

The Urinary System

The urinary system consists of the paired kidneys and ureters and the unpaired bladder and urethra. This system contributes to the maintenance of homeostasis by a complex process that involves filtration, active absorption, passive absorption, and secretion. The result is the production of urine, in which various metabolic waste products are eliminated. Urine produced in the kidneys passes through the ureters to the bladder, where it is temporarily stored and then released to the exterior through the urethra. The two kidneys produce about 125 mL of filtrate per minute; of this amount, 124 mL is absorbed in the organ, and only 1 mL is released into the ureters as urine. About 1500 mL of urine is formed every 24 h. The kidneys also regulate the fluid and electrolyte balance of the body and are the site of production of renin, a substance that participates in the regulation of blood pressure. Erythropoietin, a growth factor that stimulates the production of erythrocytes, is also produced in the kidneys. Erythropoietin also hydroxylates vitamin D₃, a steroid prohormone, to its active form.

Kidneys

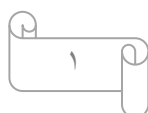
Each kidney has a concave medial border, the hilum where nerves enter, blood and lymph vessels enter and exit, and the ureter exits and a convex lateral surface. The renal pelvis, the expanded upper end of the ureter, is divided into two or three major calyces. Several small branches, the minor calyces, arise from each major calyx.

The kidney can be divided into an outer cortex and an inner medulla. In humans, the renal medulla consists of 10-18 conical or pyramidal structures, the medullary pyramids. From the base of each medullary pyramid, parallel arrays of tubules, the medullary rays, penetrate the cortex.

Each kidney is composed of 1-4 million nephrons. Each nephron consists of a dilated portion, the renal corpuscle; the proximal convoluted tubule; the thin and thick limbs of Henle's loop; the distal convoluted tubule; and the collecting tubules and ducts. Some investigators do not consider the collecting tubules and ducts to be part of the nephron. The nephron is the functional unit of the kidney.

Renal Corpuscles & Blood Filtration

Each renal corpuscle is about 200 μ m in diameter and consists of a tuft of capillaries, the glomerulus, surrounded by a double-walled epithelial capsule called glomerular (Bowman's) capsule. The internal layer (the visceral layer) of the capsule envelops the capillaries of the glomerulus. The external layer forms the outer limit of the renal corpuscle and is called the parietal layer of Bowman's capsule. Between the



two layers of Bowman's capsule is the urinary space, which receives the fluid filtered through the capillary wall and the visceral layer. Each renal corpuscle has a vascular pole, where the afferent arteriole enters and the efferent arteriole leaves, and a urinary pole, where the proximal convoluted tubule begins. After entering the renal corpuscle, the afferent arteriole usually divides into two to five primary branches, each subdividing into capillaries and forming the renal glomerulus.

The parietal layer of Bowman's capsule consists of a simple squamous epithelium supported by a basal lamina and a thin layer of reticular fibers. At the urinary pole, the epithelium changes to the simple cuboidal, or low columnar, epithelium characteristic of the proximal tubule.

During embryonic development, the epithelium of the parietal layer remains relatively unchanged, whereas the internal, or visceral, layer is greatly modified. The cells of this internal layer, the podocytes, have a cell body from which arise several primary processes. Each primary process gives rise to numerous secondary processes, called pedicels, that embrace the capillaries of the glomerulus. At a periodic distance of 25 nm, the secondary processes are in direct contact with the basal lamina. However, the cell bodies of podocytes and their primary processes do not touch the basement membrane.

The secondary processes of podocytes interdigitate, defining elongated spaces about 25 nm wide the filtration slits. Spanning adjacent processes (and thus bridging the filtration slits) is a diaphragm about 6 nm thick. Podocytes have bundles of actin filaments in their cytoplasm that give them a contractile capacity. Between the fenestrated endothelial cells of the glomerular capillaries and the podocytes that cover their external surfaces is a thick basement membrane. This membrane is believed to be the filtration barrier that separates the urinary space and the blood in the capillaries. The basement membrane is derived from the fusion of capillary- and podocyte-produced basal laminae. With the aid of the electron microscope, a central electron-dense layer (lamina densa) and, on each side, a more electron-lucent layer can be distinguished. The two electron-lucent laminae rarae contain fibronectin, which may serve to bind them to the cells. The lamina densa is a meshwork of type IV collagen and laminin in a matrix containing the negatively charged proteoglycan heparan sulfate that restricts the passage of cationic molecules. Thus, the glomerular basement membrane is a selective macromolecular filter in which the lamina densa acts as a physical filter, whereas the anionic sites in the laminae rarae act as a charge barrier. Particles greater than 10 nm in diameter do not readily cross the basal lamina, and negatively charged proteins with a molecular mass greater than that of albumin (69 kDa) pass across only sparingly.

The blood flow in the two kidneys of an adult amounts to 1.2-1.3 L of blood per minute. This means that all the circulating blood in the body passes through the



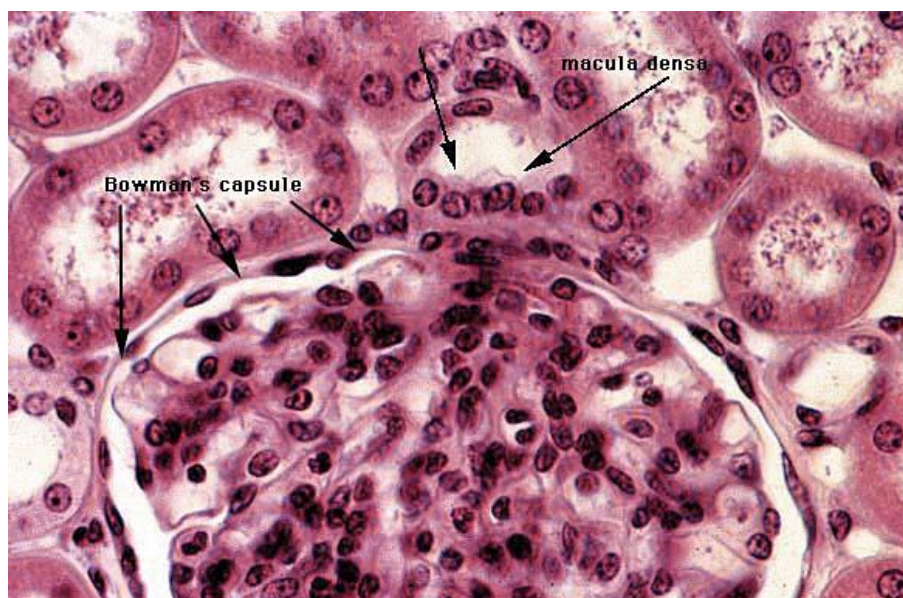
kidneys every 4-5 min. The glomeruli are composed of arterial capillaries in which the hydrostatic pressure about 45 mm Hg is higher than that found in other capillaries.

The glomerular filtrate is formed in response to the hydrostatic pressure of blood, which is opposed by the osmotic (oncotic) pressure of plasma colloids (20 mm Hg), and the hydrostatic pressure of the fluids in Bowman's capsule (10 mm Hg). The net filtration pressure at the afferent end of glomerular capillaries is 15 mm Hg.

The glomerular filtrate has a chemical composition similar to that of blood plasma but contains almost no protein, because macromolecules do not readily cross the glomerular filter. The largest protein molecules that succeed in crossing the glomerular filter have a molecular mass of about 70 kDa, and small amounts of plasma albumin appear in the filtrate.

The endothelial cells of glomerular capillaries are of the fenestrated variety, but they lack the thin diaphragm that spans the openings of other fenestrated capillaries.

In addition to endothelial cells and podocytes, the glomerular capillaries have mesangial cells adhering to their walls. Mesangial cells are contractile and have receptors for angiotensin II. When these receptors are activated, the glomerular flow is reduced. Mesangial cells also have receptors for the natriuretic factor produced by cardiac atria cells. This factor is a vasodilator and relaxes the mesangial cells, probably increasing the blood flow and the effective surface area available for filtration. Mesangial cells also have several other functions: they give structural support to the glomerulus, synthesize extracellular matrix, endocytose and dispose of normal and pathological (immune complex) molecules trapped by the glomerular basement membrane, and probably produce chemical mediators such as cytokines and prostaglandins. In the vascular pole but outside the glomerulus, there are the so-called extraglomerular mesangial cells that form part of the juxtaglomerular apparatus.



Proximal Convoluted Tubule

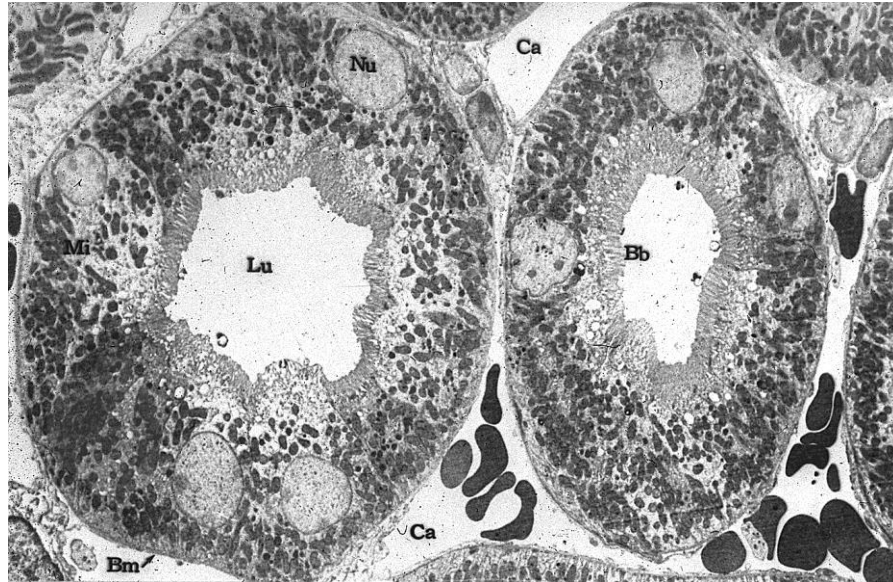
At the urinary pole of the renal corpuscle, the squamous epithelium of the parietal layer of Bowman's capsule is continuous with the cuboidal, or low columnar, epithelium of the proximal convoluted tubule. This tubule is longer than the distal convoluted tubule and is therefore more frequently seen near renal corpuscles in the renal cortex.

The cells of this cuboidal epithelium have an acidophilic cytoplasm because of the presence of numerous elongated mitochondria. The cell apex has abundant microvilli about 1 μ m in length, which form a brush border. Because the cells are large, each transverse section of a proximal tubule contains only three to five spherical nuclei.

In the living animal, proximal convoluted tubules have a wide lumen and are surrounded by peritubular capillaries. In routine histological preparations, the brush border is usually disorganized and the peritubular capillary lumens are greatly reduced in size or collapsed.

The apical cytoplasm of these cells has numerous canaliculi between the bases of the microvilli; these canaliculi increase the capacity of the proximal tubule cells to absorb macromolecules. Pinocytotic vesicles are formed by evaginations of the apical membranes and contain macromolecules (mainly proteins with a molecular mass less than 70 kDa) that have passed across the glomerular filter. The pinocytotic vesicles fuse with lysosomes, where macromolecules are degraded, and monomers are returned to the circulation. The basal portions of these cells have abundant membrane invaginations and lateral interdigitations with neighboring cells. The Na⁺/K⁺-ATPase (sodium pump) responsible for actively transporting sodium ions out of the cells is localized in these basolateral membranes. Mitochondria are concentrated at the base of the cell and arranged parallel to the long axis of the cell. This mitochondrial location and the increase in the area of the cell membrane at the base of the cell are characteristic of cells engaged in active ion transport. Because of the extensive interdigitations of the lateral membranes, no discrete limits can be observed (in the light microscope) between cells of the proximal tubule. The glomerular filtrate formed in the renal corpuscle passes into the proximal convoluted tubule, where the processes of absorption and excretion begin. The proximal convoluted tubule absorbs all the glucose and amino acids and about 85% of the sodium chloride and water contained in the filtrate, in addition to phosphate and calcium. Glucose, amino acids, and sodium are absorbed by these tubular cells through an active process involving Na⁺/K⁺-ATPase (sodium pump) located in the basolateral cell membranes. Water diffuses passively, following the osmotic gradient. When the amount of glucose in the filtrate exceeds the absorbing capacity of the proximal tubule, urine becomes more abundant and contains glucose.

In addition to these activities, the proximal convoluted tubule secretes creatinine and substances foreign to the organism, such as para-aminohippuric acid and penicillin, from the interstitial plasma into the filtrate. This is an active process referred to as tubular secretion.

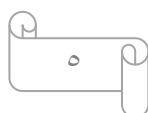


Henle's Loop

Henle's loop is a U-shaped structure consisting of a thick descending limb, a thin descending limb, a thin ascending limb, and a thick ascending limb. The thick limbs are very similar in structure to the distal convoluted tubule. In the outer medulla, the thick descending limb, suddenly narrows and continues as the thin descending limb. The lumen of this segment of the nephron is wide because the wall consists of squamous epithelial cells whose nuclei protrude only slightly into the lumen.

Approximately one-seventh of all nephrons are located near the corticomedullary junction and are therefore called juxtamedullary nephrons. The other nephrons are called cortical nephrons. All nephrons participate in the processes of filtration, absorption, and secretion. Juxtamedullary nephrons, however, are of prime importance in establishing the gradient of hypertonicity in the medullary interstitium the basis of the kidneys' ability to produce hypertonic urine. Juxtamedullary nephrons have very long Henle's loops, extending deep into the medulla. These loops consist of a short thick descending limb, long thin descending and ascending limbs, and a thick ascending limb. Cortical nephrons, on the other hand, have very short thin descending limbs and no thin ascending limbs.

Henle's loop is involved in water retention; only animals with such loops in their kidneys are capable of producing hypertonic urine and thus maintaining body water. Henle's loop creates a gradient of hypertonicity in the medullary interstitium that influences the concentration of the urine as it flows through the collecting ducts.



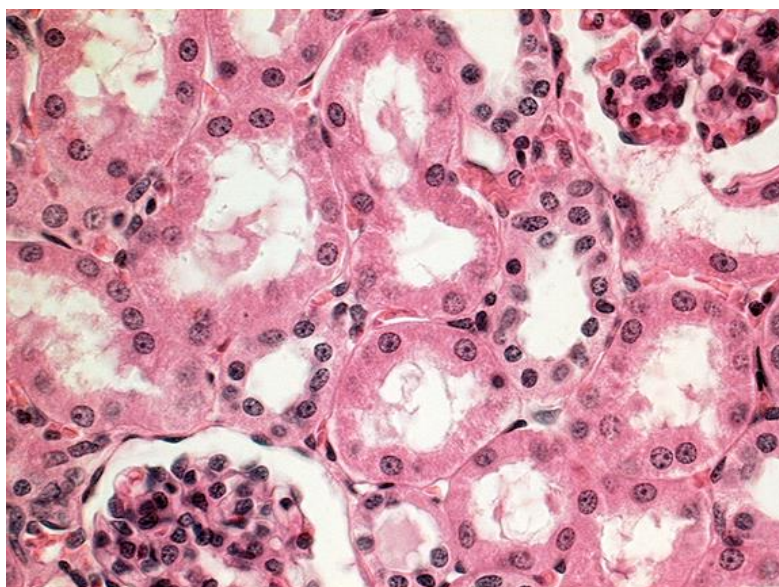
Although the thin descending limb of the loop is freely permeable to water, the entire ascending limb is impermeable to water. In the thick ascending limb, sodium chloride is actively transported out of the tubule to establish the gradient of hypertonicity in the medullary interstitium that is necessary for urine concentration. The osmolarity of the interstitium at the tips of the medullary pyramids is about four times that of blood.

Distal Convoluted Tubule

The thick ascending limb of Henle's loop penetrates the cortex; after describing a certain trajectory, it becomes tortuous and is called the distal convoluted tubule. This tubule, like the ascending limb, is lined with simple cuboidal epithelium.

The distal convoluted tubules differ from the proximal convoluted tubules (both found in the cortex) because they have no brush border, no apical canaliculi, and smaller cells. Because distal tubule cells are flatter and smaller than those of the proximal tubule, more nuclei are seen in the distal tubule than in the proximal tubule. Cells of the distal convoluted tubule have elaborate basal membrane invaginations and associated mitochondria indicative of their ion-transporting function.

The distal convoluted tubule establishes contact with the vascular pole of the renal corpuscle of its parent nephron. At this point of close contact, the distal tubule is modified, as is the afferent arteriole. In this juxtaglomerular region, cells of the distal convoluted tubule usually become columnar, and their nuclei are closely packed together. Most of the cells have a Golgi complex in the basal region. This modified segment of the wall of the distal tubule, which appears darker in microscopic preparations because of the close proximity of its nuclei, is called the **macula densa**. The cells of the macula densa are sensitive to the ionic content and water volume of the tubular fluid, producing molecular signals that promote the liberation of the enzyme renin in the circulation.



In the distal convoluted tubule, there is ion exchange if aldosterone is present in high enough concentration: Sodium is absorbed, and potassium ions are secreted. This mechanism influences the total salt and water content of the body. The distal tubule also secretes hydrogen and ammonium ions into tubular urine. This activity is essential for maintenance of the acid base balance in the blood.

Collecting Tubules & Ducts

Urine passes from the distal convoluted tubules to collecting tubules that join each other to form larger, straight collecting ducts, which widen gradually as they approach the tips of the medullary pyramids.

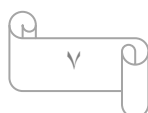
The smaller collecting tubules are lined with cuboidal epithelium and have a diameter of approximately 40 μ m. As they penetrate deeper into the medulla, their cells increase in height until they become columnar. The diameter of the collecting duct reaches 200 μ m near the tips of the medullary pyramids.

Along their entire extent, collecting tubules and ducts are composed of cells that stain weakly with the usual stains. They have an electron-lucent cytoplasm with few organelles. In collecting tubules and cortical collecting ducts, a dark-staining intercalated cell is also seen; its significance is not understood. The intercellular limits of the collecting tubule and duct cells are clearly visible in the light microscope. Cortical collecting ducts are joined at right angles by several generations of smaller collecting tubules that drain each medullary ray. In the medulla, collecting ducts are a major component of the urine-concentrating mechanism.

The epithelium of collecting ducts is responsive to arginine vasopressin, or antidiuretic hormone, secreted by the posterior pituitary. If water intake is limited, antidiuretic hormone is secreted and the epithelium of the collecting ducts becomes permeable to water, which is absorbed from the glomerular filtrate, transferred to blood capillaries, and thus retained in the body. In the presence of antidiuretic hormone, intramembrane particles in the luminal membrane aggregate to form what may be channels for water absorption.

Juxtaglomerular Apparatus

Adjacent to the renal corpuscle, the tunica media of the afferent arteriole has modified smooth muscle cells. These cells are called juxtaglomerular (JG) cells and have a cytoplasm full of secretory granules. Secretions of JG cells play a role in the maintenance of blood pressure. The macula densa of the distal convoluted tubule is usually located near the region of the afferent arteriole that contains the JG cells; together, this portion of the arteriole and the macula densa form the JG apparatus. Also a part of the JG apparatus are some light-staining cells whose functions are not well



understood. They are called extraglomerular mesangial cells or lacis cells. The internal elastic membrane of the afferent arteriole disappears in the area of the JG cells.

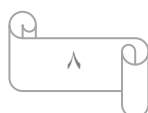
When examined with the electron microscope, JG cells show characteristics of protein-secreting cells, including an abundant rough endoplasmic reticulum, a highly developed Golgi complex, and secretory granules measuring approximately 10-40 nm in diameter. JG cells produce the enzyme renin, which acts on a plasma protein angiotensinogen to produce an inactive decapeptide, angiotensin I. As a result of the action of a converting enzyme present in high concentration in lung endothelial cells, this substance loses two amino acids and becomes an active vasopressive octapeptide, angiotensin II.

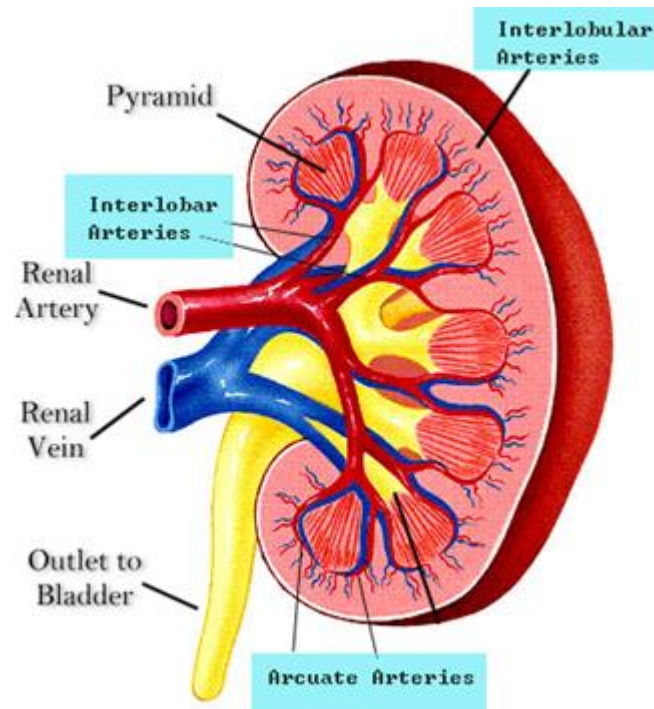
Blood Circulation

Each kidney receives blood from its renal artery, which usually divides into two branches before entering the organ. One branch goes to the anterior part of the kidney and the other to the posterior part. While still in the hilum, these branches give rise to arteries that branch again to form the interlobar arteries located between the renal pyramids. At the level of the corticomedullary junction, the interlobar arteries form the arcuate arteries. Interlobular arteries branch off at right angles from the arcuate arteries and follow a course in the cortex perpendicular to the renal capsule. Interlobular arteries form the boundaries of the renal lobules, which consist of a medullary ray and the adjacent cortical labyrinth. From the interlobular arteries arise the afferent arterioles, which supply blood to the capillaries of the glomeruli. Blood passes from these capillaries into the efferent arterioles, which at once branch again to form a peritubular capillary network that will nourish the proximal and distal tubules and carry away absorbed ions and low-molecular-weight materials. The efferent arterioles that are associated with juxtamedullary nephrons form long, thin capillary vessels. These vessels, which follow a straight path into the medulla and then loop back toward the corticomedullary boundary, are called vasa recta (straight vessels). The descending vessel is a continuous-type capillary, whereas the ascending vessel has a fenestrated endothelium. These vessels, containing blood that has been filtered through the glomeruli, provide nourishment and oxygen to the medulla. Because of their looped structure, they do not carry away the high osmotic gradient set up in the interstitium by Henle's loop.

The capillaries of the outer cortex and the capsule of the kidney converge to form the stellate veins (so called because of their configuration when seen from the surface of the kidney), which empty into the interlobular veins.

Veins follow the same course as arteries. Blood from interlobular veins flows into arcuate veins and from there to the interlobar veins. Interlobar veins converge to form the renal vein through which blood leaves the kidney.





Renal Interstitium

The space between uriniferous tubules and blood and lymph vessels is called the renal interstitium. It occupies a very small volume in the cortex but increases in the medulla. The renal interstitium contains a small amount of connective tissue with fibroblasts, some collagen fibers, and, mainly in the medulla, a highly hydrated ground substance rich in proteoglycan. In the medulla the secreting cells called interstitial cells are found. They contain cytoplasmic lipid droplets and are implicated in the synthesis of prostaglandins and prostacyclin.

Bladder & Urinary Passages

The bladder and the urinary passages store the urine formed in the kidneys and conduct it to the exterior. *The calyces, renal pelvis, ureter, and bladder* have the same basic histological structure, with the walls of the ureters becoming gradually thicker as proximity to the bladder increases.

The mucosa of these organs consists of transitional epithelium and a lamina propria of loose-to-dense connective tissue. Surrounding the lamina propria of these organs is a dense woven sheath of smooth muscle.

The transitional epithelium of the bladder in the undistended state is five or six cells in thickness; the superficial cells are rounded and bulge into the lumen. These cells are frequently polyploid or binucleate. When the epithelium is stretched, as when the bladder is full of urine, the epithelium is only three or four cells in thickness, and the superficial cells become squamous.

The superficial cells of the transitional epithelium have a special membrane of thick plates separated by narrow bands of thinner membrane that are responsible for the osmotic barrier between urine and tissue fluids. When the bladder contracts, the membrane folds along the thinner regions, and the thicker plates invaginate to form fusiform cytoplasmic vesicles. These vesicles represent a reservoir of these thick plates that can be stored in the cytoplasm of the cells of the empty bladder and used to cover the increased cell surface in the full bladder. This luminal membrane is assembled in the Golgi complex and has an unusual chemical composition; cerebroside is the major component of the polar lipid fraction.

The muscular layers in the calyces, renal pelvis, and ureters have a helical arrangement. As the ureteral muscle cells reach the bladder, they become longitudinal. The muscle fibers of the bladder run in every direction (without distinct layers) until they approach the bladder neck, where three distinct layers can be identified: The internal longitudinal layer, distal to the bladder neck, becomes circular around the prostatic urethra and the prostatic parenchyma in men. It extends to the external meatus in women. Its fibers form the true involuntary urethral sphincter. The middle layer ends at the bladder neck, and the outer longitudinal layer continues to the end of the prostate in men and to the external urethral meatus in women.

The ureters pass through the wall of the bladder obliquely, forming a valve that prevents the backflow of urine. The intravesical ureter has only longitudinal muscle fibers.

The urinary passages are covered externally by an adventitial membrane, except for the upper part of the bladder, which is covered by serous peritoneum.



Urethra

The urethra is a tube that carries the urine from the bladder to the exterior. In men, sperm also pass through it during ejaculation. In women, the urethra is exclusively a urinary organ.

Male Urethra

The male urethra consists of four parts: **prostatic, membranous, bulbous, and pendulous**. The initial part of the urethra passes through the prostate, which is situated very close to the bladder, and the ducts that transport the secretions of the prostate open into the **prostatic urethra**.

In the dorsal and distal part of the prostatic urethra, there is an elevation, the verumontanum (from Latin, meaning mountain ridge), that protrudes into its interior. A closed tube called the prostatic utricle opens into the tip of the verumontanum; this tube has no known function. The ejaculatory ducts open on the sides of the verumontanum. The seminal fluid enters the proximal urethra through these ducts to be stored just before ejaculation. The prostatic urethra is lined with transitional epithelium.

The membranous urethra extends for only 1 cm and is lined with stratified or pseudostratified columnar epithelium. Surrounding this part of the urethra is a sphincter of striated muscle, the external sphincter of the urethra. The voluntary external striated sphincter adds further closing pressure to that exerted by the involuntary urethral sphincter. The latter is formed by the continuation of the internal longitudinal muscle of the bladder.

The bulbous and pendulous parts of the urethra are located in the corpus spongiosum of the penis. The urethral lumen dilates distally, forming the fossa navicularis. The epithelium of this portion of the urethra is mostly pseudostratified and columnar, with stratified and squamous areas.

Littre's glands are mucous glands found along the entire length of the urethra but mostly in the pendulous part. The secretory portions of some of these glands are directly linked to the epithelial lining of the urethra; others have excretory ducts.

Female Urethra

The female urethra is a tube 4-5 cm long, lined with stratified squamous epithelium and areas of pseudostratified columnar epithelium. The mid part of the female urethra is surrounded by an external striated voluntary sphincter.

