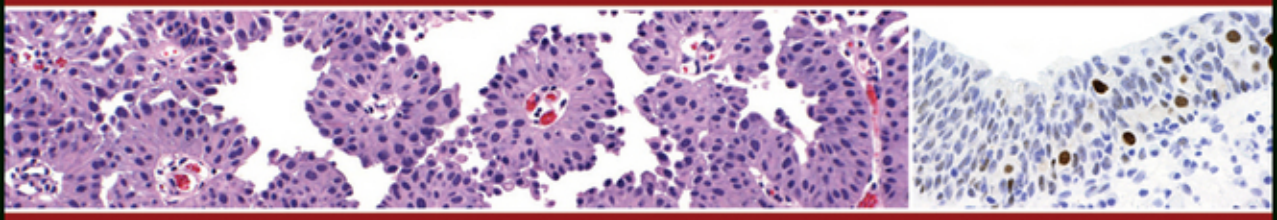
BLADDER PATHOLOGY



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Contents

Preface

The urinary bladder is subject to a unique and extraordinarily diverse array of congenital, inflammatory, metaplastic, and neoplastic abnormalities. The objective of *Bladder Pathology* is to provide contemporary, comprehensive, and evidence-based practice information for pathologists, urologists, and medical oncologists. A full spectrum of pathologic conditions that afflict the bladder and urothelium are described and illustrated. The book is aimed especially at the practicing pathologist, with an emphasis on diagnostic criteria and differential diagnoses. It is our hope that this very comprehensive book, consisting of 34 chapters, 754 pages, 112 tables, and 1741 full color photographs, will aid in the pathologist's recognition, understanding, and accurate interpretation of the light microscopic findings in bladder specimens.

This is an age of enlightenment in surgical pathology. The emergence of personalized medicine with new understandings of cancer genetics has created a paradigm shift in our practice. Greater weight continues to be placed on an evidence-based approach to diagnosis and patient management. This includes an emphasis on the scientific validation of our diagnostic methods and their meaningful application in practice. This is especially true in the management of patients with medical conditions involving the urinary bladder. Cancer of the bladder represents the fifth most common cancer in the human body, with more than 60,000 new carcinoma diagnoses annually in the United States. Many patients with bladder cancer have a prolonged survival, necessitating long-term followup, including the procurement of numerous subsequent cystoscopic biopsies and urine samples for histologic and cytopathologic evaluation. This, in turn, has generated a considerable diagnostic burden for the pathologist and cost to the health care system. It is our hope that continuing advances in the urinary bladder field can lessen the impact of these burdens on both practitioners and patients.

In the text we strive to provide a comprehensive resource for practicing surgical pathologists and their clinical colleagues so that they may better meet the daily demands and challenges of this ever-evolving field. We hope that this volume has captured our sense of excitement as we strive to stay on the cutting edge of these advances in medical practice. We have incorporated recent advances in molecular genetics of the urinary bladder with discussion of their current or potential impact on patient care. It is our intent to provide a framework by which diagnostic criteria can be compared, evaluated, and integrated with molecular and other ancillary test data.

We are indebted to many people who have been involved in the preparation of this book. We are grateful to our mentors, colleagues, and trainees who have challenged and inspired us. They include Drs. George M. Farrow, John N. Eble, David G. Grignon, Thomas M. Ulbright, Michael O. Koch, Gregory T. MacLennan, John F. Gaeta, Rodolfo Montironi, and many others. Our special thanks go to Ryan P. Christy from the Multimedia Education Division of the Department of Pathology at Indiana University, who edited the illustrations, and to Tracey Bender for her assiduous assistance in the editorial process. We also thank the staff at Wiley-Blackwell, including Thomas H. Moore, Ian Collins, Angioline Loredo, and Sheeba Karthikeyan for their invaluable support throughout the project. Finally, we earnestly solicit feedback and constructive criticism from readers so that the book may be improved in future editions.

Liang Cheng
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March 2012

Chapter 1

Normal Anatomy and Histology

Bladder Pathology, First Edition. Liang Cheng, Antonio Lopez-Beltran, David G. Bostwick.

Embryology

Early in fetal life, when cloacal dilation first appears and the hindgut ends in a blind sac, an ectodermal depression develops under the root of the tail.[1] This depression, known as the proctoderm, deepens until only a thin layer of tissue, the cloacal membrane, remains between the gut and the outside of the body. The division of the cloaca results from development of the urorectal fold that closes caudally toward the cloacal membrane. As the urorectal fold cuts progressively deeper into the cloaca, a wedge-shaped mass of mesenchyme accompanies it and forms a dense septum between the urogenital sinus anteriorly and the rectum posteriorly. This separation of the cloaca is completed before the cloacal membrane ruptures, so that its two parts open independently. When it first opens to the outside, the urogenital sinus, which is the ventral division of the cloaca, is tubular and continuous with the allantois. At this stage, it can be divided into a ventral or pelvic portion, which will become the bladder proper, and a urethral portion, which receives the mesonephric and fused müllerian ducts and later becomes the prostatic and membranous urethra in the male and the entire urethra in the female.[2]

After 8 weeks, the ventral part of the urogenital sinus expands to form an epithelial sac, the apex of which tapers into an elongated narrowed urachus. The splanchnic mesoderm surrounding both segments differentiates as interlacing bands of smooth muscle fibers and an outer fibroconnective tissue coat. By 12 weeks, the layers of the adult urethra and bladder can be recognized. This sequence of events indicates that the detrusor muscle and the urethral musculature have the same origin, constituting one uninterrupted structure.[2] This arrangement is easily observed in the female, in that the bladder and urethra form one tubular unit with expansion of the upper part. However, in the male, the structure is complicated by simultaneous development of the prostate gland. The developmental sequence is the same in both genders, and the structural arrangement in the male is only slightly more complex than that in the female.[2]

Anatomy

Gross Anatomy

The bladder is a hollow muscular organ whose main function is that of a reservoir. When empty, the adult bladder lies behind the symphysis pubis and is largely a pelvic organ. In infants and children, it is more cephalad than in adults. When full, the bladder rises above the symphysis and can readily be palpated or percussed. When overdistended, as in acute and chronic urinary retention, it may cause the lower abdomen to bulge visibly and is easily palpable in the suprapubic region. The empty bladder has an apex (superior surface), two infralateral or anterolateral surfaces, a base (posterior surface), and a neck. The apex extends a short distance above the pubic bone and ends as a fibrous cord derivative of the urachus. This fibrous cord extends from the apex of the bladder to the umbilicus between the peritoneum and the transversalis fascia. It raises a ridge of peritoneum called the median umbilical ligament. There is a peritoneal covering at the apex in both sexes that also covers a small part of the base in men.[2,3]

The apex of the bladder is apposed to the uterus and ileum in the female and to the ileum and pelvic portion of the colon in the male. The base of the bladder faces posteriorly and is separated from the rectum by the uterus and vagina in the female, and by the vasa deferentia, seminal vesicles, and ureters in the male. The anterolateral surface on each side of the bladder is apposed to the pubic bone, levator ani, and obturator internus muscles, but the central anterior bladder is separated from the pubic bone by the retropubic space, which contains abundant fat and venous plexuses. The neck of the bladder, its most inferior part, connects with the urethra. When the bladder is distended with urine, the neck remains fixed and stationary, whereas the dome rises above the pelvic cavity into the lower abdomen, touching the posterior aspect of the lower anterior abdominal wall and the small and large bowels.[3]

Beneath the urothelial lining of the inner bladder, there is loose connective tissue that permits considerable stretching of the mucosa. As a result, the urothelial mucosal lining is wrinkled when the bladder is empty but smooth and flat when distended. This arrangement exists throughout the bladder except at the trigone, where the mucous membrane adheres firmly to the underlying muscle; consequently, the trigone is always smooth, regardless of the level of distension (**Figs. 1-1** and **1-2**).

Blood Supply and Lymphatic Drainage

The bladder is supplied by the superior, middle, and inferior vesical arteries, all of which are branches of the anterior division of the hypogastric artery. Between the bladder wall proper and the outer adventitial layer, there is a rich plexus of veins that ultimately terminate in the hypogastric veins after converging in several main trunks.

The bladder lymphatics drain into the external iliac, hypogastric, and common iliac lymph nodes. There are rich lymphatic anastomoses between the pelvic and genital organs.[4–6]

Nerve Supply

The bladder is richly innervated by divisions of the autonomic nervous system.[2,7] Sympathetic nerves originate

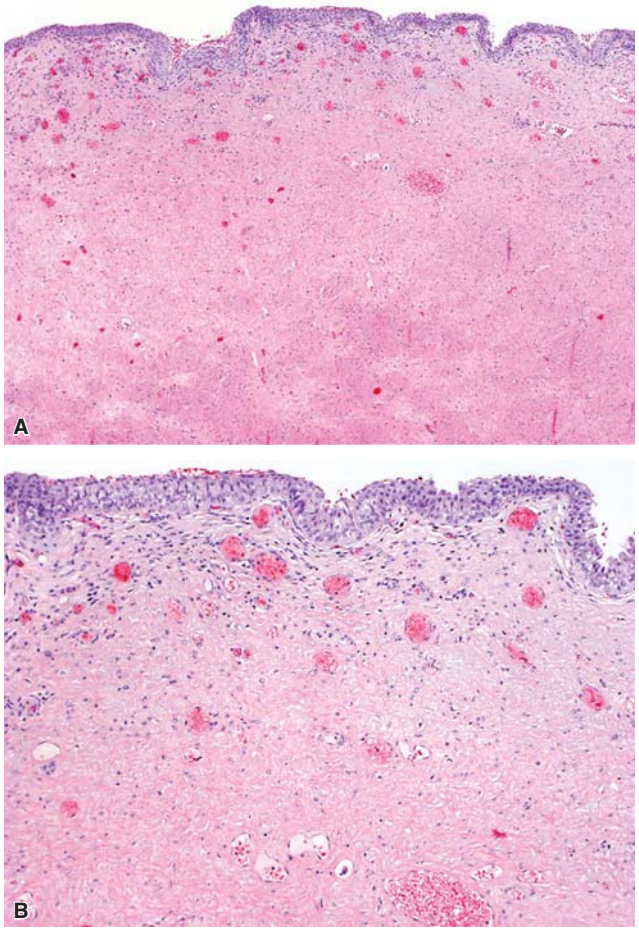


Figure 1-1 Normal trigone (A and B).

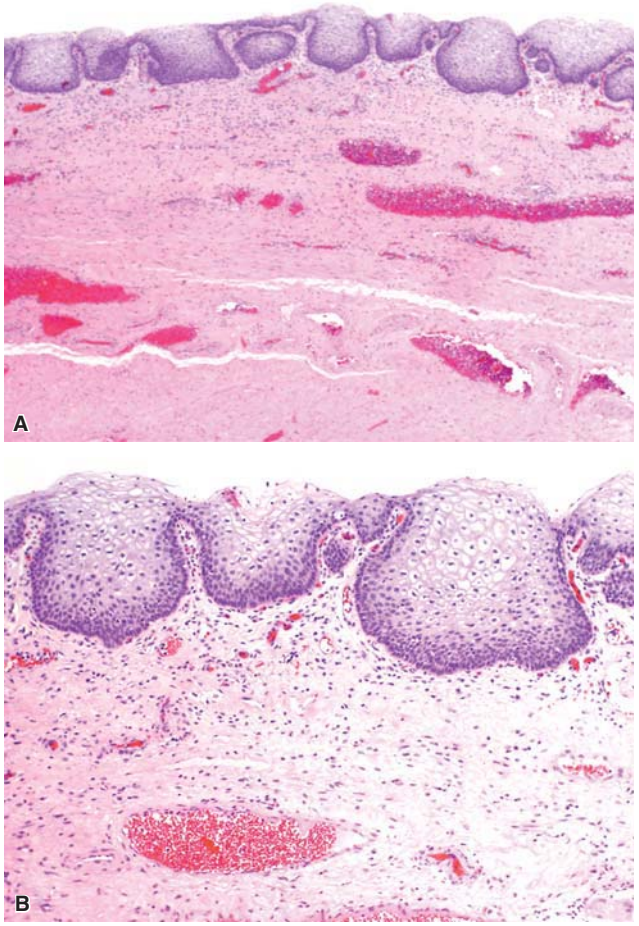


Figure 1-2 Normal trigone in a woman during the reproductive years. Note the squamous mucosa and closely packed underlying muscle (A and B).

from the lower thoracic and upper lumbar segments, mainly T11–T12 and L1–L2. These sympathetic fibers descend into the sympathetic trunk and the lumbar splanchnic nerves, connecting with the superior hypogastric plexus, an inferior extension of the aortic plexus. The latter separates into the right and left hypogastric nerves, and these extend inferiorly to join the pelvic plexus of the pelvic parasympathetic nerves. Parasympathetic nerves arise from sacral segments S2–S4, and these form the rich pelvic parasympathetic plexus. This plexus joins the sympathetic hypogastric plexus, and vesical branches emerge from this plexus toward the bladder base, innervating the bladder and urethra.[7,8]

Normal Histology

Urothelium

The urothelium is a unique stratified epithelium of variable thickness (**Figs. 1-3** to **1-6**). The number of cell layers

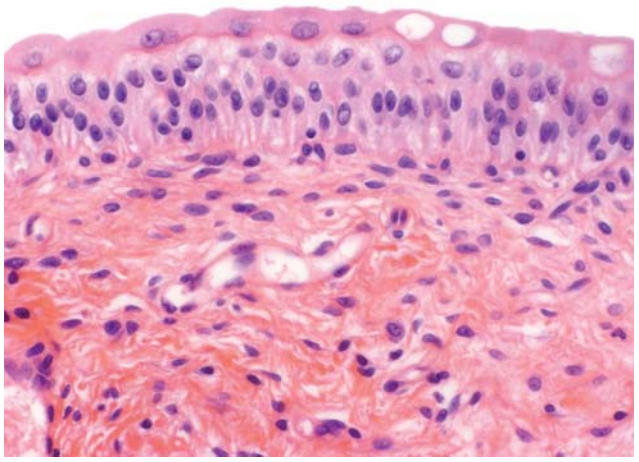


Figure 1-3 Normal urothelium. The thickness of urothelium is variable, up to seven cell layers in normal urothelium. Note the prominent superficial umbrella cells.

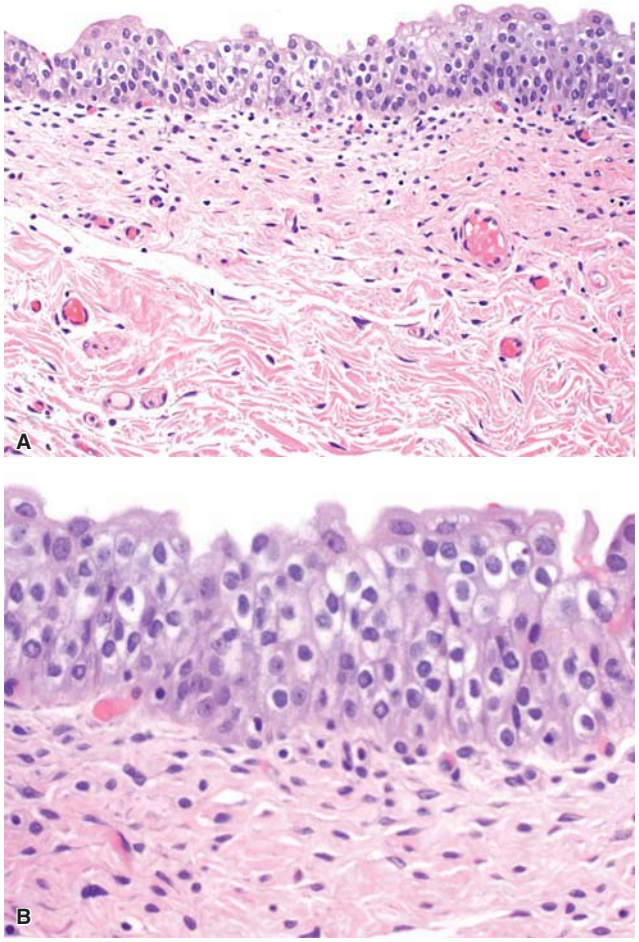


Figure 1-4 Normal urothelium (A and B). Cytoplasmic vacuolization is observed. In this preparation, the urothelium is up to seven cells in thickness (B).

depends on the degree of distension of the bladder, usually varying from three to seven layers. When distended, the bladder is three to six cell layers thick, although the typical biopsy contains about five layers; in the contracted state, it consists of six to eight layers.[9] For practical purposes, urothelium composed of more than seven cell layers is considered abnormal unless this finding can be attributed to tangential cutting of tissue.[10,11] In addition, the urothelium is thought to be monoclonal in origin, with some features of mosaicism.[12]

The normal urothelium contains a layer of large superficial cells that are frequently multinucleated, often referred to as umbrella cell thickness (**Figs. 1-7** to **1-9**). These cells have abundant eosinophilic cytoplasm, with large nuclei whose long axes are perpendicular to those of the smaller cells of the underlying basal and intermediate cell layers. The superficial cells vary in size and configuration according to the degree of bladder distension and angle

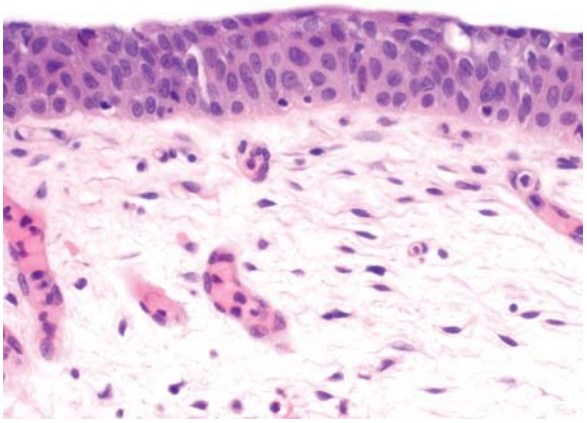


Figure 1-5 Normal urothelium. Note the orderly arrangement of the urothelial cells. The long axis of urothelial cells is often perpendicular to the mucosal surface. The superficial cells are less distinct. Prominent nuclear grooves are noted in some cells.

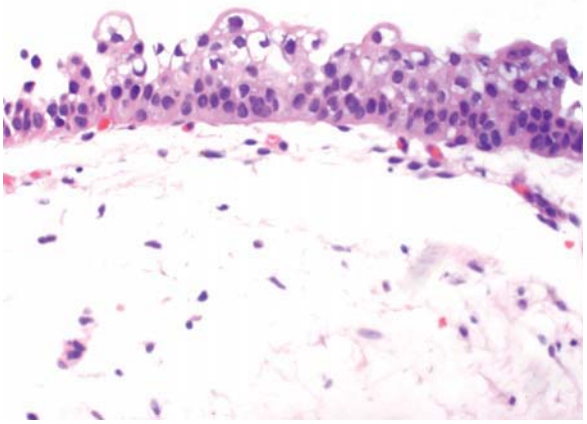


Figure 1-6 Normal urothelium. Note the variable thickness of urothelium in this preparation. The superficial cells have prominent cytoplasmic vacuolization.

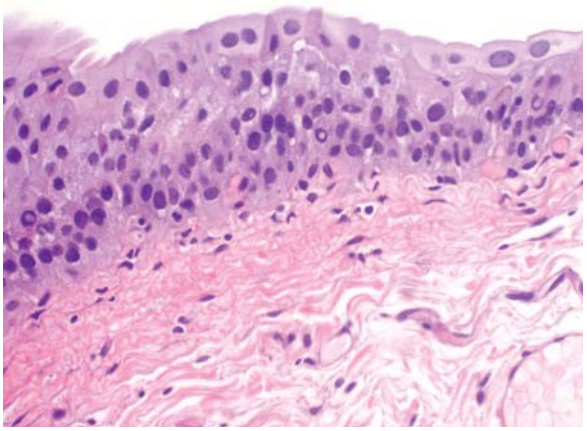


Figure 1-7 Normal urothelium. Note the prominent superficial cells. Nuclear vacuolization is occasionally seen in intermediate cells. Some variation of cell size and shape can be observed in normal urothelium and should not be interpreted as dysplasia.

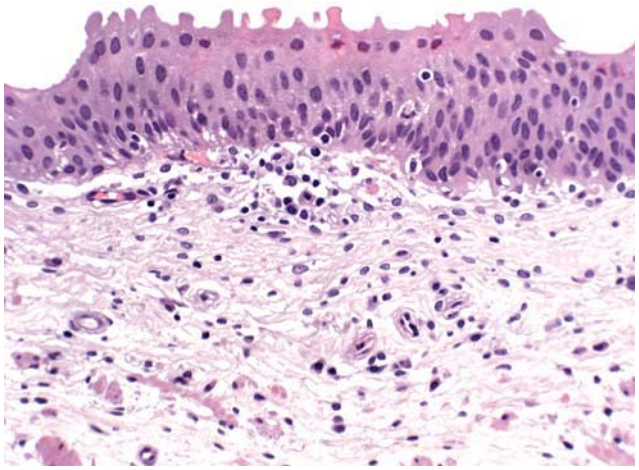


Figure 1-8 Normal urothelium. Note the prominent superficial cells.

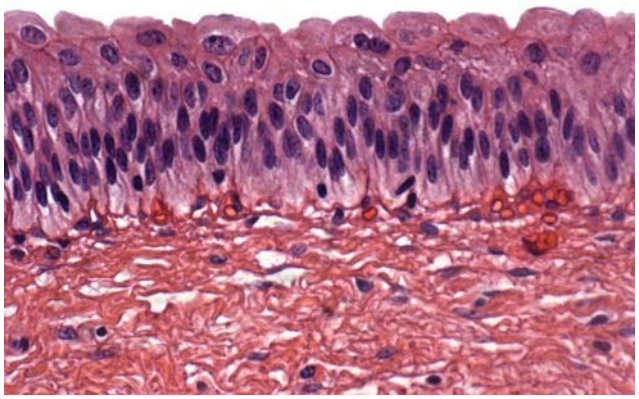


Figure 1-9 Normal urothelium. Basal and intermediate cells are located between the basal lamina and the superficial cells. Occasional prominent nuclear grooves may be seen. Note the binucleated superficial umbrella cells.

of tissue section; they may appear cuboidal in the distended bladder, but are often flattened. In addition, superficial cells are loosely attached to the underlying cells despite being interconnected with each other by extensive junctional complexes[13] and may be absent from otherwise normal urothelium in routine biopsies. Superficial umbrella cells express uroplakins and cytokeratin 20 with immunohistochemistry. The apical plasmalemma is thickened, with stiff plaques, unlike the short microvilli seen in the underlying intermediate cells.[13] However, the trigonal superficial cells of women during the reproductive years have a cobblestone pattern with long clubbed microvilli.[14] Superficial cells may persist on the surface of papillary urothelial carcinoma, particularly low grade carcinomas—a finding of potential importance in pathologic grading of bladder cancer (see also **Chapter 9**).

Basal and intermediate cells are located between the basal lamina and the superficial cells (**Figs. 1-8** to **1-10**). These cells are morphologically identical to each other, and are distinguished only by their position in the mucosa.[13] They are regularly arranged, with distinct cell boundaries and oval, round, or fusiform nuclei with occasional prominent nuclear grooves. The nuclei are located centrally in the cells and contain finely granular chromatin that often accentuates the nuclear borders. Nucleoli are usually small and difficult to detect. Mitotic figures are rare in the normal urothelium. The basal layer of epithelial cells expresses Bcl-2, while the intermediate cells express RB1 and PTEN at varying intensities. HER2 and p53 are not expressed by normal urothelial cells. Ki67, indicating proliferation, may not be expressed in a single field. The long axis of the basal and intermediate cells is perpendicular to the basement membrane. The basement membrane is usually not visible in routine hematoxylin and eosin or periodic acid–Schiff stained sections, but appears as a razor-thin layer beneath the mucosa when present. Basement membrane markers such as laminin and type IV collagen may be useful diagnostically in select cases to define the basement membrane, but are not employed routinely.[15] Delicate capillaries of the muscularis mucosae are in intimate association with the basement membrane, and invaginations or tangential cutting may create the factitious appearance of intraepithelial extension.

The urothelium is able to respond to thermal, mechanical, and chemical stimuli ("sensor functions") and has the ability to release chemicals ("transducer functions").[16] Urothelial basal cells express certain receptors and ion channels (e.g., vanilloid receptor-1), similar to afferent

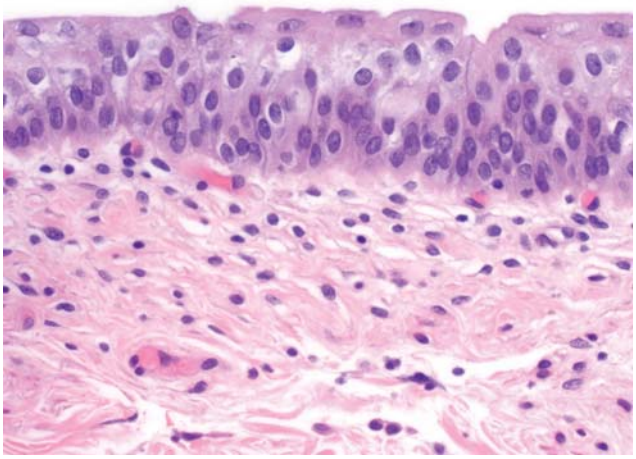


Figure 1-10 Normal urothelium. Basal and intermediate cells are more densely packed with a higher nuclear cytoplasmic ratio than that of superficial cells.

nerves.[16] The presence of afferent nerves adjacent to the urothelium suggests that these cells may be targets for transmitter release from bladder nerves or that chemicals released by urothelial cells may alter afferent excitability.

Bladder Wall

The lamina propria, located beneath the basement membrane, consists of a compact layer of fibrovascular connective tissue (**Figs. 1-11** to **1-13**). It may contain an incomplete muscularis mucosae composed of thin delicate smooth muscle fibers that may be mistaken for muscularis propria in biopsy specimens (**Figs. 1-14** to **1-16**).[17–23] The muscularis mucosae is an important diagnostic pitfall in evaluating bladder carcinoma because the management of cancer invading the muscularis propria is different from that of tumors limited to the lamina propria and surrounding the

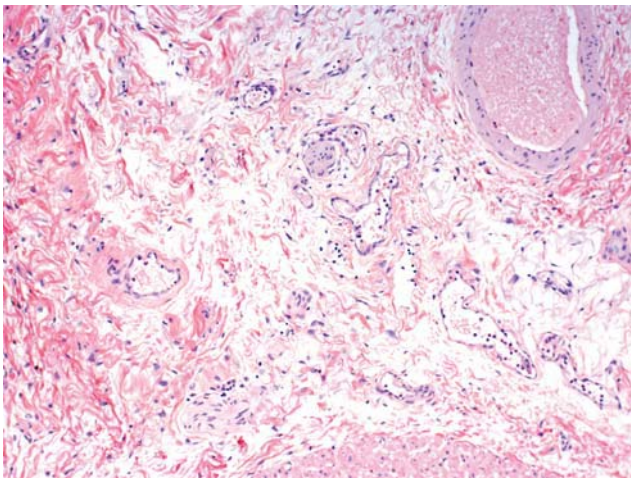


Figure 1-13 Normal lamina propria.

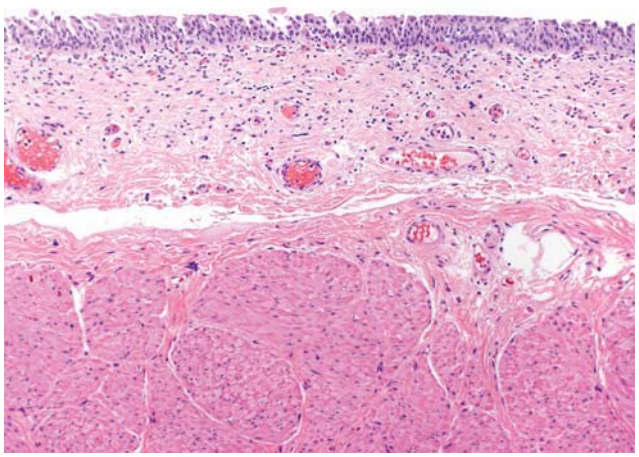


Figure 1-11 Normal lamina propria.

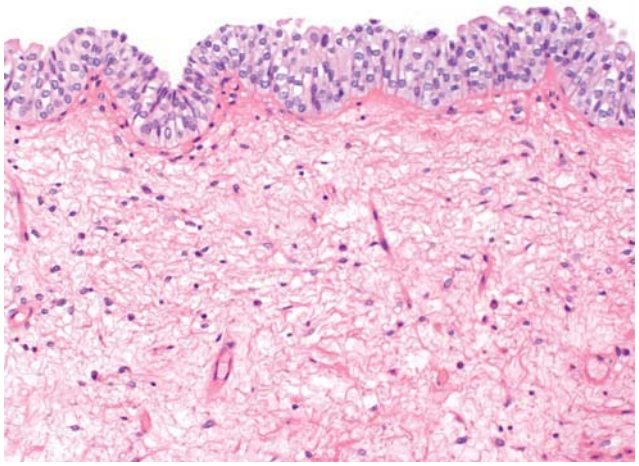


Figure 1-12 Normal lamina propria.

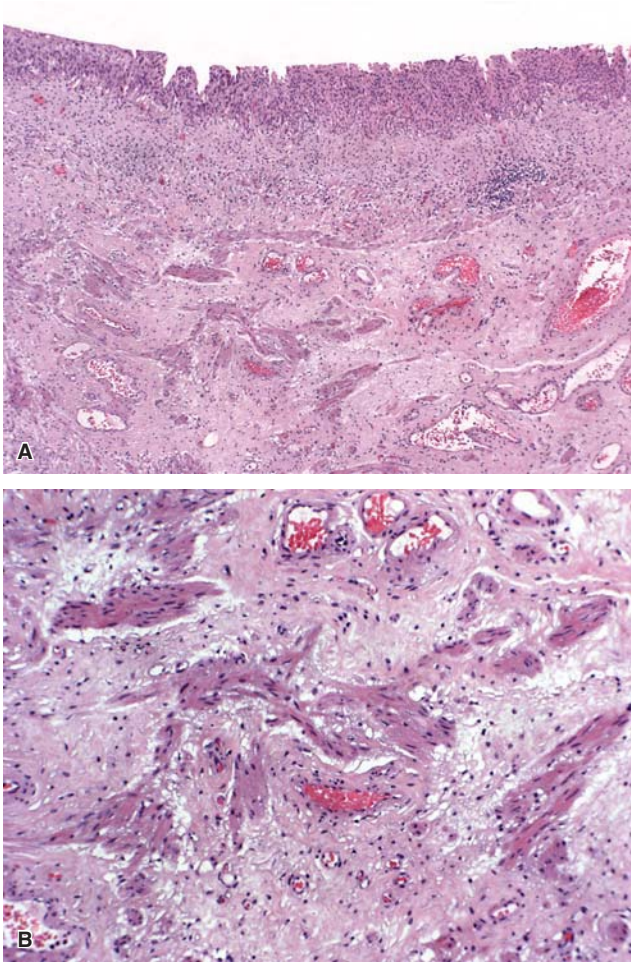


Figure 1-14 Muscularis mucosae in the lamina propria (A and B). The muscularis mucosae consists of scant delicate muscle bands interspersed with blood vessels and connective tissue stroma.

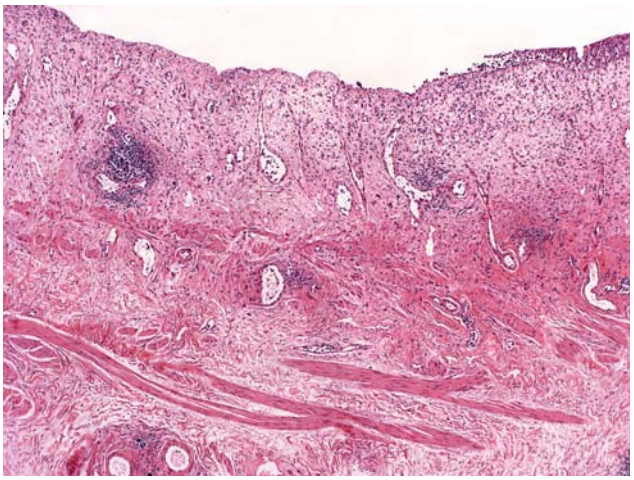


Figure 1-15 Muscularis mucosae.

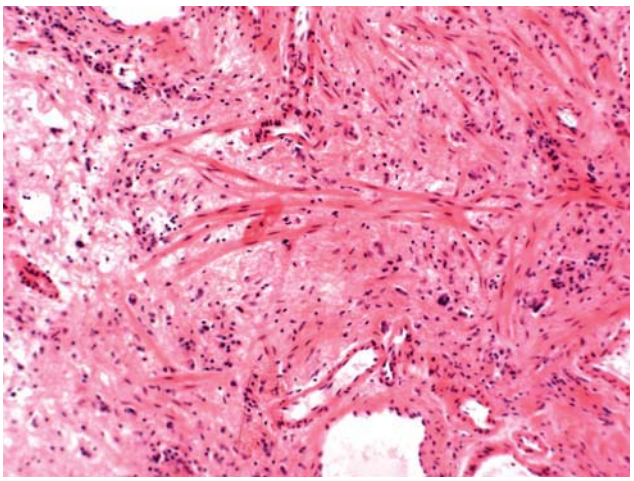


Figure 1-16 Muscularis mucosae.

muscularis mucosae. Therefore, it is important for pathologists to be aware of the existence of delicate muscle bundles within the lamina propria.[21,22,24] In biopsy specimens, these smooth muscle fibers may appear as a continuous layer, a discontinuous or interrupted layer, or as scattered thin bundles of smooth muscle fibers that do not form an obvious layer (**Fig. 1-17**).[22,25] These thin muscle fibers lie parallel to the mucosal surface, midway between the urothelium and the underlying muscularis propria.

Moderate-sized or large thick-walled blood vessels are a constant feature of the lamina propria, running parallel to the surface urothelium, in close association with the smooth muscle fibers of the muscularis mucosae (**Fig. 1-18**). However, these vessels are variable in distribution and may be close to the superficial lamina propria (**Figs. 1-19** and **1-20**). Therefore, large vessels cannot be used as a substitute for muscularis mucosae, as in some studies. It may be difficult to distinguish muscularis mucosae from muscularis

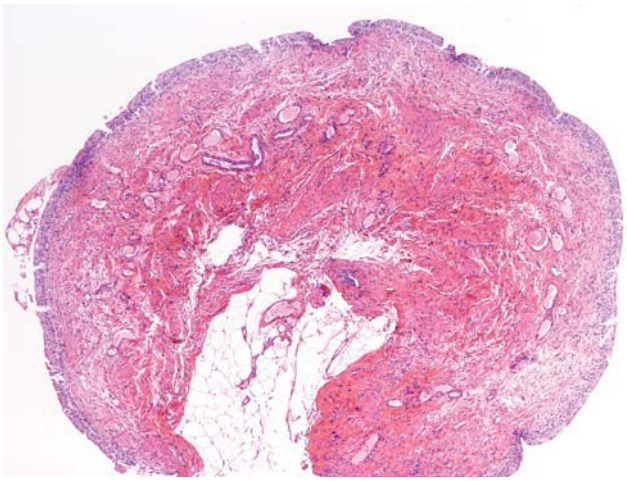


Figure 1-17 Muscularis mucosae in a biopsy specimen.

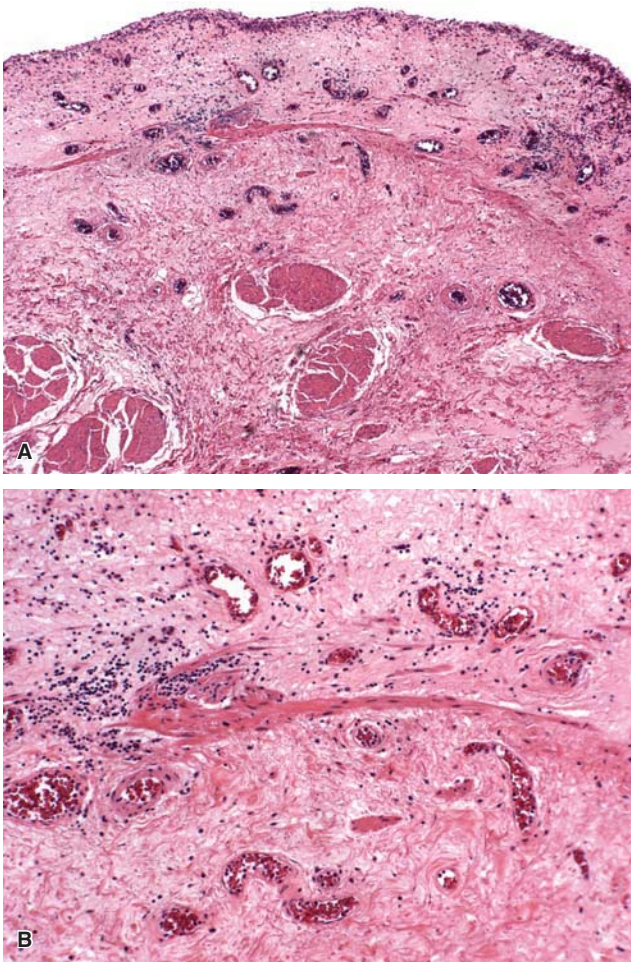


Figure 1-18 Musularis mucosae in close proximity to large vessels (A and B).

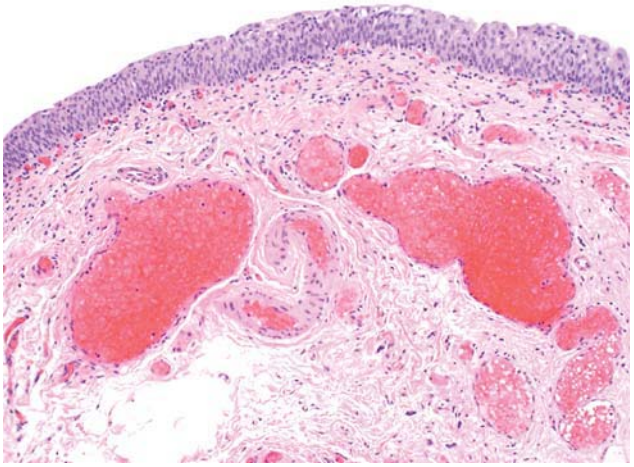


Figure 1-19 Large vessels may be seen in the superficial lamina propria and may or may not be associated with the muscularis mucosae. Therefore, large vessels cannot be used as a substitute for the muscularis mucosae.

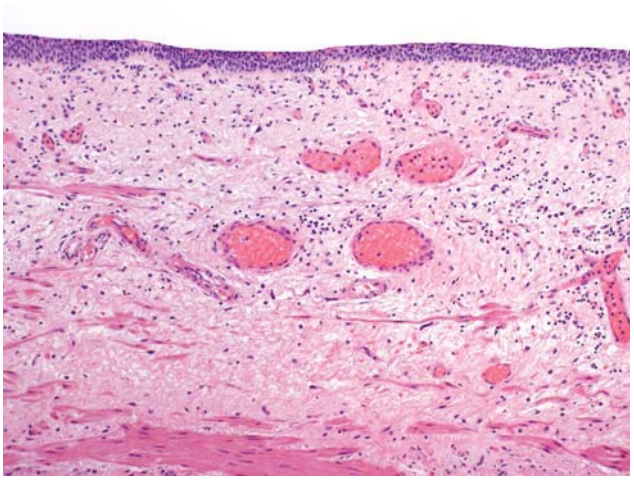


Figure 1-20 Variable distribution of large vessels and variably sized muscularis mucosae bundles.

propria (detrusor muscle). Trichome staining may be useful to resolve difficult cases.[26] Recent studies suggest that smoothelin can be a marker of interest in differentiating muscularis mucosae (negative or weak) from muscularis propria (positive and intense) (**Fig. 1-21**).[27–29]

To avoid overstaging bladder cancer, it is also important for the pathologist to be aware of the existence of fat within the lamina propria and the muscularis propria (**Figs. 1-22** and **1-23**).[30] Occasional bizarre stroma cells may be seen in the lamina propria and can be mistaken for invasive cancer cells. In difficult cases, immunostaining for cytokeratins is helpful. These bizarre stroma cells are negative for cytokeratin staining (**Figs. 1-24** and **1-25**).

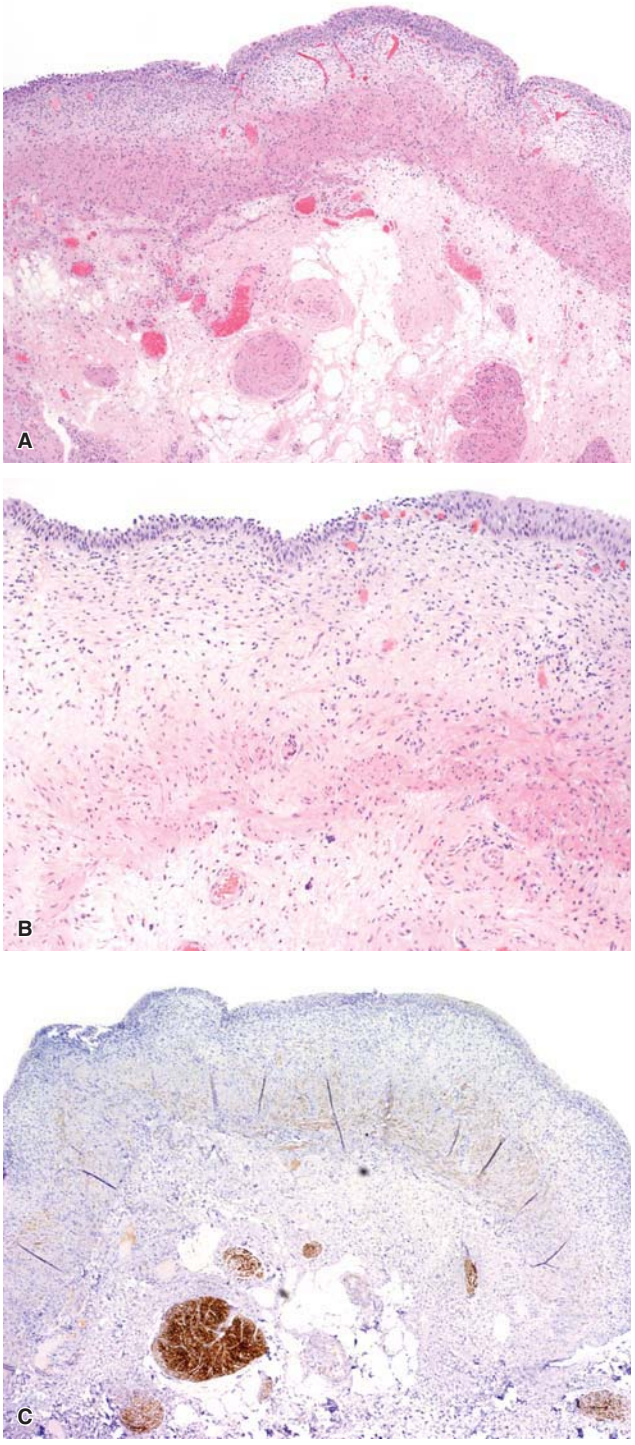


Figure 1-21 The muscularis mucosae is negative or shows weaker staining than the muscularis propria (A to C). Smoothelin usually stains strongly in the muscularis propria (detrusor muscle) (C).

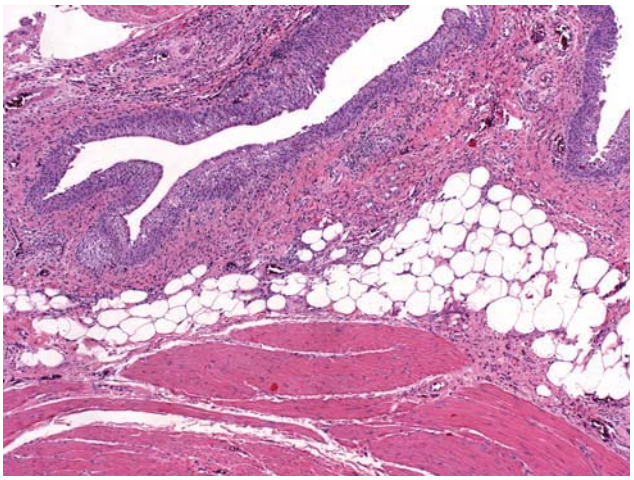
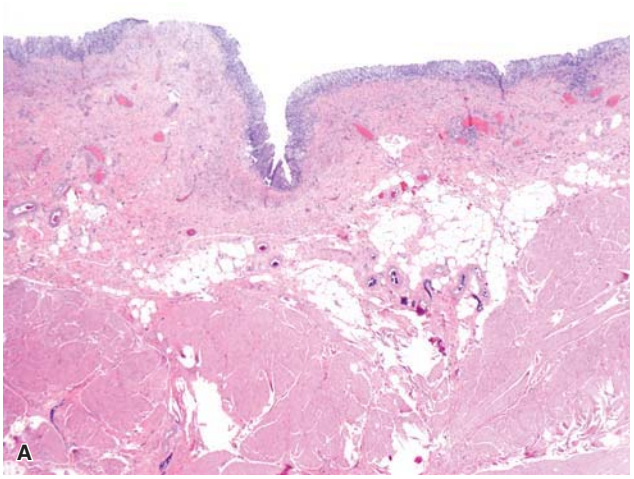


Figure 1-22 Adipose tissue can be seen in the lamina propria.



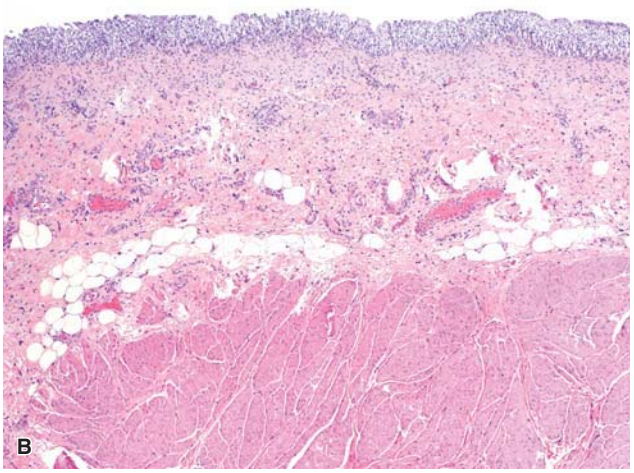
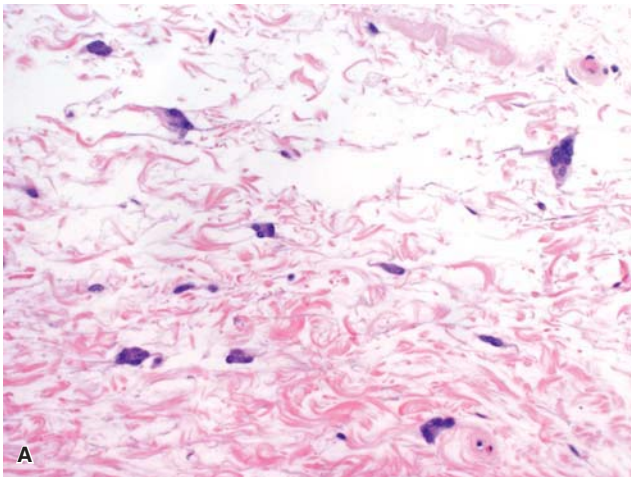


Figure 1-23 Adipose tissue is present in both the lamina propria and the muscularis propria (A and B). The presence of fat invasion in transurethral resection specimens does not indicate extravesical extension.



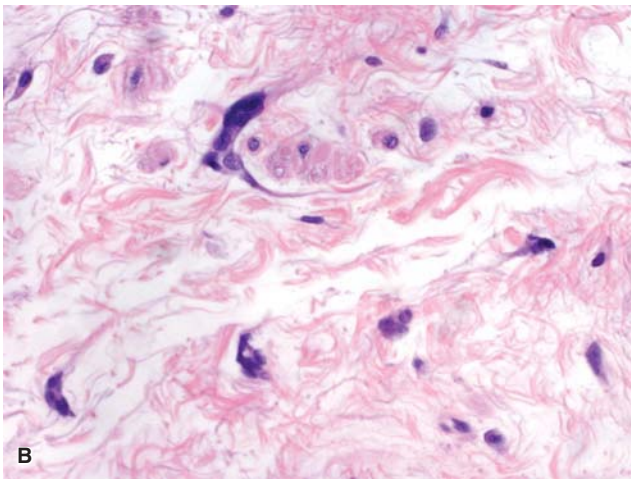


Figure 1-24 Bizarre stromal cells in the lamina propria (A and B).

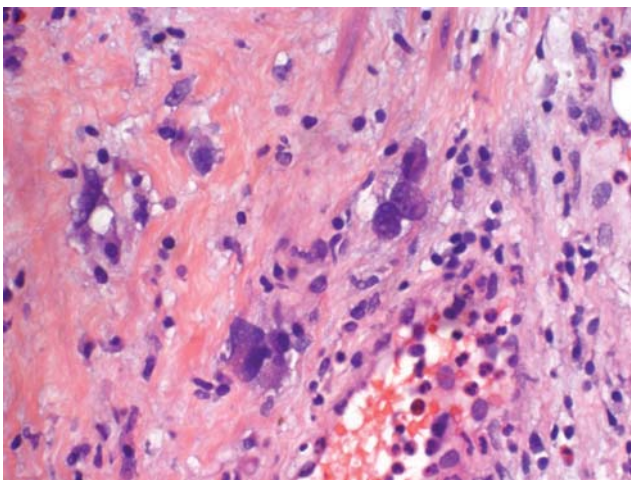


Figure 1-25 Bizarre stromal cells in the lamina propria.

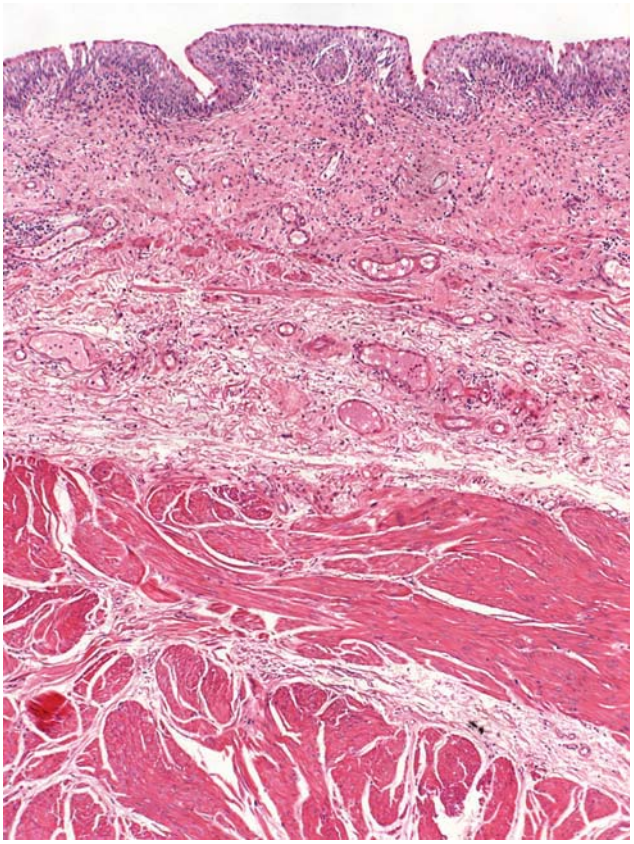


Figure 1-26 Muscularis propria (detrusor muscle). Note the contrast between the detrusor muscle and the muscularis mucosae in the lamina propria.

The muscle proper (detrusor muscle) of the bladder, the muscularis propria, is moderately thick and consists of an inner longitudinal layer, middle circular layer, and outer longitudinal layer (**Fig. 1-26**). It spirals around each ureteral orifice and increases in thickness around the internal urethral orifice, forming the internal sphincter of the bladder. The muscularis is surrounded by a coat of fibroelastic connective tissue, the adventitia, and perivesical fat.

Paraganglionic Tissue

Paraganglia are rarely found in routine sections of the urinary bladder.[31] Their presence in a bladder biopsy may be confused with neoplasm. Distinguishing features that are useful include the distinctive arrangement of cell nests, sinusoidal vascular pattern, monotonous benign cytology of the cells, and the absence of a stromal reaction.[32] Paraganglionic tissue typically demonstrates immunoreactivity with neuroendocrine markers such as chromogranin, synaptophysin, and neuron-specific enolase. The sustentacular cells exhibit immunostaining for S100 protein.

The Urachus

The urachus is an intraabdominal embryonic remnant. It contains the allantois, connecting the apex of the urinary bladder to the body wall at the umbilicus. The allantois originates in the portion of the yolk sac that gives rise to the cloacal portion of the hindgut. As the embryo grows, the urachus elongates to maintain its connection with the bladder dome and the body wall. At birth, the dome of the bladder and the umbilicus are closely opposed, and the urachus is only 2.5 to 3 mm long, with a diameter of 1 mm throughout most of its course and 3 mm where it joins the bladder.[33] The urachus lies in a space anterior to the peritoneum, bounded anteriorly and posteriorly by the umbilicovesical fascia.[34] Laterally, it is bounded by the two umbilical arteries, which, in turn, are surrounded by umbilicovesical fascia. Inferiorly, the umbilicovesical fascial layers cover the surface of the dome of the bladder. This space, the space of Retzius, is roughly pyramidal, and fascial planes separate it from the peritoneum and other structures. At the junction with the urinary bladder, the adult urachus is 4 to 8 mm wide, narrowing to about 2 mm at its superior end.

The urachus has three segments: supravesical, intramural, and intramucosal.[33] Tubular urachal remnants are found within the wall of the urinary bladder in approximately one-third of adults and are evenly distributed between men and women. There are three architectural patterns of intramural urachal canals, varying from simple tubular canals to complex branching canals (**Fig. 1-27**).[35] The mucosal portion of the urachus may have a wide diverticular opening, papilla, or a small opening flush with the mucosal surface. The majority (70%) of intramural urachal remnants are lined by urothelium; the remainder are lined by columnar epithelium, occasionally with small papillae or, rarely, mucous goblet cells or mucus-secreting columnar epithelium in women (**Figs. 1-28** and **1-29**).[35–37]

The Renal Pelvis and Ureters

The ureter and renal pelvis develop from the ampullary bud, which arises from the distal mesonephric duct during the fourth week of development. As the ureter elongates, there is a period of luminal obliteration followed by recanalization in the fifth week. Recanalization begins in the middle of the ureter and extends proximally and distally with the ureteropelvic and ureterovesical junctions; these are the last segments to recanalize. The mesonephric duct distal to the ampullary bud (the common nephric duct) is incorporated

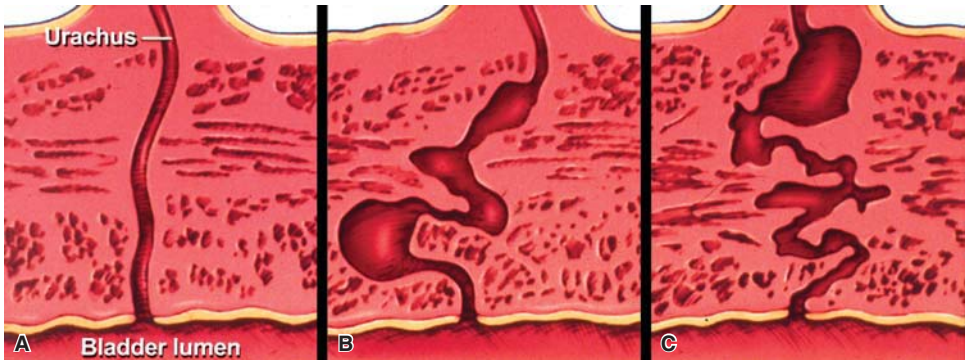


Figure 1-27 Patterns of intramural urachal canals: (A) type I, tubular canal without complexity; (B) type II; tubular canal with marked segmental dilatation and variable curvature; (C) type III, tubular canal with marked tortuosity and distortion, including segmental dilatation.

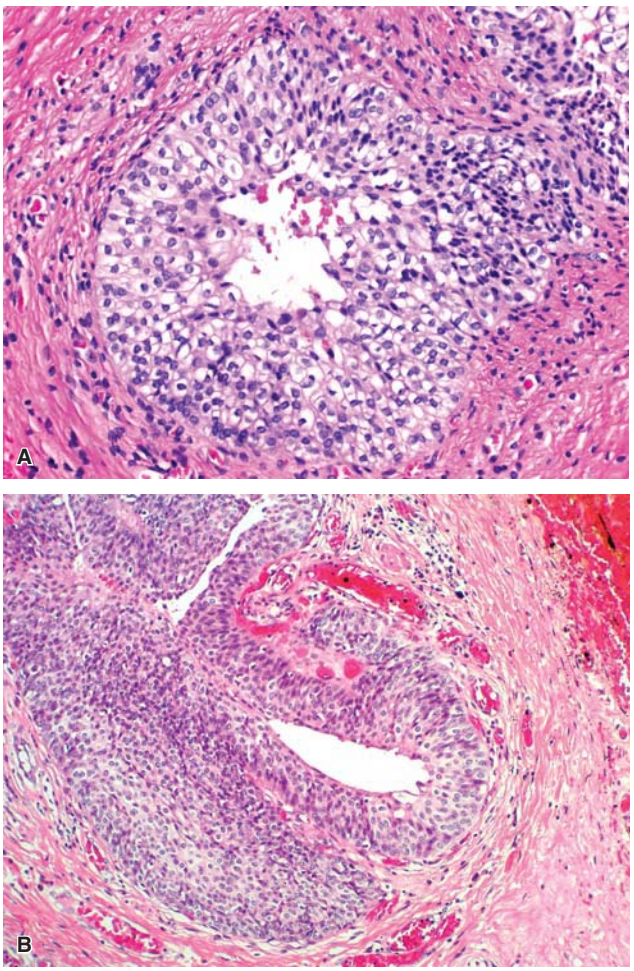


Figure 1-28 Normal urachus lined by stratified urothelium.

into the developing urogenital sinus, while the ureteral orifice migrates to the trigone and contributes to the prostatic urethra in the male.

Concomitant development of the male and female reproductive tract forms the mesonephric (wolffian) and müllerian ducts, respectively; division of the cloaca into bladder and hindgut occurs as the ureter and kidney develop. As a consequence, multiple malformations in these areas often occur together.

The lumen of the renal pelvis and ureter is lined by urothelium, which rests on a basement membrane (**Fig. 1-30**). The urothelium is composed of three to five layers of cells in the pelvis and four to seven layers of cells in the ureter. The pelvis and ureter have a continuous muscular wall that originates in the fornices of the minor calyces as small interlacing fascicles of the smooth muscle cells. The muscularis propria is not divided into distinct layers. Near the bladder, the ureter acquires an external sheath from the detrusor muscle, and the muscle fascicles become oriented longitudinally. The longitudinal fibers continue through the wall of the bladder and into the submucosa, where they surround the ureteral orifice and contribute to the trigone muscle.

The Urethra

The epithelium of the urethra is derived from the urogenital sinus, which is formed when the endodermal cloaca divides into the rectum dorsally and the urogenital sinus ventrally, separated by the urorectal septum. In women, the epithelium of the urethra is derived from endoderm of the urogenital sinus, while the surrounding connective tissue and smooth muscle arise from splanchnic mesenchyme. In men, the epithelium is also derived from the urogenital sinus except in the fossa navicularis, where it is derived from ectodermal cells migrating from the glans penis. As in women, the connective tissue and smooth muscle surrounding the male urethra is derived from splanchnic mesenchyme.

The male urethra is 15 to 20 cm long and is divided in three anatomical segments (**Figs. 1-31** and **1-32**). The

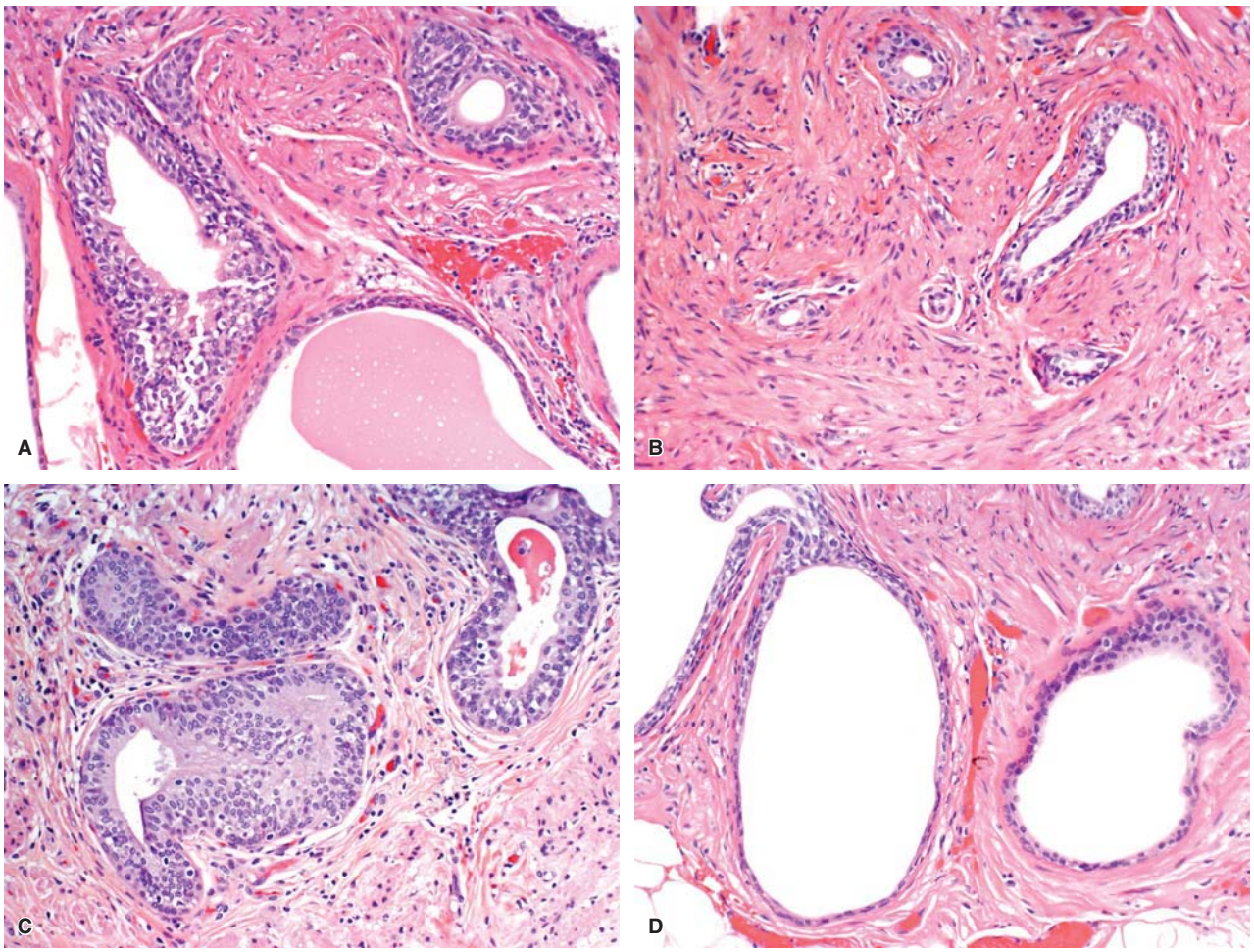


Figure 1-29 Urachal remnants (A to D).

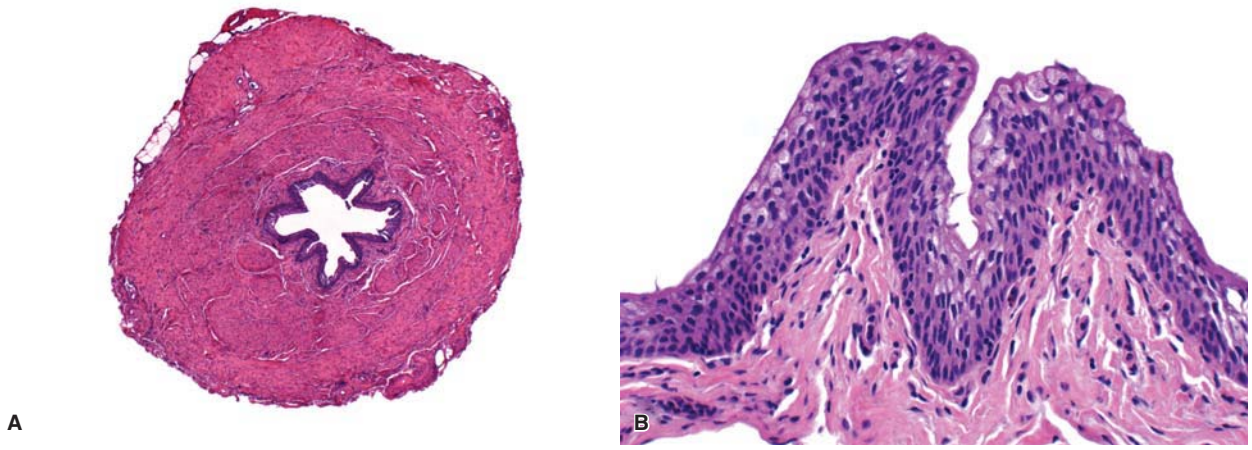


Figure 1-30 Normal ureter (A and B).

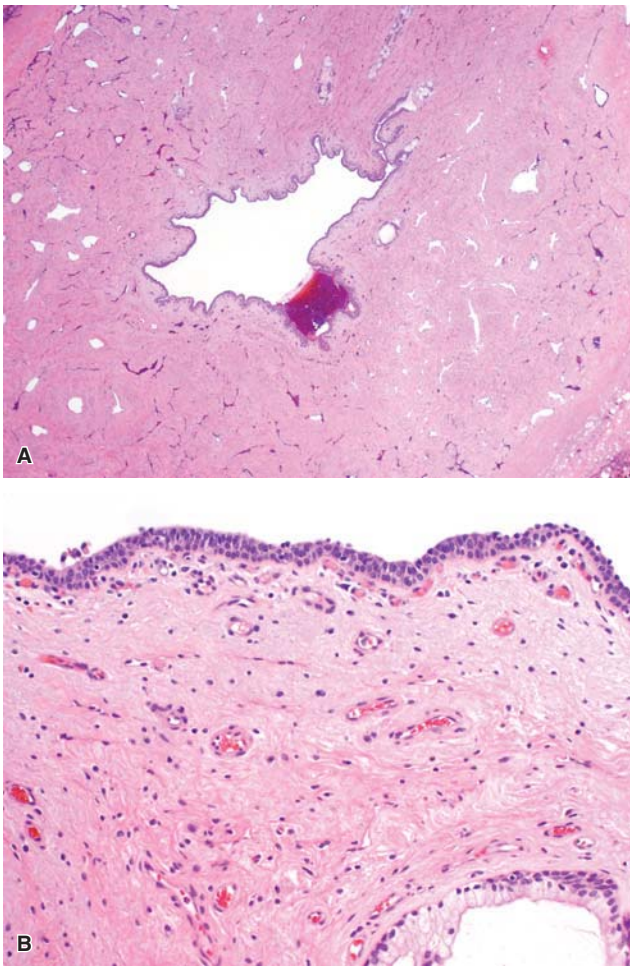


Figure 1-31 Normal urethra in a male patient (A and B).

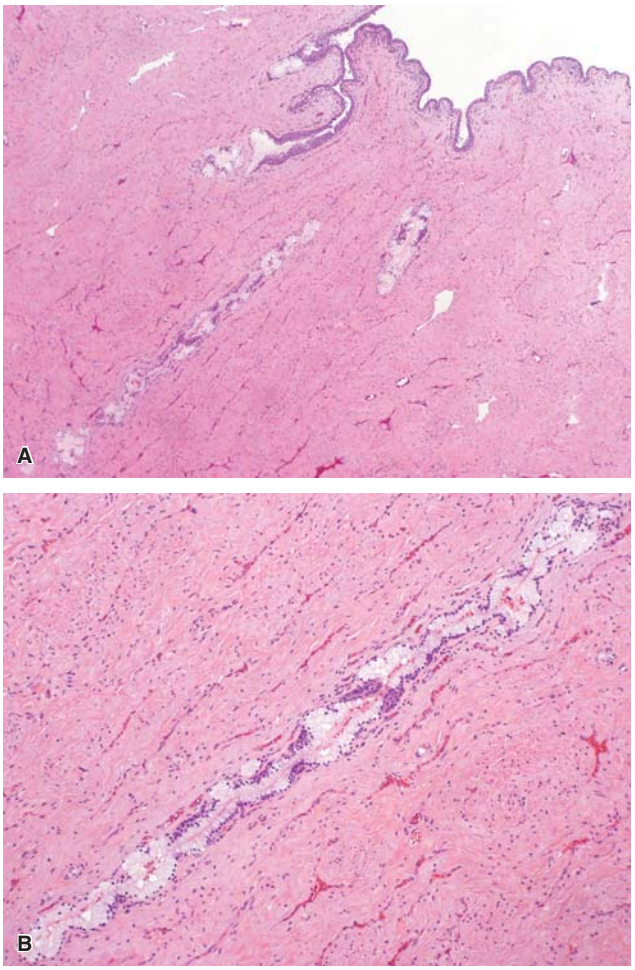


Figure 1-32 Normal urethra and periurethral glands (A and B).

prostatic urethra begins at the internal urethral orifice at the bladder neck and extends through the prostate to the prostatic apex. In the central part of the urethral crest is an eminence called the verumontanum. The verumontanum contains a slit-like opening that leads to an epithelium-lined sac called the prostatic utricle, a müllerian vestige. The ejaculatory ducts empty into the urethra on either side of the prostatic utricle. The membranous urethra extends from the prostatic apex to the bulb of the penis. Cowper glands are located on the left and right sides of the membranous urethra and their ducts empty into it. The penile urethra extends from the lower surface of the urogenital diaphragm to the urethral meatus in the glans penis. Bulbourethral glands are located in the proximal (bulbous) portion of the penile urethra. In addition, scattered mucus-secreting periurethral glands (Littre glands) are present at the periphery of the penile urethra except anteriorly (**Fig. 1-33**). The majority of unmyelinated nerve fibers penetrate the smooth muscle layers at 5 o'clock and 7 o'clock, whereas the majority of myelinated nerve fibers penetrate the striated muscles of the

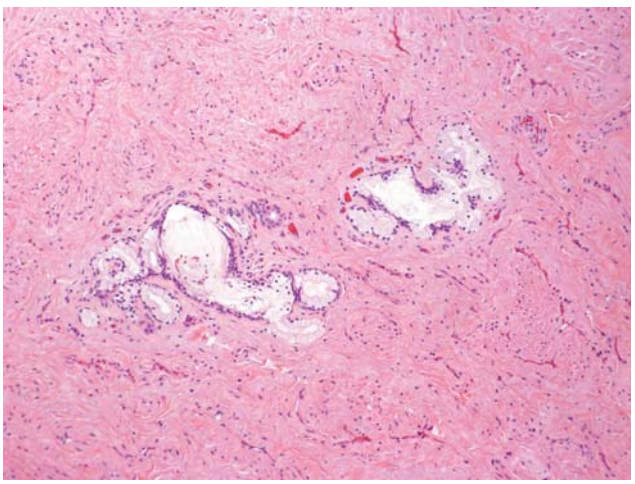


Figure 1-33 Littre glands are lined by mucus-secreting columnar cells.

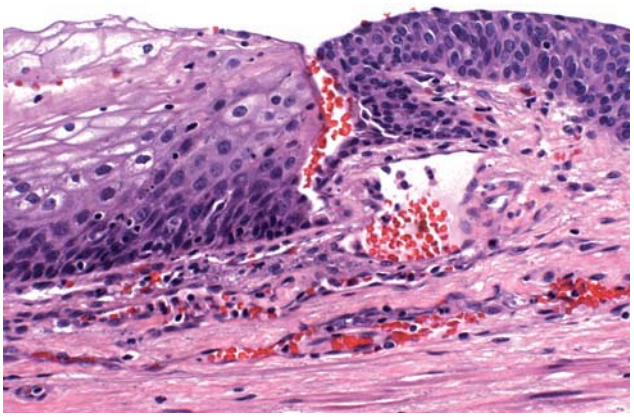


Figure 1-34 Transition from urothelium to squamous epithelium in the urethra.

prostatic capsule and of the urethral sphincter at 9 o'clock and 3 o'clock.

The type of epithelium lining the urethra varies along its length (**Fig. 1-34**). In general, urothelium lines the prostatic urethra, pseudostratified columnar epithelium lines the membranous segment and most of the penile urethra, and nonkeratinized stratified squamous epithelium lines the fossa navicularis and external urethral orifice. In females, the proximal one-third of the urethra is lined by urothelium and the distal two-thirds by nonkeratinized stratified squamous epithelium. The proximal one-third consists of a circular smooth muscle sphincter, the middle one-third of two circular layers of smooth and striated muscle fibers, and the distal one-third of a circular layer of smooth muscle fibers surrounded by an omega-shaped layer of striated muscle fibers. In the proximal one-third of the urethral sphincter, myelinated fibers run with unmyelinated fibers from the pelvic plexus. These fibers are closely related to the lateral and anterior aspects of the vagina. Unmyelinated fibers enter the smooth muscle part of the sphincter at 4 o'clock and 8 o'clock, whereas most myelinated fibers enter the sphincter at 3 o'clock and 9 o'clock. The female urethra is approximately 4 cm long, and, at its periphery, contains paraurethral Skene glands.

Immunohistochemical Findings

The urothelium has a characteristic immunophenotype. It expresses cytokeratins of both low and high molecular weights, including cytokeratins 7, 8, 13, and 19; cytokeratins 18 and 20 are present in the superficial cells.[38–41] This pattern of expression differs from that of normal stratified squamous epithelium, which shows predominantly high molecular weight cytokeratin immunoreactivity and from endometrium, endocervix, colorectum, and prostate, which demonstrate a preponderance of low molecular weight cytokeratin. High molecular weight cytokeratin immunoreactivity is restricted to the basal cell layer of the urothelium and squamous mucosa of the trigone. This can also be readily stained with antikeratin MAC387, which is not present in basal cells but in squamous cells of the trigone.[42] Other epithelial markers, such as epithelial membrane antigen, carcinoembryonic antigen, and LeuM1, are found on the surface of the urothelium. The normal urothelium synthesizes blood group isoantigens A, B, and H(O) as well as Lewis blood group antigens.[43] As mentioned above, the basal layer of urothelial cells expresses Bcl-2 while the intermediate cells express RB1 and PTEN at varying intensities. HER2 and p53 are not expressed by normal urothelial cells. Ki67, indicating proliferation, is uncommon in the normal urothelium. Prostate-specific antigen (or human glandular kallikrein 3), prostatic acid phosphatase, prostate-specific membrane antigen, and human glandular kallikrein 2 are not produced by the urothelium.

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Chapter 2

Inflammatory and Infectious Conditions

Bladder Pathology, First Edition. Liang Cheng, Antonio Lopez-Beltran, David G. Bostwick.

Table 2-1 Inflammatory Conditions

Acute and chronic cystitis
Follicular cystitis
Interstitial cystitis
Eosinophilic cystitis
Encrusted cystitis
Emphysematous cystitis
Gangrenous cystitis
Hemorrhagic cystitis
Viral cystitis
Cystitis with atypical giant stromal cells
Denuding cystitis
Granulomatous cystitis
Postsurgical
Suture granuloma
BCG-induced
Schistosomiasis
Malakoplakia
Tuberculosis
Xanthoma
Other
Other infection cystitides
Fungal
Actinomycosis
Miscellaneous cystitides

A wide variety of nonneoplastic inflammatory conditions may involve the bladder primarily or secondarily (Table 2-1).[1]

Acute and Chronic Cystitis and Their Variants

Acute and Chronic Cystitis

Most cases of acute and chronic cystitis result from infection with gram-negative coliform bacteria such as *Escherichia coli (E. Coli)*.[2,3] The most common portal of entry is the urethra. Predisposing factors include structural abnormalities of the urinary bladder, diverticula, calculi, any process or lesion that causes outflow obstruction, and systemic illnesses such as diabetes. Infectious causes of cystitis include bacterial, viral, fungal, and protozoal agents. Irritative agents that cause cystitis include trauma from instrumentation and catheterization, radiation therapy, chemotherapy, bladder calculi, and chemical irritants such as formalin, turpentine, and ether (chemical cystitis).[4,5] Some cases of cystitis are of unknown etiology. Other forms of cystitis include interstitial, eosinophilic, and follicular cystitis.[6]

In early acute bacterial cystitis, there is vascular dilatation and congestion, erythematous and hemorrhagic mucosa, and moderate to severe edema. With time, polypoid or bullous cystitis may develop, sometimes with ulceration. The urothelium may be hyperplastic or metaplastic, and, when ulcerated, is often covered by a fibrinous membrane with neutrophils and bacterial colonies (Figs. 2-1 and 2-2). Stromal edema and chronic inflammation gradually become more pronounced, particularly in the lamina propria (Fig. 2-3). If the acute inflammation persists, chronic cystitis usually develops, sometimes with prominent mural fibrosis.

In chronic cystitis, the mucosa may be thin, hyperplastic, or ulcerated, often with changes of reactive atypia (Figs. 2-4 to 2-6). Granulation tissue is typically conspicuous in the early stages, and may be replaced by dense scarring, particularly in the late healing stages. Edema may also be present (Fig. 2-7). This process may be transmural and involve

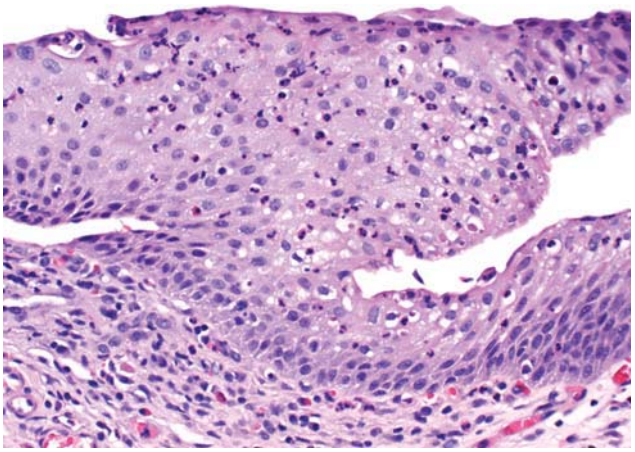

Figure 2-1 Acute cystitis. Numerous neutrophils are seen in the urothelium.

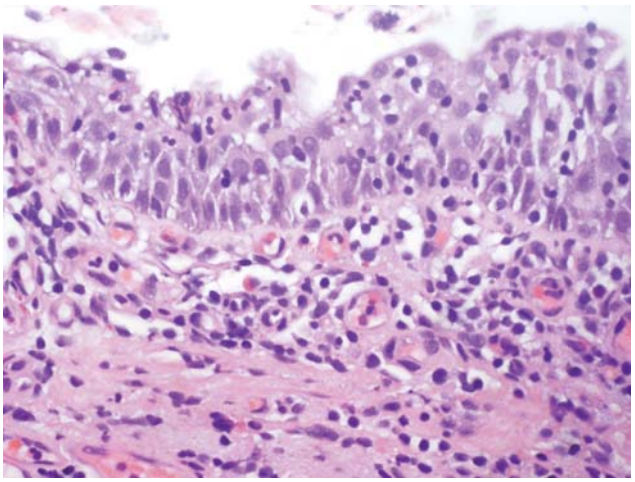

Figure 2-2 Acute cystitis. Reactive changes are commonly seen in the setting of acute cystitis and should not be mistaken for dysplasia or carcinoma in situ.

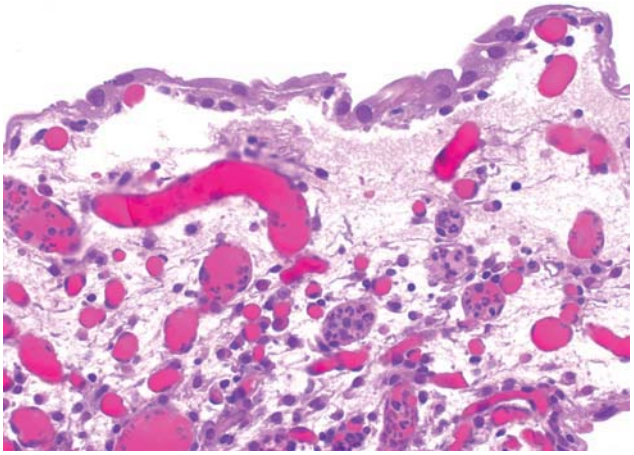

Figure 2-3 Acute cystitis. Note the stromal edema.

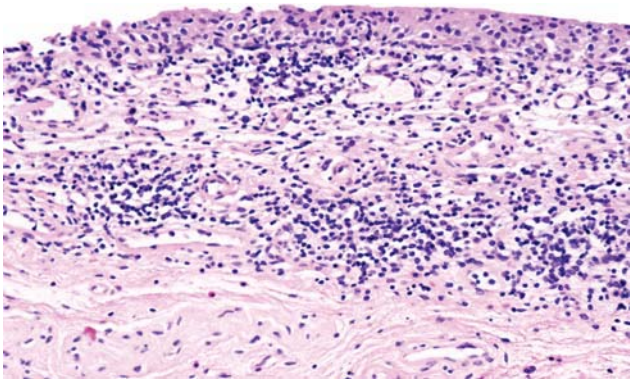

Figure 2-4 Chronic nonspecific cystitis. The mucosa is intact but thinned, and the lamina propria contains a mixed chronic inflammatory infiltrate.

perivesicular tissue. Squamous metaplasia may develop at a later stage (**Fig. 2-8**).

Papillary–Polypoid Cystitis (Papillary Cystitis; Bullous Cystitis)

Polypoid cystitis may be clinically and microscopically mistaken for papillary urothelial carcinoma.[7–9] Polypoid cystitis refers to lesions with edematous and broad-based papillae (**Figs. 2-9** to **2-12**); the designation papillary cystitis is used when thin finger-like papillae are present (**Figs. 2-13** and **2-14**). In both, there is typically abundant chronic inflammation in the stroma, accompanied by prominent and often ectatic blood vessels. Sometimes the inflammation is not prominent, and the appearance varies from papillary or polypoid cystitis to bullous cystitis, depending on the amount of stromal edema. In bullous cystitis, the lesion is wider than lesions of polypoid or papillary cystitis.[10] On cystoscopy, the lesion frequently suggests papillary urothelial carcinoma.

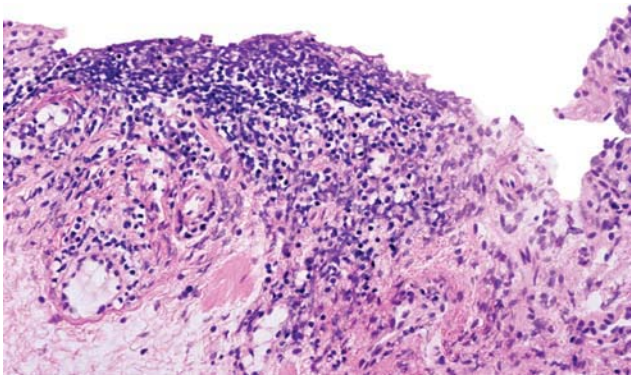

Figure 2-5 Chronic cystitis with mucosal erosion.

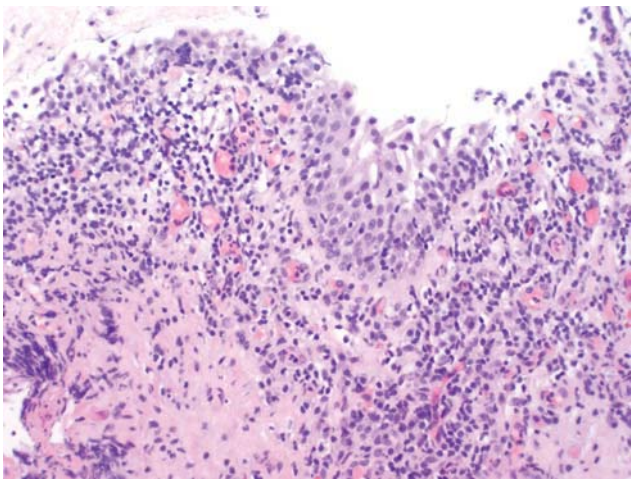

Figure 2-6 Chronic cystitis with reactive epithelial changes.

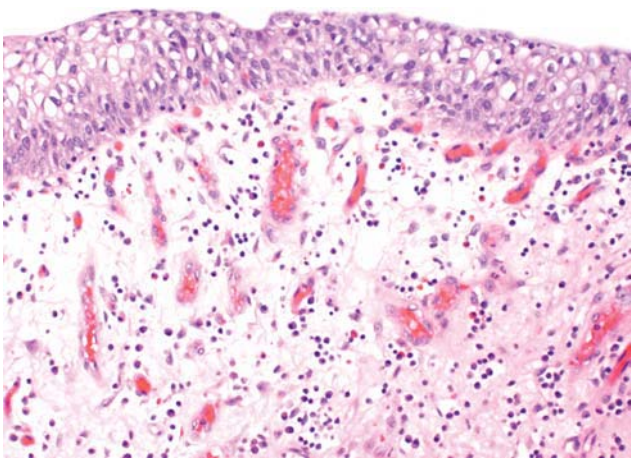

Figure 2-7 Chronic cystitis with mucosal edema. The overlying urothelium is metaplastic.

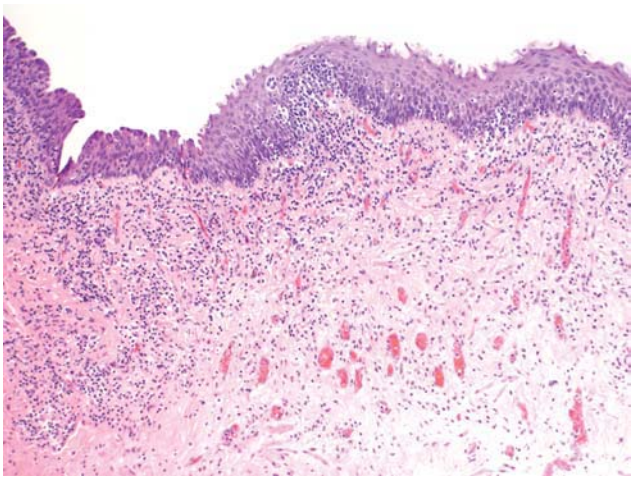

Figure 2-8 Chronic cystitis. Note the transition of normal urothelium to squamous epithelium (squamous metaplasia).

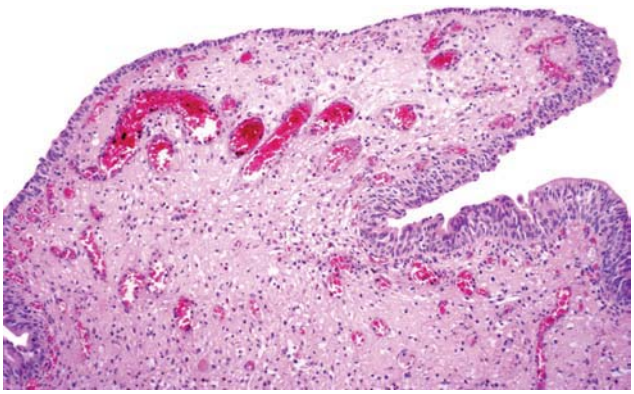

Figure 2-9 Polypoid cystitis with a broad frond of mucosa with prominent blood vessels and benign urothelial lining.

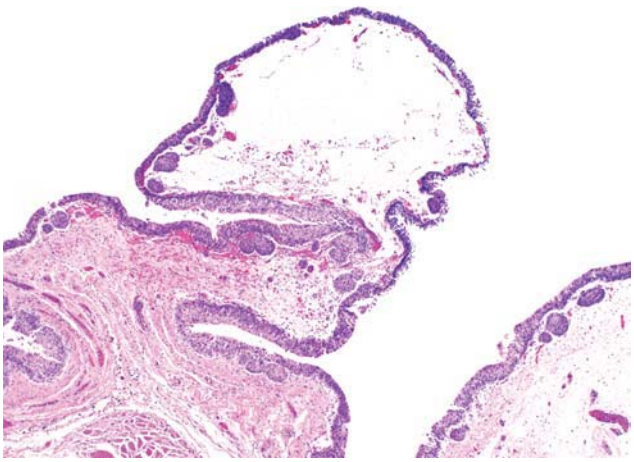

Figure 2-10 Polypoid cystitis with focal bullous formation.

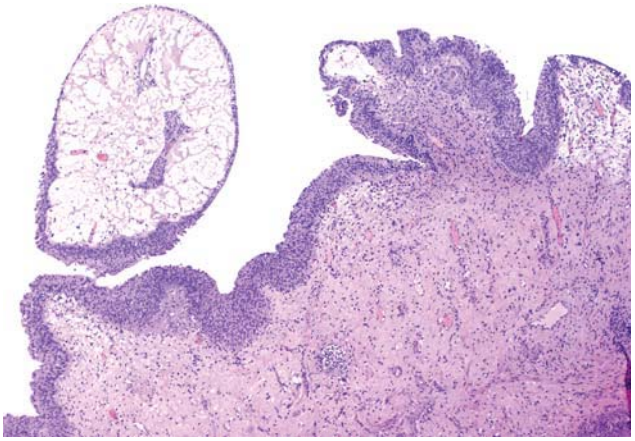

Figure 2-11 Polypoid cystitis.

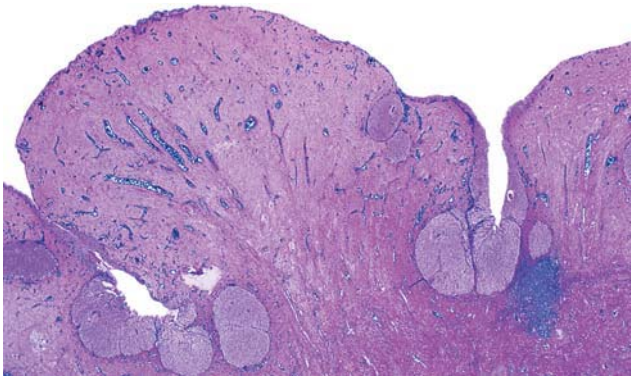

Figure 2-12 Polypoid cystitis. Broad polypoid growth that imparts a cobblestone appearance cystoscopically.

Exophytic growth of polypoid and papillary cystitis can be confused with carcinoma.[7,10] Occasionally, papillary–polypoid cystitis may be associated with reactive and metaplastic changes in the overlying or adjacent urothelium, with squamous metaplasia being the most common. The urothelium may be hyperplastic, but it lacks cytologic atypia. Less commonly, florid polypoid cystitis may suggest inverted papilloma.[10] Two clinical settings suggest that an exophytic bladder lesion is reactive or inflammatory—patients with an indwelling catheter[11,12] and those with vesical fistula.[10] Polypoid and bullous lesions are usually less than 0.5 cm in diameter, but larger, macroscopically visible lesions may involve the dome or posterior wall. The entire bladder is sometimes involved when a catheter has been present for more than six months.[10,13–15] Long-standing cases of polypoid cystitis may have a fibrous rather than an edematous stroma. The mucosal changes associated with vesical fistula may have the characteristics of reactive urothelium similar to what is seen in nonspecific chronic or acute cystitis.