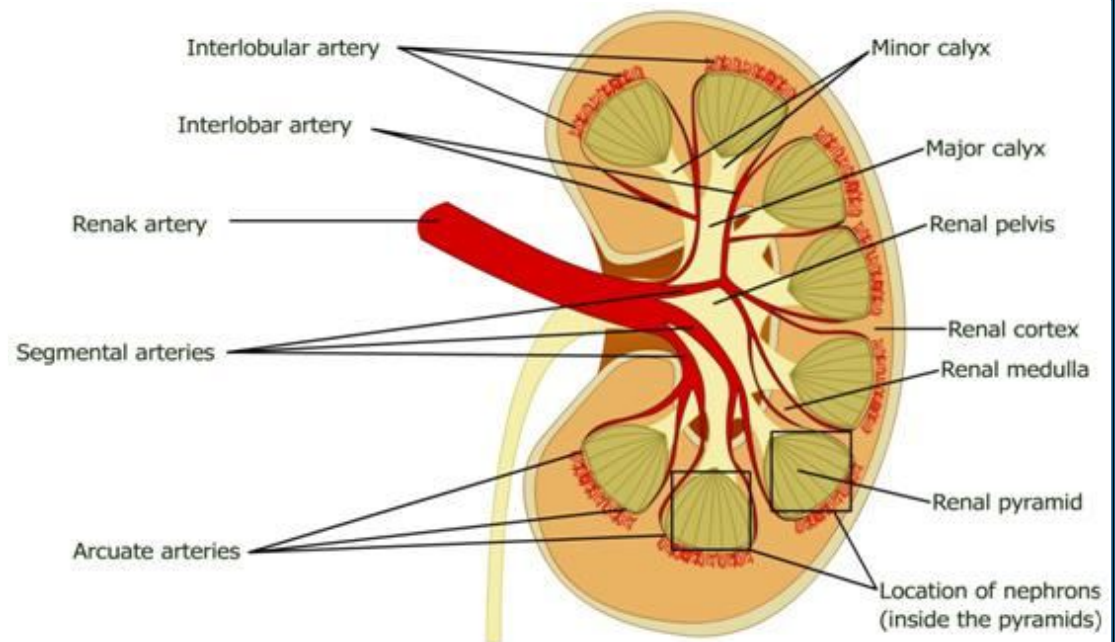


Renal Physiology



DONE BY

Saleh AlAhmadi
AbdulAziz AbuButain

SPECIAL THANKS

Abdullah AlManaa
Bilal Marwa
Ibrahim AshShoheal
Yahya Aseery

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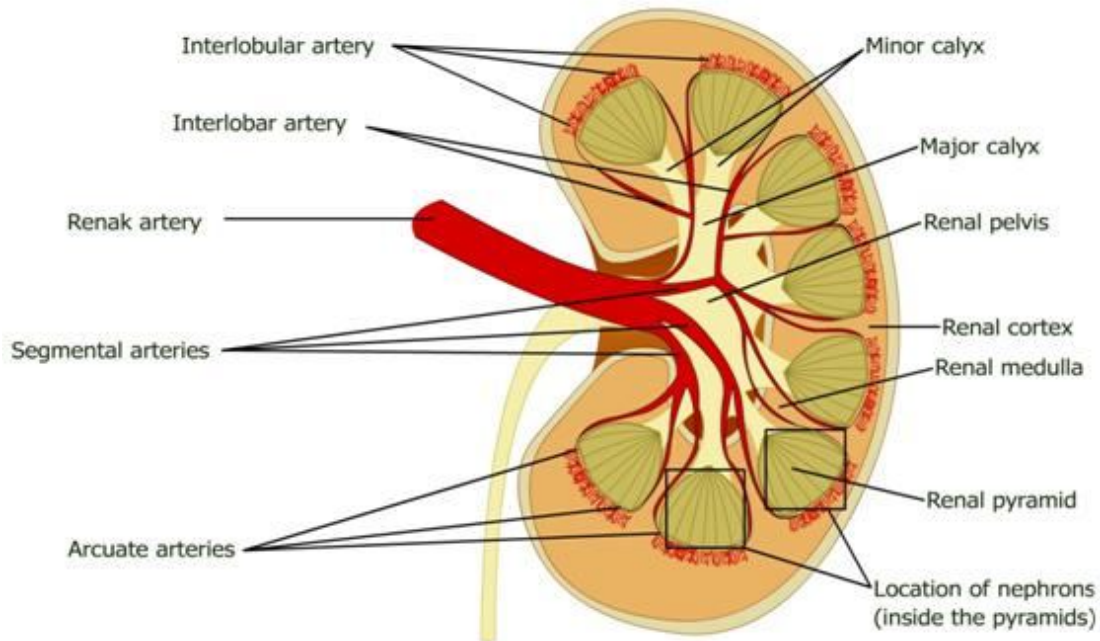
Introduction

- ❖ Functions of kidneys in homeostasis:
 - Rid the body of waste products (ingested or produced by metabolism, e.g. urea, uric acid, creatinine, bilirubin, drugs, food additives and some hormones metabolic wastes) as rapidly as they are produced.
 - Control the volume and composition of body fluids (water and electrolytes) by balancing the intake with the output, so if the intake is increased the excretion will increase as well, this function is maintained by the kidneys in large part.
 - Regulation of arterial pressure in two manners:
 - Long term regulation by blood pressure and rennin.
 - Short term regulation by nervous system.
 - Regulation of acid-base balance by excreting acids and regulating the body fluid buffer stores.
 - Erythrocytes production by secreting erythropoietin. When kidneys are exposed to hypoxia they secrete erythropoietin (kidney diseases can lead to anemia because 90% of erythropoietin is from the kidneys].
 - Regulation of vitamin D (calcitriol) production by hydroxylating the vitamin at number 1 position.
 - Functions of vitamin D:-
 - Deposition of Ca in bone.
 - Absorption of Ca from GIT
 - Regulating of Ca and phosphate
 - Glucose synthesis by gluconeogenesis during fasting.

Physiologic anatomy of the kidneys:

- ❖ The two kidneys lie in the posterior abdominal wall.
 - Surrounded by fibrous capsule that protects it.
- ❖ Each kidney weighs about 150 grams.
- ❖ The medial side is called the hilum, the renal artery and vein, lymphatics, nerve supply and ureter pass through it.
- ❖ The inner structure of the kidney is divided into two parts:
 - Outer region called: **Cortex**.
 - Inner region called: **Medulla**.
 - The medulla is composed of multiple cone-shaped masses of tissue called renal pyramids; the base of each pyramid is at the junction between cortex and the medulla. Each pyramid terminates in the papilla which projects into the renal pelvis.

- The renal pelvis is a funnel shaped continuation of the upper part of the ureter, the outer border of the pelvis is divided into 2 or 3 major calyces which will also divide into 3 minor calyces, and the minor calyces collect urine from each papilla.



Renal Blood Supply:

- ❖ 22% of CO (1100 ml/min) goes to the kidneys.
- ❖ Vessel sequence in the kidneys :-
 - Renal artery → Interlobar arteries → Arcuate arteries → Interlobular arteries (radial arteries) → Afferent arteriole → Glomerular capillaries → Efferent arterioles → Peritubular capillaries.
 - Glomerular capillaries are where large amounts of fluids and solutes are filtered.
 - Peritubular capillaries surround renal tubules and empty into vessels of the venous system which form interlobular veins, arcuate veins, interlobar veins and the renal vein.
- ❖ Kidneys are unique because they have 2 sets of capillaries: glomerular and peritubular.
 - Glomerular capillaries have high hydrostatic pressure (60 mmHg), to permits filtration.
 - Peritubular capillaries have low hydrostatic pressure (13 mmHg), to permits reabsorption.
 - Efferent arterioles help regulate hydrostatic pressure in both glomerular and peritubular capillaries.

Nephrons

- ❖ Each kidney contains about 1 million nephrons.
- ❖ After the age of 40 about 10% of functional nephrons are lost every 10 years, which means that at the age of 80; only 40% of nephrons will be functioning rather than they did at the age of 40 , but this is not a problem because of the adaptive changes in the remaining nephrons which will make them work good and excrete the proper amounts of water, electrolytes and waste products.
- ❖ Kidneys cannot regenerate new nephrons.
- ❖ Components of nephrons:
 - Bowman's capsule, which encloses the glomerular capillaries.
 - Proximal convoluted tubules.
 - Loop of Henle which is divided into 2 limbs:
 - Thin descending limb.
 - Ascending limb, which is also, has thin and thick segments.
 - Late convoluted tubules.
 - Connecting tubule → Cortical collecting tubule → Cortical collecting duct → Medullary collecting duct → Larger ducts that empty into the renal pelvis.
- ❖ In each kidney there are about 250 of very large collecting ducts each of which collects urine from 4000 nephrons.
- ❖ Types of nephrons:
 - Cortical nephrons [70%-80%]:
 - Their Bowman's capsule lies in the outer cortex and has short loop of Henle (capable of forming dilute urine).
 - Juxtamedullary nephrons [20%-30%]:
 - Their bowman's capsule lay deeper near the medulla and have long loop of Henle which sometimes reach the tips of papillae (capable of forming concentrated [>300 mOsm/kg] urine).
 - Vasculature of juxtamedullary nephrons is different from that found in cortical nephrons in that it has specialized peritubular capillaries called vasa-recta lying side by side with the loop of Henle.
 - Blood flow in the vasa-recta is very low compared with flow in the renal cortex, because most of the renal blood flow goes to the cortex and only 1-2% goes to the medulla, and this as we will discuss later is important characteristic in the kidneys for making concentrated urine.

Urine formation:

❖ Renal processes in urine formation:

1. Filtration.
2. Reabsorption.
3. Secretion.
4. Excretion.

❖ Urine excretion rate = Filtration rate - Reabsorption rate + Secretion rate

❖ Urine formation begins with filtration of large amounts of fluid (free of proteins and cellular components) from glomerular capillaries into Bowman's capsule.

- Most substances in the plasma are freely filtered so: concentration in the filtrate = their concentration in plasma
- All Proteins and half of Ca and almost all of fatty acids that are bounded to proteins are not freely filtered.

As we see in the figure:-

❖ Substance A is freely filtered, but not reabsorbed or secreted.

- E.g. creatinine.

❖ Substance B is freely filtered and partly reabsorbed.

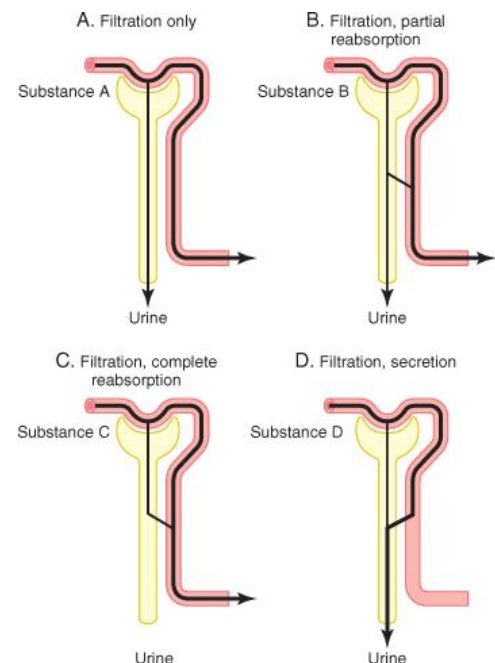
- E.g. Many electrolytes.

❖ Substance C is freely filtered and fully reabsorbed.

- E.g. Amino acids, glucose.

❖ Substance D is freely filtered and secreted, but not reabsorbed.

- E.g. Organic acid.



❖ In certain kidney diseases the negative charges of basement membrane are lost even before there are noticeable changes in the histology of the kidneys; such condition is referred to as **minimal changes nephropathy**. As a result, proteins especially albumin will be filtered and appear in the urine, a condition known as **proteinurea** or **albuminuria**.

❖ Large amounts of solutes and water are filtered and then reabsorbed because of two reasons:

1. To rapidly remove the waste products from the body
2. To allows all of the body fluids to be filtered and processed by the kidney many times each day.

Glomerular Filtration:

Filtration membrane:

- ❖ It is composed of the following:
 - Endothelium of glomerular capillaries, which has high numbers of pores (fenestrations).
 - Basement membrane, that consists of collagen and proteoglycans, which gives it the negative charge that prevent the filtration of proteins.
 - A layer of epithelial cells (podocytes) surrounding the outer surface of the basement membrane. These cells are not continuous but have foot-like processes which are separated by gaps (filtration slits). The epithelium layer also has negative charge.

Filterability of solutes is inversely related to their size:

Substance	Molecular Weight	Filterability
Water	18	1.0
Sodium	23	1.0
Glucose	180	1.0
Inulin	5,500	1.0
Myoglobin	17,000	0.75
Albumin	69,000	0.005

- ❖ As the molecular weight of the substance increases it will have less filterability through the filtration membrane, thus the membrane is selective in determining which molecules will filter according to their size and charge (positively charged molecules have higher filterability than negative ones with the same molecular size) .
- ❖ Forces favoring or opposing filtration along the filtration membrane:
 - Forces favoring filtration:
 - Hydrostatic pressure inside the glomerular capillaries (glomerular hydrostatic pressure, P_G) and this equal = 60 mmHg.
 - Colloid osmotic pressure of the proteins in Bowman's capsule, $[\pi_B]$ and this normally equal =0.
 - Because proteins are not filtered into Bowman's capsule.
 - Forces opposing filtration:
 - Hydrostatic pressure in Bowman's capsule $[P_B]$ and this equal =18 mmHg.
 - Colloid osmotic pressure of the glomerular capillaries plasma proteins $[\pi_G]$ and this equal = 32 mmHg.
- ❖ The net filtration pressure = Forces favoring filtration – Forces opposing filtration.
 $= (P_G + \pi_G) - (P_B + \pi_B) = (60 + 0) - (18 + 32) = 60 - 50 = 10 \text{ mmHg}$
- ❖ So the net filtration pressure is equal = +10 mmHg.

Determinants of GFR (Glomerular Filtration Rate)

- ❖ The total amount of filtrate formed by the kidneys per minute is called GFR.
- ❖ $GFR = K_f \times \text{Net filtration pressure}$.
 - K_f is the filtration coefficient.
 - K_f is a measure of the product of the permeability and surface area of the glomerular capillaries.
 - $K_f = GFR/\text{Net filtration pressure} = 125/10 = 12.5 \text{ ml/min/mmHg}$ of filtration pressure.
- ❖ Important values in renal processes:
 - $GFR = 125 \text{ ml/min}$ or $125 \times 60 \times 24 = 180000 = 180 \text{ L/day}$.
 - Normal urinary output = 1.5 L/day.
 - Daily reabsorption = $180 - 1.5 = 178.5 \text{ L/day}$.
 - Percent of the filtrate which has been reabsorbed = $178.5 \times 100/180 = 99.2\%$.
 - Percent excreted = $100 - 99.2 = 0.8\%$ (less than 1% becomes urine).
- ❖ Filtration Fraction:
 - Normal renal plasma flow is 650 ml/min and only 125 ml/min is filtered (GFR).
 - The filtration fraction is the fraction of the renal plasma flow that is filtered.
 - Filtration fraction = $GFR/\text{renal plasma flow} = 125/650 = 0.2$, which means (20% of the renal plasma flow is filtered into Bowman's capsule).

Factors affecting GFR

- ❖ K_f (permeability and surface area):
 - $\uparrow K_f \rightarrow \uparrow GFR$.
 - $\downarrow K_f \rightarrow \downarrow GFR$.
 - But this does not make it a primary mechanism for normal day-to-day regulation.
 - K_f can be reduced by one of the following facts :-
 - Reducing the number of functional glomerular capillaries (reducing surface area).
 - Increasing the thickness of filtration membrane (decreasing the permeability), e.g. **chronic uncontrolled hypertension** and **diabetes mellitus** by increasing the thickness of basement membrane.

❖ P_G (glomerular capillaries hydrostatic pressure):

➤ $\uparrow P_G \rightarrow \uparrow \text{GFR}$.

➤ Hydrostatic pressure is determined by the following variables:

▪ Arterial pressure:-

- \uparrow Arterial pressure $\rightarrow \uparrow P_G$.

▪ Afferent arteriole resistance:-

- \uparrow Afferent arteriole resistance (constriction) $\rightarrow \downarrow P_G$.
- \downarrow Afferent arteriole resistance (dilation) $\rightarrow \uparrow P_G$.

▪ Efferent arteriole resistance:-

- Mild constriction $\rightarrow \uparrow P_G$.

- ◆ Slight increasing in efferent arteriolar resistance will increase the resistance to outflow from glomerular capillaries and this will increase P_G and slightly increases GFR.

- Severe constriction $\rightarrow \downarrow P_G$.

- ◆ If we increase the resistance in the efferent arteriole more and more this will reduce the renal blood flow and the filtration fraction will increase (the same amount of filtrate from less amount of plasma) and this will make the colloid osmotic pressure of glomerular capillaries high (because the proteins remaining in the glomerular capillaries will be more concentrated), and because colloid osmotic pressure is an opposing force, GFR will decrease.

- Dilation $\rightarrow \downarrow P_G$.

- ◆ Dilation of the Efferent arterioles will decrease the resistance to outflow from glomerular capillaries which will make the flow very easy and this will decrease the P_G and therefore will decrease GFR.

➤ These variables are under physiologic control (the variables affecting P_G).

❖ P_B (hydrostatic pressure in Bowman's capsule):

➤ $\uparrow P_B$ in Bowman's capsule $\rightarrow \downarrow \text{GFR}$.

- In certain pathological conditions, the urinary tract will be obstructed (precipitation of Ca^{++} and uric acid which lead to stones), Bowman's capsule pressure will rise and therefore GFR will decrease because Bowman's capsule hydrostatic pressure is an opposing force.

❖ π_G (colloid osmotic pressure in glomerular capillaries [plasma protein concentration]):

➤ Effected by two factors:

- Arterial plasma colloid osmotic pressure (plasma protein concentration), as we increase the plasma protein concentration the colloid pressure will increase and GFR will decrease.

- Filtration fraction ($F_f = \text{GFR}/\text{Renal plasma flow}$), because as we increase the filtration fraction, the glomerular capillaries colloid pressure will increase (the plasma proteins will become more concentrated in the glomerulus).

✓ The filtration fraction can be increased either by:

- \uparrow GFR or \downarrow Renal plasma flow.

Physical Determinants	Physiologic/Pathophysiologic Causes
$\downarrow K_f \rightarrow \downarrow$ GFR	Renal disease, diabetes mellitus, hypertension
$\uparrow P_B \rightarrow \downarrow$ GFR	Urinary tract obstruction (e.g., kidney stones)
$\uparrow \pi_G \rightarrow \downarrow$ GFR	\downarrow Renal blood flow, increased plasma proteins
$\downarrow P_G \rightarrow \downarrow$ GFR	
$\downarrow A_P \rightarrow \downarrow P_G$	\downarrow Arterial pressure (has only small effect due to autoregulation)
$\downarrow R_E \rightarrow \downarrow P_G$	\downarrow Angiotensin II (drugs that block angiotensin II formation)
$\downarrow R_A \rightarrow \uparrow P_G$	\downarrow Sympathetic activity

Renal blood flow

- ❖ Kidneys receive extremely high blood flow compared with other organ, because they supply enough plasma for the high rates of glomerular filtration.
- ❖ Renal oxygen consumption:
 - Oxygen delivered to the kidneys far exceeds their metabolic needs, and the arterial-venous extraction of oxygen is relatively low compared with that of most other tissues.
 - A large fraction of the oxygen consumed by the kidneys is related to the high rate of active Na^+ reabsorption by the renal tubules.
 - $\uparrow \text{Na}^+$ reabsorption \rightarrow \uparrow oxygen consumption.
- ❖ Determinants of renal blood flow:
 - $(\text{Renal artery pressure} - \text{Renal vein pressure}) \div \text{Total renal vascular resistance}$.

Physiologic Control of GFR and Renal BF

- ❖ GFR is controlled by one of the following mechanisms:
 - Sympathetic nervous system.
 - Hormones and autacoids.
 - Intrinsic mechanisms (feedback control).

Sympathetic Nervous System Activation Decreases GFR

- ❖ Strong activation of sympathetic system \rightarrow Constrict renal afferent arterioles \rightarrow \downarrow renal blood flow \rightarrow \downarrow GFR.
- ❖ Sympathetic stimulation is only important in severe acute disturbances which last for minutes or hours, e.g. **brain ischemia, severe hemorrhage**.
- ❖ In a healthy resting person sympathetic tone appears to have little influence on RBF (so not influenced in day-to-day regulation).

Hormonal and Autacoids Control

- ❖ Norepinephrine, epinephrine and endothelium constrict renal blood vessels and decrease GFR
 - They work as the same manner of sympathetic system (only in severe conditions).
 - Plasma endothelium level is increased in certain diseases associated with vascular injury, e.g. **toxemia** of pregnancy, **acute renal failure** and **chronic uremia**.
- ❖ Angiotensin II:
 - Released due to:
 - Decreased arterial pressure.
 - Volume depletion (**hemorrhage** for example).
 - Angiotensin II tend to constrict efferent arterioles (mild constriction) and this will help to prevent decrease in glomerular hydrostatic pressure and GFR.
 - It will also slightly decrease renal blood flow and this mechanism will make blood flow in peritubular capillaries slower (which in turn increases reabsorption of Na and water).
- ❖ Endothelium derived relaxing factor (nitric oxide):
 - Nitric oxide is very important in maintaining renal vascular resistance low and increases GFR thus allows the kidneys to excrete normal amounts of Na and water.
- ❖ Prostaglandins and bradykinin tend to increase GFR:
 - They will not play a major role in regulating GFR and RBF in normal conditions.
 - Their job is opposing vasoconstriction to Afferent arterioles done by sympathetic stimulation, thus prevent reduction in GFR.

Auto Regulation of GFR and RBF

- ❖ The main function of auto regulation is to keep GFR and RBF constant even if there are changes in arterial blood pressure.
- ❖ The primary function of blood flow autoregulation in tissues other than the kidneys is to maintain delivery of oxygen and nutrient at a normal level and to remove waste products of metabolism, but in the kidneys the normal blood flow is higher than that required for those function (so the main function of autoregulation in the kidney is to maintain constant GFR).
- ❖ GFR normally remains autoregulated at the range 75-160 mmHg of arterial pressure, so any changes of the pressure in this range will produce a very little change in GFR.
- ❖ Without autoregulation only small increase in blood pressure (from 100 to 125) will make the GFR increases for about 25% (180L/day to 225L/day) and if tubular reabsorption is constant (178.5L/day) the total increase in urine is 30-fold, and the fluid volume will decrease rapidly which will causes death.

- ❖ But this does not happen because we have:
 - Autoregulation.
 - Adaptive mechanisms in renal tubules that allow them to increase their reabsorption (glomerulotubular balance).

Role of Tuboglomerular Feedback in Autoregulation

- ❖ There is a specialized complex of cells in the distal tubule (and lies in contact with afferent and efferent arterioles) called the macula dense. Also there are other groups of cells in the walls of afferent and efferent arterioles called juxtaglomerular cells. These 2 groups of cells form what is called (juxtaglomerular apparatus).
- ❖ Macula densa cells have sensors which indicate the NaCl concentration in distal tubules.
- ❖ The mechanism of tuboglomerular regulation is as follows:
 - If the NaCl concentration is decreased below normal in the distal tubules there will be 2 actions:
 - Decreasing the resistance in the Afferent arterioles (dilation) which will lead to \uparrow GFR.
 - Increasing rennin secretion from juxtaglomerular cells, which will increase the formation of angiotensin I, which is converted to angiotensin II.
 - Angiotensin II will mildly constrict efferent arterioles \rightarrow \uparrow glomerular hydrostatic pressure \rightarrow return GFR to normal.
- ❖ Experimental studies suggest that decreased GFR will slow the flow rate in the loop of Henle, causing increased reabsorption of Na and Cl thereby reducing the concentration of Na and Cl arriving to macula densa cells.

Myogenic autoregulation of RBF and GFR

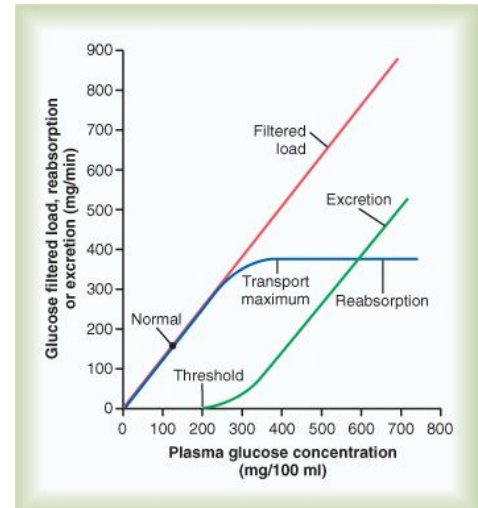
- ❖ Blood vessels (especially small arterioles) are able to resist stretch during increased arterial pressure (myogenic mechanism) thus prevents overdistention of the vessels and at the same time prevents excessive increases in RBF and GFR when arterial pressure increases.
- ❖ The responsible element in vessel constriction (stretch resistance) is specialized type of contractile cells called (mesangial cells).
- ❖ Other factors that increase RBF and GFR:
 - High protein intake and increased blood glucose.
 - A high intake of protein and glucose will make high amount of amino acids and glucose get filtered and reabsorbed, and because amino acids and glucose are reabsorbed in combination with Na, high amounts of Na are reabsorbed in the proximal tubules which means only small amount of Na will reach the distal tubules (macula densa cells), thus triggering the tuboglomerular mechanism.

Tubular Processing of the Glomerular Filtrate

- ❖ Some substances are selectively reabsorbed from the tubules back into the blood, whereas others are secreted from the blood into the lumen.
- ❖ For many substances, reabsorption plays a more important role than secretion in determining the urinary excretion rate.

Tubular Reabsorption

- ❖ Is selective & quantitatively large.
- ❖ A small change in glomerular filtration rate or tubular reabsorption can cause a large change in urine excretion. But, in reality, these changes are closely coordinated to avoid large changes in excretion.
- ❖ Glucose & amino acids are completely reabsorbed.
- ❖ Glucose concentration in plasma is equal to 60-110 g/L in the fasting state, and in the well-fed 110-180 g/L. Since 180 L of plasma are filtered daily; 180 g of glucose is reabsorbed daily.
 - 18 mg = 1mmol.
- ❖ Ion reabsorption depends on the body's needs.
- ❖ Waste products (creatinine, urea) are poorly reabsorbed.



Q: What should I do if I forget the reabsorption rate of a substance?
 Think about the importance of this substance to the body.
 For example, glucose is the most important nutrient → it is completely reabsorbed.
 Urea is a waste product → it is poorly reabsorbed & so on.

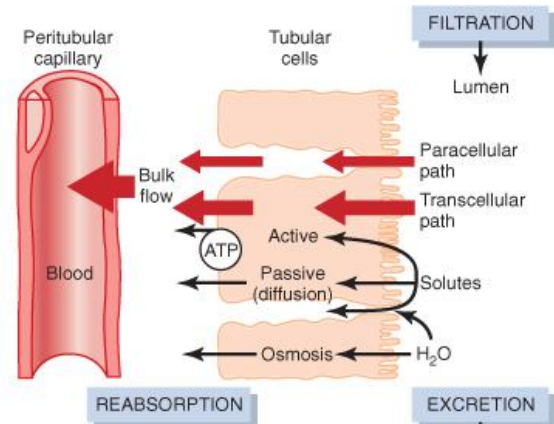
- ❖ Glomerular filtration isn't selective (everything is filtered except plasma proteins), while reabsorption is highly selective.

	Amount Filtered	Amount Reabsorbed	Amount Excreted	% of Filtered Load Reabsorbed
Glucose (g/day)	180	180	0	100
Bicarbonate (mEq/day)	4,320	4,318	2	>99.9
Sodium (mEq/day)	25,560	25,410	150	99.4
Chloride (mEq/day)	19,440	19,260	180	99.1
Potassium (mEq/day)	756	664	92	87.8
Urea (g/day)	46.8	23.4	23.4	50
Keratinize (g/day)	1.8	0	1.8	0

Active & Passive Mechanisms of Transportation

For reabsorption to occur, the substance must be transported 2 times.

- ❖ First, it has to cross the tubular epithelial membrane to the renal interstitial fluid.
- ❖ Then, it has to cross from the interstitial fluid to the peritubular capillary & hence, the blood.
- ❖ Transportation is achieved in several ways, these are:
 - 1- Transcellular transport: This occurs through the cell itself.
 - 2- Paracellular transport: This occurs through the junctional spaces between cells.
 - 3- Ultrafiltration (bulk flow): This occurs through the peritubular capillary walls, mediated by hydrostatic pressure & colloid osmotic forces.



Active Transport

- ❖ Is used to transport a substance against its electrochemical gradient.
- ❖ Requires ATP.
- ❖ Has two subtypes:
 - 1- Primary: directly associated with ATPase.
 - 2- Secondary: indirectly associated with ATPase.

Remember

- ❖ Water is always transported by osmosis (which is a passive mechanism).

Paracellular & transcellular mechanisms

- ❖ Renal tubular cells are held by tight junctions (through which paracellular transport takes place).
- ❖ Sodium moves by both mechanisms, but mostly through transcellular transport.
- ❖ Water, along with dissolved substances, is reabsorbed paracellularly.

Primary Active Transport

- ❖ Na^+ -K pumps are only found on the basolateral side of the tubular epithelial cells.
- ❖ Pumping of Na across the basolateral membrane outside the cell favors Na diffusion across the luminal membrane into the cell. This is due to:
 - 1- Na concentration: This is low inside the cell & high in the tubule.
 - 2- Negative intracellular potential (-70 millivolt).
- ❖ In the proximal tubule, there is an excessive brush border on the luminal side of the membrane, this border increases the surface area by 20-fold.

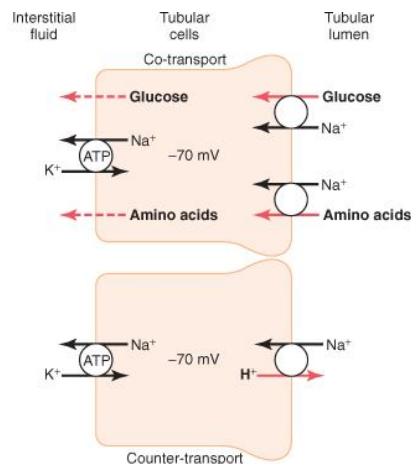
Net Reabsorption of Na

❖ Na is reabsorbed in several steps :

- 1- Across the luminal membrane, down its electrochemical gradient. (established by the Na^+ - K^+ ATPase pump on the basolateral side of the membrane).
- 2- Across the basolateral membrane against electrochemical gradient by by the Na-K ATPase pump .
- 3- By ultrafiltration from the interstitium to blood vessels.

Secondary Active Transport (Glucose & Amino Acids)

- ❖ As a substance moves down its gradient, some energy is generated. This energy is used to transport another substance against its own gradient.
- ❖ Secondary active transport is so efficient that it removes all the glucose & amino acids from the tubular lumen.
- ❖ Glucose is reabsorbed by:
 - Secondary active transport → luminal membrane
 - Passive facilitated diffusion → basolateral membrane
 - Bulk flow → peritubular capillaries.
- ✓ The same happen to amino acids 😊



Secondary Active Transport Into the Tubules

- ❖ Occurs by counter transport.
- ❖ Example: active secretion of H^+ is coupled with Na^+ reabsorption in the in the luminal membrane of the proximal tubule.
- ❖ As Na is carried to the interior of the cell, H^+ ions are forced in the other direction.

Remember

- ❖ Active transport requires energy, passive doesn't.
- ❖ Glucose is transported by both mechanisms.
- ❖ Water is transported only by passive transport (osmosis).

Pinocytosis

- ❖ Used by some parts of the tubule (especially the proximal tubule) to reabsorb large molecules such as , proteins (by a mean of endocytosis).
- ❖ After invagination of the protein to interior of the cell it is digested to amino acids (which are reabsorbed through the basolateral membrane into the interstitial fluid).
- ❖ Pinocytosis is considered a type of active transport mechanism.

Transport Maximum

- ❖ It is the limit of the rate at which a solute can be transported, secreted & reabsorbed.
- ❖ This limit is due to saturation of the transport systems, when tubular load exceeds their capacity.
- ❖ Normally, glucose doesn't exceed its threshold, so it isn't detectable in urine. Pathologically (e.g. **Diabetes mellitus**), glucose concentration in plasma is so high that it exceeds its threshold (when the filtered load exceeds capability of the tubules to reabsorb glucose) , it is then detectable in urine.
- ❖ In the proximal collecting tubule, Na does not obey the transport maximum. Instead, it obeys the gradient time transport.
 - Gradient time transport is the longer (sluggish movement) Na stays in the proximal collecting tubule the more it is reabsorbed .

Renal Threshold for Glucose

- ❖ When plasma concentration increases above 200 mg/ml, the filtered load increases to 20 mg/min & glucose begins to appear in urine.
 - The overall transport maximum of glucose is 375 mg/min, and this only can be reached when ALL nephrones have reached their maximum capacity to reabsorb glucose.
- ❖ Substances that are actively reabsorbed such as (Na) do not exhibit a transport maximum, because their transport is determined by other factors such as, 1- gradient, 2-permeability & 3- the time at which substance remains in the tubule (depends on tubular flow rate).
- ❖ Transport maximum can be increased in response to hormones such as aldosterone.

Passive Water Reabsorption is Coupled Mainly to Na Reabsorption

- ❖ Some parts of the tubule, especially the proximal tubule, are highly permeable to water, & water reabsorption occurs so rapidly even if there is only a small concentration gradient for solutes across the membrane.
- ❖ Tight junctions between cells aren't as tight as you might think & they allow significant diffusion of water & ions.
- ❖ As water moves across the tight junctions, it can also carry some solutes with it; this process is called solvent drag.
- ❖ In the loop of Henle & the collecting duct, water can't move easily across the membrane by osmosis. but, ADH can increase permeability of H₂O in the distal & collecting tubules as discussed later.
- ❖ In the proximal tubule, water permeability is always high & water is reabsorbed as rapidly as the solutes.
- ❖ In the ascending loop of Henle, water permeability is always low (almost no water is reabsorbed).

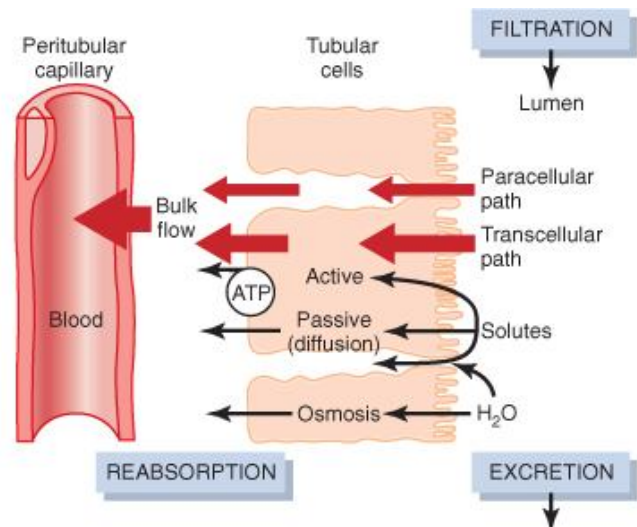
Remember

- ❖ Transport maximum of glucose is 375 mg/min, but it's never reached because not all the nephrons work at the same time or at their maximum capacity.
- ❖ Passive water reabsorption is coupled mainly to Na reabsorption.
- ❖ Tight junctions aren't really tight; they allow significant diffusion of water & ions.
- ❖ Water permeability is high in the proximal tubule & low in the loop of Henle.

Reabsorption of Chloride, Urea & Other Solutes by Passive Diffusion

Chloride (Cl⁻)

- ❖ Transport of positively charge Na⁺ out of the lumen leaves the inside negative compared to the interstitial fluid. This causes Cl⁻ ions to diffuse passively through the paracellular pathway.
- ❖ Active reabsorption of Na is closely coupled to PASSIVE reabsorption of Cl by way of an electrical potential & a Cl concentration gradient. please Look at the second figure in this page ☺.
- ❖ Also Cl is actively reabsorbed by the way of secondary active transport, which involves co-transport of Cl with Na.

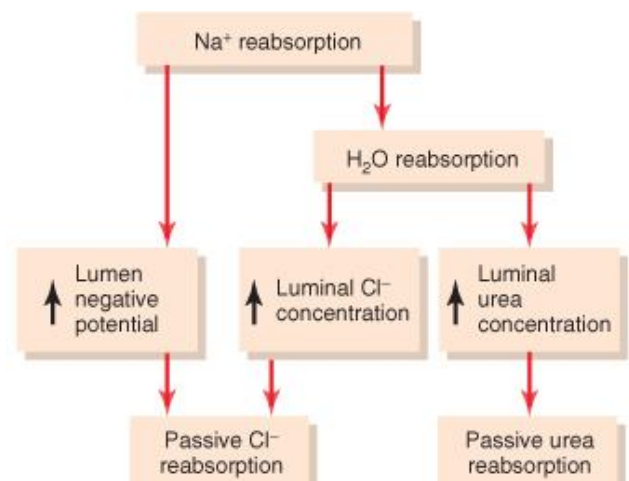


Urea

- ❖ Urea is reabsorbed passively because of the concentration gradient, which develops after the reabsorption of water by osmosis (because urea doesn't permeate the tubule as readily as water) thus making urea more concentrated in the lumen than the interstitium (the same thing also happen with Cl⁻).
- ❖ In the inner medullary collecting duct, urea is also passively reabsorbed by specific urea transporters.
- ❖ Only 50% of urea is reabsorbed, the remainder is excreted.

creatinine

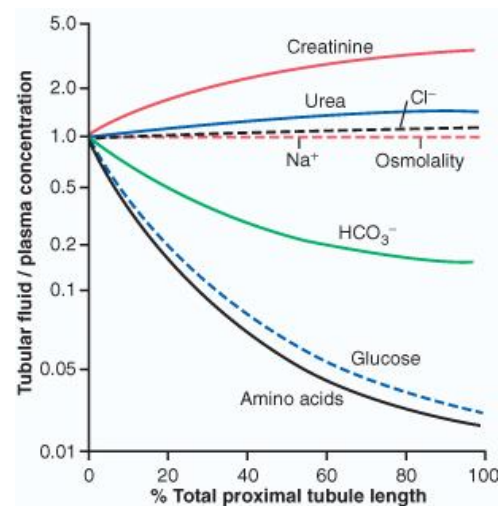
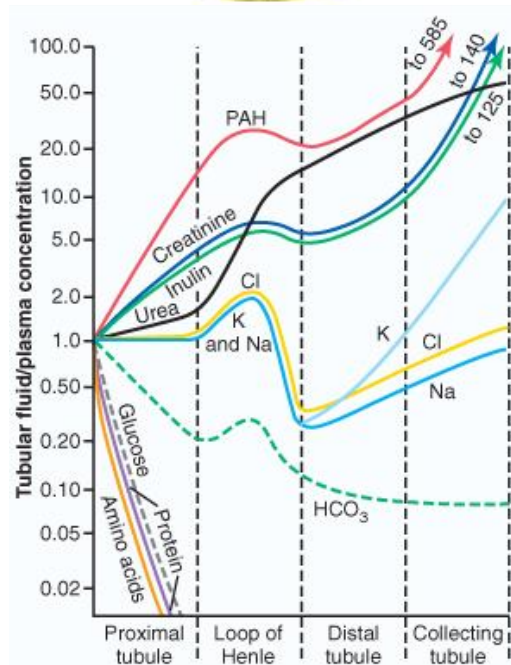
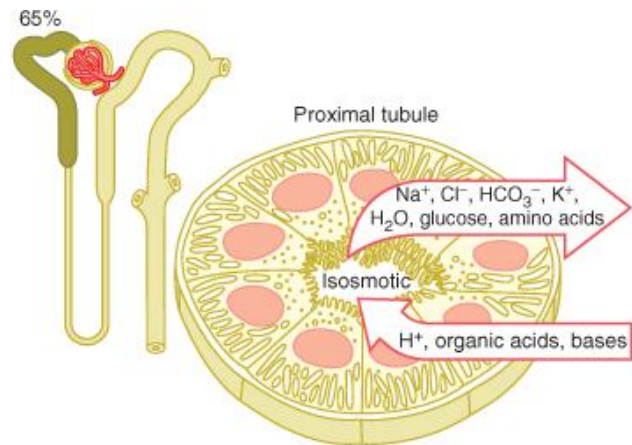
- ❖ The creatinine molecule is much larger than the urea molecule.
- ❖ creatinine is impermeable to the tubular membrane(not reabsorbed).
- ❖ Almost none of it is reabsorbed & almost all of it is EXCRETED in the urine.



Reabsorption in Different Regions of the Nephron

Proximal Tubule

- ❖ Reabsorbs almost 65% of the filtered load of Na & WATER.
- ❖ Proximal tubule cells have large number of mitochondria (to support potent active transporters) and extensive brush border on the luminal (apical) side, as well as an extensive labyrinth of the intercellular & basal channels, which together provide an extensive membrane surface area on both luminal and basolateral sides .
- ❖ The extensive membrane surface has a lot of carriers (proteins) that transport large fraction of Na+.
- ❖ Also with carriers the Na-K ATPase (on basolateral side) provides a major force for Na reabsorption (because it will make a concentration gradient) .
- ❖ In the first half of the proximal tubule, Na is transported by co-transport along with glucose , amino acids, HCO₃ and other solutes , also by counter-transport mechanism (absorption of Na while secreting H⁺ ions into the lumen).
- ❖ In the second half, too little glucose & amino acids remain to be absorbed, Leaving behind a high Cl concentration solution, Here Cl is reabsorbed passively with Na (by a mean of concentration gradient) through the para-cellular path . Please look at the 2nd figure at page 16 ☺.



Concentrations in the Proximal Tubule

- ❖ Na concentration & osmolarity remains relatively constant because of the high permeability of water.
- ❖ Concentrations of glucose, bicarbonate & amino acids decrease markedly along its length (because they are much avidly reabsorbed than water).
- ❖ Please note that we are talking about the concentration not about the amount.

Secretion of Acids & Bases

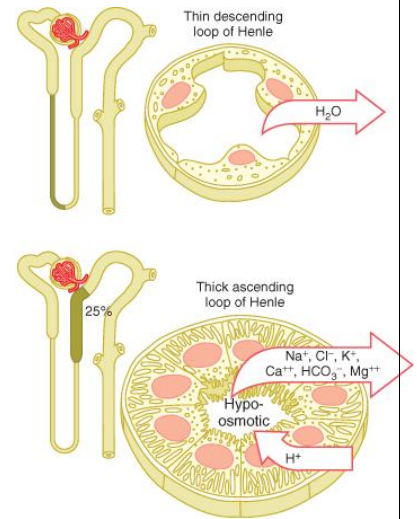
- ❖ Examples: oxaloacetate, bile salts, urate & catecholamines.
- ❖ In addition to metabolic wastes, the kidneys secrete toxins & harmful drugs.
- ❖ Para-aminohippuric acid (PAH) is rapidly excreted; about 90 % is cleared from the plasma. Thus, PAH can be used to estimate renal plasma flow.

Remember

- ❖ The proximal tubule reabsorbs almost 65% of water & Na.
- ❖ PAH can be used to estimate renal plasma flow, because it is rapidly excreted.

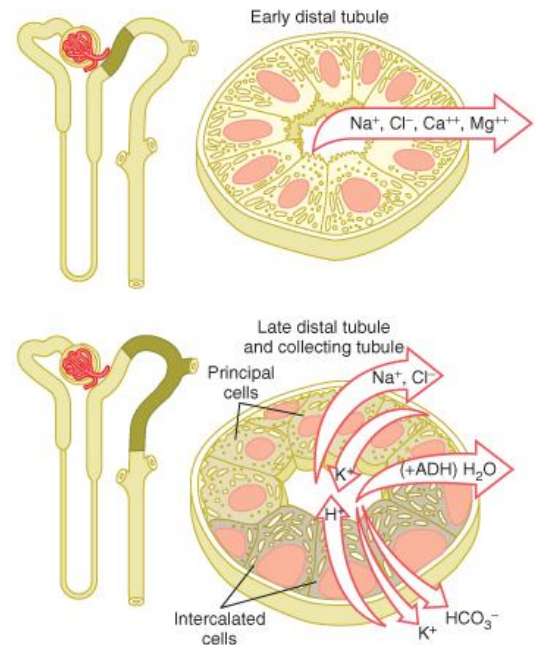
Loop of Henle

- ❖ The thin segments(descending or ascending) have no brush borders, few mitochondria & minimal metabolic activity.
- ❖ The thin descending limb is highly permeable to water only.
- ❖ 20% of filtered water is reabsorbed in the loop, almost all of it in the descending segment.
- ❖ The descending limb is only important in water reabsorption.
- ❖ The thick segment has thick epithelial cells that can actively reabsorb Na, Cl and K because of the presence of the Na- 2Cl- K co-transporter .
- ❖ About 25% of the filtration load of these ions is reabsorbed here.
- ❖ As we mentioned earlier Na-K ATPase(on the basolateral side) plays an important role in Na reabsorption by creating low intracellular Na concentration (which provides favourable gradient for Na to be absorbed).
- ❖ The thick segment also has Na-H⁺ counter-transporter.
- ❖ Also a considerable amounts of other ions such as Ca⁺⁺ , HCO₃⁻ , and Mg⁺⁺ are reabsorbed in the thick segment by passive mechanisms.
- ❖ Although the the 1-sodium 2-chloride 1-potassium co-transporter moves equal amounts of anions and cations into the cell there is a slight backleak of K⁺ creating a positive charge in the lumen which forces additional cations such as Mg⁺⁺ and Ca⁺⁺ to be absorbed through para-cellular path . ☺
- ❖ The thick ascending limb is the site of action of powerful loop diuretics, such as furosemide, butenamide & ethacrynic acid, which inhibit Na- 2Cl- K co transport.The thick ascending limb is impermeable to water. So the tubular fluid in it is very dilute(hypo-osmolarity).



Distal Tubule

- ❖ Its first part forms part of the juxtaglomerular complex (which provides feed-back control of GFR).
- ❖ It reabsorbs most ions including [Na, Cl, K], but it is impermeable to water & urea, which explains its name "the diluting segment".
- ❖ 5% of the filtered load of NaCl is reabsorbed in the early distal tubule because of the presence of Na-Cl co transporter.
- ❖ Thiazide diuretics, widely used in treating **hypertension & heart failure**, inhibit Na-Cl co-transport in the distal tubule.



Late Distal Tubule & Cortical Collecting Duct

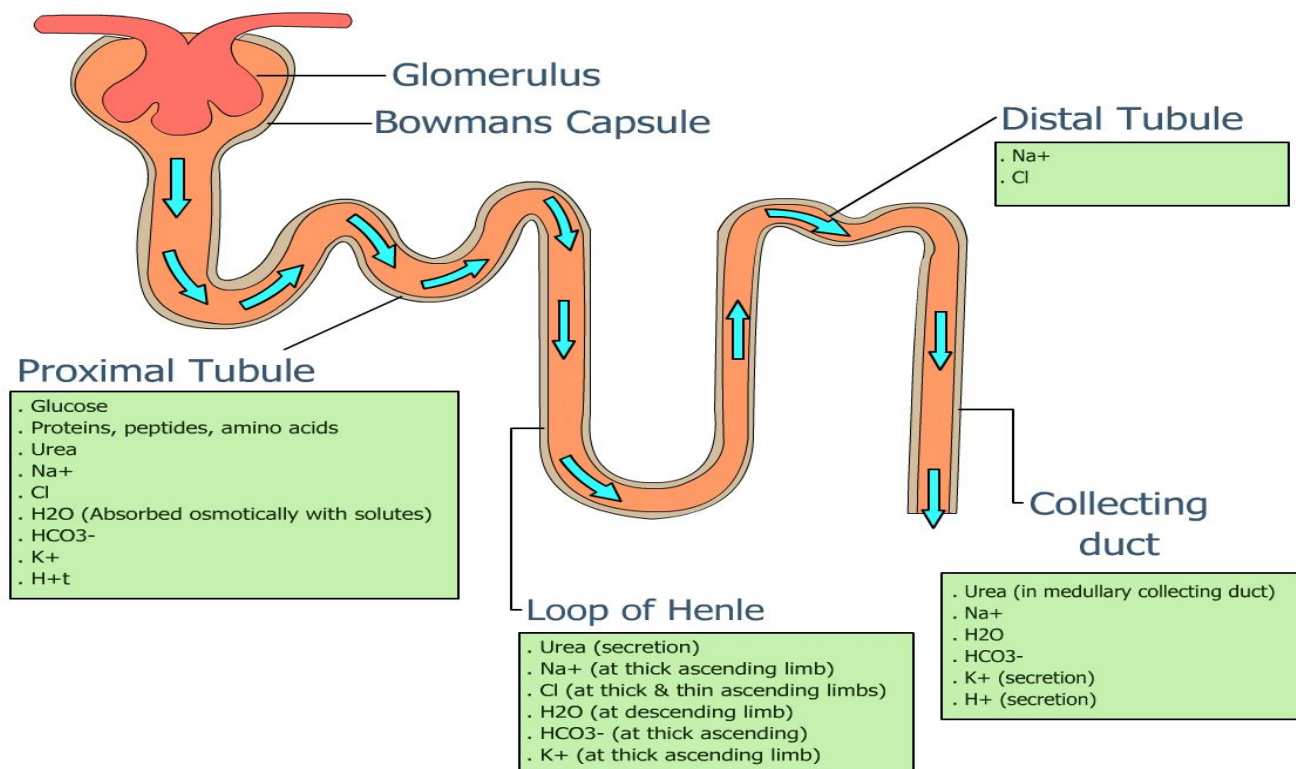
- ❖ Composed of principal cells & intercalated cells.
- ❖ Principal cells reabsorb Na & water from the lumen & secrete K ions.
- ❖ K secretion in the P-cells is due to the high activity of Na-K ATPase which tends to keep high intracellular K concentration and this will lead to diffusion of K down its concentration gradient into the lumen (secreted).
- ❖ Na channel blockers inhibit the entry of Na into the Na channels of the luminal membranes, and therefore reduce the amount of Na that can be transported across the BASOLATERAL membrane by the Na-K ATPase pump, this in turn decreases transport of K into the cells and ultimately reduces K secretion into the lumen [this mechanism is called K-sparing diuresis].
- ❖ Na channel blockers as well, as aldosterone antagonists, decrease urinary excretion of K & act as K-sparing diuretics.
- ❖ P- cells are the primary sites of action of K sparing diuretics, e.g. spironolactone, eplerenone, amiloride, & triameterene.
- ❖ Intercalated cells secrete H^+ ions by the action of H^+ -ATPase mechanism .
- ❖ H^+ ions are generated in the intercalated cells by the action of CARBONIC ANHYDRASE enzyme on water and CO_2 to form carbonic acid which dissociates into H^+ and HCO_3^- .
- ❖ For each H^+ ion secreted into the lumen, a HCO_3^- ion becomes available for reabsorption across the basolateral membrane .
- ❖ Intercalated cells can also reabsorb K ions .

Characteristics Of The Late Distal Tubule & Cortical Collecting Tubule

- ❖ Both are completely impermeable to urea.
- ❖ Almost all the urea passes on through & into the collecting duct to be excreted in the urine.
- ❖ Late distal tubule & cortical collecting tubule both reabsorb Na (the rate of reabsorption is controlled by hormones) & secrete K (controlled by aldosterone and other factors such as , concentration of K ions in the body fluids).
- ❖ Intercalated cells of these segments secrete H ions by an active ATPase pump (thus , intercalated cells play a key role in the acid-base balance of the body).
- ❖ A high level of ADH (also called vasopressin) will make them to be permeable to water, although they originally aren't (providing an important mechanism for controlling the degree of dilution or concentration of the urine).

Characteristics of the Medullary Collecting Duct

- ❖ Reabsorbs less than 10% of the filtrated water & Na.
- ❖ Permeability of the medullary collecting duct to water is controlled by ADH.
- ❖ High ADH increases water reabsorption into the medullary interstitium.
- ❖ Some urea is reabsorbed into the medullary interstitium, which helps in raising the osmolality of this region. Urea reabsorption also contributes to the kidney's ability to form concentrated urine.
- ❖ The MCD plays an important role in acid-base balance by secreting hydrogen ions (renal compensatory mechanism)



Measuring Water Reabsorption Using the Tubular Fluid/Plasma Inulin Concentration Ratio

- ❖ Inulin is used in measuring GFR due to the fact that it isn't reabsorbed nor secreted by the renal tubule.
- ❖ Inulin concentration in the tubular fluid is 3 times greater than in plasma & in glomerular filtrate, which indicates the amount of water reabsorbed along its course in the nephron.
- ❖ This means that only one third of the filtered water remains in the tubules & that the other two thirds have been reabsorbed.

Regulation of Tubular Reabsorption:

- ❖ Glomerulotubular balance: is the intrinsic ability of the tubules to increase their reabsorption rate in response to increased tubular load.
- ❖ It acts as a second line of defense to buffer the effects of spontaneous changes in GFR, while the first line of defense is the tuboglomerular feedback.
- ❖ Glomerulotubular balance refers to the fact that the total rate of reabsorption increases as the filtered load increases.
- ❖ This mechanism is independent of hormones.
- ❖ It helps to prevent overloading of the distal tubular segments when GFR increases.
- ❖ Autoregulation & glomerulotubular balance prevent large changes in fluid flow in the distal tubules when arterial pressure changes or other disturbances occur.

Peritubular Capillary & Renal Interstitial Fluid Physical Forces:

- ❖ Changes in peritubular capillary reabsorption rate can influence the hydrostatic pressure & colloid osmotic pressure of the renal interstitium.
- ❖ Normal rates for physical forces & reabsorption rates:
 - Peritubular capillary reabsorption rate = 124 ml/min
 - Reabsorption = $K_f \times$ net reabsorptive force.
- ❖ Net reabsorptive force is the sum of the hydrostatic & colloid osmotic pressures that either favor or oppose reabsorption, these include :
- ❖ Hydrostatic pressure inside the peritubular capillary, $[P_c]$ (opposing).
- ❖ Hydrostatic pressure inside the renal interstitium, $[P_{if}]$ (favoring).
- ❖ Colloid osmotic pressure of the peritubular capillary plasma proteins, $[\pi_c]$ (favoring).
- ❖ Colloid osmotic pressure of proteins in the renal interstitium, $[\pi_{if}]$ (opposing).
- ❖ Normal peritubular capillary pressure = 13 mmHg and renal interstitial fluid hydrostatic pressure = 6 mmHg, thus there is a positive opposing force that is equal to 7 mmHg.
- ❖ This is opposed by the net colloid osmotic pressure = 17 mmHg, which favors reabsorption.
- ❖ Thus, net absorptive force = 10 mmHg

- ❖ Another factor contributing to reabsorption is high filtration coefficient. Because reabsorption rate is normally 124 ml /mm & net reabsorption pressure is 10 mmHg, K_f is normally 12.4 ml/min/mmHg.

Regulation of Peritubular Capillary Physical Forces:

- ❖ Peritubular capillary hydrostatic pressure is influenced by arterial pressure & resistances of the afferent & efferent arterioles.
- ❖ Increases in arterial pressure raise peritubular hydrostatic pressure & decrease reabsorption rate, this effect is buffered by autoregulation.
- ❖ An increase in resistance of the efferent or afferent arterioles reduces peritubular capillary hydrostatic pressure & increases reabsorption rate.
- ❖ Although constricting Efferent arterioles tend to increase glomerular capillary hydrostatic pressure, it lower peritubular hydrostatic pressure and increases reabsorption. ☺
- ❖ Colloid osmotic pressure of peritubular capillaries is determined by :
 1. Systemic plasma colloid osmotic pressure.
 2. Filtration fraction (directly proportional).
 3. Renal vasoconstrictors, e.g. Angiotensin II, increase peritubular capillary pressure, which increases reabsorption by decreasing renal plasma flow & increasing filtration fraction.
- ❖ Changes in peritubular capillary K_f (permeability and surface area) can influence reabsorption rate.
- ❖ An increase in K_f raises reabsorption, while a decrease decreases reabsorption.

Renal Interstitial Hydrostatic & Colloid Osmotic Pressure

- ❖ A decrease in reabsorptive forces across the peritubular capillary membranes reduces uptake of fluid & solutes from the interstitium to the peritubular capillary.

➤ $\uparrow P_C \rightarrow \downarrow$ Reabsorption	➤ $\uparrow \pi_C \rightarrow \uparrow$ Reabsorption
➤ $\downarrow R_A \rightarrow \uparrow P_C$	➤ $\uparrow \pi_A \rightarrow \uparrow \pi_C$
➤ $\downarrow R_E \rightarrow \uparrow P_C$	➤ $\uparrow FF \rightarrow \uparrow \pi_C$
➤ \uparrow Arterial Pressure $\rightarrow \uparrow P_C$	➤ $\uparrow K_f \rightarrow \uparrow$ Reabsorption
- ❖ P_C , peritubular capillary hydrostatic pressure;
- ❖ R_A and R_E , afferent and efferent arteriolar resistances, respectively;
- ❖ π_C , peritubular capillary colloid osmotic pressure;
- ❖ π_A , arterial plasma colloid osmotic pressure;
- ❖ FF, filtration fraction;
- ❖ K_f , peritubular capillary filtration coefficient.
- ❖ When peritubular capillary reabsorption is reduced, interstitial fluid hydrostatic pressure increases & a tendency for greater amounts of solutes & water to backleak into the lumen occurs, reducing the rate of net reabsorption.

- ❖ When there is an increase in peritubular capillary reabsorption above normal, the opposite occurs.
- ❖ An initial increase in reabsorption by the peritubular capillaries reduces interstitial fluid hydrostatic pressure & raises interstitial fluid colloid osmotic pressure therefore, backleak of water and solutes into the tubular lumen is reduced .
- ❖ Forces that increase peritubular capillary reabsorption also increase the reabsorption from the renal TUBULES; conversely, hemodynamic changes that inhibit peritubular capillary reabsorption also inhibit TUBULAR reabsorption of water & solutes.

Pressure diuresis & natriuresis

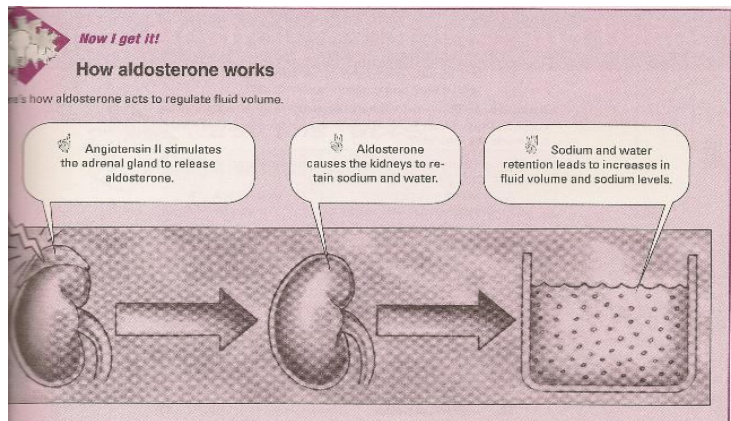
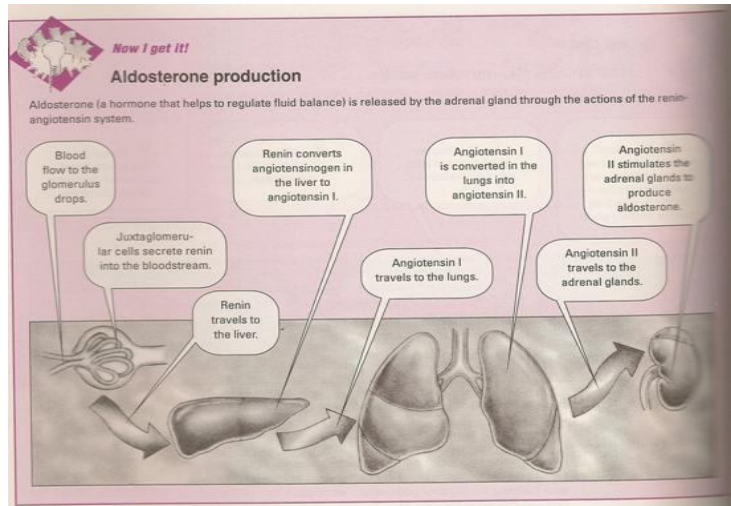
- ❖ Pressure natriuresis & diuresis occur only if autoregulation is impaired (e.g. some kidney diseases)
- ❖ Pressure natriuresis:
 - It is the increase of Na excretion due to increased arterial pressure.
- ❖ Pressure diuresis:
 - It is the increase in water excretion due to increased arterial pressure.
- ❖ An increase in arterial pressure, decreases the reabsorption percentage of the filtration load of Na & water and thus increasing the rate of urine output .
- ❖ This is due to :
 - A slight increase in peritubular capillary hydrostatic pressure & a subsequent increase in renal interstitial Fluid hydrostatic pressure (when the arterial pressure is increased ☺) tend to increase the backleak of Na and water into the tubular lumen.
 - Reduced angiotensin formation:
 - Angiotensin II increases Na reabsorption by the tubules & stimulates aldosterone secretion which further increases Na reabsorption.

Hormonal Control of Reabsorption:

Hormone	Site of Action	Effects
Aldosterone	Collecting tubule and duct	↑ NaCl, H ₂ O reabsorption, ↑ K ⁺ secretion
Angiotensin II	Proximal tubule, thick ascending loop of Henle/distal tubule, collecting tubule	↑ NaCl, H ₂ O reabsorption, ↑ H ⁺ secretion
Antidiuretic hormone(ADH)	Distal tubule/collecting tubule and duct	↑ H ₂ O reabsorption
Atrial natriuretic peptide(ANP)	Distal tubule/collecting tubule and duct	↓ NaCl reabsorption
Parathyroid hormone(PTH)	Proximal tubule, thick ascending loop of Henle/distal tubule	↓PO ₄ ⁻⁻⁻ reabsorption, ↑ Ca ⁺⁺ reabsorption

❖ Aldosterone:

- Increases Na reabsorption & increases K secretion.
- It is an important regulator of both ions.
- Its primary site of action is on the principal cells of the cortical collecting tubule.
- It stimulates the Na-K ATPase pump on the basolateral side of the cortical collecting tubule membrane.
- It also increases Na permeability of the luminal side of the membrane.
- In the absence of aldosterone (Addison's disease), there will be marked loss of Na from the body and accumulation of K
- Excess aldosterone secretion (Conn's disease) is associated with Na retention and K depletion.

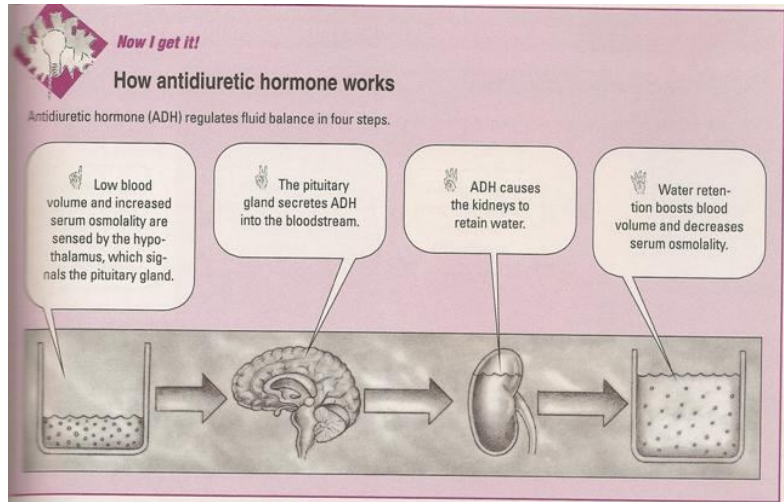


❖ Angiotensin II:

- Important in low blood pressure and/or low extra-cellular fluid volume such as hemorrhage or loss of salt & water.
- Helps to return blood pressure & extracellular volume toward normal by increasing Na & water reabsorption.
- Stimulates aldosterone secretion.
- Constricts the efferent arterioles, which has 2 effects:
 - Reduces peritubular capillary hydrostatic pressure, increasing reabsorption, especially in the proximal tubule.
 - Reduces renal blood flow, raises filtration fraction & increases concentration of proteins & colloid osmotic pressure in the peritubular capillaries.
- Directly stimulates Na reabsorption in the proximal tubules, the loop of Henle & collecting tubule by stimulating the Na-K ATPase pump.
- A secondary effect is to stimulate Na-H exchange in the luminal membrane, especially in the proximal tubule.

❖ ADH:

- Increases water reabsorption. By increasing water permeability of the distal tubule & collecting duct.
- Inserts aquaporins (specialized proteins) which when they cluster in the luminal side they form water channels (increases the permeability of H₂O).
- Plays a key role in controlling the degree of dilution of urine.
- Binds to V2 receptors in the Late DCT, collecting tubules and collecting ducts.



❖ Atrial natriuretic peptide (ANP):

- Decreases Na & water reabsorption.
- It is secreted from specific cells of cardiac atria , when distended because of plasma volume expansion.
- Increased ANP will inhibit the reabsorption of Na & water by renal tubules, especially in collecting ducts, and therefore increases urinary excretion and return blood volume back to normal.

❖ Parathyroid hormone:

- This hormone will increase Ca⁺ reabsorption in the Distal tubules. 😊

Sympathetic Nervous System

❖ Sympathetic system will decrease Na & water excretion by:

- Constricting renal arterioles and therefore ↓ GFR
- increasing rennin release & Angiotensin II formation (increasing tubular reabsorption).

Clearance Methods in Quantifying Kidney Function

❖ Renal clearance: is the volume of plasma that is completely cleared of the substance by the kidneys per unit time.

❖ Clearance refers to the volume of plasma that would be necessary to supply the amount of substance excreted in the urine per unit time.

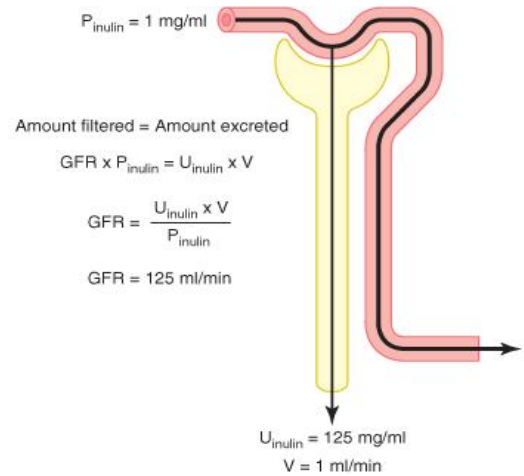
❖ $C_S = U_S \times V / P_S$.

❖ Where, C_S = clearance rate, P_S =plasma concentration, U_S = Urine concentration, V = Urine flow rate.

Substance	Clearance Rate (ml/min)
Glucose	0
Na	0.9
Cl	1.3
K	12
P	25
Insulin	125
Creatinine	140

Inulin Clearance in GFR Estimation

- ❖ Inulin is freely filtered & not reabsorbed or secreted, thus rate of excretion in urine equal the rate of substance filtered by the kidney.
 - $GFR = C_{in}$, and $C_{in} = U_{in} \times V / P_{in}$.
 - So, $GFR = U_{in} \times V / P_{in} = 125 \text{ ml/min}$.
- ❖ But inulin is not produced by the body & has to be injected, so we will replace it with creatinine.

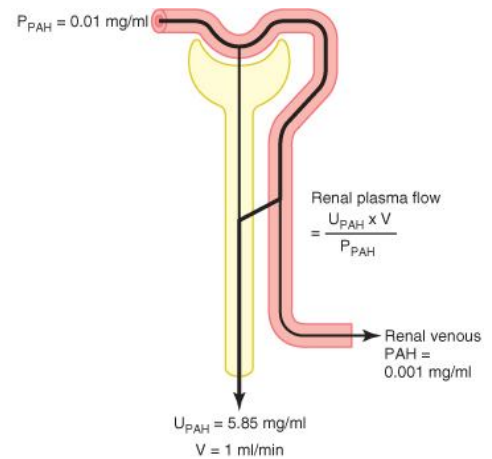


Creatinine Clearance in GFR Estimation

- ❖ creatinine does not require an intravenous infusion and is used widely.
- ❖ In creatinine there is a small amount which is secreted, so the amount excreted is more than the amount filtered, this will lead to overestimation (error).
- ❖ This error can be corrected by the machine calculating the clearance.

PAH in Renal Plasma Flow Estimation

- ❖ Para-aminohippuric acid (PAH) is freely filtered by the glomerular capillaries and is also secreted from the peritubular capillary blood into the tubular lumen.
- ❖ If a substance is completely cleared, then the clearance rate = total renal plasma flow.
- ❖ PAH is 90% cleared from plasma, therefore it can be used to estimate renal plasma flow, and we can say that:
 - $RPF = C_{PAH}$, but this is not completely true because we still have 10% in the plasma, so we can calculate the RPF as follows:
 - $RPF = \text{clearance of PAH} / \text{extraction ratio of PAH}$.
- ❖ Extraction ratio = 0.9 (because 90% is excreted in the urine).
 - Extraction ratio can be reduced in diseased kidneys, due to the inability of the damaged tubules to secrete PAH into the tubular fluid.



Calculation of Tubular Reabsorption or Secretion from Renal Clearances

- If the rate of excretion of a substance ($U_s \times V$) is less than its filtration load ($P_s \times GFR$) then some of it has been reabsorbed.
- Conversely, if the excretion rate of the substance is higher than its filtration load then the rate at which it appears in the urine represents the sum of the rate of glomerular filtration + tubular secretion.

Counter-current mechanism

counter-current multiplicaton

- water is reabsorbd from the descending limb because the medulla is hyperosmolar.
- this hyperosmolarity is due to the high concentrations of salts & urea in the medulla.
- NaCl is reabsorbed from the thick ascending limb.
- urea is reabsorbed from the collecting duct.
- Both NaCl & urea contribute to the medulla's hyperosmolarity.
- thiazide diuretics bloc NaCl reabsorption in the thick ascending loop . Thus, a large amount of urine is excreted.
- the reason for that is that salt remains in the filtrate, the medulla's osmolarity decreases , & water doesn't diffuse out .

counter-current exchanger :

- occurs in the vasa recta.
- functions to maintain the osmolarity produced by counter-current multiplication.
- salts are reabsorbed from one side & reinserted in the other side.
- water in the descending limb passes into the hyperosmolar medulla carrying o₂ & NaCl enters the blood.
- water (carrying co₂, waste products) in the ascending limb is reabsobed into the hyperosmolar blood , NaCl is left in the medulla.
- the result is that blood leaves the medulla with no significant change

Micturition

- voluntary emptying of the bladder.
- is a spinal reflex controlled by higher centers.
- the urge to urinate begins when the urinary content of the bladder reaches 400ml
- bladder distention stimulates stretch receptors in the bladder wall , leading to reflex contraction of the bladder & relaxation of the internal & external sphincters .
- inhibitory impulses from cerebral cortex inhibit this reflex , distention of the bladder stops these impulses.
- during the filling phase , the detrusor muscle is relaxed & both sphincters are contracted.
- urine is transported from the kidneys to the urinary bladder by the ureters.
- peristaltic movement of the ureter propels urine.
- the ureter opens obliquely into the bladder , this prevents urine reflux.
- fibers of the detrusor muscle are arranged spirally , circularly & longitudinally.
- internal sphincter isn't voluntary , while the external is.

*IF I HAVE A THOUSAND IDEAS AND ONLY ONE TURNS TO BE
GOOD, I'M SATISFIED*

Alfred Nobel