PHYSIOLOGY

- SHEET NO.
- WRITER : Mais Fareed
- CORRECTOR :
- DOCTOR :

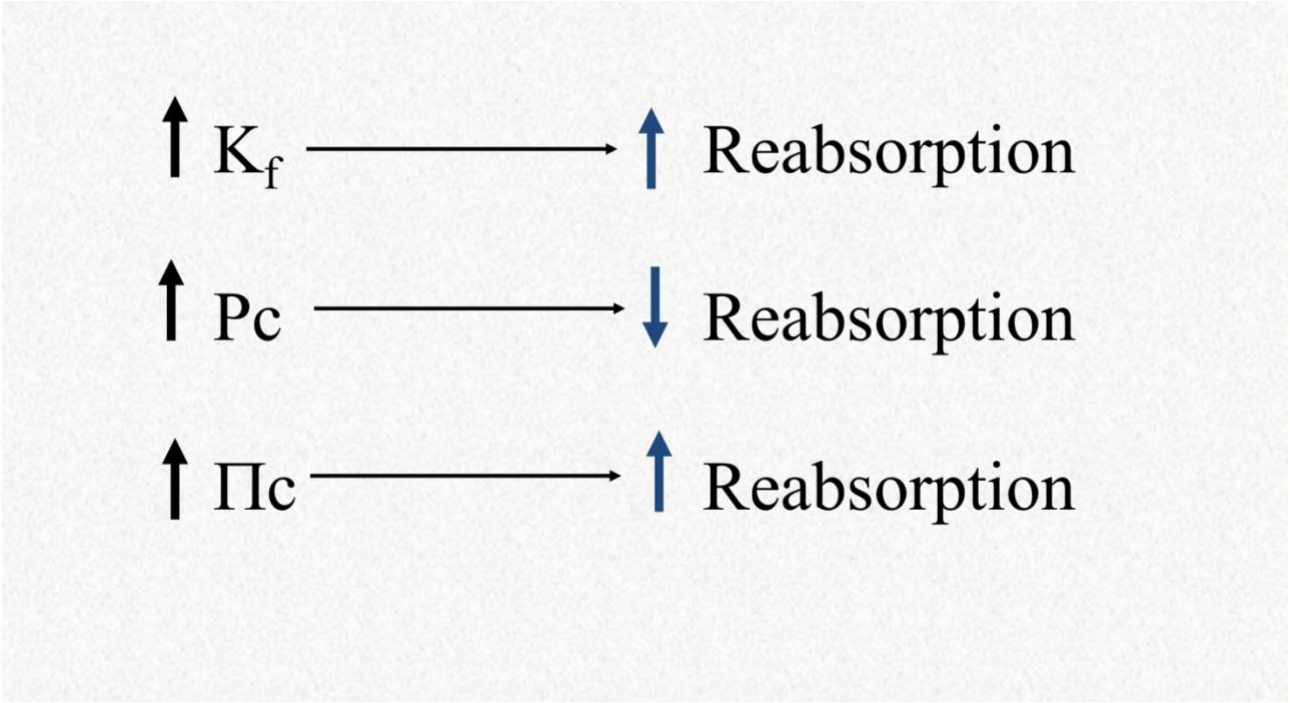
In the previous sheet we start talking about reabsorption forces and rate and how important is the regulation of reabsorption.

Peritubular Capillary Reabsorption

- Reabs (rate) = Net Reabs Pressure (NRP) * Kf = (10 mmHg) * (12.4 ml/min/mmHg) = 124 ml/min
- Reabsorption rate is directly proportional to the NRP and Kf => so as NRP increases the reabsorption increase , Kf is mostly constant (12.4 ml/min/ mmHg) but if it increased for some reasons this could cause increase in reabsorption rate .

❖ Determinants of Peritubular Capillary Reabsorption

1. If Kf increased it will increase reabsorption
2. If Capillary Hydrostatic Pressure (Pc) increased it will decrease reabsorption (according to net reabsorption equation that we've talked about in the previous sheet) because it opposing the reabsorption .
3. If Oncotic Pressur increased (with reabsorption) it will increase reabsorption .



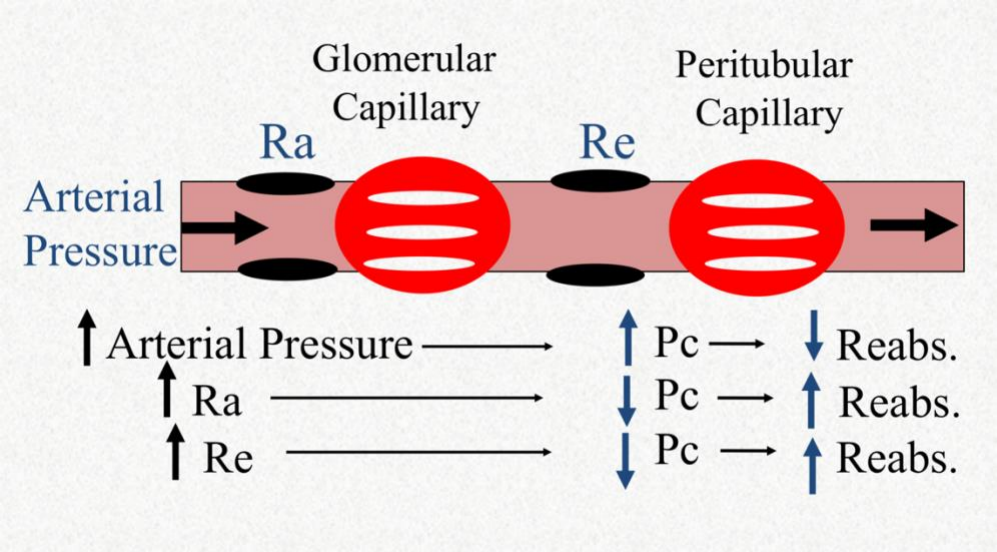
Now let's take a look at the arrangement of the glomerular capillary and Peritubular capillary and changes that can take place to either arterial pressure, afferent resistance or efferent resistance and how these changes may affect the peritubular reabsorption .

Capillary Hydrostatic Pressure:

I. Arterial Pressure => if increased (although with presence of auto regulation) it will increase the glomerular capillary pressure and this will result in increase in peritubular capillary pressure because they are continuous tube arranged in series so reabsorption will decrease.(notice we increased hydrostatic pressure in peritubular capillaries).

II. Afferent Resistance => if we increased it in afferent arteriole the peritubular capillary hydrostatic pressure decreases so it will increase the reabsorption (the opposite) and renal plasma flow will decrease (as a result of increased afferent resistance).

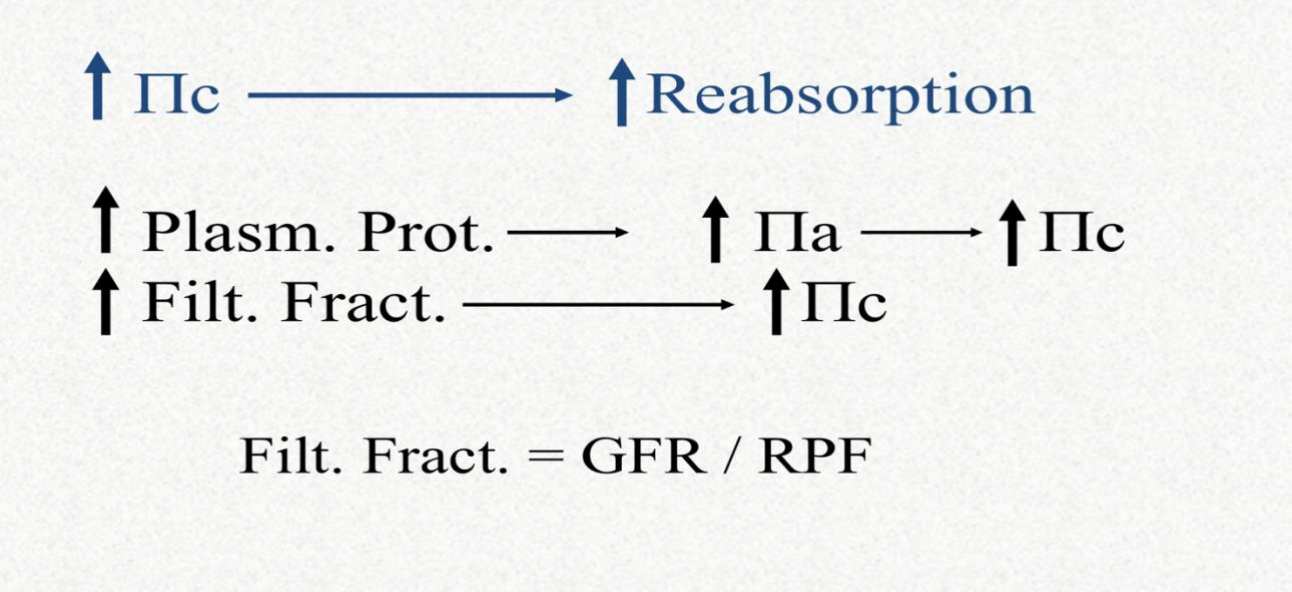
III. Efferent Resistance => if we increased it will also decrease the peritubular capillary hydrostatic pressure and it will increase reabsorption.



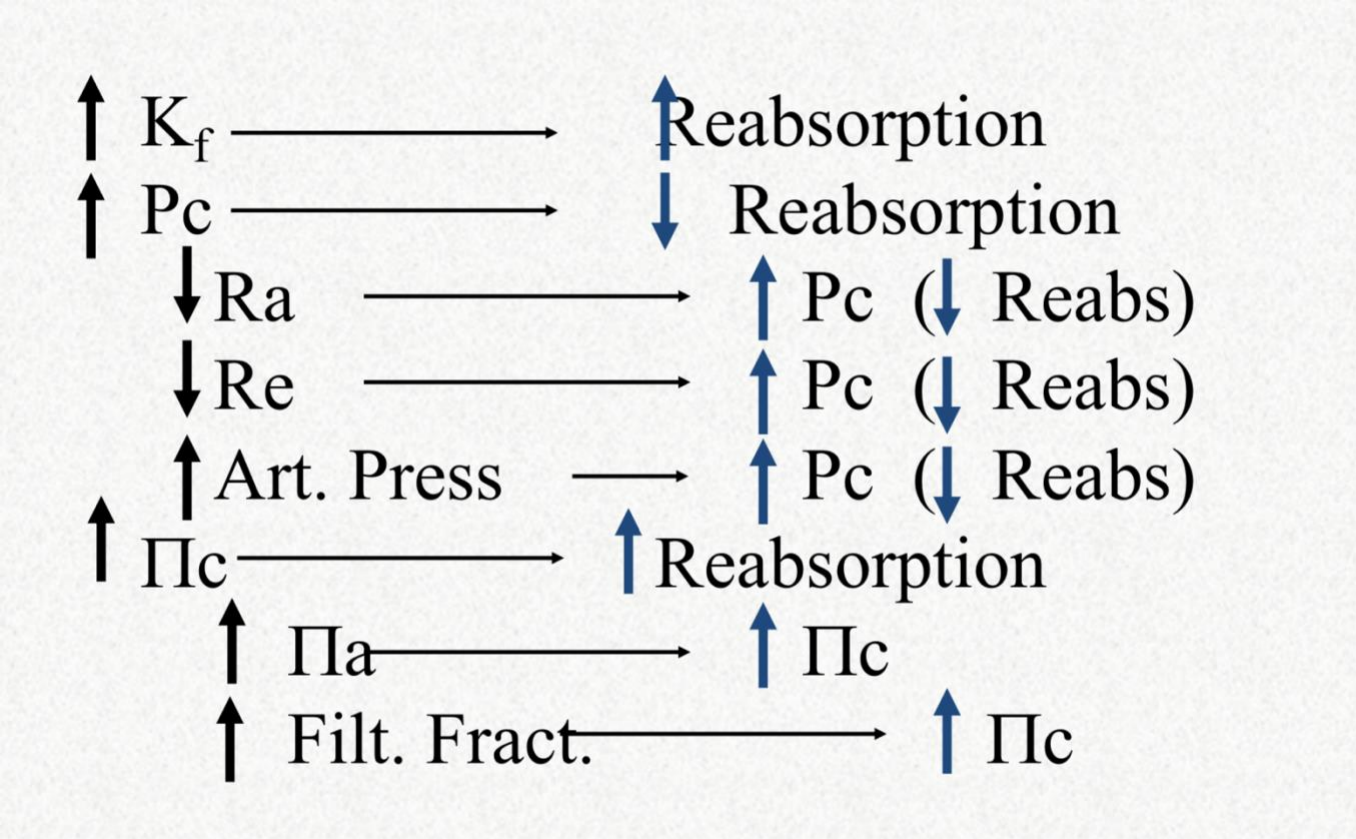
Capillary Colloid Osmotic Pressure:

- If oncotic pressure increased the reabsorption will increase
- Causes of increased oncotic pressure:
    1. Elevated arterial proteins everywhere so result in increasing oncotic pressure.
    2. Increased FF(filtration fraction) .
       FF = GFR/ RPF (so indirectly you can conclude what is the effect of renal plasma flow on reabsorption)=>>

- If we increased RPF the reabsorption will decrease, how? ↑RPF => ↓FF=> ↓oncotic pressure => ↓ reabsorption .
- May the question be (what is the effect of increased GFR on reabsorption?) ↑GFR => ↑FF=> ↑ oncotic pressure => ↑ reabsorption
- We can't change tow things at the same time (GFR and RPF)



Here is summary for what we've talked about: ↓



- So this is actually what really happens that we have reabsorption and bulk flow across the tubule and finally all that substances will enter the renal interstitium and there will undergo re absorption to the peritubular capillaries an these processes are governed by net reabsorption forces (depend completely on them).
- If net re absorption forces are normal (10 mmHg) the process will be smooth and complete reabsorption to peritubular capillary took place.
- In normal situation the leak back is very little from the reabsorbed fluids, However for any reason either increased hydrostatic pressure or decreased oncotic pressure and result in reduction in the reabsorption forces this will cause accumulation of transported substances in the interstitium and will back leak (يعني هاي الأشياء رح ترجع رجوع لل tubular fluid] and this will decrease the overall reabsorption .

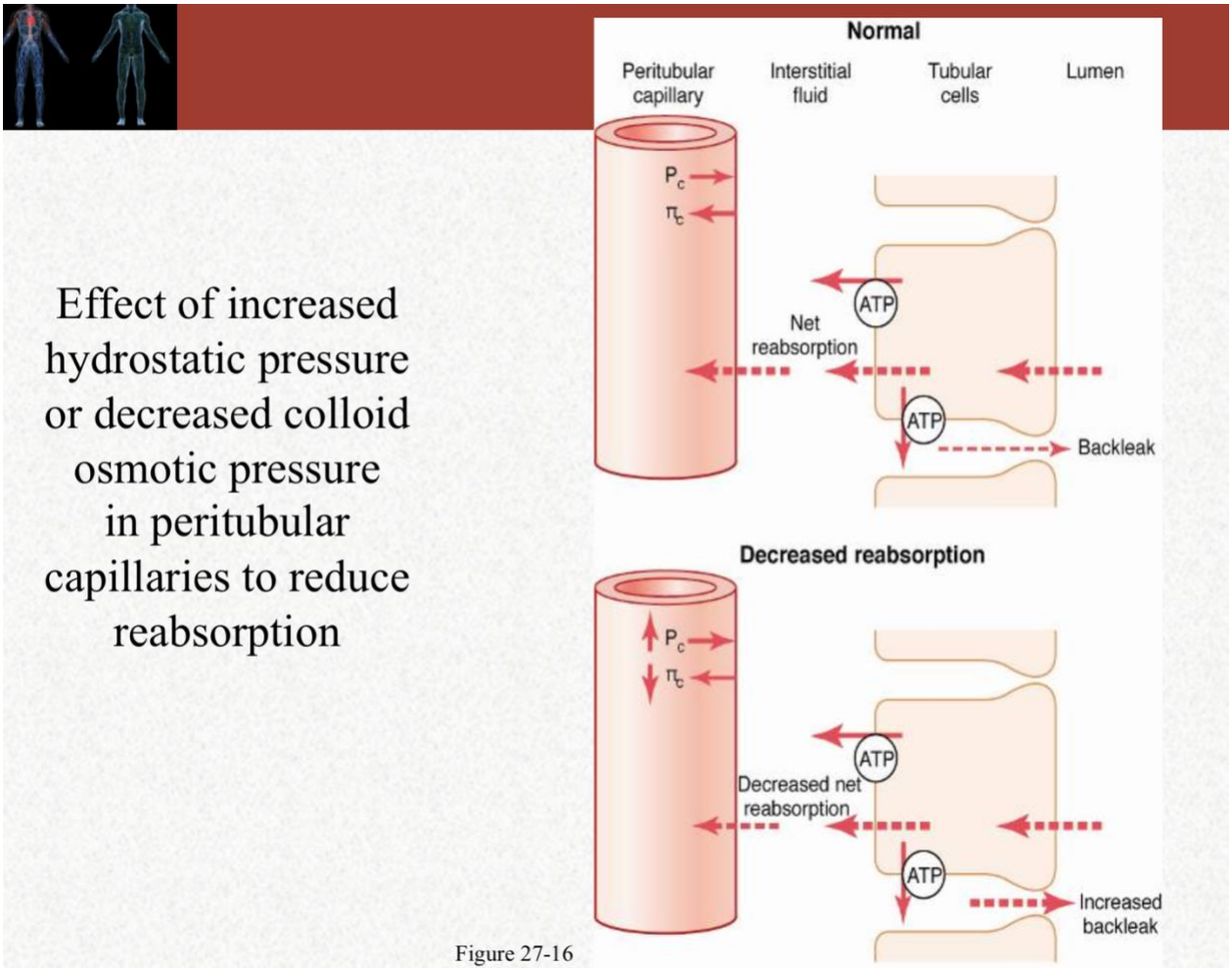
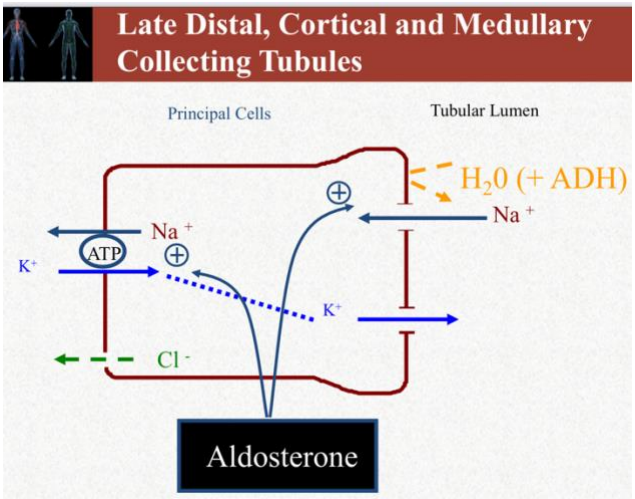


Figure 27-16

❖ Now let's talk about the **Hormonal Determinants On Reabsorption:**

I. Aldosterone => which is secreted from adrenal cortex and it's secretion stimulated by hyperkalemia (increased potassium levels) or by Ang II, it's action is that once it is in blood it will reach the tubular cells especially the principal cells and intercalated cells ,on principal cells it will stimulate Na+ reabsorption through stimulating Na+_K+ ATPase and Enac channels in late distal and collecting ducts and it also causes secretion of K+ at the same time + on intercalated cells will increase H+ secretion.

- Increases Na^+ reabsorption - principal cells
- Increases K^+ secretion - principal cells
- Increases H^+ secretion - intercalated cells



- In case of abnormal Aldosterone regulation like excessive production without feedback inhibition which is called Primary Aldosteronism (Conn's Syndrome) and this syndrome results in Na+ retention(↑re absorption), hypokalemia (↑ secretion), alkalosis (↑ H+ secretion) and hypertension (because of retention of salt and water)
- In case of Aldosterone deficiency (Addison's disease) the opposite happens so there will be Na+ wasting, hyperkalemia and hypotension.

❖ Factors that increase aldosterone secretion:

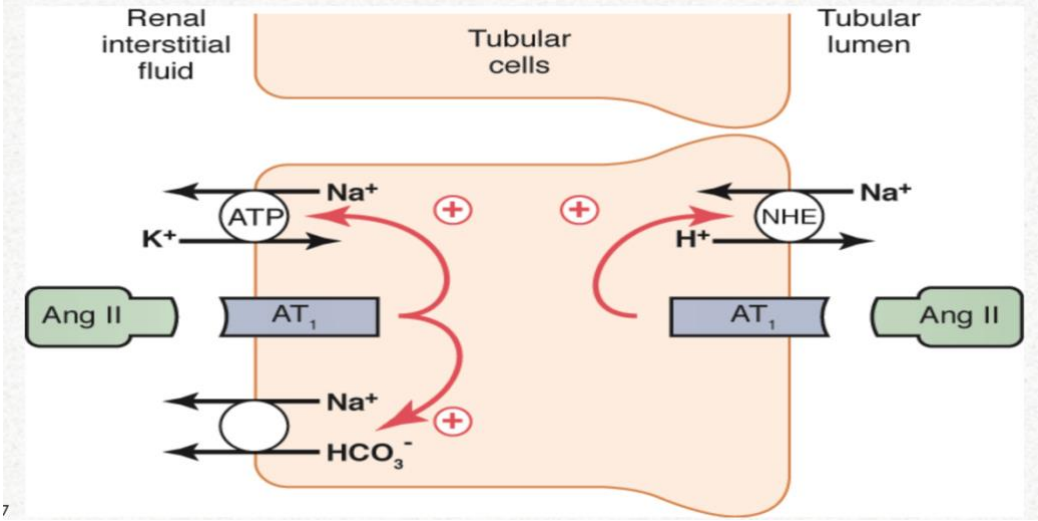
1. Angiotensin II
2. Increased K+
3. Adrenocorticotrophic hormone (ACTH) permissive role.

❖ Factors that decrease aldosterone secretion:

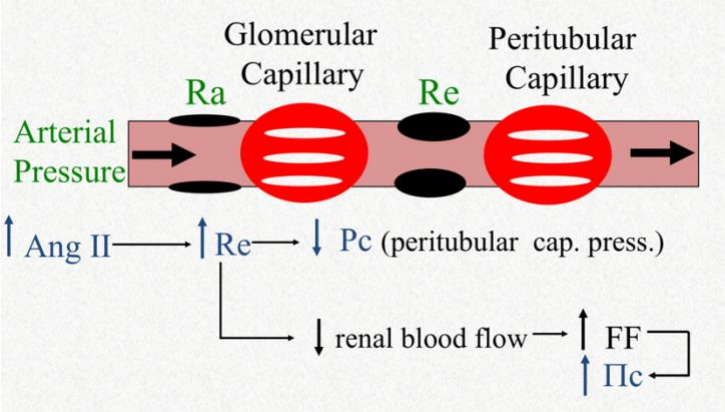
1. Atrial natriuretic factor (ANF) => causes direct inhibition on renal Ang II (which considered stimulator of aldosterone)
2. Increased Na+ concentration (osmolality)

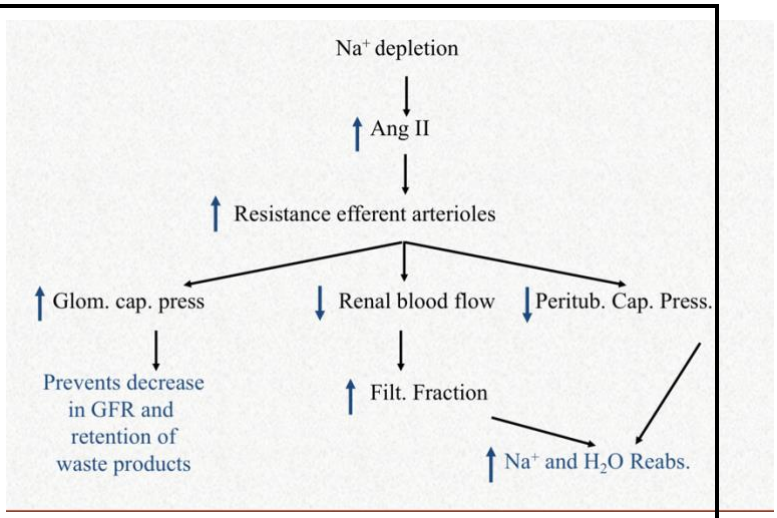
II. Angiotensin II => considered as key player in reabsorption process and one of it's ways is stimulation aldosterone secretion the other way is directly increasing Na+ Reabsorption by direct stimulation of all Na+ Reabsorption transporters from proximal duct to the nephron end (proximal, loop, distal, collecting tubules) , also Ang II has hemodynamic effect by which it causes modulation of reabsorption , how? Let's go back again to it's effect on the cells which are : preferential selective constriction of efferent arteriole so the re absorption will increase because this will decrease the hydrostatic pressure in peritubular capillary , also it increases FF because it decreases the RPF and this will increase reabsorption .

- This picture shows us how Ang II binds with AT1 receptors and stimulates Na+_K+ ATPase , Na+ _H+ exchanger and Na+_HCO3- , and there are also other examples



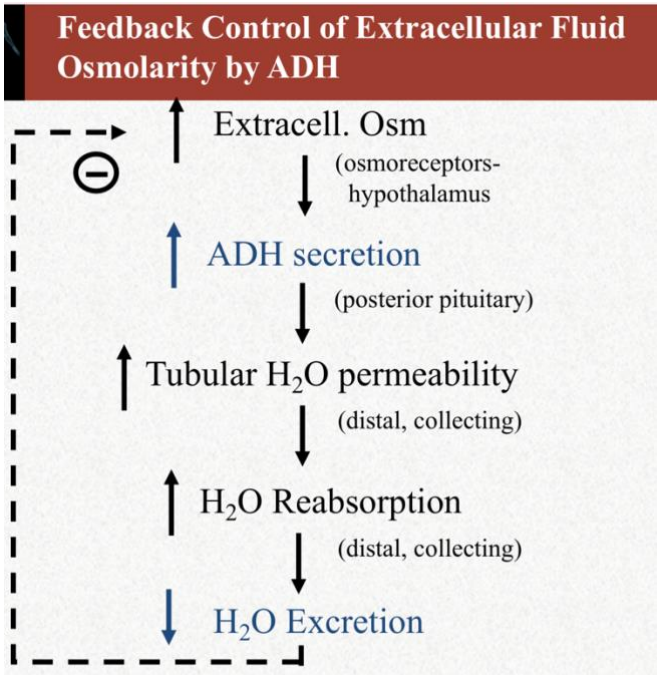
- It's hemodynamic effect here in the picture below we can see how AngII affects efferent arteriole and on reabsorption , you can notice that Ang II increased the efferent resistance so decreased hydrostatic pressure in peritubular capillaries and this in turn increase reabsorption this is the one mechanism, second mechanism is that because of constriction the renal blood flow will decrease so increasing FF which increases oncotic pressure which in turn will increase reabsorption.

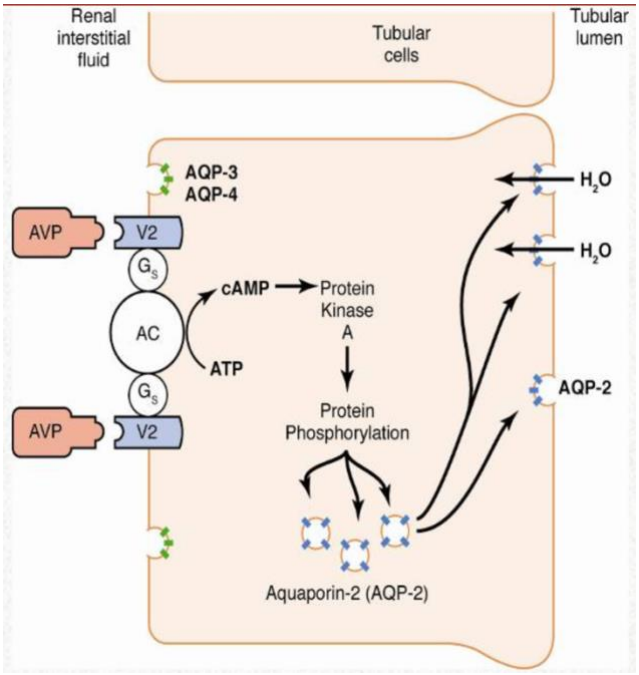




- Na depletion can lead to increased Ang II and increased resistance of efferent which will either increase glomerular capillary pressure and GFR from decreasing or it will decrease RBF and decrease peritubular capillary pressure which both will lead to increased reabsorption .
- Notice in pic 2 that increased Ang II which its target to increase BP and preserve fluids and salts to the body so why it increases GFR? Because it should save normal GFR to save the function of kidney which is elimination of waste products **.**
- In hypertension there are drugs taken to reduce BP and directed toward angiotensin II actions (block Ang II actions) like ACE inhibitors (captopril, benazipril, ramipril) Ang II antagonists (losartan, candesartin, irbesartan) Renin inhibitors (aliskirin) their effects are opposite to Ang II actions so will cause decreased aldosterone, direct inhibition of Na+ Reabsorption and decreases efferent arteriolar resistance which in turn reduces reabsorption and more Na+ excretion (Natriuresis) and Diuresis which all together cause decreased BP .

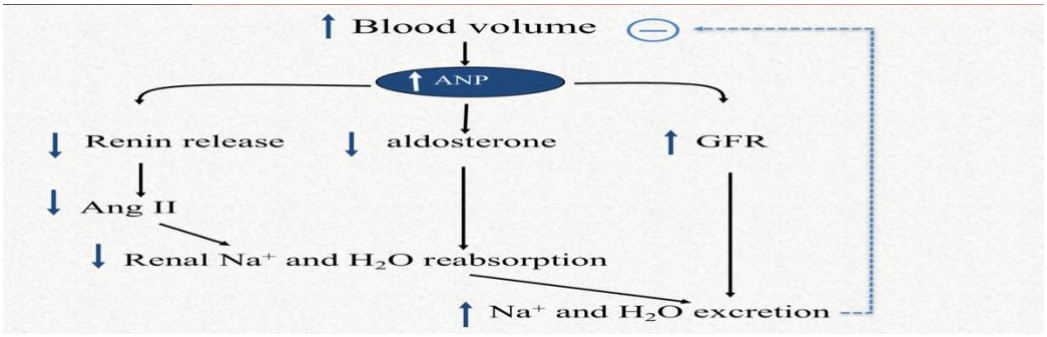
III. Antidiuretic Hormone (ADH) =>secreted by posterior pituitary gland and synthesized in hypothalamus and stored in posterior pituitary stimulated when osmolarity (osmo- receptors sense when it increases and stimulates ADH or Ang II which will stimulate ADH directly) and it's actions directed on water reabsorption as it causes insertion of aquaporin type 2 channels on luminal membrane of late and collecting ducts(when bind with V2 receptors which are GPCRs increase cAMP and phosphorylation of vesicles containing aquaporin and then they are expressed on the membrane)so increasing H2O permeability and reabsorption so conserving fluids and increasing BP , also ADH correct the osmolarity by selectively increasing reabsorption of water and decreasing osmolarity in hyperosmotic cases(tubular fluid is diluted).



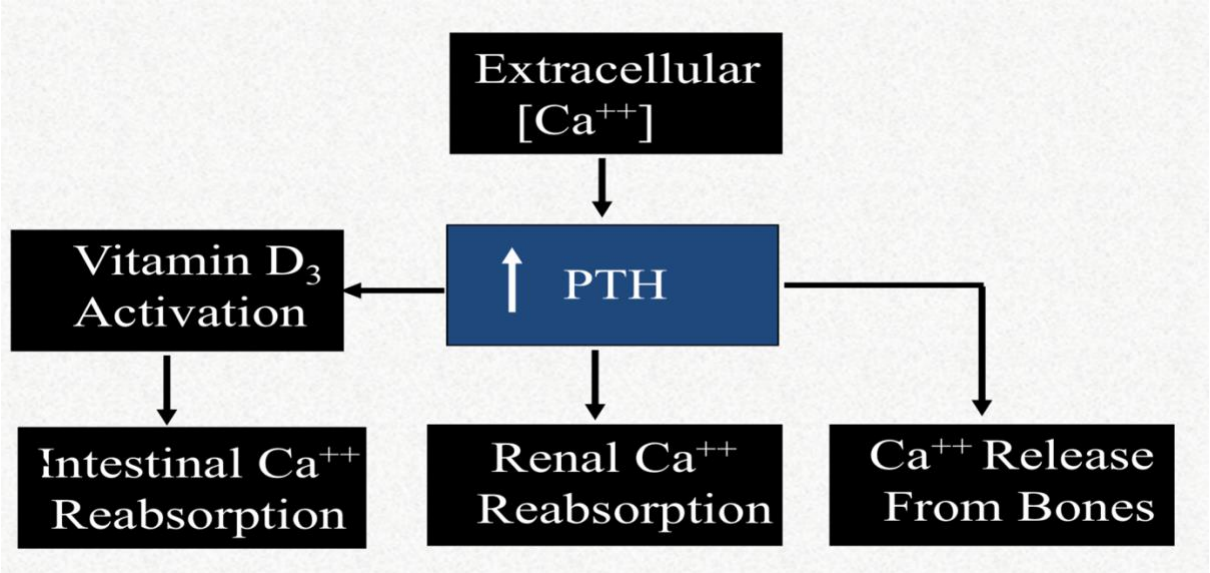


- ❖ Abnormalities of ADH :
  - i. Inappropriate ADH Syndrome (excess ADH) => a lot of water in the body so decreased plasma osmolarity and hyponatremia (dilution of Na+)
  - ii. Central Diabetes insipidus (insufficient ADH) => excessive excretion of water and urination like DM , increased plasma osmolarity hypernatremia and excess thirst.

IV. Atrial Natriuretic Peptide (ANP) => stimulated when pressure or volume increases on the atrium of the heart because of hypertension or CHF (congestive heart failure) , it's actions: direct inhibition of Na+ Reabsorption, inhibition renin release and aldosterone formation so indirectly decreases reabsorption , increase GFR because it vasodilates afferent arteriole so more excretion , helps to minimize blood volume expansion so can work as diuretic in hypertension (naturally).

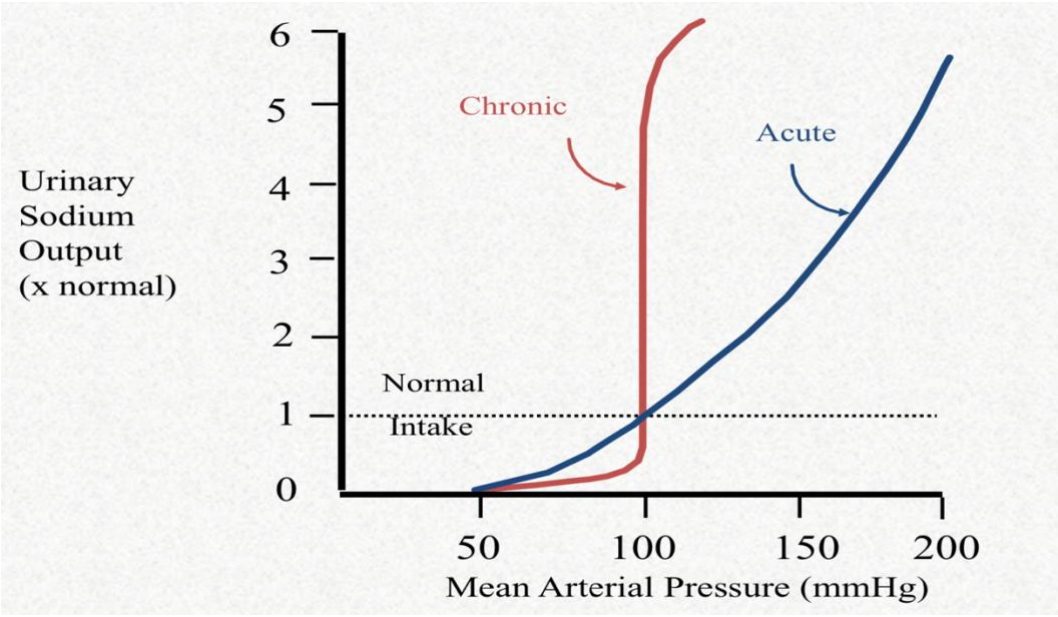


V. Parathyroid Hormone => selectively increasing Ca++ Reabsorption by kidney and gut and reduction of phosphate reabsorption and helps to increase extra cellular Ca++.



VI. Sympathetic Nervous System => Directly stimulate Na+ Reabsorption through alpha receptors in renal tubules, stimulate renin release so indirectly increases reabsorption and decreases GFR (much less than its effect on reabsorption) so in mild activation the reabsorption increases but almost doesn't have effect on GFR and only in severe stimulation there will be effect on GFR and more effect on reabsorption.

❖ <u>High Blood pressure effect on kidney:</u>



- We want to see how increasing blood pressure will affect sodium excretion in urine and we noticed from above experiment that acute increase in Mean arterial pressure will increase urinary sodium excretion, in case of chronic increase in blood pressure the increasing in urinary sodium excretion isn't gradual it is fast and sharpe because that long term inhibition of renin angiotensin aldosterone system took place which doesn't happen in case of acute as it needs time .
- How can pressure affect renal reabsorption ? Increased peritubular capillary hydrostatic pressure will decrease reabsorption , decreased renin and aldosterone and reverse their effects and finally there will be reduction in sodium reabsorption +increases its excretion, increasing release of intrarenal natriuretic factors: prostaglandins and EDRF (nitric oxide epithelial derived relaxing factor) also decrease Na+ Reabsorption.
- The effect of pressure on excretion of salts called pressure natriuresis as pressure increases the excretion of salts increases and this is followed by diuresis to correct BP .

❖ Effect of osmotic pressure on Reabsorption :

- Osmotic pressure in tubular fluid
- If certain substances didn't undergo complete reabsorption and it should be reabsorbed like glucose, if the filtered load was high (uncontrolled diabetic patient) glucose will stay in tubular fluid which will form osmotic pressure in the fluid so as a result of this reabsorption of water in late distal and collecting tubules is reduced and more excretion of tubular fluid (diuretic effect) , so this is the cause of frequent urination in diabetic patients.
- We can use mannitol which isn't reabsorbed and form osmotic pressure and diuresis (osmotic diuretic) ,not favoured in diabetic patients.

❖ Assessing kidney function:

- Plasma concentration of waste products (BUN (nitrogen) , creatinine (tells us how well the kidney is eliminating the wastes.
- Urine specific gravity => urine concentration ability testing.
- Urinalysis test reagent strips (protein, glucose)
- Albumin excretion (microalbuminuria) if there is problem in filtration membrane.
- Biobsy
- Isotope renal scans
- Imaging methods (MRI, arteriograms, iv pyelography,ultrasound)
- Clearance meythos (24-hr creatinine clearance)

- **Clearance: most important process in kidney,describes the volume of plasma that has been cleared completely of a certain substance per unit of time.** And it depends on the substance that we deal with being different with different substances, also clearance depends on renal function.
- **Renal Clearance of a substance:** is the volume of plasma completely cleared of a substance per min by the kidneys.
- **Mathematically:** what is the volume of plasma that is completely clear of this substance per time unit * plasma concentration of this substance =urinary excretion (Us* V)
- To calculate Us you need V (urine flow rate ml/min) and substance concentration in urine and measuring plasma concentration of it.

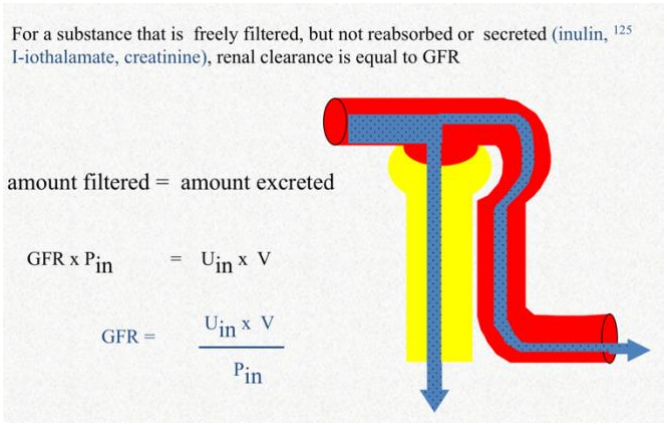
$$Cs \times Ps = Us \times V$$

$$Cs = \frac{Us \times V}{Ps} = \frac{\text{urine excretion rate}}{\text{Plasma conc. s}}$$

Where : Cs = clearance of substance S
Ps = plasma conc. of substance S
Us = urine conc. of substance S
V = urine flow rate

- <u>Clearance of different substances is different</u>
- Glucose and albumin have 0 clearance because they are completely reabsorbed, urea 70 as it is waste product and we need to get rid of it.
- Notice that clearance of inulin (exogenous substance) equals 125 which is the same GFR so we can use inulin clearance to calculate GFR by giving inulin to the patient IV ,24 hr collecting urine, measuring urinary excretion of inulin + plasma concentration of it and this could be dangerous as it may expose the patient to risk of renal failure ,so instead we can use something close to GFR which is the clearance of creatinine (140 ml/min) by estimating GFR but also we need 24 hr collection of urine. Now they are using equations by just knowing plasma creatinine (dr said she will give us these equations but they aren't for memorization) .

Substance	Clearance (ml/min)
glucose	0
albumin	0
sodium	0.9
urea	70
inulin	125
creatinine	140
PAH	600



Calculate the GFR from the following data:

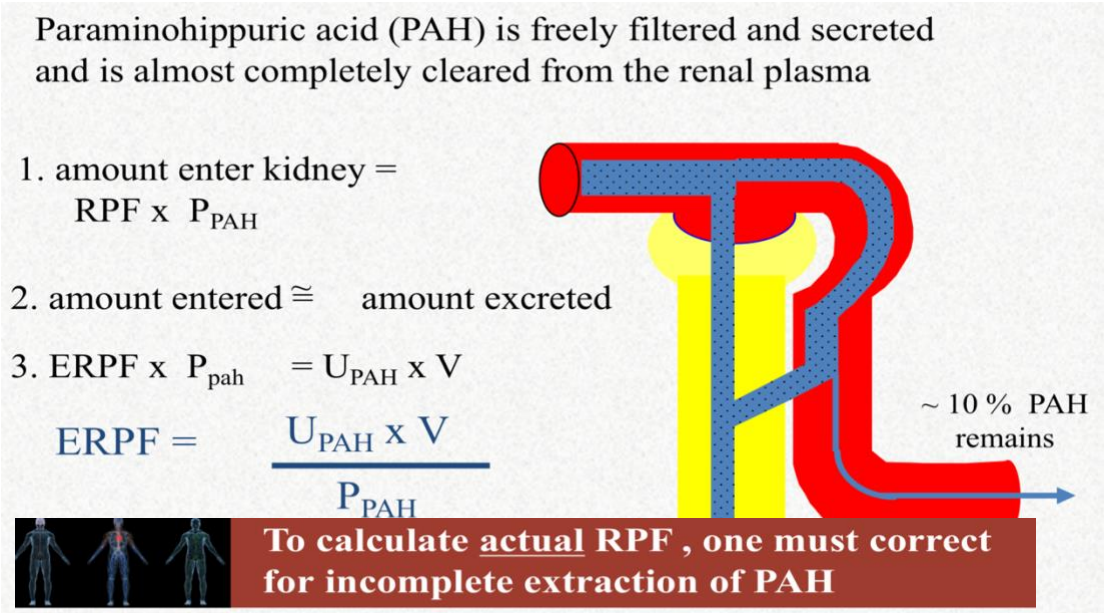
P_{inulin} = 1.0 mg / 100ml
U_{inulin} = 125 mg/100 ml
Urine flow rate = 1.0 ml/min

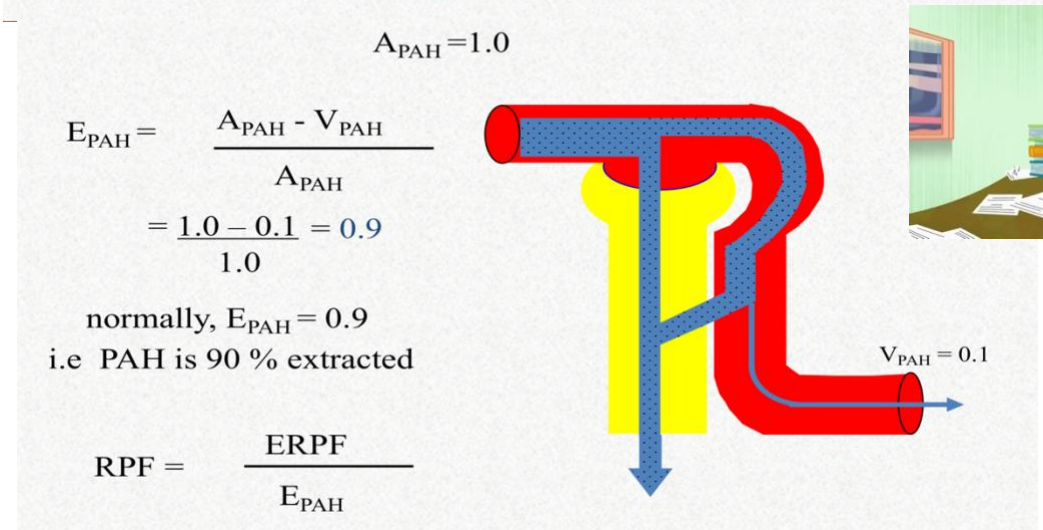
$$GFR = C_{inulin} = \frac{U_{in} \times V}{P_{in}}$$

$$GFR = \frac{125 \times 1.0}{1.0} = 125 \text{ ml/min}$$

- Theoretically if a substance is completely cleared from plasma ,it's clearance rate would equal RPF.

- So as PAH(600 ml/min) close to renal plasma flow , we can use it's clearance rate for measuring RPF. But the problem here that it doesn't completely removed in venues capillaries and gives us ERPF (effective RPF) which isn't true and need correction (because 10 % of PAH stay in venous renal blood) by measuring Extracted PAH(look at picture below) (APAH arterial PAH , VPAH venous PAH) which take venous PAH into consideration.
- Dr said that she will upload video explaining clearance equations so you can watch it for more understanding.(https://fisjo-my.sharepoint.com/:v:/g/personal/e_zayadneh_ju_edu_jo/EVfxrMv5fDZHgWF5wU3y3x0BW4Y-3tEaRCkc6iRxRnZ7rQ?e=V2r0ST)





Substance	Clearance (ml/min
inulin	125
PAH	600
glucose	0
sodium	0.9
urea	70

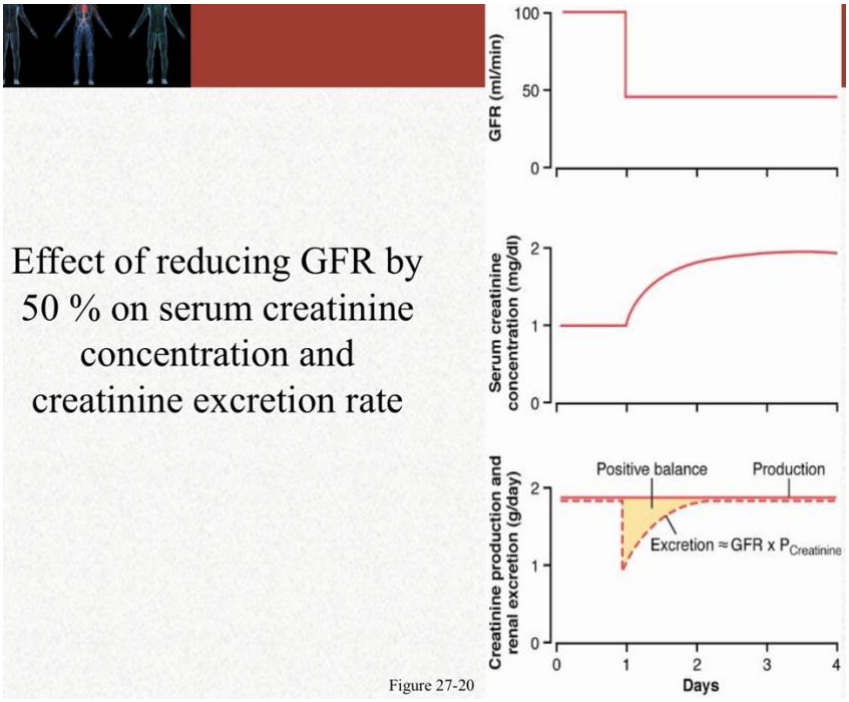
Clearance of inulin (C_{in}) = GFR

if Cx < Cin : indicates reabsorption of x

if Cx > Cin : indicates secretion of x

Clearance creatinine (C_{creat}) ~ 140 (used to estimate GFR)

Clearance of PAH (C_{pah}) ~ effective renal plasma flow



- This is very important ↑ because when there is a patient who has reduced GFR because of renal disease or loss of nephron, so firstly the GFR decreased to 50% then serum creatinine concentration will start increasing and then will be in plateau , then see the creatinine production and renal excretion firstly there is GFR reduction (the clearance or creatinine production are the same) the renal excretion will be reduced transiently then increase because Excretion = GFR * plasma creatinine concentration and as GFR has reduced then plasma creatinine concentration will increase and result in increasing of excretion and returning to normal (50% reduction of GFR and double increase in plasma creatinine concentration then no net effect on excretion rate and will be the same as before reduction of GFR) and this also applied to urea.

- In clinical settings GFR is basically estimated using creatinine estimation and by using different formulas as you can see here ↓ (not required for exam just for your knowledge)

Clinical GFR estimation equations using GFR

Online calculator:

eGFR Calculator | National Kidney Foundation

Model	Equation
Creatinine model	$36.76 + 1.91 \times Wt - 0.47 \times SCr$
Weight model	$16.25 + 1.67 \times Wt$
Cockcroft function[a]	$\frac{(130 + 0.09 \times Age) \times Wt \times (1 + 0.11 \times Sex)}{SCr}$
Jelliffe function[a]	$\frac{(2530 + 126 \times Age) \times BSA \times (1 + 0.13 \times Sex)}{SCr}$
Léger model	$\frac{(56.7 \times Wt + 0.142 \times Hght^2)}{SCr}$
Schwartz regression	$\frac{0.55 \times Hght}{SCr \times 0.01131} \times (BSA/1.73)$ if female $\left(1.5 \times Age + \frac{0.5 \times Hght}{SCr \times 0.01131}\right) \times (BSA/1.73)$ if male

Coefficients derived from modelling data set, except for Schwarz and Léger equations where the original coefficients are used. Wt: weight (kg); Age: age (years); Sex: 1 if male, 0 if female; SCr: serum creatinine ($\mu mol\,l^{-1}$); BSA: body surface area (m^2); Hght: height (cm). [a]Coefficients re-estimated from current data set using nonlinear mixed effects modelling.

- Estimation of GFR used to assist chronic kidney disease as we can divide chronic kidney diseases into stages according to their GFR(also this isn't for memorization)

Chronic kidney disease and GFR

Stage	Description	GFR (mL/min)
1	Kidney damage (protein in the urine) with normal or elevated GFR	90 or more
2	Kidney damage with mildly decreased GFR	60–89
3	Kidney damage with moderately decreased GFR	30–59
4	Kidney damage with severely decreased GFR	15–29
5	Kidney failure: end-stage renal disease (ESRD). Patients who have Stage 5 disease require dialysis or transplantation to survive.	Less than 15