Membranes and Receptors

Session 8

Lecture 8.1

Pharmacokinetics

Lecturer:

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Objectives:

- **AIMS:**
- Understand principles of drug formulation and administration, including use of different sites of administration.
- Be able to discuss oral bio-availability and factors affecting this.
- Define different ways in which drugs may interact.
- Understand the differences between zero and first order kinetics (from Work Session).
- Be able to describe mechanisms of drug elimination.

Objective-1:

Understand principles of drug formulation and administration, including use of different sites of administration

Pharmacokinetics –

“What the body does to a drug”

It refers to the absorption, distribution, metabolism, and excretion of a drug in a living organism

Pharmacodynamics:

"what the drug does to the body“ It is the study of the biochemical and physical effects of drugs and mechanisms of action of drugs in living organisms

WHAT IS MEANING OF PHARMACOKINETICS

Study of the movement of a drug into and out of the body
"What the body does to the drug"

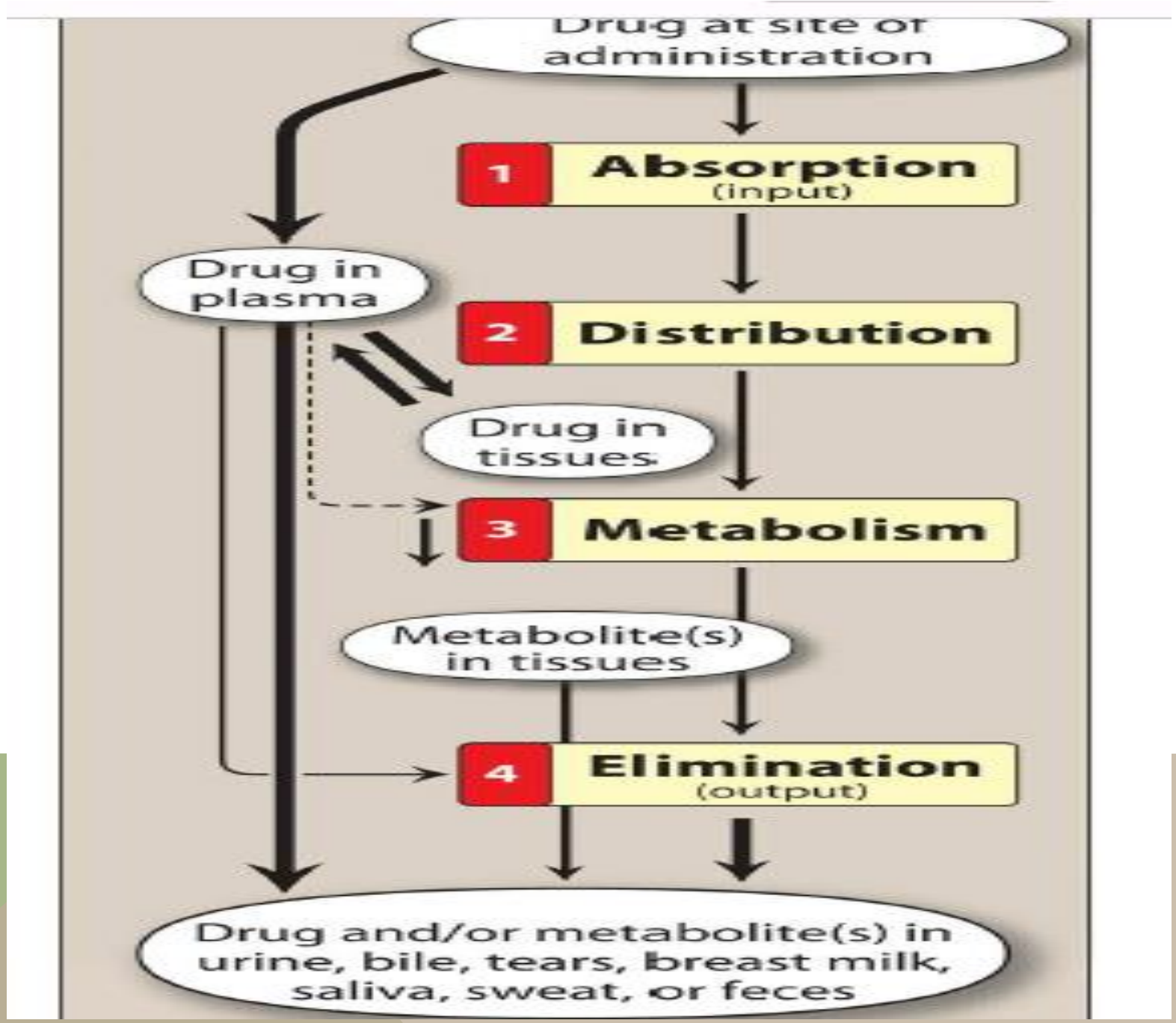
Drugs In – Drugs Out

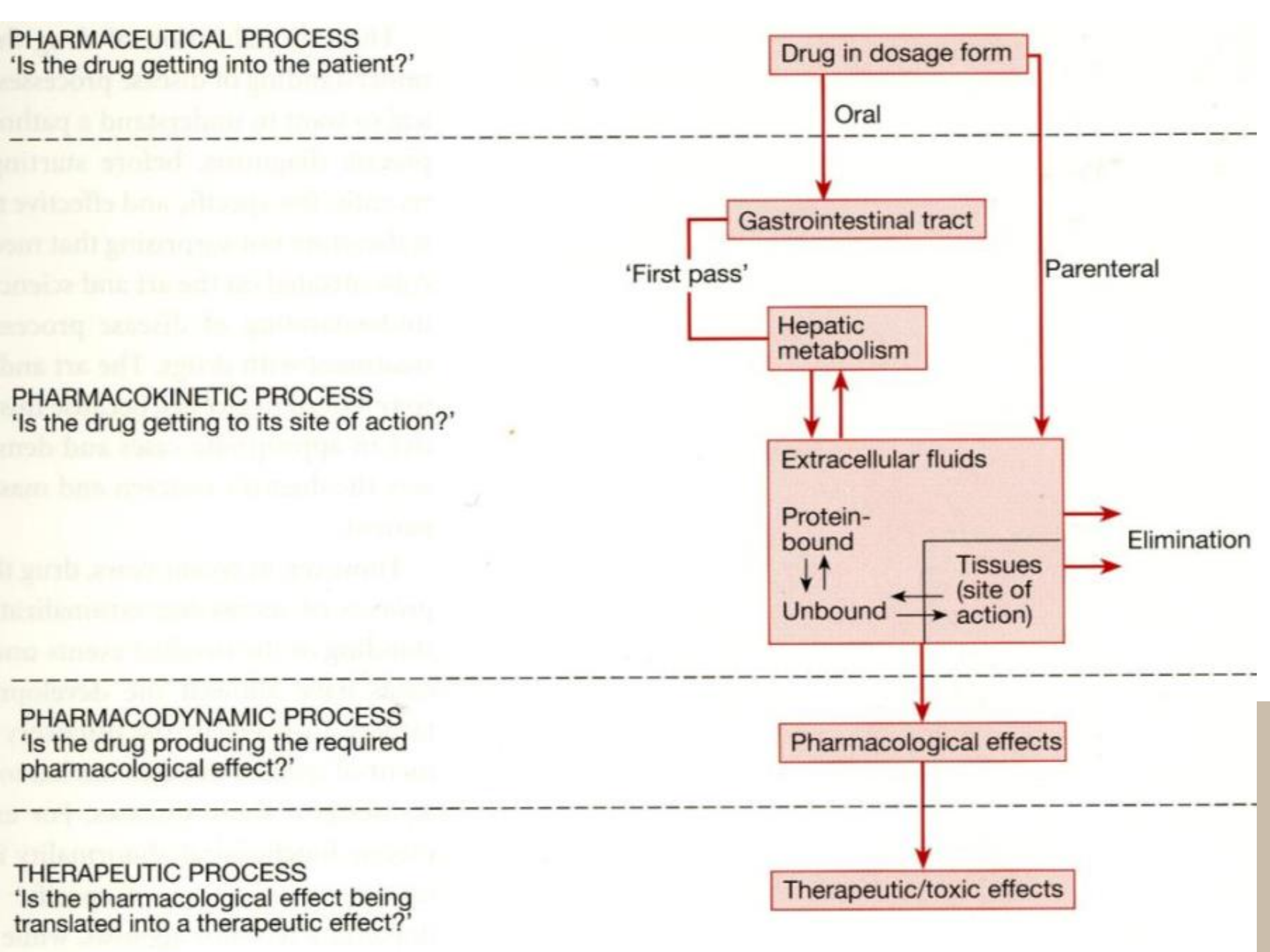
Absorption

Distribution

Metabolism

Elimination


Drug at site of administration
1 Absorption (input)
Drug in plasma
2 Distribution
Drug in tissues
3 Metabolism
Metabolite(s) in tissues
4 Elimination (output)
Drug and/or metabolite(s) in urine, bile, tears, breast milk, saliva, sweat, or feces


PHARMACEUTICAL PROCESS
'Is the drug getting into the patient?'
Drug in dosage form
Oral
Gastrointestinal tract
'First pass'
Parenteral
Hepatic metabolism
PHARMACOKINETIC PROCESS
'Is the drug getting to its site of action?'
Extracellular fluids
Protein-bound
Unbound
Tissues (site of action)
Elimination
PHARMACODYNAMIC PROCESS
'Is the drug producing the required pharmacological effect?'
Pharmacological effects
THERAPEUTIC PROCESS
'Is the pharmacological effect being translated into a therapeutic effect?'
Therapeutic/toxic effects

- **Formulation of the drug**

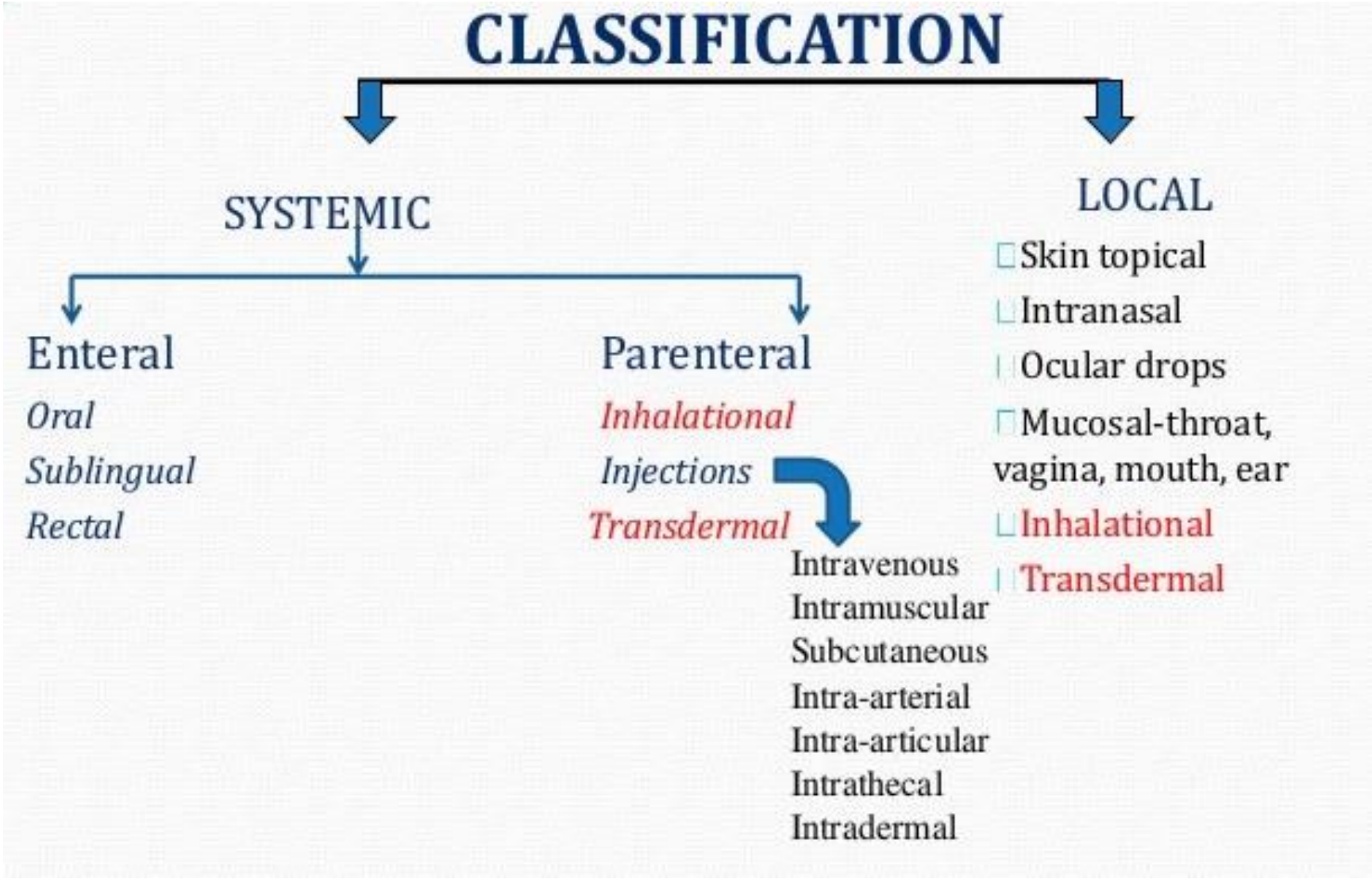
1. **Solid:** Tablet, capsule
2. **Liquid:** syrup, suspensions, emulsion

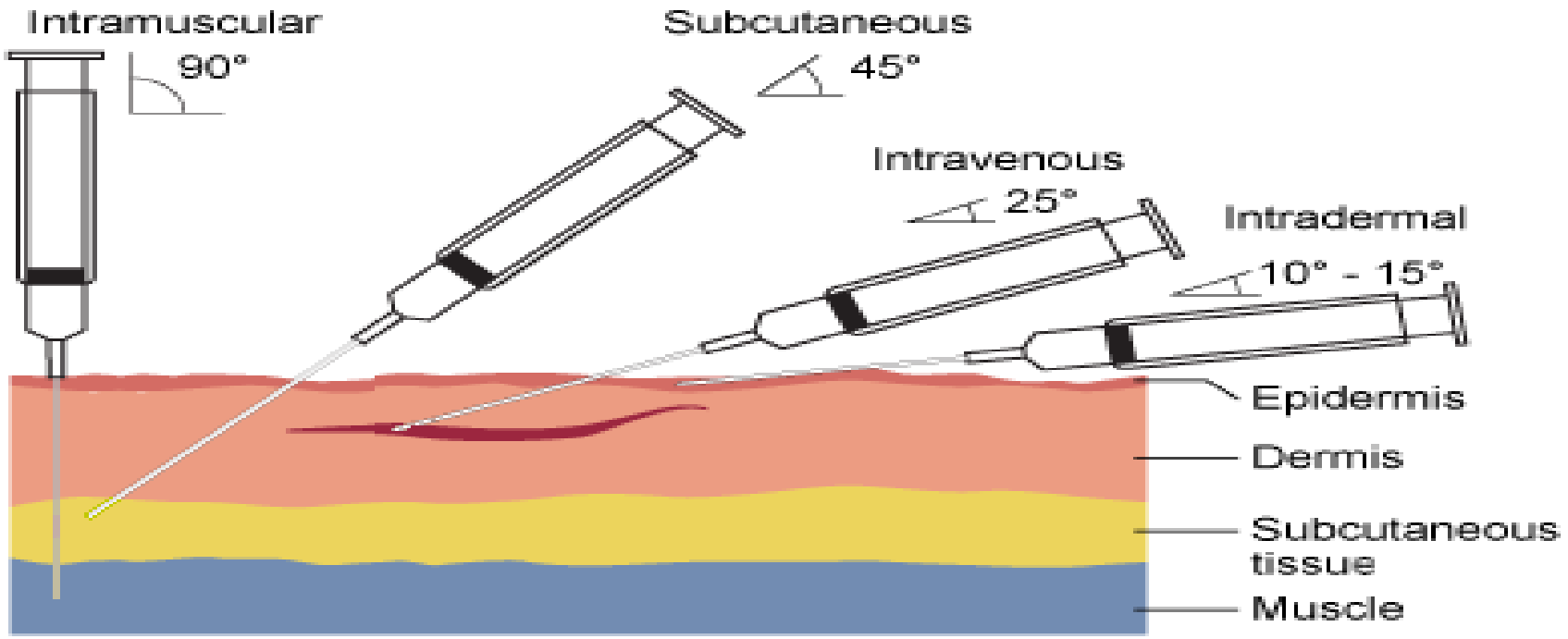
3. Injection: Ampoule, vial, IV solutions

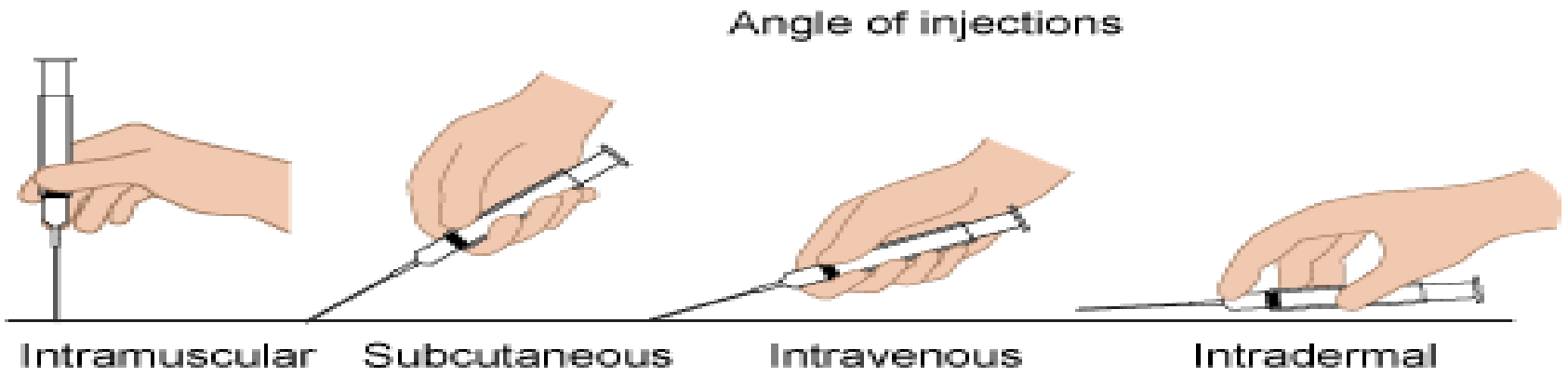
4. topical: Ointment, cream, transdermal patches, eye drops, nasal spray, suppositories

- **Site of Administration**
  - **Local** (Eye, skin, inhalation, etc)
  - **Systemic**
    - **Enteral** (Sublingual, oral, rectal)
    - **Parenteral** (Subcutaneous/intramuscular/intravenous injection, inhalation, transdermal)

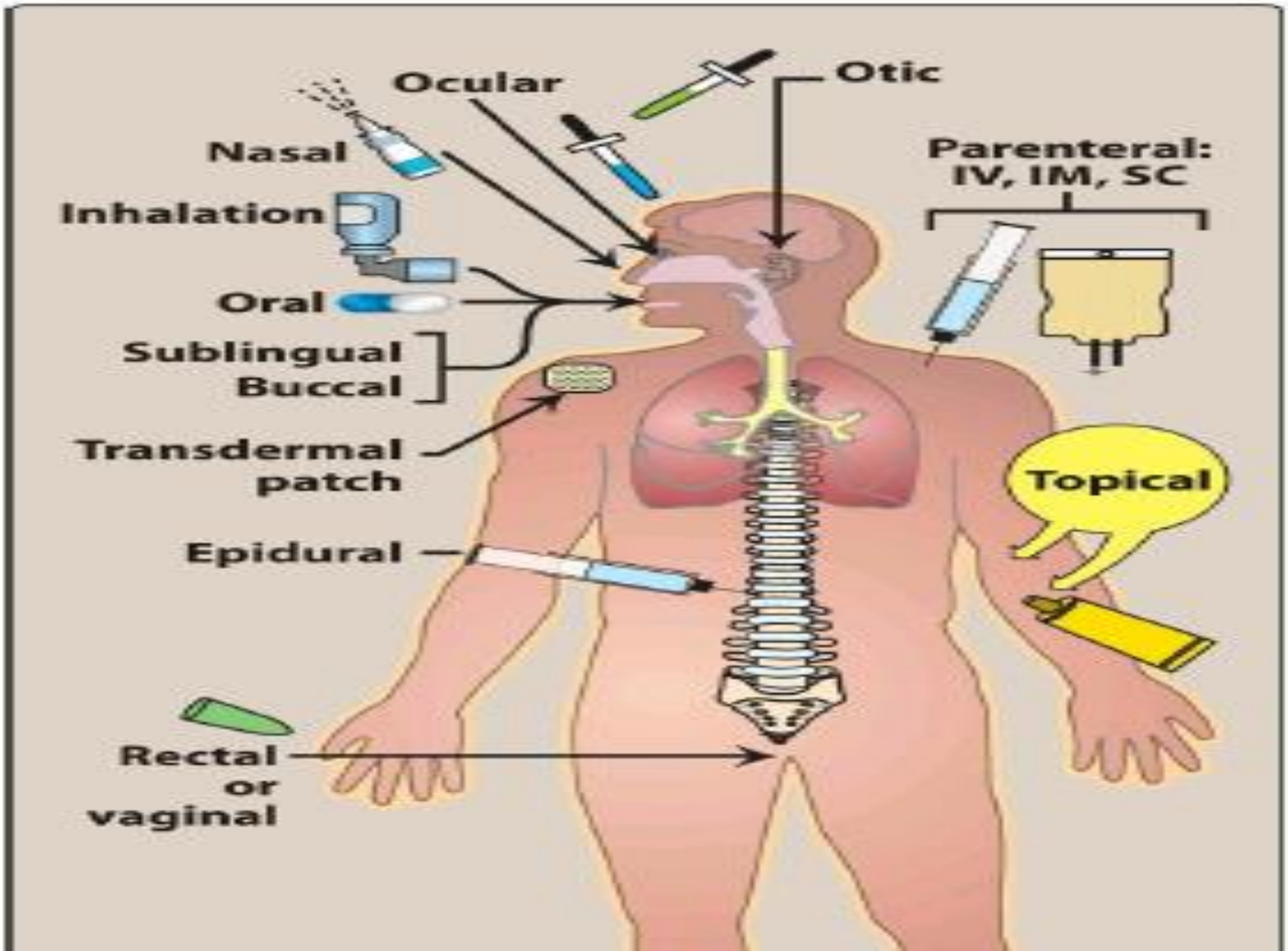
Site of Administration



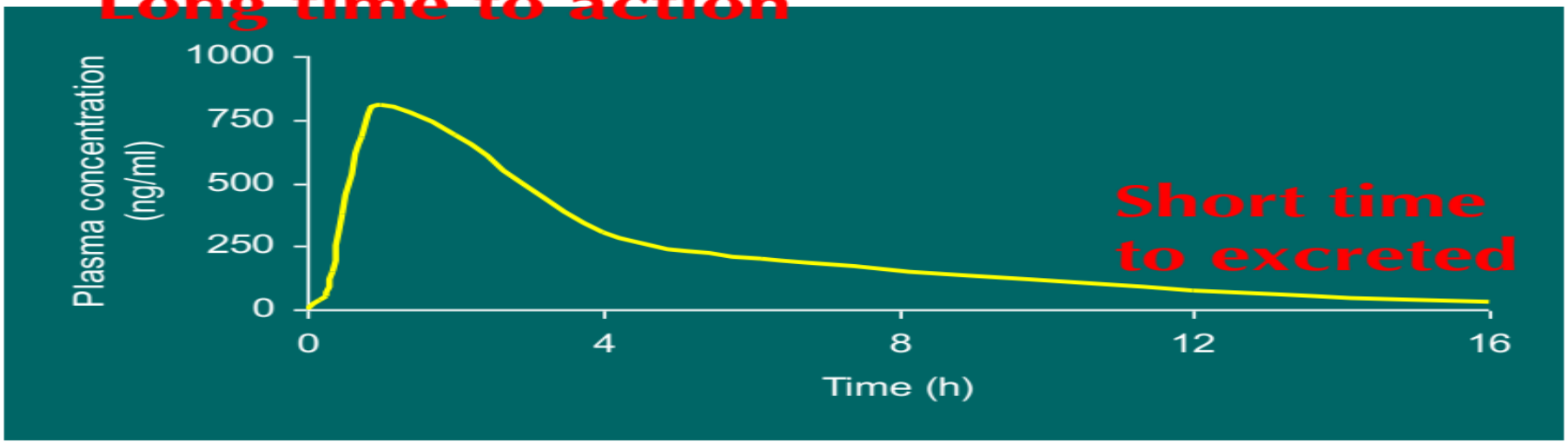

Intramuscular
90°
Subcutaneous
45°
Intravenous
25°
Intradermal
10° - 15°
Epidermis
Dermis
Subcutaneous tissue
Muscle


Angle of injections
Intramuscular
Subcutaneous
Intravenous
Intradermal

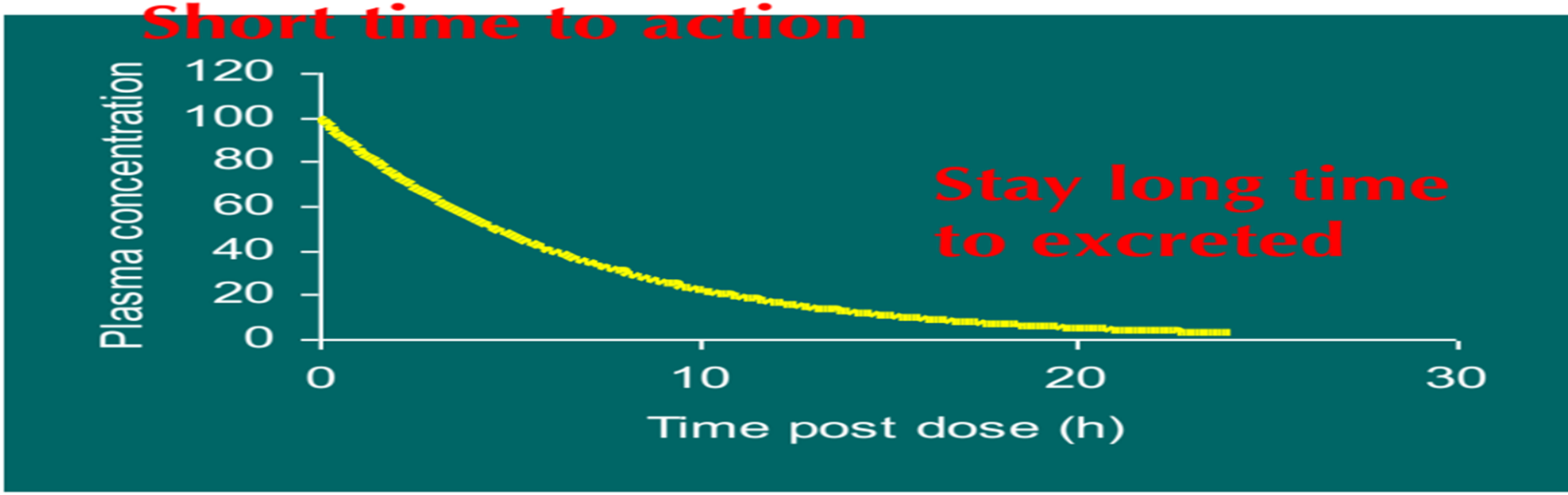
ROUTES OF DRUG ADMINISTRATION

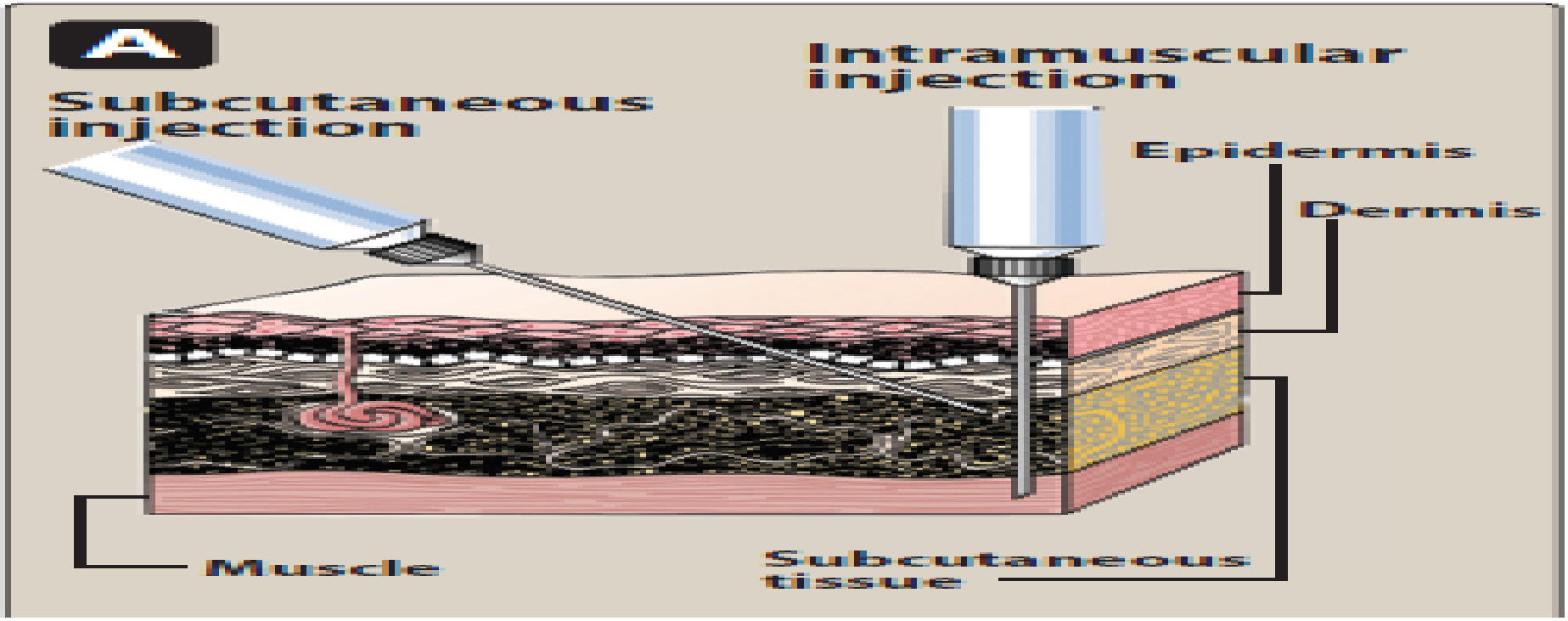


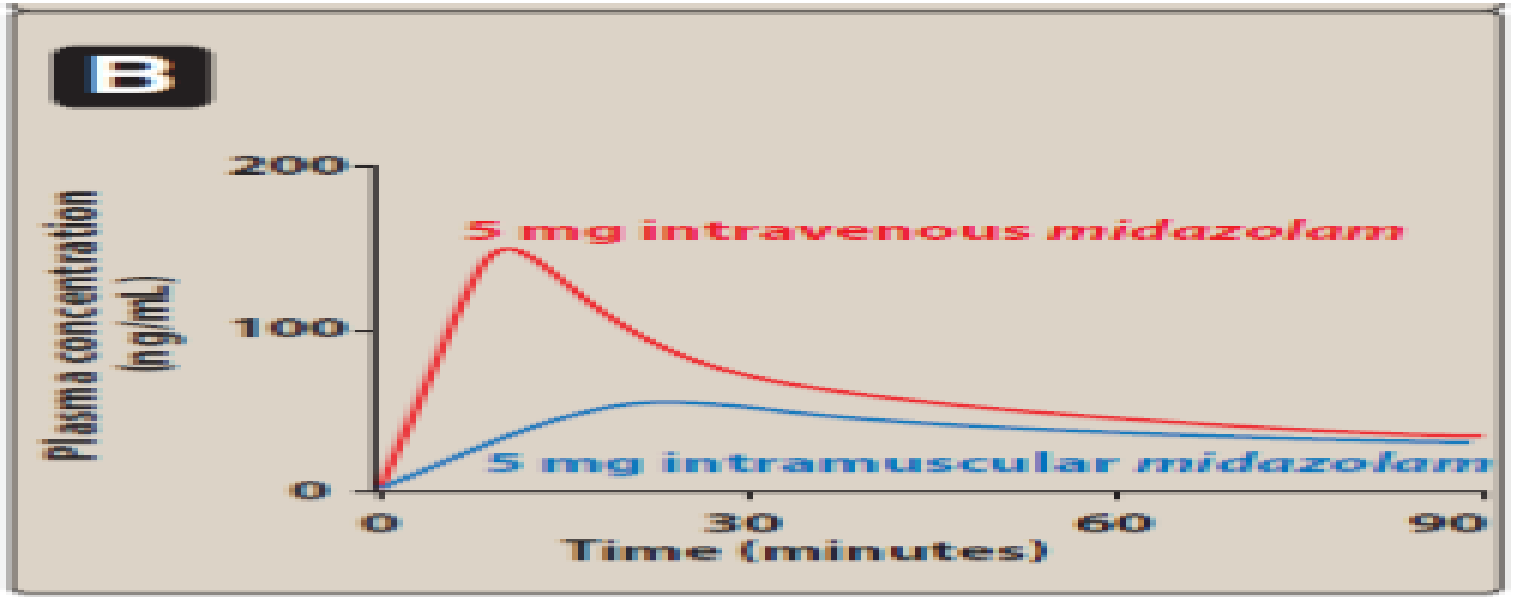
Oral Route



IV Route



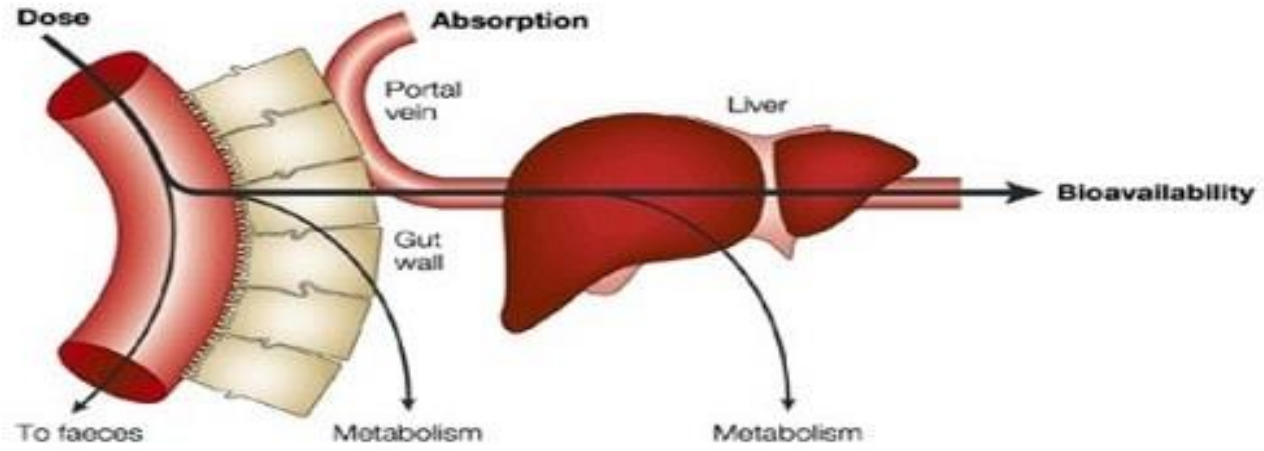

A
Subcutaneous injection
Intramuscular injection
Epidermis
Dermis
Muscle
Subcutaneous tissue

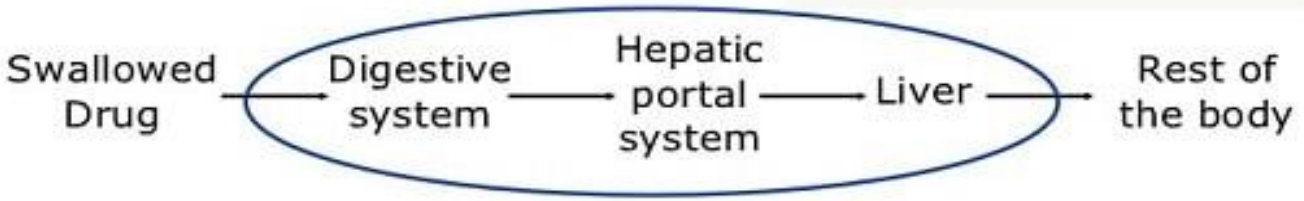

B
Plasma concentration (ng/mL)
200
100
0
5 mg intravenous midazolam
5 mg intramuscular midazolam
0
30
60
90
Time (minutes)

The first pass effect

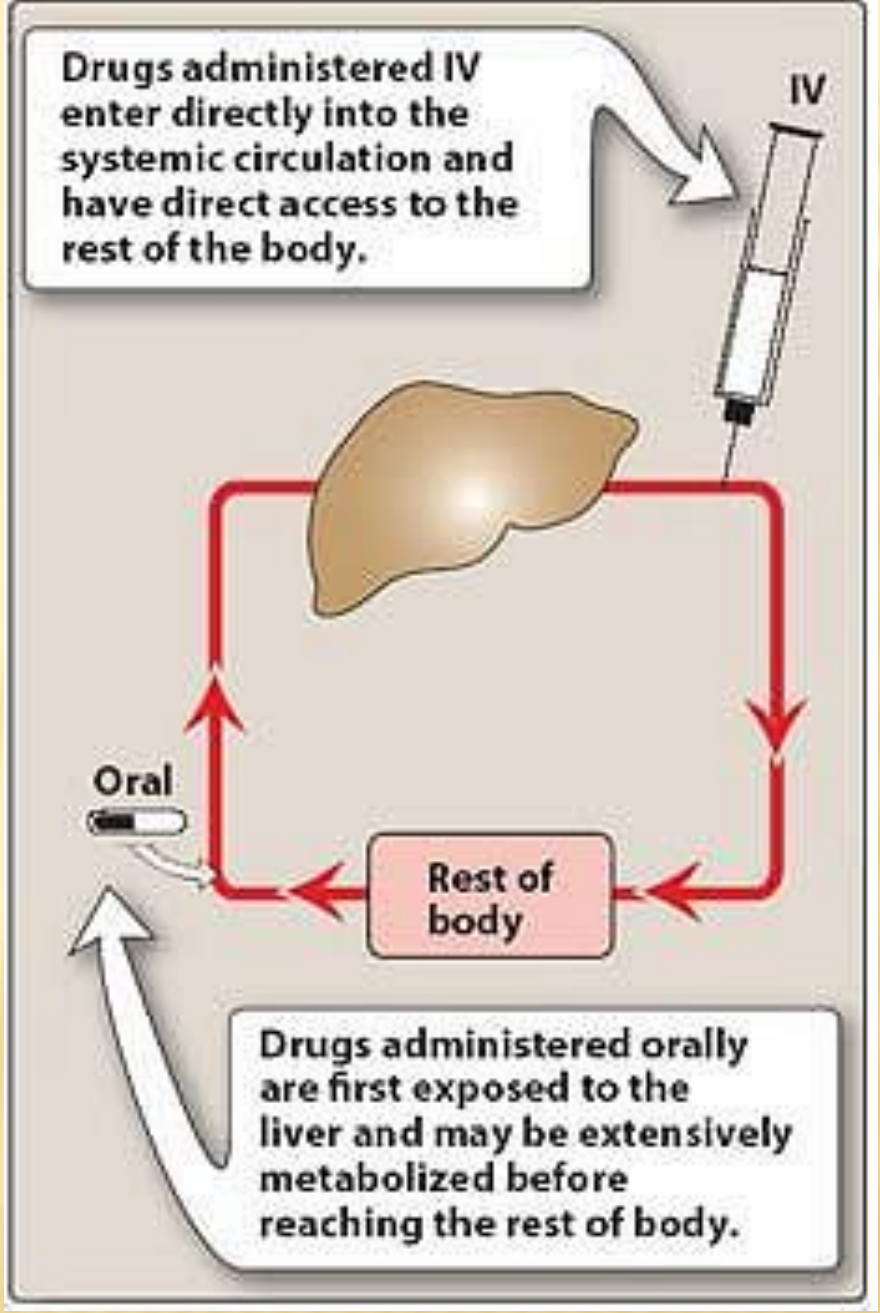
- Substances absorbed from the lumen of the ileum enter the venous blood, which drains into the hepatic portal vein and is transported directly to the liver.
- The liver is the main site of drug metabolism as it contains all of the necessary enzyme systems, so any drug absorbed from the ileum may be extensively metabolised during this first pass through the liver – the first pass effect.

- The parenteral, sublingual or rectal routes can avoid it. E.g. 90% of an oral dose of paracetamol is usually metabolised by the first pass effect.





First-pass metabolism can occur with orally administered drugs. IV = intravenous



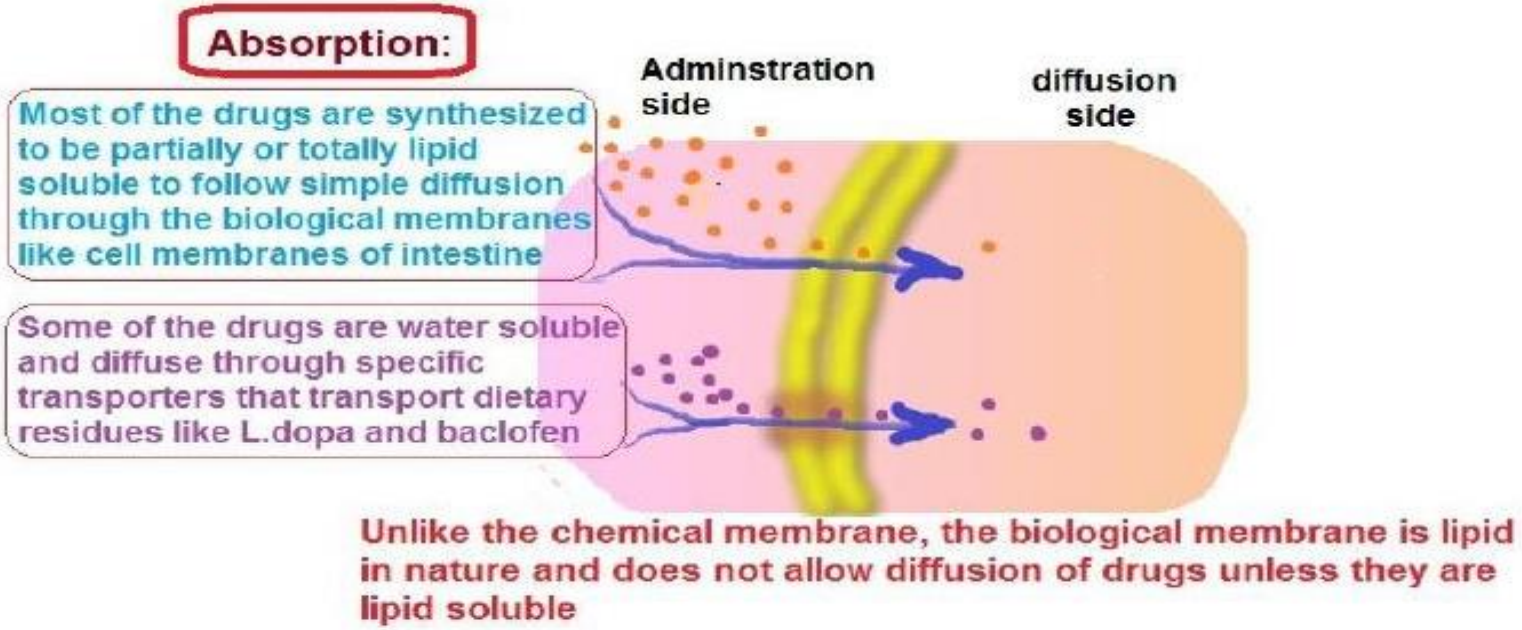
ABSORPTION OF DRUGS

Is the movement (diffusion) of drugs through a membrane.

It is of two types according to drug concentration gradient

1- Against the concentration gradient (active and facilitated) and

2- along the concentration gradient (passive which is the common for most of the drugs).



Objective-2:

Discuss oral bio-availability and factors affecting this.

BIOAVAILABILITY (F)

The fraction of a dose which finds its way into the circulation.

-For an intravenous bolus, bioavailability is 100%

-For other routes, compare amount reaching the body compartment by that route with intravenous bioavailability

Factors that influence bioavailability:

Absorption, Drug formulation, Age, Food: lipid-soluble>water-soluble,Vomiting / malabsorption, First pass metabolism.

First pass Metabolism

Any metabolism occurring before the drug enters the systemic circulation. (the ‘first-pass’ effect).

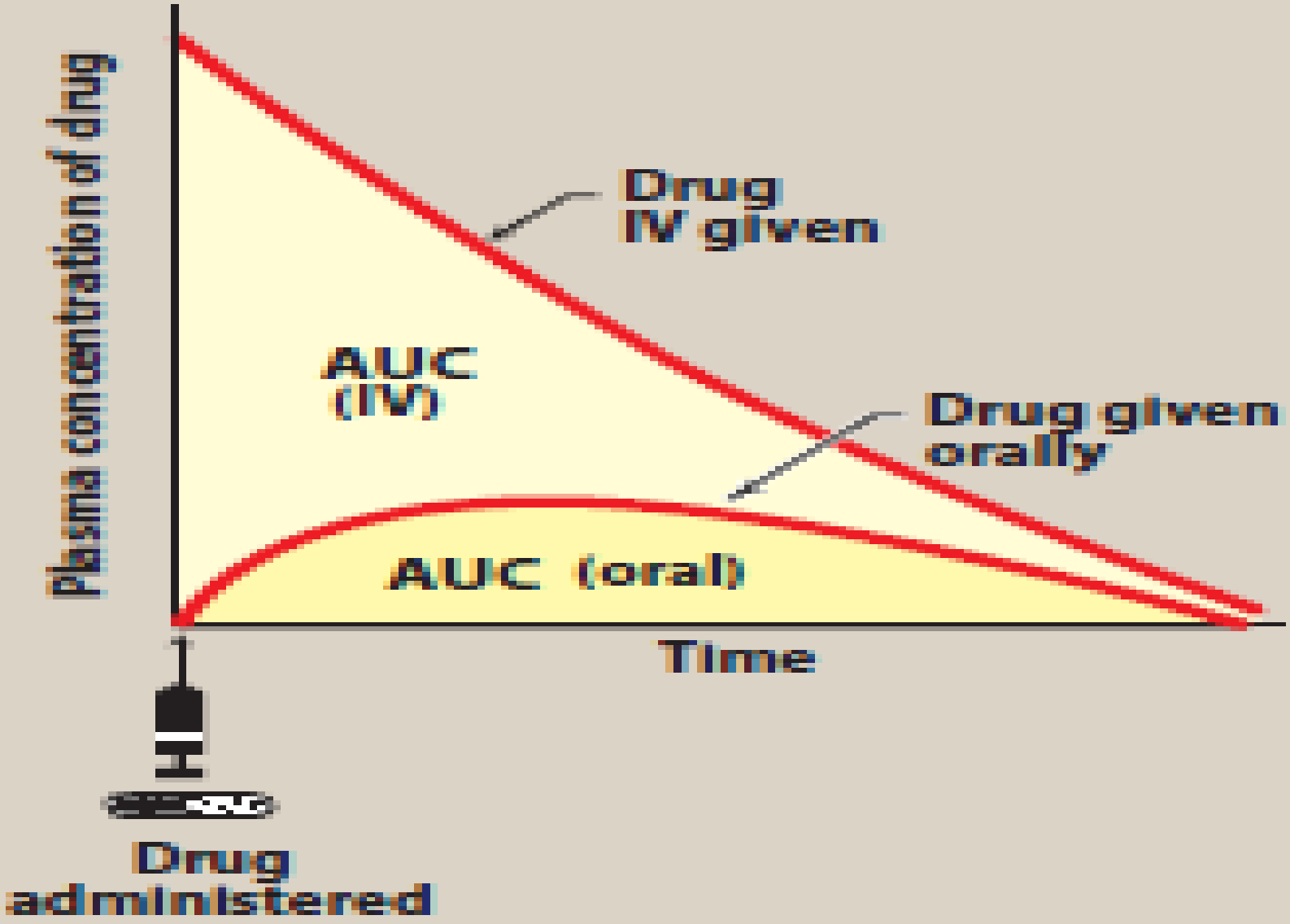
BIOAVAILABILITY CALCULATION

$$\text{Bioavailability} = \frac{\text{Amount of Drug Reaching Systemic Circulation}}{\text{Total Amount of Drug Administered.}}$$

Clinically, this is calculated by looking at the Total *Area Under the Curve* or **AUC** that describes the drugs plasma concentration over time

BIOAVAILABILITY **F = AUV oral / AUC i.v × 100**

$$\text{Bioavailability} = \frac{\text{AUC oral}}{\text{AUC IV}} \times 100$$



For example: if 100 mg of a drug are administered orally and 70 mg of this drug are absorbed unchanged, the bioavailability is 0.7 or seventy percent.

Objective-4:
Define different ways in which drugs may interact.

Drug Distribution

The distribution of a drug refers to its ability to 'dissolve' in the body

- There are two key factors:
- Protein binding
- Volume of Distribution (Vd)

Plasma Proteins

I. Many drugs bind to plasma proteins.

II. It is the free level of drug that exerts an effect, not the total. Protein binding actions can also occur

This is important if:

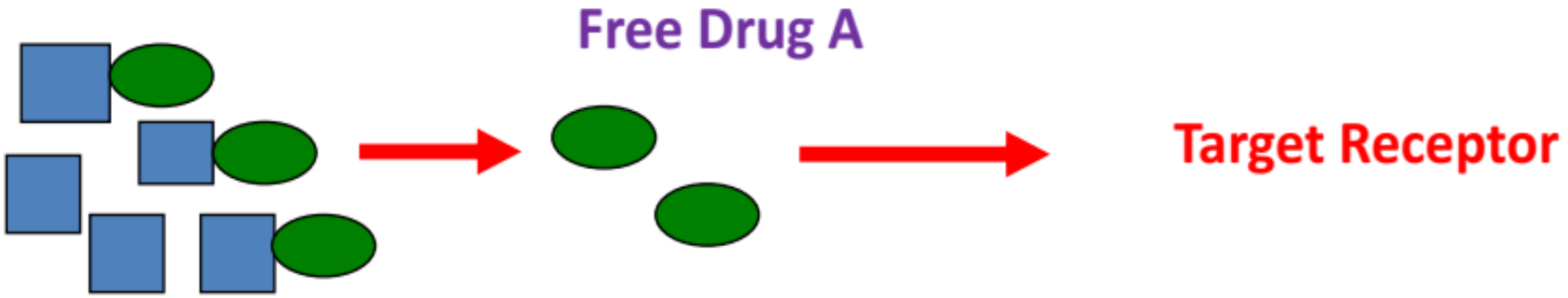
A. The drug is highly bound to albumin (>90%)

B. The drug has a small volume of distribution

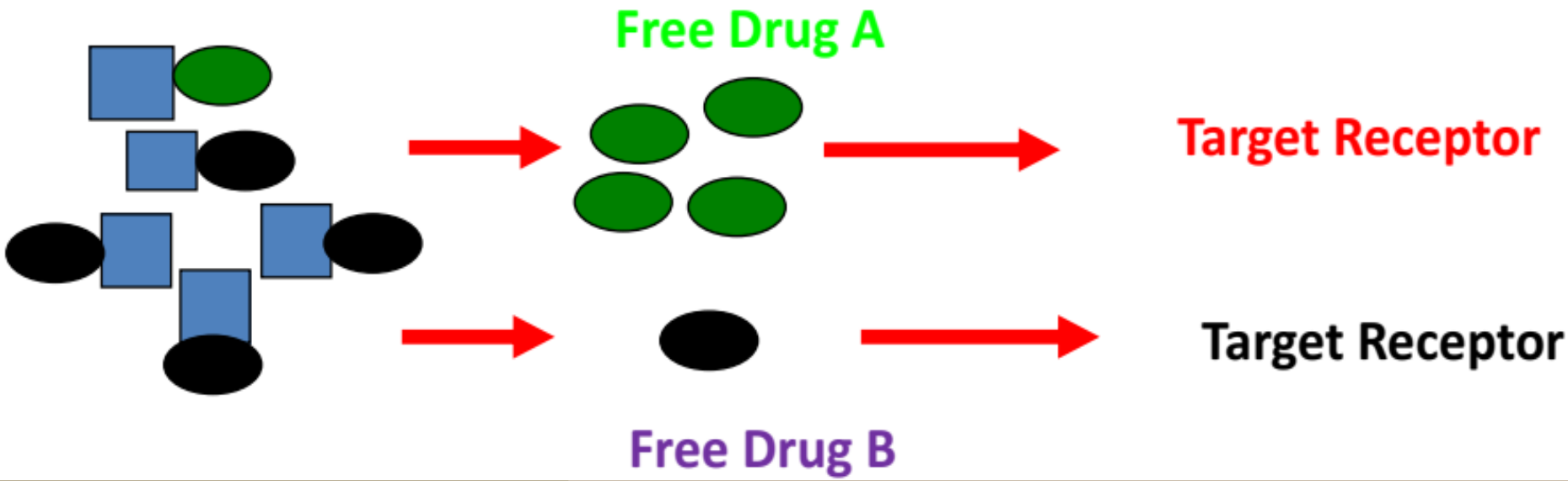
C. The drug has a low therapeutic index

- E.g. Warfarin, tolbutamide

Protein Binding Drug Interactions



Additional highly bound precipitant drug:



Object Drug	Precipitant Drug
Warfarin	Sulphonamides, aspirin, phenytoin
Tolbutamide	Sulphonamides, aspirin
Phenytoin	Valproate

Volume of distribution(Vd):

The theoretical volume into which a drug has distributed assuming that this occurring instantaneously.

Calculated as Amount Given / Plasma Concentration at Time 0

$Vd = D/C_0$

where D is the dose and C_0 the concentration at time 0.

Objective-4:
Understand the differences between zero and first order kinetics

- If drugs are metabolised by enzymes that obey Michaelis-Menten kinetics:

- $Rate\ of\ Metabolism = \frac{Vmax\ [C]}{Km + [C]}$

First order kinetics:

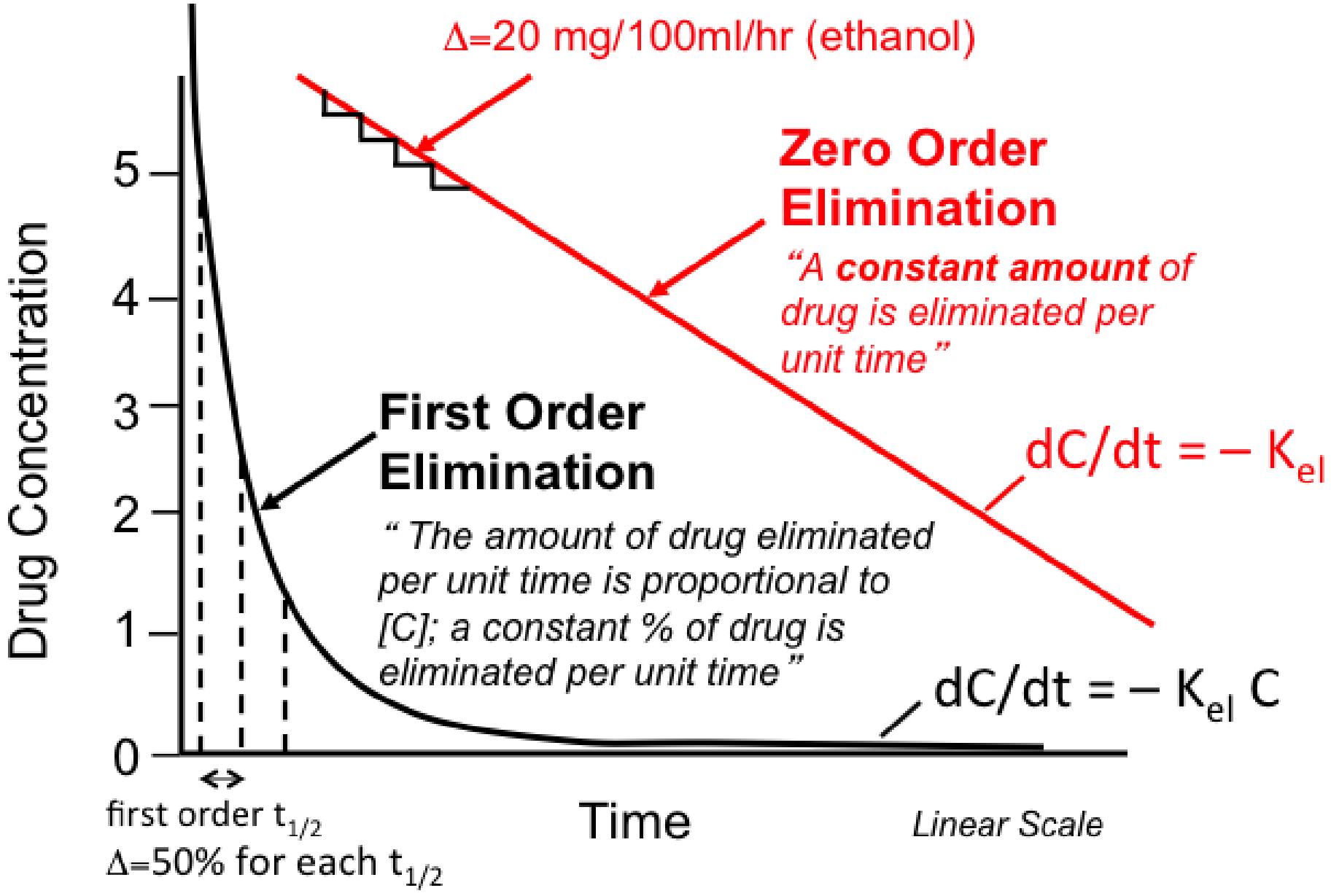
- In a situation where a drug is used at concentration [C] that is lower than K_m:
- $Rate\ of\ Metabolism = \frac{Vmax\ [C]}{Km}$
- This means that **metabolism is proportional to drug concentration** – 1^{st} Order Kinetics.
- First Order Kinetics gives a **straight line when a log scale is on the Y-axis versus time**.

Zero order kinetics:

- In a situation where drug is used at a concentration [C] much greater than K_m:

- $$Rate\ of\ Metabolism = \frac{Vmax\ [C]}{[C]}$$

- **The enzyme is saturated. The rate of decline of plasma drug level is a constant, regardless of concentration**. Zero order kinetics gives a **straight line when normal (not log) plasma concentration (Y) is plotted against time** (X).


Δ=20 mg/100ml/hr (ethanol)
Zero Order Elimination
"A constant amount of drug is eliminated per unit time"
First Order Elimination
" The amount of drug eliminated per unit time is proportional to [C]; a constant % of drug is eliminated per unit time"
dC/dt = – K_el
dC/dt = – K_el C
Drug Concentration
5
4
3
2
1
0
first order t1/2
Δ=50% for each t1/2
Time
Linear Scale

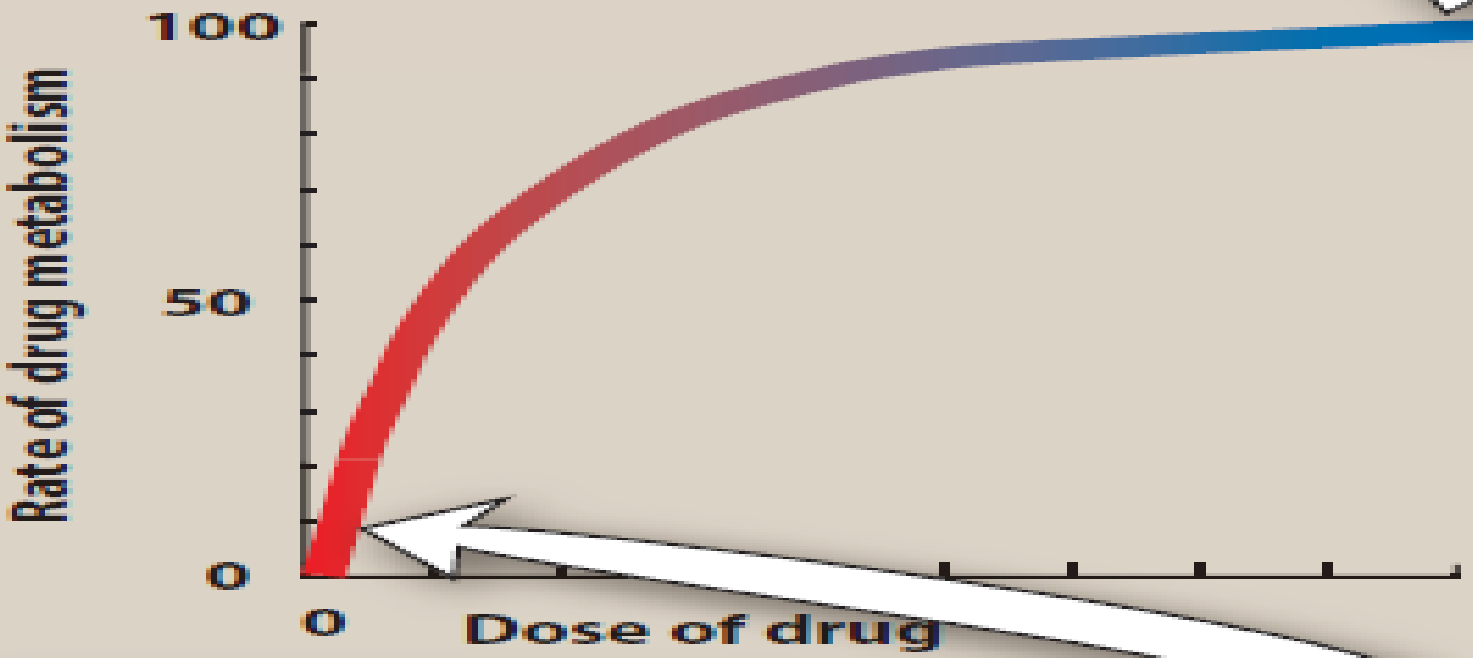
Some Important drugs that Exhibit 'Saturated' Kinetics

Relatively few drugs exhibit saturated kinetics over therapeutic doses.

There are a number of important drugs taken by very large numbers of patients, including high dose aspirin, phenytoin, verapamil, fluoxetine

Non-Linear Kinetics Can Occur with Polypharmacy

With a few drugs, such as *aspirin*, *ethanol*, and *phenytoin*, the doses are very large. Therefore, the plasma drug concentration is much greater than K_m, and drug metabolism is zero order, that is, constant and independent of the drug dose.



With most drugs the plasma drug concentration is less than K_m, and drug elimination is first order, that is, proportional to the drug dose.

Comparison

First Order Elimination	Zero Order Elimination
Fixed ratio 50% of drug Eliminated per unit of time	Fixed amount of drug Eliminated per unit of time
Not need saturable enzyme for metabolism	Need saturable enzyme for metabolism
Give liner curve	Non liner curve or saturable
Half life fixed	Half life non fixed
Safe	Danger
Most of drug eliminated from the body	A few of drug eliminated from the body

Objective-5: Describe mechanisms of drug elimination.

Drugs are eliminated from the body by:

1) Metabolism (e.g. by liver)

2) Excretion (e.g. by kidney)

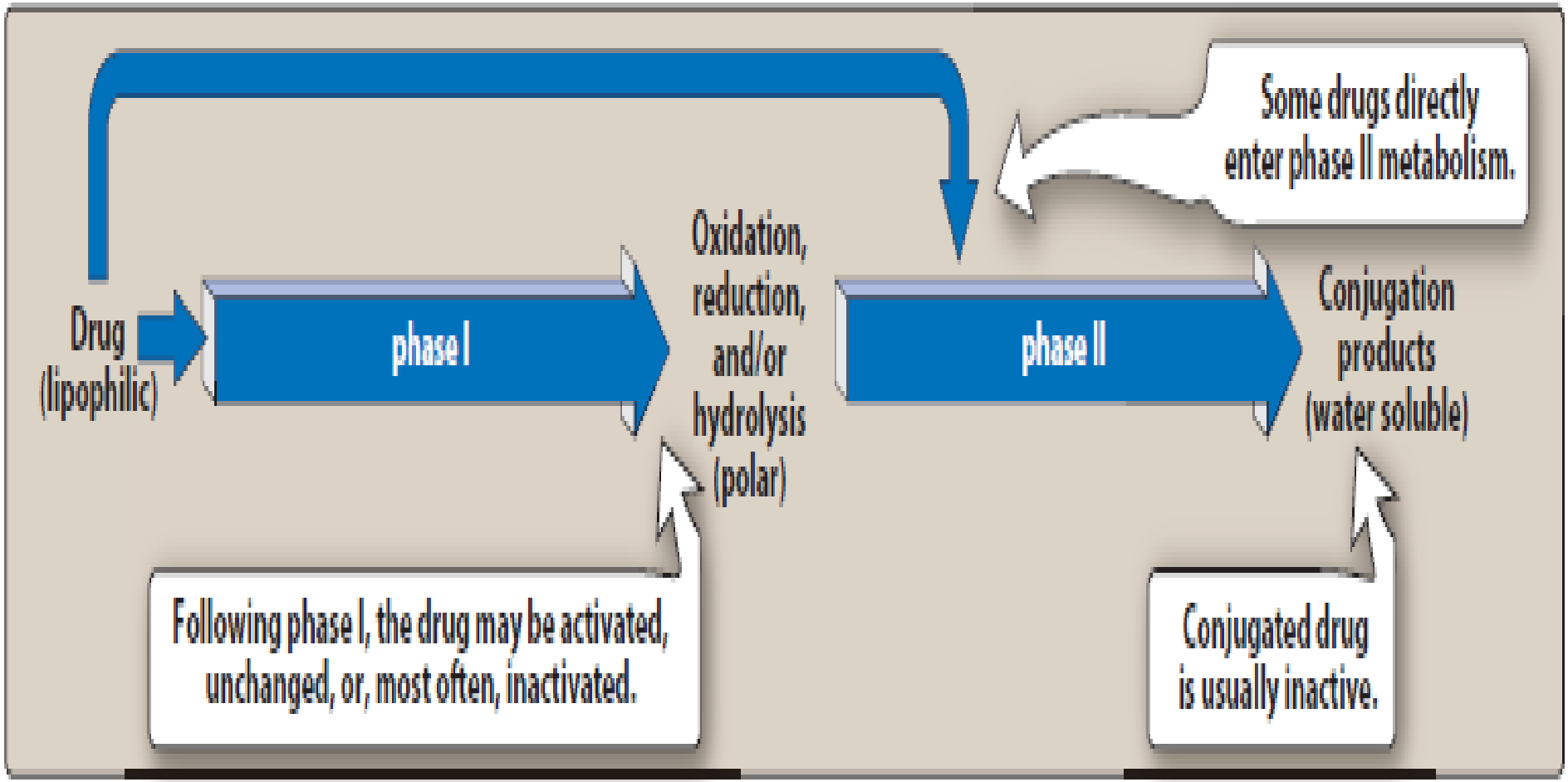
DRUG ELIMINATION

HOW DRUGS ARE ELIMINATED FROM THE BODY:

1- METABOLISM

About 90% of drugs metabolism is by the liver to make them ionized and readily excretable by the kidneys

So in hepatic or renal dysfunction many drugs clearance will be halved so consider halving drug dose


Some drugs directly enter phase II metabolism.
Drug (lipophilic)
phase I
Oxidation, reduction, and/or hydrolysis (polar)
phase II
Conjugation products (water soluble)
Following phase I, the drug may be activated, unchanged, or, most often, inactivated.
Conjugated drug is usually inactive.

soluble metabolites in the liver.

- Drugs metabolism (biotransformation) passes into two phases
- Phase I (oxidation, reduction and hydrolysis).
- Phase II (conjugation with water soluble moieties like glucuronyl)
- Biotransformation concerns only Sd i.e drug solubilization in order to be ready for excretion in urine or stool.
- Drug potency does not necessarily change during the process of solubilizition (biotransformation or detoxification).

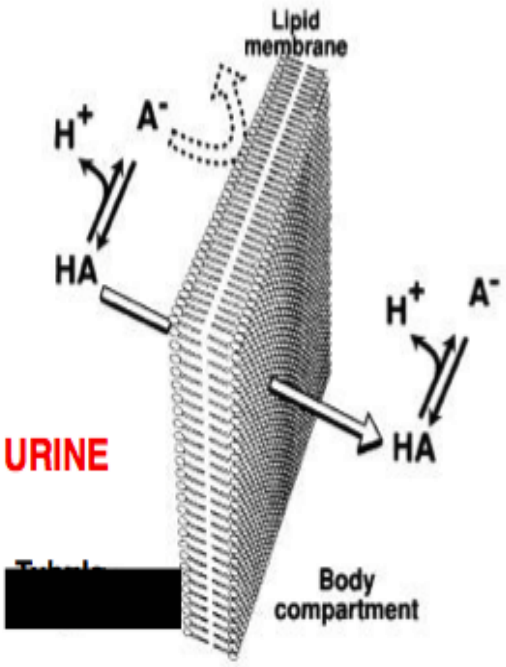
Drug activity before metabolism (solubilization)	Drug activity after metabolism
Active drug	Active metabolite
Active drug	Inactive metabolite
Inactive drug	Active metabolite

- During phase I the drugs are only partially soluble in water not sufficiently to be excreted in urine unless they pass in phase II where transferases enzymes will conjugate highly water soluble side chain (like glucuronyl, acetate or glycyl group) which renders the drugs readily excreted in urine or stool.

The excretion of drugs by the kidney

- **Only the free unbound drug is filtered through glomerular tuft.**
- Drugs can be actively secreted by the tubule (e.g. penicillin).
- **Urine pH** can determine how much of the drug is excreted: ionized drug (water soluble) is excreted in urine and not reabsorbed from renal tubules.
- Unionized drug or (lipid soluble) is reabsorbed into circulation
- So in case of over dose we can enforce drug excretion by manipulation of urine PH as drugs either weak acids or weak bases.

Renal Excretion of Drugs

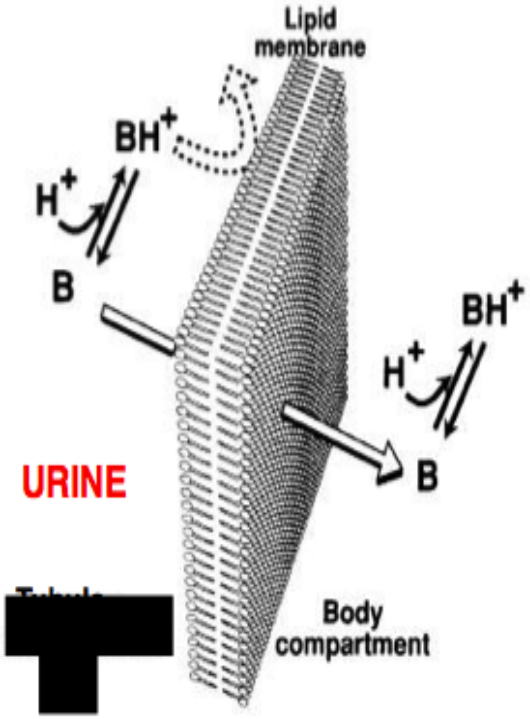


Weak Acids

Acid urine
↑ absorption

Alkaline urine
↓ absorption

Renal Excretion of Drugs

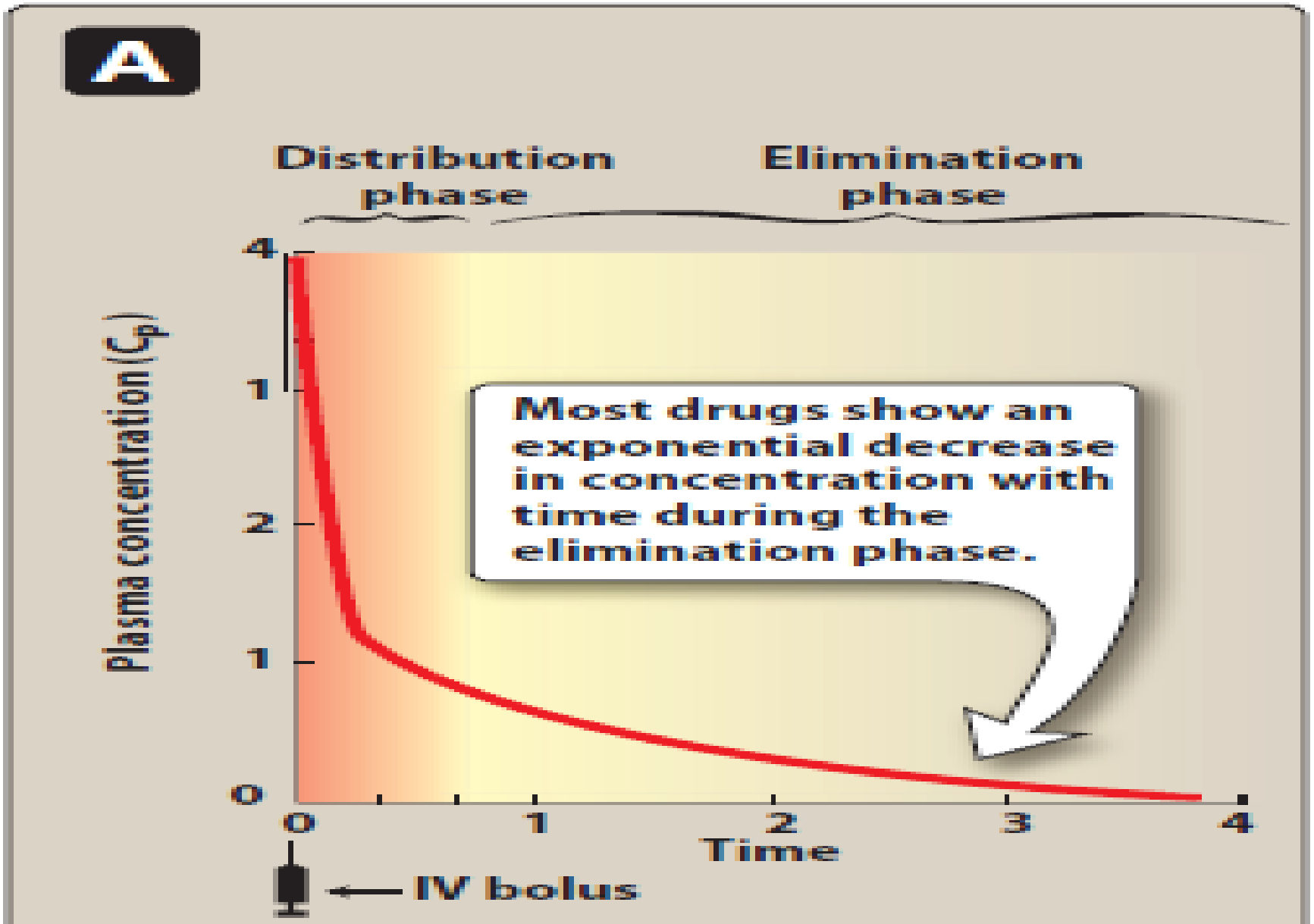


Weak Bases

Acid urine
↓ absorption

Alkaline urine
↑ absorption

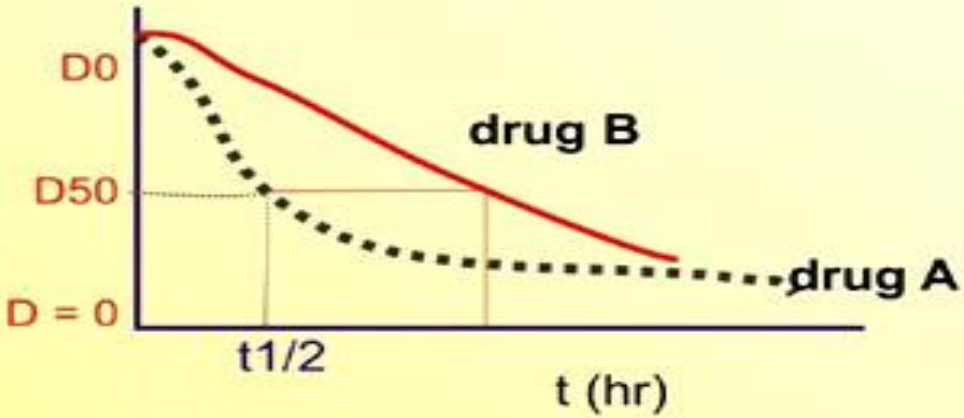
- For **weak acids**, e.g. aspirin, making the urine **alkaline** will make the drug ionised, so there will be less tubular absorption because the charged drugs stay in the tubule lumen.
- **weak bases** (e.g. amphetamine), where **acid** urine increases excretion


A
Distribution phase
Elimination phase
Plasma concentration (C_p)
4
1
2
1
0
Most drugs show an exponential decrease in concentration with time during the elimination phase.
0
1
2
3
4
Time
IV bolus

- Half-life : is the time required for the drug concentration to change by 50%

A) STEPS OF DETERMINING DRUG T1/2

1- administer a drug by any route
2- stop administration
3- measure plasma concentration immediately
4- this is D0 or Cp
5- repeat plasma measurements hourly untill Cp =0
6- these are Dt: dose at any time
7- tabulate dose against time
8- plot the graph of dose against time
9- calculate D0/2 = D50 to determine t1/2



10- apply the following drug elimination formula

$$Dt = D0\ e^{-kt}$$

k = elimination rate constant (hr^-1)= **(ln Dt/D0)/t** **and t1/2 = 0.7/k**

REACHING THERAPEUTIC LEVELS: PHARMACOKINETICS WITH REPEATED DOSING

With Repeated Dosing, the Overall Balance Between Drug In and Drug Out Determines

The 'Steady State' or Average or Plasma Level of Drug

Steady State Concentration in Plasma

Cpss = Dose Rate /Cl

The time from first repeat dose to CpSS is 5 Half Lives of the Drug

- During drug administration, a **steady state** will be reached within **5 half-lives** of that drug.
- If an immediate effect is necessary, a **loading dose** is therefore needed.

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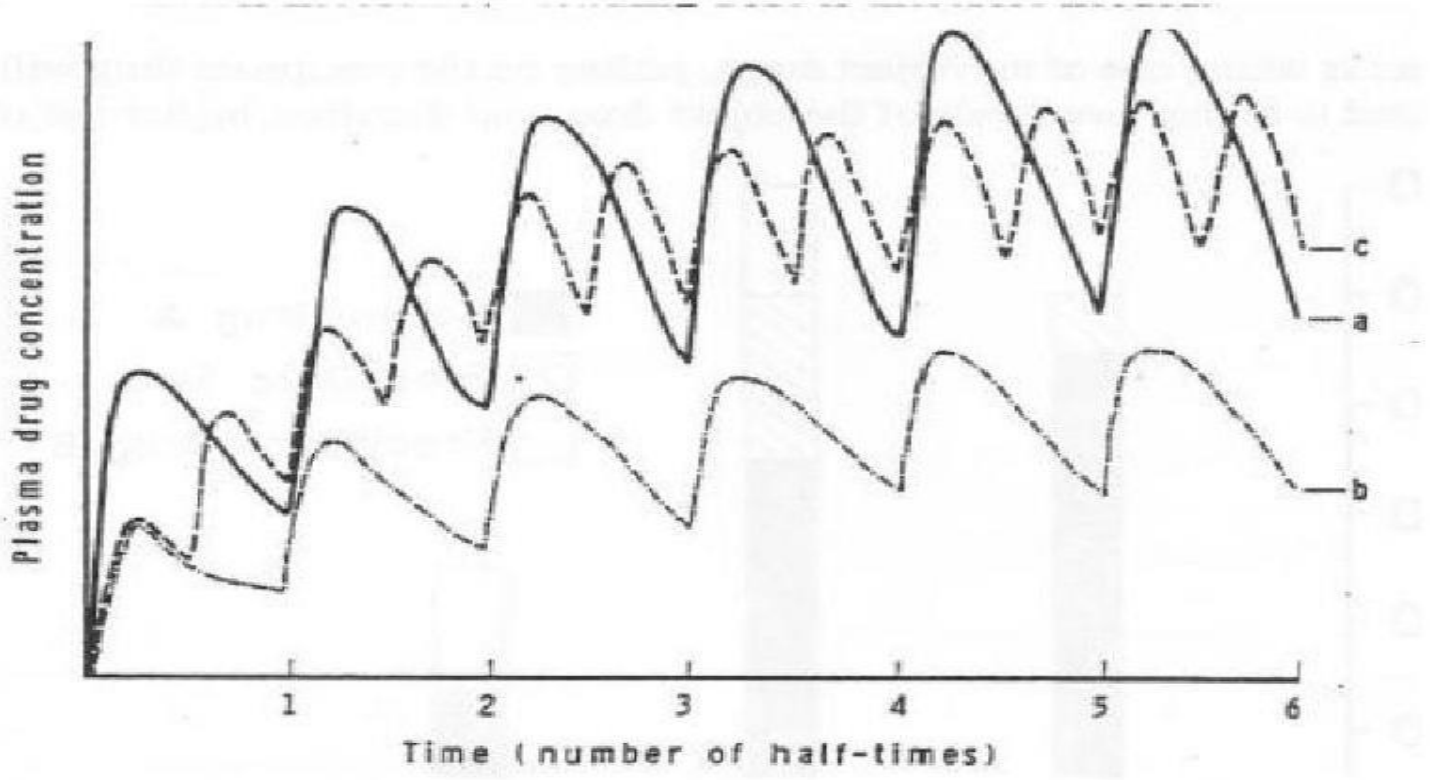

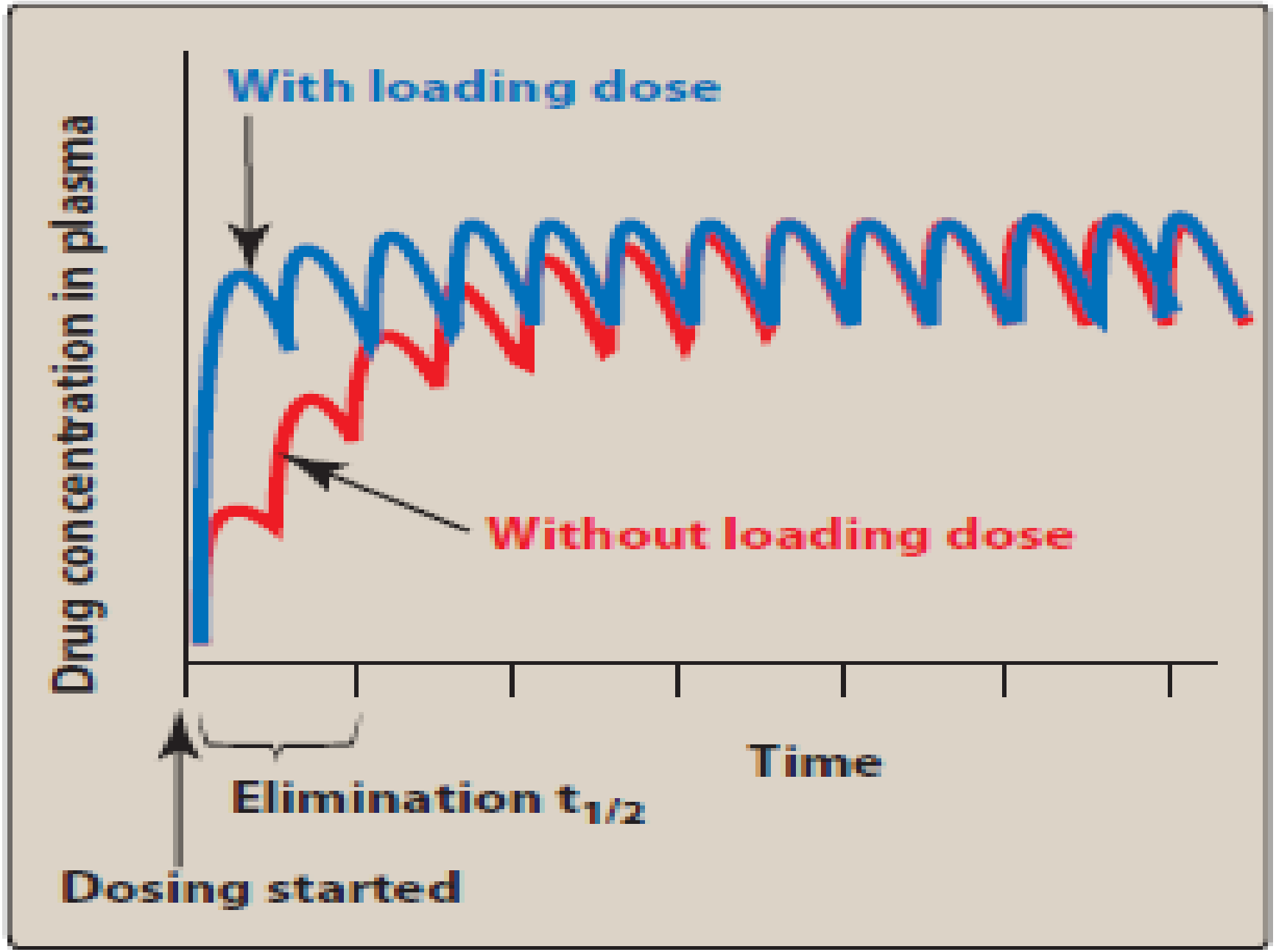
With loading dose
Drug concentration in plasma
Without loading dose
Time
Elimination $t_{1/2}$
Dosing started

The benefit of determining drug t1/2 is to estimate the time by which drug becomes in steady Cp (plasma conc.)

The benefit of determining drug order of elimination is to decide whether a drug dose can be increased safely (1st order or linear) or not (zero order or non-linear)