URO-GENITAL SYSTEM

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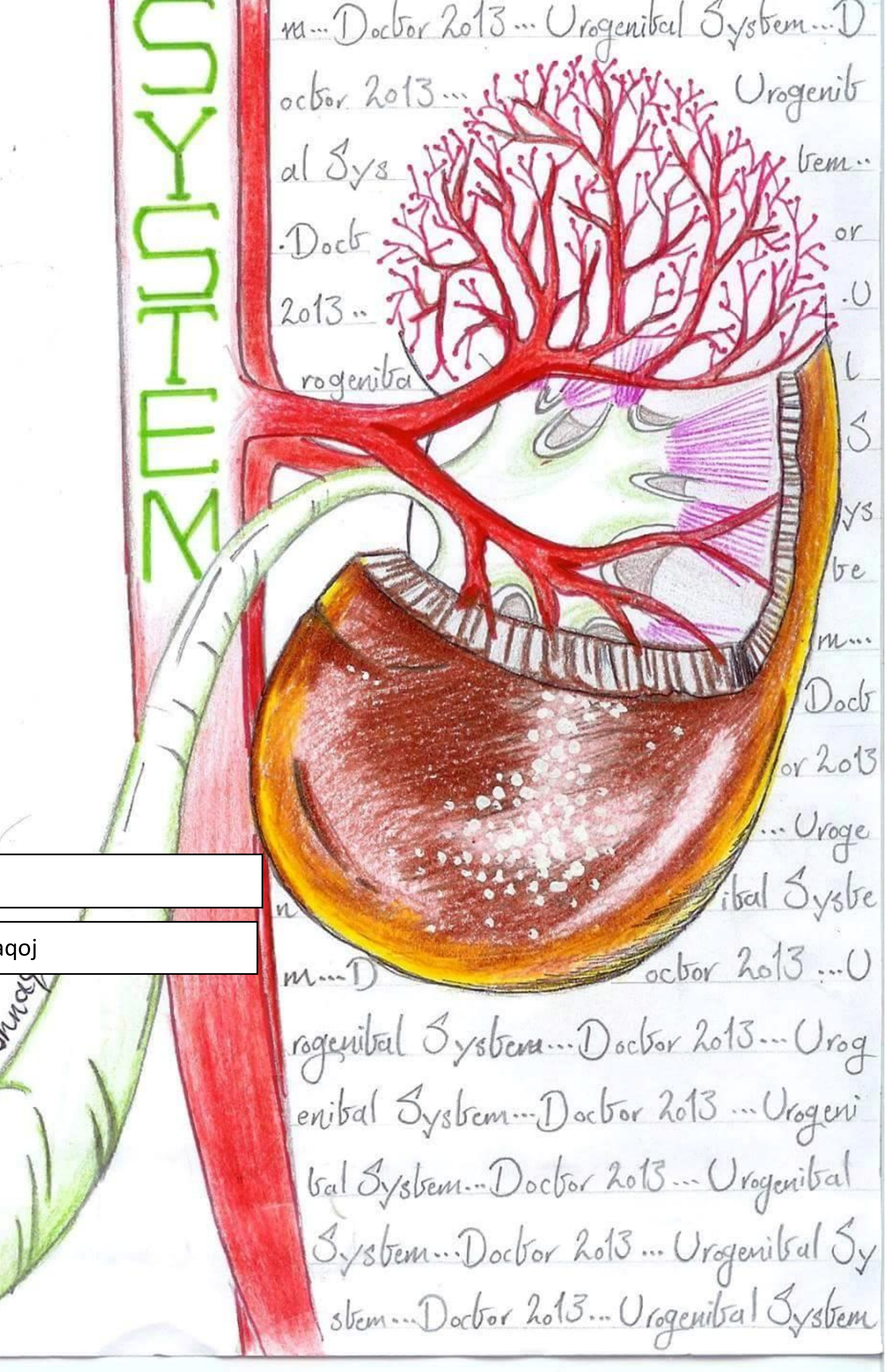

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Glomerular filtration rate (GFR) measurements:

To test for the GFR we need a substance that is freely filtered, not reabsorbed nor secreted. Inulin fits these criteria, however it is not an endogenous substance so we need to infuse it over 3 hours and try to keep its plasma concentration stable and this is troublesome, so we avoid using it for clinical purposes, and its use is limited for research.

Now the closest endogenous substance to fit the criteria is creatinine, so we can calculate its clearance which equals the GFR, creatinine however, has a setback which is that 10% of it is also excreted, so if we use creatinine to measure GFR we would end up overestimating it, this is in theory, but in real practice when we measure the plasma creatinine concentration we measure the total amount which is free and bound, bound represents 10% and is not filtered, so these errors cancel each other out ending with an accurate measurement of the GFR.

Creatinine is a waste product, it's released to the blood from the muscles at a rate of 1.5- 2gm/day, and this rate is fairly stable as it's not affected by muscle activity or other factors.

so if we say that the concentration of Creatinine is 1mg/100ml, and knowing that the GFR is 125ml/min, we can say that the filter load is equal to 1.25mg/min. so during a whole day (1.25 * 60*24) we will get around 1.5-2gm/day and we have to excrete the same amount to maintain a constant amount which is in normal conditions, however if the GFR for any reason decreased to 65ml/min(50%) for example, we have to double the concentration of the creatinine inside the plasma to maintain the 1.5-2gm/day clearance. (2mg/100ml *65ml/min= 1.3 mg/min *60*24 we get around the needed 1.5-2gm/day).

Written by Louay Zaghlol

In conclusion the plasma creatinine concentration somewhat reflects the GFR if the concentration increases you can say that the GFR has decreased in the same proportion. (1/2 GFR → double the creatinine conc., ¼ GFR → 4 times the creatinine conc.).

(Pay attention that it is only a reflection and not an actual GFR calculation)

So how to calculate the actual GFR?

As we said the clearance of creatinine is equal to the GFR, so we need to measure the clearance of Creatinine by the equation

$$Cl(cr) = \frac{U(cr)}{P(cr)} \; X \; V°$$

Where: Cl(cr) = creatinine clearance
U(cr) = concentration of creatinine in urine
P(cr) = concentration of creatinine in plasma
$V°$= Volume of urine (ml) per minute (we measure a whole day then divide by (60*24).
We can easily calculate both the concentration of creatinine in the urine and plasma, so we need to measure the volume of urine over 24 hours and we can calculate the clearance, but it's not always practical to collect the urine over 24 hours as patients may not stick with it especially old aged individuals or children. So we came up with equations that estimate the GFR to nearly 95% by only taking a blood sample and few basic information. We have many equations but we are going to use 2 only one for adults and the other for children.

1-Adult equation:

$$GFR = \frac{(140 - Age)X\ BW\ X\ (1\ or\ 0.85)\ **}{72 * Pcr}$$

Where:

BW = ideal body weight.
Pcr = plasma creatinine concentration (mg/dl).

****NOTE THAT: 1 is used for males while 0.85 for females and this is because males have more muscle mass.**

2- Children equation

$$GFR = \frac{K*height(cm)}{Pcr}$$

Where:

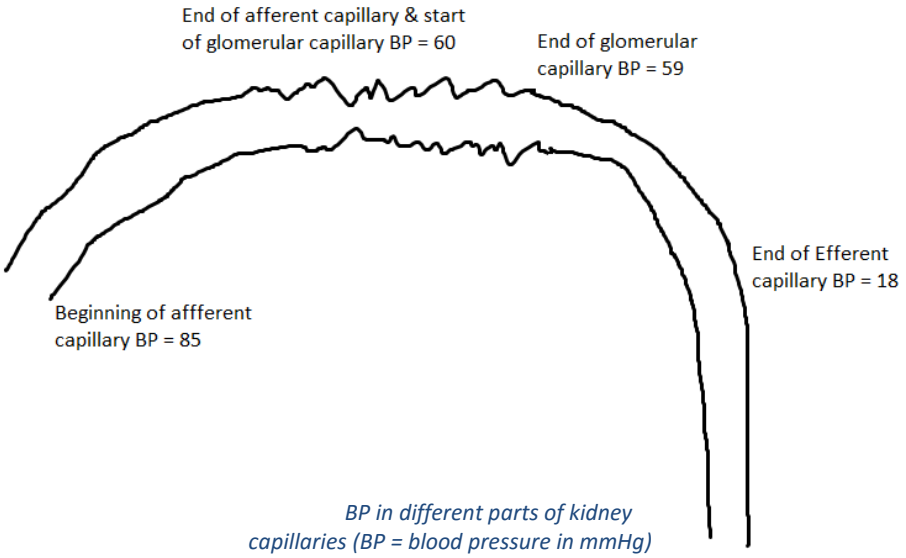
GFR is in (ml/min/1.73 m^2)

K is a constant that depends on muscle mass, which varies with a child's age.

Pcr is plasma creatinine concentration (mg/dl).

Note that: in end stage renal failure the GFR is nearly 0 so all the creatinine clearance in the urine is due to secretion as there is no filtration happening, so the creatinine clearance overestimates the GFR. So we can't use these equations, however there are other equations used for this case.

You can see from the figure that the highest drop in pressure is in the efferent capillary (has the highest resistance) and this serves to produce a driving force for higher filtration, also some drop in pressure in the afferent capillary and only minimal drop in the glomerular capillary.



BP in different parts of kidney capillaries (BP = blood pressure in mmHg)

Now what controls the GFR?

It is like any other normal filtration governed by 2 sets of forces on each side, 2 Hydrostatic pressures represented by the letter P & 2 colloidal pressures represented by the letter π, so **Pc** stands for hydrostatic pressure in the capillary which is the result of the heart pumping blood and is equal to 60mmHg, **Pbs** stands for hydrostatic pressure in the bowman's space and is equal to 18mmHg, **πc** is the colloidal pressure in the capillary due to the proteins found inside the capillary and ranges from 28-32mmHg, and finally **πbs** which is the colloidal pressure in the bowman's space and is equal to 0mmHg because there are no proteins inside it (there is protein filtered but it's minimal so we consider it as none).

The reason for the capillary colloidal pressure ranging from 28-32mmHG is due to the filtration taking place having 20% of the water exit the capillary while leaving the proteins inside the capillary the same, so the protein's concentration increases (less water) leading to higher pressure towards the end of the glomerular capillary hence the higher pressure 32mmHg (20% increase).

Now why don't we see this phenomenon in normal capillaries? Because in normal capillaries the amount of filtration is only 0.5% (20L/Day leak out, from the huge 4000L/Day reaching the capillaries) unlike the way more 20% in the kidneys (125ml/min out of the 625 ml/min), so the concentration of proteins in normal capillaries stays relatively constant throughout the length of the capillary.

What happens if a person develops a stone in his ureter or kidney?

There will be an obstruction of flow of the filtrate and this will cause a buildup of opposite hydrostatic pressure inside the bowman's space, reaching values higher than 18mmHg and this will cause a decrease in GFR which may end up stopping a whole kidney from working, moreover a stone in the urinary bladder may stop both kidneys from working, also prostate hypertrophy affects both kidney's GFR.

There are 2 types of stones, a renal kidney which causes renal colic, which is the severe pain due to a kidney stone, and this is usually benign as it causes the patient to visit the physician, on the other hand the more dangerous type of stone is the silent one which comes with dull pain which can destroy the kidney before the patient visits the physician.

Now filtration depends on driving force and permeability and as we have studied before we can put it in the equation filtration = $\Delta F \times K$

where: ΔF is difference in starling forces and is equal to 10mmHg (60-(32+18))

K is the coefficient of permeability.

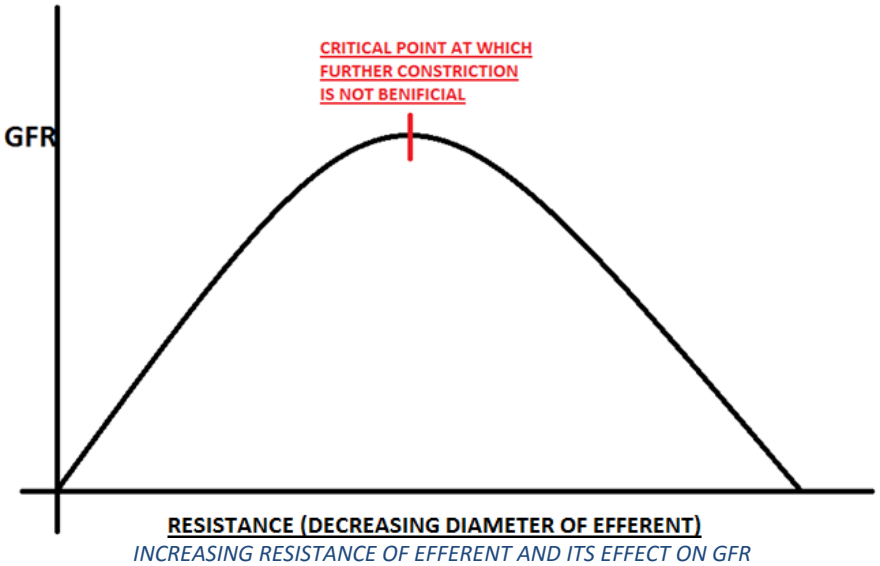
Since we know the filtration is equal to 125 ml/min. we can calculate the coefficient of permeability, which equals 12.5ml/mmHg (125/10).

Now let's recap the most important things so far:

1- Plasma creatinine reflects the GFR (inversely proportional).
2- Estimation of GFR is as good as true GFR that needs 24 hours of urine collecting which can be a challenge for you when treating certain individuals.
3- Creatinine clearance overestimates GFR in end stage renal failure.
4- The filtration across the glomerular capillaries is much higher than normal capillaries for 2 reasons: A- the diffusion coefficient is 10 times higher than a normal capillary and this is due to the structure (e.g. it is a fenestrated capillary) and B- the hydrostatic force across the glomerular capillary is way larger than that of a normal capillary.

How to manipulate the hydrostatic pressure?

By changing the diameter of the capillaries specifically the afferent and efferent, for instance increasing the diameter (dilation) of the afferent arteriole increases the amount of blood reaching the glomerular capillary hence more hydrostatic pressure, on the other hand constriction of the efferent creates higher hydrostatic pressure up to a certain point, however if the constriction is severe this will cause stasis of the blood in the glomerular capillary, although giving more time for filtration, this has a negative effect because more filtration will increase the oncotic pressure due to the very high protein concentration which counters the hydrostatic pressure and finally the filtration decreases.

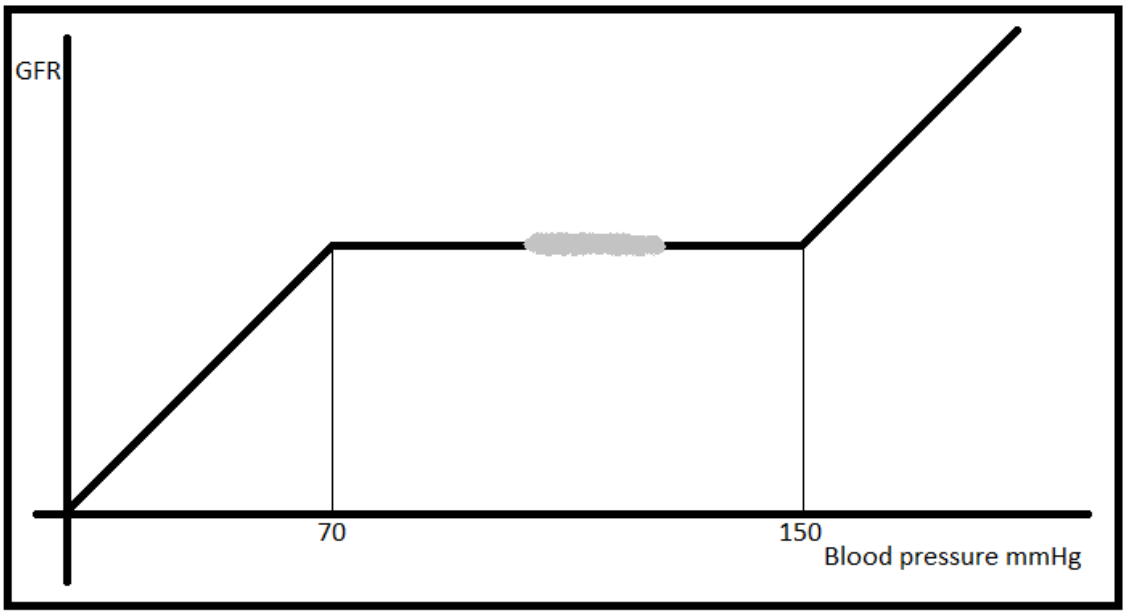


INCREASING RESISTANCE OF EFFERENT AND ITS EFFECT ON GFR

You would think that any drop in pressure below the normal average BP of 100 which gives an afferent BP of 85 and a glomerular BP of 60, would lead to stop of filtration, for example a BP of 90 would give an afferent BP of 75 and a glomerular BP of 50, so 50-(32+18) = 0, therefore the ΔF would equal 0 and hence the filtration will equal 0, and since there is normal fluctuation of BP in our bodies during the day or it decreases when we sleep, this will cause serious problems, but this does not happen due to something called autoregulation of GFR.

What does autoregulation of GFR mean?

Constant GFR in relation to BP, or in other words GFR-BP uncoupling.



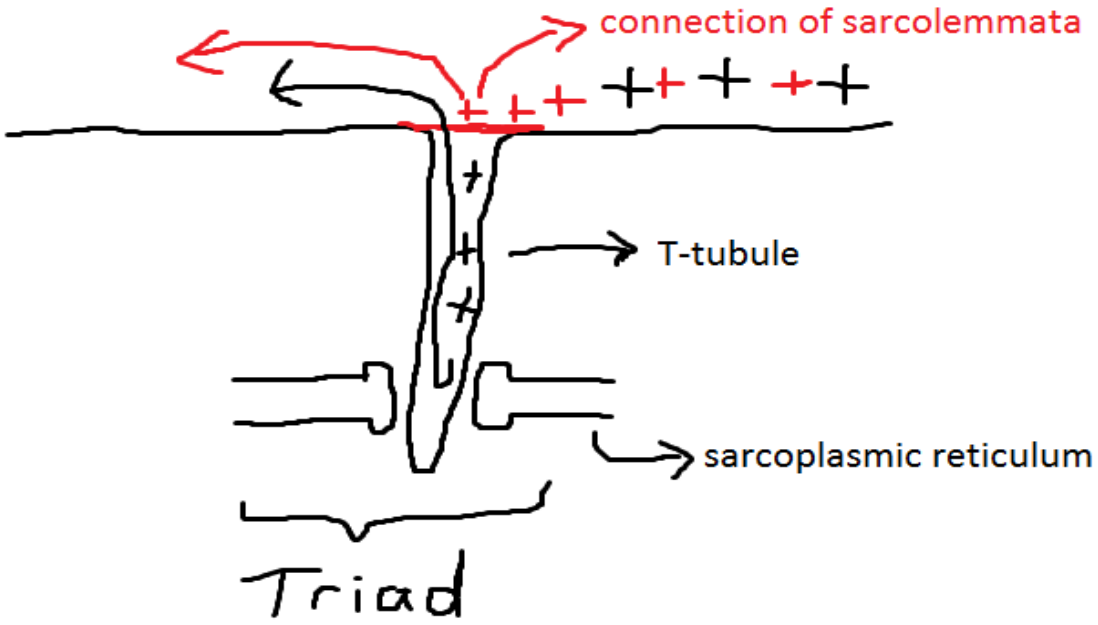
Grey area is our normal fluctuation of blood pressure, notice that the curve is linear and the GFR is kept nearly constant

Autoregulation of GFR

We have to pay attention to the critical values at which GFR-BP uncoupling stops, for example below 70, in real life if bleeding occurs, BP start to drop and this is extremely dangerous, so we have to give our patients anything like normal saline or plasma to keep the BP for dropping below 70, another case is if the surgeon can't see due to blood splattering during the operation, so he asks the anesthesiologist to decrease the BP to decrease the bleeding, the anesthesiologist must pay great attention not to drop the BP below 70 or we'll lose the patient.

The doctor here explains excitation contraction coupling and uncoupling and I see that it's irrelevant here but I'll put it anyways.

Now excitation contraction coupling is that whenever we have an excitation it is followed by contraction, what couples these together? The T-tubule, as it forms a triad with sarcoplasmic reticulum so when a signal arrives at the sarcolemma it goes through the invagination (T-tubule) to reach the sarcoplasmic reticulum and cause contraction. By a certain mechanism we cut the T-tubule and connect the sarcolemmata together this causes the spread of action potential to spare the sarcoplasmic reticulum and hence the excitation isn't followed by a contraction, this is called uncoupling.

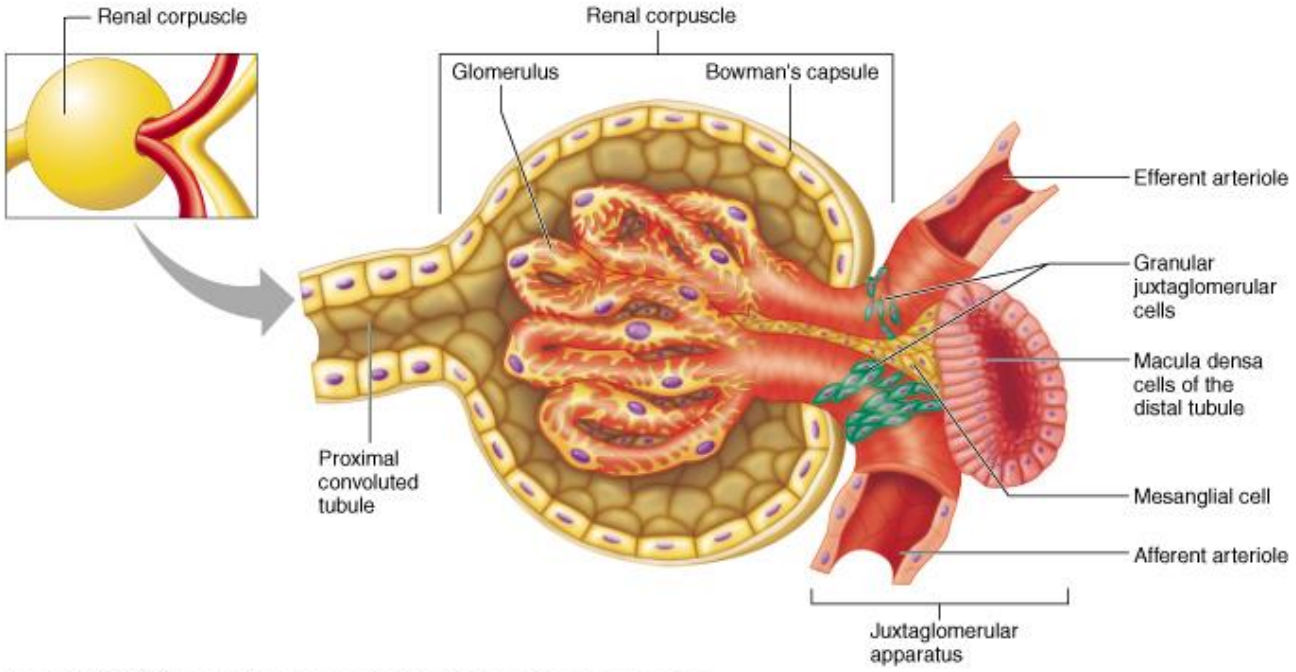


Excitation contraction uncoupling

Now this resembles somehow what happens in the kidney by uncoupling GFR and BP.

How does this the uncoupling happen in the kidney?

This happens by the so called juxtaglomerular apparatus (keep in mind that 85% of all nephrons are cortical, while the remaining 15% are juxtaglomerular nephrons), which contains something called the macula densa cells, these cells are found in the distal tubule, and they work as sensory receptors for the concentrations of sodium, potassium, calcium, potassium etc., by this they know when the GFR is low which reflects a low BP, then they send 2 different signals to neighboring cells one for granular cells (so called because they have granules containing renin) found in the efferent and afferent arterioles, these granular cells in response to the signal, release renin. And the other signal reaches the afferent arterioles causing dilation in them, which causes more blood to reach the glomerular capillaries.



The Juxtaglomerular apparatus (notice the scissor like shape formed by the macula densa and the capillaries)

Now renin is secreted from the kidney in response to decreased GFR, renin works by breaking down a 14 Amino acids molecule called angiotensinogen removing 4 amino acids, to convert it to Angiotensin I (10 amino acids peptide), now this angiotensin I is converted inside the lung by removing 2 amino acids ending up with an octapeptide called angiotensin II by an enzyme called Angiotensin converting enzyme (ACE).

Now the kidney has to do 2 goals when you are bleeding (Decreased BP), the first is that you still want to remove the waste products from your body like urea or creatinine, and this is achieved by maintaining the GFR, the other goal is to maintain body fluids, and this is done by reducing urine output. Now these 2 goals oppose each other, so how can we achieve them together?

This is done with the help of the indirectly produced angiotensin II which comes back to the kidney, in particular the efferent arteriole which has a receptor for it, there it constricts the efferent arteriole and this increases the pressure in the glomerular capillary maintaining GFR, so the first goal is achieved, now this constriction causes the BP ahead of the efferent arteriole to drop, specifically the peritubular capillaries which's job is to reabsorb water, now with this decreased BP the forces to filter decreases so this favors reabsorption *remember starling forces*, therefore achieving the two goals.

Other functions of angiotensin II include:

1- Stimulating the secretion of aldosterone from the adrenal cortex (zona glomerulosa), aldosterone in the distal tubule enhances sodium reabsorption, water follows sodium.
2- Angiotensin II by itself is a potent vasoconstrictor (the strongest) which increases BP.
3- Angiotensin II stimulates DIRECTLY the reabsorption of sodium on the proximal tubules. NOT THROUGH ALDOSTERONE.

We can see that patients on ACE-Inhibitors or Angiotensin II antagonists suffer from bleeding.

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Keep in mind that GFR must be kept constant as higher than normal GFR can cause loss of important molecules which are below 70k or are negatively charged (we'll emphasize on this point later) like sodium, potassium, glucose etc., so if large amounts are filtered, you will end up with glycosuria or aminoaciduria

Also too little GFR can cause 2 kind of problems, first one is decreased GFR on the level of a single nephron, and this causes a decrease in flow of filtrate through the tubules, (the outer diameter of the loop of Henle and the proximal tubule are 10-11 and 60 micrometer respectively), so a decrease in flow of filtrate *stasis* leads to precipitation which leads to formation of crystals which blocks the flow.

Now as a whole, a decrease in GFR of the kidney causes accumulation of materials like urea, creatinine and electrolytes, now urea and creatinine are both toxic waste products, however they differ in that creatinine levels are somewhat more stable compared to urea which may be affected by food intake (protein intake) or other factors, also creatinine level changes is limited to kidney problems unlike urea which may increase for non-renal causes like dehydration internal bleeding or burns etc.

However it's unlikely to see high creatinine levels and normal urea levels, on the other hand if you detect a high urea and normal creatinine you can be sure that it's not a renal problem, for that reason we consider creatinine to be more sensitive as a kidney function test (KFT), now accumulation of urea can cause an increase of ammonia (which is a product of urea) which is toxic to the brain and may cause brain coma, also uric acid accumulation serves as another example.

We divided the nephron into 2 parts, cortical for filtration, and medullary nephron which work on the filtrate.

We continue with the glomerular function. sometimes the kidney has a problem in filtration called glomerular problem, other times the problem is in the tubule, for example if the kidney doesn't reabsorb the calcium we will have hypercalciuria and stone formation, other times it won't reabsorb the amino acids and we will end up with aminoaciduria. Now we have to measure the amounts of proteins, amino acids or calcium in the urine over 24 hours and compare it with the database numbers to determine if a person has the condition.

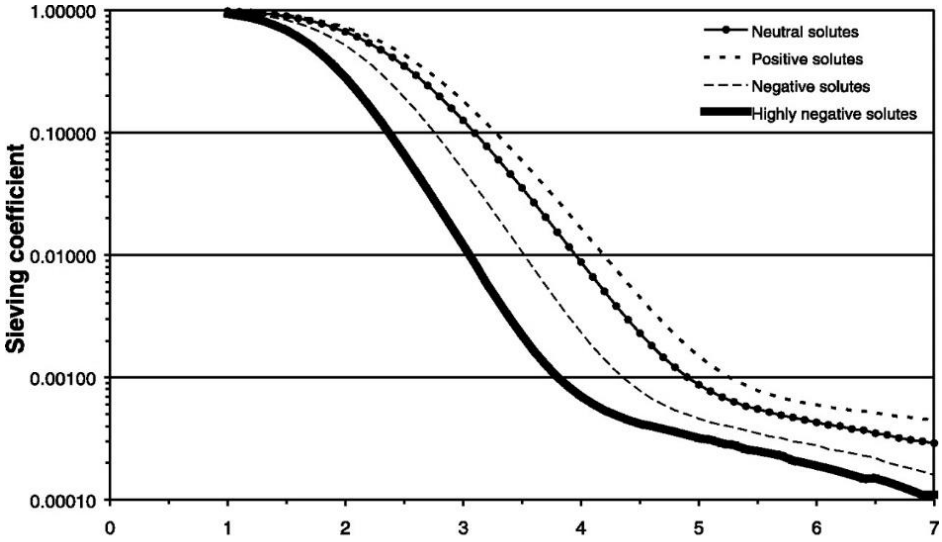
However mainly we classify renal failure according to the GFR.

Renal failure stage	GFR %
I	55-99%
II	20-45%
III	14-19%
IV	<5%

What determines which molecules pass through the glomerular capillaries?

2 factors:

1- The molecular weight, anything below 70k can pass and anything above 70k can't pass. However exceptions apply due to the 2nd point.
2- The charge of the molecule, if the molecule is negatively charged **(anions)** it needs a lower molecule weight to pass, and positively charged molecules **(cations)** can pass even with higher molecular weight, this was tested using synthetic dextran. Example on this is albumin which has around 50k molecular weight but still can't pass and this is due to its negative charge. This is because the endothelium membrane and basement membrane is negatively charged, so repulsion would occur.
   Keep in mind that this only applies to molecules with higher molecular weight near the threshold, for example chloride which is negatively charged can pass freely due to its low molecular weight.



Shifts of permeability curves due to different charges of molecules

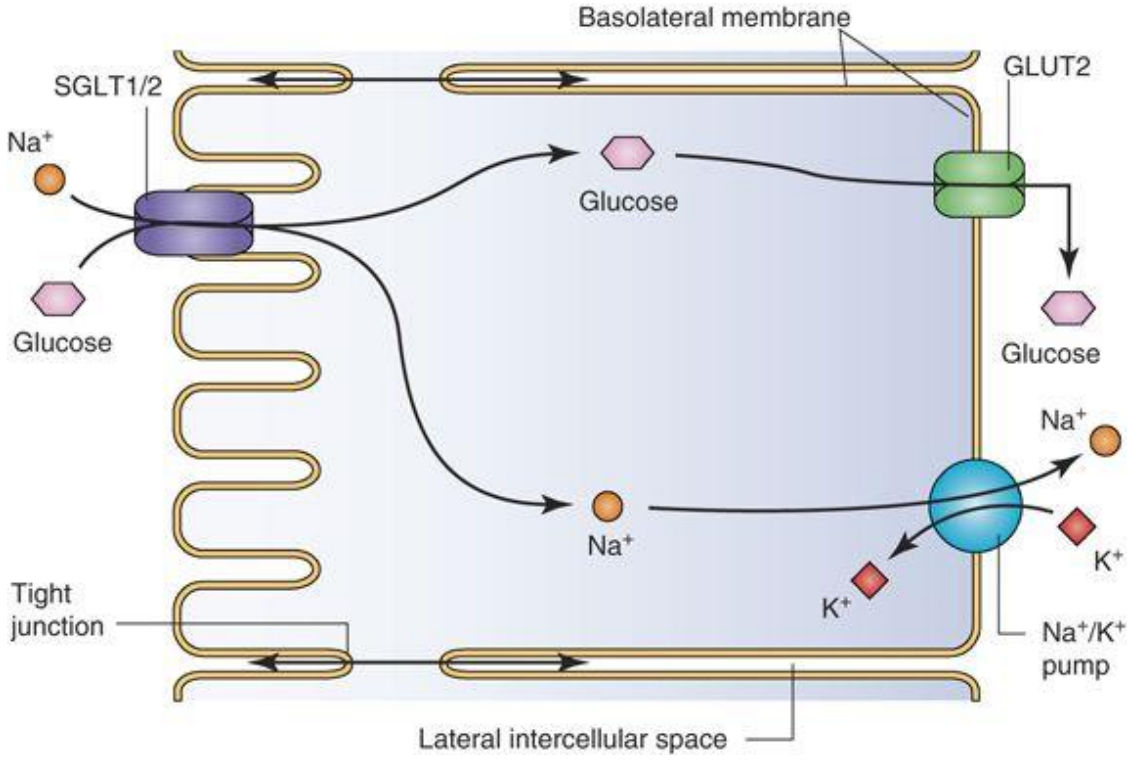
Glucose reabsorption

Fasting blood Glucose level has a normal level between 70-110gm/dL, above 126gm/dL is diabetic. Let's assume it's 100.

Now we can calculate the glucose filter load from the concentration of glucose and the GFR. With our normal values we will have a glucose filter load of 125mg/minute. (100gm/dL * 125 mL/minute *pay attention to units*).

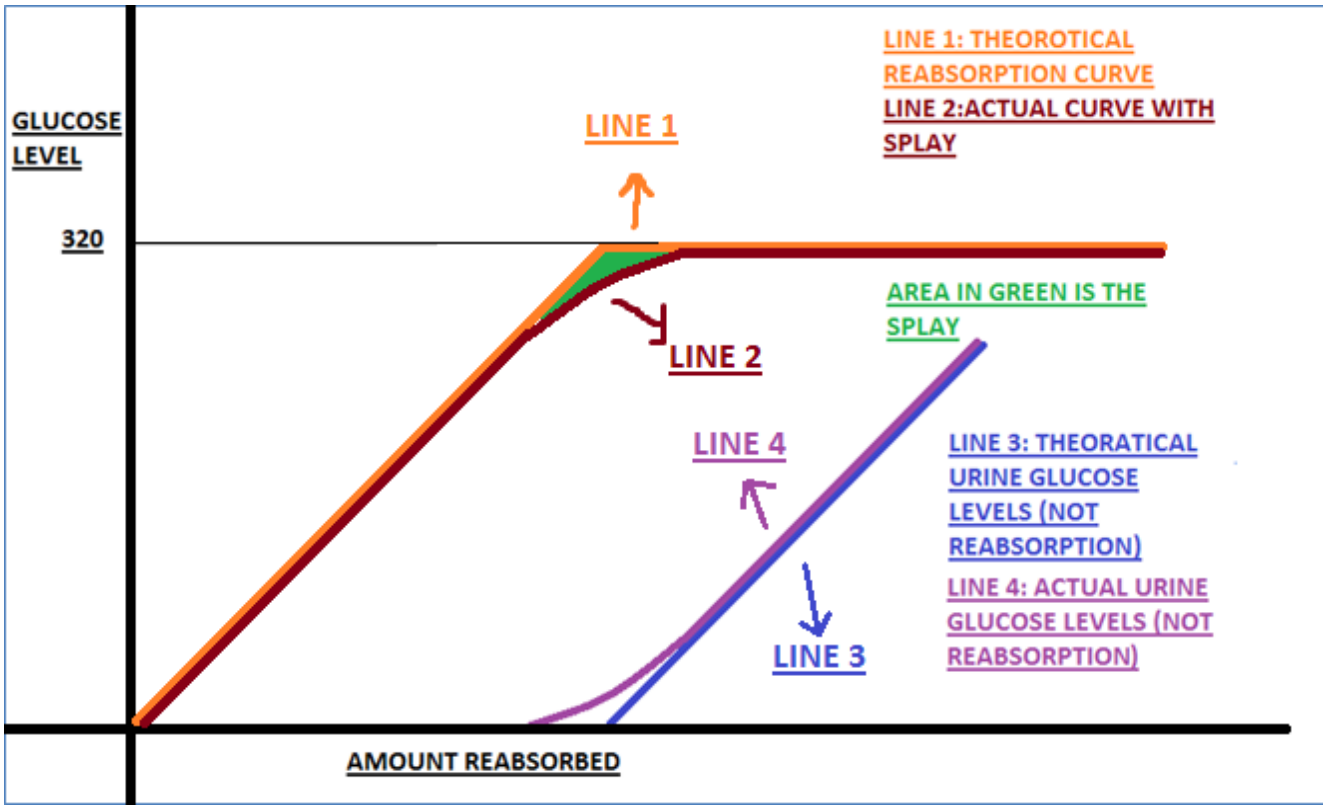
Glucose is freely filtered.

Firstly, the glucose in the proximal tubule is co-transported (secondary active transport) with sodium (from high concentration {140} to low {14} ions into the proximal convoluted tubule walls via the SGLT 1 or 2 (sodium glucose luminal transporter) cotransporter (1 has higher affinity but low capacity while 2 has lower affinity and higher capacity). Once in the tubule wall, the glucose diffuses directly into the blood capillaries along a concentration gradient (facilitated diffusion via a transporter). This blood is flowing, so the gradient is maintained. Lastly, sodium/potassium ion active transport pumps remove sodium from the tubule wall and the sodium is put back into the blood. This maintains a sodium concentration gradient in the proximal tubule lining, so the first step continues to happen. All of this happens in the first half of the proximal tubule.



What is the maximum capacity of these transporters? (Tmax)

It equals 320 mg/dL and this means that if your blood glucose levels are below 320mg/dL which is very high, there should be no glucose in the urine. So basically according to theory there rarely should be any glucose in the urine. However in real life the curve doesn't obey these rules 100% due to the fact that not all transporters will be occupied, so some glucose will escape the reabsorption. This is called splay (appearance of glucose in the urine before its Tmax).



This allows glucose to appear in urine in concentrations below 320mg/dL, specifically above 180 you expect to see glucose in the urine and is numbered +1,+2,+3 etc. check the table. (Don't memorize the number just understand the concept of numbering the higher the plasma glucose level the larger the number).

Urine dipstick designation	Approximate plasma concentration
trace	100 mg/dL [2]
1+	250 mg/dL[2] df
2+	500 mg/dL[2]
3+	1000 mg/dL[2]
4+	2000 mg/dL[2]

From this we can derive that the kidney participates only to a small extent in glucose homeostasis how?

If the glucose reaches a level of 60, it can restore it to 70, or if the glucose reaches 130 it can restore it to 120, but as we said the threshold for glycosuria is 180, and this is away from Tmax (320) and these 2 are away from normal glucose concentration, so if the glucose rises to 170 for example, the kidney cannot help in returning it to normal, in short, the further the Tmax is from the normal physiological concentration the less the participation of the kidney in that substance's homeostasis.

Another example in which the kidney **does participates** in the homeostasis, is phosphate.

Phosphate concentration is 1-2 milliMole/L in the plasma, so filter load of phosphate is around 0.1 milliMole/min., the Tmax for the reabsorption of phosphate in the kidney, is 0.1 milliMole/min., so even if you ingest more phosphate in your diet, and your plasma concentration of phosphate increase, therefore increasing the filter load of phosphate, meaning more phosphate reaches the bowman's space, only 0.1 will be reabsorbed and the rest will be excreted. Returning the plasma concentration to normal.

Here we notice that the Tmax is near the normal physiological levels of phosphate, hence it participates in the normal phosphate homeostasis.

Now if you see glucose in the urine (glycosuria) there is 2 expected scenarios, you conduct a differential diagnosis which is measuring the blood glucose level, if it was high, then it's diabetogenic (due to diabetes mellitus), if it was normal, then it is nephrogenic (due to something wrong in the kidney), the transporters here have low affinity for glucose or maybe their numbers are lower. Nephrogenic glycosuria is absolutely benign, which means its prognosis is good, it's not associated with other kidney abnormalities, and will not produce problems to the patient in the future.

Amino acids reabsorption

They are freely filtered too, they are reabsorbed also with sodium (secondary active transport) just like glucose. However sometimes we have special transporters for specific amino acids like cysteine, so if this transporter is deficient we will find cysteine in the urine (**cystinuria** which actually predisposes stones formation the kidney, the nucleus will be made of cysteine).

There are 3 types of amino acids (acidic, neutral and basic) and we have carriers for each group.

Amino acids appear in the urine due to nephrogenic problem, like nephrogenic glycosuria, both of them are called tubular problem, renal tubular acidosis is also a tubular problem. Not glomerular.

Water reabsorption

We know that 125ml of water is filtered to the glomerulus and that 1 ml is excreted, that is per minute. So 124 ml of water is reabsorbed, so 99.3% is reabsorbed while 0.7% is excreted.

Micropuncture technique

Where is this water reabsorbed and in what mechanism?

This is called segmental function of the nephron, which is to study the function of each part of the nephron, and this is done using a technique called micropuncture micropipette mentioned before to measure the concentration of important molecules in different parts of the nephron, this was first done on rats in vivo (alive), in 1924 by the richard brothers, now you can imagine the small size of the rats, their small kidneys, the fact that they were alive, breathing causing the diaphragm to push the kidneys up and down, so the micropipette must be very small in able to take around 0.25 micrometer samples, in humans you can take samples of 2 micrometers. So this whole technique is extremely hard.

Another difficulty lies in the fact that you can only reach the cortex and you cannot reach the medulla with the micropipette and also you cannot see where the micropipette is while performing this technique.

So first you have to inject a dye, if you see the dye coming back to the cortex, you can be sure than you're inside the nephron, now you will inject 2 drops of oil to stop the flow of the filtrate, and this isolates specific segments in the nephron.

Then we inject the animal with inulin, as we know inulin in the bowman's space is the same as in the plasma (freely filtered), now the fluid inside the tubules (not the glomerulus) is called the tubular fluid, now for explanation purposes, we will call the fluid inside the bowman's space the plasma because it's basically the same (not talking about proteins).

So we measure inulin in both the plasma (Bowman's capsule) and in the tubular fluid (late proximal convoluted tubule), and we divide them by each other, we will get 3. Why? Because water was reabsorbed while inulin isn't reabsorbed as we learnt earlier. But why was the answer 3 exactly? Because 2/3 of the water is reabsorbed, so what remained is 1/3, which means the same amount of inulin now is found in 1/3 of the water, which means the concentration tripled. If the answer was 2, then 50% of the water was reabsorbed, if it was 4 then 75% of the water was reabsorbed etc.

Now later they could reach the medulla by entering through the renal pelvis, and go up till you reach the loop of Henle.

Now they took 2 samples, 1 before the ascending part and the other after, they got a value (concentration of inulin before and after) of 1, what does that mean? It means that no water was reabsorbed in this segment, so they concluded that no water is reabsorbed in the ascending part of the loop of Henle, then they applied ADH and nothing changed, they concluded that ADH has no effect on the ascending loop of Henle, later they started applying drugs, to know which drug affect which segment.

Now after knowing which segments and how much they absorbed water, we started working on other substances (other than inulin) to know which segments reabsorbed or secret different substances.

Let's take sodium for example if we calculate the sodium concentration in the plasma, over the sodium concentration in the tubular fluid, we get a value of 1, and what does this mean? It means that sodium is treated the same way water is treated in the proximal convoluted tubule. Knowing that 67% of water is reabsorbed in the proximal convoluted tubule, we conclude that 67% of sodium is reabsorbed here.

As a self-test to understand what is going on, compare the value of inulin that we got earlier, which was 3, with the value of sodium which was 1, we conclude that sodium concentration remained the same, and this doesn't mean it wasn't reabsorbed, it actually was absorbed to the same extent as water.

Now we'll talk about clearance in a segment. It is the same as the clearance we talked about earlier but now we'll replace the concentrations of plasma and urine with concentrations of X before and after the segment so the equation will be as follows:

$$Cx = \frac{TFx}{Px} * V$$

Where:

Cx: Clearance of X
TFx: Conc. of X in tubular fluid (proximal tubule for example)
Px: Conc. Of X in plasma (or Bowman's capsule)
V: Fluid flow rate

Another way to know what happens to a certain substance in a specific segment is to compare the clearance of inulin to clearance of X in that specific segment. As we know inulin increases 3 times in concentration at the end of the proximal convoluted tubule, so if we measure the clearance of X and compare it to that of inulin we can reach a conclusion of how this segment affects X concentration.

This is represented by the following equation:

$$\frac{Cx}{Cin} = \frac{\frac{TFx}{Px} * V}{\frac{TFin}{Pin} * V}$$

So if Cx/Cin = 1 then this segment treats X like inulin which means that X is not reabsorbed nor secreted, if Cx/Cin = 2 this means that the same amount of X that is filtered is also SECRETED, if Cx/Cin = 0.3 this means that 0.7 of X was reabsorbed while 0.3 remained in the tubule.

Now when we started using this technique we calculated the Single nephron GFR, then we multiply by 1 million for 1 kidney, 2 million for 2 kidneys.

This subject will hopefully be elaborated on in the next lecture as I believe there are huge loopholes the doctor didn't mention.

I highly recommend going through the slides as they are more organized and contain pictures and graphs not included here.

The juice is worth the squeeze.

259102 222 0262 222628 81 3151 91028132 916232 62152 81216 79 719102 9 89 319 1 2102 4311 1251 59102 6151212223626 3151 899102 2231 32412291 5222412131 59102 02227 5102 312131 9122152 61366 1991612191 8122222281216 122152 22222121 9 4311 91324122996 231 2102 2231 9122222121 59191 3257028131321 3192262 32551218111 2231 02227 26231 719102 75932291 6181624 53151 4513111 2102 02227 122152 4311 122152 22026216291 9 81626 899102 42284212281 122152 129 2121219176262 212121 89 22316241 231 515121228

First to break the code gets 50jds enjoy.