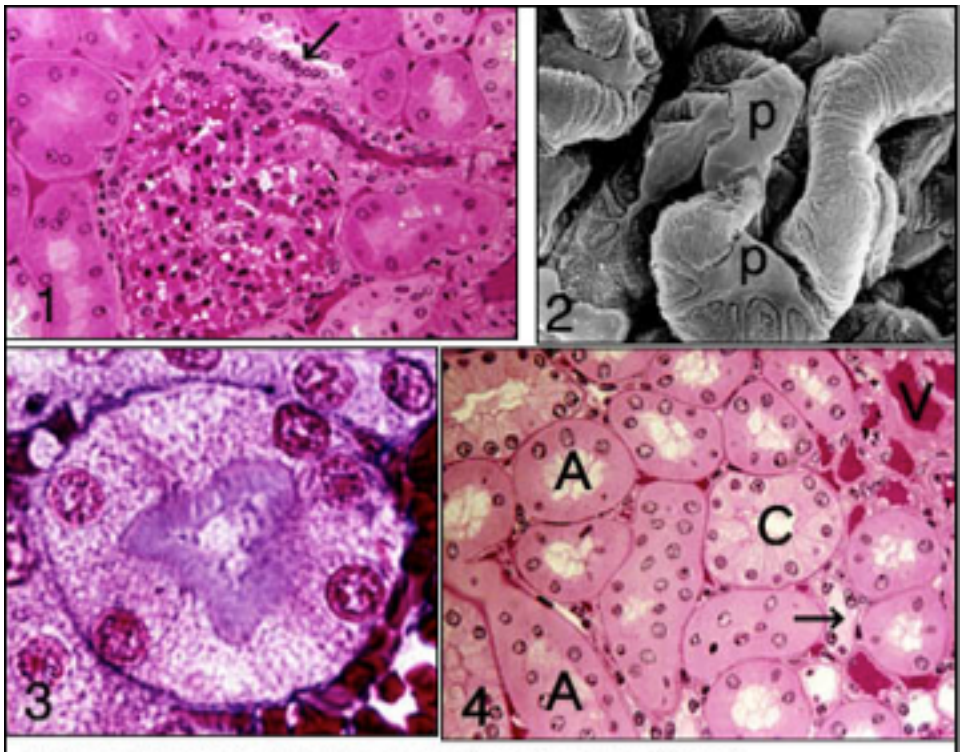
Kidney



1. A renal corpuscle. Note the adjacent macula densa (arrow).
2. An SEM of podocytes (P) covering glomerular capillaries. (Courtesy of P. Andrews).
3. A proximal convoluted tubule. Note the microvillus border.
4. Kidney Medulla. Note the thin segment (arrow), thick ascending limb of the loop of Henle (A), collecting duct (C), and vesa recta (V).

The kidneys are a pair of compound tubular glands that clear the blood plasma of metabolic wastes, regulate fluid osmolality and volume, regulate electrolyte balance, eliminate foreign chemicals, and help maintain the acid-base balance of the body. Excretion of metabolic products includes creatinine (from muscle creatine phosphate), uric acid (from nucleic acids), urea (from amino acids), metabolites of hormones and hemoglobin, as well as other substances. The kidneys also are instrumental in eliminating drugs, pesticides, and other environmental factors from the blood plasma. In addition to excretory functions, the kidneys have properties of endocrine organs and release two substances, renin and erythropoietin, directly into the bloodstream. Renin is important in regulating blood pressure and sodium ion concentration; erythropoietin influences hemopoietic activity. The kidneys also are important in activating circulating vitamin D to an active form, 1, 25-dihydroxyvitamin D3, necessary for normal absorption of calcium ion in the gastrointestinal tract.

Macroscopic Features

Human kidneys are bean-shaped organs that lie in a retroperitoneal position against the posterior abdominal wall, one on either side of the upper lumbar vertebrae. Each is contained within a thin but strong connective tissue capsule that contains fat. The renal artery and nerves

enter the kidney on the medial border at the hilum, a concavity that also serves as the point of exit for the renal vein, lymphatics, and ureter. The hilum is continuous with the renal sinus, a large central cavity surrounded by the parenchyma of the kidney and filled with loose areolar connective tissue that normally contains much fat. Nerves, lymphatics, and branches of the renal artery and vein run through the sinus. The renal pelvis is a funnel-shaped expansion of the ureter where it joins the kidney; it also passes through the sinus, dividing into two or three short tubular structures called the major calyces. These in turn divide into eight to twelve smaller units called minor calyces. Each minor calyx forms a cylindrical attachment around a conical projection of renal tissue called a renal papilla. When a hemisection of the kidney is examined macroscopically, the organization of the parenchyma into two distinct regions can be seen readily. The darker, granular appearing outer region is the cortex, which forms a continuous layer beneath the capsule. The inner region, or medulla, is paler and smoother in texture and consists of 8 to 20 cone-shaped structures called medullary pyramids, which are separated from each other by inward extensions of cortical tissue. The cortex that separates adjacent medullary pyramids makes up a renal column. The bases of the pyramids are directed toward the overlying cortex, while their apices are oriented toward the renal sinus and form the renal papillae. From the bases of the pyramids, groups of tubules extend into the cortex, giving it a striated appearance. These striations represent a continuation of medullary tissue into the cortex and constitute the medullary rays. The arrangement of cortex and medulla allows subdivision of the kidney into smaller units, the lobes and lobules. A medullary pyramid, together with its closely associated cortical tissue, forms a renal lobe, while a medullary ray, together with its associated cortical tissue, forms a renal lobule. When the kidney consists of several lobes, it is referred to as a multilobular kidney; the kidneys of humans are this type.

Microscopic Features

Each renal lobule is made up of numerous epithelial tubules called uriniferous tubules that collectively form the parenchyma of the kidney. Each uriniferous tubule can be divided into a nephron, and a collecting duct. Each of these units has a different embryologic origin.

Nephron

There are 1 to 2 million nephrons in the human kidney, each representing a functional unit of the kidney. A nephron is a blindly ending epithelial tubule that can be subdivided into several components, each differing in structure, function, and position in the kidney. During urine formation, the various segments of a nephron take part in filtration, secretion, and resorption. A typical nephron consists of a renal corpuscle, a proximal tubule with convoluted and straight portions, a thin segment, and a distal tubule that also has straight and convoluted parts. Those segments of the nephron between the proximal and distal convoluted tubules (i.e., the straight descending part of the proximal tubule, the thin segment, and the straight ascending portion of the distal tubule) are collectively referred to as the loop of Henle. The renal corpuscle and the proximal and distal convoluted tubules occur only in the cortex, whereas Henle's loop generally is confined to the medulla or to a medullary ray. The size of the nephrons and the length of their various segments vary according to the position of the parent renal corpuscle in the cortex. Renal corpuscles near the medulla are larger and the tubules are longer than are those of nephrons whose renal corpuscles are located in the periphery of the cortex. Nephrons from the subcapsular region have small renal corpuscles and their thin segments of the loop of

Henle extend for only a short distance into the medulla. Nephrons whose renal corpuscles occupy an intermediate position in the cortex show intermediate features.

Renal Corpuscle

A renal corpuscle is roughly spherical and measures 150 to 250 μm in diameter. It consists of a capillary tuft, the glomerulus, which projects into a blind expansion of the uriniferous tubule called the glomerular capsule (Bowman's capsule). The outer layer of the capsule surrounds the glomerulus as the parietal layer, which then reflects onto the glomerulus, where it is intimately applied to the glomerular capillaries to form a complete epithelial covering called the visceral layer of the glomerular capsule. The parietal layer also is known as the capsular epithelium, while the visceral layer frequently is referred to as the glomerular epithelium. The visceral and parietal layers of the capsule are separated by a narrow capsular space. The vascular pole is that area of the renal corpuscle at which the afferent and efferent arterioles enter and leave. As the afferent arteriole enters the renal corpuscle, it immediately divides into several primary branches, each of which forms a complex of capillaries (a capillary lobule) that then reunite to form the efferent arteriole. Each glomerulus is made up of several such capillary lobules. On the side opposite the vascular pole, the capsular space becomes continuous with the lumen of the proximal convoluted tubule; this region is known as the urinary pole. The parietal layer of the glomerular capsule consists of a single layer of tightly adherent squamous cells that contain few organelles. Near the urinary pole there is an abrupt transition from this simple squamous form to the large pyramidal cells that line the proximal convoluted tubule. At the vascular pole, the simple squamous capsular epithelium changes to a specialized cell type called the podocyte that forms the glomerular epithelium. Podocytes are large, stellate cells whose bodies lie some distance from the underlying capillaries, separated from them by several cytoplasmic extensions called the primary processes. These processes wrap around the glomerular capillaries and give rise to numerous secondary foot processes (pedicles) that interdigitate with similar processes from adjacent podocytes to completely invest the capillary loops of the glomerulus. The plasmalemma of the foot processes exhibits a prominent glycocalyx rich in a sialoglycoprotein called podocalyxin. The narrow clefts between the interdigitating processes form the slit pores (filtration slits), which measure about 25 nm in width. A thin slit membrane may bridge the gaps. The foot processes of the podocytes and the endothelial cells of the glomerular capillaries share a continuous common basal lamina that measures 0.1 to 0.5 μm thick. Ultrastructurally, the basal lamina consists of a central electron-dense lamina densa, a lamina rara externa adjacent to the podocyte foot processes, and a lamina rara interna adjacent to the glomerular endothelium. The lamina densa consists of type IV collagen, laminin and heparan sulfate proteoglycan. The lamina rara externa and interna consist primarily of fibronectin, which is thought to firmly attach both epithelial and endothelial cells to the lamina densa. Both cell populations are essential to establish the common basal lamina and thereafter continue to contribute to its production and maintenance.

The glomerular capillaries are lined by a fenestrated glomerular endothelium. The attenuated squamous cells show numerous large pores (fenestrae) that measure 50 to 100 nm in diameter. The renal corpuscle also shows stellate cells with long cytoplasmic processes that contain numerous filaments. These are mesangial cells, which occupy the area between the afferent and efferent arterioles at the vascular pole, where they lie in a matrix of amorphous material. These cells constitute the extraglomerular mesangium (Lacis cells) and are continuous with cells of similar appearance, the intraglomerular mesangial cells that lie between the glomerular endothelium and the basal lamina. The latter cells are thought to clear

away large protein molecules that become lodged on the common basal lamina during filtration of blood plasma. Mesangial cells may participate in the removal of older portions of the basal lamina from the endothelial side as it is added to by the podocytes. Mesangial cells are contractile and respond to angiotensin II and other vasoconstrictors. They also have receptors for the atriopeptides. The contractile activity of the mesangial cells is thought to mediate blood flow through the glomerular capillaries. Mesangial cells are of clinical importance in some kidney diseases because of their tendency to proliferate. The renal corpuscle is the filter of the nephron. The fenestrated glomerular endothelium, the common basal lamina, and the foot processes of the glomerular epithelium form the filtration barrier of the renal corpuscle. This barrier permits passage of water, ions, and small molecules from the capillaries into the capsular space, but larger structures such as the formed elements of the blood and large, irregular molecules are retained. The capillary endothelial cells prevent passage of formed elements; the common basal lamina restricts passage of molecules with a molecular weight greater than 70,000. Substances of small molecular weight (40,000 or less) cross the basal lamina and pass through the filtration slits of the surrounding glomerular epithelium to enter the capsular space. Material that collects in the capsular space is not urine but a filtrate of blood plasma.

Although materials with molecular weights larger than 45,000 or that have highly irregular shapes may pass through the endothelium and common basal lamina, they are unable to traverse the barrier provided by the foot processes of the podocytes. The filtration barrier limits passage of materials not only on the basis of size and shape but also with respect to their charge. Anionic molecules are more restricted in their passage through the filtration barrier than are neutral molecules of similar size. Heparan sulfate is a negatively charged (polyanionic) molecule of the glomerular basal lamina. The sialoprotein (podocalyxin) coats the podocyte foot processes and together with heparan sulfate gives the filtration barrier a net negative charge. The negatively charged glomerular basement membrane prevents or restricts the filtration of molecules such as albumin and other highly negatively charged molecules. Thus, the glomerular epithelium and the common basal lamina are important in limiting the kinds of materials that pass from the blood into the capsular space. The hydrostatic pressure of the blood in the glomerular capillaries supplies the energy for the filtration process. The pressure (about 70 mm Hg) provides sufficient force to overcome the colloidal osmotic pressure of substances in the blood (approximately 33 mm Hg) and the capsular pressure of the filtration membrane (about 20 mm Hg). The resulting filtration pressure (approximately 18 mm Hg) is great enough to force filtrable materials through all three layers of the filtration barrier and into the capsular space. The hydrostatic pressure exerted within the glomerular capillaries results from the unusual vascular arrangement of the glomerulus. Most vascular areas of the body are supplied by arterioles that form capillaries that then reunite into venules; but the glomerular capillaries are interposed between an afferent arteriole that conducts blood to the glomerulus and an efferent arteriole that conducts blood away from the glomerulus. This arrangement results in considerable pressure being exerted on the capillary walls and can be regulated by contraction of either arteriole. As more filtrate from the blood enters the capsular space, the rise in pressure forces the filtrate into the lumen of the proximal convoluted tubule. The capsular epithelium forms a tight seal around each renal corpuscle, preventing leakage of filtrate into the cortical tissue.

Proximal Tubule

The proximal tubule begins at the urinary pole of the renal corpuscle and is the largest segment of the human nephron. It is about 17 mm long and makes up most of the cortex. The proximal tubule is divided into a convoluted portion (pars convoluta) and a straight portion (pars recta). The convoluted portion is the longer of the two parts and is the one most frequently seen in sections of the cortex. After a tortuous course through the cortex in the region of its parent renal corpuscle, the proximal tubule takes a more direct route through the cortex to become the straight portion of the proximal tubule. It then enters the medulla or a medullary ray, where it turns toward a renal papilla as the first part of the loop of Henle. The proximal convoluted tubule consists of a single layer of large, pyramidal cells that have a well-developed microvillus (brush) border. The basolateral surfaces of these cells form an intricate system of interdigitating processes and ridges that often extend beneath neighboring cells to interdigitate with similar processes of adjacent cells. Tight junctions fuse the apices of the adjacent cells together around the tubular lumen and clearly delineate apical and basolateral cell membrane domains. The resulting separation of transmembrane (transporter) proteins is vital to the function of proximal tubular cells. Thus, a complex labyrinth of cell membranes extends from the basal region of the epithelium to near the luminal surface between individual epithelial cells. Compartmentalization of the lateral and basal regions results in a greater surface area of cell membrane, which facilitates the transport of ions and other solutes. In typical tissue sections, profiles of proximal convoluted tubules are the most common structures seen in the cortex and usually show a stellate lumen bounded by a distinct brush border. Each cell of the proximal tubule has a large spherical nucleus, but in histologic sections not all cells show a nucleus because of the large size of the cells. The cells contain a supranuclear Golgi complex and numerous rod-shaped mitochondria parallel to the long axis of the cell, closely associated with the lateral ridges and processes of the basolateral plasmalemma. The cytoplasm usually is darkly staining and granular. Structurally, the convoluted and straight parts of the proximal tubule are similar, but the cells of the straight portion are shorter, and the brush border and basolateral infoldings are less well defined than in the convoluted part. Mitochondria are abundant but are smaller and more randomly scattered. One of the main functions of the proximal tubule is absorption of the glomerular filtrate. The brush border, which consists of closely packed, elongated microvilli, increases the surface area available for absorption by about 30-fold. The microvilli are embedded in a coat of extracellular glycoprotein (glycocalyx). The apical surfaces of these cells absorb sugars and amino acids from the luminal contents in a manner similar to that of intestinal epithelial cells. Normally, all the glucose in the glomerular filtrate is absorbed in the proximal convoluted tubule. If blood glucose levels exceed the absorptive capacity of the enzymes that control the absorption of glucose, the excess spills into the urine (glycosuria).

Protein is absorbed in the proximal tubule by a system of invaginations called apical canaliculi that give rise to a series of small vesicles containing protein sequestered from the lumen. The tubular invaginations, the vesicles, and the vacuoles together make up the endocytic complex, which is actively involved in protein absorption. The vesicles coalesce to form large vacuoles that condense and ultimately fuse with lysosomes whose acid hydrolases reduce the protein to amino acids that are released back into the bloodstream. Over 65% of the sodium chloride and water of the glomerular filtrate is absorbed in the proximal tubule. Sodium ion is actively transported from the lumen, and chloride ion and water follow passively with no expenditure of energy by the cell to maintain the osmotic balance. Water passes through specialized protein channels called aquaporins. In the proximal tubule these are aquaporin-I channels, which are

not influenced by the presence of antidiuretic hormone (ADH). Aquaporin-I channels also are found in the descending thin limb of the loop of Henle. A key factor in proximal tubular cell reabsorption is a Na^+, K^+-ATPase enzyme pump located within the basolateral cell membranes that limit the complex intercellular space. The reabsorption of most substances including water is linked to the function of this Na^+, K^+-ATPase system. Glucose, amino acids, lactate, and phosphate are coupled to sodium entry across the apical plasmalemma of the cell by specific symporter (cotransport) and antiporter (countertransport) transmembrane proteins. Sodium is then moved out of the cell and into the intercellular space by the Na^+, K^+-ATPase mechanism, and glucose, amino acids, phosphate, and lactate follow by passive mechanisms. Glucose, amino acids, and lactate are usually completely removed from the tubular fluid in the first half of the proximal tubule by this mechanism. About 80% of the filtered bicarbonate is reabsorbed in the proximal tubule utilizing a Na^+/H^+- antiporter. Hydrogen ion is secreted into the lumen in exchange for bicarbonate ions. The remainder of the proximal tubule is involved primarily in the reabsorption of sodium chloride. Chloride ion concentration is high in this region because most bicarbonate, glucose, and organic anions have been preferentially reabsorbed proximally, resulting in an enriched chloride ion solution in the distal half of the proximal tubule. Here sodium is reabsorbed with chloride by parallel Na^+-H^+ and Cl^--base- antiporter transmembrane proteins within the apical plasmalemma that also is dependent on the Na^+/K^+-ATPase enzyme system of the basolateral membranes. Sodium and chloride ions in this portion of the proximal convoluted tubule also are reabsorbed following a paracellular route between neighboring epithelial cells. Other inorganic ions (50% of potassium, 65% of ionized calcium, 15% of magnesium, 85% phosphate), urea, uric acid and water-soluble vitamins (vitamin C and vitamin B complexes) also are absorbed by the proximal convoluted tubule. In addition to absorption, the proximal tubule secretes organic cations (creatine, dopamine, acetylcholine, and epinephrine) and anions (bile salts, fatty acids, urate, and para-aminohippurate) that are destined to be eliminated in the urine. Hence, this region of the nephron serves as an exocrine gland. The proximal tubule is a major site of ammonia production in the nephron as component cells metabolize glutamine. Parathyroid hormone acts to decrease phosphate resorption in the proximal convoluted tubule. Angiotensin II acts to stimulate the sodium-hydrogen antiporter, which increases hydrogen ion secretion and in addition promotes sodium, chloride, and water reabsorption.

Thin Segment

The simple cuboidal epithelium of the straight descending part of the proximal tubule (the initial segment of the loop of Henle) changes abruptly in the thin segment to an attenuated simple squamous epithelium. The luminal diameter of the nephron also decreases markedly, from 65 μm in the descending proximal tubule to about 20 μm in the thin segment. The thin segment is confined largely to the medulla of the kidney and forms the thin limb of the loop of Henle. The nuclei of the lining epithelial cells are centrally placed and cause this area of the cell to bulge into the lumen of the tubule. At the luminal surface, the brush border of the proximal tubule is replaced by short, scattered microvilli. Ultrastructurally, the cytoplasm shows fewer organelles; the lateral cell membranes have elaborate folds that interdigitate with those of adjacent cells. The cells are united at their apices by typical junctional complexes. The lateral interdigitations are less well developed near the hairpin loops. The cells rest on a relatively smooth basal lamina of moderate thickness. The length of the thin segment varies with each nephron and depends on the position of the parent renal corpuscle in the cortex. Thin segments are short or even absent from nephrons whose renal corpuscle is located near the capsule and are longest

when the renal corpuscle is located near the medulla. In these nephrons, the thin segments may extend almost to the tip of a renal papilla.

Distal Tubule

The distal tubule is divided into a straight part (pars recta), a portion that contains the macula densa (pars maculata), and a convoluted portion (pars convoluta). The straight portion of the distal tubule begins as a gradual transition from the thin segment of the nephron. The epithelium becomes cuboidal, and while a few microvilli are present, the cells lack the brush border and apical canaliculi of the proximal tubule. Interdigitating processes are present along the basolateral surfaces of the cells, and these contain numerous mitochondria. The straight part of the distal tubule constitutes the thick ascending limb of the loop of Henle and completes the looping course of this structure as it ascends through the medulla. It then re-enters the cortex to return to the parent renal corpuscle. The thick ascending limb reabsorbs about 25% of the filtered load. Reabsorption of sodium, chloride, and potassium at this location is driven by a Na^+-K^+-$2Cl^-$ symporter located in the apical plasmalemma. Sodium chloride reabsorption by cells of the thick ascending limb relies on the Na^+/K^+-ATPase enzyme system confined to the basolateral cell membrane as well as a kidney specific basolateral cell membrane chloride channel. Thus, movement of sodium across the apical cell membrane and into the cell is controlled by the transmembrane protein (symporter) that couples the movement of sodium, chloride, and potassium ions. A specific ROMK channel (an inwardly-rectifying renal potassium channel) also located within the luminal plasmalemma of cells forming the thick ascending limb recycles potassium ion back into the tubular fluid. This is necessary in order to permit sustained Na^+-K^+-$2Cl^-$ cotransport activity in cells forming the thick ascending limb of the loop of Henle. A positive membrane potential (luminal voltage) is generated and maintained by the Na^+-K^+-$2Cl^-$ cotransporter and the ROMK channel. This established positive transepithelial voltage plays an important role in the paracellular movement of cations (Na^+, K^+, Ca^{++}, Mg^{++}) from the lumen of this region of the nephron. About 15% of the remaining bicarbonate is reabsorbed at this location, as is 25% of ionized calcium, 15% of sodium, 30% of potassium, and about 70% of the magnesium from the remaining filtrate.

As it reaches the renal corpuscle, the distal tubule establishes a close relationship with the afferent arteriole, and where it contacts the arteriole, the tubule contains a group of specialized cells that form the macula densa (dense spot). This segment of the distal tube is called the pars maculata. The cells are taller and narrower than those in adjacent areas so that their nuclei are closer together, more prominent and lie just beneath the apical cell membrane. Cells of the macula densa are polarized toward the basal surface, that is, the Golgi membranes and occasional granules are found basal to the nucleus, facing the basal cell membrane. The macula densa is related to a modified region of the afferent arteriole that contains the juxtaglomerular cells and is considered to represent an endocrine portion of the kidney. This feature and the polarization of the cell suggests that the macula densa monitors the luminal fluid in the distal tubule. Cells of the macula densa also are known to produce the enzyme nitric oxide synthase. The nitric oxide released by the macula densa is thought to control vascular tone of the afferent and/or efferent arterioles, thereby influencing kidney function.

The macula densa marks the division between the ascending and convoluted portion of the distal tubule. The convoluted portion runs a tortuous course in the cortex near the renal corpuscle of its origin. The distal convoluted tubule is shorter than the proximal convoluted tubule, so fewer sections of the distal tubule are seen in histologic preparations. The lumen of the distal tubule generally is wider than that of the proximal tubules, the cells are shorter and

lighter staining, and nuclear profiles usually are seen in each cell, partly because many are binucleate. A brush border is lacking. Electron micrographs show deep, elaborate infoldings of the basolateral cell membrane associated with numerous elongated mitochondria that lie parallel to the long axis of the cell, producing the prominent basal striations of light microscopy. The cells of the distal tubules show a few luminal microvilli. The distal tubule is the site for further absorption of sodium chloride utilizing an apical thiazide sensitive sodium-chloride transporter. This transporter is driven by low intracellular sodium and chloride concentrations created by Na^+/K^+ ATPase and a basolateral cell membrane chloride channel protein. Between 5 and 10% of the remaining filtered magnesium also is absorbed in the distal convoluted tubule utilizing a luminal magnesium channel and a basolateral cell membrane sodium-magnesium exchanger. Aldosterone acts on sodium channels to stimulate sodium reabsorption and on potassium channels in cells of the distal tubule to stimulate potassium secretion. About 90% the bicarbonate in the glomerular filtrate has already been absorbed in the proximal tubule and loop of Henle. The distal tubule also is the site where ammonia is converted to ammonium ion. Thus, this segment of the nephron plays an important role in maintaining the acid-base balance of the body. Parathyroid hormone stimulates calcium ion reabsorption in cells forming the initial portion of the distal tubule. The last portion of the distal tubule can become permeable to water under the influence of antidiuretic hormone (ADH).

Loop of Henle

The loop of Henle is interposed between the proximal and distal convoluted tubules and consists of the straight portion of the proximal tubule, the thin segment, and the straight portion of the distal tubule. The loops descend in the medulla for variable distances, form hairpin loops, and then ascend through the medulla, parallel to the descending limb, to the cortex. The loop of Henle is essential for the production of hypertonic urine and is important in the conservation of body water. The loop consists of parallel limbs with tubular fluid flowing in opposite directions that act as a countercurrent multiplier system to aid in the concentration of urine. The descending thin segment is highly permeable to water but much less so to sodium and chloride ions and urea. In contrast, the ascending thin segment is impermeable to water but permeable to sodium chloride, which diffuses out of the tubule and contributes to the high osmolarity of the surrounding interstitium of the inner medulla in a passive fashion. Some ions diffuse back into the lumen of the adjacent descending limb. Cells comprising the thick ascending limb (straight portion of the distal tubule) of the loop of Henle also are impermeable to water but actively transport sodium and chloride ions out of the tubule. Such activity results in a dilute tubular fluid and contributes to an increasing hyperosmotic interstitium. Urea follows a route similar to that of these ions and makes a significant contribution to the hyperosmolarity of the interstitium. Thus, sodium and chloride ions, as well as urea, are trapped in the interstitial substance of the medulla, resulting in an increase in the osmotic concentration around the tubules in the medulla. All three passively diffuse into the descending limb but either diffuse or are actively pumped out again by the ascending limb as the cycle repeats itself over and over. The sodium chloride-urea trap thus formed establishes an osmotic gradient that increases in strength toward the renal papillae. This gradient is important for the conservation of water and formation of hypertonic urine by the terminal portion of the distal tubule and the collecting ducts.

Collecting Ducts

The collecting ducts can be subdivided according to their location in the kidney. The initial segment is found in the cortex and includes short connecting portions that unite the distal tubules of cortical nephrons to collecting ducts and arched portions that are formed by the confluence of several connecting portions from juxtamedullary nephrons. The arched portions originate deep in the cortex, which they ascend through before arching to descend within a medullary ray.

Medullary collecting ducts occur primarily in the medulla. As the ducts pass through the medulla they converge to form larger, straight collecting ducts called papillary ducts, which end at the tip of a renal papilla. The numerous openings of the papillary ducts give a sieve like appearance to the external surface of the papillae; this area has been called the area cribrosa. The external surfaces of the papillae are covered by transitional epithelium. The lining epithelium of the collecting ducts consists of principal and intercalated cells. Similar-appearing cells also are found in the last segment of the distal tubule. The principal (light) cells generally are cuboidal with centrally placed, round nuclei and lightly staining cytoplasm with characteristic, distinct cell boundaries. Ultrastructurally, the light cells show scattered, short microvilli on their apical surfaces, scattered mitochondria, and some infolding of the basal plasmalemma. They also possess a single, centrally located cilium. Principal cells reabsorb sodium and water and secrete potassium ions. The activity of this cell type is dramatically influenced by antidiuretic hormone (ADH) in fluid/volume homeostasis. In the absence of ADH the apical plasmalemma is impermeable to water and urea. In contrast, the basolateral plasmalemma is freely permeable to both. An ADH receptor (an integral membrane glycoprotein), a stimulatory G-protein and a membrane-bound adenylate cyclase are present within the basolateral plasmalemma. In the presence of ADH, cytoplasmic vesicles containing aquaporin-2 channels for water and vesicles containing channels for urea are inserted into the luminal plasmalemma of these cells making the collecting tubule permeable to both water and urea. Thus, urea reabsorbed proximally in the proximal tubule or entering the descending limb of the thin segment can be recycled back into the renal interstitium from the collecting tubule by this mechanism.

Scattered between the light cells are the intercalated (dark) cells, which have more mitochondria, stain more deeply, and show a large number of vesicles in the apical cytoplasm. The cells lack central cilia, but the apical plasmalemma shows microplicae. Some intercalated cells (cells) secrete hydrogen ions in exchange for potassium ions using an H^+/K^+-ATPase located in the apical plasmalemma. For each hydrogen ion secreted into the tubular lumen, a bicarbonate ion is released from the basolateral cell membrane using a $Cl^-/HCO3^-$ antiporter. Thus, intercalated cells secrete H^+ and reabsorb $HCO3^-$and K^+ and therefore play an important role in regulating acid-base balance. A small population of intercalated cells (cells) have been observed that function opposite the α form and secrete potassium ion. As the collecting tubules pass through the medulla, the cells increase in height to become tall columnar in the papillary ducts.

The mechanism of ammonia excretion is complex and follows a circuitous route to be excreted indirectly. Glutamine is metabolized to ammonia (NH3) and -ketoglutarate by cells forming the proximal convoluted tubule. The NH3 is converted to ammonium ($NH4^+$) intracellularly and is transported into the tubular lumen utilizing the Na^+-H^+ exchanger in which $NH4^+$ substitutes for H^+. As the luminal fluid reaches the thick ascending limb much of the $NH4^+$ is reabsorbed by the Na^+-K^+-$2CL^-$ cotransporter in which case $NH4^+$ is substituted for K^+. Within the surrounding medullary interstitium $NH4^+$ as well as NH3 contributes to the osmotic gradient maintained by

high concentrations of sodium, chloride, and urea. The collecting duct, which passes back through the interstitium, contains α-intercalated cells that contain two hydrogen transporters (H^+-ATPase and H^+-K^+-ATPase) located in the luminal plasmalemma. As hydrogen ion is secreted into the tubular fluid the lipid soluble NH_3 passes through cells of the collecting duct to enter the tubular fluid. Here the NH_3 combines with secreted hydrogen ion to form the water-soluble NH_4^+ thereby effectively "trapping" the hydrogen ion for excretion in the urine. The amount of ammonia (hydrogen ion) secreted is dependent largely on the acid/base status of the extracellular fluids. The collecting ducts function to conserve water and produce hypertonic urine. As the ducts traverse the medulla to the tips of the pyramids, they pass through the increasingly hypertonic environment established by the loop of Henle. The permeability of the collecting ducts to water is controlled by ADH. In the presence of ADH, water is drawn from the collecting ducts by osmosis because of the hypertonic environment maintained in the medullary interstitium. The loss of water from the tubular contents results in a concentrated, hypertonic urine. If ADH is lacking due to injury or disease, the kidney is unable to concentrate urine, and copious amounts of dilute urine are produced, resulting in severe dehydration. This condition is known as diabetes insipidus.

The renal interstitium fills the spaces between the tubular elements of the kidney. The cortical interstitium is relatively scant except around blood vessels and consists of fine bundles of collagen, fibroblasts, and scattered phagocytes. The medullary interstitium is more plentiful, and its cells lie parallel to the long axis of the tubules. These interstitial cells possess long, branching processes that encircle adjacent tubules and blood vessels. Pleomorphic interstitial cells filled with small lipid droplets also occur in the medullary interstitium at regular intervals between the epithelial tubules and vessels. The cells are suspected to be endocrine cells and may secrete an antihypertension factor. The medullary interstitium contains an abundant intercellular ground substance and small groups of collagen fibers.

Juxtaglomerular Apparatus

The juxtaglomerular apparatus consists of the macula densa of the distal tubule, the extraglomerular mesangium, and the juxtaglomerular cells in the wall of the afferent arteriole. The extraglomerular mesangium forms a loose mass of cells between the afferent and efferent arterioles. Component (Lacis) cells may contain granules but their precise role in the function of the juxtaglomerular apparatus is unclear. The juxtaglomerular (JG) cells appear to be highly modified smooth muscle cells in the wall of the afferent arteriole as it enters the renal corpuscle. The cells contain a number of secretory granules, well-developed Golgi complexes, and abundant granular endoplasmic reticulum. The JG cells produce renin (a proteolytic enzyme), which, when released into blood, converts a plasma protein angiotensinogen (a 2-globulin from the liver) to angiotensin I. A converting enzyme in the blood (derived from endothelial cells lining capillaries of the lung) converts angiotensin I to the polypeptide angiotensin II, which acts on the zona glomerulosa of the adrenal cortex, and stimulates the release aldosterone. Aldosterone secretion increases sodium ion absorption from the fluid within the terminal portion of the distal tubule and the cortical collecting ducts to the blood and increases movement of potassium ion from the blood to the tubular fluid. Angiotensin II also is a potent vasoconstrictor and elevates blood pressure. Within the kidney it acts a vasoconstrictor of the afferent and efferent arterioles and causes the contraction of mesangial cells. In addition, the juxtaglomerular apparatus has been implicated in the production of erythropoietin, an agent that stimulates erythropoiesis in the bone marrow. The location of the macula densa, its basal polarization, and its orientation toward adjacent JG cells suggest that

the three groups of cells may interact. The macular densa may "sense" the ion (Na^+, K^+, Cl^-) concentration in the distal tubule and thereby influence the activity of JG cells. The tubuloglomerular feedback mechanism proposed suggests a concentration-dependent uptake of Na^+, K^+, and Cl^- by a Na^+-K^+-$2Cl^-$ cotransporter located in the apical plasmalemma of macula densa cells. The result of this activity is the generation of adenosine that activates an adenosine A1 receptor in the plasmalemma of extraglomerular mesangial cells. The activation of this receptor triggers an increase in cytoplasmic calcium the resulting action potential of which is transmitted to the afferent arteriole by gap junctions resulting in vasoconstriction and inhibition of renin secretion. Local angiotensin II, prostaglandins, and nitric oxide modulate this activity. The juxtaglomerular cells also act as baroreceptors and can function independently in the release renin. Stimulation of renal sympathetic nerves results in the release of norepinephrine, which also causes renin release.

Vascular Supply

The vascular pattern of the kidneys is complex and shows regional specializations related to the organization and function of the various parts of the nephron. About 20% of the cardiac output goes to the kidneys. The renal arteries arise from the abdominal aorta and before reaching the renal sinus usually divide into branches that pass anterior and posterior to the renal pelvis to enter the renal sinus. Here they give rise to segmental arteries, which also divide to form interlobar arteries that run between renal lobes. At the cortico medullary junction, these arteries divide into several arcuate arteries that arch across the base of each medullary pyramid and give off interlobular arteries that pass into the cortex between lobules. The interlobular arteries run peripherally in the cortex, giving rise to a system of intralobular arteries that enter renal lobules and provide afferent arterioles, which supply the glomeruli of renal corpuscles. As the efferent arteriole leaves the renal corpuscle of a cortical nephron, it immediately breaks up into a peritubular capillary network that supplies the convoluted tubules. The main circulation of the renal cortex is unique in that the arterioles give rise to two distinct, sequential capillary beds: the glomerular and peritubular capillaries. Efferent arterioles from juxtamedullary nephrons, on the other hand, form several long, straight vessels, the vasa recta, that descend into the medullary pyramid and form hairpin loops. Like the loop of Henle, the loops of the vasa recta are staggered throughout the medulla. The walls of the vasa recta are thin, and the endothelium of the ascending (venous) limb is fenestrated. The vasa recta pass in close proximity to the loop of Henle, permitting passive interchange between the two elements. The vasa recta form a vascular countercurrent exchange system that removes excess water and ions. The medullary osmotic gradient is not disrupted due to the slower flow rate and the smaller volume (about 8% of the total renal blood flow) in the vasa recta and because the vasa recta also form hairpin loops in which the blood flows down the descending side of the loop and then back up the ascending side of the loop. In addition to making the collecting tubules more permeable to water, the presence of ADH results in vasoconstriction of the vessels forming the vasa recta thereby reducing the flow rate even further and protecting the established interstitial osmotic gradient from being disrupted. The venous drainage of the kidney is similar to and follows the same course as the arterial supply. However, there is no venous equivalent of the glomerulus or the afferent and efferent arterioles. The venous system of the medulla begins in the ascending limb of the vasa recta, which drains into interlobular or arcuate veins. In the peripheral cortex, capillaries unite to form small veins that assume a star-like pattern (stellate veins) as they drain into interlobular veins. The renal veins drain into the

inferior vena cava. The left renal vein differs in that it is much longer and receives venous drainage from the left gonad.