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Revised by

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Renal Clearance

Lecture 3

RENAL BLOCK
PHYSIOLOGY TEAM 437

Editing file

Objectives:

by the end of this lecture you will be able to:

- Describe the concept of renal plasma clearance.
- Use the formula for measuring renal clearance.
- Use clearance principles for inulin, creatinine etc. for determination of GFR.
- Explain why it is easier for a physician to use creatinine clearance Instead of Inulin for the estimation of GFR.
- Describe glucose and urea clearance.
- Explain why we use of PAH clearance for measuring renal blood flow.

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Concept of Clearance

Clearance is the volume of plasma that is completely cleared of a substance each minute.

Example:

Renal clearance of Substance X is defined as the ratio of excretion rate of substance X to its concentration in the plasma:

$$C_X = (U_X \times V) / P_X$$

Clearance Equation

- $C_X = (U_X X V) / P_X$
  - C_X = Renal clearance (ml/min)
  - U_X x V = Excretion rate of substance X
  - U_X = Concentration of X in urine
  - V = Urine flow rate in ml/min

Amount of substance excreted = (filtered – reablsorbed + secreted)

$$U_x V = GFR \times P_x \pm T_x$$

What is the Importance of Renal Clearance?

To quantify several aspects of renal functions:

- Rate of glomerular filtration
- Rate of blood flow
- Assess severity of renal damage
- Tubular reabsorption.
- Tubular secretion of different substances.

Renal clearance - renal plasma flow - GFR (16:29)

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Types of Clearance Tests

- **Endogenous**
  - Creatinine
  - Urea
  - Uric acid
- **Exogenous**
  - Inulin
  - Para-amino hippuric acid (PAHA)
  - Diodrast (di-iodo pyridone acetic acid)

Calculation: $\frac{U \times V}{P}$

Where:

U = concentration of substance in urine (mg/dl)

V = volume of urine excreted per minute (ml/min)

P = concentration of substance in plasma/serum (mg/dl)

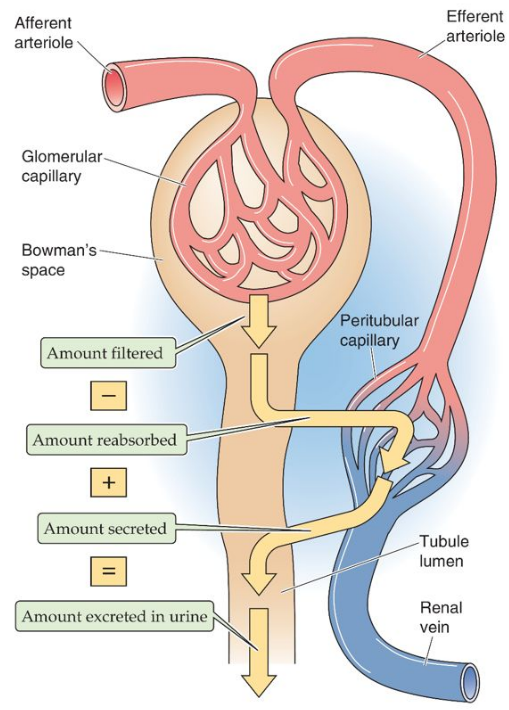
How to measure Clearance (GFR)?

Very Important

Clearance method:

Volume of plasma which is completely cleared of a substance per unit time.

- amount excreted = amount filtered – amount reabsorbed + amount secreted
- **amount filtered per minute= GFR . P_x (filtered load)**
- amount excreted per minute=$\tilde{V}$. U_x(excretion rate)



Why we measure GFR? The **level of GFR** and its **magnitude of change** over time are vital to:

- The **detection** of kidney disease
- Understanding its **severity**
- Making decisions about **diagnosis**, **prognosis**, and **treatment**.

Clearance of a solute is the volume of plasma (per unit time) needed to supply the amount of solute that appears in the urine. This CLEARANCE method uses the amount balance of an I.V. injected test substance such as inulin.

P_x = concentration of substance in plasma.

$\tilde{V}$ = urine flow rate.

U_x = concentration of substance in urine.
Inulin: Amount filtered = Amount excreted

Criteria of a substance used for GFR measurement:

Clearance = GFR

- freely filtered
- **not secreted by the tubular cells,**
- **not reabsorbed by the tubular cells.**
- should not be toxic
- should not be metabolized
- easily measurable
- NOT metabolized in the nephron

Examples of such a substance:

- **Creatinine (endogenous):**

By-product of skeletal muscle metabolism

- **Inulin (exogenous):**

It is a polysaccharide with a molecular weight of about 5200 and it fits all the above requirements. Inulin is used as an **injection** to measure GFR because it's exogenous.

1- For the above mentioned substance:

Amount filtered per minute = Amount excreted per minute.

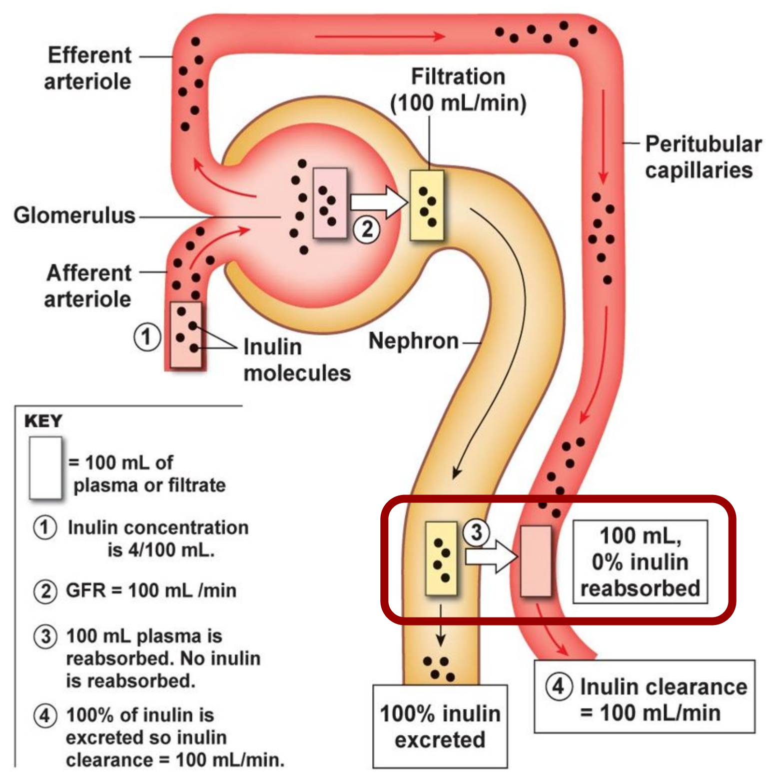
- e.g., inulin

$$GFR \cdot [P]_{Inulin} = [U]_{Inulin} \cdot \tilde{V}$$

$$Cl_{Inulin} = GFR = [U]_{Inulin} \cdot \tilde{V} / [P]_{Inulin}$$

Note: **Inulin:**

- A plant product that is filtered but **not** reabsorbed or secreted.
- Used to determine GFR and therefore nephron function.



Example

- If plasma conc. of inulin = 1 mg/100ml
- Urinary conc of Inulin = 120 mg /100ml
- Urine flow (UV) = 1 ml/min then,
  - the clearance of inulin will be?
    - 120 ml/min

Continuation of: Clearance = GFR

Clearance and GFR (4:26)

The rate of urinary excretion of a substance can be affected by glomerular filtration, tubular reabsorption, and tubular secretion.

- The amount of a substance filtered per unit time is known as the filtered load.
- The amount excreted per unit time is referred to as the excretion rate.

Fractional excretion (FE) expresses solute excretion as a percentage of its filtered load. FE is useful because changes reflect altered tubular transport rather than simple changes in GFR. FE is also known as the clearance ratio because it can be calculated as the ratio of solute clearance to creatinine clearance.

ONLY in male slides

2- For substances *reabsorbed* by the kidney:

Amount filtered per minute > Amount excreted per minute

$$GFR \cdot [P]_x > [U]_x \cdot \tilde{V}$$

$$GFR \cdot [P]_x - \text{Absorbed 'T'}^* = [U]_x \cdot \tilde{V}$$

- $Cl_{sub} < Cl_{inulin}$ Absorption from nephrons is occurring.
- Cl = 0 for glucose and amino acids (normally).
- e.g., glucose, sodium, urea. These substances are fully Reabsorbed to blood circulation

Cl = Clearance
*Absorbed 'T'= Partially transported

- **3- For substances *secreted* by the kidney:**

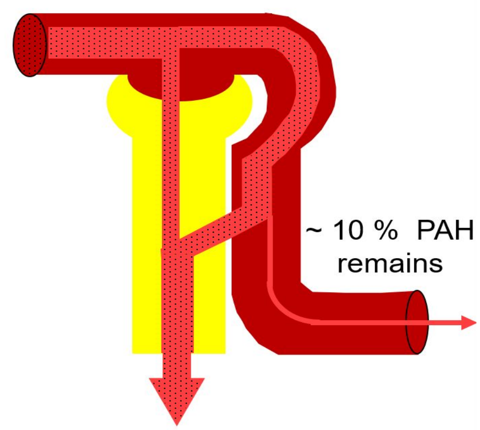
  eg. PAH, creatinine.

  amount filtered per minute < amount excreted per minute

$$GFR \cdot [P]_x < [U]_x \cdot \tilde{V}$$

$$GFR \cdot [P]_x + \text{Secreted 'T'} = [U]_x \cdot \tilde{V}$$

  12 mg/min < 60 mg/min



- $Cl_{sub} > Cl_{inulin}$ Secretion into nephrons is occurring.

Clearance method to measure RPF → Criteria of substance used eg. **PAH** → Filtered + Secreted; NOT reabsorbed

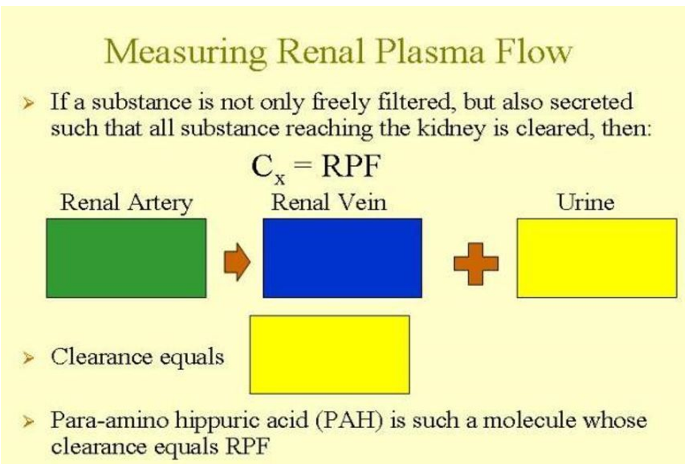
- Passage through the kidney:
  $Cl_{PAH} = RPF^* = [U]_x \cdot \tilde{V} / [P]_x$

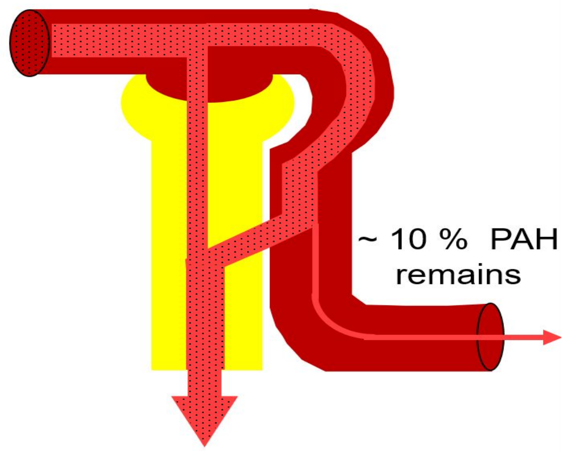
*RPF=Renal Plasma Flow

Measurement of renal blood flow

Substances used for measurement of GFR are not suitable for the measurement of Renal Blood Flow. Why?

- Inulin clearance only reflects the volume of plasma that is filtered and not that remains unfiltered and yet passes through the kidney.
- It is known that only 1/5 of the plasma that enters the kidneys gets filtered.
- Therefore, other substances to be used with special criteria.
- To measure renal blood flow we will have to measure renal plasma flow first and then from the hematocrit we calculate the actual blood flow.





Use of PAH Clearance to Estimate Renal Plasma Flow.

Para-Aminohippuric acid (PAH) is freely filtered and secreted

and is almost completely cleared from the renal plasma.

1. amount enter kidney = RPF x P_{PAH}
2. amount entered = amount excreted
3. ERPF* x $P_{PAH} = U_{PAH}$ x V (*effective renal plasma flow).

$$ERPF = \frac{U_{PAH} \times V}{P_{PAH}}$$

ERPF = Clearance PAH

Example of such substance:
Para-aminohippuric acid (PAH)
90% of plasma flowing through the kidney is completely cleared of PAH.

For the measurement of renal plasma flow, we will again need a substance that is:

- freely filtered
- **Rapidly secreted by the tubular cells,**
- not reabsorbed by the tubular cells.
- should not be toxic
- easily measurable

How to measure renal blood flow?

PAH clearance(C) example: If the concentration of PAH in the urine and plasma and the urine flow are as follows:

- Conc. of PAH in urine=25.2 mg/ml
- Urine flow=1.1 ml/min
- Conc. of PAH in arterial blood=0.05 mg/ml
- Then CPAH or Renal Plasma Flow= (25.2 x 1.1)/0.05 = 560 ml/ min

$$RPF = RBF \times (1\text{-hematocrit})$$

(وسطين في طرفين)

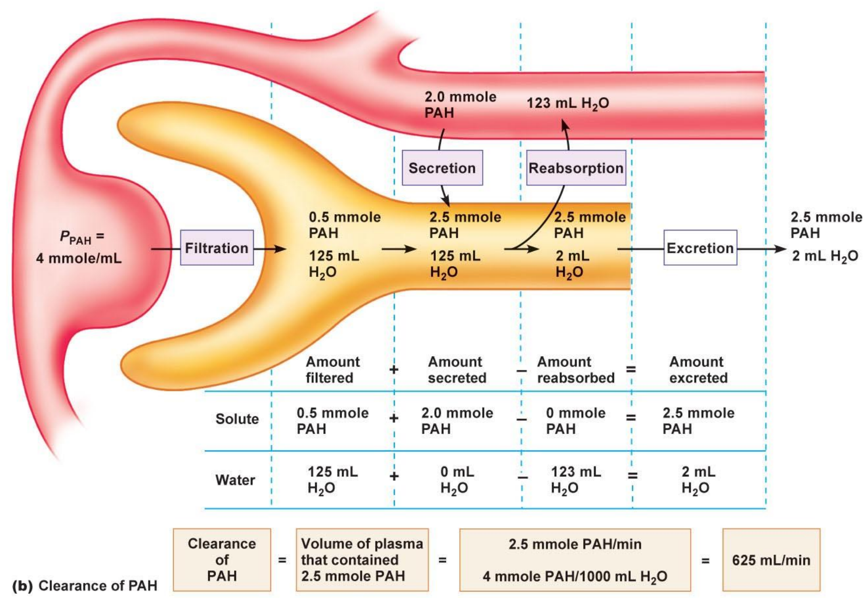
$$RBF = \frac{RPF}{(1\text{- Hematocrit})}$$

Remember

Answer: let's say the hematocrit is 45%, then renal blood flow will be:

- (560 x 100)/(100-45)= 1018 ml/min

Extra



(b) Clearance of PAH

Importance of renal clearance:

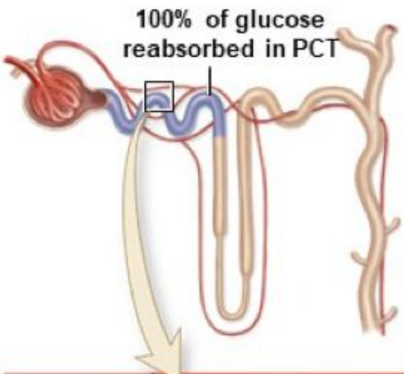
1. Renal Clearance gives an indication of the kidneys' function.
2. Clearance can also be used to determine renal handling of a substance.
3. Clearance values can also be used to determine how the nephron handles a substance filtered into it.
4. In this method the clearance for inulin or creatinine is calculated and then compared with the clearance of the substance being investigated.

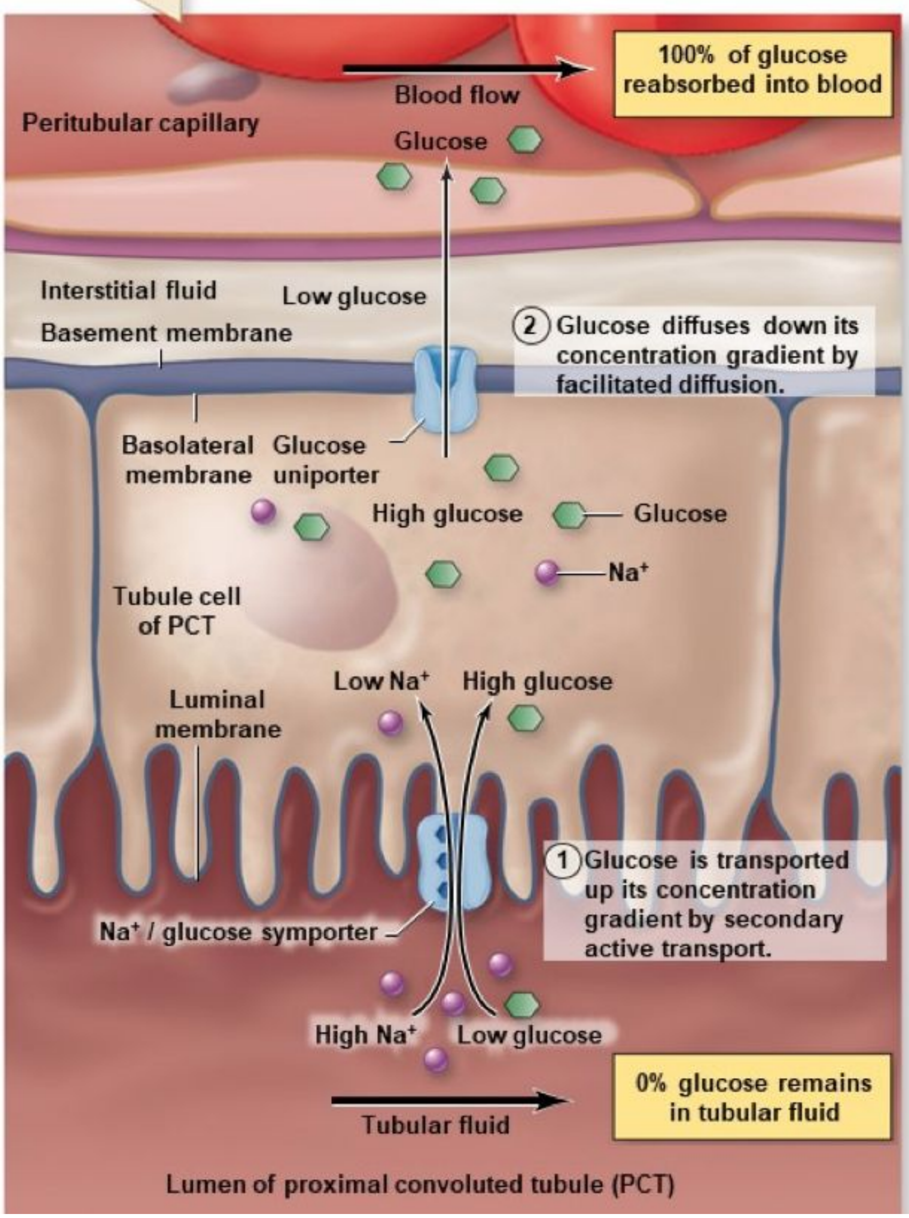
Glucose Reabsorption

ONLY in male slides

- From tubular lumen to tubular cell:
- Sodium co-transporter (carrier-mediated secondary active transport).
- Uphill transport of glucose driven by electro-chemical gradient of sodium, which is maintained by Na-K pump present in basolateral cell membrane.
- From tubular cell to peritubular capillary:

  Facilitated diffusion (carrier-mediated passive transport)





- Glucose has a specific channel (glucose carrier) that has the ability/characteristic to be saturated.
- Glucose enters against its concentration gradient with the help of sodium.

Comparison of Clearance of a Substance with Clearance of Inulin

1) = **inulin** clearance; only filtered not reabsorbed or secreted
2) < **inulin** clearance; reabsorbed by nephron tubules
3) > **inulin** clearance; secreted by nephron tubules

Calculation of Tubular Reabsorption or Secretion from Renal Clearance

Substances that are **completely reabsorbed** from the tubules (amino acids, glucose), **clearance** = **zero** because the urinary secretion is zero.

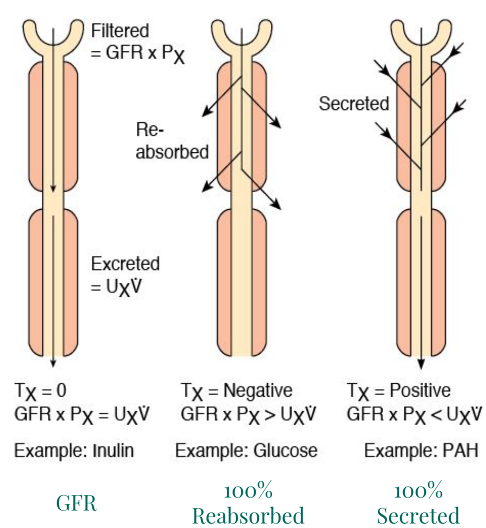
Substances **highly reabsorbed** (Na), its **clearance** < **1% of the GFR**.

Reabsorption rate can be calculated =

Filtration rate- excretion rate = (GFR X P*)-(U* X V)
* The substance needed to be assessed.

- If excretion rate of a substance is greater than the filtered load, then the rate at which it appears in the urine represents the sum of the rate of glomerular filtration + tubular secretion:
- Secretion* = (U* X V)- (GFR X P*)

* indicate the substance



Filtration fraction

It is the ratio of GFR to renal plasma flow.

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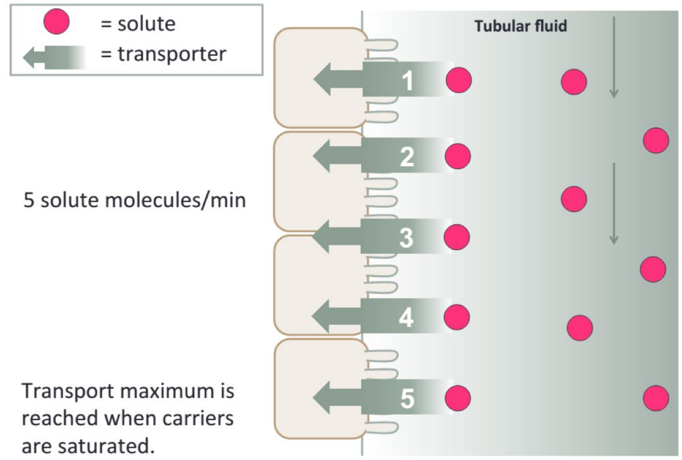
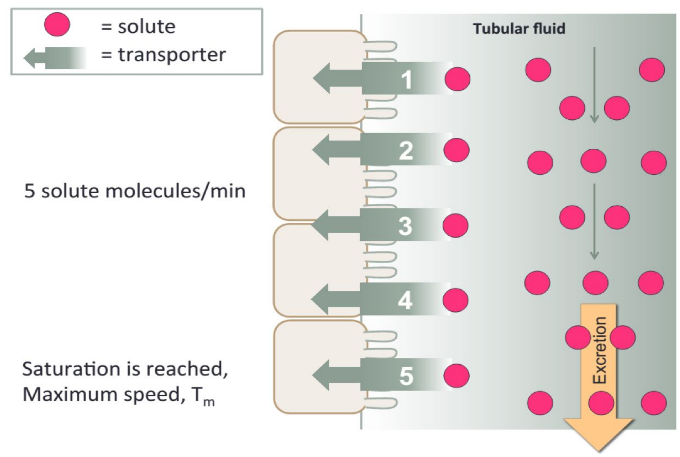
Tubular Transport Maximum

- It is the maximal amount of a substance (in mg) which can be transported (reabsorbed or secreted) by tubular cells/min.
- Many substances are reabsorbed by carrier mediated transport systems e.g. glucose, amino acids, organic acids...
- Carriers have a maximum transport capacity (T_m) which is due to saturation of the carriers. **If T_m is exceeded, then the excess substrate enters the urine.**
- Glucose is freely filtered, so whatever its [plasma] that will be filtered.

> - For example, if I had 100 glucose molecules and the limit of T_m is 50, only 50 are removed and the rest are left.
> - But mostly the limit of T_m in our bodies is double the amount of glucose.
>
> **Important**





Tubular Transport Maximum

- In man for plasma glucose up to 180 mg/dl, all will be reabsorbed. Beyond this level of plasma [glucose], it appears in the urine = renal plasma threshold for glucose.
- (If plasma [glucose] = 275 mg/dl, 275 mg/dl will be filtered, 180 mg/dl reabsorbed and 95 mg/dl excreted.)

> - If it exceeds 275 or 250, glucose must enter the urine.
> - After, some people will have glucose in the urine and others won't have it, because the limit of T_m differs between people.
> - Renal Plasma Threshold for Glucose: the highest concentration of glucose in which no excretion of glucose in urine happens.
>
> **Important**

- Kidney does NOT regulate [glucose], (insulin and glucagon). Normal [glucose] of 90 mg/dl, so T_m is set way above any possible level of (non-diabetic) [glucose] at 375 mg/min. Thus, ensure that all this valuable nutrient is normally reabsorbed. The appearance of glucose in the urine of diabetic patients = glycosuria, is due to failure of insulin, NOT, the kidney.

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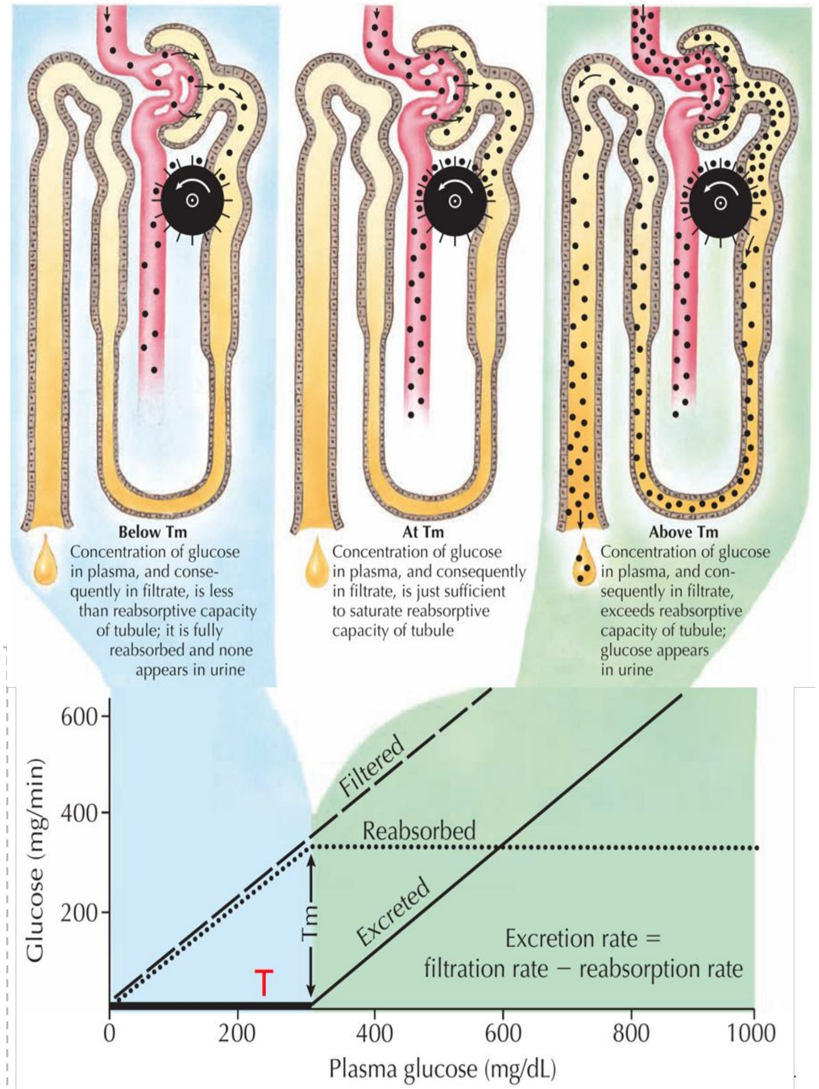
Once T_m is reached for all nephrons, further ↑ in tubular load are not reabsorbed, but are then excreted.

Threshold (T) is the plasma conc. at which tubular load just exceeds T_m for reabsorption, where below threshold all solute molecules are reabsorbed, and above threshold, some solutes are not. **(T_m was in mg/min)**



Glucose curve (very important):

- The filteraton is always increasing

(note that the line is rising constantly even at 700 mg/100ml)

filtration= GFR . P_x

-The excretion start at glucose threshold (180 mg/100ml)

How to calculate excretion ?

$$\frac{\text{GFR} \cdot P_x}{100} - (T_m) = \text{excretion}$$

e.g. calculate glucose(G) excretion:

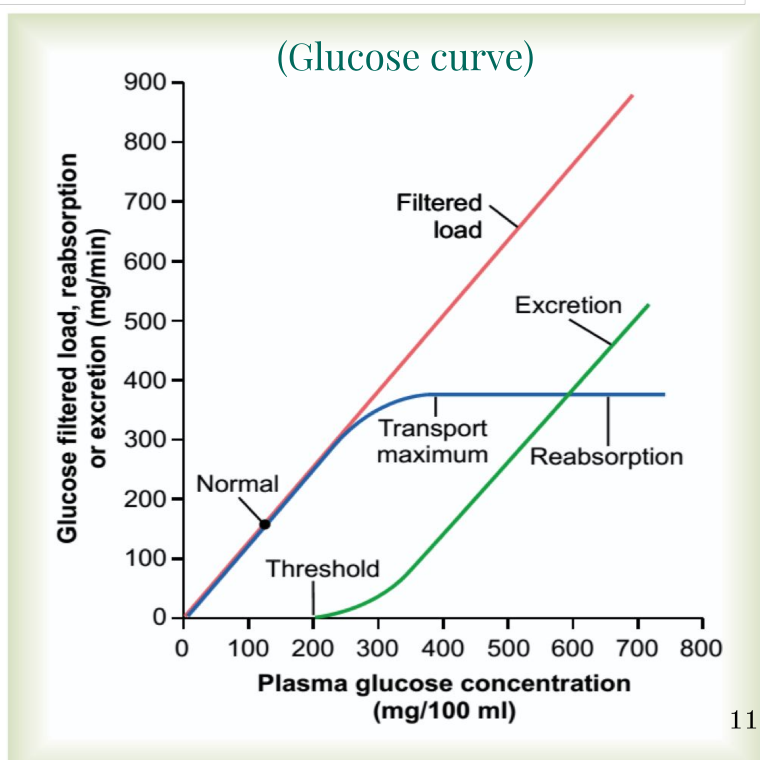
GFR=125 (ml/min)

plasma G conc.=200mg/100ml

T_m =180

(125 . 200) / 100 = 250-180

Glucose excretion = 70 mg/min



Why divide by 100?

(because P_x is mg/100ml

Important Extra Explanation From Doctor

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Summary of Important Points:

- Clearance is a “quantitative concept” which is useful for evaluating several aspects of renal function. If one liter of plasma contains one milligram of a substance, and we remove that entire mg, then the *clearance* is **one liter** (not one mg). If we removed one tenth of a mg, then the clearance would be one tenth of a liter. *Renal clearance* describes the removal of substances from “a volume of” plasma (excretion) per time period (usually per minute).

- If a substance is **not** excreted then the renal clearance is zero. If a substance could be **100% removed** from plasma, then the clearance would be the entire volume of plasma processed by the kidneys (=**renal plasma flow**, ml/min!!). Para-amino-hipuric acid (PAH) is **almost** entirely removed from plasma by the kidneys (85-90%), so the clearance of PAH is **almost** equal to RPF (actually 85-90% of RPF). Similarly, if a substance (like inulin) is freely filtered, but not reabsorbed or secreted, then the amount excreted (removed) = the amount filtered. Thus the clearance of inulin is equal to the volume filtered, **the glomerular filtration rate** (GFR).

Note: Some substances are handled by the kidneys in a very specific fashion and this can be useful in determining kidney function.

<u>Example:</u> if it were possible for the kidneys to **completely** remove a substance from plasma then the clearance of that substance is identical to RPF!

<u>Example:</u> if a substance is freely filtered but is **not** transported by the tubules, then that which is filtered is also excreted. Therefore, only the filtrate is "cleared" and the clearance of that substance is identical to the GFR!

Q1/Given the following information for a freely filterable substance

GFR = 120 mL/min
Plasma concentration = 3 mg/mL
Urine flow rate = 2 mL/min
Urine concentration = 10 mg/mL

we can conclude that:

a) The kidney tubules reabsorbed 340 mg/min
b) The kidney tubules reabsorbed 200 mg/min
c) The kidney tubules secreted 200 mg/min
d) The kidney tubules secreted 340 mg/min
e) Net transport is 0 mg/min

Amount Filtered per minute = (GFR X [Sub]plasma)
= 120 ml/min X 3 mg/ml = 360 mg/min
Amount Excreted per minute = ([sub]urine X Urine flow rate)
= 2 ml/min X 10 mg/ml = 20 mg/min
Amount Filtered per minute > **Amount Excreted per minute**
Amount Transported per minute = **Filtered – Excreted**
= 360 - 20 = 340 mg/min

الكمية اللي صار لها reabsorption

Q2/A patient is infused with PAH to measure renal blood flow. She has a urine flow rate of 1 mL/min, a plasma [PAH] of 1 mg/mL, a urine [PAH] of 600 mg/mL, and a hematocrit of 45%. What is her RBF?

a) 555 mL/min
b) 600 mL/min
c) 660 mL/min
d) 1,091 mL/min
e) 1,333 mL/min

$$Cl_{PAH} = RPF = \frac{[U]_x \cdot \tilde{V}}{[P]_x} = \frac{600 \text{ mg/mL x 1 mL/min}}{1 \text{ mg/min}} = 600 \text{ mL/min}$$

$RPF = RBF \times (1\text{-hematocrit})$

$RBF = 600 / (1-0.45) = 1{,}091$ mL/min

ONLY in male slides

$RPF = RBF \times (1\text{-hematocrit})$
(وسطين في طرفين)

$$RBF = \frac{RPF}{(1- \text{Hematocrit})}$$

Remember

Summary

- Renal clearance
  1. Filtration only
  2. Filtration, partial reabsorption
  3. Filtration, complete resorption
  4. Filtration, secretion

- Renal clearance of Substance X is defined as the ratio of excretion rate of substance X to its concentration in the plasma:

$$C_X = (U_X \text{ X } V)/ P_X$$

- Amount of substance excreted =
  (filtered – reabsorbed + secreted)

$$U_x V = GFR \text{ x } P_x \pm T_x$$

- Amount filtered per min (filtered load) =

$$GFR \,.\, P_x$$

- Amount Excreted per min (excretion load) =

$$\tilde{V} \,.\, U_x$$

- GFR =

$$Cl_{Inulin} = GFR = [U]_{Inulin} \,.\, \tilde{V} / [P]_{Inulin}$$

- RPF =

$$Cl_{PAH} = RPF = [U]_x \,.\, \tilde{V} / [P]_x$$

- RBF =

$$RPF / (1\text{-hematocrit})$$

Quiz

1) Criteria of a substance used for GFR measurement:
  a) Not freely filtered
  b) Secreted by the tubular cells
  c) Should be toxic
  d) Not reabsorbed by the tubular cells

2) For the measurement of renal plasma flow a substance needs to be:
  a) Not freely filtered
  b) Toxic
  c) Completely secreted
  d) Reabsorbed

3) If the clearance of a substance is less than the clearance of inulin it is?
  a) Only filtered not reabsorbed or secreted
  b) Reabsorbed by nephron tubules
  c) Secreted by nephron tubules
  d) Filtered, reabsorbed, and secreted

4) A substance that is completely reabsorbed from the tubules:
  a) Inulin
  b) Amino acids
  c) Para-Aminohippuric acid (PAH)
  d) Creatinine

5) Amount of substance excreted =
  a) The ratio of GFR to renal plasma flow
  b) Amount filtered-reabsorbed+secreted
  c) Amount filtered+reabsorbed+secreted
  d) Amount filtered-reabsorbed-secreted

6) Substance clearance that is used to measure the renal plasma flow:
  a) Glucose
  b) Inulin
  c) Paraminohippuric acid (PAH)
  d) Na

1) D
2) C
3) B
4) B
5) B
6) C

Thank you for checking our work

Male Team:

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