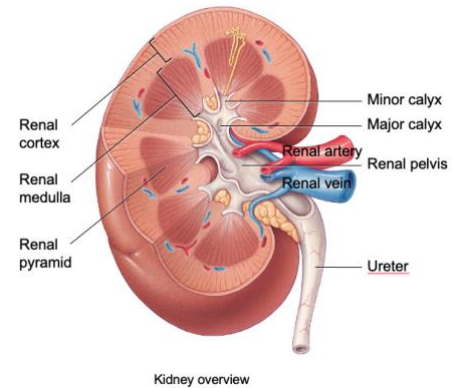
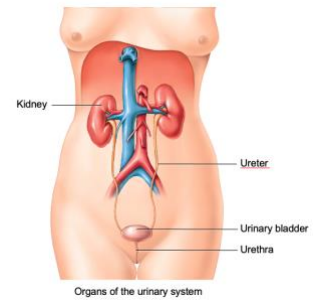


- I. Overview of Renal Physiology – The kidneys do most of the work within the urinary system. Other parts are mainly passageways and storage areas. The functions of the kidneys include the following:
  - A. **Excretion of wastes** – By forming urine, kidneys help excrete wastes from body. Some wastes excreted in urine result from metabolic reactions. These include urea and ammonia from deamination of amino acids; creatinine from breakdown of creatine phosphate; uric acid from catabolism of nucleic acids; and urobilin from breakdown of hemoglobin. These products are collectively known as nitrogenous wastes because they are waste products that contain nitrogen. Other wastes excreted in the urine are foreign substances that have entered the body, such as drugs and environmental toxins.
  - B. **Regulation of blood ionic composition** – Kidneys help regulate the blood levels of several ions by adjusting the of these ions that are excreted into urine, including sodium ions ( $\text{Na}^+$ ), potassium ions ( $\text{K}^+$ ), calcium ions ( $\text{Ca}^{2+}$ ), chloride ions ( $\text{Cl}^-$ ), and phosphate ions ( $\text{HPO}_4^{2-}$ ).
  - C. **Regulation of blood pH** – Kidneys excrete a variable amount of hydrogen ions ( $\text{H}^+$ ) into the urine and conserve bicarbonate ions ( $\text{HCO}_3^-$ ), which are an important buffer of  $\text{H}^+$  in blood. Both activities help regulate blood pH.
  - D. **Regulation of blood volume** – Kidneys adjust blood volume by returning water to blood or eliminating it in urine. An increase in blood volume increases blood pressure; a decrease in blood volume decreases blood pressure.
  - E. **Regulation of blood pressure** – Kidneys help regulate blood pressure by secreting the enzyme renin, which activates the renin–angiotensin–aldosterone pathway. Increased renin causes increase in blood pressure.
  - F. **Maintenance of blood osmolarity** – By separately regulating loss of water and loss of solutes in the urine, kidneys maintain a relatively constant blood osmolarity close to 300 milliosmoles per liter (mosmol/liter). (The osmolarity of a solution is a measure of the total number of dissolved particles per liter of solution. The particles may be molecules, ions, or a mixture of both. A similar term, osmolality, is the number of particles of solute/kg water. Since it is easier to measure volumes of solutions than to determine the mass of water they contain, osmolarity is used more commonly than osmolality).
  - G. **Production of hormones** – Kidneys produce two hormones. Calcitriol, the active form of vitamin D, helps regulate calcium homeostasis, and erythropoietin stimulates the production of erythrocytes.

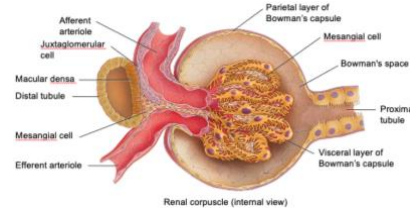
## II. Organization of the Kidneys

### A. Kidneys

1. Paired bean-shaped organs just above the waist
2. Kidney structure
  - a. Contains an outer layer called the cortex
  - b. Contains an inner area called the medulla
  - c. Renal pyramids – Several cone-shaped structures located within the renal medulla
  - d. Major and minor Calyces (singular is calyx)
  - e. Renal pelvis that leads urine into ureter and then urinary bladder



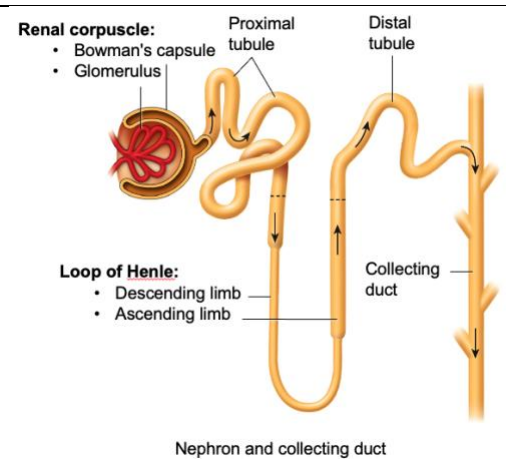
3. Functional unit of the kidney is the nephron
  - a. Nephron parts:
    - 1) **Renal corpuscle** – where blood plasma is filtered. The two components of a renal corpuscle are the **glomerulus** (a capillary network) and **Bowman's capsule**, or **glomerular capsule**, a double-walled epithelial cup that surrounds the glomerular capillaries



- 2) **Renal tubule** – Once blood plasma is filtered at the renal corpuscle, the filtered fluid passes into the renal tubule, which consists of a single layer of epithelial cells that lines a lumen. The renal tubule has three main sections: **proximal tubule, loop of Henle, and distal tubule.**

The renal corpuscle, proximal tubule, and distal tubule lie within the renal cortex; the loop of Henle extends into the renal medulla, makes a hairpin turn, and then returns to the renal cortex. From the renal corpuscle, filtered fluid first enters the proximal tubule. The term proximal denotes that this part of the renal tubule is closest to the site where the renal tubule attaches to Bowman's capsule. Most of the proximal tubule is convoluted, which means that it is coiled rather than straight. From the proximal tubule, filtered fluid enters the loop of Henle, also known as the nephron loop. The first part of the loop of Henle dips into the renal medulla, where it is called the descending limb. It then makes

that hairpin turn and returns to the renal cortex as the ascending limb. From the loop of Henle, filtered fluid enters the distal tubule. The term distal denotes that this part of the renal tubule is farther away from the site where renal tubule attaches to Bowman's capsule. The distal tubule is also convoluted. The distal tubules of several nephrons empty into a single collecting duct. Multiple collecting ducts in turn unite to form larger ducts that drain into the minor calyces. Note that as fluid passes through the nephron and collecting duct, it is referred to as either filtrate, filtered fluid, or tubular fluid, and its composition can be modified. Once the fluid exits the collecting ducts, it is referred to as urine, and its composition cannot be altered.



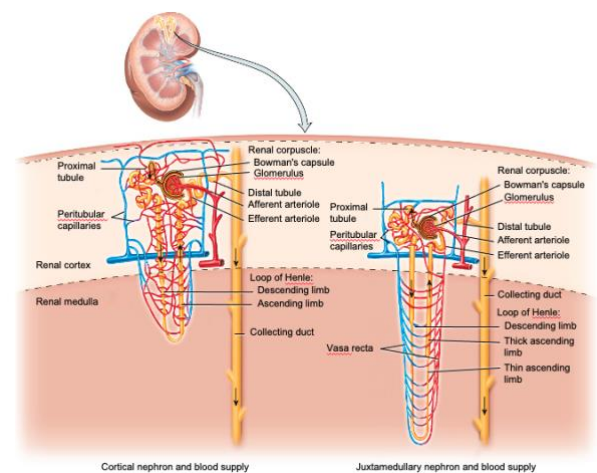
#### 4. Types of nephrons

##### a. Cortical

- 1) 80% of the kidney's nephrons are cortical nephrons.
- 2) Their renal corpuscles lie in the outer portion of the renal cortex, and they have short loops of Henle that lie mainly in the cortex and penetrate only into the outer region of the renal medulla

##### b. Juxtamedullary

- 1) The other 20% of the nephrons are juxtamedullary nephrons.
- 2) Their renal corpuscles lie deep in the cortex, close to the medulla, and they have a long loop of Henle that extends into the deepest region of the medulla
- 3) Ascending limb of the loop of Henle consists of two portions: a thin ascending limb followed by a thick ascending limb
- 4) Nephrons with long loops of Henle enable the kidneys to excrete very dilute or very concentrated urine



## 5. Blood supply to kidney

- a. Very extensive – as the kidneys remove wastes from the blood and regulate its volume and ionic composition
- b. **Renal artery** leads to the **afferent arteriole**, which:
- c. Leads to **glomerulus**
- d. Blood leaves glomerulus through **efferent arteriole**, which divides to form:
- e. **Peritubular capillaries** that carry blood back to the **renal veins** and surround:
  - 1) The tubular parts of both cortical and juxtamedullary nephrons that are within the renal cortex.
  - 2) Short loops of Henle of cortical nephrons.
- f. **Vasa recta** – long loop-shaped capillaries that extend from some efferent arterioles, that surround long loops of Henle of juxtamedullary nephrons

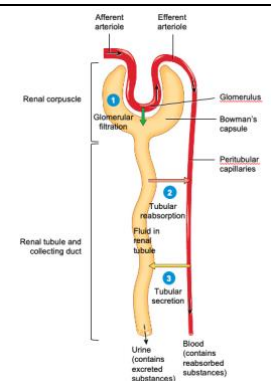
## 6. Juxtaglomerular apparatus

- a. Important in regulating kidney function
- b. Part of the distal tubule and afferent arteriole come in contact
- c. Consist of:
  - 1) Macula densa – specialized cells in this region
  - 2) Juxtaglomerular cells (JG) – modified smooth muscle fibers

## III. Overview of Renal Physiology

### A. To produce urine you perform three basic tasks

1. **Glomerular filtration** – In the first step of urine production, water and most solutes in blood plasma move across the wall of glomerular capillaries into Bowman's capsule and then into the renal tubule.
2. **Tubular reabsorption** – As filtered fluid flows through the renal tubule and collecting duct, tubule and duct cells reabsorb about 99% of the filtered water and many solutes. Reabsorption is the movement of substances from fluid in the tubular lumen to blood in the peritubular capillaries. This process allows useful substances to be returned to the bloodstream. The remaining 1% of filtered fluid that is not reabsorbed contains substances that the body does not need (wastes, drugs, excess ions, etc.) and will eventually be excreted into the urine.
3. **Tubular secretion** – As fluid flows through the renal tubule and collecting duct, tubule and duct cells also secrete wastes and other substances that are not useful to



the body. Secretion is the transfer of substances from blood in the peritubular capillaries to fluid in the tubular lumen. This process serves as an additional mechanism for removing unneeded substances from the bloodstream.

#### IV. Glomerular Filtration

A. Occurs at the renal corpuscle

B. Consists of glomerulus and Bowman's capsule

1. Bowman's capsule

a. Organized into two layers

1) Parietal layer – Single cell layer of epithelial cells

2) Visceral layer – Podocytes

2. Renal corpuscle

a. Contains filtration membrane

1) Made of glomerulus and visceral (podocyte) layer of Bowman's capsule, forming a leaky barrier

2) Permits filtration of:

i. Water and small solutes

3) Prevents filtration of:

i. Blood cells and nearly all plasma proteins

4) Substances filtered from the blood cross three barriers—the endothelium of the glomerulus, the **basement membrane of the glomerulus, and the visceral layer of Bowman's**

i. **Endothelium of the glomerulus.** Glomerular endothelial cells are quite leaky because they have fenestrations (pores) that measure 70–100 nm in diameter. This size permits passage to water and all solutes in blood plasma. However, the fenestrations are too small to allow blood cells to filter through the endothelium. Located among the glomerular capillaries and in the cleft between afferent and efferent arterioles are mesangial cells.

ii. **Basement membrane of the glomerulus.** a porous layer of acellular material between the endothelium and the podocytes, consists of collagen fibers and negatively charged glycoproteins. The pores within the basement membrane allow water and most small solutes to pass through. However, the negative charges of the

glycoproteins repel plasma proteins, most of which are anionic; the repulsion hinders filtration of these proteins.

- iii. **Visceral layer of Bowman's capsule.** Recall that the visceral layer of Bowman's capsule consists of podocytes, and each podocyte contains footlike processes called pedicels that wrap around glomerular capillaries. The spaces between pedicels are the filtration slits. A thin membrane, the slit membrane, extends across each filtration slit; it contains pores that permit the passage of molecules that have a diameter smaller than 6–7 nm, including water, glucose, vitamins, hormones, amino acids, urea, ammonia, and ions. Negatively charged glycoproteins that cover the slit membrane oppose the filtration of plasma proteins. Because of the negative charges associated with the podocyte layer and basement membrane and the small size of the slit membrane pores, less than 1% of albumin, the smallest and most abundant plasma protein, can pass through the filtration membrane and enter the glomerular filtrate.

5) The principle of filtration—the use of pressure to force fluids and solutes through a membrane—is the same in glomerular capillaries as in capillaries elsewhere in the body. However, the volume of fluid filtered by the renal corpuscle is much larger than in other capillaries of the body for three reasons:

- i. Glomerular capillaries present a large surface area for filtration because they are long and extensive. Mesangial cells regulate how much of this surface area is available for filtration. When mesangial cells are relaxed, surface area is maximal, and glomerular filtration is very high. Contraction of mesangial cells reduces available surface area, and glomerular filtration decreases.
- ii. Filtration membrane is thin and porous. Despite having several layers, the thickness of the filtration membrane is only 0.1 mm (100  $\mu\text{m}$ ). Glomerular capillaries also are about 50 times leakier than capillaries in most other tissues, mainly because of their large fenestrations.

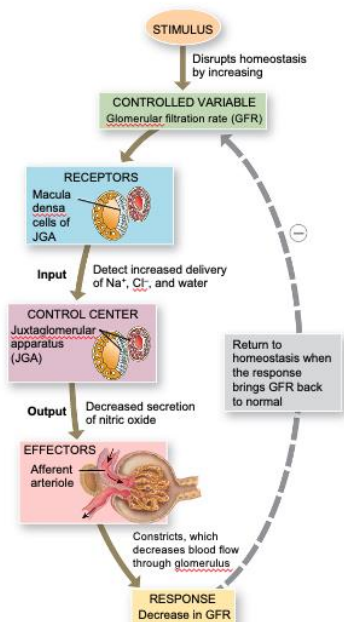
- iii. Glomerular capillary blood pressure is high. Because the efferent arteriole is smaller in diameter than the afferent arteriole, resistance to the outflow of blood from the glomerulus is high. As a result, blood pressure in glomerular capillaries is considerably higher than in capillaries elsewhere in the body.

#### C. Glomerular Filtration Is Determined by the Balance of Four Pressures

1. **Glomerular capillary hydrostatic pressure (PGC)** – is the blood pressure in glomerular capillaries. Generally, PGC is about 55 mmHg. It promotes filtration by forcing water and solutes in blood plasma through the filtration membrane.
2. **Bowman's space hydrostatic pressure (PBS)** – is the hydrostatic pressure exerted against the filtration membrane by fluid already in Bowman's space and renal tubule. PBS opposes filtration and represents a “back pressure” of about 15 mmHg.
3. **Plasma colloid osmotic pressure ( $\pi_{GC}$ )** – is due to the presence of proteins such as albumin, globulins, and fibrinogen in blood plasma of glomerular capillaries.  $\pi_{GC}$  also opposes filtration and is typically about 30 mmHg.
4. **Bowman's space colloid osmotic pressure ( $\pi_{BS}$ )** – which is due to the presence of proteins in the fluid in Bowman's space, promotes filtration. Under normal conditions, the fluid in Bowman's space has very little protein, so  $\pi_{BS}$  is 0 mmHg. However, when the filtration membrane is damaged, protein can enter from blood into Bowman's space, causing  $\pi_{BS}$  to increase

#### D. Glomerular filtration rate (GFR)

1. Amount of filtrate formed per minute
2. A measure of kidney function
3. On average is about 180 L/day
4. Regulated many different ways
  - a. **Autoregulation** – The kidneys themselves help maintain a constant renal blood flow and GFR despite normal, everyday changes in blood pressure, like those that occur during exercise. Consists of two mechanisms that work together to maintain nearly constant GFR over a wide range of systemic blood pressures:
    - 1) **Myogenic mechanism** – occurs when stretching triggers contraction of smooth muscle cells in walls of afferent arterioles. As blood pressure rises, GFR also rises because renal blood flow increases. However, the



Tubuloglomerular feedback

elevated blood pressure stretches the walls of afferent arterioles. In response, smooth muscle fibers in wall of afferent arteriole contract, which narrows arteriole's lumen. As a result, renal blood flow decreases, thus reducing GFR to its previous level. Conversely, when arterial blood pressure drops, smooth muscle cells are stretched less and thus relax. Afferent arterioles dilate, renal blood flow increases, and GFR increases. The myogenic mechanism normalizes renal blood flow and GFR within seconds after a change in blood pressure.

- 2) **Tubuloglomerular feedback** – is so-named because part of renal tubules—*the macula densa*—provides feedback to the glomerulus. When GFR is above normal due to elevated systemic blood pressure, filtered fluid flows more rapidly along renal tubules. As a result, the proximal tubule and loop of Henle have less time to reabsorb Na<sup>+</sup>, Cl<sup>-</sup>, and water. Macula densa cells are thought to detect the increased delivery of Na<sup>+</sup>, Cl<sup>-</sup>, and water and to inhibit release of nitric oxide (NO) from cells in the juxtaglomerular apparatus (JGA). Because NO causes vasodilation, afferent arterioles constrict when level of NO declines. As a result, less blood flows into glomerular capillaries, and GFR decreases. When blood pressure falls, causing GFR to be lower than normal, the opposite sequence of events occurs, although to a lesser degree. Tubuloglomerular feedback operates more slowly than myogenic mechanism.

- b. **Neural regulation** – Like most blood vessels of the body, those of the kidneys are supplied by sympathetic fibers of the autonomic nervous system (ANS) that release norepinephrine. Norepinephrine causes vasoconstriction through activation of α<sub>1</sub> receptors, which are particularly plentiful in smooth muscle fibers of afferent arterioles. At rest, sympathetic stimulation is moderately low, the afferent and efferent arterioles are dilated, and renal autoregulation of GFR prevails. With moderate sympathetic stimulation, both afferent and efferent arterioles constrict to the same degree. Blood flow into and out of the glomerulus is restricted to the same extent, which decreases GFR only slightly. With greater sympathetic stimulation, however, as occurs during exercise or hemorrhage, vasoconstriction of the afferent



arterioles predominates. As a result, blood flow into glomerular capillaries is greatly decreased, and GFR drops. This lowering of renal blood flow has two consequences: (1) It reduces urine output, which helps conserve blood volume. (2) It permits greater blood flow to other body tissues.

- c. **Hormonal regulation** – Two hormones contribute to regulation of GFR. Angiotensin II reduces GFR; atrial natriuretic peptide (ANP) increases GFR. Angiotensin II is a very potent vasoconstrictor that narrows both afferent and efferent arterioles and reduces renal blood flow, thereby decreasing GFR. Cells in the atria of the heart secrete atrial natriuretic peptide (ANP). Stretching of atria, as occurs when blood volume increases, stimulates secretion of ANP. By causing relaxation of the glomerular mesangial cells, ANP increases the capillary surface area available for filtration. Glomerular filtration rate rises as the surface area increases.

Type of Regulation	Major Stimulus	Mechanism and Site of Action	Effect on GFR
<b>Renal Autoregulation</b>			
<b>Myogenic mechanism</b>	Increased stretching of smooth muscle fibers in afferent arteriole walls due to increased blood pressure.	Stretched smooth muscle fibers contract, thereby narrowing the lumen of the afferent arterioles.	Decrease.
<b>Tubuloglomerular feedback</b>	Rapid delivery of $\text{Na}^+$ and $\text{Cl}^-$ to the macula densa due to high systemic blood pressure.	Decreased release of nitric oxide (NO) by the juxtaglomerular apparatus causes constriction of afferent arterioles.	Decrease.
<b>Neural regulation</b>	Increase in level of activity of renal sympathetic nerves releases norepinephrine.	Constriction of afferent arterioles through activation of $\alpha_1$ receptors and increased release of renin.	Decrease.
<b>Hormone Regulation</b>			
<b>Angiotensin II</b>	Decreased blood volume or blood pressure stimulates production of angiotensin II.	Constriction of both afferent and efferent arterioles.	Decrease.
<b>Atrial natriuretic peptide (ANP)</b>	Stretching of the atria of the heart stimulates secretion of ANP.	Relaxation of mesangial cells in glomerulus increases capillary surface area available for filtration.	Increase.

## V. Tubular Reabsorption and Tubular Secretion

### A. Filtration

1. Amount of filtrate that enters the proximal convoluted tubule is large
2. A volume greater than the plasma in half an hour
3. Because so much gets filtered many things must be taken back

### B. Secretion

## 1. Transfer of material from blood to tubule

### C. Reabsorption

#### 1. Two routes

##### a. Paracellular

##### 1) Substances travel between cells

##### b. Transcellular

##### 1) Substances travel through cells

##### 2) Uses transporters

#### 2. Through transcellular pathway

##### a. Requires use of transport proteins

##### b. Much of it occurs through secondary active transport using $\text{Na}^+$

##### c. Important to have $\text{Na}^+/\text{K}^+$ pump which will maintain concentration gradients

##### d. Water

##### 1) Passive (obligatory) ~ 80%

- i. Follows the solutes that get reabsorbed
- ii. Occurs passively in all places

##### 2) Facultative ~ 20%

- i. Happens in the later parts of the kidney (distal convoluted tubule and throughout collecting duct)
- ii. Hormone regulated (antidiuretic hormone)

### D. Reabsorption and secretion

#### 1. Different substances are reabsorbed or secreted to varying degrees in different parts of the renal tubule

##### a. Reabsorption and secretion – proximal convoluted tubule (PCT)

##### 1) Largest amount of solute and reabsorption. The PCT contains a brush border of microvilli along their apical membranes which increase the surface area for reabsorption and secretion.

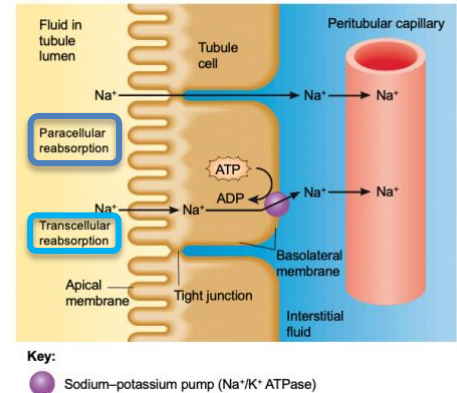
##### 2) Water, $\text{Na}^+$ , $\text{K}^+$ , $\text{Ca}^{++}$

- i. 65%

##### 3) Organic solutes

- i. 100%

Reabsorption routes: paracellular reabsorption and transcellular reabsorption

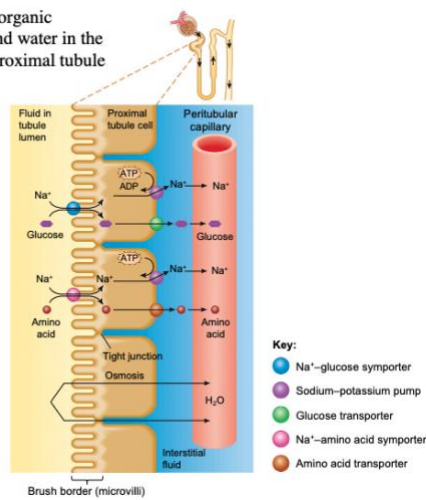


#### 4) Bicarbonate

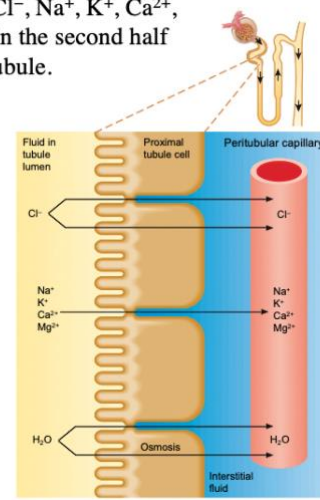
i. 80–90%

#### 5) Most occurs through $\text{Na}^+$ cotransport

Reabsorption of organic nutrients,  $\text{Na}^+$ , and water in the first half of the proximal tubule



Reabsorption of  $\text{Cl}^-$ ,  $\text{Na}^+$ ,  $\text{K}^+$ ,  $\text{Ca}^{2+}$ ,  $\text{Mg}^{2+}$ , and water in the second half of the proximal tubule.



#### b. Reabsorption and secretion – loop of Henle

1) Chemical composition of filtrate is different but still isosmotic

2) Reabsorption continues

3) Water – only in descending limb

i. 15%

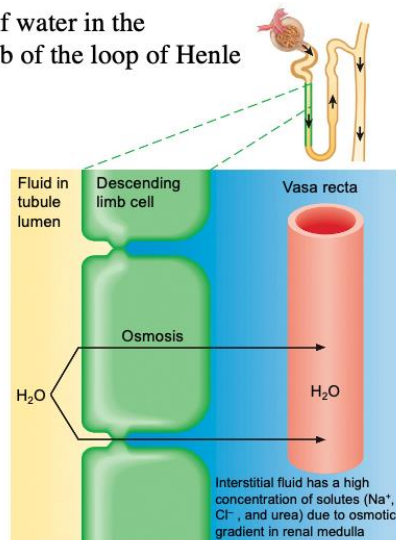
4) Ions – only in ascending limb

i. 20–30%

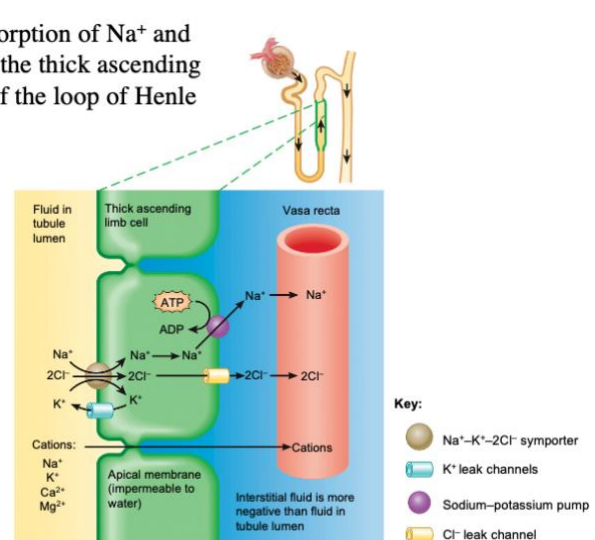
5) Bicarbonate

i. 10–20%

Reabsorption of water in the descending limb of the loop of Henle



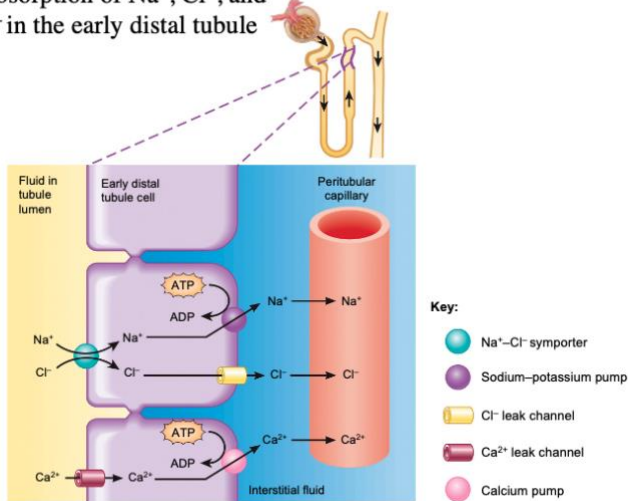
Reabsorption of  $\text{Na}^+$  and  $\text{Cl}^-$  in the thick ascending limb of the loop of Henle



### c. Reabsorption and secretion – early distal tubule

- 1) Little reabsorption takes place
- 2) Mostly  $\text{Na}^+$  and  $\text{Cl}^-$
- 3) Carried out but the  $\text{Na}^+/\text{Cl}^-$  symporters

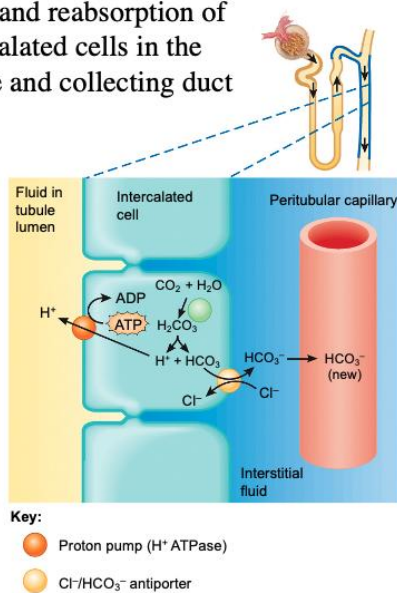
Reabsorption of  $\text{Na}^+$ ,  $\text{Cl}^-$ , and  $\text{Ca}^{2+}$  in the early distal tubule



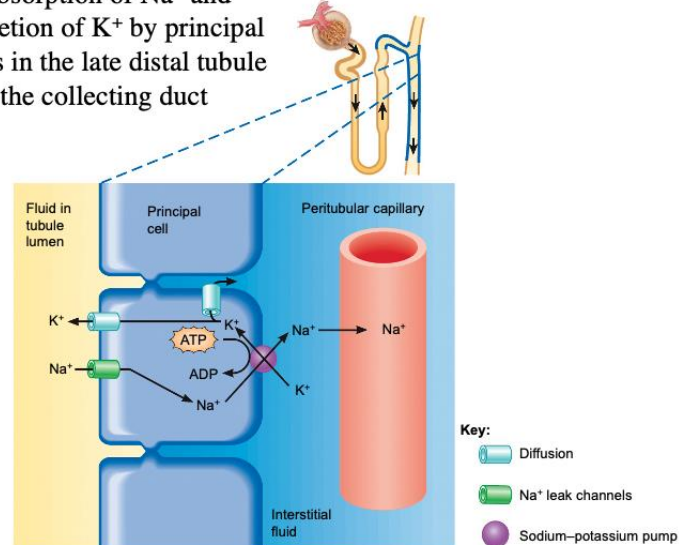
### d. Reabsorption and secretion – late distal tubule and collecting duct

- 1) Two different cell types present
  - i. Principal cells
    1. Reabsorb  $\text{Na}^+$
    2. Secrete  $\text{K}^+$
  - ii. Intercalated cells
    1. Reabsorb  $\text{HCO}_3^-$
    2. Secrete  $\text{H}^+$

Secretion of  $\text{H}^+$  and reabsorption of  $\text{HCO}_3^-$  by intercalated cells in the late distal tubule and collecting duct



Reabsorption of  $\text{Na}^+$  and secretion of  $\text{K}^+$  by principal cells in the late distal tubule and the collecting duct



## E. Hormonal control of secretion and absorption

### 1. Antidiuretic hormone (ADH)

- a. Also known as vasopressin
- b. ADH is produced by neurons in the hypothalamus and is stored and released from the posterior pituitary gland
- c. Secreted in response to increased plasma osmolarity and decreased blood volume
- d. Stimulates facultative water reabsorption. Promotes water reabsorption by inserting aquaporins into the collecting duct

### 2. Other hormones

#### a. Renin-angiotensin-aldosterone system

- 1) Triggered when blood pressure and blood volume decrease
- 2) Decreased filtration
- 3) Stimulates reabsorption of  $\text{Na}^+$  which facilitates reabsorption of water
- 4) Renin secreted by juxtaglomerular cells
- 5) Angiotensin converting enzyme secreted by lungs
- 6) Aldosterone produced and secreted by adrenal cortex
  - i. Secreted in response to low blood volume and increased plasma potassium
  - ii. Targets the late distal tubule and collecting duct
  - iii. Increases sodium reabsorption
  - iv. Increases potassium and hydrogen secretion

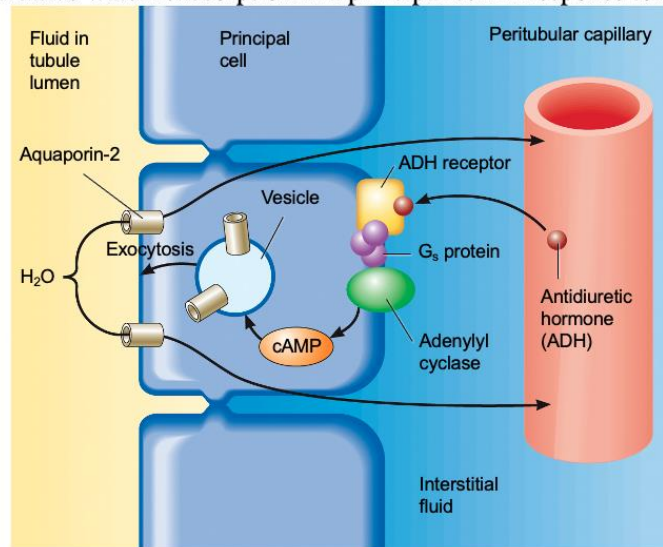
#### b. Atrial natriuretic peptide (ANP)

- 1) Inhibit reabsorption of  $\text{Na}^+$
- 2) Increases urine output

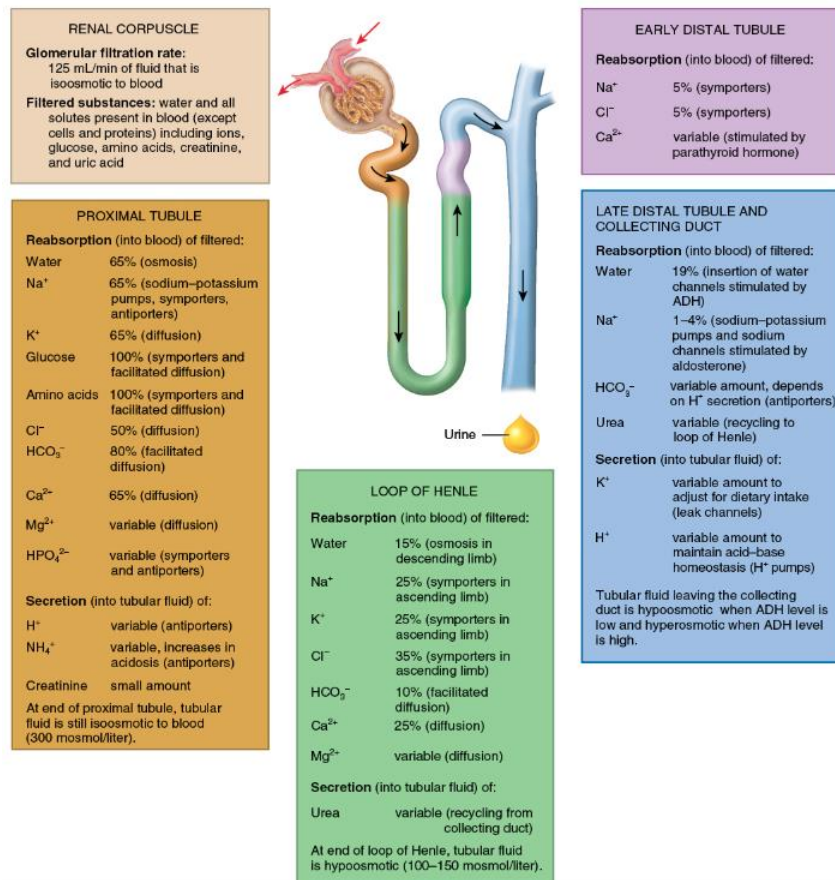
#### c. Parathyroid hormone

- 1) Stimulates the reabsorption of  $\text{Ca}^{++}$

### Facultative water reabsorption in a principal cell in response to ADH



### Summary of filtration, reabsorption, and secretion in the nephron and collecting duct.



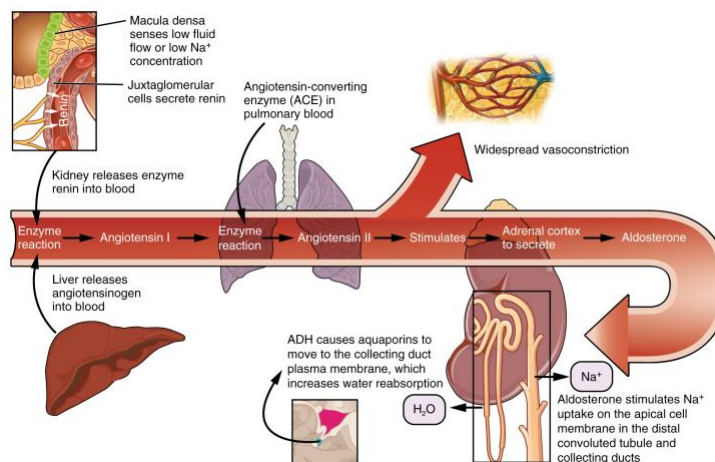
## VI. Regulating Blood Pressure: The Renin Angiotensin Aldosterone System (RAAS)

- A. A structure associated with the nephron—the juxtaglomerular apparatus (JGA), which is located adjacent to the efferent and afferent arterioles at the transition point between the ascending limb of the nephron loop and the distal tubule. It plays an important role in regulating blood pressure. The JGA consists of two groups of cells: the juxtaglomerular



cells of the afferent arteriole and the macula densa cells of the distal tubule. When blood pressure in the renal corpuscle drops, the cells of the JGA release the enzyme renin. The level of renin increases in the blood which will then convert angiotensinogen (a plasma protein produced by the liver), into angiotensin I. This now circulates around the body and once blood arrives at the capillaries, particularly the ones of the lungs, the enzyme: angiotensin- converting enzyme converts angiotensin I into the hormone angiotensin II.

- B. A series of subsequent reactions in the blood plasma results in the production of angiotensin II, which has three major effects: (1) It directly stimulates blood vessels to constrict; (2) it stimulates the posterior pituitary to release antidiuretic hormone (ADH), which stimulates the reabsorption of water by the kidneys; and (3) it stimulates the adrenal cortex to release aldosterone, which induces the kidneys to reabsorb sodium (and thus water via the resulting osmosis). The constriction of blood vessels raises blood pressure directly; the reabsorption of water resulting from the action of ADH and aldosterone increases blood volume, which also increases blood pressure. When blood pressure rises to within its homeostatic range, the JGA stops releasing renin.



## VII. Production of Dilute and Concentrated Urine

Even though your fluid intake can be highly variable, the total volume of fluid in your body normally remains stable. Homeostasis of body fluid volume depends in large part on the ability of the kidneys to regulate the rate of water loss in urine. Normally functioning kidneys produce a large volume of dilute (hypoosmotic) urine when fluid intake is high, and a small volume of concentrated (hyperosmotic) urine when fluid intake is low or fluid loss is large. ADH controls whether dilute urine or concentrated urine is formed. In the absence of ADH, urine is very dilute. However, a high level of ADH stimulates reabsorption of more water into blood, producing a concentrated urine.

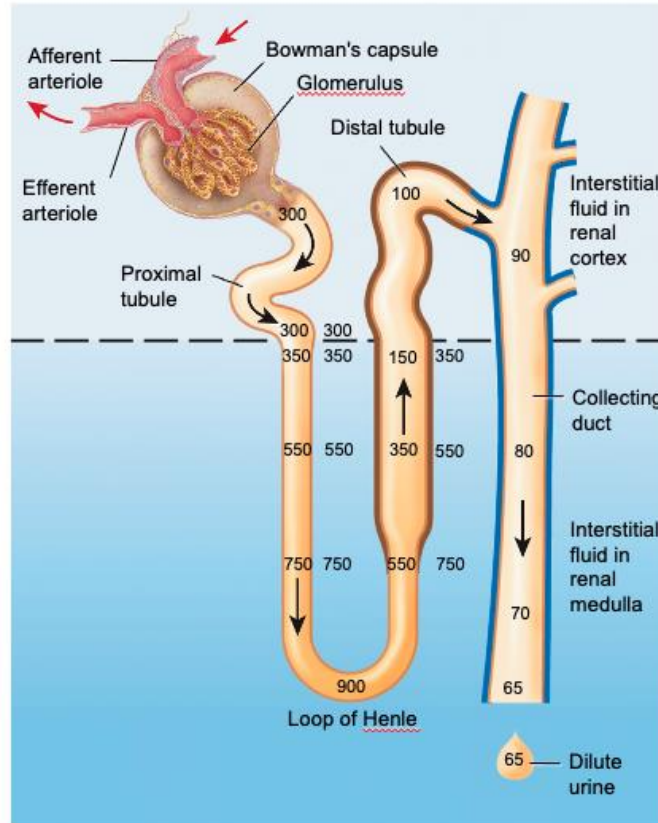
## **A. Production of dilute urine allows the kidneys to get rid of excess water**

1. Glomerular filtrate has the same ratio of water and solute particles as blood; its osmolarity is about 300 mosmol/liter. As previously noted, fluid leaving the proximal tubule is still isoosmotic to blood plasma. When dilute urine is being formed, the osmolarity of the fluid in the tubular lumen increases as it flows down the descending limb of the loop of Henle, decreases as it flows up the ascending limb, and decreases still more as it flows through the rest of the nephron and collecting duct. These changes in osmolarity result from the following conditions along the path of tubular fluid:

- a. Because the osmolarity of the interstitial fluid of the renal medulla becomes progressively greater, more and more water is reabsorbed by osmosis as tubular fluid flows along the descending limb toward the tip of the loop. As a result, the fluid remaining in the lumen becomes progressively more concentrated.
- b. Cells lining the thick ascending limb of the loop of Henle have symporters that actively reabsorb  $\text{Na}^+$ ,  $\text{K}^+$ , and  $\text{Cl}^-$  from the tubular fluid. The ions pass from the tubular fluid into thick ascending limb cells, then into interstitial fluid, and finally some diffuse into the blood inside the vasa recta.
- c. Although solutes are being reabsorbed in the thick ascending limb, water permeability of this portion of the nephron is always quite low, so water cannot follow by osmosis. As solutes—but not water molecules—are leaving the tubular fluid, the osmolarity of the tubular fluid drops to about 150 mosmol/liter. Fluid entering distal tubule is thus more dilute than plasma.
- d. While the fluid continues flowing along the early distal tubule, more solutes, but only a small number of water molecules, are reabsorbed. The cells of the early distal tubule are not very permeable to water and are not regulated by ADH.
- e. Finally, the principal cells of the late distal tubule and collecting duct are impermeable to water when the blood concentration of ADH is very low. Because additional solutes but very few water molecules are reabsorbed in these regions when there is a very low blood ADH level, tubular fluid becomes progressively more dilute as it flows onward. By the time the tubular fluid drains into the renal pelvis, its concentration can be as low as 65–70

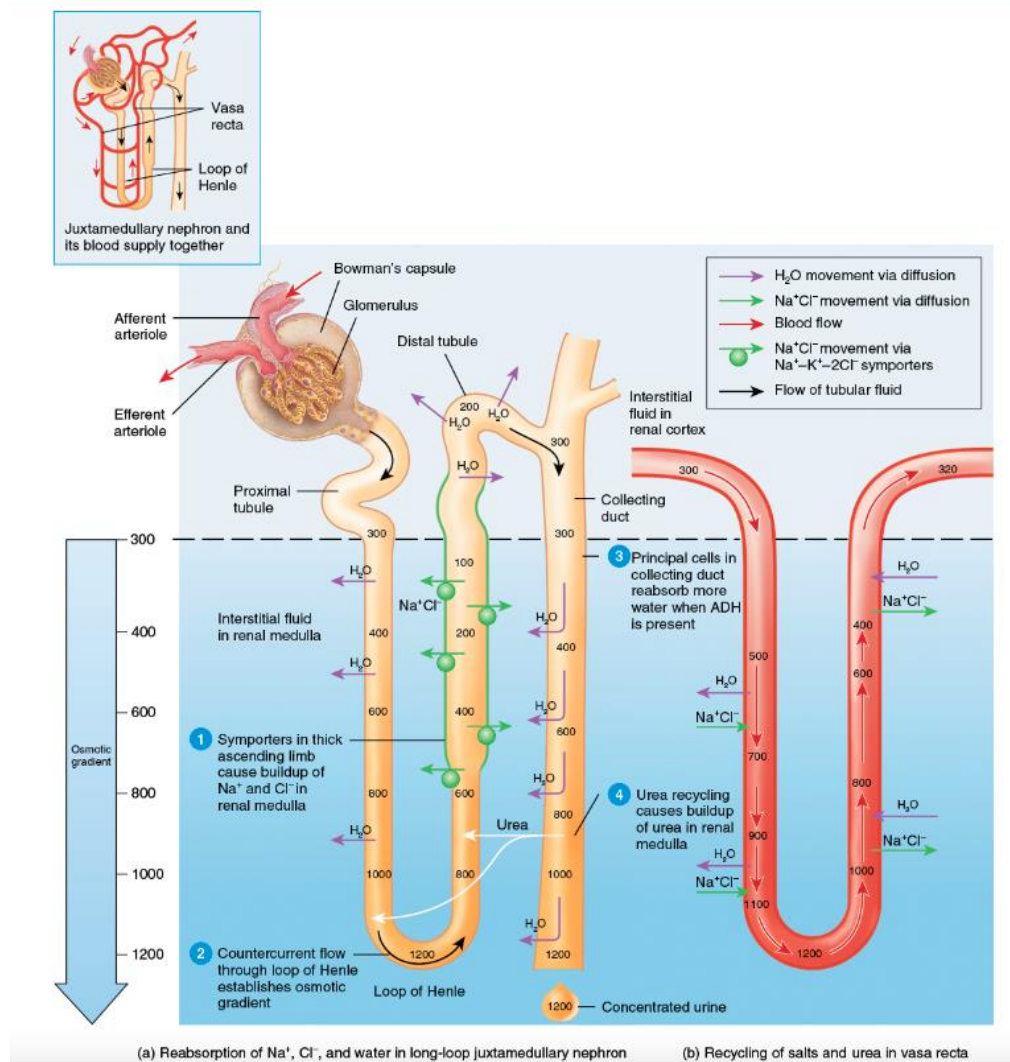


mosmol/liter. This is four times more dilute than blood plasma or glomerular filtrate.



- B. Mechanism of concentrated urine production** – When water intake is low or water loss is high (such as during heavy sweating), the kidneys must conserve water while still eliminating wastes and excess ions. Under the influence of ADH, the kidneys produce a small volume of highly concentrated urine. Urine can be four times more concentrated (up to 1200 mosmol/liter) than blood plasma or glomerular filtrate (300 mosmol/liter).
- The ability of ADH to cause excretion of concentrated urine depends on the presence of an osmotic gradient of solutes in the interstitial fluid of the renal medulla.
  - The three major solutes that contribute to this high osmolarity are  $\text{Na}^+$ ,  $\text{Cl}^-$ , and urea.
  - Two main factors contribute to building and maintaining this osmotic gradient:
    - differences in solute and water permeability and reabsorption in different sections of the long loops of Henle and the collecting ducts and
    - the countercurrent flow of fluid through tube-shaped structures in the renal medulla. Countercurrent flow refers to the flow of fluid in opposite directions. This occurs when fluid flowing in one tube runs counter (opposite) to fluid flowing in a nearby parallel tube. Two types of countercurrent mechanisms

exist in the kidneys: countercurrent multiplication and countercurrent exchange.



- **countercurrent multiplication** – process by which a progressively increasing osmotic gradient is formed in the interstitial fluid of the renal medulla because of countercurrent flow.
  - Production of concentrated urine by the kidneys occurs in the following way:
    - i. Symporters in thick ascending limb cells of the loop of Henle cause a buildup of  $\text{Na}^+$  and  $\text{Cl}^-$  in the renal medulla. In the thick ascending limb of the loop of Henle, the  $\text{Na}^+ - \text{K}^+ - 2\text{Cl}^-$  symporters reabsorb  $\text{Na}^+$  and  $\text{Cl}^-$  from the tubular fluid. Water is not reabsorbed in this segment, however, because the cells are impermeable to water. As a result, there is a buildup of  $\text{Na}^+$  and  $\text{Cl}^-$  ions in the interstitial fluid of the medulla.
    - ii. Countercurrent flow through the descending and ascending limbs of the loop of Henle establishes an osmotic gradient in the renal medulla. Because tubular fluid constantly

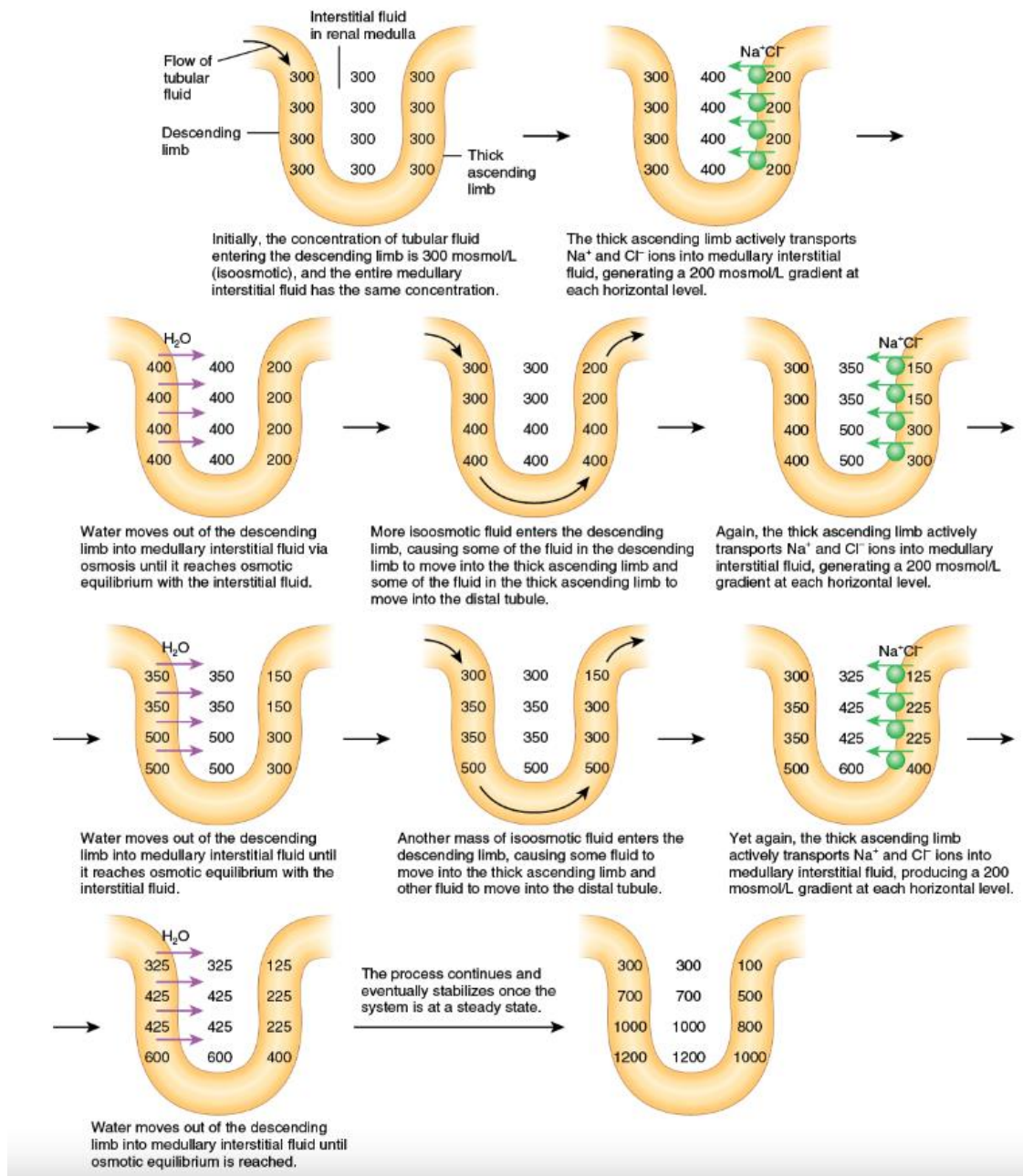
moves from the descending limb to the thick ascending limb of the loop of Henle, the thick ascending limb is constantly reabsorbing  $\text{Na}^+$  and  $\text{Cl}^-$  ions. Consequently, the reabsorbed  $\text{Na}^+$  and  $\text{Cl}^-$  become increasingly concentrated in the interstitial fluid of the medulla, which results in the formation of an osmotic gradient that ranges from 300 mosmol/liter in the outer medulla to 1200 mosmol/liter deep in the inner medulla. The descending limb of the loop of Henle is very permeable to water but impermeable to solutes except urea. Because the osmolarity of the interstitial fluid outside the descending limb is higher than the tubular fluid within it, water moves out of the descending limb via osmosis. This causes the osmolarity of the tubular fluid to increase. As the fluid continues along the descending limb, its osmolarity increases even more: At the hairpin turn of the loop, the osmolarity can be as high as 1200 mosmol/liter in juxtamedullary nephrons. As you have already learned, the ascending limb of the loop is impermeable to water, but its symporters reabsorb  $\text{Na}^+$  and  $\text{Cl}^-$  from the tubular fluid into the interstitial fluid of the renal medulla, so the osmolarity of the tubular fluid progressively decreases as it flows through the ascending limb. At the junction of the medulla and cortex, osmolarity of tubular fluid has fallen to about 100 mosmol/liter. Overall, tubular fluid becomes progressively more concentrated as it flows along the descending limb and progressively more dilute as it moves along the ascending limb.

- iii. Cells in the collecting ducts reabsorb more water and urea. When ADH increases the water permeability of the principal cells, water quickly moves via osmosis out of the collecting duct tubular fluid, into the interstitial fluid of the inner medulla, and then into the vasa recta. With loss of water, the urea left behind in the tubular fluid of the collecting duct becomes increasingly concentrated. Because duct cells deep in the medulla are permeable to it, urea diffuses from the fluid in the duct into the interstitial fluid of the medulla.
- iv. Urea recycling causes a buildup of urea in the renal medulla. As urea accumulates in the interstitial fluid, some of it diffuses into the tubular fluid in the descending and thin ascending limbs of the long loops of Henle, which are also permeable to urea. However, while the fluid flows through the thick ascending limb, distal tubule, and cortical portion of the collecting duct, urea remains in the lumen because cells in these segments are impermeable to it. As fluid flows along collecting duct, water reabsorption continues via osmosis because ADH is present. This water reabsorption further increases the concentration of urea in the tubular fluid, more urea diffuses into the

interstitial fluid of the inner renal medulla, and the cycle repeats. The constant transfer of urea between segments of the renal tubule and the interstitial fluid of the medulla is termed urea recycling. In this way, reabsorption of water from the tubular fluid of the ducts promotes the buildup of urea in the interstitial fluid of the renal medulla, which in turn promotes water reabsorption. The solutes left behind in the lumen thus become very concentrated, and a small volume of concentrated urine is excreted.

- **countercurrent exchange** – is the process by which solutes and water are passively exchanged between the blood of the vasa recta and interstitial fluid of the renal medulla because of countercurrent flow. Note that the vasa recta also consists of descending and ascending limbs that are parallel to each other and to the loop of Henle. Just as tubular fluid flows in opposite directions in the loop of Henle, blood flows in opposite directions in the descending and ascending parts of the vasa recta. Because countercurrent flow between the descending and ascending limbs of the vasa recta allows for exchange of solutes and water between the blood and interstitial fluid of renal medulla, the vasa recta is said to function as a countercurrent exchanger.
- Blood entering the vasa recta has an osmolarity of about 300 mosmol/liter. As it flows along the descending part into the renal medulla, where the interstitial fluid becomes increasingly concentrated,  $\text{Na}^+$ ,  $\text{Cl}^-$ , and urea diffuse from interstitial fluid into the blood, and water diffuses from the blood into the interstitial fluid. But after its osmolarity increases, the blood flows into the ascending part of the vasa recta. Here, blood flows through a region where the interstitial fluid becomes increasingly less concentrated. As a result,  $\text{Na}^+$ ,  $\text{Cl}^-$ , and urea diffuse from the blood back into interstitial fluid, and water diffuses from interstitial fluid back into the vasa recta. The osmolarity of blood leaving the vasa recta is only slightly higher than the osmolarity of blood entering the vasa recta. Thus, the vasa recta provides oxygen and nutrients to the renal medulla without washing out or diminishing the osmotic gradient. Whereas the long loop of Henle establishes the osmotic gradient in the renal medulla by

countercurrent multiplication, the vasa recta maintains the osmotic gradient in the renal medulla by countercurrent exchange.



## VIII. Evaluation of Kidney Function

A. Routine assessment of kidney function involves evaluating both the quantity and quality of urine and the levels of wastes in the blood.

1. Urinalysis - analysis of the physical, chemical, and microscopic properties of urine

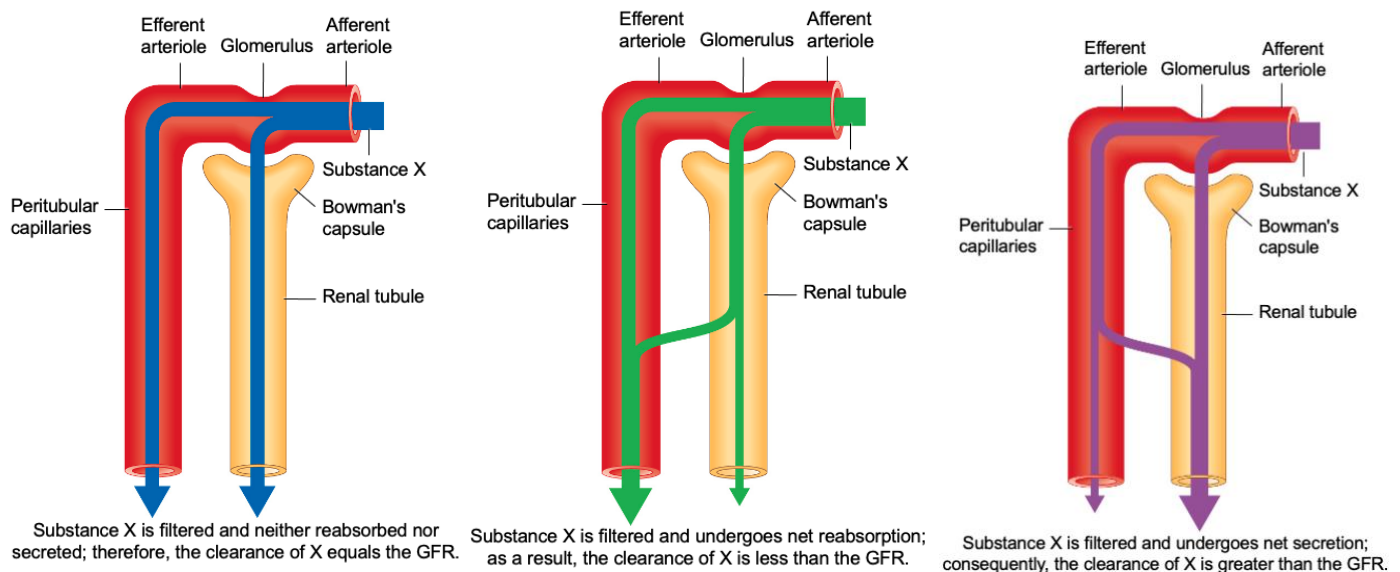
a. Blood urea nitrogen (BUN) - which measures the blood nitrogen that is part of the urea resulting from catabolism and deamination of amino acids. When glomerular filtration rate decreases severely, as may occur with renal disease

or obstruction of the urinary tract, BUN rises steeply. One strategy in treating such patients is to minimize their protein intake, thereby reducing the rate of urea production.

- b. Plasma creatinine – which results from catabolism of creatine phosphate in skeletal muscle. Normally, the blood creatinine level remains steady because the rate of creatinine excretion in the urine equals its discharge from muscle. A creatinine level above 1.5 mg/dL (135 mmol/liter) is usually an indication of poor renal function.

- 2. Renal plasma clearance – indicates how effectively the kidneys are removing a substance from blood plasma.

- a. Even more useful than BUN and blood creatinine values in the diagnosis of kidney problems is an evaluation of how effectively the kidneys are removing a given substance from blood plasma and excreting it into urine.



- 3. Renal failure – occurs because of inadequate kidney function

- a. Acute renal failure (ARF)

- 1) When the kidneys almost completely stop working
- 2) Main feature is suppression of urine flow
- 3) Causes include low blood volume (for example, due to hemorrhage), decreased cardiac output, damaged renal tubules, kidney stones, and certain drugs.
- 4) Causes a multitude of problems:
  - i. There is edema due to salt and water retention

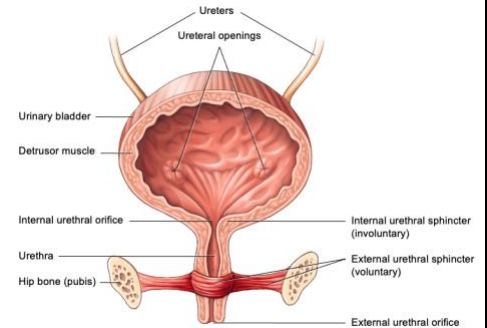
- ii. Acidosis due to an inability of the kidneys to excrete acidic substances
  - iii. In the blood, urea builds up due to impaired renal excretion of metabolic waste products and potassium level rises, which can lead to cardiac arrest.
  - iv. Often, there is anemia because the kidneys no longer produce enough erythropoietin for adequate erythrocyte production.
  - v. Because the kidneys are no longer able to produce calcitriol, which is needed for adequate calcium absorption from the small intestine, osteomalacia (softening of bones) also may occur.
- b. Chronic renal failure (CRF)
- 1) Progressive and irreversible decline in kidney function
  - 2) may result from other kidney disorders or from traumatic loss of kidney tissue.
  - 3) develops in three stages
    - i. **Diminished renal reserve** – nephrons are destroyed until about 75% of the functioning nephrons are lost. At this stage, a person may have no signs or symptoms because the remaining nephrons enlarge and take over the function of those that have been lost.
    - ii. **Renal insufficiency** – Occurs once 75% of the nephrons are lost. Characterized by a decrease in glomerular filtration rate (GFR) and increased blood levels of nitrogen-containing wastes and creatinine. Also, the kidneys cannot effectively concentrate or dilute the urine.
    - iii. **End-stage renal failure** – Final stage, occurs when about 90% of the nephrons have been lost. At this stage, GFR diminishes to 10–15% of normal, oliguria is present, and blood levels of nitrogen-containing wastes and creatinine increase further. People with end-stage renal failure need dialysis therapy and are possible candidates for a kidney transplant operation.

## IX. Urine Transportation, Storage, and Elimination

### A. Urine transportation



1. Once urine is formed in the kidneys, it drains into the minor and major calyces and then into the renal pelvis.
2. From the renal pelvis, urine drains into the ureters
3. Ureters carry urine to the urinary bladder
4. Bladder store urine
5. Excreted through the urethra.



## B. Micturition reflex

1. Micturition – also known as urination or voiding
  - a. Discharge of urine from the bladder
  - b. occurs via a combination of involuntary and voluntary muscle contractions.
2. Coordinated events controlled by spinal cord micturition centers
  - a. When the volume of urine in the urinary bladder exceeds 200–400 mL, pressure within the bladder increases considerably, and stretch receptors in its wall transmit action potentials into the spinal cord.
  - b. Simultaneously, the micturition center inhibits somatic motor neurons that innervate skeletal muscle in the external urethral sphincter.
  - c. Upon contraction of the urinary bladder wall and relaxation of the sphincters, urination takes place.
  - d. Urinary bladder filling causes a sensation of fullness that initiates a conscious desire to urinate before the micturition reflex actually occurs.
3. Urethra conveys urine out to the environment
  - a. Opening of the urethra to the exterior is called the external urethral orifice, which is located between the clitoris and vaginal opening in a female and at the tip of the penis in males
  - b. In both males and females, the urethra is the terminal portion of the urinary system and the passageway for discharging urine from the body.