Renal Physiology

The kidneys have several functions including the following:

[1] Regulate water and electrolytes balance.

[2] 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**..

A waste is any substance that is useless to the body or present in excess of the body's needs. A metabolic waste is a waste substance produced by the body. Thus the food residue in feces, for example, is a waste but not a metabolic waste, since it was not produced by the body and, indeed, never entered the body's tissues. Metabolism produces a great quantity of wastes that are lethal to cells if allowed to accumulate. Some of the most toxic examples are small nitrogen-containing compounds called nitrogenous wastes. About 50% of the nitrogenous waste is urea, a by-product of protein catabolism. Proteins are broken down to amino acids, and then the -NH2 group is removed from each amino acid. The -NH2 forms ammonia, which is exceedingly toxic but the liver quickly, converts it to urea. Other nitrogenous wastes in the urine include uric acid and creatinine, produced by the catabolism of nucleic acids and creatine phosphate, respectively. Although less toxic than ammonia and less abundant than urea, these wastes are far from harmless. 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] 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] Acid-base regulation (along with the lungs and body buffers) through excreting acids and by regulating the body buffer stores.

[5] Regulation of erythrocyte production from the bone marrow by secreting erythropoietin which stimulate the bone marrow to produce erythrocytes.

[6] 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 gluconeogenesis occurs in the liver, but a substantial fraction occurs in the kidneys, particularly during a prolonged fast.

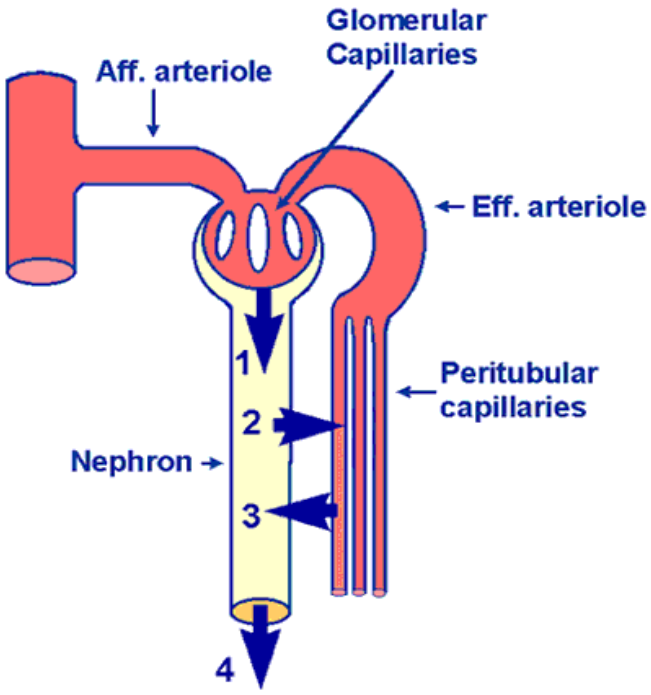
Renal function is based on four steps:

Blood from renal arteries is delivered to the glomeruli. At 1/5 of cardiac output, this is the highest tissue-specific blood flow.

1. Glomeruli form ultrafiltrate, which flows into renal tubules.

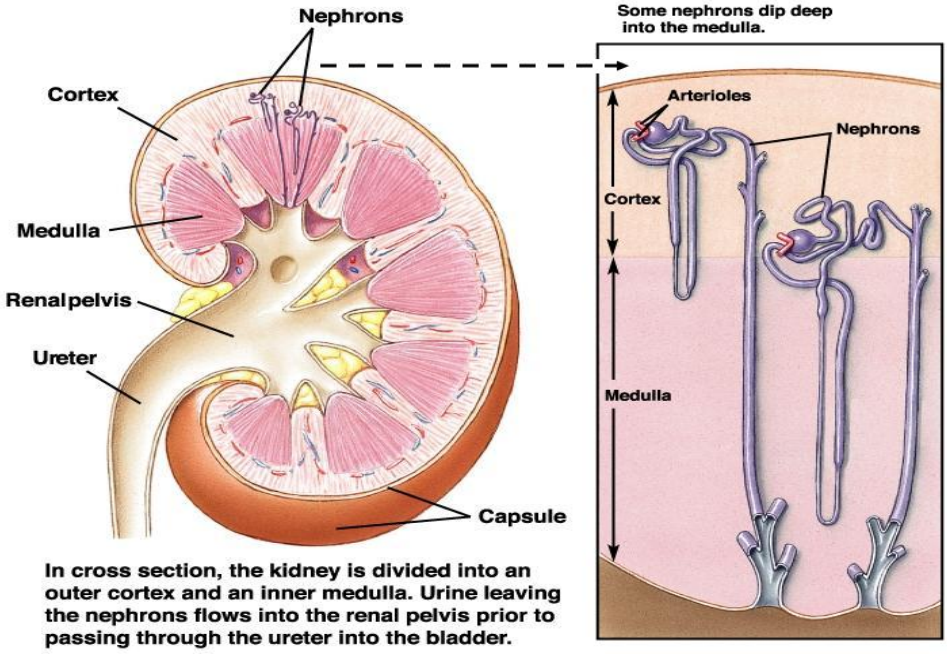
2 and 3 Tubules reabsorb and secrete solute and water from the ultrafiltrate.

4. Tubular fluid leaves the kidney via the ureter to the bladder

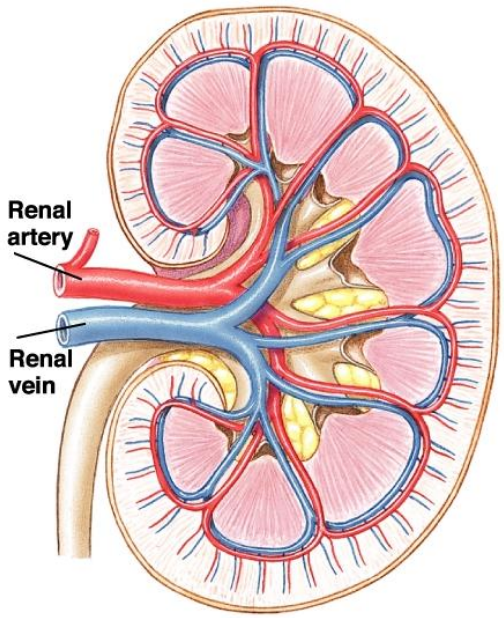


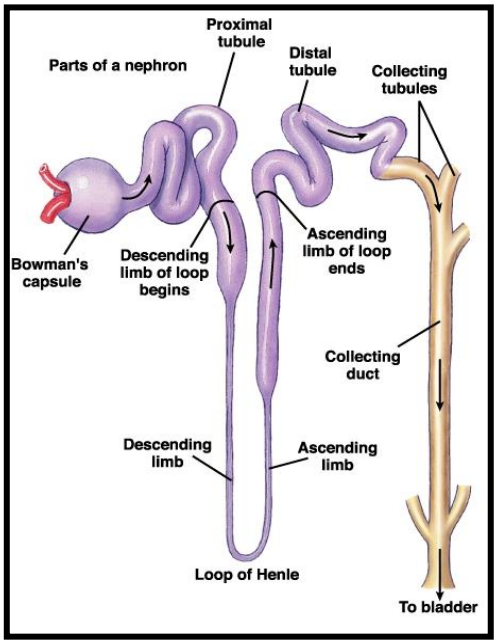
and out through the urethra.

Anatomy and function of the kidney



In cross section, the kidney is divided into an outer cortex and an inner medulla. Urine leaving the nephrons flows into the renal pelvis prior to passing through the ureter into the bladder.



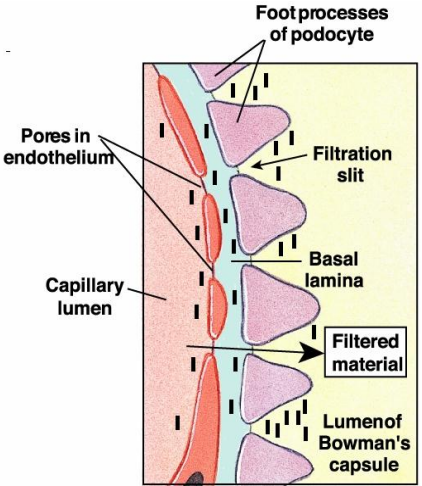


The kidney consists of: **[A] Nephron. [B] Blood vessels. [C] Nerves**

(A) 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 million nephrons in each kidney in human. Kidneys cannot regenerate new nephrons and their number decrease with aging, each nephron consists of:

[A] Bowman`s capsule: It is the invaginated blind end of the tubule that encased the **glomerulus** (which is a branching capillaries). The pressure in the glomerular capillaries is higher than that in other capillary beds.

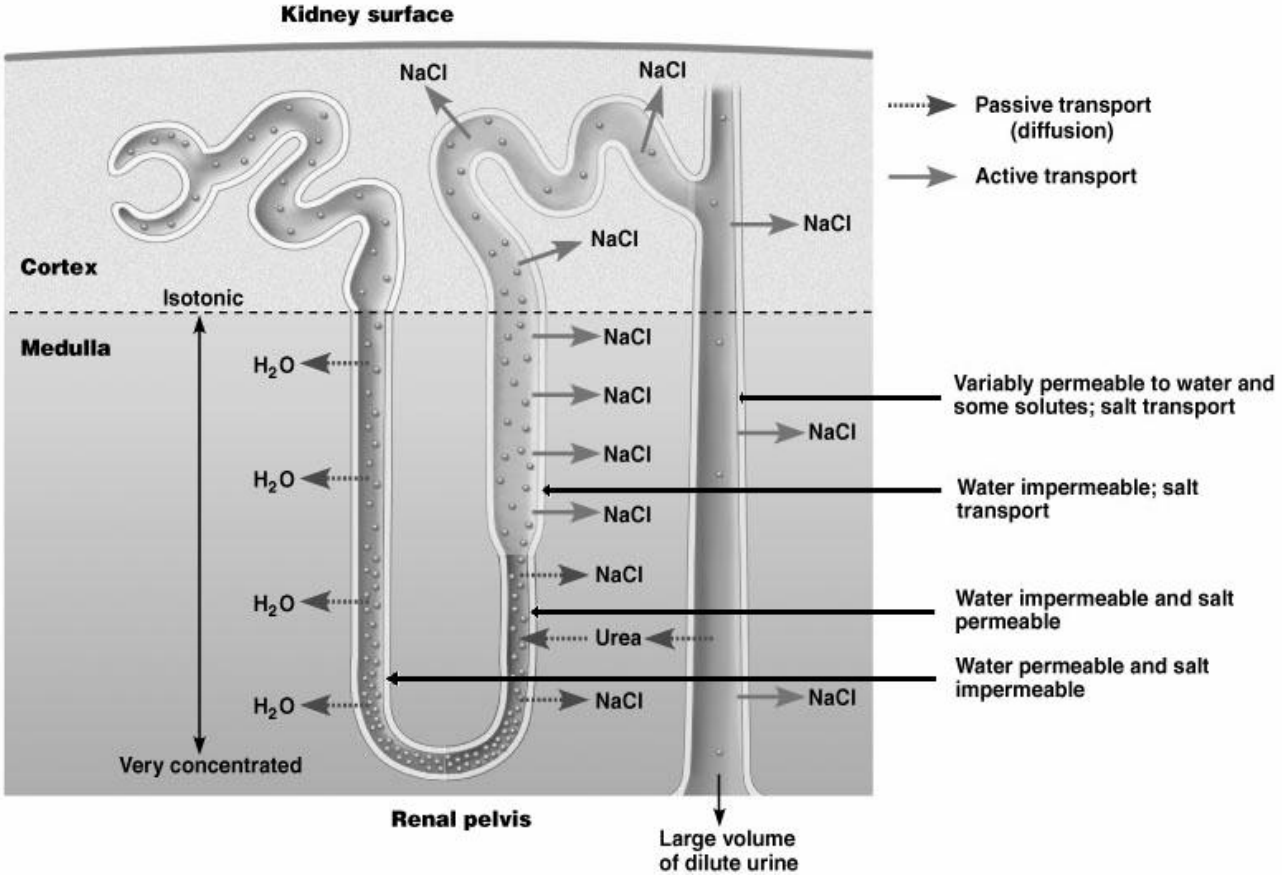
The membrane of the glomerular capillaries is called the **glomerular membrane**. The average total area of glomerular capillary endothelium across which filtration occurs (i.e. the glomerular membrane) is about 0.8 m^2. In general, this membrane is different from other capillary membranes by having 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). Narrow filtration that slits between these projections are bridged by a membrane protein called **nephrin**, which also contributes signifi cantly to the filtration barrier.



Fixed negative charges are present in the basement membrane and the filtration slits, and account for electrical repulsion of negatively charged macromolecules by the filtration barrier. Another type of cells is also present between the basal lamina and the endothelium called mesangial cells, which are contractile cells and play a role in the regulation of glomerular filtration besides other functions.

Yet, 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 the presence of thousands of small holes which are called **fenestrae** in the endothelial cells, by the presence of **large spaces** in the basement membrane, and by incontinuity of the cells that form the epithelial layer which are finger-like projections that forms slits between themselves called **slit-pores**.

[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


Kidney surface
NaCl
NaCl
Passive transport (diffusion)
Active transport
NaCl
NaCl
Cortex
Isotonic
Medulla
NaCl
H_2O
NaCl
Variably permeable to water and some solutes; salt transport
NaCl
NaCl
H_2O
Water impermeable; salt transport
NaCl
NaCl
H_2O
Water impermeable and salt permeable
Urea
Water permeable and salt impermeable
H_2O
NaCl
NaCl
Very concentrated
Renal pelvis
Large volume of dilute urine

[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. The proximal tubule resorbs from the filtered material **Na+, K+, Cl-,** nearly all **glucose** and **amino acids** and a proportional amount of **water**. The mechanism for glucose and amino acid reabsorption involves co-transport with Na^+ across the proximal tubule apical membrane. In addition, the proximal tubule also resorbs **urea**, **phosphate**, **Mg**, **sulfate, lactate, acetoacetate ions, vitamins** and **lipid-soluble substances**. Approximately 99% of the water filtered by the glomerulus is also resorbed by the whole renal tubule segments; and about 65% of the filtered water is resorbed by the proximal tubule.

In addition, the proximal tubule epithelium also **secretes H+, organic acids**, **bases,** and **certain drugs**, such as penicillin into the tubule fluid. The proximal tubule is the site of glomerulotubular balance as we will see later.

- **Proteins** are absorbed through the brush border of the proximal tubule by the process of **pinocytosis**.

Although the amount of Na in the tubular fluid decreases markedly along the proximal tubule, the concentration of Na and the total osmolarity remains relatively constant (isotonic) because water permeability of the proximal tubules is so great

that water reabsorption proportional to Na reabsorption. The proximal tubule is also the site for secretion of organic acids and bases (bile salts, oxalate, urate, Catecholamines), drugs, and toxins.

- Reabsorption of HCO_3^- occurs primarily in the proximal tubule indirectly through the absorption of CO_2 from proximal tubular fluid.

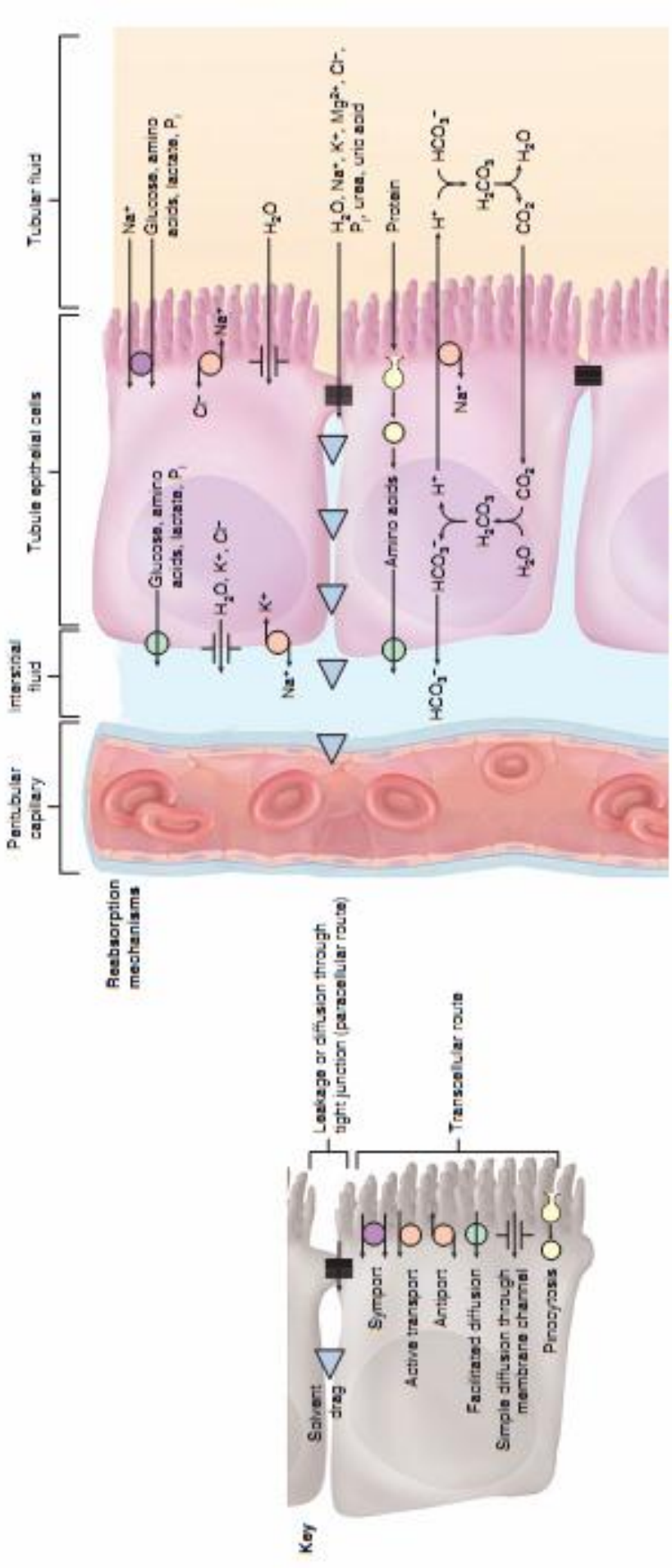
[2] Loops of Henle: The nephrons with their glomeruli located in the outer portion of the renal cortex have short loops of Henle **(cortical nephrons**, **70%),** where as those with glomeruli in the juxtamedullary region of the cortex (**juxtamedullary nephrons**, **30%)** have long loop extending down into medullary pyramids. The juxtamedullary nephrons are important for urine concentration. They also reabsorb a higher proportion of glomerular filtrate than cortical nephrons and are said to be "salt-conserving." In states where effective circulating blood volume is reduced, a higher proportion of renal blood flow (RBF) is directed to the juxtamedullary nephrons, helping to conserve extracellular fluid volume.

Loops of Henle include: The thin descending segment, the thin ascending segment, and the thick ascending segment.

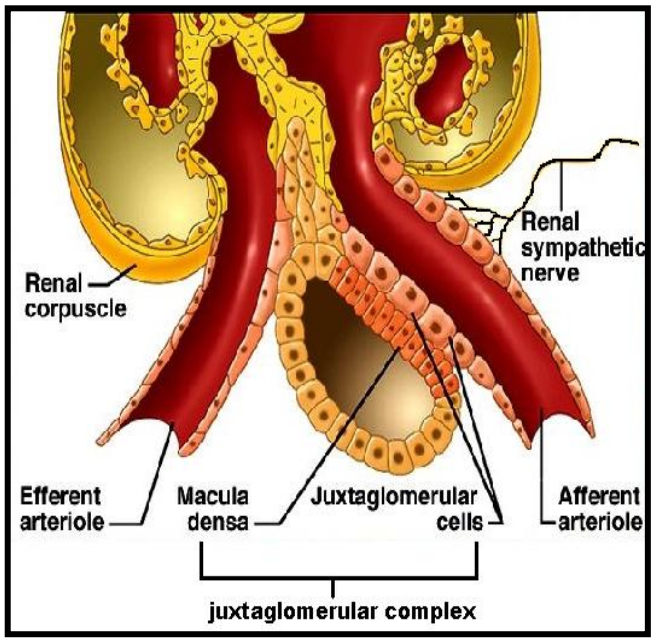
The thin descending segment of the loop of Henle: The epithelia cells of it are very thin with no brush border and very few mitochondria. They are highly permeable to **water** but nearly impermeable to sodium and most other ions. About 20% of the filtered water is reabsorbed in the descending thin limb 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 the ascending thin limb is impermeable to water, no water reabsorption is taking place in this area of the nephrone.

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. Therefore, this segmant 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.



Mechanisms of Reabsorption in the Proximal Convoluted Tubule.



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^-, Mg) are reabsorbed in the loop of Henle mainly in the thick ascending limb.

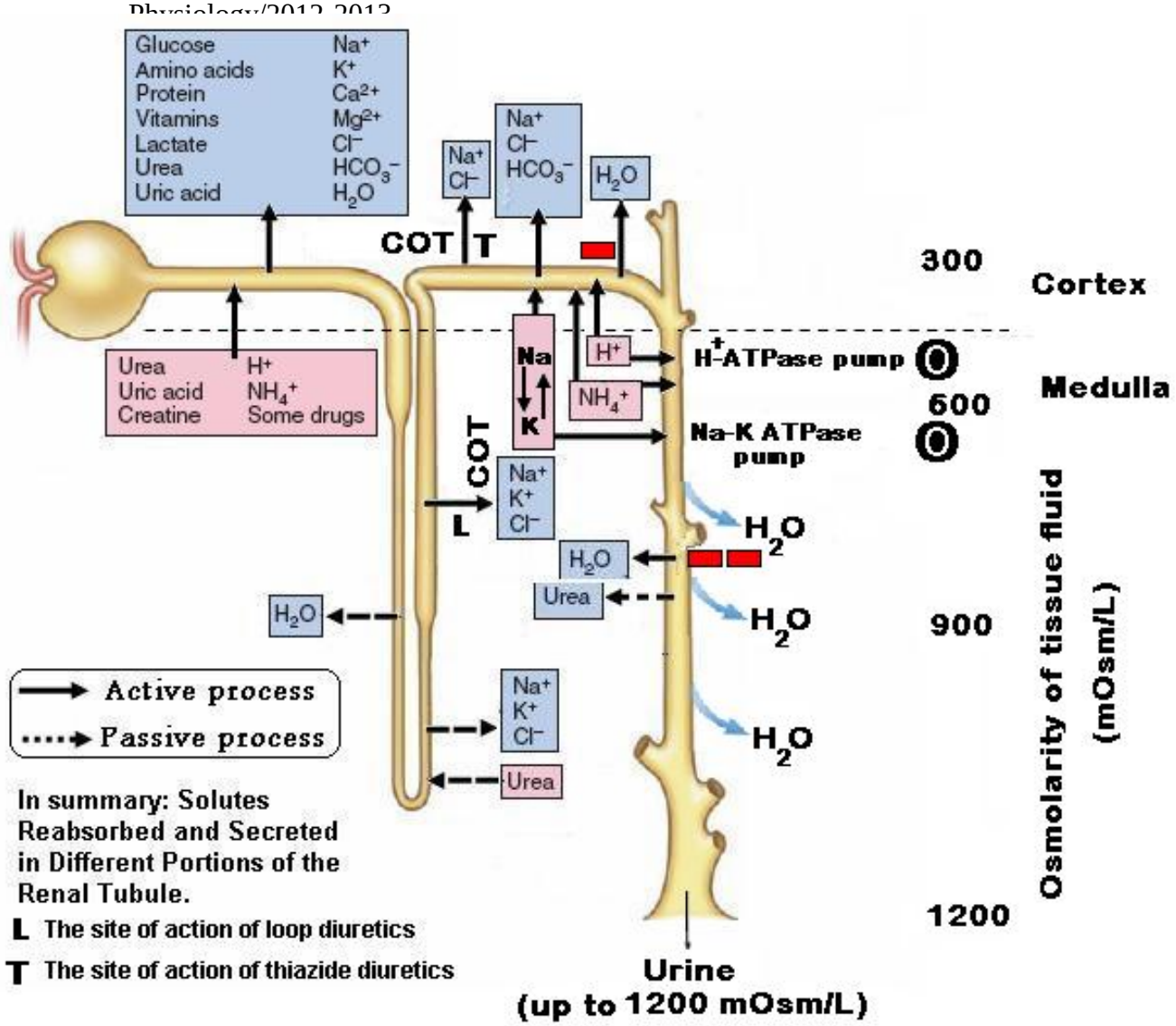
Because the thick segment of the ascending loop of Henle is impermeable to water, most of the water delivered to this segment remains in the tubule, despite the reabsorption of large amounts of solute. Thus, the tubular fluid in the ascending limb becomes very dilute as it flows toward the distal tubule (hypotonic).

[3] Distal convoluted tubule: 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.


Glucose
Amino acids
Protein
Vitamins
Lactate
Urea
Uric acid
Na+
K+
Ca2+
Mg2+
Cl−
HCO3−
H2O
Na+ Cl−
Na+ Cl− HCO3−
H2O
COT
T
300
Cortex
Urea
Uric acid
Creatine
H+
NH4+
Some drugs
Na
K
H+
NH4+
H+-ATPase pump
Na-K ATPase pump
600
Medulla
COT
L
Na+ K+ Cl−
H2O
H2O
Urea
H2O
H2O
H2O
900
Active process
Passive process
Na+ K+ Cl−
Urea
In summary: Solutes Reabsorbed and Secreted in Different Portions of the Renal Tubule.
L The site of action of loop diuretics
T The site of action of thiazide diuretics
1200
Urine
(up to 1200 mOsm/L)
Osmolarity of tissue fluid (mOsm/L)
Under the effect of aldosterone
Under the effect of ADH

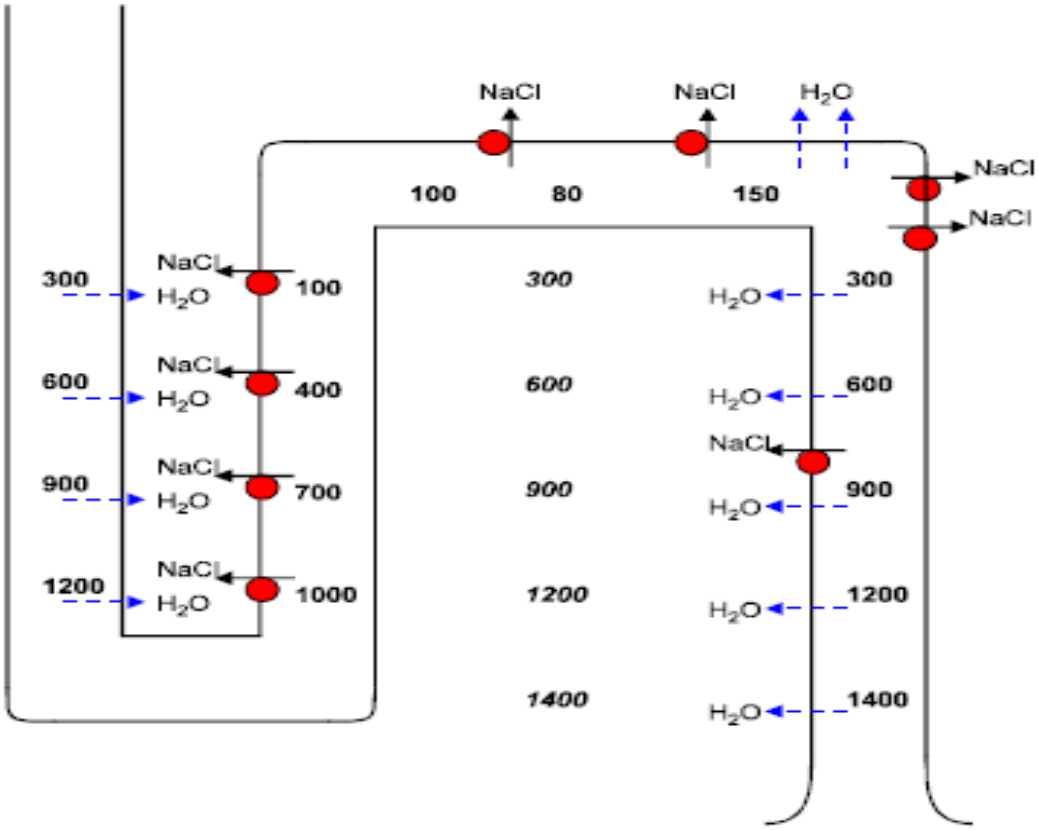
- **Reabsorb Na ions** while **secrete K ions** through increase the activity of *Na-K ATPase countertransporter* at the basolateral side of the cells under the effect of the hormone aldosterone.
- **Reabsorb K** ions while **secrete H ions** via *H-K ATPase countertransporter* at the luminal border 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.

[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 epitheliums of the medullary collecting ducts are involved in:

- **Na ions reabsorption** while **secrete K ions** under the effect of aldosterone through increase the activity of *Na-K ATPase countertransporter*.
- Vasopressin-stimulated **water reabsorption**.
- **H ions secretion** and bicarbonate ions transport (by *H-ATPase pump*) under the effect of aldosterone.

It is the final site for urine processing, and reabsorb less than 10% of the filtered water and Na. It plays an extremely important role in determining the final urine output of water and solutes.

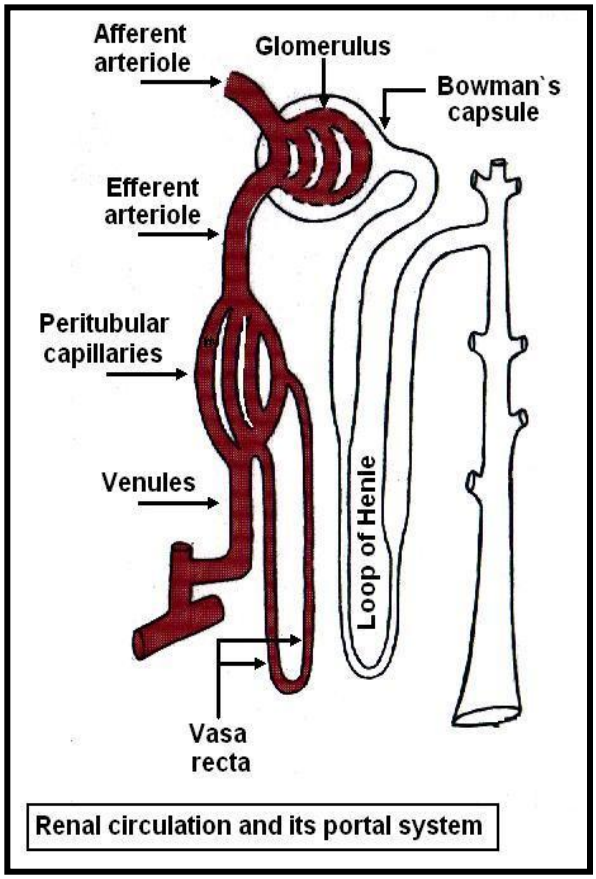
- Its permeability to water is under the control of ADH similar to the cortical collecting duct.
- It is permeable to urea (unlike the cortical collecting duct) which is increased in the presence of ADH.
- It is capable of secreting H ions against concentration gradient.



At each horizontal level, the medullary interstitium is concentrated by the transport of solute from the ascending loop of Henle as the descending loop of Henle is freely water permeable, ie water passively leaves the tubule concentrating the luminal contents these two processes proceed at each horizontal level so that the final concentration of solute deep in the medullary interstitium is ~ 1200-1400 mosmol/l the gradient at each horizontal level across the ascending loop of Henle remains at only 200 mosmol/l, while that across the descending loop of Henle is near zero therefore, the osmolality in the ascending loop of Henle is always less than that of the descending loop of Henle the fluid leaving the thick ascending loop of Henle for the distal tubule is ~ 200 mosmol/l below plasma, ie. **~ 100 mosmol/l.**

(B) Blood vessels: The renal fraction of the total cardiac output is about 21% (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.

In the juxtamedullary glomeruli, long efferent arterioles extend from the glomeruli down into the outer medulla and then divide into specialized long and straight capillary loops called **vasa recta** extended downward into the medulla to lay side by side with the lower parts of thin segments of juxtaglomerular loops of Henle all the way to the renal papillae. Then, like the loop of Henle, they also loop back toward the cortex and empty into the cortical veins. This specialized network of capillaries in the medulla plays an essential role in the formation of concentrated urine.



Renal circulation and its portal system

[C] Nerve supply: The kidney has a rich adrenergic sympathetic nerve supply distributed to the:

[A] Vascular smooth muscle to cause vasoconstriction.

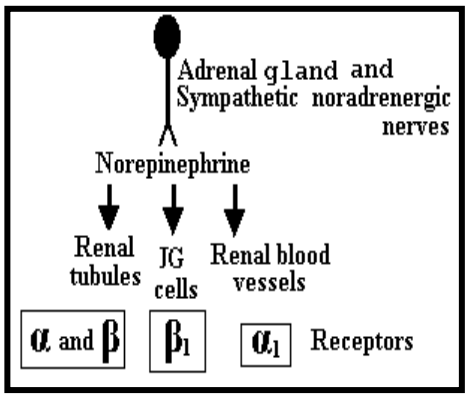
[B] Juxtaglomerular cells to cause renin secretion.

[C] Tubular cells to stimulate Na and water reabsorption.

There is no significant parasympathetic innervation

Glomerular function:

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). 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:

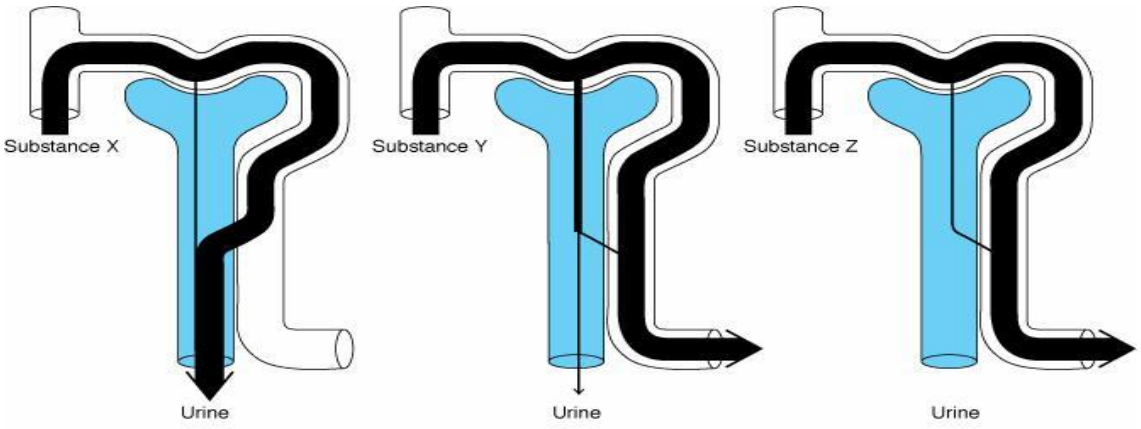


[1] Size of the molecules: Neutral substance with effective molecular diameter of less than 4 nm are freely filtrated, and those with diameter more than 8 nm (80 A), filtration is zero. Between these two values, filtration is inversely proportional with diameter.

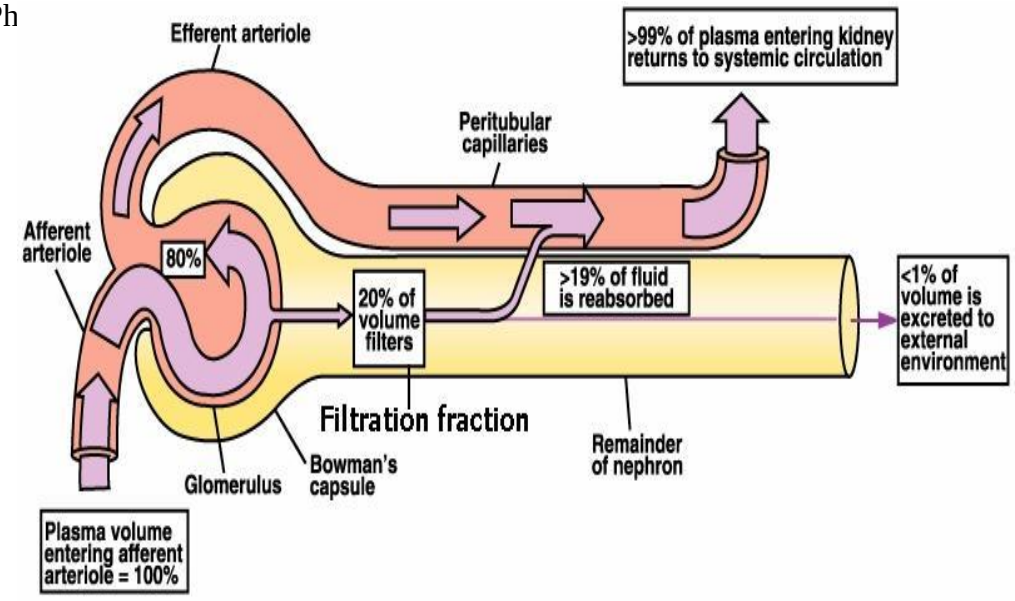
[2] The electrical charges of the molecules: This is because the inner side of the pores of the glomerular membrane is negatively charged repelling other negatively charged molecules that tend to pass through pores. For these two reasons, the glomerular membrane is almost completely impermeable to all 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%.



Renal manipulation of 3 hypothetical substances, X, Y, and Z. Substance X is filtered and secreted but not reabsorbed. Substance Z is filtered but is completely


Efferent arteriole
>99% of plasma entering kidney returns to systemic circulation
Peritubular capillaries
Afferent arteriole
80%
20% of volume filters
>19% of fluid is reabsorbed
<1% of volume is excreted to external environment
Filtration fraction
Remainder of nephron
Glomerulus
Bowman's capsule
Plasma volume entering afferent arteriole = 100%

Renal Function Tests: There are several tests for diagnosing kidney diseases, evaluating their severity, and monitoring their progress. Here we examine two methods used to determine renal clearance and glomerular filtration rate.

Renal clearance: is the volume of blood plasma from which a particular waste is completely removed in 1 minute. It represents the net effect of three processes: Glomerular filtration of the waste + Amount added by tubular secretion - Amount reclaimed by tubular reabsorption = Renal clearance

The substance used to measure the clearance should fulfill the following criteria: [A] freely filtered. [B] Neither reabsorbed nor secreted by the tubules. [C] Not metabolised or stored in the kidney. [D] Not toxic and not affecting the GFR. Such of these substances are inulin, creatinine, and Para-aminohippuric acid.

In principle, we could determine renal clearance by sampling blood entering and leaving the kidney and comparing their waste concentrations. In practice, it is not practical to draw blood samples from the renal vessels, but clearance can be assessed indirectly by collecting samples of blood and urine, measuring the waste concentration in each, and measuring the rate of urine output. Suppose the following values were obtained for urea: U (urea concentration in urine) = 6.0 mg/mL, V (rate of urine output) = 2 mL/min, P (urea concentration in plasma) = 0.2 mg/mL.

Renal clearance (C) is $C = UV/P = (6.0 \text{ mg/mL})(2 \text{ mL/min})/ 0.2 \text{ mg/mL} = 60 \text{ mL/min}$

This means the equivalent of 60 mL of blood plasma is completely cleared of urea per minute. If this person has a normal GFR of 125 mL/min, then the kidneys have cleared urea from only 60/125 = 48% of the glomerular filtrate. This is a normal rate of urea clearance, however, and is sufficient to maintain safe levels of urea in the blood.

Using clearance to estimate GFR:

GFR can be measured indirectly by calculating the clearance of a substance. The substance is called **glomerular marke** such as **Inulin**. For inulin, GFR is equal to the renal clearance. Inulin is a low-molecular-weight polysaccharide that is small enough to pass freely through the glomerular filtration barrier. Inulin is neither reabsorbed nor secreted by the nephron and cannot be metabolized. Therefore, the rate of inulin filtration equals the rate of inulin excretion in urine so the volume of plasma cleared per minute equals GFR. Inulin usually is not used clinically because it must be intravenously infused. Suppose, for example, that a patient's plasma concentration of inulin is P = 0.5 mg/mL, the urine concentration is U =30 mg/mL, and urine output is V = 2 mL/min. This person has a inulin clearance = UV/P = (30 mg/mL)(2 mL/min)/ 0.5 mg/mL = 120 mL/min. Therefore, for inulin, its clearance is equal to GFR.

In clinical practice, GFR is more often estimated from creatinine excretion. This has a small but acceptable error of measurement, and is an easier procedure than injecting inulin and drawing blood to measure its concentration.

However, measurement of endogenous **creatinine** clearance is more suitable because it does not need intravenous infusion as in inulin.

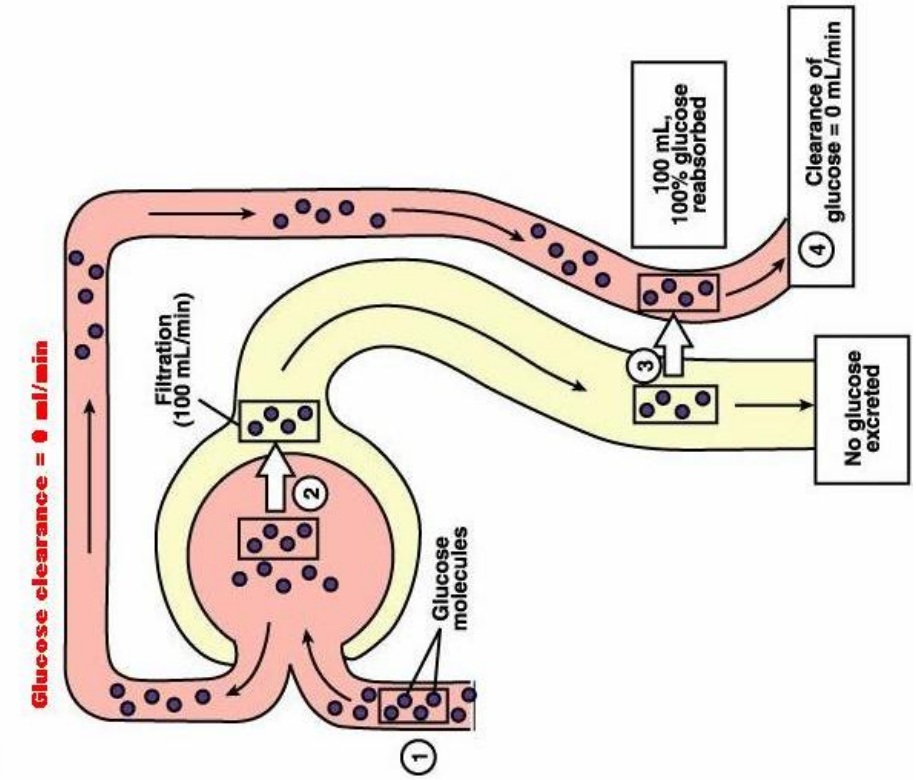
Using clearance to estimate RBF:

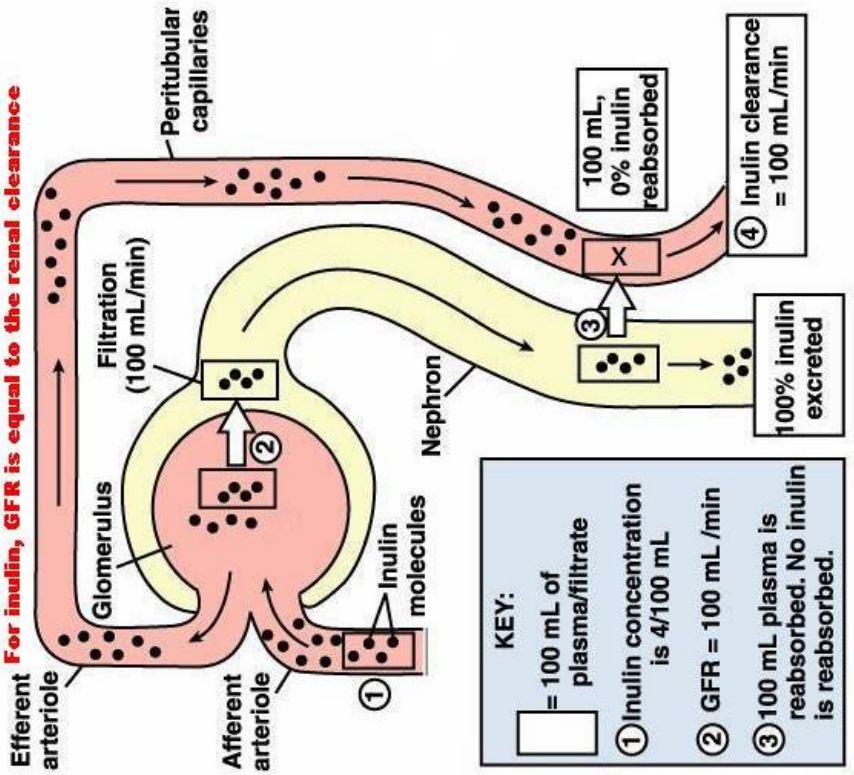
Para-aminohippuric acid (PAH) clearance is used as a measure of renal blood (plasma) flow (RPF): **PAH**, like inulin in its criteria. However, it is different from inulin in that it is cleared from the plasma by a **single passage** through the kidney and the remaining PAH in the plasma after the glomerular filtrate is formed, is secreted into the tubules by the proximal tubule, i.e zero PAH in renal vein. Where a substance is completely cleared from the plasma by a single passage through

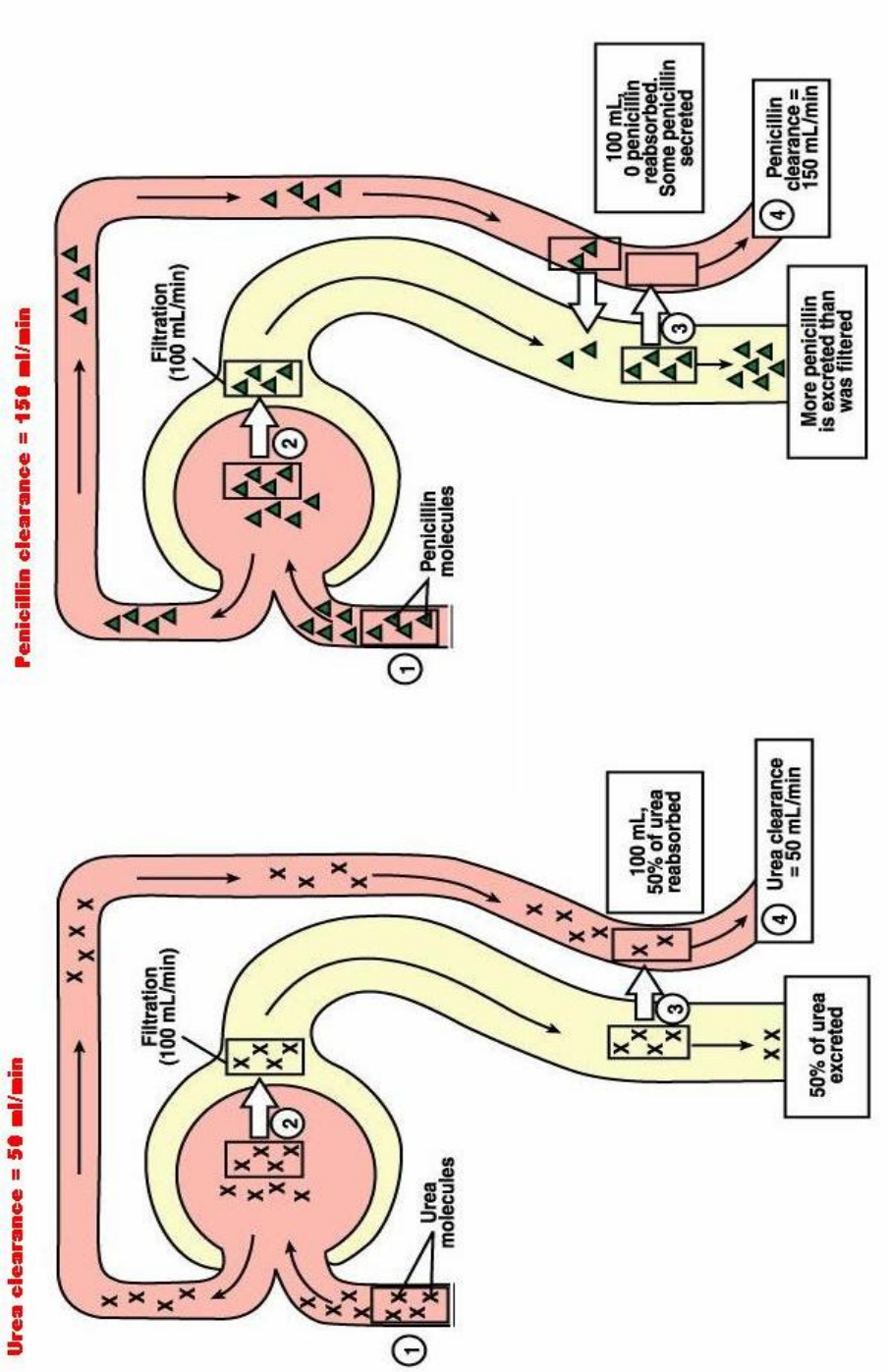
the kidney and all the cleared material is excreted in the urine, the clearance is equal to the renal plasma flow. Therefore:

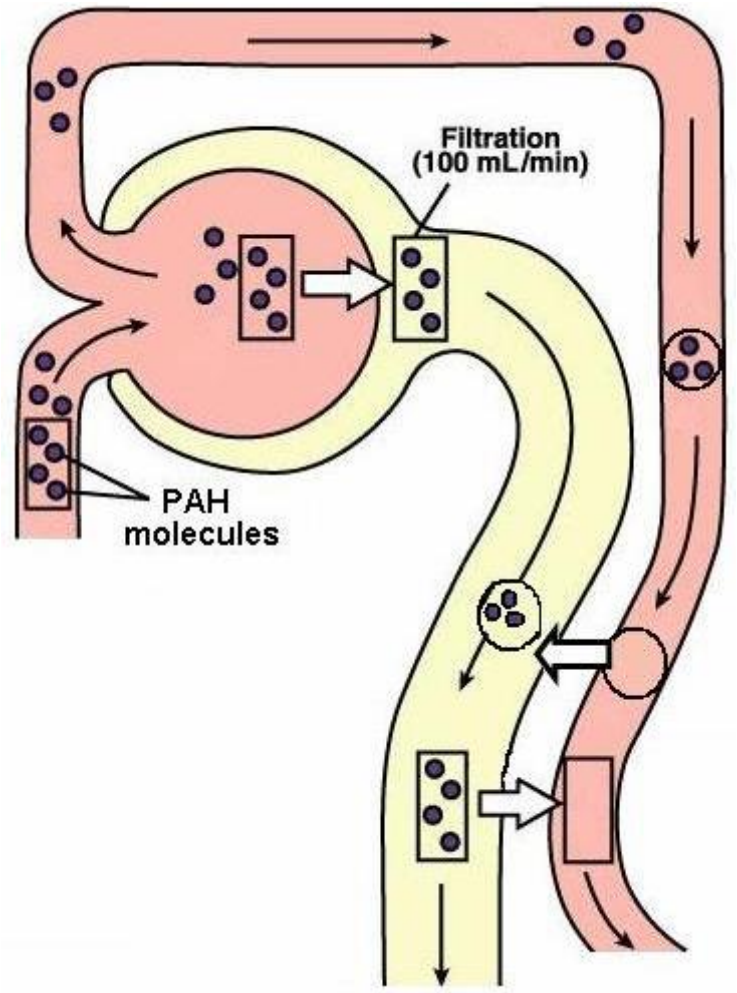
$$\text{Renal plasma flow (RPF)} = \frac{\text{Con. of PAH in urine X ml of urine/min}}{\text{Con. Of PAH in the plasma}}$$

$$\text{Renal blood flow (RBF)} = \frac{\text{RPF}}{1 - \text{Hct}}$$






Penicillin clearance = 150 ml/min
Filtration (100 mL/min)
Penicillin molecules
100 mL, 0 penicillin reabsorbed. Some penicillin secreted
Penicillin clearance = 150 mL/min
More penicillin is excreted than was filtered
Urea clearance = 50 ml/min
Filtration (100 mL/min)
Urea molecules
100 mL, 50% of urea reabsorbed
Urea clearance = 50 mL/min
50% of urea excreted


Filtration
(100 mL/min)
PAH
molecules

Factors that affect GFR: GFR is determined by:

[1] The filtration pressure is the net pressure forcing fluid through glomerular membrane (the Starling forces) which is determined by:

[A] Glomerular capillary hydrostatic pressure: This can be affected by several factors:

[1] Renal blood flow: Increase blood flow through the nephrons greatly increases the GFR for two reasons: (A) The increasing flow increases the glomerular pressure which enhances filtration. (B) The increased flow through the nephrons allows less time for plasma proteins to be more concentrated at the venous end of the glomerular capillaries bed. Therefore, oncotic pressure has far less inhibitory influence on glomerular filtration.

***[2] Afferent arteriolar constriction*:** Leads to decrease the rate of blood flow into the glomeruli and also decrease the glomerular pressure and decrease the GFR, and vice versa.

***[3] Efferent arteriolar constriction*:** A slight efferent arteriolar constriction increases the glomerular pressure causing slight increase in GFR. However, moderate and severe efferent arteriolar constriction causes a paradoxical decrease in the GFR despite the elevated glomerular pressure. This is due to the fact that plasma in this case will remain for long period of time in the glomerulus, and extra large portion of plasma will filter out. This will increase the plasma colloid osmotic pressure to excessive level causing a decrease in the GFR.

[B] A change in Bowman's capsule hydrostatic pressure: Increasing the hydrostatic pressure in Bowman's capsule (as in urinary tract obstruction) reduces GFR and vice versa.

[C] A change in glomerular capillary colloid osmotic pressure: A decrease in the glomerular capillary colloid osmotic pressure increases GFR and vice versa.

[D] An increase in the Bowman's colloid osmotic pressure: This may occur in diseases that causes filtration of proteins across glomerular membrane and consequently increases GFR.

[2] The capillary filtration coefficient, *which* is the product of the permeability and filtering surface area of the capillaries. It can be affected by:

[A] The changes in the permeability of the glomerular capillaries, which may be changed in disease state with consequent changes in the GFR.

[B] The thickness and the surface area of the capillary bed across which filtration is taking place which can be changed with a consequent change in the GFR. An example of such change is contraction or relaxation of mesangial cells in response to various substances can induce a decrease or an increase in the effective filtration surface area and eventual changes in the GFR.

In summary:

GFR can be affected by

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

A. Glomerular capillary hydrostatic pressure which is affected by:

I. Renal blood flow.
II. Afferent arteriolar constriction.
III. Efferent arteriolar constriction.

B. Bowman's capsule hydrostatic pressure.
C. Glomerular capillary colloid osmotic pressure.
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.

Factors affect urine volume: These factors play a significant role in determining the rate of fluid volume excretion (i.e. the urine).

[1] Presence of excessive quantities of osmotic particles (Osmotic diuresis): An important example on the osmotic diuresis is the diabetes mellitus in which the proximal tubules fail to reabsorb all the glucose, as normally occurs. Instead, the nonabsorbed glucose passes the entire distance through the tubules and carries with it a large portion of the tubular water. Osmotic diuresis also occurs when substances that are poorly or cannot be reabsorbed by the tubules are filtered in excessive quantities from the plasma into glomerular filtrate. Examples of such substances are sucrose, mannitol, and urea.

[2] Plasma colloid osmotic pressure: A sudden increase in plasma colloid osmotic pressure instantaneously decreases the rate of fluid volume excretion. The cause of this is due to (A) a decrease in GFR and (2) an increase tubular reabsorption.

[3] Sympathetic stimulation: Sympathetic stimulation causes constriction of the afferent arterioles via α_1 receptors stimulation. It greatly decreases the glomerular pressure and simultaneously decreases GFR. At the same time, the blood flow into the peritubular capillaries is decreased and consequently, the capillary pressure is decreased, thus increasing tubular reabsorption. Also sympathetic stimulation stimulate juxtaglomerular complex (via β_1 receptors) to release renin.

[4] Arterial pressure: Under normal condition (when the renal autoregulatory mechanism is intact), a change in blood

pressure causes a slight change diuresis and natriuresis. Unlike in renal diseases (when the renal autoregulatory mechanism is impaired), small increase in arterial pressure often causes marked increase in urinary excretion of Na and water. This results from two separate effects: (A) the increase in arterial pressure increases glomerular pressure, which in turn increases GFR, thus leading to increased urine output. (B) The increase in arterial pressure also increases the peritubular capillary pressure, thereby decreasing tubular reabsorption.

[5] Hormonal control: Such as:

ADH: When excess antidiuretic hormone is secreted by the posterior pituitary gland, the effect is to increase the water permeability of the distal tubule, collecting tubule and collecting duct with a consequent decrease the urinary volume output acutely. However, when excess ADH is secreted for long periods of time, the acute effect of decreasing urinary output is not sustained. The reason is that other factors, such as the arterial pressure, colloid osmotic pressure, and concentrations of the osmolar substances in the glomerular filtrate all change in the direction that leads eventually to a urinary volume output equal to the daily need.

Aldosterone: This is secreted by the zona glomerulosa cells of the adrenal cortex by its action on the principal cells of the cortical collecting tubule to increase Na reabsorption and to increase K secretion.

Angiotensin II:

[1] It stimulates aldosterone secretion, which in turn increases Na and water reabsorption.

[2] It constricts the efferent arterioles and consequently increases Na and water reabsorption through the following mechanisms:

[A] When the angiotensin constricts the efferent arterioles, this reduces the peritubular capillary pressure causing an increase in

the rate of reabsorption of water and electrolytes from the tubular system especially from the proximal tubule, because the balance forces at the capillary membrane is now in favor of absorption.

[B] Because of the constriction of the efferent arterioles, the blood flow through glomeruli is decreased while the GFR is still near normal. This will lead that a very high proportion of plasma fluid to filter through the glomerular membrane into tubules. Therefore, the concentration of the plasma proteins in the blood leaving the glomeruli becomes very high and this concentrated plasma flows on into the peritubular capillaries. As the result, the colloid osmotic pressure in these capillaries is greatly increased, which is an additional factor that enhances reabsorption of water and salt.

[C] There is evidence that angiotensin also has a direct effect on the distal tubules in causing increased active reabsorption of Na.

[3] It act directly especially on the proximal tubule to increase Na and water reabsorption (by stimulating Na-K ATPase pump at the basolateral membrane of the tubular cell) and Na-H exchange (at the luminal side of the tubular cell).

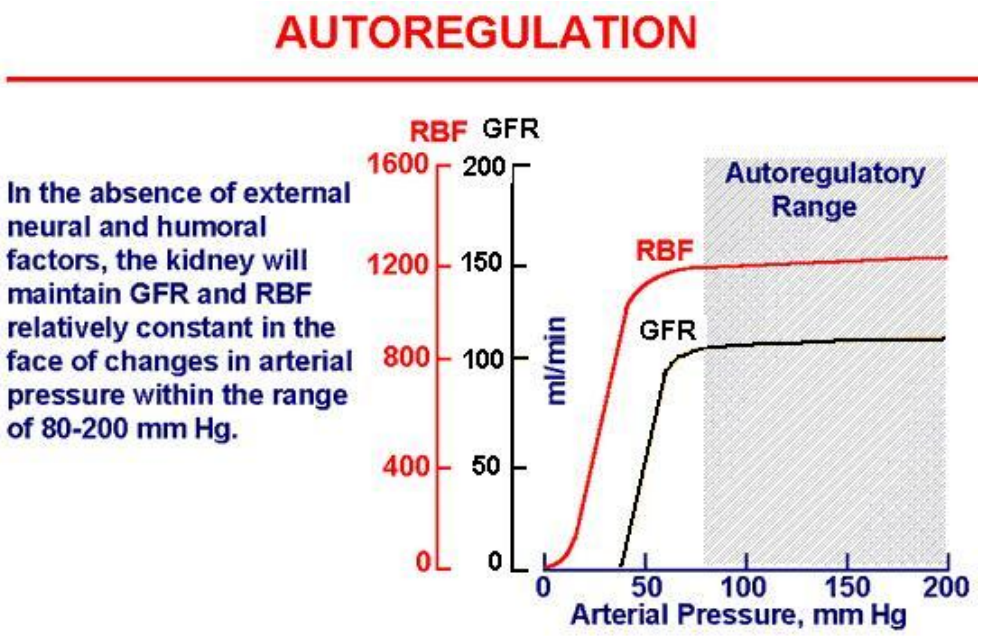
[4] Mesangial cells constrict in response to angiotensin II and reduce the capillary filtration coefficient resulting in an overall decrease in GFR.

Atrial natriuretic peptide: It is released from specific cells of the cardiac atria upon distension as a result of plasma volume expansion. It inhibits the reabsorption of Na and water by the renal tubules especially in the collecting ducts with consequent increase in the urinary output.

Parathyroid hormone: It increases the reabsorption of Ca and Mg ions from the ascending limb of loop of Henle and distal tubule. It inhibits the reabsorption of phosphate from the proximal tubule.

Autoregulation of GFR (and renal blood flow): It is the feedback intrinsic mechanisms by which the kidneys normally keep the renal blood flow (and consequently GFR) relatively constant, despite marked changes in arterial blood pressure.

GFR (125 ml/min) and renal blood flow (1200 ml/min) normally they have to remain relatively constant for both kidneys even the blood pressure changes from 75-160 mm Hg.



This is because that even a 5% too great or too little rate of glomerular filtration can have considerable effects in causing either excess loss of solutes and water into the urine, or at the other extreme too little of necessary excretion of waste products. There are specialized negative feedback mechanisms which add together to provide the degree of GF and renal blood flow that is required. These negative feedback mechanisms are:

- **[A] Tubuloglomerular feedback mechanism**
- **[B] Myogenic mechanism**

[A] Tubuloglomerular feedback mechanism: This occurs through JG complex.

[1] The afferent arteriolar vasodilator and vasoconstrictor feedback mechanisms: A low GFR causes a low flow rate of tubular fluid which leads to overreabsorption of Na and Cl ions in the ascending limb of the loop of Henle and therefore decreases the ions concentration at the macula densa. This decrease in ion concentrations initiates a signal (not completely understood) from the macula densa to the juxtaglomerular cells to dilate the afferent arteriole which results to an increased blood flow into the glomerulus causing an increase in glomerular pressure and hence GFR back toward the required level. If GFR rises, however, it increases the flow of tubular fluid and the rate and more delivery of NaCl in the ascending limb of the loop of Henle and therefore increases the ions concentration at the macula densa. The macula densa apparently senses variations in flow or fluid composition and initiates a signal (not completely understood) from the macula densa to the juxtaglomerular cells to constrict the afferent arteriole which results to a decreased blood flow into the glomerulus causing a decrease in glomerular pressure and hence GFR back toward the required level.

[2] The efferent arteriolar vasoconstrictor feedback mechanism: Too few Na and Cl ions at the macula densa are believed to cause JG cells to release renin and this in turn causes the formation of angiotensin II which constricts mainly the efferent arterioles (much more than the afferent arterioles). Therefore, the constriction of the efferent arterioles causes the pressure in the glomerulus to rise leading to increase in GFR back to normal. Renin is an enzyme that release from renal juxtaglomerular cells and acts on a substrate angiotensinogen. The cascade reaction is as shown in figure below.

Renin release is increased if:

- Renal perfusion pressure is decreased,

- Renal blood flow is decreased,
- Stimulation of renal nerves.

[B] Myogenic mechanism: This mechanism of stabilizing the GFR is based on the tendency of smooth muscle to contract when stretched. When the arterial pressure rises, it stretches the wall of the arteriole, and this in turn causes a secondary contraction of the arteriole. This decreases the renal blood flow and GFR back toward normal, thus opposing the effect of the rising arterial pressure to increase the flow. Conversely, when the pressure falls too low, an opposite myogenic response allows the artery to dilate and therefore increases the flow and GFR.

Glomerulotubular balance: It is the ability of the tubules to increase reabsorption rate in response to increased tubular load, which means that when the GFR increases, the rate of tubular reabsorption increases in exact proportion to the increase in filtration. Glomerulotubular balance is especially good in the proximal tubules and loop of Henle and less effective in the more distal segments of the tubular system. This slight lack of glomerulotubular balance in the distal tubular segments can lead to a tremendous increase in urine output when the GFR is increased. Also, very slight changes in rate of reabsorption of tubular fluid can cause equally as great alteration in urine output. The mechanistic basis of glomerulotubular balance is poorly understood but appears to act completely independently of neuroendocrine regulatory mechanisms and is likely an intrinsic property of the nephron itself. It seems likely that changes in GFR result in modification of the Starling Forces in the Peritubular Capillaries resulting in proportionally increased or decreased total nephronic resorption. Glomerulotubular balance is a critical mechanism which protects distal segments of the nephron from being overloaded in contexts of short-term increases in GFR. Distal segments of the nephron have a very

limited capacity to increase tubular resorption of water and solutes; consequently, a large increase in distal flow rates would result in catastrophic loss of fluid in the urine. Glomerulotubular balance thus guarantees that the majority of additional tubular flow, due to increases in GFR, is resorbed by proximal segments of the nephron which are significantly more capable of resorbing large fluid volumes. It should be pointed out that glomerulotubular balance can be thought of as a second layer of protection which follows mechanisms of Tubuloglomerular

Effect of "perfect" Glomerulotubular Balance on the mass of sodium leaving the proximal tubule

GFR (L/min)	P_{Na} (mmol/L)	Filtered (mmol/min)	Reabsorbed proximally (66.7% of filtered; mmol/min)	Leaving proximal (mmol/min)
0.124	145	18	12	6
0.165	145	24	16	8
0.062	145	9	6	3

Feedback that attempt to maintain nearly constant rates of GFR. In response to a primary change in GFR, the percentage of the filtered sodium reabsorbed proximally remains approximately constant (about 65%). The fraction not reabsorbed also remains approximately constant (about 35%).

The net result of fixed fractional reabsorption is to reduce the magnitude of difference in sodium leaving the proximal tubule The mechanisms responsible for matching changes in tubular reabsorption to changes in GFR are completely intrarenal (ie, glomerulotubular balance requires no external neural or hormonal input. Glomerulotubular balance is actually a second line of defense preventing changes in renal hemodynamics per se from causing large changes in sodium excretion. The first line of defense is autoregulation of GFR as described previously. GFR autoregulation prevents GFR from changing too much in direct response to changes in blood pressure, and glomerulotubular balance blunts the sodium-

excretion response to whatever GFR change does occur. Thus, tubuloglomerular feedback and glomerulotubular balance are processes that allow a large fraction of the responsibility for homeostatic control of sodium excretion to reside in those primary inputs that act to influence tubular reabsorption of sodium independently of GFR changes.

Tubular load of a substance: Is the total amount of the substance that filters through the glomerular membrane into tubules per minute.

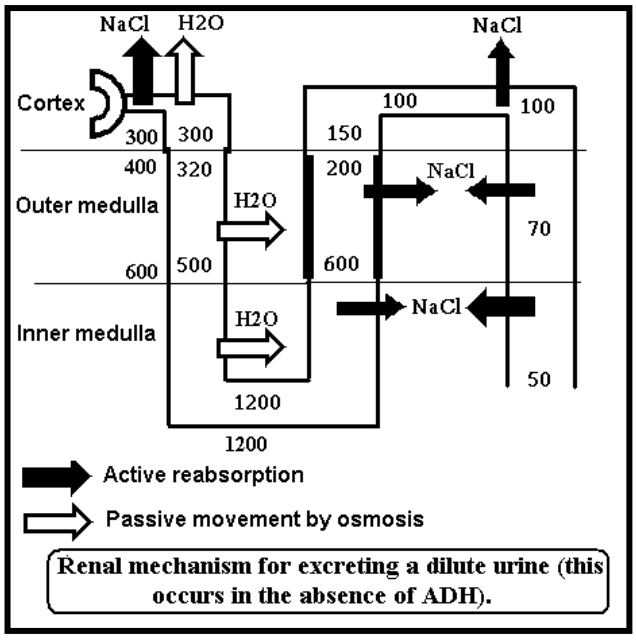
Tubular load = conc. of the substance in the filtrate x GFR. It is expressed in gm/min. For example, if the plasma concentration of glucose is 100 mg/100 ml plasma, so the tubular load of glucose is equal to:

$$\frac{100\ \text{mg}}{100\ \text{ml}} \times \frac{125\ \text{ml}}{\text{min}} = 125\ \text{mg/min}$$

Tubular transport maximum (T_m): It is the maximum rate (in mg/min) for actively reabsorbing or secreting substance by the tubule. For example, the T_m for glucose average 320 mg/min for adult human being, and if the tubular load becomes greater than 320 mg/min, the excess above this amount is not reabsorbed but instead passes on into the urine. The serum level of the substance below which none of it appears in the urine and above which progressively larger quantities appear is called the **threshold concentration** of that substance. The renal threshold for glucose occurs at a plasma glucose concentration somewhat below the value at which the renal Tm for glucose is reached. In fact, glucose begins to spill into the urine when its tubular load exceeds 220 mg/min which correspond to a concentration of glucose in plasma of 180 mg/100 ml when kidneys are operating

at their normal glomerular filtration rate of 125 ml/min. This phenomenon, termed **splay**, occurs because not all of the two million nephrons have the same Tm for glucose, and those with lower Tm for glucose begin losing glucose to the urine before those with higher Tm for glucos.

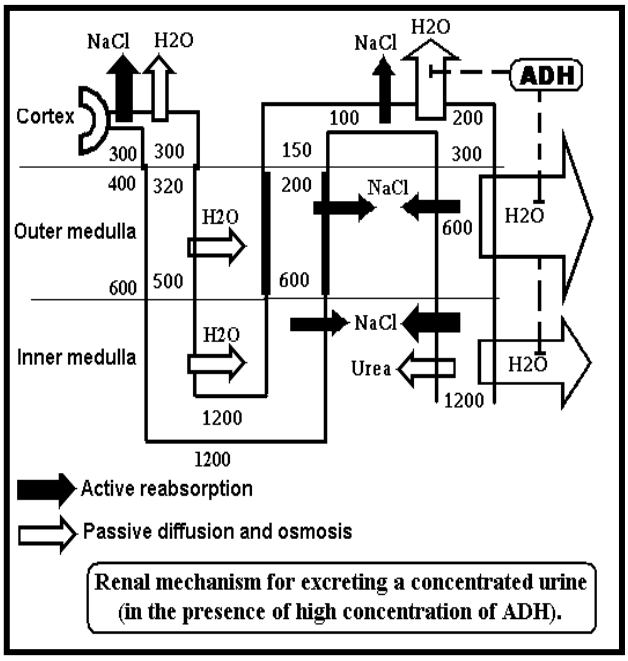
Renal Mechanisms for excreting diluted or concentrated urine: The kidneys can excrete urine with an osmolarity as low as **50 mOsmol/l**, a concentration that is only about sixth the osmolarity of normal extracellular fluid. Conversely, when there is a deficit of water and extracellular fluid osmolarity is high, the kidney can excrete urine with a concentration of about **1200 to 1400 mOsmol/l**. Equally important, the kidney can excrete a large volume of dilute urine or a small volume of concentrated urine without major changes in rates of excretion of solutes such as Na and K. This ability to regulate water excretion independently of solute excretion is necessary for survival, especially when fluid intake is limited. When the osmolality of the body fluids fall too low, i.e. when the fluids become too dilute, the kidney automatically excrete a great excess of water in urine causing the urine to be diluted and therefore increasing the body fluid osmolality back toward normal. Conversely, when the osmolality of body fluids is too great, the kidney automatically excrete an excess of solutes in urine causing the urine to be concentrated thereby reducing the body fluid osmolality again back toward normal.



Renal mechanism for excreting a dilute urine (this occurs in the absence of ADH).

[1] The Renal mechanism for excreting dilute urine: As fluid flows through the proximal tubule, solutes and water are reabsorbed in

equal proportions, so that little change in osmolarity occurs, that is the proximal tubule fluid remains isotonic to the plasma, with an osmolarity of about 300 mOsmol/l. As fluid passes down the descending loop of Henle, water is reabsorbed by osmosis and the tubular fluid reaches equilibrium with the surrounding interstitial fluid of the renal medulla, which is very hypertonic, of about 1200 mOsmol/l, i.e. four times the osmolarity of the original glomerular filtrate. Therefore, the tubular fluid becomes more concentrated as it flows into the inner medulla. In the ascending limb of the loop of Henle, especially the thick segment, Na, K, and Cl are avidly reabsorbed. However, this portion of the tubular segment is impermeable to water. Therefore, the tubular fluid becomes more dilute as it flows up the ascending loop of Henle into the early distal tubule, with the osmolarity decreasing progressively to about 100 mOsmol/l by the time the fluid enters the early distal tubular segment. Thus, the fluid leaving the early distal tubular segment is hypotonic with an osmolarity of only about one third the osmolarity of plasma. As the dilute fluid in the early distal tubule passes into the late distal tubule, cortical collecting tubule, and collecting duct, there is additional reabsorption of NaCl. This portion of the tubule is also impermeable to water (in the absence of ADH), and additional reabsorption of solutes causes the tubular fluid to become even more diluted with an osmolarity of about 50 mOsmol/l.



[2] Renal mechanism for excreting concentrated urine: The basic requirements for forming concentrated urine is a **high level of ADH:** This increases the permeability of the distal tubules and collecting ducts to water, thereby allowing these tubular segments to avidly reabsorb water. The signal that tells the kidney whether to excrete diluted or concentrated urine is the hormone called **antidiuretic hormone (ADH)** or **vasopressin** that is secreted from the posterior pituitary gland. When the body fluids are too concentrated, the posterior pituitary gland secretes large amount of ADH, which causes the kidney to excrete excessive amounts of solutes but to conserve water in the body. Conversely, in the absence of ADH the kidney excretes dilute urine, thus removing excessive amount of water from the body fluids and causing them to become concentrated once again.

The high osmotic gradient along the renal medullary interstitial fluid: Which means 300 mOsmol/l at the cortex, about 800 mOsmol/l at the outer medulla, and as high as 1200-1400 mOsmol/l at the inner medulla. This gradient is **produced:**

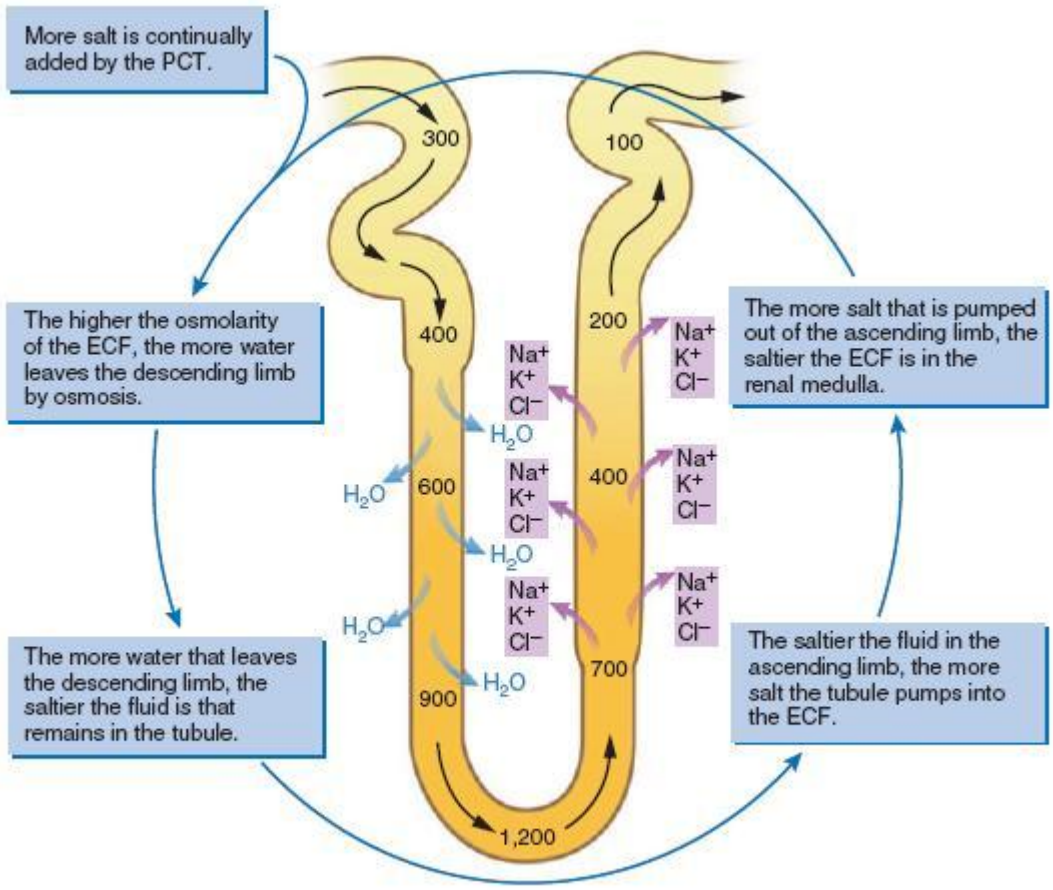
- By the operation of the loops of Henle as **countercurrent multipliers** and
- By medullary interstitial urea concentration (**urea cycle**)

And is **maintained**

- By the operation of the vasa recta as **countercurrent exchangers** in addition to
- By the **Slight medullar blood flow**

[1] Countercurrent multipliers: In general, a "countercurrent system" is a system in which the inflow runs *parallel to*, *counter to (opposite to)*, and in *close proximity* to the outflow *for some distance*. This occurs for both the loop of Henle and the vasa recta of the renal medulla.

The operation of each loop of Henle as a countercurrent multiplier depends on the following:



The Countercurrent Multiplier of the Nephron Loop.

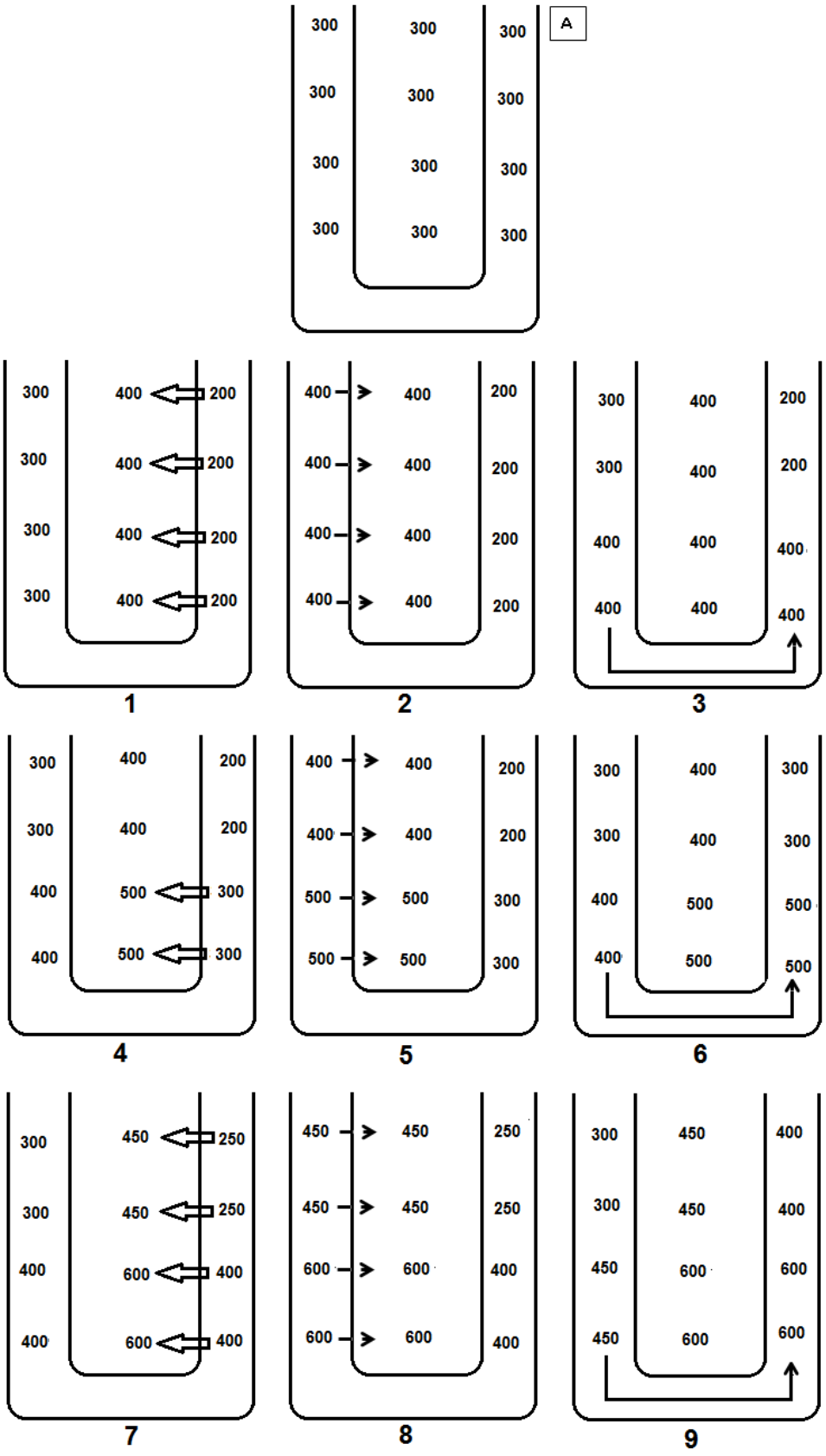
[1] Active transport of Na, K, Cl, and other ions out of thick ascending limb from the tubular lumen to the interstium. This pump able to create about 200 Mosmol concentration gradient between the interstial fluid and the tubular lumen.

[2] Diffusion of water by osmosis from the thin descending loop of Henle to the interstial fluid.

[3] Facillitated diffusion of large amounts of urea from the inner medullary collecting ducts into the medullary interstitium.

All of the above processes are essential to produce the increasing osmotic gradient along the medullar interstial fluid.

With these characterisatics of the loop of Henle in mind, let us



now discuss how the renal medulla becomes hyperosmotic:

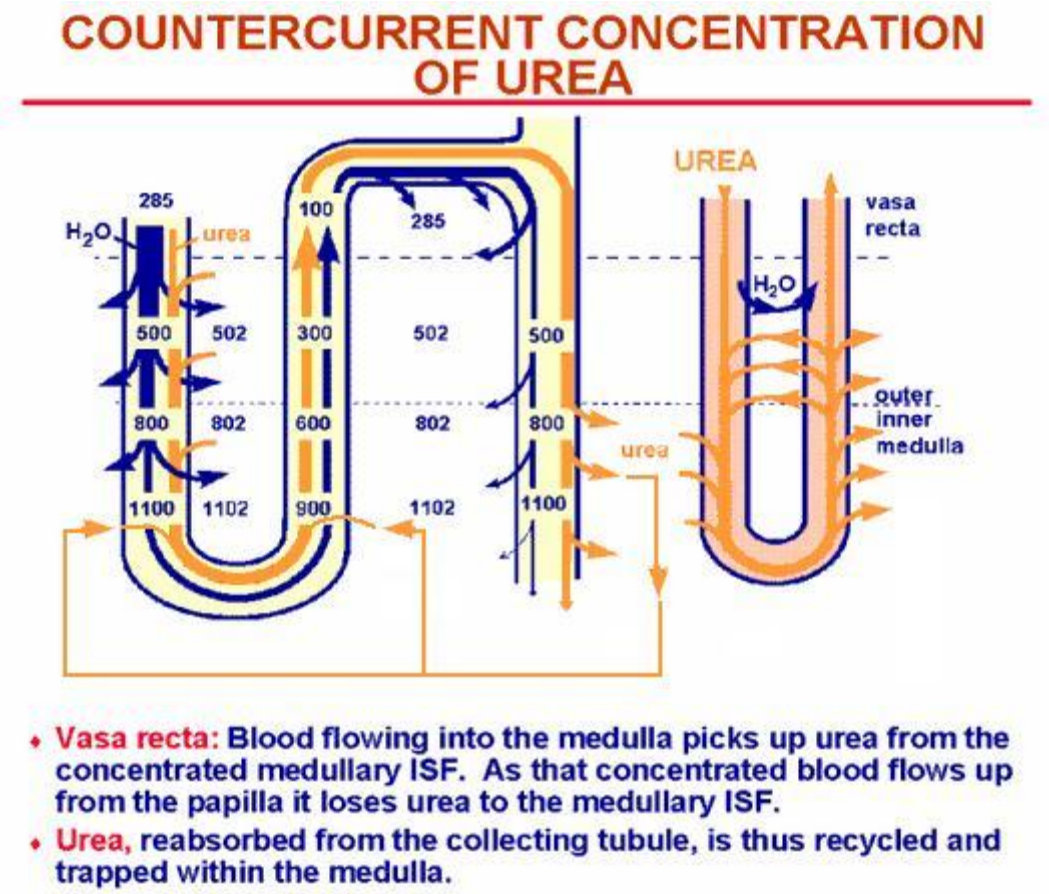
1. First assume that the loop of Henele is filled with a concentration of 300 mOsmol/L, the same as that leaving the proximal tubule (figure A)
2. The active pump of the thick ascending limb on the loop of Henele is turned on, reducing the concentration inside the tubule and raising the interstitial concentration; this pump establishes a 200 mOsmol/L concentration gradient between the tubular fluid and interstitial fluid (step 1).
3. The tubular fluid in the descending limb loop of Henele and the interstitial fluid quickly reach osmotic equilibrium because of osmosis of water out of the descending limb. The interstitial fluid is maintained at 400 mOsmol/L because of continued transport of ions out of the thick ascending loop of Henele (step 2).
4. Additional flow of fluid into the loop of Henele from proximal tubule causes the hyperosmotic fluid previously formed in the descending limb to flow into the ascending limb (step 3).
5. These steps are repeated over and over (steps 4,5,6, and 7,8,9) with the net effect of adding more and more solute to the medulla in excess of water. With sufficient time, this process gradually traps solutes in the medulla and multiplies the concentration gradient established by the active pumping of ions out of the thick ascending loop of Henele, eventually raising the interstitial fluid osmolarity to 1200-1400 mOsmol/L.

The urea cycle: Urea contributes about 40-50% of the osmolarity of the renal medullary interstitium when kidney is forming maximally concentrated urine. While reabsorption of urea occurs in several tubule segments, the reabsorption of urea that occurs in the collecting duct differs from reabsorption in all other segments. This is because the urea permeability of the collecting duct is increased by antidiuretic hormone (ADH). In the absence of ADH, the collecting duct is nearly impermeant to both water and urea. In the presence of ADH, the permeability to water of the entire collecting duct is increased and portions of the collecting duct also show an increase in permeability to urea, greatly increasing urea reabsorption.

- At the proximal tubule: about 40% of the filtered urea is reabsorbed; however, because 60-80% of the filtered water is reabsorbed, the fluid leaving the proximal tubule has a urea concentration 2-3x that of plasma.
- At the loop of Henle (thin descending and ascending limbs): Somewhat permeable to urea. The high interstitial concentration of urea causes some of the interstitial urea to enter the lumen of the loop.
- At the thick ascending, distal tubule and cortical segment of the collecting duct: All are imperable to urea; as water is reabsorbed, urea becomes concentrated in the lumen.
- At the medullary collecting duct: Slightly permeable to urea, and this permeability is increased under the effect of ADH. As water is reabsorbed, the urea remaining within the duct becomes progressively more concentrated, which therefore diffuses out of the lumen into the interstitium in accordance with its concentration gradient

Since the thick ascending limb of the loop of Henle, the distal convoluted tubule, and the cortical sections of the collecting duct are impermeable to urea, its concentration increases downstream in these parts of the nephron. ADH can make the inner medullary collecting duct more permeable to urea. Urea now diffuses back into the interstitium (where urea is responsible for about 40% of the high osmolality there) then transported back into the descending limb of the loop of Henle, comprising **the recirculation of urea.**

About 40% of total osmolarity in the inner medulla is due to the presence of urea. A high ADH level causes the expression of uniporters for urea transport in the collecting duct, accounting for high interstitial urea concentration. High urea concentration draws water out of the descending limb of the loop of Henle by osmosis. This concentrates NaCl in the descending limb, creating a diffusion gradient for NaCl to move passively out of the thin ascending limb into the interstitium. The importance of urea is illustrated in patients with a low protein intake who have a reduced capacity to concentrate their urine because of lower urea levels. Children younger than 1 year have a reduced urine-concentrating ability because of lower urea levels; young children utilize proteins for rapid body growth and as a result do not produce much urea.



The net effect of the steps noted above is to recirculate or trap urea in the renal medulla, raising the osmotic activity of interstitial fluid (contributes about half of the osmolality; NaCl contributes most of the rest)

Note 1: Not all urea is reabsorbed or trapped; in fact, because much of the nephron is only slightly permeable to urea, urea is concentrated in the tubular fluid as water is reabsorbed, so urea normally becomes concentrated in the urine.

Note 2: During a water diuresis when a large amount of dilute urine is excreted, urea does not become concentrated as the fluid in the collecting duct passes through the renal medulla, so not much urea diffuses into the interstitium. This results in an interstitial osmolality about half maximum (600 mOsm/kg)

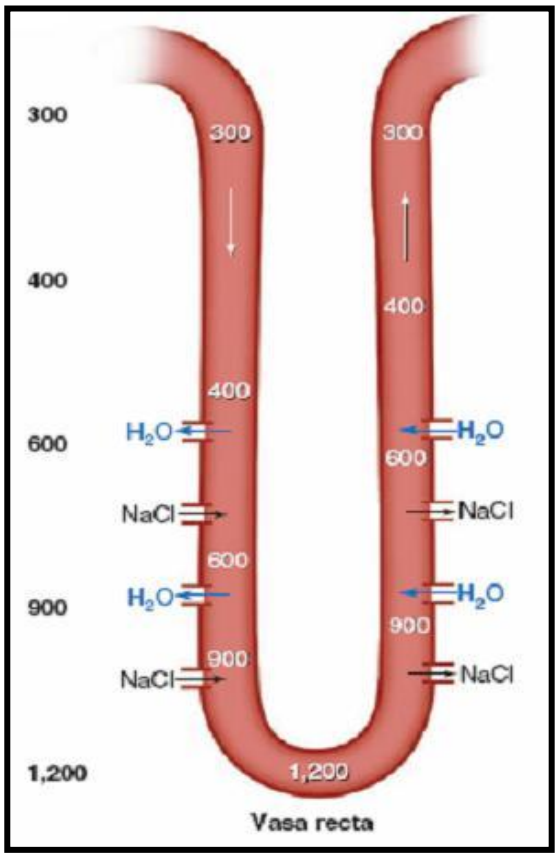
Note 3: Patients on protein restricted diets have impaired ability to form concentrated urine. The fundamental role of urea in contributing to urine concentrating ability is evidenced by the

fact that people, who fed a high protein diet, yielding large amounts of urea as a nitrogenous waste product, can concentrate their urine much better than people whose protein intake and urea production are low.

To deliver nutrients to the cells of the medulla without carrying away extensive amounts of solute, which would weaken the osmotic gradient ie to **maintain** this high interstitial fluid osmotic gradient, the solutes are prevented from being washed out to the circulation by:

[1] One characteristic of the medullary blood flow is that it is very slow representing less than 2% of the total renal blood flow.

[2] A second characteristic is the shape of the loop of the vasa recta capillaries that run parallel to the loop of Henle. Much fluid and solute exchange occurs between the medullary ISF and the vasa recta in both directions. Because of the parallel loop arrangement of the vasa rectae and the loop of Henle, there is little net change in the concentration of the medullary ISF. Therefore, the action of vasa recta is a **countercurrent exchanger**. The exchange mechanism works as follows:



1. Blood moving down the descending portion of the vasa recta loop passes through areas of increasing osmolarity.
2. Responding to osmotic pressure, water diffuses out of the blood into the interstitium. At the same time, sodium and chloride ions diffuses into the blood

as a result of its higher concentration in the interstitium.

3. If this blood now left the medulla, the sodium and chloride ions would be removed and lost to the osmotic gradient. However, the capillary actually reverses direction, so the conditions also reverse.

5. The viscous blood moves up the ascending portion of the vasa recta through areas of decreasing osmolarity. The blood regains the water by osmosis and loses most of the solutes back into the interstitium.

• The net result is that the blood has brought nutrients to the cells of the medulla without carrying away extensive amounts of solute, which would weaken the osmotic gradient.

These two effects cause the osmolal concentration in the capillary blood to raise progressively higher to a maximum concentration of 1200 mOsmol/l at the tip of vasa recta. Then, as the blood flows back up through the ascending limbs of vasa recta, all the extra NaCl and urea start to diffuse back out of the blood into the interstitial fluid while water diffuse back into the blood. Therefore, by the time the blood leaves the medulla, its osmolality is only slightly greater than that of the blood that had initially entered the vasa recta. As a result, the blood flowing through the vasa recta carries only a minute amount of the medullary interstitial solutes away from the medulla.

Urea excretion: The rate of urea excretion determined by:

[1] Concentration of urea in the plasma.

[2] GFR.

In general, the quantity of urea that passes on through the tubules into the urine average between 40-60% of the urea filtered. In many renal diseases the GFR of the two kidneys falls below normal and therefore excretion of urea is decreased. However, the body continues to form large quantities of urea which means that urea will progressively collect in the body

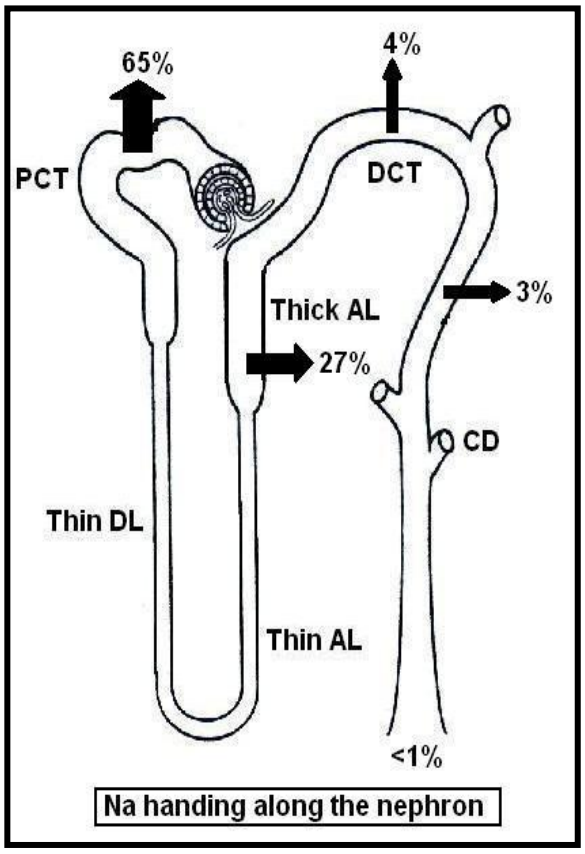
fluids until the plasma concentration rises very high. Then the quantity of urea filtered in the glomerular filtrate (conc. of urea in the plasma x GFR) eventually will become great enough to allow excretion of the urea as rapidly as it formed. Many other waste products that must be excreted by the kidneys obey the same principles for excretion as urea such as creatinine, uric acid.

The kidneys can excrete urea with minimum quantities of water and this can be achieved by two mechanisms:

[1] Formation of concentrated urine in the presence of ADH.

[2] Recirculation of urea from the collecting duct into the thin limb of the loop of Henle so that it passes upward through distal tubule, collecting tubule and then collecting duct again. In this way, urea can recirculate through these terminal portions of the tubular system several times before it is excreted and each time around these circuits contributes to the high concentration of urea so that very little water is excreted along with urea. Thus, this urea recirculation mechanism (which is also called **urea cycle**) through the loop of Henle, the distal tubule, and the collecting tubule and duct in a way to concentrate urea in the medullary interstitium and in the urine at the same time.

Na secretion: The quantities of Na that pass through glomerular filtrate each day is so huge and the kidneys adjust the final amount of Na that issue into the urine so that it will balance the daily intake of Na while keeping the Na concentration in the body fluids constant. In order to achieve this goal, the tubular system of the kidney has to perform two jobs: **[1]** To reabsorb nearly all of it and **[2]** To adjust very carefully the remaining amount that is excreted for maintaining appropriate amounts of Na in the body fluids. The reabsorption of Na by the tubular system and excretion the excess of it is conducted by the following mechanisms:



Na handing along the nephron

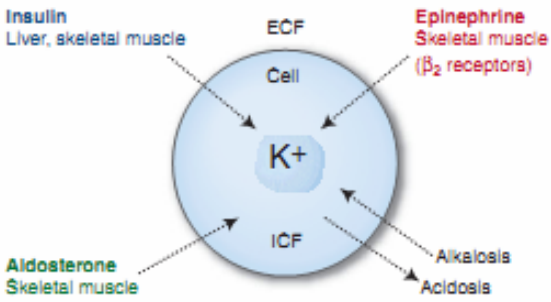
[A] Proximal tubule: At which 65% of Na is reabsorbed in addition to the Cl and water. Reabsorption of Na is done by active transport process.

[B] Thick portion of ascending limb of Henle: At which about 27% of Na is reabsorbed by active process, but not associated with water because this segment of loop of Henle is not permeable to water. The rest of 8% of Na will pass into the distal tubule.

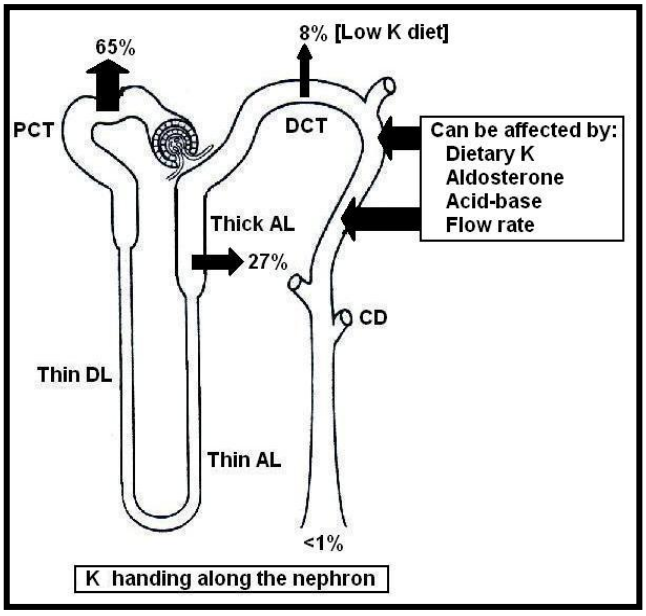
[C] Na reabsorption in the distal tubule, cortical collecting tubule, and the collecting ducts is controlled by **aldosterone**. In the presence of large amounts of aldosterone, almost the last amount of tubular Na are reabsorbed from these portions of the tubular system by active transport process coupled at least partially with active transport of K into the cells in opposite direction (i.e. K being exchanged for Na and therefore, none of Na enters the urine).

POTASSIUM BALANCE

About 98% of K+ in the body is in the intracellular fluid and is exchangeable with the extracellular fluid K+. The extracellular fluid [K+] is controlled within the range of 3.5 mEq/L to 5.5 mEq/L. Control of the extracellular fluid [K+] is essential to prevent membrane potential disruption because K+ conductance determines the resting membrane potential of most cells.



Factors affecting internal K+ homeostasis. Arrows indicate the net direction of K+ flux between the extracellular fl uid (ECF) and the intracellular fl uid (ICF) in response to each stimulus.



The plasma K+ is affected by shifts between the intracellular fluid and extracellular fluid (**internal K+ homeostasis**) and by the balance between K+ ingestion and excretion (**external K+ homeostasis**). Aldosterone is the central hormone controlling K+ balance and produces effects on both internal and external homeostasis. An increase in the extracellular fluid [K+] stimulates aldosterone secretion directly.Consequently, cellular uptake of K+ in skeletal muscle is increased, which reduces extracellular fluid [K+], and renal K+ excretion is stimulated to remove excess K+.

Potassium secretion: To maintain normal body K balance, only one eighth of the total daily tubular load of K can be excreted which must be carefully controlled. The reabsorption of K by

the tubular system and excretion the excess of it is conducted by the following mechanisms:

[A] Proximal tubules and loop of Henle: Large amount of K are reabsorbed by active transport from proximal tubule (65%) along with Na ions and from the thick portion of the ascending limb of loop of Henle (27%) via Na-K-2Cl cotransporter leaving only about 8% of the original filtered K to enter the distal tubule.

[B] Distal tubules and cortical collecting tubules: The remaining small amount of K is actively reabsorbed in the distal tubules and cortical collecting tubules (via H-K ATPase countertransporter at the luminal membrane of tubular cells) which depend on the dietary K intake. Consequently, all the filtered K is actually reabsorbed back to the blood, which would eventually be lethal because of the toxic effects of K accumulation in the body. Therefore, active **K secretion** occurs in the principal cells in the late distal tubule and the cortical collecting duct (under the efect of aldosterone in an exchange to Na ions) is the principal means by which the tubular system controls the rate of K loss in the urine.

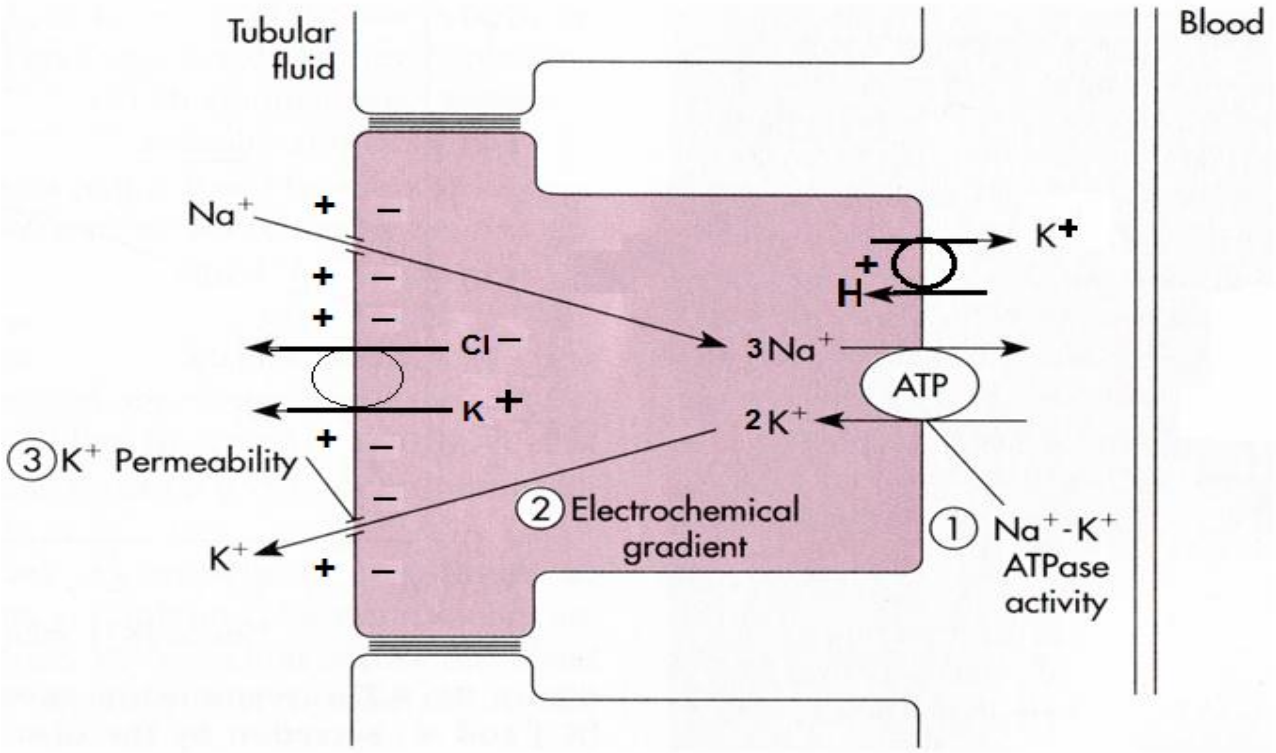
The mechanisms of K secretion:

On a high K diet or **high plasma K concentration:**

1. **Aldosterone** is increased leading to an increase in the activity of Na-K ATPase at the basolateral side of the tubular cells. This causes depolarization of the luminal cell membrane and also increases the intracellular K concentration.
2. At the luminal membrane, K^+ is passively secreted into the lumen through passive K channels. The magnitude of this passive secretion is determined by the chemical and

electrical driving forces on K across the luminal membrane

3. Na^+ passively transported from tubular fluid to tubular cell according to electrochemical gradients.
4. A K-Cl cotransport in the apical membrane may laso contribute to K secretion.



On low K diet or low plasma K concentration, intracellular K decreases, so that the driving force for K secretion decreases. Also, the tubular α-intercalated cells are stimulated to reabsorb K by H-K ATPase.

Aldosterone increases Na-K ATPase activity at the basolateral side of the tubular principal cells thereby increasing the intracellular K, consequently the driving force for K secretion. Therefore, in hyperaldosteronism there is an increase in K secretion which leads to hypokalaemia. While in hypoaldosteronism, there is a decrease in K secretion which leads to hyperkalaemia.

In **acidosis**, the blood contains excess H ions, therefore, H enters the cell across the basolateral membrane in an exchange with K (via H-K countertransporter) which leaves the cells. As a result, the intracellular K concentration and the driving force for K secretion decreases. The reverse occurs in **alkalosis** (increase in K secretion).

Diuretics that increase flow rate through the distal tubule (such as thiazide and loop diuretics) cause dilution of the luminal K concentration, increasing the driving force (concentration gradient between the tubular fluid and tubular cell) for K secretion. As a result of increased K secretion, these diuretics cause hypokalaemia. In contrast, K-sparing diuretics either antagonize the action of aldosterone (such as spironolactone) or act directly on the principal cells (such as triameterene and amiloride) to decrease K secretion and cause hyperkalaemia.

High Na ions entered the distal tubules increases the rate of Na reabsorption in an exchange to K ions. Consequently, Na load can cause excess secretion of K ions and consequently hypokalaemia.

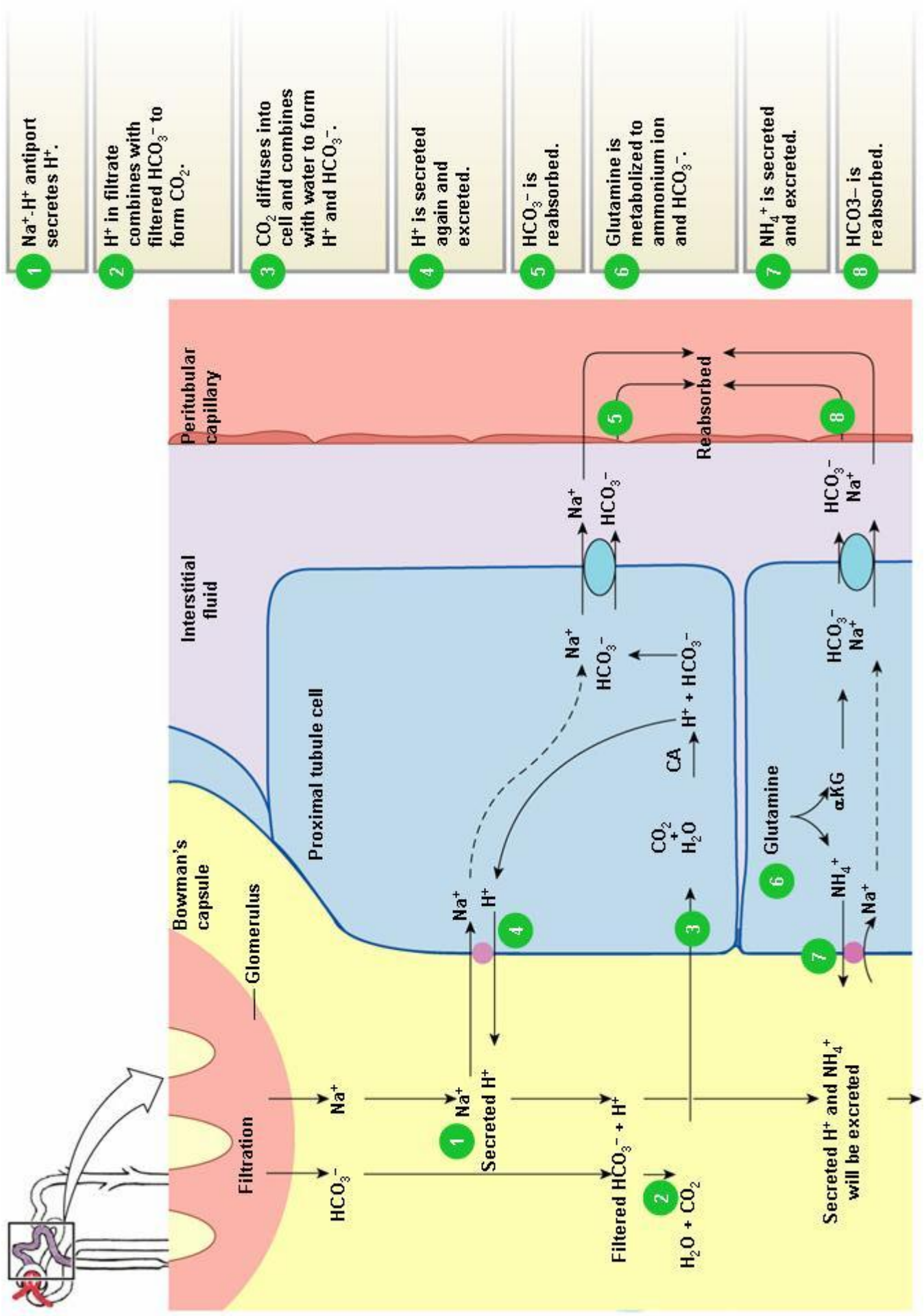
Excess anions in the lumen cause an increase in K secretion by increasing both the negativity of the lumen and the electrical driving force for K secretion.

In summary urinay K secretion is increased in:
• **High K diet**

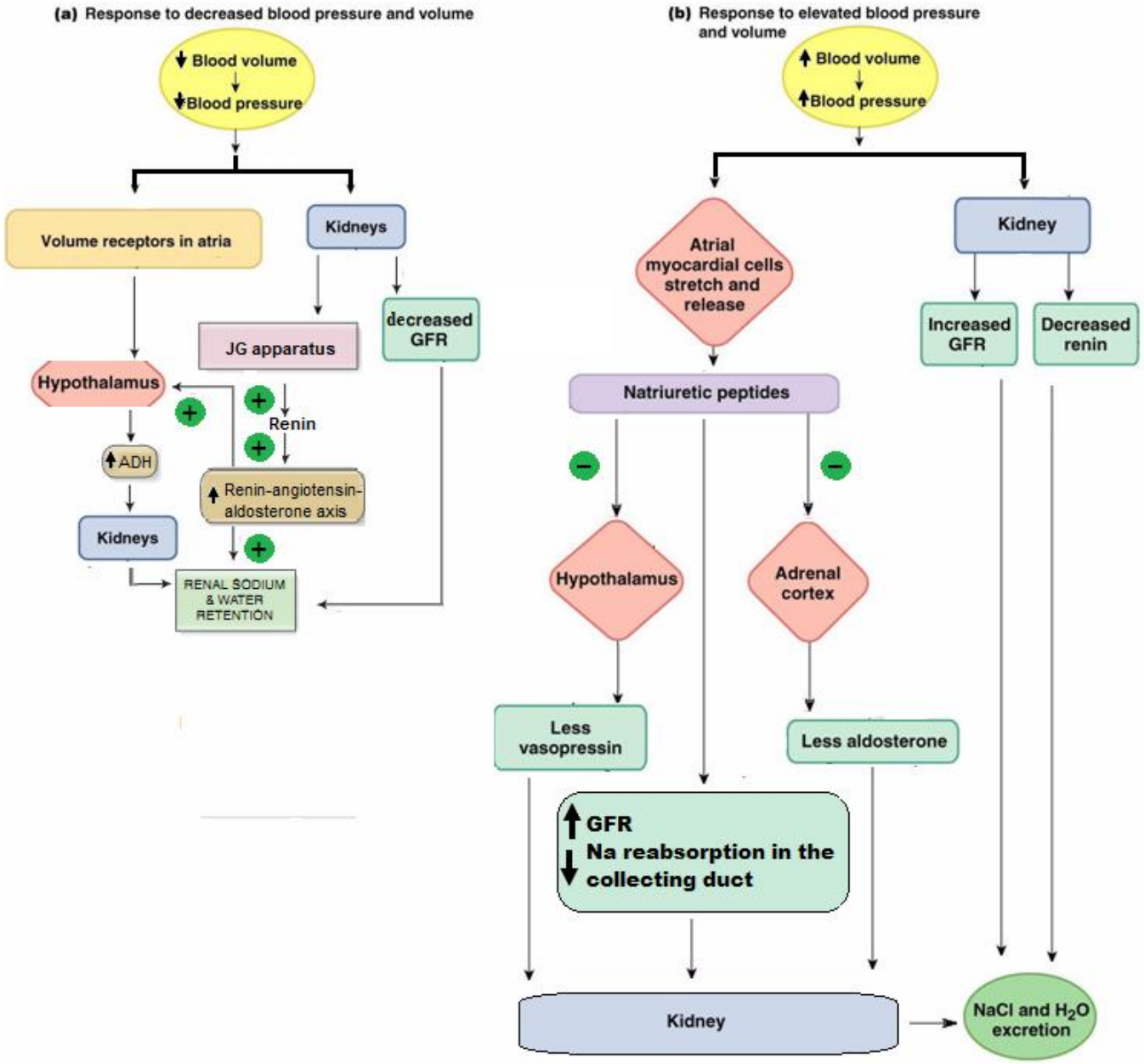
- **High plasma K concentration**
- **Aldosterone excess**
- **Alkalosis**
- **Diuretics and diuresis**
- **High tubular Na**
- **Excess tubular anions**

H^+ secretion: The epithelial cells of the proximal tubules, thick segment of the ascending limb of the loop of Henle, distal tubules, collecting tubules, and collecting ducts all secrete H^+ into the tubular fluid in an exchange with Na^+ ions and HCO_3^- into the extracellular fluids. This is an example of secondary active transport; extrusion of Na ions from the cells into the interstitium by Na^+-K^+ ATPase lowers the intracellular Na^+, and this causes Na^+ to enter the cell from the tubular lumen, with coupled extrusion of H^+. The H^+ comes from intracellular dissociation of H_2CO_3 , and the HCO_3^- that is formed diffuses into the interstitial fluid. Thus, for each H^+ ion secreted, one Na^+ and one HCO_3^- ion enter the interstitial fluid. The Na^+ ion and HCO_3^- then are transported together from the epithelial cell into the extracellular fluid. The mechanism by which this occurs is illustrated in the figure. Since the chemical reactions for secretion the H^+ begin with CO_2, the greater the CO_2 concentration, the more rapidly the reaction proceed, and the greater becomes the rate of H^+ secretion.

Therefore, any factors that increase the CO_2 concentration in the extracellular fluids, such as decreased respiration or increased metabolic rate, also, increase the rate of H^+ secretion. Conversely, any factor that decreases the CO_2, such as excess pulmonary ventilation or decreased metabolic rate, decreases the rate of H^+ secretion.


1 Na+-H+ antiport secretes H+.
2 H+ in filtrate combines with filtered HCO3− to form CO2.
3 CO2 diffuses into cell and combines with water to form H+ and HCO3−.
4 H+ is secreted again and excreted.
5 HCO3− is reabsorbed.
6 Glutamine is metabolized to ammonium ion and HCO3−.
7 NH4+ is secreted and excreted.
8 HCO3− is reabsorbed.
Peritubular capillary
Interstitial fluid
Proximal tubule cell
Bowman's capsule
Glomerulus
Filtration
Reabsorbed
Na+
HCO3−
CA
H+ + HCO3−
CO2 + H2O
Glutamine
αKG
NH4+
Secreted H+
Filtered HCO3− + H+
H2O + CO2
Secreted H+ and NH4+ will be excreted

Renal regulation of extracellular fluid volume: The basic mechanism for fluid volume control is the same as the basic mechanism for arterial pressure control. The renal role is illustrated in the diagram.



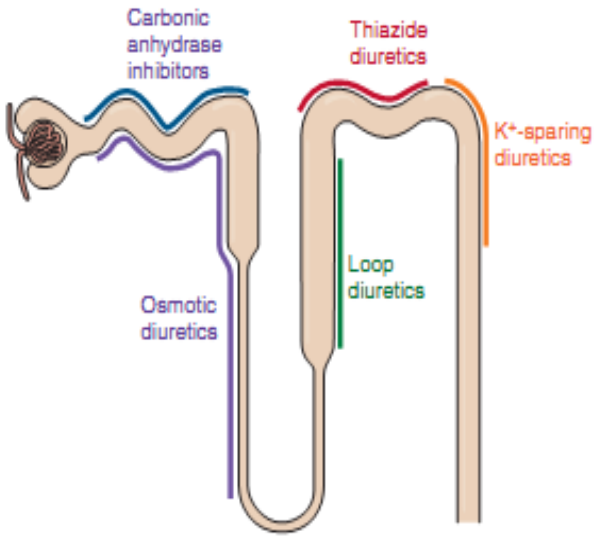
Renal handling of phosphate: 85% of the filtered phosphate is reabsrobed in proximal tubule by Na-phosphate cotransport. The rest of the filtered load of phosphate (15%) is excreted in urine. Phosphate excretion is therefore highly dependent on GFR, and renal insufficiency quickly results in inadequate phosphate excretion. Increased plasma phosphate is a common feature of renal insufficiency. Parathyroid hormone (PTH) inhibits phosphate reabsorption in proximal tubule by inhibiting Na-phosphate cotransport.

Renal handling of Ca: 60% of plasma Ca is filtered across the glomerular capillaries. About 90% of the filtered Ca is reabsorb by **passive paracellular Na-Ca cotransport** processes in the proximal tubule and thick ascending limb, and the electrochemical forces driving it are dependent directly or indirectly on sodium reabsorption. Therefore, loop diuretics that inhibit Na reabsorption also increase the urinary Ca loss. However, 8% of the filtered Ca is reabsorbing **actively (Na-Ca countertransport)** in the distal tubule. PTH, vitamin D, and thiazide diuretics all stimulate Ca^{2+} reabsorption in the distal tubule. Therefore, thiazide diuretics used in treatment of hypocalcaemia

Diuresis: Is defined as an increase in the urine flow rate; **diuretics** are agents that induce diuresis. Most diuretics used clinically are organic acids that are efficiently secreted by the proximal tubule; they act by inhibiting various luminal membrane Na+ reabsorption from the tubules, which in turn causes natriuresis (increased Na output) and this in turn causes diuresis (increased water output or also called polyuria). The increased water output, in most cases, occurs secondary to inhibition of tubular Na reabsorption because Na remaining in the tubules acts osmotically to decrease water reabsorption.

Because the renal tubular reabsorption of many solutes, such as K, Cl, Mg, and Ca, is also influenced secondarily by Na reabsorption, many diuretics raises renal output of these solutes as well. The effect of most diuretics on renal output of salt and water subsides within a few says. This is due to activation of other compensatory mechanisms initiated by decreased extracellular fluid volume such as reduced arterial blood pressure with consequent reduction of GFR and increases renin secretion. All these responses together override the chronic effects of the diuretics on urine output. The figure illustrates sites of action for different classes of diuretics.

Loop diuretics (e.g., furosemide) inhibit the Na/2Cl/K cotransporter in the thick ascending limb. Explosive increases in urine flow occur because this nephron segment normally reabsorbs 20–25% of filtered Na+. Because of their powerful diuretic effect, loop diuretics are particularly useful when diuresis is needed (e.g., pulmonary edema). Thiazide diuretics (e.g., hydrochlorothiazide) inhibit Na-Cl cotransport in the distal tubule. Thiazides are less potent loop diuretics because a lower proportion of the filtered load is reabsorbed in the distal tubule compared to the loop of Henle. Thiazides are considered first-line agents in the treatment of hypertension, but they can also be used in a variety of conditions, including symptomatic relief of edema and calciuria.



Sites of action of major classes of diuretics.

Agents that act on the principal cells in the cortical collecting duct are called **K+-sparing diuretics** because

inhibition of reabsorption at this site also inhibits K+ secretion. Amiloride is an example of this class of diuretic, which acts by blocking apical Na+ channels in the principal cells. Aldosterone antagonists (e.g., spironolactone) belong to the group of K+-sparing diuretics and act by reducing the expression and activity of Na+ transport proteins in the cortical collecting duct.

K+-sparing agents have a weak diuretic effect because less than 5% of filtered Na+ is reabsorbed at this site. However, agents in this group can be helpful in the treatment of certain specific disorders.

Carbonic anhydrase inhibitors (e.g., acetazolamide) dramatically reduce bicarbonate reabsorption in the early proximal tubule, producing a weak diuresis. Because of their weak diuretic effect, carbonic anhydrase inhibitors are rarely used for this purpose. Acetazolamide is commonly used in the treatment or prophylaxis of altitude sickness and in reducing intraocular pressure associated with glaucoma.

Osmotic diuretics are nonreabsorbed solutes present in the tubule lumen; they cause water to remain in the lumen and to be passed into the urine. An example of osmotic diuresis discussed previously is untreated diabetes mellitus, when the glucose Tm is exceeded and glucose remains in the tubule lumen. The proximal tubule and thin descending limb of the loop of Henle are the main sites of action because these areas have the highest membrane water permeability and are affected most by osmotic gradients. The inert sugar mannitol can be used to clinically induce an osmotic diuresis. Mannitol can be helpful in the treatment of patients with head injuries to reduce intracranial pressure by producing a fluid shift out of the brain.

The urine: Even in health the volume and composition of urine may vary widely from day to day depending on the type of food, amount of fluid taken or lost. The yellow color of normal urine

is due mainly to the pigment urochrome. The color of the urine in general varies according to its concentration. Freshly passed urine has hardly any smell, but when it is allowed to stand it develops an ammoniacal odor, owing to the bacterial decomposition of urea to ammonia. The specific gravity of the urine in health can vary between 1.001 and 1.040 according to the concentration of dissolved solids, but usually lies between 1.010 and 1.025. In terms of pressure these figures mean variation from 300 to 1300 mOsmol/l according to the urine flow. In renal disease the kidney becomes unable to alter the concentration of urine to meet the needs of the body and the specific gravity remains fixed at about 1.010 which represents an osmolarity of about 300 mOsmol/l, the same as that of plasma.