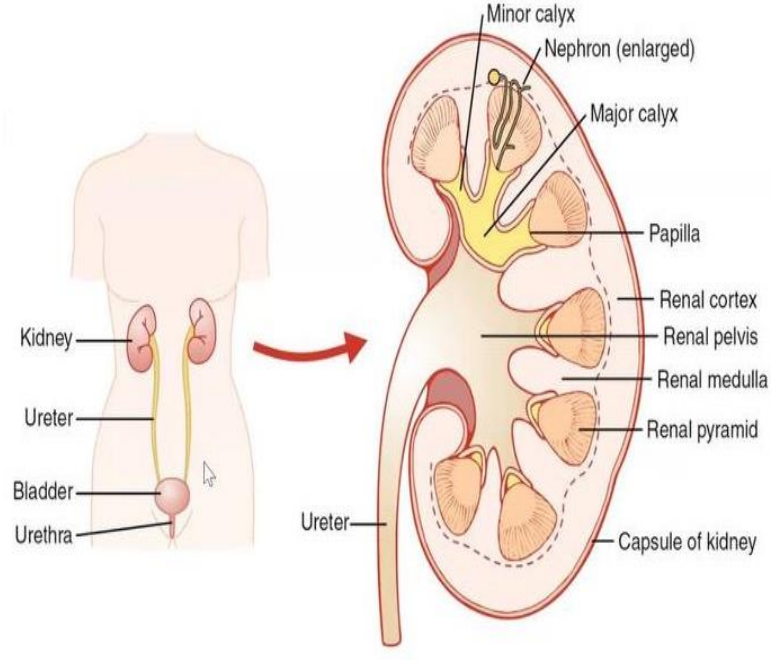
Renal System

Physiology

Pharmacy stage II, Semester I
2025-2026

Renal Physiology

- The urinary system is composed of two kidneys, two ureter, urinary bladder, and urethra.
- The kidneys act on the plasma first converting it to ultra filtrate to which it later add and remove substances so that the final product is urine.
- The kidneys have several functions, including the following:



1 - Kidneys **regulate** water and electrolytes balance: If intake is less than excretion, the amount of that substance in the body will decrease, and vice versa.

2 - Kidneys **responsible** for excretion of metabolic waste products like

- **urea** from the metabolism of amino acids,
- **creatinine** from muscle creatine,
- **uric acid** from nucleic acid,
- **bilirubin** the end product of Hb breakdown,
- metabolites of various **hormones** and foreign chemicals like **drugs** and **toxins**.
- Hormones in the blood are removed in many ways, mostly in the liver, but a number of hormones are removed in parallel by renal processes.
- The level of nitrogenous waste in the blood is typically expressed as blood urea nitrogen **(BUN)**. The urea concentration is normally 7 to 18 mg/dL. An abnormally elevated BUN is called **azotemia** and may indicate renal insufficiency.
- **Azotemia** may progress to uremia, a syndrome of diarrhea, vomiting, dyspnea, and cardiac arrhythmia stemming from the toxic effects of nitrogenous wastes. Convulsions, coma, and death can follow within a few days. Unless a kidney transplant is available, renal failure requires hemodialysis to remove nitrogenous wastes from the blood.

3 - Kidneys play essential role in **regulation** of arterial pressure both in long-term regulation (through excretion of variable amounts of sodium and water) and in short-term regulation (through secretion of vasoactive factors or substances such as renin).

4 - Kidneys contribute to **acid-base regulation** (along with the lungs and body buffers) through excreting acids and by regulating the body buffer stores.

5 - Kidneys responsible for **regulation** of erythrocyte production from the bone marrow by secreting **erythropoietin** which stimulate the bone marrow to produce erythrocytes.

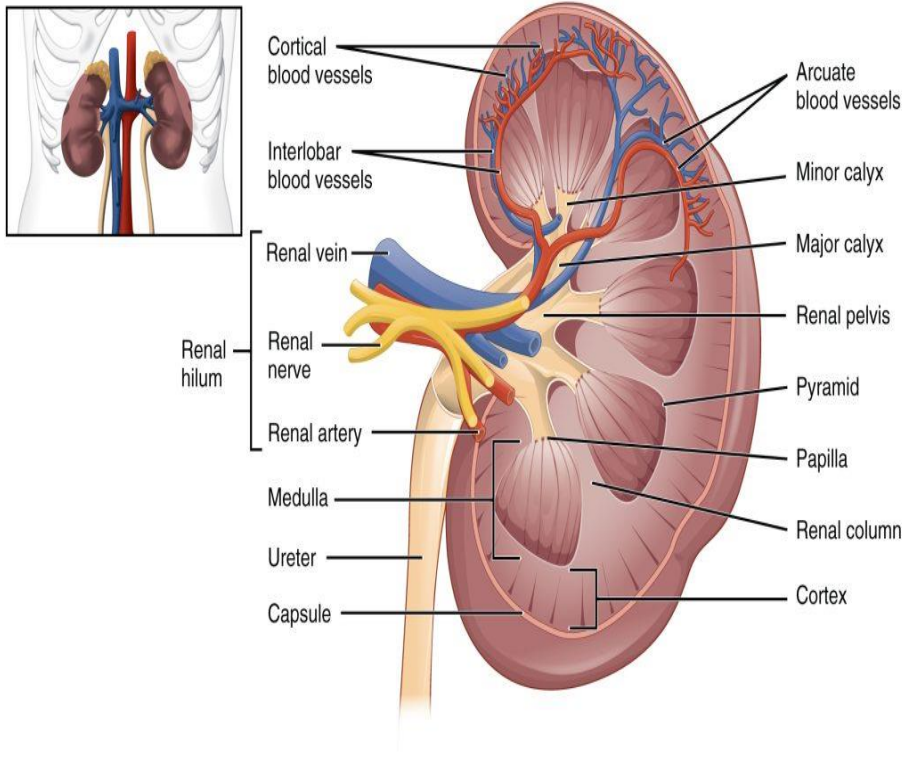
6 - Kidneys **regulate** 1,25-dihydroxy vit. D_3 production which is essential in regulation of Ca and phosphate.

7 - In kidneys, **gluconeogenesis** can take place. Most gluco-neogenesis occurs in the liver, but a substantial fraction occurs in the kidneys, particularly during a prolonged fast.

Anatomy and function of the kidney

Kidneys

- Bean-shaped paired organs covered with fibrous capsule
- Interior of kidney has 2 layers: Renal cortex& Renal Medulla
- • Renal pyramids; cone-shaped pieces of tissue that point toward medial opening of kidney
- Renal Papillae; Tips of pyramids with tiny penings for release of urine from pyramids
- Renal columns; Tissue between pyramids
- Urine from renal papillae empties into cuplike depression called minor calyx— unite to form major calyx.
- Major calyces unite to form funnel-shaped basin called Renal Pelvis (hollow, innermost chamber of kidney)



B. Ureters

- Tube from each kidney that drains urine from pelvis of kidney to the urinary bladder
- Smooth muscle in wall with mucous lining
- Peristalsis pumps urine away from kidney

C. Urinary Bladder

- Stores urine until acceptable time and place to urinate
- Is a hollow sac lined with epithelium capable of stretching greatly
- Capacity: 500ml
- Detrusor muscle—generates APs in response to stretch

D. Urethra

- Single tube continuous with neck of bladder which drains urine from bladder to outside of body

Functional units of kidney (Nephron)

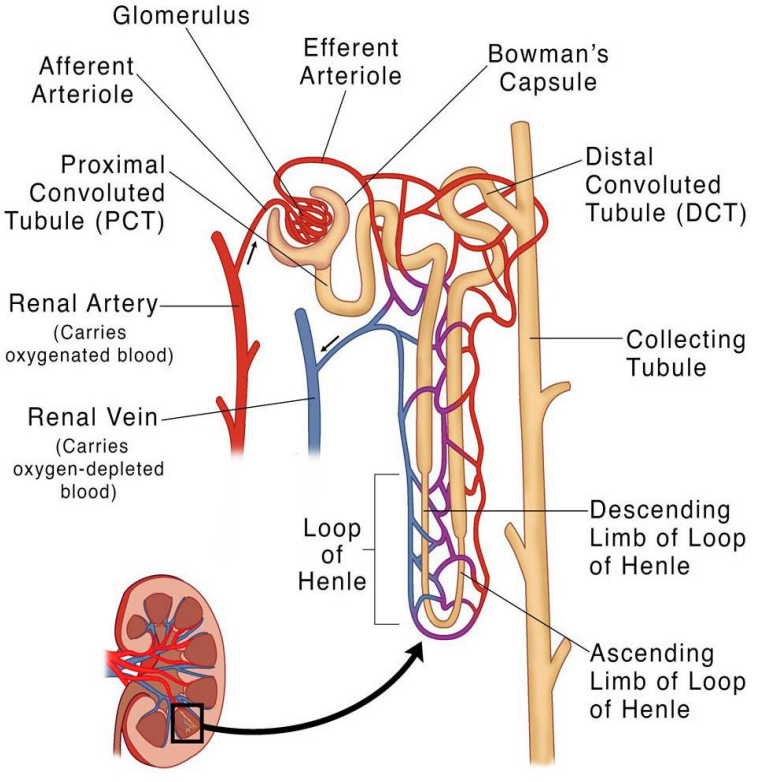
The kidney:

The kidney divided into cortex and medulla, and consists of:

[1] Nephron, [2] Blood vessels and [3] Nerves.

[1] The Nephron:

- It is a tubular system and it is the basic functional unit of the kidney that capable of forming urine by itself.
- There are about 1.3 million nephrons in each kidney in human. Kidneys cannot regenerate new nephrons and their number decrease with aging.
- The human being needs 1/3 of the 1.3 million nephrons in order to survive.

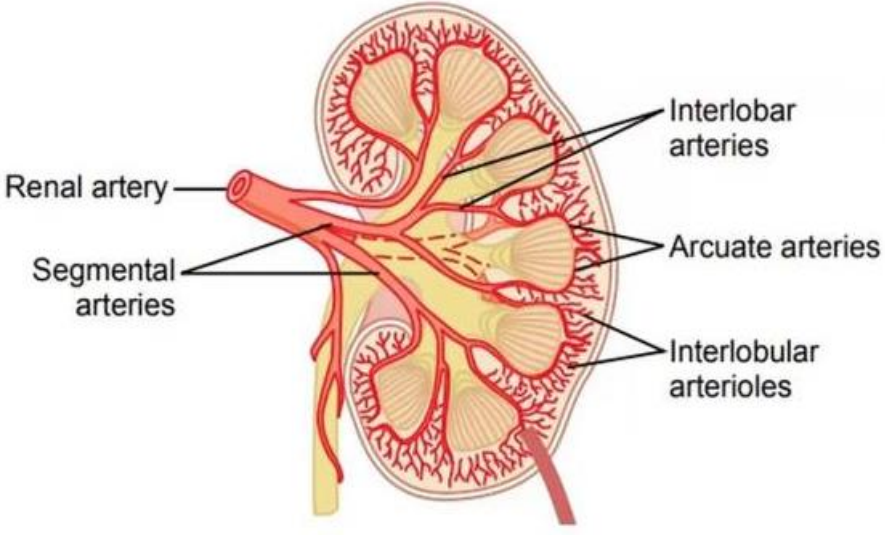


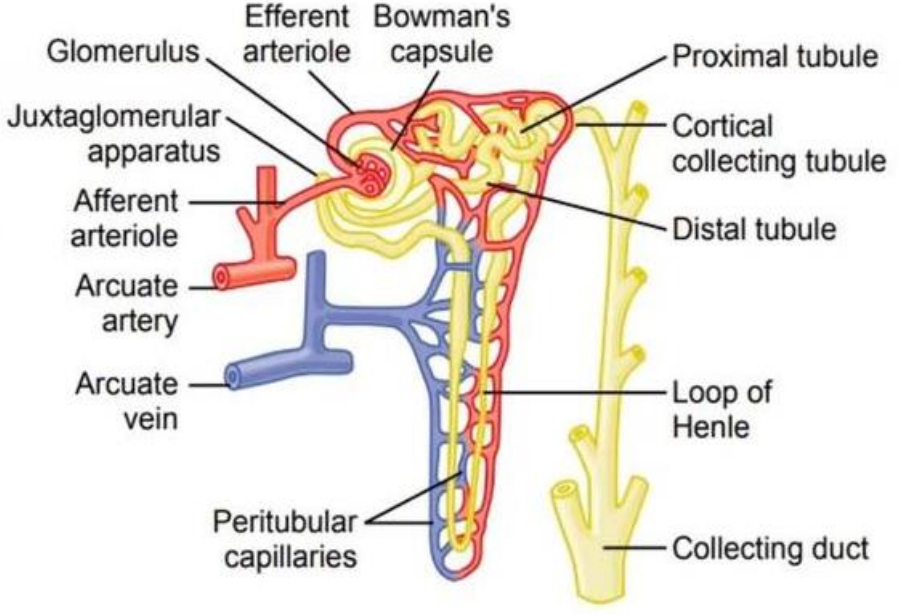
Renal Blood Supply

Blood vessels:

- The renal fraction of the total cardiac output is **about 22%** (vary from 12-30%). In resting adult, the blood flow in renal cortex is about 98% of the total renal blood flow while in medulla is only 2% of the total renal blood flow. This is why the O_2 consumption of cortex is much higher than that of medulla.
- Arterial system of the kidney is technically **a portal system**, because branches twice in the following arrangement: Renal artery ➔ Segmantal artery ➔ Interlobar artery ➔ arcuate artery ➔ Interlobular artery ➔ Afferent arteriole ➔ branching capillaries in Bowman`s capsule (glomerulus) ➔Efferent arterioles ➔ branching around the tubules so called (Peritubular capillaries) ➔ Venules ➔ Interlobular veins ➔ arcuate vein ➔ interlobar vein ➔ Renal veins.
- Most of the peritubular capillary network lies in the renal cortex alongside the proximal, distal, and collecting tubules.

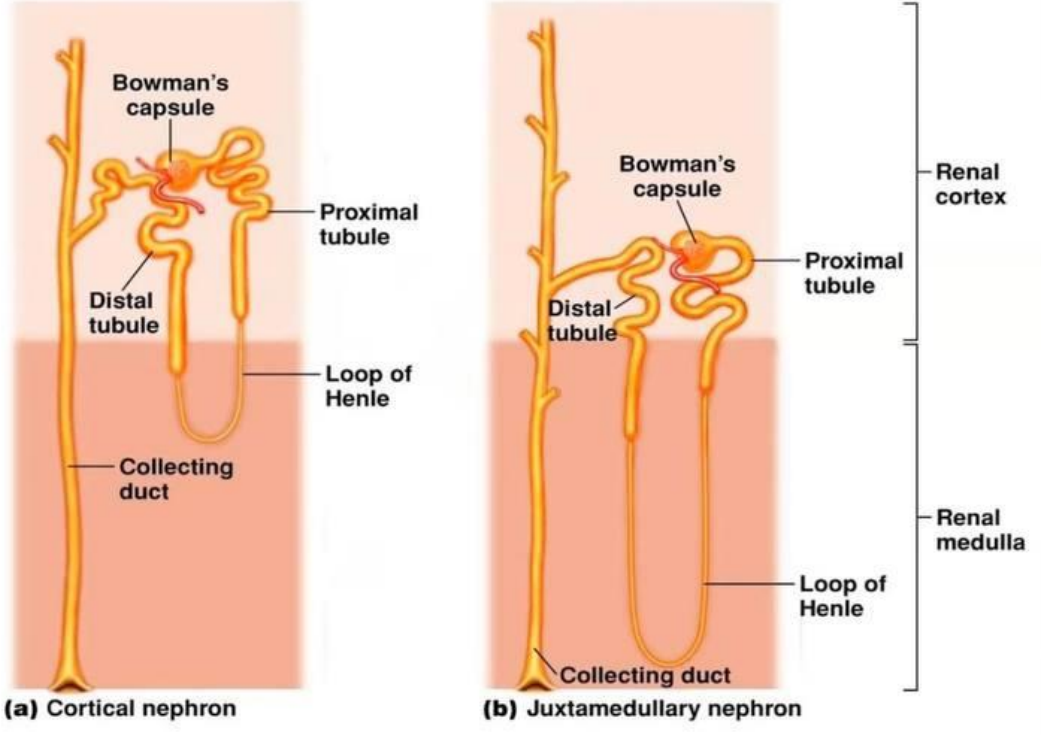
Renal Blood Supply





Types of nephron

- Cortical nephrons
- Juxtamedullary nephrons
  - 20-30%
  - Vasa recta

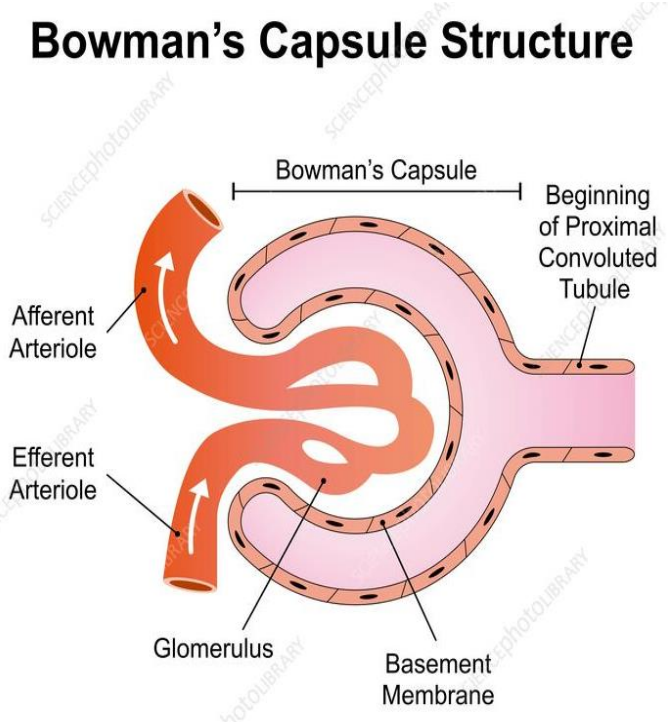


Nephron structure

1- **Bowman's capsule or glomerular capsule**;

completely surrounds glomerulus and receives fluid that is filtered out of glomerulus. Glomerular capsule and its glomerulus make up the Renal Corpuscle.

- **Glomerulus** = a ball-like network of blood capillaries filters water and solute from blood producing blood filtrate that enters urinary tubules
- The membrane of the glomerular capillaries is called the **glomerular membrane (s**
- In general, this membrane is different from other capillary membranes by **having three layers** instead of two. These three layers are endothelial layer of the capillary itself, a basement membrane (basal lamina), and a layer of epithelial cells (podocytes).

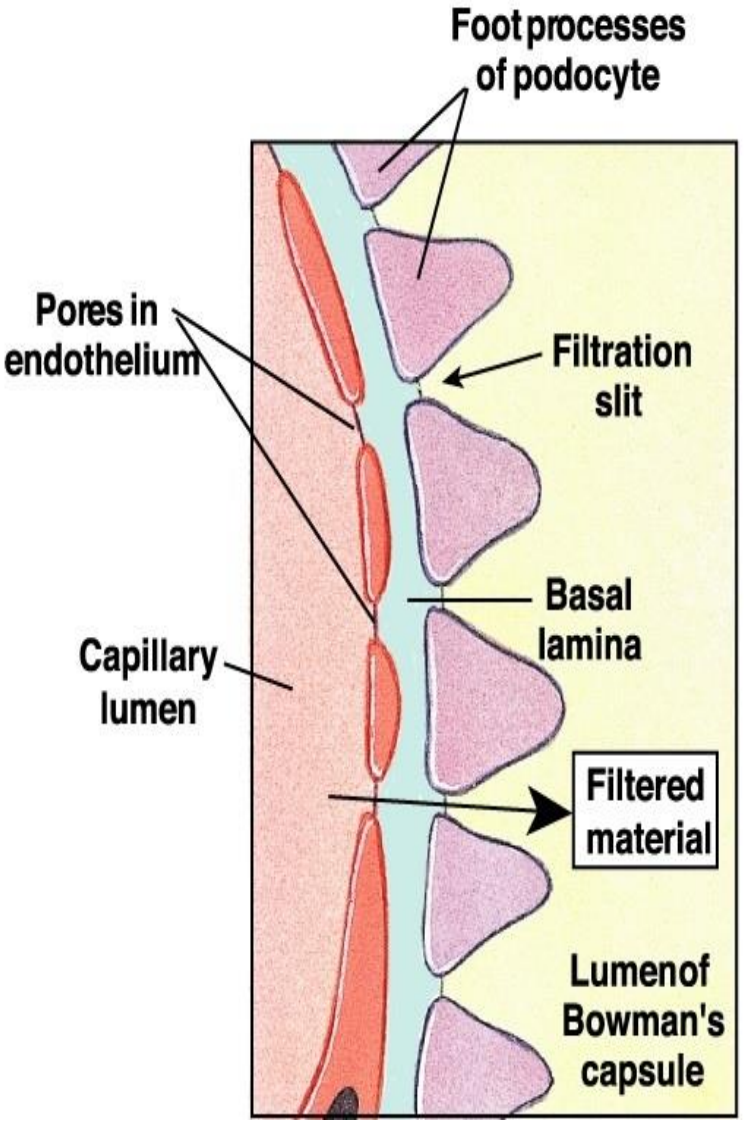


❖ despite the number of layers, the **permeability** of the glomerular membrane is from 100-500 times as great as that of the usual capillary. The tremendous permeability of the glomerular membrane is caused by:

1- The presence of thousands of small holes which are called **fenestrae** in the endothelial cells.

2 - The presence of **large spaces** in the basement membrane.

3 - Incontinuity of the cells that form the epithelial layer which are finger-like projections that forms slits between themselves called **slit-pores** (Filtration Slit).



Four major regions of the nephron:

1. Proximal convoluted tubule (PCT)

- Close to beginning of nephron
- Highly coiled tubule extending from glomerular capsule
- Contains millions of microvilli
- Contains abundant mitochondria In renal cortex

2. *Nephron loop or loop of Henle.*

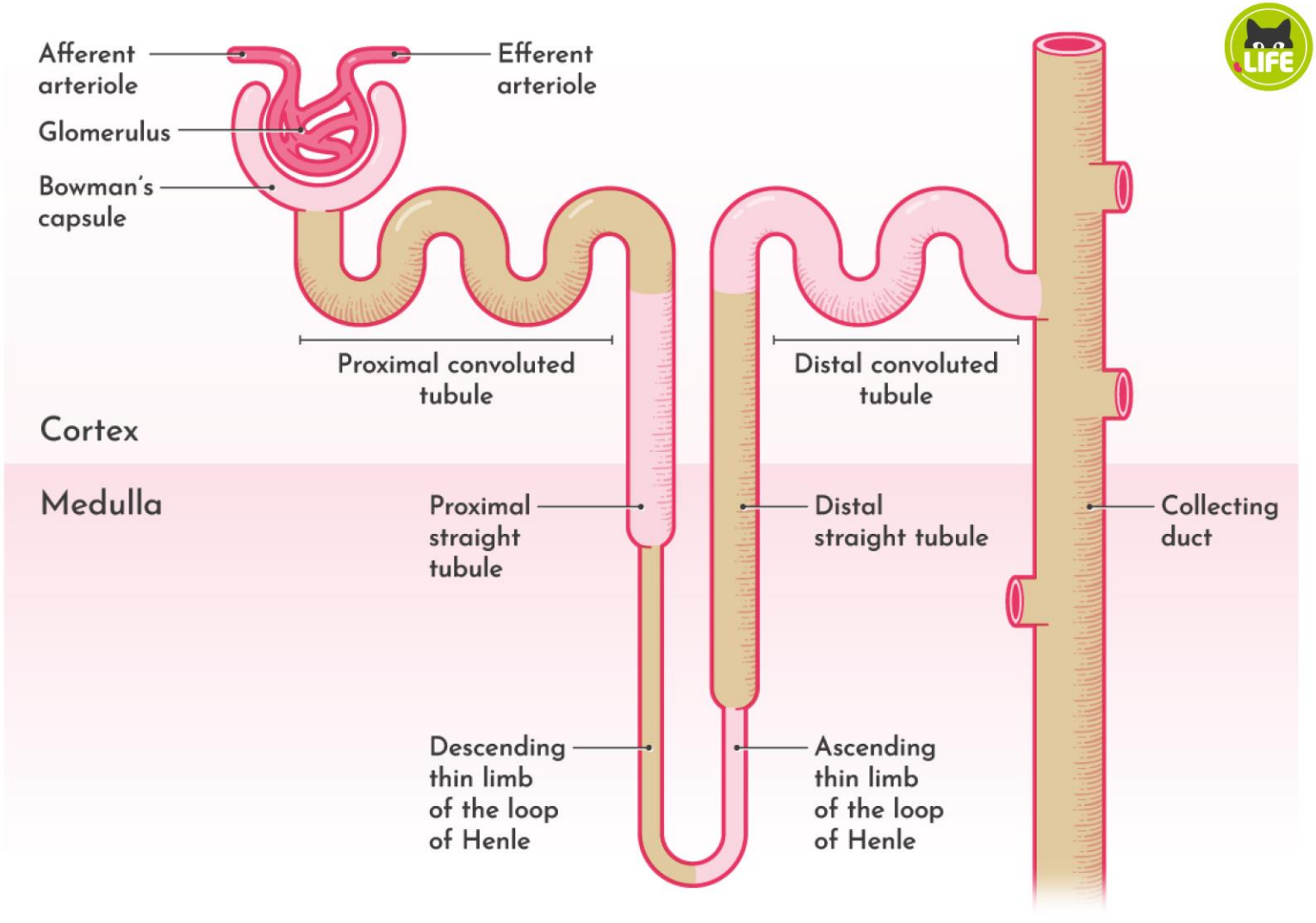
- formed when the PCT straightens out and makes a hairpin loop (like a U) dipping down into medulla, loops from cortex □ medulla □ cortex

3. Distal convoluted tubule (DCT)

- Drains filtrate from nephron loop
- **Shorter** than proximal tubules and few microvilli
- formed when the nephron loop returns to the cortex and winds and twists again before emptying into collecting tubule

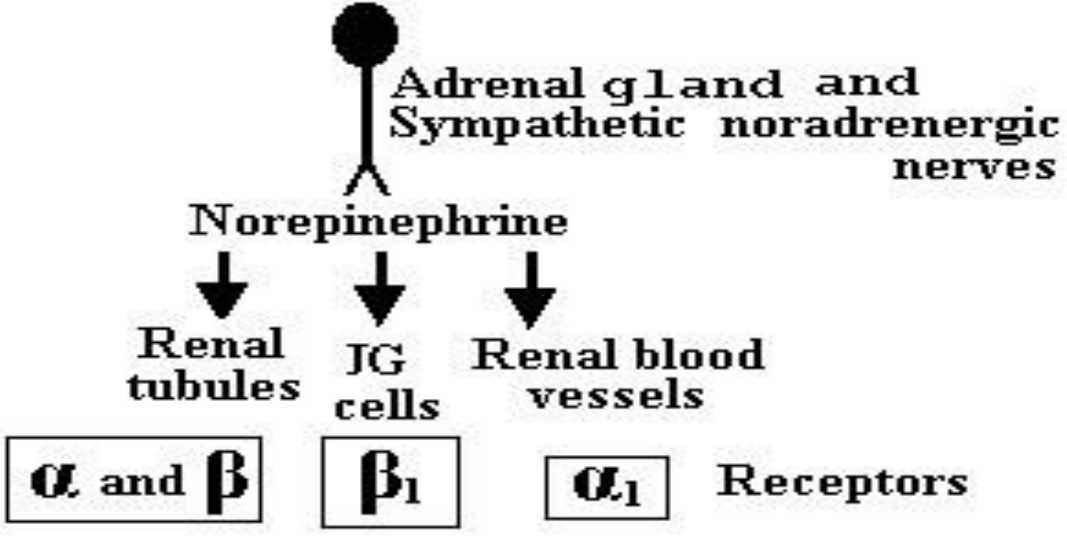
4. Collecting tubule or Collecting Ducts

- collect urine from up to 8 different distal convoluted tubules
- urine flows down the collecting tubule → into calyces in the kidney to renal pelvis → out the kidney through the ureter


Afferent arteriole
Efferent arteriole
Glomerulus
Bowman's capsule
Proximal convoluted tubule
Distal convoluted tubule
Cortex
Medulla
Proximal straight tubule
Distal straight tubule
Collecting duct
Descending thin limb of the loop of Henle
Ascending thin limb of the loop of Henle

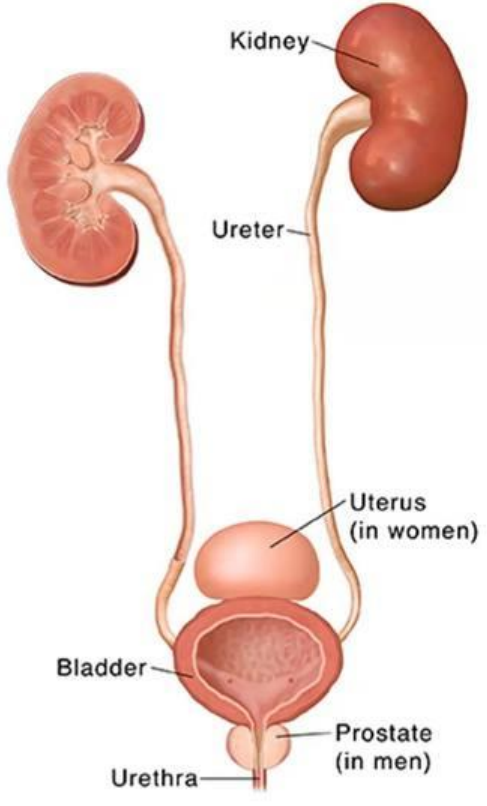
Nerve supply:

- The kidney has a rich adrenergic sympathetic nerve supply distributed to the:
- 1 - Vascular smooth muscle to cause vasoconstriction.
- 2 - Juxtaglomerular cells to cause renin secretion.
- 3 - Tubular cells to stimulate Na and water reabsorption.
- There is no significant parasympathetic innervation



Transport of Urine from the Kidney Through the Ureters and into the Bladder

- Urine that is expelled from the bladder has essentially the same composition as fluid flowing out of the collecting ducts.
- The walls of the ureters contain smooth muscle and are innervated by both sympathetic and parasympathetic nerves, (+ intramural plexus of neurons).

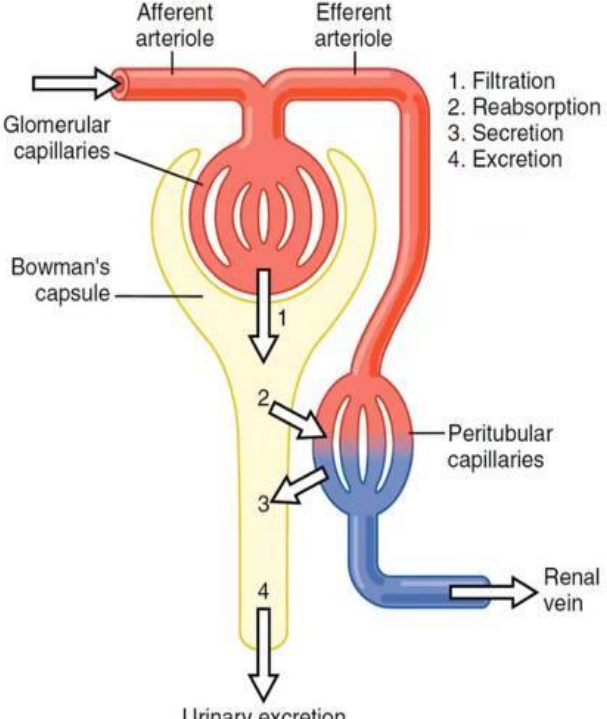


Processes of Urine Formation

- glomerular filtration
- **reabsorption** of substances from the renal tubules into the blood
- **secretion** of substances from the blood into the renal tubules

- Urinary excretion rate = Filtration rate - Reabsorption rate + Secretion rate

They are regulated according to the needs of the body.

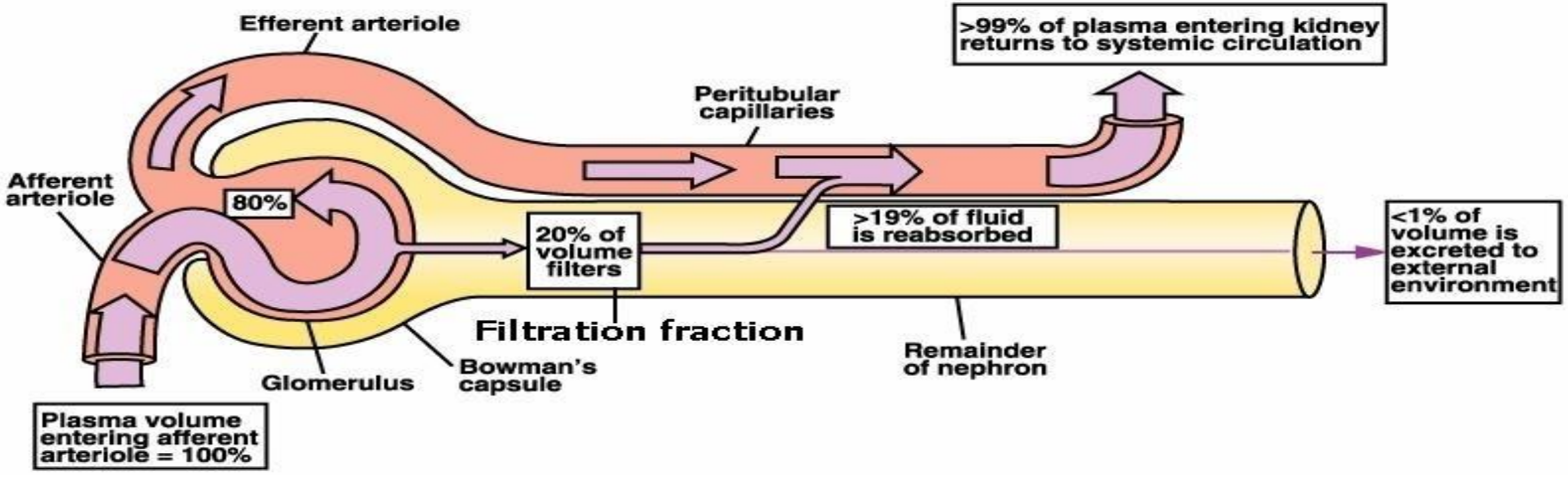


Excretion = Filtration – Reabsorption + Secretion

Glomerular filtration rate (GFR)

- **Glomerular filtration rate (GFR):**
- It is the fluid that filtrate through the glomerulus into Bowman`s capsule each minute in all nephrons of both kidneys which is about **125 ml/min** or **180 L/day** in males (10% lower in female). This is equivalent to 7.5 L per hour or 180 L per day, since the total blood volume averages about 5.5 L, this means that the total blood volume is filtered into the urinary tubules every 40 minutes. The high GFR of the glomerular membrane is due to very high permeability of the capillaries of the glomerulus, which is about 100-500 times as great as that of the usual capillary. Yet, despite the tremendous permeability of the glomerular membrane, it has an extremely high degree of selectivity. The selectivity of the glomerular membrane depends on:
- **[1] Size of the molecules**: Neutral substance with effective molecular diameter of less than 4 nm are **freely filtrated**, and those with diameter more than 8 nm (80 A), **filtration is zero**. Between these two values, filtration is inversely proportional with diameter.

- **[2] The electrical charges of the molecules:**
- This is because the inner side of the pores of the glomerular membrane is negatively charged **repelling** other negatively charged molecules that tend to pass through pores.
- For these two reasons, the glomerular membrane is almost completely **impermeable** to all plasma proteins but is **highly permeable** to all other dissolved substances in normal plasma.
- The composition of the glomerular filtrate is the same as plasma **except** that it has no significant amount of proteins.
- The **filtration fraction** is the fraction of the renal plasma flow that becomes glomerular filtrate. Since the normal plasma flow through both kidneys is 650 ml/min and the normal GFR is 125 ml/min, the average filtration fraction is about 1/5 or 19%.



GFR can be affected by:

[1]: The filtration pressure, which is influenced by:

A. Glomerular capillary hydrostatic pressure (60mm Hg) which is affected by:

I. Renal blood flow.

II. Afferent arteriolar constriction.

III. Efferent arteriolar constriction.

B. Bowman's capsule hydrostatic pressure (18mm Hg).

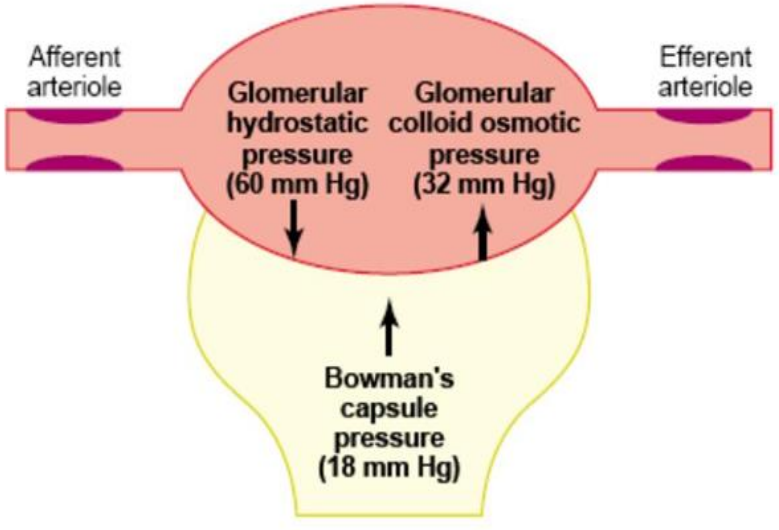
C. Glomerular capillary colloid osmotic pressure (32mm Hg)

D. Bowman's colloid osmotic pressure.

[2]: The capillary filtration coefficient (K_f), which can be affected by:

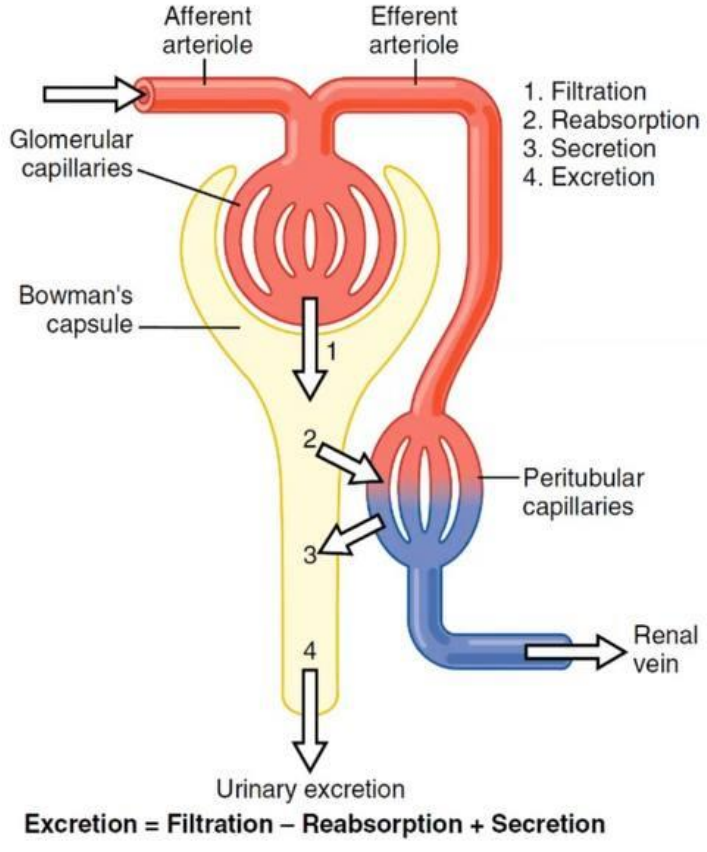
A. The permeability of the glomerular capillaries.

B. The thickness and surface area of capillary bed.



Renal Tubular Reabsorption and Secretion

- **Renal Tubular Reabsorption and Secretion**
- Filtrate flows sequentially through the successive parts of the nephron.
- Urinary excretion = Glomerular filtration – Tubular reabsorption+ Tubular secretion



Reabsorption and Secretion

- **Reabsorption ;**

selected materials of value to the body are removed from tubular filtrate and passed back into the blood returned to the body. 99% of the filtrate is

- **Secretion ;**

transport of solutes from plasma directly into the tubular fluid to:

✓ dispose of substances not already in filtrate (drugs).

✓ toeliminate undesirable substances that have been reabsorbed.

✓ controlling blood pH.

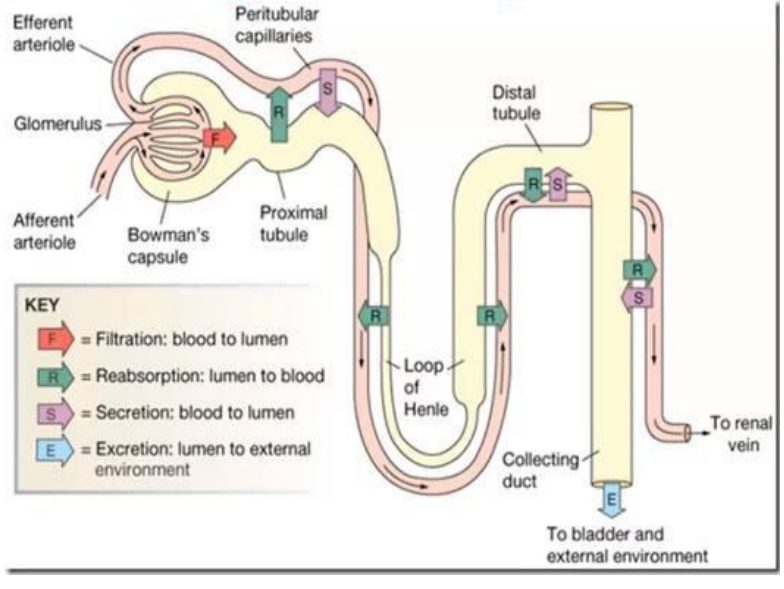
✓ toget rid of excess K.+

Filtration vs Reabsorption

- Filtration = Glomerular filtration rate × Plasma concentration

- glomerular filtration and tubular reabsorption are quantitatively large and closely coordinated.

- tubular reabsorption is highly selective but filtration is not.

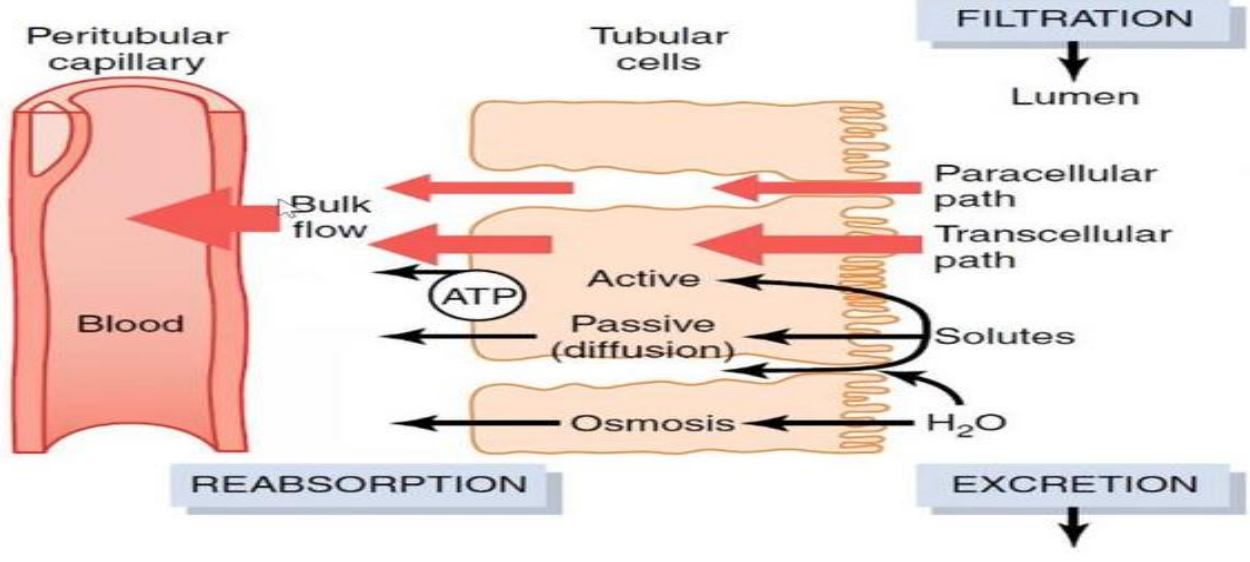


Reabsorption mechanism

Tubular Reabsorption Includes **Passive and Active Mechanisms** For a substance to be reabsorbed, and can be Reabsorption by **Paracellular bath and Transcellular bath** it must first be transported:

(1) across the tubular epithelial membranes into the renal interstitial fluid and then

(2) through the peritubular capillary membrane back into the blood.



Tubular Reabsorption Has a Maximum Rate

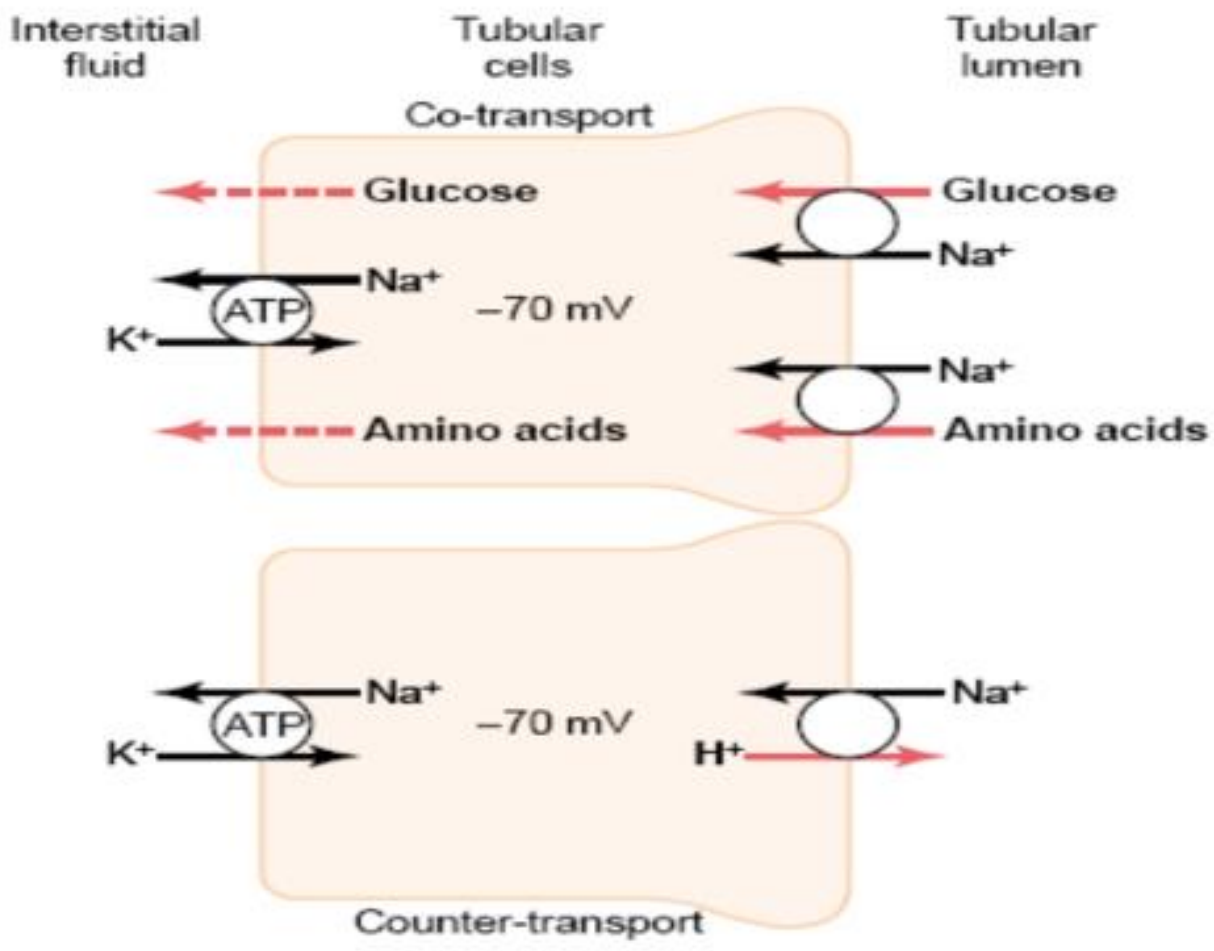
- Most of the solutes filtered into the tubule are reabsorbed because they are too valuable to throw away (glucose & amino acids).

1- In many cases reabsorption is by active transport, requiring ATP **Example of active transport: Na, K pump**:

- Most of the filtered Na is reabsorbed by the Na pump in the proximal tubule (~65%) Na pumping in the ascending loop of Henle sets of osmotic gradients that are used to regulate water (~25%)
- Fine tuning of Na is done by Na pumps in the distal tubule and collecting duct, which are controlled by the hormone, aldosterone

2- Some reabsorption is by secondary active transport the flows are indirectly coupled to the active transport of another substance (such as Na)

Example of secondary active transport: Glucose reabsorption The proximal tubule has a mechanism for cotransport of Na & glucose.


Interstitial fluid
Tubular cells
Tubular lumen
Co-transport
Glucose
Glucose
Na+
Na+
ATP
K+
−70 mV
Na+
Amino acids
Amino acids
Na+
ATP
K+
−70 mV
Na+
H+
Counter-transport

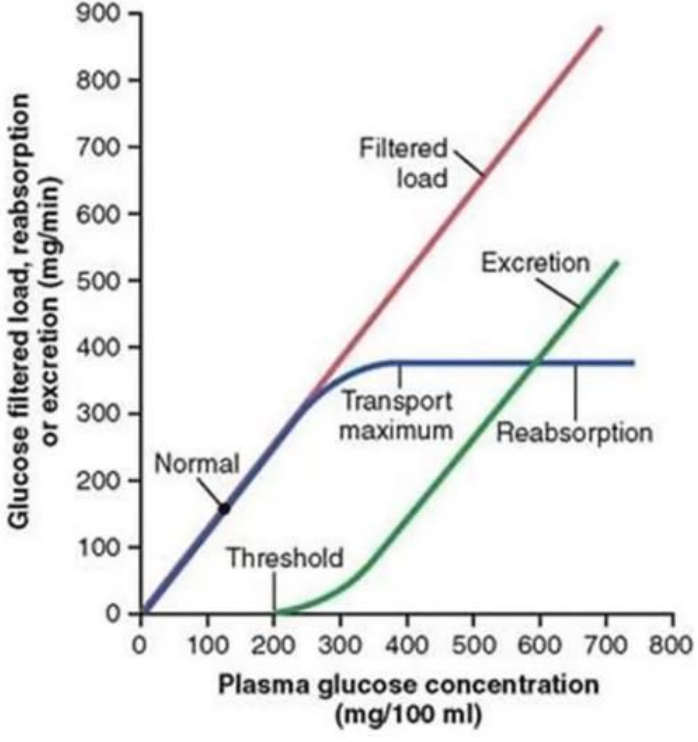
The kidneys "maximum capacity" for reabsorption of a substance is the transport maximum (Tm), or renal threshold.

- e.g. normal blood glucose level is 2.5 to 5.3 mmol/1 (45 to 95 mg/100 ml). If the level rises above the transport maximum of about 9 mmol/1 (160 mg/100 ml) glucose appears in the urine (Glycousuria) **because all the carrier sites are occupied and the mechanism for active transfer out of the tubules is overloaded**.
- When that occurs, some glucose will be excreted into the urine (glucosuria) **diabetes mellitus**.

▪ Note: small amounts of glucose may spill into the urine when plasma concentrations of glucose are low. **This occurs because some of the nephrons have lower tubular maximum rates than others**.

- Maximum transport rate is limited by the number of pump or carrier molecules in the cell membrane

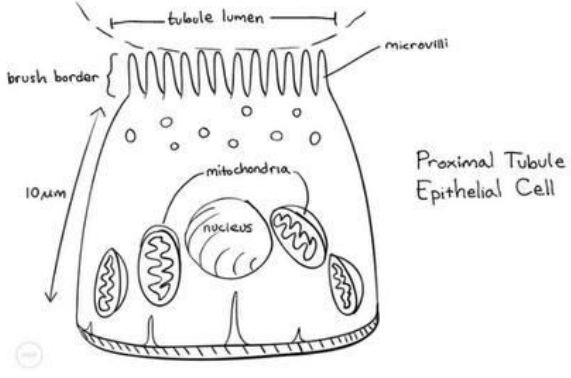
Transport maximum

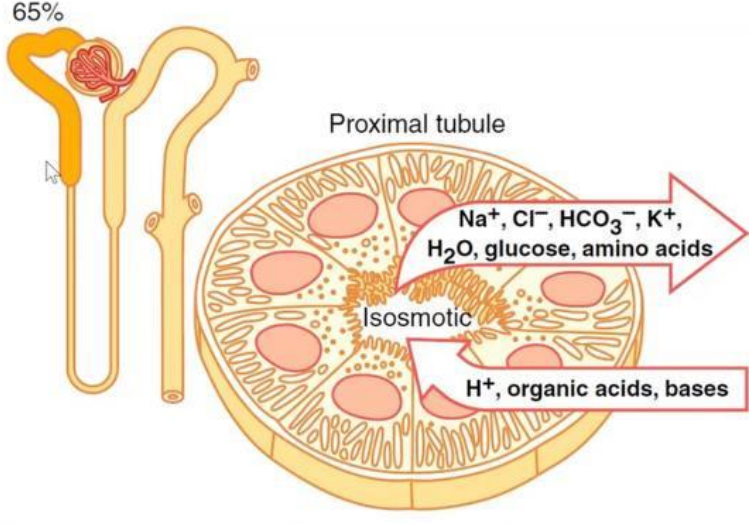


Reabsorption and Secretion Along Different Parts of the Nephron

Proximal Tubular Reabsorption

- Proximal Tubules Have a High Capacity for Active and Passive Reabsorption. Why?!!
  - highly metabolic and have large numbers of mitochondria
  - extensive membrane surface area (brush border….)
  - loaded with protein carrier for co-transport and counter-transpo





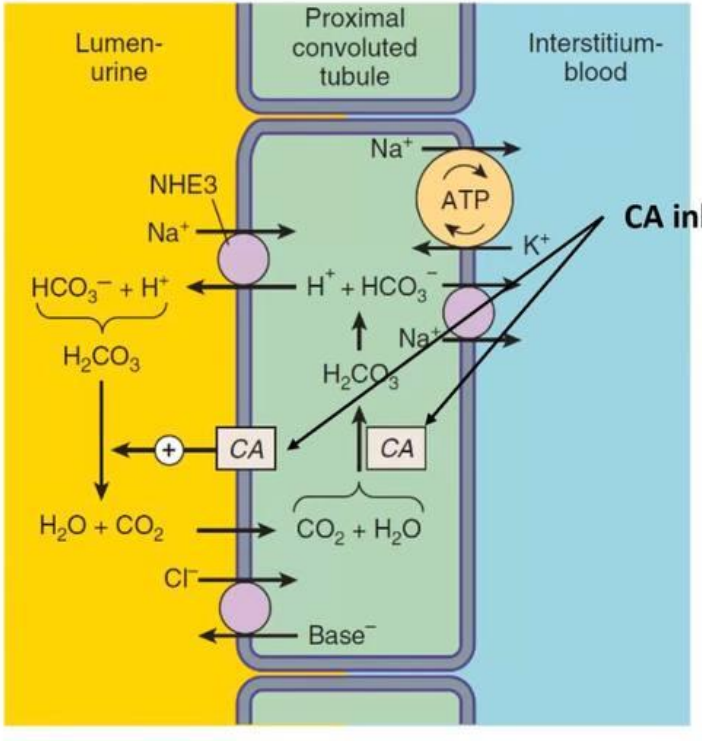
B - The Tubule:

- Throughout its course, the tubule is made up of a single layer of epithelial cells resting on a basement membrane. (Note: All epithelial cell layers rest on a basement membrane). The structural and immunocytochemical characteristics of these epithelial cells vary from segment to segment of the tubule. A common feature is the presence of tight junctions between adjacent cells that physically link them together. The tubule divided in:

1 - Proximal tubules:

- It includes **proximal convoluted** tubule and **proximal straight** tubule. They lie in the renal cortex along with the glomerulus. The epithelial cells of the proximal tubule are highly metabolic cells, with large number of mitochondria to support extremely rapid active transport processes and they are interdigitated with one another and are united by apical tight junction but contain lateral intercellular space. It contains a brush border due to the presence of microvilli.
- Reabsorption in the proximal tubule is essentially **isotonic**; i.e. the osmolality of fluid in all parts of the proximal tubule is approximately to that of plasma.

Proximal Tubule

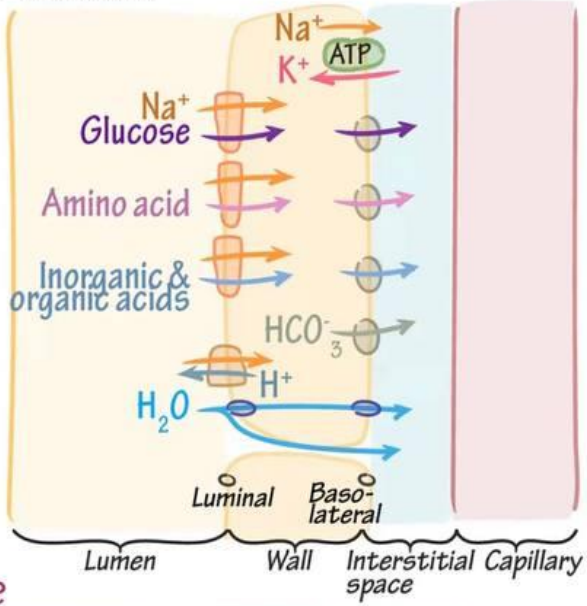


CA inhibitor (acetazolamide)

Sodium Reabsorption

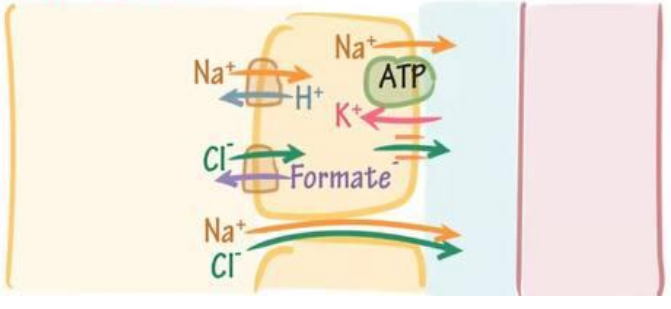
Early Proximal Tubule

Na^+ <> Nutrients, Acids, H^+ secretion



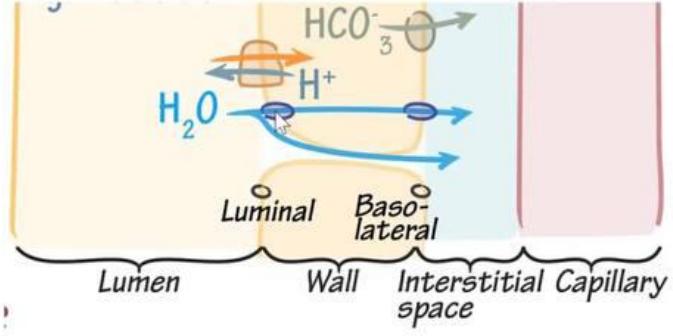
Late Proximal Tubule

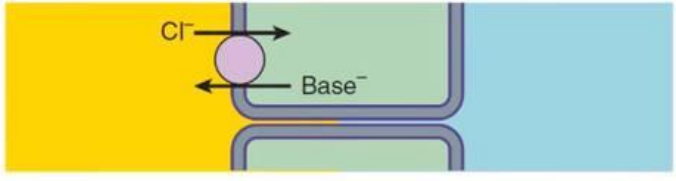
Na^+ <> Cl^-



Proximal Tubule

- Osmolarity, remains essentially the same all along the proximal tubule.
  - Water follow Na^+
- Secretion of organic acids and bases such as bile salts, uric acid, and drugs.





2 - Loops of Henle:

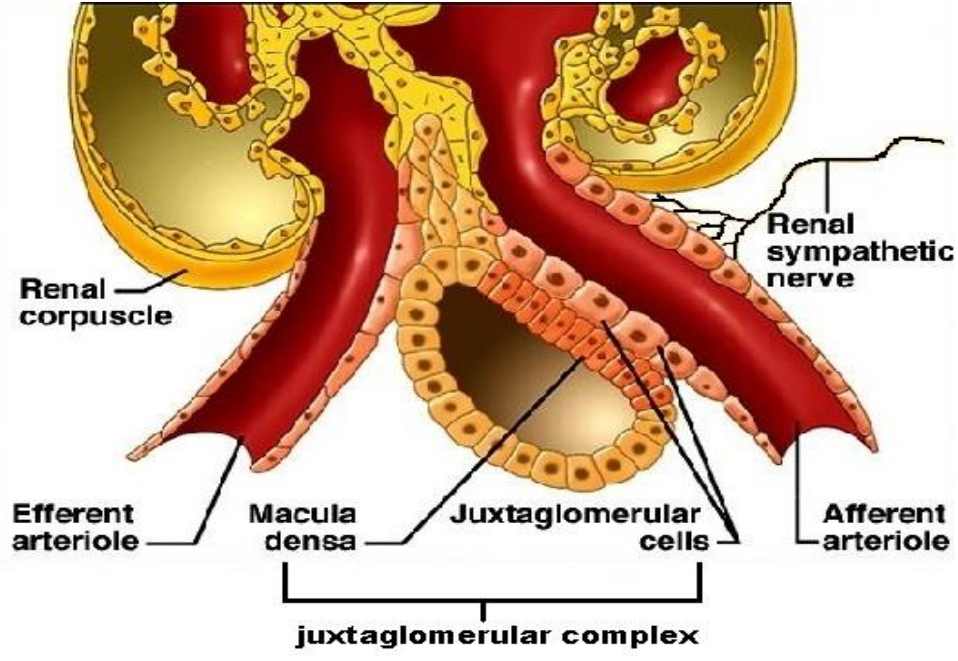
- ✓ The nephrons with their glomeruli located in the outer portion of the renal cortex have short loops of Henle **(cortical nephrons**, **70%),** where as those with glomeruli in the juxtamedullary region of the cortex (**juxtamedullary nephrons**, **30%)** have long loop extending down into medullary pyramids.
- ✓ Loops of Henle **include**: The thin descending segment, the thin ascending segment, and the thick ascending segment.
- ✓ **The thin descending segment of the loop of Henle**: The epithelia cells of it are very thin with no brush border and very few mitochondria. They are highly permeable to **water** but nearly impermeable to urea, sodium and most other ions. About 20% of the filtered water is reabsorbed in the descending thin limb loop of Henle.
- ✓ **The thin ascending segment of the loop of Henle**: The epithelia cells of the ascending thin segment, on the other hand, are far less permeable to water but more permeable to **urea** and **NaCl** than is the descending portion. Because of the ascending thin limb is impermeable to water, no water reabsorption is taking place in this area of the nephron.

✓ **The thick ascending segment of the loop of Henle**:

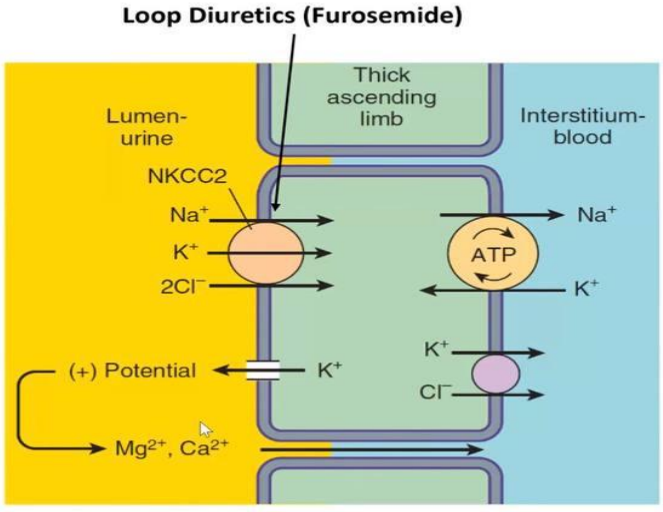
- The epithelial cells of the ascending thick segment are similar to those of the proximal tubules except that they have a rudimentary brush border and much tighter tight junction. The cells adapted for strong active transport of **Na, K,** and **Cl** ions. On the other hand, the thick segment is almost entirely impermeable to both water and urea. Therefore, no water reabsorption is taking place in this area of the nephrone, and this segment is called the diluting segment.
- It is the only segment in which active **Cl** pumping normally occur. This active transport of ions can be inhibited by drugs called loop diuretics such as frusemide, ethacrynic acid, and bumetanide, which consequently abolish the intraluminal positivity. Eventually the passive absorption of Na ions ceases.

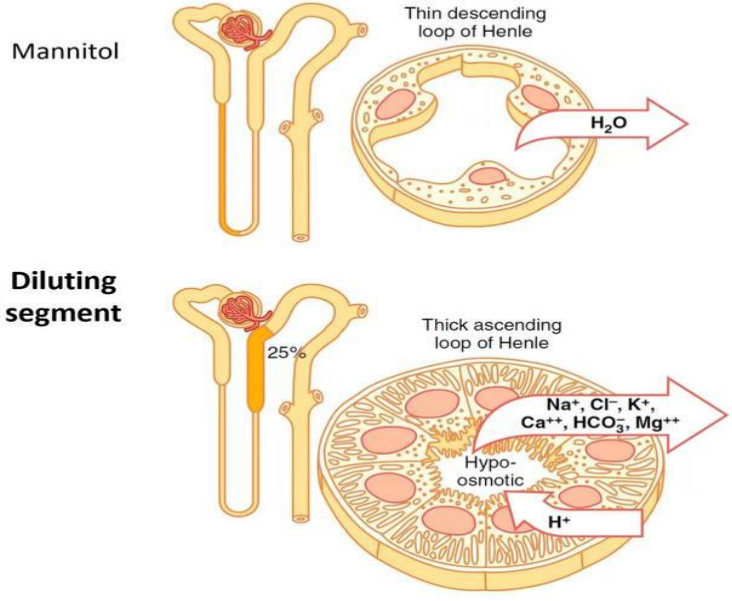
- This thick ascending segment ascends all the way back to the same glomerulus from which the tubule originated and passes tightly through the angle between the afferent and efferent arterioles. The cells of this portion of the thick ascending segment which are in complete attachment with the epithelial cells of the afferent and efferent arterioles are called **Macula densa.**
- The specialized smooth muscle cells of the afferent arterioles that come in contact with the macula densa are called **juxtaglomerular cells** (JG cells) which contain renin granules. Macula densa and JG cells plus few granulated cells between them are collectively known as **juxtaglomerular complex or apparatus** which has a dense adrenergic neural innervation.

- About 25% of filtered loads of **Na**, **Cl**, and **K** (and other ions such as **Ca**, **HCO_3^-** and **Mg**) are reabsorbed in the loop of Henle mainly in the thick ascending limb.
- Because the thick segment of the ascending loop of Henle is impermeable to water, most of the water delivered to this segment remains in the tubule, despite the reabsorption of large amounts of solute. Thus, the tubular fluid in the ascending limb becomes very dilute as it flows toward the distal tubule (**hypotonic**).



LOOP OF HENLE



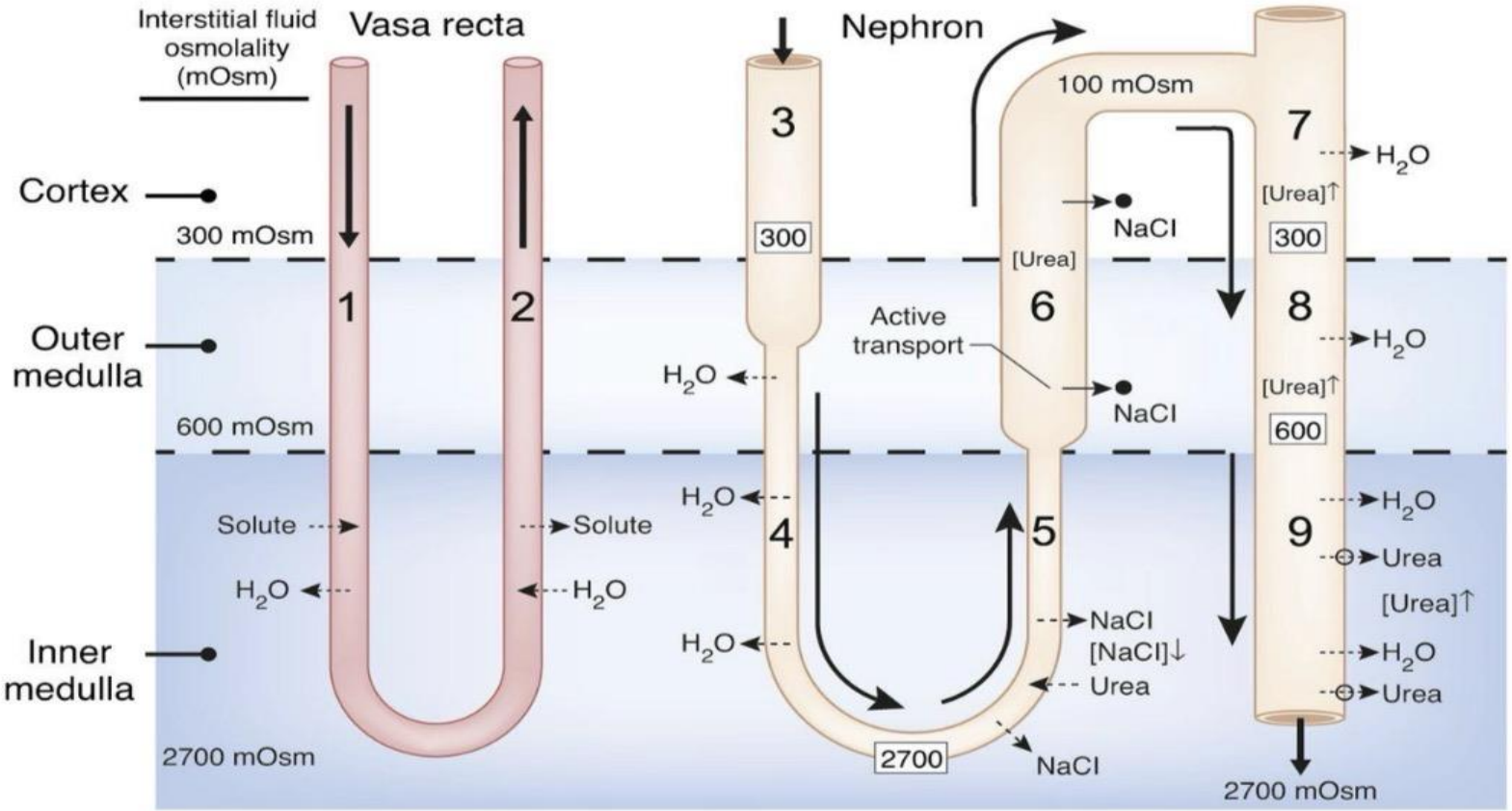


- The TAL reabsorbs **$Na^+ + K^+ + 2Cl^-$** via the **NKCC2** cotransporter (apical).
- **Na^+/K^+-ATPase** on the basolateral side pumps Na^+ to blood and brings K^+ into the cell.
- Some **K^+ recycles to the lumen via ROMK**, generating a **lumen-positive voltage** that drives **paracellular Mg^{2+} and Ca^{2+}** reabsorption.
- Thin descending limbHighly permeable to water, poor solute transport.Water leaves into the hyperosmotic medulla → tubular fluid becomes concentrated.
- Thick ascending limb as the “diluting segment”Impermeable to water but reabsorbs ~25% of filtered NaCl (plus some Ca^{2+}, HCO_3^-, Mg^{2+}).Because salts are reabsorbed without water, fluid leaving the TAL is hypo-osmotic.The segment also secretes a small amount of H^+, contributing modestly to acid–base handling.

Countercurrent mechanism

Refers to inter-actions between the descending and ascending limbs, decreasing water concentration in descending limb encounters an increasing solute concentration → fluid flowing in opposite directions right alongside each other, (multiplies the concentration of interstitial fluid of renal medulla, very high at deepest part of medulla)

- urea exiting from collecting duct adds to high osmolality (and re-enters ascending limb)

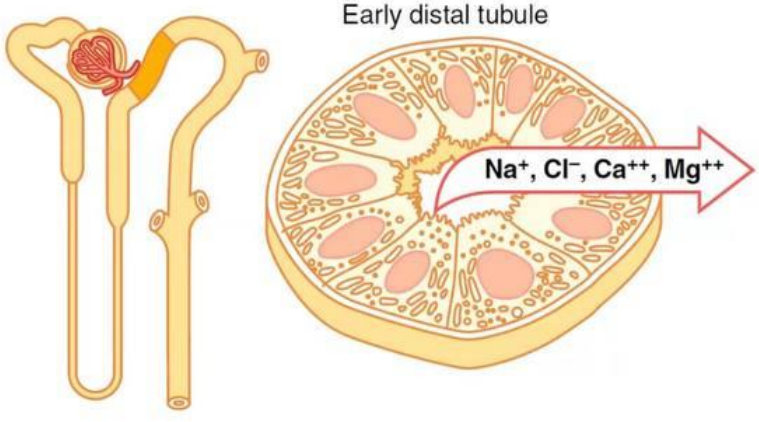


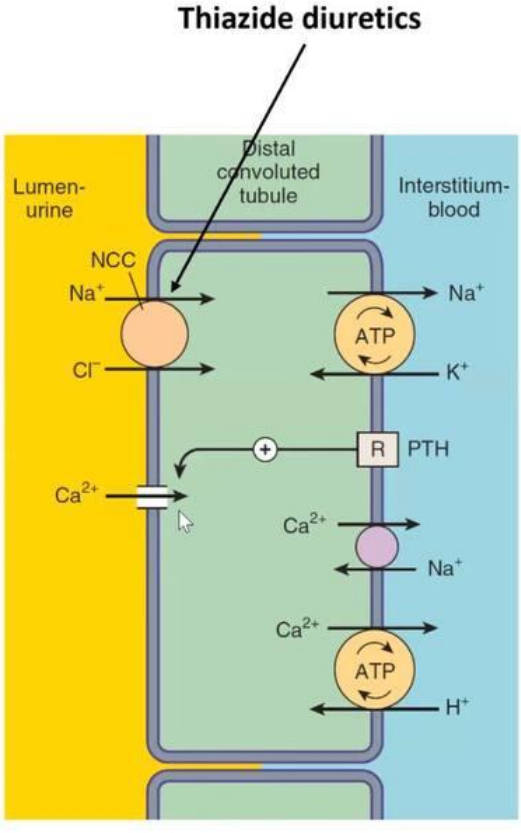
1 descending vas rectum
2 ascending vas rectum
3 proximal tubule
4 descending thin limb
5 ascending thin limb
6 thick ascending limb
7 cortical collecting duct
8 outer medullary collecting duct
9 inner medullary collecting duct

3 - Distal convoluted and Collecting tubules : They lie in the renal cortex.

- The distal tubule (also called the diluting segment) has almost the same characteristics as the thick segment of ascending limb of the loop of Henle. It reabsorbs **Na** ions and other ions but is almost entirely impermeable to both water and urea. This segment is the site of action of special type of diuretics called thiazide and loop diuretics.
- **Reabsorption of water** can occurs in the distal tubule but **only** in the presence of antidiuretic hormone (ADH, or vasopressin). With high level of ADH, these tubular segments are permeable to water, but in the absence of ADH, they are virtually impermeable to water.
- **Reabsorb Na ions** while **secrete K ions** through increase the activity of *Na-K ATPase countertransporter* at the basolateral side of the cells under the effect of the hormone aldosterone.
- **Reabsorb K** ions while **secrete H ions** via *H-K ATPase countertransporter* at the luminal border of the cell.
- **Secretion of H ions** (by *H-ATPase pump*) at the luminal border of the cells after being generated inside the cell by the action of carbonic anhydrase on water and CO_2 to form carbonic acid which then dissociates into H ions and HCO_3^- ions. Then the available $HCO3^-$ ions are reabsorbed across the basolateral membrane. Aldosterone also increases H ion secretion by stimulating the *H-ATPase pump*.

DISTAL CONVOLUTED TUBULE





In the **distal convoluted tubule**, calcium enters the cell from the lumen through **Transient Receptor Potential Vanilloid 5 (TRPV5)** on the **apical** side.

It then leaves the cell into the blood across the **basolateral** side via the **Sodium–Calcium Exchanger 1 (NCX1)** and the **Plasma Membrane Ca^{2+}-ATPase (PMCA)**.

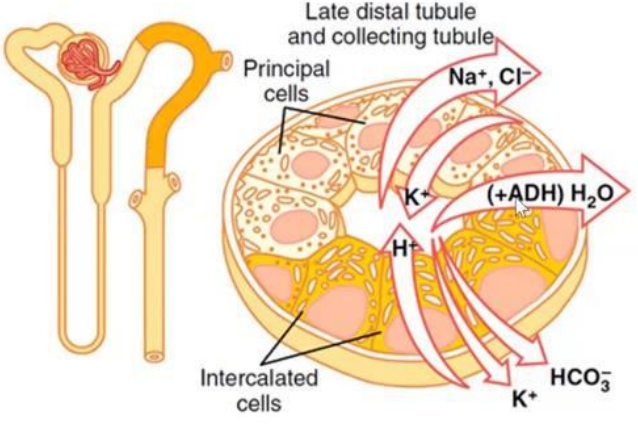
Parathyroid Hormone (PTH) boosts these pathways, so **more Ca^{2+} is reabsorbed into blood → less Ca^{2+}**

4 - Collecting tubules and ducts:

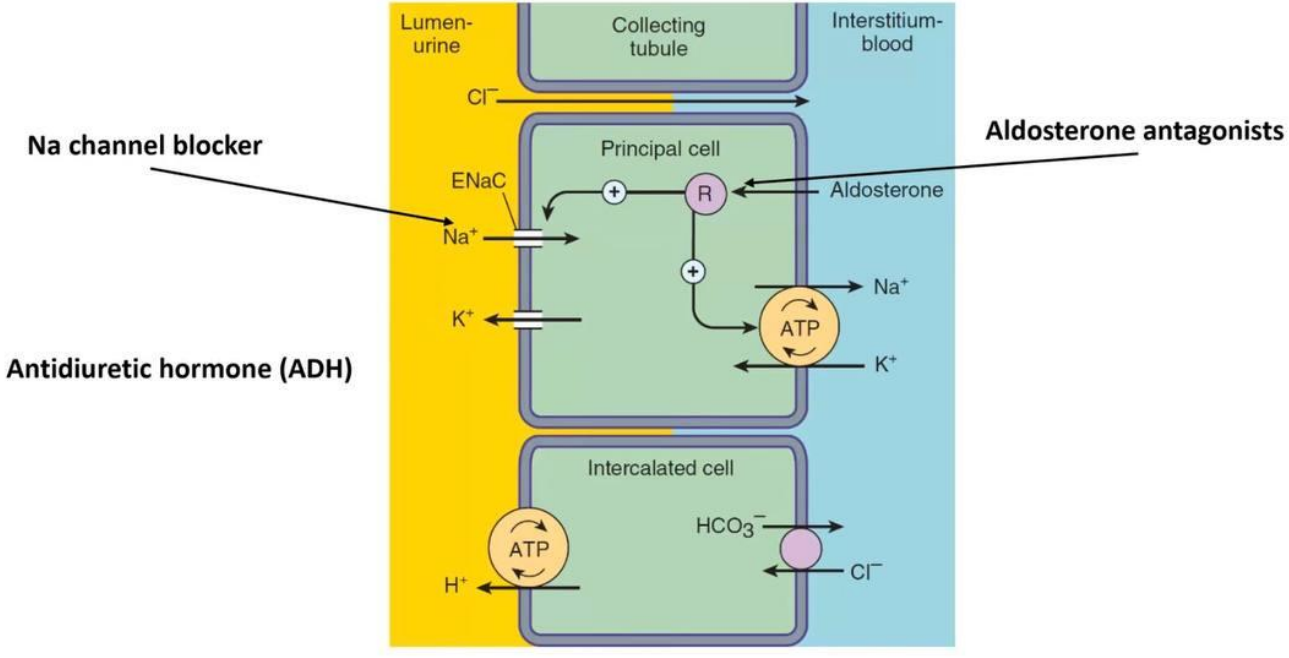
- About eight distal tubules coalesce to form the collecting tubule which turns once again away from the cortex and passes downward into medulla where it becomes the collecting ducts.
- The epithelium of collecting ducts is made up of principal cells **(P cells)** which are involved in Na ions reabsorption and vasopressin-stimulated water reabsorption, and intercalated cells **(I cells)** which are concerned with acid secretion and bicarbonate transport.

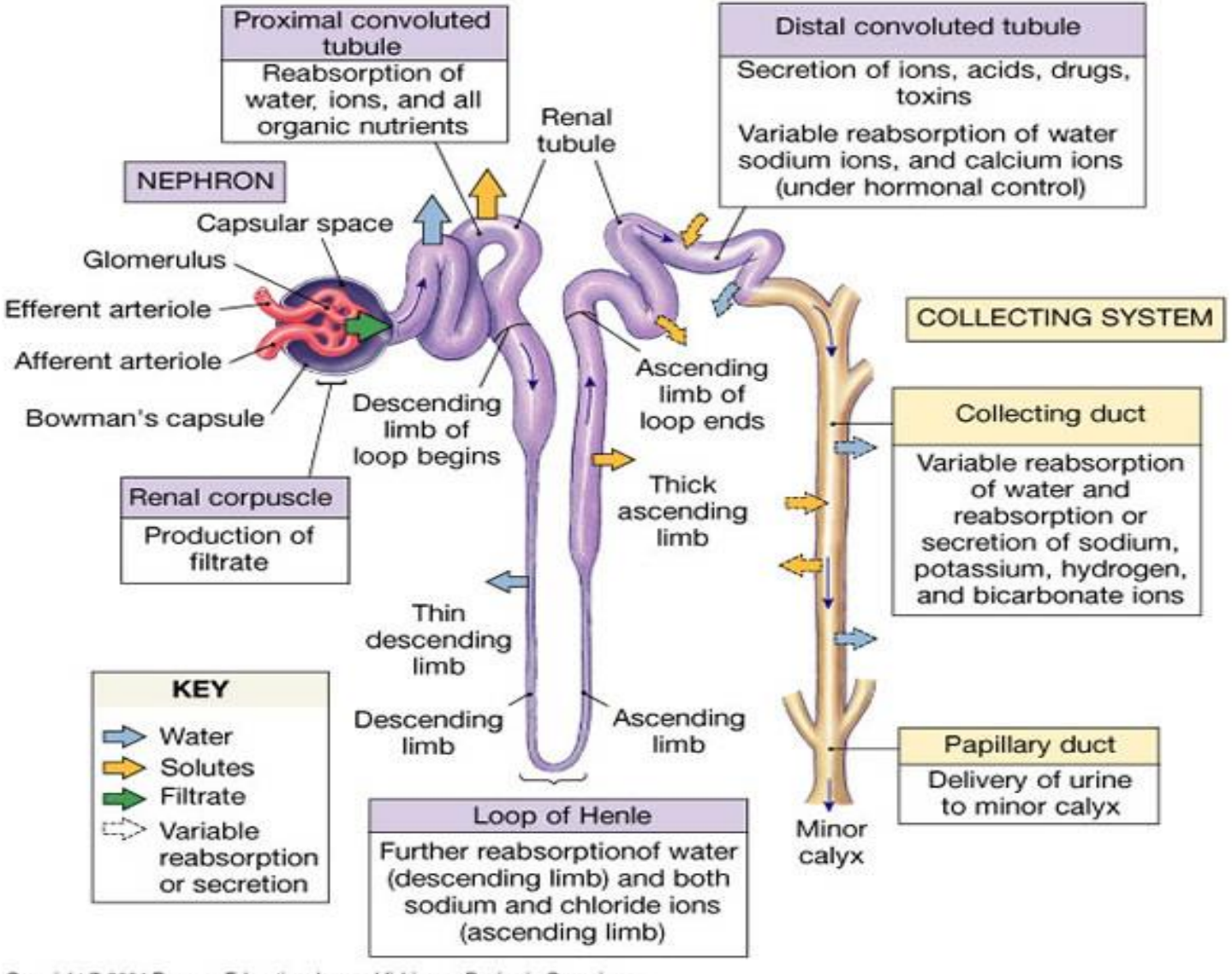
COLLECTING TUBULE SYSTEM

- The connecting tubule, the collecting tubule, and the collecting duct
- responsible for **only 2–5%** of NaCl reabsorption by the kidney, But?!
  - The final site of NaCl reabsorption
  - Site of action of mineralocorticoids
  - Site of K+ secretion

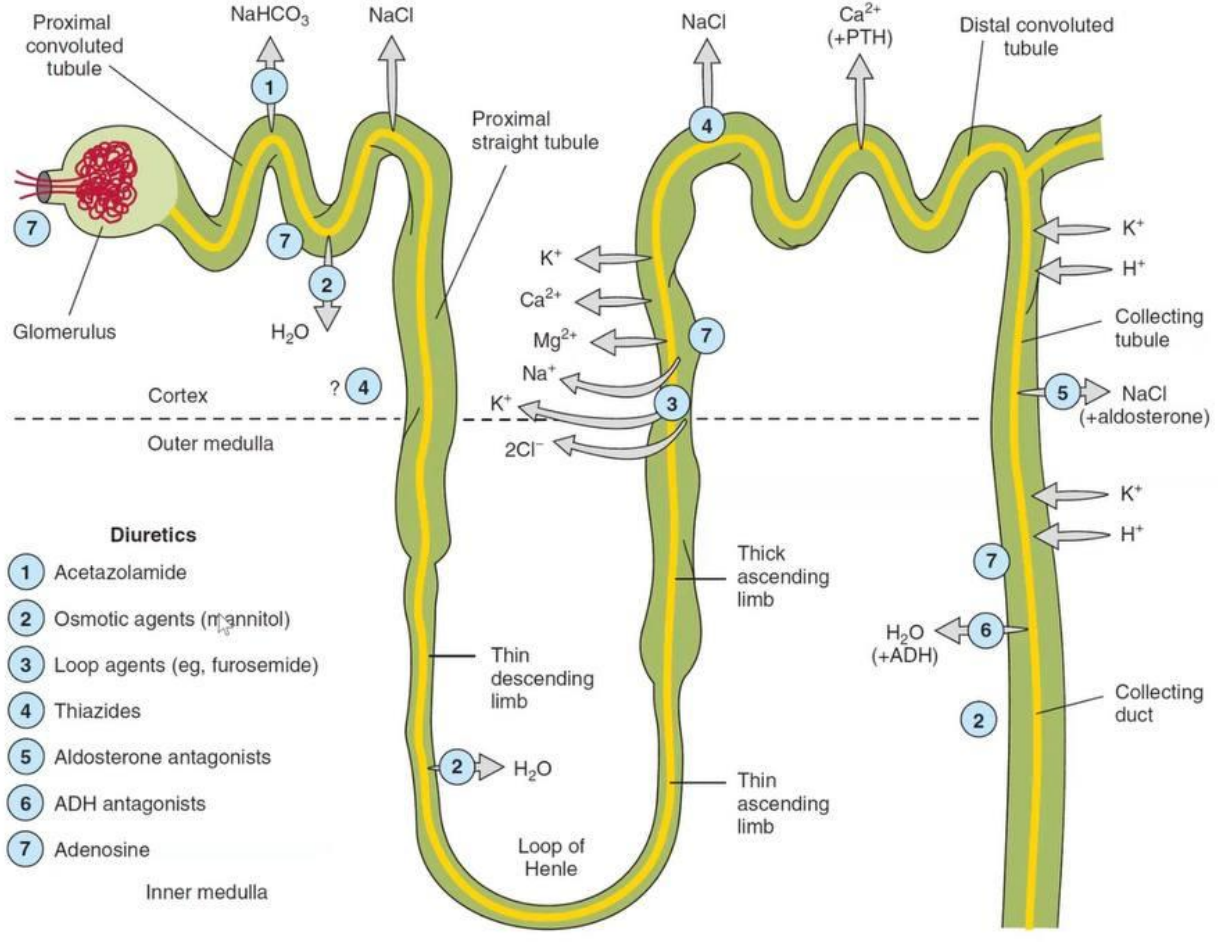


COLLECTING TUBULE SYSTEM





The Summary


Proximal convoluted tubule
$NaHCO_3$
NaCl
NaCl
Ca^{2+} (+PTH)
Distal convoluted tubule
Proximal straight tubule
Glomerulus
H_2O
Cortex
Outer medulla
Inner medulla
K^+
Ca^{2+}
Mg^{2+}
Na^+
K^+
$2Cl^-$
Collecting tubule
NaCl (+aldosterone)
K^+
H^+
Thick ascending limb
Thin descending limb
Thin ascending limb
Loop of Henle
H_2O (+ADH)
Collecting duct
Diuretics
1 Acetazolamide
2 Osmotic agents (mannitol)
3 Loop agents (eg, furosemide)
4 Thiazides
5 Aldosterone antagonists
6 ADH antagonists
7 Adenosine