# Lecture-2

## Review of the previous lecture:

-Kidney's function is to clean the blood by the removing of the waste plus adding some valuable substances

-kidney failure will lead to death for many reasons, for example:
- Increase plasma urea and creatinine concentrations
- Electrolyte imbalance
* K imbalance (hyperkalemia): lead to cardiac arrhythmias
- * Ca imbalance: affects bone (kidney is one of three organs for $Ca^{++}$ homeostasis: Bone, GIT and kidneys)

- pH disturbance: metabolic acidosis.

- Kidney secret erythropoietin→ kidney failure may lead to anemia

- Kidney regulates the volume of blood: kidney failure → hypertension, malignant hypertension → pulmonary edema

# Today's Lecture:

- **Renal Blood Flow (RBF)**
- **Glomerular Filtration Rate (GFR)**

# Renal blood flow

- High blood flow (~22 % of cardiac output)

- High blood flow needed for high GFR

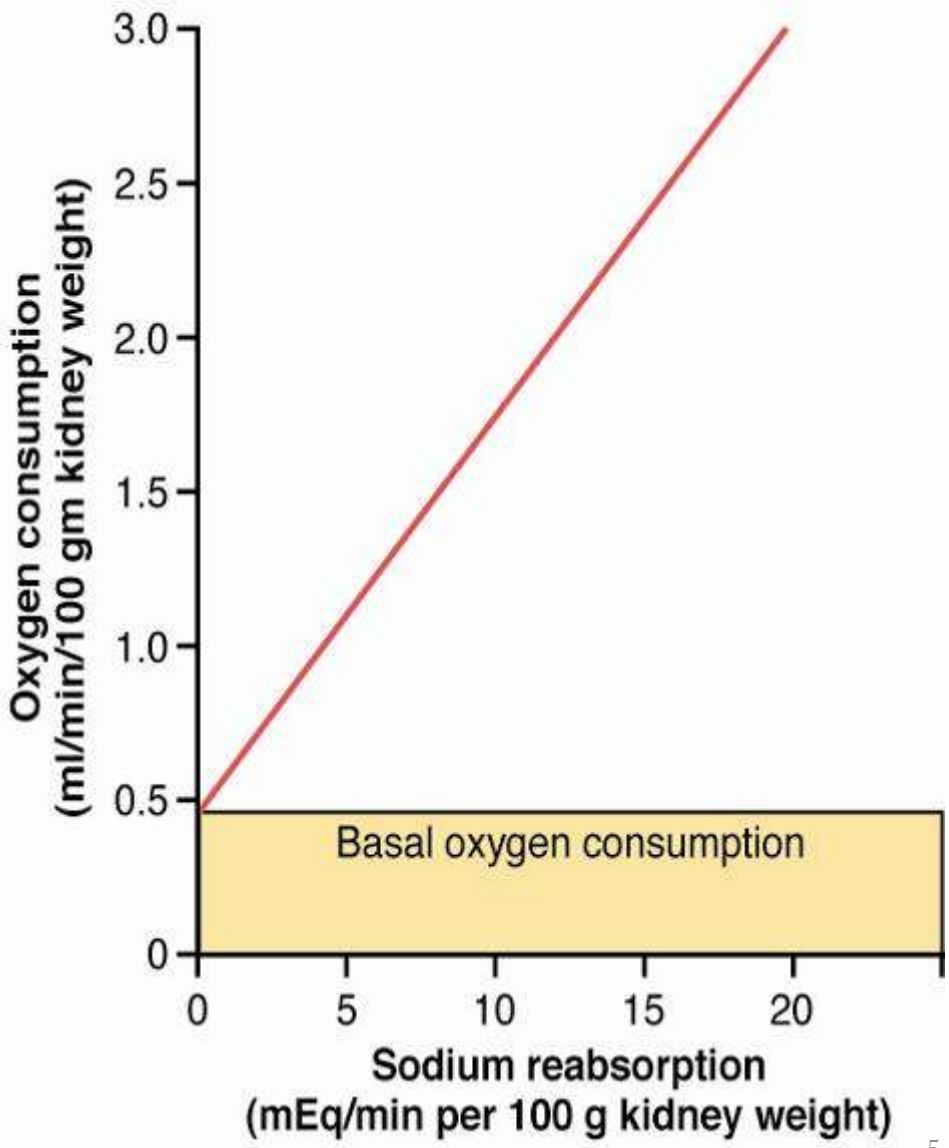
- Oxygen and nutrients delivered to kidneys normally greatly exceeds their metabolic needs

- A large fraction of renal oxygen consumption is related to renal tubular sodium reabsorption

# RBF

- Kidneys are reconditioning organs i.e. Receive too much blood. RBF= 20-25% of Q.
- If RBF decreases →→Renal Failure
- The A-V oxygen difference is small.
- However, $O_2$ CONSUMPTION in the kidney (ml $O_2$/g $tissue_2$ weigh) is twice as that for brain.
- This $O_2$ consumption is directly related to $Na^+$ reabsorption. If GFR is high → $Na^+$ reabsorption is high→$O_2$ consumption is high. When GFR is severely depressed (Acute RF) → decrease need for $O_2$

# Renal oxygen consumption and sodium reabsorption



# Blood Flow to Different Organs

| Tissue | Blood flow (ml/g/min) | A-V difference Vol% |
|---|---|---|
| Heart | 0.8 | 11 |
| Brain | 0.5 | 6.2 |
| Sk muscles | 0.03 | 6 |
| Liver | 0.6 | 3.4 |
| Kidney | 4.2 | 1.4 |
| Carotid bodies | 20 | 0.5 |

# How to measure Renal Blood Flow?

Through this equation:

$$RBF = \frac{\text{Renal Plasma Flow}}{1\text{-Hct}}$$

So, if we assume that the RBF is 1250 ml and the Hct is 45%, the Renal Plasma Flow is ≈ **685 ml.**

# How to measure Renal Plasma Flow (RPF) :

- RPF : how much plasma enter both kidneys per minute.
- We use a substance X that is completely removed (cleaned) from the blood once it reaches the kidneys: i.e. Renal vein concentration of X = 0
- Once “X” comes to the peritubular capillaries is completely secreted.
- The substance used commonly here is the PAH (para-aminohippuric acid.)

# Before we proceed to RPF measurement: we must understand the concept of clearance “C” in renal physiology

-Cx: Is volume of plasma/min provide X for excretion/min.

-Unit of clearance: [Volume/time such as ml/min]

***<u>Examples:</u>***

- **We have 650 ml plasma with specific amount of X, after leaving the kidney through renal vein all of the plasma was cleaned from X (100%): Clearance = 650 ml/min**

- **We have 650 ml plasma with specific amount of Y, we find the entire amount in the renal vein and nothing in the urine, then clearance = 0 ml/min**

- **We have 650 ml plasma with specific amount of Z, after leaving the kidney we find half of the amount of Z. Clearance will be 50% of the 650 = 325 ml/min**

**Law of Conservation of Mass:**

**Amount excreted/min = Amount provided for excretion (by artery)/min**

$$Ax = Vx + Ux$$

- Ax: is the amount of "X" entering the kidneys through the renal artery
- "X" leaves the kidney through:
- 1. renal vein (Vx) or 2. urine (Ux).

If we assume that venous concentration of X "Vx" equals to zero, then:

$$\mathbf{Ax = Ux}$$

**AX=RPF (ml/min) * Px**

**UX= UOP (ml/min) * Ux**

**Therefore, RPF = (U/P)x * UOP**

• *Additional criteria must be met before using "x" as RPF marker:*
*"X: is not accumulated, produced or metabolized in the kidney. It does not affect kidney function*

# PAH :

## Paramino hippuric acid

PAH is a substance used to measure RPF (RPF marker),

how?

Through the equation, the amount of the substance that enters the kidney has to be excreted in the urine, so we need a substance that <u>is totally excreted by filtration and secretion without any reabsorption to the vein</u> and these criteria are found in PAH.

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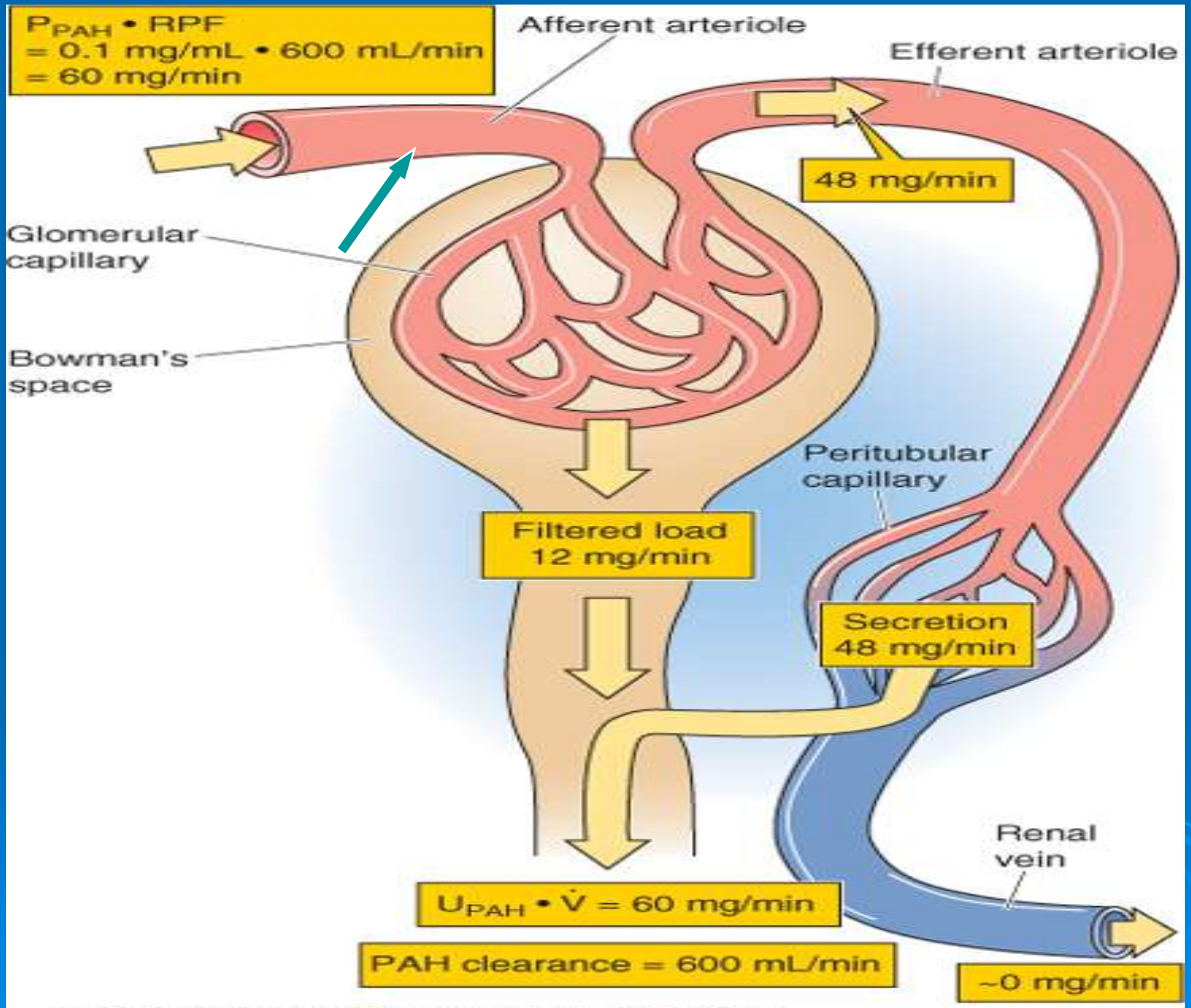
# PAH CURVE for FILTRATION and SECRETION

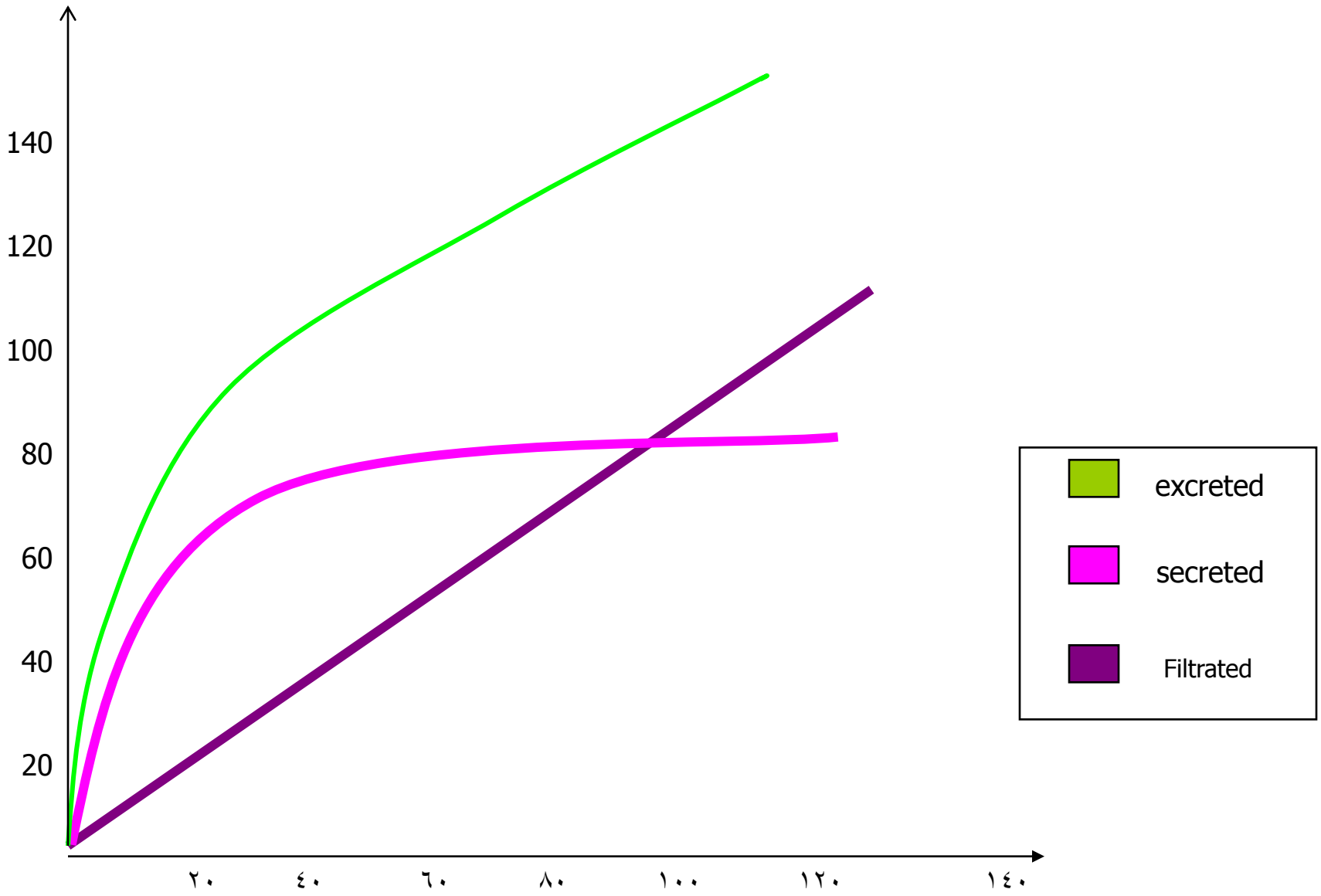
- Filtration is passive.
- Secretion is active (saturation, Tmax).
- Filtered load : how much is filtered per minute.
- Filtered load is proportional to its plasma conc. (linear)
- Since GFR = 125……filtration counts for 125/650 = 20 % of excretion of PAH in urine.
- Secretion counts for 80 %.
- Secretion exhibit Tmax; ( Transport maximum.)
- The excretion curve is the sum of the above two curves.

**The source of PAH in the urine:**

1. **filtration 20%**
2. **secretion 80%**
3. **No reabsorption.**



# PAH CURVE for FILTRATION and SECRETION :



***Remember***:

*PAH is completely cleared from plasma in the kidney.*

- When we increase the PAH in the plasma, the filtration will increase proportionally (as filtration is a passive active).
(remember: 20% of the substance is filtered

- But secretion (which is an active process) after a certain concentration will reach its Tmax and no more increase in secretion. The rest will return through the renal vein and thus not all plasma will be cleaned.

- So at a certain concentration the kidney will not be able to clear the whole plasma from the substance.

**- If PAH delivered to peritubular capillaries exceedds 80 mg/min (Tmax = 80 mg/min) this will underestimate RPF**

- Amount excreted per min in the urine = amount provided for excretion per min.
- $U_{PAH} \times V = P_{PAH} \times C_{PAH}$

$C_{PAH}$ = minimum volume of plasma per unit time which provided PAH for excretion in the urine in the same unit time (ml/min).

# Example

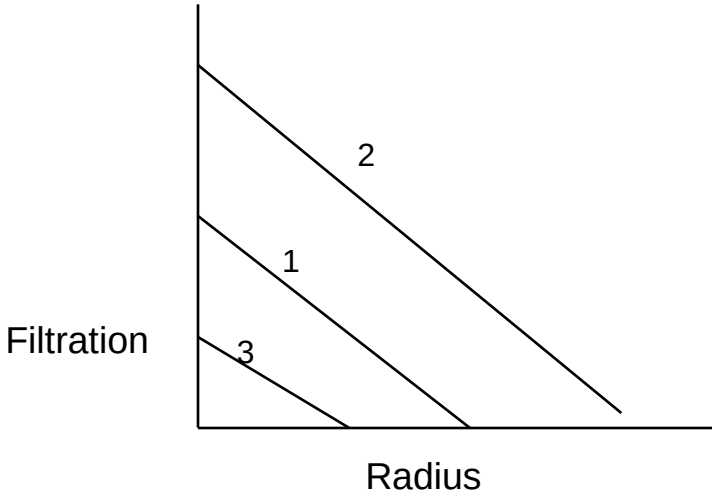
- If the concentration Of PAH in blood (say 1 mg/ml) and its concentration in the urine is 650 mg/ml), and the UOP = 1 ml/min. Conclusion: RPF= 650 ml/min
- But actually this is not the case. Because 10 % of renal blood goes to nourish the kidney structures such as capsule, medulla, calices, pelvis etc. This portion never reach afferent arteriole and thus does not participate in renal function.
- Therefore, 90 % is the effective RPF= $C_{PAH}$ = 585 ml/min
- The 100 % is called true or total tRPF.
- tRPF = eRPF ÷ 0.9= tRPF= 650 ml/min .
- NOTE : RPF is **not** a routine clinical test.
- $C_{PAH}$ underestimate the RPF. The $C_{PAH}$ represents the effective RPF. The true RPF is 10% higher.
- Extraction of PAH= 90%

# Glomerular Filtration Rate

- As in systemic capillaries, filtration in the kidneys is also affected by Starling Forces (Hydrostatic & Osmotic pressure in & out ).
- Here, Bowman's capsule stands for the interstitium surrounding the systemic capillaries

- Any substance with a MW less than 70 K can be filtered, and the filtration is inversely related with its radius:

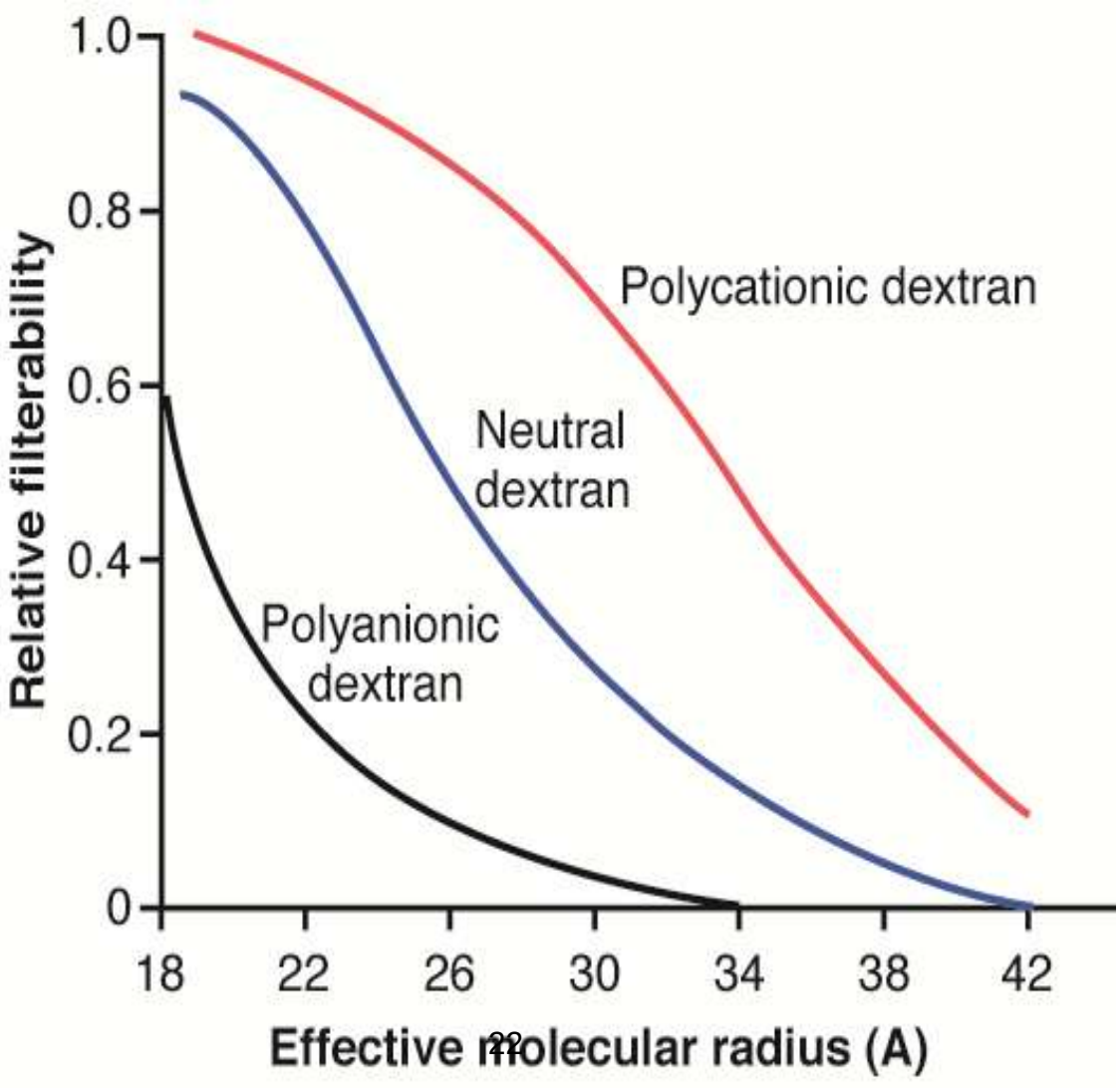
(1) a neutral substance
(2) Cations…more filtration
(3) Anion: less filtration




***Note:***

Hemoglobin MW is less than 70 K. However, it is not filtered because Hb is bounded to protein: in hemolysis we can see Hb in the urine (pink urine).

# Effects of size and electrical charge of dextran on filterability by glomerular capillaries.



- **Measuring GFR**

- **GFR is a tool used to classify different stages in renal disease:**
- **1. Decreased Renal reserve. When 50% of the nephrons are destroyed (One kidney without compensation). GFR drops to 50%. Homeostasis is perfectly maintained. Urea and creatinine are within normal range (Cr 0.7-1.4 mg/dl).**
- **2. Renal Insufficiency: When GFR drops to 20-50%. The earliest sings is isosthenuria or polyuria with isotonic urine. Azotemia, anemia, and hypertension appear too.**

- **3. Renal Failure: GFR drops to less than 20% N. All signs and symptoms of uremia (urine in the blood) are present.**

- **4. End-stage Renal Disease ESRD: Occurs when GFR drops to less than 5% N. At this stage, dialysis or transplantation are necessary for survival. Is an administrative term rather than medical term. It means that person should be covered by government insurance, because replacement therapy is mandatory.**

# Implications of measuring GFR

- Many chronic diseases affect renal function. One major example is diabetes mellitus, which causes micro-angiopathy in the renal vasculature. This in turn alters glomerular filtration.
- You will see in the example later that the GFR is way below normal, even though Pcr is still at the upper limit of normal range. The reason is that serum creatinine remains around normal even when the GFR is reduced to less than half of its normal value. Kidney impairment is present, but it is not serious.

# Measuring GFR

- 125ml/min of plasma is filtered in Bowman's capsule,
- 1 ml/min of urine excreted and
- 124 ml is reabsorbed (>99%).

- How to measure GFR?

-We need a substance that is: freely filtered, not secreted and not reabsorbed.

INULIN is an exogenous substance that meets these criteria

**Filtrate Load of Inulin**: the amount of Inulin filtered / min which is equal to the amount *excreted in the urine/min*

Inulin is a Glomerular marker. (Inulin clearance = GFR)

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**Again**

**Excreted amount/min = amount provided for excretion throug filtration/min**

$$U_{inulin} * V = P_{inulin} * GFR$$

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- Since Inulin is an exogenous substance it is only used for research purposes such as in micropuncture experiments…we will come back to this technique later

# Hence, We need an endogenous substance such as:

# CREATININE:

- Creatinine: Comes from high energy bound, muscle phosphocreatinine (PC)
    - Plasma creatinine by itself (without creatinine clearance) is a good indicator of renal function because it does not relate to food intake or level of exercise.
    - ***Small molecule (MW is 114)..freely filtered***
    - ***Its concentration in plasma (0.7 -1.4 mg/dl)***
- ***Freely filtered, not reabsorbed but SLIGHTLY SECRETED***
- Creatinine in the urine comes from 90% filtered and 10% through secretion. This might overestimates the measurement of GFR, unless it is self-corrected as we will see later
- To convert mg/dl of creatinine to μmol/l, multiply by 88.4
- To convert μmol /l of creatinine to mg/dl, divide by 88.4.

***Through this equation:***

$$\text{Creatinin Clearance (tGFR)} = \frac{U_{Cr}}{P_{Cr}} * V$$

**Last point to describe:**
**10% of <u>Cr in urine</u> comes from secretion which overestimates the GFR.**
**But it was found that 10% of <u>Cr in plasma</u> is bounded to proteins (so, they cancel each others)**

**Ccr is good estimation of GFR.**

# Estimating GFR in adults and children

- The bottom line is that equations for estimation of GFR are available and accurate. I will describe three of them. Pcr and anthropometric measures are utilized without the need for 24 hour urine collection.
- Gradual loss of renal function with age is a normal process (1% each year after the age of 40y ), as in the case of the female patient in the coming example. Although her GFR is markedly reduced, it is probable that she has normal renal function (relatively). Even if she has hypertension, it is most likely due to age-related vascular degenerative processes.
- Notice that estimations of GFR are unacceptable in cases of end-stage renal disease.

$$eC_{Cr} = \frac{(140 - \text{Age}) \times \text{Mass (in kilograms)} \times [0.85\ if\ Female]}{72 \times \text{Serum Creatinine (in mg/dL)}}$$

- Values for women are 85% of the predicted.
- Second equation
- GFR= 186* (serum creatinine in mg/dl)$^{-1.154}$ (age in years)$^{-0.203}$
- Third Equation" **Schwartz Formula in Children**
- GFR (mL/min/1.73 $m^2$) = k * Height (cm) / Serum Creatinine (mg/dl)
- k = Constant.
- k = 0.33 in premature Infants
- k = 0.45 in Term infants to 1 year old
- k = 0.55 in Children to 13 years
- K=0.65 for male children older than 13 y

# Estimating GFR in adults

- Let us take the example of an 85 year old geriatric female patient.
- Weight = 60 kg, Pcr = 1.5mg/dl

- eGFR = [(140 – 85) * (75kg)] / (1.5 * 72) * 0.85 = 26ml/min/1.73$m^2$

# Estimation of GFR in a pediatric patients

- **The Schwartz Equation**
- GFR can be estimated in a pediatric patient simply using plasma creatinine without all the hassle of 24 hour urine collection.
- **The equation is eGFR =**

**(k * height) / Pcr (in mg/dl)**

# Estimation of GFR in a pediatric patients

Example: for 6-y old child:

k = 0.55, h = 110cm, Pcr = 0.33mg/dl

- eGFR = (0.55 * 110) / 0.33 = 183ml/min/1.73$m^2$

| Age (y) | GFR ml/min /1.73 $m^2$ | |
|---|---|---|
| | Males | Females |
| 20-29 | 94-140 | 72-110 |
| 30-39 | 59-137 | 71-121 |
| 40-49 | 76-120 | 50-102 |
| 50-59 | 67-109 | 50-102 |
| 60-69 | 54-98 | 45-75 |
| 70-79 | 49-79 | 37-61 |
| 80-89 | 30-60 | 27-55 |
| 90-99 | 26-44 | 26-42 |
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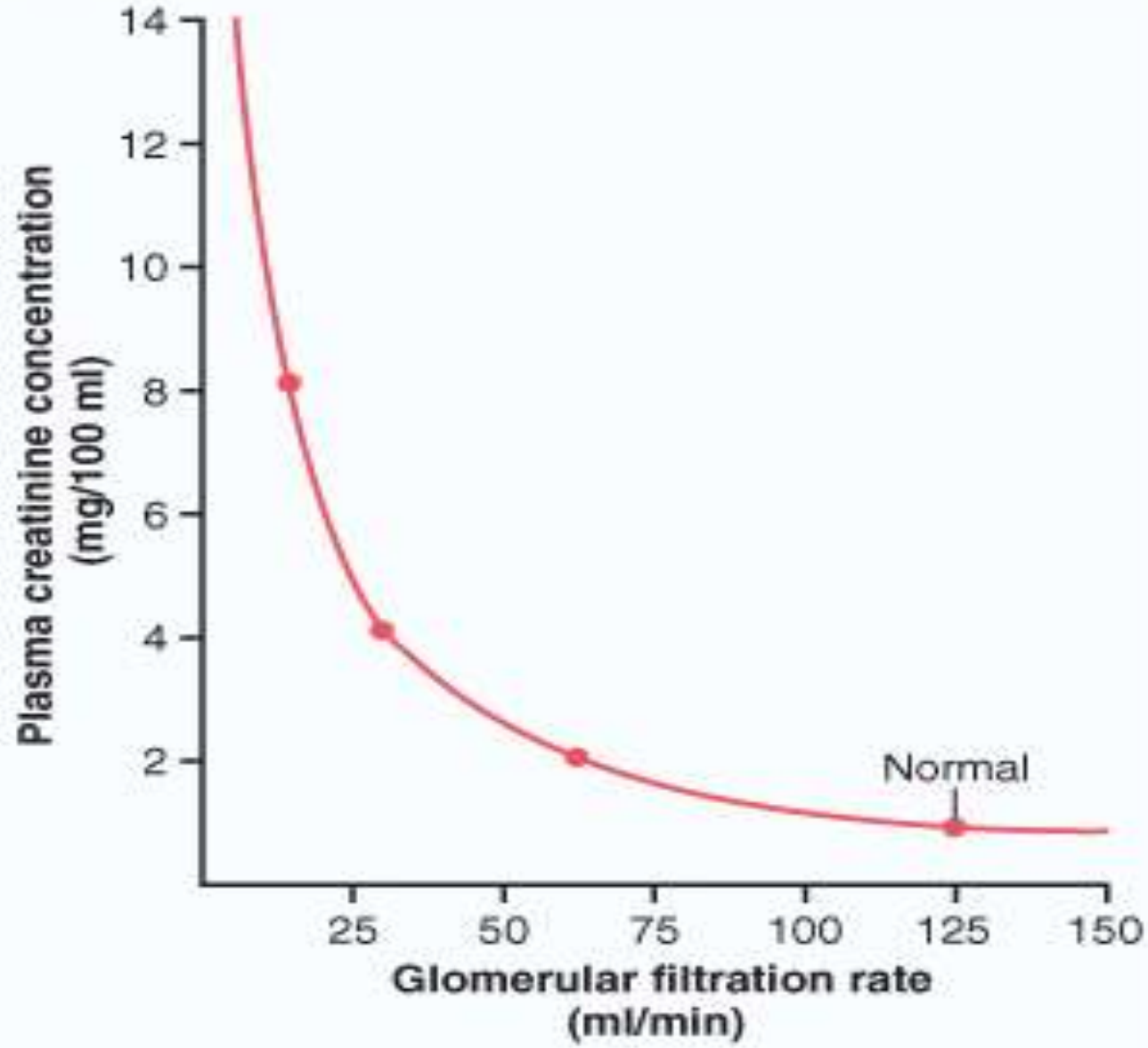
Plasma creatinine concentration (mg/100 ml)
14
12
10
8
6
4
2
Normal
25
50
75
100
125
150
Glomerular filtration rate (ml/min)