Urinary system

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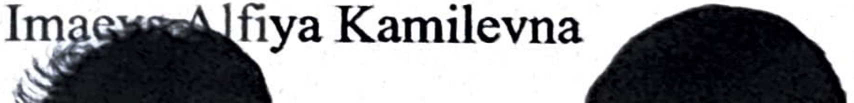
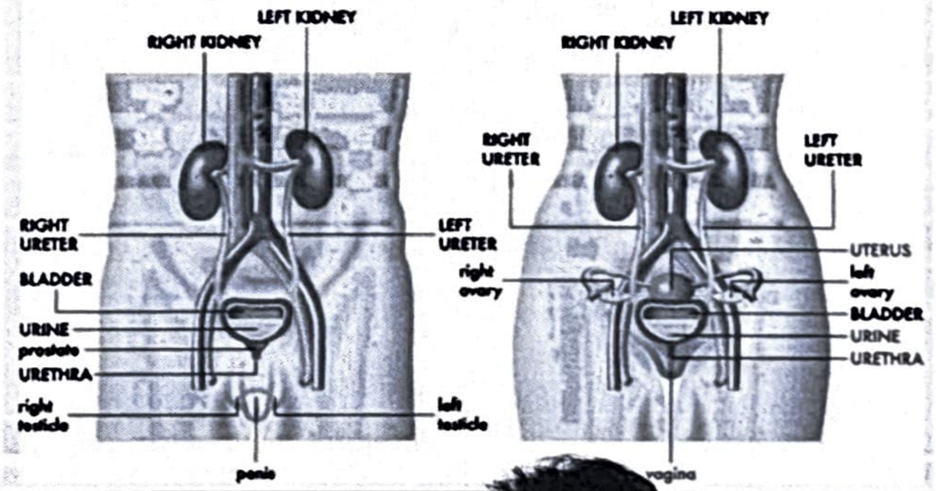


URINARY SYSTEM

The urinary system consists of the paired kidneys and ureters, the bladder, and the urethra. This system's primary role is to ensure optimal properties of the blood, which the kidneys continuously monitor. This general role of the kidneys involves a complex combination of renal functions:

- Regulation of the balance between water and electrolytes (inorganic ions) and the acid-base balance;
- Excretion of metabolic wastes along with excess water and electrolytes in urine, the kidneys' excretory product which passes through the ureters for temporary storage in the bladder before its release to the exterior by the urethra;
- Excretion of many bioactive substances, including many drugs;
- Secretion of renin, a protease important for regulation of blood pressure by cleaving circulating angiotensinogen to angiotensin I;
- Secretion of erythropoietin, a glycoprotein growth factorthat stimulates erythrocyte production in red marrow when the blood O2 level is low;
- Conversion of the steroid prohormone vitamin D, initially produced in the skin, to the active form (1,25-dihydroxyvitamin D3 or calcitriol);
- Gluconeogenesis during starvation or periods of pro- longed fasting, making glucose from amino acids to supplement this process in the liver.



KIDNEY EMBRYOGENESIS

During approximately weeks 4 and 5, three sets of excretory structures emerge; two regress, and the third eventually matures to the adult form.

- These systems develop and regress from cranial to caudal, and overlap chronologically.

Pronephros

•Emerges early in week 4 in intermediate mesoderm, which is located along the posterior abdominal cavity.

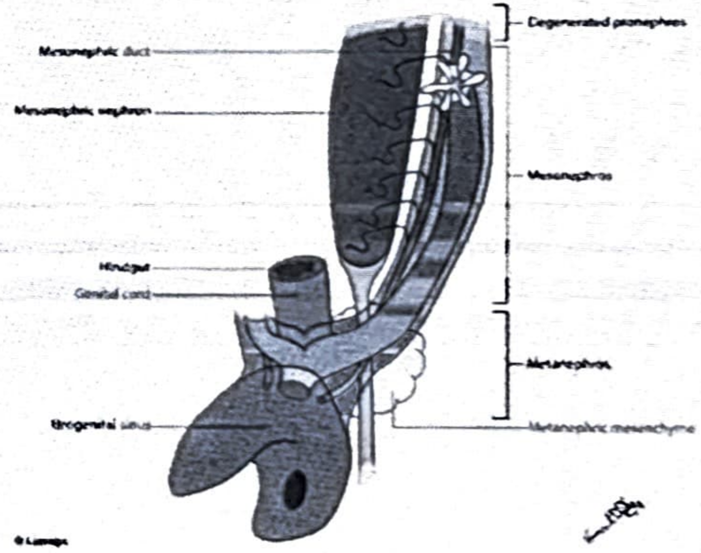
•— Both the urinary and genital systems arise from a common ridge in the intermediate mesoderm. Primary nephritic ducts (aka, pronephritic ducts) arise in the cervical segments as rods of condensed mesoderm, which then undergo epithelialization.

•Five to seven nephritic vesicles (aka, nephrotomes) form simultaneously in the mesoderm; these small, hollow balls of epithelia are nonfunctional, and completely regress within a week of emerging.

•The pronephros is a vestigial structure in humans, but is responsible for excretion in early vertebrates (i.e., lampreys).

— As the pronephros regresses during week 4, the mesonephros emerges in the thoracic region.

Renal Embrology



Mesonephros

•Primary nephritic ducts continue their growth caudally (as their cranial ends degenerate).

•— Their elongation is driven by mesenchymal-epithelial cell conversions taking place at their caudal tips; they extend from the thoracic region to the middle lumbar region. Mesonephric buds and tubules develop in the mesoderm, also in cranial to caudal direction (the cranial-most mesonephric buds regress as caudal buds emerge).

•The tubules form connections to the ducts, which are now called the mesonephric (aka, Wolffian) ducts.

•— Overall, more than 40 mesonephric buds will form, but, because older buds regress as new buds form, there are never this many present at once.Eventually, the mesonephric ducts elongate and fuse with the urogenital sinus (be aware that some texts state that the connection occurs earlier, with the cloaca).

•The mesonehpros degenerates in the female (for the most part; remnants can be found as the epoophoron, paraoophoron, and Garner cyst); in the male, it persists to contribute to the reproductive duct system.

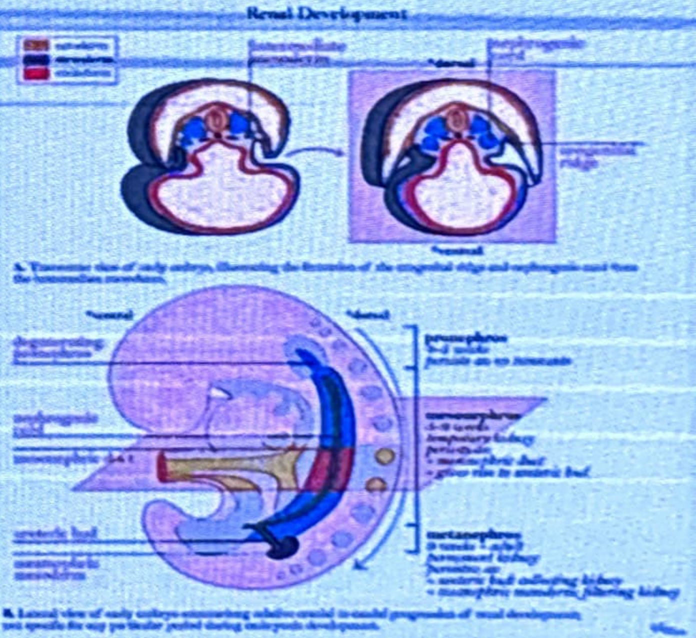
Metanephros

•Definitive kidney Ureteric bud arises as an outgrowth of the mesonephric duct, near its connection with the urogenital sinus.

•— This process is driven by the interaction between glial cell line-derived neurotrophic factor (GDNF), and receptor-tyrosine-protein kinase (Ret), which is released by the undifferentiated mesonephric mesenchyme. The bud grows towards, and, eventually into, the metanephric mesoderm (aka, blastema).

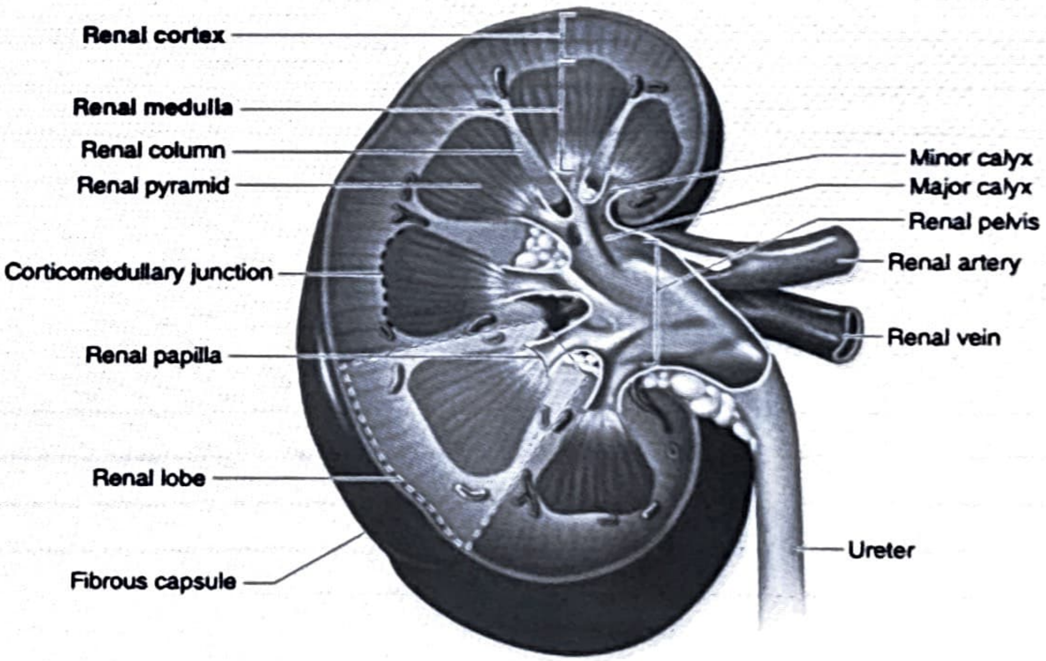
•Upon contact, cellular interactions between the ureteric bud and the metanephric mesoderm drive repeated rounds of bifurcation the ureteric bud and the generation of excretory units (**<u>the nephrons</u>**) in the mesoderm (these processes are discussed in detail, elsewhere).

•Metanephros development, specifically nephrogenesis, continues post-natally.



KIDNEYS

Approximately 12-cm long, 6-cm wide, and 2.5-cm thick in adults, each kidney has a concave medial border, the hilum—where nerves enter, the ureter exits, and blood and lymph vessels enter and exit—and a convex lateral surface, both covered by a thin fibrous capsule. Within the hilum tthe upper end of the ureter expands as the renal pelvis and divides into two or three major calyces. Smaller branches, the minor calyces, arise from each major calyx. The area surrounding the renal pelvis and calyces contains adipose tissue. The parenchyma of each kidney has an outer renal cortex, a darker stained region with many round corpuscles and tubule cross sections, and an inner renal medulla consisting mostly of aligned linear tubules and ducts. The renal medulla in humans consists of 8-15 conical structures called renal pyramids. Each pyramid plus the cortical tissue at its base and extending along its sides constitutes a renal lobe. The tip of each pyramid, called the renal papilla, projects into a minor calyx that collects urine formed by tubules in one renal lobe.

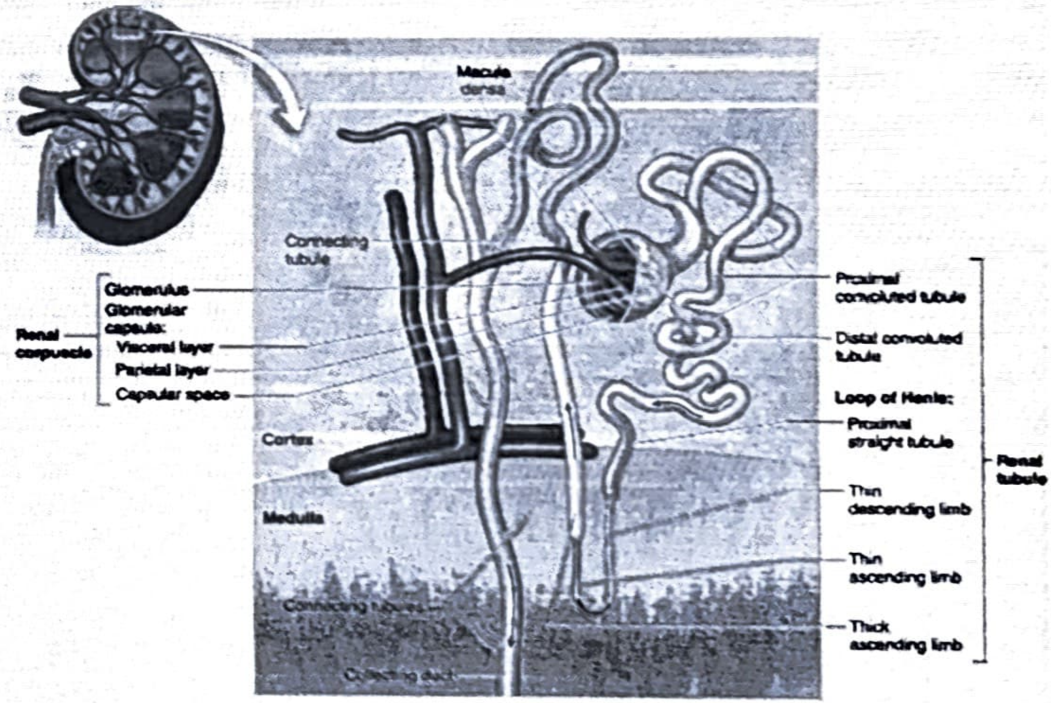


NEPHRON

Kidneys each contain 1-4 million functional units called nephrons, each consisting of a corpuscle and a long, simple epithelial renal tubule with three main parts along its length. The major divisions of each nephron are:

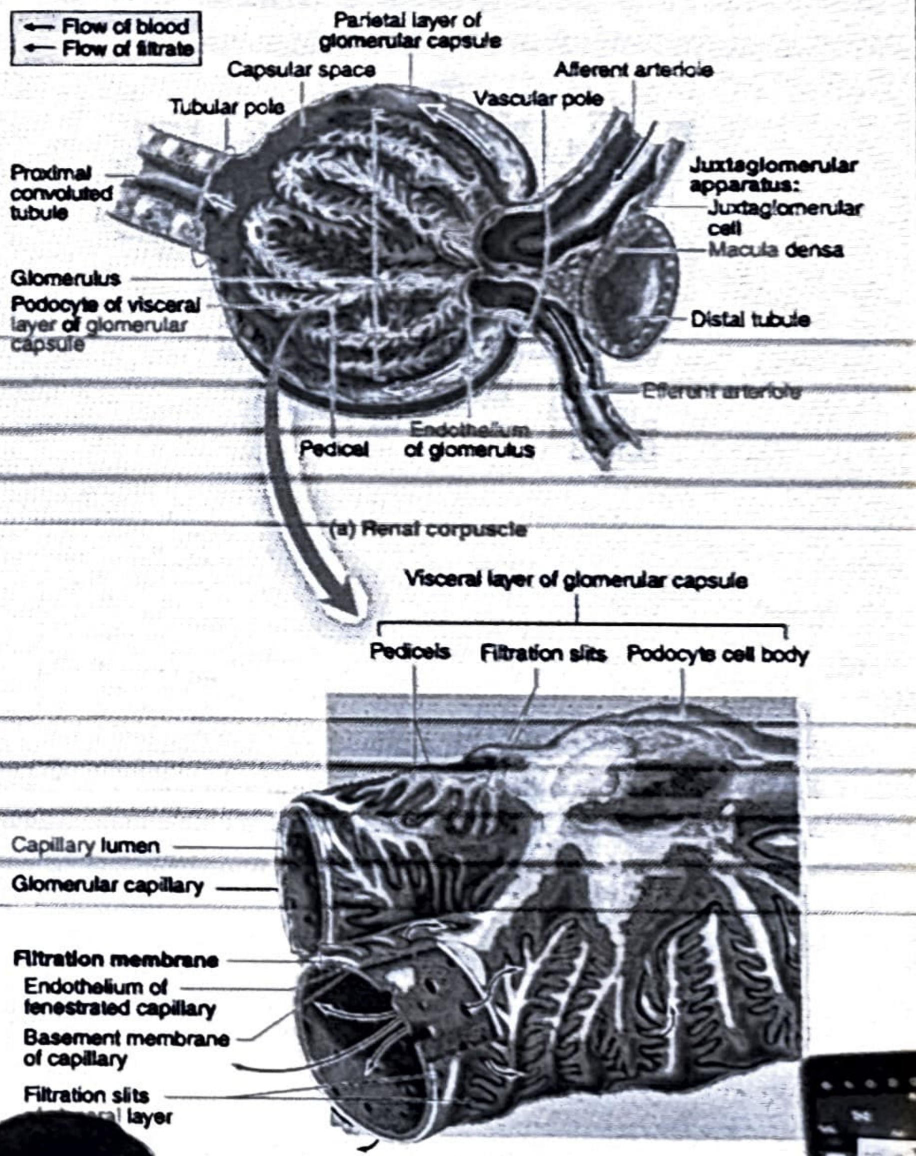
- Renal corpuscle, an initial dilated part enclosing a tuft of capillary loops and the site of blood filtration, always located in the cortex;
- Proximal tubule, a long convoluted part, located entirely in the cortex, with a shorter straight part that enters the medulla;
- Loop of Henle (or nephron loop), in the medulla, with thin descending and a thin ascending limb;
- Distal tubule, consisting of a thick straight part ascending from the loop of Henle back into the cortex and a convoluted part completely in the cortex;
- Connecting tubule, a short minor part linking the nephron to collecting ducts.

Connecting tubules from several nephrons merge to form collecting tubules that then merge as larger collecting ducts. These converge in the renal papilla, where they deliver urine to a minor calyx. Cortical nephrons are located almost completely in the cortex while juxtamedullary nephrons (about one-seventh of the total) lie close to the medulla and have long loops of Henle.



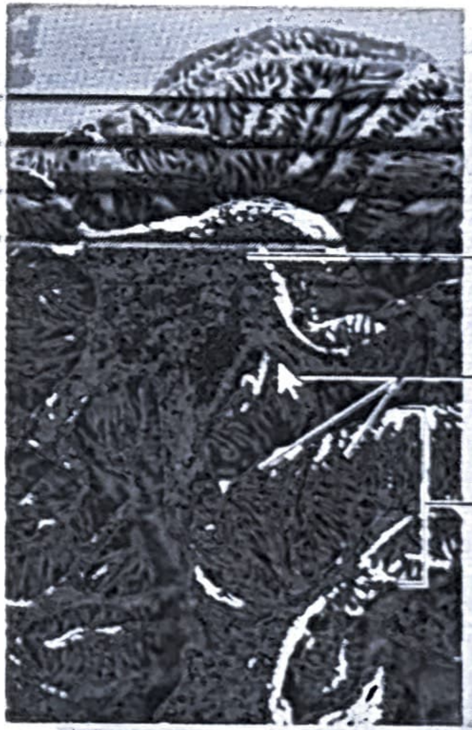
RENAL CORPUSCLES

At the beginning of each nephron is a renal corpuscle, about 200 µm in diameter and containing a tuft of glomerular capillaries, surrounded by a double-walled epithelial capsule called the glomerular (Bowman) capsule. The internal or visceral layer of this capsule closely envelops the glomerular capillaries, which are finely fenestrated. The outer parietal layer forms the surface of the capsule. Between the two capsular layers is the capsular (or urinary) space, which receives the fluid filtered through the capillary wall and visceral layer. Each renal corpuscle has a vascular pole, where the afferent arteriole enters and the efferent arteriole leaves, and a tubular pole, where the proximal convoluted tubule (PCT) begins. The outer parietal layer of a glomerular capsule consist of a simple squamous epithelium supported externally by a basal lamina. At the tubular pole, this epithelium changes to the simple cuboidal epithelium that continues and forms the proximal tubule.



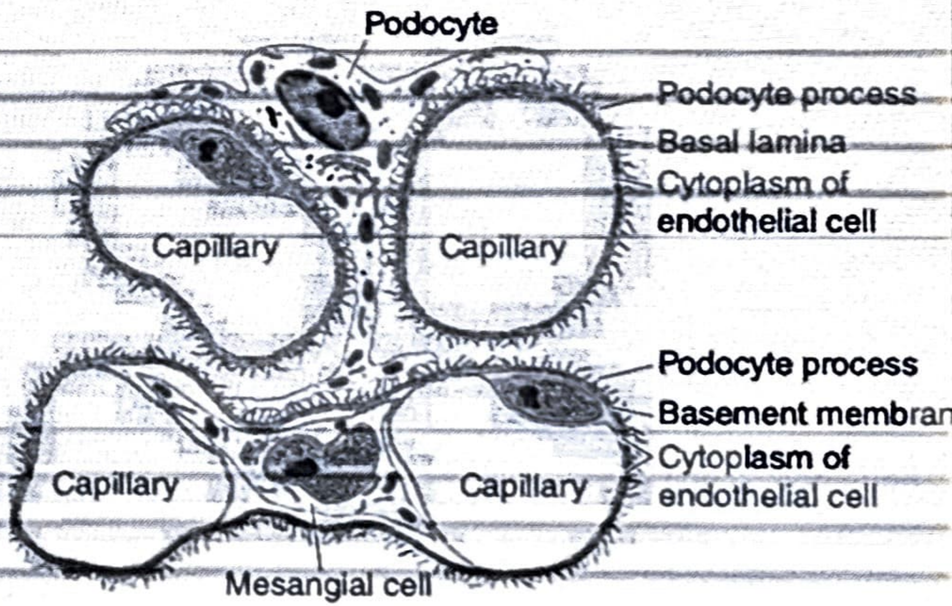
(c) Filtration membrane

The visceral layer of a renal corpuscle consists of unusual stellate epithelial cells called podocytes which together with the capillary endothelial cells compose the apparatus for renal filtration. From the cell body of each podocyte several primary processes extend and curve around a length of glomerular capillary. Each primary process gives rise to many parallel, interdigitating secondary processes or pedicels (L. pedicellus, little foot). The pedicels cover much of the capillary surface, in direct contact with the basal lamina. Between the interdigitating pedicels are elongated spaces or filtration slit pores, 25- to 30-nm wide. Slit diaphragms are modified and specialized occluding or tight junctions composed of nephrins, other proteins, glycoproteins, and proteoglycans important for renal function. Projecting from the cell membrane on each side of the filtration slit, these polyanionic glycoproteins and proteoglycans interact to form a series of openings within the slit diaphragm, with a surface that is negatively charged.

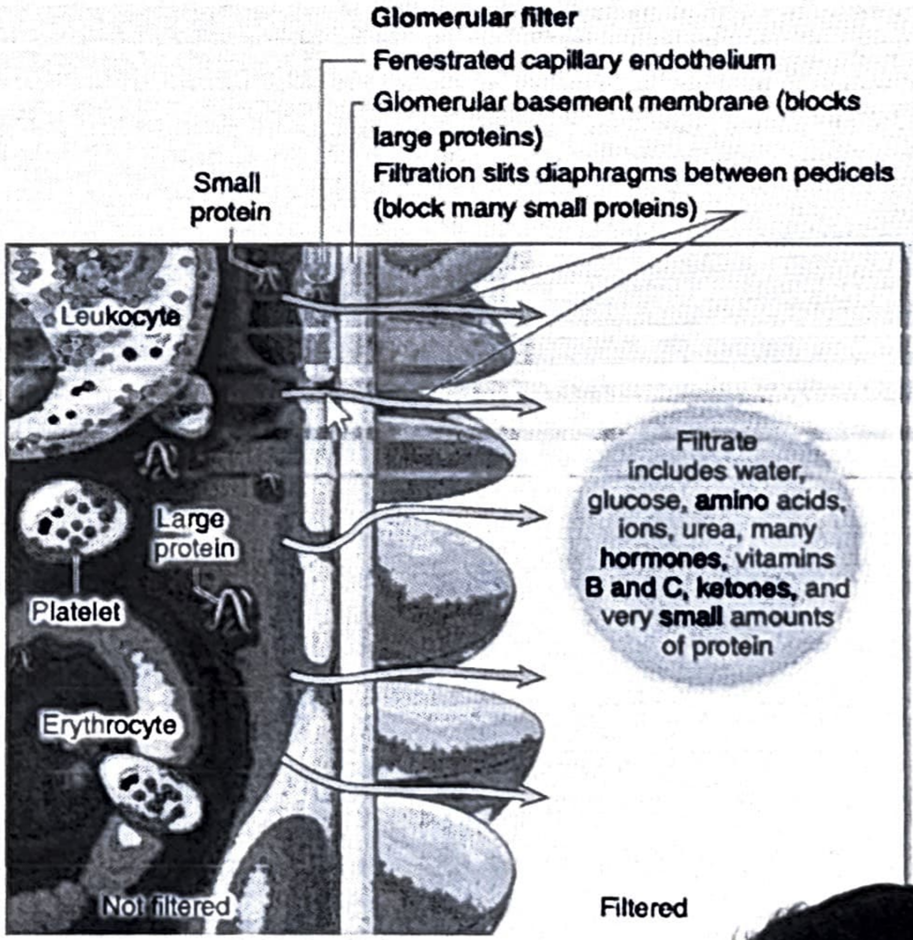


Renal corpuscles also contain mesangial cells (Gr. mesos, in the midst + angion, vessel), most of which resemble vascular pericytes in having contractile properties and producing components of an external lamina. Mesangial cells are difficult to distinguish in routine sections from podocytes, but often stain more darkly. They and their surrounding matrix comprise the mesangium, which fills interstices between capillaries that lack podocytes. Functions of the mesangium include the following:

- Physical support of capillaries within the glomerulus
- Adjusted contractions in response to blood pressure changes, which help maintain an optimal filtration rate
- Phagocytosis of protein aggregates adhering to the glomerular filter, including antibody-antigen complexes
abundant in many pathological conditions
- Secretion of several cytokines, prostaglandins, and other factors important for immune defense and repair in the glomerulus

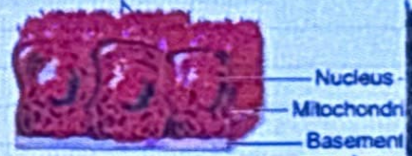


The glomerular filtration barrier consists of three layered components: the fenestrated capillary endothelium, the glomerular basement membrane (GBM), and filtration slit diaphragms between pedicels. The major component of the filter is formed by fusion of the basal laminae of a podocyte and a capillary endothelial cell.



PROXIMAL CONVOLUTED TUBULE

Cells in many parts of the nephron tubule and collecting system reabsorb water and electrolytes, but other activities are restricted mainly to specific tubular regions. At the tubular pole of the renal corpuscle, the simple squamous epithelium of the capsule's parietal layer is continuous with the simple cuboidal epithelium of the proximal convoluted tubule (PCT). These long, tortuous tubules fill most of the cortex. PCT cells are specialized for both reabsorption and secretion. Over half of the water and electrolytes, and all of the organic nutrients glucose, amino acids, vitamins, etc), filtered from plasma in the renal corpuscle are normally reabsorbed in the PCT. These molecules are transferred directly across the tubular wall for immediate uptake again into the plasma of the peritubular capillaries. Transcellular reabsorption involves both active and passive mechanisms, with the cells having a large variety of transmembrane ion pumps, ion channels, transporters, enzymes, and carrier proteins. Water and certain solutes can also move passively between the cells (paracellular transport) along osmotic gradients through leaky apical tight junctions.

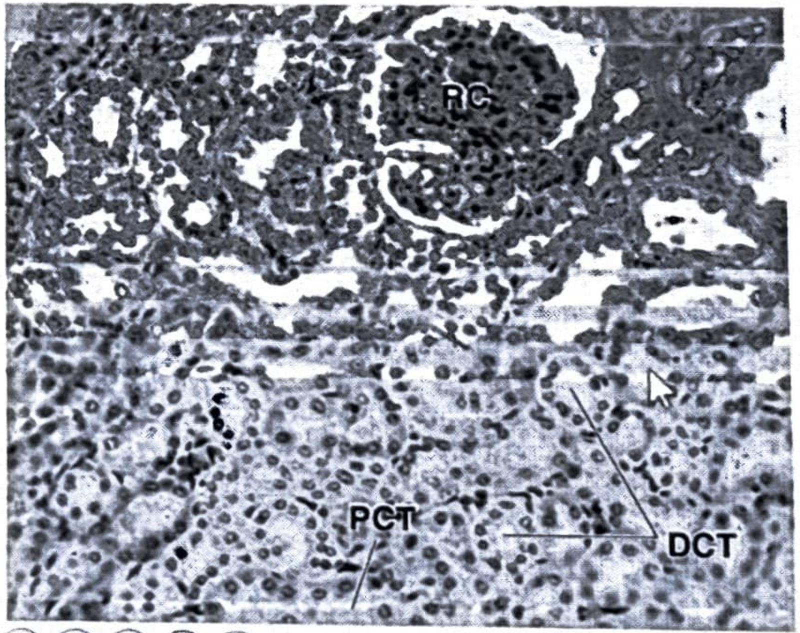


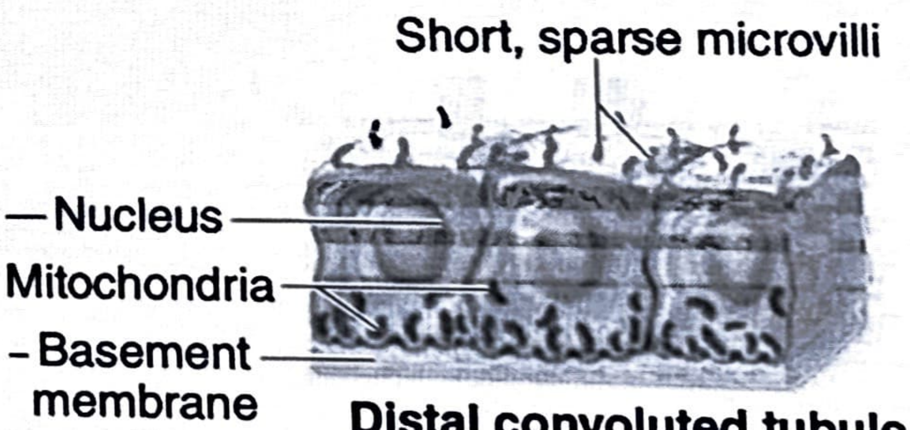
(c) Convoluted tubule epithelia

TEM reveals important features of the cuboidal cells of the proximal convoluted epithelium: the long, dense apical microvilli (MV), the abundant endocytotic pits and vesicles (V) in the apical regions near lysosomes (L). Small proteins brought into the cells nonspecifically by pinocytosis are degraded in lysosomes and the amino acids released basally. Apical ends of adjacent cells are sealed with zonula occludens, but the basolateral sides are characterized by long invaginating folds of membrane along which many long mitochondria (M) are situated. Water and the small molecules released from the PCTs are taken up immediately by the adjacent perit capillaries (C). Between the basement membranes of the tubule and the shown here is an extension of a fibroblast (F). (X10,500)

DISTAL CONVOLUTED TUBULE

The ascending limb of the nephron is straight as it enters the cortex and forms the macula densa, and then becomes tortuous as the distal convoluted tubule (DCT. Much less tubular reabsorption occurs here than in the proximal tubule. The simple cuboidal cells of the distal tubules differ from those of the proximal tubules in being smaller and having no brush border and more empty lumens. Because distal tubule cells are flatter and smaller than those of the proximal tubule, more nuclei are typically seen in sections of distal tubules than in those of proximal tubules. Cells of the DCT also have fewer mitochondria than cells of proximal tubules, making them less acidophilic. The rate of Na+ absorption here is regulated by aldosterone from the adrenal glands.





Distal convoluted tubule

HISTOLOGIC FEATURES AND MAJOR FUNCTIONS OF REGIONS WITHIN RENAL TUBULES.

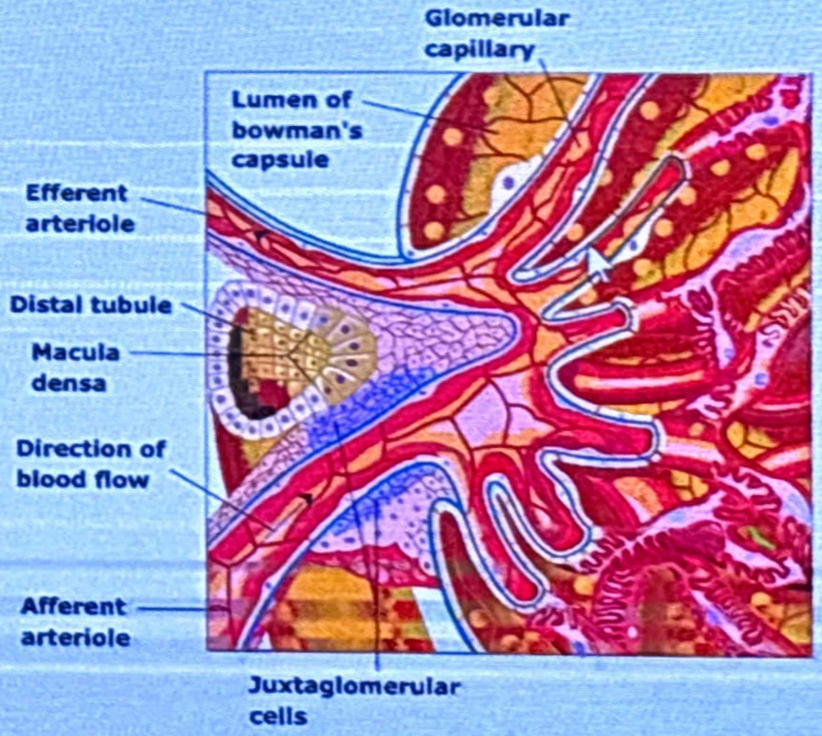
Region of Tubule	Histological Features	Locations	Major Functions
PCT	Simple cuboidal epithelium; cells well-stained, with numerous mitochondria, prominent basal folds and lateral interdigitations; long microvilli, lumens often occluded	Cortex	Reabsorption of all organic nutrients, all proteins, most water and electrolytes; secretion of organic anions and cations, H^+, and NH_4^+
Loop of Henle			
Thin limbs	Simple squamous epithelium; few mitochondria	Medulla	Passive reabsorption of Na^+ and Cl^-
TAL	Simple cuboidal epithelium; no microvilli, but many mitochondria	Medulla and medullary rays	Active reabsorption of various electrolytes
DCT	Simple cuboidal epithelium; cells smaller than in PCT, short microvilli and basolateral folds, more empty lumens	Cortex	Reabsorption of electrolytes
Collecting system			
Principal cells	Most abundant, cuboidal to columnar; pale-staining, distinct cell membranes	Medullary rays and medulla	Regulated reabsorption of water & electrolytes; regulated secretion of K^+
Intercalated cells	Few and scattered; slightly darker staining	Medullary rays	Reabsorption of K^+ (low-K^+ diet); help maintain acid-base balance

DCT, distal convoluted tubule; PCT, proximal convoluted tubule; TAL, thick ascending limb.

JUXTAGLOMERULAR APPARATUS

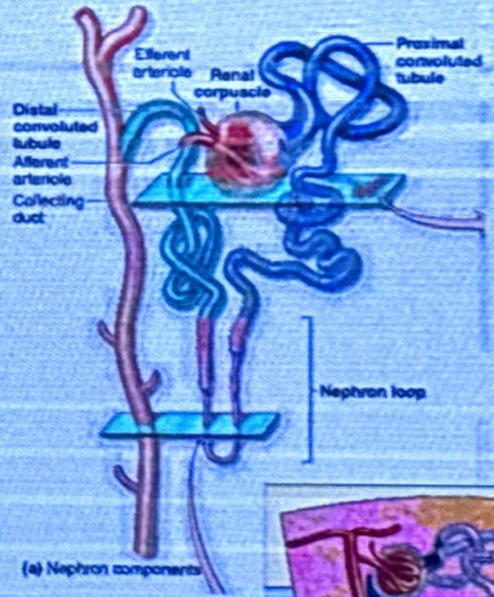
Where the initial, straight part of the distal tubule contacts the arterioles at the vascular pole of the renal corpuscle of its parent nephron, its cells become more columnar and closely packed, forming the macula densa (L. thickerbspot). This is part of a specialized sensory structure, the juxtaglomerular apparatus (JGA) that utilizes feedback mechanisms to regulate glomerular blood flow and keep the rate of glomerular filtration relatively constant.

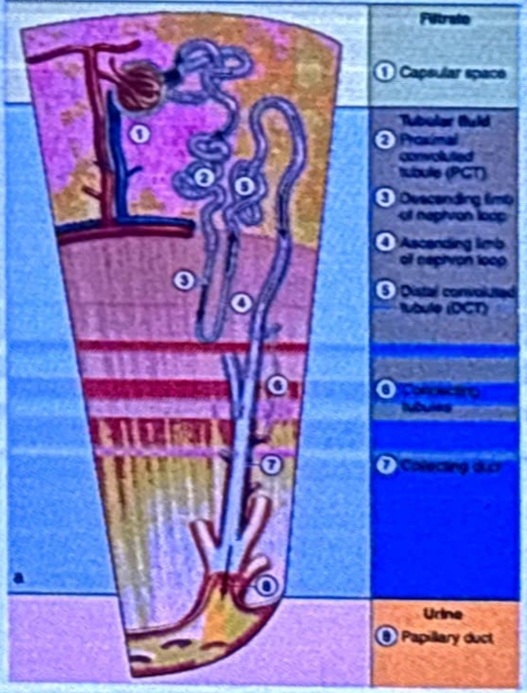
Cells of the macula densa typically have apical nuclei, basal Golgi complexes, and a more elaborate and varied system of ion channels and transporters. Adjacent to the macula densa, the tunica media of the afferent arteriole is also modified. The smooth muscle cells are modified as juxtaglomerular granular (JG) cells, with a secretory phenotype including more rounded nuclei, rough ER, Golgi complexes, and granules with the protease renin. Also at the vascular pole are lacis cells (Fr. lacis, lacework), which are extraglomerular mesangial cells that have many of the same supportive, contractile, and defensive functions as these cells inside the glomerulus.

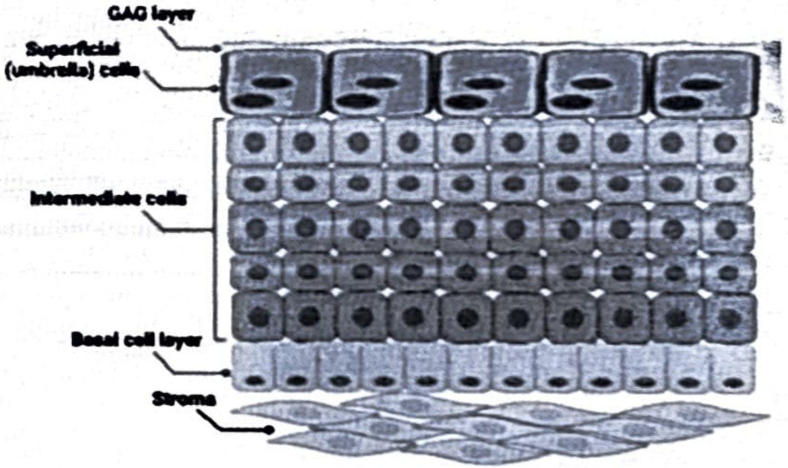


LOOP OF HENLE

The PCT continues with the much shorter proximal straight tubule that enters the medulla and continues as the nephron's loop of Henle. This is a U-shaped structure with a thin descending limb and a thin ascending limb, both composed of simple squamous epithelia. The straight part of the proximal tubule has an outer diameter of about 60 µm, but it narrows abruptly to about 30 µm in the thin limbs of the loop. The wall of the thin segments consists only of squamous cells with few organelles (indicating a primarily passive role in transport) and the lumen is prominent. The thin ascending limb of the loop becomes the thick ascending limb (TAL), with simple cuboidal epithelium and many mitochondria again, in the outer medulla and extends as far as the macula densa near the nephron's glomerulus. The loops of Henle and surrounding interstitial connective tissue are involved in further adjusting the salt content of the filtrate. Cuboidal cells of the loops' TALs actively transport sodium and chloride ions out of the tubule against a concentration gradient into the hyaluronate-rich interstitium, making that compartment hyperosmotic.





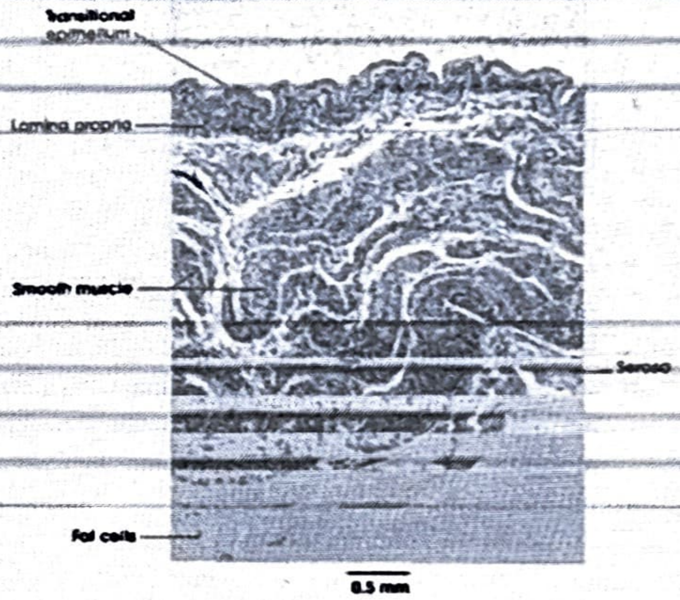


Urine is transported by the ureters from the renal pelvis to the urinary bladder where it is stored until emptying by micturition via the urethra. The walls of the ureters are similar to that of the calyces and renal pelvis, with mucosal, muscular, and adventitial layers and becoming gradually thicker closer to the bladder. The mucosa of these organs is lined by the uniquely stratified urothelium or transitional epithelium.

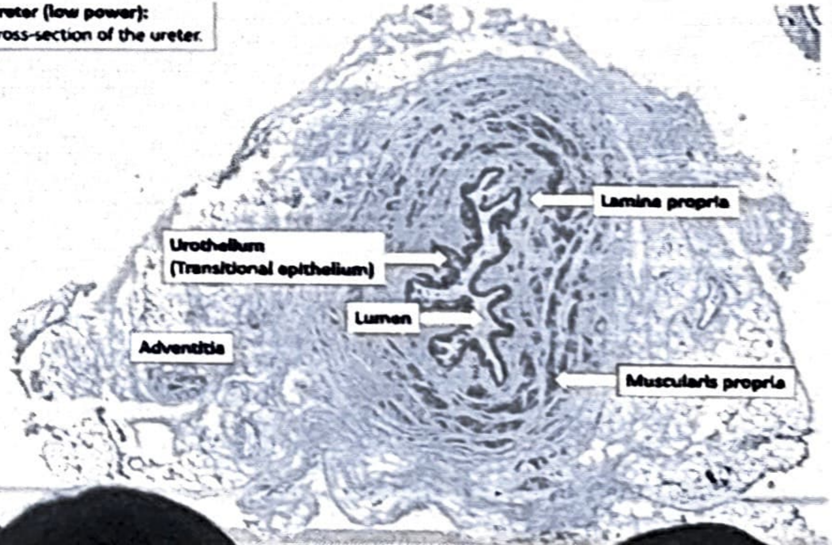
This mucosal surface layer plays an important barrier role, preventing absorption of urine's toxic substances such as acid and urea and defending against pathogen entry from the external environment. The urothelium consists of three cell types: basal, intermediate, and superficial cells, also known as umbrella cells or facet cells. The basal cells are the most undifferentiated urothelial cell type, located at the basement membrane of the lumen and serving a progenitor role. The intermediate cells are highly proliferative, forming multiple cell layers depending on the species. In times of injury or infection, intermediate cells are responsible for rapidly regenerating the urothelium. On the apical surface, fully differentiated umbrella cells are responsible for maintaining the impermeability and high-resistance barrier function of the urothelium. Umbrella cells sometimes binucleated, which are highly differentiated to protect the underlying cells against the potentially cytotoxic effects of hypertonic urine.

Urothelium is surrounded by a folded lamina propria and submucosa, followed by a dense sheath of interwoven smooth muscle layers and adventitia. Urine is moved from the renal pelvises to the bladder by peristaltic contractions of the ureters.

The **BLADDER'S** lamina propria and dense irregular connective tissue of the submucosa are highly vascularized. The bladder in an average adult can hold 400-600 mL of urine, with the urge to empty appearing at about 150-200 mL. The muscularis consists of three poorly delineated layers, collectively called the detrusor muscle, which contract to empty the bladder. Three muscular layers are seen most distinctly at the neck of the bladder near the urethra. The **URETERS** pass through the wall of the bladder obliquely, forming a valve that prevents the backflow of urine into the ureters as the bladder fills. All the urinary passages are covered externally by an adventitial layer, except for the upper part of the bladder that is covered by serous peritoneum.



Ureter (low power): Cross-section of the ureter.



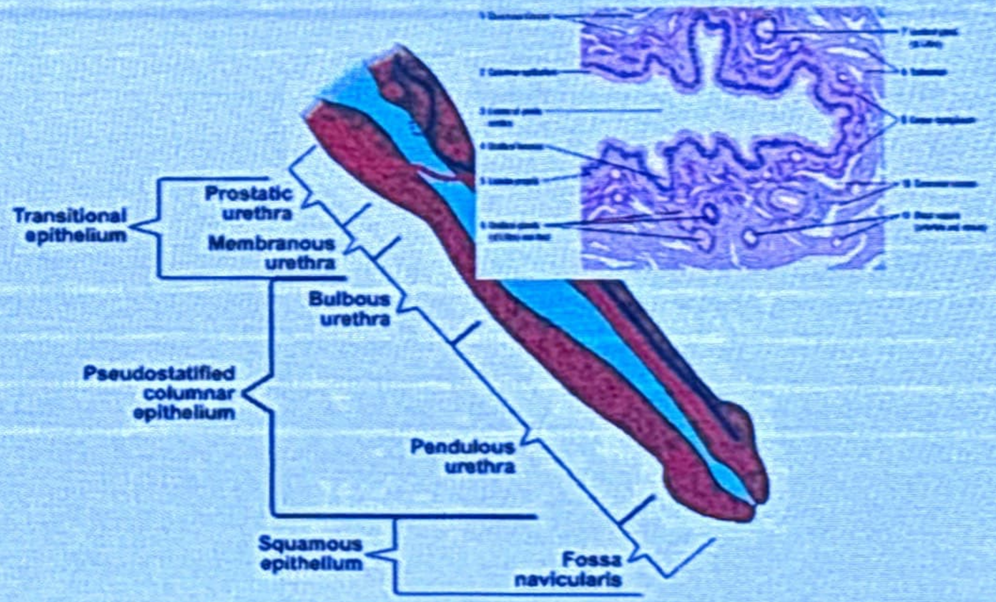
The **URETHRA** is a tube that carries the urine from the bladder to the exterior. The urethral mucosa has prominent longitudinal folds, giving it a distinctive appearance in cross section. In men, the two ducts for sperm transport during ejaculation join the urethra at the prostate gland.

The **male urethra** is longer and consists of three segments:

■ The prostatic urethra, 3-4 cm long, extends through the prostate gland and is lined by urothelium.

■ The membranous urethra, a short segment, passes through an external sphincter of striated muscle and is lined by stratified columnar and pseudostratified columnar epithelium.

■ The spongy urethra, about 15 cm in length, is enclosed within erectile tissue of the penis and is lined by stratified columnar and pseudostratified columnar epithelium, with stratified squamous epithelium distally.



In women, the urethra is exclusively a urinary organ. The **female urethra** is a 3- to 5-cm-long tube, lined initially with transitional epithelium which then transitions to nonkeratinized stratified squamous epithelium continuous with that of the skin at the labia minora. The middle part of the urethra in both sexes is surrounded by the external striated muscle sphincter.