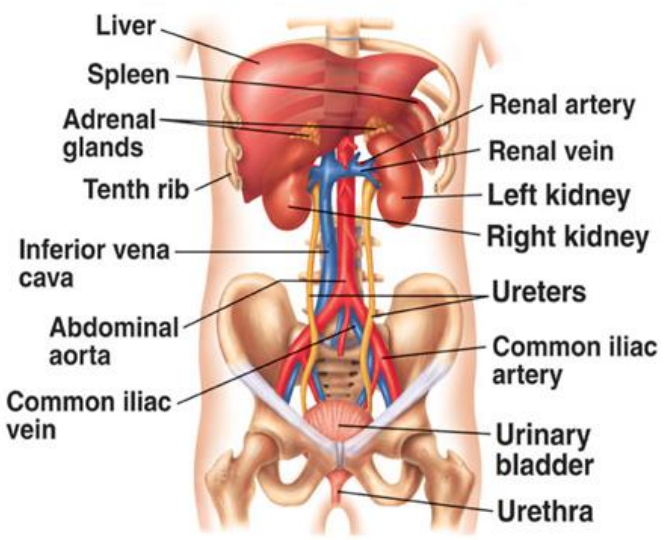
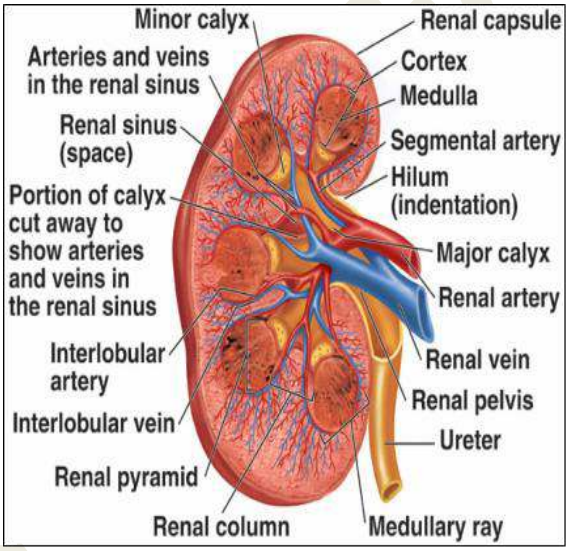
PHYSIOLOGY OF URINARY SYSTEM

Organ system that produces, stores & carries urine. Includes two kidneys, two ureters, the urinary bladder, two sphincter muscles & the urethra. Humans produce about 1.5 liters of urine over 24 hours, although this amount may vary according to the circumstances. More fluid intake generally rises urine production. Raised perspiration & respiration may drop the amount of fluid excreted through the kidneys. Medications (as diuretics) interfere with urine production.



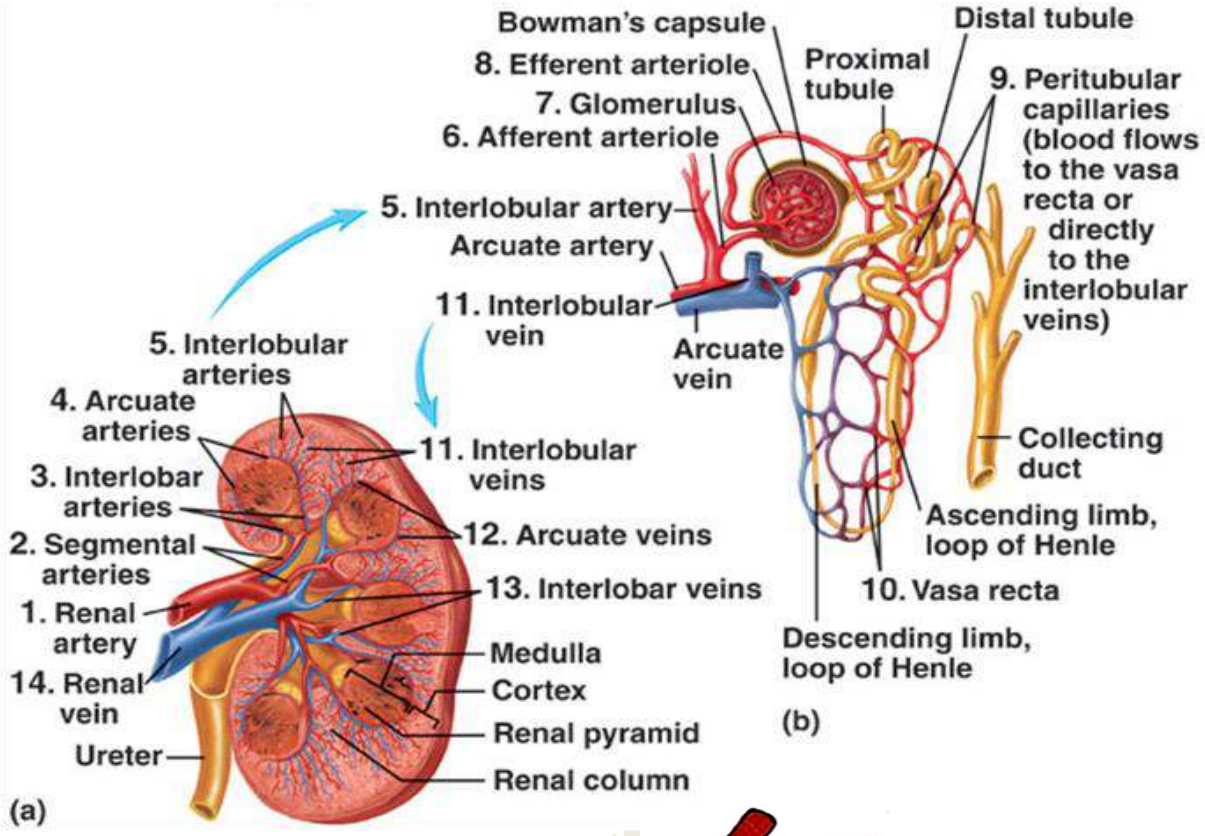


Kidney is paired organ (weight about 300 g), Composed of two parts cortex (isotonic urine) and medulla (hypertonic urine). Each kidney consists of 8-10 conical pyramids with bases in the cortex & apices project toward the pelvis. Each pyramid has outer cortex & inner medulla. Medulla in turn subdivided into outer & inner zones. The outer zone splits into outer & inner stripes. Each pyramid pours its urine into a minor calyx, and then every 2-3 calyces unite to form a major calyx. Major calyces unites to form the renal pelvis that leads urine through the ureter. Renal pelvis emerges through the hilum of kidney from which renal artery, enters & renal vein leaves. Two ureters pour into single urinary bladder from which urethra emerges.

Renal blood supply

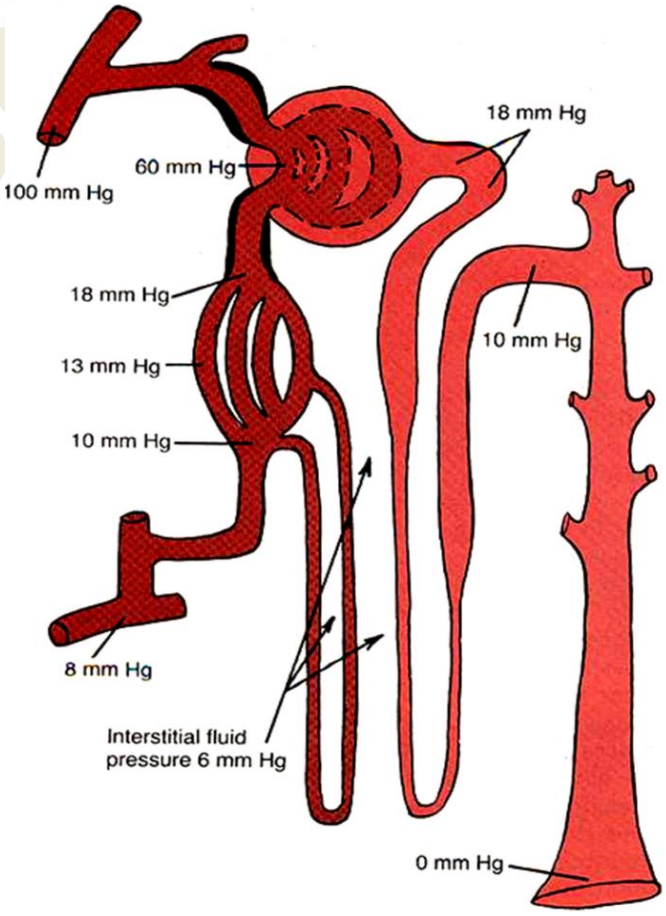
About 25% of the resting cardiac output (1.25 L\min) supplies the 300 grams of renal tissue with much greater flow to the cortex (97%) than to the medulla.

- Arterial tree: Renal, segmental, interlobar, arcuate & interlobular arteries. Afferent (then glomerular capillaries), efferent arterioles & peritubular capillaries (vasa recta). Hence, Systemic blood is carried out of the glomerulus by an efferent arteriole instead of a venule, as is observed in most other capillary**.**
- Venous tree: Interlobular, arcuate, interlobar, segmental and renal veins.



Characteristics of the renal blood flow:

1. Large blood flow: 200 ml/min (20% of cardiac output) & (94%) to the cortex
2. 1ry & 2ry capillary networks:
   - Primary network: glomerular capillary network, between afferent and efferent arterioles, high hydrostatic pressure (60 mmHg), favor glomerular filtration.
   - Secondary network: peritubular capillary network, made by branch of efferent arterioles, low pressure (13 mmHg), favor tubular reabsorption.
3. Autoregulation of renal blood flow.
4. Tubuloglomerular feedback.
5. Nervous and humoral regulation.
6. High RBF not reflect high O_2 intake as kidney use only 8% of all O_2 intake.



N.B.

- There are 2 sets of capillaries & 2 sets of arterioles!!
- The only circulation where there are capillaries, which are drained by arterioles

Dr. Hayder

Glomerular capillary bed	Peritubular capillary bed
1. Receives bl from afferent art.	Receives bl from efferent art.
2. High pressure bed 45- 55 mmHg	Low pressure bed 10- 13 mmHg
3. Represents arterial end of cap.	Represents venous end of cap.
4. Allows fluid filtration.	Allows fluid reabsorption.

(Renal Major Capillaries)

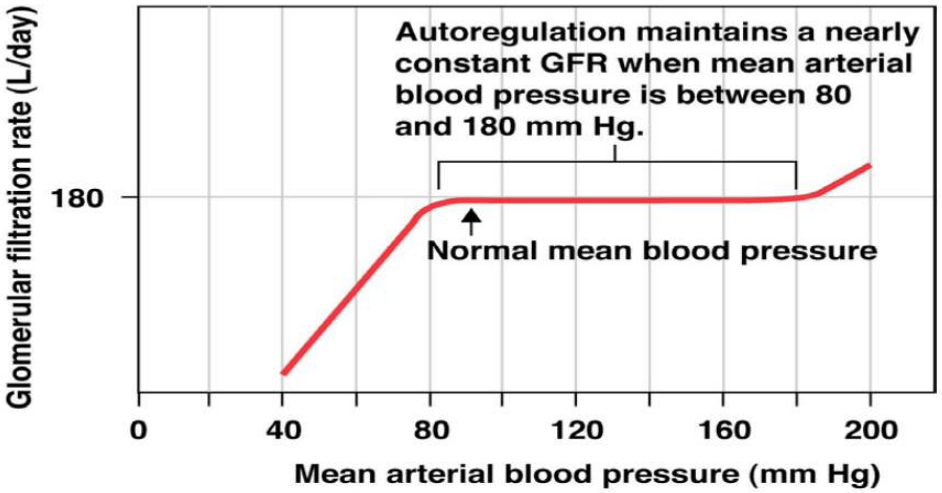
Autoregulation of RBF determines GFR:

- RBF is about 20% of the cardiac OP: very large flow relative to the weight of the kidneys (≈ 350 g).
- RBF also modifies solute & water reabsorption and delivers nutrients to nephron cells.
- RBF kept constant in BP of 80-180 mmHg by varying renal vascular resistance. I.e. the resistances of the interlobular artery, afferent arteriole and efferent arteriole.
- RBF autoregulation is vital to prevent large changes in GFR that would greatly affect urinary output & to allow normal renal excretion of water & solute.
- RBF autoregulation occurs in denervated & isolated kidney. I.e. its "intrinsic property".

A) Autoregulation of the renal blood flow

@ DEF; RBF is kept relatively constant between ABP; 80-180 mmHg, It is present in denervated, isolated kidney, This proving that this property is *intrinsic property*.

- Beyond blood pressure range 80 – 180 mmHg, there is no autoregulation.



Impact of autoregulation:

- *With autoregulation:* GFR=125m/min (180L/day) but tubular reabsorption178.5L/day results in 1.5L/day of urine.

- *Without autoregulation*: Small ↑ in BP 100 to 125mm Hg, ↑GFR by 25% (180 to 225L/day). If tubular reabsorption constant, urine flow of 46.5 L/day!!

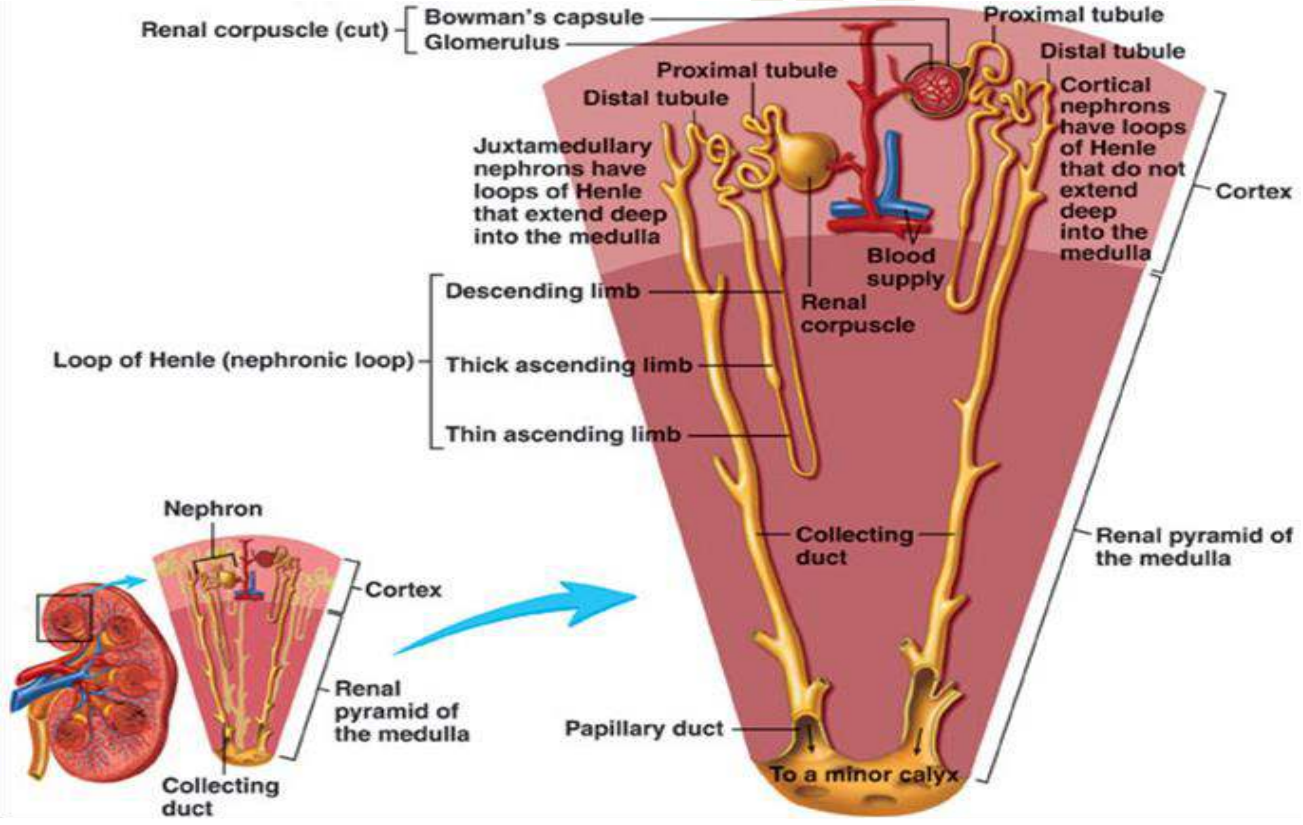
Nephrons

The structural and functional unit of kidney is called **nephron**. More than one million nephrons are present in each kidney. The kidney cannot regenerate new nephrons. Nephrons are composed of two major parts:

1) A glomerulus 2) A long tube

Glomerulus, which is a globular tuft of capillaries supplied by **afferent arteriole** and drained by **efferent arteriole** and enclosed inside tightly sealed **Bowman's capsule**. Blood that is filtered inside the glomerulus is transferred from Bowman's capsule to the renal tubules.

The first segment of renal tubules is the proximal tubule, which starts as a tortuous tubule called **proximal convoluted tubule (PCT)** or called **pars convoluta**, which then straightens to be called the **proximal straight tubule (PST)** or called **pars recta**.



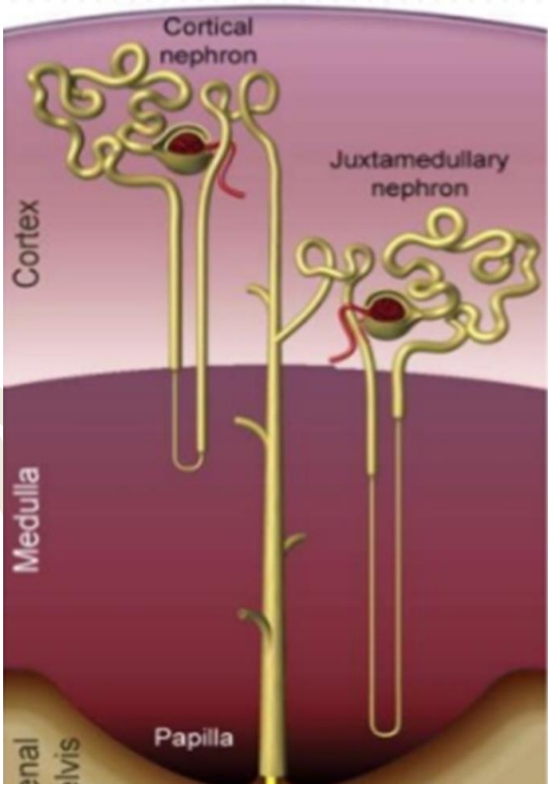
At the junction between outer and inner stripes of outer medullary zone, starts the **thin descending limb of Henle's loop (tDHL)**. **tDHL** turns back to become the **thin ascending limb of Henle's loop (tAHL)** which thickens at the junction between the inner and outer medullary zones to be referred to as **ascending limb of Henle's loop (TAHL)** which enters the cortex again as **distal tubule**.

The distal tubule passes between the afferent and efferent arterioles of the same nephron making with the afferent arteriole a special contact called **juxtaglomerular apparatus (JGA)** and then continues as **distal convoluted tubule (DCT)**.

Distal convoluted tubules unite as **collecting tubules**, which pour in larger collecting tubes, & then **cortical and medullary collecting ducts** to end in **main duct** of renal pyramid supplying the **minor calyx**.

Types of nephrons:

There are two types of nephrons:



Cortical nephrons:

More numerous) 70%-80% (lying in the outer layer of cortex. The tubular system is relatively short, no tAHL & efferent narrower than afferent arterioles. Has peritubular capillaries, but no vasa recta. Na reabsorption occurs mainly here, & JG apparatus is well developed hence, share in the process of an autoregulation.

Juxtamedullary nephrons:

Less numerous (20-30%), lie in the inner third of cortex, long tubules with long tAHL dip deeply down into the medulla toward the pyramids & efferent wider than afferent arteriole (because efferent arteriole here supplies a much extensive peritubular capillary network) so vasa recta is active. Urine concentration occurs mainly here, but no autoregulation as the JG apparatus is absent.

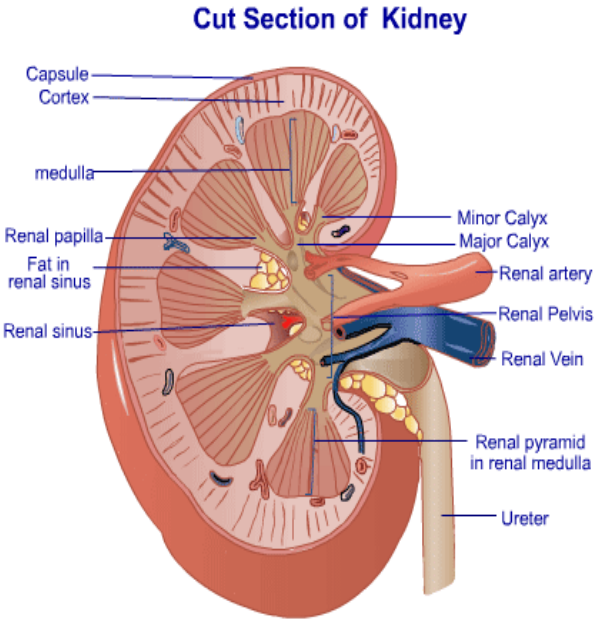
So, why is the loop of Henle useful?

The longer the loop, the more concentrated the filtrate in the medulla become.

Importance: the collecting tubule runs through the hyperosmotic medulla more ability to reabsorb H2O.

Renal pelvis

The major function of the renal pelvis is to act as a funnel for urine flowing to the ureter. It is the point of convergence of two or three major calices .A branch of the renal pelvis called a calyx surrounds each renal papilla**.**



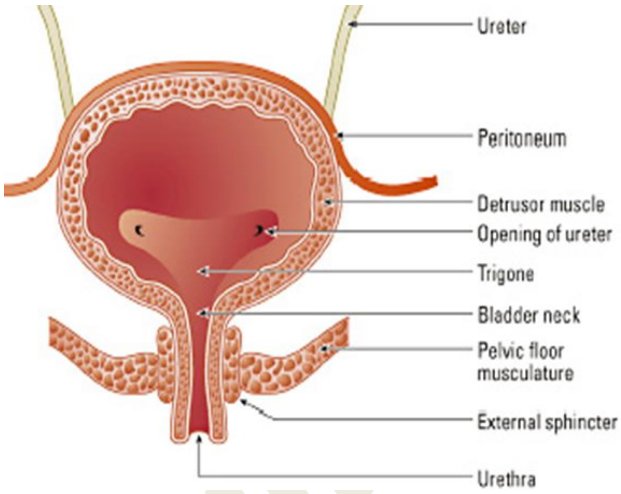
Ureters

The ureters are about 200 to 250 mm long, urine is collected in the renal pelvis (or pyelum), which connects to the ureters, which carry urine to the bladder.The urine

peristaltically forced downward through smooth muscular tissue in the ureteric walls.

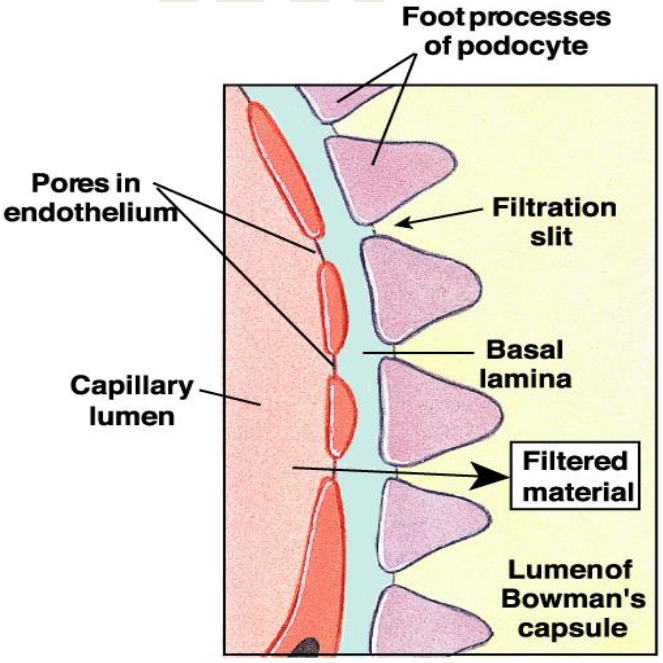
Urinary Bladder

A balloon shape hollow muscular organ. It can stores up to 500 ml of urine comfortably (2- 5 hours). Its sphincters (circular muscles) regulate the flow of urine from the bladder. Internal urethral sphincter in the beginning of urethra (smooth muscle – involuntary) while, external (skeletal muscle – voluntary). In males, both sphincters are more powerful, able to retain urine for twice as long as females.



Glomerular capillary membrane

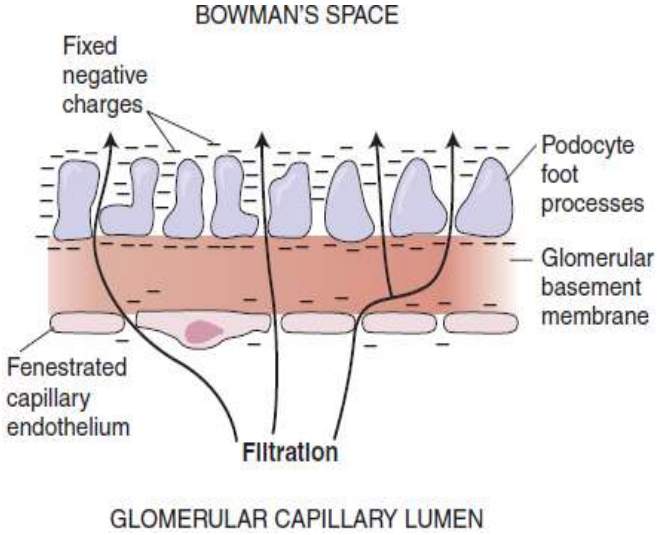
It is composed of three layers. The **single layer of capillary endothelial cells** lies on **basement membrane** and covered by the visceral layer of Bowman's capsule which is called **podocytes**. The endothelial layer is fenestrated such that even some plasma proteins (but not cells) can pass through its fenestrae. Yet; the proteins cant exit the basement membrane despite its very high permeability (more than 100 times the permeability of other capillary membranes in human body). Other filtered materials and ions, however can pass easily through the membrane and the slit pores between the feet of podocytes.



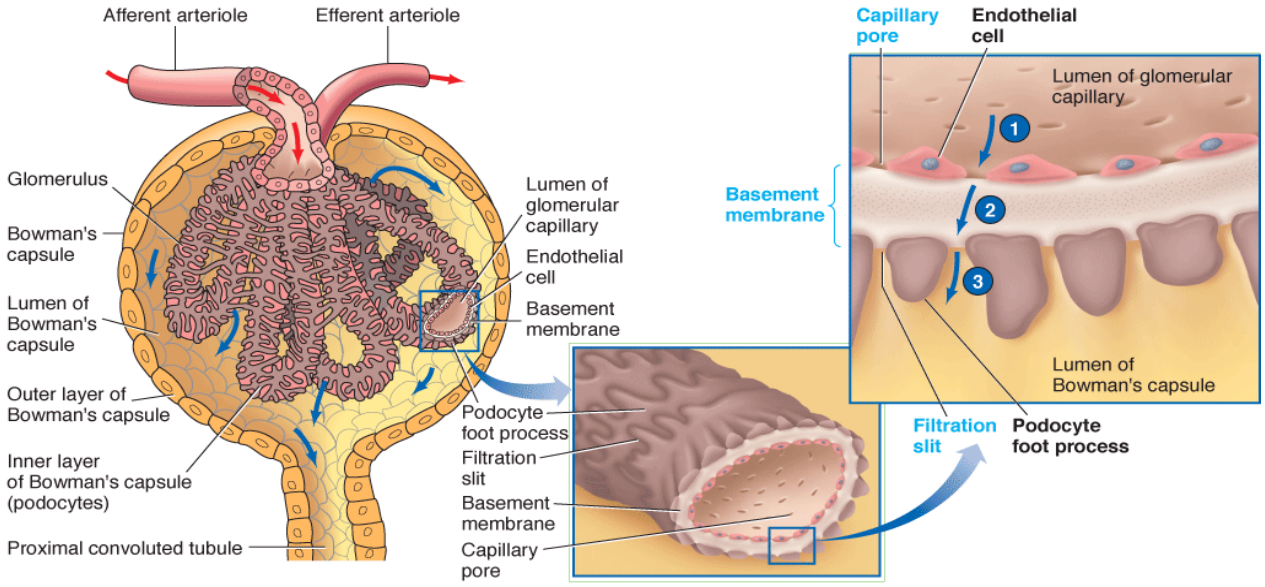
(Glomerular filtration membrane & podocyte)

Filterability of the Membrane:

Filterability is a term used to describe membrane selectivity based on the molecular size and charge. Pore size would favor plasma protein (albumin) passage, but negative charge on protein is repelled by the (-) charged basement membrane



(proteoglycan filaments & podocytes). Loss of this (-) charge causes proteinuria.



To be filtered, a substance must pass through

1. the pores between the endothelial cells of the glomerular capillary
2. an acellular basement membrane
3. the filtration slits between the foot processes of the podocytes of the inner layer of Bowman's capsule

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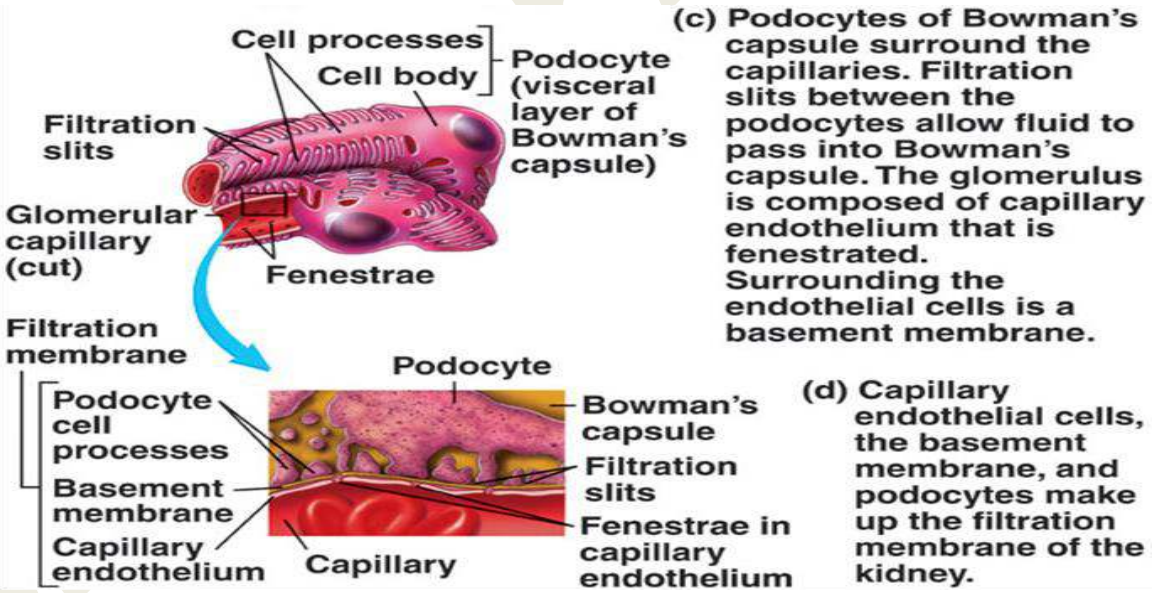


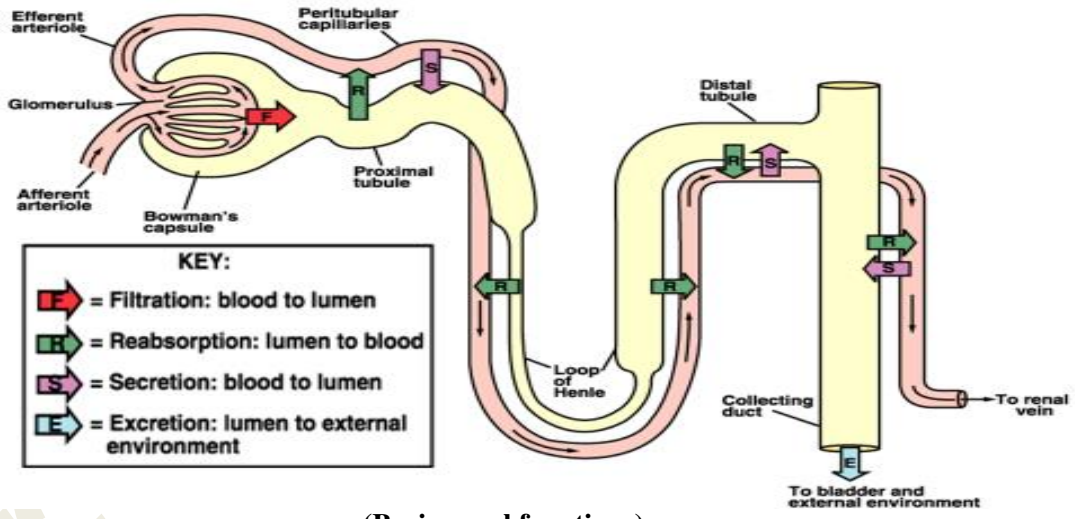
Function of the kidney

- Regulation of ECF **volume, osmolarity & composition.**
- Regulation of **blood pressure.**
- Regulation of **acid-base balance.**
- Regulation of **bone metabolism** by regulation of **excretion of calcium & phosphate ions** & formation of active the form of **vit. D3** (1, 25 dicalcipherol).

- Production of hormones: **erythropoietin, renin, prostaglandins, atrial natriuretic peptide, kallikreins & active form of vit. D3.**
- Excretion of various **metabolic waste products, drugs, toxic substances:**
  - Urea from protein breakdown
  - Uric acid from nucleic acid breakdown
  - Creatinine from muscle creatine breakdown
  - End products of hemoglobin breakdown

Basic Renal Terminology

Glomerular filtration rate (GFR): amount of fluid pass into Bowman's capsule / min.
Renal blood flow (RBF): amount of blood flowing through the kidney / (min).
Filtration: process by which substances enter Bowman's capsule.
Reabsorption: process by which substances move from inside to outside the tubule (from lumen to blood).
Secretion: process by which substances move from outside to inside the tubule (blood to lumen) made by epithelial cells itself or blood substance are transported into renal tubular lumen.
Excretion: substances that pass from the kidney into the bladder.



(Basic renal functions)

The ability of the kidney to move specific substances selectively into & out of the tubule in a very controlled & coordinated manner makes normal kidney function so critical to life.

Glomerular filtration:

Fluid and small solutes dissolved in the plasma such as glucose, amino acids, Na, K, Cl, HCO_3^- , other salts, and urea pass through the membrane and become part of the filtrate.

- The glomerular membrane hold back blood cells, platelets and most plasma proteins.
- The filtrate is about 20% of the plasma.

- Ultrafiltrate: Most substances in the plasma (except protein) are freely filtrated, so that their concentrations in Bowman's capsule are almost the same as in the plasma.

Substance	Plasma	Glomerular Filtrate
Ions (mEq/L)		
Na	142	142
K	5	5
Cl	103	103
HCO	28	28
Organic Molecule (mg/dl)		
Protein	1000-5000	5-11
Glucose	100	100
Urea	26	26
Uric acid	3	3
creatinine	1.1	1.1

(Composition of Plasma Vis Glomerular Filtrate)

Renal clearance

When certain amount of substance (x) is cleared away from plasma and excreted in urine, it is called **renal clearance** of that substance (C_x) . Not all of the substance filtered from glomerular capillaries appears in urine, instead; some of this substance may be reabsorbed back to the blood via peritubular capillaries, while additional amounts of the same substance may be secreted from tubular cells to tubular lumen to appear in urine.

$$C_x = GFR - TR + TS$$

Where: GFR is the **glomerular filtration rate** of x
TR is the **tubular reabsorption** of x
TS is the **tubular secretion** of x

Significance of renal clearance:

- Estimate renal function؛
- Determine glomerular filtration rate (GFR)
- Determine renal blood flow (RBF)
- Presume renal tubular transport effect
- Free-water clearance

Glomerular filtration rate (GFR)

Glomerular filtration is passive non-selective process. When renal plasma flows from afferent to efferent arterioles, ≈ 20% of its contents filtered by glomerular filtration from glomerular capillaries to Bowman's capsule. This is called the **filtration fraction (FF)**

GFR = Renal Plasma flow (RPF) * FF

GFR = RPF * 20%

RPF = Renal Blood Flow (RBF) * (1-hematocrit)

= 1250 ml\min * 0.5

= 625 ml\min

GFR = 625 ml\min * 20%

GFR = 125 ml\min

Hence, about 180 liters of plasma are filtered by renal glomeruli every day. But, about 179 liters are reabsorbed by renal tubules back to the circulation and only about 1 liter is excreted as urine every day.

Measurements of GFR and RBF

A substance used to measure GFR and RBF must fulfill the following requirements:

1. It must not be toxic.
2. It must not be stored, or metabolized by kidney.
3. It must not be produced, secreted or reabsorbed by renal tubules.
4. It must not affect GFR or RBF by itself.
5. Freely filterable at glomerulus
6. Does not bind to plasma proteins
7. Low concentrations are enough

Measurement of GFR

Endogenous substance as **creatinine** or exogenous substance as **inulin** fairly fulfills most of the previously mentioned requirements to measure GFR.

$$\mathbf{GFR = C_{in} = U_{in} * V \setminus P_{in}}$$

Where C_{in} = Clearance of inulin

U_{in} = Urinary concentration of inulin

V = Urine flow

P_{in} = Plasma concentration of inulin

Measurement of RBF

Measurement of RBF can be calculated after measurement of RPF as follows:

$$\mathbf{RBF = RPF \setminus (1\text{-hematocrit})}$$

RPF can be measured by measurement of clearance of (x) substance that is completely 100% extracted from plasma and excreted in urine during its passage from afferent to efferent arterioles (extraction ratio = 1.0).

$$\mathbf{RPF = C_x \setminus E_x}$$

Where C_x is clearance of x

E_x is extraction ratio of x But, E_x is 1.0

So $\mathbf{RPF = C_x}$

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Such substance (x) is not found yet. But, there is another substance called Paraaminohippuric acid **(PAH)** that is about 90% extracted, so, its extraction ratio is said to be 0.9 ($\mathbf{E_{PAH} = 0.9}$).

$$\mathbf{RPF = C_{PAH} \setminus E_{PAH}}$$
$$\mathbf{= C_{PAH} \setminus 0.9}$$

Factors affecting GFR

The following equation summarizes some factors influencing GFR

$$\mathbf{GFR = K_f * (net\ ultrafiltration\ pressure)}$$
$$\mathbf{= K_f * (P_G + \Pi_B - P_B - \Pi_G)}$$
$$\mathbf{= K_f * (60 + 0 - 18 - 32)}\ \text{respectively}$$
$$\mathbf{= K_f * (+10\ mmHg)}$$

Where: $\mathbf{K_f}$ is ultrafiltration coefficient, which is the effective ultrafiltration (surface area multiplied by glomerular capillary permeability).

$\mathbf{P_G}$ is glomerular capillaries' hydrostatic pressure

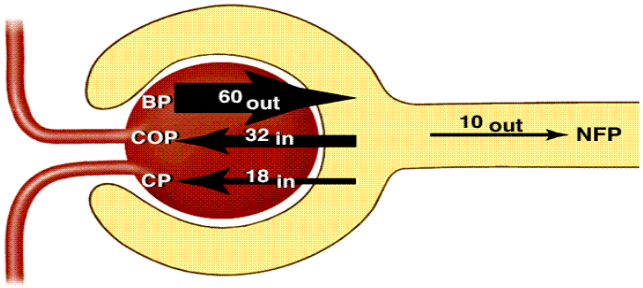
$\mathbf{\Pi_B}$ is osmotic pressure of colloids inside Bowman's capsule

$\mathbf{P_B}$ is hydrostatic pressure inside Bowman's capsule

$\mathbf{\Pi_G}$ is osmotic pressure of colloids inside glomerular capillaries

The latter four factors are called **Starling forces**

(Net Filtration Pressure)



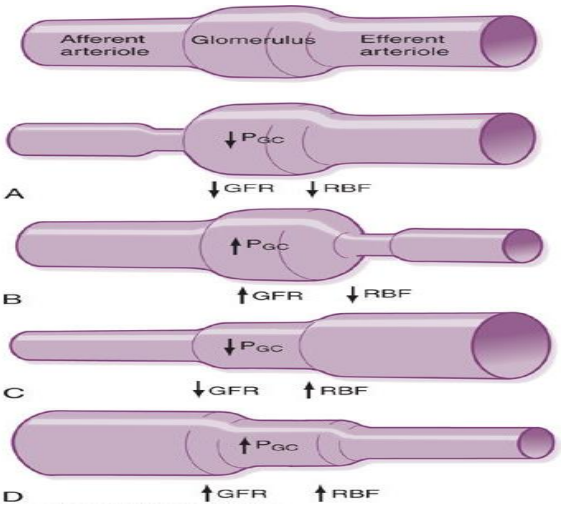
Capillary blood pressure (BP)	60 mmHg out
Colloid osmotic pressure (COP)	– 32 mmHg in
Capsular pressure (CP)	– 18 mmHg in
Net filtration pressure (NFP)	10 mmHg out

Other factors affecting GFR are:

- **RBF:** when RBF increases GFR also increases
- **FF:** when FF increases GFR also increases

] Because GFR=RPF * FF

- **Vasoconstriction of afferent arterioles** decreases GFR (decreased P_G)
- **Slight vasoconstriction of efferent arterioles** increases GFR (increased P_G)
- **Severe vasoconstriction of efferent arterioles** decreases GFR (increased Π_G)



(Effects of different Afferent arterioles states on GFR & Efferent arterioles)

Control of GFR

Control of GFR is by one or more of the followings:

- Sympathetic nervous activity
- Hormones and autacoids
- Autoregulation
- Plasma levels of amino acids and **glucose**

1- Sympathetic nervous activity: Strong sympathetic activity decreases GFR e.g., in severe hemorrhage and in cerebral ischemia while the role of parasympathetic (vagal) innervations is yet unknown.

2- Hormones and autacoids: Hormones are small chemical substances that are secreted from endocrine glands and transported by blood to work at distant organs while autacoids are chemical substances that are secreted and act locally.

Adrenaline (epinephrine), nor-adrenaline (nor-epinephrine), angiotensin II, aspirin and endothelin *decrease* GFR. Nitric oxide, prostaglandin & bradykinin *increase* GFR.

3- Autoregulation: Autoregulation involves afferent not efferent arterioles. Autoregulation is important to prevent large changes in GFR that would greatly affect urinary output. Two regulatory processes are faced in the regulation of GFR:

a. Juxtaglomerular feedback mechanism: Juxtaglomerular apparatus (JGA) consists of specific distal convoluted tubular epithelial cells called **macula densa** (which contains **osmoreceptors** that are sensitive to any increase or decrease in concentration of NaCl) in close contact with specific smooth muscle cells in the wall of afferent arterioles called **Juxtaglomerular cells**.

Macula Densa cells in distal tubule sense levels of Na with Na-K-2Cl cotransporter . If Na levels are high, releases adenosine, which acts on afferent & efferent arterioles (reduces filtration). Adenosine constricts afferent arteriole by **A1** adenosine receptor & adenosine dilates efferent arteriole by **A2** adenosine receptor.

Decreased amounts of NaCl near osmoreceptors of macula densa sends impulses to JG cells to relax resulting in vasodilatation of afferent arterioles, increase blood flow to glomerular capillaries, and increase GFR.

When ***GFR is decreased***, **tubular flow slows down** resulting in **increased tubular reabsorption of NaCl**. This will **decrease NaCl near the osmoreceptors** of macula

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densa. Macula densa will send impulses to the **JG cells to relax** resulting in **vasodilatation of afferent arterioles**. This will **increase blood flow to the glomerular capillaries** which will in turn ***increase GFR***.

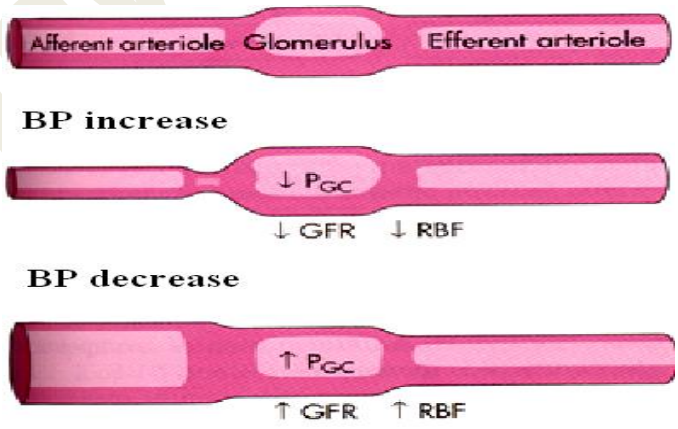
The reverse occurs when ***GFR is increased***; **tubular flow quickens** resulting in **decreased tubular reabsorption of NaCl**. This will **increase NaCl near the osmoreceptors** of macula densa. Macula densa will send impulses to the **JG cells to contract** resulting in **vasoconstriction of afferent arterioles**. This will **decrease blood flow to the glomerular capillaries**, which will in turn ***decrease GFR***.

Renin is also produced by JG cells in response to any increase in GFR or RBF, which will result in production of angiotensin I and then angiotensin II to decrease GFR and RBF.

Impact of Autoregulation:

- Autoregulation:
  - GFR = 180 L/day and tubular reabsorption = 178.5 L/day
  - Results in 1.5L/day in urine
- Without Autoregulation:
  - Small ↑ in BP 100 to 125mm Hg, ↑GFR by 25% (180 to 225L/day)
  - If tubular reabsorption constant, urine flow of 46.5 L/day

b. Myogenic mechanism: Increased RBF that causes increase in GFR; is at the same time the cause of distension of afferent arterioles and stretch of smooth muscles lining their walls. This stretch results in myogenic contraction of these smooth muscles leading to vasoconstriction of afferent arterioles and decreased RBF and GFR.



Myogenic Mechanism of the autoregulation

4- Plasma levels of amino acids and glucose: This mechanism depends on the fact that tubular reabsorption of amino acid and glucose is unlimited and so, when plasma levels of amino acids and glucose increase; tubular reabsorption will also increase resulting in decreased amounts of NaCl near the osmoreceptors of macula densa. Macula densa will send impulses to the JG cells to relax resulting in vasodilatation of

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afferent arterioles. This will increase blood flow to the glomerular capillaries which will in turn increase GFR.

Tubular reabsorption

A highly selective process may be **passive** or **active**. Some substances are **completely reabsorbed** like **amino acids** and **glucose**. Some substances are **mostly reabsorbed** like **bicarbonates** and some **other electrolytes**. Some other substances are **mostly reabsorbed in the presence of specific factors like hormones** but their reabsorption is reduced when these hormones are reduced or absent like **water** reabsorption, which is increased in the presence of **antidiuretic hormone**, and **sodium** ions reabsorption that is increased in the presence of **aldosterone** and\or **angiotensin II** hormones. Many substances are reabsorbed **along with other substances** like **chloride ions,** which follow **sodium ions**, and **sodium chloride** salt, which follows **water**. Some substances are **50% reabsorbed** (and 50% excreted) like **urea**. Some other substances are about **completely excreted** like **creatinine** and some **drugs** and **poisons**.

Why large amounts of solutes are filtered & then reabsorbed by the kidneys?

1- Allows the kidneys to rapidly remove waste products from the body that depend primarily on GFR

2- Allows all body fluids to be filtered many times each day. Because the entire plasma volume is only ≈ 3 liters, while the GFR is ≈180 L/day, the entire plasma can be filtered ≈ 60 times each day (precise & rapid) control of the body fluids.

There is a glomerulotubular balance such that when GFR increases; tubular reabsorption also increases. However, this is not eternal; in reality, the active transport processes of reabsorption may be saturated when the tubular lumen is overloaded with filtered substances. The maximum tubular load of certain substance above which an active transport process of tubular reabsorption is saturated and reabsorption is ceased is called **transport maximum** (**Tm**) of that substance. The maximum plasma concentration of certain substance above which this substance starts to appear in urine is called **renal threshold** of that substance which equals **Tm\GFR**

Transport maximum of glucose (**TmG**) is about 325 mg\min and its ideal renal threshold is 325\125 = 2.6 mg\ ml = 260 mg\100 ml

But the actual renal threshold for glucose is about 180 mg\100 ml and this difference may be due to that not all of renal tubules have the same Tm and that some of the filtered glucose molecules before Tm bypass reabsorption.

Factors affecting tubular reabsorption

The same previously mentioned Starling forces affect tubular reabsorption in addition to other factors. The following equation summarizes some of these factors.

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TR = *Kf* * (net reabsorption pressure)

TR = *Kf* * (*Pif* – *Pc* + *Πc* - *Πif*)

TR = *Kf* * (6 mmHg – 13 mmHg + 32 mmHg – 15 mmHg)

TR = *Kf* * (+10 mmHg)

Where ***Kf*** is a constant that depends on the surface area of effective reabsorption, distance of reabsorption and tubular capillary permeability

Pif is interstitial fluid hydrostatic pressure
Pc is peritubular capillaries' hydrostatic pressure
Πc is peritubular capillaries' osmotic pressure of colloids
Πif is interstitial fluid osmotic pressure of colloids

} **Starling forces**

Control of tubular reabsorption:

1-Sympathetic activity: Increase tubular reabsorption of sodium ions.

2- Hormonal activity:

A- Aldosterone: Secreted from **adrenal cortex** and acts on **principal cells** of **distal tubules** to increase **reabsorption of sodium ions and excretion of potassium ions**. It increases **permeability** of **luminal membrane** to sodium ions and stimulates **sodium- potassium pump** in **basolateral membrane**.

Adrenal insufficiency (**Addison's disease**) results in excessive sodium loss and potassium retention while adrenal hyperactivity (**Cushing syndrome**) results in sodium retention and potassium depletion.

B- Angiotensin II: Produced by the lungs from **angiotensin I** this in turn produced in the liver from **angiotensinogen** (**renin**). Angiotensin acts directly (or indirectly after stimulation of aldosterone) to increase sodium ions reabsorption.

C- Antidiuretic hormone (vasopressin): Secreted from posterior pituitary gland and it acts on distal and collecting tubules and ducts to increase water reabsorption and urine concentration.

D- Atrial natriuretic peptide (ANP): Produced by cardiac atria in response to any increase in blood volume and acts especially on collecting ducts to decrease sodium &water reabsorption and so, increase urine excretion to restore normal blood volume.

<u>A few Situations Encountered in Life:</u>

Increase Fluid Volume /Decrease Osmolarity
- Drink pure H2O
- Excrete dilute urine

Norm Fluid Volume /Increase Osmolarity
- Salty popcorn (no drink)
- Highly concentrated urine of low volume

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E- Parathyroid hormones: Produced by parathyroid glands and act especially on thick ascending limbs of Henle's loops (and distal convoluted tubules) to increase calcium and magnesium ions reabsorption and decrease phosphate reabsorption.

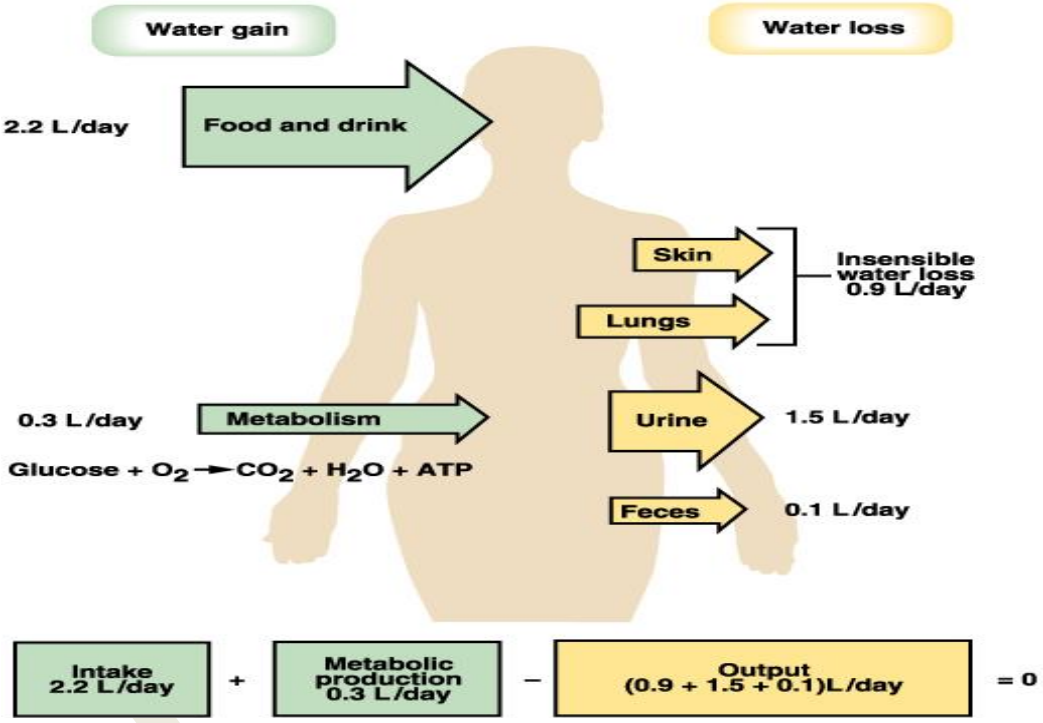
Sources of Water Output & Input

Water input

- Food & drink = 2.2 L/day
- Cellular respiration: Glucose + O_2 → CO_2 + H_2O = 0.3 L/day

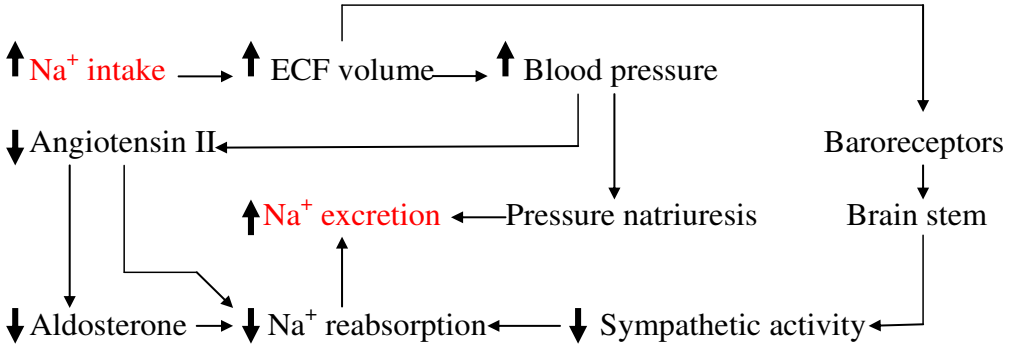
Water output

- Urine = 1.5 L/day
- Fecal matter = 100 mL/day
- Evaporative{skin & respiration} = 900 mL/day



Regulation of ECF osmolarity

Normal ECF osmolarity is about 280-300 mosm\L and it is mostly dependent on sodium ions concentration (142 mEq\L). Normal daily sodium ions intake must equals its daily output = 10-20 mEq.



Plasma osmolarity (P_{osm}) in healthy subjects is calculated from plasma sodium concentration (P_{Na+})

$$P_{osm} = 2.1 * P_{Na+}$$

However, in patients with renal diseases, plasma concentrations of other substances like urea and glucose are also calculated.

When P_{osm} decreases; kidneys excrete large amounts of diluted urine (down to 50 mosm\L) while when P_{osm} increases; kidneys excrete small amounts of highly concentrated urine (up to 1200 mosm\L).

The human body must get rid of not less than 600 mosm of metabolic wastes/day. So, it is very necessary to excrete not less than 0.5 liters of highly concentrated urine daily.

$$\frac{600 \text{ mosm\day}}{1200 \text{ mosm\L}} = 0.5 \text{ L\day}$$ this is the **minimum obligatory urine volume**

According to this equation, when kidney losses its ability to produce concentrated urine; the minimum obligatory urine volume will increase resulting in excessive loss of body fluids (a disease called diabetes insipidus).

According to the same equation, excessive intake of hyperosmotic fluids like seawater will seriously increase the P_{osm} and, thence, the minimum obligatory urine volume even with the maximum renal capability of urine concentration resulting in death from dehydration due to excessive loss of body fluids.

The ability of kidney for concentration of urine requires the presence of **hyperosmotic medulla** created by **countercurrent mechanism** and **urea recirculation** in concert with **ADH**.

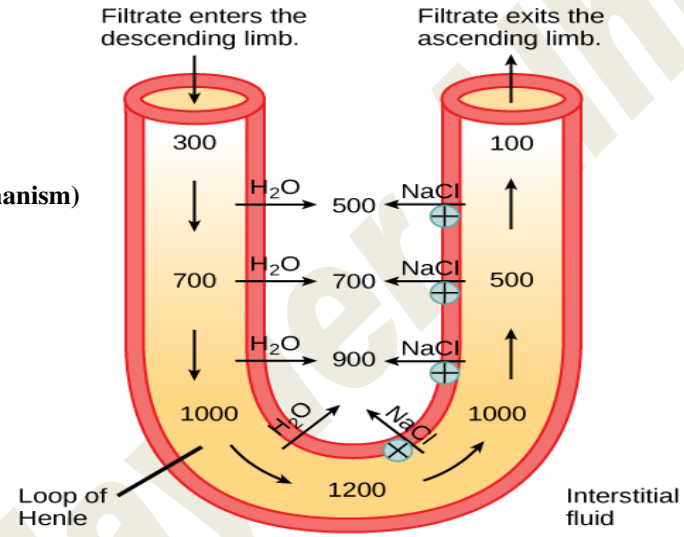
Volume \ Osmolarity	Decrease	No change	Increase
Increase	Drinking large amount of water	Ingestion of isotonic saline	Ingestion of hypertonic saline
No change	Replacement of sweat loss with plain water	Normal volume and osmolarity	Eating salt without drinking water
Decrease	Incomplete compensation for dehydration	Hemorrhage	Dehydration (e.g., sweat loss or diarrhea)

Renal regulation of salt and water balance (Relationship of osmolarity and volume)

Countercurrent mechanism

An osmotic gradient is formed in the interstitial space around the loop of Henle that raises from ‘’the top to the bottom’’ of the loop. The action of the ‘’tritransporter’’ of the epithelial cells of the ascending limb, the water permeability of the descending limb, and the shape of the loop give such osmotic gradient. The process by which this occurs is called counter-current multiplication. The descending and ascending limbs of Henle's loop and vasa recta run a long distance parallel, counter and in close proximity to each other carrying solutes toward medulla and water toward systemic circulation resulting in hyperosmotic medulla. Ascending limbs of Henle's loop are called **countercurrent multipliers** because they continuously bring new NaCl to medulla while ascending vasa recta are called **countercurrent exchangers** because they continuously drawback water

(Counter current mechanism)

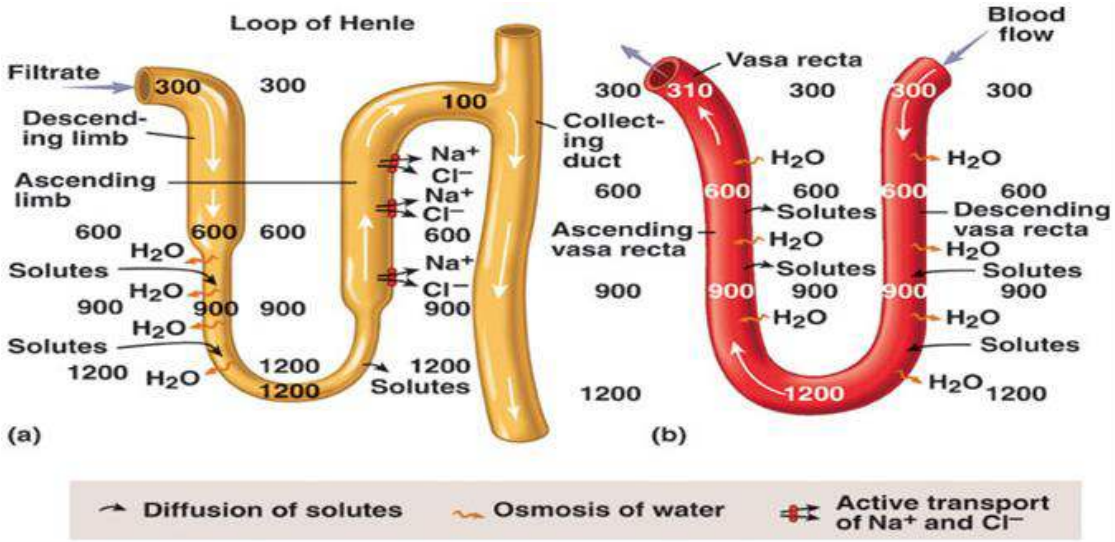


from medulla to the systemic circulation. The major bulk of tubular reabsorption of water and solutes (about 65%) occurs in proximal tubules. So, tubular fluid reaches the thin segments within its original osmolarity (300 mosm\L).

About 15% of water reabsorption occurs in tDHL which is carried back to the systemic circulation via ascending vasa recta. But tDHL is impermeable to solutes which stay within thin segment not reabsorbed. So, tubular fluid reaches the ascending limbs highly hyperosmotic (1200 mosm\L).

Starting from tAHL, all the following segments are impermeable to water in absence of ADH but very little amounts of solutes are passively reabsorbed in tAHL. So, tubular fluid reaches the following segment still hyperosmotic (900 mosm\L).

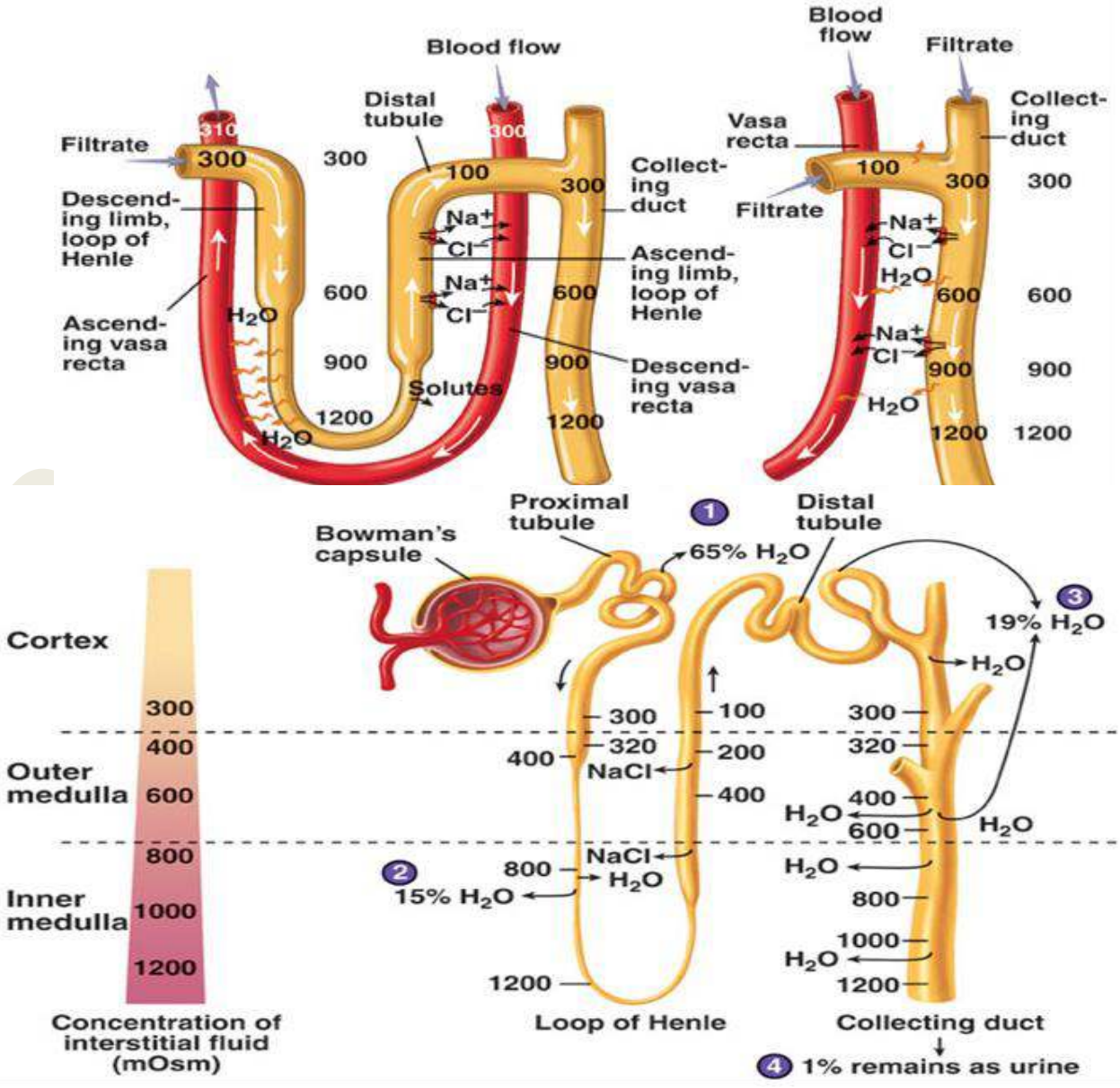
The major active reabsorption of electrolytes occurs in TAHL (about 30%) which is mainly due to $1Na^{+}$-$2Cl^{-}$-$1K^{+}$ active cotransport process which works against as much



as 200 mosm\L concentration gradient. So, tubular fluid reaches distal tubules hypoosmotic (100 mosm\L).

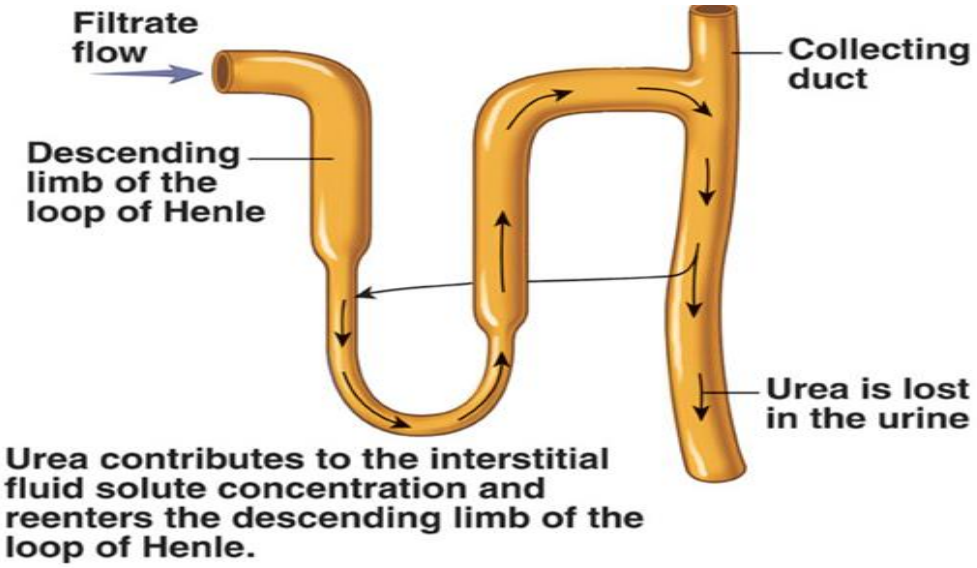
The remaining reabsorption processes of electrolytes (5%) occur in distal segments.

The net result is hyperosmotic medulla, which favors further water reabsorption (about 19%) from collecting ducts by ADH & only about 1% of filtered water is excreted in urine. While in absence of ADH, about 20% of filtered water is excreted.



Urea recirculation

Recirculation of urea is responsible for about 40% of the process of urine concentration when urea is reabsorbed from medullary colleting tubules to the medullary interstitium to be secreted again from the tubular cells of thin segments to their lumen where the cycle is repeated again and again.



Types of Renal Tubululer Transports :

Passive transport

- Simple: only Na +
- Co-transport: with Cl-, glucose, aminoacids & phosphates
- Anti-transport: Na+ inside, H+ or Ca2+ out

Active transport

- Na+/K+ pump dependent on ATP energy.

Body control of ECF osmolarity

1- **Osmoreceptors-ADH feedback**
2- **Thirst center in brain stem**
3- **Salt appetite center in brain stem**

Osmoreceptor cells lie in anterior hypothalamus, are sensitive to any increase in Na+ concentration, and send signals to supraoptic nuclei, which stimulate the posterior pituitary gland to increase secretion of ADH that increases water reabsorption. Vasopressin secretion is also stimulated by decreased blood volume, decreased blood pressure, nausea, vomiting, morphine and nicotine. Vasopressin secretion is inhibited by increased blood volume, increased blood pressure and alcohol intake.

Increased osmolarity also stimulates the **thirst center** in brain stem to increase the desire for water intake and also to increase secretion of ADH. Thirst center is also

stimulated by decreased ECF volume, decreased blood pressure, angiotensin II and dryness of mouth, pharynx and esophagus while it is inhibited by decreased ECF osmolarity, increased ECF volume, increased blood pressure and gastric distension.

Decreased osmolarity stimulates **salt appetite** center in the brain stem to increase the desire for salt intake.

Regulation of blood volume and pressure

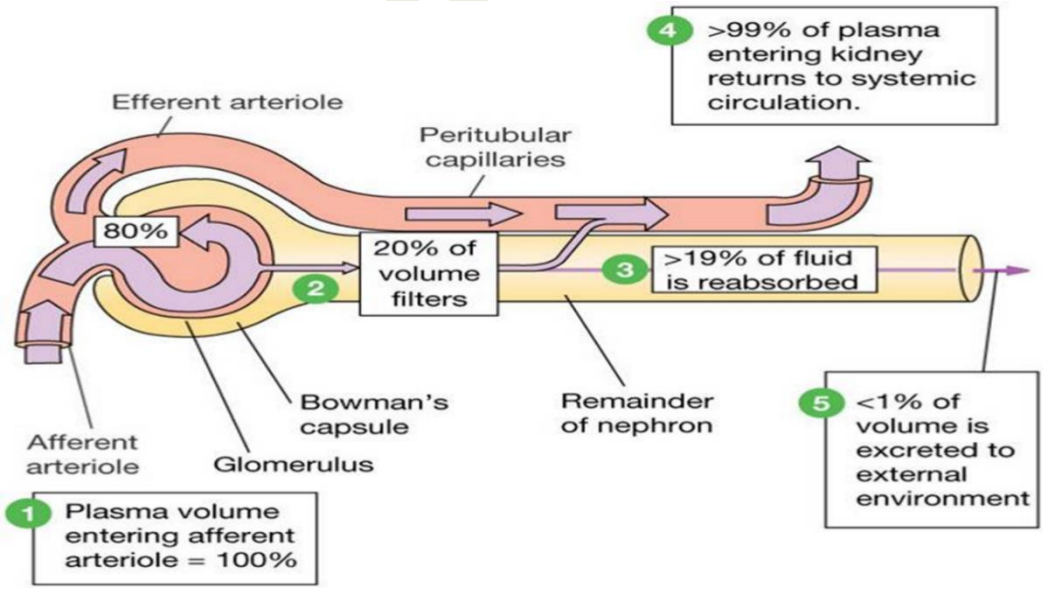
Blood volume is kept constant despite the tremendous changes in fluids intake from 0.1^{th} to 10 times normal. This constant blood volume is due to:

1- Small increase in blood volume results in large increase in cardiac output.
2- Small increase in cardiac output results in large increase in blood pressure.
3- Small increase in blood pressure results in large increase in urine excretion.

which immediately hinders and reverses the raising blood volume and pressure.

Acute increase in blood pressure is balanced by direct increase in Na^+ excretion due to increase in GFR and decrease in Na^+ reabsorption with increase in Na^+ leak back to the tubular lumen. Pressure induced increase in Na^+ excretion is called **pressure natriuresis**, which is always accompanied by **pressure diuresis** (pressure-induced increase in urine excretion).

Chronic increase in blood pressure is balanced by decrease in angiotensin II production, which results in decrease in Na+ reabsorption directly, or indirectly by decreasing aldosterone production from adrenal cortex.



Body regulation of acid-base balance

General considerations:

- Metabolism of food generates acid.
- Acid in the body is in two forms: fixed and volatile.

- Kidneys remove excess fixed acid؛
- Lungs remove excess volatile acid .
- Acidemia is excess H ions in the blood ؛
- Alkalemia is excess bicarbonate ions in the blood.

Any change in hydrogen ions concentration **[H^+]** will affect all cellular and body functions due to its effects on many reactions. Normal [H^+] in ECF is only 0.00000004 mol\L, so; it is better to use pH (which is –log [H^+] = 7.4).

Nobody can survive more than hours when pH raises to 8.0 or falls to 6.8 (more or less than normal by 0.6). Regulation of [H^+] is by one or more of the following systems: *Chemical acid-base buffer systems in body fluids, respiratory and renal regulation of acid-base balance.* Buffer system is functioning within seconds up to 2 hours only » then the respiratory comes within hours » after that the kidney comes within days and will participate in the process of acid base balance and its affect stay for the long run.

A. Buffer systems are:

1- **Bicarbonate buffer system**: It is the most important buffer system in ECF. The following reaction occurs when [H^+] is increased:

$$H^+ + HCO_3^- \rightarrow H_2CO_3 \rightarrow H_2O + CO_2$$.....(CO_2 to be expired by the lungs)

While when [OH^-] is increased, the following reaction occurs:

$$OH^- + H_2CO_3 \rightarrow H_2O + HCO_3^-$$ .....($HCO3^-$ to be excreted by kidneys)

The power of dissociation constant (**pK**) for bicarbonate system is 6.1 and accordingly, **Henderson-Hassel Bach** equation states that:

$$pH = 6.1 + \log [HCO_3^-] \backslash 0.03\ PCO_2$$

When HCO_3^- decreases, pH is decreased **metabolic acidosis**
When PCO_2 increases, pH is decreased **respiratory acidosis**
When HCO_3^- increases, pH is increased **metabolic alkalosis**
When PCO_2 decreases, pH is increased **respiratory alkalosis**

2- Phosphate buffer system: It is important buffer system in renal tubular fluids & intracellular. Its pK is 6.8 and the following reaction occurs when [H^+] increases:

$$H^+ + HPO_4^{2-} \rightarrow H_2PO_4^-$$

When [OH^-] is increased the following reaction occurs:

$$OH^- + H_2PO_4^- \rightarrow HPO_4^{2-} + H_2O$$

3- Protein buffer systems: Are the most available intracellular buffer systems but also work extracellularly. One of the most important protein buffers is hemoglobin in red blood cells.

$$H^+ + Hb \rightarrow HHb$$

4- Ammonium buffer system: Is the last choice buffer system in renal tubules when bicarbonate and phosphate buffer systems are saturated. Ammonium is

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formed from metabolism of glutamine inside renal tubular cells. The following reaction occurs when [H^+] increases:

$$H^+ + NH_3 \rightarrow NH_4^+$$

When [OH^-] is increased the following reaction occurs:

$$OH^- + NH_4^+ \rightarrow NH_4OH$$

B. Respiratory regulation

Respiratory regulation of acid-base balance is via stimulation or inhibition of the respiratory center in the brain stem by the central chemosensitive areas which are bilateral aggregations of neurons beneath the ventral surface of medulla that are sensitive to changes in H^+ and PCO_2. The result is hyper- or hypo- ventilation respectively.

Double normal alveolar ventilation reduces PCO_2 and raises pH from 7.4 to 7.63 while 1\4th normal alveolar ventilation raises PCO_2 and reduces pH to 6.95 because pH is inversely related to PCO_2 according to Henderson-Hasselbach equation.

c. Renal regulation:

Occurs by excretion of acidic or alkaline urine. Normally, daily renal secretion of H^+ is about 4400 mmol. Bicarbonates system buffers 4320 mmol in renal tubules and the other 80 mmol are buffered by phosphates and then ammonium buffer systems. Most of renal tubular cells utilize secondary active transport to secrete H^+ like Na^+-H^+ antiport, but the intercalated cells of distal tubules utilize primary active transport called proton pump.

Physiology of micturition

Urinary excretion is vital function for keeping normal metabolism & homeostasis of internal environment in the human body. Micturition is the disposing urine from the bladder through the urethra out of the body & is usually under voluntary control. Urinary incontinence: inability to control urination & is more in women than men. The reverse is urinary retention: inability to urinate. While nocturnal enuresis mean incontinence during the night (effects of emotions).

Urine enters urinary bladder in spurts synchronous with the regular peristaltic contractions of ureteric smooth muscles (1-5 times per minute) and the oblique insertion of ureters into the vicinity of bladder walls prevents back flow of urine to the ureters.

Kidney have no vagus nerve fibers innervation. Urinary bladder receives parasympathetic innervations from S2, S3 and S4 via pelvic nerves. Sympathetic innervations come from L1, L2 and L3 via hypogastric nerves after relay in inferior mesenteric ganglion. Somatic sensory and motor innervations come from S2, S3 and

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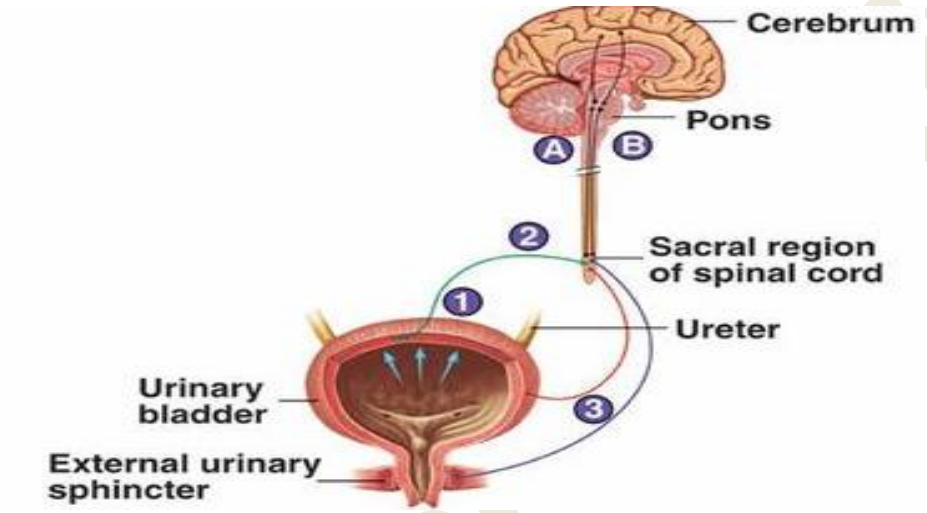
S4 via pudendal nerves. Sensory innervations also travel with autonomic innervations via pelvic and hypogastric nerves. Kidney have no vagus nerve fibers innervation.

The first urge to void is felt at bladder volume of 150 ml and the marked sense of fullness is at about 400 ml. However, this can be relieved by the property of plasticity of smooth muscles.



Voluntary micturition is thought to be initiated after relaxation of muscles of pelvic floor, which may cause sufficient downward pull on detrusor muscle, which induces excitation of stretch receptors in the bladder wall to initiate reflex contraction. The afferent and efferent limbs of voiding reflex travel with pelvic nerves to the sacral portion of spinal cord and threshold for this reflex is adjusted by the activity of facilitatory and inhibitory centers in the brain. Facilitatory areas are in pontine region and posterior hypothalamus while inhibitory area is in midbrain.

Other reflex that share in the physiology of micturition is the "Renorenal reflex". Sensory nerves located in the renal pelvic wall are activated by stretch of the renal pelvic wall, which may occur during diuresis or ureteral spasm/occlusion. Activation of these nerves leads to an increase in afferent renal nerve activity, which causes a decrease in efferent renal nerve activity & an increase in urine flow rate & urinary sodium excretion.

The internal urethral sphincter is made up of bands of smooth muscles on either sides and plays no role in micturition, but in male, it prevents retrograde ejaculation (reflux of semen into the urinary bladder during ejaculation). The external sphincter is skeletal muscle and it contracts voluntarily to delay micturition or interrupt its starting. The ability to delay micturition until the opportunity to void is available is a learning ability of brain in adults.

After micturition, female's urethra empties by gravity while male's urethra empties by several contractions of bulbocavernosus muscle.

Pathological Terms:

UTI: Urinary Tract Infection
Nephritis: Inflammation of the kidneys
Hydronephrosis: dilation of the renal pelvis
Anuria: no urinary output
Dysuria: painful urination
Enuresis: lack of bladder control
Oliguria: scanty urination
Polyuria: excessive urination
Incontinence: involuntary discharge of urine or feces
Diuretic: Increase urine output
Antidiuretic: Decrease urine output

Changes of Renal System with Aging Include

- Decline in the number of functional nephrons
- Reduction of GFR
- Reduced sensitivity to ADH
- Problems with the micturition reflex.

Dr. Hayder Alhindy