UNIVERSITY OF PUTHISASTRA

PRINCIPALE OF PHARMACOKINETIC

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Academic Year: 2021 - 2022

COURSE OBJECTIVES

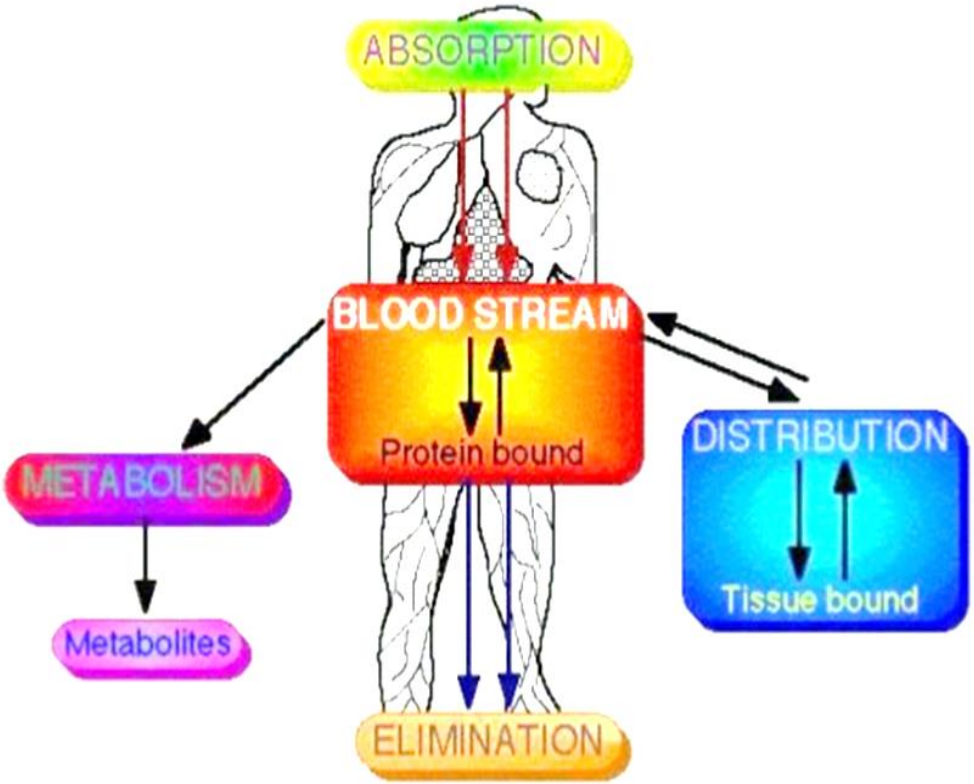
After studying this chapter, student will be able to:

- Understand the concept of pharmacokinetic clearly.
- Describe the main process of **ADME:**
  - **A**bsorption
  - **D**istribution
  - **M**etabolism
  - **E**limination

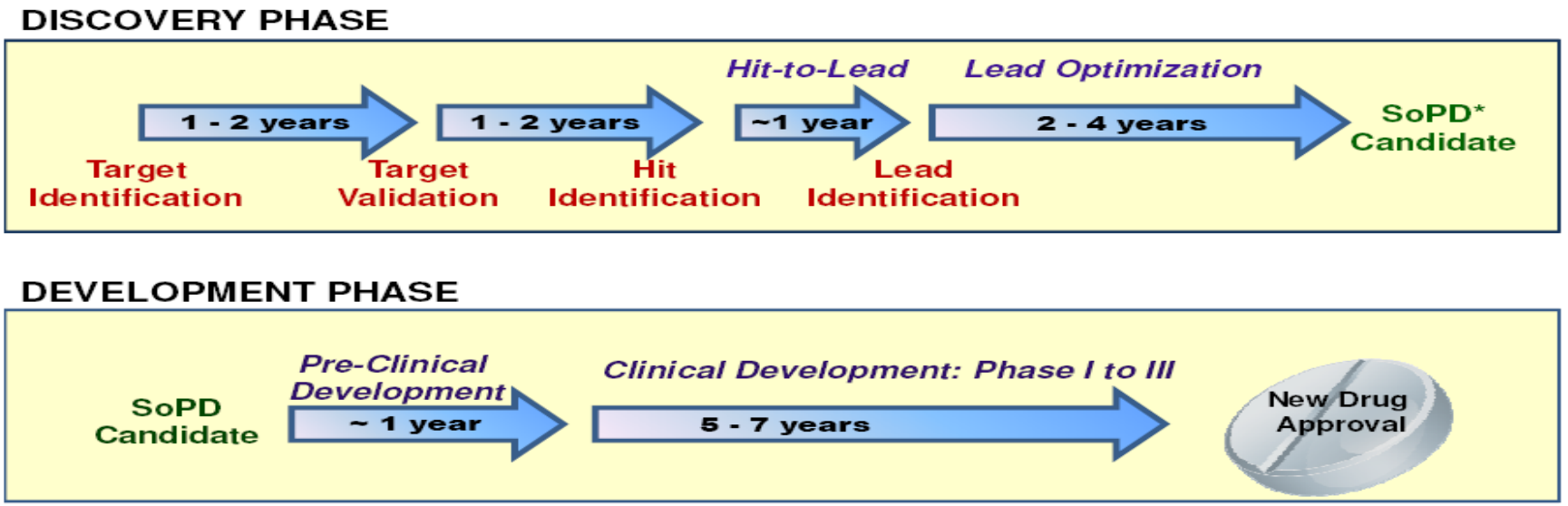
Pharmacokinetics

COURSE OUTLINE

- Definition of Pharmacokinetic
- Absorption
- Distribution
- Metabolism
- Elimination



DRUG RESEARCH & DEVELOPMENT



Drug discovery and development

- 10-15 years to develop a new medicine
- Likelihood of success: 10%
- Cost $800 million – 1 billion dollars (US)

PHARMACOKINETIC

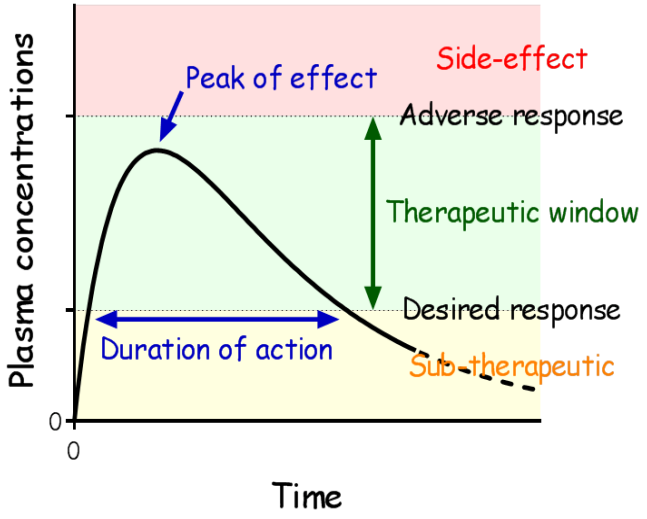
What does it mean?

- Pharmacokinetics is the study of how a drug reaches its target in the body and how it is affected on that journey. **Ex:** Effect of the body on the drug.
- The study of the disposition of a drug. The disposition of a drug includes the processes of **ADME.**
- The fundamental characteristic of pharmacokinetic study is drug removal from the body.
- Pharmacokinetics cannot be studied alone without a similar equal response that is produced by the body upon receiving the drug, called as *PHARMACODYNAMICS*

PHARMACOKINETIC

Why do we study Pharmacokinetic (PK)?

- We administer drugs (dose) because we seek a certain effect (response), but a complex chain of events links the administered dose to the observed response.
- Patients may suffer:
  - Toxic drugs may accumulate
  - Useful drugs may have no benefit because doses are too small to establish therapy.
  - A drug can be rapidly metabolized



Pharmacokinetics

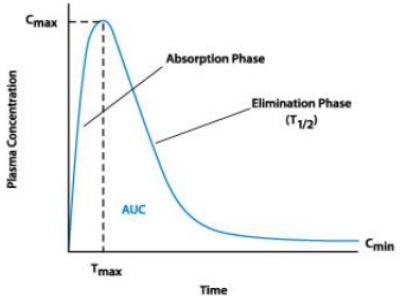
PHARMACOKINETIC

- The processes that characterize PK are summarized in the **ADME** scheme.

  - **Absorption**
  - **Distribution**
  - **Metabolism**
  - **Excretion**

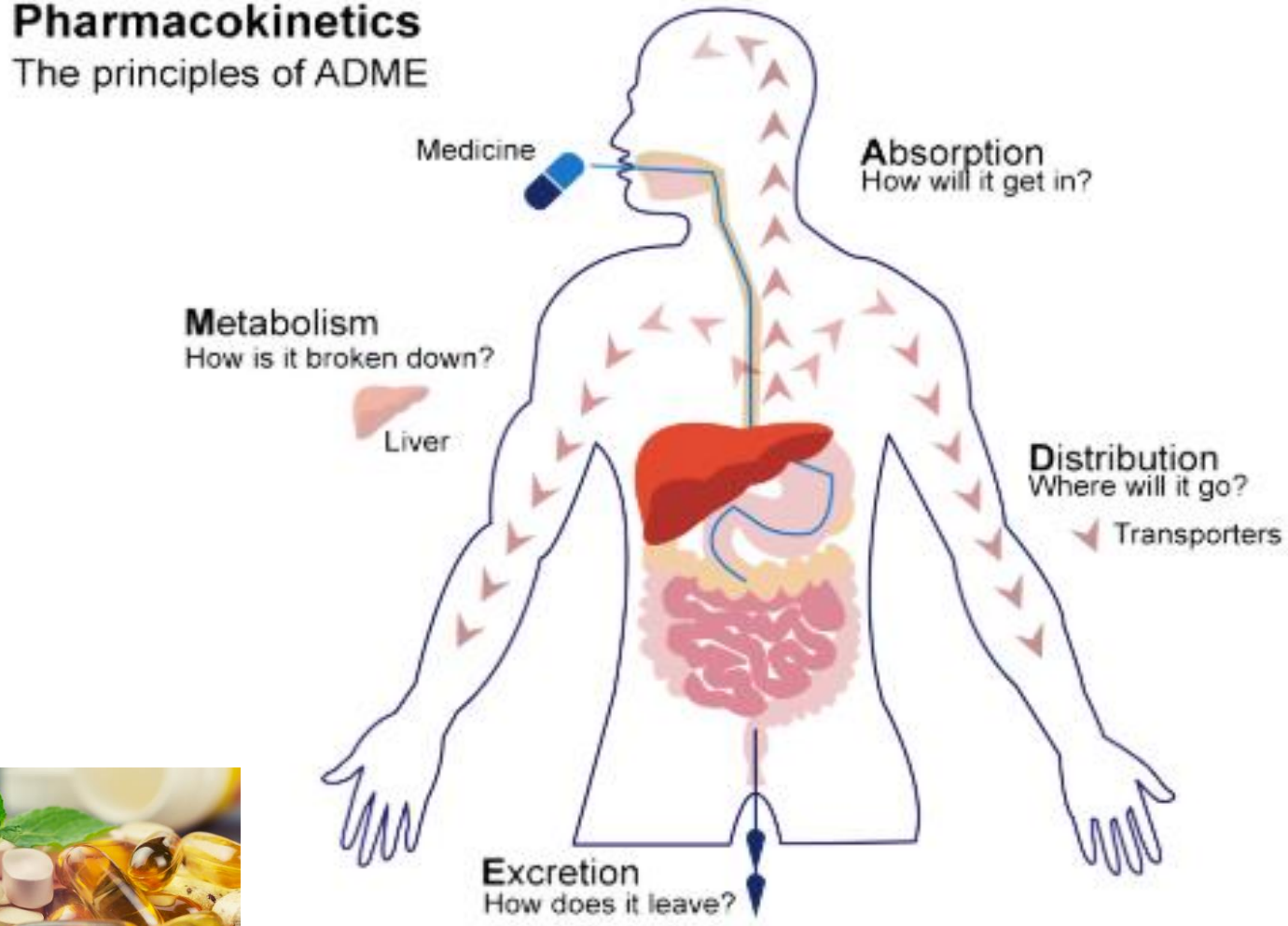
  } Elimination

} Disposition



Pharmacokinetics

PHARMACOKINETIC



Pharmacokinetics

PHARMACOKINETIC

These four features (ADME) include:

- **Absorption:** The rate and extent to which drug is absorbed by the body.
- **Distribution:** The rate and extent to which drug is distributed in the bodily fluids and tissues from distinct absorption sites. This is expressed by volume of distribution **(Vd)**.
- **Metabolism:** The rate and extent to which drug undergo enzymatic action required to break down the drug into its active form or proceed to elimination.
- **Elimination:** It is another important key feature describing rate and extent to which drug is eliminated from the body after attaining peak plasma conc. And producing its action.

ABSORPTION

- Absorption is the entry of drug with blood via the biological membrane from the site/route of administration.
- The process by which drug proceeds from the site of administration to the site of measurement (blood stream) within the body.
- Necessary for the production of a therapeutic effect.
- Most drugs undergo gastrointestinal absorption. This is extent to which drug is absorbed from gut lumen into portal circulation
- **Exception:** IV drug administration

Pharmacokinetics

ABSORPTION

IV Route vs Oral Route

I.V Drug	Oral Drug
Immediately	Delayed
completely	incomplete

Pharmacokinetics

ABSORPTION

The Process of Absorption:

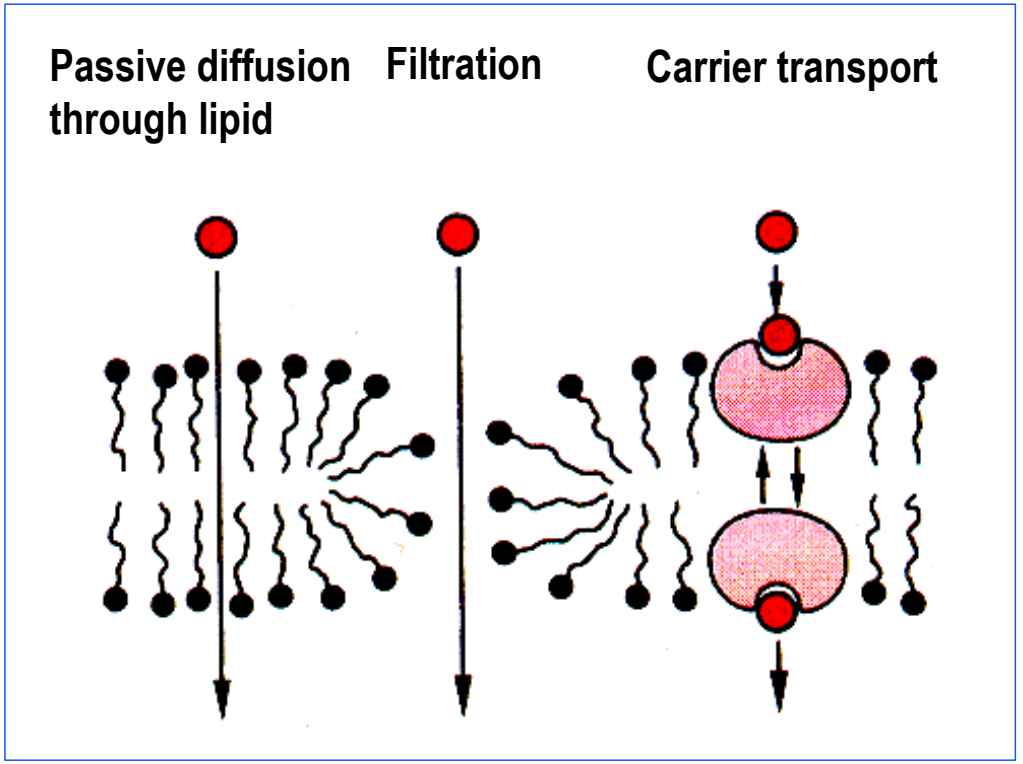
- The most common and preferred method of administration is the oral route.
- Absorption depends on:
  - Hydrophilic/hydrophobic properties, polarity and ionization of the drug
  - Passage through membranes to reach the blood
  - Passive diffusion of lipid soluble species

Pharmacokinetics

ABSORPTION

The Process of Absorption:

- **Passive transport:**
  - *Passive diffusion*
  - *Filtration*
- **Specialized transport:**
  - *Carrier transport*
    - Active transport
    - Facilitated diffusion
  - *Pinocytosis...etc.*



ABSORPTION

Absorption & Ionization

Non-ionised drug

↓

More lipid soluble drug

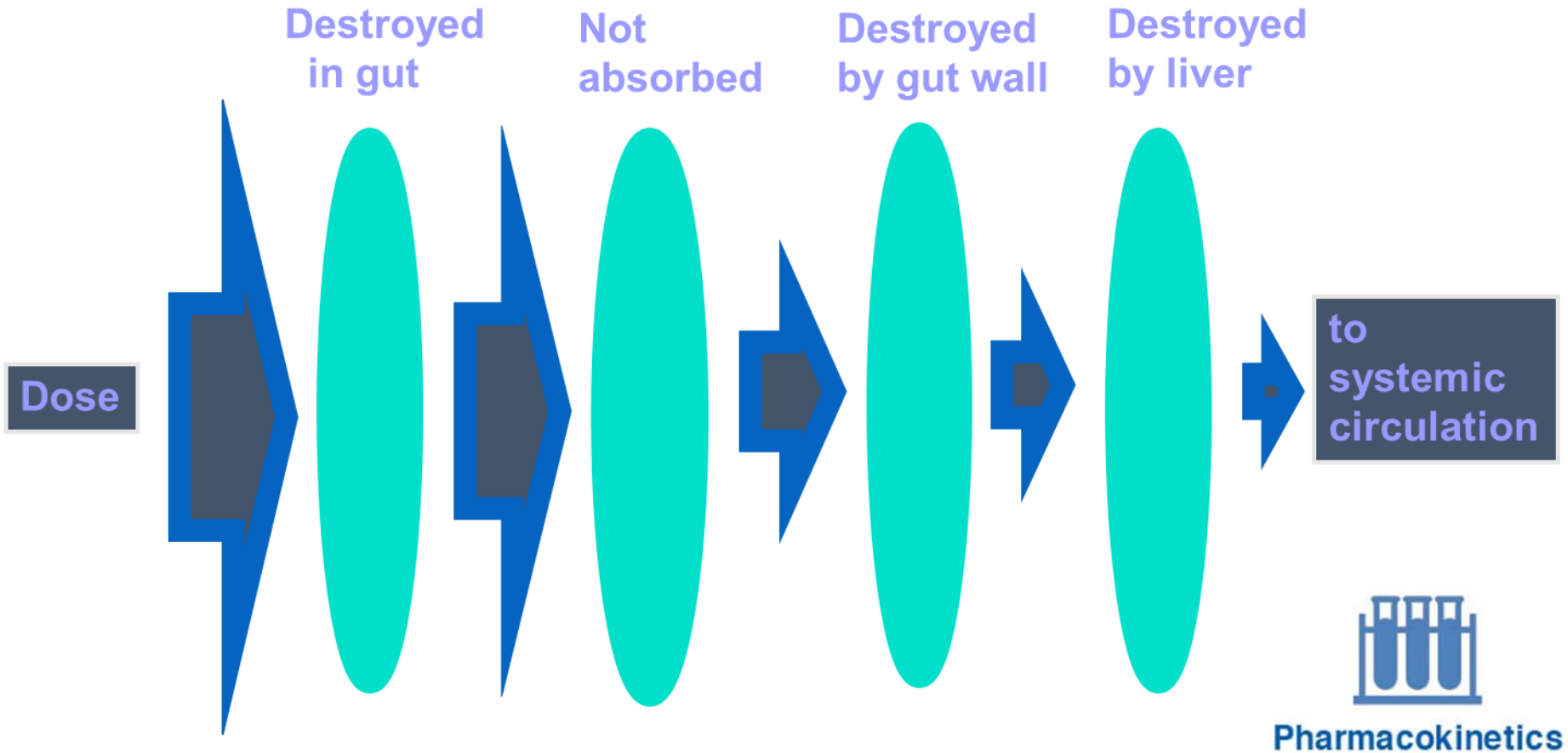
↓

Diffuse across cell membranes more easily

Pharmacokinetics

ABSORPTION

First Pass Metabolism

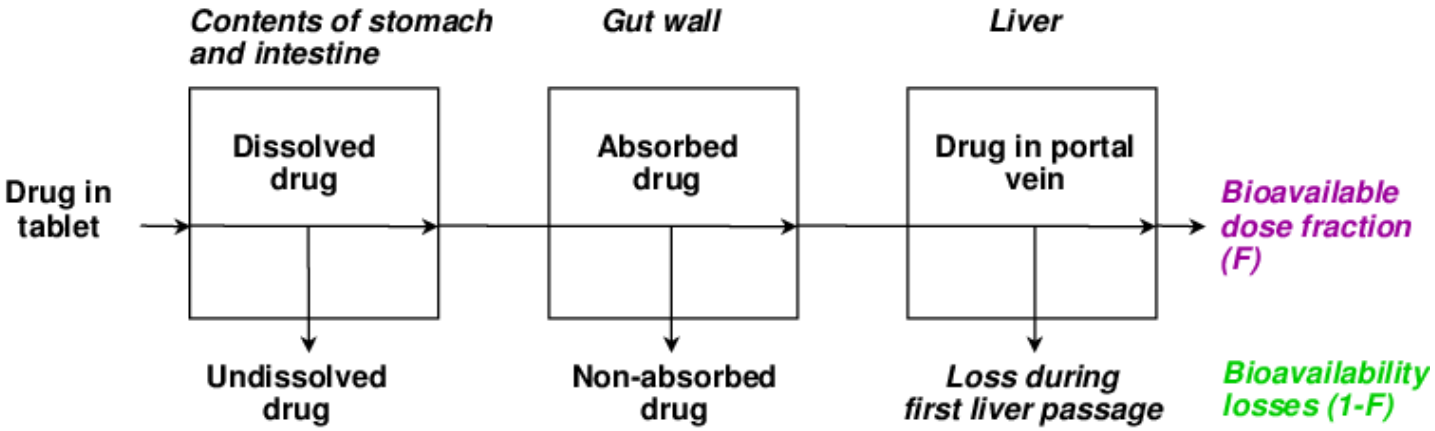


Pharmacokinetics

ABSORPTION

BIOAVAILABILITY

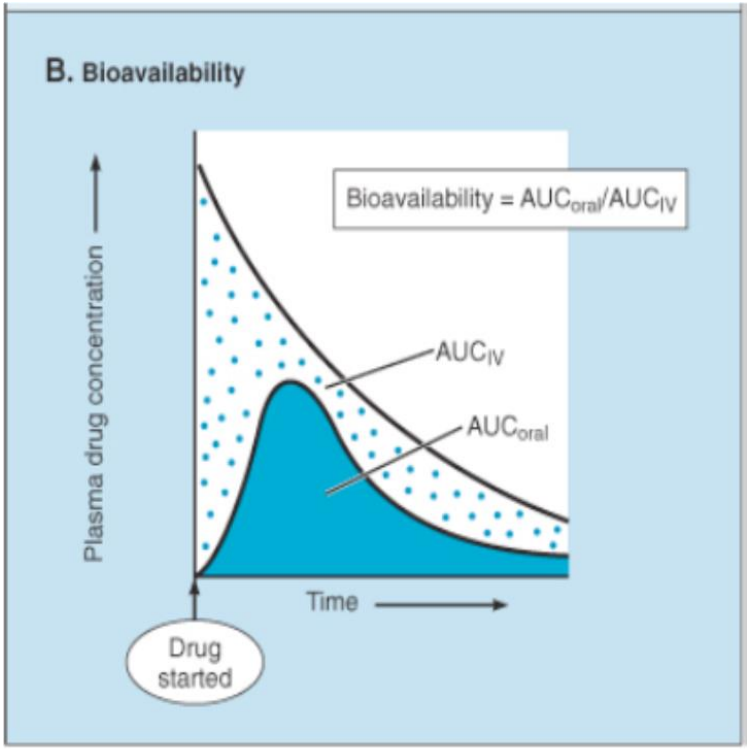
- **Bioavailability:** the fraction of the administered dose reaching the systemic circulation.
- **Significance:** Dosage of drugs with a high hepatic extraction.



ABSORPTION

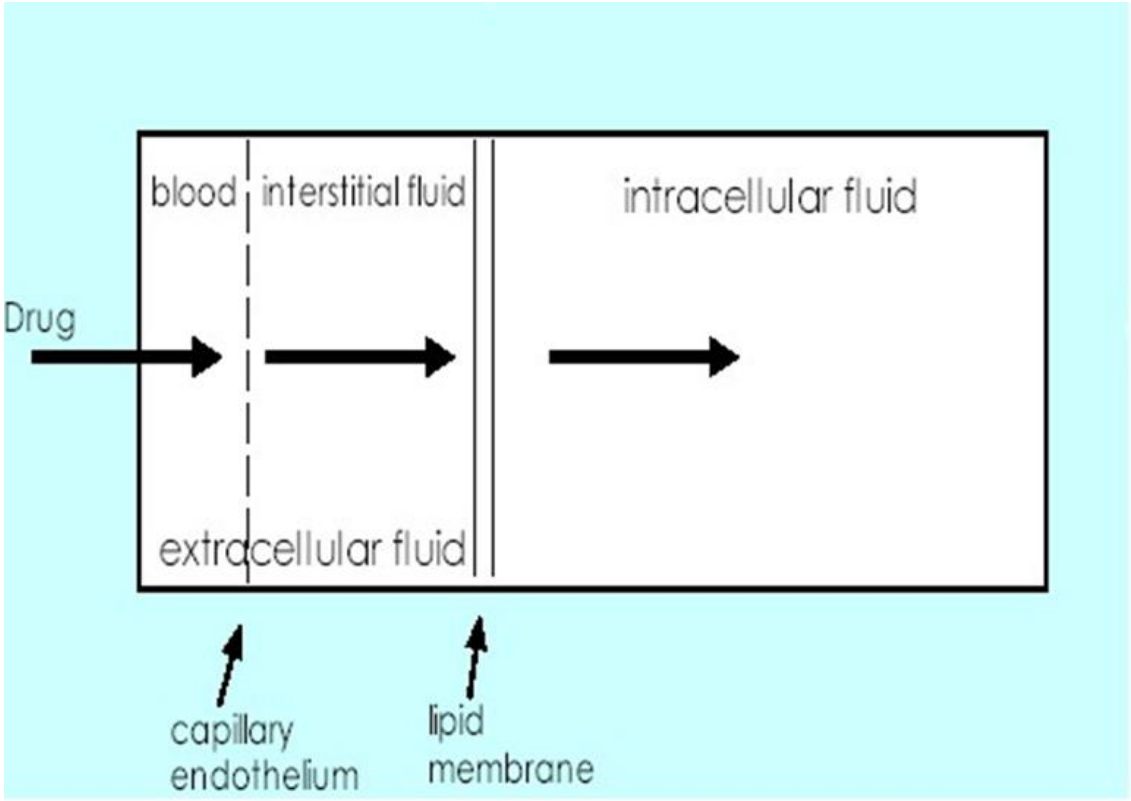
DETERMINATION OF BIOAVAILABILITY

- A drug given by the intravenous route will have an absolute bioavailability of 1 (F=1 or 100% bioavavailable).
- While drugs given by other routes usually have an absolute bioavailability of less than one.
- The absolute bioavailability is the area under curve (AUC) non-intravenous divided by AUC intravenous.



DISTRIBUTION

- **Distribution:** The movement of drug from the blood to and from the tissues.



Pharmacokinetics

DISTRIBUTION

- **Distribution is determine by:**
  - Partitioning across various membranes
  - Binding to tissue components
  - Binding to blood components (RBC, plasma, protein)
  - Physiological volume

Pharmacokinetics

DISTRIBUTION

- All of the fluid in the body (referred to as the total body water), in which a drug can be dissolved, can be roughly divided into three compartments:
  - intravascular (blood plasma found within blood vessels)
  - interstitial/tissue (fluid surrounding cells)
  - intracellular (fluid within cells, i.e. cytosol)

- The distribution of a drug into these compartments is dictated by it's physical and chemical properties

DISTRIBUTION

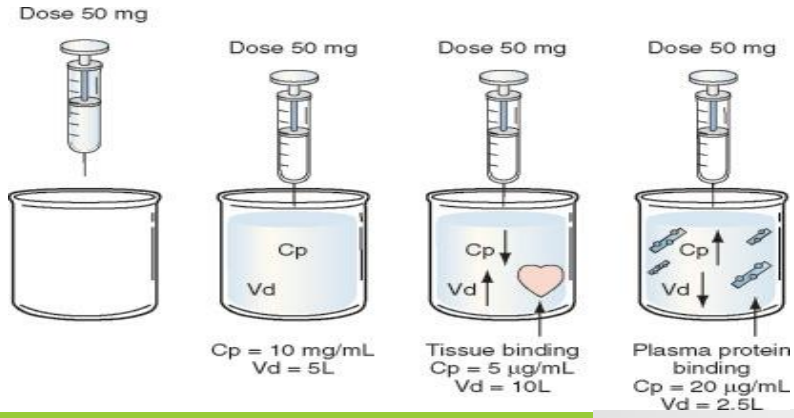
TOTAL BODY WATER

Vascular	Extravascular	Intracellular
3 L	9 L	28 L
4% BW	13% BW	41% BW

DISTRIBUTION

VOLUME OF DISTRIBUTION (Vd)

- Volume of Distribution (V_d) is the amount of drug in body/plasma drug concentration.
- Volume of distribution (V_d) is a theoretic concept that relates the amount of drug in the body **(Dose)** to the concentration **(C)** of drug that is measured (in blood, plasma, and unbound in tissue water)



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DISTRIBUTION

VOLUME OF DISTRIBUTION (Vd)

FORMULA:

The volume of distribution is given by the following equation:

$$V_D = \frac{\text{total amount of drug in the body}}{\text{drug blood concentration}}$$

- In expressing the apparent Vd in terms of % body weight, a 1L volume is assumed to be equal to the weight of 1kg.

- For example, if the V_D is 3500 ml for a subject weighing 70 kg, the V_D expressed as percent of body weight is

$$\frac{3.5\ \text{kg}}{70\ \text{kg}} \times 100 = 5\%\ \text{of body weight}$$

DISTRIBUTION

VOLUME OF DISTRIBUTION (Vd)

Volume of Distribution for Some Drugs:

DRUG Vd (L)

- **Cocaine 140**
- **Clonazepam 210**
- **Amitriptyline 1050**
- **Amiodarone ~5000**

Pharmacokinetics

DISTRIBUTION

VOLUME OF DISTRIBUTION (Vd)

Factors Affecting Drugs Vd:

- **Blood flow** (rate varies widely as function of tissue):

  - Muscle = slow

  - Organs = fast

- **Capillary structure:** Most of capillary are “leaky” and do not impede diffusion of drugs

- **Blood-brain barrier (BBB)** formed by high level of tight junctions between cells (distributed by osmotic)

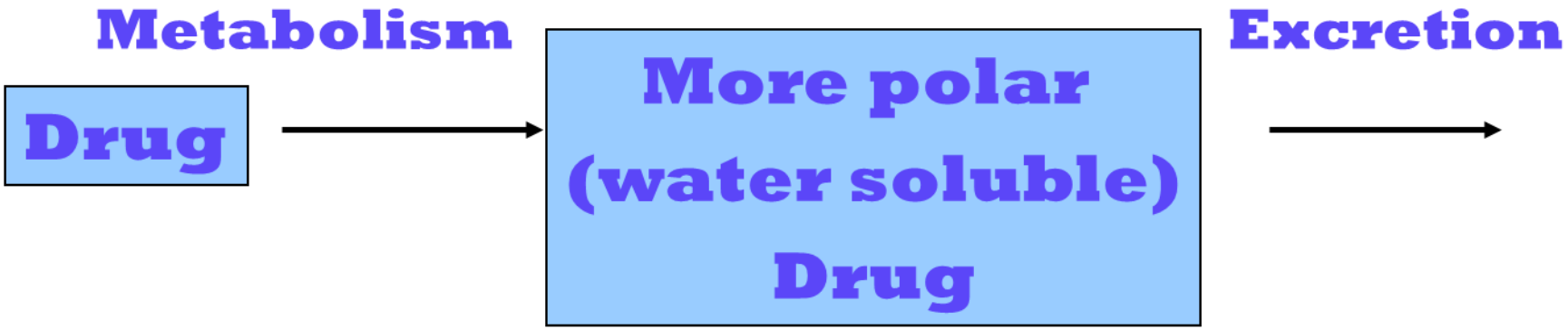
DISTRIBUTION

Plasma Protein Binding

- Many dugs bind to plasma proteins in the blood steam
- Plasma protein binding limits distribution
- A drug that binds protein diffuses less efficiently, than a drug that doesn't.

METABOLISM (BIOTRANSFORMATION)

- Defined as the conversion from one chemical form to another.
- A process by which lipid soluble drugs are converted to water soluble for their excretion
- Enzymes are typically involved in metabolism



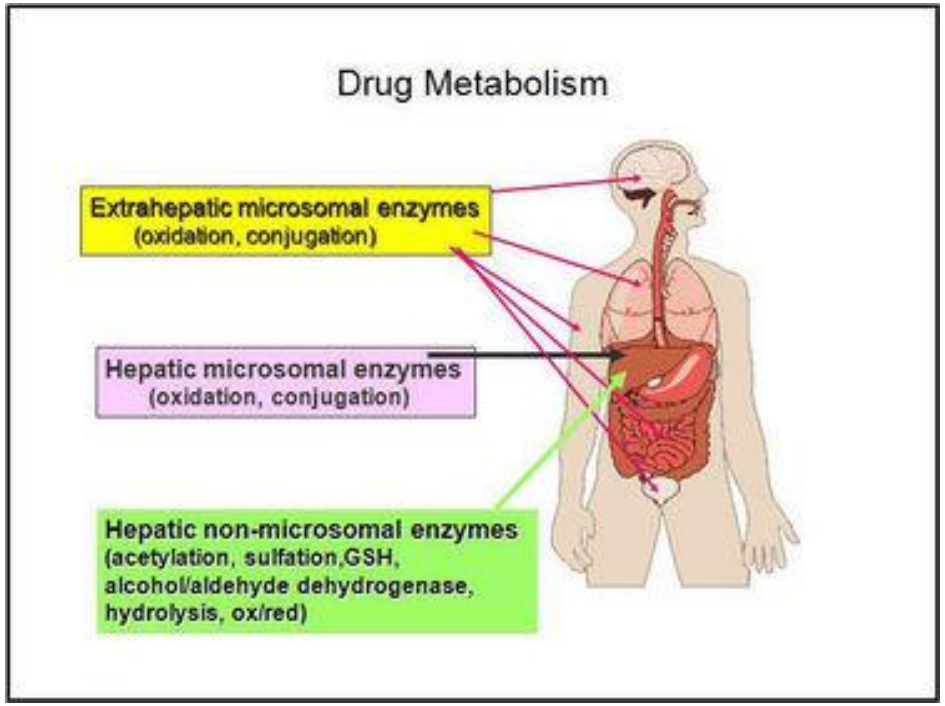
METABOLISM (BIOTRANSFORMATION)

Objective:

- To inactive pharmacological effect
- To enhance pharmacological effect (diazepam to oxazepam)
- To convert prodrugs into active drugs:
  - Aspirin to salicylic acid
  - Codeine to morphine

Sites

- The major site: Liver (microsomal enzyme systemic hepatocyte)
- Secondary organs:
  - Intestines
  - Stomach
  - Blood
  - Brain, - Lung
  - Kidney, - Skin (epithelial cell)



METABOLISM

- From 1898 through to 1910 heroin was marketed as a non-addictive morphine substitute and cough medicine for children. Bayer marketed heroin as a cure for morphine addiction
- Heroin is converted to morphine when metabolized in the liver.


BAYER Pharmaceutical Products

HEROIN—HYDROCHLORIDE

is pre-eminently adapted for the manufacture of cough elixirs, cough balsams, cough drops, cough lozenges, and cough medicines of any kind. Price in 1 oz. packages, $4.85 per ounce; less in larger quantities. The efficient dose being very small (1-48 to 1-24 gr.), it is

The Cheapest Specific for the Relief of Coughs

(In bronchitis, phthisis, whooping cough, etc., etc.)

WRITE FOR LITERATURE TO

FARBENFABRIKEN OF ELBERFELD COMPANY

SELLING AGENTS

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METABOLISM

Phases of Metabolism

❖ *Phase I:*

- Convert parent compound into a more polar (hydrophilic) metabolite by adding or unmasking functional groups. Ex: Oxidation
- Often these metabolite are inactive
- May be sufficiently polar to be excreted readily

METABOLISM

Phases of Metabolism

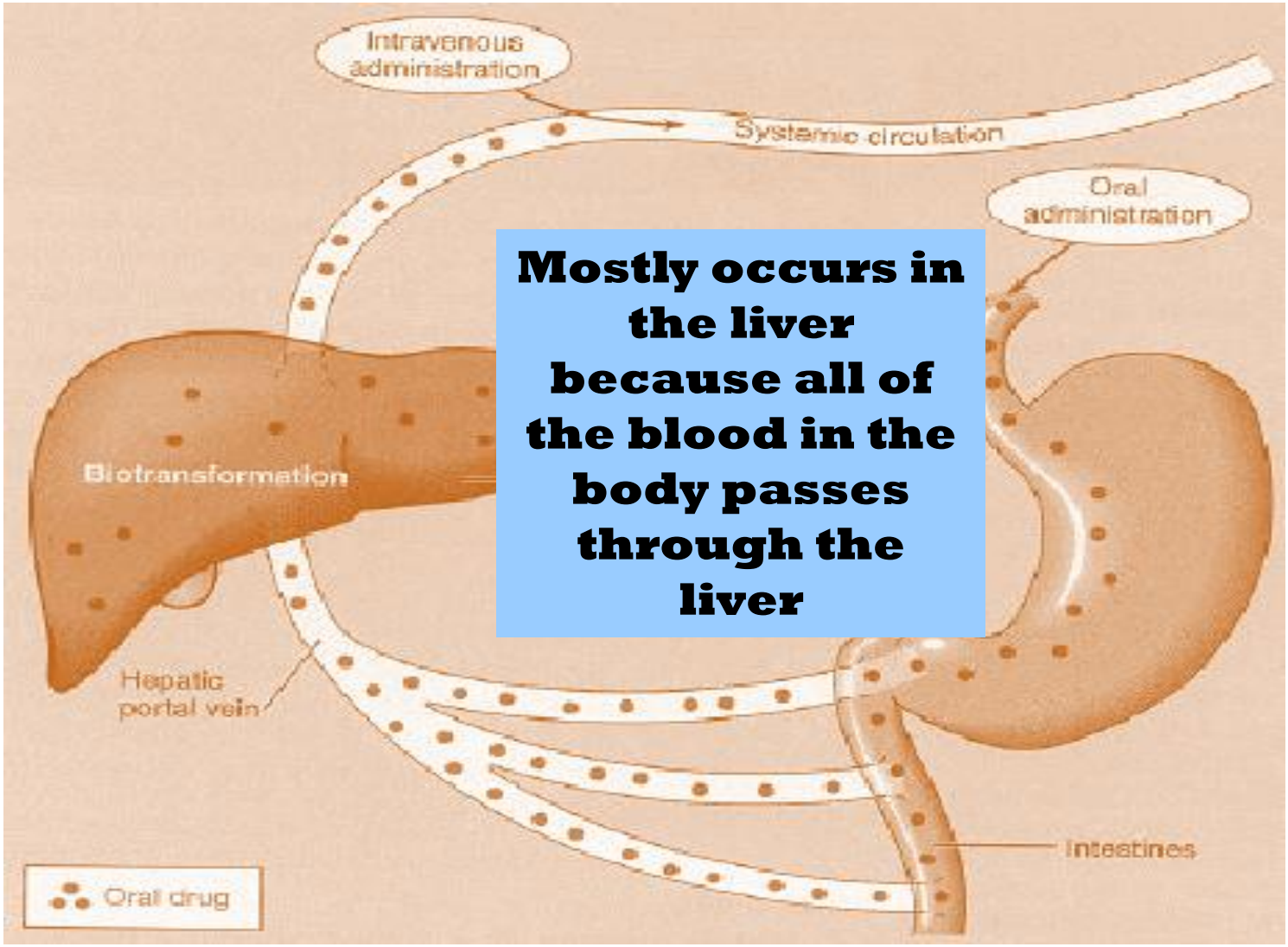
❖ *Phase II:*

- Conjugation with endogenous substrate to further increase aqueous solubility.

- Conjugation with glucuronide, sulfate, acetate, amino acid

Pharmacokinetics

METABOLISM

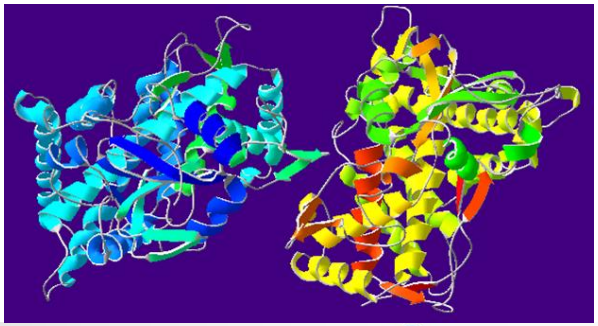


Mostly occurs in the liver because all of the blood in the body passes through the liver

METABOLISM

The Most important Enzymes

- Microsomal Cytochrome P450 (monooxygenase family of enzymes, which oxidize drugs)
- Act on structurally unrelated drugs
- Metabolize the widest range of drugs



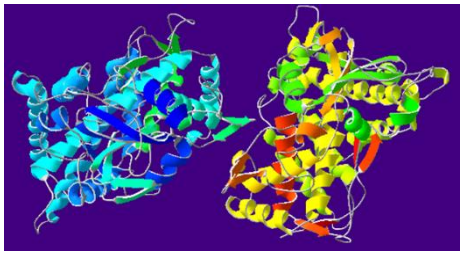
METABOLISM

CYP Family of Enzymes

- Found in liver, small intestine, lung, kidney and placenta.
- Major source of catalytic activity for drug oxidation
- Estimated that 90% or more of human drug oxidation can be attribute to 6 main enzymes:

  1- CYP1A2 2- CYP2D6 3-CYP2C9

  4- CYP2C9 5- CYP2C19 6-CYP3A4



- ***In different people & different population and activity of CYP oxidases differs.***

Pharmacokinetics

METABOLISM

Human Liver P450 Enzymes

There are numerous P450 isoforms of which the following are important:

P450 Isoform	Percentage of human liver (%)
CYP1A2	15
CYP2A6	4
CYP2B6	1
CYP2C9	20
CYP2D6	5
CYP2E1	10
CYP3A4	30

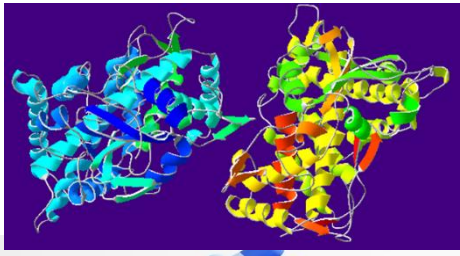
CYP3A4 → account for >50% of all prescribed metabolism

Pharmacokinetics

METABOLISM

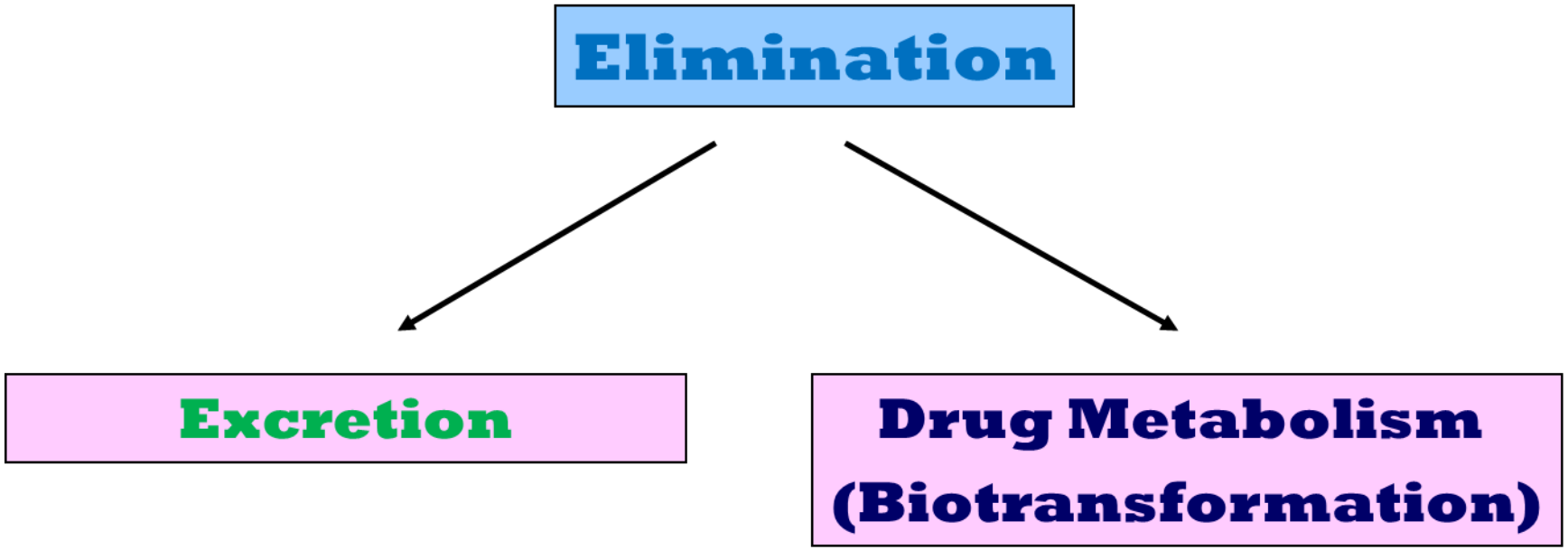
Inhibitor and Inducer of Microsomal Enzymes

- **Inhibitors:** Cimetidine prolongs action of drugs or inhibits action of those biotransformed to active agents (pro-drugs)
- **Inducers:** Barbiturates, carbamazepine shorten action of drugs or increase effects of those biotransformed to active agents.
- **Blockers:** Acting on non-microsomal enzymes (MAOI, Anticholinesterase drugs)



ELIMINATION

- The irreversible removal of the parent drugs from the body.



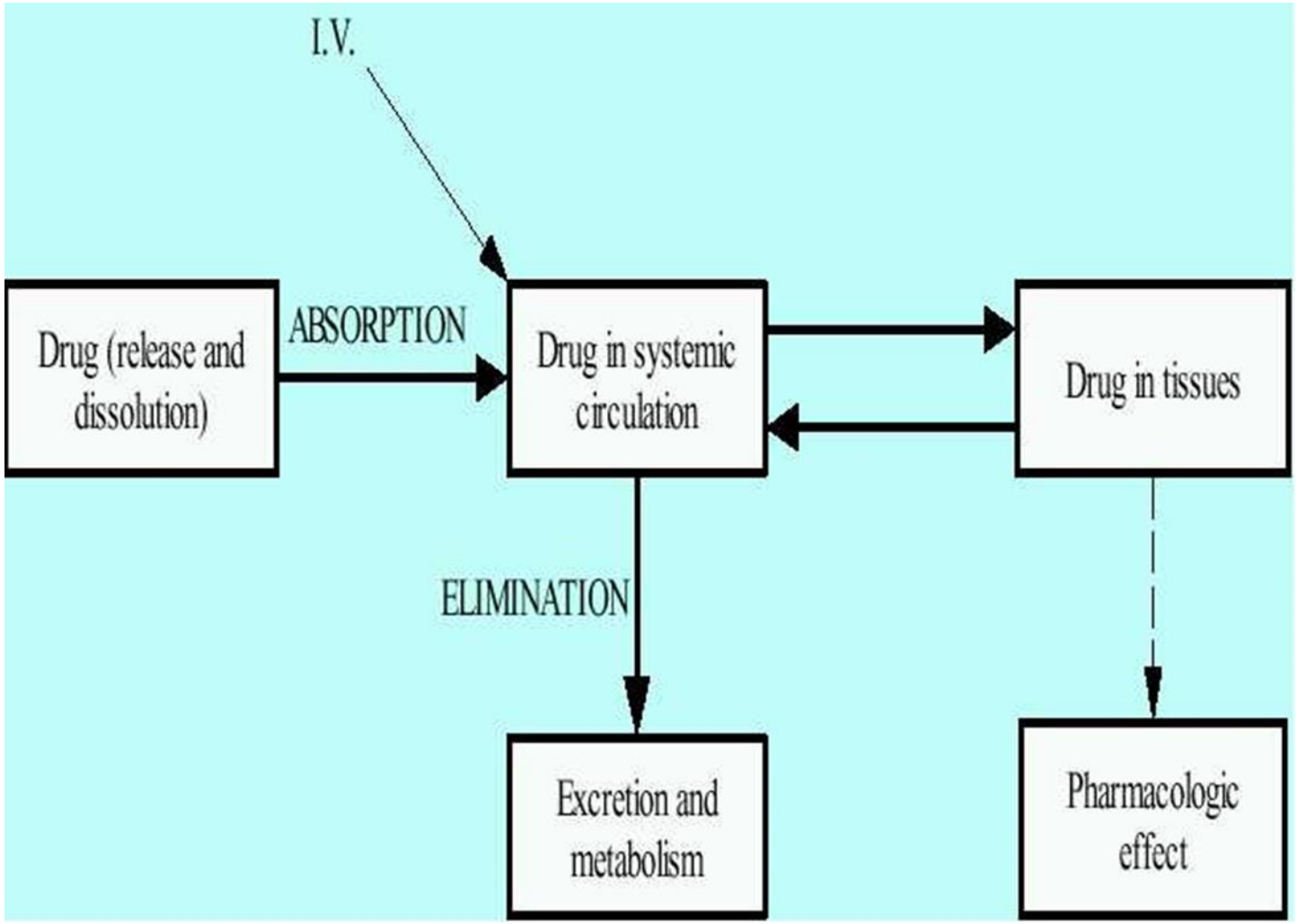
Pharmacokinetics

EXCRETION

- The main process that body eliminates “unwanted” substance.
- Most common route-biliary or renal
- Other routes – lung (through exhalation), skin (through perspiration)
- Lipophilic drugs may require several metabolism steps before they are excreted.

Pharmacokinetics

EXCRETION



Pharmacokinetics

EXCRETION

CLEARANCE

- **Definition:** Clearance may be define as the rate of urinary exertion divided by the average concentration of excreted substance in the plasma.
- Clearance can be calculated as:

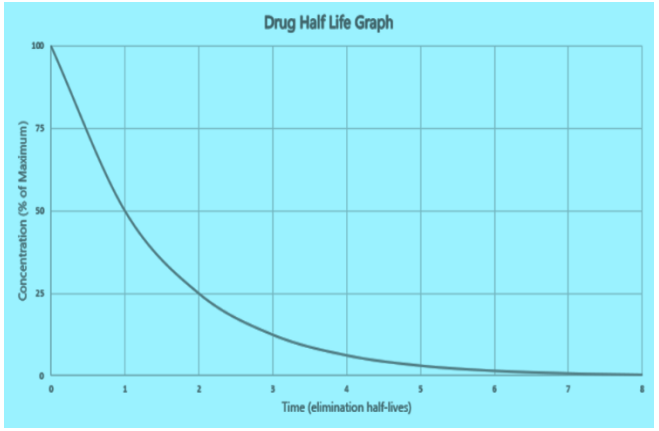
$$Cl = \frac{\text{Rate of elimination}}{C},$$ where C is plasma concentration..

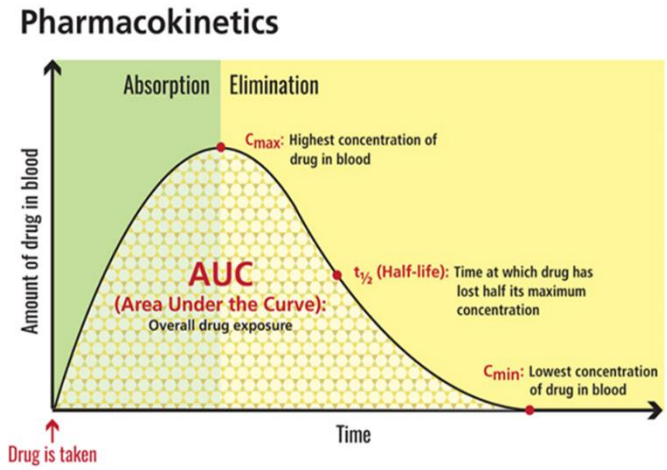
Pharmacokinetics

EXCRETION

HALF-LIFE OF A DRUG

- It is defined as the time it takes for the concentration of the drug in the plasma or the total amount in the body to be reduced by 50%. In other words, after one half-life, the concentration of the drug in the body will be half of the starting.
- In general, the effect of the drug is considered to have a negligible therapeutic effect after 4 half-lives, that is, when only 6.25% of the original dose remains in the body.





EXCRETION

HALF-LIFE OF A DRUG

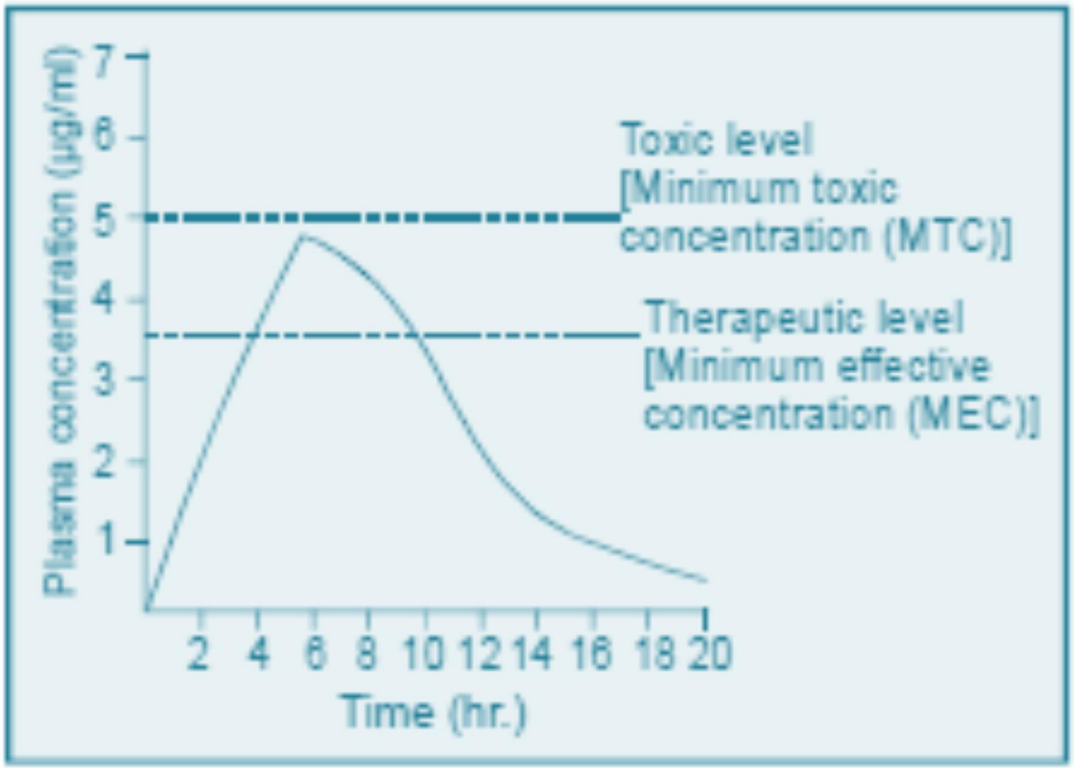


Fig. 1.4.4: Drug concentration in plasma vs time curve of drug administered orally.

EXCRETION

HALF-LIFE OF A DRUG

Example:

- Taking a 100 mg dose of an intravenous drug with a half-life of 15 minutes as an example, the following is true:
  - 15 minutes after the drug administration, 50 mg of the drug remains in the body.
  - 30 minutes after the drug administration, 25 mg of the drug remains in the body.
  - 45 minutes after the drug administration, 12.5 mg of the drug remains in the body.
  - 1 hour after the drug administration, 6.25 mg of the drug remains in the body.

EXCRETION

HALF-LIFE OF A DRUG

FORMULA:

$$t\frac{1}{2} = \frac{0.693 \times Vd}{CL}$$

Logarithm of 2

Volume of distribution

Clearance

Half-life

Pharmacokinetics

EXCRETION

HALF-LIFE OF A DRUG

FORMULA:

The elimination half life ($t_{1/2}$) from elimination phase is

$$t_{1/2} = \frac{\text{Log } 2}{k}$$

k = Elimination rate constant (total amount of drug in the body removed per unit time).

$$k = \frac{CL}{V}$$

Clearance is the measure of the body's ability to eliminate a drug.

$$\text{Therefore } t_{1/2} = 0.693 \times \frac{V}{CL}$$

And, having known the biological half-life ($t_{1/2}$), the elimination rate constant (kE) can be calculated

$$kE = 0.693 / t_{1/2}$$

Pharmacokinetics

DRUG INTERACTON

Definition

- Drug interactions may be defined as an alteration in duration and/or onset of action of the pharmacokinetic and/or pharmacodynamics of one drug produced by another drug.

General Aspects

- The multiple drug therapy produced a combined effect, which may be antagonistic or synergistic in nature.
- The drug may interact with the another drug at any point during their absorption, distribution, metabolism and excretion.

DRUG INTERACTON

i.	**Interaction due to the formation of chelate complex**		
	Antacids	Tetracycline, isoniazid, atenolol, chlorpromazine penicillamine, digoxin, ranitidine	Decreased absorption
	Antacids	Bishydroxycoumarin	Increased absorption
	Cholestyramine	Warfarin, phenylbutazone, digitoxin, cephalexin and chlorothiazide	Decreased absorption
	Activated charcoal	Tolbutamide, theophylline, phenytoin, digoxin, carbamazepine, valproate	Decreased absorption
	Activated charcoal	Piroxicam, theophylline & phenobarbital	Increased absorption
	Mineral oils	Fat soluble vitamins	Decreased absorption
	Iron preparation	Methyldopa	Decreased absorption
ii.	**Interaction due to the alteration in gastric pH**		
	Antacids	Cimetidine	Decreased absorption
	Cimetidine	Tetracycline	Decreased absorption
iii.	**Interaction due to increase in gastric motility**		
	Metoclopramide	Digoxin, cimetidine	Decreased absorption
	Metoclopramide	Chlorothiazide, acetaminophen	Increased rate of absorption
iv.	**Interaction due to decrease in gastric motility**		
	Antacids	Isoniazid, phenytoin, propranolol and benzodiazepines	Decreased rate of absorption
	Amitriptyline	Bishydroxycoumarin	Increased absorption
v.	**Interaction due to alteration of gut**		
	Cimetidine	Lidocaine, propranolol, verapamil, imipramine	Increased absorption

Drug affected	Drug interacting	Effect
Gastrointestinal system		
Carbenoxolone	Amiloride, spironolactone	Inhibition of ulcer healing.
Cimetidine	Antacids	Reduced absorption if taken simultaneously.
Metoclopramide	Anticholinergic drugs such as atropine, benzhexol, propantheline, narcotic analgesics	Antagonism – they have opposing effects on gastrointestinal activity.
Cardiovascular system		
Antiarrhythmic drugs	Any combination of two or more	Increased myocardial depression.
Disopyramide	Potassium salts, amiodarone	Hyperkalaemia, increased risk of ventricular arrhythmias due to prolongation of QT interval.

Drug displaced	Displacing agent
Coumarin	Diazoxide, ethacrynic acid, phenylbutazone, NSAIDs
Tolbutamide	Dicumarol, phenylbutazone
Phenytoin	Tolbutamide, NSAIDs
Diazepam	Heparin

NSAIDs = Nonsteroidal antiinflammatory drugs.

Drug (inducing part)	Drug induced
Chloral hydrate	Bishydroxycoumarin
Phenobarbital	Bishydroxycoumarin, digitoxin, phenylbutazone, phenytoin
Phenytoin	Carbamazepine, cimetidine, theophylline, oral

Drug causing inhibition	Drug inhibited
Bishydroxycoumarin	Tolbutamide
Disulfiram	Phenytoin, theophylline, warfarin
Isoniazid	Phenytoin
Phenylbutazone	Tolbutamide, phenytoin

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Any questions?