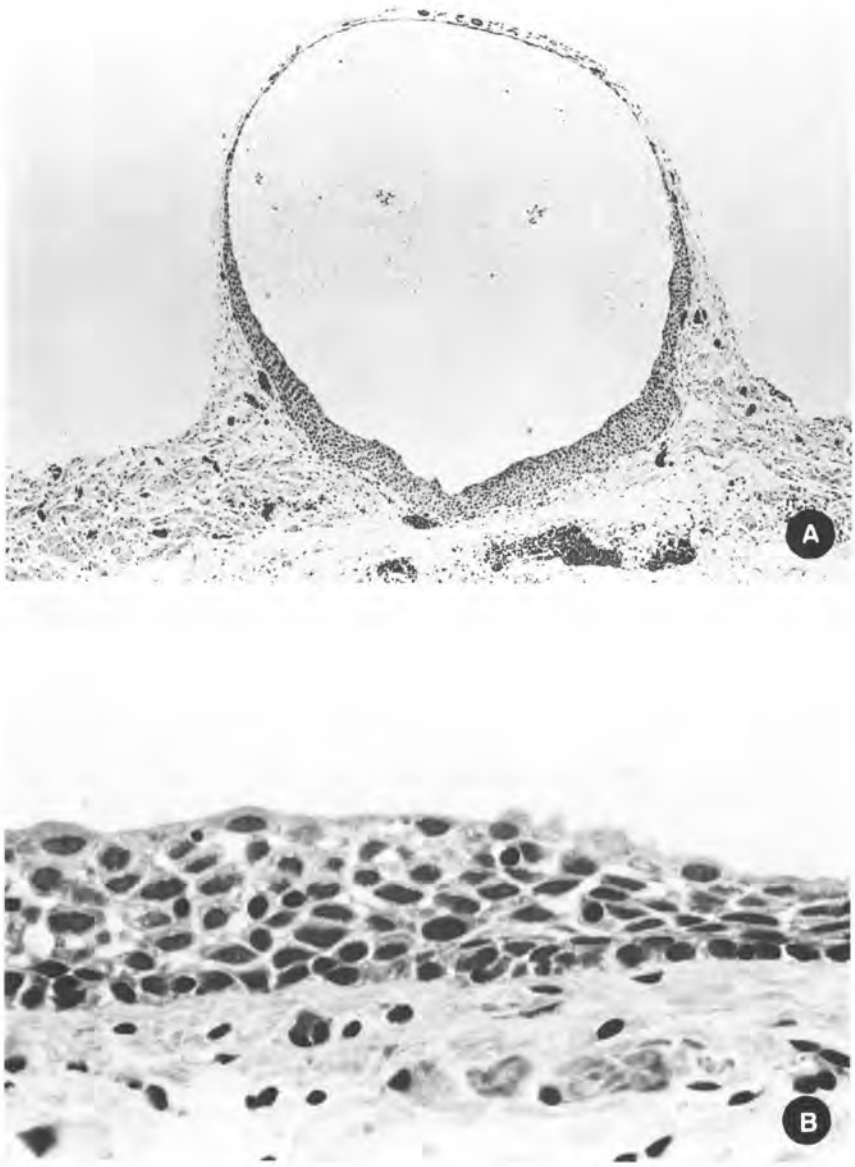

FIGURE 6-56 **(A)** Cystic Walthard cell rest in tubal serosa lined by transitional epithelium. **(B)** Detail of lining epithelium.

Carcinosarcoma, Adenosarcoma, and Endometrial Stromal Sarcoma

Carcinosarcoma (malignant mixed mesodermal tumor) and endometrial stromal sarcoma arise by neometaplasia or from endometriosis and accordingly are classified with the neoplasms of surface epithelial origin. Their clinical behavior is similar to that of their more frequent uterine counterparts, and they are discussed in more detail in Chapter 4.

Carcinosarcoma is found predominantly in postmenopausal women who present with pelvic pain, abdominal distention, or weight loss.[219–229] An adnexal mass is generally palpable, and a significant percentage of patients have ascites. At operation, more than 80% of the tumors have spread beyond the ovary, and bilateral ovarian involvement is common. The tumor is large, with an average diameter of 15 cm. The most typical appearance is that of a cyst with solid gray or tan mural nodules, but some tumors are completely solid. Hemorrhage and necrosis frequently are present. Microscopically, carcinosarcoma is a biphasic neoplasm that has epithelial and mesenchymal components (Color Figure 6-7). The epithelial component can be any type of surface epithelial carcinoma, but serous, endometrioid, and undifferentiated carcinoma are most frequent. The mesenchymal component is sarcomatous, and as a rule a mixture of several types of sarcoma is present. The types that are most common are fibrosarcoma, endometrioid stromal sarcoma, leiomyosarcoma, chondrosarcoma, and rhabdomyosarcoma. Immunohistochemical testing for cytokeratin and other epithelial markers helps identify the epithelial component in a predominantly mesenchymal neoplasm.[230,231] Immunostains for myoglobin and desmin help identify rhabdomyoblasts.[230–232] Women with carcinosarcoma of the ovary have a poor prognosis, and more than 75% of these women die within 1 year of diagnosis.

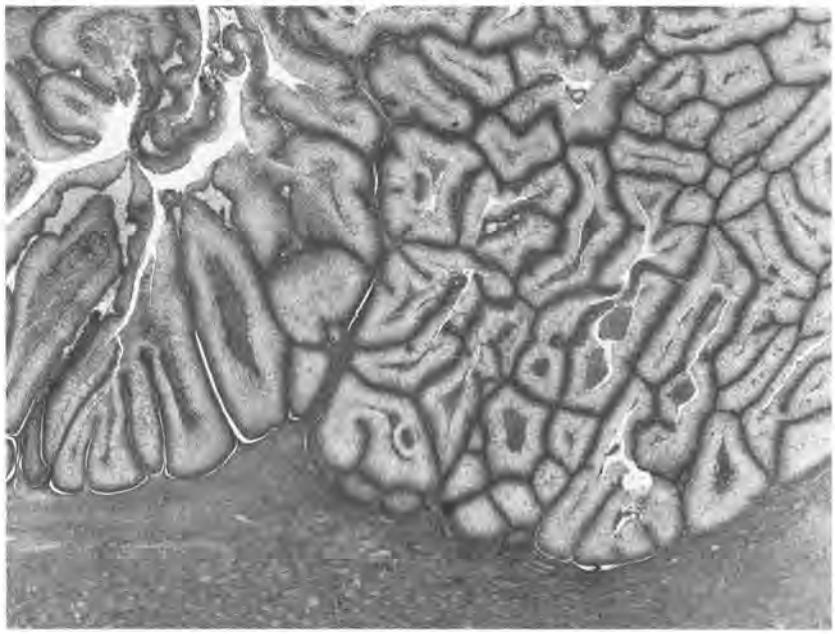

FIGURE 6-57 Proliferating Brenner tumor.

Carcinosarcoma may respond to combination chemotherapy, but the response is not durable.[233]

The *differential diagnosis* between carcinosarcoma and immature teratoma is important because the treatment and prognosis are different. Carcinosarcoma occurs in postmenopausal women, whereas immature teratoma arises in children and young women. Both tumors contain epithelium and mesenchyme, but these elements are adult and cytologically malignant in carcinosarcoma, and embryonal in teratoma.[225] Immature neuroepithelium, which is prominent in immature teratoma, is not observed in carcinosarcoma of the ovary.

Adenosarcoma of the ovary is an intermediate type of mixed mesodermal tumor. It has a sarcomatous mesenchymal component, but the epithelium is benign.[234,235] The stroma, which is fibrous or resembles endometrial stroma, is most cellular around the epithelium. Adenosarcoma is capable of local spread and metastasis, but most patients survive.[234,235]

Endometrial stromal sarcoma arises in women who average 54 years of age.[236,237] The main symptoms are abdominal swelling or pain. There is bilateral ovarian involvement in 50% of women with stromal sarcoma, extraovarian spread in nearly 80%, and pelvic endometriosis in a high proportion of cases. The tumors average 11 cm in diameter, and most are partly cystic or entirely solid. The cut surfaces are tan, yellow, or white, and hemorrhage or necrosis is often noted. Low-grade stromal sarcoma is composed of cells that resemble proliferative-phase endometrial stromal cells.[236,237] They have uniform round, oval, or spindled dark nuclei, inconspicuous nucleoli, and scanty cytoplasm with ill defined cell borders. Cytologic atypia is minimal, and mitotic figures are infrequent. Nests and cords of tumor cells infiltrate the ovarian parenchyma. Vascular invasion is prominent once the tumor invades beyond the ovary. High-grade stromal sarcoma is composed of cells that are more atypical and generally exhibit greater mitotic activity.[237] Women with low-grade stromal sarcoma have a relatively favorable prognosis, even when there is extraovarian spread.[237] The value of treatment with progesterone, radiation therapy, or chemotherapy is unclear, although beneficial results are observed in some patients. High-grade stromal sarcoma pursues a more aggressive clinical course.

The main differential diagnosis is endometrial stromal sarcoma of the uterus metastatic to the ovary and thecoma. Endometrial stromal sarcoma of the uterus frequently invades the adnexa, including the ovary. Women with stromal sarcoma of the ovary often have stromal sarcoma of the uterus, and it is difficult to determine whether the tumor in the ovary represents a metastasis or a separate primary site. Certainly, any woman with stromal sarcoma of the ovary should undergo careful evaluation of the uterus, and hysterectomy should be part of the surgical treatment.[237] Low-grade stromal sarcoma of the ovary often contains fibrous areas that raise the question of thecoma. Thorough histologic evaluation reveals more typical areas of stromal sarcoma. Thecoma, unlike stromal sarcoma, is rarely bilateral and rarely associated with endometriosis, and it almost never infiltrates into ovarian stroma or veins.

Aspiration Biopsy Cytology of Epithelial Tumors

Ovarian tumors usually are not aspirated in the United States, for several reasons. Women with these neoplasms undergo laparotomy for diagnosis and treatment regardless of the results of aspiration. In

addition, there is concern that a cystic ovarian neoplasm may rupture or leak during or after aspiration. Nevertheless, ovarian masses occasionally are aspirated, and aspiration cytology can be useful in the follow-up of patients with malignant tumors.[238–241]

Aspirates from benign epithelial tumors are usually of low cellularity. They contain occasional sheets or papillary clusters of cohesive epithelial cells with uniform normochromatic nuclei and a variable amount of cytoplasm (Color Figure 6-8). Ciliated cells are observed in aspirates from women with serous tumors. The cells from mucinous tumors have a honeycomb arrangement when seen on end, and they contain mucin vacuoles (Color Figure 6-9).

Malignant tumors yield more cellular aspirates. In serous carcinoma, papillary clusters, irregular sheets and balls of cells, and loosely cohesive groups of cells are seen (Color Figure 6-10). The nuclei are large, hyperchromatic, and more variable than in benign neoplasms. Mucinous carcinoma is characterized by irregular clusters of cells with hyperchromatic, atypical nuclei and variably sized cytoplasmic mucin vacuoles. Recognizable glands are often identified in aspirates from endometrioid carcinoma, and foci of squamous differentiation may be present (Color Figure 6-11). Aspirates from clear cell carcinoma contain polygonal cells with abundant clear or granular eosinophilic cytoplasm.

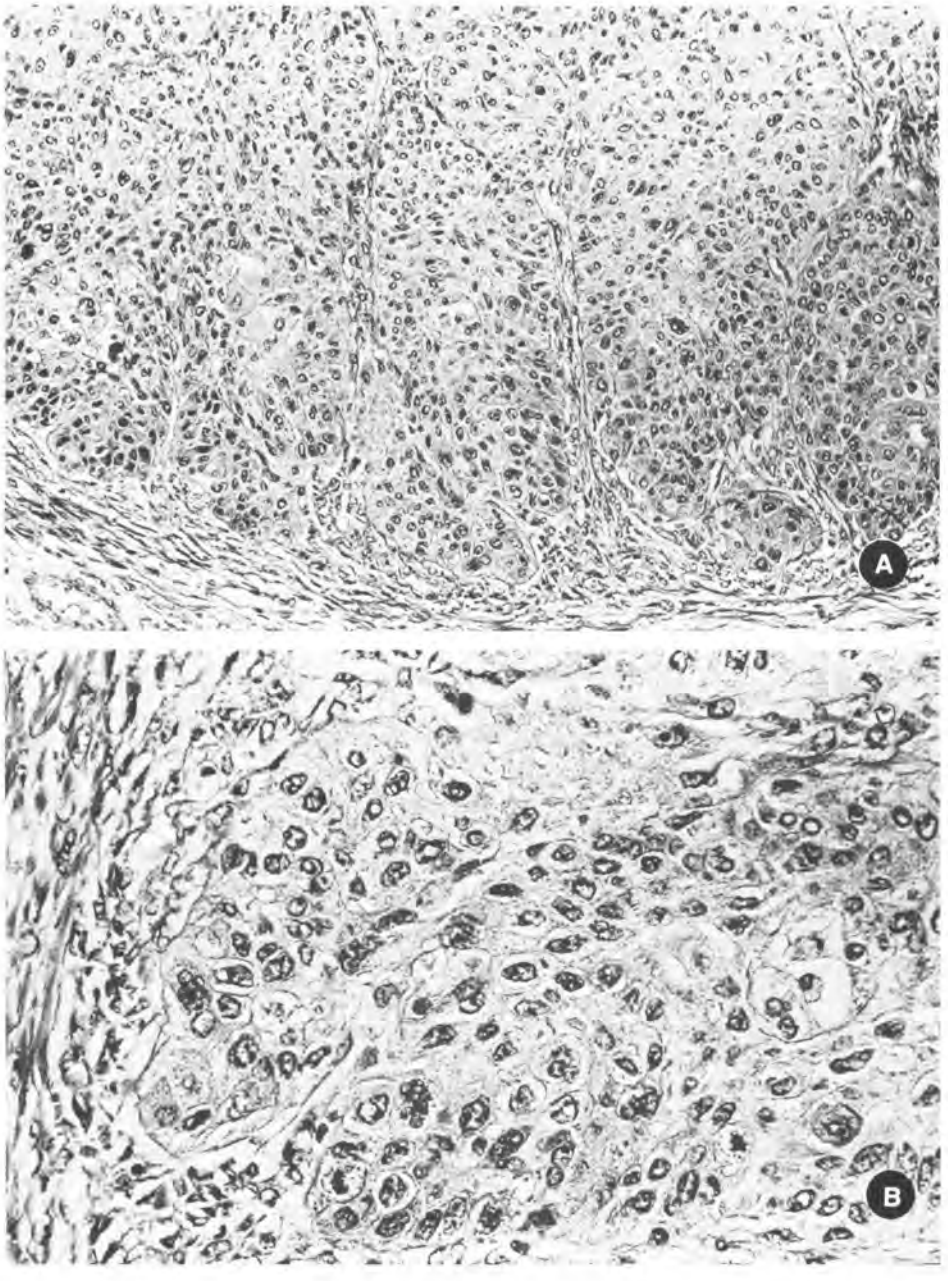

FIGURE 6-58 **(A)** Malignant Brenner tumor. Cytologically malignant transitional epithelium invades the ovarian stroma. **(B)** Detail of malignant cells.

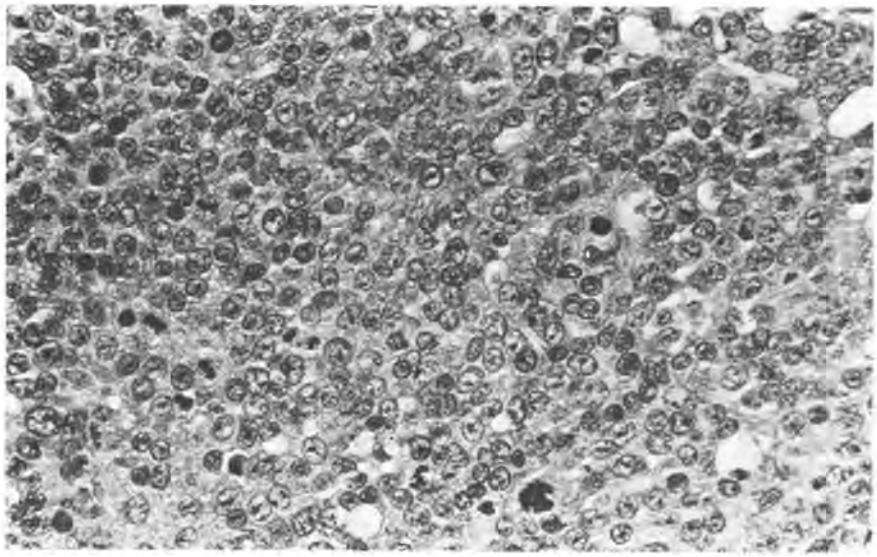

FIGURE 6-59 Undifferentiated carcinoma. This sheet of malignant epithelial cells has no specific pattern of differentiation.

Sex Cord/Stromal Tumors

The neoplasms discussed in this section are derived from the sex cords or ovarian mesenchyme (Table 6-5). They comprise 5% to 12% of all ovarian neoplasms.[242–244] The benign tumors in the fibroma-thecoma group are common. Other sex cord stromal tumors and mesenchymal tumors are uncommon or rare. The most frequent malignant ovarian sex cord stromal tumor is the granulosa cell tumor.

Adult Granulosa Cell Tumor

Granulosa cell tumor is the most common malignant sex cord stromal tumor. It constitutes 1% to 2% of all ovarian tumors.[242,244,245] There are two histologic types of granulosa cell tumor. The *adult type,* discussed in this section, is the most frequent. It develops almost exclusively in women who are 20 years of age or older. The *juvenile granulosa cell tumor,* discussed in the next section, occurs mainly in children, but occasional cases are observed in mature women.

Clinical Findings. Adult granulosa cell tumors occur in women 15 to 80 years of age. The average patient age is about 52 years, and more than half are postmenopausal.[246–250] Granulosa cell tumors occasionally are detected in pregnant women (in about 1% to 2% of cases).[246,248,251] Postmenopausal bleeding is the most frequent symptom in older women. Premenopausal women generally have disturbances of menstruation, such as menorrhagia, metrorrhagia, or amenorrhea. There is a relation between estrogen-producing tumors of the ovary and endometrial hyperplasia and carcinoma. A third or more of women with granulosa cell tumors of the ovary have endometrial hyperplasia.[246,249,250] Endometrial adenocarcinoma, which is usually well-differentiated and superficial, is detected in 2% to 13% of patients.[248–250,252] About 25% of patients have only nonspecific symptoms such as abdominal distention or abdominal pain. Acute abdominal symptoms caused by rupture or torsion of the tumor occur in 5% to 10% of cases.[250] The duration of symptoms is 6 months or less in half of the patients.[252] An adnexal mass is palpable in 60% of women with granulosa tumors. Many novel substances have been detected in the serum of patients with granulosa cell tumors, including müllerian-inhibiting substance,[253] inhibin,[254] and follicle regulatory protein.[255] One or

TABLE 6-5
Sex Cord/Stromal Tumors

Granulosa cell tumor
Adult type
Juvenile type
Thecoma-fibroma group
Thecoma
Typical
Luteinized
Fibroma
Typical
Cellular
Fibrosarcoma
Fibrothecoma
Stromal tumor with minor sex cord elements
Sclerosing stromal tumor
Sertoli cell tumor
Sertoli-Leydig cell tumor
Well differentiated
Intermediate differentiation
Poorly differentiated
Retiform
. . . with heterologous elements.
Sex cord tumor with annular tubules (SCTAT)
Gynandroblastoma
Lipid cell (steroid cell) tumor
Unclassified
Stromal luteoma
Leydig cell tumor
Soft tissue tumor not specific to ovary
Unclassified

more of these may prove to be a useful tumor marker.

Rarely, granulosa cell tumors produce androgenic hormones that cause varying degrees of virilization.[249,251,256–258] Androgenic granulosa cell tumors occur at all ages, but 70% occur in women 15 to 35 years of age.[257] The most frequent symptoms caused by androgenic granulosa tumors are hirsutism, enlargement of the clitoris, deepening of the voice, and amenorrhea.

Eighty to 90% of granulosa cell tumors are confined to the ovary (stage I) at the time of diagnosis.[248,250,252] Bilateral tumors are uncommon (<5%). Extraovarian spread, when observed, is to the peritoneum and liver.[249,259]

Macroscopic Appearance. Granulosa cell tumors vary from small, incidentally discovered nodules a few millimeters in diameter to large neoplasms 30 cm or greater in diameter. Granulosa cell tumors may be entirely solid, but most are partly or largely cystic (Color Figure 6-12). The solid areas are pink, tan, brown, or light yellow and can be firm or soft. Zones of necrosis and hemorrhagic regions are frequent. The cysts typically contain clear or yellow fluid, but intracystic hemorrhage is common. Rare granulosa cell tumors are very large and entirely cystic with a thin tan wall. An increased proportion of such tumors are androgenic.[257,258]

Microscopic Appearance. The neoplastic cells resemble normal granulosa cells. They are small, round, cuboidal, or fusiform and are uniform in size. The nuclei are round or oval and hyperchromatic, and they frequently have longitudinal grooves and a single nucleolus (Figs. 6-60 and 6-62*B*). The cytoplasm is pale, and cell borders are ill defined. Luteinized cells with abundant eosinophilic cytoplasm are present in some neoplasms, particularly in those that occur in pregnant women and in those that cause androgenic symptoms.[257,260] Mitotic figures, nuclear pleomorphism, and atypia are uncommon.

The varied histologic appearance of these neoplasms is due to the arrangement of the tumor cells. Many patterns have been described, but they frequently are mixed and have no prognostic significance. The *microfollicular* pattern is most typical (see Fig. 6-60). Cuboidal or cylindrical granulosa cells grow around small spaces (Call-Exner bodies) that contain eosinophilic material and cellular debris. The Call-Exner bodies are distributed among cords and sheets of granulosa cells. The *macrofollicular* pattern is composed of variably sized follicles lined by stratified granulosa cells. The *trabecular* pattern contains long simple or stratified cords of granulosa cells surrounded by stroma (Fig. 6-61). The *insular* pattern is distinguished by nests and islands of granulosa cells within the stroma. The cells grow in disorganized sheets in the *solid* or *diffuse* pattern (Fig. 6-62), whereas they form irregular undulating cords in the *gyriform* or *watered-silk pattern.* Granulosa cell tumors contain a variable amount of fibrothecomatous stroma, which has no effect on the clinical behavior of the tumor.

Immunocytochemical studies reveal that neoplastic granulosa cells react with antibodies to vimentin.[261–264] The results with antikeratin antibodies depend on the antibody that is used. A negative reaction generally is obtained with polyclonal antibodies, but monoclonal antibodies against the low-molecular-weight cytokeratins 8 and 18 (Cam 5.2, AE1/3) are positive in 30% to 60% of granulosa tumors.[261–264] Of the positive tumors, about half are diffusely positive, and the other half contain only focally reactive cells. Other antibodies that are reported to react with granulosa cell tumors are desmoplakin (in frozen sections) and S-100 protein.[261,265] Granulosa cell tumors give a negative reaction with antibodies to epithelial membrane antigen, carcinoembryonic antigen, monoclonal antibody B72.3, and neuron-specific enolase.[261,263]

Electron microscopic study discloses that the tumor cells have hyperchromatic nuclei. The cytoplasm contains numerous intermediate filaments, ribosomes, and round or elongated mitochondria. The Golgi complex is well developed, and there are many desmosomes between the tumor cells. Scattered cells contain mitochondria with tubular cristae, smooth endoplasmic reticulum, and lipid droplets.[265–267] The latter cells probably are the site of hormone production.

More than 80% of granulosa cell tumors are diploid.[248,268–270] Ploidy analysis does not appear to provide significant prognostic information.[268,270,271] Karyotype analysis of several granulosa cell tumors and other types of stromal tumors revealed trisomy 12.[272,273] Additional tumors need to be studied to verify that this finding is characteristic of granulosa cell tumor.

The cytology of granulosa cell tumor is similar in peritoneal fluid specimens and aspirates.[274–278] The nuclei are small, round or oval, and hyperchromatic. Some nuclei have longitudinal grooves, and most contain small nucleoli. The cells typically have scanty amphophilic cytoplasm. Smears prepared from aspirates are hypercellular and contain clumps of cells and individual cells (Color Figure 6-13). Microfollicular structures are a helpful diagnostic feature if present.

Differential Diagnosis. The differential diagnosis includes undifferentiated carcinoma, malignant lymphoma, primary or metastatic carcinoid, small cell carcinoma, and granulosa cell proliferations of pregnancy. *Metastatic adenocarcinoma* and *primary undifferentiated carcinoma* are the neoplasms most frequently misdiagnosed as granulosa cell tumor. Carcinoma cells have large, atypical, pleomorphic nuclei, and mitotic figures are frequent. Because most granulosa cell tumors are DNA diploid, the presence of a DNA aneuploid cell population should prompt consideration of a carcinoma.[271] Mucin often can be

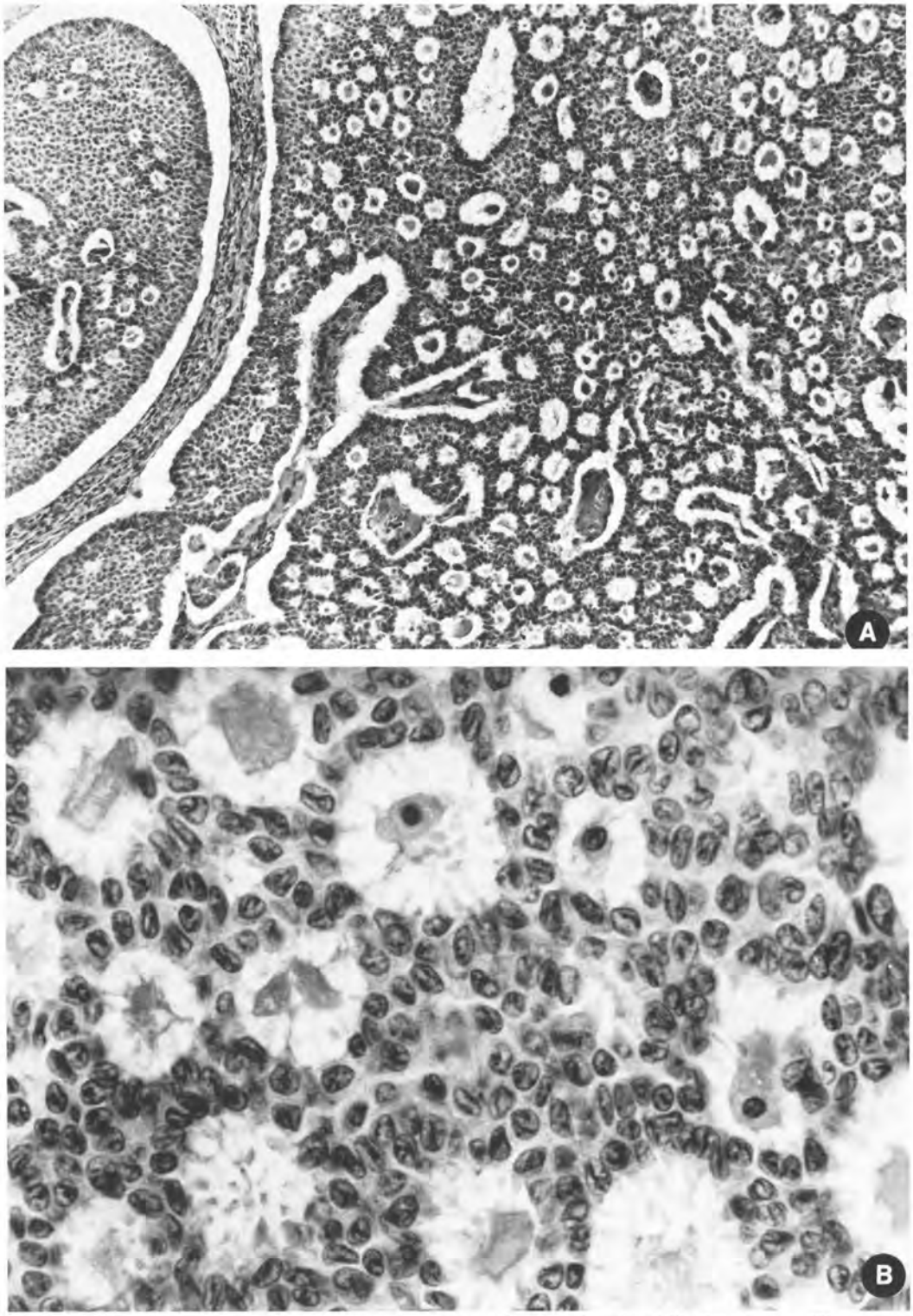

FIGURE 6-60 **(A)** Granulosa cell tumor growing in a predominantly microfollicular pattern. **(B)** High magnification view showing Call-Exner bodies and tumor cells with characteristic grooved nuclei.

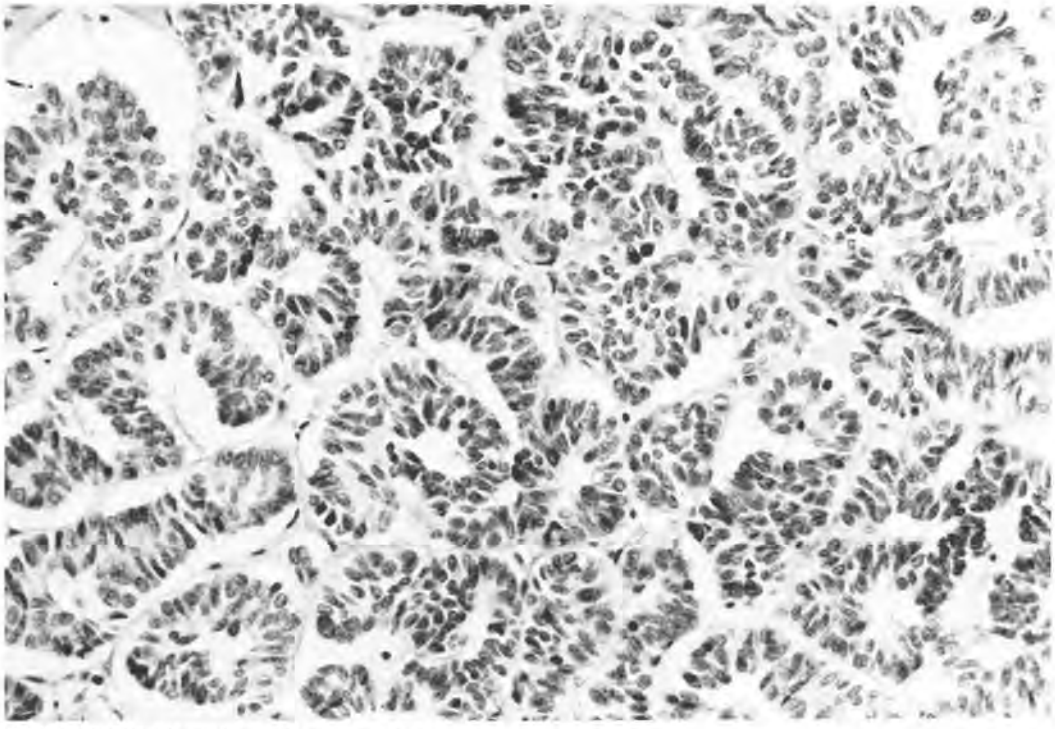

FIGURE 6-61 Granulosa cell tumor: trabecular pattern.

identified in carcinoma cells or glands with appropriate special stains. Carcinoma cells have a different immunophenotype than granulosa cells. Carcinoma cells typically give a positive reaction with cytokeratin, epithelial membrane antigen, monoclonal antibody B72.3, and carcinoembryonic antigen, and may be vimentin negative. Adult granulosa cell tumors may exhibit cytokeratin positivity and generally are vimentin positive, but they do not react with the other antibodies.

Lymphoma can mimic a granulosa cell tumor growing in a diffuse pattern. Lymphoma usually is bilateral, and typically there is extensive extraovarian disease. Lymphoma cells are noncohesive and lack nuclear grooves. They have coarser nuclear chromatin than granulosa cells. Immunostains for cytokeratin and vimentin are negative, whereas those for leukocyte common antigen and other hematopoietic antigens are positive.

Carcinoid tumors have small, round, dense nuclei, instead of the ovoid, grooved nuclei typical of granulosa cells. The neurosecretory granules in their cytoplasm can be identified by argentaffin or argyrophil stains or by electron microscopy. Immunostains for chromogranin are positive. Primary ovarian carcinoids are unilateral, homogeneous, and often associated with other teratomatous elements. Metastatic carcinoids usually are bilateral and multinodular.

Small cell carcinoma of the ovary resembles granulosa cell tumor because it grows in a diffuse pattern and may contain macrofollicles. It occurs in a younger population than does adult granulosa cell tumor (nearly all patients are younger than 40 years), and patients with small cell carcinoma often have hypercalcemia. The tumor cell nuclei are not grooved and are more variable and hyperchromatic than they are in granulosa cell tumor. Mitotic figures are more frequent. Except for the macrofollicles, none of the typical patterns of granulosa cell tumor is present. The immunohistochemical features overlap with granulosa cell tumor, but there is a greater percentage of cytokeratin positivity, and many small cell carcinomas are neuron-specific enolase or chromogranin positive.

Granulosa cell proliferation in the ovary of a pregnant woman can resemble a small adult granulosa cell tumor.[279] Such proliferations are small, multifocal, confined to the antrum of an atretic follicle, and do not exhibit the typical morphology of a granulosa cell tumor in pregnancy.[260] For the differential diagnosis with *Sertoli-Leydig cell tumor,* see the section on that tumor.

Clinical Behavior and Treatment. The standard treatment for granulosa cell tumor is total abdominal hysterectomy and bilateral salpingo-oophorectomy. Unilateral salpingo-oophorectomy is acceptable treatment for young women with stage IA neoplasms if conservation of fertility is wanted. In one series, however, several women treated by unilateral salpingo-oophorectomy had a recurrence in the female genital tract at a site that would have been removed by hysterectomy and bilateral salpingo-oophorectomy.[248] It is unclear how many of these were really

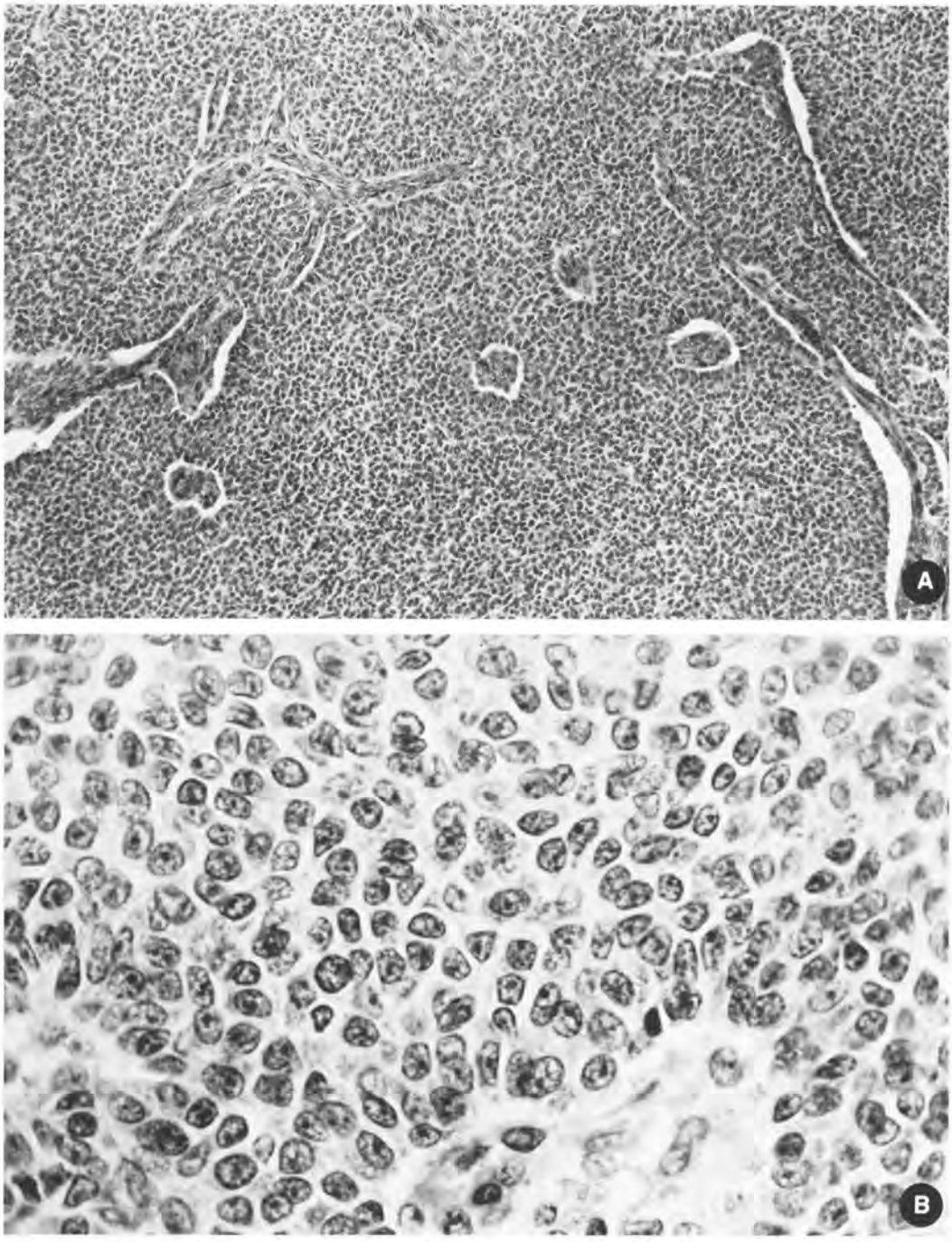

FIGURE 6-62 Granulosa cell tumor: solid or diffuse pattern of growth. **(A)** Low-power magnification. **(B)** Detail.

granulosa cell tumors. Neither adjuvant chemotherapy nor postoperative radiation therapy is administered to patients with stage IA granulosa cell tumors. Metastases are almost uniformly intra-abdominal, and, because of the slow growth rate of these neoplasms, surgical excision is the most appropriate treatment. About two thirds of patients with advanced or recurrent granulosa cell tumor respond to chemotherapy with cisplatin, doxorubicin, and cyclophosphamide or a similar regimen, but long-term complete remissions are unusual.[280] The effectiveness of radiation therapy in the treatment of advanced or recurrent disease is unclear, but it is frequently advocated.[248,250]

All granulosa cell tumors should be regarded as neoplasms of LMP, although most have a benign clinical evolution. Overall, 20% to 30% of adult granulosa cell tumors recur.[247–250] The recurrence rate is about 10% for stage IA tumors.[247] When intra-abdominal spread is present at diagnosis (stage

III), about two thirds of the patients die of tumor.[247,248] Granulosa cell tumors grow slowly, and metastases frequently are detected more than 5 years after initial treatment.[248,250] Disease-free intervals of more than 20 years followed by recurrence are not rare.

The prognosis is difficult to determine, but some pathologic features correlate with clinical outcome.[247,249,250] Large tumors (greater than 15 cm in diameter), bilateral tumors, and those that have ruptured or spread beyond the ovary have a less favorable prognosis. Granulosa cell tumors with moderate or marked atypia or with more than 2 mitotic figures per 10 high-power fields are more likely to recur. There is no correlation between the microscopic pattern and the clinical outcome. The ploidy cannot be used to predict the prognosis.[268,270]

Juvenile Granulosa Cell Tumor

Less than 5% of granulosa cell tumors occur in children and teenagers. A few of these are similar to the granulosa cell tumor seen in adults,[281] but most have distinctive clinical and pathologic features and have been termed *juvenile granulosa cell tumors.*[281–285] Infrequent examples of juvenile granulosa cell tumor are found in women older than 18 years.

Clinical Findings. Juvenile granulosa cell tumors occur over a wide spectrum of patient ages. They have been described in a stillborn infant and in a 67-year-old woman.[281,282] The average patient age is 15 years, and most juvenile granulosa cell tumors occur in children.[281–285]

More than 75% of premenarchal girls with granulosa cell tumors have isosexual precocious pseudopuberty, as manifested by development of the breasts, growth of pubic and axillary hair, endometrial proliferation with anovulatory bleeding, and increased bone age. A vaginal smear typically shows estrogen effect. Older children have menstrual abnormalities, abdominal distention, or a palpable abdominal mass. An adnexal mass is palpable in more than 70% of patients. Occasional patients develop acute abdominal symptoms due to torsion or rupture of their tumors. At operation, juvenile granulosa cell tumors are unilateral, and more than 95% are confined to the ovary (stage I). The prognosis is worse for patients with positive peritoneal cytology (stage IC), so it is important to examine peritoneal washings for the presence of tumor cells. Juvenile granulosa cell tumors occasionally are found in patients with Ollier's or Maffucci's syndromes.[282,284,286,287]

Macroscopic Appearance. The tumors measure 2.5 to 30 cm in diameter; the average diameter is 12 cm. Most are solid with cystic areas, but some are entirely solid, and a small percentage are largely cystic. The solid areas are nodular and yellow or tan. Hemorrhage is seen in about half of the tumors, and necrosis in a few of them.

Microscopic Appearance. Many juvenile granulosa cell tumors have a lobulated or nodular appearance at low magnification. Macrofollicular and solid growth patterns dominate the histologic picture (Fig. 6-63). The macrofollicles are lined by one or more layers of neoplastic granulosa cells. The follicles are uniform in some tumors and irregular in shape and size in others. The neoplastic cells are large, with round, dark nuclei, and a variable amount of cytoplasm. Nuclear grooves usually are not seen in juve-

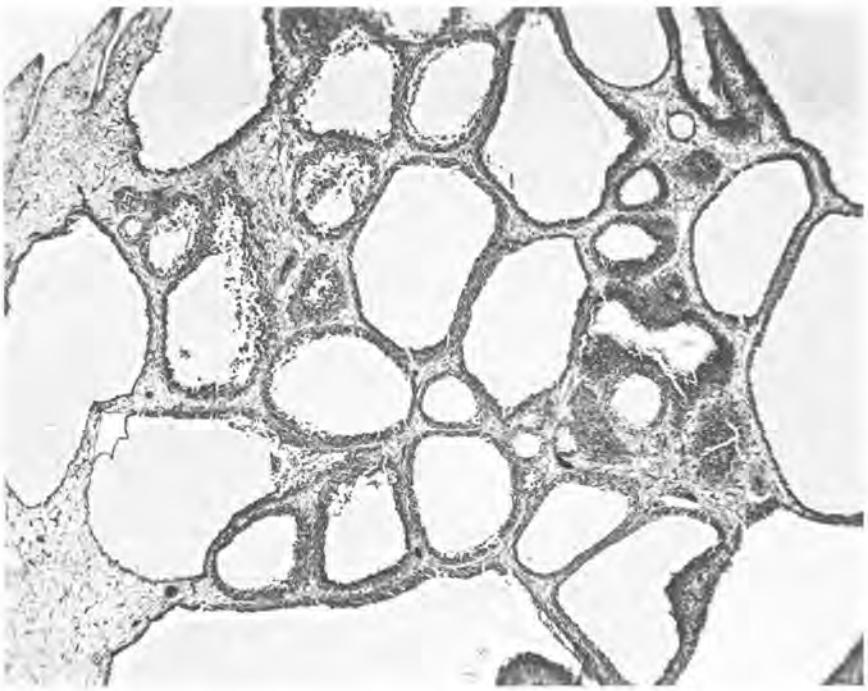

FIGURE 6-63 Juvenile granulosa cell tumor with a macrofollicular pattern of growth. (Zaloudek CJ, Norris HJ: Granulosa tumors of the ovary in children: A clinical and pathologic study of 32 cases. Am J Surg Pathol 6: 503–512, 1982)

nile granulosa cell tumors. Most neoplasms contain luteinized cells (Fig. 6-64). Cytologic atypia and mitotic activity are increased compared with adult granulosa cell tumors. There are an average of 6 mitotic figures per 10 high-power microscopic fields.

Few immunocytochemical studies have been performed on juvenile granulosa cell tumors. The tumor cells are vimentin positive and carcinoembryonic antigen negative.[261,285] Cells that react with antibodies against low-molecular-weight cytokeratins and neuron-specific enolase are found in about 50% of juvenile granulosa cell tumors.[261,285]

Ultrastructurally, the cytoplasm of nonluteinized tumor cells contains rough endoplasmic reticulum, free ribosomes, small mitochondria, and inconspicuous smooth endoplasmic reticulum. The cells are joined by immature desmosomal attachments. Other cells contain organelles associated with steroid production, including large mitochondria (some with tubular cristae), abundant smooth endoplasmic reticulum, and large lipid droplets.

Tumor cell DNA content does not appear to correlate with clinical behavior. About 40% of juvenile granulosa cell tumors contain an aneuploid cell population, but the clinical outcome is equally favorable in diploid and aneuploid tumors.[288]

Cytologic study reveals granulosa cells in aggregates, singly, or in irregular clusters.[289] The nuclei are central and have fine chromatin and small nucleoli. Nuclear grooves are absent. There is a moderate amount of granular cytoplasm.

Differential Diagnosis. The main differential diagnostic considerations are adult granulosa cell tumor and small cell carcinoma. In the first case, the age of the patient is helpful, because *adult granulosa cell tumors* occur in older patients. Juvenile tumors are composed of larger, more pleomorphic granulosa cells, and there is greater nuclear atypia and mitotic activity. Luteinized cells are more frequent in juvenile granulosa cells. At low magnification, juvenile granulosa cell tumor has a lobulated or nodular growth pattern that is not seen in adult tumors. Finally, the typical patterns observed in adult granulosa cell tumors are not seen in juvenile tumors, in which macrofollicular and diffuse patterns dominate. There are many similarities between *small cell carcinoma* and juvenile granulosa cell tumor, and it can be difficult to differentiate between them. Both neoplasms develop mainly in young patients, but small cell carcinoma is associated with hypercalcemia in 60% of cases, whereas juvenile granulosa cell tumor produces symptoms caused by abnormal estrogen production. Small cell carcinoma grows in a diffuse pattern and may contain irregular macrofollicles. It does not exhibit the nodular low-power pattern seen in juvenile granulosa cell tumor. Mitotic activity generally is more pronounced in small cell carcinoma, and atypical mitotic figures are more likely. Immunohistochemistry can be helpful in the differential diagnosis.[261] Small cell carcinoma is more likely to be cytokeratin positive. In contrast to granulosa cell tumor, about 50% of small cell carcinomas are vimentin negative. Many small cell carcinomas are chromogranin positive; granulosa cell tumor does not react with this antibody.

Clinical Behavior and Treatment. Most juvenile granulosa cell tumors are confined to one ovary (stage IA) at diagnosis and are treated successfully by

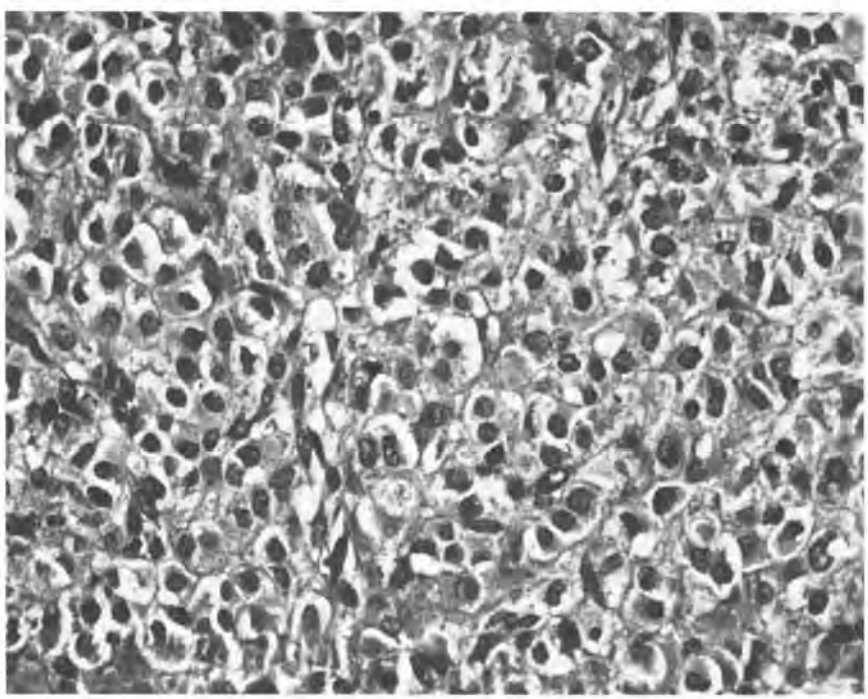

FIGURE 6-64 Juvenile granulosa cell tumor. The tumor cells are partly luteinized and have a moderate amount of granular eosinophilic cytoplasm.

unilateral salpingo-oophorectomy. Because of the young age of most patients, hysterectomy and bilateral salpingo-oophorectomy is reserved for those few patients who have advanced disease (stage II or III). The long-term survival in large series is greater than 90%.[281,282,285] Patients with positive peritoneal cytology or extraovarian tumor spread have an increased risk of recurrence.[282] Recurrence and death from tumor takes place within 3 years of diagnosis. No effective treatment for recurrent or metastatic neoplasms has been identified.

Thecoma

The thecoma is a neoplasm derived from the ovarian stroma that contains cells resembling those of the theca interna. Thecomas constitute about 7% of all sex cord stromal tumors of the ovary.[290]

Clinical Findings. Thecomas occur in women 20 to 80 years of age. Most patients are perimenopausal or postmenopausal, with an average age of slightly greater than 50 years.[245,246,252,290] Luteinized thecomas occur in somewhat younger women, and more than 30% are detected in patients younger than 30.[40] The clinical presentation depends on the patient's menopausal status. Postmenopausal patients typically present with postmenopausal bleeding, although about 25% of these patients have only nonspecific symptoms such as abdominal distention. Premenopausal women frequently have menstrual abnormalities such as irregular bleeding or amenorrhea, pelvic or abdominal pain, or abdominal distention. A few thecomas, usually of the luteinized type, are virilizing.[40,251] Endometrial hyperplasia is detected in about 15% of women with thecomas and as many as 26% to 29% have endometrial carcinoma.[252,291] At operation, 5% of patients have bilateral tumors.[245,246] Extraovarian spread does not occur except in rare malignant tumors with thecomatous features.

Macroscopic Appearance. Thecomas range from small, incidentally discovered tumors less than 1 cm in diameter to large neoplasms more than 20 cm in diameter. The average diameter is 7 cm. The consistency ranges from firm to hard. The cut surface is gray, tan, white, or yellow (Fig. 6-65 and Color Figure 6-14). Thecomas often contain cysts of various sizes containing yellow serous fluid. Calcified regions may be present.

Microscopic Appearance. Thecomas are composed of irregular, whorled, anastomosing fascicles of ovoid or fusiform cells that frequently are separated by hyalinized connective tissue plaques (see Fig. 6-65). The tumor cells have round or oval nuclei containing finely dispersed chromatin. The cytoplasm is slightly eosinophilic and can be homogeneous or vacuolated. Fat stains performed on unfixed frozen sections demonstrate cytoplasmic lipid droplets. Reticulin stains reveal a fibrillar network surrounding individual theca cells. A rich capillary network is present between the bundles of theca cells. Rare tumors in young women contain extensive areas of calcification.[292]

Variably sized clusters of polygonal luteinized stromal cells are found in some stromal tumors. Such tumors are referred to as *luteinized thecomas*, whether the background stromal pattern is that of thecoma, fibrothecoma, or fibroma.[39,40] Luteinized thecomas can produce estrogenic (50%) or androgenic (11%) effects or can be nonfunctional (39%).[40] Nearly all androgenic thecomas are luteinized thecomas.

Rare stromal tumors containing theca cells or luteinized cells invade adjacent organs, recur after adequate excision, or metastasize. Features that raise the possibility of malignancy include large size, hypercellularity, and frequent mitotic figures (4 or more mitotic figures per 10 high-power fields).[40,293]

Immunostains for vimentin are positive in thecoma, whereas those for cytokeratin are negative.[262] Immunostains for enzymes involved in steroidogenesis reveal that thecoma contains the enzymes required for cholesterol side-chain cleavage and 17α-hydroxylation but that an enzyme required for aromatization of androgen to estradiol is absent.[294] This suggests that the tumor cells, like the theca cells in the normal ovary, are capable of producing androgens, but that conversion to estrogen takes place elsewhere, within the ovary or in the periphery.

Electron microscopy discloses a spectrum of cell types, including some with features of smooth muscle cells.[267,295,296] Spindle-shaped mesenchymal cells with prominent Golgi complexes, short branching profiles of rough endoplasmic reticulum, and occasional lipid droplets predominate. Cells with abundant 10-nm intermediate filaments are found, as are cells with dilated smooth endoplasmic reticulum, lipid, and large mitochondria with tubular or straight cristae.

A cytogenetic abnormality, trisomy 12, is reported to characterize thecoma and several other sex cord stromal tumors.[272,297,298]

Differential Diagnosis. The histologic appearance of thecoma overlaps with that of fibroma. The term *fibrothecoma* is commonly used for a fibroma that contains occasional, plump, spindled theca cells. Such tumors generally are hormonally inactive.

Clinical Behavior and Treatment. Thecomas are almost invariably benign neoplasms, and surgical excision is the appropriate treatment. Rare malignant tumors with unequivocal thecomatous differentiation have been described.[40,242,251,293] However, most neoplasms reported as "malignant thecoma" are sarcomatoid granulosa cell tumors, fibrosarcomas, or other types of malignant mesenchymal tumors.

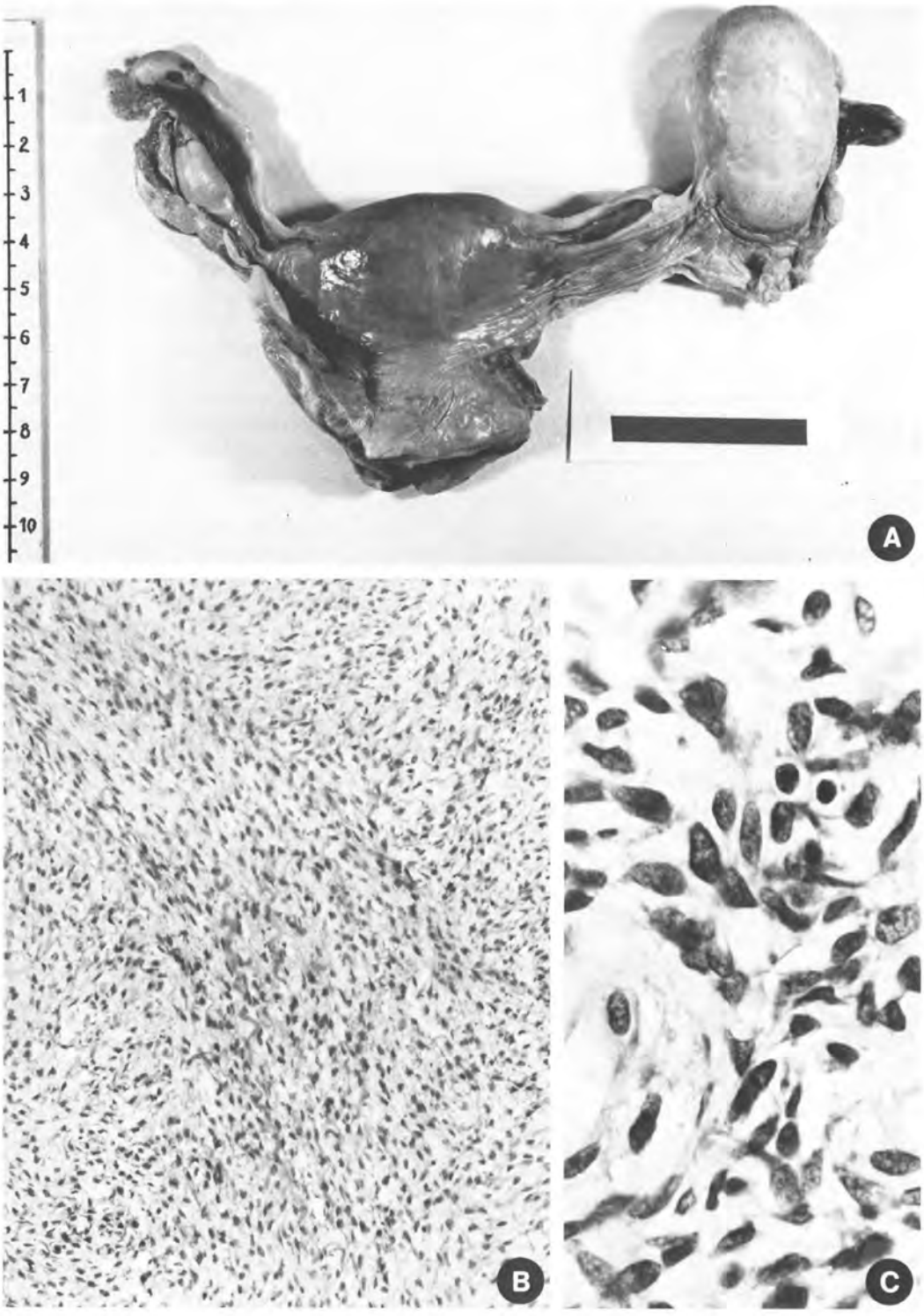

FIGURE 6-65 Thecoma. **(A)** Macroscopic appearance. **(B,C)** Microscopic appearance.

Fibroma and Related Neoplasms

The fibroma is a benign tumor that is composed of fibroblasts and collagen fibers and arises in the ovarian stroma. It represents 1% to 5% of all ovarian tumors and is by far the most common sex cord stromal tumor.[243,290] Malignant fibroblastic tumors of the ovary are rare.[299]

Clinical Findings. The clinical presentation is not specific. Fibroma occurs in patients 20 to 80 years of age, with an average age of slightly less than 50 years.[290] Many fibromas are asymptomatic and are discovered at operation for some other problem. Large tumors cause abdominal discomfort or distention and about 30% are associated with ascites.

Meigs' syndrome is a condition in which an ovarian fibroma is accompanied by ascites and hydrothorax.

Macroscopic Appearance. The fibroma is a firm, white tumor with a smooth, multinodular surface. Many fibromas are smaller than 1 cm in diameter, but tumors larger than 10 cm are not uncommon. The cut surface is solid and pearly white (Fig. 6-66*A*). There may be foci of necrosis and hemorrhage in large tumors. Five to 10% of fibromas are bilateral. Cellular fibroma and fibrosarcoma are larger and softer.

Microscopic Appearance. Fibromas are composed of spindle cells that grow in whorled and anastomosing bundles (see Fig. 6-66*B*). The nuclei are fusiform and uniform from cell to cell. A variable amount of collagenous stroma is admixed with the fibroblastic tumor cells; the stroma is occasionally so prominent that it dominates the histologic picture. Occasionally, small irregular or tubular collections of sex cord cells are present within a fibroma or fibrothecoma. Rare sex cord elements do not adversely affect the prognosis of such tumors, which are designated as *fibromas with sex cord elements.*[300]

Rare fibroblastic tumors are hypercellular neoplasms in which the spindle-shaped cells are arranged in a herringbone or storiform pattern. Hypercellular fibroblastic tumors that exhibit mild to moderate nuclear atypia and 3 or fewer mitotic figures per 10 high-power fields are designated as *cellular fibromas.* Those in which the degree of nuclear atypia is moderate or marked and in which there are 4 or more mitotic figures per 10 high-power fields are designated as *fibrosarcoma.*[299]

Ultrastructural studies suggest that fibromas and thecomas are derived from the same cell type and that they differ only in the proportion of collagen-forming and steroid-forming cells.[267,295] Cytogenetic studies reveal that trisomy 12 is a consistent abnormality in ovarian fibroma.[272,273,297]

Clinical Behavior and Treatment. The fibroma is a benign neoplasm that is treated adequately by surgical excision. Cellular fibroma is capable of locally aggressive growth if it is incompletely excised. Fibrosarcoma is a malignant mesenchymal tumor with a poor prognosis. It is treated by complete excision and chemotherapy.[299]

Sclerosing Stromal Tumor

The sclerosing stromal tumor is an uncommon benign tumor that arises predominantly in young women in the second and third decades of life.[301–304] The most typical presentation is with menstrual irregularity and pelvic pain. Sclerosing stromal tumors range from 1.5 to 17 cm in diameter. They typically are solid, firm neoplasms with nodular white or yellow cut surfaces. Rare examples are cystic.[305] At low magnification, sclerosing stromal tumor has a pseudolobular appearance produced by an admixture of densely cellular nodules and less cellular fibrous or edematous zones (Fig. 6-67). The cellular population ranges from spindle-shaped fibroblastic cells to polygonal cells with eosinophilic or vacuolated cytoplasm. Most tumor cells are vimentin positive. Scattered cells display smooth muscle differentiation, which can be demonstrated by immunohistochemistry or electron microscopy.[306] A tendency to sclerosis and to marked vascularity is typical. The sclerosing stromal tumor is benign and is treated by excision.

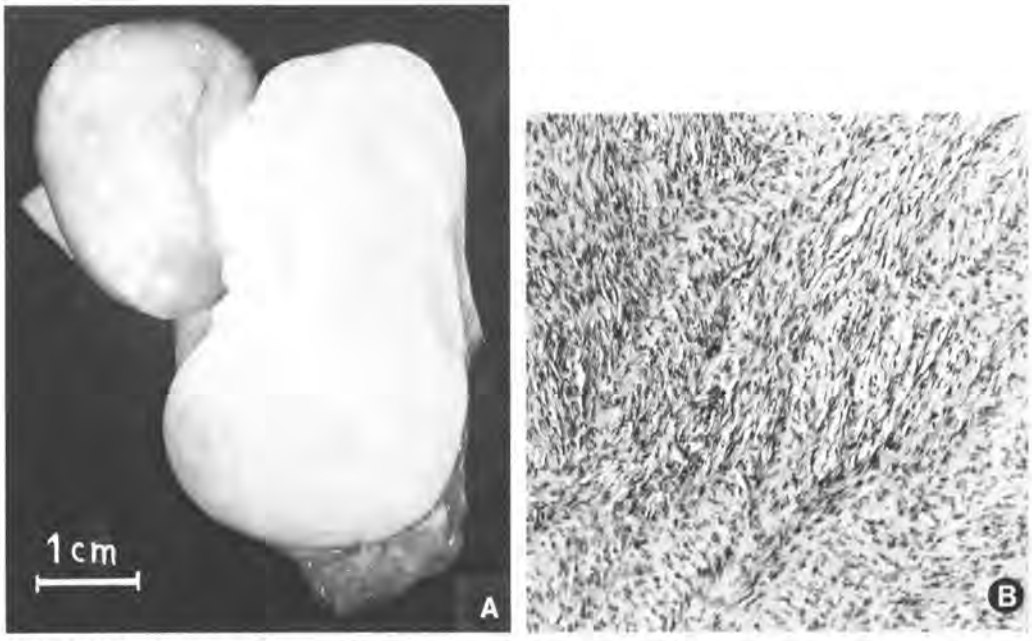

FIGURE 6-66 Ovarian fibroma. **(A)** Macroscopic appearance. **(B)** Microscopic appearance.

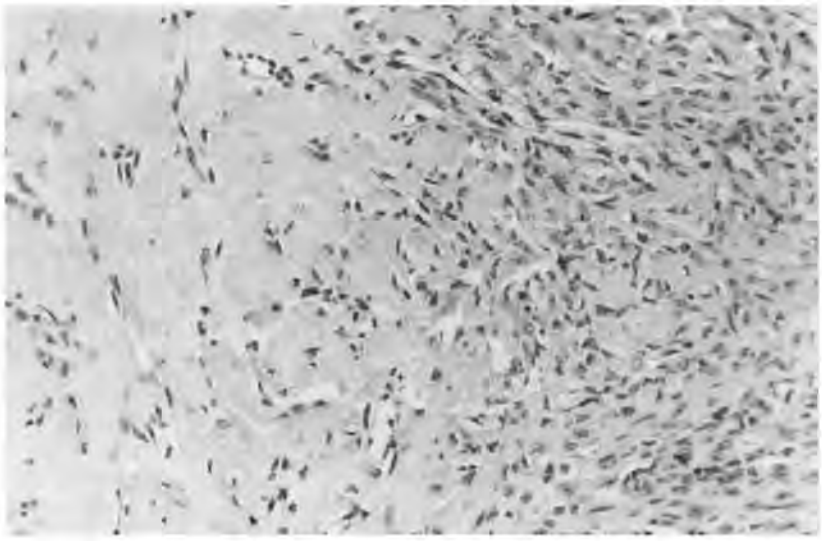

FIGURE 6-67 Sclerosing stromal tumor. The cellular region is shown on the right, and the acellular hyalinized area with prominent vessels is on the left.

The main differential diagnosis is with massive edema, which also occurs in young women. Sclerosing stromal tumor is an expansile neoplasm that displaces normal ovarian structures. In contrast, the latter are present within areas of massive edema. We have seen Krukenberg's tumors initially misdiagnosed as sclerosing stromal tumors; a stain for mucin should prevent this error.

Sertoli-Leydig Cell Tumor

Sertoli-Leydig cell tumors are rare neoplasms, comprising less than 1% of ovarian tumors. About one half are virilizing. They are classified into two main clinicopathologic groups: (1) well-differentiated Sertoli-Leydig cell tumors (10% of the total); and (2) Sertoli-Leydig cell tumors of intermediate and poor differentiation. About 25% of the latter contain areas of heterologous or retiform differentiation.

Clinical Findings. Sertoli-Leydig cell tumors typically arise in young women, but they occasionally are detected in children and in women over 60 years of age. The average age is 24 years, and 75% of patients are younger than 30.[133,307,308] Women with well-differentiated Sertoli-Leydig cell tumors average 40 years of age, 10 to 15 years older than those with the more common intermediate and poorly differentiated tumors.[133,307,308] Sertoli-Leydig cell tumors that contain areas of retiform differentiation develop in young patients; the average age is 16 years.[146,309,310]

About 50% of Sertoli-Leydig cell tumors are hormonally active.[133,307,308] These tumors cause symptoms that range from menstrual disorders to virilization. Common menstrual abnormalities include irregular bleeding, oligomenorrhea or amenorrhea, and, in older women, postmenopausal bleeding. Well-developed features of virilization are observed in about 40% of patients, who most typically have amenorrhea, deepening of the voice, and hirsutism. Other signs of virilization include temporal alopecia, hypertrophy of the clitoris, and acne. Serum levels of testosterone and urine levels of 17-ketosteroids are increased in virilized patients.

The 50% of patients whose tumors are not hormonally active present with nonspecific findings such as abdominal distention, abdominal mass, or abdominal pain. Five to 10% of patients present with acute abdominal symptoms caused by torsion or rupture of the tumor. Sertoli-Leydig cell tumors occasionally are discovered in asymptomatic women. Rare examples produce α-fetoprotein, which is useful as a tumor marker.[146,309-315]

At operation, Sertoli-Leydig cell tumors are nearly always confined to one ovary. Extraovarian spread is uncommon. Tumor rupture is an important adverse prognostic finding; it is detected in 5% to 15% of cases.[307]

Macroscopic Appearance. The well-differentiated Sertoli-Leydig cell tumor presents as an encapsulated unilateral mass 1.5 to 10 cm in diameter.[316] The average diameter is 5 cm. Well-differentiated tumors are generally solid and have a yellow or yellow-tan cut surface.

Intermediate and poorly differentiated tumors are larger. They range from small tumors less than 1 cm in diameter to large neoplasms 35 cm in diameter. The average diameter is 15 cm. Poorly differentiated tumors tend to be larger than those of intermediate differentiation, but there is considerable overlap. Most Sertoli-Leydig cell tumors are partly solid and partly cystic, but tumors that are mainly solid or mainly cystic are not uncommon. Solid areas vary from firm to soft and are gray-pink, yellow, or orange.

Microscopic Appearance. The *well-differentiated Sertoli-Leydig cell tumor* contains well-formed hollow or

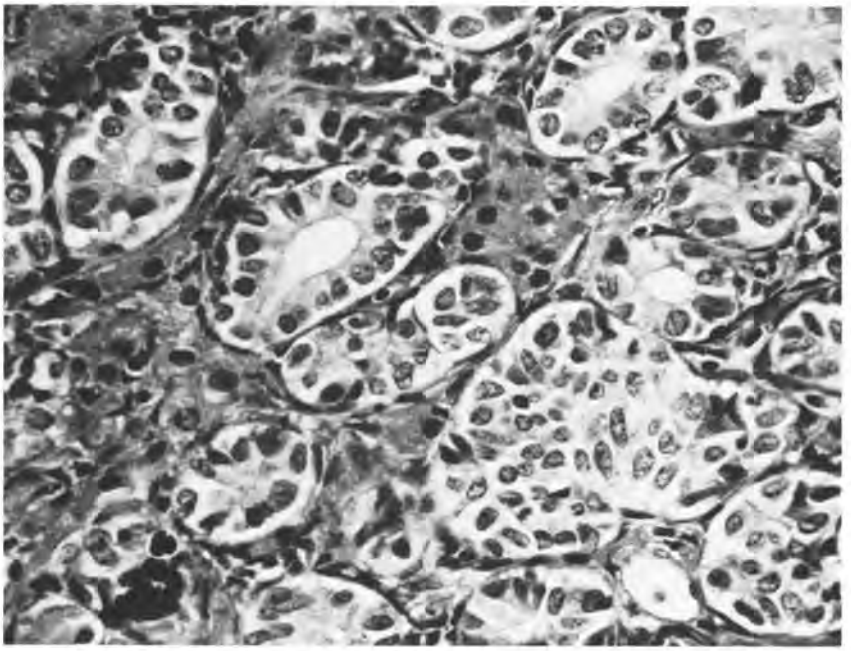

FIGURE 6-68 Well-differentiated Sertoli-Leydig cell tumor. Sertoli tubules and Leydig cells can be seen.

closed tubules lined by columnar Sertoli cells. These are admixed with large, polygonal cells with eosinophilic cytoplasm, compatible with Leydig cells (Fig. 6-68) and mature fibrous stroma. Crystals of Reinke are only rarely identified within the Leydig cells. Cytologic atypia and mitotic activity are minimal.

There are well-formed Sertoli tubules in some *intermediate and poorly differentiated Sertoli-Leydig cell tumors,* but in most tumors the Sertoli cells are organized in solid cords (Fig. 6-69). Retiform tubules are present in 10% to 25% of intermediate and poorly differentiated neoplasms and occasionally are the dominant histologic finding. Retiform tubules are long and branching and are lined by low columnar to cuboidal cells with scanty cytoplasm and hyperchromatic, oval nuclei (Fig. 6-70). Papillae often are present within retiform tubules. Mitotic figures generally are inconspicuous in tubular cells of all types, but there are numerous mitotic figures in occasional tumors with retiform tubules. Some tumors contain tubules lined by cytologically atypical Sertoli cells, but this does not appear to be of prognostic significance. The tubules are set in a background of immature gonadal stroma and Leydig cells. It is the presence of immature stroma that sets intermediate and poorly differentiated Sertoli-Leydig cell tumors apart from the well-differentiated neoplasms (Fig. 6-71).[133] The stroma is most prominent in poorly differentiated neoplasms, where it constitutes the bulk of the tumor. Sertoli tubules and Leydig cells are often inconspicuous in poorly differentiated neo-

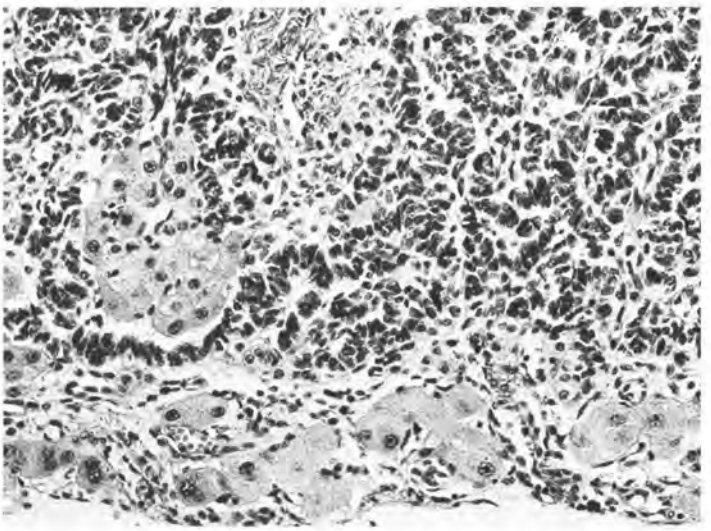

FIGURE 6-69 Intermediate Sertoli-Leydig cell tumor with clusters of Leydig cells and cord-like arrangements of Sertoli cells.

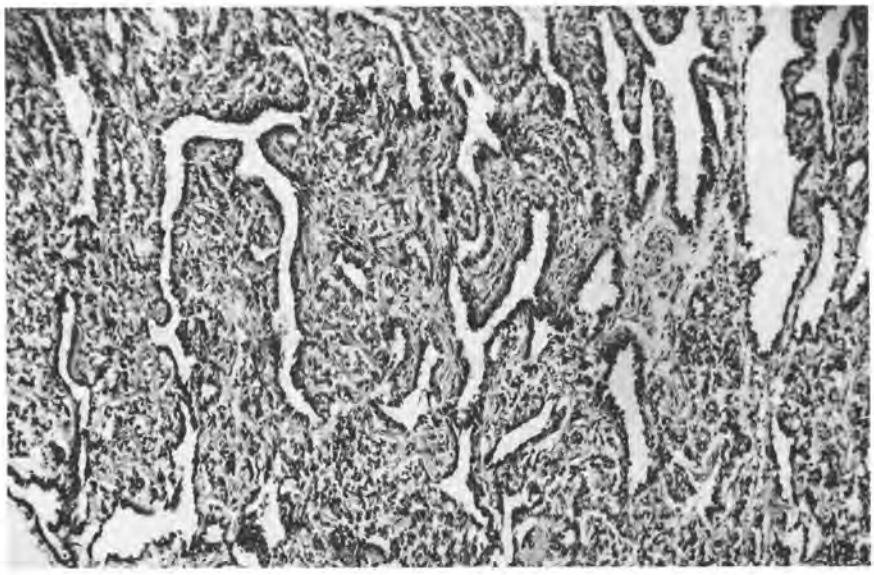

FIGURE 6-70 Retiform tubules in a Sertoli-Leydig cell tumor. The tubules are branching and are lined by cuboidal epithelial cells. (Zaloudek CJ, Norris HJ: Sertoli-Leydig tumors of the ovary: A clinicopathologic study of 64 intermediate and poorly differentiated neoplasms. Am J Surg Pathol 6:503–512, 1982)

plasms. There generally is minimal stromal cell atypia, but mitotic figures, which average 4 to 5 per 10 high-power fields, are easy to find. Heterologous elements are present in 20% to 25% of intermediate and poorly differentiated Sertoli-Leydig cell tumors. Mucinous epithelium of intestinal type is the most common of these (Fig. 6-72), but carcinoid, neuroblasts, cartilage, and striated muscle also have been described.[133,317,318]

The neoplastic Sertoli cells within the tubules react with antibodies to cytokeratin, whereas the stromal cells and Leydig cells, which are cytokeratin negative, react with antibodies to vimentin.[262,264] Rare Sertoli-Leydig cell tumors secrete α-fetoprotein. Immunostains for α-fetoprotein are positive in Leydig cells, Sertoli cells, or so-called hepatoid cells in such neoplasms.[312–315] The gastrointestinal epithelium in heterologous tumors contains cells that are argyrophilic and immunoreactive for chromogranin, serotonin, and peptides such as corticotropin, somatostatin, and calcitonin.[319] Testosterone is present in Leydig cells and in stromal cells and Sertoli cells.[320] There is immunoreactivity with antibodies against P-450 cytochromes in Leydig cells, Sertoli cells, and stromal cells, indicating that all are potential sites of steroidogenesis.[321]

Ultrastructural studies confirm that the Leydig cells are a source of hormone secretion. Leydig cells contain the prominent vesicular smooth endoplasmic reticulum and mitochondria with tubular cristae that characterize steroid hormone-producing cells.[322,323] Sertoli cells are surrounded by a basal lamina, and there are desmosomes between the cells. Their cytoplasm contains small mitochondria, rare smooth vesicles, and occasional microfilaments. Some cells contain lipid droplets.

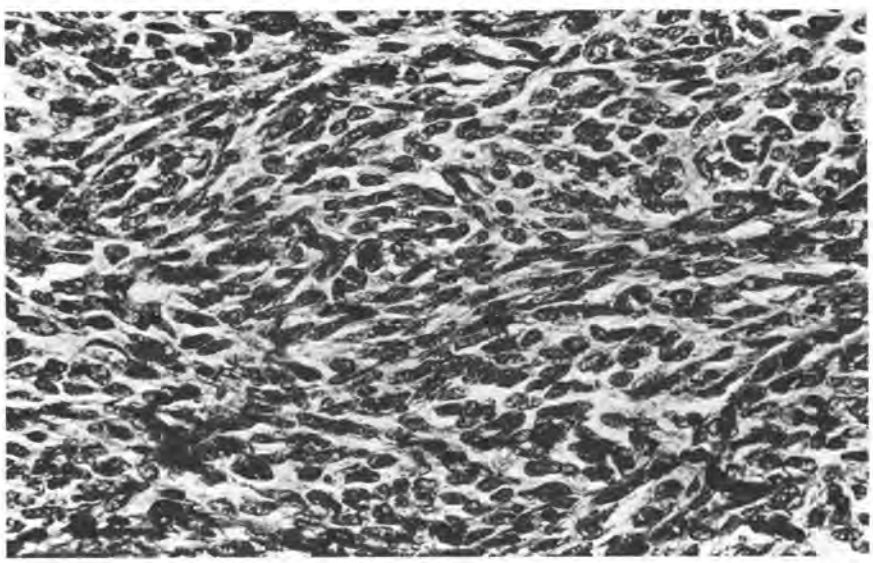

FIGURE 6-71 Immature gonadal stroma in a poorly differentiated Sertoli-Leydig cell tumor.

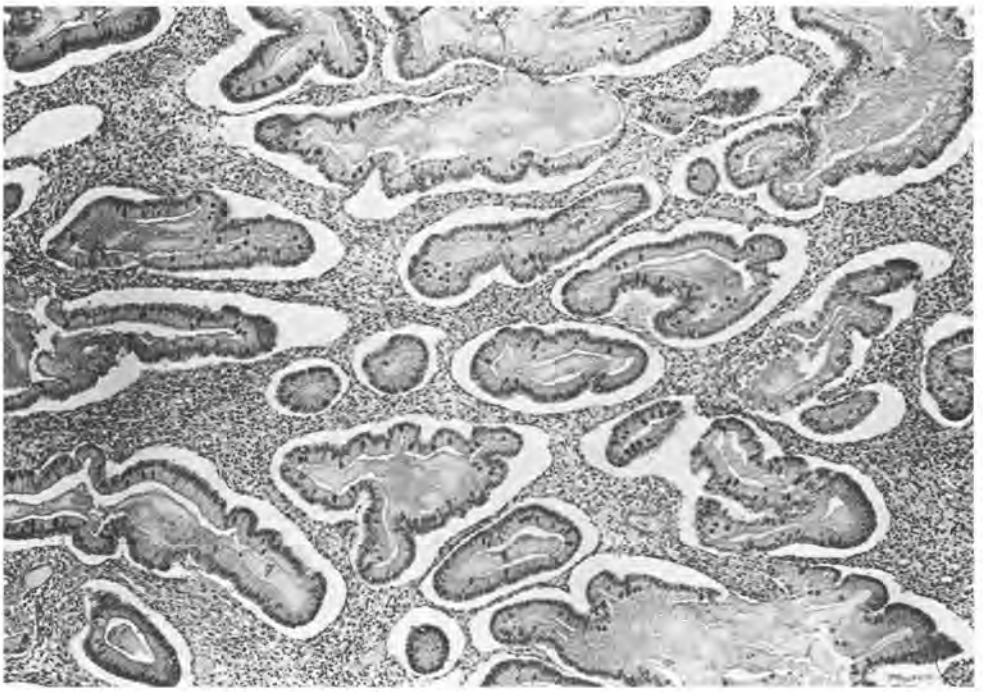

FIGURE 6-72 Sertoli-Leydig cell tumor: heterologous mucinous epithelium (mucicarmine stain).

Differential Diagnosis. The differential diagnosis of Sertoli-Leydig cell tumor includes granulosa cell tumor and unclassified sex cord/stromal tumors, endometrioid carcinoma, metastatic adenocarcinoma, and yolk sac tumor.

Granulosa cell tumor and Sertoli-Leydig cell tumor commonly contain small areas resembling the other tumor type. Well-formed tubules and Leydig cells are not seen in granulosa cell tumor, and the typical histologic patterns of granulosa cell tumor are not seen in a Sertoli-Leydig cell tumor. Heterologous differentiation is unique to the Sertoli-Leydig cell tumor. A small proportion of sex cord/stromal tumors are too poorly differentiated to designate except as unclassified sex cord/stromal tumors.

Endometrioid carcinoma can simulate a Sertoli-Leydig cell tumor, particularly when luteinized stromal cells are present within or around it.[185,186] These tumors occur in an older patient population and are hormonally inactive. They often are bilateral and associated with pelvic endometriosis. Sertoliform endometrioid carcinomas are mixed with more typical areas of endometrioid carcinoma, contain squamous metaplasia, and lack the immature stroma that characterizes a Sertoli-Leydig cell tumor.

Metastatic adenocarcinoma, particularly the tubular Krukenberg tumor, can raise the question of Sertoli-Leydig cell tumor.[324] Most cases of metastatic carcinoma are detected in older patients, and the metastatic deposits are multifocal and bilateral. The tubules are lined by cytologically malignant cells that exhibit a degree of nuclear atypia and mitotic activity not seen in the Sertoli cells lining the tubules of a Sertoli-Leydig cell tumor.

When a retiform tubular pattern is prominent, a Sertoli-Leydig cell tumor can be confused with a *yolk sac tumor,* or even with a serous epithelial tumor. The presence of virilizing clinical symptoms and of areas of more typical Sertoli-Leydig cell differentiation is helpful in arriving at the correct diagnosis. Yolk sac tumors have a primitive embryonal stroma and generally contain cells that exhibit greater cytologic atypia and mitotic activity than is seen in a Sertoli-Leydig cell tumor. Immunohistochemistry typically demonstrates α-fetoprotein in a yolk sac tumor, but rare Sertoli-Leydig cell tumors also contain this substance.

Clinical Behavior and Treatment. The treatment is mainly surgical. Unilateral salpingo-oophorectomy is sufficient in most cases.[133,307] Total abdominal hysterectomy is warranted in older patients and in those with unfavorable prognostic findings, such as rupture, extraovarian spread, a poorly differentiated neoplasm with frequent stromal cell mitoses, or heterologous mesenchymal differentiation (eg, cartilage or skeletal muscle, or foci of neuroblastoma).[133,307]

Well-differentiated Sertoli-Leydig cell tumors do not recur or metastasize after adequate excision.[133,316] Most intermediate and poorly differentiated Sertoli-Leydig cell tumors follow a benign clinical evolution, and excision of the neoplasm brings about disappearance of many of the symptoms of virilization and a return to normal hormonal activity. The 5-year survival in one report was 92%, whereas in another study 18% of the tumors were clinically malignant.[133,307] Most recurrences are detected within the first 5 years after treatment. Chemotherapy appears beneficial in about half of the patients who receive it.[280,307]

Leydig Cell Tumor

Nearly all ovarian Leydig cell tumors arise in the hilus of the ovary, presumably from hilus cells.[36,325] Leydig cell tumors in this location are sometimes referred to as *hilus cell tumors.* Occasional Leydig cell tumors originate from the ovarian stroma and are designated as *non-hilar* or *stromal Leydig cell* tumors.[37,38,40]

Clinical Findings. Most Leydig cell tumors are discovered in postmenopausal women; the average age is 58 years.[36,325] The typical clinical presentation is with hirsutism or true masculinization (ie, acne, masculine voice, and clitoral hypertrophy), which regresses after resection of the tumor. Serum levels of testosterone are elevated, but levels of urinary 17-ketosteroids generally are within normal limits.[36] Amenorrhea is common in premenopausal women, and older women frequently have postmenopausal bleeding. Study of the endometrium reveals hyperplasia in a high percentage of cases, a finding that is most likely secondary to peripheral conversion of testosterone to estrogen. In many cases, symptoms are present for several years before the diagnosis is established. Leydig cell tumors usually are too small to be palpable. They are detected because of the hormonal symptoms that they cause or are an incidental finding at operation for some other reason.

Macroscopic Appearance. These neoplasms present as small spherical brown or yellow-brown masses situated in the ovarian hilus or, rarely, in the medulla and cortex. They are poorly delimited from surrounding tissues and are of homogeneous consistency. The average diameter is 3 to 5 cm, with tumors as small as 0.7 cm and as large as 15 cm having been reported. Virtually all are unilateral.

Microscopic Appearance. *Hilar Leydig cell tumors* are unencapsulated and are composed of round or polygonal cells that are similar to the hilus cells present in the normal ovary.[36,325] Neoplastic cells are sometimes increased in size and are irregular in shape. Their nucleus is small, round, and hyperchromatic. The cytoplasm is granular and eosinophilic (Fig. 6-73). Some cells contain lipid droplets, and many contain yellow-brown lipochrome pigment, which is responsible for the color of the tumor. Reinke crystals are rod-like structures with round or square ends (Fig. 6-74). These can be identified in the cytoplasm of the tumor cells in about 50% of hilar Leydig cell tumors. The cytoplasm often contains round, eosinophilic, hyaline spheres.

There are two types of non-hilar Leydig cell tumors. Pure *non-hilar Leydig cell tumors* are composed exclusively of Leydig cells.[37] *Stromal Leydig cell tumors* contain Leydig cells mixed with a fibromatous or thecomatous stromal component.[38,40] By definition, crystals of Reinke must be identified within tumor cell cytoplasm for diagnosis of a non-hilar Leydig cell tumor. Because only 50% of hilar Leydig cell tumors contain crystals, some non-hilar Leydig cell tumors undoubtedly are unrecognized and are classified as stromal luteoma[326] or luteinized thecoma.[40]

Electron microscopic studies reveal abundant agranular endoplasmic reticulum and many large mitochondria. The crystals of Reinke are composed of a protein lattice, and the intracellular pigment granules appear similar to those of testicular Leydig cells.[327–329]

Differential Diagnosis. The main differential diagnostic consideration in hilar Leydig cell tumor is *hilus cell hyperplasia.* Hilus cell hyperplasia is typically bilateral and does not form a visible tumor.

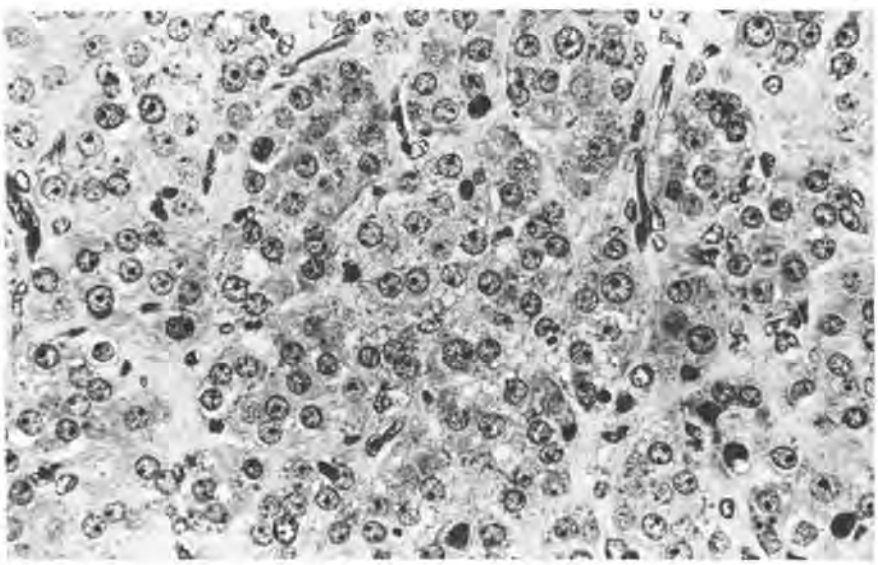

FIGURE 6-73 Hilar Leydig cell tumor composed of uniform polygonal cells.

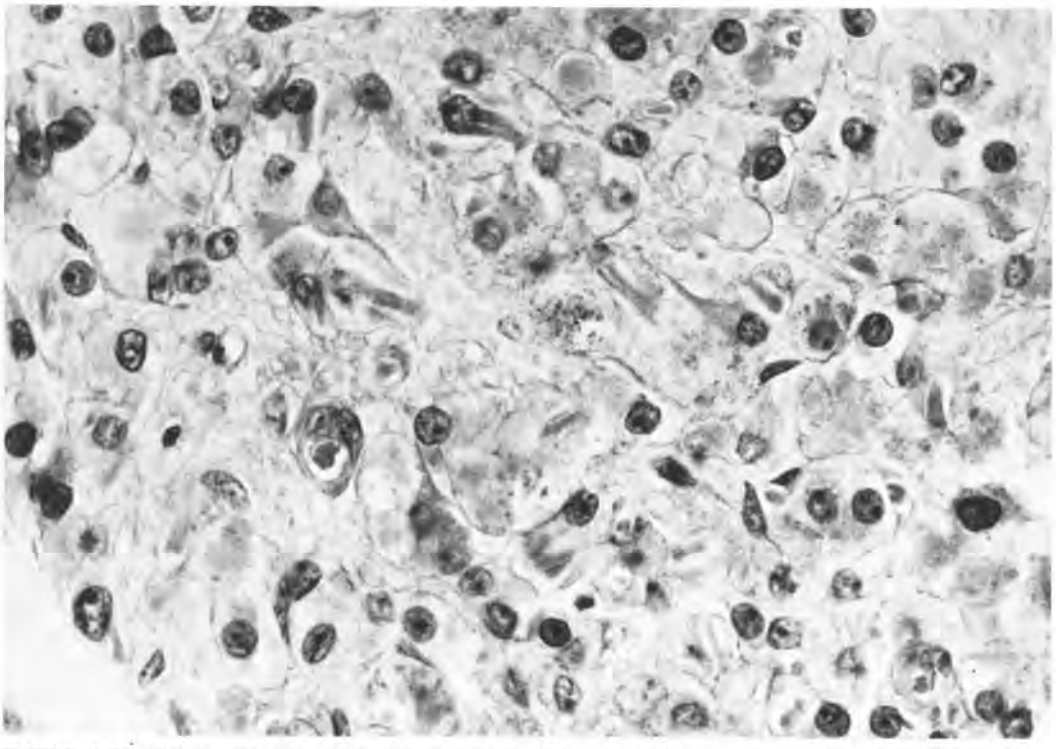

FIGURE 6-74 Reinke crystals within the cytoplasm of Leydig cells.

Microscopically, hilus cell hyperplasia is multinodular and bears a normal relation to the nerves in the ovarian hilus. Hilar Leydig cell tumors are unilateral and grossly visible, and they displace normal hilar structures. Non-hilar Leydig cell tumors must be differentiated from *stromal luteoma*[326] and stromal Leydig cell tumors from *luteinized thecoma.*[40] This distinction rests on the identification of crystals of Reinke within Leydig cells in Leydig cell tumors.

Clinical Behavior and Treatment. Malignant Leydig cell tumors are rare; only two cases have been reported.[36,325] Virtually all Leydig cell tumors are clinically benign and are cured by surgical excision.[36–38,40,325]

Stromal Luteoma

The stromal luteoma is an uncommon neoplasm that occurs predominantly in postmenopausal women.[326] Most patients have abnormal uterine bleeding, and an endometrial biopsy often reveals hyperplasia. Rare stromal luteomas are virilizing. One third of these tumors are an incidental finding at operation or autopsy. The stromal luteoma is a small unilateral neoplasm; all reported examples are less than 3 cm in diameter. The cut surface is gray, white, yellow, or brown. The tumor is located in the ovarian stroma and is composed of cells that resemble Leydig cells. They are polygonal, with granular eosinophilic cytoplasm and small, round, centrally placed nuclei. Differentiation from a Leydig cell tumor is based on the non-hilar location of the stromal luteoma and on the absence of cytoplasmic crystals of Reinke. Other ovarian abnormalities typically are present, including stromal hyperthecosis, which is often bilateral, and hilus cell hyperplasia. The stromal luteoma is a benign neoplasm.

Sertoli Cell Tumor

Pure Sertoli cell tumors are rare. They differ from Sertoli-Leydig cell tumor by virtue of the absence of Leydig cells and of immature gonadal stroma.

Clinical Findings. Sertoli cell tumors most often arise in women of reproductive age. Most patients are in their mid-30s, but these neoplasms can occur in children and postmenopausal women.[330,331] Two thirds of the tumors are hormonally active. Of these, 70% secrete estrogen and 30% produce androgens. Patients with hormone-secreting neoplasms present with irregular bleeding, precocious pseudopuberty, or virilization, depending on their age and the type and amount of hormone that is secreted. The one third of patients with hormonally inactive neoplasms have nonspecific symptoms such as pain or abdominal swelling. Small tumors may be incidental findings.

Macroscopic Appearance. Sertoli cell tumors are unilateral, circumscribed tumors with an average di-

ameter of 5 to 7 cm. Their cut surfaces are fleshy and tan or yellow, with cysts present in some neoplasms.

Microscopic Appearance. These neoplasms are composed of Sertoli cells and a supporting connective tissue framework. Leydig cells and immature stromal cells are absent. The Sertoli cells are columnar, with small, round to oval nuclei and granular eosinophilic or clear cytoplasm. They line elongated tubules or are arranged in solid cords that are two or three cells thick. This arrangement is referred to as a *simple tubular pattern* in contrast to the *complex tubular pattern* that is more characteristic of the closely related sex cord tumor with annular tubules. Some Sertoli cell tumors are composed of tubules that are lined by cells with abundant, clear, lipid-rich cytoplasm (Fig. 6-75). Such neoplasms are referred to as *lipid-rich Sertoli cell tumors.*

Clinical Behavior and Treatment. Most Sertoli cell tumors have a benign evolution and are treated adequately by unilateral salpingo-oophorectomy.[330,331] Rare poorly differentiated or invasive neoplasms recur or metastasize and cause the patient's death.

Sex Cord Tumor With Annular Tubules

The sex cord tumor with annular tubules (SCTAT) is designated as an unclassified sex cord/stromal tumor because the most appropriate classification is a point of controversy. Some authors view the SCTAT as a granulosa cell tumor,[332–335] whereas others consider it to be a variant of the Sertoli cell tumor.[330,336]

Clinical Findings. The SCTAT occurs in two clinical settings. First, about one third occur in women with the *Peutz-Jeghers syndrome,* a hereditary condition characterized by the presence of mucocutaneous melanin pigmentation and hamartomatous intestinal polyps.[333,337] Virtually all female patients with this syndrome have SCTATs, which are usually microscopic, multicentric, and bilateral. Most are asymptomatic and are discovered incidentally. SCTATs also occur in patients who do not have the Peutz-Jeghers syndrome.[330,333,334,337,338] In the latter setting, the neoplasms are discovered in patients 6 to 76 years of age. The average age is 36 years.[337] Premenarchal girls may have precocious pseudopuberty.[333,337] Older patients frequently have menstrual dysfunction or postmenopausal bleeding, depending on their age. An adnexal mass is palpable in about 50% of patients. A novel assay for müllerian-inhibiting substance revealed an increased serum level of that substance in one patient with a SCTAT.[253] SCTATs that are not associated with the Peutz-Jeghers syndrome generally are unilateral, solitary, and grossly apparent.

Macroscopic Appearance. In patients with the Peutz-Jeghers syndrome, the neoplasms are small and sometimes microscopic. They are multifocal, frequently bilateral, tan or yellow solid tumors (Color Figure 6-15). Foci of calcification are often present. Neoplasms that are not associated with the Peutz-Jeghers syndrome vary more in appearance, ranging from less than 1 cm to 20 cm in diameter, with fleshy, tan, or yellow cut surfaces.

Microscopic Appearance. SCTATs are composed of simple or, more frequently, complex annular tubules set in a fibrous stroma (Fig. 6-76). The tumor cells are columnar, with clear cytoplasm and hyperchromatic, round, basal nuclei (Fig. 6-77). Atypia and mitotic figures are rare. Tubular lumina are often absent. In solid areas, apposed columnar tumor cells have a paired arrangement, with their nuclei located at opposite poles of the cells. Round cores of hyaline material are present within the nests of cells, and similar material may form part of the stroma of larger neoplasms.

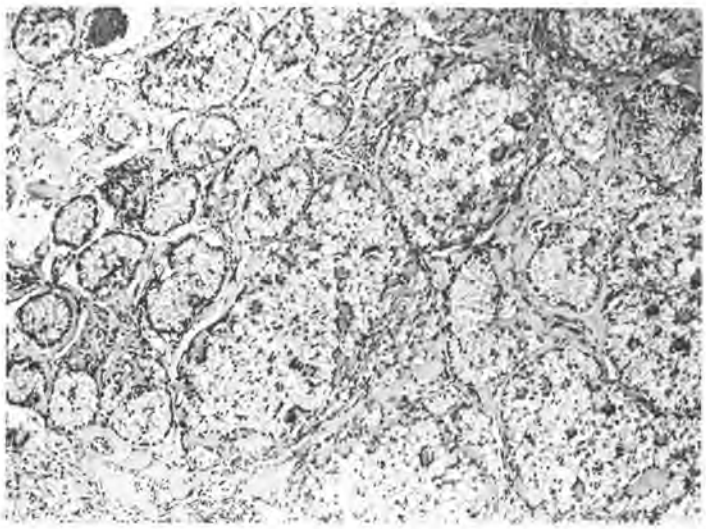

FIGURE 6-75 Sertoli cell tumor with abundant lipid-rich cytoplasm.

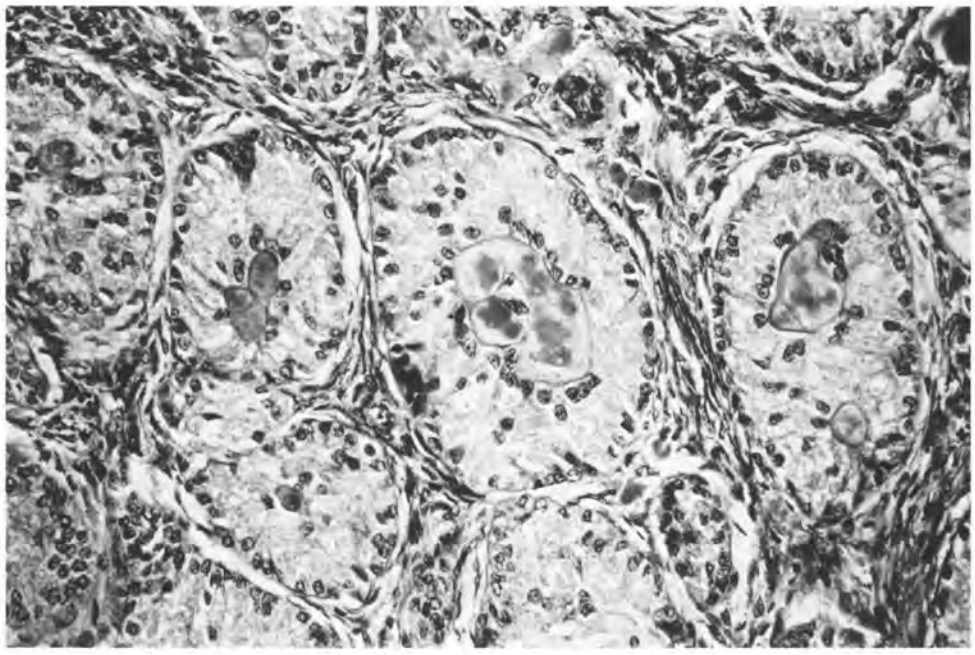

FIGURE 6-76 This sex cord tumor with annular tubules had the characteristic multifocal pattern of tumors associated with Peutz-Jeghers syndrome.

The immunocytochemical features of the SCTAT have not been characterized adequately, but many cases have been studied with the electron microscope.[330,332,334–336,339] Basement membrane material surrounds tumor cell nests and fills the central spaces within the nests, forming the hyaline cores seen by light microscopy. Most tumor cells contain cytoplasmic filaments. Some authors interpret bundles of filaments as Charcot-Böttcher filaments and conclude that SCTATs are Sertoli cell tumors.[330,336,339] Others do not identify Charcot-Böttcher filaments and interpret the ultrastructure as most compatible with that of a granulosa cell tumor.[332,334,335]

Cytologically, the SCTAT resembles a granulosa cell tumor. The tumor cells are small, with uniform nuclei and scanty pale cytoplasm. They are arranged singly, in trabeculae, in solid groups, or in rosette-like structures. The latter are reminiscent of the Call-Exner body seen in granulosa cell tumor. Hyaline cores, if present within the rosettes, may provide a clue to the correct diagnosis.[340]

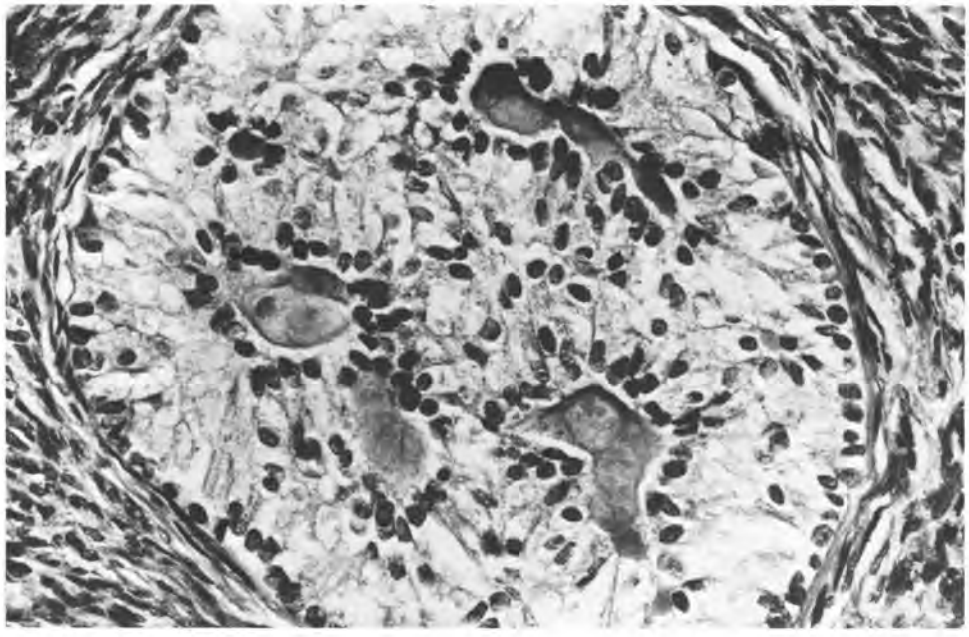

FIGURE 6-77 Sex cord tumor with annular tubules showing hyaline deposits and antipodal arrangement of cells.

Clinical Behavior and Treatment. The SCTAT is almost invariably an incidental finding in patients with the Peutz-Jeghers syndrome. The tumors are too small to palpate, and they rarely produce sufficient estrogen to cause symptoms. No treatment is necessary for asymptomatic patients.[337] Some patients with Peutz-Jeghers syndrome develop minimal deviation adenocarcinoma of the endocervix, so lifetime surveillance by a gynecologist is appropriate. A second, extremely rare sex cord/stromal tumor of the ovary occurs in children with Peutz-Jeghers syndrome and causes sexual precocity.[341]

In patients who do not have the Peutz-Jeghers syndrome, SCTAT is unilateral. Young women with localized disease (stage IA) can be treated by salpingo-oophorectomy. Older women and those with more advanced tumors are treated by hysterectomy and bilateral salpingo-oophorectomy. About 15% of SCTATs not associated with Peutz-Jeghers syndrome are clinically malignant.[337,338] It is difficult to predict which tumors will metastasize, but those in which frequent mitotic figures or stromal invasion are identified should be regarded with suspicion.

Lipid Cell Tumors (Steroid Cell Tumors)

Lipid cell or steroid cell tumors are a heterogeneous group of stromal tumors that cannot be more specifically classified. Most of the tumors in this group are composed of a mixture of cells resembling Leydig cells and cells resembling adrenal cortical cells.[342,343]

Clinical Findings. Lipid cell tumors occur in patients 3 to 80 years of age. The average age is 45 years. Most patients are virilized or hirsute. Other presentations include abdominal swelling or pain, menstrual dysfunction, or postmenopausal bleeding. Levels of urinary 17-ketosteroids and serum testosterone typically are elevated.[342,343] Most tumors are confined to the ovaries at diagnosis, and bilateral tumors are rare (6% of cases).[342] Pelvic, peritoneal, or distant metastases are present in 10% to 20% of patients.[342,343]

Macroscopic Appearance. Lipid cell tumors range from less than 1 cm to more than 20 cm in diameter. The average size is about 7 cm. Most are solid and have tan, yellow, or orange cut surfaces. Hemorrhage and necrosis are present in less than 25% of lipid cell tumors.

Microscopic Appearance. Some tumor cells resemble Leydig cells except that crystals of Reinke are not present. These cells are polygonal, with abundant eosinophilic cytoplasm and central round nuclei that contain a small nucleolus. The second major cell type resembles an adrenal cortical cell and has abundant vacuolated pale cytoplasm and a central vesicular nucleus (Fig. 6-78). A mixture of these two cell types is typical, but one or the other may predominate. Fat stains are positive in most adrenal-type cells. Mitotic figures are infrequent in lipid cell tumors, and nuclear atypia is absent or modest. Markedly atypical cells and frequent mitotic figures are observed in a minority of cases.

Immunohistochemical analysis for steroidogenic enzymes reveals intense staining of the tumor cells, which is compatible with steroid production.[321] Electron microscopic study provides evidence of steroid production within the tumor cells.[344] They contain abundant smooth endoplasmic reticulum, numerous mitochondria with tubular cristae, lipid droplets, and dense lysosomal bodies.

Clinical Behavior and Treatment. Young patients with stage IA neoplasms can be treated by salpingo-oophorectomy. Older patients and those with advanced tumors are treated by hysterectomy and bilateral salpingo-oophorectomy. Hirsutism and signs of virilization generally regress after removal of the

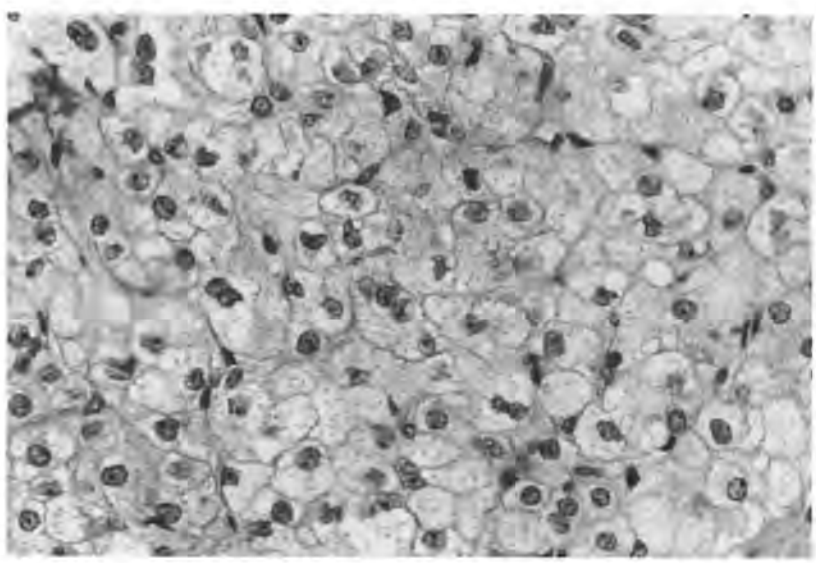

FIGURE 6-78 Lipid cell tumor: adrenal type cells with abundant foamy cytoplasm.

tumor. A significant proportion of lipid cell tumors (25% to 43%) are clinically malignant.[342,343] Recurrences generally are detected within the first several years after initial treatment, but about 20% are not detected for 5 years or more.[342] Pathologic features that help identify malignant lipid cell tumors include large size, the presence of hemorrhage or necrosis, 2 or more mitotic figures per 10 high-power fields, and moderate or marked nuclear atypia.

Gynandroblastoma

The gynandroblastoma is a rare ovarian tumor in which there are substantial areas of "testicular" (Sertoli cell or Sertoli-Leydig cell) and granulosa cell differentiation. Only about a dozen cases are well documented in the literature.[345-347] Clinically, most patients with gynandroblastoma have symptoms of masculinization. The tumor is unilateral and 1 to 18 cm in diameter.[345] The exterior is smooth, and the cut surface is cystic and multilocular, with interspersed solid white or yellow areas of variable prominence. Microscopically, tubular and cord-like structures similar to those seen in a well-differentiated Sertoli or Sertoli-Leydig cell tumor are present in intimate relation with solid nests and sheets of typical granulosa cells, within which Call-Exner bodies frequently are found. The stroma may be inconspicuous or may consist of spindle-shaped cells resembling theca cells. Occasional luteinized cells or Leydig cells are seen. All elements of the tumor are well differentiated, and cytologic atypia is minimal. All gynandroblastomas thus far reported have been clinically benign. The treatment is surgical excision.

Other Nonepithelial Tumors

Nonspecific Mesenchymal Tumors

Virtually any type of soft tissue tumor can arise in the ovary. These tumors do not differ in appearance or behavior from similar neoplasms that occur elsewhere in the body. Smooth muscle tumors are the most common mesenchymal tumors of the ovary. Most are benign leiomyomas,[348,349] but leiomyosarcoma[350-352] is sometimes observed. The lipoleiomyoma is an unusual neoplasm composed of fat and smooth muscle.[353,354] Hemangioma and myxoma are other types of benign soft tissue tumor that are seen in the ovary.[355-357] Primary sarcomas of the ovary are rare.[221,358] This group includes fibrosarcoma and endometrial stromal sarcoma, which were discussed earlier in this chapter, and rhabdomyosarcoma,[359] chondrosarcoma,[360] osteosarcoma,[361] and malignant schwannoma.[362]

Malignant Lymphoma

Less than 1% of women with lymphoma have the initial presentation of their disease in the ovary.[363] Such women present with an abdominal or pelvic mass or pelvic pain and have unilateral or bilateral ovarian tumors at laparotomy. Extraovarian lymphoma is observed at operation or shortly thereafter in most cases, indicating that ovarian lymphoma is usually part of a disseminated disease process. A few long-term survivors treated only by oophorectomy never develop extraovarian lymphoma, indicating that rare cases of primary ovarian lymphoma do occur.[363-365] Both ovaries are involved in more than 50% of cases. The tumors measure 2 cm to more than 20 cm in diameter, with an average diameter of about 15 cm. The cut surface is fleshy and pink, tan, or gray. Microscopically, all ovarian lymphomas are of the non-Hodgkin's type; Hodgkin's disease is not reported in the ovary.[363-366]

Small non-cleaved cell lymphoma of Burkitt's or non-Burkitt's type occurs with greatest frequency in children and young women and is characterized by a diffuse proliferation of small non-cleaved lymphoid cells. Mitotic figures are frequent, and phagocytic histiocytes often are present in large numbers, producing the starry-sky appearance typical of this lymphoma.

Large cell lymphoma is most common in adults. It is diffuse and composed of large cleaved or non-cleaved lymphoid cells or of immunoblasts (Fig. 6-79). The latter have vesicular nuclei with a prominent nucleolus and a moderate amount of basophilic cytoplasm. Lymphoma of the ovary rarely exhibits a follicular pattern. All immunophenotyped ovarian lymphomas have been of B-cell type.[367,368] Survival depends on the clinical stage and the histologic type of the lymphoma.[363-366] *Leukemia* can involve the ovary, and a few examples of *granulocytic sarcoma* of the ovary have been reported.

Small Cell Carcinoma

Small cell carcinoma is a biologically aggressive neoplasm of uncertain histogenesis that occurs predominantly in young women.[369-374]

Clinical Features. Small cell carcinoma occurs in women 13 to 55 years of age, but most of these tumors arise in young women who are younger than 30.[370-372] The average age is 25 years. The typical clinical presentation is with abdominal pain, nausea or vomiting, or an abdominal mass. About two thirds of patients have hypercalcemia, but this is rarely responsible for the presenting symptoms. Most tumors are confined to the ovary at diagnosis, though extraovarian spread is not unusual. Bilateral tumors are uncommon except in patients with extensive intra-abdominal tumor dissemination.

Macroscopic Appearance. Small cell carcinoma measures 8 to 27 cm, with an average diameter of 15 cm. It is a solid, nodular, gray or tan tumor that contains small cysts. Zones of hemorrhage and necrosis are common.

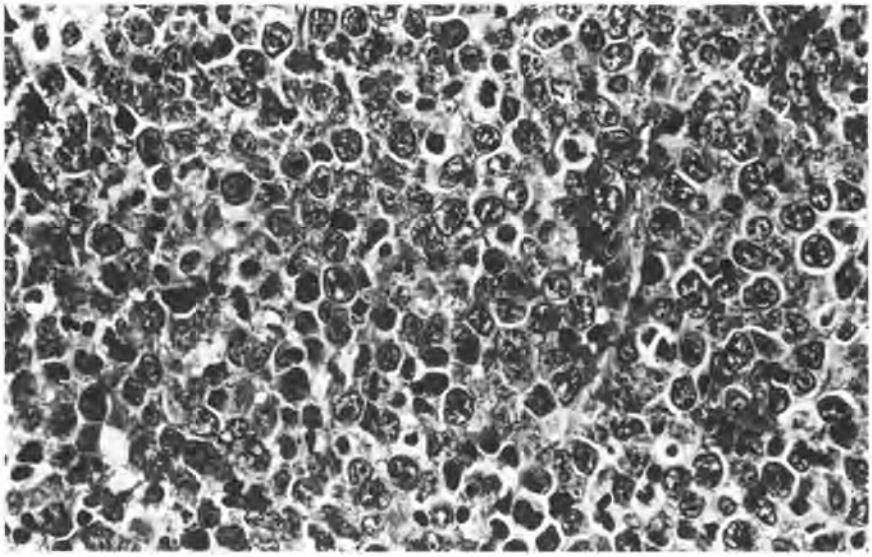

FIGURE 6-79 Large cell lymphoma involving the ovary.

Microscopic Appearance. Most tumors are composed of uniform small cells with round, oval, or fusiform nuclei and scanty cytoplasm (Color Figure 6-16). The nuclei are hyperchromatic, but the chromatin is fine. Nucleoli, if present, are small. Nuclear grooves are uncommon. There are frequent mitotic figures. Irregular follicle-like structures filled with lightly eosinophilic material are a characteristic finding in small cell carcinoma. There is focal or extensive variation from the typical morphology in one third of these neoplasms. Some tumors contain a malignant spindle cell component, and others contain large cells with abundant eosinophilic cytoplasm and vesicular nuclei with prominent nucleoli.[369,372]

Immunohistochemical testing for low-molecular-weight cytokeratins generally is positive.[261,372] One third of small cell carcinomas are immunoreactive for epithelial membrane antigen, and more than half react with antibodies against vimentin.[261,372] Neuron-specific enolase is positive in more than two thirds of small cell carcinomas, and occasional tumors are immunoreactive for parathyroid hormone.[261,371] Testing for α-fetoprotein is negative, but there is focal weak reactivity with antibodies against α_1-antitrypsin in some tumors.[372]

Ultrastructurally, small cell carcinoma has features of an epithelial neoplasm.[370–373] Groups of tumor cells are delimited by a discontinuous basal lamina, and there are desmosome-like junctions between adjacent cells. Lumina are rare, and the cells lining them have microvilli. The nuclei frequently are indented, and some contain nucleoli. The most characteristic ultrastructural feature is the presence of prominent, dilated cisterns of rough endoplasmic reticulum filled with amorphous, moderately electron-dense material. Phagolysosomes, polyribosomes, and mitochondria are noted. Dense-core neurosecretory granules were observed in 3 of 4 tumors studied by one group,[371] but were not detected by others,[370,372,373] despite a careful search for them.

The morphology is variously interpreted as suggesting that small cell carcinoma is a type of sex cord stromal tumor,[373] a neuroendocrine tumor,[371] or a germ cell tumor related to yolk sac tumor.[372] The histogenesis is uncertain, and small cell carcinoma is designated as an unclassified ovarian carcinoma.

Differential Diagnosis. The main differential diagnostic considerations are malignant lymphoma and juvenile granulosa cell tumor. In contrast to small cell carcinoma, *lymphoma* is commonly bilateral and frequently involves the abdominal lymph nodes or the spleen. Immunohistochemical staining is helpful, because lymphoma reacts with leukocyte common antigen and various B-cell antibodies, whereas small cell carcinoma reacts with cytokeratin and neuron-specific enolase.

The differentiation from *juvenile granulosa cell tumor* can be difficult, particularly if macrofollicular structures are present in the tumor. Juvenile granulosa cell tumor frequently produces estrogenic symptoms, whereas small cell carcinoma causes hypercalcemia. Luteinized tumor cells are not present in small cell carcinoma. The pattern of immunoreactivity of the neoplasm can be helpful. Juvenile granulosa cell tumor is more likely to be vimentin positive, and small cell carcinoma is more likely to be cytokeratin positive or to exhibit a positive reaction for epithelial membrane antigen.[261] Both neoplasms are immunoreactive for neuron-specific enolase.[261] The demonstration by electron microscopy of dilated rough endoplasmic reticulum containing amorphous material favors a diagnosis of small cell carcinoma.

Undifferentiated carcinoma occasionally is considered in the differential diagnosis. It occurs in older women, is more pleomorphic, and usually contains some foci of differentiated epithelial carcinoma. *Metastatic small cell carcinoma* of bronchial or other origin lacks follicular structures, occurs in older

women, is usually bilateral, and contains dense-core neurosecretory granules that are revealed by electron microscopy.

Clinical Behavior and Treatment. Small cell carcinoma is an aggressive neoplasm with high mortality even when disease is localized at diagnosis.[369] Although the average patient is young, the optimal surgical treatment probably is hysterectomy with bilateral salpingo-oophorectomy. There is no effective adjuvant treatment. The response to radiation therapy or chemotherapy is limited,[370,374] and overall survival is less than 20%.[370–372,374]

Germ Cell Tumors

Tumors derived directly from germ cells include dysgerminoma and embryonal carcinoma. Germ cell tumors also include those tumors derived indirectly from germ cells by embryonic (eg, teratoma) or extraembryonic (eg, choriocarcinoma and yolk sac tumor) differentiation (Table 6-6). Benign cystic teratomas are among the most common ovarian tumors.[243] Malignant germ cell tumors are rare and occur most often in children and in women younger than 30 years.

Dysgerminoma

Dysgerminoma is the most common malignant germ cell tumor of the ovary.[243,244,375,376] Nevertheless, it is a rare neoplasm, accounting for only 1% to 2% of all malignant ovarian tumors.

Clinical Features. Dysgerminoma develops mainly in children and young women.[18,377–381] Nearly all patients are between 5 and 55 years of age. The average age is 22 years, and 85% to 90% of patients are 30 years of age or younger.[382]

The clinical presentation is nonspecific. The most common symptoms are abdominal mass, increasing abdominal girth, and abdominal pain.[377,378,381,383] Twenty percent of patients have menstrual abnormalities.[379] Hormonally active tumors are rare, and patients with these tumors have secondary amenorrhea and increased levels of human chorionic gonadotropin.[384,385] Some patients with dysgerminoma have elevated levels of serum lactic dehydrogenase, which can serve as a useful tumor marker.[386,387] Levels of serum α-fetoprotein are within normal limits.[386] The average duration of symptoms before diagnosis is about 5 months.[378] Dysgerminoma is the most frequent malignant neoplasm arising in patients with gonadal dysgenesis.[380,382,388]

Most patients with dysgerminoma have localized disease. Tumor is confined to the ovaries (stage I) in 70% to 80% of cases.[377,378,381,386] Dysgerminoma is typically unilateral, but in contrast to other types of malignant germ cell tumors, bilateral growth (stage IB) occurs in 5% to 10% of cases.[377,381] Involvement of the contralateral ovary can be detected only by microscopic examination in about 50% of the bilateral cases. Biopsy of a grossly normal contralateral ovary is therefore frequently recommended if treatment is to be by unilateral salpingo-oophorectomy.[377,389] Dysgerminoma metastasizes by way of the lymphatics to the para-aortic lymph nodes.[380,386]

Macroscopic Appearance. Dysgerminoma occurs more frequently in the right ovary than in the left.[382] It is a firm, nodular tumor with smooth surfaces. It is usually large when detected, with an average diameter of 15 cm. The cut surface is fleshy and gray, tan, or white (Color Figure 6-17). Some tumors have a lobulated appearance. Hemorrhage and necrosis are common in large tumors.

Microscopic Appearance. The microscopic appearance is identical to that of seminoma of the testis. The tumor cells are medium-sized and polyhedral with round, vesicular nuclei that have reticular chromatin and prominent nucleoli. Mitotic figures are frequent. The cytoplasm, which is best preserved in tissue fixed in Bouin's or B-5 fixative, is abundant and clear or granular (Fig. 6-80). Cytoplasmic glycogen is found in some tumors. The tumor cells grow in cords or irregular nests separated by fibrous septa (Fig. 6-81). A lymphocytic infiltrate, located predominantly within the septa, is a consistent finding. Lymphoid follicles with germinal centers may be present. Epithelioid cells, multinucleated giant cells, and granulomas are seen in some tumors. Rarely, a granulomatous or fibrous reaction is extensive enough to obscure the underlying neoplastic cells. Zones of necrosis are found in some neoplasms, especially the large ones. Neoplasms in which the degree of atypia is greater than usual and in which there is a high mitotic rate (more than 30 mitotic figures per 10 high-power fields) have been termed *anaplastic dysgerminoma* by some authors; however, the prog-

TABLE 6-6
Germ Cell Tumors

Dysgerminoma
Yolk sac tumor (endodermal sinus tumor)
Embryonal carcinoma
Polyembryoma
Choriocarcinoma
Teratoma
Immature
Mature
Solid
Cystic (dermoid cyst)
Monodermal
Struma ovarii
Carcinoid
Neuroectodermal tumor
Mixed germ cell tumor
Gonadoblastoma

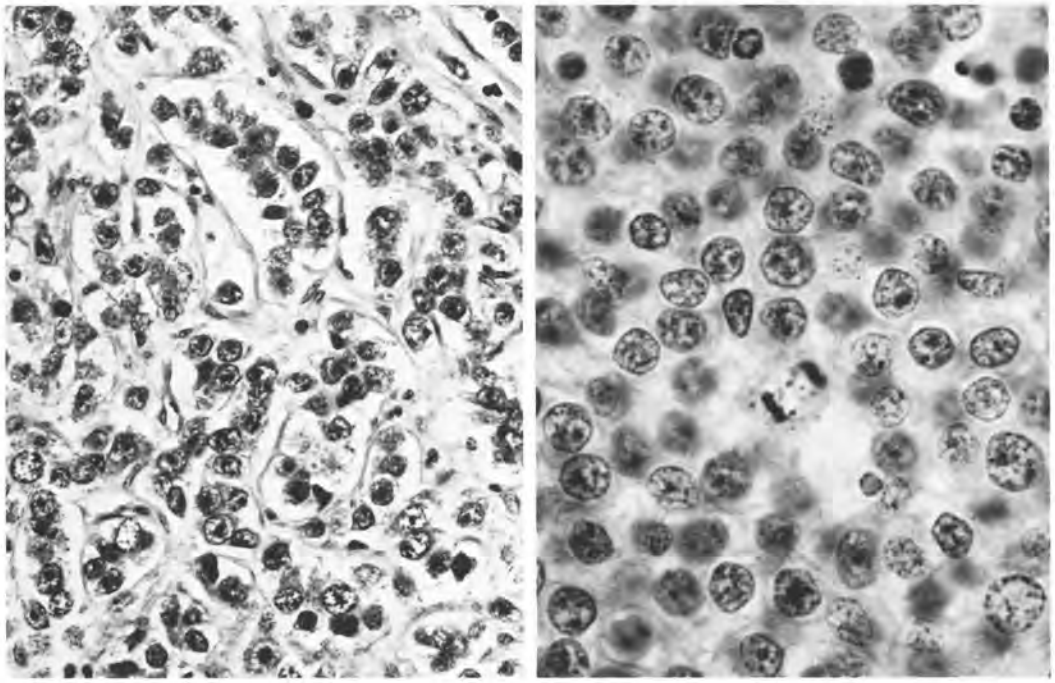

FIGURE 6-80 Dysgerminoma. Note the vesicular nuclei and clear cytoplasm.

nosis in such cases is comparable to that of typical dysgerminoma.[378] About 5% of dysgerminomas contain syncytiotrophoblastic giant cells (Fig. 6-82). No other nondysgerminomatous differentiation is found in these tumors, which are termed *dysgerminoma with syncytiotrophoblastic giant cells.*[385]

The immunohistochemistry of dysgerminoma is similar to that of testicular seminoma. Monoclonal antibodies against cytokeratin are particularly useful because germinoma cells give a negative reaction, whereas embryonal carcinoma, yolk sac tumor, and surface epithelial carcinomas exhibit positive cyto-

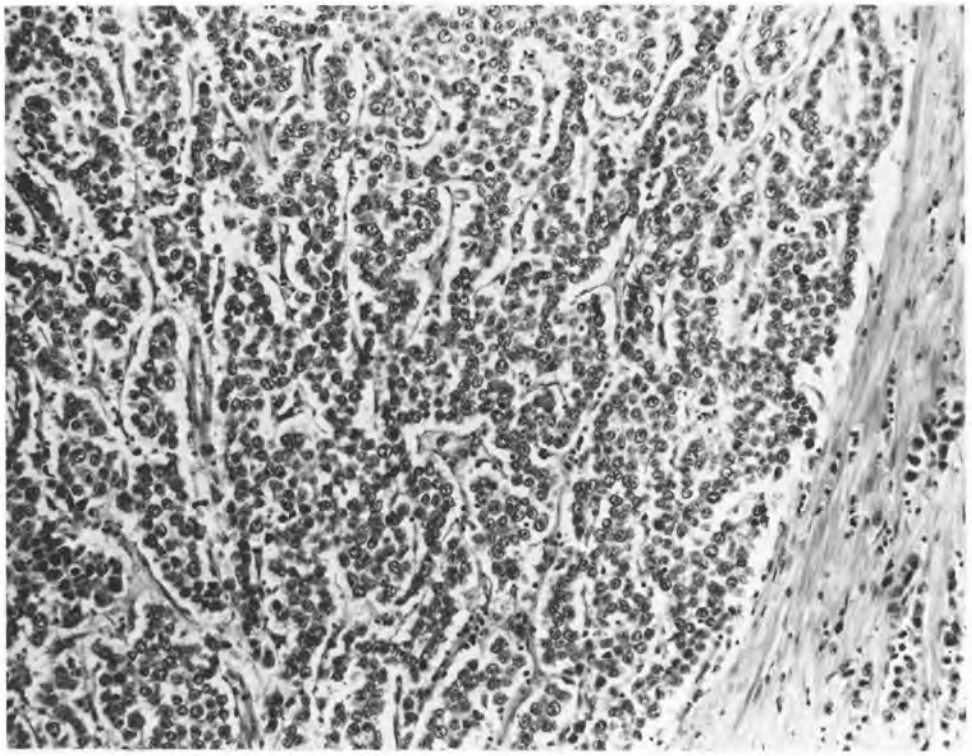

FIGURE 6-81 Dysgerminoma. This microscopic pattern shows the characteristic nests of germinoma cells separated by delicate fibrous septa.

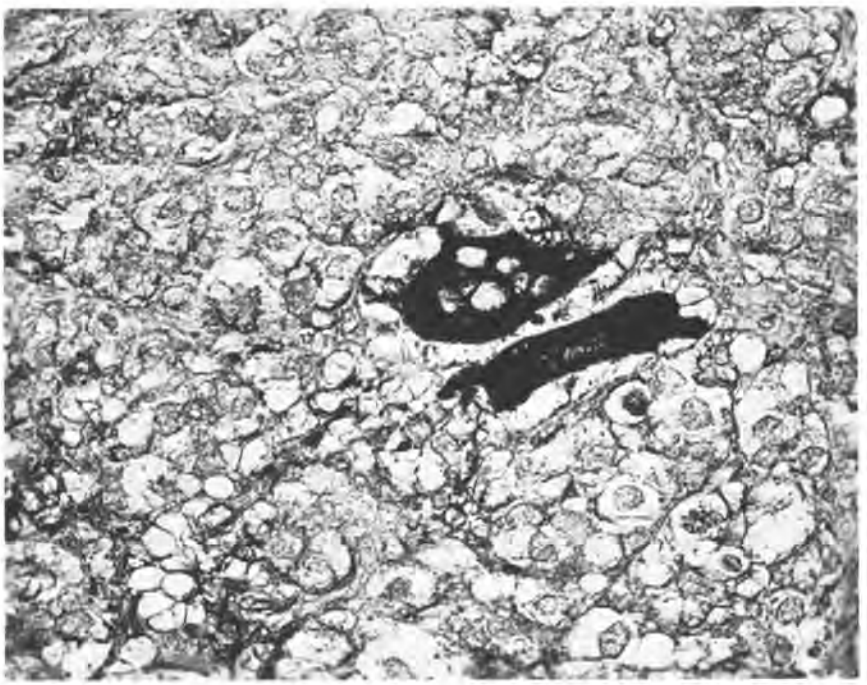

FIGURE 6-82 Dysgerminoma. An immunocytochemical reaction for human chorionic gonadotropin yields a positive reaction in the cytoplasm of the syncytiotrophoblastic giant cells.

plasmic staining.[390] Germinoma cells exhibit a positive reaction for placental alkaline phosphatase, as do other types of malignant germ cell tumors.[391,392] The syncytiotrophoblastic giant cells that rarely occur in dysgerminoma exhibit positive cytoplasmic staining for human chorionic gonadotropin.[385] Barring one exceptional case, the mononuclear germinoma cells are negative for human chorionic gonadotropin.[393] Immunostains for α-fetoprotein are negative.

Ultrastructurally, dysgerminoma cells most closely resemble oogonia.[394] They are polygonal with round central nuclei, prominent irregular nucleoli, and sparse cytoplasmic organelles. The cytoplasm contains scattered polyribosomes, annulate lamellae, scattered lysosomes, and aggregates of glycogen. There are rare desmosome-like attachments between cells.

Dysgerminoma has a characteristic cytologic appearance.[395,396] Tumor cells are found singly and in small sheets. They have large round nuclei with prominent nucleoli and a moderate amount of clear (alcohol-fixed) or basophilic (air-dried) cytoplasm (Color Figure 6-18). There is a characteristic basophilic, striated background in fine-needle aspirates that is best appreciated in air-dried smears. Lymphocytes and, in some cases, epithelioid cells are admixed with the dysgerminoma cells.

Ploidy analysis of dysgerminoma reveals that there are no diploid tumors.[397] Most dysgerminomas are aneuploid, but a sizable minority have a DNA index around 2 and may be polyploid. There is no correlation between the ploidy and the prognosis.

Differential Diagnosis. Dysgerminoma has a characteristic microscopic appearance, and most cases are easily recognized. The differential diagnosis includes embryonal carcinoma, clear cell carcinoma, malignant lymphoma, and metastatic malignant melanoma.

Patients with *embryonal carcinoma* frequently have symptoms caused by tumor secretion of human chorionic gonadotropin.[398] The tumor cells have irregular, pleomorphic nuclei. They grow in cohesive sheets and may form abortive glands. Immunostains for cytokeratin and α-fetoprotein are positive in mononuclear tumor cells. Syncytiotrophoblastic giant cells are almost always present in embryonal carcinoma, but they are rarely seen in dysgerminoma. There is no lymphocytic or granulomatous infiltrate. Ovarian embryonal carcinoma is a much rarer tumor than dysgerminoma.

Clear cell carcinoma occurs in an older age group than dysgerminoma and is more frequently bilateral. Carcinoma cells are more cohesive and frequently form glands and papillae. Immunostains for cytokeratin and other epithelial markers are positive.

Lymphoma may occur in the same age group as dysgerminoma.[363–365,399] Involvement of the ovaries is generally secondary; bilateral ovarian involvement is associated with lymphadenopathy or involvement of other extranodal sites. Malignant lymphocytes are smaller than dysgerminoma cells, and the nuclei contain coarse chromatin clumps and have less prominent nucleoli. Lymphoma cells infiltrate the ovarian stroma and surround, but often do not displace, normal ovarian structures. The fibrous septa that are characteristic of dysgerminoma are not present. Immunostains for leukocyte common antigen are positive, and the presence of other lymphocyte antigens usually can be demonstrated.

Metastatic melanoma most often is bilateral and multinodular.[400] Melanoma cells frequently have prominent eosinophilic macronucleoli and intranuclear inclusions of cytoplasm. The amphophilic or eosinophilic cytoplasm may contain melanin pigment. Positive immunostains using the HMB-45 antibody and antibodies against S-100 protein are of great assistance in correctly identifying melanoma.

Clinical Behavior and Treatment. Dysgerminoma has a favorable prognosis; the 5-year survival rate exceeds 90%.[377,379,380,383] Until recently, dysgerminoma was treated by surgical removal of the tumor followed by radiation of the pelvis and para-aortic lymph nodes. This treatment gave excellent results even in patients with extraovarian tumor spread.[378,401] Patients with unilateral encapsulated dysgerminoma (stage IA) have an excellent prognosis when treated by unilateral salpingo-oophorectomy without any adjuvant therapy.[377,381] This is the preferred treatment for such patients, who have a 5-year survival rate of greater than 95%.[386,389] Some authorities advocate biopsy of the contralateral ovary even if it appears normal because of the risk (about 5%) of occult dysgerminoma.[377] There is a slightly increased risk of local recurrence with conservative therapy, but survival is not compromised because relapses can be treated effectively.[377,379] Most recurrences are detected within 2 years, with a maximum time to recurrence of 4 years.[379,402] The standard treatment for advanced disease (stage >IA) is total abdominal hysterectomy, bilateral salpingo-oophorectomy, limited debulking, and additional treatment with chemotherapy or radiation therapy. If preservation of fertility is of paramount importance, the uterus and one ovary, if uninvolved by tumor, may be conserved.[386] Chemotherapy, especially cisplatin-based regimens, is highly effective against dysgerminoma.[403,404] The combination of bleomycin, etoposide, and cisplatin, for example, was used successfully to treat more than 90% of patients with advanced (stage III and IV) dysgerminoma.[405] Chemotherapy is more effective than radiation therapy if there is bulky tumor or if there are multiple sites of involvement. Normal menses and pregnancy are possible after radiation therapy,[378,379] but chemotherapy may pose less risk of infertility.[386,406] Chemotherapy will probably replace radiation therapy as the first-line postsurgical treatment for dysgerminoma, except when there are only small localized masses of recurrent or residual disease.[386]

Yolk Sac Tumor (Endodermal Sinus Tumor)

Yolk sac tumor is the second most common malignant germ cell tumor of the ovary. It constitutes about 1% of ovarian cancers.[375] Originally described as a tumor of mesonephric origin, it is now known to develop by differentiation of malignant germ cells into extraembryonic yolk sac structures.[407,408]

Clinical Features. Yolk sac tumors occur almost exclusively in children and young women.[409–413] Patients generally are between 5 and 45 years of age; the median age is 19 years. The tumor occurs infrequently in women older than 45.

The clinical signs are nonspecific. Most patients complain of abdominal pain.[411] Abdominal distention or a palpable abdominal mass is commonly noted.[413] About one third of patients have a fever of unexplained origin.[409] Tumor rupture or torsion produces acute abdominal symptoms in 10% of patients. Abnormal vaginal bleeding is an uncommon symptom that occurs in only about 5% of cases. The duration of symptoms is typically short, ranging from days in patients with acute abdominal symptoms to 3 months.[412] Alpha-fetoprotein is detected in the serum of most patients with yolk sac tumors.[409,412,414] Some patients have increased levels of CA-125 antigen.[414]

About 50% of patients have tumor confined to the ovary at diagnosis.[409–411] Involvement of the contralateral ovary is not seen except in advanced cases with extensive metastases.[411] It is therefore not necessary to biopsy or excise the contralateral ovary in patients with yolk sac tumor. Extraovarian spread is to the peritoneum and omentum, the para-aortic lymph nodes, and the liver. Extraovarian disease is confined to the pelvis (stage II) in about 10% of cases. More extensive metastases are present in the remaining 40%.

Macroscopic Appearance. Yolk sac tumors are large, with an average diameter of 16 cm.[409,411,412] The cut surface is predominantly solid with multiple small cysts. The tumors have a variegated appearance, with tan, white, and gray tissue admixed with areas of hemorrhage and necrosis.

Microscopic Appearance. Four major microscopic patterns have been described, and most neoplasms show a mixture of patterns.[411] The *reticular* pattern is most common. It is composed of a loose sieve-like meshwork of microcystic spaces lined by a single layer of flattened or cuboidal cells with clear or amphophilic cytoplasm and atypical, hyperchromatic nuclei (Fig. 6-83). The *festoon* or *pseudopapillary* pattern is composed of anastomosing spaces and papillae lined by columnar cells with clear or amphophilic cytoplasm and fusiform, hyperchromatic nuclei. Schiller-Duval bodies are papillary structures with a vascular, mesenchymal core covered by flattened to columnar tumor cells that project into tubules or cystic spaces (Fig. 6-84). Schiller-Duval bodies are characteristic of yolk sac tumor and are observed in two thirds of cases. In the *polyvesicular vitelline* pattern, cysts lined by cuboidal or columnar epithelial cells are surrounded by variably cellular mesenchymal stroma.[415] The *solid* pattern is characterized by sheets of small to medium-sized undifferentiated cells with a moderate amount of ampho-

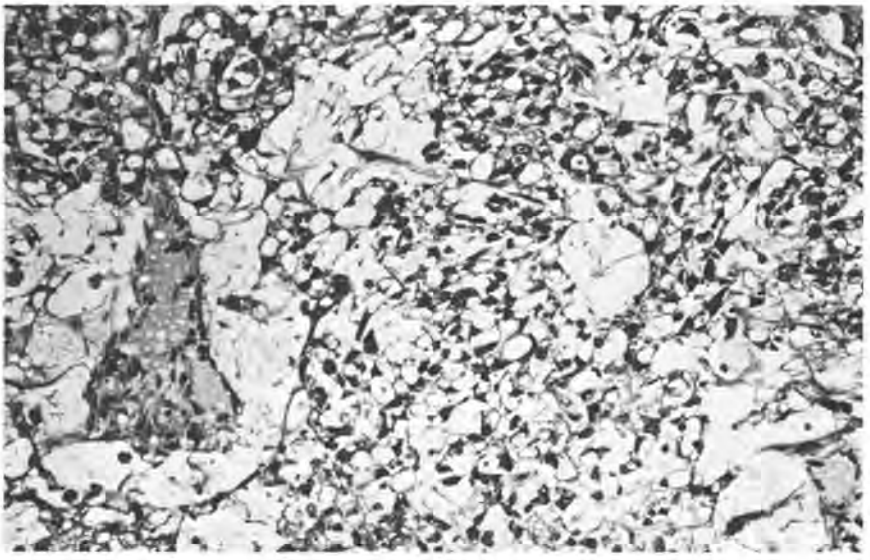

FIGURE 6-83 Yolk sac tumor, growing in a predominantly reticular pattern.

philic or clear cytoplasm. A constant finding in yolk sac tumors is eosinophilic, periodic acid-Schiff (PAS)-positive, diastase-resistant hyaline globules (see Fig. 6-84*A*). These globules are most numerous in the reticular and festoon patterns. Abundant extracellular hyaline PAS-positive material, usually seen in reticular or solid areas, is a characteristic finding in yolk sac tumors.[412,416] This material, which ultrastructurally resembles basement membrane and is composed of laminin and type IV collagen, has been interpreted as indicative of parietal yolk sac differentiation.[416] Small enteric glands lined by columnar cells and goblet cells are seen in 50% of yolk sac tumors. Myxoid stroma containing spindle or stellate cells is prominent in 25% of yolk sac tumors.[409] The spindle cells react with antibodies to cytokeratin and vimentin.[417] They may give rise to the differentiated mesenchymal components (eg, cartilage, striated muscle, and bone) that occasionally are seen in yolk sac tumors. The spindle cell component appears to be more resistant to chemotherapy than the epithelium. Luteinized stromal cells are present in or around 15% to 20% of yolk sac tumors. Syncytiotrophoblastic giant cells are present in rare cases.[412,418]

Several unusual growth patterns have been described. These are usually admixed with more typical patterns, facilitating their recognition as yolk sac tumors. *Hepatoid* yolk sac tumors are composed of sheets of large polygonal cells that resemble liver cells (Color Figure 6-19).[419] They have abundant eosinophilic or clear cytoplasm, well-defined cell borders, round central nuclei, and prominent nucleoli. *Glandular* yolk sac tumors are composed predominantly of glands of endometrioid[183] (Color Figure 6-20) or intestinal[420,421] type.

The immunocytochemical reaction that best characterizes yolk sac tumor is a positive reaction with antibodies against α-fetoprotein. Positive staining is observed in more than 75% of yolk sac tumors and is seen in tumor cell cytoplasm, in secretions within cyst and gland lumina, and in some hyaline bodies.[200,411–413,418] Tumor cells with hepatoid, endometrioid, and intestinal patterns are positive for α-fetoprotein. Immunostains for α_1-antitrypsin,[419,422] cytokeratin,[417,418] and placental alkaline phosphatase[391,392] are positive. The extracellular hyaline material in yolk sac tumors is laminin-positive.[416] Immunostains for human chorionic gonadotropin are negative except for positive cytoplasmic staining in the syncytiotrophoblastic giant cells that are rarely seen in yolk sac tumors.[412,413]

Ultrastructurally, yolk sac tumor cells vary in size and shape. The nuclei are irregular but relatively uniform in size. Prominent nucleoli are present only in a minority of tumor cells. There are microvilli on the luminal surfaces of the cells. Adjacent cells are joined by tight junctions at their luminal borders and by desmosomes elsewhere. The cytoplasm contains uniform mitochondria, abundant glycogen that may be present in large aggregates, and rough endoplasmic reticulum that is focally dilated and filled with electron-dense material. Two ultrastructural features are characteristic of yolk sac tumor.[407,415,416,423,424] First, there is abundant extracellular, amorphous, electron-dense, basement-membrane-like material. Second, intracytoplasmic electron-dense material forms rounded aggregates that are not membrane-bound and that correspond to the hyaline bodies seen by light microscopy.

The cytologic appearance of yolk sac tumor is similar in body cavity fluids and in fine-needle aspirates.[423,425,426] Tumor cells are arranged in clusters, with few isolated single cells. They have primitive nuclei and prominent nucleoli. Two cell types have been described. One has distinct cell borders and homogeneous cytoplasm with occasional small vacuoles. The other has indistinct cell borders and many variably sized cytoplasmic vacuoles, producing a bubbly

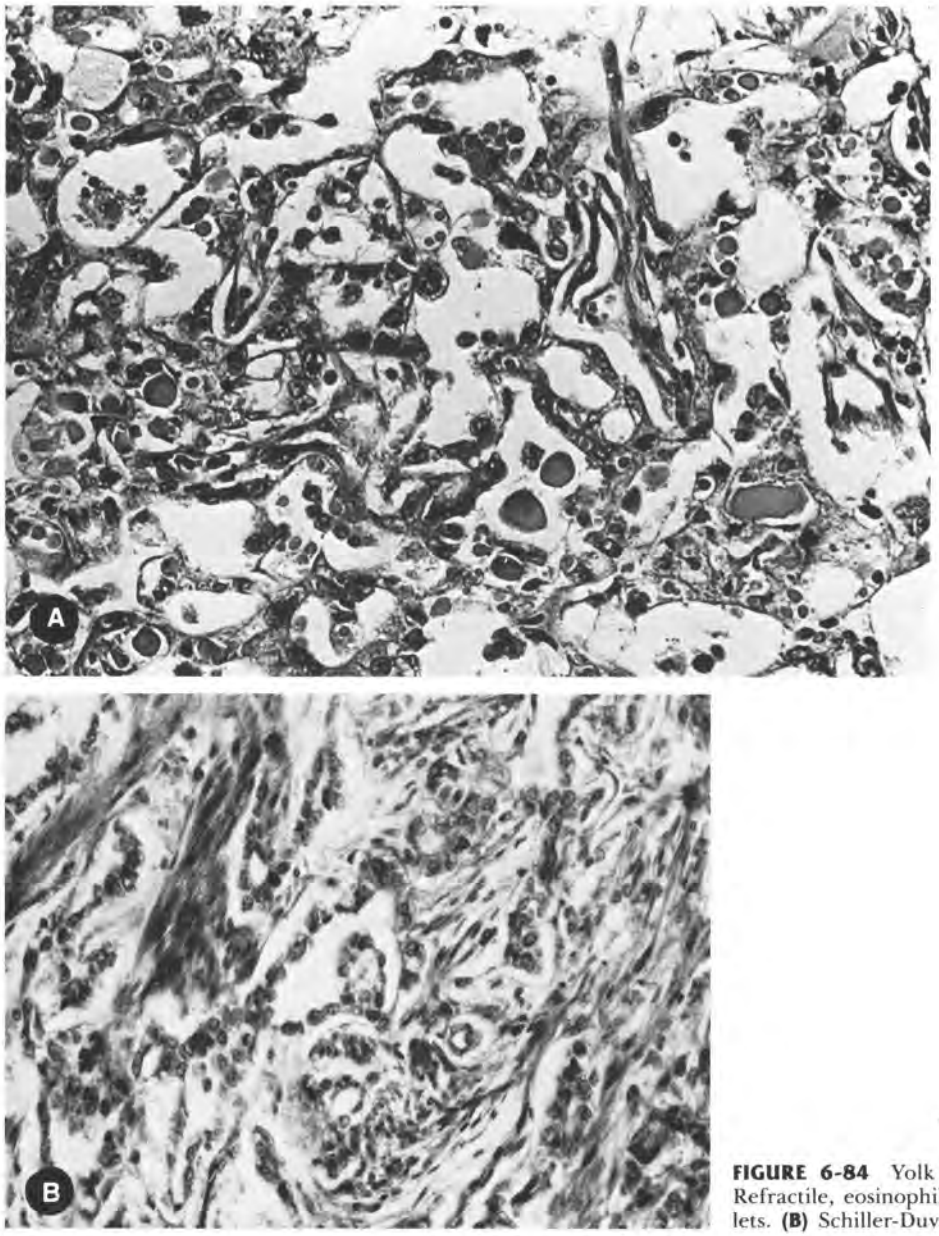

FIGURE 6-84 Yolk sac tumor. **(A)** Refractile, eosinophilic hyaline droplets. **(B)** Schiller-Duval body.

appearance. The distinctive intracytoplasmic and extracellular hyaline bodies and extracellular eosinophilic hyaline material are best visualized in air-dried smears.[423]

Nuclear DNA content has been analyzed in only a few yolk sac tumors.[427] Most are aneuploid, but the ploidy correlates poorly with the clinical outcome.

Differential Diagnosis. The differential diagnosis of yolk sac tumor includes clear cell carcinoma, other types of surface epithelial carcinoma, and embryonal carcinoma. Before Teilum showed that yolk sac tumor was of germ cell origin, pathologists thought that yolk sac tumor and clear cell (or mesonephroid) carcinoma were variants of the same neoplasm.[408]

Clear cell carcinoma occurs in an older patient population than yolk sac tumor and is more likely to be bilateral. Tubules and papillae are lined by cells with clear cytoplasm and by distinctive hobnail cells. Solid areas in clear cell carcinoma are composed of sheets of polygonal cells with clear cytoplasm and uniform nuclei. In yolk sac tumor, the solid areas contain sheets of small to medium-sized cells with primitive nuclei and frequent mitotic figures. The primitive spindle cell stroma seen in yolk sac tumor is absent in clear cell carcinoma, as are the characteristic growth patterns of yolk sac tumor, including Schiller-Duval bodies. Hyaline globules and extracel-

lular hyaline material may be present in clear cell carcinoma and are a potential cause of diagnostic difficulty.[428] Immunostains may help to differentiate between clear cell carcinoma and yolk sac tumor: a positive stain for α-fetoprotein coupled with a negative reaction with the Leu-M1 antibody is reported to characterize yolk sac tumor.[200]

Rare examples of yolk sac tumor contain areas of glandular growth that resemble *endometrioid carcinoma.*[183] The youth of the patient, the aggressive nature of the tumor, the presence of other patterns of yolk sac tumor, and positive immunostains for α-fetoprotein and α_1-antitrypsin support a diagnosis of yolk sac tumor. Rare epithelial *hepatoid carcinomas* occur in the ovary.[429] These are differentiated from yolk sac tumor by their occurrence in an older patient population and by the absence of other typical patterns of yolk sac tumor.

Embryonal carcinoma is a malignant germ cell tumor that is closely related to yolk sac tumor. Embryonal carcinoma cells are larger and more pleomorphic, however, and grow mainly in a solid pattern, with only rare and poorly formed glands. Syncytiotrophoblastic cells, which secrete human chorionic gonadotropin, are frequently present. As a result, hormonally induced symptoms are common in patients with embryonal carcinoma but rare in those with yolk sac tumor.

Clinical Behavior and Treatment. The prognosis of yolk sac tumor was poor before the widespread use of combination chemotherapy. The clinical course was characterized by rapid growth, development of metastases, and high mortality, even when the tumor appeared localized at operation. Kurman and Norris reported only a 13% 3-year survival in a large series of patients, most of whom did not receive adequate chemotherapy.[411] Yolk sac tumors are rarely bilateral, so unilateral salpingo-oophorectomy with limited debulking of extraovarian tumor is the recommended initial surgical treatment. Radiation therapy is ineffective in the treatment of yolk sac tumor.[409,430] The development of multiagent chemotherapy has radically altered the prognosis for patients with yolk sac tumor. Adjuvant vincristine, dactinomycin, and cyclophosphamide administered to patients with stage I neoplasms results in a survival rate of about 80%, and survival of patients with advanced disease approaches 50%.[409,431,432] Recent experience with chemotherapy regimens containing cisplatin document comparable results in stage I and improved survival in patients with advanced disease.[433–438] Measurement of serum α-fetoprotein levels is an effective method of monitoring the response to treatment.[414] An increase in the α-fetoprotein level may indicate the presence of recurrent tumor long before there is any clinical or radiologic evidence of recurrence. The role of second-look laparotomy is unclear.[436] Residual tumor has been identified in a few patients at second-look surgery despite a negative α-fetoprotein result.[439]

Embryonal Carcinoma

Embryonal carcinoma occurs only rarely in the ovary. The ovarian neoplasm is morphologically identical to embryonal carcinoma of the testis.

Clinical Features. Embryonal carcinoma occurs in children and young women.[398,412,413] The age ranges from 4 to 28 years, with a median age of 15 years. The most common presentation is with a pelvic or abdominal mass. More than 50% of patients complain of abdominal pain. Hormonally mediated symptoms are noted in 60% of cases. Pregnancy tests are frequently positive, and serum levels of human chorionic gonadotropin-β (β-hCG) are elevated in most patients.[398] Half of the premenarchal patients present with precocious pseudopuberty.[398] Postpubertal patients typically have menstrual abnormalities. Most embryonal carcinomas of the ovary produce α-fetoprotein. In patients with this neoplasm, β-hCG and α-fetoprotein are useful tumor markers.

Tumor is confined to one ovary (stage IA) in 60% of cases.[398] No bilateral (stage IB) cases have been reported. Metastatic spread is to the pelvic and abdominal peritoneum.

Macroscopic Appearance. Embryonal carcinoma is a soft, solid neoplasm. The average diameter is 17 cm. The cut surface is fleshy and tan or gray. Areas of hemorrhage and necrosis are almost always present, as are small cysts.

Microscopic Appearance. The tumor cells grow predominantly in sheets and nests. There are occasional clefts, glands, or papillary structures. The neoplastic cells have large, vesicular nuclei with coarse chromatin and one or two prominent nucleoli. The cytoplasm is abundant and clear or amphophilic (Fig. 6-85). Syncytiotrophoblastic giant cells are present in most embryonal carcinomas. They are admixed with the mononuclear embryonal carcinoma cells or, more frequently, are seen at the periphery of the cell nests. The stroma is loose and edematous or cellular, composed of small, primitive-appearing spindle cells.

Immunocytochemical studies reveal human chorionic gonadotropin within the cytoplasm of the syncytiotrophoblastic giant cells.[398,412,413] Occasional large mononuclear cells are positive for human chorionic gonadotropin. Such cells react with antibodies to human placental lactogen and most likely are intermediate trophoblastic cells. Alpha-fetoprotein is detected within mononuclear embryonal carcinoma cells in 70% of cases.[398]

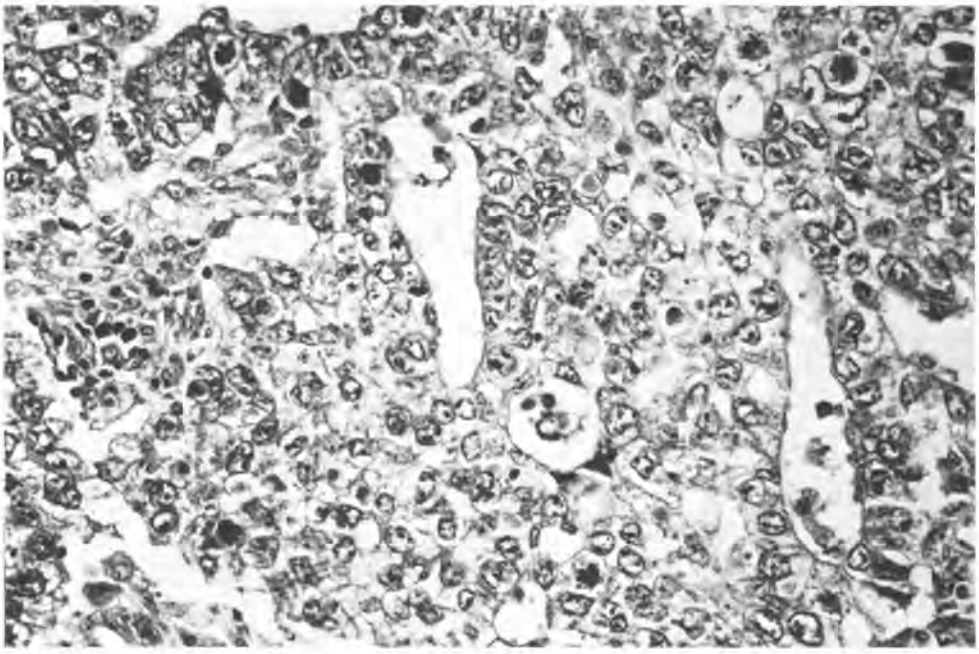

FIGURE 6-85 Embryonal carcinoma. Sheets of large atypical cells and poorly formed glandular clefts.

Differential Diagnosis. The differential diagnosis includes dysgerminoma and poorly differentiated carcinoma of surface epithelial origin. Embryonal carcinoma cells are more irregular than *dysgerminoma* cells; the nuclei are more pleomorphic, and the cytoplasm is more amphophilic. Glands and papillae are not seen in dysgerminoma. In contrast to embryonal carcinoma, dysgerminoma cells do not react with antibodies to cytokeratin or α-fetoprotein. Syncytiotrophoblastic giant cells are found much more frequently in embryonal carcinoma. *Poorly differentiated carcinoma* of surface epithelial origin occurs in an older age group than embryonal carcinoma and frequently is bilateral. No syncytiotrophoblastic giant cells are present, and immunostains for α-fetoprotein and hCG are negative.

Clinical Behavior and Treatment. Localized embryonal carcinoma is treated by unilateral salpingo-oophorectomy. Bilaterality has not been reported, and biopsy of the contralateral ovary is not recommended. Standard surgical treatment of advanced (stage >IA) disease is total abdominal hysterectomy, bilateral salpingo-oophorectomy, and limited debulking. Unilateral salpingo-oophorectomy and limited debulking surgery followed by chemotherapy can be considered for advanced tumors when conservation of fertility is important, if the contralateral ovary and uterus are uninvolved.

Before effective combination chemotherapy was available, embryonal carcinoma often progressed rapidly. Survival in stage IA was only 50%.[398] Combination chemotherapy is effective in embryonal carcinoma but response rates are difficult to determine because embryonal carcinoma of the ovary is so rare. Some patients with advanced disease can be cured with cisplatin-based chemotherapy regimens.[438]

Serum assays for human chorionic gonadotropin and α-fetoprotein are useful in the evaluation and follow-up of patients with embryonal carcinoma. If serum levels of either or both markers remain elevated after treatment, or if they become elevated during follow-up, the patient has recurrent or metastatic tumor. Serum markers are a sensitive method of monitoring patients with embryonal carcinoma because increased levels often are noted weeks or months before a recurrence is detected by clinical or radiographic examination.

Choriocarcinoma

Pure primary ovarian choriocarcinoma of germ cell origin is extremely rare.[375,440,441] Only 0.04% of ovarian tumors on file at the Armed Forces Institute of Pathology were choriocarcinomas.[375] Choriocarcinoma is seen more frequently as a component of a mixed germ cell tumor.

Clinical Features. Choriocarcinoma of the ovary occurs only in children and young women. Presenting symptoms include abdominal pain and abdominal bleeding. Premenarchal children may have precocious pseudopuberty.[440] Pregnancy tests are positive, and serum levels of β-hCG are elevated.[440,442,443]

Macroscopic Appearance. Choriocarcinoma is a large, soft, purple-red tumor between 4 and 25 cm in diameter.[440] The cut surface is hemorrhagic and necrotic.

Microscopic Appearance. A large portion of the tumor is hemorrhagic and necrotic. Viable tumor cells are best seen at the periphery, where cytotrophoblastic and syncytiotrophoblastic cells grow in a plexiform pattern. The cytotrophoblastic cells have abundant, clear cytoplasm and well-defined cell borders. They have irregular vesicular nuclei, some of which have prominent macronucleoli. The syncytiotrophoblastic cells have multiple hyperchromatic nuclei and abundant basophilic or amphophilic vacuolated cytoplasm. Immunostains for human chorionic gonadotropin disclose a positive cytoplasmic reaction in the syncytiotrophoblastic giant cells.[443]

Differential Diagnosis. *Gestational choriocarcinoma* is the most important differential diagnostic consideration. If the patient is premenarchal, the choriocarcinoma is of germ cell origin.[440,441] Metastatic or primary gestational choriocarcinoma is as common as primary choriocarcinoma of germ cell origin in young women.[441] There are no morphologic differences between gestational choriocarcinoma and choriocarcinoma of germ cell origin. The clinical history may help in the differential diagnosis. The choriocarcinoma can be proved to be of gestational origin if a paternal component can be identified in the tumor cell genome by DNA analysis.[444]

Clinical Behavior and Treatment. Choriocarcinoma of the ovary is treated by surgical excision followed by combination chemotherapy. Most patients are children or young women, so unilateral salpingo-oophorectomy is the surgery of choice. Total abdominal hysterectomy and bilateral salpingo-oophorectomy may be required if the contralateral ovary or uterus is involved. Favorable results have been described, even with suboptimal chemotherapy.[440] Recent reports indicate that patients with advanced disease can be treated successfully with platinum-containing chemotherapy protocols.[438]

Teratoma

The benign cystic teratoma (or dermoid cyst) is the most common ovarian neoplasm. It comprises between 26% and 44% of all ovarian tumors.[243,244] The other types of teratoma are all uncommon. Teratomas originate from germ cells. They have a female sex chromatin pattern (positive), and nearly all cases have a 46,XX karyotype. Experimental studies suggest that most teratomas originate by parthenogenesis from single haploid germ cells.[445] Restriction fragment length polymorphism analysis supports an origin from a single germ cell after the first meiotic division, with failure of the second meiotic division.[446] Some teratomas may originate from cells that have failed to complete the first meiotic division.[446]

Mature (Benign) Teratoma. These are cystic or, rarely, solid tumors containing tissues derived from the three embryonic germ layers: ectoderm, mesoderm, and endoderm. The common benign cystic teratoma is frequently referred to as a *dermoid cyst.*

Clinical Features. Benign teratomas occur in patients of all ages, but 85% are detected in patients between 20 and 50 years of age.[244] The peak incidence is in patients between 20 and 29 years of age. Benign teratomas grow slowly, and small neoplasms are asymptomatic. Symptoms such as pelvic pressure or pain appear when the tumor attains a large size. About 10% of benign cystic teratomas are bilateral.[376] Potentially serious complications include torsion and rupture.

Macroscopic Appearance. Benign teratomas range in size from small neoplasms several centimeters in diameter to large neoplasms weighing several kilograms. They are round, and their surfaces are smooth. Their consistency varies from firm to soft. The cut surface has a unilocular or multilocular cystic appearance (Color Figure 6-21). The cysts contain tufts of hair, yellow grumous material, or oily or serous liquid. Firm, white cartilage, gritty bone, and intact teeth may be identified (Fig. 6-86). Soft, gelatinous, gray-tan material corresponding to glial tissue, and brown, translucent zones of thyroid tissue frequently are present. Dense, solid foci within an otherwise cystic teratoma are unusual and should be sampled carefully for histologic study. A few mature (benign) teratomas are entirely solid, but these can be differentiated from immature teratoma only by microscopic study.

Microscopic Appearance. Benign teratomas contain a variable admixture of ectodermal, mesodermal, and endodermal structures. Ectodermal derivatives such as skin, hair follicles, and adnexal sebaceous and sweat glands are encountered most often (Fig. 6-87). When they are the main structures, the tumor is commonly referred to as a *dermoid cyst.* Other commonly observed tissues include neural (usually glial) tissue, choroid plexus, digestive tract mucosa (including endocrine cells), respiratory mucosa, renal tissue, adipose tissue, smooth or striated muscle, peripheral nerve, thyroid tissue, dental structures, bone or cartilage, and a loose connective tissue framework that surrounds the other elements (Figs. 6-88 and 6-89). Individual tissues occasionally dominate to the extent that the tumor can be considered a monodermal teratoma. Cystic spaces lined by flattened epithelium or granulation tissue and surrounded by multinucleated giant cells and lipophages are found in some teratomas. The foreign-body granulomatous reaction is caused by disruption of the epithelium with liberation of the cyst contents into the surrounding tissue.

FIGURE 6-86 Macroscopic appearance of an ovarian teratoma, showing an abortive tooth.

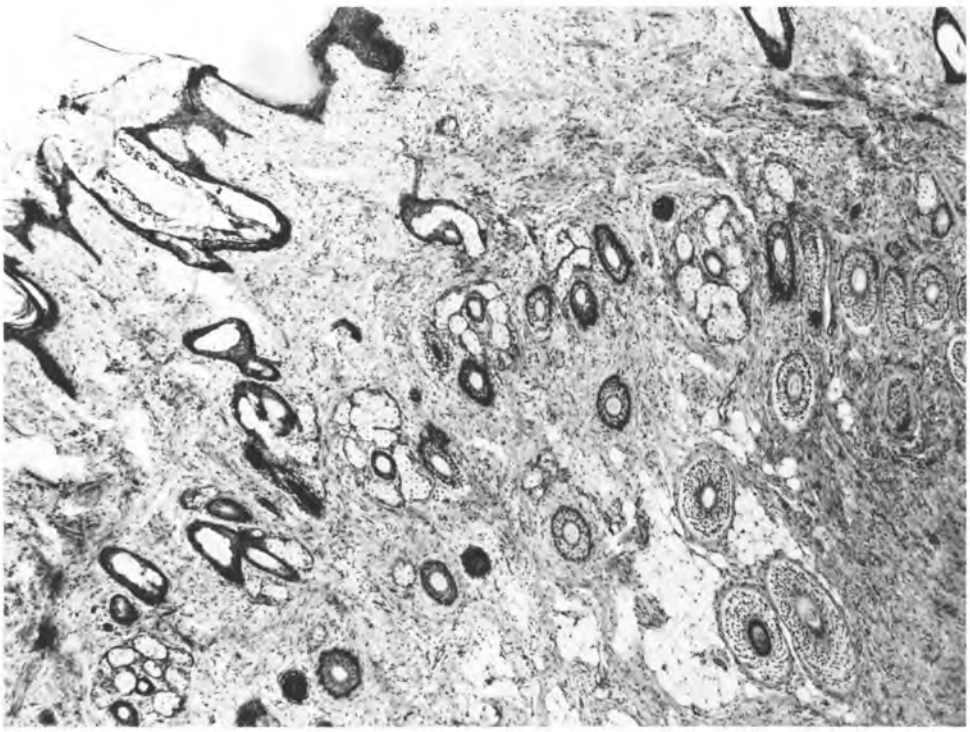

FIGURE 6-87 Squamous epithelium, sebaceous and sweat glands, and hair follicles in a benign cystic teratoma.

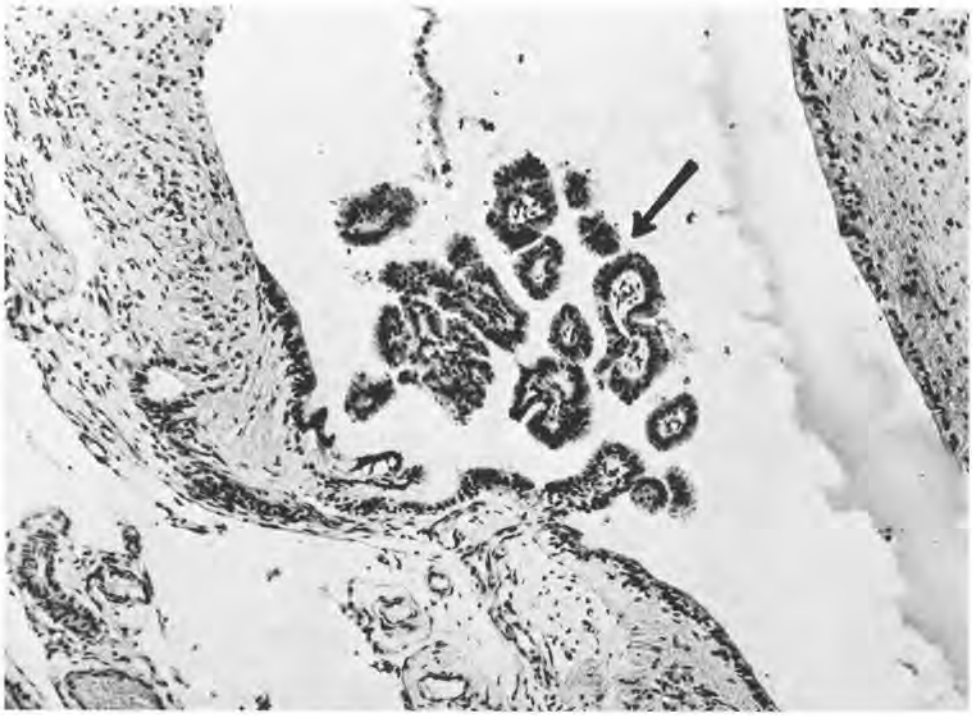

FIGURE 6-88 Glia and choroid plexus (*arrow*) in a benign cystic teratoma.

Clinical Behavior and Treatment. Mature teratomas are benign neoplasms and can be treated conservatively. Cystectomy is adequate treatment, particularly in children and young women. Peritoneal glial implants are detected in rare patients with mature solid teratoma of the ovary.[447,448] The implants are composed of mature glia (grade 0) and do not adversely affect survival.

Malignant transformation occurs in 1% to 3% of benign cystic teratomas.[449,450] This complication is typically seen in postmenopausal women, but it also occurs in premenopausal women and children. In contrast to immature teratoma, which is composed of embryonal tissues, the malignant tumors that arise in benign cystic teratoma resemble typical adult neoplasms. Squamous carcinoma is the most common malignant tumor arising in a benign cystic teratoma, accounting for about 90% of cases.[451,452] The remainder are adenocarcinoma, sarcoma, melanoma, or other rare tumor types.[453,454] The prognosis for patients with a malignant neoplasm arising in a benign cystic teratoma is unfavorable; most die within 1 year of diagnosis.

Immature Teratoma. Immature teratoma is the third most common malignant germ cell tumor of the ovary, representing 20% of such tumors at a major cancer center.[431]

Clinical Features. Immature teratoma occurs in children and young adults. The age of occurrence ranges from 6 to 40 years, with an average age of about 20 years.[431,455–459] The clinical presentation is with abdominal pain, palpable abdominal mass, or abdominal distention. Rare patients have acute abdominal symptoms due to torsion or rupture of the neoplasm.[460] The duration of symptoms ranges from 1 day to 6 months, with an average of 1 month.[460] Serum levels of α-fetoprotein are elevated in 30% to 50% of patients and may serve as a useful tumor marker.[460–462] Levels of the tumor marker CA-125 are frequently elevated in patients with immature teratoma.[461] Localized tumors (stage I) are found in 50% to 80% of patients. Bilateral (stage IB) immature teratoma is not reported. The contralateral ovary is only involved in patients with advanced disease, in whom its involvement reflects metastatic spread.[457,459,460] Metastatic spread is transcoelomic to the pelvic and abdominal peritoneum and the omentum. A benign cystic teratoma is present in the contralateral ovary in 10% to 15% of cases.[457,460,463]

Macroscopic Appearance. These are unilateral tumors of firm consistency. They range from 6 to 30 cm in diameter; the average diameter is 18 cm. The cut surface typically is partly cystic and partly solid. Cysts bearing a resemblance to a dermoid cyst are noted in 26% of cases.[463] The solid portion of the tumor is gray to brown and varies from soft and fleshy to hard and gritty. Chondroid differentiation is occasionally identified as a hard gray or white translucent area.

Microscopic Appearance. Tissues derived from all three germ cell layers are present, but ectodermal and mesodermal derivatives predominate. Typical

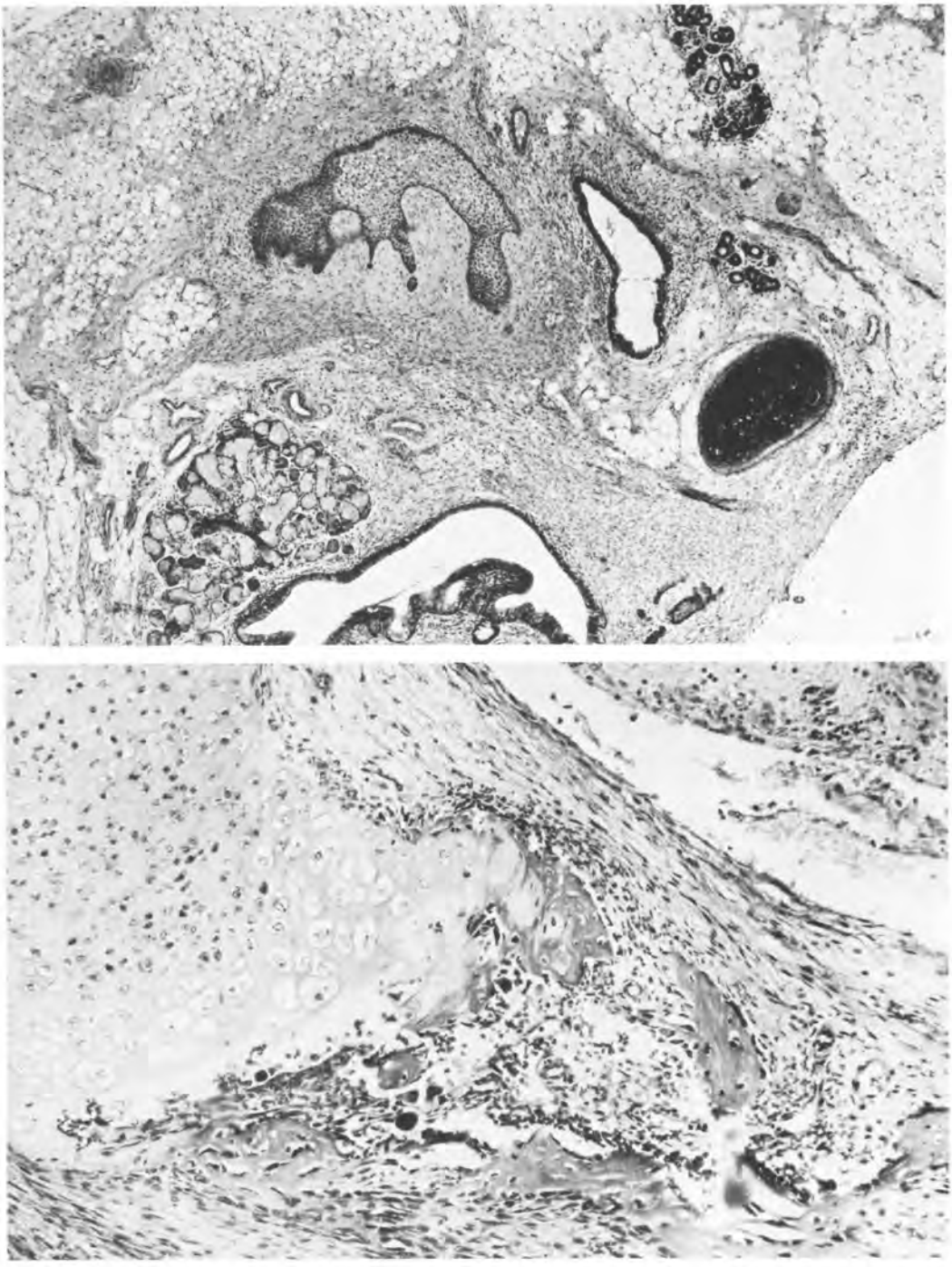

FIGURE 6-89 Benign teratoma. **(A)** Squamous and gastrointestinal epithelium. **(B)** Cartilage and bone.

ectodermal derivatives include skin, skin appendages, and neuroectoderm. Neuroectodermal elements are the most easily recognized and measured immature tissues (Fig. 6-90). They include sheets of immature neuroepithelium, neuroepithelial tubules (Fig. 6-91) and rosettes, neuroblastic elements, immature glia, and primitive retina with melanin pigmentation. The most common mesodermal tissues include cartilage, bone, and embryonal stroma. Embryonal stroma, a readily identified indicator of immaturity, is composed of small, densely cellular fusiform cells that exhibit mitotic activity. Endodermal differentiation is mainly represented by intestinal and bronchial structures. Immature teratoma must be graded because the prognosis depends on the grade and stage. Immaturity is measured using a grading system that rates teratomas from grade 0 (a neoplasm composed entirely of mature tissues) to grade

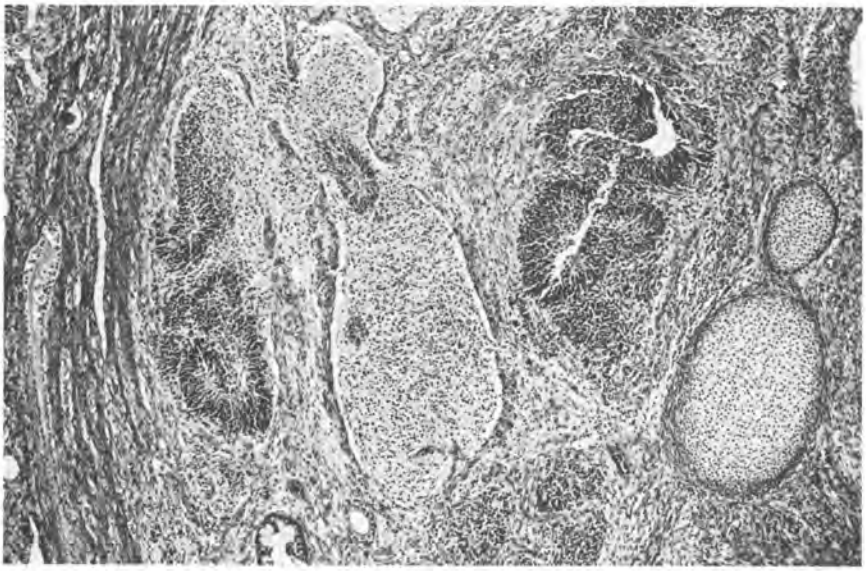

FIGURE 6-90 Immature teratoma with neuroepithelium and embryonal cartilage.

3 (a neoplasm containing abundant immature tissue; Table 6-7).[459] Metastases from an immature teratoma may be grade 0, but the primary ovarian neoplasm must, by definition, be grade 1, 2, or 3 (Fig. 6-92).

Rare examples of immature teratoma are composed predominantly or entirely of immature neuroectodermal structures including sheets of small round cells, primitive neuroepithelium, rosettes, and glia.[455,464] Such neoplasms have been termed *malignant neuroectodermal tumor.*[464]

Immunohistochemical evaluation of immature teratoma reveals positive staining of glia with antibodies to glial fibrillary acidic protein (GFAP).[225,465,466] Fibrillary and cell body staining are encountered. This reaction occasionally helps identify inconspicuous foci of glial differentiation. Primitive neuroepithelial elements do not stain with GFAP. There is a positive staining reaction with antibodies to neurofilaments in some tumors.[225,465] Neuron-specific enolase stains glial elements and, with less intensity, neuroepithelium.[465] Endodermal derivatives such as intestinal and respiratory epithelium contain argyrophilic cells, which react with a variety of antibodies against neurohormonal peptides.[225] In accord with the clinical finding of increased serum α-fetoprotein in as many as 50% of cases, there is positive staining for α-fetoprotein in such yolk sac endodermal derivatives as gland-like vesicles, intestinal epithelium, and liver.[225,462]

Electron microscopic study reveals glial elements, immature neuronal cells, occasional immature ependymal-type cells, and primitive undifferentiated cells.[465]

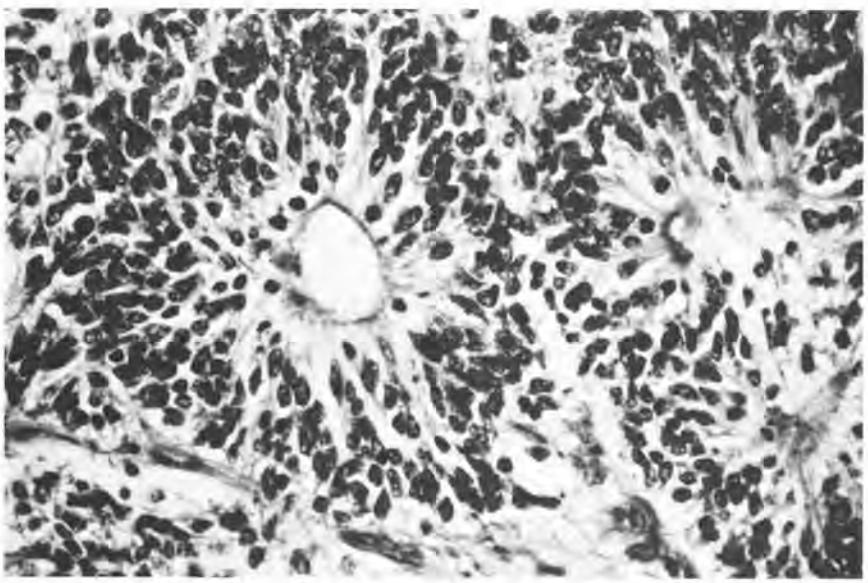

FIGURE 6-91 Neuroepithelium forming tubules in an immature teratoma.

TABLE 6-7
Histologic Grading of Immature Teratoma of the Ovary

Grade	*Immature Tissue*	*Neuroepithelium*
0	Mature tissues only	None
1	+	Rare, not more than 1 LPF per slide
2	++	Common, not more than 3 LPF per slide
3	+++	Prominent, 4 or more LPF per slide

LPF, low-power field(s).

Differential Diagnosis. Immature teratoma must be differentiated from mature cystic or solid teratoma and from carcinosarcoma. Most *mature teratomas* are predominantly cystic. They contain only mature tissues, which tend to be arranged in an organized pattern. In contrast, immature teratoma is likely to have extensive areas of solid growth. Disorganized immature tissues are admixed with mature elements. Immature neuroepithelium is the most common immature element, but it should not be confused with mature cerebellar tissue. Primitive embryonal stroma is frequently noted. *Carcinosarcoma* is a highly malignant neoplasm of surface epithelial derivation. It occurs almost exclusively in postmenopausal women and is composed of malignant adult neoplastic epithelium and mesenchyme, often including heterologous elements. Immunohistochemistry may help in the differential diagnosis, because carcinosarcoma does not display immunoreactivity to neurohormonal peptides, α-fetoprotein, neurofilaments, or GFAP. Finally, immature teratoma is a frequent constituent of *mixed germ cell tumor*, so adequate sampling to exclude other tumor types is essential for accurate diagnosis.

Clinical Behavior and Treatment. Conservation of fertility is important in most patients, so surgical treatment should be conservative. Patients with localized (stage IA) tumors can be treated by unilateral salpingo-oophorectomy. Involvement of the contralateral ovary is so rare that biopsy is unnecessary. A tumor in the contralateral ovary is most likely a benign cystic teratoma, which should be managed by cystectomy.[460] More advanced tumors are treated by unilateral salpingo-oophorectomy and excision of extraovarian tumor. Effective chemotherapy is available, and if the contralateral ovary is not involved it may be conserved. If preservation of fertility is not an issue, or if the contralateral ovary is involved, hysterectomy and bilateral salpingo-oophorectomy are appropriate. A study conducted at the Armed Forces Institute of Pathology before the availability of effective chemotherapy provides a historical baseline for prognosis in immature teratoma.[459] Survival depended on stage and grade. Survival in stage IA was 100% for grade 1, 70% for grade 2, and 33% for grade 3 tumors. Survival with advanced disease was about 50%, but too few tumors were studied to relate both grade and stage to prognosis. Based on these historical results, treatment of stage IA, grade 1 immature teratoma is by surgery alone. Patients with stage IA, grade 3 immature teratoma and those with advanced disease receive chemotherapy. Treatment of patients with stage IA, grade 2 tumors is controversial, with some authors advocating chemotherapy[460,461,467] and others not.[455,456] The combination of vincristine, dactinomycin, and cyclophosphamide, as well as cisplatin-containing regimens and

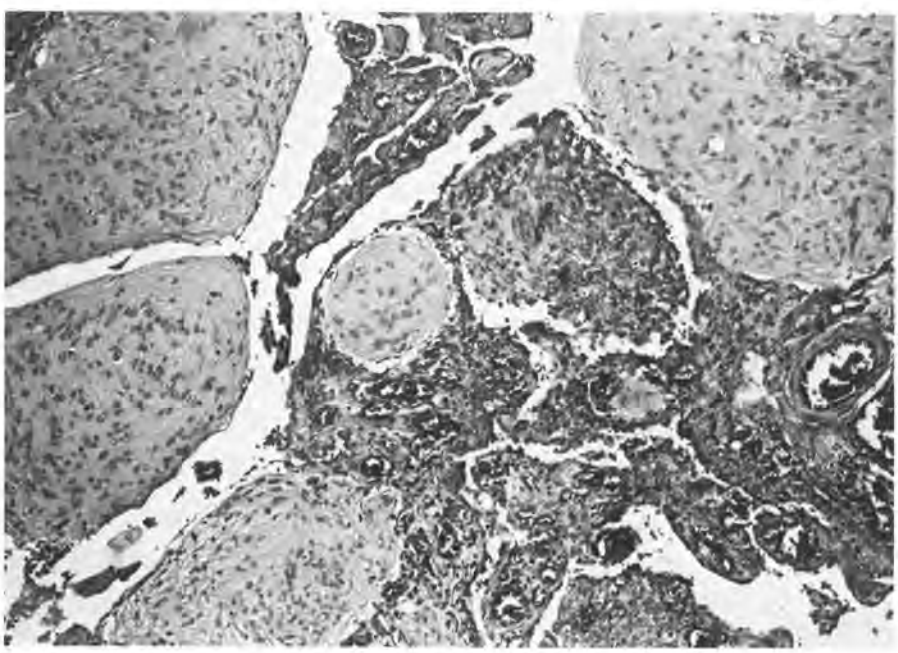

FIGURE 6-92 This peritoneal implant, which was derived from an immature teratoma, is composed entirely of benign glial tissue with reactive mesothelial and vascular hyperplasia.

doxorubicin, are effective adjuvant chemotherapies, with survival rates of 90% to 100% in patients with localized disease.[468] Patients who have residual gross tumor or recurrent tumor have a less favorable outcome. About 55% of such patients can be cured with chemotherapy regimens that include cisplatin.[438]

The prognosis in immature teratoma depends on the stage and grade of the primary tumor and on the grade of the peritoneal implants. In some instances, the peritoneal implants contain only mature tissues; such implants usually are composed exclusively or partly of mature glia (see Fig. 6-92). Grade 0 implants behave in a clinically benign manner and do not adversely affect the prognosis.[448,457,459,460,469–471]

Monodermal Teratomas

Struma Ovarii. Struma ovarii is a monodermal teratoma composed totally or in overwhelming proportion of thyroid tissue.[472] It accounts for 1% to 3% of benign teratomas of the ovary. The term *struma ovarii* is not used for dermoid cysts that contain small areas of thyroid tissue or for teratomas composed predominantly of other elements. Adequately documented cases producing hyperthyroidism are rare.

Most strumas are encapsulated neoplasms several centimeters in diameter. On cross section, they are red, with a shiny, meaty appearance (Fig. 6-93). Microscopic examination shows normal thyroid tissue (see Fig. 6-93) or thyroid tissue showing degenerative changes such as hemorrhage, cyst formation, and fibrosis. Microfollicular adenomatoid nodules may resemble granulosa cell tumor or carcinoid, creating a possible source of confusion. Immunohistochemical staining for thyroglobulin reveals a positive reaction in struma ovarii, confirming the diagnosis.

The clinical behavior is benign, and simple excision is adequate treatment. Any of the histologic types of thyroid carcinoma may arise in a struma. Most examples have been classified as carcinoma on histologic grounds alone, but cases with metastases have been reported.[472–477] Malignant struma is treated by total hysterectomy with bilateral salpingo-oophorectomy, thyroidectomy, and therapeutic doses of iodine 131.

Carcinoid Tumor. Carcinoid tumors of the ovary are rare. They are considered to be monodermal teratomas because most are associated with other teratomatous elements. Pure carcinoids occur in the ovary; most of these probably develop in and subsequently overgrow a teratoma. It is theoretically possible for a carcinoid to arise from neuroendocrine cells in mucinous tumors.

Most patients present with nonspecific symptoms. The carcinoid syndrome occurs in about one third of patients with insular carcinoid, mainly those with large neoplasms.[478] It is rarely associated with other types of primary ovarian carcinoid. The clinical presentation can be dramatic with flushing, diarrhea, and heart disease. The carcinoid syndrome can occur in the absence of metastases because venous blood from the ovaries does not pass through the liver. Metastatic intestinal or bronchial carcinoids also may be encountered in the ovary. These, too, may be associated with the carcinoid syndrome.

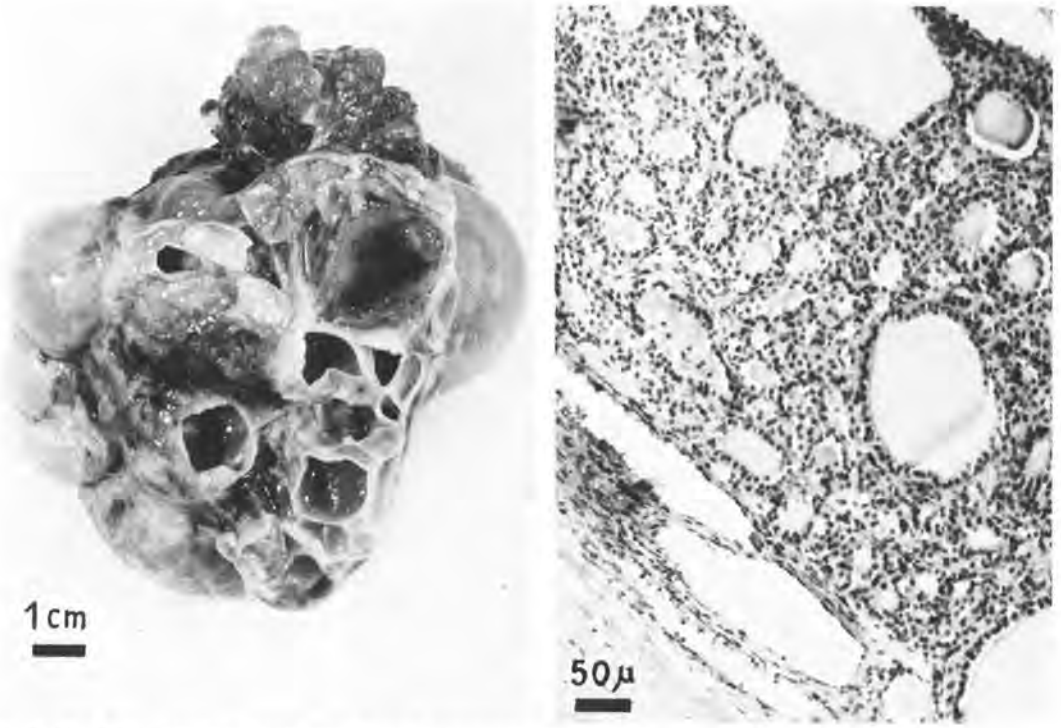

FIGURE 6-93 Struma ovarii: gross and microscopic appearance.

Carcinoids are firm, tan or yellow, solid tumors. They are unilateral and frequently arise in the wall of a benign cystic teratoma. They are composed of uniform round or cuboidal cells with round nuclei, coarse nuclear chromatin, and a moderate amount of clear or eosinophilic cytoplasm (Fig. 6-94). Fine, dark granules can be demonstrated in the cytoplasm by argentaffin or argyrophil stains. Many peptide hormones can be detected in carcinoid cells by immunohistochemistry, and neuroendocrine granules are observed in ultrastructural studies (Fig. 6-95).[479,480] Four main microscopic patterns have been described, and mixed patterns often are noted. The *insular* pattern is most common and is composed of sheets and islands of neoplastic cells surrounded by fibrous stroma.[478] The cells grow in ribbons in the *trabecular* pattern (see Fig. 6-94*B*).[481,482] *Strumal carcinoid* contains carcinoid and thyroid follicular epithelium that are intimately admixed, at least focally (Color Figures 6-22 and 6-23).[483–485] Finally, rare cases of primary *mucinous carcinoid* arise in the ovary.[486,487] These contain glands lined by columnar or cuboidal cells and goblet cells. Metastasis from a mucinous carcinoid tumor of the appendix must be excluded.

Teratomatous elements are often found adjacent to an ovarian carcinoid. Their identification is important evidence that the neoplasm is primary in the ovary and not metastatic. Unlike the primary ovarian carcinoid, metastatic tumors are usually bilateral, multinodular, and unassociated with other teratomatous elements. An extraovarian primary can be demonstrated by appropriate clinical studies.[480,488]

The primary ovarian carcinoid is a slowly growing neoplasm that is treated adequately by excision. Most are unilateral, and salpingo-oophorectomy is appropriate treatment for young patients. Carcinoid tumor of the ovary has a favorable prognosis. Metastases and tumor-related deaths are infre-

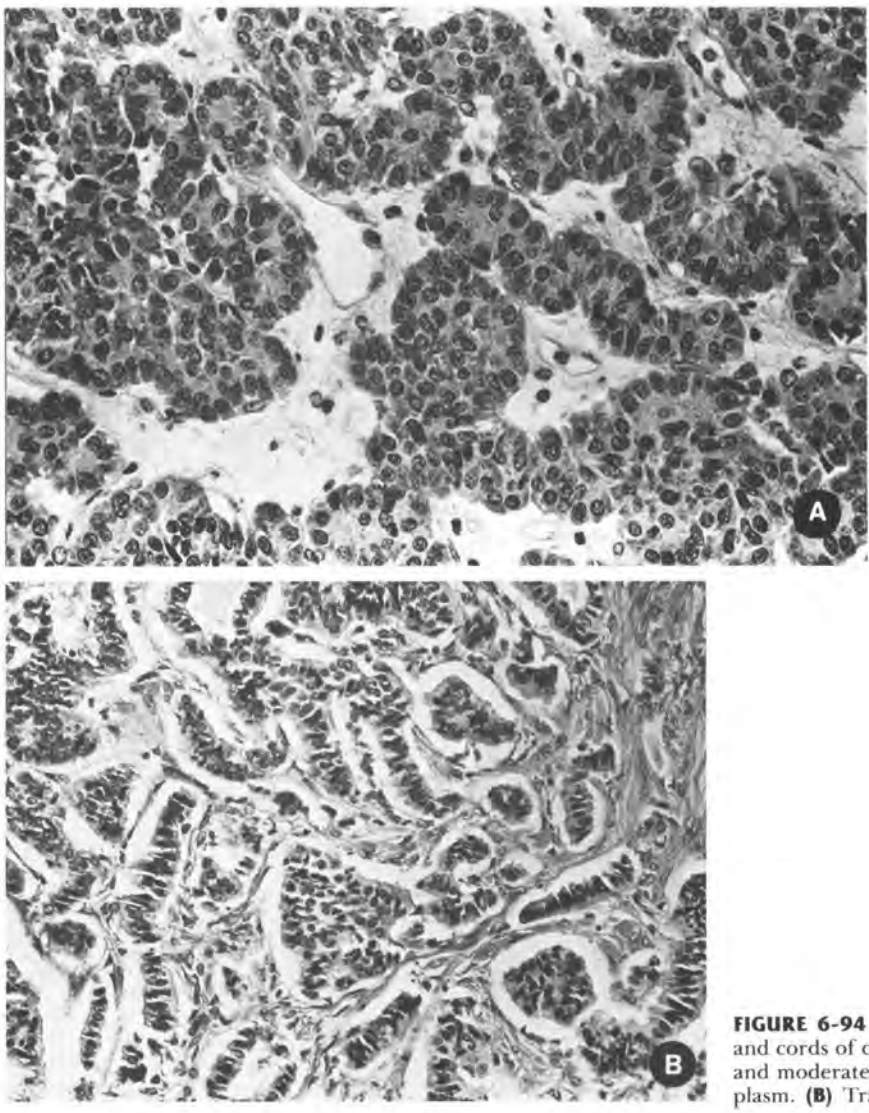

FIGURE 6-94 Carcinoid tumor. **(A)** Nests and cords of cells with regular, round nuclei and moderate amounts of eosinophilic cytoplasm. **(B)** Trabecular growth pattern.

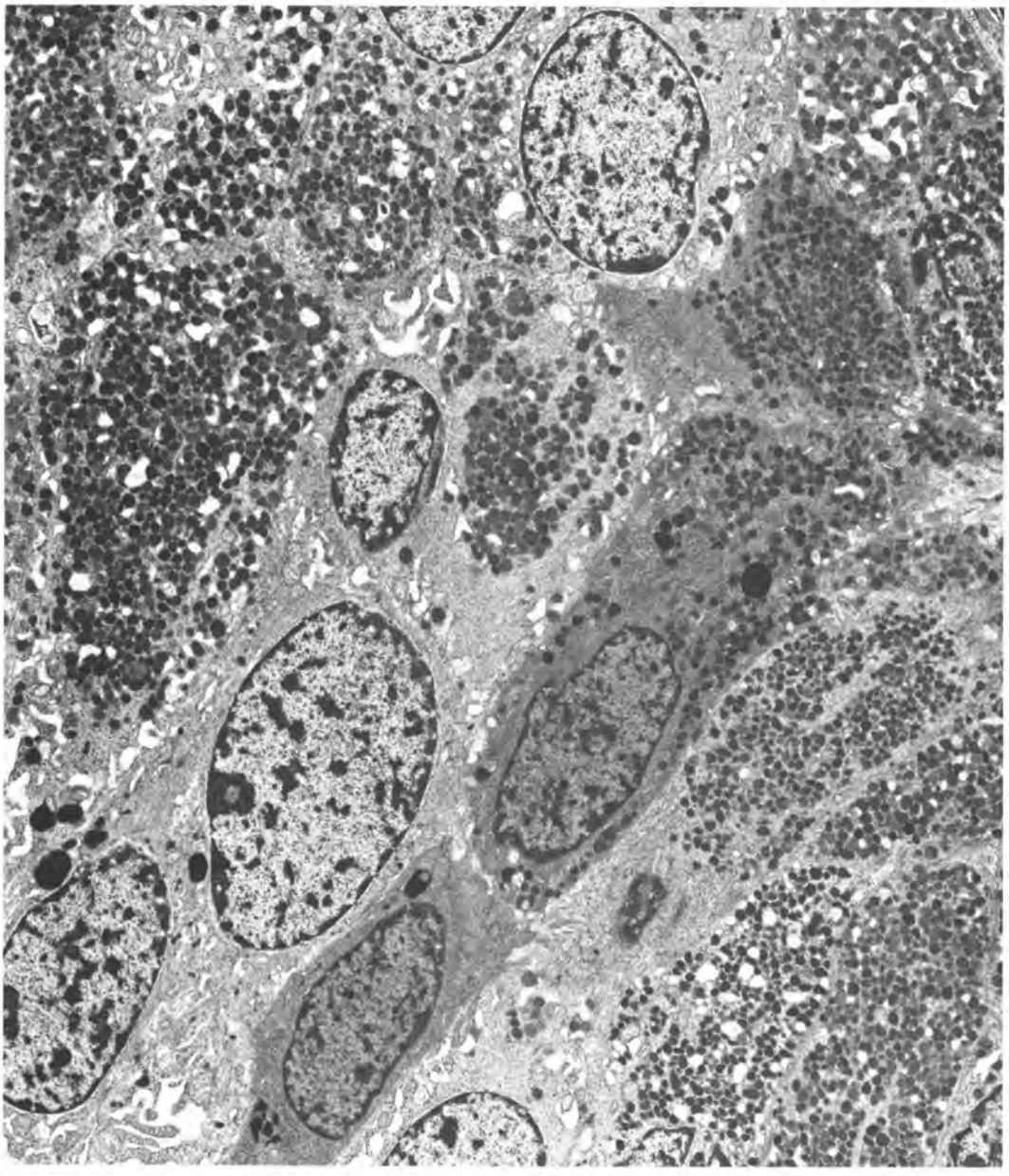

FIGURE 6-95 Ultrastructure of carcinoid tumor. The cytoplasm contains numerous granules of varying electron density and bundles of microfilaments (×5200). (Courtesy of Dr. J. M. Orenstein, George Washington University, Washington, DC).

quent. Based on the limited information in the literature, mucinous carcinoid may exhibit more aggressive behavior than other types of carcinoid. In the absence of metastases, symptoms abate rapidly after removal of the neoplasm.

Malignant Mixed Germ Cell Tumor

Malignant mixed germ cell tumors are composed of mixtures of the various pure types of germ cell tumor. Such neoplasms comprise 5% to 20% of all malignant germ cell tumors.[489,490] The presence of benign teratomatous elements does not qualify a neoplasm for inclusion in this category.

Clinical Features. Mixed germ cell tumors occur in children and in young women 5 to 33 years of age. The average patient age is 16 years. The most typical clinical presentation is with a palpable abdominal mass and abdominal pain. Acute abdominal symptoms occur in 15% to 20% of patients. Precocious pseudopuberty is detected in one third of prepubertal children with mixed germ cell tumors.[489] Older children and adults may have amenorrhea or abnormal vaginal bleeding. A positive pregnancy test or an increased level of serum human chorionic gonadotropin is discovered in 50% of patients, and the serum levels of α-fetoprotein are elevated in 50% of patients. The duration of symptoms is 1 day to 6

months, with an average of 4 weeks.[490] Most patients (57% to 66%) have stage I tumors at diagnosis.[489,490]

Macroscopic Appearance. Mixed germ cell tumors are large neoplasms. Their average diameter is 15 cm; fewer than 10% measure less than 10 cm in diameter. The appearance of the cut surface depends on the elements that are present. Areas of dysgerminoma are fleshy and gray or tan. Yolk sac tumor is variable in color and contains small cysts. Choriocarcinoma is hemorrhagic. Immature teratoma is white or tan and often contains cysts and translucent areas of cartilaginous differentiation. Most mixed germ cell tumors are unilateral. A small percentage of the tumors that contain dysgerminoma are bilateral.[490]

Microscopic Appearance. About 80% of mixed germ cell tumors contain two malignant elements. Three germ cell elements are found in 15% of these neoplasms, and the remainder contain four or more different elements. The various elements may be admixed or they may be found in separate, adjacent parts of the tumor (Fig. 6-96). Dysgerminoma is the most frequent element in mixed germ cell tumor. Yolk sac tumor and immature teratoma are each found in more than 50% of mixed germ cell tumors. Embryonal carcinoma, choriocarcinoma, and polyembryoma are observed less frequently.[489–491]

Clinical Behavior and Treatment. Early reports suggested that the prognosis depended on the size of the tumor, its stage, and the types and amounts of the various germ cell components.[489,492] More recent reports describing patients who received modern combination chemotherapy indicate that stage is the only significant determinant of prognosis.[490]

The initial treatment of malignant mixed germ cell tumor is surgical. Tumors confined to one ovary (stage IA) are treated by unilateral salpingo-oophorectomy. The standard treatment for those patients with more advanced tumors is total abdominal hysterectomy and bilateral salpingo-oophorectomy. Conservation of an uninvolved uterus and a contralateral ovary can be considered in some patients with advanced disease if conservation of fertility is desired. More than 50% of stage I tumors treated by surgery alone recur, indicating that occult metastases are present at diagnosis in most cases.[489,490,492] All patients therefore require postoperative chemotherapy, except those whose tumors are stage IA and contain only dysgerminoma and grade I immature teratoma. More than 70% of stage I patients treated with combination chemotherapy are cured.[490] Patients with more advanced tumors have a survival rate of about 50%.[438,467,490]

Gonadoblastoma

Gonadoblastoma is a rare tumor composed of germ cells and sex cord cells.[493–496] It arises almost exclusively in abnormal gonads.[496–498]

Clinical Features. Gonadoblastoma has been detected over a wide age group, ranging from 6 months to 45 years. The average age at diagnosis is 18 years, and 80% of patients are less than 20 years old.[497] The most common clinical presentation is with primary or, less often, secondary amenorrhea. Occasional tumors are detected during a physical examination, at operation for an acute abdomen, or during evaluation of adnexal calcifications detected on abdominal or pelvic radiographs. Most patients are phenotypic females, but gonadoblastoma also occurs in phenotypic males. Phenotypic females have a normal or short vagina that ends in a small cervix. The uterus is small in 75% of patients, and the fallopian tubes are small or rudimentary in 35%. Many patients are mildly virilized.[496] The most common

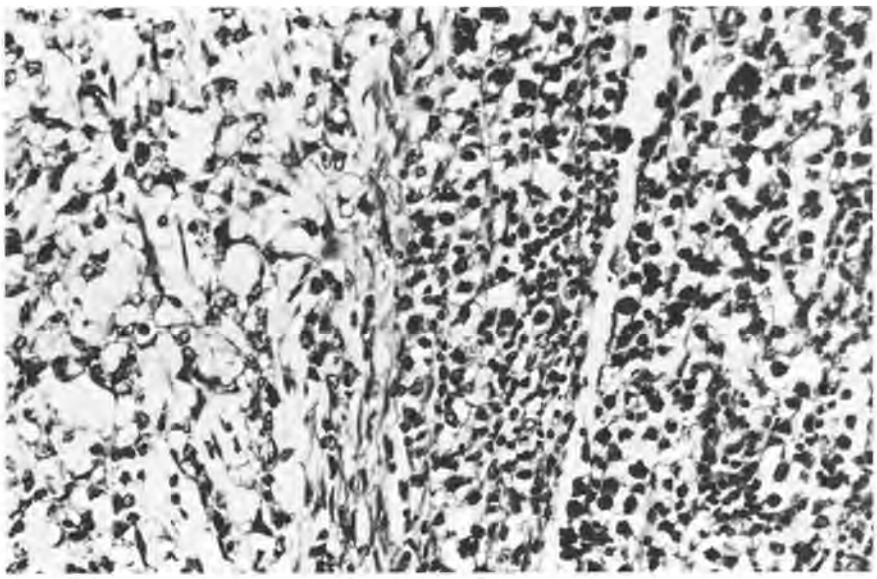

FIGURE 6-96 Malignant mixed germ cell tumor: yolk sac tumor (*left*) and dysgerminoma (*right*).

karyotypes are 46,XY and 45,X/46,XY. A Y chromosome or a Y-chromosome fragment is detected in more than 90% of patients.[497]

Macroscopic Appearance. Gonadoblastoma arises in abnormal gonads, including streak gonads, indeterminate gonads, and dysgenetic testes.[496] The neoplasms are small, ranging from microscopic to 2 to 3 cm in diameter. More than 40% are bilateral. The cut surface is tan or white and often there are visible calcified areas.

Microscopic Appearance. Gonadoblastoma is composed of nests of germ cells and sex cord cells. The germ cells are large, polygonal cells with abundant clear cytoplasm, vesicular nuclei, and prominent nucleoli (Fig. 6-97). They resemble germinoma cells. They are surrounded by smaller cells of sex cord origin, which may resemble granulosa or Sertoli cells. They surround a single germ cell, a group of germ cells, or a small space containing eosinophilic hyaline material (see Fig. 6-97). The stroma between the epithelial nests is frequently luteinized in postpubertal patients, and there are many microcalcifications.

Immunocytochemical testing reveals that the sex cord elements react with antibodies to vimentin and cytokeratin. The hyaline material reacts with antilaminin antibodies, compatible with basement membrane material.[499] The germ cells resemble dysgerminoma cells by electron microscopy.[493,499] The sex cord cells contain cytoplasmic bundles of Charcot-Böttcher filaments, a finding compatible with differentiation toward Sertoli cells.[499]

Differential Diagnosis. Rare examples of other types of *combined germ cell-stromal tumors* have been described, including a neoplasm with an epithelial component.[500,501] The absence of cell nests and the hyaline cores within them serves to differentiate such neoplasms from gonadoblastoma. Sex cord tumor with annular tubules (SCTAT) is differentiated from gonadoblastoma and from the other types of combined tumors by the absence of germ cells. Microscopic gonadoblastoma-like lesions occur in fetal and infant ovaries in the absence of genetic abnormalities. These lesions are associated with follicular atresia, and their relation with gonadoblastoma is unclear.[502,503]

Clinical Behavior and Treatment. Gonadoblastoma is benign unless overgrown by a germinoma or some other type of malignant germ cell tumor. Bilateral gonadectomy is indicated when a gonadoblastoma is discovered.[497,498] The gonads are nonfunctional from a reproductive point of view. Gonadoblastoma is frequently bilateral, and removal of both gonads precludes virilization or evolution of a malignant germ cell tumor. The risk that a malignant germ cell tumor will arise in an abnormal gonad in a patient with a Y chromosome is estimated at 25%.[504] Most of the malignant germ cell tumors that arise in gonadoblastoma are germinomas,[496,497,505] but other, more aggressive, types of germ cell tumor occur.[496,497,505,506] We have seen a single case of Sertoli-Leydig cell tumor arising in a gonadoblastoma.

Metastatic Tumors

Gastrointestinal, breast, and uterine carcinomas frequently metastasize to the ovaries.[171,201,507–513] Although metastatic cancer comprises 10% of all ovarian cancers seen in surgical material, the percentage of metastatic tumors that pose diagnostic problems, presenting clinically as primary ovarian neoplasms, is much smaller.

In older series compiled when the primary endocrinologic treatment for breast cancer was surgical removal of the ovaries, 30% to 50% of the metastatic cancers identified in the ovaries were from the breast (Fig. 6-98). These were usually incidental microscopic findings in grossly unremarkable or slightly enlarged ovaries. Large metastatic deposits easily mistaken for primary neoplasms were rare. Antiestrogenic drugs such as tamoxifen have largely replaced oophorectomy in the endocrinologic treatment of breast cancer, and the surgical pathologist now sees ovarian metastases from breast cancer only occasionally.[510,513] In modern surgical series, most metastatic neoplasms detected in the ovaries are from gastrointestinal primary sites.[171,201,507–509,512] These not infrequently present as primary ovarian neoplasms, with the primary gastrointestinal tumor detected only after the ovarian neoplasm has been removed and studied by the pathologist. The gastrointestinal cancers responsible for ovarian metastases are metastatic from the colon and rectum, stomach and biliary tract, in order of decreasing frequency.[514]

Ovarian metastases are most likely to affect functioning ovaries. Invasion takes place by the lymphatic or hematogenous route, by serosal implantation of neoplastic cells disseminated by the fallopian tubes into the peritoneal cavity, or by direct extension from adjacent organs such as the large intestine or appendix.

Macroscopic Appearance

Metastatic ovarian cancers vary in appearance. The entire ovary may be replaced by a solid white mass of firm or rubbery consistency. Metastatic colorectal cancer often presents as a large unilocular or multilocular cystic neoplasm with solid areas. Other metastatic carcinomas form multiple nodules in the cortex and medulla and on the serosa. Small metastases may not be readily visible because their color and consistency are similar to those of the surrounding ovarian parenchyma. Normal-appearing ovaries occasionally exhibit widespread lymphatic permeation by metastatic tumor.

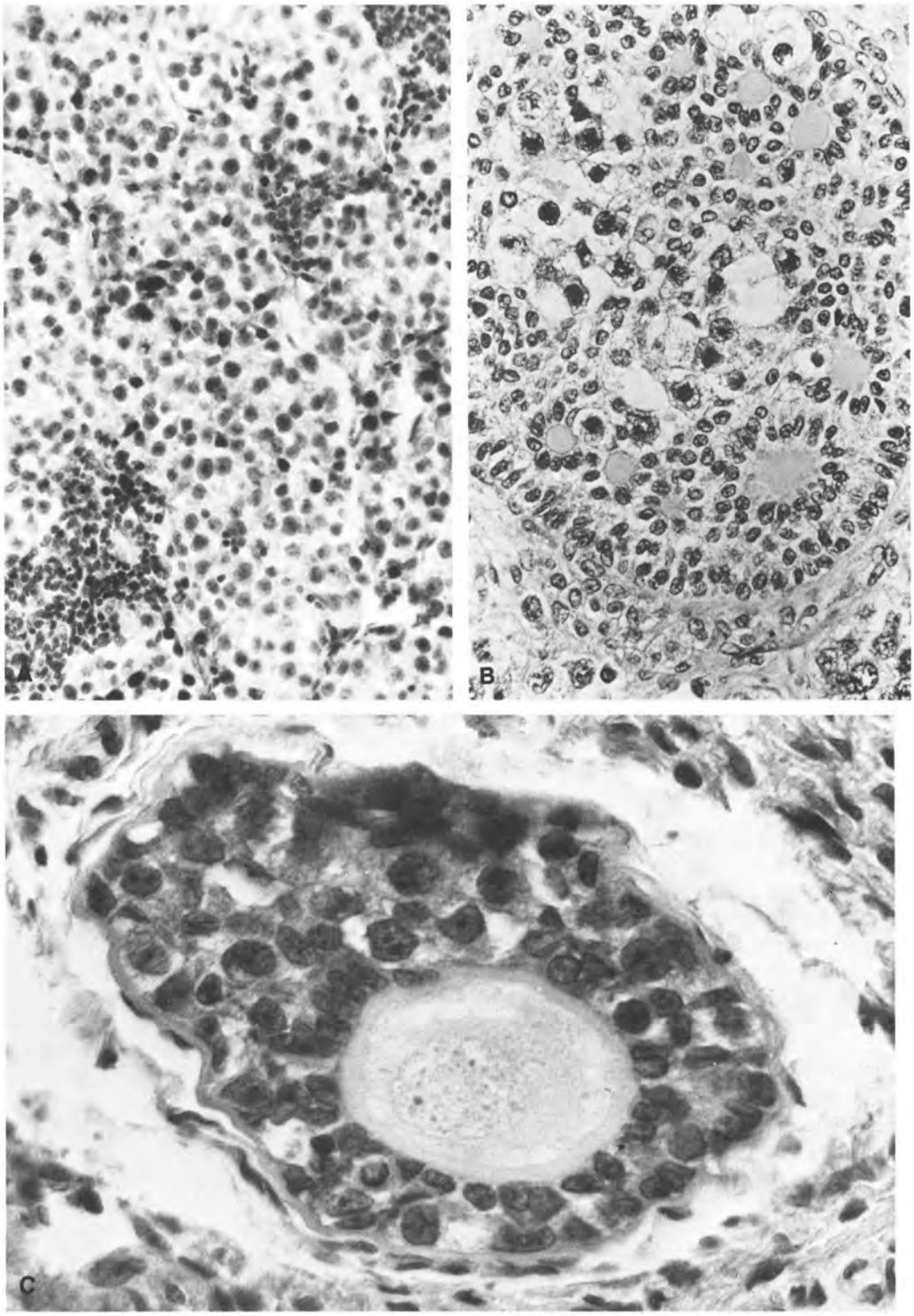

FIGURE 6-97 Gonadoblastoma. **(A)** Focus of germinoma. **(B)** Nest of sex cord elements containing scattered large germ cells. **(C)** The space surrounded by sex cord cells resembles a Call-Exner body. (Courtesy of Dr. Jean de Brux, Paris, France).

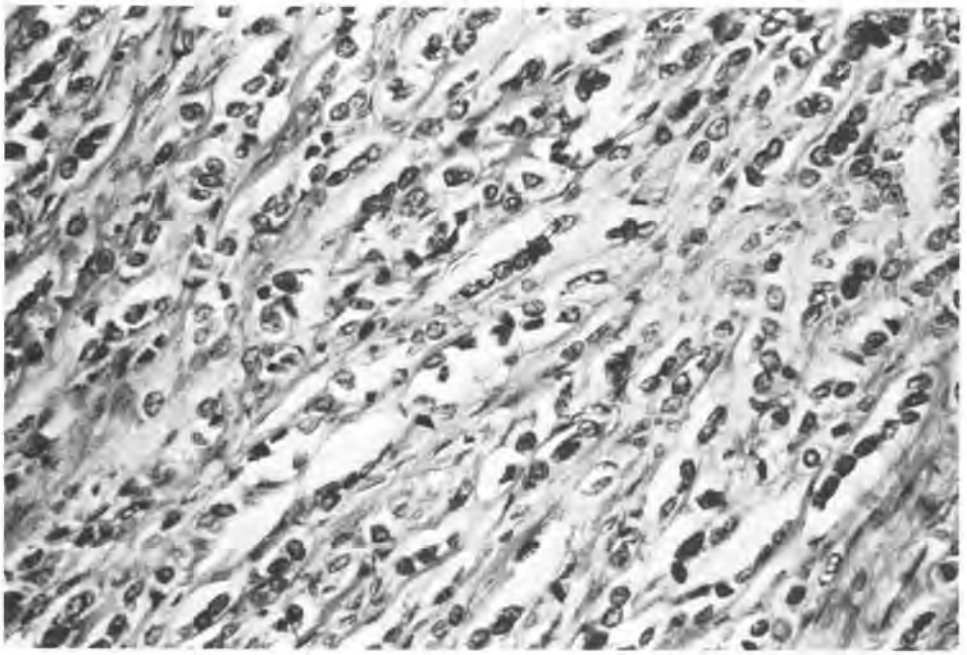

FIGURE 6-98 Metastatic breast cancer in the ovary.

When the uterus and ovaries are both involved by adenocarcinoma, it may be difficult to determine the point of origin of the tumor. Statistically, endometrial carcinoma with ovarian metastasis is more frequent than ovarian carcinoma with uterine metastasis. In most instances, however, the findings are best interpreted as simultaneous primary cancers in the endometrium and ovary. This is particularly true when the endometrial carcinoma is superficial and well differentiated, because metastases are unlikely in such a setting.

Microscopic Appearance

Metastatic carcinoma reproduces the appearance of the primary tumor to a variable degree. The most useful clue that a cancer is metastatic is that it is bilateral and multifocal. The neoplastic cells may diffusely infiltrate the parenchyma (see Fig. 6-98) or grow in discrete rounded nodules. Implants on the surface of the ovary are common. Metastatic carcinoma may be visible within lymphatic spaces in the ovary, especially the hilum, and in the mesovarium. The stromal cells in and around some metastatic cancers are luteinized. The luteinized cells occasionally secrete enough estrogen or androgen to cause clinical symptoms.

Metastatic colorectal adenocarcinoma often simulates a primary adenocarcinoma of the ovary, and the correct diagnosis can be difficult, even after microscopic examination.[171,172,507,512] This type of metastatic carcinoma typically grows in a multicystic pattern with extensive necrosis. The malignant cells lining the cystic spaces are stratified or grow in a cartwheel or cribriform pattern (Color Figure 6-24). Metastatic colorectal cancer resembles endometrioid carcinoma if goblet cells are absent or inconspicuous. Helpful differential diagnostic features are the presence of the attributes of metastatic carcinoma listed above, segmental necrosis of glands, greater nuclear atypia than anticipated in a tumor composed of well-formed glands, and the absence of squamous metaplasia.[171] If goblet cells are present, the differential diagnosis is with mucinous carcinoma of the ovary. Many of the differential diagnostic features previously mentioned are helpful. In addition, primary mucinous carcinoma of the ovary often contains areas resembling a benign or LMP mucinous tumor, in which endocervical-type cells are present.

Metastatic carcinoid tumor is histologically identical to a primary ovarian carcinoid.[488] Bilaterality, multifocality, and the absence of other teratomatous elements suggest that a carcinoid tumor is metastatic, usually from an intestinal primary site.

Krukenberg tumor is a form of metastatic cancer in which malignant signet-ring cells invade an abundant and hypercellular stroma.[515–517] The primary carcinoma usually is located in the stomach, but signet-ring cell carcinoma of the breast, colon, and gallbladder can give rise to this type of ovarian metastasis. Krukenberg tumors are most frequent in patient populations in which there is a high incidence of gastric carcinoma, such as in women of Japanese extraction. The ovaries typically retain their shape but are symmetrically or asymmetrically enlarged. They are firm and yellow-white. The cut surface is honeycombed with small mucinous cysts, and there are foci of hemorrhage and necrosis (Fig. 6-99*A*). Microscopically, the signet-ring cells are found as isolated single cells, or they grow in variably sized nests, cords or tubules.

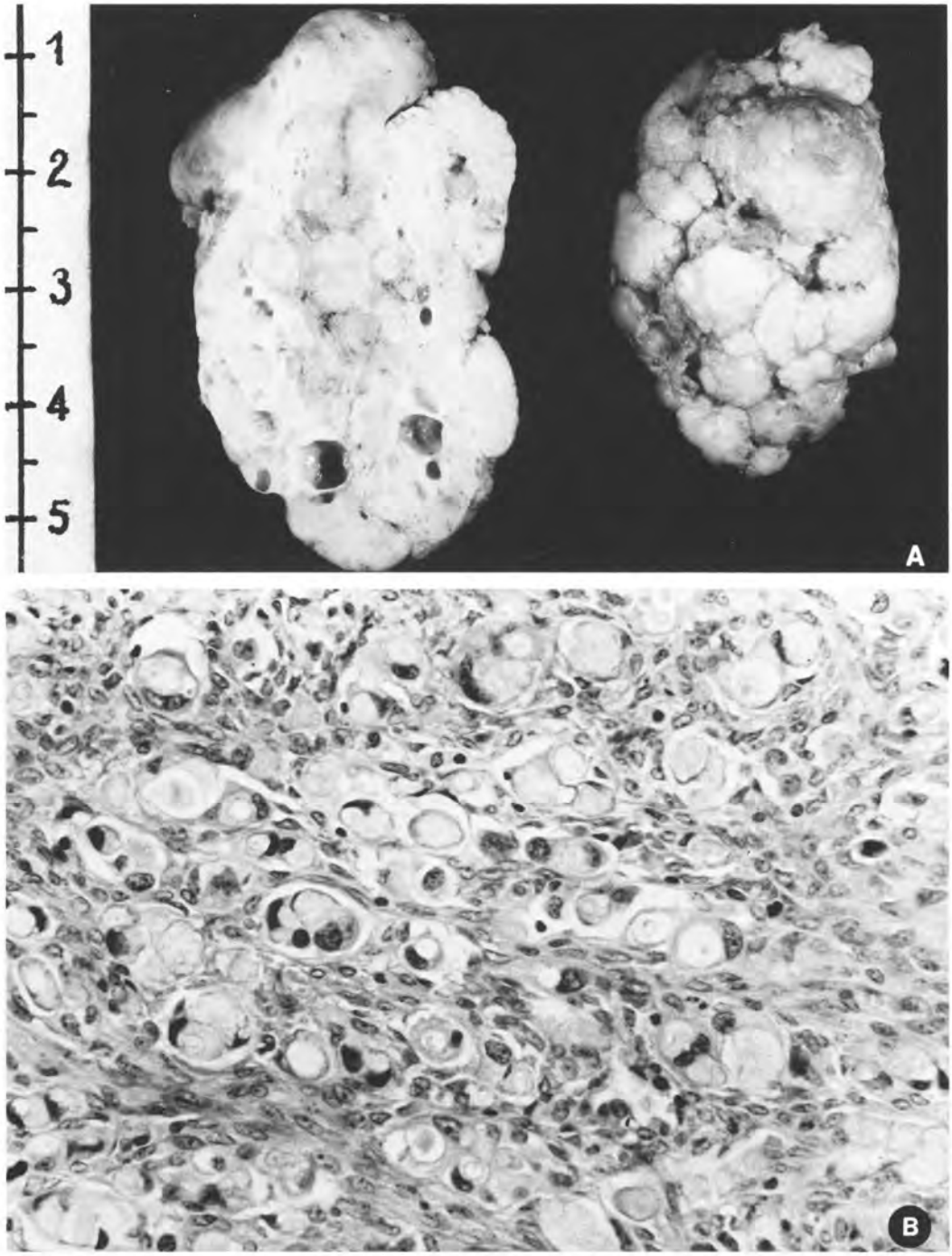

FIGURE 6-99 Ovarian metastasis from gastric carcinoma (Krukenberg tumor). **(A)** Gross appearance. **(B)** Microscopic appearance showing signet-ring cells.

A Krukenberg tumor that contains prominent tubules may be designated as a *tubular Krukenberg tumor.*[324,518] The malignant cells contain round cytoplasmic mucin globules that compress and flatten the hyperchromatic nucleus against one cell border (see Fig. 6-99*B*). The stroma is abundant and hypercellular. It is focally edematous and it may contain pools of mucin. The stroma is occasionally so prominent that it obscures the malignant cells, but they can easily be identified in sections stained with periodic acid-Schiff or mucicarmine stains or with immunohistochemical stains for epithelial markers such as cytokeratin, epithelial membrane antigen, or carcinoembryonic antigen. In rare cases, an extraovarian primary tumor cannot be identified in a woman with a typical Krukenberg tumor. Such tumors have been designated as primary Krukenberg tumors. The diagnosis of primary Krukenberg tumor should be made with caution because an occult gastrointestinal primary may remain undetected even after

painstaking investigation. It is best to consider all Krukenberg tumors as metastatic until proved otherwise.

Parovarian Tumors and Cysts

Almost any type of ovarian tumor can occur in the broad ligament or elsewhere in the parovarium, perhaps arising in accessory ovarian tissue. The following discussion emphasizes lesions that are encountered in these sites more frequently than in the ovary itself.

Adrenal Cortical Rests and Tumors

Accessory adrenal cortical tissue is rarely present within the ovary, but it is common in a paragonadal location. Small, circumscribed *adrenocortical rests* composed of polygonal adrenal-type cells with abundant clear, vacuolated cytoplasm and small vesicular nuclei are present in more than 20% of women (Fig. 6-100). Tumors resembling adrenal cortical adenomas may arise in this accessory adrenal tissue, and we have seen a myelolipoma develop in one case.

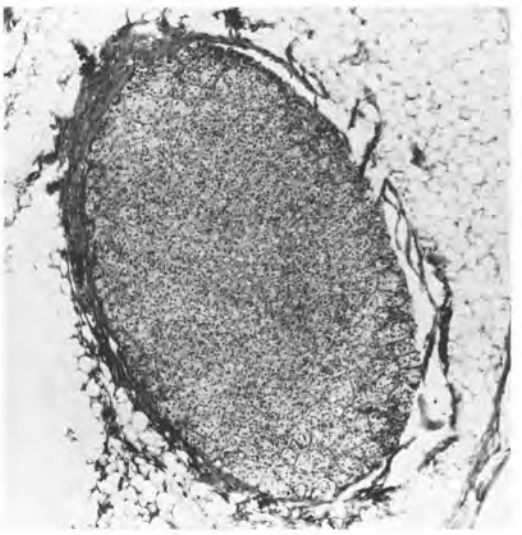

FIGURE 6-100 Parovarian adrenocortical rest.

Hydatid of Morgagni

These common benign cysts arise from müllerian vestiges. They are situated below the fallopian tube and usually are an incidental finding. They are occasionally large enough to present clinically as an adnexal mass. They are translucent cysts, usually small, that contain clear or pale yellow fluid. They may be unilocular or multilocular (Fig. 6-101). Microscopically, they are lined by cuboidal to columnar epithelium, often of tubal type, resting on a musculoconnective tissue wall.

Female Adnexal Tumor of Probable Wolffian Origin

The female adnexal tumor of probable wolffian origin is a distinctive adnexal tumor that arises within

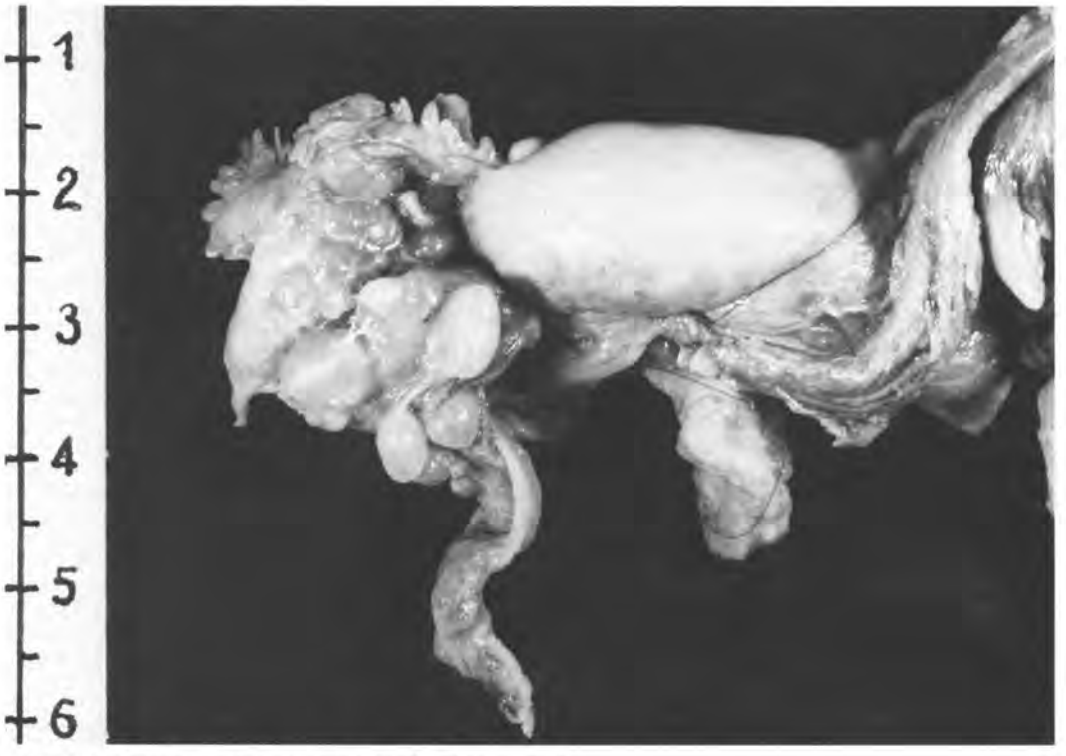

FIGURE 6-101 Parovarian cysts (hydatids of Morgagni).

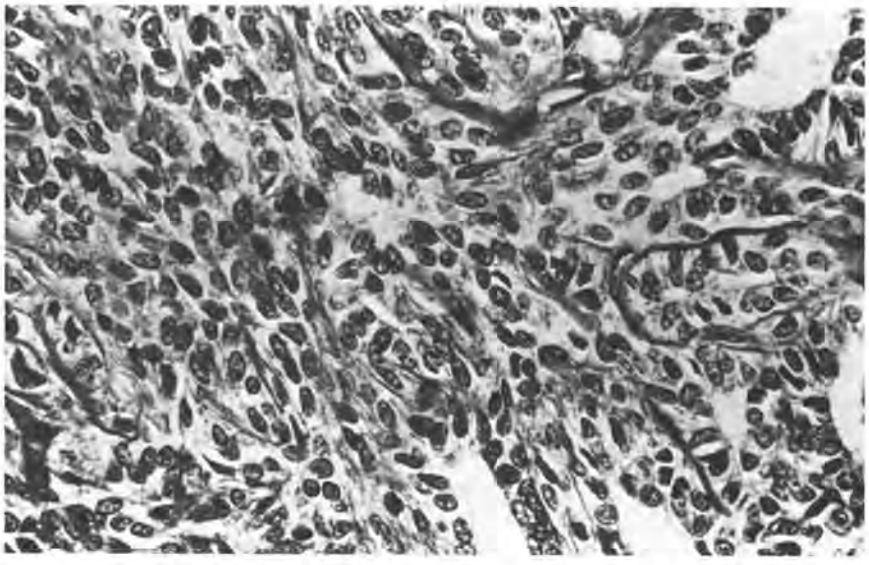

FIGURE 6-102 Adnexal tumor of probable wolffian origin (juxtaovarian tumor).

the broad ligament attached to the mesosalpinx, or within the ovary itself. It may be derived from mesonephric remnants, which are common in this area.[519–521] Most examples are found in middle-aged women, but the neoplasm occurs over a wide age range. The clinical presentation is nonspecific. The tumor is solid and ranges from 2 to 20 cm in diameter. The cut surface is solid and white or gray. The tumor is composed of uniform epithelial cells growing in diffuse, trabecular, tubular (Fig. 6-102), and microcystic patterns. Mitotic activity or cytologic atypia is uncommon. Prominent peritubular basement membranes are characteristic and are best demonstrated with the reticulin stain. Most of these neoplasms are benign, but rare malignant examples are reported. Malignant tumors of wolffian origin exhibit increased mitotic activity or cytologic atypia, overgrowth of spindle cells, or lymphatic invasion.

Adenomatoid Tumor

In the female genital tract, adenomatoid tumors are most common in the fallopian tube or the myometrium. Adenomatoid tumors rarely occur in or immediately adjacent to the ovary.[522] Most measure less than 1 to 2 cm in diameter. They are composed of tubules lined by cuboidal cells and surrounded by fibrous stroma. Adenomatoid tumors are benign neoplasms of mesothelial derivation.

Smooth Muscle Tumors of the Broad Ligament and Round Ligament

Intraligamentary leiomyomas present as firm, white, round nodules surrounded by a thin fibrous capsule. The cut surface demonstrates the typical whorled structure of a smooth muscle tumor. Microscopically, they are similar to uterine leiomyomas. Leiomyosarcoma can arise in the broad ligament.

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7 The Female Peritoneum

In the 1980s, several new clinicopathologic entities primarily involving the female peritoneum were described, and several other previously known conditions were characterized more fully. These findings probably were the result of the increased use of exploratory laparotomy with extensive peritoneal sampling in women with tumors of the genitalia, but they may also be partly due to an increased incidence of some of these conditions.

Because of the gynecologic emphasis of this text, conditions that affect the male and female peritoneum similarly are mentioned only briefly, whereas those that are significantly more prevalent in or limited to women are given more extensive coverage. Endometriosis, although not exclusively a peritoneal condition, is included here because most of its manifestations are related to peritoneal localizations of the disease.

EMBRYOLOGY

The peritoneum is formed from the lateral mesoderm, which splits into a somatic and a splanchnic layer. These layers are associated with the ectoderm and entoderm, respectively, and enclose the intraembryonic coelom, a cavity that later forms the pleural and peritoneal cavities. The peritoneal cavity is formed from the portion of the intraembryonic coelom that is caudal to the septum transversum. The peritoneal cavity subsequently divides into the lesser and greater sacs, which communicate through the epiploic foramen.

ANATOMY

The peritoneum is a continuous serous membrane that lines the abdominal wall (parietal peritoneum) and is reflected over the abdominal and pelvic viscera (visceral peritoneum). The space between these two layers is the peritoneal cavity. Because the two layers are normally in contact, however, this cavity is largely a potential one.

The lesser sac of the peritoneum is known as the omental bursa and is related only to the dorsal surface of the stomach and the closely surrounding structures. The remainder of the peritoneal cavity (the portion to which we refer throughout this chapter) is known as the greater sac. The abdominal viscera are either attached to the abdominal wall and partly covered by the peritoneum (the *retroperitoneal viscera*) or completely surrounded by the peritoneum and suspended from the abdominal wall by *mesenteries*, sheets of connective tissue containing blood and lymph vessels and covered by the peritoneum.

Further consideration of the complex anatomy of the peritoneum is beyond the scope of this chapter, but three points should be emphasized with particular reference to the female peritoneum. First, although in the male the peritoneum is a completely closed sac, in the female the free ends of the fallopian tubes open directly into the peritoneal cavity, providing a conduit to the external environment. Second, the pelvic peritoneum in women is considerably more irregular than that in men because of its numerous folds, fossae, recesses, and cul-de-sacs.[1] These include the vesicouterine and rectouterine

cul-de-sacs; the paravesical, parauterine, pararectal, and ovarian fossae; and the tubo-ovarian recess. These complex nooks and crannies often are sites for the development of infection, adhesions, and foci of endometriosis and metastatic carcinoma. Finally, the relation of the peritoneum to the female genitalia should be considered. The germinal epithelium of the ovaries is derived from and directly continuous with the pelvic peritoneum. The serous coats of the fallopian tubes, uterine corpus, and cervix are peritoneal, and the so-called ligaments from which these various organs are suspended are covered by peritoneum. The cervix is not covered anteriorly by peritoneum, because the vesicouterine cul-de-sac extends caudad only as far as the junction between the uterine corpus and cervix.

HISTOLOGY

In its resting state, the peritoneum is lined by a single layer of low cuboidal cells, which are underlaid by a thin layer of nonspecific fibrous mesenchymal tissue. This subserous mesenchymal layer contains a small network of capillaries, lymphatics, and nerve fibers. Ultrastructurally, the mesothelial cells contain microvilli on their apical surfaces and numerous pinocytotic vesicles. The nucleus occupies a large portion of the cell, and intracytoplasmic organelles are not prominent.

CYTOLOGY

Because peritoneal mesothelial cells usually are examined cytologically in effusions, which by definition are pathologic, opportunities to observe normal cells are limited. In addition, free-floating cells in an effusion take on different characteristics from the same cells attached to a serous membrane. Therefore, the following discussion of "normal" peritoneal cytology must assume at least slight variation from the true physiologic norm.[2-4]

The mesothelial cells appear as solitary elements, gathered in small clusters, and in sheets. The individual cells generally are round to polygonal and measure from 10 to 20 μm in diameter. The nucleus is centrally located and occupies about one-half the cell diameter. The nuclear membrane is prominent, and there is a finely dispersed chromatin network with occasionally one or two prominent nucleoli. The cytoplasm is homogeneous and is basophilic to faintly eosinophilic.

The cells adhere well to one another in clusters and sheets and appear uniform in size, shape, and nuclear morphology. Papillary clusters are frequently seen in cases of "irritation" but should not be observed in the absence of pathology. In addition to mesothelial cells, macrophages and various leukocytes are frequently encountered in peritoneal fluid specimens.

INFLAMMATORY LESIONS

Although inflammatory lesions of the peritoneum are common, they are discussed here only briefly for two reasons. First, they are as likely to occur in males as in females. Second, they are usually diagnosed bacteriologically rather than histologically and only infrequently generate material for the surgical pathologist.

Peritonitis is most commonly due to infectious and chemical causes. *Infectious peritonitis* is usually bacterial and may be primary or secondary. The primary form is rare and usually is caused by pneumococci or streptococci. Secondary bacterial peritonitis usually is due to perforation of a viscus, usually within the gastrointestinal tract (eg, peptic ulcer, diverticulum, or tumor), and the resulting peritonitis is both bacterial and chemical. Bohnen and colleagues found a mortality rate of 38% in generalized peritonitis but noted a much lower mortality rate (about 10%) if the initiating condition was acute appendicitis or a perforated duodenal ulcer.[5] In women, a common cause of peritonitis is acute bacterial salpingitis. In the staging system of Monif, salpingitis with peritonitis is considered stage II salpingitis, whereas the ruptured tubo-ovarian abscess is considered stage IV and a potentially life-threatening situation (see Table 5-1).[6]

Other types of infectious peritonitis result from *tuberculosis* and *actinomycosis*. These infections may be difficult to diagnose because of the absence of an obvious primary lesion elsewhere. Singh and associates found percutaneous peritoneal biopsy helpful in making the diagnosis in 64% of patients with tuberculous peritonitis (Fig. 7-1).[7] Although acid-fast bacilli are seldom found on smears of peritoneal fluid, a culture often is more rewarding.

Chemical peritonitis may be caused by an almost endless list of agents. The most common source of chemical peritonitis is rupture of a portion of the gastrointestinal tract, but iatrogenic causes are also common. In particular, material from surgical gloves (previously talc and now more commonly starch) has been demonstrated to produce a foreign-body granulomatous response, which generally becomes evident 1 to 4 weeks after a surgical procedure. The offending agent should be demonstrable within histiocytes and foreign-body giant cells, thereby avoiding the mistaken diagnosis of an infectious granulomatous peritonitis. Sources of foreign-body granulomata in the female peritoneum include contrast media used for hysterosalpingography, contents of a ruptured ovarian dermoid cyst, and meconium disseminated at cesarean section.[8]

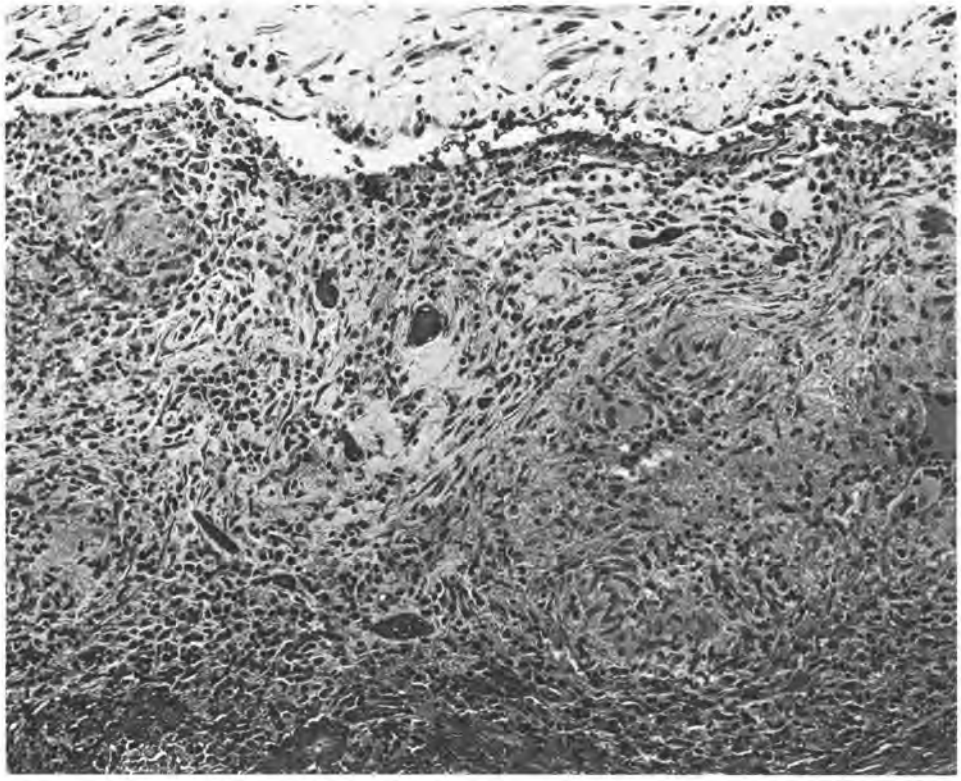


FIGURE 7-1 Peritoneal tuberculosis: granulomas on serosal surface of tube.

The peritoneum can be the site of an inflammatory response in autoimmune diseases such as *systemic lupus erythematosus* and *familial Mediterranean fever.* The latter condition, which is also known as familial recurrent polyserositis or periodic fever, is an inherited disease of unknown cause, characterized by acute self-limited attacks of fever and signs of peritonitis, pleuritis, and arthritis. Familial Mediterranean fever is clinically important because it can mimic surgical causes of peritonitis and because generalized amyloidosis tends to develop in these patients.[9]

ADHESIONS

Peritoneal adhesions unfortunately are a common problem in both men and women and are encountered frequently in the practice of surgical pathology. Although adhesions may develop as a consequence of inflammatory lesions, they most often pose a significant clinical problem after abdominopelvic operations. An extensive study of the mechanisms of development of postoperative peritoneal adhesions suggested that intraoperative bleeding is the most important etiologic factor.[10] In this study, intraoperative drying of the serosa appeared to be an important potentiating factor, and the presence of talc, infection, and tissue necrosis was important in some instances.

Although peritoneal adhesions initially are composed predominantly of proliferating fibroblasts and mesothelial cells, blood, and fibrin, they eventually become densely collagenous and can cause intestinal obstruction. The usual treatment is surgical lysis of the adhesions, and the pathologist must search the submitted material carefully for evidence of a specific cause. This is particularly true if the initial surgical operation was for cancer, because a few recurrent cancer cells may be masked by massive fibroplasia. The pathologist must be equally careful when adhesions develop in a postradiotherapeutic rather than postoperative setting. In this situation, the opposite danger exists: misdiagnosis as recurrent cancer of bizarre cellular atypias that have developed in fibroblasts or endothelial cells as a result of radiation therapy.

Other iatrogenic causes of extensive peritoneal fibrous adhesions include drugs, notably β-adrenergic blocking agents such as practolol. The generalized condition produced by these drugs has been designated *sclerosing peritonitis.*[11]

CYSTS

True peritoneal cysts are rare. Walker and Putnam analyzed 33 cases of omental, mesenteric, and retroperitoneal cysts and suggested classification of these cysts into four major groups:

1. Embryonic and developmental
2. Traumatic or acquired
3. Neoplastic
4. Infectious and degenerative.[12]

Although 27 of the 33 cases occurred in females, many cysts were of enteric, genitourinary, or lymphatic origin and thus would not qualify as being derived from the peritoneum. Most traumatic and infectious cysts are actually pseudocysts because they are not lined by epithelium or mesothelium.

The most common true cystic lesion of the peritoneum that we have encountered in women has been designated *cystic mesothelioma* or *multilocular peritoneal inclusion cysts* (see the following section on benign tumors).

HYPERPLASIAS, METAPLASIAS, AND BENIGN TUMORS

Reactive Hyperplasia

Whenever the peritoneum is irritated, the mesothelium can proliferate to an alarming degree, forming papillary, glandular, and solid structures that may be confused with malignant mesothelioma or metastatic adenocarcinoma. Rosai and Dehner noted this situation within hernia sacs,[13] but we have encountered it frequently in many other peritoneal locations. In women, reactive hyperplasia is particularly likely to be encountered in pelvic inflammatory disease. In this situation, if there are extensive adhesions between the ovary and fallopian tube, the proliferating mesothelial cells may be found at the center of the inflammatory mass and not near any obvious serosal surface, making their correct identification even more difficult. Considerable anisonucleosis and nuclear pleomorphism may be present in these hyperplastic foci, but the overall appearance is still that of mesothelial cells: polygonal cell outlines, low nuclear–cytoplasmic ratios, glassy cytoplasmic appearance, and absence of stainable mucin (Fig. 7-2). Mitoses may be present but generally are few in number.

Cytologically, the cells may appear atypical, but their mesothelial origin is usually recognizable.[2–4] They can probably best be recognized by identifying intermediate forms between the atypical, often gigantic reactive cells and other classic benign mesothelial cells (Color Figure 7-1). In addition, the large, atypical mesothelial cells, although hyperchromatic, usually lack the internal structural aberrations suggestive of malignancy, such as coarsely clumped chromatin and condensation of chromatin along the nuclear membrane. If the atypia is of inflammatory origin, large numbers of inflammatory cells are usually present in the peritoneal effusion or washing specimen, and their prominence is helpful (although not infallible) in the differential diagnosis from a malignant peritoneal process.

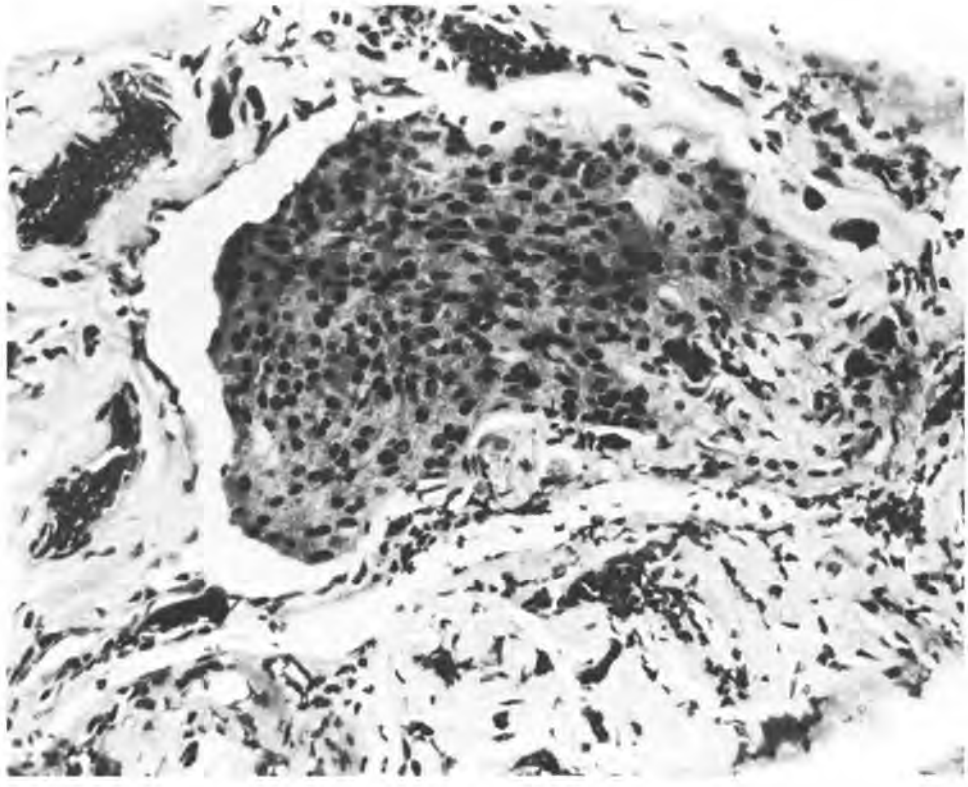


FIGURE 7-2 Mesothelial cell proliferation in hernia sac.

Flow cytometric analysis of peritoneal fluid specimens has been suggested as a useful adjunct to classic cytologic examination. Comparative studies in women with benign and malignant gynecologic diseases, however, have noted unacceptably high false-positive and false-negative results with flow cytometry.[14,15]

Endosalpingiosis

The term *endosalpingiosis* was coined by Sampson in 1930 to delineate persistent or recurrent nests of tubal epithelium in salpingectomy scars.[16] Sampson thought that these cells had an aggressive potential, and he noted similar cells in various peritoneal locations, including the ovarian surfaces. The term has subsequently come to be identified with any proliferation of müllerian-type epithelium on a peritoneal surface, although, as the name suggests, these proliferations most often are of the tubal epithelial type. Although these lesions were little more than a rarely seen histologic curiosity as recently as 20 years ago, they are being found with increasing frequency as gynecologic oncologists have become more aggressive in performing exploratory laparotomy in gynecologic cancer. Because they are encountered frequently in biopsy specimens from cases of ovarian or endometrial adenocarcinoma, often of relatively low grade, their differential diagnosis from metastatic adenocarcinoma poses an increasingly vexing problem to the pathologist.

Etiology

The causes suggested for this condition are the same as those suggested for endometriosis, and it is not unusual to find endometriosis and endosalpingiosis coexisting in a patient.[17] Because direct transitions from normal to slightly hyperplastic mesothelium to foci of endosalpingiosis can often be demonstrated, we favor the concept of a müllerian metaplastic histogenesis in most cases. We believe that endosalpingiosis frequently coexists with müllerian neoplasms of the upper female genital tract because we have encountered it in about 10% to 15% of cases of stage I serous carcinomas and borderline tumors of the ovary. This coexistence has been noted with equal or greater frequency in several published series.[18,19]

On the other hand, Zinsser and Wheeler noted the presence of tubal inflammatory disease in all cases of omental endosalpingiosis and concluded that tubal epithelial regurgitation with subsequent peritoneal implantation is the most common histogenetic pathway.[16] As in endometriosis, this question remains unresolved, and more than one etiologic mechanism may exist.

Clinical Findings

Unlike endometriosis, endosalpingiosis seems almost invariably to be a totally asymptomatic condition. Only rarely are symptomatic cases reported.[20] The lesions are discovered during the course of surgery for another condition, usually an ovarian or endometrial tumor or tubal inflammatory disease. It is surprising that this condition was not found in omental specimens at autopsy by Zinsser and Wheeler, because similar müllerian glandular inclusions have been reported in abdominal and pelvic lymph nodes in 5% to 41% of women at autopsy.[16,21]

Macroscopic Appearance

The lesions of endosalpingiosis may be grossly cystic or papillary. More often they present as small gray-white, firm, and occasionally calcified nodules measuring 1 to 2 mm in diameter (Color Figure 7-2) or as incidental findings on histologic examination of grossly unremarkable structures. They may be found on any peritoneal mesothelial surface but seem to have a predilection for the omentum, posterior uterine serosa, ovarian surface, and rectouterine cul-de-sac. The serosal surfaces of the fallopian tubes, bowel, bladder, and diaphragm are also common sites.

Microscopic Appearance

The lesions are composed of glands, papillae, cysts, and small solid cell nests. The cells are often organized as a single layer of cuboidal cells of mesothelial type but also show transitions to various types of müllerian epithelium, which by definition must include tubal epithelium (Figs. 7-3 and 7-4). When tubal metaplasia is clear-cut, one should be able to identify ciliated, secretory, and intercalated cells (Fig. 7-5). The glandular epithelium may also resemble endometrium, endocervix, or urothelium (Fig. 7-6). The latter metaplastic pathway is rare unless one includes the *Walthard's cell rests* commonly seen on the serosal surface of the fallopian tube under the rubric of endosalpingiosis.

Considerable chronic inflammation and fibrosis may accompany, entrap, and eventually obliterate the cellular elements in these proliferations. Calcification is common and usually takes the form of small concentric psammoma bodies. Sometimes it is difficult to find residual viable cells within a large mass of psammoma bodies and fibrous tissue (Fig. 7-7).

Cytologic Appearance

Because endosalpingiosis has been discussed in detail only in recent years, its cytologic appearance is still being defined.[22,23] In a peritoneal lavage spec-

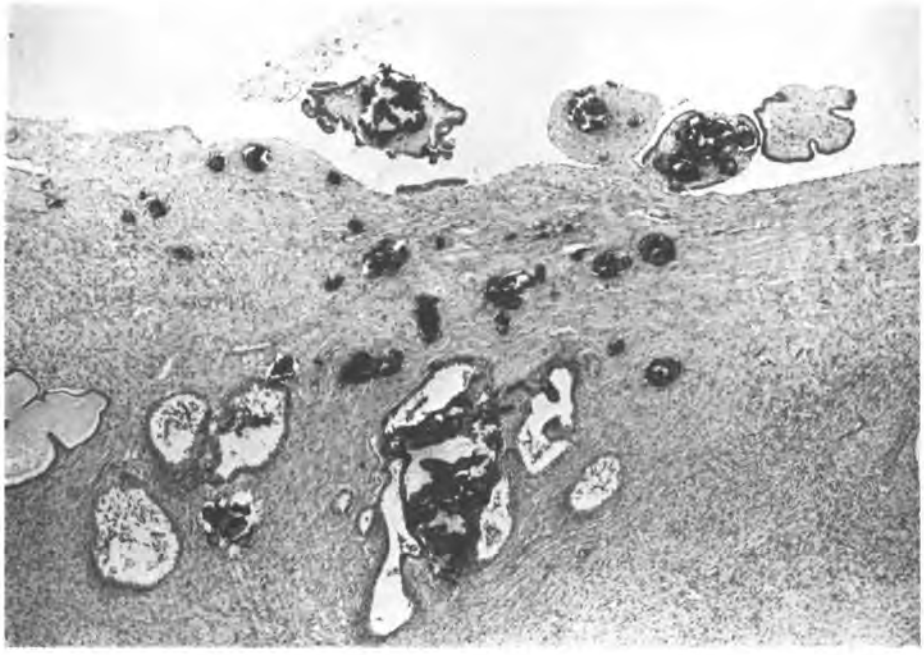


FIGURE 7-3 Endosalpingiosis of ovary. Note the numerous microcalcifications and growth both at and below the serosal surface. (Farhi DC, Silverberg SG: Pseudometastases in female genital cancer. Pathol Annu 17 [Part I]:47–76, 1982)

imen (which is the usual source of cytologic material in endosalpingiosis), the most useful diagnostic criterion is the presence of transitions from cells of epithelial, often atypical, appearance to those of classic benign mesothelial cells. Although the cells may be large and atypical, they lack the classic cytologic criteria of malignancy. Psammoma bodies may be numerous within the peritoneal cavity (Color Figures 7-3 and 7-4) and are not diagnostic of malignancy or even of neoplasia.[24] Papillary formations with psammoma bodies may be seen in the vaginal smears of women with endosalpingiosis, and this should always be considered as an alternative to the diagnosis of carcinoma.

Differential Diagnosis

The most important differential diagnosis of endosalpingiosis is with a malignant tumor of the peritoneum, usually metastatic adenocarcinoma but occa-

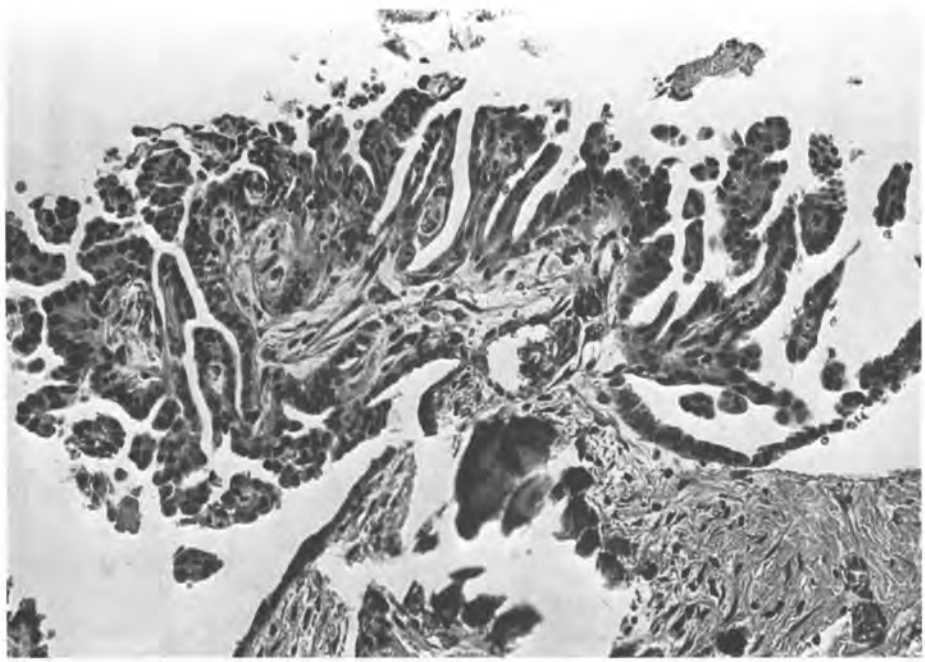


FIGURE 7-4 Endosalpingiosis of ovarian surface: detail.

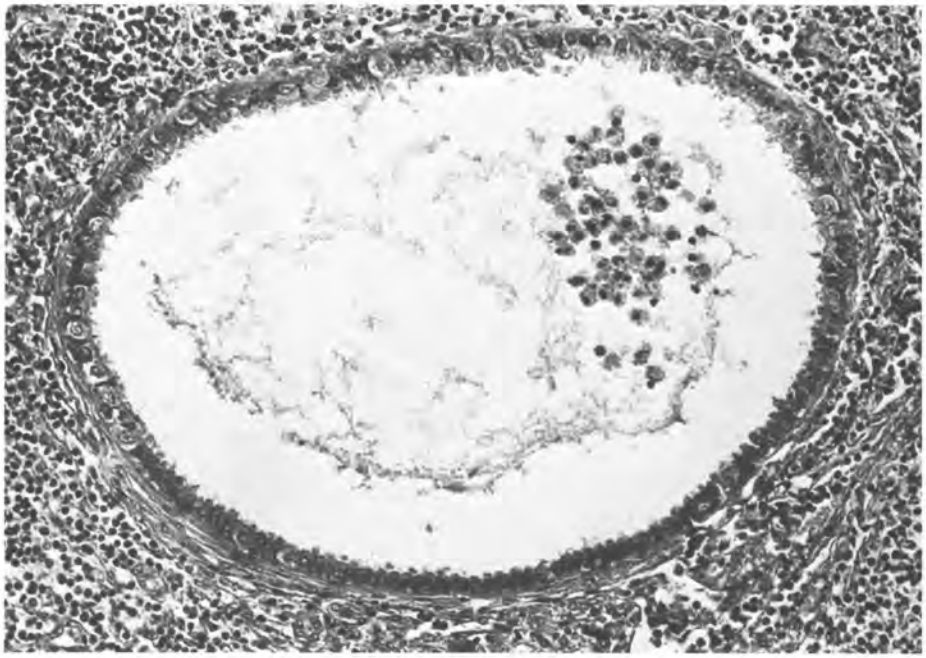


FIGURE 7-5 Detail of endosalpingiosis gland showing tubal-type epithelium.

sionally malignant mesothelioma. The finding of transitions to obvious mesothelial cells should rule out the diagnosis of metastatic carcinoma, even when a carcinoma is present in the ovary or endometrium. The absence of tumor elsewhere and the presence of tubal inflammatory disease strongly support the diagnosis of endosalpingiosis. Of equal or greater importance, in most cases, are the cytologic features of the epithelium itself. The presence of a tubal pattern, particularly if ciliated cells are numerous, is virtually diagnostic of endosalpingiosis. Even if such a pattern is not easily identified, the overall appearance should be bland, with atypia that is no more than slight to moderate and with only rare mitotic figures. There should be no destructive stromal invasion, although this may be difficult to differentiate from the inflammatory and sclerosing response by which the spontaneous regression of many foci of endosalpingiosis apparently takes place. Psammoma bodies may be seen in both endosalpingiosis and metastatic adenocarcinoma, but if the primary tumor elsewhere lacks psammoma bodies or a papillary ar-

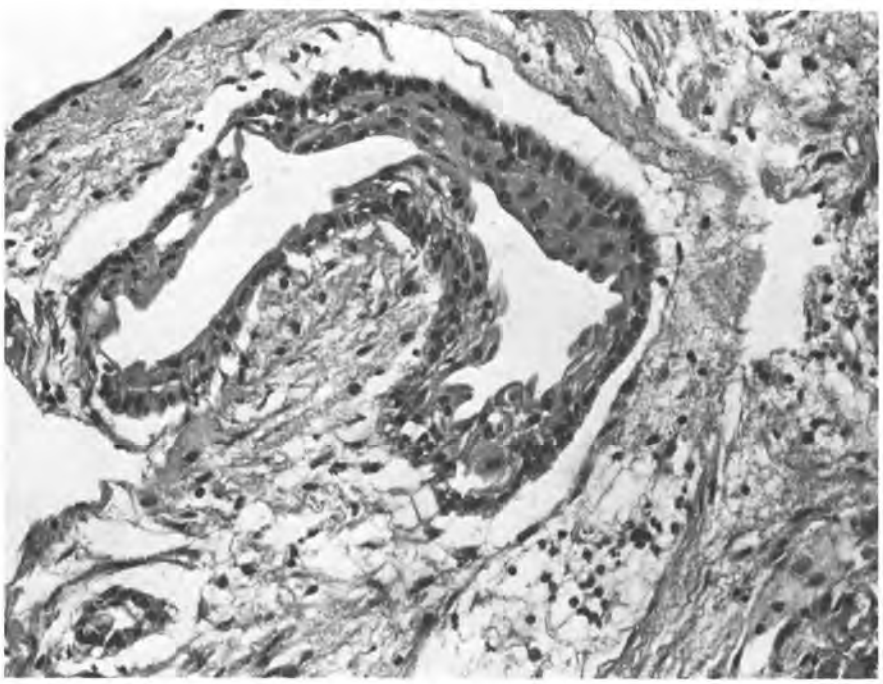


FIGURE 7-6 Endosalpingiosis of intestinal serosa showing urothelial metaplasia.

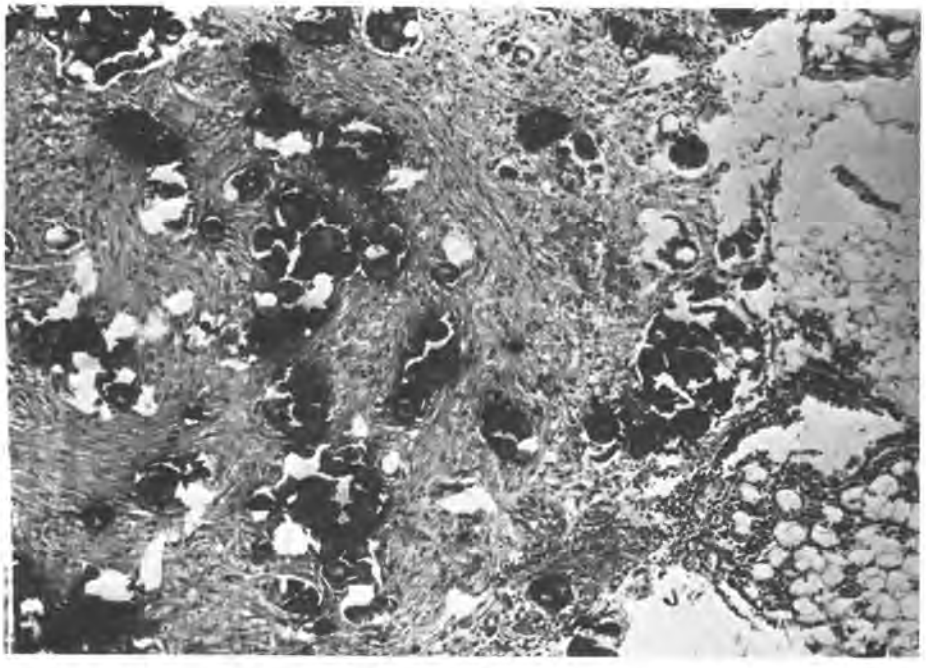


FIGURE 7-7 "Healed" endosalpingiosis of omentum, with fibrosis and microcalcifications. No residual viable cells are present.

chitecture, their presence in a mesothelial nodule otherwise consistent with endosalpingiosis would suggest benignity. The absence of a back-to-back or cribriform pattern is helpful. The differential diagnosis with malignant mesothelioma includes all these factors but is made simpler by the observation that classic mesothelioma of the peritoneum rarely occurs in women. When it does, it is almost invariably a macroscopically visible, diffuse, infiltrating tumor rather than the small, often microscopic proliferations of endosalpingiosis.

More difficult than the differentiation from metastatic adenocarcinoma is that from *serous tumor of low malignant potential* (*borderline tumor*[25,26] or *micropapillomatosis of low malignant potential*[27]) of the peritoneum, which may occur in the presence or absence of serous borderline tumor of the ovary. Bell and Scully have considered peritoneal proliferative lesions to be serous borderline tumors if they are composed of tubal-type epithelium exhibiting papillary projections, tufting, or detachment of cell clusters, even when they arise on the background of endosalpingiosis.[25,26] We believe that some lesions that we would consider to be atypical or even typical endosalpingiosis are overdiagnosed by these criteria (Fig. 7-8). We prefer to diagnose peritoneal borderline tumors by the same criteria used for ovarian borderline tumors (ie, cytologic criteria of malignancy without stromal invasion; see Chap. 6).

If the same criteria that are used for ovarian lesions are applied to peritoneal serous lesions, terms such as *noninvasive epithelial implants*, *noninvasive desmoplastic implants*, and *invasive implants* are no longer necessary.[28] These terms appear to be applied differently by different authors in describing the spectrum of neoplastic proliferations seen in various peritoneal sites in women with ovarian serous borderline tumors. We use only two diagnostic categories for these lesions—serous borderline tumor or invasive serous carcinoma (Figs. 7-9 through 7-11). Lesions with a tubal-type epithelium and a reactive stroma but without the usual architectural and cytologic features of serous carcinoma are usually regressing endosalpingiosis. Those with a reactive stroma and malignant cellular features are serous carcinomas, and serous tumors without evidence of stromal invasion but with tufting, cellular stratification and exfoliation, nuclear atypia, and mitotic activity are borderline tumors.

These distinctions are important because of differences in *prognosis*. The evolution of endosalpingiosis appears to be benign, and cases of carcinoma or borderline tumors should not be staged higher because of the finding of endosalpingiosis at exploratory laparotomy. In rare cases, the apparent development of a malignant or borderline tumor in a benign glandular inclusion has been reported (Fig. 7-12), usually when a similar tumor is present in the endometrium or ovary, and more often in a lymph node inclusion than in one of the more common sites of endosalpingiosis.[21,29] Nevertheless, the possibility of such a transformation must be kept in mind. Some or all multifocal serous carcinomas and serous borderline tumors arising from peritoneal surfaces may have developed in foci of endosalpingiosis, but this phenomenon has not been demonstrated conclusively and must remain speculative. Endosalpingiosis appears to require no treatment. Because the condition usually is diagnosed after its removal, it is difficult to be certain of its natural history if untreated. However, cases of spontaneous regression have been reported.

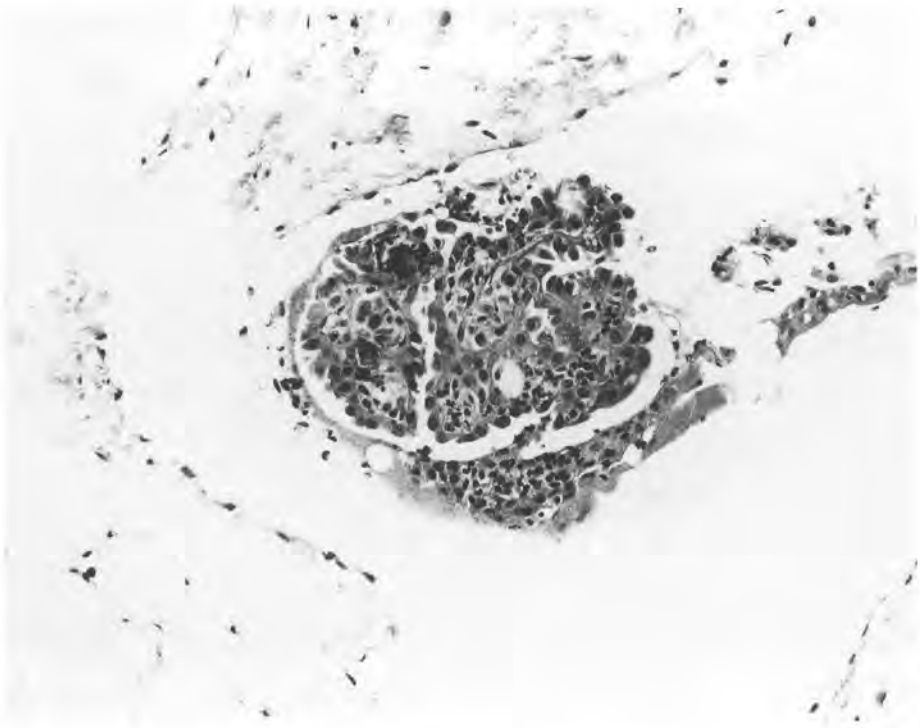


FIGURE 7-8 Atypical endosalpingiosis of omentum. There is papillary tufting and moderate nuclear atypia but no stratification or exfoliation of cell clusters. The patient had an ovarian serous tumor of low malignant potential.

The prognostic significance of peritoneal serous borderline tumors, on the other hand, is somewhat controversial. When they occur in the absence of an ovarian tumor, these tumors usually have a totally benign follow-up. Some patients may experience episodes of small bowel obstruction as a result of persistent or recurrent borderline tumors. Progression to invasive cancer and tumor-related death is rare.[25–27]

There is considerably less unanimity concerning the clinical significance of peritoneal serous borderline tumors and invasive carcinomas accompanying serous borderline tumors of the ovary. As summarized by Gershenson and Silva, some authors believe that only "invasive implants" worsen the prognosis, whereas an equal number report no significant difference in the outcome of patients with "invasive" or

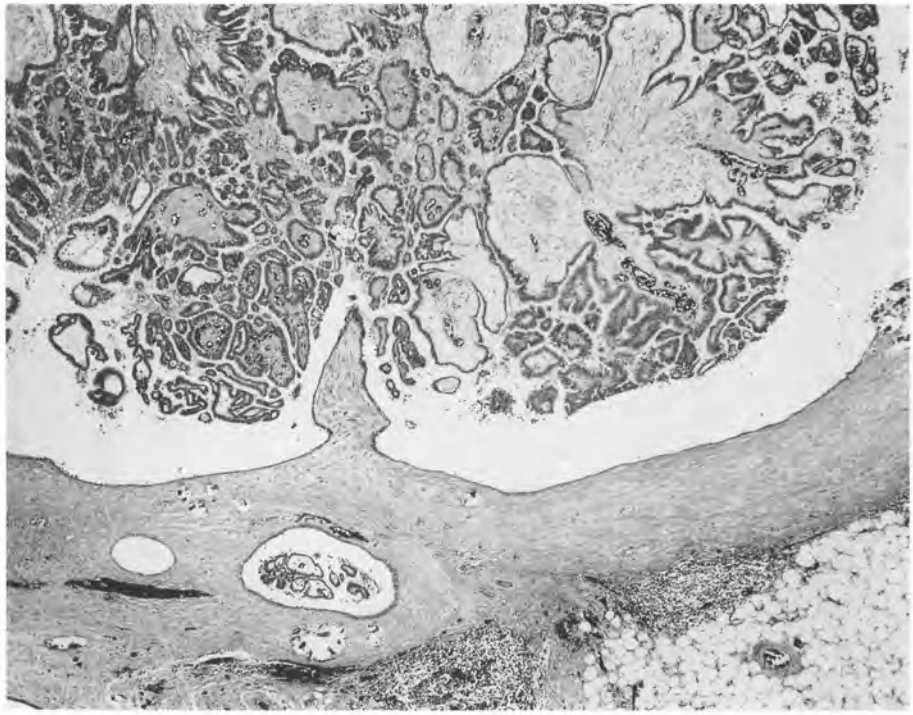


FIGURE 7-9 Serous tumor of low malignant potential in omentum. The patient had histologically identical tumors of both ovaries.

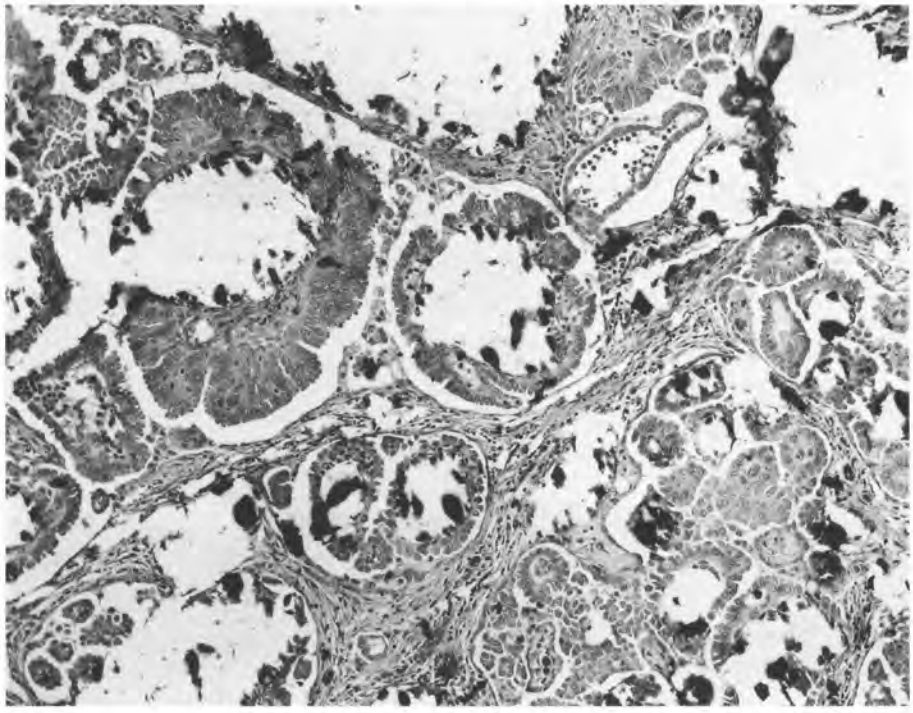


FIGURE 7-10 Serous tumor of low malignant potential in omentum. The tumor is heavily calcified, but papillary tufting, stratification, nuclear atypia, and exfoliation of cell clusters are easily seen. There is no stromal invasion. The patient had an ovarian serous tumor of low malignant potential.

"noninvasive" implants.[30] These differences may be based on differing diagnostic criteria or merely on the small numbers of cases in most reported series. In a review of my (SGS) recent, equally small, and unreported material, we found that patients with either of these lesions fared equally well.

Another controversial aspect of these "implants" is their *pathogenesis*. Many authors (including ourselves) have believed that they represent multifocal primary peritoneal neoplasia (the so-called field effect), but Segal and Hart have presented strong evidence in favor of their being true implants from the primary ovarian borderline tumor.[31] In their series, peritoneal implants were found in 29 of 47 patients (62%) whose ovarian tumors were found to have exophytic growth on the serosal surface, compared with 2 of 51 patients (4%) without exophytic tumor. Until this question is resolved completely, we

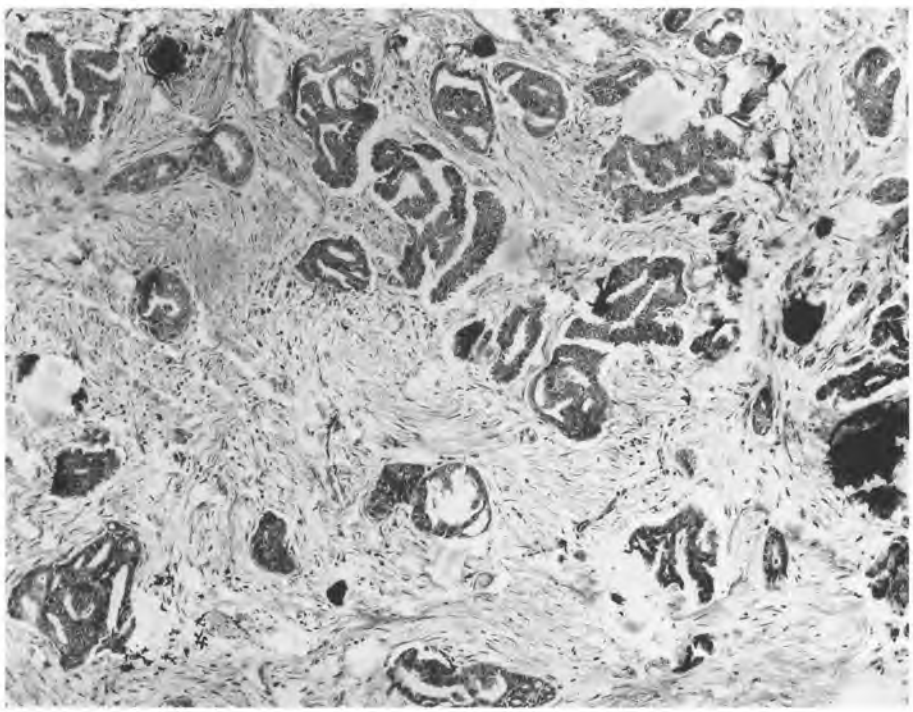


FIGURE 7-11 Invasive serous carcinoma of omentum. The patient had a synchronous ovarian serous tumor of low malignant potential.

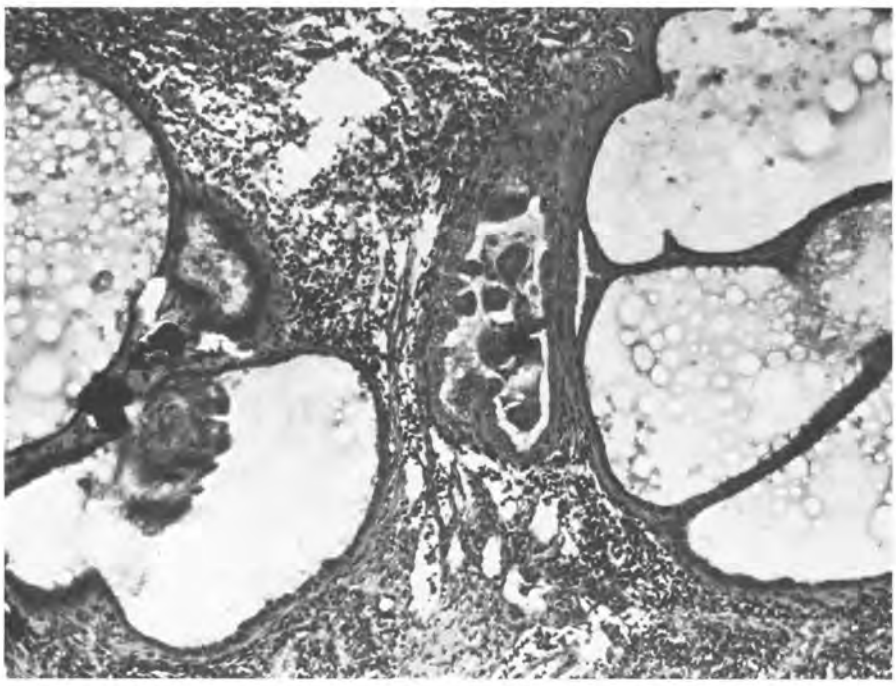


FIGURE 7-12 Development of a borderline serous tumor in an otherwise typical focus of endosalpingiosis (*right*) in a pelvic lymph node. A borderline serous tumor was also present in the ovary. (Farhi DC, Silverberg SG: Pseudometastases in female genital cancer. Pathol Annu 17 [Part 1]:47–76, 1982)

recommend the designation of these lesions as peritoneal serous borderline tumors or as invasive serous carcinoma—which are strictly morphologic diagnoses—rather than as noninvasive or invasive implants, which implies a specific pathogenesis. Primary serous carcinoma of the peritoneum is a different lesion from a clinical point of view and is discussed later in this chapter.

Benign glandular inclusions of müllerian type occur frequently in pelvic and paraortic lymph nodes of women (Fig. 7-13).[21,32,33] The same diagnostic criteria for differentiation of endosalpingiosis from metastatic adenocarcinoma should be applied in this situation (Fig. 7-14). An additional helpful observation is the involvement of the subcapsular sinusoid in metastatic cancer versus its lack of involvement by the benign glandular inclusions.

Another differential diagnosis of endosalpingiosis is endometriosis. The two conditions coexist and probably have identical pathogenetic mechanisms, and the distinction may be more apparent than real. However, it should be attempted because endometriosis is related clinically to infertility, pain, and other symptoms, and endosalpingiosis is not. In endometri-

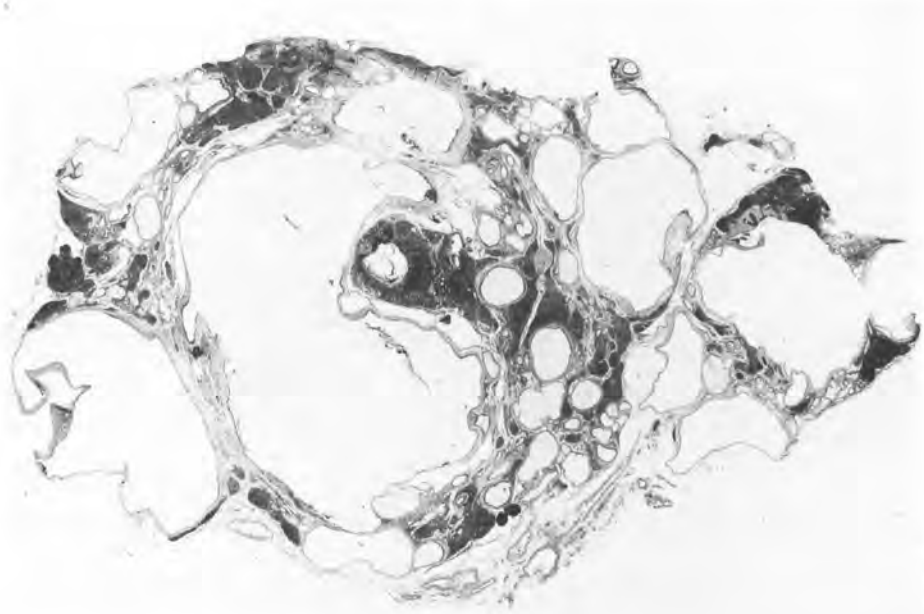


FIGURE 7-13 Pelvic lymph node largely replaced by benign glandular inclusions, lined by flattened and tubal-type epithelium.

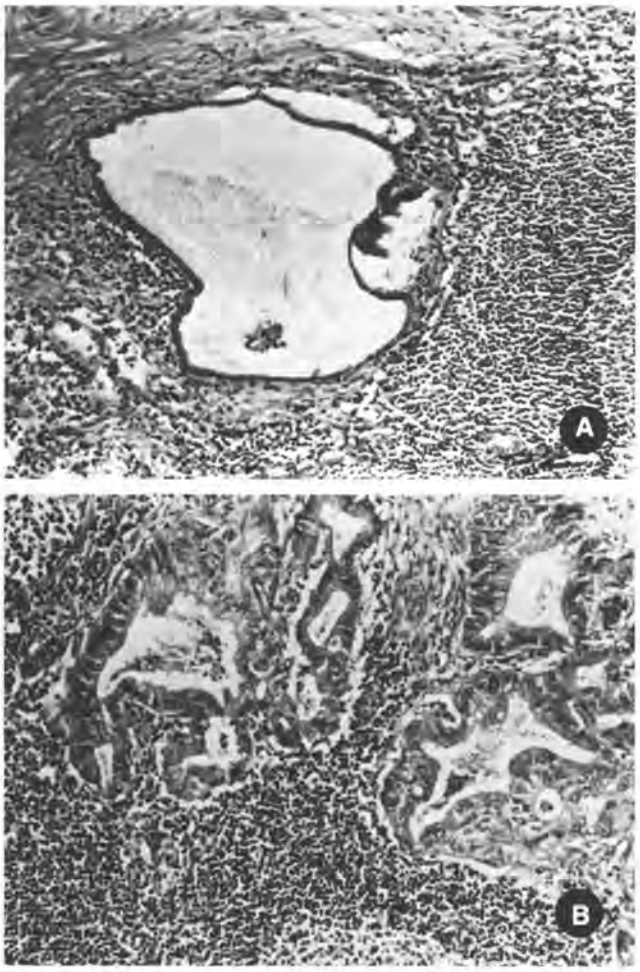


FIGURE 7-14 Comparison of benign glandular inclusion **(A)** and metastatic adenocarcinoma **(B)** in a pelvic lymph node. Both illustrations are from the same node. (Farhi DC, Silverberg SG: Pseudometastases in female genital cancer. Pathol Annu 17 [Part I]:47–76, 1982)

osis, the classic triad of endometrial epithelium, endometrial stroma, and old or recent hemorrhage should be present, whereas in endosalpingiosis the epithelium is more commonly of tubal type and, even when endometrial, should not be surrounded by stroma and hemorrhage.

Endometriosis

Endometriosis is one of the most common—and most important clinically—of those peritoneal conditions limited to or markedly more common in women. Endometriosis is not found only in peritoneal sites, however, and although we have included it among the metaplasias, its pathogenesis is uncertain.

Endometriosis is defined most simply as the presence of benign endometrial epithelium and stroma in an ectopic site. The condition has been divided into *endometriosis interna* (or *adenomyosis*), which involves the myometrium, and *endometriosis externa*, which generally is found in extrauterine localizations but is also found in the uterine serosa in the absence of myometrial involvement. Adenomyosis is discussed in Chapter 4; our discussion here is confined to the external variant of endometriosis. Sites other than the uterine serosa are, in descending order of frequency, the ovary, pelvic peritoneum, rectovaginal septum, fallopian tube, rectum and sigmoid, cervix, uterine ligament, vagina, other pelvic and abdominal locations, and rare scattered sites entirely outside the pelvis and abdomen.[34–38]

Pathogenesis

The pathogenesis of endometriosis has been debated for more than half a century, and the issue is by no means settled. There is ample clinical and experimental evidence favoring each of the main theories of pathogenesis. These theories are:

1. Retrograde menstruation and implantation
2. Coelomic metaplasia
3. Lymphatic or hematogenous dissemination.

Theory of Implantation. Sampson was the first major figure to champion the theory of implantation.[39] He hypothesized that retrograde menstruation with expulsion of endometrial fragments through the tubal lumina into the peritoneal cavity would lead to implantation and development of these fragments in most of the common sites of endometriosis.[40] This theory corresponds well with the usual distribution of clinical endometriosis and with experimental studies that induce endometriosis by implantation in animals and humans.[41,42] The implantation theory is also supported by reports of so-called scar endometriosis, in which the lesion develops in a surgical scar related to an episiotomy, a recently cauterized cervix, or an excised Bartholin's gland.[43]

Opponents of this theory point to the rarity of documented retrograde menstruation, the apparent lack of viability in most fragments of menstrual endometrium, and the occasional foci of endometriosis in sites where retrograde menstruation would not be likely to play a role (eg, pleuropulmonary endometriosis).[38]

Theory of Coelomic Metaplasia. Meyer adapted the theory of coelomic metaplasia from the ideas of von Recklinghausen.[44] The theory proposes that the peritoneal mesothelium undergoes müllerian metaplasia into endometrial-type tissues. It is supported by the knowledge that the müllerian ducts and the peritoneal serosa have a common coelomic origin. Other supportive data (which usually are anecdotal) include the development of endometriosis in patients without intrauterine endometrium[45] and the association of endometriosis with other types of epithelial and mesenchymal proliferations presumably derived by mesothelial metaplasia.[17,46] This theory might explain intrathoracic endometriosis, because all but two

of the reported cases have been pleural or subpleural.[38] However, even rarer localizations that are not abdominal, pelvic, or thoracic would be difficult to explain using this theory.

Theory of Lymphatic or Hematogenous Dissemination. A theory of lymphatic or hematogenous dissemination would appear to explain those rare cases that are dissonant with the other two theories. Endometrial fragments can be found in myometrial vascular spaces during menstruation and in other phases of the menstrual cycle,[47,48] and endometriosis in pelvic lymph nodes has been attributed to lymphatic spread.[49] Most of the common pelvic and abdominal sites of endometriosis, however, are better explained by one or both of the previously cited theories.

Other Theories. Other phenomena have been invoked to explain why endometriosis develops in some women but not in others. The theory of metaplasia, in particular, cannot explain the absence of endometriosis in normal males and premenarchal females without an additional hormonal explanation. The few cases reported in males and in phenotypic females with gonadal dysgenesis generally have been associated with the use of exogenous hormones.[50,51] Studies in monkeys have indicated that although implantation endometriosis can be initiated without ovarian steroid hormones, maintenance depends on estrogen, progesterone, or both.[52] However, almost all studies of hormone receptors in human endometriosis have found that these receptors are present in lower concentrations in ectopic endometrium than in normal intrauterine endometrium in the same patients and may be absent entirely from the endometriotic foci.[53–56]

A heritable tendency toward the development of endometriosis has been suggested,[57,58] and immunologic abnormalities have been noted in patients with endometriosis.[59–61] These factors may be causative or secondary.

Symptoms

Endometriosis appears during the period of gonadal activity and stabilizes or regresses after a natural or artificial menopause. Some cases are asymptomatic and represent incidental surgical findings, whereas others cause painful pelvic manifestations connected with the menstrual cycle and show signs of compression of adjacent organs. The most frequent clinical manifestations are dysmenorrhea, menometrorrhagia, dyspareunia, infertility, and lumbar or rectal pain.[34,35,62,63]

The pain associated with endometriosis is usually aggravated during menstruation and appears to be due to bleeding into and around the foci of disease. Some studies suggest that dysmenorrhea is a consequence of the prostaglandins produced by the endometriotic implants, but other studies indicate that women with and without endometriosis have no significant differences in prostaglandin levels.[64] The pathogenesis of the other symptoms, particularly infertility, is equally difficult to explain. Although infertility in anatomically advanced cases of endometriosis is probably best attributed to replacement or obstruction of normal reproductive structures, the infertility frequently encountered in the presence of minimal endometriosis remains to be explained.[65] Various types of ovulatory dysfunction, including luteinization of an unruptured follicle (the so-called LUF syndrome), have been suggested as the cause of infertility in these cases, as have increased prostaglandin production and autoimmunity to endometrial or ovarian tissue.[34,59,60]

Other clinical manifestations of endometriosis are based on specific locations. For example, endometriosis has been reported to cause ureteral obstruction and to mimic acute appendicitis and rectosigmoid carcinoma.[36]

Clinical Staging

Classification of the severity of endometriosis is important in determining prognosis and treatment and in comparing different methods of treatment. The system of classification of pelvic endometriosis most frequently used is the revised classification of the American Fertility Society (Table 7-1).[66] Extrapelvic endometriosis has been classified by Markham and colleagues (Table 7-2).[67]

Macroscopic Appearance

Endometriosis presents diffusely or as isolated nodules that vary in size but generally do not surpass a few millimeters in diameter. Appearance and size vary with the phase of the menstrual cycle; the nodules become congested and painful during the menstrual phase. In the ovary, endometriosis presents as firm red-brown or blue cysts of several millimeters in diameter on the surface of the organ.[68] A section made through these foci reveals white or yellow tissue surrounding a more hemorrhagic central zone. When these tissues are voluminous, they may occupy a large part of the ovary and deeply invade the cortex. These cysts contain altered blood and their contents often are brown, prompting the common term, *chocolate cysts of the ovary* (see Color Figure 6-4). They are distended during menstrual periods and may rupture or develop fistulas into the ovarian stroma or the pelvic peritoneal cavity.

In the uterosacral ligaments, the rectovaginal septum, the round ligaments, and the umbilicus, foci of endometriosis are single or multiple small, blue nodules. The nodules vary in size, and the largest may be palpable. When they appear under the peritoneal or tubal serosa, these nodules have a stellate aspect with blue centers. More rarely, tubal endome-

TABLE 7-1
American Fertility Society Classification of Endometriosis: 1985

Disorder		***Extent***		
Endometriosis		***<1 cm***	***1–3 cm***	***>3 cm***
Peritoneum				
	Superficial	1	2	4
	Deep	2	4	6
Ovary				
R	Superficial	1	2	4
	Deep	4	16	20
L	Superficial	1	2	4
	Deep	4	16	20
Posterior Cul-de-sac Obliteration		***Partial*** 4		***Complete*** 40
Adhesions		***<1/3 Enclosure***	***1/3–2/3 Enclosure***	***>2/3 Enclosure***
Ovary				
R	Filmy	1	2	4
	Dense	4	8	16
L	Filmy	1	2	4
	Dense	4	8	16
Tube				
R	Filmy	1	2	4
	Dense	4*	8*	16
L	Filmy	1	2	4
	Dense	4*	8*	16

*If the fimbriated end of the fallopian tube is completely enclosed, change the point assignment to 16.

Total of Above: 1–5 = stage I (minimal); 6–15 = stage II (mild); 16–40 =stage III (Moderate); > 40 = stage IV (severe).

American Fertility Society: Classification of endometriosis: 1985. Fertil Steril 43:351–352, 1985

TABLE 7-2
Classification and Staging of Extrapelvic Endometriosis

Classification of Extrapelvic Endometriosis
- Class I: Endometriosis involving the intestinal tract
- Class U: Endometriosis involving the urinary tract
- Class L: Endometriosis involving the lung and thoracic cage
- Class O: Endometriosis involving other sites outside the abdominal cavity

Staging of Extrapelvic Endometriosis
- Stage I No organ defect
  1. Extrinsic: surface of organ (serosa, pleura)
     a. <1 cm lesion
     b. 1 to 4 cm lesion
     c. >4 cm lesion
  2. Intrinsic: mucosal, muscle, parenchyma
     a. <1 cm lesion
     b. 1 to 4 cm lesion
     c. >4 cm lesion
- Stage II Organ defect*
  1. Extrinsic: surface of organ (serosa, pleura)
     a. <1 cm lesion
     b. 1 to 4 cm lesion
     c. >4 cm lesion
  2. Intrinsic: mucosal, muscle, parenchyma
     a. <1 cm lesion
     b. 1 to 4 cm lesion
     c. >4 cm lesion

*Organ defect would depend on the organ of involvement and would include but not be limited to obstruction and partial obstruction of the urinary tract and the intestinal tract and hemothorax, hemoptysis, and pneumothorax resulting from pulmonary involvement.

Markham SM, Carpenter SE, Rock JA. Extrapelvic endometriosis. Obstet Gynecol Clin North Am 1989;16(1):193.

triosis simulates a hematosalpinx. This deeply pigmented appearance, although characteristic of mature lesions, may not be seen in early lesions such as those often encountered in laparoscopic staging procedures.[69–71] These initial lesions may be white, yellow, or red and may progress to the brown or blue appearance with time. The pain associated with the menstrual period is caused by the vascular tension that results from the periodic growth of these masses. The vulvar localization, of which relatively few cases have been reported, occurs mainly in women who have sustained obstetric vulvar trauma or an episiotomy. It often is not associated with involvement of the usual pelvic sites.[36]

Similarly, superficial cervical endometriosis is common after endometrial curettage combined with cervical conization, whereas deep cervical involvement usually is an extension from the cul-de-sac.[36] Intestinal, ureteral, pleural, pulmonary, and cutaneous localizations have been described (Color Figure 7-5).

Microscopic Appearance

Endometriosis is composed of glands, cellular stroma, and, in some cases, smooth muscle fibers (Fig. 7-15). The glands are lined by columnar, cuboidal, or flattened epithelial cells. The ciliated cells found in normal endometrium are also found in endometriosis. The stroma may be difficult to find or may be considerably more abundant than the glandular component. Unlike adenomyosis, the endometrium in external endometriosis generally responds to ovarian hormones and may show secretory changes in the second half of the cycle and decidual transformation during pregnancy.

Endometriosis is difficult to recognize when repeated hemorrhages have modified the tissue, leaving only glands lined by flattened epithelium or cysts completely devoid of epithelium. If hemorrhage is pronounced, macrophages laden with hemosiderin or, more commonly, lipofuscin or hemofuscin are found in the stroma. These cells are characteristic and may be the only clue to the diagnosis. However, if extensive sectioning fails to reveal glands or stroma of endometrial type, the diagnosis of endometriosis can only be suggested rather than confirmed.

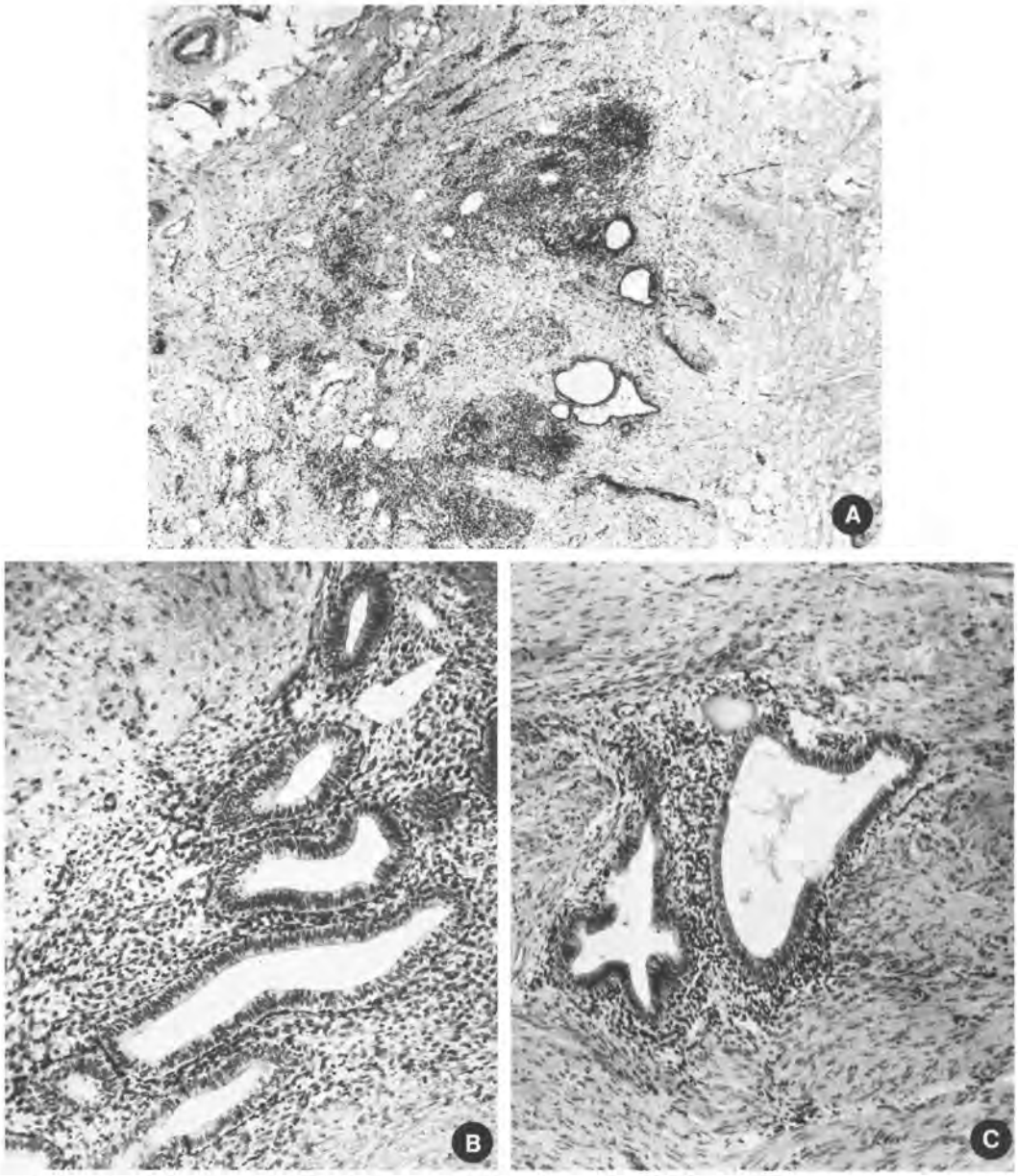


FIGURE 7-15 Endometriosis. **(A)** Lymph node; **(B)** rectal wall; and **(C)** sigmoid.

Several variations in appearance have been characterized recently. *Stromal endometriosis*, in which glands cannot be identified, is most common in the ovary and the cervix.[72] The absence of glands leads to a differential diagnosis with low-grade endometrial stromal sarcoma and other stromal neoplasms, including sex cord-stromal tumors in the ovary and Kaposi's sarcoma in the cervix.[36,72] *Necrotic pseudoxanthomatous nodules* are apparently a manifestation of end-stage endometriosis and are seen particularly in perimenopausal and postmenopausal women.[73] These nodules involve the ovaries and peritoneum and consist of central necrosis surrounded by palisaded pseudoxanthoma cells, hyalinized fibrous tissue, or both. Typical endometriosis is found elsewhere. *Endomyometriosis* is a variant in which extensive proliferation of smooth muscle results in the formation of uterus-like masses in the ovary, broad ligament, omentum, and other locations.[74] An alternative explanation for these masses is that they are congenital malformations. Other variations seen in endometriosis include stromal calcification, ossification, myxoid change, and inflammatory infiltrates, the latter possibly following superimposed infection.

Hormonal lesions may be reflected in the ectopic endometrium. For example, varying degrees of endometrial hyperplasia may be seen, particularly in ovarian endometriosis, and may coexist with similar images of hyperplasia in the intrauterine endometrium. Rare cases of endometriosis—again particularly in the ovarian localization—show marked cytologic atypia of the glandular epithelium without

architectural evidence of hyperplasia or carcinoma (Fig. 7-16). This *atypical endometriosis*, which should be diagnosed only when the atypia is not a reaction to underlying inflammation, has been reported as coexisting with and progressing to carcinoma, usually of the clear cell or endometrioid type (Fig. 7-17).[75,76] Chalas and colleagues have suggested that a high AgNOR (silver-staining nucleolar organizing region) count in atypical endometriosis may predict the development of carcinoma.[76]

Finally, peripheral reactive fibrosis is often seen and contributes to the increase in volume of the mass. Extensive fibrous adhesions may form, even to the point of causing a "frozen pelvis." Neither the formation of these adhesions nor the perineural or vascular invasion occasionally encountered in otherwise typical endometriosis should by itself be accepted as evidence of malignancy.[36]

Cytologic Examination

Cytologic examination is rarely performed in endometriosis. The overall appearance is benign, and epithelial and stromal cells may be seen.[38] Ceroid or iron pigment in histiocytes may falsely suggest the diagnosis of malignant melanoma.[77] Increased numbers of macrophages may be seen in peritoneal fluids from infertile endometriosis patients.[78]

Malignant Transformation

Ectopic endometrium shares with intrauterine endometrium the ability to undergo malignant change, although this transformation occurs in less than 1% of patients with endometriosis. Mostoufizadeh and Scully, for example, found 11 cases of carcinoma in more than 1800 reported cases of ovarian endometriosis.[79] Brooks and Wheeler pointed out that almost one fourth of the cases of malignant tumors arising in endometriosis were in extraovarian sites.[80]

Endometrioid carcinoma of the ovary may be of endometriotic origin, but this can be proved in only a small proportion of cases (up to 24% of cases reported in the literature). Clear cell carcinoma and mucinous müllerian borderline tumor are the only other ovarian epithelial tumors frequently associated with endometriosis (see Chap. 6). Proof of malignant transformation in endometriosis should consist of the two strict criteria formulated by Sampson: the presence of a focus of benign endometriosis at the origin of the tumor, and the demonstration of transition between the benign and malignant zones (Fig. 7-18). A malignant tumor may arise from any of the constituents of endometriosis: glandular epithelium, endometrial stroma, or smooth muscle fibers. Carcinomatous transformation of the glandular epithelium is most common. The appearance of stromal sarcoma, leiomyosarcoma, carcinosarcoma, or adenosarcoma is more unusual.

Treatment

There are strong proponents of both medical and surgical treatment for endometriosis. Medical treatment includes oral contraceptives, other progestational agents, and danazol, a synthetic steroid derivative of ethisterone with antigonadotropic properties.[62,81] Other agents are Gn-RH-a, a long-acting

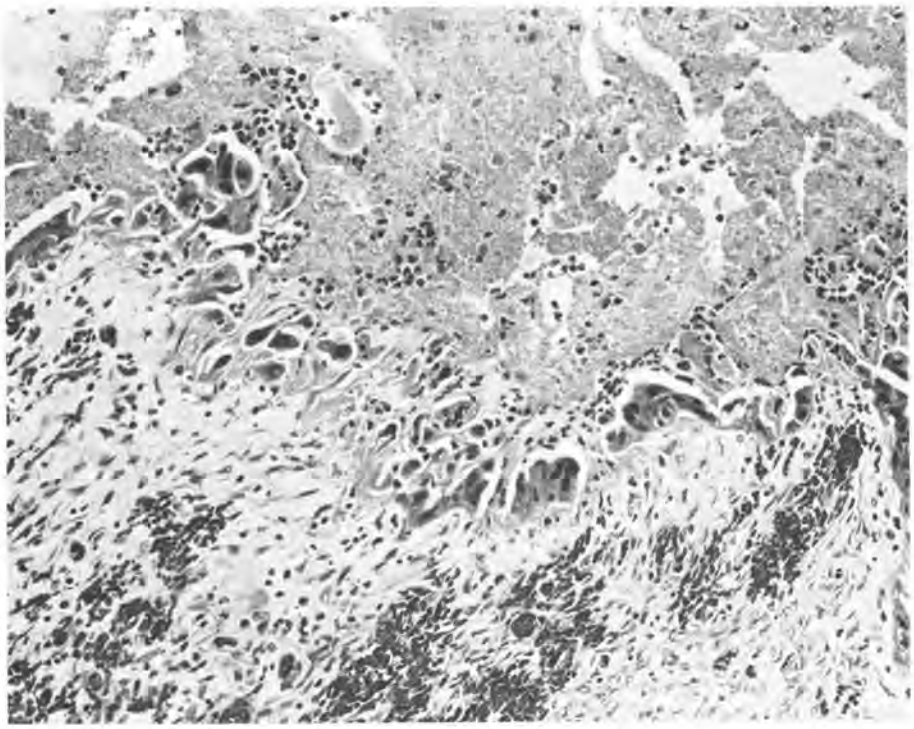


FIGURE 7-16 Atypical endometriosis of ovary. Bizarre proliferated cells project into a blood-filled cavity. They are underlaid by hemorrhagic endometrial stroma.

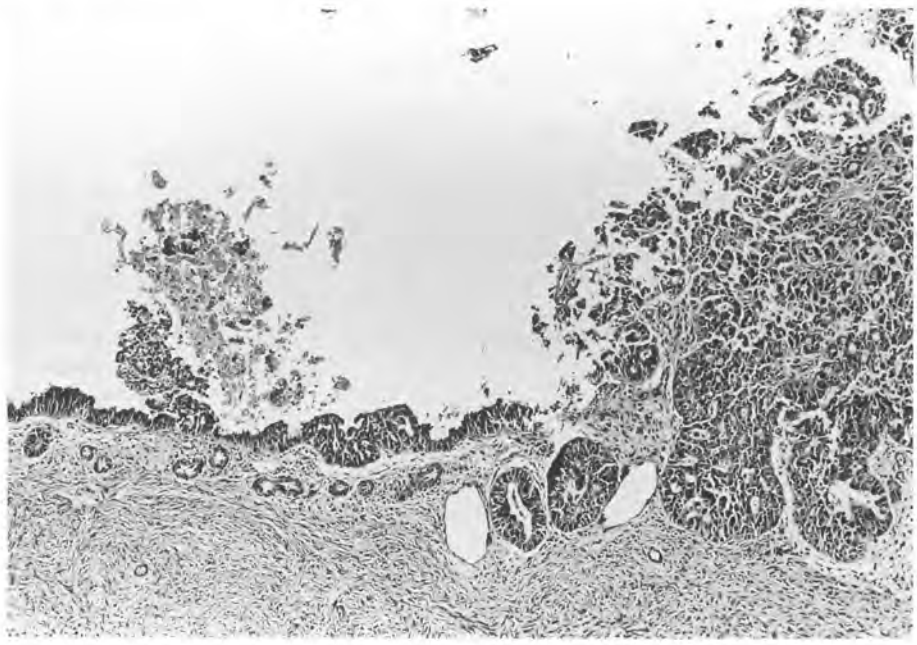


FIGURE 7-17 Ovarian cyst lining shows atypical endometriosis (*left*) in continuity with endometrioid carcinoma (*right*). (LaGrenade A, Silverberg SG: Ovarian tumors associated with atypical endometriosis. Hum Pathol 19:1080–1084, 1988)

gonadotropin-releasing hormone agonist, and gestrinone, an antiprogesterone steroid.[81–83] The results of different therapeutic measures are just beginning to be compared by the standardized approach permitted by the new clinical staging system (see Table 7-1).

The histologic changes brought about by the long-term administration of progestational agents are the same in clinical endometriosis and in the experimental disease in monkeys: decidual reaction followed by necrosis and fibrosis of the endometriotic foci. With danazol therapy, a pseudomenopause is created; small lesions regress completely, whereas large and thick-walled lesions decrease in size and may develop new adhesions.[62] The uterus, tubes, and ovaries atrophy with this form of treatment. Similar changes are seen in gestrinone-treated patients. Some lesions, however, show no change after therapy. The effectiveness of medical therapy can be monitored in some cases by serial determinations of plasma CA-125 levels.[84]

Surgical treatment is often necessary for diag-

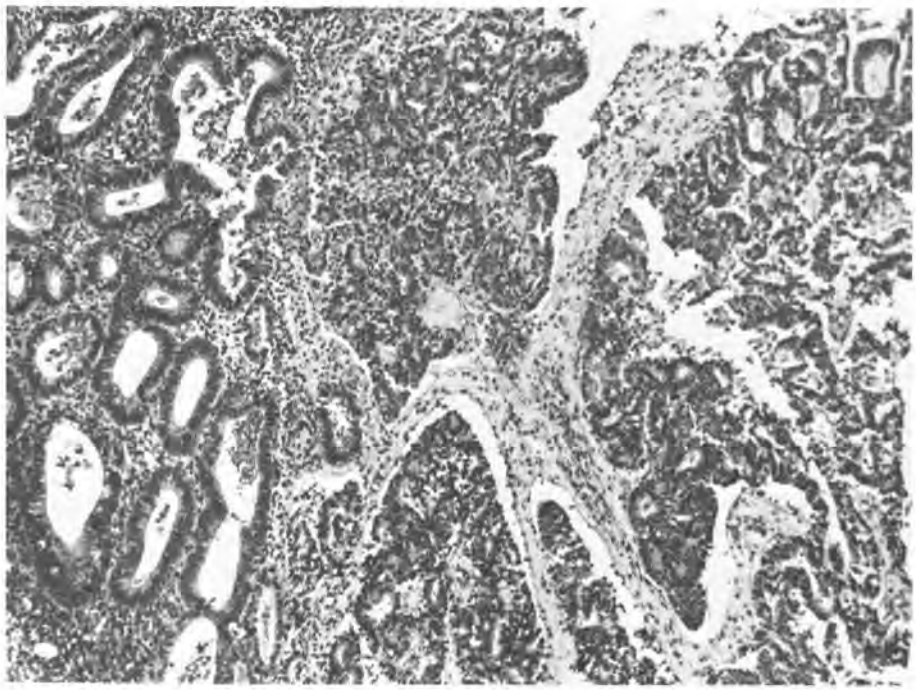


FIGURE 7-18 Adenocarcinoma (*right*) arising in endometriosis (*left*) of the vaginal wall. This patient had a synchronous carcinoma of the intrauterine endometrium without myometrial invasion.

nostic purposes and is indicated in the event of failure of hormonal therapy.[65,85] Surgery sometimes becomes necessary in the event of a serious complication such as obstruction or massive hemorrhage. The surgery may be local if the focus is easily resectable, or radical if the lesion is extensive or diffuse. Both medical and surgical therapies are more effective in cases of mild endometriosis. Clinical recurrence is frequent. In a review of the literature, Wheeler and Malinak found recurrence rates of 2% to 47% after conservative surgery, 17% to 29% after the establishment of pseudopregnancy with progestational agents, and 39% after danazol therapy.[86]

Endocervicosis

Far rarer than endosalpingiosis and endometriosis is a lesion known as endocervicosis, in which benign müllerian metaplasia results in the formation of mucinous epithelium resembling that of the endocervix. This lesion is usually an incidental finding in pelvic lymph nodes or the pelvic peritoneum but has been reported as a symptomatic mass in the posterior wall of the urinary bladder.[87,88] The differential diagnosis is with metastatic (or, in the bladder, primary) mucinous adenocarcinoma.

Leiomyomatosis Peritonealis Disseminata

A rare condition, leiomyomatosis peritonealis disseminata is found in women of reproductive age and is characterized by the presence of widespread peritoneal nodules. Although the first case was reported in 1952, subsequent case reports have accumulated so slowly that the 1982 report by Tavassoli and Norris[89] of 20 cases comprised about half of the reported cases in the literature at that time,[90] and only about 20 additional cases have been reported since then.[91] The condition has stimulated discussion, however, because of the discrepancy between the gross appearance of the lesions, which resemble a disseminated malignant tumor, and their uniformly benign evolution.

The condition occurs in women of reproductive age, many of whom are pregnant or postpartum (43% of cases) or taking contraceptive steroids or other hormones (27%) at the time of diagnosis.[91] The lesions are usually discovered incidentally, often at the time of cesarean section, laparoscopic tubal ligation, or other exploratory procedures associated with pregnancy. Because this lesion is often associated with unusual hormonal situations, it is widely assumed that its pathogenesis is related to hormonal imbalances. Fujii and colleagues were able to induce peritoneal nodules containing smooth muscle cells in guinea pigs by administering estrogen and progesterone.[92] The origin of the lesions appears to be in the subcoelomic mesenchyme, as discussed in detail by Ober and Black.[93]

Clinical Findings

Clinically, these are generally asymptomatic lesions that are discovered at the time of an exploratory procedure, usually a cesarean section or postpartum tubal ligation. Women with abdominal or pelvic symptoms almost always have coexistent disease such as endometriosis or uterine leiomyomata.[22,91]

Macroscopic Appearance

Macroscopically, there is a frightening picture of dozens to hundreds of small, well-demarcated, firm, gray to white nodules diffusely involving the peritoneal surfaces. These nodules usually measure 2 to 3 mm in diameter but may grow as large as 2 to 3 cm or even larger.

Microscopic Appearance

Microscopically, the nodules are composed of well-circumscribed whorled masses of uniform and benign-appearing smooth muscle cells (Fig. 7-19). Decidual cells may be admixed in those cases occurring in pregnant or postpartum women. Pleomorphism, nuclear atypia, and mitotic figures are absent or minimal. Collagenous sclerosis and inflammation may be present, but necrosis is absent. Foci of endometriosis or endosalpingiosis are present in continuity with the nodules in 10% of the cases.[94]

Ultrastructurally, the typical appearance is that of smooth muscle cells, with myofibrils, dense bodies, pinocytotic vesicles, and basal lamina. Some researchers have commented on the presence of cells resembling myofibroblasts and decidual cells, and of endometriosis.[46,89]

The evolution of these lesions has been generally benign, although two reported cases have been interpreted as progressing to leiomyosarcoma.[95,96] In several cases, the lesions have been shown to regress after the cessation of the abnormal hormonal stimulus (termination of pregnancy or of oral contraception). In a few cases, the lesions have recurred (or persisted) with a subsequent pregnancy. This association with hormonal stimuli is consistent with the presence of estrogen and progesterone receptors in the smooth muscle cells of the lesion.[97] It would appear from the reported cases that treatment should be conservative.

Deciduosis

Just as the subcoelomic mesenchyme apparently can proliferate and result in the development of smooth muscle nodules, a somewhat different pathway of development may produce solitary or multiple nodules of decidua in pregnant women.[94,98–100] As in leiomyomatosis peritonealis disseminata, these nodules are almost always asymptomatic findings discovered during the course of laparotomy for other indications,

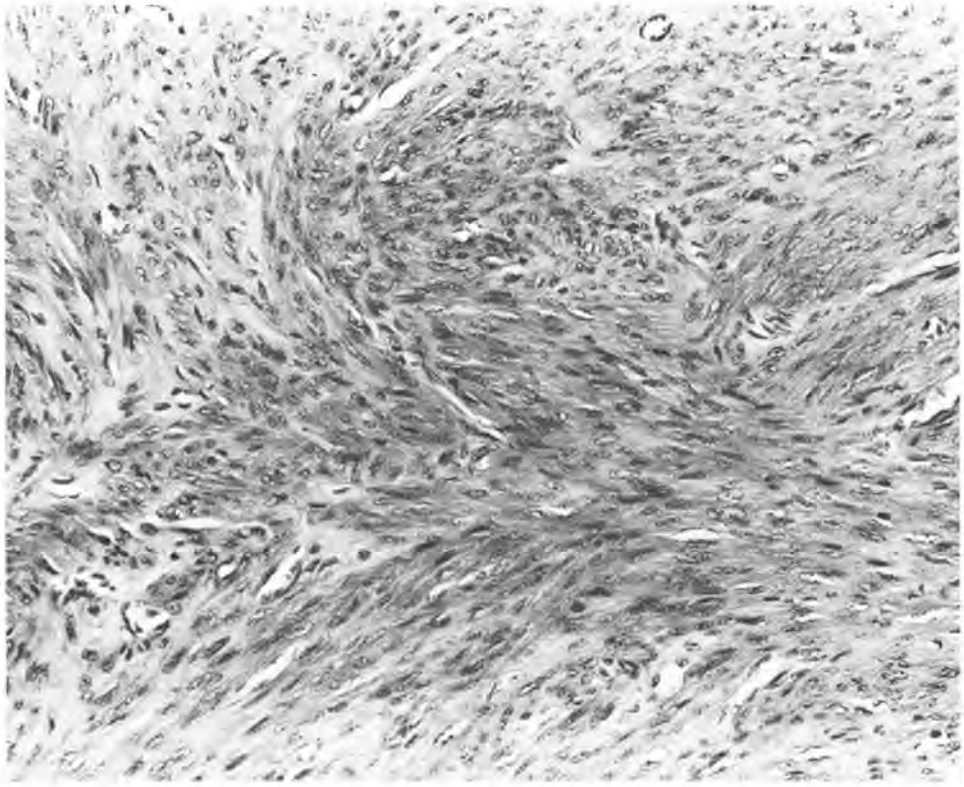


FIGURE 7-19 Benign smooth muscle proliferation in leiomyomatosis peritonealis disseminata.

although rare cases have been associated with massive intraperitoneal hemorrhage.[98,99] Similar foci of ectopic decidua may be seen in the cervix, the fallopian tubes, and pelvic and paraortic lymph nodes (Fig. 7-20). In one series, they were found in the tubal serosa in 5.5% of postpartum tubal ligation specimens.[98] In these situations, their major significance is the possibility of being misinterpreted as carcinoma, usually of squamous type.[100] Because decidual cells may show some cytologic atypia, the differential diagnosis depends on their low nuclear–cytoplasmic ratio, voluminous glassy eosinophilic cytoplasm, sharply demarcated cell borders, lack of intercellular bridges, and absence of destructive or proliferative stromal invasion. If doubt remains, the lack of immunoreactivity of decidual cells for cytokeratins should be helpful.

Splenosis

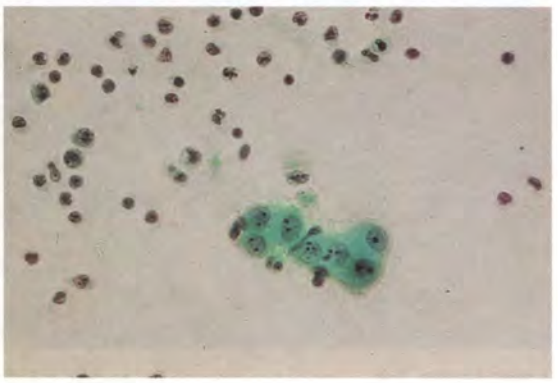
Splenosis is a rare condition in which traumatic splenic rupture results in the implantation of splenic fragments throughout the peritoneal cavity.[101] It is no more common in women than in men but is notable in women because of its tendency to mimic endometriosis in its gross appearance. The nodules usually are an incidental finding at laparotomy and involve, in descending frequency, the small bowel, omentum, parietal peritoneum and large intestinal serosa, and diaphragm. Their dark purple color may suggest hemorrhagic foci of endometriosis. Histologic examination quickly resolves this problem.

Benign Mesotheliomas

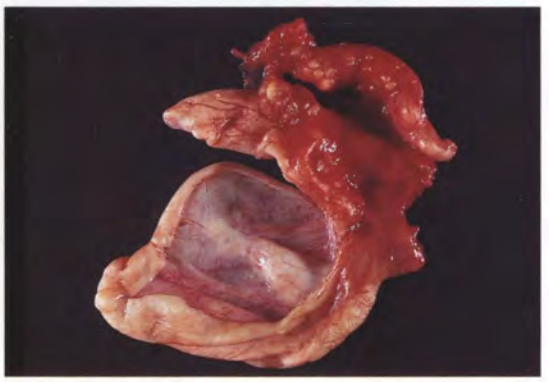
For many years, when the term *mesothelioma* was used to refer to a peritoneal lesion, the assumption was made that this represented a diffuse malignant process. In the past few decades, it has become apparent that a large variety of benign peritoneal mesotheliomas may be encountered and that they are far more common in women than the classic malignant mesothelioma.

Four benign or putatively benign patterns of peritoneal mesothelioma have been delineated: localized fibrous tumors, papillary mesotheliomas, cystic mesotheliomas, and adenomatoid tumors. The *localized fibrous tumor* is a common tumor of the pleura and a rarity in the peritoneum.[102,103] It is not limited to or overwhelmingly more common in women. Its other names, localized fibrous mesothelioma and submesothelioma, reflect the debate between advocates of a mesothelial origin and a fibroblastic derivation. The most recent ultrastructural and immunohistochemical (keratin-negative, vimentin-positive) studies support the latter theory.[103] As the name used here suggests, the lesion is localized, solitary, and composed of a uniform spindle cell proliferation with varying amounts of collagen. A focally or diffusely prominent hemangiopericytic pattern is often present. Atypia and mitotic activity are minimal, and lesions studied by flow cytometry have been diploid.[103] The evolution is benign.

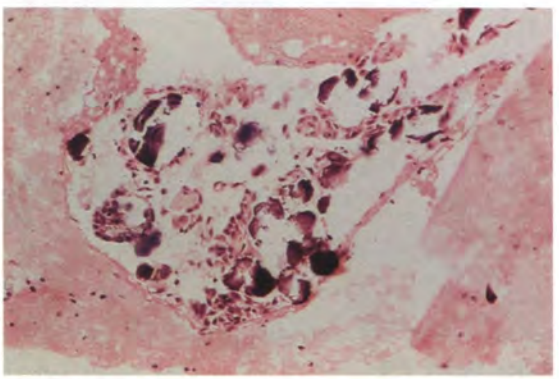
The *adenomatoid tumor* has been convincingly demonstrated to be of peritoneal mesothelial origin, but it is almost always found in women in the fallo-



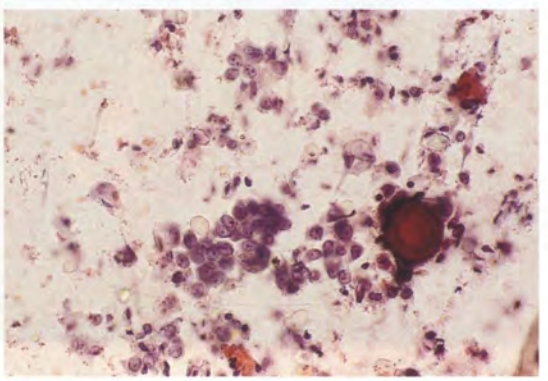
Color Figure 7-1



Color Figure 7-2



Color Figure 7-3



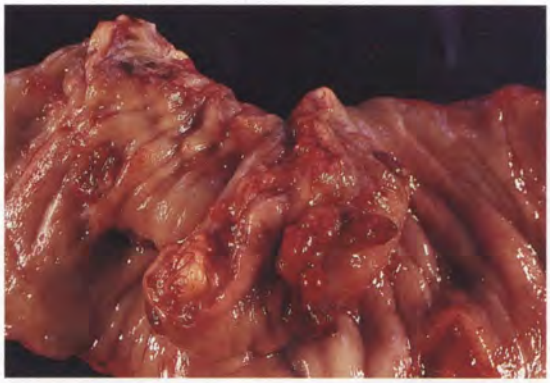
Color Figure 7-4

Color Figure 7-1 Reactive mesothelial cell atypia.

Color Figure 7-2 Endosalpingiosis of the tubal serosa accompanying a benign ovarian cyst.

Color Figure 7-3 Endosalpingiosis. Psammoma bodies and a few benign cells in peritoneal fluid cell block.

Color Figure 7-4 Endosalpingiosis in peritoneal washing: benign cells and psammoma body.



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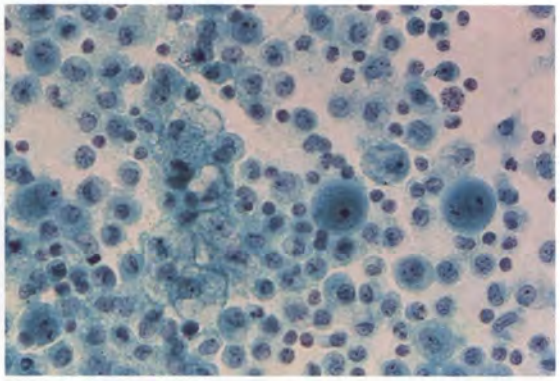

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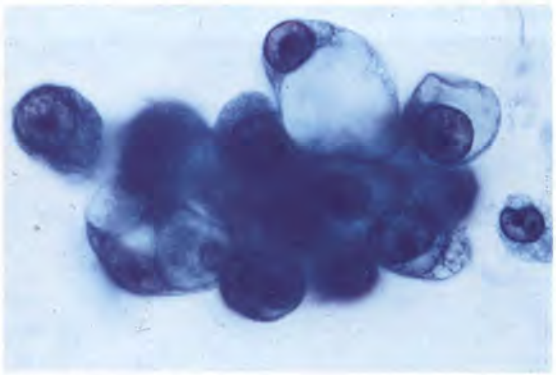


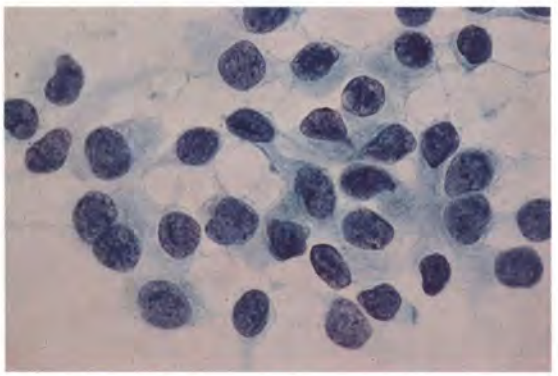
Color Figure 7-8

Color Figure 7-5 Intestinal endometriosis. Nodular red serosal lesions extend through the bowel wall and ulcerate the mucosa.

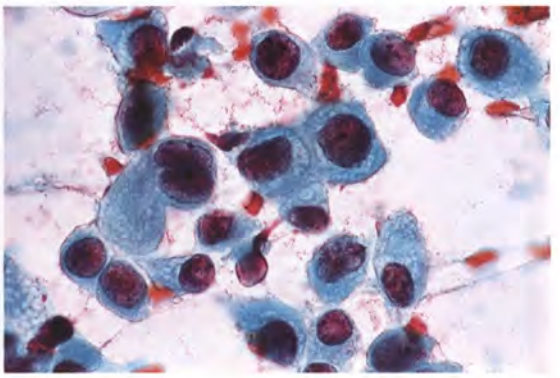
Color Figure 7-6 Malignant mesothelioma. Mesothelial cells range from small to large and bizarre.

Color Figure 7-7 Serous carcinoma of mesentery. Patient had undergone a hysterectomy with bilateral salpingo-oophorectomy for benign disease 14 years earlier (see Fig. 7-27 for microscopic appearance).

Color Figure 7-8 Metastatic adenocarcinoma in peritoneal fluid: mucin-secreting malignant cells. (Courtesy of Dr. Poonam Chandra, George Washington University, Washington, DC)



Color Figure 10-1



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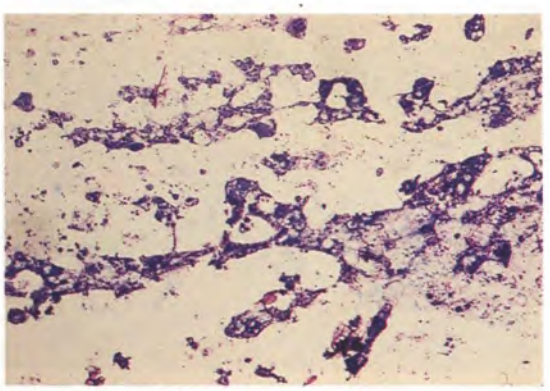

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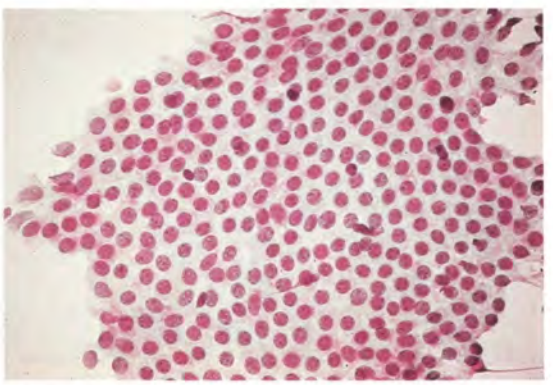


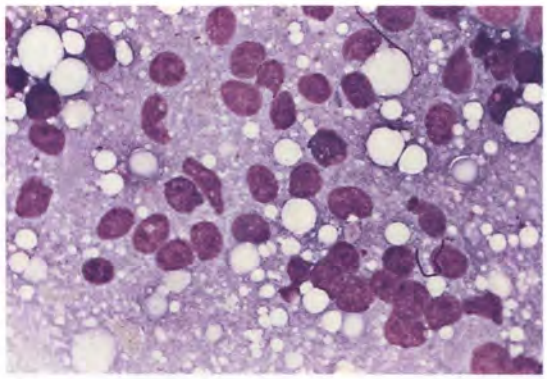
Color Figure 10-4

Color Figure 10-1 Fine-needle aspirate from infiltrating duct carcinoma. Poorly cohesive cells with increased nuclear–cytoplasmic ratios and nuclear hyperchromatism are shown. This tumor was moderately well differentiated.

Color Figure 10-2 Fine-needle aspirate from poorly differentiated infiltrating duct carcinoma. There is increased pleomorphism compared with that shown in Color Figure 10-1.

Color Figure 10-3 Fat necrosis: smear shows necroinflammatory background with no ductal cells.

Color Figure 10-4 Fine-needle aspirate from fibroadenoma. A large sheet of uniform ductal epithelial cells is shown in a honeycomb array, with peripheral blunt branches.



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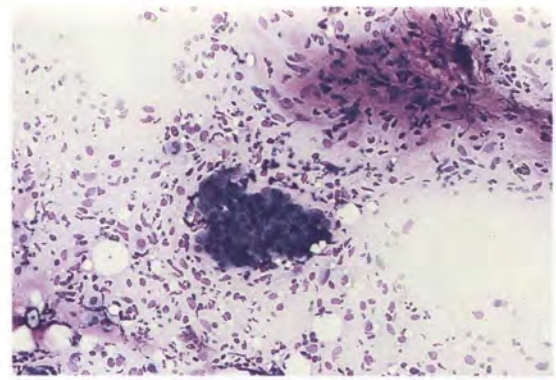

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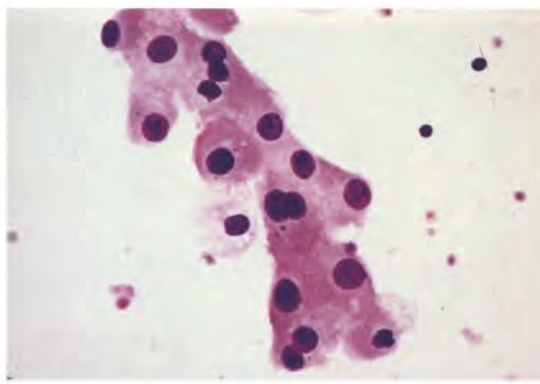

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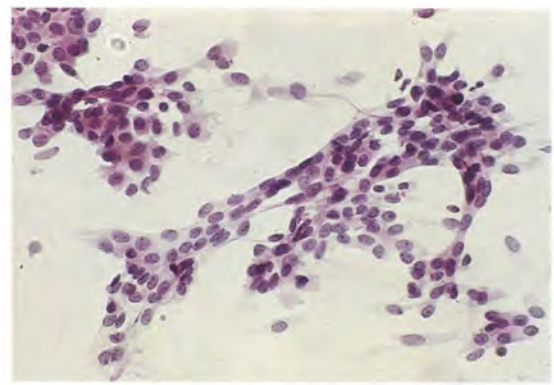


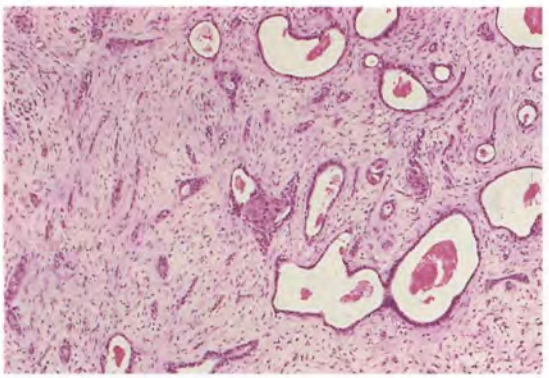
Color Figure 10-8

Color Figure 10-5 Lactational hyperplasia. An air-dried Diff-Quick-stained smear shows poorly cohesive ductal cells with mildly atypical nuclei and intracytoplasmic lipid vacuoles.

Color Figure 10-6 Low-grade phyllodes tumor. Cytologic picture of benign ductal cells and hypercellular stroma.

Color Figure 10-7 Intraductal papilloma: benign ductal cells showing apocrine metaplasia in smear from nipple discharge.

Color Figure 10-8 Nipple adenoma (subareolar papillomatosis). Intraoperative smear of biopsy specimen emphasizes cytologic benignity.



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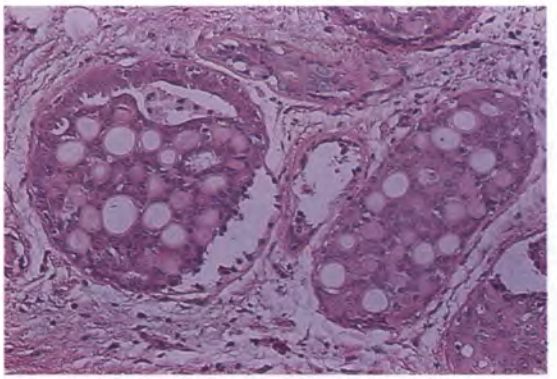
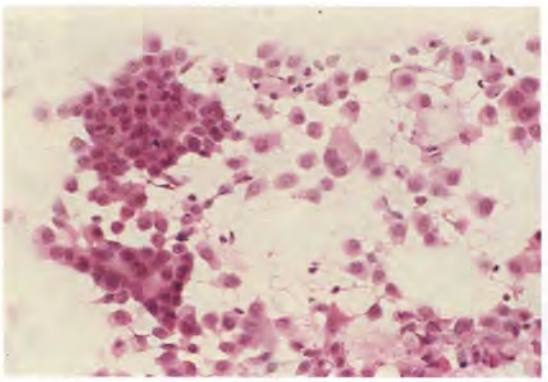
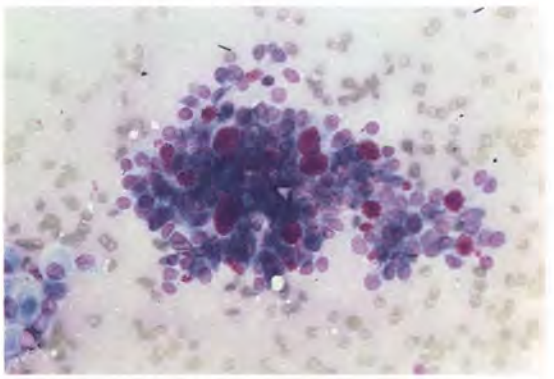


Color Figure 10-10



Color Figure 10-11



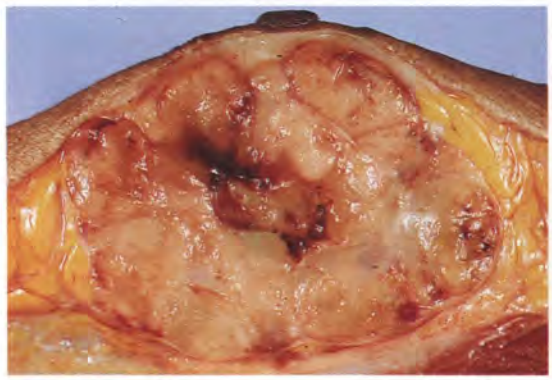
Color Figure 10-12

Color Figure 10-9 Syringomatous adenoma of nipple. Infiltrating dilated and comma-shaped glandular structures, some with squamous metaplasia, in a nonreactive stroma. (Courtesy of Dr. Mirka Jones, Armed Forces Institute of Pathology, Washington, D.C.)

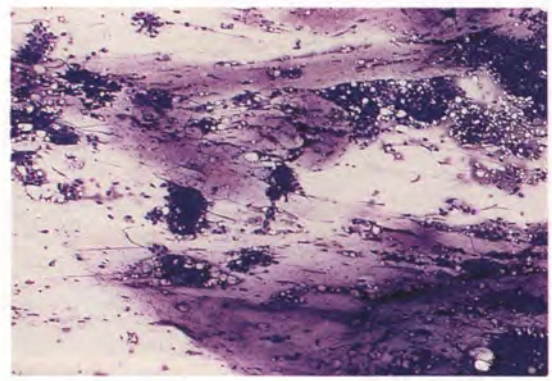
Color Figure 10-10 Collagenous spherulosis. This was an incidental microscopic finding in a breast biopsy performed for another indication.

Color Figure 10-11 Intraductal carcinoma. Smear shows cohesive and dyshesive malignant ductal cells.

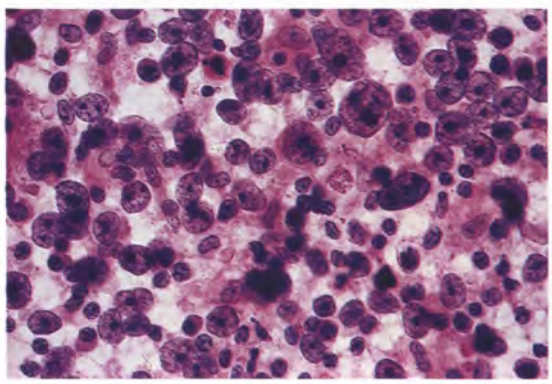
Color Figure 10-12 Adenoid cystic carcinoma. Smear from fine-needle aspirate shows small, uniform tumor cells in hyaline background. (Courtesy of Dr. Sana Tabbara, The George Washington University Medical Center, Washington DC)



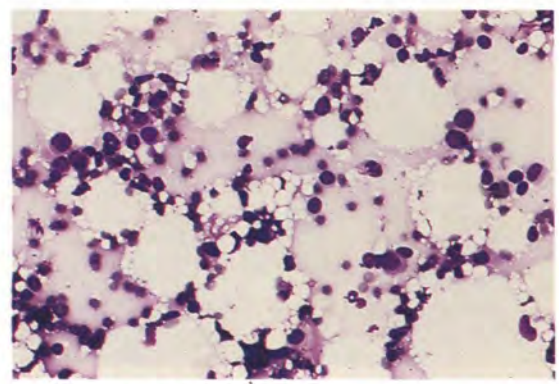
Color Figure 10-13



Color Figure 10-14



Color Figure 10-15



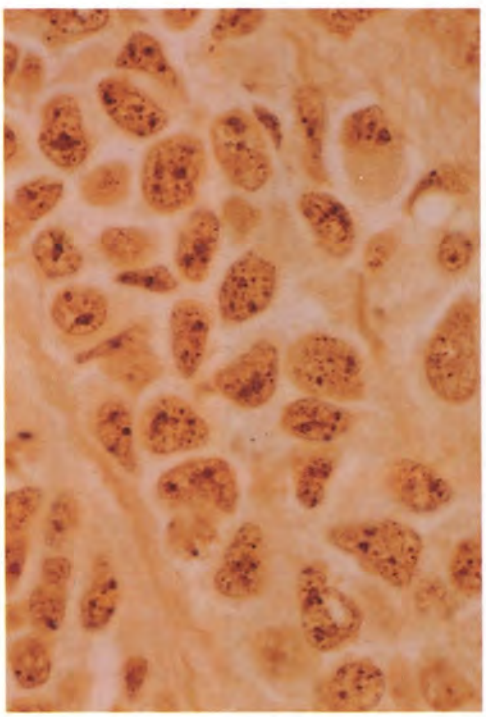
Color Figure 10-16

Color Figure 10-13 Mucinous carcinoma. A large, well-circumscribed, gelatinous gross appearance is typical.

Color Figure 10-14 Mucinous carcinoma. Smear shows clusters of small tumor cells in voluminous extracellular mucinous background (Diff-Quick stain).

Color Figure 10-15 Medullary carcinoma. Cytologic appearance of large, bizarre, dyshesive carcinoma cells and small lymphocytes.

Color Figure 10-16 Infiltrating lobular carcinoma. The most cellular region of a paucicellular smear shows small tumor cells in small clusters and as single cells.



Color Figure 12-1

Color Figure 12-2

Color Figure 12-1 AgNORs in serous papillary adenocarcinoma of the ovary. The specimen was fixed in 10% formalin for 18 hours and then embedded in wax. AgNORs are seen as black dots. They sometimes appear in aggregates within the nucleus.

Color Figure 12-2 Simultaneous immunohistochemistry and in situ hybridization of c-*myc* in serous papillary adenocarcinoma of the human ovary. The brown colorimetric diaminobenzidine reaction represents immunoreactivity of *c-myc,* and the black dots represent hybridization signals on autoradiography. This technique allows the expression of c-*myc* at mRNA and protein levels in the same tumor cells.

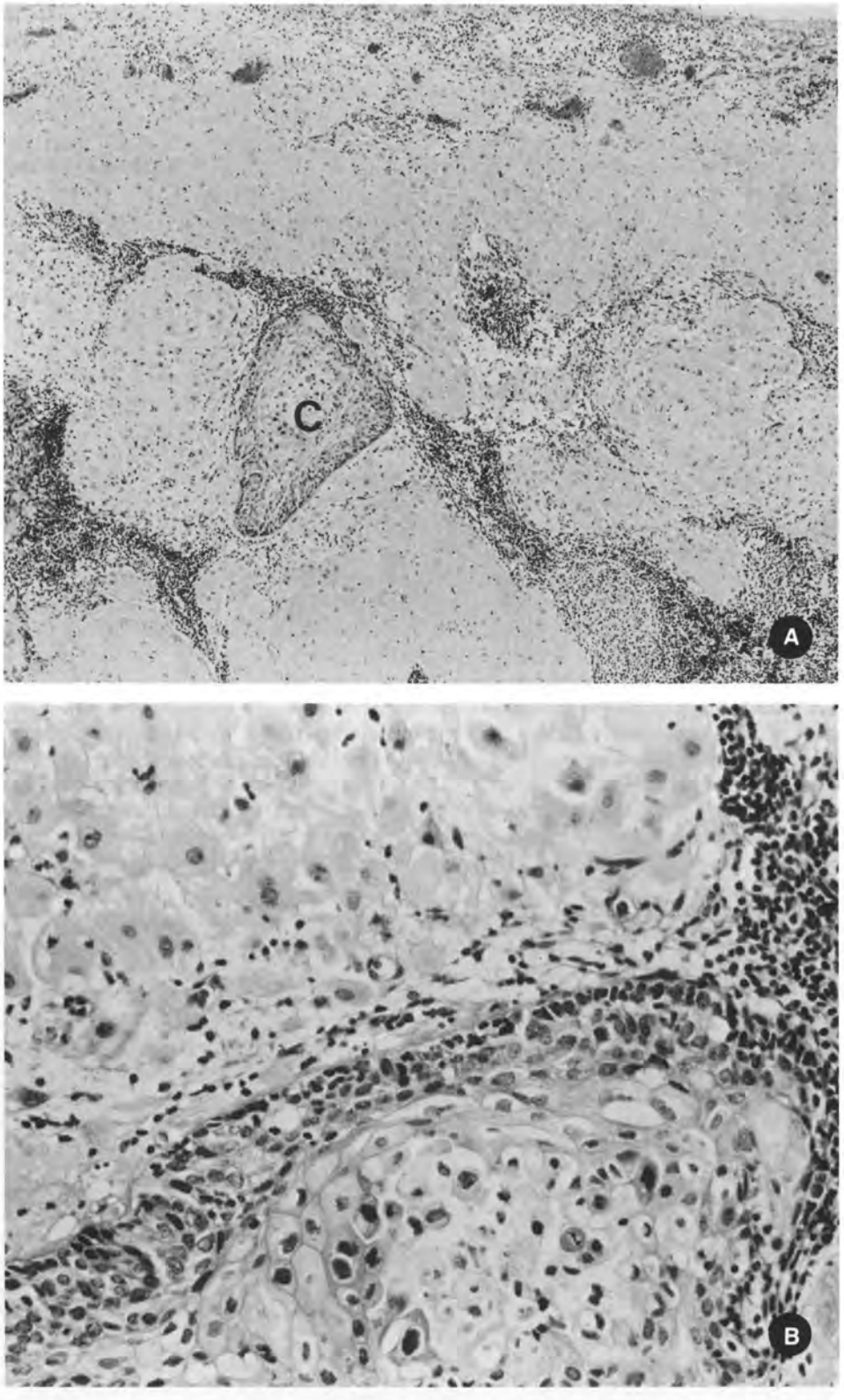


FIGURE 7-20 Decidua and metastatic cervical squamous carcinoma in pelvic lymph node of pregnant patient. **(A)** Low-power (single focus of carcinoma is marked *C*); **(B)** detail with decidua (*top*) and carcinoma (*below*).

pian tube or the uterine corpus. However, structures resembling those seen in adenomatoid tumors have been induced experimentally in animals in subperitoneal nodules produced by sex steroids, and rare examples of adenomatoid tumor arising in peritoneal sites outside the uterus and fallopian tube have been reported.[104,105] For further discussion of this tumor, see Chapters 4 and 5.

Since the initial case report in 1952, more than 120 cases of *cystic mesothelioma* have been reported, most in young or middle-aged women.[91,106–110] These tumors present as multiloculated cystic

masses in the abdomen and pelvis, with the usual clinical complaint of pain or a palpable mass. They vary in size, ranging from smaller than 1 cm in diameter to 20 cm or greater, whereas the individual cysts comprising the tumor vary in diameter from millimeters to centimeters (Fig. 7-21). The cysts contain thin watery secretions and are lined predominantly by a single layer of flattened to cuboidal mesothelial-like cells (Fig. 7-22). Occasional papillary tufts may be encountered (Fig. 7-23), as may foci of squamous metaplasia and mild to moderate cytologic atypia with occasional mitotic figures. The stroma between the cysts is generally thin and collagenous to myxoid. It may contain focal mild inflammatory cell infiltration.

Ultrastructurally, the lining cells of the cysts are confirmed to be of mesothelial origin by the presence of microvilli, desmosomes, and intracytoplasmic microfilaments.[106,107] About 40% of patients with adequate follow-up data have experienced recurrences, often after several years, but there are no reports of distant metastasis or death due to the tumor. The main differential diagnosis is with *cystic lymphangioma,* which is grossly and microscopically similar but occurs predominantly in males and children, and often in the mesentery.[110] Histologic and ultrastructural distinctions are based on the fact that the cystic lymphangioma is lined by endothelial rather than mesothelial cells and contains smooth muscle within the intercystic stroma. Unlike cystic mesothelioma, the lymphangiomas rarely recur.[110]

The main controversy surrounding this lesion concerns its fundamental nature. The term *cystic* or *multicystic mesothelioma* is used by those investigators who consider it a neoplasm,[108] whereas the term *multilocular peritoneal inclusion cysts* is preferred by those who conclude that these cases are reactive.[91,109] The latter view is encouraged by the finding that a history of previous abdominal surgery, pelvic inflammatory disease, or endometriosis was present in 84% of cases in one large series.[109] Those who take the former view are happier to quote the lower figure of 27% in another series.[108] The recurrence rate of 40% supports the neoplastic adherents, whereas their opponents state that these recurrences are merely examples of reactions to new adhesions formed at surgery. To make matters more confusing, some supporters of the reactive origin hypothesis claim that rare cases of true multicystic mesotheliomas do exist and can be recognized by the presence of markedly atypical mesothelial cells and the absence of a prominent inflammatory component.[91] We have not been able to appreciate this difference. We use the term *cystic mesothelioma,* and, whatever its origin, we emphasize the frequently recurrent but benign evolution of this lesion.

The most difficult benign mesotheliomas to characterize are those with a papillary architecture. Foyle and colleagues have divided papillary tumors of the peritoneum occurring in women into four groups.[102] *Diffuse papillary mesothelioma* is the least common type and is identical to the diffuse malignant mesothelioma known for decades and occurring far more frequently in men. *Papillary carcinoma* refers to a malignant tumor identical to serous carcinoma of the ovary but occurring in patients without

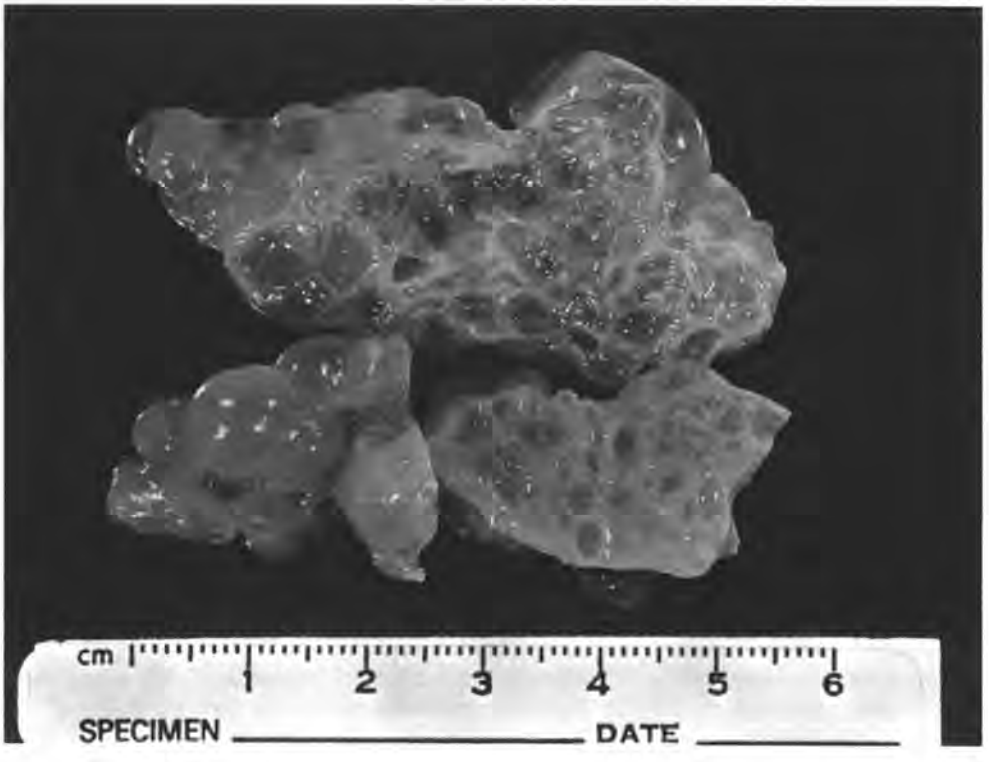


FIGURE 7-21 Macroscopic appearance of cystic mesothelioma.

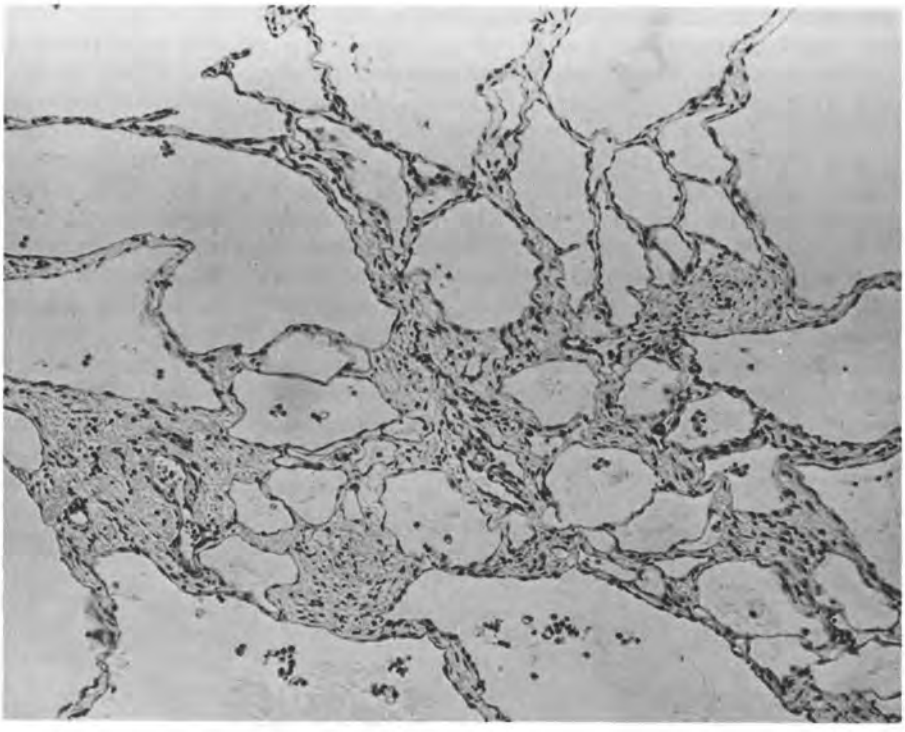


FIGURE 7-22 Low-power photomicrograph of cystic mesothelioma.

an ovarian primary tumor. *Atypical diffuse mesothelioma* was the term used to describe lesions intermediate in appearance between the first two. Because these are all malignant tumors, they are discussed in a later section of this chapter. More pertinent to the present section is the fourth group, *well-differentiated diffuse papillary mesothelioma.* As the name indicates, these are diffuse papillary proliferations that are confined to the omentum or are widespread on peritoneal surfaces. The experience of Foyle's group was subsequently updated to 22 cases,[111] and a total of about 35 cases have been published.[106,112–114] Although some of these mesotheliomas occurred in men and in postmenopausal women, the usual presentation was as an incidental finding in women of reproductive age. The lesions usually are multiple and small, although solitary lesions with an identical histologic appearance were described by Goepel.[112]

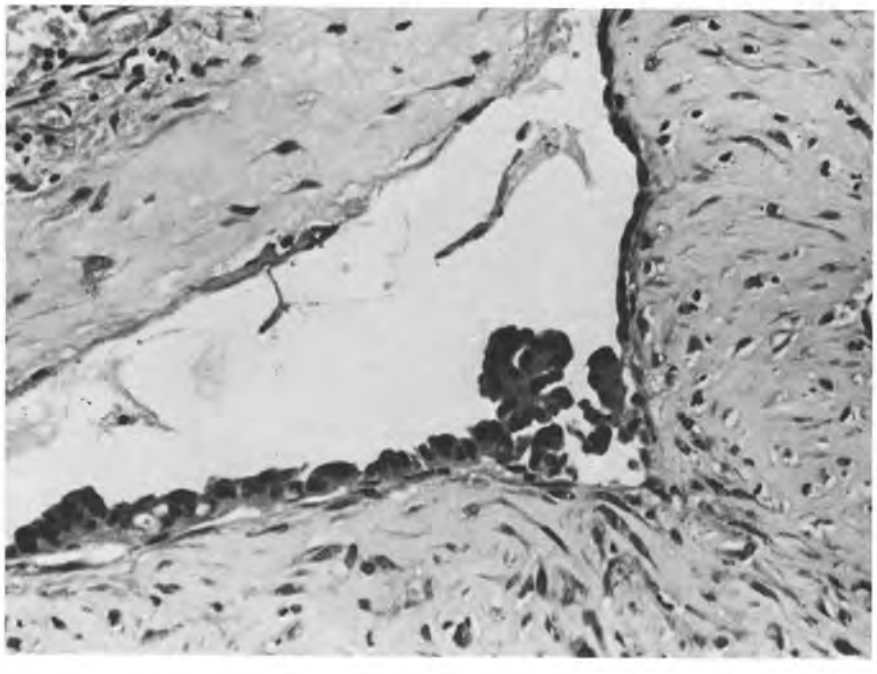


FIGURE 7-23 Cystic mesothelioma. Detail shows focal slightly atypical proliferation of mesothelial cells.

The most commonly involved sites are the omentum and pelvic peritoneum.

Histologically, these tumors are tubulopapillary or purely papillary. The papillary areas show coarse branching fronds with prominent fibrovascular cores. The lining cells are low cuboidal and uniform, with generally inconspicuous nucleoli and few mitotic figures (Fig. 7-24). In the tubular areas, there may be slightly more pleomorphism, but always less than in malignant diffuse mesothelioma. The absence of cell stratification, necrosis, and stromal invasion is helpful in the differential diagnosis. So few of these benign mesotheliomas have been reported that their cytologic appearance is poorly characterized.[113] We would, however, expect it to appear somewhat similar to reactive mesothelial hyperplasia and endosalpingiosis.

When all the lesions found in a patient are typical of well-differentiated diffuse papillary mesothelioma, the evolution appears to be benign, although persistence or recurrence has been noted for as long as 29 years.[102] However, these lesions have coexisted with or evolved into diffuse malignant mesothelioma in some patients.[91,114] Other patients have died, usually after a protracted course, although it is unclear whether the tumor or its therapy was most responsible.[111] All lesions should be removed and examined histologically, and the prognosis should be determined by the histologically most aggressive pattern.

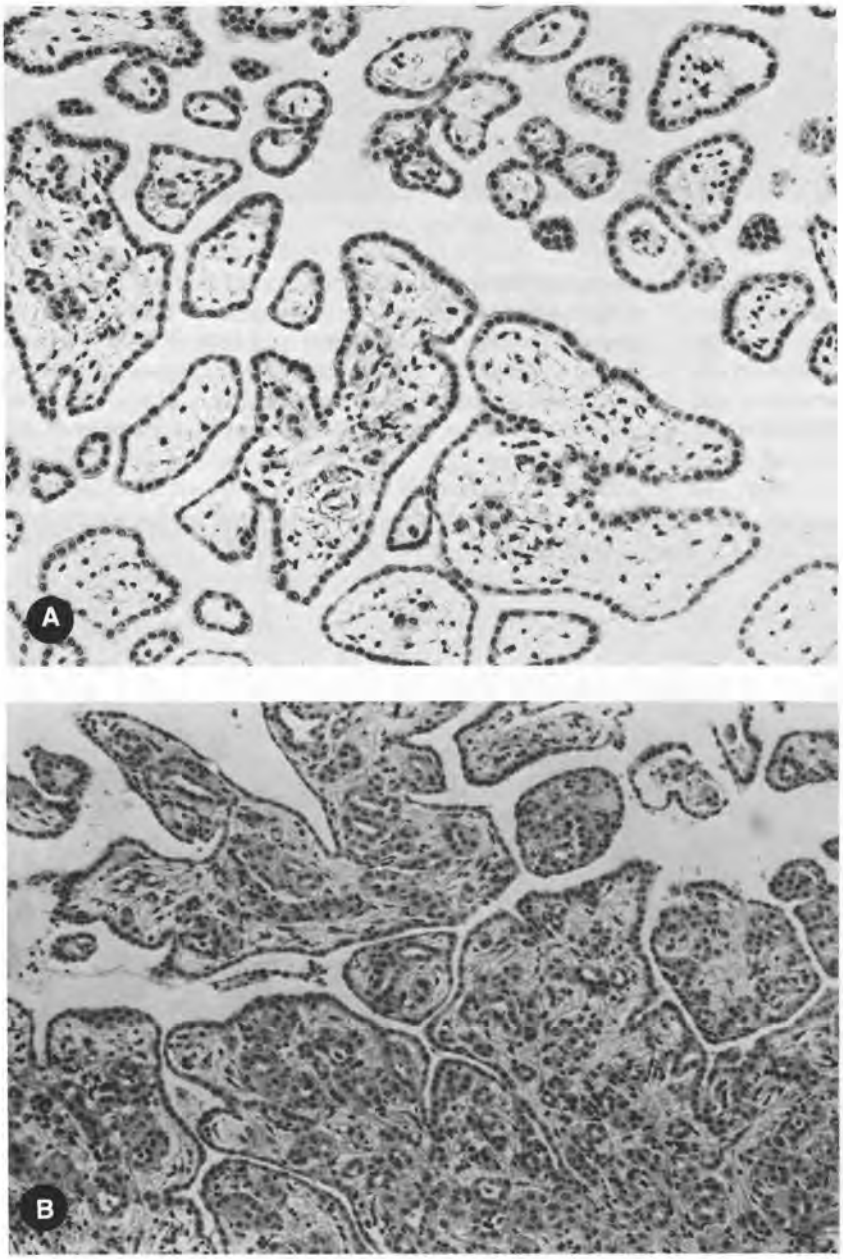


FIGURE 7-24 Well-differentiated papillary mesothelioma. **(A)** Papillary pattern; **(B)** tubulopapillary pattern. (**A:** Foyle A, Al-Jabi M, McCaughey WTE: Papillary peritoneal tumors in women. Am J Surg Pathol 5:241–249, 1981. **A** and **B** courtesy of Dr. W.T.E. McCaughey.)

MALIGNANT TUMORS

Malignant Mesothelioma

Malignant mesothelioma is a tumor that has been studied for many years, but a somewhat recent observation has been its rarity in women. Kannerstein and Churg, for example, encountered only 6 women among 83 patients with pathologically confirmed malignant peritoneal mesotheliomas.[115] Similarly, only 3 of 25 papillary peritoneal tumors in women reported by Foyle and associates were classic malignant mesotheliomas.[102] Because of the relative paucity of these tumors among women, they are not covered in detail in this chapter. They must be considered briefly, however, because of their importance in the differential diagnosis of benign mesothelial hyperplasias, metaplasias, and tumors, on the one hand, and metastatic and primary peritoneal carcinomas on the other.

Unlike these lesions in the differential diagnosis, classic malignant mesothelioma in women is associated with asbestos exposure, as it is in its more common manifestation in men.[107] The tumor is virtually always symptomatic because of its diffuse and invasive nature.

Macroscopic Appearance

Macroscopically, the diffuse tumor involvement of peritoneal surfaces presents with small nodules and large plaque-like masses. Intraperitoneal viscera are matted together by masses of tumor and are frequently invaded. Nodal and distant metastases generally present as a late event.

Microscopic Appearance

As in the more common pleural tumors, the microscopic picture varies from a purely epithelial to a mixed epithelial-sarcomatoid pattern (Fig. 7-25). The pure sarcomatoid pattern is rare.[116,117] In the epithelial pattern, papillae, tubules, and solid nests are seen. Psammoma bodies may be encountered, but these are more common in papillary adenocarcinomas. The cells show the usual cytologic criteria of malignancy.

Differential Diagnosis

The differential diagnosis is with benign mesothelial proliferations and carcinomas. The gross appearance, the presence of stromal invasion, and the finding of extensive necrosis, cell stratification, nuclear enlargement, hyperchromatism, and frequent mitotic figures generally are sufficient to establish the malignant nature of the process. At the cytologic level, this distinction may be much more difficult, but the presence of large clusters of cells, multinucleated cells, and malignant-appearing nuclei in some cells should suggest the diagnosis.

The differential diagnosis from adenocarcinoma is even more difficult, and it is not uncommon for

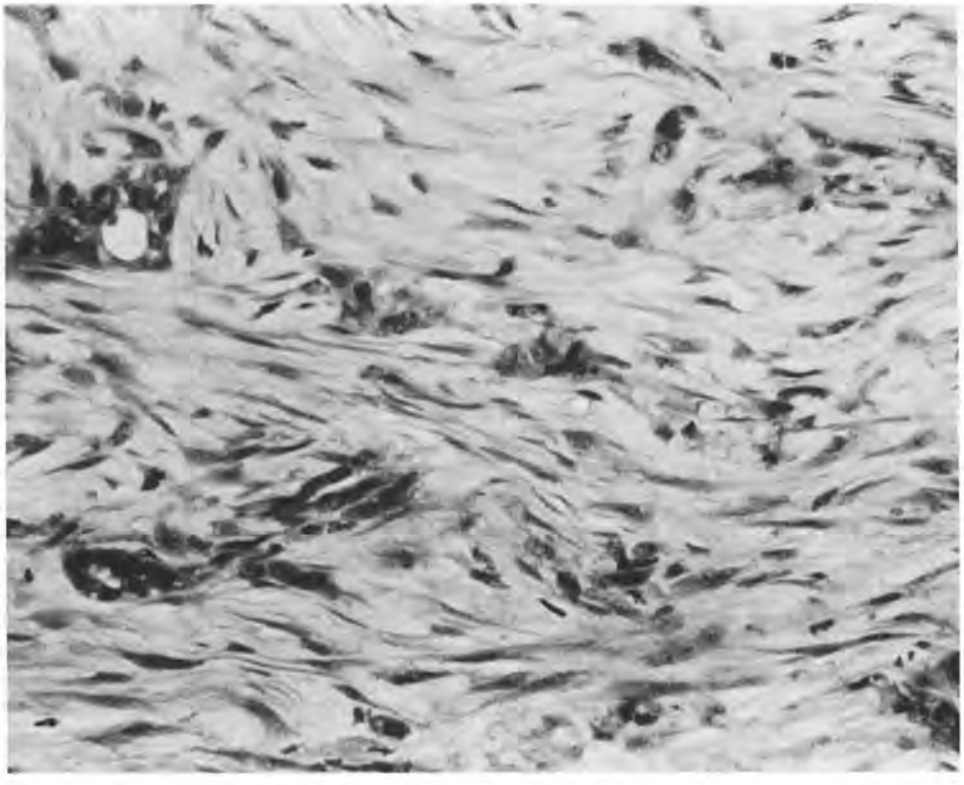


FIGURE 7-25 Malignant mesothelioma, showing malignant tubular and stromal elements.

the final diagnosis not to be established until postmortem examination. At the light microscopic level, the presence of malignant stromal cells is virtually diagnostic (save for the rare possibility of a metastatic carcinosarcoma), but more commonly the tumors are of pure epithelial type. Histochemical, immunohistochemical, and ultrastructural criteria have been suggested by various researchers, but we have found none of them to be infallible. At the histochemical level, Kannerstein and Churg emphasized the presence of intracytoplasmic colloidal iron-positive secretion, which was removed by hyaluronidase in many of their mesotheliomas.[115] In metastatic epithelial neoplasms, the mucosubstances present were not dissolved by hyaluronidase. Immunohistochemically, the most useful antigens have been carcinoembryonic antigen (CEA), Leu-M1 (CD15), TAG-72 (recognized by monoclonal antibody B72.3), and the antigen recognized by monoclonal antibody BER-EP4, all of which are demonstrable in most adenocarcinomas and in few or no mesotheliomas.[118,119]

Ultrastructurally, the emphasis has been on the presence in mesotheliomas of long and slender microvilli without a glycocalyx (Fig. 7-26), the quantitative increase in the numbers of intermediate filaments in mesotheliomas compared with adenocarcinomas, and the absence of specific findings seen in some adenocarcinomas, such as abundant mucin, numerous cilia, glycocalyx, rootlets of microvilli, and neurosecretory-type dense core granules.[118,120,121] When ultrastructural examination is available, it is probably the most reliable study that can be used.

The cytologic differential diagnosis is difficult.[2,3,122] In most instances, the pathologist is able to suggest but not make the unequivocal diagnosis of malignant mesothelioma on examination of an ascitic fluid specimen (Color Figure 7-6). Numerous papillary clusters of cells showing the usual cytologic criteria of malignancy should be present. The clusters are often large and demonstrate a three-dimensional morphology compared with the generally flat clusters of benign mesothelial cells. The individual cells are considerably larger than benign mesothelial cells, but unlike the cells of a metastatic adenocarcinoma, they show apparent transitions to cells with obvious mesothelial morphology (ie, abundant cytoplasm, a distinct, clear cell border, and a small nucleus). The cytoplasm is occasionally vacuolated, but usually much less so than in adenocarcinoma. However, a secretory type of peritoneal mesothelioma has been reported, in which many vacuoles of mucolipid are present.[123] Occasionally, prominent microvilli can be observed at the light microscopic level in cytologic material. If a cell block is prepared, some of the histochemical and immunohistochemical techniques mentioned previously may be used, and ultrastructural and flow cytometric study of cells from an effusion may be helpful.

Prognosis and Treatment

The prognosis of malignant mesothelioma is dismal. Although distant metastases may develop as a late event or not at all, the extensive local progression of the tumor almost invariably leads to death within a few years of diagnosis. Treatment is largely supportive.

Adenocarcinoma of Presumed Mesothelial Origin

Although it has been accepted for some time that many, if not all, of the malignant "epithelial" tumors of the ovary are ultimately of mesothelial origin, it is only within the past few years that evidence has accumulated to suggest that similar tumors may arise outside the ovaries.

Their pathogenesis is probably analogous to that of endosalpingiosis and some cases of endometriosis and involves a simultaneous or sequential process of metaplasia and neoplasia. Although any of the histologic patterns of "epithelial" ovarian cancer (serous, mucinous, endometrioid, clear cell, transitional cell, and mixed mesodermal) may be encountered as a primary extraovarian mesothelial-derived tumor, the vast majority are serous. Ovarian serous carcinomas usually are widely disseminated in the peritoneal cavity at the time of diagnosis, and it is possible that this phenomenon represents a multifocal origin rather than an ovarian primary with metastases.[124,125] Similarly, we believe it is likely that the "intra-abdominal carcinomatosis after prophylactic oophorectomy in ovarian-cancer-prone families" reported by Tobacman and colleagues[126] and the "serous surface papillary carcinomas of the ovary" reported by Gooneratne and associates[127] represent the same entity, as do the "papillary carcinomas of the peritoneum" of Foyle and colleagues.[102]

The clinical presentation and gross appearance of these lesions are identical to those of metastatic serous carcinoma of ovarian origin, with the following exceptions: the ovaries are absent, having been removed previously, usually for benign disease (Color Figure 7-7); the ovaries are present but uninvolved with tumor; or the ovaries are present and only minimally involved. In the latter situation, a case can be made that ovarian surface involvement, even if limited to microscopic foci, represents the source of the peritoneal dissemination.[127] The proportion of disseminated serous carcinomas diagnosed as extraovarian in origin varies from 7% to 18% in recently published series from different countries, with the difference more likely due to varying diagnostic criteria than to true geographic variation.[128–131] The criteria for the diagnosis of primary extraovarian carcinoma used by the Gynecologic Oncology Group are reproduced here:

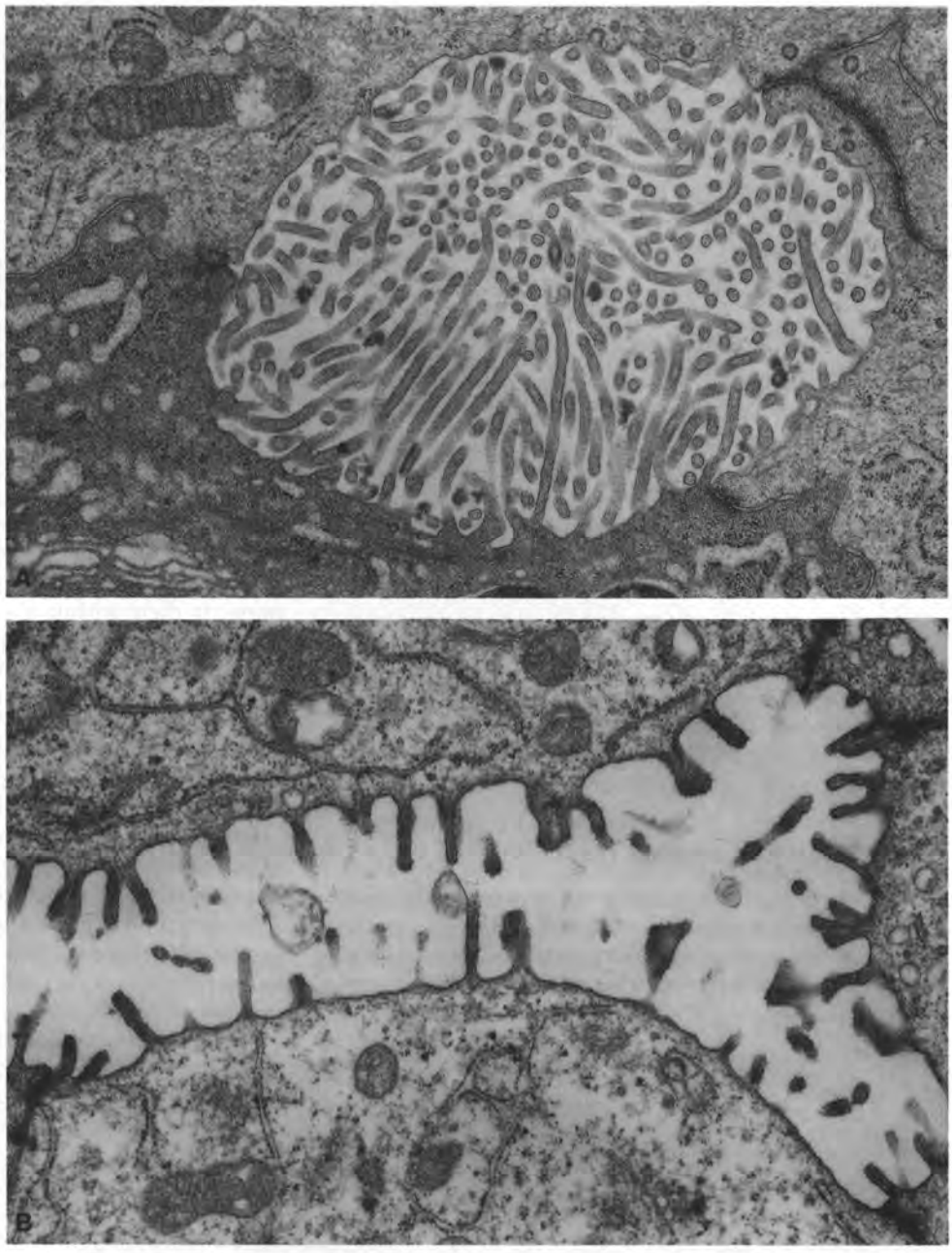


FIGURE 7-26 Electron micrographs of the lumina of malignant mesothelioma **(A)** and serous carcinoma of ovary **(B).** The height to width ratio of microvilli in **A** exceeds 10:1, compared with about 4:1 for microvilli of the serous carcinoma. Note the glycocalyx coating the microvilli in the lower figure only. (×25,000; courtesy of Jan M. Orenstein, MD, PhD, George Washington University, Washington, DC)

Both ovaries are either physiologically normal in size or enlarged by a benign process. In the judgment of the surgeon and the pathologist, the bulky tumor is in the peritoneum and the degree of tumor involvement at one or more extraovarian sites is greater than on the surface of either ovary.

Microscopically, the ovarian component is one of the following: (1) nonexistent; (2) confined to ovarian surface epithelium with no evidence of cortical invasion; (3) involves ovarian surface and underlying cortical stroma but with any given tumor size less than 5 × 5 mm; (4) tumor less than 5 × 5 mm within ovarian substance associated with or without surface disease.

The histological and cytological characteristics of the tumor are predominantly serous type—that is, similar or identical to ovarian serous papillary adenocarcinoma, any grade.

Patients who had an oophorectomy performed prior to the diagnosis of extraovarian peritoneal serous papillary carcinoma (EPSPC) must fit one of the following two catego-

ries: (1) the pathology report is required to document benign ovaries, and all slides of normal ovaries must be submitted for review if the oophorectomy was performed within five years of the diagnosis of EPSPC; (2) if the oophorectomy occurred more than five years prior to the diagnosis of EPSPC, the pathology report of the benign ovaries is required, and an attempt to obtain the slides must be made.

Microscopic Appearance

Microscopically, these tumors are identical to serous carcinomas of ovarian origin (Fig. 7-27). They are usually poorly differentiated, lack the malignant stromal elements that may be seen in malignant mesothelioma, and are much more likely to contain numerous psammoma bodies than are classic malignant mesotheliomas.

Ultrastructural Findings

Ultrastructural study of a few cases has shown the presence of the type of secretory granules commonly encountered in ovarian serous carcinomas, as well as shorter and blunter microvilli than those of classic mesotheliomas.

Immunohistochemical Findings

Immunohistochemical results are similar to those for ovarian serous carcinoma and aid in the distinction from malignant mesothelioma (see Malignant Mesothelioma earlier in this chapter). A panel of immunohistochemical markers including CEA and Leu-M1 can be used to differentiate small tumor nodules (positive for both) from benign epithelial and mesothelial proliferations.[132]

Prognosis

The prognosis in these cases was originally thought to be worse than that for correspondingly disseminated ovarian serous carcinoma, but most recent studies have indicated that the response rates to platinum-based chemotherapeutic regimens and the ultimate survival are comparable.[128–131]

Foyle and colleagues, in their report of 25 papillary peritoneal tumors in women, grouped 4 cases under the classification of "atypical diffuse mesothelioma."[102] These tumors were said to occupy an intermediate position histologically between typical diffuse malignant mesothelioma and the papillary carcinomas that we have just described. One of the patients died within a year, but the other 3 patients demonstrated a more prolonged course. Although such an intermediate group probably exists, we advise caution in making this diagnosis because we recently encountered an identical tumor that eventually proved to be a metastatic pancreatic carcinoma.

Finally, primary peritoneal malignant tumors of ovarian type occasionally are of histologic types other than serous, such as mucinous and clear cell adenocarcinomas (Fig. 7-28).[133,134] Unlike extraovarian serous carcinomas, these tumors usually form a solitary mass and are found most frequently in the retroperitoneum or mesentery. Their natural

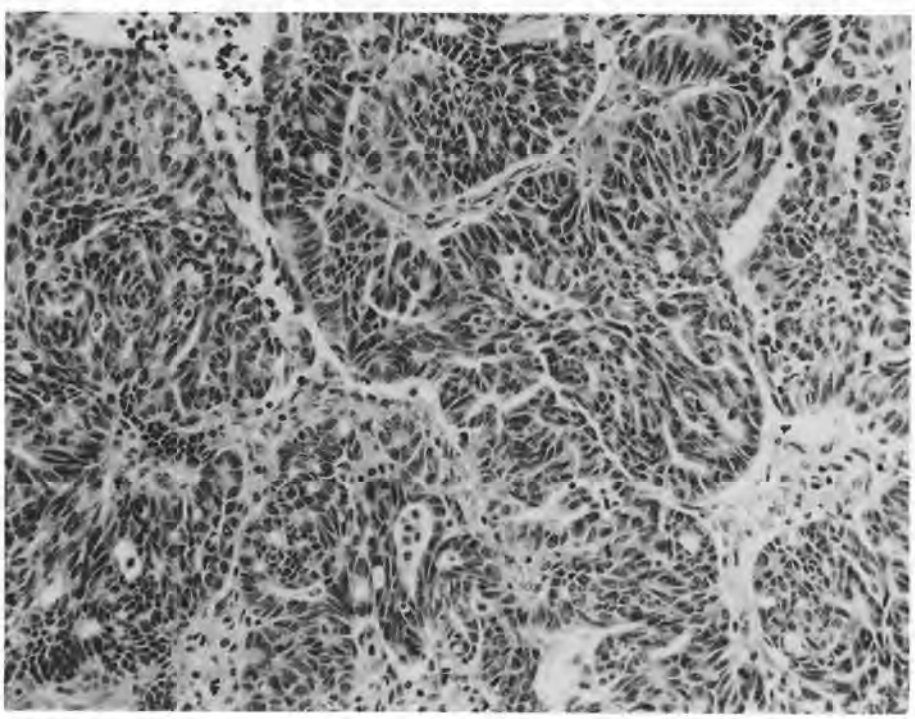


FIGURE 7-27 Serous carcinoma of the peritoneum. This patient had undergone bilateral oophorectomy 14 years earlier for a benign condition (see Color Figure 7-7).

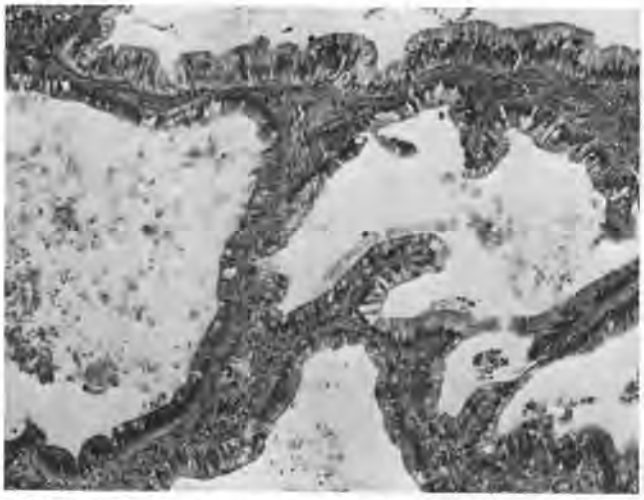


FIGURE 7-28 Retroperitoneal borderline mucinous tumor. The ovaries were grossly normal. (Farhi DC, Silverberg SG: Pesudometastases in female genital cancer. Pathol Annu 17 [Part I]:47–76, 1982)

history remains poorly defined because of the small number of cases reported. Benign epithelial tumors of ovarian type are reported in peritoneal and retroperitoneal locations.[135]

Metastatic Tumors

Although we have devoted a large portion of this chapter to the discussion of primary malignant peritoneal tumors, the pathologist encounters metastases to the peritoneum far more frequently. The differential diagnosis of metastatic carcinoma includes many of the reactive, metaplastic, and neoplastic conditions described in this chapter, and it is always important to consider the possibility of these conditions before rendering a diagnosis of metastatic carcinomatosis, with its attendant dramatic therapeutic and prognostic implications.

Any malignant tumor may metastasize to the peritoneum. In women, the cancers most likely to be discovered on biopsy are those of the ovary, endometrium, and large intestine. The metastatic breast cancers formerly encountered during oophorectomy or adrenalectomy have declined in number with the decreased popularity of these operations, and metastatic breast cancer is encountered in the peritoneum by the surgical pathologist today primarily in cases in which it results in intestinal obstruction. Cervical carcinomas seldom metastasize to the peritoneum, although peritoneal wash cytologies may be positive. Positive findings are more common with cervical adenocarcinoma than with squamous cell carcinoma.[136]

Clinically, metastatic peritoneal cancer is often manifested by increased abdominal girth secondary to ascites. About as often, the metastatic disease is asymptomatic and is detected by biopsy at the time of exploratory laparotomy or by cytologic examination of peritoneal fluid.

Macroscopic Appearance

Macroscopically, metastatic cancer may vary from grossly undetectable to multiple pearly white nodules of a few millimeters each to massive peritoneal plaques with extensive adhesions leading to a "frozen pelvis." This latter appearance is encountered more frequently with ovarian tumors than with other primaries.

Microscopic Appearance

The microscopic appearance of the metastatic tumor should be similar to that of the primary tumor from which it arose. This is important in the differential diagnosis, because foci of endosalpingiosis are often identified by their different appearance from the primary endometrial or cervical tumor with which they may be associated. In the differential diagnosis of metastatic serous ovarian carcinoma, the presence of a papillary architecture and psammoma bodies in endosalpingiosis may be confusing. Any peritoneal nodules associated with borderline ovarian tumors (see Chap. 6) should be carefully classified as benign, borderline, or invasive malignant, although, as discussed earlier, it is unclear whether invasive "implants" augur a worse prognosis than borderline ones.[30]

Cytologic Diagnosis

Cytologic diagnosis of metastatic carcinoma in peritoneal fluids is one of the most difficult problems in the field of diagnostic cytology. There are many benign conditions that can result in the observation of atypical mesothelial cells in a peritoneal fluid, and some of these conditions (such as endosalpingiosis) seem to occur with greater frequency in women who have female genital cancer. It behooves the pathologist not to overdiagnose such a specimen as malignant, even if he or she is tempted to do so by knowledge of the presence of a primary carcinoma. A cytologic diagnosis of metastatic carcinoma should depend on the presence of several groups of cells with clearly malignant features, such as cellular enlargement, increased nuclear—cytoplasmic ratio, an abnormal, coarsely clumped chromatin pattern, and abnormal mitotic figures (Fig. 7-29 and Color Figure 7-8). Other useful findings include the production of mucin and the presence of many cell aggregates with a three-dimensional configuration and of two or more sex chromatin bodies in a single cell.[2–4] Although these characteristics identify most metastatic cancers in women, other findings may point to specific tumor types: melanin pigment in malignant melanoma, bizarre spindle cells in metastatic sarcomas, and so-called Indian-filing in some cases of metastatic mammary carcinoma.

Among primary carcinomas of the female genital tract, peritoneal cytologic findings are positive in at least one half of the cases of ovarian carcinoma,[137,138] less frequently in endometrial carcinoma,[139,140] and

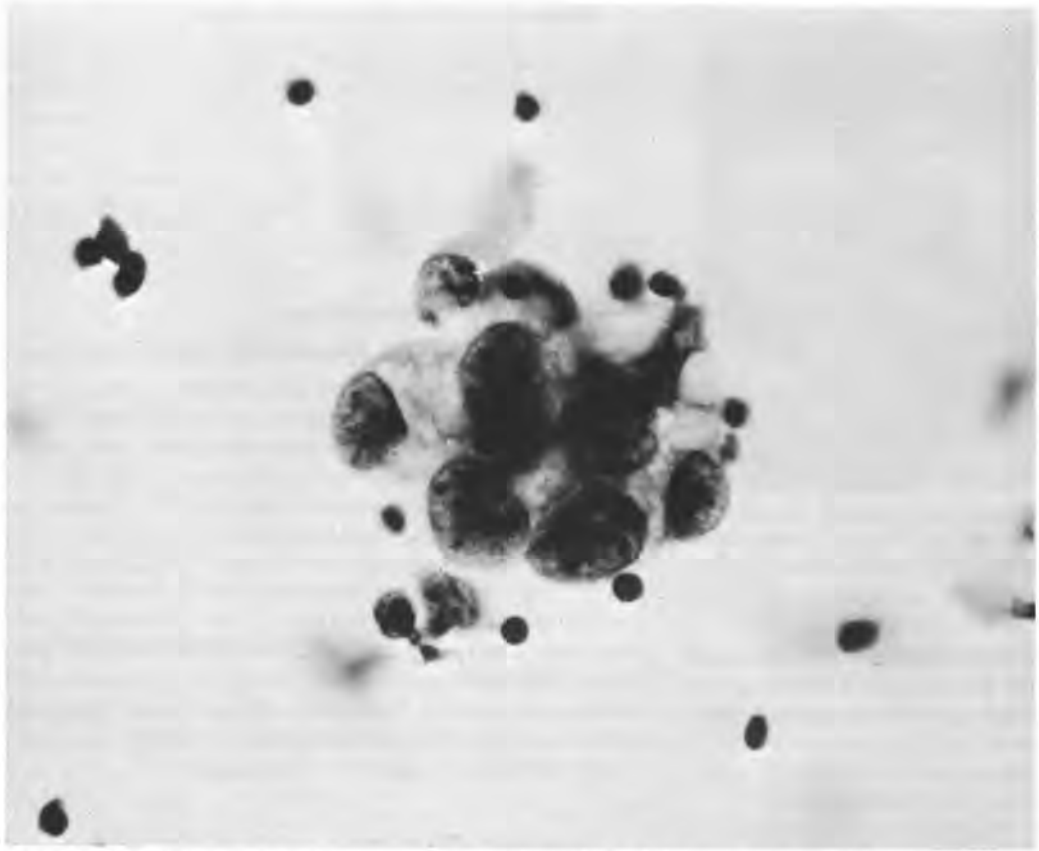


FIGURE 7-29 Cluster of malignant cells in peritoneal fluid from a woman with primary adenocarcinoma of the endometrium.

least frequently (less than 10% of cases) in carcinoma of the cervix.[136] The prognostic significance of a positive peritoneal cytology in these tumors has been debated, but in general it seems to correlate best with high-stage and high-grade tumors and may add fairly little to an already poor prognosis. In ovarian cancer, however, the FIGO (International Federation of Gynecology and Obstetrics) staging system recommends that a stage I or II cancer be assigned to subgroup Ic or IIc on the basis of a positive peritoneal cytology or the presence of ascitic fluid.

Special Variants

Two rare but interesting conditions that should be considered under the heading of metastatic tumors to the peritoneum are *pseudomyxoma peritonei* and *gliomatosis peritonei.* The former term refers to a clinical syndrome of mucinous ascites of any origin, but most often the syndrome is associated with a mucinous tumor of the ovary or appendix (and often both). The pathogenesis of the peritoneal lesion is controversial. Some investigators consider these associated ovarian and appendiceal tumors to be borderline or low-grade malignant,[141] whereas others are equally convinced of their benignity.[142] The peritoneal lesions may represent metastases but may also represent a metaplastic phenomenon such as has been suggested in cases of endosalpingiosis and endometriosis. Young and colleagues have recently postulated that when pseudomyxoma peritonei occurs in association with mucinous tumors of both the ovary and appendix, the appendiceal tumor represents the origin of the peritoneal lesion.[143] In any event, pseudomyxoma peritonei presents grossly as loculated, yellow-brown, glairy mucus on peritoneal surfaces, often leading to dense adhesions and an "omental cake." Microscopically, mucinous cells that generally show minimal atypia are found (sometimes with difficulty) floating in large pools of extracellular mucin. The condition is generally considered to be incurable, but patients may survive with persistent disease for many years. Repeated paracenteses with intraperitoneal installation of chemotherapeutic agents or hyaluronidase may be helpful.

The term *gliomatosis peritonei* refers to the presence of benign glial implants on peritoneal surfaces in association with an immature teratoma of the ovary (see Chap. 6). This tumor seems to have a peculiar tendency to mature into benign tissues. In one large series, extraovarian tumor foci usually were better differentiated than the associated primary ovarian tumors.[144] Mature components other than glia may be seen, and the phenomenon has been seen in lymph nodes and other metastatic sites (Fig. 7-30), but the usual presentation is that of multiple, small peritoneal nodules composed of histologically benign neuroglia (Fig. 7-31). If the glial implants are

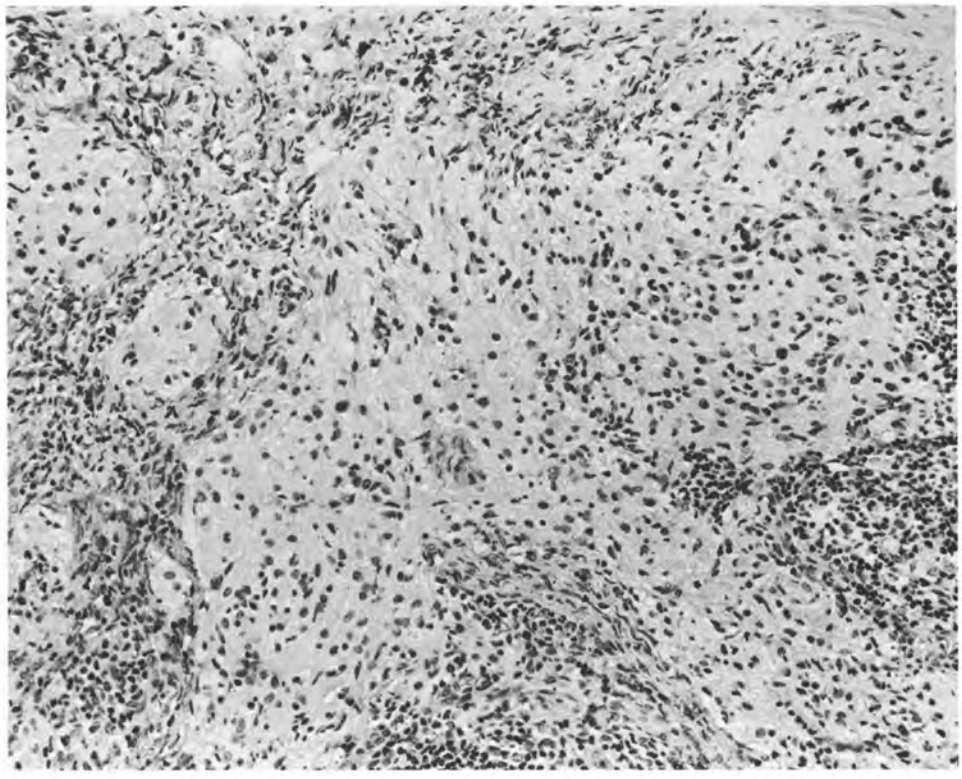


FIGURE 7-30 Mature glial tissue in the sinusoids of a pelvic lymph node. The patient had immature teratoma of the ovary.

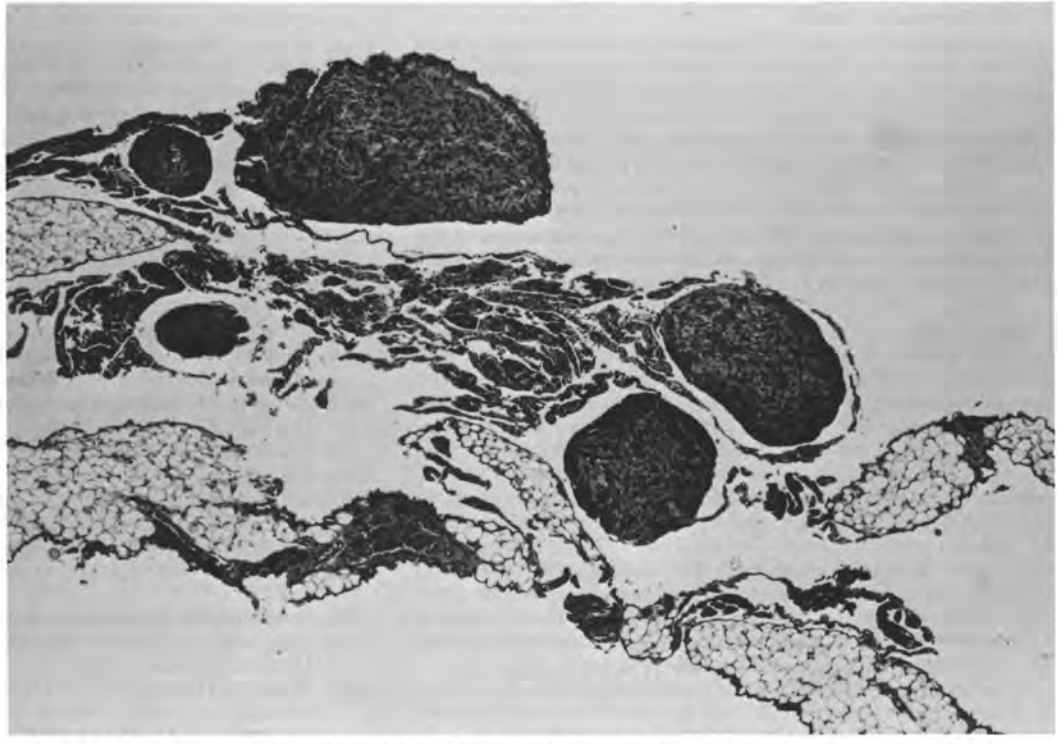


FIGURE 7-31 Multiple peritoneal nodules of benign glial tissue (gliomatosis peritonei) associated with ovarian immature teratoma.

all mature (grade 0), they do not unfavorably influence the prognosis, which then depends largely on the grade of the primary ovarian tumor.[144–146] Multiagent chemotherapy is instituted if the primary tumor is of high grade or if immature implants are found, but in a grade I immature teratoma of the ovary with only grade 0 implants, the prognosis is excellent without any adjuvant therapy. Second-look laparotomies in these latter patients generally have shown either persistence or regression (but not growth) of the implants.[147]

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8 The Placenta

Janice M. Lage

The placenta is the most vital fetal organ: a fetus cannot survive without its placenta. The placenta serves the most basic metabolic needs of the fetus, including respiration, nourishment, and excretion. A diseased placenta will continue to function to some extent until it is destroyed completely. The fetal sequelae resulting from placental compromise depend on the severity of the insult, the adequacy of residual placental function, and the time remaining in utero. In many cases, the delivered placenta contains a morphologic record of the antecedent intrauterine events.

Because the placenta is the most accessible of all fetal organs and contains a record of intrauterine events, it should not be routinely discarded at delivery. All placentas should be examined by the attendant at delivery, usually the obstetrician-gynecologist. In most cases, the newborn is healthy, and the placenta, being normal on examination, may be discarded after neonatal well-being has been ensured. Unfortunately, untoward outcomes do occur, and the placentas from these deliveries should be examined by a pathologist. Table 8-1 lists the indications for placental examination by a pathologist.

Because medicolegal concerns focus attention on placental examination as a morphologic record of antenatal conditions and intrapartum events, it is essential that the practicing general pathologist perform an adequate gross examination and take appropriate samples for microscopic examination. In addition, photographs of any gross placental lesions, particularly those associated with fetal or neonatal death, may be pivotal in the outcome of a legal action.

This chapter provides a basic description of placental pathology, focusing on the salient gross and microscopic placental lesions encountered in daily practice. The intricacies of placental embryology are well-covered elsewhere and are not included in this book. Many excellent texts are available to aid the examiner in evaluating particularly difficult or unusual specimens.[12,13,17,48]

EARLY DEVELOPMENT

By accessing the maternal circulatory system, the placenta obtains essential biological support for the fetus. This is first achieved by implantation of the blastocyst into the uterine endometrium, which begins around postovulatory day 6 or 7 and is completed near day 10 (menstrual cycle day 24).[1-2] The blastocyst burrows into the decidualized endometrium, and its trophoblastic shell initially proliferates radially, forming the scaffolding for the definitive villi that begin to develop during the second week after implantation. By the third week, blood lakes created between invading villi coalesce, forming the intervillous space (Fig. 8-1). Invagination of the extraembryonic mesenchyme into the villi initiates the development of villous capillaries. Developing fetal blood cells appear in primitive villous capillaries about 28 days after conception (Fig. 8-2).[3]

The definitive placenta forms from the basally oriented villi of the chorion frondosum (Fig. 8-3). Peripheral divisions of the main stem villi form secondary and tertiary villi. This villous branching ex-

pands the interface between the fetal trophoblast and the maternal blood, enhancing transfer of oxygen and nutrients. Those villi directed toward the endometrial cavity, the chorion laeve, atrophy due to inadequate nutrition.

The implantation site contains cytotrophoblast, syncytiotrophoblast, and intermediate trophoblast, with the latter predominating (Fig. 8-4). Mononuclear trophoblast invades the maternal spiral arteries. This trophoblastic invasion of the maternal spiral arteries peaks at the 12th week and continues, progressing to the level of the junction between the spiral arteries and the myometrial radial arteries.[2] Intravascular trophoblast invades outwardly through the vessel walls, splaying apart and destroying muscular and elastic fibers. Concomitantly, endometrial stromal trophoblast invades the spiral arterial walls from the endometrial stroma. The destructive vascular invasion by trophoblast eventuates in markedly dilated, fibrotic vessel walls, which increase uteroplacental blood flow while precluding vasoconstriction. Between the 14th and 20th weeks, a second wave of trophoblast invades deeper into myometrial segments of the spiral arteries, further enhancing blood flow.

TABLE 8-1
Indications for Placental Examination

Fetal Indications
- Untoward obstetric outcome
- Stillbirth
- Small or large neonate for gestational age
- Known or suspected intrauterine infection, maternal toxoplasmosis
- Malformations or deformations, oligohydramnios, chromosomal anomalies
- Multiple gestation

Maternal Indications
- Abnormal pregnancy: poor fetal growth, hyperemesis, α-fetoprotein abnormalities
- Preterm labor
- Premature rupture of membranes
- Abruption or unexplained vaginal bleeding
- Maternal fever, septicemia, chorioamnionitis
- Maternal disorders affecting pregnancy: preeclampsia/eclampsia, hypertension, diabetes, blood dyscrasias, malignancy

Placental Indications
- Cloudy, foul-smelling membranes
- Excessively large or small placenta for gestational age
- Abnormalities of shape
- Placental hematoma(s) and thrombi
- Abnormalities of umbilical cord: cysts, knots, single umbilical artery, webs, bands
- Abnormalities of chorionic membranes: white spots on fetal surface, yellow streaking, extrachorial gestation, cysts

TYPES OF TROPHOBLAST

By microscopy, three types of trophoblast are identified: cytotrophoblast, syncytiotrophoblast (syncytium), and intermediate trophoblast (Fig. 8-5). The cytotrophoblast forms single, polygonal to oval cells with vesicular nuclei, prominent nucleoli, moderate amount of clear to granular cytoplasm, and distinct cell borders. Cytotrophoblastic mitotic activity is brisk during the first trimester and virtually inapparent by term. The syncytiotrophoblast represents an amalgamation of cytotrophoblastic cells forming a large, multinucleated "cell" with abundant, dense, amphophilic to violaceous cytoplasm with multiple vacuoles. The nuclei shrink, resulting in more condensed, pyknotic chromatin. The syncytiotrophoblast is incapable of cell division but remains metabolically active. The third type of trophoblast, previously termed *X cells,* is now known as *intermediate trophoblast.*[4] This trophoblast is characterized by discrete cells, which may be uninucleate, binucleate, or multinucleate. Their cell shape ranges from round and polygonal with abundant eosinophilic to amphophilic cytoplasm to spindle-shaped with attenuated cytoplasm. Nuclei of the intermediate trophoblast are hyperchromatic and may be lobulated. Nucleoli are inconspicuous.

Trophoblast may be divided into two groups: villous or extravillous. Villous trophoblast encompasses that trophoblast overlying the villi: cytotrophoblast, syncytiotrophoblast, and scant intermediate trophoblast (see Fig. 8-5). Most extravillous trophoblast is intermediate trophoblast with some syncytiotrophoblast and cytotrophoblast (see Fig. 8-4). Extravillous trophoblast may be found in the uterine implantation site, both intravascularly and within endometrial stroma and myometrium, placental septa, and placental membranes.

ANATOMY

Viewed from the maternal surface, the placental disc is formed of 15 to 20 so-called maternal cotyledons, nodules of villous tissue created and demarcated by the *placental septa* (see Fig. 8-4). The placental septa are infoldings of decidua and implantation-site trophoblast that are pulled up into the placental parenchyma by their attachment to more slowly growing anchoring villi. The maternal cotyledons have no functional significance (see Fig. 8-3).

In contrast, a *fetal cotyledon* describes all villous tissues derived from a main stem villus (see Fig. 8-3) and consists of an anatomic unit with a single stem artery from one of the umbilical arteries. A placental *lobule* is the villous tissues derived from a secondary stem villus. The functional unit of the placenta is the *tertiary villus,* also called the *terminal villus.* Fetal metabolic needs are satisfied by active and passive transport of nutrients, gases, and hormones across the vasculosyncytial membranes of terminal villi.

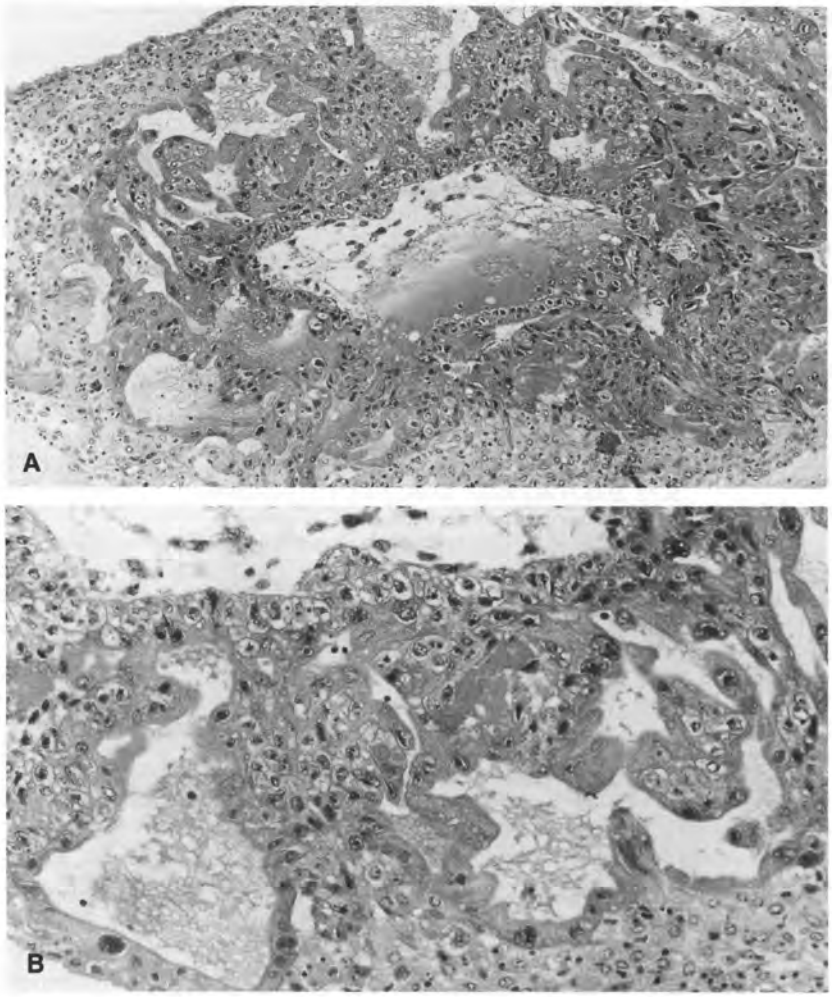

FIGURE 8-1 **(A)** Day 10 to 11. The blastocyst is embedded in the superficial endometrium. The embryo is not present in the exocoelomic cavity in this section. The trophoblastic shell is composed of syncytiotrophoblast and cytotrophoblast. **(B)** Blood lacunae are formed by invading cytotrophoblast and syncytiotrophoblast. (Lage JM. Diagnostic dilemmas in gynecologic and obstetric pathology. Semin Diagn Pathol 7(2):146–155, 1990)

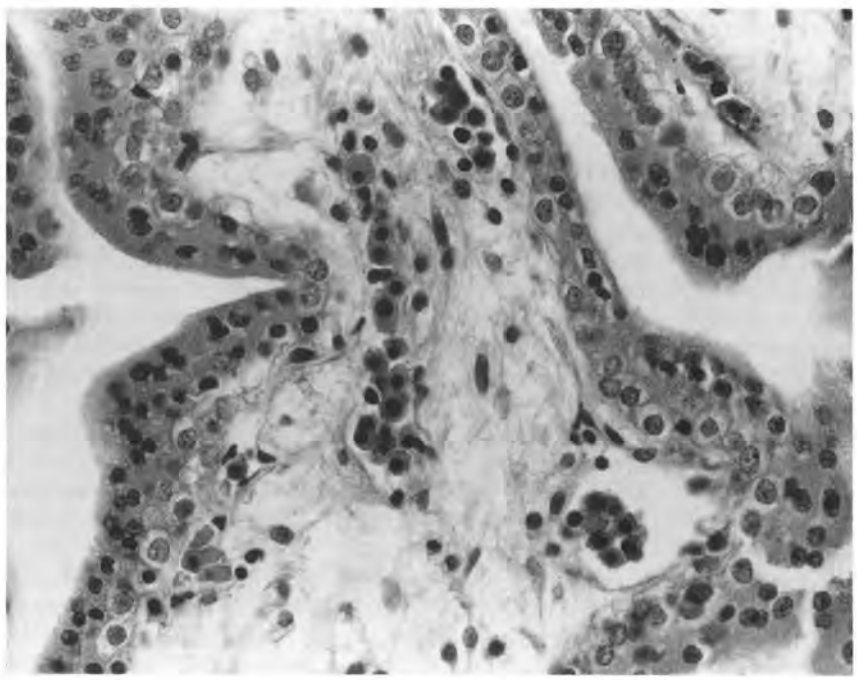

FIGURE 8-2 An immature villus with villous capillaries containing nucleated red blood cells. The villus surface is composed of two layers: inner cytotrophoblast and outer syncytiotrophoblast. The stroma contains fibroblastic stromal cells and macrophages (Hofbauer cells).

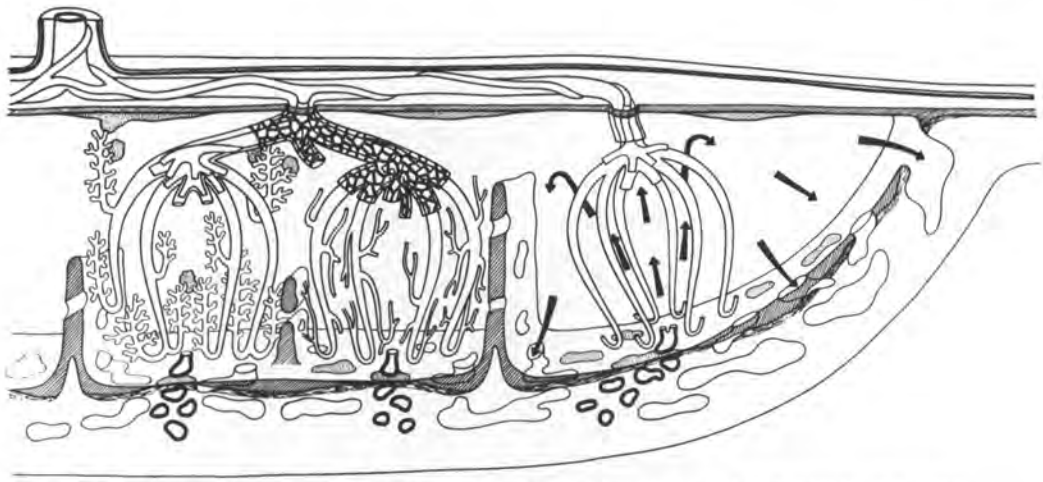

FIGURE 8-3 Placental structure. *Top*: The umbilical cord inserts into the chorionic plate (amnion, chorionic vessels [*light lines*] from umbilical cord arteries and vein, and chorion). Umbilical arteries branch onto the surface of the chorionic plate and penetrate the placental villous parenchyma. They divide with the villous branches to the tertiary villus, where the vessels closely approximate the maternal intervillous space, then pass back to the chorionic plate, ultimately fusing to form the umbilical vein. The basal plate is the interface between the placental villous tissue and maternal endometrium. Maternal uteroplacental arteries or spiral arteries (*heavy lines*) perfuse the intervillous spaces, and uteroplacental veins (superficial endometrial sinusoids, *light lines*) drain blood from the intervillous spaces. Fetal cotyledons may be single (*right*) or multiple (*left*). The maternal cotyledon is outlined by slanted lines. Arrows indicate direction of maternal blood flow.

The size of tertiary villi decreases throughout gestation. In the first trimester, the tertiary villi measure 170 μm in diameter; by second trimester, 70 μm; and by term, 40 μm. The presence and number of syncytiotrophoblastic knots reflects villous maturation: the closer to term, the more syncytial knots. A placenta may be described as immature or mature based on villous size and amount of syncytial knots. Mature placentas, usually after 34 weeks' gestation, contain small tertiary villi, and there is close approximation of capillary vascular endothelium to attenuated syncytium facing the maternal intervillous space. There is scant villous mesoderm, little if any cytotrophoblast, and syncytial knots on roughly 30% to 40% of villi. Placentas lacking these features are termed *immature*. Placental maturity does not connote gestational maturity. A term placenta associated with fetal α-thalassemia will remain histologically immature even when delivery occurs at 40 weeks' gestation.

The umbilical cord contains two arteries carrying deoxygenated blood from the fetus to the placenta, and one vein carrying oxygenated blood from the placenta back to the fetus. The extraplacental fetal membranes are composed of amnion, chorion, and decidua. The umbilical cord and extraplacental membranes may be described as placental adnexa.

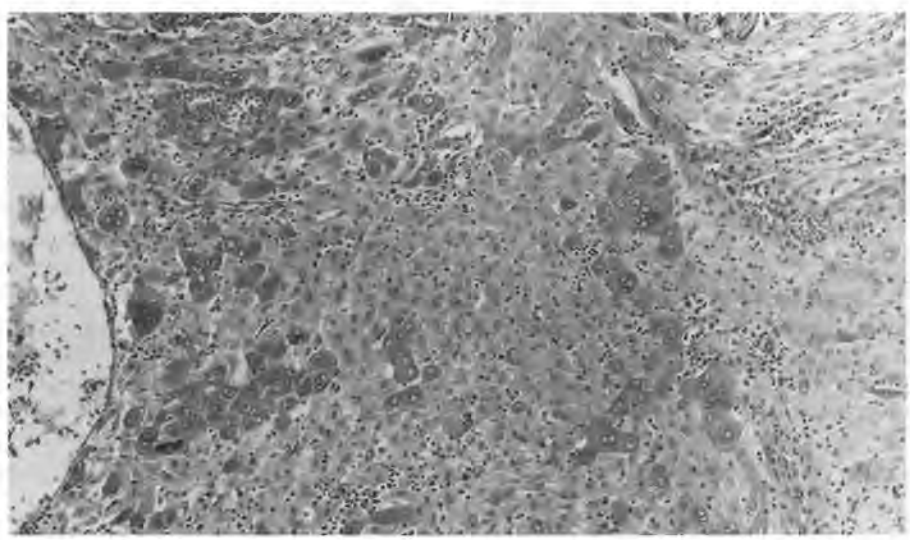

FIGURE 8-4 Decidualized endometrium with implantation-site trophoblast composed of mononucleated and multinucleated trophoblast. This histologic finding confirms intrauterine pregnancy. (Lage JM. Diagnostic dilemmas in gynecologic and obstetric pathology. Semin Diagn Pathol 7(2):146–155, 1990)

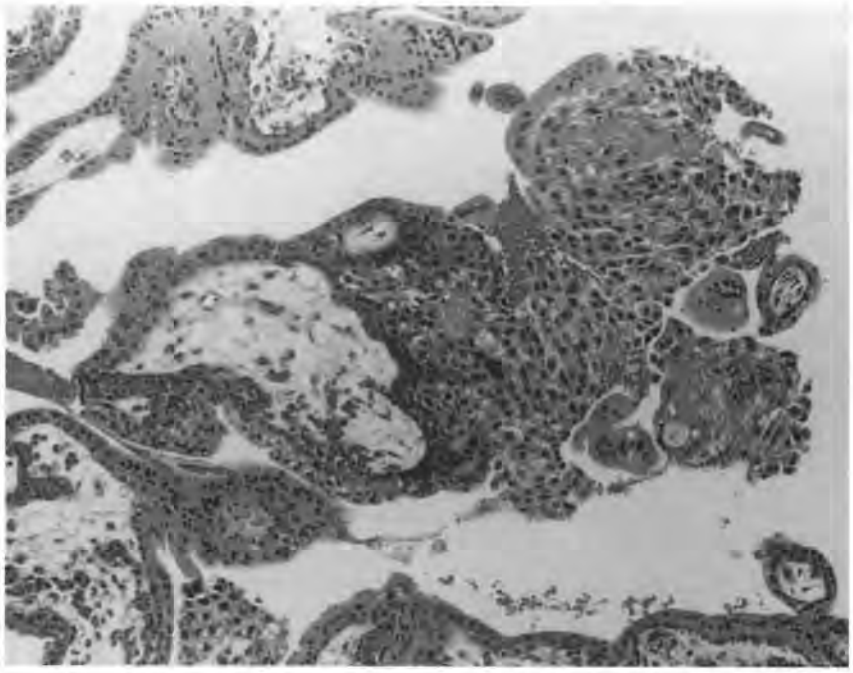

FIGURE 8-5 First-trimester villus with basal proliferation of cytotrophoblast (nearest villus), intermediate trophoblast (central core of trophoblast), and multinucleated syncytiotrophoblast (facing the maternal intervillous space).

EVALUATION OF EARLY CONCEPTUSES: SPONTANEOUS ABORTUSES, ELECTIVE TERMINATIONS, AND ECTOPIC PREGNANCIES

The pathologist's role in the evaluation of uterine curettings from an early conceptus is to document the presence and normality of fetal tissues: embryo, villi, or trophoblast (see Fig. 8-4). The gross specimen should be examined by someone with knowledge of normal fetal and placental morphology. Fetal tissues recognized grossly or found microscopically confirm intrauterine pregnancy. Identifying placental villous tissue verifies intrauterine pregnancy; however, any gross diagnosis requires microscopic confirmation because decidua may simulate villi. Implantation-site trophoblast or syncytiotrophoblast alone also confirms intrauterine pregnancy.

The extent of microscopic examination is determined by the nature of the specimen. In most institutions, identification of grossly normal fetal and villous tissues appears adequate in elective terminations of pregnancy with no abnormal maternal or fetal history. Microscopic examination is reserved for specimens with abnormal clinical history, gross fetoplacental abnormalities, or scant tissue. Although uterine curettings after a spontaneous abortion or complete abortion may contain only scant villous tissue, this is not the case for curettings from an elective termination (therapeutic abortion). In this case, identification of only a small amount of placental tissue is abnormal, and the following possibilities should be considered: clinically unknown or unsuspected spontaneous or missed abortion, ectopic pregnancy, or incomplete uterine evacuation. When confirmation of intrauterine pregnancy is lacking (ie, no fetal or villous tissue and no trophoblast), the pathologist is obligated to notify the clinician that an ectopic pregnancy cannot be excluded regardless of the clinical circumstances. An immediate verbal report regarding the possibility of ectopic pregnancy must be given. The clinician also should be notified when the pathologist suspects that the uterine curettings contain a paucity of villous tissue for the gestational age in an elective termination.

Microscopic examination of all spontaneous abortuses is required to document the presence of villous tissues and to exclude hydatidiform mole. Cytogenetic analysis of fetal or placental tissues should always be performed after the third spontaneous abortion or when gross fetal anomalies are present. Excellent recent texts describe normal fetal histology and development.[5,6]

The villi of a missed or spontaneous abortus may be small and sclerotic or large and edematous. In the *hydropic abortus,* the villi are diffusely enlarged and balloon-shaped, but the villous trophoblast is attenuated (see Fig. 8-6). Villous cavitation, both real and as a result of tangential sectioning of the chorion plate, may be apparent. Diagnosis of hydatidiform mole is excluded as there is no trophoblast hyperplasia. More than 50% of missed abortions have chromosomal anomalies.[7] Excluding triploidy and partial hydatidiform moles, chromosomal anomalies such as autosomal trisomies, 45,X, tetraploidy, and mosaicisms are not associated with specific villous morphologic alterations.[7]

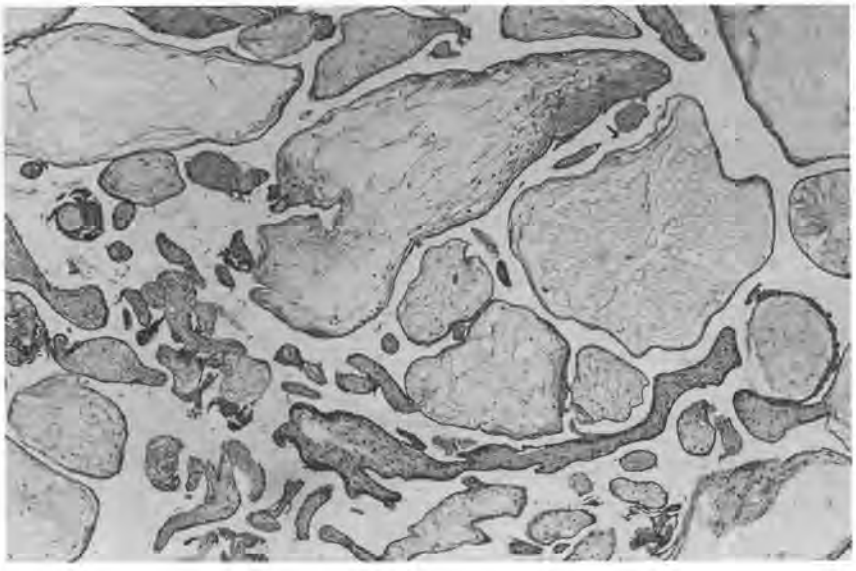

FIGURE 8-6 Hydropic abortus with a spectrum of villus sizes, attenuated trophoblast, and focal cavitation. (Lage JM. Diagnostic dilemmas in gynecologic and obstetric pathology. Semin Diagn Pathol 7(2):146–155, 1990)

GROSS EXAMINATION

There are many protocols for gross placental examination. An example is provided in Appendix 8-1. The placenta can be kept refrigerated for several days without significant destruction of morphology. The two most important physical requirements for gross examination are appropriate gear designed to protect the prosector from blood splashes (eg, goggles, mask, hat, gloves, gown, and shoe covers) and a large sink with running water and an adjacent cleared surface.

Placental dimensions are measured and the disc shape recorded. Fetal surface, membranes, and cord are examined. The umbilical cord is measured and the number of vessels recorded. One or two sections of umbilical cord are taken, preferably not from the placental insertion site. A membrane roll (or jelly-roll) is prepared and fixed. The adnexa are then trimmed and the placental disc weighed. The placenta is turned over and the maternal surface examined. Any blood clots are measured and noted. The completeness of the maternal surface is assessed. Slicing the entire disc from decidua to chorionic plate allows inspection and palpation of parenchyma. The color of the villous parenchyma is recorded. All lesions, particularly infarcts, thrombi, hematomas, or undefined nodularity, are measured and described. If no lesions are identified, three routine cassettes containing the following should be submitted:

1. Umbilical cord and membrane roll
2. Random section of peripheral parenchyma (avoid atrophic areas)
3. Random section of central parenchyma.

Any gross lesion should be sampled for microscopic examination. Transverse parenchymal sections should include the full thickness from chorionic plate to the basal plate, with chorionic plate vessels cut in cross section if possible. Representative tissue blocks (or the entire placenta) should be fixed overnight and trimmed the next day. Placental parenchyma is excessively bloody and requires prolonged fixation. Fresh tissues submitted for routine processing and sectioning the following day usually result in inadequate fixation and, although interpretable, are suboptimal.

Placental Weight

The weight of a normal placenta increases with gestational age. Published charts compare normal placental weights by gestational age for whites and blacks.[9] These weights are based on trimmed, unfixed placentas. Roughly, by 20 weeks' gestational age, the placental weight should not exceed 150 g, or, at 30 weeks' gestational age, 375 g.[8] A term placenta weighs 400 to 600 g. A heavy placenta, or *placentomegaly,* is associated with maternal and fetal disorders, some of which are listed in Table 8-2. Most common is fetal macrosomia, which results from maternal diabetes or, less frequently, from Beckwith-Wiedemann syndrome.[10] A metabolic storage disorder may be diagnosed by unusual vacuolation of villous and extravillous trophoblast and villous stromal cells (see Fig. 8-7).[11] A small placenta is often associated with a small baby, suggesting intrauterine growth retardation. Others have dismissed the value of placental weights, suggesting that differences from the norm may be accounted for by variation in the amount of fetal blood retained in the placenta, a function of the time of cord clamping.[12]

TABLE 8-2
Conditions Associated With Placentomegaly

Diabetes mellitus, maternal
Blood dyscrasia, fetal-maternal
Neoplasm, fetal or maternal
Storage disorder, fetal
Chronic fetal infection
Fetal macrosomia
Multiple gestations
Anemia, maternal or fetal
Hydrops fetalis, not otherwise specified

Placental Shape

Placental shapes vary greatly. Some shapes are variants of normal with no clinical significance, whereas others are associated with potential fetal morbidity and mortality. Figure 8-8 illustrates the spectrum of singleton placental forms. Placentas usually are discoid and can be as large as 15 to 20 cm at term.

Succenturiate or Accessory Placenta (Placenta Succenturiata)

Extra lobules of placental parenchyma separated from the main disc are termed *accessory* or *succenturiate lobes* and constitute the most common variation of placental shape in singletons (Fig. 8-9). Succenturiate placentation occurs in roughly 3% of placentas.[13] It refers to a single (and rarely multiple), detached, smaller placental lobule, whose connection to the main disc is by way of chorionic vessels in the fetal membranes with minimal or no underlying parenchyma (see Fig. 8-9). The umbilical cord tends to insert centrally into the main mass. In most, the membranous chorionic vessels are completely unprotected by underlying villous parenchyma, placing them at risk for rupture, particularly when crossing the cervical os. Antepartum traumatic (iatrogenic) rupture of such vessels has resulted in rapid fetal exsanguination and death. In addition to fetal risks in succenturiate placentation, severance and retention of the accessory lobe may result in postpartum maternal hemorrhage.

Bilobate or Bipartite Placenta (Placenta Bilobata)

The bilobed or bipartite placenta consists of two separate placental masses of equal size joined by an isthmus composed of thinned parenchyma or membranes (Fig. 8-10). The umbilical cord tends to insert near the center of the isthmus or on the membranes near the isthmus. This type of placentation generally is not associated with poor fetal outcome. Depending on the architecture of the umbilical and chorionic vessels, there is some potential for antepartum disruption similar to that caused by the succenturiate placenta (Fig. 8-11). Bilobate placentation has been associated with older women of high gravidity, with infertility, and with increased manual placental extraction.[14] *Trilobate* and *multilobate* placentas are similar to bilobate placentas except that three or more lobes of similar sizes are present. The multiplex placentations (*placenta duplex, triplex,* and *multiplex*) are similar to the multilobed placentas except that in multiplex placentas each lobule is perfused directly from the umbilical cord rather than through chorionic vessels derived from the single dominant lobe as in multipartite placentations.

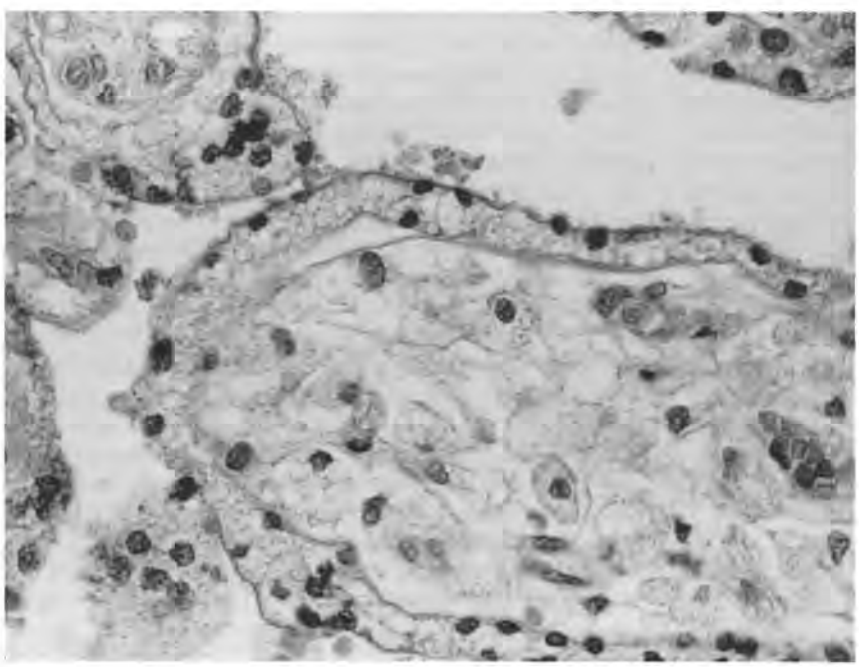

FIGURE 8-7 Fetal storage disorder, a GM_1 gangliosidase deficiency, is reflected in vacuolation of villous syncytiotrophoblast and stromal cells. Both cytotrophoblast and intermediate trophoblast of basal plate (not shown here) were vacuolated.

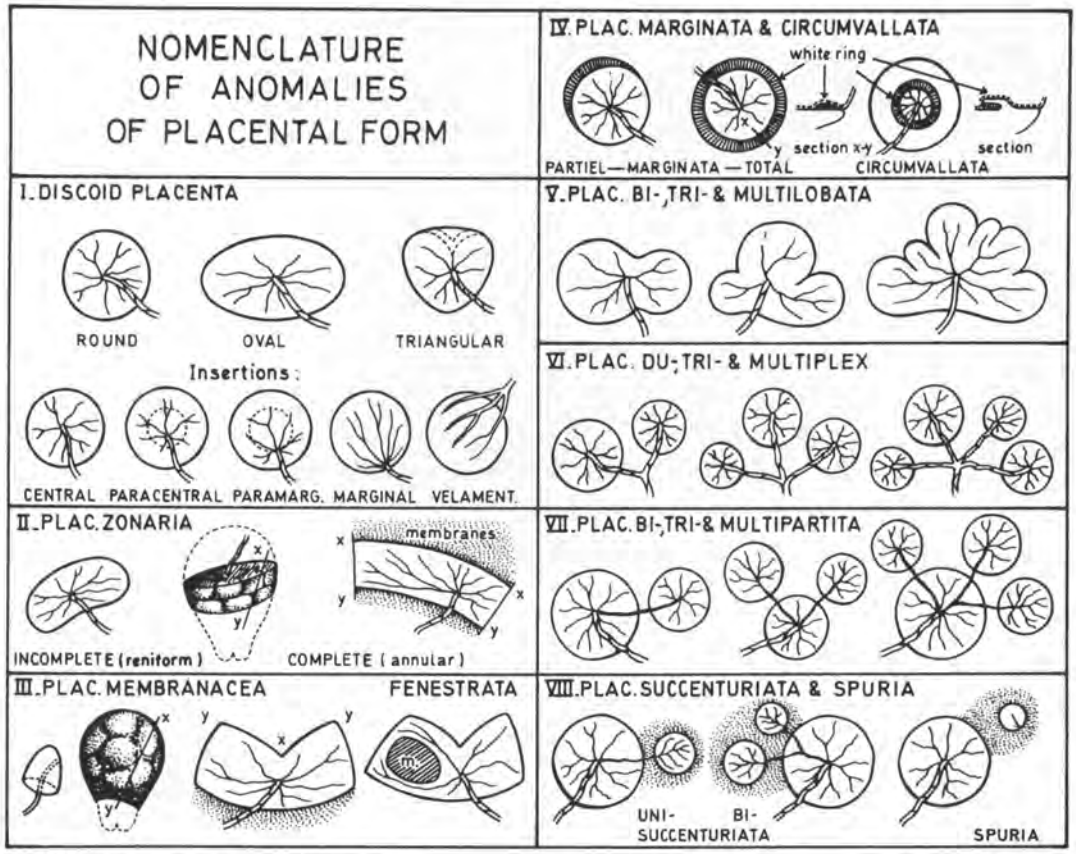

FIGURE 8-8 Anomalies of placental form.

Other Abnormal Placental Shapes

The most extreme form of multilobation is the *placenta membranacea* (*diffusa*). This type of placentation is common in animals and is the norm for sheep. In our experience, placenta membranacea has an incidence of roughly 1 in 20,000 to 30,000 births. The placenta consists of numerous (15 to 30), 2- to 3-cm masses of chorionic villi dispersed throughout the entire gestational sac. It is as if the chorion laeve failed to atrophy and a single dominant placental disc never formed. Each lobule of villi tends to have a single chorionic artery and vein connecting directly to the umbilical cord or to another lobule. Placenta membranacea usually is placenta previa and may well be placenta accreta. It is associated with increased vaginal bleeding during pregnancy and, more commonly, with postpartum bleeding, often due to retained placental tissues.

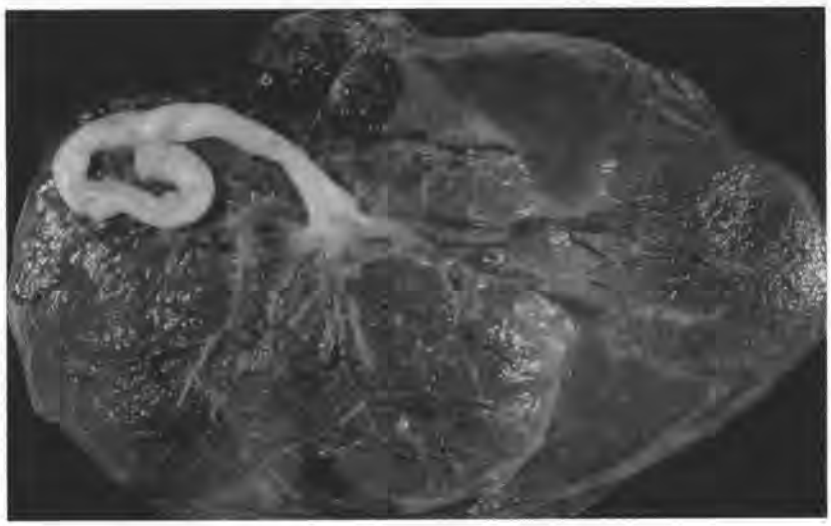

FIGURE 8-9 Succenturiate placenta (placenta succenturiata), a variant of placenta bipartita. Chorionic vessels travel unsupported through the placental membranes to the accessory lobe. Vessels of the accessory lobe unite with those of the main disc on the chorionic plate before entering the umbilical cord.

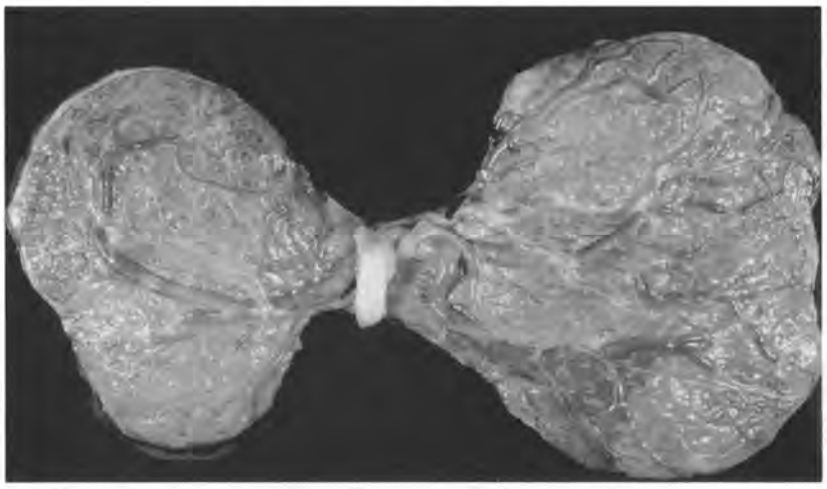

FIGURE 8-10 Bilobed placenta (placenta bipartita). The umbilical cord inserts centrally into membranes between the two placental discs.

In the *ring-shaped* placenta (*complete placenta zonaria*), the villous tissue is annular, forming a doughnut-like ring. When fixed, it can stand up on its own. This type of placentation is uncommon and in our experience occurs in about 1 in 50,000 births. The umbilical cord may insert onto the membranes.

A *fenestrate* placenta (*placenta fenestrata*) has a localized, approximately 2-cm, round to oval absence of villous tissue, generally within a central or paracentral portion of the chorionic plate. This curious villous defect has not been ascribed to any known predisposing factors.

Abnormal Membrane Insertions

In normal *marginal insertion,* the placental membranes insert at the edge of the chorionic plate. *Placenta extrachorialis* describes the general category of abnormal membrane insertion, of which there are two main types: *circummarginate (placenta marginata)* and *circumvallate (placenta vallata*; see Fig. 8-8). In the circummarginate placenta, the membrane insertion appears normal except that there is a 1- to 2-cm white plaque along a portion or the entire circumference of the chorionic plate (Fig. 8-12). On microscopy, this subchorionic white plaque consists of maternal decidua and some implantation-site trophoblast with the placental villi tucked under the intervening endometrium. There seem to be minimal sequelae associated with circummarginate membrane insertion.

In contrast, in circumvallate membrane insertion the extraplacental membranes are folded back onto themselves resulting in a deep "V" on the fetal surface, distal to which a layer of endometrium is sandwiched between the extraplacental membranes and the marginal chorionic villi (Fig. 8-13). Circumvallate placentation may be associated with prior marginal placental separation. Pregnancy outcome generally is normal. A full spectrum of intermediate forms of membrane insertions ranging from circummarginate to circumvallate have been observed.

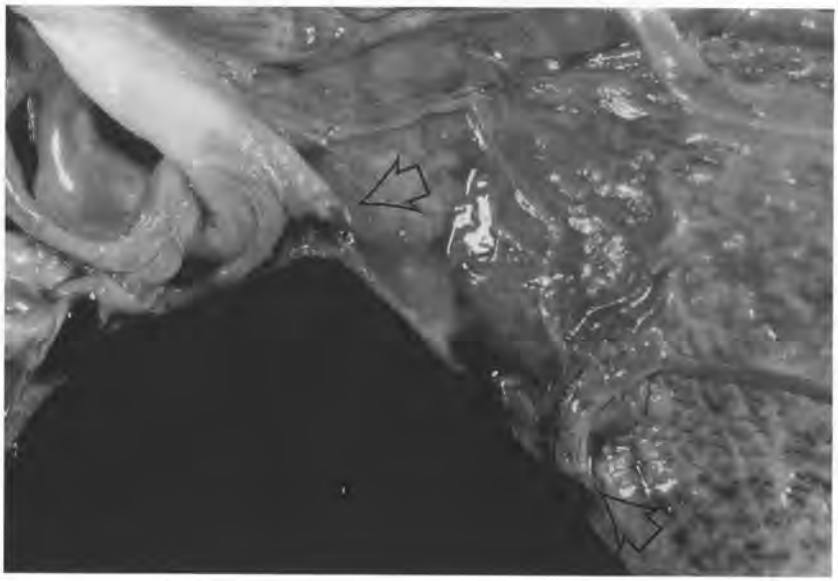

FIGURE 8-11 This umbilical artery is lacerated at the umbilical cord insertion site (same placenta as in Fig. 8-10).

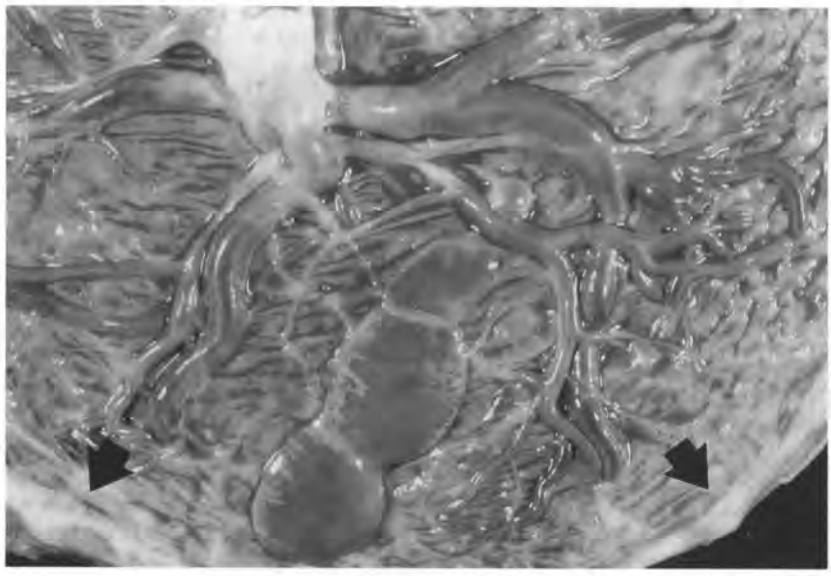

FIGURE 8-12 Circummarginate membrane insertion is indicated by the rim of white tissue at the placental margin (*arrows*). Innocuous subchorionic cysts are seen on the fetal surface.

PLACENTA CRETA

Placenta accreta refers to an abnormal adherence of the placenta to the uterus after delivery of the fetus. It is a clinical diagnosis. Pathologists have proffered a variety of histologic criteria to support its diagnosis. The most common, a lack of decidua intervening between villi and myometrium, may be a subjective call. Any placental tissue remaining in the uterus after the third stage of delivery implies abnormal adherence. By this definition, villous tissue in a postpartum hysterectomy specimen connotes placenta accreta. Villi may be implanted directly onto myometrium, with little to no intervening fibrin, implantation-site trophoblast, or decidua. Most commonly, the retained villi are associated with scant implantation-site trophoblast and fibrin, with minimal, if any, decidua. Placenta accreta may be focal or extensive, involving the entire placenta. Most often, placenta accreta is focal, and the scant amount of residual villous tissues in a postpartum hysterectomy belies the gravity of this potentially life-threatening process.

Placenta increta refers to villi within the myometrium, usually involving previous cesarean section or myomectomy scars. In some, there is no history of previous uterine instrumentation. The placentation of all ectopic pregnancy sites including fallopian tubes, cornua, and cervix is increta or percreta.

The most severe and life-threatening abnormal placentation is *placenta percreta,* in which villi penetrate through the uterine wall to the serosa. Placenta percreta may cause bleeding at any point in gestation, with severe postpartum hemorrhage occurring if manual or surgical placental extraction is attempted. All forms of placenta creta are associated

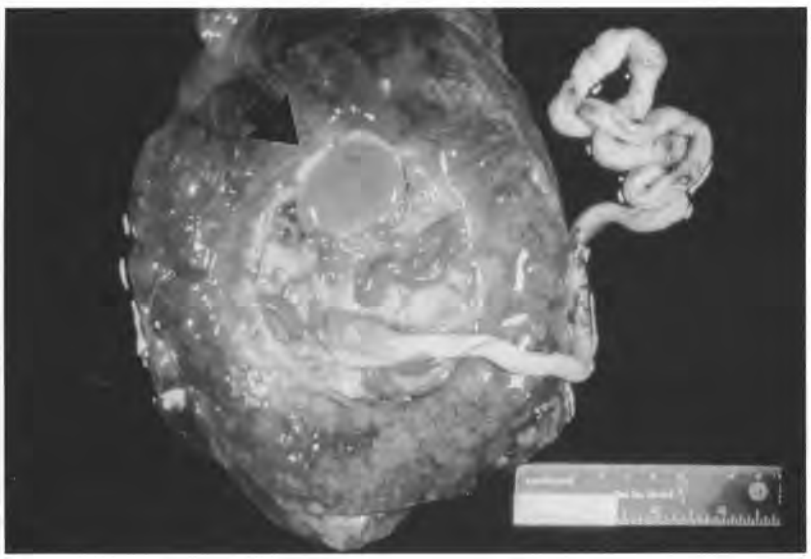

FIGURE 8-13 Circumvallate membrane insertion. Placental membranes are doubled back onto the fetal surface (*arrow*).

with increased postpartum bleeding, which may necessitate hysterectomy for control. Uterine inversion, although uncommon, is a serious and potentially lethal complication resulting from failure to diagnose placenta creta.

UMBILICAL CORD

The normal umbilical cord measures 40 to 70 cm in length at term, is 1 to 2 cm in diameter, and contains three vessels. The umbilical vessels are cushioned within Wharton's jelly, a myxomatous substance providing structural support. The amnion forming the surface of the cord is contiguous with the amnion of the placental membranes.

Gross structural abnormalities of the cord involve its insertion into the placental disc, the number and structure of vessels and vestigial remnants, its shape, and intrinsic tumors. The most common abnormality of the cord, inflammation of cord vessels relating to chorioamnionitis, is presented in the section dealing with placental infections.

Umbilical cords measuring less than 40 cm in length are arbitrarily designated *short,* whereas those more than 70 cm in length are called *long.* An umbilical cord that appears short at placental examination may simply be incomplete, with a section of cord having been submitted for blood gas analysis or an unusually long portion left attached (temporarily) to the infant. Truly short cords have been associated with congenital anomalies such as gastroschisis, amnionic band syndrome, abnormal fetal brain development, and low intelligence quotients in childhood.[15] They generally are associated with a lack of fetal movement, whereas long cords have been associated with excessive fetal movement. Entrapment of fetal parts (nuchal cord), formation of true knots, and cord prolapse are the main risks associated with a long cord. In the rare total absence of the umbilical cord, termed *acordia,* the fetal abdomen is juxtaposed to the placenta (Fig. 8-14). These fetuses generally do not survive.

FIGURE 8-14 In the total absence of the umbilical cord (acordia), the fetal abdomen is juxtaposed to chorionic vessels.

Normally, the umbilical cord inserts centrally or slightly eccentrically into the chorionic plate (see Fig. 8-9). Insertion at the edge of the placental disc is termed *marginal* (battledore), and occurs in around 6% of cases. Studies analyzing the association between marginal cord insertion and fetal sequelae have yielded conflicting results. Recently, Davies found marginal cord insertion associated with fetal growth retardation.[16]

In 1% of placentas, the cord inserts directly into the fetal membranes. This is called *membranous* (velamentous) insertion. The fetal vessels may be traumatized or compressed due to a lack of underlying placental parenchyma (Fig. 8-15).[17] Membranous insertion of the cord in twins is seven times more common than in singletons. Membranous vessels crossing over the cervical os, *vasa previa,* may be ruptured during labor or delivery, leading to fatal fetal exsanguination. Robinson found fetal structural deformities, including hip dislocation and skull malformations, associated with membranous cord insertion.[18]

The normal cord contains two arteries and one vein. Absence of one umbilical artery, termed *single umbilical artery,* occurs in 1% of placentas and is more frequent in twins and in whites.[19,20] It is associated with congenital anomalies, most often involving the genitourinary and cardiovascular systems, chromosomal anomalies, stillbirth, and neonatal death. Leung found renal anomalies in 19% of fetuses with single umbilical artery who were studied by obstetric ultrasonography.[19] Others have suggested that there is no predilection for specific types of anomalies associated with single umbilical artery.[17] Because the umbilical arteries may fuse near the chorionic insertion site, sections of cord documenting vascular content should be taken proximal to the insertion site. In some states in the United States, the delivering physician is required by law to document the number of umbilical cord vessels at birth.

A *true knot* in the umbilical cord is found in about 1% of deliveries and most often is inconsequential. Normally, a true knot slides up and down

FIGURE 8-15 Membranous insertion of umbilical cord.

the cord and does not restrict blood flow. Umbilical cords with two or three knots, or a knot "tied twice" have been observed. True knots are an uncommon cause of intrauterine fetal death (Fig. 8-16). A true knot is described as occlusive when associated with a marked narrowing of the cord on one side of the knot and dilatation on the other. The *false knot* is not a knot at all (Fig. 8-17). It consists of a varicosity or tortuosity of an umbilical vessel and, unless associated with a thrombus, leads to no sequelae.

Vascular structural abnormalities of cord vessels include thrombosis, stenosis, and aneurysms. Complete thrombosis of the umbilical vein is lethal. Partial thrombosis may result in placental hydrops (Fig. 8-18). Thrombosis of one umbilical artery is not life-threatening. Occasionally, an umbilical artery is stenotic. Arterial stenosis has been suggested as a cause of single umbilical artery. Aneurysms of the umbilical vein have been associated with fetal systemic vascular malformations (Fig. 8-18).

In its early form, the primitive umbilical cord contains the omphalomesenteric duct, the allantoic duct, and the vitelline artery and vein. The *omphalomesenteric duct* connects the fetal yolk sac with the small intestine at the site of a Meckel's diverticulum. It atrophies during the 7th to 16th week. Vestigial remnants of the omphalomesenteric duct may be found in the periphery of the cord in Wharton's jelly near the amnionic surface. The duct is lined by cuboidal to columnar, intestinal-type epithelium, often

FIGURE 8-17 False knot of umbilical cord.

mucin-containing, which may be hyperplastic or metaplastic. Adenomas of small or large intestinal-type epithelium and a variety of mesodermally derived composite lesions, parallelling those of a Meckel's diverticulum, may develop within omphalomesenteric duct remnants (Fig. 8-19). In rare cases, such a lesion prolapses out the omphalomesenteric duct, through Wharton's jelly, and onto the cord surface, forming a pedunculated, beefy-red polyp.

Remnants of the *allantoic duct* are more common but less interesting. In early fetal life, the allantoic duct serves as a conduit for the fetal bladder. True to its association with the urinary tract, it is lined by a transitional-type epithelium that remains flat to cuboidal, with scant clear cytoplasm. The duct is often encountered in routine sections of the umbilical cord, lying between the umbilical arteries. Remnants of the vitelline vessels may be found in the term cord. They have no known clinical significance in the mature placenta.

There are rare umbilical cord cysts containing Wharton's jelly (Fig. 8-20). The more exotic, benign vascular tumors of the umbilical cord include *hemangiomas* (angiomyxomas) and *teratomas.* Although most cord hemangiomas are benign, the larger ones

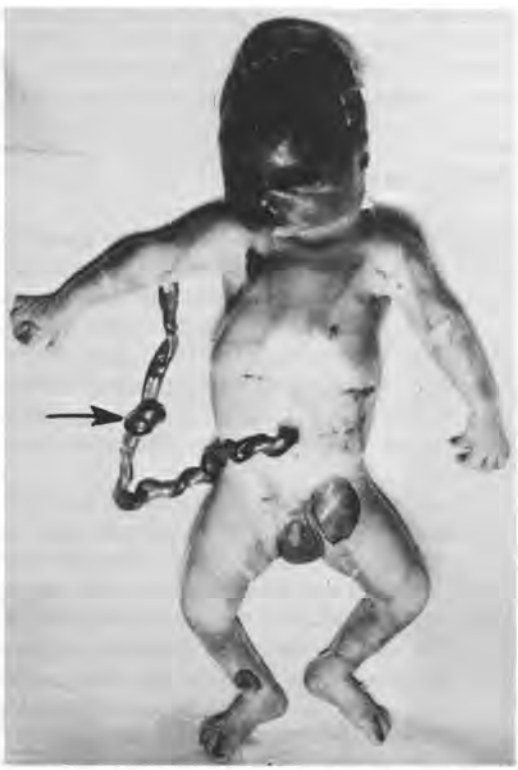

FIGURE 8-16 True knot in umbilical cord resulting in fetal death in utero.

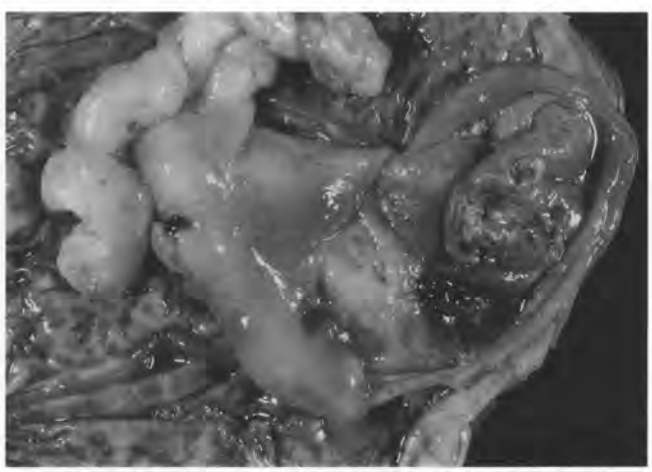

FIGURE 8-18 Aneurysm of umbilical vein associated with a large thrombus.

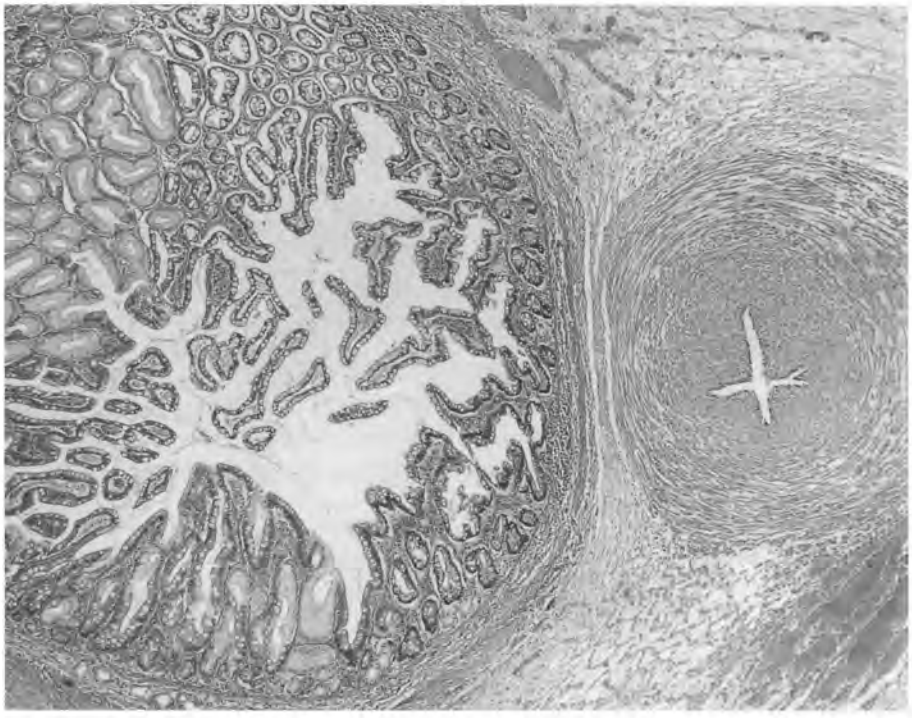

FIGURE 8-19 Intestinal-type epithelium within an omphalomesenteric duct remnant of an umbilical cord in a term infant.

may shunt blood or compress umbilical cord blood flow (Fig. 8-21). Some have obstructed delivery or have been associated with stillbirth.[21,22] Rare umbilical cord teratomas have been reported.[23] Some of these may represent included twins.

Bacteria can infect the cord, giving it an overall cloudy appearance. In contrast, *fungal colonization* by *Candida* species produces multiple, creamy yellow nodules, typically 3 to 4 mm in diameter and located just under the amnion. By microscopy, spores and hyphal forms are seen on hematoxylin and eosin-stained sections (Fig. 8-22) and are highlighted by periodic acid-Schiff or silver stains. The newborn may have disseminated skin nodules or may be totally normal. Candidal septicemia and pneumonia are rare.

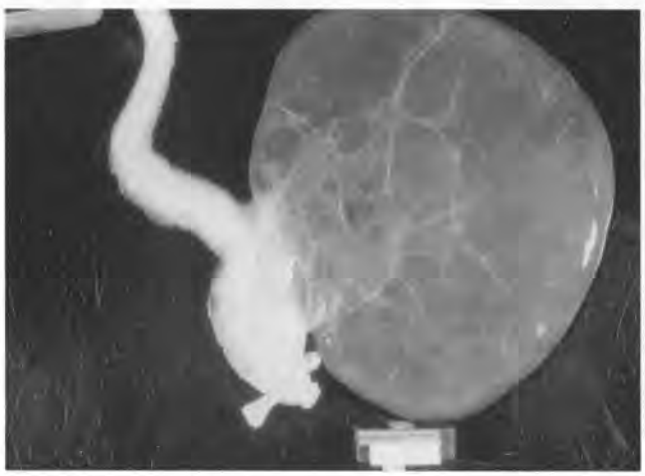

FIGURE 8-20 Umbilical cord cyst containing Wharton's jelly.

The amnion of the cord may undergo metaplastic changes, including squamous metaplasia and columnar metaplasia (see discussion later in this chapter). Deposits of amnion nodosum are usually located at the base of the cord, although the amnion overlying the chorionic plate tends to be involved more extensively. Amnionic bands may entwine, constrict, or occlude the cord.

PLACENTAL MEMBRANES

The fetus floats in amnionic fluid enclosed within the amnionic cavity. The amnionic sac enlarges and obliterates the chorionic cavity and fuses with the chorion. The uterine cavity itself is obliterated near the end of the third month by the fusion of the chorion laeve and its attached decidua capsularis to the decidua vera (decidua parietalis). The amnion, chorion laeve, and decidua form the extraplacental membranes.

The amnion is composed of a single layer of flattened to cuboidal epithelial cells (amniocytes) atop a mesoblastic connective tissue layer. The chorion contains extravillous trophoblast and is adjacent to the maternal decidua. Within the chorion laeve of the extraplacental membranes are remnants of atrophic villi. The decidua is composed of decidualized endometrial stroma, endometrial glands, and spiral arteries. Macrophages are present in all three layers. Microscopic examination of the membranes provides valuable information about acute and chronic placental infection, meconium or blood exposure, ma-

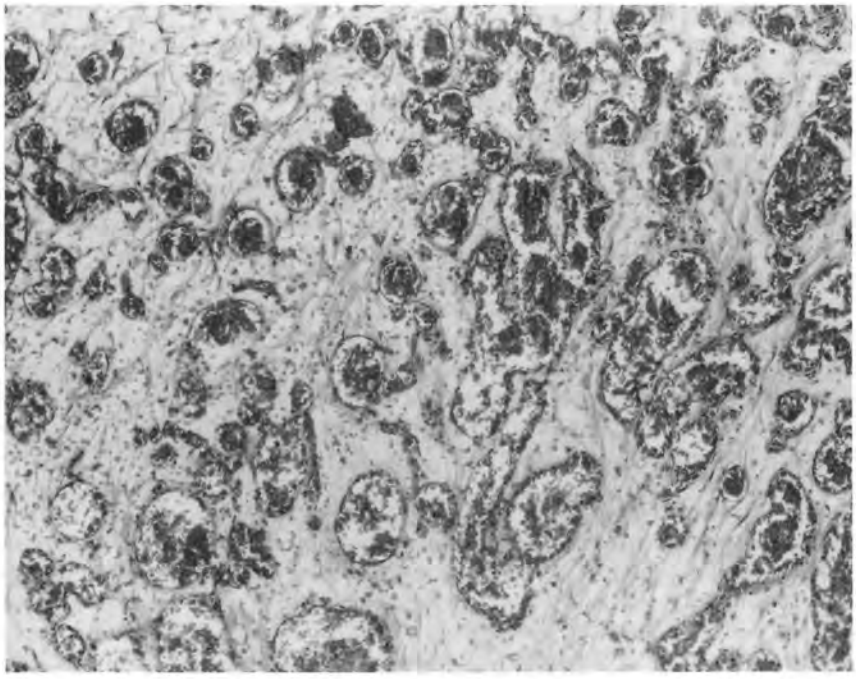

FIGURE 8-21 Hemangioma of umbilical cord.

ternal disorders affecting uteroplacental perfusion, and the amount of amnionic fluid.

Chorioamnionits

Chorioamnionitis is diagnosed pathologically by maternal leukocytes infiltrating into the chorioamnionic membranes. Chorioamnionitis is rare in the first trimester. In the second trimester, it is a common cause of premature labor, premature rupture of membranes, and stillbirth. At term, it is often observed histologically but is rarely associated with poor neonatal outcome if delivery is achieved within the first 24 hours.[24] Chorioamnionitis is discussed in more detail in the section on placental infections.

Meconium

Fresh meconium is dark green and viscous. It is water-soluble and easily cleared in tissue processing. In

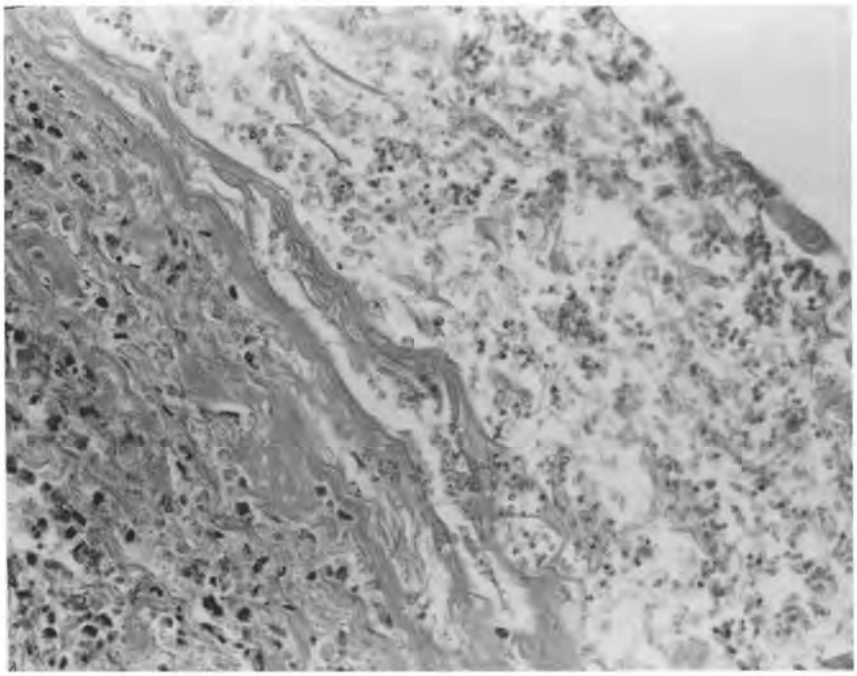

FIGURE 8-22 Umbilical cord with collection of spores and hyphal forms of *Candida* species on surface of cord. There is superficial invasion of the umbilical cord and acute inflammation.

histologic sections, it is light yellow, finely granular, dusty, and far less bright yellow than hematoidin. Hemosiderin is coarsely granular and yellow-brown to brown and, unlike meconium, is refractile.

The timing and response to meconium exposure in vivo is not well characterized. Apparently, meconium initially causes focal epithelial necrosis, followed by amnionic columnar metaplasia with ballooning and cytoplasmic vacuolization.[17] Associated subamnionic macrophages engulf meconium pigment (Fig. 8-23). Imbued meconium can be found in macrophages of the chorion, umbilical cord, or decidua. The high degree of water solubility accounts for the marked disparity between the intense green to brown discoloration of the fetal surface in meconium-stained placentas and for the subtlety of histologic findings.

In vitro studies suggest that meconium appears within chorionic macrophages about 3 hours after fetal release (see Fig. 8-23).[25] There is some evidence to suggest that meconium induces necrosis of umbilical cord vascular smooth muscle, thereby causing vasospasm and decreasing fetal blood flow.[26] Meconium staining of the placenta is not invariably associated with fetal meconium aspiration.[27]

All green-stained placentas are not the result of meconium passage. Green discoloration may reflect hemosiderin deposits from metabolized blood of placental thrombi, hematomas, abruptions, fetal hemolysis, and marginal hemorrhages. Sometimes it is difficult to differentiate meconium from hemosiderin; in such cases, an iron stain is helpful.

Amnion Nodosum

Amnion nodosum consists of nodular deposits of fetal vernix caseosum and debris atop ulcerated amnion (Fig. 8-24). It is always associated with oligohydramnios. The deposits may be numerous (more than 100), elevated, yellow to cream-colored. They measure 2 to 5 mm in diameter. In contrast to squamous metaplasia, they are easily removed by firm scraping. Although they center around the umbilical cord insertion and extend centrifugally from the juxtaumbilical chorionic plate, some deposits may be found on the extraplacental membranes.

Microscopic examination often reveals an ulcerated amnion, which may be attenuated but intact. The nodule consists of an eosinophilic hump of debris: parakeratotic fetal squames, hair, and amorphous granular material (Fig. 8-25). At the edges, regenerating amnion may partially cover the nodule. Amnion nodosum, apart from its association with oligohydramnios, is related to structural anomalies of the fetal urinary tract and may result from bilateral renal agenesis, cystic dysplastic kidneys, ureteral atresia or agenesis (bilateral), absence of the urinary bladder, posterior urethral valves with marked obstruction, urethral stenosis, or atresia. Oligohydramnios from preterm rupture of membranes usually results in fewer deposits of amnion nodosum than does bilateral renal agenesis. Amnion nodosum should prompt careful monitoring and evaluation of the newborn's urinary tract.

Squamous Metaplasia

Squamous metaplasia may involve the amnion of the umbilical cord and the placental membranes. It is grossly similar to amnion nodosum except that the nodules are smaller and whiter. Firm scraping will not remove a nodule of squamous metaplasia because it is an inherent part of the amnion. By microscopy, it consists of multilayered squamous epithelium

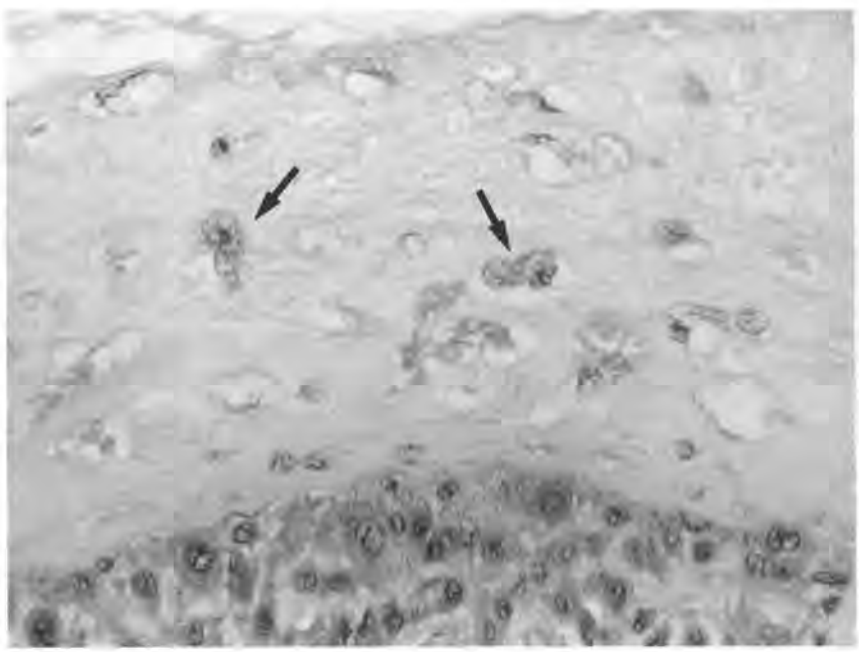

FIGURE 8-23 Placental membranes with subamnionic macrophages imbued with finely particulate, granular meconium (*arrows*). Meconium is also present in superficial macrophages in the chorion. Amnionic epithelium is avulsed.

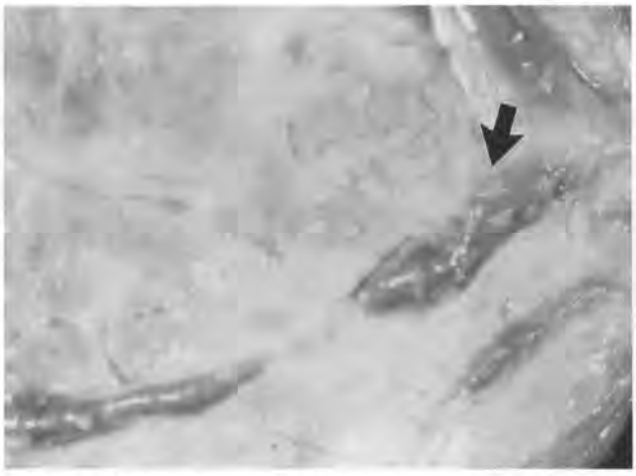

FIGURE 8-24 Fetal surface of placenta showing nodular deposits of amnion nodosum on amnion overlying chorionic vessels (*arrow*). Fetus had bilateral renal agenesis.

complete with keratohyalin granules and occasionally with dense ortho- or parakeratosis (Fig. 8-26). It has no known clinical significance and its importance derives from differentiating it from amnion nodosum. Microscopy should be performed in all cases of nodular deposits on the fetal surface.

Amnionic Vacuolization

Fetal gastroschisis is associated with a distinctive vacuolization of the amnion. The eosinophilic cytoplasm of the amnion contains a single vacuole or a few small to medium-sized clear vacuoles. In contrast to the columnar metaplasia associated with meconium exposure, the nuclei of amnionic vacuolization in gastroschisis are normal and not pyknotic. This type of vacuolization generally is not found with fetal omphalocele.

Amnionic Band Syndrome

Amnionic band syndrome (amnion rupture sequence) results from a premature rupture of the amnion. The fetus is no longer housed in the amnionic cavity, but within a cavity lined by subamnionic connective tissues or chorion.[28] The strings or bands of the ruptured amnion and its connective tissue may entrap, disrupt, or amputate developing fetal structures. The resultant malformations depend on the timing of the rupture and the site of entrapment. Rupture in early gestation leads to major malformations, such as craniofacial defects, some types of encephaloceles and meningoceles, and possibly gastroschisis. Usually severe oligohydramnios ensues, with resultant pulmonary hypoplasia, positional deformations of extremities, and Potter facies. Amputation of an arm, leg, or even the head may occur. The fetus, even with good Apgar scores at birth, often dies shortly after birth of pulmonary insufficiency.

Rupture later in pregnancy is less destructive, although bands may entrap fingers, toes, or feet, resulting in amputation, constriction, or deformation (Fig. 8-27). Examination of the placenta shows avulsion of the amnion with erosion of the subamnionic connective tissue. Remnants of amnionic bands encircle the base of the umbilical cord or entrap fetal parts. Amputated fetal parts may become attached to the placenta or may be free-floating, delivered with the placenta and adnexa.[29] Rarely, the infant adheres to the placenta. Defects associated with amnionic

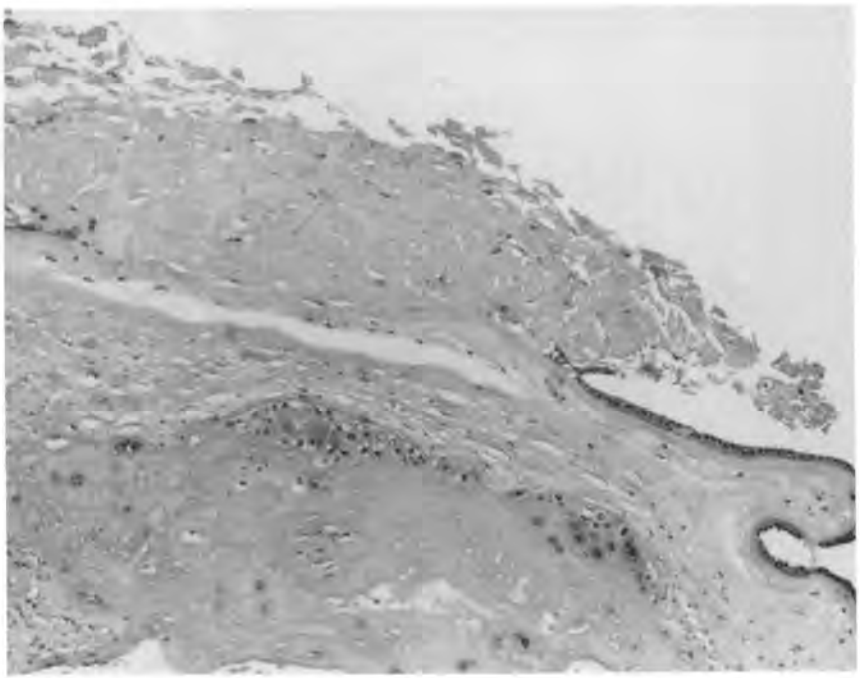

FIGURE 8-25 Amnion nodosum involving the placental chorionic plate. Ulcerated amnion is replaced by a mound of fetal squames, debris, and lanugo. Fetus had bilateral renal agenesis.

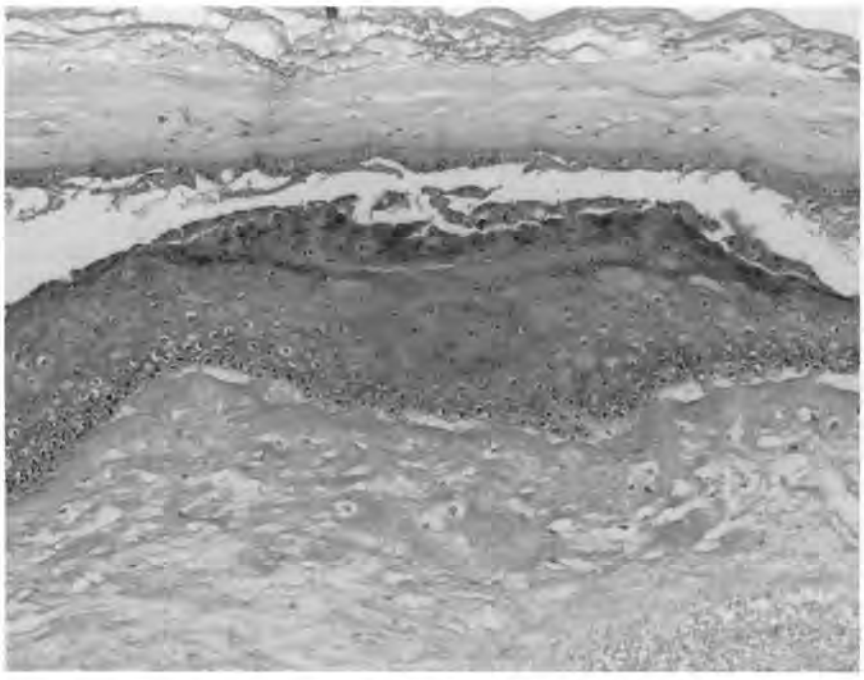

FIGURE 8-26 Membrane roll showing squamous metaplasia of amnion (*center*). Amnion is converted into squamous epithelium complete with keratohyalin granules and parakeratosis. The normal amnion is opposite the nodule of squamous metaplasia.

band formation are sporadic and, in most cases, are not associated with chromosomal anomalies or recurrences. Although it was initially feared that second-trimester amniocentesis would result in an increase in amnionic band formation, no such association has been observed.[30]

Decidual Vasculopathy

Pathology in the decidual vessels of the extraplacental membranes (decidua parietalis) provides data regarding the status of maternal circulation during gestation. *Decidual vasculopathy* (or *early atheromatous change, acute atherosis*) is a pathologic finding in abnormal placentas that affects maternal vessels that do not undergo the physiologic vascular changes of pregnancy. It is not found in normal, uncomplicated pregnancies.[31] Decidual vasculopathy is most commonly associated with preeclampsia, eclampsia, small-for-gestational-age infants,[31–33] and hypertension.[34–35] It is found less frequently with diabetes mellitus,[34,36] collagen vascular diseases such as lupus erythematosus,[37] and renal disorders. Even among women with preeclampsia, only 25% have decidual vasculopathy in random sections of the membranes. Submitting an extra sample of the membrane roll increases the diagnostic yield; two samples of the membrane roll should be submitted for microscopic examination in high-risk placentas.

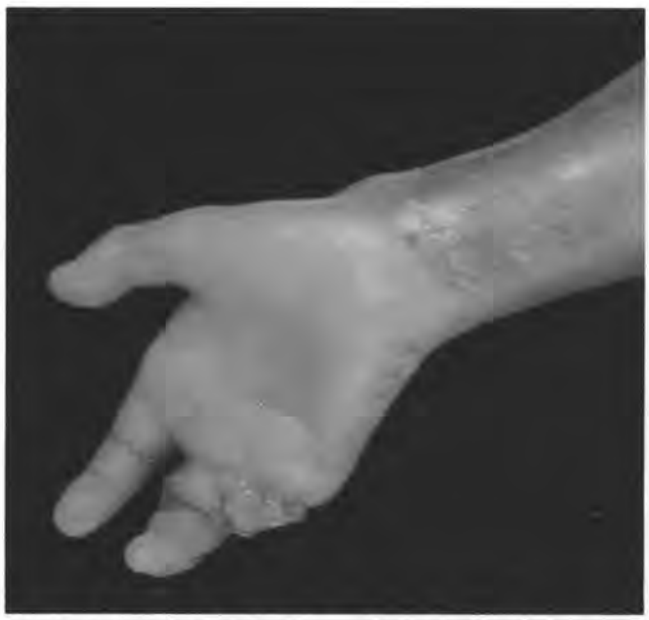

FIGURE 8-27 Fetal hand with amnionic band constricting the fingers, deforming and amputating the digits.

Microscopically, decidual vasculopathy takes three distinct forms:

1. Thickening or hyalinization of arteriolar vessel walls with mild perivascular mononuclear cell infiltrate
2. Marked arteriolar wall thickening with onion-skinning (Fig. 8-28)
3. Moderate arteriolar wall thickening with fibrinoid necrosis, focal or complete occlusion of vascular lumen, infiltrate of mononuclear cells (lymphocytes and plasma cells), and lipid-rich macrophages (lipophages; Figs. 8-29 and 8-30). In rare cases, the macrophages contain cholesterol clefts.

Finding vasculopathy in the maternal decidual vessels of the extraplacental membranes is important because it reflects the status of the vessels in the pla-

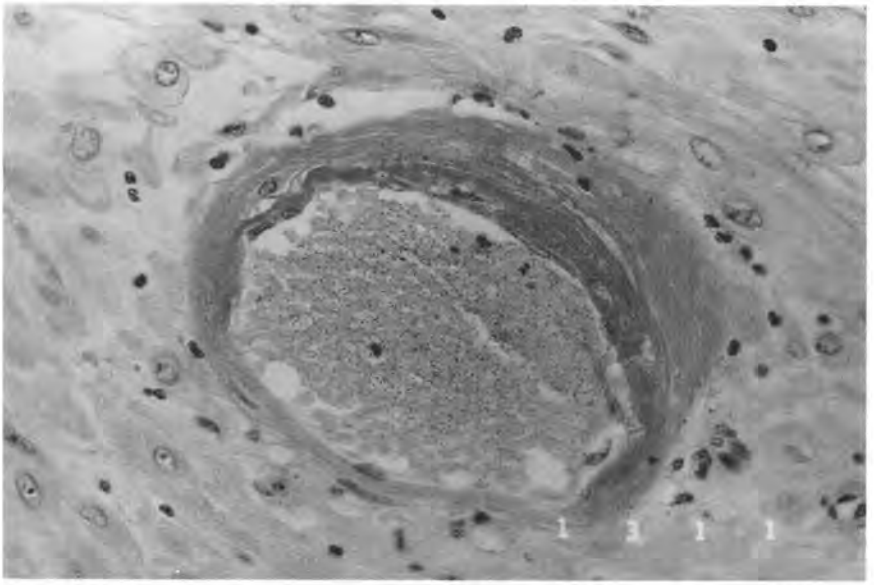

FIGURE 8-28 Decidual vasculopathy with marked dilation of decidual arteriole, hyalinization of vessel wall, dense crescentic fibrin deposit, and sparse mononuclear cell infiltrate. Section taken from extraplacental membranes.

cental bed of the implantation site. The vascular lesions of preeclampsia affect the spiral arteries of the decidua parietalis (away from the implantation site), the basal arteries, and the deep myometrial portions of the spiral arteries serving the implantation site.[38] Khong found that acute atherosis also involved the decidual segments of the spiral arteries of the placental bed in pregnancies complicated by preeclampsia or small-for-gestational-age infants (Fig. 8-30).[39] Destruction of vascular walls by fibrinoid necrosis with focal or complete luminal occlusion or thrombosis decreases placental perfusion and results in parenchymal infarcts. It has been suggested that decidual vasculopathy represents the localized results of an inappropriate fetal-maternal immunologic reaction because it is histologically similar to the vascular lesions of allograft transplant rejection.[40]

MULTIPLE GESTATION AND ITS COMPLICATIONS

Twin gestations provide an opportunity to study the interactions of nature and nurture in forming human life. Because the uterus was designed to support one gestation at a time, twins constitute a reproductive error. Prematurity is the rule in twin births, with perinatal mortality rates three times higher than in singletons.[41–43] Congenital malformations,

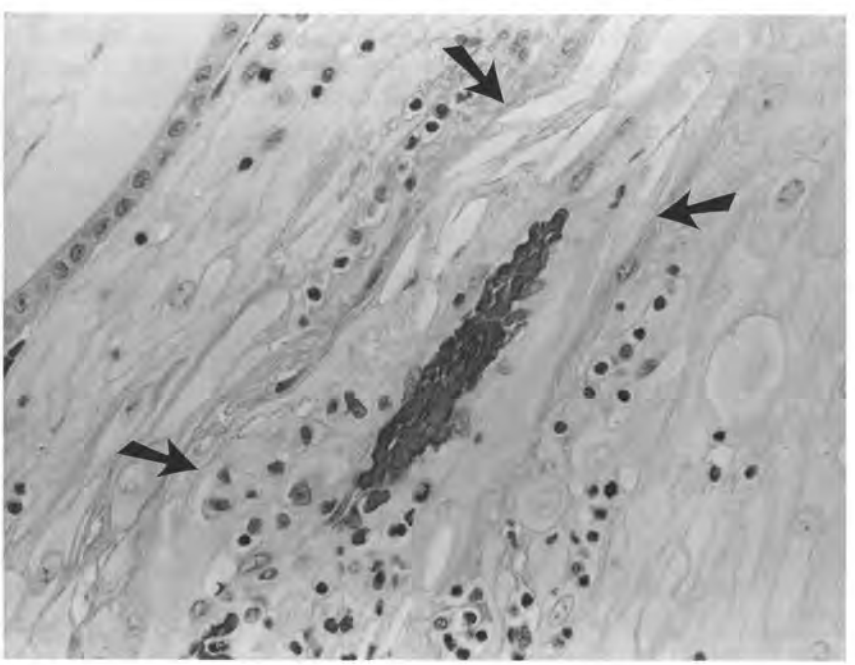

FIGURE 8-29 Extraplacental membranes showing decidual vasculopathy with expansion of maternal vessel (*arrows*) by numerous macrophages, some containing cholesterol clefts, embedded in loose eosinophilic fibrinoid material. There is moderate mononuclear cell infiltrate of vessel and surrounding decidua. Amnion (*upper left*) and minimal chorion can be seen.

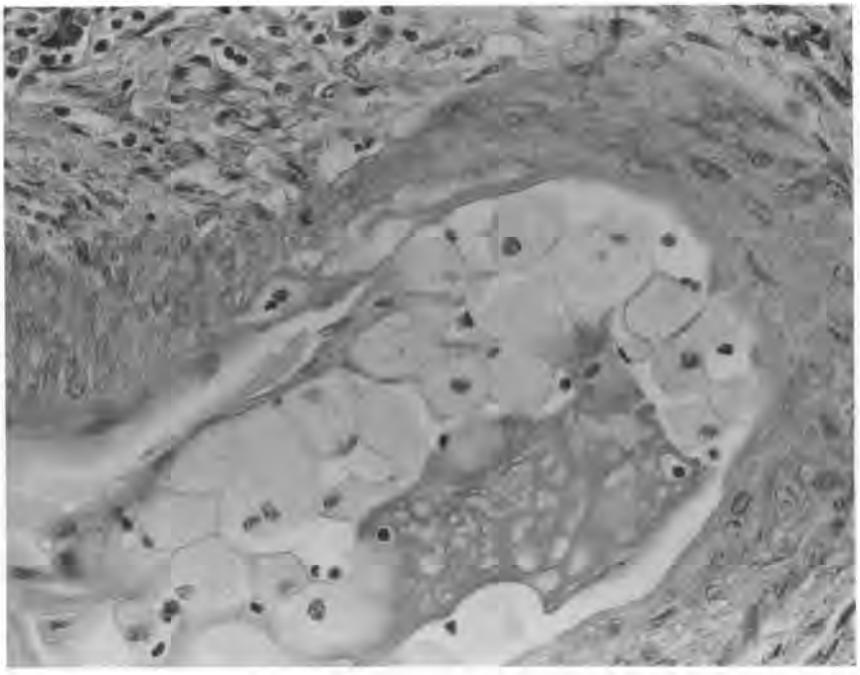

FIGURE 8-30 Decidual vasculopathy with numerous lipophages, scattered mononuclear cells, and central fibrin. Section of decidua from the basal plate of placenta subtending a large placental infarct.

particularly congenital heart disease and central nervous system anomalies, occur more frequently in identical twins.[44]

Twin gestations are the most common type of multiple gestation. In Western countries, there is 1 twin birth for every 80 births.[45] Naturally occurring births of higher order are significantly less common, with the frequency of triplets at $1:80^2$, quadruplets, $1:80^3$, and quintuplets, $1:80^4$.

There are two types of twins: monozygous and dizygous. *Monozygous twins* (identical twins) are derived from the fertilization of one oocyte by one spermatozoon and are genetically identical. *Dizygous twins* (fraternal twins) are derived from two separate fertilization events: two different oocytes are fertilized by two different spermatozoa. Dizygous twins are no more alike than any other full sibling pair. There are rare cases of half-identical twins derived from fertilization of an ova and its polar body. Even more rare are cases of twin ova fertilized by spermatozoa from different fathers.

The rate of monozygous twinning is relatively constant throughout the world at 3.5 per 1000 births and is not associated with any known predisposing factors.[43,44,46] Depending on the population, monozygotes account for as many as one-third of all twin births. In contrast, the incidence of dizygous twinning depends on multiple factors. Dizygous twinning increases with family history of twins, advanced maternal age (highest between ages 35 and 40), increased parity, and exposure to exogenous gonadotropins. Among whites, dizygotic twinning occurs in about 8 per 1000 births. Asian women have a rate one half as frequent, and black women twice as great.[46] In Nigeria, where the rate of dizygous twinning is at its highest, twin births in the Yoruba tribe account for 1 per 22 to 25 births.[46,47]

The most common question posed on the birth of twins is whether the twins are identical or fraternal. Twins derived from a single zygote are genetically identical and monozygous.[45] Those from two different zygotes (dizygous) are fraternal. Examination of the placenta in conjunction with knowledge of the sex of each twin allows ascertainment of zygosity in about 55% of twin births.[49] In a series of 250 consecutive twin placentas past 20 weeks' gestational age, 1.5% were monoamnionic-monochorionic; 29.6% were diamnionic-monochorionic; 34% were diamnionic-dichorionic, fused; and 35.2% were diamnionic-dichorionic, separate.[50] Further evaluation of the twins in this series from the eastern United States revealed that 41% were monozygous and 59% dizygous. Of the monozygous twins, 70% were monochorionic and 30% dichorionic, with fused or separate placentas. All dizygous twins had dichorionic placentation.

The physical characteristics of the twin placenta or placentas depend on the zygosity, the proximity of the two implantation sites, and the time of fission of the zygote in monozygous twins (Table 8-3). A twin or multiple gestation may have one or more amnion, chorion, and placental mass. Placentation is the term used to describe the anatomic relations among these various elements. In some instances, zygosity may be inferred from knowledge of placentation.

The timing of zygote fission determines the type of placentation. Four potential types of placentation may form in monozygous twins (see Table 8-3).[45,50] If the blastocyst divides before the 3rd day, the placentas are indistinct from those of dizgyous twins: each twin has its own amnion, chorion, and placental disc, and the placenta is termed *diamnionic-dichorionic.* Proximity of uterine implantation sites determines whether each disc remains separate or fuses

TABLE 8-3
Relationship Between Number of Placental Discs, Composition of Dividing Septum, and Inferred Zygosity

Type of Twin Placenta(s)	*Number of Placental Masses*	*Dividing Septum*	*Amnions in Dividing Septum*	*Chorions in Dividing Septum*	*Zygosity*
Monoamnionic-monochorionic	1	No	—	—	Monozygous
Diamnionic-monochorionic	1	Yes	2	0	Monozygous
Diamnionic-dichorionic, fused	Apparently 1*	Yes	2	2	Monozygous or dizygous
Diamnionic-dichorionic, separate	2	No†	—	—	Monozygous or dizygous

*The two fused placentas often resemble one large placental disc.
†Although separate diamnionic-dichorionic placentas will ultimately contain areas of placental fusion either of the extraplacental membranes or of the discs themselves, there is no dividing septum.

(Figs. 8-31 through 8-33). When the twinning event occurs after the chorion has already formed, between the 3rd to 8th day, both fetuses will share the same chorion, but each will have its own amnion. This type of placenta is called *diamnionic-monochorionic* (Fig. 8-34). Division of the blastocyst after formation of amnion and chorion, between the 8th and 13th days, yields two fetuses housed within the same chorioamnion, termed *monoamnionic-monochorionic* (Fig. 8-35). Although there are four types of placentation associated with monozygous twinning, only in monochorionic placentation is monozygosity ensured. Zygosity cannot be determined from placental examination in dichorionic placentation, because monozygous and dizygous gestations may result in dichorionic placentation.

Only two types of placentas may form in dizygous gestations (see Table 8-3 and Figs. 8-31 through 8-33). Because the conceptuses are derived from separate fertilizations, each forms a separate placenta with a separate amnion, chorion, and placental disc. Due to space constraints, the two placentas eventually come in contact with each other. In some cases, this involves only the extraplacental membranes, and both discs remain separate (see Fig. 8-31). In others, large portions of the placental discs fuse, giving the impression of one placenta (see Fig. 8-32). Except in rare cases, two separate placentas imply diamnionic-dichorionic placentation. A recently reported bipartite diamnionic-monochorionic placenta was an exception to this rule.[51]

For placentas with dividing septa, a membrane roll (jelly-roll) should be prepared from the intact septum. Although a T section of the septum with underlying chorion has been recommended, we find that it disrupts the vasculature of the chorionic plate and, depending on how tightly it is rolled, may be somewhat difficult to interpret. After taking tissue for a membrane roll, the septum should then be examined grossly to ascertain its composition. The septum from dichorionic placentas is relatively opaque and contains two amnions and two chorions (Fig. 8-36), with a few scattered villi from either side (Fig. 8-37). The latter finding is particularly helpful when the septum has been severely disrupted during delivery. The septum of a monochorionic placenta, however, is translucent, composed of only two layers of amnion, and devoid of chorion or chorionic villi

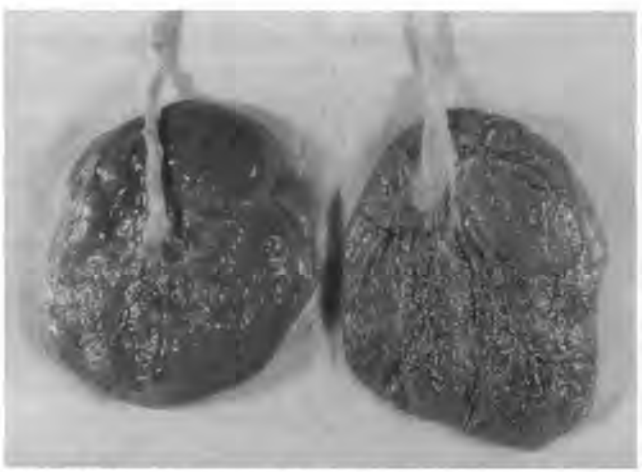

FIGURE 8-31 Diamnionic-dichorionic twin placentas, separate. Placenta on left had chorioamnionitis and meconium within amnionic macrophages. Placenta on right was normal.

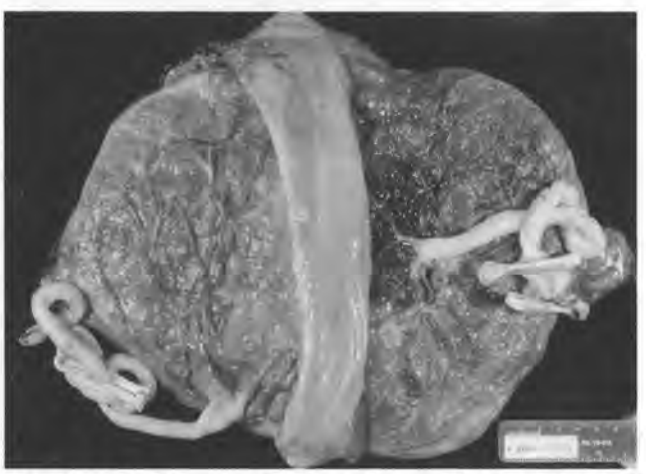

FIGURE 8-32 Diamnionic-dichorionic twin placentas, fused. Dividing septum is composed of two layers of amnion and two layers of chorion.

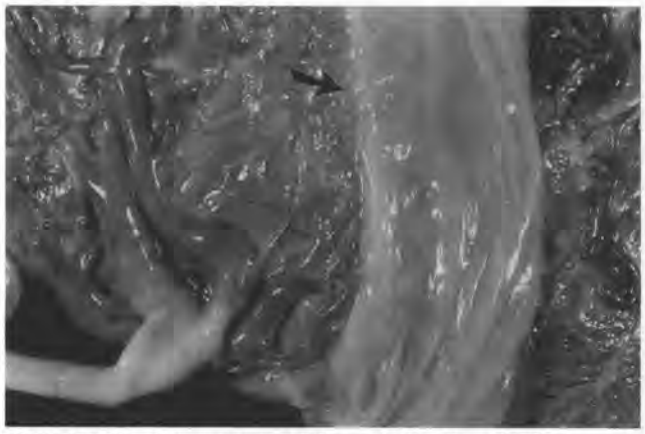

FIGURE 8-33 Closer view of Figure 8-32. The dividing septum is opaque, and the junction between the two placentas forms a ridge at the base of the septum (*right of arrow*) that is characteristic of fused dichorionic placentas. Tiny chorionic vessels course along the chorionic surface and onto the dividing septum for a short distance (*arrow*).

(Fig. 8-38). Microscopic confirmation offers histologic documentation.

Examination of placentas from multiple gestations such as triplet (Fig. 8-39) and quadruplet (Fig. 8-40) gestations is performed similarly to that of twin gestations. The pathologist must note the exact source of sections, particularly with respect to the dividing septa, on gross sketch and on tissue cassettes and slides.

Conjoined Twins

Conjoined twins are formed by incomplete fission of an embryo late in development, on or after the 13th day of gestation.[45] They are uncommon, occurring once in every 100,000 births. More than 70% are female, for unknown reasons.[45] Their placentation is always monochorionic. Although there is great variety in the joining sites, most show partial to complete fusion of the chest, termed *thoracopagii.* In some, only part of the body was duplicated, with the remainder remaining singleton (Fig. 8-41). Associated umbilical cord anomalies include partial or complete fusion or forking (Fig. 8-42).

FIGURE 8-34 Diamnionic-monochorionic twin placenta with translucent dividing septum composed of two layers of amnion. (Lavery PJ, ed: The human placenta. Rockville, MD, Aspen, 1987)

FIGURE 8-35 Monoamnionic-monochorionic twin placenta. There is no dividing septum in this type of placentation. (Lavery PJ, ed: The human placenta. Rockville, MD, Aspen, 1987)

Vascular Anastomoses in Twin Placentas

Virtually all monochorionic placentas contain vascular anastomoses linking the fetal circulations,[52] but they are less frequent in monoamnionic-monochorionic placentas.[53] Most fused dichorionic placentas have no vascular anastomoses between the two fetal circulations, although exceptions have been reported.[54,55]

Vascular anastomoses across the chorionic plate are visible on gross inspection. Most frequently these take the form of arterial-to-arterial or venous-to-venous connections. Less common are arterial-to-venous or venous-to-arterial anastomoses. The easiest way to check for suspected anastomoses is by visual inspection of the fetal surface, and then by injecting air (20 to 40 mL) into a large chorionic vessel while constricting the umbilical cord. Vascular anastomoses are demonstrated when air tracks from vessels on one twin to those of the co-twin. Reinjection confirms initial impressions. If needed, radiographs of barium-injected anastomoses can serve as a permanent record.

The consequences of these vascular links depend largely on their nature, number, and net circulatory result. Those that connect vessels of similar pressures (eg, artery-artery or vein-vein) are of little consequence. If unbalanced, potentially life-threatening sequelae may result from shunting of blood from one twin to the other by artery-vein or vein-artery anastomoses.

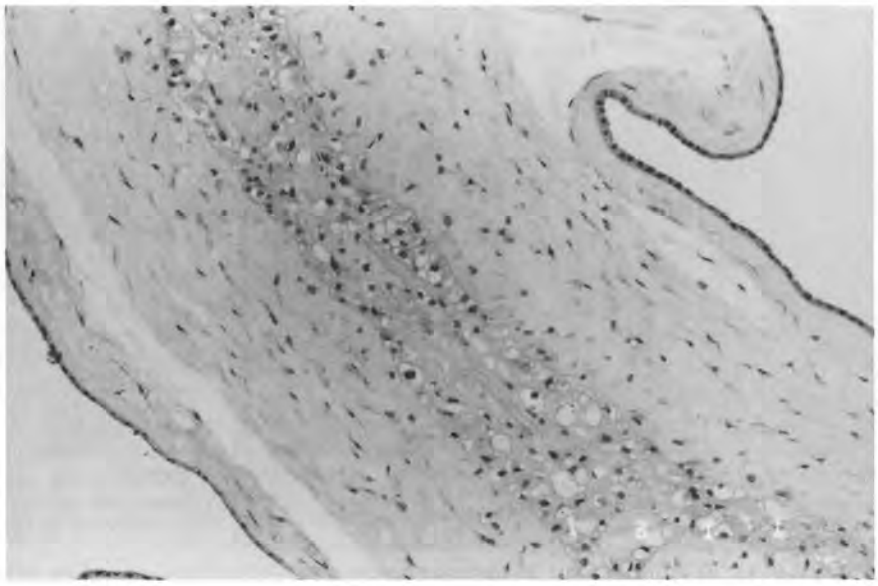

FIGURE 8-36 Dividing septum in diamnionic-dichorionic twin placentas showing two amnions (*lower left* and *upper right*) and partial fusion of the two chorions (*center*).

Dizygous twins usually have completely separate placental circulatory systems. Joining of the fetal circulations in dizygous twins may result in blood group chimerism, identified by two red blood cell groups in one twin. Precursor blood cells are passed between fetuses at a stage when the tolerance of the immature immune system allows these cells to engraft and proliferate. More than 30 pairs of such dizygous twins with blood group chimerism have been described.[45,48,56] Vascular anastomoses have been documented in fused placentas from dichorionic twins.[54,55]

Twin Transfusion Syndrome

The twin transfusion syndrome, a consequence of unidirectional blood shunting between the twins by unbalanced chorionic anastomoses, is one of the most serious hazards of monochorionic twining. The risk is greatest in diamnionic-monochorionic twins, in whom the incidence is 5% to 16%.[56,57] In its extreme form, both twins die.[58] The donor twin transfuses the recipient twin with every beat of its heart. The donor becomes malnourished, small, pale, and growth-retarded (Fig. 8-43), eventuating in a severely anemic fetus with high output heart failure. There is massive extramedullary hematopoiesis in virtually all organs, including the placenta. The recipient becomes plethoric and macrosomic, developing congestive heart failure with hepatomegaly due to volume overload (see Fig. 8-43). The pathology of the monochorionic placenta in twin transfusion syndrome reflects the circulatory status, the donor's portion being pale, hydropic, and immature, with

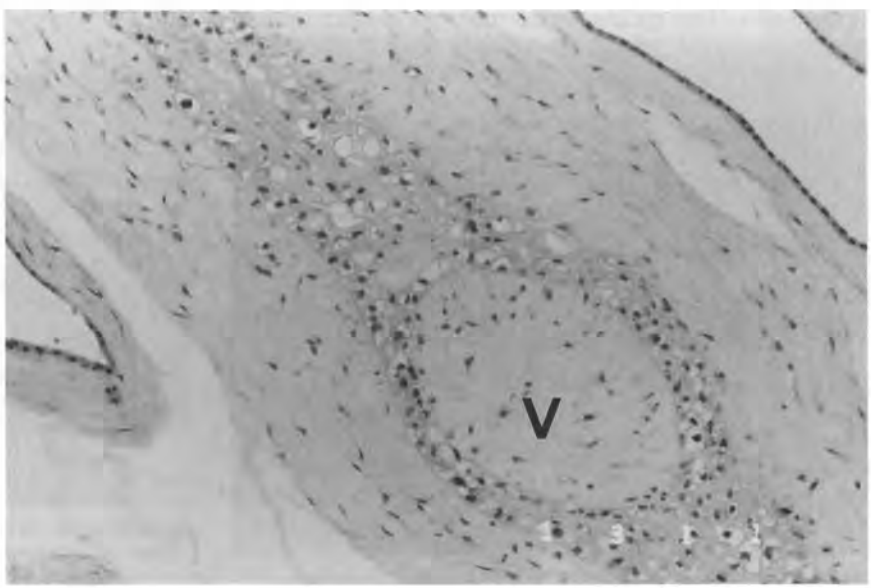

FIGURE 8-37 A residual villus (*V*) from the chorion laeve within the dividing septum confirms dichorionic placentation.

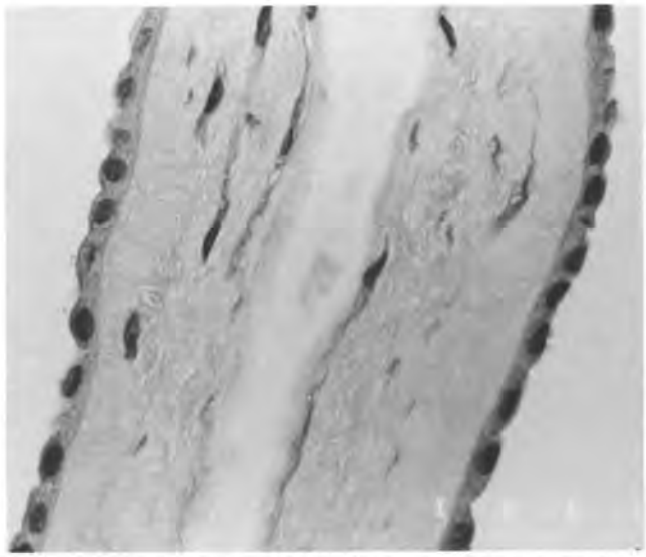

FIGURE 8-38 Dividing septum of the diamnionic-monochorionic placenta. The septum is composed of two layers of amnion and is totally devoid of chorion.

villous vessels packed with extramedullary hematopoiesis (Figs. 8-44 through 8-46). The recipient's portion is congested and more mature (see Figs. 8-44 and 8-45). On the death of one twin, usually the recipient, the shunting temporarily reverses and finally stops. The pathology observed depends on when the sequence is interrupted, either by delivery or fetal death, and, if death occurs, on the interval between fetal death and delivery.

Acardiac Twin

The formation of an acardiac twin, formerly called an *acardiac monster,* is another disastrous consequence of vascular anastomoses in monochorionic twins. As the name implies, this twin has no heart or has a rudimentary heart; often, the twin has no head (Fig. 8-47). The incidence of this abnormality is 1 in

FIGURE 8-39 Triplet placenta, triamnionic-trichorionic.

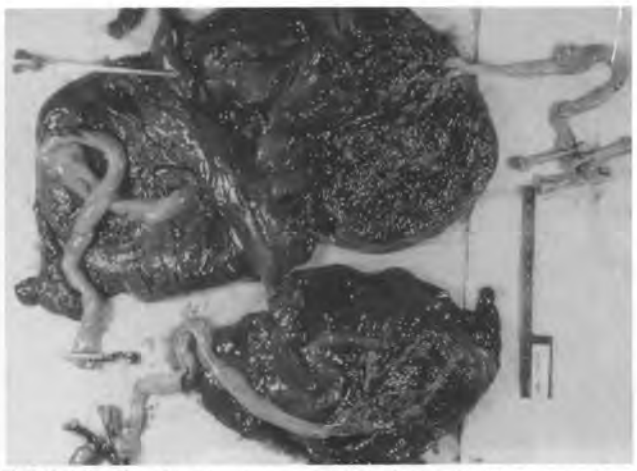

FIGURE 8-40 Quadruplet placenta. Three infants were liveborn, and one died in utero. The placenta of the stillborn fetus is indicated by the probe.

100 monozygous twin gestations or 1 in 30,000 deliveries.[48] Recent Doppler studies have proved the long-believed but previously unsubstantiated theory regarding the etiology of the acardiac twin: it is caused by a reversal of vascular perfusion.[59] The acardiac twin is perfused by vascular anastomoses from its partner's placenta rather than from its own placenta (see Fig. 8-47). This results in two problems: (1) the acardiac twin receives blood by the umbilical arteries rather than by the umbilical vein, and (2) the blood it receives is low in oxygen, having already passed through the co-twin's body. The lower extremities get the first pass of blood and are the most normal morphologically. Those structures perfused later are less normal, and the last on the line are overtly malformed, atretic, or absent (agenesis). Thus, the heart and head are usually substantially malformed or absent. Some acardiac twins are remarkably dysmorphic, composed of a ball with skin enclosing a mass of disorganized visceral, cartilaginous, and bony structures, prompting some to

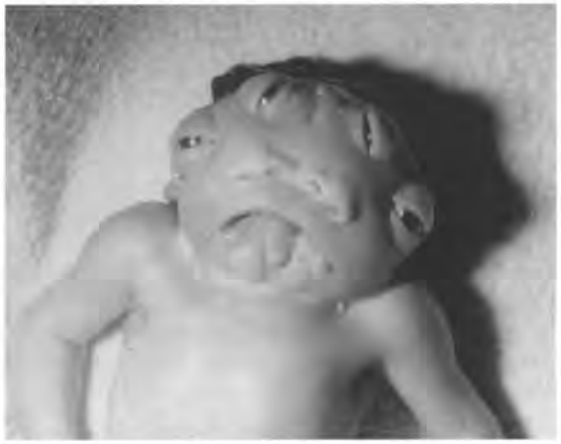

FIGURE 8-41 Anencephalic partially conjoined twins with duplication of head and upper spine. Remainder of fetal corpus was singleton. (Courtesy of Dr. Kristina Amyot, Albany, New York)

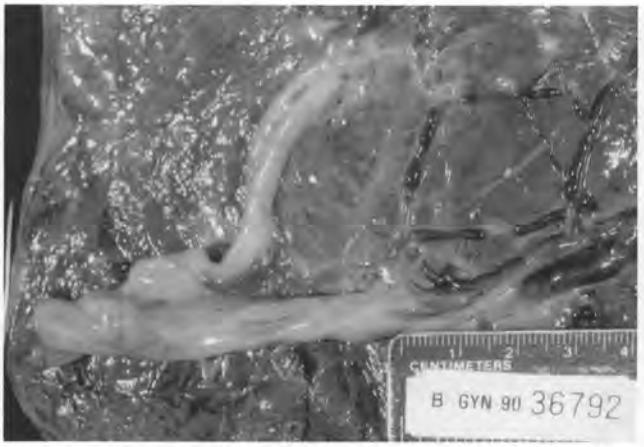

FIGURE 8-42 Forked umbilical cord in conjoined twins. The smaller cord contained a single umbilical artery.

question whether a birth certificate should be issued for the acardiac co-twin.

Fetus in Fetu

Fetus in fetu refers to a monozygous twin that grew within the body of its co-twin. It generally is found within the abdomen of its co-twin;[60] Dr. Shirley G. Driscoll saw such a fetus in the neck of a stillbirth (personal communication). Cytogenetic analysis of a pair of such twins demonstrated that the liveborn twin and included *fetus in fetu* had identical karyotypes.[60] Although both are monozygous twins, the acardiac is differentiated from the *fetus in fetu* by physical separation from its partner. Yet some *feti in fetu* contain morphologic anomalies that closely resemble those of acardiac twins.[59,60] It appears that these commonalities may result from a reversal of

FIGURE 8-43 Monozygous twins with twin transfusion syndrome. There is a marked discrepancy between fetal sizes. The donor twin (*left*) is small and undernourished. Oligohydramnios is reflected by positional deformation of right foot (talipes equinovarus deformity). The left foot was amputated during delivery. The recipient twin (*right*) is hydropic with visceromegaly.

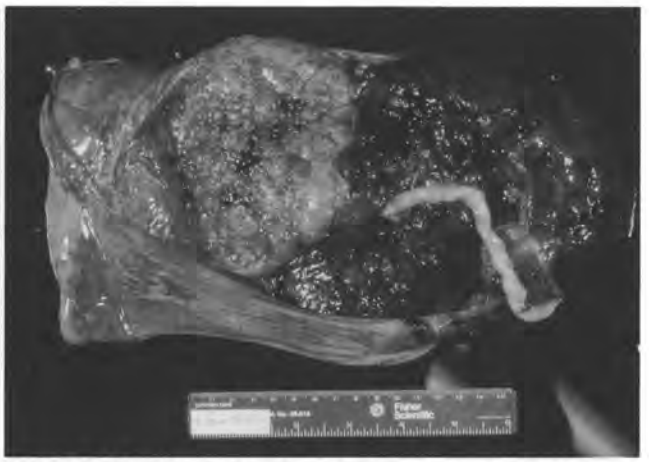

FIGURE 8-44 Maternal surface of monochorionic twin placenta in twin transfusion syndrome. The donor portion (*left*) is small, pale, and spongy. The recipient portion (*right*) is enlarged, congested, and hemorrhagic. The umbilical cord is reflected over the maternal surface.

blood perfusion patterns similar to that described in acardiac twins.

Congenital Malformations

Although twinning itself, particularly monozygous twinning, constitutes a reproductive error, additional congenital malformations are two to three times more frequent in twins than singleton.[61] Among twins, malformation rates are highest in monozygous twins. These malformations include anencephaly (see Fig. 8-41), holoprosencephaly, cloacal exstrophy, Vater association, sirenomelia, and sacrococcygeal teratoma. Velamentous insertion of the umbilical cord and single umbilical artery are seven times more frequent in twins.[48] It is possible that the single umbilical artery in twins results from perturbations

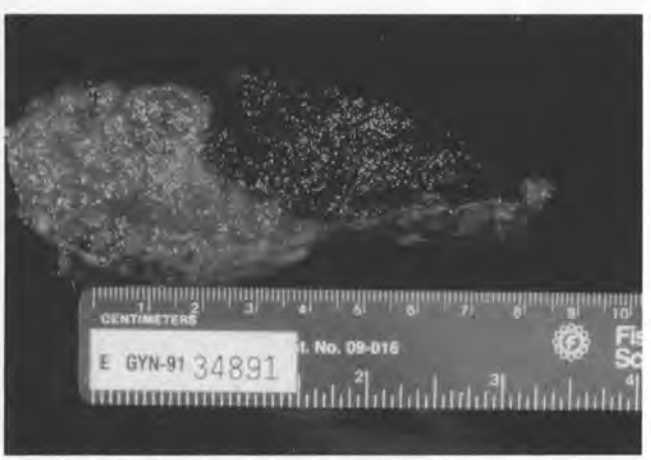

FIGURE 8-45 Cross section of placenta showing marked contrast of donor placental parenchyma (*right*) and recipient placental parenchyma (*left*). The same specimen is shown in Figure 8-44.

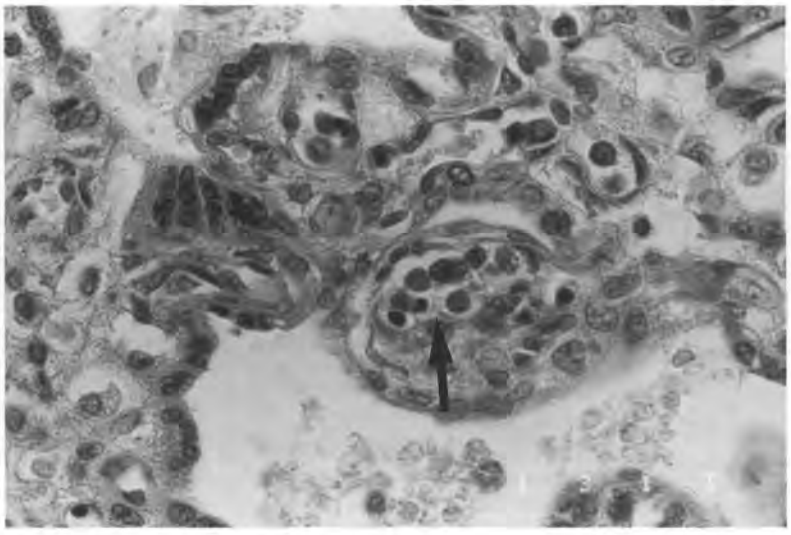

FIGURE 8-46 Donor placenta of twin transfusion syndrome with erythroblasts in fetal capillaries (*arrows*),

of placental growth and may not be associated with the same incidence and severity of congenital anomalies as in singletons.

Fetal Death in Utero

Perinatal mortality in recognized twin gestations is about 10%.[17] Early fetal loss is far greater. In a seminal ultrasonographic study, 71% of twin gestations diagnosed before 10 weeks' gestation were delivered as singletons.[62] One twin "vanished" before delivery. However, all twin gestations diagnosed after 15 weeks' gestation were delivered as twins. Overall perinatal mortality rates are roughly twice as high in monochorionic twins compared with dichorionic twins, with monoamnionic twins having the highest perinatal mortality rate.[63] Monoamnionic twins are prone to premature delivery, fetal death in utero (presumably related to cord accident), and lower birth weights.[64] In a recent study, monoamnionic monochorionic twins of more than 20 weeks' gestational age showed 65% double survival rate and 70% overall survival.[64] Similar fetal death rates of 10% to 40% have been reported for monoamnionic twins.[65,66]

Fetus Compressus and Fetus Papyraceous

When death occurs in one twin during the first 3 months, all fetoplacental remnants may be resorbed. Death later in gestation results in a compressed but intact fetus, encased within the membranes, termed *fetus compressus* (Figs. 8-48 and 8-49). Further desiccation of fetal tissues results in a paper-thin, macerated, mummy-like appearance, termed *fetus papyraceous* (Fig. 8-50). There is significant overlap between these two categories. At delivery of a term

FIGURE 8-47 Acardiac twin showing umbilical vasculature derived from placental chorionic vascular anastomoses. The lower body is more completely formed than the upper body. (Courtesy of Dr. David Genest, Boston, Massachusetts)

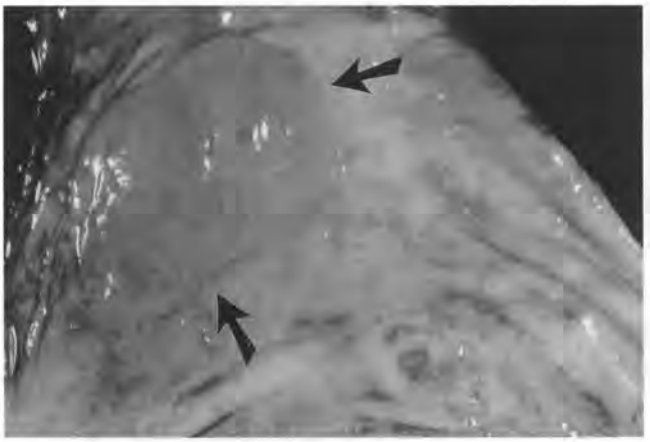

FIGURE 8-48 A fetus compressus enclosed within membranes (*arrows*). The extraplacental membranes of the surviving co-twin encircle the fetus compressus and its atrophic placenta.

FIGURE 8-50 Maternal surface of monochorionic twin placenta with one twin a fetus papyraceous. The portion of the placenta supplying the fetus papyraceous was thin, fibrotic, and avascular. The surviving co-twin was healthy at birth.

gestation in which there was early intrauterine death of a co-twin, it is often hard to find any evidence of the antecedent twin, sometimes called a "vanishing twin" (see Fig. 8-48). Radiographs of the placenta and membranes may be helpful in disclosing fetal bones. Microscopic examination of a thickening or focal opacity of the fetal membranes may reveal cartilage and bony remnants.[67]

Placental villi of the dead twin may be recognized, particularly if the fetus survived well into the later half of gestation. If fetal death occurs within 1 month of delivery, the villi most commonly are smaller than expected for gestational age, with large syncytiotrophoblastic knots and recanalized blood vessels. Villous vascular recanalization, termed *hemorrhagic endovasculitis,* initially was thought to be associated with and causal of, rather than incidental to, fetal death in utero.[68] By microscopy, recanalization of the chorionic stem vessels by proliferating endothelium results in the formation of small blood-filled channels (Fig. 8-51). The muscular coat remains relatively unperturbed. Apparent extravasation of entrapped and fragmented red blood cells creates a buckshot appearance. Subsequent studies demonstrated identical pathology in normal placentas that were maintained by artificial perfusion for a few days after delivery, implying that the initiating event is cessation of fetal circulation.[69]

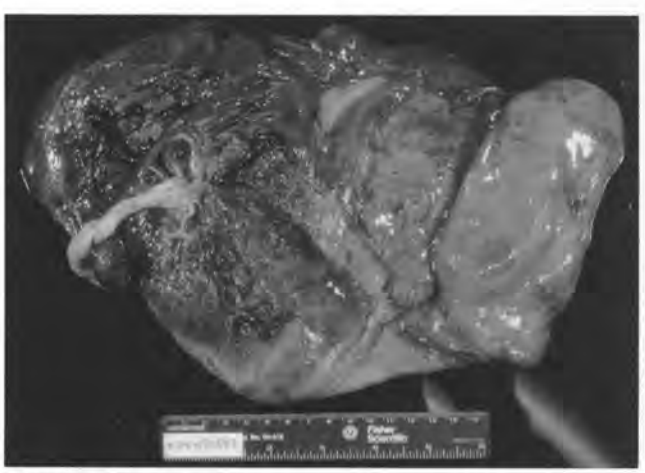

FIGURE 8-49 A fetus compressus that is slightly more mature than fetus in Figure 8-48 is enclosed within fetal membranes (*right*).

PLACENTAL INFECTIONS

General Concepts

The two main types of fetoplacental infection are *acute infection* and *chronic infection.* Infections may involve both placenta and fetus, or one alone. There are two main routes of placental infection: ascending and hematogenous. *Ascending infections* are transmitted by the vagina and cervix directly into chorioamnion or by intermediary endometrial decidua. *Hematogenous infections* are caused by maternal blood-borne pathogens entering the intervillous space and crossing into placental villi, or by infection of decidua, which leads to involvement of placental structures. Ascending infections tend to be acute, whereas hematogenous infections more commonly are chronic.

Acute Chorioamnionitis

Acute chorioamnionitis is the most common cause of preterm birth throughout the world. Although pathologists and clinicians both diagnose chorioamnionitis, they do not use the same criteria.[70] Clinically, chorioamnionitis is diagnosed based on signs and symptoms of maternal infection, such as fever and tachycardia without an extrauterine source, bacteria on cultures or Gram stain of amniotic fluid, or foul-

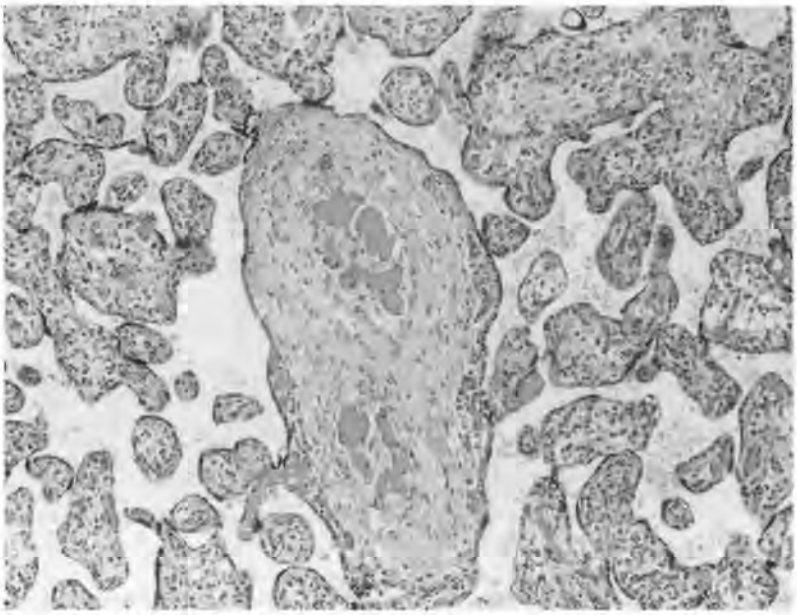

FIGURE 8-51 Vascular recanalization of chorionic stem vessel following fetal death in utero. Endothelial proliferation following cessation of fetal circulation results in repartitioning of vessel lumen.

smelling placenta at delivery. Clinically apparent chorioamnionitis has an incidence of 123 per 1000 births.

Pathologic diagnosis of chorioamnionitis, based on inflammatory cells in the placental membranes, occurs in 18% of term deliveries and in 32% of preterm deliveries.[71] Chorioamnionitis was found in 7.5% of placentas from elective cesarean deliveries performed before labor began.[71] In recent studies, 44%[72] to 72%[73] of placentas with histologically confirmed chorioamnionitis contained pathogenic organisms. This rate increased to 82% when there was a clinical diagnosis of chorioamnionitis.[73] In the latter study, more than 50% of pathogens were anaerobes.[73] The pathogens catalogued in individual studies vary depending on the patient populations, on whether anaerobic cultures were performed, and in some instances on the specific interests of the investigators. Organisms commonly isolated include *Staphylococcus epidermidis,* Gram-positive anaerobic cocci, group B β-hemolytic streptococcus, *Escherichia coli, Staphylococcus aureus, Listeria monocytogenes, Bacteroides* species, *Gardnerella vaginalis, Neisseria gonorrhoeae, Ureaplasma urealyticum,* and *Mycoplasma hominis.*

Chorioamnionitis is the most frequent pathologic diagnosis of placentas examined and is associated with increased neonatal morbidity in some studies.[72] However, chorioamnionitis is rarely associated with infants who develop signs of birth asphyxia (metabolic acidemia, seizures in the immediate newborn period, or Apgar scores of 3 or less)[24] in *term* gestations.[74] Recent studies suggest that no untoward fetal outcome is associated with chorioamnionitis if delivery is achieved within 24 hours.[75] Antepartum or neonatal death from intrauterine infection is uncommon. When it does occur, antemortem or postmortem blood cultures (in neonatal sepsis) and lung cultures (in congenital aspiration pneumonia) often reveal the same pathogens as those cultured from placenta or cervix. These results support the clinical view that chorioamnionitis is strongly associated with placental and, less commonly, fetal infections. One caveat must be added: as with other organ systems, all inflammatory lesions are not infectious in etiology. The possibility of membranitis resulting from noninfectious causes such as trauma or autoimmune processes cannot be excluded.

The controversy regarding rupture of membranes and chorioamnionitis is like the story of the chicken and the egg: Which came first? It seems logical that rupture of the membranes allows vaginal flora access to the amnionic cavity. It is just as plausible that infection may spread through contiguous structures to the amnionic cavity when the membranes are intact. Chorioamnionitis has been found with and without membrane rupture. The most widely accepted scenario is that chorioamnionitis weakens the membranes, inciting subsequent rupture.

Pathology of the Placenta in Chorioamnionitis

Grossly, chorioamnionitis is characterized by a heavy placenta with thickened, yellow-white to tan, cloudy membranes that may be foul-smelling (Fig. 8-52). A variety of pathologic terms have been used to describe its associated microscopic findings. *Acute chorioamnionitis* is defined by *maternal* leukocytic infiltrate of chorioamnion (Figs. 8-53 through 8-55). The term *chorionitis* may be applied to neutrophilic infiltrates confined to the chorion that have not crossed into the subamnionic connective tissue. The incidence and relevance of chorioamnionitis compared with chorionitis are not well characterized. Applicable factors may include the extent of membrane sampling, the proximity to the site of mem-

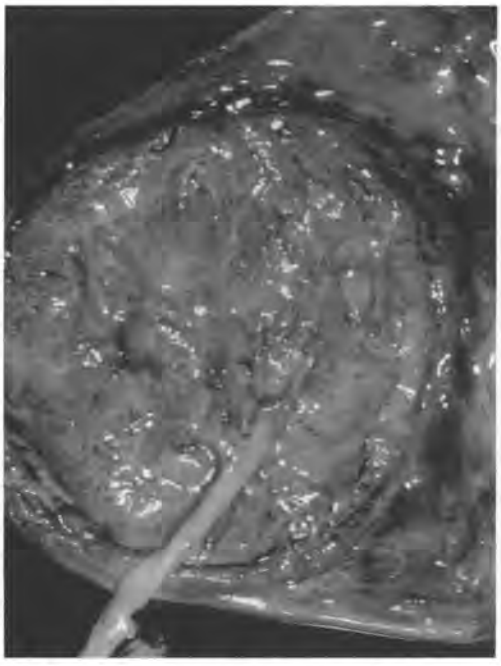

FIGURE 8-52 Fetal surface of placenta with chorioamnionitis. Membranes are thickened, opaque, and yellow-white.

brane rupture, and the duration of infection. Membrane rolls prepared from the site of rupture enhance the diagnostic yield.[76] Sometimes chorioamnionitis is not evident in the membrane roll, although it can be inferred by chorionic plate inflammation or umbilical vasculitis. Deciduitis, composed of neutrophils migrating from decidual vessels, invariably accompanies chorioamnionitis and chorionitis (see Fig. 8-53).

Umbilical Cord Inflammation (Funisitis)

Migration of *fetal leukocytes* through the muscular walls of the umbilical vessels, usually through the umbilical vein first and then through the arteries, is termed *umbilical cord vasculitis* or *funisitis* (Figs. 8-56 and 8-57). *Umbilical phlebitis* refers to inflammation involving the umbilical vein. A cord with extensive inflammation in which all the vessels and Wharton's jelly contain migrating fetal neutrophils may be described as umbilical panvasculitis and perivasculitis.

In long-standing umbilical inflammation, rings of degenerating inflammatory cells encircle the umbilical vessels in a pattern similar to an Ouchterlony immunodiffusion plate. Calcification may develop. Although most umbilical cord inflammation involves fetal leukocytes, in syphilis and toxoplasmosis the infiltrate may be lymphoplasmocytic. Although it is commonly believed that acute chorioamnionitis precedes funisitis, the temporal relations between these lesions are not well characterized. It is probably safe to assume that in most cases umbilical inflammation implies some sort of fetoplacental infection.

Chorionic Plate Vasculitis

In a fashion analogous to that of the umbilical cord, migration of *fetal leukocytes* from the chorionic vessels through the muscular walls toward the amnion constitutes *chorionic vasculitis*. It has been suggested that the hallmarks of ascending infection follow an ordered sequence: deciduitis, chorioamnionitis, and umbilical cord vasculitis, with chorionic plate vasculitis last in the sequence. This may be true, but there is no evidence documenting this sequence.

Villous Edema

Villous edema results from accumulation of excess stromal fluid and is characterized by a punched-out, Swiss-cheese appearance of the villous stroma (Fig. 8-58). It may be found in many pathologic states including those causing hydrops fetalis: blood dyscrasias, fetoplacental infection, and congenital anoma-

FIGURE 8-53 Extraplacental membrane roll showing chorioamnionitis with necrotic amnion (*arrow*) and dense neutrophilic infiltrate of amnion, chorion, and maternal decidua. Sclerotic villi of chorion laeve are visible (*right*).

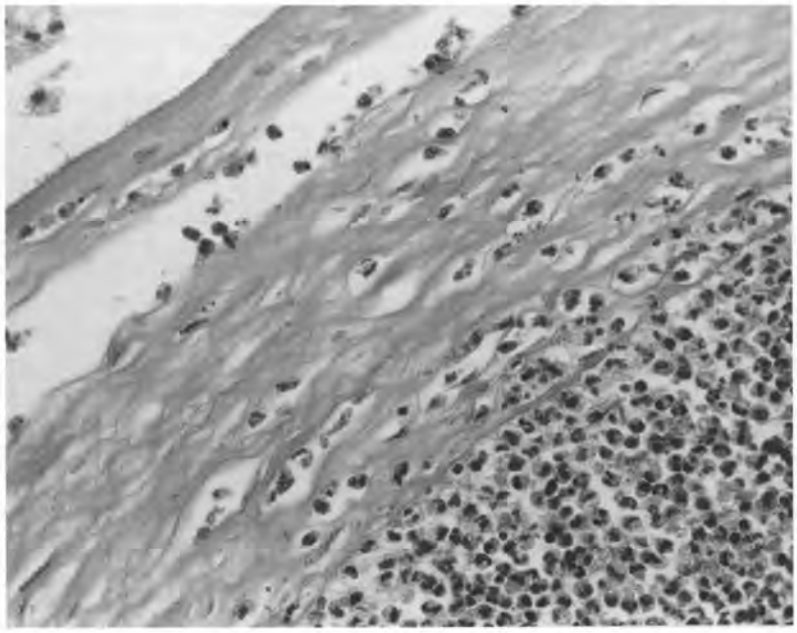

FIGURE 8-54 A high-power magnification of Figure 8-53 showing inflammation of the amnion. There is a large collection of neutrophils (*lower right*) between the amnion and underlying chorion (not pictured).

lies, particularly those impeding venous return to the heart. Naeye found villous edema in 87% of placentas with chorioamnionitis.[77] Its severity and extent were associated positively with the cord arterial blood pH values, low Apgar scores, vigorous resuscitation at birth, need for assisted ventilation later, frequency of hyaline membrane disease, and neonatal mortality.[77]

Acute Fetal Infection

Transplacental passage of particularly virulent organisms results in acute fetal infection (early onset neonatal sepsis) in 3 to 5 births per 1000. The fetus is infected by swallowing or aspirating infected amnionic fluid or hematogenously through infection of placental villi, umbilical cord vessels, or chorionic plate vessels. Fetal infection generally is manifested by congenital fetal aspiration pneumonia resulting from inhalation of infected amnionic fluid containing viable bacterial organisms (Fig. 8-59). Swallowing of infected fluid results in bacterial colonization of the gastrointestinal tract with subsequent parenchymal invasion producing enteritis, pancreatitis, or rarely gastritis. Bacteria can be identified by lung, blood, or spleen cultures.

Beta-hemolytic streptococcus is the prototypic organism for this condition. Despite early and appro-

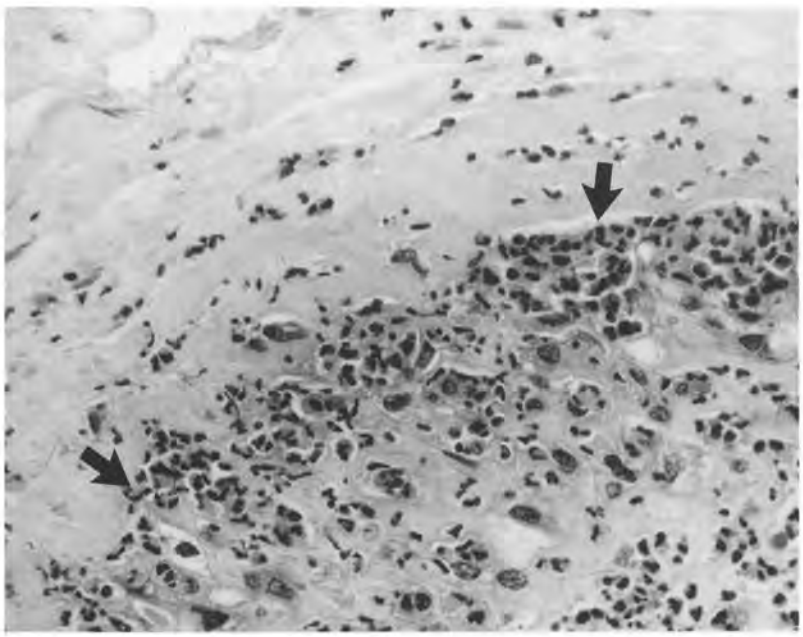

FIGURE 8-55 Chorioamnionitis showing maternal neutrophils invading from the decidua through the chorion (*arrow*) and into the amnion (*upper left*).

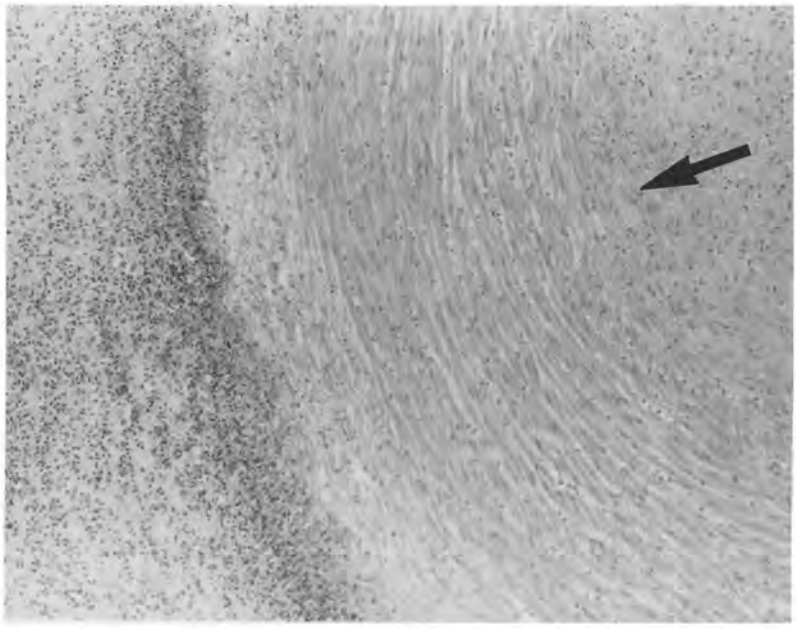

FIGURE 8-56 Umbilical cord with funisitis showing marked, concentric, neutrophilic inflammation of the umbilical artery with fetal neutrophils migrating from the vessel lumen to the amnionic cavity. The arrow indicates the direction of fetal neutrophilic migration.

priate pharmacotherapy, there is a high perinatal mortality rate associated with acute fetal infection, particularly in preterm neonates. Other commonly identified organisms include *Staphylococcus epidermidis, Escherichia coli* and *Ureaplasma urealyticum.*[78]

Chronic Fetal Infection

Chronic fetal infections may involve the fetoplacental unit or the fetus or placenta alone. In chronic fetoplacental infection, clinically apparent disease occurs in 1 to 2 births per 1000. The placental villi become colonized, and the infection may remain localized within the villi or may spread systemically by accessing fetal villous vasculature. With some infectious agents (eg, herpes simplex), the fetus may succumb to systemic disease in utero even though the delivered placenta shows minimal stigmata of infection.

Chronic Villitis

The hallmark of chronic placental infection is *chronic villitis.* Chronic villitis is defined by a mononuclear inflammatory cell infiltrate involving villi (Fig. 8-60). It may be focal or diffuse and is often basal. The infiltrate consists mostly of lymphocytes and mononuclear histiocytic cells, with occasional plasma cells.

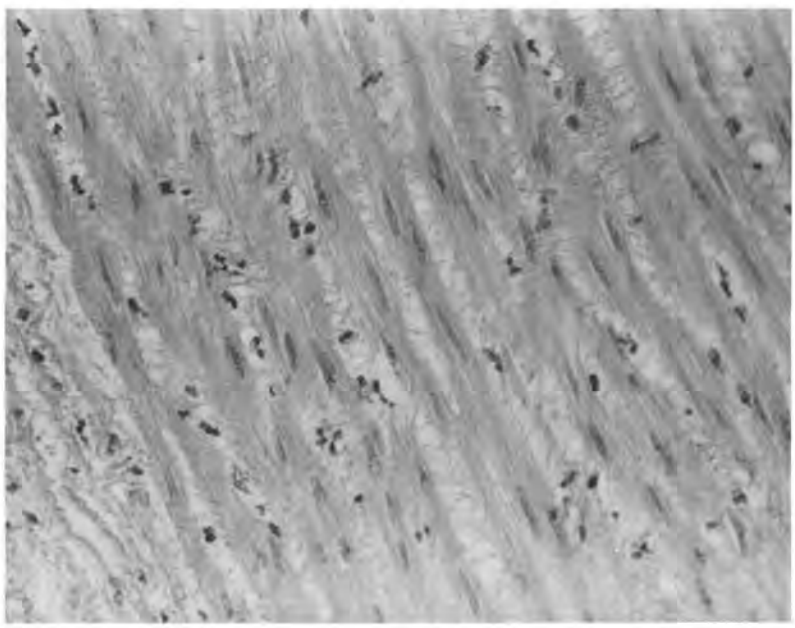

FIGURE 8-57 High-power magnification of same specimen as Figure 8-56 showing fetal neutrophils between the muscle fibers of the umbilical artery.

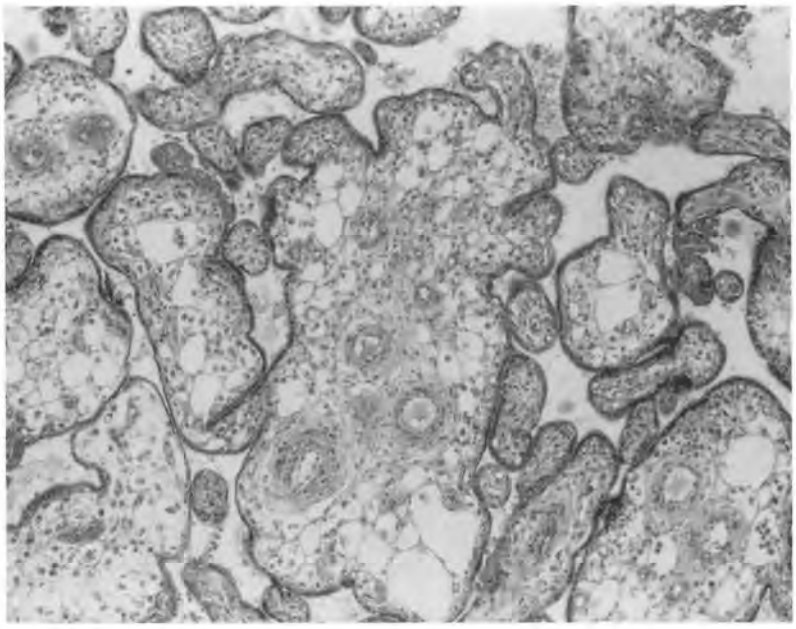

FIGURE 8-58 Villous edema involving a second-trimester placenta. Villous stromal edema forms collections of clear spaces, giving a "Swiss cheese" appearance to the stroma.

Immunohistochemical studies of these lesions demonstrate predominantly helper T lymphocytes and activated macrophages that react with monoclonal antibodies to D-related human leukocyte antigen.[79]

The incidence of chronic villitis depends on the population studied and the number of sections examined per placenta. In general, about 10% of placentas contain chronic villitis. Prevalances of 13.6%[80] and 7.6%[81] have been reported. In a recent study examining an average of 13.4 blocks per placenta, chronic villitis was identified by histology or immunohistochemistry in 76% of normal term placentas.[82]

Although chronic villitis is a common and distinct pathologic lesion, pathogens are rarely found. Characteristic infiltrates are associated with some agents, but inferences of a specific organism based on villous histopathology in the absence of diagnostic pathogens remains speculative. Assays of umbilical cord immunoglobulin M (IgM) values as an index of fetal infection document increased IgM values in less than 10% of cases with chronic villitis.[83] This has led some to proffer that chronic villitis, although definitely associated with infection in some placentas, is most commonly the result of an immunologic reaction.[79] Others counter this notion by suggesting that the immunologic reaction results from, or is associated with, the placental infection.

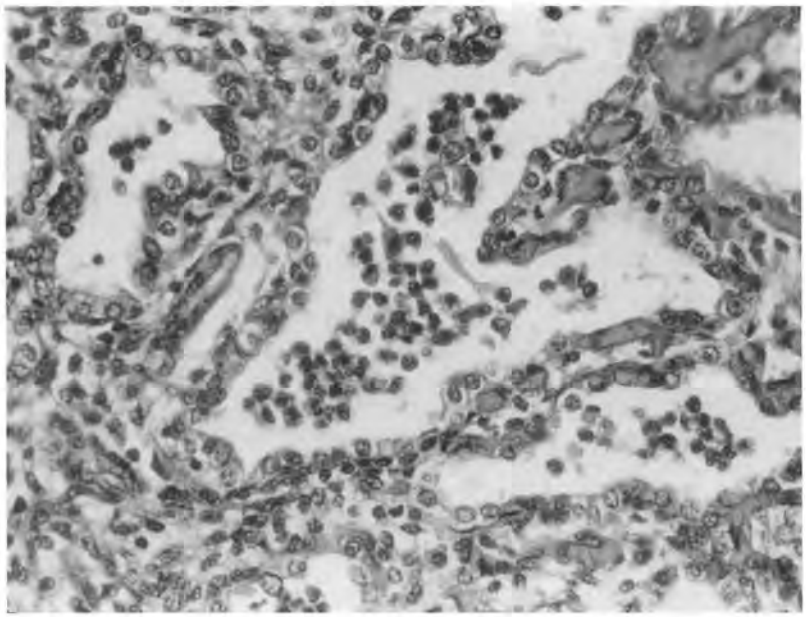

FIGURE 8-59 Fetal lung with congenital aspiration pneumonia. Numerous maternal neutrophils and fetal squames are aspirated into fetal alveoli. Interstitial fetal neutrophils were present elsewhere.

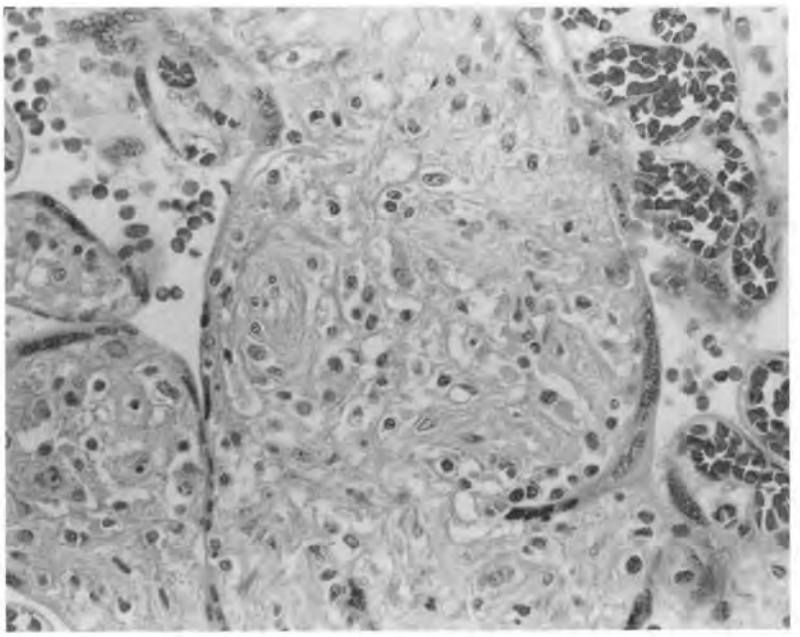

FIGURE 8-60 Term placenta with focus of chronic villitis characterized by expanded villous stroma with mononuclear cell infiltrate composed of lymphocytes and histiocytes. Plasma cells may be seen in some cases.

Chronic Chorioamnionitis

Chronic chorioamnionitis, a condition of uncertain etiology, is defined by chronic inflammatory cells within the chorioamnion (Fig. 8-61). In a recent study of chronic chorioamnionitis, no specific pathogen was identified.[84] Chronic chorioamnionitis with chronic umbilical panvasculitis and perivasculitis is commonly associated with spirochetal infections, such as by *Treponema pallidum.*

Chronic Fetal Infection

The most common signs of fetal infection in utero include growth retardation and preterm birth. An enlarged placenta (placentomegaly), particularly with hydrops or chronic villitis, suggests fetal infection. Autopsy findings in fetal or neonatal death due to infection include hydrops, jaundice, purpura, skin rashes, eye lesions, hepatosplenomegaly, central nervous system anomalies, and parenchymal plasma cells.

Specific Pathogens

Bacterial Organisms

Beta-Hemolytic Streptococcus. More than 50% of serious neonatal infections are caused by group B

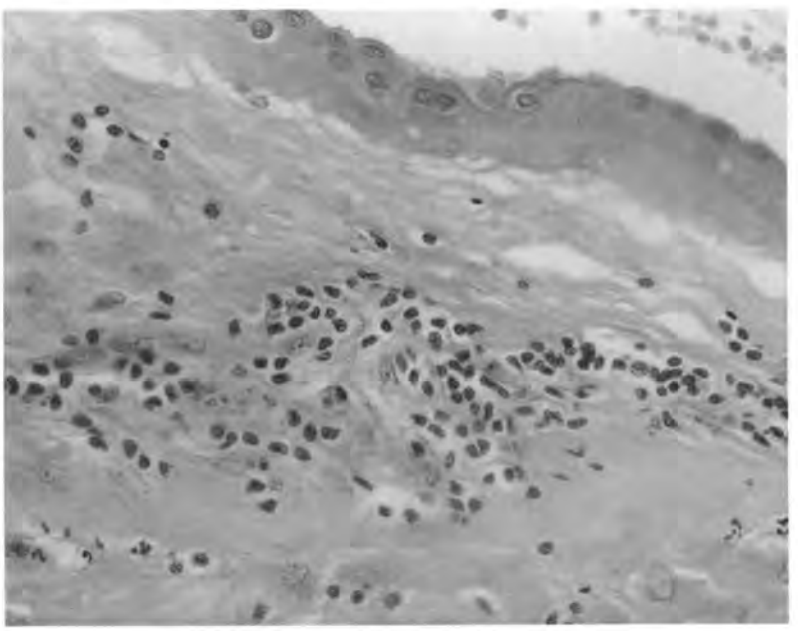

FIGURE 8-61 Chronic chorioamnionitis characterized by lymphocytic infiltrate of the chorion and amnion.

β-hemolytic streptococcus. Maternal colonization ranges from 5% to 50% with perinatal transmission rates of 0.5%.[85] In the United States, 3 of every 1000 infants develops a streptococcal congenital aspiration pneumonia, sepsis, or meningitis.[86] Despite appropriate treatment, the combined neonatal morbidity and mortality rate associated with group B β-hemolytic streptococcal infection exceeds 50%. Although β-hemolytic streptococcus is the most common offender, *Staphylococcus aureus* is moving to the top of the list at some centers. Novak and Platt found chorioamnionitis in 64% of placentas associated with early onset group B streptococcal neonatal sepsis, funisitis in 27%, and organisms on the fetal membranes in 41%.[87] Villous edema was present and was focal in 23% and diffuse in 18%.[87]

Grossly, placentas with streptococcal infection have cloudy membranes and may be heavy for gestational age. Occasionally, the membranes are yellow-white, opaque, and foul-smelling. Early infection, particularly in immature placentas, may be inapparent on gross examination.

Microscopy shows chorioamnionitis ranging from mild or moderate chorionitis to severe, necrotizing chorioamnionitis with numerous bacterial colonies (Fig. 8-62; see also Figs. 8-53 and 8-54). The umbilical cord shows panvasculitis and perivasculitis, often with concentric rings of inflammatory cells and many necrotic surrounding cord vessels (see Figs. 8-56 and 8-57). The most intense inflammation is directed toward the amnionic surface. In some instances, cocciform bacterial colonies sit atop the amnion with little underlying inflammation (see Fig. 8-62). We have seen rare cases of fetal death from congenital aspiration pneumonia with culture-proved β-hemolytic streptococcus infection of lung and spleen without any significant placental inflammation. The villi in streptococcal infections are often edematous and have a Swiss-cheese appearance (see Fig. 8-58). Septic intervillositis and fetal chorionic vasculitis with thrombus formation occur in advanced cases.

Listeria Monocytogenes. *Listeria monocytogenes* is a diphtheroid bacillus responsible for outbreaks of listeriosis. It has been associated with abortions and fetal death in cattle and other animals, including humans. It is a facultative intracellular bacterium whose eradication requires macrophage- and T-cell-mediated immunity. Growth of *L. monocytogenes* is enhanced by cold temperatures. Maternal infection usually occurs after consumption of milk, milk products such as cheese, and meat products contaminated by infected manure. Maternal infection results in decidual seeding that spreads to involve the placenta. Intrauterine fetal infection carries a high perinatal mortality rate. In an infected fetus or a stillborn or liveborn delivered with disseminated disease, the condition is termed *granulomatosis infantiseptica.*[88]

Placental pathology is virtually pathognomonic in fully developed listeriosis. Macroscopically, multiple, small, yellow-white foci dot the cut surfaces of the placental villi. By microscopy, these consist of multifocal, villous micro- to macroabscesses with villous necrosis; smaller lesions show acute villitis (Fig. 8-63). Neutrophils and fibrin surround affected villi, and a characteristic acute villitis develops. Numerous neutrophils accumulate in an artificially created subtrophoblastic space and then invade the villous stroma. Occasionally, multinucleated giant cells are formed in villous abscesses (see Fig. 8-63). Sometimes there is chorioamnionitis, but it is far less extensive than in the average β-hemolytic streptococcal chorioamnionitis. The diphtheroid organisms of lis-

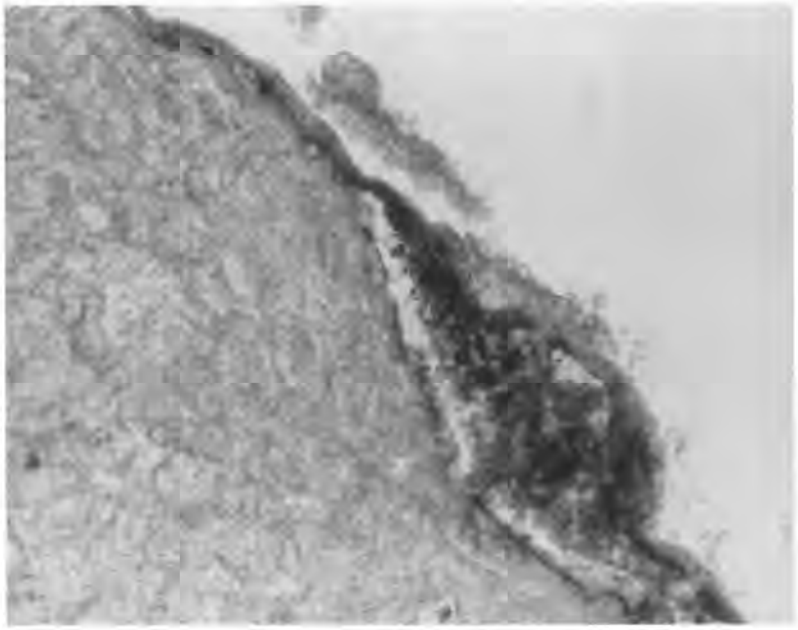

FIGURE 8-62 Amnion of extraplacental membranes showing a large subepithelial collection of cocciform bacterial colonies.

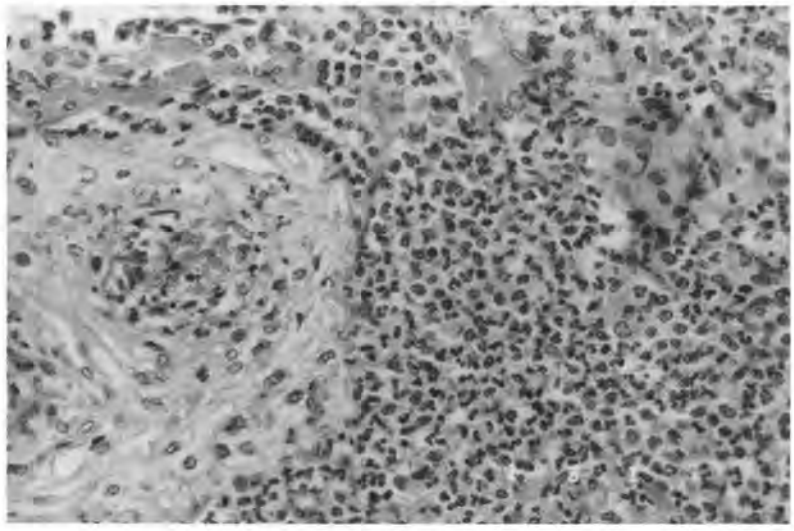

FIGURE 8-63 Acute intervillositis with slight acute villitis in a placenta infected with *Listeria monocytogenes*. There is a massive accumulation of maternal leukocytes in the intervillous space, with focal acute inflammation involving the villus (*left*). A poorly formed multinucleated giant cell can be seen (*upper right*).

teriosis seem to accumulate and proliferate preferentially in the amnion overlying the chorionic plate or in the villous abscesses, and, although difficult to identify in some cases, they are best highlighted by Brown-Brenn or Gram stains. Cold-enrichment of the placenta (ie, storage in the refrigerator overnight or on a long weekend) favors demonstration of organisms.

Syphilis. Syphilis, a disease thought to be relegated to historical texts, has made a dramatic resurgence within our communities. The smallest of us have taken the lion's share of the burden, since unrecognized congenital syphilis may be lethal in utero.

Treponema pallidum, the spirochete that causes syphilis, is hematogenously transmitted to the placenta during maternal spirochetemia. Although it was suggested that infection could not occur in early gestation, this is not the case. Grossly, placentas infected with syphilis are pale, bulky, edematous, and heavy. Focal lesions are not recognized.

Early infection with *T. pallidum*, as with *Toxoplasma* species, may invoke no inflammatory response. Abundant spirochetes, best seen on Warthin-Starry stains, are found in Wharton's jelly and are totally devoid of surrounding host reaction. As infection continues, a chronic necrotizing funisitis develops,[89] often containing lymphocytes, plasma cells, and much karyorrhectic debris. Necrotizing funisitis is not specific for syphilis because it may develop in viral and bacterial infections. The placenta reflects the spirochetal infection and the associated fetal anemia by showing a characteristic chronic villous vasculitis (Fig. 8-64). Villous capillaries contain circulating nucleated red blood cells and erythroblasts.

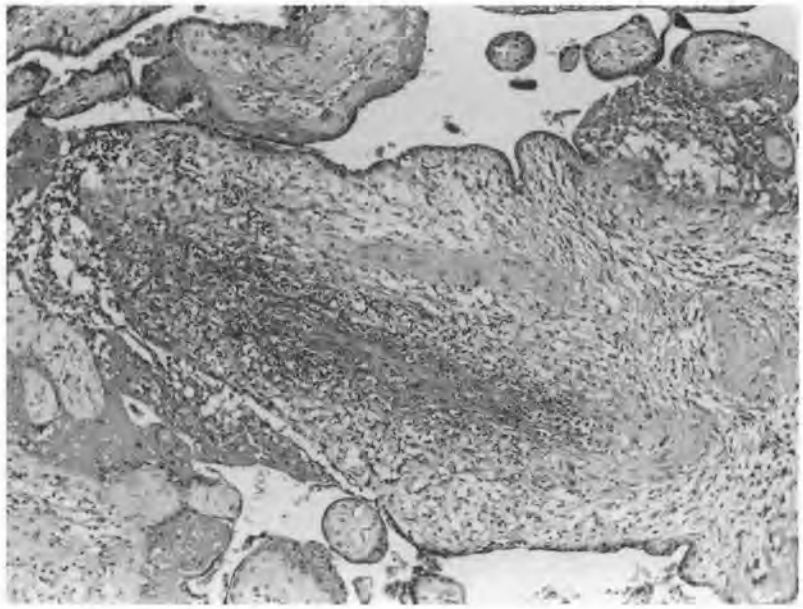

FIGURE 8-64 Necrotizing villous vasculitis in a near-term placenta infected with syphilis. Villi are expanded by a mononuclear cell infiltrate that is centered on and destroying vessel walls. The hydropic fetus was stillborn.

Other Bacteria, Genital Mycoplasma, Ureaplasma, and Chlamydia. Placental infections caused by virtually all known fetal and neonatal pathogens have been described. The literature is replete with case reports demonstrating the pathology associated with specific agents. In *Ureaplasma urealyticum, Mycoplasma hominis,* and *Chlamydia* placental infections, the placental pathology is nonspecific, usually consisting of chorioamnionitis and funisitis. Further data regarding these agents can be found elsewhere.[78]

Viral Infections

Cytomegalovirus. Cytomegalovirus (CMV), one of the *Herpesviridiae,* is the most common cause of perinatal infections, with an incidence ranging from 8 to 22.2 per 1000 births. In the United States, 3000 to 4000 infants are born each year with symptomatic disease.[90] In many, congenital CMV infection is unrecognized. Late sequelae include unilateral or bilateral deafness, blindness, and mental retardation. Virus reaches the placenta by hematogenous dissemination during the viremic phase of primary or recurrent maternal infection. A maternal-fetal transmission rate of 20% to 50% has been reported.[91] Although fetal infection may occur at any time during gestation, the greatest sequelae are associated with infection in early and mid-gestation, particularly when the mother is unsensitized. Neonatal CMV infection is common and is associated with minimal or no sequelae.

Grossly, the placenta infected with CMV may be small, normal, or large for gestational age. In recent and severe infection, it is commonly edematous, pale, and heavy, particularly when fetal anemia is present. In early infections, the placental weight may be normal.

CMV is a major cause of chronic villitis. Microscopically, CMV is characterized by a necrotizing villitis, described by some as "acute" and by others as "chronic" (Figs. 8-65 and 8-66). It is "acute" in the sense that the infection is active and ongoing, and "chronic" because lymphocytes and plasma cells constitute the inflammatory infiltrate. The villi are edematous and show foci of ongoing, active villous destruction with thrombosis of villous capillaries, necrosis of stroma and overlying trophoblast, lymphocytic and plasmacytic infiltration, hemosiderin deposition, calcification, and stromal hyalinization. Over time, there is villous stromal scarring (see Figs. 8-65 and 8-66). The severe, destructive lesions may be focal, with remaining villi relatively normal or slightly hypercellular. CMV is diagnosed by finding the pathognomonic violaceous, intranuclear and cytoplasmic inclusions in endothelial cells, stromal cells, Hofbauer cells or, much less commonly, trophoblast. The stromal Hofbauer cells may be prominent, showing unusual configurations.[92,93] Villous endothelial destruction results in an acute vasculitis that progresses to an obliterative vasculitis. Viral inclusions may be found in decidua, amnionic macrophages, and amnion.[94] The stromal inflammatory cells have been characterized as T cells and fetal plasma cells, the latter secreting IgG and IgM.[92] If no inclusions are identified in initial sections of necrotizing villitis, additional villous tissue should be examined microscopically. Newer approaches to the diagnosis of viral placentitis include immunoperoxidase staining, in situ hybridization, and polymerase chain reaction.

In long-standing lesions, viral inclusions may be inconspicuous or absent. The necrotizing deciduitis associated with CMV placentitis supports the notion that fetal CMV infection may result from reactivation of latent virus in the endometrium.[95] There has been

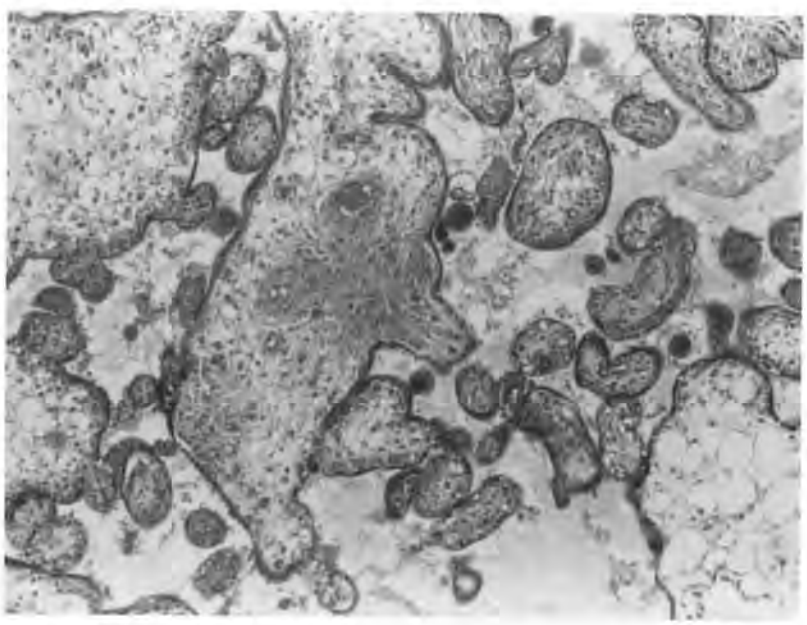

FIGURE 8-65 Acute necrotizing villitis in cytomegalovirus infection of placenta. Note the villous edema of the surrounding villi. The central villus depicts two foci of villous necrosis.

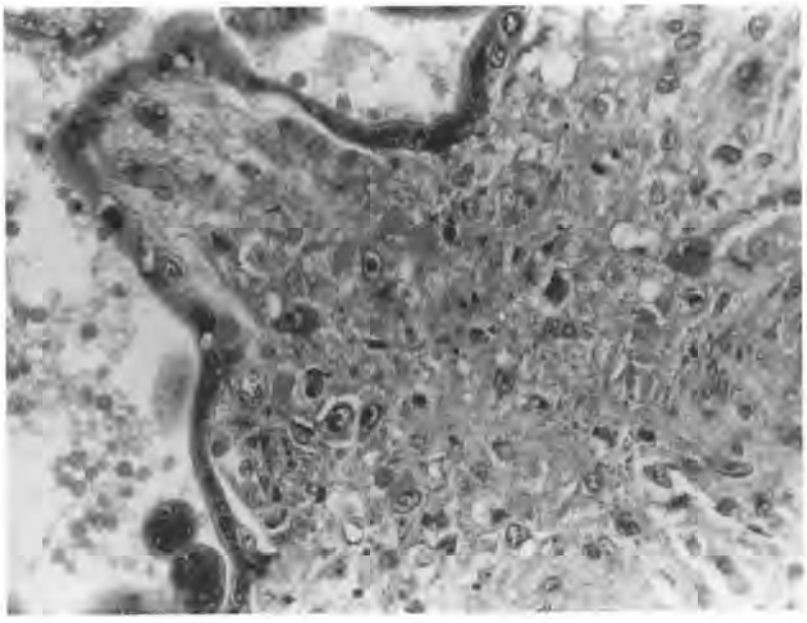

FIGURE 8-66 A magnification of Figure 8-65 demonstrating effects of cytomegalovirus infection of placenta. Villous stroma is necrotic and eosinophilic, and stromal cells contain both "owl-eye" intranuclear and granular cytoplasmic viral inclusions.

some correlation between the extent and severity of placental involvement and the clinical outcome.[96] In lethal congenital CMV infections, the fetus is jaundiced and anemic and has hepatosplenomegaly. Viral inclusions are found in the epithelia and mesenchyme of many fetal organs, including the lung, thymus, thyroid follicles, pancreatic and bile ducts, glomeruli, and renal tubules. Central nervous system involvement may result in hydrocephalus, microcephaly, and microcalcifications. Surviving children may have cataracts, chorioretinitis, and deafness.

Herpes Simplex Virus Types 1 and 2. The incidence of neonatal herpes simplex virus (HSV) infections is estimated to range from 1 in 2500 to 1 in 10,000 deliveries.[97-99] Eighty percent of HSV infection in the neonate is of type 2, and 20% is type 1. In the United States, 16.4% of adults are seropositive for HSV type 2.[100] Asymptomatic shedding of virus occurs in 0.35% to 2.3% of pregnant women.[101,102] Fetal transmission of HSV in a primary maternal infection is associated with an increased frequency of spontaneous abortions, congenital malformations, and stillbirth.[97,98] Maternal seropositivity for HSV type 2, but not for HSV type 1, reduces the neonatal transmission of HSV type 2 infection.[102] Recurrent infection is the most common form of infection during pregnancy.[100,102] Perinatal transmission occurs in 33% of women with a primary infection, compared with 3% with reactivated infection.[101] HSV is most commonly acquired intrapartum, although rare cases of hematogenous dissemination have been documented. Neonatal HSV infection is associated with a 50% mortality rate despite treatment with vidarabine or acyclovir.[103]

The hallmarks of antenatal HSV infection of the placenta are not well characterized. Even when the fetus is stillborn and when autopsy discloses multifocal destructive hepatic and pulmonic parenchymal lesions, placental findings may be minimal and nonspecific (Fig. 8-67). Typical ground-glass nuclear inclusions of HSV in the placenta are rare.[104,105] Inclusions have been demonstrated in chorion.[105] Garcia described a placenta infected with HSV that showed intranuclear inclusions in decidual cells, chronic chorioamnionitis, chronic lymphoplasmacytic villitis with Langhans'-type giant cells containing necrotic foci centered on villous vessels, and villous trophoblast necrosis with fibrin deposition.[106] A recent study of neonatal HSV infections depicted villous stromal cells containing viral antigens by immunohistochemistry and virions by electron microscopy.[107] Others have reported acute or subacute necrotizing membranitis with amnionic necrosis,[96,104,108] mononuclear or plasmacytic chronic chorioamnionitis,[108] agglutination of villi, fibrinoid necrosis or thrombosis of villous vessels, bland placental necrosis,[96,109] and necrotizing deciduitis. Benirschke illustrates a remarkable plasmacytic infiltrate of membranes with a subamnionic blister.[17] Herpetic placentas can be identified by polymerase chain reaction,[110] and infected cells may be mapped by directly labeled oligonucleotide probes.[111]

The infant may develop vesicular skin lesions, hepatoadrenal necrosis, and meningoencephalitis. In lethal cases, the fetal lung and liver show extensive geographic necrosis with residual ground-glass nuclear inclusions at the periphery of necrotic zones (see Fig. 8-67).

Varicella. Chickenpox is caused by infection by varicella-zoster virus, another member of the *Herpesviridiae*. Congenital fetal infection results from intrauterine transmission of maternal infection by viremia

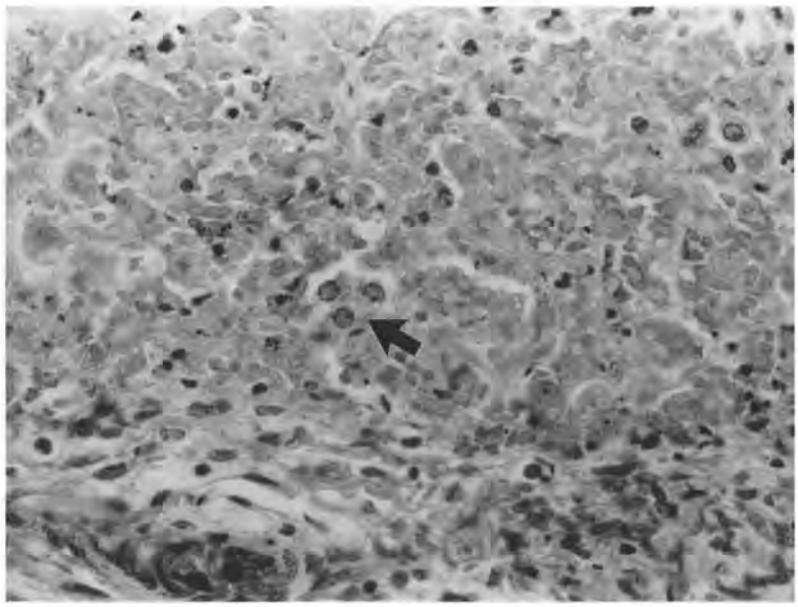

FIGURE 8-67 Neonatal liver in congenital herpes simplex virus 2 infection. There were large, sharply demarcated areas of hepatic necrosis containing ground-glass nuclear inclusions (*arrow* indicates three involved cells). The infant died 3 weeks after birth from a systemic herpetic infection.

in an unsensitized gravida. Primary infection occurs at an incidence of 1 to 5 per 10,000 pregnancies,[112,113] with perinatal transmission in 26%.[114] Infection in the first trimester may be associated with chorioretinitis, cataracts, cutaneous scars, and limb hypoplasia.[115,116] Neonates infected antepartum may be born with the chickenpox rash or may develop it within a week or so after birth.

Placental findings depend on the duration of infection and, as in all viral infections, the extent to which the placenta is sampled for microscopic examination. In one case, villous involvement produced grossly recognized "rice seeds."[117] Varicella may be characterized by acute necrotizing villitis or granulomatous villitis. Early lesions are composed of focal, acute, necrotizing villitis that is similar to but not associated with the degree of destructive necrosis found in CMV infection. Even in these early lesions, multinucleated histiocytic giant cells may be striking (Fig. 8-68). Along with eosinophilic intranuclear viral inclusions, these cells help to differentiate varicella from CMV placentitis. As the disease progresses, an extensive granulomatous villitis develops.

Parvovirus B-19. Parvovirus B-19 was discovered serendipitously in 1975 during screening of blood for hepatitis B.[118] It is the cause of the childhood exanthem erythema infectiosum, also known as *fifth disease.* It also causes aplastic crisis in chronic hemolytic anemia, a chronic rheumatoid arthritis, and

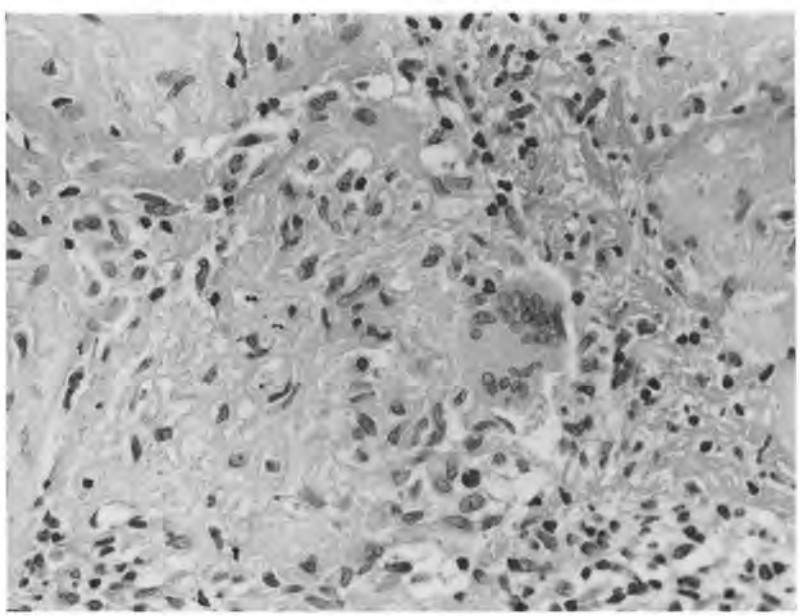

FIGURE 8-68 Placenta in congenital varicella-zoster infection. Villous outlines are obscured by a dense, fibrinous exudate containing mononuclear cells and a multinucleated giant cell. Villous parenchyma showed slight liquefaction. Apart from this focus, the other villi showed only chronic villitis. The baby was hospitalized for chickenpox 6 days after delivery.

chronic bone marrow suppression. Its association with spontaneous abortion is well-described in the veterinary literature. In humans, it has been reported to cause spontaneous abortions and nonimmune hydrops fetalis due to aplastic anemia or myocarditis. Congenital parvovirus infection has been diagnosed and treated successfully in utero.[119] In children, apart from fever, catarrhal symptoms, and a rash, it is a benign disease with anemia occurring only rarely.

Placental infection is most likely to occur by a hematogenous route in a nonsensitized woman. In a study of 10 women with clinically proved disease, fetal transmission was documented in 3 cases, and anomalies were described in 1 fetus.[120] The placental pathology mirrors the degree of fetal anemia. The placenta may be heavy, bulky, and pale. Fetal villous capillaries contain numerous nucleated red blood cells with erythroblasts. Erythropoiesis may be found in the villi. Parvovirus infection involves red blood cell precursors and nucleated red blood cells. Infected nuclei are enlarged and distended by a homogeneous, glassy-red to violaceous, intranuclear inclusion. These inclusions are like those of HSV infection except that they are more violaceous. It is uncommon to see these affected cells in the placenta, even when there is extensive fetal involvement. We have seen similar inclusions in developing fetal organs such as the lung, thyroid, kidney, and skeletal muscle. It appears that the inclusions may involve a variety of immature fetal mesenchymal and epithelial cells, not only the red blood cells within these structures.

Depending on the fixative used, similar-appearing cells are found in early first-trimester placentas in which the nucleated red blood cells are derived from the yolk sac. It is not clear whether all such placentas contain parvovirus infection, or whether this unusual nuclear appearance is the result of erythroblastosis of yolk sac or villous stromal origin. Similarly, certain decalcifying solutions used in our institution for bone marrow decalcification create intranuclear inclusions in erythroid precursors that are indistinguishable from parvovirus. After excluding other causes of hemolytic and nonhemolytic hydrops, parvovirus infection should be considered if a hydropic placenta contains numerous nucleated red blood cells. In formalin-fixed tissues, pathognomonic viral inclusions are sufficient for a diagnosis of parvovirus infection. If parvovirus is suspected, serologic analysis of maternal or fetal IgM and IgG for parvovirus-specific antibodies or a polymerase chain reaction for parvoviral DNA in placenta or fetal tissues should be performed.

Hepatitis B. Hepatitis B infection may be transmitted hematogenously to the placenta and fetus. Asymptomatic hepatitis B infection was found in 0.66% of women in a low-risk group.[121] Although the infection usually develops postnatally, presumably by enteric infection, rare transplacental infection has been documented, suggesting that the placenta serves as an intermediary.[122]

Placental findings in congenital hepatitis B infection are primarily related to elevated maternal bilirubin levels. Khudr and Benirschke described bilirubin in chorionic macrophages and villous Hofbauer cells.[123] In a severe case, villous tissue curetted from an icteric woman was deep yellow-green, and the villi had bile pigments by microscopy.[17] Apart from placental cells stained by bile and villous edema,[124] specific placental parenchymal changes do not seem to occur in most cases of hepatitis B infection.

Human Immunodeficiency Virus (HIV). The World Health Organization estimates that more than 3 million women of reproductive age are infected with human immunodeficiency virus.[125] Maternal to fetal transmission of the human immunodeficiency virus type 1 (HIV-1), which causes the acquired immune deficiency syndrome (AIDS), occurs in about 24% to 30% of cases.[126,127] Perinatal transmission increases as maternal CD4 lymphocyte counts decrease.[128] It is estimated that 0.05% of all neonates born in the United States are infected with the HIV virus.[128] Within a group of high-risk women, 7.1% were found to be antibody-positive.[129] Neonatal seroconversion in congenital infection may not occur until after infancy. In a recent study, measurement of neonatal HIV-IgA levels showed a high overall sensitivity and specificity for determining neonatal infection.[130] Life expectancy is severely reduced both for the mother and infected neonate. Treatment is supportive at best, and no cure or preventive vaccine has been developed.

Although many investigators have examined carefully the placentas of women with known HIV positivity or AIDS, few morphologic findings have been described. This may reflect an inability to determine which placentas are infected, or it may be that infection results in minimal placental pathology. Jauniaux and colleagues studied placentas from 49 HIV-infected mothers and found no distinct lesions.[131] This agrees with our experience. Lewis and associates found HIV in trophoblast, Hofbauer cells, and embryonic blood cell precursors using immunocytochemistry and in situ hybridization.[127] Villous destruction does not seem to occur in HIV infection. As with all human tissues, full protective precautions must be taken; in placental examination, this includes gown, gloves, mask, and eye protection.

Rubella. The highest incidence and greatest severity of sequelae result from congenital rubella infection during the first trimester. As with all viral placentitides, the pathology depends on the severity and stage of maternal or placental infection. In acute maternal infection, the placenta tends to be smaller than normal. Gross lesions are not observed. Microscopy shows focal necrotizing villitis with acute villous endovasculitis; the latter is characteristic of congen-

ital rubella infection.[132] Severe endothelial necrosis of villous vessels may fragment red blood cells but is not associated with villous stromal hemorrhage. Additional vascular pathology includes endothelial cushions and old calcified thrombi.[93] Obliteration of villous blood flow results in shrunken, avascular villi, and villous agglutination may result from trophoblast injury with subsequent fibrin deposition. Eosinophilic cytoplasmic viral inclusions may be found in endothelial cells, stromal cells, macrophages, and trophoblast.[133,134] In contrast to CMV placentitis, the villitis of rubella is not associated with stromal hemosiderin deposition or villous edema.

The fetal sequelae of congenital rubella infection depend on the gestational age of the fetus. Fetal death in utero may occur when infection occurs in the first trimester. Just as in the placenta, the virus is vasculotropic, destroying fetal blood vessel walls and resulting in ischemia and parenchymal organ abnormalities. Nonlethal sequelae of early infection include the following:

Congenital malformations, particularly involving the cardiovascular system
Intrauterine growth retardation
Interstitial pneumonitis
Hepatomegaly with parenchymal necrosis
Focal extramedullary hematopoiesis
Periportal round cell infiltrates
Bile stasis and jaundice
Splenomegaly with anemia, purpura, and thrombocytopenia
Small, fibrotic spleen
Cataracts
Deafness
Microcephaly and mental retardation.

Plasma cells in fetal lymph nodes connote premature B cell maturation. Widespread immunization of children for rubella has decreased the incidence of overt congenital rubella infections. The long-term effects of live vaccines remain unknown. Reinfection of previously immunized women has been reported.[135,136]

Other Viral Infections. In general, viral infection of the placenta results in villous destruction with mononuclear and plasma cell infiltrates, in viral inclusions with or without giant cells, and in villous agglutination. In *mumps* infection, presence of the paramyxovirus can be inferred by eosinophilic cytoplasmic inclusions in villous fibroblasts and decidual cells.[137] Maternal-fetal transmission of *measles* infection was associated with fetal stillbirth in one reported case. Measles viral antigens were found in the syncytiotrophoblast and decidua by immunoperoxidase and immunofluorescence studies.[138] There were agglutination of villi with trophoblast necrosis, diffuse intervillous fibrin, and mononuclear cells.[138] Placental infection by the *Epstein-Barr virus* in maternal infectious mononucleosis resulted in perivasculitis and necrotizing deciduitis, acute chorionitis, villous edema, necrotic trophoblast, and obliterative villous vasculitis with mononuclear and plasmacytic inflammation.[139,140]

No specific placental lesions are described for the picornavirus infections of *poliomyelitis, ECHO virus*, and *Coxsackie B virus.* Garcia and colleagues reported villitis and intervillositis in placentas with ECHO 33 and ECHO 27 infection.[141] Placental hydrops resulting from severe fetal myocarditis may develop in Coxsackie B infection.

Parasitic and Protozoan Infections

Toxoplasma gondii. In developed nations, the most common parasitic infection that the placental pathologist is likely to encounter is the coccidian *Toxoplasma gondii.* Cats serve as the primary hosts. Cultures in contact with cats, particularly cat litter boxes and outdoor sandboxes, are at risk for toxoplasma from fecal contamination by oocysts. Humans, sheep, and pigs become hosts for the secondary cycle. Congenital toxoplasmosis is more common in France due to the consumption of infected raw meat (ie, steak tartare or undercooked meat) containing cysts and tachyzoites. Transplacental transmission in seronegative women results in primary fetal infection in about 50% of women. Fetal infection in early pregnancy may result in severe abnormalities, including hydrocephalus, seizures, central nervous system calcifications, hydrops fetalis, and chorioretinitis leading to blindness. Transmission is more common later in pregnancy, with the consequences being less severe. In infected infants, new lesions may appear late into childhood.[142]

Placental *Toxoplasma* infection may be overlooked by the most experienced obstetric pathologist. Congenital *Toxoplasma* infections often are missed because of the total lack of inflammation surrounding the cysts and because high-power examination (×200 to 400) is required to identify the organisms.

Grossly, the placenta in toxoplasmosis is similar to that of villitis in general: heavy, edematous, and pale. Some have a normal weight. Microscopic examination discloses villitis, with a spectrum of lesions ranging from subtle lymphocytic chronic villitis with minimal villous fibrosis to a proliferative villitis with lymphoplasmocytic infiltrates eventually terminating in fibrosis. Villous endarteritis and focal necrosis may occur.[143] The encysted organisms are 200 μm in diameter and can be found in the amnion, the subamnionic macrophages of the chorioamnionic membranes, the umbilical cord, and even within the trophoblast (Fig. 8-69).[144] Most often, the cysts and sometimes even the newly released organisms remain totally unperturbed within the subamnionic connective tissue. Occasionally slight calcification and single cell necrosis trumpet their presence. Over time, rupture of cysts with extrusion of free organisms sparks a chronic lymphoplasmocytic infiltrate. A chronic funisitis may develop in the cord. The released sin-

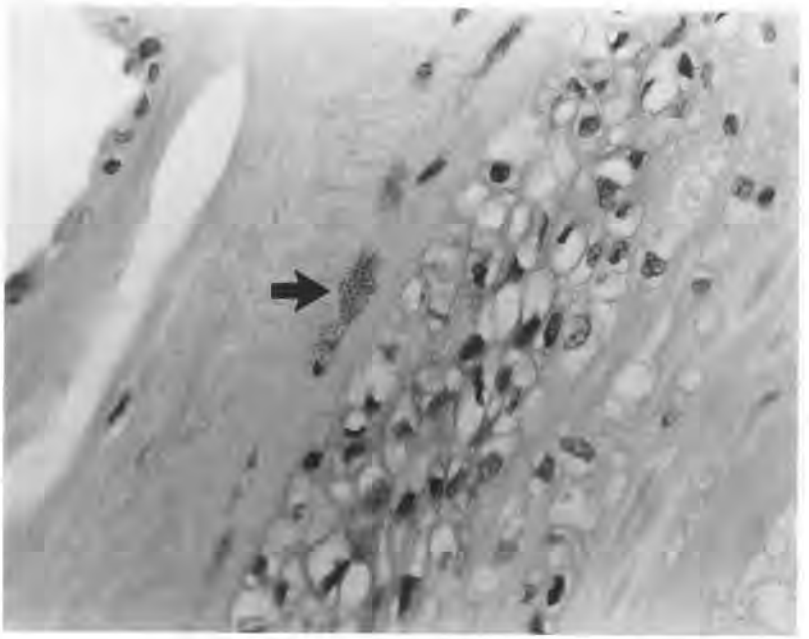

FIGURE 8-69 Congenital toxoplasmosis infection disclosing encysted organisms within macrophages (*arrow*) of subamnionic connective tissues of extraplacental membranes.

gle, small, crescent-shaped organisms are 2 to 4 μm by 4 to 8 μm. Periodic acid-Schiff stains are positive. The decidua shows chronic lymphoplasmacytic inflammation and rarely contains parasites.

Chagas' Disease. Maternal–fetal transmission of Chagas' disease, caused by infection with *Trypanosoma cruzi,* occurs by hematogenous dissemination to the placenta. The trypanosome infects trophoblast and Hofbauer cells, and then enters the fetal circulation. Infected placentas are heavy and pale, showing a chronic destructive villitis with fibrin deposition and intervillositis, ending in villous destruction with scarring.[145,146]

Villitis of Unknown Etiology

Unfortunately, all discussions of chronic villitis must end with villitis of unknown etiology. In placentas with genuine chronic villitis, failure to identify the offending agent by morphologic recognition of the organism, by history, or by serologic studies occurs in 6% to 33.8% of cases.[147] In 1973, Altshuler coined the term *villitis of unknown etiology* to describe such cases.[148] Russell found focal chronic villitis of unknown etiology in 7.6% of placentas.[81] It has been associated with fetal growth retardation and perinatal mortality and may recur in subsequent gestations.[80,81,149] It is not clear whether the villitis is due to an unknown infection or is the result of an immune-mediated phenomenon.[147] Some suggest that an unrecognized infection invokes an immune response, whereas others opine that the entire process is immunologic and devoid of an infectious component.[147,150] Clearly, further investigation is warranted.

Fungal Infections

Organisms of *Candida* species are the most common fungi to involve the placenta and its adnexa. This infection is described and illustrated earlier in this chapter in the section on the umbilical cord.

PARENCHYMAL PLACENTAL LESIONS

Infarcts

In the placenta, as in other tissues, infarcts occur when perfusion stops. Inciting events in the placenta include alterations in maternal blood flow through the maternal uterine arteries and premature separation of the placenta from its implantation site. Most infarcts result from disturbances in uteroplacental perfusion and are associated most frequently with maternal disorders such as preeclampsia. In preeclampsia and other diseases, decidual vasculopathy (atheromatous change) of the uterine vessels diminishes the luminal diameter, obstructing and ultimately preventing adequate placental perfusion. At this point, infarction occurs. Much less commonly, infarcts are associated with a retroplacental hematoma. Infarcts may occur anywhere within the villous parenchyma, but they are more frequently basal and peripheral.

Placental infarcts are uncommon in immature placentas. At term, small infarcts occupying less than 5% of the total parenchyma may be found in 25% of placentas and are inconsequential.[151] The significance of a placental infarct depends on many factors: most important are the number and extent of the in-

FIGURE 8-70 Placenta with wedge-shaped marginal infarct.

farcts. When more than 10% of the placenta is infarcted, fetal well-being is jeopardized. There is a rough correlation between the quantity of infarcted villous tissue and the degree of fetal compromise.

Placental infarcts take on a variety of gross and microscopic appearances. On gross examination, a recent, fresh infarct is well-demarcated, beefy red, and more firm than the surrounding parenchyma (Fig. 8-70). In fresh infarcts, demarcation from normal parenchyma is more easily palpated than visualized. As the infarct ages, it becomes brown and then turns yellow to white. The oldest infarcts look like white scars.

On microscopic examination, the villi in a recent infarct are crowded together, diminishing the normal intervillous space (Fig. 8-71). The villous vessels are congested and dilated, and blood may extravasate into the stroma. Trophoblast nuclei become hyperchromatic, and karyorrhexis ensues (Fig. 8-72). Scant fibrin is deposited at the periphery of the infarct and in the intervillous space. Usually there is a minimal to slight maternal neutrophilic infiltrate surrounding the infarct, although it may be totally absent.

Less commonly, infarcts result from decreased maternal villous perfusion due to the interposition of an underlying retroplacental hematoma. Blanc has suggested that a villous infarct associated with a retroplacental hematoma evinces similar but slightly different histology: The intervillous space between infarcted villi is enlarged and congested when the infarct is due to retroplacental hematoma and is collapsed when it is a result of maternal vasculopathy.[152]

As the infarct ages, there is a loss of nuclei in the trophoblast and villous stromal and vascular cells, and the dead villi eventually become pale pink on hematoxylin-eosin staining (Figs. 8-73 and 8-74*A*). The fetal stem artery of the infarcted villi thromboses. Later, the infarct consists of pale white scaffolds of "ghost villi" outlined by fibrin. Viable villi adjacent to an infarct are small, containing more multinucleated syncytial giant cells than those distant from the infarct.

Infarcts are more frequent when there is a maternal history of preeclampsia or hypertension.[151] Large areas of infarcted villi encircling small foci of preserved villi are most commonly associated with severe obstruction of maternal blood flow to the placenta, which may result in intrauterine death, fetal hypoxia, or growth retardation.[151] Most commonly, the pathology of the affected maternal vessels is not evident in the decidua underlying the infarct, although occasionally the superficial decidual vessels show characteristic vasculopathic changes. The identification of decidual vasculopathy is enhanced by examination of the decidua parietalis (in the extraplacental membranes). If present, decidual vasculopathy suggests a similar affliction in some retroplacental implantation-site vessels.

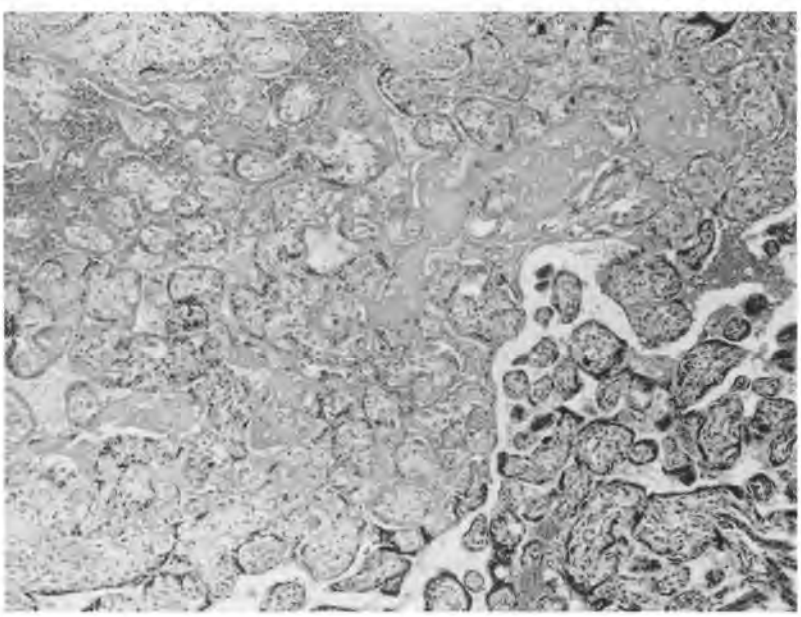

FIGURE 8-71 Recent villous infarct, low-power magnification, characterized by villous crowding with interspersed fibrin and early trophoblast necrosis.

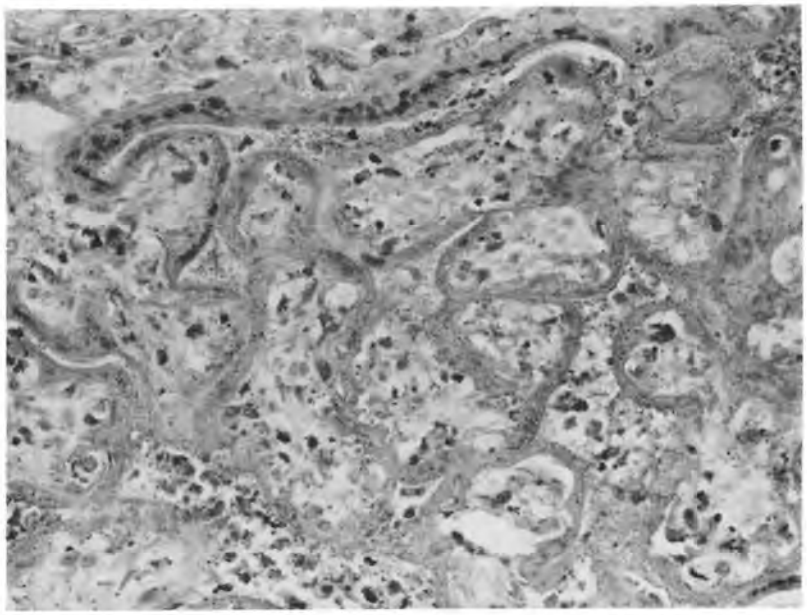

FIGURE 8-72 Recent villous infarct (higher power magnification of specimen in Fig. 8-71), showing focal pallor of trophoblast nuclei, trophoblast necrosis, villous stromal necrosis with nuclear debris, and fragmentation of nuclei in intervillous space.

Fibrin Deposition

Intervillous fibrin deposition occurs in 22% of term placentas and, less commonly, in preterm placentas or in those pregnancies complicated by preeclampsia, essential hypertension, or diabetes mellitus.[12,13,153] Most term placentas contain some subchorionic fibrin grossly recognizable as tiny, white to yellow subchorionic streaks on the fetal surface. Many have a 1- to 2-cm plaque of subchorionic fibrin that is inconsequential. Naeye has correlated an absence of subchorionic fibrin with fetal hypoactivity, cerebral palsy, low childhood intelligence quotient, fetal hypotonia, trisomy 21, and short umbilical cord.[154]

Microscopically, fibrin is often found in the subchorionic space. Not uncommonly, tiny foci of fibrin deposition surround scattered villi within the placental parenchyma. It is believed that eddy currents are greatest under the chorionic plate, resulting in some destruction of the trophoblast surface with adherence of fibrin and platelets. Occasionally, villi underlying a subchorionic plaque become entrapped within the fibrin. Although fibrin is acellular, it may entrap maternal red blood cells. Fibrin deposits on villous trophoblast and intermediate trophoblast (from the placental septa and cell islands) invoke trophoblastic proliferation to some extent, possibly as a reaction to the fibrin stranglehold (see Fig.

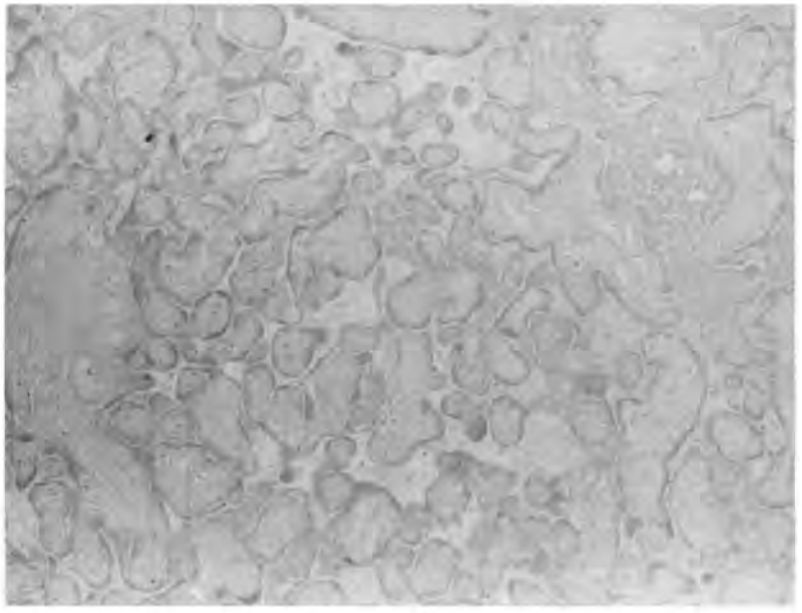

FIGURE 8-73 Remote villous infarct, low-power magnification, with bland homogenization of villous stroma and few trophoblastic nuclear outlines remaining.

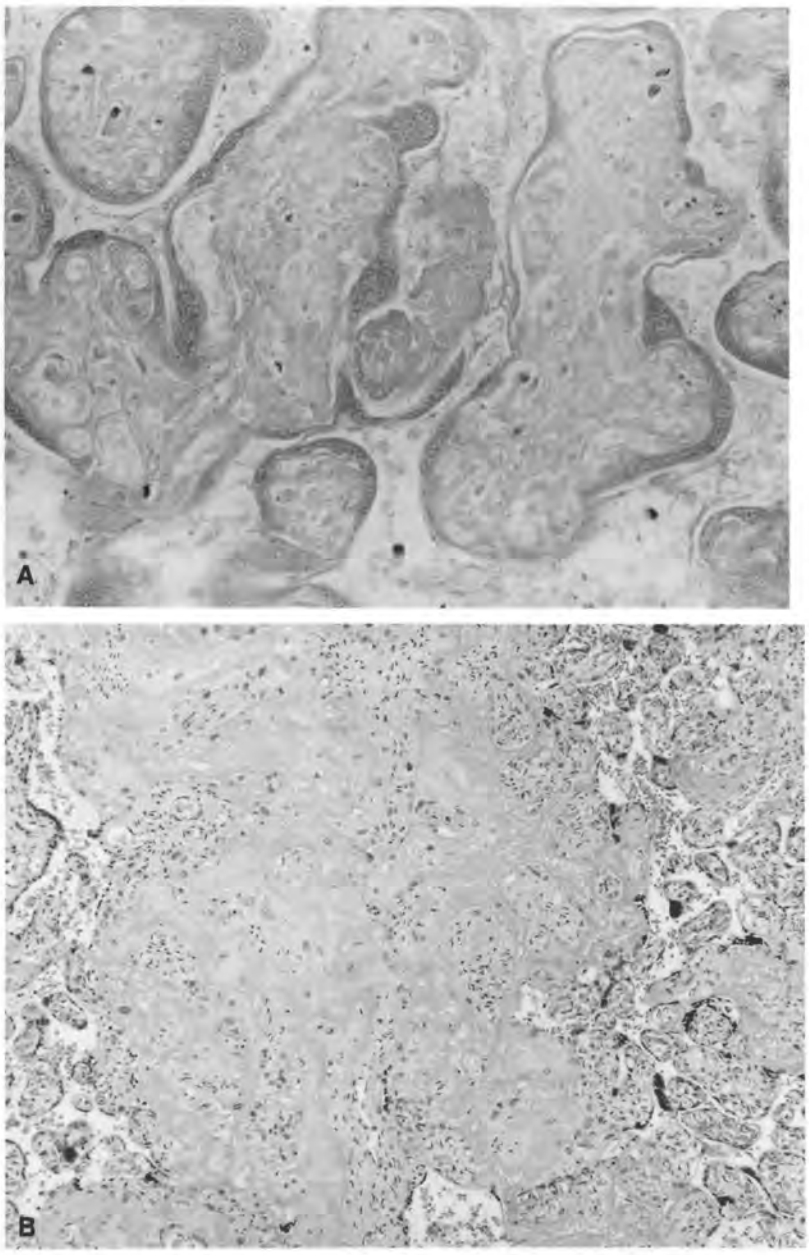

FIGURE 8-74 **(A)** Remote villous infarct (higher magnification of specimen in Fig. 8-73) showing crowded villi, amorphous stroma with few cellular outlines, and ghost nuclei of syncytiotrophoblast. **(B)** Intervillous fibrin deposition: fibrin encircles normal villi, invoking a proliferation of intermediate trophoblast.

8-74*B*). The proliferating trophoblast, usually intermediate trophoblast, may mimic primary and metastatic malignancy by its cytologic atypia and mitotic activity.

There are unusual states of extensive fibrin deposition in which virtually all the villi are surrounded by a fibrin blanket, described by some as "massive intervillous fibrin deposition" (the so-called glitter infarct).[155] It is often associated with excessive decidual fibrin deposition with chronic inflammation and infarction of basal villi, termed *maternal floor infarction.*[17] There appears to be a relation between the two, because they often coexist in the same placenta. Both are associated with fetal growth retardation and poor perinatal outcome, and they may recur in subsequent pregnancies. In many, the fetus is stillborn. It is unclear whether the stillbirth is the result of, or etiology for, both maternal floor infarction and massive intervillous fibrin deposition.

Placental Hematomas and Abruption

Placental hematomas occur at many sites. Grossly, a hematoma may be *retroplacental, marginal, retromembranous,* or *subamnionic* (Fig. 8-75). All are derived

FIGURE 8-75 Retroplacental hematoma (*upper left*) and marginal hematoma (*lower left*) viewed from maternal surface of placenta.

from maternal blood except for the subamnionic hematoma, which is fetal in origin and often results from undue traction on the umbilical cord to hasten placental delivery. Microscopic examination of placental hematomas shows layering of fibrin and red blood cells (Fig. 8-76).

The most dangerous of the placental hematomas, *massive retroplacental hematoma*, usually results from a tear in a decidual spiral artery. The leaking blood forms a large retroplacental blood clot. The hematoma may be large enough to dissect the placenta entirely off the decidua, resulting in a complete abruption and total loss of placental perfusion, which, without immediate delivery, leads to fetal death in utero. If the placenta remains partially attached (partial abruption), the villous tissue overlying the abruption usually becomes infarcted.

Retroplacental hematomas occur in 4.5% of placentas.[13] The incidence increases threefold in pregnancies complicated by preeclampsia.[13] Retroplacental hematomas, particularly when large, are associated with increased perinatal mortality. A diagnosis of retroplacental hematoma may be obvious in a placenta with attached hematoma, or it may be inferred based on the amount of clotted blood received with a placenta in the specimen container, or based on the presence of a large, fixed, smooth depression on the maternal surface indicating its former location. All retroplacental hematomas should be described, measured, and recorded. Although there is often an association between a retroplacental hematoma and a clinical diagnosis of abruption, the two do not go hand in hand. A clinical diagnosis of abruption may be associated with a placenta showing no pathologic evidence of hematoma, and the corollary is true: a retroplacental hematoma may not be associated with a clinical diagnosis of, or sequelae from, abruption.

The so-called marginal sinus bleed or tear is a small hematoma that sometimes develops along the placental margin (see Fig. 8-75). The blood spreads centrifugally, extending retromembranously and retroplacentally. A large marginal hematoma may result in antepartum maternal hemorrhage with "port wine" amnionic fluid. If the hematoma is long-standing, there may be hemosiderin deposition in macrophages of membranes and decidua. This hematoma is of no clinical significance to the fetus.

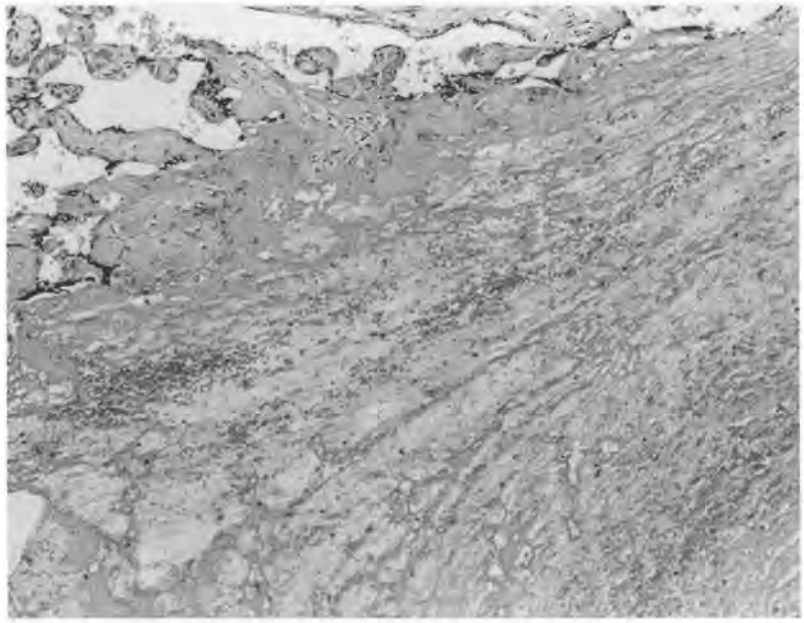

FIGURE 8-76 Microscopy of retroplacental hematoma showing layers of fibrin and red blood cells separating basal plate from maternal decidua. This case was associated with a clinical diagnosis of abruption.

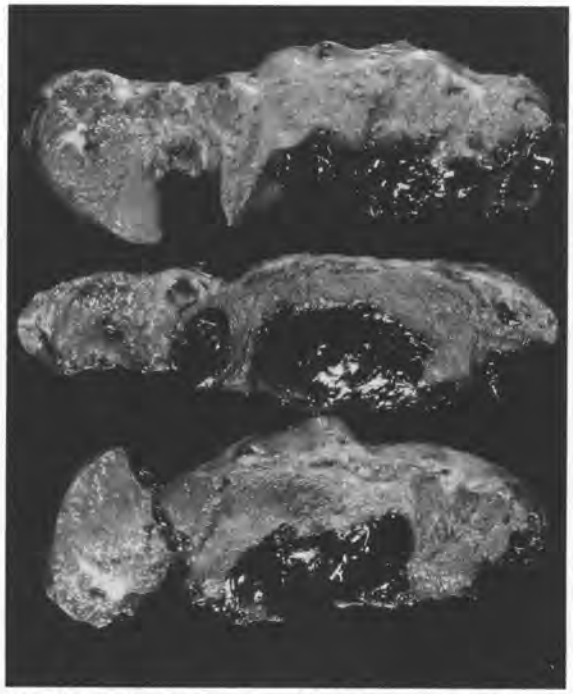

FIGURE 8-77 Placenta with multiple large, recent intervillous thrombi associated with infarction of surrounding villi.

Intervillous and Subchorionic Thrombi

An *intervillous thrombus* is a space-occupying, intraplacental blood clot that displaces surrounding villi. Intervillous thrombi may be single or multiple and usually are situated midway between the chorionic plate and the basal plate (Fig. 8-77). They commonly measure 1 to 2 cm in diameter but may exceed 3 to 4 cm. Intervillous thrombi are found in up to 40% of all placentas.[13] When fresh, an intervillous thrombus is mahogany-red, soft, and gelatinous (see Fig. 8-77). Over time, the thrombus firms as the blood components layer out, and a laminated appearance ensues. The initial mahogany-red color fades to white. Sometimes an intervillous thrombus may be difficult to differentiate grossly from an infarct.

Microscopically, it is composed of red blood cells and fibrin (Fig. 8-78). An aged thrombus is laminated, with alternating layers of red blood cells and fibrin (Fig. 8-79). Intervillous thrombi never organize. The blood of an intervillous thrombus is a mixture of maternal and fetal blood. Fetal blood loss into an intervillous thrombus is purported to cause fetal-maternal hemorrhage[156] and may prompt maternal sensitization to fetal red blood cell antigens.[157] Surrounding villi are displaced but usually are not infarcted. Occasionally, stromal villous hemorrhages are found.

Massive subchorial thrombosis, which is greater than 1 cm in thickness, has been called *Breus' mole.* It represents a recent subchorionic thrombus that protrudes into the amnionic cavity or down to the basal plate, or both. As it matures, it becomes laminated and may enlarge, displacing and disrupting a large amount of normal parenchyma. These thrombi are associated with fetal death in utero and are maternal in origin.[13,48,158]

Fetal Artery Thrombosis

Thrombosis of a fetal artery results in loss of fetal villous perfusion. The involved villi are grossly similar to infarcted villi. The lesion is pyramidal, appearing triangular on full-thickness cross sections, with its apex pointing to the chorionic plate. As the lesion ages, the villi become white and shrink.

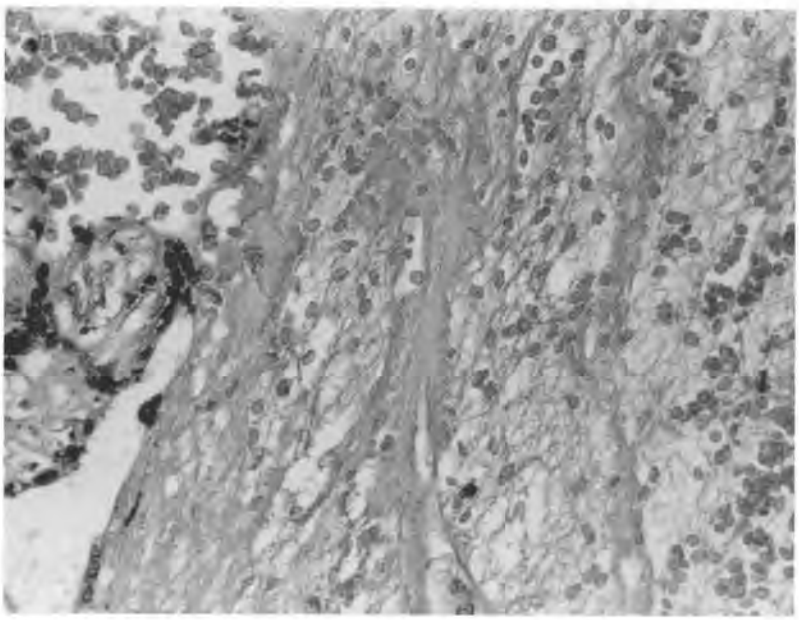

FIGURE 8-78 Recent intervillous thrombus with fibrin entrapping red blood cells. Adjacent villus is viable.

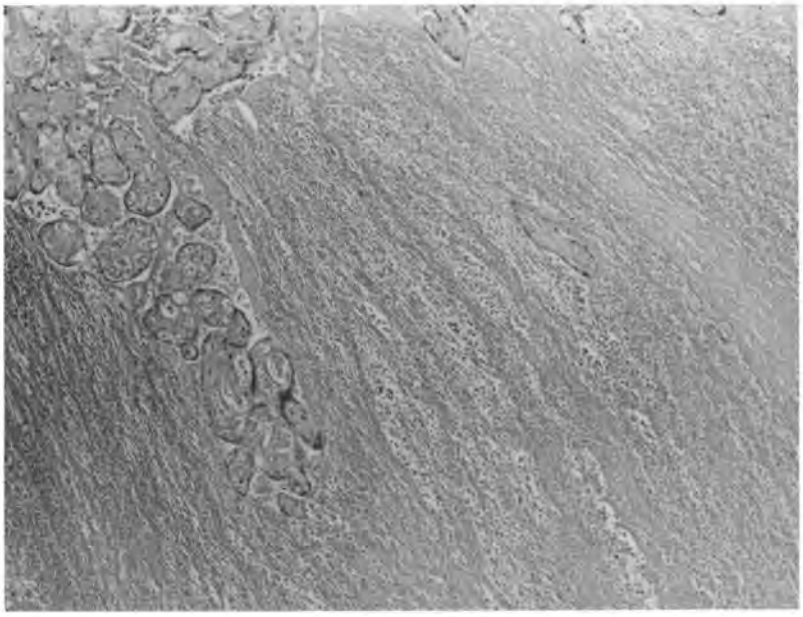

FIGURE 8-79 An older, laminated intervillous thrombus showing thick layers of fibrin and entrapped red blood cells. Adjacent villi are infarcted.

Microscopically, the thrombosis may involve a fetal chorionic artery or, just distal to that, a mainstem villous artery (Fig. 8-80). The villi most distal to the thrombosis are completely avascular, with those more proximal showing fibromuscular sclerosis of stem villous vessels, most likely a reactive change (Fig. 8-81). In distal villi, fibrous obliteration of the villous vessels is accompanied by stromal hyalinization. In some foci, maternal perfusion of the intervillous space continues, and the syncytiotrophoblast remains viable and may form large knots. A localized fetal artery thrombosis is more common in diabetics[13,36] and occurs in 4.5% of full-term placentas.[13] In some placentas, thrombosis of 20% to 30% of the villi apparently has been inconsequential to the fetus.[12] Greater degrees of villous avascularity, approaching 50%, have resulted in fetal death.[12]

PLACENTAL PATHOLOGY ASSOCIATED WITH MATERNAL AND FETAL DISORDERS

Maternal Disorders

The scope of this chapter allows only an introduction to the placental findings associated with maternal disorders. The most common maternal conditions affecting the placenta—preeclampsia, essential hypertension, diabetes mellitus, and maternal malig-

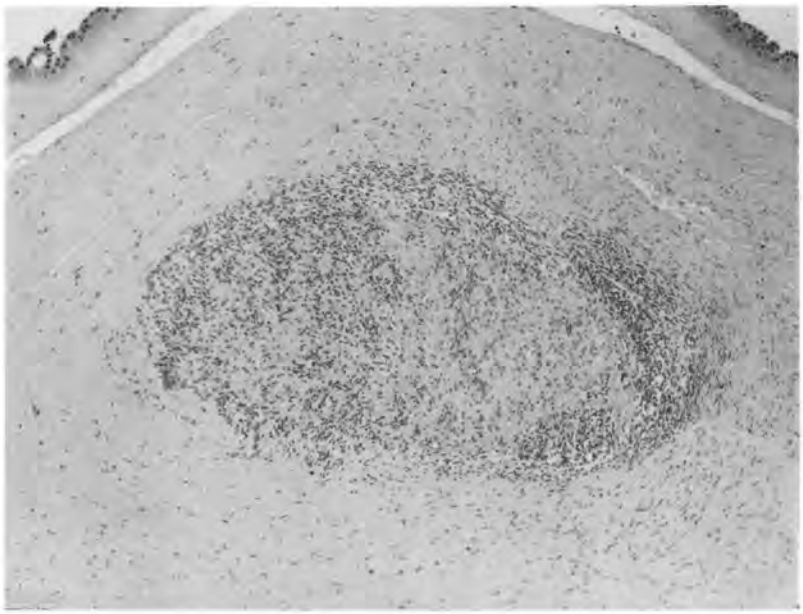

FIGURE 8-80 Thrombosis of a fetal artery of the chorionic plate.

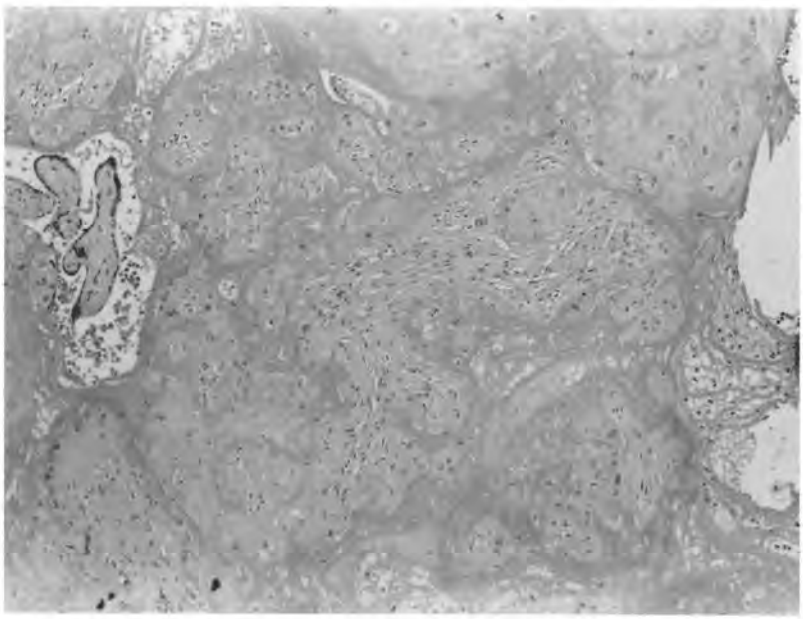

FIGURE 8-81 Villi distal to the thrombus depicted in Figure 8-80. There is dense intervillous fibrin deposition and fibromuscular sclerosis. Note the lack of villous blood vessels and a few uninvolved villi (*left*).

nancy—are discussed in this section. For a review of other less common maternal diseases such as intrahepatic cholestasis of pregnancy,[12] sickle cell disease and trait (Fig. 8-82),[159–163] maternofetal rhesus incompatibility,[17,164] systemic lupus erythematosus,[12,13] and maternal exposure to toxins,[12,13] the reader should consult the literature cited.

Preeclampsia (Toxemia of Pregnancy) and Eclampsia

Preeclampsia is one of the most serious maternal disorders whose onset is occasioned solely by pregnancy. Preeclampsia is defined by hypertension and proteinuria or generalized edema developing after 20 weeks' gestation. It becomes eclampsia when accompanied by a maternal seizure. Despite extensive research, the etiology of preeclampsia remains unknown.

Although the literature reviewing placental pathology associated with preeclampsia is voluminous, much of it remains conflicting. Most investigators agree that in preeclampsia the placenta tends to be smaller than normal, and that infarcts, particularly recent ones, and retroplacental hematomas are more common.[12,165,166] The amount and extent of infarction seem proportional to the severity of preeclampsia: 33% of placentas in mild preeclamptics have infarcts, compared with 60% for those with severe disease.[12] Apart from these lesions, the noninfarcted

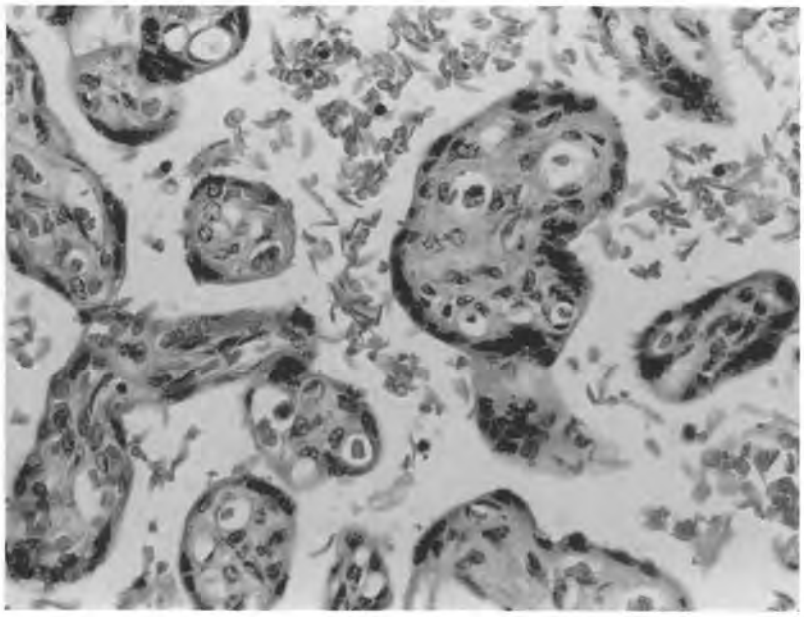

FIGURE 8-82 Maternal sickle cell disease. The maternal red blood cells in the intervillous space are sickled. Fetal hemoglobin F protects fetal cells against sickling, and the fetal status with regard to sickle cell trait or disease cannot be ascertained by placental examination.

villi tend to have a more prominent cytotrophoblastic layer and a thickened basement membrane.[12] In some, there are excessive syncytiotrophoblastic knots (so-called Tenney-Parker knots; Fig. 8-83), decreased number of and smaller villous vessels, and narrowing of fetal stem arteries.[167–169] Maternal vascular changes, known as decidual vasculopathy (eg, acute atherosis, acute atheromatous changes), are presented in the preceding section on the fetal membranes. It has been suggested that many of the placental changes in preeclamptics result from the lack of a second wave of trophoblastic invasion of maternal myometrial arteries: The vascular muscle and elastic lamina remain intact. This precludes further vascular dilatation and increased placental perfusion, which are essential for normal fetal growth in later pregnancy.

Essential Hypertension

Clinically, the term *essential hypertension* refers to hypertension preceding 20 weeks' gestation. Pregnancy-induced hypertension is defined as hypertension occurring later in pregnancy and unaccompanied by proteinuria and edema. The placental findings in essential hypertension are similar to those of preeclampsia: infarcts, retroplacental hematomas, increased cytotrophoblast, and thickening of the trophoblastic basement membrane. In addition, and differentiating it from preeclampsia, an unusual form of decidual vasculopathy (hyperplastic arteriosclerosis) has been described in essential hypertension. It consists of vessels with increased overall diameter, markedly thickened glassy-eosinophilic walls, and proliferations of the intima that result in luminal narrowing and uteroplacental ischemia.[170–172] Hyperplastic arteriosclerosis is best observed in the uterine radial arteries and is seen less frequently in the intramyometrial implantation-site vessels. There appear to be minimal fetal sequelae in pregnancies with uncomplicated essential hypertension.[12,173,174]

Diabetes Mellitus

Maternal diabetes mellitus is associated with fetal macrosomia and increased neonatal morbidity. In general, the placental hallmark of maternal diabetes mellitus, whether gestational or not, is placentomegaly. Some of the largest and heaviest placentas, excluding those from erythroblastosis fetalis, are from diabetic mothers. The placenta is bulky and thickened by edematous villi. In some, the placenta is normal or small for gestational age. Single umbilical artery is 3 to 5 times more common in diabetics, as are some congenital malformations, particularly those involving the cardiovascular system.[36,175] The cord itself, like the macrosomic placenta and fetus, is larger than expected.

Microscopically, the increased villous bulk is translated into villous immaturity and villous edema. The cytotrophoblastic layer is prominent and shows persistent mitotic activity. The trophoblastic basement membrane is thickened. Fibrinoid necrosis of villi is more common in diabetics.[176] In addition to acute atherosis, Driscoll has described an additional type of decidual vasculopathy in 50% of diabetics consisting of arteriolar medial hypertrophy, hyalinization, and onion-skinning.[36]

Hydrops Placentalis: Immune and Nonimmune

Within this broad category are a large number of lethal or severely debilitating fetal diseases, the pathol-

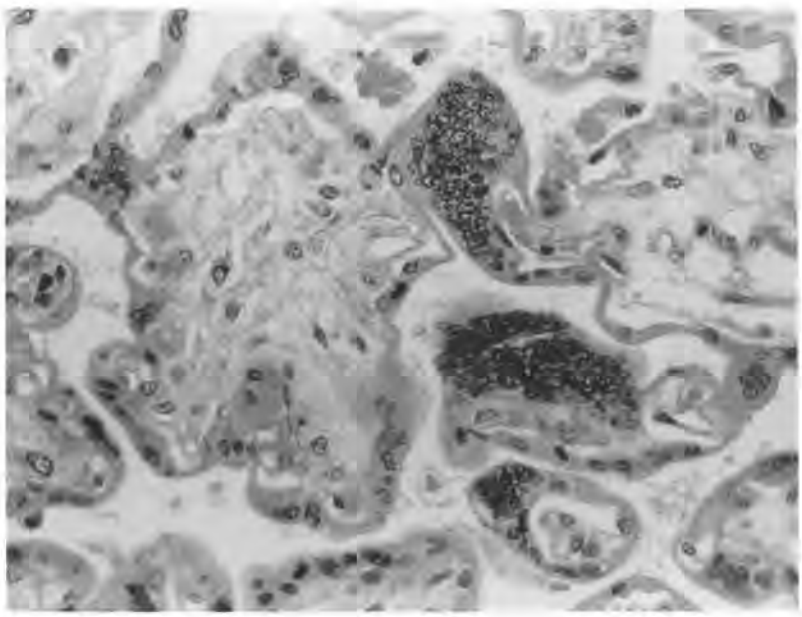

FIGURE 8-83 Tenney-Parker syncytiotrophoblastic knots in placenta from a woman with preeclampsia.

ogy of which directly involves, or is reflected in, the placenta. Extreme villous edema has been termed *villous hydrops* or *hydatid change* and refers to an excessive accumulation of clear watery fluid resulting in the formation of grossly visible, swollen, grape-like placental villi. Villous hydrops may be diagnosed early in gestation by obstetric ultrasonography and is often associated with hydrops fetalis, a condition consisting of an abnormal accumulation of watery, serous fluid in the fetal tissues.

Hydropic placentas tend to be large, heavy, bulky, pale, and spongy. Microscopically, the villi are immature and edematous. The cytotrophoblast is conspicuous, and cell proliferation is evidenced by increased mitotic activity. Fetal capillaries contain nucleated fetal red blood cells and erythroblasts (see Fig. 8-46). In many instances, the placental changes reflect fetal anemia, heart failure, or increased venous pressures. For a concise and clear review of the pathophysiology of fetal hydrops, the reader is referred to the recent comprehensive article by Machim.[177]

Formerly, the most common cause of hydrops placentalis was Rhesus blood group incompatibility. With the advent of the immune globulin preparation (RhoGAM) in the 1960s, the incidence of maternal sensitization has decreased markedly. Because of improved diagnosis and treatment of affected fetuses, marked placental hydrops due to Rh disease is uncommon. Leading the list of causes of placental hydrops are congenital malformations with and without associated genetic disorders, infections, α-thalassemia, blood group incompatibilities due to ABO and Kell antigens, red cell dyscrasias, congenital nephrotic syndrome (Finnish nephrosis), fetal-maternal hemorrhage, and storage disorders.

OTHER VASCULAR LESIONS OF THE PLACENTA

Chorangiosis is a term describing a distinct increase in the number of villous vessels, which has been correlated with poor neonatal outcome (Fig. 8-84).[178] The validity of this lesion has been challenged by some who claim that it represents filling and distension of previously collapsed vessels. Chorangiosis defined by Altshuler's criteria of "ten villi, each with ten or more vascular channels in ten or more noninfarcted and nonischemic zones of at least three different placental areas" (using a 10× objective) is uncommon in routine placental material. The rarity of this lesion in our experience and its association with high-risk pregnancies lends support to the contention that increased villous vascularity relates to poor neonatal outcome. Clearly, further investigation is warranted.

PLACENTAL CALCIFICATION

Calcification of the placenta increases throughout gestation. First-trimester placentas are rarely calcified. Scattered calcific deposits occur in the second trimester, and by term most placentas have scattered calcifications. Ultrasonographic determination of placental calcification is expressed as grades ranging from 1 to 3. Neither histologic nor ultrasonographic assessments of placental calcifications can be used to determine pulmonary maturity. Although the amount of placental calcification is variable, there are no studies demonstrating a relation between calcification and neonatal outcome.

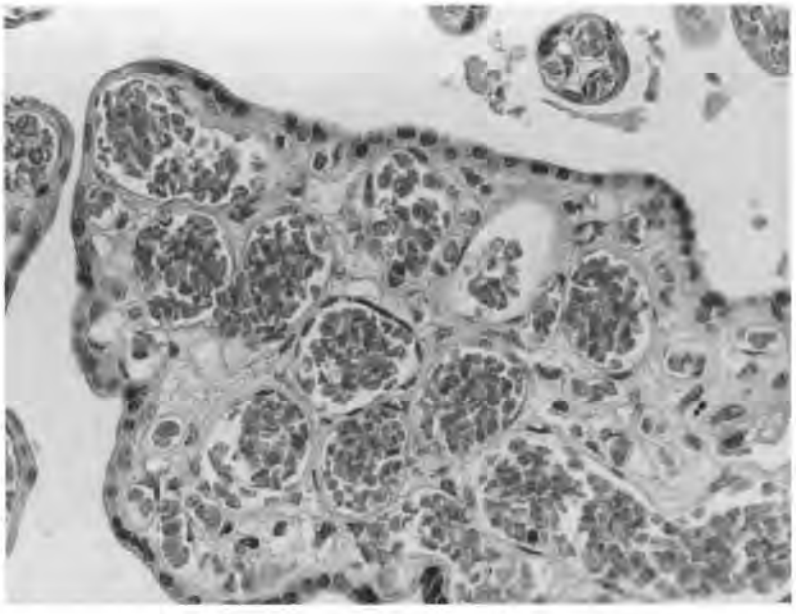

FIGURE 8-84 Chorangiosis of placenta depicting a villus with more than 10 vessels. Diagnosis requires multiple fields containing similar such villi.

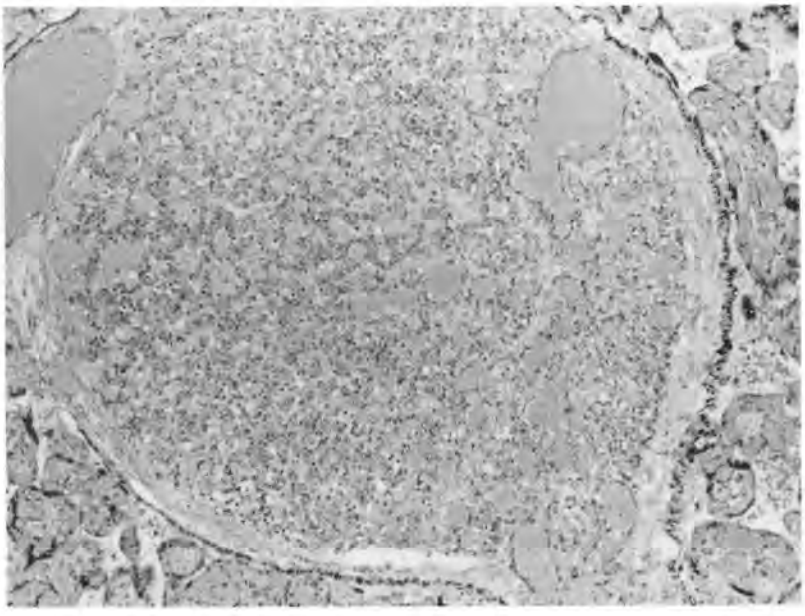

FIGURE 8-85 Microscopic chorangioma illustrating vascular proliferation within the confines of a single villus.

TUMORS OF THE PLACENTA

Benign Tumors

The most common benign tumor to involve the placenta is a *chorangioma.* It is composed of a localized proliferation of fetal blood vessels and villous stroma, generally occurring within the confines of one or a few villi. Most are small and recognized by microscopy alone (Fig. 8-85). Large tumors may form a rounded mass, bulging into the amniotic cavity (Fig. 8-86). Such large tumors are often associated with polyhydramnios and hydrops fetalis from vascular shunting; thrombocytopenia, hemolysis, or disseminated intravascular coagulation; and, in some, intrauterine death. Although mitotic activity may be brisk in some chorangiomas, no metastases have been reported.

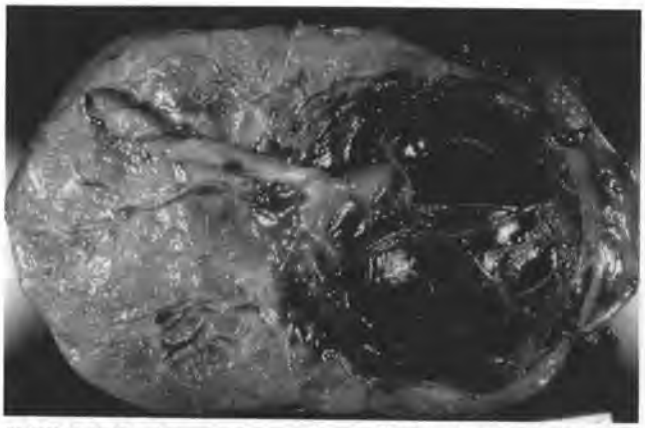

FIGURE 8-86 Large chorangioma of the placenta forming a hemorrhagic mass that bulges from the fetal surface toward the amnionic cavity.

Uncommonly, *placental teratomas* have been found embedded between the amnion and the chorion in the placenta or in subamnionic location in the umbilical cord. Their histopathology is akin to that of the mature (cystic) teratoma of the ovary: skin and fat are virtually always present. No malignant placental teratoma has been reported. The origin of placental teratomas is controversial. Faulty migration of germ cells from the yolk sac represents the most likely theory, with unrecognized twin gestations (similar to acardiac fetuses) remaining an alternative mechanism.[179]

Malignant Tumors

Melanoma is reported to be the most common malignant tumor to metastasize to the placenta,[180] although in our practice metastatic breast carcinoma is more common by far. Any hematogenously disseminated tumor may metastasize to the placenta, and a gynecologic malignant tumor may involve the placenta by direct extension. Circulating malignant cells from fetal tumors such as neuroblastoma and lymphoma can escape the confines of the villous capillaries and invade the stroma. Choriocarcinoma is discussed below.

GESTATIONAL TROPHOBLASTIC DISEASES

Hydatidiform mole, the most common gestational trophoblastic tumor, results from an abnormal fertilization event. In hydatidiform moles, as in the other trophoblastic tumors, neoplasia is due to uncontrolled trophoblastic proliferation. Trophoblastic tumors may be subclassified dichotomously as tumors

with villi–hydatidiform mole, partial and complete; and tumors without villi–choriocarcinoma and placental site trophoblastic tumor. The World Health Organization classification of gestational trophoblastic tumors is presented in Table 8-4.

Based on genetic and morphologic criteria, hydatidiform moles are divided into two types: partial hydatidiform mole and complete hydatidiform mole.[181,182] A pathologic distinction between these hydatidiform moles is necessary as they are associated with differing clinical outcomes. A 10% to 30% incidence of gestational trophoblastic disease follows complete mole, compared with 5% for partial mole.[183] Although its overall incidence may be falling, choriocarcinoma may develop after complete mole;[184] however, it rarely occurs after partial mole.[185]

The *incidence* of molar pregnancies varies throughout the world, ranging from 1 in 4500 deliveries in the United States[186] to 1 in 1300 deliveries in Israel[187] and 1 in 85 to 373 deliveries in Indonesia.[188] The mean age of women with partial and complete moles is similar, near 28 years.[183] Women with complete or partial mole are more likely to have a personal or family history of previous gestational trophoblastic disease, and personal history of two or more previous spontaneous miscarriages, infertility and smoking.[189] Having had one complete mole increases a patient's risk of a subsequent mole by 100-fold. Both groups tend to present with abnormal vaginal bleeding, with complete mole more commonly associated with increased uterine size for dates, toxemia, thyrotoxicosis, theca lutein cysts and hyperemesis.[190]

The standard *treatment* for both types of hydatidiform mole is uterine evacuation, generally by dilatation and curettage. Follow-up consists of monitoring serum or urine β human chorionic gonadotropin (hCG) levels. Although spontaneous remission follows most molar evacuations, any consistent plateau or rise in hCG values should prompt treatment with chemotherapy.

There are marked *genetic* differences in hydatidiform moles. The complete mole is diploid by cytogenetic studies[191] and generally is diploid or tetraploid by flow cytometric studies (Fig. 8-87). In contrast to the genotype of normal diploid placenta, the 46 chromosomes of a complete mole are totally paternal in origin, termed androgenetic.[191] About 90% of complete moles are derived from the fertilization of an empty ovum by a haploid spermatozoon which then duplicates its DNA (homozygous complete mole). The remaining 10% are produced from fertilization of an empty ovum by two different spermatozoa resulting in a mixture of homozygous and heterozygous alleles (heterozygous complete mole). There is no difference in the natural history of homozygous versus heterozygous complete moles. Maternal mitochondrial DNA is preserved in complete mole, supporting the postulated "empty-ovum" theory.[192]

In contrast, the partial mole is triploid, having 69 chromosomes: the maternal pronucleus with its haploid DNA is conserved and, instead of fertilization by one haploid set of paternal DNA, *two* haploid sets of paternal DNA are added.[181] Thus, there is a

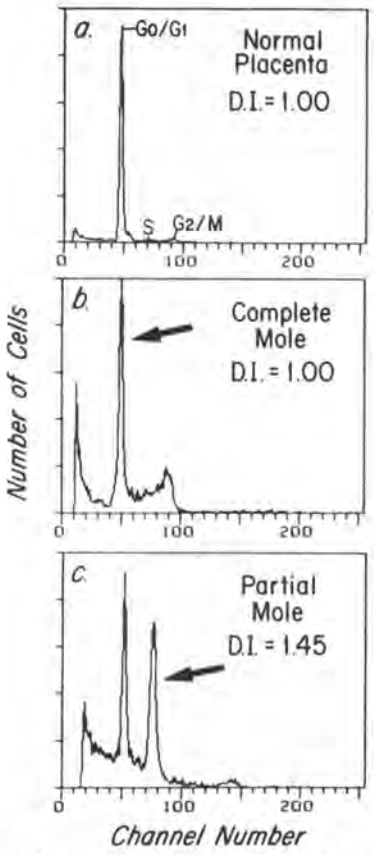

FIGURE 8-87 DNA histograms. **(A)** Diploid hydropic abortus. **(B)** Diploid complete hydatidiform mole. **(C)** Triploid partial hydatidiform mole. Channel number reflects nuclear DNA content. The DNA index (D.I.) is the ratio of the test sample modal G0/G1 DNA content to control (diploid) modal G0/G1 DNA content. G0/G1 peaks of complete mole **(B)** and partial mole **(C)** are indicated by arrows. The G0/G1 peak of the complete mole contains the same DNA content as the added control lymphocytes; therefore, the D.I. = 1.0. (Lage JM, Driscoll SG, Yauner DL, Olivier AP, Mark SD, Weinberg DS. Hydatiform moles: application of flow cytometry in diagnosis. Am J Clin Pathol 89: 596–600, 1988)

TABLE 8-4
World Health Organization Classification of Gestational Trophoblastic Diseases

Hydatidiform mole
Complete
Partial
Invasive hydatidiform mole
Choriocarcinoma
Placental site trophoblastic tumor
Trophoblastic lesions, miscellaneous
Exaggerated placental site
Placental site nodule or plaque
Unclassified trophoblastic lesion

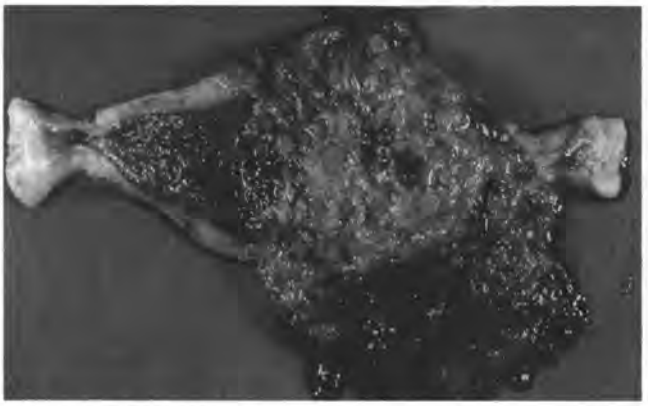

FIGURE 8-88 Complete hydatidiform mole in a gravid hysterectomy specimen.

predominance of paternal DNA in partial and complete mole. In the partial mole, the retained maternal haploid component serves to mollify the histologic expression and natural history of the disease.

Complete Hydatidiform Mole

Pathology

The complete mole has such a characteristic *macroscopic appearance* that it may be diagnosed by the ultrasonographer, attendant at delivery, or pathologist (Fig. 8-88). The placenta is voluminous, far exceeding that expected for gestational age. The villi swell, forming numerous grossly recognizable vesicles (Fig. 8-89). The size of the vesicles depends on the age of the mole and the manner of evacuation, and the largest villous vesicle averages 1.6 cm in maximum diameter.[183] No fetal parts are found.

Microscopic examination discloses diffuse, marked villous enlargement due to massive stromal edema. The edema displaces the mesenchymal stroma centrally, creating an acellular clear space called a central cistern (villous cavitation). There is marked proliferation of cyto- and syncytiotrophoblast (Fig. 8-90). Some villi have remnants of villous vessels with degenerating nucleated red blood cells. Well-formed villous vessels with abundant nucleated red blood cells are not characteristic of complete hydatidiform mole. The endomyometrial implantation site contains large, hyperchromatic trophoblast.

Evolution

Most women with complete mole undergo spontaneous gonadotropin remission after molar evacuation. In 10% to 30%, chemotherapy is required to eradicate residual molar villi or trophoblast.[183,190] The incidence of pathologically confirmed choriocarcinoma after complete mole seems to be decreasing in the United States, developing in less than 1% to 2%. In a recent study of 150 women with complete mole followed at a trophoblastic disease center, 33 received chemotherapy for persistence, and none developed choriocarcinoma.[184]

Most commonly, there is no attempt to obtain tissue for pathologic evaluation of metastases because the risks of operation outweigh the information gained. Accordingly, the clinical term "persistent gestational trophoblastic disease (or tumor)" was coined to encompass all types of molar residua. The chemotherapeutic regimens used to treat persistent disease are based on a variety of clinical parameters, focusing on the clinical extent of disease, hCG values, and type of antecedent gestation.

Endometrial curettings in patients with persistent gestational trophoblastic disease after complete hydatidiform mole usually contain residual molar villi and avillous, or implantation-site, trophoblast. Frank choriocarcinoma is rare. A diagnosis of choriocarcinoma should be contemplated only after the

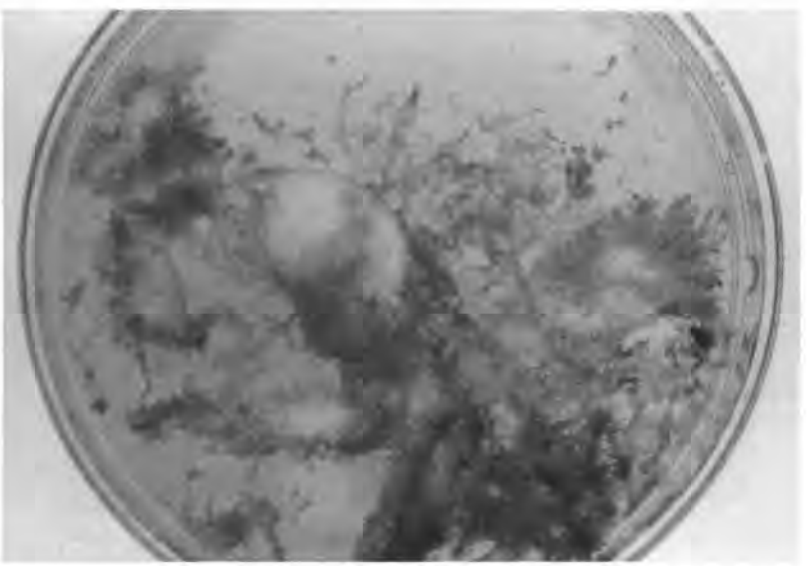

FIGURE 8-89 Molar villi floated in saline in a petri dish (same specimen as in Fig. 8-88). Villi are swollen, filled with fluid, and covered by hyperplastic trophoblast that may be recognized grossly as fibrillary projections from villous surfaces.

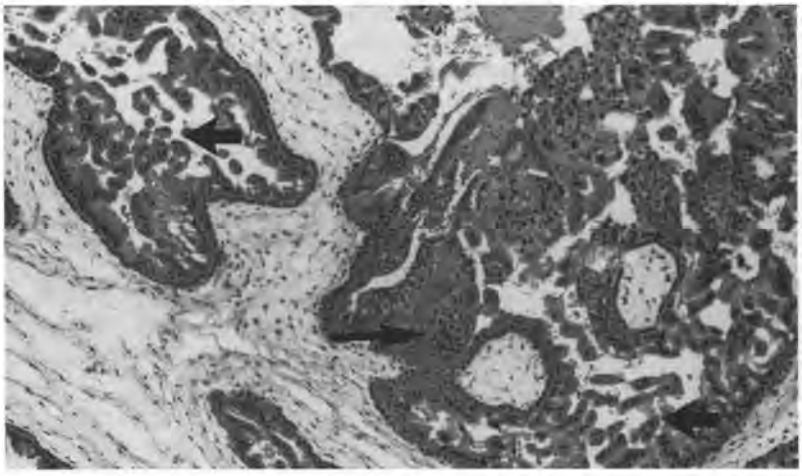

FIGURE 8-90 Complete hydatidiform mole showing collapsed villus with prominent uninucleate cytotrophoblast hyperplasia (*long arrow*) and multinucleated syncytiotrophoblast hyperplasia (*short arrows*). Villous stroma lacks blood vessels and red blood cells.

entire specimen has been carefully examined microscopically and the possibility of residual villous tissue is excluded (see section on choriocarcinoma). A pathologic diagnosis of choriocarcinoma significantly alters clinical treatment.

Complete Hydatidiform Mole in a Twin Gestation

Because twinning occurs with a frequency of 1 in 80 gestations, it is not too uncommon for a complete mole to be accompanied by a normal twin. About 1% to 2% of hydatidiform moles are from twin gestations.[183,193] Interpretation of pathology in such cases is facilitated by previous ultrasonographic recognition of a twin gestation, by receipt of a hysterectomy specimen (Fig. 8-91), or by knowledge of a liveborn normal co-twin.

If the mole is evacuated by curettage and the abnormal, molar villi are admixed with normal villi, the initial gross examination may point to partial mole. Microscopically, the complete mole is differentiated from partial mole by much more exuberant trophoblastic hyperplasia involving cytotrophoblast and syncytiotrophoblast, and more extensive and pronounced villous cavitation. The complete mole lacks villous scalloping and the two populations of villi characteristic of partial mole (vide infra). In contrast to partial mole, a twin fetus accompanying complete mole is generally without congenital anomalies.

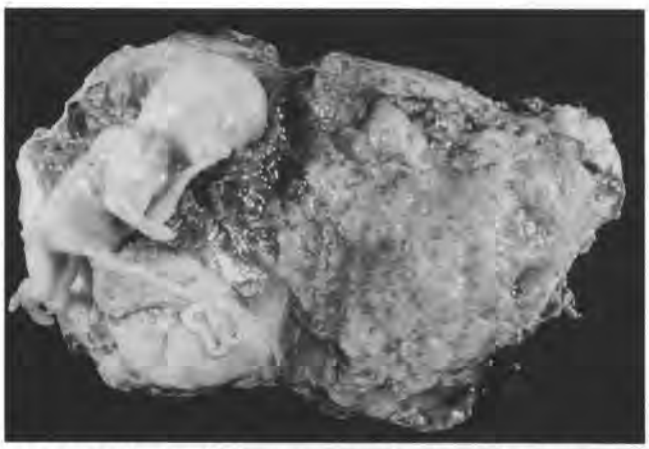

FIGURE 8-91 Gravid hysterectomy showing twin pregnancy: complete hydatidiform mole and and normal twin with umbilical cord and placenta intact. (Lage JM, Mark SD, Roberts DJ, Goldstein DP, Bernstein MR, Berkowitz RS: A flow cytometric study of 137 fresh hydropic placentas: correlation between types of hydatidiform moles and nuclear DNA ploidy. Obstet Gynecol 79:403–410, 1992)

Partial Hydatidiform Mole

A partial hydatidiform mole is derived from an abnormal conceptus that contains an extra haploid set of DNA, is termed triploid (see Fig. 8-87), and has a total of 69 chromosomes. Both the fetus and its placenta are triploid and abnormal. By *gross examination,* the amount of villous tissue in most partial moles is greater than expected for gestational age. In one study, the average maximum villous diameter was 0.51 cm.[183] Fetal tissues are virtually always present and often anomalous.

Though a partial mole may be suspected on gross examination, the diagnosis rests with *microscopy* (Table 8-5). In contrast to the diffuse villous enlargement of the complete mole, there are two populations of villi in partial moles, with some enlarged and some normal to small and sclerotic[181,182] (Fig. 8-92). The villous outline is scalloped (Fig. 8-93) resulting in stromal trophoblastic inclusions (Fig. 8-94). The sine qua non of partial mole is focal trophoblastic hyperplasia (Fig. 8-95; see also Fig. 8-92). The trophoblast hyperplasia ranges from minimal to moderate and chiefly involves the syncytiotrophoblast (see Fig. 8-95). Frank villous cavitation occurs, but to a much lesser degree. Villous blood vessels contain nucleated red blood cells. In older, late second trimester partial moles, villous vessels may form bizarre, gaping, anastomotic channels[182] reminiscent of vascular malformations (Fig. 8-96). Although fragmented and occa-

TABLE 8-5
Gross and Microscopic Differences Between Hydropic Abortus, Partial Hydatidiform Mole, and Complete Hydatidiform Mole

	Hydropic Abortus	***Partial Hydatidiform Mole***	***Complete Hydatidiform Mole***
Amount of Tissue	Scant	Increased for gestational age	Markedly increased
Villous Swelling	Diffuse swelling, involves chorion laeve	Two populations with focal villous swelling	Diffuse swelling
Villous Cavitation	Focal	Focal	Common to extensive
Trophoblast Hyperplasia	None	Focal, involving syncytiotrophoblast	Extensive
Villous Scalloping and Villous Stromal Inclusions	Usually balloon-shaped villi, no scalloping	Focal	Absent
Fetal Tissue	Usually absent, trisomy 18 a notable exception	Usually intact or fragmented fetal parts	Absent
DNA Content	Diploid, often with abnormal karyotype	Triploid: 69 XXX, 69 XXY, rarely 69 XYY	Diploid, paternal

sionally autolyzed, fetal tissues usually are found in partial moles. In older fetuses, anomalies may involve any organ system, but fusion of the fingers or toes, termed syndactyly, is a tipoff to triploidy.[194,195] The implantation site usually contains enlarged, somewhat hyperchromatic, nuclei.

The *natural history* of partial mole is well-documented.[183,196–200] Most women with partial mole undergo spontaneous gonadotropin remission after molar evacuation. About 5%, and in some series, 1% or so, require reevacuation or chemotherapy.[193,198] Although infrequent, choriocarcinoma has followed partial mole.[185,200]

Distinction of Partial Mole from Hydropic Abortus

In many instances the most difficult diagnostic distinction for the obstetric pathologist is between the partial mole and the hydropic abortus (see Table 8-5). The villi of both are focally enlarged, edematous, and even cavitated. Microscopic examination demonstrates a total lack of trophoblastic hyperplasia in the hydropic abortus. Its villi are balloon-shaped, regular, and covered by thin, attenuated trophoblast. Most hydropic abortuses lack fetal tissues and are diploid or near-diploid by karyotype or flow cyto-

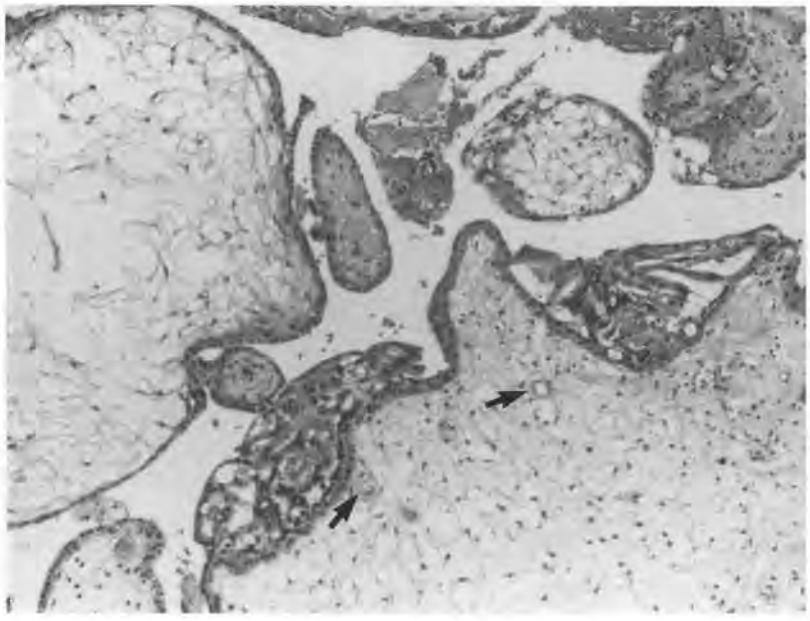

FIGURE 8-92 Partial hydatidiform mole showing two populations of villi: large, edematous villi with focal syncytiotrophoblastic hyperplasia and smaller, focally sclerotic villi. Fetal capillaries are indicated by arrows. Villous edema of villus (*upper left*) is beginning to coalesce, forming the precursor to a small, central cistern.

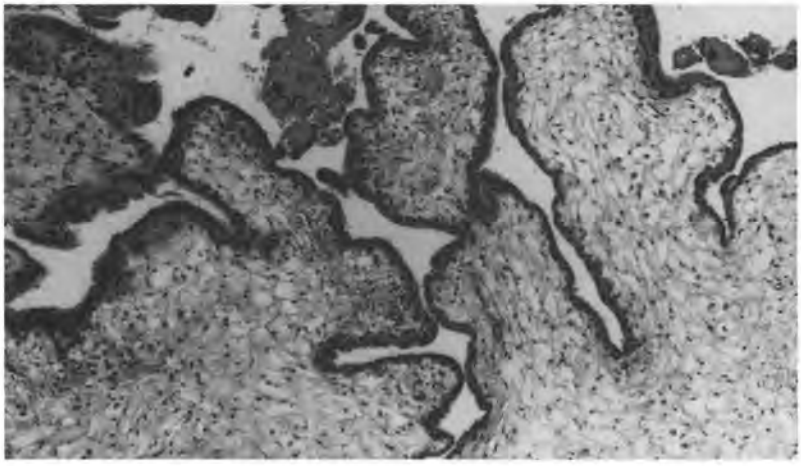

FIGURE 8-93 Partial hydatidiform mole showing enlarged villi with scalloped villous outlines.

metric analysis, although trisomy of a single or a few chromosomes is common.

In contrast, most partial moles are triploid (see Fig. 8-87). The total volume of villous tissue in partial moles far exceeds that in hydropic abortuses. Furthermore, in partial moles the villous outlines are scalloped, forming trophoblastic inclusions, and trophoblast hyperplasia is focally evident. Fetal tissues are more readily found in partial moles.

Third Type of Hydatidiform Mole

Some diploid hydatidiform moles have more phenotypic similarities to partial mole than to complete mole.[181,185,201] Some have maternal and paternal DNA.[201] This has prompted some to opine that a third category of molar gestation might exist: that of diploid partial mole. A conceptus could have a relative "predominance" of a specific paternal DNA locus if there were a deletion of the comparable maternal locus. This uniparental disomy could result in a molar phenotype, albeit slightly different from the triploid partial mole. Because our knowledge regarding molar gestations is simplistic, any placenta with trophoblast hyperplasia that cannot be further subtyped should be diagnosed as "hydatidiform mole," and appropriate hCG monitoring should follow regardless of DNA content or parental origin.

Invasive Hydatidiform Mole

Hydatidiform moles, partial and complete, can invade the uterine wall, resulting in a tumor that is beyond the reach of the curette. Invasive mole is the most common form of persistent gestational trophoblastic disease after complete mole. Molar villi invade the myometrium in a manner identical to that of placenta increta and may even perforate the

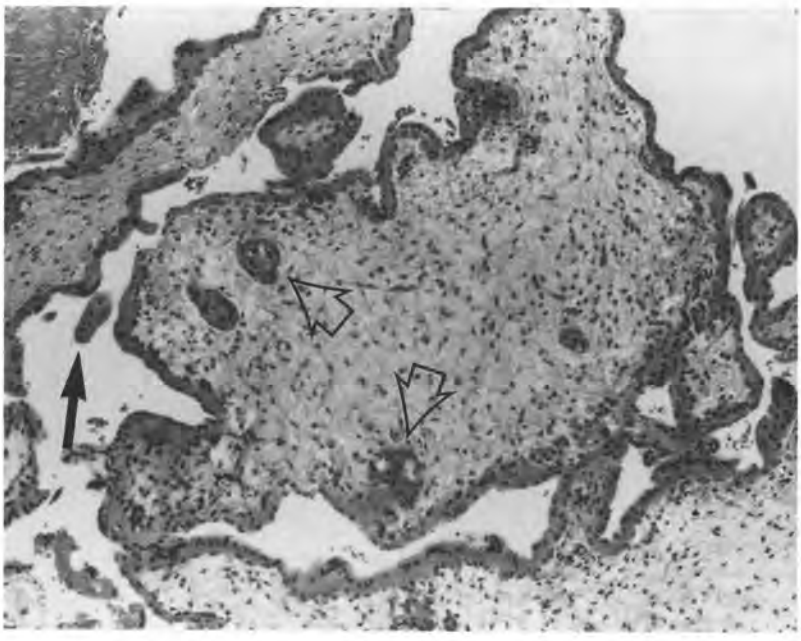

FIGURE 8-94 Partial hydatidiform mole with enlarged villus containing stromal trophoblastic inclusions (*open arrows*). Syncytiotrophoblastic notch (*closed arrow*) in intervillous space appears detached from adjacent villi.

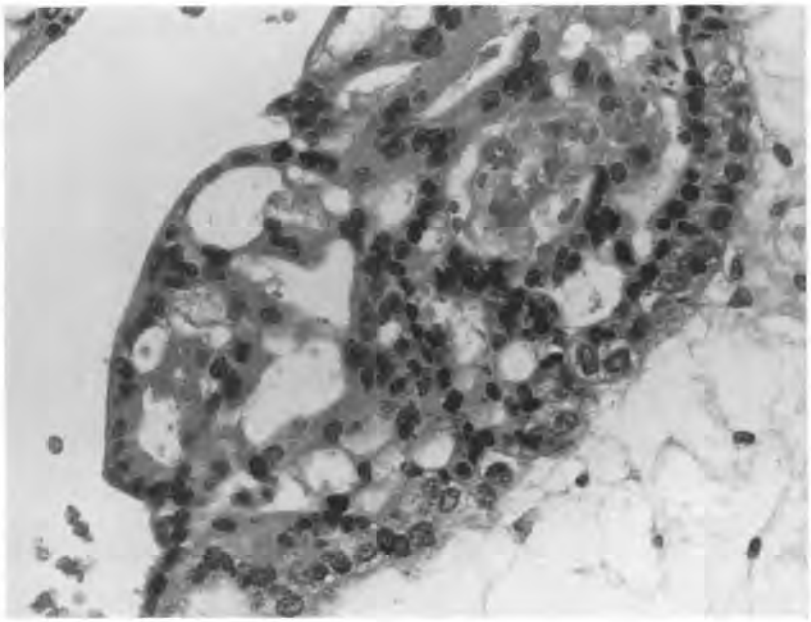

FIGURE 8-95 Partial hydatidiform mole depicting trophoblastic hyperplasia composed of mounds of lacy syncytiotrophoblast. A single layer of cytotrophoblast is present.

uterine serosa. In most cases, invasive mole is effectively treated by chemotherapy, although some require hysterectomy.

Placental Site Lesions

Placental Implantation Site and Placental Site Nodule and Plaque

The implantation site is composed predominantly of intermediate trophoblast (see Fig. 8-5). This type of trophoblast is generally uninucleate, with a single moderate-size nucleus and clear to eosinophilic cytoplasm. After fetal death, degenerative changes in the intermediate trophoblast result in marked nuclear pyknosis and hyperchromasia. Usually all implantation-site trophoblast has disappeared from the postgravid uterus by 4 to 6 weeks postpartum or postevacuation. Abnormally retained implantation-site trophoblast may form single cells or masses of cells within the endomyometrium. In the past, this was called "retained implantation-site trophoblast."

Recent studies have described another form of retained implantation-site trophoblast composed of discrete, round to oval, eosinophilic nodules with radially oriented intermediate trophoblast in a hyalinized stroma.[202,203] These nodules of intermediate trophoblast have been termed *placental site nodules (or plaques)*. A placental site nodule is depicted in Figures 8-97 and 8-98. In most cases, placental site nodules are derived from residua of placental septal trophoblast (Fig. 8-99) or from cell islands that become embedded in the endomyometrium. Signifi-

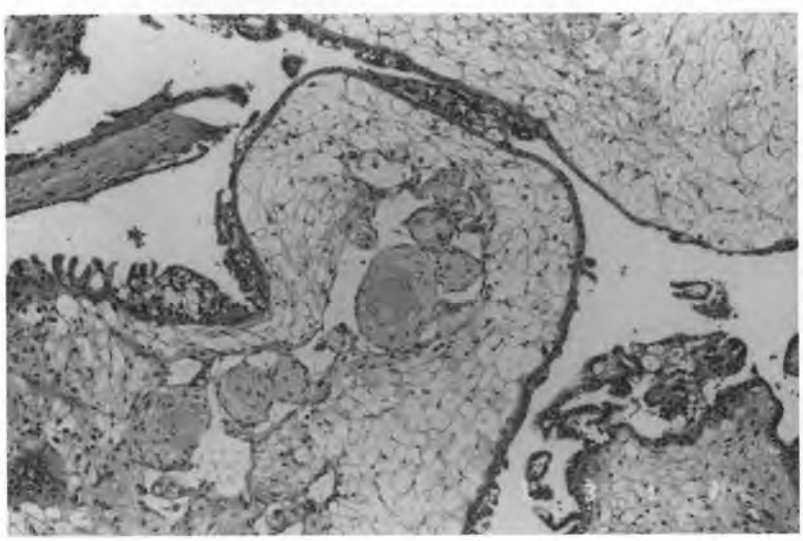

FIGURE 8-96 Partial hydatidiform mole, late second-trimester specimen, with enlarged, edematous villi containing aberrant, maze-like villous vessels, piles of hyperplastic syncytiotrophoblast, and syncytiotrophoblastic notches. Flow cytometry confirmed triploid DNA content.

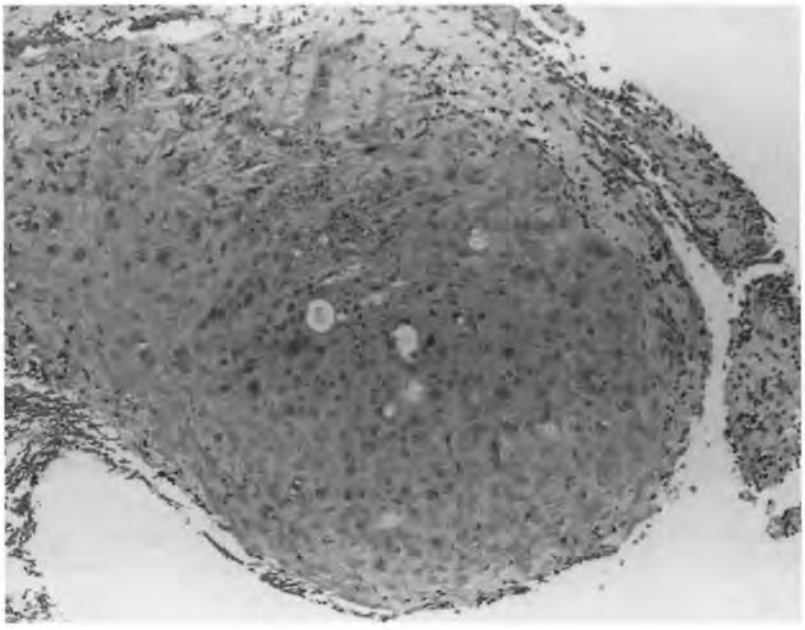

FIGURE 8-97 Placental-site nodule in endometrial curettings. Nodule is predominantly acellular, composed of eosinophilic hyalinized material with preservation of residual central intermediate trophoblast. This lesion showed positive immunostaining for keratin and human placental lactogen.

cant mitotic activity such as >1/10 to 20 high-power (×400) fields should raise the possibility of placental site trophoblastic tumor. Uterine curettage appears to be effective treatment in most cases. Careful follow-up is warranted as there is no basis for assuming that persisting placental site nodules might not serve as a precursor of, or be associated with, a placental site trophoblastic tumor in some instances.

Placental Site Trophoblastic Tumor

The placental site trophoblastic tumor (PSTT) is a rare malignant tumor developing in women who have been pregnant previously.[204–209] It is composed of intermediate trophoblast that secretes small amounts of β-hCG. Grossly, tumor nodules are hemorrhagic and fleshy and may occur at any site in the uterus. Microscopically, it consists of invasive sheets and nodules of monotonous, malignant-appearing, intermediate trophoblast that splay apart, but do not destroy, myometrial fibers (Fig. 8-100). The tumor is strongly hPL positive, with focal hCG positivity. Surgery remains the mainstay of treatment, because the tumor—unlike choriocarcinoma—responds poorly to chemotherapy. Most recurrences tend to be local, although systemic metastases may be fatal.[206,208] Only 10% to 15% of PSTTs behave malignantly, and behavior cannot always be predicted by histopathologic

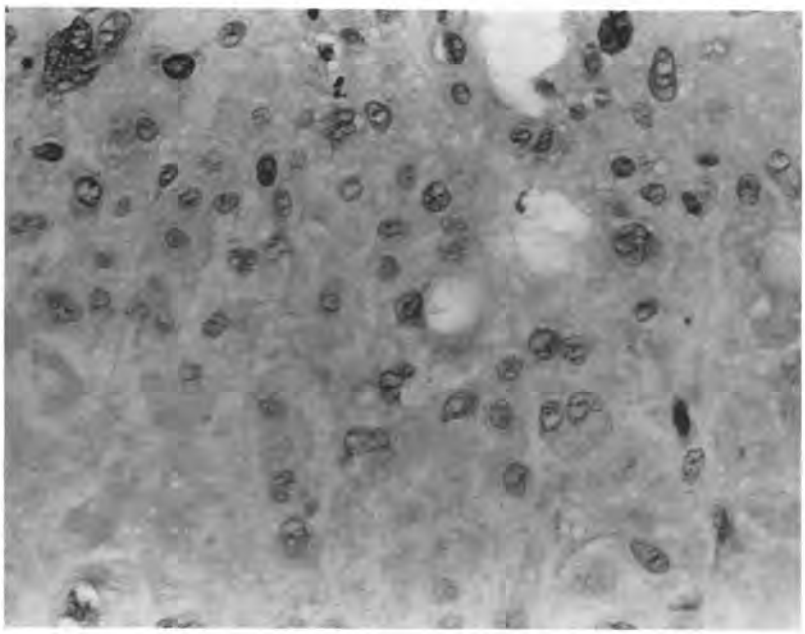

FIGURE 8-98 Placental-site nodule, higher magnification of Figure 8-97, showing loosely formed columns of uninucleate and multinucleate intermediate trophoblast without mitotic activity.

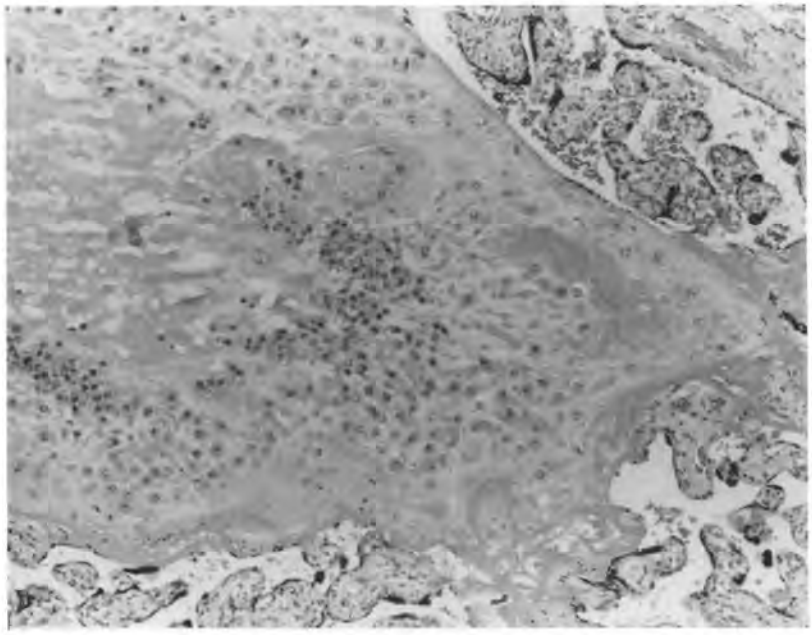

FIGURE 8-99 Placental septum from a normal term placenta showing intermediate trophoblast surrounded by acellular fibrinoid. Anchoring villi are attached to surface of placental septum. Placental-site nodules most likely represent residua of normal placental septa or cell islands.

analysis.[204–209] It has been suggested that numerous mitotic figures (over 5 per 10 high-power fields), extensive necrosis, and strong and diffuse hCG immunoreactivity are more frequently associated with malignant behavior.[207,209]

Placental site trophoblastic tumor must be differentiated from choriocarcinoma as the clinical management differs significantly. Choriocarcinoma is characterized by a proliferation of intermediate trophoblast and cytotrophoblast with foci of diagnostic syncytiotrophoblast (Fig. 8-101). Tumor necrosis and hemorrhage are pronounced. Choriocarcinoma is strongly hCG-positive by immunohistochemistry, and elevated serum β-hCG values suggest choriocarcinoma. Placental site tumor is devoid of syncytiotrophoblast and is far less necrotic. Its tumor cells are immunoreactive for hPL with minimal hCG staining. Serum β-hCG is virtually always low in women with placental site trophoblastic tumors. Both tumors are keratin-positive.

Gestational Choriocarcinoma

Reported incidences of choriocarcinoma range from 1 in 20,000 livebirths[210] and 1 in 40,000 deliveries[186] in the United States to 1 in 570 to 1 in 1650 deliveries in Indonesia.[188] The risk of gestational chorio-

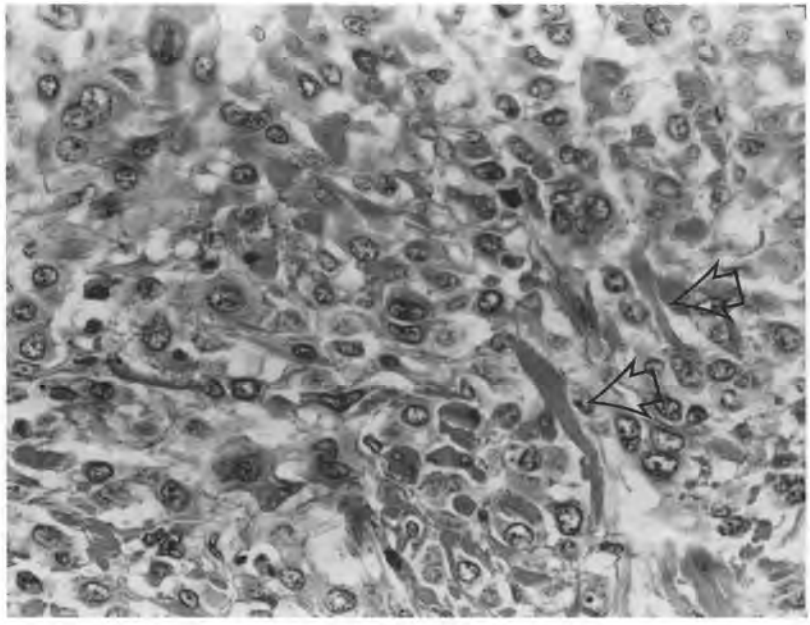

FIGURE 8-100 Placental-site trophoblastic tumor composed of sheets of intermediate trophoblast invading the myometrium. Tumor splays apart the individual myometrial myocytes (*arrows*) without inducing significant necrosis or hemorrhage.

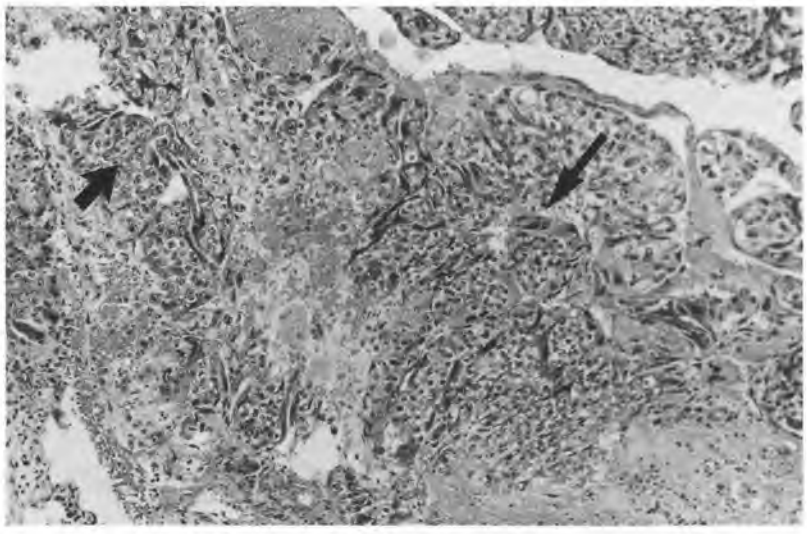

FIGURE 8-101 Choriocarcinoma showing extensive tumor necrosis and hemorrhage. Viable tumor consists of nests of cytotrophoblast (*short arrow*) capped by syncytiotrophoblast (*long arrow*).

carcinoma depends on the nature of the antecedent pregnancy: 50% of gestational choriocarcinomas follow complete hydatidiform mole, 25% follow spontaneous abortion, 22.5% follow normal pregnancy, and 2.5% follow ectopic pregnancy.[211]

Choriocarcinoma most commonly affects the uterus and is manifested by vaginal bleeding. Numerous bizarre presentations have been reported, reflecting the extent of widespread, systemic metastases present at the time of initial diagnosis. The tumor is characterized by hCG production, and hCG level relates to tumor burden.

Although postmolar gestational choriocarcinoma may be virtually uniformly cured by chemotherapy, the same is not true for choriocarcinoma developing after normal delivery. This may reflect the increased time interval between onset of tumor and diagnosis as well as differences in DNA content and parental source. The DNA of postmolar choriocarcinoma is usually totally androgenetic, being derived from the complete mole,[212] whereas postgestational choriocarcinoma contains the normal, biparental DNA of the delivered infant or fetus.[212–214]

Grossly, choriocarcinoma is recognized by its strikingly dark red, hemorrhagic appearance. Uterine choriocarcinomas may be polypoid, projecting into the endometrial cavity, or solely intramyometrial, or diffusely replacing the entire corpus and cervix. Large areas may be necrotic. When metastatic, tumor nodules tend to be well-circumscribed, hemorrhagic and necrotic.

Microscopically, the degree of tumor necrosis, hemorrhage and infarction is unsurpassed by most malignant tumors. Diligent searching for viable tumor reveals islands of uninucleate intermediate trophoblast and cytotrophoblast alternating with

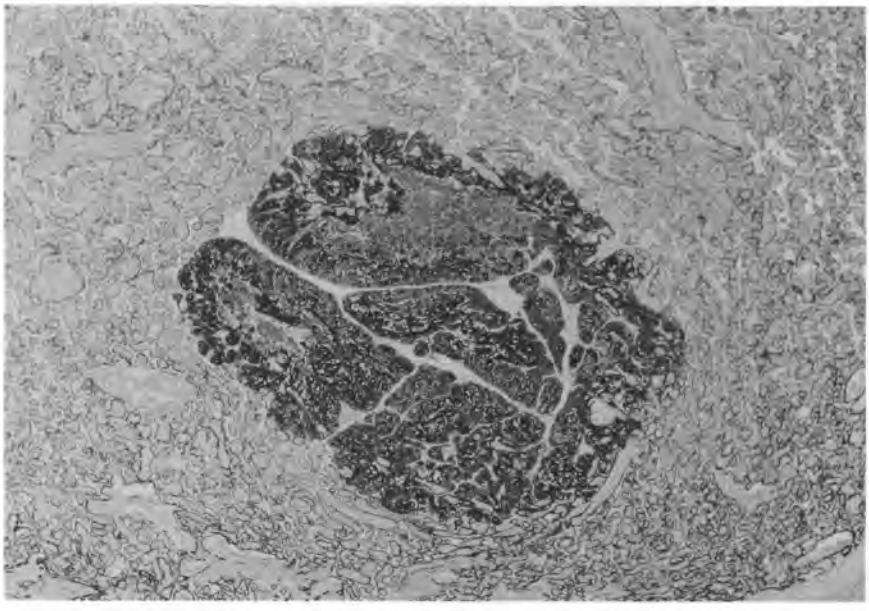

FIGURE 8-102 Choriocarcinoma in a term placenta. Keratin immunostaining (AE1/AE3 Boehringer-Mannheim, Indianapolis, IN) highlights malignant cytotrophoblast and syncytiotrophoblast surrounded by normal term villi. Tumor islands contain much central necrosis. (Lage JM, Roberts DJ. Choriocarcinoma in a term placenta: Pathologic diagnosis of tumor in an asymptomatic patient with metastatic disease. Int J Gynecol Pathol 12:80–85, 1993.)

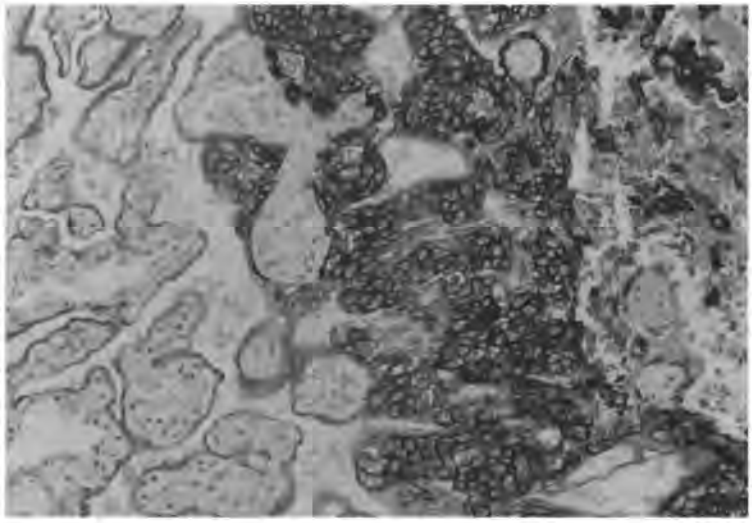

FIGURE 8-103 Choriocarcinoma in a term placenta, higher magnification of Figure 8-102, keratin immunostain (AE1/AE3, Boehringer-Mannheim, Indianapolis, IN). Tumor develops from trophoblast of normal-appearing villi and proliferates, forming avillous nodules of choriocarcinoma. Note the central necrosis of one tumor nodule at right. (Lage JM, Roberts DJ. Choriocarcinoma in a term placenta: Pathologic diagnosis of tumor in an asymptomatic patient with metastatic disease. Int J Gynecol Pathol 12:80–85, 1993.)

syncytiotrophoblast (see Fig. 8-101). The syncytiotrophoblast tends to remain peripherally located, encircling nodules of uninucleate trophoblast. Small clusters of syncytiotrophoblast demarcate the somewhat larger foci of uninucleate trophoblast giving the tumor an overall biphasic appearance. Although the cells of many undifferentiated tumors may simulate the appearance of uninucleate trophoblast, the presence of syncytiotrophoblast, characterized by multinucleation and abundant violaceous to blue cytoplasm, is required to diagnose choriocarcinoma. Syncytiotrophoblastic nuclei tend to be small and inconspicuous, with occasional eosinophilic nucleoli, although larger nuclei are sometimes seen. In contrast, the uninucleate trophoblast (cytotrophoblast and intermediate trophoblast) has greater cytologic atypia, with cells containing large, lobulated and even bizarre nuclei, coarse chromatin, and prominent nucleoli. The cytoplasm tends to be clear to granular and slightly eosinophilic in cytotrophoblast, and dense, amphophilic to eosinophilic in intermediate trophoblast.

Choriocarcinoma has a predilection for early and extensive vascular space invasion, leading to systemic metastases even when tumor volume is small. Destructive endometrial and myometrial invasion are identified in hysterectomy specimens (now rarely seen) and may be seen in uterine curettings. Large sheets of tumor cells differentiating into syncytiotrophoblast and cytotrophoblast or intermediate trophoblast, absence of villous tissue, and destructive endomyometrial invasion have been offered as criteria required for the diagnosis of choriocarcinoma in uterine curettings.[215] Choriocarcinoma is strongly immunopositive for keratin and hCG, with weak immunopositivity for hPL.

Choriocarcinoma, like the placental site tumor, is devoid of villi, the only exception being those tumors arising in association with a placenta.[216,217] In such cases, the villous origin of the malignant trophoblast is easily discerned (Figs. 8-102 and 8-103). The presence of molar villi from a partial or complete hydatidiform mole obviates a diagnosis of choriocarcinoma, even if sheets of obviously malignant trophoblast are identified. Chemotherapy with surgery as an adjunctive modality offers cure in 81% of all women and in 71% of those with metastatic tumor.[218] Although choriocarcinoma may arise from a placenta at any point in gestation, fetal metastases are uncommon, but uniformly lethal. Presentation in an infant or fetus in the absence of any evidence of maternal tumor has been reported.[219]

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APPENDIX 8-1
Protocol for Gross Placental Examination

WOMEN'S & PERINATAL PATHOLOGY **PLACENTAL EXAMINATION**

NAME **AGE:** Path.*

UH* **EDC** Date Dr.:

HISTORY: Prenatal and labor

INFANT: _____ lb. _____ oz. Term Premature Alive

Stillborn Macerated Sex

Other

(Twins Sex: 1: 2: Weight: 1: 2:)

GROSS EXAMINATION (In case of multiple gestation, use one form for placenta of each infant):

WEIGHT: _____ gm. **DIMENSIONS:** _____ × _____ × _____ cm.

CORD: _____ cm. Insertion: _____ cm. from margin. Membranous_____

Color: _____ No. of vessels: _____ Other: _____

FETAL SURFACE: Color: _____ Dull: _____ Opaque Membranes: _____

Subchorionic fibrin: None: _____ Slight: _____ Moderate: _____ Extensive: _____

Other:

MEMBRANES OF SAC: Complete: _____ Uncertain: _____ Incomplete:_____

Insertion: Marginal _____% Circummarginate _____% Circumvallate _____%

Edema _____ Nearest pt. of rupture _____ cm.

Decidual Necrosis (Extent and Location):

Other:

(Twin Dividing Membranes: Amnions _____ Chorions _____)

MATERNAL SURFACE: Complete: _____ Uncertain: _____ Incomplete: _____

Depressions: Location & Dimensions (apparent cause?):

*Designate as #1 and #2, if so labeled when received. Designate as A and B, if arbitrarily labeled.

PLACENTAL EXAMINATION (continued)

Path. #

MATERNAL SURFACE (continued):

Old Hemorrhage: _____ Dimensions _____ × _____ × _____cm.

Retroplacental _____ Retromembranous _____ Distant from margin: _____cm.

Recent Hemorrhage: _____ Dimensions _____ × _____ × _____ cm.

Retroplacental _____ Retromembranous _____ Distant from margin: _____cm.

Calcification: Slight _____ Moderate _____ Extensive _____

Other:

CUT SURFACE: Color (Normal, Pale, Congested, Mottled) _____

Consistency (Spongy, Firm, Gritty) _____

Intervillous Thrombi: Laminated: Number, Dimensions _____

Not Laminated: Number, Dimensions _____

Marginal Sinus Thrombi (Describe) _____

Infarcts: Color, Dimensions & Location: _____

Other:

GROSS SUMMARY:

FINAL DIAGNOSIS:

REMARKS:

Examined by: _____

Courtesy of Brigham and Women's Hospital, Boston

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9 Ectopic Pregnancy

Ectopic pregnancy is significant because of its clinical consequences and the frequency with which it occurs. About 0.3% of all pregnancies are ectopic, and the frequency is increasing worldwide.[1-4] In the United States, ectopic pregnancy accounts for up to 10% of maternal deaths, and mortality is even higher than that in black women.[1,5]

Ectopic pregnancy is the consequence of an anomaly of implantation of the ovum. For various reasons, which are not always understood, the migration of the fertilized egg is sometimes disturbed. Implantation, instead of taking place in the endometrial cavity, is brought about in a uterine cornu, the fallopian tube, or, more rarely, in the ovary, cervix, or peritoneal cavity.

Most ectopic pregnancies evolve for a period of a few weeks and are terminated by the death of the fetus, which is caused by hemorrhage or by rupture of the walls containing the ectopic conceptus (due to distention or corrosive action of the villi). However, a significant percentage of cases continue into the second or even the third trimester, and deliveries of live infants occasionally take place.

In addition to decidual transformation of the endometrium, other endometrial histologic changes may suggest the existence of an ectopic pregnancy (Arias-Stella phenomenon; see Chap. 4). The abnormal localization of the implantation site causes hemorrhage in the placenta. The decidual mucosa may separate from the endometrial wall as a single cast or as multiple fragments. This expulsion follows the death of the fetus after an interval varying from a few hours to a few days. The decidual fragments are infiltrated by leukocytes, and the glands show a regressive appearance of postmenstrual type. The absence of chorionic villi, trophoblastic cells, and fetal parts in a uterine evacuation specimen for induced abortion should always be noted and investigated thoroughly. The failure to recognize ectopic pregnancies in this situation has led to maternal death.[6]

ETIOLOGY

The etiology of ectopic pregnancy is not entirely understood, and diverse mechanisms are invoked to explain ectopic implantation of the conceptus. The migration of the ovum may be disturbed by mechanical factors, including tubal chronic inflammation, compression of the pathway of migration by intrinsic or extrinsic tumors, diverticula, or endometriosis.[7,8] The most important factor in tubal ectopic pregnancy is previous tubal inflammatory disease. This is true whether salpingitis is implicated by clinical history,[4] antibody studies for *Chlamydia trachomatis* or other organisms,[3] or direct histopathologic examination of the uninvolved tube.[8-11] A few studies have identified salpingitis in as low a proportion as 29% of the tubes involved by ectopic pregnancies.[2] However, most studies found the prevalence of salpingitis to be in the range of 90%, which was significantly greater than the percentages found for control tubes[9,11] and included even tubes that were laparoscopically normal.[10] In recurrent ectopic pregnancies in tubes previously treated conservatively, the underlying tubal disease (including salpingitis isthmica nodosa) seems to be the major causal factor.[12] In women who were exposed in utero to diethylstilbestrol (DES), tubal

malformations rather than inflammatory lesions appear to be responsible for the increased frequency of tubal ectopic pregnancy.[7,13]

Another suggested cause of ectopic pregnancy is the presence of ectopic endometrial tissue (endometriosis) in the tube, which favors implantation at that site, although this is an uncommon association.[4,9] In some cases, there may be increased receptivity of the tubal mucosa to ovular implantation. In other cases, delayed ovulation and inadequate development of luteal endometrium may lead to failure of normal implantation, with subsequent menstrual bleeding impeding the progress of the ovum in the tube; this mechanism is considered uncertain.[14] It is possible that still unknown anomalies of the ovum may be responsible for nidation.

Induced abortion is claimed to increase the incidence of subsequent ectopic pregnancy.[15,16] More recent studies have denied this association unless there is postabortal infection, in which case the effects are mediated through the pathway of salpingitis.[17,18]

In women with intact intrauterine contraceptive devices (IUDs), almost 5% of all pregnancies are ectopic, apparently because the IUD is far more effective in reducing intrauterine than extrauterine pregnancies.[4] However, the rate of ectopic pregnancies per thousand woman-years of IUD use is not increased.[19,20]

Other iatrogenic causes of ectopic pregnancy have been postulated. These include ovulation induction with clomiphene citrate, human pituitary gonadotropin, or human chorionic gonadotropin, suggesting that the pathogenesis involves an endocrine disturbance, such as unusually high estrogen levels;[21] in vitro fertilization with insertion of the embryo directly into the fundus, which supports the theory of retrograde menstrual flow after delayed ovulation;[22] and failed tubal sterilization procedures, particularly laparoscopic and especially electrocoagulation, emphasizing the role of mechanical tubal factors.[23]

Previous ectopic pregnancy greatly increases the risk for another ectopic gestation and for infertility.[4,8,12,24] The risk factors probably include the therapeutic tubal surgery itself and the underlying tubal inflammation that may have been responsible for the first tubal pregnancy.

TUBAL PREGNANCY

Tubal pregnancy is by far the most frequent type of ectopic pregnancy. More than 97% of 1559 ectopic pregnancies in two large series were tubal localizations.[25,26] Implantation takes place most often in the ampullary portion, less frequently in the isthmic portion, and rarely in the interstitial portion of the tube.[9,27] Bilateral tubal pregnancy has been reported in more than 150 cases.[28] Simultaneous intra- and extrauterine pregnancy has been reported in more than 500 cases.[29]

Tubal pregnancy is characterized by the following symptoms, in descending order of frequency: lower abdominal pains, bloody vaginal discharge, and periods of amenorrhea, nausea, and vomiting. The most common objective findings are cervical tenderness, uterine contractions and other signs of early pregnancy, abdominal tenderness, fluid in the abdominal cavity, and a tender adnexal mass. Rupture is accompanied by violent pains, abdominal rigidity and rebound tenderness, and signs of incipient or actual shock secondary to internal hemorrhage. Common positive findings in the clinical history include a history of infertility for several years before the current incident, a history of previous salpingitis, and, more rarely, a history of a previous ectopic pregnancy. The incidence of repeated contralateral ectopic pregnancy ranges from 7% to 27%.[25,30] Repeated ipsilateral tubal pregnancy is becoming more common after conservative operative therapy.[2,12,24]

Macroscopically, the tube is enlarged and takes an ovoid shape. The serosa is stretched and congested (Fig. 9-1). Placental villi progressively erode into the wall until they provoke rupture of the tube. In some cases, hemorrhage is so pronounced that it leads to fetal death before rupture takes place. This hemorrhage is due to destruction of an arterial or arteriolar wall and leads to weakening of the implantation of the ovum with rupture of the capsule surrounding it (Fig. 9-2).

Microscopically, in some cases, there is a well-developed decidual reaction in the submucosal stroma. This reaction is usually minimal compared with that in the endometrium, and it presents in the form of small cell nests.[31] That portion of the tubal mucosa that is not directly involved by the placental tissues shows abundant leukocytic infiltrates. The gestational tissue itself is often completely or largely intraluminal, although invasion of the tubal wall may occur earlier in isthmic than in ampullary cases.[2,8,32] Villi are sometimes found only after a protracted search or not at all, with the final histopathologic diagnosis being hematosalpinx. In conservatively treated cases (less than salpingectomy), the embryo frequently is not identified.

In other cases, fetal death is not accompanied by hemorrhage or rupture, and the fetoplacental tissues undergo fibrotic regression. The pathologist may discover hyalinized and sclerotic debris of placental villi on examination of a tube resected at a later date for other clinical indications.[33] Secondary calcification and fetal mummification are rarer sequelae.

If the trophoblastic tissues have undergone such a degree of degeneration that their hormonal activity has ceased, biological tests for pregnancy may be negative. Other diagnostic maneuvers that may be of value include endometrial curettage, examination under anesthesia, culdoscopy, and culdocentesis (aspiration of nonclotting blood is suggestive but not di-

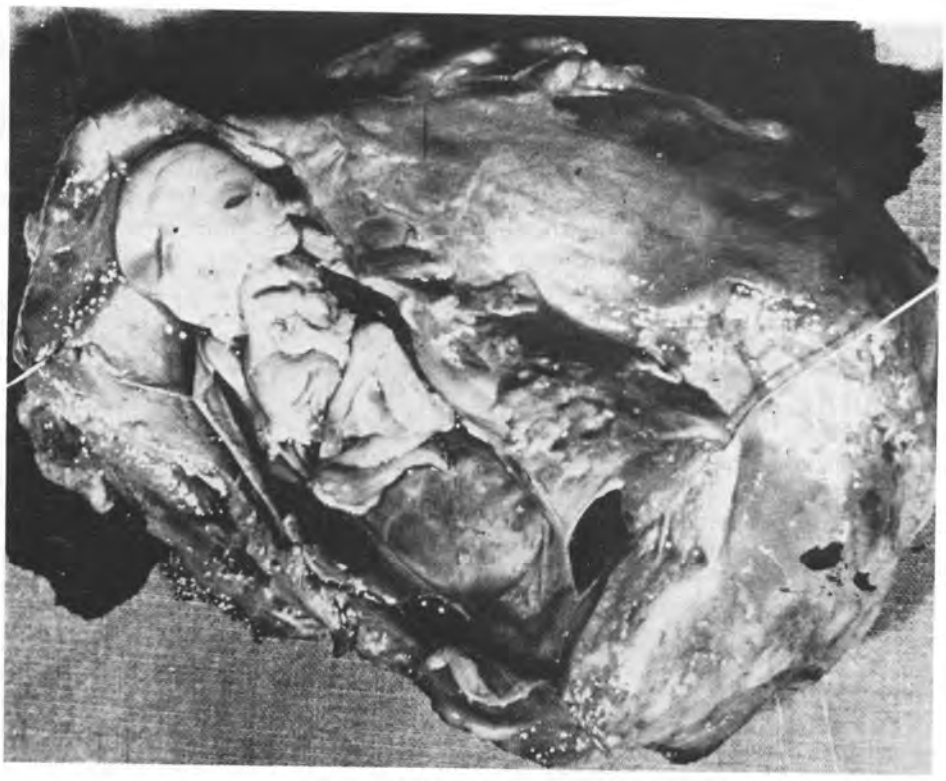

FIGURE 9-1 Ruptured tubal pregnancy.

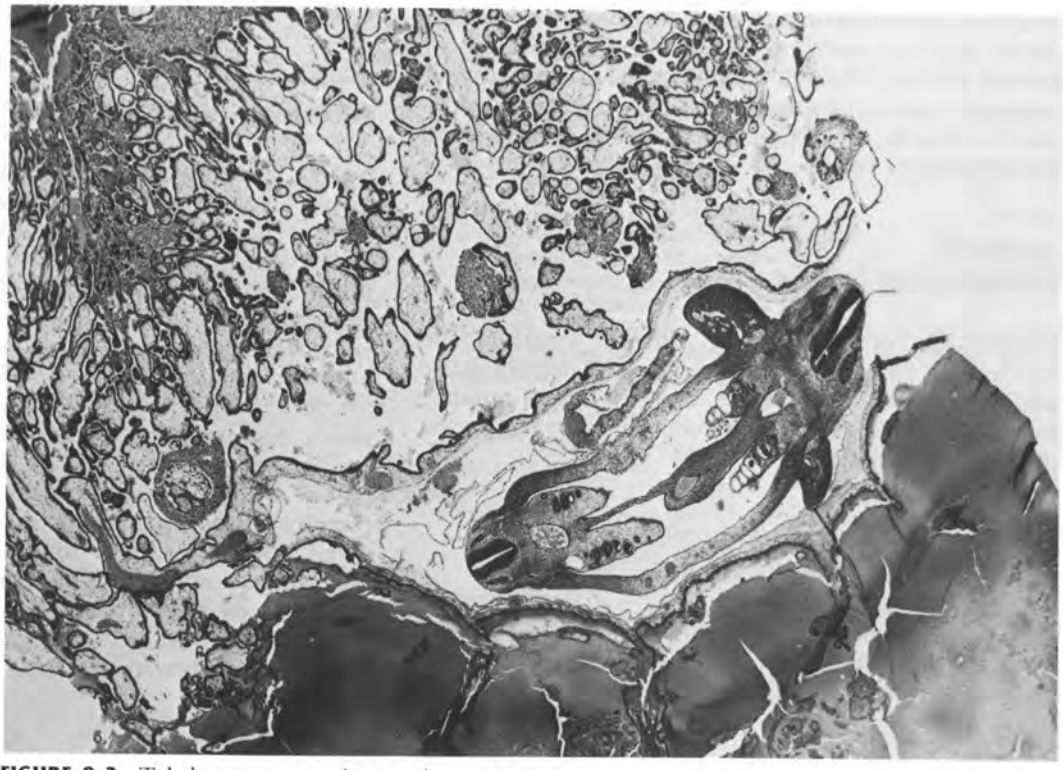

FIGURE 9-2 Tubal pregnancy: microscopic appearance.

agnostic of ectopic pregnancy). A newer modality that has been of great value is ultrasonography.[27]

The maternal mortality in tubal pregnancy is around 0.1%, and fetal mortality is nearly 100%.[5] Less than 50% of women treated for tubal pregnancy are able to conceive thereafter, and a contralateral tubal pregnancy develops in many of these women.[24,30] As a general rule, the severity of chronic inflammation in the excised tube is inversely related to the chance for a subsequent normal pregnancy.[8,30]

ANGULAR PREGNANCY

Angular or cornual pregnancy is characterized by the implantation of the ovum in a uterine cornu. This rare event generally terminates in abortion before the fourth month. Examination of the uterus reveals a soft hemorrhagic zone in one of the cornua, from which fetoplacental debris can be recovered.

INTRAMURAL PREGNANCY

Intramural pregnancy refers to a conceptus completely surrounded by myometrium and showing no connection with the endometrium or the tube. This is a rare presentation.[34] The fertilized ovum may enter the myometrium from the endometrial or serosal surface. Postulated mechanisms include adenomyosis, previous uterine trauma, abnormal endometrial glands, increased trophoblastic activity, and perforation of uterine blood vessels.

ISTHMIC PREGNANCY

Ovular implantation in the cervical canal at the isthmus is frequently complicated by hemorrhage and rupture of the uterine wall. If the pregnancy evolves, dystocic accidents such as placenta previa must be considered.

CERVICAL PREGNANCY

Development of the ovum in the cervical tissues leads to serious hemorrhages at the time of placental separation. This type of pregnancy almost always results in abortion. The maternal mortality rate is 30%.[35]

Macroscopic examination shows a voluminous, soft, hemorrhagic, and necrotic cervix contrasting with a small corpus uteri. Histologic examination confirms the diagnosis of ectopic pregnancy by demonstration of fetoplacental debris in the cervix, without corporeal attachment.

OVARIAN PREGNANCY

More than 400 cases of primary ovarian pregnancy are reported in the literature; they are estimated to account for 0.17% to 4.7% of all ectopic pregnancies.[36,37] The true value is probably closer to the lower figure. The criteria that must be satisfied before this diagnosis is made are as follows:

1. The tube must be intact and separate from the ovary, with no microscopic evidence of tubal pregnancy.
2. The gestational sac must be in the normal position of the ovary and connected to the uterus by the utero-ovarian ligament.
3. Ovarian tissue must be demonstrated in the wall of the gestational sac.

The localization of the products of conception may be intrafollicular or extrafollicular. The former is thought to be the result of a disturbance of ovulation, whereas the latter may be due to inhibition of discharge of the ovum secondary to mechanical factors (eg, inflammation, hypoplastic tube, uneven ovarian surface, or endometriosis).

Although most of these cases terminate in abortion in the first trimester, full-term live births have been reported in about 1 in 25 cases. A significant percentage of these infants are malformed.

ABDOMINAL PREGNANCY

Several hundred cases of abdominal pregnancy have been described. This presentation is said to occur once for each 15,000 live births,[38] and once for each 70 ectopic gestations.[39] It may be primary or, more often, secondary to an expelled ovarian or tubal pregnancy.

The placenta can develop among the intestinal loops or on an appendix epiploica, although it most often develops on the peritoneal surface. The pregnancy may result in a viable infant as a result of secondary vascularization from the peritoneum. About half of these infants are born alive, but most subsequently do not survive. A dead fetus, if not recognized and removed immediately, may undergo skeletonization, saponification (replacement of the soft parts by fats and soaps), suppuration or abscess formation, or lithopedion formation (sterile calcification). The maternal mortality rate is approximately 10%.[39]

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10 The Breast

EMBRYOLOGY

Phylogenetically, the breast originates in sweat gland tissue and arises as a cutaneous appendage. It appears in the 8-mm embryo as a longitudinal cutaneous thickening situated on each side of the midline and extending from the axillary to the inguinal region.[1,2] These mammary crests regress rapidly except in the thoracic region, and in the 20-mm embryo the only one persisting is the precursor of the future mammary gland (Fig. 10-1). When regression is incomplete, aberrant (supernumerary) mammary glands develop.

In the fifth month of fetal life, 15 to 20 epithelial buds arise on the deep surface of the mammary crest and ramify to form the outlines of the lactiferous ducts. In the eighth month, the epithelial cords develop lumina. Proliferation of the connective tissue stroma of the central region forms the nipple. Apocrine glands develop around the nipple to form Montgomery's glands.[3] Once at this stage, the breast is not modified further until birth. At this time, under the influence of maternal hormones, the primordial lactiferous ducts ramify and briefly secrete a milky substance (colostrum or "witch's milk") containing fat globules, protein granules, and corpuscles of Donné.

At puberty, the evolution of the gland begins again and is completed. The main lactiferous ducts develop numerous prolongations (secondary lactiferous ducts) and terminate in small saccular structures lined by cuboidal epithelium (alveoli). Each main duct and its ramifications constitute a mammary lobe, of which there are 15 to 20 in each breast. The proliferation of these epithelial structures is accompanied by development of the vasculoconnective tissue framework and adipose tissue.

ANATOMY

The breast is composed of a glandular apparatus and fibroadipose tissue; it rests on a musculo-connective tissue bed.[1,2] In the center of its convex surface is an epidermis-covered, circular, pigmented region measuring about 2 cm in diameter, known as the *areola*. The nipple is situated at the center and forms a cylindrical excrescence of about 1 cm in diameter. Surrounding the nipple are the tubercles of Montgomery.[3] The arteries of the breast are branches of the internal mammary, external mammary, and intercostal arteries.

The lymphatics merit a more detailed description because they play an important role in the dissemination of malignant tumors of the breast.[4,5] Some of the perilobular, perialveolar, and ductal, and all the cutaneous lymphatics drain into the areolar plexus, from which three lymphatic groups arise: external, internal, and inferior. Many of the deep lymphatics of the breast bypass the areolar plexus and drain directly into these groups. The external mammary lymphatics form several large trunks, which flow peripherally around the external border of the pectoralis major muscle and terminate in the nodes surrounding the external mammary vessels. These nodes are in direct continuity with the other nodes of the axilla.

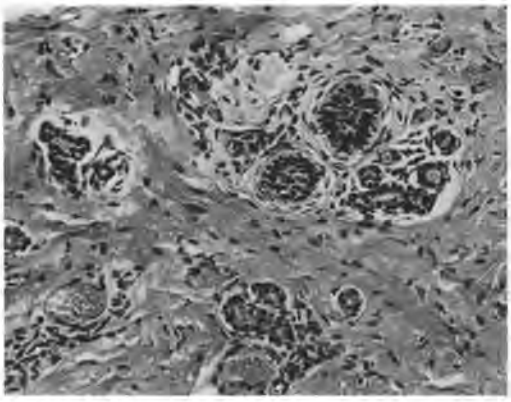


FIGURE 10-1 Fetal mammary gland.

The axillary nodes, from 10 to 30 in number, constitute five groups: (1) the group of the axillary vein; (2) the external mammary group; (3) the scapular group; (4) the central group; and (5) the subclavicular group.

The interpectoral nodes of Rotter provide a potential direct pathway to the subclavicular group, bypassing the lower axillary nodes, but they are usually of little significance. The internal mammary lymphatics arise in the internal part of the areolar plexus, traverse the intercostal spaces, and flow into the nodes of the internal mammary vessels; they measure from 1 to 3 mm each and number 6 to 8. From there, the lymphatic chains proceed into the supraclavicular lymphatic system and the mediastinal nodes.

The inferior or inframammary lymphatics originate in the deep surface of the breast and flow into the anterior pectoral nodes and then into the axillary or subclavicular nodes. There are also lymphatic trunks coursing to the supraclavicular nodes and to the lymphatics of the contralateral breast. Finally, lymphatic pathways lead to the paravertebral chains. Injection studies using colloidal gold have shown that 97% of the lymph flows to the axillary nodes and 3% to the internal mammary chain.[6] Intramammary nodes have been reported in 28% of carcinomatous breasts and were involved by metastatic cancer in one third of all cases in which they were present.[5] Intramammary nodes are also frequently encountered as mammographically detected masses in benign breasts.[7]

The nerves of the breast come from the second through sixth intercostals and from the cervical and brachial plexus.

HISTOLOGY

The main lactiferous ducts consist of a stratified lining of superficial columnar cells and deep cuboidal cells underlain by a layer of myoepithelial cells. A fibroelastic lamina surrounds this glandular structure (Fig. 10-2). The secondary lactiferous ducts are of smaller caliber but have the same structure.

The acini are composed of cuboidal cells partially surrounded by discontinuous myoepithelial cells. During the nursing period, the cuboidal cells become columnar, and their apical poles are charged with fatty secretory droplets (apocrine secretion).

The ductules or terminal ducts connect ducts with their lobules and acini. They represent the cutoff point for the elastic fibers in the periductal stroma, have the greatest proliferative activity of all mammary epithelial units, and may represent the site of origin of most breast cancers.[8,9]

Electron microscopy has permitted us to understand better the fine structure of myoepithelial and epithelial cells (Figs. 10-3 and 10-4).[10,11] The myoepithelial cells have clear cytoplasm that is poor in cellular organelles and rich in fibrillar bundles of smooth muscle type. The epithelial cells have dense to clear cytoplasm corresponding to an uneven distribution of organelles. Cytokeratin and actin filaments are visible in the cytoplasm. The morphology of the epithelial cells varies with the phase of the menstrual cycle. Estrogen stimulates epithelial proliferation corresponding to a greater RNA synthesis, with increased nuclear density and a high mitotic count. Ultrastructural studies reveal an increase in number and size of the Golgi apparatus, ribosomes, and mitochondria. Progesterone induces the dilatation of ducts and secretion by the alveolar epithelial cells. Only in the third month of pregnancy and thereafter does secretory activity develop fully. Growth factors are also important in mammary development and function.[12] Argyrophilic cells are rare in normal breast tissue; some of them are hormonally active.

Premenstrual fullness is attributable to increasing interlobular edema and ductular and acinar proliferation. Steroid receptors and membrane-bound peptide receptors are involved in these mechanisms.[12]

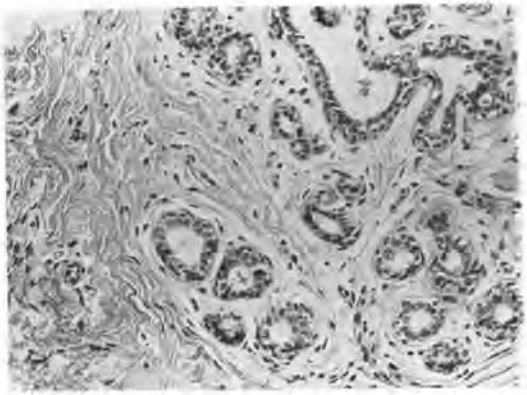


FIGURE 10-2 Normal mammary terminal ductule (*upper right*) and lobule. Note the epithelial and surrounding myoepithelial cells and the loose intralobular and dense inter- or perilobular stroma.

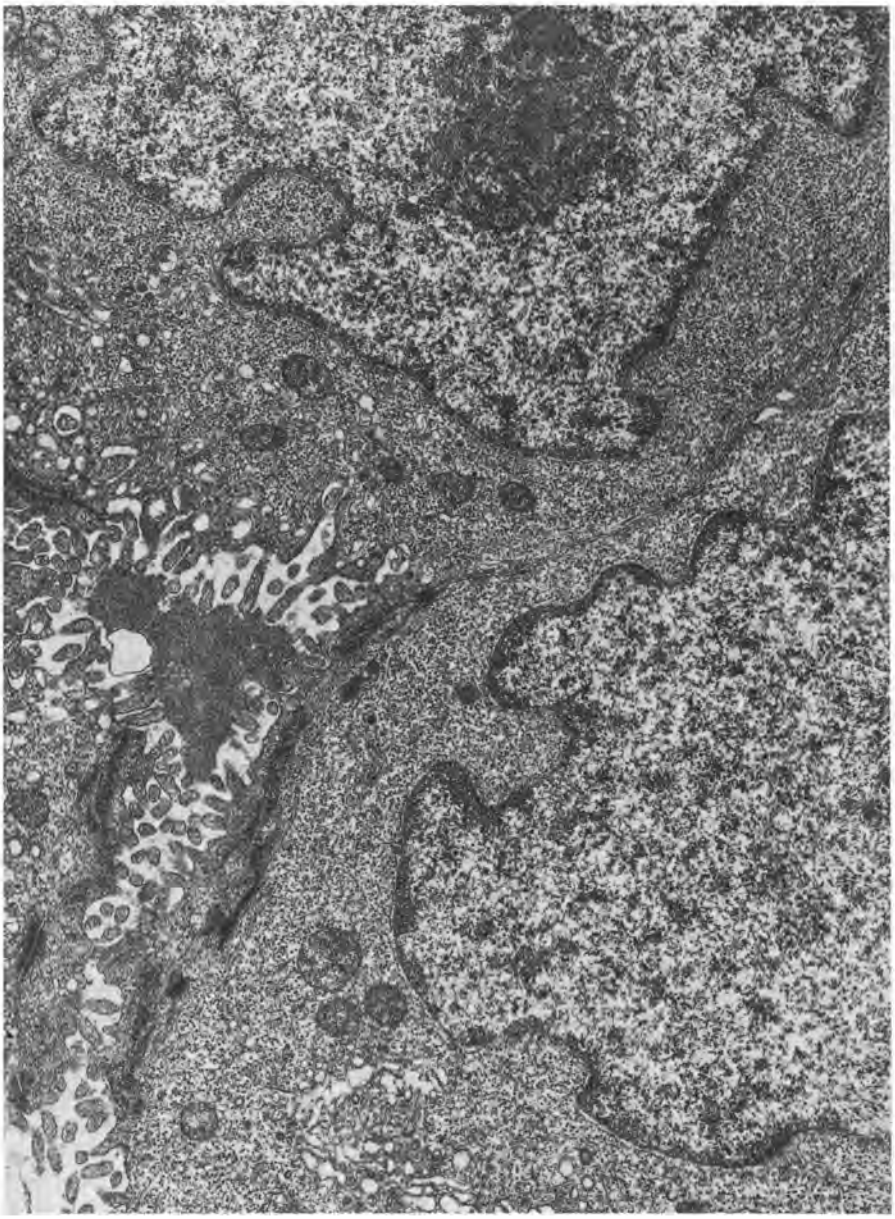


FIGURE 10-3 Electron micrograph of luminal aspect of normal mammary terminal duct. Note the numerous microvilli, tight junctions, and desmosomes.

During pregnancy, the breast undergoes a period of proliferation and remarkable hyperplasia (Fig. 10-5). These changes are a result of the activity of sex steroid hormones, prolactin, placental lactogen, and chorionic gonadotropin. The ducts form new digitations that terminate in numerous acini. During the nursing period, the epithelial cells develop marked secretory activity, with the production first of colostrum and later of milk. The secretory cells produce fat, lactose, and proteins through apocrine and merocrine mechanisms. Thus, the breast passes through three phases of development: at birth, at puberty, and during pregnancy.[12] It undergoes atrophy after the menopause (Fig. 10-6).

The intralobular connective tissue stroma is poor in collagen fibers and adipose tissue. It participates in the histophysiologic modifications of the mammary gland.[12,13] On the contrary, the perilobular connective tissue is thick and does not undergo histologic transformation during the various stages of development of the breast.

The nipple is covered by pigmented epidermis showing numerous papillae penetrating into the dermis. The stroma contains smooth muscle fibers, which constitute the areolar muscle, and accessory mammary glands derived from apocrine glands (glands of Montgomery).[3] At the periphery of the areola are found sebaceous and sweat glands and a few hair follicles.

MALFORMATIONS

Absence of the nipple (athelia) or of the breast (amastia) is rare. The latter may be unilateral or bilateral and is often associated with other congenital

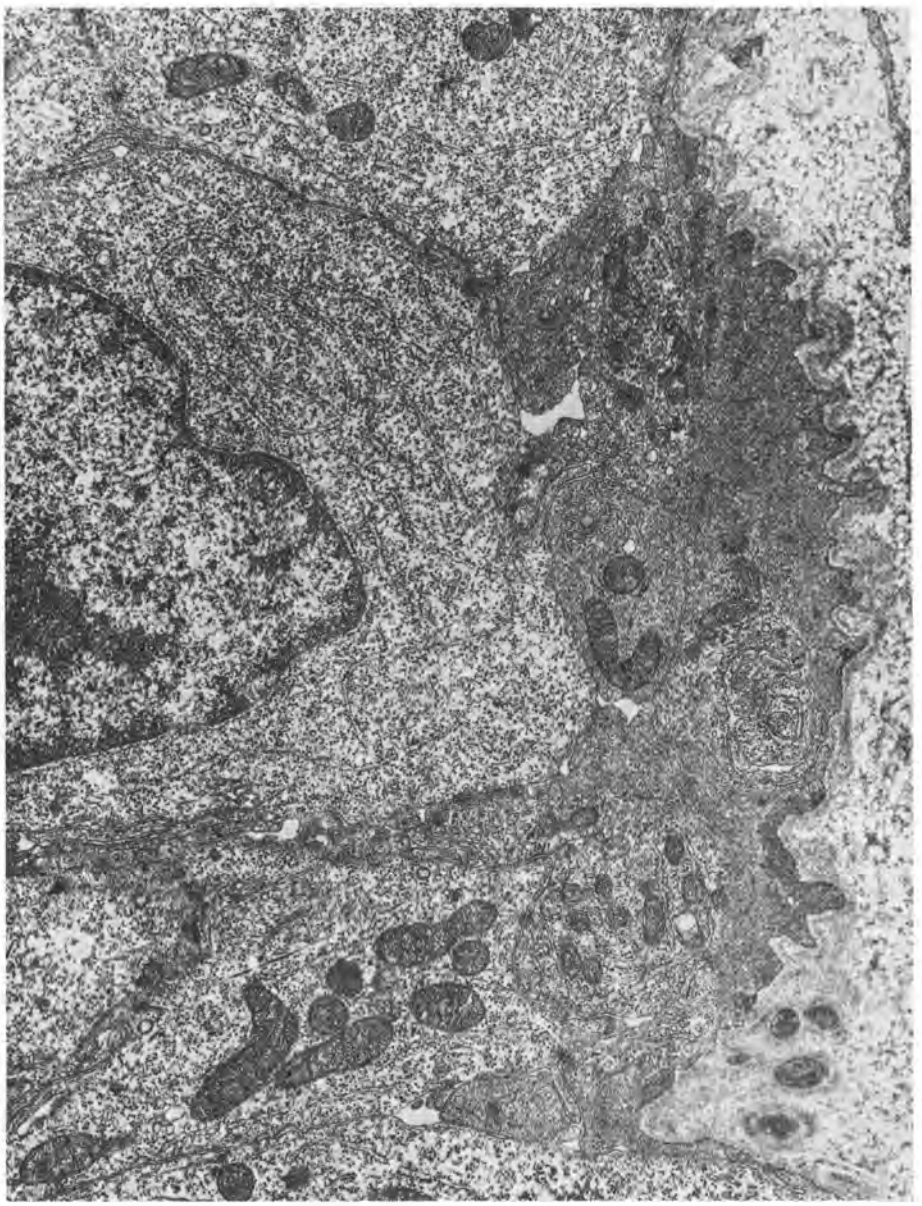


FIGURE 10-4 Basal aspect of the terminal duct shown in Figure 10-3. The dark cell at right is a myoepithelial cell, with hemidesmosomes bordering a basement membrane, to the right of which are collagen fibers. The light cells at left are the epithelial cells whose apical portions are seen in Figure 10-3.

anomalies. More common is the presence of supernumerary nipples (polythelia) or of supernumerary glands (polymastia). The aberrant formations are most often found in the path of the primitive mammary crest. They may be single or multiple, rudimentary or voluminous, and may show signs of secretory activity. They may be sites of benign or malignant tumors; axillary polymastia is a problem in this regard.

MAMMARY HYPERTROPHY

Mammary hypertrophy is found in the young girl of 8 to 10 years of age or at puberty. It is also seen in association with constitutional precocious puberty. It consists of unilateral or bilateral abnormal development of the mammary parenchyma. Before puberty, it may be provoked by a functional ovarian tumor, a luteal cyst, an adrenal cortical tumor, or a cyst of the third ventricle. In a certain number of cases, thorough investigation fails to reveal an underlying cause. Puberty usually brings about spontaneous amelioration. Mammary hypertrophy developing after puberty advances progressively and sometimes attains monstrous proportions, necessitating surgical treatment.[14] The hypertrophy may be unilateral. Histologically, the hyperplasia involves the ducts as well as connective tissue stroma and adipose tissue.

DIAGNOSIS OF BREAST LESIONS

Tumors constitute the major category in breast pathology, and the major reason for breast diagnosis is ultimately to diagnose and treat malignant tumors.

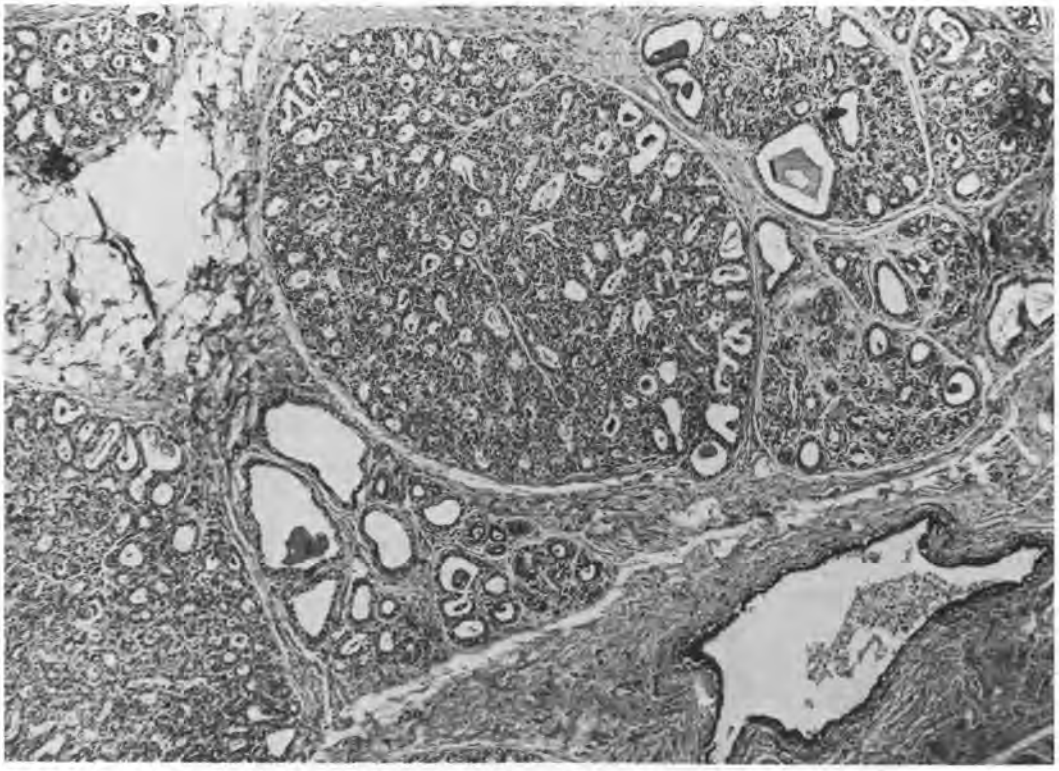


FIGURE 10-5 Lactating breast. Microscopic appearance.

The situation has changed markedly from 100 or even 20 years ago, when the patient generally presented to her physician with a self-detected mass, a biopsy was performed to determine whether the mass was cancer, and immediate operative treatment—usually without any adjuvant nonoperative therapy—was undertaken on the basis of that diagnosis.

In current practice, on the other hand, there are many variations from this classic scenario. First, most biopsies are performed in women who participate in screening programs in which abnormalities are detected radiographically, and many of these abnormalities are not palpable by the patient or the examining physician. Second, fewer and fewer operations for breast cancer are performed as one-stage procedures based on an intraoperative diagnosis. In most cases, the diagnostic procedure is separated from a subsequent therapeutic procedure by a period of days or even weeks. Third, it is now recognized that, rather than a simple diagnosis of benign versus malignant, numerous lesions exist which, although themselves benign, are premalignant or serve as markers of breasts at increased risk of developing cancer in the future. Finally, the therapeutic options for invasive cancers—as well as for preneoplastic conditions—now include various types of mastectomy and more limited operative procedures, as well as a vast array of adjuvant radiotherapeutic, hormonal, and chemotherapeutic options. The final choice or choices from this extensive menu depend on the specific diagnosis made by the pathologist and on additional features specific to each patient.

Clinical Diagnostic Techniques

As mentioned above, the classic—and for many years the only—diagnostic technique available to the clinician was inspection and palpation of the breast. At the beginning of the era of microscopic diagnosis, noted clinicians such as Velpeau could state that obvious cancers should be removed, and that there was no chance that "active and reasoned experience can ever be replaced by microscopic anatomy."[15]

In subsequent years, an extensive literature arose to prove that clinical impressions of the benignity or malignancy of palpable breast masses were often incorrect, and therefore must always be confirmed by biopsy. Even this literature is now largely of historic interest because of the decreasing proportion of mammary lesions presenting as palpable masses. Thus, a number of noninvasive techniques have arisen to assist the clinician in formulating an impression of a breast lesion.

Thermography and *infrared photography* depend on the difference between the skin temperature over a lesion and that over adjacent uninvolved breast tissue.[16] *Ultrasonography*, which uses high-frequency sound waves, is a totally noninvasive technique, like thermography, but both of these lack diagnostic precision and therefore should not be used as a

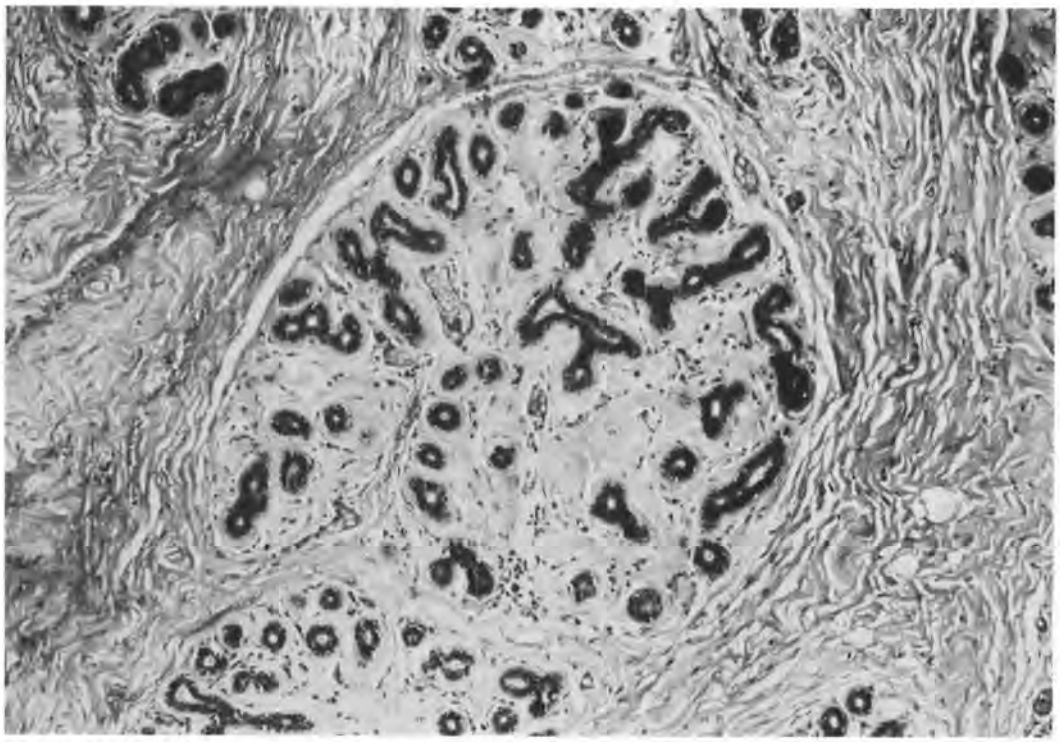


FIGURE 10-6 Perilobular fibrosis in an atrophic breast.

screening method in asymptomatic women.[16,17] *Galactography* (radiography after injection of the ducts with radiopaque dye) and *fiberoptic ductoscopy*[18] may identify lesions in cases of nipple discharge but cannot diagnose them accurately. With the latter technique, biopsy material can be obtained from the lesion. The most valuable technique is *mammography* (and its variant *xeroradiography*), a type of soft-tissue radiography of the breast. Mammography is of particular value in the detection of small, clinically impalpable malignant tumors, including those that have not yet invaded the stroma.[19–21] Although initially limited by its high percentage of error, mammography has shown a substantial change in the quality of its results because of improved image receptors and examination hardware and the increased experience of radiologists. This has been accompanied by a decrease in the dose of radiation to the patient, minimizing the potential danger of the technique. When used in conjunction with ultrasonography, which has a good ability to differentiate between solid and cystic masses, it provides complementary information. Unlike thermography, mammography has proved to be a useful technique for screening of asymptomatic women. About 25% of biopsies performed in this circumstance contain cancer, of which almost half are noninvasive.[22]

A certain diagnosis can be provided only by histologic examination. In instances of biopsy for mammographically suspicious or positive lesions, contralateral breast biopsy in patients with mammary cancer, specimens with noninfiltrating cancer, or any large biopsy with no grossly evident lesion, radiographic examination of the specimen can be an invaluable aid to the pathologist.[19,23,24]

Pathologic Diagnostic Methods

In addition to the purely clinical and noninvasive techniques discussed above—all of which essentially function to identify specific lesions for which a pathologic diagnosis must be obtained—there are numerous techniques available for transferring diagnostic tissues or cells from the patient to the pathology laboratory. These are discussed in general terms in this section, and the cytopathologic and histopathologic appearances of specific lesions are discussed under the headings of those lesions.

Fine-Needle Aspiration Biopsy

Fine-needle aspiration (FNA) cytology is easily performed, cost-effective, accurate, safe, and well accepted by patients. The technique is now well recognized after an eclipse of more than 40 years,[25] and many reports in the world literature reveal a high diagnostic efficiency.[26–29] This procedure is performed with an 18- to 22-gauge needle attached to a 20-mL syringe. Suction (which has been shown to be optional[30]) permits withdrawal of minuscule tissue fragments, which are smeared on a slide and fixed, preferably in 95% alcohol or with a commercial spray fixative. An air-drying technique can also be

used with staining by the Romanovsky or Diff-Quik technique. Rapid staining and examination are useful to verify that adequate material has been obtained and, in some instances, to reassure an anxious patient. Malignant cells are recognized by their manner of desquamation in plaques and by their cytologic alterations (Fig. 10-7; Color Figures 10-1 and 10-2).

The general diagnostic criteria applied in clinical cytology are used here: variations of the nuclear shape and size, modifications of the chromatin structure, enlargement of nucleoli, staining affinities of cytoplasm, and modifications of the cellular size and form.[26,28,29] In addition to diagnosing malignancy, aspiration cytology is able to recognize some particular forms of cancer such as colloid and signet-ring cell, medullary, and papillary cancers; squamous carcinomas and comedocarcinomas; and various sarcomas (see discussions of these tumors). Immunohistochemical methods for demonstrating hormonal receptors in aspiration smears are available.[31]

FNA cytology of palpable lesions provides a simple means of differentiating between cystic and solid breast masses. Clear fluid from cystic lesions can be discarded, because experience has shown the absence of suspicious cellular elements. If a solid area remains after the aspiration, or if the mass recurs, the procedure should be repeated.[32] The technique has given excellent diagnostic results (about 10% false-negative and less than 0.1% false-positive reports) in the hands of pathologists expert in the interpretation of this material.[27] Unsatisfactory specimens are less often obtained when pathologists perform the aspiration and immediately check the material for adequacy.[28,29]

The value of FNA in the evaluation of nonpalpable lesions is less well documented. It is only by chance that the needle will penetrate a microscopic lesion in the absence of a stereotactic procedure. Hook-wire systems have improved the location of minute pathologic foci and provide a relatively stable guide for the surgeon.[33] Nevertheless, we think that FNA has not replaced open biopsy for the diagnosis of suspicious nonpalpable lesions. Negative aspirations should be evaluated in concert with the mammographic findings, because nonpalpable lesions may have been sampled inadequately.

Core-Needle Biopsy

The core-needle biopsy method, which produces best results when using a rotating trocar coupled with a motor turning at great speed, has the advantage of permitting true tissue biopsies to be obtained.[34] The disadvantage (as with other incisional techniques, including FNA) is that the specimen available may be from the tissue surrounding a lesion rather than from the lesion itself when the latter is small. FNA tends to produce more accurate results than core-needle biopsy.[27]

Cytologic Examination of Nipple Secretions

Nipple secretions may be spread on a slide, fixed in alcohol-ether or air-dried, stained, and examined.

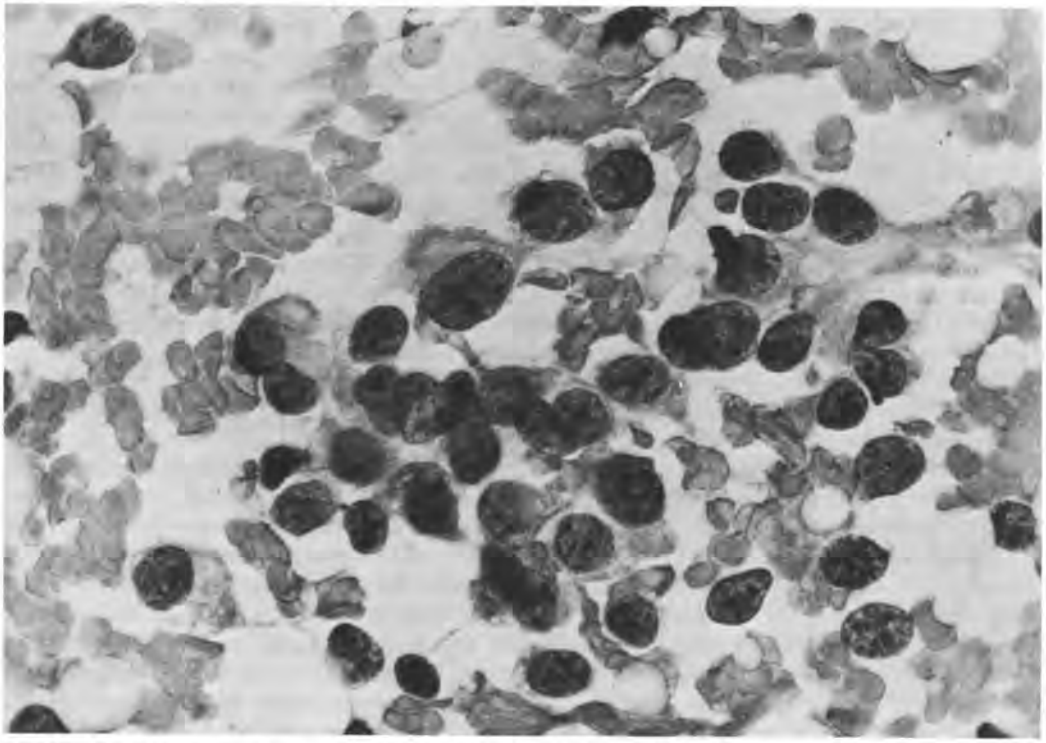


FIGURE 10-7 Mammary duct carcinoma: neoplastic cells in needle aspiration smear.

Spontaneous nipple discharge is usually produced by benign lesions involving large ducts, but cancer (usually intraductal) is occasionally the culprit.[35] When secretion is discrete, massage may be necessary. Even when this latter manipulation is used, most benign and malignant breast lesions do not produce nipple discharge. An additional disadvantage of this technique is the frequent necessity of extensive manipulation of the lesion, which may facilitate metastatic dissemination in cases of malignancy.

Open Surgical Biopsy

Open surgical biopsy remains the method of choice in many institutions. The fragment removed by the surgeon is immediately examined by the pathologist, and the most suspicious zones may be submitted for intraoperative histologic (frozen section) or cytologic examination. This technique permits rapid histologic interpretation, on the basis of which further excision, whether conservative or radical, may be planned. Immediate interpretation, however, may be difficult or even impossible; this is particularly the case for in situ carcinomas and atypical but benign intraductal lesions, some examples of sclerosing or microglandular adenosis, and paucicellular or well-differentiated infiltrating carcinomas. In these doubtful cases—and in many institutions in all cases—the surgeon must wait for the examination of permanent sections before proceeding.

In many institutions, intraoperative cytology is used as an adjunct to, or even a replacement for, the traditional frozen section examination in intraoperative pathologic consultation. The technique is more rapid than frozen section, and it enables the pathologist to study several regions of a suspicious tissue fragment. As with FNA cytology, alcohol-fixed or air-dried techniques may be used. The criteria used for diagnosis are similar to those used in FNA cytology.

Intraoperative cytology has three advantages over frozen section that are particularly important in breast pathology. First, intraoperative cytology preserves tissue from small tumors for use in adjunctive studies, such as receptor analysis and flow cytometry. Second, it eliminates diagnostic problems caused by architecturally atypical but cytologically benign lesions, such as sclerosing papillomas, radial scars, and sclerosing adenosis. Third, it avoids artifactual distortion of tissues by freezing, particularly in intraductal and intralobular lesions, in which permanent sections become difficult to interpret after such artifacts are introduced.

Accuracy rates for intraoperative cytology have been found to be comparable to those for frozen sections in the hands of experienced pathologists.[36,37] The field is perilous for the novice, however. A pathologist who is familiar with the frozen section technique should perform frozen sections and cytologic preparations in parallel for an extended period of time before electing to substitute cytology for frozen section examination.

How reliable is intraoperative diagnosis of breast lesions? Because frozen sections are performed more frequently for lesions of the breast than for any other site, this is a question that is frequently asked by the surgeon and the novice pathologist. Obviously, the adequacy of frozen section diagnosis depends largely on the pathologist's familiarity with the procedure; the institution that performs 10 procedures each year will have poorer results than the institution that performs 1000 each year. With this reservation in mind, we can summarize the classic literature as follows: false-positive diagnoses are extremely rare, false-negative diagnoses account for 0.5% to 1.5% of diagnoses reviewed, and another 1% to 3% of diagnoses are deferred to the examination of permanent sections.[36]

These published figures reflect the era in which the usual breast cancer was a large, palpable mass discovered by the patient herself or her physician. At the present time, when many tumors are "minimal" lesions discovered during the course of a screening mammographic examination, and when the practice of immediate mastectomy after frozen section has fallen into disfavor, we find that many more (up to 10% or 15%) intraoperative diagnoses are deferred, and that the false-negative rate may rise because of sampling error in macroscopically benign biopsy specimens. The main points of intraoperative pathologic consultation in many of these cases may be to confirm by immediate specimen radiography that the proper area has been removed by the surgeon, and to rule out the presence of a gross tumor that requires tissue processing for special studies. In most of these cases, gross examination alone may suffice.[38] In gross tumors, even if immediate mastectomy is not scheduled, an imprint or frozen section diagnosis is useful to confirm that the tissue sample frozen immediately for hormone receptor analysis is carcinoma and does represent viable tumor tissue.

Processing and reporting of mammographically directed biopsies represent a new and in many ways different chapter in breast biopsy pathology, and they require close cooperation among the surgeon, the radiologist, and the pathologist. Recommendations for the collaborative management of such cases have been published and are summarized in Table 10-1.[23,24,39–41] For small biopsies, all tissue received by the pathologist should be submitted for microscopic examination. With larger specimens, the submission of all areas of radiographic calcification and fibrous parenchyma in mammographically directed biopsy specimens,[40] and of 10 blocks of fibrous parenchyma in grossly lesion-free biopsy specimens resulting from the presence of a palpable mass,[41] has been demonstrated to be cost-effective and diagnostically adequate.

TABLE 10-1.
Steps in the Evaluation of Patients with Mammographically Detected Nonpalpable Lesions with Microcalcifications

1. Careful mammographic evaluation before biopsy to establish the extent of the microcalcifications
2. Biopsy with needle localization
3. Specimen radiography to confirm excision
4. Examination of the specimen radiograph by the pathologist and comparison with the gross specimen
5. Inking of the specimen margins by the pathologist followed by careful gross dissection, examination, and description
6. Submission of a portion of a grossly apparent invasive carcinoma measuring greater than 1.0 cm for ancillary studies (eg, receptors, flow cytometry)*
7. Postbiopsy mammography to confirm that all suspicious microcalcifications have been removed
8. Careful microscopic examination of permanent sections to confirm the presence of microcalcifications, diagnose any lesions present, and determine the relation of tumor (if present) to the inked resection margins.

*We [C.G., S.S.] recommend that frozen sections not be performed on specimens showing no gross tumor, an apparent intraductal lesion, or an apparent invasive carcinoma of 1.0 cm or less in greatest diameter, and that such specimens be submitted for careful microscopic examination of permanent sections, with or without intraoperative scrape or imprint cytology.

Adapted from Schnitt SJ, Silen W, Sadowsky NL et al: Ductal carcinoma in situ (intraductal carcinoma) of the breast. N Engl J Med 318:898–903, 1988

INFLAMMATORY DISEASES OF THE BREAST

Acute Mastitis

The risk of infection is greatest in the lactating gland. Obstruction of the major breast ducts may provoke milk stasis, which progresses to noninfectious mastitis and eventually to infectious mastitis. The leukocyte count is less than 10 per millimeter of milk in noninfectious mastitis but may be greater in infectious mastitis.[42] Bacterial contamination occurs through the fissured nipple and is propagated by means of the lymphatics toward the lactiferous ducts. The bacteria present are common skin inhabitants such as streptococci, *Haemophilus* species, and *Micrococcus pyogenes.* The breast is red and edematous; a purulent nipple discharge is seen. The ductal epithelium is infiltrated by leukocytes and subsequently undergoes necrosis. At this stage, the lesions may regress under the influence of antibiotics or, more rarely, progress to abscess formation. At the periphery of the suppurative zone are seen intense vascular congestion and edema and an abundant stromal histioleukocytic infiltrate. In addition to these abscesses related to the lactiferous ducts, we must mention subcutaneous abscesses (supramastitis) and deep abscesses (inframastitis).

Mondor's disease or thrombophlebitis of the superficial chest wall (thoracoepigastric) veins is a rare, usually self-limited condition.[43] The diagnosis is usually evident to the clinician, so that the pathologist rarely encounters the lesions as an excised specimen. Histologically, it consists of an obliterative endophlebitis with thrombosis and severe alteration of the adventitia and intima. It may accompany carcinoma of the breast.[43]

Chronic Mastitis

Chronic abscess of the breast is of the same etiology as acute abscess. It consists of a purulent pocket surrounded by a thick fibrous wall. Histologic examination reveals leukocytic and histiocytic infiltration of the wall, which is dense, thick, and sclerotic.

Galactocele should be classified among the chronic abscesses.[44] It is a cystic lesion of variable dimensions containing altered liquid and viscous milk. The cyst wall consists of fibrous tissue containing leukocytes and macrophages. A prominent foreign-body giant cell reaction may be present (Fig. 10-8). Galactocele has been described in patients receiving oral contraceptives and suffering from galactorrhea. Diagnostic aspiration can cure the lesion.

Granulomatous mastitis, described by Kessler and Wolloch, is a lobular lesion characterized by noncaseous granulomas in which no organisms are identified.[45] An immunologic mechanism identical to the one observed in granulomatous thyroiditis has been suggested to explain this lesion.

Another probable autoimmune mastitis is the condition that has been called *lymphocytic mastopathy*[46] and, because of its frequent association with insulin-dependent diabetes mellitus, *diabetic mastopathy.*[47] The histologic features include lymphocytic ductitis and lobulitis with lobular atrophy and sclerosis, lymphocytic vasculitis, and dense keloid-like fibrosis (Fig. 10-9). The infiltrating lymphocytes have been described as predominantly B cells. The focal distribution of the infiltrate and the rarity of small lymphocytic lymphomas in the breast help in the differential diagnosis from malignant lymphoma.

Chronic subareolar abscess may occur in women during the reproductive years. It probably results from the obstruction of major lactiferous ducts due to foci of hyperkeratotic squamous metaplasia, a mechanism similar to the development of epidermal inclusion cysts. This obstruction creates an obstructive mastopathy with parenchymal alterations due to the granulomatous process.

Mammary tuberculosis is no longer common in Western countries. It is encountered in young women and often is secondary to pulmonary, lymph nodal, or costal tuberculosis; more rarely, it represents a solitary primary focus. It is accompanied by voluminous caseous axillary lymphadenopathy. Macroscopically, the lesion consists of soft, yellow, granular lesions disseminated in the breast. When abscesses form, they may fistulize to the skin. A sclerosing and nonabscess-forming type may simulate cancer. Histologic examination reveals Langhans' giant cell granulomata. Culture of

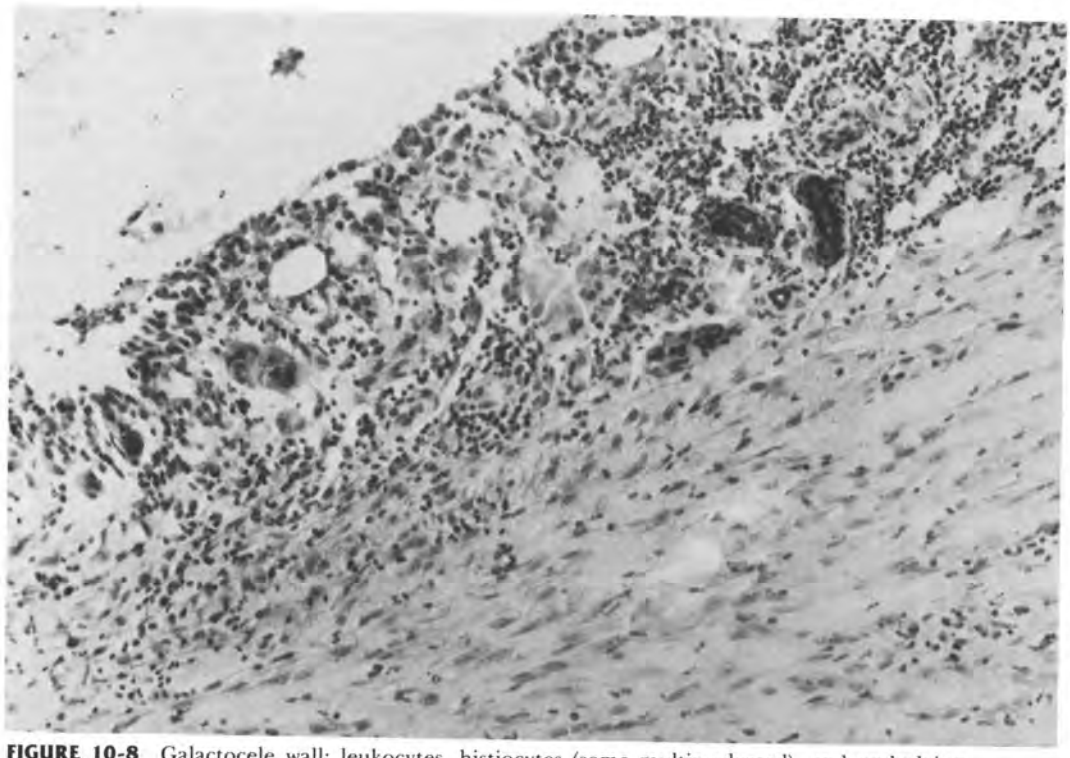


FIGURE 10-8 Galactocele wall: leukocytes, histiocytes (some multinucleated), and underlying fibrosis.

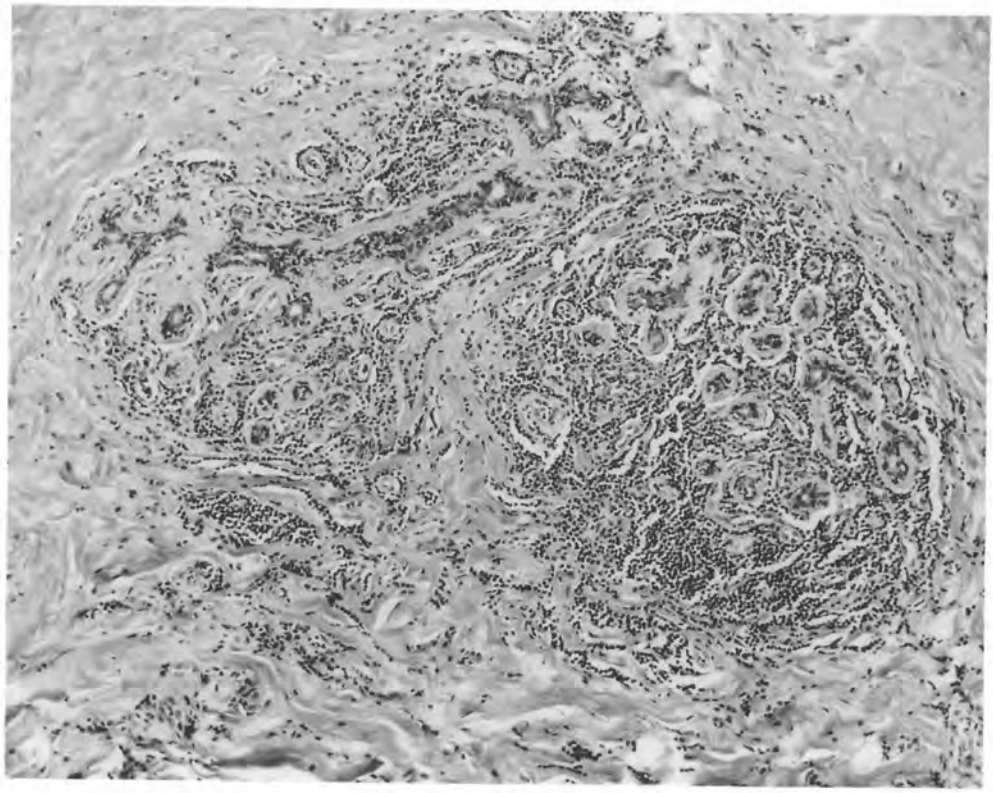


FIGURE 10-9 Lymphocytic mastopathy. Atrophic terminal ducts and lobules are surrounded and infiltrated by a dense infiltrate of small lymphocytes. This patient was not diabetic.

the tubercle bacillus or guinea pig inoculation confirms the diagnosis.

Mammary syphilis is a rare lesion. Primary chancre has been described in the older literature among wet nurses contaminated by infants with congenital syphilis. The lesion appears at the base of the nipple. Rare examples of secondary syphilis (cutaneous syphilids) and tertiary gummas have been reported.[48]

Mammary actinomycosis is rare and is secondary to a pulmonary focus. It presents as a fistulizing nodular induration. *Actinomyces bovis* may be identified in the purulent fistulous drainage.

Other inflammatory lesions that we merely mention because of their great rarity are the mammary localizations of *sarcoidosis*,[49] *blastomycosis, hydatid cyst, filariasis*, and *scleroderma. Mammary necrosis* as a complication of anticoagulant therapy with sodium warfarin (Coumadin) should be mentioned; vasculitis, thrombi, hemorrhage, and necrosis are found in these rare cases, which may represent a manifestation of a Schwartzman phenomenon.[50] *Wegener's granulomatosis* may occur in the breast,[51] as may localized vasculitis of no clinical significance.

Duct Ectasia

Mammary duct ectasia is manifested by the presence in the mature woman of dilated principal lactiferous ducts accompanied by adjacent granulomatous and chronic inflammatory lesions.[52] Synonyms are *periductal mastitis, chronic mastitis, comedomastitis, plasma cell mastitis, mastomalacia,* and *varicocele tumor.* It may be confused grossly with intraductal carcinoma. Clinically, it presents as subareolar induration accompanied by serous or sanguineous nipple discharge and retraction or deformation of the nipple. The rather slow development of these lesions and the secondary inflammatory complications clinically suggest an abscess. The complications regress after anti-inflammatory therapy but reappear periodically, the cause not having been suppressed. The nipple discharge and nipple inversion produced by duct ectasia and periductal fibrosis are not encountered in cases of fibrocystic change.

If the clinical and pathologic features of the disease are well defined, the precise mechanism of development of the lesion is not known. Is periductal inflammation the initial pathologic manifestation or is it the stasis of ductal contents? Pregnancy and lactation have been implicated in the development of the lesions, but this relation has been denied; moreover, this condition has been described in men.[53] Dixon and colleagues suggest that the primary change is periductal inflammation followed by ductal fibrosis and later ductal dilatation.[52] They have observed that the periductal inflammation is more frequent in young patients, whereas duct dilatation and secondary nipple retraction are more commonly seen in older patients.

Macroscopic Appearance. The subareolar zone is firm and shows several blue or brown voluminous ducts containing creamy or necrotic fluid. The ducts are surrounded by gray or necrotic inflammatory tissue. Compression of the dilated ducts expels the creamy discharge.

Microscopic Appearance. Two lesions are prominent: the presence of dilated ducts with thick fibrotic walls and giant cell inflammatory granulomata. The lesion appears to begin as duct dilatation, followed by rupture of the duct wall (Fig. 10-10). The cell debris, lipid contents of the duct, and lipophages spread into the adjacent stroma and induce the formation of a granulomatous inflammatory reaction, which sometimes simulates a tuberculous lesion. The granuloma organizes around lipid deposits and contains epithelioid cells and plasma cells. The abundance of plasma cells explains the term *plasma cell mastitis* that previously designated the lesion. Hemosiderin deposits are found in the macrophages. Distortion and destruction of the elastic tissue are always present. Foam cells are abundant. Retraction of the nipple is caused by secondary fibrosis. Histologic examination of the lesion erases the clinical suspicion of malignancy and avoids needless mutilative surgery.

Fat Necrosis

Fat necrosis of the breast is a lesion that frequently is mistaken for carcinoma.[54–56] This benign condition presents as a pseudotumorous mass with cutaneous retraction, ecchymoses, pain, and redness of the overlying skin. It is most commonly encountered in women with voluminous fatty breasts. In half the cases, the lesion is post-traumatic; more rarely, it may consist of necrosis secondary to an inflammatory focus. It is encountered in mastectomy specimens at a previous biopsy or FNA site and as a sequel to radiation therapy for breast cancer.[56]

Macroscopic Appearance. The biopsy specimen shows a poorly circumscribed indurated zone with yellow or gray foci of necrosis. Small cysts, fatty deposits, and hemorrhagic foci are sometimes visible. In advanced lesions, marked fibrosis, occasionally accompanied by calcification, is seen. Even on gross examination, the dense, granular, firm tissue may suggest a malignant lesion.

Microscopic Appearance. Histologic examination reveals necrosis of adipose cells with an inflammatory infiltrate rich in plasma cells, lymphocytes, and histiocytes. The macrophages are filled with lipids and appear as large cells with clear and microvacuolar cytoplasm (Fig. 10-11). Subsequently, a foreign-body granuloma rich in epithelioid cells and giant cells is formed around the fatty deposits and choles-

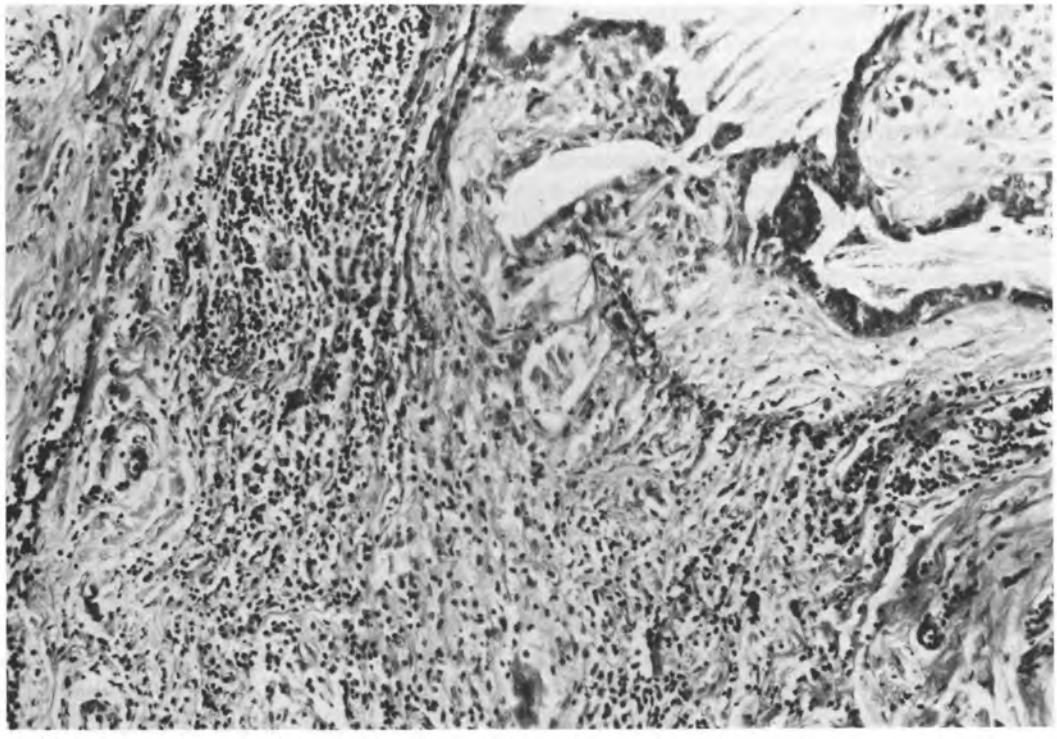


FIGURE 10-10 Plasma cell mastitis (duct ectasia).

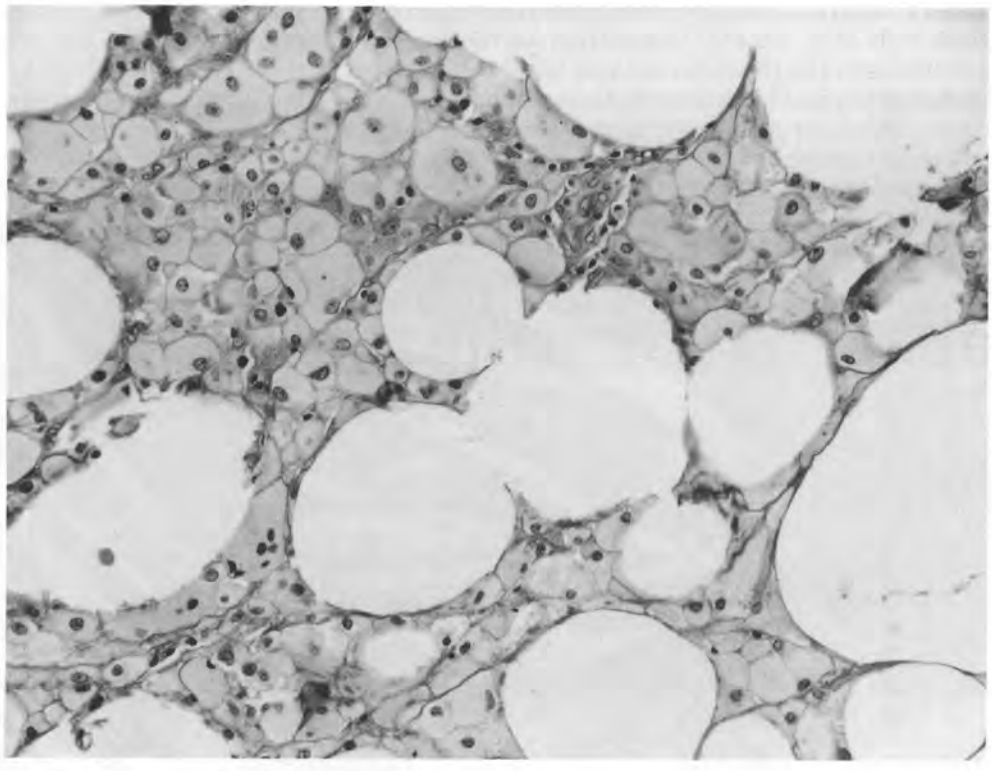


FIGURE 10-11 Fat necrosis. Adipose tissue is infiltrated by foamy macrophages.

terol crystals (Fig. 10-12). The lesion evolves toward fibrosis, which is responsible for the nipple retraction. Histologic examination is essential to arrive at the correct diagnosis and avoid overtreatment.

Duct ectasia with severe periductal mastitis is sometimes misinterpreted as fat necrosis. A clinical history of breast injury and the presence of necrosis may help to clarify the diagnosis. *Fine-needle aspiration* may provide diagnostic material, consisting of foam cells with vesicular nuclei, giant histiocytes, and leukocytes (Color Figure 10-3). Unlike carcinoma, ductal cells are absent or few in number. The evolution is benign, and local excision is curative.

Paraffinoma

For cosmetic reasons, women may receive intramammary injections or implants of paraffin or silicone. These substances may provoke the formation of chronic abscesses, foreign body granulomata, and cutaneous fistulas.[57,58] The clinical history, combined with the finding on physical examination of one or several tender, firm, well-circumscribed nodules, is usually diagnostic, but it is not rare to see carcinoma develop within a silicone granuloma.[57] The excised lesion is recognizable by the presence of a white, glistening, glairy substance, which histologically shows the foreign body surrounded by a prominent inflammatory reaction, usually with many foreign-body giant cells (Fig. 10-13). Penetration of the injected material into the thoracic wall and pleural cavity has been reported. This lesion is, fortunately, rare.

Because of recent publicity concerning leakage of silicone implants, many women are choosing to have their implants removed. The pathologist receiving specimens from such procedures should carefully examine the implants for evidence of rupture or leakage, and submit any surrounding mammary tissue received for microscopic examination.

INFARCTION

Although infarction is uncommon, it is important for two clinical reasons. The first of these is that infarcts presenting as localized masses may mimic carcinoma; they appear in young women during pregnancy or lactation[59] and usually involve fibroadenomas, adenomas, intraductal papillomas,[60] or lactating mammary tissue. Fixation of the lesion to the surrounding tissues, hardness, and sometimes enlarged axillary lymph nodes create a clinical impression of malignancy. The underlying lesion may be difficult to demonstrate if the infarct is extensive and chronic. It is sometimes difficult to determine if infarction appears in preexisting fibroadenoma or occurs in hyperplastic lobules; in the absence of pregnancy, infarction of fibroadenoma is rare. Mammary infarcts are significant in that, particularly in the older woman, they may be associated with other, potentially lethal, thromboembolic complications in other regions of the body. This is especially true in those cases that occur in women taking anticoagulant medication and in women who have Wegener's gran-

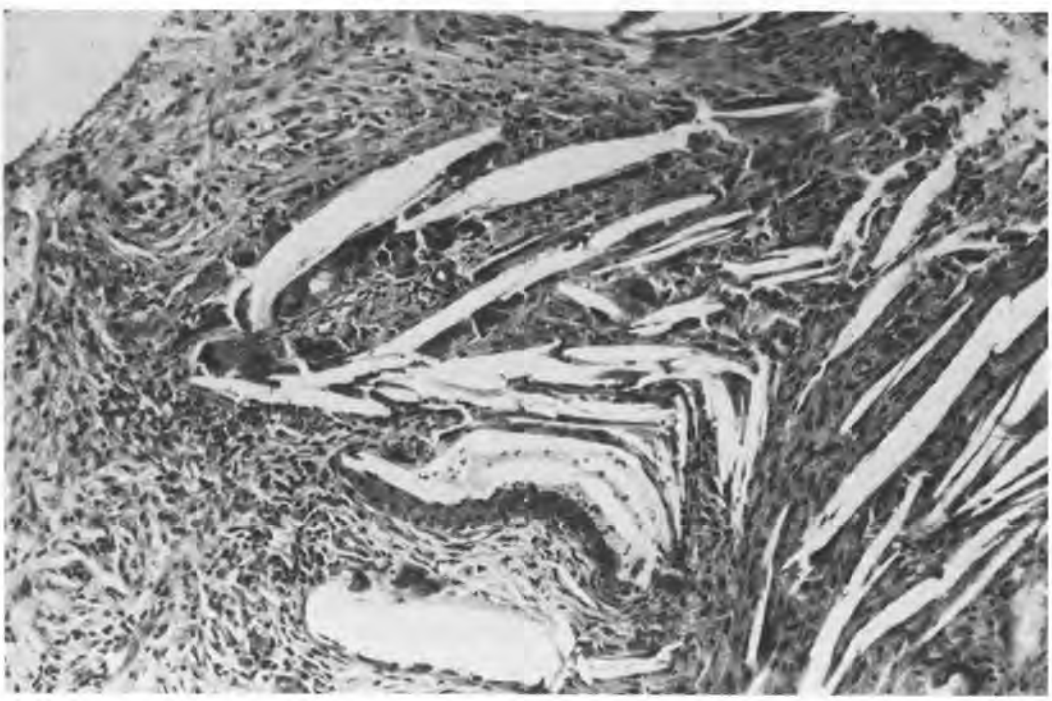


FIGURE 10-12 Fat necrosis: foreign body granuloma surrounding fatty deposits and cholesterol crystals.

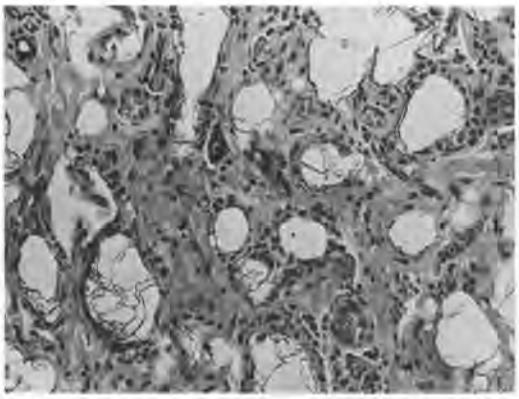


FIGURE 10-13 Paraffinoma: foreign material surrounded by histiocytes and giant cells.

ulomatosis,[51,61] thrombophlebitis migrans disseminata, and mitral stenosis with heart failure. In these situations, vascular lesions (arterial or venous) are usually prominent, whereas these are rarely found in pregnant or lactating women with a mammary infarct. Thus, the pathogenesis in the latter situation is assumed to be increased hemodynamic demand of lactating tissue. Occasionally, vascular occlusions are found in the infarcted tissues.

Macroscopic Appearance. The lesion is usually small, solitary, and well demarcated in the young woman but may involve the entire breast and the overlying skin in the older woman on oral anticoagulants. Infarction of multiple fibroadenomas has been reported.

Histologic Appearance. Ischemic necrosis, with or without extensive hemorrhage, is the main finding. "Ghost" outlines of previously viable tissue may be present if the infarct is recent. The distorted and compressed ductal formations at the periphery of the lesion should not be interpreted as infiltrating carcinoma. Squamous metaplasia of ductal epithelium may be so prominent as to provoke confusion with squamous carcinoma. Although carcinomas may, on occasion, become focally or even extensively infarcted, some evidence of the underlying tumor is always present. The persistence of a two-cell–layered epithelium argues against the malignant nature of the infarcted tissue.

MAMMARY INVOLVEMENT IN INHERITED SYSTEMIC DISEASES

The breast may be involved in several systemic diseases of inherited type. Among these manifestations are mammary subcutaneous neurofibromas in generalized neurofibromatosis, mammary fibromatosis in Gardner's syndrome,[62] and lobular agenesis in cystic fibrosis.[63] Women with the complex of cardiac and cutaneous myxomas, spotty pigmentation, endocrine overactivity, and schwannomas may have mammary manifestations including myxoid fibroadenoma, myxomatosis, and ductal adenoma with tubular features.[64,65] The skin overlying the breast may demonstrate the same lesions as extramammary skin in inherited and noninherited systemic diseases.

More importantly, benign and malignant breast lesions have been reported in women with Peutz-Jeghers and Cowden's syndromes,[64] and breast carcinoma itself is commonly familial (see the section on carcinoma).

BENIGN TUMORS

Fibroadenoma (Adenofibroma)

The fibroadenoma is a slowly growing benign lesion composed of epithelial and connective tissue elements distributed in variable proportions. It may represent a nodular hyperplasia of epithelial and stromal tissues and is not a tumor in the usual sense of the word. It is the third most commonly seen breast disease, after fibrocystic change and carcinoma. It develops in young women, particularly between 20 and 40 years of age, and rarely appears after this age. It is extremely rare in the male breast.

Etiology. Genital hormones appear to play a promotional role: the tumor develops during the period of gonadal activity, enlarges during pregnancy, and undergoes variations in volume and sensitivity in relation to the menstrual cycle. Fibroadenomas of huge dimensions may be encountered during adolescence. Estrogen administration may lead to vascular congestion, edema, and leukocytic infiltration within the tumor. Infarction may occur during pregnancy,[59] as may florid epithelial proliferation.[66] The latter has been reported with oral contraceptive agents, but a controlled study failed to confirm this as a significant finding.[67]

Clinical Appearance. Fibroadenoma is a well-circumscribed and freely movable, round, lobular tumor of a firm and elastic consistency. It does not adhere to adjacent tissues, skin, or chest wall, and it is not painful.

Macroscopic Appearance. The appearance of the tumor is characteristic. It is a well-limited, spherical, pink or white, lobular mass. When the epithelial elements are abundant, the color tends toward deep pink to light tan. Section reveals smooth, shiny fibrous tissue of lobulated structure (Fig. 10-14*A*). A leaf-like structure with deep clefts may be present. The surface of the tumor bulges above the plane of section as a consequence of the elasticity of the connective tissue framework.

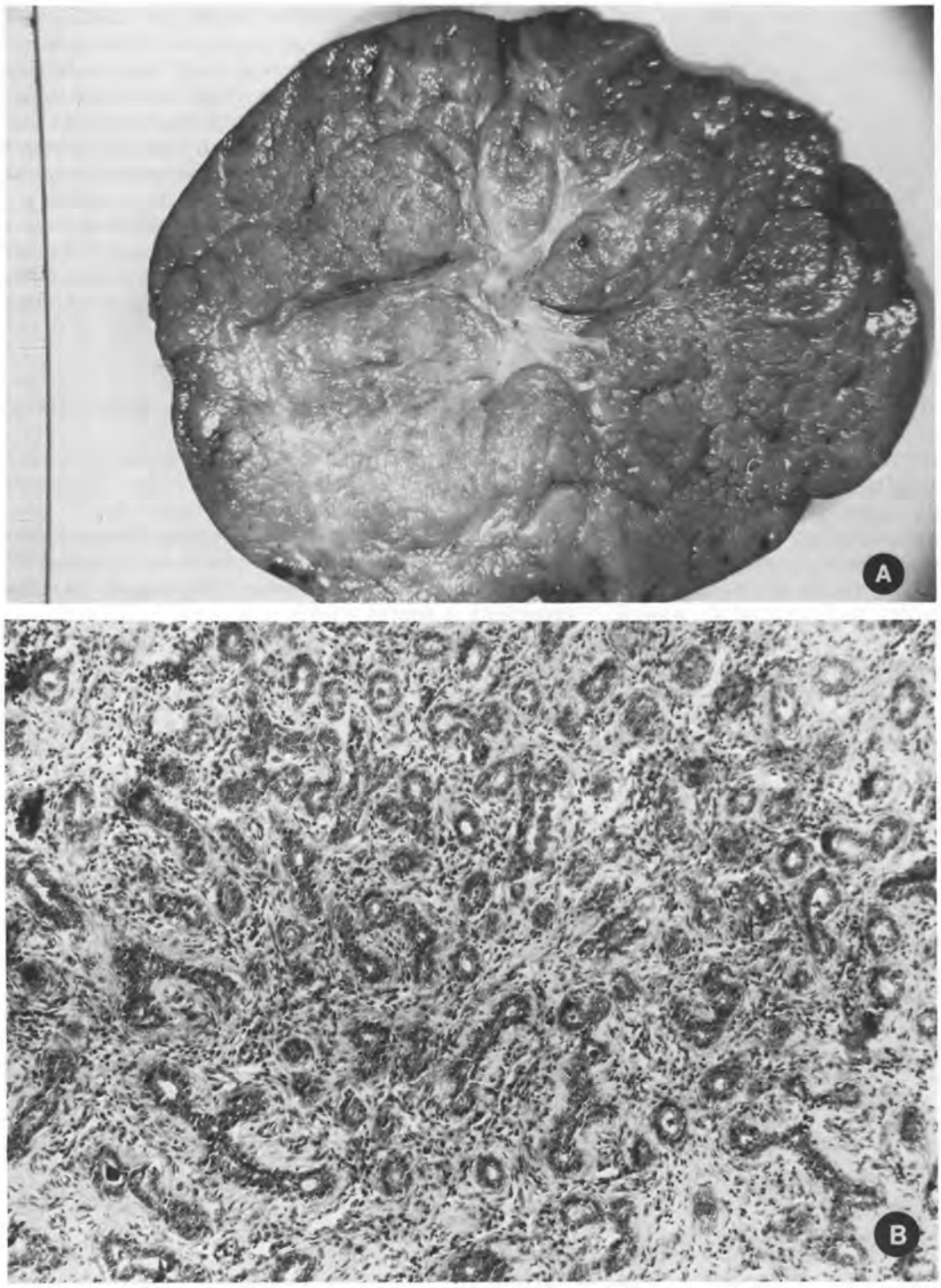


FIGURE 10-14 Pericanalicular fibroadenoma. **(A)** Macroscopic appearance. **(B)** Microscopic appearance.

Microscopic Appearance. Fibroadenomas may be subclassified according to the abundance and disposition of the epithelial formations. When these are numerous, the tumor is called a *tubular* or *pericanalicular fibroadenoma* (Fig. 10-14*B*). The tubular epithelial structures are ramified, of variable diameter, lined by columnar or cuboidal cells analogous to those of the lactiferous ducts, and surrounded by cuffs of connective tissue. Apocrine epithelium occasionally is present. The tubular lumina may be easily seen or reduced to small slits. The tubules may show varied appearances, depending on the planes in which they are sectioned.

The connective tissue framework is dense and richly cellular; the elements composing it are elongated and disposed in whorling fascicles that have a

concentric disposition in the immediate vicinity of the epithelial formations. Numerous collagen fibers are present. Capillary vascularization is discrete. Foci of edema and myxoid or, more rarely, cystic degeneration may be present. Giant multinucleated cells of reactive nature have been described. In about 2% of cases, the epithelial formations are so overwhelmingly predominant and the connective tissue stroma so sparse that the tumor is known as an *adenoma*.[66,68]

In the *intracanalicular fibroadenoma*, connective tissue proliferation dominates the picture, and the epithelial tubules are compressed and deformed by the stroma (Fig. 10-15). The tubules and ducts become compressed, flattened, and curved in on themselves so that they no longer show true central lumina. Epithelial proliferation forms thin ramifying cell cords, which enclose round masses. The subclassification into pericanalicular and intracanalicular patterns, although consecrated by usage, does not imply differences in behavior and is of little practical significance.

Not too infrequently, epithelial proliferation may be seen within the fibroadenoma to a degree that appears alarming, especially when combined with moderate cytologic atypia. However, the development of carcinoma within a fibroadenoma is an extremely rare event, and these proliferative changes are of no clinical significance. True carcinomas arising in fibroadenomas are usually noninfiltrating (in situ lobular or, less frequently, intraductal carcinomas).[69,70] Rarely, pictures of squamous, cartilaginous, osseous, or adipose metaplasia are seen within the tumor.

In adolescents, fibroadenomas may grow rapidly and attain a large size, arousing clinical concern.[71] These juvenile lesions reveal marked epithelial proliferation without ductal compression and high stromal cellularity. Cellular atypia is not present. Differential diagnosis with phyllodes tumor may be considered, but the latter lesion almost always occurs in older patients and is characterized by at least focal stromal overgrowth and mild to marked stromal atypia.

A rare variant of fibroadenoma with the presence of argyrophilic cells has been reported by Azzopardi and colleagues.[72] The ductal outer layer shows a marked proliferation, which overshadows the inner layer; these large cells with a vesicular nucleus are argyrophilic with the Bodian silver impregnation technique. Azzopardi suggests a probable endocrine nature of the lesion.

Differential Diagnosis. Fibroadenoma is common and characteristic, but may on occasion pose a diagnostic problem in its distinction from phyllodes tumor, hamartoma, tubular or ductal adenoma, or adenosis tumor. The only clinically significant problem is with phyllodes tumor (see below), because the others all behave clinically like fibroadenomas.

Cytologic Appearance. In FNA biopsies or intraoperative lesional smears, cellularity is high. Broad sheets of uniform epithelial cells are present, often in a honeycomb pattern (Color Figure 10-4), and they characteristically contain numerous clefts and

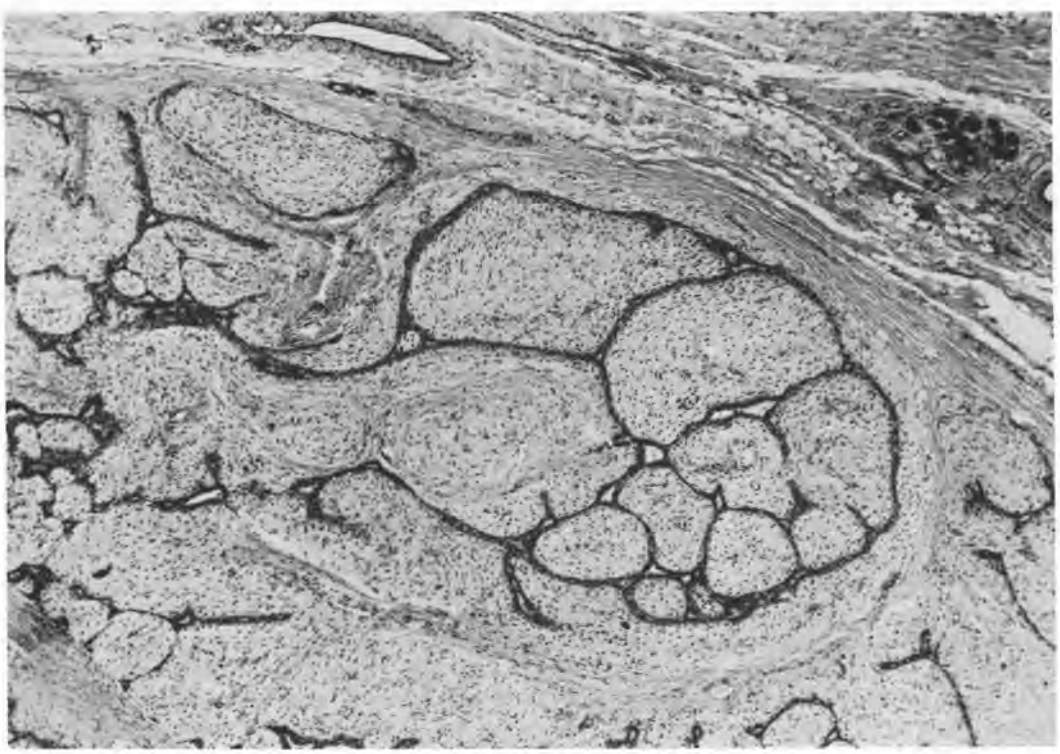


FIGURE 10-15 Intracanalicular fibroadenoma.

branches. These cell clusters are tightly cohesive, but single cells with ovoid nuclei lacking surrounding cytoplasm are also numerous, as are fragments of fibrous stroma. The apocrine cells and foam cells seen frequently in fibrocystic changes tend to be absent in fibroadenomas, but overlap occurs between the two lesions. Focal epithelial atypia is common in fibroadenomas, and may rarely lead to a misdiagnosis of carcinoma.[73] True carcinoma (almost always in situ lobular or ductal) may also be seen within a fibroadenoma, and has an excellent prognosis when treated conservatively.[69,70]

Lactational changes (Color Figure 10-5) may also mimic carcinoma, particularly in air-dried smears, because the cohesive nature of the epithelial cells is not well demonstrated. The presence of numerous intracytoplasmic lipid globules suggests the correct diagnosis.

Evolution and Prognosis. Growth is slow but may continue over a period of years to produce a voluminous tumor. These tumors stabilize or regress at the menopause, and they occasionally become calcified. The treatment of choice (mainly for diagnostic purposes) is surgical excision. These are radioresistant tumors. Although hormonal factors are thought to play a significant role in their genesis, endocrine therapy has been ineffective.

Phyllodes Tumor (Cystosarcoma Phyllodes)

Phyllodes tumor is essentially a fibroepithelial tumor characterized by marked proliferation of the connective tissue stroma and often by great size as well. It appears in middle-aged women with greatest frequency, but it has been reported in teenagers and in elderly women. Many of the cases reported in teenagers, however, are probably really examples of juvenile or giant fibroadenoma.[74] Phyllodes tumor generally contains progesterone receptors but not estrogen receptors.[75]

Phyllodes tumor characteristically grows slowly at first, and then rapidly, often attaining considerable dimensions. This tumor represents about 1% of all mammary fibroadenomas. The name of cystosarcoma phyllodes was given to this tumor by Müller, who first described it in 1838.[76] He used this term to indicate a cystic and fleshy tumor, but confusion has been caused subsequently by the implication of malignancy. In actuality, only about 10% to 25% of these tumors are malignant.[77–80] The term *phyllodes tumor* is therefore more appropriate for this lesion.

Clinical Appearance. This is a spherical, firm, usually well-circumscribed tumor, which may easily attain a diameter of 10 to 20 cm within a few months. Cutaneous ulceration, however, is a late manifestation even in these huge tumors and is of trophic rather than neoplastic character.

Macroscopic Appearance. The lesion consists of a well-circumscribed multinodular mass. Although the classic description is that of a voluminous tumor, typical lesions have been reported that measured as little as 2 cm in diameter, emphasizing the fact that it is the histologic appearance that is diagnostic. Section of the tumor reveals firm, white nodules separated by fibrous septa. In large tumors, foci of necrosis, hemorrhage, and cystic degeneration are numerous (Fig. 10-16).

Microscopic Appearance. Proliferation of stromal cells is intense, with the epithelial formations being rare and almost lost in the hyperplastic stroma. In many cases a tumor that at first appears to be purely mesenchymal reveals its true nature only after examination of many sections, when finally a few epithelial structures are found. However, it must be clear that these are an integral part of the tumors, and not merely normal ducts that have been overgrown by the tumor, before the diagnosis of phyllodes tumor is made. The connective tissue cells are large, with voluminous, elongated, and sometimes hyperchromatic nuclei and clear cytoplasm. They are disposed in anastomosing and whorled bundles that form multiple round nodules. Immunohistochemical and ultrastructural studies reveal a proliferation of myofibroblasts.[81–83] Heterologous stromal elements other than fibromyxoid tissue can be present, including bone, cartilage, and striated muscle. In some cases, the epithelial components may be abundant and form cysts and florid proliferations. Carcinoma can occur within a phyllodes tumor in rare cases.

The distinction between the benign and malignant forms is important but sometimes difficult to make. Because stromal cellular atypia immediately adjacent to the epithelial formations is common to both varieties, the regions that should be examined to make the distinction are those that are far removed from these formations, particularly at the periphery of the tumor (Fig. 10-17).

In the malignant form, cellular anarchy is more accentuated, nuclear and cytoplasmic atypia and mitotic figures are numerous, and the tumor borders tend to be infiltrating rather than well circumscribed (see Fig. 10-17). Stromal overgrowth (large regions of pure stromal proliferation) is commonly seen. Because of the frequent difficulty in dividing these tumors into benign and malignant forms, some authors prefer to include a "borderline" group for the intermediate cases. Our recommendation is to use only two categories, expressed as low-grade and high-grade tumor. In any event, the report of the pathologist to the surgeon should always state in some form the degree of histologic atypia of the tumor. However, the pathologist and surgeon must realize that cytologically benign lesions occasionally behave in a malignant fashion or recur locally as the malignant variant and, conversely, that a high percentage of malignant lesions are cured by conservative surgery.

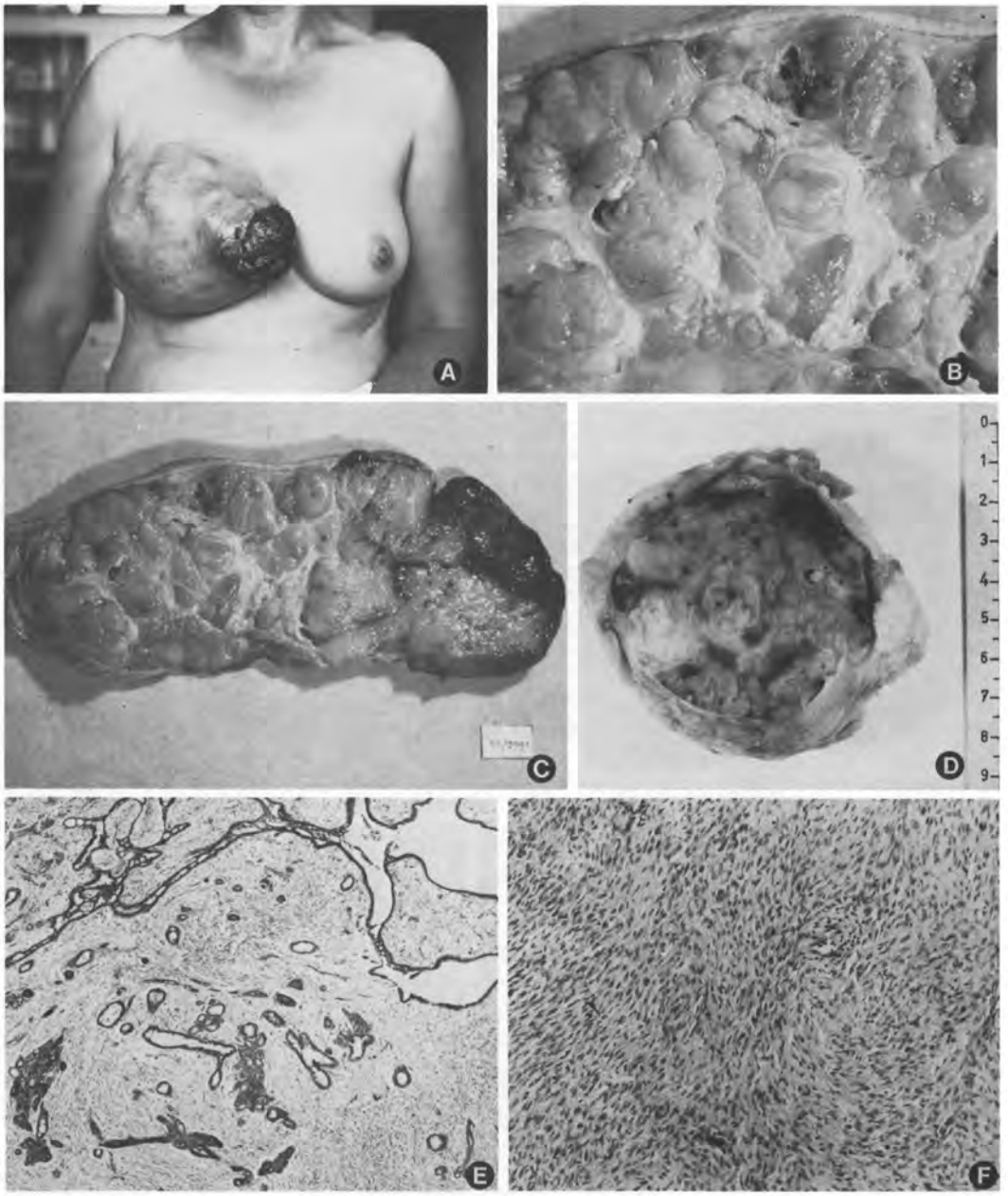


FIGURE 10-16 Cystosarcoma phyllodes: benign form.

Different prognostic factors have been tested, including tumor margins, mitotic activity, stromal overgrowth, stromal cellular atypism, and necrosis, but conflicting results have been obtained.[78–80,84,85] Ploidy studies have been found to be useful in some series[84] but not in others.[80,85]

Cytologic Appearance. A few cases have been reported in which the diagnosis was suggested by FNA cytology.[86,87] Phyllodes tumor is characterized by a high cellularity of stromal fragments with bipolar naked nuclei, clusters of ductal cells with overlapping nuclei, giant cells of foreign-body type, and foam cells (Color Figure 10-6). The appearance is similar to that described above for fibroadenoma but with more stromal cellularity and atypia.

Evolution and Prognosis. The evolution of the benign tumors is rapid; the volume and the threat of cutaneous ulceration demand rapid surgical intervention. Local recurrence after an inadequately wide excision is not uncommon but does not indicate conversion to malignancy, which rarely occurs. The malignant forms grow rapidly locally and have the potential for hematogenous metastases; the most frequent sites are lung, pleura, and bone. Lymph node metastases have been reported but are so rare that they do not constitute a significant hazard. The me-

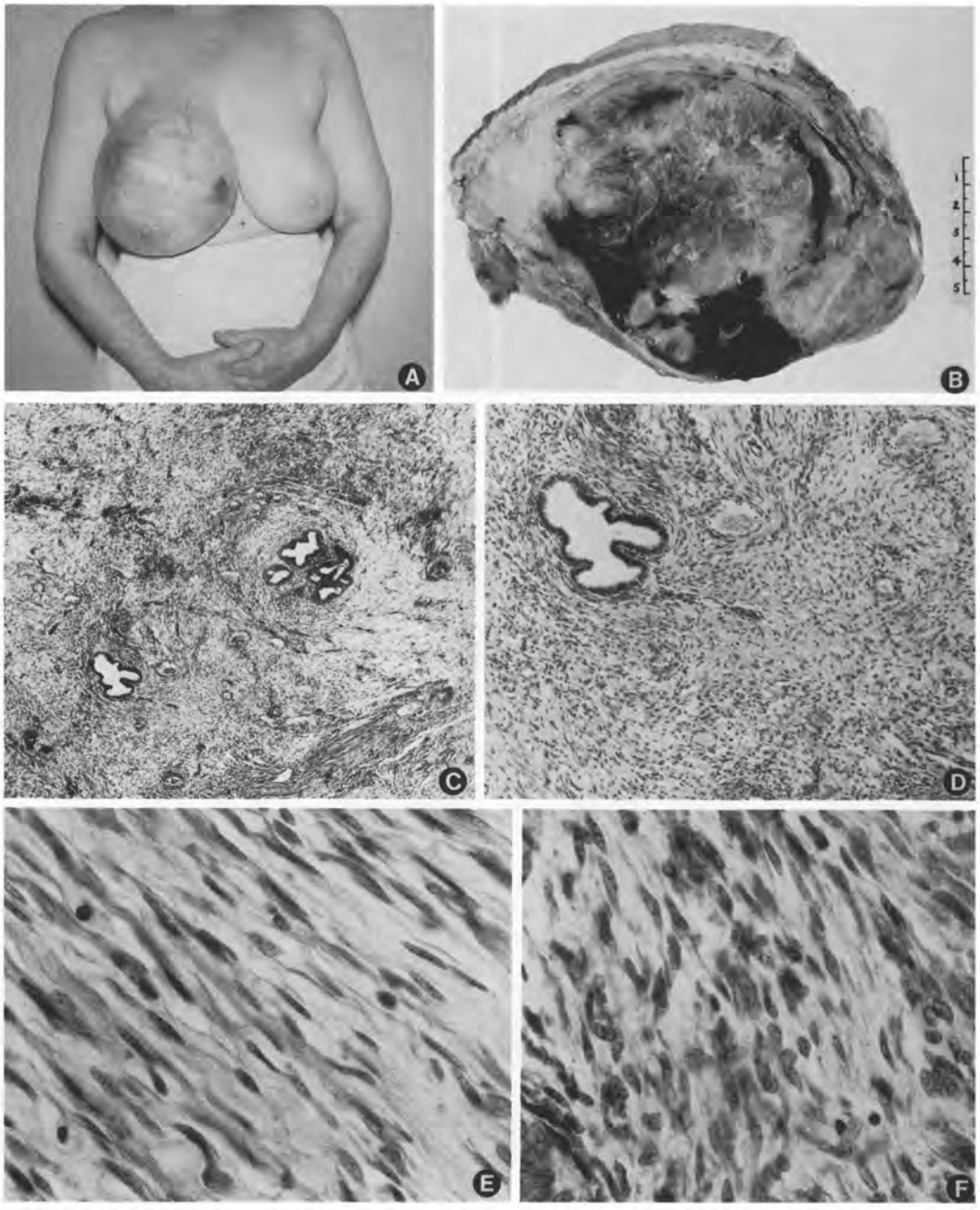


FIGURE 10-17 Cystosarcoma phyllodes: malignant form.

tastases consist histologically of the stromal elements of the tumor only, with the exception of a single reported case in which stromal and epithelial elements metastasized.[88]

Surgical treatment may consist of local excision if the tumor is benign and not too large. Voluminous or malignant phyllodes tumors are best treated by simple mastectomy. Adjuvant radiation therapy does not seem to change the prognosis.

Differential Diagnosis. Although the differential diagnosis between the benign and malignant forms (see above) is discussed extensively in the literature—albeit with no uniform conclusion—an equally vexing problem involves the distinction between a fibroadenoma with an unusual degree of stromal proliferation and the lowest grade lesion acceptable as a phyllodes tumor. In our opinion, the age of the patient (adolescent and very young women rarely have phyllodes tumors) and the size of the tumor (with 2 cm as a useful but not perfect dividing line) often are helpful adjuncts to purely histologic features. For the diagnosis of phyllodes tumor, the stromal proliferation should be diffuse rather than focal and should be accompanied by at least some cytologic atypia. Ultrastructural studies have demonstrated basement

membrane reduplication at the epithelial-stromal junction in fibroadenoma and focal ruptures of basement membrane in phyllodes tumor,[83] but it remains to be seen if this can be demonstrated at the light microscopic level by immunohistochemical stains for basement membrane components. In any event, borderline tumors should be excised adequately rather than shelled out.

At the other end of the spectrum, high-grade phyllodes tumors with a sparse ductal component should be differentiated from pure fibrosarcoma, liposarcoma, and malignant fibrous histiocytoma of the breast, which generally have a poorer prognosis. Many sections may be required to demonstrate the ductal elements, which must be well within the tumor rather than entrapped at the periphery.

Intraductal Papilloma

Also known as *papillary adenoma, papillary cystadenoma,* and *dendritic adenoma,* intraductal papillomas are found within the principal lactiferous ducts and are composed of epithelial vegetations with central connective tissue axes.[89–91] These lesions are relatively uncommon. They appear at any age, but preferentially between 30 and 50 years. They frequently pose the diagnostic problem of differentiation from intraductal carcinoma. They should be differentiated from the far more common intraductal "papillomatosis," better known as *intraductal hyperplasia* or *epitheliosis,* a multicentric involvement of secondary ducts usually seen as part of the spectrum of fibrocystic changes (see below).

Clinical Appearance. This lesion manifests itself by (1) spontaneous or induced serous or bloody nipple discharge, (2) the presence of a small subareolar tumor of a few millimeters in diameter, and (3) rarely, nipple retraction. Galactography or ductoscopy often permits localization of the tumor.[18] Cytologic examination of the discharge reveals numerous epithelial cells of benign appearance.

Macroscopic Examination. Within a dilated or cystic duct is found a soft, friable, red or yellow, papillomatous formation attached by a short, thin stalk to the duct wall. These tumors usually approximate 5 mm in diameter and show superficial hemorrhagic ulceration.

Microscopic Examination. The tumor is composed of multiple papillae, each of which consists of a connective tissue axis on which are disposed the cuboidal or columnar epithelial cells (Fig. 10-18). These structures frequently ramify and are coupled together to form pseudoglandular cavities of diverse sizes and shapes; proliferation of solid cell nests is commonly seen. Apocrine metaplasia may be present, but it is much more common in the multifocal intraductal "papillomatosis" of fibrocystic change. The cells show moderate secretory activity and are disposed in two or three layers, which include a variable number of myoepithelial cells. Bizarre and atypical nuclear and cytoplasmic anomalies are absent, and mitoses are rare. Small foci of sclerosis and hyalinization are frequently seen; these are sequelae of hemorrhage, ulceration, or arterial thrombosis in the stalks.

Cytologic Appearance. Cytologic examination of the serous or bloody nipple discharge shows uniform cells with vesicular nuclei, fine granular chromatin, and homogeneous cytoplasm (Color Figure 10-7). Nucleoli are inconspicuous. These cells are isolated or display very typical cohesive papillary structures. Distinction from carcinoma is based on the absence of nuclear and cytoplasmic atypia and the lesser degree of cellularity. Myoepithelial cells may be represented by dark, elongated, naked nuclei.

Differential Diagnosis. The distinction between a benign but moderately atypical intraductal papilloma and a low-grade intraductal papillary carcinoma may be difficult to make.[89,92–95] Benign lesions are more frequently misdiagnosed as malignant than vice versa. The presence of notable cytologic atypia (unless limited to cells showing apocrine metaplasia) should characterize an intraductal papillary lesion as malignant, as should abnormal mitotic figures, the absence of vasculo-connective tissue axes in the stalks of the papillae, and the presence of cell strands bridging the duct lumen and forming a pattern like the spokes of a cartwheel (cribriform pattern). The holes between the spokes, however, should be round and uniform, because slit-like and non-uniform spaces are frequently seen in benign papillomas and papillomatoses. Central necrosis also suggests malignancy but may be seen rarely in benign lesions. Myoepithelial cells are numerous in intraductal papillomas and absent to sparse in carcinomas, and they can be demonstrated immunohistochemically using antibodies to muscle-specific actin and, less reproducibly, to high-molecular-weight keratins and S-100 protein.[93] If myoepithelial cells are easily seen without special stains, benignity is strongly favored. Apocrine metaplasia, as mentioned previously, is far more common in benign than in malignant lesions, particularly when it is focal; the rare apocrine carcinoma shows this change diffusely. The presence of true stromal invasion, of course, characterizes a tumor as indisputably malignant. However, marked sclerosis within and around a benign intraductal papilloma occasionally produces an appearance of "pseudoinvasion," with which the pathologist must be familiar.[92] This sclerosis is usually densely hyalinized, as opposed to the more myxoid and inflamed fibroelastotic stroma of infiltrating carcinoma (Fig. 10-19).

Infarction of a papilloma, associated with marked distortion of the ductal structures, is important to recognize because it may simulate invasive

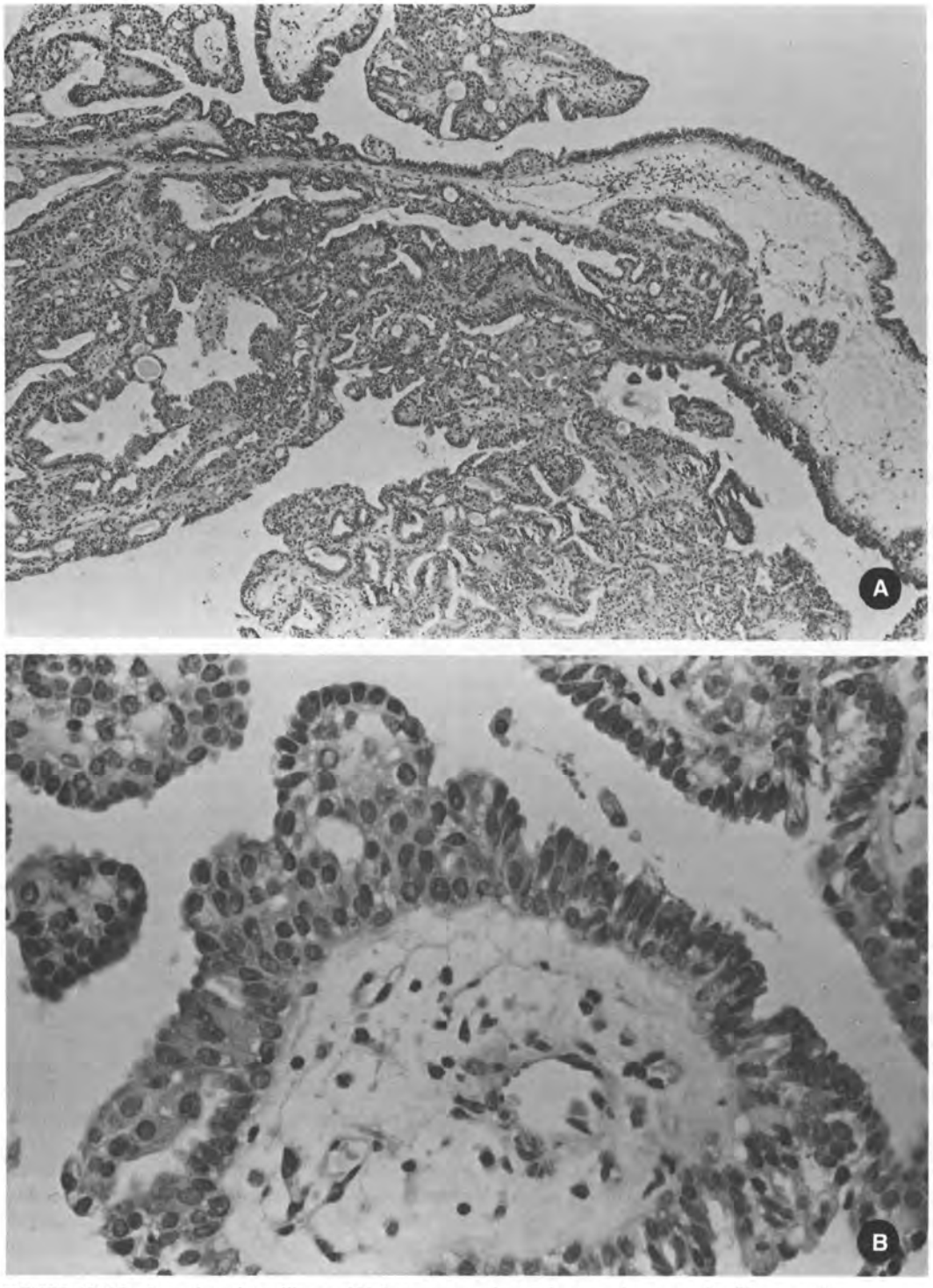


FIGURE 10-18 Intraductal papilloma. **(A)** Low-power photomicrograph—note the fibrovascular connective tissue stalks. **(B)** Detail of benign-appearing ductal epithelial cells and underlying myoepithelial cells.

carcinoma.[60] Squamous metaplasia sometimes present in papillomas should not be overdiagnosed as differentiated squamous carcinoma.[60] In metaplasia, the squamous elements are devoid of nuclear atypia and atypical mitoses.

Under the term *juvenile papillomatosis,* localized masses with grossly visible cysts (so-called "Swiss cheese" disease) and prominent intracystic and intraductal proliferations have been described in adolescents and young women (Fig. 10-20).[96] This proliferation can range from banal to florid to atypical hyperplasia. Coexistent adenosis, fibrosis, and radial

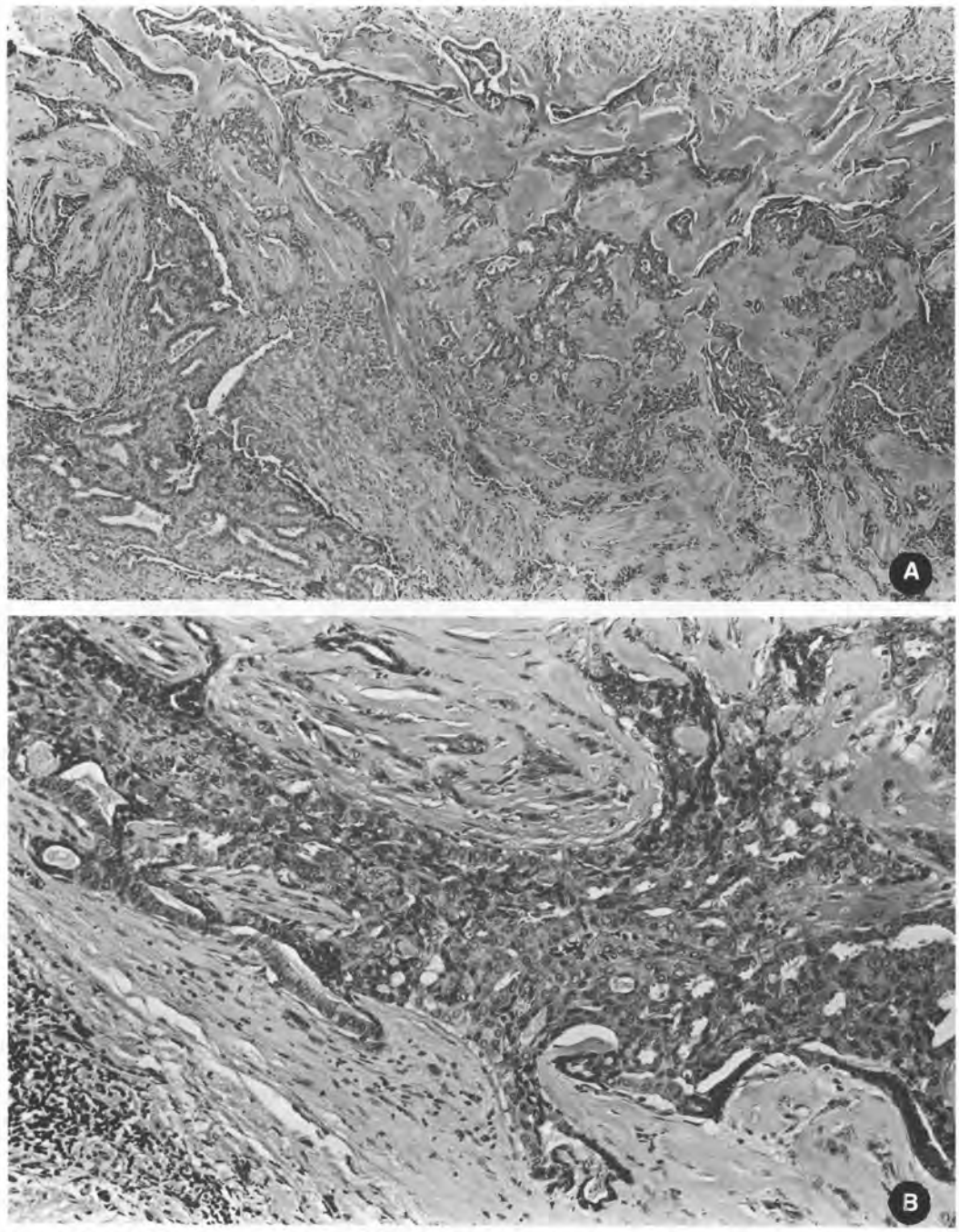


FIGURE 10-19 Sclerosing papilloma. Hyalinized stroma **(A)** within and **(B)** around the ductal proliferation creates a pseudoinfiltrative pattern. The benign cytologic appearance of the lesion is demonstrated in **B**.

scars are frequently encountered. FNA cytology confirms the benign polymorphous picture and includes many foam cells as well as normal and atypical ductal cells. This lesion should be differentiated from the diffuse "papillomatosis" accompanying fibrocystic changes in older women, in which no mass is macroscopically evident, and from solitary or multiple papillomas. Juvenile papillomatosis also occurs in adult women—up to 35 years of age in the series of Rosen and Kimmel,[96] so the name is somewhat misleading. Long-term follow-up of these lesions is necessary because our knowledge of their malignant potential is scanty. Rosen and Kimmel suggest that carcinoma is more likely to develop in women with a positive family history and recurrent bilateral lesions.[96]

Another recently characterized lesion that probably is a variant of intraductal papilloma is *ductal adenoma of the breast.*[97] This is a lesion of medium-sized to large ducts, usually single but occasionally multiple, that is solid and may show worrisome cytologic

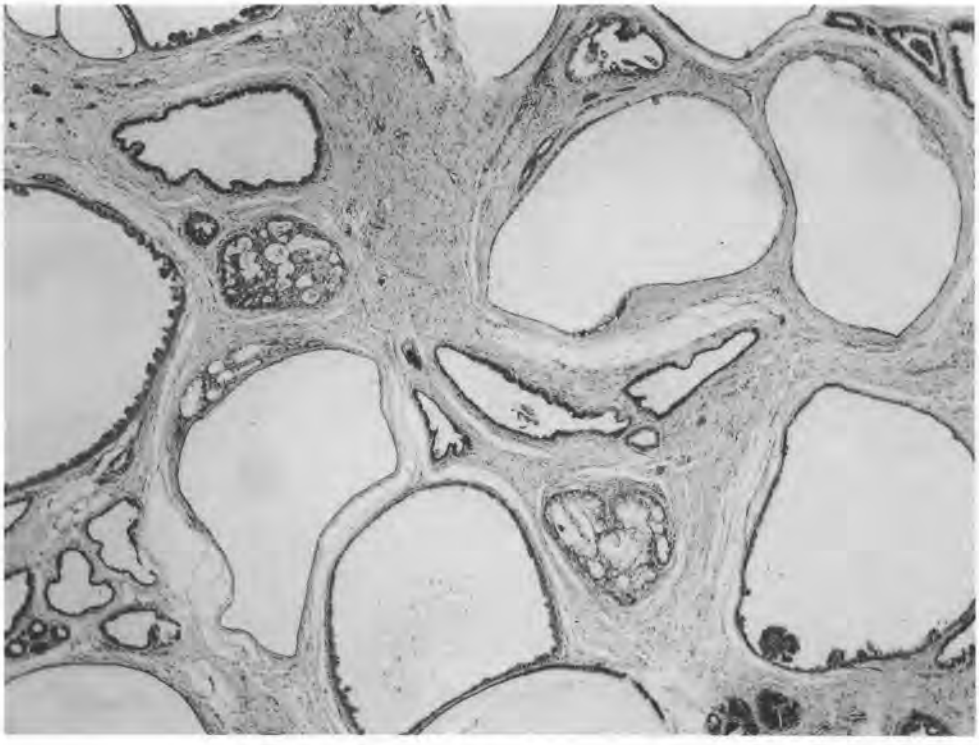


FIGURE 10-20 Juvenile papillomatosis. Multiple cystically dilated ducts show varying degrees of intracystic epithelial proliferation.

atypia and pseudoinfiltration. Myoepithelial cells and intact basement membrane can be demonstrated immunohistochemically, and the lesion does not recur after local excision.

Evolution. Although numerous studies have suggested that the multiple intraductal hyperplastic lesions of fibrocystic change probably form a continuous spectrum from benign to malignant, with the dividing line poorly defined, solitary intraductal papillomas are totally benign lesions in almost all cases.[98–100] Although some authors have noted an increased risk of subsequent carcinoma in patients treated for intraductal papilloma, others have felt that in most of these cases the original lesion was probably underdiagnosed. In any event, excision should be complete to avoid local recurrence. Actual focal or complete malignant transformation within an intraductal papilloma is rare; such a lesion should be treated as intraductal carcinoma (Fig. 10-21). In the uncommon case of multiple intraductal papillomas, the risk of subsequent carcinoma is higher than that of the usual solitary lesion.[99]

Adenoma of the Nipple

Adenoma of the nipple presents as a nodule immediately beneath the nipple, often with crusting or ulceration of the nipple, and is often misdiagnosed clinically as Paget disease or an intraductal papilloma or carcinoma. The lesion may be accompanied by a bloody discharge and soreness of the nipple and appears more frequently during the fourth and fifth decades. Synonyms are *subareolar papillomatosis, florid papillomatosis, papillary adenoma,* and *erosive adenomatosis.*

Macroscopically, the lesion is a solitary, well-circumscribed, usually solid mass with a density ranging from soft to firm. It infiltrates indistinctly the nipple and the subareolar region.

The *histologic appearance* is identical to that of hidradenoma papilliferum, a type of sweat gland adenoma, but no sweat glands are seen, and the lesion appears to arise in mammary ducts (Figs. 10-22 and 10-23). The characteristic features are ducts filled by branched papillary projections with central connective tissue axes, lined by a double layer of cells (epithelial and myoepithelial). The cells are always uniform, and mitotic activity is usually low. Necrosis is rare. Apocrine snouts, squamous cysts, solid nests of cells, and peripheral fibrosis with pseudoinvasion are frequently seen.[101–103] Fibrosis with subsequent epithelial distortion may be considerable, and it should be noted that this is not a purely intraductal lesion.

The *cytologic appearance* in FNA or intraoperative smears (Color Figure 10-8) is characterized by high cellularity, with uniform ductal epithelial cells in clusters and occasionally singly, as well as myoepithelial cells, variable numbers of inflammatory cells and macrophages, and some necrotic debris.[104] Nuclear atypia is absent or minimal.

The *evolution* of this lesion is benign, and it is cured by local excision. Because intraductal papil-

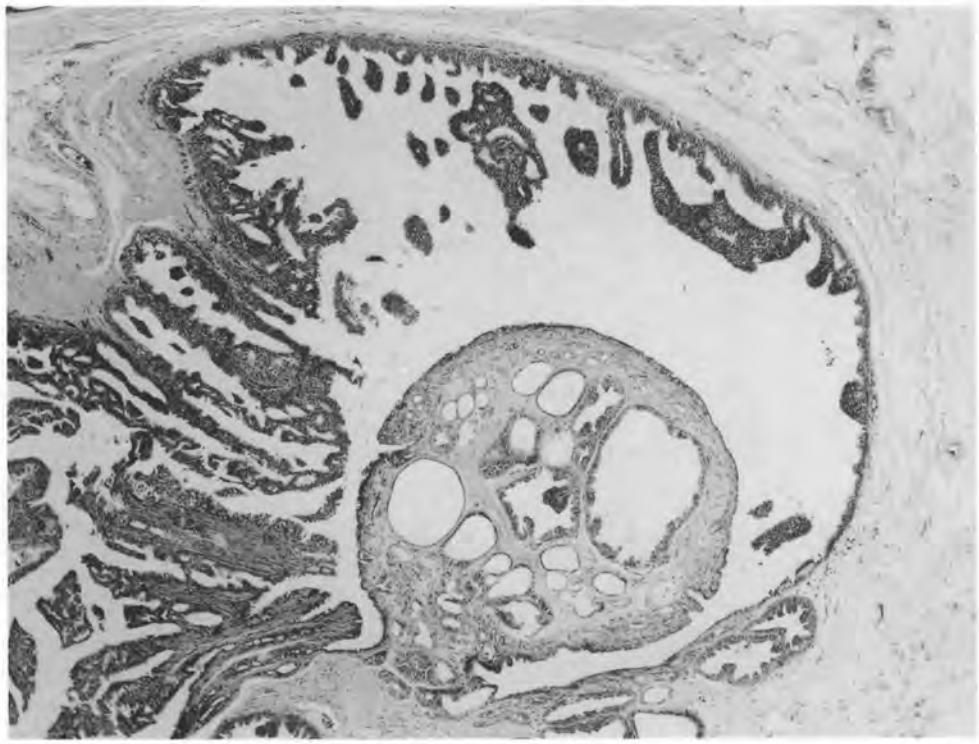


FIGURE 10-21 Intraductal papilloma (the round polypoid lesion on a stalk) coexisting in the same duct with extensive micropapillary proliferation diagnosable as intraductal carcinoma when it involves two or more complete duct profiles.

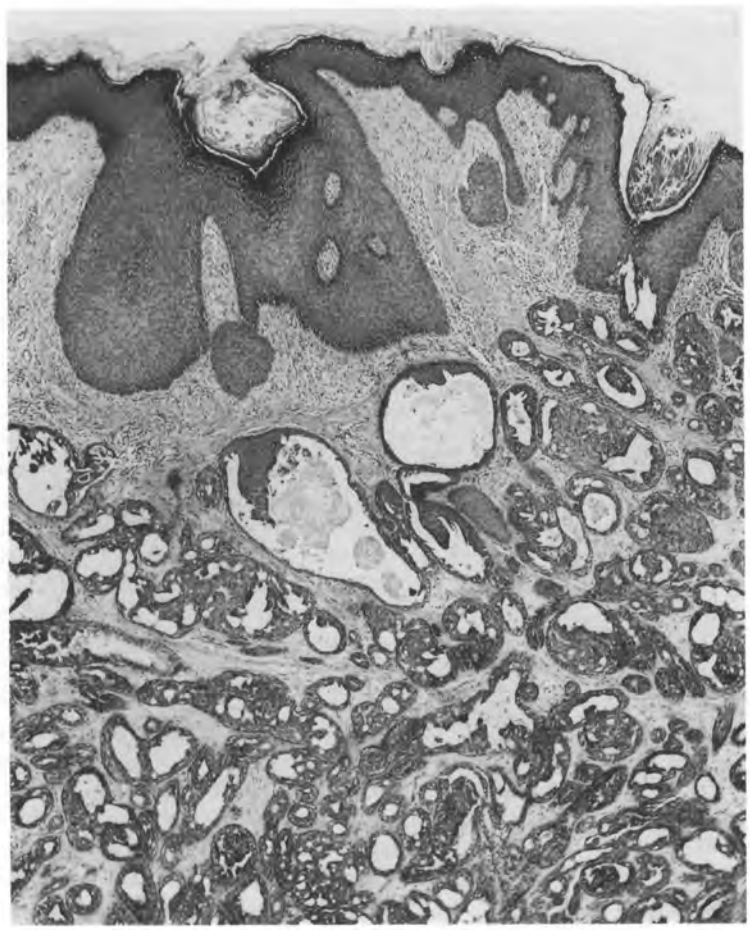


FIGURE 10-22 Adenoma of the nipple. Note the extension to the nipple epidermis. Squamous epithelium is present within some of the dilated ducts in the center of the figure. Lack of circumscription is apparent.

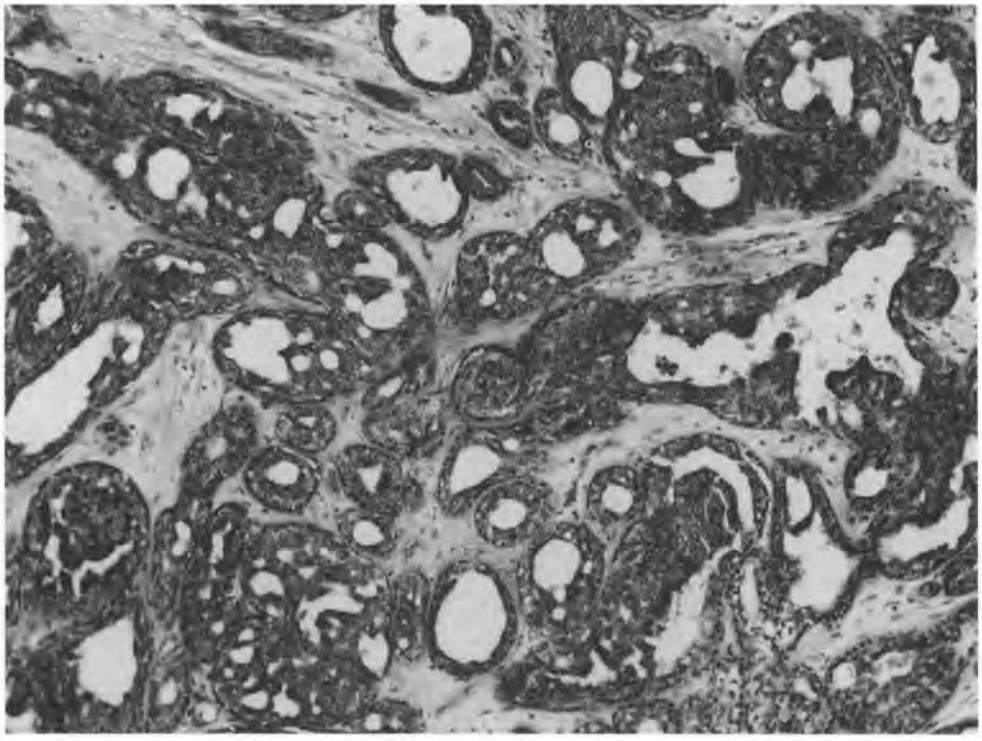


FIGURE 10-23 Adenoma of the nipple. Ducts are surrounded by prominent myoepithelial cell layer.

loma and intraductal or invasive carcinoma have been seen elsewhere in the same breast on a number of occasions, their presence should always be excluded.[101,103]

Sweat and Salivary Gland-Type Tumors

In addition to adenoma of the nipple, rarer lesions showing the histologic picture of benign sweat gland or salivary gland tumors have been reported. These include *clear cell hidradenoma* (clear cell myoepithelioma),[105] *eccrine spiradenoma,*[105] *pleomorphic adenoma* (benign mixed tumor)[106] and *syringomatous adenoma of the nipple.*[107] Follow-up of these lesions has been uniformly benign. Syringomatous adenoma of the nipple (Color Figure 10-9) is particularly important to recognize, because it may mimic certain patterns of mammary carcinoma. Diagnostic features include the typical location as well as the usual slit-like lumina, cell stratification, squamous metaplasia, absence of cytologic atypia, and lack of a stromal response.

In addition, there is a group of mammary tumors of low or incompletely characterized malignant potential that deserve mention in this section. *Adenoid cystic carcinoma* is traditionally included in the classification of ductal carcinomas and is discussed in that section. However, in many ways it should be thought of as belonging here because it is of salivary gland type.

A more recently described group of lesions that are best described here are the *myoepithelial lesions* of the breast. Tavassoli has classified these as myoepitheliosis, adenomyoepithelioma, and myoepithelial carcinoma.[108] By far the most common—although still a rare mammary lesion—is *adenomyoepithelioma*, a solitary gross tumor with well- or poorly circumscribed margins. The characteristic feature is a bimorphic cellular proliferation, with both ductal and myoepithelial cells, often arranged as ductal cell-lined tubules surrounded by concentric bands of clear myoepithelial cells (Figs. 10-24 and 10-25). The latter may be predominantly spindled and are best identified by positive immunostaining for muscle-specific actin or S-100 protein. The lesion appears to be benign, although it can recur locally if inadequately excised, and 2 of 27 adenomyoepitheliomas in Tavassoli's series had carcinoma arising within them. Three cases in this series were multifocal microscopic lesions with a similar cellular population, designated as myoepitheliosis, whereas a single case of myoepithelial carcinoma was an infiltrating malignant tumor composed purely of myoepithelial cells.

Collagenous spherulosis is another recently described lesion that has been shown to be of combined epithelial and myoepithelial cell origin.[109] It is usually an incidental microscopic finding but may rarely form a palpable mass. The characteristic microscopic feature is the presence of whorls of dense hyalinized collagen interspersed with the two cell types (Color Figure 10-10). The lesion is benign.

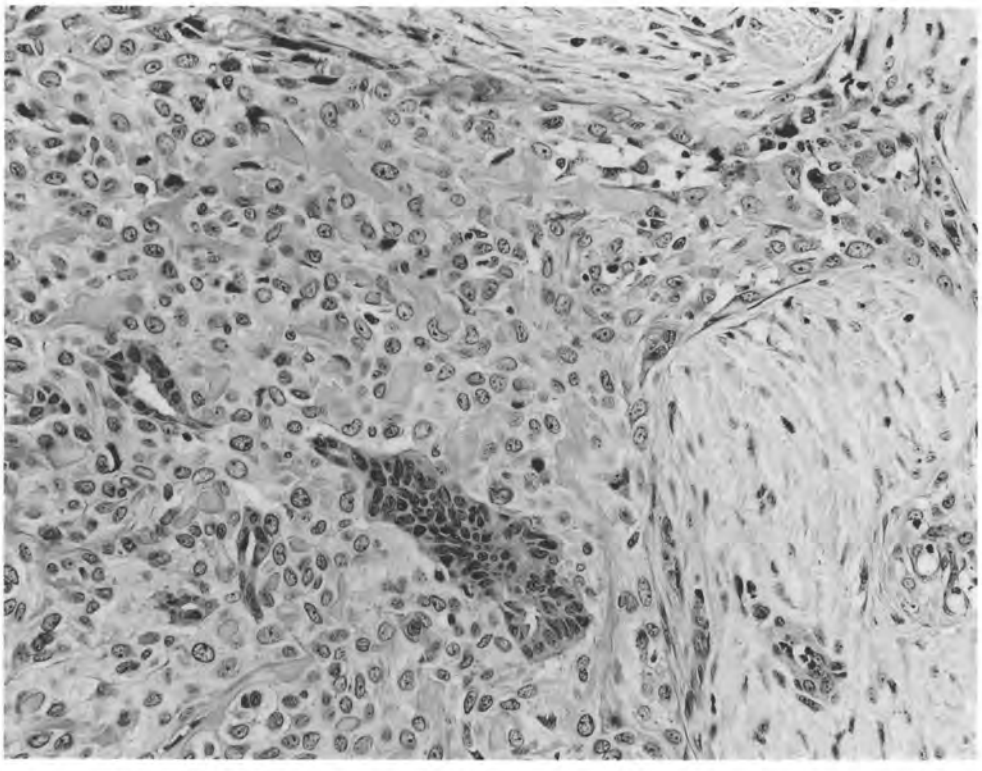


FIGURE 10-24 Adenomyoepithelioma. Bland-appearing ductal structures are surrounded by a circumscribed proliferation of ovoid myoepithelial cells, and the entire complex is bordered by fibrotic stroma.

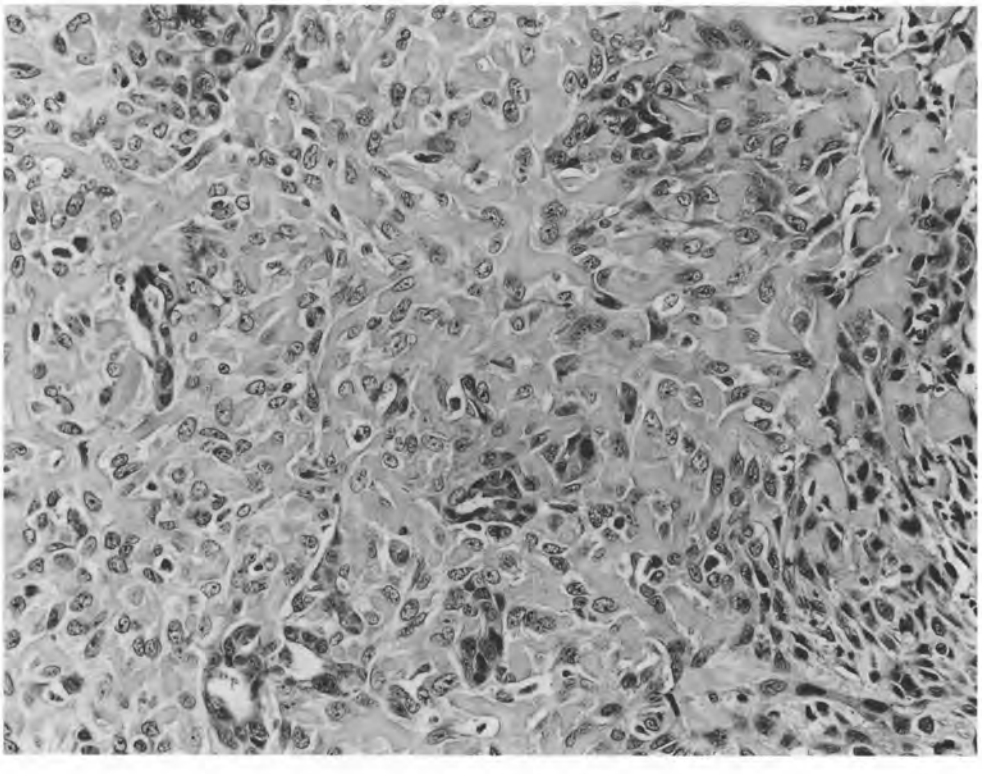


FIGURE 10-25 Adenomyoepithelioma. These myoepithelial cells are more spindled than those in Figure 10-24 and show some atypia and mitotic activity.

Lipoma

Lipoma of the breast is seen in women between 40 and 60 years of age, in the form of a well-demarcated, soft, round mass, the diameter of which is generally in the range of 1 to 5 cm. It is surrounded by a thin fibrous capsule.

The *macroscopic appearance* is clearly that of a benign lesion, and can easily be confused with normal adipose tissue except for its encapsulation. The *histologic picture* is that of banal adipose tissue. The form known as *adenolipoma* consists of a lipoma in which a few mammary lobules are found included in the tumorous fatty proliferation; this is probably better included under the heading of hamartoma.[110,111] This is also true for chondrolipoma.[112]

Hamartoma

The term *hamartoma* recently has been used to describe benign, encapsulated growths with the gross appearance of fibroadenomas but histologically resembling normal breast tissues (Fig. 10-26). This lesion differs from fibroadenoma in that the stroma does not take an active part in the tumorigenesis, fat is usually present, and apocrine metaplasia is often seen.[110,111]

Lactoma (Lactating Adenoma)

Although not a true tumor, this lesion is discussed here because it presents to the clinician as a well-defined tumorous mass during late pregnancy and lactation and is often excised for diagnostic purposes. It consists of a well-demarcated but unencapsulated, small, spherical mass composed of histologically normal-appearing lactating mammary tissue.[66,68] This is a proliferative rather than a neoplastic lesion and, as such, regresses spontaneously after the nursing period if it is untreated.

A somewhat similar lesion may be encountered in the breasts of women taking oral contraceptives or other medications, particularly antipsychotic and antihypertensive drugs.[113] The proliferation in these cases may be localized (Fig. 10-27) or diffuse and is frequently an incidental microscopic finding. Malignant transformation has not been reported.

Granular Cell Tumor

Granular cell tumor is also known as *Abrikosov's tumor* and *granular cell myoblastoma*. Almost 100 cases of granular cell tumor of the breast have been reported.[114]

The macroscopic appearance of these lesions may lead to confusion with carcinoma, because they present as firm, rounded masses that usually adhere to surrounding tissues. They appear to arise most often in the upper and medial segments of the breast. Their histologic and cytologic appearances are characteristic and allay fears about malignancy. A histologic description is given in Chapter 1.

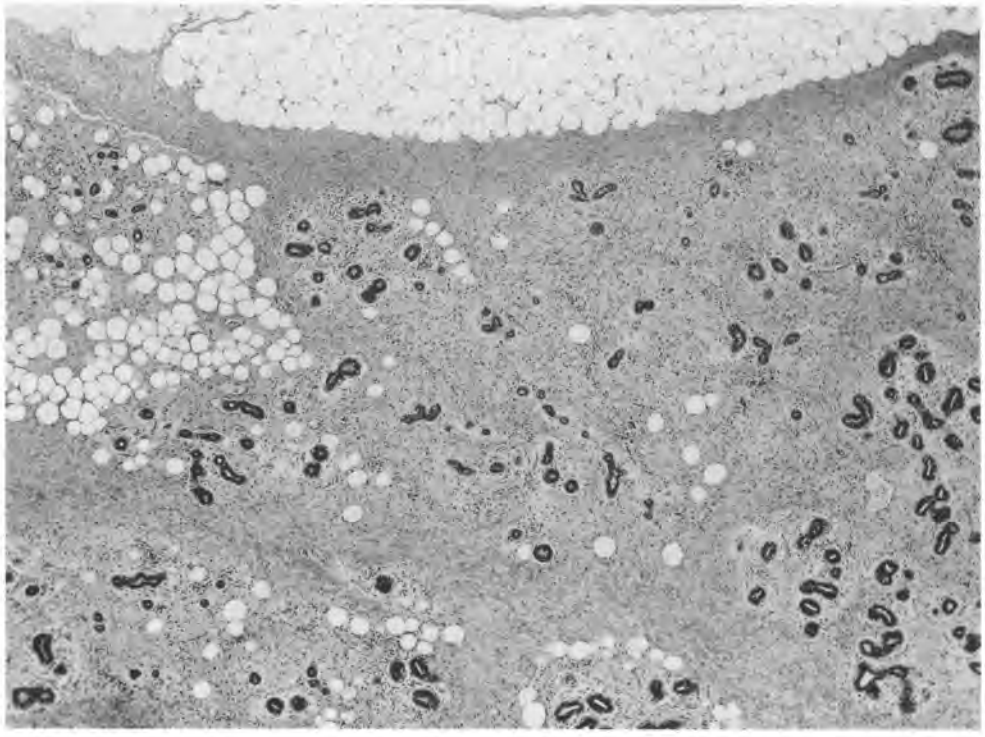


FIGURE 10-26 Hamartoma. This lesion was removed as a probable fibroadenoma. It consists of randomly scattered ductules, fibrous stroma, and fat, and it is well demarcated from adjacent adipose tissue.

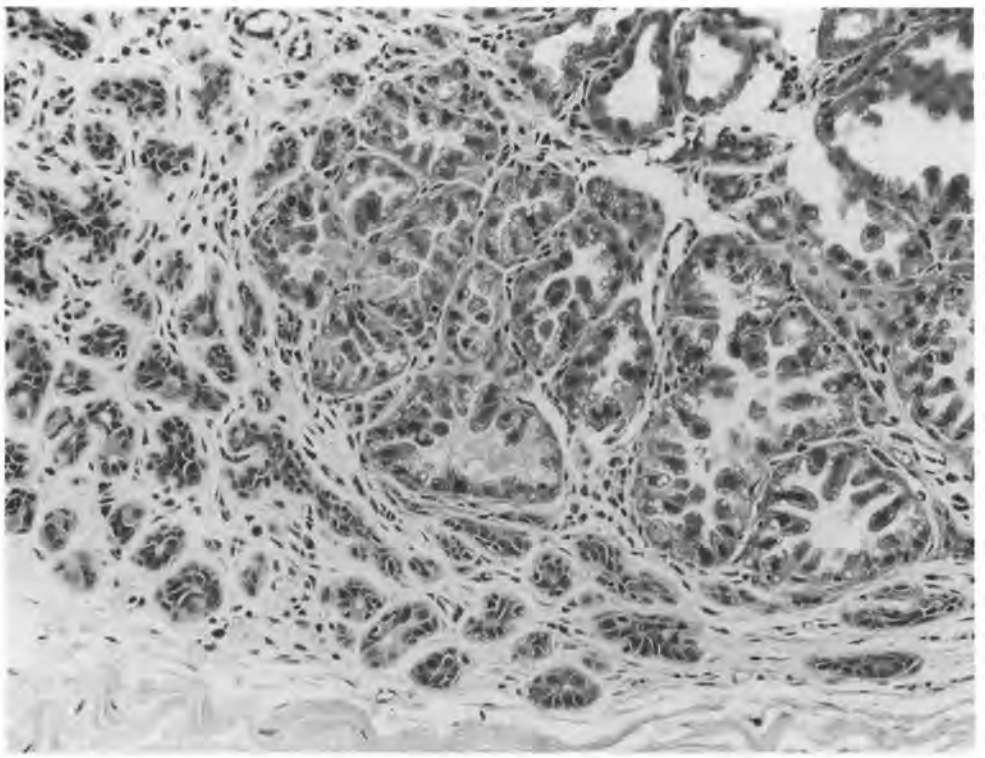


FIGURE 10-27 Secretory (lactational) hyperplasia seen focally as an incidental microscopic finding. Note the enlarged hyperchromatic nuclei, which should not raise the suspicion of carcinoma in this setting.

Leiomyoma

Rare cases of mammary leiomyoma have been described.[115] Leiomyoma develops from the chest wall musculature, smooth muscle of the skin, and vascular or areolar muscle.

Hemangioma and Related Vascular Lesions

Pathologists who were trained more than 20 years ago will remember having been taught that any vascular lesion occurring in mammary parenchyma (as opposed to the skin overlying or muscle underlying the breast proper) was by definition an angiosarcoma, regardless of how benign it might appear. This concept is of historical interest only, because a number of benign vascular lesions of the breast have now been documented. The most common of these is the *perilobular hemangioma,* a sharply circumscribed and usually perilobular lesion (Fig. 10-28) that generally measures less than 1.5 mm and is an incidental microscopic finding (angiosarcomas are large, grossly visible tumors).[116,117] Lesueur found an 11% prevalence of these lesions in a forensic autopsy series.[117] Histologically, they are identical to benign hemangiomas seen elsewhere.

Other less common vascular lesions in the breast include *venous hemangiomas,*[118] *angiomatosis*[119] (a rare lesion in which variably-sized but benign-appearing vessels are distributed uniformly through the tumor), *hemangioma with atypical histologic features*[120] (which has been shown to be benign), and *hemangiopericytoma.*[121]

A related but nonvascular lesion is *pseudoangiomatous hyperplasia of mammary stroma,* a benign keloid-like fibrosis containing slit-like spaces that are not lined by endothelial cells, as demonstrated by negative immunostaining for factor VIII-related antigen and *Ulex europaeus* lectin. This lesion was found as an incidental microscopic finding in 23% of breast biopsy specimens in one series.[122] It occasionally forms a palpable mass.

The main clinical significance of all these lesions is that they may be diagnosed by the unwary pathologist as angiosarcoma. Basically, angiosarcoma is always grossly infiltrative and is usually a large tumorous mass containing (at least focally) atypical and mitotically active endothelial cells. This tumor is discussed in greater detail later in this chapter.

Other Benign Masses

A number of other benign lesions may present as palpable or mammographically detected intramammary masses. These include normal or pathologic *intramammary lymph nodes,*[7,123] *plasma cell granuloma* (inflammatory pseudotumor),[124] *fibromatosis*[125], and *mucocele-like tumor.*[126,127] All of these resemble their counterparts seen in other parts of the body. The mucocele-like tumor is important in the differential diagnosis of mucinous carcinoma and is discussed with that tumor.

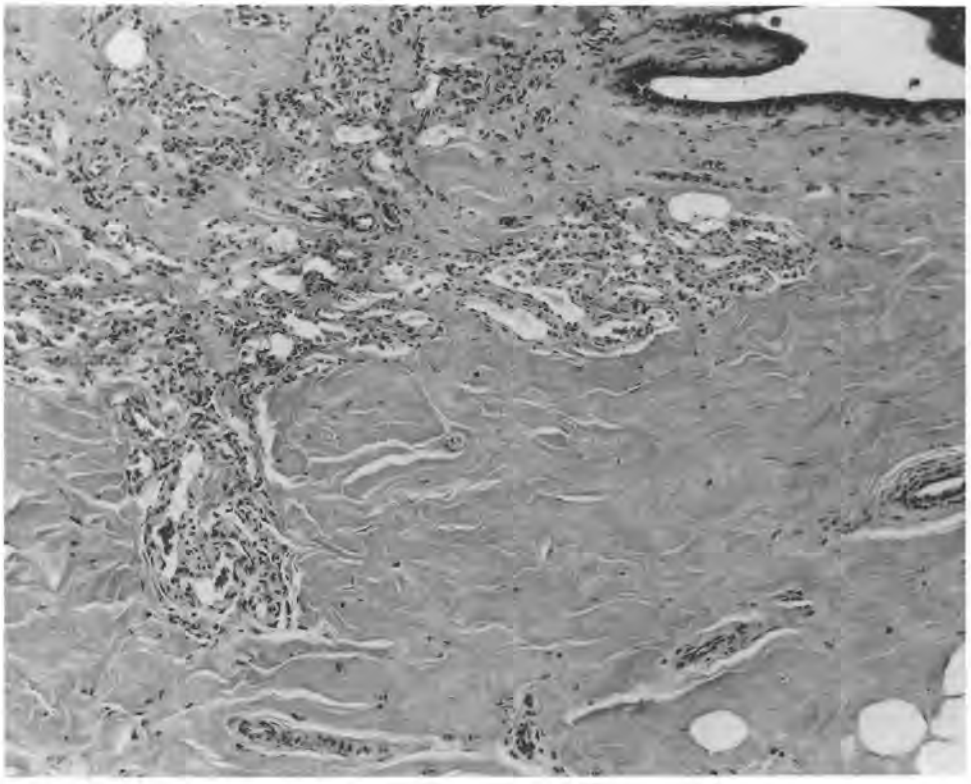


FIGURE 10-28 Perilobular hemangioma. This microscopic lesion (seen almost in its entirety here) is adjacent to a lobule, the terminal duct of which is seen in the photomicrograph.

FIBROCYSTIC CHANGES

Fibrocystic changes represent a condition formerly known under a great variety of names, including *fibrocystic disease, chronic cystic mastitis, fibrocystic mastopathy, fibrocystic dysplasia, fibroadenomatosis, mazoplasia, mastodynia, cystic dysembryoplasia, chronic mammitis, Reclus' disease,*[128] and *Schimmelbusch's disease.*[129] This multitude of names reflects the confusion in the definition of the fibrocystic complex of clinical, gross, and histopathologic changes. Because at least some of the histopathologic changes are encountered in most women in their reproductive years, the tendency—which we applaud—is not to characterize these changes as a "disease."[130,131] We do, however, continue to use the term *fibrocystic changes* diagnostically, as a means of notifying the surgeon that a submitted sample cannot be characterized as normal resting breast tissue.[132]

The main significance of the lesions discussed under this heading lies in what they do not represent—a cancerous or highly precancerous condition. However, numerous studies have demonstrated a slightly increased risk (in the range of twofold or less) of cancer development in the breasts of women bearing these lesions.[100,133,134] Whether this indicates a real premalignant potential, or merely indicates a different level of concern and follow-up of women who have had benign breast biopsies, remains to be determined. In any event, we have chosen to separate the discussion of atypical lobular and ductal hyperplasias—which are most commonly seen in association with the fibrocystic complex—because these latter lesions are (1) associated with considerably higher (on the order of fourfold) risk of subsequent cancer, and (2) more difficult to differentiate at the histopathologic level from lesions that are considered to be noninvasive cancers.

Etiology

The etiology of a non-disease is difficult to define. Nevertheless, it is clear that women with clinically significant fibrocystic changes (in other words, those who come to biopsy) are probably different in some ways from women who never develop such changes. Women in whom these same changes can be demonstrated at autopsy are also different from women in whom they cannot. It is generally agreed that the prevalence of fibrocystic lesions is probably related to hormonal disequilibria to which the breast is subject during the course of reproductive life, which in turn are related to genetic background, age, parity, lactational history, and administration of exogenous hormones.[132] In one autopsy study in which women of different racial groups were compared, those groups at greater risk for the development of breast cancer showed more fibrocystic changes.[135]

Clinical Features

The first clinical manifestation is usually the discovery by the patient of an intramammary nodule. In-

tracystic tension may produce discomfort and tenderness to palpation. The cysts may appear rapidly and disappear just as rapidly by rupture or resorption. Symptoms are characteristically aggravated in the premenstrual period and usually involve both breasts. The manifestations of the condition decrease after menopause.

Clinical examination reveals one or several firm, moderately movable nodules, which may give the impression of "beads on a string." Skin retraction is absent, and nipple discharge is rarely seen. The consistency of these nodules depends on the tension of the fluid within the cysts and the prominence of associated fibrosis.

Sclerosing adenosis is usually an incidental microscopic finding, but it may rarely present as a clinically detectable mass (*adenosis tumor*).[136,137] The other components of the fibrocystic process are generally incidental findings, with the exception of radial scars, which may be appreciated as individual lesions by palpation or mammography.

Many biopsies showing fibrocystic changes are obtained as the result of mammographically detected abnormalities in asymptomatic women with no palpable masses. In many instances, the primary feature that provokes the biopsy is the presence of microcalcifications.

Macroscopic Appearance

The biopsy specimen is usually characterized by the presence of small cysts in a white fibrous parenchyma. The classic color of the cysts is blue (so-called blue-dome cysts), but yellow, green, and brown cysts also are encountered. They may reach a few centimeters in diameter or may be so small that they are identified only at histologic examination. The cyst walls are small and shiny unless intraductal or intracystic proliferative lesions are present, in which case a velvety, tan to white inner surface may be seen. The intracystic fluid may be clear and straw-colored, viscous and green, or even creamy yellow or brown.

In occasional cases, multiple gross cysts with intracystic papillary proliferations are seen forming a localized mass in the breast of a young woman. This "Swiss cheese" pattern has been characterized as *juvenile papillomatosis*.[96]

Noninvasive and invasive cancers may be found within a breast biopsy in which the dominant features are fibrocystic. The pathologist should search carefully for regions of increased firmness with a granular, chalky appearance, often with yellow streaks radiating into the surrounding benign tissues. Such lesions generally prove to be infiltrating carcinomas, but radial scars may have a similar gross appearance. Intraductal carcinomas may be recognized as foci of soft papillomatous proliferation or of comedo-type necrosis within dilated ducts. Again, benign intraductal lesions can show these gross appearances, and other intraductal carcinomas may not be detectable grossly. Lobular carcinoma in situ is almost always an incidental microscopic finding.

Microscopic Appearance

Fibrocystic changes are characterized by the presence of several basic microscopic lesions, excluding the atypical lesions to be discussed later:

- Lactiferous cysts
- Stromal fibrosis
- Apocrine metaplasia
- Sclerosing adenosis
- Radial scars
- Secondary inflammation
- Intraductal epithelial hyperplasia.

Lactiferous Cysts

Lactiferous cysts usually are surrounded by a dense fibrous stroma (Fig. 10-29*A*). The lining epithelium may be cuboidal, flattened, or even missing entirely and replaced by a fibrous wall (Fig. 10-29*B*). Sometimes the cells become charged with lipids, are desquamated into the cyst lumina, and form plaques of large cells with finely vacuolated cytoplasm. The cysts may be isolated, compressed against each other, or ramified. They are formed from the principal or secondary lactiferous ducts and are surrounded by discrete lymphoplasmacytic infiltrates. In some cases, lipid-laden cells become agglomerated, and cholesterol crystals appear in the necrotic debris. Secondary calcification may take place in benign lesions (Fig. 10-30) but should always arouse a suspicion of malignancy.

Stromal Fibrosis

Stromal fibrosis is a constant finding, but its degree varies from one case to another and from one area to another in the same case. Fibrosis encircles the lobules and the ducts, and in a more advanced stage atrophic epithelial structures are compressed by an abundant stroma containing collagen and acid mucopolysaccharides. Hyalinization, calcification, and ossification may be observed in longstanding lesions. The reactive desmoplastic stroma associated with infiltrating carcinoma and characterized by large spindled cells in a fibroelastotic background with myxoid and inflammatory changes is by definition absent.

Apocrine Metaplasia

Apocrine metaplasia is often found in cystic epithelia. It affects primary and secondary ducts equally. The lining cells are large, with abundant pale eosinophilic cytoplasm and small round nuclei; the apical pole swells and herniates into the cyst lumen (Fig. 10-31). They may involve an entire duct or only part of a duct, and may be seen in both flat and prolifer-

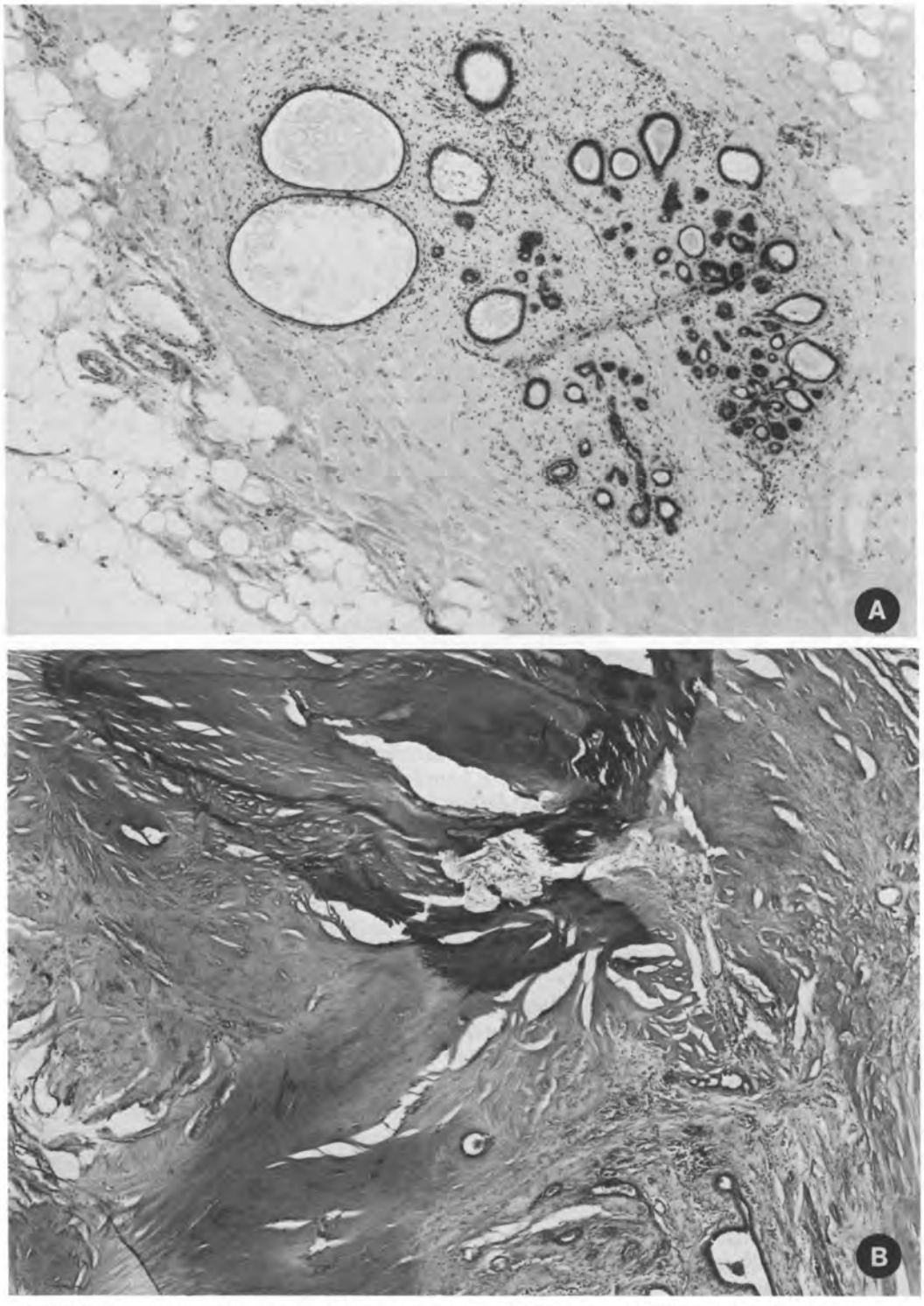


FIGURE 10-29 Fibrocystic change. **(A)** Focal duct cysts. **(B)** Secondary fibrosis and calcification.

ated epithelia. Whether these cells are truly analogous to those of apocrine sweat glands has been the subject of several investigations. Although some authors stress the similarities, most feel that the mammary cells are not truly apocrine.[138] They are actively proliferating and secreting cells, and might better be referred to as *oncocytes* because of their numerous mitochondria. The apocrine cells may, on occasion, show moderate cellular atypia.

Sclerosing Adenosis

Sclerosing adenosis represents a particular clinicopathologic picture, recognized since the 1940s, in

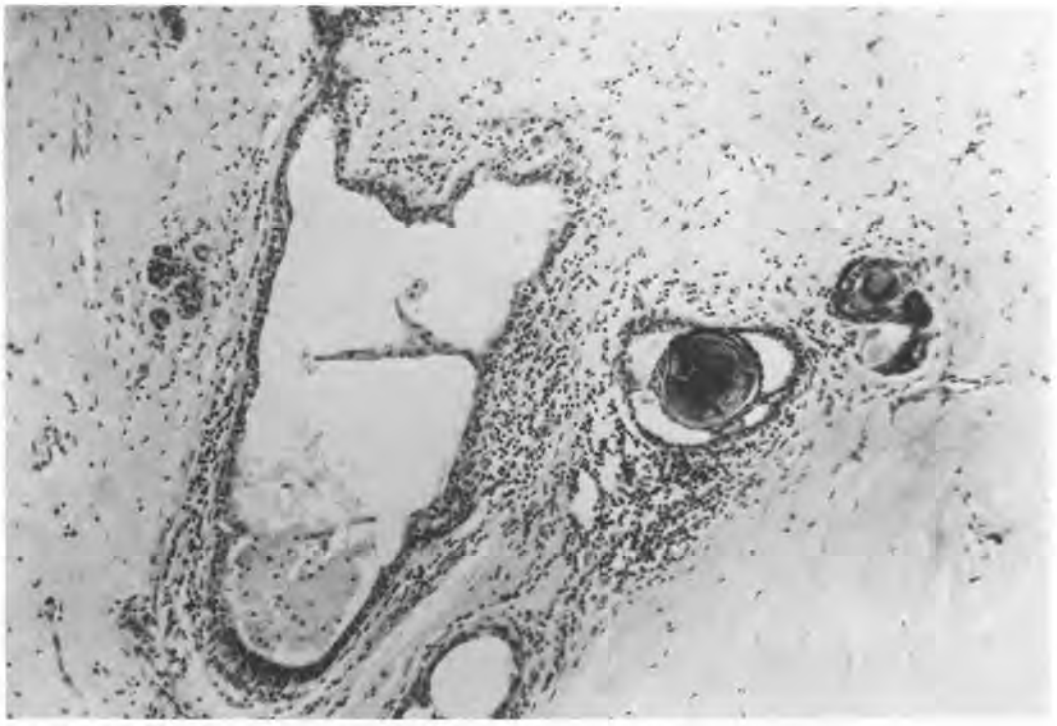


FIGURE 10-30 Lactiferous duct cysts with intracystic calcification.

which the proliferation of the myoepithelium constitutes the dominant lesion (Fig. 10-32).

In the initial phase, some ductules proliferate intensely in the form of ducts or cell cords compressed against each other. The lobular structure persists, and bizarre cell atypias are not seen. This hyperplasia involves primarily the myoepithelial cells, which are seen as elongated elements with acidophilic cytoplasm in which myofibrils are occasionally visible without special stains. This is followed by hyperplasia of the epithelial cells and proliferation originating in ductal budding. Ultrastructural studies confirm the involvement of the myoepithelial cells in the development of sclerosing adenosis.[139] Myoepithelial cells are characterized by the presence of filaments and dense bodies in the cytoplasm and are underlain by basal lamina. Their presence in these lesions can be confirmed by immunohistochemical positivity for muscle-specific actin and (less reliably) S-100 protein.

In the subsequent phase, marked interstitial fibrosis takes place, breaking up the glandular formations into such small pieces that a false appearance of neoplastic infiltration is created. On rare occasions, even perineural infiltration may be present.[140] The epithelial cords are finally completely submerged in a fibrotic and hyalinized connective tissue framework, but they always retain a vague lobular disposition.

This lesion is too frequently misdiagnosed as carcinoma, particularly on frozen section, and it is important to be aware of its existence and appearance (Table 10-2). Intraoperative or FNA cytology (smears or imprints) always appears benign.[36,137] Malignant transformation occurs extremely rarely and is usually lobular or ductal carcinoma in situ.[141,142] Atypical apocrine metaplasia is a benign but histologically worrisome focal lesion that may also be encountered within sclerosing adenosis.[143] Different opinions have been expressed concerning the existence of an elevated risk of carcinoma associated with sclerosing adenosis. Two studies provide arguments for the reassignment of sclerosing adenosis to a category of slightly elevated cancer risk.[144,145] The pathologist should perform a careful search for atypical lobular or ductal hyperplasia, which represent more grave risk factors, when sclerosing adenosis is observed.

Radial Scar

The radial scar lesion also is known as *infiltrating epitheliosis, nonencapsulated sclerosing lesion,* and *indurative mastopathy.* It is sometimes detected by mammography or may present as an incidental finding in tissues excised in cases of fibrocystic change. It is single or multiple. Its mean size is around 1 cm in diameter. Macroscopically, it consists of a firm, regular, gray-white lesion with a central depressed retraction.

Microscopically, it is characterized as a radial stellate lesion consisting of a dense, central, fibroelastotic core with entrapped ductal structures (Fig. 10-33). These structures exhibit varying degrees of adenosis, hyperplasia, and ductal cystic dilatation. The cells lining these epithelial structures generally lack cytologic atypia. Mitoses are very rare.

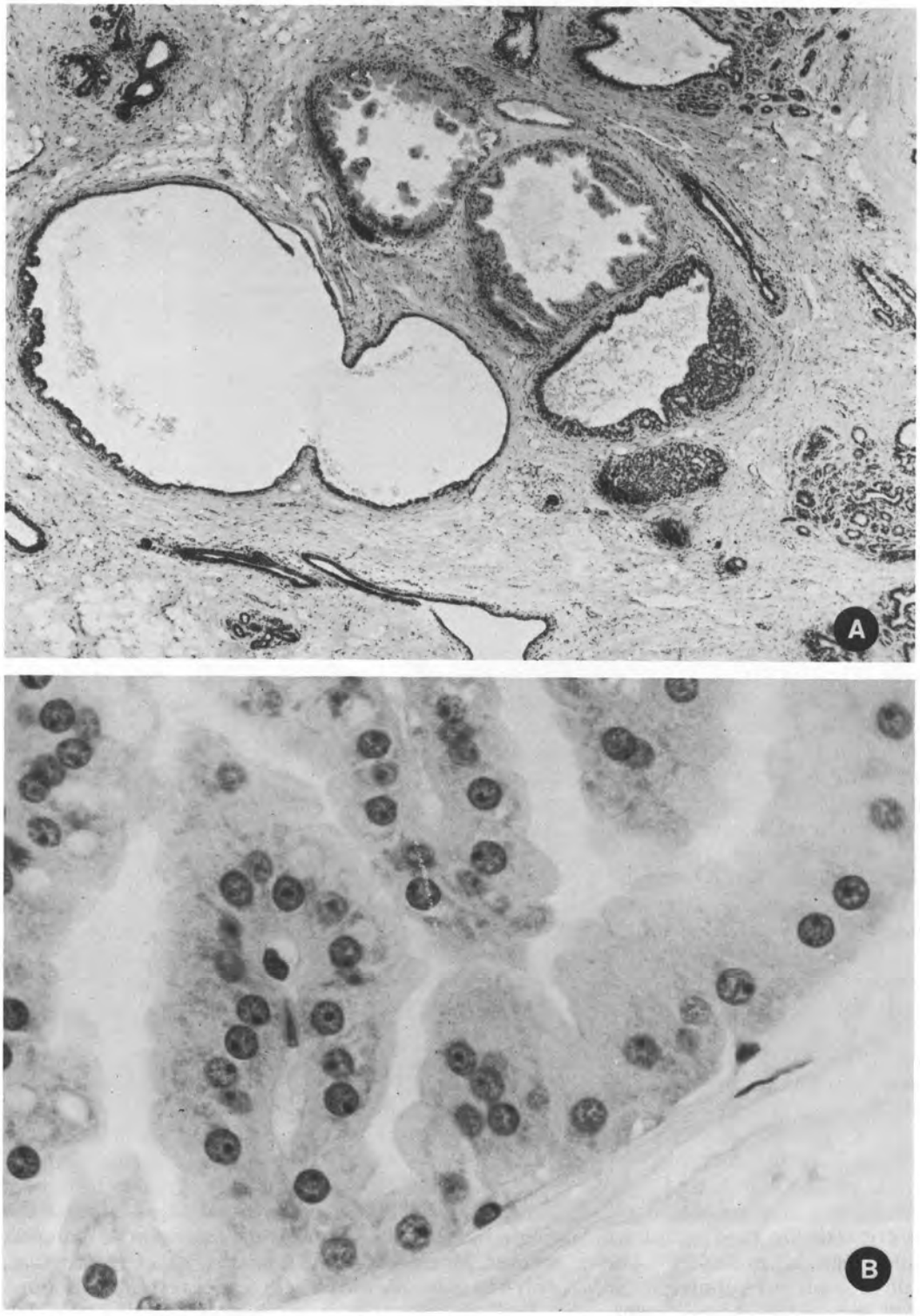


FIGURE 10-31 Apocrine metaplasia. **(A)** Low magnification. **(B)** Detail.

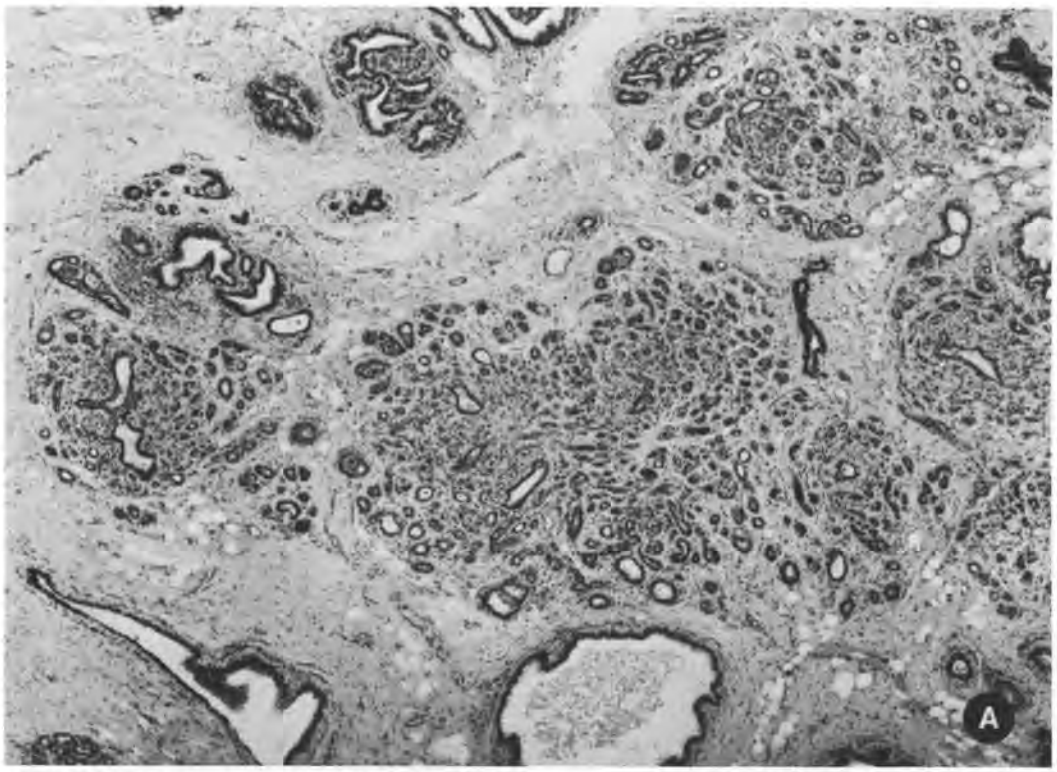


FIGURE 10-32 Sclerosing adenosis.

The lesion worries the pathologist for two reasons. First, it has some histologic similarities with tubular carcinoma, and second, for some authors it may represent a precursor of tubular or other types of carcinoma.[146,147] The absence of infiltration of the adjacent stroma and the presence of myoepithelial cells characterize a radial scar.

In any case, the lesion should be considered as part of the fibrocystic complex and shares with it the potential risks of cancer development.

Secondary Chronic Inflammation

Secondary chronic inflammation is characterized by the presence of plasma cells and polymorphonuclear leukocytes in the vicinity of ruptured cysts. It is a local complication; an inflammatory process is not an essential constituent of fibrocystic change. These reactive changes should not be confused with a primary mastitis or the inflammatory stroma accompanying a carcinoma.

Intraductal Epithelial Hyperplasia (Epitheliosis; Papillomatosis)

Intraductal epithelial hyperplasia is defined as an increase in epithelial cell numbers above the normal bilayered structure (epithelial and myoepithelial cells). It may involve the lobule, the terminal duct, or any part of the ductal system. However, the lesion by convention is considered to be a ductal rather than a lobular proliferation. The term *epithelial hyperplasia* is preferred to *epitheliosis* and *papillomatosis* because it suggests the hyperplastic character of the lesions and reflects the probable continuous progression from typical hyperplasia to atypical hyperplasia, carcinoma in situ, and eventually invasive carcinoma.

Two proposed classifications of the entire spectrum of proliferative mastopathy are summarized in Tables 10-3 and 10-4.[100,148] The distinction among these lesions involves many subjective features, and reproducibility among different observers may be difficult to obtain.[94,95] These statements are similar to those that have been made for many years with reference to intraepithelial lesions of the uterine cervix, and the same degree of caution must be exercised in the interpretation of these mammary alterations. Despite this more or less continuous spectrum, we believe that it is useful to separate the typical hyperplasias to be considered here from the atypical forms, both because the latter are defined by their distinction from in situ carcinoma and because they carry a higher risk of progression to carcinoma. Thus, a lack of resemblance to in situ carcinoma is implied in the definition of typical hyperplasia.

Typical intraductal hyperplasia is characterized by a proliferation in which there is an increase in cell numbers to more than the normal two layers (Figs. 10-34 through 10-36). There is formation of bridges, tufts, arcades, and fenestrated sheets preserving the presence of lumina in the new proliferations, as well as cell nests that appear solid in at least

(Text continued on page 556)

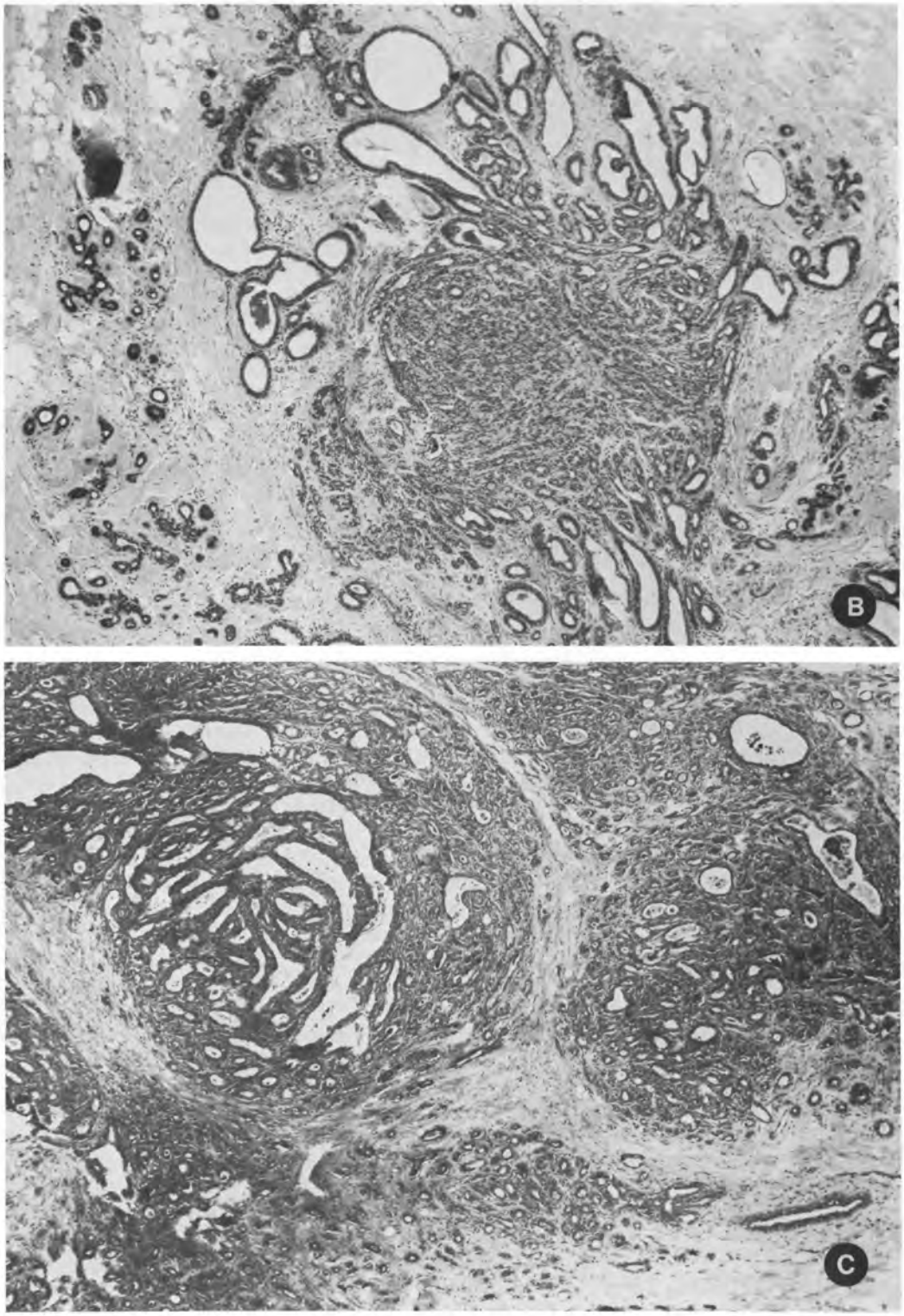


FIGURE 10-32(B,C) *(continued)*

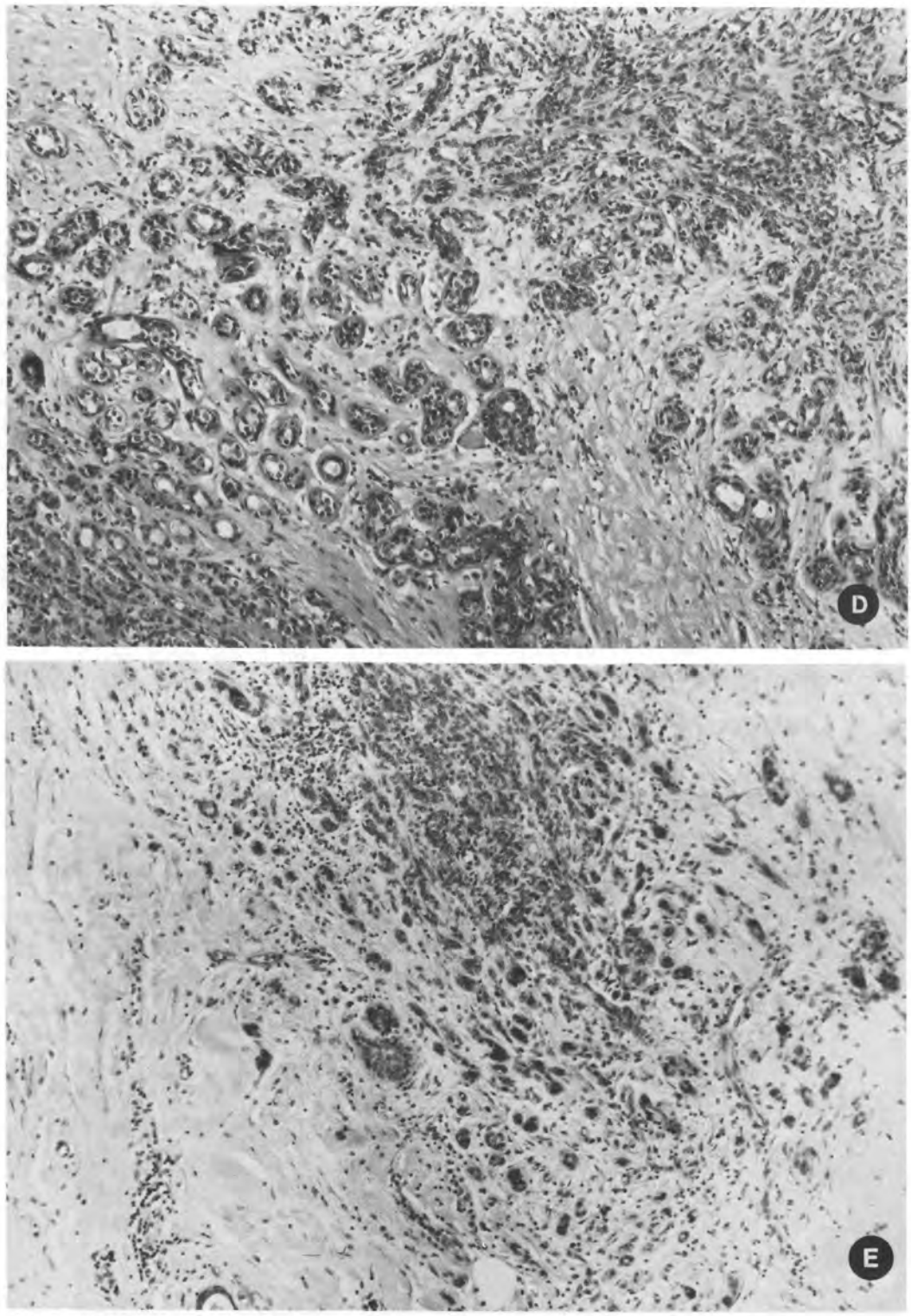


FIGURE 10-32(D,E) *(continued)*

TABLE 10-2.
Differential Diagnosis of Sclerosing Adenosis Versus Infiltrating Carcinoma

	Sclerosing Adenosis	***Carcinoma***
Distribution	Multifocal	Usually one dominant mass
Architecture	Lobular pattern preserved	Irregular
Borders	Circumscribed	Infiltrating (usually)
Lumina	Sclerosed centrally, often preserved peripherally	Uniform throughout
Swirling	Prominent	Rare
Stroma	Fibrotic, hyalinized	Fibroelastotic, myxoid, inflamed, sometimes normal; almost never hyalinized
Cell Type	Epithelial and myoepithelial	Epithelial
Nuclear Atypia	Absent to minimal	Slight to marked
Focal Apocrine Change	Frequently present	Rare

some histologic sections. The lumina generally are irregular in size and shape, with numerous compressed slit-like spaces. The cells are small, irregularly shaped, and arranged at least focally in a swirling or streaming pattern. There is a lack of cellular uniformity, so that it is usually easy to demonstrate the presence of more than one cell type, and ovoid to spindled cells are admixed with rounder ones. Nuclear hyperchromasia, prominent nucleoli, and mitotic figures are absent or present only very focally.

This discussion of ductal hyperplasia raises the question of whether similar proliferative but not atypical lesions occur in lobules. According to Page and colleagues, such lesions do not exist (or at least are not included in their classification of epithelial hyperplasia of the breast).[149] Fechner and Mills recognize *lobular hyperplasia* without atypia, but they indicate that its premalignant potential is unknown.[150] Carter also illustrates lobular hyperplasia and defines it as intralobular proliferation of cells that are not appreciably enlarged or atypical, do not distend the lobules, and are accompanied by at least some myoepithelial cells.[151] We accept this definition, along with the caveat of Fechner and Mills that we do not know the clinical significance of this lesion. It does not seem to have any association with fibrocystic changes, and it may or may not represent the lower end of the spectrum in which lobular carcinoma in situ is the other end.

Another lesion involving lobules, the clinical significance of which is also unknown, is the picture

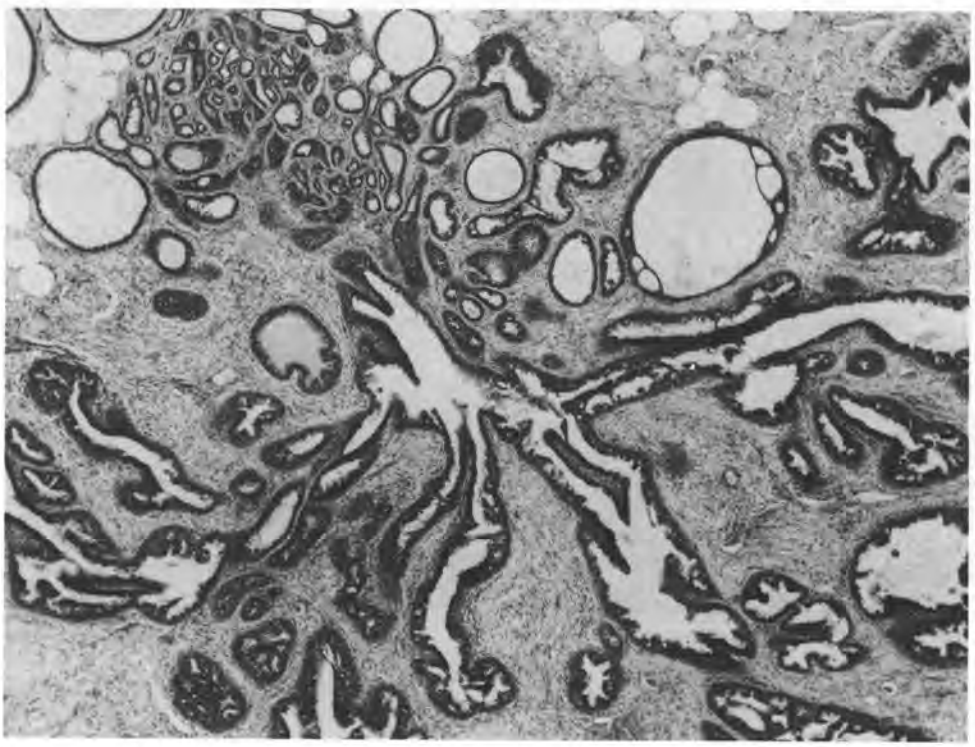


FIGURE 10-33 Radial scar. Central sclerosis and radial ductal proliferation are surrounded by foci of sclerosing adenosis and intraductal hyperplasia.

TABLE 10-3.
Mammary Epithelial Proliferative Disease Characterized by Cancer Risk

Cancer Risk	*Morphologic Features*
No increased risk	No proliferative disease: Adenosis (including florid) Apocrine change Duct ectasia Mild epithelial hyperplasia of usual type
Slightly (1.5–2×) increased risk	Usual hyperplasia, moderate or florid Sclerosing adenosis Papilloma
Moderately (4–5×) increased risk	Atypical ductal hyperplasia Atypical lobular hyperplasia
High (8–10×) risk	Lobular carcinoma in situ Noncomedo ductal carcinoma in situ

Adapted from Page DL, Dupont WD: Anatomic markers of human premalignancy and risk of breast carcinoma. Cancer 66:1326–1335, 1990

that has been known classically as *blunt duct adenosis* and is now more generally referred to as *unfolded lobules.*[152] These basically are cystically dilated lobules that resemble ducts but are too close to one another to represent true preexisting ducts (Fig. 10-37). Tangential sectioning of the epithelium within unfolded lobules can produce images falsely resembling hyperplasia, but true hyperplasias, including atypical hyperplasias, can develop in these structures.

ATYPICAL HYPERPLASIAS AND IN SITU CARCINOMAS

The lesions discussed in this section are intimately related to one another in three senses. First, the histologic pictures within the spectra of atypical hyperplasias and in situ carcinomas—whether for lobular or ductal lesions—are similar and pose difficult differential diagnostic problems. Second, all these lesions are associated with a markedly increased risk for the subsequent development of invasive cancer, although, as we shall see, the details of the magnitude of risk depend on the specific diagnosis and on other clinical factors, such as a family history of breast cancer. Finally, these lesions all share the property of being diagnosed most frequently by mammography or as incidental findings in breast tissues removed for other indications, rather than presenting as palpable masses.

Intraductal and intralobular carcinomas are defined as malignant transformation of the epithelium without infiltration of the underlying stroma. Although previously these lesions accounted for no more than 10% of all mammary carcinomas, they are now seen more and more frequently as the result of the widespread application of screening mammography.[98] When radiographically suspicious microcalcifications are present and biopsy is performed, more than 50% of the malignant tumors identified are noninvasive, with most of these being ductal rather than lobular.[22,98] The processing of these mammographically directed biopsies represents an important new chapter in breast pathology for the

TABLE 10-4.
Diagnostic Criteria and Cancer Risk for Nonapocrine Intraductal Hyperplasias and Carcinomas

Category	*Criteria*	*Risk of Invasive Carcinoma*
Ordinary or regular intraductal hyperplasia (IDH)	Multiple cell types, variable cellular and nuclear appearance, irregular/peripheral fenestrations, stretched or twisted epithelial bridges, focal cell streaming or spindling, unevenly distributed nuclei	2.6%
Atypical intraductal hyperplasia (AIDH)	Cell population monotonous and uniformly distributed, subtly increased nuclear–cytoplasmic ratio, round nuclei; architectural pattern of IDH or cribriform, micropapillary or stratified spindle cell papillary pattern not exceeding 2 mm in aggregate cross-sectional ductal diameters	9.8%*
Intraductal carcinoma (IDC)	Criteria for AIDH exceeding 2 mm in aggregate diameter or a cytologically obviously malignant lesion	Not stated

*Increased in the presence of sclerosing adenosis or a positive family history of breast carcinoma.

Adapted from Tavassoli FA, Norris HJ: A comparison of the results of long-term follow-up for atypical intraductal hyperplasia and intraductal hyperplasia of the breast. Cancer 65:518–529, 1990

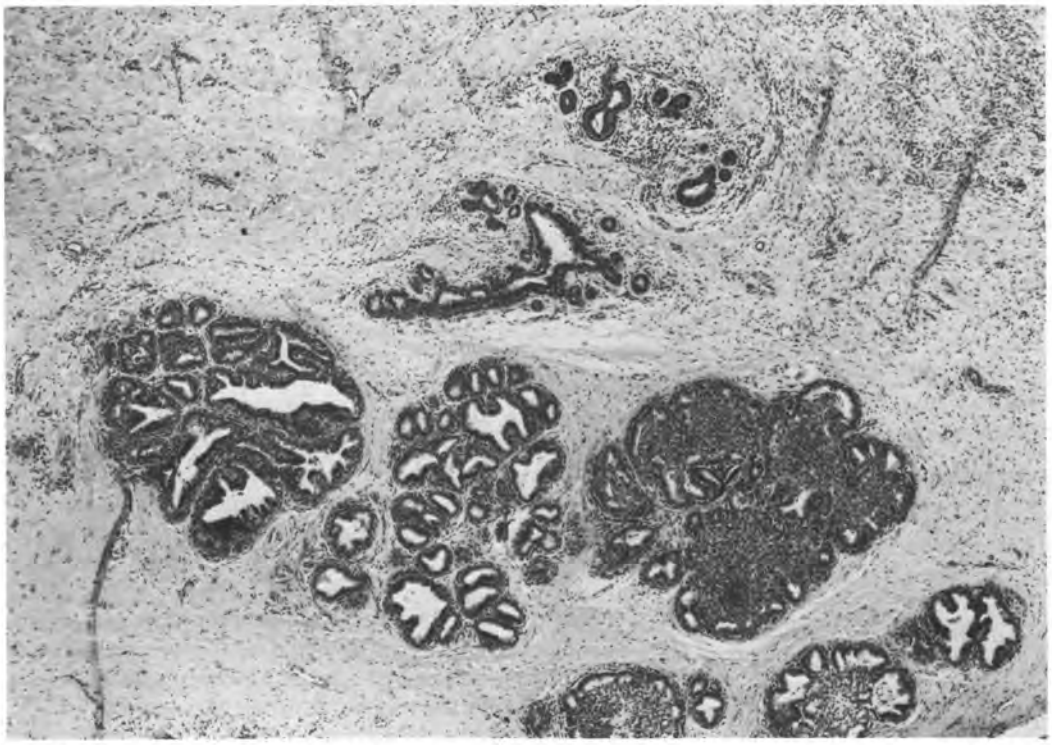


FIGURE 10-34 Typical intraductal hyperplasia of predominantly solid type.

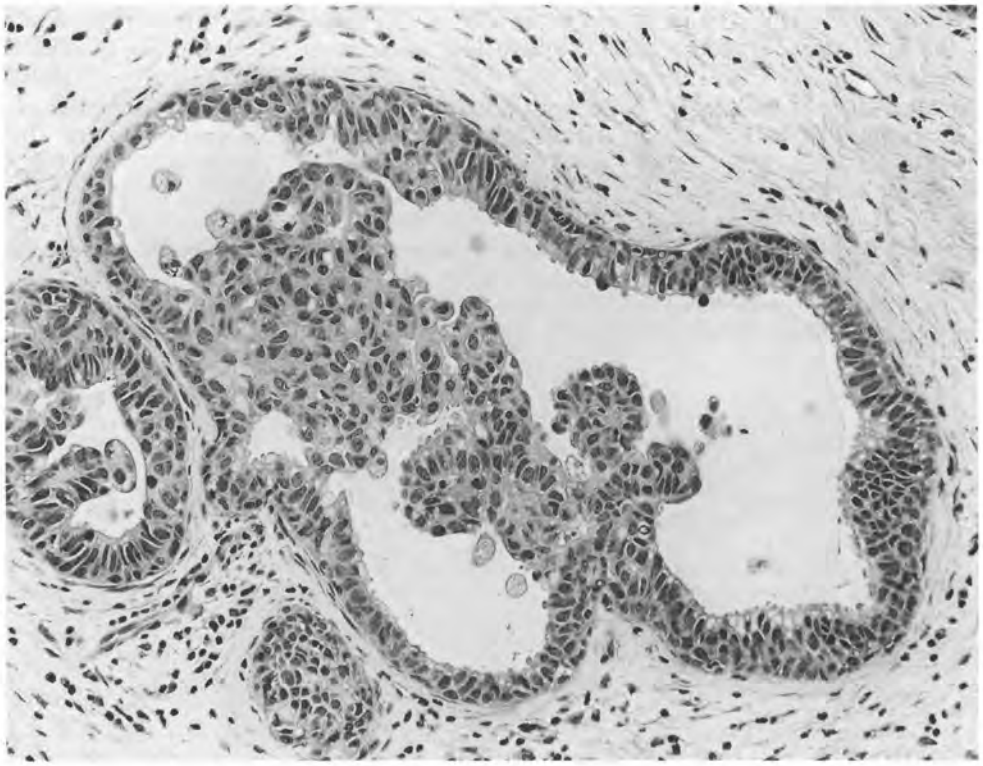


FIGURE 10-35 Typical hyperplasia: papillary and solid proliferation. Note the small size and irregular shapes of hyperplastic cells, with some spindling and swirling.

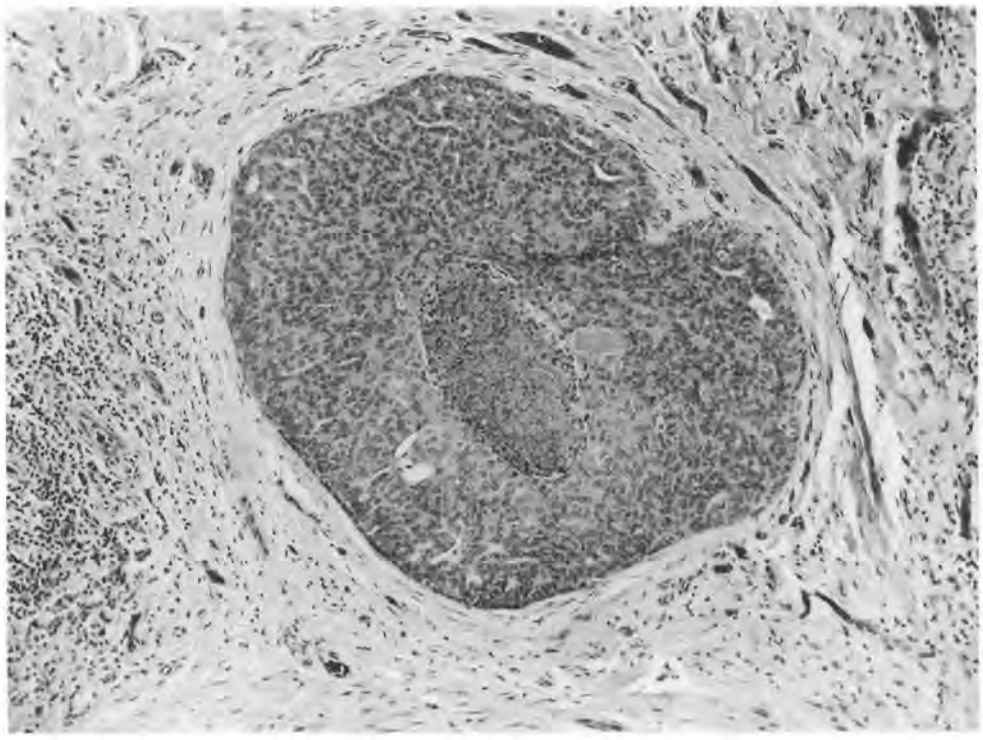


FIGURE 10-36 Typical hyperplasia. The lumina formed in this proliferation vary in size and shape. Central necrosis, although more common in intraductal carcinoma, is occasionally seen in completely benign lesions such as this one.

practicing pathologist, and the reader is referred to our earlier discussion on diagnostic approaches and to pertinent references[23,24] for a discussion of the technical details.

Despite the similarities mentioned above between lobular carcinoma in situ (LCIS) and ductal carcinoma in situ (DCIS), there are significant differences.[100] It is thought that LCIS represents a risk indicator of later invasive carcinoma rather than a fully malignant true precursor lesion, because the eventual invasive cancer may occur anywhere in the ipsilateral or contralateral breast and has an equal likelihood of being lobular or ductal in type. On the other hand, when invasive carcinoma follows DCIS, it appears in the same breast and even in the same quadrant, and is almost invariably of ductal type, indicating that DCIS represents a true precursor of invasive carcinoma.

Ductal Carcinoma In Situ (Intraductal Carcinoma)

Ductal carcinoma in situ (DCIS), which accounted for less than 5% of cases of mammary carcinoma in the pre-mammography era, is reported today to represent 15% to 22% of breast carcinomas.[22,98,100,153] Studies suggest that two forms of DCIS exist. The first is a lesion that does not form a palpable mass, is usually not recognizable macroscopically in excised tissues, and is histologically of non-comedo type. The second form is comedocarcinoma, in which a mass may be formed and clusters of distended ducts filled with creamy yellow to brown necrotic material may be recognized grossly.[154–158] Either form may be associated with a serosanguineous nipple discharge. Mammography reveals the presence of microcalcifications of granular, linear, or branching type. This finding is not specific, because only 25% of biopsies performed for these calcifications contain carcinoma, and 50% of these carcinomas are invasive.[22,98]

Microscopic Appearance. Intraductal carcinoma is distinguished by proliferation of the lining epithelia of the lactiferous ducts without stromal invasion. These epithelial proliferations occur in three common and two rare architectural patterns. The three common forms are:

- Micropapillary, in which papillae (usually lacking connective tissue axes) project into the lumen (Figs. 10-38 and 10-39)
- Cribriform, in which the tumor cells form bridges over uniform spaces, producing a uniformly punched-out pattern referred to as "cartwheels" or "Roman bridges" (Figs. 10-40 and 10-41)
- Comedocarcinoma, in which the lumina are filled with solid plugs of large, pleomorphic tumor cells, in which central necrosis becomes a prominent feature (Fig. 10-42).

The two less common types are:

- Solid, in which solid plugs of tumor cells that are less anaplastic than those of comedocarci-

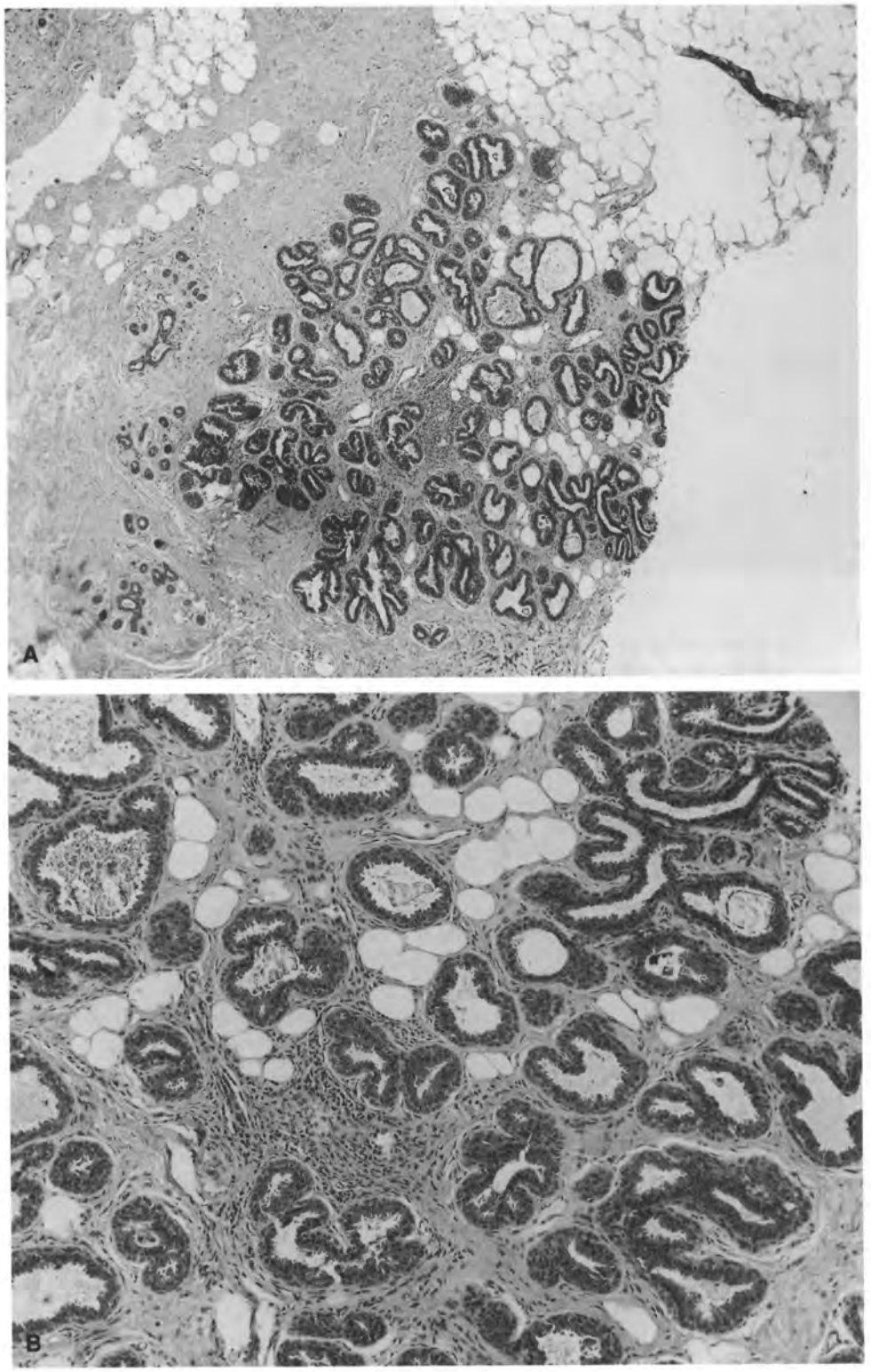


FIGURE 10-37 Unfolded lobules. **(A)** Low-power view showing the crowding of the enlarged and dilated lobules. **(B)** Detail showing double layer of cells without true hyperplasia or atypia.

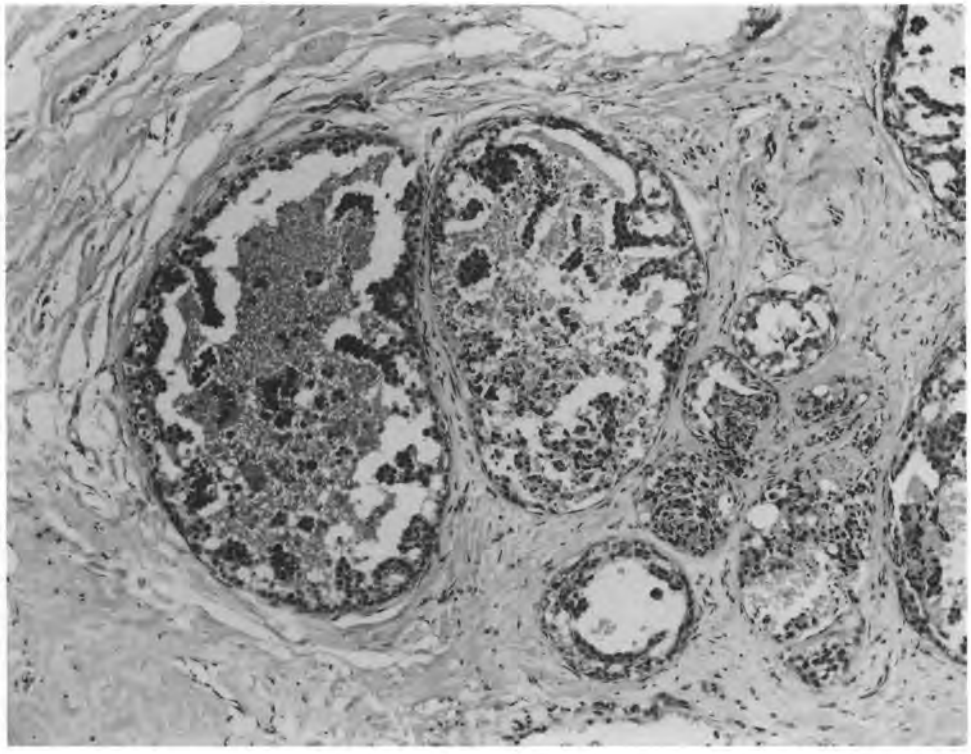


FIGURE 10-38 Intraductal carcinoma, micropapillary type. Low-power view of a group of involved ductal profiles.

noma fill duct lumina (Fig. 10-43) without (or occasionally with) the development of central necrosis (although solid intraductal cellular proliferations without necrosis are more frequently benign)

Papillary stratified spindle cell, in which large papillae with central connective tissue axes are lined by tall columnar cells with their nuclei oriented perpendicular to the basement membrane (Fig. 10-44).

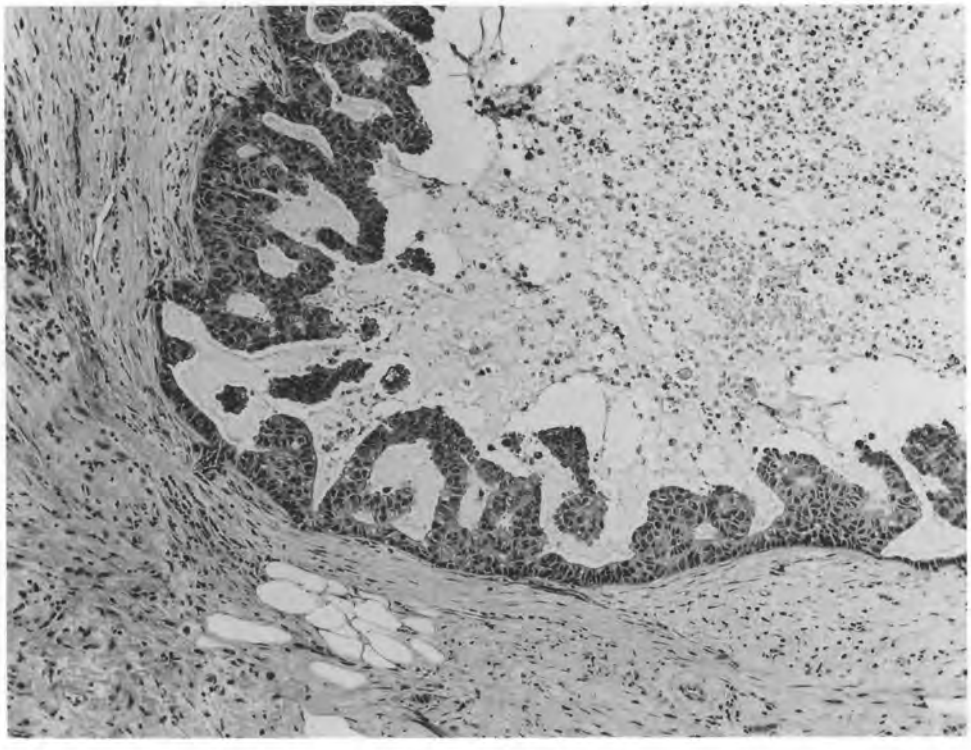


FIGURE 10-39 Intraductal carcinoma, micropapillary type. Detail of an involved duct showing small papillae lacking connective tissue axes and lined by a uniform cell population. Some papillae have fused to form so-called Roman bridges.

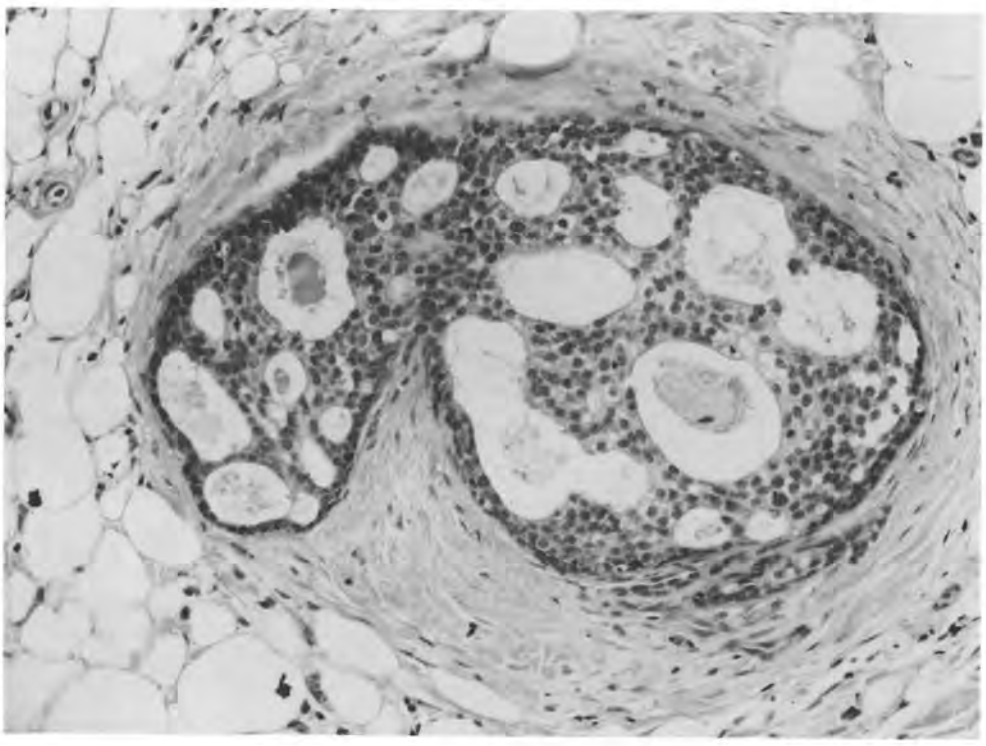


FIGURE 10-40 Intraductal carcinoma, cribriform type. Note the punched-out pattern of regular lumina and the uniform round cells without spindling or swirling.

A sixth type, so-called clinging carcinoma, is more poorly documented as representing carcinoma rather than a form of atypical hyperplasia.[159] In this pattern, a few layers of dyspolaric atypical cells line ducts with minimal architectural abnormalities. Even rarer variants are a mucinous type (Fig. 10-45), which may accompany infiltrating mucinous (colloid) carcinoma; hypersecretory duct carcinoma (Fig. 10-46), in which the malignant ducts are cystically dilated and contain colloid-like material; and intraductal carcinoma showing prominent apocrine differentiation (Fig. 10-47).

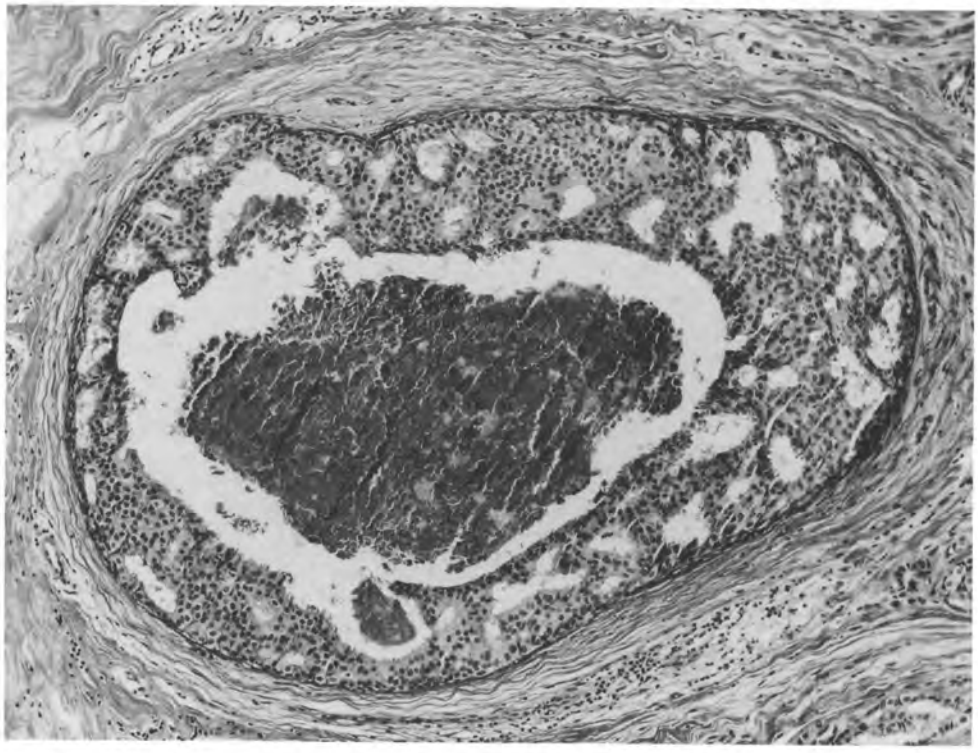


FIGURE 10-41 Intraductal carcinoma, cribriform type. This duct displays prominent central necrosis.

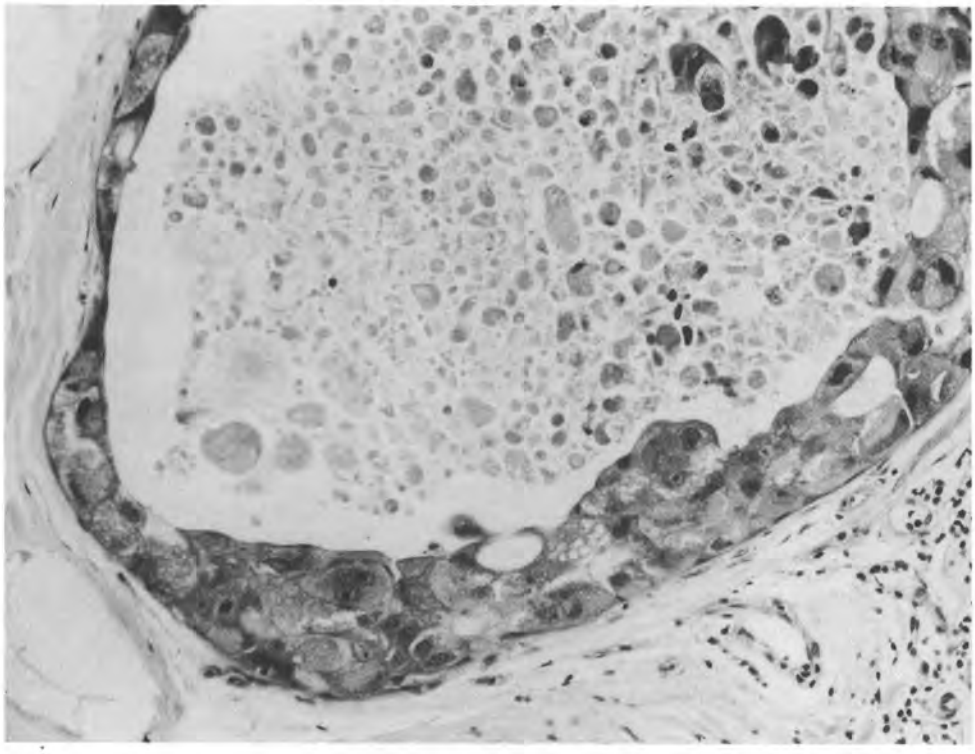


FIGURE 10-42 Intraductal comedocarcinoma. Tumor cells are large and pleomorphic and grow in a solid sheet. Central necrosis is present.

The cells forming the tumor range from small and uniform in the cribriform type to large, pleomorphic, and bizarre in comedocarcinoma, with intermediate differentiation in the other forms. Nevertheless, the prognosis of completely noninvasive intraductal carcinoma is identical in all forms; lymph nodal metastases are extremely rare, as is death resulting from tumor.[154–162]

Diagnosis of a mammary carcinoma as intraductal requires multiple sections to rule out minute foci of stromal invasion. A diagnosis therefore cannot be guaranteed based on a frozen section.[162–164] If

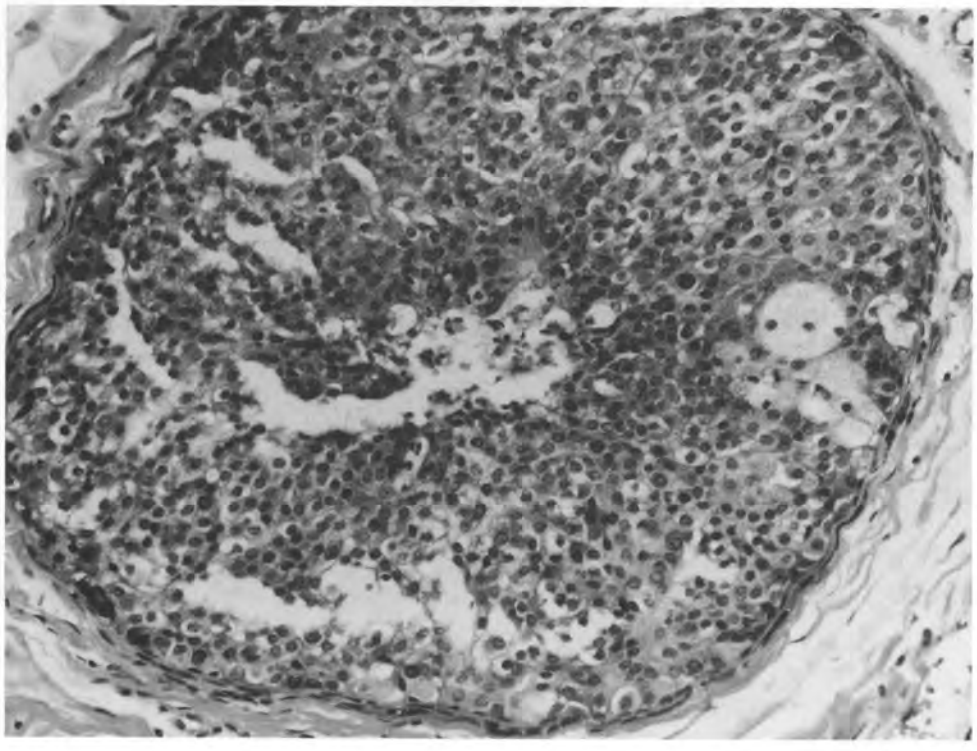


FIGURE 10-43 Intraductal carcinoma, solid type. Despite the solid growth of this tumor, the cells are relatively small and uniform (compare with Fig. 10-42, at the same magnification), and a plug of central necrotic debris is not seen.

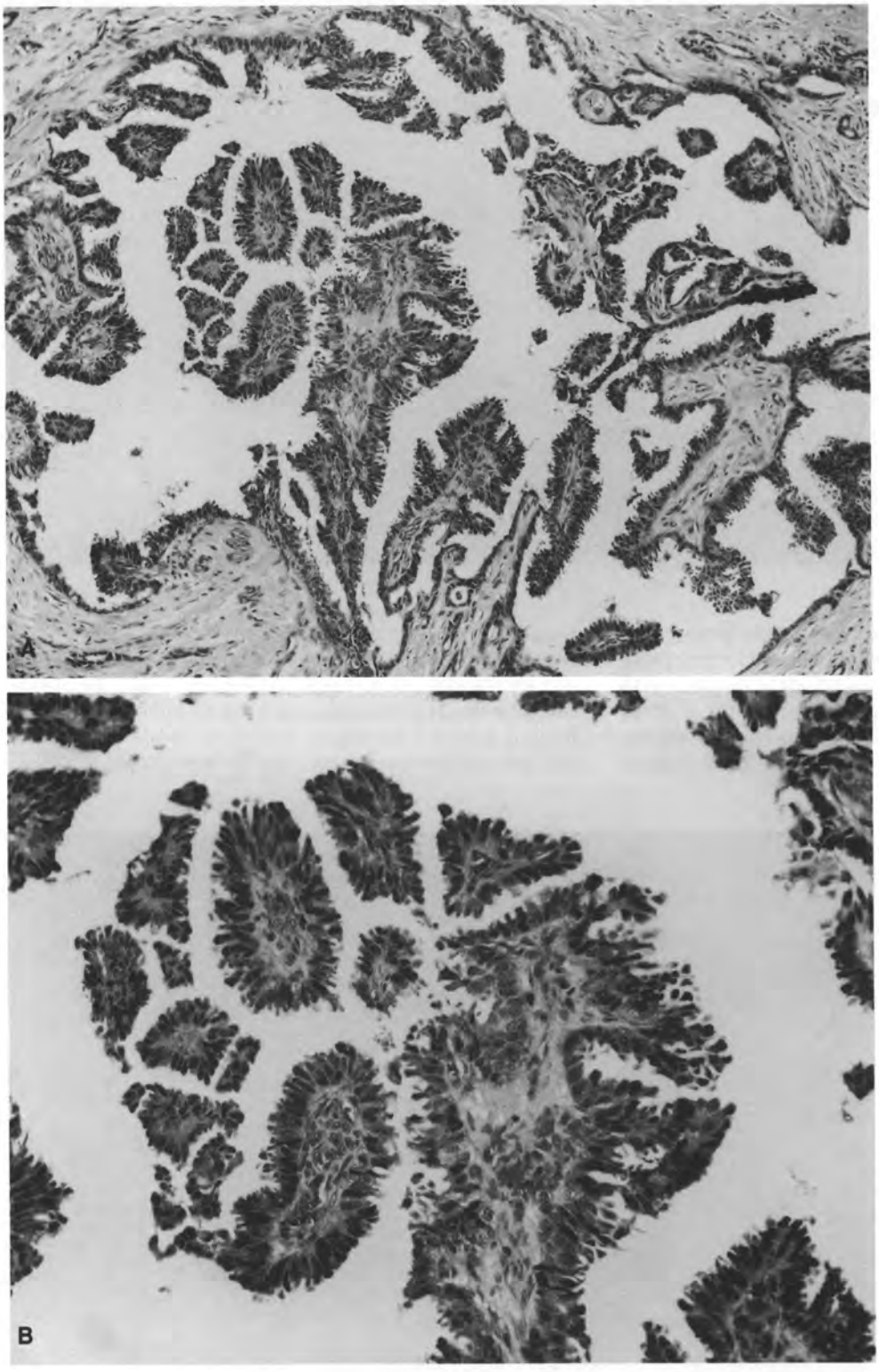


FIGURE 10-44 Intraductal carcinoma, papillary stratified spindle cell type. **(A)** Papillary growth pattern with central connective tissue axes. **(B)** The papillae are lined by tall columnar cells oriented perpendicular to the basement membrane, with no underlying myoepithelial cells.

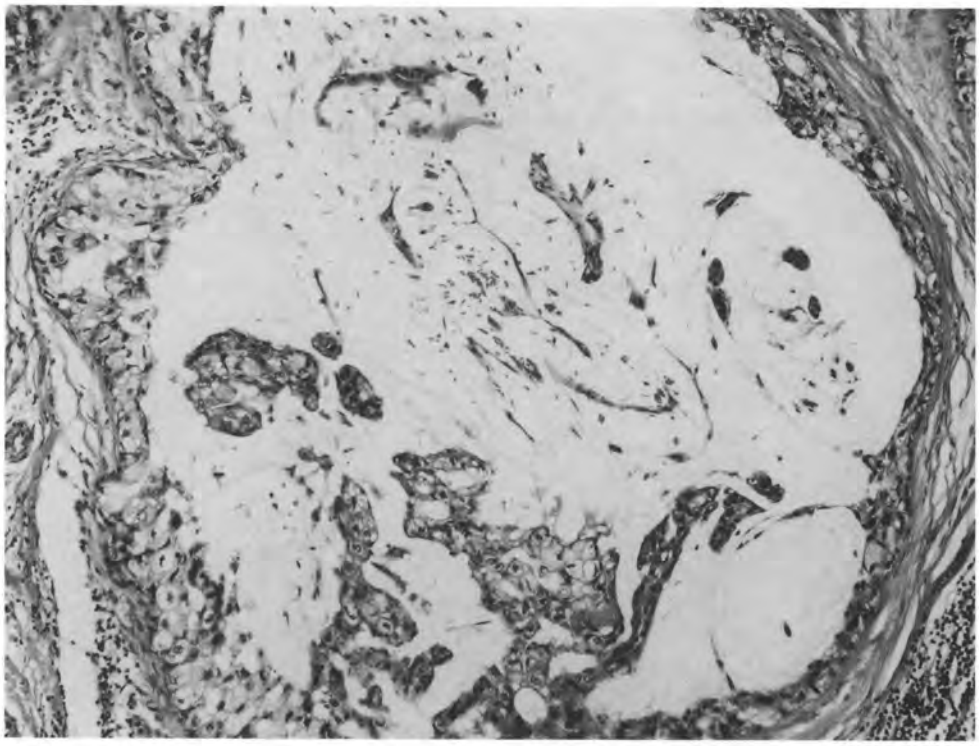


FIGURE 10-45 Intraductal carcinoma, mucinous type. Voluminous intracellular and extracellular mucin is present. This breast was removed for mucinous (colloid) carcinoma.

the diagnostic problem is suspected in advance, frozen sections should not be performed, because freezing artifact renders the interpretation of subsequent permanent sections more difficult. At least eight blocks should be examined to exclude the presence of stromal infiltration. This careful study is important because the incidence of nodal metastases and a lethal course rise sharply when there is even limited invasion of the stroma (Fig. 10-48), although in this situation these eventualities are less likely than with diffusely infiltrative cancer.[163–167] Invasion can be demonstrated ultrastructurally in many instances

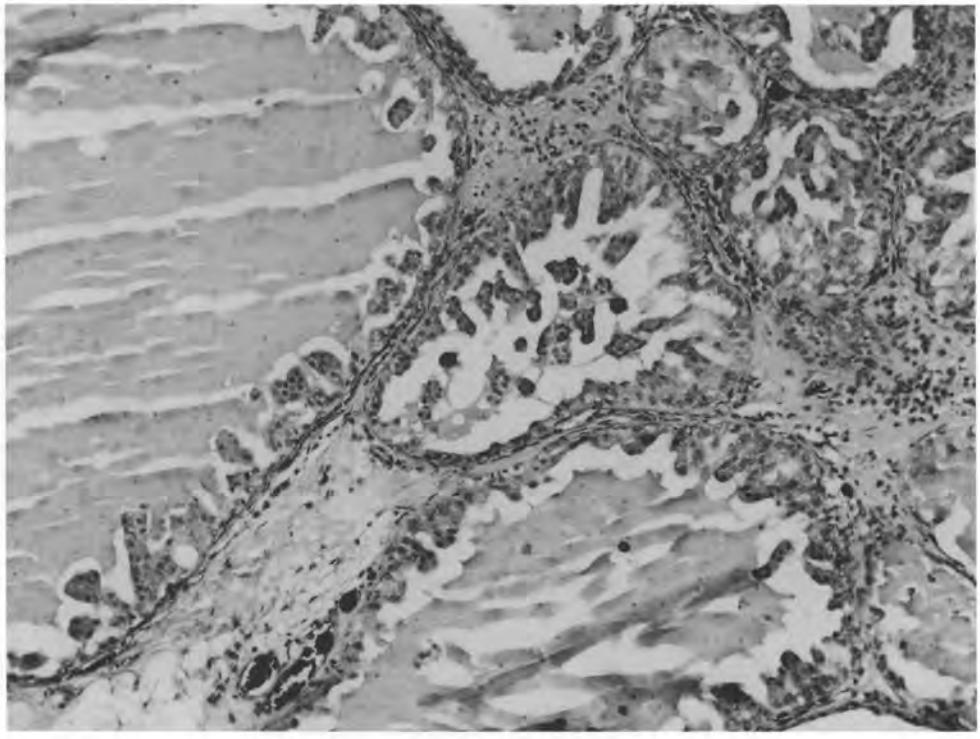


FIGURE 10-46 Intraductal carcinoma, hypersecretory type. This micropapillary tumor has cystically dilated ducts filled with colloid-like material.

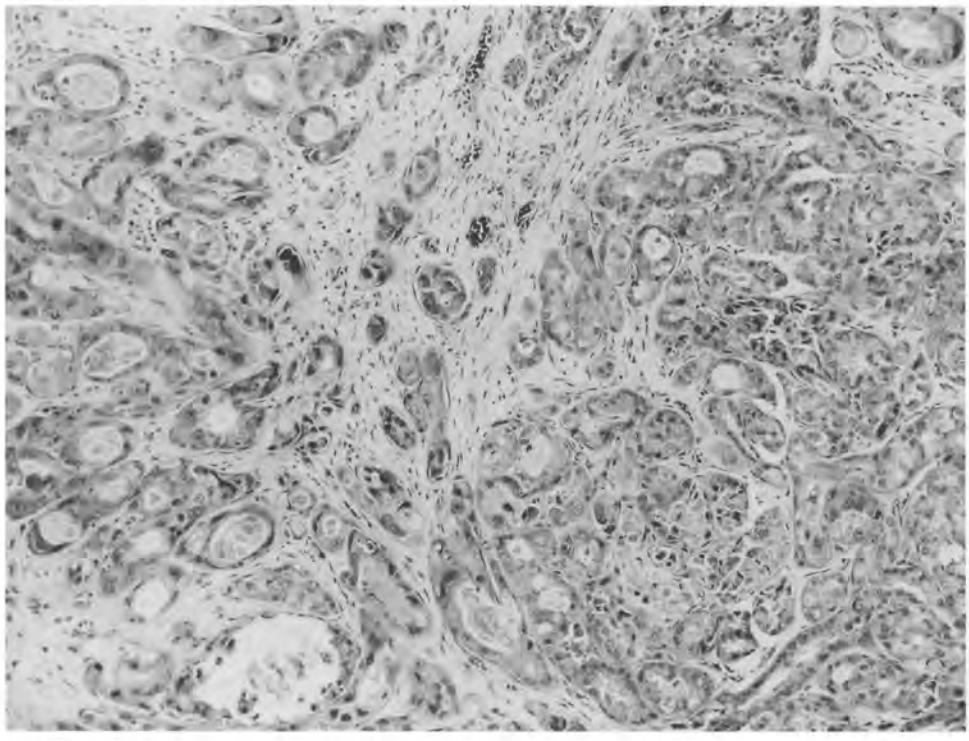


FIGURE 10-47 Intraductal carcinoma, apocrine type, arising in sclerosing adenosis. The sclerosing architecture raises the differential diagnosis of infiltrating carcinoma, but the usual stromal reaction is absent.

when it cannot be seen with the light microscope, but prognostically the light microscopic findings are the important ones. The presence of smooth muscle actin in myoepithelial cells may help in the differential diagnosis, because these cells are said to be lacking in early invasive foci.[168] Immunohistochemical studies for laminin and type IV collagen may be useful.[169] Ultimately, classic light microscopy remains diagnostic.

Differential Diagnosis. The comedo type of DCIS is usually easily diagnosed by virtue of the large

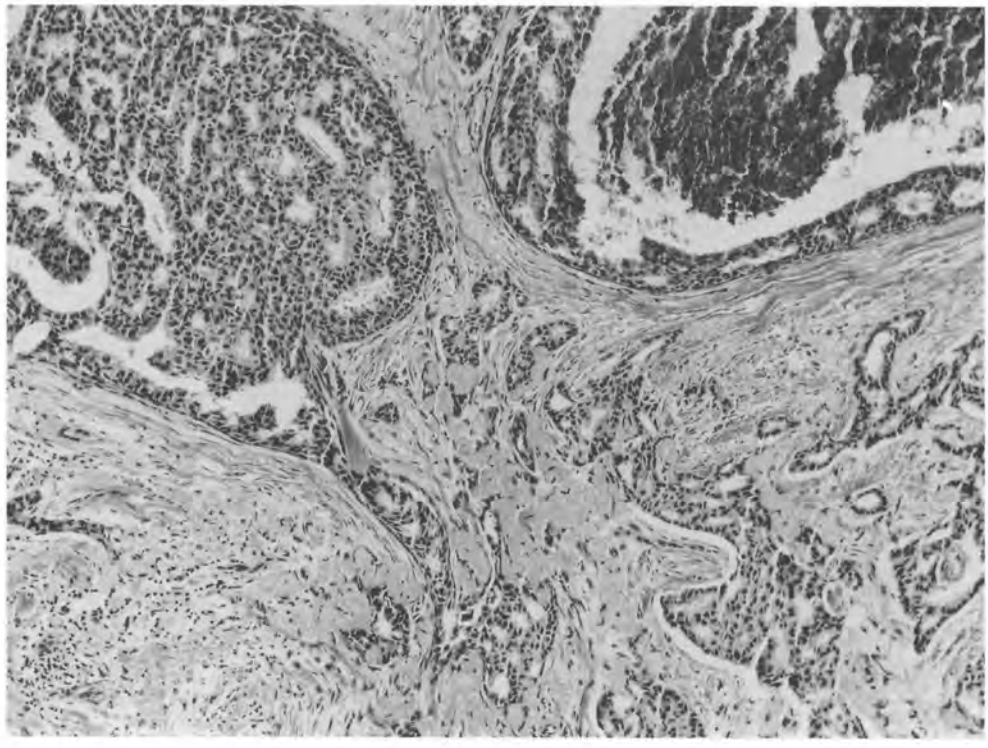


FIGURE 10-48 Intraductal carcinoma, cribriform type, with focal stromal infiltration.

number of ducts involved, the marked atypia and mitotic activity of the tumor cells, and the central necrosis. On the other hand, diagnostic problems are common with the non-comedo forms, which in our experience are more often overdiagnosed than underdiagnosed. If the diagnosis of intraductal carcinoma is being considered, the pathologist should always ask himself or herself into which subtype the lesion fits and be sure that the criteria for that subtype are met. Quantitative criteria are important. Page and colleagues[100] demand that at least two ductal profiles be completely involved by the malignant changes, and Tavassoli and Norris[148] demand that the lesion measure at least 2 mm in diameter. In practice, these criteria usually yield the same results, because two or more adjacent involved ducts usually measure more than 2 mm. Lesser degrees of involvement, or lesions that meet some but not all of the qualitative criteria for the diagnosis of non-comedo DCIS, are diagnosed as atypical ductal hyperplasia (see below).

In theory, ductal hyperplasias without atypia should not enter into the differential diagnosis of DCIS, but in practice they frequently do.[94] The same statement can be made for solitary and multiple intraductal papillomas, juvenile papillomatosis, nipple adenoma, and radial scar, all of which are discussed in more detail in earlier sections. In our experience, the most common reason for diagnostic confusion between these lesions and DCIS is suboptimal histotechnique. This problem is frequently compounded by the fact that frozen sections have been performed on these tissues, and the subsequent artifact in the permanent sections may make the diagnosis difficult if not impossible to render. Therefore, we cannot emphasize too strongly the admonition against performing frozen sections on grossly benign mammographically directed biopsy specimens or in instances in which DCIS is suspected clinically or grossly.

Cytologic Appearance. Because DCIS is only occasionally a palpable lesion, few reports have characterized its FNA cytologic characteristics. One report emphasized that an inadequate specimen was obtained in 44% of the cases, and only 37% were considered diagnostic or suspicious for malignancy.[170] Compared with positive smears from infiltrating duct carcinomas, those from DCIS showed less irregular nuclear spacing and less pronounced nuclear overlapping, and they were more likely to be hypocellular and to contain benign epithelial cells and macrophages. Our experience supports the conclusion of the authors of this study that FNA cannot reliably differentiate DCIS from infiltrating duct carcinoma.

Because the comedo type of DCIS is generally more extensive, often forming a palpable mass, and is cytologically more anaplastic, the likelihood of a positive diagnosis of cancer is greater in FNA cytology of this subtype. The malignant cells are large and poorly differentiated (Color Figure 10-11) and are arranged largely in relatively cohesive groups, with fewer single tumor cells seen compared with infiltrating carcinomas.[171] Necrotic cellular debris may be prominent. As with non-comedo DCIS, the distinction of this form of DCIS from its microinvasive or more extensively invasive counterpart is difficult and probably should not be attempted.

Treatment. *Treatment,* as for other breast cancers, is still controversial. It should be based on what is clearly known about the lesion:[154–162,165,166,172–174]

- When intraductal carcinoma is diagnosed on frozen section, or even on permanent sections of an incisional biopsy, stromal infiltration may be found in 5% to 10% of subsequent material examined.
- Axillary lymph node metastases are found in 1% or less of well-documented cases of intraductal carcinoma without stromal infiltration, and distant metastases are even less frequent.
- If intraductal carcinoma is untreated after biopsy (usually because of misdiagnosis as a benign lesion), the risk of recurrent carcinoma is about 50% within 10 years, and many of these cancers recur rapidly and are infiltrating.
- Although intraductal carcinoma is frequently multifocal and bilateral, the vast majority of clinical recurrences in untreated cases are at the same site in the same breast.

These data may be interpreted to suggest mastectomy as the elected treatment in view of the incidence of multicentric disease, or very wide local excision or quadrantectomy with or without radiation therapy in view of the low risk of recurrence outside the involved quadrant. Probably the best interpretation is that treatment should be individualized, and the patient should be an active participant in the decision and should be aware of the risk involved.

Radiation therapy often is used with conservative surgery in the treatment of DCIS. Some reports suggest that radiation therapy is less active against DCIS than against invasive carcinoma.[174] In any event, local recurrence rates appear to be halved by the addition of radiation therapy, with rates of 10% to 54% reported for excision alone, compared with rates of 4% to 21% for excision with radiation.[173] Even after local recurrence, about 80% of patients can be treated successfully.

The relation of the microscopic findings to results of treatment for DCIS are still being established. Nevertheless, there is a definite indication that intraductal comedocarcinoma is more likely to progress to infiltrating carcinoma if not successfully treated initially. This impression fits with the biologic data that comedocarcinomas are more frequently aneuploid and receptor-negative and more

frequently express the protein product of the c-*erb*-B2 oncogene than do non-comedo type intraductal carcinomas.[175–177] Large or widespread DCIS lesions would appear to be at greater risk of recurrence after conservative treatment as well.

Atypical Ductal Hyperplasia

Atypical ductal hyperplasia (ADH) is in the middle of the spectrum that includes ductal hyperplasia without atypia at its lower end and in situ ductal carcinoma at its upper end. Although we hope that an acceptable definition for ADH independent of these other entities will be established, at the moment ADH is best defined by what it does not represent—specifically, DCIS. ADH may be thought of as a lesion that possesses some but not all of the characteristics of DCIS.

In ADH, the epithelial cells have a monotonous appearance and display round, often centrally located nuclei with a moderately increased nuclear–cytoplasmic ratio. Hyperchromasia, if present, is discrete. Rosette-like arrangement of the nuclei may be observed. The architectural features may be cribriform, micropapillary, spindle cell papillary, or solid with secondary lumens. There is no central necrosis. Peripheral fenestration is present.

The diagnosis of ADH is usually made because these features, classic for non-comedo DCIS, are present filling only one duct profile or incompletely filling more than one duct profile (Fig. 10-49).[149] In the system of Tavassoli and Norris, the lesion measures less than 2 mm in diameter.[148] An equally compelling reason for making the diagnosis of ADH is that the lesion quantitatively but not qualitatively satisfies the diagnostic criteria for non-comedo DCIS. In such an instance, the lesion is generally well-differentiated and involves only a few ducts, and it is appropriate to choose the less malignant diagnosis and avoid overtreatment.

ADH carries a risk of development of subsequent carcinoma that is intermediate between those of proliferative breast disease without atypia and in situ carcinoma.[98,100,134,148] The relative risk is generally quoted as fourfold, but it should be remembered that a relative risk of four still represents an absolute risk of less than 10% for the development of carcinoma.

Lobular Carcinoma In Situ

Lobular carcinoma in situ (LCIS) is the noninfiltrating form of lobular carcinoma. Despite the fact that it was first described independently in 1941 by Foote and Stewart[178] and Muir,[179] its natural history has been defined only recently. Its mean age of incidence is in the forties, but it may occur at any age; two thirds of the patients are premenopausal. Bilaterality is found at diagnosis in about one third of the cases. The lesion is defined as a proliferation of uniform abnormal cells that distends and fills at least one half of the acini in at least one lobular unit (Figs. 10-50 and 10-51).[149] These cells are definitely larger than normal lobular cells but are not volumi-

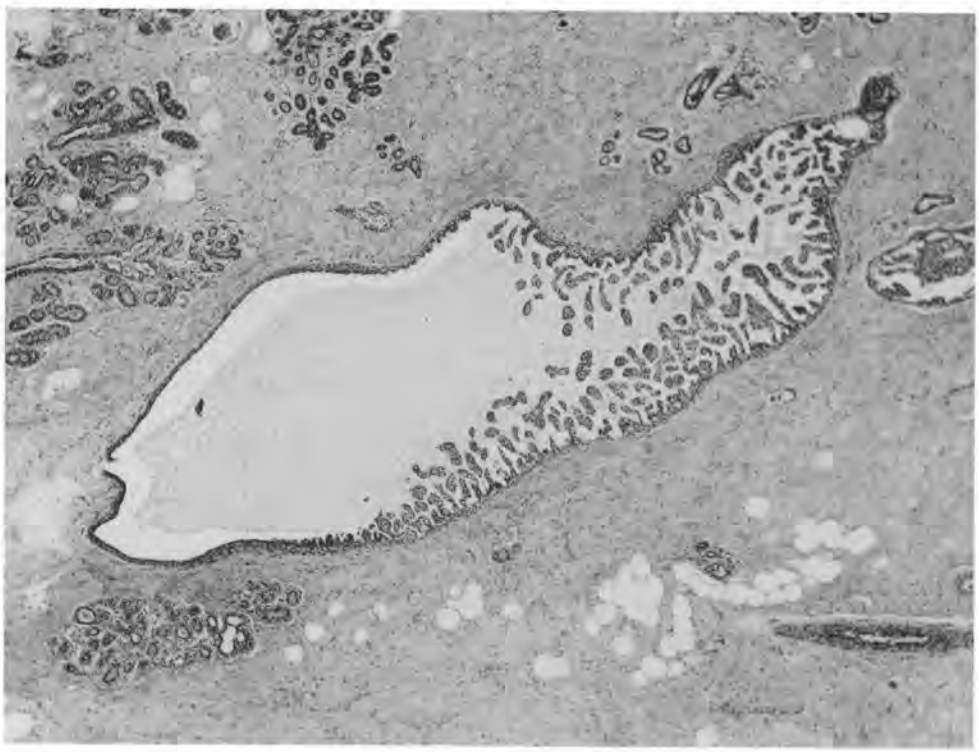


FIGURE 10-49 Atypical ductal hyperplasia. A micropapillary intraductal carcinoma pattern involves less than one complete duct profile.

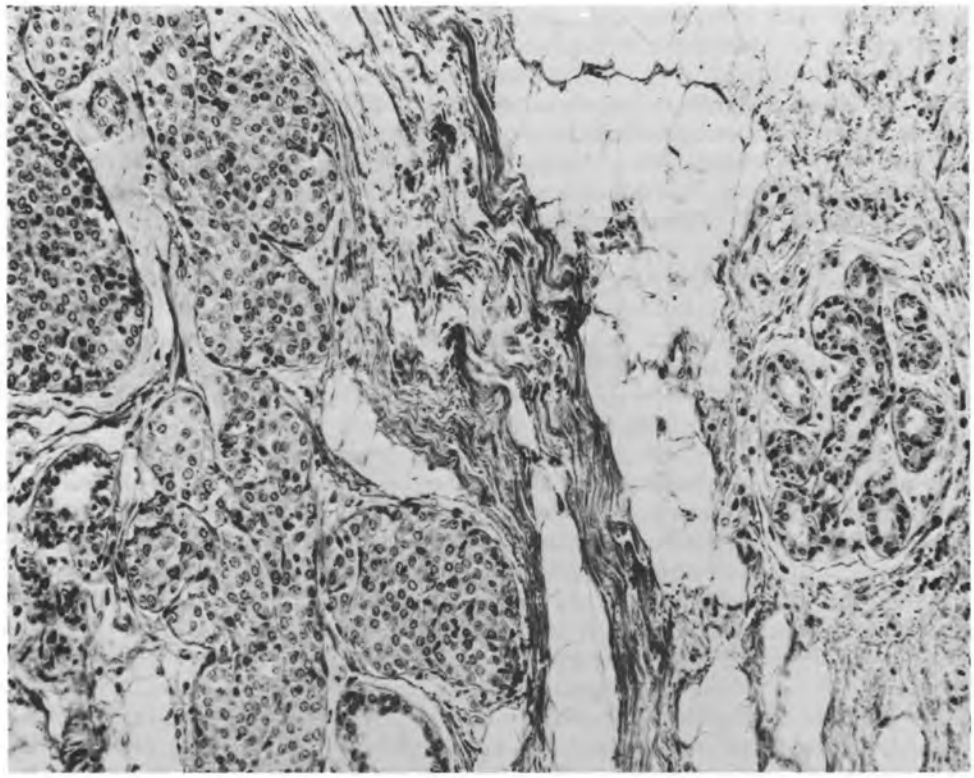


FIGURE 10-50 In situ lobular carcinoma. Contrast the lobular size on left with the normal lobule on right.

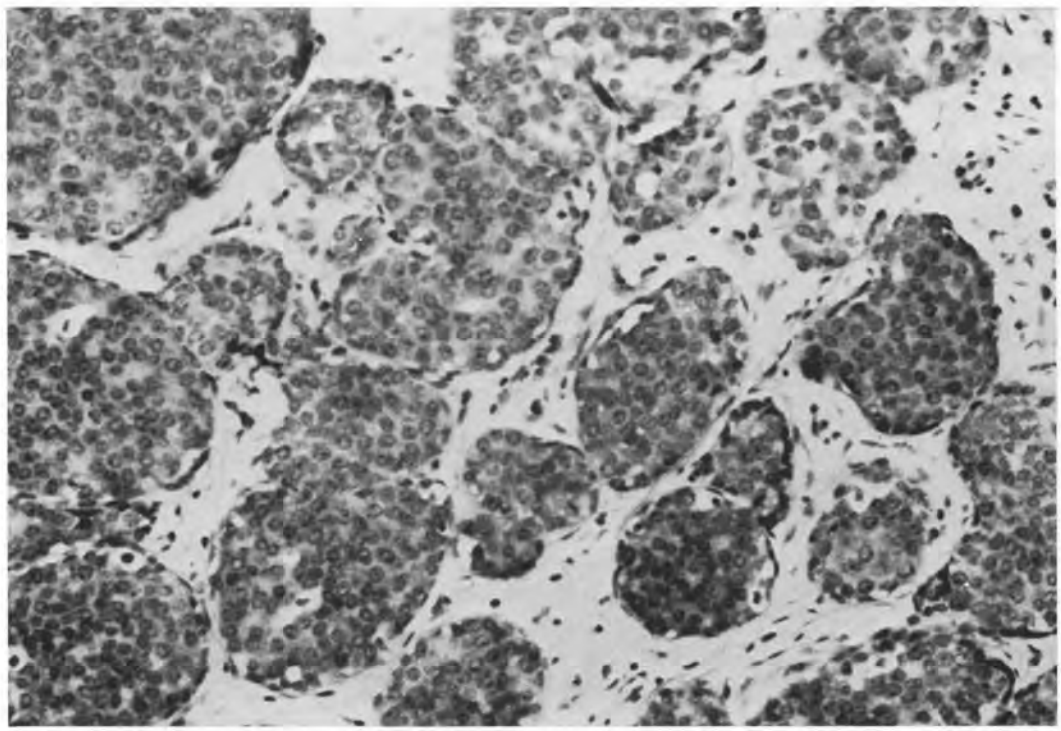


FIGURE 10-51 In situ lobular carcinoma, showing uniformity of neoplastic cells.

nous. They lack cohesion or regular orientation. Their nuclei are round and normochromatic. Nucleoli are small but usually apparent. The cytoplasm is moderately eosinophilic. Intracytoplasmic lumina containing neutral mucosaccharides may be common and represent a characteristic finding (Fig. 10-52). These "bullseye" or "targetoid" structures are a common feature of infiltrating lobular carcinoma as well. Normal or benign hyperplastic lobules are usually found adjacent to the neoplastic lobules, the contrast aiding in the recognition of the lesion. Neoplastic cells may infiltrate adjacent ductules in a pagetoid fashion between the ductal epithelial cells and the myoepithelial elements. The diagnosis, like many others in mammary pathology, is usually made under the scanning lens of the microscope, because the enlarged acini with obliterated lumina are characteristic. On frozen section, pictures of benign but atypical lobular hyperplasia are often confusing, and for this reason we never make a definitive diagnosis of LCIS until we have the opportunity of examining the permanent sections.

The significance of this lesion is that, like intraductal carcinoma, it is a marker of increased risk for the development of infiltrating carcinoma. Unlike intraductal carcinoma, LCIS may not be the lesion from which the infiltrating carcinoma actually develops. The statistics and their translation into therapeutic action are even more vehemently argued than those for intraductal carcinoma.[98,180–186]

The main similarities and differences may be summarized as follows:

- LCIS occurs on the average in younger women than DCIS and is even less likely to present as a palpable or otherwise symptomatic lesion, the diagnosis almost invariably being incidental (in a biopsy performed for another lesion, usually fibrocystic change) or mammographic.
- Occult stromal infiltration is much less frequently associated with an initial diagnosis of LCIS than of DCIS.
- Positive axillary lymph nodes are as rare or rarer with pure LCIS than with DCIS.
- LCIS is somewhat less likely than DCIS to progress to infiltrating cancer if untreated (15% to 35% in published series, compared with an average of 50% for DCIS).
- When recurrence and progression take place in LCIS, the interval is usually greater than with DCIS (often 20 years or more).
- A minimum of one third to a maximum of one half or more of the recurrent cancers occur in the contralateral breast, probably only partially as a result of the greater tendency of LCIS than DCIS to be multifocal (50% or more) and bilateral.
- Although a greater proportion of infiltrating carcinomas after LCIS are of infiltrating lobular type than in unselected series of breast cancer, about half are ductal.

The main therapeutic recommendations include lifetime follow-up, in which mammography should

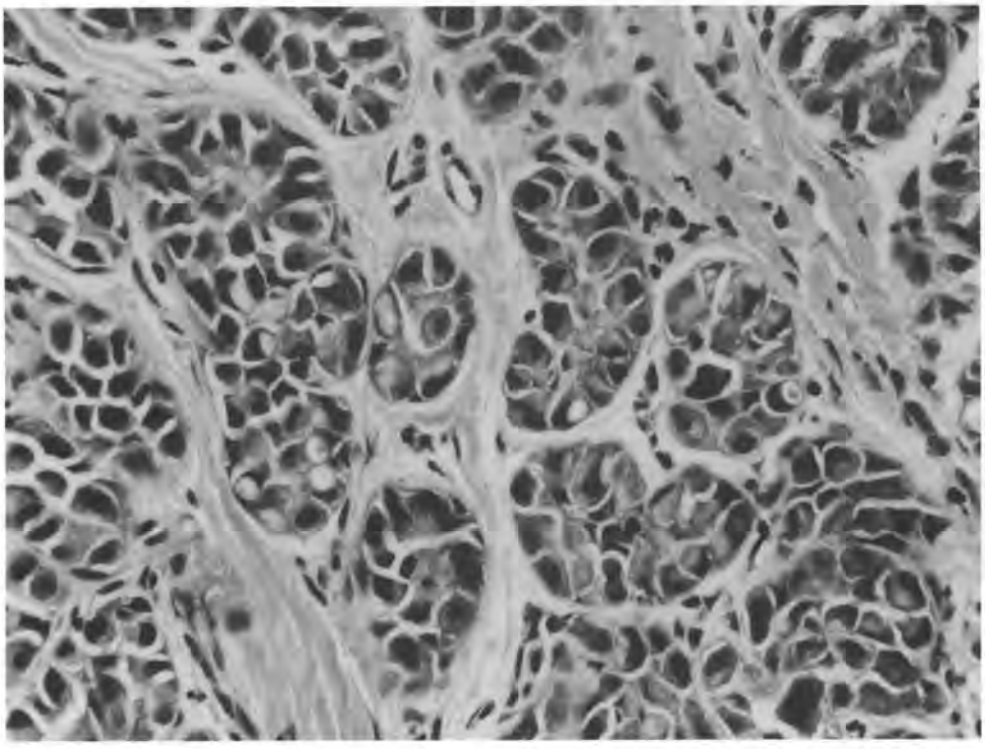


FIGURE 10-52 In situ lobular carcinoma with numerous intracytoplasmic lumina (signet-ring cells).

play an important role, although it is not infallible;[187,188] ipsilateral total mastectomy with contralateral biopsy (mirror image, upper outer quadrant, or mammographically directed); and bilateral total mastectomy. We believe that all of these options should be presented to the patient, although the pendulum has clearly swung toward conservatism in recent years.

Differential Diagnosis. The main differential diagnosis is with atypical lobular hyperplasia and is discussed below. Less commonly, LCIS may be confused with non-comedo DCIS extending into lobules (lobular cancerization; Fig. 10-53). However, the lobular extensions of DCIS often contain some residual cribriform spaces or papillae, whereas LCIS is totally solid. The cells of DCIS are less uniform, usually larger, and may be mitotically active; some central necrosis is frequently present. More typical DCIS involving larger ductal spaces is usually present nearby, although DCIS and LCIS can certainly coexist in the breast, so that the presence of one should not rule out the other.

LCIS in unusual locations may be difficult to diagnose. For example, if the only disease in a section is in small ducts, the differential diagnosis with DCIS and atypical lobular hyperplasia is even more problematic. LCIS within a fibroadenoma usually demonstrates the classic features,[69,70] but LCIS occurring within a focus of sclerosing adenosis is easy to overlook,[141,142] because the usual uniform large round acini are compressed and irregular. Here it is important to recognize the typical LCIS cells filling whatever acini are still recognizable as such.

In sclerosing adenosis, and occasionally without it, the differential diagnosis between LCIS and infiltrating lobular carcinoma (particularly the alveolar variant) may be raised. The latter lesion is usually a palpable or grossly detectable mass that consists of more round nests of tumor cells than would be appropriate to a lobular unit. It invokes the usual stromal reaction to invasive carcinoma.

Atypical Lobular Hyperplasia

Just as ADH is best defined by its relation to DCIS, atypical lobular hyperplasia (ALH) is characterized by its relation to LCIS. Because we have defined LCIS (see previous section) as a proliferation of uniform abnormal cells that distends and fills at least one half of the acini in at least one lobular unit, the definition of ALH is then a qualitatively similar cellular proliferation that differs quantitatively from LCIS in that it does not (1) distend or (2) fill the acini, or (3) it does distend and fill acini, but less than one-half of the acini in one lobular unit (Fig. 10-54). The criterion of LCIS that most often is not met is filling of acini, in that intercellular (not intracellular) lumina are present focally. It also is common for the acini to be filled but not distended. This is best demonstrated by comparing their diameters with those of the acini of the closest uninvolved lobular unit. As with LCIS, ALH is generally detected incidentally or

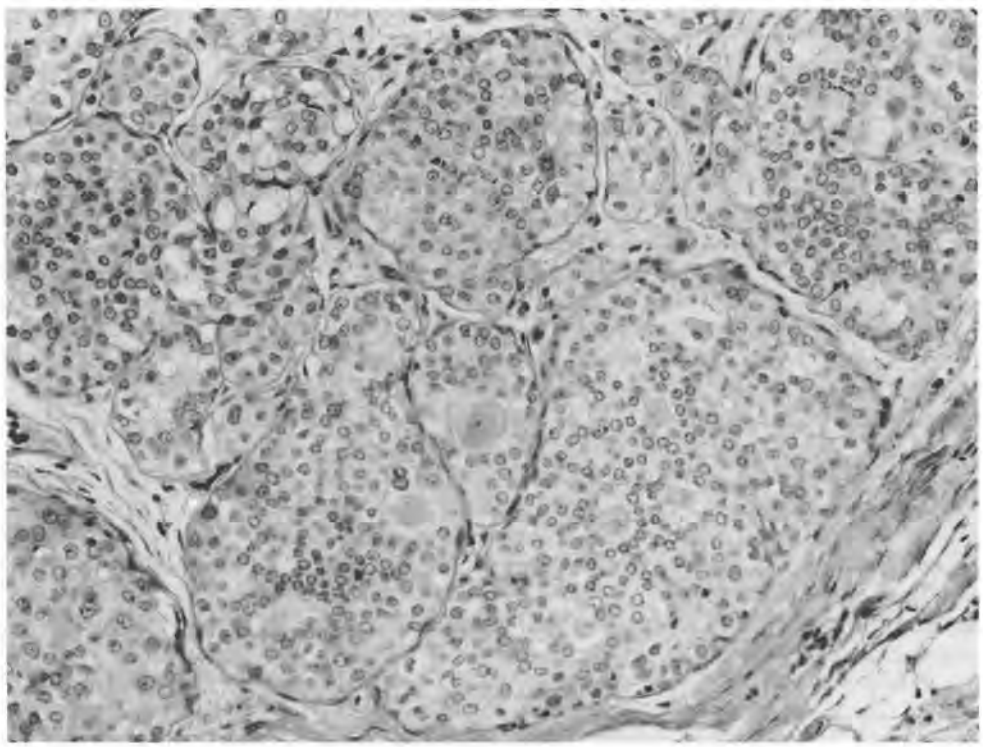


FIGURE 10-53 Lobular cancerization. A cribriform intraductal carcinoma has extended into the lobular unit; note the numerous small lumina. Most cases of lobular cancerization show more pleomorphism and necrosis.

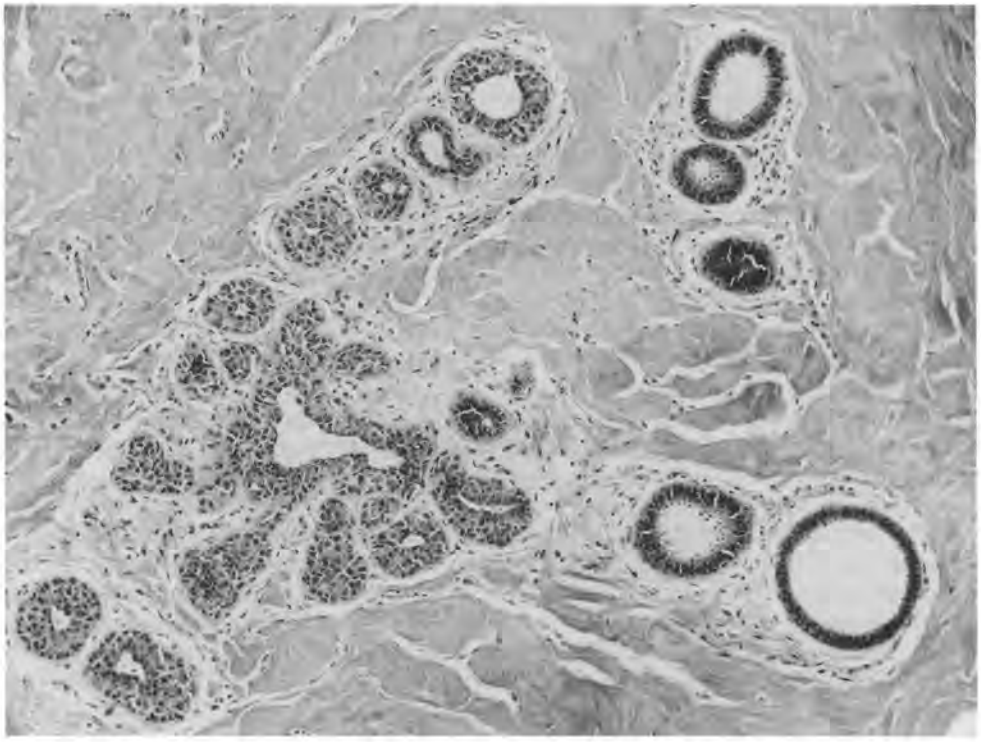


FIGURE 10-54 Atypical lobular hyperplasia. The acini in this lobular unit are slightly distended (as are adjacent uninvolved unfolded lobules) but not filled by the proliferated atypical cells. The terminal duct is also involved by the same process.

mammographically and does not form palpable masses. It also is found predominantly in premenopausal and perimenopausal women.

The term *lobular neoplasia* is sometimes used to include both ALH and LCIS and sometimes is used as a synonym for ALH.[181] Because of this imprecision, we prefer to avoid this term. Nonetheless, ALH and LCIS form a continuous spectrum, perhaps with banal lobular hyperplasia at the lower end.

The *clinical significance* of ALH, again like LCIS, is that it is a marker of increased risk for the development of invasive breast cancer. The relative risk, as with ADH, is about fourfold (absolute risk slightly less than 10%). As with LCIS, subsequent cancers may be of lobular or ductal type and may occur in either breast. The risk of uncomplicated ALH is doubled in the presence of a family history of breast cancer in a first-degree relative (mother, sister, or daughter) and is almost doubled when the ALH extends into ducts beyond the lobular unit (Fig. 10-55).[98,100,189] The usual *management* is careful and lifelong follow-up.

The *differential diagnosis* of ALH is predominantly with LCIS, as discussed above. Although the distinction is basically quantitative, it should be remembered that LCIS may involve only a single lobular unit and ALH may involve many. ALH extending into ducts (see Fig. 10-55) is difficult if not impossible to differentiate from LCIS extending into ducts unless the lobular unit primarily involved can be evaluated by the usual criteria. Lobular hyperplasia without atypia, unfolding lobules, and atypical ductal proliferations extending into lobules may also pose diagnostic problems (see the section on LCIS).

MALIGNANT EPITHELIAL TUMORS

The malignant epithelial tumors of the breast constitute the most important group of cancers in women. More than 5% of all women in the United States develop breast cancer, and some estimates are even higher. In Japan, on the other hand, it is a relatively rare disease (although increasing in frequency), whereas in most European countries the incidence is intermediate between these two extremes but closer to that of America.[190] The incidence curve rises progressively after the age of 35 years and reaches its peak between 50 and 60 years (Fig. 10-56). Mammary cancer is uncommon below the age of 30 years[191] and is very rare below 20 years.[192] It appears with greater frequency and earlier in life in women whose mothers or other primary relatives have also had mammary cancer.[193]

Etiology and Epidemiology

Probably more studies have been done on the epidemiology of breast cancer than of any other human malignant tumor, but the etiology of this neoplasm is still unknown. However, clinical and experimental data point out certain factors that favor its appearance. These generally fall into the major headings of genetic, dietary, and hormonal factors, and there are probably numerous interrelations both within and between these major categories.

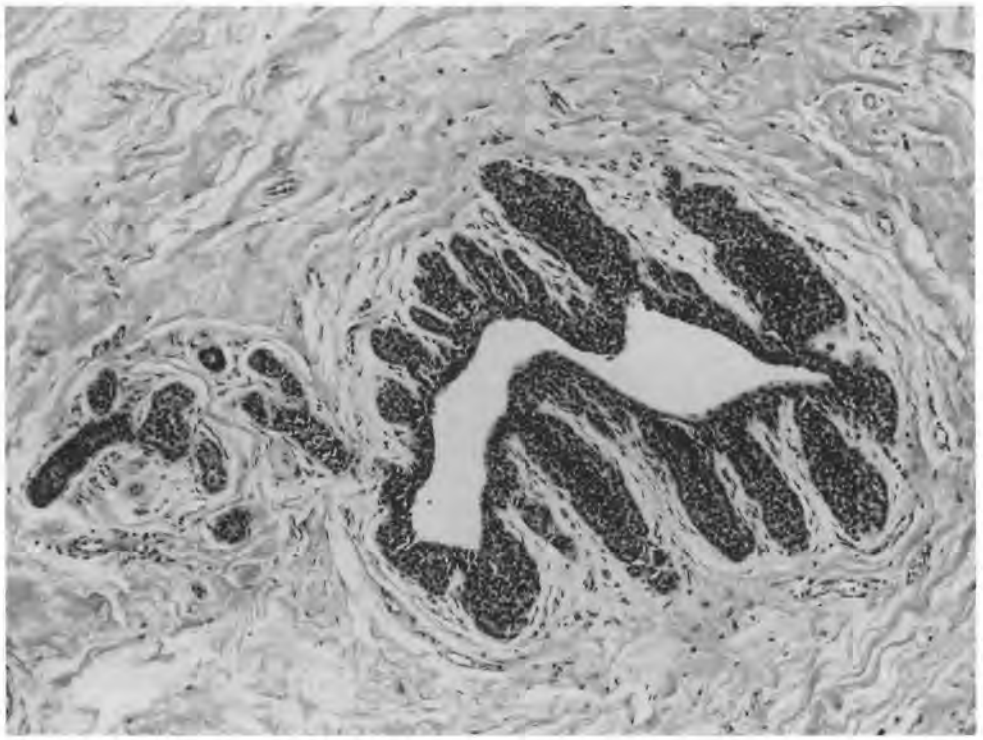


FIGURE 10-55 Atypical lobular hyperplasia with ductal extension. The buds of atypical lobular cells form an architectural pattern easily recognizable at low magnification.

Genetic Factors

Studies related to genetic factors in breast cancer development focus predominantly on populations and families. As mentioned above, breast cancer is much more common in American and European women than in Japanese and Chinese women, but even in America there are differences among such populations as white non-Hispanic, white Hispanic, and Native American.[135] Breast cancer rates in the daughters and granddaughters of Japanese immigrants to the United States show a gradual rise, but not to the level of the Caucasian population.[194] These and other population differences generally have been thought to be related to dietary and hormonal factors more than to genetic ones.

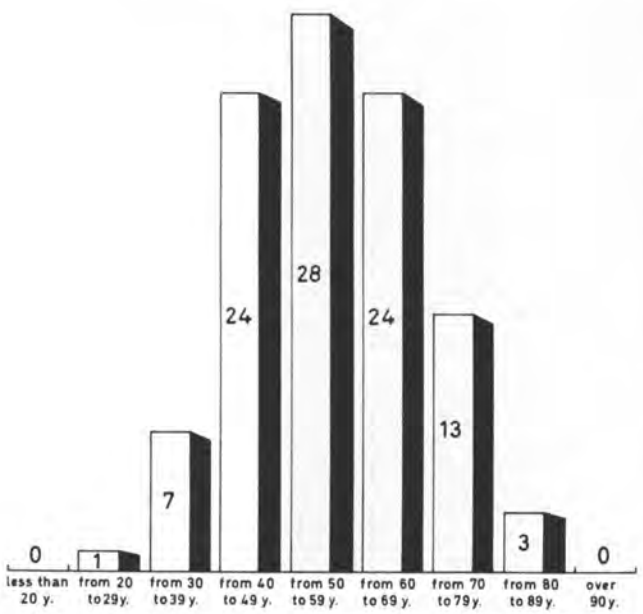


FIGURE 10-56 Frequency of appearance (in percentage) of mammary cancers as a function of age (6590 cases).

On the other hand, there are certainly strong indications of a genetic basis for the development of breast cancer in families.[193] Two major findings have been known for many years. First, a family history of breast cancer increases a woman's risk twofold to threefold. Second, patients with familial breast cancer are younger when the diagnosis is made and have a higher frequency of bilateral disease than patient with sporadic breast cancer. Studies conducted on families with high frequencies of breast cancer already have identified four distinct inherited patterns of the disease. These include a predisposition to breast cancer only; a predisposition to breast and ovarian cancer; Cowden's disease, which includes breast cancer, thyroid neoplasms, and multiple hamartomas of the skin and oral cavity; and the Li-Fraumeni syndrome, which includes soft-tissue and bone sarcomas, brain tumors, leukemias, and adrenal cortical carcinoma.[193] More such syndromes will probably be reported in the future. The specific chromosomal lesion involved has been identified in some of these situations (see Chap. 12 for further discussion).

Dietary Factors

Numerous dietary factors have been studied in an attempt to determine their relation to breast can-

cer.[195–198] The long-held opinion has been that a Western diet plays a significant role in increasing the risk of breast cancer in the Western world, but the exact mechanisms involved have been controversial. It has been found recently that a diet high in animal fats elevates plasma levels of sex hormones and decreases the concentration of sex hormone binding globulin, thus increasing the availability of these steroids for peripheral tissues.[195] Obese women, who are at a greater risk for the development of breast cancer, have been found to have lower sex hormone-binding globulin levels.[196] On the other hand, the consumption of soy protein in the Asian diet may be protective, perhaps due to the phytoestrogens in these products.[197] Alcohol consumption has been associated with an increased risk of breast cancer in some studies but not in others, and the mechanism involved is still unknown.[198] These and other dietary factors are still under investigation, but the general assumption is that they ultimately relate to alterations in hormonal levels.

Hormonal Factors

Hormonal factors involved in mammary carcinogenesis are in many ways the most difficult to investigate, because it is postulated that the hormonal events that take place early in life may influence the development of breast cancer many years later. Nevertheless, it has been recognized for many years that, for example, late age at menarche, early artificial or natural menopause, early term pregnancy, and breast feeding are factors that appear to be protective against the development of breast cancer. The exact hormonal mechanisms involved have been searched for in human and animal studies, with considerable differences in the results obtained. There seems to be a definite interplay among genetic, dietary, and hormonal factors, so that, for example, upper body obesity—influenced by inheritance and diet—is a marker for hyperandrogenemia, which is associated with an increased risk of breast cancer.[199]

It is not surprising that, considering the known effect of endogenous hormones on the development of breast cancer, the attention of many epidemiologists has turned to a possible relation with exogenous hormone administration.[200–203] Most studies have not demonstrated a significantly increased risk for estrogen replacement therapy or oral contraception, but several have shown possible risk factors in subsets of women (eg, younger versus older women, long-term versus short-term use, and current users versus former users). Use of these hormones is a matter of informed choice, with individual considerations of the risk-benefit ratio.

Given what is known about breast cancer epidemiology, certain investigators have suggested the possibility of breast cancer prevention by alterations in diet, hormonal milieu, or both.[204–206] It is still far too early to comment on these suggestions, which will require trials involving many thousands of women, careful monitoring of compliance, and analysis of the results only after many years.

Classification

Different classifications of malignant neoplasms of the breast have been proposed, but the most widely used is the one established by the World Health Organization (WHO; Table 10-5).[207] This classification does not include many lesions described or better characterized in recent years, and accordingly the ensuing discussion will use a modification of it.

Malignant epithelial tumors (carcinomas) of the breast classically have been thought to be derived from the lactiferous ducts or from the acinar structures of the breast lobules. More recent studies have suggested that most if not all breast cancers actually originate in the ductules (terminal ducts).[208,209] By far the most common type of carcinoma seen in all populations is infiltrating duct carcinoma of not otherwise specified type, which occurs alone or in combination with other histologic types in about 70% of all cases. The proportion of noninfiltrating ductal and lobular carcinomas has increased in recent years in screened populations, and the remainder of the tumors consist of the specific histologic types of infiltrating carcinoma mentioned in the WHO classification, as well as others that will be discussed. Primary sarcomas and carcinosarcomas of the breast are rare tumors, as are leukemic, lymphomatous, and metastatic lesions.

TABLE 10-5.
World Health Organization Classification of Malignant Epithelial Tumors of the Breast

1. Noninvasive
   a. Intraductal carcinoma
   b. Lobular carcinoma in situ
2. Invasive
   a. Invasive ductal carcinoma
   b. Invasive ductal carcinoma with a predominant intraductal component
   c. Invasive lobular carcimona
   d. Mucinous carcinoma
   e. Medullary carcinoma
   f. Papillary carcimona
   g. Tubular carcinoma
   h. Adenoid cystic carcinoma
   i. Secretory (juvenile) carcinoma
   j. Apocrine carcinoma
   k. Carcinoma with metaplasia
      i. Squamous type
      ii. Spindle-cell type
      iii. Cartilaginous and osseous type
      iv. Mixed type
   l. Others
3. Paget's disease of the nipple

Clinical Signs

All the malignant epithelial tumors of the breast present with similar signs and symptoms. In most cases, the patient consults a physician because she has noted the presence of a painless breast mass. With the introduction of mammography, more lesions are detected at a subclinical level.

More rarely, the tumor manifests itself by nipple discharge, retraction or erosion, cutaneous redness or roughening, local pain or tenderness, an axillary mass, or evidence of disseminated metastatic disease, such as bone pain (Fig. 10-57). The median period of time elapsed between the first symptom and the first medical consultation is 6 to 12 months, which underscores the advisability of disseminating to the public more information regarding the technique and necessity of breast self-examination, the necessity of seeking immediate medical consultation on the discovery of a mass, and the value of routine mammography after the age of 40 years or earlier in high-risk groups.

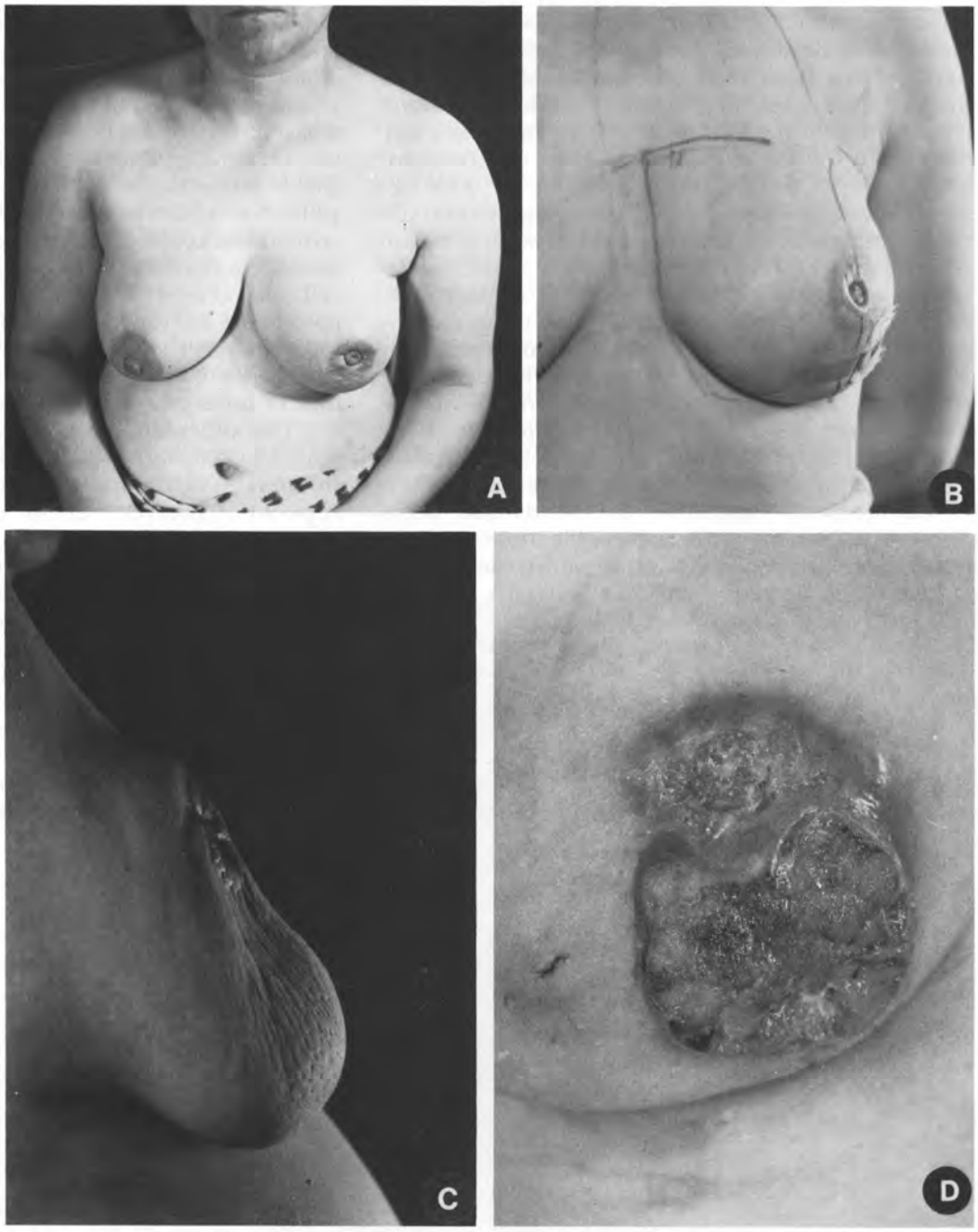


FIGURE 10-57 Mammary duct carcinoma. **(A,B)** Retraction of nipple. **(C)** Retraction of nipple and *peau d'orange*. **(D)** Carcinoma ulcerating through skin.

On the other hand, even the earliest possible diagnosis and treatment does not result in a 100% cure rate. Many authors have noted that, with the exception of asymptomatic tumors and those treated within 1 month of the onset of symptoms, those tumors treated after a long symptomatic period tend to show a more favorable prognosis than those treated with less delay. The reason for this appears to be that slowly growing tumors of low malignant potential will be tolerated by the patient for a longer time before she consults a physician, whereas rapidly growing, highly malignant tumors will alarm their hosts sooner. Some tumors, by their nature and their interaction with the host, can be treated even after considerable delay with good results, whereas others may be fated from their onset to terminate unhappily. This concept of "biologic predeterminism," which is new in the field of oncology and is still not accepted by many authors, has been discussed by MacDonald[209a] and by Gershon-Cohen.[209b] The latter author, by means of serial mammographic studies, has estimated "doubling times" in several breast cancer cases and has indicated that about three fourths of the life histories of these tumors take place in the preclinical phase. Others, using mathematical models, have suggested that tumors can only rarely be detected before metastases have already taken place. Perhaps the key to improving our therapeutic results is held in those techniques, such as mammography or methods yet to be developed, that are capable of detecting breast cancers before they become clinically apparent. It already has been noted that patients with impalpable tumors diagnosed by screening procedures are much more likely to have noninvasive and "minimal" invasive tumors, with less likelihood of metastatic disease.[19–22,210,211]

Invasive Carcinomas

Infiltrating Duct Carcinoma

Infiltrating duct carcinoma (IDC) is also known as *invasive ductal carcinoma, carcinoma of no special type* (not otherwise specified [NOS], *carcinoma with productive fibrosis, scirrhous carcinoma, stellate carcinoma,* and *carcinoma simplex.* The WHO classification is one of exclusion: IDC is the most frequently encountered malignant tumor of the breast not falling into any of the other categories of invasive mammary carcinoma.

The tumor arises, in order of decreasing frequency, in the upper outer quadrant, the central region, the upper inner quadrant, the lower outer quadrant, or the lower inner quadrant.[212,213] The diameter of the tumor is most often between 1 and 5 cm.

Macroscopic Appearance. The macroscopic appearance varies, but two main types are encountered. The first and more frequent appearance is that of a round or ovoid hard mass, more or less adherent to adjacent tissues. Section reveals gray-yellow or white tissue with a granular surface, the central region of which is depressed. Attentive examination shows yellow or white streaks disposed in radial fashion around the center of the tumor; these streaks correspond to fibroelastic stroma separating neoplastic cell cords (Fig. 10-58).[214,215] The peripheral fibroadipose tissue adheres to the tumor and emphasizes its radial pattern. When cut, the tumor has a characteristic gritty consistency, which has been likened to that of an unripe pear.

The other appearance, less common, is represented by a spherical yellow-pink mass of softer consistency, which appears better demarcated from adjacent structures. Section in this instance shows white, granular, homogeneous tissue, with only moderate peripheral retraction. This different picture is attributed to more limited fibrosis.

Occasionally, there are several tumor nodules present macroscopically in a breast. Subserial whole organ sections have shown that multiple nodules are actually present in about half of all cases of infiltrating cancer.[216] Although even random sections confirm this in a lower percentage of cases,[217,218,219] clinical recurrences in the breast after partial mastectomy and radiation therapy occur in less than 20% of cases.[220–222]

FIGURE 10-58 Mammary duct carcinoma: macroscopic appearance on section.

When the skin is involved, it becomes thickened, indurated, and invaginated over the tumor. Velpeau compared this appearance of the skin to that of a firm hide (carcinoma en cuirasse).[15]

A certain number of breast cancers are bilateral from their onset. These may represent rapid metastatic involvement of the contralateral breast or two independent tumors.[223,224]

Microscopic Appearance. The neoplastic glandular formations are disposed in cords, solid cell nests, tubes, glands, anastomosing bundles, and mixtures of all of these. They are disseminated in a stroma, the prominence of which varies from one tumor to another and from one region to another within a single tumor (Figs. 10-59 through 10-61). There is an abundant framework of collagen, reticulin, and elastic fibers. The epithelial cells present diverse cytologic anomalies. All appearances are encountered, from the small cell with a moderately hyperchromatic regular nucleus to the monstrous cell with a voluminous, lobulated, irregular, and hyperchromatic nucleus. The number of mitoses is variable. Cytoplasm is found in variable abundance.

The stroma may be reduced to a few thin bundles or it may consist of many large homogeneous plaques.[214,215] Hyaline degeneration is uncommon. The neoplastic cell cords rapidly overflow the parenchyma of the breast lobules and infiltrate the adjacent adipose tissue as centrifugal cellular streaks that confer on the tumor its star-shaped gross appearance.

Many tumors express one or more characteristics of the specific tumor types in the classification, but these minor foci do not influence the prognosis, which is more favorable only if the lesions are entirely or mostly composed of the specific patterns.

Histologic Grading. The variable appearance of IDC has led to numerous grading systems, most of which correlate to some extent with biologic tumor behavior. The best validated and most reproducible of these, which has the advantage of using both architectural and cytologic features, is the Nottingham system, a modification of the Bloom and Richardson method as reported by Elston and Ellis.[225] This system is summarized in Table 10-6. Elston and Ellis reported acceptable concurrence (more than 90%) between two pathologists independently using this system, and an excellent correlation with prognosis in a series of almost 2000 cases. They recommend that all invasive breast cancer be graded in this manner, but our preference is to limit its use to IDC not otherwise specified (IDC-NOS), because most histologic subtypes discussed below have unique natural histories and histologic features.

Electron Microscopic Appearance. Electron microscopic studies of mammary carcinomas have contributed interesting morphologic data (Figs. 10-62 and 10-63) but have failed to accomplish the two main tasks in which success might be hoped for: (1) to delineate absolute criteria for differentiating benign from malignant lesions, and (2) to establish a rational

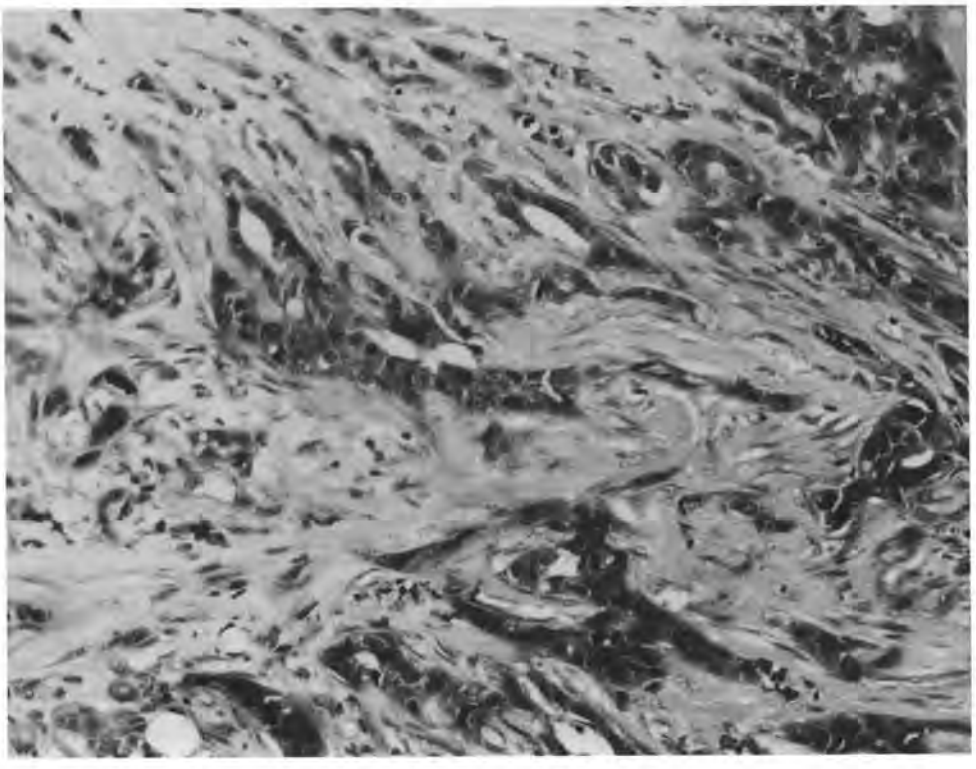


FIGURE 10-59 Infiltrating duct carcinoma, not otherwise specified. The infiltrating ductal formations contain lumina and are lined by cells showing relatively slight pleomorphism and mitotic activity.

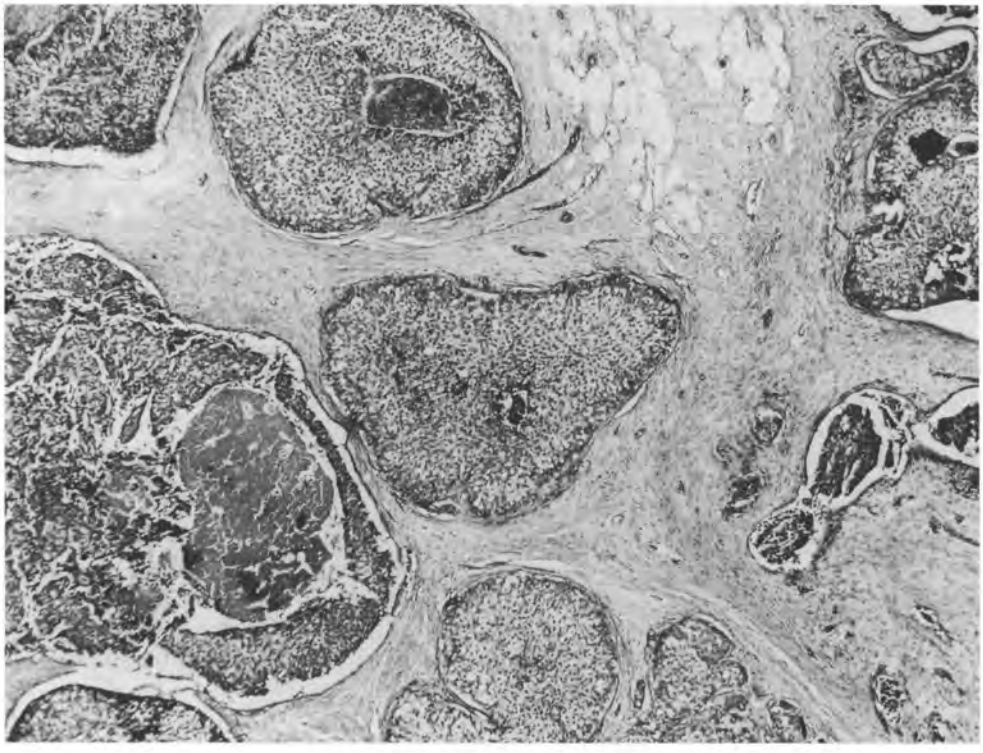


FIGURE 10-60 Infiltrating duct carcinoma, not otherwise specified. In this tumor, large nests of poorly differentiated tumor cells with foci of central necrosis (mimicking intraductal comedocarcinoma) invade through a reactive stroma.

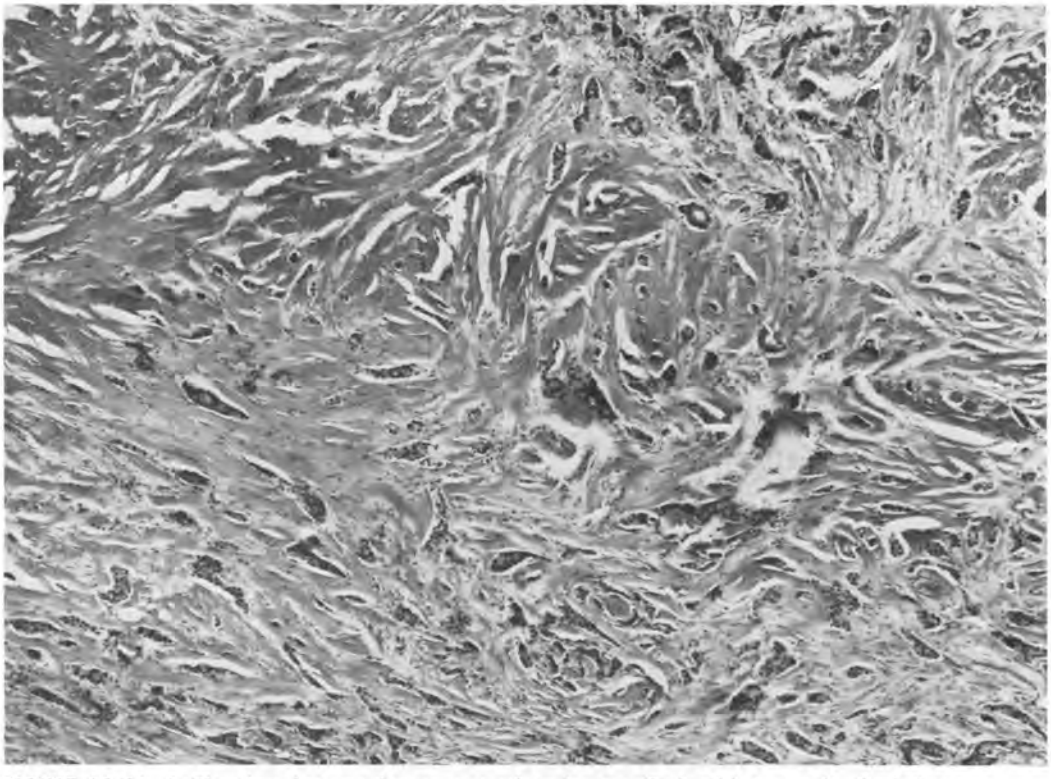


FIGURE 10-61 Infiltrating duct carcinoma, not otherwise specified. This tumor is of scirrhous type, showing a paucicellular pattern and a dense fibroelastotic stroma.

TABLE 10-6.
Combined Architectural and Cytologic Grading System for Infiltrating Duct Carcinoma

Feature	*Assessment*	*Numerical Score**
Tubule formation	In >75% of tumor	1
	10%–75%	2
	<10%	3
Nuclear pleomorphism	Small, regular uniform cells	1
	Moderate increase in size and variability	2
	Marked variation	3
Mitotic counts at tumor periphery	0–9/10 HPF†	1
	10–19	2
	20 or more	3

*The three scores are added together. A final tally of 3 to 5 = grade I (well differentiated); 6 or 7 = grade II (moderately differentiated); and 8 or 9 = grade III (poorly differentiated).

†HPF = high-power fields, defined by use of a Leitz Ortholux microscope with wide-angle eyepieces and 25× objective (field area 0.274 mm^2). This must be recalculated for other microscopes.

Adapted from Elston CW, Ellis IO: Pathological prognostic factors in breast cancer. I. The value of histological grade in breast cancer: Experience from a large study with long-term follow-up. Histopathology 19:403–410, 1991

classification of breast cancers based on their exact cell of origin. With regard to the former task, several studies have shown a spectrum from hyperplastic and atypical to malignant lesions.[10,11] The presence of such structures as intracytoplasmic lumina and fibrils and the absence of basal lamina appear to be more frequent in malignant tumors but certainly are not pathognomonic; other features such as nuclear hyperchromatism, increased nuclear–cytoplasmic ratio, and so forth, can be detected as easily (if not more so) with the light microscope.

A histogenetic classification based largely on ultrastructure has been attempted by Murad.[226] He defines a myoepithelial cell (scirrhous), a ductal epithelial cell (medullary), and a ductular (lobular) carcinoma, but he fails to account for other known variants in this rather controversial study. At present, the identification of the various forms of mammary carcinoma still depends on light microscopy.

Cytologic Appearance. The criteria for a diagnosis of carcinoma in an FNA specimen are similar to standard cytologic criteria of malignancy in other organs.[26,28,29] In IDC, the smears generally are highly cellular and are composed of single tumor cells and large clusters, usually in a hemorrhagic background (see Color Figures 10-1 and 10-2). The clusters often show a loss of the tight cellular cohesiveness seen in aspirates from fibroadenomas and other benign conditions that show numerous cell clusters. They lack the bimorphism of most benign breast aspirates, in which the single cells demonstrate bipolar nuclei and little or no cytoplasm. At higher magnification, the cells are large and exhibit anisonucleosis, high nuclear–cytoplasmic ratios, hyperchromatism, and nuclei that are often eccentrically situated and occasionally bizarre. The degree of atypia in the aspirate generally reflects the differentiation of the tumor, but the correlation is not perfect.

Differential Diagnosis. The most frequent histopathologic differential diagnostic problems associated with IDC-NOS relate to its distinction from other types of infiltrating mammary carcinomas, especially those with a more favorable prognosis. In general terms, the safest statement that can be made is that one of the favorable rarer types (eg, tubular, adenoid cystic, papillary, cribriform, mucinous, and medullary) should not be diagnosed unless the tumor in question is a perfect fit with the classic features of that type. Suggestive but atypical variants are best diagnosed as IDC and graded appropriately. Most of the favorable histologic types must be pure or at least dominant (the rule varies with the type) to maintain their favorable natural history; therefore, when one of these types occurs together with IDC-NOS, the proportion of each should be specified in the surgical pathology report. The diagnostic features of the various subtypes are discussed individually below.

Less common but potentially more serious diagnostic problems concern the distinction of IDC from a noninfiltrating duct carcinoma (DCIS) or a benign lesion. The problem of sclerosing adenosis is probably overemphasized in the literature and usually involves tubular carcinoma more than IDC (see Table 10-2 for the most useful differential diagnostic features). Nipple adenomas, radial scars, and sclerosing papillomas can present problems and are discussed above. They are all cytologically benign lesions and most of them have prominent myoepithelial cells (demonstrable by standard light microscopy or, when necessary, by immunohistochemistry). They all have classic—albeit different—architectural features that are generally lacking in the more haphazardly arranged IDC. The reactive, inflamed, myxoid to fibroelastotic stroma of IDC is in sharp contrast to the totally unreactive stroma of nipple adenoma and the generally hyalinized stroma of a sclerosing papilloma.

DCIS can present a major diagnostic problem, particularly when it occurs within an architecturally abnormal lesion such as sclerosing adenosis or a radial scar (see Figs. 10-32, 10-33, and 10-47). The background lesion, however, is usually apparent, and the diagnosis of IDC should be made only rarely in this situation. Another problem with DCIS involves tangential sectioning through a branch of an involved duct, giving the false appearance of extension of a tongue of tumor out into the stroma. In this situation, additional levels through the block may be helpful if they demonstrate more obvious stromal infiltration. If they do not, we prefer to be conservative and retain the diagnosis of DCIS, because a

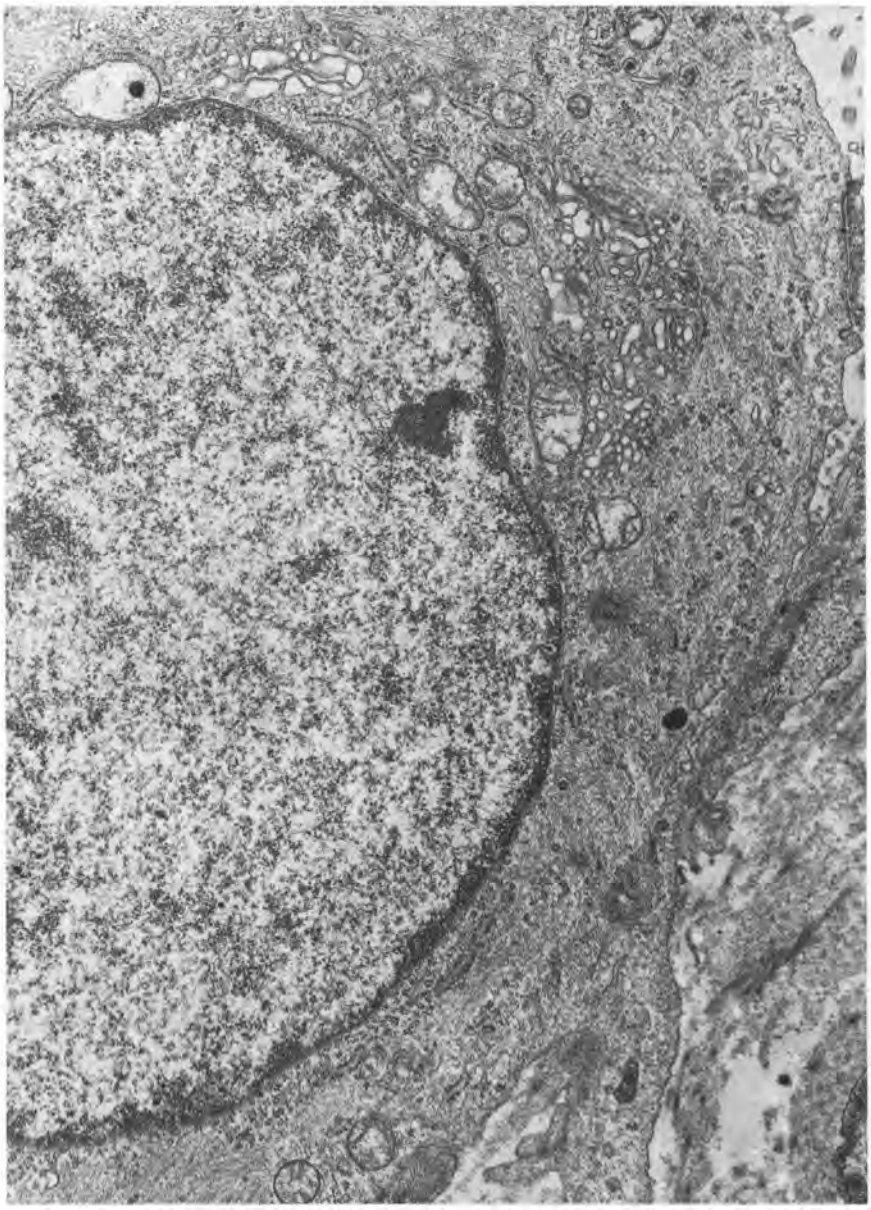


FIGURE 10-62 Infiltrating duct carcinoma: electron micrograph shows tumor cell in intimate contact with collagen fibers at lower right. Myoepithelial cells and basement membrane are absent here. Golgi apparatus, free ribosomes, and microfibrils are prominent.

single microscopic tongue of invasive carcinoma is unlikely to alter the natural history of the tumor. IDC and other mammary carcinomas present differential diagnostic problems when they are detected in a metastatic focus in the absence of a known primary tumor in the breast, or when both a breast primary and a different primary adenocarcinoma have been diagnosed in the past. Despite claims to the contrary, we know of no antibody in immunohistochemical use that is totally specific for breast cancer, so the final estimation—and it often is just that—must still be made on the basis of the basic light microscopic features.

Prognostically Favorable Variants of Infiltrating Carcinoma

Because IDC-NOS makes up about 70% of all primary infiltrating carcinomas of the breast, the less common variants are defined by virtue of (1) their distinctive histopathologic and (occasionally) gross pathologic features, and (2) their prognostic differences, if any, from IDC-NOS. Most of the variants that have been well characterized are associated with a more favorable prognosis, although in some instances this advantage is present only when the variant is present in its pure form, and in others minor proportions of admixed IDC-NOS apparently do not worsen the prognosis. In some of the prognostically favorable variants, it is difficult to determine whether the clinical behavior is determined by the histologic type alone, or by type in concert with such factors as tumor size and grade. Finally, some of the types that are generally thought to be prognostically favorable by most authors have not had such an excellent prognosis when studied by others, and data derived from the era of treatment by radical mastec-

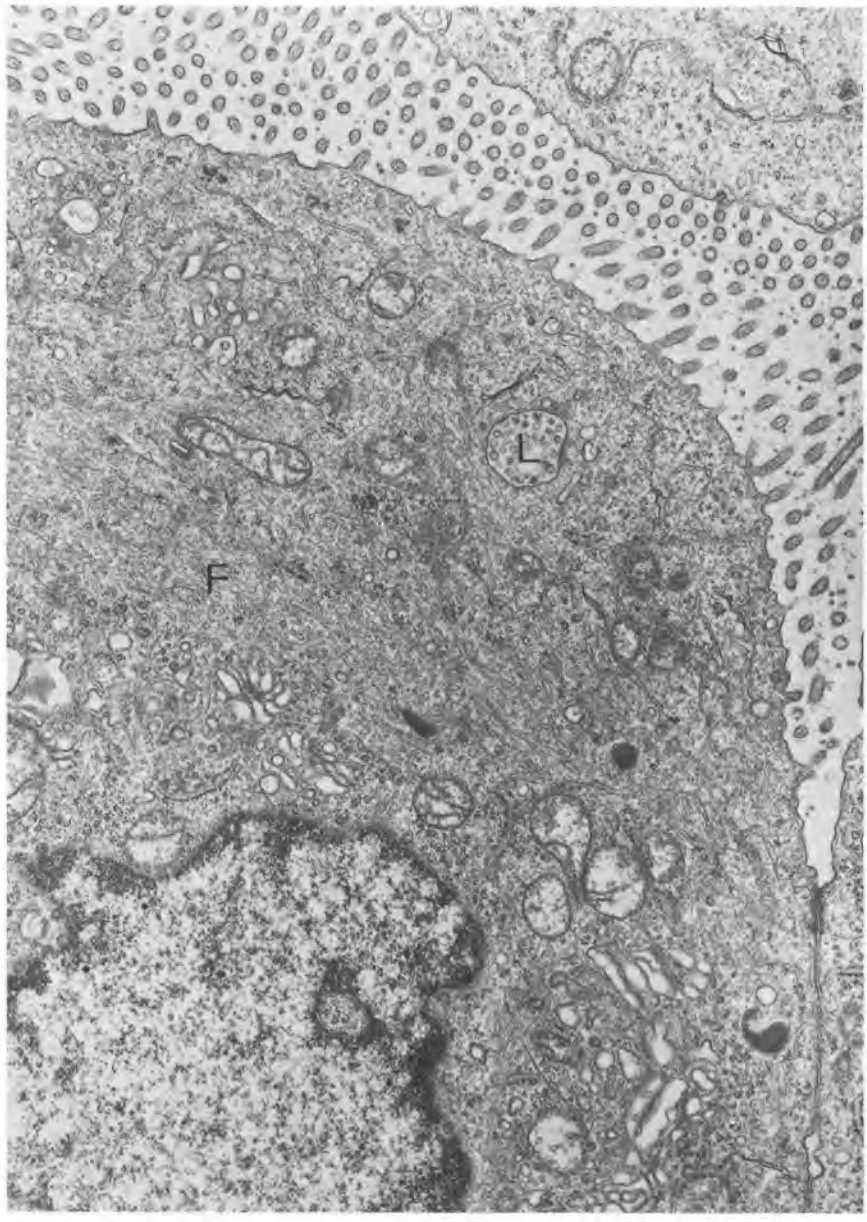


FIGURE 10-63 Infiltrating duct carcinoma: electron micrograph shows considerable similarity to benign mammary ductal epithelial cells, but with numerous microfibrils (*F*) and small intracellular lumen (*L*).

tomy alone are being supplanted by new studies in which the treatment is often conservative surgery with adjuvant radiation therapy, chemotherapy, or both. This is a rapidly changing field, and the reader must keep up with new developments.

A final caveat in this area concerns the tendency for breast cancer tissues to be submitted for numerous prognostic studies in which tumor histopathology is not taken into consideration. Particularly when the cancer is small to begin with—as is often the case today—it becomes more and more difficult to be sure what proportion of a tumor the prognostically favorable variant really represents.

Tubular Carcinoma. When it was first fully characterized in the 1970s, tubular carcinoma was considered to be a rare tumor, representing no more than 1% of all infiltrating carcinomas of the breast. With the advent of mammographic screening, the proportion of tubular carcinomas in most series has increased to close to 10% of all infiltrating cancers.[227-232] A corollary of this observation is the fact that tubular carcinomas tend to be small, usually measuring about 1 cm or less in greatest dimension, and rarely measuring more than 2 cm. It is generally thought that tubular carcinoma represents a stage in the growth phase of IDC, and that if the tumor is allowed to grow to a large size, it will ultimately assume the IDC-NOS morphology.

Clinically, these tumors are often impalpable and are usually discovered by mammography. When a tubular carcinoma is palpable, it generally appears as a small, hard, stellate mass. Skin and nipple retraction are very rare. The age distribution is similar to that of patients with IDC-NOS.

Macroscopically, there is little to differentiate tu-

bular carcinoma from IDC-NOS except its small size. Some tumors are so small (1 to 2 mm) that they even escape detection on examination of the gross biopsy specimen and are initially diagnosed on microscopic examination.

Microscopically, the tumor is characterized by the presence of oval or round tubular structures with open lumina surrounded by a single layer of small, rather uniform cells (Figs. 10-64 through 10-66). The tumor often grows in a stellate pattern but may lack any special form, simply infiltrating around and between benign ducts and into adjacent fat. The ducts may be compressed into an angulated teardrop shape or may grow together to form a focal cribriform pattern (see Fig. 10-66). Stroma between the malignant tubular structures is usually reactive, but it may be hyalinized or even unremarkable. Occasional tubular carcinomas arise within a radial scar, and they share some of the architectural features of that lesion. The tumor cells are, by definition, well differentiated. Mitotic figures are rare, necrosis is absent, and tumor cell stratification is absent or minimal. Myoepithelial cells are not seen.

The above description applies to pure tubular carcinoma, but many cases are admixed with intraductal, in situ lobular, or other infiltrating carcinoma patterns.

Differential Diagnosis. The most important differential diagnosis is with benign sclerosing lesions such as sclerosing adenosis (see Table 10-2) and radial scar. The most useful features of tubular carcinoma in making this distinction are the infiltrative pattern, the uniformity and open appearance of the tubular structures, the presence of a reactive stroma, and the absence of a myoepithelial cell layer. When the presence or absence of myoepithelial cells is in doubt, they can be identified immunohistochemically with antibodies to actin and S-100 protein[233] or ultrastructurally.[139] A more difficult differential diagnosis is with the rare condition known as *microglandular adenosis* (Fig. 10-67).[234–236] This lesion may present as a palpable mass of several centimeters or may be an incidental microscopic finding. There is a haphazard distribution of small round glands extending through fibrous stroma and fat, without any surrounding stromal reaction. The gland lumina usually contain dense hyaline eosinophilic material that is generally PAS-positive. The cell cytoplasm may be clear and often can be demonstrated to contain glycogen. Nuclear atypia and mitotic figures are absent. Although this condition is benign, it may be associated with simultaneous or subsequent carcinoma.[236] The main differentiating features from tubular carcinoma are the smaller size of the glands, the absence of a reactive stroma, and the hyaline material present within the lumina.

Other differential diagnostic problems for tubular carcinoma involve its distinction from other forms of infiltrating carcinoma, particularly cribriform and infiltrating duct NOS. The former distinction is largely of interest to the histologic purist, because the clinical behavior of tubular and cribriform carcinomas is identical. The distinction from IDC-NOS is more important, because the latter has a poorer prognosis (see below).

Clinical Features and Prognosis. It is universally agreed that pure tubular carcinoma, whether or not admixed with patterns of noninfiltrating carcinoma, has an excellent prognosis, with distant metastases and death recorded only rarely. More controversial is the prognostic significance of admixed infiltrating carcinoma of other histologic types. Most authors allow up to 25% of IDC-NOS within the definition of tubular carcinoma with a favorable prognosis.[227,230,232] However, we believe that if part of the tumor has been submitted for nonhistologic studies, and any IDC-NOS is present in the material examined histologically, the possibility of distant metas-

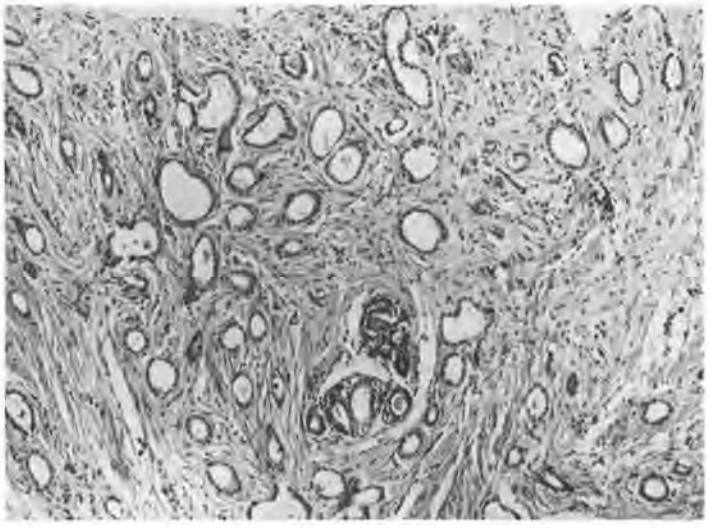


FIGURE 10-64 Tubular carcinoma. Uniform tubular structures in a reactive stroma swirl around benign ducts at bottom center.

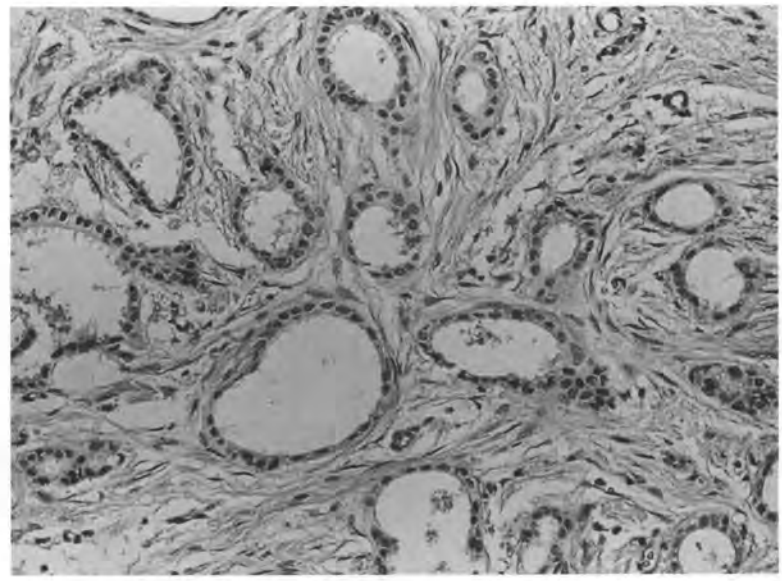


FIGURE 10-65 Tubular carcinoma. Note the stellate pattern, open tubular structures, and single layer of well-differentiated tumor cells.

tases may exist. As mentioned above, the not infrequent coexistence of infiltrating cribriform carcinoma does not worsen the prognosis of tubular carcinoma.

Axillary lymph node metastases are not rare in tubular carcinoma, occurring in about 10% to 15% of cases in most series. Even node-positive cases do not seem to be at much risk for the development of distant metastases, because these occur in 2% or less of all cases. Tubular carcinomas are virtually always estrogen and progesterone receptor-rich and diploid.

Infiltrating Cribriform Carcinoma. Infiltrating cribriform carcinoma is a recently described tumor that comprises slightly more than 3% of infiltrating carcinomas of the breast.[237,238] The size of the tumor is usually between that of tubular carcinoma and that of IDC-NOS, and foci of either or both of these may be present in tumors that are predominantly cribriform. This relation led Venable and colleagues to suggest that infiltrating cribriform carcinoma may represent a transitional form as small tubular carcinomas mature into larger IDCs.[238]

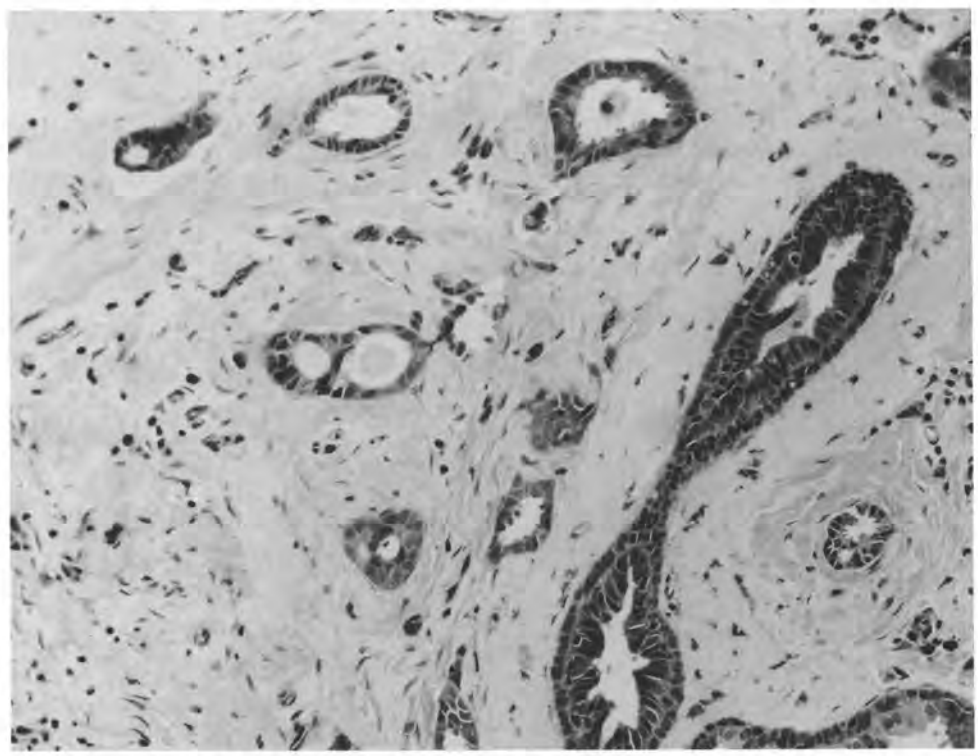


FIGURE 10-66 Tubular carcinoma. Compare the single-layered carcinoma with the benign duct at lower right, which contains a prominent myoepithelial cell layer. Some of the carcinomatous tubules are teardrop-shaped, whereas two others are fused to form the beginning of a cribriform pattern.

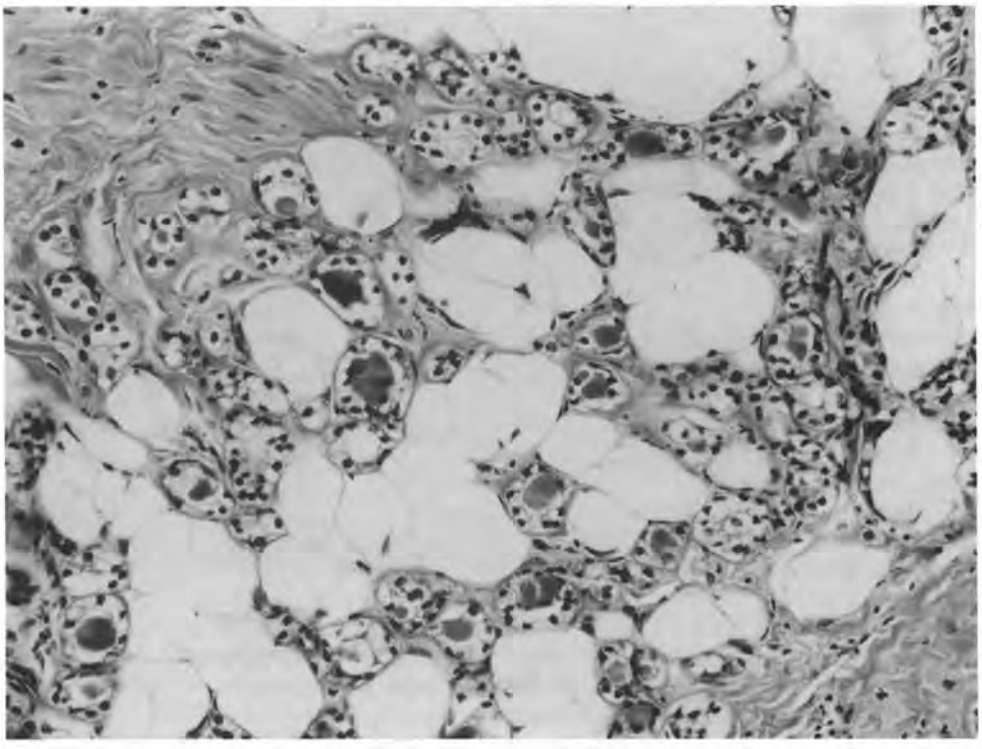


FIGURE 10-67 Microglandular adenosis. Small glandular structures lined by a single cell layer and containing dense eosinophilic material in their lumina infiltrate haphazardly into connective tissue and fat.

Microscopically, the tumor is characterized by irregular infiltrating islands of tumor displaying rather uniform cribriform spaces lined by moderately- to well-differentiated cells (see Fig. 10-68). The word *infiltrating* is part of the name of this tumor to differentiate it from the cribriform pattern of DCIS, which it closely resembles and which forms one of the major differential diagnoses. Important differentiating features are the angular nature of the islands in the infiltrating tumor and the reactive intervening stroma. The other main lesions to be considered in the differential diagnosis are tubular, infiltrating duct, and adenoid cystic carcinomas. The latter entity, which is the most difficult to differentiate from infiltrating cribriform carcinoma, is discussed below.

Clinical Features and Prognosis. In the reports of Page and colleagues[237] and Venable and colleagues,[238] no patient died of recurrent or metastatic infiltrating cribriform carcinoma, although metastases to axillary lymph nodes were not infrequent. Venable and colleagues emphasized that these always involved three or fewer nodes if IDC-NOS did not comprise more than 50% of the infiltrating component of the primary tumor. Mixed cribriform-tubular carcinomas did well regardless of the respective proportions of these two histologic types. The

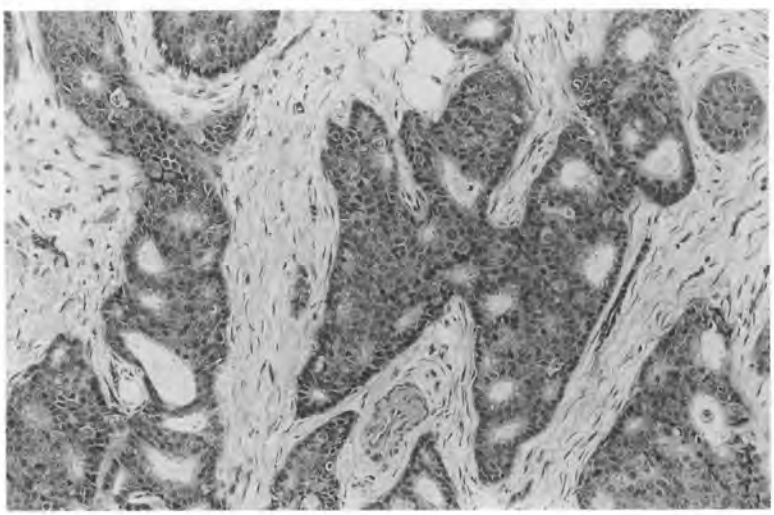


FIGURE 10-68 Infiltrating cribriform carcinoma. Irregularly shaped nests of small, uniform cells form regular cribriform spaces. The intervening stroma is spindled and edematous.

favorable prognosis of these two histologic types was also confirmed in the large study of Ellis and colleagues.[239]

Cytologic Features. The cytologic features of infiltrating cribriform carcinoma and tubular carcinoma are not well established in the literature. We have found that FNA biopsies and intraoperative smears of these two lesions resemble those of very well-differentiated IDCs. In both tumors, lumen formation is occasionally seen and may suggest the specific diagnosis.

Adenoid Cystic Carcinoma. Adenoid cystic carcinoma is a rare primary neoplasm of the breast.[240–242] A recent review suggests that only 140 cases have been reported.[242] It represents far less than 1% of all breast carcinomas.

Macroscopically, the tumors are usually small, well-circumscribed, and white-gray, with a mean diameter ranging from 2 to 3 cm. A significant number occur in the subareolar region, but nipple discharge is not noted.

Microscopically, the tumor is identical to its more common salivary gland counterpart. The tumor cells are arranged in cribriform (Fig. 10-69), trabecular, tubular, or solid patterns, with mixtures of these occurring in many tumors. The tumor cells are small with a round, hyperchromatic nucleus and sparse cytoplasm. The stroma is often myxoid or hyaline and surrounds the epithelial structures. Myoepithelial cells can generally be demonstrated immunohistochemically.

In typical cribriform areas, basement membrane material invaginates into the tumor cell nests to form PAS-positive hyaline cores. As in adenoid cystic carcinoma of salivary glands, perineural infiltration is common.

The *cytologic features* are characteristic and consist of small, uniform neoplastic cells with round, moderately hyperchromatic nuclei grouped in small clusters or large sheets and dispersed in an intercellular matrix that stains pale pink or green with the Papanicolaou stain and intensely red in Giemsa-stained specimens.[243] Frequently, lakes of hyaline stroma are surrounded by a layer of epithelial cells, suggesting the characteristic feature of this tumor at the histopathologic level (Color Figure 10-12).

The *differential diagnosis* of this tumor is predominantly with infiltrating cribriform carcinoma. The main differentiating features characteristic of adenoid cystic carcinoma are the presence of extracellular basement membrane material within pseudocysts; the presence of myoepithelial cells within the tumor; the absence of a noninfiltrating component; the absence of an admixture of tubular or IDC; and the absence of estrogen and progesterone receptors. Infiltrating cribriform carcinoma is virtually always estrogen receptor-positive and usually progesterone receptor-positive.

The *prognosis* of adenoid cystic carcinoma is excellent, with axillary nodal metastases and distant metastases being rare. Few cases with long-term follow-up have been reported in which conservative surgical treatment was undertaken.

Mucinous (Mucoid, Colloid, Gelatinous) Carcinoma. In most mammary carcinomas, there is discrete mucin production in the glandular cells. However, when extracellular mucin comprises 50% or more of tumor volume the tumor is called a *mucinous carcinoma* (Fig. 10-70). This tumor originally was characterized by Saphir[244] in 1941 as having a favorable prognosis, and numerous subsequent studies have confirmed this observation.[212,239,245–247] In its pure form, the tumor comprises about 2% of all mammary carcinomas.

Clinically, the tumor tends to occur in older

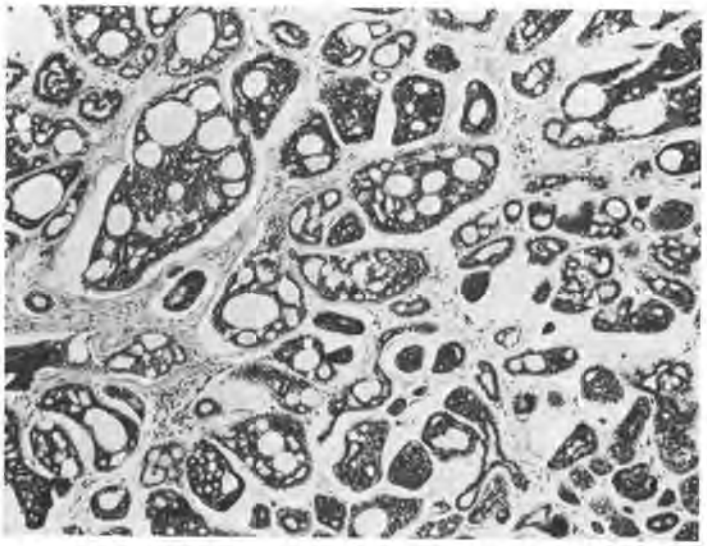


FIGURE 10-69 Adenoid cystic carcinoma: microscopic appearance. Invaginations of basement membrane material into cystic cavities are seen.

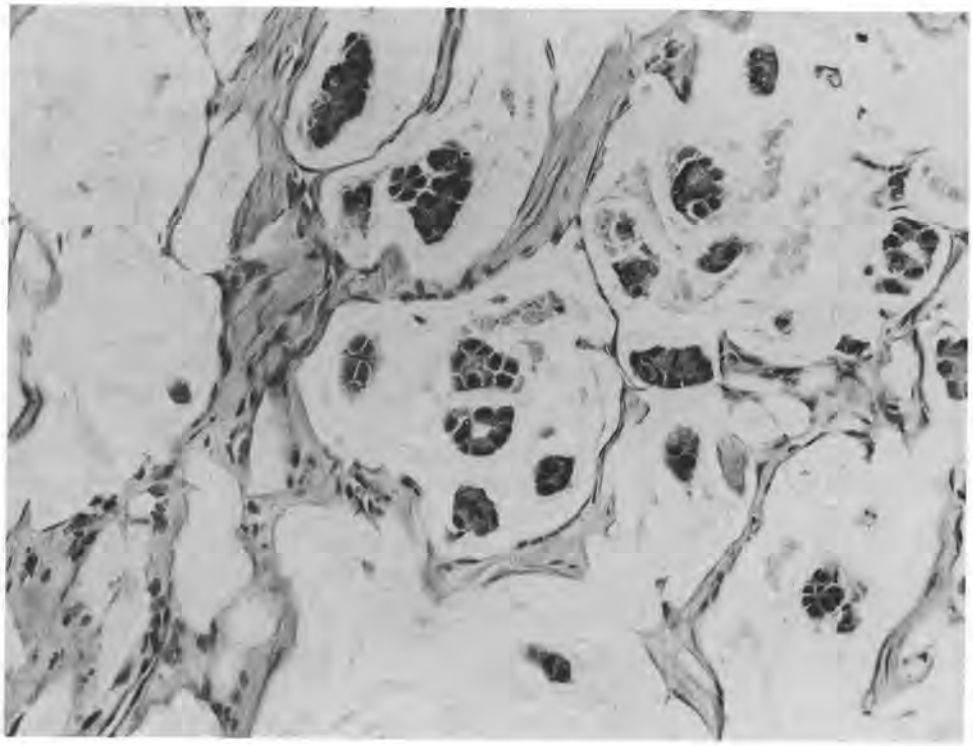


FIGURE 10-70 Mucinous carcinoma. Small glandular structures lined by well-differentiated tumor cells float in lakes of extracellular mucin.

women as a slowly expanding, well-circumscribed, soft mass. It frequently has expanded to a large size by the time that histopathologic diagnosis is made.

The *gross appearance* of the tumor is well circumscribed, soft, and gelatinous. This gross appearance is characteristic (Color Figure 10-13), although it may occasionally be confused with an unusually large and soft fibroadenoma.

Microscopically, the characteristic appearance is one of small solid or glandular nests of well-differentiated tumor cells floating in lakes of extracellular mucin (see Fig. 10-70). For the tumor to display its favorable prognosis, this pattern must be seen uniformly throughout the tumor, because even small amounts of IDC-NOS dilute the clinical behavior. Intraductal carcinoma, on the other hand, does not worsen the prognosis. When it is present, it is usually of non-comedo type and may display voluminous extracellular mucin (Fig. 10-71).

Neuroendocrine differentiation, characterized by the presence of cells showing argyrophilia, immunohistochemical positivity for chromogranin or synaptophysin, or dense-core neurosecretory granules by electron microscopy, is a common feature of mucinous carcinoma but does not seem to alter the prognosis when present.[248,249]

Cytologic examination reveals cellular cohesive groups and isolated cells in a background of abundant mucin (Color Figure 10-14). The nuclei are regular in size and shape, and the chromatin is finely dispersed. In those tumors in which an admixture of IDC-NOS is present, nuclear abnormalities are focally more pronounced. Intracellular (as opposed to extracellular) mucin usually is not prominent.

The *differential diagnosis* is with the rare benign condition known as *mucocele-like tumor of the breast*.[250,251] This lesion is characterized by a palpable mass composed of multiple cysts containing mucinous material, with rupture and discharge of acellular mucin into the surrounding stroma. These tumors may closely resemble mucinous carcinoma at both the cytologic and histologic levels. In the series of Ro and colleagues, all mucocele-like tumors were associated with microscopic foci of either mucinous carcinoma or ADH with abundant intraluminal mucin.[250] These authors caution against considering this tumor an entirely benign lesion.

The *prognosis* of pure mucinous carcinoma is favorable, although not as favorable as that of tubular, cribriform, and adenoid cystic carcinomas. In most series, despite the frequent large size of the tumors, only 10% to 15% of patients have died of metastatic carcinoma. When a minor IDC component is present, the prognosis is intermediate between that of pure mucinous carcinoma and the usual IDC.[239,245–247,252] Early reports suggest that conservative surgery and radiation therapy are effective in the treatment of this tumor type.[253]

Papillary Carcinoma. Although papillary carcinomas generally have been considered to be prognostically favorable mammary carcinomas, it often has been unclear in the literature whether the tumors being analyzed were papillary variants of intraductal carcinoma, papillary intracystic carcino-

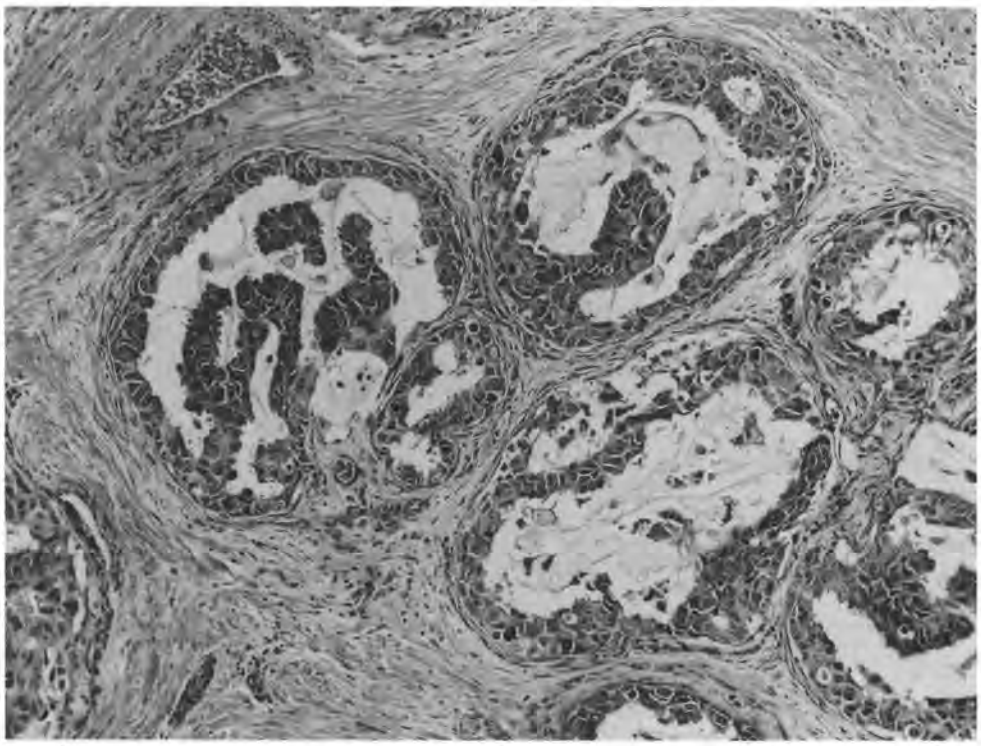


FIGURE 10-71 Intraductal carcinoma with voluminous intraluminal mucin. This lesion was associated with an infiltrating mucinous carcinoma.

mas,[254,255] or invasive papillary carcinomas.[256] Classic intraductal carcinoma has already been discussed in an earlier section, but the other two forms of papillary carcinoma are considered here.

Intracystic papillary carcinoma usually presents as a bulky, soft, well-circumscribed mass in an older woman. Microscopically, the lesion is confined to a large cystic space, but it may extend into adjacent smaller ducts (Fig. 10-72). Stromal infiltration is absent or very focal. These tumors are usually curable by wide local excision alone, and certainly by mastectomy.

Even less common is *invasive papillary carcinoma,* which may actually represent several rare entities but is defined as any infiltrating carcinoma containing papillary formations. Many of the tumors reported by Fisher and colleagues may have represented examples of mucinous carcinoma with some papillary growth, whereas others were histologically similar to serous papillary carcinoma of the ovary.[256] As a group, the 5-year disease-free survival rate was in the range of 90%, although 30% of cases with axillary dissection had nodal metastases.

Secretory Carcinoma. Secretory carcinoma is a rare type of mammary carcinoma that has been known as *juvenile carcinoma,* but several reports have indicated that the tumor also occurs in adults.[257–260] The tumor is usually well circumscribed grossly and is characterized histologically by the presence of vacuolated cells arranged in solid, cystic, or ductal patterns (Fig. 10-73). The secretory material is present in the cytoplasm and in extracellular secretions. The material is PAS-positive, diastase-resistant, and mucicarmine-negative. Ultrastructural examination reveals the presence of numerous membrane-bound secretory vacuoles. The exact nature of this secretory material remains unknown, but the tumor appears to be different from the *glycogen-rich clear cell carcinomas* recently reported.[261]

The intracytoplasmic vacuoles that are a characteristic feature of secretory carcinoma may also be seen in FNA cytologic material and may result in the correct diagnosis being made preoperatively.[260] When secretory carcinoma occurs in a patient younger than 20 years, it is apparently always curable by surgery alone. In older patients, axillary nodal metastases are not uncommon, and death as a result of distant metastases has been reported in rare cases. Nevertheless, the prognosis is still considerably more favorable than for IDC-NOS.

Medullary Carcinoma. The special tumor variants that have been discussed up to this point all share a well-differentiated nuclear appearance and a favorable prognosis that is acknowledged by virtually all authors. Medullary carcinoma is an exception to both of these rules. One of the characteristic features of the tumor is its high-grade nuclear morphology, and the favorable prognosis initially noted by Moore and Foote[262] has been confirmed by most[263–268] but not all[239,269] authors.

Clinically and mammographically, medullary carcinoma presents as a lobulated circumscribed mass more or less similar to fibroadenoma. Microcalcifiations are rare. The tumor often acquires a large

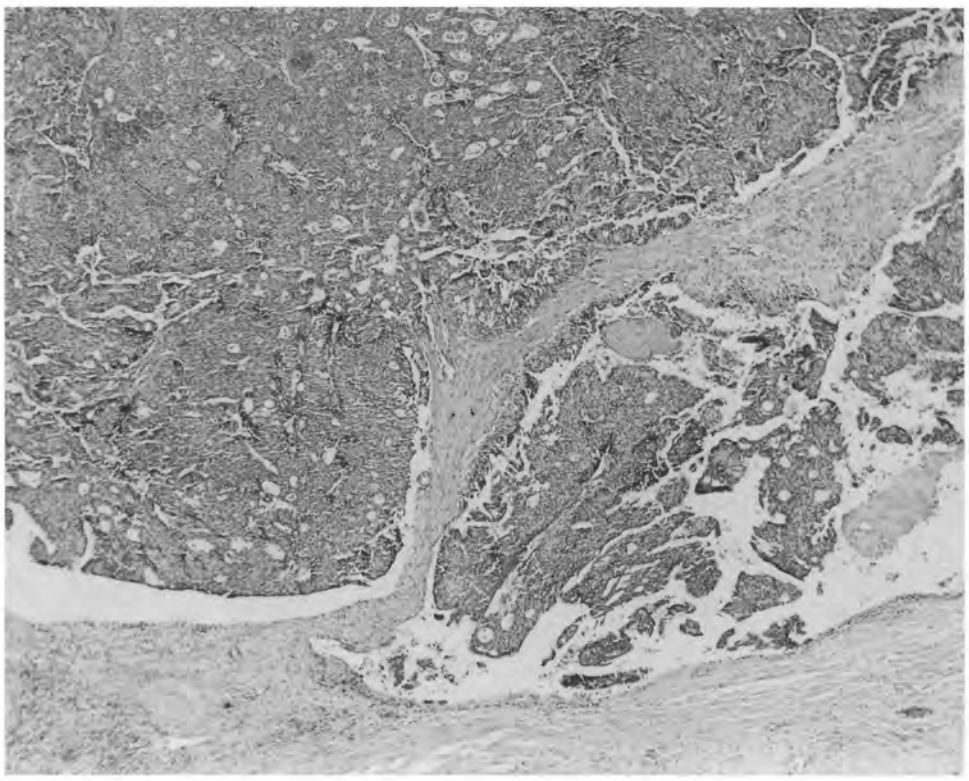


FIGURE 10-72 Intracystic papillary carcinoma. Only a portion of this tumor, which was confined to a large cystic cavity, is shown here.

volume without becoming adherent to the skin or surrounding tissues.

Macroscopically, the tumor is spherical and well demarcated, with a rubbery consistency and yellow-white color (Fig. 10-74). Foci of necrosis and hemorrhage are often prominent.

The classic *microscopic features* of this tumor are shown in Figures 10-75 and 10-76 and are outlined in Table 10-7. These features include the following:

- A predominantly circumscribed border
- A so-called syncytial growth pattern (a solid growth without glandular or papillary features)

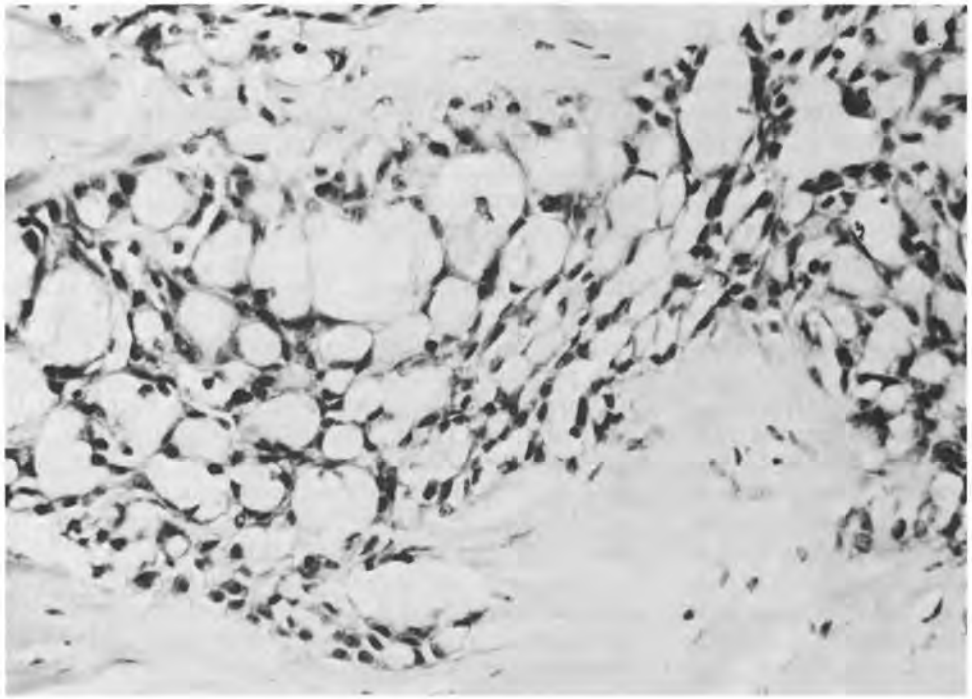


FIGURE 10-73 Secretory carcinoma. Note the feathery secretory material in cells and lumina.

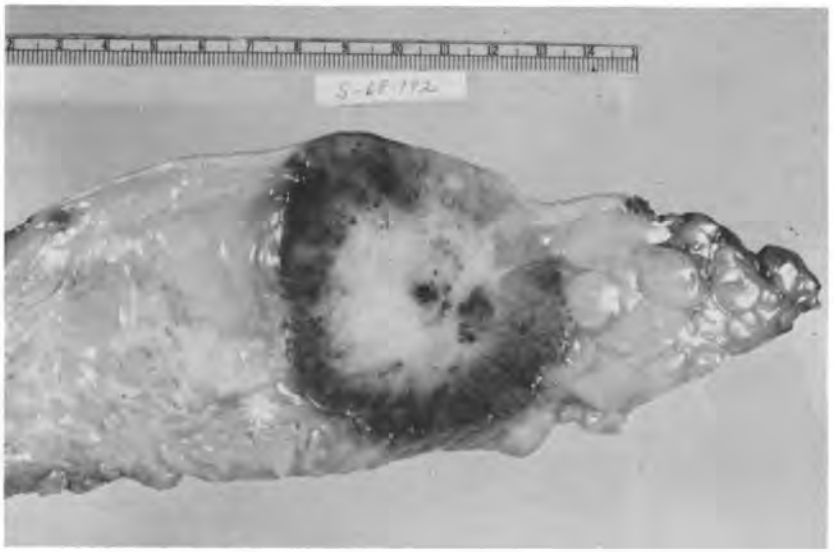


FIGURE 10-74 Medullary carcinoma: macroscopic appearance.

- The presence of a prominent stromal lymphoplasmacytic infiltrate
- Nuclei that are generally poorly differentiated or, at best, moderately differentiated.

Ridolfi and colleagues proposed in 1977 a category of *atypical medullary carcinoma* for tumors that met some but not all of the criteria for classic medullary carcinoma, and they suggested that the prognosis in this group was intermediate between the favorable prognosis of classic medullary carcinoma and the less favorable IDC-NOS.[264] More recently, Wargotz and Silverberg[267] and Pedersen and colleagues[268] have tried to simplify the diagnostic criteria, because it appears that many breast cancers with inflammatory stroma are overdiagnosed as medullary,[265,266] perhaps leading to the differences in opinion concerning the prognostic significance of this diagnosis. In our system, the term *atypical medullary carcinoma* is not used, and the diagnosis of IDC is mandatory if any of the primary criteria mentioned above are not met, and also if two or more of three secondary criteria (complete microscopic circumscription, moderate to marked mononuclear infiltrate, and absence of surrounding in situ carcinoma) are not met (see Table 10-7).

FIGURE 10-75 Medullary carcinoma. Low-power photomicrograph showing tumor circumscription, foci of necrosis, and lack of glandular or papillary differentiation.

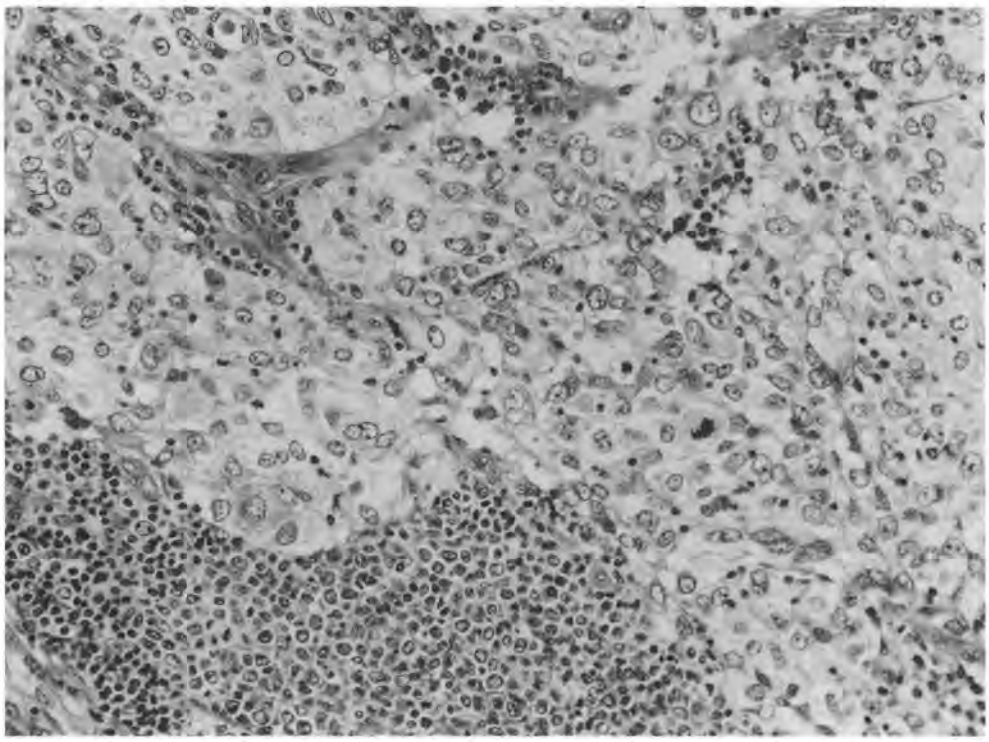


FIGURE 10-76 Medullary carcinoma. Detail of solid sheets of pleomorphic tumor cells and lymphoid infiltrate.

Ultrastructural studies have shown that the tumor cells are characterized by specialization of the cell surfaces into microvilli, formation of ducts and solid islands, and moderately well-developed rough endoplasmic reticulum.[270,271] They resemble the true epithelial cells of the mammary duct.

These tumors rarely, if ever, contain estrogen or progesterone receptors. In typical cases, FNA or intraoperative *cytology* (Color Figure 10-15) shows pleomorphic malignant epithelial cells interspersed with numerous lymphocytes and plasma cells. Glandular and papillary formations are not seen, and bizarre lobulated nuclei with macronucleoli are common. Unfortunately, medullary-like IDCs (defined by the histologic criteria discussed above) can have identical cytologic features, so the diagnosis is not precise until the entire tumor is studied histopathologically.

The *prognosis* of typical medullary carcinoma is thought to be favorable by most authors. In our series, the 5-year survival rate was greater than 90%.[267] Axillary nodal metastases are fairly common, but the prognosis in most series is better than that of IDC-NOS in node-negative and node-positive cases.

Because the usual prognostic features for breast carcinoma (tumor grade, receptor status, and ploidy) are all unfavorable in medullary carcinoma, an explanation must be sought for the probably favorable prognosis. Most widely studied has been the lymphoid infiltrate that is a characteristic feature of these tumors.[272] It has been suggested that these cells become effector cells capable of killing the tumor cells by mechanisms similar to those of natural killer lymphocytes.

TABLE 10-7.
Proposed Histologic Criteria for the Diagnosis of Medullary Carcinoma

*Primary**
1. Predominantly circumscribed border
2. Syncytial growth $\geq$ 75%
3. Presence of admixed stromal mononuclear infiltrate
4. Grade 2 or 3 nuclei
5. Absence of glandular features

Secondary†
1. Microscopically completely circumscribed
2. 2+ to 3+ mononuclear infiltrate
3. Absence of in situ carcinoma

*Diagnosis of infiltrating duct carcinoma is mandatory if any one of these criteria is not met.

†Diagnosis of infiltrating duct carcinoma is mandatory if two or more of these criteria are not met.

Adapted from Wargotz ES, Silverberg SG: Medullary carcinoma of the breast: A clinicopathologic study with appraisal of current diagnostic criteria. Hum Pathol 19:1340–1346, 1988

Other Infiltrating Carcinomas

In addition to the prognostically favorable histologic types of mammary carcinoma mentioned above, there are a number of other variants that are prognostically neutral or unfavorable when compared with IDC-NOS. These types are discussed in the following sections.

Infiltrating Lobular Carcinoma. The most common of the histologic types with no probable prognostic significance is infiltrating lobular carcinoma, which comprises between 5% and 10% of all infiltrating carcinomas of the breast. We emphasize the word "probable" because the prognostic significance of lobular carcinoma is still uncertain. In recent monographs on breast pathology, lobular carcinoma is referred to as a prognostically favorable type of breast cancer by Page and Anderson and an unfavorable type by Carter.[149,151] Furthermore, some authors note prognostic differences between different histologic subtypes of infiltrating lobular carcinoma, whereas others deny this assertion.[239,273–277]

Clinically and *macroscopically*, infiltrating lobular carcinoma is essentially identical to IDC, presenting as a stellate, firm, infiltrative mass of variable size. Several studies have noted a higher frequency of bilaterality in infiltrating lobular carcinoma than in IDC.[273,278]

Microscopically, the so-called classic pattern described initially is still the most common (Fig. 10-77). In this pattern, the neoplastic cells line up in long rows one cell thick, surrounded by fairly abundant stroma, in a single-file pattern. The tumor cells also exhibit a circumferential growth around uninvolved benign ducts. There is no tendency to form glandular or papillary structures, nor are wide sheets of cells noted. The individual cells are small and show little cytologic atypia.

In addition to this classic form, alveolar, solid, mixed, tubulolobular, and pleomorphic variants have been described. In the alveolar pattern, the tumor grows in round aggregates of 20 or more cells, reminiscent of LCIS but with obvious stromal infiltration (Fig. 10-78). In the solid variant, the tumor cells grow in a sheet-like pattern or in irregularly shaped nests (Fig. 10-79). The mixed group shows a combination of classic, alveolar, or solid growth patterns in a single tumor. In all these tumor types, the cytologic appearance of the tumor cells is identical, as it is in tubulolobular carcinoma,[279] in which the cells additionally form small tubules with definite lumina (Fig. 10-80). On the other hand, a group of tumors showing the architectural features of classic infiltrating lobular carcinoma but with a much greater degree of cytologic pleomorphism have been described as the pleomorphic variant of lobular carcinoma.[277] These tumors also are characterized by an eosinophilic, slightly granular cytoplasm and immunohistochemical positivity for the antigen GCDFP-15, suggesting apocrine differentiation.

Ultrastructurally, the most prominent feature of infiltrating lobular carcinoma is the frequency of intracellular lumina (Fig. 10-81). The exact cell of origin is not clear from these studies.[280–282] *Cytologically*, infiltrating lobular carcinoma of classic type differs from IDC by virtue of paucicellular smears or aspirates containing smaller tumor cells arranged singly or in small groups rather than forming larger ductal aggregates (Color Figure 10-16). Because of their low cellularity and lack of marked atypia, these tumors are well-known causes of false-negative cytologic diagnoses.[283] The solid, alveolar, and mixed patterns, on the other hand, may be diagnosed incorrectly as IDC because of the more abundant cellularity of cytologic material from these tumors. A prominent feature in all the variants is intracytoplasmic vacuoles representing the intracellular lumina demonstrated ultrastructurally.

The most difficult *differential diagnosis* of infiltrating lobular carcinoma is with malignant lymphoma or a leukemic infiltrate, and we have seen cases misinterpreted in both directions. If any doubt exists of the correct diagnosis, immunohistochemical stains for keratins and leukocyte common antigen should easily resolve the problem. Lobular carcinomas are also confused histologically with IDCs, especially of the paucicellular scirrhous variety. In this situation, the characteristic small uniform cells of lobular carcinoma should be present before this diagnosis is made.

The *prognosis* is controversial, with some authors claiming better survival than for IDC-NOS and others considering lobular carcinoma to be prognostically unfavorable. Within the histopathologic spectrum of infiltrating lobular carcinoma itself, most authors consider the so-called nonclassic types (alveolar, solid and mixed) of worse prognosis than the classic types,[273–275] whereas others deny this assertion.[276] Nesland and colleagues believe that the alveolar growth pattern signifies neuroendocrine differentiation and is not prognostically unfavorable.[276] Ellis and colleagues find the solid pattern to be unfavorable, but all the others to have a relatively good prognosis.[239] Weidner and Semple state that tumors with the classic architectural features of infiltrating lobular carcinoma but nuclei of grade of 2 or 3 have a poorer prognosis, and label the latter tumors the *pleomorphic variant.*[284] This term is used differently by Eusebi and his colleagues, who also find that their "pleomorphic lobular carcinoma" is an aggressive tumor, with 9 of their 10 cases recurring or proving lethal within short intervals from diagnosis.[277] We have recently noted that the presence of light microscopically detected intracellular lumina (signet-ring cells) in more than 10% of the cells of an infiltrating lobular carcinoma is associated with a poorer prognosis (see the following section).

Several authors believe that infiltrating lobular carcinoma is more likely to be bilateral than IDC. Nevertheless, several studies have demonstrated that conservative surgical therapy and radiation therapy provide as good local control of the primary tumor in cases of lobular carcinoma as in IDC.[285,286]

A recent autopsy study has suggested that metastasis to unusual sites such as peritoneum and retroperitoneum, hollow viscera, internal genital organs, leptomeninges, and myocardium is more common with lobular than ductal carcinoma.[287] The metastases to these and other sites are characterized by a

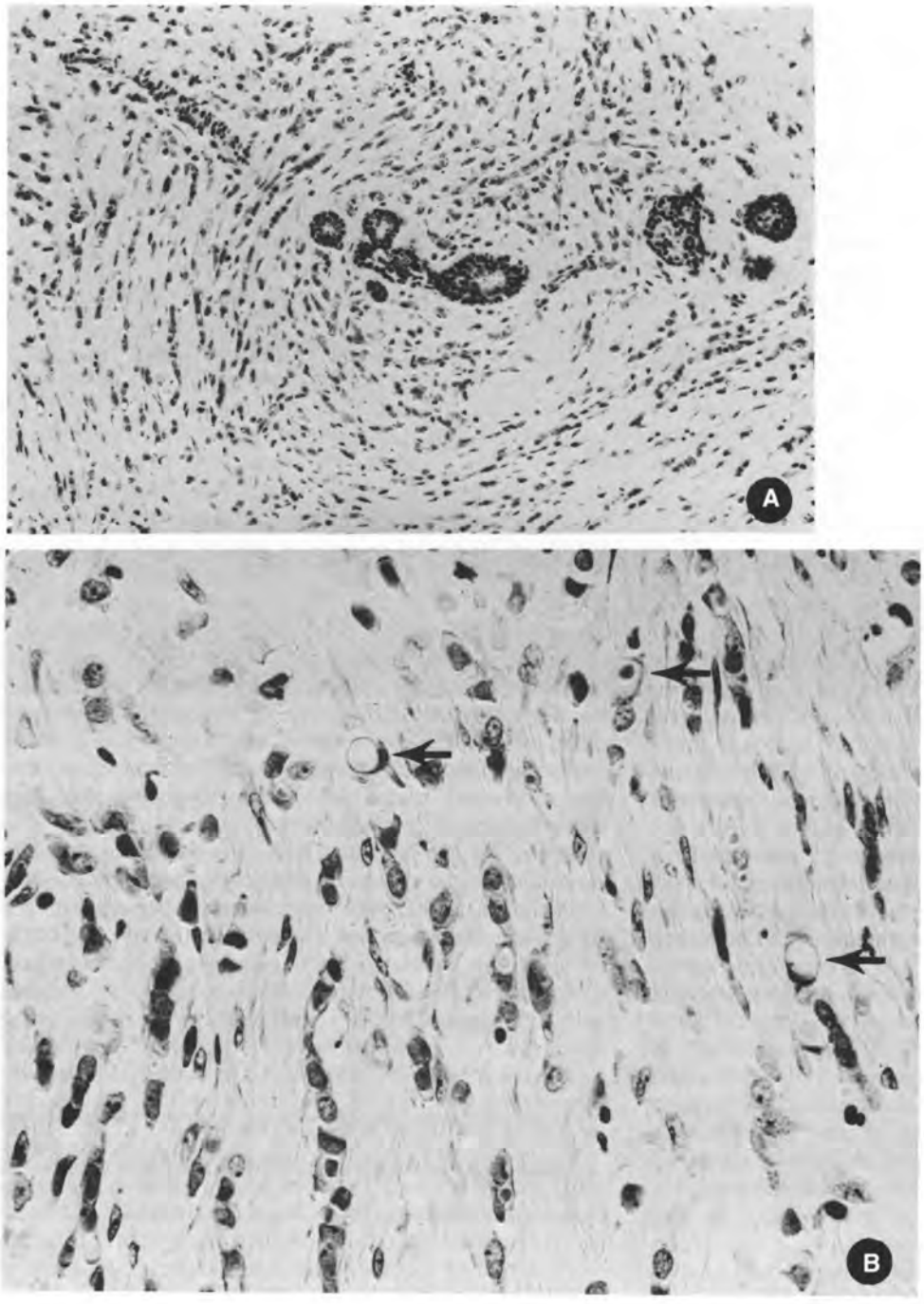


FIGURE 10-77 Infiltrating lobular carcinoma, classical type, with numerous signet-ring cells. **(A)** Low-power view showing single tumor cells swirling around benign ductules. **(B)** Detail of tumor cells with intracellular lumina containing mucin (*arrows*).

diffuse growth that infiltrates in a lymphoma- or leukemia-like manner. As with the primary tumor, immunohistochemistry may be necessary to identify the lesions correctly.

Infiltrating lobular carcinoma has been stated to be more often positive than IDC for estrogen receptors, probably because low nuclear grade is usually part of the definition.[288] The alveolar variant, according to Shousha and colleagues, is the most likely to be receptor-positive.[288]

Signet-Ring Cell Carcinoma. In the late 1970s and early 1980s, a number of studies were published on a variant of breast cancer that usually had the architectural features of classic infiltrating lobular carcinoma but was additionally characterized by the presence of numerous signet-ring cells.[289–291] These cells displayed nuclei that were compressed to the periphery by large globular intracytoplasmic inclusions, many of which showed a "bull's eye" appearance with a central dense mucicarminophilic core surrounded

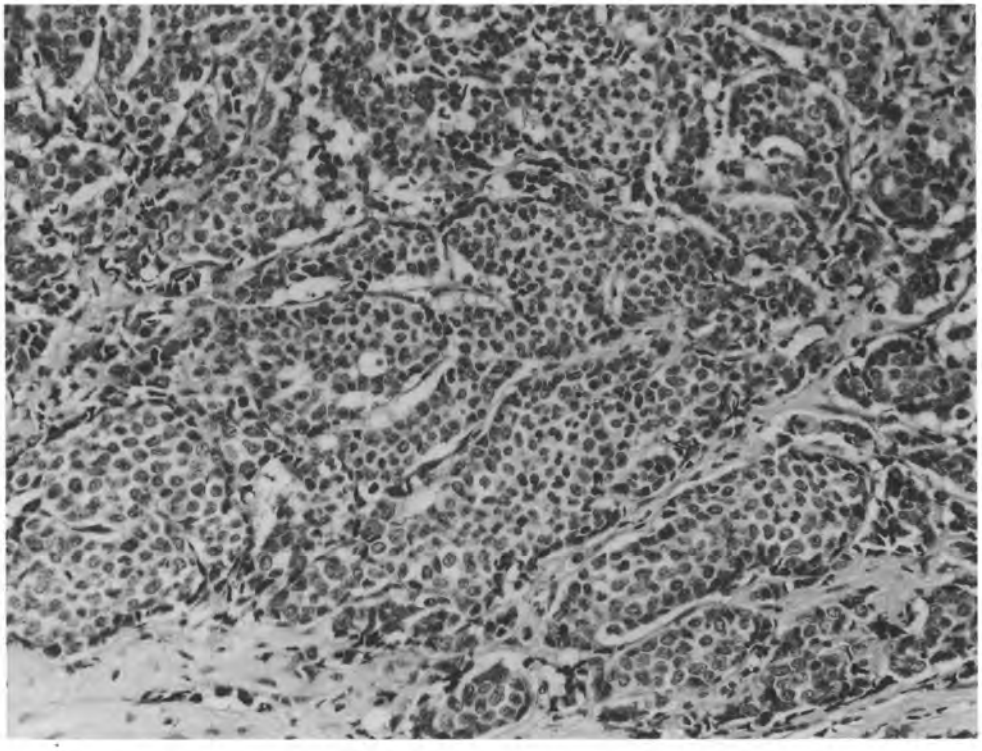


FIGURE 10-78 Infiltrating lobular carcinoma, alveolar type. The rounded nests of small uniform cells suggest in situ lobular carcinoma.

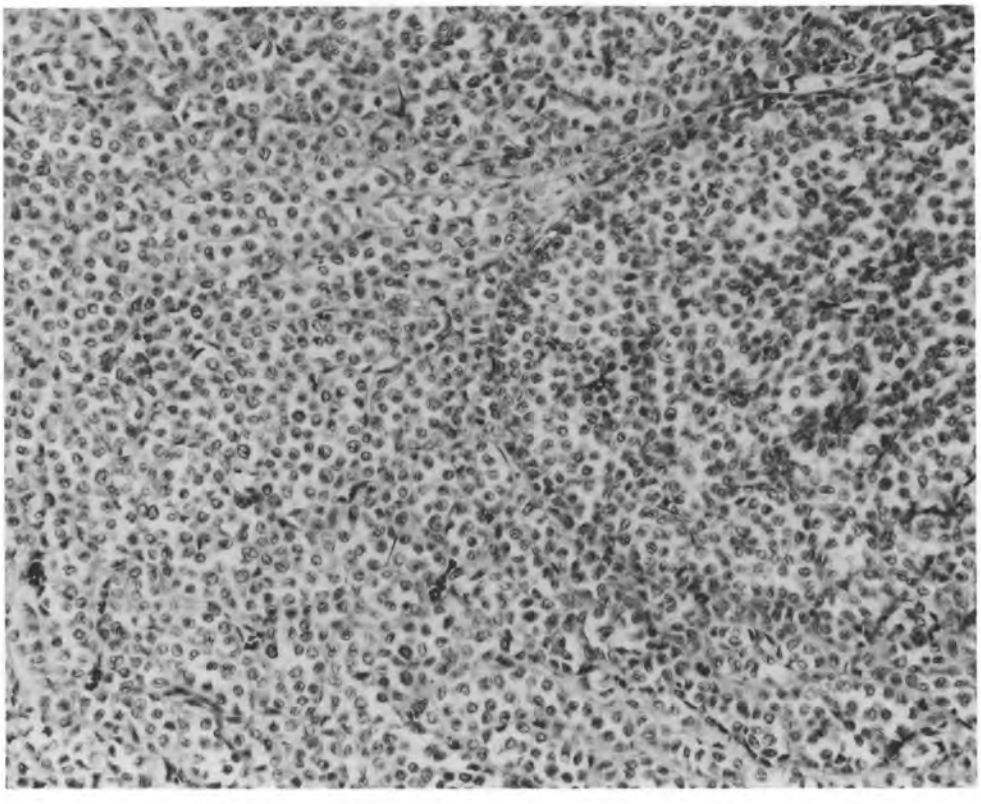


FIGURE 10-79 Infiltrating lobular carcinoma, solid type, with suggestion of alveolar pattern at right.

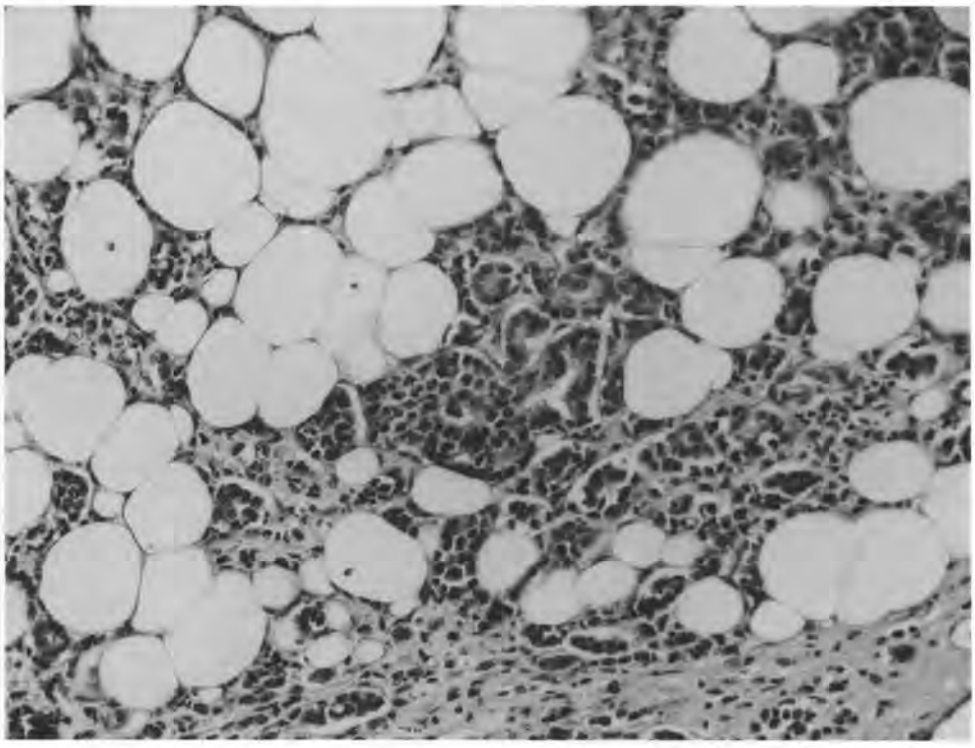


FIGURE 10-80 Infiltrating tubulolobular carcinoma: small cells focally form tubules. Elsewhere this was a mixed classical and solid lobular carcinoma.

by an empty space (see Fig. 10-77). Steinbrecher and Silverberg first suggested that this type of tumor was a mucinous variant of infiltrating lobular carcinoma and that it had a poorer prognosis than other lobular carcinomas,[289] and most other publications on the subject agreed.

At the George Washington University Medical Center and the Hospital of The University of Pennsylvania, we have recently reviewed all our infiltrating lobular carcinomas and have found that the great majority include at least some signet-ring cells. There is a tendency for the prognosis to be poorer as the proportion of these cells increases, with 10% of signet-ring cells appearing to represent a dividing line between favorable and unfavorable cases. Accordingly, we prefer to diagnose these tumors as infiltrating lobular carcinoma, then specifying both the architectural type (eg, classic, alveolar, solid) and the prominence of signet-ring cells if they comprise more than 10% of the tumor cell population.

Apocrine Carcinoma. The term *apocrine carcinoma* is used for an infiltrating carcinoma in which the ductal or glandular structures are lined by large cells with abundant eosinophilic cytoplasm, recalling the apocrine cells of sweat glands (Fig. 10-82). Intraductal carcinomas in which the malignant cells are exclusively apocrine also occur,[292,293] but intraductal proliferations with focal apocrine changes are almost always benign. In a classic publication, Frable and Kay showed that the prognosis of apocrine carcinoma was no different than that for equally differentiated IDCs of non-apocrine type.[292] More recent studies have expanded on but not changed this impression.[293] On the other hand, the apocrine variant of lobular carcinoma, known as *pleomorphic lobular carcinoma,*[277] does appear to be associated with a particularly unfavorable prognosis.

Neuroendocrine Tumors. In 1977, Cubilla and Woodruff reported 8 cases of a distinctive small cell tumor of the breast containing argyrophilic granules by light microscopy and neurosecretory-type granules on electron microscopic examination, and they designated this tumor *primary carcinoid tumor of the breast.*[294] Subsequent studies have indicated that argyrophilia may be seen in from 5%[72] to 50%[295] of breast carcinomas if appropriate stains are done. Many of these are otherwise typical IDCs and appear to have the usual prognosis for this tumor type. A higher than expected proportion are mucinous carcinomas and appear to share the favorable prognosis of that tumor variant.[248,249] A small proportion of the argyrophilic tumors resemble either the alveolar variant of infiltrating lobular carcinoma[273,276] or the mammary counterpart of small cell or oat cell carcinoma of the lung.[248,296] These *small cell carcinomas* are notable, as are their pulmonary counterparts, for clinical aggressiveness and early metastatic dissemination.

Metaplastic Carcinoma. Metaplastic carcinomas are a heterogeneous group of uncommon neoplasms characterized by foci of squamous, spindle cell, osseous, or chondroid differentiation. Most of these tumors have at least some ductal component, but this

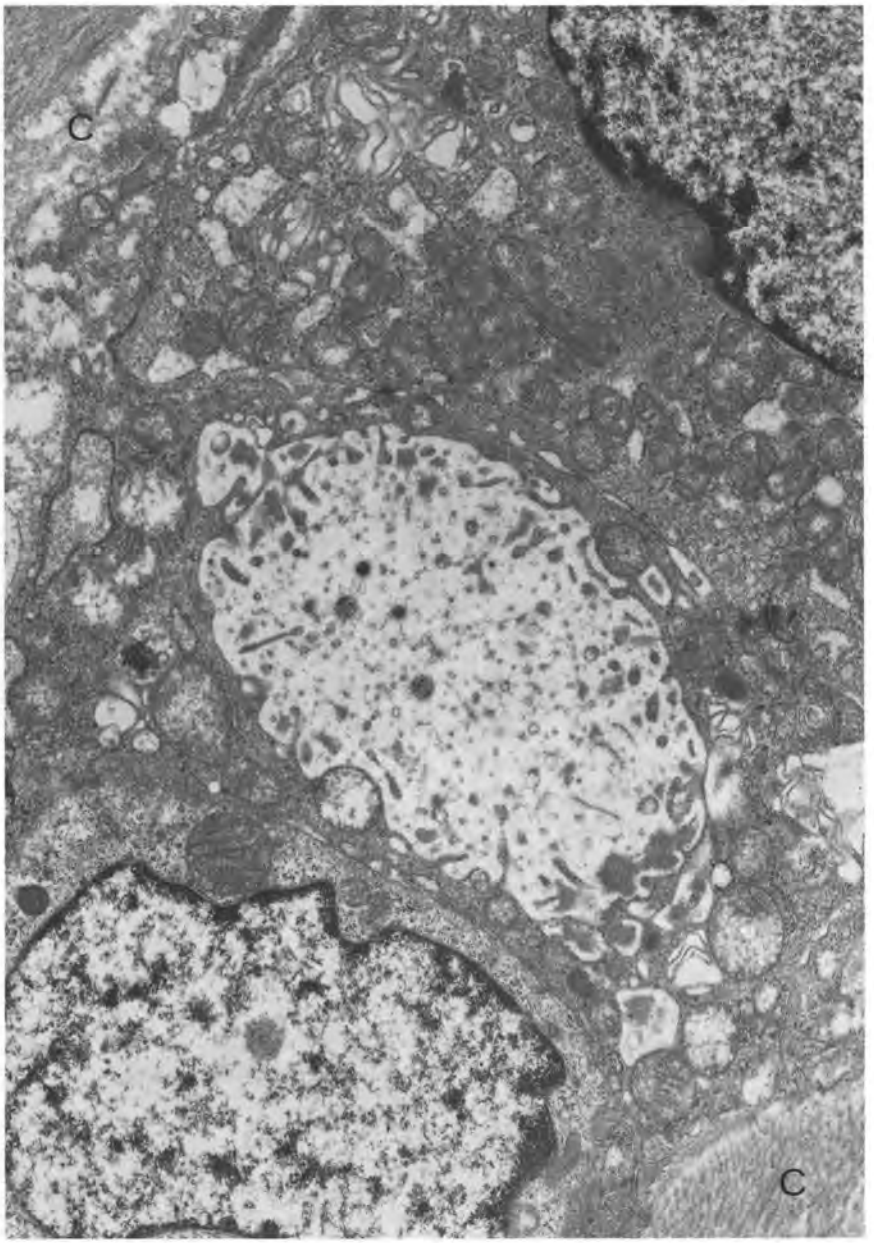


FIGURE 10-81 Infiltrating lobular carcinoma: single-file arrangement of tumor cells surrounded by collagen. Intracellular lumina (*center*) are larger and more numerous than in infiltrating duct carcinoma.

may be difficult or even impossible to find. Confusion about the true nature, classification, and clinical significance of these lesions is exemplified by the fact that even manuscripts from the same department have used different classification systems.[297–302] The largest and most thoroughly studied series of cases has been that of Wargotz and Norris, which we summarize here and in Table 10-8.[298–302]

Basically, Wargotz and Norris divide their metaplastic carcinomas into five separate types. *Matrix-producing carcinoma* is defined as overt carcinoma with direct transition to a cartilaginous or osseous stromal matrix without an intervening spindle cell zone. *Spindle cell carcinoma* is characterized by a dominant spindle cell proliferation composed of bland-appearing bipolar cells with insignificant pleomorphism and low mitotic activity, growing in fascicles and producing collagen (Fig. 10-83). To make this diagnosis, either in situ or infiltrating carcinoma must be present merging with the spindle cell component or the epithelial nature of the spindle cells must be proved by immunohistochemistry or electron microscopy.

In *carcinosarcoma* (Fig. 10-84), the neoplasm is biphasic, with both the epithelial and the spindle cell component appearing histologically malignant. Pure *squamous cell carcinoma* of ductal origin is characterized as an infiltrating carcinoma that is exclusively squamous (Fig. 10-85) without involvement of the skin, or as an intraductal carcinoma that is exclusively squamous. Finally, *metaplastic carcinoma with osteoclastic giant cells* consists of an intraductal or in-

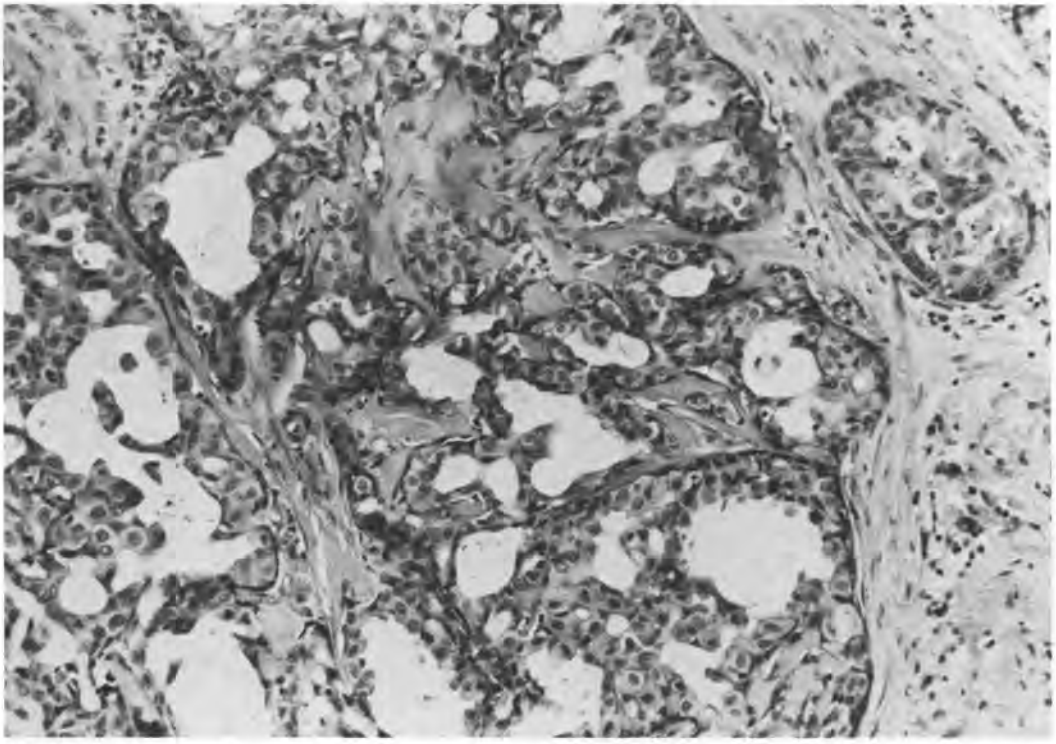


FIGURE 10-82 Apocrine carcinoma.

filtrating carcinoma contiguous to or admixed with a bland-appearing spindle cell stroma or a sarcomatous stroma in which osteoclastic-like giant cells are intermingled.

In the forms dominated by spindle cells—particularly bland-appearing spindle cells—immunohistochemistry may be necessary to demonstrate the epithelial derivation of this cell population.[303] Epithelial antigens may demonstrate somewhat subtle epithelial elements and may mark the apparent mesenchymal elements in many of these cases.

In the material of Wargotz and Norris, spindle cell carcinoma was the most common of the five types reported, consisting of almost half of the total cases, whereas carcinosarcoma was easily the second most common type. The bland appearance of spindle cell carcinoma must be emphasized, because we have seen cases of this sort misdiagnosed as fibromatosis or reactive scarring. We believe that any infiltrative spindle cell population in the breast that cannot be explained by previous trauma or surgery should be investigated immunohistochemically.

In the publications of Wargotz and Norris, the 5-year survival rates ranged between 63% and 68% for all tumor types except carcinosarcoma, which had a poorer survival of 49%. It is not clear what the survival rate was for IDC-NOS during this time period at the same institution, but in all likelihood only carcinosarcoma had a significantly less favorable prognosis.

The main *differential diagnosis* of most of these lesions is with pure sarcomas of the breast, and the main clinical significance of making the distinction is that metaplastic carcinomas are far more likely to involve axillary lymph nodes.

TABLE 10-8.
Metaplastic Carcinomas of the Breast

Type	*No. of Cases*	*5-Year Survival(%)*
Matrix-producing carcinoma	26	68
Spindle cell carcinoma	100	64
Carcinosarcoma	70	49
Pure squamous cell carcinoma of ductal origin	22	63
Metaplastic carcinoma with osteoclastic giant cells	29	68

Wargotz ES, Norris HJ: Metaplastic carcinomas of the breast. V. Metaplastic carcinoma with osteoclastic giant cells. Hum Pathol 21:1142–1150, 1990

Lipid-Rich Carcinoma. Lipid-rich carcinoma is another rare mammary tumor, characterized by sheets of epithelial cells containing intracytoplasmic lipid (Fig. 10-86).[304] The histologic pattern, particularly in metastases, may mimic that of a lymphoma. Another significant differential diagnosis is with the signet-ring cell type of infiltrating lobular carcinoma, which can be differentiated by a positive PAS or mucin stain.

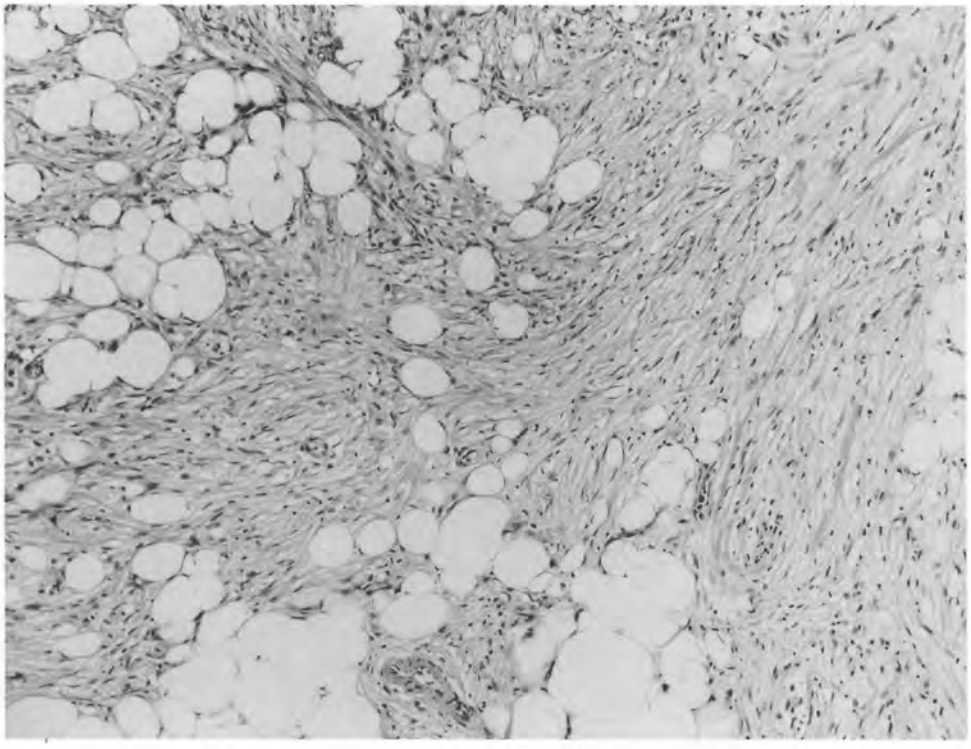


FIGURE 10-83 Spindle cell carcinoma. Fascicles of bland spindle cells infiltrate adipose tissue.

Van Bogaert and Maldague have subdivided the lipid-rich tumors into three types: histiocytoid (the most common), sebaceous, and a type with apocrine-like features.[305] They emphasize a similarity of the first type to the histiocytoid mammary carcinoma reported by Hood and colleagues that frequently metastasized to the eyelid.[306] This latter tumor, however, was said to be negative when stained for lipids. The prognosis in the few lipid-rich carcinomas appropriately analyzed has been poor, but they have tended to be high-grade carcinomas, so that the prognostic significance of the lipid component is not clear.

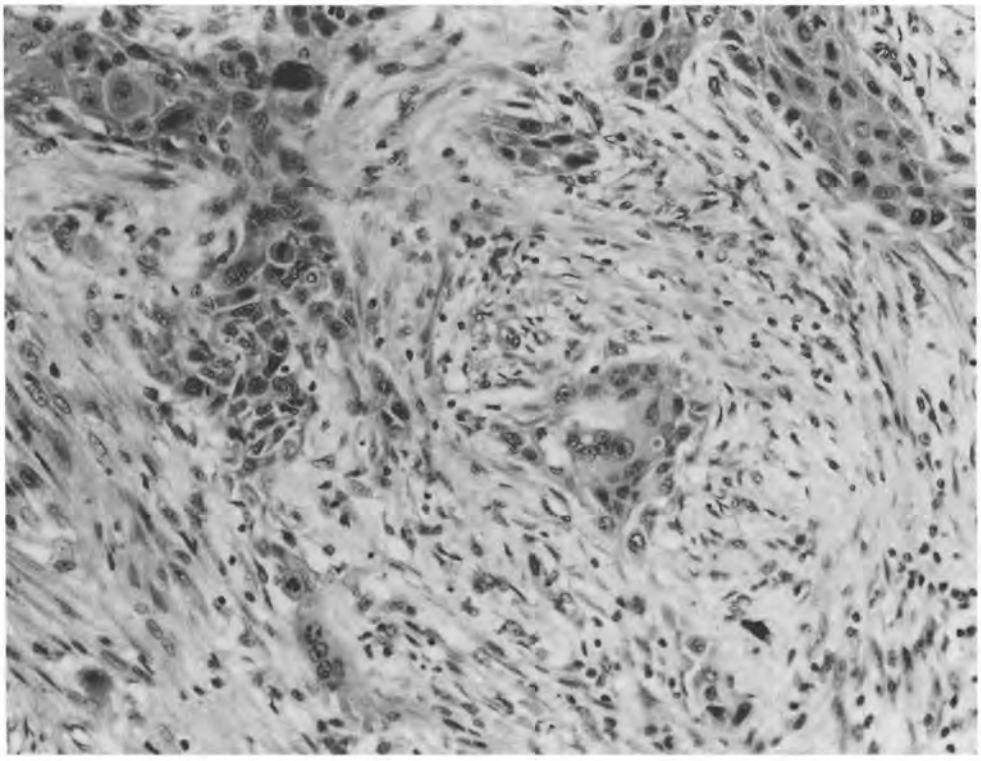


FIGURE 10-84 Carcinosarcoma. Both the epithelial and the stromal components of this tumor appear histologically malignant.

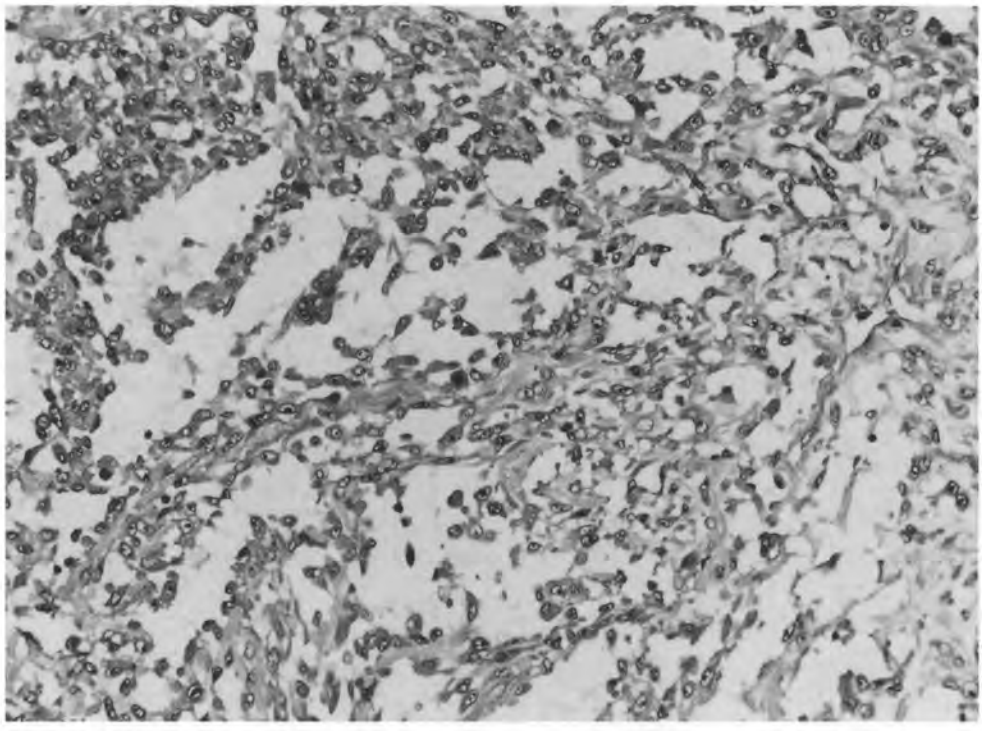


FIGURE 10-85 Squamous cell carcinoma of ductal origin. In this example, the malignant squamous cell nests display a cavitated pattern resembling angiosarcoma (acantholytic squamous cell carcinoma).

Types of Carcinoma Characterized by Their Site of Involvement

In addition to the variants of mammary cancer discussed above, which are characterized by the histologic appearance of the tumor itself, two specific types are characterized by their location within the breast. Paget's disease is a mammary carcinoma involving the epidermis of the nipple, whereas inflammatory carcinoma is a breast cancer that has spread within dermal lymphatics.

Paget's Disease. Paget's disease, described in 1874 by Paget,[307] is a cutaneous alteration of the nipple

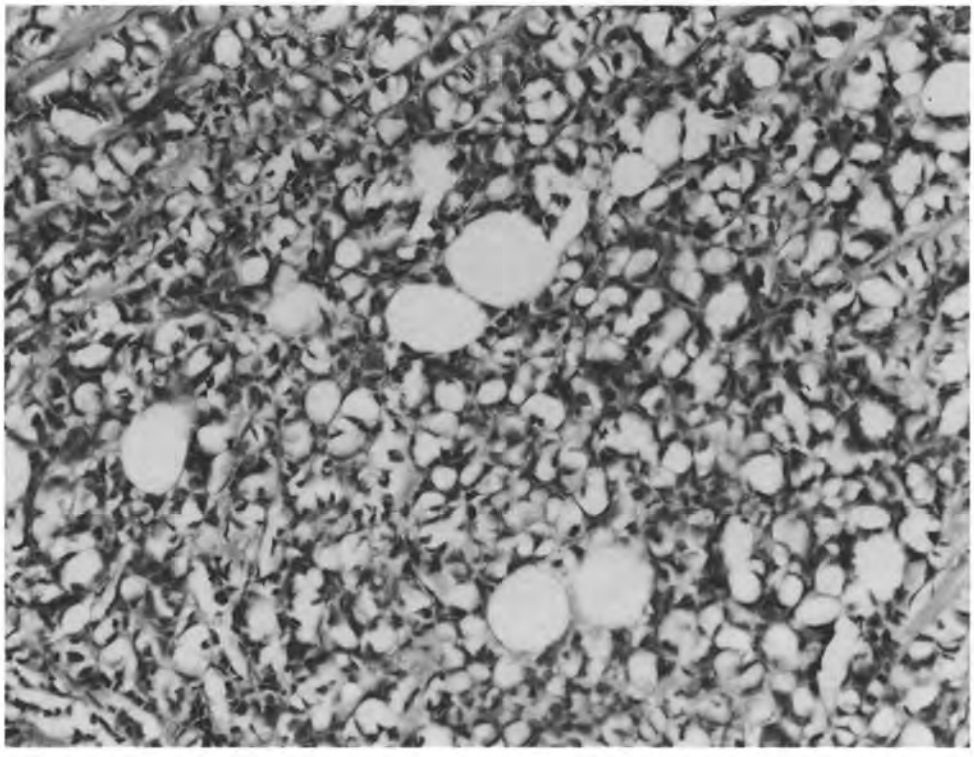


FIGURE 10-86 Lipid-rich carcinoma. Prominent lipid vacuoles distend the tumor cell cytoplasm.

almost always associated with an underlying mammary carcinoma. Paget erroneously thought that the skin lesion was benign but induced the cancer below. It is characterized clinically by a crusted and verrucous lesion of the skin of the nipple (Fig. 10-87). It is encountered especially in women older than 40 years, and is associated with about 5% of mammary carcinomas. The lesion begins as a more or less round, red, pruritic plaque with a granular surface, which eventually ulcerates and bleeds. It is surrounded by a squamous collar, which tends to grow toward the periphery. The nipple becomes progressively retracted and finally disappears in the neoplastic mass. This evolution may extend over several years, the underlying tumor mass not becoming palpable until the end of this period in some cases. When no tumor is palpable at the time of diagnosis, the underlying carcinoma is usually intraductal, and the prognosis is excellent. When a palpable tumor is present, the tumor is usually infiltrative, axillary and other metastases may have taken place, and the prognosis is that of the infiltrating carcinoma. In the absence of a palpable mass,

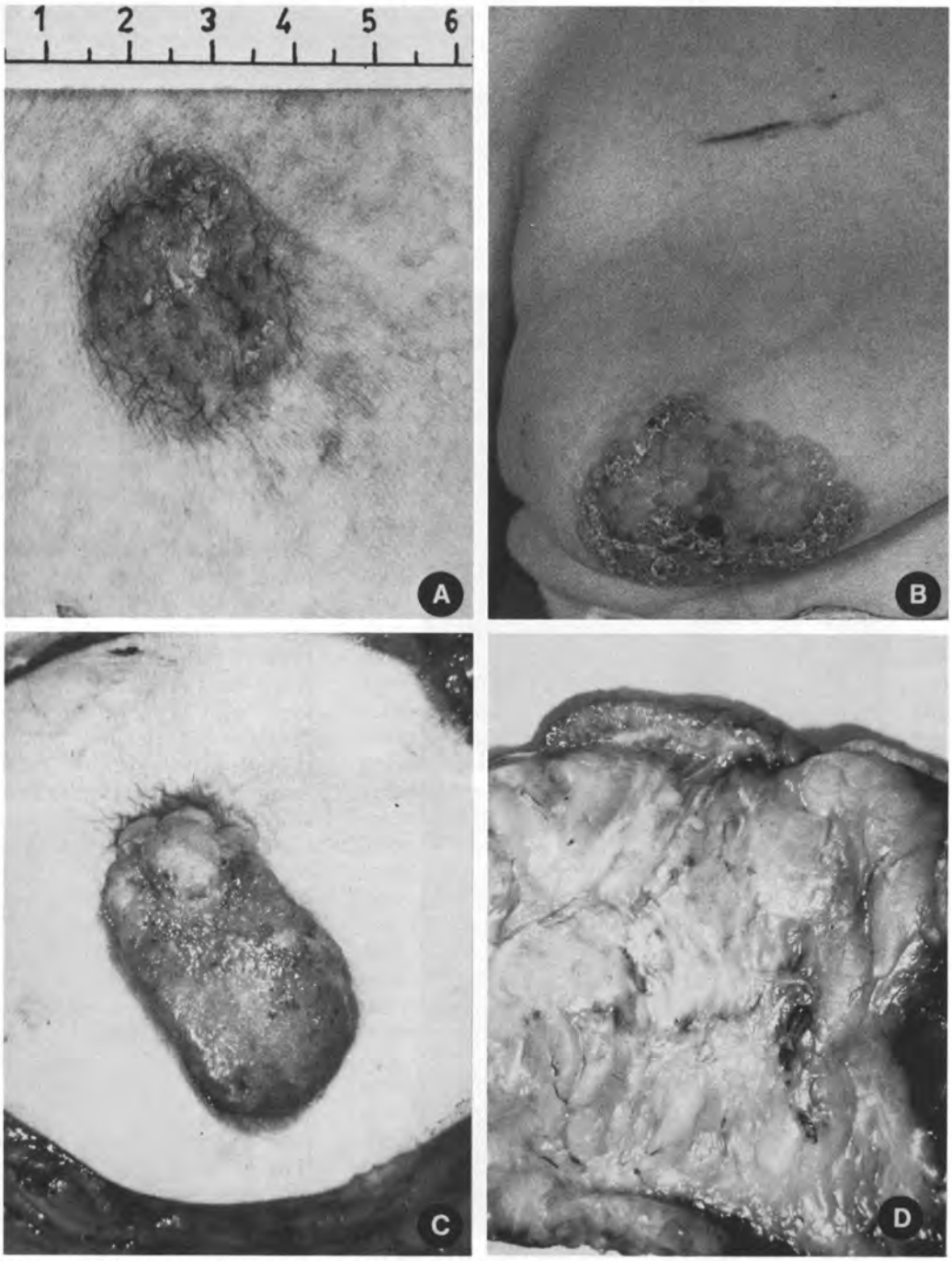


FIGURE 10-87 Paget's disease: macroscopic appearances.

mammography may detect a nodule, microcalcifications, or abnormal architectural changes that may reveal the underlying carcinoma.

Microscopically, Paget's disease is characterized by invasion of the epidermis of the nipple by large, round, neoplastic cells with voluminous clear cell cytoplasm, disposed singly or in small groups (Fig. 10-88). Outlines of gland formation are occasionally distinguishable. The Paget cells are usually located in deep layers of the epidermis, but they also may be found in the superficial layers as dyskaryotic cellular debris. They may also largely replace the nipple epidermis, giving an appearance similar to that of Bowen's disease or in situ squamous carcinoma; the term *anaplastic Paget's disease* has been used in this situation.[308] An inflammatory infiltrate of the underlying dermis or the involved epidermis is occasionally seen.

When the main lactiferous ducts underlying the nipple are examined carefully, the same neoplastic cells usually are found infiltrating the ductal epithelium as isolated cells (Fig. 10-89) or small cords. In the great majority of cases, examination of mastectomy specimens reveals a typical mammary carcinoma of intraductal or infiltrating duct type or both (96% in the series of Dixon and colleagues).[309]

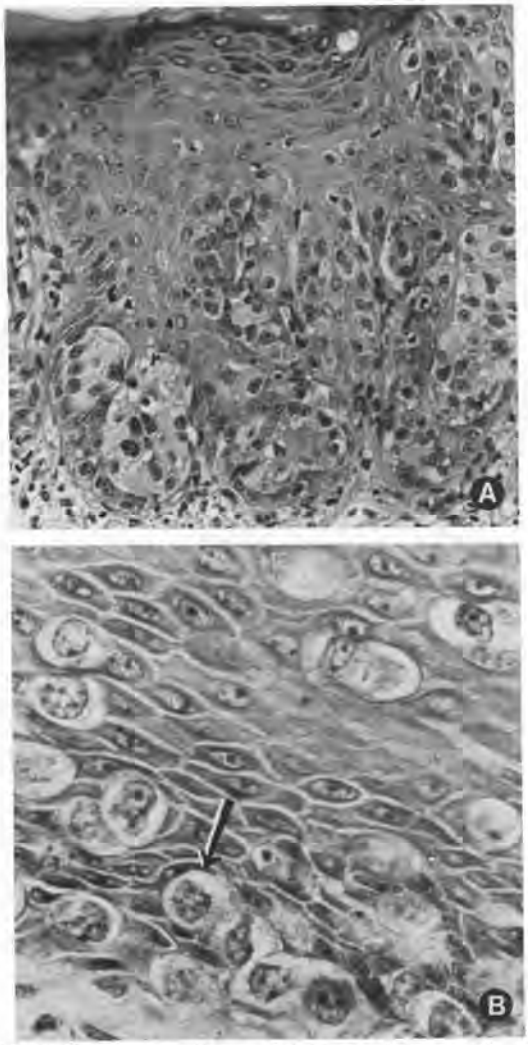


FIGURE 10-88 Paget's disease. **(A)** Nests of Paget cells. **(B)** Detail of Paget cells (*arrow*).

What is the primary site of the tumor? Toker has demonstrated intraepidermal clear cells in about 10% of normal nipples, which may be the cells from which the tumor arises.[310] Similarly, the ultrastructural study of Sagebiel has suggested in situ transformation of epidermal cells to Paget cells.[311] On the other hand, the almost consistent association with an underlying duct carcinoma suggests either a "field cancerization" or invasion of the epidermis by tumor cells growing up the ducts.[309] The origin of the neoplastic cells in the nipple is still controversial.

The *differential diagnosis* of Paget's disease involves other intraepidermal and infiltrating tumors of the nipple, including Bowen's disease (in situ squamous carcinoma), malignant melanoma, and basal cell carcinoma.[308,312,313] All these conditions are far rarer than Paget's disease. A positive stain for mucin is diagnostic, but many cases of Paget's disease stain negatively. Some authors conclude that immunohistochemical staining—specifically for carcinoembryonic antigen (CEA), epithelial membrane antigen (EMA), gross cystic disease fluid protein (GCDFP-15), cytokeratin CAM 5.2, and c-*erb*-B2—is more reliable.[308,312]

The *prognosis* of Paget's disease depends entirely on the underlying carcinoma, and the treatment should be aimed at that tumor as well.

Inflammatory Carcinoma. Inflammatory carcinoma is characterized clinically by the presence of cutaneous edema (*peau d'orange*), erythema of greater than one third of the breast, and diffuse brawny induration with or without a discrete underlying mass (Fig. 10-90).[314–316] The diagnostic pathologic sign is histologic evidence of carcinomatous invasion of dermal lymphatics (Fig. 10-91). Although histologic confirmation of carcinoma is necessary before treatment can be instituted, numerous studies have indicated that either the clinical or the histopathologic definition may be used to characterize a carcinoma as of inflammatory type. Parenthetically, it should be noted that the name of the tumor does not imply an acute or chronic inflammatory infiltrate seen histologically.

The condition is rare and is encountered in from 1% to 4% of all carcinomas of the breast. It may be associated with any histologic type. Mammography shows a diffuse increased density of the affected parenchyma or a tissue mass and an increase in skin thickness. The tumor mass is often difficult to palpate in the swollen and massively indurated breast. The skin of the breast is red, warm, tender and edematous.

The clinical significance of this type of cancer is that, regardless of the tumor type or grade, the prognosis is extremely poor. For many years, mastec-

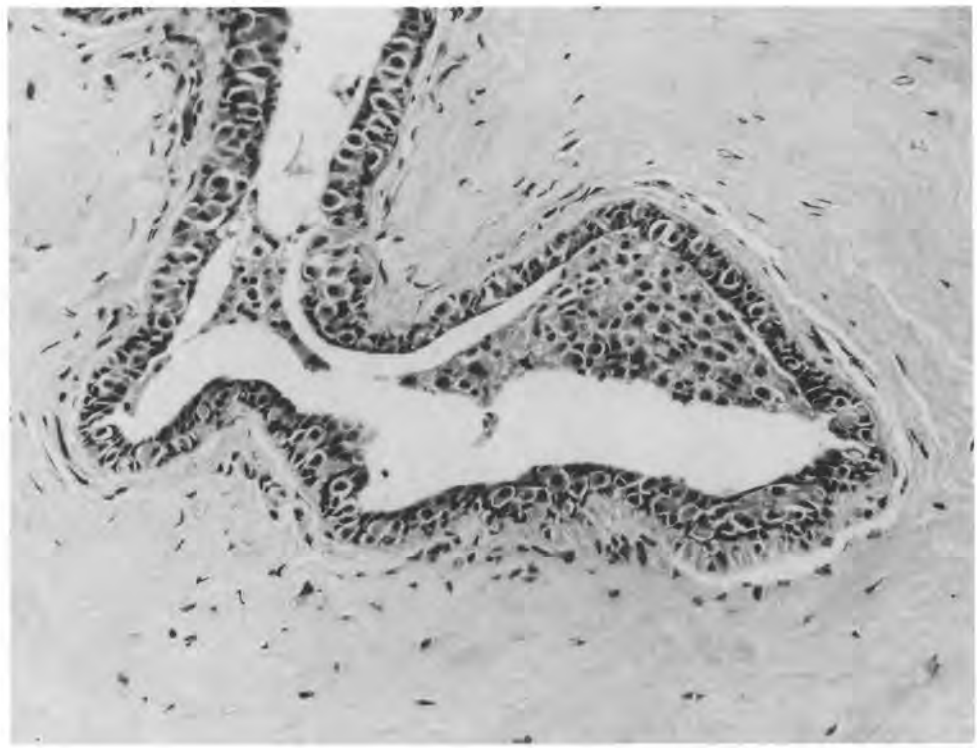


FIGURE 10-89 Pagetoid cancerization of a mammary duct.

tomy was not even attempted, because 5-year survival was almost unknown. Recent investigators have obtained 5-year survival rates in the vicinity of 30% with a combination of irradiation, surgery, and chemotherapy.[315,316]

Prognostic Factors in Breast Carcinoma

The previous discussion in this chapter has emphasized some of the areas of histopathologic typing and grading of carcinomas of the breast that are said to be of prognostic significance. The reader has undoubtedly realized by now that many of the factors are controversial. The same statement may be applied to other histopathologic, clinical, and laboratory features of breast carcinoma that have been claimed to be of significance in planning therapy and estimating the prognosis.

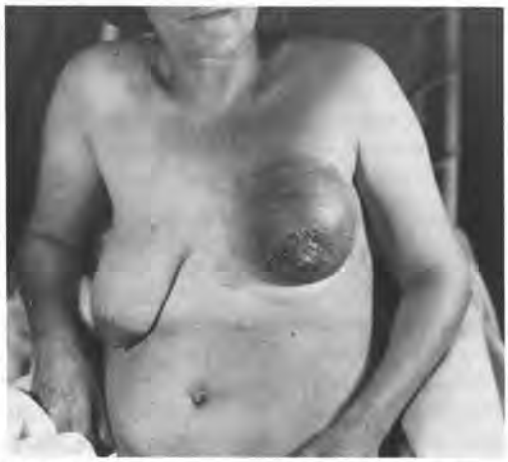


FIGURE 10-90 Inflammatory carcinoma (carcinomatous mastitis) appearing a few weeks after delivery in a 37-year-old woman.

Some (but by no means all) of the prognostic factors reported in breast carcinoma are listed in Table 10-9. It should be obvious from perusal of this table that we have entered the age of information overload with regard to breast cancer. Furthermore, we have also entered an age in which—thanks to screening programs leading to early detection—the size of the tumor presented to the pathologist has generally become smaller than that seen in past years. Therefore, the pathologist must become more selective about what to do with tumor tissue; the paradox is that, as more tissue is diverted to nonhistologic studies, fewer of the pertinent histologic observations are capable of being made.

The purpose of conveying prognostic information to the clinician treating a patient with breast cancer also has changed. Years ago, all patients underwent radical mastectomy, and prognostic information was used largely to inform the patient or her family what her likelihood of survival was. In unfavorable situations, adjuvant radiation therapy or chemotherapy might be used, but more often these modalities were used only for recurrent carcinoma. In the current era, on the other hand, prognostic factors are used prospectively to determine what type of operative treatment should be undertaken and what type of adjuvant therapy should be given. An often valid assumption is that favorable

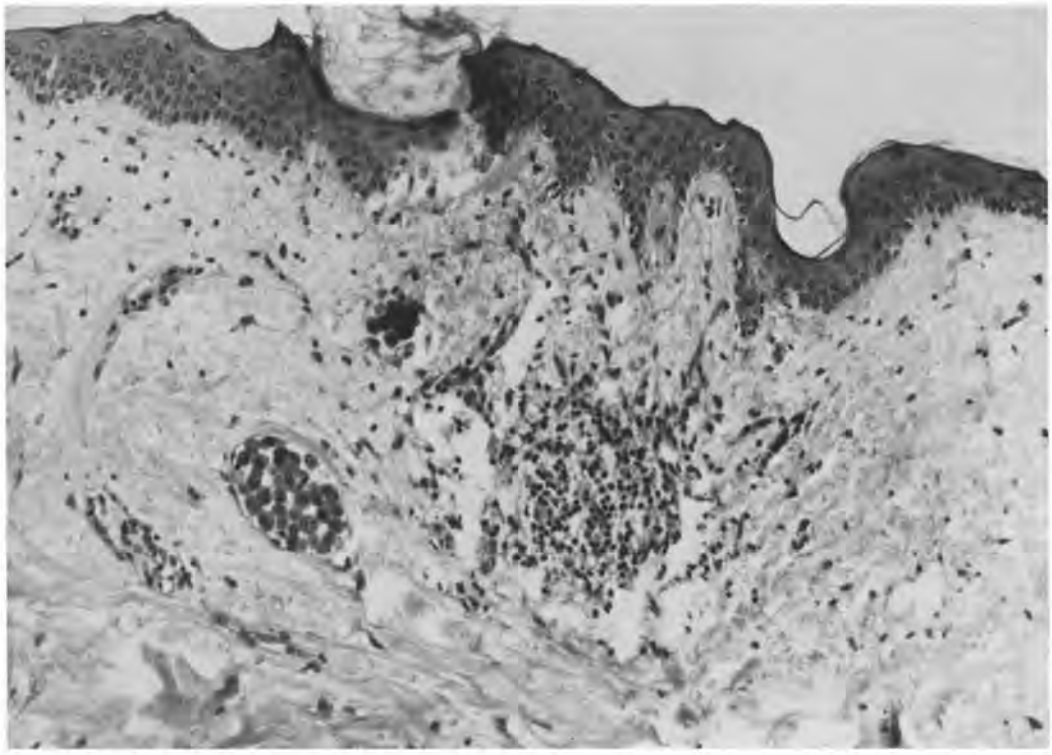


FIGURE 10-91 Inflammatory carcinoma: neoplastic infiltration of subcutaneous lymphatics.

prognostic factors will be used to define that small subset of patients who do not receive adjuvant therapy.[317–319]

Few investigations have compared the entire spectrum of prognostic factors available. Many of the published manuscripts have reported the value of only a single determination, or perhaps the comparison of a single determination with two or three others. Almost never has the cost of the various determinations been taken into account. In this era of cost-conscious medicine, we believe that cost-benefit ratios of performing specific determinations need to be investigated.

Clinical Prognostic Factors

As Table 10-9 indicates, many clinical determinations affect the prognosis of a woman with breast cancer. Older women are believed by many to have a poorer prognosis, and their general physical condition may make them ineligible for certain types of treatment. In the United States, black women with breast cancer do more poorly than white women, partially but not totally on the basis of more extensive disease at the time of diagnosis. The role of pregnancy has been debated for years, with some authorities claiming a poorer outcome for breast cancer in pregnant or lactating women and others denying this assertion.[320,321] Clinical evidence of a large tumor, a locally extensive tumor (see the discussion of inflammatory carcinoma above), or distant metastases will alter the clinical stage, which in turn will usually alter the treatment.

A few words should be included here about staging of breast cancer. Although it would appear that at least clinical staging should be uniform and noncontroversial, in actuality there are four different staging systems—the Columbia, Manchester, International, and American systems—each of which has its proponents. In general terms, both the International Union against Cancer (UICC) and the American Joint Committee for Cancer (AJCC) use a comparable TNM system, with the T stage reflecting the size of the primary tumor, the N stage the extent of regional lymph node metastases, and the M stage the presence or absence of distant metastases.[322–325] This TNM system is presented in Table 10-10. Both primary tumor factors and axillary node factors are indicative of the ability of the tumor to spread to distant sites, because the exact M status may not be known at the time of initial treatment.

"Routine" Gross and Microscopic Pathologic Prognostic Factors

The list of factors included in Table 10-9 is long but by no means comprehensive. It indicates that the final surgical pathology report in a case of breast cancer ought to comment on as many of these factors as is feasible given the specimen examined.[326] Histologic tumor type and tumor grade have been discussed above and will not be covered again here.

TABLE 10-9.
Selected Prognostic Factors in Breast Carcinoma

Clinical
Age
Race
Pregnancy/lactation
Tumor size estimate
Locally extensive tumor*
Distant metastases*
General physical condition
"Routine" Gross/Microscopic Pathology
Tumor size*
Axillary node involvement*
Histologic tumor type(s)
Histologic grade
Lymphatic invasion
Blood vessel invasion
Lymphoid host response
Pushing vs infiltrating border
Tumor necrosis
Stromal elastosis
Mitotic activity
Nuclear grade
Proportion of noninvasive carcinoma†
Resection margins†
Multifocality/multicentricity†
Other
Hormone receptors
Ploidy
S-phase fraction
Oncogene overexpression
Tumor suppressor genes
Proliferative indices
Morphometric analyses
Microvessel quantitation
Cathepsin D
P-glycoprotein

*Used in determination of stage and independently.
†To evaluate breast conservation surgery.

The tumor size should be measured carefully by the first pathologist to come in contact with the specimen, often in the intraoperative situation. The reporting of axillary node involvement is controversial, because it is not entirely clear how many nodes must be obtained by the surgeon, what techniques are necessary for the pathologist to identify them grossly, how thoroughly lymph nodes submitted for histologic examination should be sectioned, and whether immunohistochemical detection of additional metastases adds information of prognostic value.[327-329] Our general impression is that the more carefully lymph node specimens are examined, the more micrometastases will be found, and the less clinically significant this information will be.

Tumor invasion of blood vessels and lymphatic spaces provides important prognostic information, but in a different manner. Blood vessel invasion appears to be associated with poorer survival regardless of the status of the axillary lymph nodes,[269,330] whereas peritumoral lymphatic space invasion serves more as a marker of the likelihood of metastases in the axillary lymph nodes.[331,332] Both types of vascular invasion must be distinguished from shrinkage artifact around nests of tumor in stroma—a determination that is sometimes easier to speak or write about than to attempt in practice.

Mitotic activity is included in most grading systems, but it is thought by some authors to be an independent prognostic factor of major significance.[333-335] The best method of expressing mitotic activity is unclear, with both mitotic figures per 10 high-power fields and mitotic figures per 1000 cells proposed as different methods.

The other factors listed in Table 10-9 are probably of less clinical significance with respect to tumor-free survival. In conservative surgical procedures, however, the presence of an extensive intraductal component, multifocal tumor, or positive resection margins may indicate that the patient requires more extensive surgery (perhaps mastectomy) for local tumor control.[220-222,336,337] A similar approach is used to predict the efficacy of primary radiation therapy.[338,339]

Other Prognostic Factors

Table 10-9 again represents only a partial list of nonroutine factors (histologic or otherwise) for which prognostic implications have been claimed. Levels of estrogen and progesterone receptors head the list because, as specific predictors of a tumor's response to hormonal therapy, these determinations

TABLE 10-10.
TNM Clinical Stages for Carcinoma of the Breast, 1988

TNM Stage	*Primary Tumor (T) (cm)*	*Nodal Metastases (N)**	*Distant Metastases (M)*
0	In situ	No	No
I	≤ 2	No	No
IIA	≤ 2	Yes	No
	$> 2 \leq 5$	No	No
IIB	$> 2 \leq 5$	Yes	No
	> 5	No	No
IIIA	> 5	Mobile or fixed	No
	> 5	Fixed	No
IIIB	Skin or chest wall	Any	No
	Any	Internal mammary	No
IV	Any	Any	Yes†

*Pertains to ipsilateral axillary nodes unless otherwise stated.
†Including supraclavicular nodes.
Adapted from Beahrs OH, Henson DE, Hutter RVP, Kennedy BJ, eds: American Joint Committee on Cancer: Manual for staging cancer, 4th ed, pp 149–154. Philadelphia, JB Lippincott, 1992

remain the only ones that provide both prognostic and therapeutic information.[340–344] Fortunately, the biochemical method has been superseded in many laboratories by methods that can determine receptors directly on histologically examined tissue.[342–344]

DNA ploidy and S-phase fraction studies have been reported enthusiastically by many authors, but recent review articles and large studies have suggested that the data should be used with care.[345–348] These studies can be performed both on archival paraffin-embedded tissues and on FNA biopsies. The study of oncogenes and antioncogenes (tumor suppressor genes) has taken on an increased significance in breast cancer in recent years, but reservations have been expressed on the interpretation of these data as well.[349–354] Indices of tumor proliferation other than those that are determined by flow cytometry—such as bromodeoxyuridine and thymidine labeling, argyrophilic nucleolar organizer region counts, Ki67 scores, and similar techniques—are also said to provide useful information.[355–359] Again, it is still not clear whether any of these techniques offer enough additional information beyond routine studies such as tumor grade and mitotic activity to justify the increased labor and cost involved in their performance.

A similar statement might be made of morphometric techniques,[360,361] which, although microscopic pathologic determinations, are hardly routine. They certainly can be said to have less interobserver variability than the routine studies.

Microvessel quantitation is a new prognostic indicator in breast carcinoma.[362] The microvessels are identified by immunohistochemistry using antibodies to endothelial markers. Higher microvessel counts within tumors tend to be associated with a higher frequency of distant metastasis. Again, it remains to be determined whether the additional effort is justified on a cost-benefit basis.

Other markers, such as cathepsin D and P-glycoprotein, have been studied.[363,364] The latter shows some correlation with chemotherapy resistance, but more studies must be done to evaluate its overall clinical significance. Cathepsin D seems to be less important today than it was thought to be several years ago.

In summary, numerous nonroutine prognostic markers are available. With the single exception of estrogen and progesterone receptor determination, further studies are necessary to document the usefulness, reproducibility, and cost-benefit ratio for each of these markers.

The Surgical Pathology Report in Cases of Infiltrating Carcinomas of the Breast

Given the extensive therapeutic menu available to the patient and her physicians, it is more important than ever that the surgical pathology report in a case of breast cancer convey the information necessary for intelligent therapeutic decisions to be made. The compilation of this information begins when the pathologist first encounters the specimen, because at this point a careful measurement of tumor size must be made and recorded, and the decision must be made with regard to how much of the gross tumor tissue (if any) is to be sent for nonhistologic studies, and which studies are to be requested. The complexities of this decision have been discussed above, but for the purposes of the surgical pathology report it should be noted that we always include a statement about which special studies were requested. Ultimately, the results of these studies—receptors, flow cytometry, oncogenes, and so forth—are integrated into the final surgical pathology report, usually in the form of addenda.

A careful and thorough *gross description* continues to be a mainstay of the surgical pathology report in breast cancer, as in other diseases. In addition to the measurement of tumor size, the location of the tumor—relative to margins in a local excision specimen, and to breast quadrant as well in a mastectomy—should be recorded, as should grossly evident multicentricity, skin involvement, and axillary nodal metastases.

Microscopic observations to be recorded are primarily those that have been mentioned above as being of major prognostic significance. The tumor type or types (with the proportion of each if more than one type is found), tumor grade (at least in all cases of IDC-NOS), presence or absence of lymphatic and blood vessel invasion, evaluation of the host lymphoid response, and evaluation of the character of the tumor border, tumor necrosis, and stromal elastosis should be included. In institutions in which protocols call for this information separate from histologic grade, the nuclear grade of the tumor and an estimation of its mitotic activity may be recorded separately. Multicentricity or multifocality should be noted when present. In breast conservation surgical specimens, the proportion of intraductal carcinoma and its localization (within or immediately adjacent to versus distant from the infiltrating component) should be clearly stated, as should the condition of the resection margins.

Beyond these general comments, specific circumstances call for specific observations to be included in the surgical pathology report. Treatment or research protocols at certain institutions may call for information other than that mentioned here, and the pathologist at such institutions must comply with these requests. Because some patients will have had radiation therapy, hormonal therapy, or chemotherapy before the initial operative treatment, or biopsy or excision of a recurrence, it is important for the pathologist to recognize the effects of these treatments on normal and neoplastic breast tissues and to be able to differentiate residual or recurrent carcinoma from therapy-induced changes.[365–367]

Because so many factors require comment in the surgical pathology report, a standard protocol is use-

ful in most institutions, so that errors of omission are not committed. In many departments, this is done by means of a computer-generated list of observations to be made. It is important for the pathologist to be able to add additional comments when they are appropriate.

Evolution

Local tumor extension takes place by infiltration of the lactiferous ducts, the connective tissue network, and the mammary adipose tissue. Infiltration appears to occur after a much shorter noninvasive phase in ductal than in lobular carcinomas.

Lymphatic dissemination within the breast proceeds by two pathways: the centripetal route toward the areolar and retroareolar plexus, and the deep route toward the prepectoral fat (Fig. 10-92). Invasion of local lymphatics is responsible for edema, cutaneous infiltration (*peau d'orange*), and multiple foci of tumor within the breast, especially beneath the nipple. Lymphatic permeation even without lymph node invasion is a local manifestation of histologic aggressiveness, but the accurate histopathologic assessment of lymphatic involvement is difficult.[368,369] The axillary lymph nodes are invaded in most cases in older series, but in a much smaller proportion of cases detected in screening programs.[165,370,371] The clinical estimation of lymph node involvement is often inaccurate; many cases with clinically negative nodes actually have metastases. The converse is also true, in that greatly enlarged clinically positive nodes may merely be the seat of hyperplastic changes or fatty infiltration. The nodes of the internal mammary chain are also frequently involved by metastases. Their involvement appears to be favored by three factors: the presence of axillary metastases, a large (5 cm or more) primary tumor, and a tumor located centrally or medially in the breast. Intramammary lymph nodes may be present in the mammary parenchyma and should be recognized as such.[7] Their involvement by tumor has a prognostic value, particularly in stage I carcinomas. Invasion of the supraclavicular nodes signals the presence of metastases disseminated beyond the possibility of surgical cure and is a grave prognostic sign.[372] More distant nodes subsequently involved are the cervical, mediastinal, and inguinal nodes.

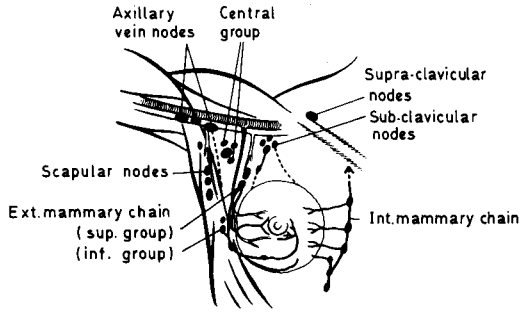


FIGURE 10-92 Diagram of the lymph nodes draining the breast.

Hematogenous metastases lead to generalized dissemination of cancer in the bones, lungs, liver, ovaries, adrenals, pleura, peritoneum, and other sites.[373,374] An interesting and unexplained phenomenon is the occasional finding of metastatic mammary cancer massively involving one organ or system (usually liver, bones, or lungs) without significant replacement of other organs.[375–377] The commonly involved bones, in decreasing order of frequency, are the vertebrae, pelvis, femur, humerus, skull, ribs, and clavicle.

Morphologic changes may be present in bone marrow adjacent to foci of metastatic tumor. These consist of medullary fibrosis and increased numbers of erythroblasts, eosinophils, plasma cells, and monocytes. The mechanism of production of this medullary reaction is not known. Micrometastases in bone marrow can be detected immunohistochemically at initial treatment in 25% of cases and are associated with decreased survival.[378]

Breast cancer metastases in bone are, like most other types of cancer, usually osteolytic, but in about 10% of cases the metastases are osteoblastic. Although prostatic carcinomatous metastases are usually blastic, breast cancer is one of the few metastatic lesions in women commonly producing this picture. Hypercalcemia is a frequent finding in mammary cancer with osseous metastases, but it is occasionally encountered in patients without osseous involvement as well; a direct metabolic action by the tumor, probably hormonal in nature, has been postulated in these cases.[373,379] Some data suggest the role of a direct route to bones by retrograde venous seeding. The presence of bone metastases caudad to the lumbosacral junction is said to be predictive of visceral metastases.[375]

Pulmonary involvement in metastatic breast cancer can take many different forms, but diffuse lymphangitic spread[380] is more common, and large solitary metastases rarer, than in other types of cancer. Pulmonary metastases are often accompanied by pleural involvement with recurrent pleural effusions that are difficult to treat successfully.[381]

Local chest wall recurrences after mastectomy arise from neoplastic cells in the deep lymphatics that migrate superficially to constitute multiple subcutaneous nodules of variable size (Fig. 10-93). They usually appear first at or near the mastectomy scar, later extending to involve the entire thoracic region. They may not become evident until several years after initial treatment, but in any event they usually herald widespread metastatic disease.[382]

These and other late recurrences constitute an important clinical and pathologic problem. It is not rare to see recurrences appearing 10 or even 20 years after initial therapy. The reasons for this peculiar behavior in certain cases are not known; exhaustion of immunologic defense mechanisms has been suggested, but this is little more than pure hypothe-

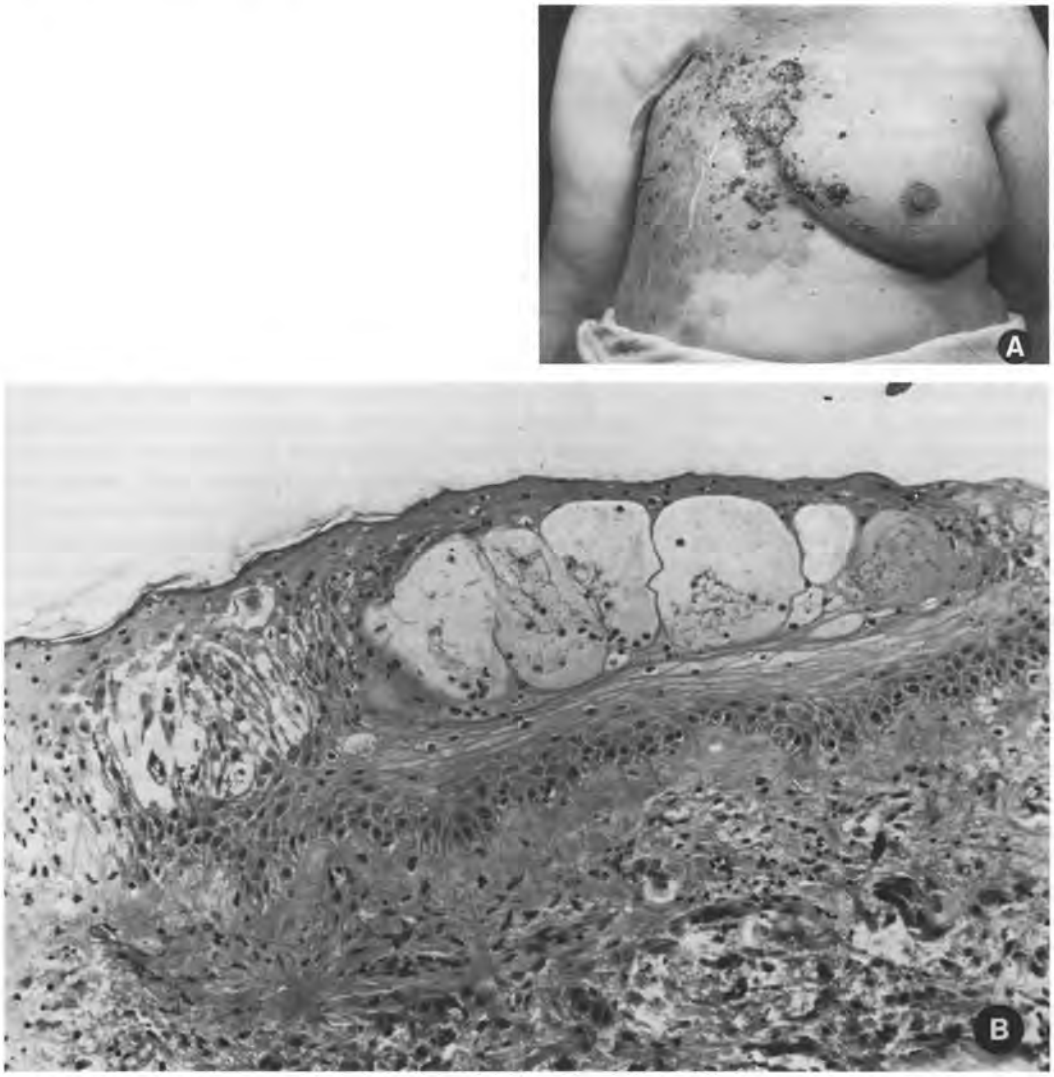


FIGURE 10-93 Infiltrating duct carcinoma. **(A)** Local cutaneous recurrence. **(B)** Dermal neoplastic invasion with bullous degeneration of overlying epidermis (local recurrence).

sis.[383] This phenomenon is much more common in breast cancer than in cancers of most other sites: between 5 and 10 years after treatment, from 14% to 18% of patients apparently cured at 5 years will develop recurrences, and virtually all of these patients will eventually die of their disease. It is meaningless to speak of 5-year "cure" in this disease.

Many of these late recurrences occur in the contralateral breast. For example, in the series of 1458 breast cancer patients followed by Robbins and Berg, 94 developed carcinoma in the opposite breast, representing a fivefold increase over the breast cancer expectancy in a similar population without the first tumor.[384] Stewart underscored this problem when he stated that "the most frequent precancerous lesion of the breast is a cancer of the opposite breast."[385] In these cases, it is not always possible to determine if this represents a metastatic lesion or a new primary cancer (Table 10-11).[386] Subserial whole organ sectioning, however, indicates that the true incidence of bilateral breast cancer may approach 100%.[216,217,219,387]

Primary malignant tumors of other sites develop in breast cancer patients as frequently as contralateral breast cancer (13% of cases in the large series of

TABLE 10-11.
Pathologic Distinction Between Second Primary Mammary Cancer and Metastasis to Contralateral Breast

Second Primary Cancer	*Metastasis*
In mammary tissue	In fat
Usual distribution (UOQ)	Midline or axillary tail
Solitary	Multiple
Infiltrating margins	Pushing margins
Any histologic type	Like primary tumor (high grade)
In situ changes present	In situ changes absent

Rosen and colleagues[388]) and are responsible for many more deaths. Most lethal nonmammary cancers in this series arose in the ovary, stomach, pancreas, and lung.

Therapy

Changes in the primary therapy of breast cancer have progressed so rapidly that it is almost useless to summarize them in great detail in any text that will be published after a hiatus of more than a few months. Nevertheless, we will attempt a brief summary of the state of the art at this time.

First, as discussed above, the primary operative treatment of operable breast cancer has changed dramatically, with few radical mastectomies being performed in the Western world, and a trend toward more and more patients having breast conservation procedures (tylectomy, lumpectomy, local excision) rather than modified radical mastectomy.[389,390] The great majority of these patients will receive postoperative radiation therapy, and some may have received preoperative radiation therapy to convert a large tumor into a smaller one more amenable to breast conservation surgery.[390,391] Preoperative chemotherapy is used in the same manner.[392] The analysis of biopsies, excisions, and fine-needle aspirations of breasts after previous chemotherapy or radiation therapy may pose diagnostic pitfalls for the pathologist.

In addition to its preoperative and postoperative adjuvant roles, radiation therapy may be the only treatment for primary breast cancer in patients deemed to be inoperable because of tumor extent or other medical factors, in patients who refuse surgical treatment, and in certain other instances.[391,393]

Another development in the treatment of breast cancer is that this neoplasm is now considered to be a systemic rather than a localized disease, even in the absence of demonstrable distant metastases. Axillary lymph node dissection is an important part of the primary surgical treatment, because the status of the nodes is a primary factor in determining whether adjuvant hormonal or nonhormonal chemotherapy will be given. Patients with involved lymph nodes are now routinely treated with chemotherapy if they are premenopausal and with tamoxifen (an antiestrogen) if they are postmenopausal, especially if their tumors contain estrogen receptors.[394,395] More controversial is the question of adjuvant therapy in the treatment of node-negative breast cancers, with some studies recommending treatment for all patients and others suggesting that prognostic factors such as tumor size, receptor status, proliferation indices, and others be used to define a subset of node-negative patients who do not need adjuvant therapy.[394–397] Particularly important in making these decisions is expanded information that is accruing concerning the risk of both nonhormonal chemotherapy and tamoxifen.[394,397,398] Tamoxifen has also been suggested as prophylaxis against the development of breast cancer in high-risk women.[204–206]

Treatment of patients with distant metastases is less controversial, although new hormonal and nonhormonal chemotherapeutic regimens are being developed at a rapid rate.[373] The median survival after the development of metastases is about 2 to 3 years in most series,[373,374,377] although the pattern of metastatic spread may result in significantly shorter or longer survival. For example, patients who develop purely osseous metastases[376,377] tend to have much longer survival than patients whose metastases are predominantly visceral. Unlike primary breast cancer, there are studies suggesting that the survival of patients with metastatic breast cancer has not increased significantly over the past 25 years.[374]

MALIGNANT NONEPITHELIAL NEOPLASMS

Malignant Soft-Tissue Tumors (Sarcomas)

Primary sarcomas of the breast are rare (0.6% of mammary malignant tumors at the Institut Bordet and less than 1% in other reported series).[399] In most series, the most common form is malignant phyllodes tumor (periductal fibrosarcoma and liposarcoma). These tumors have been discussed in an earlier section.

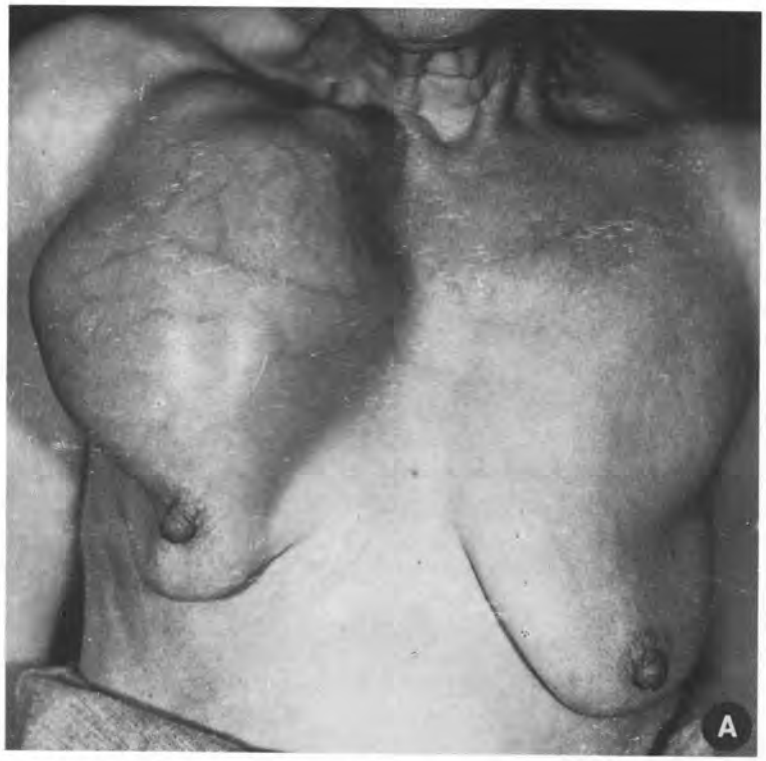
Of the remaining primary sarcomas of the breast, the most common in older series is fibrosarcoma[400] and in recent series malignant fibrous histiocytoma.[399] Jones and colleagues have suggested that these two neoplasms be classified together because they have many features in common and a single tumor may contain foci resembling the classic appearance of each.[401]

As a group, the mammary sarcomas share certain clinical features. They tend to present as bulky masses, usually without evidence of metastatic dissemination. Axillary nodal metastases are rare, and dissemination occurs almost exclusively by the hematogenous route.

These tumors often recur locally before they metastasize, and local control is often difficult to obtain with surgical procedures short of mastectomy. Finally, unlike mammary carcinoma, the vast majority of all recurrences occur within the first 5 years after initial treatment.

Fibrosarcoma and Malignant Fibrous Histiocytoma

Although the relative proportions of these two tumors vary in different reported series, they represent together more than 50% of all pure mammary sarcomas.[399–401] As with other sarcomas, they present as large, firm, poorly limited, rapidly growing masses (Fig. 10-94).



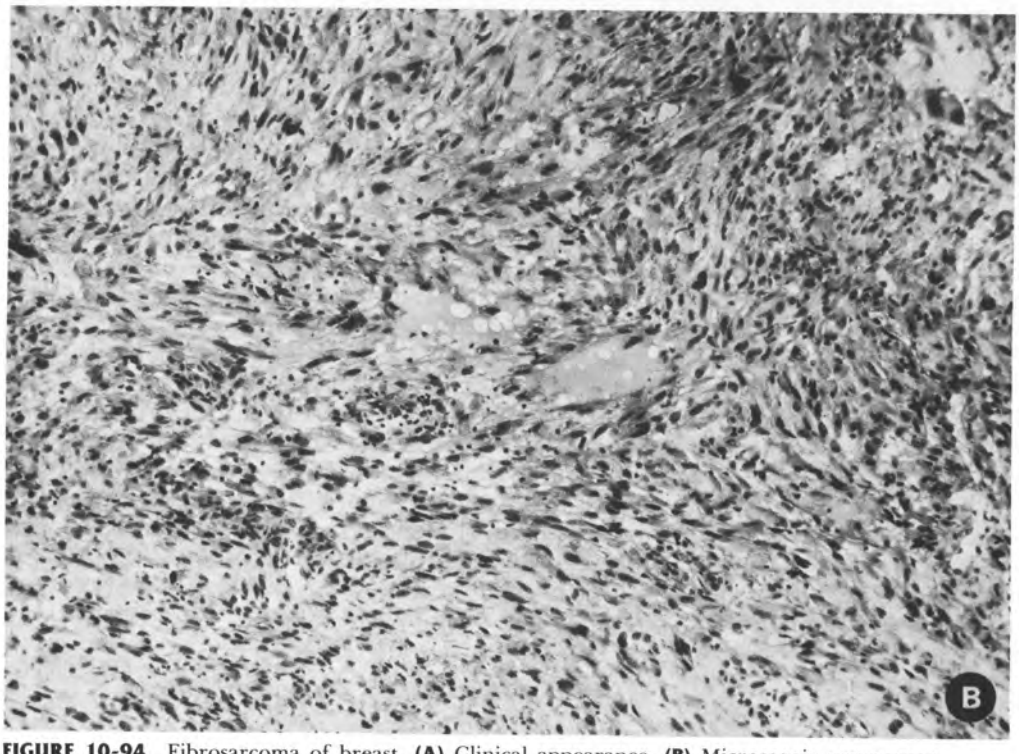


FIGURE 10-94 Fibrosarcoma of breast. **(A)** Clinical appearance. **(B)** Microscopic appearance.

Microscopically, they are composed of fusiform cells with hyperchromatic, often bizarre nuclei, with variable numbers of mitotic figures. The cells are arranged in a herringbone or storiform pattern according to the fibrosarcomatous or malignant fibrous histiocytomatous differentiation. Jones and associates found that the herringbone pattern was associated with a more favorable prognosis, as was low-grade atypia and mitotic activity.[401]

Liposarcoma

Liposarcomas form large, rounded masses of soft to firm yellow tissue. Histologically, they resemble the myxoid or the pleomorphic type of liposarcoma seen elsewhere. Unlike the other mammary sarcomas, they display a tendency to metastasize by the lymphatic as well as the hematogenous route.[402]

Other Nonvascular Sarcomas

Stromal sarcoma of the breast is a term that was popularized by Berg and colleagues in 1962 to unify the diagnosis of all connective tissue sarcomas of the breast other than malignant phyllodes tumor.[403] More recent studies suggest—and we agree—that it is more useful to classify mammary sarcomas as accurately as possible according to histopathologic type.[399,404] In addition to the forms mentioned above, rare examples of leiomyosarcoma,[405] clear cell sarcoma,[399] malignant peripheral nerve sheath tumor,[399] and alveolar soft part sarcoma[399] have been reported. Occasional osteosarcomas and chondrosarcomas have been described, but these may represent matrix-forming metaplastic carcinomas, as recently characterized by Wargotz and Norris.[298]

Differential Diagnosis

The differential diagnosis of the sarcomas mentioned thus far, in addition to each other, is primarily with metaplastic carcinomas and malignant phyllodes tumors, both of which have been described in more detail in earlier sections of this chapter. A careful search of many sections for histologically malignant (in the former case) or benign (in the latter) epithelial elements is essential to the correct diagnosis. Immunostaining for epithelial markers may be necessary to rule out the diagnosis of one of the forms of metaplastic carcinoma.

Other differential diagnostic possibilities, particularly for the low-grade sarcomas, include benign lesions such as fibromatosis, fasciitis, and fat necrosis. These are also discussed earlier in this charter and in standard texts of soft-tissue tumor pathology.

Angiosarcoma

Angiosarcoma of the breast, although rare, is one of the most lethal of all mammary neoplasms.[406] Although it was once taught that all vascular tumors of the breast proper (as opposed to the overlying skin or underlying chest wall) were sarcomatous, it is now known that a variety of benign vascular and pseudovascular lesions can be seen in the breast.[116–122] These are discussed in greater detail in an earlier section of this chapter. Unlike these lesions, angiosarcomas almost always present as large palpable masses of firm consistency and pink color, honeycombed with darker red foci. They consist of blood vessels the lining cells of which show varying degrees of differentiation (Figs. 10-95 through 10-97). Several studies have shown a definite relation between tumor

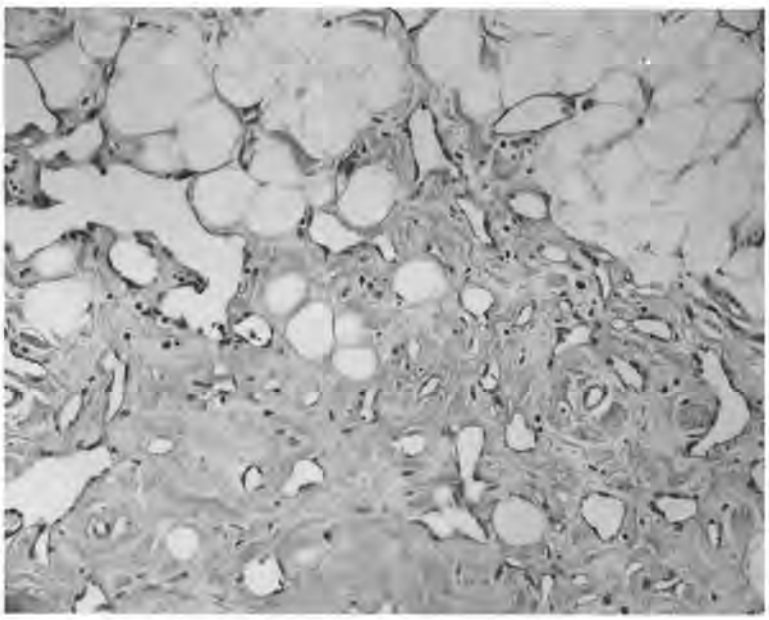


FIGURE 10-95 Well-differentiated angiosarcoma. The blood vessels in this field are infiltrative and irregular in shape, but they lack papillary or solid features and atypia.

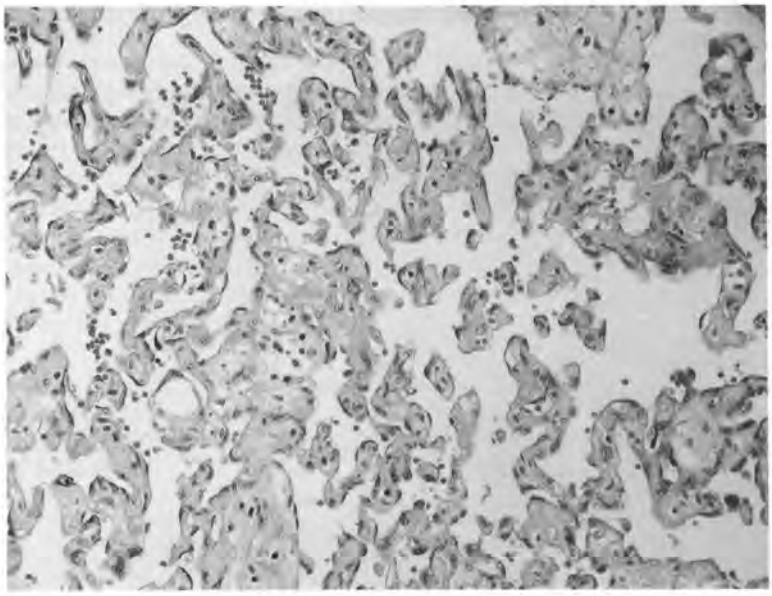


FIGURE 10-96 Moderately differentiated angiosarcoma. Papillary tufting is prominent, but cytologic atypia is still slight.

grade and prognosis, with a poor survival rate (20% or less) for poorly differentiated tumors.[407,408] Well-differentiated angiosarcomas may be difficult to differentiate from benign hemangiomas; the main features favoring a diagnosis of angiosarcoma are a tumor size large enough to form a palpable mass and the presence of communicating vascular channels.

Most patients with mammary angiosarcoma are young, and some have been pregnant at the time of diagnosis, raising the suspicion of hormone dependence. Cases with estrogen receptors have been reported, but it is not clear whether the receptors were actually in the tumor cells or in infiltrated benign mammary tissue.[409]

Angiosarcomas of the breast have been reported after lumpectomy and radiation therapy for breast carcinoma,[410,411] but these appear to be cutaneous rather than true mammary angiosarcomas. Cutaneous angiosarcoma is obviously part of the differential diagnosis of mammary angiosarcoma, as are the benign vascular lesions mentioned above. An additional differential diagnostic possibility is an acantholytic squamous cell carcinoma, such as that illustrated in Figure 10-85. Immunostains for endothelial and epithelial markers are important here.

Postmastectomy Lymphangiosarcoma

Postmastectomy lymphangiosarcoma (Stewart-Treves syndrome)[412] was first described in 1948, and subsequently close to 200 cases have been reported. Although not a breast tumor per se, it merits consider-

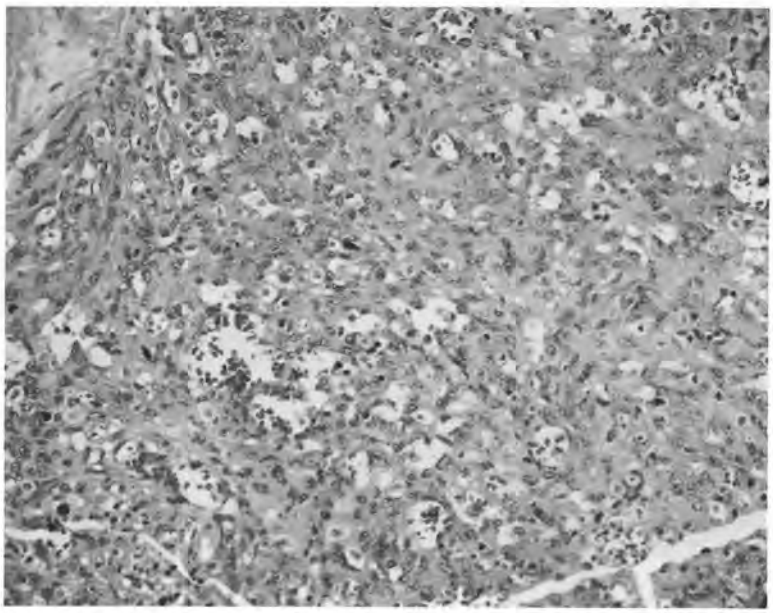


FIGURE 10-97 Poorly differentiated angiosarcoma. Tumor growth is largely in the form of spindled cells with nuclear atypia and mitotic figures. A background of blood-filled vascular channels identifies the tumor as angiosarcoma.

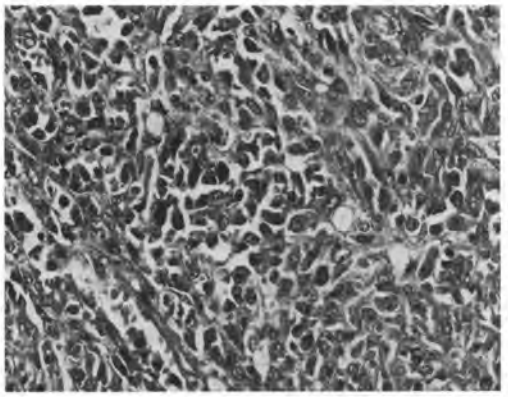


FIGURE 10-98 Postmastectomy lymphangiosarcoma: microscopic appearance.

ation here because of its tendency to develop in lymphedematous arms after mastectomy. Considerably rarer is the appearance of this tumor in lower extremities that are the site of chronic lymphedema of different etiology, but this occurrence supports the concept of the etiologic significance of lymphatic stasis. The lesion first presents as a cutaneous ecchymosis or nodule, rapidly becoming multiple and coalescent; reported cases have appeared an average of almost 10 years after mastectomy. Histologic examination usually easily demonstrates the lymphatic character of the tumor (Fig. 10-98), but a small biopsy specimen may occasionally be confused with metastatic mammary carcinoma. Ultrastructural and immunohistochemical studies may be necessary in such cases to confirm the vascular and nonepithelial nature of the tumor.[413,414] The prognosis is poor.

Lymphoid and Hematopoietic Neoplasms

Mammary localizations of malignant lymphomas[415–417] and leukemic infiltrates[418] are not rare, but they usually are part of the spectrum of disseminated malignant disease. We have seen cases of lymphoma that were difficult to differentiate from lobular, lipid-rich, or medullary carcinoma (Fig. 10-99). Immunostains for leukocyte common antigen and epithelial markers assist in this differential diagnosis. A chloracetate esterase stain identifies the granules of a granulocytic leukemic infiltrate. So-called lymphoid pseudotumors are occasionally encountered in the breast; they are characterized by a pleomorphic but benign cytologic appearance and the frequent formation of follicles with germinal centers.[419] They are benign. More easily differentiated lymphoid lesions are benign intramammary lymph nodes[7] and lymphocytic mastopathy.[46,47]

The *prognosis* of malignant lymphomas depends on the clinical stage and the histologic type, with primary mammary lymphomas of low stage and low histologic grade having a more favorable prognosis. These primary lymphomas are thought to be of B cell type, and may originate in preexisting lymphocytic mastopathy.[415,417]

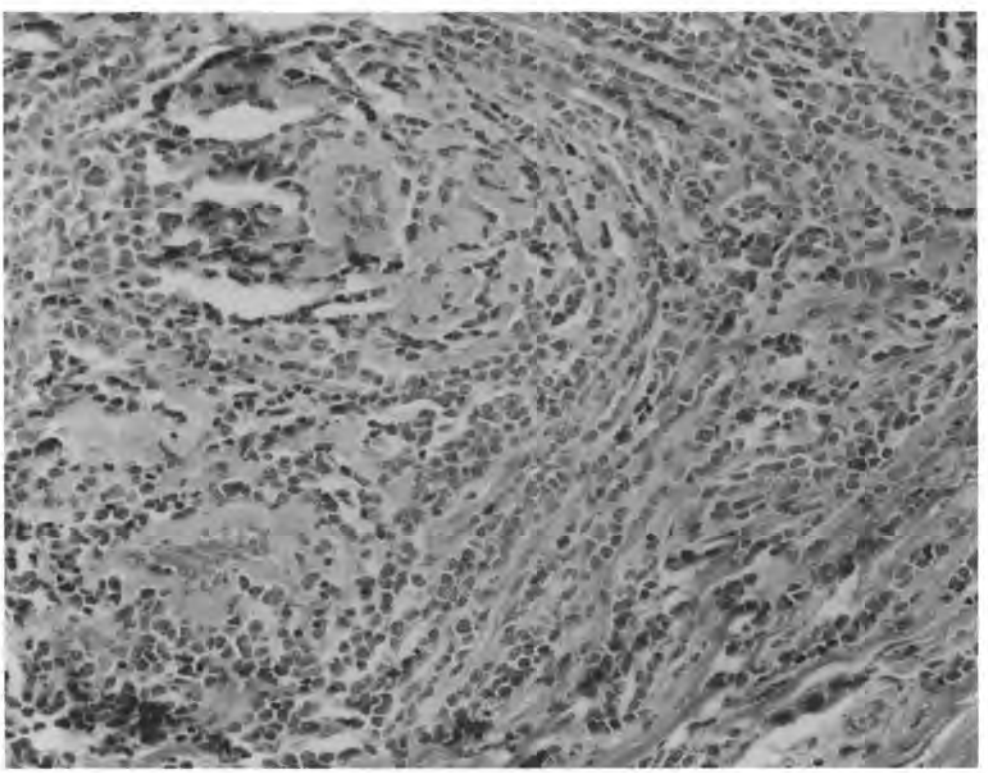


FIGURE 10-99 Malignant lymphoma, small cell type, of breast. Tumor cells swirl around residual benign ducts in the same manner as in classical infiltrating lobular carcinoma. The tumor cells were immunohistochemically positive for leukocyte common antigen and negative for cytokeratins and epithelial membrane antigen.

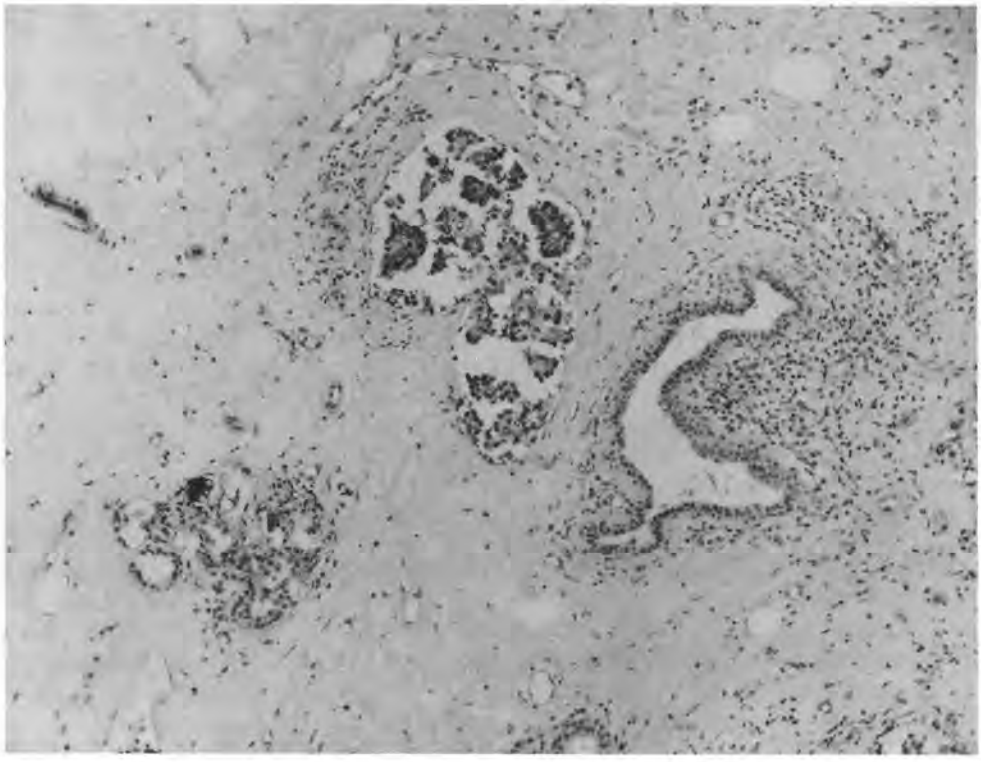


FIGURE 10-100 Metastatic serous carcinoma of ovary in breast tissue. Note involvement of periductal vascular space.

TUMORS METASTATIC TO THE BREAST

Metastatic involvement of the breast is uncommon as an autopsy finding and is a great rarity as a clinical phenomenon; only a few dozen cases of the latter have been reported, whereas the former occurs in about 5% of patients dying of malignant neoplasms other than breast cancer.[420,421] The most common primary tumors seen, other than malignant lymphomas and leukemias, are carcinomas (of the stomach, uterus, ovary, and thyroid) and malignant melanomas. These are generally recognized by the clinical history, the absence of a single dominant mass, and the presence of diffuse lymphatic or vascular infiltration (Fig. 10-100). Primary tumors of the breast—both carcinomas and sarcomas—appear simultaneously or at a later date in the opposite breast with a much greater frequency than do primary tumors of other organs.[386,387]

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11 Extragenital Pathology in Obstetrics and Gynecology

Hernando Salazar and Richard J. Stock

Most disease processes can occur in women of any age, regardless of their reproductive state. However, there are specific extragenital problems that occur as causes, complications, or secondary effects of gynecologic or obstetric conditions and may alter reproductive function. This chapter discusses the most important extragenital problems related to gynecologic and obstetric practice, focusing on those that may come to the pathologist by way of biopsy or autopsy material. The problems are presented by organ system.

ENDOCRINE SYSTEM

About 30% of patients with amenorrhea-galactorrhea syndrome also have a prolactin-producing adenoma of the pituitary gland.[1-4] Hyperprolactinemia also results from blockage or destruction of the prolactin-producing dopaminergic centers or their hypothalamic-hypophyseal tracts by tumors (eg, craniopharyngioma, meningioma, or pituitary neoplasms other than prolactinomas), inflammatory lesions (eg, sarcoid or tuberculous granulomas), degenerative lesions (eg, amyloidosis), traumatic or surgical stalk transection, or irradiation.[5,6] Hyperprolactinemia may be secondary to hormonal therapy (eg, estrogens, oral contraceptives, or thyrotropin-releasing hormone), anesthesia, dopamine or dopamine-receptor blocking agents (eg, reserpine, methyldopa, MAO inhibitors, phenothiazines, and opiates), hypothyroidism, renal failure, chronic nipple stimulation, or ectopic production of prolactin by neuroendocrine tumors (eg, lung and kidney).[6] Most of these patients are infertile but regain their fertility and can become pregnant once prolactin levels drop close to normal after surgical (transsphenoidal partial hypophysectomy) or medical (bromocriptine) treatment.[7-9]

In the past, pituitary tumors associated with amenorrhea-galactorrhea syndrome were usually classified as "nonfunctional" or "chromophobic" adenomas because they were formed by degranulated cells that did not stain with the standard methods.[10] It was not until 1971, when the identification of prolactin-producing cells of "lactotrophs" by immunoassay was standardized, that prolactinomas were recognized as functional neoplasms capable of causing hyperprolactinemia.[11-14]

Prolactin-producing adenomas are the most common tumors of the human pituitary gland.[15,16] Most are microadenomas measuring less than 1 cm in diameter, but they may be larger (macroadenomas) and capable of causing deformation of the sella or compression of the hypothalamus, optic chiasm, and other neighboring structures. Macroadenomas may be diagnosed clinically and radiologically by standard radiographic techniques. The diagnosis of microadenomas requires computed tomography (CT) scans because they usually do not produce deformities of the sella.

Before the introduction of bromoergocriptine (bromocriptine), a potent antiprolactin agent that is now the preferred method of treatment of prolactinomas, the only therapeutic approaches were surgery and radiation.[17] Surgical removal of the tumor by partial transsphenoidal hypophysectomy has been the source of specimens suitable for biochemical and

morphologic studies. Prolactin-secreting pituitary adenomas are usually "chromophobic" with standard stains because they contain scant secretory granules (Fig. 11-1). The prolactin content of the neoplastic cells is high, although it does not take the form of granules.[18,19]

Ultrastructurally, the cells are large and oval with irregular nuclei and abundant cytoplasm rich in mitochondria and rough endoplasmic reticulum. There is a prominent Golgi system. The secretory granules usually are scant and small (<100 nm in diameter), in sharp contrast to the characteristic large and irregular granules of the normal lactotrophs (600 to 800 nm in diameter). The neoplastic lactotrophs apparently are incapable of forming normal granules. The high prolactin content is present as particulate or homogeneous, medium-dense material within the endoplasmic reticulum cisternae and Golgi apparatus or as discrete droplets with abnormal granular organization (Fig. 11-2). The secretory granules are frequently released ectopically into the intercellular spaces rather than through the vascular pole of the cells into the capillaries.[18,19]

The content of prolactin in the tumor can be assessed qualitatively by immunocytochemical labeling with specific antiprolactin antibodies.[20] It can be assessed quantitatively by incubation of tumor fragments and measurement of hormone levels in the effluent, expressed as nanograms per milligram of tissue.[18]

There is moderate hyperplasia of the nonsecretory stellate cells surrounding the microadenomas, the significance of which is not clear.[21] Significant hyperplasia of lactotrophs within the parenchyma surrounding the adenoma may account for the residual elevated serum prolactin levels observed after "complete" removal of the tumors.[22,23]

The pituitary gland normally increases in size during pregnancy. The size increase is probably due to a physiologic hyperplasia of lactotrophs and somatotrophs, with corresponding increases in the levels of prolactin and growth hormone secondary to the normal increase of placental estrogen during pregnancy.[6] Estrogen seems to exert direct and indirect (antidopaminergic) stimulating actions on lactotrophs. This may explain the chronic hyperprolactinemia observed in patients receiving hormone contraceptives. However, galactorrhea is absent in these cases, probably due to the inhibitory effect of estrogen and progesterone on the breast's lactogenic functions. Contrary to previous indications that oral contraceptives or estrogen therapy would result in the development of prolactinomas,[24–28] multicenter studies with large numbers of patients have failed to prove such a cause-effect relation.[29,30]

Postpartum Pituitary Necrosis (Sheehan's Syndrome)

Although pituitary necrosis resulting in hypopituitarism had been known as part of the so-called Simmonds' syndrome (panhypopituitarism with cachexia), it was Sheehan who first recognized the problem of an ischemic necrosis or infarction of the pituitary gland during the postpartum period (Sheehan's syndrome).[31] The mechanism by which hypophyseal infarction sometimes occurs in these patients seems to be part of a general circulatory deficit secondary to postpartum uterine bleeding. Systemic

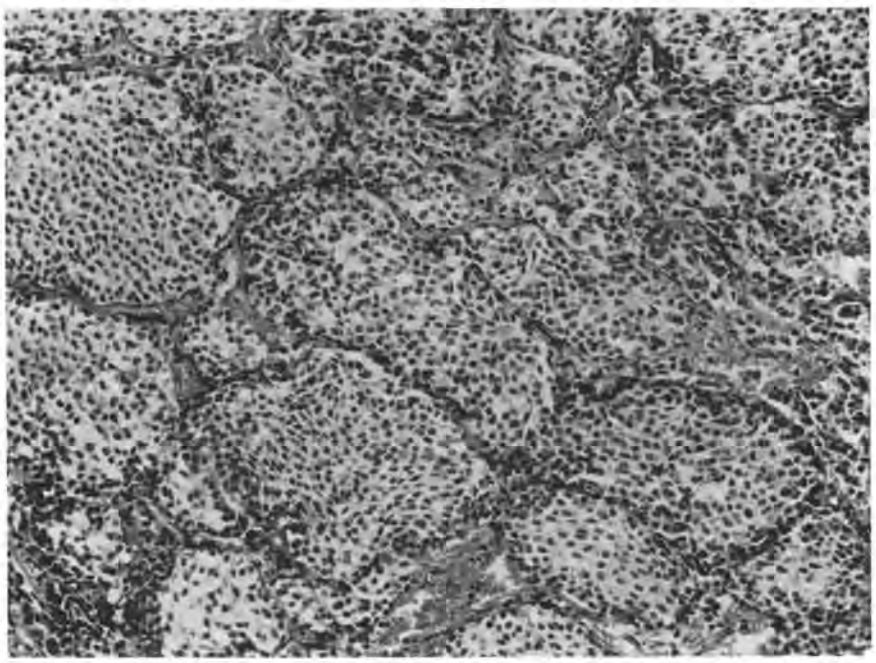

FIGURE 11-1 Panoramic view of a pituitary adenoma removed by transsphenoidal partial hypophysectomy from a 25-year-old patient with hyperprolactinemia, galactorrhea, and history of oral contraception. The tumor is lobulated and formed by cords and masses of monotonous, uniform cells with clear unstained (degranulated) cytoplasm. High prolactin content was demonstrated by a prolactin-specific peroxidase-antiperoxidase (PAP) method.

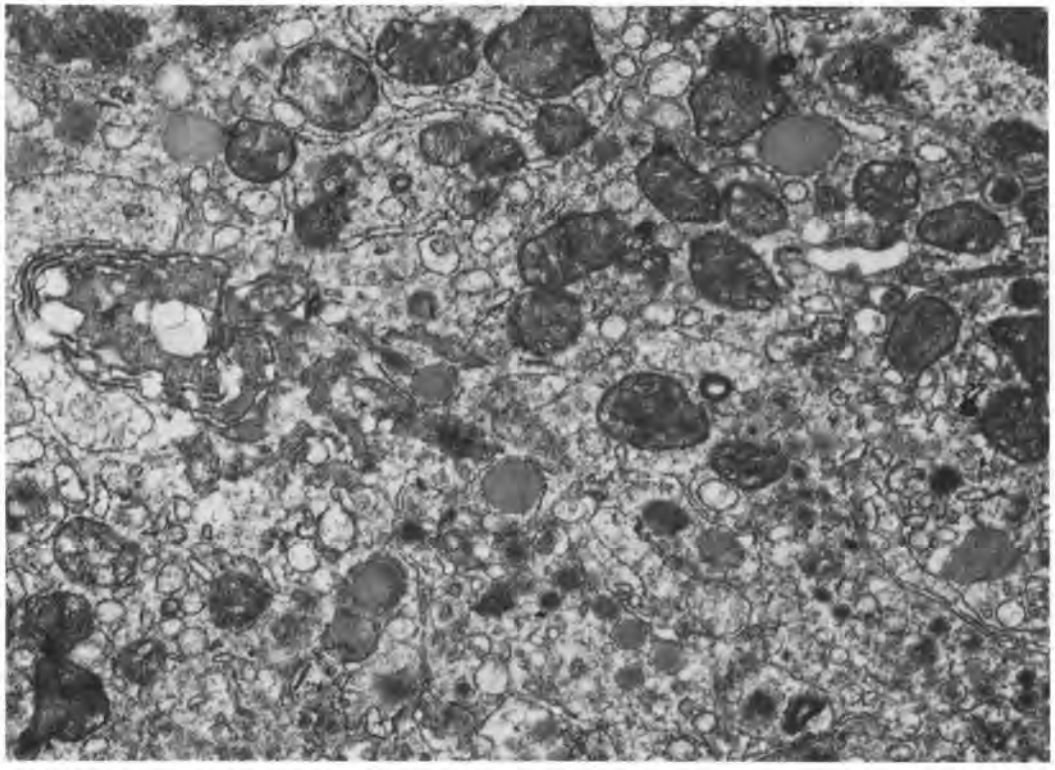

FIGURE 11-2 Portion of lactotroph in a prolactin-producing microadenoma removed from a 22-year-old woman with galactorrhea-amenorrhea. Serum prolactin levels were 490 ng/mL (normal < 25 ng/mL) and tumor levels were 1.24 μg/mg of tissue (normal <0.37 μg/mg). Note well-developed organelles, small membrane-bound secretory granules, and poorly formed granules with decreased density and amorphous material of similar density in Golgi structures. These suggest abundant hormonal content but abnormal packing of secretory granules (×47,000).

vascular collapse and shock are, in turn, probably related to hypofibrinogenemia and disseminated intravascular coagulation. The acute infarction of the hypertrophied gland at the end of gestation results in rapid loss of most or all of the hypophyseal trophic hormones. Often, the entire gland is involved, although the neurohypophysis is sometimes preserved.

The magnitude of the clinical picture depends on the extent of the infarct. If more than 75% of the gland is necrotic, the result is severe panhypopituitarism with morphologic changes and functional deficits of the target organs.[32–35] Lactation is terminated, and the thyroid, adrenals, and gonads atrophy. This is followed by amenorrhea, loss of libido, loss of pubic and axillary hair, trophic and pigmentary changes of the skin, general muscle weakness, decreased tolerance to cold temperature, and other conditions of endocrine deficit. If the posterior lobe is compromised, the problem is complicated by diabetes insipidus.

Grossly, the pituitary gland appears enlarged and congested and has a burgundy-red discoloration. It is friable in the necrotic areas if the infarction is recent. After some time, healing by fibrosis occurs, and the gland appears small, firm, gray-brown, and irregular due to scarring. Microscopically, the necrotic areas are replaced by dense, poorly vascularized fibroconnective tissue with islands of preserved parenchyma usually containing largely degranulated cells (Fig. 11-3). The noninfarcted areas may show compensatory hyperplasia and hypergranulation. Recovery is highly variable.

Diabetes Mellitus and Pregnancy

The advances of the past decades in the understanding of diabetes and abnormal glucose metabolism have resulted in great improvements in the management of the pregnant diabetic patient. These improvements have translated into decreased fetal and neonatal morbidity and mortality. Before 1922, no infant of a diabetic mother survived.[36] With the availability of insulin, the infant survival rate improved to about 70% in 1960 and to more than 90% in the 1980s, reaching the neonatal mortality rate of the general population.[37] Likewise, the recognition and adequate management of patients with so-called diabetes of pregnancy (transient abnormal glucose metabolism of gestation), which occurs in about 2.5% of all pregnancies, have prevented maternal and fetal morbidity and death.

Adult-onset (type II) diabetes differs etiologically and pathogenetically from juvenile, insulin-depen-

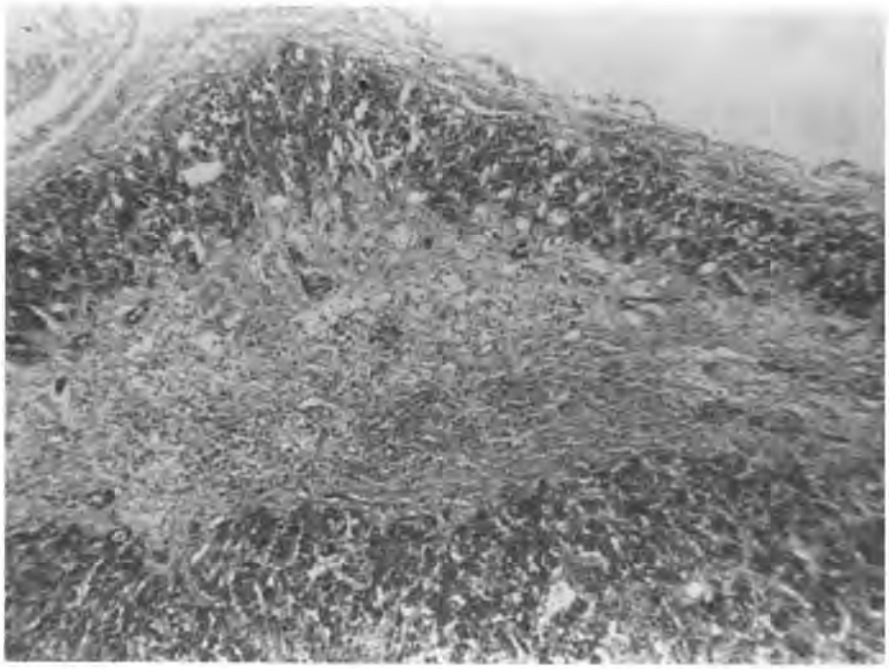

FIGURE 11-3 Adenohypophysis with a large central infarct in the process of healing. Note the density of cells in the preserved areas and fibroblastic proliferation in the infarcted area.

dent (type I) diabetes. In adult-onset diabetic pregnancies, decreased insulin secretion and markedly reduced insulin sensitivity are pathophysiologically important, independent of the effect of obesity.[38,39] The main pathogenetic mechanism in juvenile diabetes, on the other hand, is an absolute deficiency of insulin.

During pregnancy, whether normal or diabetic, metabolic changes occur in a biphasic fashion, with significant changes at about the 27th week of gestation (the beginning of the third trimester). These changes are related to factors of maternal fuel utilization, such as storage of adipose tissue, insulin secretion and resistance, glucose utilization, and concentrations of high-density lipoprotein cholesterol.[40,41] At about the 27th week, the diabetic mother switches from a glucose-based to a lipid-based source of energy from stored reserves and insulating fats. This saves glucose and other nutrients for fetal nutrition and growth, with a significant increase in transplacental transport to the fetus. This may explain the fetal macrosomia of diabetic pregnancies, with uncontrolled glucose assimilated by the fetus. Infant survival is directly related to the degree of control of maternal glucose.[42] At the time of metabolic transition in the mother, gestational diabetes usually becomes apparent or ketoacidosis occurs in the pregnant diabetic. The management of the diabetic pregnancy, therefore, is geared to the regulation of concentrations of plasma glucose and other circulating fuels.

Microvascular disease or diabetic microangiopathy is the most significant complication, resulting in renal, retinal, cardiac, cutaneous, and soft-tissue chronic ischemia.[43]

Diabetic Nephropathy

Diabetic nephropathy is a progressive disease of the microvasculature of the glomerulus that results in increased permeability to protein, glomerular scarring, and, finally, irreversible peripheral edema and chronic progressive renal failure.[44–46] The risk of developing nephropathy varies from 30% to 50% in type I and type II diabetes. The incidence of nephropathy among pregnant diabetic women is about 5% in the general population and 10% to 25% in obstetric referral centers.

Histologic changes in the kidney precede the clinical diagnosis of nephropathy by several years. These changes consist primarily of basement membrane thickening of afferent and efferent glomerular arterioles. Nodular or diffuse intercapillary sclerosis of the glomerular tuft results from increased accumulation of plasma proteins on the capillary basement membranes and the mesangium (Fig. 11-4). Progression of these abnormalities leads to gradual glomerular sclerosis, secondary tubular atrophy, and chronic renal failure. By the time azotemia appears and creatinine clearance drops to less than 25 mL/min, hypertension occurs and accelerates the progression of the vascular disease, contributing to mortality.

Diabetic nephropathy has implications for pregnancy mainly because it is complicated by hypertension and results in a high incidence of preeclampsia, accelerated hypertension, fetal distress, fetal growth retardation, and perinatal mortality. Pregnancy in itself apparently does not accelerate or worsen the progression of nephropathy in the diabetic patient. The main objective in the management of these

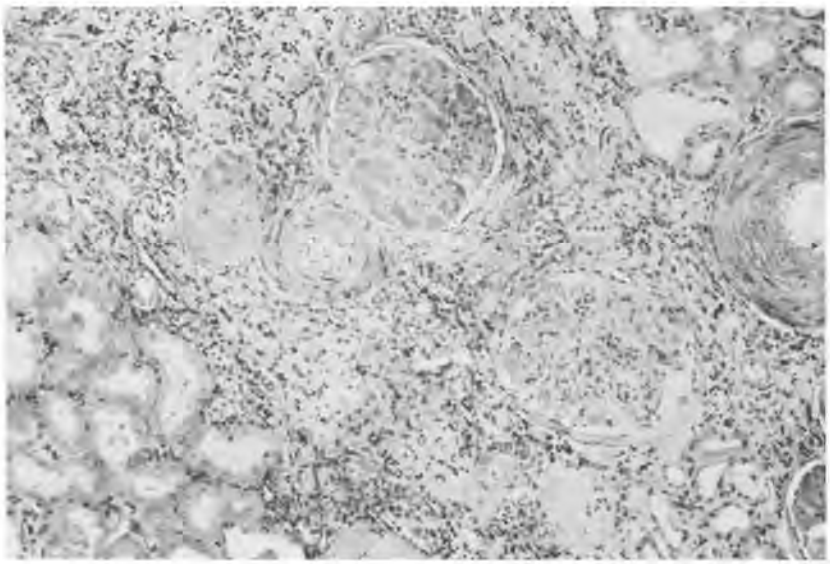

FIGURE 11-4 Diabetic nephropathy, showing both nodular glomerulosclerosis (Kimmelstiel-Wilson lesion) and severe arterial and arteriolar sclerosis. (Courtesy of Dr. A. Andrew Abraham, George Washington University, Washington, DC)

pregnancies is to save the fetus and the mother, and preterm delivery is frequently required. Improvements in perinatal and neonatal intensive care facilities have greatly reduced the perinatal morbidity and mortality associated with the preterm delivery of infants of diabetic mothers. The incidence of spontaneous abortions and congenital malformations is much higher in diabetic mothers with poor glycemic control.[47]

Diabetic Retinopathy

Retinopathy is the most prevalent form of microvascular lesion in diabetics.[48,49] It is generally divided into three main types according to the kind and magnitude of the lesions:

1. Nonproliferative or background retinopathy is characterized by microaneurysms, microhemorrhages, hard exudates, and edema. Unless these lesions occur in the perimacular area, vision is not affected.
2. Preproliferative retinopathy is characterized by intraretinal microvascular abnormalities, microhemorrhages, and soft or "cotton-wool" exudates. This lesion may progress to neovascularization.
3. Proliferative retinopathy is the final stage, with extensive neovascularization at the disc and elsewhere. Fibrosis, preretinal and massive vitreal hemorrhages, and retinal detachment result in permanent loss of vision.

The pathogenesis of diabetic retinopathy is not clear. It does not seem to be based, as is the case elsewhere, on thickening of the capillary basement membranes. Instead, it is based on a breakdown of the blood-retinal barrier with vascular damage, leakage of blood and plasma proteins, hyperglycemia-induced hypercoagulation, and decreased fibrinolysis, with endothelial deposits, microthrombosis, and proliferation of pericytes and fibroblasts.[50]

The role of pregnancy as a complicating factor in diabetic retinopathy is not clear. Apparently, it depends on the magnitude of the problem. Background nonproliferative retinopathy progresses in severity during pregnancy, with a maximum peak in the third trimester, and regresses postpartum. Problems occur in pregnant patients with active proliferative retinopathy, mainly due to intraocular hemorrhage, and blindness may occur during pregnancy. The proliferating neovascularization of the disc and other areas progresses through pregnancy if untreated. Laser-beam pararetinal photocoagulation and therapeutic abortion are indicated in cases of florid discal neovascularization in early pregnancy. Cases in therapeutic or spontaneous remission at the onset of pregnancy do not seem to progress to catastrophic stages.

Because excessive elevation of blood glucose levels for prolonged periods is the most important factor in the origin and development of diabetic retinopathy, strict glycemic control is the most crucial therapeutic measure for the prevention and control of retinal sequelae in diabetic patients. The following risk factors have been identified in diabetic pregnant subjects:[48]

- Pregnancy per se accelerates the natural progression of retinopathies.
- Hyperglycemia and hypertension potentiate this acceleration.
- The rate of acceleration depends on the duration of diabetes and the state of the retina at the onset of pregnancy.
- Rapid normalization of blood glucose may be counterproductive, requiring intensive surveillance and aggressive retinal therapy.

VASCULAR SYSTEM

Thromboembolism Associated With Pregnancy and Contraception

Virchow first described clots in the lungs that had arisen elsewhere in the body, excluding the pulmonary arteries, and termed this process *embolia.*[51] He postulated that the intravascular clots were the result of vascular trauma, vascular stasis, and a state of hypercoagulability (Virchow's triad). Although our knowledge of the clotting mechanism has grown by leaps and bounds in the last few decades, our concepts of the actual causes of thrombosis and embolization still remain fairly nonspecific and within the boundaries of Virchow's triad.

There are several possible risk factors for thrombosis and embolization in the obstetric or gynecologic patient. In general, pregnancy has been viewed as a high-risk state.[52,53] However, it appears that the period of highest relative risk is the postpartum period; the antepartum period does not appear to be associated with excess risk. In contrast to popular belief, there is no evidence that varicose veins constitute a positive risk factor. Prolonged immobilization, pelvic surgery, obesity, increasing age, and malignancy do constitute increased risks. It has been postulated that oral contraceptives and estrogens, when used for lactation suppression, are associated with increased risks for thromboembolic phenomena.[54–57] Peculiar to pregnancy and the use of oral contraceptives are the rare occurrences of highly localized vascular intimal proliferation, sometimes with thrombosis, that may involve the pulmonary, renal, hepatic, ovarian, and intracranial vessels, including the sagittal sinuses (Fig. 11-5). Pulmonary embolization, on the other hand, is a problem of major clinical significance in obstetric practice, particularly in the postpartum period. Although the incidence of death secondary to pulmonary embolism is decreasing, it is still the second leading cause of death in the post-cesarean section patient.[58]

Of Virchow's triad, vascular trauma has predominated as the focal point in thrombosis research. Major steps in the initiation of localized coagulation are localized platelet aggregation, subsequent release of adenosine diphosphate, and availability of platelet factor 3. There is little evidence that this chain of events is actually responsible for localized thrombosis in humans. Rather, it is believed that vascular stasis and altered coagulability play major roles because they occur in the area of the venous valves. In the postpartum state, significant alterations occur in the diameters and pressures of the ovarian veins, which are important sites of thrombosis. Principles other than changes in procoagulant and anticoagulant factors must be considered. Rheologic aspects may play a significant role, especially when considering the changing vessel diameters and flow patterns.[59] Hypercoagulability in pregnancy is thought to exist and may be related to the increases in all the plasma factors involved in the coagulation mechanism, except for factors XI and XIII.

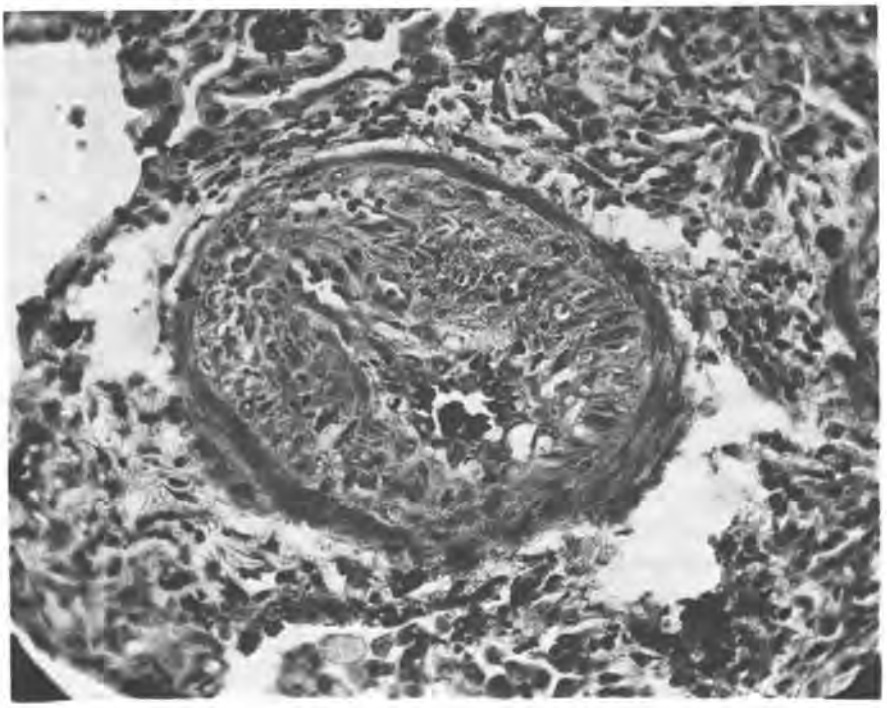

FIGURE 11-5 Branch of a pulmonary artery in a pregnant woman: marked cellular intimal proliferation with almost complete luminal obliteration. (Irey NS, Norris HJ: Intimal vascular lesions associated with female reproductive steroids. Arch Pathol 96: 227–234, 1973. (Courtesy of Dr. Henry J. Norris and the Armed Forces Institute of Pathology, Washington, DC)

Oral Contraception and Cardiovascular Disease

Initial studies of oral contraceptive use focused on the alterations in coagulation activation factors and fibrinolytic systems. Changes were identified that affected both systems, but whether the overall effect clinically resulted in increased risk for thrombosis generally was not clear.[60] Many epidemiologic studies have suggested an increased risk of cardiovascular disease with oral contraceptive use. Unfortunately, these studies have been hampered by the many oral contraceptives available and their changing formulation with time, by the fact that women use different contraceptives for varying periods, by the generally unreliable information regarding the use of a product, and by variable familial, work, and medical conditions or habits that might contribute to cardiovascular events.[61,62] In general, there appears to be an increased risk of venous thrombosis with the use of preparations with high estrogen doses (most of which are no longer on the market).[63]

More recent studies have focused on changes in serum cholesterol, triglycerides, and lipoproteins. The progestins, especially formulations containing levonorgestrel, tend to affect adversely the markers for coronary heart disease.[64] Epidemiologic studies do not suggest a increased risk after discontinuation of oral contraceptives.[65]

Lower-Extremity Thrombophlebitis in Pregnancy

Deep vein thrombosis is difficult to diagnose accurately. Depending on the criteria used, the incidence in pregnancy ranges from 1.9 in 1000 to 30 in 100. This problem is rare antepartum but is 10 times more frequent in the postpartum period. It is correlated with increased age, traumatic and operative deliveries, preeclampsia, dehydration, anemia, prolonged bed rest, infection, and nutritional deficiencies. Often these major problems arise in the postpartum state, in which pulmonary embolization constitutes a major threat. In the event of a death secondary to pulmonary embolism and suspected deep vein thrombosis of the lower extremities, it is imperative to evaluate these vessels at autopsy. This is done in routine autopsies by "milking" the veins of the leg while observing the free flow of blood from the transected pelvic vessels. If there is a high degree of suspicion, the vascular spaces of the legs should be opened and examined thoroughly.

Ovarian Vein Thrombosis and Thrombophlebitis

In the third trimester of pregnancy, the ovarian veins increase in diameter as much as 60-fold to about 26 mm.[66] Although venous pressure does not appear to rise in pregnancy, there is a precipitous fall in the ovarian vein pressure immediately postpartum and a shift in the pattern in venous drainage from the uterus. These changes are probably the major factors associated with the occurrence of ovarian vein thrombosis in the immediate postpartum period.[67] The clinical picture of this condition is characterized by fever, abdominal pain, and, at times, a palpable mass. The differential diagnosis often includes appendicitis, because ovarian vein thrombosis more often occurs on the right side. Diagnosis frequently is made at the time of exploratory laparotomy. Cultures from the vessels usually are negative. This is in contrast to a frequent occurrence of positive cultures from ovarian vein thrombosis associated with septic abortion or pelvic inflammatory disease. Ovarian vein thrombi are probably the major source of postpartum pulmonary emboli; therefore, examination of these vessels at autopsy is imperative.

Renal Vein Thrombosis

Renal vein thrombosis appears to be a rare complication of pregnancy and has been said to be secondary to uterine compression of the inferior vena cava.[68] The main symptoms often consist of lumbar or abdominal pain, which is associated with proteinuria if the process is acute. The process may be gradual and first identified by the discovery of a mass on abdominal postpartum examination. Besides the occlusion of vessels, the histologic changes noted in the kidneys are similar to those of membranous glomerulonephritis. Interstitial edema occurs, and there may be mild to moderate atrophy of the convoluted tubules. In more chronic cases, interstitial fibrosis and severe tubular atrophy may be seen.

Hepatic Vein Thrombosis (Budd-Chiari Syndrome)

Occlusion of the hepatic venous outflow tract is a rare condition that was described by Budd in 1845 and Chiari in 1898. The cause may be tumor or localized venous thrombosis. The latter has been associated with conditions in which there is an underlying predisposition to thrombosis, such as polycythemia rubra vera or paroxysmal nocturnal hemoglobinuria. The occurrence of this syndrome in pregnancy and with the use of oral contraceptives has been attributed to induced changes in the coagulation factors, but the possibility of estrogen- or progesterone-induced intimal vascular changes cannot be excluded.[69,70] In pregnancy and with oral contraceptives, the onset of symptoms is sudden, developing over a period of 1 to 3 months.

Clinically, patients present with abdominal pain and distention, hepatomegaly, and ascites. Jaundice usually is not present at the time of diagnosis, and liver enzyme studies are not helpful. The hepatic scintiscan may be useful in diagnosis; however, hepatic vein catheterization is the most important diagnostic technique.

Liver biopsy generally shows intense vascular congestion, localized necrosis, and cell atrophy. Demonstration of thrombi in the small hepatic sinusoids or antral veins is unusual. The histologic findings in general reflect localized ischemia and, although nonspecific, may be useful in suggesting the appropriate diagnosis.

The Budd-Chiari syndrome in association with pregnancy has a poor prognosis, with a mortality of about 50%.[71] The prognosis does not appear to be as grave when the syndrome occurs in association with the use of oral contraceptives, and remission has occurred with discontinuation of the medication. Death, if it occurs, is usually within a period of 6 to 12 months. At autopsy, the hepatic veins are found to be occluded by thrombi. The inferior vena cava is patent. In rare cases, associated portal, mesenteric, and splenic vein thrombi have been seen. Liver changes, in addition to thrombosis of central and suprahepatic veins, vary from marked dilatation and congestion of sinusoids to focal necrosis resulting from ischemia. Extravasation of blood into Disse's spaces and progressive atrophy of hepatocytes in the less congested areas are characteristic. Coalescing fibrosis of centrilobular regions is the form of healing in surviving cases.

Intracranial Thrombosis

Cerebral venous and dural sinus thrombi occur in several conditions, including pregnancy.[72,73] Intracranial thrombosis most commonly occurs in the latter part of pregnancy but has been reported in the first trimester. The hypercoagulable state of pregnancy has been implicated, as has the predisposition of the cortical venous system to thrombotic episodes by virtue of the lack of valves, low pressure, fibrous septa, and transient changes in pressure during pregnancy.

Intracranial thrombosis has been associated with the use of oral contraceptives.[72,73] These hormones may cause arterial changes including eccentric intimal thickening with clumping of the internal elastic membrane and the occurrence of plaques. These findings are most often noted in strokes associated with the use of oral contraceptives. Although it is frequently stated that cerebral venous thrombosis in pregnancy and the puerperium is not uncommon, occurring in about 1 in 10,000 pregnancies, few cases have been reported.

Clinical manifestations frequently include headache with or without convulsions. When accompanied by convulsions, cerebral venous thrombosis may be confused with eclampsia; however, hypertension is absent. Focal neurologic signs or coma may be presenting features. Definite antemortem diagnosis is made by cerebral angiography. CT scans can reliably and noninvasively suggest the diagnosis. The mortality is high, and the autopsy findings include cerebral edema, basilar herniation, multiple petechial hemorrhages, and organizing venous thrombosis. In pregnancy-associated intracranial venous thrombosis, the sinus endothelial proliferation described in cases associated with oral contraceptive use is not observed as frequently.

Pulmonary Thromboembolism

Pulmonary thromboembolism in patients receiving oral contraceptives usually is believed to be secondary to alterations in the coagulation process similar to those seen in pregnancy.[74] Some reports suggest that the pathogenesis of pulmonary thromboembolism in oral contraceptive users may be different from that in pregnancy, in that the pulmonary vascular obstruction usually is secondary to local vascular changes and subsequent thrombosis rather than to an embolic phenomenon (see Fig. 11-5).

Pulmonary embolism is the second leading cause of death in pregnancy.[74,75] It is the leading cause of death in cesarean section patients. The major clinical signs of pulmonary embolism are dyspnea and tachypnea. The classic signs of hemoptysis—pleural friction rub, gallop rhythm, cyanosis, and sharp chest pain—are present in less than 25% of these patients. The most helpful auxiliary studies include arterial PO_2, electrocardiogram, chest x-ray films, lung scans, and pulmonary arteriography. The latter constitutes a definitive diagnostic tool but usually is reserved for those patients in whom surgery is contemplated. Massive pulmonary embolism occurs suddenly, usually from the second postpartum day to several weeks postpartum. The risk increases with age, parity, restricted activity, traumatic or operative deliveries, dehydration, anemia, and the use of estrogens to suppress lactation.

One of the major problems in delineating the probable causes and origins of pulmonary embolism has been the incomplete reporting of the investigation of deaths secondary to suspected pulmonary embolism. In cases in which a careful search was conducted, about one half of the thrombi originated in the pelvic veins. In cases of death occurring soon after delivery, the emboli may be unorganized and therefore difficult to differentiate from postmortem clotting. In autopsies of sudden death shortly after delivery, opening the pulmonary veins in situ might reveal folds in the obstructing clot that would be diagnostic of embolization (Fig. 11-6).

To define risk factors that may be associated with anesthesia or surgical techniques used during cesarean section, every effort should be made to identify the sources of the emboli. This type of information may allow modification of techniques or procedures to lessen the risk of pulmonary embolism after cesarean section.

Chorionic Embolism

Chorionic tissue can be identified in the maternal circulation throughout pregnancy. Chorionic tissue has been found sequestered in the pulmonary vasculature postpartum and is considered a normal event.

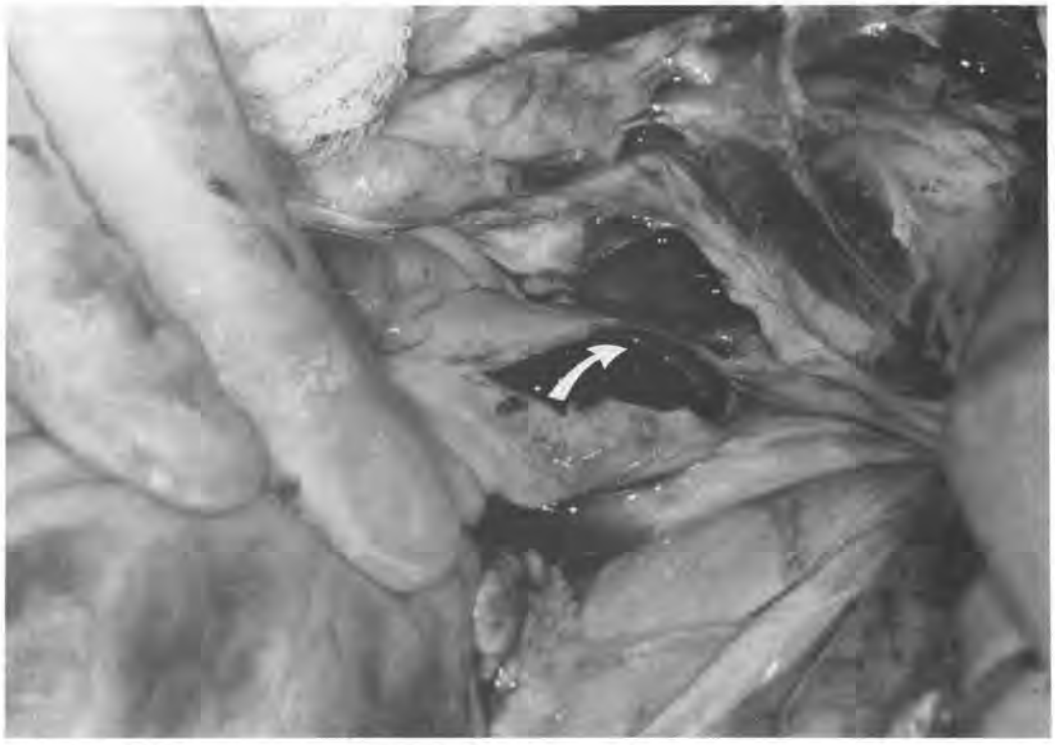

FIGURE 11-6 Pulmonary embolism. This patient died within 4 hours of a cesarean section. At the time of surgery, marked broad ligament and ovarian vein varicosities had been noticed without evidence of thrombosis. The fresh, folded embolus (*arrow*) that can be seen obstructing the main pulmonary artery originated from the right ovarian vein.

Acute pulmonary embolism with chorionic tissue has been identified in association with hydatidiform mole and choriocarcinoma. In hydatidiform mole, it is usually associated with uterine evacuation, occurring in about 10% of cases, and is self-limited and rarely fatal.[76]

Fat Embolism

Fat embolism appears to be encountered more frequently when the pregnant patient sustains bone and extensive soft-tissue injuries.[77] The predominant symptoms are tachypnea, hypotension, altered consciousness, petechial rash about the neck and shoulders, and pyrexia. Hypoxemia, leukocytosis, and hypocalcemia are frequently present. Demonstration of fat globules in sputum, circulating blood, and spinal fluid may be of help in the diagnosis, but they are not specific. At autopsy, neutral fat should be looked for in frozen section material from the lungs and choroid plexus. Fat embolism may play some role in amniotic fluid embolism and may be a component of air embolism.

Air Embolism

Air embolism is associated with many different types of operative procedures and circumstances, but it appears to be most common in association with pregnancy.[78] After Leonet reported the first death associated with pregnancy in 1845, most of the reported gynecologic fatalities of air embolism were associated with pregnancy, except those in which the precipitating events were diagnostic pneumoperitoneum, tubal insufflation, or, rarely, hysterectomy.[79] In 1960, Nelson reviewed all the cases reported to be associated with pregnancy and the puerperium and estimated that the incidence of air embolism was about 1 in 100,000 live births.[79] Of the 199 proved fatal cases of embolism, 40% were associated with attempted illegal abortion, most of them by douching with various substances.

Two factors are necessary for venous air embolization. First, there must be a partially open venous space. Second, the air pressure must exceed the venous pressure. The mechanism suggested for air entry before labor is the forcing of air through the cervix, with displacement of the membranes in the lower uterine segment and entry into the exposed rich vascular bed. A douche bulb can provide 200 to 300 mL of air with a fluid mixture in this fashion. The rich, open vascular spaces associated with delivery provide easy access to the vascular system. The hemodynamic changes associated with delivery, along with decompression of the abdomen and Trendelenburg's position, are believed to create negative venous pressure that potentiates air embolism.

The effect of the bolus of air in the venous system is almost immediate. Clinically, there is marked apprehension, tachycardia with loss of pe-

ripheral pulse, dyspnea, cyanosis, and vascular collapse. In arterial air embolism, the lethal dose is considerably less, and the mechanism of death is secondary to cerebral embolism, which produces neurologic manifestations, including blindness. Ophthalmologic examination may reveal air in the retinal vessels.

Gynecologic laparoscopy is a common procedure in which large volumes of gas are injected into the peritoneal cavity. The most commonly used gases are carbon dioxide and nitrous dioxide, both of which have high solubility constants. Usually, large intravascular volumes are required to cause a symptomatic embolism. Fatal gas embolism secondary to laparoscopy has been reported.[80] Laser ablation of the endometrium has been associated with at least 2 deaths from gas embolization; the use of air and nitrogen were involved.[81] In operative hysteroscopy, the uterine cavity is distended by a fluid medium. With operative trauma to the wall, intravasation of fluid easily occurs, and acute fluid overload with pulmonary edema is a common complication. With the advent of laser ablation using artificial sapphire tips, an additional cooling mechanism must be used to keep the sapphire tip from overheating. This has been accomplished by use of a gas flow around the fiber, usually air, nitrogen, or carbon dioxide, which is the source of the gas embolization in fatal cases. Air embolism can be associated with forced infusion of blood, insertion of subclavian catheters or central venous lines, and the placement of the needle for epidural anesthesia.[82]

The autopsy findings in venous air embolism are usually evident, with air frequently found in the uterine vessels, the veins of the broad ligament, the inferior vena cava, and the right heart. Pulmonary congestion and right heart dilatation are dominant findings. In performing the autopsy, no major veins should be transected until the inferior vena cava is adequately exposed and examined for air and the right heart opened under water. This may be achieved by filling the chest cavity with water or carefully clamping all the major heart vessels and transferring the heart to a water-filled basin. The gas found within the heart and great vessels can be trapped and analyzed by such devices as the Erben and Nadvornik apparatus.

Antemortem air embolism must be differentiated from septic death associated with a gas-forming organism and from postmortem gas formation secondary to gas-forming bacilli. In the former, the clinical course is different; blood culture should identify the problem in both cases. In both situations, gas is found in arteries and veins. In the rare case of arterial gas embolism, gas may be found in the coronary arteries and the brain, particularly the choroid plexus. The main central nervous system finding is that of disseminated foci of ischemic necrosis.

Most cases of air embolism are seen in pregnancy and associated with the use of a vaginal douche, cunnilingus, or aberrant sexual activity. These histories may not be readily available and must be carefully ferreted out. A detailed description of the external and internal genitalia should be made. When the event is associated with delivery, the uterus should be examined carefully for lacerations or rupture.

Amniotic Fluid Embolism

Amniotic fluid embolism is one of the most dangerous and untreatable conditions in obstetrics.[58,82,83] Although previously recognized, the clinical entity was not widely appreciated until the publication by Steiner and Lushbaugh in 1941.[84] It is characterized by hypotension, hypoxia, and coagulopathy, with an incidence of anywhere from 1 in 3,400 to 1 in 80,000 deliveries.[85,86] Amniotic fluid embolism accounts for 5% to 10% of maternal deaths, and when combined with pulmonary thromboembolism represents the leading group of causes of maternal mortality in the United States.[85] The syndrome usually occurs in the term patient in labor or immediately postpartum, but it has been described in the first and second trimesters and, in rare cases, hours to days after delivery. The dramatically acute symptoms are sometimes heralded by chills, apprehension, emesis, and a need for micturition, followed by sudden respiratory distress, cyanosis, cardiovascular collapse, and coma. Eighty percent of patients die within 6 hours of onset of symptoms, with 25% to 50% of those dying in the first hour. For those surviving the first hour, coagulation problems develop in 30% to 45% and are manifested by a range of changes from minor drops in the platelet counts to full-blown disseminated intravascular coagulation. Coagulation problems constitute the presenting symptom in about 12% of cases.[86,87]

Because the respiratory symptoms are so acute and the main autopsy finding consists of intravascular amniotic debris in the pulmonary vasculature, it has long been postulated that the symptom complex is precipitated by a sudden and massive intravasation of amniotic fluid. For this reason, particular attention was directed at the clinical notations of tumultuous labor patterns and the use of oxytocin with chlorobutanol (Pitocin). Because of the acuteness of the onset of symptoms, the differential diagnosis includes ruptured uterus, eclampsia, pulmonary embolism, air embolism, abruptio placentae with shock, supine hypotension syndrome, myocardial infarction, cerebrovascular accident, Gram-negative sepsis, bilateral pneumothorax, aspiration syndrome, and anaphylactic reaction to an administered drug.

Amniotic fluid embolism is rare. Only slightly more than 300 cases are recorded in the literature, many of them single case reports, often with incomplete clinical and pathologic data.[86] The single major diagnostic feature is the autopsy finding of amniotic fluid debris in the pulmonary vasculature, which usually is described as consisting of squamous epithelial cells, mucin, fat, and fetal hair.[87] These findings,

combined with the acute nature of the pulmonary symptoms, has been viewed in the past as evidence for an acute obstructive or possible anaphylactoid reaction to a massive intravasation of fluid with subsequent cor pulmonale. There have been only a limited number of animal studies, and their results have yielded conflicting data regarding the effects of intravenous infusion of amniotic fluid with and without meconium.[86] The only two studies carried out in primates have shown that amniotic fluid infusion is clinically innocuous.[86] In more recent years, careful clinical documentation of hemodynamic events in affected patients has tended to refute the earlier view that the clinical symptoms are a result of mechanical obstruction or anaphylactoid reaction.[87] The findings in larger series of carefully compiled autopsies and in cytologic analyses of right heart blood in affected and unaffected patients have altered past suggestions about the sequence of events and mechanisms of response in patients with amniotic fluid embolism.[87,88]

The patient suffering from amniotic fluid embolism tends to be older (average age of 32) and is more often parous (88%). Most cases occur at term and during the course of labor. Sudden dyspnea accompanied by hypotension and cardiorespiratory arrest occur in nearly 80% of the cases, with subsequent convulsions in 10%. It has been postulated that the acute symptoms are secondary to pulmonary hypertension, transient right ventricular dysfunction, and interpulmonary vascular shunting with arterial hypoxia and acidosis. Of those patients surviving the first hour, hemodynamic observations fail to identify evidence of pulmonary hypertension, and it is presumed that there was resolution of any acute changes. Left ventricular dysfunction or failure is identified with resultant pulmonary edema. The myocardial dysfunction is believed to be due to the initial hypoxia and acidosis, which may in part account for the subsequent findings of renal failure, hepatic injury, and cerebral edema.

The autopsy findings usually are not dramatic. Right heart dilatation is sometimes identified in sudden death, which tends to refute the mechanical obstruction theory of the presumed initial right heart failure. The more usual macroscopic findings include the following: pulmonary edema (consistent with left heart failure); pulmonary, subendocardial, subepicardial, and subcapsular hepatic hemorrhages; multiple organ vascular congestion; and cerebral edema. The pulmonary vasculature often appears to be bloodless, but on microscopic examination contains squames, mucin, lanugo, fat, and leukostasis.[87] The quantity of intravascular material identified does not completely correlate with the duration of symptoms before death and, in fact, may be sparse.[87]

Squames, mucin, fat, and lanugo may not be readily appreciated in slides stained with hematoxylin and eosin (Fig. 11-7). Squames must be differentiated from detached endothelial cells, especially when the interval between death and autopsy is prolonged. Multiple frozen sections of lung should be obtained and stained for fat, which is good evidence for the diagnosis of amniotic fluid embolism without

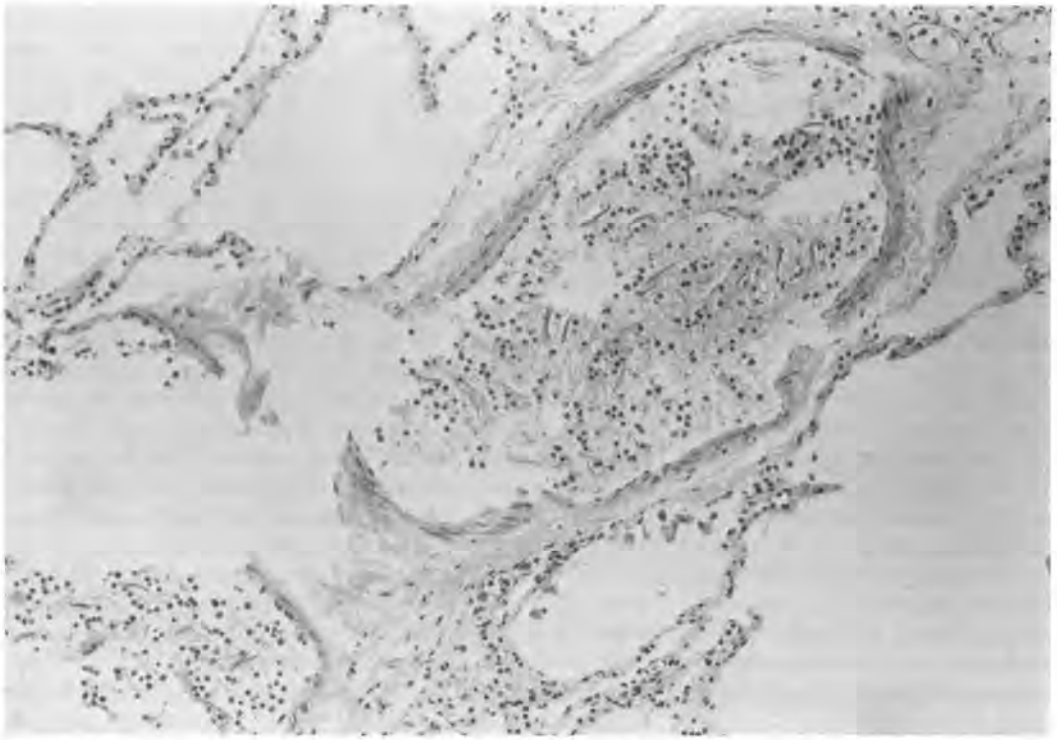

FIGURE 11-7 Amniotic fluid embolism. Numerous neutrophils, flat squamous cells, and amorphous material fill the pulmonary vascular spaces.

the risk of contamination or misdiagnosis that exists with the identification of squames. Multiple pulmonary sections should be stained for mucin, using Mowry's colloidal iron stain, and for squames, using Alcian green-phloxine. Lanugo is best seen with polarized light and is rarely identified. Mucin positivity is the most common finding. Unlike the presence of trophoblastic tissue in the lungs of pregnant patients, the finding of amniotic debris in the maternal circulation has always been considered abnormal and pathognomonic of amniotic fluid embolism. Amniotic debris has been found in the systemic circulation. It has been reported in the vessels of the myocardium, cerebrum, kidneys, pancreas, gallbladder, pituitary, adrenals, small bowel, and spleen. Apparently, no clinical significance is attached to these latter findings.[87]

In recent years, it has been thought possible to diagnose amniotic fluid embolism by examining right heart blood.[88,89] On centrifugation, three distinct zones have been noted in right heart blood of patients with the clinical syndrome of amniotic fluid embolization. The topmost layer is usually positive for mucin, the presence of which may be confirmed by cytologic preparations. Squames are usually identified in cell block material taken from the uppermost layer. However, the presence of squames alone may be an artifact, because squames may be identified in right heart blood recovered from non-pregnant women.[90,91] Because the initial reports suggested that a positive diagnosis could be made on the basis of squames in the blood from the right heart circulation, amniotic fluid embolism has a tendency to be overdiagnosed.

The idea that a massive intravasation occurs abruptly is partially supported by the frequent autopsy finding of uterine lacerations.[87] Vascular access for the amniotic fluid has been postulated to occur by one of the following three mechanisms:

1. Via the endocervical veins, in that as the fetal head descends, it blocks the birth canal, and the transmitted pressure of the contractions drives the trapped fluid into the traumatized and opened cervical veins[92]
2. Via the placental site secondary to premature placental separation, which allows access to large maternal veins (premature separation was clinically evident in 45% of the cases in one series)[83]
3. By way of the uterine wall.

Careful examination of the uteri of women who died of amniotic fluid embolism has disclosed partial rupture or localized tears with venous sinuses filled with amniotic debris.[87] Trauma to the endometrial surface has been implicated. Amniotic fluid embolism occurs in a disproportionate number of women in association with an intrauterine device and has been associated with intrauterine catheters, cesarean sections, and intrauterine manipulations. The observation of uterine intravascular amniotic debris and blood clot is not necessarily correlated with the occurrence of amniotic fluid embolization.

When death occurs early after the onset of symptoms, large numbers of neutrophils and histiocytes with phagocytized meconium-like debris have been observed to obstruct the pulmonary vessels. This suggests that amniotic fluid containment may be a mediator for the clinical response. Meconium and prostaglandins have been implicated; the latter, especially prostaglandin F_2, are found in the amniotic fluid in patients in labor. This theory would not explain amniotic fluid embolism occurring in the first and second trimesters.

The bleeding diathesis that may occur is not readily explained. The picture is that of disseminated intravascular coagulation, with an increase in serum fibrinolytic activity, thrombocytopenia, hypofibrinogenemia, and fibrin split products. Amniotic fluid has been shown to contain an activator of factor X; however, the amount present in amniotic fluid is not sufficient to precipitate a systemic effect.

Disseminated Intravascular Coagulopathy

Disseminated intravascular coagulopathy (DIC) is a clinical syndrome that occurs during the course of several different disease states. The manifestations probably can best be regarded as a consequence of the formation of thrombin. The thrombin catalyzes the activation and consumption of certain coagulant proteins and the production of fibrin thrombi. The consumption of fibrin leads to hypofibrinogenemia, which in pregnancy may be associated with any of the conditions associated with DIC listed below:

Abruptio placentae
Intrauterine fetal death with retention
Intra-amniotic injection of saline
Amniotic fluid embolism
Septic abortion
Retained placenta
Toxemia
Transfusion reaction
Septicemia

The laboratory diagnosis is made in patients with evidence of hemorrhage or thrombosis by the findings of a decreased platelet count, hypofibrinogenemia, prolonged prothrombin time, and fibrin degradation products. The histologic findings are those of multiple, small-vessel fibrin thrombi in different organ systems (Fig. 11-8).

LIVER

Toxemia of Pregnancy

Acute toxemia of pregnancy, a complex disorder of the third trimester of pregnancy (after the 24th week), is characterized by edema, hypertension, and

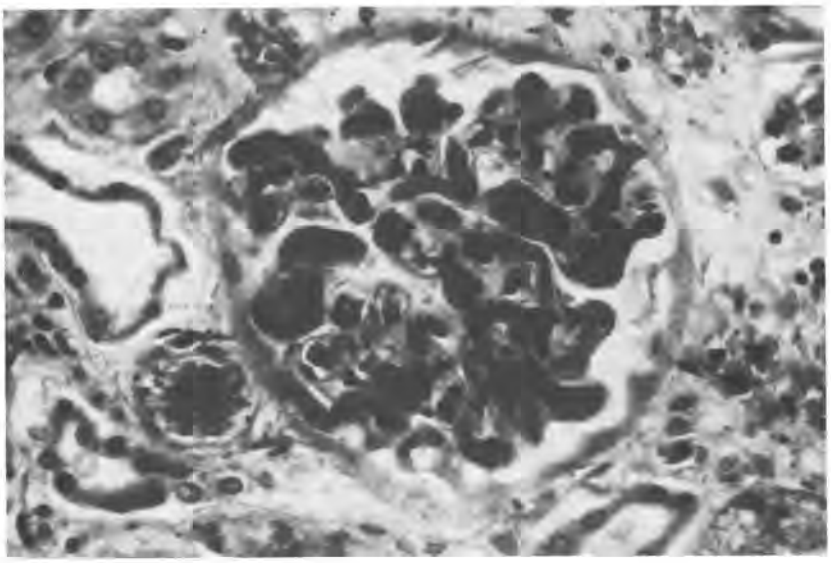

FIGURE 11-8 Renal glomerulus in a case of disseminated intravascular coagulation (DIC). Multiple fibrin thrombi are demonstrated well in this periodic acid-Schiff stain. (Courtesy of Dr. A. Andrew Abraham, George Washington University, Washington, DC)

proteinuria. It usually is classified into two groups: preeclampsia, which may be mild or severe, and eclampsia.[93–97] In mild preeclampsia, patients have edema of the face and hands, hypertension of at least 140/90 mm Hg, and persistent proteinuria (1+ to 2+). In severe preeclampsia, these signs are increased and there is marked edema, including anasarca and pulmonary edema. The blood pressure rises to at least 166/110 mm Hg, and the proteinuria is of the order of 5 g or more per 24 hours (3+ to 4+). Oliguria of less than 500 mL per 24 hours, visual and cerebral disturbances, headaches, and epigastric pain are common in severe preeclampsia. If the patient develops convulsions, becomes comatose, or both, the diagnosis of eclampsia is made.

In recent years, the HELLP syndrome (hemolysis, elevated liver enzymes, and low platelets) has been characterized as a form of severe preeclampsia.[98] The syndrome is related to a marked increase in maternal and perinatal morbidity and mortality. The hematologic and serologic changes can be identified before the appearance of proteinuria and hypertension and are identified in 23% of proteinuric hypertensive patients.[99] It is particularly in association with this syndrome that hepatic necrosis, subcapsular hemorrhage, and renal dysfunction are encountered.

In the United States, preeclampsia occurs in about 5% to 10% of all pregnancies. Eclampsia represents only 0.1% to 0.2% of all pregnancies, or 2% of all cases of preeclampsia.[100] Although these conditions may occur in multiparous women, they are more prevalent in primigravidas. Progress in prenatal care during the past decades has notably reduced the incidence of severe preeclampsia and eclampsia, and therefore of fetal and maternal morbidity and mortality.

The systemic complications of severe preeclampsia and eclampsia include abruptio placentae, hypofibrinogenemia, hemolysis, cerebral hemorrhage (a common cause of death), retinal hemorrhage, pulmonary edema, glomeruloendotheliosis with secondary oliguria, and liver necrosis and hemorrhage.[94,101] In this section, only the hepatic alterations in preeclampsia and eclampsia are discussed.[97,102–105]

The liver changes in toxemia of pregnancy are just part of the systemic vascular disorder resulting, presumably, from renin activation (the trigger mechanism is unknown). This is followed by retention of sodium in the vascular walls, which in turn induces a generalized vascular hyperreactivity to pressor substances (catecholamines and angiotensin) with development of an insidious vasospastic state characteristic of toxemia.[97,99,104–106] The vasospasm is considered the basic cause for the hypertensive state and the changes seen in different organs in preeclampsia and eclampsia.

Less than 50% of toxemic patients present with liver function changes, which usually consist of elevated alkaline phosphatase levels, moderate elevations in transaminase levels, and decreased platelet levels (HELLP syndrome). Markedly elevated lactate dehydrogenase levels are associated with liver necrosis, whereas alkaline phosphatase and γ-glutamyltransferase levels apparently are not related to the occurrence or extent of liver necrosis.[99] Hepatic injury may be detected before clinical signs by ultrasonography.[107] Elevation in bilirubin levels is rare, and only 10% of patients with eclampsia develop jaundice.[108]

Only in severe cases are the functional changes complicated by hepatic necrosis and hemorrhage and, eventually, spontaneous rupture.[101,109] These lesions may be fatal. A sudden complaint of right upper quadrant pain, accompanied by hepatomegaly, elevated serum levels of hepatic enzymes, fever, and leukocytosis, should suggest the presence of liver necrosis and hemorrhage. At times oliguria and shock complete the clinical picture.

The main histologic findings consist of fibrinous thrombosis of sinusoids with panlobar, multifocal periportal hemorrhage. In severe cases, multiple areas of intraparenchymal and subcapsular hemorrhage may occur, as well as centrilobular ischemic necrosis with inflammatory exudate (Fig. 11-9). Liver rupture, a potentially fatal complication, may occur in rare severe cases.[110-114]

Liver biopsy is a hazardous procedure usually not attempted in the eclamptic patient. Most of the morphologic changes have been described from autopsy material.

Liver Tumors and Steroid Therapy

Since the introduction of oral contraceptive drugs in 1960, contraceptive steroids have been implicated in liver function alterations resulting in intrahepatic cholestasis, abnormal bromsalphthalein (BSP) excretion, jaundice, and neoplastic and nonneoplastic mass lesions. Other nonspecific alterations of the hepatocyte can be seen in pregnancy and with estrogen replacement therapy, chiefly the presence of megamitochondria with crystalline inclusions (Fig. 11-10), intracellular bile inclusions, and cholestasis.[115]

During the past decades, there have been numerous reports of liver tumors associated with a history of steroid contraception.[116-127] Although the lesions have been diagnosed using a variety of terms, they can be grouped into three main categories: focal nodular hyperplasia, hepatocellular adenoma, and hepatocellular carcinoma.[118,121,122,125,128,129]

Focal Nodular Hyperplasia

Focal nodular hyperplasia is a nonneoplastic, tumorous lesion of the liver that affects women more often than men, is most frequent in the third and fourth decades of life, and is frequently associated with hormonal contraception.[125,128,130-132] Most patients with this association are symptomatic and are more likely than focal nodular hyperplasia patients not using oral contraception to develop spontaneous rupture of the liver with hemoperitoneum, a potentially fatal complication.[133]

In asymptomatic patients, the lesion may be found incidentally at the time of surgery for other conditions. When symptomatic, patients commonly present with acute or chronic abdominal pain and a palpable mass. Liver function tests are negative, but a CT scan is usually diagnostic. The lesion is usually single (in rare cases it is multiple) and less than 5 cm in diameter. It is frequently located at the surface of the liver and may be pedunculated. Although not encapsulated, it is well circumscribed, firm, fibrous, and distinct from the adjacent hepatic tissue. It characteristically contains a central stellate scar.

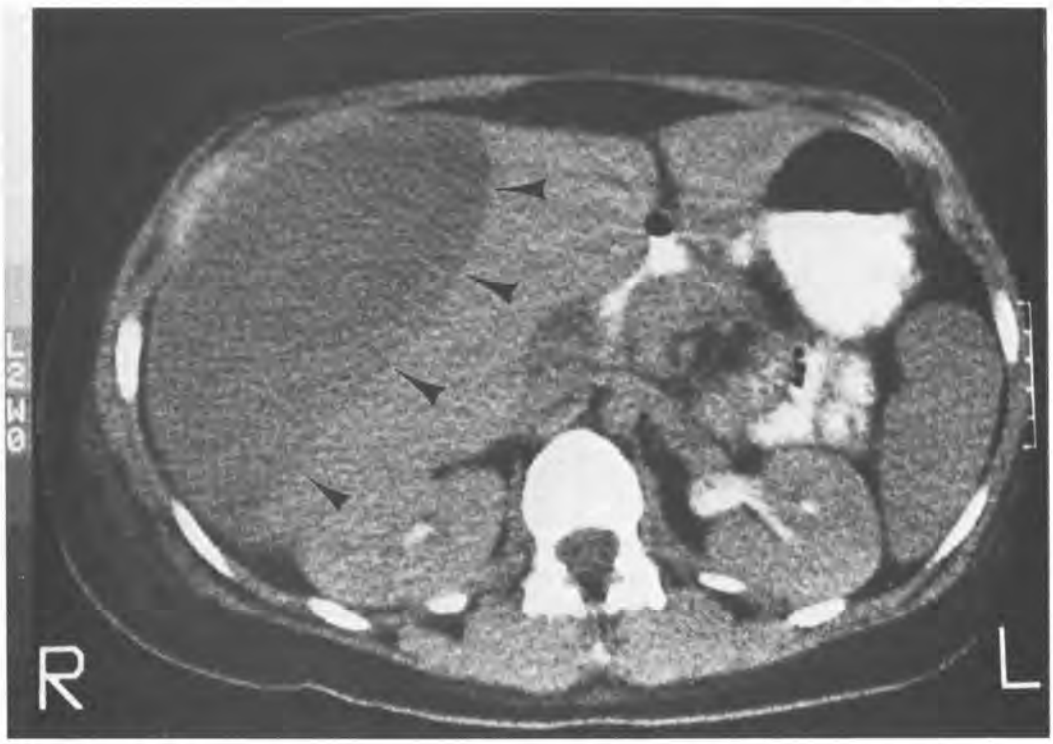

FIGURE 11-9 CT scan of a spontaneous subcapsular hematoma of the liver in severe preeclampsia. This patient presented with severe epigastric pain immediately postpartum associated with marked elevation of liver enzymes. Both ultrasound and CT scan revealed a large subcapsular lesion (*arrows*). Fine-needle aspiration confirmed the lesion to be an encapsulated hematoma. Resolution occurred without surgery over a period of 7 months.

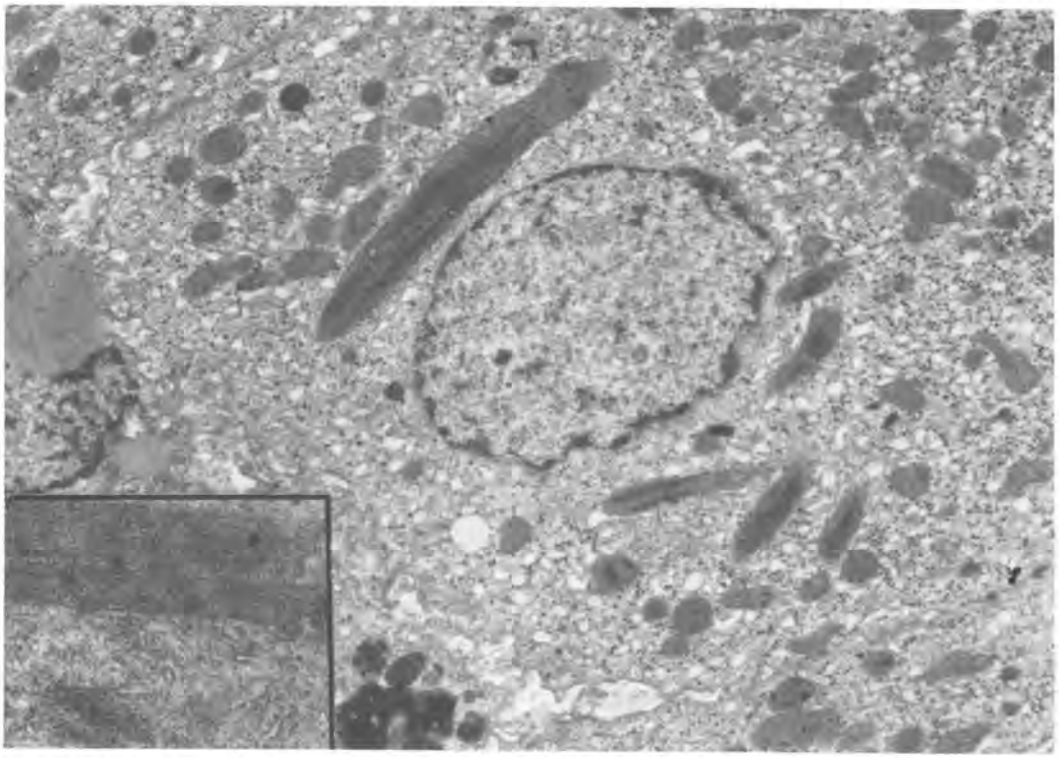

FIGURE 11-10 Hepatocyte with abundant mitochondria, some of them gigantic and containing crystalline structures (*detail in inset*). Note the dispersed glycogen granules and well-developed endoplasmic reticulum. The specimen is from the liver biopsy of a 28-year-old woman who took oral contraceptives for 5 years (×9800; inset, ×69,200).

Histologically, the lesion is composed of multiple small, confluent nodules of normal-appearing hepatocytes arranged in compact plates and cords around irregular foci of hyperplastic bile ducts and small blood vessels, within a fibrous collagenous stroma with lymphocytic infiltration (Figs. 11-11 and 11-12). Hemorrhage may occur within the tumor or may progress to rupture of the liver and hemoperitoneum, a catastrophic complication that requires immediate surgical treatment and occurs particularly in cases associated with steroid contraception.[132] The lesions of focal nodular hyperplasia may regress spontaneously after discontinuance of the steroid medication.

Hepatocellular Adenoma

Hepatocellular adenoma is the benign liver lesion most commonly associated with oral steroid contraception.[118,119,128,134–136] This lesion was rare until the 1970s, ten years after the introduction of hormonal contraception. Since then, an increasing number of reports have confirmed this association, supporting a causal relation. Adenomas also occur in female and male patients receiving androgens for therapeutic reasons.

Clinically, most patients are symptomatic, presenting with chronic right upper quadrant or epigastric pain or pressure and usually with a palpable mass. If intratumorous or subcapsular hemorrhage has occurred, the complaint is of acute upper abdominal pain. If rupture of the liver and hemoperitoneum complicate the problem, the picture is that of an acute abdomen. Liver function tests are within normal limits. Hepatic angiography and CT scan are diagnostic of the tumor mass. Needle biopsies may be considered with caution due to the high risk of hemorrhage. Like focal nodular hyperplasia, adenomas may regress after discontinuance of the steroid medication.[137,138]

Macroscopically, these tumors are usually single, although about 25% are multiple. They are well-circumscribed and partially encapsulated masses of lobulated, firm, gray-tan tissue that contrast with the surrounding darker and homogeneous liver parenchyma. These adenomas are usually larger than focal nodular hyperplasias, but most measure less than 10 cm in diameter. They are usually located in the right lobe of the liver. Some may be very large and can be located in the left lobe (Fig. 11-13). These tumors may become hemorrhagic and may result in liver rupture and hemorrhage. Greatly dilated veins are characteristically present within and around these hepatocellular adenomas, a factor that plays an important role in hemorrhagic complications.

Histologically, these tumors are composed of closely packed cords and masses of slightly pleomorphic hepatocytes with clear granular cytoplasm, sepa-

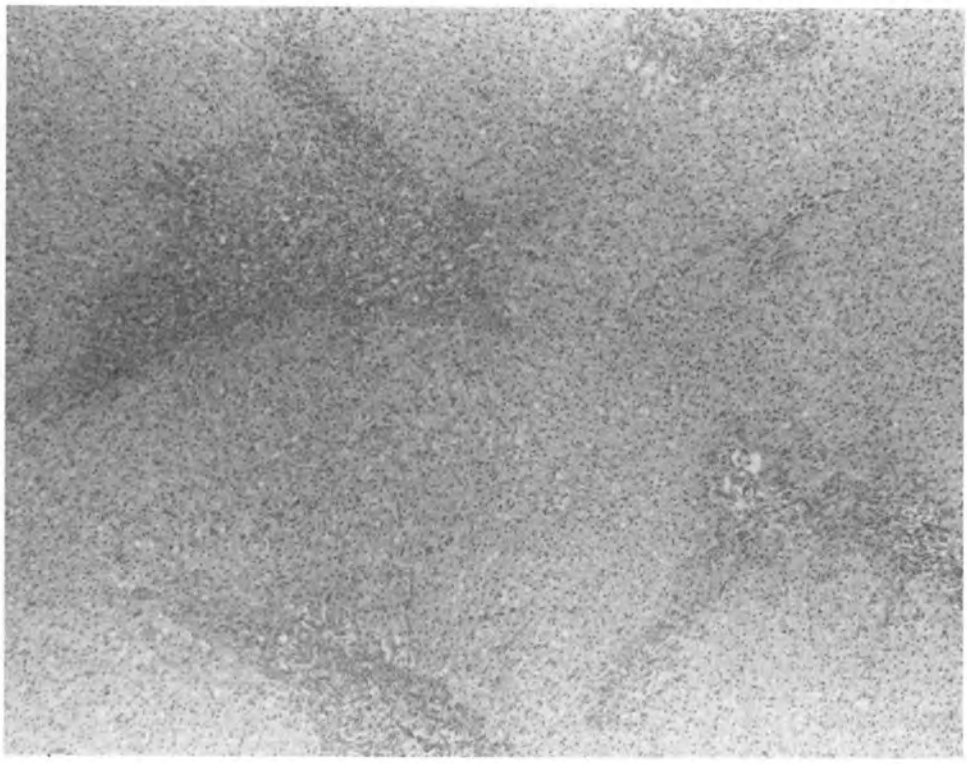

FIGURE 11-11 Panoramic view of focal nodular hyperplasia of the liver in a patient with a history of oral contraception. The irregular dark areas correspond to foci of fibrosis containing vascular proliferation and hyperplasia of bile ducts. They are separated by normal-appearing parenchyma.

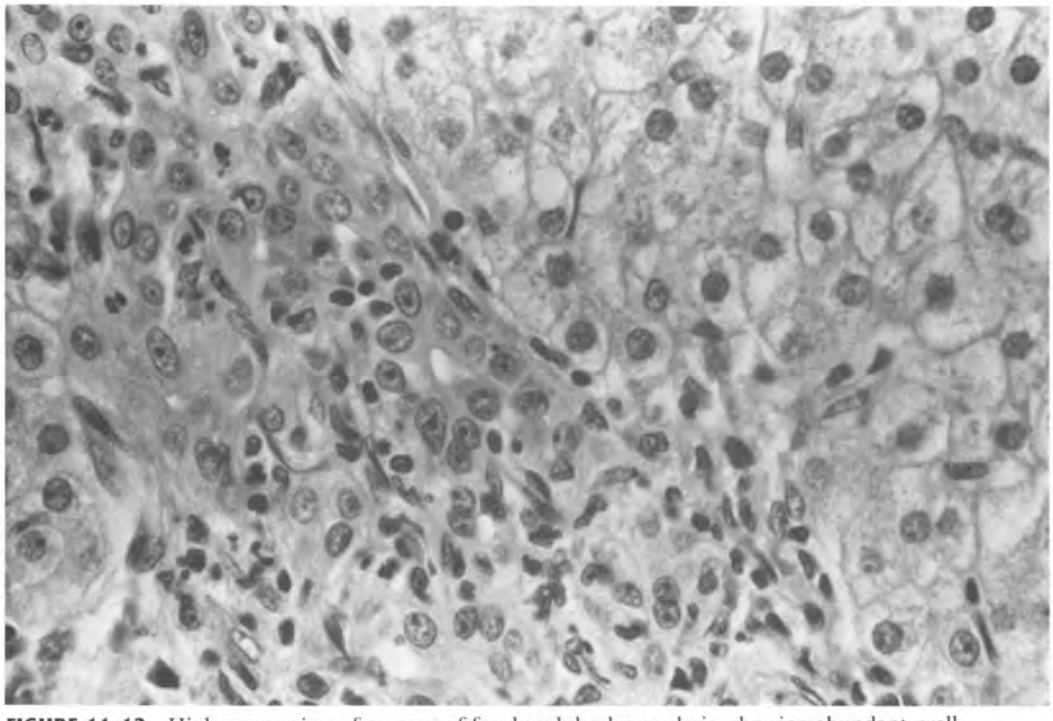

FIGURE 11-12 High-power view of an area of focal nodular hyperplasia, showing abundant, well-preserved cords of hepatocytes surrounding a triangular zone of fibrosis with bile duct hyperplasia, proliferation of small blood vessels, and predominantly mononuclear inflammatory infiltrate.

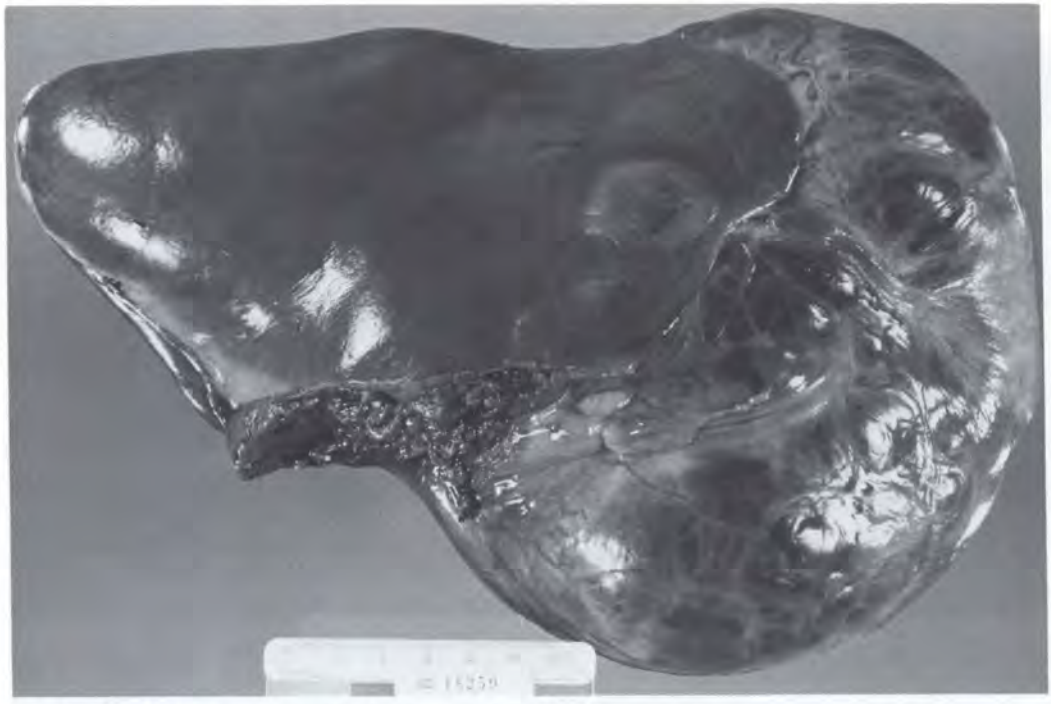

FIGURE 11-13 Large hepatocellular adenoma (18 × 16 × 12 cm) occupying most of the left lobe of the liver. A partial lobectomy was performed in this patient, who had a long history of oral contraception before conception. The tumor was found at 12 weeks of gestation. Therapeutic abortion failed to induce regression of the tumor. Its cut surface was lobulated, focally necrotic, and hemorrhagic, thus confirming a CT scan impression. The tumor was negative for estrogen and progesterone receptors, but the adjacent normal liver was positive.

rated by irregular sinusoids, with obliteration of the lobular hepatic architecture and absence of portal spaces and central veins (Fig. 11-14). Dilated veins are present randomly throughout the tumors. Bile ducts are absent. Fatty metamorphosis may be present focally. Areas of ischemic necrosis and hemorrhage are frequently seen. Resection is the treatment of choice (see Fig. 11-13).

Hepatocellular Carcinoma

Hepatocellular carcinoma is a distinctive malignant neoplasm. It is epidemiologically associated with environmental factors, mainly chemical exposure, and is related to viral hepatitis, cirrhosis, irradiation, and steroid therapy.[120,129,139–144] In geographic areas of high prevalence, these tumors affect young and middle-aged adults, mainly men (5:1). In areas of low frequency, such as Europe and North America, they usually occur in elderly men.

A possible etiologic relation between hepatic malignant tumors and long-term use of steroid hormones (contraceptive steroids and anabolic androgens) has been evolving in recent years on the basis of strong circumstantial evidence.[120,127,139–141,145] This evidence for a relation is strongly suggested by a marked increase in the relative risk with continuous use of oral contraceptives for more than 5 years. The risk is postulated to be secondary to estrogen; however, a recent study did not show an increased risk with long-term use of replacement estrogen.[146] More than 100 cases of oral contraceptive-associated hepatocellular carcinoma have been reported since 1977, and although there is no proof of a causal relation, the epidemiologic evidence suggests a strong correlation that must be considered seriously and evaluated.[127,146] This becomes especially evident when the common risk factors of alcoholism and hepatitis B virus are absent.[127]

Most of these contraceptive-associated malignant hepatic tumors have been hepatocellular carcinomas occurring in young women, a population at minimal risk for this type of lesion in the past. The tumors appear de novo, with the exception of a few alleged to have resulted from malignant transformation of an adenoma. In addition to their ability to metastasize, these tumors had spontaneous rupture with severe hemorrhage in about 10% of cases.

Histologically, hepatocellular carcinomas are differentiated from focal nodular hyperplasia by the absence of central scarring and vascular and bile duct proliferation and by the presence of architectural and cytologic criteria of malignancy. These latter criteria (irregular cell nests, trabeculae, and acini; infiltrating tumor borders; cellular atypia and pleomorphism; presence of numerous mitotic figures) are even more important in the differential diagnosis of hepatocellular adenoma, because both lesions are

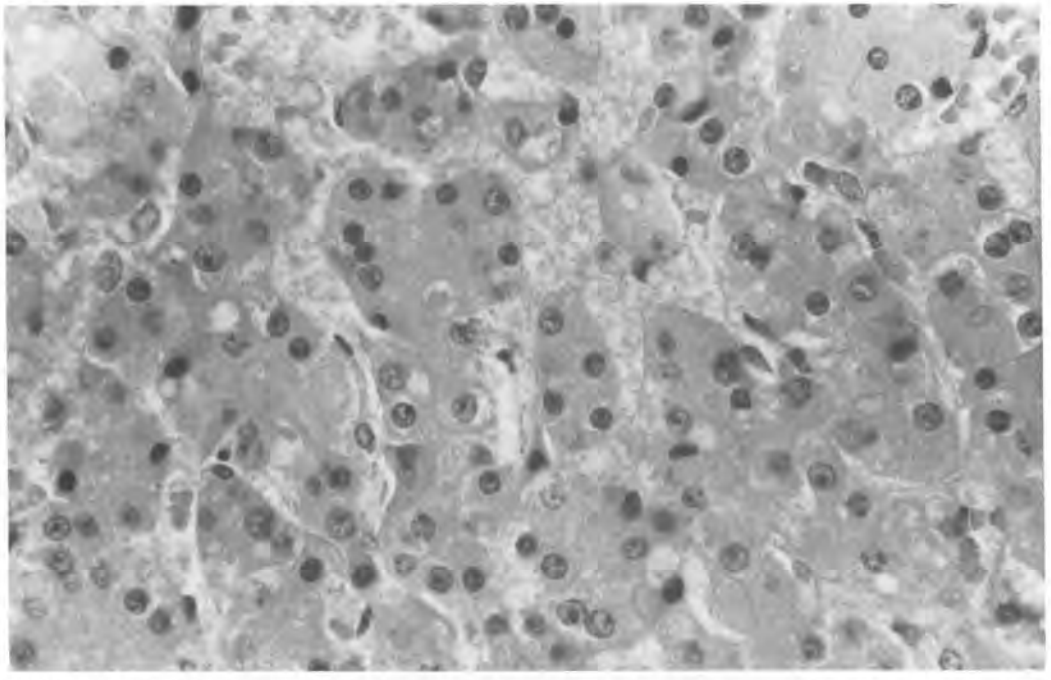

FIGURE 11-14 Needle biopsy of the hepatocellular adenoma shown in Figure 11-13. Note the irregular cords and sheets of slightly pleomorphic hepatocytes with focal necrosis and hemorrhage.

monomorphous proliferations of hepatocytes only, but adenomas lack the malignant phenotype. In young women, many of the carcinomas are of the *fibrolamellar oncocytic* type, a recently characterized and prognostically favorable variant in which cords and nests of large eosinophilic cells that show ultrastructural features of oncoctyes (packed with large and pleomorphic mitochondria) are separated by prominent bands of dense collagen (Figs. 11-15 and 11-16).[147,148]

Spontaneous Rupture of the Liver

Spontaneous rupture of the liver is not a common occurrence. Usually the patients are older, multiparous, in the third trimester of pregnancy, and hypertensive.[110–113] Eclampsia is diagnosed in only about 25% of the cases. Usually, the patient presents with epigastric pain, right upper quadrant pain, or both. The pain may have been present for several weeks. Usually, there is marked elevation of all liver enzymes. Spontaneous rupture of a subcapsular hematoma usually occurs in association with delivery. Hemoperitoneum, shock, and death occur in 60% of cases. The subcapsular hematoma is usually seen in association with histologic findings of fibrin emboli in the sinusoids and hepatic arterioles, with periportal hemorrhagic necrosis. Unlike the diffuse subcapsular hematomas noted in eclamptic patients, the hematomas in spontaneous hepatic rupture usually are confined to the anterior and superior aspects of the liver. In pregnant patients presenting with epigastric or right upper quadrant pain, it has been recommended that hepatic scans or ultrasound be performed to detect the subcapsular hematoma before rupture. This may be achieved by CT scan. Most of these instances are associated with the HELLP syndrome. Hemangiomas, amebic abscesses,

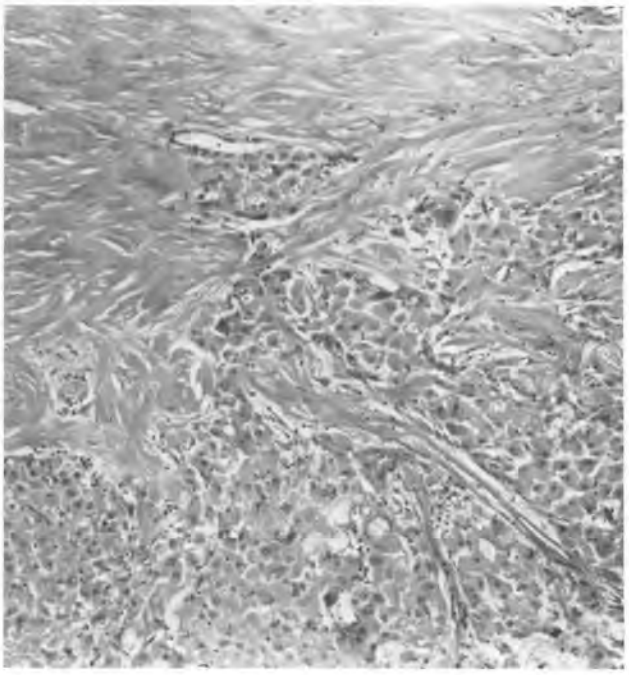

FIGURE 11-15 Fibrolamellar oncocytic hepatocellular carcinoma in a 23-year-old woman. Dense, laminated collagen separates solid nests of tumor cells.

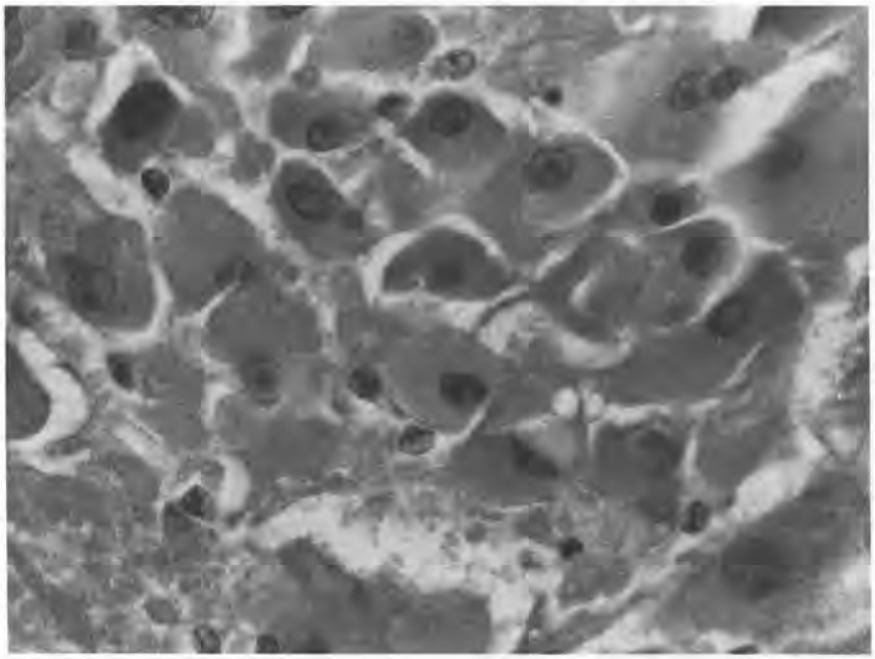

FIGURE 11-16 The tumor cells (oncocytes) in fibrolamellar oncocytic hepatocellular carcinoma are characterized by large size, pleomorphism, and voluminous eosinophilic granular cytoplasm packed with mitochondria.

and hepatic adenomas and carcinomas have been noted as rare causes of hepatic rupture in pregnancy. Fine-needle aspiration may be useful in confirming the nature of the observed hepatic defect. Large-bore needle biopsies should be avoided because they are more likely to precipitate a surgical emergency.

SEXUAL, CONTRACEPTIVE, AND SANITARY PRACTICES

Death Related to Sexual Activity

Unlike men, women almost never suffer an acute myocardial infarct during sexual activity. However, air embolism secondary to cunnilingus or air injection for eroticism does occur (see the section on air embolism). Although death due to airway obstruction secondary to an aspirated condom is evident, asphyxiation secondary to aspiration of semen or the impaction of the penis in the hypopharynx may not be readily evident. Diagnosis may be established by tracheobronchial cytology for the identification of sperm.

Complications of Intrauterine Contraception

Although intrauterine contraceptive devices (IUDs) were first introduced early in this century, not until the advent of inert plastic materials did a multitude of devices appear on the medical scene. The main problems with the devices included intrauterine retention, uterine cramping, bleeding, and myometrial embedding of the devices. Critical illness and deaths associated with intrauterine devices were first reported in 1968 by Scott.[149] The deaths attributed to the IUD were secondary to septicemia occurring shortly after insertion. Two deaths occurred secondary to amniotic fluid embolism, with devices that were found to be partially protruding through the myometrium. Subsequent problems with septicemia occurred mostly with the Dalkon Shield. With this device, the element responsible for infection was the multifilament string that protruded through the cervix (Fig. 11-17). This string allowed bacteria to migrate through its protected interstices and into the endometrial cavity. Intrauterine infection became an especially important problem when pregnancy occurred in the patient wearing the Dalkon Shield. More recent evaluation of IUDs has revealed little in the way of an increased risk for pelvic inflammatory disease.[150]

Beyond these immediate problems was the question of the fate of the IUD that perforated through the myometrium into the peritoneal cavity. Originally, some IUDs such as the Bromberg Bow were of a "closed" loop construction. In the peritoneal cavity, a loop of bowel could become entrapped within the closed loop of this device, resulting in intestinal obstruction.[151] IUDs are now made of relatively inert polyethylene plastic impregnated with barium salts. The salts enable the device to be seen by radiographic procedures. Some devices are "medicated," containing elemental copper or a progestin (Cu7, Tatum T, Dalkon Shield, Progestasert). The devices containing copper tend to invoke an intense fibrous reaction when located in the endometrial cavity. Perforation of the uterus is usually thought to be a consequence of insertion. If the uterus is perforated, the device may simultaneously perforate adjacent

structures such as the bladder or colon. The nonmedicated devices usually provoke little peritoneal reaction and therefore can be located and removed by means of laparoscopy, but the copper-wrapped (Cu7, Tatum T) and copper-impregnated (Dalkon Shield) devices tend to be encapsulated by fibrous tissue.

Under experimental conditions, the copper devices are immobilized by fibrous tissue, and visceral perforation is not seen. Clinically, there have been well-documented cases of perforation of the appendix, jejunum, and colon by copper-wrapped devices that do not appear to be secondary to perforation at the time of insertion.

Other complications of intrauterine contraception are discussed in the chapters on the uterine corpus (Chap. 4), the fallopian tube (Chap. 5), and ectopic pregnancy (Chap. 9).

LAPAROSCOPIC AND PELVISCOPIC INJURIES

Laparoscopy is achieved with a trocar that is sharply and blindly introduced transcutaneously into the peritoneal cavity. Pelviscopy involves operative manipulation, usually via additional abdominal wall puncture sites. Peritoneal insufflation with carbon dioxide (CO_2) is usually achieved via a Verres needle, which is 2 mm in diameter, followed by a primary trocar of 10 to 12 mm diameter, and by secondary trocars ranging from 5 to 10 mm in diameter. The most frequently used primary trocars have sharp pyramidal tips that cut through the anterior abdominal wall fascia when the instrument is thrust against the tented lower abdominal wall. Trocars with conical tips are available but are much less frequently used; the conical tip is somewhat blunted and has no cut-

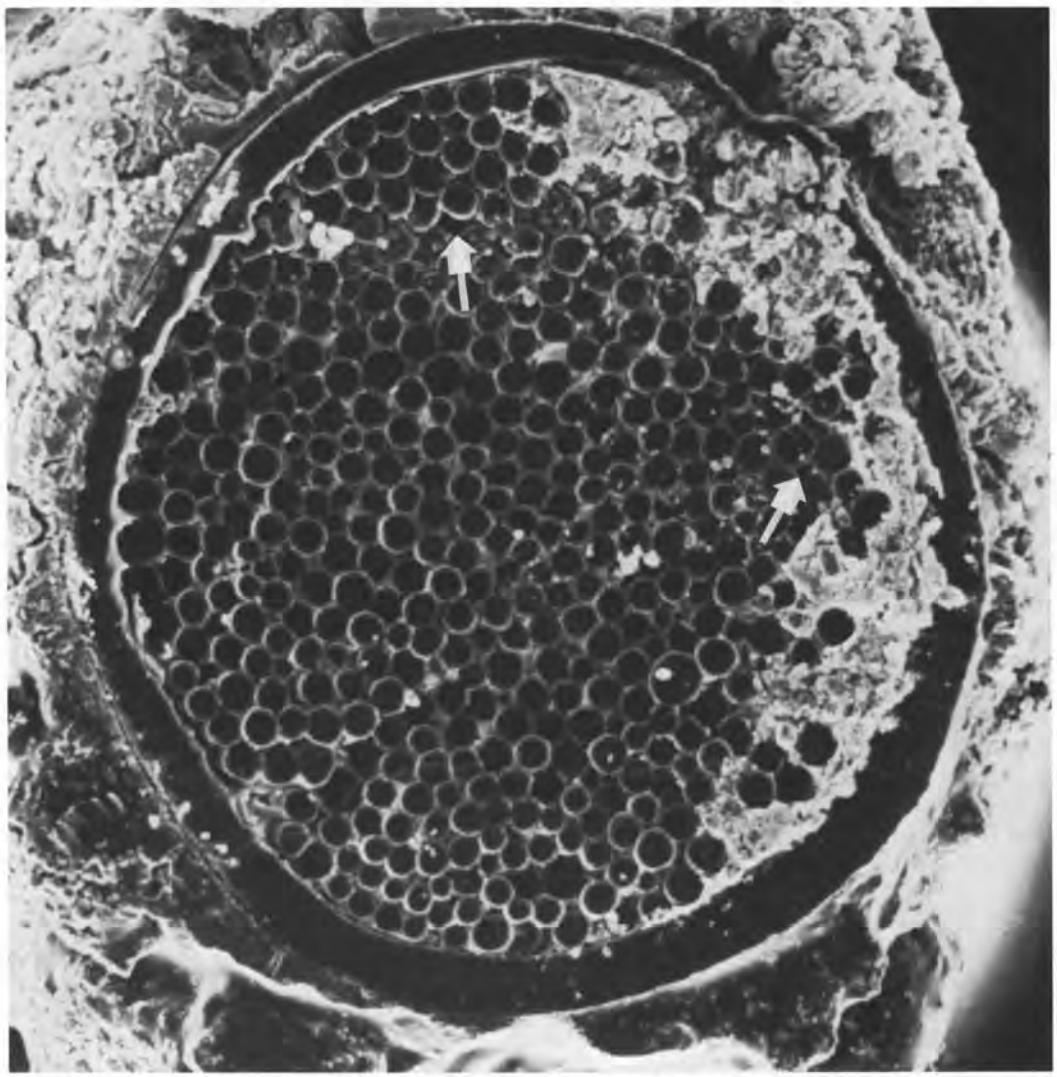

FIGURE 11-17 Scanning electron photomicrograph of a cross section of the tail of an intrauterine contraceptive device (Dalkon Shield) that had been in place for 12 years. Note the multifilament structure with internal spaces (*arrow*) that permit safe movement of bacteria.

ting edge. The Verres needle and primary trocar are inserted around or within the umbilicus and directed in the midline toward the hollow of the pelvis. Secondary trocars are usually inserted off the midline, through the rectus muscle, and the internal puncture site is usually viewed from the primary trocar site through a laparoscope. Recently, disposable pyramidal trocars have become available and are widely used because they are exceedingly sharp. This characteristic tends to reduce the force necessary to penetrate the anterior abdominal wall and hence may reduce uncontrolled thrust injuries to the peritoneal contents and the retroperitoneal structures.[152] The disposable pyramidal-tipped trocars have a retractable plastic shield that is supposed to advance over the sharp pyramidal point once anterior wall penetration is achieved. Gynecologic operative procedures by laparoscopy (pelviscopy) include the use of scissors, scalpels, clips, thermocoagulation, monopolar and bipolar electrical coagulation, and lasers.

The single most common use of laparoscopy is for female sterilization. The most serious direct complication has arisen from the use of intraperitoneal electrofulguration by monopolar techniques.[153] During the 1970s, unrecognized bowel injury with delayed perforation, sepsis, and death related to these techniques led to significant modifications of the electrosurgical generators and to a trend away from the use of monopolar electrical current to bipolar current and to the development of mechanical devices designed to obstruct the fallopian tubes. Another associated injury is intravasation of the insufflating gas with gas embolization.[153] The medium used most often is CO_2, which because of its solubility constant requires large volumes before symptoms are precipitated. The clinical and pathologic changes are discussed under the topic of gas embolization.

Other significant injuries that occur secondary to laparoscopic and pelviscopic procedures include penetration and laceration injuries occurring with the Verres needle or trocar and electrical burns and laser injuries to structures near the operative sites.[154] Complications necessitating laparotomy are reported in about 3 of 1,000 cases, and deaths are reported in 1 in 11,000 procedures.[154] Lethal vascular injuries have occurred secondary to Verres needle and trocar injuries to the aorta, vena cava, or the common iliac vessels. Most often, deaths follow obvious trocar injuries to the major vessels.[155] Verres needle vascular injuries can be detected by careful dissection of the major vessels. In these cases, there usually is extensive retroperitoneal hemorrhage.

Unrecognized gastrointestinal injuries of a significant nature are common and often become medicolegal issues. The nature of these injuries is important in ascertaining causation and instituting or designing preventive techniques or equipment. The main question has been whether there are distinctive histologic changes attributable to a thermally induced injury versus a perforation-type injury.[156,157] From the clinical perspective, surgically induced perforations manifest within a day or so after the injury, whereas perforations induced by thermal injury occur some days later. With sterilization by unipolar electrofulguration, death most commonly followed sepsis that developed after presumed electrical bowel injury with subsequent perforation. The exact mechanism for the injury is unknown, although it was attributed to spark gapping, inadvertent touching of adjacent bowel with an active electrode or hot instrument, or even by the heat retained within the fulgurated tissue itself. In 1981, this led to an admonition by the American Association of Gynecologic Laparoscopists that methods other than unipolar sterilization should be used for female sterilization.

Levy and colleagues studied the effects of four types of intestinal injuries in rabbits at 24, 28, 72, and 96 hours.[156] They felt that there were distinct differences between electrical injuries (unipolar and monopolar) and puncture injuries. As in a previous report by Thompson and Wheeless in a small series of human cases with presumed unipolar electrical injury, it was noted that, in contrast to a puncture injury, electrically induced injuries had coagulative necrosis with a relative absence of white cell infiltrates within the lesion site.[157] In contrast to the observations of Thompson and Wheeless, Levy and colleagues did not correlate more extensive necrosis of the outer muscular bundle of the bowel with an electrical injury. From our own observations of 3 known electrical injuries and 3 puncture injuries, the former injury to the outer muscle layer was notably more extensive and somewhat characteristic, as Thompson and Wheeless reported.[157] We have noted similar patterns of injury to the muscularis of the fallopian tube after unipolar and bipolar electrofulguration procedures (Figs. 11-18 and 11-19). Puncture injuries tend to tear or cut muscle bundles, with muscular retraction being somewhat greater in the outer muscle bundle. The sharp nature of the injury is usually apparent, even in injuries to the bladder, where the muscle pattern is not as distinct as in the bowel (Figs. 11-20 and 11-21). The excised bowel segment at the perforation site should be sectioned carefully to exclude a surgically independent cause of perforation, such as a ruptured diverticulum.

Large and small bowel puncture injuries occur most often because of adhesions and frequently are unrecognized by the surgeon because the segment of involved bowel adheres to the anterior abdominal wall at the peritoneal trocar site. The surgeon, therefore, is unable to recognize the possibility at the time of surgery unless a 360° scan of the anterior peritoneum is carried out and the bowel is visualized coming up to the trocar site. For an accurate assessment of the cause of injury, careful observations at the time of corrective surgery should be recorded.

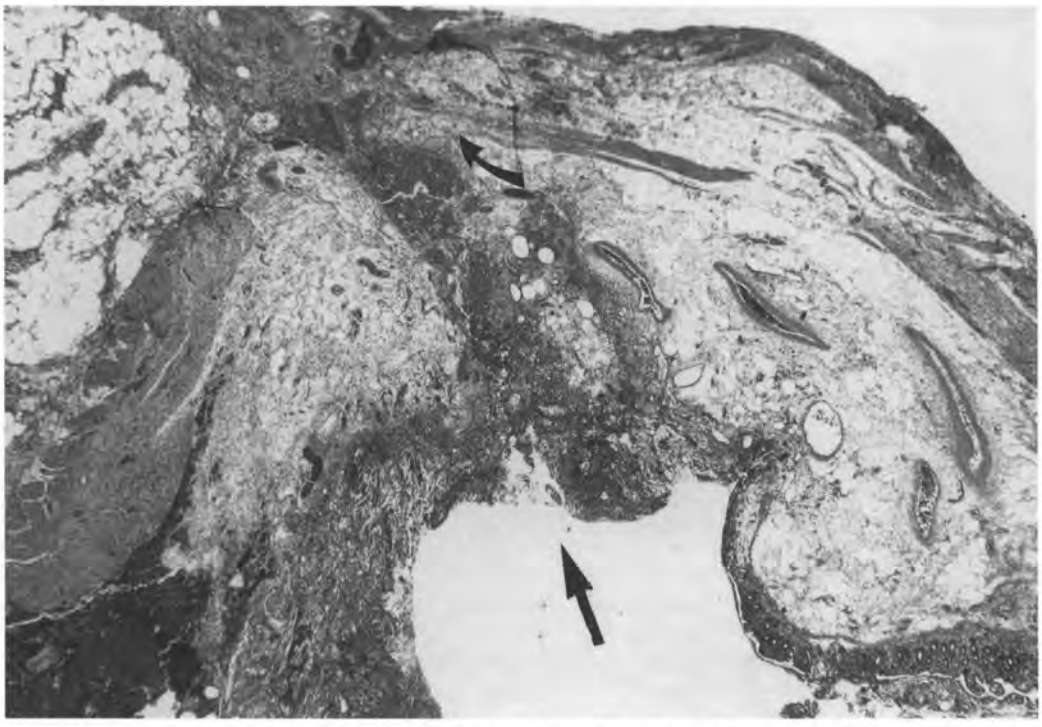

FIGURE 11-18 Exit trocar injury to the small bowel (*straight arrow*) with stretching, tearing, and acute inflammatory infiltrate involving the muscularis (*curved arrow*). The injury occurred during a laparoscopic sterilization procedure 8 hours before this specimen was taken and was identified by bowel contents leaking through the umbilical trocar site.

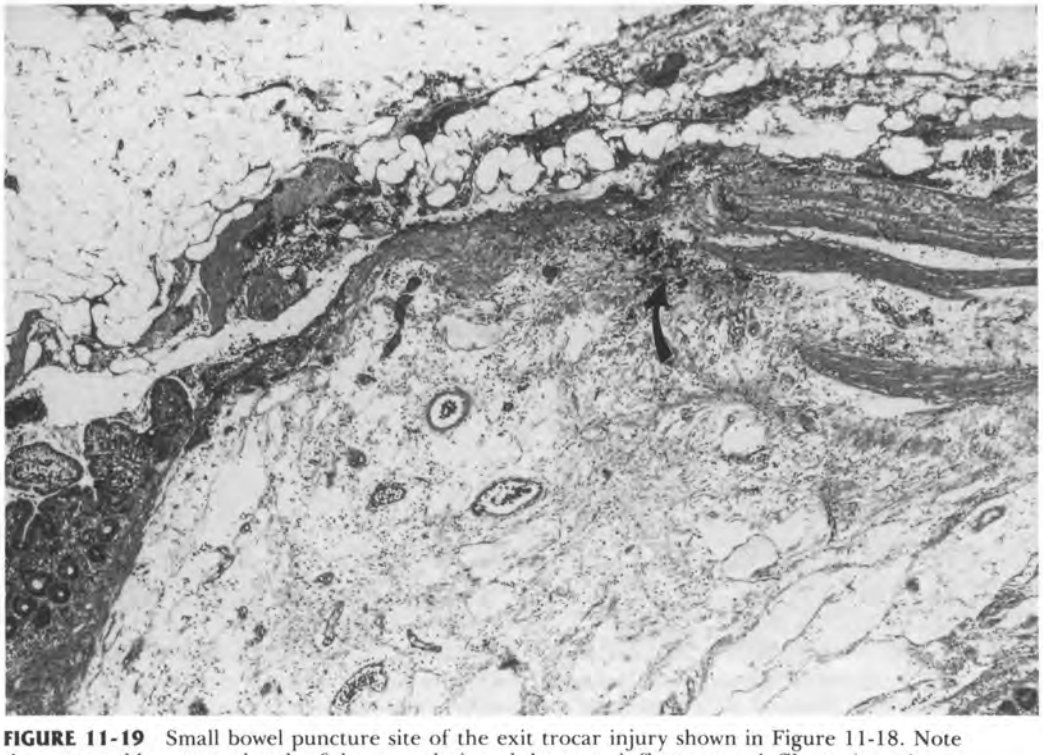

FIGURE 11-19 Small bowel puncture site of the exit trocar injury shown in Figure 11-18. Note the retracted but severed ends of the muscularis and the acute inflammatory infiltrate (*arrow*).

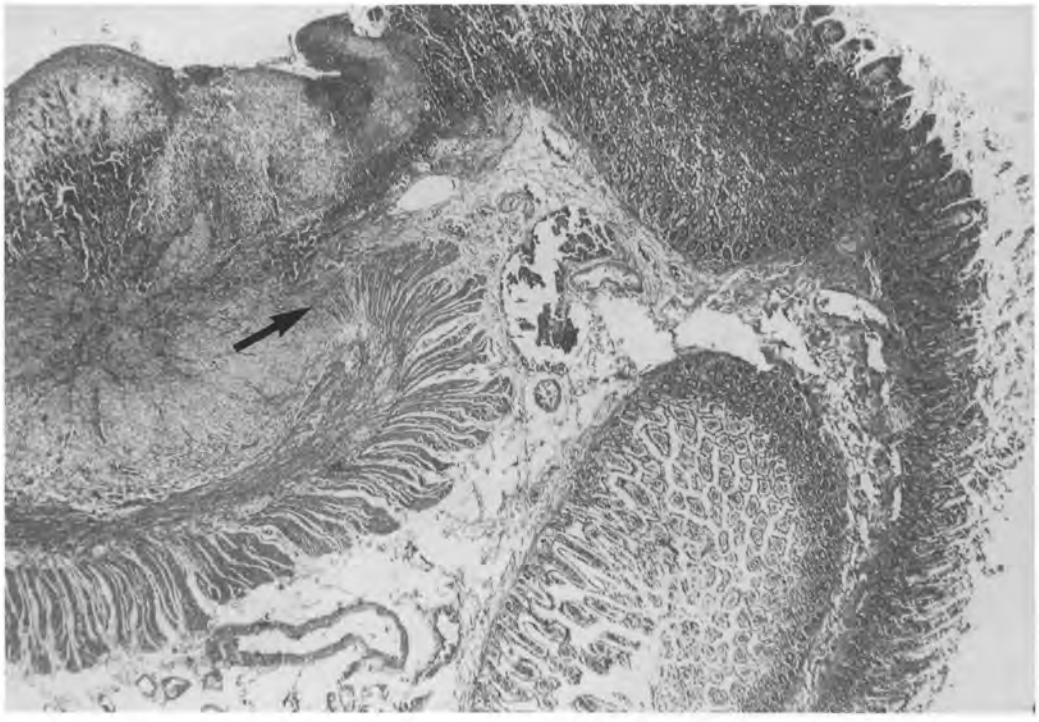

FIGURE 11-20 Site of a perforation 6 days after lysis of bowel adhesions using monopolar electrosurigcal devices. Note the contracted muscularis with more marked loss of the outer muscle layer (*arrow*).

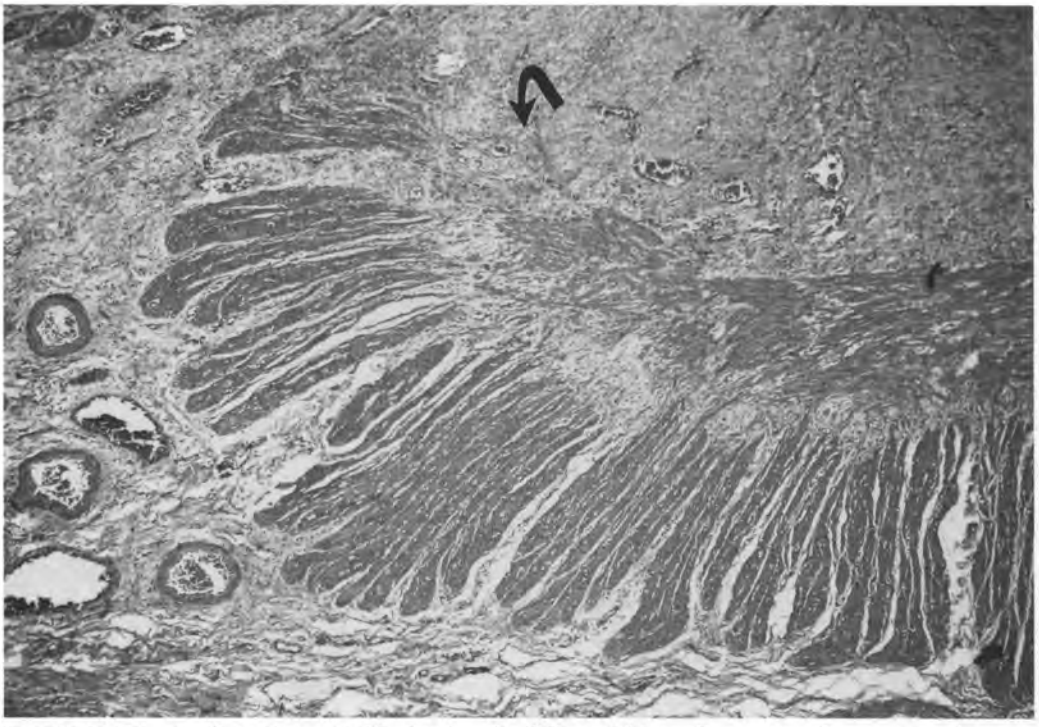

FIGURE 11-21 Detail of Figure 11-20, showing the differential loss of outer muscle mass (*arrow*) with contraction pattern and little local acute inflammatory infiltrate.

VAGINAL DOUCHING

Air embolism is a potential hazard of vaginal douching during pregnancy (see the section on air embolism). Air and fluids injected intravaginally may pass through the endometrial cavity and fallopian tubes to enter the peritoneal cavity, much in the same fashion as in diagnostic tests such as hysterosalpingography. Two problems may be seen secondary to such an event. First, the patient may present with abdominal discomfort and, if in the process of medical evaluation an upright x-ray film of the abdomen is obtained, free air may be visualized beneath the diaphragm. This could lead to an unnecessary laparotomy with a preoperative diagnosis of ruptured viscus. The second problem is the intraperitoneal instillation of nonsterile fluid, irritating chemicals, or both. Acute bacterial salpingitis or peritonitis or chemical peritonitis may ensue. Some researchers believe that talc powders are implicated in the pathogenesis of malignant epithelial tumors of the ovary.

TOXIC SHOCK SYNDROME

Toxic shock syndrome was originally described in 1978 by Todd and associates.[158] They showed a relation between the syndrome and the finding of *Staphylococcus aureus,* phage group 1, in mucosal or sequestered sites. The systemic syndrome is a multisystem illness with a wide range of signs and symptoms. The Centers for Disease Control definition for the syndrome includes the following:

Fever of 38.9°C (102°F) or higher
Diffuse macular erythroderma
Hypotension
Systemic symptoms involving three or more of the following organ systems: gastrointestinal, muscular, mucosal membranes, renal, hepatic, hematologic, or central nervous system
Desquamation 1 to 2 weeks after the onset of the illness
Negative serologic tests (Rocky Mountain spotted fever, leptospirosis, or measles)
No evidence of another cause for the illness.

The toxic shock cases rapidly gained national attention because they were reported in large numbers among young, previously healthy women who were menstruating.[159] By October 1981, 1330 cases were reported to the Centers for Disease Control, with a case fatality rate of 5.9%.[160] Although toxic shock syndrome has been reported in males and is associated with a multitude of surgically and nonsurgically caused focal infections, about 90% of cases occur in women at or near the time of menstruation, most of whom have been using tampons. Early in the 1980s, epidemiologic data suggested that the syndrome had a direct relation with the chemical composition and absorbency capacity of newer tampons introduced in the late 1970s.[161] Although the chemical composition of these tampons has been modified, toxic shock syndrome remains a risk for tampon users, especially those in their late teens. The mechanism for initial mucosal injury was thought to be secondary to vaginal mucosal drying with point ulceration, allowing staphylococcal colonization.[160] There has been some question regarding the association of toxic shock syndrome with features other than menstruation and the use of tampons. Lanes and colleagues noted a positive association with a recent history of vaginitis and a negative association with oral contraceptive use.[162] After high absorbency tampons were withdrawn from the market in 1981 and the absorbency of other tampons was lowered through 1985, the incidence of menstrual-associated toxic shock syndrome has markedly decreased. The fatality rate has declined to about 2%.

Recently, cases of toxic shock syndrome have been reported in association with the use of vaginal contraceptive sponges made of polyurethane. The symptoms and signs are not related to menstruation. Toxic shock syndrome also has been reported in association with genital laser procedures, and there have been similar clinical presentations secondary to group A streptococcal infections involving spontaneous abortion.[163,164]

The major cause for the syndrome complex is almost always an infection with a strain of *S. aureus* that produces exoprotein toxins. Most of the menstrual-associated toxic shock cases are related to *S. aureus* strains producing toxic shock syndrome toxins.[165] Other toxins, particularly enterotoxins B and C, can produce identical symptoms, as can some of the streptococcal toxins.

The histopathologic changes noted in fatal cases are similar to the changes previously reported in scarlet fever.[166] The predominant pathologic lesion appears to be that of vascular injury. The main findings have been in the skin, vaginal mucosa, lung, liver, and kidney. Mucosal edema, ulceration, and perivasculitis are seen in the vagina. In the lung, pulmonary congestion, alveolar hemorrhage, edema, and hyaline membrane formation are frequently noted. Periportal inflammation and microvesicular fatty change are seen in the liver. The renal changes are most consistent with acute tubular necrosis. In addition, occasional cases of adrenal hemorrhage have been recorded.

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12 New Technologies in Gynecologic Pathology

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CYTOMETRY

Measurement of DNA content has been a valuable technique in the study of gynecologic tumors for many years.[1] The clinical relevance of DNA content is based on the linkage between extensive chromosome aberrations and shifts from euploidy with loss of modal value. The goal is to better assess prognostic indicators by supplementing subjective histologic type and grading with more objective measurements.

Methodology

There are basic differences between flow cytometry (FCM) and static DNA analyzers. FCM favors the measurement of a huge number of signals, supposed to be single unaltered cells, so that the information on the quantity of "events" is valuable. In static devices, the technique is based on the stoichiometric character of the Feulgen stain, which is directly proportional to the amount of DNA in the nucleus. Individual cells are submitted interactively to a skilled observer, and each single cell is taken into consideration. Superpositions, fragments, and benign accompanying cells are discarded, making the total number of measured cells much lower (200 to 300 nuclei). This interactive morphonuclear analysis allows a stepwise multiparametric discriminant analysis, selecting for each pathologic entity between the most significant morphometric (nuclear area) and densitometric (DNA index) parameters and analyzing the spatial distribution and condensation of the chromatin.[2]

Both FCM and ICM (interactive computerized cytometry) can be applied to fine-needle aspiration material if adequately sampled. A cell suspension at a minimal concentration of 2×10^6 cells/mL in buffer solution is needed for FCM; full details of the procedure are explained elsewhere.[3,4] For ICM, smears can be obtained from aspirates, surgical specimens, or resuspension of paraffin-embedded blocks.[5] Small aneuploid stem lines and intratumoral heterogeneity are detected more easily in aspirates than in tumor pieces.[6] The smears are immediately fixed in EFA (96% ethanol, 75 vol; 40% neutral formol, 20 vol; 5% acetic acid, 5 vol). They can be stored at 4°C.

Comparison of FCM with ICM shows 80% agreement in ploidy assessment. However, some cases judged as diploid by FCM were reclassified as aneuploid by ICM. It is therefore recommended that FCM diploid cases be confirmed by an ICM analysis.[7] The major pitfalls in the accuracy of interactive computerized cytometry arise in the reproducibility of the sampling and staining procedures and in the standardization of the digital analyses.[8]

Ovary

Abnormal karyotypes and DNA values in ovarian cancer have been found in some reports to be independent adverse prognostic indicators of patient survival.[9] The DNA index combined with the number of aneuploid clones and the S-phase fraction is prognostically significant.[10] The DNA content in

both primary tumors and metastatic ascites is predominantly hypodiploid and paratriploid.[11–15] Aneuploid tumor cells are more often identified in advanced cases than in earlier stages of the disease.[3] Paratriploid tumors also are more disseminated at the time of diagnosis, which could be due to an early loss of chromosomes followed by duplication of the hypodiploid clones leading to near triploidy.[16] Neardiploid tumors have a more favorable prognosis.[17]

Tumors of low malignant potential (borderline tumors) should perhaps be reassessed in the light of their DNA analysis. Five of 35 of these ovarian borderline tumors studied by our group (unpublished data) were hyperdiploid and aneuploid, suggesting that they should be considered early carcinomas.

Corpus Uteri

In endometrial carcinoma, diploid tumors have a better prognosis than aneuploid tumors,[17] and the ploidy group is related to the degree of differentiation. Attempts to differentiate between atypical hyperplasia and carcinoma give inconclusive results by DNA analysis, because diploidy with occasional peridiploidy is present in atypical hyperplasia and in early carcinoma.[9] Morphometry sometimes helps in the differential diagnosis of papillary carcinoma with or without a background of atypical hyperplasia.[18]

Cervix

Premalignant lesions show two groups of modal values, one at the diploid level and one at the hypertriploid-tetraploid level, with in situ carcinoma having undergone less change than invasive carcinoma. Histograms obtained from severe dysplasia and carcinoma in situ were found sufficiently different compared with those from mild lesions to be proposed as an automatic prescreening procedure for cancer diagnosis.[19]

Changes in nuclear shape and chromatin structure observed in cervical intraepithelial neoplasia (CIN) have been compared with normal cells on reference smears. Not surprisingly, significant deviations were also detected close to the intraepithelial lesion in histologically normal-appearing cells, auguring possible recurrence after surgical excision or ablation of the visible lesion.[20] The risk is highlighted by the demonstration of human papillomavirus in the nuclei of "normal" epithelium adjacent to lesions and persisting in the residual tissue after local treatment.[21]

A comparative study between a group of pure CIN III cases and selected CIN areas adjacent to the invasive component of cervical cancers revealed significant differences in a panel of photometric features. The CIN lesions associated with invasive cancer all showed features consistent with potentially progressive lesions, whereas the pure CIN cases could be divided into a similar cluster (62% of patients younger than 45 years, and 27% of those older than 45 years) and a separate cluster suggesting the possibility of regression.[22]

Cervical squamous cell carcinomas are near diploid or hypertriploid.[23] DNA analyses tend to suggest that tumors with large nuclei and a triploid to tetraploid range have a better survival rate and late distant metastases. Those peridiploid tumors with a worse prognosis can be identified histologically as of the small cell type.[17]

Breast

Many prognostic indicators have already proved to be relevant in breast cancer, and every new machine-generated parameter or combination of parameters must provide nonredundant information. They can be used to quantify objectively the subjective appraisal of the shape, size, and hyperchromatism used in the scoring of Bloom and Richardson.[24] They are equally informative with fresh imprints or with smears from fine-needle aspiration.[25,26]

DNA content and its derivatives (DNA index, DNA malignancy grade) have been correlated more or less successfully with histologic grading, receptor status, and lymph node status.[27,28] Involvement of the axillary lymph nodes is most important in the prediction of disease-free interval.[29] By DNA measurements, both node-negative and node-positive cases can be split into separate prognostic subgroups.[30]

Correlation of aneuploidy with tumor size is biased by the frequency of diploid, small, nonpalpable tumors easily detected by mammography during their indolent course. Aneuploidy often precedes the invasive stage; aneuploid tumors grow more rapidly, and their aggressive behavior is correlated with absent estrogen receptors and poorly differentiated histologic type.[30–33]

Measurements of the nuclear area in invasive cancers are in agreement with the concept that less aggressive tumors contain cells with smaller nuclei.[25,34] These measurements have been used to differentiate between atypical ductal hyperplasia and in situ carcinoma.[35]

Nuclear DNA distribution is supposed to predict the outcome of the disease, but results from different groups remain contradictory. Clinical application to the care of individual patients should be considered questionable. In this regard, study of the S-phase fraction in combination with ploidy[27] or the combined use of DNA content and histologic characterization[9] seem better than either method alone. For some authors, there is no clear relation between histogram distribution of DNA and 5-bromodeoxyuridine (BrdU) labeling index. There may be tumors with hyperdiploid or frankly aneuploid cells but with low S-phase fraction, raising the question of the biological significance of these aneuploid cells.[36]

Another promising application is the study of morphometric and textural modifications of breast tumor cells related to their response during chemotherapy.[37] These studies promise to be useful in the identification of chemosensitive stem lines and may help to develop new therapeutic strategies.

Conclusion

The ability of DNA ploidy to predict recurrence and survival is more reliable in early stages of cancer, but ploidy and other cytometric determinations do not facilitate the early diagnosis of malignancy. Moreover, no single parameter threshold has a specific meaning. When assessing the information that a single parameter provides, it is necessary to consider whether that factor has a direct impact on other relevant prognostic factors.

DNA content is a stable, easily measured marker of tumor cells. It gives valuable information about the biology of the cell, which must not be confused with the clinical behavior of the clone. How these measurements may be applied to the management of individual patients with cancer remains controversial. The measurements should not be used for individual therapeutic decisions.

IMMUNOHISTOCHEMICAL ANALYSIS OF CELL CYCLE-RELATED ANTIGENS

Cell kinetic information is becoming a valuable adjunct to histopathologically based tumor classification. It is well known that the identification of proliferating compartments in human tumor tissues is important in predicting biological behavior. Among the various methods used to assess cell proliferation or cell kinetics in human surgical specimens submitted to pathology laboratories, immunohistochemical analysis of cell cycle-related antigens has several advantages over other reported methods, including thymidine labeling index, BrdU, and FCM: cellular and tissue architectures are maintained (especially compared with FCM), the method is relatively simple and rapid, and the use of radioactivity is avoided. Therefore, immunohistochemical detection of cell cycle-related antigens has the potential to become important in assessment of tumor cell kinetics in pathologic material routinely submitted to the laboratory. This section reviews the three cell cycle-related nuclear antigens most extensively studied in human tumors by immunohistochemical methods.

DNA Polymerase α

DNA polymerase α is an enzyme that plays a central role in DNA replication in mammalian cells.[38] The production of a monoclonal antibody against DNA polymerase α provided a new method for detecting proliferative activity of both tumor cells and normal cells with high proliferative activity.[39] The enzyme is localized in the nucleus at the G_1/S or G_2 phase and in the cytoplasm at the M phase of cultured human cells; it is not detected in resting cells.[40] DNA polymerase α was extensively studied immunohistochemically in various human neoplasms by Tsutsumi and colleagues.[41] In human gynecologic tumors, Mushika and associates reported that the proportion of cells positive for DNA polymerase α increased progressively in dysplasia, carcinoma in situ, and invasive squamous carcinoma of the cervix.[42] However, immunostaining of DNA polymerase α requires frozen sections, and in our experience the results are easily affected by fixation. Therefore, analysis of DNA polymerase α is not widely used in diagnostic laboratories.

Ki67

Ki67 is a mouse monoclonal antibody that was produced by Gerdes and colleagues in 1983.[43] The precise nature and composition of the antigen are unknown, but it is considered to be a nuclear antigen present in all phases of the cell cycle except for the G_0 phase.[44] It has been postulated that the number of cells with positive immunoreactivity of Ki67 per total number of tumor cells represents the number of cells cycling at any one time (ie, the growth fraction). However, Ki67 labeling obtained by immunohistochemistry in various tumors has not necessarily been consistent with flow cytometric studies and the usual clinical and histologic parameters used to predict clinical outcome.[45] Ki67 labeling also requires frozen sections, as in the case of DNA polymerase α, but can be demonstrated on cytologic smears if appropriately processed.[46] Ki67 labeling eventually may be worth incorporating into a routine diagnostic service, but it awaits further investigations to be established as an independent prognostic indicator.

Proliferating Cell Nuclear Antigen

Proliferating cell nuclear antigen (PCNA) was discovered initially by Miyachi and associates as a nuclear antigen that reacts with an autoantibody in the sera of some patients with systemic lupus erythematosus.[47] Subsequent studies have revealed that the expression of this 36-kd nuclear antigen correlates with the late G_1 and S-phase of the cell cycle.[48] PCNA later turned out to be an auxiliary protein of DNA polymerase δ and is considered to play an important role in the initiation of cell proliferation.[49] Recently, Hall and colleagues employed monoclonal antibody PC-10, which recognizes a fixation- and processing-resistant epitope of PCNA and thus is appropriate for immunohistochemistry in routinely processed surgical pathology specimens.[50] With the introduc-

tion of this antibody, immunolocalization of PCNA has a practical advantage over that of Ki67 and DNA polymerase α for assessing cell kinetics on tissue sections: PCNA can be detected to some extent in formalin-fixed and paraffin-embedded specimens. This makes retrospective studies of cell kinetics possible. However, PCNA immunoreactivity is considerably influenced by tissue preparation, especially choice of fixatives and duration of fixation. In addition, intra- and interobserver errors in interpretation are still prominent. The PCNA labeling index has been demonstrated to be consistent with the Ki67 labeling index,[50,51] BrdU incorporation,[50] and flow-cytometric S-phase analysis,[52] although conflicting data have been reported. Contradictory results have been reported in correlation of the PCNA labeling index with the clinical outcome of various malignant tumors.

The variability of PCNA data obtained in previous investigations may be due to lack of sensitivity in the immunohistochemical detection system, lack of uniformity in preparing the tissue specimens, the choice of antibodies, or differences in scoring methods (eg, how to interpret weakly stained PCNA immunoreactivity). At this juncture, PCNA labeling is best assessed by (1) using immediately and briefly fixed (10% formalin or 4% paraformaldehyde) and paraffin-embedded specimens; (2) employing a monoclonal antibody against a tissue-processing-resistant epitope of PCNA; and (3) counting all PCNA-reactive nuclei as positive regardless of intensity of immunostain. Under these conditions, PCNA was successfully and reproducibly localized in our laboratory in surgical pathology materials including gynecologic specimens (Figs. 12-1 and 12-2). We recommend incorporating PCNA immunohistochemistry into the techniques available in pathology laboratories.

AgNORS

Nucleolar organizer regions (NORs) are loops of ribosomal DNA (rDNA) present in the nuclei of cells that possess ribosomal RNA (rRNA) genes.[53] These rRNA are transcribed by RNA polymerase I and ultimately direct the synthesis of protein. Therefore, NOR numbers appear to reflect cellular and nuclear activity. NORs can be easily visualized by a silver impregnation technique originally described on metaphase chromosome spreads and then applied to histologic sections. Since Crocker and Nar reported a one-step silver staining technique for nucleolar organizer regions applicable to routinely processed formalin-fixed and paraffin-embedded tissues,[54] the method has been widely used in the study of human neoplasms. The argyrophilic structures obtained by a one-step silver stain (AgNORs) are NOR-associated nonhistone nucleoproteins.

AgNORs appear as multiple granular, well-defined, black, silver-stained intranuclear structures, sometimes in aggregates within the nucleolus (Color Figure 12-1). In human ovarian epithelial tumors (Sasano and associates, unpublished observations), the mean number of AgNORs per nucleus is correlated with histologic nuclear grade (Fig. 12-3) and histologic type of the neoplasms (Fig. 12-4). However, Wilkinson and colleagues studied AgNORs in human endometrial lesions and found no significant differences of the mean number of AgNORs per nucleus among intraendometrial neoplasia, hyperplastic mucosa, and normal proliferative mucosa, with a slight increase in invasive adenocarcinoma.[55]

AgNOR staining and counting is a relatively easy and simple method, and only a darkroom facility is required when performing this stain in diagnostic pathology laboratories. AgNORs are, however, associ-

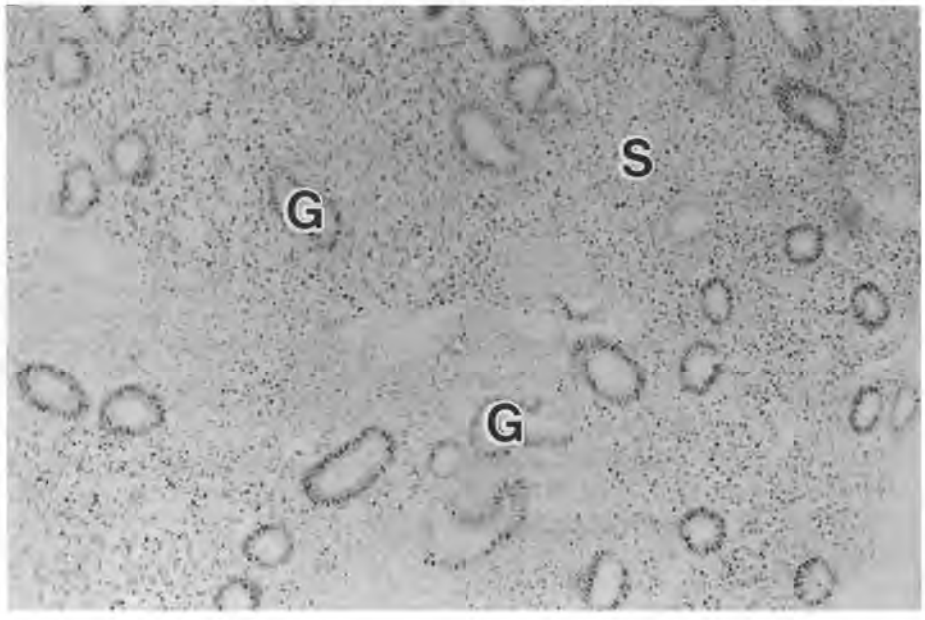

FIGURE 12-1 Immunolocalization of proliferating cell nuclear antigen in proliferative human endometrium. Immunoreactivity is observed in stroma (*S*) and glands (*G*).

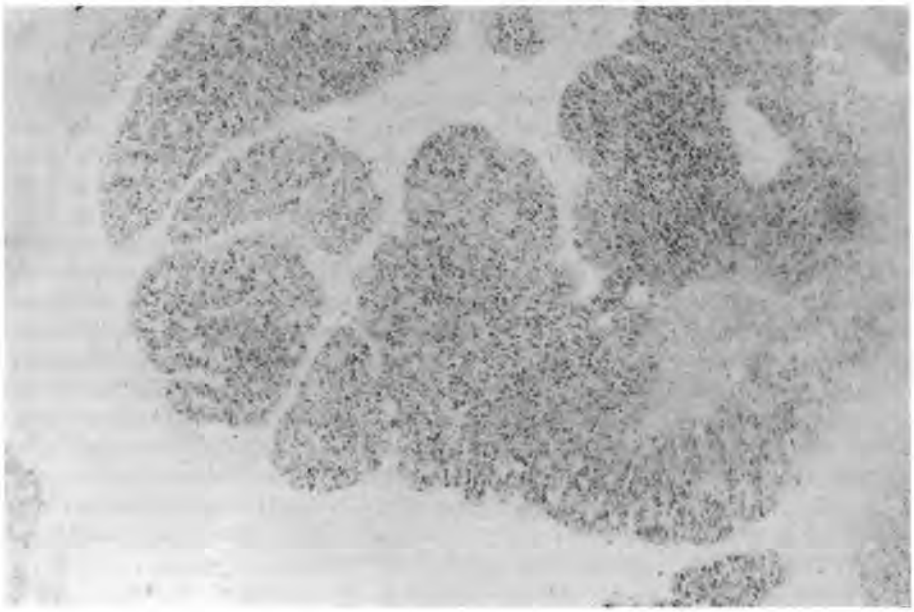

FIGURE 12-2 Immunolocalization of proliferating cell nuclear antigen (PCNA) in poorly differentiated endometrial adenocarcinoma. Almost all the tumor cells are positive for PCNA.

ated with several major technical problems, including intra- and interobserver errors in counting the silver grains, and the effects of fixation (increasing fixation time resulting in a tendency for the smaller intranucleolar dots to coalesce).[56] In addition, increasing numbers of reports have demonstrated no relation between AgNORs and prognosis, clinical course, cell proliferation indices, and DNA ploidy.[57] Therefore, the practical value of AgNORs remains to be evaluated at this juncture.

KARYOTYPING

At the beginning of the century, Boveri expressed the theory that mitotic anomalies lead to malignant transformations.[58] The results of cytogenetic studies conducted on animal and human tumors over the subsequent three quarters of a century have favored this hypothesis, and chromosome anomalies are today considered a major event in carcinogenesis.[59] The current karyotype nomenclature is based on the banding techniques of the 1970s,[60] which individualized 500 to 600 chromatin segments and was crucial in proving that almost all tumor metaphases are actually abnormal.[61]

For a couple of decades, cytogenetic studies have been more rewarding in human leukemia than in solid tumors, because the higher mitotic rate and natural suspension state of bone marrow aspirates fa-

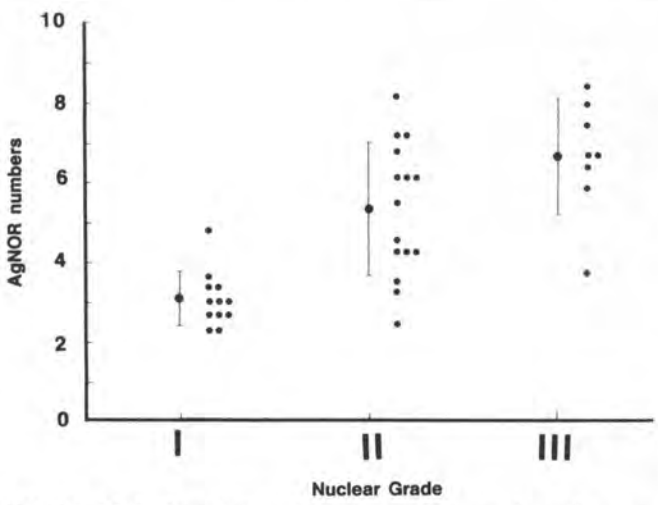

FIGURE 12-3 Correlation between nuclear grade and mean number of AgNORs per nucleus in serous and mucinous carcinoma of the ovary.

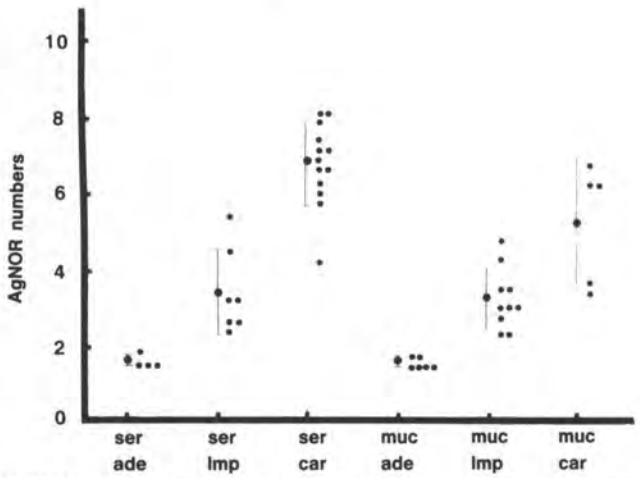

FIGURE 12-4 Correlation between histologic types of ovarian serous and mucinous neoplasms and pooled mean AgNOR numbers per nucleus. *ser ade,* serous cystadenoma; *ser lmp,* serous adenocarcinoma of low malignant potential; *ser car,* serous adenocarcinoma; *muc ade,* mucinous cystadenoma; *muc lmp,* mucinous adenocarcinoma of low malignant potential; *muc car,* mucinous carcinoma.

vored cytogenetic analyses in the leukemias. Although appropriate studies of chromosomes in solid tumors are still few (less than 20% of more than 14,000 cancer cases in one major analysis[62]), they prove that nonrandom specific changes occur in solid tumors the same way they do in leukemias and lymphomas, hallmarked by an abnormal clone with markers and consistent chromosome breakpoints in the whole cell population.

It is now well established that chromosome rearrangements are nonrandom and often specific for the histologic pattern of the neoplastic proliferation.[63] Some cytogenetic findings are pathognomonic of tumor subtypes, such as t(X;18) in synovial sarcoma, t(12;16) in myxoid liposarcoma, and t(11;22) in Ewing's sarcoma, or of their embryologic origin (iso12p in testicular germ cell tumors).[64,65] This morphology-associated profile may be helpful in cases of uncertain differentiation or origin and is becoming accepted as an aid in the diagnosis of soft-tissue tumors. Despite the fact that epithelial tumors are much more common than sarcomas, sarcomas still constitute the bulk of the reports. This is because their chromosome rearrangements are unique and simple, as they are in hematologic neoplasms, and because they may retain a relative karyotypic stability through clinical progression and metastasis.

The recurrent chromosome breakpoints of benign tumors are not the same as those of their malignant counterparts. There may be specific regions preferentially affected in certain benign neoplasms.[66] It is, however, possible that the underlying cause is the same, although the biological effects depend on the affected breakpoints distinguishing benign neoplasms from their malignant counterparts.[67] Probably at its very beginning, a tumor is still polyclonal and occasionally multicentric. One or a small number of cells initiate the process of neoplasia by monoclonal selection, with the genetic alteration itself allowing the outgrowth of the dominant cell by clonal expansion. The tumors remain monoclonal but heterogeneous, composed of different subclones with subsequent (secondary) chromosome changes selected by their growth advantage, their drug resistance, and the more aggressive biological behavior they can offer.

At the time of surgery and sampling for cytogenetic studies, carcinomas are already fully developed. Their karyotype at that stage is far more complex and is blurred by many secondary changes often not related to a specific disease. Significant primary changes tend to be obscured, and their analysis is puzzling; interpretation is time-consuming and sometimes meaningless. Nevertheless, detection of minor DNA changes remains beyond the resolution of "metaphase cytogenetics" and needs more sophisticated methods, such as molecular genetics or in situ hybridization. This promising new approach uses fluorescent DNA probes specific to known regions of the genome to measure numerical heterogeneity in tumors and even in normal tissues and to demonstrate structural rearrangements.[68,69] Combining in situ hybridization on nuclei isolated from fresh tissue and metaphase cytogenetics will certainly improve the interpretation of complex karyotypes.[70] The major advantage of interphase cytogenetics is that it requires only a small number of cells, its sensitivity allowing the detection of minimal residual disease.[68]

Karyotyping is the first step of recognition of the chromosome profiles of the tumors. Once the profile is characterized, interphase cytogenetics becomes relevant to the study of a larger series, including archival material, allowing an assessment of the prognostic significance of every deviation from normal.

Malignant Tumors

Ovary

The first karyotypic studies in the ovary were conducted on metastatic fluids or cell lines and yielded confusing results. Throughout the bulk of this complex information, chromosomes 1 and 6 and, to a lesser degree, chromosome 11 remain the more consistently involved in structural rearrangements (Fig. 12-5).[14,71–73]

Published studies deal mostly with the common epithelial adenocarcinomas, which represent more than 80% of all ovarian cancers. A t(6;14) translocation was described in 12 papillary cystadenocarcinomas,[74] but it could not be confirmed as specifically and systematically involved in ovarian carcinomas.[72,75–77] However, aberrations of 6q could be an important constituent of ovarian cancer, having been recognized in various histologic types and cell lines.[72,78,79] Chromosome 7 has also been reported in structural or numerical rearrangements.[76,80–82]

In a recent survey, structural rearrangement breakpoints in 53 ovarian carcinomas appeared nonrandomly clustered in certain chromosome regions and could be related to tumor-specific allele loss.[16] The potential existence of a tumor suppressor gene has been suggested in deletions of 6q and 17p, whose loss favors transformation.[83] In the survey, 7 of the 53 carcinomas of the ovary displayed simple karyotypic changes: 5 had numerical changes only (2 of these being trisomic 12) and 2 had a single translocation as the sole anomaly.[16] Such simple karyotypic changes appear to be preferentially demonstrated in well-differentiated carcinomas or in borderline tumors.[84,85] These changes might precede complex aneuploidies acquired during the progressive dedifferentiation of the tumor, according to the theory of clonal evolution as a cause of more aggressive phenotype.[84,86]

Complex karyotypes are more frequent in serous papillary tumors than in mucinous and clear cell carcinomas.[16] Among 46 cases with complex aberrations, chromosomes 1, 3, and 6 were commonly altered, as already mentioned in previous studies; chromosome 19p arms were affected 26 times, and q arms 14 times. Twelve tumors had a breakpoint in

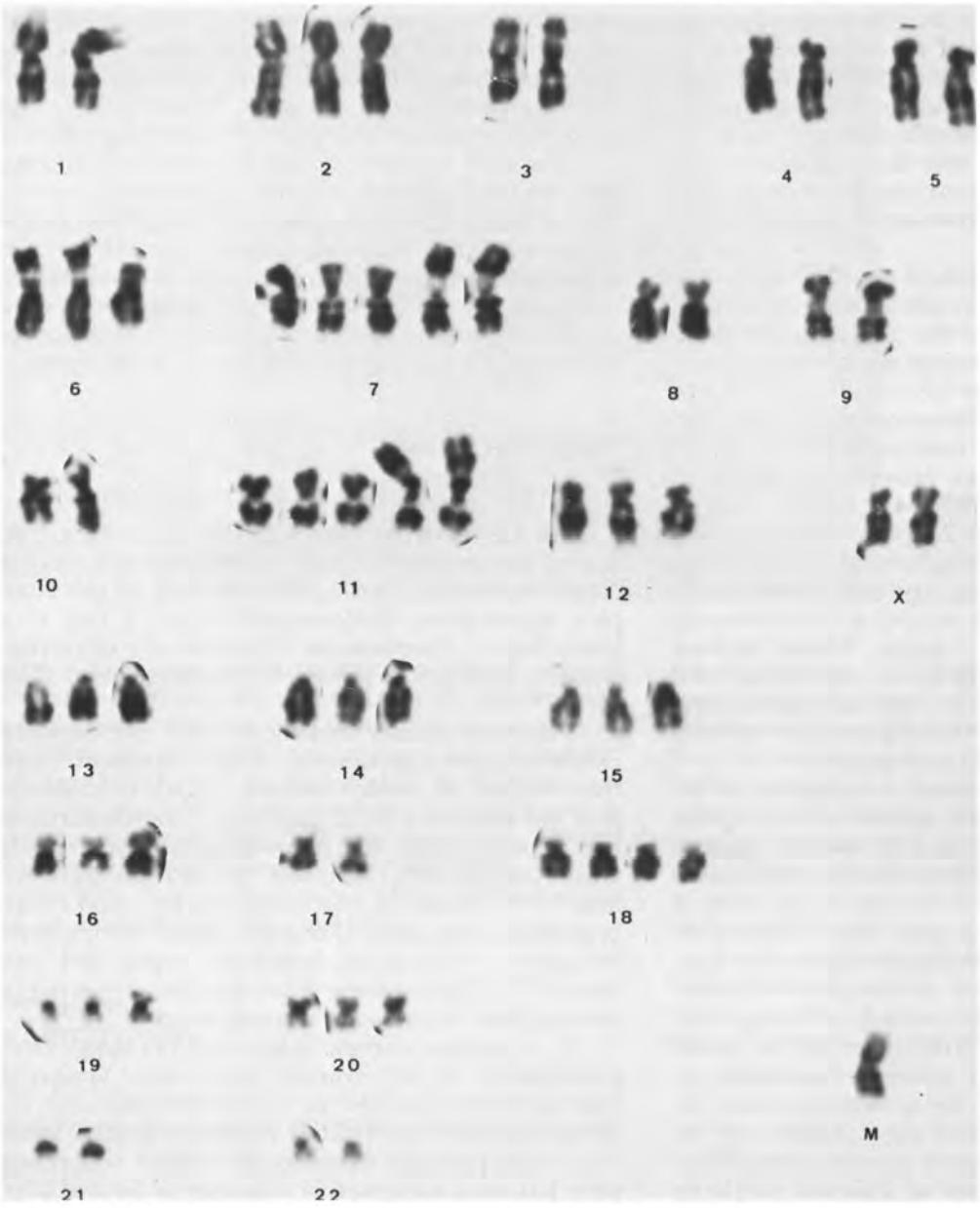

FIGURE 12-5 Karyotype from an ovarian metastatic ascites. Tetraploidization with subsequent losses and structural anomalies affects almost all pairs. Short arms of chromosome 6 are deleted; p arms of derivative chromosome 7 contain a homogeneous staining region; and abnormal chromosomes in pair 11 are der (1;11). (Verhest A, Van Schoubroek F, Lambot M: Identification of abnormal chromosomes in a metastic ovarian tumor. Abstract from the 5th European Congress of Cytology. European Federation of Cytology Societies, Milano, 1975)

11p13. Nevertheless, a common cytogenetic event in the development of ovarian carcinoma has not been detected. A study by Atkin and associates suggested an inverse correlation between the presence of chromosome 1 and survival rate,[75] but this correlation was not significant in another series.[81]

Carcinosarcoma (malignant mixed mesodermal tumor) has been reported only twice: isochromosome for the short arms of nb 5 was noted, and both cases were also triploid.[75,87] Nonepithelial tumors are still poorly documented: two studies of immature teratomas suggest a possible link between poor prognosis and deviations in karyotype.[88,89] Cytogenetic studies of sex cord-stromal tumors deal mainly with the fibroma-thecoma group, in which trisomy 12 was found as a nonrandom change. The same anomaly is shared by some granulosa cell tumors[85,90,91] and uterine leiomyomas.[92] Two reported cases of granulosa cell tumor are comparable, with a structural rearrangement of 6q leading to loss of genetic material.[93,94]

Once again, these simple numerical or structural

anomalies may reflect a low-grade malignant potential,[84] as they do in epithelial tumors. It is premature to draw any prognostic conclusion, however, because 6q breakpoints are found in a broad spectrum of carcinomas, including those of ovarian origin.[62]

Breast

Breast cancer is the most frequently occurring cancer in women living in Europe and North America. It displays a variable and somewhat unpredictable outcome, even in small tumors, and therefore is in need of accurate predictors of behavior. Technical difficulties encountered in solid tumor cytogenetic studies are conspicuous in breast cancer; therefore, specificity of primary changes remains to be confirmed. A recent large study claims a rate of success of 18% (banded karyotypes available), with a final tally of 26 meaningful cases.[95] The results show the great instability of the population, often without clearly defined modal values. Two ductal carcinomas with early invasion had a diploid karyotype; most tumors were in the triploid range, sometimes with a hypodiploid sideline. One or more sites were involved in almost 80% of the published observations on chromosome 1, and chromosomes 3 and 11 were affected in 45% of the cases.[62,95] In other series, rearrangements of chromosomes 6, 7, 11, 16, and 17 were noted;[96–99] they are not considered as primary but rather as secondary (acquired during tumor progression), and they may confer a selective advantage in cell proliferation. In another study, trisomic cells for chromosomes 1 and 18 were detected by in situ hybridization in an otherwise diploid DNA pattern.[100]

Several regions on chromosome 1 are the targets of rearrangements that result in genic imbalance between alleles,[96,97,99,101] implicated in breast cancer development.[102] Loss of chromosome 16 is another interesting feature.[98,99] This loss is sometimes preceded in a first evolutionary step by long-arm rearrangements leading to homozygosity of the 16q21-24 segment in early carcinomas. This segment thus has been proposed as a site of a putative breast cancer suppressor gene relevant to cancer initiation.[95] This chromosome could be discarded in later stages by further multiple abnormalities related to tumor progression. Allelic defect is not limited to chromosome 16 in breast cancer.[98,103] A 17p deletion has been identified,[104,105] including the locus of the p53 gene.[106] The protein product of this gene plays a role in the regulation of the cell cycle and is considered a potential antioncogene (see below).

As expected, loss of heterozygosity (LOH) and oncogene amplification are not limited to breast cancer; 1q, 3p, 11p, 13q, and 17p sites of mutation are shared with other epithelial tumors of the lung, gastrointestinal tract, and kidney and urinary tract, and with some sarcomas.[107]

Somatic mutations have been related to other prognostic factors, such as hormone receptors and histologic grade.[108] However, no significant association with disease-free interval and overall survival can be accurately drawn due to the lack of reproducibility of the results among different authors. Lack of uniformity in the statistical management of the data is another pitfall.[107,109] Quantitative DNA analysis appears more relevant to prognostic assessment.

Corpus Uteri

In a recent comprehensive survey, only 25 cases of cytogenetically analyzed endometrial carcinoma could be collected from the literature.[15] More recently, 24 new observations have been reported in detail.[110] Trisomy and tetrasomy 1q appear the most consistent anomaly in these series, with a mean frequency of 75%. Breakpoints on chromosome 1 are common in human neoplasia but are generally considered nonspecific.[111] Trisomy as a sole anomaly would suggest a real primary change, possibly related to the early stage of development of carcinoma. Although trisomy 10 is the second most frequent anomaly,[110,112] about 30% of stage I carcinomas remain diploid or beyond the resolution of current banding techniques. Whether those "normal" mitoses originate from cancer cells or from stromal benign cells is still controversial.

No correlation could be found between chromosome patterns and prognostic parameters such as age, hormonal status, histologic grade, and TNM stage.[110] There thus seems to be little chance to get any relevant information relating to progression to carcinoma from karyotypic rearrangements in borderline endometrial lesions.

Carcinosarcomas (malignant mixed mesodermal tumors) are reported to present complex abnormalities with no identical rearrangements.[110]

Cervix

Invasive Carcinoma. Cytogenetic mapping of genes involved in the initiation, development, and progression of cancer provides some clues to which regions are more susceptible to mutagenicity. It appears that cytogenetic changes related to cervical cancer are variable, some directly related to the neoplastic transformation itself, others to the viral integration process or to the step of progression to invasive cancer. These nonrandomly distributed structural rearrangements affect highly significantly both arms of chromosomes 1 and 11, but also 3p, 6q, 17p, 18p, and 21q in deletions, duplications or translocations.[113] Duplication resulted in iso17q in one case, with anomalies emerging early in the microinvasive phase.[78] No correlation could be drawn with the histologic type,[113] but chromosome 1 rearrangement is suggested to be linked with a proliferation advantage for the cell.

Cervical Intraepithelial Neoplasia (CIN). Cytogeneticists have been attracted from the beginning to this model of human carcinogenesis. The continuous slow evolution through the dysplastic changes fluctuating from regression to relapse has shown precocious minimal structural anomalies and modal deviations.[114] Multiple preinvasive lesions with different karyotypes in the same cone biopsy raised the question of the multiclonality of such lesions before their clonal expansion.[115]

The high rate of failure in obtaining a sufficient number of suitable mitoses (about 1 per 1000 cells) has led and still leads to the wide use of morphometric and densitometric analyses of the interphase nuclei. For the same reasons, no relevant information is available for carcinomas of the vagina and the vulva.

Benign Tumors

Diploidy remains the rule in benign conditions. However, clonal evolution in the ovary was reported more than 20 years ago,[116,117] and in a recent survey trisomy 12 was detected in 3 cases of mucinous and serous cystadenomas.[118]

The recent recognition of nonrandom, clonal chromosome abnormalities in benign tumors rests largely on the study of *leiomyomas* of the corpus uteri. Series are numerous from different groups of investigators.[119,120] Recurrent findings point out that breakpoints affect specific regions such as 7q21 in deletions or 12q14 in translocation. This last band is also involved in benign lipomas, which suggests that the same growth-controlling genes might affect mesenchymal cells in different types of benign soft-tissue tumors but are different from those of their malignant counterparts.[121] Trisomy 12,[92] ring chromosomes, and monosomy 22 are other nonrandom abnormalities described in leiomyomas.[119] Specific regions on chromosomes 1, 7, and 13 and t(12;14) could be important at the molecular level in the control of muscle cell proliferation.[120,122] A normal chromosome complement is retained in about 50% of benign uterine leiomyomas, but 80% of cellular and atypical leiomyomas show clonal abnormalities.[122] The possibility of clonal evolution with additional anomalies is worth keeping in mind because of a relation with increased cellularity and mitotic activity; such cases could be of some unexplained clinical significance.[123]

Fibroadenoma is to the breast what leiomyoma is to the corpus uteri: the most frequent benign tumor, generally considered as an innocuous lesion without risk of malignant transformation. Few studies deal with this tumor. Clonal structural rearrangement was present in one fourth of the cases in a recent series,[124] focusing on 12p anomaly as already noted in a previous report.[125] It is suggested that in the "coproliferation" of epithelial and mesenchymal cells, cytogenetic aberrations are limited to vimentin-positive metaphases.[126]

Borderline epithelial breast lesions remain to be clearly defined before being compared cytogenetically, because they still generate many controversies.[127] Malignant but preinvasive epithelial proliferations do not yield reproducible or convincing results.[128] Because of their focal and widely dispersed nature, they will probably be investigated more satisfactorily by techniques such as in situ hybridization or immunohistochemistry, which can preserve their architecture.

Technical Addendum

The technical difficulties in obtaining a sufficient number of suitable mitoses are beginning to be overcome by the use of collagenase for disaggregation and methotrexate for synchronization.[129,130] A 5-cm^3 specimen in sterile growth medium is enough for transportation to the laboratory. The initiation of the procedure should be as fast as possible and requires a perfect collaboration with the surgeon and the pathologist, who will ensure both good clinical information and a representative, viable sample of the tumor.

ONCOGENES AND TUMOR SUPPRESSOR GENES

Understanding the fundamental nature of human malignancy has been the central theme of a large body of molecular biological research performed during the last two decades. This work has led to the identification of dominantly acting DNA sequences whose expression appears to be associated with conversion of normal cells to cancer cells. These DNA sequences are known as *oncogenes* and were first identified in the genomes of acutely transforming rodent and avian retroviruses, which efficiently transform cells and induce tumors in vivo within 2 to 3 weeks. During the retroviral life cycle, retroviruses incorporate certain genes from their infected hosts in a process known as *transduction.* These transduced DNA sequences have turned out to be so-called viral oncogenes. These findings demonstrated that the genetic sequences responsible for neoplastic transformation by the retroviruses are actually of mammalian or avian DNA origin. There generally are genetic differences between retroviral oncogenes and cellular progenitors because transduction is frequently associated with genetic mutations, including point mutations, deletions, and genetic substitutions. The homologous genes present in mammalian or avian DNA generally are referred to as *cellular oncogenes* or *proto-oncogenes.*

Occasionally, retroviral oncogenes are fused products of more than one cellular oncogene, and oncogenes in some human retroviruses are not homologous to any genes present in eukaryotes but are still

responsible for oncogenic activity by the virus.[131] Increasing numbers of cellular and viral transforming genes are continuing to be detected, characterized, and reported in many scientific journals. Many readers may have noticed the prefixes "v-" or "c-" preceding the names of these genes in various articles. The term v-*onc* denotes an actual retroviral oncogene (ie, the gene of an acutely transforming retrovirus that causes malignant transformation in target cells). On the other hand, c-*onc* denotes a cellular oncogene or proto-oncogene as described above, derived from normal cells, which usually requires activation to cause cellular transformation.

Structure and Function of Oncogenes

The fact that cellular oncogenes are conserved in DNA sequences in mammals led to the postulation that oncogene products might play important roles in normal cell growth and differentiation. Experimental studies have revealed that oncogenes appear to be regulated in a specific manner during fetal development, and that transcription levels for different cellular oncogenes vary in the same tissues at different stages of development. Oncogene products have been investigated and placed into a number of functional categories based on their location in the cell or on knowledge of their action at the cellular level.

Classification

Proto-oncogenes are classified into five major categories.[132,133] The first and largest class of proto-oncogenes encodes protein kinases. This group of proto-oncogenes can be further subclassified into two functional groups: those encoding tyrosine-specific kinases (including *src, abl, fes, fgr, ros, rel, yes,* and *syn*) and those that encode proteins that have a kinase-like domain but do not possess detectable tyrosine kinase activity in vitro (which include *raf, pks, kit, mos,* and *sea*).[133]

The second class of proto-oncogenes is the so-called *ras* family and consists of H-*ras,* K-*ras* and N-*ras.* The *ras* family has different degrees of homology in their effector regions. Each of the genes in the *ras* family is composed of four coding exons with identical intron spacing, and each encodes a 21,000-d polypeptide (p21)[134] that binds GTP and GDP and has a GTPase and autokinase activity. It is located on the plasma membrane when active. The p21 of the different members of the *ras* oncogene family differ slightly in their carboxyl terminus. Members of the *ras* oncogene family containing activating point mutations are generally capable of transforming cell lines.

The third class of proto-oncogenes encodes growth factors themselves. This group includes the *int* and *sis* genes. The *int*-1 gene was identified in mammary neoplasms and encodes a protein in the fibroblast growth factor family. The proto-oncogene v-*sis* is derived from genes encoding a platelet-derived growth factor (PDGF), with 92% homology with the nonglycosylated β-chain of PDGF.

The fourth class encodes polypeptide growth factor receptors or proteins with the characteristic transmembrane structure of a growth factor receptor. This group of proto-oncogenes includes *erb*-A, *erb*-B, *fms,* and *kit.* Characteristically, these proteins span the cell membrane and possess an intracellular cytoplasmic domain and an extracellular domain. Binding of ligands to the extracellular domain of these growth factor receptors generally leads to the activation of the intrinsic tyrosine kinase activity of the intracellular cytoplasmic domain of the receptor molecule, which subsequently results in the induction of cell proliferation.

The last class of proto-oncogenes are those located in the nucleus. They are considered to regulate gene expression with possible DNA binding. This class of proto-oncogenes includes the *myc* group (c-*myc,* N-*myc* and L-*myc*), *myb, fos, ets*-1, *ets*-2, and *ski.* Some of these genes have been demonstrated to encode nuclear proteins that bind regulatory regions in DNA, which subsequently regulate transcription of cellular genes. Gene products of these proto-oncogenes are also considered to play major roles in the transition from quiescence to proliferation in the cell cycle.

Oncogene Activation

Proto-oncogenes or cellular oncogenes derived from normal cells usually do not cause cellular transformation. Therefore, many studies have attempted to explain how cellular oncogenes become involved in the biology of malignant tumors. The data indicate that for proto-oncogenes to play any role in neoplastic transformation and progression, they must go through the process called *activation.* Activation of proto-oncogenes occurs as a result of structural changes that create qualitative changes in their genes and expression levels or quantitative changes in their genes and encoded proteins. The types of structural changes that can cause activation include point mutations, chromosomal rearrangements, and DNA amplification. These changes in the DNA can lead to increased expression of the protein, enhanced activity of the protein, or deregulation of protein expression. The best characterized system demonstrating activation of oncogenes by point mutations occurs in the *ras* gene family, in which point mutations interfere with the binding of *ras* protein to the GAP protein.

DNA amplification of various oncogenes has been documented in numerous human tumors. Gene amplification may be associated with readily recognizable chromosomal abnormalities but, in most cases, DNA amplification of proto-oncogenes occurs without significant quantitative change of the entire DNA content of the cells. Some amplification genes are also rearranged or mutated. Amplification of proto-oncogene can lead to overexpression, by in-

creasing the amount of DNA template available for mRNA production. An increased level of oncogene expression is believed to be a prerequisite for the selective growth advantage exhibited by cells containing additional gene copies. It could also be the principal contribution of gene amplification to tumorigenesis.[135]

Despite these features of proto-oncogene activation, in most naturally occurring human tumors, activation of a single proto-oncogene probably does not lead to immediate malignant transformation. Experiments have indicated that naturally occurring human cancers result from multiple events that may involve activation of more than one proto-oncogene, as well as loss of other cellular genes that suppress the development of the tumor cell type (tumor suppressor genes).

Laboratory Methods to Detect Oncogene Abnormalities in Clinical Laboratories

The initial step in studying whether a proto-oncogene may be involved in the biological or clinical behavior of a human neoplasm is to determine whether it has been activated through one of the processes previously described (point mutation, gene rearrangement, overexpression, or amplification) or through other processes. From the practical standpoint, methods to detect changes of cellular oncogenes in clinical laboratories are classified based on the level of oncogene abnormality the pathologist attempts to study (ie, at the DNA, mRNA, or protein level). The major methods classified by this schema are summarized in Table 12-1. The remainder of this section briefly describes the characteristics of these respective methods, with particular emphasis on advantages and disadvantages from the standpoint of diagnostic laboratories.

TABLE 12-1.
Major Methods to Detect Changes of Cellular Oncogenes in the Clinical Laboratory

I.	DNA levels
	1. Dot/slot blot hybridization
	2. Southern blot hybridization and restriction fragment length polymorphism
	3. Polymerase chain reaction–dot/slot blot hybridization and nuclear sequencing
	4. Others
II.	mRNA levels
	1. Northern blot hybridization
	2. In situ hybridization
III.	Protein levels
	1. Immunoblotting
	2. Immunohistochemistry

DNA Levels

DNA transfection techniques have led to the isolation of genes that cause transformation of NIH3T3 cells, but transfection assays are still tools of basic science laboratories, as is insertional mutagenesis assay. Therefore, DNA abnormalities are generally examined on immobilized DNA sequences, with the possible exception of nucleotide sequencing in the clinical laboratory setting.

Dot/Slot Blotting. This technique is the most simple of the DNA hybridization methods and has been used in various clinical laboratories. The technique itself is based on hybridization of a single-stranded radiolabeled probe on immobilized target sequences on a membrane. After washing the membrane, autoradiographs or colorimetric reactions can reveal binding of the DNA probe employed. After stripping the membrane and reprobing with a control probe, one can examine the presence or absence of DNA amplification by comparing the intensity of hybridization between the proto-oncogene DNA probes and the control probes. This technique is simple and straightforward and can examine DNA extracted from formalin-fixed and paraffin-embedded materials to some extent. A major disadvantage is that it is impossible to determine what sizes of DNA fragment one is analyzing (ie, whether increased hybridization signals really represent DNA amplification). This disadvantage is augmented by the fact that results are occasionally in conflict with the data obtained by Southern blotting. Therefore, dot/slot hybridization may remain a method of studying the degree of DNA amplification in cases known to have oncogene DNA amplification, but the technique is being largely replaced by Southern blot hybridization.

Southern Blot Hybridization and Restriction Fragment Length Polymorphism. The principle of Southern blot hybridization is summarized in Figure 12-6. Southern blot analysis can provide information on (1) gene structure, including gene rearrangement or chromosomal alteration; (2) the copy number of a particular gene, including the presence or absence of DNA amplification (Fig. 12-7) and the degree of amplification by dilution of the applied DNA (Fig. 12-8); and (3) the presence of polymorphism in the DNA sequences. Southern blot hybridization is still the best method for the study of oncogene abnormalities, especially with regard to the first two sets of information. Diagnostic pathologists must have at least basic knowledge about this method.

Restriction fragment length polymorphism (RFLP), which can demonstrate the presence of point mutations, is also studied by Southern blot analysis by digestion of DNA with appropriate restriction endonuclease. This method is based on the fact that, without DNA mutations, all the restriction sites are present in the stretch of DNA that hybri-

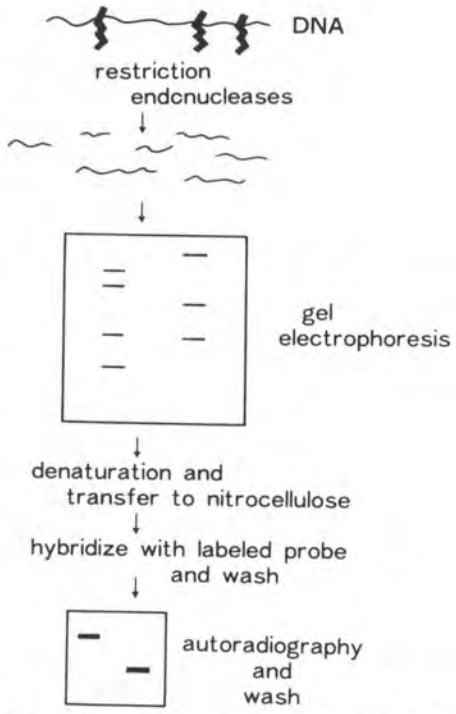

FIGURE 12-6 The principle of Southern blot hybridization analysis.

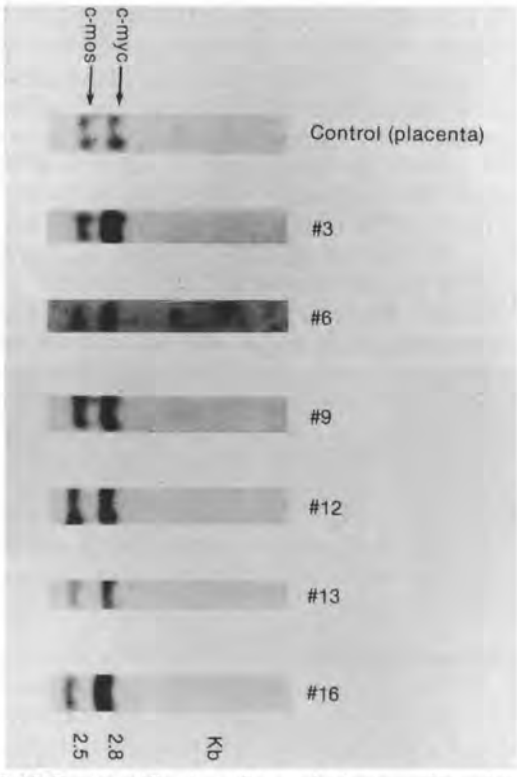

FIGURE 12-7 Amplification of *c-myc* in 6 cases of ovarian carcinoma. Lanes are from an autoradiograph of a Southern blot of Hind III-digested DNA from normal placenta and 6 ovarian carcinomas. The intensity of signal of *c-myc* relative to that for the placental control DNA indicates amplification of the *c-myc* oncogene in the tumors. (Sasano H, Garrett CT, Wilkinson DS et al: Proto-oncogene amplification and tumor ploidy in human ovarian neoplasms. Hum Pathol 21:382–391, 1990)

dizes to the probe when an appropriate restriction enzyme is employed. The recent use of allele-specific oligonucleotide probes has contributed to the detection of point mutations of oncogenes.

Polymerase Chain Reaction–Dot/Slot Hybridization. Since its introduction in 1985, the polymerase chain reaction (PCR) has transformed the way DNA analysis is carried out in clinical and research laboratories.[136] The PCR reaction is based on the annealing and extension of two oligonucleotide primers that flank the target region in duplex DNA.[136] Thus, PCR technique overcomes the problem of detecting DNA abnormalities that occur at low frequency in the target population as well as the problem of too little DNA for analysis. Amplified DNA fragments may be run on a gel and visualized with ethidium bromide staining, but generally the DNA is analyzed by hybridization, direct sequencing, or the RNase A mismatch cleavage method. Because of the extreme

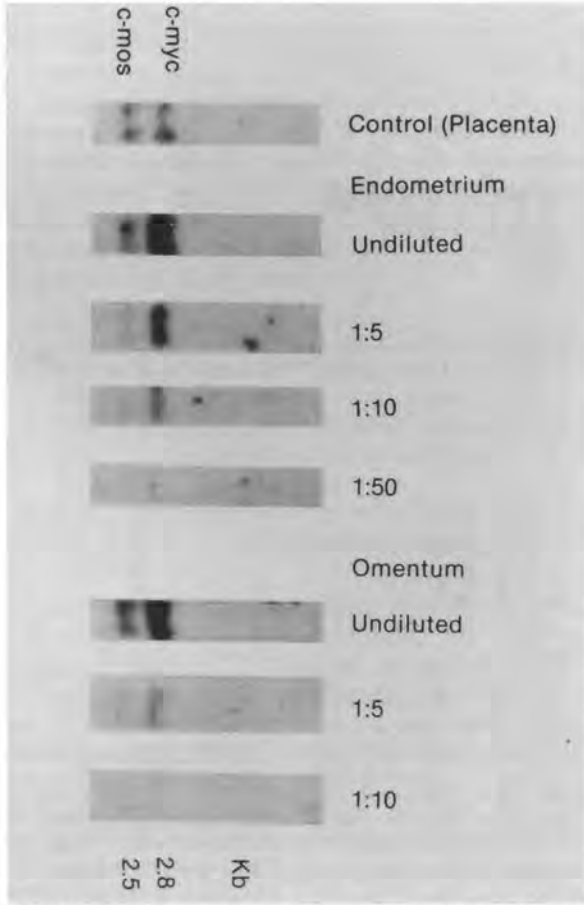

FIGURE 12-8 Dilution study of *c-myc* amplification in DNA extracted from endometrial and omental tumors analyzed by Southern blot hybridization. DNA from the endometrial tumor exhibited about 10-fold *c-myc* amplification. DNA from the omental lesion showed about 5-fold *c-myc* amplification. (Sasano H, Comerford J, Wilkinson DS et al: Serous papillary adenocarcinoma of the endometrium: Proto-oncogene amplification, flow cytometry, estrogen and progesterone receptors and immunohistochemical analysis. Cancer 65:1545–1551, 1990)

sensitivity of PCR, DNA contamination can become a serious problem.

The major application of PCR to oncogene analysis is the detection of point mutations. PCR is able to detect minor structural changes, rearrangements, or both in single-copy genes. PCR has been used effectively to test tumors (including human gynecologic neoplasms) for single nucleotide mutations with the H-, K-, and N-*ras* cellular genes (Fig. 12-9). The presence of the mutation may not be diagnostic of malignancy but does provide information concerning one of the abnormal growth-controlling mechanisms within the neoplastic cells.

It is true that determination of the specific sites of point mutation can be achieved only by nucleotide sequencing of PCR products. However, DNA sequencing is time-consuming, labor-intensive, and expensive to perform, despite advances in automation. Therefore, to determine the presence of point mutations, it is more feasible to analyze PCR products by selective oligonucleotide probe hybridization, RNAase A cleavage, or the single-strand conformation polymorphism method. These methods can provide information comparable to DNA sequencing in most diagnostic laboratories.

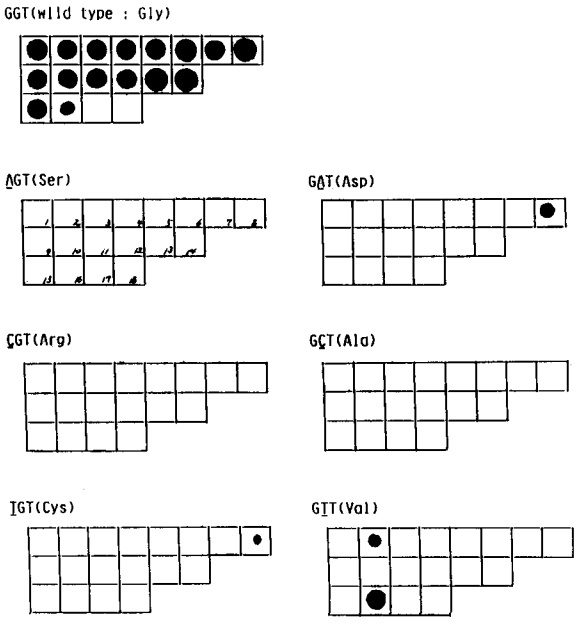

FIGURE 12-9 Detection of K-*ras* codon 12 mutation. Polymerase chain reaction and dot blot hybridization were done three times in each case. Point mutations were recognized in three cases in this figure: No. 6, GGT → GAT (endometrial carcinoma); No. 15, GGT, GAT, and GCT (cervical adenocarcinoma); No. 16, GGT → GTT (cervical adenocarcinoma). Control cases are shown from No. 18 to No. 21: No. 18, human placenta as negative control; No. 19, SW 480 (100%) as positive control (GGT → GTT); No. 20, SW 480 (10%); No. 21, SW 480 (5%). (Sato S, Ito K, Ozawa N, et al: Analysis of point mutations at codon 12 of k-ras in human endometrial carcinoma and cervical adenocarcinoma by dot blot hybridization and polymerase chain reaction. Tohoku J Exp Med 165:131–136, 1991.)

Other Methods. Other methods to study abnormalities of proto-oncogenes of human tumors at the DNA level are pulse field gel electrophoresis[137] and fluorescent in situ hybridization. They may be less cumbersome and labor-intensive than the transfection method or insertional mutagenesis, as described above, but they are not used routinely in diagnostic laboratories.

mRNA Levels

The first step in analyzing gene expression of proto-oncogenes in human tumors is to determine whether their mRNA is present in the specimen obtained. Techniques for the analysis of gene expression include one that examines immobilized mRNA on membranes (Northern blot analysis) and one that studies the localization of mRNA in tissue sections (in situ hybridization) by the use of radioactively labelled or nonisotopic probes.

Northern Blot. Total RNA obtained from fresh or quick-frozen tissue is fractionated and separated in a denaturing gel during electrophoresis, as was described in the section on Southern blot analysis. RNA is then transferred after electrophoresis to a nylon or nitrocellulose membrane, followed by hybridization with a specific radiolabeled or nonisotopic probe, washing, and development of a colorimetric reaction. Northern blot can demonstrate the molecular size of mRNA transcripts and the degrees of expression of a particular transcript. Overexpression of proto-oncogenes can be observed by this technique after reprobing with such control probes as β-actin. Northern blot analysis is thus considered a standard method of analyzing proto-oncogene expression in human neoplasms.

From the practical standpoint, it is difficult to install this technique in diagnostic laboratories because the technique is time-consuming and labor-intensive. Great care must be taken during the procedure, including sampling of the specimen, to avoid degrading the fragile RNA by RNase contamination. Thus, in the study of proto-oncogenes, Northern blot is a powerful tool in basic science laboratories but may not play such an important role in diagnostic laboratories dealing with surgical pathology specimens.

In Situ Hybridization. Northern blot analysis, like Southern blot analysis, treats the specimen as a mass and cannot provide information on the localization of mRNA expression, which is a serious disadvantage when studying human specimens. Human solid tumors, including almost all gynecologic tumors, are composed of stroma and cancer cells, and Northern blot analysis cannot demonstrate cancer cell-specific mRNA expression of proto-oncogenes. In situ hybridization is a technique that visualizes RNA mole-

cules in a tissue section through hybridization with a radiolabeled or nonisotopic probe of the specimen affixed to a glass slide. As an example, in situ hybridization analysis of the c-*myc* oncogene in human ovarian carcinoma is shown in Figure 12-10. The results of in situ hybridization are easily influenced by tissue preparation, choice of probes, and conditions of hybridization and washing.

A method by which we have consistently demonstrated good and reproducible hybridization signals is summarized in Figure 12-11. Fixation of tissues in 4% paraformaldehyde and subsequent paraffin embedding have provided reliable retention of the mRNA targets as well as excellent preservation of cell and tissue architecture compared with frozen sections.[138,139] Oligonucleotide probes generally permit greater specificity than cDNA or cRNA probes because redundant or conserved nucleotide sequences can be avoided during probe design and synthesis. In our experience, radiolabeled probes have a much higher sensitivity than the nonisotopic probes available, including digoxigenin. Therefore, the combination of 4% paraformaldehyde-fixed, wax-embedded specimens with radiolabeled oligonucleotide DNA probes is probably the ideal method for in situ hybridization. In addition, one can perform immunohistochemistry and in situ hybridization on the same tissue sections with the appropriate choice of chromogens. This simultaneous immunohistochemistry and in situ hybridization on the same section allows study of the expression of proto-oncogenes in the same carcinoma cells (Color Figure 12-2).

Thus, mRNA in situ hybridization can provide information regarding both the localization of mRNA expression and, to some extent, the level of expression. This technique has a potential wide appeal to surgical pathologists because the analysis is performed on tissue sections, making it possible to correlate mRNA expression with histopathologic findings. In situ hybridization cannot provide qualitative information regarding the size or structure of the mRNA, and the technique itself is still time-consuming and labor-intensive. Therefore, further improvements—especially introduction of much better colorimetric agents—are required for this technique to be widely used in diagnostic laboratories.

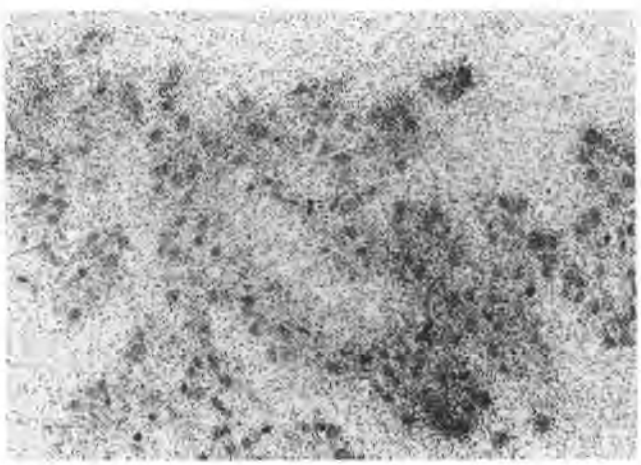

FIGURE 12-10 In situ hybridization of c-*myc* in a case of serous papillary adenocarcinoma of the ovary. Hybridization signals are observed as black dots on autoradiography. Intense hybridization signals were observed in the tumor cells.

Protein Levels

Analysis of proto-oncogene expression in human cancers by determining protein levels is in most cases performed by employing specific antibodies against the oncogene products. Technically, analysis is classified into two groups: Western (or immunoblotting) and immunohistochemistry. For practicing pathologists, the latter method is probably the easiest of all of the techniques discussed thus far for the study of oncogene abnormalities. However, as in the case of in situ hybridization, results are easily influenced by tissue preparation—especially fixation—and the choice of antibodies. Many of the oncogene products are transmembrane or nuclear proteins, and extra care should be taken not to disrupt their intracellular localization and antigenicity when performing immunostains. A large number of antibodies are commercially available, including antibodies against *ras*-p21, c-*myc*, N-*myc*, c-*erb*-B2, EGFR, and c-*fos*. Pathologists or technologists in charge of histopathology laboratories should check the following points before ordering these antibodies:

1. The antibodies should be usable for immunostaining of routinely processed surgical pathology specimens.
2. The antibodies should have been generated against processing-resistant epitopes of the molecule.
3. The specificity of the antibodies must have been checked by immunoblotting.

Some commercially available antibodies against oncogene products are not suitable for immunostaining of surgical pathology material. Even if immunostains can be performed successfully on tissue sections, it is still difficult to interpret the immunoreactivity obtained, for two main reasons. First, immunohistochemistry cannot provide information on the quantity of the products. Second, the oncogene products examined by immunohistochemistry are also present in nonneoplastic cells, with the possible exception of c-*erb*-B2.

In summary, immunohistochemistry of oncogene products can be easily done in most diagnostic pathology laboratories if one chooses appropriate methods of tissue preparation and suitable antibodies, but great care should be taken in interpreting the findings.

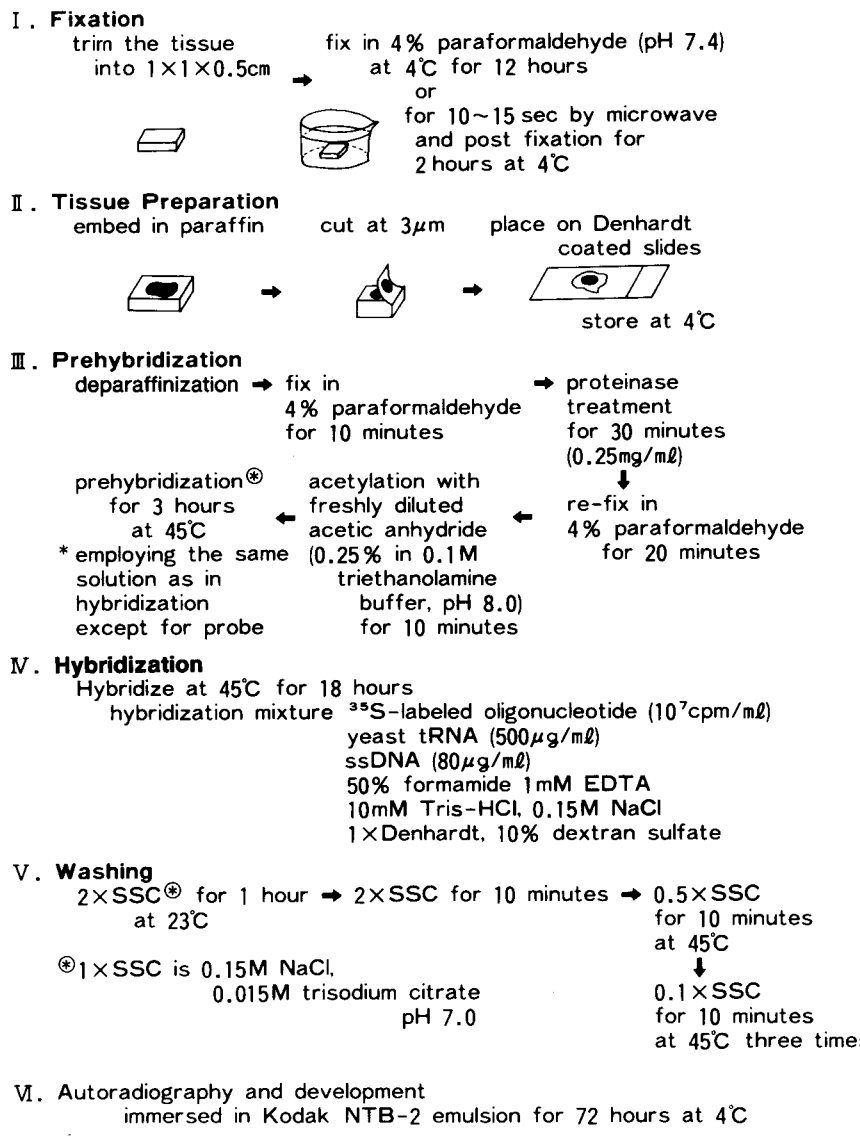

FIGURE 12-11 In situ hybridization methods routinely used in our laboratory. (Courtesy of the Department of Pathology, Tohoku University School of Medicine)

Oncogenes in Human Gynecologic Tumors

At this point, no definitive correlation has been established between abnormalities of cellular oncogenes and the biological behavior or clinical outcome of any gynecologic cancers. However, considerable evidence suggests that activation of cellular oncogenes is involved in the pathogenesis or development of at least some of these tumors. This section reviews the frequency with which cellular oncogene abnormalities have been found in ovarian, cervical, and endometrial cancers.

Ovarian Cancer

Ovarian cancer remains a common and lethal disease. It is the most common cause of death from gynecologic cancer and the fourth most common cause of female cancer death in the United States.[140] There is now a greater understanding of the numerous prognostic factors that are predictive for outcome of patients with ovarian cancer. These prognostic variables provide not only a framework for appropriate selection of therapy, but also a valid comparison between treatment options. In this regard, there have been an increasing number of studies that indicate that activated oncogenes should be among the factors considered.

Results of major published studies are summarized in Table 12-2.[141-164] This table shows the conflicting results obtained regarding the involvement of the *ras* oncogene group and *c-erb*-B2. The protooncogene *c-erb*-B2 probably has associated tyrosine kinase activity similar to that of EGFR, and the immunohistochemistry of *c-erb*-B2 is well established in human ovarian cancer (Fig. 12-12). Slamon and colleagues reported a high prevalence of *c-erb*-B2 amplification in human ovarian cancer.[141] They claimed that both amplification and overexpression were associated with decreased survival of the patients.[141] Press and associates subsequently reported similar findings.[142] Other reports have observed neither the

TABLE 12-2.
Summary of Major Studies on Abnormalities of Proto-oncogenes in Ovarian Cancer

Investigators	*Oncogenes Examined*	*Type of Abnormality*	*Summary of Results*
Sasano et al[145]	c-*erb*-B2	Amplification	0/12
	int 2	Amplification	1/12
	c-*myc*	Amplification	6/12
Zang et al[151]	c-*erb*-B1	Amplification	0/15
	c-*erb*-B2	Amplification	3/15
Berchuck et al[152]	c-*erb*-B2	Overexpression (immunohistochemistry)	Intense staining is associated with poor survival.
Slamon et al[141]	c-*erb*-B2	Amplification	20/31*
Zhou et al[153]	c-K-*ras*	Amplification	3/7
	c-H-*ras*	Amplification	1/12
	c-*myc*	Amplification	3/12
	c-*erb*-B-2	Amplification	1/12
Masuda et al[154]	c-*myc*	Amplification	3/11
	c-*erb*-B-2	Amplification	1/11
	c-*erb*-B-1	Amplification	0/5
	c-K-*ras*	Amplification	2/5
	c-H-*ras*	Amplification	1/11
	myb	Amplification	0/8
	N-*myc*	Amplification	0/4
	sis	Amplification	0/6
Van't Veer et al[155]	c-K-*ras*	Amplification	3/37
		Point mutation	0/30
Fukumoto et al[156]	c-K-*ras*	Amplification	2/8
		Point mutation	None
Boltz et al[157]	c-K-*ras*	Amplification	2/81†
Enomoto et al[158]	K-*ras*	Transfection	0/7
		Point mutation	2/13
Press et al[142]	c-*erb*-B2	Amplification	31/120
		Overexpression (Northern blot)	23/67
		Overexpression (immunohistochemistry)	69/72
Garuti et al[143]	c-*erb*-B2	Amplification (Northern blot)	0/20
Chien et al[159]	K-*ras*	Amplification	4/12
		Overexpression (Northern blot)	4/12
Schreiber et al[148]	c-*myc*	Amplification	5/30
Sasano et al[160]	c-*myc*	Overexpression (immunohistochemistry)	No significant difference of immunostain between invasive carcinoma and carcinoma of LMP
Ito et al[144]	EGFR	Overexpression (immunohistochemistry)	
	c-*erb*-B2	Overexpression (immunohistochemistry)	
Haas et al[161]	*ras* group	Transfection	1/18 active in serous papillary carcinoma
Watson et al[162]	c-*myc*	Overexpression (flow cytometry)	Overexpression in serous papillary carcinoma
Polacarz et al[163]	c-*myc*	Overexpression (immunohistochemistry)	Difference of staining pattern among mucinous neoplasms

(continued)

TABLE 12-2. *(continued)*

Investigators	Oncogenes Examined	Type of Abnormality	Summary of Results
Rodenburg et al[147]	*ras* group	Overexpression (immunohistochemistry)	More intense staining in carcinoma than in normal ovary‡
Slamon et al[149]	*abl*	Overexpression (mRNA)	0/6
	fes	Overexpression	0/6
	fos	Overexpression	6/6
	fms	Overexpression	4/6
	c-*myc*	Overexpression	6/6
	myb	Overexpression	0/6
	c-H-*ras*	Overexpression	6/6
	c-K-*ras*	Overexpression	4/6
Lee et al[164]	c-H-*ras*	Rearrangement	1/17
		Allele loss	5/17

*Overexpression generally correlated with amplification.

†Specimen consisted of 26 patients and seven xenografted ovarian cancer cell lines.

‡No correlation of *ras* expression with histologic type of ovarian cancer, tumor ploidy, or clinical outcome.

frequency nor the correlation with clinical outcome reported by Slamon.[143–145] Therefore, it is premature to assign any role to the *c-erb*-B2 oncogene in the development or progression of human ovarian carcinoma.

The *ras* oncogenes are the most frequently identified transformation-associated genes found in human solid tumors. The frequency of mutation or amplification of *ras,* especially K-*ras,* in ovarian cancer is in the range of 10% to 25% (see Table 12-2), which is consistent with the reported prevalence of activated *ras* in other human solid cancers.[146] However, Rodenburg and colleagues reported no correlation of *ras* expression with histologic type of ovarian cancer, tumor ploidy, or clinical outcome.[147] Therefore, the biological significance of *ras* oncogenes in human ovarian carcinoma requires further evaluation.

Expression of the c-*myc* proto-oncogene is highly regulatable and usually is correlated with cell proliferation; c-*myc* activation, overexpression, or both have been demonstrated in from 17%[148] to 100%[149] of ovarian cancers. Adequate information regarding the clinical characteristics and outcomes of patients with ovarian cancers that overexpress the c-*myc* oncogene is not available in all reports. However, the presence of c-*myc* amplification (see Fig. 12-7) was reported to be associated with a higher degree of nu-

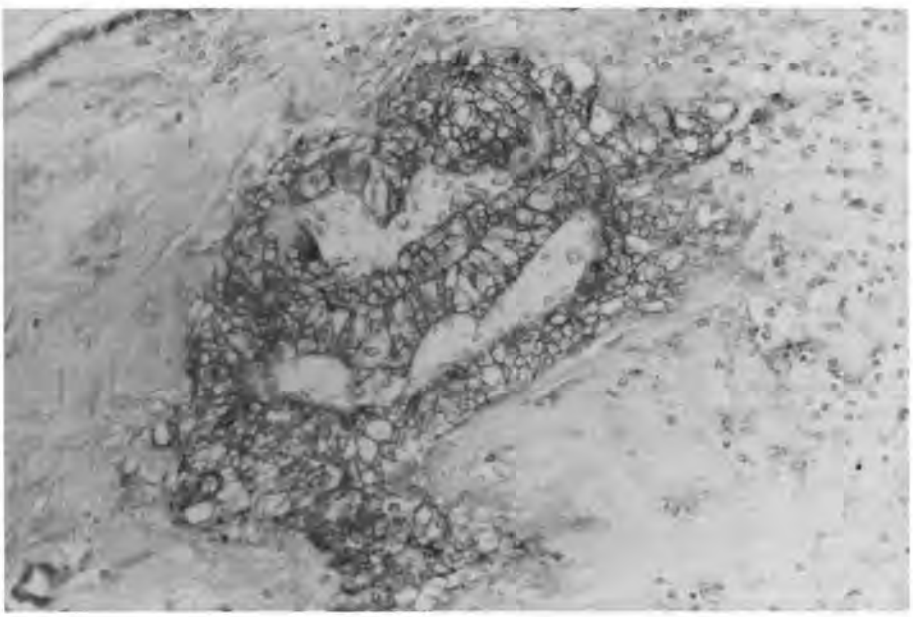

FIGURE 12-12 Mucinous adenocarcinoma of the ovary showing c-*erb*-B2 immunolocalization. Immunoreactivity was present at the cell membrane and in the cytoplasm.

clear atypia and high mitotic rate,[145] which are established as prognostic factors in human ovarian cancer.[150] Direct correlation of c-*myc* activation with clinical outcome in patients with ovarian cancer awaits further investigation.

Uterine Cervical Cancer

Results of major studies on proto-oncogene abnormalities in uterine cervical cancer are summarized in Table 12-3. Invasive carcinoma of the uterine cervix is the second most frequent cancer in women worldwide. The biological behavior of cervical cancer is complicated by the possible involvement of human papillomavirus (HPV) in carcinogenesis. Therefore, many studies of proto-oncogenes have been performed in cervical invasive carcinoma and its precursors to clarify the correlation with HPV and with malignant transformation of HPV-related lesions.[165–182] Numerous reports (summarized in Table 12-3) suggest that certain proto-oncogenes are involved in the development and progression of uterine cervical cancers.

Most studies have focused on c-*myc*. The data from both amplification and overexpression are not necessarily consistent, but it appears that activation of c-*myc* occurs in advanced stages of carcinoma, suggesting its possible role in tumor progression.[165–167] Bourhis and colleagues recently reported that overexpression of c-*myc* is a strong and independent indicator of the risk of overall relapse and distant metastases, even in early-stage carcinoma.[168] Durst and associates suggested that one mechanism by which HPV might induce neoplasia was through integration into cellular DNA in the proximity of c-*myc* and induction of c-*myc* expression.[169] This finding may be reevaluated in light of recent findings that suggest that the tumor-inducing properties of HPV may be related more to inhibition of tumor suppressor genes than to activation of proto-oncogenes.[170]

Results of c-*erb*-B2 studies in uterine cervical squamous carcinoma are consistent with the overall low frequency of c-*erb*-B2 abnormalities in squamous cell carcinomas in general. In addition, even in cervical squamous cancer cells with c-*erb*-B2 abnormalities, the results may merely reflect the conserved potential of glandular differentiation in exocervical squamous epithelia and their malignant counterparts.[171] Most of the proto-oncogene studies were performed on uterine cervical squamous cell carcinoma, with the exception of that of Sato and colleagues, who studied the immunohistochemical localization of c-*myc*, c-*erb*-B2, and EGFR in 7 cases of cervical adenocarcinoma.[172] These were positive in 5, 2, and 7 of the cases, respectively. Because cervical adenocarcinoma is known to be an aggressive tumor, further investigations are needed to clarify which proto-oncogenes play roles in the pathogenesis and development of this tumor.

Endometrial Carcinoma

The results of major studies on oncogene abnormalities in human endometrial carcinoma are summarized in Table 12-4. When analyzing abnormalities of proto-oncogenes in clinical samples of human endometrial carcinoma, it is important to note that many of these tumors are intimately associated with hyperplasia. Therefore, proto-oncogene studies should be performed by a morphology-based technique such as in situ hybridization or immunohistochemistry; otherwise, the carcinoma itself may not be the lesion studied. Enomoto and colleagues proposed that point mutations in codon 12 of K-*ras* are significant events in the etiology of adenocarcinoma of the endometrium,[158] but other reports have shown a lower frequency of c-K-*ras* point mutation.[182,183] This discrepancy may be due to the degree of contamination of nontumor cells, but further studies are required.

Other studies have indicated a possible correlation of clinical outcome in human breast carcinoma with abnormalities of c-*erb*-B2[141,184] and c-*myc*.[184] Some endometrial carcinomas may depend on sex steroid hormones, as in breast cancer, and both human breast and endometrial cancers share common clinical risk factors. Therefore, it is reasonable to postulate possible roles of these two proto-oncogenes in the biological behavior of human endometrial carcinoma. Abnormalities of these two oncogenes have been reported recently in human endometrial carcinoma (see Table 12-4).[185–189]

A high degree of c-*myc* amplification was reported in endometrial serous papillary adenocarcinoma (see Fig. 12-8), which is known to be associated with aggressive biological behavior and poor prognosis.[185] Borst and associates reported that amplification of the c-*erb*-B2 or c-*myc* oncogene was correlated with clinically advanced-stage disease and poorly differentiated lesions, indicating that oncogene amplification may predict biologically aggressive endometrial cancers.[187] Berchuck and colleagues demonstrated a correlation of high expression of c-*erb*-B2 with increased mortality in patients with endometrial cancer.[188] Further studies are needed, but c-*myc* and c-*erb*-B2 appear to play important roles in the biological behavior of human endometrial carcinoma.

Tumor Suppressor Genes

The molecular biology of cancer encompasses far more than the simple activation of oncogenes. Cancer has been recognized as a genomic disease, which progresses stochastically through a series of steps to ultimately produce malignant neoplasia. In most human cancers, neoplastic transformation involves activation of oncogenes (as described earlier) and simultaneous escape from the control of counterbalancing suppressor genes.[190]

TABLE 12-3.
Summary of Major Studies on Abnormalities of Proto-oncogenes in Uterine Cervical Cancer

Investigators	*Oncogenes Examined*	*Type of Abnormality*	*Summary of Results*
Riou et al[166]	c-H-*ras*	Locus analysis Point mutation	Loss of one allele in 36% 24%*
DiLuca et al[173]	c-*myc*	Amplification	0/14
Ocadiz et al[174]	c-*myc*	Amplification	17/35
Baker et al[175]	c-*myc*	Amplification	14/44
Hendy-Ibbs et al[176]	c-*myc*	Overexpression (flow cytometry)	Normal cervix higher than carcinoma
Riou et al[165]	c-*myc*	Overexpression (Northern and slot blot)	25/72
Hughes et al[177]	c-*myc*	Overexpression (immunohistochemistry)	Normal cervix more positive than carcinoma
Sagae et al[178]	*ras*(p21)	Overexpression (immunohistochemistry)	57.1%† 54.2%‡ 38.7%§
Berchuck et al[179]	c-*erb*-B2	Overexpression (immunohistochemistry)	1/26
	EGFR	Overexpression (immunohistochemistry)	22/26
Hayashi et al[180]	*ras*(p21)	Overexpression (immunohistochemistry)	6/52‖
	EGFR	Overexpression (immunohistochemistry)	3/52
Riviere et al[181]	c-*erb*-B2	Overexpression (Northern blot)	3/27
	c-*myc*	Overexpression (Northern blot)	5/18
Riou et al[167]	c-*myc*	Amplification Overexpression (Northern blot)	35/182 70/151#
Bourhis et al[168]	c-*myc*	Amplification Overexpression (Northern blot)	8/93 31/93
Brumm et al[171]	c-*erb*-B2	Overexpression (Northern blot) Overexpression (immunohistochemistry)	3/8 2/8
Sato et al[172]	c-*erb*-B2	Overexpression (immunohistochemistry)	2/7**
	c-*myc*	Overexpression (immunohistochemistry)	5/7**
	EGFR	Overexpression (immunohistochemistry)	7/7**
Sato et al[182]	K-*ras*	Point mutation	2/7**

*Mutation at codon 12.
†Keratinizing type of squamous cell carcinoma.
‡Large cell nonkeratinizing type.
§Small cell type.
‖Positive cases have higher incidence of lymph node metastasis.
#Overexpression associated with aggressive biological behavior.
**Cervical adenocarcinoma.

TABLE 12-4.
Summary of Major Studies on Abnormalities of Proto-oncogenes in Endometrial Cancer

Investigators	*Oncogenes Examined*	*Type of Abnormality*	*Summary of Results*
Sasano et al[185]	c-*myc*	Amplification	1/4
	int-2	Amplification	0/4
	c-*erb* B-2	Amplification	0/4*
Kacinski et al[186]	*fms*	Overexpression (in situ hybridization)	High levels of expression
	fos		
	c-*erb* B-2		
	c-K-*ras*		
Long et al[183]	*ras* group (p21)	Overexpression (immunohistochemistry)	Higher rate of positivity in high grade carcinoma†
Brumm et al[171]	c-*erb*-B2	Overexpression (Northern)	4/11
Enomoto et al[158]	c-K-*ras*	Point mutation	4/10
Borst et al[187]	c-*erb*-B2	Amplification	11/16
	c-*myc*	Amplification	10/15
Berchuck et al[188]	c-*erb*-B2	Overexpression (immunohistochemistry)	9/95
Nasim et al.[220]	c-K-*ras*	Point mutation	2/12
Sato et al[182]	c-K-*ras*	Point mutation	3/21
Sato et al[172]	c-*erb*-B2	Overexpression (immunohistochemistry)	7/23
	EFGR	Overexpression (immunohistochemistry)	21/23
Sato et al[189]	c-*myc*	Overexpression (in situ hybridization)	Intense hybridization in high grade carcinoma

*Amplification was seen only in serous papillary carcinoma, not in classical endometrioid carcinoma.
†Positivity of p21 was also seen in stromal cells.

The genetic predisposition to certain malignant neoplasms was first postulated because certain forms of cancer cluster in families that demonstrated certain chromosomal abnormalities inherited as an autosomal dominant Mendelian trait. From this observation, the presence of genes that predispose individuals to the development of cancer by loss of their function has been postulated. The putative genes have been called *tumor suppressor genes, recessive oncogenes, antioncogenes,* and *cancer predisposition genes.* Laboratory studies have indicated that loss of function may occur through mutation or deletion of these genes in a variety of malignant neoplasms.[191–193]

Two types of experimental evidence have pointed to the identification of tumor suppressor genes. The first type of evidence is provided by somatic cell hybridization: malignant cells fused to nonmalignant cells of the same species remain nonmalignant as long as these cells retain certain chromosomes donated by the parents. The loss of these sets of chromosomes results in the malignant phenotype in the hybrid cells.[194] In addition, cancer cell proliferation and the transformed phenotype can be suppressed by contact with normal cells[195] or by the introduction of individual chromosomes into the tumor cells of interest.[196] Mapping of putative tumor suppressor genes to specific chromosomes derived from normal cells has been attempted by analyzing the loss of chromosomes in the hybrid cells that re-express tumorigenicity.

The second type of evidence has come from the study of familial hereditary predisposition to cancers such as retinoblastoma. Cytogenetic and molecular studies have indicated that loss of genes on specific chromosomal loci occurs frequently in certain types of tumors. This may be explained by the so-called genetic instability associated with malignant transformation, but it is also true that recurrent and nonrandom chromosomal abnormalities are present

in a variety of tumors, although all these chromosomal deletions may not necessarily indicate the presence of tumor suppressor genes.[191]

Tumor suppressor genes have been postulated to encode proteins that regulate normal growth and to suppress neoplastic development indirectly. These genes may act recessively so that both maternal and paternal copies of the gene product must be inactivated for the involvement of tumor suppressor genes in the development of malignant phenotypes. Numerous chromosome abnormalities have been proposed as putative tumor suppressor genes, but at this juncture there are only three well-established and widely accepted tumor suppressor genes in human cancer. These are the retinoblastoma (*RB*) gene on chromosome 13q, the p53 gene on chromosome 17p,[196] and the DCC gene on chromosome 18q.[197] The retinoblastoma gene is located on the long arm of chromosome 13 (13q 14), and the expression of this gene is altered in virtually all cases of retinoblastoma[198–200] and in some other tumors.[198] Retinoblastoma cells lack a functional Rb protein and their tumor-forming propensity is suppressed by introducing the wild-type *Rb*-1 gene into the cells. Increasing evidence suggests that retinoblastoma protein plays a critical role in control of the cell cycle.[201]

The p53 protein was first identified as a host cell protein bound to T antigen, the dominant transforming oncogene of the DNA tumor virus SV-40.[202] This gene, which is located on the short arm of chromosome 17, was at first considered a proto-oncogene rather than a tumor suppressor gene because transfection of mutant variants into cells along with *ras* oncogene leads to malignant transformation.[203] It was subsequently shown that the study above actually employed mutated p53 genes and that the wild-type gene is incapable of the transformation described.[194]

The gene DCC, which is located on the long arm of chromosome 18, was originally described by Fearon and colleagues in 1990.[197] This gene is considered to play a role in the pathogenesis of human colorectal neoplasia through alteration of the normal cell-cell interactions controlling growth.[197]

Tumor Suppressor Genes in Human Gynecologic Tumors

Studies on involvement of tumor suppressor genes, mostly the retinoblastoma gene and p53, and on chromosomal deletion in human gynecologic cancers are summarized in this section. Emphasis is placed on their clinical significance and on clinical methods of laboratory detection.

Chromosomal Allelic Deletion. Certain genetic predispositions to develop gynecologic cancers have been known for years. In these cases, it has been postulated that the patient inherits one defective tumor suppressor gene from one parent and then inactivates the other gene through spontaneous mutation or deletion in cells that give rise to the tumor.[193] Therefore, tumors that arise in individuals without such a genetic predisposition must be associated with inactivation or loss of both normal alleles.[193] This is generally detected by observing that a tumor contains only one of the two alleles for a given gene that is present in the corresponding normal tissue. Therefore, allelic deletion in tumor cells generally represents the loss of a functioning tumor suppressor gene on the deleted allele and retention of a mutated nonfunctional cancer suppressor gene on the remaining allele.[193] Studies on allelic loss or loss of heterozygosity (LOH) in human gynecologic tumors are summarized in Table 12-5.[204–211]

Retinoblastoma (RB) Gene. Analysis of the retinoblastoma gene is usually done by detecting DNA abnormalities in the specimen, because immunohistochemical study of the *RB* product is not well established. *RB* gene abnormalities have not been

TABLE 12-5.
Summary of Loss of Heterozygosity in Human Gynecologic Tumors

Investigators	Tumor Site	Chromosome	Frequency
Yokota et al[204]	Uterine cervix	3p	9/9
Lee et al[164]	Ovary	11p (c-H-*ras*)	5/10
Sato et al[205]	Ovary	3p	6/33
		7p	3/7
		11p	7/29
		17p	13/28
		17q	12/31
		19p	11/32
		19q	4/16
		20	4/32
		21	0/12
		22	2/10
Okamoto et al[206]	Endometrium	Loss of heterozygosity at 27 loci in 10 chromosomes	
Ehlen et al[207]	Ovary	High frequency in 3p, 6q, 11p	
Eccles et al[208]	Ovary	17p	69%
		17q	77%
Russell et al[209]	Ovary	17q	10/13
Viel et al[210]	Ovary	11p (c-H-*ras*)	4/7
Lee et al[211]	Ovary	6q	9/14
		17p	6/8(D17S28)
			9/14(DI7S30)
		11p	5/11
Riou et al[166]	Uterine cervix	11p	10/28

studied extensively in human gynecologic tumors. Sasano and colleagues recently demonstrated a possible involvement of the *RB* gene in an ovarian carcinoma of low malignant potential with aggressive behavior.[212] One of 16 cases of ovarian carcinoma demonstrated evidence of homozygous deletion of the gene (Fig. 12-13). This tumor was classified histologically as being of low malignant potential but behaved in an aggressive fashion, suggesting that the structural alteration of the *RB* gene was involved in the behavior of this tumor. Recently Li and associates demonstrated allelic loss at the *RB* locus in 6 of 20 cases of human ovarian cancer.[213] What is becoming of great interest in the story of involvement of the *RB* gene in human gynecologic cancer is the fact that the oncogenic HPV types encode transformation proteins (E7) that form complexes with the protein product of the *RB* gene.[170] Further study should clarify the possible role of the *RB* gene and its gene products in the clinical behavior of human gynecologic cancers, especially HPV-associated lesions.

p53. Increasing numbers of studies of p53 have been reported in a variety of human neoplasms, and gynecologic cancers are no exception. The major studies of p53 abnormalities in human gynecologic cancer are summarized in Table 12-6.[214–216]

The major methods of detecting p53 abnormalities (ie, the presence of mutated p53) in human surgical pathology specimens are the nucleic acid-based approach and immunohistochemical methods. The nucleic acid-based approach was initially the detection of DNA abnormalities by direct sequencing of PCR products (Fig. 12-14). In human cancers, most activating mutations seem to be present in a portion of the gene spanning codons 132 to 281 (corresponding to exons 5, 6, 7, 8, and 9), which is known to include the SV-40 large T-binding domain as well as four highly conserved sequence blocks.[196] The patterns of DNA mutations vary from DNA point mutation to deletions of variable length. Although activating mutations are not necessarily confined to these areas, most studies have used PCR-amplified DNA fragments of these regions. Direct nucleotide sequencing of these fragments is a well established conventional method of detecting p53 abnormalities. However, the method is not used in diagnostic laboratories because of its time-consuming, expensive, and cumbersome nature. Recently, a relatively simple and sensitive method for detection of structural alterations of DNA fragments, known as the SSCP (single-strand conformation polymorphism) technique, was developed.[217] This technique employs radiolabeled PCR fragments, which allow the mutated molecule to be separated before sequencing (Fig. 12-15). This method is much simpler and less time-consuming then conventional DNA direct sequencing but is still cumbersome and labor-intensive, and the use of radioactivity prevents its widespread use in diagnostic laboratories.

It has been demonstrated that p53 mutations, which cause amino acid substitutions, appear to change the structure of the protein, resulting in a

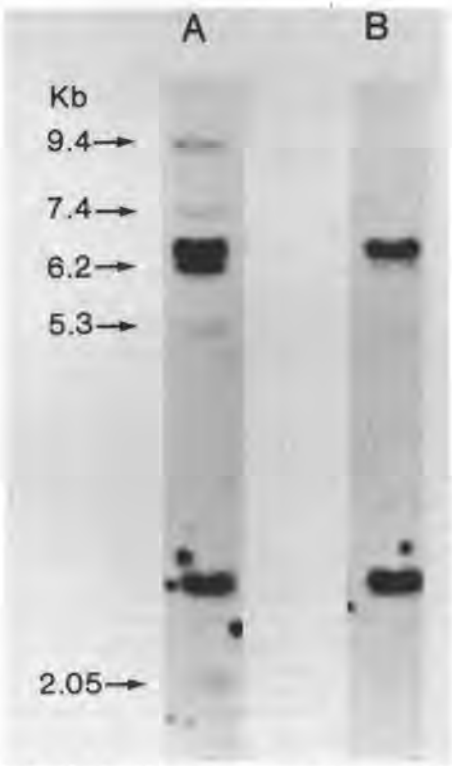

FIGURE 12-13 Southern blot analysis of control DNA (*lane A*) and endometrioid carcinoma of low malignant potential (*lane B*) using a probe to the *RB* gene and a probe to monitor DNA transfer. The intensity of the band monitoring the amount of DNA on the filter (two intense bands in this figure) was nearly identical in the control and tumor tissues. Compared with the control tissue in lane A, the 9.4-kb and 7.4-kb bands detected by the probe to the *RB* gene were deleted in lane B. (Sasano H, Comerford J, Silverberg SG, Garrett CT: Analysis of abnormalities of the retinoblastoma gene in human ovarian and endometrial carcinoma. Cancer 66:2150–2154, 1990)

TABLE 12-6.
Analysis of p53 Abnormalities in Gynecologic Tumors

Investigators	*Tumor Site*	*Methods*	*Results (Mutations)*
Okamoto et al[206]	Endometrium	PCR-SSCP DNA sequencing	3/24
Mazars et al[214]	Ovary	PCR-SSCP	11/30
Marks et al[215]	Ovary	Immunohistochemistry	54/107
Kihana et al[216]	Ovary	PCR-SSCP DNA sequencing	11/22

PCR, polymerase chain reaction; *SSCP*, single-strand conformation polymorphism.

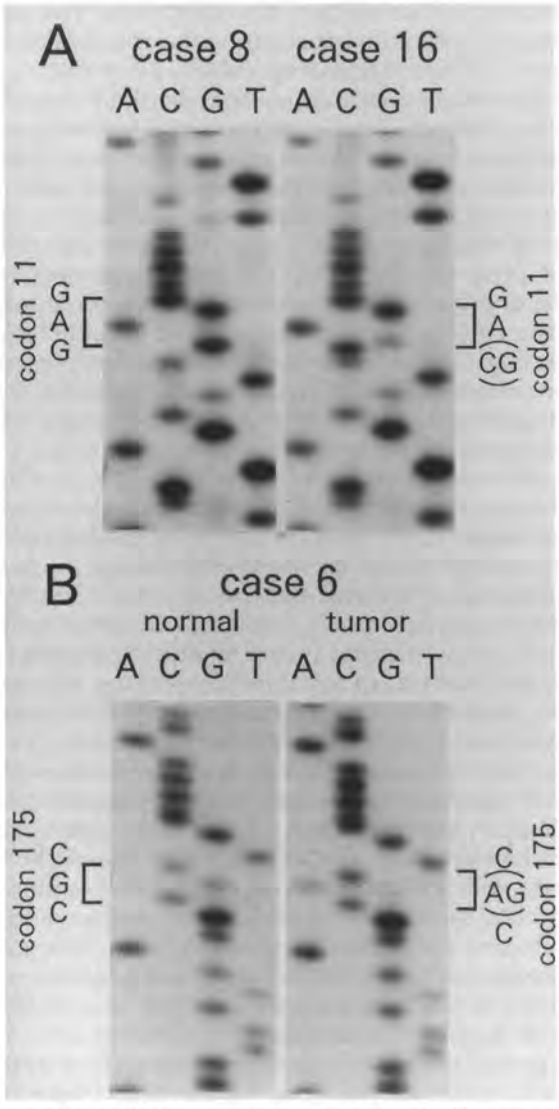

FIGURE 12-14 Direct sequencing analysis of p53 gene mutations in human ovarian carcinoma. **(A)** Sequencing of DNA of tumor tissues from cases 8 and 16 (serous papillary adenocarcinoma) around codon 11. **(B)** Sequencing of DNA from tumor and normal tissue from case 6 (serous papillary adenocarcinoma) around codon 175. Point mutational alterations were detected at codon 11 (sense, CAG from GAG) in case 16 and at codon 175 (sense, CAC from CGC) in case 6 tumor. Case 8 and normal tissue from case 6 demonstrated the wild-type sequence. (Kihana T, Tsuda H, Okada S et al: Analysis of abnormalities of p53 tumor suppressor gene in ovarian cancer. Jpn J Cancer Res 50:107, 1991; Courtesy of Dr. Kihana, Ehime University School of Medicine, Ehime, Japan)

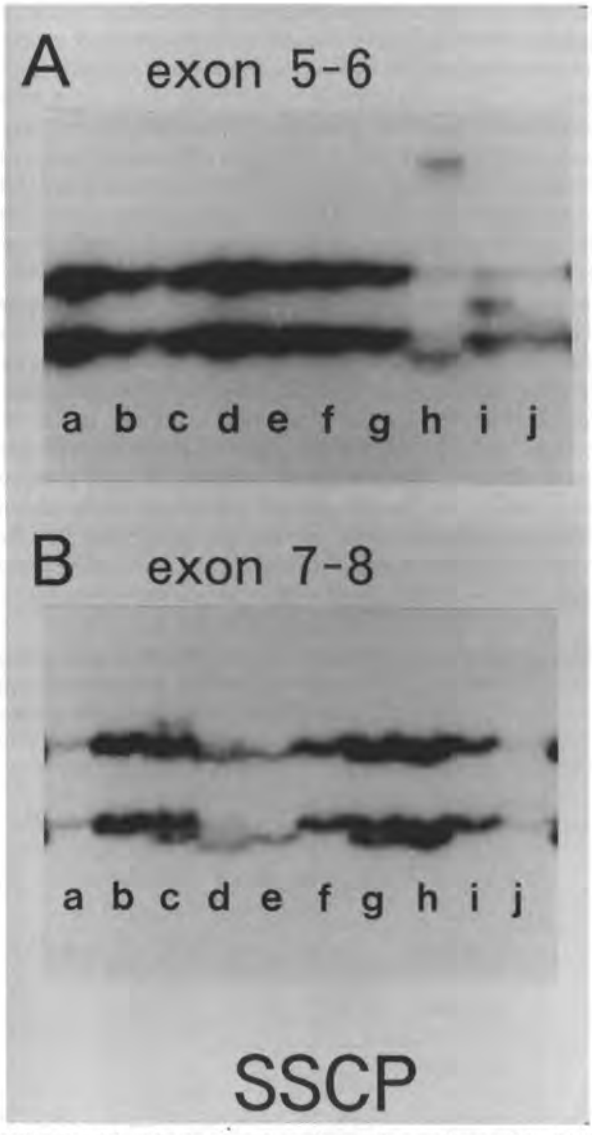

FIGURE 12-15 Single-strand conformation polymorphic (SSCP) analysis of PCR-amplified DNA fragments of p53 in human ovarian cancer. **(A)** Analysis of exon 5–6 of the p53 gene using a gel with glycerol at room temperature. Lanes A and B show fragments of normal and tumor DNA from the same case. Lanes C through J show tumor tissue DNA from carcinoma cases. Mobility shift of single-stranded fragments, differing from normal control DNA in lane A, was detected in lanes H, I, and J. **(B)** Analysis of exon 7–8 of the p53 gene on gel without glycerol at room temperature. Lane A represents normal tissue, and lanes B through J show fragments of tumor DNA. By SSCP analysis of the PCR product encompassing exons 7 and 8, two or four constitutional bands were observed for each case because of DNA polymorphism within the intron between exons 7 and 8 of the p53 gene. Mobility shift was detected in lanes C, D, and J. (Kihana T, Tsuda H, Okada S et al: Analysis of abnormalities of p53 tumor suppressor gene in ovarian cancer. Jpn J Cancer Res 50:107, 1991; Courtesy of Dr. Kihana, Ehime University School of Medicine, Ehime, Japan)

longer half-life, which can be detected as overexpression of p53.[218] In various human neoplasms, overexpression of the p53 protein as determined by immunohistochemistry is closely correlated with the presence of a DNA mutation in the p53 gene. Therefore, simple immunohistologic methods can provide strong evidence of such a p53 DNA mutation. Immunolocalization of p53 has two other advantages over a conventional nucleic acid-based approach to detecting p53 abnormalities. First, immunostaining is a rapid, inexpensive, and straightforward method of identifying p53 mutations. The second and more important advantage is that the expression of p53 can be localized and correlated with other histopathologic parameters (Fig. 12-16).

A nucleic acid-based approach usually involves contamination by nonmalignant and nonviable

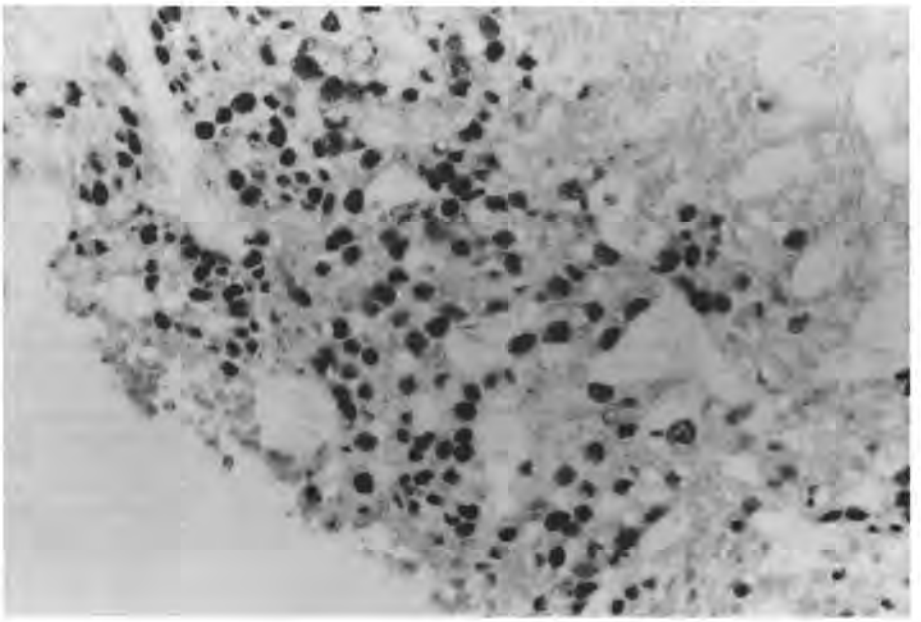

FIGURE 12-16 Immunolocalization of p53 in human ovarian carcinoma. Immunoreactivity, which represents overexpression of p53, is seen exclusively in the nuclei of carcinoma cells. The specimen was fixed in 4% paraformaldehyde for 18 hours and then embedded in paraffin.

cancer cells, because the tissue is processed as a mass. Therefore, the results are strongly influenced by the percentage of viable cancer cells present in the specimen examined. An immunohistochemical approach has a number of drawbacks, including the difficulty of demonstrating immunoreactivity in routinely processed specimens and of detecting all mutated forms of the p53 gene. These difficulties may be overcome by future technical advances. Despite these potential drawbacks, the immunohistochemical approach to p53 is considered to be of potential value in the study of human cancers including gynecologic tumors, especially for surgical pathologists.

Abnormalities of p53 appear to be correlated strongly with malignant phenotypes, but no significant correlation has been reported between p53 abnormalities and prognosis or clinical outcome in a variety of human tumors, including ovarian carcinoma. The practical value of detecting p53 abnormalities is thus limited both by technical difficulties and by the lack of immediate prognostic and therapeutic application of the results. However, the strong relation between p53 and malignant transformation is of potential value in differentiating premalignant conditions, and the possible involvement of p53 with the behavior of HPV-associated gynecologic lesions may be important in the near future.[219]

Conclusion

Increasing evidence suggests that proto-oncogenes and tumor suppressor genes are involved in the development or progression of human gynecologic cancer, or both. Although conventional morphologic approaches will no doubt remain an indispensable tool of the surgical pathologist in the diagnosis and evaluation of these tumors, the development of novel technologies and new knowledge of the molecular features of neoplastic transformation will provide an opportunity to improve our understanding of their behavior. It is important for those engaged in the care of patients with gynecologic tumors to follow and understand the developments in this field.

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