The glomerular membrane has 4 layers:

A. Endothelial walls of capillaries, which is perforated by thousands of small holes called "fenestrae" (70-100nm in diameter).

B. Basement membrane of those capillaries (basal lamina), which is formed of loose collagen bundles and proteoglycan filament with wide large spaces in between. The basal lamina does not contain visible gaps.

C. Epithelial cells of Bowman's capsules (called podocytes) with its filtration slits.

It is the most outer layer of interrupted epithelial cells arranged in a finger like projections (pseudopodia) forming slits called "filtration slit pores" (25nm in diameter) through which filtrate passes.

D. Filtration slit diaphragm:- It is a specific basement membrane of the podocytes, which is the second layer of the Bowman's capsule and considered as the fourth layer of the glomerular membrane.

❑The substances that pass from blood in the glomerular capillaries to reach renal tubules (glomerular filtrate) must pass through the capillary pores, then capillary basement membrane, then filtration slits of podocytes and finally slit diaphragm. This filtrate never cross the cell wall of the podocytes.

** Factors affecting GFR:

1. Hydrostatic pressure of the glomerular capillaries (60mm Hg) .
2. Hydrostatic pressure in Bowman's capsule (18 mmHg) .
3. Oncotic pressure of plasma proteins (32 mmHg).
4. Permeability of glomerular membrane .
5. Systemic blood pressure
6. Sympathetic stimulation

1- Hydrostatic pressure of the glomerular capillaries

- There are a direct relationship between glomerular capillary pressure and GFR.
- This pressure is affected by the diameter of afferent & efferent arterioles.
- constriction of affarent arterioles will diminish the glomerular capillary pressure that decreases GFR.
- dilatation of afferent arteriole increase the glomerular capillary pressure & GFR.
- Mild constriction of efferent arteriole increase the GFR, while severe constriction of efferent arteriole will decrease GFR due to diminish renal blood flow.

2– Hydrostatic pressure in Bowman's capsule

It is the antagonising force for filtration. Increase of this pressure by stone formation or any other obstruction in the urinary tract as tumours or fibrosis leads to marked diminish in filtration and if the obstruction is severe and maintained it will affect kidney function.

3 – Oncotic pressure of plasma proteins:

- It is also an antagonising force for filtration.
- Diminish formation of plasma proteins as in liver diseases or marked loss of it as in kidney disease increase GFR.
- The Oncotic pressure of plasma proteins is here high (32 instead of 28 mm Hg) because the filtered fluid is protein free filtrate which increases the concentration of plasma proteins.

4 – Permeability of glomerular membrane:

It is affected by:-

A. Total surface area of filtration (determined by total number of healthy nephrons)

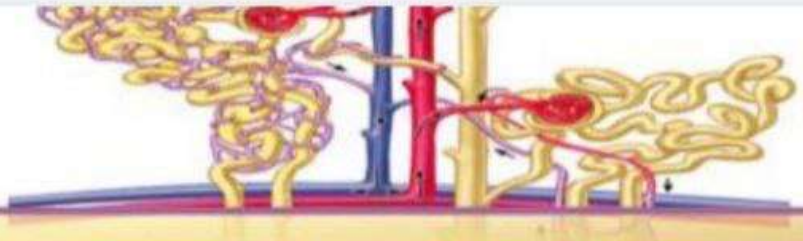
B. The state of intra-glomerular mesangial cells (defensive cells). When contract decreases the effective filtration area with subsequent decrease in GFR while its relaxation increase the GFR.

This permeability is assessed by measuring what is called Filtration Coefficient (F_k) which is the volume of fluid filtered by all the nephrons in both kidney/minute/per 1 mm Hg net filtration pressure.

$$(F_k) = \frac{\text{GFR}}{\text{Pressure}} = \frac{125}{10} = 12.5 \text{ ml/minute/1 mm Hg.}$$

5 – Systemic blood pressure:

The GFR remains more or less constant between blood pressure 70 and 180 mmHg due to auto-regulation of renal blood flow. Yet in severe haemorrhage and shock when the ABP decrease below 70 mmHg there is marked decrease in GFR, and it may even stop in severe shock with subsequent acute renal failure. On the other hand, marked elevation of blood pressure above 210mmHg causes an increase in GFR and urine formation phenomena called "pressure diuresis".



6 – Sympathetic stimulation:

Marked sympathetic stimulation as in severe exercise or intense emotional stress diminishes GFR by constricting the renal artery.

There are specific contractile cells between neighbouring capillaries "mesangial cells" that play a role in regulation of the glomerular filtration, as it contract and relax.

Factors affecting mesangial cells

Contraction	Relaxation
Endothelins	Atrial natriuretic peptide
Angiotensin II	Dopamine
Histamine	PGE2
Vasopressin	
Noradrenalin	
Thromboxane A_2	
PGF2	

Origin & distribution of renal blood vessels:

Renal artery (100 mmHg) ⇩

Inter-lobar artery ⇩

Arcuate artery ⇩

Inter-lobular artery (85 mmHg) ⇩

Afferent arteriole ⇨ Glomerulus ⇨ **Efferent arteriole** ⇨ ***Peritubular capill.***

(60 - 80 mmHg) (60 mmHg) (18 mmHg) ***Vasa recta*** in JM nephron

⇧ Inter-lobular vein ⇧

⇧ Arcuate vein ⇧

⇧ Inter-lobar vein ⇧

Renal vein (4 mmHg) ⇧

(13 mmHg

sympathetic innervations to kidney and its effects ?

A. Pathway:-

The sympathetic preganglionic fibers come from the lower thoracic and upper lumbar segments of the spinal cord.

The postganglionic sympathetic fibres supply:

- The afferent and efferent arterioles.
- The proximal and distal tubules.
- The juxtaglomarular cells.
- The Loop of Henle(Thick part)

B. Effect of sympathetic stimulation:

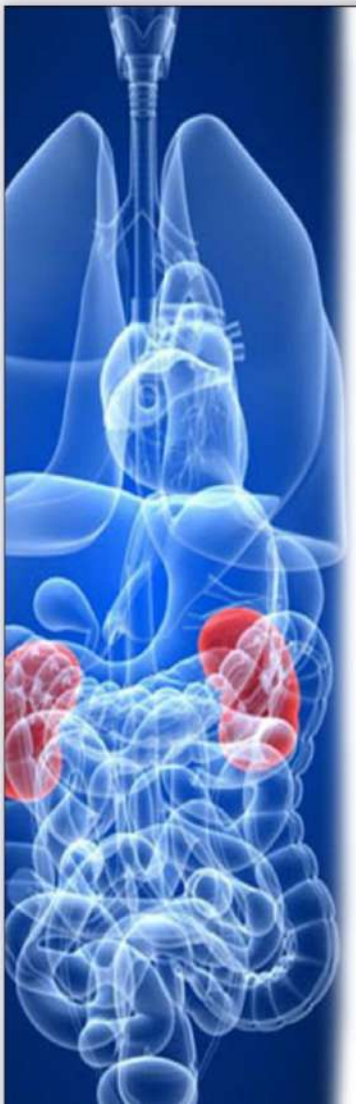
1. V.C of afferent arterioles ($\alpha 1$ receptors) → decreased glomerular filtration and renal blood flow.
2. Increased renin secretion (β_1 receptors at the juxtaglomerular cells).
3. Increased Na+ reabsorption by the renal tubular cells →decreases Na + execration.

Factors controlling renal blood flow (RBF)

A. Nervous factors

Stimulation of the sympathetic supply to the kidney diminishes RBF through constricting renal artery. and this greatly reduces GFR & urine formation.

e.g. muscular exercise



B. Haemodynamic factors

1. Drop in blood pressure as in haemorrhage or severe shock markedly reduces RBF to the degree that causes acute renal failure.
2. During pregnancy renal blood flow may be increased by 50% due to increase Blood volume & Progesterone which causes VD.
3. Sudden standing from recumbent position diminishes RBF by about 20%.

C. Hormonal factors

1. Angiotensin II and norepinephrine diminishes RBF.
2. Endothelin cause renal VC and decrease RBF.
3. Acetylcholine and dopamine cause renal vasodilatation.
4. Nitric oxide (NO) → renal VD

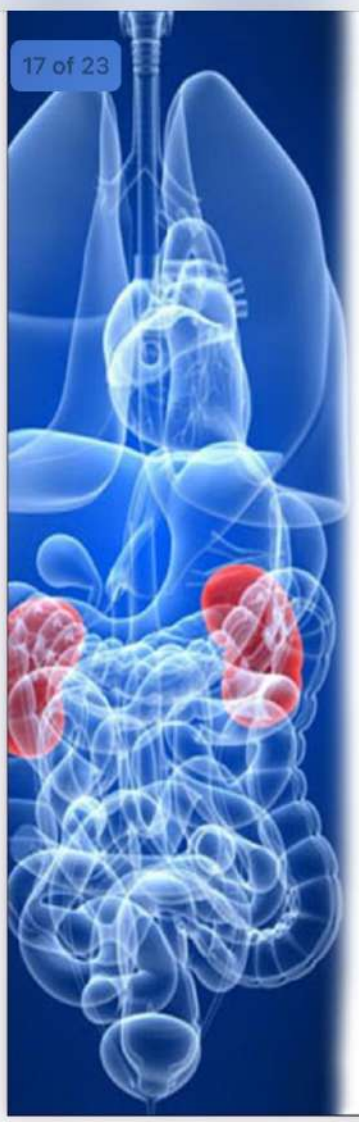
D. Auto-regulation of the renal blood flow:

- A fall of ABP to 50 mmHg may completely stop urine output, while a rise to 210 mmHg may increase the urine output 7 – 8 times.
- The kidneys have an auto regulatory mechanism, and the blood pressure may vary from 70 to 180 mm Hg with little change in RBF or GFR.

The mechanism may be:

a- Myogenic: an increase in ABP → stretch of arterial wall → increase rate of depolarisation in its smooth muscles → constriction of the arterioles → diminish blood flow.

b- Intra-renal tissue pressure theory: the kidney is surrounded by tight capsule, any increase in blood flow → increase in the intrarenal pressure that diminishes excess blood flow.



C- Tubulo-glomerular feedback:-

If rate of flow through the first part of DCT is increased, the glomerular filtration decreases (and vice versa).

Mechanism of tubuloglomerular feedback.

Increase NaCL in the DCT
in front of macula densa cells

Decrease renin secretion by JG cell
in the afferent arteriole

Abolish V.C effect of renin angiotensin
system on efferent arteriole

Increase Na-K ATPas activity

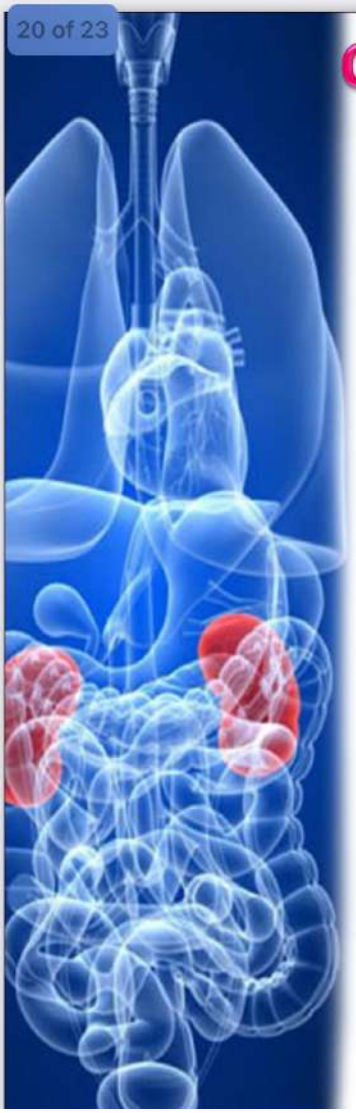
Increase ATP hydrolysis

More adenosine is formed

Adenosine is secreted from the basal membrane of the cells and act via adenosine A1 receptors on the macula densa cells to increase their release of Ca^{2+} to vascular smooth muscles in afferent arteriole

send a signal that cause
VC of afferent arterioles

Decrease GFR



Q) What happen when the ABP rises from 100 to 180 mmHg?

In this condition, constriction (narrowing) of afferent arterioles occurs, so both the RBF & GFR are kept relatively constant (or increase slightly) in spite of the increased ABP. The afferent arteriolar V.C is produced by either the myogenic mechanism or the tubuloglomerular feedback mechanism.

Q) What happens when the ABP falls from 100 to 70 mmHg?

A. V.D of the afferent arterioles by releasing a prostaglandin (PGI2).

B. V.C of the efferent arterioles by secreting renin which increase the formation of angiotensin II.

- The former increases the RBF while the later increases the renal vascular resistance , and both increase the glomerular capillary pressure , so the GFR is kept relatively constant(or decrease slightly) in spite of the decreased ABP.

Decrease ABP→ decease glomerular hydrostatic pressure→ decrease GFR → decrease in NaCL load and Decrease flow in DCT→ Stimulation of macula densa cells

+ Juxtaglomerular cells

To secret Renin

Increase Angiotensin II

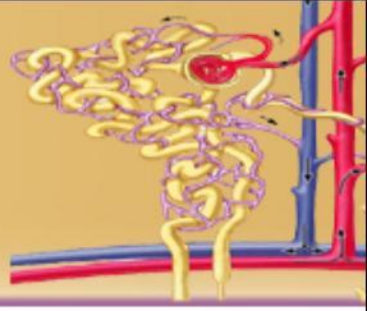
V.C of efferent arteriole That increase efferent arteriolar resistance

releasing a prostaglandin (PGI2).

V.D of Afferent arterioles that decrease afferent arteriolar resistance

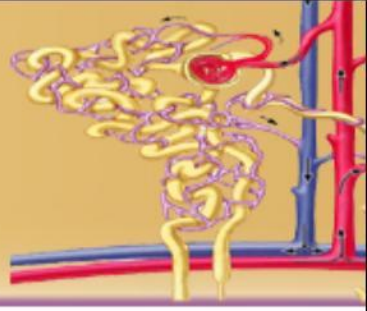
increase GF. Pressure → restore GFR

The tubuloglomerular feedback.



C. Water reabsorption in the DCT and collecting tubules:

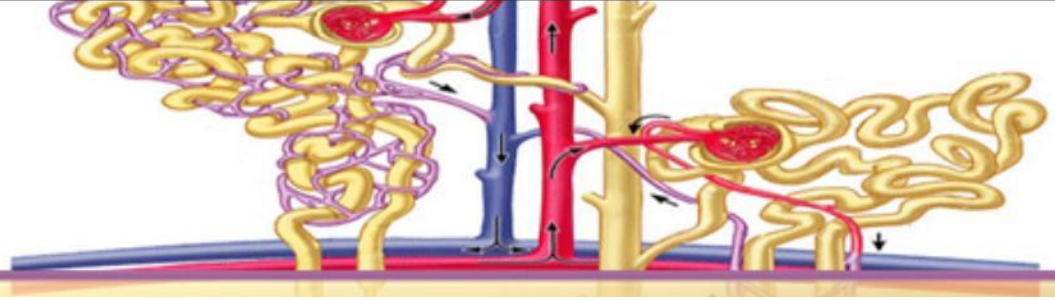
1. In the **first portion of DCT** a little amount of filtered water is reabsorbed. This segment is considered as continuation of thick ascending limb of Henel's loop i.e., **relatively impermeable to water** and here there is continuation of removal of solutes.

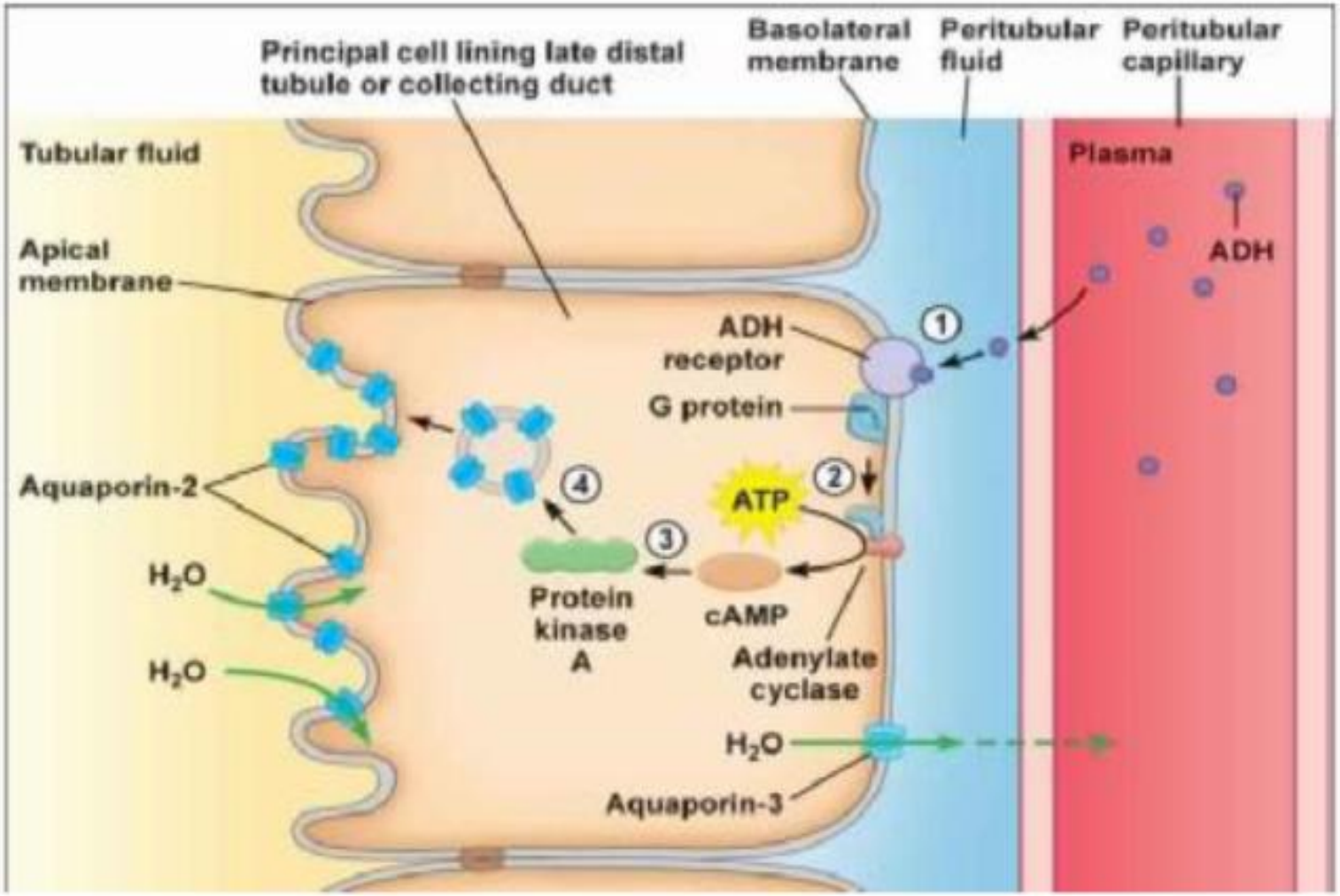


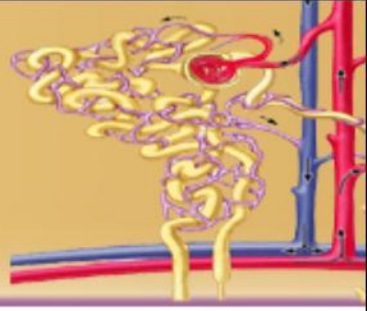
2. In late portion of DCT and collecting ducts:

In this part, about **(10- 14.2 %)** of water is reabsorbed by what is called **'facultative water reabsorption"** i.e., depends on circulating ADH.

- The hormone acts through water channels called **"aquaporine –2"** located in the principal cells of the collecting tubules leading to increase luminal membrane permeability to water.



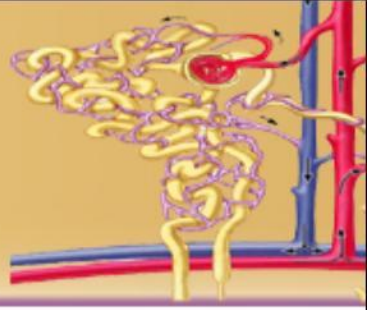

Principal cell lining late distal tubule or collecting duct
Basolateral membrane
Peritubular fluid
Peritubular capillary
Tubular fluid
Plasma
ADH
Apical membrane
ADH receptor
1
G protein
2
ATP
Aquaporin-2
4
3
H_2O
Protein kinase A
cAMP
Adenylate cyclase
H_2O
H_2O
Aquaporin-3



Auto-regulation of the water content in urine output

- it is the ability of the kidney to excrete either concentrated or dilute urine
- in cases of marked water diuresis urine volume may reach up to **14 L/day** with urine osmolarity

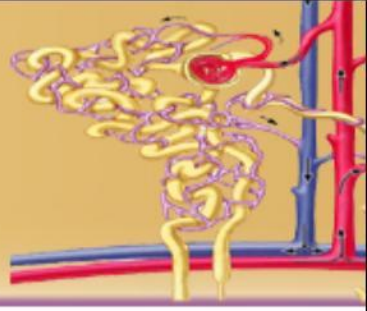
50 mosmol / L ,**while** in water deficit urine volume may be reduced to **500ml/day** with urine osmolarity **1400 mosmol / L**



- This function is determined by the amount of water reabsorption in the renal tubules. Since water reabsorption is **obligatory in the PCTs & Loop of Henle**, final adjustment of the urine volume & osmolality (concentration) depends only on the extent of **facultative water reabsorption in the CDs**, which is determined by

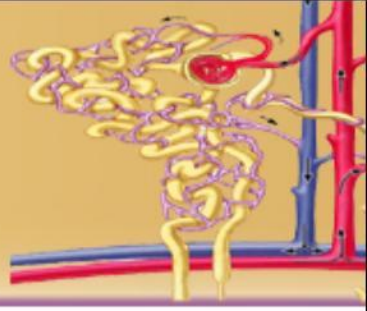
two main factors:

- **ADH**
- **hyper- osmolarity of the medullary interstitium**

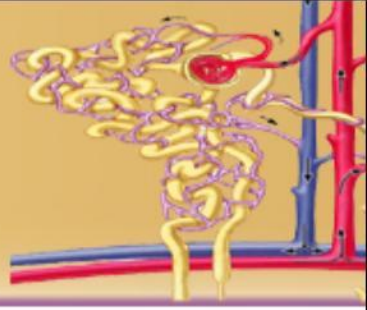


1. The ADH blood level: This hormone renders the CDs (and the DCTs to little extent) highly water permeable

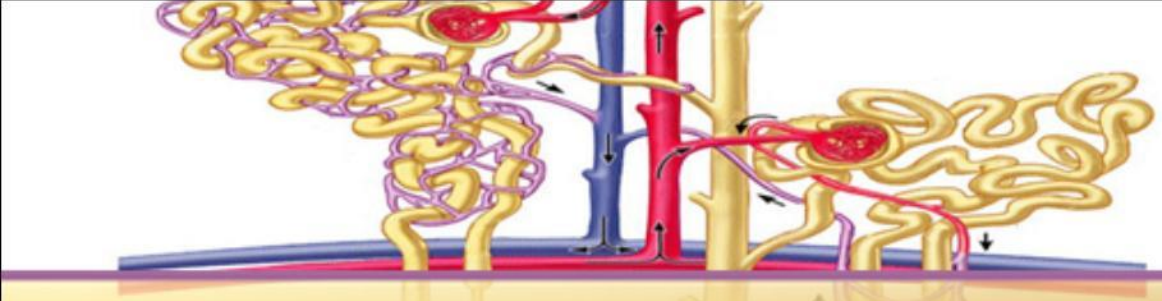
2. The hyper-osmolality of the medullary interstitium : This is developed by the renal counter current mechanism, and it is the force that cause passive water reabsorption from the CDs into the renal medulla.



- At normal level of ADH urine volume is about 1.5 litres daily with an osmolality about 400 mosmol/litre
- At high rate of ADH secretion there is more water reabsorption and consequently, more urine concentration, this results in excretion of concentrated urine with high osmolarity.



- At the low rate of ADH secretion the urine dilution occurs.
- This decreases the water-permeable area in the CDs (thus the reabsorbed amount of water is decreased leading to excretion of a large volume of urine with a lower osmolarity than normal).



Counter current mechanisms

It is the (**Power of the kidney to concentrate urine**).

- The aim of this mechanism is to **create & maintain hyperosmolarity** of renal medullary interstitium → this increases the water reabsorption from CD

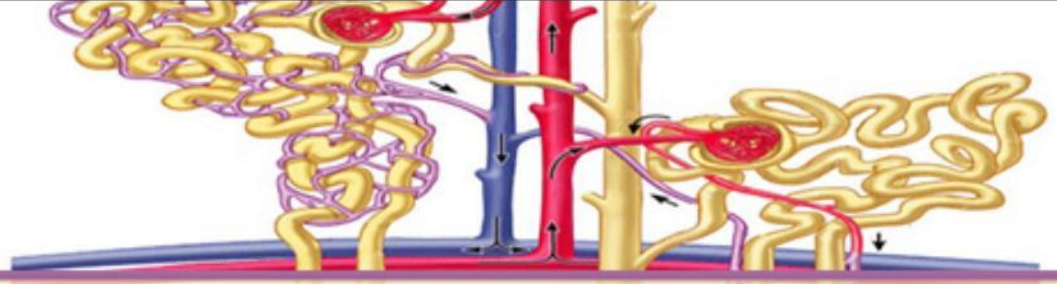
- By this mechanism, there are **4 folds** multiplication of tonicity across the renal medulla:

- In superficial layers of renal medulla = 300 mosmol/L.
- In deep layers of renal medulla = 1200 - 1400 mosmol/L.

- Two **synergistic** mechanisms work together at the same time:

I) Countercurrent **multiplier** mechanism. (***create*** the hypertonicity).

II) Countercurrent **exchanger** mechanism. (***maintain*** the hypertonicity).



Countercurrent multiplier mechanism:

- **It is the function of:** Loop of Henle

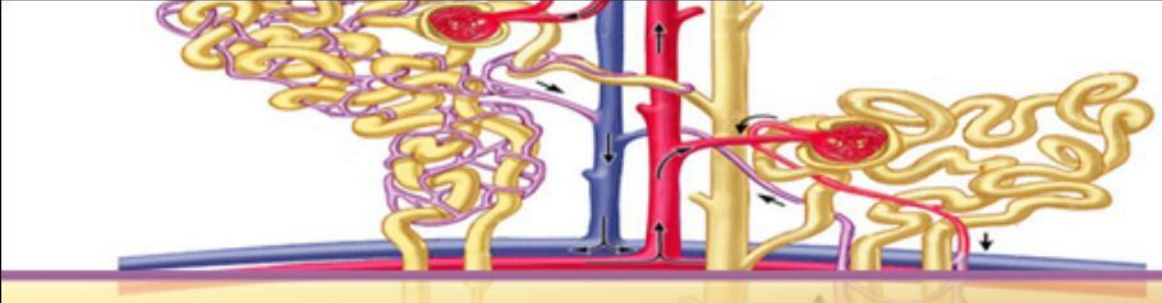
Aim: **Creation** of hypertonicity in deep renal medullary interstitium.

- This leads to shift of water **from** the CD **to** the renal medullary interstitium and **then to** the blood flow of vasa recta.
- **Steps of countercurrent multiplier:**

1. In thick ascending loop of Henle:

- Active transport of Na+ followed by cotransport of K+ & Cl-

- It is called (1Na+, 1K+, 2Cl-) active pump
- This shift of ions to renal medullary interstitium is **not followed** by water reabsorption because thick ascending limb is impermeable to water.



2. In descending loop of Henle:

- The water of the tubular fluid is continuously moved to the interstitium (by osmosis).

- Na+ & other ions remain inside lumen with **progressive** increasing of their concentration because the descending limb is permeable to water only.

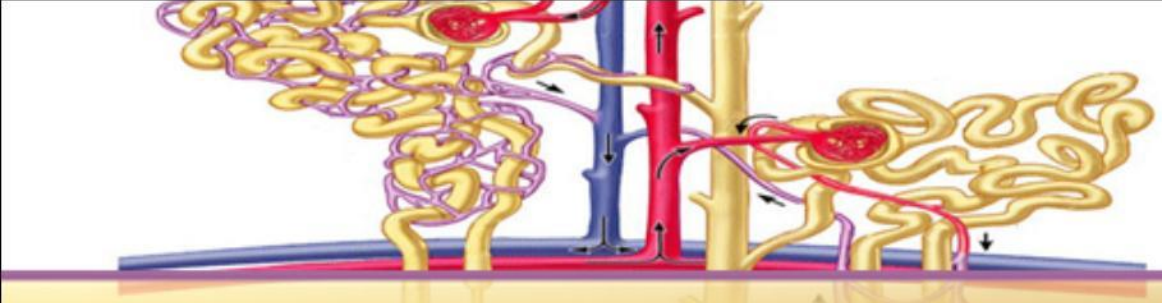
3. In thin part of ascending loop of Henle:

- Some of NaCl diffuses passively out to the medullary interstitium.

- This leads to:

a) ⇧ Osmolarity of medulla.

b) ⇩ NaCl in the ascending limb.



4. Repetition:

- Repetition of the first step and so on.

Unique characters of loop of Henle:

1) Two currents of fluids run in opposite direction: parallel and near to each other

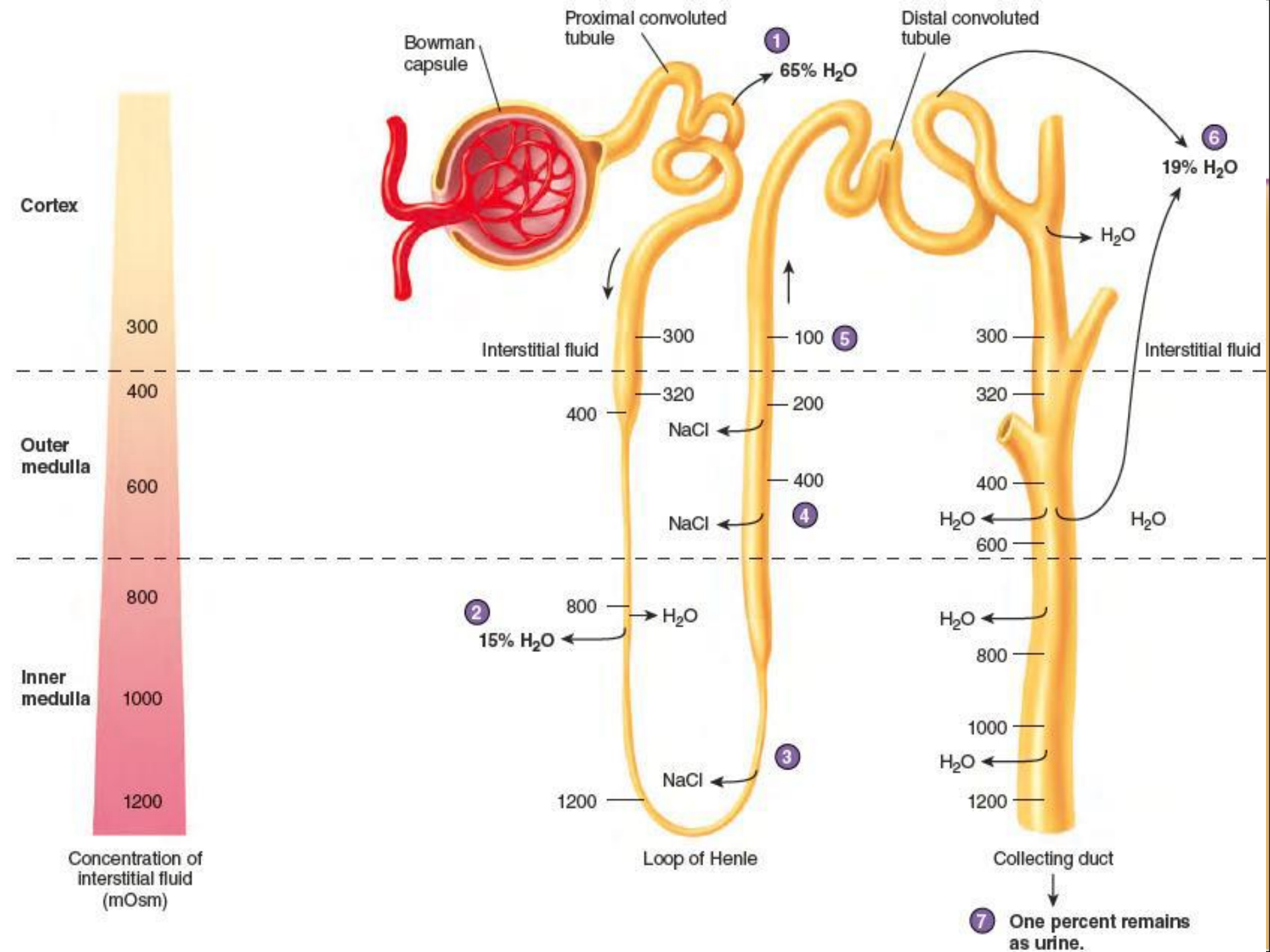
(descending & ascending limbs).

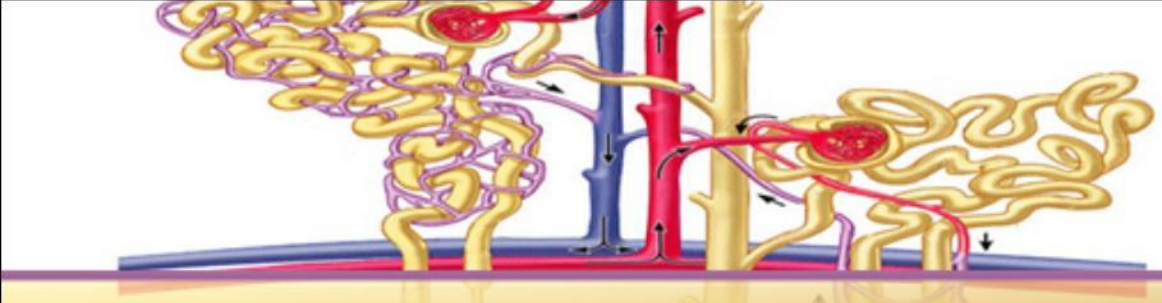
2) Difference in permeability of two limbs:

a) **Ascending limb:** permeable to Na+ but impermeable to water.

b) **Descending limb:** permeable to water but impermeable to Na+.

3) Source of energy: derived from ATP (for sodium pump) in the thick ascending part of the loop of Henle.


Proximal convoluted tubule
Distal convoluted tubule
Bowman capsule
1
65% H_2O
6
19% H_2O
H_2O
Cortex
300
Interstitial fluid
300
100
5
Interstitial fluid
400
320
200
Outer medulla
NaCl
400
600
400
NaCl
4
H_2O
H_2O
600
800
2
800
H_2O
15% H_2O
H_2O
800
Inner medulla
1000
1000
3
H_2O
NaCl
1200
1200
Concentration of interstitial fluid (mOsm)
Loop of Henle
Collecting duct
7
One percent remains as urine.



2) Countercurrent exchanger mechanism:

- **It is the function of** Vasa recta .

Aim: **Maintenance** of hypertonicity of renal medullary interstitium by:

a) Removal of excess water from renal medullary interstitium.

b) Trapping of solutes (NaCl & urea) in renal medullary interstitium.

Steps of counter current exchanger:

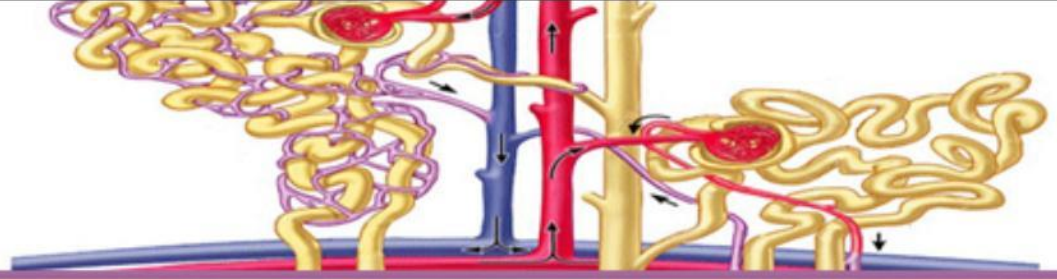
1. In the descending limb of vasa recta:

- Both **NaCl & urea** diffuse from renal medulla to the blood.

Due to their high concentration in renal medulla.

- **Water** leaves the descending limb to the hypertonic medulla.

Due to the hydrostatic pressure in the descending limb is more than osmotic pressure of plasma proteins.



2. In the ascending limb of vasa recta:

- Some of **NaCl & urea** diffuse out into the medullary interstitium
- ***Due to their high concentration in the ascending limb of vasa recta.***
- **Water** is reabsorbed into the ascending limb.
- ***Due to increased concentration of plasma proteins.***

Reabsorbed water represents the water that leaves the descending loop of Henle & the collecting ducts.

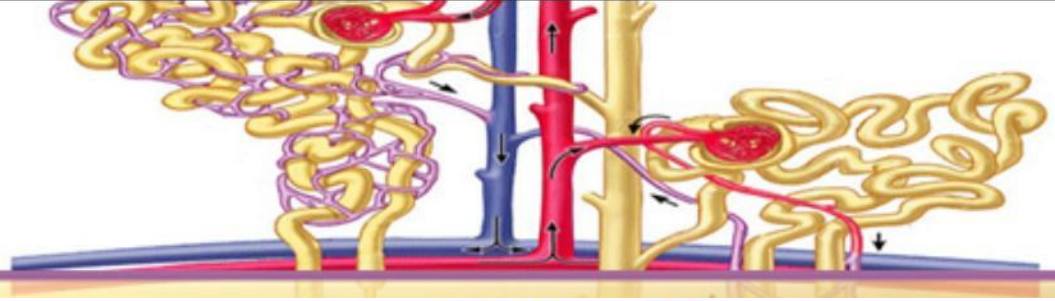
- So, water absorbed in the vasa recta > water leaves the vasa recta.

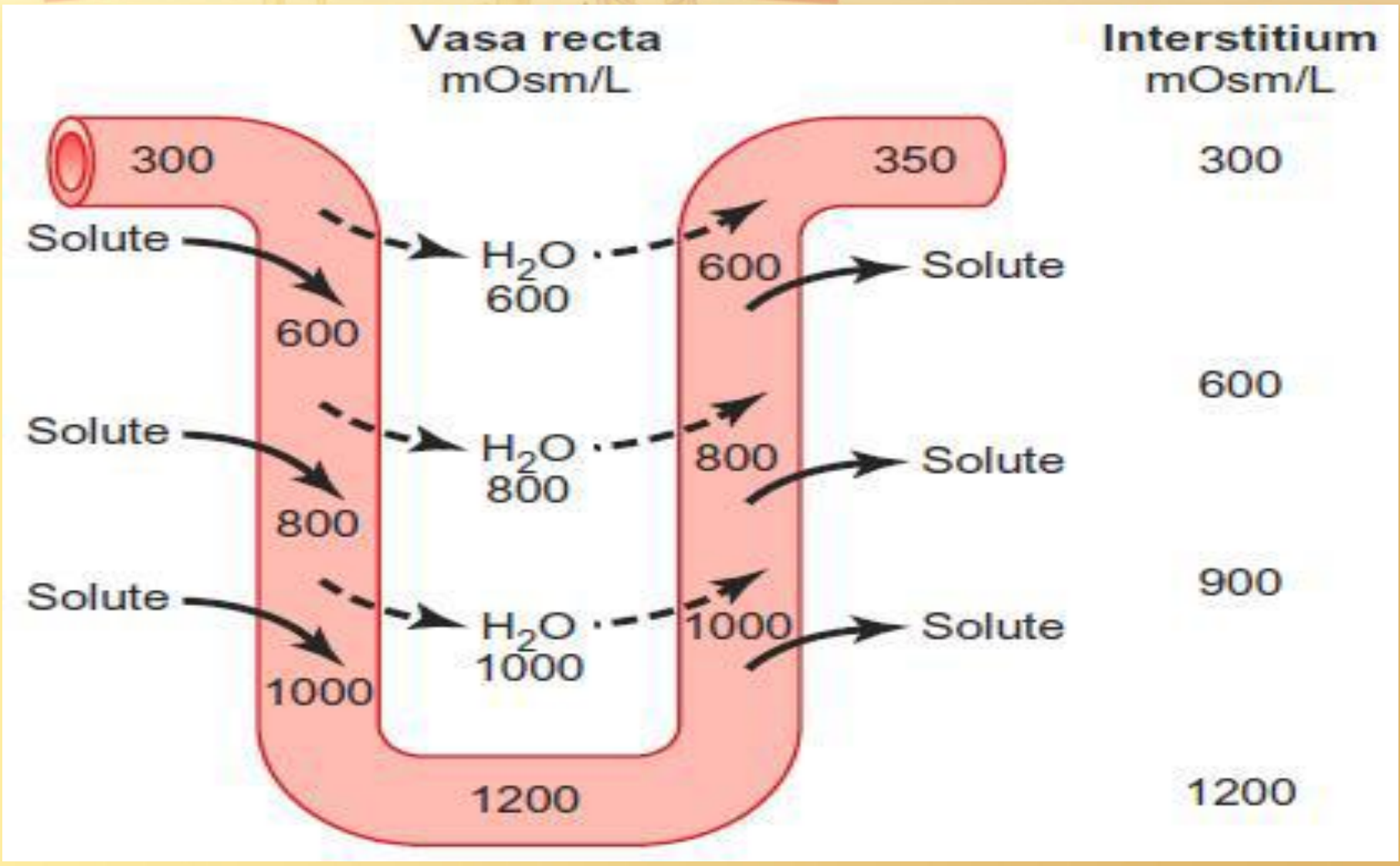
Unique characters of vasa recta:

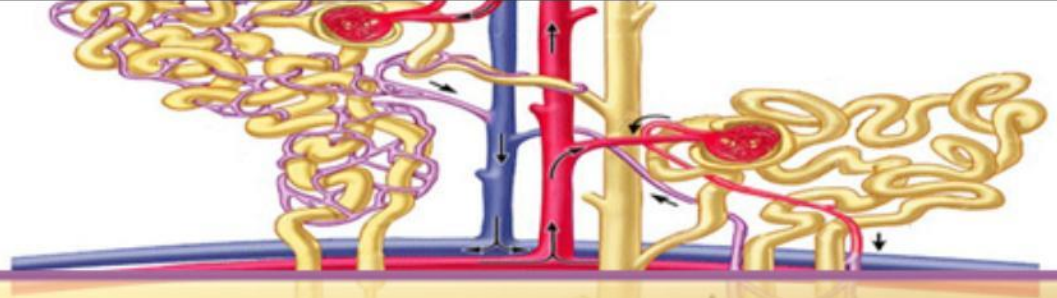
1) **S**ame **high** permeability in both limbs.

2) **S**luggish circulation to allow exchange.

3) Low pressure. (slow & Low)




Vasa recta
mOsm/L
Interstitium
mOsm/L
300
350
300
Solute
H_2O
600
600
Solute
600
600
Solute
800
H_2O
800
800
Solute
900
Solute
1000
H_2O
1000
1000
Solute
1200
1200



Unique characters present in the medulla

1. Medullary interstitial fluid is **hyperosmotic**.

- The hyper-osmolality of renal medulla is important to produce concentrated urine, because without this mechanism even large doses of ADH cannot produce such concentrated urine.

2. Many of fluids run in opposite directions, parallel to and near to reach other(**countercurrents**).

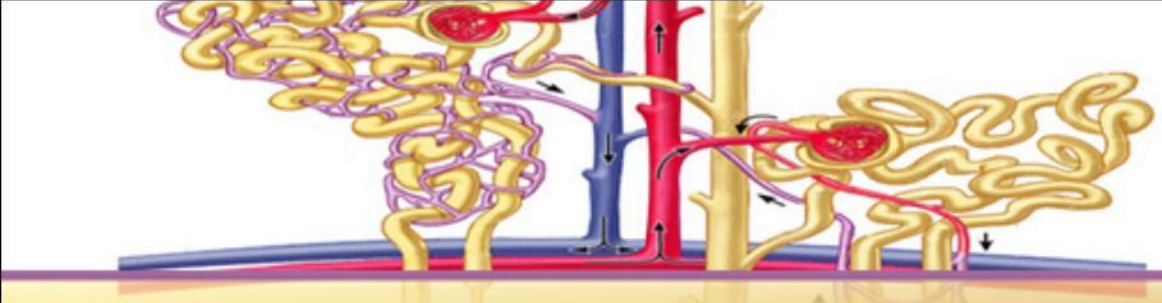
3. Difference in permeability of both two limbs of the loop.

4. Source of energy mostly derived from ATP (for sodium pump).

➢ **N.B. Causes of hyperosmolarity of renal medullary interstitium:**

1) Countercurrent mechanisms (**60%** of hyperosmolarity).

2) Urea cycle (**40%** of hyperosmolarity).



Urea cycle (Re circulation of urea)

Definition: Passive diffusion of **urea** following **water** from the medullary collecting ducts into the medullary interstitium due to its concentration gradient.

Steps:

1. Water reabsorption from the medullary CD by the high osmolarity of renal medulla ⇨ ⇧ concentration of urea in CD.

2. Urea diffuses from **CD to renal medullary interstitium** (following water reabsorption helped by ADH).

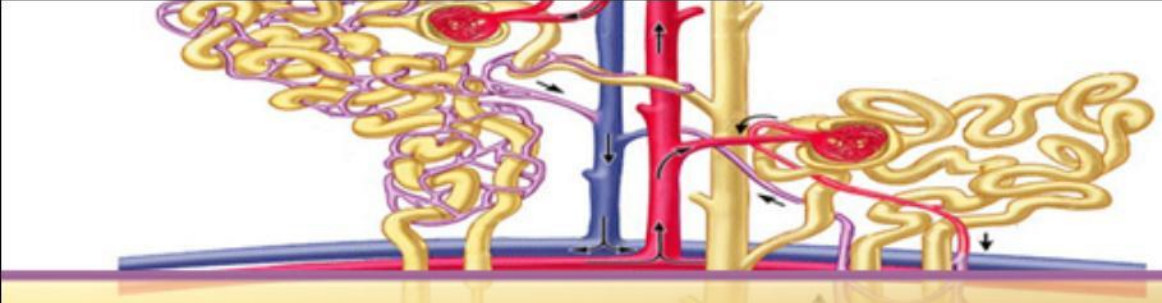
This increase the osmolarity in renal medulla.

3. Then, urea enters from renal medullary interstitium to the lumen of the *descending and thin ascending parts of loop of Henle.*

4. Then, urea is **trapped** inside the lumen of **thick ascending limb.**

This part is **impermeable** to H2O & urea.

5. Urea **re-circulation** again till it reaches the *medullary collecting ducts* to start a new cycle and so on.



Importance:

1) It is responsible for **40%** of hypertonicity of renal medulla *(add 500 mosmol/liter to renal medulla).*

2) It plays important role in **urine concentration**

N.B. The only parts that are **permeable** to urea are **medullary collecting duct**,

descending & **thin ascending limb** of Henle's loop & **PCT** (partial permeable).

But **Thick ascending** part of loop of Henle, **DCT** & **cortical** collecting tubules are all **impermeable to urea**.