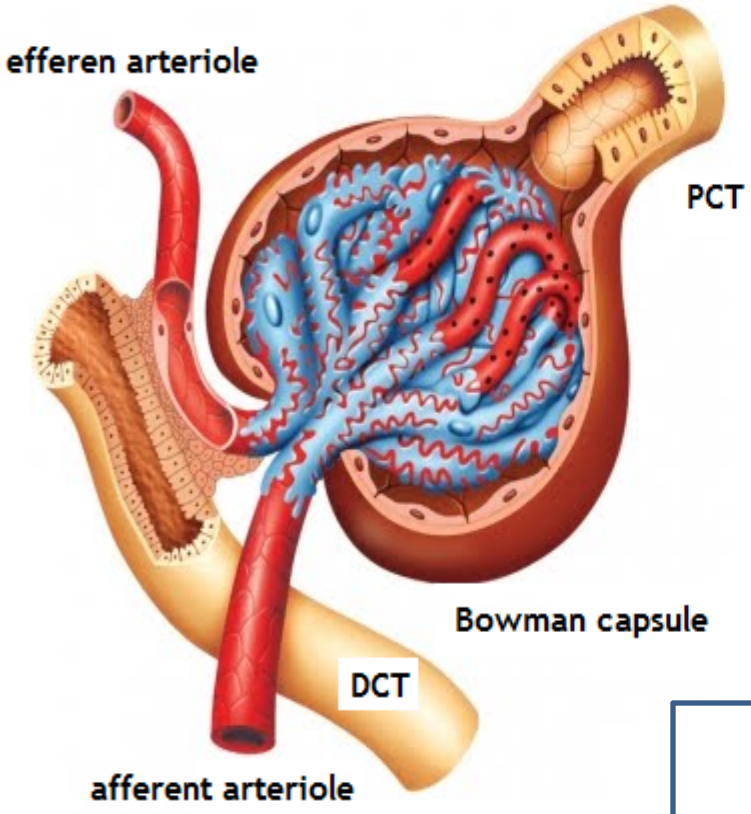
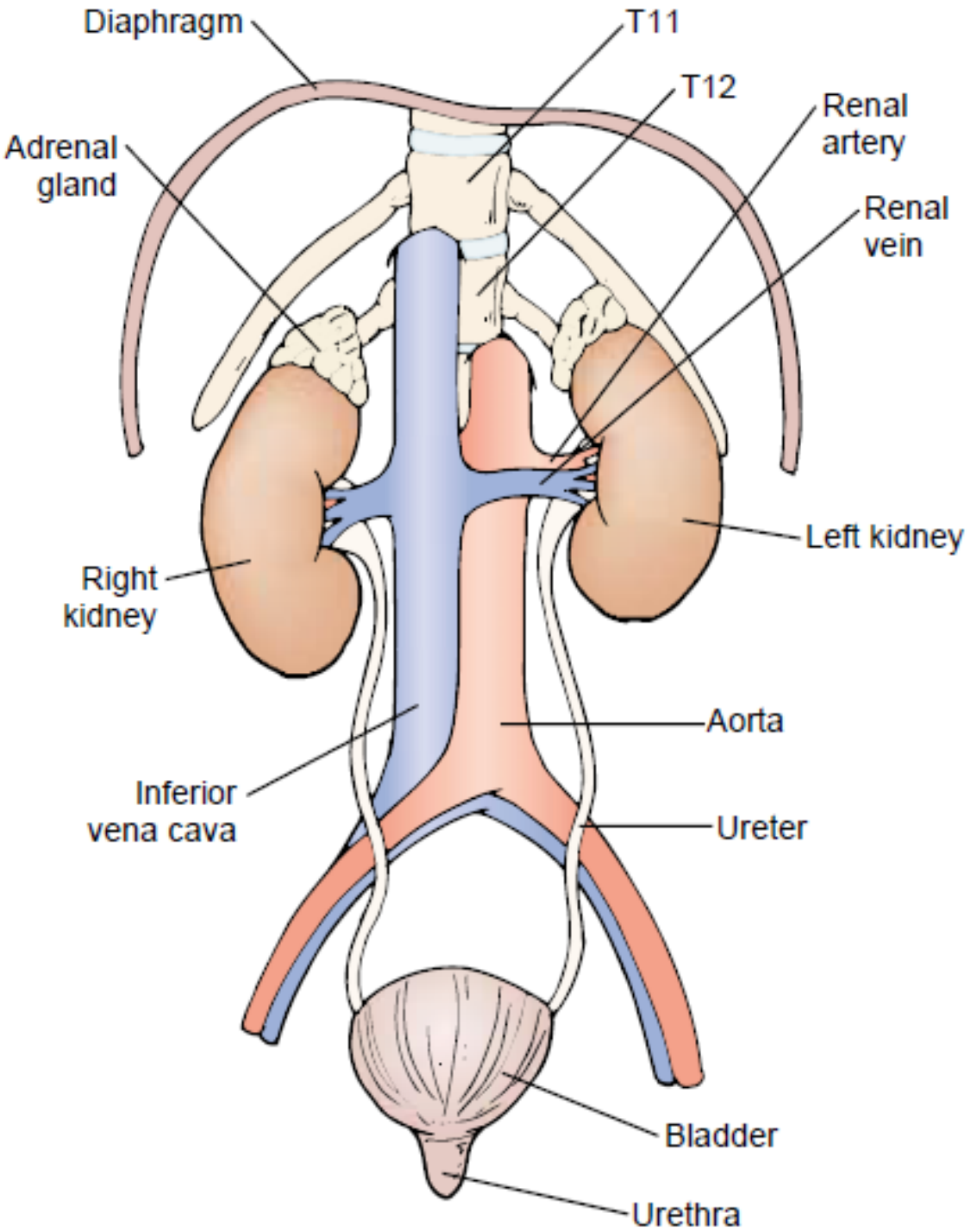
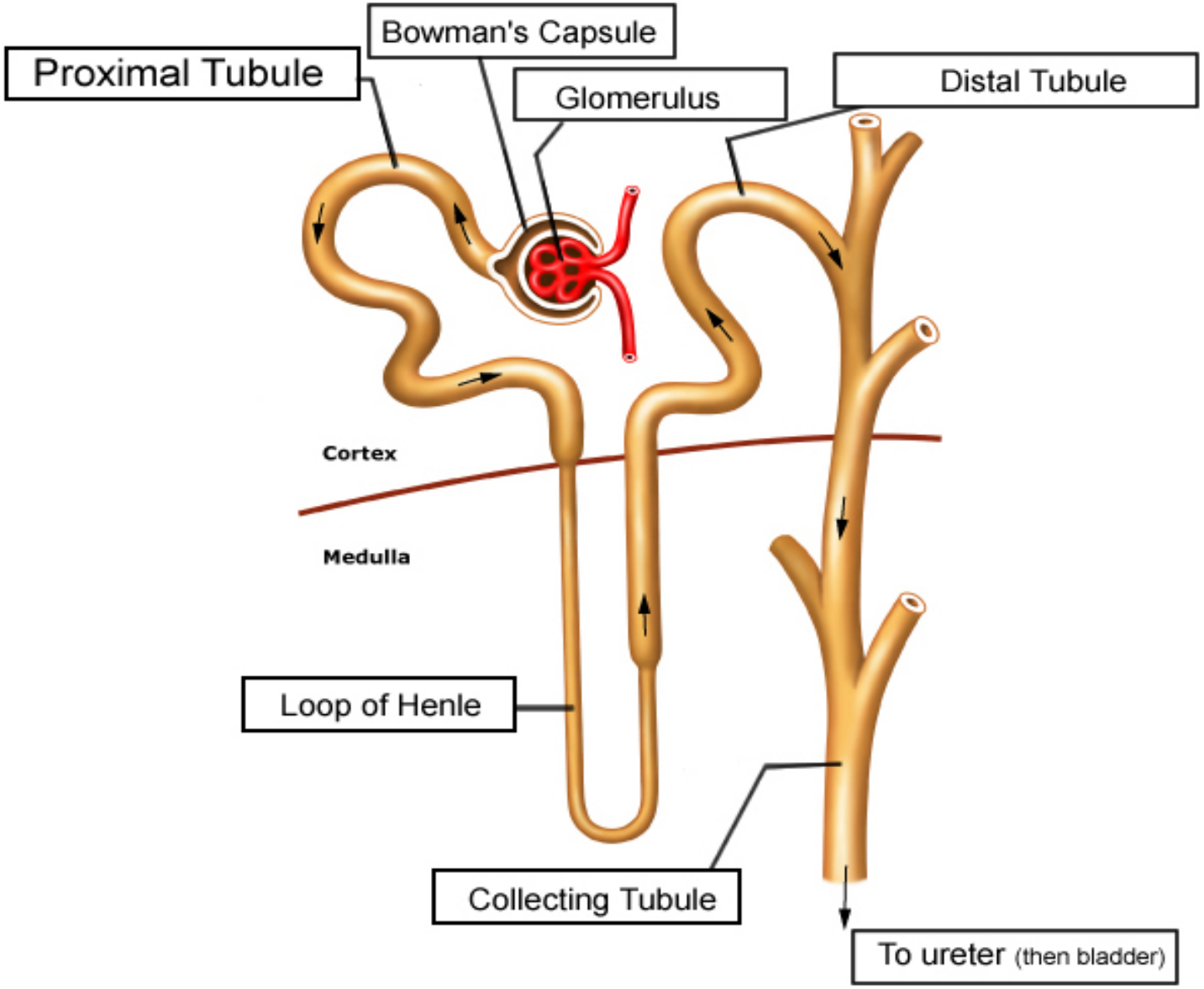


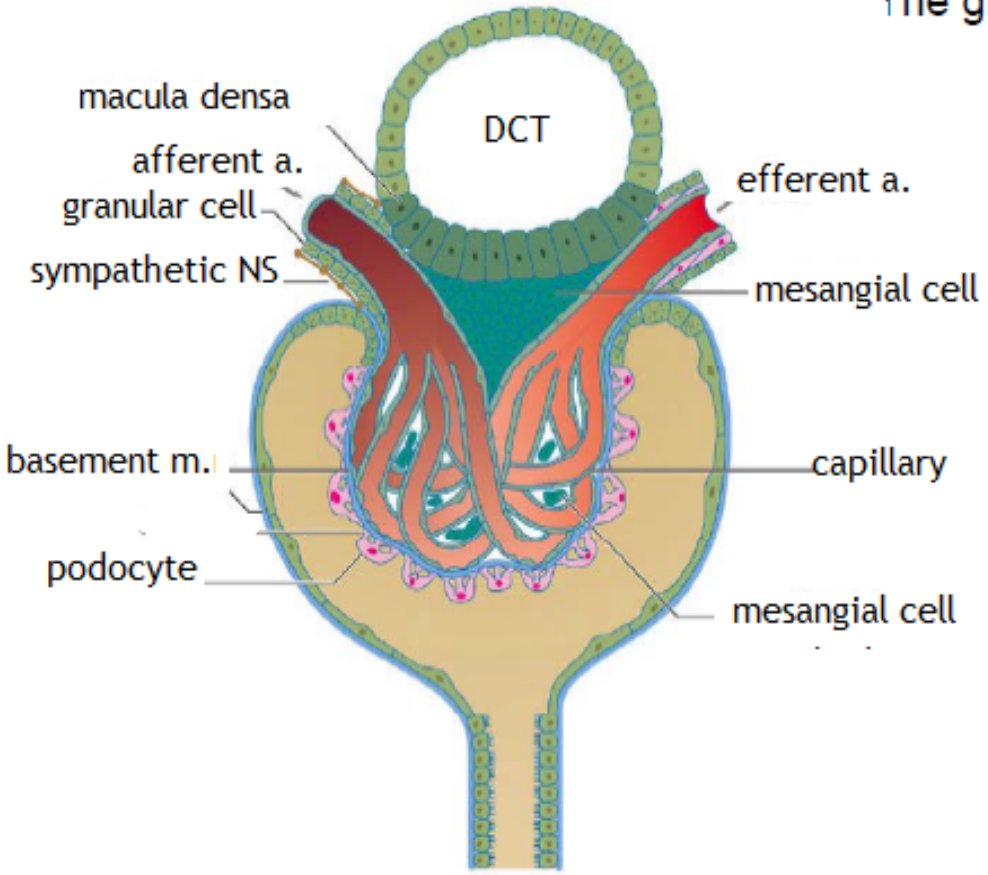
GLOMERULAR FILTRATION


Diaphragm
T11
T12
Renal artery
Adrenal gland
Renal vein
Left kidney
Right kidney
Aorta
Inferior vena cava
Ureter
Bladder
Urethra

Nephron

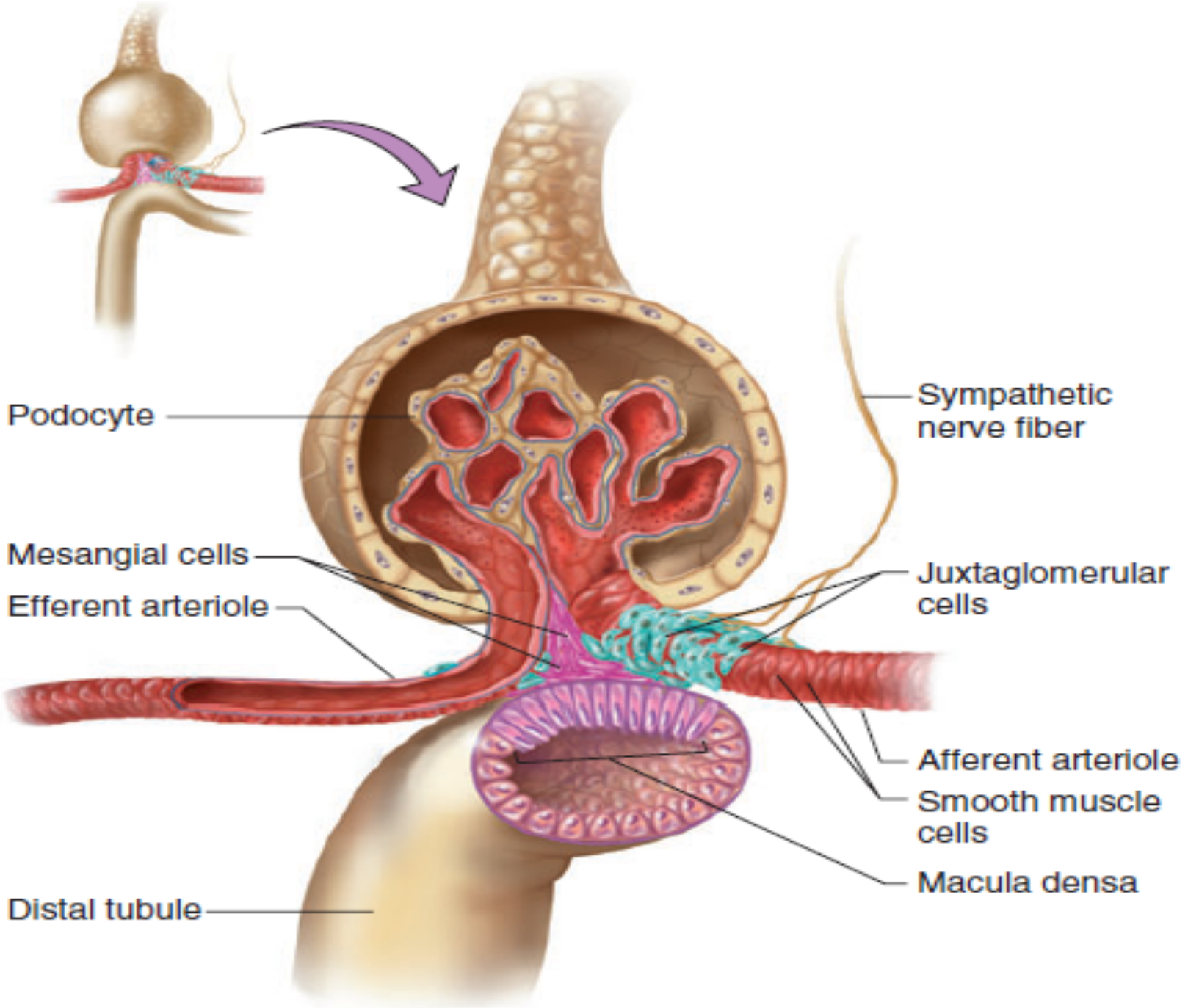

Bowman's Capsule
Proximal Tubule
Glomerulus
Distal Tubule
Cortex
Medulla
Loop of Henle
Collecting Tubule
To ureter (then bladder)

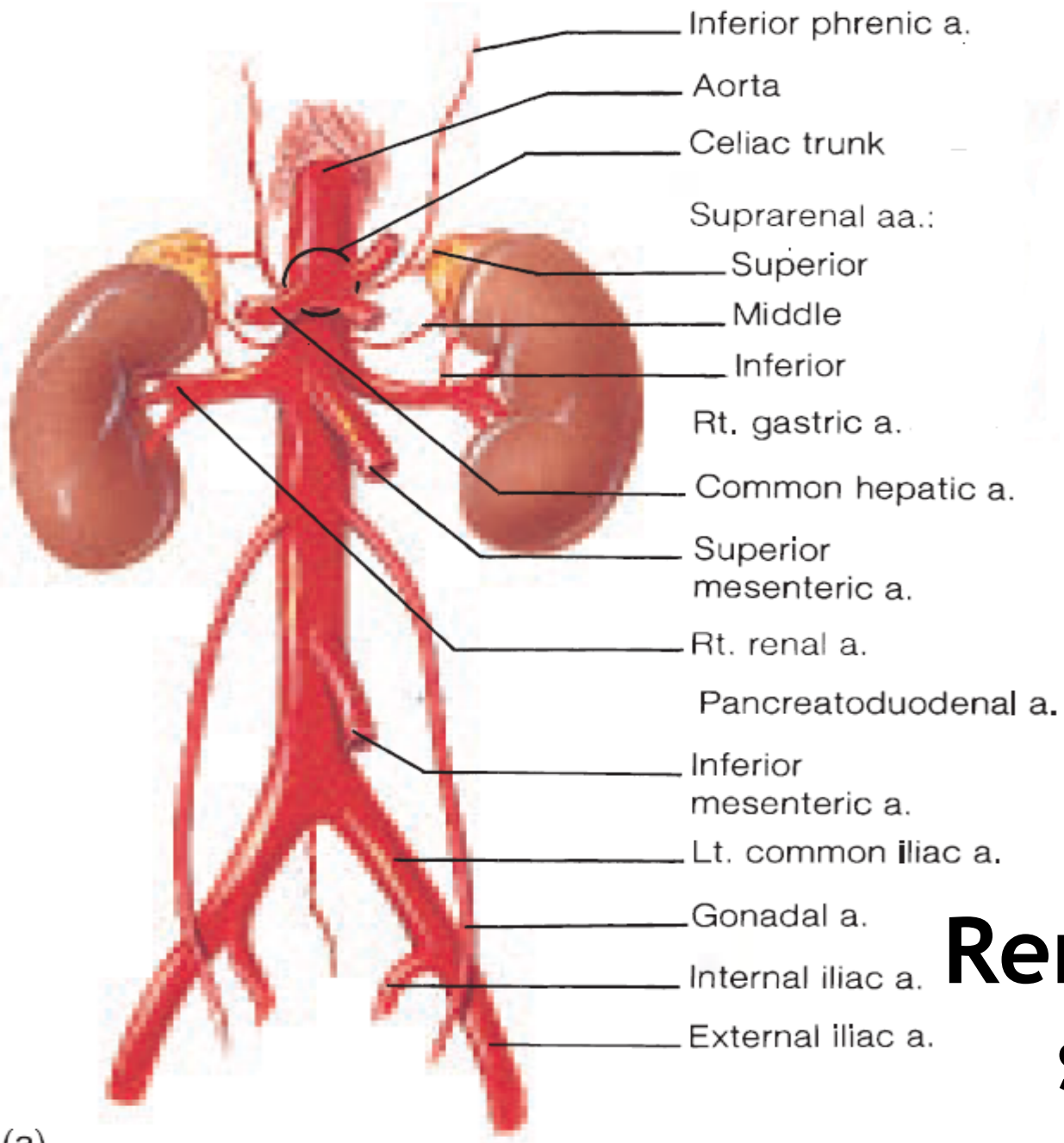
The Glomerulus



The glomerulus filters the plasma in blood

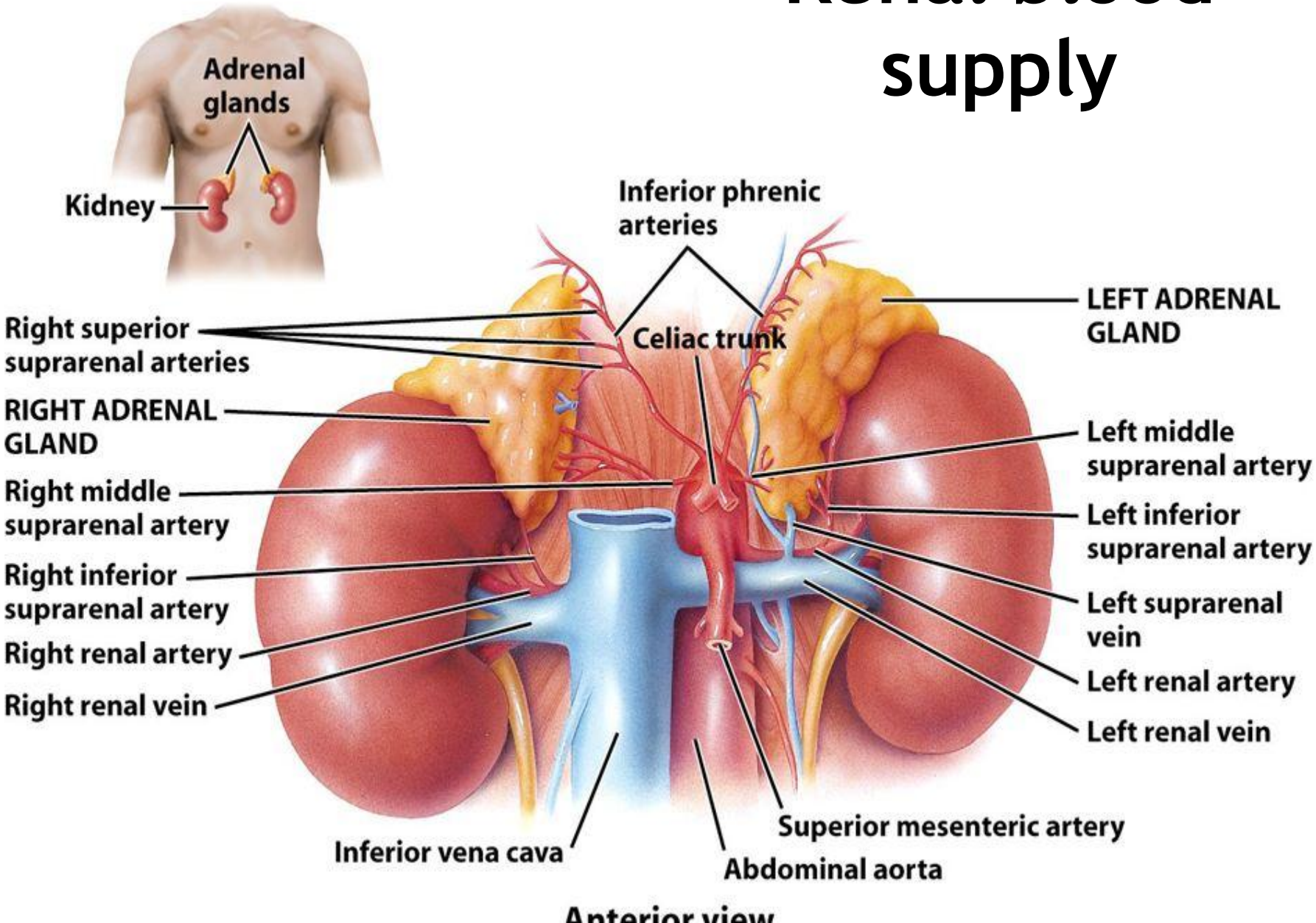
1. Bowman's capsule
2. Afferent arteriole – blood flow in
   - Sympathetic innervation for control of renal blood flow and plasma filtration
3. Glomerular Tuft (capillaries)
   - The leakiest blood vessels in the body
4. Efferent arteriole – blood flow out
   Not regulated
5. **Juxtaglomerular apparatus**
   Macula Densa and granule cells
   - hormonal regulation


Podocyte
Mesangial cells
Efferent arteriole
Distal tubule
Sympathetic nerve fiber
Juxtaglomerular cells
Afferent arteriole
Smooth muscle cells
Macula densa



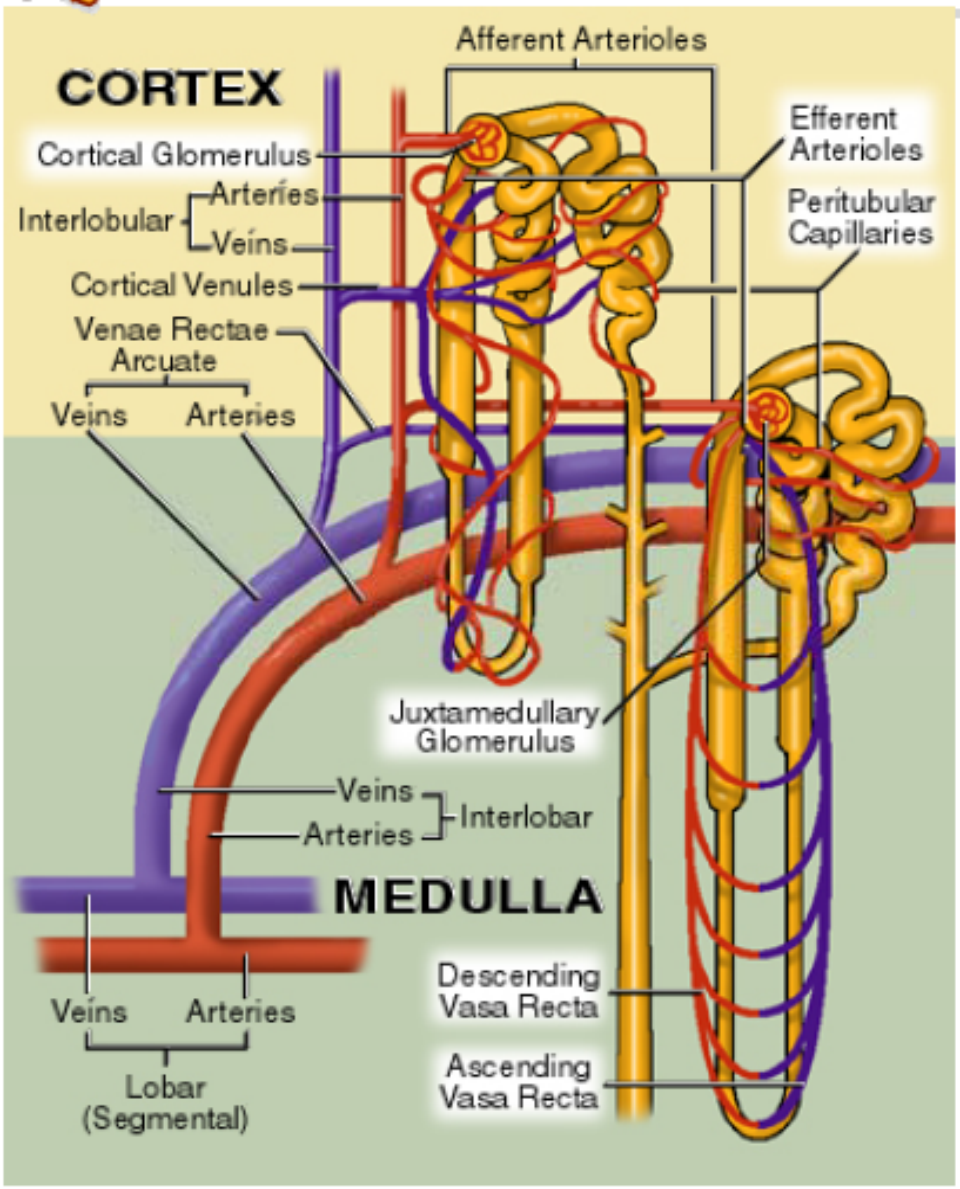
Renal blood supply

Renal blood supply



Right lung
Diaphragm muscle
Inferior vena cava
Right kidney
Celiac trunk
Common hepatic artery
Superior mesenteric artery
Right common iliac artery
Right external iliac artery
Right external iliac vein
Left lung
Heart
Left renal artery
Left kidney
Abdominal aorta
Inferior mesenteric artery

Renal Blood Supply

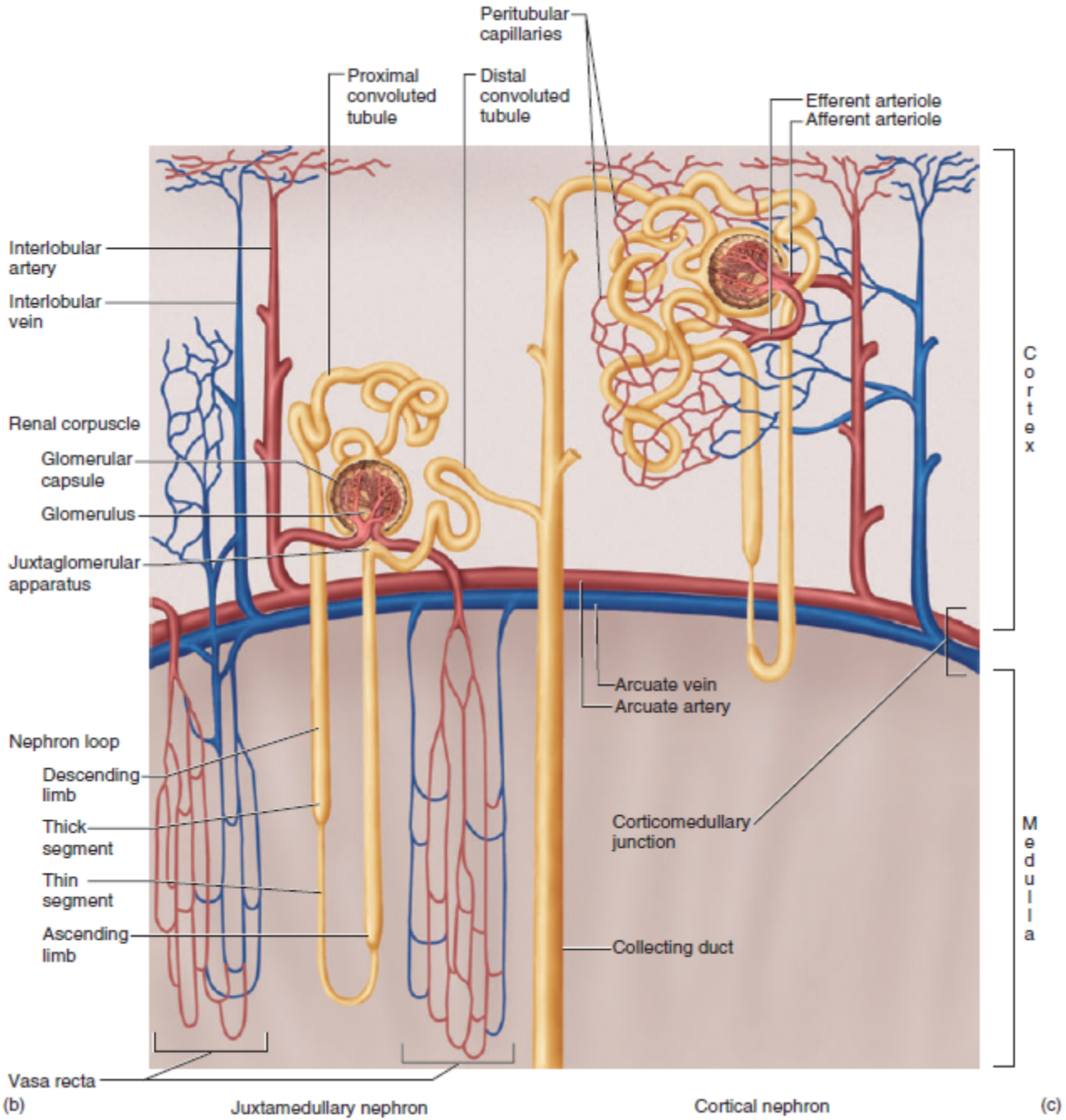


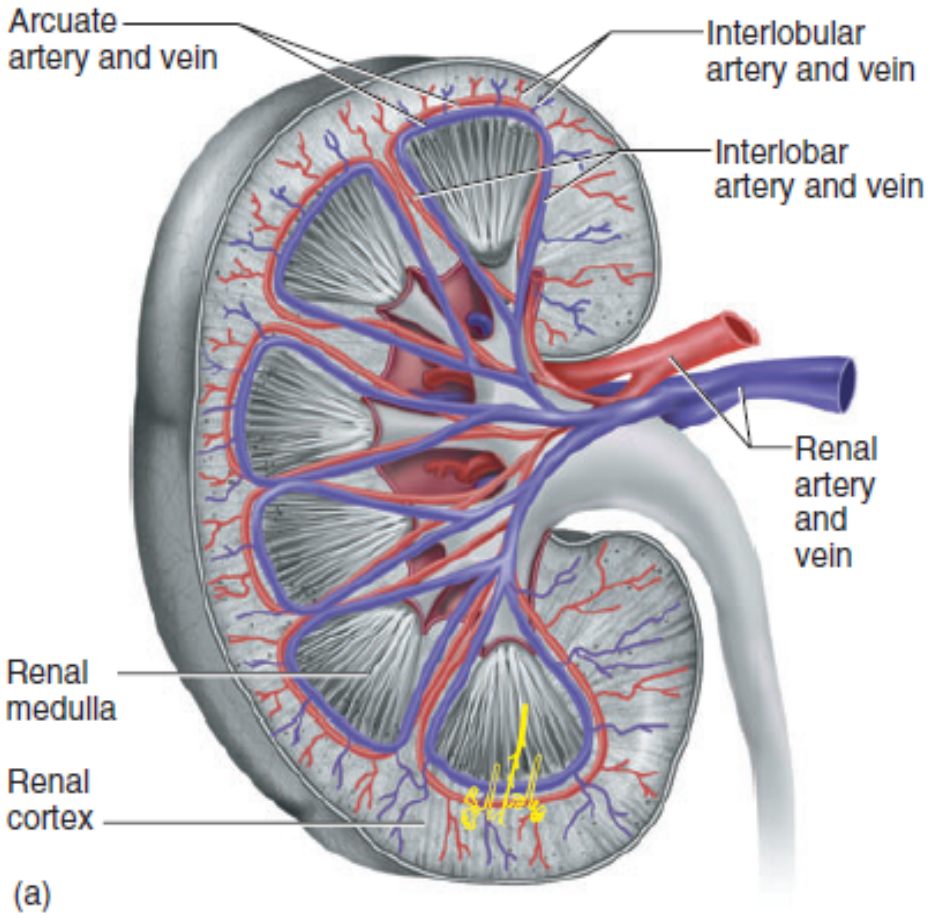
- Aorta
- Left and right renal arteries
- Arcuate artery (boundary of Cortex and Medulla

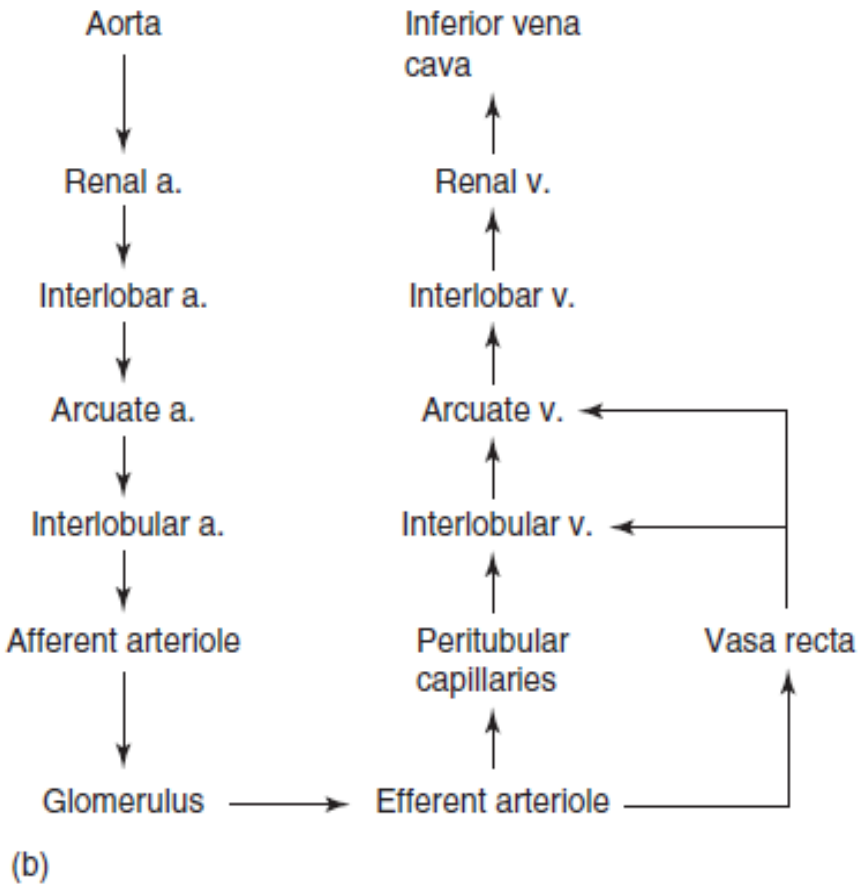
- Afferent arteriole
- Glomerular capillaries
- Efferent arteriole

- Peritubular capillaries

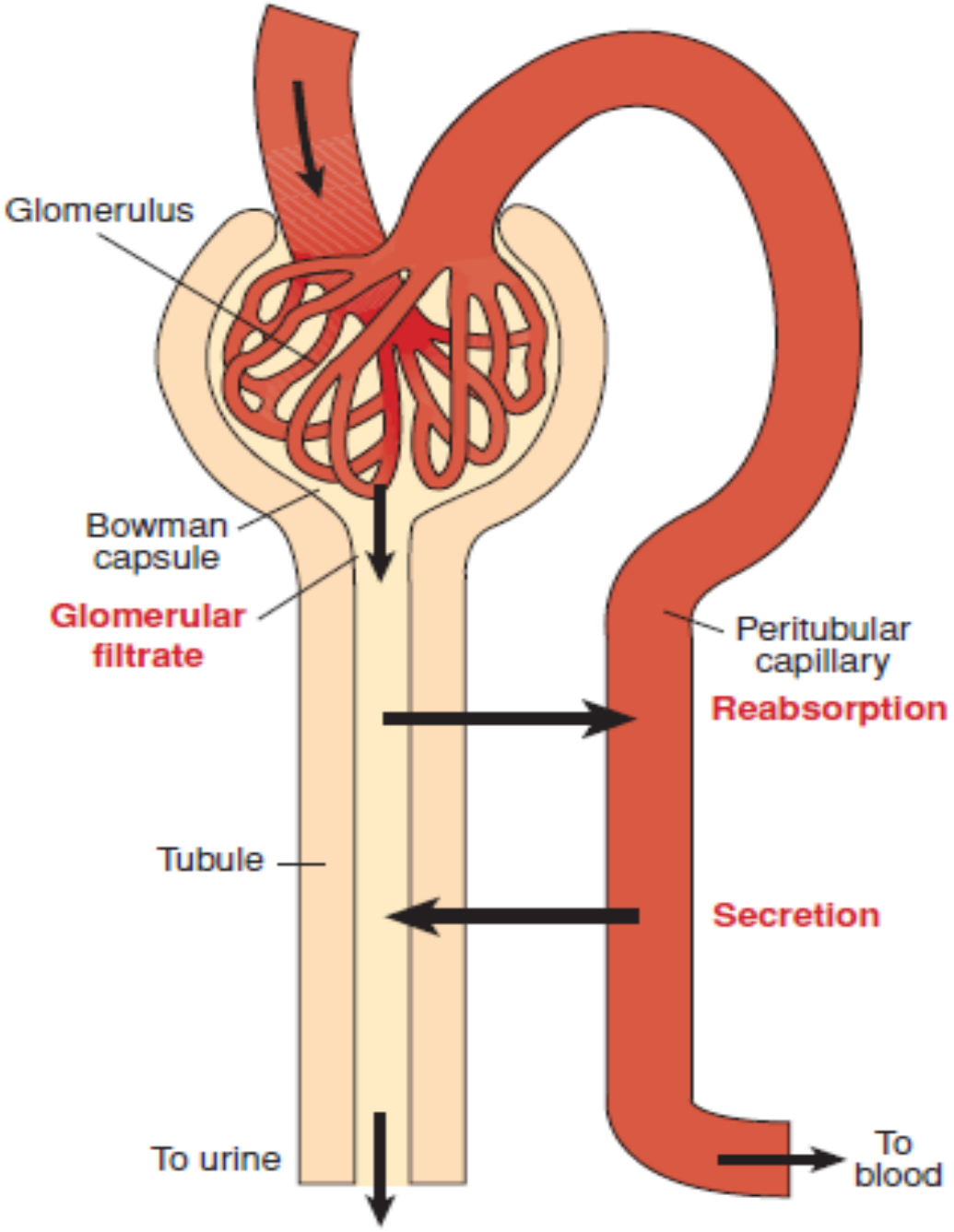
- Interlobular/arcuate vein
- Right and left renal veins
- IVC


Peritubular capillaries
Proximal convoluted tubule
Distal convoluted tubule
Efferent arteriole
Afferent arteriole
Interlobular artery
Interlobular vein
Renal corpuscle
Glomerular capsule
Glomerulus
Juxtaglomerular apparatus
Cortex
Arcuate vein
Arcuate artery
Nephron loop
Descending limb
Thick segment
Thin segment
Ascending limb
Corticomedullary junction
Medulla
Collecting duct
Vasa recta
(b)
Juxtamedullary nephron
Cortical nephron
(c)


Arcuate artery and vein
Interlobular artery and vein
Interlobar artery and vein
Renal artery and vein
Renal medulla
Renal cortex
(a)

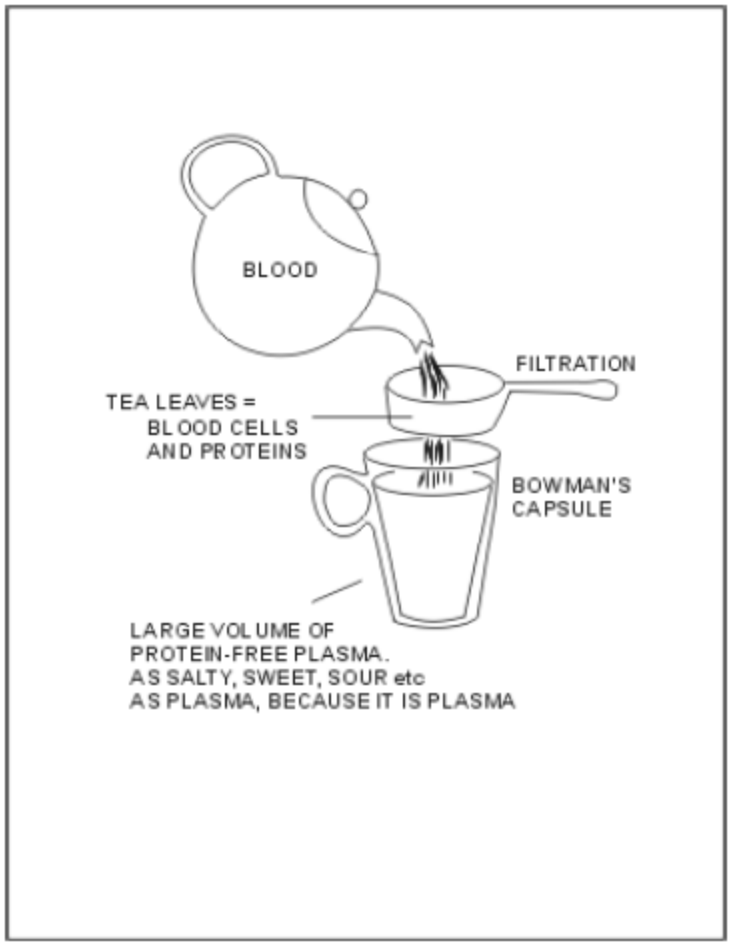

Aorta
Renal a.
Interlobar a.
Arcuate a.
Interlobular a.
Afferent arteriole
Glomerulus
Efferent arteriole
Peritubular capillaries
Vasa recta
Interlobular v.
Arcuate v.
Interlobar v.
Renal v.
Inferior vena cava
(b)

Urine Formation



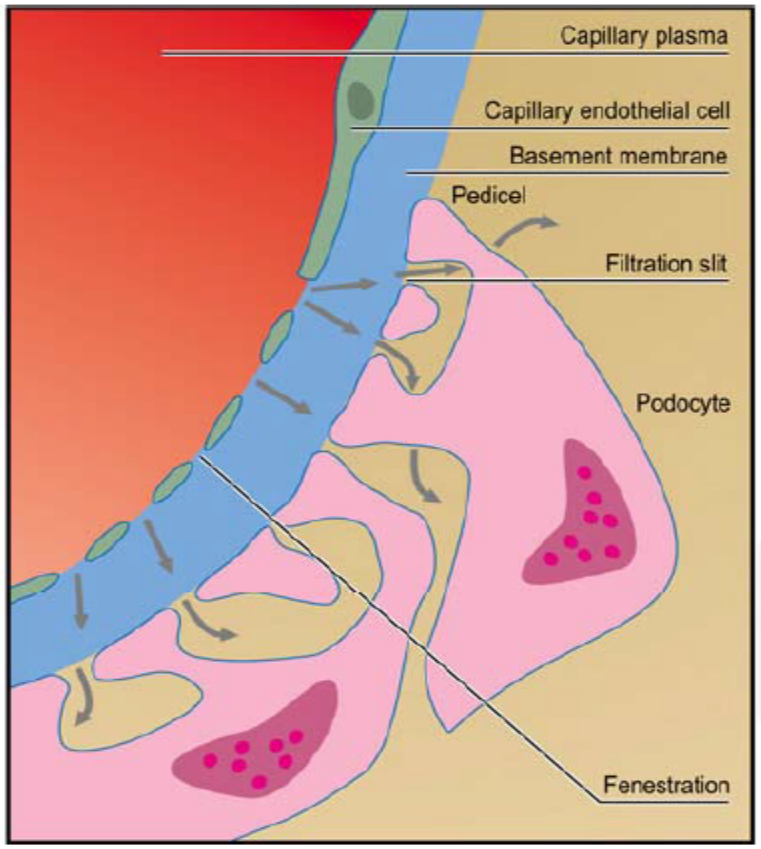
What is Filtered and How?

Glomerular Filtration



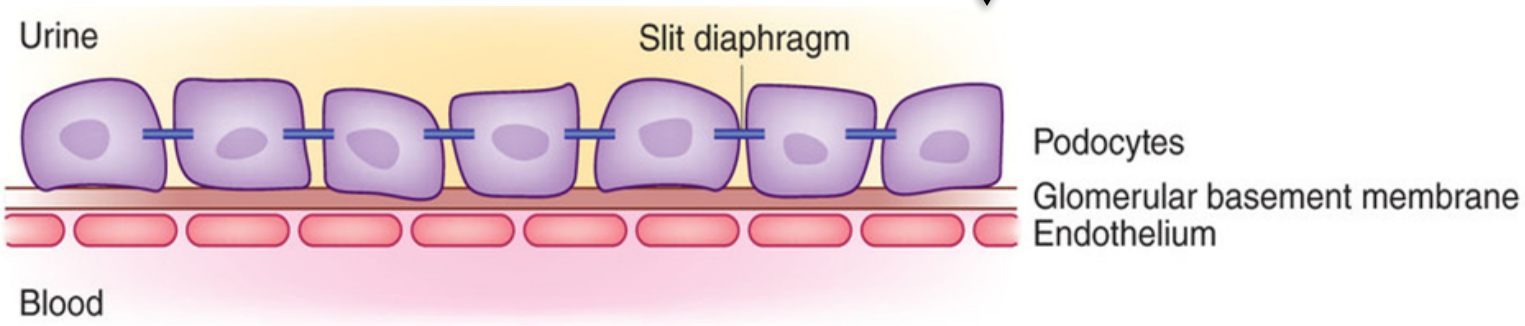
- filter approximately 20% of plasma each time the blood passes through the kidneys
- filter approximately 125 ml of plasma per min
- Or 180 litres of fluid per day
- total circulation volume = 3-5 litres
- 65 times per day on average

The Filtration barrier

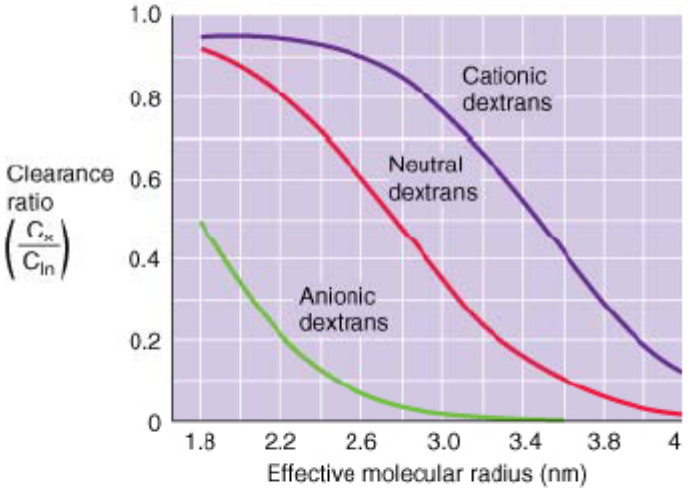


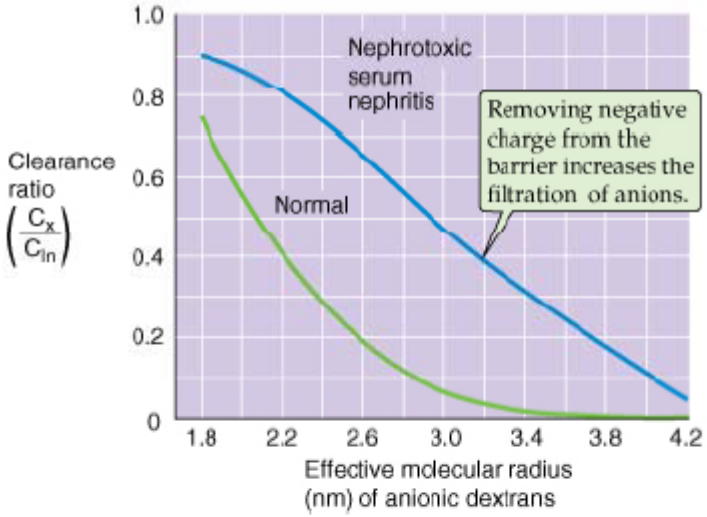
3 layers to pass through …

1. Capillary endothelium permeable
   - Water, salts, glucose
   - Filtrate moves between cells
2. Basement membrane
   - Acellular gelatinous layer of collagen/glycoproteins
   - Permeable to small proteins
   - Glycoproteins repel protein movement صد
3. Podocyte layer
   - Pseudopodia interdigitate forms filtrations slits



Effect of charge on filtration

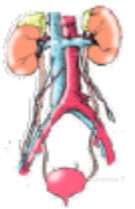




In many disease processes the negative charge on the filtration barrier is lost so that proteins are more readily filtered - a condition called **proteinuria**

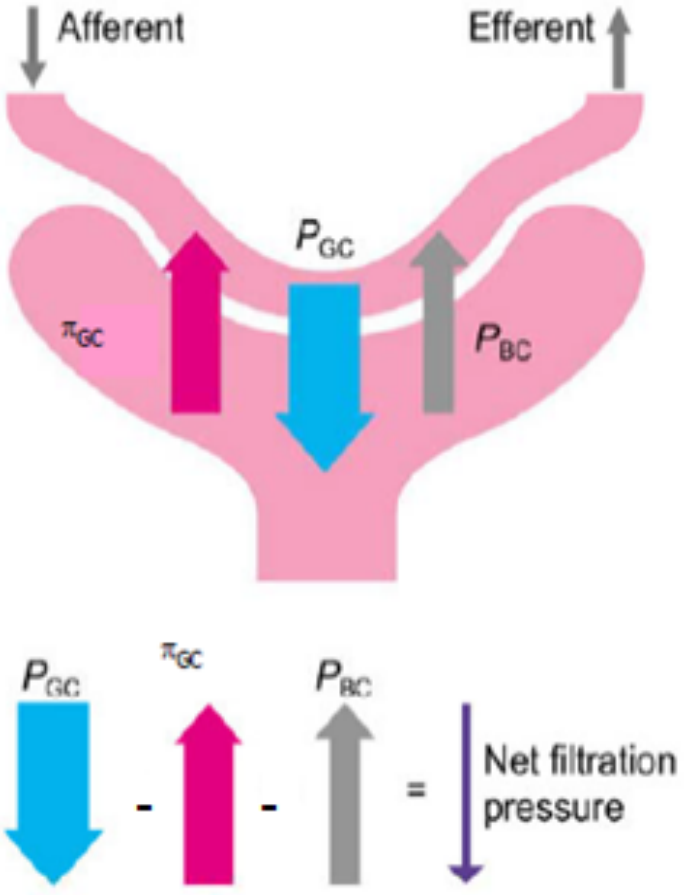
The result of all that filtering!

Substance	Plasma and ultra-filtrate
Glucose mg/d/l	100
Na^+ mmol/l	140
Urea mg/d/l	15
Creatinine mg/d/l	1



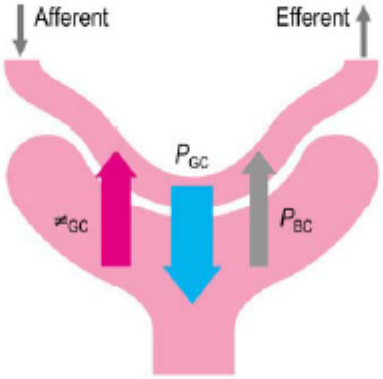
What forces plasma through the barrier?

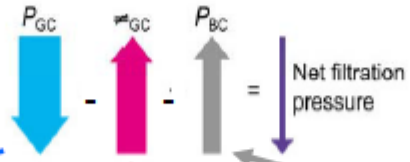
Plasma Filtration



- Physical forces are the only forces involved in the filtering of plasma form tubular fluid
- There are three forces involved
  1. Hydrostatic pressure in the capillary – regulated (P_{GC})
  2. Hydrostatic pressure in the Bowman's capsule (P_{BC})
  3. Osmotic pressure difference between the capillary and tubular lumen (π_{GC})

Plasma Filtration





net filtration pressure

A – (B+C)
55-(30+15)

=
10mmHg

A	B	C
hydrostatic pressure in plasma	hydrostatic pressure in tubule	osmotic pressure in glomerulus
Favours filtration	Opposes filtration	Opposes filtration
55mmHg	30mmHg	15mmHg

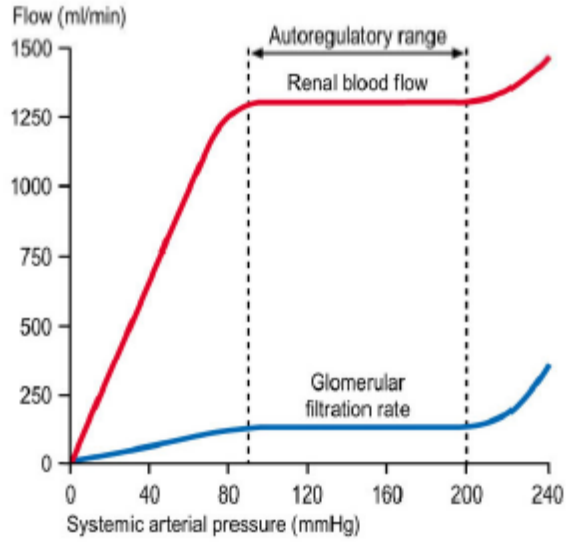
Regulation of GFR

Extrinsic

Intrinsic

((autoregulation

Autoregulation- myogenic



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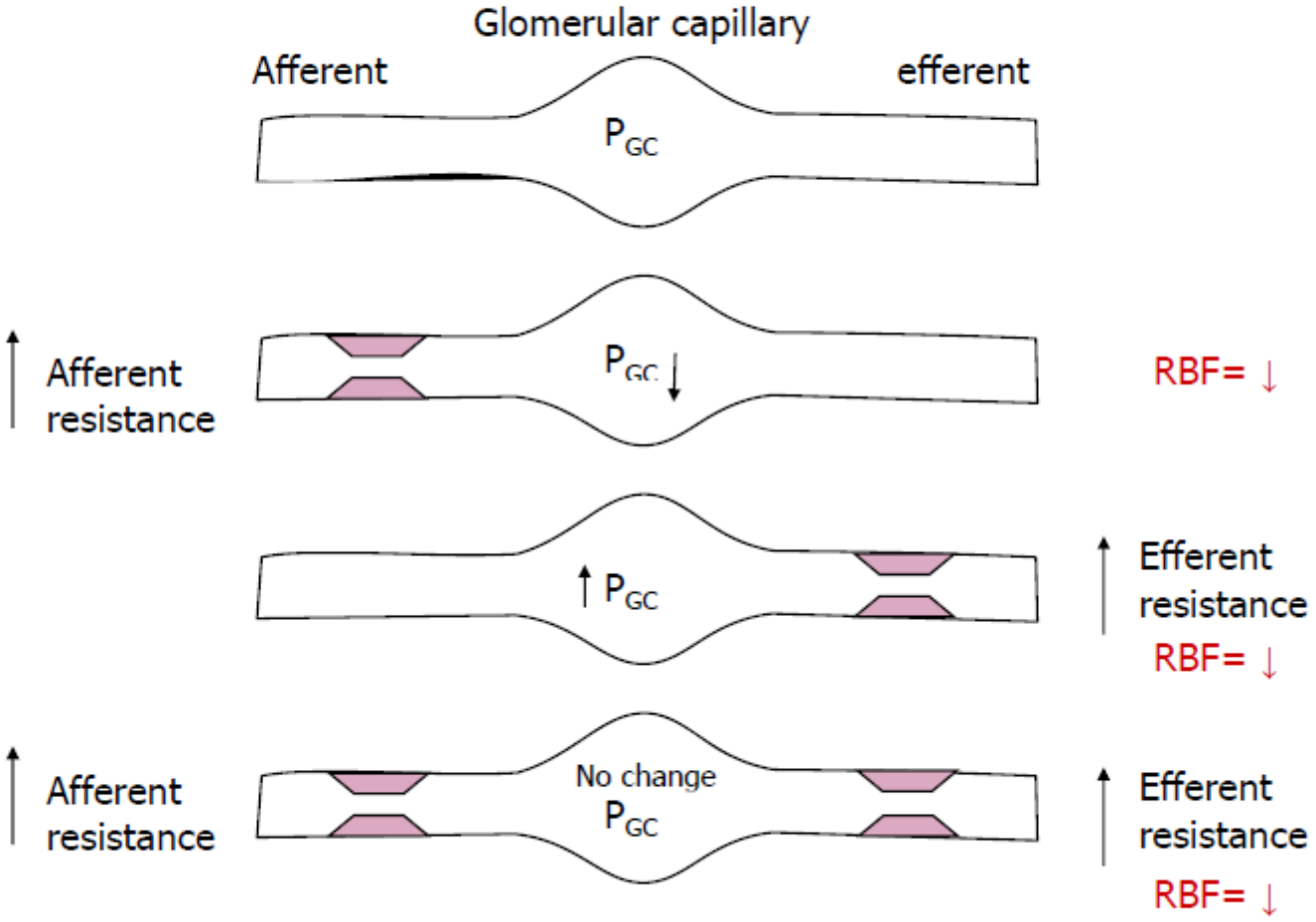
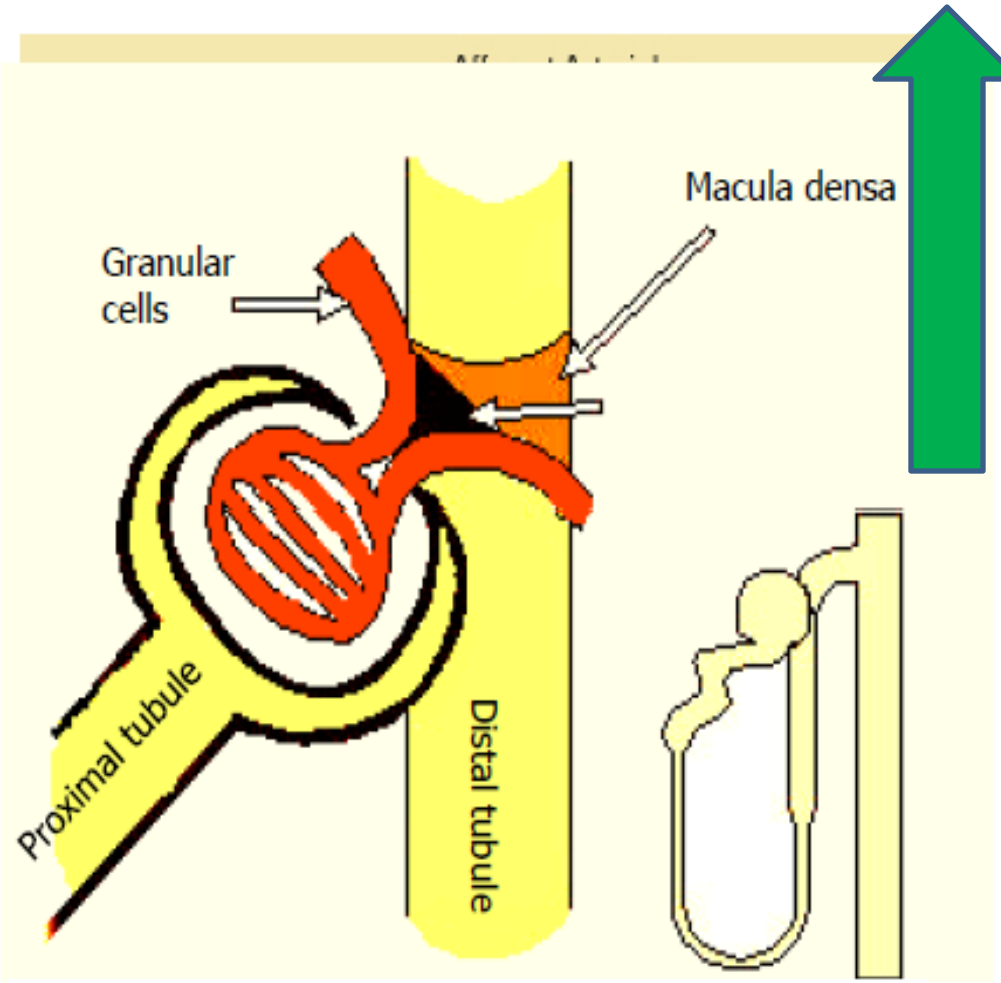
Auto-regulatory mechanisms keep GFR within normal limits

- Autoregulation of the afferent arterioles
- ↑ bp → afferent arteriole constriction
- ⇒ GFR is unchanged
- ↓ bp → afferent arteriole dilatation
- ⇒ GFR is unchanged
- Autoregulation is able to maintain GFR when blood pressure is within physiological limits (80-180 mmHg)

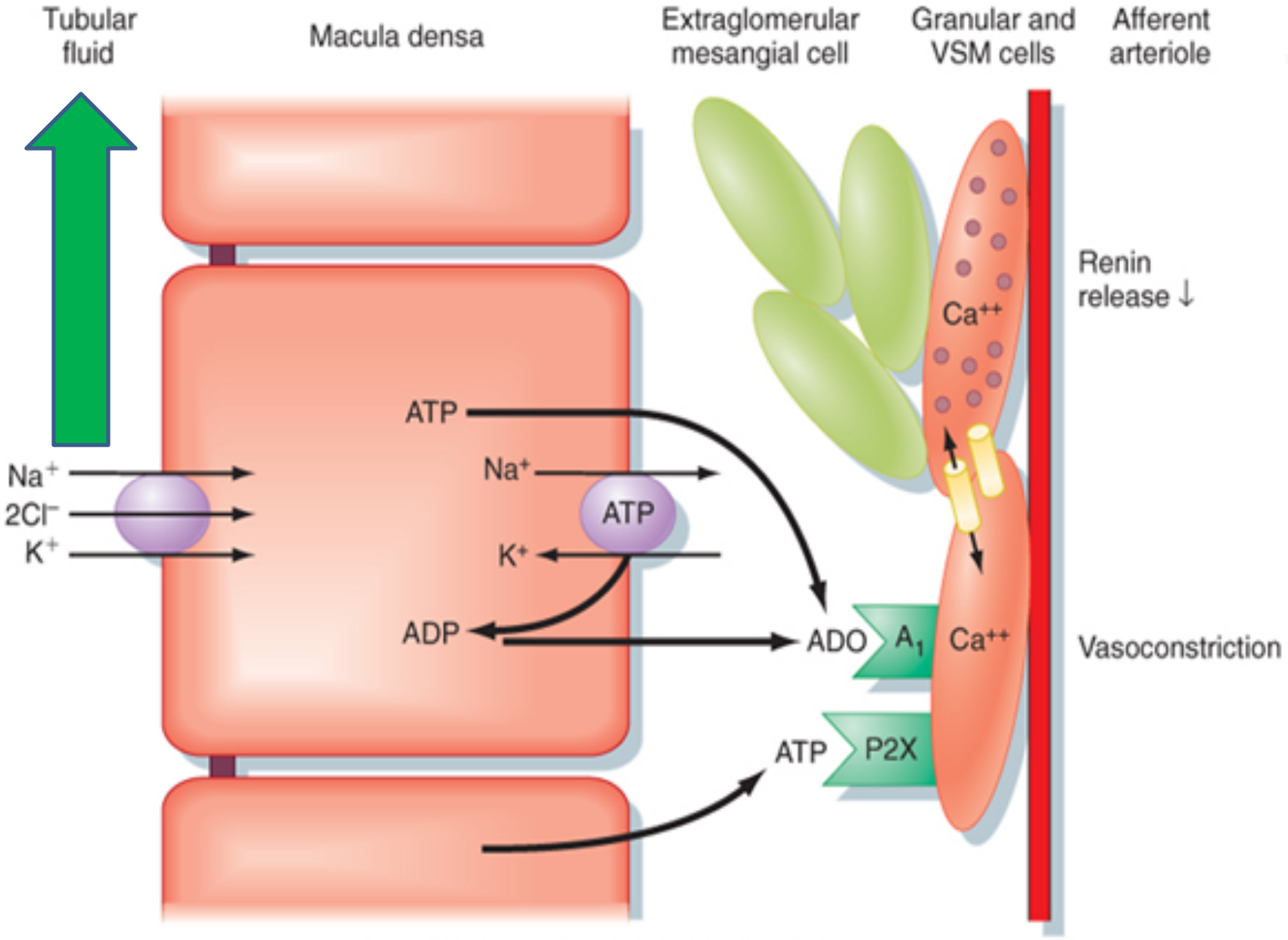
Afferent or efferent constriction

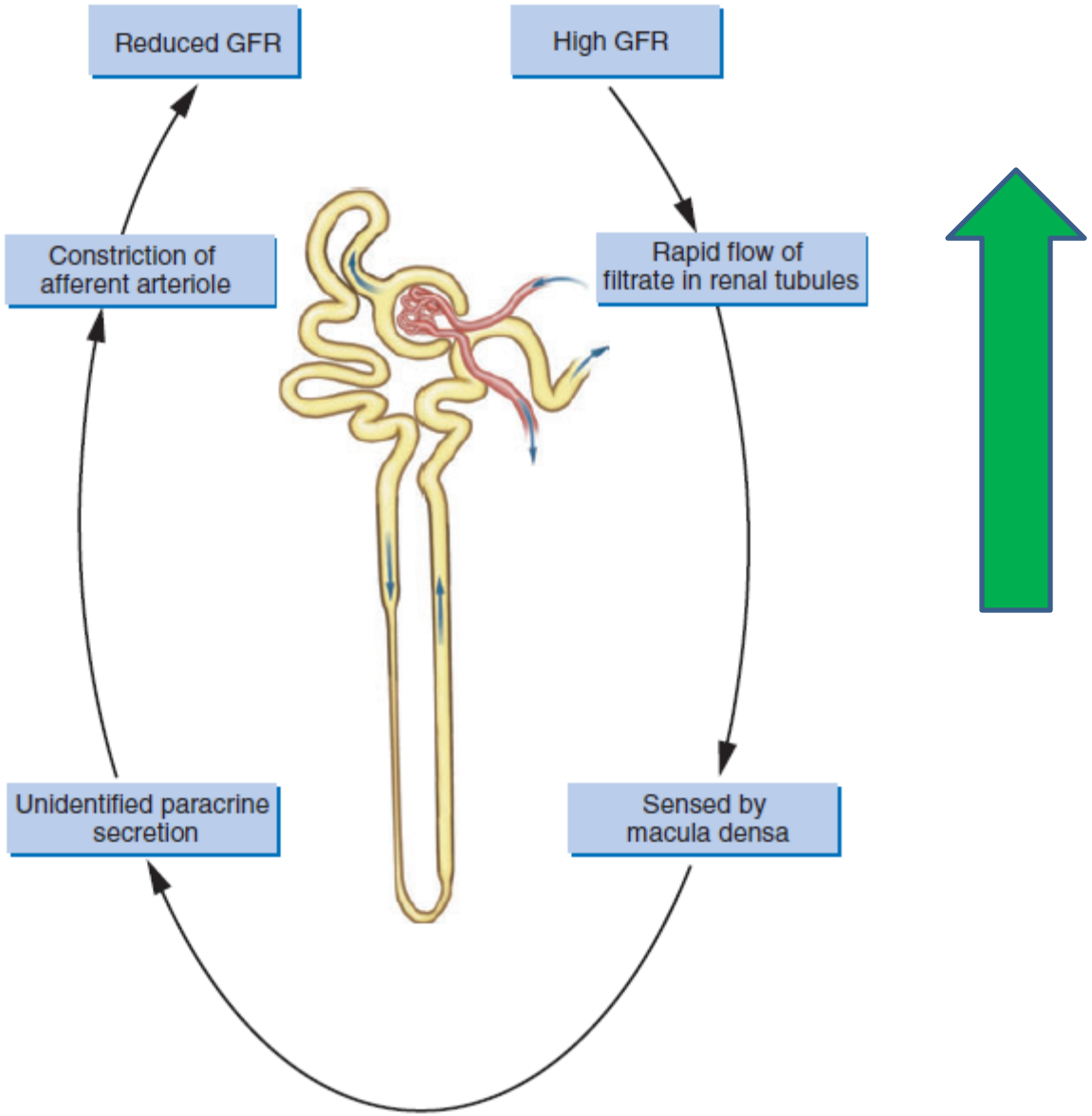


Autoregulation-TG feedback

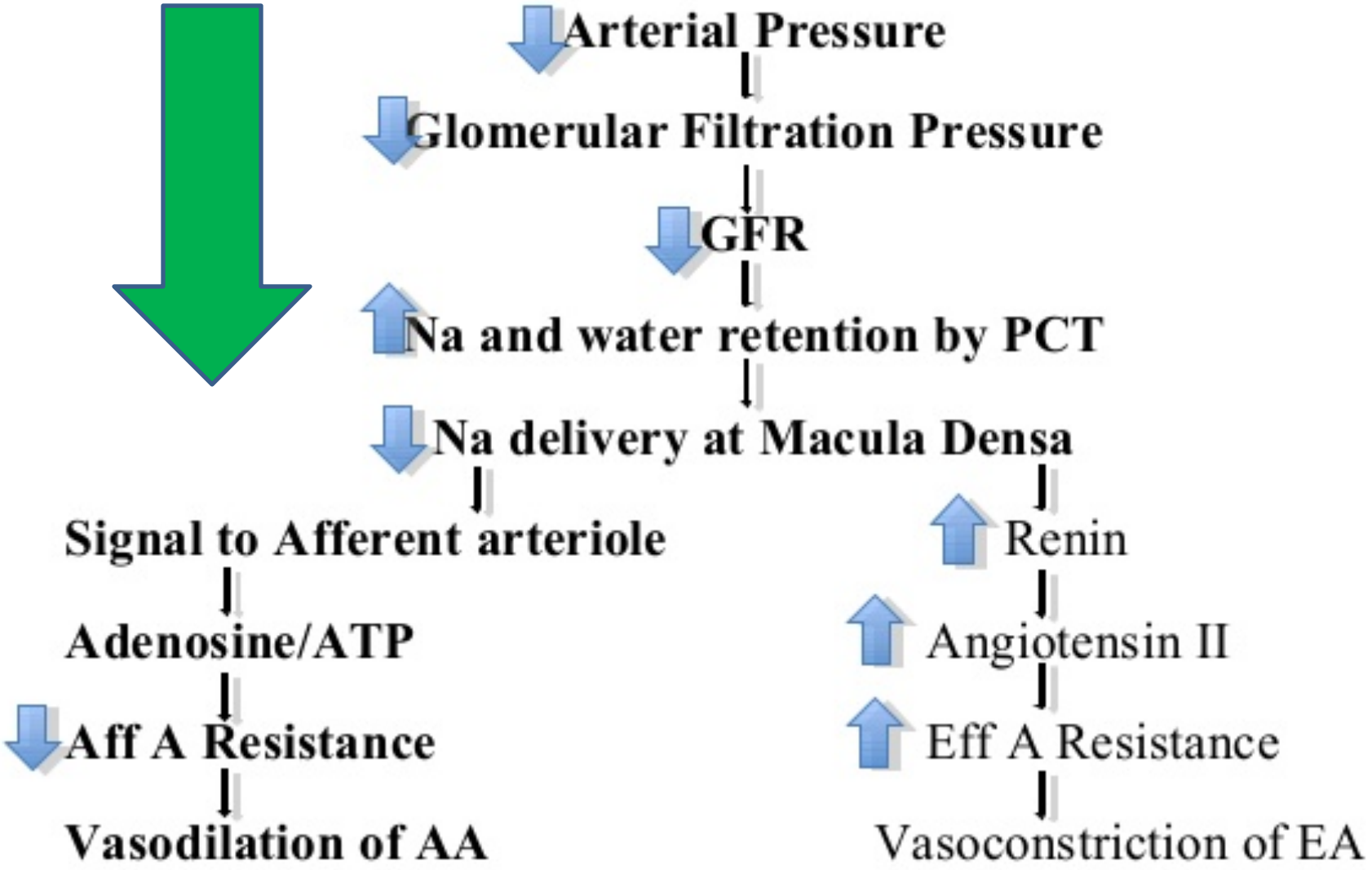


- ↑ In arterial pressure = ↑glomerular capillary pressure ↑RPF and ∴↑GFR
- ↑GFR leads to ↑[Na] and [Cl] in DT
- Resulting depolarization allows Ca^{2+} entry into MD ➔smooth muscle contraction
- ↓ **Renin secretion**


Tubular fluid
Macula densa
Extraglomerular mesangial cell
Granular and VSM cells
Afferent arteriole
Renin release ↓
Ca++
ATP
Na+
2Cl−
K+
Na+
ATP
K+
ADP
ADO
A1
Ca++
Vasoconstriction
ATP
P2X

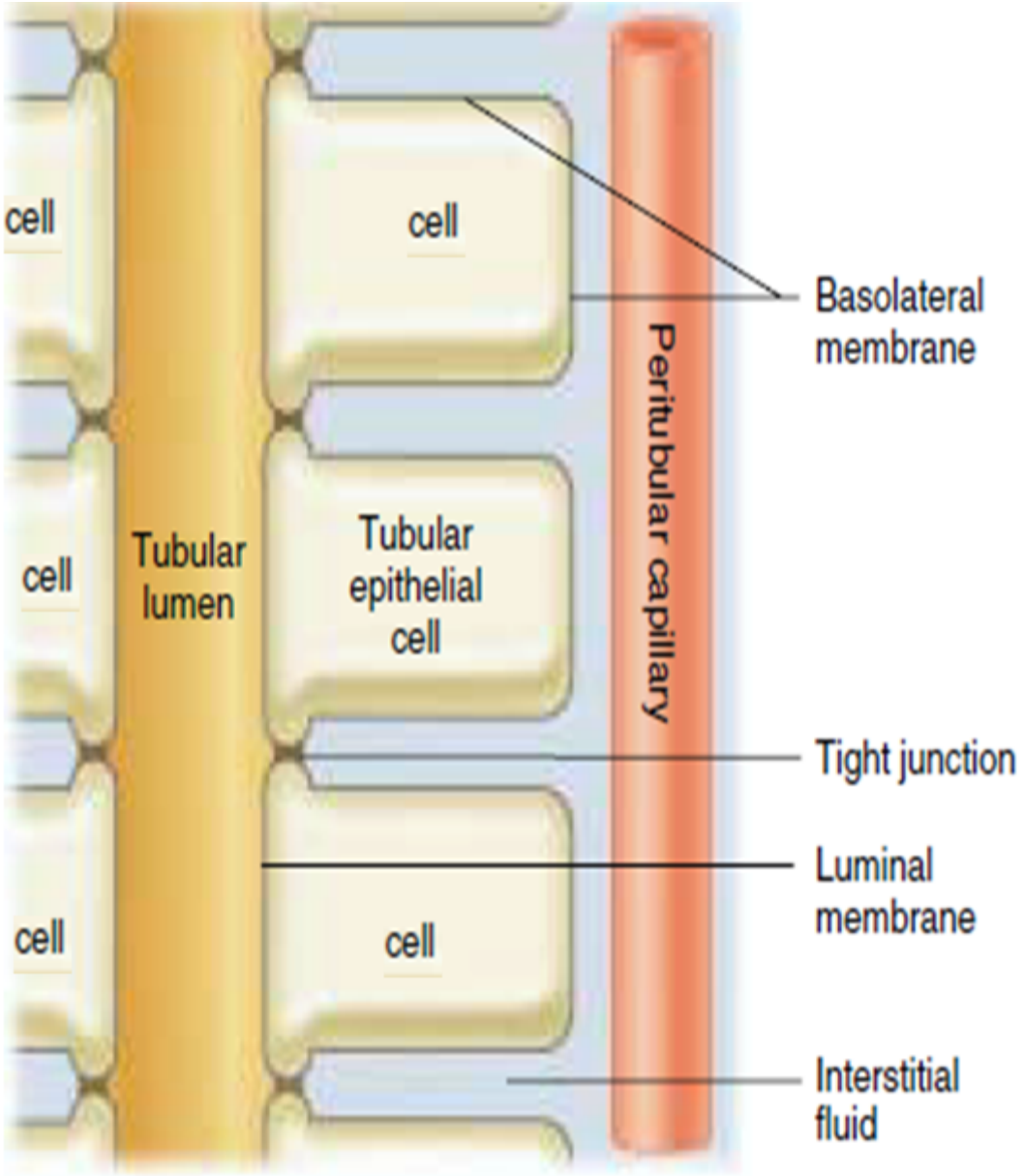

Reduced GFR
High GFR
Constriction of afferent arteriole
Rapid flow of filtrate in renal tubules
Unidentified paracrine secretion
Sensed by macula densa

Tubuloglomerular feedback continued.

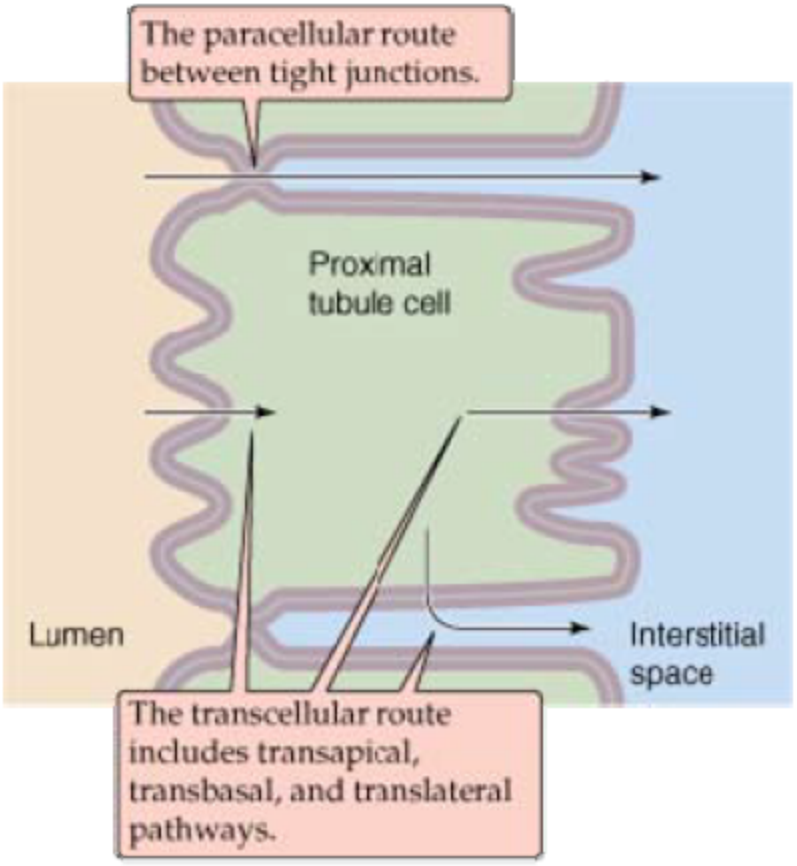


Tubular

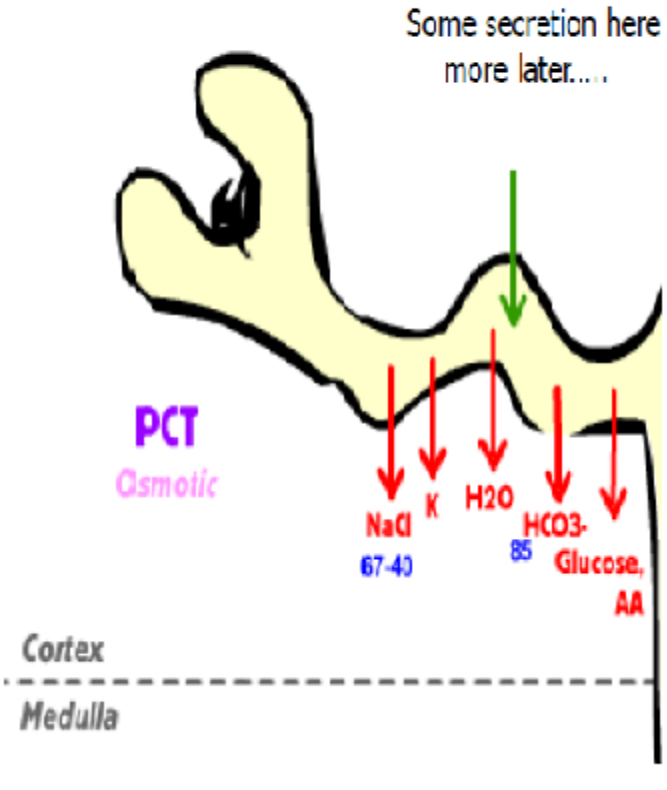
Re

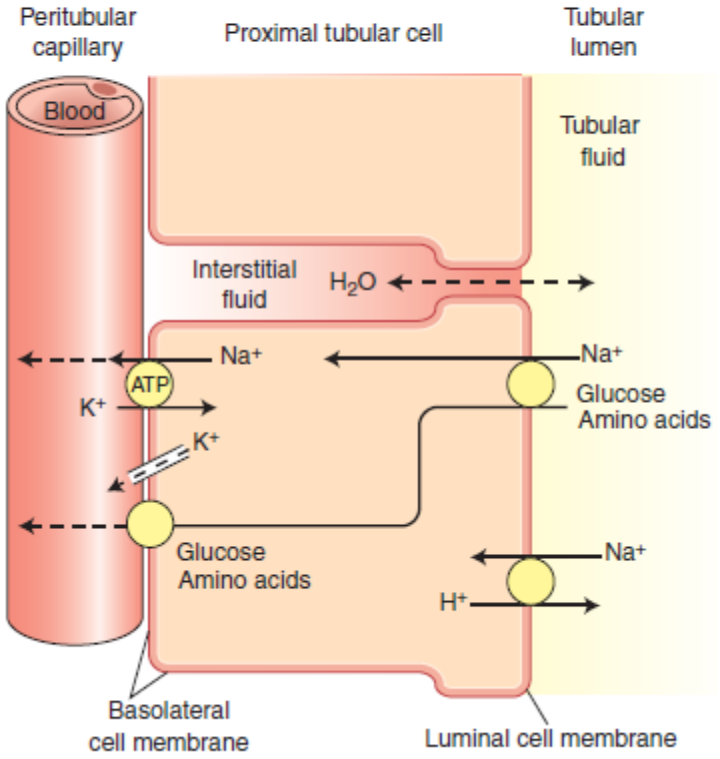

cell
cell
cell
cell
Tubular lumen
Tubular epithelial cell
Peritubular capillary
Basolateral membrane
Tight junction
Luminal membrane
Interstitial fluid

Paracellular and transcellular

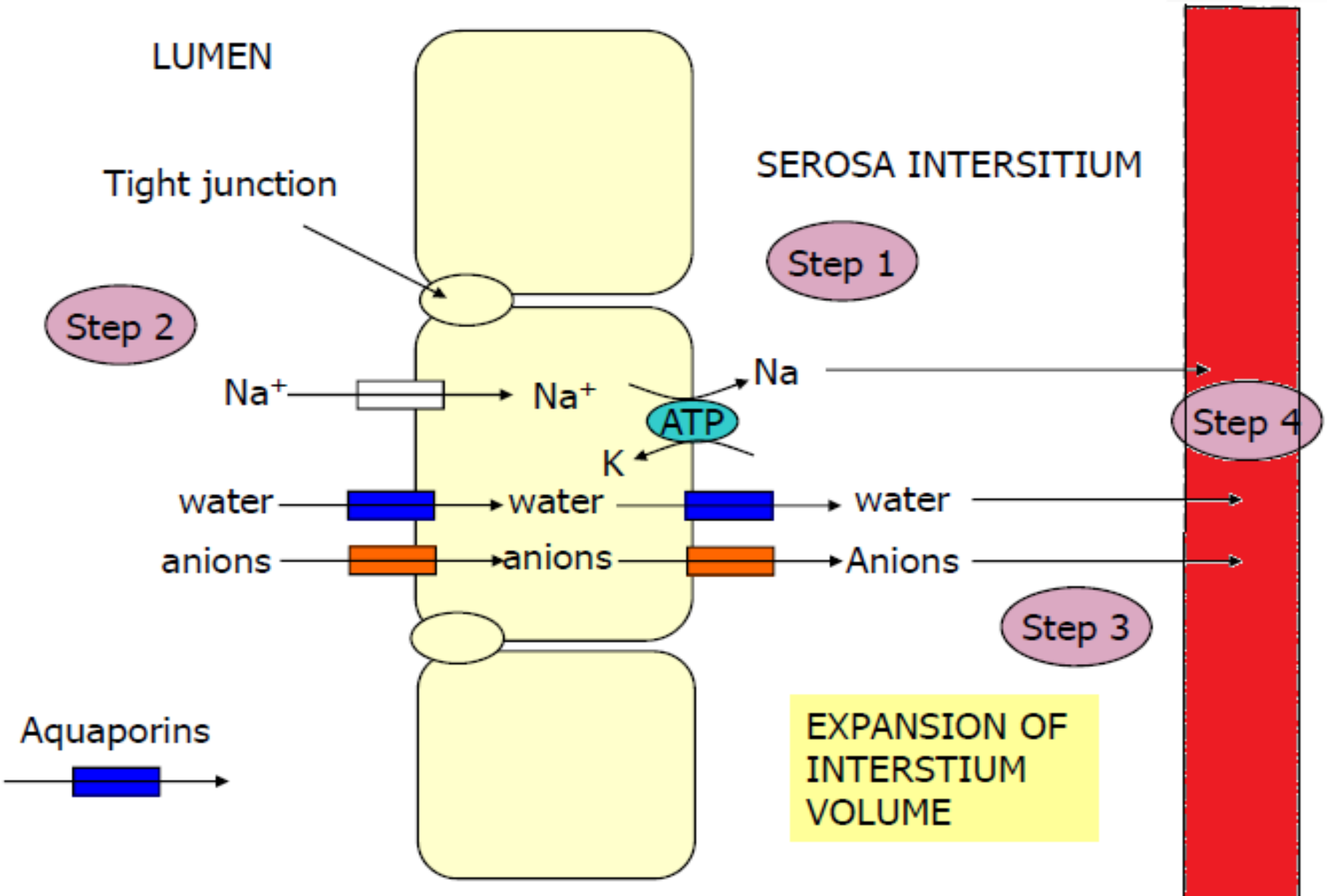


Proximal tubule

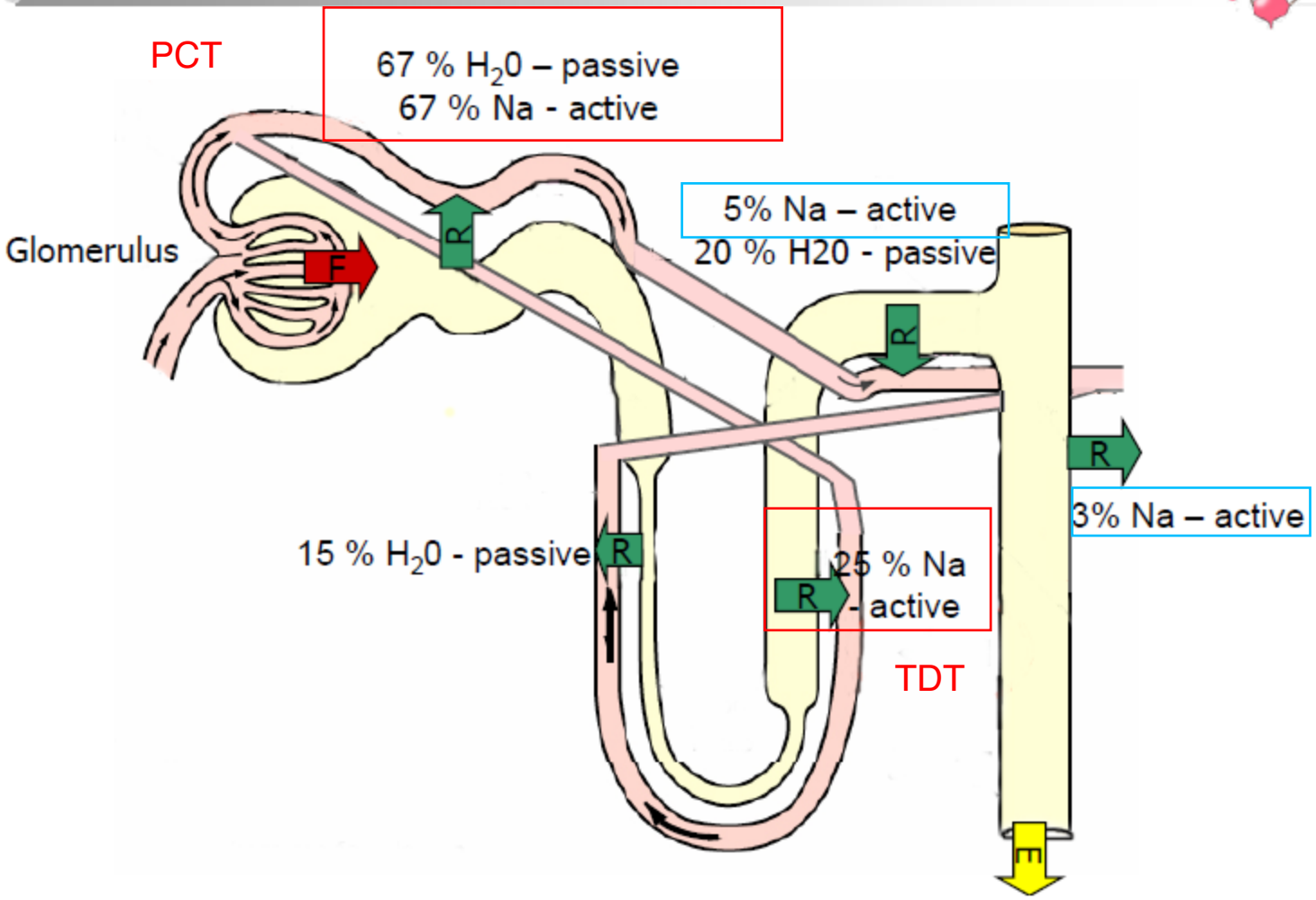




Sodium Sodium reabsorption is the key to everything else,because it creates an osmotic and electrical gradient that drives the reabsorption of water and the other .solutes

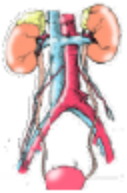


Tubular reabsorption (Na & H_20)

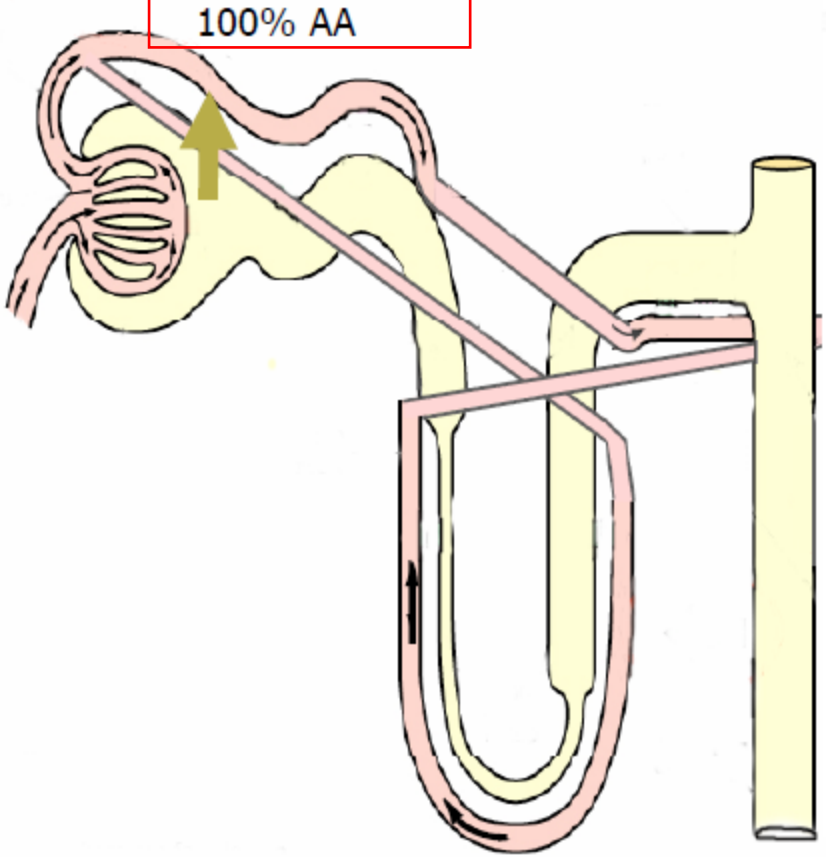


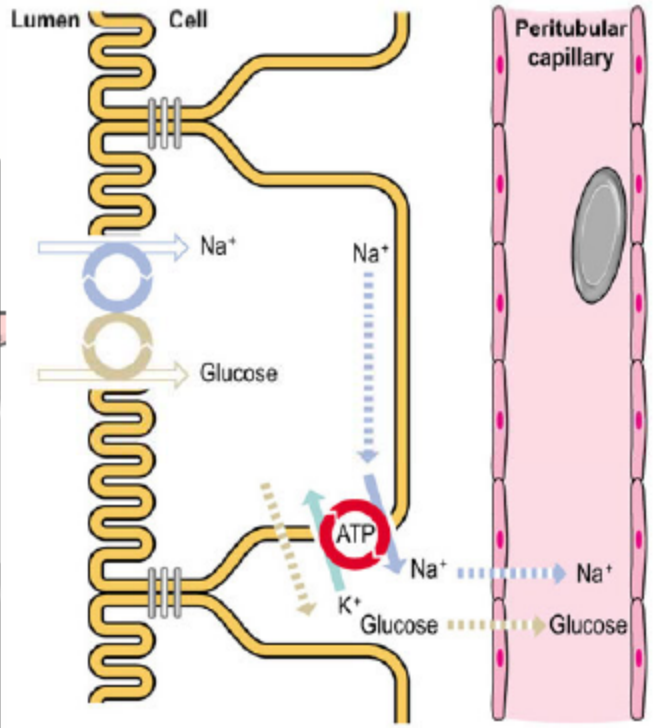
-For drugs

Organic substances



100% Glucose
100% AA





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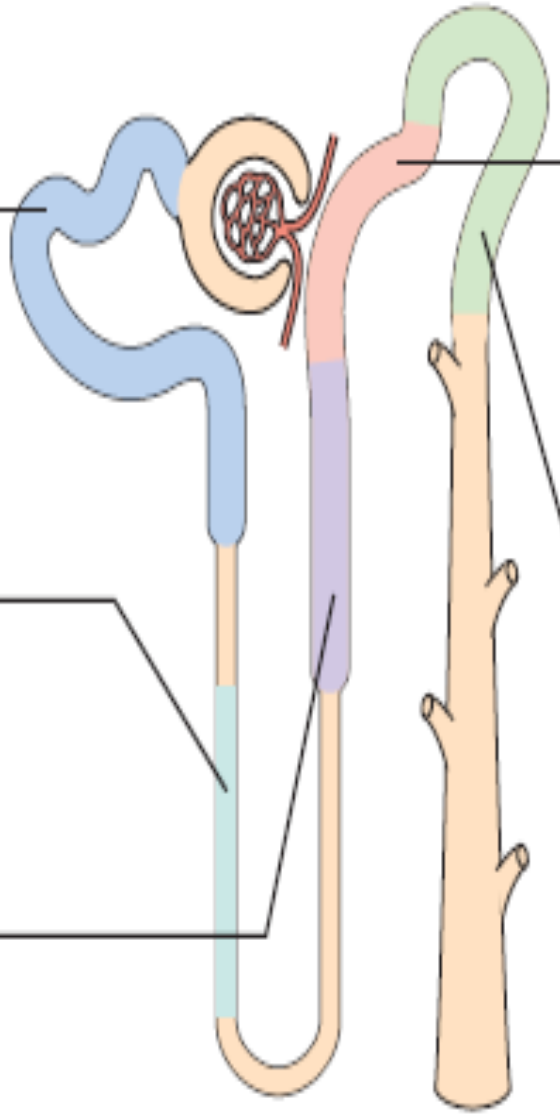
Summary reabsorption

- All plasma constituents are at the same concentration in the glomerular filtrate as in the plasma
- Reabsorption is highly selective 2 step process [lumen ➔interstitium ➔peritubular capillary]
- Movement can be transcellular or paracellular but transport occurs primarily though cells unlike glomerular filtration
- Channels and transporters promote trans-membrane flux of solute that can not pass through lipid bi-layer this is energy dependent
- Reabsorption of solute and water is linked to active Na reabsorption.
- Water and solute reabsorbed into interstitium is driven into capillary by starling forces.



Proximal tubule
- *Reabsorption:* Na^+, Cl^-, HCO_3^-, K^+, H_2O, glucose, amino acids
- *Secretion:* H^+, organic acids and bases

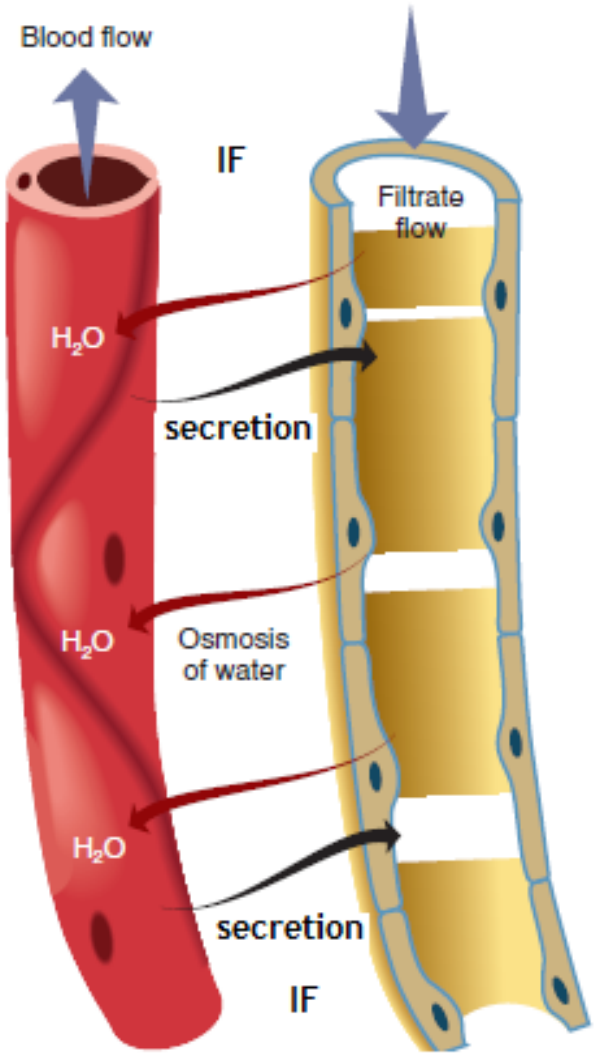
Thin descending loop of Henle
- *Reabsorption:* H_2O

Thick ascending loop of Henle
- *Reabsorption:* Na^+, Cl^-, K^+, Ca^{++}, HCO_3^-, Mg^{++}
- *Secretion:* H^+

Early distal tubule
- *Reabsorption:* Na^+, Cl^-, Ca^{++}, Mg^{++}

Late distal tubule and collecting duct
- **Principal cells**
  Reabsorption: Na^+Cl^-
  Secretion: K^+;
  ADH-mediated H_2O reabsorption
- **Intercalated cells**
  Reabsorption: HCO_3^-, K^+
  Secretion: H^+

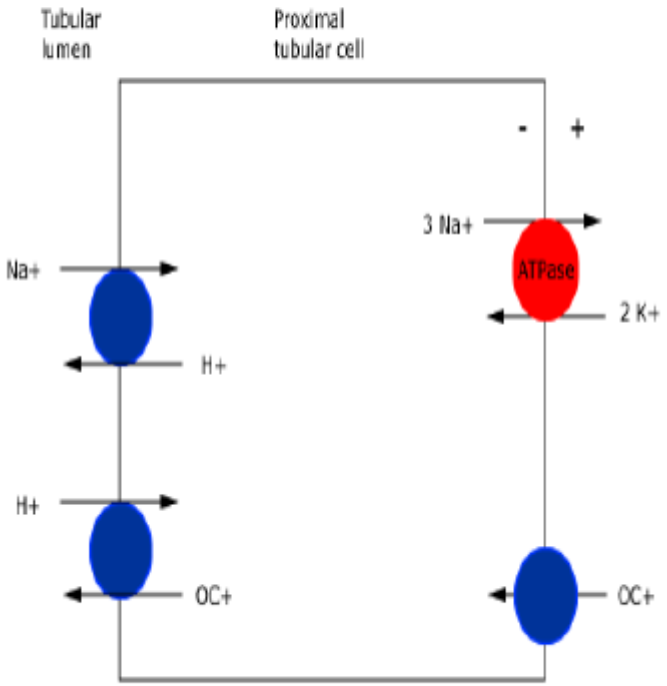
Tubular Secretion



Tubular Secretion

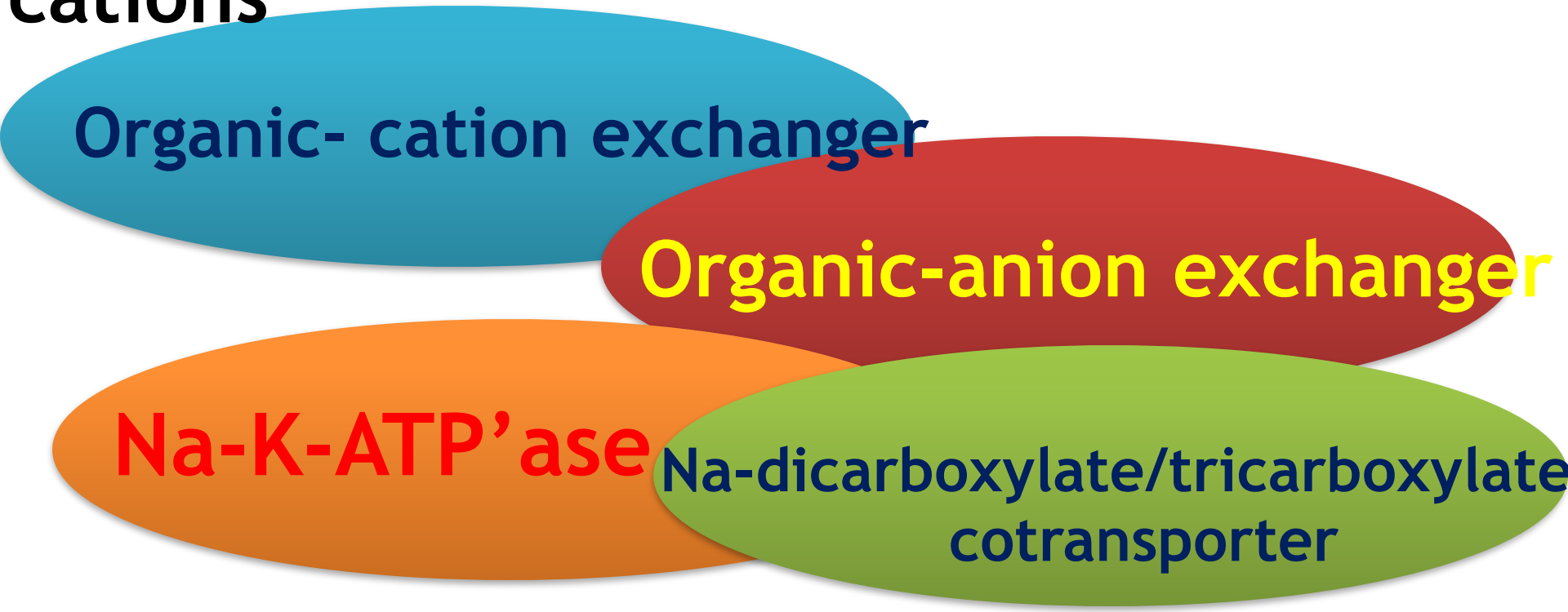
- Like tubular reabsorption, tubular secretion involves transepithelial transport mechanisms
- This provides a second route of entry for solutes that need to be secreted into the tubular fluid
- This is useful since only 20% of the plasma is filtered each time blood passes through the kidney
- Substances secreted into the tubular fluid are:
  - Protons (H^+)
  - Potassium (K^+)
  - Organic anions and cations

Organic cation secretion



- Model for organic cation (OC+) secretion in the proximal tubule.
- Entry by passive carrier- mediated diffusion across the basolateral membrane down favourable concentration and electrical gradients created by the Na-K-ATPase pump.
- Secretion into the lumen occurs by a H+-OC+ exchanger that is driven by the H+ gradient created by the Na+-H+ antiporter.

The four major carrier proteins involved in the secretion of organic anions and cations



Summary organic secretion

- several organic cation transporters analogous to organic anion transporters
- Cations compete with each other for transport this adds a T_m limitation
- Cations enter the basolateral by one of several OCT (uniporters) and leave apical membrane into lumen via antiporter which exchanges H^+ for organic cation

Cations		Anions	
Endogenous	Drugs	Endogenous	Drugs
ACH	sulfonamides	urate	penicillin
dopamine	Morphine	bile salts	salicylate
adrenaline	Atropine	fatty acids	NAS
histamine	Isoproterenol		
serotonin			

Clearance

Of ceratinine , urea , uric acid

Clearance is defined as the volume of plasma rendered free of a given substance in 1 minute. **Clearance is calculated as the ratio of urinary excretion rate to plasma concentration.**

$$C_P = (U_p \times V) \div P_p$$

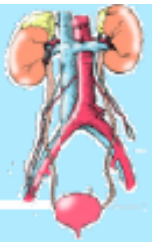
C_P = Renal clearance of solute P

U_P = Urine concentration of solute P

V = Urine flow rate

P_p = Plasma concentration of solute P

Clearance rate



- P is an imaginary compound but a real "P" would be inulin.

$$\text{Clearance rate } (\text{ml.min}^{-1}) = \frac{\text{Urine concentration of substance} \times \text{Urine flow rate } (\text{ml.min}^{-1})}{\text{Plasma concentration of the substance}}$$

$$125 \ (\text{ml.min}^{-1}) = \frac{125\text{mg/ml} \times 1\text{ml.min}^{-1}}{1\text{mg/ml}}$$

- If a compound behaves like "P" then it is completely cleared from the plasma that is filtered ∴the rate it appears in urine = GFR

Flow of plasma in the kidney

Every min 625ml of plasma goes to the kidney- renal plasma flow

(500ml not filtered)

(125ml filtered = GFR)

Fluid in plasma

500ml initially enters the peritubular capillaries

Fluid in urine

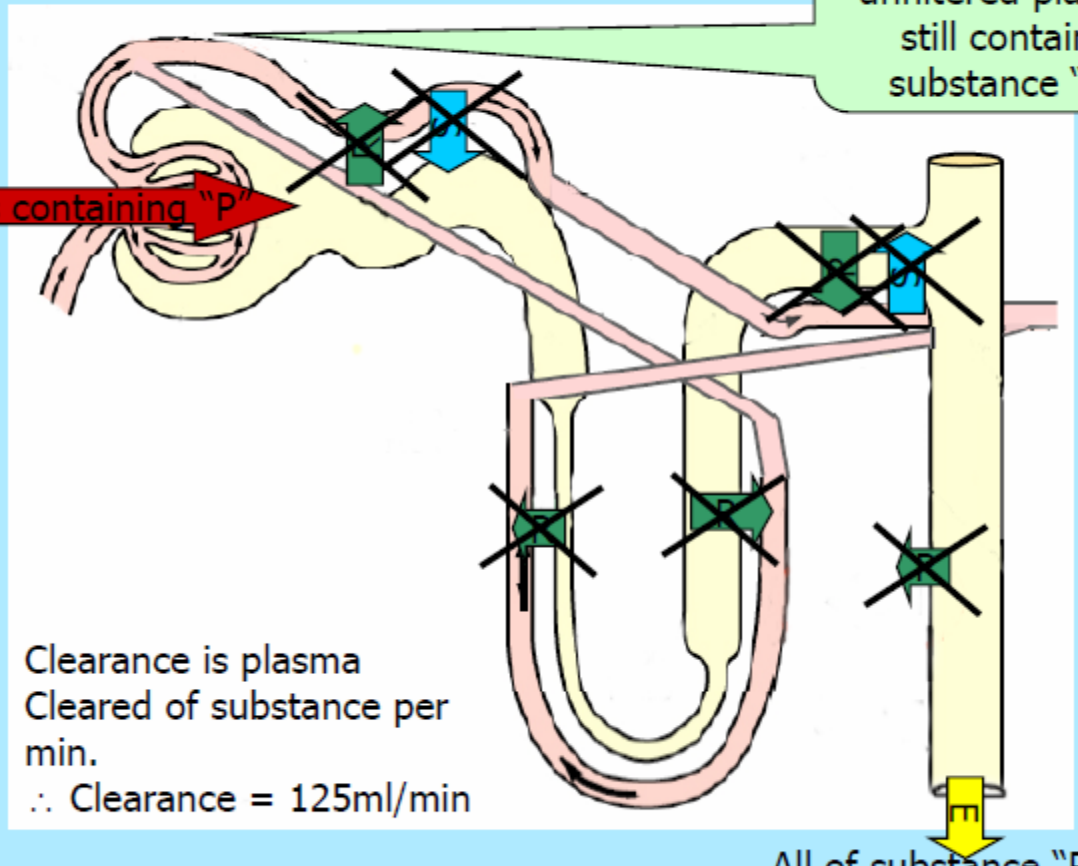
1. Anything filtered and not reabsorbed
2. Any thing not filtered but secreted

Composition of filtrate in the bowman's capsule is IDENTICAL to plasma (- large proteins)

Plasma Clearance

500mls of unfiltered plasma still contains substance "P"

125mls containing "P"



Clearance is plasma Cleared of substance per min.

∴ Clearance = 125ml/min

All of substance "P" In the 125ml filtrate ends up in urine

• *Using clearance to estimate GFR*

GFR = important of know renal function

- **Estimates of GFR are used clinically as an index of renal function and to assess the severity and the course of renal disease. A fall in GFR means the disease is progressing, where an increase in GFR suggests a recovery. One of the important methods used to determine GFR is using the concept of clearance.**

Clinically why do you need to know what the GFR's is?

- severity of renal disease , and to know patient need kidney transplantation or not
- function of renal

Fate of substances filtered

	% reabsorbed	% excreted
Water	99	1
Sodium	99.5	0.5
Glucose	100	0
Urea	50	50
Phenol	0	100

Does everything behave like inulin?

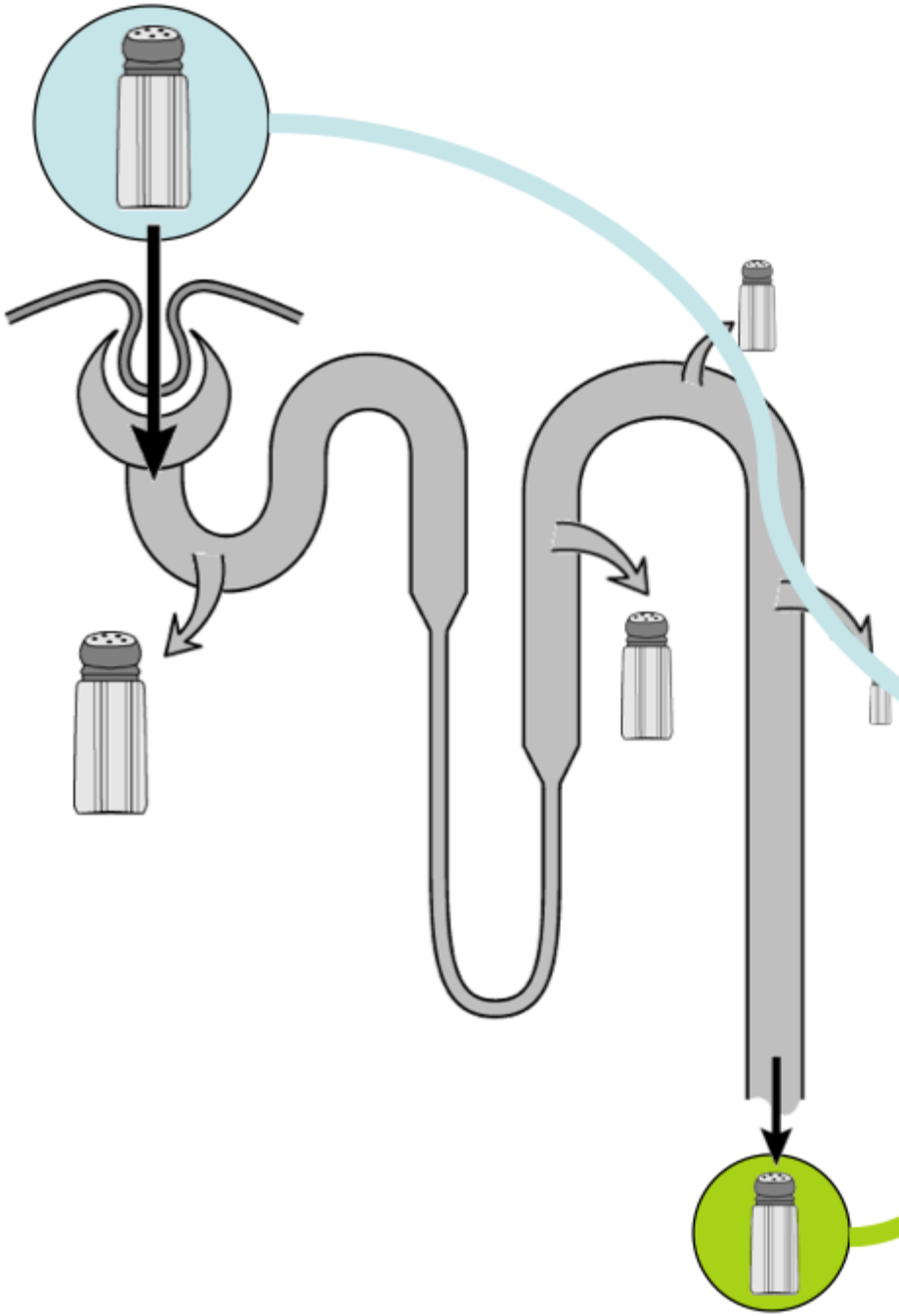
Normal clearance values (ml/min)		
Inulin	125	Not reabsorbed not secreted
Glucose		
PAH		

Clearance of PAH is ∴ = to renal plasma flow

(Fractional excretion (FE expresses solute excretion as a .percentage of its filtered load

$$FE_{Na} = (U_{Na} * P_{cr}) / (U_{cr} * P_{Na}) * 100$$

Calculating the fractional sodium excretion (FENa) can be useful in the setting of acute renal failure ((ARF



Fractional excret
of sodium:

Excreted N

Filtered Na

Assessing the patient with acute renal failure – Laboratory analysis

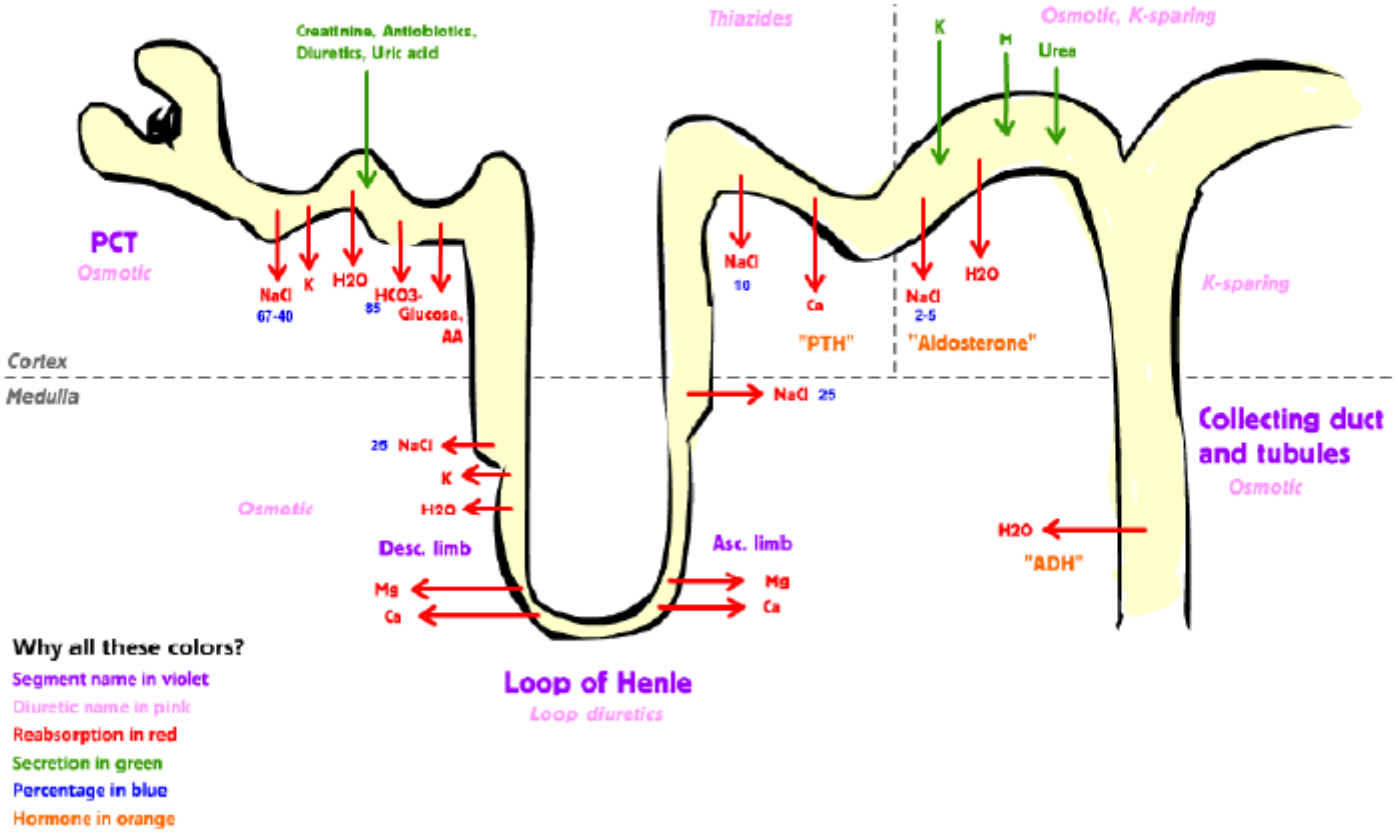
- Fractional excretion of sodium:

$$FE_{Na} = \frac{(Urine_{Na+} \times Plasma_{Creatinine})}{(Plasma_{Na+} \times Urine_{Creatinine})} \times 100$$

It is the Simple measurement of Tubular Excretory function

- $FE_{Na} < 1\%$ → **Prerenal**
- $FE_{Na} > 2\%$ → Epithelial tubular injury (**acute tubular necrosis**), obstructive uropathy
- *If patient receiving diuretics, can check FE of urea.*

Summary



Why all these colors?

Segment name in violet

Diuretic name in pink

Reabsorption in red

Secretion in green

Percentage in blue

Hormone in orange

Normal ranges	
Serum biochemistry	
Sodium	136 – 145 mmol/l
Potassium	3.5 - 5.0 mmol/l
Bicarbonate	21 – 30 mmol/l
Urea	3.6 - 7.1 mmol/l
Creatinine	50 -120 mmol/l
Calcium	2.1 - 2.5 mmol/l
pH	7.38 - 7.42

Urinary V plasma

Substance	Concentration		
	Urine	Plasma	U/P ratio
Glucose mg/d/l	0	100	0
Na^+ mmol/l	90	140	0.6
Urea mg/d/l	900	15	60
Creatinine mg/d/l	150	1	150