

Kidney Structure and Function.

Learning Objectives.

At the end of this section, you should be able to :

- 1. describe the structure of the kidney;**
- 2. understand the vascular organisation of the kidneys;**
- 3. describe how filtration occurs in Bowman's capsule;**
- 4. understand the role of the nephron in the production of urine;**
- 5. appreciate the hormonal control of urine production;**
- 6. appreciate the role of the kidney homeostasis and blood pressure maintenance;**
- 7. understand the concept of 'clearance'.**

The kidneys can suffer extensive damage and still maintain their extremely important role in the maintenance of homeostasis. As long as about one third of one kidney remains functional, survival is possible. If the kidneys stop functioning completely death will result without medical intervention.

The role the kidneys play in controlling the composition and volume of body fluids is essential, the kidneys being the major excretory organs of the body. They remove most waste products from the blood, and play a major role in controlling blood volume and pressure, the concentration of ions in the blood, pH of the blood, red blood cell production, and vitamin D metabolism. The skin, liver, lungs, and intestines eliminate some waste products, but if the kidneys fail to function, other excretory organs cannot adequately compensate.

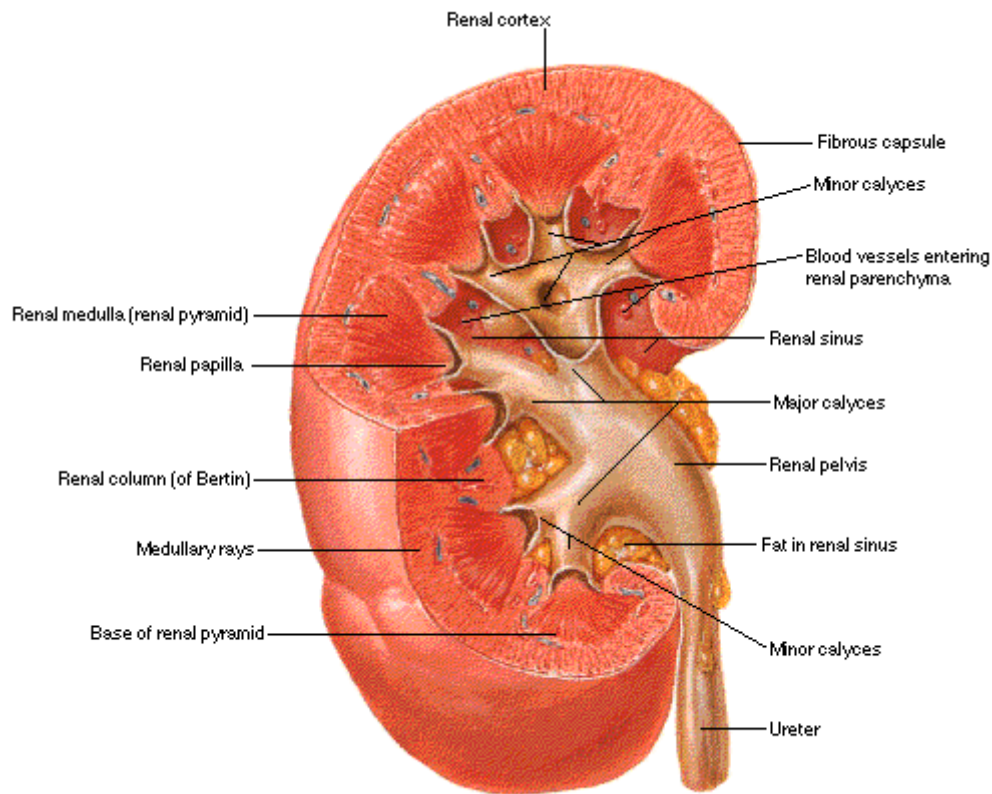
The urinary system consists of two kidneys; a single, midline urinary bladder; two ureters, which carry urine from the kidneys to the urinary bladder; and a single urethra, which carries urine from the bladder to the outside of the body.

The Kidneys

The kidneys are bean-shaped organs, each about the size of a tightly clenched fist. They lie on the posterior abdominal wall behind the peritoneum and on either side of the vertebral column near the lateral borders of the psoas muscles. The superior pole (top) of each kidney is protected by the rib cage, and the right kidney is slightly lower than the left because of the presence of the liver above it. Each kidney measures about 11 cm long, 5 cm wide, 3 cm thick and weighs about 130 g. A fibrous connective tissue layer, called the renal capsule, encloses each kidney, and around the renal capsule is a dense deposit of adipose tissue, the renal fat pad, which protects the kidney from mechanical shock. The kidneys and surrounding adipose tissue are anchored to the abdominal wall by a thin band of connective tissue, the renal fascia.

On the medial side of each kidney is a small area called the hilum where the renal artery and nerves enter and the renal vein and ureter exit. The hilum opens into a cavity called the renal sinus, which contains fat and connective tissue.

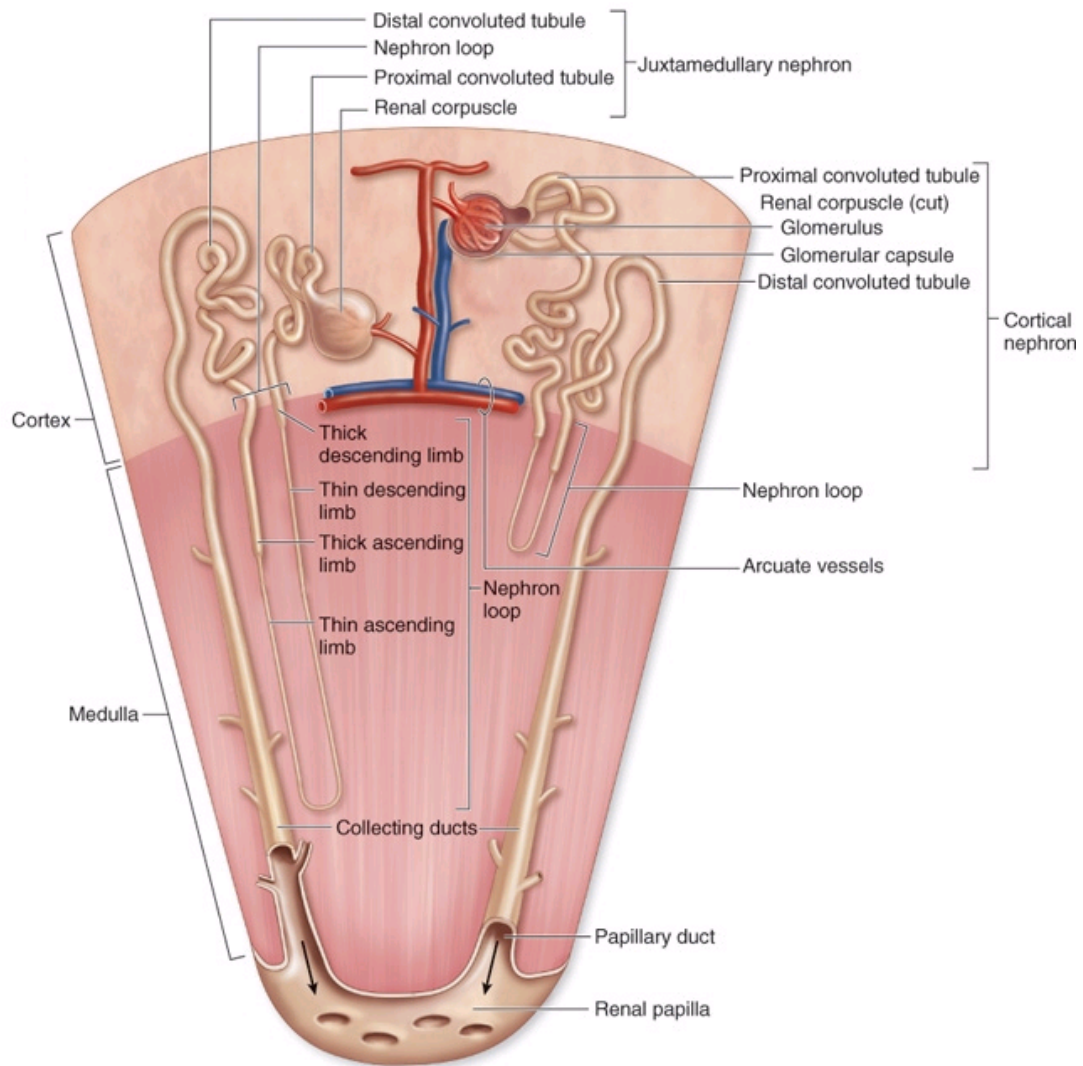
The kidney is divided into an outer cortex and an inner medulla that surrounds the renal sinus. The medulla consists of a number of cone-shaped renal pyramids, which appear triangular when seen in a longitudinal section of the kidney. Extensions of the pyramids, called medullary rays, project from the pyramids into the cortex, and extensions of the cortex, called renal columns, project between the pyramids. The base of each pyramid is located at the boundary between the cortex and the medulla, and the tips of the pyramids, the renal papillae, are pointed toward the centre of the kidney.



Funnel-shaped structures called minor calyces surround the renal papillae. Minor calyces from several pyramids join together to form larger funnels called major calyces. There are 8-20 minor calyces and 2 or 3 major calyces per kidney. The major calyces converge to form an enlarged channel called the pelvis, which is located in the renal sinus. The renal pelvis then narrows to form a small-diameter tube, the ureter, which exits the kidney and connects to the urinary bladder. Urine formed within the kidneys passes through the renal papillae into the minor calyces. From the calyces, urine moves into the major calyces, collects in the renal pelvis, and exits the kidney through the ureter.

The basic histologic and functional unit of the kidney is the nephron, which consists of an enlarged terminal end called the renal corpuscle, a proximal tubule, a loop of Henle (nephric loop), and a distal tubule. The distal tubule empties into a collecting

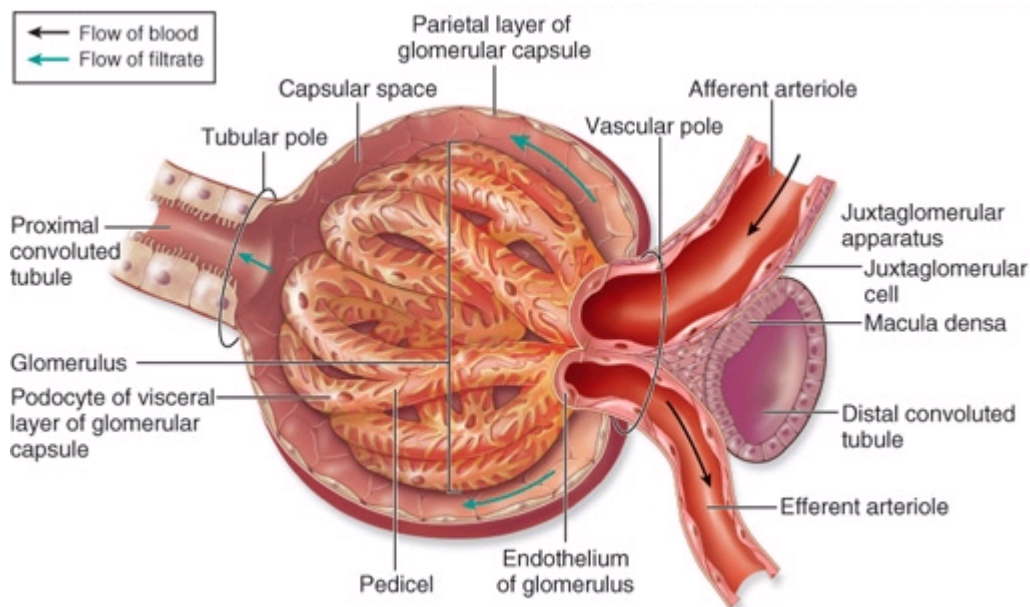
duct, which carries the urine from the cortex of the kidney to the calyces. The renal corpuscles, proximal tubules, and distal tubules are in the renal cortex. The collecting tubules and parts of the loops of Henle enter the renal medulla.



There are approximately 1,300,000 nephrons in each kidney, and one third of them must be functional to survive. Most nephrons measure 50-55 mm in length, although the nephrons with renal corpuscles located within cortex near the medulla are longer than those in cortex nearer to the exterior of the kidney. Nephrons whose renal corpuscles lie near the medulla are called juxta-medullary nephrons and make up about 15% of all nephrons. The juxta-medullary nephrons have longer loops Henle,

which extend farther into the medulla than the loops of Henle of nephrons whose renal corpuscles originate in the superficial cortex.

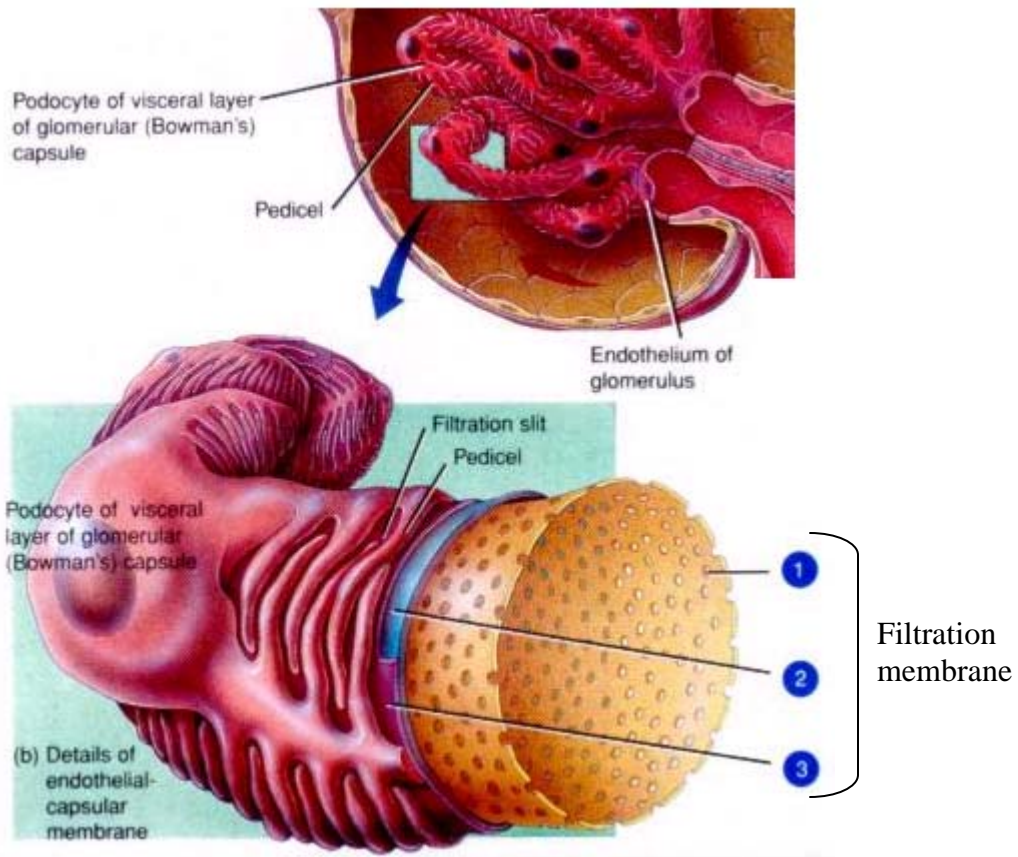
Each renal corpuscle consists of the enlarged end of a nephron called Bowman's capsule and a network of capillaries called the glomerulus. The wall of Bowman's capsule is indented to form a double-walled chamber, and the indentation is occupied by the glomerulus, which is said to resemble a ball of string. Fluid passes from the glomerulus into Bowman's capsule.



The cavity of Bowman's capsule opens into the proximal tubule, which carries fluid away from the Bowman's capsule. The outer, parietal layer of Bowman's capsule is composed of simple squamous epithelium which becomes cuboidal at the beginning of the proximal tubule. Surrounding the glomerulus is the inner layer of Bowman's capsule, called the visceral layer, and consists of specialised cells called podocytes.

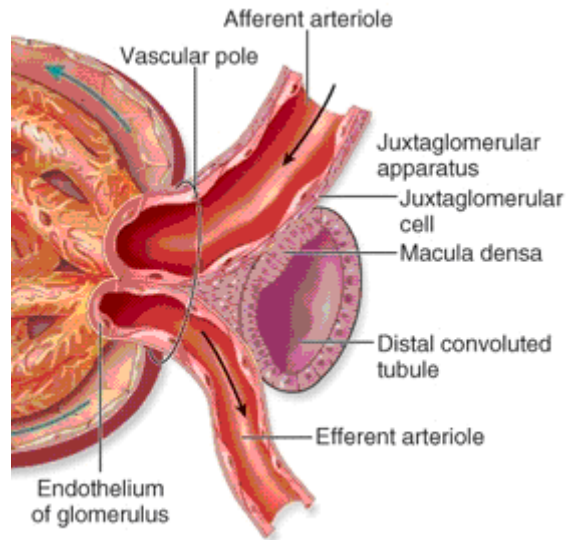
The walls of the glomerular capillaries are lined with endothelial cells that have openings called fenestrae. The visceral layer of Bowman's capsule surrounds the

glomerular capillaries with gaps called filtration slits between the podocyte processes surrounding the capillaries. There is a basement membrane between the endothelial cells of the glomerular capillaries and the podocytes of Bowman's capsule. The capillary endothelium, the basement membrane, and the podocytes of Bowman's capsule make up the filtration membrane. In the first step of urine formation, fluid passes from the glomerular capillaries into the lumen of Bowman's capsule across this filtration membrane.



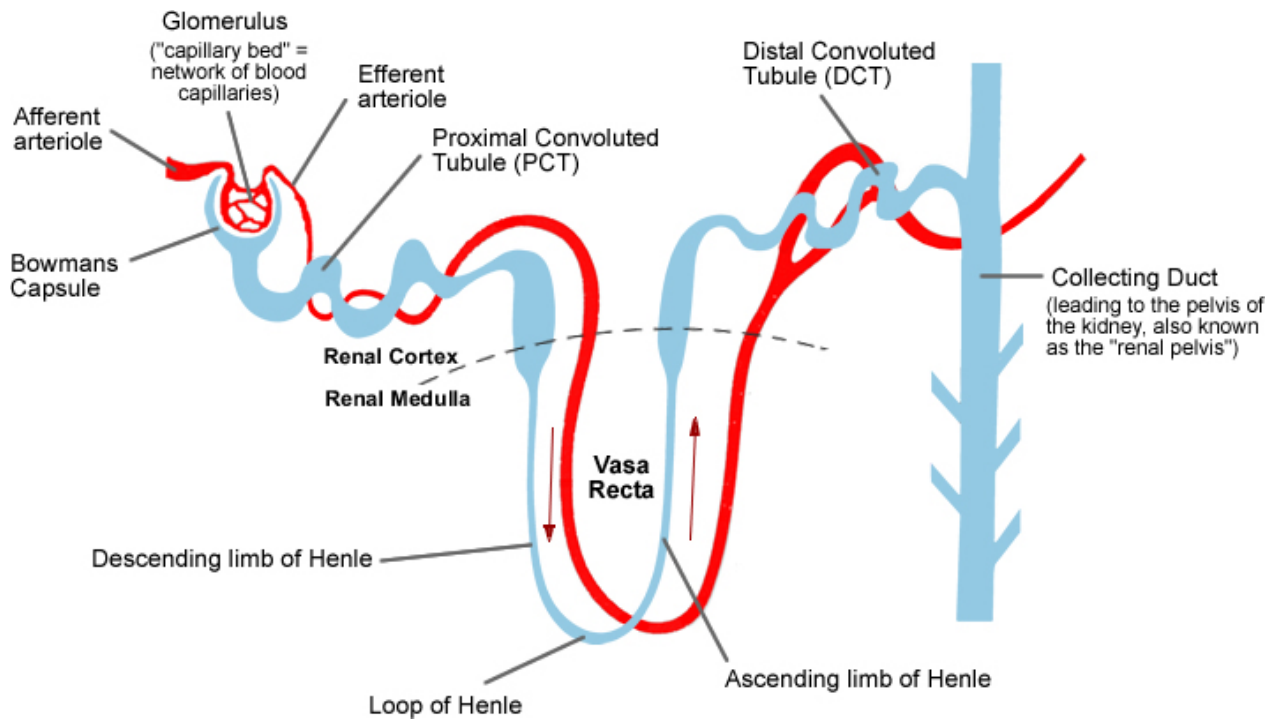
The glomerulus is supplied by an afferent arteriole and is drained by an efferent arteriole. These arterioles both have a layer of smooth muscle. At the point where the afferent arteriole enters the renal corpuscle, the smooth muscle cells are modified to form cuff around the arteriole. These modified cells are called juxta-glomerular cells. A part of the distal tubule of the nephron lies adjacent to the renal corpuscle between the afferent and efferent arterioles. The specialised tubule cells in this area are

collectively called the macula densa. The juxta-glomerular cells of the afferent arteriole and macula densa cells are in intimate contact with one another, and together they are called the juxta-glomerular apparatus.

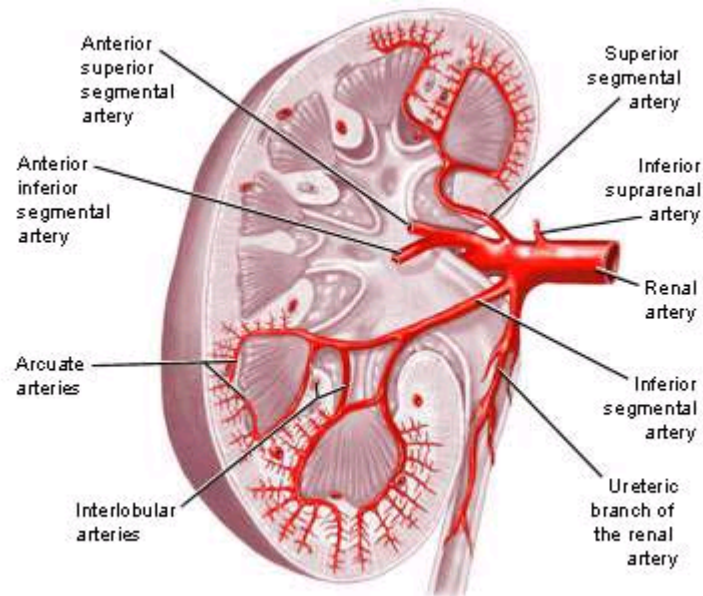


The proximal convoluted tubule is around 14mm in length, and its walls are composed of simple cuboidal epithelium. The cells are broader at the base, and have microvilli on the surface which projects into the lumen.

The loops of Henle are continuations with the proximal tubule, with each loop having a descending and ascending limb. The first section of the descending limb is similar in structure to the proximal tubule. The loops of Henle that extend into the medulla become very thin near to the end of the loop, and the lumen is narrowed. As the loop begins to ascend, the lumen is still narrow, but soon becomes wider as it ascends further. The thick part of the loop returns towards the renal corpuscle and ends by giving rise to the distal tubule near to the macula densa. The distal tubules are not as long as the proximal tubules. The distal tubules drain into the collecting ducts, which form much of the medullary rays. They extend through the medulla to the tips of the renal pyramids.

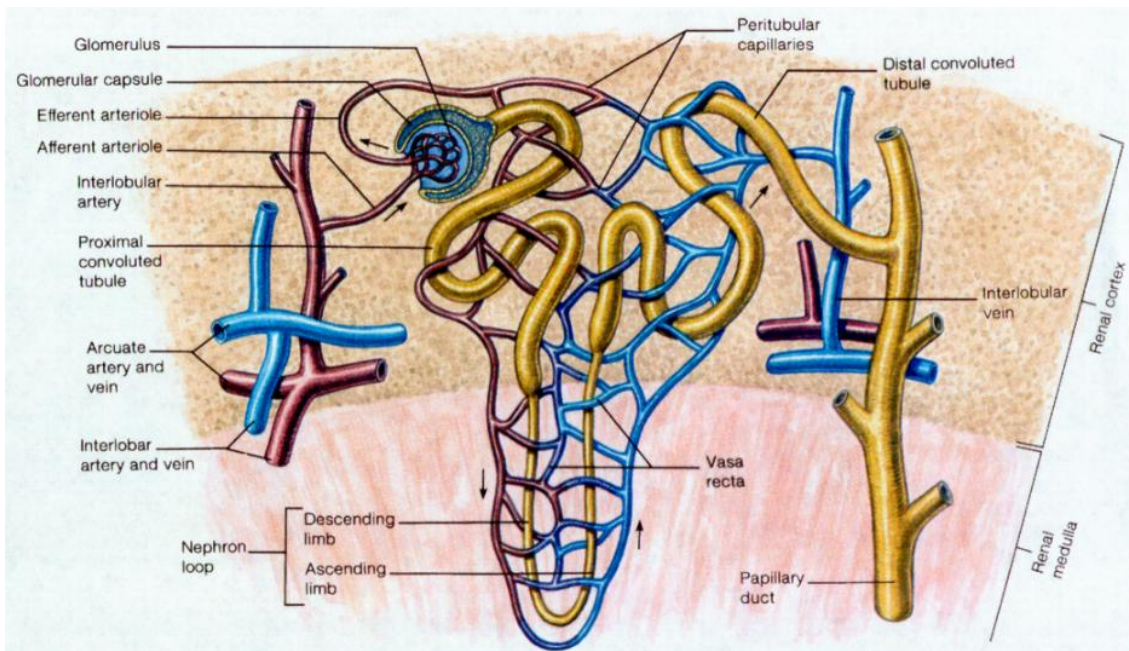


Arteries and Veins of the Kidneys



A renal artery branches off the abdominal aorta and enters the renal sinus of each kidney. Segmental arteries diverge from the renal artery to form interlobar arteries, which ascend within the renal columns toward the renal cortex. Branches from the interlobar arteries diverge near the base of each pyramid and arch over the base of the pyramids to form the arcuate arteries. Interlobular arteries project from the arcuate arteries into the cortex, and the afferent arterioles are derived from the interlobar arteries or their branches. The afferent arterioles supply blood to the glomerular capillaries of the renal corpuscles.

Efferent arterioles arise from the glomerular capillaries and transport blood away from the glomeruli. After each efferent artery exits the glomerulus, it gives rise to a plexus of capillaries called the peritubular capillaries around the proximal distal tubules. Specialised parts of the peritubular capillaries, called vasa recta, pass into the medulla with the loops of Henle and then back towards the cortex. The peritubular capillaries drain into interlobular veins, which in turn drain into the arcuate veins. The arcuate veins empty into the interlobar veins, which drain into the renal vein. The renal vein exits the kidney and connects to the inferior vena cava.



Ureters and Urinary Bladder

The ureters extend inferiorly and medially from the renal pelvis at the renal hilum to reach the urinary bladder, which stores urine. The urinary bladder is a hollow muscular container that lies in the pelvic cavity just posterior to the symphysis pubis. The size of the bladder depends on the presence or absence of urine. The ureters enter the bladder inferiorly on its postero-lateral surface, and the urethra exits the bladder inferiorly and anteriorly.

At the junction of the urethra with the urinary bladder, smooth muscle of the bladder forms the internal urinary sphincter. The external urinary sphincter is skeletal muscle that surrounds the urethra as the urethra extends through the pelvic floor. The sphincters control the flow of urine through the urethra.

KEY LEARNING POINTS.



- 1. The kidneys play a major role in excretion, and also in controlling the composition and volume of body fluids.**
- 2. The functional unit of the kidney is the nephron.**
- 3. Nephrons are made up of the renal corpuscle, the proximal convoluted tubule, the loop of Henle, the distal convoluted tubule, and the collecting duct.**
- 4. The renal corpuscle contains Bowman's capsule, and this is where filtrate is produced.**
- 5. The filtration unit is made up of the wall of a glomerular capillary, the visceral layer of Bowman's capsule, and podocytes.**
- 6. The kidneys are supplied with blood by branches from the abdominal aorta, forming the renal artery.**

Urine Production

(hint – you might find it easier to follow the whole process if you print off a large copy of the diagram of the nephron from page 9, and refer to this as you work through this section)

Urine formation results from the following three processes:

1. **Filtration** a. Filtration is the movement of materials across the filtration membrane into the lumen of Bowman's capsule to form filtrate.

2. **Reabsorption** b. Solutes are reabsorbed across the wall of the nephron by transport processes, such as active transport and co-transport.

 c. Water is reabsorbed across the wall of the nephron by osmosis.

3. **Secretion** d. Solutes are secreted across the wall of the nephron into the filtrate.

Filtration, reabsorption, and secretion are the three major processes critical to the formation of urine. Filtration is movement of fluid across the filtration membrane as a result of a pressure difference. The fluid entering the nephron becomes the filtrate. Reabsorption is the movement of substances from the filtrate back into the blood. In general, most of the water and useful solutes are reabsorbed, but waste products and other substances in the filtrate are not. Secretion is the active transport of substances into the nephron. Urine produced by the nephrons consists of the substances filtered and secreted into the nephron minus those substances that are reabsorbed.

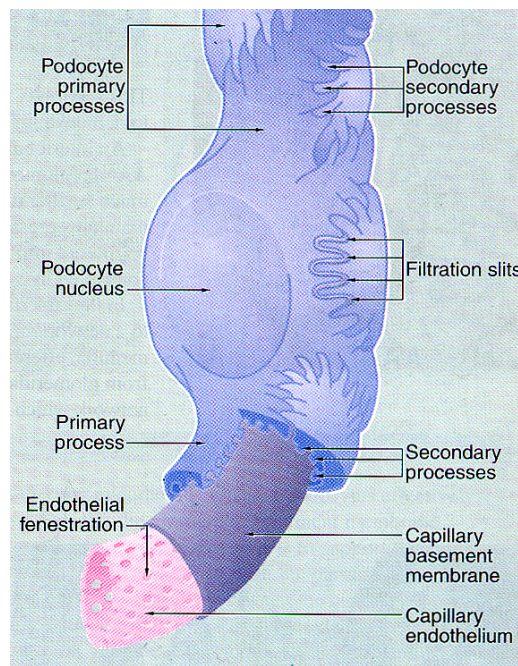
Filtration

The part of the total cardiac output that passes through the kidneys is called the renal fraction, which varies from 12% to 30% of the cardiac output in healthy resting

adults, although it averages 21% to produce a renal blood flow rate of 1176 mL/min. The plasma that flows through the kidneys each minute, called the renal plasma flow rate, is equal to the renal blood flow rate multiplied by the portion of the blood that is made up of plasma (approximately 55%) therefore $1176 \text{ mL/min} \times 0.55 = 646.8 \text{ mL plasma/minute}$.

The part of the plasma flowing through the kidney that is filtered through the filtration membranes into lumen of Bowman's capsules to become filtrate is called filtration fraction. The filtration fraction averages 19% of the plasma flowing through the kidney ($650 \text{ mL plasma/min} \times 0.19 = 123.5 \text{ mL plasma/min}$). Therefore, approximately 125 mL filtrate is produced each minute. The amount of filtrate produced each minute is called the glomerular filtration rate (GFR), which is equivalent to approximately about 180 litres of filtrate produced daily. Because only 1-2 litres of urine is produced each day by a healthy person, it is obvious that not all of the filtrate becomes urine. Approximately 99% of filtrate volume is reabsorbed in the nephron, and less than 1% is eliminated as urine.

Filtration Barrier



The filtration membrane is a filtration barrier that prevents the entry of blood cells and proteins into the lumen of Bowman's capsule but allows other blood components to enter. The filtration membrane is many times more permeable than a typical capillary. Water and solutes of a small molecule diameter readily pass from the glomerular capillaries through the filtration membrane into Bowman's capsule, whereas larger molecules cannot. The fenestrae of the glomerular capillary, the basement membrane, and the podocytes prevent molecules bigger than 7nm in diameter, or with a molecular mass of 40,000 daltons, passing through. Most plasma proteins are larger than 7nm and therefore they cannot pass through, and are retained in the glomerular capillaries. Albumin, which is slightly smaller than 7nm, enters the filtrate in small amounts so it is normal for the filtrate at this stage to contain small amounts of protein. Hormones are also small enough to pass through the barrier. Proteins like albumin that are small enough to pass through are reabsorbed by endocytosis in the proximal convoluted tubule, and therefore little protein is found in the urine of a healthy person.

Filtration Pressure

The formation of filtrate depends on a pressure gradient called the filtration pressure, which forces fluid from the glomerular capillary through the filtration membrane into the lumen of Bowman's capsule. The filtration pressure results from the sum of the forces that move fluid out of the glomerular capillary into the lumen of Bowman's capsule and those that move fluid out of the lumen of Bowman's capsule into the glomerular capillary. The glomerular capillary pressure (GCP), which is the blood pressure inside the capillary, moves fluid out of the capillary into Bowman's capsule. The glomerular capillary pressure averages approximately 45 mm Hg, which is much higher than that in most capillaries. Opposing the movement of fluid into the lumen of Bowman's capsule is the capsule pressure (CP), which is approximately 10 mm Hg, caused by the pressure of filtrate already inside Bowman's capsule. The colloid osmotic pressure (COP) resulting from the presence of unfiltered plasma proteins remaining within the glomerular capillary, produces an osmotic force of about 28

mm Hg, which also moves fluid to the glomerular capillary from Bowman's capsule. The filtration pressure is therefore around 7 mm Hg. This is calculated as follows:

$$\begin{aligned} \text{Filtration pressure} &= \text{glomerular capillary pressure} - \text{capsule pressure} - \text{colloid osmotic pressure} \\ 7 \text{ mm Hg} &= 45 \text{ mm Hg} - 10 \text{ mm Hg} - 28 \text{ mm P} \end{aligned}$$

The higher glomerular capillary pressure results from a low resistance to blood flow in the afferent arterioles and glomerular capillaries and from a higher resistance to flow in the efferent arterioles. As the diameter of a vessel decreases, resistance to flow through the vessel increases, and pressure upstream from the point of decreased vessel diameter is higher than the pressure down-stream from the point of decreased diameter. The efferent arteriole has a small diameter, and the blood pressure is higher within the glomerular capillaries because of the low resistance to blood flow in the afferent arterioles and glomerular capillaries, and also because of the higher resistance to blood flow in the efferent arteriole. Also the pressure is lower in the peritubular capillaries which are downstream from the efferent arterioles.

Consequently, filtrate is forced across the filtration membrane into the lumen of Bowman's capsule. The low pressure in the peritubular capillaries allows fluid to move into them from the interstitial fluid. The smooth muscle cells in the walls of the afferent and efferent arterioles can alter the vessel diameter and glomerular filtration pressure.

Tubular Reabsorption

The filtrate leaves the lumen of Bowman's capsule and flows through the proximal tubule, the loop of Henle, and the distal tubule, and then into the collecting ducts. As it passes through these structures, many of the substances in the filtrate undergo tubular reabsorption. Inorganic salts, organic molecules, and about 99% of the filtrate volume leave the nephron and enter the interstitial fluid. These substances then enter the low-pressure peritubular capillaries and flow through the renal veins to enter general circulation .

Solutes transported from the lumen of the nephron to the interstitial fluid include amino acids, glucose, and fructose, as well as sodium, potassium, calcium, bicarbonate, and chloride ions. These substances are transported across the epithelial cells of the nephron by a process called cotransport.

Water follows the solutes that are reabsorbed across the wall of the nephron. As the solutes in the nephron are reabsorbed, water follows the solutes by the process of osmosis. Variation in the transport processes in each portion of the nephron and variation in the permeability characteristics of each portion of the nephron allow 99% of the volume of the filtrate to be reabsorbed. The small volume of the filtrate that forms urine contains a relatively high concentration of urea, uric acid, creatinine, potassium ions, and other substances that are toxic in high concentrations. Regulation of solute reabsorption and the permeability characteristics of portions of the nephron allow the regulation of urine concentration so that a small volume of very concentrated urine or large volume of very dilute urine can be produced.

Transport in the Proximal Tubule

A process basic to all cotransport processes in the nephron is the active transport of sodium ions across the basal cell membrane, from the cytoplasm to the interstitial fluid, creating a low concentration of sodium inside the cells. At the basal cell membrane, ATP provides the energy required to transport sodium ions out of the cell in exchange for potassium ions. Because the concentration of sodium ions in the lumen of the tubule is high, there is a large concentration gradient from the lumen of the nephron to the intracellular fluid of the cells lining the nephron. This concentration gradient for sodium ions is the source of energy for the transport of other ions into the cell.

Within the apical membrane, which separates the lumen of the nephron from the cytoplasm of the nephron cells, there are carrier molecules for substances such as amino acids, glucose, phosphate, lactate, and chloride ions. Each of these carrier molecules binds specifically to one of the substances to be transported and to sodium

ions. The concentration gradient for sodium ions provides the source energy that moves both the sodium ions and the other molecule or ion bound to the carrier molecule from the lumen into the cell of the nephron. Once the cotransported molecules are inside of the cell, they cross the basal membrane of the cell by facilitated diffusion.

In the proximal tubule, amino acids, glucose, sodium ions, potassium ions, bicarbonate ions, and chloride ions are among the solutes transported across the wall of the nephron against their concentration gradients. The proximal tubule is permeable to water. As solute molecules are transported from the nephron to the interstitial fluid, water therefore moves by osmosis in the same direction. By the time the filtrate has reached the end of the proximal tubule, its volume has been reduced by approximately 65%. Because the wall of the nephron is permeable to water, the concentration of the filtrate in the proximal tubule remains about the same as that of the interstitial fluid.

Transport in the Loop of Henle

The loop of Henle descends into the medulla of the kidney where the concentration of solutes in the interstitial fluid is very high. The thin segment of the descending loop of Henle is highly permeable to water and moderately permeable to urea, sodium, and most other ions. It is adapted to allow passive movement of solutes through its wall, although water passes through much more rapidly than solutes. As the filtrate passes through the thin segment of the loop of Henle, water moves out of the nephron by osmosis, and some solutes move into the nephron. By the time the filtrate has reached the end of the thin segment of the loop of Henle, the volume of the filtrate has been reduced by another 15%, and the concentration of the filtrate is equal to the high concentration of the interstitial fluid (1200 mOsm/L).

NB - An osmole (Osm) is a measure of the number of particles in solution. One osmole is the molecular weight, in grams, of a solute divided by the number of ions or particles into which it dissociates in solution. A milliosmole (mOsm) is one one-thousandth of an osmole. The

osmolality of a solution is the number of osmoles in a kilogram of solution. Water moves by osmosis from a solution with a lower osmolality to a solution with a higher osmolality. Thus water moves by osmosis from a solution of 100 mOsm/kg toward a solution of 300 mOsm/kg .

The ascending limb of the loop of Henle is impermeable to water. Solute molecules such as sodium, potassium, and chloride ions, however, are transported from the nephron into the interstitial fluid. Cotransport is responsible for the movement of potassium and chloride ions with sodium ions across the apical membrane of the ascending limb of the loop of Henle.

Once inside the cells of the ascending limb, chloride and potassium ions diffuse across the cell membrane into the interstitial fluid from a higher concentration inside the cells to a lower concentration outside of the cells.

Because the ascending limb of the loop of Henle is impermeable to water and because ions are transported out of the nephron, the concentration of solutes in the tubule is reduced to about 100 mOsm/kg by the time the fluid reaches the distal tubule. In contrast, the concentration of the interstitial fluid in the cortex is about 300 mOsm/kg. Thus the filtrate entering the distal tubule is much more dilute than the interstitial fluid surrounding it.

Transport in the Distal Tubule and Collecting Duct

Sodium and chloride ions are actively transported across the wall of the distal tubules and collecting ducts. In addition, the collecting ducts extend from the cortex of the kidney where the concentration of the interstitial fluid is approximately 300 mOsm/kg through the medulla of the kidney where the concentration of the interstitial fluid is very high. The permeability of the distal tubules and collecting ducts to water is under hormonal control. Antidiuretic hormone (ADH) increases the permeability of the cell membranes to water, but the cell membranes are relatively impermeable to water in the absence of ADH. When ADH is present, water moves

by osmosis out of the distal tubule and collecting duct, whereas in the absence of ADH, water remains in the nephron.

In the proximal tubules, 65% of the filtrate volume is reabsorbed, and 15% of the filtrate volume is reabsorbed in the thin segment of the loops of Henle. About 80% of the volume of the filtrate is therefore reabsorbed in these structures. When ADH is present, another 19% is reabsorbed in the distal tubules and collecting ducts.

Changes in the Concentration of Solutes in the Nephron

Urea enters the glomerular filtrate and is present in the same concentration as it is in the plasma. As the volume of the filtrate decreases in the nephron, the concentration of urea increases because renal tubules are not as permeable to urea as they are to water. Only 40%-60% of the urea is passively reabsorbed in the nephron, although about 99% of the water is reabsorbed. In addition to urea, urate ions, creatinine, sulfates, phosphates, and nitrates are reabsorbed but not to the same extent as water. They therefore become more concentrated in the filtrate as the volume of the filtrate becomes smaller. These substances are toxic if they accumulate in the body, so their accumulation in the filtrate and elimination in urine help maintain homeostasis.

Some drugs, environmental pollutants, and other foreign substances that gain access to the circulatory system are reabsorbed from the nephron. These substances are usually lipid-soluble, non-polar compounds. They enter the glomerular filtrate and are reabsorbed passively by a process similar to that by which urea is reabsorbed. Because these substances are passively reabsorbed within the nephron, they are not rapidly excreted. The liver attaches other molecules to them by a process called conjugation, which converts them to more water-soluble molecules. These more water-soluble substances do not pass as readily through the wall of the nephron, are not reabsorbed from the renal tubules, and consequently are more rapidly excreted in the urine. One of the important functions of the liver is to convert non-polar toxic

substances to more water-soluble forms, thus increasing the rate at which they are excreted in the urine.

Tubular Secretion

Some substances, including by-products of metabolism that become toxic in high concentrations and drugs or molecules not normally produced by the body, are moved into the nephron by tubular secretion. As with tubular reabsorption, tubular secretion can be either active or passive.

KEY LEARNING POINTS.



- 1. Urine is formed via filtration, reabsorption, and secretion.**
- 2. The kidneys require on average 21% of cardiac output for normal function.**
- 3. The filtration barrier prevents the entry of erythrocytes and proteins into filtrate, but allows smaller structures to pass through, including water, ions, glucose, and some hormones.**
- 4. Once the filtrate leaves Bowman's capsule, it passes into the proximal tubule, where there is active transport of sodium ions and other solutes out of the tubule.**
- 5. This increase in solute concentration outside of the tubule encourages water to move out of the tubule also, by a process of osmosis, reducing the volume of the filtrate by approximately 65%.**
- 6. Further water moves out of the nephron in the loop of Henle in its descending loop.**

KEY LEARNING POINTS contd....

- 7. The ascending loop of Henle is impermeable to water, but permeable to solutes, and these further move out of the nephron.**
- 8. In the distal tubule sodium and chloride ions are actively transported out of the nephron.**
- 9. The permeability of the distal tubules and collecting ducts is under the control of Antidiuretic hormone.**
- 10. When ADH is present water is reabsorbed; when it is absent, water stays in the distal tubule and collecting ducts.**
- 11. Approximately 99% of the filtrate originating from Bowman's capsule is reabsorbed, leaving around 1% to be excreted as urine.**

Urine Concentration Mechanism

When a large volume of water is consumed, it is necessary to eliminate the excess without losing excessive electrolytes or other substances essential for the maintenance of homeostasis. Under this condition the kidneys produce a large volume of dilute urine. If drinking water is not available, producing dilute urine leads to rapid dehydration. When water intake is restricted, the kidneys produce a small amount of concentrated urine that contains sufficient waste products to prevent their accumulation in the circulatory system. The kidneys are able to produce urine with concentrations that vary between 65 and 1200 mOsm/kg whilst maintaining an extracellular fluid osmolality very close to 300 mOsm/kg.

The ability of the kidney to concentrate urine depends on maintaining a high medullary concentration gradient. The interstitial fluid concentration is about 300 mOsm/kg in the cortical region of the kidney and becomes progressively higher in the medulla. The interstitial osmolality reaches about 1200 mOsm/kg near the tips of the renal pyramids. Maintenance and production of the high solute concentration in the kidney medulla depend on the vasa recta, the loop of Henle, and the distribution of urea.

The vasa recta function to remove excess water and solutes from the kidney medulla without changing the high concentration of solutes in the medullary interstitial fluid. The vasa recta also supply blood to the medulla of the kidney. As filtrate moves through the nephron and the collecting duct, water and solutes are reabsorbed from the filtrate into the surrounding interstitial fluid. The reabsorbed water and solutes enter the peritubular capillaries and flow from there into the general circulation.

The vasa recta are countercurrent systems, in which fluid flows in parallel tubes but in opposite directions, and heat, or substances such as water or solutes, diffuse from tubes carrying fluid in one direction to tubes carrying fluid in the opposite direction, so that the fluid in both sets of tubes have nearly the same composition.

NB A simple illustration of a counter current system is the heat exchange system which prevents a penguin's feet from freezing. In their case, this takes the form of 'counter current heat exchangers' at the top of the legs. The arteries, which supply warm blood and oxygen to the penguin's feet break up into many small vessels which are closely linked to similar numbers of venous vessels bringing cold blood back from the feet. So, when heat is lost from the arterial vessels, the venous vessels running in the opposite direction pick it up and carry it back through the body, rather than out through the feet. This means that in the very remote regions of the skin, cells get oxygen but heat isn't lost through this skin.



The vasa recta make up a countercurrent system because the blood flows through them to the medulla and, after the vessels turn near the tip of the renal pyramid, the blood flows in the opposite direction. As blood flows toward the medulla, water moves out of the vasa recta, and some solutes diffuse into them. As blood flows back toward the cortex, water moves into the vasa recta, and some solutes diffuse out of them. The composition of the blood at both ends of the vasa recta is nearly the same, with the volume and osmolality slightly greater as the blood once again reaches the cortex.

The loops of Henle are countercurrent multiplier systems, which increase the concentration of sodium ions within the medulla while making the filtrate dilute. Countercurrent multiplier systems are countercurrent systems that are assisted by active transport mechanisms that move solutes from the lumens of the ascending limbs of loops of Henle to the interstitial fluid. The countercurrent multiplier functions of the loops of Henle make the concentrating function of the kidney more efficient than it would be with a simple countercurrent system.

As filtrate descends into the medulla of the kidney through the descending limbs of the loops of Henle, water diffuses out of the nephrons into the more concentrated interstitial fluid and is removed by the vasa recta. The walls of the ascending limbs of

the loops of Henle are not permeable to water, however, and active transport mechanisms move large amounts of solutes such as sodium and chloride ions out of the filtrate and into the interstitial fluid. Although some of the sodium and chloride ions diffuse into the descending limbs of the loops of Henle or the vasa recta, more sodium and chloride ions are transported from the ascending limbs into the interstitial fluid of the medulla. Thus active transport of solutes from the ascending limbs of the loops of Henle helps to maintain a high concentration of solutes in the interstitial fluid of the medulla, while the filtrate in the ascending limbs, the loops of Henle decrease in osmolality from 1200 mOsm/kg to 100 mOsm/kg.

Urea

Urea molecules are responsible for a substantial part of the high osmolality in the medulla of the kidney. Urea molecules diffuse into the descending limbs of the loops of Henle from the interstitial fluid. The ascending limbs of the loops of Henle and the distal tubules are not permeable to urea. The collecting ducts are permeable to urea, however, and urea diffuses out of them into the interstitial fluid of the medulla. The urea within the interstitial fluid of the medulla can cycle several times from the interstitial fluid into the descending limbs and from the collecting duct back into the interstitial fluid. Consequently, a high urea concentration is maintained in the medulla of the kidney which adds to the high solute concentration in the medulla.

Summary of Changes in Filtrate Volume and Concentration

In the average person, about 180 litres of filtrate enters the proximal tubules daily. Substances such as glucose, amino acids, sodium ions, calcium ions, potassium ions, and chloride ions are actively transported, and water moves by osmosis, from the lumens of the proximal tubules into the interstitial fluid. The excess solutes and water then enter the peritubular capillaries. Consequently, approximately 65% of the filtrate volume is reabsorbed as water, and solutes move from the proximal tubules

into the interstitial fluid, and the osmolality of both the interstitial fluid and the filtrate is maintained at about 300 mOsm/L.

The filtrate then passes into the descending limb of the loops of Henle, which is highly permeable to water and solutes. As the descending limb penetrates deep into the medulla of the kidney, the surrounding interstitial fluid has progressively greater osmolality. Water diffuses out of the nephron as solutes slowly diffuse into it. By the time the filtrate reaches the deepest part of the loops of Henle, its volume has been reduced by an additional 15% of the original volume and its osmolality has increased to about 1200 mOsm/kg. By the time the filtrate has reached the tip of the loops of Henle, at least 80% of the filtrate volume has been reabsorbed.

After passing through the descending limbs of the loop of Henle, the filtrate enters the ascending limbs, or the thick segments. The thick segments are not permeable to water but sodium, chloride, and potassium ions are transported from the filtrate into the interstitial fluid. The movement of ions, but not water, across the wall of the ascending limbs, causes the osmolality of the filtrate to decrease from 1200 to approximately 100 mOsm/kg by the time the filtrate again reaches the cortex of the kidney. As a result, the filtrate in the nephron is dilute compared with the concentration of the surrounding interstitial fluid, which has an osmolality of about 300 mOsm/kg.

The filtrate enters the distal tubules after passing through the loops of Henle. Near the end of the distal tubules, the wall of the tubules can be permeable to water, providing ADH is present. Water diffuses from the lumen of the nephron to the interstitial spaces.

The filtrate then flows into the collecting ducts which pass through the medulla of the kidney with its high concentration of solutes. If ADH is present, water diffuses from the collecting ducts into the interstitial fluid. By the time the filtrate passes through the collecting ducts, another 19% of the filtrate is reabsorbed. Thus 1% of the

filtrate remains as urine and 99% of the filtrate is reabsorbed. The osmolality of the filtrate at the end of the collecting ducts is approximately 1200 mOsm/kg.

In addition to the dramatic decrease in filtrate volume and increase in filtrate osmolality, there is a marked alteration in the filtrate composition. Waste products such as creatinine and urea as well as potassium, hydrogen, phosphate, and sulfate ions are present at a much higher concentration in urine than in the original filtrate because of the removal of water from the filtrate. Many substances are selectively reabsorbed from the nephron, and others are secreted into the nephron so that beneficial substances are retained in the body and toxic substances are eliminated.

KEY LEARNING POINTS.



- 1. The larger amount of water that is consumed, the more necessary it becomes to eliminate the excess without losing essential solutes.**
- 2. The vasa recta function to remove excess water and solutes, without altering the necessary high concentration of solutes within the medullary interstitial fluid.**
- 3. this occurs by a counter-current mechanism, where fluid flows in parallel tubes, but in opposite directions, with diffusion of fluid or solutes occurring between the tubules.**
- 4. The loops of Henle are counter-current multiplier systems, increasing the numbers of sodium ions within the medullary interstitial fluid whilst retaining water within the nephron. They are counter-current systems, aided by active transport.**

Regulation of Urine Concentration and Volume

Urine can be dilute or very concentrated and it can be produced in large or small amounts. Urine concentration and volume are regulated by mechanisms that maintain the extracellular fluid osmolality and volume within narrow limits.

Filtrate reabsorption in the proximal tubules and the descending limbs of the loops of Henle is obligatory, which means it is not under neural nor hormonal control, and remains relatively constant. However, filtrate reabsorption in the distal tubules and collecting ducts is regulated and can change dramatically, depending on the conditions to which the body is exposed.

If homeostasis requires the elimination of a large volume of dilute urine, a large volume of filtrate is produced, and the dilute filtrate in the distal tubules and collecting ducts can pass through them with little change in concentration. On the other hand, if conservation of water is required to maintain homeostasis, slightly less filtrate is produced and water is reabsorbed from the filtrate as it passes through the distal tubules and collecting ducts. This results in the production of a small volume of very concentrated urine. Regulation of urine volume and concentration involves hormonal mechanisms, autoregulation, and the nervous system.

Hormonal Mechanisms

Antidiuretic Hormone (ADH)

The distal tubules and the collecting ducts remain relatively impermeable to water in the absence of ADH. When little ADH is secreted, a large part of the 19% of the filtrate that is normally reabsorbed in the distal tubules and the collecting ducts becomes part of the urine. People who do not secrete sufficient ADH often produce 10-20 litres of urine per day and develop major problems such as dehydration and ion imbalances. Insufficient ADH secretion results in a condition called diabetes

insipidus; the word 'diabetes' implies the production of a large volume of urine, and the word insipidus implies the production of a clear, tasteless, dilute urine. This condition is in contrast to diabetes mellitus, which implies the production of a large volume of urine that contains a high concentration of glucose, 'mellitus' referring to 'honeyed', or 'sweet'.

ADH is secreted from the posterior pituitary gland. Pressure receptors that monitor blood pressure in the atria of the heart, large veins, carotid sinuses, and aortic arch, influence ADH secretion when the blood pressure increases or decreases in excess of 5%-10%.

When blood osmolality increases, or when blood pressure declines significantly, ADH secretion increases and acts on the kidneys to increase the reabsorption of water. The reabsorption of water by the kidneys decreases blood osmolality and increases blood pressure. Conversely, when blood osmolality decreases or when blood pressure increases, ADH secretion declines. The reduced ADH levels cause the kidneys to reabsorb less water and to produce a larger volume of dilute urine. The increased loss of water in the urine increases blood osmolality and decreases blood pressure.

Ethanol intake reduces the amount of ADH produced, which explains why drinking alcohol increases the need to urinate, as less water is reabsorbed in the collecting ducts, resulting in increased quantities of dilute urine.

Renin -Angiotensin -Aldosterone

Renin is an enzyme secreted by cells of the juxtaglomerular apparatus. The rate of renin secretion increases if blood pressure in the afferent arteriole decreases, or if the sodium ion concentration of the filtrate passing by the macula densa cells of the juxtaglomerular apparatuses decreases. Renin enters the general circulation, acting on angiotensinogen to convert it to angiotensin I. Subsequently, a proteolytic enzyme called angiotensin-converting enzyme (ACE) converts angiotensin I to

angiotensin II. Angiotensin II is a potent vasoconstrictor substance that increases the peripheral resistance, causing blood pressure to increase. Angiotensin II also increases the rate of aldosterone secretion, the sensation of thirst, salt appetite, and ADH secretion.

The rate of renin secretion decreases if blood pressure in the afferent arteriole increases, or if the sodium ion concentration of the filtrate increases as it passes by the macula densa of the juxtaglomerular apparatuses. A large decrease in the concentration of sodium ions in the interstitial fluids acts directly on the aldosterone-secreting cells of the adrenal cortex to increase the rate of aldosterone secretion. Angiotensin II is much more important than the blood level of sodium ions, however, in regulating aldosterone secretion.

Aldosterone is a steroid hormone secreted by the cortical cells of the adrenal glands, and passes through the circulatory system from the adrenal glands to the cells in the distal tubules and the collecting ducts. Aldosterone molecules diffuse through the plasma membranes and bind to receptor molecules within the cells. The combination of aldosterone molecules with their receptor molecules increases synthesis of the protein molecules that are responsible for the active transport of sodium ions across the epithelial cells of the nephron. As a result, the rate of sodium ion transport out of the filtrate back into the blood increases.

Decreased secretion of aldosterone decreases the rate of sodium ion transport. As a consequence, the concentration of sodium ions in the distal tubules and the collecting ducts remains high. Because the concentration of filtrate passing through the distal tubules and the collecting ducts has a greater than normal concentration of solutes, the capacity for water to move by osmosis from the distal tubules and the collecting ducts is diminished, urine volume increases, and the urine has a greater-than-normal concentration of sodium ions.

Atrial Natriuretic Hormone

A polypeptide hormone called atrial natriuretic hormone is secreted from cardiac muscle cells in the right atrium of the heart, when blood pressure in the right atrium increases. Atrial natriuretic hormone inhibits ADH secretion and sodium ion reabsorption in the kidney, which leads to the production of a large volume of dilute urine. The resulting decrease in blood volume increases blood pressure. Atrial natriuretic hormone also dilates arteries and veins, which reduces peripheral resistance and lowers blood pressure.

Autoregulation

Autoregulation is the maintenance within the kidneys of a relatively stable GFR over a wide range of systemic blood pressures. For example, the GFR is relatively constant as systemic blood pressure changes between 90 and 180 mm Hg.

Autoregulation involves changes in the degree of constriction in the afferent arterioles. The precise mechanism by which autoregulation is achieved is unclear, but, as systemic blood pressure increases, the afferent arterioles constrict and prevent an increase in renal blood flow and filtration pressure across the filtration membrane of the renal corpuscle. Conversely, a decrease in systemic blood pressure results in dilation of the afferent arterioles, thus preventing a decrease in the renal blood flow and filtration pressure across filtration membrane in the renal corpuscle.

Autoregulation is also influenced by the rate of flow of filtrate by cells of the macula densa. An increased flow is detected by the macula densa, which sends a signal to the juxtaglomerular apparatus to constrict the afferent arteriole. The result is a decrease in the filtration pressure across the filtration membrane of the renal corpuscle.

Effect of Sympathetic Stimulation on Kidney Function

Sympathetic neurons with noradrenaline as their neurotransmitter innervate the blood vessels of the kidneys. Sympathetic stimulation constricts the small arteries and afferent arterioles, decreasing renal blood flow and filtrate formation.

Intense sympathetic stimulation, such as during shock or intense exercise, decreases the rate of filtrate formation to only a few milliliters per minute. Small changes in sympathetic stimulation have a minimal effect on renal blood flow and filtrate formation. Autoregulation maintains renal blood flow and filtrate formation at a relatively constant rate unless sympathetic stimulation is intense.

In response to severe stress or circulatory shock, renal blood flow can decrease to such low levels that the blood supply to the kidney is inadequate to maintain normal kidney metabolism. As a consequence, kidney tissues can be damaged and thus be unable to perform their normal functions. This is one of the reasons that shock should be treated quickly.

KEY LEARNING POINTS.



- 1. Urine concentration and volume is regulated by hormonally, by autoregulation, and by the sympathetic nervous system.**
- 2. Hormonal control involves ADH, the renin-angiotensin-aldosterone system, and by atrial natriuretic hormone.**
- 3. Autoregulation is where the kidney alters afferent arteriolar diameter in order to maintain a stable GFR.**
- 4. Sympathetic stimulation constricts small arteries and afferent arteriole to decrease renal blood flow, and filtrate formation.**

Regulation of Body Fluid Volume

Water intake varies from person to person and is strongly influenced by habit. Most water enters the body through ingested liquids and solid foods, but approximately 10% of body water is produced by cellular metabolism. Water output occurs by several routes and is equal to water intake. Approximately 40% of water loss occurs through evaporation from the lungs, diffusion through the skin, secretion of glands, perspiration, and in the faeces, whereas approximately 60% is excreted by the kidneys in the urine. Major functions of the kidneys are the production of a small volume of concentrated urine when it is necessary to conserve water, or a large volume of dilute urine when it is necessary to lose water. In this way the kidneys help maintain body fluid osmolality and volume within a narrow range of values.

It is possible for the volume of extracellular fluid to increase or decrease, even if the osmolality of the extracellular fluid is maintained within a narrow range of values. Mechanisms exist to regulate the extracellular fluid volume.

Cells that are sensitive to changes in blood pressure are important in the regulation of extracellular fluid volume. Carotid sinus and aortic arch baroreceptors monitor blood pressure in large arteries, and cells of the juxtaglomerular apparatus are sensitive to pressure changes within the afferent arterioles. These pressure receptors respond to changes in arterial blood pressure, including pressure changes resulting from increases or decreases in blood volume. Receptors are also located in the walls of the atria and large veins that are sensitive to forces that stretch their walls. The small changes in pressure that occur in response to increases or decreases in the volume of venous blood are examples. In addition, cells of the macula densa are sensitive to the sodium ion concentration in the filtrate. Together these receptors play important roles in the regulation of the extracellular fluid volume.

An increase or decrease in the extracellular fluid volume increases or decreases the pressure of arterial and venous blood. The pressure receptors of the aortic arch,

carotid sinus atria, large veins, and juxtaglomerular apparatuses detect the pressure changes and activate neural mechanisms and three major hormonal mechanisms.

Neural mechanisms.

Neural mechanisms change the frequency of action potentials carried by sympathetic neurons to the afferent arterioles of the kidney in response to increases or decreases in blood volume. When the pressure receptors detect an increase in arterial and venous blood pressure, the frequency of action potentials carried by sympathetic neurons to the afferent arterioles decreases. Consequently, the afferent arterioles dilate. This increases the glomerular capillary pressure, which increases the filtration pressure, resulting in an increase in the GFR and an increase in the filtrate volume and urine volume. Because of autoregulation, a large increase in blood pressure is required to substantially increase the filtration pressure.

When the pressure receptors detect a decrease in arterial and venous blood pressure, there is an increase in the frequency of action potentials carried by sympathetic neurons to the afferent arterioles. Consequently the afferent arterioles constrict. This decreases the glomerular capillary pressure, which decreases the filtration pressure, resulting in a decrease in the GFR and a decrease in the filtrate volume and urine volume. Because of autoregulation, a large decrease in blood pressure is required to substantially decrease the filtration pressure.

Renin-angiotensin-aldosterone mechanism.

The renin-angiotensin-aldosterone mechanism responds to small changes in blood volume, and changes in the sodium ion concentration in the filtrate. An increase in blood volume can cause an increased blood pressure in the afferent arterioles, which results in a decreased rate of renin secretion by the juxtaglomerular cells. The concentration of sodium ions in the filtrate passing the cells of the macula densa increases when the volume of filtrate flowing through the nephron increases. The macula densa cells respond to the increased sodium ion concentration by decreasing renin secretion from the juxtaglomerular cells.

The decrease in renin secretion results in a decreased conversion of angiotensinogen to angiotensin I, which results in a decrease in the conversion of angiotensin I to angiotensin II. The reduced angiotensin II level causes a decrease in the rate of aldosterone secretion from the adrenal cortex. The decreased aldosterone reduces the rate of sodium ion reabsorption, primarily from the distal tubules and collecting ducts. Consequently, more sodium ions remain in the filtrate and fewer sodium ions are reabsorbed. The effect is to increase the osmolality of the filtrate and to reduce the osmolality of the extracellular fluid. Because the mechanisms that regulate extracellular fluid osmolality function simultaneously, ADH secretion decreases in response to the reduced osmolality of the extracellular fluid and, consequently, less water is reabsorbed in the distal tubules and collecting ducts of the kidney. The water remains, with the excess sodium ions, in the filtrate. Thus, the volume of urine produced by the kidney increases and the extracellular fluid volume decreases.

An increase in renin secretion results in an increased conversion of angiotensinogen to angiotensin I, which results in an increase in the conversion of angiotensin I to angiotensin II. The increased angiotensin II causes an increase in the rate of aldosterone secretion from the adrenal cortex. The increased aldosterone increases the rate of sodium ion reabsorption, primarily from the distal tubules and collecting ducts. Consequently, fewer sodium ions remain in the filtrate and more sodium ions are reabsorbed. The effect is to decrease the osmolality of the filtrate and to increase the osmolality of the extracellular fluid. Because the mechanisms that regulate extracellular fluid osmolality function simultaneously, there is an increase in ADH secretion in response to the increased osmolality of the extracellular fluid and, consequently, more water is reabsorbed in the distal tubules and collecting ducts of the kidney. Thus the volume of urine produced by the kidney decreases and the extracellular fluid volume increases.

Atrial natriuretic hormone mechanism.

This mechanism is important in the regulation of extracellular fluid volume, especially in response to increases in extracellular fluid volume. An increase in

pressure in the atria of the heart, which usually results from an increase in blood volume, stimulates the secretion of atrial natriuretic hormone. Atrial natriuretic hormone decreases sodium ion reabsorption in the distal tubules and collecting ducts and, therefore, increases the rate at which sodium ions and water are lost in the urine. Thus, increased atrial natriuretic hormone decreases the extracellular fluid volume.

A decrease in pressure in the atria of the heart inhibits the secretion of atrial natriuretic hormone. The decreased atrial natriuretic hormone decreases the inhibition on sodium ion reabsorption in the distal tubules and collecting ducts and, therefore, the rate at which sodium ions are reabsorbed increases. As sodium ion reabsorption increases water reabsorption also increases. Thus, decreased atrial natriuretic hormone tends to result in decreased urine volume and an increase in the extracellular fluid volume.

Antidiuretic hormone mechanism.

The ADH mechanism plays an important role in regulating extracellular fluid volume in response to large changes in blood pressure (of 5% - 10%). An increase in blood pressure results in a decrease in ADH secretion. As a result the reabsorption of water from the lumen of the distal tubules and collecting ducts decreases, resulting in a larger volume of dilute urine. This response helps decrease the extracellular fluid volume and blood pressure.

A decrease in blood pressure results in an increase in ADH secretion. Consequently, the reabsorption of water from the lumen of the distal tubules and collecting ducts increases, resulting in a smaller volume of concentrated urine. This response helps increase the extracellular fluid volume and blood pressure.

KEY LEARNING POINTS.



- 1. Body fluid volume is regulated by a number of systems – baroreceptors and hormonal control are mainly responsible for this.**
- 2. Baroreceptors are sensitive to changes in blood pressure, and when they detect a change in blood pressure they active neural and hormonal mechanisms.**
- 3. Neural mechanisms change the frequency of action potentials carried by the sympathetic system to the afferent arterioles of the kidney, altering their diameter.**
- 4. A decrease in blood pressure can also stimulate the release of renin, which stimulates the conversion of angiotensin I to angiotensin II, bringing about vasoconstriction, and a resulting increase in blood pressure.**
- 5. An increase in blood pressure within the atria of the heart stimulates increased production of atrial natriuretic hormone, which decreases sodium reabsorption in the distal tubules and collecting ducts, increasing water and sodium excretion.**
- 6. ADH secretion is reduced with an increase in blood pressure, allowing more water to be retained in the collecting ducts, and therefore excreted.**

Clearance and Tubular Maximum

Plasma clearance is a calculated value representing the volume of plasma that is cleared of a specific substance each minute. For example, if the clearance value is 100 mL/min for a substance, the substance is completely removed from 100mL of plasma each minute.

The plasma clearance can be calculated for any substance that enters the circulatory system according to the following formula :

$$\text{Plasma clearance (mL/min)} = \text{Quantity of urine (mL/min)} \times \frac{\text{Concentration of substance in urine}}{\text{Concentration of substance in plasma}}$$

Plasma clearance can be used to estimate GFR if the appropriate substance is monitored. The GFR is reduced when the kidney fails. Measurement of the GFR indicates the degree to kidney damage has occurred. Such a substance must have the following characteristics:

- (1) it must pass through the filtration membrane of the renal corpuscle as freely as water or other small molecules,
- (2) it must not be reabsorbed,
- (3) it must not be secreted into the nephron,
- (4) it must be neither metabolised nor produced in the kidney.

Inulin is a polysaccharide that has these characteristics. As filtrate is formed, it has the same concentration of inulin as plasma, but as the filtrate flows through the nephron, all of the inulin remains in the nephron to enter the urine. As a consequence all of the volume of plasma that becomes filtrate is cleared of inulin and the plasma clearance for inulin is equal to the rate of glomerular filtrate formation.

Plasma clearance can also be used to calculate renal plasma flow. Substances with the following characteristics, however, must be used:

- (1) the substance must pass through the filtration membrane of the renal corpuscle,
- (2) it must be secreted into the nephron at a sufficient rate so that very little of it remains in the blood as the blood leaves the kidney.

Para-aminohippuric acid (PAH) meets these requirements. As blood flows through the kidney, all of the PAH is either filtered or secreted into the nephron. The clearance calculation for PAH is therefore a good estimate of the volume of plasma flowing through the kidney each minute. Also, if the haematocrit is known, the total volume of blood flowing through the kidney each minute can be easily calculated.

The concept of plasma clearance can be used to make the measurements described previously, or it can be used to determine the means by which drugs or other substances are excreted by the kidney. A plasma clearance value greater than the inulin clearance value suggests that the substance is secreted by the nephron into the filtrate.

The tubular load of a substance is the total amount of the substance that passes through the filtration membrane into the nephrons each minute. Normally, glucose is almost completely reabsorbed from the nephron by the process of active transport. The capacity of the nephron to actively transport glucose across the epithelium of the nephron is limited, however. If the tubular load is greater than the capacity of the nephron to reabsorb it, the excess glucose remains in the urine.

The maximum rate at which a substance can be actively reabsorbed is called the tubular maximum. Each substance that is reabsorbed has its own tubular maximum, determined by the number of active transport carrier molecules and the rate at which they are able to transport molecules of the substance. For example, in people suffering from diabetes mellitus the tubular load for glucose can exceed the tubular maximum by a substantial amount, allowing glucose to appear in the urine. Urine

volume is also greater than normal because the glucose molecules in the filtrate reduce the effectiveness of water reabsorption by osmosis.

Diuretics

Diuretics are agents that increase the rate of urine formation. Although the definition is simple, a number of different physiologic mechanisms are involved.

Diuretics are used to treat disorders such as hypertension and several types of oedema that are caused by conditions such as congestive heart failure and cirrhosis of the liver. Use of diuretics can lead to complications, however, including dehydration and electrolyte imbalances.

Inhibitors of sodium ion reabsorption include thiazide-type diuretics. They promote the loss of sodium ions, chloride ions, and water in urine. These diuretics are given to some people who have hypertension. Inhibitors of sodium ion reabsorption, such as bumetanide, furosemide, and ethacrynic acid, specifically inhibit transport in the ascending limb of the loop of Henle. These diuretics are frequently used to treat congestive heart failure, cirrhosis of the liver, and renal disease.

Potassium-sparing diuretics are antagonists to aldosterone or directly prevent sodium ion reabsorption in the distal tubules and collecting ducts. Thus they promote sodium ion and water loss in the urine. These diuretics are used to reduce the loss of potassium ions in the urine and therefore preserve, or "spare," potassium ions. They are often used in combination with inhibitors of sodium ion reabsorption and are effective in preventing excess potassium loss in the urine.

Osmotic diuretics freely pass by filtration into the filtrate, and they undergo limited reabsorption by the nephron. These diuretics increase urine volume by elevating the osmotic concentration of the filtrate, thus reducing the amount of water moving by osmosis out of the nephron. Urea, mannitol, and glycerine have been used as osmotic diuretics. Although they are not commonly used, they are effective in

treating people who are suffering from cerebral oedema, and oedema in acute renal failure.

Xanthines, including caffeine and related substances, act as diuretics, partly because they increase renal blood flow and the rate of glomerular filtrate formation. They also influence the nephron by decreasing sodium and chloride reabsorption.

Alcohol acts as a diuretic, although it is not used clinically for that purpose. It inhibits ADH secretion from the posterior pituitary and results in increased urine volume.

KEY LEARNING POINTS.



- 1. Plasma clearance represents the amount of plasma which is cleared of a substance each minute.**
- 2. It can be used to estimate GFR, which is an indicator of kidney function.**
- 3. Plasma inulin can be used as a measure of GFR as it is completely cleared from the plasma, without and reabsorption nor secretion, and is therefore removed completely, and excreted.**