Basic concepts and processes in Pharmacology

- Pharmacokinetics
- Pharmacodynamics
- Drug reactions
- Drug interactions:
  - Drug-drug interactions
  - Drug-food interactions

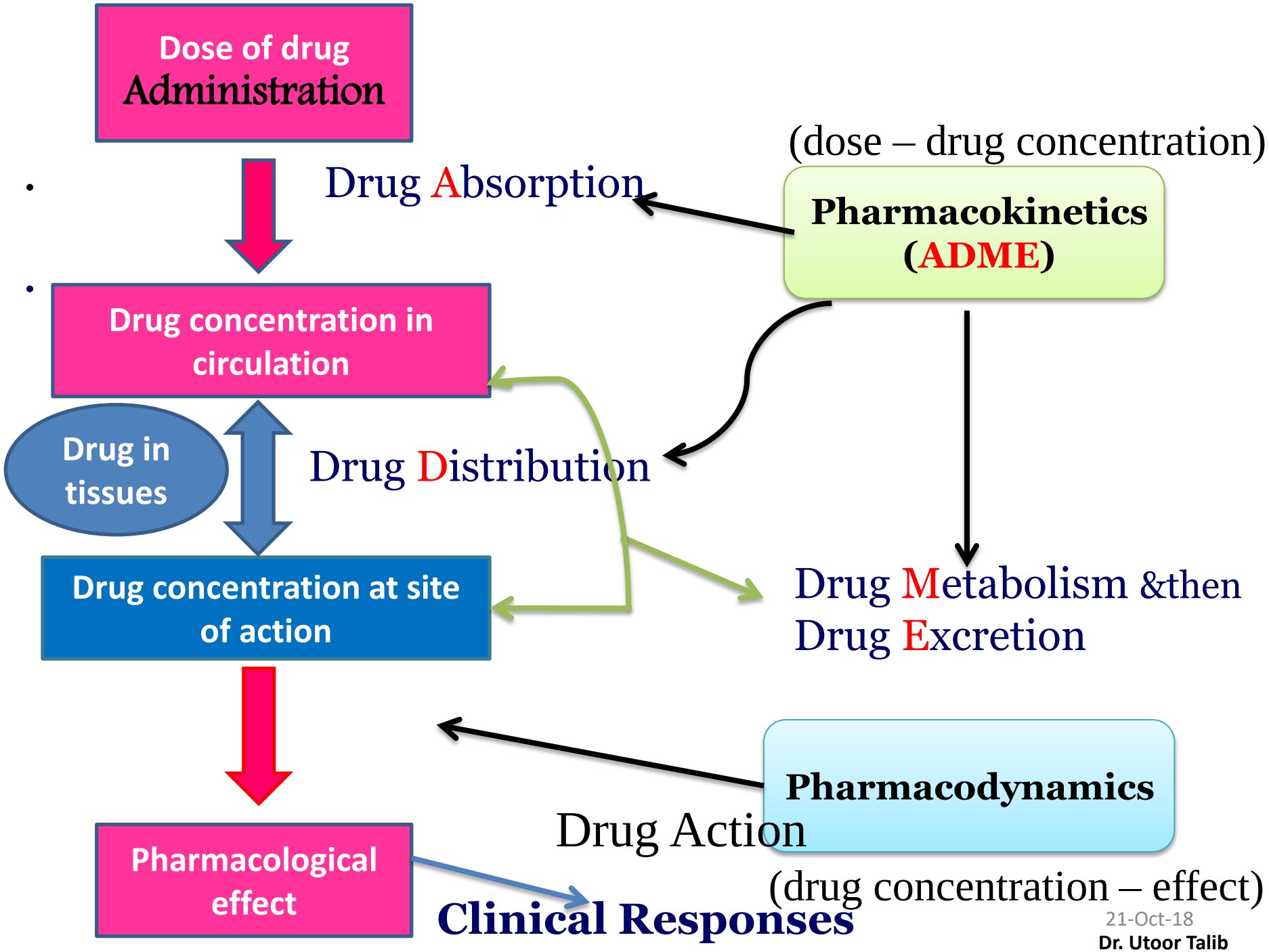
Lecture 3
Pharmacokinetics

Objectives:

Upon completion of this lecture, student will be able to answer the following questions:

1. Define and differentiate between Pharmacokinetics and Pharmacodynamics
2. What are pathways and mechanisms by which drugs across cell membranes
3. What are the pharmacokinetic processes and factors that affect each process.
4. Define the following terms: First Pass Effect, Bioavailability, Drug half-life, onset of drug action, peak concentration, duration of drug action. Steady state concentration, Therapeutic and toxic concentration, and Therapeutic range.

- The most important factors that determine the intensity of drug responses:
  - **Pharmacokinetics**
  - **Pharmacodynamics**
- It's important to understand the difference between pharmacokinetics (drug movement) and pharmacodynamics (drug action)
- **Pharmacokinetics:** derived from two Greek words:
  - *Pharmakon* = " Drug"
  - *Kinetics* = " Movement or Motion "
- **Pharmacokinetics:** the study of drug movement throughout the body.
- In practical terms, it describes how the body deals with the drug after taken, including the processes of **A**bsorption, **D**istribution, **M**etabolism, and **E**xcretion (**ADME**) – i.e., what happens to a drug from the time it is administered until it leaves the body.


Dose of drug
Administration
Drug Absorption
(dose – drug concentration)
Pharmacokinetics
(ADME)
Drug concentration in circulation
Drug in tissues
Drug Distribution
Drug concentration at site of action
Drug Metabolism &then
Drug Excretion
Pharmacodynamics
Drug Action
Pharmacological effect
(drug concentration – effect)
Clinical Responses

What are the importance of pharmacokinetics?

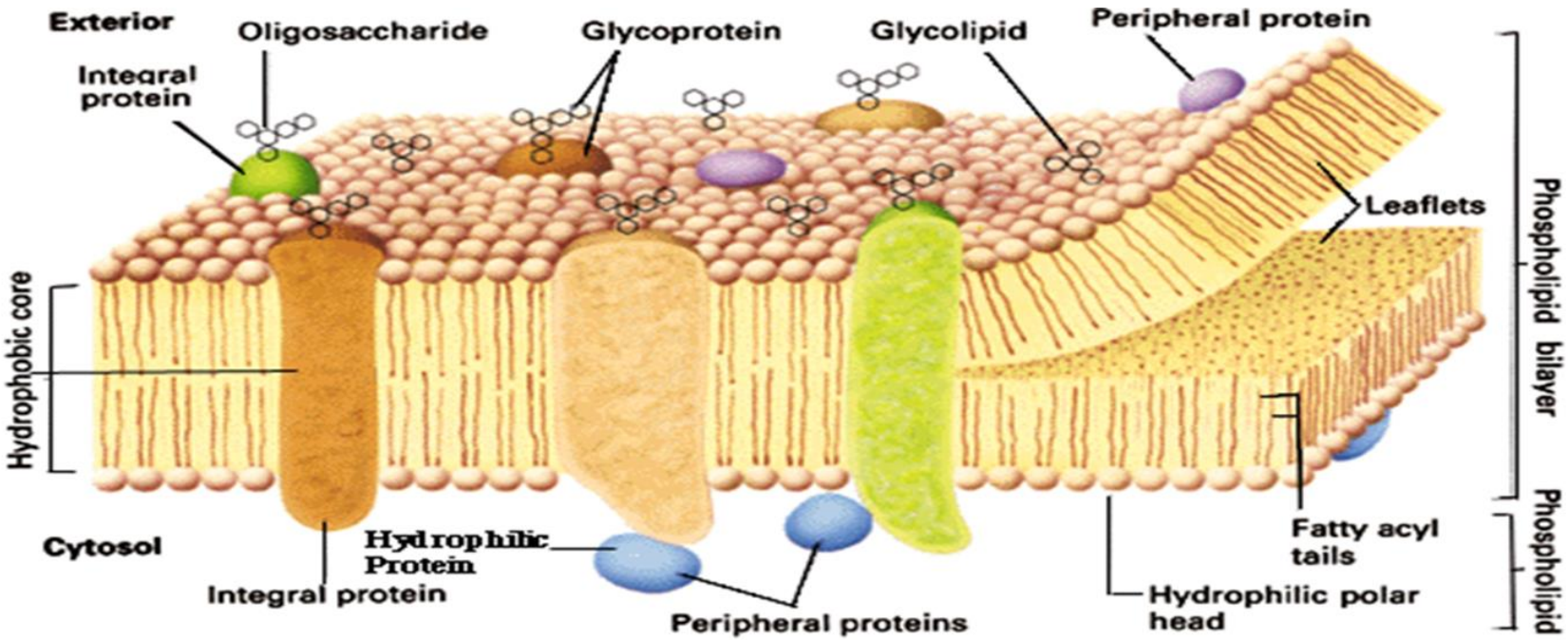
Pharmacokinetic processes determine

- the concentration of a drug at its sites of action
- the speed of onset of the drug action,
- the intensity of the drug's effect, and
- the duration of drug action or time course of responses

- All 4 phases of pharmacokinetics (**ADME**) involve drug movement.

How drugs move through the body?

- **Passage of drugs across membranes**
- To move throughout the body, drugs must cross membranes.



- The basic membrane structure consists of a double layer of molecules known as phospholipids. Phospholipids are simply lipids (fats) that contain an atom of phosphate. The large objects embedded in the membrane represent protein molecules, which serve a variety of functions like (a) contributing structure to the membrane (b) acting as enzyme (c) acting as carrier for transport of substances (d) acting as receptors.

- Drugs must cross membranes to enter the blood from their site of administration. e.g., a drug taken by mouth must cross the plasma membranes of the mucosal cells of the GIT to enter the bloodstream. Once in the blood, drugs must cross membranes to leave the vascular system and reach their sites of action. In addition, drugs must cross membranes to undergo metabolism and excretion.

- What are pathways by which drugs across cell membranes?

Drug pathways to cross cell membranes

There are three main pathways by which drugs across cell membranes:

1) **Channels or pores:** e.g., small ions, such as potassium and sodium.
2) **Transport system**:
3) The most common pathway is **Direct penetration** of the membrane itself. E.g., lipid soluble drugs

- Membranes are composed primarily of lipids; therefore, to directly penetrate membranes, a drug must be lipid soluble (lipophilic).
- Certain kinds of molecules are not lipid soluble and therefore cannot penetrate membranes. This group consists of polar molecules (water soluble) and ions. These agents may use other means to gain entry, such as protein carriers or active transport.

- **Mechanisms by which drugs cross-cell membranes**

Drugs are transported to and from target cells by:

a) Passive transport

1. Simple diffusion

2. Filtration

b) Specialized transport

1. Facilitated diffusion

2. Active transport

3. Endocytosis.

- **Define drug absorption**
- **What are factors affecting drug absorption?**

- **Absorption**
- Absorption is a process following administration of drug and defined as the **movement of a drug from its site of administration into the blood circulation through biological membranes.**
- It is the process by which a drug is made available for use in the body
- The rate of drug absorption determines the onset of drug action (how soon effects will begin).
- The amount of drug absorbed or the extent of drug absorption determines its intensity.
- In case of intravenous or intra-arterial administration the drug bypasses absorption processes and it enters into the circulation directly.

- **Factors Affecting Drug Absorption**
- The rate at which a drug undergoes absorption is influenced by the physical and chemical properties of the drug itself and by physiologic and anatomic factors at the absorption site.
- **Rate of dissolution**
- **Surface area**
- **Blood flow**
- **Lipid solubility**
- **pH partitioning**

- **Discuss:**

How the route of drug administration affects the rate and amount of absorption?

The route of administration affects the rate and amount of absorption.

Routes and Absorption		
Route	**Barriers to Absorption**	**Absorption Pattern**
Oral	Medications must pass through the layer of epithelial cells that line the GI tract.	Varies greatly due to the following variables: • Stability and solubility of the medication • GI pH and emptying time • Presence of food in the stomach or intestines • Other medications currently being administered • Forms of medications (enteric coated pills, liquids)
Subcutaneous and intramuscular	The capillary wall has large spaces between cells; therefore there is no significant barrier.	The rate of absorption is determined by: • Solubility of the medication in water o Highly soluble medications will be absorbed in 10 to 30 min. o Poorly soluble medications will be absorbed more slowly. • Blood perfusion at the site of injection o Sites with high blood perfusion will have rapid absorption. o Sites with low blood perfusion will have slow absorption. • Temperature of the tissue: cold causes vasoconstriction and decreases absorption; heat causes vasodilation and increases absorption
Intravenous	No barriers	Immediate & Complete – administered directly into blood
Mucous membranes	Medications must pass through the layer of epithelial cells	• Perfusion or blood flow to the area • Integrity of the mucous membranes • Length of time retained in area
Topical (skin)	Medications must pass through the layer of skin.	• Perfusion or blood flow to the area • Integrity of skin
Inhalation	Medications must pass through the layer of epithelial cells of respiratory tract	• Perfusion or blood flow to the area • Integrity of lung lining • Ability to administer drug properly

What we mean by First pass effect?

First pass effect

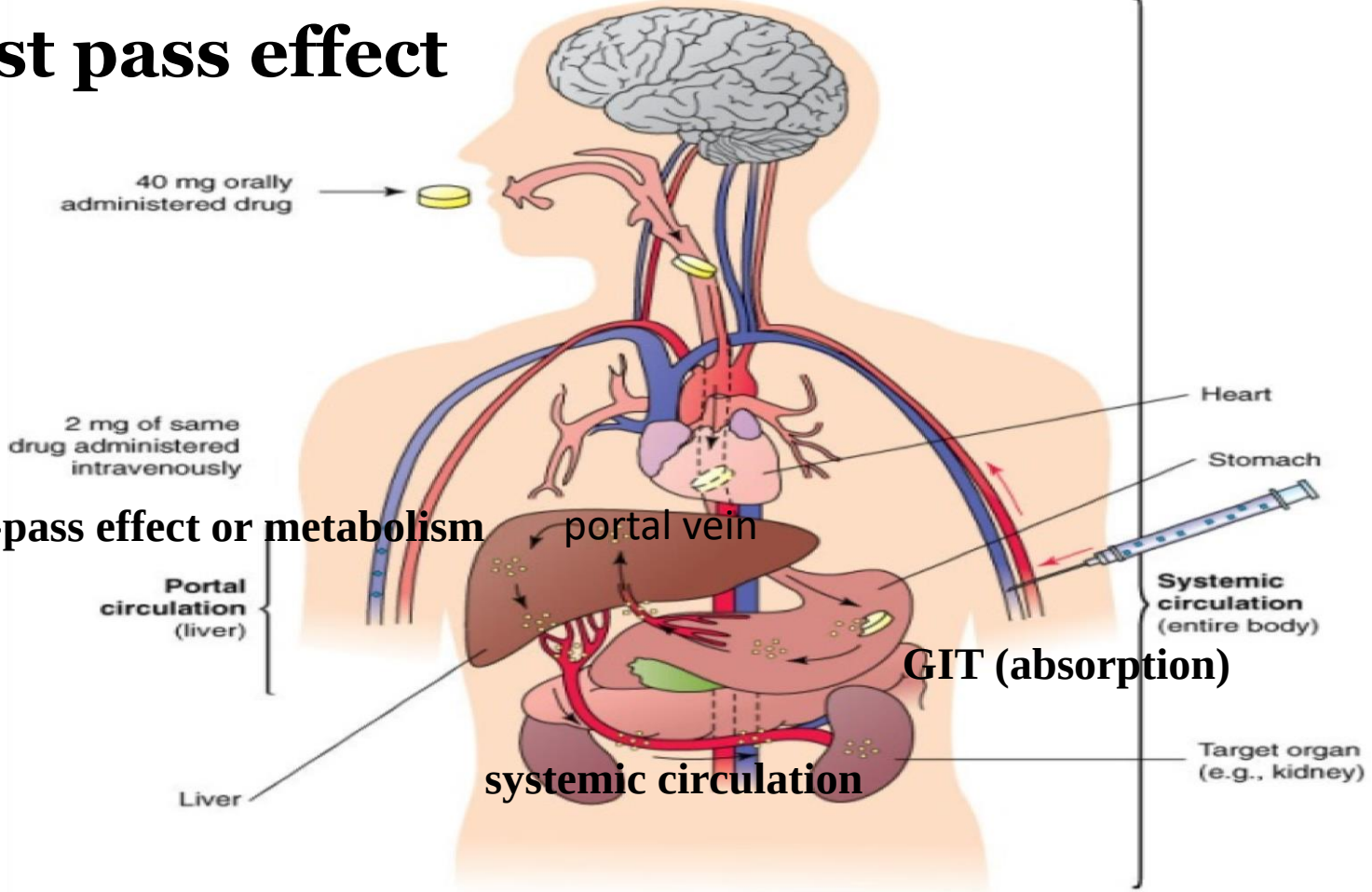


Fig. 2-3. First-pass effect is the metabolism of a drug by the liver before its systemic availability.

A medication given orally → absorbed from the GIT → they are carried directly to the liver via the hepatic portal vein. In the liver drug may be subjected to metabolism before it reaches the systemic circulation and distributes round the body.

- **First Pass Effect:** refers to the rapid hepatic inactivation of certain oral drugs before they reaches the systemic circulation .
- To circumvent the first-pass effect, a drug that undergoes rapid hepatic metabolism is often administered parenterally. This permits the drug to temporarily bypass the liver, thereby more drug reaches the circulation/ more of the drug is bioavailable and reach therapeutic levels in the systemic circulation.
- First-pass effect occurs to lesser extent with PR administration because drug absorbed in colon bypasses the portal system: colon (absorption) → internal pudendal veins → systemic circulation.

What is the significance of first pass effects or metabolism?

- The significance of first pass metabolism is limits or reduces ***a drug's bioavailability.***
- **Bioavailability** (F): is the percentage of administered dose(the amount of drug) that reaches the systemic circulation in unchanged state to produce a biological effect (by any route).
- Drugs that given IV are virtually 100% bioavailable; an oral drugs are virtually always less than 100% bioavailable because some is not absorbed from the GI tract and some undergoes first pass metabolism. Drugs with a low bioavailability may be ineffective orally and needs to be administered parenterally.

What are Factors that affecting bioavailability?

- **Factors affecting bioavailability:**
- Route of administration
- Dosage form: dosage form is a major determinant of a drug's bioavailability.
- First-pass effect.
- Drug absorption
- Drug solubility in gut.

Define drug distribution

What are Factors that affecting distribution?

Distribution

- Distribution is defined as the movement of drugs throughout the body (drugs move between different body compartments to reach target site of action).
- Once a drug is injected or absorbed into the bloodstream, it is carried by the blood and tissue fluids to its sites of pharmacologic action, metabolized, and then excreted.
- **distribution depends on several factors**

1) Drug's solubility – water or lipid soluble
2) Blood flow: Cardiac output and perfusion of the tissues – adequacy of blood circulation (good blood profusion = good flow/distribution)

- Areas of rapid distribution: heart, liver, kidneys, brain
- Areas of slow distribution: muscle, skin, fat
- Peripheral vascular or cardiac disease may delay med. distribution

3) Plasma proteins and tissue binding.
4) Barriers to drug distribution: Blood–brain barrier & Placental barrier

What are the consequences of plasma protein drugs binding?

1) Protein binding can restrict drug distribution.

- Most drugs circulate partly free (unbound) in plasma and partly protein bound. Only free drug molecules can leave the vascular system. The free fraction is the pharmacologically active and it is the one removed by metabolism and excretion.
- Drugs can form reversible bonds with various proteins in the body mainly albumin – which act as carriers.
- Albumin is a large molecule and because of its size, albumin always remains in the bloodstream. Therefore the protein–drug complex is relatively large and cannot enter into capillaries. As a result, bound drug molecules cannot leave the bloodstream and reach their sites of action, or undergo metabolism or excretion until the drug-protein bond is broken.

- The free and bound fractions are in equilibrium – i.e., as the free drug is removed, it will be replaced by drug released from bound fraction. Protein binding allows part of a drug dose to be stored and released as needed.
- Some drugs are tightly bound and are released very slowly. These drugs have a very long duration of action because they are not free to be broken down or excreted. E.g., warfarin (an anticoagulant) is strongly protein binding, (99%) of drug molecules in plasma are bound and leaving only 1% free
- Some drugs are loosely bound; they tend to act quickly and to be excreted quickly. E.g., gentamicin (an antibiotic) is weak protein binding, less than 10% of drug molecules in plasma are bound and leaving more than 90% free.

2) Protein binding can be a source of drug interactions

- If albumen molecules are low (malnourished, burns, blood loss) there are more free unbound drug in plasma – increasing levels of free drug can increase the intensity of drug responses. If plasma drug levels rise sufficiently, toxicity can result.
- If more drug molecules than protein molecules, each molecule of albumin has only a few sites to which drug molecules can bind. there are more free unbound drug in plasma – increasing levels of free drug can increase the risk of drug - to drug interaction, which can either increase or decrease the effect of a drug.

Barriers to drug distribution: Blood–brain barrier

- The term blood-brain barrier (BBB) refers to the unique anatomy of capillaries in the CNS – it is a protective system that keeps many things (e.g., potentially toxic substances, poisons) away from the CNS. There are tight junctions between the cells that compose the walls of most capillaries in the CNS. These junctions are so tight that they prevent drug passage. Only drugs that are lipid soluble or have a transport system can cross the BBB to a significant degree. Drugs that are not lipid soluble – ionized or polar drugs distribute poorly to the CNS – including certain chemotherapeutic agents and toxic compounds.
- BBB can be a significant obstacle to therapy of CNS disorders. The barrier can, for example, impede access of antibiotics to CNS infections.
- The BBB is not fully developed at birth. As a result, newborns have heightened sensitivity to medicines that act on the brain. Likewise, neonates are especially vulnerable to CNS toxicity.

Barriers to drug distribution: Placental barrier

- Many drugs readily pass through the placenta and affect the developing fetus in pregnant women.
- Placental Drug Transfer: The membranes of the placenta separate the maternal circulation from the fetal circulation.
- However, the membranes of the placenta do NOT constitute an absolute barrier to the passage of drugs, lipid-soluble, nonionized compounds readily pass from the maternal bloodstream into the blood of the fetus. In contrast, compounds that are ionized, highly polar, or protein bound are largely excluded.
- Drugs that have the ability to cross the placenta can cause serious harm. Some compounds can cause birth defects, ranging from low birth weight to physical anomalies and alterations in mental aptitude

- **Define: Drug Metabolism**
- **What are the therapeutic consequences of drug metabolism?**
- **What are factors that affecting the rate of drug metabolism?**

- **Drug Metabolism:** known as biotransformation, is defined as the enzymatic alteration of drug structure – process of chemically converting a drug to a form that is usually more easily removed from the body. This occurs primarily in the liver, but also takes place in the kidneys, lungs, bowel, and blood.
- **Hepatic Drug-Metabolizing Enzymes**: Most drug metabolism that takes place in the liver is performed by the **hepatic microsomal enzyme system**, also known as the **P450 system**. The term P450 refers to cytochrome P450, a key component of this enzyme system. It is important to appreciate that cytochrome P450 is not a single molecular entity, but rather a group of 12 closely related enzyme families. Three of the cytochrome P450 (CYP) families—designated **CYP1, CYP2**, and **CYP3—metabolize** drugs. The other nine families metabolize endogenous compounds (e.g, steroids, fatty acids). Each of the three P450 families that metabolize drugs is itself composed of multiple forms, each of which metabolizes only certain drugs.

• Therapeutic consequences of drug metabolism

1) The most important consequence of drug metabolism **is acceleration of renal drug excretion**. Kidneys, which are the major organs of drug excretion, are unable to excrete drugs that are highly lipid soluble. Hence, by converting lipid-soluble drugs into more hydrophilic (water-soluble) forms, metabolic conversion can accelerate renal excretion of many agents
2) Drug inactivation: metabolism can convert pharmacologically active compounds to inactive forms.
3) Increased therapeutic effect Metabolism can increase the effectiveness of some drugs. E.g., conversion of codeine into morphine: the analgesic activity of morphine is so much greater than that of codeine.
4) Activation of Pro-drugs into active forms
   - ❑ A pro-drug is a compound that is pharmacologically inactive as administered and then undergoes conversion to its active form via metabolism.
5) Decreased or increased toxicity: by converting drugs into inactive forms, metabolism can decrease toxicity. Conversely, increased toxicity when metabolism increase the potential for harm by converting relatively safe compounds into forms that are toxic. E.g., conversion of paracetamol into a hepatotoxic metabolite.

Factors affecting the rate of drug metabolism

Several factors can influence the rate at which drugs are metabolized.

1. *Age*: The drug-metabolizing capacity ↓ in infant & old people. The liver does not develop its full capacity to metabolize drugs until about 1 year after birth, infants are especially sensitive to drugs, and care must be taken to avoid injury. Similarly, the ability of older adults to metabolize drugs is commonly decreased. Drug dosages may need to be reduced to prevent drug toxicity.
2. *Sex*: males metabolized drugs more than females.
3. *Genetics* – genetic (inherited) allows some people to metabolize drugs rapidly and others to metabolize them more slowly.

- *4. Nutritional status*: hepatic drug metabolizing enzymes require a number of co-factors to function. In malnourished pt, these co-factors may be deficient, causing drug metabolism to be compromised.
- *5. Induction and Inhibition of Drug-Metabolizing Enzymes.* Drugs that act on the liver to increase rates of drug metabolism are **inducers**. This process of stimulating enzyme synthesis is known as **induction**. As the rate of drug metabolism increases, plasma drug levels fall.
- Drugs that act on the liver to decrease rates of drug metabolism are called **inhibitors**. This process is known as **inhibition**. slower metabolism can cause an increase in active drug accumulation. This can lead to an increase in adverse effects and toxicity.

- *6. First-Pass Effect* : If the capacity of the liver to metabolize a drug is extremely high, that drug can be completely inactivated on its first pass through the liver. As a result, no therapeutic effects can occur. E.g., Nitroglycerin
- *7. Competition between drugs*: when two drugs are metabolised by the same metabolic pathway, they may compete with each other for metabolism, and may, thereby ↓ the rate at which one or both drugs is metabolised. If metabolism is depressed enough, a drug can accumulate to dangerous levels.
- *8. Pathological condition:* Certain diseases can reduce metabolism. E.g., liver diseases, heart failure

- Define drug Excretion
- What are steps of renal drug excretion?
- What are factors that modify renal drug excretion

Excretion

- Excretion is the removal of a drug and their metabolites from the body. Kidneys are the main organ of drug excretion, (especially for those that are water soluble and not volatile).
- Excretion also takes place through the liver, lungs, bowel, biliary system, breast milk, and exocrine glands.
- **Elimination**: The combination of metabolism plus excretion is called elimination.

Excretion primarily through the kidneys by:

- Glomerular filtration:
- Passive tubular reabsorption:
- Active tubular secretion:

• Factors that modify renal drug excretion

- ✓ **Age**
- ✓ **Renal dysfunction**
- ✓ **Blood flow**
- ✓ **PH-dependent ionization**
- ✓ **Competition for active tubular transport**

What we mean by the following terms:

- **Plasma Drug Levels**
- **Minimum Effective Concentration**
- **Therapeutic and toxic drug concentration**
- **Onset of drug action, peak concentration, and duration of action**
- **Drug half-life**
- **Steady state concentration**
- **loading and maintenance drug doses**

THANK YOU FOR YOUR ATTENTION

ANY QUESTION??