PHARMACOKINETICS

Session workouts:-

i) Definition

ii) To explain the 4 steps of pharmacokinetics

iii) Describe the mechanisms of movement of drugs a cross the biological cell membrane

iv) To enumerate Factors that influence the rate and extent of absorption of a drug

Definition;

Refers to the study of absorption, distribution, metabolism (biotransformation) and excretion of drugs, i.e. the movement of drugs into, within or out of the body. Or simply (what the body does to the drug).

DRUGS ABSORPTION

- Drug absorption is the movement of a drug from the site of administration into the fluid of the body that will carry it to the site(s) of action (target organ). For a drug to reach its site of action, it must pass through various biological cell membranes depending on the route of administration.

The mechanisms of movement of drugs a cross the biological cell membrane

There are a number of mechanisms of drug absorption:-

- Passive (simple) diffusion of water and lipid soluble drugs
- Pinocytosis and phagocytosis
- Active transport
- Facilitated diffusion
- Passive filtration
- Passage via gap junction

- **Passive diffusion:** is movement of particles from an area of high concentration to an area of low concentration. (Good for small particles).
- **Facilitated diffusion**: is passive diffusion that uses special carrier molecules (Good for big molecules), occurs by the **carrier proteins.**

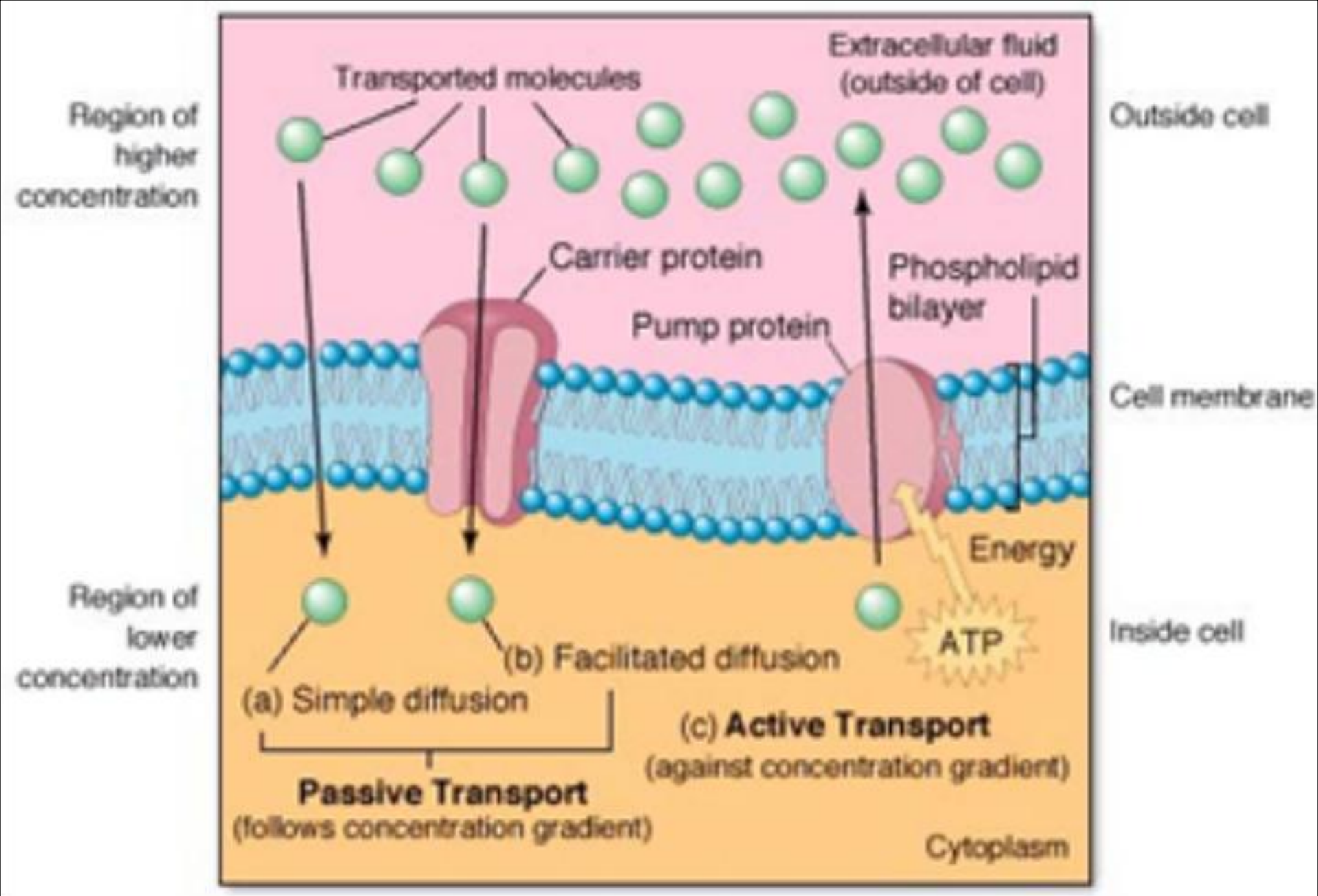
  NB, when the rate of diffusion is proportional to the concentration of the drug at the administered area is referred to as first order kinetics

ZERO ORDER KINETICS

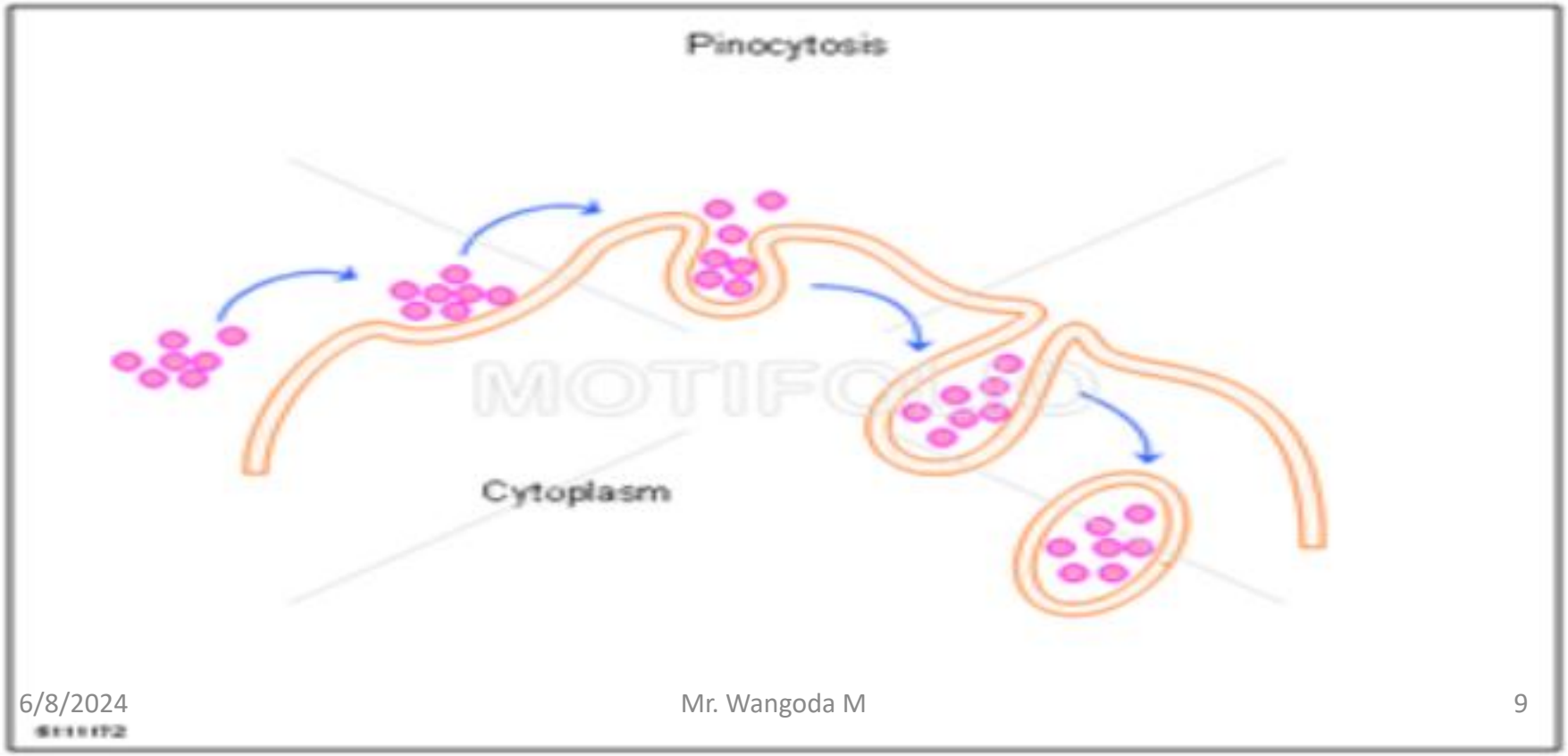
- Is when the absorption occurs independently from the concentration of the drug. .Concentration has no effect on the diffusion rate of the drug, and the absorption occurs at a constant speed.
- No energy is required

Mechanism of mov't cont'

- **Active transport**: involves movement of molecules against the concentration gradient from areas of low concentration of molecules to an area of high concentration of molecules.
- It involves both a carrier molecule and energy (good for accumulation of a drug within a part of the body)


Region of higher concentration
Region of lower concentration
Transported molecules
Extracellular fluid (outside of cell)
Outside cell
Carrier protein
Pump protein
Phospholipid bilayer
Cell membrane
Energy
ATP
Inside cell
(a) Simple diffusion
(b) Facilitated diffusion
(c) Active Transport
(against concentration gradient)
Passive Transport
(follows concentration gradient)
Cytoplasm

- **Pinocytosis/phargocytosis:** Molecules are physically taken into the cell by engulfing.
- **Pinocytosis** is engulfing liquids
- **Phagocytosis** is engulfing solid particles.



Factors that influence the rate and extent of absorption of a drug;

i) **Disintegration and dissolution**: The drugs taken orally should break up into individual particles to be absorbed; then has to dissolve in the gastrointestinal fluids, and in case of a drug given subcutaneously or intramuscularly, the drug molecules have to dissolve in tissue fluid.

ii) **Formulation of drug**: substances added to a drug like starch and lactose may sometimes interfere with absorption.

iii) **Particles size**: some drugs are better absorbed when they are of small particles, e.g. corticosteroids, griseofulvin, digoxin, Aspirin and tolbutamide. For some drugs that must act on the gut and absorption is not desired, the particle size should be kept large.

iv) Solubility of the drug: lipid soluble drugs are absorbed faster and better by dissolving in the phospholipids.

v) PH levels: ionized drugs are poorly absorbed while unionized drugs are lipid soluble and are well absorbed. Acidic drugs remain unionized in acidic medium of the stomach and are rapidly absorbed, e.g. aspirin and barbiturates. Basic drugs are unionized when they reach the alkaline medium of the intestine, e.g. pethidine and ephedrine. Strong acids and bases are highly ionized and therefore poorly absorbed, e.g. heparin and streptomycin

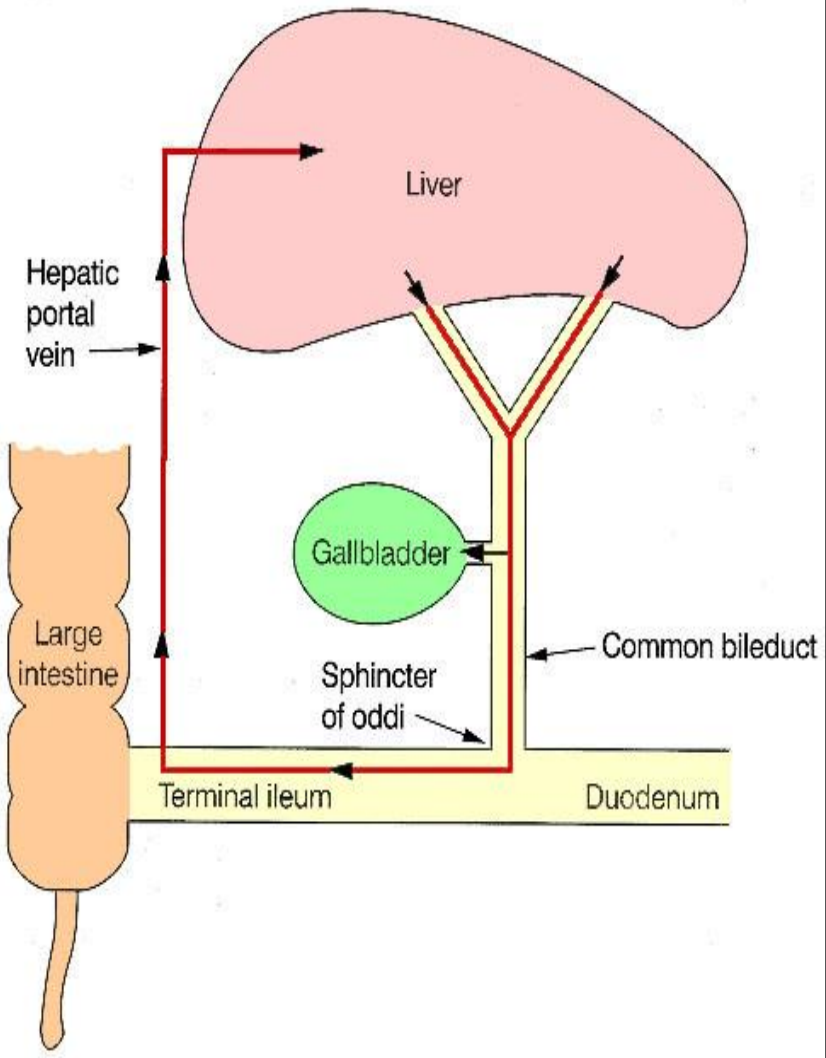
vi) Total surface area available for absorption: the intestines is rich in microvilli, this offers a large surface for absorption.

vii) Contact time at absorption site: if the drug moves through the gastrointestinal tract very quickly, as in severe diarrhea, it will not be well absorbed or anything that delays the transport of drugs from the stomach to intestines delays the rate of absorption of the drug.

viii) Presence of food: delays gastric emptying, dilutes the drug, delay absorption, drugs may form complexes with food constituents and such complexes are poorly absorbed, e.g. tetracyclines chelate calcium present in food and certain drugs like ampicillin and rifampicin as will absorbed only on the empty stomach.

First Pass Effect

- Drugs that are absorbed via the GIT are circulated to the liver first via the hepatic portal vein
- Liver then acts as a filter
- Only part of the drug is circulated systemically
- The combination of processes is termed the ‘First Pass’ effect



ix) Metabolism: some drugs may be degraded in the gut, e.g. nitroglycerine, insulin; such drugs should be given using alternative routes.

x) Diseases: diseases of the gut like malabsorption and achlorhydria result in reduced absorption of drugs.

xi) Blood flow to the absorption site: blood flow to the intestines is much greater than blood flow to the stomach. Thus absorption from the small intestines is much favoured over that from the stomach.

‘’NB: ROUTES OF DRUG ADMINISTRATION WILL BE COVERED BY MR OLUK”

DRUG DISTRIBUTION

STDs should be able to:-

i)Define the term drug distribution

ii) Name various sites where drugs are distributed to

iii) Mention the Factors that affect distribution of drugs

iv) Describe the Properties of plasma protein-drug binding

Definition:

Drug distribution is the process by which a drug leaves the blood stream and enters the extracellular fluids and tissues.

- Once drugs have been absorbed from various sites of extravascular administration they are distributed to: Total plasma compartment, extravascular fluid, total body water, intravascular and interstitial fluid, other sites, e.g. the fetus may take up some drugs, others may be stored in the body fat, e.g. thiopental

Factors affecting distribution of drugs:

- **Binding of drugs to plasma proteins**: most drugs bind to plasma proteins; Acidic drugs mainly bind to albumin and basic drugs bind to alpha-acid glycoprotein. Binding increases the absorption and reduces the distribution, metabolism and excretion. The free or unbound fraction of the drug is the only form available for action, metabolism and excretion, while the protein bound form serves as reservoir. Thus protein binding prolongs the duration of action of the drugs.
- **Membrane permeability**
- **Blood perfusion rate**

- **Affinity of drug to tissue components**
- **Weight considerations**
- **Barriers to drug distribution eg Brain-blood barrier, Placenta barrier**
- **Binding to Plasma Proteins:**

  The most important protein that binds the drugs in blood is albumin for most of the drugs.

Especially, the acidic drugs (salicylates, vitamin C, sulfonamides, barbiturates, penicillin, tetracyclines, warfarin, probenesid etc.) are bound to albumin.

Basic drugs (streptomycin, chloramphenicol, digitoxin, coumarin etc.) are bound to alpha-1 and alpha-2 acid glycoproteins, globulins, and alpha and beta lipoproteins.

Properties of plasma protein-drug binding

Saturable:

One plasma protein can bind a limited number of drug molecule

Non-selective:

More than one kind of drug which has different chemical structures or pharmacological effects can be bound to the space on plasma protein

Reversible:

The bonds between the drug and plasma protein are weak bonds like hydrogen or ionic bonds.

METABOLISM OF DRUGS

STDs should be able to:-

i) Define the various terms involved with drug metabolism

ii) State the Importance of metabolism

iii) Name the enzymes inolved in drug metabo.lism

iv) Explain the Types of bio-transformations

v) Explain the Clinical importance of microsomal enzyme induction

vi) Enumerate the Factors that affect the Biotransformation of drugs

vii) Explain the term Hepatic Clearance

Drug metabolism or biotransformation is the process of biochemical alteration of the drug in the body and the products formed after these reactions are called **“drug metabolites”**.

The metabolites that are formed after biotransformation are generally more polar, more easily ionized compounds compared to the main (original) drug. So, these metabolites can be excreted from the body easily.

The most important organ of metabolism is the liver. Also some drugs are metabolized by the kidneys, gut mucosa, lungs, blood, placenta and skin

Some drugs which don't have any activity in vitro, may gain activity after their biotransformation in the body. These types of drugs are called "**pro-drug**" or "**inactive precursor**".

Drug examples that gain activity after biotransformation (pro-drugs

Drug examples that gain activity after biotransformation (pro-drugs

PRO-DRUG	EFFECTIVE METABOLITE
• Chloral hydrate	• Trichloroethanol
• Cortisone	• Hydrocortisone
• Enalapril	• Enalaprilate
• Lovastatin	• Lovastatin acid
• Clofibrate	• Clofibric acid
• L-DOPA	• Dopamine

Drug examples that is transformed to less active compounds after biotransformation

DRUG	LESS ACTIVE METABOLITE
• Aspirin	• Salicylic acid
• Meperidine	• Normeperidine
• Lidocaine	• De-ethyl lidocaine (dealkylated)

Importance of metabolism

- Formation of more polar compounds that are water soluble and are easily eliminated
- Detoxification
- Prodrug activation. Prodrug is an inactive drug which gets converted into an active form in the body. Eg ?

Enzymes responsible for metabolism of drugs

- Microsomal enzymes . these are present in the smooth endoplasmic reticulum of the liver, kidney and GIT eg glucuronyl transferase, dehydrogenase, hydroxylase and cytochrome P450.
- Non-microsomal enzymes: present in the cytoplasm,& mitochondria of different organs eg esterases, amidases and hydrolase

Types of biotransformations

- Chemical reactions of biotransformation can take place in two phases, namely:
- Phase I: (Non-synthetic reaction)
- Phase II: (synthetic reactions)or (conjugation rxns)
- **Phase I reactions** convert the drug to a more polar metabolite by oxidation, reduction or hydrolysis.
- **Oxidation reactions** are the most important metabolizing reactions, mostly catalyzed by mono-oxygenases present in the liver. If the metabolite is not sufficiently water soluble to be excreted, it undergoes phase II reactions

- **Phase II reactions**: in phase II reaction water soluble substances present in the body like; glucuronic acid, glutathione or amino acid combine with the drug (phase II metabolite) to form a highly polar compound which is inactive and gets readily by the kidney. Large molecules are excreted through bile.
- Glucuronidation is the most common phase II reaction, others are sulfate, conjugation, acetylation and methylation reactions.

- **Enzyme induction**: some drugs increase the synthesis of certain microsomal enzymes (CYP). This process speeds the metabolism of the inducing drug itself and other drugs metabolized by microsomal enzymes.

Clinical importance of microsomal enzyme induction

- **Drug interactions**: enzyme induction may be responsible for drug interactions which may result in therapeutic failure of some drugs due to reduced duration of action, e.g. failure of oral contraceptives in patients taking rifampicin.
- **Enzyme inhibition (inhibitors)** some enzymes inhibit microsomal enzyme activity; drugs like cimetidine and ketaconazole bind to these enzymes and competitively inhibit the metabolism of substances like testosterone., chloramphenical, erythromycin, cimetidine, kateconazole, ciprofloxacin and verapamil

Factors That Affect The Biotransformation of Drugs

- Induction or inhibition of microsomal enzymes
- Genetic differences
- Age
- Gender
- Liver diseases
- Environmental factors

NB ,In newborns cytochrome P450 enzymes and glucuronosyltransferases are not sufficient.

So, biotransformation of some drugs (diazepam, digoxin, acetaminophen, theophylline etc…) is very slow in newborns.

Hepatic Clearance

- It can be described as “the volume of plasma cleared from the drug via metabolism in liver per unit time (ml/min)”
- It is an indicator of the metabolic rate of the drugs.
- Drugs can be divided into 3 groups according to their hepatic clearances:
  - Drugs with **high** hepatic clearance (Drugs with **high extraction ratio**)
  - Drugs with **low** hepatic clearance (Drugs with **low extraction ratio**)
  - Other drugs

Drugs with high hepatic clearance (Drugs with high extraction ratio):

- Generally these are high-lipophilic drugs
- Absorption ratios from the gastrointestinal tract is 100% or very close to 100%.
- The pre-systemic elimination of these drugs is very high; so because of this reason systemic bioavailability of these drugs are low.
- The ratio between the oral and parenteral dose of the drug is high (high difference in dose between oral and parenteral route)

Drugs with low hepatic clearance (Drugs with low extraction ratio):

- Metabolic rates of these drugs in liver are low.
- Elimination rate of these drugs **are not affected** considerably with the changes in hepatic blood flow.
- However, the induction/inhibition of metabolizing enzymes affects the metabolism rate.

Other drugs:

- These drugs are the ones between the above two groups.
- Hepatic clearances of these drugs are affected in high amounts by both hepatic blood flow and metabolizing capacity of the biotransformation enzymes.

DRUG EXCRETION (DRUG ELIMINATION)

- This is the removal of a drug from the body.
- The major organs of excretion are the kidneys, intestines, biliary system and lungs, and drugs can also be excreted in small amounts in the saliva, sweat and milk.

  Renal elimination is the most important.
- The excretion of drugs in the milk is in small amounts and is of no significance to the mother. But for the suckling infant, it may sometimes be important, especially of the infant's immature metabolic or excretory mechanisms.
- Examples of drugs that could be toxic to suckling infants when taken by the mother are Theophylline, anticancer drugs, salicylates, chloramphenical, nalidixic acid, phenobarbitone, Beta blockers

RENAL EXCRETION

- Drugs and metabolites are excreted from the kidneys by 2 ways.

a) Glomerular filtration

b) Tubular secretion

- Tubular reabsorption is not an excretion way; however there is no doubt that it effects the excretion of drugs from the body by the kidney.

Glomerular filtration

- **Simple passive diffusion** plays role in glomerular filtration.
- The filtration rate is 110-130 ml/min.
- They are filtered from the glomerulus into proximal tubules except the bound fraction of drug molecules to the plasma proteins. Because albumin cannot be filtered from the glomerulus, the drugs cannot pass through into the proximal tubules.

b) Tubular secretion:

- There are 3 important points about the tubular secretion mechanism of the drugs:
  - Tubular secretion occurs mainly in the **proximal tubules**.
  - **Active transport** is the main mechanism for tubular secretion.
  - The **efficiency (performance) of** the excretion by tubular secretion is higher than glomerular filtration route. Clearance maximum in glomerular filtration is approximately 120 ml/min, whereas the clearance maximum of tubular secretion is about 600 ml/min.

c) Tubular reabsorption:

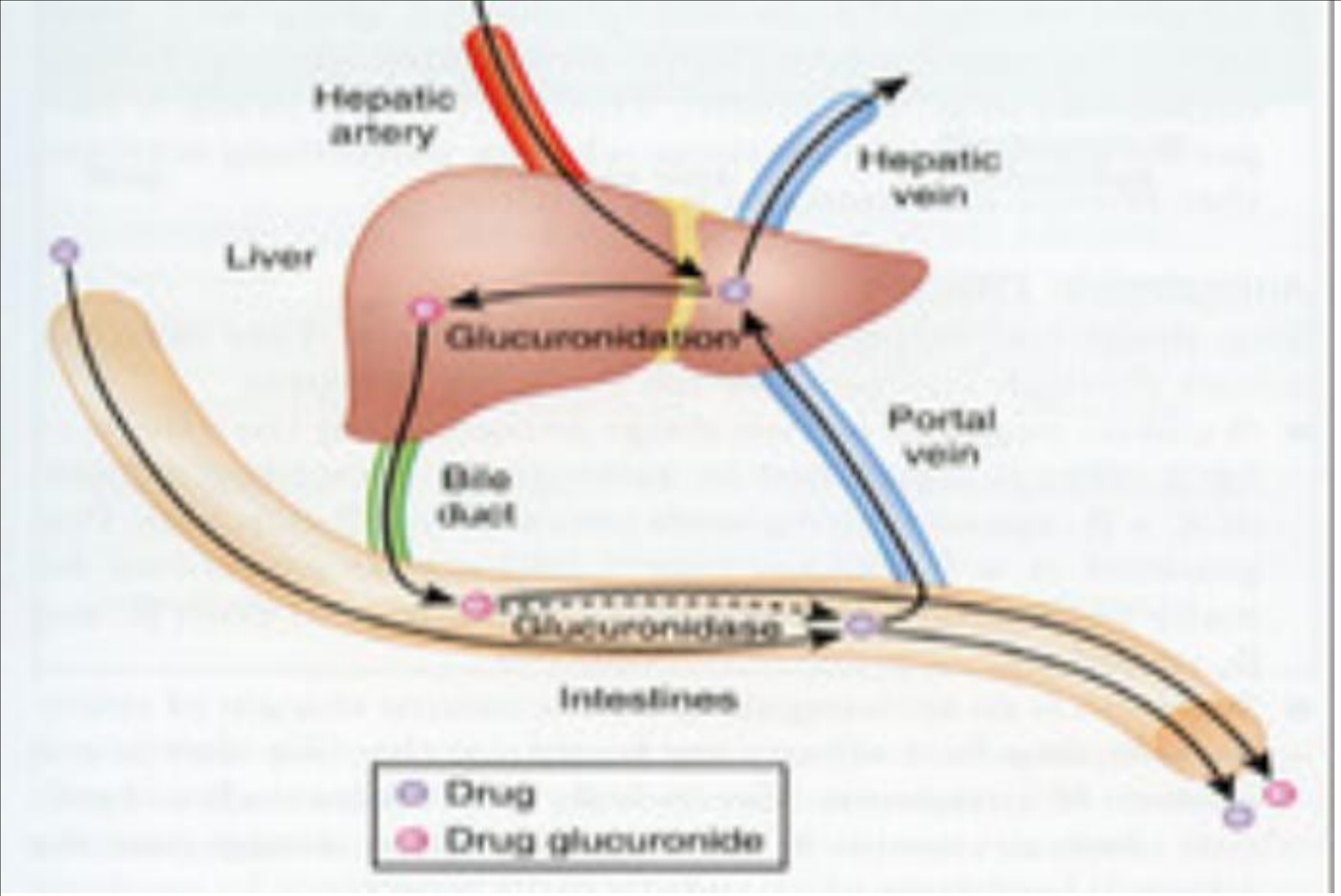
- This mechanism works in an opposite (counter) way by reducing the drug or metabolite excretion.
- Tubular reabsorption occurs **mainly in distal tubules** and partially in proximal tubules.
- It occurs by **simple passive diffusion** generally.

d) BILIARY EXCRETION

- These substances are generally secreted into the billiary ducts from the hepatocytes by **active transport** and finally they are drained into the intestines.
- Especially, highly ionized polar compounds (conjugation products) can be secreted into the bile in remarkable amounts.
- After biotransformation, metabolites are drained into the small intestine by biliary duct.

- Drug metabolites in the small intestine are broken down again in the small intestine and **reabsorbed back** reaching the liver by portal vein again.
- This cycle between the liver and small intestine is called the enterohepatic cycle.
- Especially the drugs which are metabolized by the **conjugation reactions** go under enterohepatic cycle.
- This is important, because enterohepatic cycle prolongs the duration of stay of the drugs in our body which leads an increase in the duration of their effect.

- Drug examples that go under the enterohepatic cycle in remarkable amounts.
  - Chlorpromazine
  - Digoxin
  - Indomethacin
  - Chloramphenicol


Hepatic artery
Hepatic vein
Liver
Glucuronidation
Portal vein
Bile duct
Glucuronidase
Intestines
Drug
Drug glucuronide

e) ARTIFICIAL EXCRETION WAYS

- **Haemodialysis** is one of the options among the artificial excretion ways for the drugs.
- It is used especially for the treatment of **acute drug intoxications** to eliminate the drug from the body and also in renal failure.
- f). **Gaseous or the volatile substances** can pass from the blood circulation into the alveoli by passing across the endothelium and epithelium of the alveolar membrane.

IMPORTANT PARAMETERS IN DRUG ELIMINATION (CLEARANCE & HALF LIFE)

CLEARANCE

- It can be described as **the volume of plasma** cleared from the drug per unit time (ml/min).
- **Total Body Clearance**: It is the plasma volume cleared from the drug per unit time via the elimination of the drug from all biotransformation and excretion mechanisms in the body.
- **Renal Clearance**: It can be described as **the rate of the excretion of a drug from kidneys**. So in other words, renal clearance is the volume of plasma cleared from the non-metabolized (unchanged) drug via the excretion by kidneys per minute.

- There are **four important factors** that affect the renal clearance of the drugs:
  - Plasma protein binding of the drug.
  - Tubular reabsorption ratio of the drug.
  - Tubular secretion ratio of the drug.
  - Glomerular filtration ratio of the drug.

HALF-LIFE ($t_{1/2}$):

- It is the time it takes for the plasma concentration or the amount of drug in the body to be reduced by **50%** via different elimination mechanisms.

- Drug excretion is commonly expressed in terms of half life ($t_{1/2}$)
- This is the time required for the concentration of the drug in the plasma to decrease by one-half of it's initial value
- Drug half life is variable and can be long or short
- Subsequent doses are given to raise the concentration levels to a peak

Loading Doses

- Are used when the medical condition demands high concentrations very quickly
- This is achieved by an initial dose that is twice the maintenance dose


The End