كلية الطب البيطري – جامعة تكريت

ماجستير أدوية

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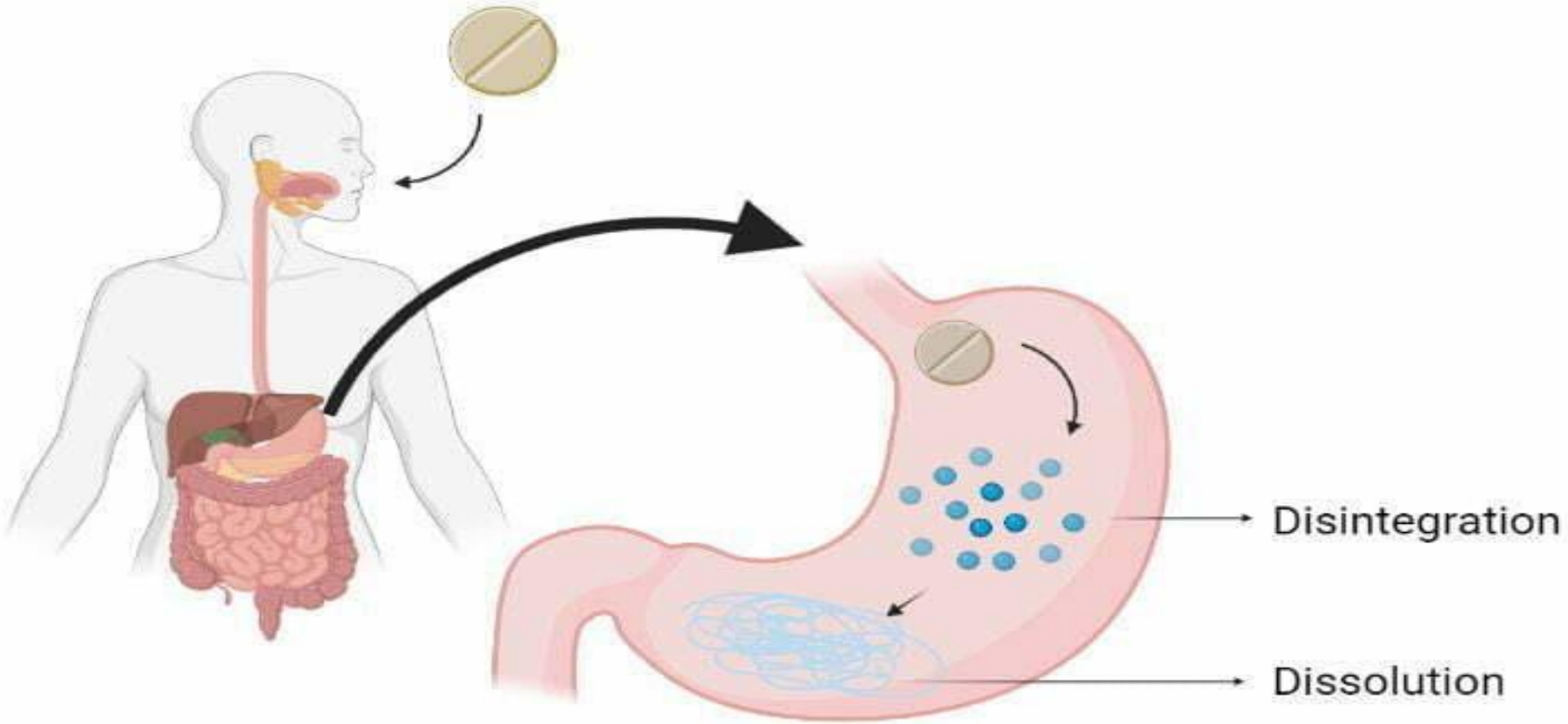
2024-2025 \ First Term 2

Advanced Pharmacology

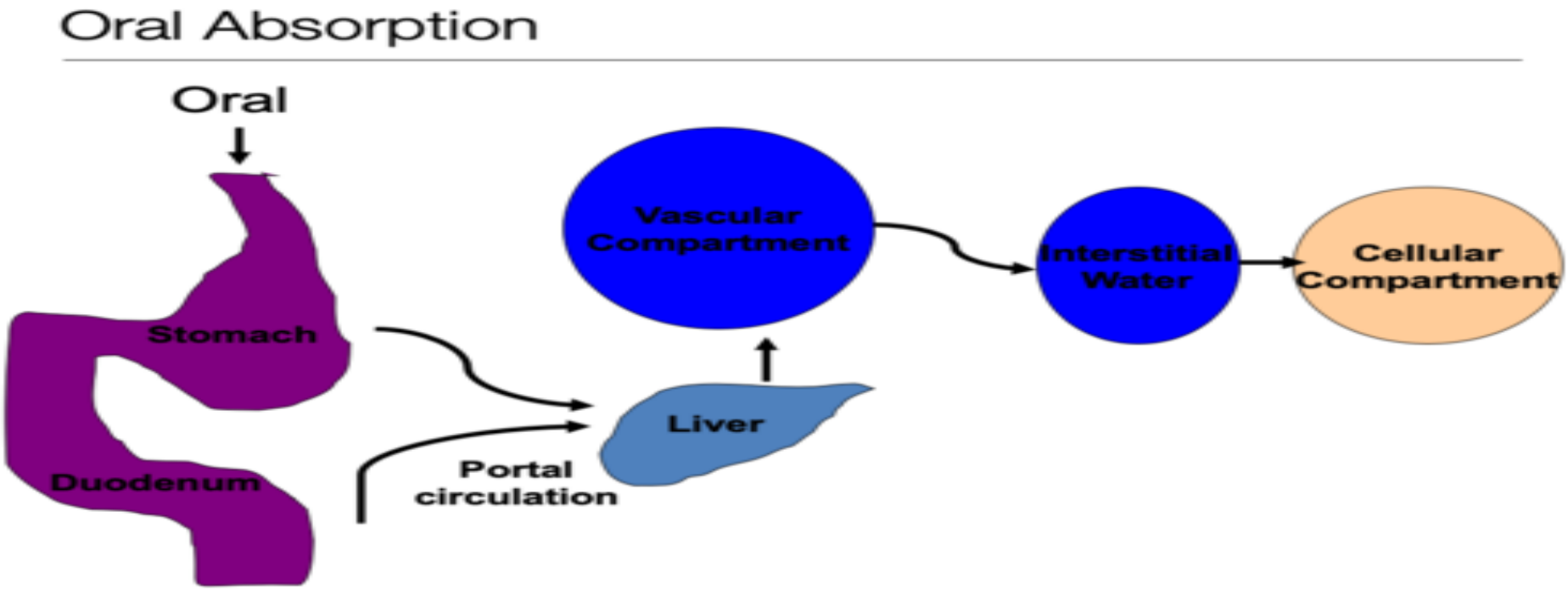
PHARMACOKINETICS VARIABLES: ADME

DRUG ABSORPTION



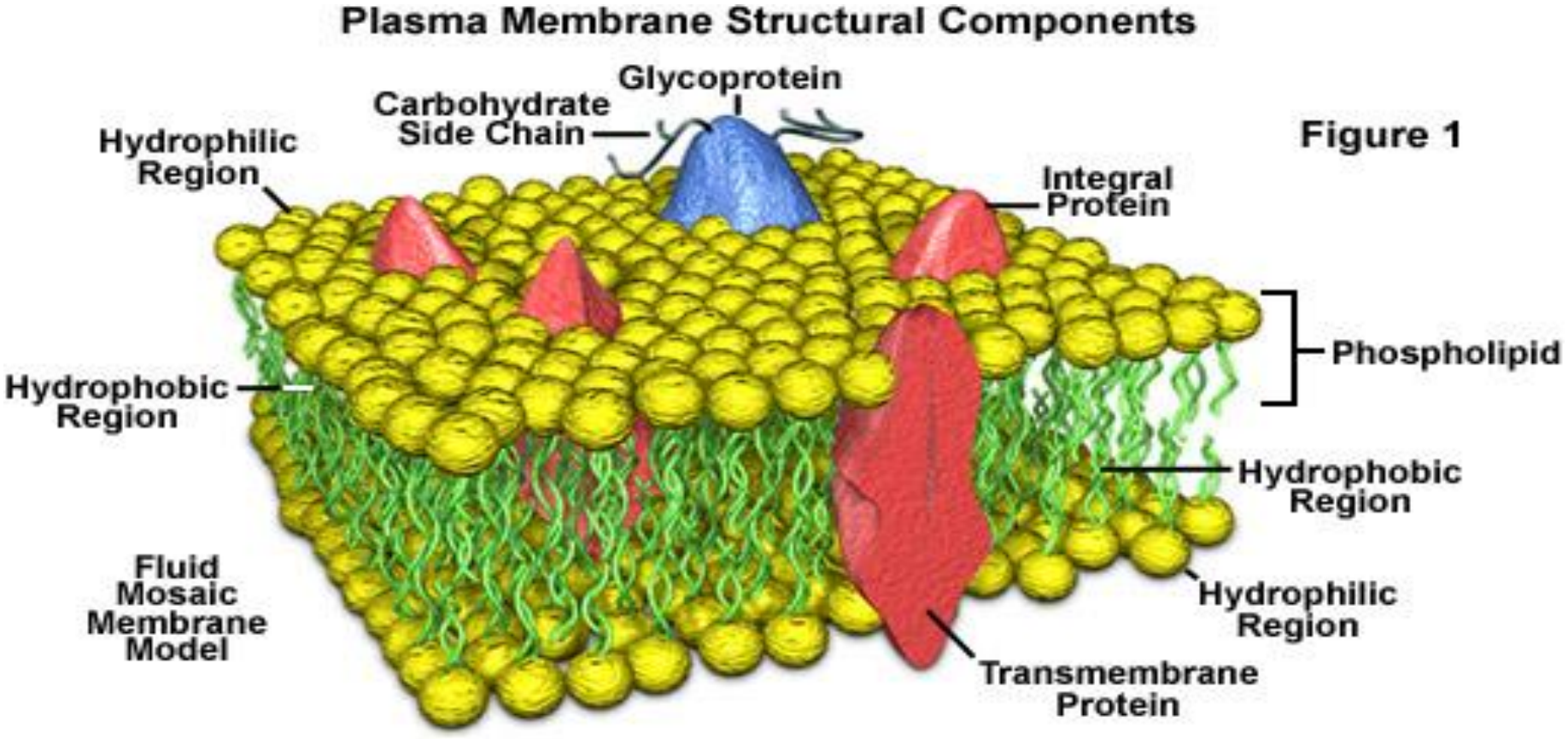
ABSORPTION

It is a passage of the drug from its site of administration to the plasma or systemic circulation.



Drug transport across cell membrane

- The movement of drug molecules between different compartments in the body involve diffusion through lipid barriers (membranes).



- **Mechanisms by which drug molecules penetrate cell membranes include:**

1. Passive diffusion through the lipid membranes.
2. Carrier-mediated transport.
3. Diffusion though aqueous pores (aquaporins).
4. Pinocytosis

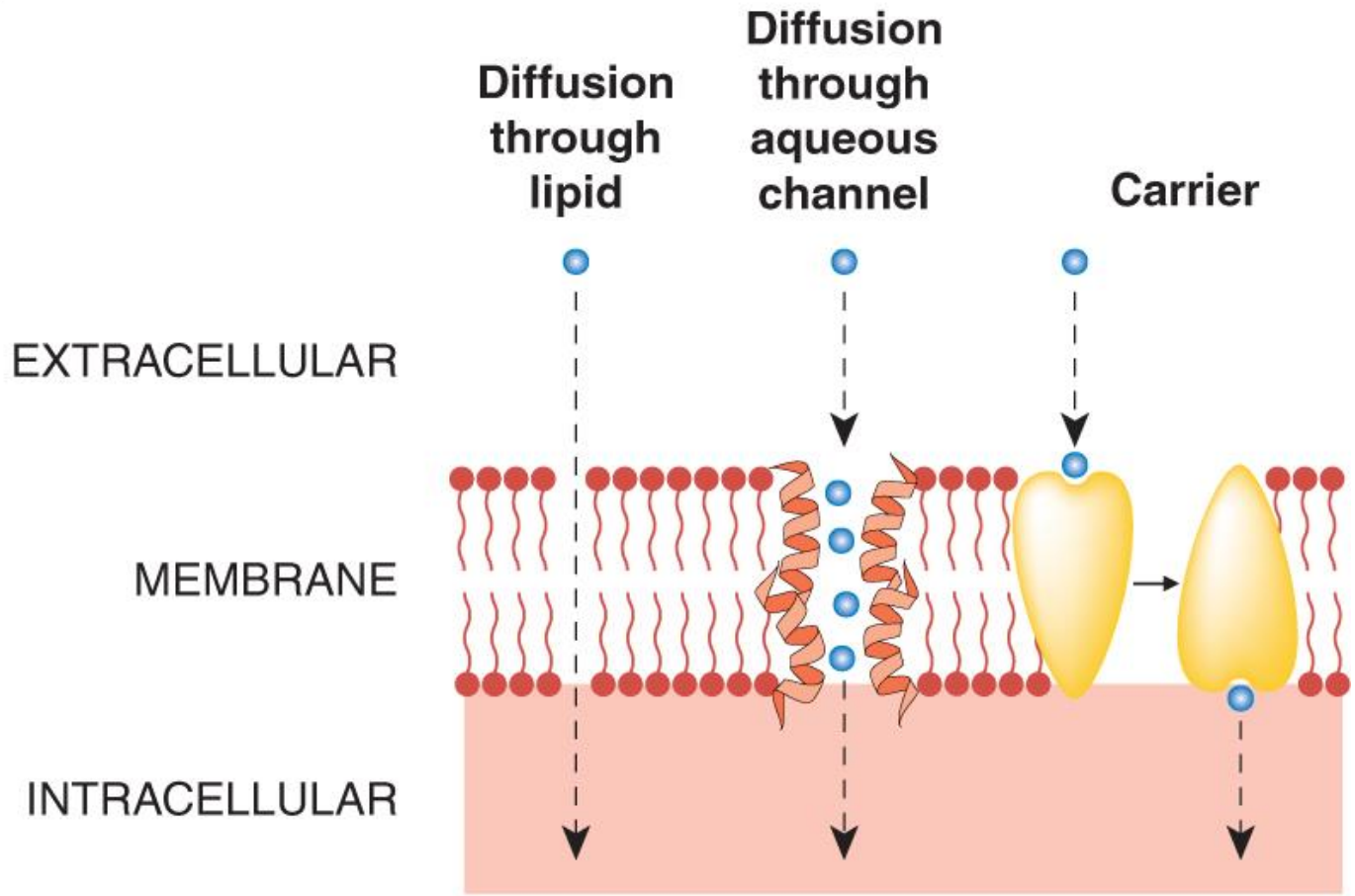
1. <u>Passive diffusion:</u>

The cell membrane is lipoprotein in nature. Therefore passive diffusion depends on:

a. Lipid solubility of the drug
b. The conc. gradient of the drug
c. The surface area of the membrane

- **Characteristics of passive diffusion:**
- The drug move from region of high conc. to low conc. in a rate proportional to the conc. gradient.
- The drug's lipid solubility is the major determinant of the rate of passive diffusion (MW is less important).
- It does not need a carrier, nor energy, the driving force is the conc. gradient.
- Transfer is not inhibited by the presence of other substances with similar chemical structure i.e. . No competition.

Mechanisms by which drugs can cross cell membranes



- Ionization affects:

  lipid solubility of the drug: The cell membrane is impermeable to the ionized form of a drug but relatively permeable to the unionized form. A general rule is that only non-ionized (lipid soluble) drugs pass quickly through membranes.

  Ionized species are too polar to pass easily. i.e. acidic drugs are non-ionized at ↓pH (↑ lipid soluble, well absorbed) while the basic drugs are (↓lipid soluble, not absorbed). Fully ionized compounds can not be absorbed (strong acids & bases).

2. Carrier-mediated transport:

Can be active or facilitated transport.

a. Active transport:

aminoacids, glucose, vit B1& B6

- **Characters:**
- The carrier requires energy
- Against conc. gradient
- Active transport play important role in the renal and biliary excretion of many drugs and their metabolites (renal excretion organic acids and bases)

b. Facilitated transport:

It differs from active in that: doesn't need energy, in the direction of the conc. gradient & less specific than active transport but it is a saturable process and subjected to competition by similar compounds

3. **Aqueous diffusion:**

Through aqueous pores (↓ M.W substances, water, urea & organic electrolytes). Capillaries of the brain & testis lack these pores.

4. **Endocytosis (pinocytosis):**

Transport of macromolecules such as insulin into CNS.

Drug Absorption from the gastrointestinal tract

- Intestine is the most important site for drug absorption in the GIT.
- Characterize by a very large surface area, provided by the existence of villi and microvilli.
- Most drugs are absorbed from the intestine by passive diffusion at a rate determined by the ionization and lipid solubility of the drug molecules.
- Some drugs (e.g. levodopa , fluorouracil) are absorbed by a carrier-mediated transport mechanisms.

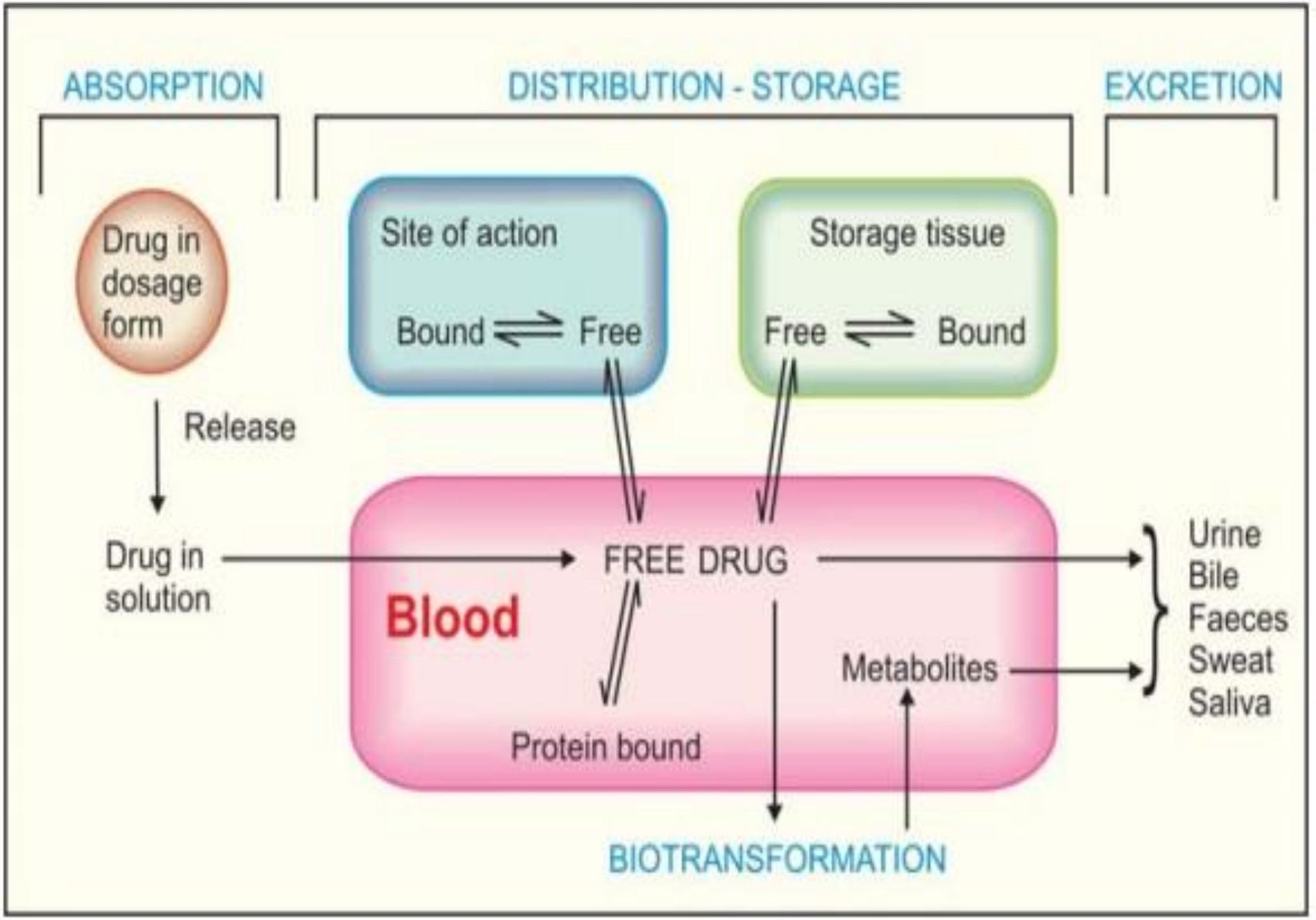
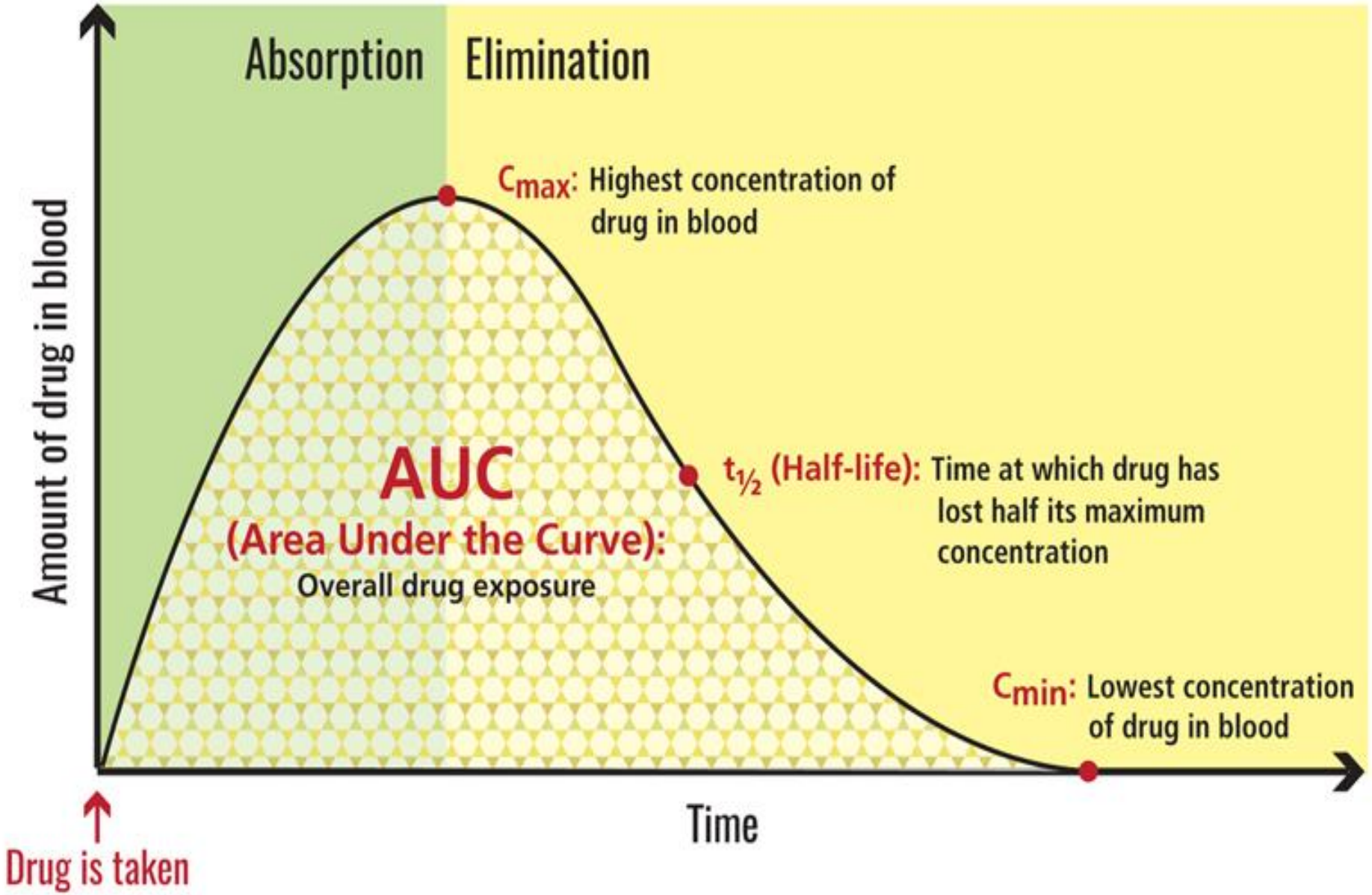


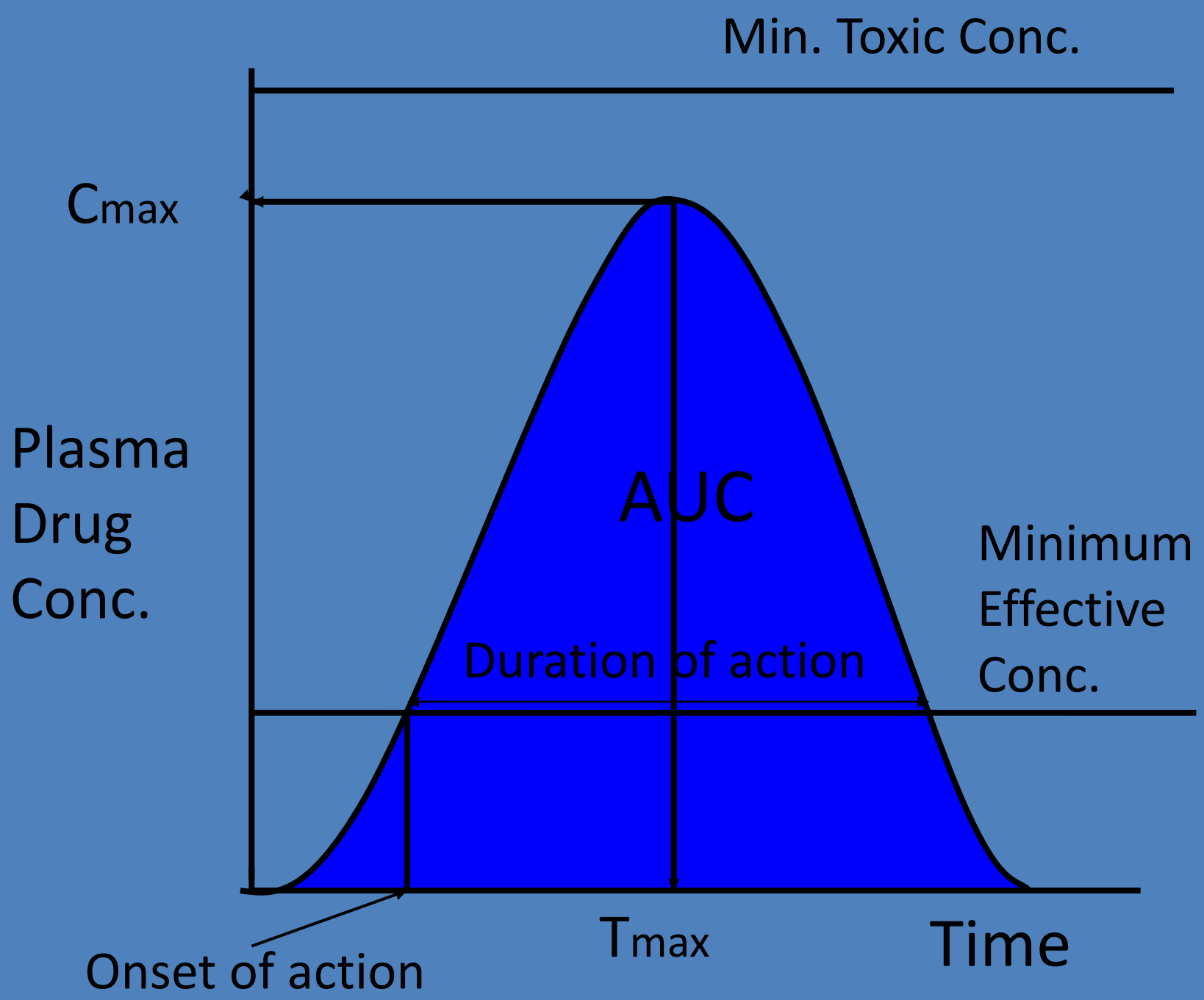
Fig. 2.1: Schematic depiction of pharmacokinetic processes

Bioavailability

- It is the fraction of the administered dose that reaches the systemic circulation as intact drug & the rate at which this occurs.
- Determination of bioavailability:
- It is measured from the plasma drug concentration-time curve following I.V & other route (oral) of administration, by comparing area under curve (AUC) of a drug after a particular route of administration with AUC achieved by I.V. route.

Pharmacokinetics




Min. Toxic Conc.
Cmax
Plasma
Drug
Conc.
AUC
Minimum
Effective
Conc.
Duration of action
Onset of action
Tmax
Time

- Parameters:

1. The peak conc (Cmax): related to the efficacy & should be within the therapeutic window
2. The time taken to reach the peak conc (Tmax):

   Related to the rate of drug absorption

   ↓Tmax → faster absorption.
3. Area under plasma drug conc-time curve (AUC): related to the extent of absorption (the amount of the drug that is absorbed)

   Absolute bioavailability= $\frac{(AUC)_{o}}{(AUC)_{i.v}}$
4. Minimum Effective plasma conc (MEC)
5. Minimum toxic conc (MTC) or maximum safe conc.
6. Therapeutic window
7. Onset of action
8. Duration of action

Factors affecting drug bioavailability

1. **Intestinal motility (I.M):**

   The greater the intestinal motility the shorter is the contact time at the absorption site, the lesser the absorption of the drug. It is affected by:

- Drugs: atropine & hyoscine (↓I.M), metoclopramide & domperidone (↑I.M), e.g. hyosine increase the absorption of riboflavin while metoclopramide significantly reduces digoxin conc.
- Diseases: diarrhea & hyperthyrodism (↑I.M).

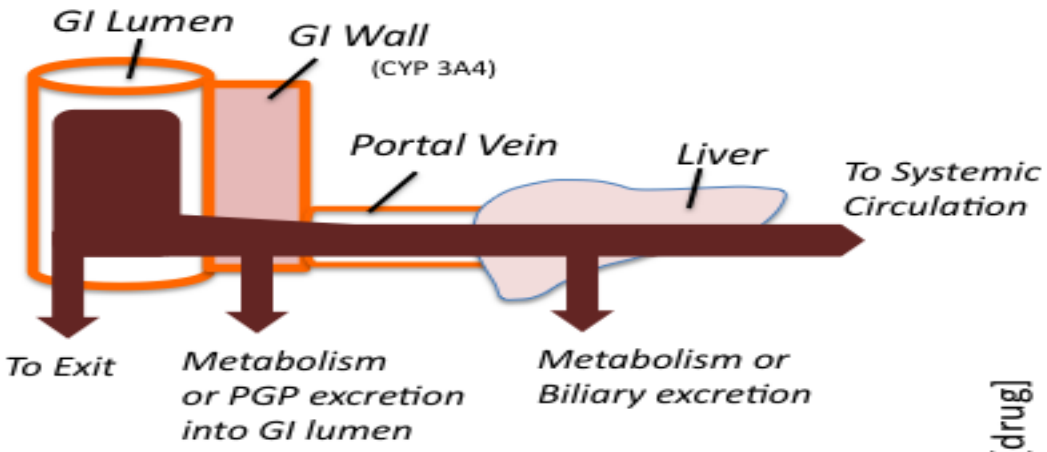
2. **Gastric emptying rate (G.E.R):**

- The rate at which the stomach delivers drugs to the small intestine.

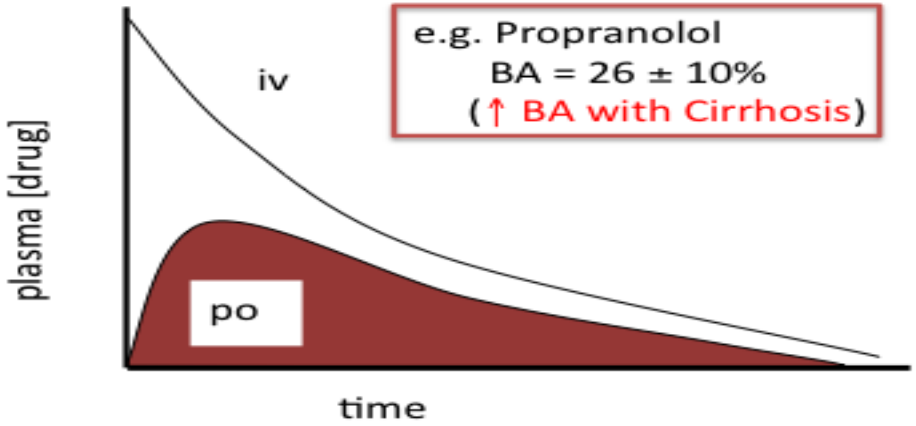
- Since most drugs (including weak acids), are optimally absorbed from the small intestine, any factor that promotes GER increases the absorption of drugs while reduction in GER is likely to reduce the overall rate of drugs absorption.

Bioavailability

- the fraction absorbed into the systemic circulation is the drug's bioavailability



$$BA = \frac{AUC_{po}}{AUC_{iv}} \times 100$$



3. **Surface area at the absorption site:**

   ↑Surface area ↑ absorption e.g. intestinal mucosa & pulmonary alveolar epithelium

4. **Blood flow to the GIT:**
   Voluminous & vigorous in the intestine, affected by stress , hypovolumia & heart failure (↓ blood flow). Supine position (↑ blood flow).

5. **Gastrointestinal pH:**

   The pH of GIT fluids varies along the length of the GIT (stomach 1-3.5, small intestine 5-8, and large intestine 8).

- It affects aqueous solubility:
- The dissolution rate of a poorly soluble weak acidic drug is enhanced in alkaline environment while a poorly soluble weak basic drug dissolve more readily in acidic environment.

6. **1st pass metabolism:**

   It reduces the oral bioavailability of drugs

7. **Food:** affects drug absorption by

a. ↓GER: delayed drug absorption. But a meal reduces the irritation from irritant drug & fatty meal increases the absorption of lipophylic drugs such as griseofulvin

b. Complexation of food component with drugs:

   food containing divatent & trivalent metals (Al^{3+}, Ca^{2+}, Fe^{3+} & Mg^{2+}) chelates with tetracycline & flouroquinolones.

c. Stimulates gastrointestinal secretion (Hcl , pepsin & bile salts) →↑degradation of unstable drugs

   Bile salts can form insoluble, non-absorbable complexes with some drugs (neomycin, Kanamycin and nystatin).

d. Competition between food component & some drugs for the same absorption site:

   The absorption of levodopa may be inhibited by certain amino acids (tyrosine and phenylalanine), resulting from the break down of ingested proteins.

e. Increased viscosity of the GIT content: ↓dissolution rate and absorption of the drug.

f. Food leads to transient increase in blood flow to the liver →saturation of the metabolizing enzymes in the liver → ↓ 1st pass effect →↑ bioavailability e.g propranolol

- Absorption of some drugs is not affected by food e.g. oxazepam, prednisolone, doxycycline and others.

8. Complexation:

- With drugs: tetracycline+ antacids

  Cholestyramine + warfarin or thyroxine

- With food component

9. **Drug stability:**

Some drugs may be subjected to acid or enzymatic hydrolysis in GIT e.g. penicillin G, insulin & erythromycin (enteric coated tablets or prodrug)

10. **Formulation of the drug:**

a. Particle size of the powder:
The smaller the particle size the higher is the dissolution rate, the greater is the absorption of the drug.

- Drugs whose bioavailability is enhanced by particle size reduction include: tolbutamide, digoxin, spiranolactone, griseofulvin and aspirin (micronized tablets).

b. The dosage form:
The absorption of the drug decreases in the following order, according to the type of the dosage form:

Aqueous solutions > aq. suspension > soft gelatin capsule > hard gelatin capsule > uncoated tablet > coated tablet.

11. **Adsorption:**
charcoal ↓absorption of many drugs.
12. **Route of administration:**
absorption is faster from i.v. > inhaled > i.m. > oral > dermal administration

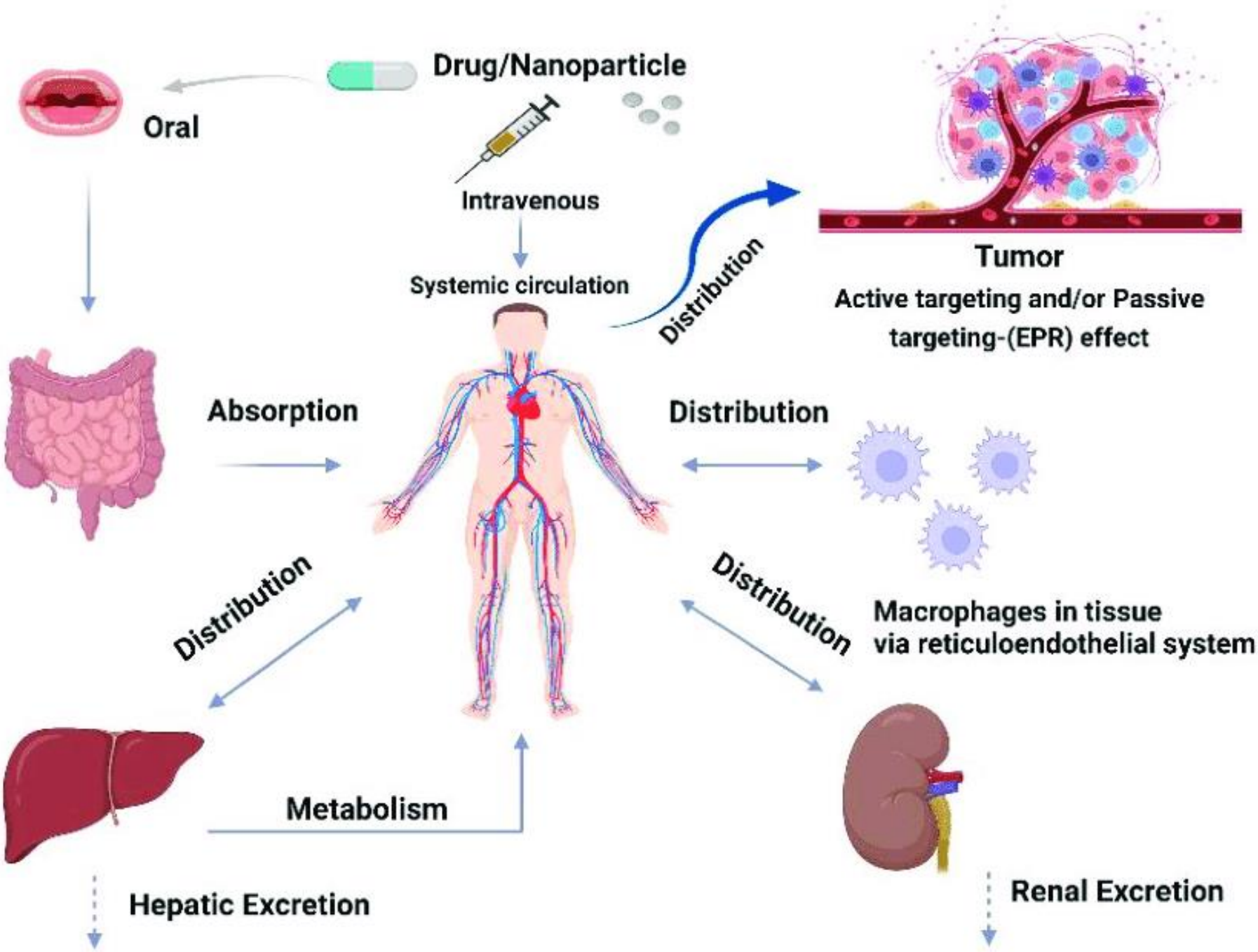
Distribution

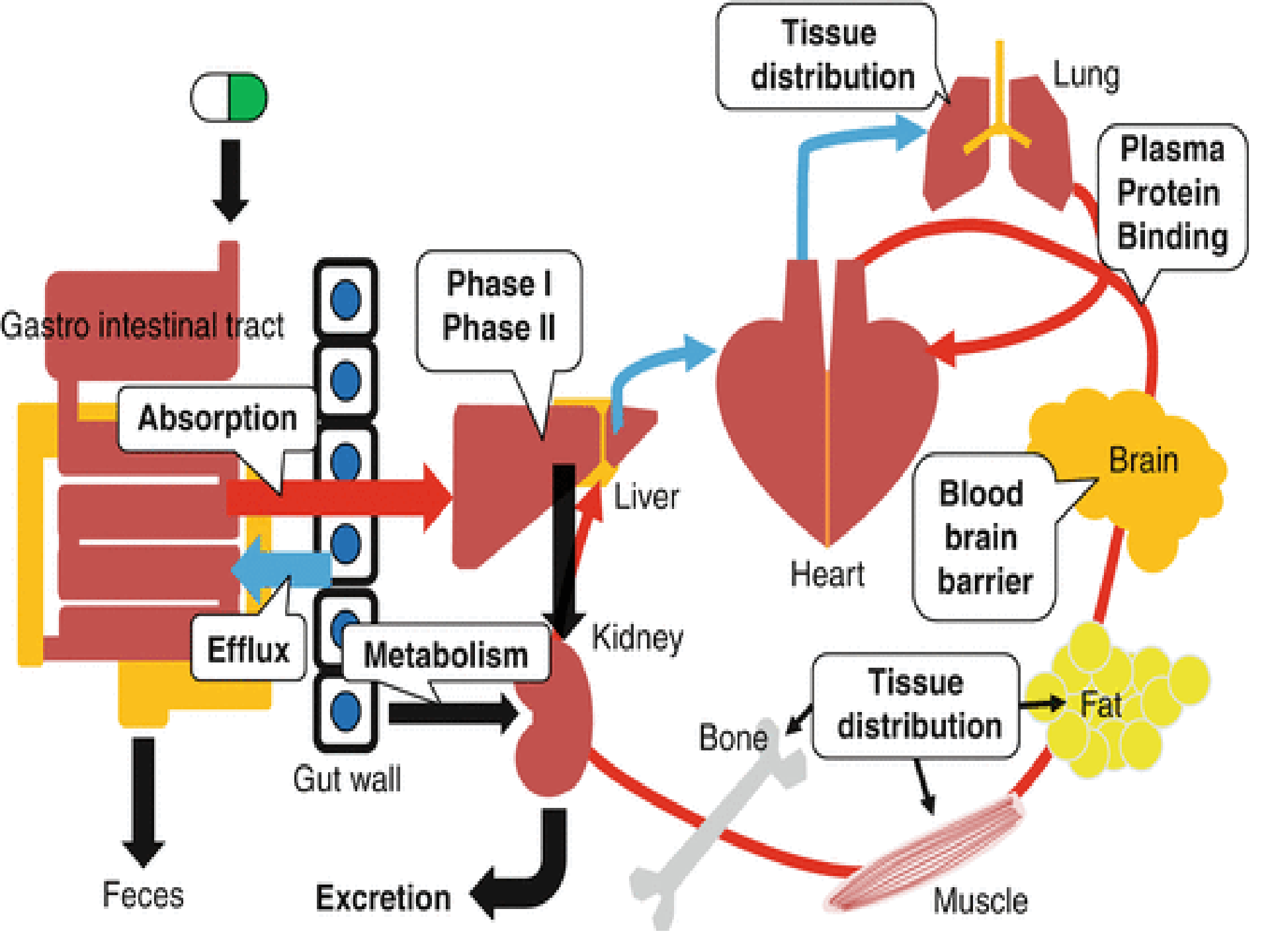
Is the process by which the drug reversibly leaves the blood stream & enters the interstitial and/or other cellular fluids.

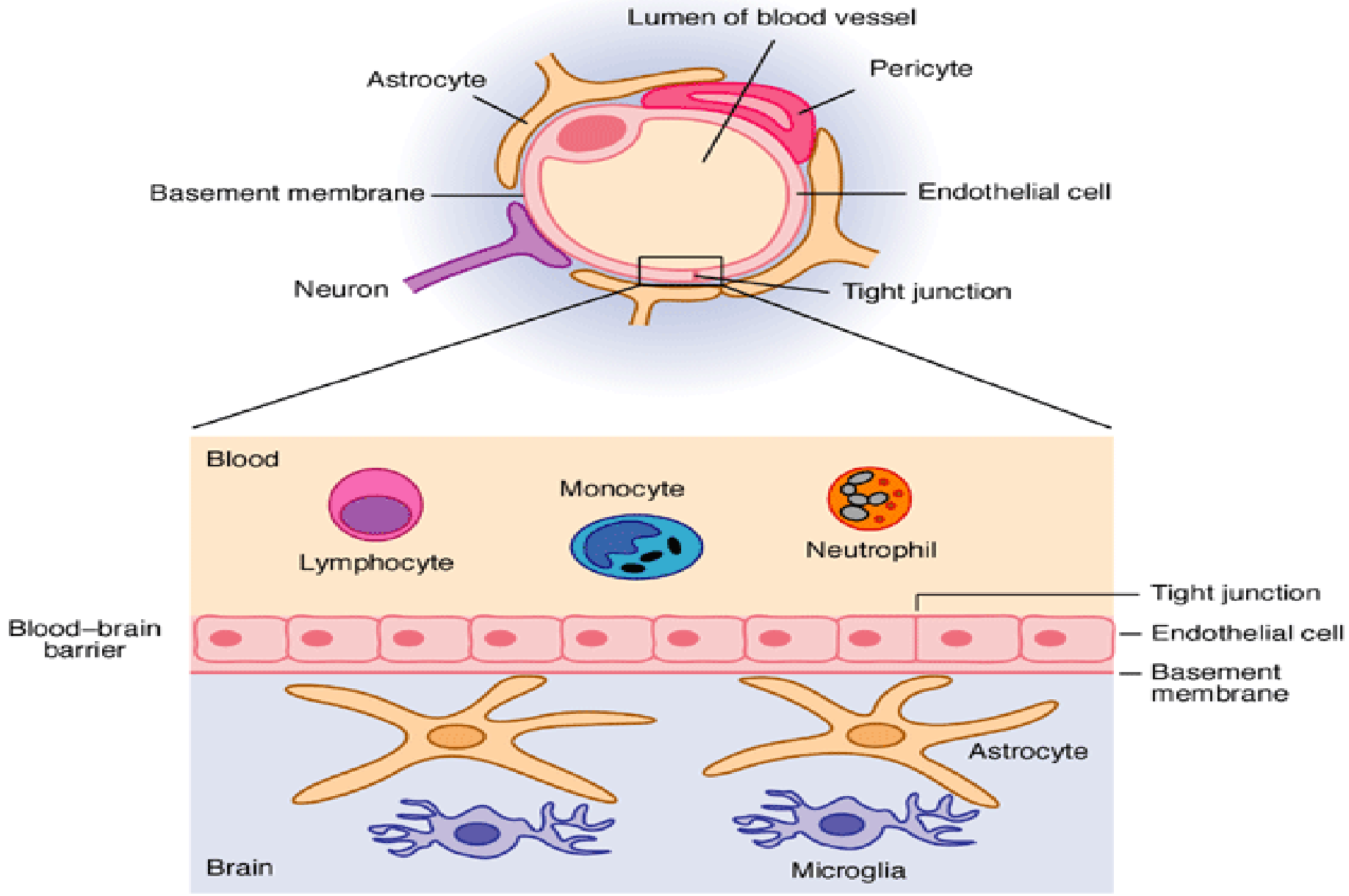
- Distribution of the drug depends on:

1. Blood flow: fast distribution (highly perfused organs), slow distribution (muscle, skin & fats).
2. Capillary permeability: depends on lipid solubility of the drug & capillary nature, e.g. tight junction between endothelial cells in B.B.B.
3. Binding to plasma proteins & tissues:

- **Binding of drugs to plasma proteins:**
- It is non-selective & reversible.
- Drugs exist in free & bound form (pharmacologically inactive). Distribution occurs for free drugs only.
- Drugs can bind to plasma proteins such as albumin (most important, binds acidic drugs), α_1 acid-glycoprotein (binds some basic drugs) & β-globulin (binds hormones & some basic drugs).


Drug/Nanoparticle
Oral
Intravenous
Systemic circulation
Distribution
Tumor
Active targeting and/or Passive targeting-(EPR) effect
Absorption
Distribution
Distribution
Distribution
Macrophages in tissue via reticuloendothelial system
Metabolism
Hepatic Excretion
Renal Excretion

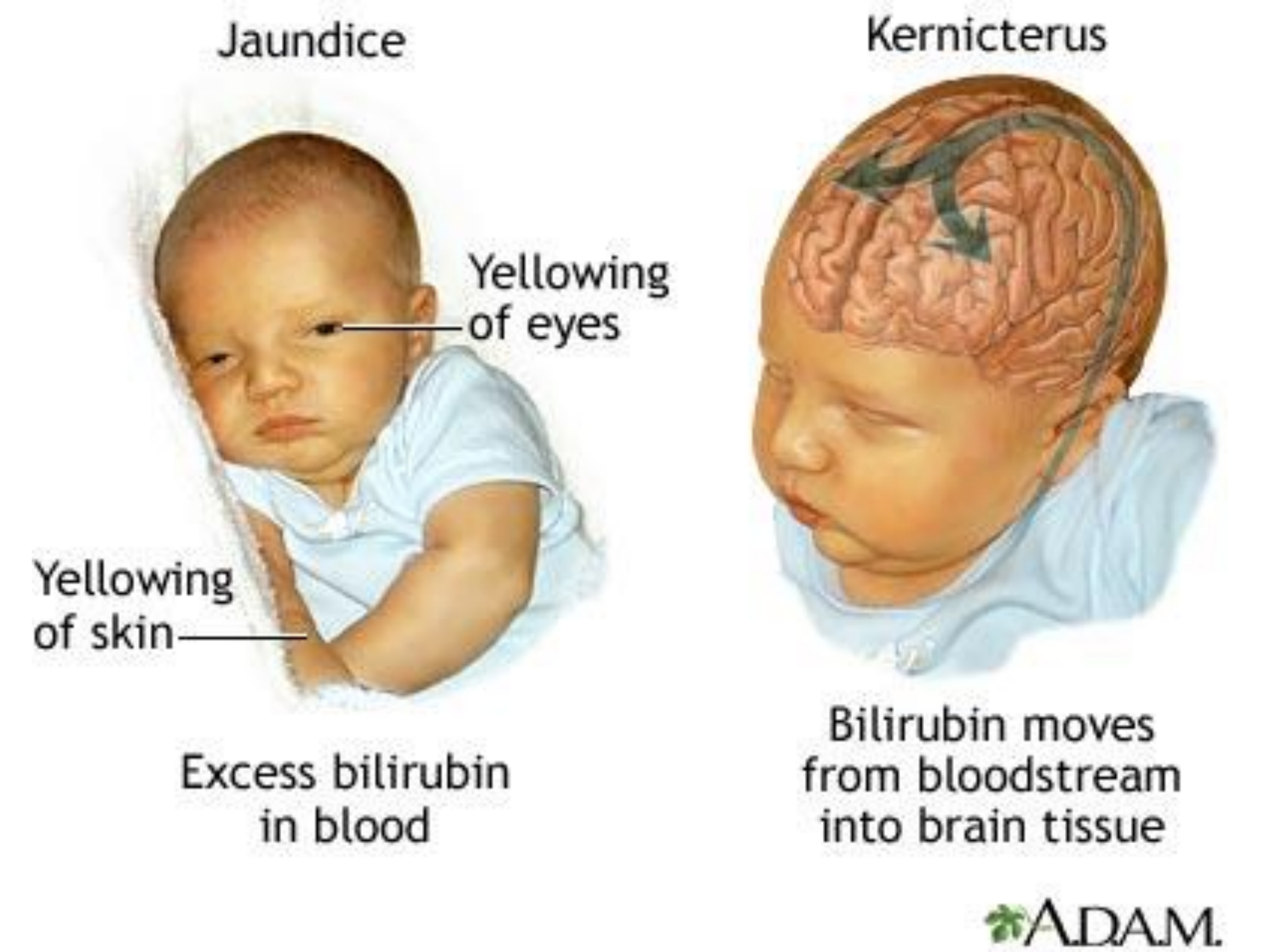

Tissue distribution
Lung
Plasma Protein Binding
Phase I
Phase II
Gastro intestinal tract
Absorption
Liver
Heart
Brain
Blood brain barrier
Efflux
Metabolism
Kidney
Tissue distribution
Fat
Bone
Gut wall
Feces
Excretion
Muscle



The blood–brain barrier (BBB)

- Protein binding of drugs limits their distribution (for free drug only) & glomerular filtration (doesn't change the free drug conc) but it doesn't limit active tubular secretion (↓free drug conc, only the solute is filtered, dissociation of drug-protein complex).
- **Significance of drug binding to plasma proteins:**
- Protein binding displacement:

  Drugs highly bound to plasma proteins compete or displace others from their binding sites leading to drug interactions . e.g. displacement of tolbutamide or warfarin by salicylates → hypoglycemia or bleeding.
- displacement of bilirubin by sulfonamides in premature babies → kernicterus disease.
- Drug toxicity: results from
- Hypoalbuminemia.
- If the displacing agent ↓elimination of the displaced drug.


Jaundice
Yellowing of eyes
Yellowing of skin
Excess bilirubin in blood
Kernicterus
Bilirubin moves from bloodstream into brain tissue
A.D.A.M.

- Competition between drugs for protein binding can rarely leads to clinically important drug interactions due to the following: 1. The majority of drugs occupy only small fraction of the binding sites at therapeutic plasma conc. 2. displacement of a drug from its binding sites leads to transient increases in the free drug conc. followed by increased elimination.

- **Binding of drugs to tissues or organs:**
- Many drugs accumulate in tissues (drug reservoir) e.g. chloroquine accumulates in tissue rich in melanin (retina), tetracycline (bones & teeth), amiodarone (liver & lung), Lipid soluble drugs (fats).

- Accumulation in body fats depends on
- fat : water partition coefficient (↑fat : water partition coeff. ↑accumulation in fats)

1. Blood supply: Low, but chronic administration → accumulation in fats e.g. thiopental.

- **Redistribution** of the drug from its site of action into other tissues or sites terminates the effect of the drug e.g. redistribution of ↑ lipid soluble drugs that act on the brain such as thiopental which is characterized by very rapid distribution to the brain (rapid onset) & slow distribution to fats which lower the drug conc in the plasma followed by ↓drug conc. in brain (rapid termination).

- **Diffusion of drugs across special barriers:**

1. Blood brain barrier (B.B.B):

B.B.B is impermeable to many drugs such as anticancer .Distribution of insufficiently lipid soluble drugs to CNS is restricted but actively transported & ↑lipid soluble drugs can distribute to CNS.

- **Factors increasing B.B.B. permeability to drugs:**

a) Inflammation:(meningitis treated by benzyl penicillin)

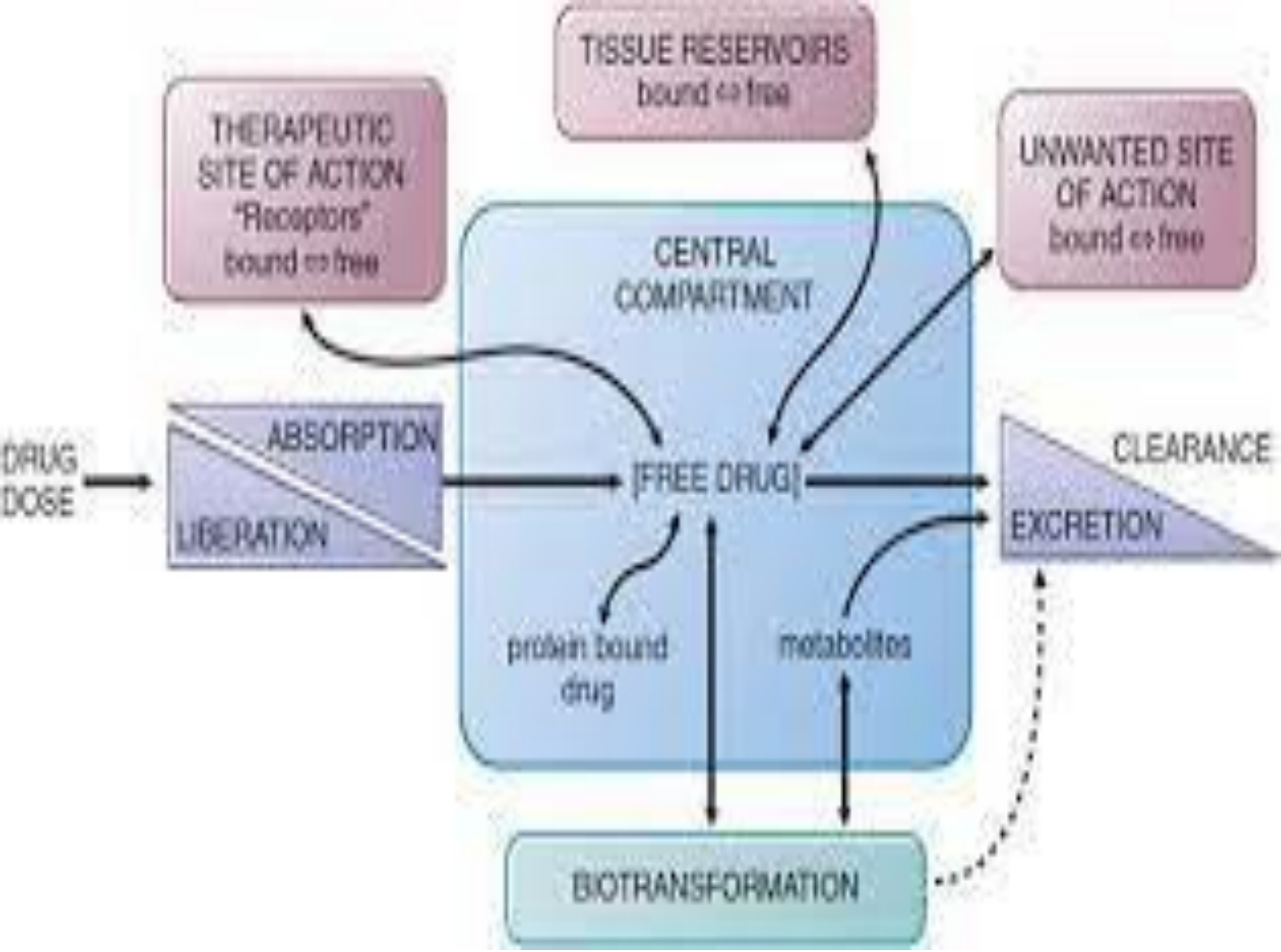
b) Extreme stress (pyridostigmine, acts peripherally)

c) Some peptides such as bradykinin (to improve chemotherapy penetration during brain tumor).

d) Mobile phone radiation

2. The placenta:

Allows the passage of lipid soluble drugs e.g. benzodiazepines, opiates & β-blockers.


TISSUE RESERVOIRS
bound ⇔ free
THERAPEUTIC SITE OF ACTION "Receptors"
bound ⇔ free
UNWANTED SITE OF ACTION
bound ⇔ free
CENTRAL COMPARTMENT
DRUG DOSE
ABSORPTION
LIBERATION
[FREE DRUG]
CLEARANCE
EXCRETION
protein bound drug
metabolites
BIOTRANSFORMATION

DRUG ELIMINATION

- It is irreversible loss of the drug from the body occurs by metabolism & excretion

  DRUG METABOLISM (biotransformation)
- It is a biochemical changes that generate more polar & inactive metabolite readily excreted from the body.
- The main site of drug metabolism is the liver (can occur in GIT, kidney, blood & lung)
- a) Suxamethonium hydrolyzes by plasma cholinesterase.
- b) tyramine and salbutamol are metabolized in the gut wall.

- The metabolizing enzymes may be located in the endoplasmic reticulum, mitochondria, cytosol or lysosomes.
- **The role of drug metabolism:**

1. ↑polarity &↓lipid solubility of the drug: to enhance excretion of the drug.
2. Alter the pharmacological activity of the parent drug:

- Drug inactivation (most of drugs)
- Conversion of inactive drug (prodrug) into active metabolite (cortisone→ hydrocortisone)
- Conversion of active drug into active metabolite.
- Conversion to toxic metabolite (methanol → formaldehyde)

Inactive drug (prodrug)	Active drug	Active metabolite	Toxic
Prednisone	Prednisolone		
Zidovudine	Zidovudine triphosphate		
	Diazepam	Nordiazepam	Oxazepam
	Morphine	Morphine 6- glucuronide	
	Acetylsalicylic acid	Salicylic acid	
	Halothane		Trifluroacetic acid
	Methoxyflurane		Fluoride
	Paracetamol		N-acetyl-p- benzo-quinoneimine

- **Phases of drug metabolism:**

1. Phase I (non-synthetic or functionalization reaction)
2. Phase II (biosynthetic reaction)

- The products of phase 1 are often more reactive and some time more toxic than the parent drug.

1. Phase I:

a. Oxidation reactions
b. Hydrolysis reactions
c. Reduction reactions

- They introduce a relatively reactive group (OH, NH_2 or SH) into the drug→ more polar.
- They are catalyzed by microsomal or non-microsomal enzymes.

- **Hepatic Microsomal Drug –Metabolizing Systems**

- They are embedded in the membranes of endoplasmic reticulum of the liver (hepatic microsomal enzymes).
- They are localized intracellularly , so the common feature of drugs metabolized by these enzymes are their high lipid solubility.
- Less important for polar drugs unless they have an specific transport mechanisms and a greater portion of these drugs are excreted unchanged in urine.
- Cytochrome P_{450}: is the most important enzyme in drug metabolism (hemoprotein). CYP_{450} is affected by drugs (inducers or inhibitors) and age.

- CYP_{450} exists in large numbers of subfamilies ”isoenzymes” with different selectivity e.g.

  CYP_{3A4} :metabolizes 50% of medications e.g. benzodiazepines, Ca-channel blockers…..etc

  CYP_{2D6}: metabolizes 30% of medications e.g. TCA, B-blockers…..etc

  CYP_{1A2}: metabolizes paracetamol, warfarin & caffeine.

- **Microsomal enzymes catalyzes:**
- 1) glucuronide conjugations .
- 2) most of oxidation reactions of drugs while reduction and hydrolysis are catalyzes by both microsomal and non-microsomal enzymes.

- **Phase II reactions:**

  Are conjugation reactions where the metabolite formed by phase1 is conjugated with endogenous constituent such as glucuronic acid, glutathione, sulphate, acetic acid, or methyl group.
- Usually results in pharmacologically inactive and more polar compounds, excreted in urine or bile.
- Catalyzed by conjugating enzyme mainly cytosolic drug-metabolizing enzyme.
- Require energy.

TABLE 4–3 Phase II reactions.

Type of Conjugation	Endogenous Reactant	Transferase (Location)	Types of Substrates	Examples
Glucuronidation	UDP glucuronic acid	UDP glucuronosyltransferase (microsomes)	Phenols, alcohols, carboxylic acids, hydroxylamines, sulfonamides	Nitrophenol, morphine, acetaminophen, diazepam, *N*-hydroxydapsone, sulfathiazole, meprobamate, digitoxin, digoxin
Acetylation	Acetyl-CoA	*N*–Acetyltransferase (cytosol)	Amines	Sulfonamides, isoniazid, clonazepam, dapsone, mescaline
Glutathione conjugation	Glutathione (GSH)	GSH-*S*-transferase (cytosol, microsomes)	Epoxides, arene oxides, nitro groups, hydroxylamines	Acetaminophen, ethacrynic acid, bromobenzene
Glycine conjugation	Glycine	Acyl-CoA glycinetransferase (mitochondria)	Acyl-CoA derivatives of carboxylic acids	Salicylic acid, benzoic acid, nicotinic acid, cinnamic acid, cholic acid, deoxycholic acid
Sulfation	Phosphoadenosyl phosphosulfate	Sulfotransferase (cytosol)	Phenols, alcohols, aromatic amines	Estrone, aniline, phenol, 3-hydroxy-coumarin, acetaminophen, methyldopa
Methylation	*S*-Adenosylmethionine	Transmethylases (cytosol)	Catecholamines, phenols, amines	Dopamine, epinephrine, pyridine, histamine, thiouracil
Water conjugation	Water	Epoxide hydrolase (microsomes) (cytosol)	Arene oxides, *cis*-disubstituted and mono-substituted oxiranes Alkene oxides, fatty acid epoxides	Benzopyrene 7,8-epoxide, styrene 1,2-oxide, carbamazepine epoxide Leukotriene A_4

Factor affecting drug metabolism

1. Enzyme induction:

- The ability of some drugs or chemicals to increase microsomal enzyme activity (↑synthesis or↓ degradation).
- Enzyme induction can results in : a) acceleration of metabolism and usually a decrease in response of the inducer and co-administered drug. b) it may increases or decreases drug toxicity.
- Characters :
- i) the onset of induction occurs after few days and pass-off 2-3 weeks after withdrawal of the inducer

- Examples:

a. Barbiturates(CYP_{3A4},CYP_{2C19}) b. Rifampicin (CYP_{3A4})

c. Phenytoin (CYP_{3A4}) d. Glucocorticoids (CYP_{3A4})

e. Ethanol (CYP_{2E1}) f. carbamazepine (CYP_{3A4})

g. Diet & Environmental factors (smoking (benzpyrene), charcoal broiled meat (CYP_{1A2})

- Enzyme induction→ drug-drug interactions:

  Enzyme inducer + drug → ↓ drug effect

  Phenobarbitone + warfarin → ↓ warfarin effect

- Enzyme induction→ tolerance:

  Auto-induction of some drugs (barbiturates & phenytoin) → pharmacokinetic tolerance.

- Enzyme induction→ drug toxicity:

  Ethanol + paracetamol →↑ risk of hepatotoxicity.

- Therapeutic application of enzyme inducer: Phenytoin ↑steroid metabolism in Cushing's syndrome. Barbiturates are given to mothers before delivery to induce early appearance of enzymes in neonates → ↓ risk of kernicterus disease caused by sulfonamides.

2. Enzyme inhibition:

- The ability of some drugs or chemicals to decease microsomal enzyme activity (↓ synthesis or ↑ degradation).
- Examples:

a. Cimetidine b. Erythromycin or clarithromycin (CYP_{3A4})

c. Quinidine (CYP_{2D6}) d. Chloramphenicol ($CYP_{2B1)}$

e. Ketoconazole (CYP_{3A4}) f. Grapefruit juice (CYP_{3A4})

g. Ciprofloxacin h. Metronidazole

- Therapeutic application of enzyme inhibitor:

a. Captopril & enalapril inhibits ACE
b. Allopurinol Inhibits xanthine oxidase

- Enzyme inhibition→ drug interaction:

  Enzyme inhibitor + drug →↑drug effect (toxicity)
- Terfenadine or Astemazole + grapefruit juice or erythromycin → cardiac arrhythmia. (Terfenadine is replaced by its active metabolites fexofenadine)
- Cimetidine inhibits the metabolism of warfarin or theophylline → bleeding or theophylline toxicity.

3. Gender:

- Sex-dependent variations in drug metabolism have been well documented in rats, where young adult male rats metabolize drugs more faster than mature female rats.
- Similar differences in drug metabolism also exist in human for ethanol, propranolol, benzodiazepines and salicylates.i.e. ↓oxidation of estrogen & benzodiazepine in female relative to male

4. Age:

↓hepatic microsomal enzyme activity in neonates esp. premature babies→ kernicterus (sulfonamides) & gray baby syndrome (chloramphenicol).

- Age-related decrease in hepatic enzyme activity & hepatic blood flow → ↓drug metabolism in elderly.

5. Diseases:

- Liver & cardiac disease ↓drug metabolism. e.g. ↑$t_{1/2}$ of diazepam and chlordiazepoxide in patients with liver cirrhosis and viral hepatitis.
- Hypothyrodism ↑$t_{1/2}$ of digoxin.
- Infections, inflammation & cancer (release of inflammatory mediators, cytokines & nitric oxide) impair drug metabolism.

6. Diet & environmental factor:

- Charcoal broiled food, cruciferous vegetables & cigarette smoking are CYP_{1A2} enzyme inducers
- Grapefruit juice (furanocoumarin) is CYP_{3A4} inhibitor

7. Circadian rhythm:

   The metabolism rate of some drugs varies during the 24 hours of the day, e.g. the metabolism of theophylline & diazepam is faster at night & slower during the day.

- Chronotherapy (chronopharmacology) deals with human circadian rhythms and their impact on pathology and treatment of diseases.

8. Genetic polymorphisms in drug metabolizing enzymes: lead to interindividual variation in drug response.

9. Ethnic differences:

   Chinese differ from Whites in ethanol metabolism, producing higher levels of acetaldehyde.

   (Chinese are more sensitive to ethanol than Whites)

10. Chemical nature, dose & route of administration of the drug:
    overdose of a drug → saturation of some of the metabolic pathways and prevalence of others→ toxicity (e.g. paracetamol).

References

- Lipinncot’s Pharmacology.
- Katzung et al, Basic and clinical pharmacology.