UGS MODULE
PHYSIOLOGY(LECTURE 3)
RENAL CLEARANCE

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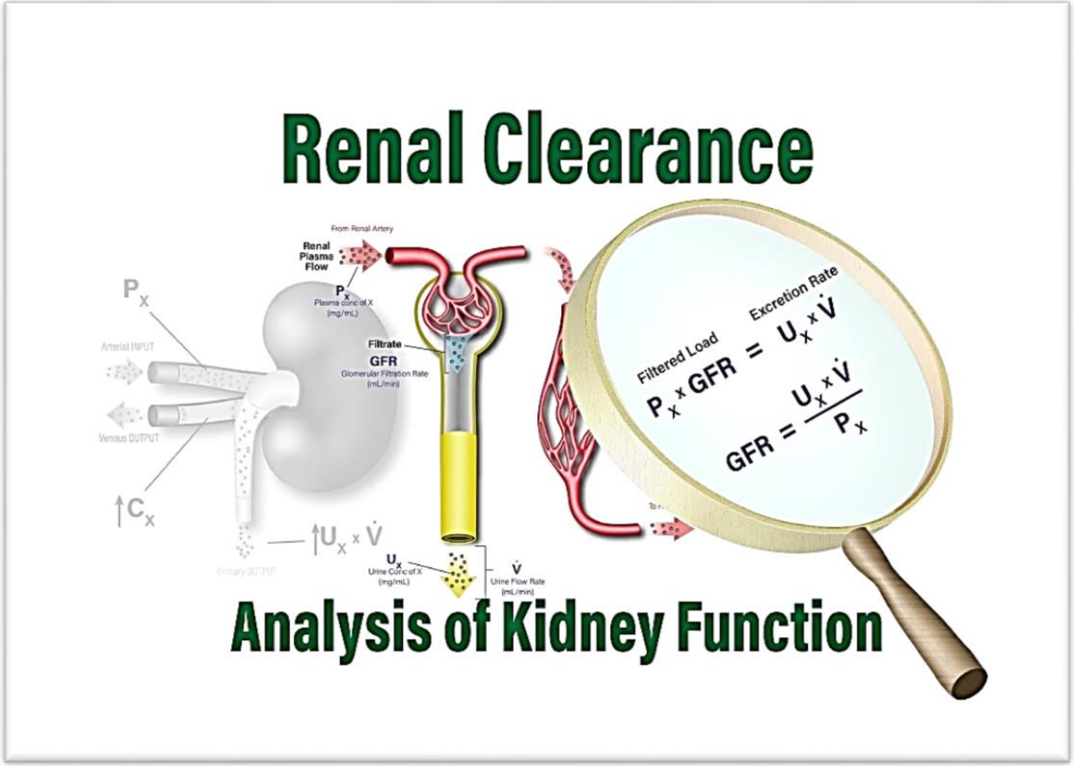


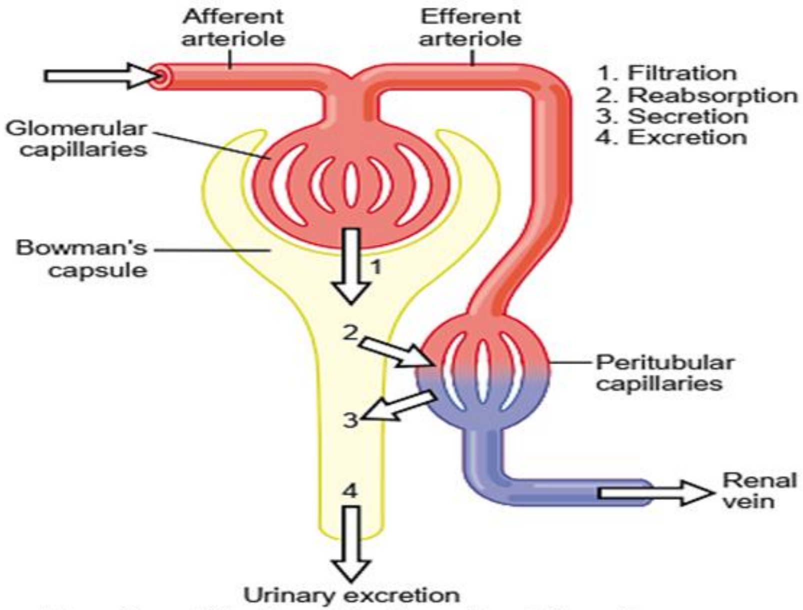
In general, the nephrons are associated with filtration, reabsorption, secretion, and excretion:

- The **filtered load (FLx) of a substance:**
  - ✓ The amount of a specific substance filtered per unit time.
  - ✓ It is equal to the plasma concentration of the substance (Px) times GFR.
  - ✓ $FLx = Px \times GFR$.
- The **urinary excretion** (Ex) of a substance:
  - ✓ It is the urine concentration of the substance (Ux) times the volume of urine produced per unit time (V).
  - ✓ $Ex = Ux \times V$.
- **Reabsorption rate of a substance (Rx):**
  - ✓ It is equal to the filtered load (FLx) of the substance minus the urinary excretion of a substance (Ex).
  - ✓ $Rx = FLx - Ex$.
- **Substances that are secreted (e.g., creatinine, PAH, H^+, K^+):**
  - ✓ The secretion rate of a substance (Sx) is equivalent to the excretion rate minus the filtered load of the substance.
  - ✓ $Sx = Ex - FLx$.

Renal Clearance

- **The renal clearance of any substance is the volume of plasma from which that substance is completely removed ("cleared") by the kidneys per unit time.**

- **Renal clearance is one of renal function tests that depends on combined blood and urine analysis.**



The clearance equation incorporates the urine and plasma concentrations of the substance, and the urine flow rate and is usually reported in ml/min.

Equation of clearance:

Clearance is calculated by using an equation that is determined as follows:

1. The amount of substance (x) cleared from the plasma/minute =the amount of this substance excreted in urine/minute.

2. The amount of substance (x) cleared from plasma/minute= C_x X P_x

C_x = volume of plasma cleared from substance (x) per minute = ml /min

P_x = concentration of substance per ml in plasma = mg /ml

3. The amount of substance (x) excreted in urine/minute= V X U_x, where

V is the volume of urine/minute (ml/minute).

U_x is the concentration of substance/ml urine (mg/ml).

4. Since both amounts are equal, then

C_x X P_x = V X U_x, therefore

$$C_x = \frac{V\,xUx}{P_x}$$

This is **the equation of clearance (C) and it shows that the clearance value of any substance is obtained by finding its amount excreted in urine/minute (VxU), then dividing this amount by the concentration of this substance/ml plasma (P)**.

The clearance of various substances is not the same **depending on the mode of handling of each substances in the nephron** (i.e. what happens to the substance in the nephron).
Substances that are secreted in renal tubules have high clearance, while those reabsorbed have low clearance.

N.B. As the substance is freely filtrated so, its concentration in plasma(P_x) = its concentration in glomerular filtrate (GF_x).

When substance x passes through the renal tubule, the following possibilities can occur before being excreted in urine:

1. The substance is freely filtered in glomeruli and is neither reabsorbed nor secreted in the renal tubules, so;

The amount filtered/minute = the amount excreted/ minute

$GFR \; X \; GF_x \quad = \quad V \; X \; U_x$

GFR= $\frac{V \; X \; Ux}{GFx}$

Since the substance is freely filtered

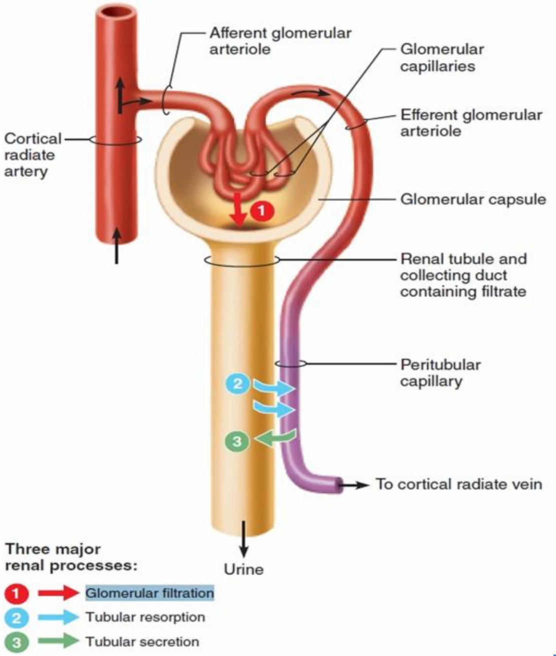
So, its concentration in plasma = its concentration in filtrate

$P_x \quad = \quad GF_x$

So,

GFR= $\frac{V \; XUx}{Px}$ **= C**

e.g. inulin



Unfortunately, there is no endogenous substance that exactly meets these requirements (i.e., the substance is freely filtered, but neither reabsorbed nor secreted), Inulin does meet these criteria.

Inulin Clearance:

- Inulin is a polysaccharide. Its M.W is about 5200.
- Its mode of handling in the nephron is as follows:
  - **It is freely filtered in the glomeruli (i.e. its concentration in plasma= its concentration in glomerular filtrate).**
  - **It is neither reabsorbed nor secreted in the renal tubules, so the amount filtered/minute=the amount excreted in urine/minute.**
  - Accordingly, the **volume of plasma that is cleared from inulin/minute (inulin clearance) is that volume filtered in the glomeruli/minute i.e. the GFR**.

For this reason, **determination of inulin clearance is often used for measurement of GFR** as follows:

1. The amount of inulin filtered/minute= GFR X GF_{IN}

And since GFR=C_{IN} and GF_{IN}=P_{IN}

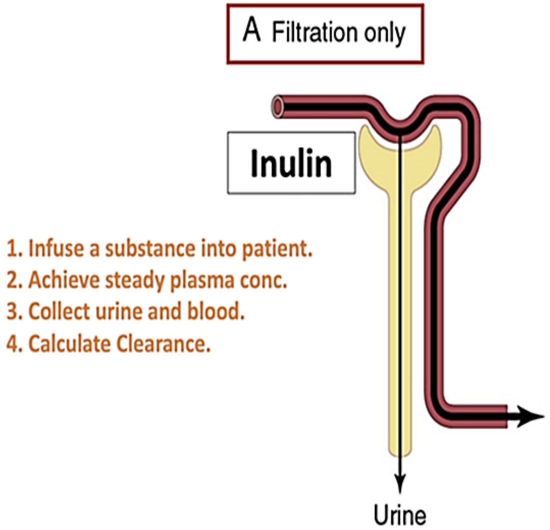
So, the filtered amount= C_{IN} X P_{IN}

2. The amount of inulin excreted/minute= V X U_{IN}

Since 1 and 2 are equal

C_{IN} X P_{IN} = V X U_{IN} and accordingly

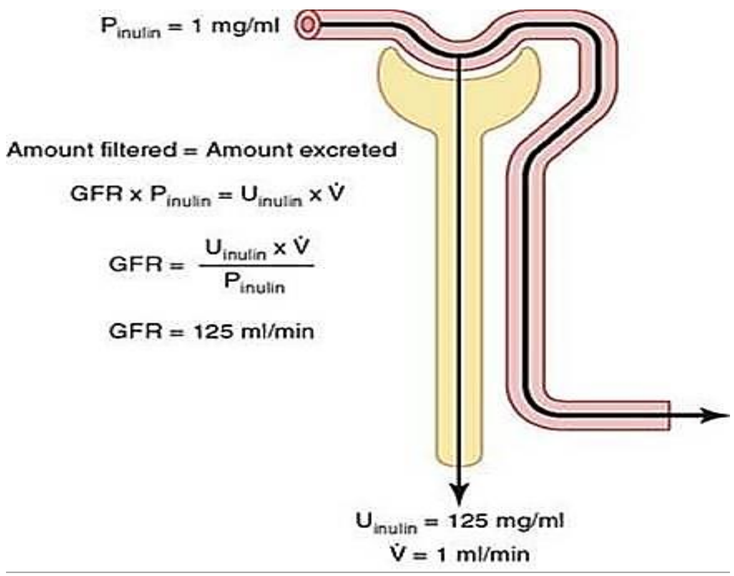
C_{IN} (GFR)= $\frac{V\ X\ UIN}{P_{IN}}$ = about 125 ml/minute.



- **Significance of inulin clearance:**

- **It measures GFR.**
- **It is used as a reference value:**

Substances having lower clearance than that of inulin (e.g. urea) means that they are reabsorbed in the renal tubules while those having higher clearances (e.g. creatinine) means they are secreted.



- Infusing inulin to determine clearance is not routinely used because of the invasive nature of the procedure.
- Instead, the renal clearance of the **endogenous substance creatinine is used to approximate GFR**.

Creatinine Clearance:

- ✓ Creatinine is a by-product of muscle metabolism and is freely filtered by the kidneys.
- ✓ It is not reabsorbed, but there is about 10% secretion into the renal tubules from the peritubular capillaries, and thus, creatinine clearance overestimates GFR by about 10% but is close enough to be highly useful in most clinical situations.

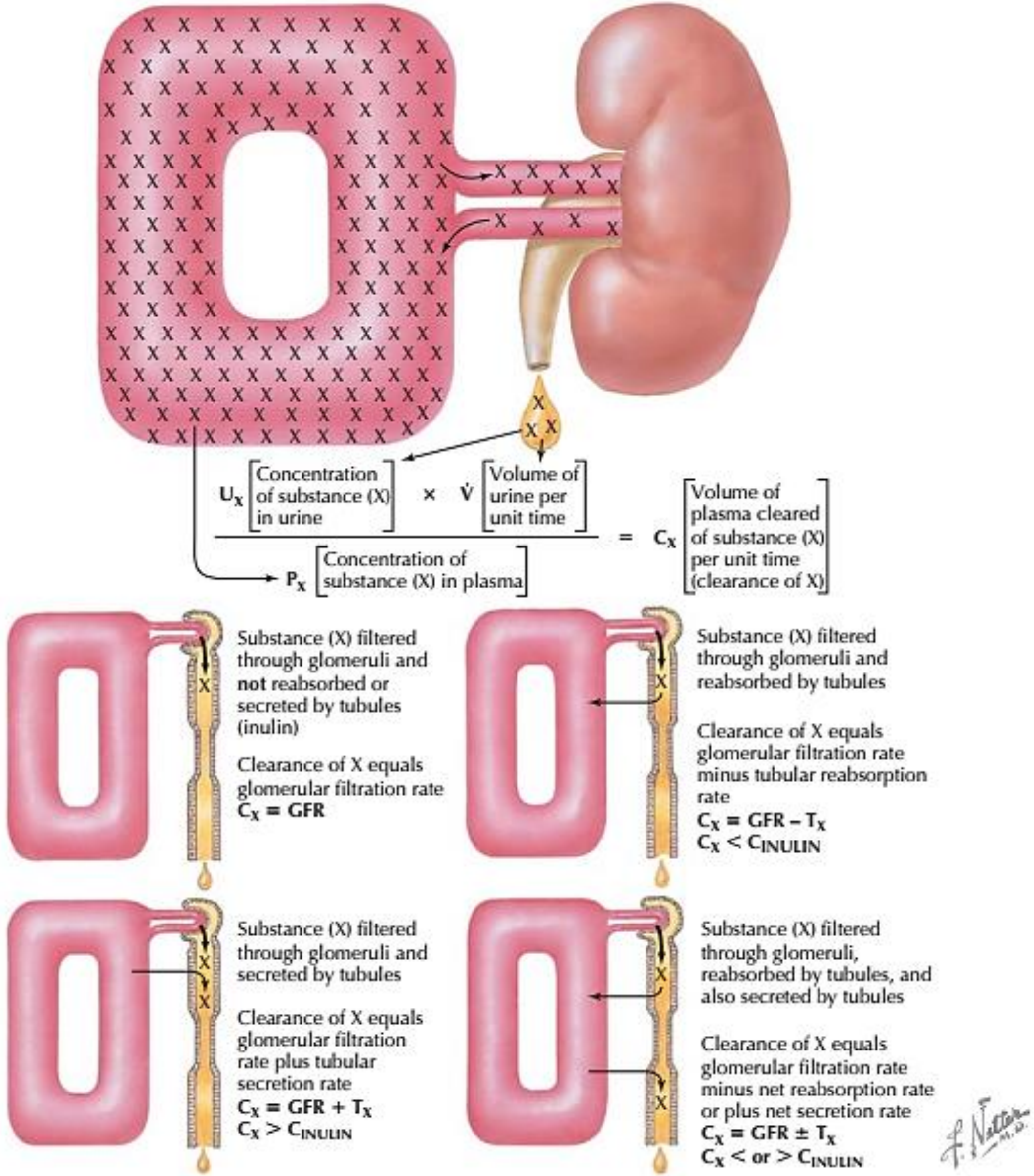


Figure 16.6 **Renal Clearance Principle** "Clearance" describes the volume of plasma that is cleared of a substance per unit time. The renal clearance of a substance provides information on how the kidney handles that substance. Since inulin is freely filtered, and not reabsorbed or secreted, all of the filtered inulin is excreted in the urine. Thus, C_{in} is equated with the glomerular filtration rate (GFR), and the net handling of other substances can be determined, depending on whether their clearance is greater than (net secretion), less than (net reabsorption), or equal to C_{in}.

2. If the substance is :

- **Freely filtered (in glomeruli)**
- **Partially reabsorbed and not secreted in the renal tubules:**

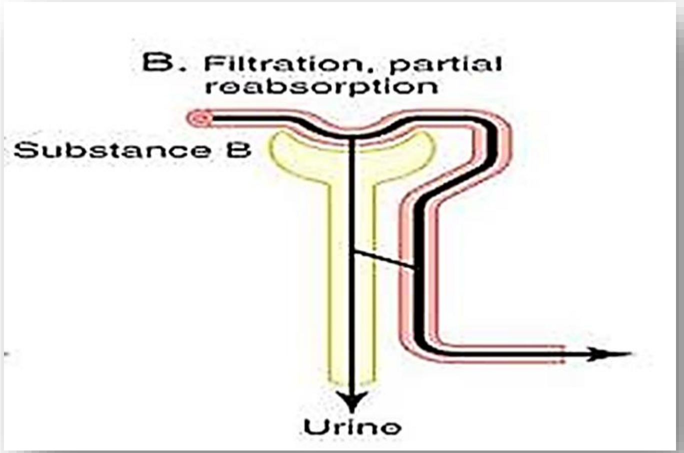
The amount excreted in urine/minute < the amount filtered/minute.

i.e. $V \times U < GFR \times P$

So, $\frac{V \times U}{P} < GFR$ i.e. **GFR > clearance of this substance.**

e.g. urea.

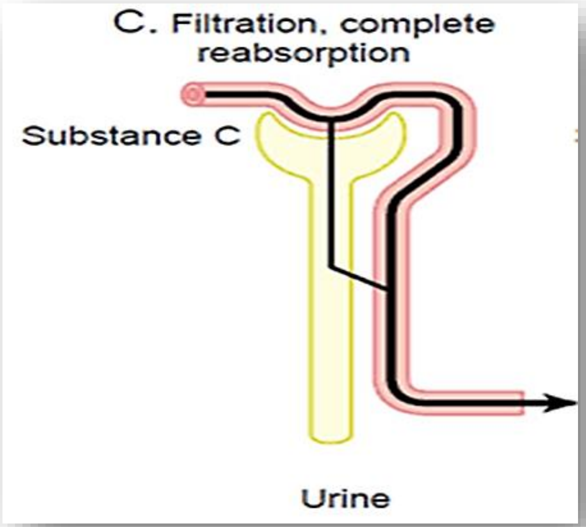
Urea clearance is normally about 70 ml/minute.



3. **<u>If the substance is:</u>**

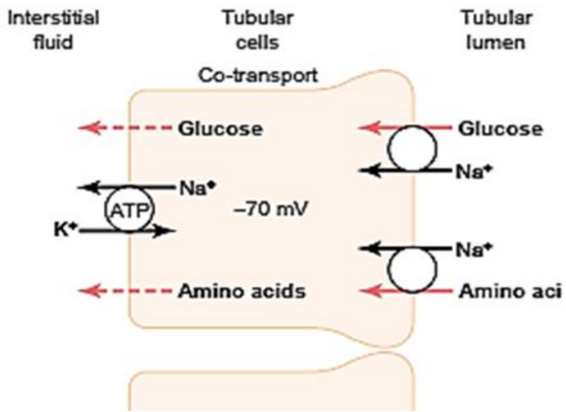
- ✓ **<u>Freely filtered in glomeruli</u>**
- ✓ **<u>Completely reabsorbed and not secreted in the renal tubules :</u>**

The amount of substance excreted in urine/minute =zero
So, the clearance of this substance **= zero**.
e.g. Glucose
Normally, glucose is completely reabsorbed (PCT) under normal conditions.
This means that all RPF/minute has not been cleared from glucose.



Glucose Transport and Tm_G

- **Glucose absorption is an example of secondary active transport.**
- **For glucose transport, the rate-limiting step is the number of specific transporters (sodium-dependent glucose transporter (SGLT)-2) available in PCT.**
- Glucose and Na^+ bind to the sodium-dependent glucose transporter (SGLT)-2 in the apical membrane, and glucose is carried into the cell as Na+ moves down its electrical and chemical gradient. The Na^+ is then pumped out of the cell into the interstitium, and the glucose exits by facilitated diffusion via glucose transporter (GLUT)-2 into the interstitial fluid.
- There is a **limit to the amounts of glucose that they can be transported per unit time known as the transport maximum (Tm). This is because the binding sites on the membrane transport proteins become saturated when the concentration of the transported substance increases to a certain level.**



- The **sodium-glucose carriers have a high transport maximum (Tm), and under normal conditions**, the filtered load of glucose is low enough that the transporters can carry all of the glucose back into the blood, leaving none in the tubular fluid and urine. Thus, **the renal clearance of glucose is normally zero**.
- However, if the FL of glucose is high, there may be too much glucose present in the tubular fluid and the carriers can become saturated.
- **The renal threshold for glucose: It is the plasma level at which glucose first appears in the urine. It is the point where the first nephrons exceed their Tm, resulting in glucose in the urine (glucosuria). It is about 200 mg/100 ml in arterial plasma**.
- When the plasma glucose concentration (and hence the filtered load of glucose) is under the renal threshold, all of the glucose in tubular fluid will be reabsorbed.
- However, when it exceeds the threshold, the transporters are saturated (Tm exceeded in some nephrons) and glucose appears in the urine.
- **The Tm_G is about 375 mg/min in men and 300 mg/min in women.**
- In people with significant hyperglycemia (for example, in poorly controlled diabetes mellitus), the plasma glucose concentration often exceeds the threshold value of 200 mg/100 ml, so that the filtered load exceeds the ability of the nephrons to reabsorb glucose.
- In other words, although the capacity of the kidneys to reabsorb glucose can be normal in diabetes mellitus, the tubules cannot reabsorb the large increase in the filtered load of glucose. In addition, the high filtered load of glucose can also lead to significant disruption of normal renal function (diabetic nephropathy).

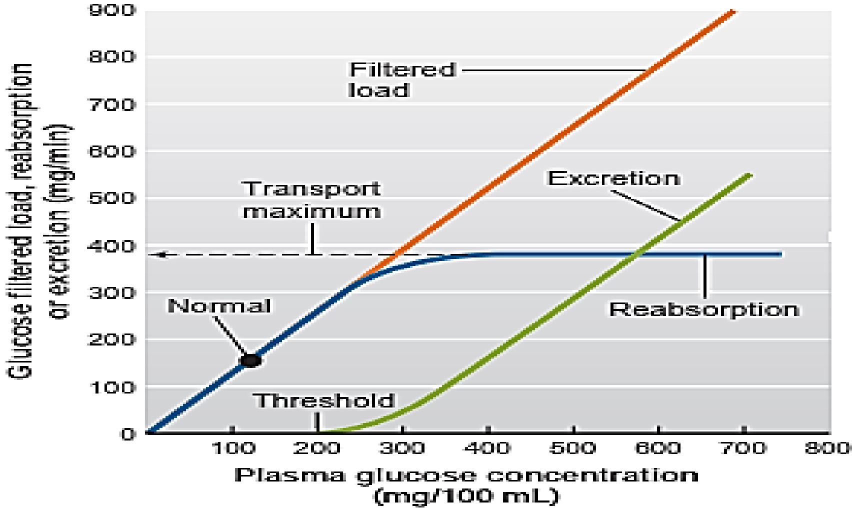
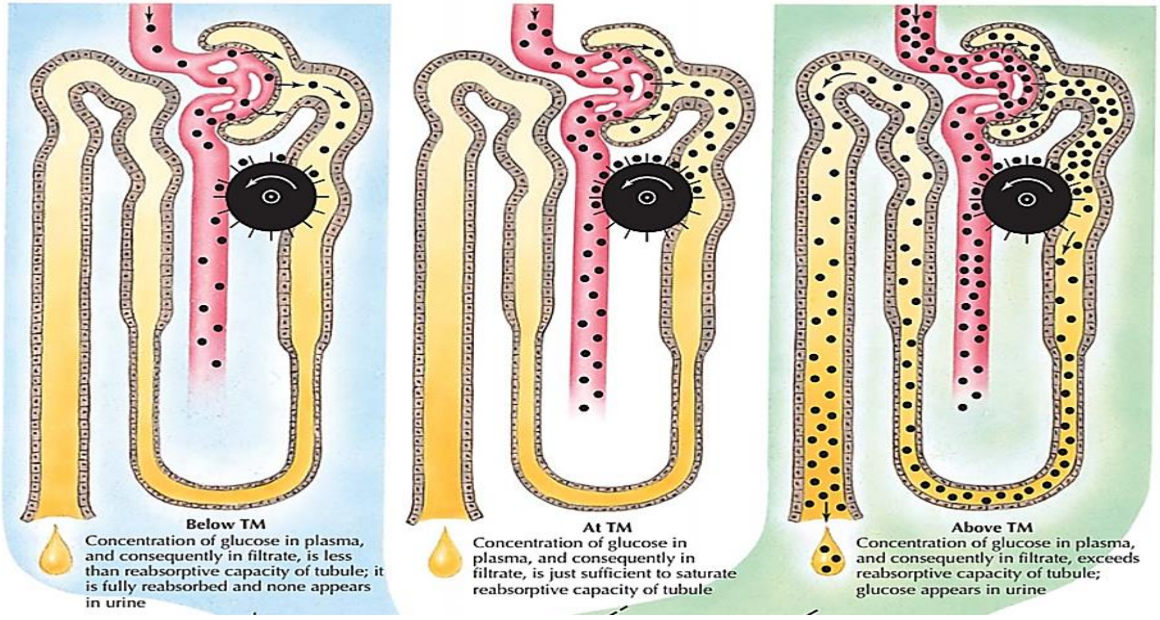


Figure 14.11 The relationship between plasma glucose concentration and the rate of glucose filtered (filtered load), reabsorbed, or excreted. The dotted line shows the transport maximum, which is the maximum rate at which glucose can be reabsorbed. Notice that as plasma glucose exceeds its threshold, glucose begins to appear in the urine.



(4) If the substance is

- ✓ **Freely filtered in glomeruli**
- ✓ **Partially secreted and not reabsorbed in the renal tubules**

then,

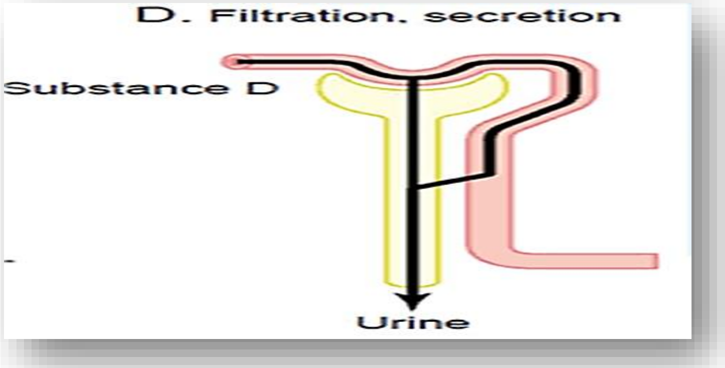
The amount excreted in urine/minute > amount filtered/minute.

i.e. $V \times U > GFR \times P$ so, $\frac{VxU}{p} > GFR$

The clearance of the substance > GFR.

The clearance of this substance is greater than inulin clearance, meaning that a greater volume of plasma than 125 ml has been cleared from this substance/minute.

e.g. Creatinine clearance (normally about 140 ml/minute).

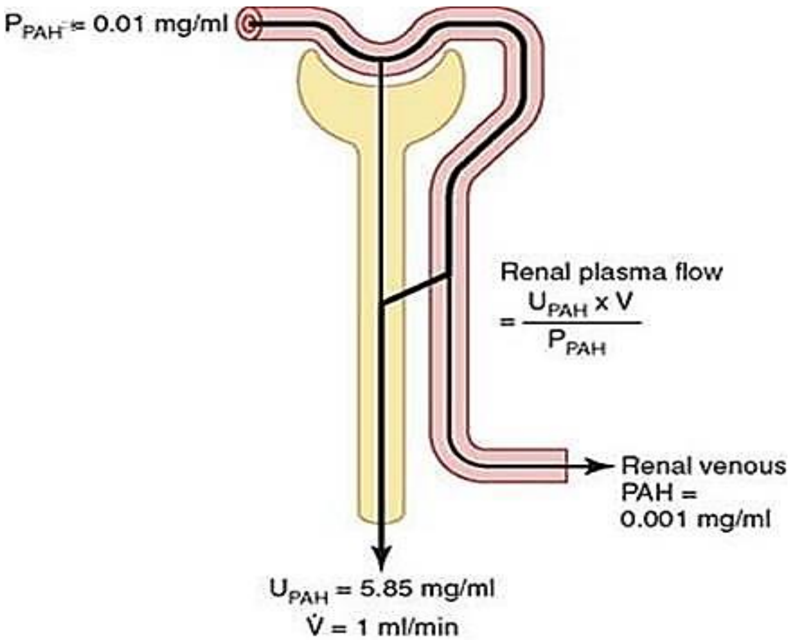


(5) <u>If the substance is</u>

- **<u>Freely filtered in glomeruli</u>**
- **<u>Completely secreted in the renal tubules and not reabsorbed.</u>**

- So that the **renal venous blood is nearly free of the substance then,**
- **Consequently, all the plasma that enters the kidney per unit time is cleared of this substance.**
- **Therefore, the clearance of this substance = RPF (ml/minute).**
- **RPF** can be measured by infusing **p-aminohippuric acid (PAH)** and determining its urine and plasma concentrations.
- PAH is filtered by the glomeruli and secreted by the tubular cells,
- When PAH is infused at low doses, 90% of the PAH in arterial blood is removed in a single circulation through the kidney.
- So, the value obtained should be called the **effective renal plasma flow (ERPF)** to indicate that the level in renal venous plasma was not measured.

- **Extraction ratio** = Percentage of PAH removed from arterial plasma (90%).
- In humans, **ERPF** (= Clearance of PAH) averages about **585 ml/min**.
- So, 585 ml/minute represents 90 % of actual RPF.
- **Actual RPF= 585 X100/90= 650 ml/minute.**



- **From the renal plasma flow, the renal blood flow can be calculated by dividing by 1 minus the hematocrit.**
- **If Hematocrit (Hct) = 45%, then plasma represents (55%) (i.e. 1-Hct) of total blood volume.**

$$\mathbf{RBF = RPF \times \frac{1}{1-Hct}}$$

$$\mathbf{= 650 \times \frac{1}{0.55} = \text{about } 1200 \text{ ml/minute.}}$$

Significance of renal clearance:

- **It is one of renal function tests.**
- **Measurement of GFR by inulin clearance.**
- **Measurement of RPF by PAH clearance.**
- **Estimation of filtration fraction (FF).**


Thank
you