PHARMACOKINETIC

LECTURE BY :
MAJID K. BASHARA
DEPARTMENT OF PHARMACOLOGY

OBJECTIVE

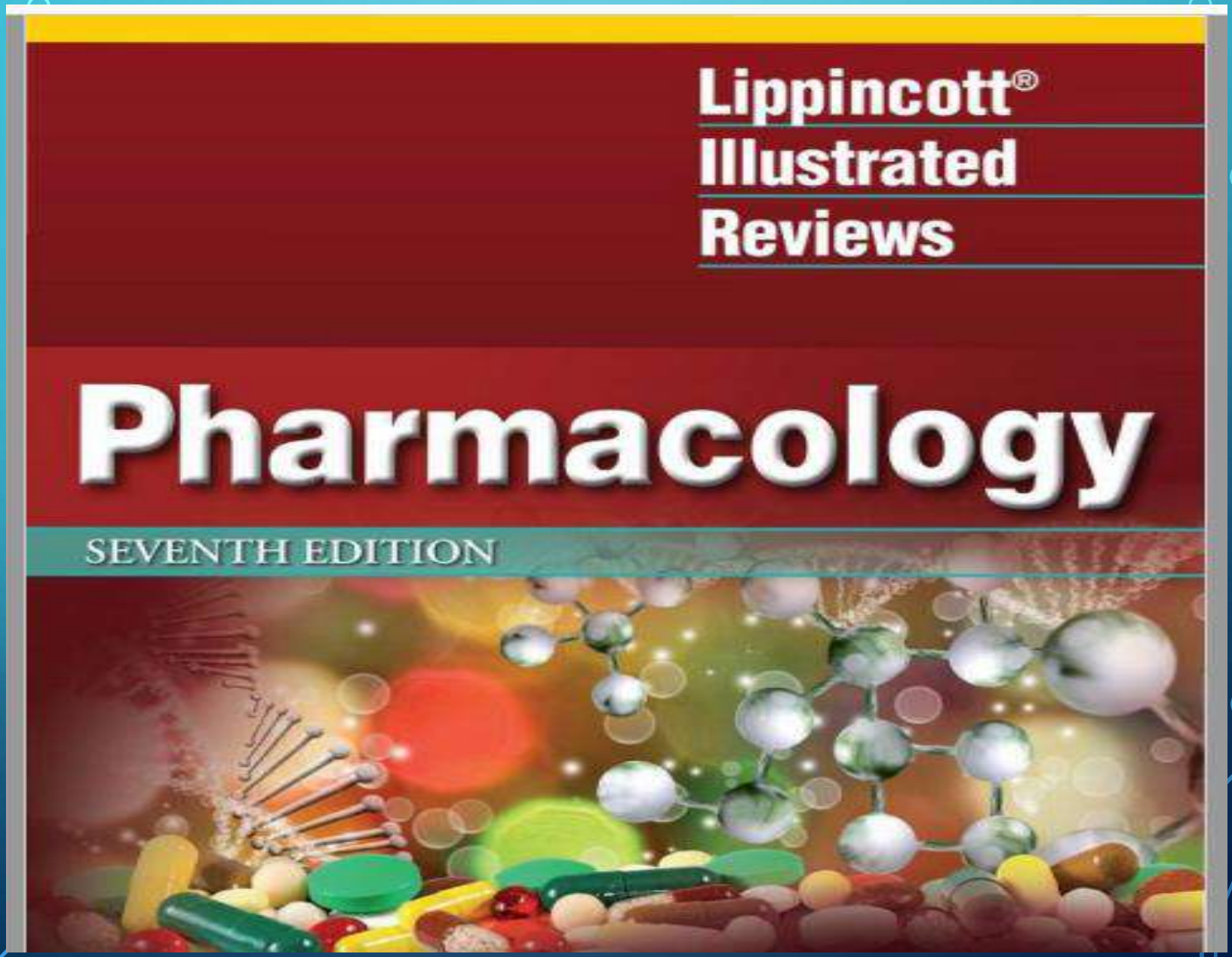
LEARNING THE MECHANISM OF

ABSORPTION

DISTRIBUTION

METABOLISM

ELIMINATION


Lippincott®
Illustrated
Reviews
Pharmacology
SEVENTH EDITION

WHAT IS THE PHARMACOLOGY

Pharmacology is a branch of medicine, • biology and pharmaceutical sciences concerned with drug or medication action.

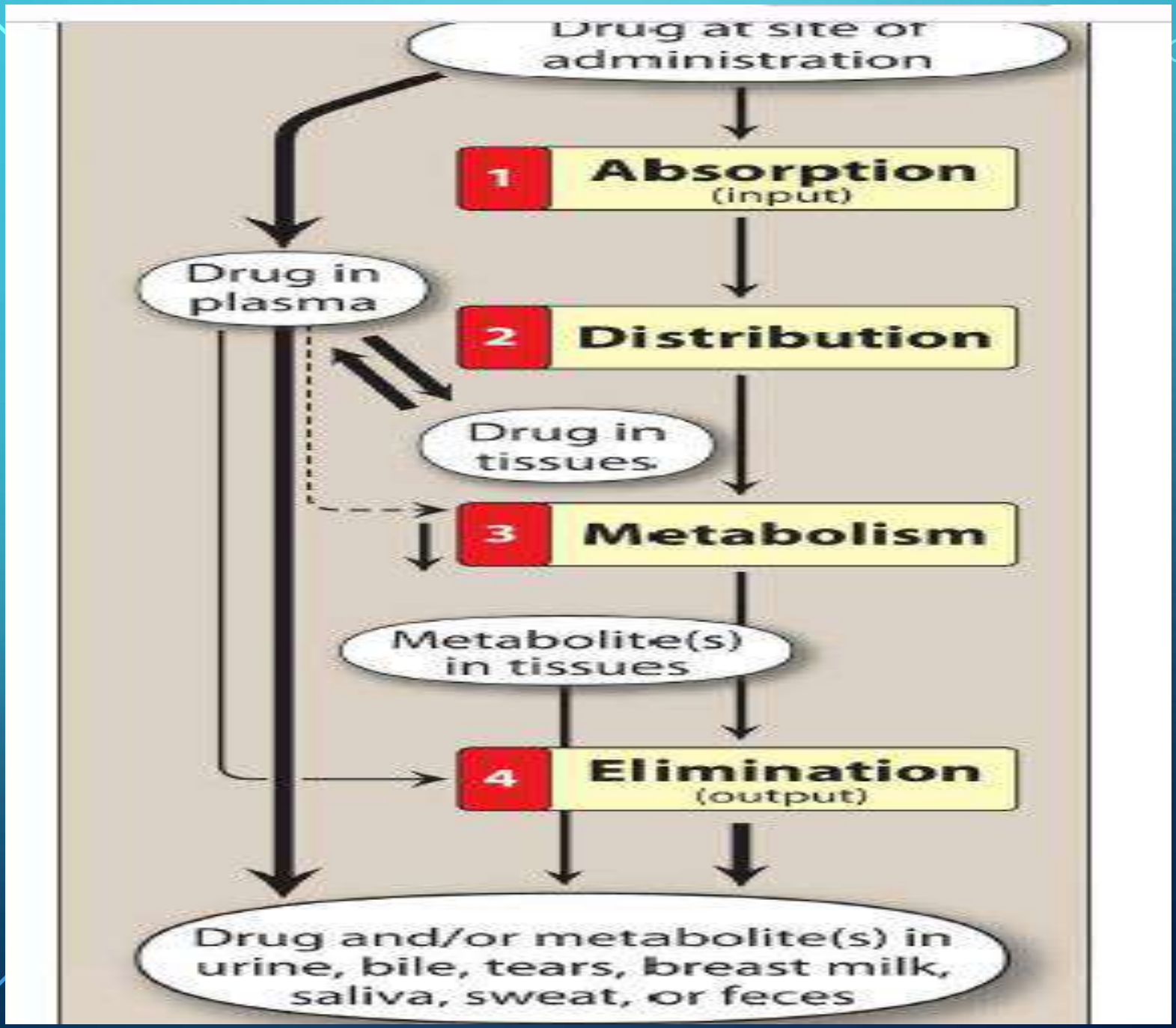
PHARMACOLOGY MEANS :

- *Pharmacodynamics is defined as how the body reacts to the drugs
- *Pharmacokinetics is the study of the bodily absorption, distribution, metabolism, and excretion of drugs.

WHAT IS MEANING OF PHARMACOKINETICS

mean how the human body handling the drug •

- 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

ROUTES OF DRUG ADMINISTRATION

A. Enteral •

1. Oral •

a. Enteric-coated preparations •

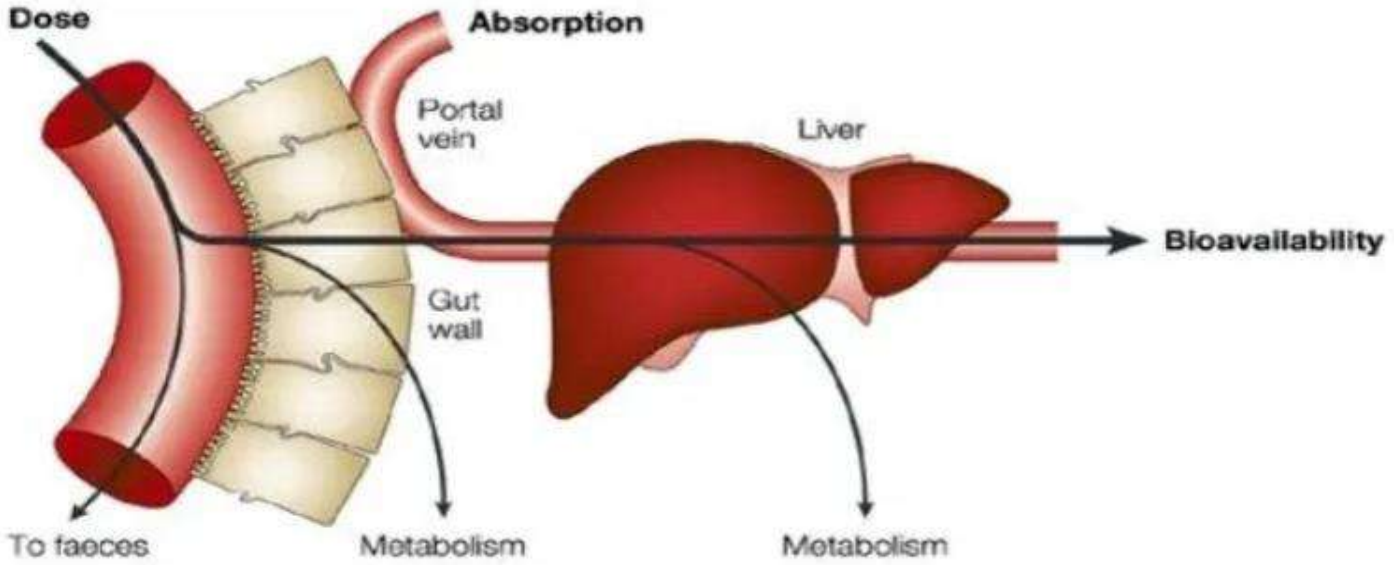
b. Extended-release preparations •

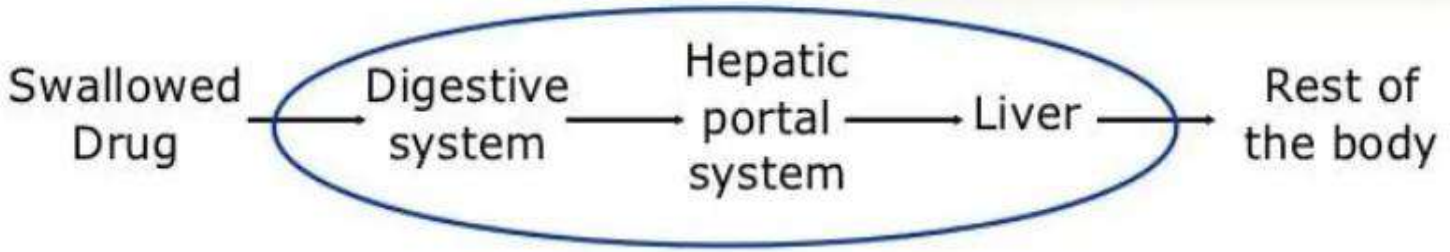
2. Sublingual/buccal •

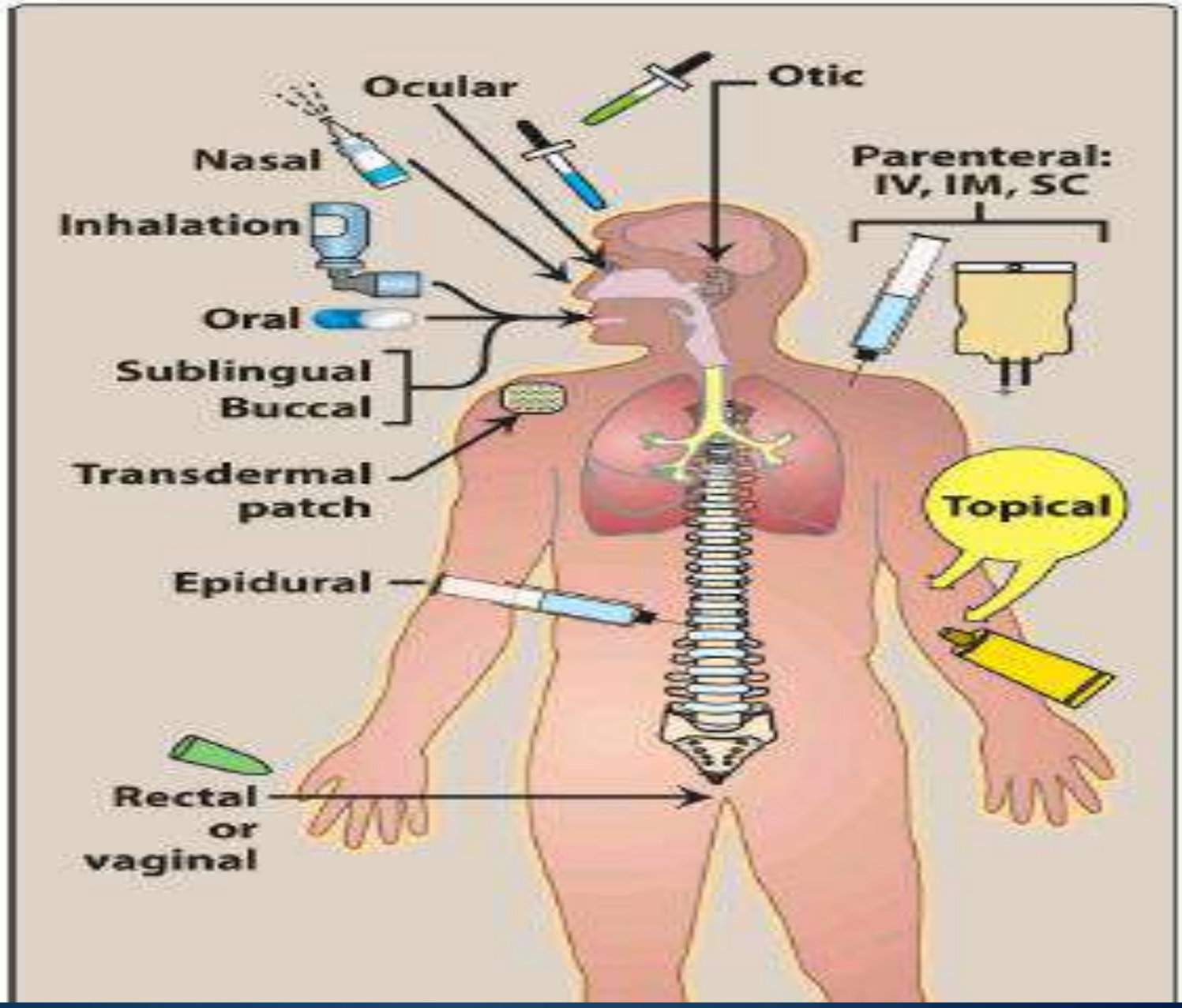
- first pass effect is a phenomenon in which a drug gets metabolized at a specific location in the body that results in a reduced concentration of the active drug upon reaching its site of action or the systemic circulation.

- Drugs with significant first-pass effect are imipramine, morphine, propranolol, buprenorphine, diazepam, midazolam, pethidine, tetrahydrocannabinol (THC), ethanol (drinking alcohol), cimetidine, lidocaine, chlorpromazine, and nitroglycerin (NTG).

First Pass Metabolism






Ocular
Otic
Nasal
Parenteral:
IV, IM, SC
Inhalation
Oral
Sublingual
Buccal
Transdermal
patch
Topical
Epidural
Rectal
or
vaginal

ROUTES OF DRUG ADMINISTRATION

B. Parenteral •

1. Intravenous (IV) •

2. Intramuscular (IM) •

3. Subcutaneous (SC) •

ROUTES OF DRUG ADMINISTRATION

C. Other •

1. Oral inhalation •

2. Nasal inhalation •

3. Intrathecal / intraventricular •

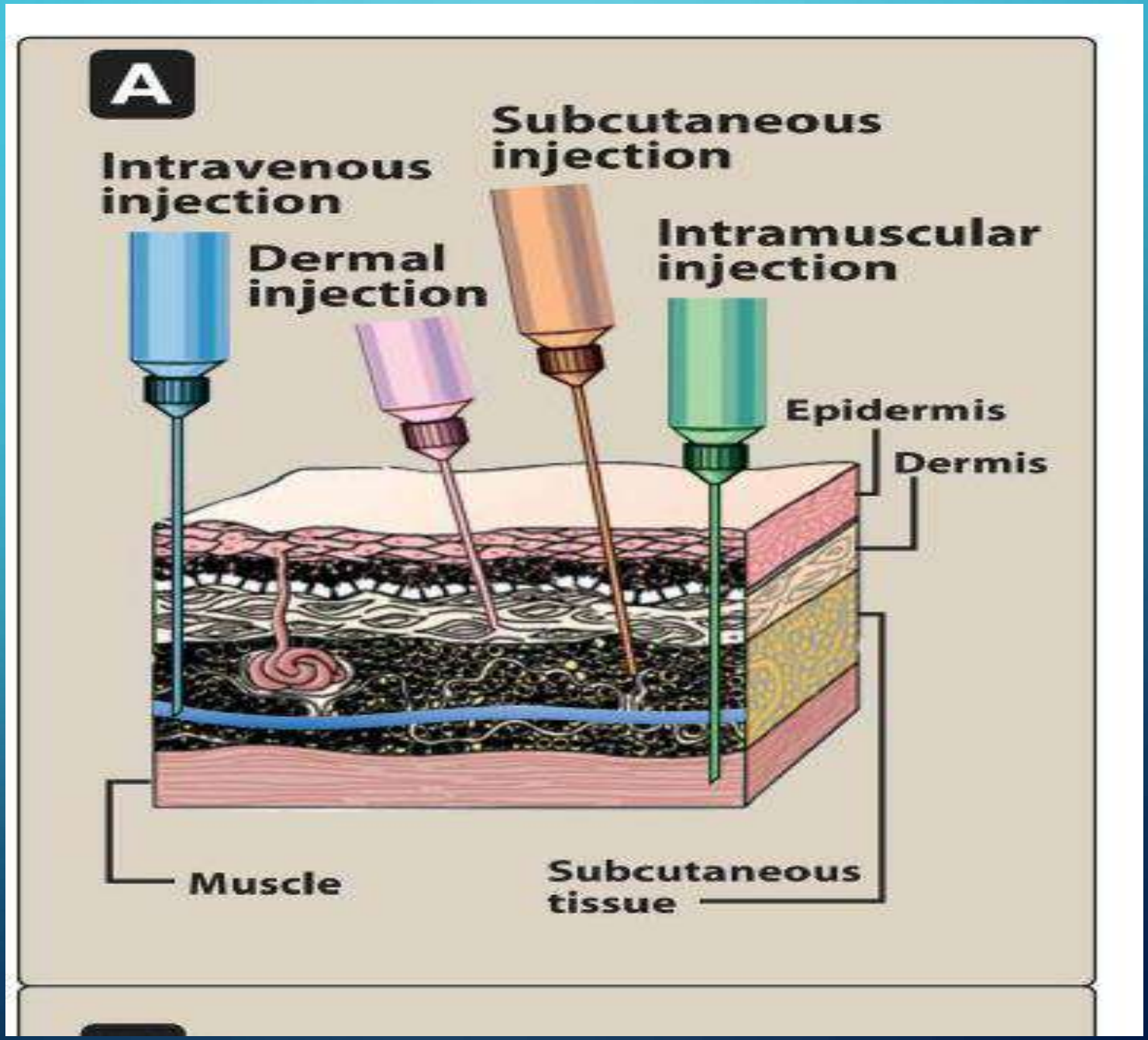
4. Topical •

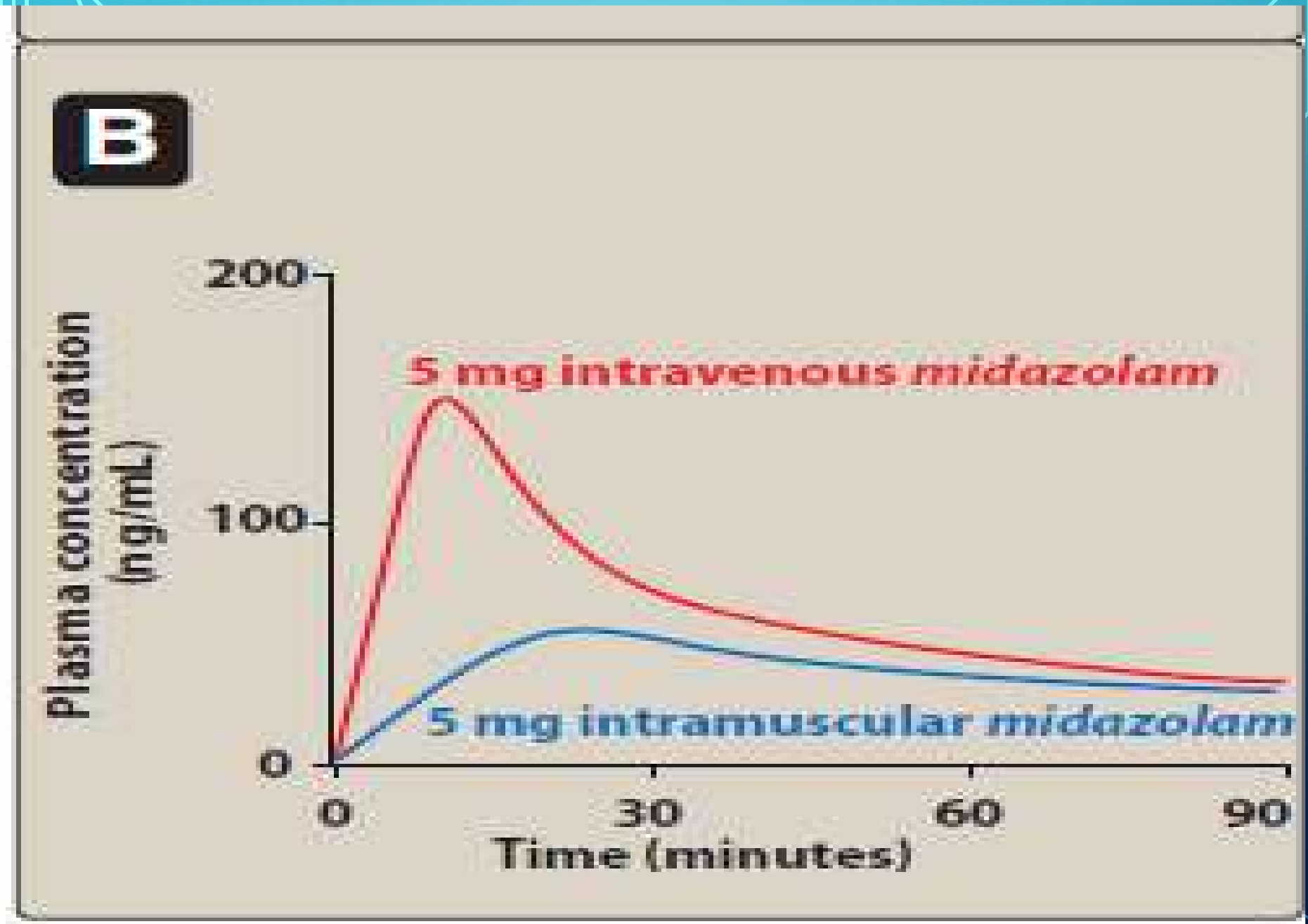
6. Rectal •

intrathecal means injection into the spinal canal, or into the subarachnoid space so that it reaches the cerebrospinal fluid (CSF) and is useful in spinal anesthesia, chemotherapy, or pain management applications

Common Routes of Administration

Route	Bioavailability	Characteristics
IV	100%	Most rapid onset
IM	75-100%	Large volumes often feasible; may be painful
SC	75-100%	Smaller volumes than i.m. may be painful
Oral (PO or enteral)	0-100%	Most convenient 1st pass effect
Rectal*	30-100%	Less 1st pass effect
Inhalation	5-100%	Often rapid onset (Rx: asthma)
Transdermal	80-100%	Slow absorption & onset of action; no 1st pass; long duration of action


A
Intravenous injection
Subcutaneous injection
Dermal injection
Intramuscular injection
Epidermis
Dermis
Muscle
Subcutaneous tissue


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

ABSORPTION

- Absorption is the transfer of a drug from the site of administration to the bloodstream

ABSORPTION OF DRUGS

- Mechanisms of absorption of drugs from the GI tract
  1. Passive diffusion e.g most drugs
  2. Facilitated diffusion e.g glucose
  3. Active transport e.g ions, vitamins, sugars, amino acids
  4. Endocytosis e.g neurotransmitter

PASSIVE DIFFUSION

- The driving force for passive diffusion of a drug is the concentration gradient across a membrane separating two body compartments.

FACILITATED DIFFUSION

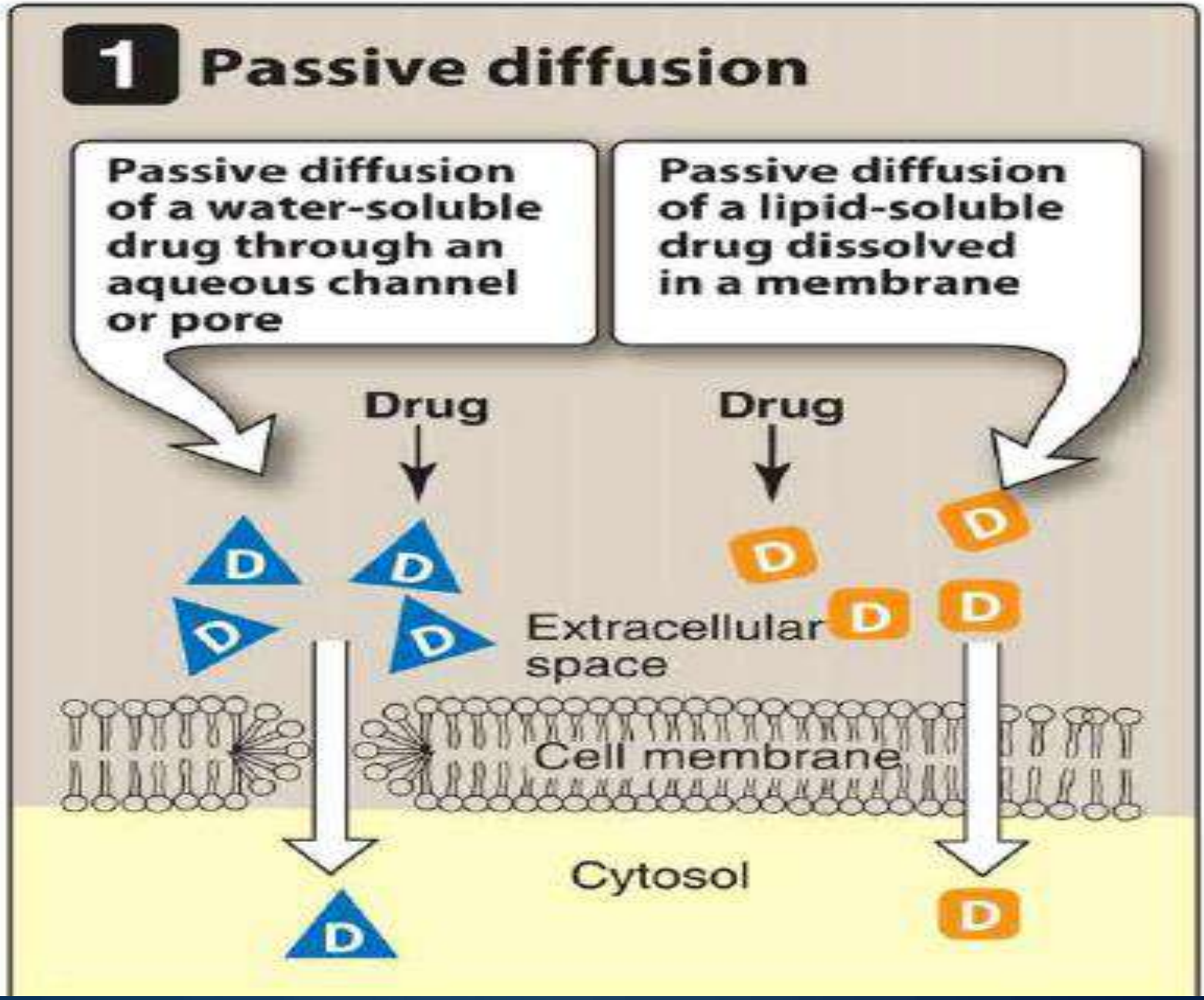
- specialized transmembrane carrier proteins that facilitate the passage of large molecules. These carrier proteins undergo conformational changes, allowing the passage of drugs or endogenous molecules into the interior of cells.

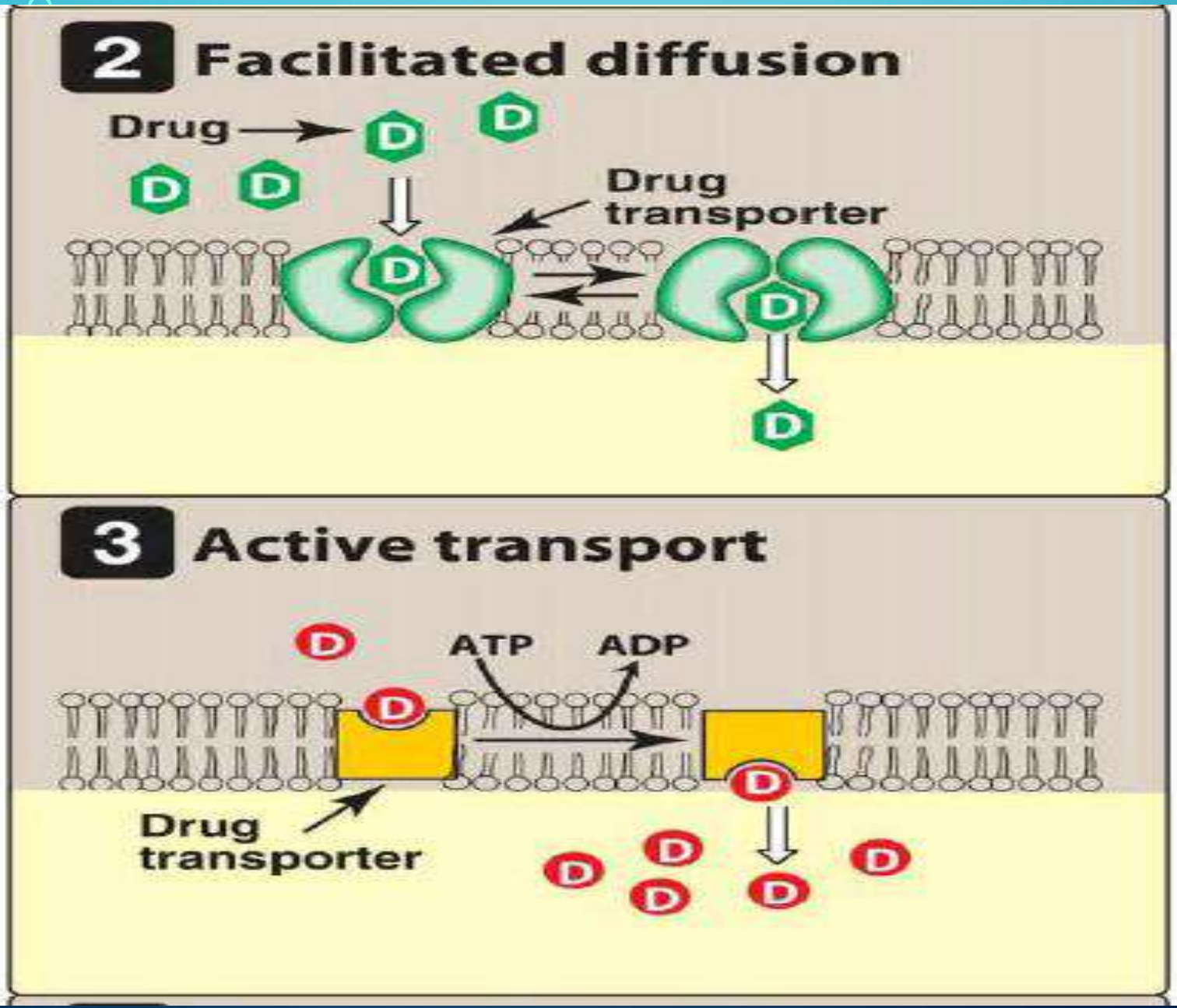
ACTIVE TRANSPORT

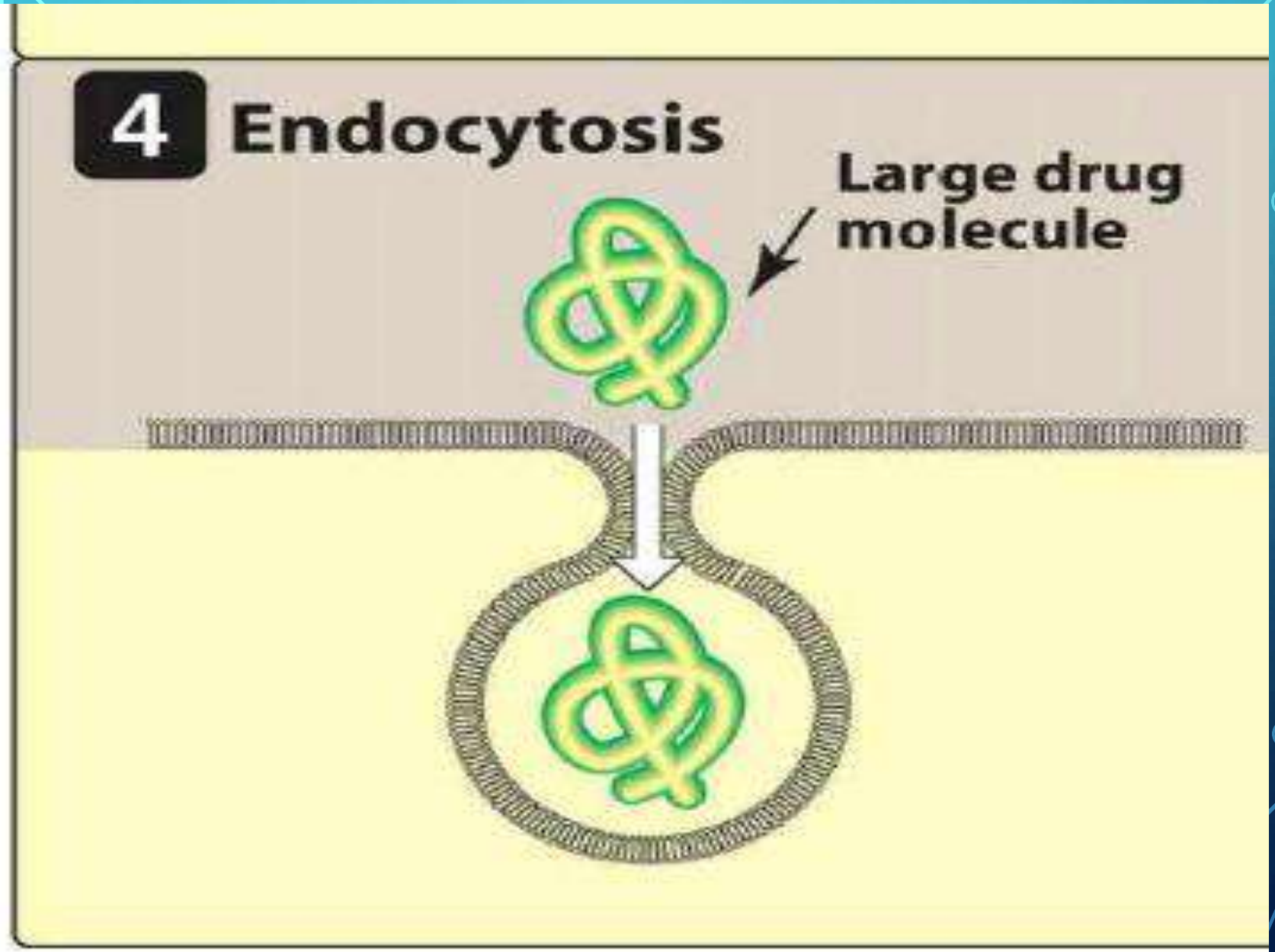
- involves specific carrier proteins that span the membrane. However, active transport is energy dependent, driven by the hydrolysis of adenosine triphosphate (ATP).

ENDOCYTOSIS AND EXOCYTOSIS

- This type of absorption is used to transport drugs of exceptionally large size across the cell membrane. Endocytosis
- involves engulfment of a drug by the cell membrane and transport into the cell by pinching off the drug-filled vesicle.
- Exocytosis is the reverse of endocytosis.


1 Passive diffusion
Passive diffusion of a water-soluble drug through an aqueous channel or pore
Passive diffusion of a lipid-soluble drug dissolved in a membrane
Drug
Drug
D
Extracellular space
Cell membrane
Cytosol


2 Facilitated diffusion
Drug
D
Drug transporter
3 Active transport
ATP
ADP
Drug transporter


4 Endocytosis
Large drug molecule

FACTORS INFLUENCING ABSORPTION

1. Effect of pH on drug absorption •
2. Blood flow to the absorption site •
3. Total surface area available for absorption •
4. Contact time at the absorption surface •
5. Expression of P-glycoprotein •

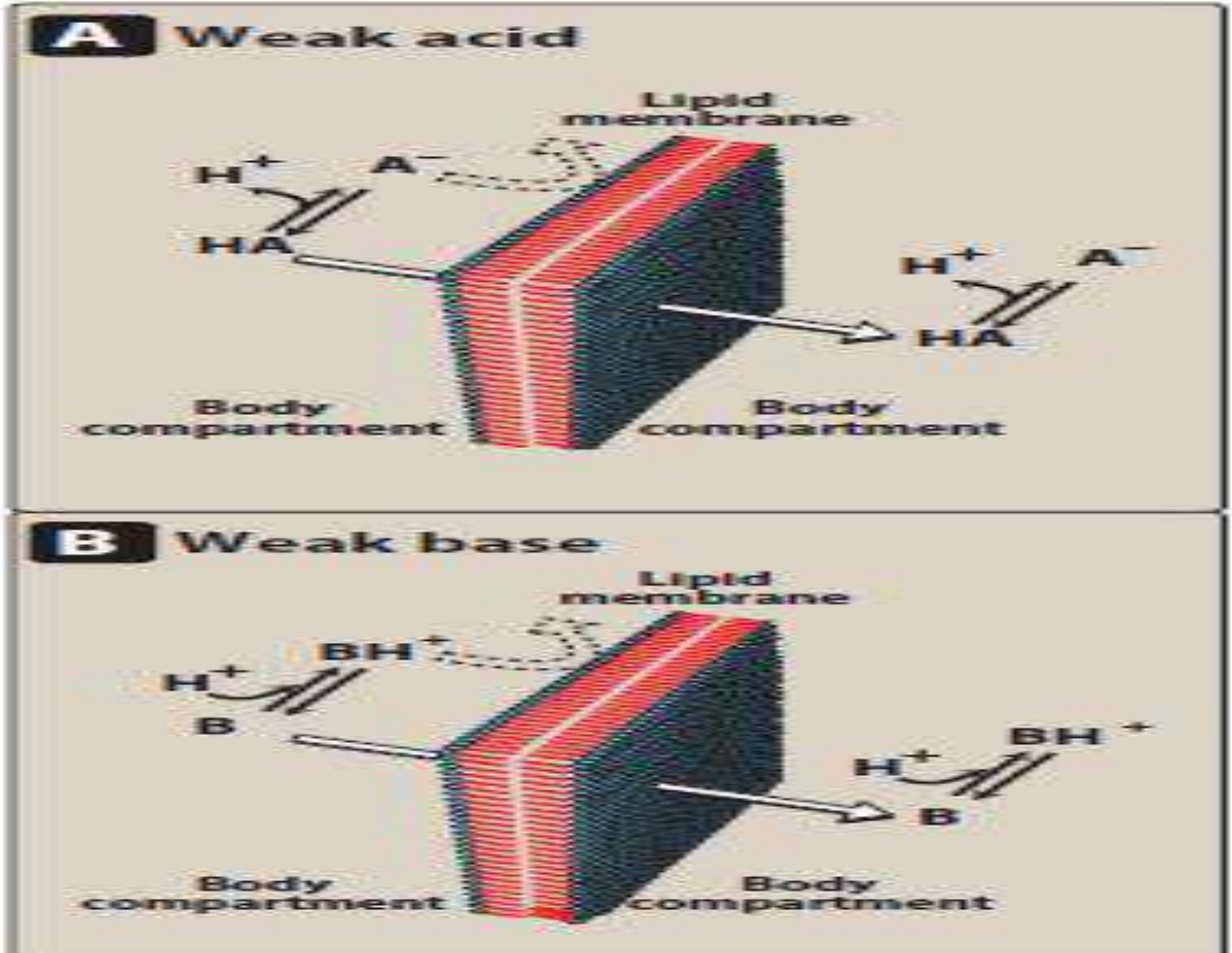
HENDERSON-HASSELBALCH EQUATION

$$pH = pK_a + \log([A^-]/[HA])$$

$$pH = pK_a + \log([\text{ionized}]/[\text{unionized}])$$

NOTE

- Un ionized form of drug is lipid soluble
- Ionized form of drug is water soluble


A Weak acid
Lipid membrane
H+
A−
HA
H+
A−
HA
Body compartment
Body compartment
B Weak base
Lipid membrane
BH+
H+
B
BH+
H+
B
Body compartment
Body compartment

BIOAVAILABILITY

- Bioavailability is the rate and extent to which an administered drug reaches the systemic circulation

BIOAVAILABILITY

1. Determination of bioavailability •
2. Factors that influence bioavailability •

a. First-pass hepatic metabolism •

b. Solubility of the drug •

c. Chemical instability •

d. Nature of the drug formulation •

SOLUBILITY OF THE DRUG

For a drug to be readily absorbed, it must be

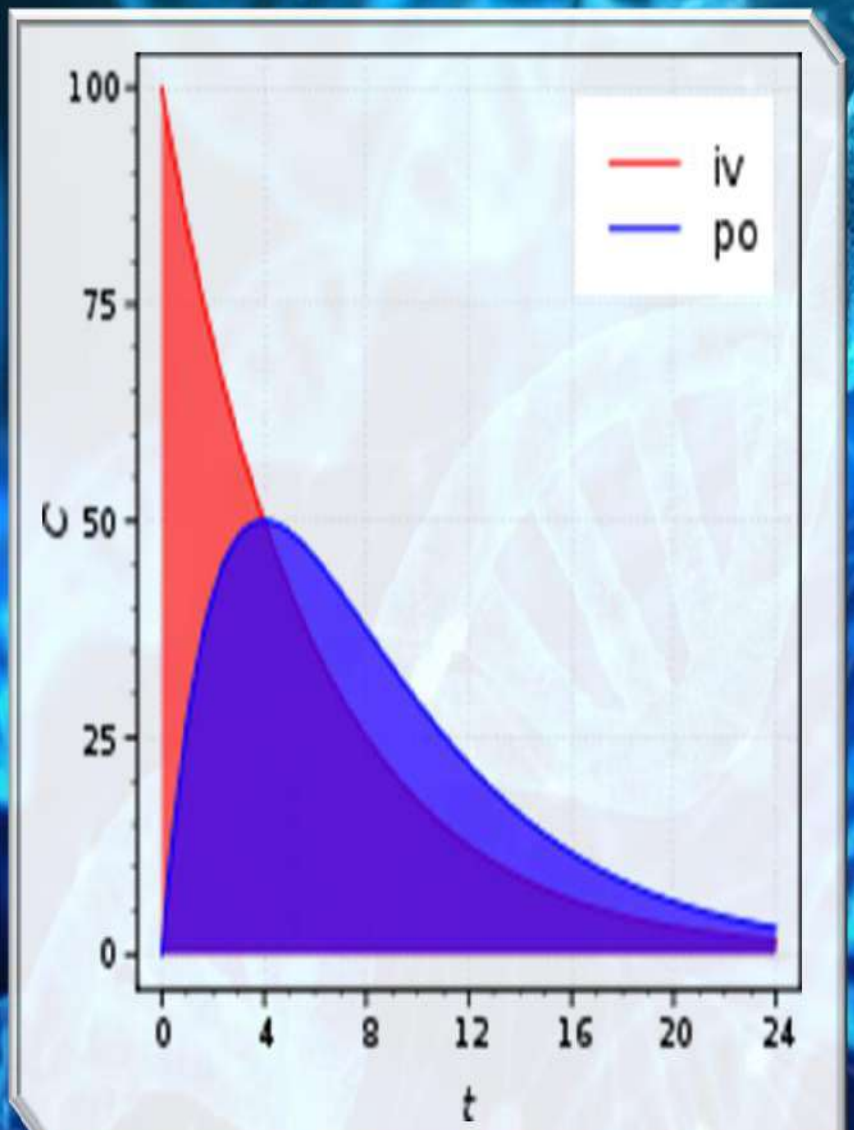
- largely lipophilic, yet have some solubility in aqueous solutions. This is one reason why many drugs are either weak acids or weak bases.

CHEMICAL INSTABILITY

- Some drugs, such as penicillin G, are unstable in the pH of gastric contents. Others, such as insulin, are destroyed in the GI tract by degradative enzymes.

NATURE OF THE DRUG FORMULATION

- Drug absorption may be altered by factors unrelated to the chemistry of the drug. For example, particle size, salt form, crystal polymorphism, enteric coatings, and the presence of excipients (such as binders and dispersing agents)
- .

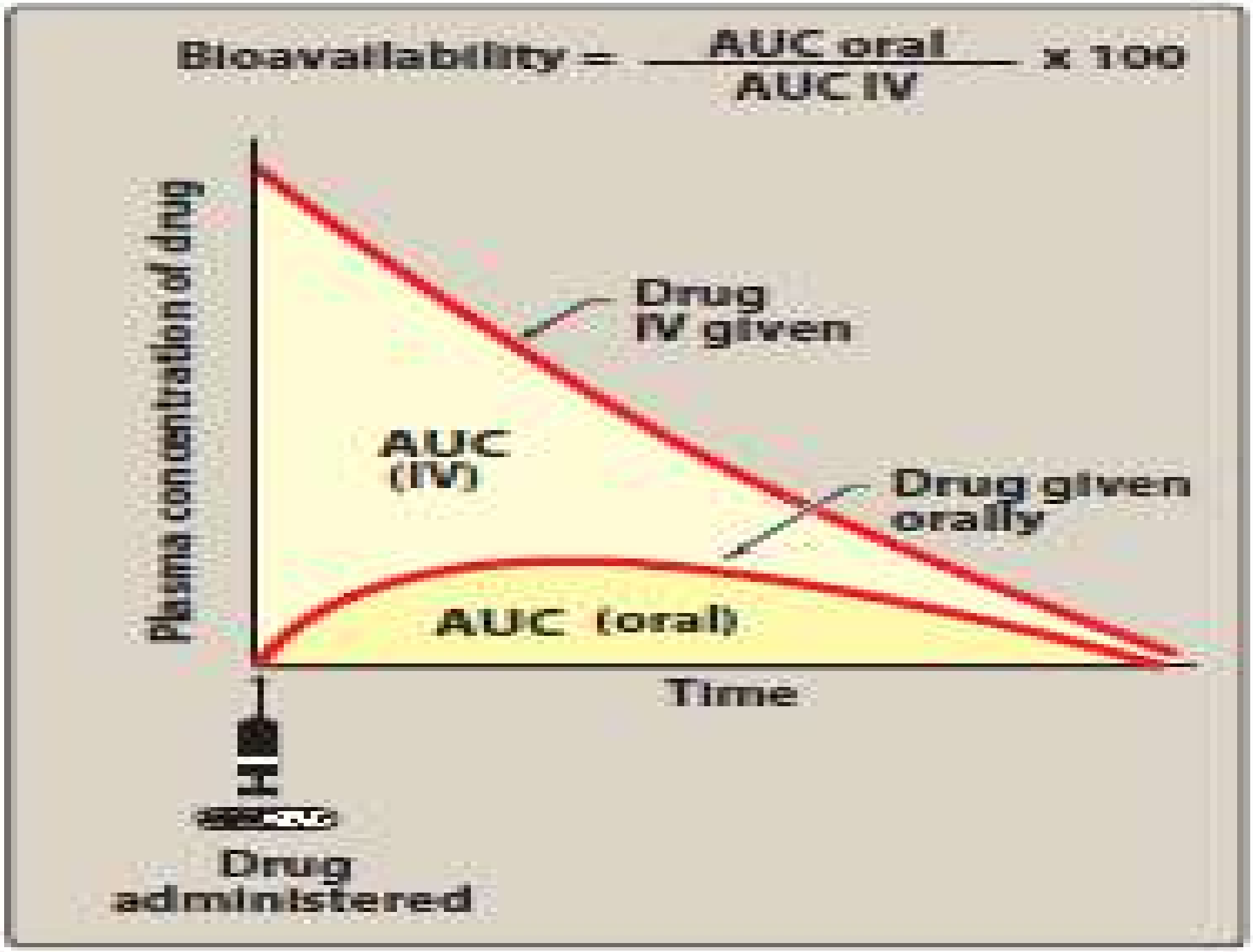


Bioavailability

Bioavailability is understood to be the extent and the rate to which a substance or its active moiety is delivered from a pharmaceutical form and becomes available in the general circulation.

BIOAVAILABILITY CALCULATION

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


Bioavailability = AUC oral / AUC IV x 100
Plasma concentration of drug
Drug IV given
AUC (IV)
Drug given orally
AUC (oral)
Time
Drug administered

DRUG DISTRIBUTION

- process by which a drug reversibly leaves the bloodstream and enters the extracellular fluid and tissues.

DRUG DISTRIBUTION

A. Blood flow •

B. Capillary permeability •

C. Binding of drugs to plasma proteins and tissues •

1. Binding to plasma proteins •

2. Binding to tissue proteins: •

D. Lipophilicity •

BLOOD FLOW

- blood flow to “vessel-rich organs” (brain,
- liver, and kidney) is greater than that to the skeletal muscles. Adipose tissue, skin, and viscera have still lower rates of blood flow.

CAPILLARY PERMEABILITY

- In the liver and spleen, a significant portion of the basement membrane is exposed due to large, discontinuous capillaries through which large plasma proteins can pass . In the brain, the capillary structure is continuous, and there are no slit junctions .

BINDING TO PLASMA PROTEINS

- Reversible binding to plasma proteins sequesters drugs in a nondiffusible form and slows transfer out of the vascular compartment. Albumin is the major drug-binding protein, and it may act as a drug reservoir

BINDING TO TISSUE PROTEINS

- Many drugs accumulate in tissues, leading to higher concentrations in tissues than in interstitial fluid and blood.
- Drugs may accumulate because of binding to lipids, proteins, or nucleic acids. Drugs may also undergo active transport into tissues

D. LIPOPHILICITY

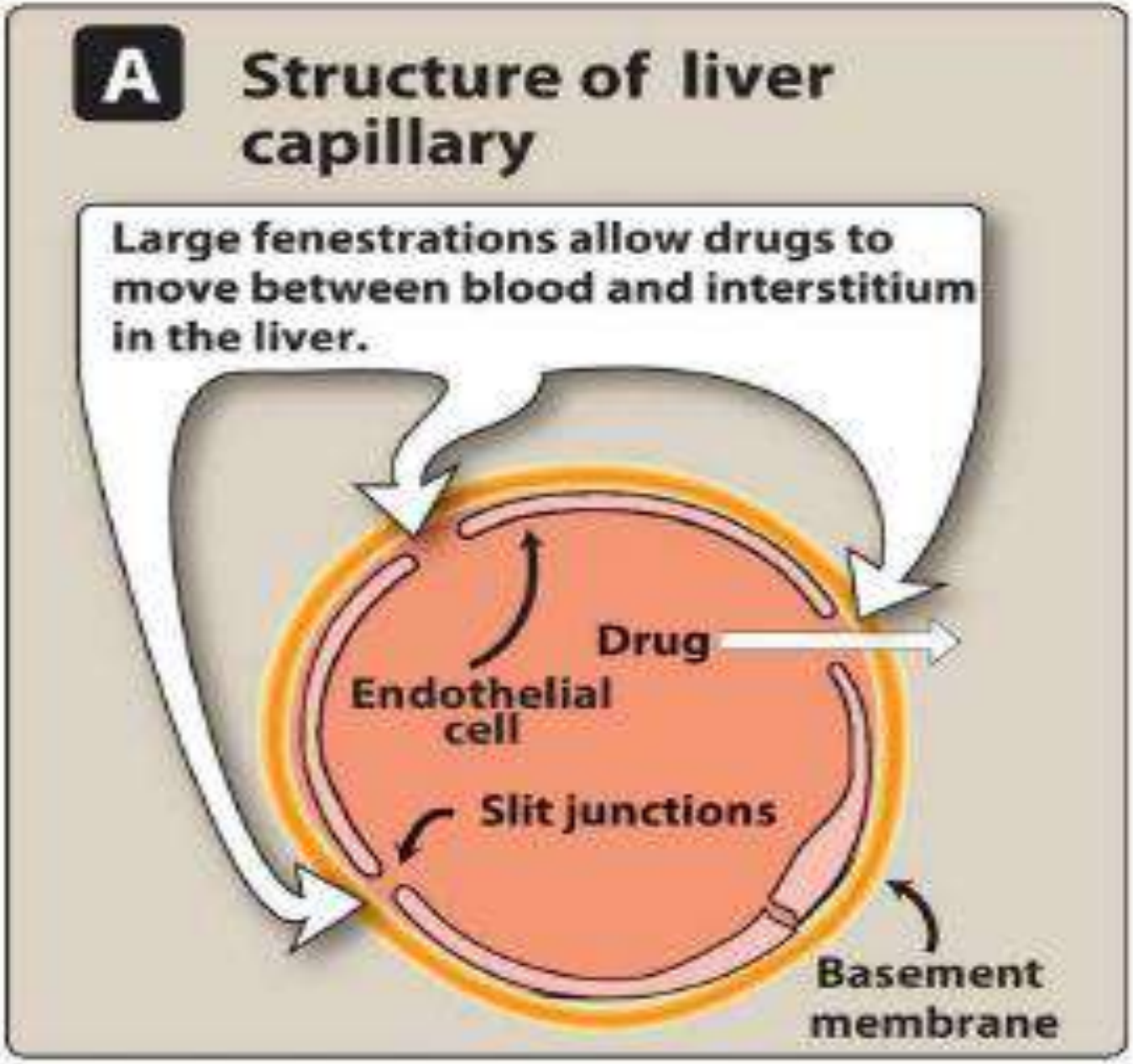
- Lipophilic drugs readily move
- across most biologic membranes. These drugs dissolve in the lipid membranes and penetrate the entire cell surface. The major factor influencing the distribution of lipophilic drugs is blood flow to the area.

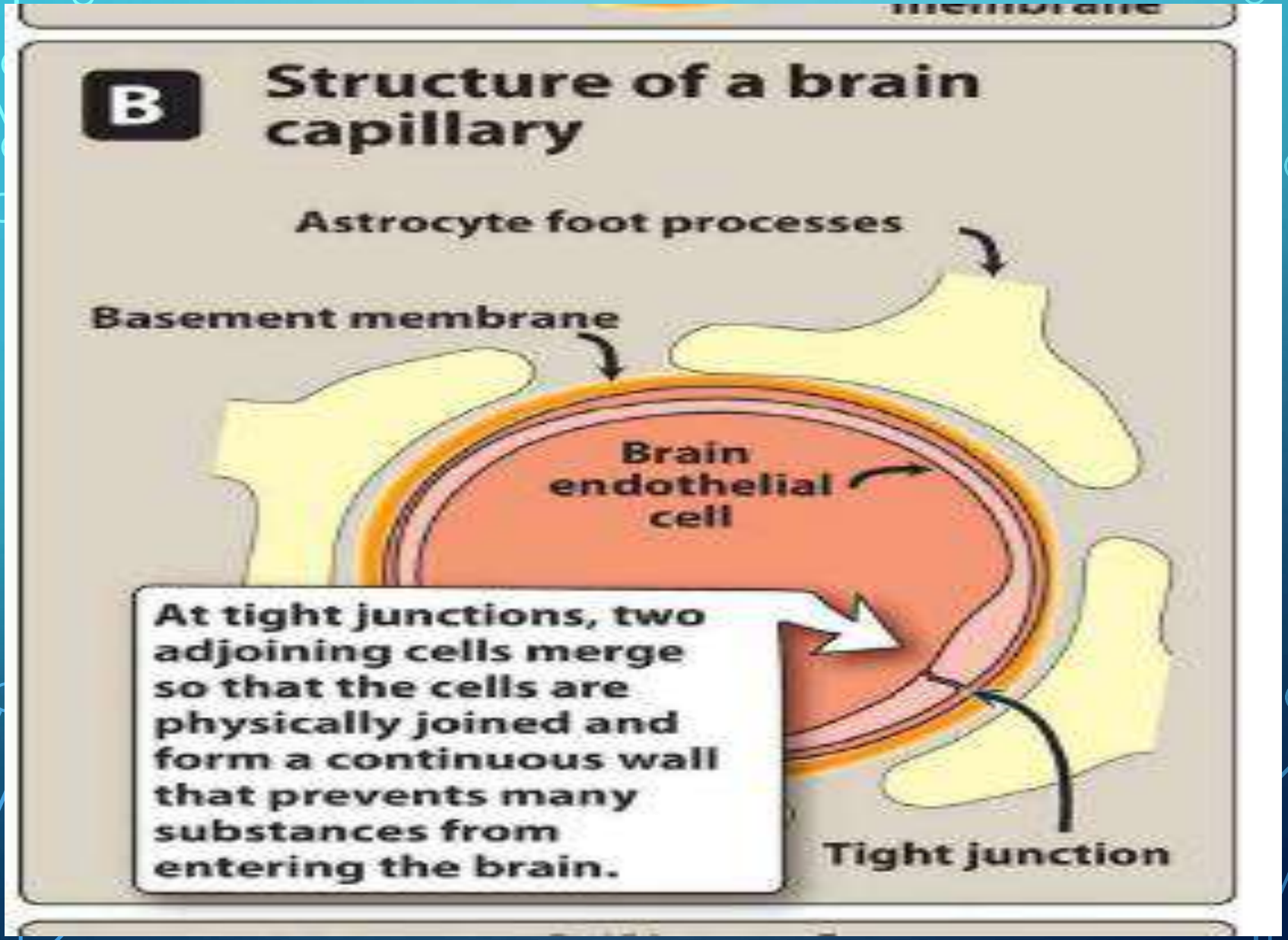
DRUG DISTRIBUTION

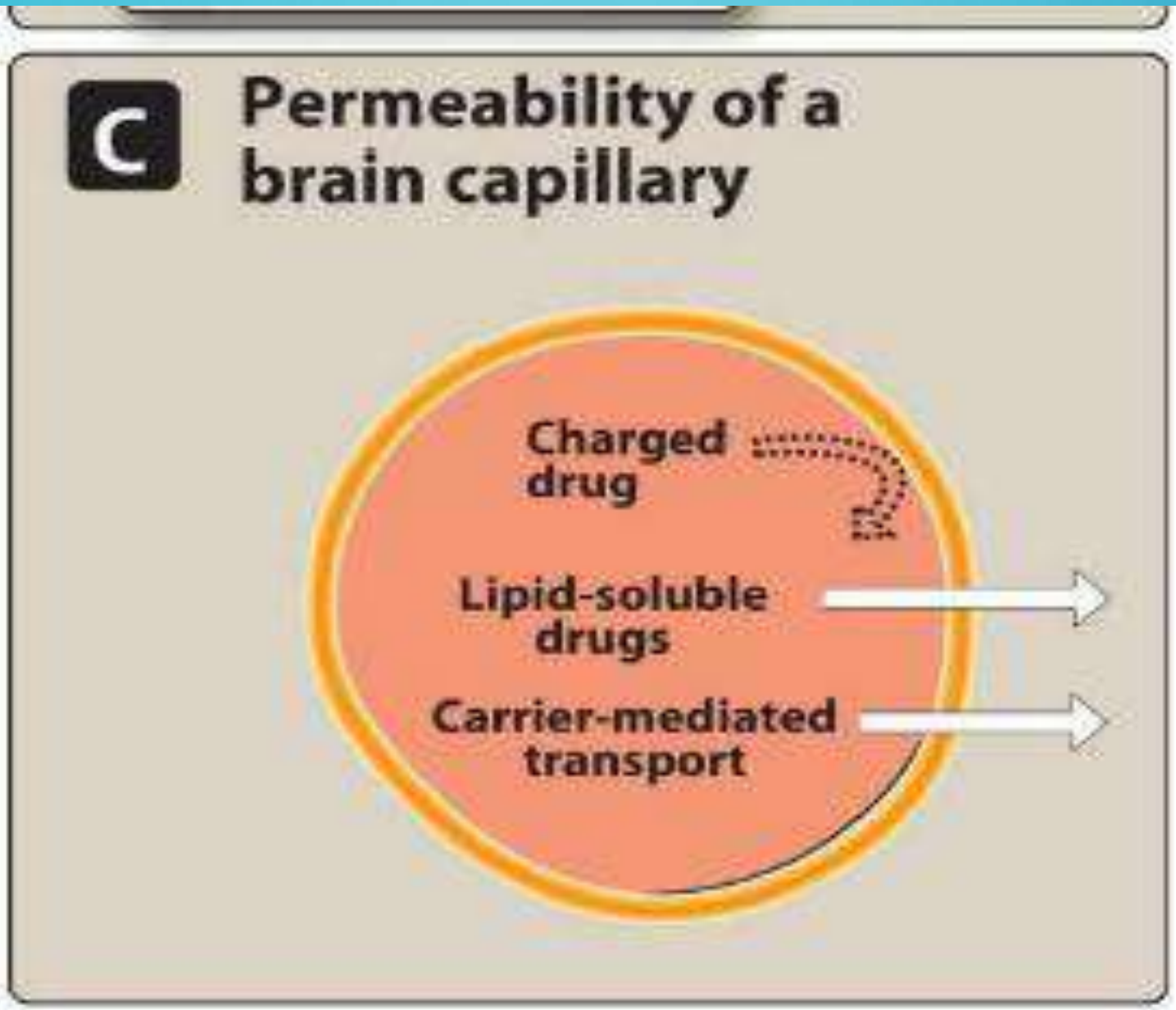
E. Volume of distribution •

Vd = dose of drug in the body / C o •

C o = drug conc. In the plasma at zero time •


A
Structure of liver capillary
Large fenestrations allow drugs to move between blood and interstitium in the liver.
Drug
Endothelial cell
Slit junctions
Basement membrane


B
Structure of a brain capillary
Astrocyte foot processes
Basement membrane
Brain endothelial cell
At tight junctions, two adjoining cells merge so that the cells are physically joined and form a continuous wall that prevents many substances from entering the brain.
Tight junction


C
Permeability of a brain capillary
Charged drug
Lipid-soluble drugs
Carrier-mediated transport

- For example, if 10 mg of drug is injected into a patient and the plasma
- concentration is extrapolated back to time zero, and C0 = 1 mg/L
- then Vd = 10 mg/1 mg/L = **10 L**.

DRUG DISTRIBUTION

water compartmentsin the body

a. Plasma compartment (4L)

b. Extracellular fluid (14L)

c. Total body water(42L)

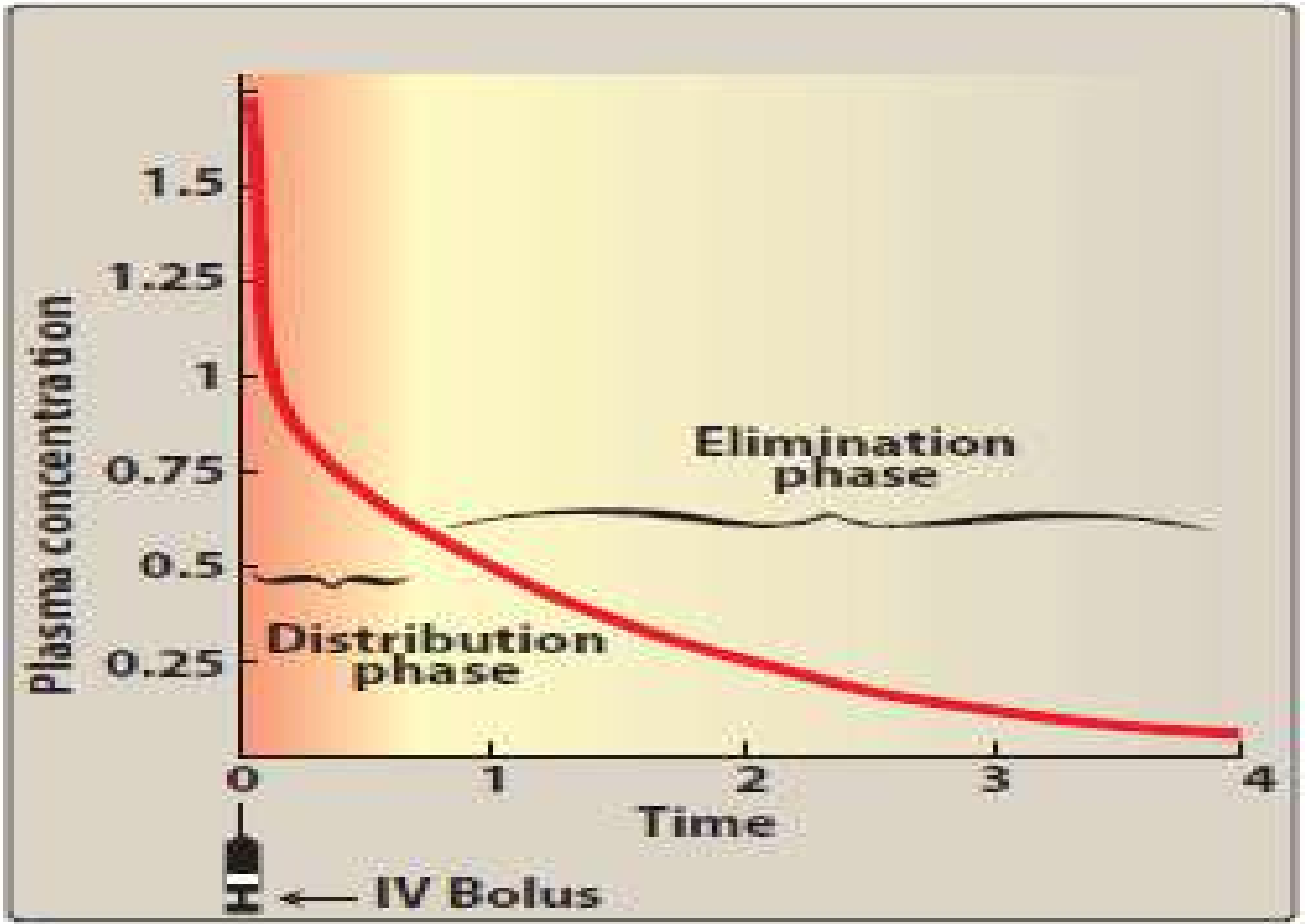
VOLUME OF DISTRIBUTION

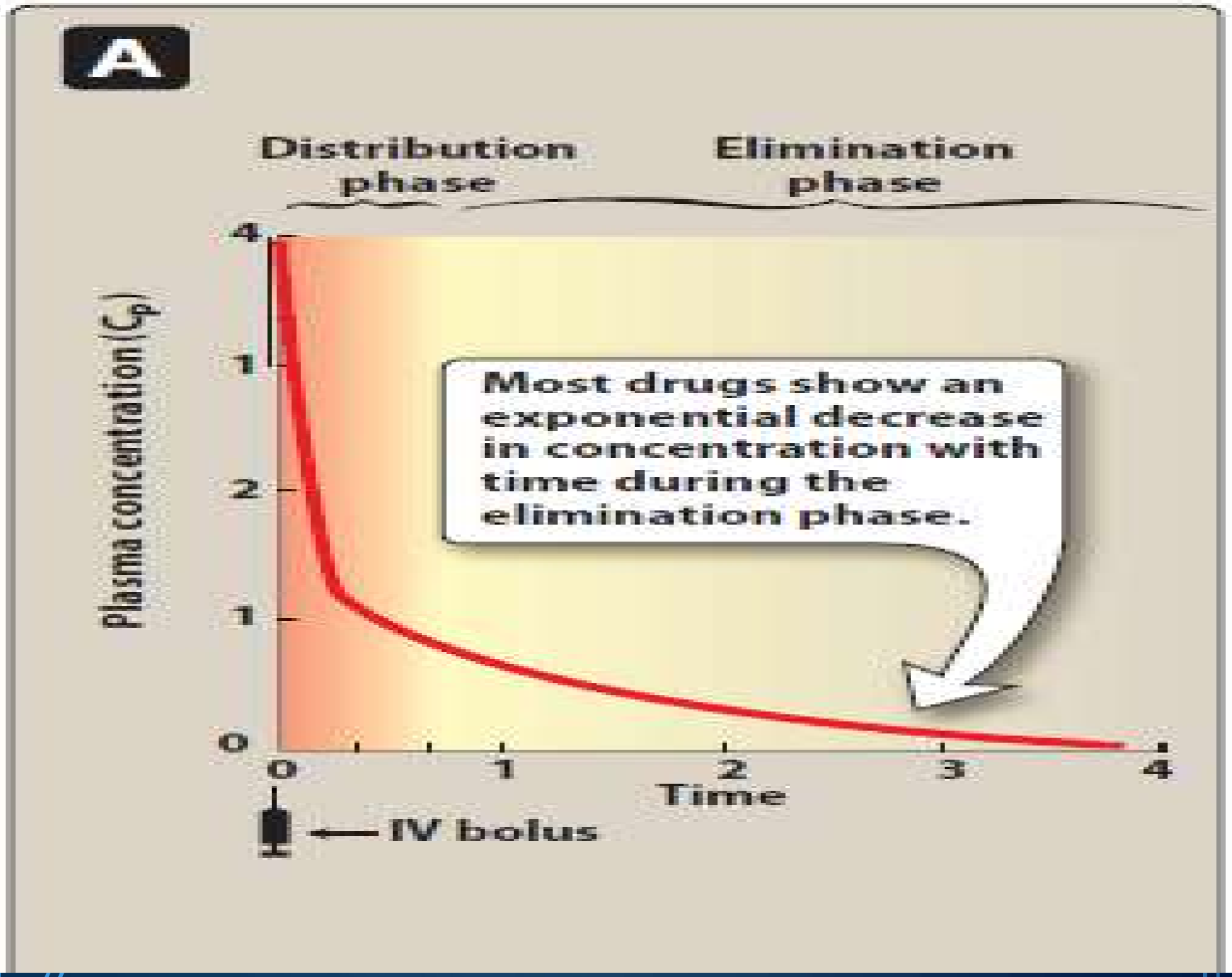
4. Effect of Vd on drug half-life

$t_{1/2} = 0.693 \times Vd / CL$

any factor that increases Vd can

increase the half-life and extend the duration of action of the drug


Plasma concentration
1.5
1.25
1
0.75
0.5
0.25
Elimination phase
Distribution phase
0
1
2
3
4
Time
IV Bolus


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

Substance	Volume of distribution (L)	Broad class
Adalimumab	5	Small: Mainly retained in the blood.
Warfarin	7	
Gentamicin	16	
Theophylline	35	Medium: Distributed fairly evenly between blood and tissues.
Cimetidine	140	
Digoxin	510	Large: Majority of drug moves out of blood into the tissues.
Doxepin	1,600	
Chloroquine	15,000	

DRUG CLEARANCE THROUGH METABOLISM

- Once a drug enters the body, the process of elimination begins. The three major routes of elimination are hepatic metabolism, biliary elimination, and urinary excretion.

- Elimination is irreversible removal of drug from the body. It involves biotransformation (drug metabolism) and excretion. Excretion is removal of intact drug from the body.
- Together, these elimination processes decrease the plasma concentration exponentially

CALCULATION OF CLEARANCE

A. KINETICS OF METABOLISM

1. First-order kinetics •

$$v = \text{Rate of drug metabolism} = \frac{V_{max}[C]}{K_m}$$

2. ZERO-ORDER KINETICS

With a few drugs, such as aspirin, ethanol, and phenytoin, the doses are very large. Therefore, [C] is much greater than Km, and the velocity equation becomes

ZERO-ORDER KINETICS

$$v = \text{Rate of drug metabolism} = \frac{V_{max}[C]}{[C]} = V_{max}$$

REACTIONS OF DRUG METABOLISM

1. Phase I •

a. Phase I reactions utilizing the P450 system: •

(oxidation , reduction , hydrolysis) •

CYP3A4/5, •

CYP2D6, •

CYP2C8/9, •

CYP1A2 •

- In phase I ,CYP450 enzymes catalyze several reactions, including oxidation, sulphoxidation,
- aromatic hydroxylation, aliphatic hydroxylation, N-dealkylation, O-dealkylation, and
- deamination. Among all, oxidation is the primary reaction, which leads to addition of
- 1 or more oxygen atom(s) to the parent drug

P450 SYSTEM

- [1] Nomenclature
- [2] Specificity
- [3] Genetic variability
- [4] Inducers
- [5] Inhibitors

NOMENCLATURE

- The family name is indicated by the Arabic number that follows CYP, and the capital letter designates the subfamily, for example, CYP3A . A second number indicates the specific isozyme, as in CYP3A4.

SPECIFICITY

- Because there are many different genes that encode multiple enzymes, there are many different P450 isoforms.
- These enzymes have the capacity to modify a large number of structurally diverse substrates. In addition, an individual drug may be a substrate for more than one isozyme.

Genetic variability

Variations in P450 activity may alter drug efficacy and the risk of adverse events. CYP2D6, in particular, exhibits genetic polymorphism.

- CYP2D6 mutations result in very low capacities to metabolize substrates. For example, some individuals obtain no benefit from the opioid analgesic *codeine*, because they lack the CYP2D6 enzyme that activates the drug.

- *clopidogrel* carries a warning that patients who are CYP2C19 “poor metabolizers” have a diminished antiplatelet effect when taking this drug and an alternative medication should be considered. *Clopidogrel* is a prodrug, and CYP2C19 activity is required to convert it to the active metabolite

PHASE I REACTIONS NOT INVOLVING THE P450 SYSTEM

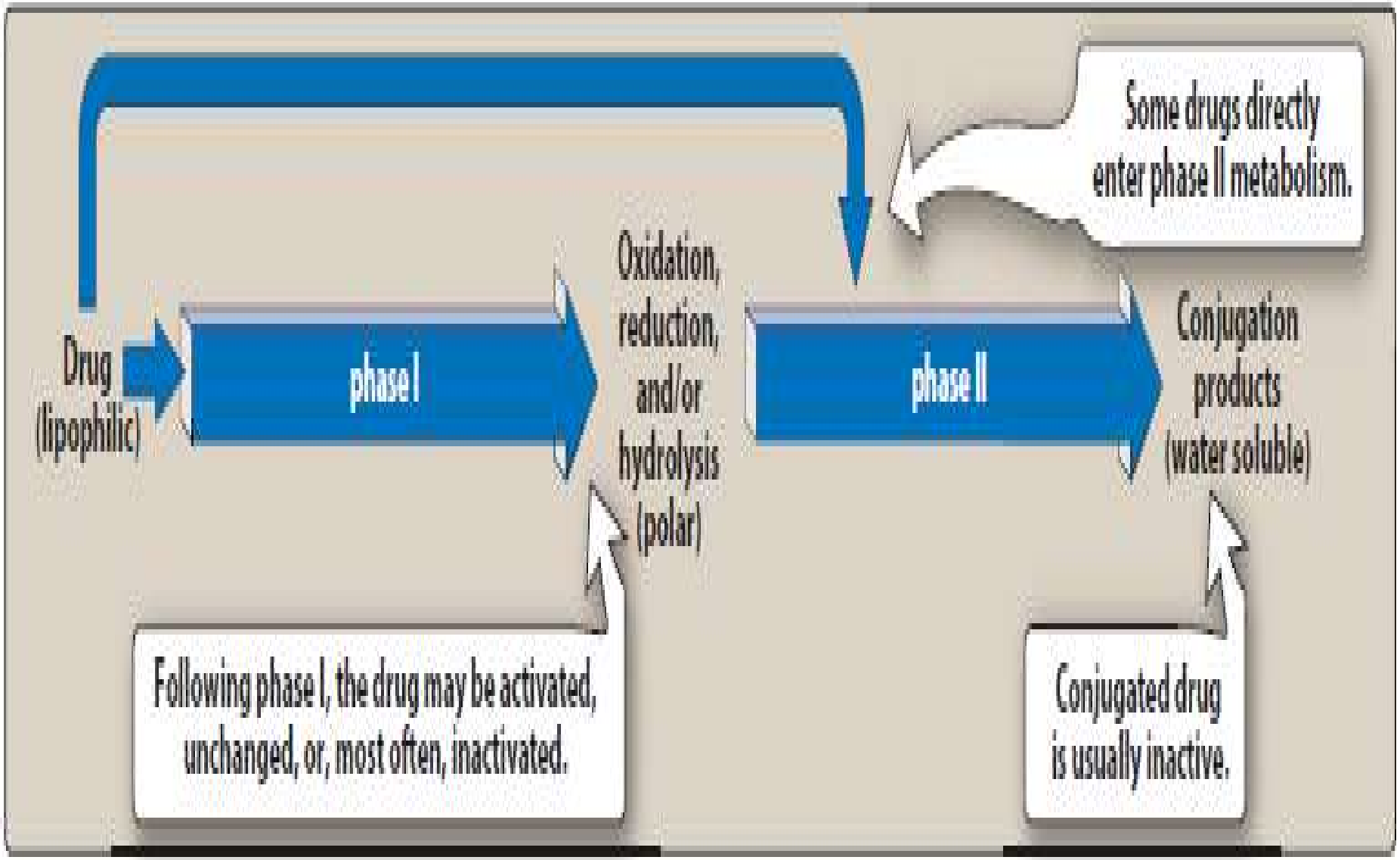
- These include amine oxidation (for example, oxidation of catecholamines or histamine), alcohol dehydrogenation (for example, ethanol oxidation), esterases (for example, metabolism of aspirin in the liver), and hydrolysis (for example, of procaine).

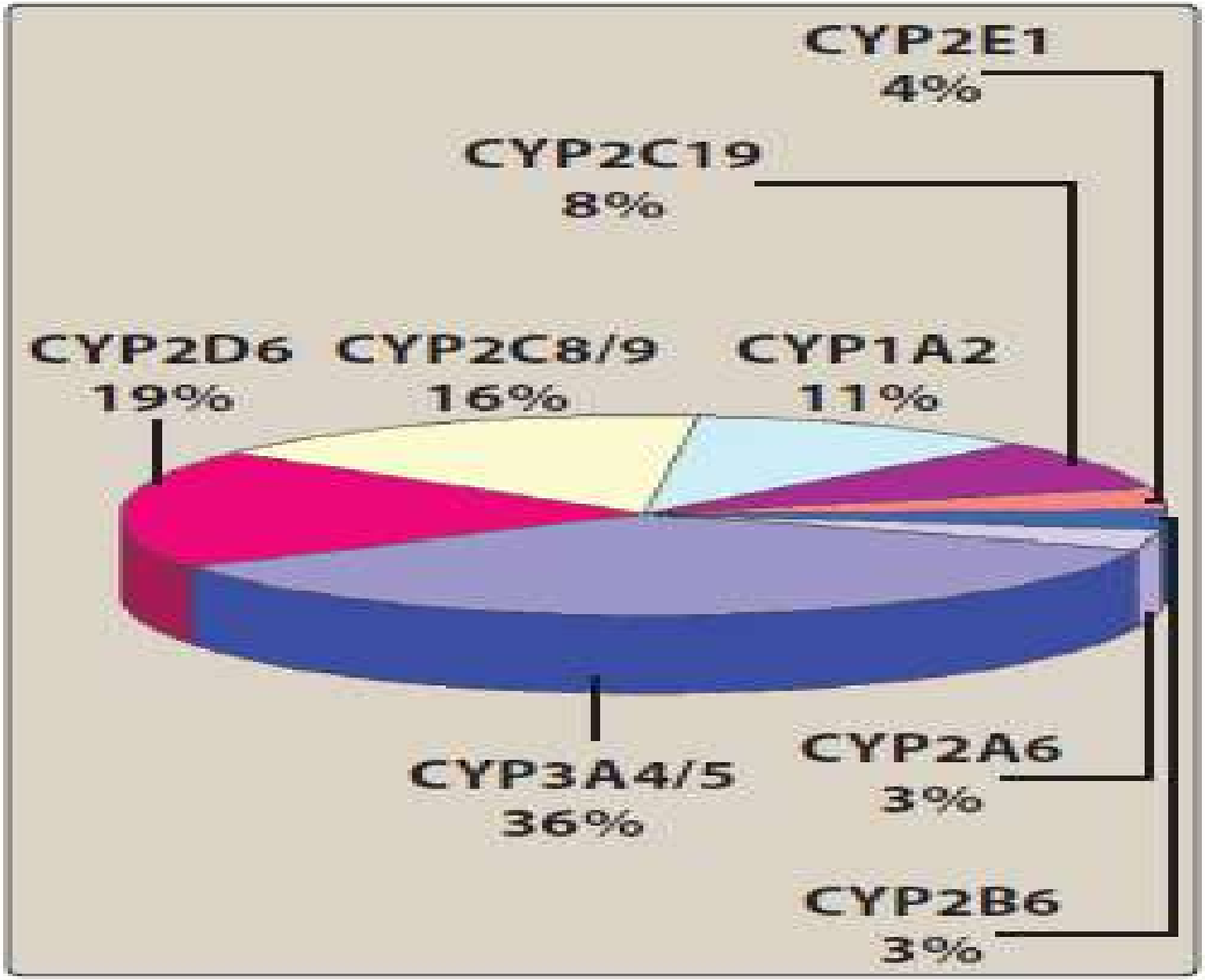
2. Phase II •

Usually involved conjugation with sulfuric acid , •
acetic acid ,or glucuronic acid

The most common phase II drug-metabolizing enzymes are

- UDP-glucuronosyltransferases (UGTs), sulfotransferases (SULTs),
- N-acetyltransferases (NATs),
- glutathione S-transferases (GSTs),
- thiopurine S-methyltransferases (TPMTs),
- and catechol O-methyltransferases (COMTs).


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.


CYP2E1
4%
CYP2C19
8%
CYP2D6
19%
CYP2C8/9
16%
CYP1A2
11%
CYP3A4/5
36%
CYP2A6
3%
CYP2B6
3%

Isozyme: CYP2C9/10

COMMON SUBSTRATES	INDUCERS
Warfarin *Phenytoin* *Ibuprofen* *Tolbutamide*	*Phenobarbital* *Rifampin*

Isozyme: CYP2D6

COMMON SUBSTRATES	INDUCERS
Desipramine *Imipramine* *Haloperidol* *Propranolol*	None*

Isozyme: CYP3A4/5

COMMON SUBSTRATES	INDUCERS
Carbamazepine *Cyclosporine* *Erythromycin* *Nifedipine* *Verapamil*	*Carbamazepine* *Dexamethasone* *Phenobarbital* *Phenytoin* *Rifampin*

CYP INHIBITORS

- Inhibition of drug metabolism can lead to significant increases in plasma drug concentration and resultant adverse effects or drug toxicity

- Numerous drugs inhibit one or more of the CYP-dependent biotransformation pathways of *warfarin*. For example, *omeprazole* is a potent inhibitor of three CYP isozymes involved in *warfarin* metabolism

DRUG CLEARANCE BY THE KIDNEY

- Drugs must be sufficiently polar to be eliminated from the body. Removal of drugs from the body occurs via a number of routes; the most important is elimination through the kidney into the urine.

RENAL ELIMINATION OF A DRUG

- A drug passes through several processes in the kidney before elimination: glomerular filtration, active tubular secretion, and passive tubular reabsorption.

1. GLOMERULAR FILTRATION

- Drugs enter the kidney through renal arteries, which divide to form a glomerular capillary plexus. Free drug (not bound to albumin) flows through the capillary slits into the Bowman space as part of the glomerular filtrate

2. PROXIMAL TUBULAR SECRETION

- Drugs that were not transferred into the glomerular filtrate leave the glomeruli through efferent arterioles, which
- divide to form a capillary plexus surrounding the nephric lumen in the proximal tubule.

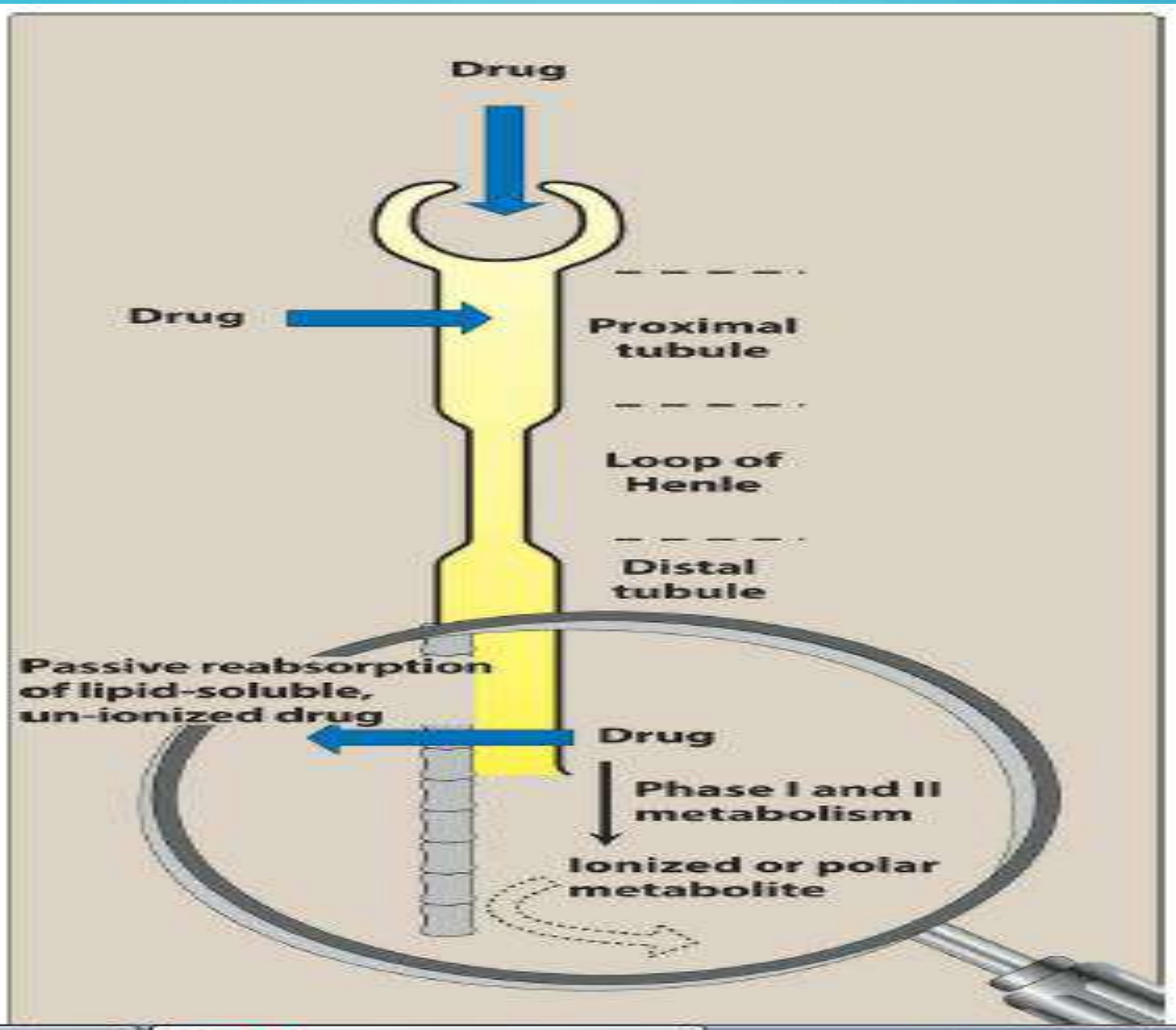
- Secretion primarily occurs
- in the proximal tubules by two energy-requiring active transport systems: one for anions (for example, deprotonated forms of weak acids) and one for cations (for example, protonated forms of weak bases)

3. DISTAL TUBULAR REABSORPTION

- As a drug moves toward the distal convoluted tubule, its concentration increases and exceeds that of the perivascular

- space. The drug, if uncharged, may diffuse out of the nephric lumen, back into the systemic circulation

- Manipulating the urine pH to increase the fraction of ionized drug in the lumen may be done to minimize the amount of back diffusion and increase the clearance of an undesirable drug. Generally, weak acids can be eliminated by alkalinization of the urine, whereas elimination of weak bases may be increased by acidification of the urine. This process is called “ion trapping.”


Drug
Drug
Proximal tubule
Loop of Henle
Distal tubule
Passive reabsorption of lipid-soluble, un-ionized drug
Drug
Phase I and II metabolism
Ionized or polar metabolite

TOTAL BODY CLEARANCE

$$CL_{total} = CL_{hepatic} + CL_{renal} + CL_{pulmonary} + CL_{other}$$

CLINICAL SITUATIONS RESULTING IN CHANGES IN DRUG HALF-LIFE

Patients who

may have an increase in drug half-life include those with 1) diminished renal or hepatic blood flow, for example, in

cardiogenic shock, heart failure, or hemorrhage; 2) decreased ability to extract drug from plasma, for example, in

renal disease; and 3) decreased metabolism, for example, when a concomitant drug inhibits metabolism or in hepatic

insufficiency, as with cirrhosis.

- In contrast, the half-life of a drug may be decreased by increased hepatic blood flow, decreased protein binding, or increased metabolism. This may necessitate higher doses or more frequent dosing intervals.

DESIGN AND OPTIMIZATION OF DOSAGE REGIMEN

- the clinician must select the appropriate route of administration, dosage, and dosing interval.

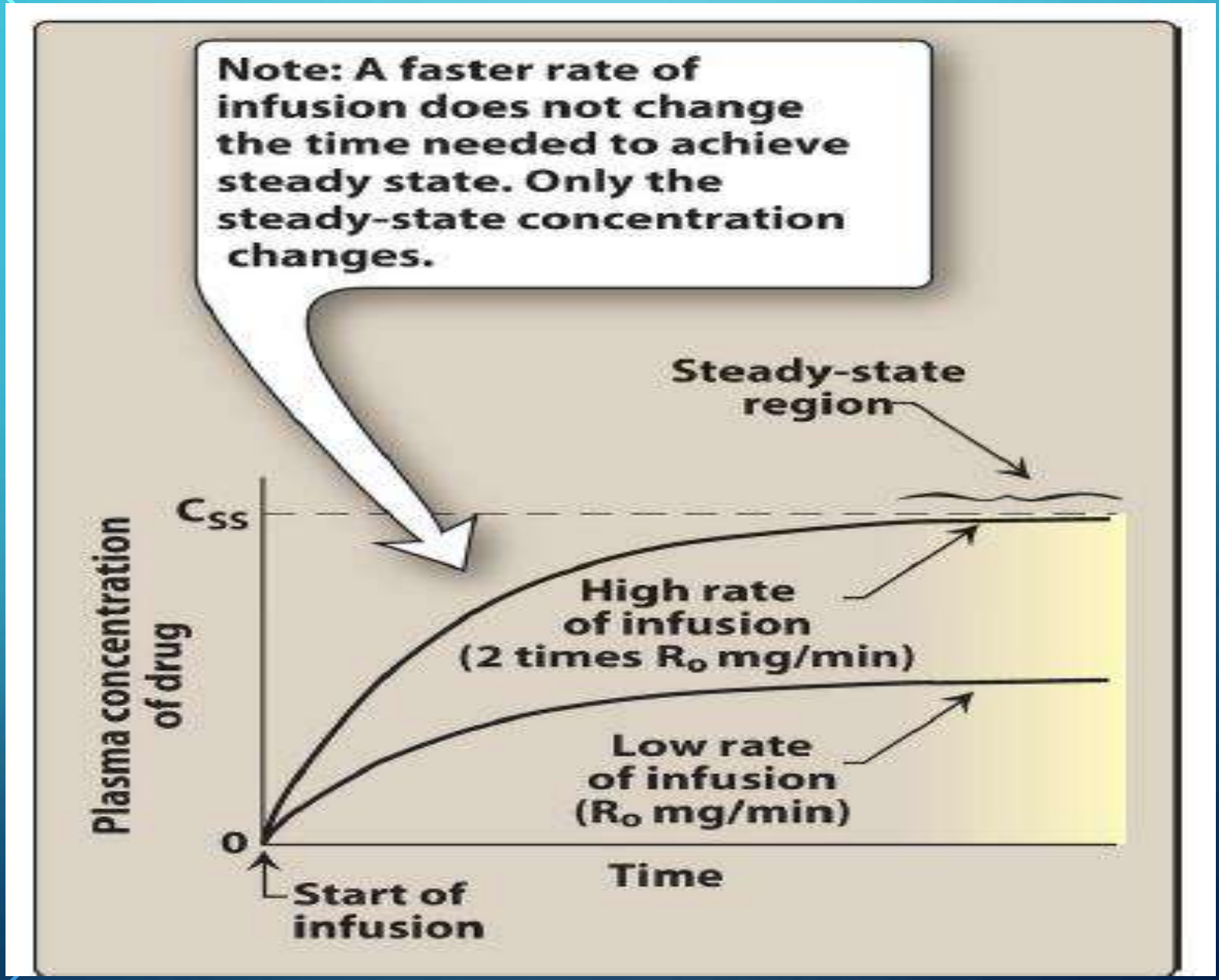
- Continuous or repeated administration results in accumulation of the drug until a steady state occurs. Steady-state concentration is reached when the rate of drug elimination is equal to the rate of drug administration, such that plasma and tissue levels remain relatively constant.
-

STEADY STATE CONCENTRATION

- the rate of drug elimination is equal to the rate of drug administration

CONTINUOUS INFUSION REGIMENS

- the rate of drug entry into the body is constant. Most drugs exhibit first-order elimination, that is, a constant fraction of the drug is cleared per unit of time. Therefore, the rate of drug elimination increases proportionately as the plasma concentration increases


Note: A faster rate of infusion does not change the time needed to achieve steady state. Only the steady-state concentration changes.
Steady-state region
C_{ss}
High rate of infusion (2 times R_o mg/min)
Low rate of infusion (R_o mg/min)
Plasma concentration of drug
0
Time
Start of infusion

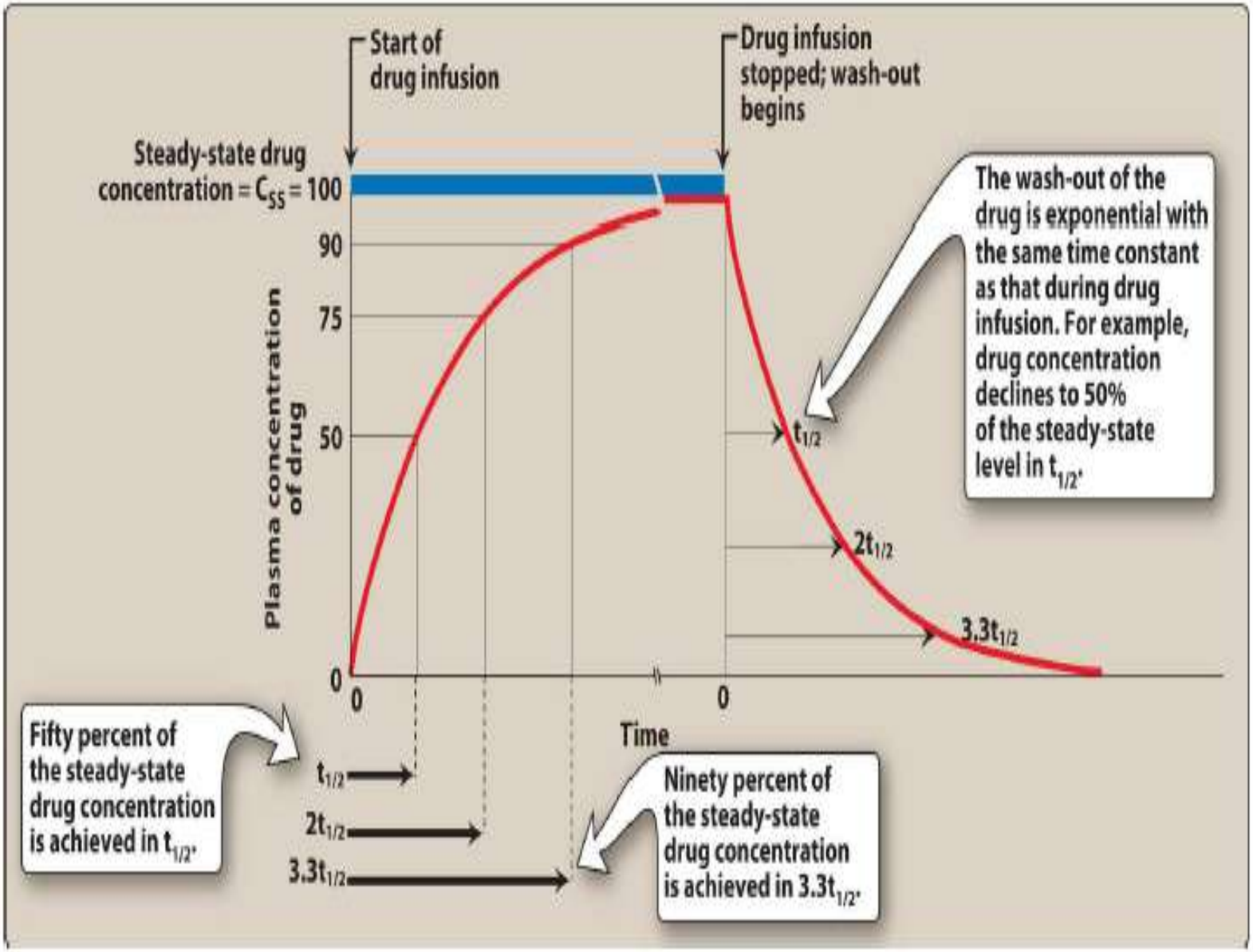
Influence of infusion rate on steady-state concentration

- The steady-state plasma concentration (C_{ss}) is directly proportional to the infusion rate. For example, if the infusion rate is doubled, the C_{ss} is doubled

- Furthermore, the Css is inversely proportional to the clearance of the drug. Thus, any factor that decreases clearance, such as liver or kidney disease, increases the Css of an infused
- drug (assuming Vd remains constant). Factors that increase clearance, such as increased metabolism, decrease the Css.

TIME TO REACH STEADY-STATE DRUG CONCENTRATION

- a drug reaches steady state in about
- 4 to 5 half-lives

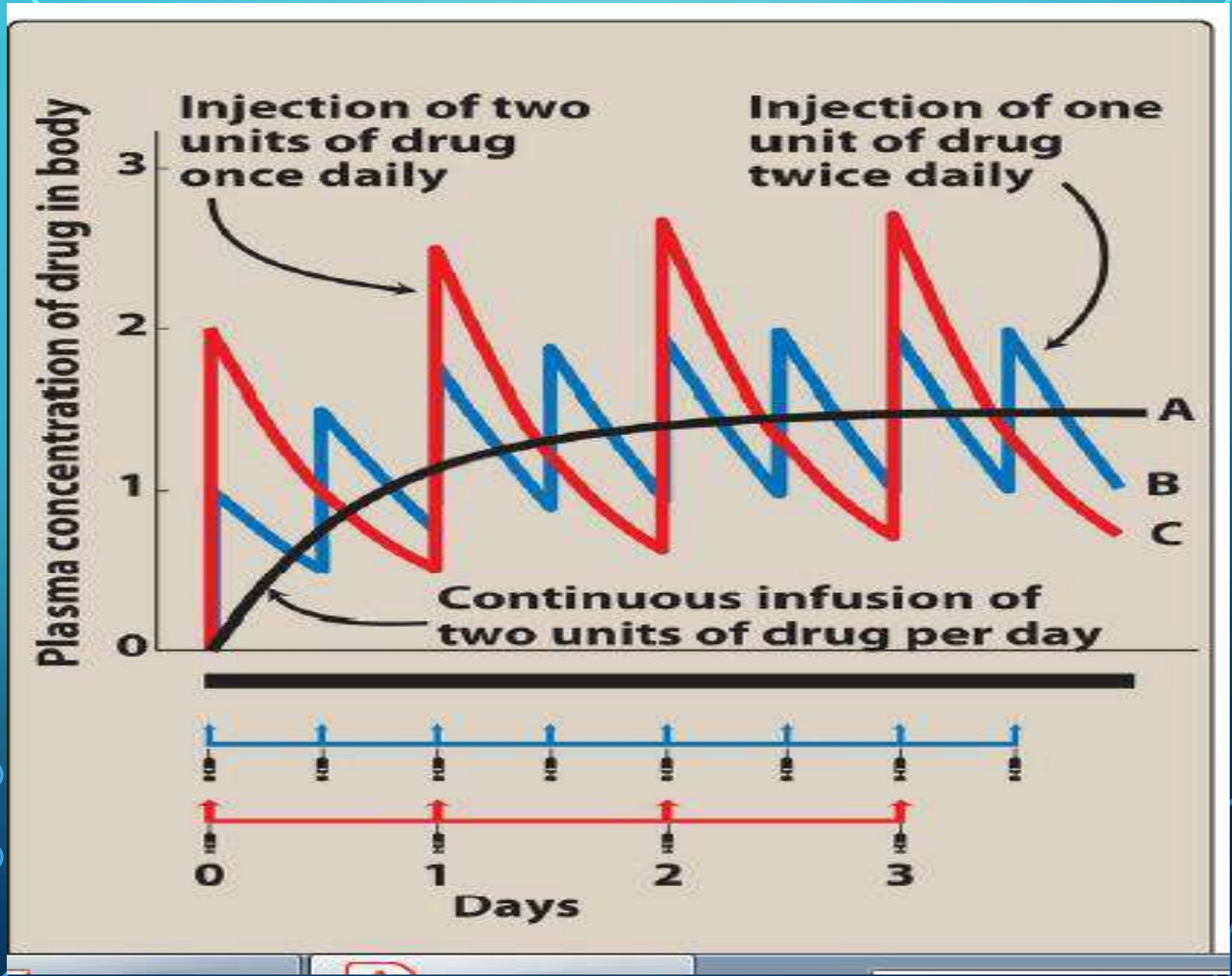

Start of drug infusion
Drug infusion stopped; wash-out begins
Steady-state drug concentration = C_{SS} = 100
90
75
50
0
Plasma concentration of drug
$t_{1/2}$
$2t_{1/2}$
$3.3t_{1/2}$
The wash-out of the drug is exponential with the same time constant as that during drug infusion. For example, drug concentration declines to 50% of the steady-state level in $t_{1/2}$.
0
0
Time
Fifty percent of the steady-state drug concentration is achieved in $t_{1/2}$.
$t_{1/2}$
$2t_{1/2}$
$3.3t_{1/2}$
Ninety percent of the steady-state drug concentration is achieved in $3.3t_{1/2}$.

FIXED-DOSE/FIXED-TIME REGIMENS

- Administration of a drug by fixed doses rather than by continuous infusion is often more convenient. However, fixed doses of IV or oral medications given at fixed intervals result in time-dependent fluctuations in the circulating level of drug,

MULTIPLE IV INJECTIONS

- When a drug is given repeatedly at regular intervals, the plasma concentration increases until a steady state is reached

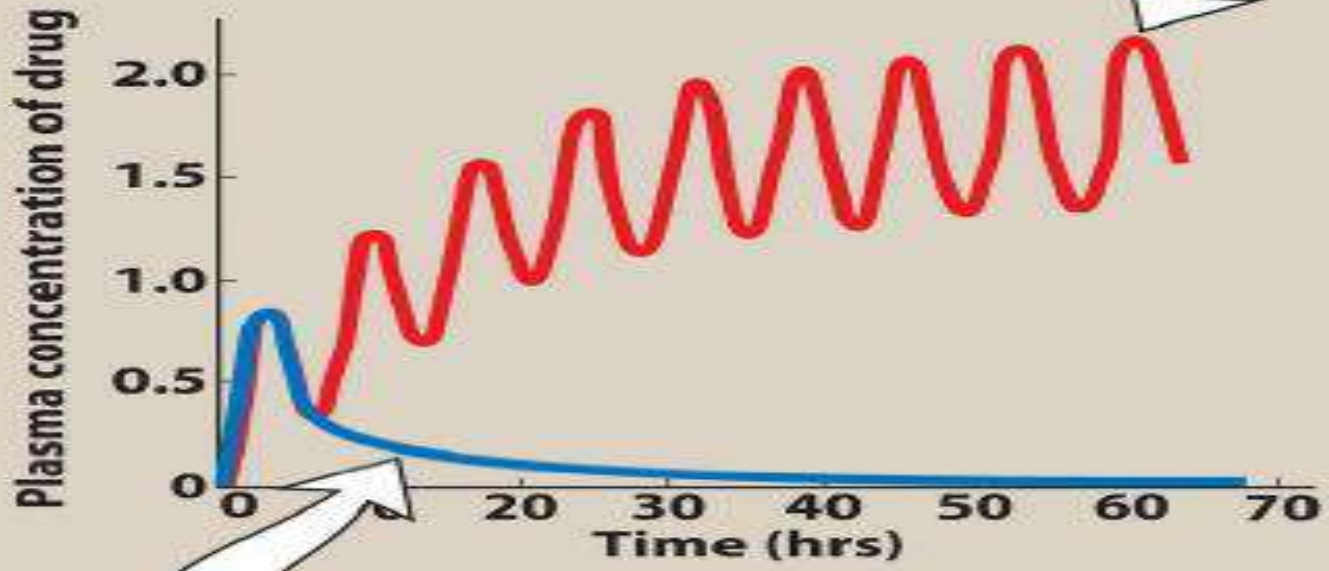

Plasma concentration of drug in body
3
2
1
0
Injection of two units of drug once daily
Injection of one unit of drug twice daily
A
B
C
Continuous infusion of two units of drug per day
0
1
2
3
Days

MULTIPLE ORAL ADMINISTRATIONS

- Most drugs administered on an outpatient basis are oral medications taken at a specific dose one, two, or more times daily. In contrast to IV injection, orally administered drugs may be absorbed slowly, and the plasma concentration of the drug is influenced by both the rate of absorption and the rate of elimination

REPEATED FIXED DOSE

Repeated oral administration of a drug results in oscillations in plasma concentrations that are influenced by both the rate of drug absorption and the rate of drug elimination.



SINGLE FIXED DOSE

A single dose of drug given orally results in a single peak in plasma concentration followed by a continuous decline in drug level.

OPTIMIZATION OF DOSE

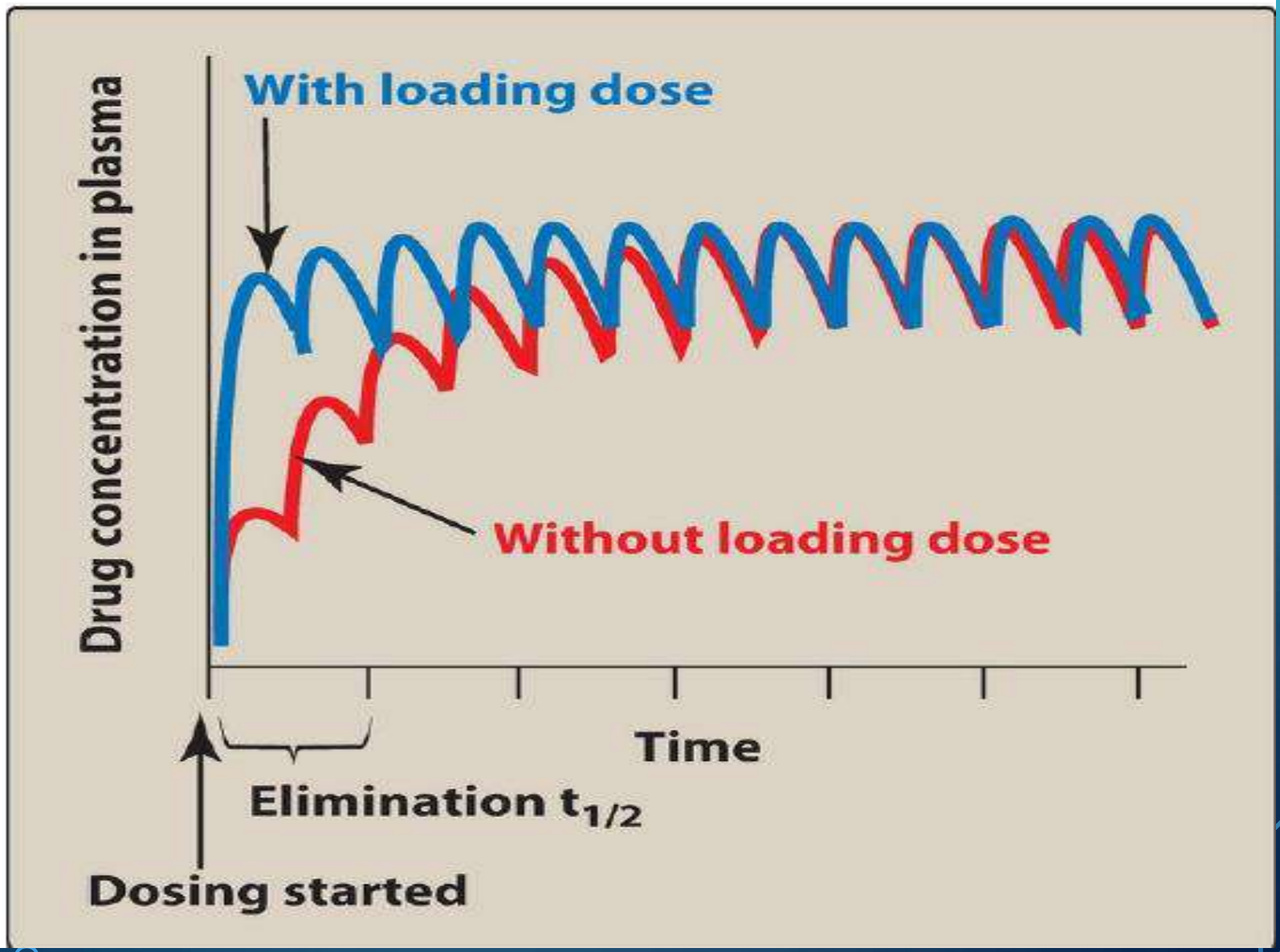
- The goal of drug therapy is to achieve and maintain concentrations within a therapeutic response window while minimizing toxicity and/or adverse effects. With careful titration, most drugs can achieve this goal. If the therapeutic window of the drug is small (for example, *digoxin* or *lithium*),

MAINTENANCE DOSE

- Drugs are generally administered to maintain a C_{ss} within the therapeutic window. It takes 4 to 5 half-lives for a drug to achieve C_{ss}. To achieve a given concentration, the rate of administration and the rate of elimination of the drug are important

LOADING DOSE

- Sometimes rapid obtainment of desired plasma levels is needed (for example, in serious infections or arrhythmias). Therefore, a “loading dose” of drug is administered to achieve the desired plasma level rapidly, followed by a maintenance dose to maintain the steady state


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

CALCULATION OF LOADING DOSE

- Loading dose = (V_d) × (desired steady-state plasma concentration)/F