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The Urinary Tract

A Comprehensive Guide to Patient Diagnosis and Management

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Our thanks to our families for their support and patience during the making of this book.

Foreword

As cofounder and president of the Bladder Cancer Advocacy Network, I am so pleased to see this comprehensive guide to the diagnosis and management of urinary tract diseases. As a "below the belt" condition, bladder cancer, and more benign bladder conditions, suffers from a lack of awareness and understanding—both from the medical community as well as the general population.

Drawing on the expertise of specialists across the country from multiple disciplines, this thorough and practical textbook is an essential tool for all physicians and physicians-in-training for understanding the specific issues and complexities that arise in the treatment of bladder cancer, as well as other urinary tract diseases. Early and correct diagnosis, along with the most appropriate treatment for the specific stage and grade of the patient's disease, is keys to survival in bladder cancer. I believe that when utilized, this Guide will improve patients' lives.

On behalf of bladder cancer patients and their families, along with family members who have lost loved ones to this disease, I applaud the work and effort of the editors and contributors to this valuable treatise.

Bethesda, MA, USA — Diane Zipursky Quale

Preface

Diseases of the urinary tract—whether benign or malignant—can present challenges in diagnosis and patient management. Increasing awareness of the complexity of urinary tract disease has prompted the formation of several national and international working groups focused on this anatomic region to better address outstanding questions in the field.

It is clear that one factor contributing to delayed progress in understanding and treating urinary tract disease is the sometimes limited communication between pathologist and treating physician. With the expansion of subspecialty publications, new diagnostic pathology entities in bladder cancer may be limited to a pathology-only audience; similarly, new treatment methods and their impact in clinical care may be viewed primarily by an urologist and oncologist audience. The lack of crosstalk and collaborative communication in such situations can lead to missed opportunities in disease understanding and management. In light of this, we took a novel approach to designing this textbook: each chapter is written by a pathologist and treating physician, often assigned from different institutions. We deliberately structured our text in this manner to not only highlight challenging areas that arise in the "crosstalk" arena but also address potential institutional differences in the management of urinary tract patients.

This book covers urethral, bladder, and upper tract disease, with emphasis on selected benign conditions—such as polypoid lesions, diverticular disease, and inflammatory processes—and most neoplastic processes. Neoplasia is addressed from a clinical and pathological perspective, with chapters addressing urothelial carcinoma and variant histology, as well as a chapter describing mesenchymal lesions. Additional chapters address anatomy and histology of the urinary tract, the role of urine cytology, pathology-endoscopy correlates, chemotherapy for neoplasia, and the molecular pathogenesis of bladder cancer.

Our primary goal in designing this text is to provide a comprehensive guide to the diagnosis and management of urinary tract disease for physicians and other health-care providers who diagnose and treat patients with urinary

tract disease. We hope that by emphasizing potentially problematic areas for each disease entity, we can not only draw attention to areas of needed improvement but also stimulate the necessary discussions to solve these outstanding problems.

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Part I

The Urinary Tract

Anatomy, Embryology, and Histology

1

Renee Dintzis and Jennifer McBride

Embryonic Origin of the Urinary Tract

Although the urinary and genital systems function as two separate systems, they are intimately related anatomically and embryologically. Both develop from a longitudinal elevation of intermediate mesoderm along the posterior aspect of the body wall identified as the urogenital ridge. The urogenital ridge is divided into the nephrogenic cord that gives rise to the urinary system and the gonadal ridge that gives rise to the genital system. The following sections will focus on the development of the urinary system structures including the kidneys, ureters, urinary bladder, and urethra.

Kidneys

In the developing human embryo, three successive sets of kidneys form along the posterior body wall. The initial set—the pronephroi—appears early in the fourth week as rudimentary nonfunctional structures (Fig. 1.1). These initial structures are localized in the cervical region and are composed of a small cluster of cells with tubular ducts that open caudally into the cloaca, the terminal part of the hindgut. While the collective mass of the pronephroi degenerates by the end of the fourth week, a length of the pronephric ducts endures as a precursor to the next set of kidneys.

The second set of kidneys appears late in the fourth week as the mesonephroi immediately caudal to the initial pronephroi (Fig. 1.1a). This second set is well developed and continues to function until approximately the ninth week of fetal development when the permanent kidneys become fully developed. As the mesonephric tubules grow medially they surround a cluster of capillaries to form a glomerulus and the surrounding Bowman's capsule; collectively, these structures are referred to as a renal corpuscle. Laterally, the mesonephric tubules enter the mesonephric (Wolffian) ducts, originally the pronephric ducts, and continue caudally to open into the cloaca (Fig. 1.1a). While the mesonephroi degenerate near the end of the first trimester, the mesonephric ducts persist in the male and contribute to the formation of the genital system including the seminal vesicles, ejaculatory ducts, epididymis, and vas deferens.

The third and permanent set of kidneys—the metanephroi—begins to develop early in the fifth week and to become functional in approximately the ninth week. The metanephroi develop from two sources: the metanephric diverticulum (ureteric bud), an outgrowth of the mesonephric

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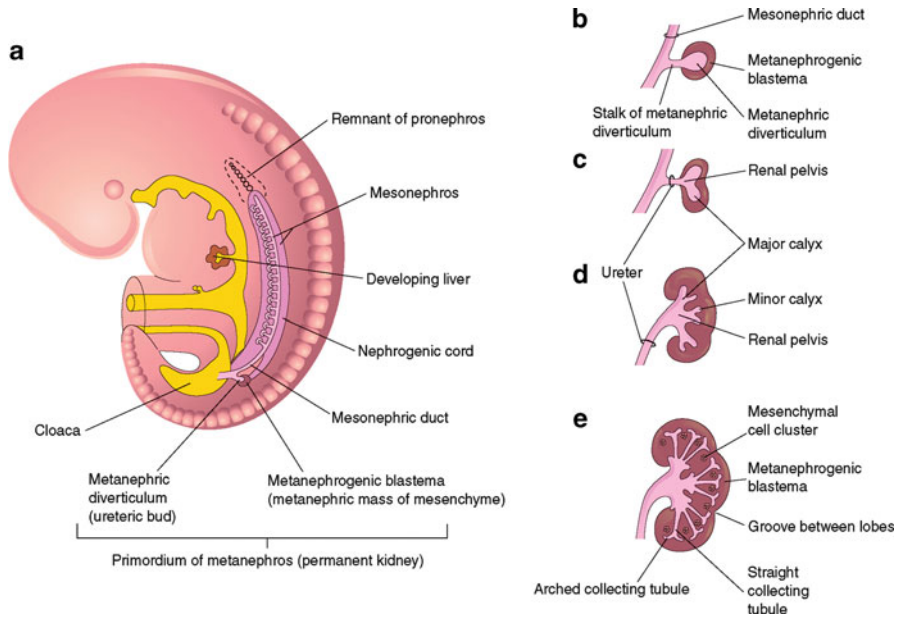

Fig. 1.1 Lateral view of the developing metanephros in a 5-week embryo (reprinted with permission from Moore and Persaud [4])

duct adjacent to its entrance into the cloaca, and the metanephrogenic blastema (metanephric mass of mesenchyme) that arises from the caudal aspect of the nephrogenic cord (Fig. 1.1a). The connecting stalk of the metanephric diverticulum develops into the ureters, and the cranial portion infiltrates the metanephrogenic blastema, subsequently causing the bulb of the diverticulum to subdivide repetitively into several branches. This branching pattern will form the primitive renal pelvis, major and minor calyces, and the collecting tubules (Fig. 1.1b–e). After penetrating the metanephrogenic blastema, the distal end of each collecting tubule induces the cells in the blastema to form metanephric vesicles that develop into S-shaped metanephric tubules with the proximal end invaginated by a glomeruli (Fig. 1.2). These tubules become distal convoluted tubules, proximal convoluted tubules, and the nephron loop (of Henle). Along with the glomeruli and its capsule, these tubules comprise a nephron or excretory unit. At its "distal" end each distal convoluted tubule is confluent with a collecting tubule, thus establishing a confluence between Bowman's capsule and the collecting unit.

Continuing up until the 32nd week of gestation the number of kidney glomeruli steadily increases. Nephrons also continue to form until birth when nephron development and formation is completed, with approximately 1–2 million nephrons in each kidney. At birth, the kidney has a lobulated appearance that diminishes during infancy as the nephrons and surrounding tissues continue to grow.

Initially, the metanephric kidneys are located in the pelvis just ventral to the sacrum. By the ninth week of development, the kidneys have ascended from the pelvis into the abdomen to reach their adult position along the posterior abdominal wall. Increased growth of the lumbar and sacral regions induces kidney ascent. As they ascend, the kidneys receive arterial branches from surrounding blood vessels. While in the pelvis, the kidneys receive arterial blood supply from the common iliac arteries. During their ascent, the kidneys are supplied by the aortic arterial branches until they reach the abdominal aorta, at which point they receive blood supply from the permanent renal arteries. The more caudal arterial branches from the common iliac

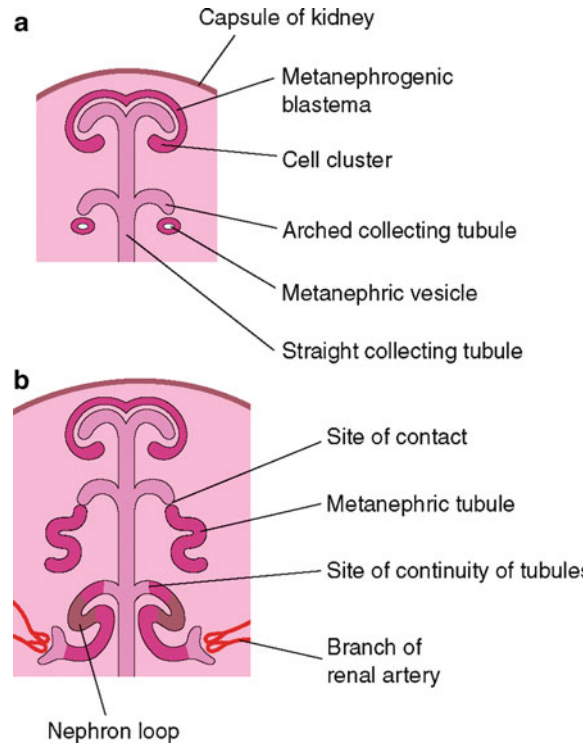

Fig. 1.2 Nephron development from the metanephric tubules. (**a**) Initiation of nephrogenesis, week 8. (**b**) Uriniferous tubules are formed by continuity of the collecting tubules with the metanephric tubules (reprinted with permission from Moore and Persaud [4])

and distal aorta degenerate as the kidneys migrate rostrally; however, some vessels may remain as accessory renal arteries. These accessory arteries directly reflect the changing blood supply to the kidneys during development. Typically, these arteries branch off the aorta near the renal artery to enter the hilum of the kidney. Branches that course anterior to the ureter to enter the inferior pole of the kidney may lead to obstruction of the ureter resulting in obstructive hydronephrosis.

Bladder and Ureters

The bladder and urethra develop from the urogenital sinus that is formed during the fourth to seventh week of gestation, when the cloaca is divided by the urorectal septum into an anal canal posteriorly and urogenital sinus anteriorly (Fig. 1.3a). Three divisions of the urogenital sinus are identified: an upper or cranial part that forms the majority of the bladder, a middle pelvic section that will become the entire urethra in females as well as the bladder neck and prostatic urethra in males, and a caudal phallic part that extends towards the genital tubercle. Early during bladder development, the bladder is continuous with the allantois, a sac-like structure that collects liquid waste and exchanges gases used by the embryo. Eventually, the allantois constricts and forms a fibrous cord—the urachus—that connects the apex of the bladder to the umbilicus and that subsequently forms the median umbilical ligament in the adult (Fig. 1.3b, c).

As the bladder develops, the caudal aspects of the mesonephric ducts are absorbed into the bladder wall and contribute to the formation of the trigone. As a result, the ureters that initially developed from the mesonephric ducts enter the bladder separately. During kidney ascent, the ureteral openings migrate superolaterally to enter the base of the bladder at an oblique angle, whereas the mesonephric duct openings move

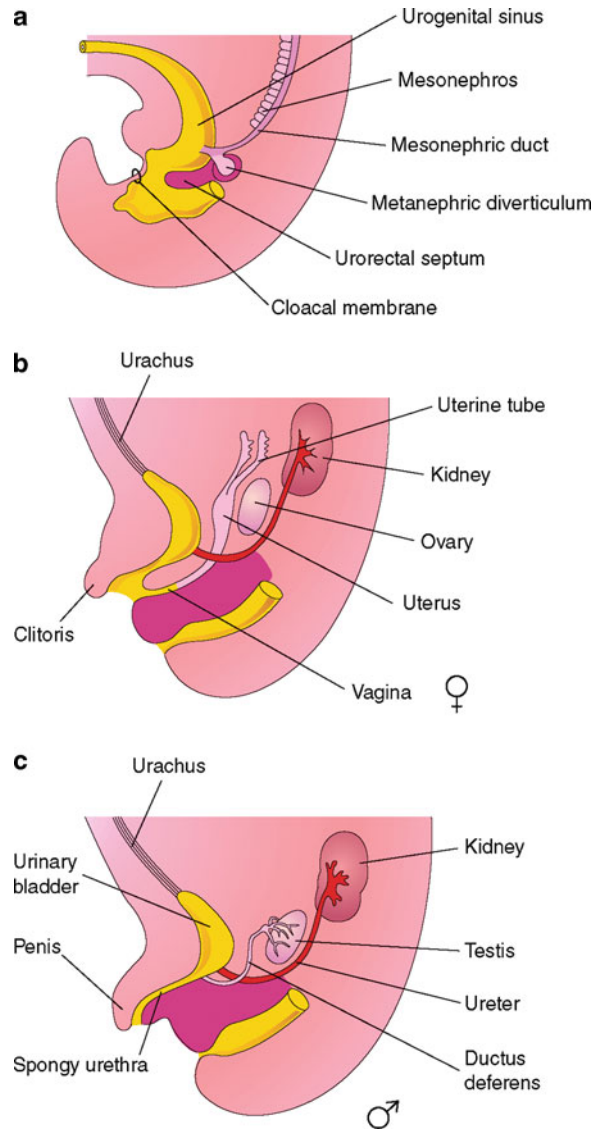

Fig. 1.3 Lateral view of the 5-week embryo. (**a**) Development of the urogenital sinus and rectum formed by division of the cloaca. (**b**) Male urogenital sinus and rectum at 12 weeks. (**c**) Female urogenital sinus and rectum at 12 weeks (reprinted with permission from Moore and Persaud [4]

close together to form the ejaculatory ducts in the prostatic urethra. In females, the distal ends of the mesonephric ducts degenerate.

Urethra

In both sexes, the majority of epithelium lining the urethra is derived from the urogenital sinus endoderm, while surrounding smooth muscle and connective tissues originate from splanchnic mesenchyme. The distal epithelium of the male urethra is derived from the glandular plate ectoderm that migrates from the glans penis to line the navicular fossa and join the spongy urethra. Near the end of the third month, the epithelium lining the prostatic urethra develops outgrowths that infiltrate the surrounding mesenchyme to form the prostate gland in males and urethral and paraurethral glands in females.

Anatomy of the Urinary Tract

Kidney

Structure

The kidneys function primarily to maintain fluid volume and composition and secondarily to regulate homeostatic functions such as acid–base balance and blood pressure. The kidneys are retroperitoneal organs positioned lateral to the vertebral column at the T12–L3 level in the supine position. The right kidney sits slightly lower due to its relationship with the liver above, while the left kidney sits closer to the midline, is somewhat narrower and generally 1 cm longer. Blood vessels, nerves, lymphatics, and the ureters enter and exit the bean-shaped organs through the concave hilum on the medial surface.

In the living tissue, the parenchyma of the kidney appears reddish brown and is divided into an outer cortex and inner medulla, the organization of which can be seen clearly in longitudinal section. The cortex contains a filtration apparatus that consists of an extensive vascular supply, collecting tubules and ducts, convoluted and straight tubules, and renal corpuscles. As the cortex arches over the medullary pyramids it sends intervening projections called renal columns into the medulla towards the renal sinus, a cavity within the kidney containing, nerves, vessels, calyces, and the renal pelvis. These renal columns are considered structures of the renal medulla. The inner medulla contains 6–12 pale conical-shaped medullary pyramids with the base of each pyramid oriented towards the cortex and an apex, or renal papilla oriented towards the renal sinus. Each renal papilla drains urine into a cup-like minor calyx, with 2–3 minor calyces combining to form a major calyx. Within the renal sinus the major calyces then converge to drain into the renal pelvis, the dilated proximal portion of the ureters.

Fascia and Relationships

Surrounding the kidneys are alternating layers of fascia and adipose tissue. The fascial layer in immediate contact with the kidney is the renal capsule—a histological component of the kidney itself. Encompassing the renal capsule is a mass of extraperitoneal fat referred to as perinephric fat (Fig. 1.4). Anterolateral to the kidney, two membranous layers split from the surrounding transversalis fascia and course medially enclosing the perinephric fat as renal (Gerota's) fascia. The anterior layer continues medially and fuses with the connective tissue of the inferior vena cava and aorta or may join with the anterior layer from the opposing side. The posterior layer also continues medially to fuse with fascia of the psoas major muscle. Inferiorly, both layers surround the ureter. Superiorly, these layers cover the adjacent adrenal gland with an intervening septum separating the gland from the kidney. The final layer, paranephric fat, is positioned along the posterolateral aspect of the kidney between the posterior layer of renal fascia and transversalis fascia.

Blood Vessels and Lymphatic Drainage

The kidneys receive blood from the left and right renal arteries that arise from the abdominal aorta just inferior to the superior mesenteric artery at the L1-L2 vertebral level (Fig. 1.5). Both arteries are positioned posterior to the renal veins as they project laterally towards the renal hilum. Due to the location of the abdominal aorta slightly left of midline, the right renal artery is longer than the left renal artery and passes posterior to the inferior vena cava. As the renal arteries approach the hilum they split into anterior and posterior branches that divide into multiple segmental arteries perfusing the parenchyma of the kidneys. Extrahilar or accessory arteries are common and usually branch off the abdominal aorta superior or inferior to the main renal artery trunk.

The renal veins leave the renal hilum to drain into the inferior vena cava at the L1 vertebral level. Due to the location of the inferior vena cava to the right of midline, the left renal vein is longer than the right renal vein and passes posterior to the superior mesenteric artery as it crosses the midline to join the inferior vena cava (Fig. 1.6).

Lymphatic vessels from the kidneys follow the renal veins to drain into the left and right lateral lumbar (caval or aortic) nodes near the origin of the renal arteries.

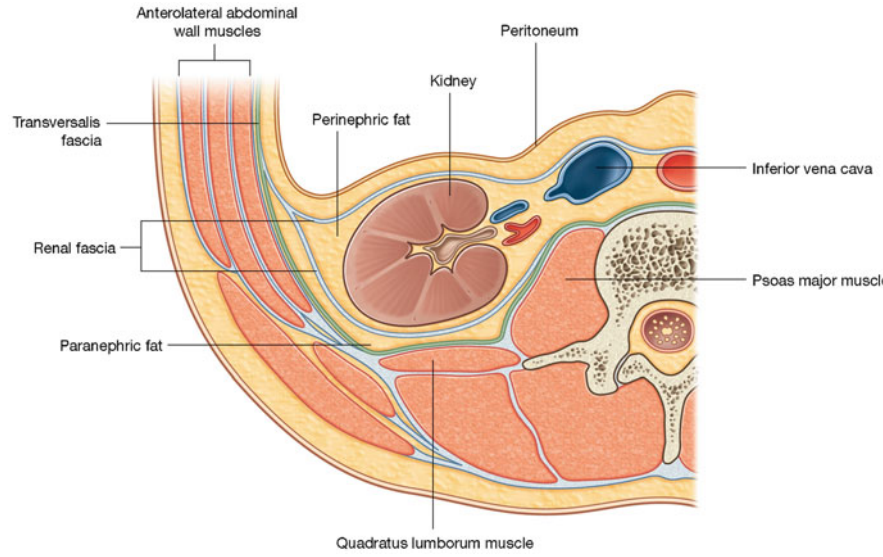

Fig. 1.4 Relationship of the surrounding fat and fascia to the kidney (reprinted with permission from Drake et al. [1, 2])

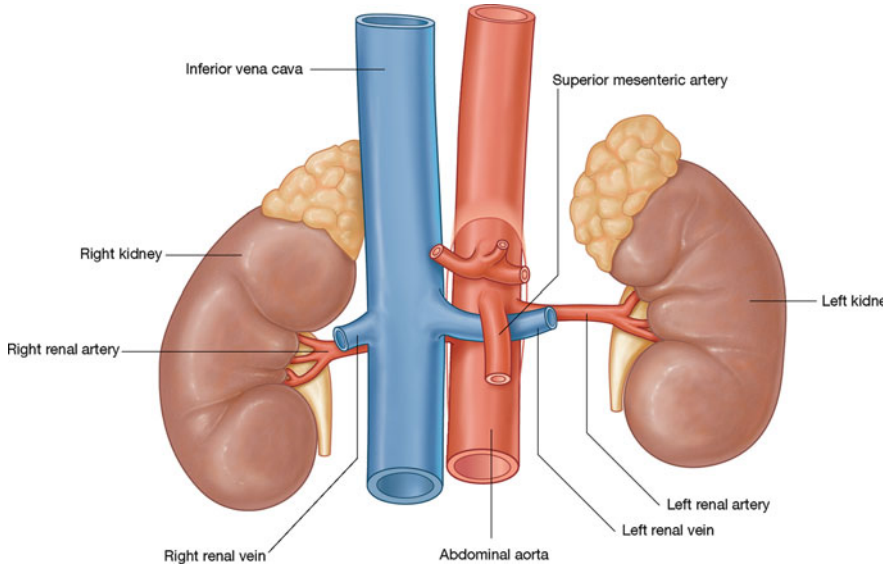

Fig. 1.5 Arterial and venous blood supply to the kidney (reprinted with permission from Drake et al. [1, 2])

Innervation

Innervation of the kidneys originates from sympathetic nerve fibers from T1-L1 spinal cord levels traveling in the renal plexus along the surface of the renal artery. This plexus receives postganglionic fibers from the celiac plexus and preganglionic fibers from the least splanchnic and first lumbar splanchnic nerves. Nerves from the renal plexus travel along the renal arteries to enter the hilum of the kidney for innervation of the tubules, glomeruli, and blood vessels. While parasympathetic fibers are present in this plexus, these fibers do not appear to play a role in kidney function.

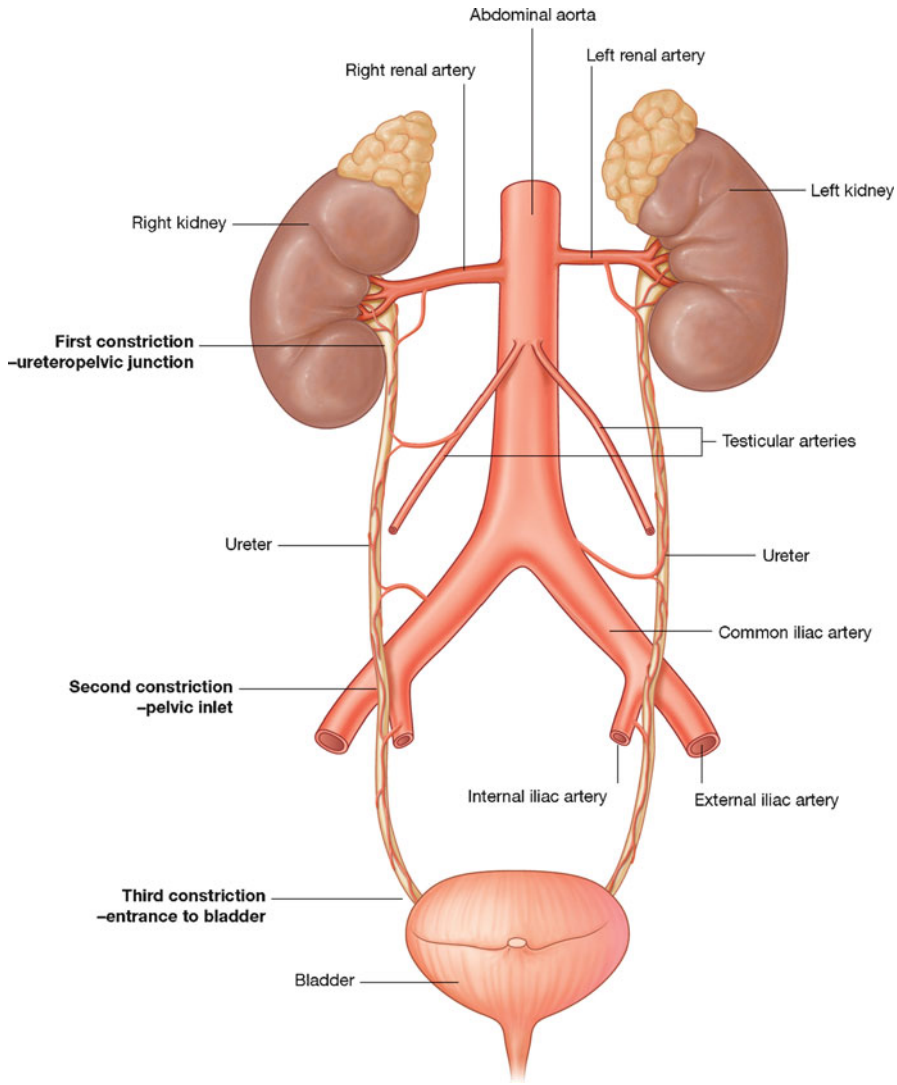

Fig. 1.6 Areas of constriction along the course of the ureter (reprinted with permission from Drake et al. [1, 2])

Ureters

Pathway and Relationships

The ureters are muscular ducts that transmit urine from the kidneys to the urinary bladder. In adults, the ureters are approximately 3–4 mm in diameter, 25–30 cm long and course retroperitoneally between the renal pelvis of the kidneys and base of the urinary bladder. As the renal pelvis projects inferiorly from the hilum of the kidneys, it narrows to connect with the ureters at the ureteropelvic junction (Fig. 1.6). This is the first of three constriction points along the path of the ureter where renal calculi or other debris may become lodged. Other areas where the ureters may be anatomically constricted include the pelvic inlet as the ureters pass anterior to either the distal common iliac artery or proximal external iliac artery and the ureterovesical junction as the ureters pass through the bladder wall.

Along their course towards the pelvic cavity the ureters are related to several different struc-

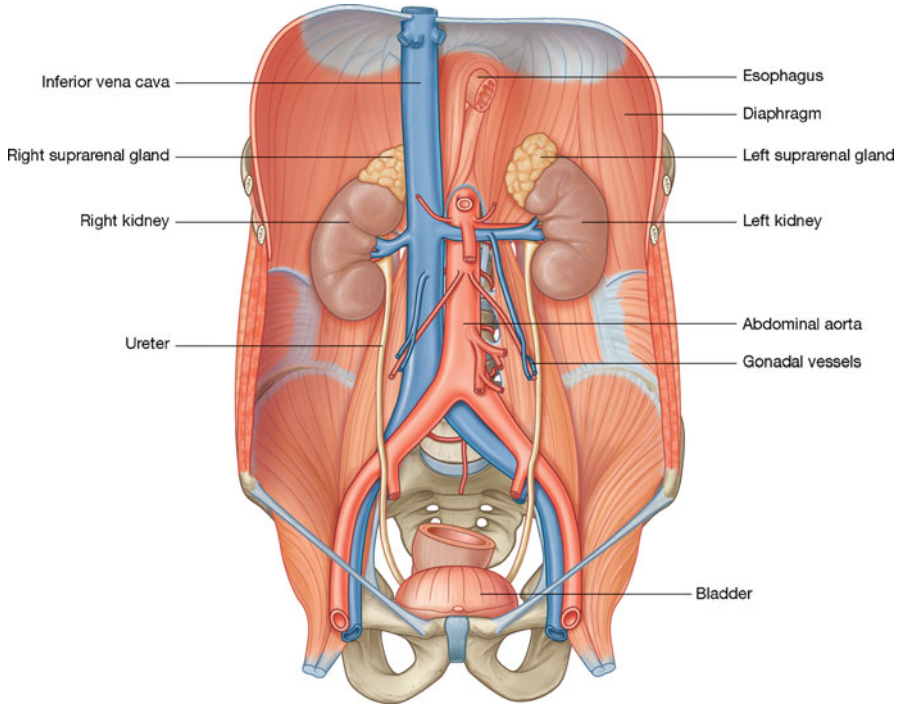

Fig. 1.7 Relationship of the ureters to posterior abdominal wall structures (reprinted with permission from Drake et al. [1, 2])

tures. At the ureteropelvic junction, the left ureter is lateral to the aorta whereas the right ureter is lateral to the inferior vena cava (Fig. 1.7). In the abdomen, both ureters pass anterior to the psoas major muscle, genitofemoral nerve, and are crossed obliquely on their anterior surface by the gonadal vessels. Continuing inferiorly, the left ureter is positioned lateral to the inferior mesenteric vein through much of its path and courses posterior to the jejunal and sigmoid portions of the small and large bowel. From its point of origin the right ureter is situated posterior to the descending duodenum and is crossed anteriorly by the right colic and ileocolic arteries inferiorly. Near its entrance into the pelvic cavity it is located posterior to the terminal portion of the ileum.

After passing through the pelvic inlet, the ureters are positioned along the posterior aspect of the lateral pelvic wall, anterior to the internal iliac artery and initial segment of the anterior trunk of the internal iliac. Upon reaching the ischial spine the ureters turn anteromedially to enter the outer wall of the bladder. Along their course in the pelvis, the ureters pass over the fascia of the obturator internus, levator ani muscles, and are located medial to the umbilical artery, inferior vesical artery, uterine artery (in the female), and obturator nerve, artery, and vein.

In addition to the previously mentioned relationships, the ureters are associated with different structures present in the male and female pelvic cavity. In females, once the ureters have crossed the pelvic brim they are located posterior to the ovaries and travel anteriorly and medially in the uterosacral folds (Fig. 1.8a). Near the base of the broad ligament they pass inferior to the uterine arteries and continue on to the base of the bladder. After crossing the pelvic brim in males, the ureters pass anteriorly and medially in the sacrogenital folds (Fig. 1.8b). As they travel towards the base of the urinary bladder they lie inferior to the ductus deferens and anterior to the seminal vesicles.

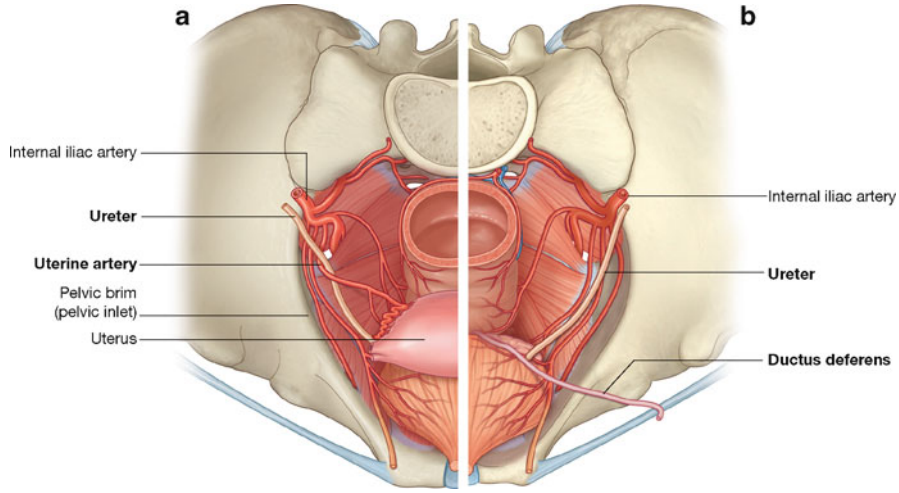

Fig. 1.8 Relationship of the ureters to the pelvic cavity. (**a**) In the female. (**b**) In the male. (reprinted with permission from Drake et al. [1, 2])

Blood Vessels and Lymphatics

Arterial branches perfusing the ureters arise directly from the aorta as well as the renal, gonadal, common iliac, internal iliac, vesical, and uterine arteries (Fig. 1.6). While the distribution of these anastomosing vessels to the ureters is variable, branches from the renal arteries and inferior vesical arteries appear to be the most consistent. Venous drainage from the ureters follows a pattern similar to the arterial supply.

Lymphatic fluid from superior regions of the ureters may follow lymphatic vessels from the kidneys or drain into lateral aortic nodes next to the lumbar vertebrae. Vessels from the mid-region of the ureters coalesce in common iliac nodes and inferior portions drain into nodes related to the common, external, and internal iliac vessels.

Innervation

Nerve fibers innervating the ureters arise from sympathetic fibers from T12 to L1 and parasympathetic fibers from S2 to S4 spinal cord levels. These fibers reach the superior, intermediate, and inferior regions of the ureter by passing through the renal, abdominal aortic, superior hypogastric, and inferior hypogastric plexuses. The functional role of these fibers is to modulate contractile events. Initiation of contraction is believed to occur through possible pacemaker sites in the minor calyces. Contraction initiated in the minor calyces is then propagated through the adjacent major calyces to maintain flow of urine away from the kidney parenchyma.

Pain associated with extreme distention or spasm of the ureter is primarily referred to cutaneous areas innervated by the T11-L2 spinal cord levels. Areas affected would most likely include the lateral and posterior abdominal wall, pubic region, scrotum, labia majora, and anterior aspect of the proximal thigh.

Bladder

Structure

The hollow urinary bladder is a reservoir for temporary storage of urine conveyed by the ureters from the kidneys. When empty, the bladder is located entirely in the pelvic cavity and takes on a pyramidal shape with a superior surface, two inferolateral surfaces, an apex, and a base. As it fills, the bladder extends anteriorly and superiorly into the abdominal cavity and has a dome-like appearance (Fig. 1.9). In children, the bladder is mostly in the abdominal cavity and continues descending to reach the pelvic cavity after puberty. The bladder wall has several layers

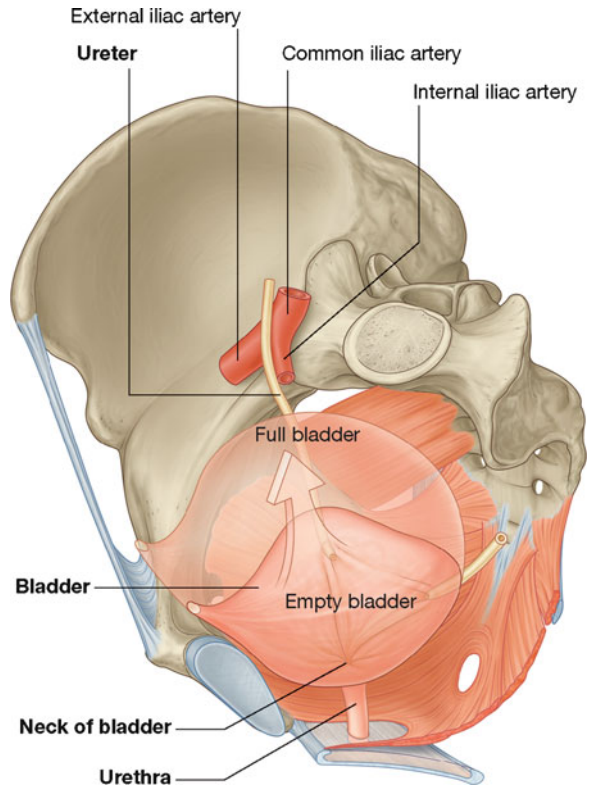

Fig. 1.9 Shape and orientation of the urinary bladder when full and empty (reprinted with permission from Drake et al. [1, 2])

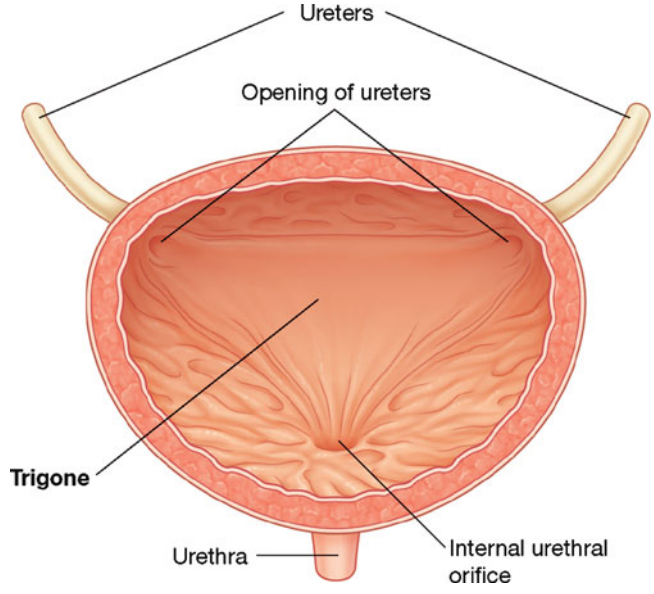

Fig. 1.10 Interior surface of the urinary bladder base showing the trigone (reprinted with permission from Drake et al. [1, 2])

of smooth muscle that allows it to distend for accommodation of urine and to contract for voiding when the bladder becomes full. Internally, along the base of the bladder is a smooth area known as the trigone. This is a triangular-shaped region that connects the openings of the two ureters superiorly and urethra inferiorly (Fig. 1.10).

Fascia, Relationships, and Ligaments

The entire superior surface of the bladder in males and majority of the superior surface in females is covered by peritoneum that is continuous with the median and medial umbilical folds on the anterior abdominal wall. This reflection of peritoneum creates the supravesical fossa. Posteriorly in the male, the peritoneum extends to the base of the bladder, forms the lining of the rectovesical pouch (Fig. 1.11a), and terminates laterally as the sacrogenital folds. In females, the peritoneum extends posteriorly without reaching the base of the bladder and reflects onto the body and isthmus of the uterus to form the lining of the vesico-uterine pouch (Fig. 1.11b). In both males and females, the inferolateral surface of the bladder is devoid of peritoneum and is separated from the pubis and puboprostatic ligament in males, or pubovesical ligament in females, by the retropubic space (of Retzius).

The bladder is bordered by several different structures in the male and female pelvic cavity. The anterior surface is in contact with the pubic symphysis, retropubic fat pad, and anterior abdominal wall. Laterally, it is related to the obturator internus superiorly and levator ani muscles inferiorly. The remaining surfaces of the bladder are associated with different structures depending on location in the male or female. In the male, the neck of the bladder is in contact with the superior aspect of the prostate gland. Posteriorly are the rectovesical pouch, ductus deferens, and seminal vesicles. The superior aspect is related to the peritoneal cavity, ileum, and sigmoid colon. In the female, the neck of the bladder rests on the urogenital diaphragm. Immediately posterior to the bladder is the vagina

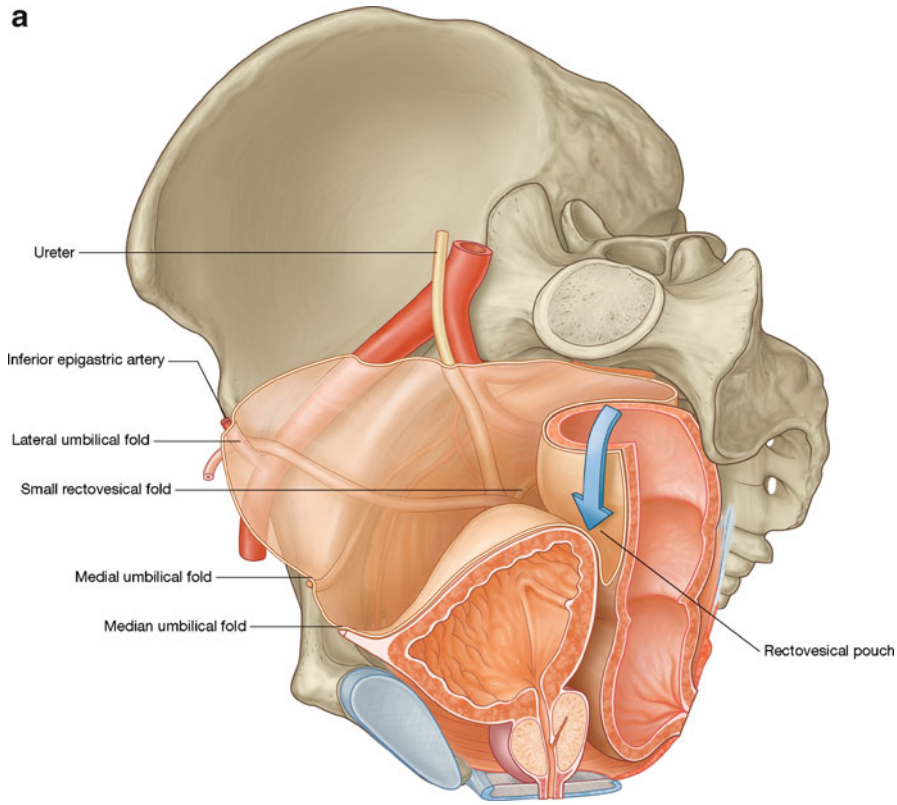

Fig. 1.11 Peritoneum lining the pelvis. (**a**) In the male. (**b**) In the female (reprinted with permission from Drake et al. [1, 2])

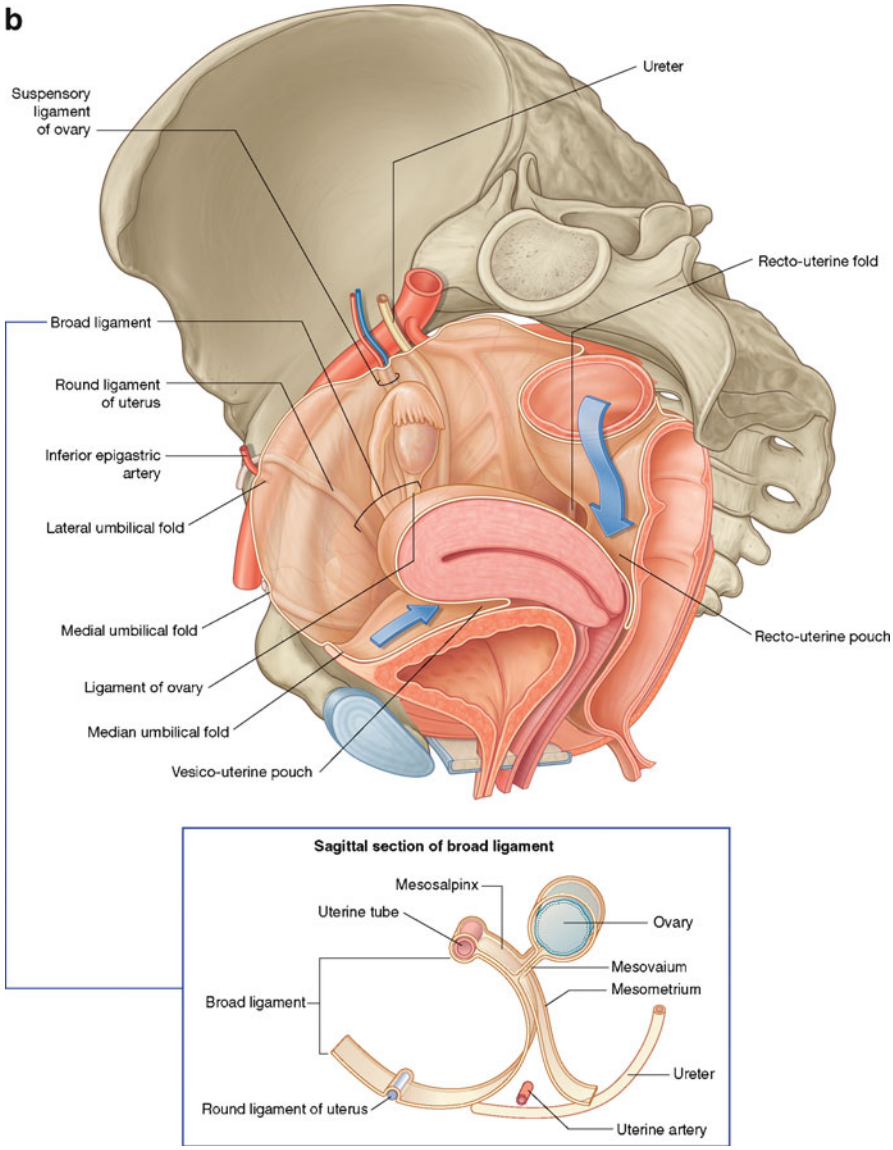

Fig. 1.11 (continued)

and lower portion of the uterus. The superior aspect is related to the peritoneal cavity, vesicouterine pouch, and body of the uterus.

Stabilization of bladder position is achieved by condensations of pelvic fascia and peritoneum that connect the bladder to the anterior abdominal wall, pubis, lateral pelvis, and rectum. Anteriorly, the obliterated urachus or median umbilical ligament connects the apex of the bladder to the umbilicus on the anterior abdominal wall. Rarely, extravasation of urine into the patent urachal remnant can result in urachal cyst or fistula. In the female pelvis, anterior extensions of the tendinous arch of pelvic fascia connect the bladder to the pubis as the pubovesical ligaments (Fig. 1.12a). Inferiorly the tendinous arch connects with the visceral fascia of the vagina as the paracolpium to assist the vagina in bearing the weight of the bladder. The male counterpart to the pubovesical ligament is the puboprostatic