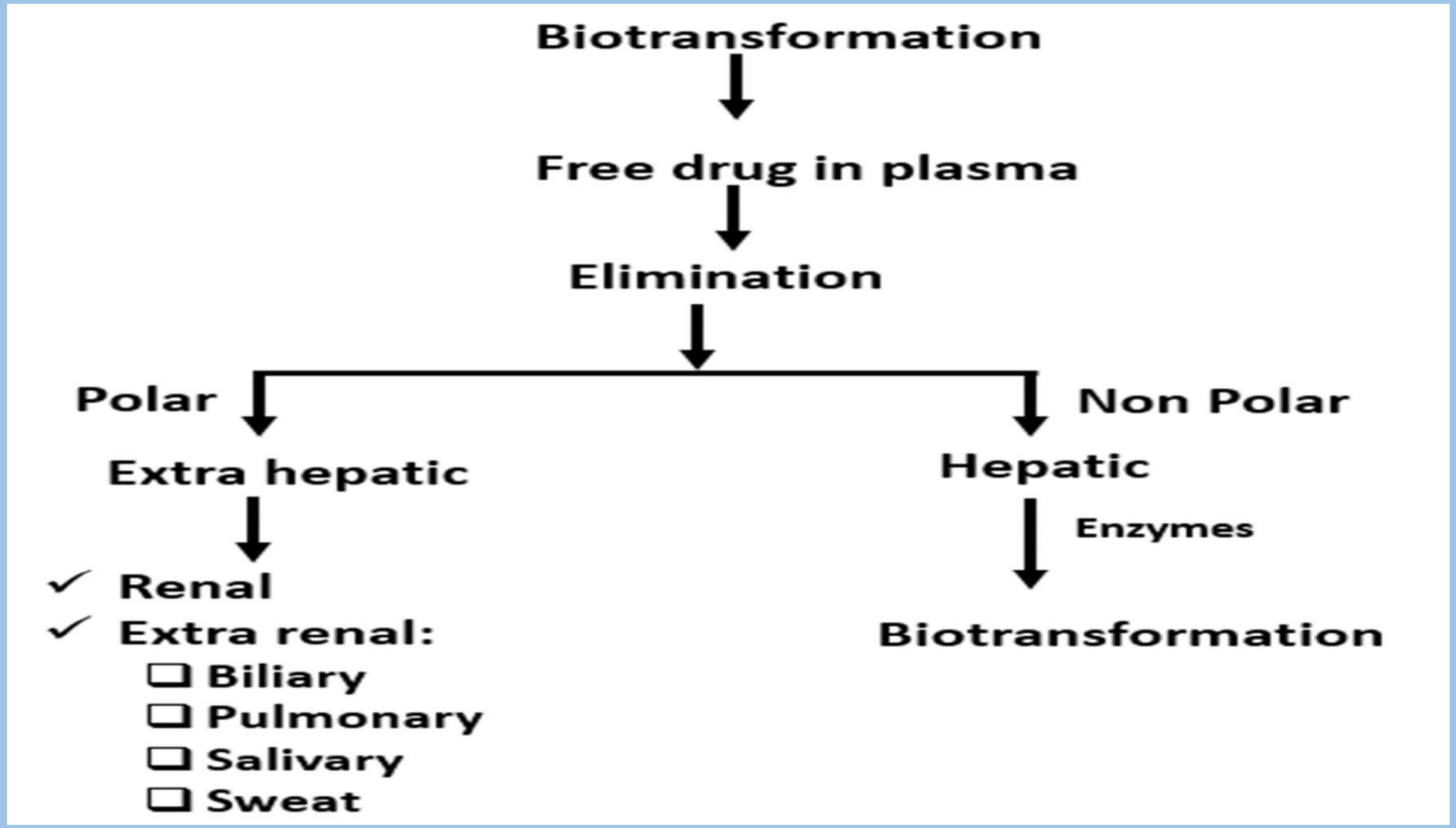
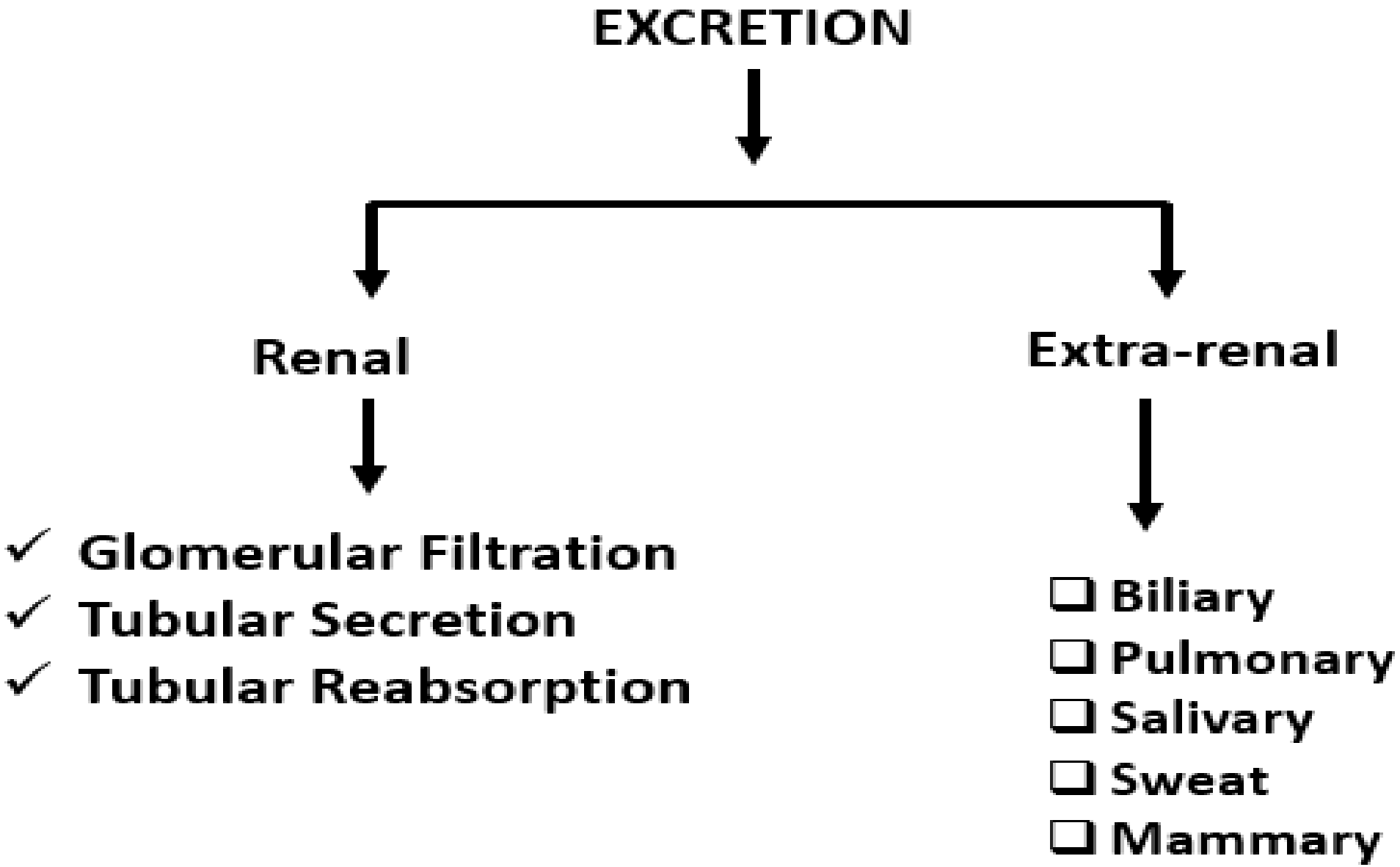
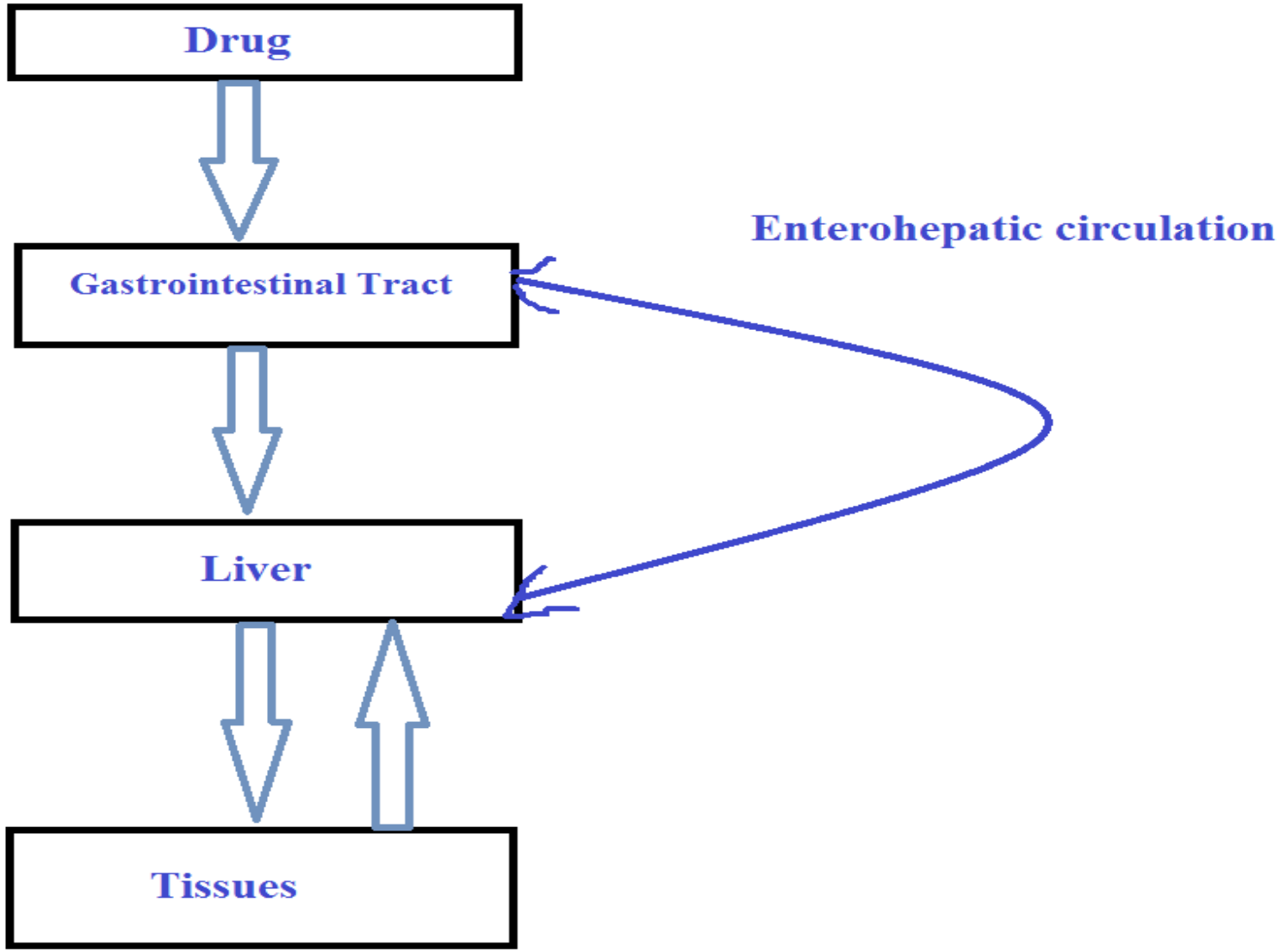

Biotransformation
Free drug in plasma
Elimination
Polar
Non Polar
Extra hepatic
Hepatic
Enzymes
✓ Renal
✓ Extra renal:
❑ Biliary
❑ Pulmonary
❑ Salivary
❑ Sweat
Biotransformation


EXCRETION
Renal
Extra-renal
✓ Glomerular Filtration
✓ Tubular Secretion
✓ Tubular Reabsorption
❑ Biliary
❑ Pulmonary
❑ Salivary
❑ Sweat
❑ Mammary



Enterohepatic Circulation

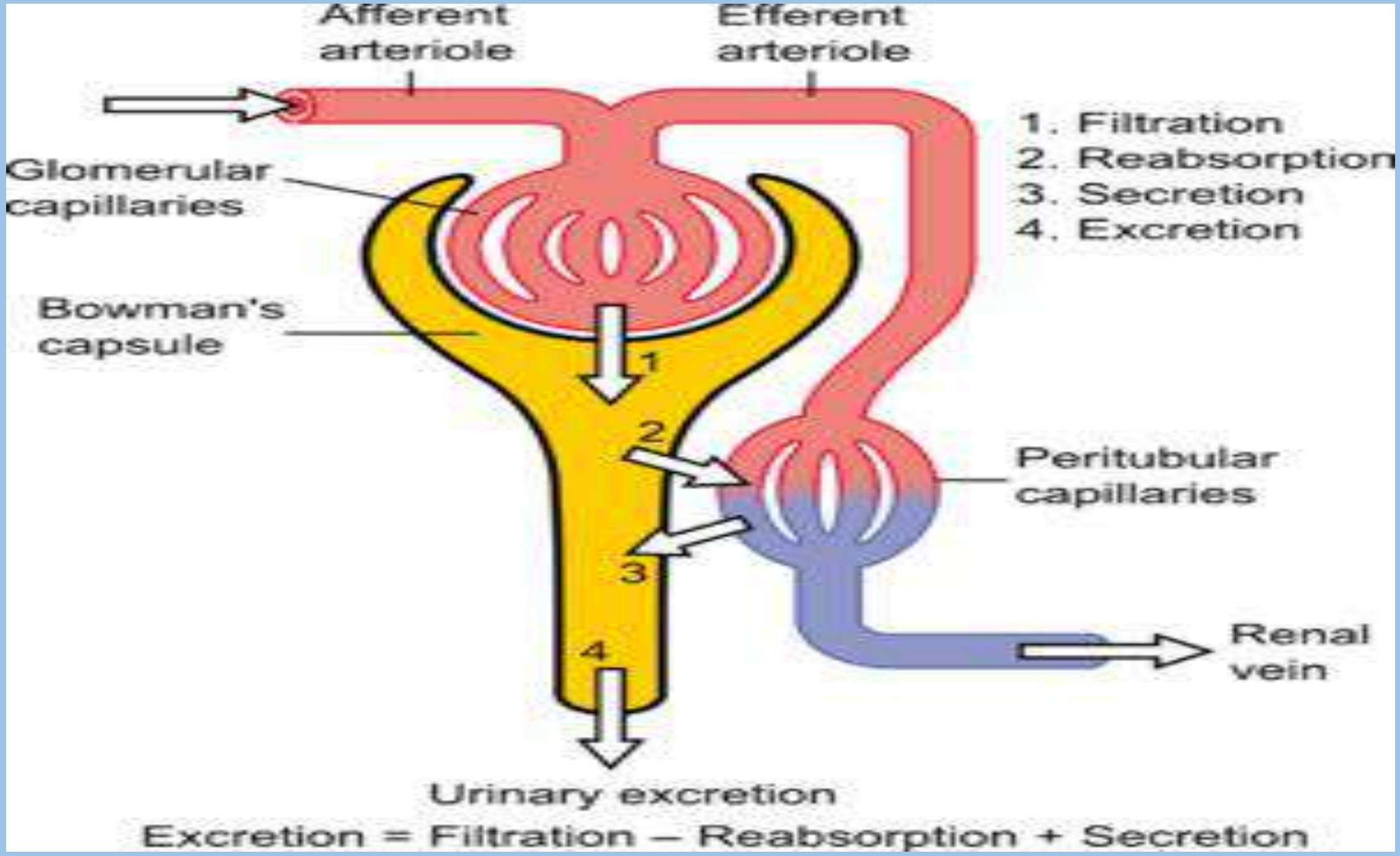
- **Physiological Importance of Renal Excretion:**

1. Elimination of unchanged or toxic metabolites.
2. Regulation of aqueous equilibrium.
3. Regulation of mineral equilibrium.
4. Maintenance of the pH of blood.
5. Kidney has two functions: Secretion of (Renin and Erythropoietin)

- **Pharmacological Importance of Renal Excretion:**

1. Investigation and research" Sample media": from experimental data we can predict the pharmacokinetic parameters as: $t_{1/2}$, Ke, CLr, CLT, CLm, Clextra and bioavailability.
2. Dossification (Renal function). Posology???????
3. Toxicity: Caused by drugs as Gentamycin.
4. Therapeutic or clinical efficiency: Nitrofurantoin (Filtration only)

- **The principle processes that determine the urinary excretion of drugs are:**
- Glomerular filtration.
- Active Tubular secretion.
- Passive Or Active Tubular re-absorption.


Afferent arteriole
Efferent arteriole
1. Filtration
2. Reabsorption
3. Secretion
4. Excretion
Glomerular capillaries
Bowman's capsule
1
2
Peritubular capillaries
3
4
Renal vein
Urinary excretion
Excretion = Filtration – Reabsorption + Secretion

1. Glomerular Filtration

- About 20 % of the renal blood supply (1.2 L/min) is directed to the glomerulus.
- Glomerular Filtration Rate (GFR) = 120-130 mL/min aproximately (180 L/day).
- Passive Process.
- Mwt < 69000 Da of molecules undergo filtration.
- Water soluble substances are eliminated by renal excretion.
- Drugs such **inulin** are not actively secreted or reabsorbed. They are used to measure the glomerular filtration rate (GFR).
- Creatinine is used clinically to assess GFR.

- **Factors Affecting The Filtration Rate:**

✓Membrane Surface area.

✓Membrane thickness.

✓Number and size of pores.

✓Solid substance in the filtrate liquid.

✓Viscosity.

✓Temperature.

✓Pressure gradient :

(Pressure on the membrane surface/ Pressure under the membrane) → Effective Pressure of Filtration (**E.P.F**).

E.P.F = Blood Pressure – (Colloid osmotic pressure + Intra-capsular pressure)

= 65 mmHg –(25 mmHg + 15 mHg)

= 25 mmHg

2. Active Tubular Secretion

- Occurs mainly in Proximal tubules.
- It increases drug concentration in filtrate.
- Drugs undergo active secretion have excretion rate values greater than normal GFR.
- Active tubular secretion shows competition effects.
- For ex, probenecid (a weak acid) competes for the same system as penicillin, decreasing the rate of penicillin excretion.

- Two secretion mechanisms are identified:

1. System for secretion of organic acids/anions:

- Penicillin, salicylates,(aspirin), sulfonamides, Probenecid, Uric acid

2. System for secretion of organic bases/cations:

- Atropine, morphine, catecholamine, quinine, neostigmine

3.Tubular re-absorption

- Drugs undergo tubular re-absorption have excretion rates less than the GFR.
- Re-absorption increases half life of a drug.
- Re-absorption may be active or passive.
- The extent of tubular secretion is controlled by :
    1. Drug’s lipophilicity.
    2. pH of filtrate (Urine) & pKa of drug.
    3. Filtrate flow.

➢ **Influence of the pH of urine and pKa of drug on its capacity for tubular reabsorption.**

- For weak electrolyte drugs, urine pH affects the ratio of non-ionized & ionized drug:

a) If the drug exists primarily in the non-ionized or lipid-soluble form, then it is reabsorbed more easily from the lumen of the nephron.

b) If the drug exists primarily in the ionized or water-soluble form, then it is excreted more easily in urine.

c) Depending on the pKa of the drug, alteration of the urine pH alters the ratio of ionized to non-ionized drug and affects the rate of drug excretion. For example, alkalization of the urine by the administration of sodium bicarbonate increases the excretion of salicylates (weak acid).

➢ Influence of Filtrate flow on the capacity for tubular reabsorption

- An increase in urine flow caused by simultaneous administration of a diuretic decrease the time for drug reabsorption. Consequently more drug is excreted.

➢ Factors affecting renal excretion of drug

1.Factors affecting the glomerular filtration:

Increased perfusion →increased excretion (Vasodilators, Cardio-stimulant ”Caffeine”).

2.Factors affecting the carrier mediate system:

Competency: Probenecid + Penicillin.

Inhibition of energetic system: Diuretics ;Thiazide.

3.Factors affecting the passive diffusion(Physicochemical properties of drug):

pH of urine & pKa of drug.

MWt, Drug liposolubility, Vd.

4.Pathological Factors

Hypo-function of kidney : elderly.

Mathematical treatment

- Renal (CLr).
- Renal excretion constant (Ku)
- Problems and training.

➢ Concept and determination of clearance

Of the concepts in the pharmacokinetics clearance has the greatest potential for clinical application. It is also the most useful parameter for the evaluation of an elimination mechanism.

❑There are several definitions of clearance which are pharmacokinetically equivalent:

- "Is the volume of fluid containing drug which is cleared of drug per unit time"

e.g. if the clearance of penicillin is 15mL/min in a patient with an apparent Vd o 12 liters, then 15 mL of the 12 liters is cleared of drug per minute.

- "Is the rate of drug elimination divided by the plasma concentration at that time"

$$\text{Clearance} = CL = \frac{dxu}{dt.Cp} = \frac{mg}{min.mg/mL} = mL/min$$

$$\mathbf{CL.\ Cp = \frac{dxu}{dt}} \qquad \mathbf{where\ [\ \frac{dxu}{dt} = VE\ (rate\ of\ drug\ excretion) = Cp\ .\ Ku\ .Vd\ ]}$$

➢ Concept and determination of clearance

- "Is the product of the first-order elimination rate constant and apparent Vd"

$$CLr = \frac{(d.x_u/dt)}{Cp} \quad \text{where } [\frac{d.x_u}{dt} = Cp \,.\, Ku \,.Vd\,]$$

$$CLr = \frac{Cp.\, Ku \,.\, Vd}{Cp} = Ku \,.\, Vd$$

Total Drug Clearance = Total body Clearance

CLT= CLr + CLm + Clext.r

Ke . Vd = Ku. Vd + Km . Vd +Kext.r .Vd

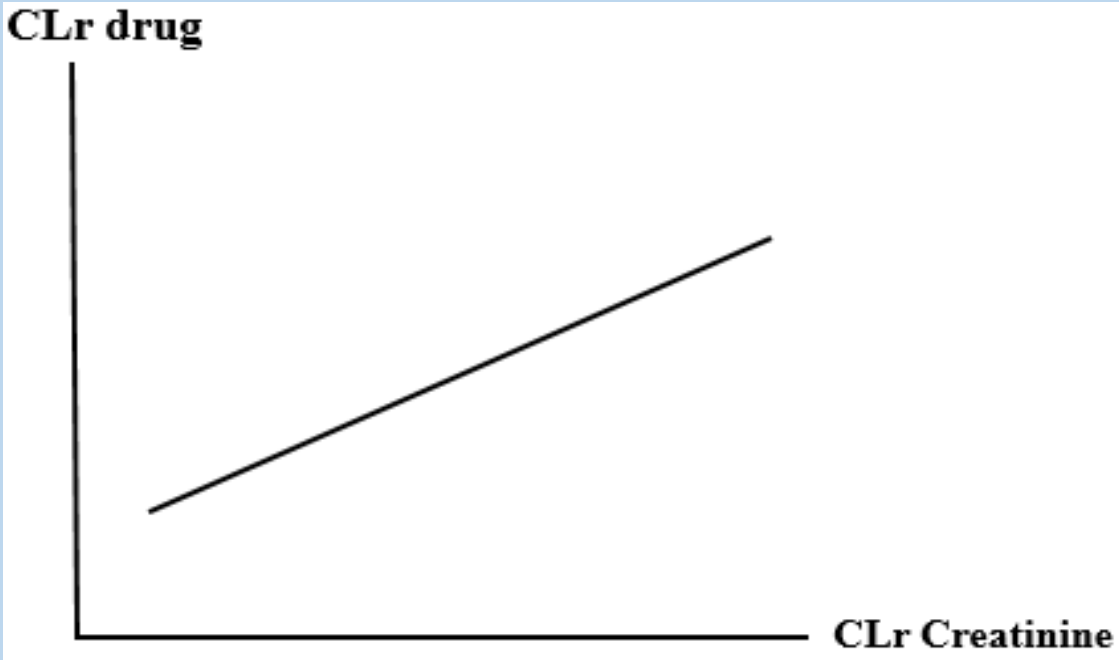
- " Is a measure of the apparent volume(in mL) of plasma containing the amount of drug excerted, metabolized, eliminated per minute."

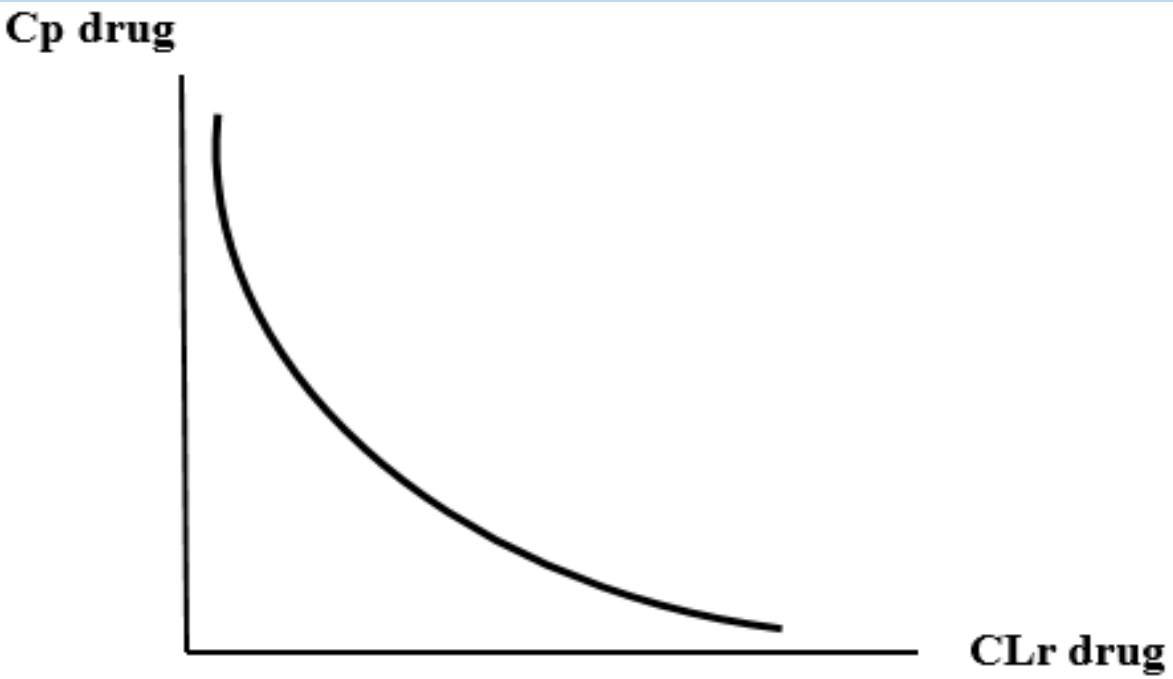
➢ Concept and determination of clearance

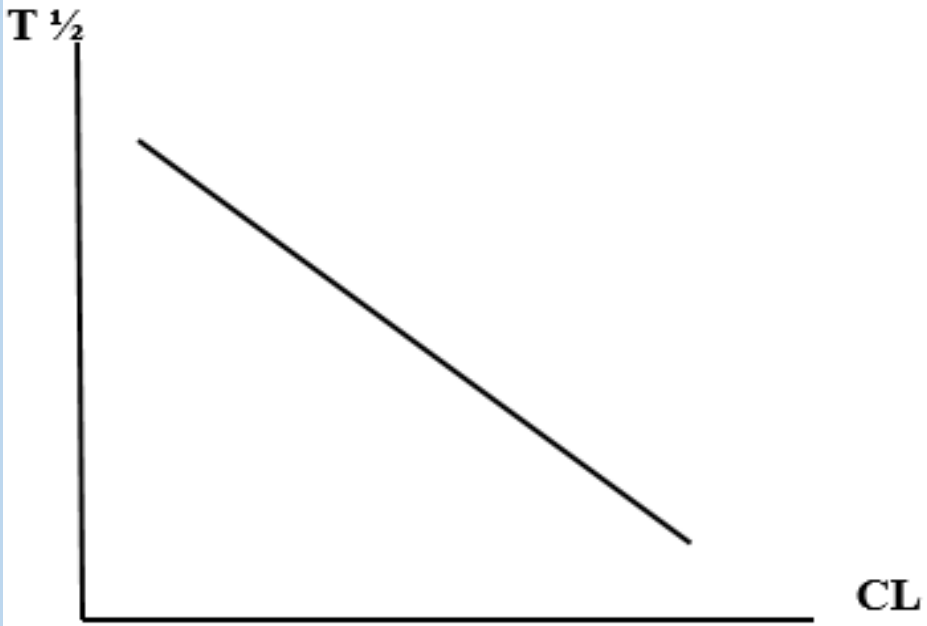
- By comparing the clearance value for the drug to that of a standard reference drug (such as inulin which is cleared through the kidney by glomerular filtration only). The physiologic clearance process for the first drug may be inferred. For example, note the clearance ratio of the renal clearance (CLr) of the drug in the question to the CL of a drug such as inulin presented in the following table

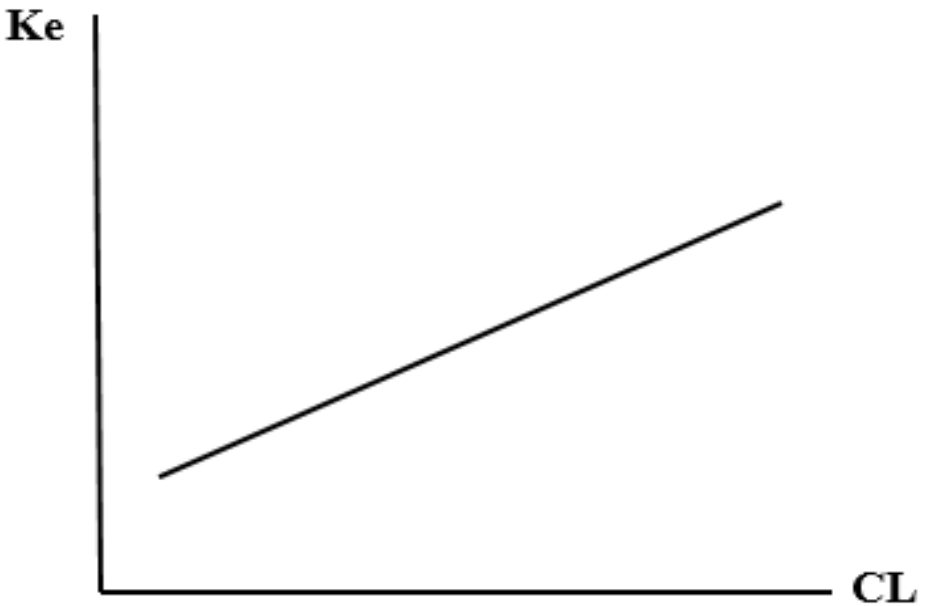
Clearance Ratio	Probable Mechanism of renal Excretion
$\frac{\text{CL drug}}{CL\ inulin} < 1$	**Drug is partially reabsorbed**
$\frac{\text{CL drug}}{CL\ inulin} = 1$	**Drug is filtered only**
$\frac{\text{CL drug}}{CL\ inulin} > 1$	**Drug is actively secreted**

- The clearance of inulin will be equal to the GFR= 130 mL/min.


CLr drug
CLr Creatinine


Cp drug
CLr drug


T ½
CL


Ke
CL

➢ Determination of renal clearance (CLr)

$$VE = VF + VS - VR \quad /Cp$$

$$\frac{VE}{Cp} = \frac{VF}{Cp} + \frac{VS - VR}{Cp} = CLr$$

When $VE = \frac{dx\text{-}u}{dt}$ then $CLr = \frac{(d\text{-}x\text{-}u/dt\text{-})}{Cp}$;

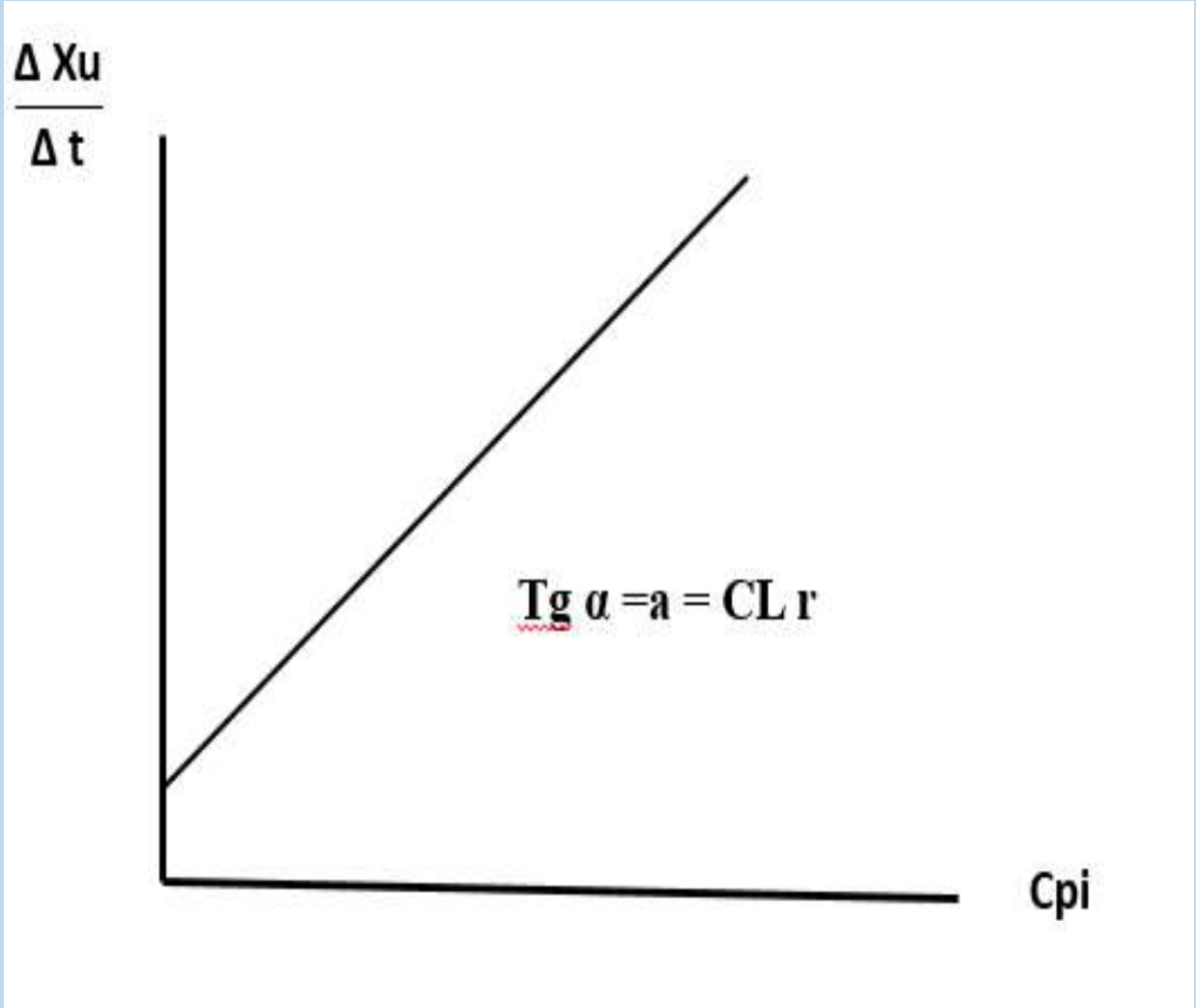
$$CLr \,.Cpi = \frac{\Delta\, Xu}{\Delta\, t}$$

a. X = y

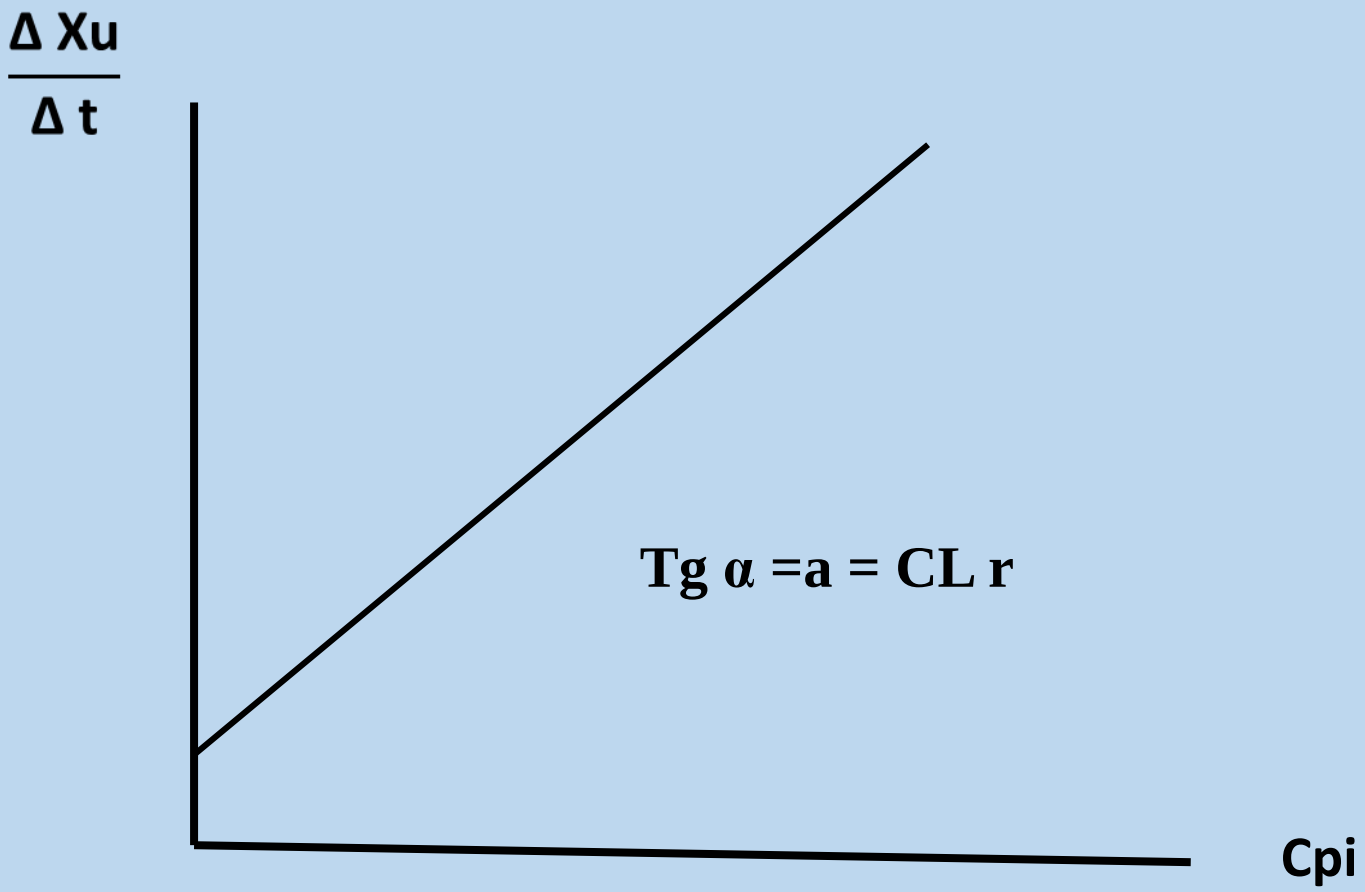
When $\Delta\, Xu = Xu2 - Xu1$

$\Delta\, t = t2 - t\,1$

$$Cpi = Cpo\,.\,e^{-ke.ti} \qquad Where\ ti = \frac{t1 + t2}{2}$$



➢ Determination of renal clearance



➢ Determination of renal clearance

$$VE = VF + VS - VR \qquad /Cp$$

$$\frac{VE}{Cp} = \frac{VF}{Cp} + \frac{VS - VR}{Cp} \; ; \; VF = GFR \,.\, \alpha \,.\, Cp$$

$$CLr = GFR \,.\, \alpha + \frac{VS - VR}{Cp} \qquad / \; GFR \,.\, \alpha$$

$$\frac{CLr}{GFR \,.\, \alpha} > 1 \quad \text{Filtration \& Secretion (VS>VR)}$$

$$\frac{CLr}{GFR \,.\, \alpha} = 1 \quad VS = VR \text{ or } \; VS = 0 \text{ and } VR = 0$$

$$\frac{CLr}{GFR \,.\, \alpha} < 1 \; \text{Filtration \& Reabsorption}$$

➢ Determination of renal clearance

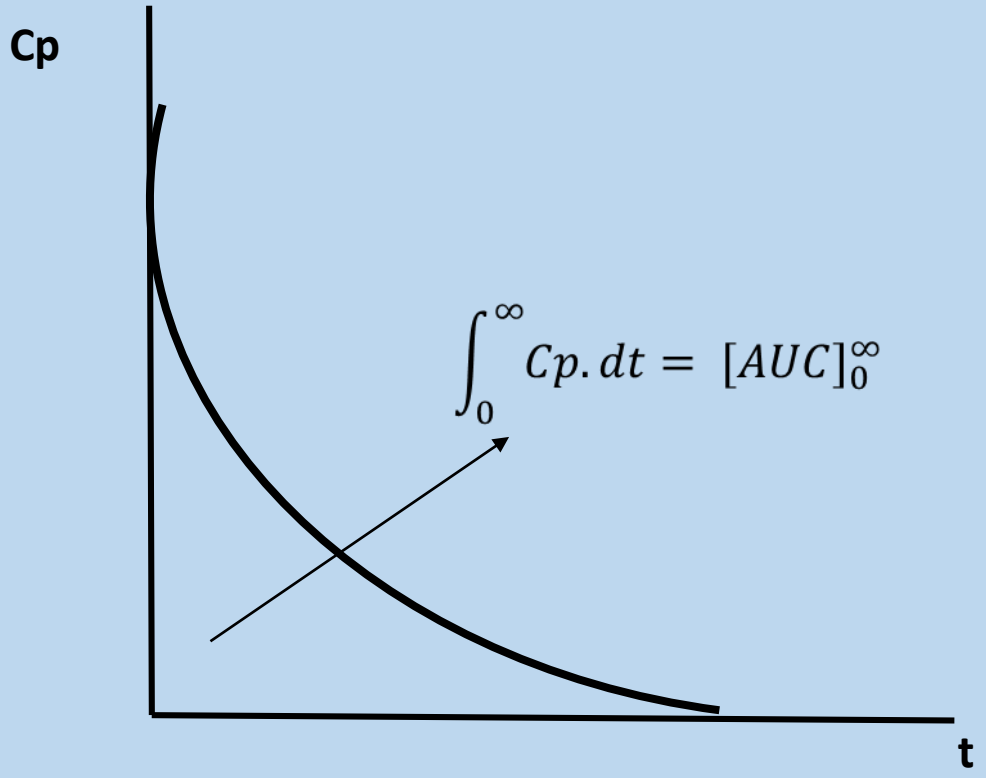
$$CLr = \frac{VE}{Cp} = \frac{dxu/dt}{Cp}$$

dXu = CLr . Cp.dt By integration

$$\int_0^\infty dXu = CLr \cdot \int_0^\infty Cp.dt$$

$$Xu^\infty = CLr \cdot [AUC]_0^\infty$$

$$CLr = \frac{Xu^\infty}{[AUC]_0^\infty}$$



➢ Determination of renal excretion constant (Ku)

1.

$CLr = Vd.\ Ku$, $CLr = \frac{VE}{Cp}$ and $Vd = \frac{Xt}{Cpt}$

$\frac{VE}{Cp} = \frac{Xt}{Cpt} . Ku$, $\frac{dXut}{dt . Cp} = \frac{Xt}{Cpt} . Ku$

$\frac{dXut}{dt} = Xt.\ Ku$

If the administration is iv in bolus:

$Ct = Co . e^{-ke.t}$, $Xt = Xo . e^{-ke.t}$

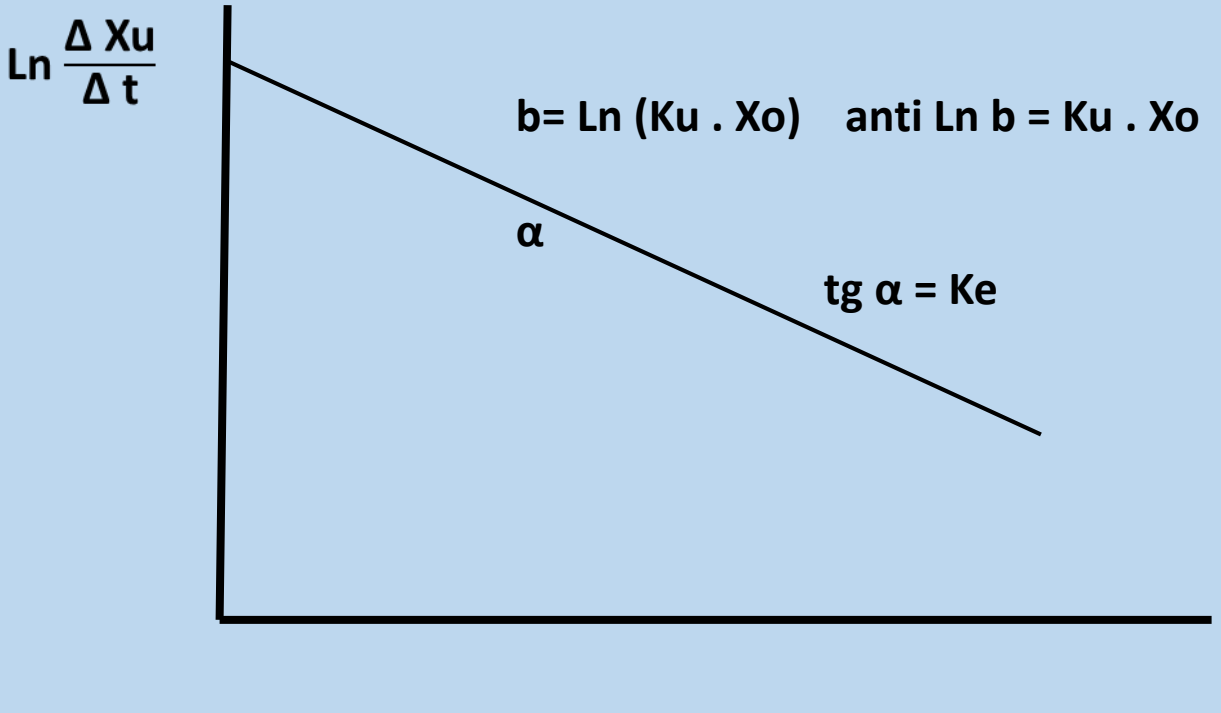
$\frac{dXut}{dt} = Ku . Xo . e^{-ke.t}$

$$\text{Ln}\ \frac{dXu.t}{dt} = \text{Ln}\ (\text{Ku.Xo}) - \text{Ke}\ .\text{t}$$

$$\text{Ln}\ \frac{\Delta\ \text{Xu}}{\Delta\ \text{t}} = \text{Ln}\ (\text{Ku}\ .\ \text{Xo}) - \text{Ke}\ .\ \text{ti}$$

y b a X

Xut	t	Δ Xut	Δ t	ti
Xu1	t1	Δ Xu1=Xu2- Xu1	Δ t1= t2 –t1	$ti1=\frac{t1+t2}{2}$
Xu2	t2	Δ Xu2=Xu3- Xu2	Δ t2= t3 –t2	$ti2=\frac{t2+t3}{2}$
Xu3	t3	Δ Xu3=Xu4- Xu3	Δ t3= t4 –t3	$ti3=\frac{t3+t4}{2}$
Xu4	t4	……	…….	…….



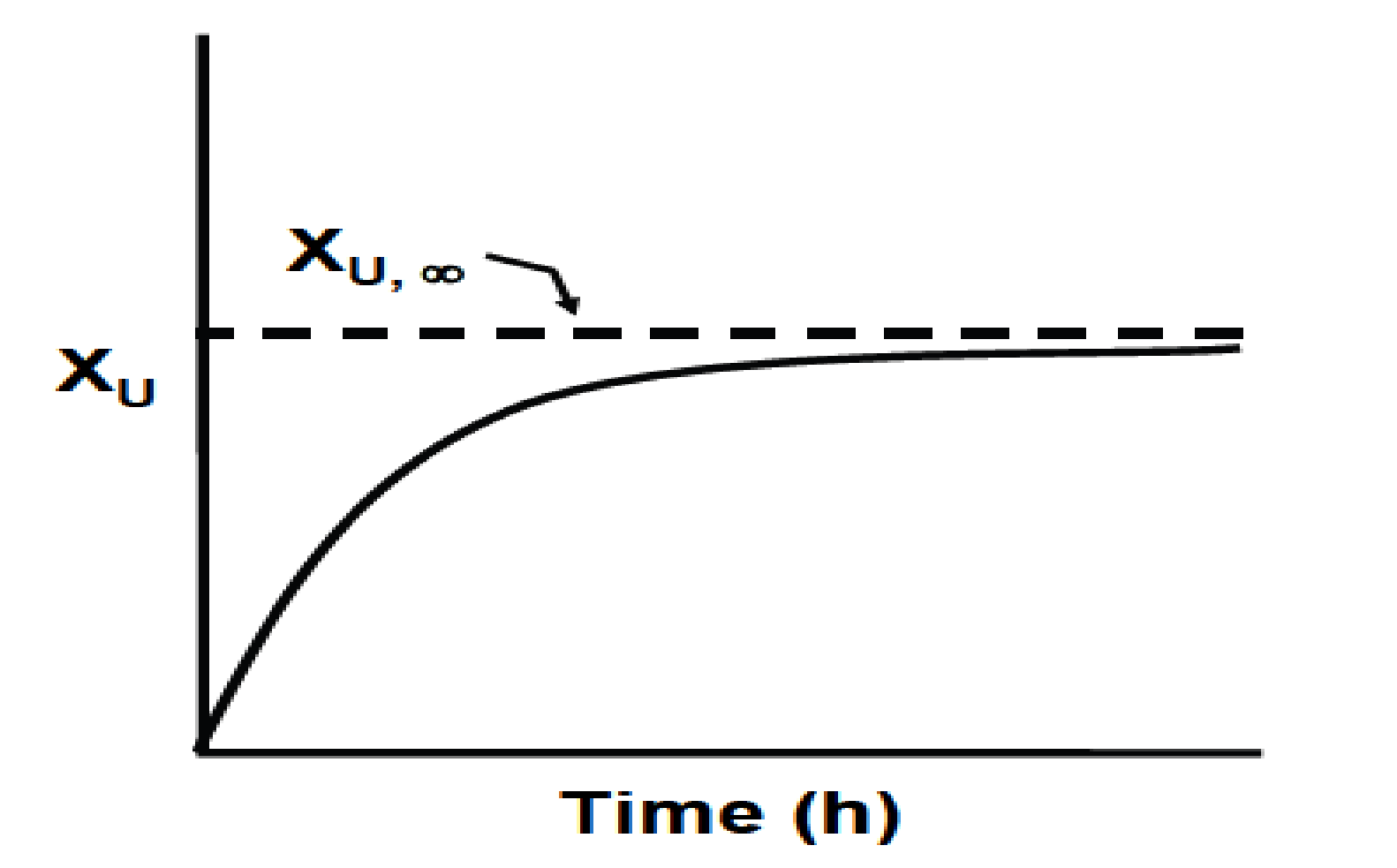
$$Ku = \frac{anti\ Ln\ b}{Xo}$$

$$Ke = \frac{0.693}{t1/2}$$

$$Ke = \frac{Ln\ Co - Ln\ Ct}{t}$$

$$Ke = \frac{Ln\ [\frac{\Delta\ Xu}{\Delta\ t}]2 - Ln\ [\frac{\Delta\ Xu}{\Delta\ t}]1}{ti2 - t\ i1}$$

2-Accumulative values of Xu



2-Accumulative values of Xu

$$\frac{dXut}{dt} = Ku \,.\, Xo \,.\, e^{-ke.t}$$

$$dXut = Ku \,.\, Xo \,.\, e^{-ke.t}\ dt$$

$$\int_0^t dXut = Ku.\ Xo \,.\, \int_0^t e^{-ke.t}\ dt$$

$$[Xu]_0^t = Ku \,.\, Xo\ [\frac{e^{-ke.t}}{-ke}]_0^t \qquad e^0 = 1$$

$$Xut = Ku \,.\, Xo\ [\frac{e^{-ke.t}}{-ke} - \frac{1}{-ke}]$$

$$\mathbf{Xut = \frac{Ku \,.\, Xo}{ke}\,[1 - e^{-ke.t}]}$$

When t = ∞

$e^{\infty} = 0$

$$\boldsymbol{Xu^{\infty} = \frac{Ku \,.\, Xo}{Ke}}$$

$$\mathbf{Ku = \frac{Xu^{\infty}}{Xo}\ ke}$$

$$\mathbf{Km = \frac{Xm^{\infty}}{Xo}\ ke}$$

3-

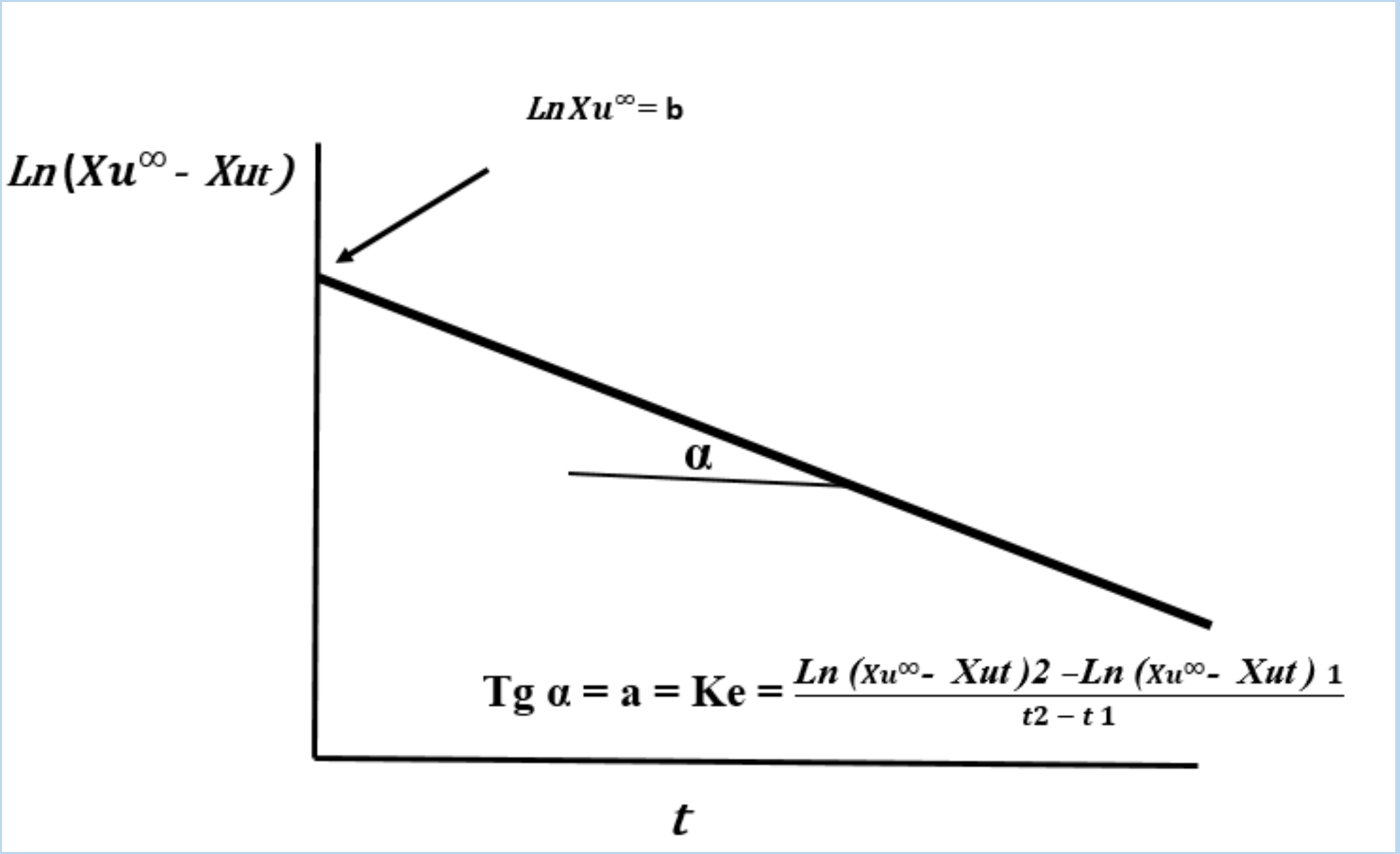
$$Xu_{to} = Xu^{\infty} \cdot (1 - e^{-ke.t})$$

$$Xu_t = Xu^{\infty} - Xu^{\infty} \cdot e^{-ke.t}$$

$$(Xu^{\infty} - Xu_t) = Xu^{\infty} \cdot e^{-ke.t}$$

$$Ln(Xu^{\infty} - Xu_t) = Ln\,Xu^{\infty} - Ke \cdot t$$

y b a x


$Ln\,Xu^{\infty} = b$
$Ln\,(Xu^{\infty} - Xut)$
α
$Tg\ \alpha = a = Ke = \frac{Ln\,(Xu^{\infty} - Xut)2 - Ln\,(Xu^{\infty} - Xut)\,1}{t2 - t\,1}$
t

1

$$CLT = CLr + CLm + CLextra\ (if\ any)$$

$$Vd.Ke = Ku.Vd + Km.Vd + CLextra.Vd$$

$$Ke = Ku + Km + Kextra\ (if\ any)$$

↓

100%.

Xo

CLT

$$X_o = X_u^\infty + X_m^\infty$$

$$1 = f_u + f_m$$

$$f_u = \frac{X_u^\infty}{X_o} \quad , \quad f_m = \frac{X_m^\infty}{X_o}$$

[2]

Determination of Cl_r

[1] $Cl_r \cdot Cp = \frac{\Delta Xu}{\Delta t}$

[2] $\frac{Cl_r}{GFR.\alpha} = 1 + \frac{VS - VR}{GFR.\alpha.\ Cp}$

[3] $Cl_r = \frac{Xu_0^{\infty}}{[AUC]_0^{\infty}}$

[3]

Determination of K_u

[1] $\ln \frac{\Delta x_{ut}}{\Delta t} = \ln(K_u \cdot x_0) - K_e \cdot t$

$y = b \pm a \cdot x$

$K_u = \frac{\text{Anti}\ln b}{x_0}$, $K_e = \frac{\ln c_0 - \ln c_t}{t}$

$K_e = \frac{\ln\left(\frac{\Delta x_{ut}}{\Delta t}\right)_2 - \ln\left(\frac{\Delta x_{ut}}{\Delta t}\right)_1}{t_{i2} - t_{i1}}$

[2] $x_{ut} = \frac{K_u \cdot x_0}{K_e} \cdot \left[1 - e^{-K_e \cdot t}\right]$

$t = \infty$

$x_u^\infty = \frac{K_u \cdot x_0}{K_e}$, $x_m^\infty = \frac{K_m \cdot x_0}{K_e}$

[3] $\ln\left(x_u^\infty - x_{ut_c}\right) = \ln x_u^\infty - K_e \cdot t$

$y = b \pm a \cdot x$

Excretion Problems

1. An antibiotic was given by intravascular bolus injection at a dose of 500 mg. The apparent volume of distribution was 21L and the elimination half life was 6 hours. Urine was collected for 48 hours and 400 mg of the unchanged drug was recovered.

A. What is the fraction of the dose excreted unchanged in the urine

B. Calculate: ke, Clr, TBCl and Clm of the drug

Excretion Problems

2. After 5 hours of IV bolus administration of 300 mg of a drug, where its distribution follows one compartment open model, 3 µg/ml of plasma concentration was obtained, if the Vd=12 L and the Clr = 3 L/h.

Calculate the maximum amount of drug excreted by urine.

Excretion Problems

3. A disease such as viral hepatitis can affect the elimination of some drugs. An IV bolus administration of 30 mg of indocyanine green (ICG) was given to 60 kg subject during and after the recovery of viral hepatitis produced the following data:

During hepatitis (mg/L)	After hepatitis (mg/L)	Time (hours)
7.2	5.1	2.5
5.7	2.5	5.0
4.3	1.3	7.5
3.3	0.74	10.0
2.6	0.39	12.5
2.1	0.19	15

Calculate the following parameters after and during the recovery of acute viral hepatitis: $t_{1/2}$, Ke, Vd and the TBCl

Excretion Problems

4. If we consider tow medicaments A and B and their pharmacokinetic parameters are reflected in the following table

Pharmacokinetic parameters	Drug (A)	Drug (B)
Ke	0.055 h^{-1}	0.070 h^{-1}
Protein binding	76%	20%
Xu	100 mg	400mg
Cp (3h)	10.59 µg/ml	4.08 µg/ml
X_0	500mg	500mg
GFR	130 ml/min	130 ml/min

Indicate which mechanism is predominant in the renal excretion for each medicament?

Excretion Problems

5. From the following table, the following parameters were taken:

Pharmacokinetic parameters	Drug A	Drug B
P. plasma binding	70%	40%
Clr L/h	15	4.1
TBCl L/h	19.2	4.8

a) Indicate how much % of the drug will be eliminated by extra renal via for each drug
b) In which drug the tubular secretion is predominant mechanism if the GFR is 130 ml/min
c) Calculate the km for both drugs if the Vd = 15 L