Lecture No. 4

The composition of the ultrafiltrate is:

Plasma minus protein

How do we know that for sure?

By using the micropuncture technique (taking a sample from Bowman's capsule in vivo and analyze it)

*** Examples of Modification of the ultrafiltrate:**
In the proximal tubule, 100 % of filtered glucose is reabsorbed by a carrier mediated transport mechanism
2° active transport.

In the apical luminal side of the cell we have Na^+ - Glucose luminal transporters:
SGLT 1&2
SGLT 1 : high affinity, low capacity.
SGLT 2 : modest affinity, high capacity.

*** Here, Na^+ is transported down its gradient, but glucose is actively transported against its gradient.**
BUT, if we don't have Na^+, No glucose will be absorbed.

TUBULAR FUNCTION

GTC "GLUCOSE TITRATION CURVE"

- Renal threshold for glucose is 180mg/dl. What does this tell you?
- This implies that the kidney is not involved in glucose homeostasis under normal physiological conditions because the threshold is far from the physiological range (70 – 110mg/dl) which must be tightly controlled.
- The kidney does however participate in the homeostasis of other substances. One good example is phosphate. The normal plasma concentration of this anion is 1mmol/l, and the transport maximum for reabsorption is 0.1mmol/min.
- What do these numbers tell us? Let's examine them more closely. Every minute 125ml of plasma is filtered, and a maximum of 0.1mmol of phosphate is reabsorbed. For every 1 liter to be filtered, a maximum of 0.8mmol is reabsorbed, which is very close to the plasma concentration of 1mmol/l. Therefore, regardless of how much phosphate is ingested, the maximum amount to be reabsorbed corresponds to the normal plasma concentration. So the kidney participates in phosphate homeostasis.

*** At the basolateral membrane, glucose is transported by facilitated diffusion.**

Any carrier-mediated transport exhibits Tmax (saturation) Tmax means if the delivered G to proximal tubules is too much (more than the capacity of the carriers), then it won't be reabsorbed completely, instead, it will be excreted in the urine → Glucosuria.

Glucose MW is small (180), → freely filtered. Freely filtered means: its concentration in the plasma is the same as in Bowman's space.

- Plasma concentration of glucose is between 70 – 110 mg/dl)

-The filtered load of glucose?

It's the amount of glucose filtered per minute.

Filtered load = Plasma conc. * GFR

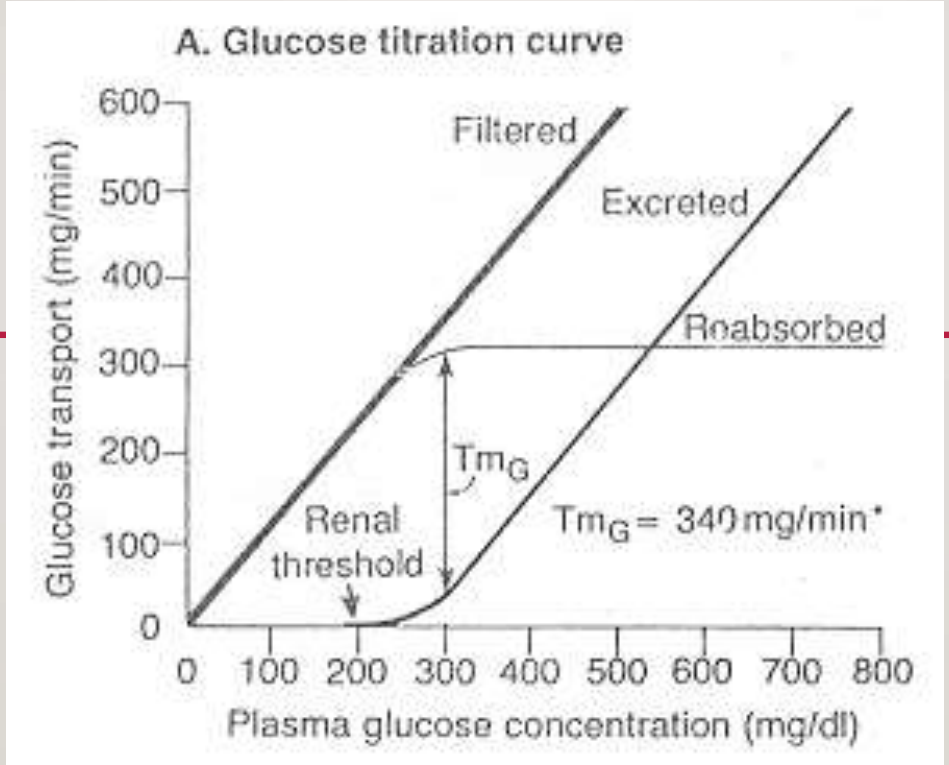
= 100 mg / dl * 1.25 dl/min.

= 125 mg / min

Now, if we increase plasma G conc→↑ Filtration (Linear relationship).

- Reabsorption will increase until we reach Tmax

*** Tmax for glucose is 320 mg/dl, or 375 mg/min (filtered load)**



This curve is called: Glucose Titration Curve GTC.

Until plasma concentration of glucose is 180 mg/dl, we have no excretion ►→ 100% of glucose is reabsorbed.

At normal or even slightly higher than normal, all G are reabsorbed, meaning that kidney is not a major regulator for G. Since threshold & Tm for Glucose are far above normal plasma G level (slight ↑ or ↓ plasma [G] → still 100% of the filtered load is reabsorbed).

Threshold **:**

The conc. of glucose in plasma at which glucose starts to appear in urine = ~~(180 mg/dl venous blood) or (200 mg/dl arterial blood)~~

Theoretically, Threshold & Tmax should match, but practically they do not.→ that is why we see *Splay*

Splay is deviation of the threshold from Tmax

<u>OR</u>: appearance of glucose in urine before Tmax is reached

When increasing plasma [Glu] more than 320 mg/dl …the excreted fraction increases since reabsorption remains constant.

To measure Tmax, we must supply suprasaturated concentrations. … Increase in G conc. →increase chance of the carrier to catch G

- If we have Glucosuria, it may be:

1. Diabetogenic ⟶ because of diabetes
2. Nephrogenic ⟶ the number of glucose carriers in this person is less than normal ⟶ less threshold ⟶ any small rise in the plasma glucose conc. (ex: after meals) will induce glucosuria.

Nephrogenic Glucosuria is benign, not associated with other renal problems, & will not cause any problem later on…good prognosis….you do not need to mention it.
Conclusion: if the patient glucosuria, do a blood glucose level test (e.g FBS), if normal, then it's nephrogenic….just ignore it .

KIDNEY FUNCTION

- KIDNEY FUNCTION IS IMPORTANT TO ASSESS IN MANY CLINICAL SETTINGS.
- A COMMONLY PERFORMED TEST IS CREATININE CLEARANCE AS A MEASURE OF GFR.
- TWENTY FOUR HOUR URINE COLLECTION IS REQUIRED FOR ACCURATE CREATININE TESTING.
- HOWEVER, THIS IS NOT ALWAYS POSSIBLE AS IN THE CASE OF DEMENTED ELDERLY, SMALL CHILDREN, UNCOOPERATIVE PATIENTS, ETC...
- CONSEQUENTLY, SCIENTISTS USED DIFFERENT METHODS AND EQUATIONS TO ESTIMATE GFR (THE VALUE OBTAINED THUS LABELED EGFR).

Tests used to assess Kidney Function

- First,

C_{cr}=tGFR

Mentioned previously

• Second,

KFT: ***blood tests*** to assess kidney function:
Plasma urea (P_{urea}), Plasma Creatinine (P_{cr}), Electrolyte.
- If Pcr is in it s normal range (0.7-1.4 mg/dl), this does not always exclude kidney impairment… you should notice the range is wide "double". Pcr depends on muscle mass: for example if Pcr today is 0.8 mg/dl and after few weeks it increases to 1.4 mg/dl…this indicates decrease in GFR….so previous reading is important if available.

* Still, plasma creatinine is the best indicator as KFT. It is more important than urea because urea is subjected to other variables. (Like in cases of dehydration or GI bleeding), it's plasma level increases without kidney damage.

* Creatinine also rises due to increase muscle mass (body builders). Elderly have less muscle mass.

Third,

Another tests involve *urine analysis* ;

*** urine is very informative and easy to deal with.**
*** We can test:**
1. Volume of urine (24 h Urine collection)
2. Presence or absence of Glucose, proteins, RBCs, WBC, casts, etc…
3. SG
4. Color
5. pH

Segmental Physiology of the nephron

Glucose **is reabsorbed by secondary active transport in the Proximal Tubules. How did we know ?**
Answer: Using the micropuncture technique:
When we take a sample from the late proximal tubule → Zero glucose; this mean → 100% of the filtered glucose is reabsorbed in the proximal tubules.

The same thing applies to the *amino acids* which are 100% reabsorbed in proximal tubules, through different carriers:

- **one for neutral amino acid**
- **one for acidic amino acids**
- **one for alkaline amino acids**

*** And there are special carriers for special amino acids like Cystein.**

• The Micropuncture Technique

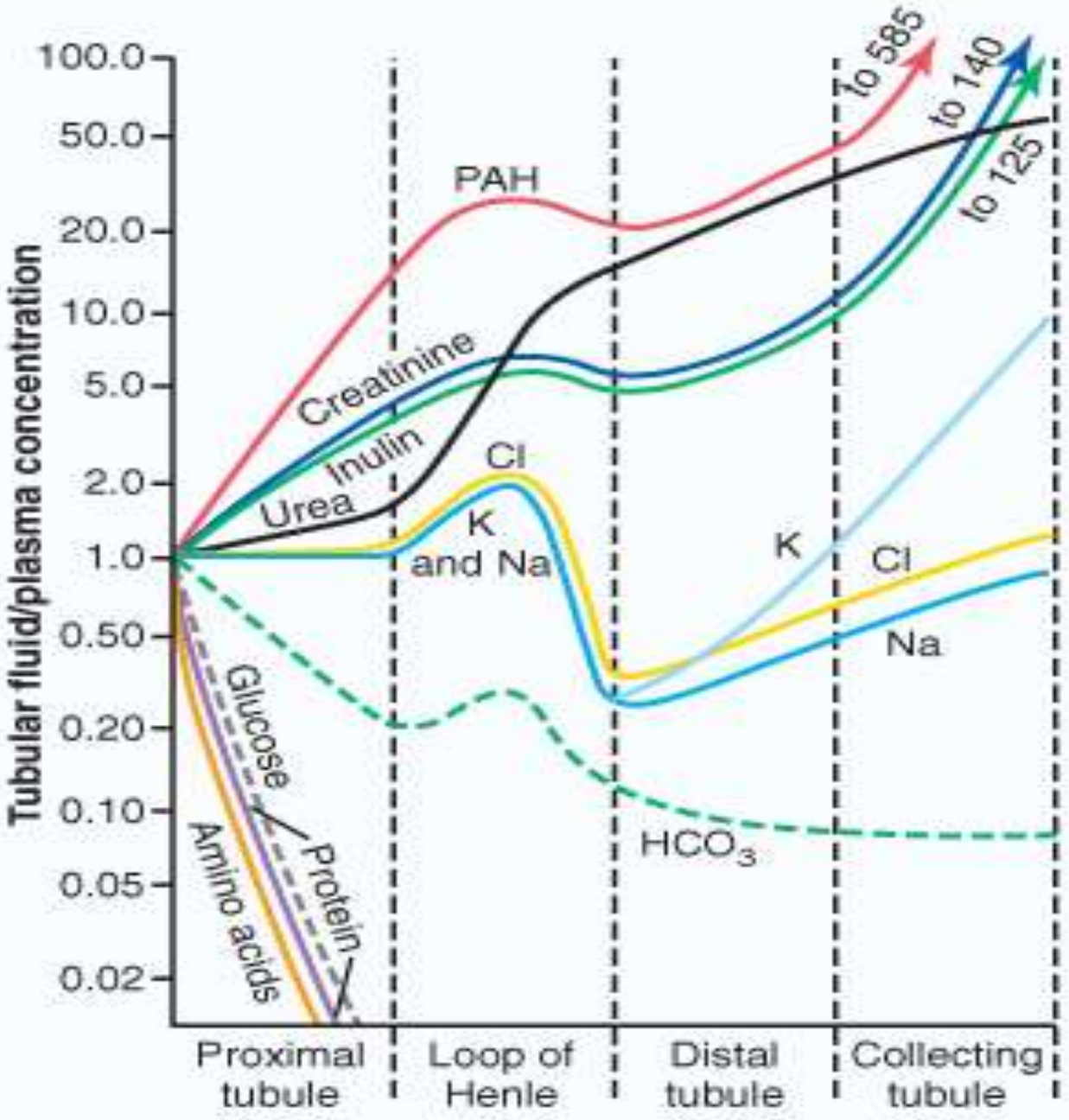
•When we study the kidney & perform the micropuncture technique, we do this *in vivo* , because the interstitium is very unique and we can't offer it *in vitro (osmotic gradient)*

• We isolate the segment that we want to study (in vivo) by injecting 2 drops of oil, by a pipette that has a diameter of 2 µm & the sample we get is in terms of nano litres.

• We can measure SNGFR (Single Nephron GFR) by measuring free flow from Bowman's capsule collecting ultrafiltrate for 10 min and do our calculations

SEGMENTAL VARIATION IN THE TUBULAR SYSTEM

- **The ratio of a substance's concentration in the tubular fluid to its levels in the plasma changes along the course of the tubular system depending on how it is handled.**
- **The next Figure describes these changes. Notice how levels of glucose and amino acids drop to extinction even before the tubular fluid completes its passage through the proximal tubule.**
- **The TF/P for sodium remains 1 in the proximal tubule since Na+ and water are reabsorbed in the same proportion.**
- **For inulin, however, TF/P reaches 3 in the proximal tubule since 65% of water and none of the inulin is reabsorbed.**
- **Regarding PAH, its levels in the proximal tubule are higher than those of the others. The reason is that it is not only filtered, but also actively secreted and not reabsorbed.**


Tubular fluid/plasma concentration
100.0
50.0
20.0
10.0
5.0
2.0
1.0
0.50
0.20
0.10
0.05
0.02
PAH
Creatinine
Inulin
Urea
Cl
K
and Na
Glucose
Amino acids
Protein
HCO3
To 585
to 140
to 125
K
Cl
Na
Proximal tubule
Loop of Henle
Distal tubule
Collecting tubule

Generally,

if we want to study semental physiology of the nephron, or just know each segnet handles substance X, we do micropuncture technique….it will tell us how that segment of the nephron handles this substance.

If "x" is freely filtered then [X] in Bowman's capsule is equal to [X] in plasma……If:

$$\frac{TF_x}{P_x} = 1$$

What is your conclusion??

Mostly, we conclude that this substance is reabsorbed at the same proportion as water…

….but how much water has been reabsorbed across that specific segment?

To know that we must utilize inulin

if $\frac{TF_{In}}{P_{In}} = 3$

This means that 2/3 of the water was reabsorbed

Also 2/3 of substance X must have been reabsorbed too

By taking two samples (at the beginning and at the end of any segment) and measuring substance X conc at both sides (notice: we are using the concept of clearance).

Clearance of substance X across that segment.

$$C_X = \frac{TF_X}{P_X} * V$$

Where

Cx : Clearance of X

TF_X : Conc. of X in tubular fluid (proximal tubule for example)

P_X : Conc. Of X in plasma (or Bowman's capsule)

V: Fluid flow rate

Now, comparing with inulin:

$$\frac{C_X}{C_{in}} = \frac{\frac{TF_X}{P_X} * V}{\frac{TF_{[inulin]}}{P_{[inulin]}} * V}$$

* If $\frac{Cx}{Cin} = 1$

This means that this substance was handled by that specific segment exactly as inulin: not reabsorbed, not secreted.

* If $\frac{Cx}{Cin} = 2$

This means that the same amount of X that is filtered was also secreted to the tubule.

* If $\frac{Cx}{Cinulin} = 0.3$

This means that 0.7 of X was reabsorbed & 0.3 only remained in the tubule.

***Notes*:**

- In nephrectomy, other nephrons may compensate partially.
- We may have congenital one kidney & that's okay if it's functioning well & has no malformations
- Silent malignant Kidney stone :if present, it might give only a discomfort feeling, different from colicky pain.

- Renal colicky pain – caused by stones – is benign, bc it alarms the patients always to go to doctor.

- obstruction by stone might damage the kidney, because it will increase Bowman's capsular hydrostatic pressure & oppose the filtration.

  This leads to cortical atrophy → permanent kidney damage.

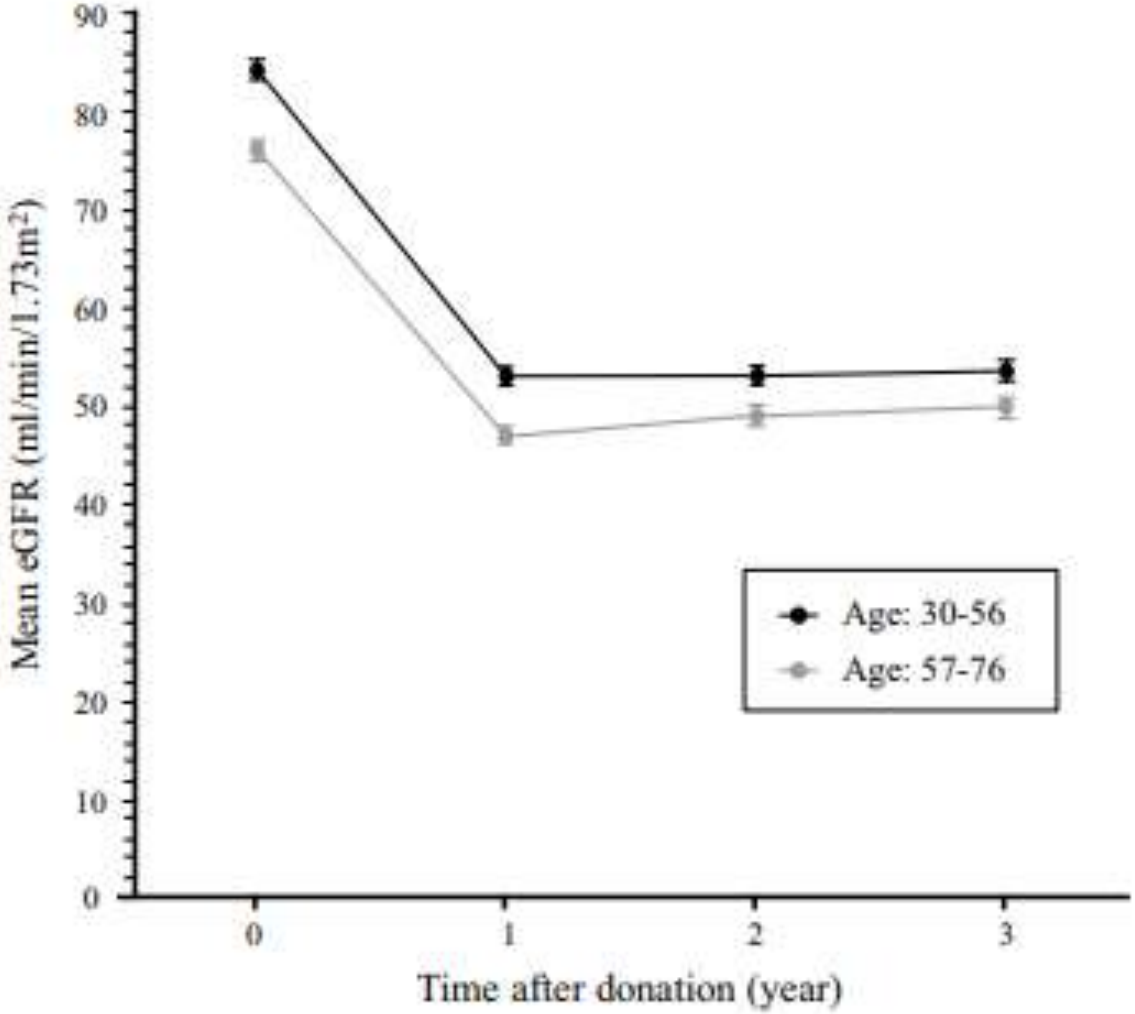


Fig. 3 Serial kidney function of living kidney donors at 1, 2, and 3 years after donation