1 Embryology, Anatomy, and Histology of the Kidney

Jennifer M. McBride

Development of the Kidney

During embryonic development, the urinary system emerges from the dorsal body wall as a longitudinal elevation of intermediate mesoderm known as the urogenital ridge (Fig. 1.1a, b). Located along each side of the aorta, the urogenital ridge gives rise to both the urinary system as the nephrogenic cord and the genital system as the gonadal ridge. The following is a description of kidney development from rudimentary nonfunctional structures of the nephrogenic cord to definitive functional organs.

Early in the fourth week, the primitive kidneys or pronephroi appear as elevations along the cervical region of the developing embryo [1]. These transitory structures consist of epithelial buds which extend ventromedially and pronephric ducts which extend caudally to eventually open into the cloaca of the hindgut (Fig. 1.2a). By the end of the fourth week, the pronephroi have degenerated with the pronephric ducts persisting to become incorporated into the second set of kidneys as the mesonephric (Wolffian) duct (Fig. 1.2b).

J.M. McBride, Ph.D. (✉)
Cleveland Clinic, Lerner College of Medicine of Case Western Reserve University, Cleveland Clinic/NA24, 9500 Euclid Avenue, Cleveland, OH 44195, USA
e-mail: mcbridj@ccf.org

During the fourth week, the mesonephroi emerge caudal to the pronephroi and function as interim structures until full development of the permanent kidneys around week 9. Along the length of the mesonephric (Wolffian) ducts (formerly pronephric ducts), mesonephric tubules begin to emerge on either side of the vertebral column extending from the upper thoracic region to mid-lumbar levels (Fig. 1.3a, b), with cranial tubules regressing by the end of week 5. The remaining tubules located in the upper three lumbar levels differentiate into cup-like pouches which extend medially to meet loops of capillaries emerging from the aorta (Fig. 1.3c). These structures are collectively referred to as a renal corpuscle and consist of the cup-like glomerular capsule and capillary plexus (Fig. 1.3d). During week 9, the mesonephric ducts regress in the female but persist in the male as part of the genital duct system including the ductus deferens, duct of epididymis, ejaculatory ducts, and seminal vesicles.

During the fifth week, the definitive kidneys or metanephroi begin to develop. Two sources give rise to the definitive kidneys: the ureteric bud (metanephric diverticulum) and the metanephrogenic blastema (metanephric mass of mesenchyme) (Fig. 1.4a). The ureteric buds emerge as outgrowths of the mesonephric ducts adjacent to their entrance into the cloaca. As they elongate, the ureteric buds invade the metanephrogenic blastema which grows from the caudal

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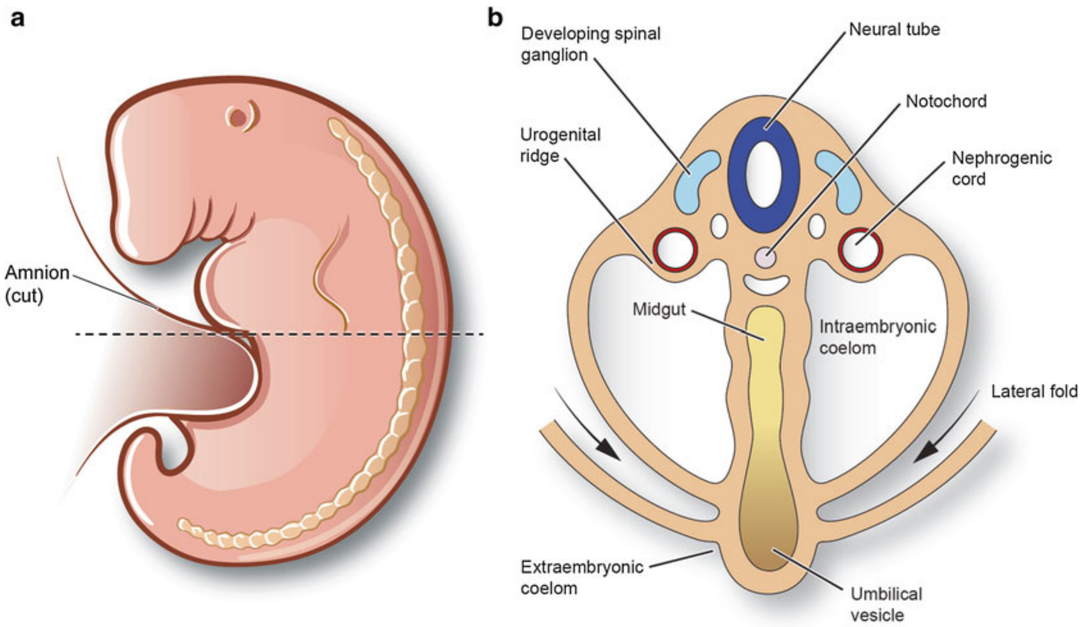

Fig. 1.1 (**a**) Lateral view of embryo in fourth week. (**b**) Transverse section demonstrating development of the urogenital ridge from the intermediate mesoderm (reprinted with permission, Cleveland Clinic Center for Medical Art & Photography © 2015. All Rights Reserved)

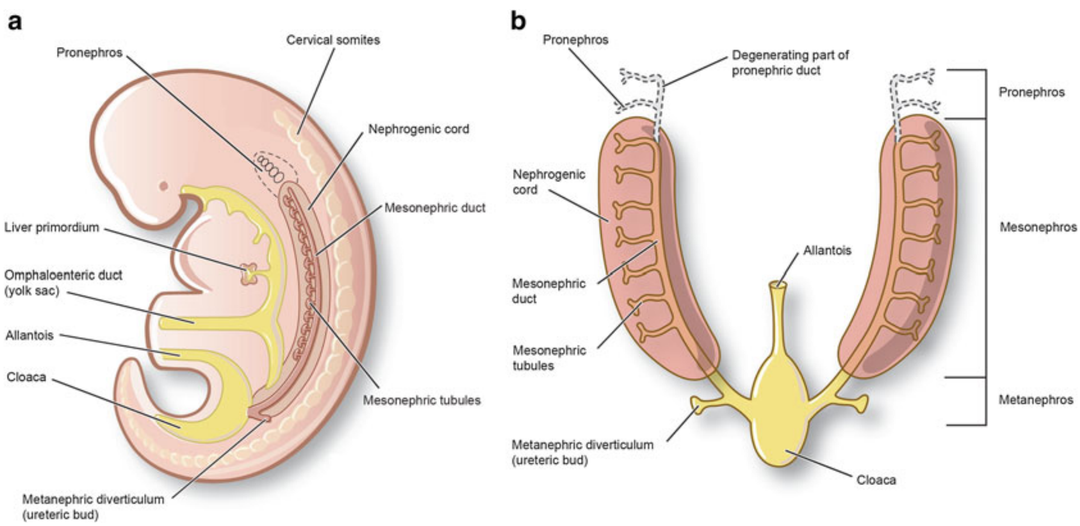

Fig. 1.2 Depiction of the nephric system transitions from the fourth to fifth week. (**a**) Lateral illustration of embryo in the fifth week with the development of the transitory pronephroi and pronephric ducts which open caudally into the cloaca. (**b**) Ventral view (reprinted with permission, Cleveland Clinic Center for Medical Art & Photography © 2015. All Rights Reserved)

aspect of the nephrogenic cord. Penetration of the metanephric mesenchyme induces the ureteric bud to undergo a series of repetitive branchings, leading to formation of the renal collecting ducts and tubules, calyces, and primitive renal pelvis (Fig. 1.4b–d). Reciprocally, the distal end of the bud induces the metanephric mesenchyme to condense and form metanephric vesicles which

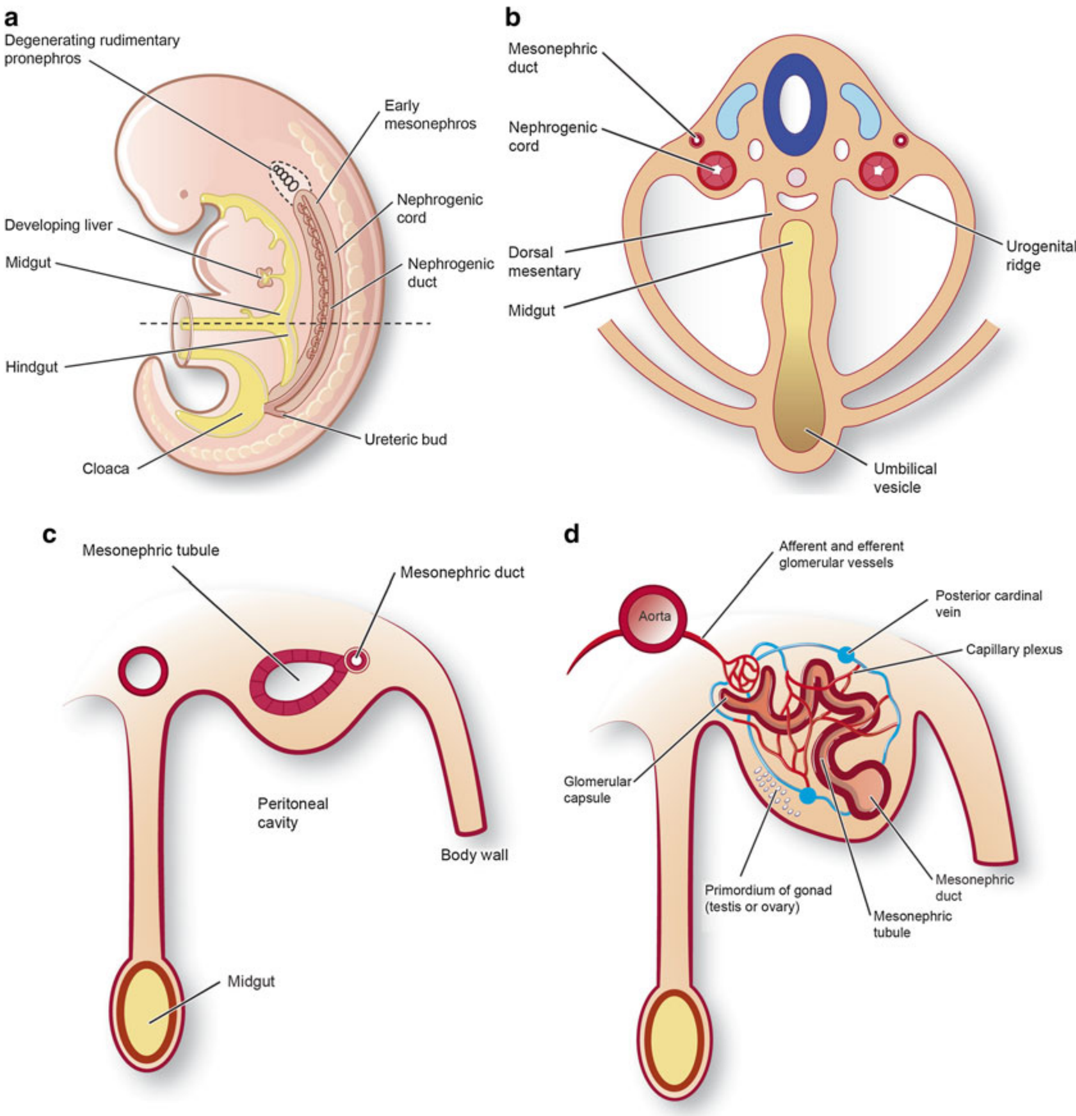

Fig. 1.3 (**a**) Lateral view indicating degeneration of the pronephros and emergence of the mesonephros. (**b**) Ventral view. (**c**) Sequential development of the mesonephric tubules from weeks 5 to 11. (**d**) The medial aspect of the mesonephric tubules extends to meet loops of capillaries emerging from the aorta (reprinted with permission, Cleveland Clinic Center for Medical Art & Photography © 2015. All Rights Reserved)

will further develop into a series of metanephric tubules (Fig. 1.5a, b). The connection formed between the lumens from these S-shaped metanephric tubules with that of the ureteric duct results in the formation of the definitive uriniferous tubule (Fig. 1.5c). These uriniferous tubules will further differentiate into proximal convoluted tubules, distal convoluted tubules, and the nephron loop including descending and ascending nephron loops (Fig. 1.5d).

During the tenth week, the metanephroi become functional as the distal convoluted and collecting tubules begin to adjoin. In addition, the population of glomeruli further increases during this time up until week 32 of gestation. Nephrons also continue to form with approximately two million nephrons present in each kidney at term.

Between weeks 6 and 9, the kidneys withdraw from the pelvis and ascend along either side of the aorta to reach their permanent location along

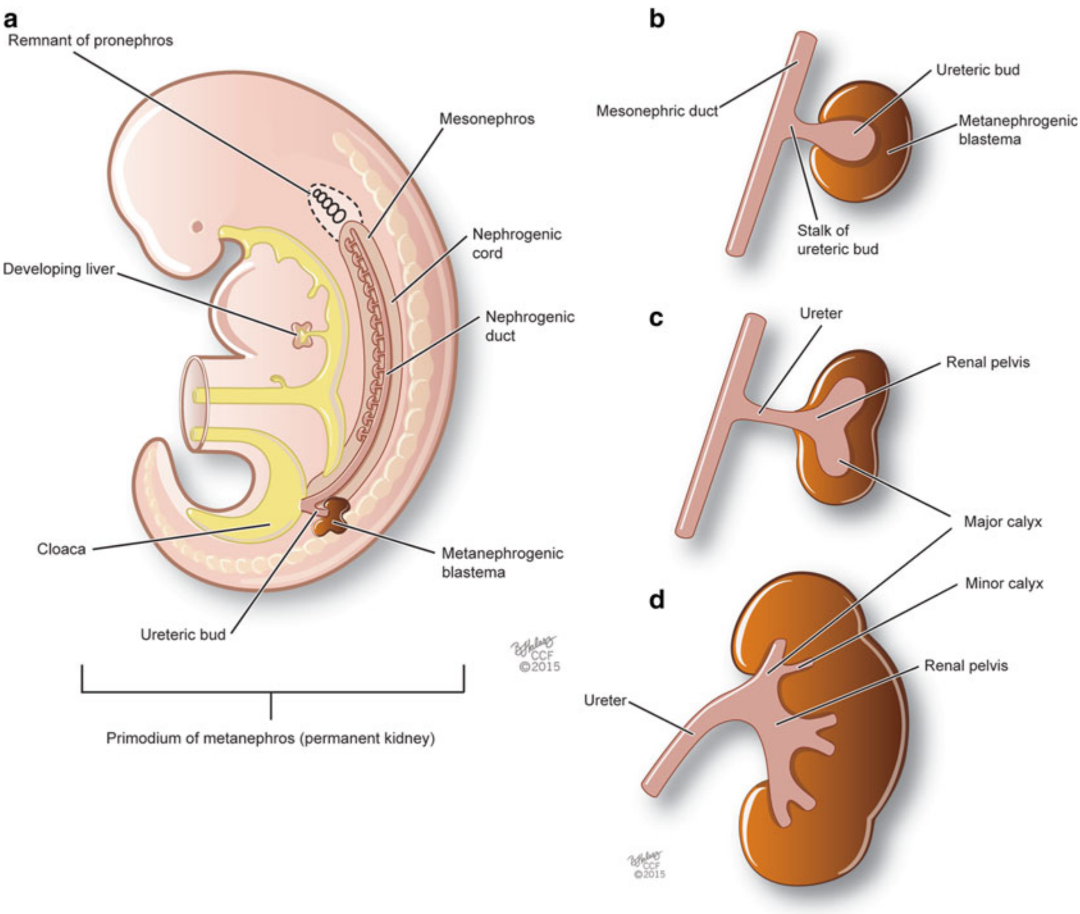

Fig. 1.4 Metanephros development from the ureteric bud and metanephrogenic blastema. (**a**) Lateral view of an embryo in the fifth week of development. (**b**–**d**) Sequential branching of the ureteric bud as it penetrates the metanephric mesenchyme (reprinted with permission, Cleveland Clinic Center for Medical Art & Photography © 2015. All Rights Reserved)

the posterior abdominal wall of the lumbar region (Fig. 1.6a–d). During their ascent, the kidneys' original blood supply from the common iliac arteries disappears with branches from successive levels of the aorta taking their place. After contacting the suprarenal glands, the kidneys become fixed in their position with primary arterial supply deriving from the abdominal aorta. Caudal arterial branches may remain as accessory renal arteries; typically, these branches arise from the aorta to enter the hilum of the kidney.

Anatomy of the Kidney

Overall Structure

The kidneys are reddish-brown bean-shaped structures located retroperitoneally along the posterior abdominal wall (Fig. 1.7). While posture and dynamic changes of the diaphragm can modify their relationship to surrounding structures, in the supine position, the kidneys typically extend

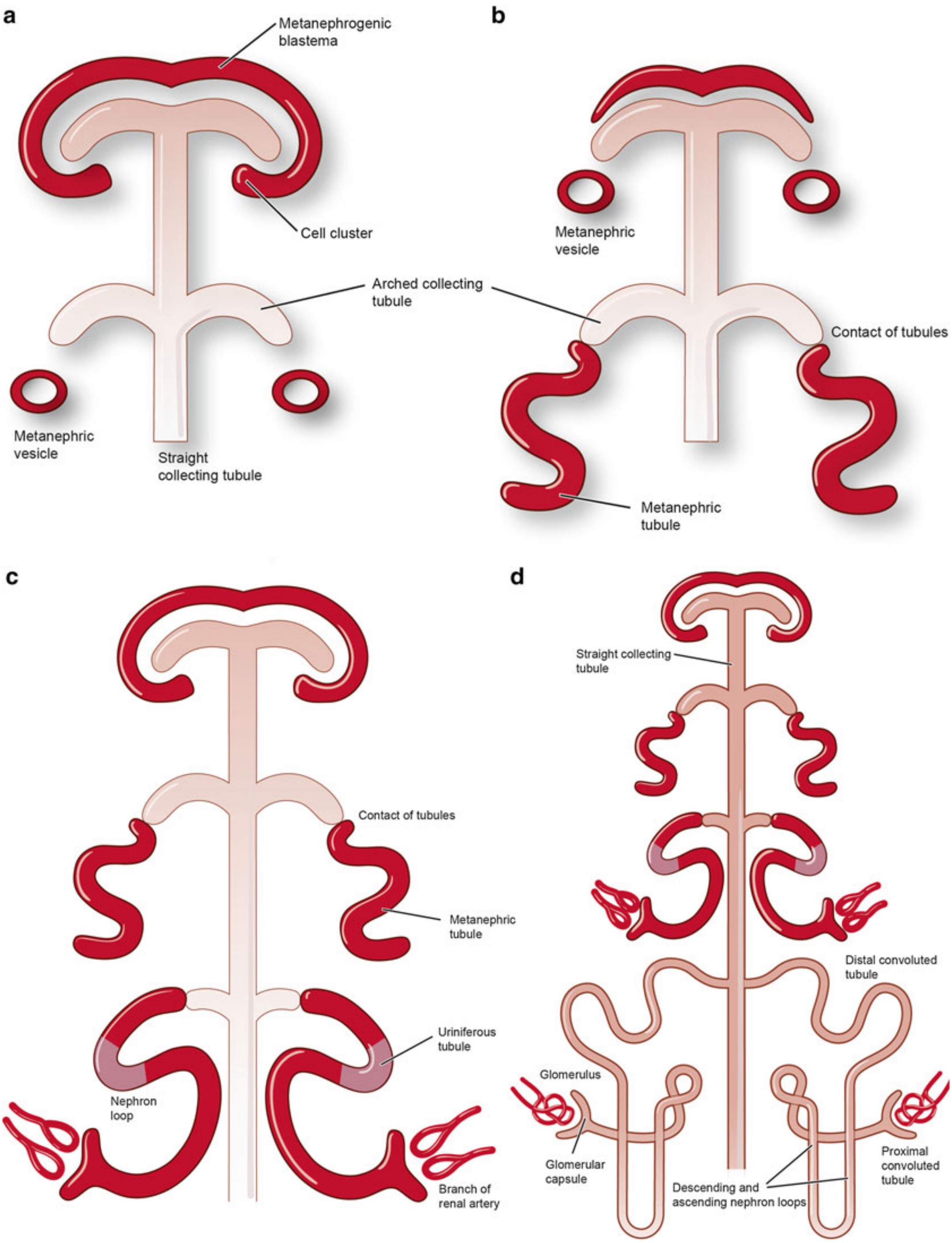

Fig. 1.5 Development of nephrons. (**a**) The distal end of the ureteric bud develops into a series of metanephric tubules. (**b**–**d**) These S-shaped structures, along with the ureteric duct, will form the uriniferous tubules (reprinted with permission, Cleveland Clinic Center for Medical Art & Photography © 2015. All Rights Reserved)

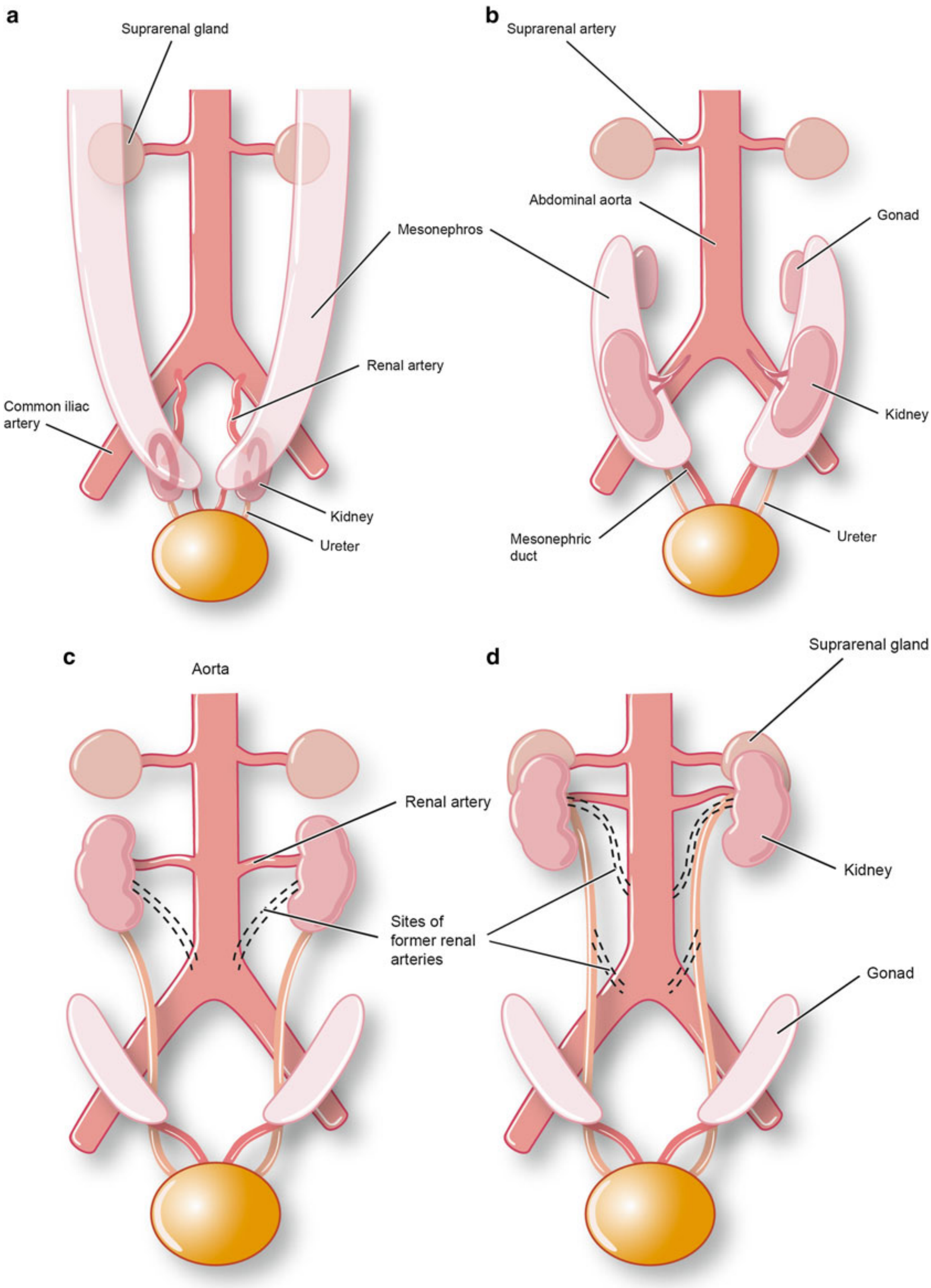

Fig. 1.6 Ventral abdominopelvic view of embryo from weeks 6 to 9. (**a**–**d**) The kidneys ascend alongside of the aorta to reach their permanent location in the lumbar region of the posterior abdominal wall (reprinted with permission, Cleveland Clinic Center for Medical Art & Photography © 2015. All Rights Reserved)

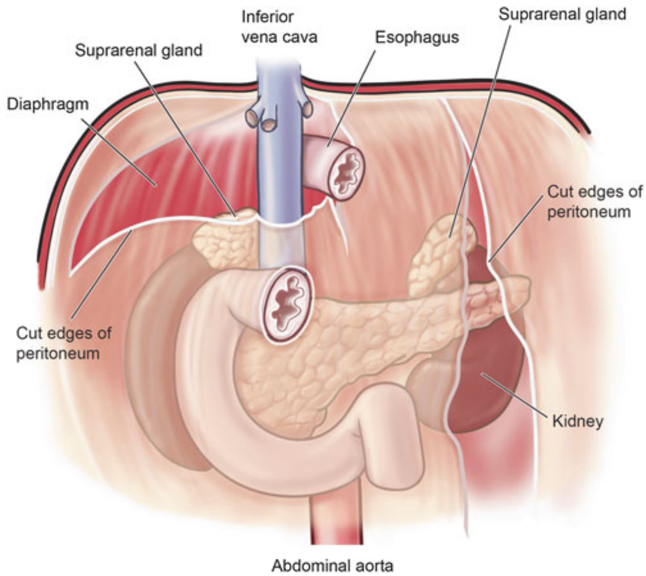

Fig. 1.7 Retroperitoneal location of the kidneys along the posterior abdominal wall (reprinted with permission, Cleveland Clinic Center for Medical Art & Photography © 2015. All Rights Reserved)

from vertebral levels TXII–LIII. The right kidney occupies a position slightly lower due to its relationship with the liver superiorly. Conversely, the left kidney rests slightly closer to the midline, has a narrower profile, and is somewhat longer. On its medial surface, the kidneys are occupied by blood vessels, nerves, lymphatics, and the renal pelvis entering and exiting the concave-shaped hilum which faces anteriorly and medially.

Adjacent Structures

Due to their position in the paravertebral gutters along the posterior abdominal wall, the kidneys are in contact with the surfaces of several structures directly or through an intervening layer of peritoneum. Anteriorly, the left kidney is related to the spleen, suprarenal gland, stomach, pancreas, jejunum, descending colon, and left colic flexure (Fig. 1.8a). Alternatively, the anterior surface of the right kidney is related to the liver, suprarenal gland, small intestine, right colic flexure, and descending part of the duodenum. Posteriorly, both kidneys are related to the psoas major muscle, quadratus lumborum muscle, transversus abdominis muscle, diaphragm, costodiaphragmatic recess, eleventh rib (left kidney only), twelfth rib, subcostal nerve, ilioinguinal nerve, and iliohypogastric nerve (Fig. 1.8b).

Fascial Contributions

The retroperitoneal connective tissue is organized around the kidneys to form interchanging layers of fascia and adipose tissue. In immediate contact with the kidney is the renal capsule, a fibrous layer which encapsulates the kidney, but it is histologically distinct from the renal parenchyma. Surrounding the renal capsule is the perinephric (perirenal) fat, an accumulation of adipose tissue from the extraperitoneal fatty layer (Fig. 1.9). Adjacent to the anterolateral aspect of the kidney and enclosing the perinephric fat are two layers extending from transversalis fascia that surround the kidney and are referred to as renal (Gerota's) fascia. Towards the midline, the anterior layer of renal fascia adjoins to the connective tissue of the inferior vena cava, aorta, or anterior layer from the opposing side. The posterior layer of renal fascia travels medially to adjoin to the fascia covering the anterior surface of the psoas major muscle. In addition to covering the

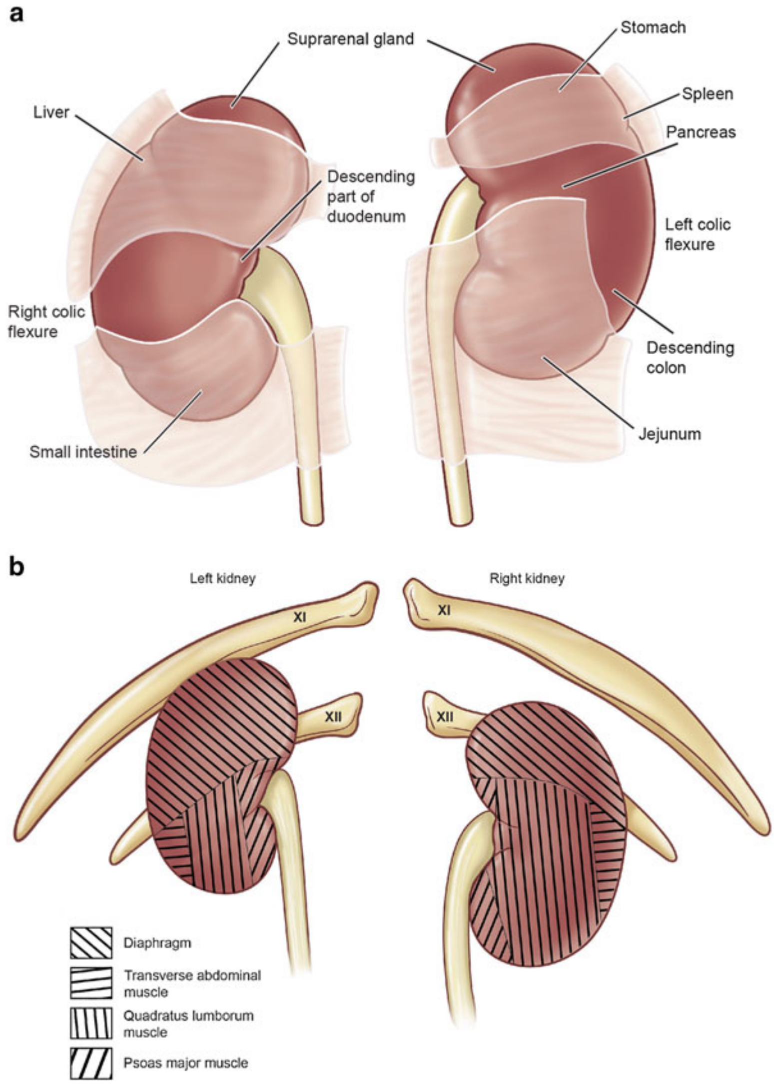

Fig. 1.8 Relationship of surrounding structures to the kidney. (**a**) Anterior surface. (**b**) Posterior surface (reprinted with permission, Cleveland Clinic Center for Medical Art & Photography © 2015. All Rights Reserved)

kidney, renal fascia also encapsulates the suprarenal gland superiorly; however, an intervening septum ordinarily separates the two structures. A final outermost layer of adipose tissue, paranephric fat, is found posteriorly and lateral to the kidney residing between the posterior layer of renal fascia and transversalis fascia.

Arterial Supply, Venous Drainage, and Lymphatics

The renal arteries are the primary arterial supply to the kidneys and extend off of the abdominal aorta between vertebral levels LI and LII (Fig. 1.10). Comparatively, the right renal artery emerges from the aorta slightly more superior and passes posterior to the inferior vena cava as it extends towards the kidney. As they course towards the kidney, the renal arteries give off several nonrenal branches which perfuse the adjacent renal capsule, ureters, and suprarenal glands. Just prior to reaching the renal hilum, they divide into five segmental arteries: superior/apical, anterosuperior, anteroinferior, inferior, and posterior. These terminal arteries are responsible for perfusing corresponding regions of the kidney. Clinically, this allows for identification of

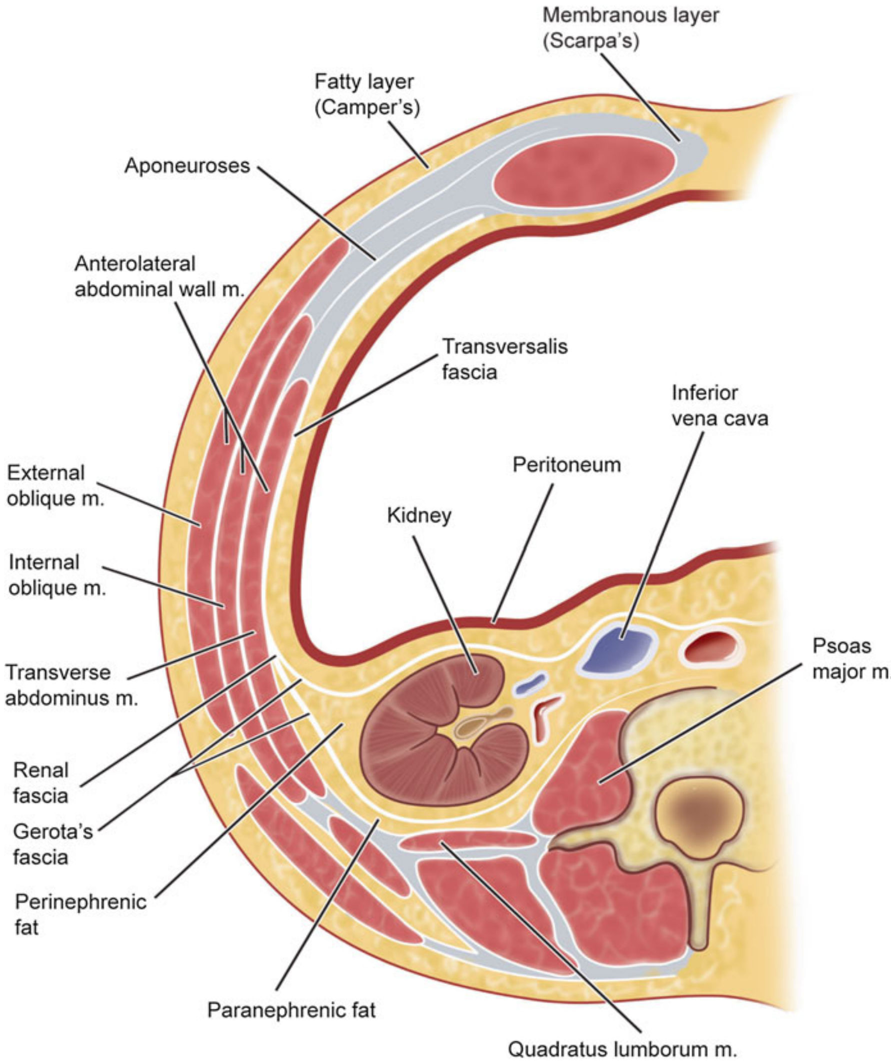

Fig. 1.9 Illustration of fascia and adipose tissue surrounding the kidney (reprinted with permission, Cleveland Clinic Center for Medical Art & Photography © 2015. All Rights Reserved)

surgically resectable renal segments as the segmental branches exhibit very little anastomotic properties. Accessory renal arteries may also be present, originating directly from the abdominal aorta to enter the hilum or other level (extrahilar arteries) of the kidney.

Positioned anterior to the renal arteries are the renal veins that arise from several small branches exiting the renal hilum. Both veins converge on the inferior vena cava residing just right of midline (Fig. 1.11). Due to the positioning of the inferior vena cava, the left renal vein is longer in length and passes anterior to the aorta and posterior to the descending segment of the superior mesenteric artery. This vascular relationship can be significantly compromised with the development of an aneurysm in either the aorta or superior mesenteric artery.

Lymphatic drainage from the kidneys, ureters, and suprarenal glands all coalesce into the left

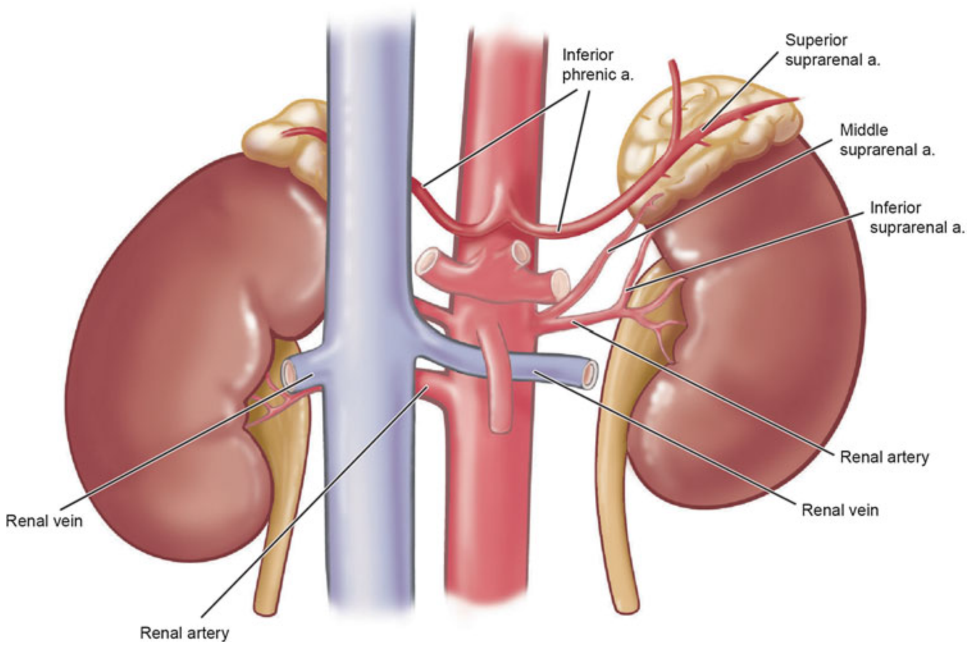

Fig. 1.10 Arterial supply to the kidney (reprinted with permission, Cleveland Clinic Center for Medical Art & Photography © 2015. All Rights Reserved)

and right lateral lumbar (caval or aortic) nodes (Fig. 1.12). These nodes are located near the source of the renal arteries bilaterally [2].

Innervation

The kidneys receive nervous system input from the sympathetic nervous system originating from T12 to L1 levels of the spinal cord. These fibers form a renal plexus along the surface of the renal arteries and receive contributions from the celiac plexus, least splanchnic, and first lumbar splanchnic nerves (Fig. 1.13). Upon reaching the kidney, these fibers are responsible for regulating renal blood flow, salt and water reabsorption by the nephron, and glomerular filtration rate. In contrast to sympathetic nerve function, parasympathetic innervation does not appear to play a significant role in regulating kidney function [3].

Histology of the Kidney

Renal Capsule

Externally, the kidney is surrounded by the renal capsule, a fibrous connective tissue structure weakly attached to the kidney surface. The capsule includes two discrete layers: an inner layer of myofibroblasts and an outer layer of collagen fibers and fibroblasts [4]. At the hilum, the capsule penetrates the area of the sinus to contribute to the connective tissue covering of the calyces and renal pelvis.

Parenchyma

Overview

When viewing the hemisected kidney, two regions are clearly visible: the centrally located medulla with inner and outer segments and the

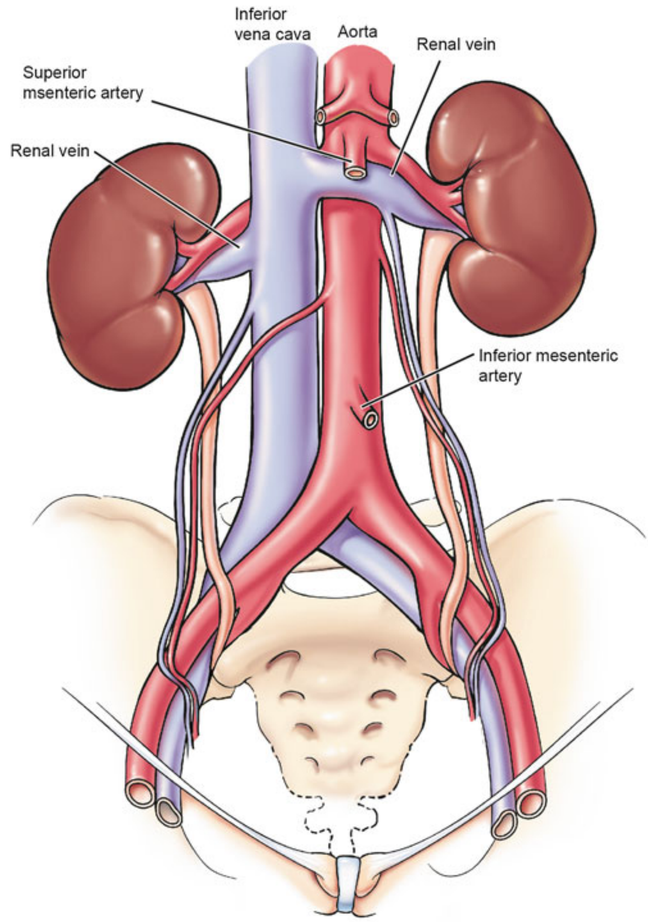

Fig. 1.11 Venous drainage from the kidney (reprinted with permission, Cleveland Clinic Center for Medical Art & Photography © 2015. All Rights Reserved)

overlying cortex which is subdivided into an outer cortex and a juxtamedullary cortex sitting adjacent to the medullary pyramids (Fig. 1.14). Within each kidney, 8–12 conical-shaped medullary pyramids exist with their bases directed towards the overlying cortex. Between each pyramid, a segment of cortex interjects to form a renal column (of Bertin). The association of the medullary pyramids and their surrounding cortical tissue constitute a renal lobe, with the total number of lobes in the kidney determined by the number of pyramids present. Another level of organization of kidney parenchyma is the lobule which consists of a central medullary ray and the cortical tissue surrounding it. Interstitial tissue throughout the parenchyma is extremely scarce, consisting mostly of reticular tissue and some collagenous fibers which surround blood vessels, large papillary ducts, and glomerular capsules.

Cortex

In the fresh state, the cortex appears brownish red, a coloring indicative of the extensive blood flow passing through the complex network of vasculature. Every minute, the kidneys receive approximately 20 % of the cardiac output, with 90 % directed towards the cortex and 10 % to the medulla. Populating the cortex are renal corpuscles and various segments of the tubule system including convoluted and straight tubules of the nephron, collecting tubules, and collecting ducts (Fig. 1.15). The renal corpuscle represents the initial, dilated portion of the nephron. Closer examination of this sphere-shaped structure

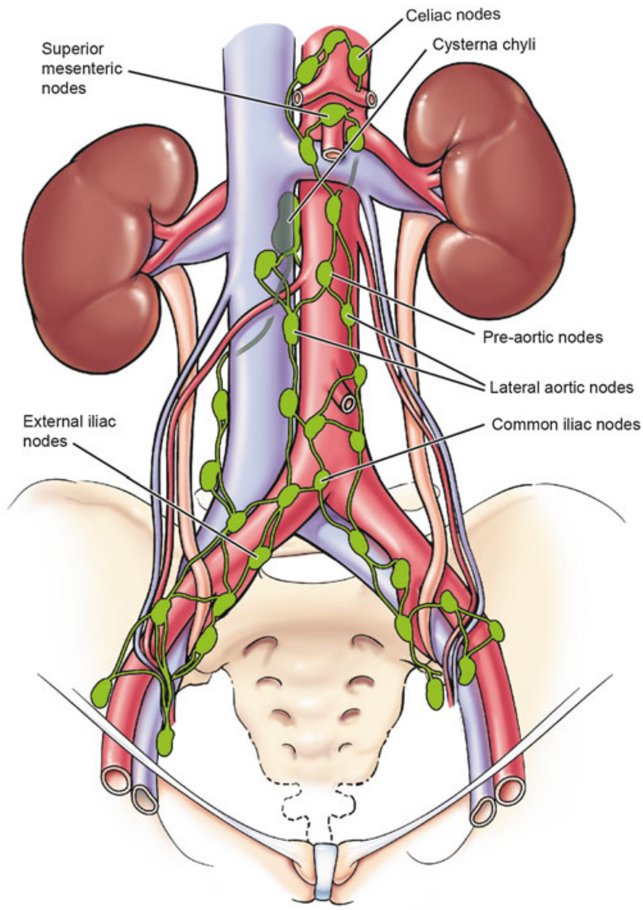

Fig. 1.12 Lymphatic drainage from the kidneys to the lateral lumbar (caval or aortic) nodes (reprinted with permission, Cleveland Clinic Center for Medical Art & Photography © 2015. All Rights Reserved)

reveals an accompanying capillary system known as the glomerulus. Situated between areas of renal corpuscles and their closely approximated convoluted and collecting tubules are areas of medullary rays which consist of straight tubules of the nephrons and collecting ducts.

Medulla

The medulla consists of 8–12 conical-shaped medullary pyramids and intervening areas of cortical tissue referred to as renal columns (Fig. 1.14). These structures contain the same cortical structures as described previously but are regarded as part of the medulla. Organizationally, the medullary pyramid and its surrounding cortical tissue constitute a lobe of the kidney, with 8–12 lobes present in a human kidney. Each lobe is further subdivided into lobules which consist of a central medullary ray and surrounding cortical tissue. Within the medullary pyramids are straight tubules and collecting ducts which are accompanied by the vasa recta, a capillary network oriented in parallel to the tubules and ducts. The medullary pyramids are divided into an outer and inner medulla with the inner segment oriented towards the apical end or papilla. Each of these divisions contains specific segments of the nephron. The inner medulla contains the descending thin limbs, ascending thin limbs, and inner medullary collecting ducts. The outer medulla is further subdivided into an outer stripe with proximal straight tubules, distal straight tubules, and outer medullary collecting ducts and an inner stripe with descending thin limbs, distal straight tubules, and outer medullary collecting ducts. The collecting ducts open into a perforated region

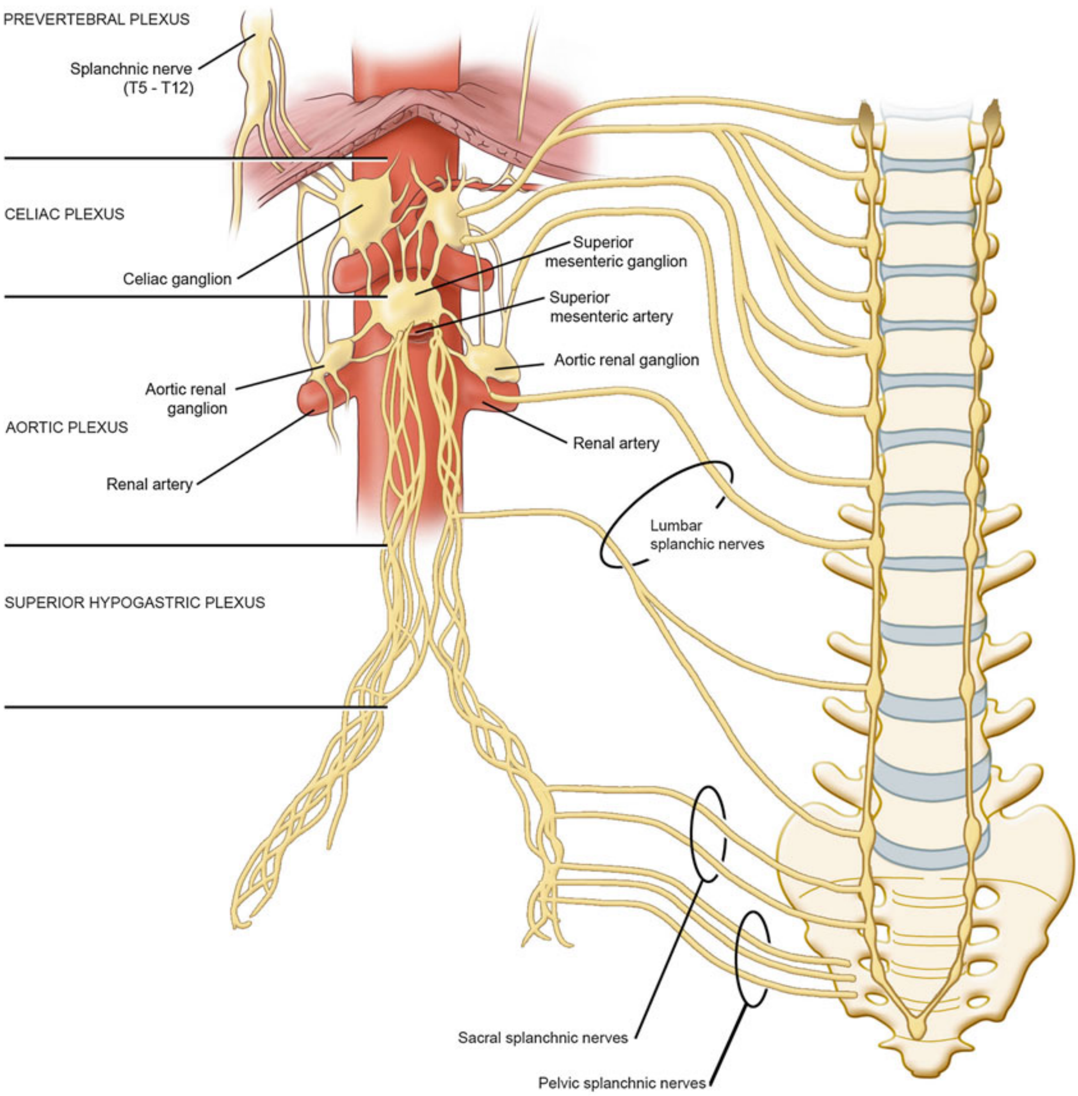

Fig. 1.13 Sympathetic innervation to the kidneys (reprinted with permission, Cleveland Clinic Center for Medical Art & Photography © 2015. All Rights Reserved)

of the papilla known as the area cribrosa. Each papilla projects into a cup-like minor calyx which is an extension of the renal pelvis.

Renal Corpuscle

The renal corpuscles consist of a tuft of glomerular capillaries surrounded by the visceral and parietal layers of Bowman's capsule (Fig. 1.16a, b). Each corpuscle has a vascular pole with an afferent and efferent arteriole, as well as a urinary pole in which the proximal tubule arises. Lining the lumen of the capillaries is a layer of fenestrated simple squamous endothelium, with fenestrations spanning 60–100 nm. Immediately adjacent to the basement membrane of the capillary wall is the visceral layer of Bowman's capsule. It is comprised of podocytes or visceral epithelial cells which give off primary processes and then secondary processes called pedicels or foot processes (Fig. 1.17). As the foot processes

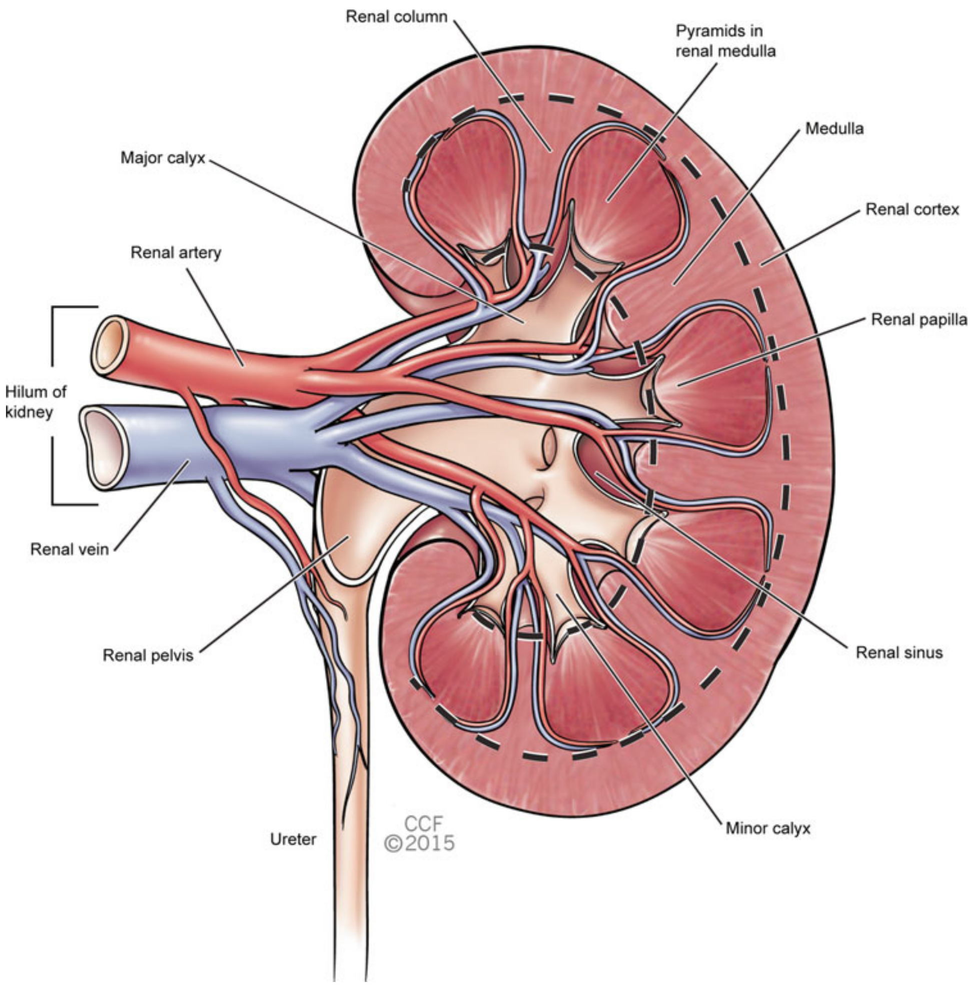

Fig. 1.14 Depiction of kidney structure in the hemisected kidney (reprinted with permission, Cleveland Clinic Center for Medical Art & Photography © 2015. All Rights Reserved)

interdigitate with one another around the capillary, filtration slits with a diameter of 20–25 nm are formed. Each slit is covered by a filtration slit diaphragm to limit the passage of smaller molecules. Together, the capillary endothelium, glomerular basement membrane, and the visceral layer of Bowman's capsule form the filtration apparatus of the kidney. Surrounding these structures is the external or parietal layer of Bowman's capsule. This layer consists of simple squamous epithelium supported by an indistinct basement membrane.

Between the loops of the glomerular capillaries and around the vascular pole are mesangial cells which play a significant role in maintaining the structure and support of the glomerular filtration barrier. While the primary role of mesangial cells is phagocytosis and structural support, they also proliferate in response to glomerular injury. In addition, these cells retain contractile properties which allow them to regulate glomerular distension in response to increases in blood pressure.

Nephron

Functionally, the nephron is responsible for the production of urine. In humans, there are approximately two million nephrons present in each kid-

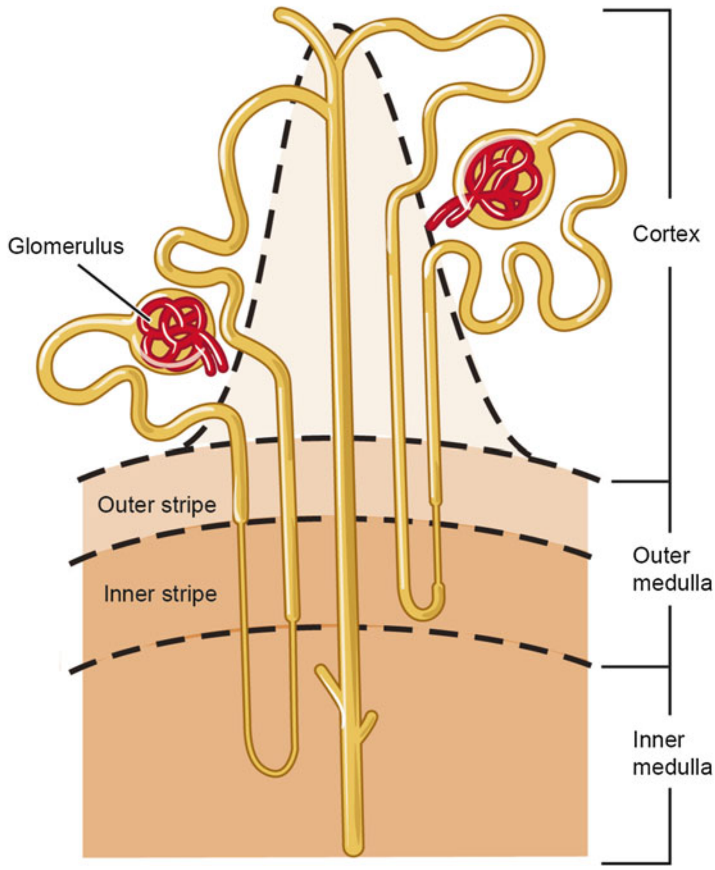

Fig. 1.15 Diagram of adult kidney indicating the relationship of nephrons to their collecting tubules and ducts within the cortex and medulla (reprinted with permission, Cleveland Clinic Center for Medical Art & Photography © 2015. All Rights Reserved)

ney. The initial segment is comprised of the renal corpuscle with its glomerulus and surrounding renal or Bowman's capsule (Fig. 1.15). Blood entering the glomerular capillary loops passes first through an afferent arteriole and then drains from the efferent arteriole, both of which are located at the vascular pole of Bowman's capsule. On the opposite side of the renal corpuscle is the urinary pole, where the proximal convoluted tubule originates. The remaining tubular segments of the nephron include the proximal thick segment, thin segment, and distal thick segment.

Nephron Tubules

As mentioned previously, the proximal convoluted tubule represents the initial tubule segment stemming from the urinary pole of the renal corpuscle. This segment takes a tortuous course through the cortex before entering the medullary ray as the proximal straight tubule or thick descending limb of the loop of Henle to enter the medulla (Fig. 1.15). Continuing as the thin descending limb, within the medulla it makes a turn to head back towards the cortex as the thin ascending limb. Entering the medullary ray of the cortex, it transitions into the distal straight tubule or thick ascending limb of the loop of Henle. After leaving the medullary ray, the distal straight tubule makes contact with the vascular pole of its renal corpuscle. The epithelial cells of the tubule near the afferent arteriole of the glomerulus are modified to form the macula densa. After leaving the corpuscle, the tubule becomes the distal convoluted tubule which empties into a collecting duct within the medullary ray by way of an arched collecting tubule or connecting tubule (Fig. 1.15).

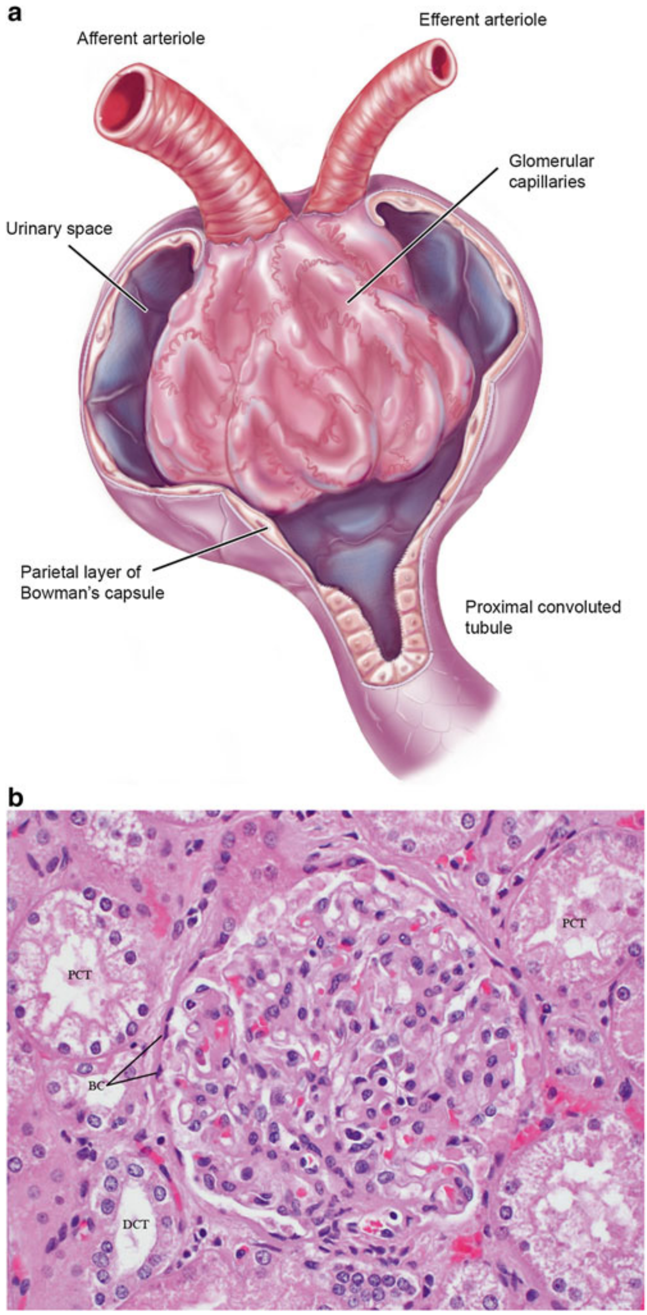

Fig. 1.16 The renal corpuscle. (**a**) Schematic representation. (**b**) Light micrograph. Note the parietal layer of Bowman's capsule (BC), surrounding proximal convoluted tubules (PCT) and distal convoluted tubules (DCT) (reprinted with permission, Cleveland Clinic Center for Medical Art & Photography © 2015. All Rights Reserved)

Proximal Convoluted Tubule

The lumen of the proximal convoluted tubule is lined by cuboidal cells with a prominent brush border consisting of apically located microvilli (Fig. 1.16b). Another distinguishing feature is the basal striations, which contain a high concentration of vertically oriented mitochondria. Functionally, the increased surface area offered by the brush border makes this segment of the nephron the primary site of reabsorption, with approximately 65% of the total ultrafiltrate per day being reabsorbed here. With the aid of transmembrane proteins, Na^+/K^+-ATPase pumps, and AQP-1, the majority of salts and water

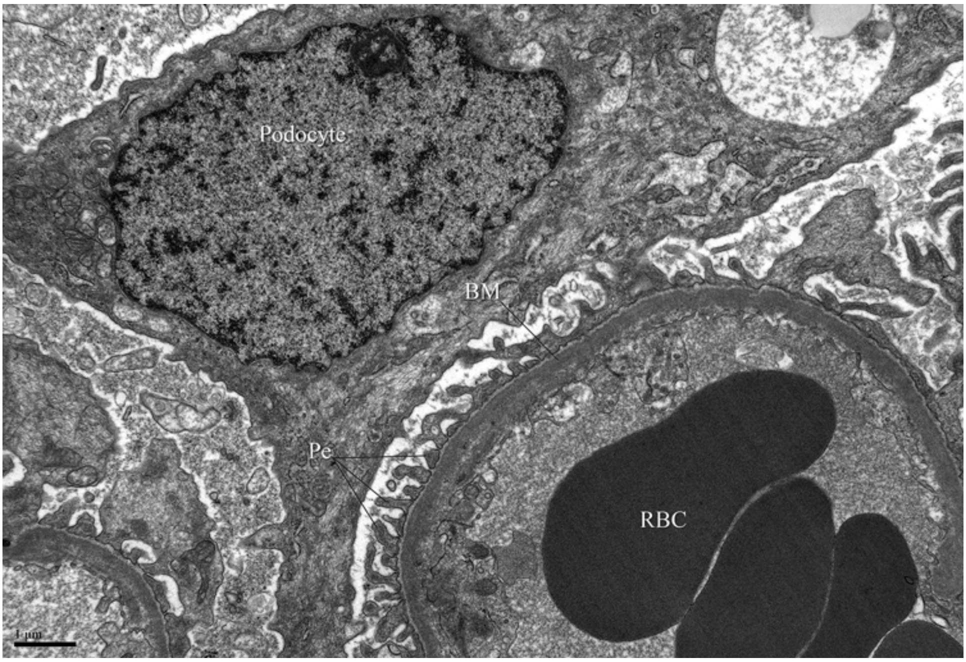

Fig. 1.17 Transmission electron micrograph of a glomerular capillary and neighboring podocyte. Pedicels (Pe) of the podocyte rest on the basement membrane adjacent to the endothelium of the fenestrated glomerular capillary (courtesy of Jesus Macias, University of California at San Diego)

are absorbed within the proximal convoluted tubule. In addition, the proximal convoluted tubule also reabsorbs glucose, amino acids, and polypeptides.

Loop of Henle

With a less prominent role in reabsorption, the cuboidal-shaped cells of the proximal straight tubule have a much shorter brush border and smaller, less intricate basal domain and randomly oriented mitochondria. The thin segment is lined with simple squamous epithelium with cells further subdivided at the electron microscopy level into types I–IV based on contact with neighboring cells, abundance of intracellular organelles, as well as the presence and morphology of microvilli. At the level of the descending thin limb, water passively diffuses out to the interstitial space, while a small amount of NaCl and urea enters into the nephron lumen. In contrast, NaCl passively diffuses out to the interstitial space at the level of the thin ascending limb. The thin ascending limb is also impermeable to water.

Transitioning into the distal straight tubule, the cells lining the lumen exhibit a cuboidal shape, fewer microvilli, extensive basolateral plications, and numerous basal located mitochondria. At this level, NaCl is actively pumped out of the nephron lumen and into the medullary interstitium. Near the vascular pole, the cells of the straight tubule take on a columnar shape and are more numerous. As the cells appear crowded and somewhat overlapping, this area is referred to as the macula densa, a component of the juxtaglomerular apparatus. The distal convoluted tubule is the continuation of the distal straight tubule within the cortical labyrinth. It is similar in structure and appearance. Exchange of Na^+ and K^+ at this level is mediated through aldosterone secreted by the adrenal glands. Under this influence, Na^+ is reabsorbed and K^+ is secreted.

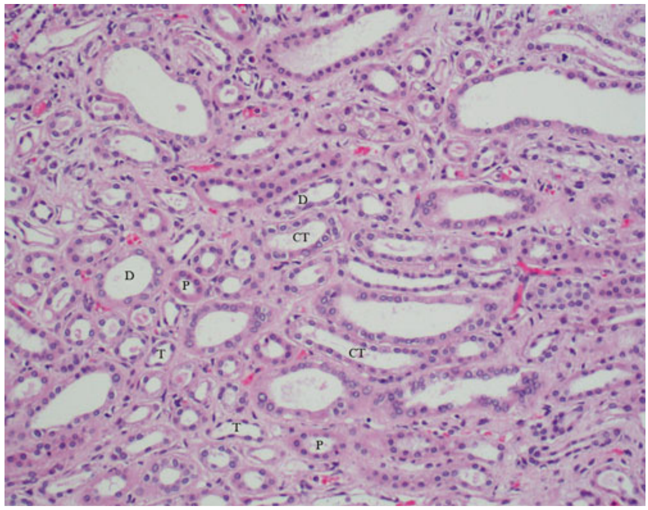

Fig. 1.18 Light micrograph from the outer potion of the medulla region. Note the presence of proximal straight tubules (P), distal straight tubules (D), collecting tubules (CT), and thin segments (T)

Collecting Tubules and Ducts

Connecting to the distal convoluted tubules are collecting tubules (Fig. 1.18) which then transition into collecting ducts. Both of these structures are comprised of simple epithelium. In general, the cells of the collecting ducts transition from squamous to cuboidal in nature as they pass from outer to inner medulla and become columnar near the renal papilla. The two principal cell types in the collecting tubules and collecting ducts are light cells or collecting duct cells and dark cells or intercalated cells. The collecting duct cells are greater in number and are identified by their pale-staining cytoplasm and sparse microvilli. These cells possess several aquaporin channels and thus play a role in water permeability in the collecting ducts. In contrast, the intercalated cells are less abundant and exhibit a dark staining cytoplasm. These cells secrete H^+ or bicarbonate and thus play an important role in acid–base balance.

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