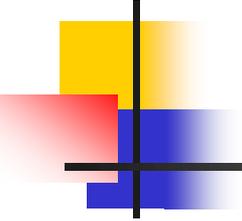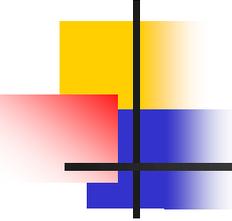# Pharmacokinetics (II)

Dr Mohammed Alsbou

Professor of Clinical Pharmacology

Department of Pharmacology

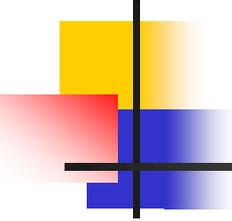**Faculty of Medicine, Mutah University**

Drug Distribution

- Is the process by which a drug leaves blood stream & enters interstitium (extracelullar fluids) and/or cells of the tissues
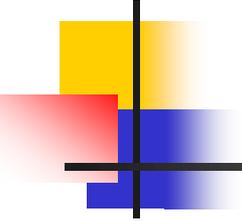
Drug distribution depends on:

- Blood flow to tissue capillaries
- Capillary permeability
- Degree of binding to plasma & tissue proteins

Drug distribution depends on:

❑ **Blood flow to tissue capillaries:**

○ Blood flow to tissue capillaries vary

○ blood flow to **brain, liver & kidney is higher than** that to skeletal muscles & adipose tissue

- **Capillary permeability** is determined by:
  - Drug structure: **Hydrophobic drugs**, which have no net charge, readily move across biologic membranes. They dissolve in lipid membranes and, therefore
  - **hydrophilic drugs,** which have a positive or negative charge, do not readily penetrate cell membranes, and therefore, must go through slit junctions
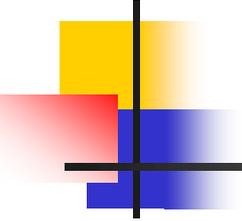
- Capillary structure: (brain continuous, liver discontinuous)
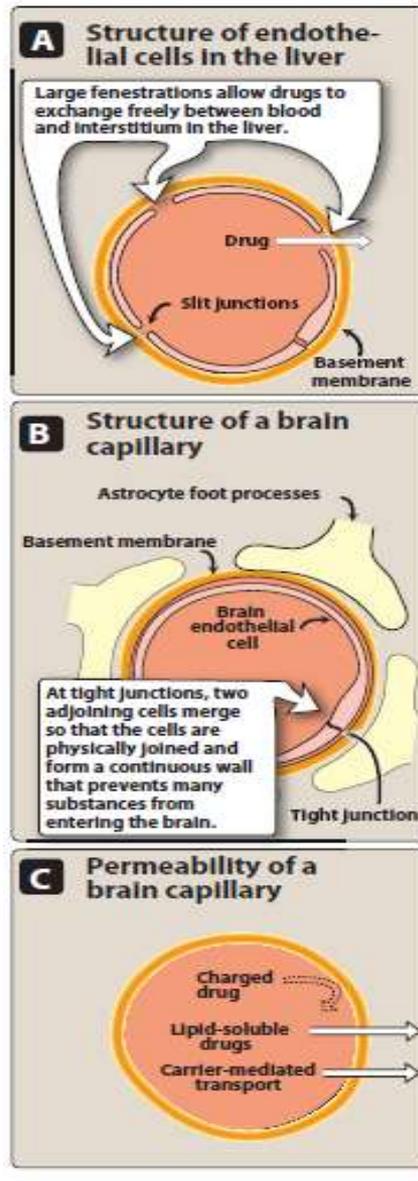
Cross-section of liver and brain capillaries
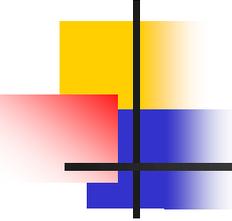
Blood-Brain Barrier (BBB)

- To enter brain, drug must pass through endothelial cells of capillaries of CNS or activelly transported (specific transporters)

  - **Lipid-soluble drugs** readily penetrate into CNS because they can dissolve in membrane of endothelial cells

  - **Ionised or polar drugs** fail to enter CNS because they are unable to pass through endothelial cells of CNS

The blood–brain barrier (BBB)

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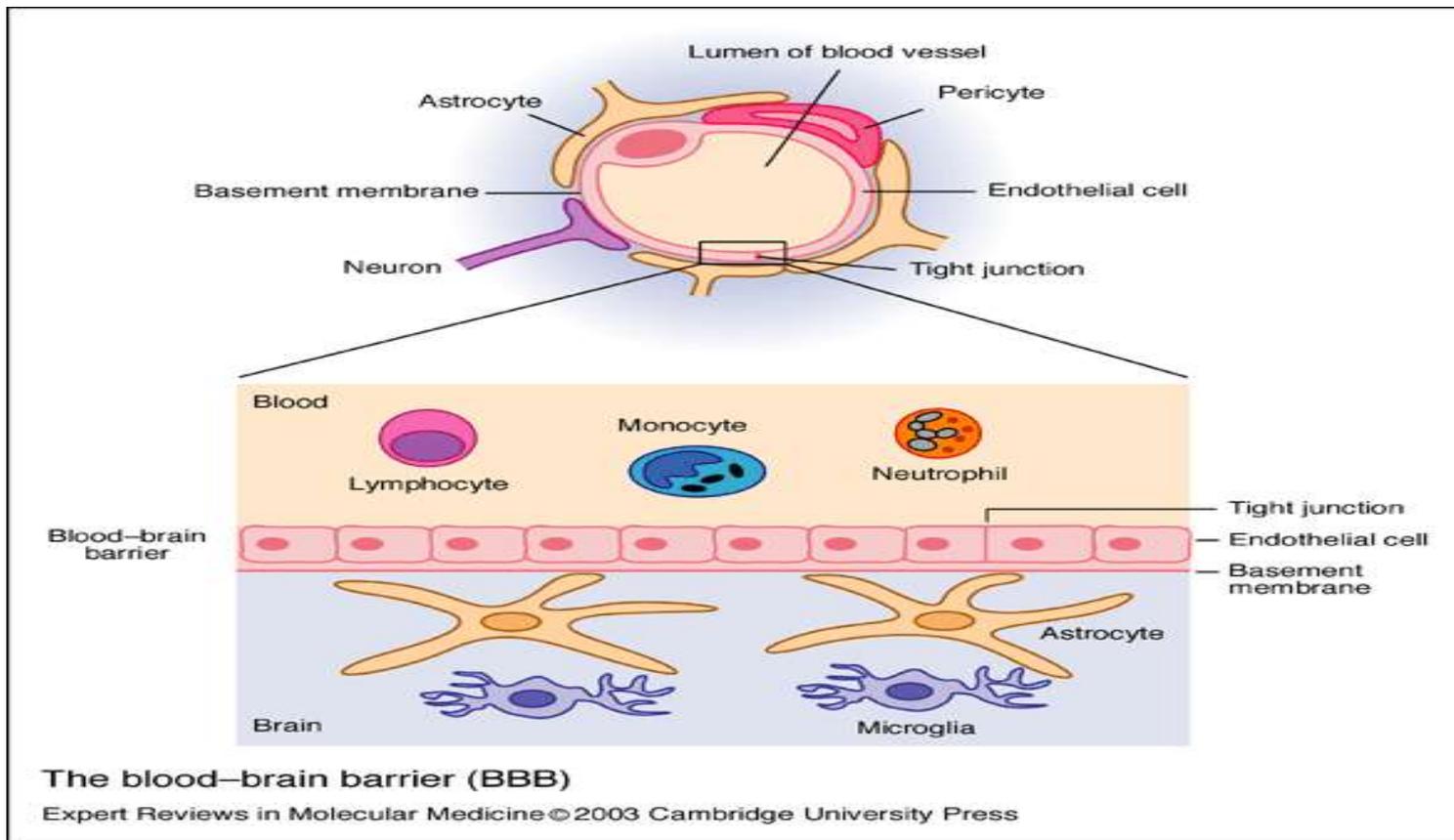
The BBB is created by the tight apposition of endothelial cells lining blood vessels in brain, forming a barrier between circulation and brain parenchyma (e.g. astrocytes, microglia)
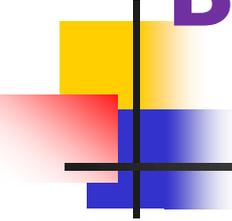
# Binding of drugs to plasma protein

- **Plasma albumin** is major drug-binding protein
 - **Bound drugs** are pharmacologically **inactive**
 - **Only free drug (unbound drug)** can act on target sites in tissues **(active)**
- As concentration of **free drug** decreases due to elimination (metabolism, excretion), bond drug dissociate from protein
 - **Hypoalbumunemia** may alter level of free drug
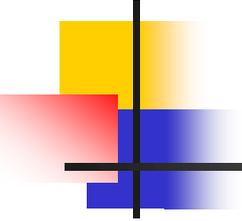
Drug Metabolism

- Drugs are eliminated by biotransformation and/or excretion into urine or bile
- Metabolism transform **lipophilic drugs** into **more polar** products
- **Liver** is major site of drug metabolism
- Other sites kidney, intestines
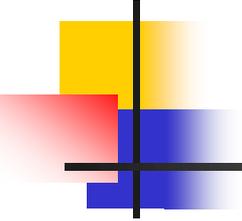
- Some drugs are administered as **inactive compound (pro-drug)** & must be metabolised to their active forms
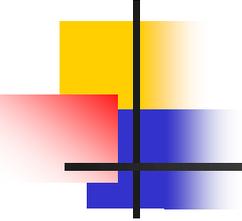
Kinetics of metabolism

- **First-order kinetics:**

- Metabolism is catalyzed by enzymes

  - **At low doses**, drug metabolism **is first order** – rate of metabolism is directly proportional to drug dose
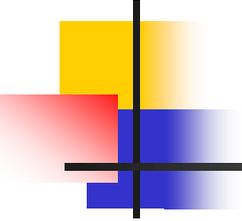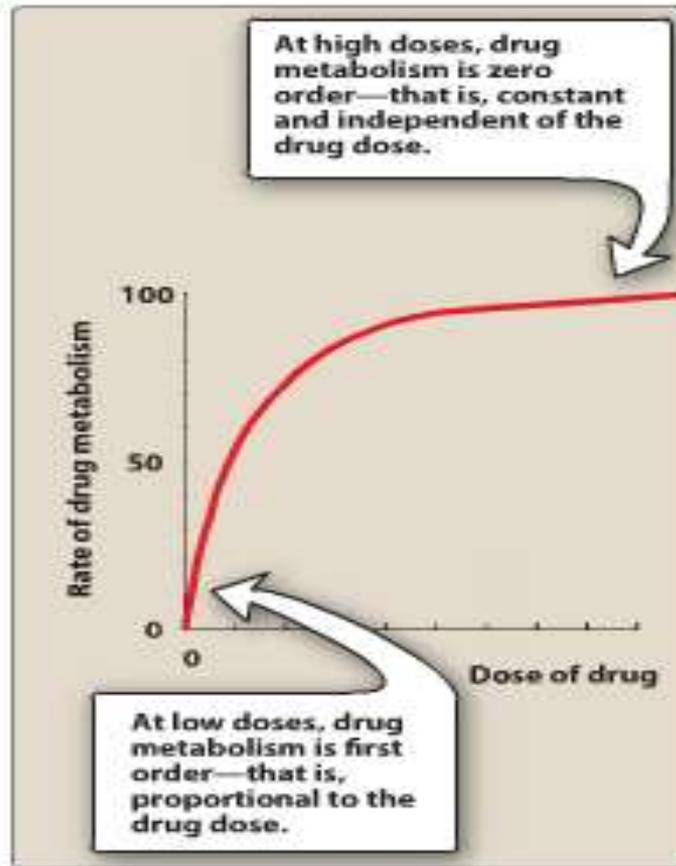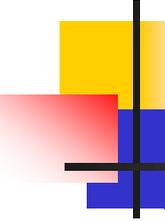
Kinetics of metabolism

- **Zero-order kinetics:**

- **At high doses**, drug metabolism **is zero order** (no-Linear) that is constant & independent of drug dose (because the enzyme is saturated by high free-drug concentration)
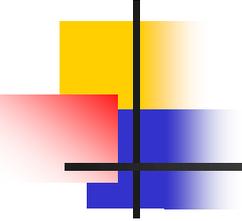
Effect of drug dose on rate of metabolism

Reactions of metabolism

- Kidney cannot eliminate lipophilic drugs that readily cross cell membranes and reabsorbed in distal tubules

- **Lipid-soluble drugs** must be metabolised in liver using two reactions called:
 - **Phase I**
  - **Phase II**

Phase I

- Converts lipophilic molecules into more polar molecule by introducing or unmasking **polar functional group** such as –OH or –NH2

- Phase I reactions are catalsyed by **cytochrome P450 system** (also called microsomal mixed function oxidase)
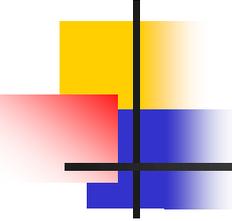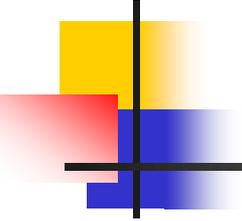
Cytochrome P450 system

- Designated as **CYP**

- Is composed of many families of heme-containing isozymes that are located in most cells primarily in liver & GI tract

- There are many different genes & many different enzymes known as **P450 isoforms**
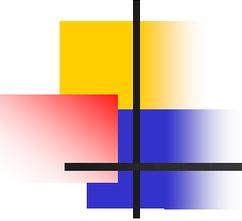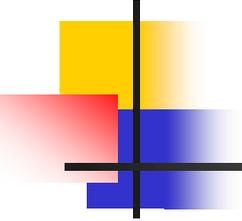
- **Most isoforms involved in metabolism of drugs are:**
  - **CYP3A4=** (60% of drugs)
  - **CYP2D6=** (25% of drugs)
  - **CYP2C9=** (15% of drugs)
  - **CYP2C19=** (15% of drugs)

Genetic Variability

- These enzymes exhibit **genetic variability**, which has implication for individual dosing regimens, determining responsiveness & risk of adverse drug reactions

CYP 450 inducers

- Certain drugs phenobarbital, rifampin, carbamazepine increase synthesis of CYP enzymes

- Thus increase metabolism of drugs metabolised by these CYP enzymes, decrease plasma concentration & decrease therapeutic effect
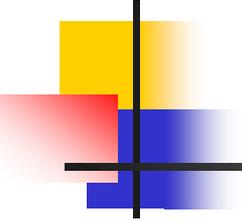
CYP 450 inhibitors

- Inhibition of CYP isozymes can lead to serious adverse events

- Important CYP inhibitors are erythromycin, ketoconalzole, omeprazole

- Omeprazole is a potent inhibitor of three of CYP isozymes responsible for *warfarin metabolism*

- If two drugs are taken together, plasma concentrations of *warfarin increase,* which leads to increase risk of hemorrhage and other serious bleeding reactions
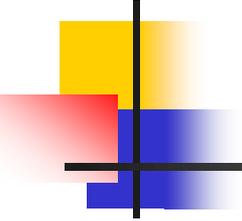
- Natural substances such as grapefruit juice may inhibit drug metabolism

- Grapefruit juice inhibits CYP3A4 and, thus,

drugs such as amlodipine & clarithromycin, which are metabolized by this system, have greater amounts in systemic circulation— leading to higher blood levels & potential to increase therapeutic and/or toxic effects of drugs
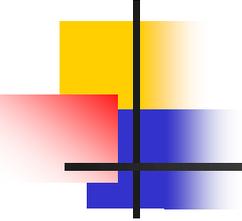
Phase II

- This phase consists of conjugation reactions
- If the metabolite from Phase I metabolism is sufficiently polar, it can be excreted by kidneys
- However, many Phase I metabolites are too lipophilic to be retained in kidney tubules
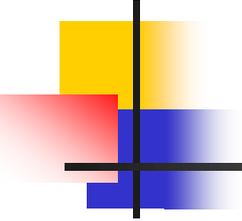
- A subsequent **conjugation reaction** with an endogenous substrate, such as glucuronic acid, sulfuric acid, acetic acid, or an amino acid

- Results in polar, usually more **water-soluble compounds** that are most often **therapeutically inactive**
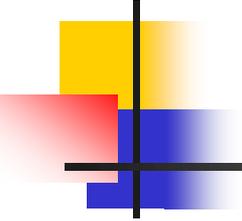
Phase II

- **Glucuronidation** is the most common and important conjugation reaction

- Drugs possessing **–OH, HN2, COOH** group may enter phase II directly & become conjugated without phase I

Biotransformation of drugs

Drug → Phase I → Oxidation, reduction, and/or hydrolysis → Phase II → Conjugation products

Some drugs directly enter Phase II metabolism.

Following Phase I, the drug may be activated, unchanged, or most often, inactivated.

Conjugated drug is usually inactive.