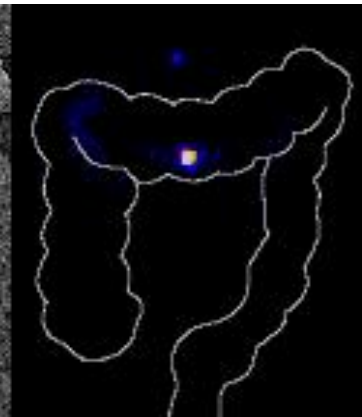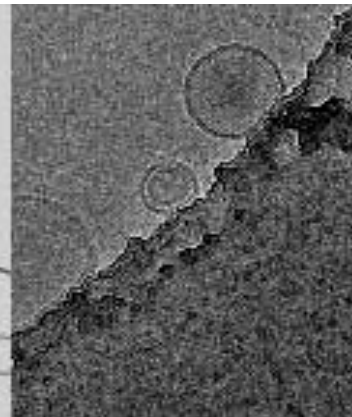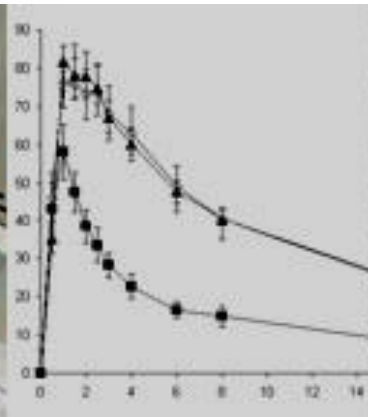# BIOPHARMACEUTICS
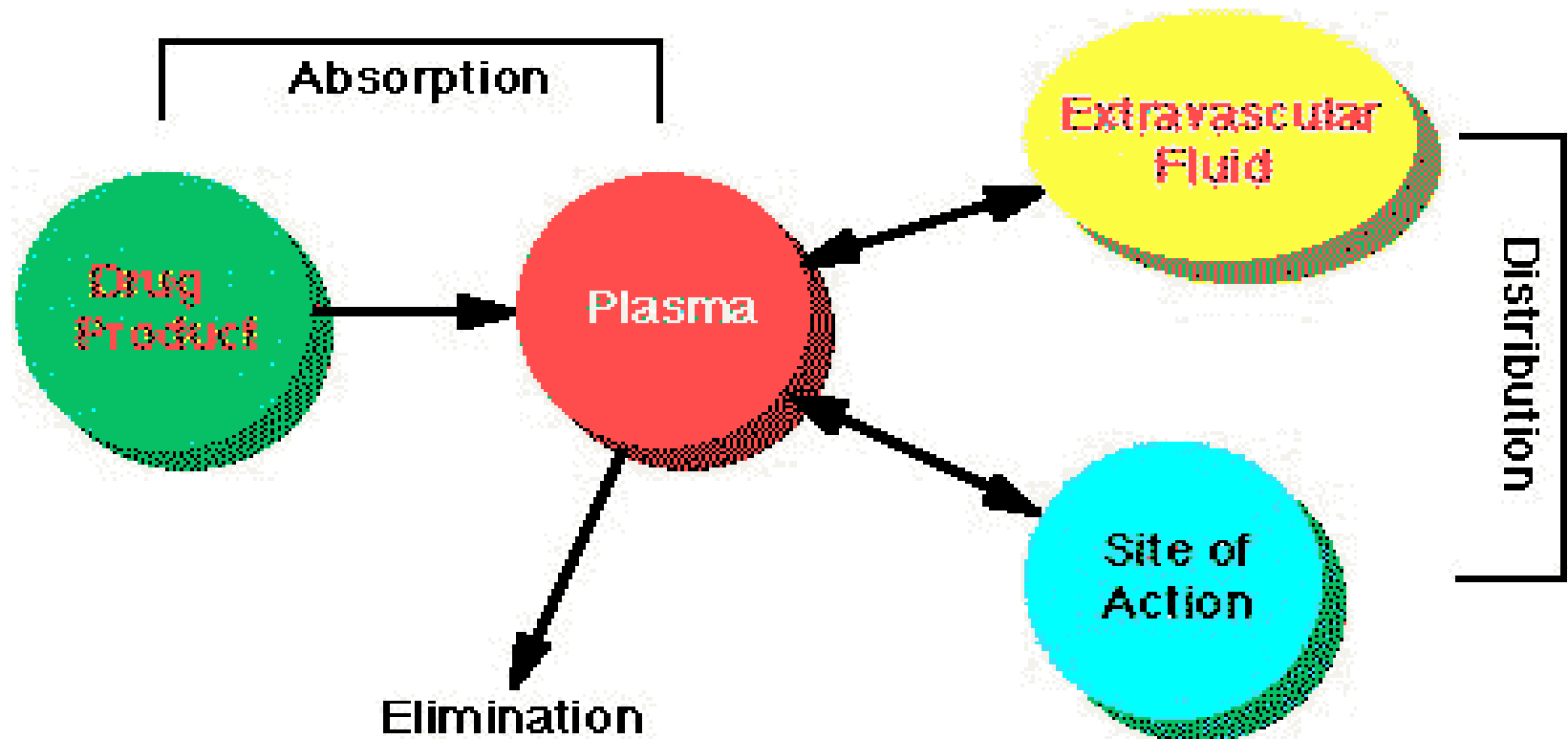
Introduction to bipharmaceutics:

- **Biopharmaceutics:** the study of how the physicochemical properties of drugs, dosage forms and routes of administeration affect the rate and extent of the drug absorption.

- Thus, biopharmaceutics involves factors that influence the:

1) protection and stability of the drug within the product;

2) the rate of drug release from the product;

3) the rate of dissolution of the drug at the absorption site; and

4) the availability of the drug at its site of action .

Introduction to bipharmaceutics (Cont.):

Scheme demonstrating the dynamic relationships among the drug, the product, and pharmacologic effect.

Introduction to bipharmaceutics (Cont.):

- **ADME:** is an (term) acronym in pharmacokinetics and pharmacology for **a**bsorption, **d**istribution, **m**etabolism, and **e**xcretion, and describes the disposition of a pharmaceutical compound within an organism.

- **Pharmacokinetics:** The study and characterization of the time course (kinetics) of drug absorption, distribution, metabolism and elimination (ADME).

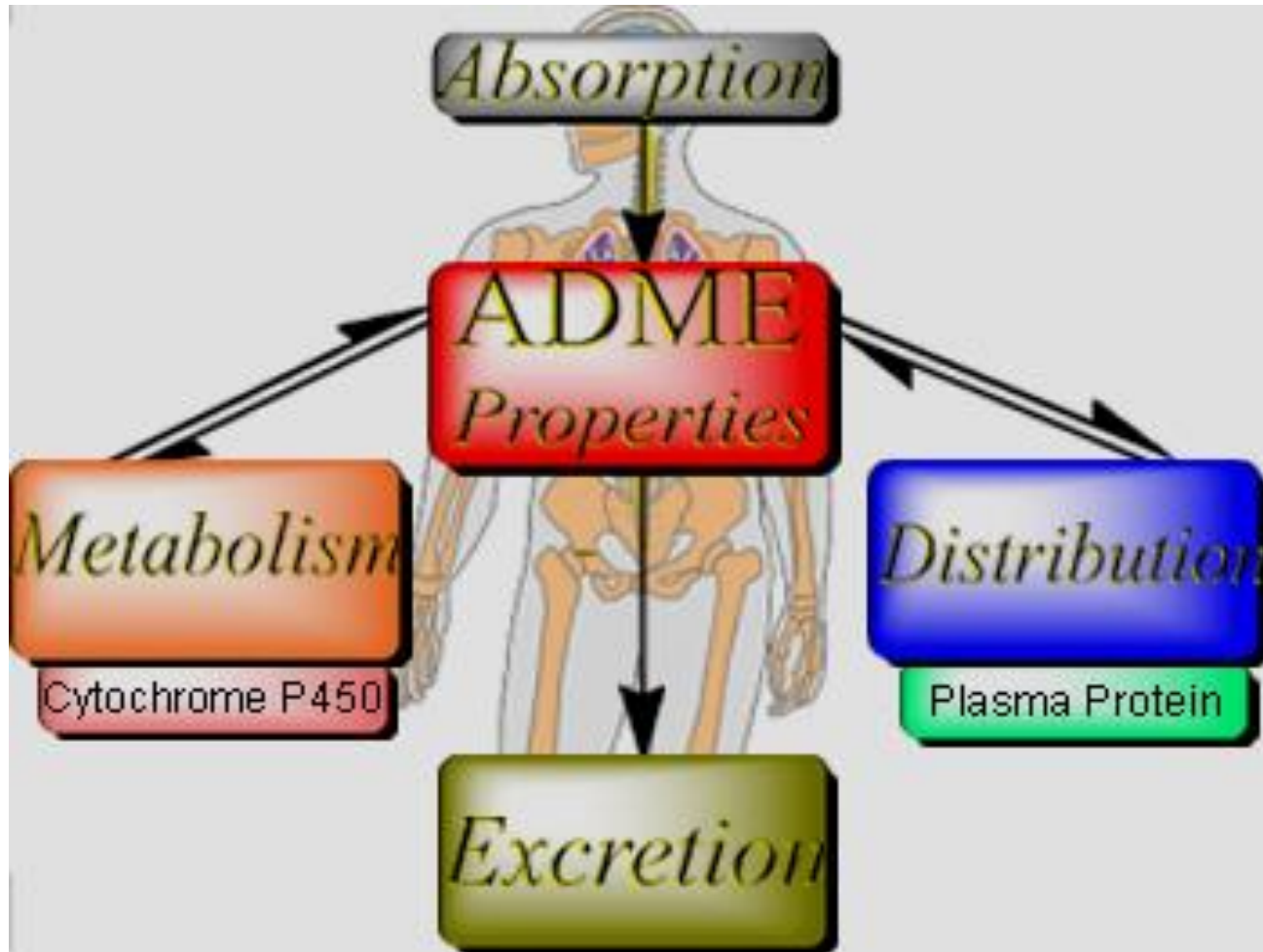# Introduction to bipharmaceutics (Cont.):

ADME PROCESSES

Absorption
Distribution
Metabolism
Excretion
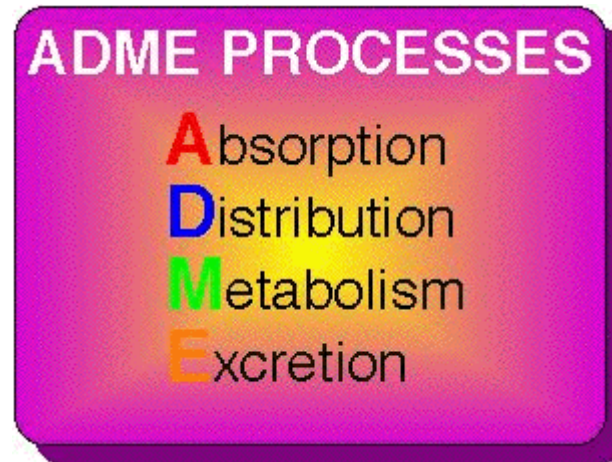
- **Absorption:** is the process of a substance entering the body(plasma).
- **Distribution:** is the dispersion of substances throughout the fluids and tissues of the body.
- **Metabolism:** is the irreversible transformation of parent compounds into daughter metabolites.
- **Excretion:** is the elimination of the substances from the body.

Introduction to bipharmaceutics (Cont.):

Introduction to bipharmaceutics (Cont.):
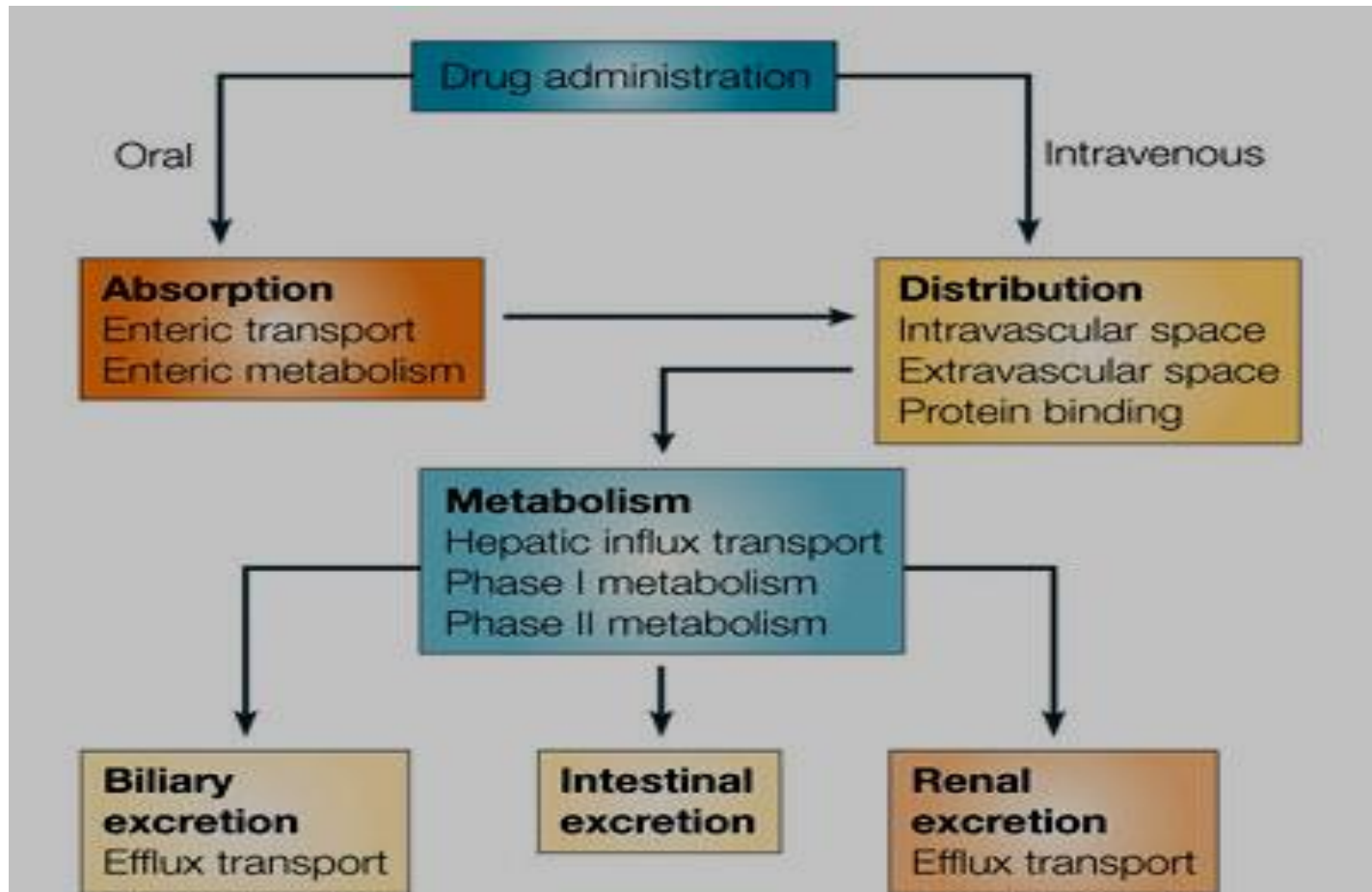
Introduction to bipharmaceutics (Cont.):

- **Bioavailability:** The rate and extent of drug absorption.
- **Bioavailable dose:** The fraction of an administered dose of a particular drug that reaches the systemic circulation intact.
- **Plasma level-time curve:**
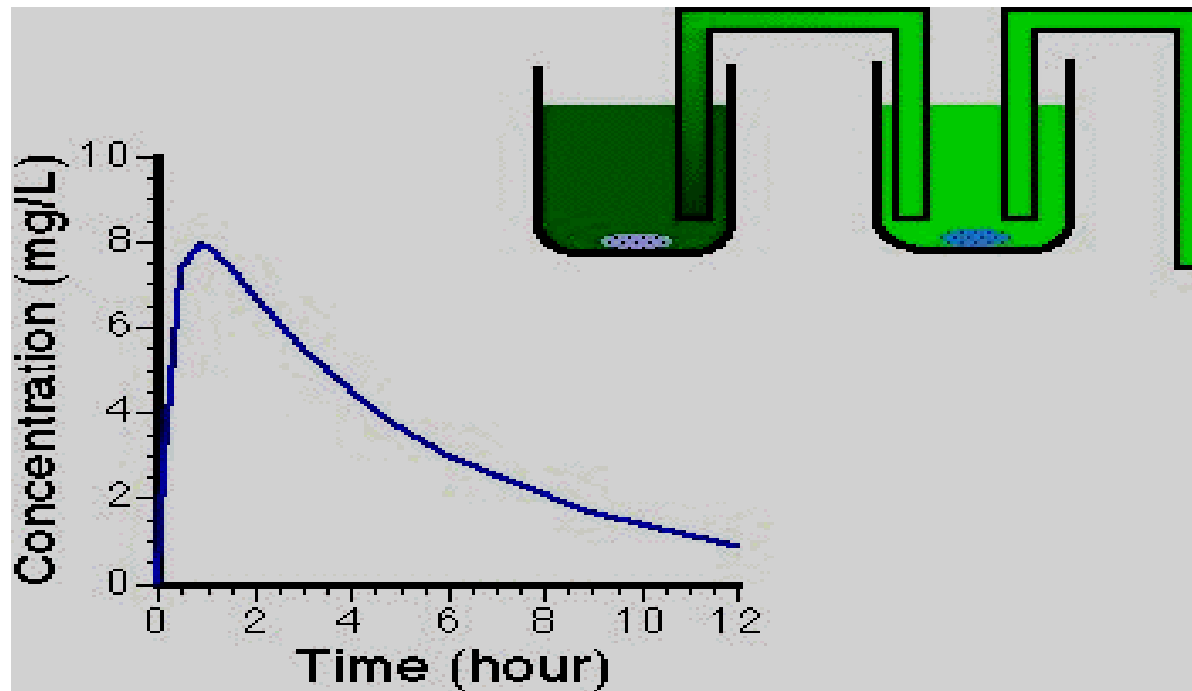
Introduction to bipharmaceutics (Cont.):

- The plasma level-time curve is generated by measuring the drug concentration in plasma samples taken at various time intervals after a drug product is administered.

- The concentration of drug in each plasma sample is plotted against the corresponding time at which the plasma sample was removed.
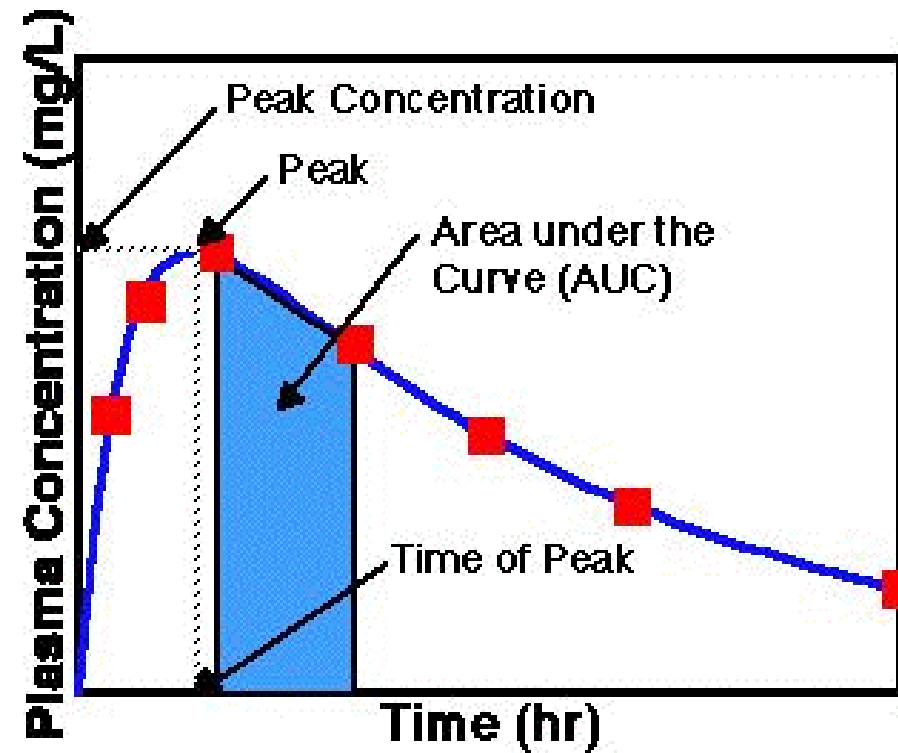
Introduction to bipharmaceutics (Cont.):
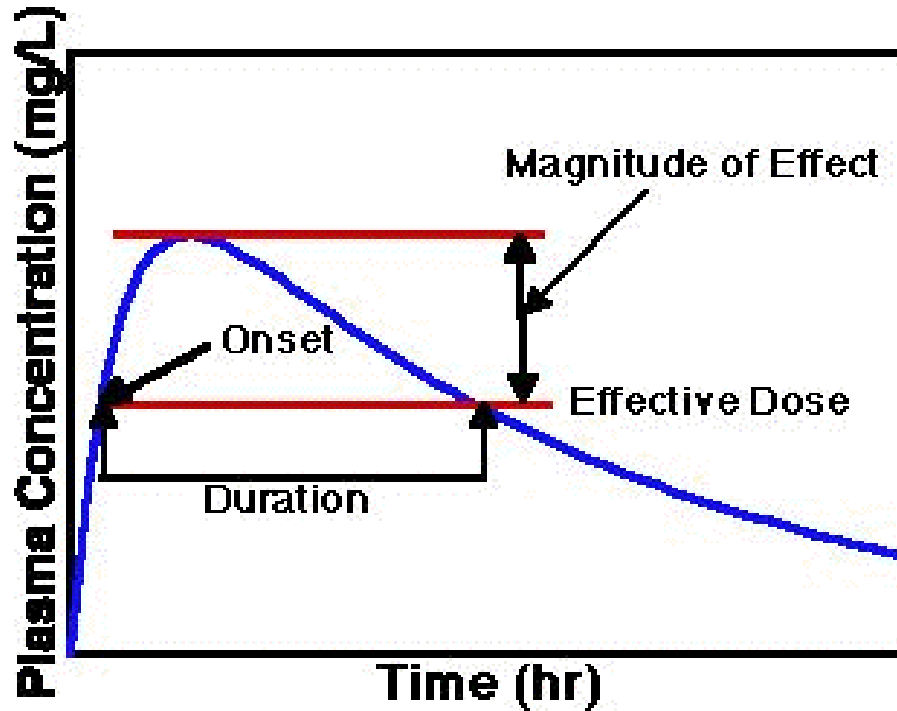
Introduction to bipharmaceutics (Cont.):

- **Drug Product Performance Parameters:**

1- Minimum effective concentration (MEC): The minimum concentration of drug needed at the receptors to produce the desired pharmacologic effect.

2- Minimum toxic concentration (MTC): The drug concentration needed to just produce a toxic effect.

3- Onset time: The time required for the drug to reach the MEC.

4- Duration of action: The difference between the onset time and the time for the drug to decline back to the MEC.

Introduction to bipharmaceutics (Cont.):

5- The time of peak plasma level: The time of maximum drug concentration in the plasma and is proportional to the rate of drug absorption.

6- The peak plasma level: The maximum drug concentration, usually related to the dose and the rate constants for absorption and elimination of the drug.

7- Area under the curve: It is related to the amount of drug absorbed systemically.

Absorption

Main factors affecting oral absorption:

I Physiological factors.

II Physical-chemical factors.

III Formulation factors.

I Physiological factors affecting oral absorption:

1- Membrane physiology.

2- Passage of drugs across membranes.

3- Gastrointestinal physiology.

I.   Characteristics of GIT physiology and drug absorption

II.   Gastric emptying time and motility

III.   Effect of food on drug absorption

Physiological factors influencing bioavailability:

1- Membrane physiology:
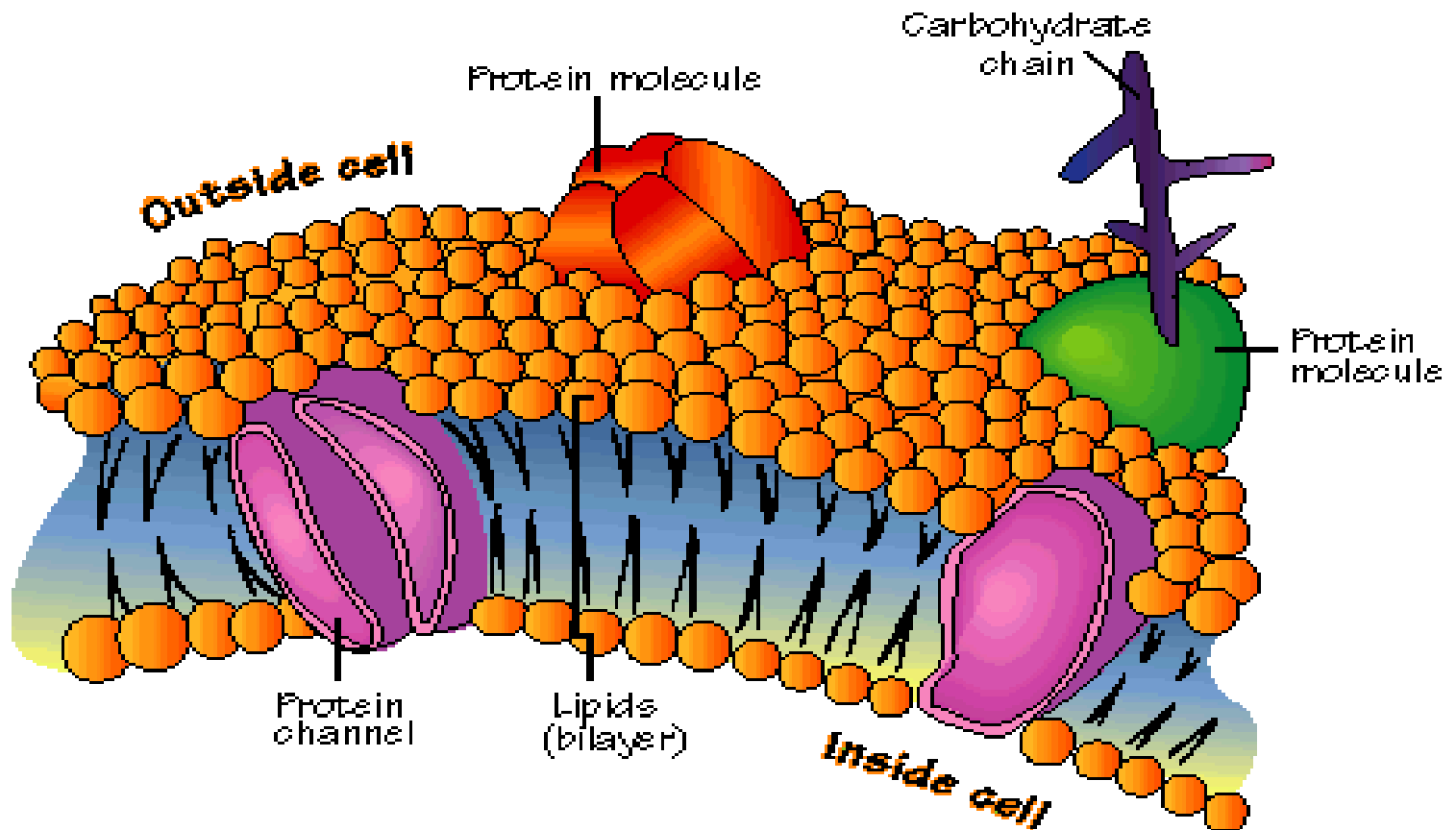
1- Membrane physiology (Cont.):

- The cell membrane is the barrier that separates the inside of the cell from the outside.

- The cell membrane is made up of phospholipids, proteins, and other macromolecules.

- The phospholipids make up a bilayer. It contains hydrophilic and hydrophobic molecules.

- The proteins in the cell membrane are located within the phospholipid bilayer.

- So, the biologic membrane is mainly lipid in nature but contains small aqueous channels or pores.

2-Passage of drugs across membranes:

••Transport across the membranes:

1- Carrier mediated:
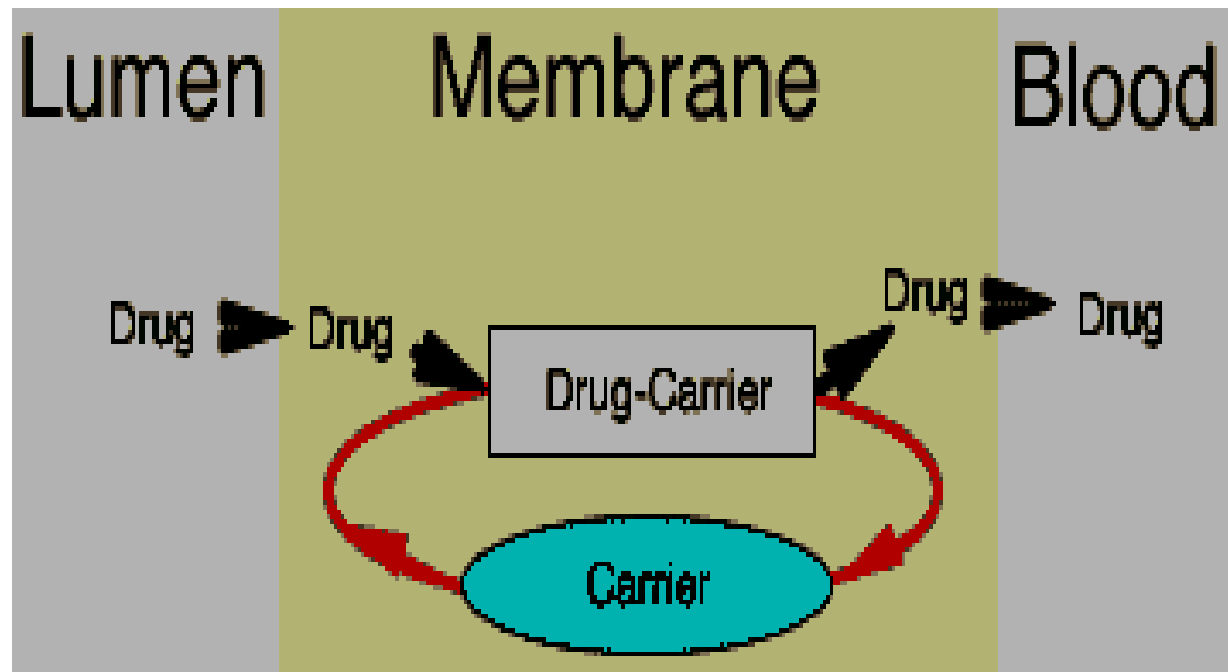
2-Transport across the membranes (Cont.):

A- Active transport:

- A few lipid-insoluble drugs (e.g.5-flurouracil) that resemble natural physiologic metabolites (e.g. glucose, amino acids) are absorbed from the GIT by this process.

- Transport of a drug against concentration gradient (from regions of low drug concentrations to regions of high concentrations).

- It is an energy-consuming system.

- The carrier molecule may be highly selective for the drug molecule, therefore, drugs of similar structure may compete for sites of adsorption on the carrier (competitive inhibition is possible)

- Because only a certain amount of carrier is available, all the adsorption sites on the carrier may become saturated if the drug concentration gets very high.
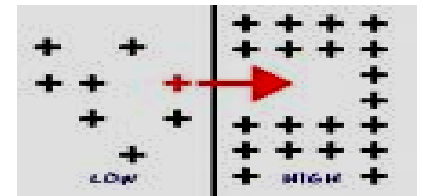
2-Transport across the membranes (Cont.):
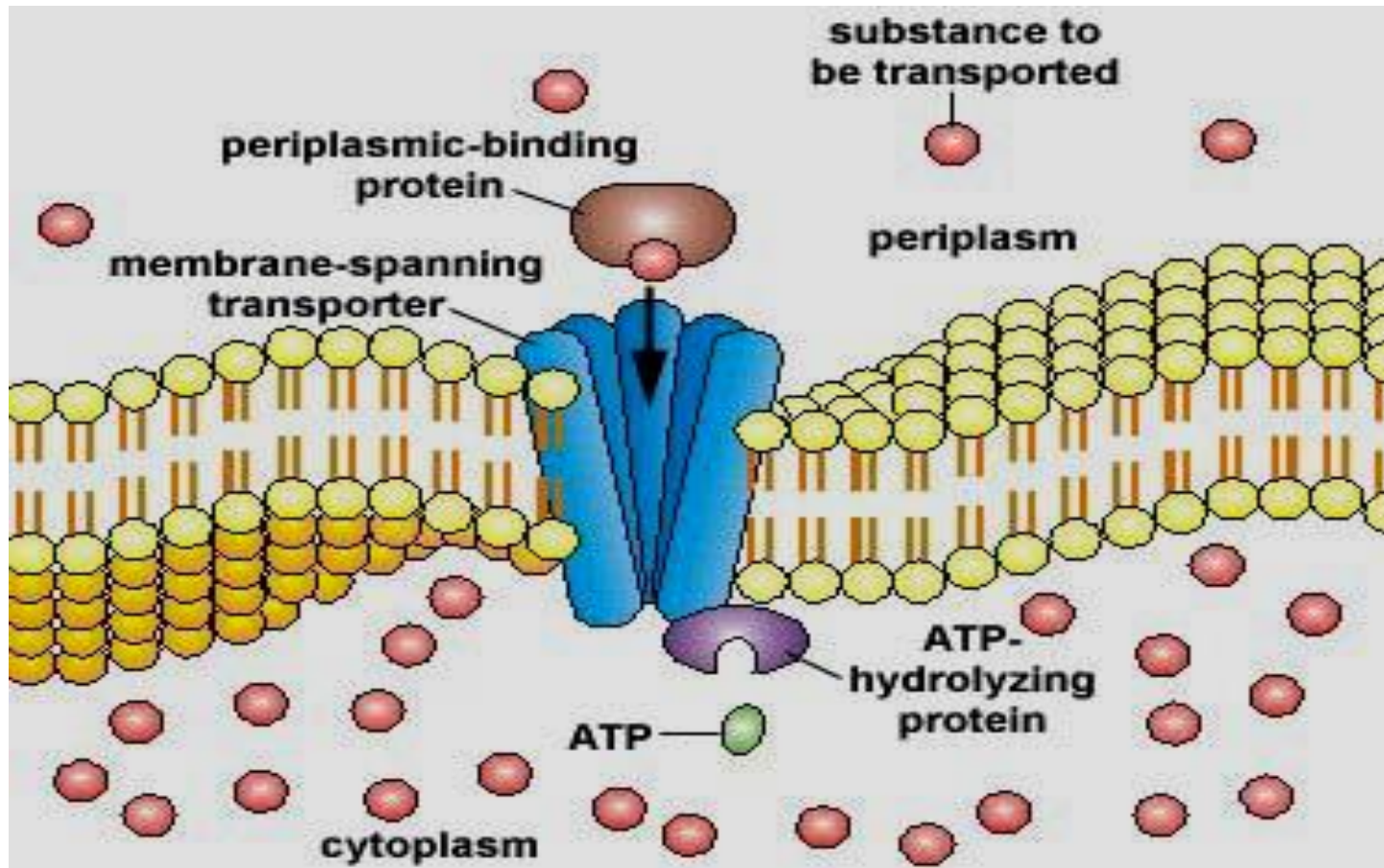
2-Transport across the membranes (Cont.):

B- Facilitated diffusion:

- Play a very minor role in absorption.

- A drug carrier is required but no energy is necessary. e.g. vitamin B12 transport.

- Saturable if not enough carrier and structurally selective for the drug and shows competition kinetics for drugs of similar structure.

- No transport against a concentration gradient only downhill but faster.

Facilitated diffusion

Outside cell	Low concentration of solute	Outside cell
Inside cell	High concentration of solute	Inside cell
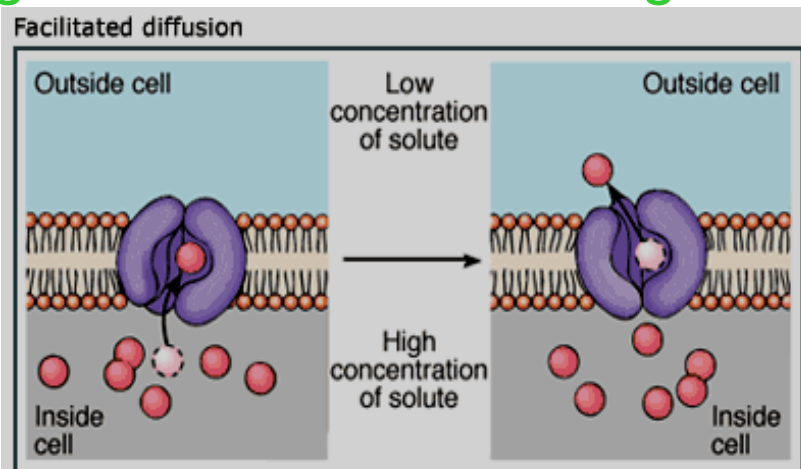
2-Transport across the membranes (Cont.):

2- Passive diffusion:

- Most drugs cross biologic membranes by passive diffusion.

- Diffusion occurs when the drug concentration on one side of the membrane is higher than that on the other side.

- The process is passive because no external energy is expended.

- The driving force for passive diffusion is the difference in drug concentrations on either side of the cell membrane.
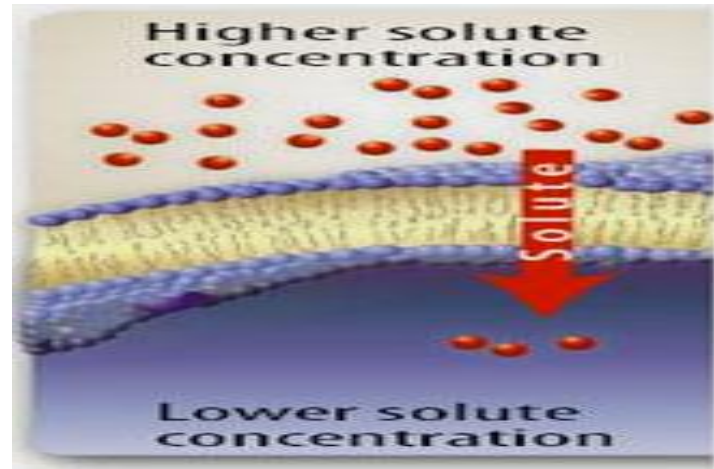
2-Transport across the membranes (Cont.):
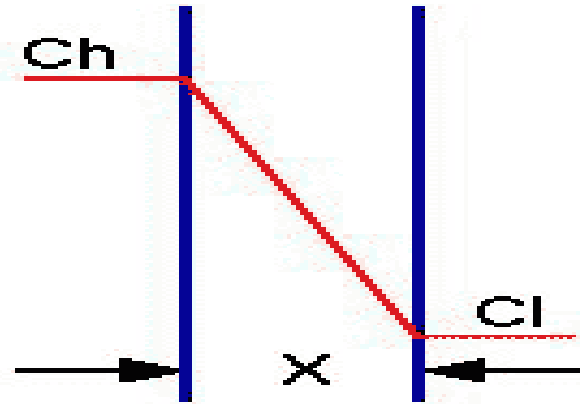
Diagram of Passive Transport with a Concentration Gradient

-The rate of transport of drug across the membrane can be described by Fick's first law of diffusion:-

$$\text{Rate of diffusion} = \frac{dM}{dt} = -\frac{D \bullet A \bullet (Ch - Cl)}{x}$$

Fick's First Law, Rate of Diffusion

2-Transport across the membranes (Cont.):

■ The parameters of this equation are:-

D: diffusion coefficient. This parameter is related to the size and lipid solubility of the drug and the viscosity of the diffusion medium.

As lipid solubility increases or molecular size decreases then D increases and thus dM/dt also increases.

A: surface area. As the surface area increases the rate of diffusion also increase.

The surface of the intestinal lining (with villae and microvillae) is much larger than the stomach. This is one reason absorption is generally faster from the intestine compared with absorption from the stomach.

2-Transport across the membranes (Cont.):

x: membrane thickness. The smaller the membrane thickness the quicker the diffusion process. As one example, the membrane in the lung is quite thin thus inhalation absorption can be quite rapid.

(Ch -Cl): concentration difference.
The drug concentration in blood or plasma will be quite low compared with the concentration in the GI tract. It is this concentration gradient which allows the rapid complete absorption of many drug substances.

- Normally Cl << Ch then:-

$$\frac{dM}{dt} = -\frac{D \bullet A \bullet Ch}{x}$$

constant, ka

2-Transport across the membranes (Cont.):
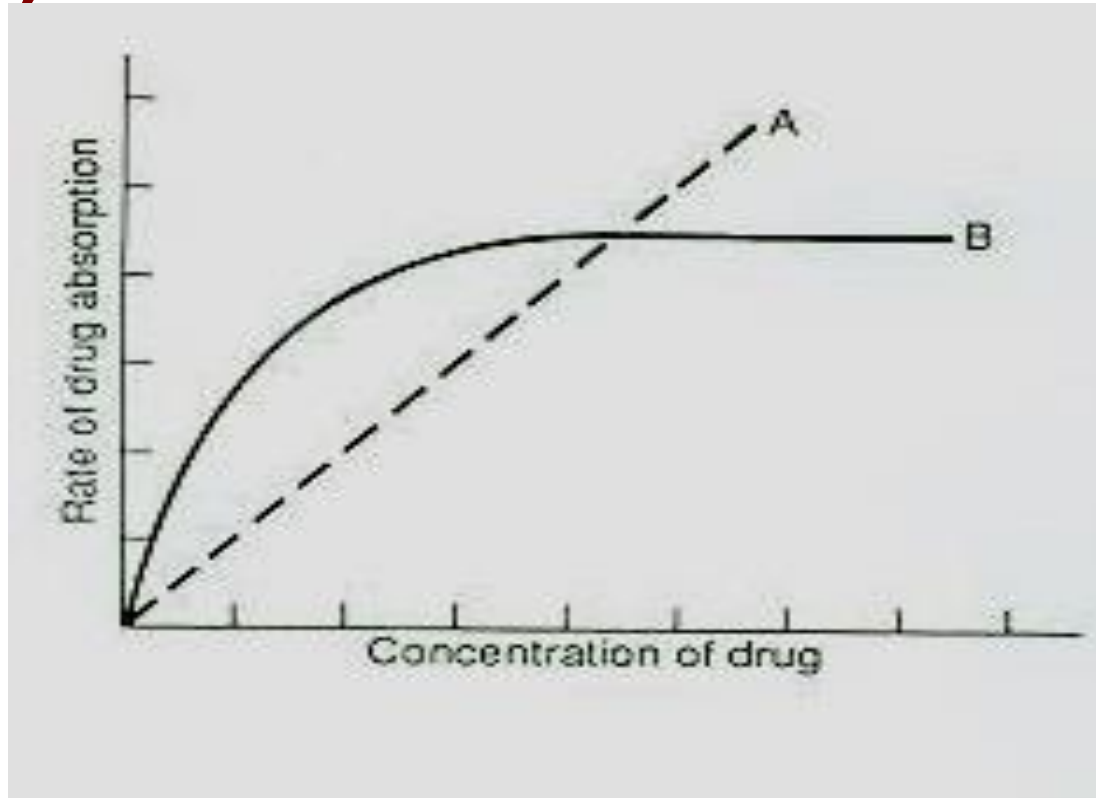
Relationship between drug concentration and absorption rate For a passive process (Curve A) and for a carrier-mediated Process (Curve B).

2-Transport across the membranes (Cont.):
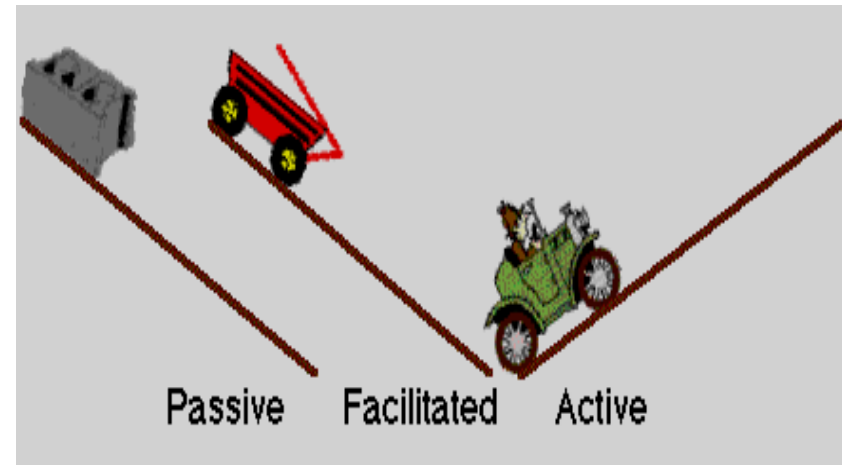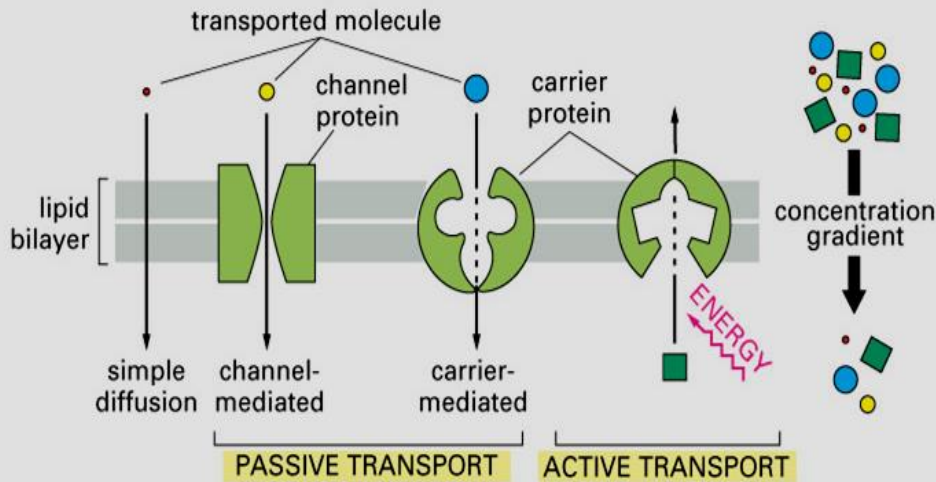
Illustration of Different Transport Mechanisms

2-Transport across the membranes (Cont.):

3- Vesicular transport:

- It is the process of engulfing particles or dissolved materials by the cell.

- Pinocytosis and phagocytosis are forms of vesicular transport that differ by the type of material ingested.

Pinocytosis: refers to the engulfment of small molecules or fluid.

Phagocytosis: refers to the engulfment of larger particles or macromolecules.

- During pinocytosis or phagocytosis, the cell membrane invaginates to surround the material, and then engulfs the material into the cell. Subsequently, the cell membrane containing the material forms a vesicle or vacuole within the cell.

- Vesicular transport is the proposed process for the absorption of Vitamin A, D, E, and K, peptides in new born.

2-Transport across the membranes (Cont.):

VESICLE

PLASMA MEMBRANE

Endocytosis

Outside of cell

Cytoplasm
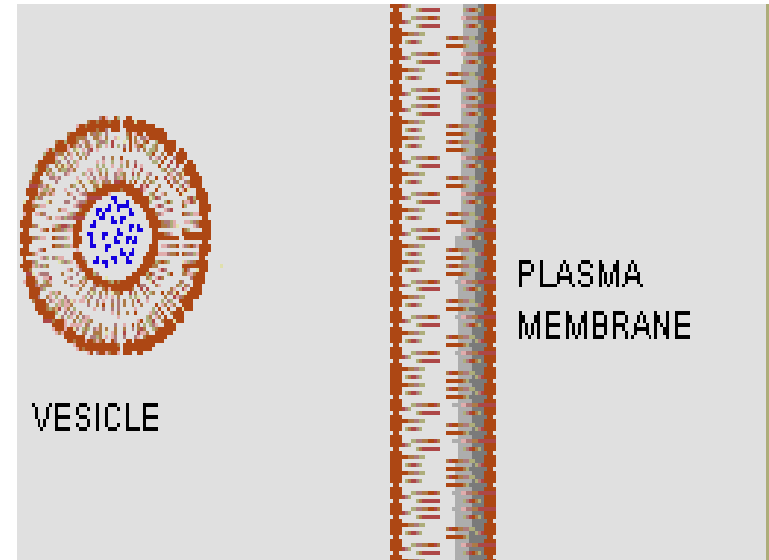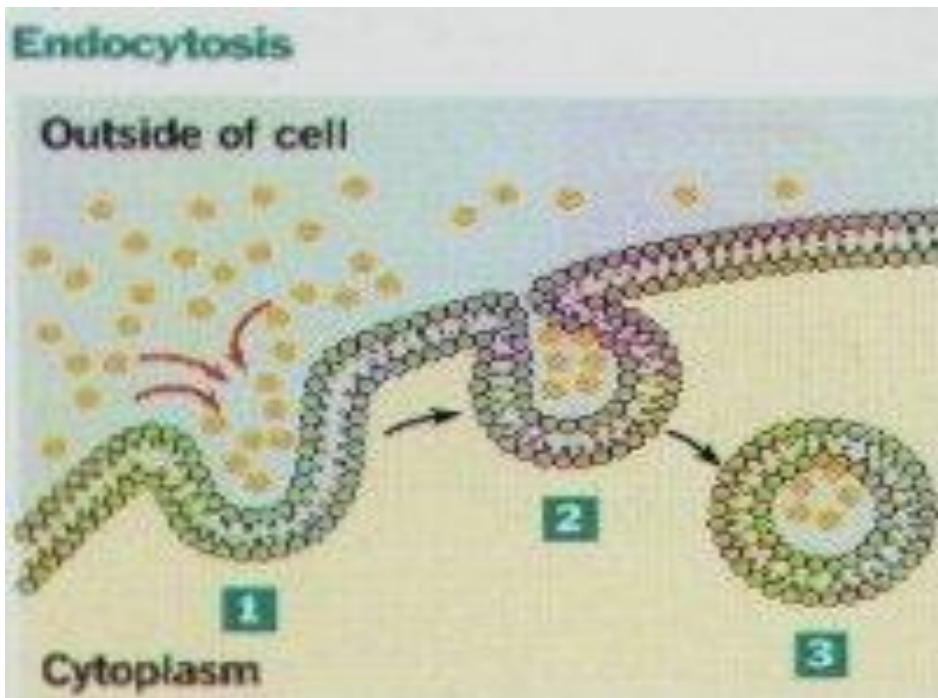
2-Transport across the membranes (Cont.):

4- Pore (convective) transport:

- A certain type of protein called transport protein may form an open channel across the lipid membrane of the cell.

- Very small molecules, such as urea, water and sugars are able to rapidly cross the cell membrane through these pores.

5- Ion pair formation:

- Strong electrolyte drugs are highly ionized or charged molecules, such as quaternary nitrogen compounds.

- These drugs penetrate membranes poorly. When linked up with an oppositely charged ion, an ion pair is formed in which the overall charge of the pair is neutral. This neutral complex diffuses more easily across the membrane.

- e.g. the formation of an ion pair for propranolol (basic drug) with oleic acid.

Transport of Substances Across a Membrane by Channel Proteins
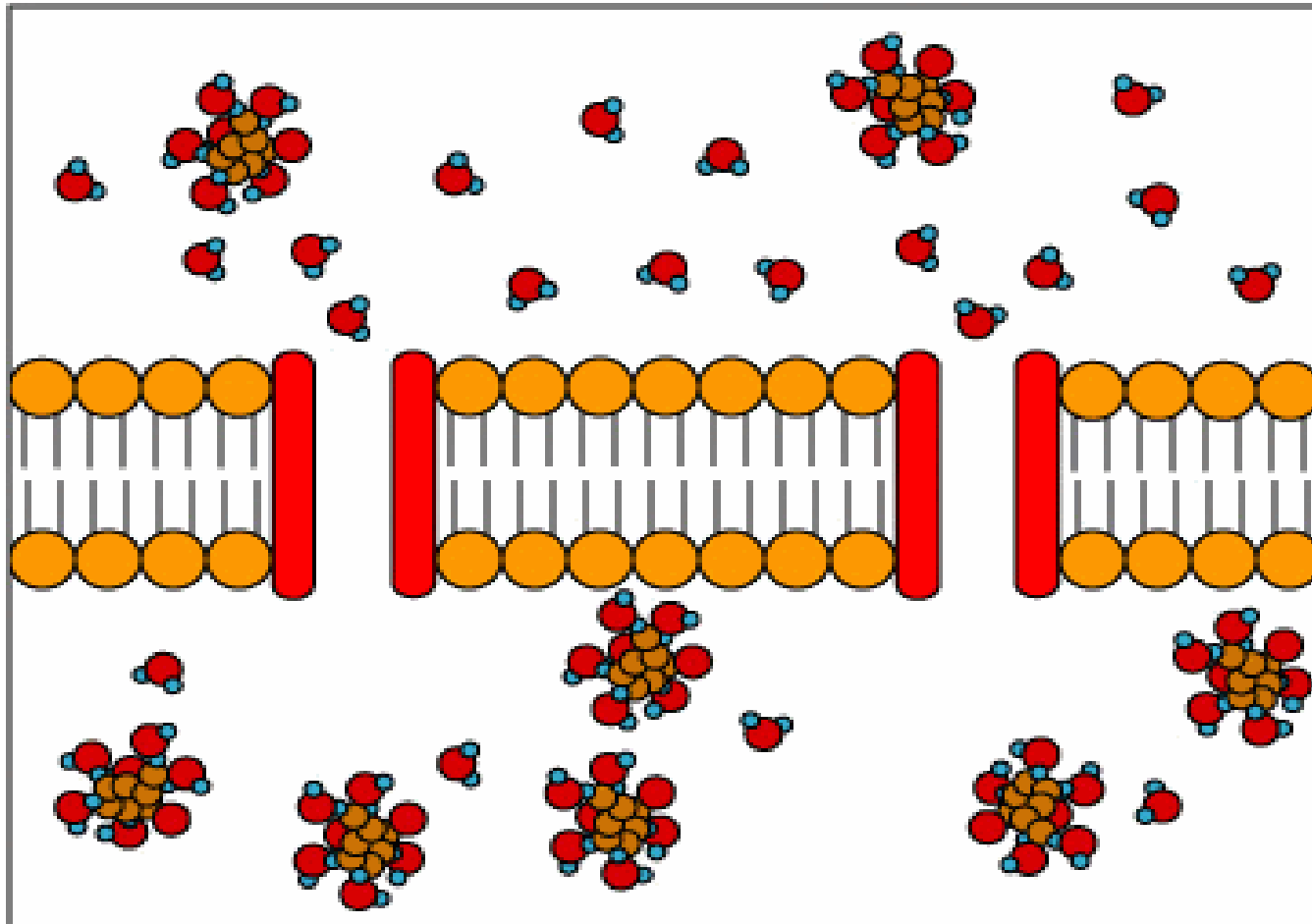
2-Transport across the membranes (Cont.):
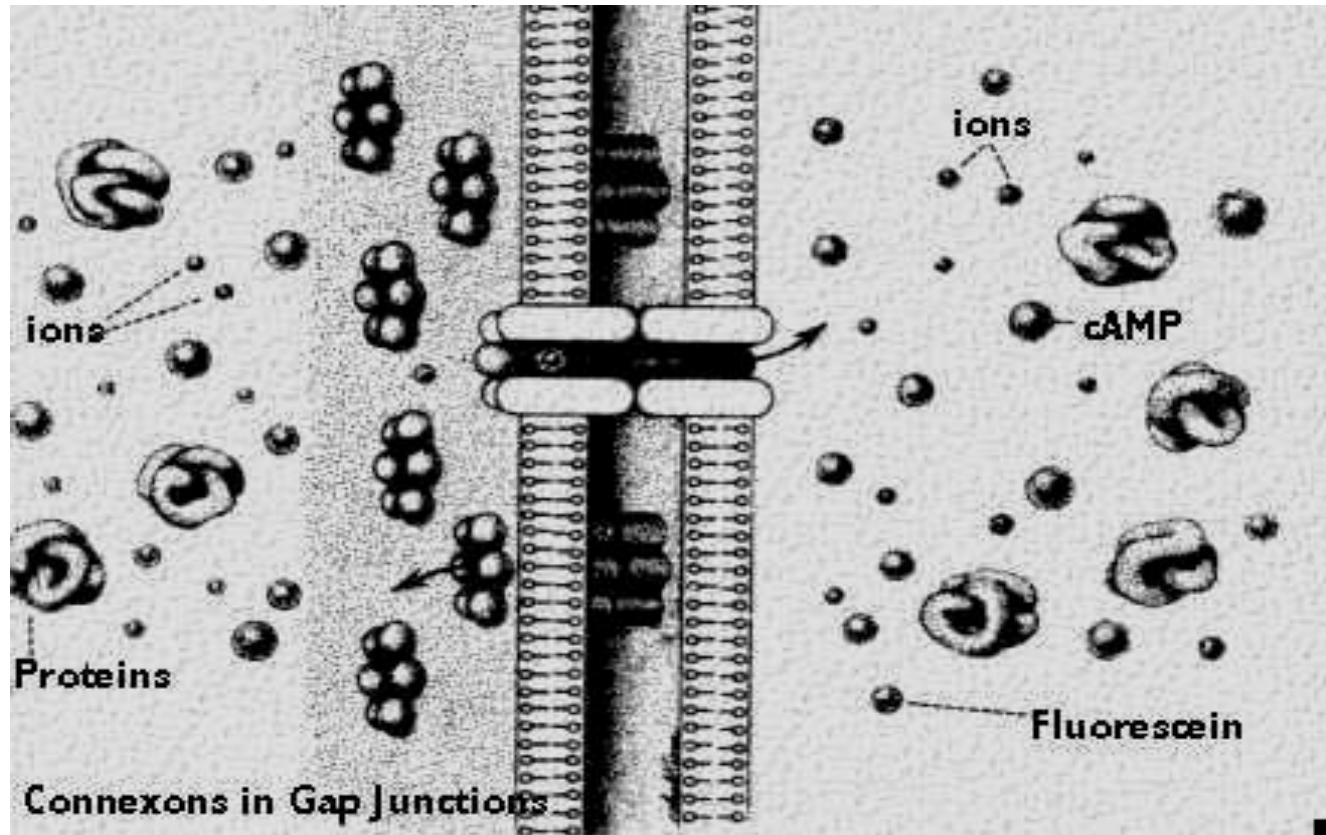
Mechanism of ion pair transport of drugs

3- Gastrointestinal (GI) Physiology:

- The gastrointestinal tract is a muscular tube approximately 6 m in length with varying diameters.

- It stretches from the mouth to the anus and consists of four main anatomical areas: the oesophagus, the stomach, the small intestine and the large intestine or colon.

- The majority of the gastrointestinal epithelium is covered by a layer of mucous. This is a viscoelastic translucent aqueous gel that is secreted through out the GIT, acting as a protective layer and a mechanical barrier.

Gastrointestinal (GI) Physiology (Cont.):
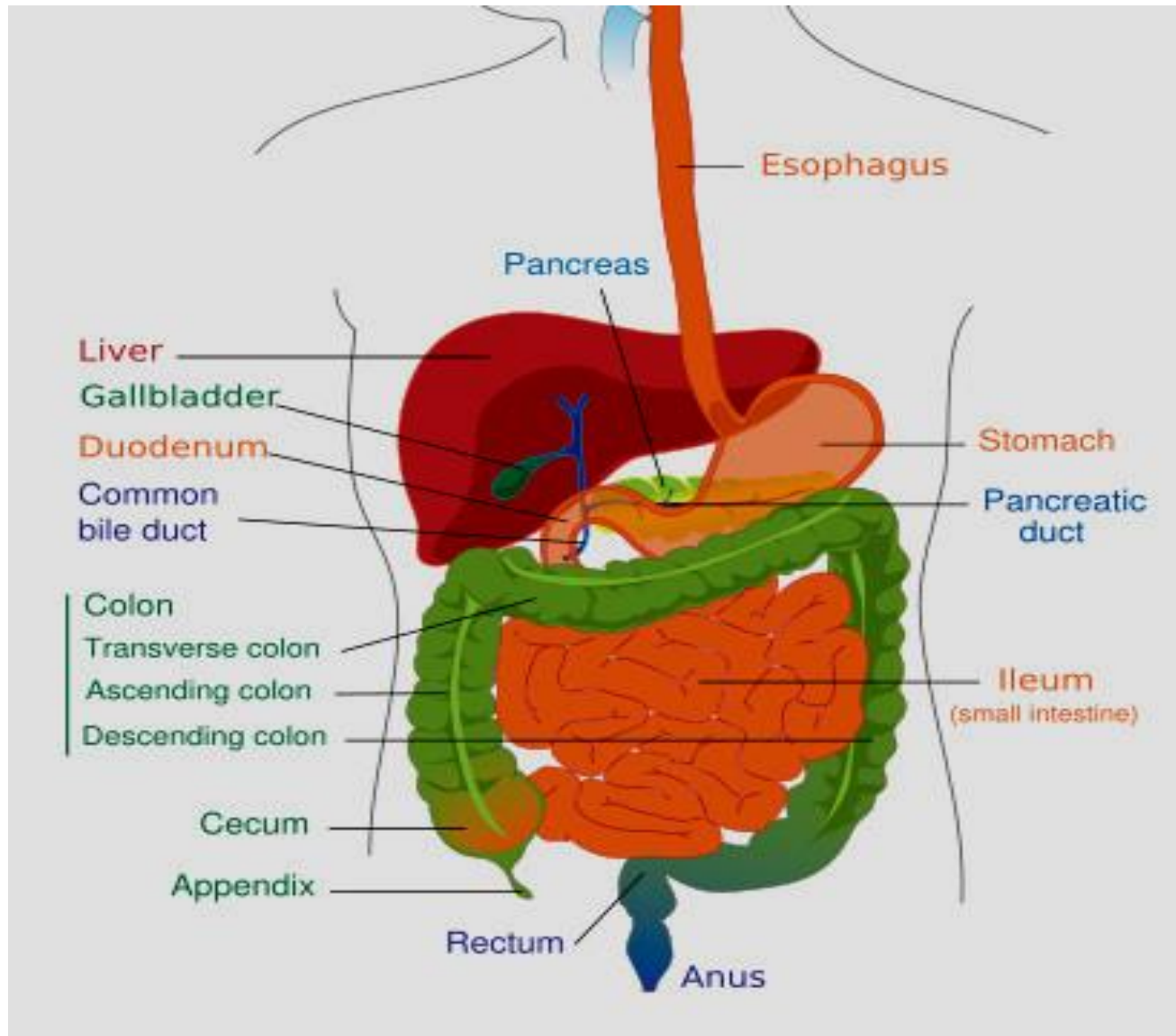
Gastrointestinal (GI) Physiology (Cont.):
I. Characteristics of GI physiology and Drug Absorption:

Organs	pH	Membrane	Blood Supply	Surface Area	Transit Time	By-pass liver
Buccal	approx 6	thin	Good, fast absorption with low dose	small	Short unless controlled	yes
Oesophagus	5-6	Very thick no absorption	-	small	short, typically a few seconds, except for some coated tablets	-

I. Characteristics of GI physiology and Drug Absorption (cont.):

Organs	pH	Membrane	Blood Supply	Surface Area	Transit Time	By-pass liver
Stomach	1.7-3.5	normal	good	small	30 min (liquid) - 120 min (solid food)	no
Duodenum	5 - 7	normal	good	Very large	very short,	no

I. Characteristics of GI physiology and Drug Absorption (cont.):

Organs	pH	Membrane	Blood Supply	Surface Area	Transit Time	By-pass liver
Small Intestine	6 – 7.5	normal	good	Very large	About 3 hours	no
Large intestine	6.8 - 7	-	good	Not very large	long, up to 24 hours	Lower colon, rectum yes

I. Characteristics of GI physiology and Drug Absorption (cont.):

The environment within the lumen:

Gastrointestinal pH

- As we observed from the previous tables, the pH of fluids varies along the length of the GIT.

- The gastrointestinal pH may influence the absorption of drugs in a variety of ways:

A- It may affect the chemical stability of the drug in the lumen e.g. penicillin G, erythromycin

B- affect the drug dissolution or absorption e.g. weak electrolyte drug

Luminal enzymes

- The primary enzyme found in gastric juice is pepsin. Lipases, amylases and proteases are secreted from the pancreas into the small intestine.

- Pepsins and proteases are responsible for the digestion of protein and peptide drugs in the lumen.

I. Characteristics of GI physiology and Drug Absorption (cont.):

- The lipases may affect the release of drugs from fat / oil – containing dosage forms.

- Bacteria which are localized within the colonic region of the GIT secrete enzymes which are capable of a range of reactions.

- e.g. Sulphasalazine which is a prodrug used to target the colon.

Bacterial enzymes

Sulphasalazine ────────────────→   active drug

(5-aminosalycylic acid)

treat inflammatory bowel disease
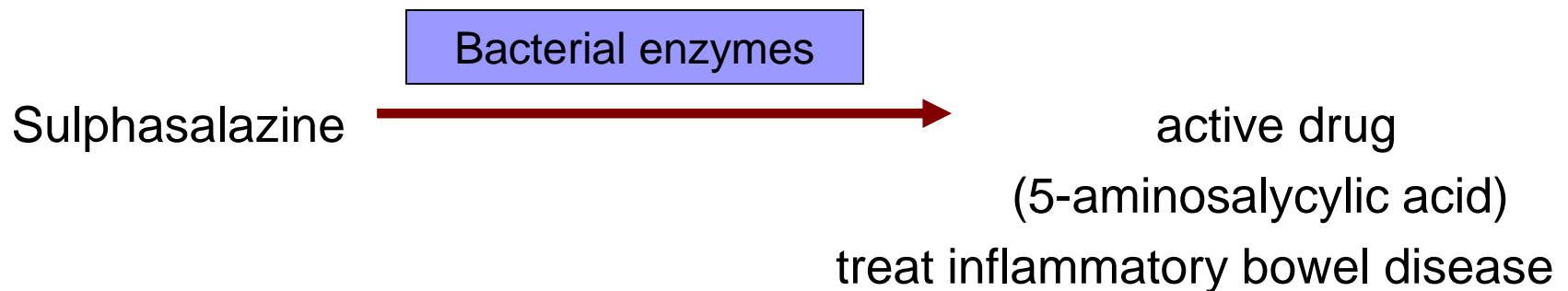
I. Characteristics of GI physiology and Drug Absorption (cont.):

Disease state and physiological disorders

- Local diseases can cause alterations in gastric pH that can affect the stability , dissolution and absorption of the drug.

- Partial or total gastrectomy results in drugs reaching the duodenum more rapidly than in normal individuals. This may result in an increased overall rate of absorption of drugs that are absorbed in the small intestine.

- However, drugs that require a period of time in the stomach to facilitate their dissolution may show reduced bioavailability in such patients.

I. Characteristics of GI physiology and Drug Absorption (cont.):

The unstirred water layer

- It is a more or less stagnant layer of water and mucous adjacent to the intestinal wall.

- This layer can provide a diffusion barrier to drugs.

- Some drugs (antibiotics e.g. tetracycline) are capable of complexing with mucous, thereby reducing their availability for absorption.

II **Gastric emptying and motility:**

- The time a dosage form takes to traverse the stomach is usually termed: the gastric residence time, gastric emptying time or gastric emptying rate.

▪ Generally drugs are better absorbed in the small intestine (because of the larger surface area) than in the stomach, therefore quicker stomach emptying will increase drug absorption.

- For example, a good correlation has been found between stomach emptying time and peak plasma concentration for acetaminophen. The quicker the stomach emptying (shorter stomach emptying time) the higher the plasma concentration.

- Also slower stomach emptying can cause increased degradation of drugs in the stomach's lower pH; e.g. L-dopa.

II Gastric emptying and motility:
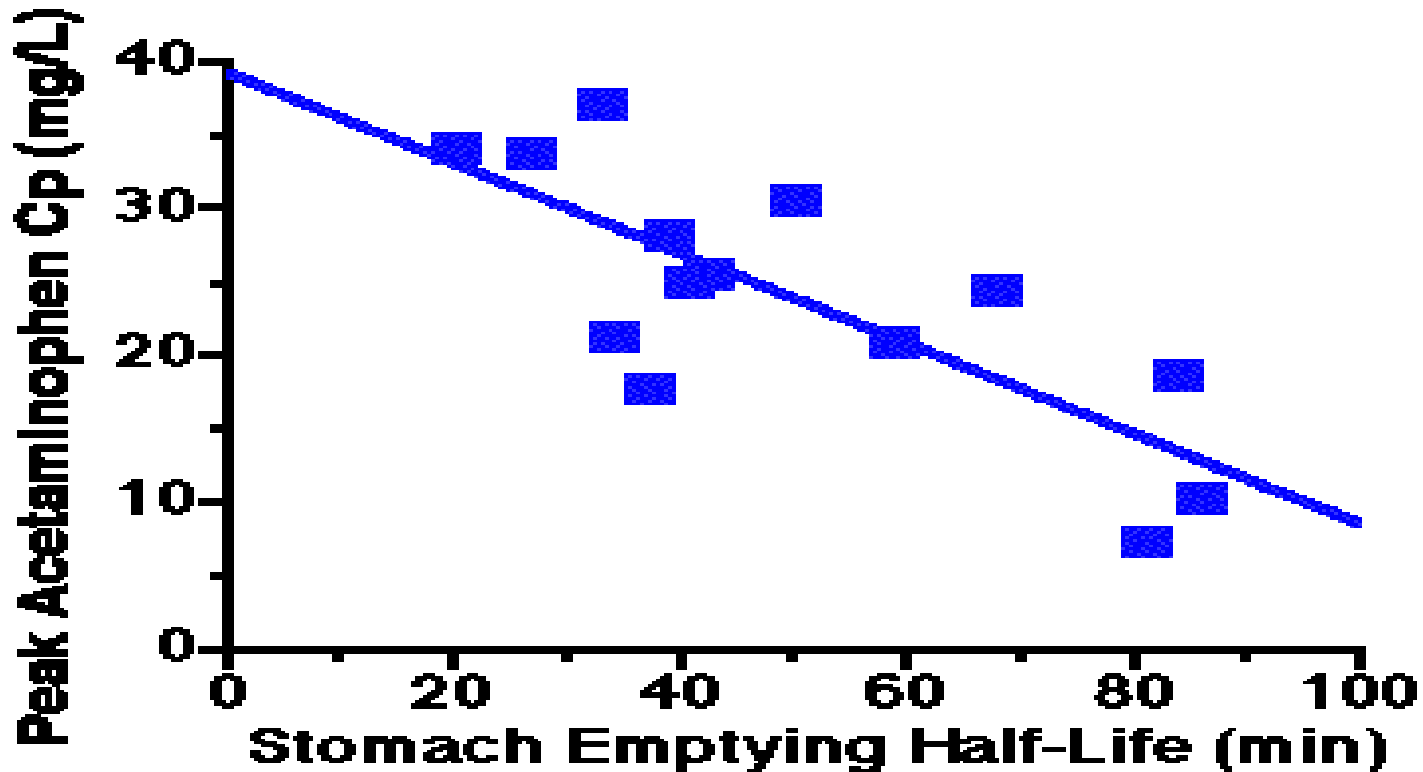
Dependence of peak acetaminophen plasma concentration as a function of stomach emptying half-life

II Gastric emptying and motility:

Factors Affecting Gastric Emptying

Volume of Ingested Material	As volume increases initially an increase then a dcrease. Bulky material tends to empty more slowly than liquids
Type of Meal	
Fatty food	Decrease
Carbohydrate	Decrease
Temperature of Food	Increase in temperature, increase in empting rate
Body Position	Lying on the left side decreases emptying rate. Standing versus lying (delayed)
Drugs	
Anticholinergics (e.g. atropine)	Decrease
Narcotic (e.g. morphine)	Decrease
Analgesic (e.g. aspirin)	Decrease

ll Gastric emptying and motility:

Factors Affecting Gastric Emptying

Viscosity	Rate of emptying is greater for less viscous solutions
Emotional states	- Stressful emotional states increase stomach contraction and emptying rate - Depression reduces stomach contraction and emptying
Disease states	-Rate of emptying is reduced in: Some diabetic patients, hypothyrodism -Rate of emptying is increased in: hyperthyrodism
Excercise	Reduce emptying rate

III Effect of Food:

- The presence of food in the GIT can influence the rate and extent of absorption, either directly or indirectly via a range of mechanisms.

A- Complexation of drugs with components in the diet

e.g.Tetracycline forms non-absorable complexes with calcium and iron, and thus it is advised that patients do not take products containing calcium or iron, such as milk, iron preparations or indigestion remedies, at the same time of day as the tetracycline.

B- Alteration of pH

Food tends to increase stomach pH by acting as a buffer. This liable to decrease the rate of dissolution and absorption of a weakly basic drug and increase that of a weakly acidic one.

III Effect of Food (cont.):

C- Alteration of gastric emptying

Fats and some drugs tend to reduce gastric emptying and thus delay the onset of action of certain drugs.

D- Stimulation of gastrointestinal secretions

- Gastrointestinal secretions (e.g. pepsin) produced in response to food may result in the degradation of drugs that are susceptible to enzymatic metabolism, and hence a reduction in their bioavailability.

- Fats stimulate the secretion of bile. Bile salts are surface active agents which increase the dissolution of poorly soluble drugs (griseofulvin).

  Bile salts can form insoluble and non-absorbable complexes with some drugs, such as neomycin and kanamycin.

III Effect of Food (cont.):

E-Competition between food components and drugs for specialized absorption mechanisms

There is a possibility of competitive inhibition of drug absorption in case of drugs that have a chemical structure similar to nutrients required by the body for which specialized absorption mechanisms exist.

F- Increased viscosity of gastrointestinal contents

The presence of food in the GIT provides a viscous environment which may result in:

- Reduction in the rate of drug dissolution
- Reduction in the rate of diffusion of drug in solution from the lumen to the absorbing membrane lining the GIT.

Hence, there is reduction in drug bioavailability.

III Effect of Food (cont.):

G- Food-induced changes in presystemic metabolism

- Certain foods may increase the bioavailability of drugs that are susceptible to presystemic intestinal metabolism by interacting with the metabolic process.

- E.g. Grapefruit juice is capable of inhibiting the intestinal cytochrome P450 (CYP3A) and thus taken with drugs that are susceptible to CYP3A metabolism which result in increase of their bioavailability.

H- Food-induced changes in blood flow

- Food serve to increase the bioavailability of some drugs (e.g. propranolol) that are susceptible to first-pass metaolism.

- Blood flow to the GIT and liver increases after a meal. The faster the rate of drug presentation to the liver; the larger the fraction of drug that escapes first-pass metabolism. This is because the enzyme systems become saturated.

III Effect of Food (cont.):
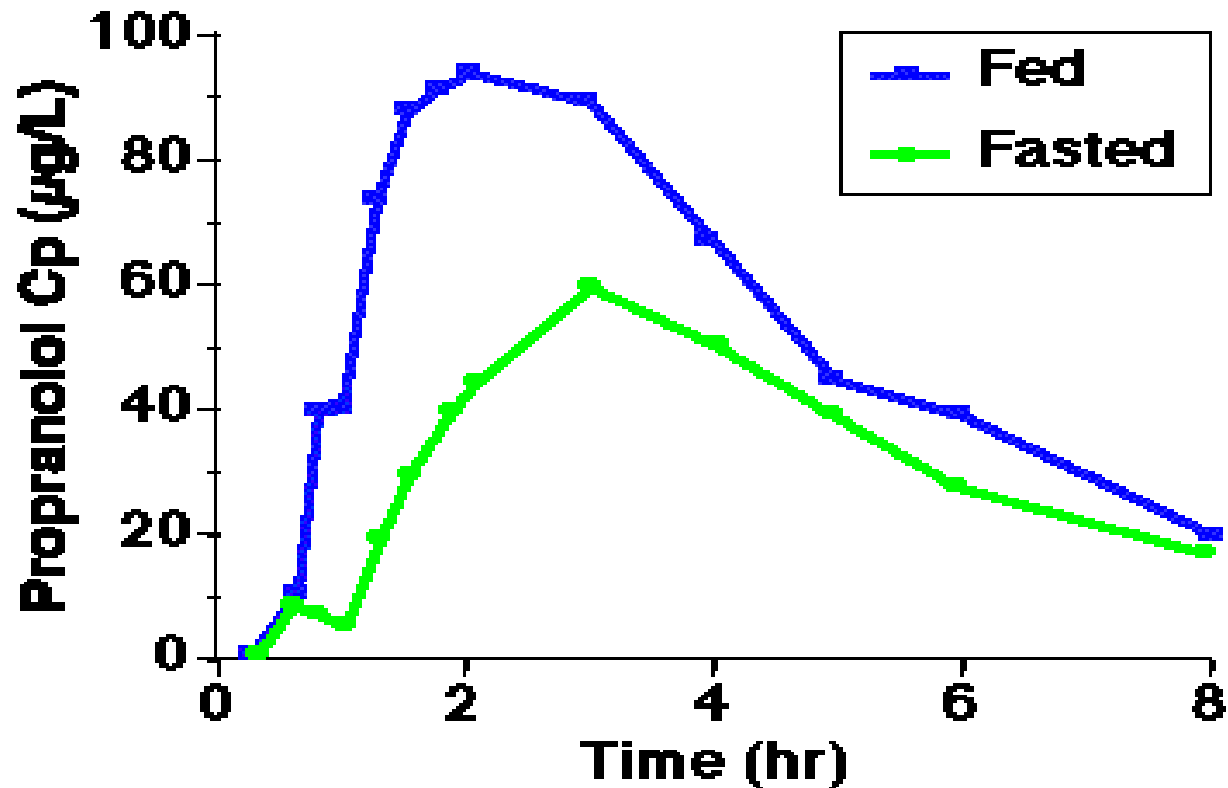
Effect of Fasting *versus* Fed on Propranolol Concentrations

Presystemic metabolism:

Definition: The metabolism of orally administered drugs by gastrointestinal and hepatic enzymes, resulting in a significant reduction of the amount of unmetabolized drug reaching the systemic circulation.

Gut wall metabolism

- This effect is known as first-pass metabolism by the intestine.

- Cytochrome P450 enzyme, CYP3A, that is present in the liver and responsible for the hepatic metabolism of many drugs, is present in the intestinal mucosa and that intestinal metabolism may be important for substrates of this enzyme e.g. cyclosporin.

-

Presystemic metabolism:

Hepatic metabolism

- After a drug is swallowed, it is absorbed by the digestive system and enters the hepatic portal system. It is carried through the portal vein into the liver before it reaches the rest of the body.

- The liver metabolizes many drugs (e.g. propranolol), sometimes to such an extent that only a small amount of active drug emerges from the liver to the rest of the circulatory system.

- This *first pass* through the liver thus greatly reduces the bioavailability of the drug.

Presystemic metabolism (Cont.)

Nature Reviews | Drug Discovery
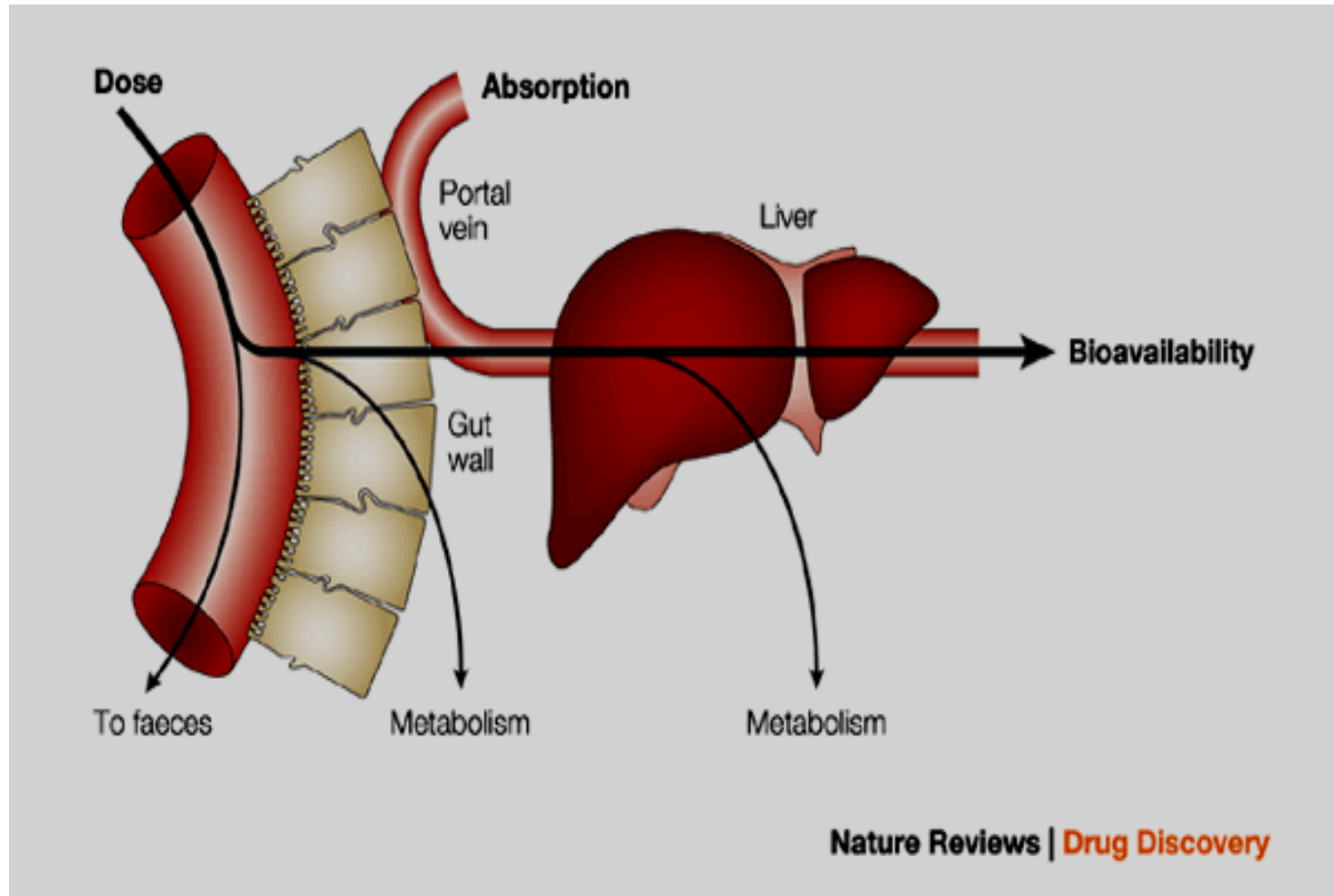
Hepatic metabolism (Cont.)
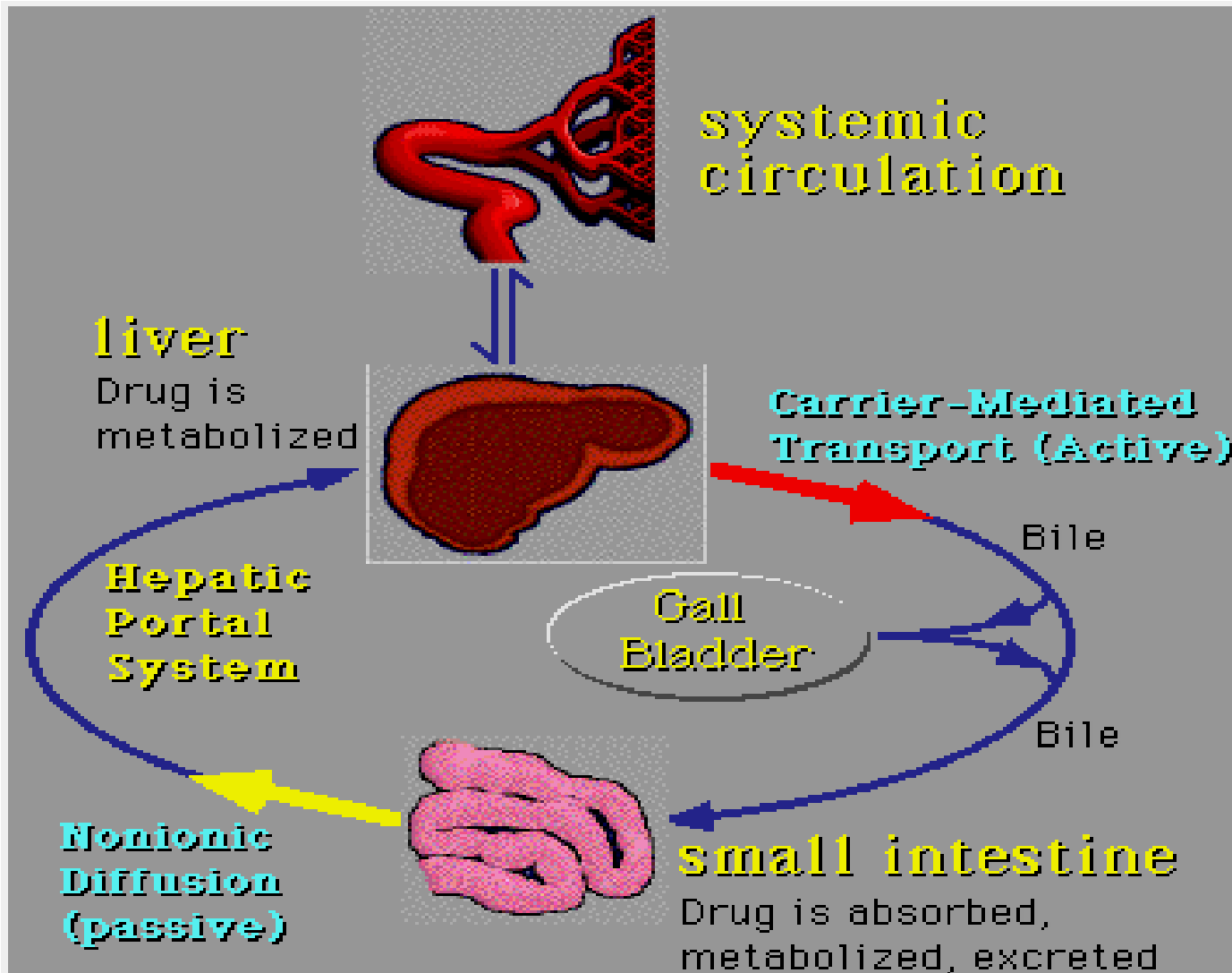
II Physical-Chemical Factors Affecting Oral Absorption:

Physical-chemical factors affecting oral absorption include:

A- pH-partition theory

B- Lipid solubility of drugs

C- Dissolution and pH

D- Drug stability and hydrolysis in GIT

E- Complexation

F- Adsorption

A. pH - Partition Theory:

- According to the pH-partition hypothesis, the gastrointestinal epithelia acts as a lipid barrier towards drugs which are absorbed by passive diffusion, and those that are lipid soluble will pass across the barrier.

- As most drugs are weak electrolytes, the unionized form of weakly acidic or basic drugs (the lipid-soluble form) will pass across the gastrointestinal epithelia, whereas the gastrointestinal epithelia is impermeable to the ionized (poorly-lipid soluble) form of such drugs.

- Consequently, the absorption of a weak electrolyte will be determined by the extent to which the drug exists in its unionized form at the site of absorption.

A. pH - Partition Theory (Cont.):
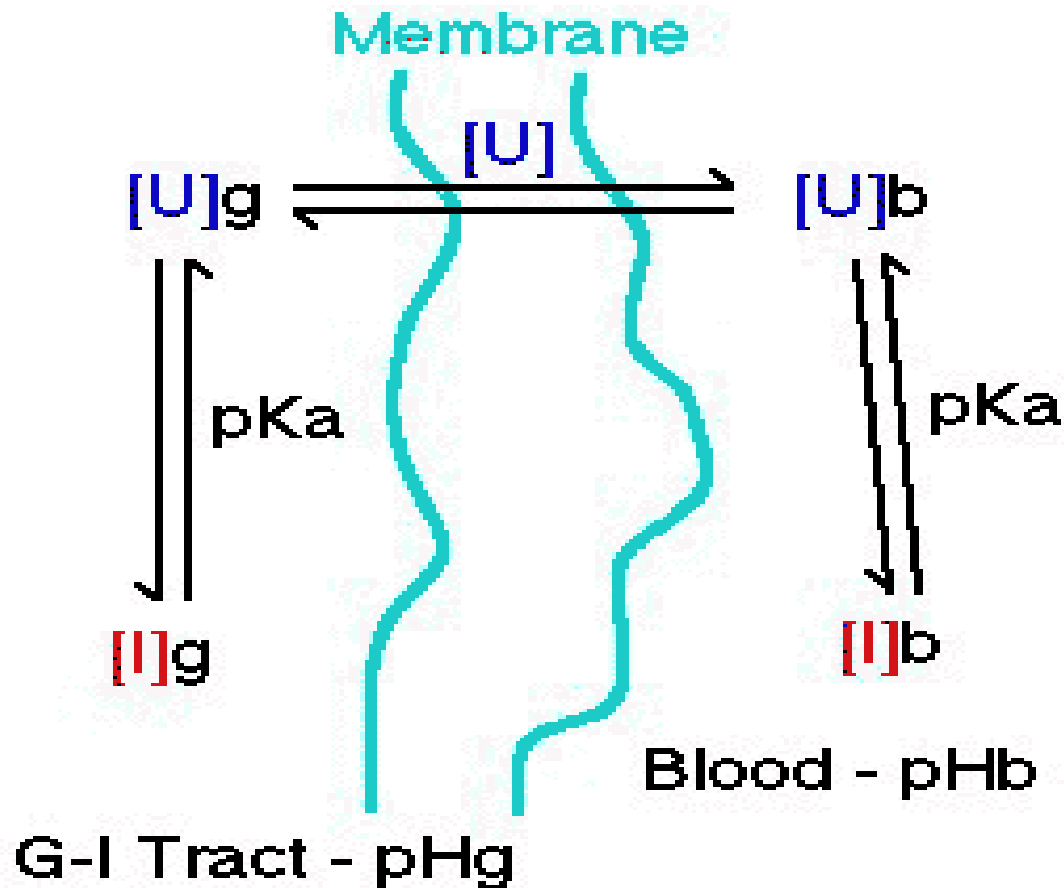
Diagram Showing Transfer Across Membrane

A. pH - Partition Theory (Cont.):

- The extent to which a weakly acidic or basic drug ionizes in solution in the gastrointestinal fluid may be calculated using *Henderson - Hasselbach equation.*

** Weak acids (e.g. aspirin):

$$HA \rightleftharpoons H^+ + A^-$$

$$Ka = \frac{a_{H^+} \bullet a_{A^-}}{a_{HA}} \approx \frac{[H^+] \bullet [A^-]}{[HA]}$$

Dissociation Constant equation - Weak Acids

taking the negative log of both sides

A. pH - Partition Theory (Cont.):

$$-logKa = -log[H^+] - log\frac{[A^-]}{[HA]}$$

Rearranging gives the following equation:

$$pKa - pH = log\frac{[U]}{[I]} = log\frac{[HA]}{[A^-]}$$

Henderson - Hasselbach Equation - Weak Acids

A. pH - Partition Theory (Cont.):

**Weak Bases:

$$pKa - pH = log\frac{[I]}{[U]} = log\frac{[HB^+]}{[B]}$$

Henderson - Hasselbach Equation - Weak Bases

Limitations of the pH-partition hypothesis:

-Despite their high degree of ionization, weak acids are highly absorbed from the small intestine and this may be due to:

1- The large surface area that is available for absorption in the small intestine.

2- A longer small intestine residence time.

A. pH - Partition Theory (Cont.):

3- A microclimate pH, that exists on the surface of intestinal mucosa and is lower than that of the luminal pH of the small intestine.

B. Lipid solubility of drugs:

- Some drugs are poorly absorbed after oral administration even though they are non-ionized in small intestine. Low lipid solubility of them may be the reason.

- The best parameter to correlate between water and lipid solubility is **partition coefficient**.

Partition coefficient (p) = [L] conc / [W] conc

where,   [L] conc is the concentration of the drug in lipid phase.

[W] conc   is the concentration of the drug in aqueous phase.

- The higher p value, the more absorption is observed.

C. Drug Dissolution:

- Many drugs are given in solid dosage forms and therefore must dissolve before absorption can take place.

$$Solid \xrightarrow{\text{Dissolution}} Solution \xrightarrow{\text{Absorption}} Blood$$
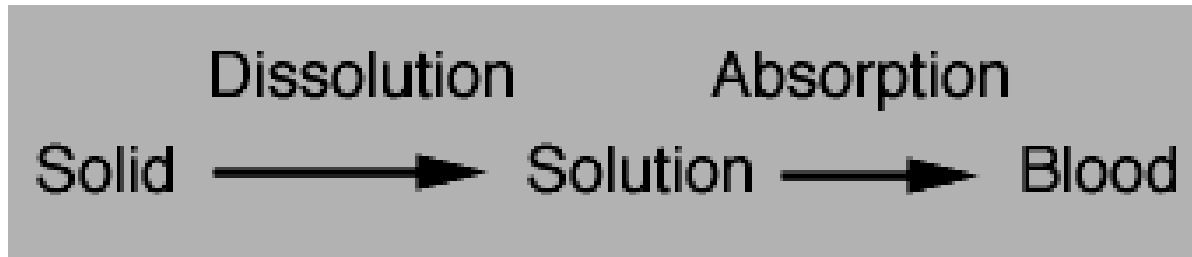
- If dissolution is the slow, it will be the rate determining step (the step controlling the overall rate of absorption) then factors affecting dissolution will control the overall process.

C. Drug Dissolution (cont.):

- Drug dissolution is considered to be diffusion controlled process through a stagnant layer surrounding each solid particle.

Solid drug

Bulk solution Well mixed Uniform concentration

Unstirred layer. Quite small film of liquid surrounding the solid drug particle
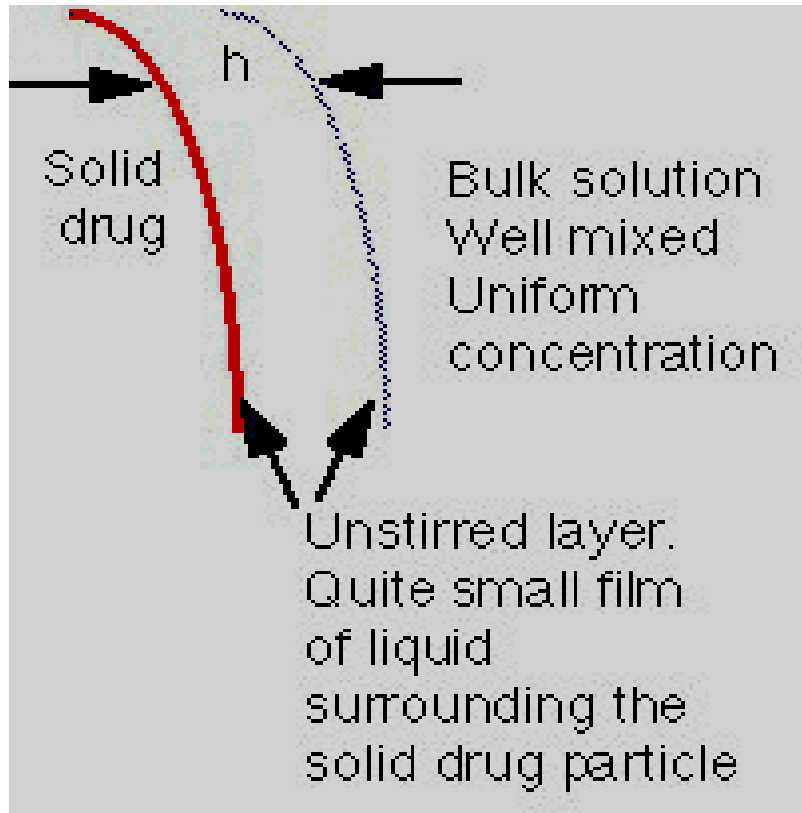
Diagram Representing Diffusion Through the Stagnant Layer

C. Drug Dissolution (cont.):

- The dissolution of drugs can be described by the **Noyes-Whitney equation:**

$$\text{Rate of Solution} = \frac{D \bullet A \bullet (Cs - Cb)}{h}$$

- Where D is the diffusion coefficient, A the surface area, Cs the solubility of the drug, Cb the concentration of drug in the bulk solution, and h the thickness of the stagnant layer.
-If Cb is much smaller than Cs then we have so-called "Sink Conditions" and the equation reduces to

$$\text{Rate of Solution} = \frac{D \bullet A \bullet Cs}{h}$$

C. Drug Dissolution (cont.):

Factors affecting drug dissolution in the GIT:

I Physiological factors affecting the dissolution rate of drugs:

- The environment of the GIT can affect the parameters of the Noyes-Whitney equation and hence the dissolution rate of a drug.

A- Diffusion coefficient, D:

- Presence of food in the GIT ⟶ increase the viscosity of the gastrointestinal fluids ⟶ reducing the rate of diffusion of the drug molecules away from the diffusion layer surrounding each undissolved drug particles **(↓ D)** ⟶ decrease in dissolution rate of a drug.

C. Drug Dissolution (cont.):

B- Drug surface area, A:

Surfactants in gastric juice and bile salts increase the wettability of the drug ⟶ increase the drug solubility via micellization.

C. The thickness of diffusion layer, h:

An increase in gastric and/or intestinal motility decrease the thickness of diffusion layer around each drug particle ⟶ increase the dissolution rate of a drug.

D. The concentration, C, of drug in solution in the bulk of the gastrointestinal fluids:

C. Drug Dissolution (cont.):

Increasing the rate of removal of dissolved drug by absorption through the gastrointestinal-blood barrier and increasing the intake of fluid in the diet ⟶ will decrease in C ⟶ rapid dissolution of the drug.

II Physicochemical factors affecting the dissolution rate of drugs:

A- Surface area, A:

- The smaller the particle size ⟶ the greater the effective surface area of drug particle ⟶ the higher the dissolution rate.

C. Drug Dissolution (cont.):

- *Methods of particle size reduction include:* mortar and pestle, mechanical grinders, mills, solid dispersions in readily soluble materials (PEG's).

- However very small particles can clump together. Therefore a wetting agent such as Tween 80 can have a beneficial effect on the overall absorption.
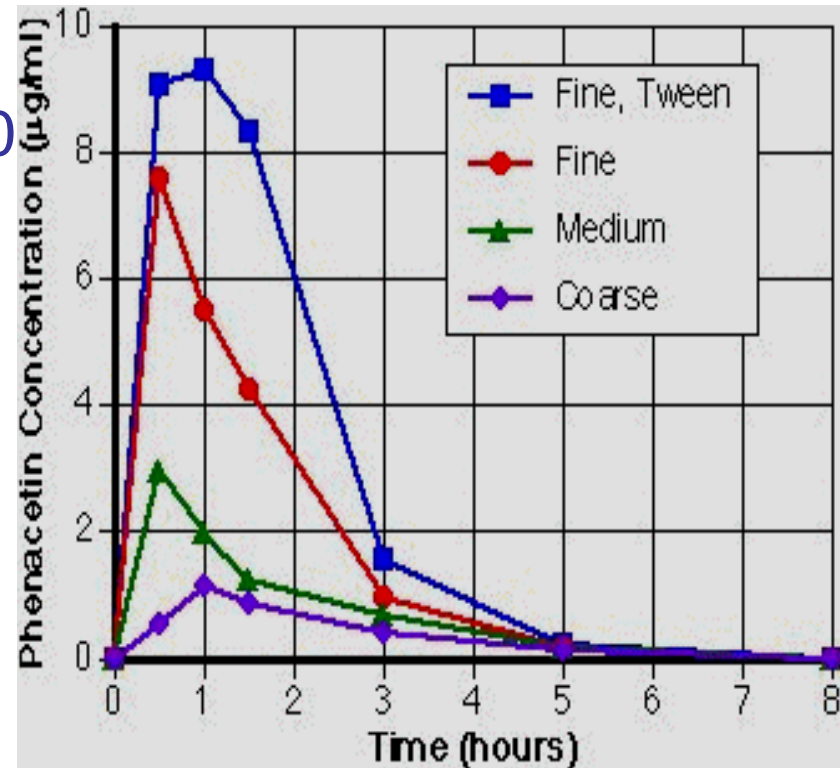
C. Drug Dissolution (cont.):

B-Diffusion coefficient, D:

The value of D depends on the size of the molecule and the viscosity of the dissolution medium.

C- Solubility in the diffusion layer, C_s:

- The dissolution rate of a drug is directly proportional to its intrinsic solubility in the diffusion layer surrounding each dissolving drug particle.

C. Drug Dissolution (cont.):

D- Salts:

- **Salts of weak acids and weak bases generally have much higher aqueous solubility than the free acid or base.**

- The dissolution rate of a weakly acidic drug in gastric fluid (pH 1 – 3.5) will be relatively low.

- If the pH in the diffusion layer increased, the solubility, C_s, of the acidic drug in this layer, and hence its dissolution rate in gastric fluids would be increased.

C. Drug Dissolution (cont.):

- The pH of the diffusion layer would be increased if the chemical nature of the weakly acidic drug was changed from that of the free acid to a basic salt (the sodium or potassium form of the free acid.

- The pH of the diffusion layer would be higher (5-6) than the low bulk pH (1-3.5) of the gastric fluids because of the neutralizing action of the strong (Na^+, K^+) ions present in the diffusion layer.

- The drug particles will dissolve at a faster rate and diffuse out of the diffusion layer into the bulk of the gastric fluid, where a lower bulk pH.

C. Drug Dissolution (cont.):

- Thus the free acid form of the drug in solution, will precipitate out , leaving a saturated solution of free acid in gastric fluid.

This precipitated free acid will be in the form of:

- very fine,

- non-ionized,

- wetted particles which have a very large surface area in contact with gastric fluids, facilitating rapid redissolution when additional gastric fluid is available.

Drug Dissolution (cont.):
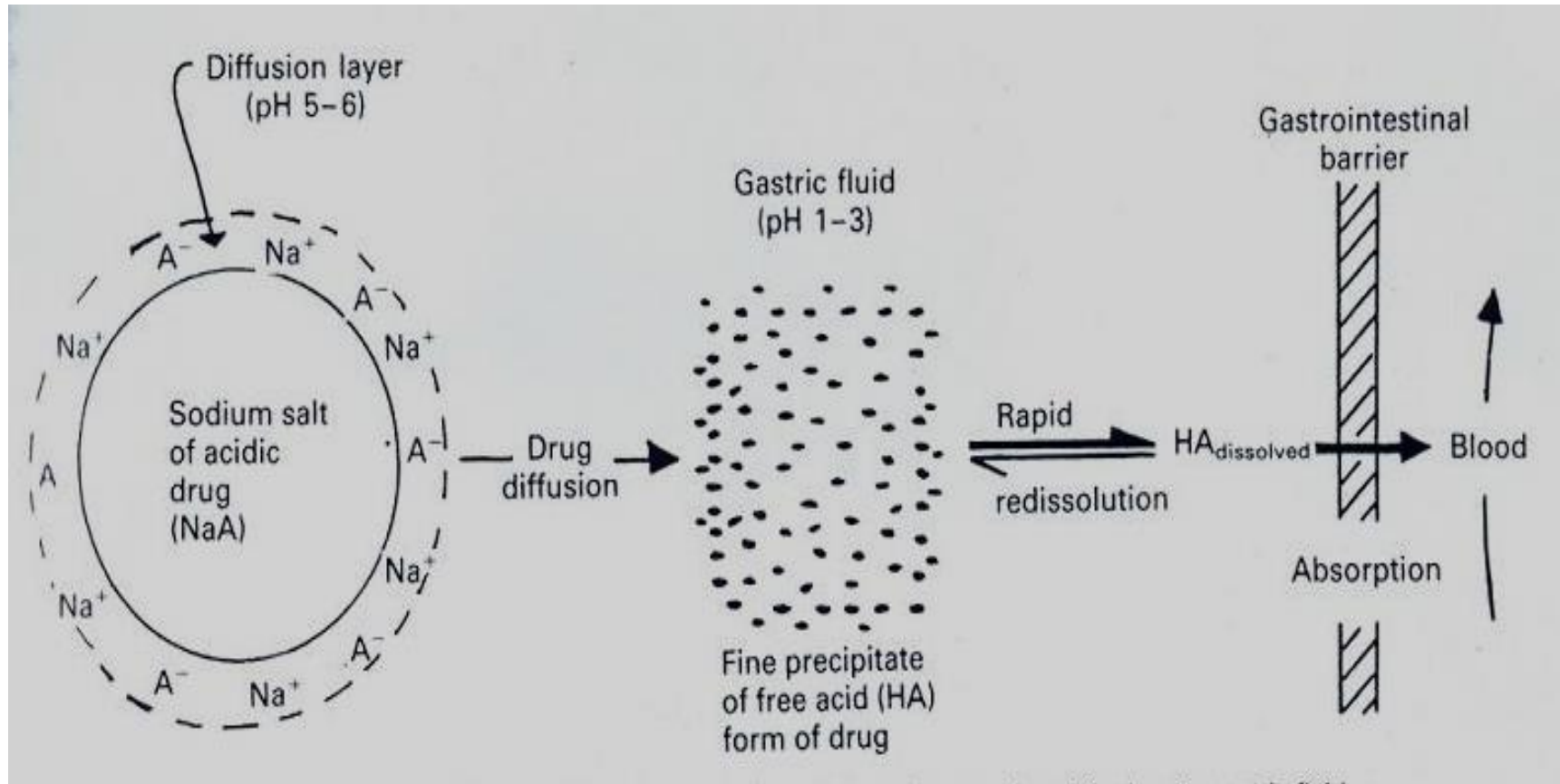
Dissolution process of a salt form of a weakly acidic drug in gastric fluid.

Drug Dissolution (cont.):

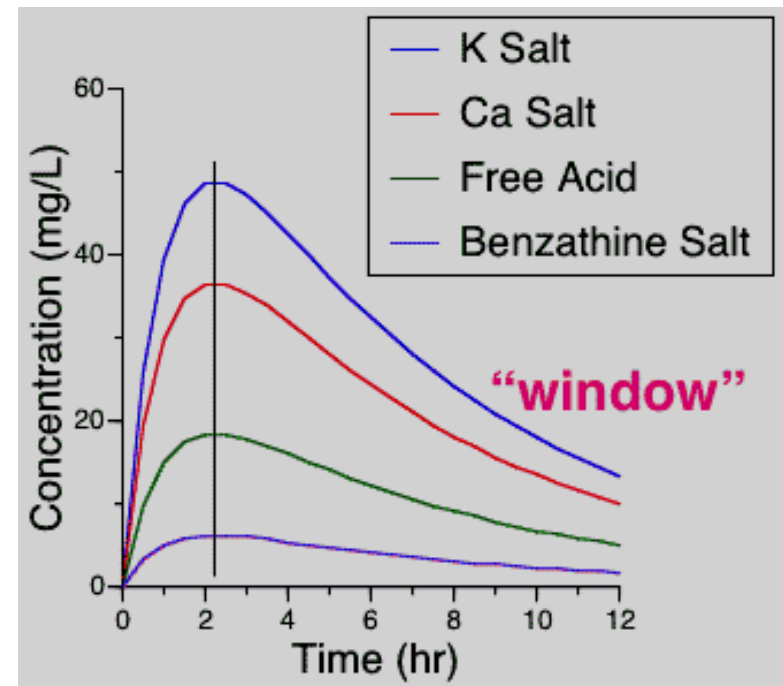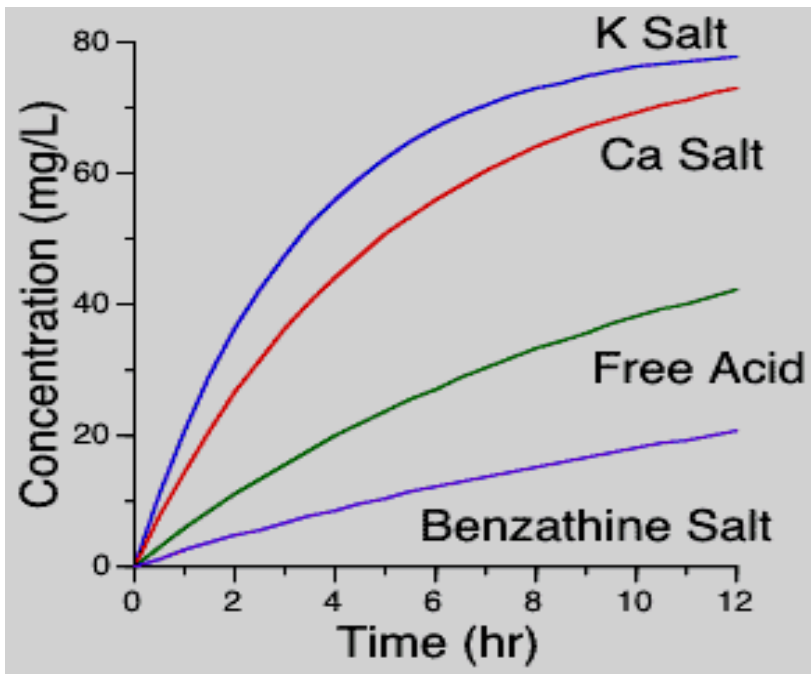- One example is the dissolution and bioavailability profiles of Penicillin V with various salts.

These results might support the use of the benzathine or procaine salts for IM depot use and the potassium salt for better absorption orally.

Drug Dissolution (cont.):

E- Crystal form:

1- Polymorphism:

- Some drugs exist in a number of crystal forms or polymorphs. These different forms may have different solubility properties and thus different dissolution characteristics.

- Chloramphenicol palmitate is one example which exists in three crystalline forms A, B and C.

A ⟶ is the stable polymorph

B ⟶ is the metastable polymorph (more soluble)

C ⟶ is the unstable polymorph

- The plasma profiles of chloramphenicol from oral suspensions containing different proportions of

Drug Dissolution (cont.):

Polymorphic forms A and B were investigated.

-The extent of absorption of
Chloramphnicol increases as the
Proportion of the polymorphic form
B is increased in each suspension.
This is attributed to the more rapid
Dissolution of the metastable
Polymorphic form B.
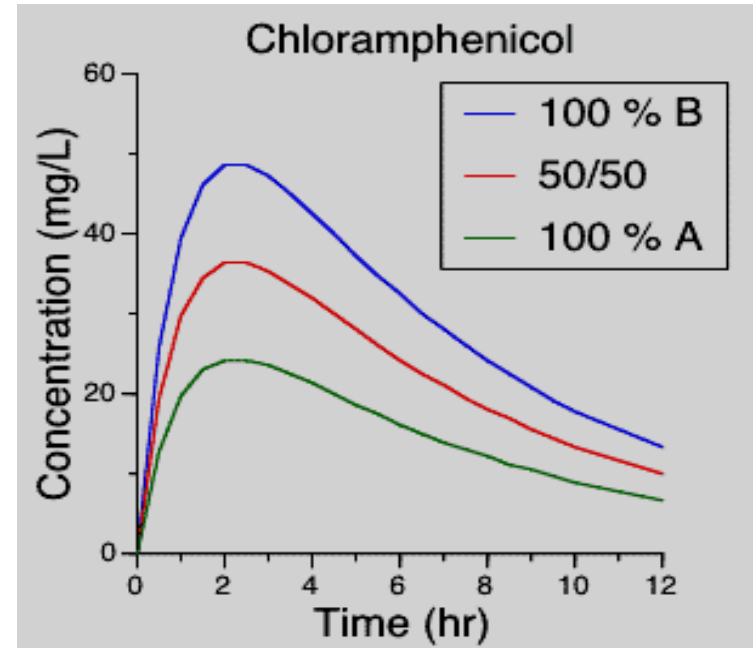
- Shelf-life could be a problem as the more soluble (less stable) form may transform into the less soluble form (more stable).

Drug Dissolution (cont.):

2- Amorphous solid:

- The amorphous form dissolves more rapidly than the corresponding crystalline form.

- The more soluble and rapidly dissolving amorphous form of novobiocin antibiotic was readily absorbed following oral administration of an aqueous suspension to humans. However, the less soluble and slower-dissolving crystalline form of novobiocin was not absorbed (therapeutically ineffective).

- The amorphous form of novobiocin slowly converts to the more stable crystalline form, with loss of therapeutic effectiveness.

Drug Dissolution (cont.):

3- Solvates:
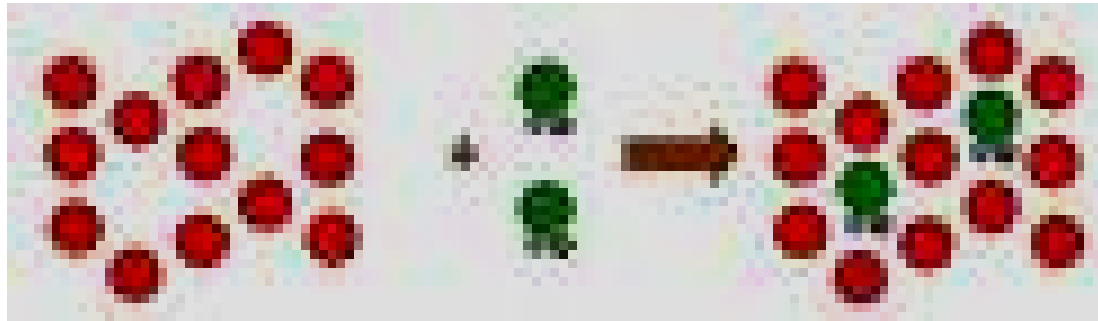
Solvates: If the drug is able to associate with solvent molecules to produce crystalline forms known as solvates.

Hydrates: drug associates with water molecules.

- The greater the solvation of the crystal, the lower are the solubility and dissolution rate in a solvent identical to the solvation molecules.

Drug Dissolution (cont.):

- The faster-dissolving anhydrous form of ampicillin was absorbed to a greater extent from both hard gelatin capsules and an aqueous suspension than was the slower-dissolving trihydrate form.

D- Drug stability and hydrolysis in GIT:

- Drugs that are susceptible to acidic or enzymatic hydrolysis in the GIT, suffer from reduced bioavailability.

- How to protect drugs (erythromycin) from degradation in gastric fluid ??

1- Preparing enteric coated tablets containing the free base of erythromycin. The enteric coating resists gastric fluid but disrupts or dissolves at the less acid pH range of the small intestine.

2- The administration of chemical derivatives of the parent drug. These prodrugs (erythromycin stearate) exhibit limited solubility in gastric fluid, but liberate the drug in the small intestine to be absorbed.

E- Complexation:

- Complexation of a drug may occur within the dosage form and/or in the gastrointestinal fluids, and can be benefecial or deterimental to absorption.

1- Intestinal mucosa (mucin) + Streptomycin = poorly absorbed complex

2- Calcium + Tetracycline = poorly absorbed complex (Food-drug interaction)

3- Carboxyl methylcellulose (CMC) + Amphetamine = poorly absorbed complex (tablet additive – drug interaction)

4- Lipid soluble drug + water soluble complexing agent = well-absorbed water soluble complex (cyclodextrin)

F- Adsorption:

- Certain insoluble susbstances may adsorbed co-administrated drugs leading to poor absorption.

- Charcoal (antidote in drug intoxication).

- Kaolin (antidiarrhoeal mixtures)

- Talc (in tablets as glidant)
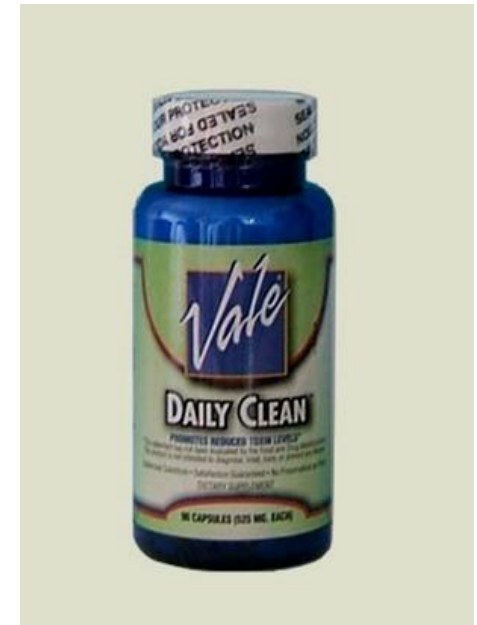
III Formulation Factors Affecting Oral Absorption:

- The role of the drug formulation in the delivery of drug to the site of action should not be ignored.

- Since a drug must be in solution to be absorbed efficiently from the G-I tract, you may expect the bioavailability of a drug to decrease in the order solution > suspension > capsule > tablet > coated tablet.

A. *Solution dosage forms:*

- In most cases absorption from an oral solution is rapid and complete, compared with administration in any other oral dosage form.

III Formulation Factors Affecting Oral Absorption (Cont.):

- Some drugs which are poorly soluble in water may be:

1- dissolved in mixed water/alcohol or glycerol solvents (cosolvency),

2- given in the form of a salt (in case of acidic drugs)

3- An oily emulsion or soft gelatin capsules have been used for some compounds with lower aqueous solubility to produce improved bioavailability.

III Formulation Factors Affecting Oral Absorption (Cont.):

B. Suspension dosage forms:

- A well formulated suspension is second to a solution in terms of superior bioavailability.

- A suspension of a finely divided powder will maximize the potential for rapid dissolution.

- A good correlation can be seen for particle size and absorption rate.

- The addition of a surface active agent will improve the absorption of very fine particle size suspensions.

III Formulation Factors Affecting Oral Absorption (Cont.):
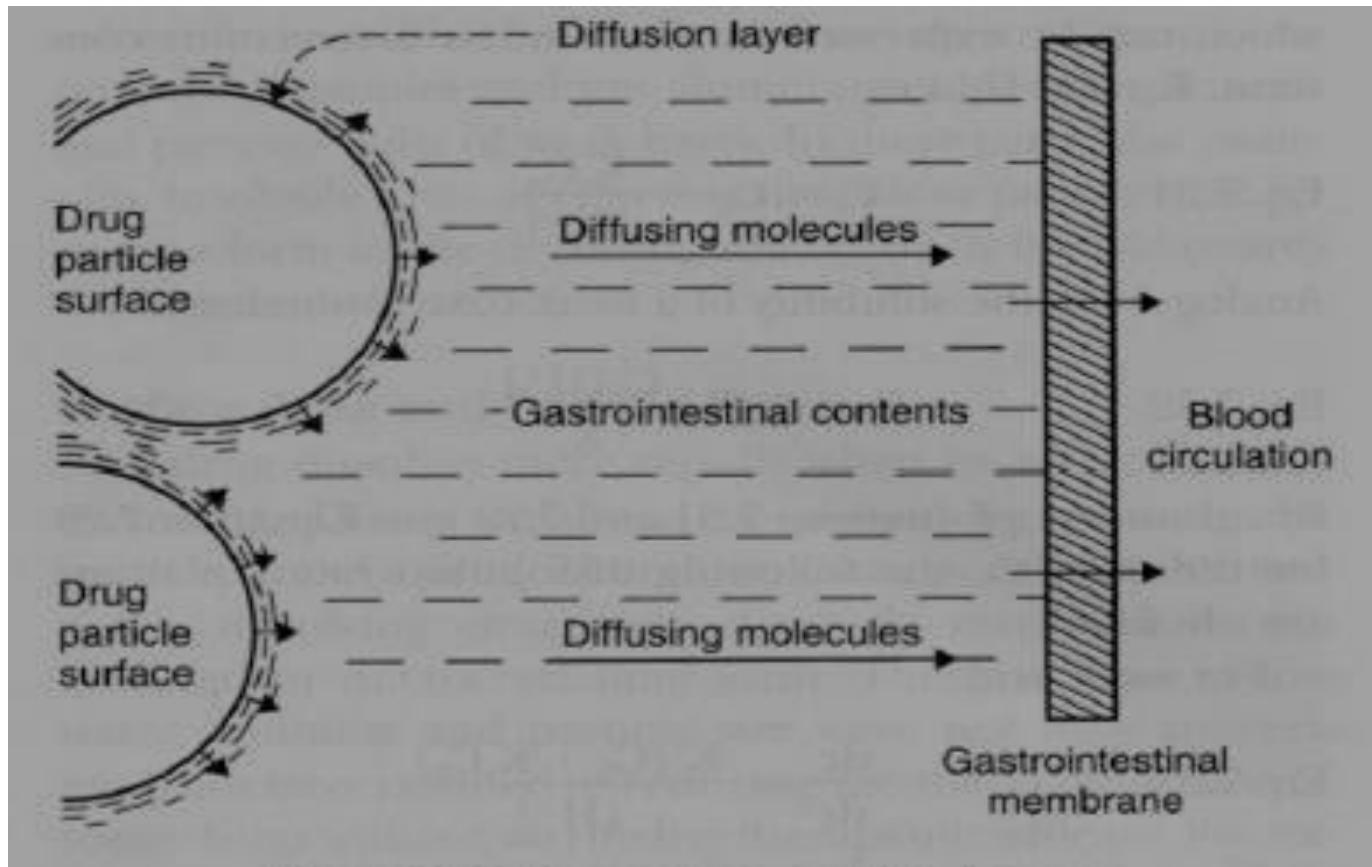
Absorption of drugs from aqueous suspensions

III Formulation Factors Affecting Oral Absorption (Cont.):

C. Capsule dosage forms:

- The hard gelatin shell should disrupt rapidly and allow the contents to be mixed with the G-I tract contents.

- If a drug is hydrophobic a dispersing agent should be added to the capsule formulation. These diluents will work to disperse the powder, minimize aggregation and maximize the surface area of the powder.

- Tightly packed capsules may have reduced dissolution and bioavailability.

III Formulation Factors Affecting Oral Absorption (Cont.):

D. Tablet dosage forms:
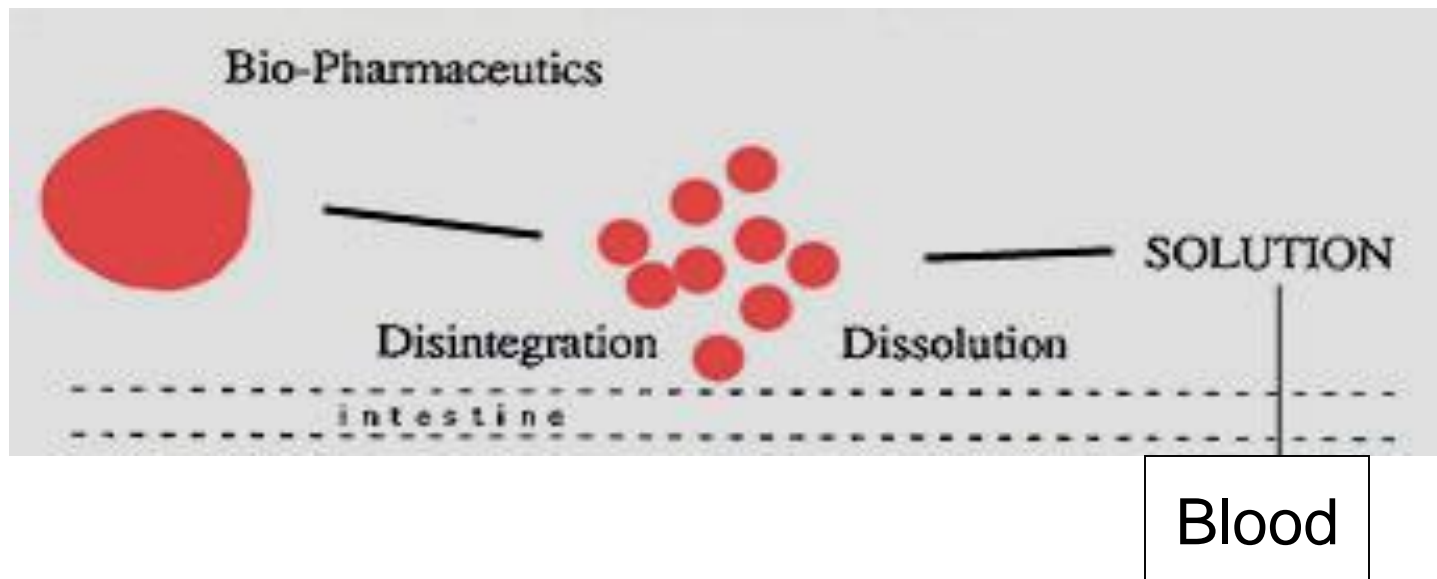
III Formulation Factors Affecting Oral Absorption (Cont.):

- The tablet is the most commonly used oral dosage form.
- It is also quite complex in nature.

1-Ingredients

Drug : may be poorly soluble, hydrophobic

Lubricant : usually quite hydrophobic

Granulating agent : tends to stick the ingredients together

Filler: may interact with the drug, etc., should be water soluble

Wetting agent : helps the penetration of water into the tablet

Disintegration agent: helps to break the tablet apart

III Formulation Factors Affecting Oral Absorption (Cont.):

- Coated tablets are used to mask an unpleasant taste, to protect the tablet ingredients during storage, or to improve the tablets appearance.

This coating can add another barrier between the solid drug and drug in solution. This barrier must break down quickly or it may hinder a drug's bioavailability.

- *Sustained release tablet*

Another form of coating is enteric coated tablets which are coated with a material which will dissolve in the intestine but remain intact in the stomach.

Distribution:

Drug distribution: means the reversible transfer of drug from one location to another within the body.

- The distribution of drugs in the body depends on:

1- their lipophilicity

2- protein binding.

Low plasma binding or high tissue binding or high lipophilicity usually means an extensive tissue distribution.

Distribution:

- In pharmacokinetics, the distribution is described by the parameter V, the apparent volume of distribution.

- At equilibrium, V will theoretically not be lower than 7 L in a 70-kg person, but it has no upper limit.

Drug distribution patterns:

-The extent to which a drug distributes affects the half-life of the drug and the fluctuation of the concentration at steady state.

Distribution can be thought of as following one of four types of patterns:

1-The drug may remain largely within the vascular system. Plasma substitutes such as dextran are an example of this type, but drugs which are strongly bound to plasma protein may also approach this pattern.

Drug distribution patterns (Cont.):

Body Water in Various Organs

2

4

1

Blood

Specific Organ or Tissue for example Thyroid, Bone, Fat

3

General Organs for example Muscle, Liver
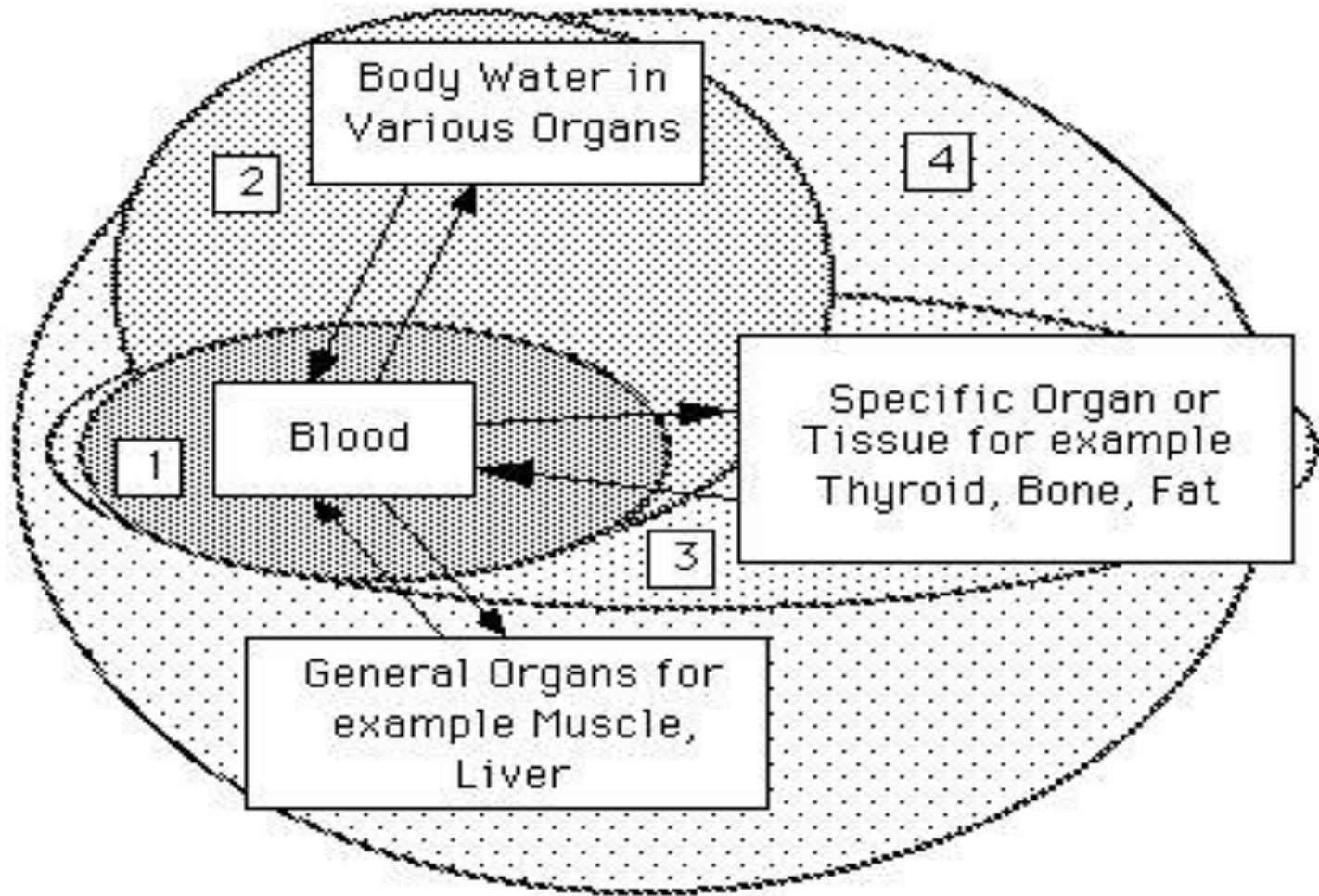
Diagram Representing Various Volumes Distribution Patterns

Drug distribution patterns (Cont.):

2- Some low molecular weight water soluble compounds such as ethanol and a few sulfonamides become uniformly distributed throughout the body water.

Drug distribution patterns (Cont.):

3- A few drugs are concentrated specifically in one or more tissues that may or may not be the site of action.

Iodine is concentrated by the thyroid gland.

The antimalarial drug chloroquine may be present in the liver at concentrations 1000 times those present in plasma.

Drug distribution patterns (Cont.):

Tetracycline is almost irreversibly bound to bone and developing teeth.

Consequently tetracyclines should only be given to young children or infants in extreme conditions as it can cause discoloration and mottling of the developing second set of teeth.

Another type of specific concentration may occur with highly lipid soluble compounds which distribute into fat tissue.

Drug distribution patterns (Cont.):

4- Most drugs exhibit a non-uniform distribution in the body with variations that are largely determined by the ability to pass through membranes and their lipid/water solubility.

The highest concentrations are often present in the kidney, liver, and intestine usually reflecting the amount of drug being excreted.

Drug distribution patterns (Cont.):

- Apparent volume of distribution (V) is a useful indicator of the type of pattern that characterizes a particular drug.

- A value of V in the region of 3-5 liter (in an adult) would be compatible with pattern 1. This is approximately the volume of plasma.

- Pattern two would be expected to produce a V value of 30 to 50 liter, corresponding to total body water.

- Agents or drugs exhibiting pattern 3 would exhibit very large values of V. Chloroquine has a V value of approximately 115 L/ kg .

- Drugs following pattern 4 may have a V value within a wide range of values.

Drug distribution patterns (Cont.):

Volumes of body fluids	
Fluid substances	**Volume (liter)**
Extracellular Fluid	19
Plasma	3
Interstitial fluids	16
Intracellular fluids	23
Total body water	42

Factors affecting drug distribution:

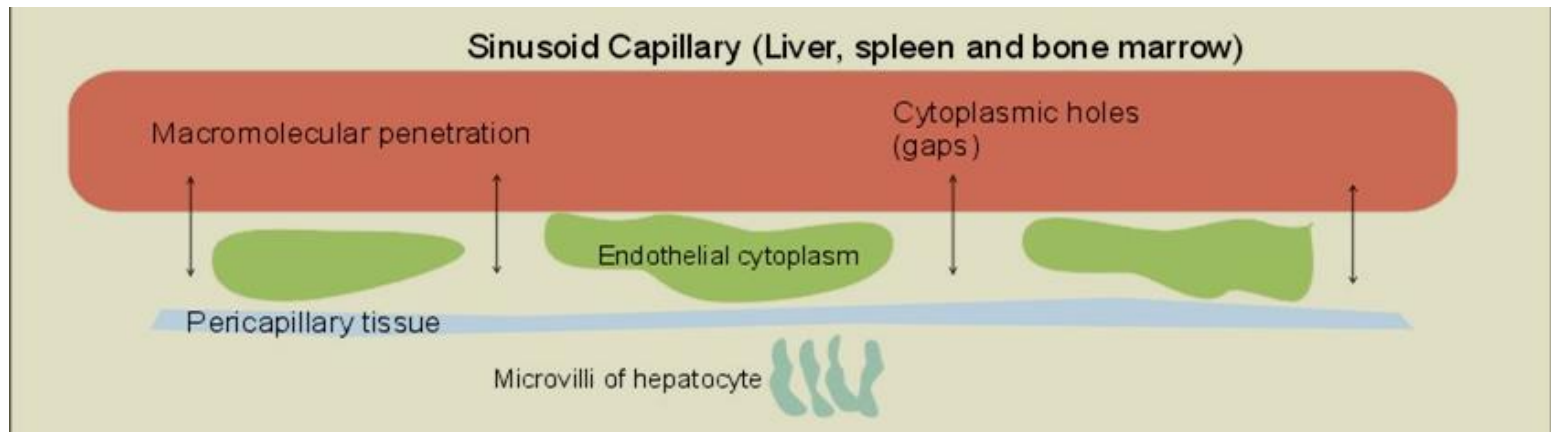| Factors Affecting Distribution	
A- Rate of distribution	B- Extent of Distribution
1. Membrane permeability 2. Blood perfusion	1. Lipid Solubility 2. pH – pKa 3. Plasma protein binding 4. Tissue drug binding
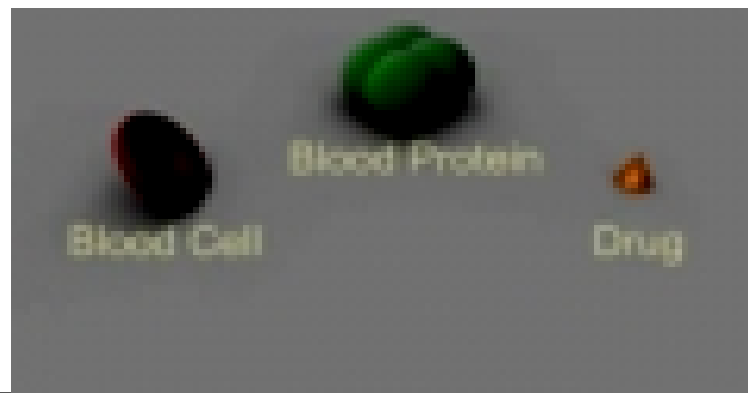
Factors affecting drug distribution (Cont.):

A. Rate of distribution

1. Membrane permeability:

- Capillary walls are quite permeable.
- Lipid soluble drugs pass through very rapidly.
- Water soluble compounds penetrate more slowly at a rate more dependent on their size.
- Low molecular weight drugs pass through by simple diffusion. For compounds with molecular diameter above 100 Å transfer is slow.
- For drugs which can be ionized the drug's pKa and the pH of the blood will have a large effect on the transfer rate across the capillary membrane.
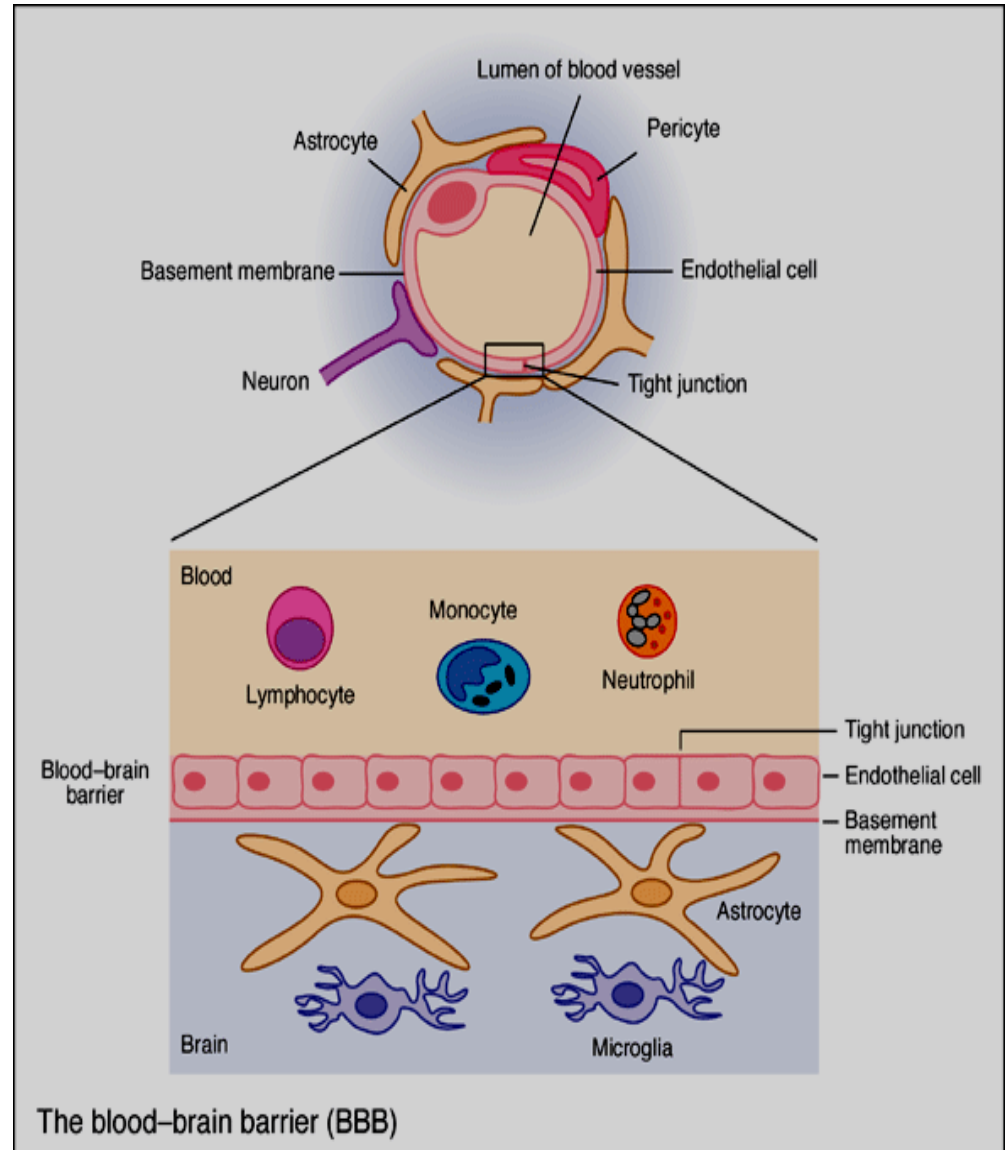
Factors affecting drug distribution (Cont.):

- There are two deviations to the typical capillary structure which result in variation from normal drug tissue permeability.

i) Permeability is greatly increased in the renal capillaries by pores in the membrane of the endothelial cells, and in specialized hepatic capillaries, known as sinusoids which may lack a complete lining. This results in more extension distribution of many drugs out of the capillary bed.

Sinusoid Capillary (Liver, spleen and bone marrow)
Macromolecular penetration
Cytoplasmic holes (gaps)
Endothelial cytoplasm
Pericapillary tissue
Microvilli of hepatocyte

II) On the other hand, brain capillaries seem to have impermeable walls restricting the transfer of molecules from blood to brain tissue.

-Lipid soluble compounds can be readily transferred but the transfer of polar substances is severely restricted.

- This is the basis of the "blood-brain" barrier.

The blood–brain barrier (BBB)

Factors affecting drug distribution (Cont.):

2. Blood perfusion rate:

■ The rate at which blood perfuses to different organs varies widely:

Blood Perfusion Rate		
Organ	Perfusion Rate (mL/min/mL of tissue)	Percent of cardiac output (CO)
Bone	0.02	5
Brain	0.5 - 0.55	14 - 15
Fat	0.01 - 0.03	2 - 4
Heart	0.6 - 0.7	4
Kidneys	4.0 - 4.5	22 - 24
Liver	0.8 - 0.95	25 - 27
Muscle	0.025 - 0.030	15
Skin	0.04 - 0.05	5 - 6

Brain
0.5 ml/min/ml tissue

Muscle
0.025 ml/min/ml tissue
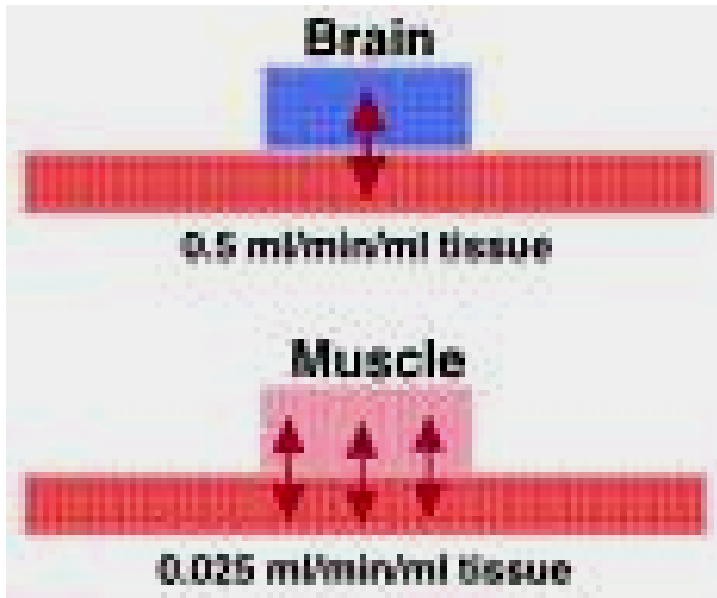
Factors affecting drug distribution (Cont.):

- The rate at which a drug reaches different organs and tissues will depend on the blood flow to those regions.

- Equilibration is rapidly achieved with heart, lungs, liver, kidneys and brain where blood flow is high.

- Skin, bone, and depot fat equilibrate much more slowly.

Factors affecting drug distribution (Cont.):

B. Extent of Distribution

1.Lipid Solubility:

- Lipid solubility will affect the ability of the drug to bind to plasma proteins and to cross lipid membrane barriers.

- Very high lipid solubility can result in a drug partitioning into highly vascular lipid-rich areas. Subsequently these drugs slowly redistribute into body fat where they may remain for long periods of time.

Factors affecting drug distribution (Cont.):

2. Effects of pH:

- The rate of movement of a drug out of circulation will depend on its degree of ionization and therefore its pKa.

- Changes in pH occuring in disease may also affect drug distribution. For example, blood becomes more acidic if respiration is inadequate.

3. Plasma protein binding:

- Extensive plasma protein binding will cause more drug to stay in the central blood compartment. Therefore drugs which bind strongly to plasma protein tend to have lower volumes of distribution. (↑ protein binding = ↓ V)

Factors affecting drug distribution (Cont.):

- Albumin comprises 50 % of the total proteins binds the widest range of drugs. Acidic drugs commonly bind to albumin, while basic drugs often bind to α1-acid glycoproteins and lipoproteins.

- *Forces involved:*

- Groups on the protein molecules that are responsible for **electrostatic interactions** with drugs include:

  - ☐ NH3+ of lysine
  - ☐ N- terminal amino acids
  - ☐ NH2+ of histidine
  - ☐ S- of cysteine
  - ☐ COO- of aspartic and glutamic acid residues.

Factors affecting drug distribution (Cont.):

- In order to achieve stable complexes, the initial electrostatic attraction is reinforced by **van der Waal's forces** and **hydrogen bonding**.

What is the effect of protein binding on drug action?

1. Extensive plasma protein binding will decrease the amount of absorbed drug (decrease peak plasma level).

2. Elimination of a highly bound drug may be delayed. Since the concentration of free drug is low, drug elimination by metabolism and excretion may be delayed. This effect is responsible for prolonging the effect of the drug digoxin.
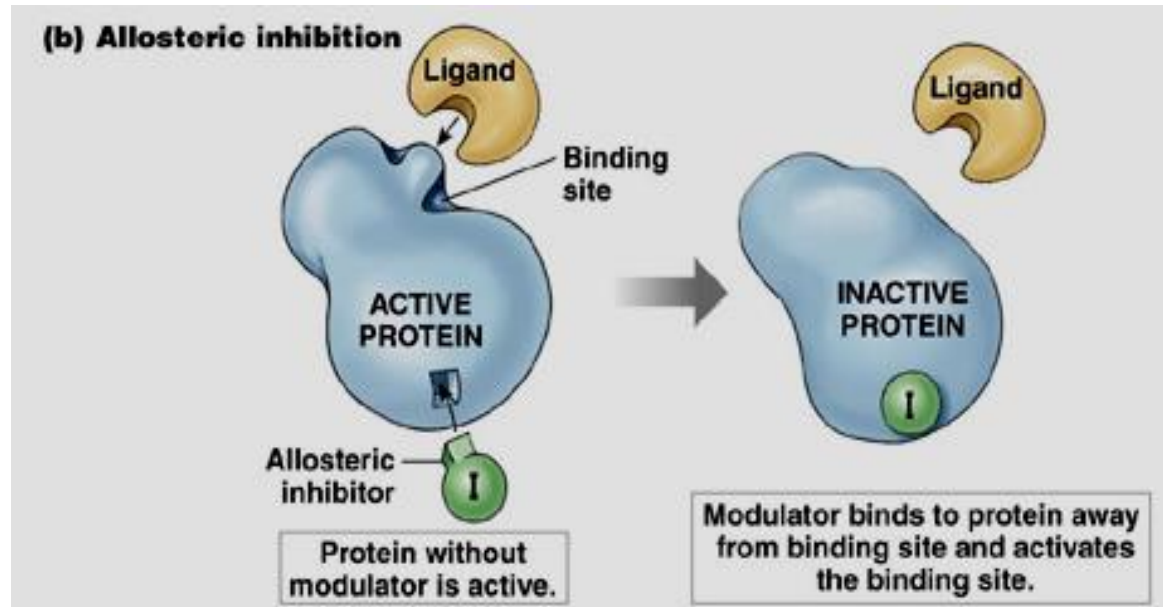
Factors affecting drug distribution (Cont.):

3. Changes in the concentration of plasma proteins will influence the effect of a highly bound drug.

A low plasma protein level may occur in:

- old age

- malnutrition

- illness such as liver disease (remember that most plasma proteins are made in the liver), or chronic renal failure where there is excessive excretion of albumin.

In each case the result is a smaller proportion of drug in bound form and more free drug in the plasma. The greater amount of free drug is able to produce a greater therapeutic effect and reduced drug dosages may be indicated in these cases.

Factors affecting drug distribution (Cont.):

(b) Allosteric inhibition

Ligand

Binding site

ACTIVE PROTEIN

Allosteric inhibitor

Protein without modulator is active.

Ligand

INACTIVE PROTEIN

Modulator binds to protein away from binding site and activates the binding site.

4. There may be competition between drugs, in which agents that are bound very tightly, such as coumarin anticoagulants, are able to displace less tightly bound compounds from their binding sites.

Factors affecting drug distribution (Cont.):

- In general, plasma protein binding is reversible and obeys the law of mass action:

(free drug) + (albumin) $\xrightarrow[k_2]{k_1}$ **(drug-albumin complex)**
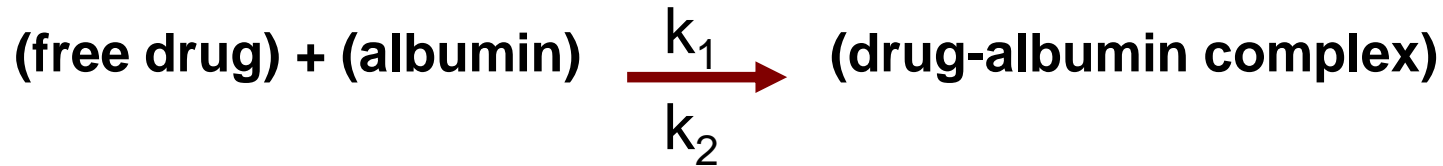
where k1 and k2 are the association and dissociation rate constants, respectively.

At equilibrium:
$$K_D = \frac{k_2}{k_1} = \frac{[\text{free drug}] \times [\text{albumin}]}{[\text{drug-albumin complex}]}$$

- where KD is the equilibrium dissociation constant. It is a measure of the affinity of the drug for albumin:

Factors affecting drug distribution (Cont.):

- The lower the KD $\longrightarrow$ the higher the affinity.

- The higher the KD $\longrightarrow$ the lower the affinity.

- As the concentration of drug increases in plasma, the percent that is bound will decrease.

Factors affecting drug distribution (Cont.):

4. Tissue drug binding (tissue localization of drugs):

- In addition to plasma protein binding, drugs may bind to intracellular molecules.

- The affinity of a tissue for a drug may be due to: binding to tissue proteins or to nucleic acids, or in the case of adipose tissue, dissolution in the lipid material.

e.g. The concentration of chloroquine in the liver is due to the binding of the drug to DNA.

e.g. Barbiturates distribute extensively into adipose tissue, primarily because of their high lipid solubility.

e.g. Tetracyclines bind to bone thus should be avoided in young children or discoloration of permanent teeth may occur.

Factors affecting drug distribution (Cont.):

Other distribution considerations

1.Weight considerations:

A- Body composition of the very young and the very old may be quite different from 'normal', that is the average subject in whom the parameter values may have been originally determined.

B- Another group of patients in which body composition may be greatly altered from `normal' is the obese. These patients have a higher proportion of adipose tissue and lower percentage of water.

Thus for drugs which are relatively polar, volume of distribution values may be lower than normal.

For example the apparent volume of distribution of antipyrine is 0.62 l/kg in normal weight subjects but 0.46 l/kg in obese patients.

Other drugs such as digoxin and gentamicin are also quite polar and tend to distribute into water rather than adipose tissue.
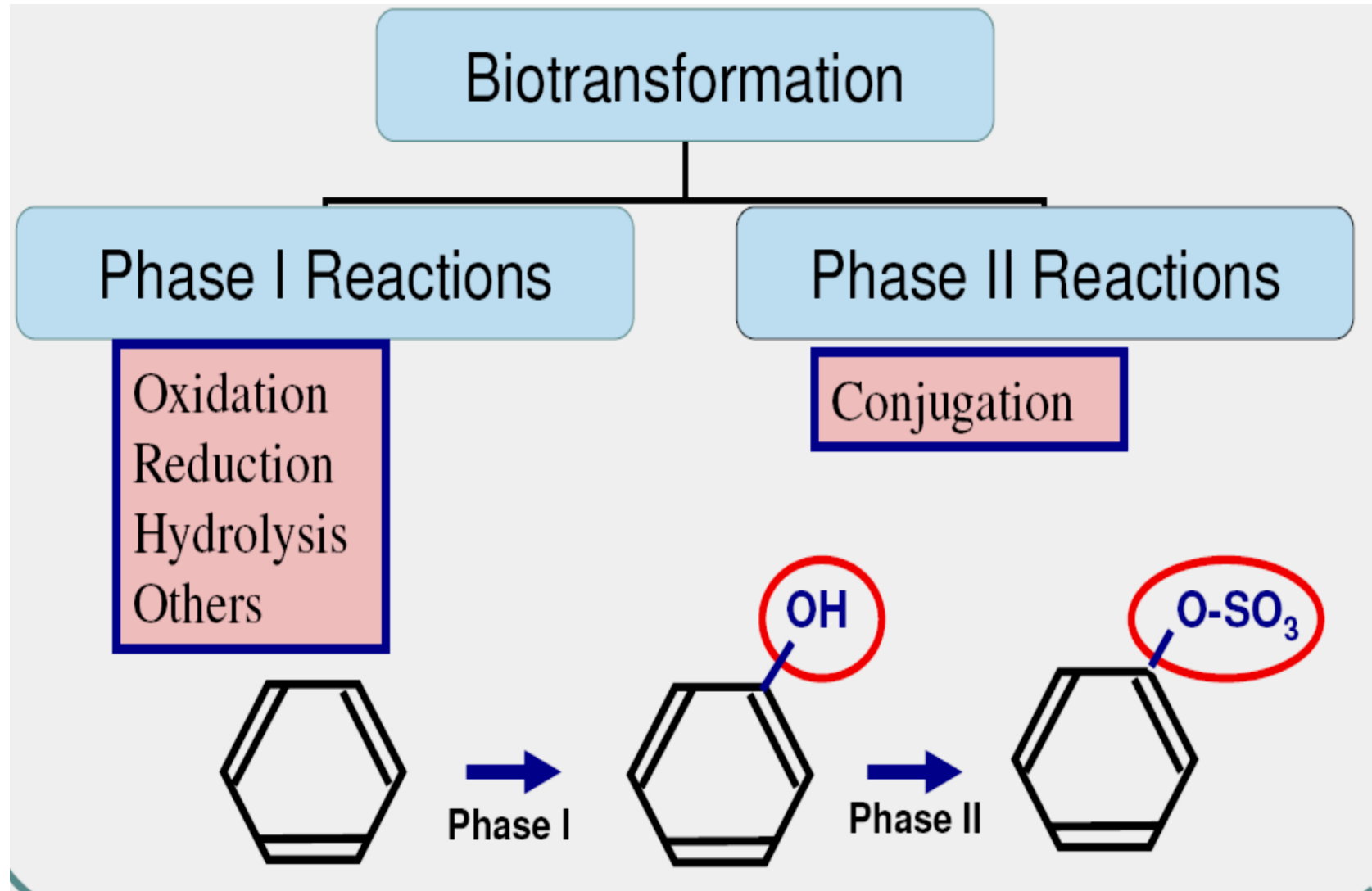
Drug metabolism:

- **Metabolism is defined as:** The irreversible biotransformation of drug in the body → typically involves making it more polar to enhance renal excretion

- Drug metabolism often converts lipophilic chemical compounds into:
  - more hydrophilic, more water soluble
  - have their actions decreased (become less effective) or increased (become more effective)
  - May be converted to less toxic or more toxic metabolites or to metabolites with different type of effect or toxicity

- The metabolism of drugs takes place mainly in the liver (the smooth endoplasmic reticulum of the liver cell) . However, other organs such as the kidney, lung, intestine and placenta can also be involved in this process.

Drug metabolism (Cont.):

- Occasionally the metabolite is less water soluble.

- A significant example is the acetyl metabolite of some of the sulfonamides.

- Some of the earlier sulfonamides are acetylated to relatively insoluble metabolites which precipitated in urine, crystalluria.

- Now the more commonly used sulfonamides have different elimination and solubility properties and exhibit less problems.

Two types of Metabolic Reactions
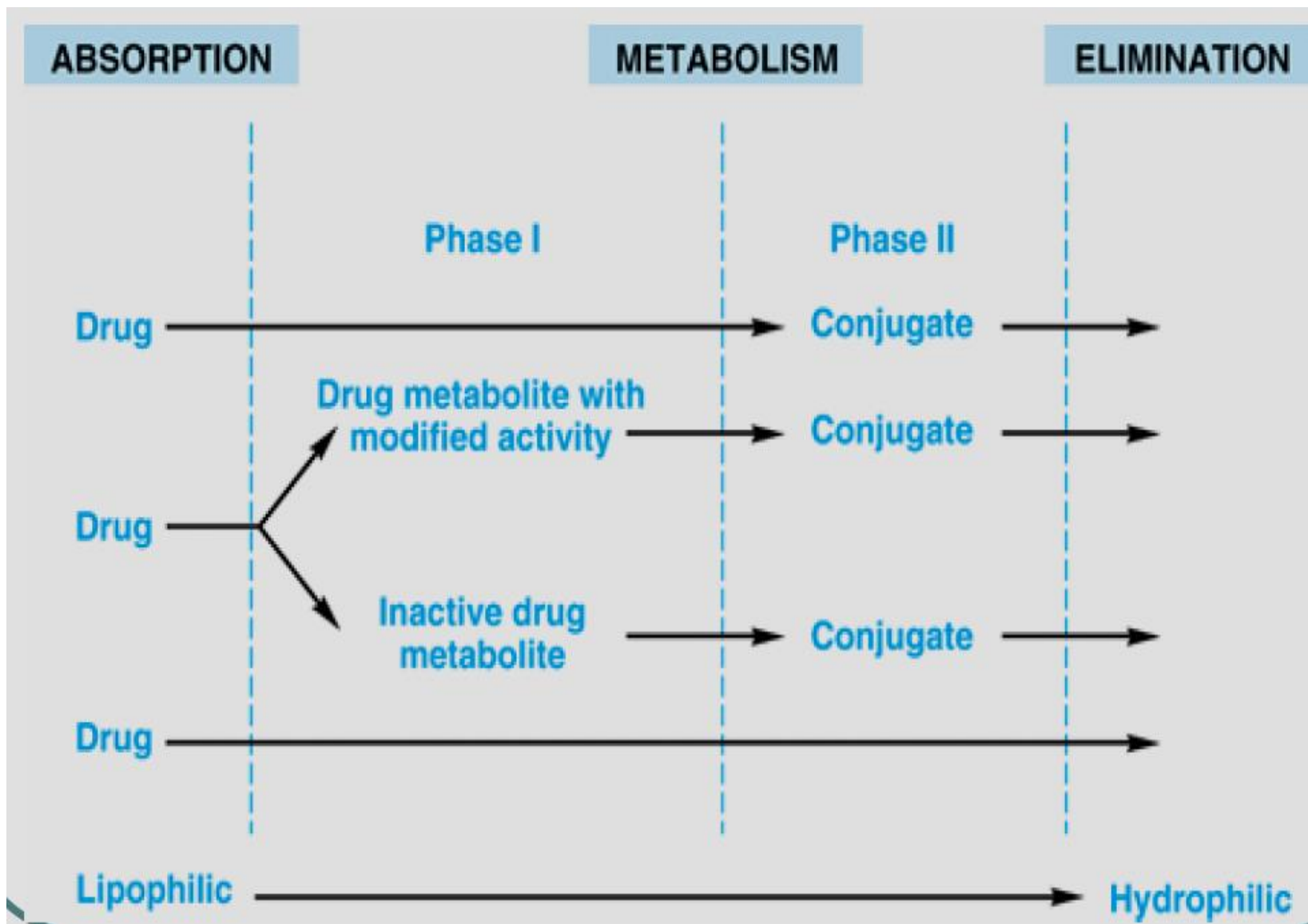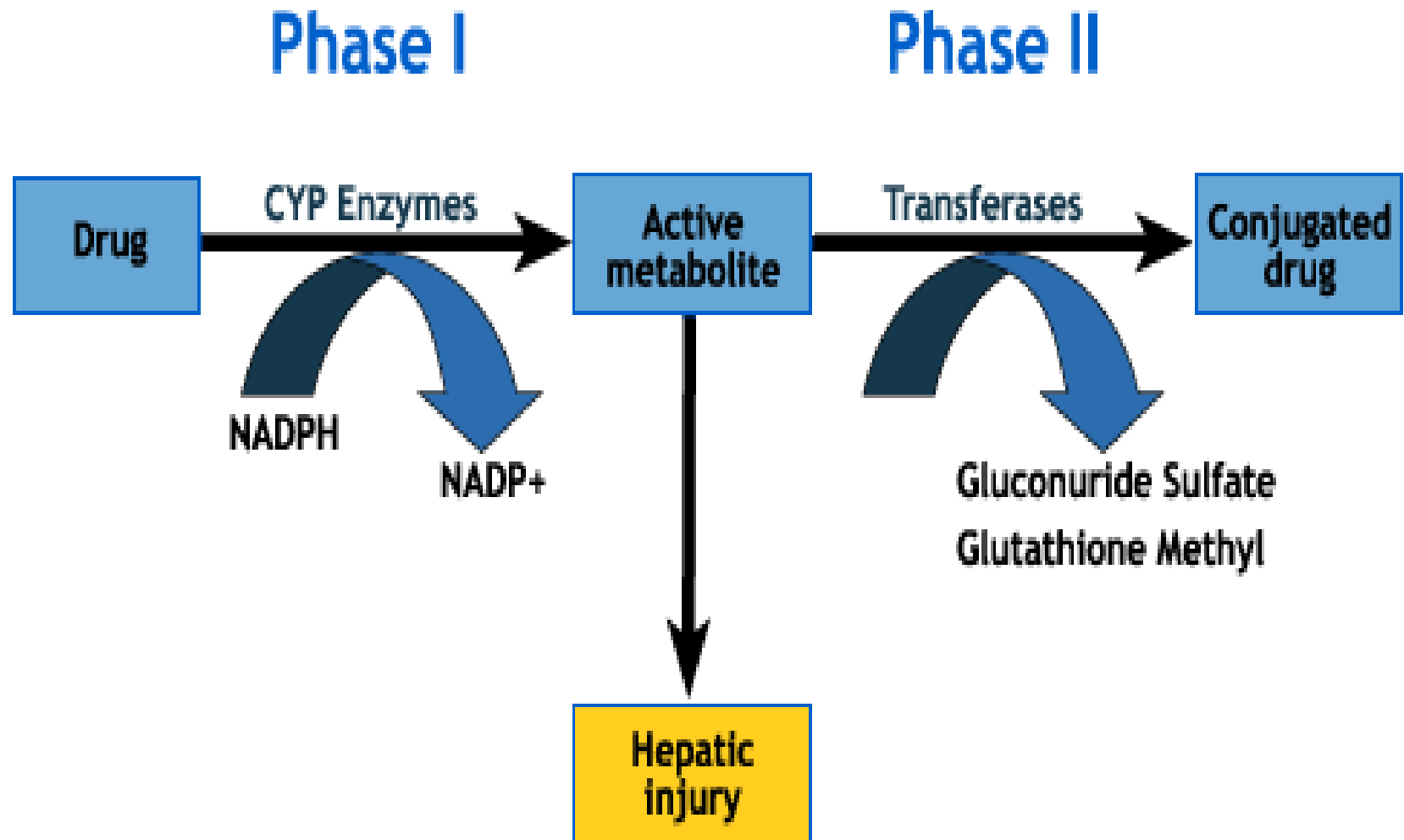
Phases of metabolism:
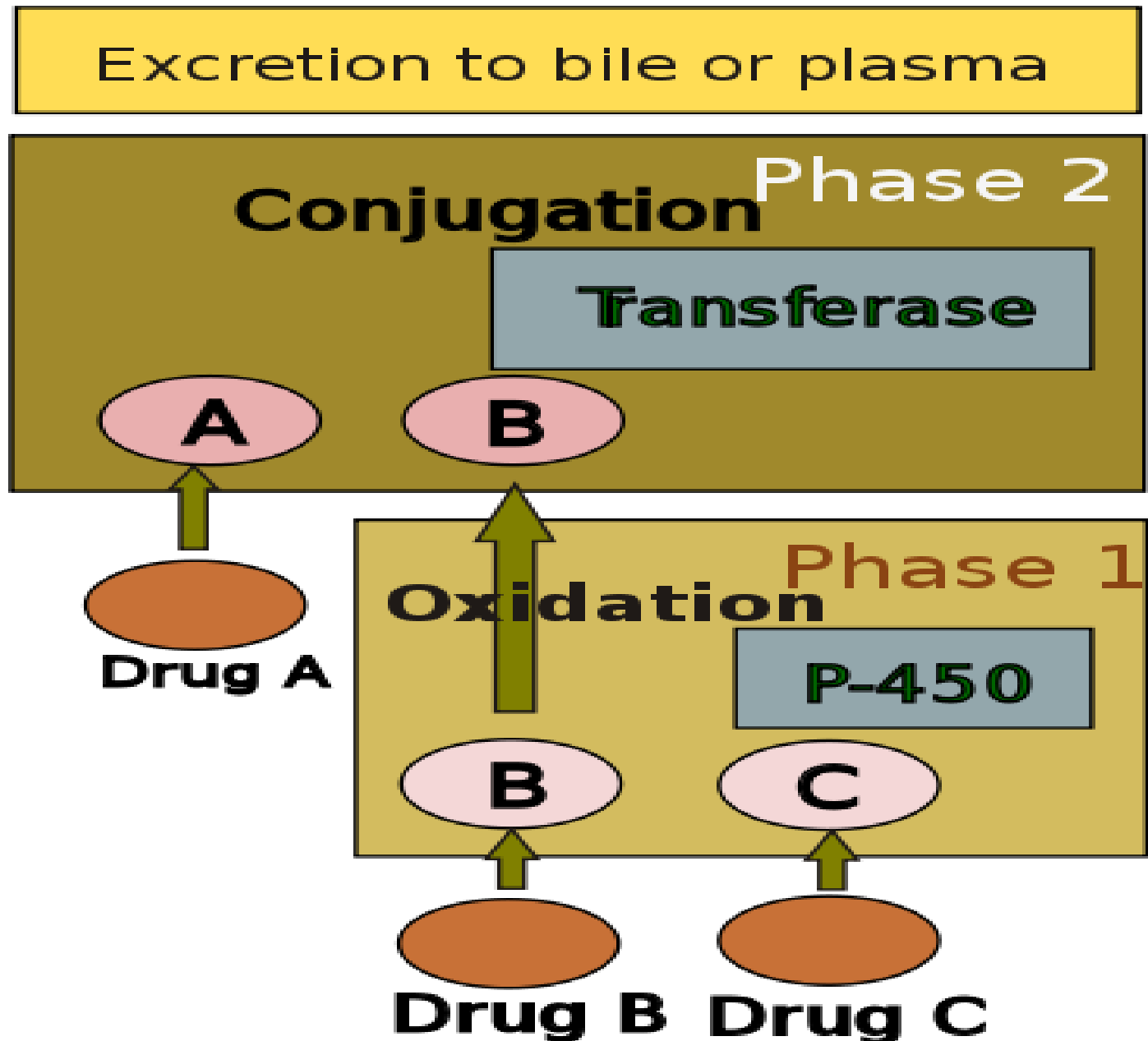
Phases of metabolism:

Phase I reactions:

- Change drugs to more hydrophilic metabolites which are more readily excreted

- Introduce into the drug molecule sites for phase II reactions

- May be less toxic (but not always)

- Mostly occur in the endoplasmic reticulum (microsomes) of liver cells.

- Usually involve oxidation, reduction, hydrolysis or other reactions

Phase I reactions:

1- Oxidation

Oxidation is the addition of oxygen and/or the removal of hydrogen, carried out by oxidases . Most oxidation steps occur in the endoplasmic reticulum. These oxidative reactions typically involve a cytochrome P450, NADPH and oxygen.

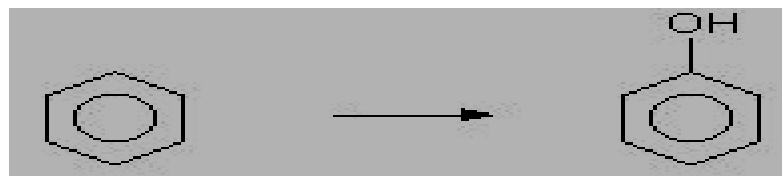Common reactions include :-

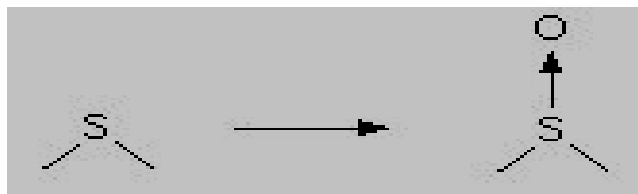- **Alkyl group ----> alcohol**
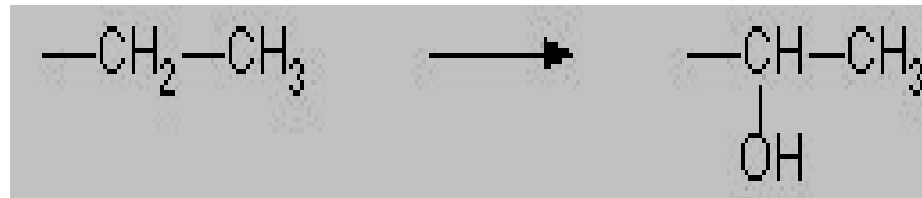
- **Aromatic ring ----> phenol**

Phases of metabolism (Cont.):

for example phenytoin

Oxidation at S or N

for example chlorpromazine

2.Reduction
Add a hydrogen or remove oxygen

azo (-N=N-) or nitro groups (-NO2) -----> amines (-NH2)

for example nitrazepam

Phases of metabolism (Cont.):

3.Hydrolysis

Addition of water with breakdown of molecule.

Esters ---> alcohol and acid

$$R-O-C=O \quad (CH_3) \longrightarrow ROH \ + \ CH_3-COOH$$
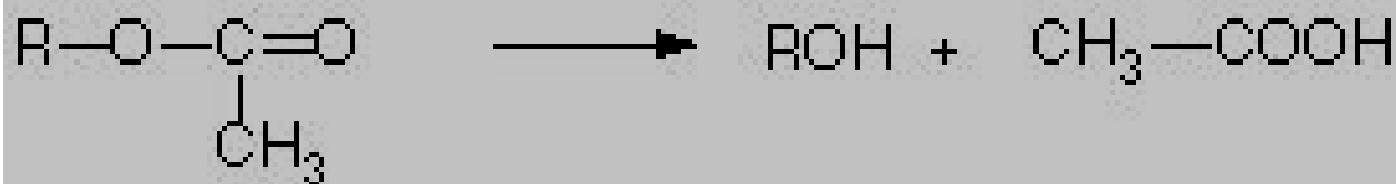
- for example aspirin to salicylic acid

Phase II

1.Conjugation

Conjugation reactions covalently add large, polar endogenous molecules to parent drug or Phase I metabolite →inactive and excretable

(glucuronide, glutathione, sulfate, acetate, amino acids etc)

Phases of metabolism (Cont.):

- **Glucuronidation**

This is the main conjugation reaction in the body. This occurs in the liver. Aliphatic alcohols and phenols are commonly conjugated with glucuronide. Thus hydroxylated metabolites can also be conjugated. for example morphine

- **Acylation**

Acylation, especially acetylation with the acetyl group, e.g. sulfonamides

- **Glycine**

Glycine addition (NH2CH2COOH) for example nicotinic acid

- **Sulfate**

Sulfate (-SO4) for example morphine, paracetamol

Drug metabolism (Cont.):

- In most cases the metabolites are inactive, however, occasionally the metabolite is also active, even to the extent that the metabolite may be the preferred compound to be administered. The original drug may take on the role of a pro-drug. For example:-

<p style="text-align:center;color:green">codeine ---> morphine</p>

<p style="text-align:center;color:green">primidone ---> phenobarbital</p>

- Drug metabolism can be quantitatively altered by drug interactions. This alteration can be an increase by induction of enzyme activity or a reduction by competitive inhibition.

Drug metabolism (Cont.):
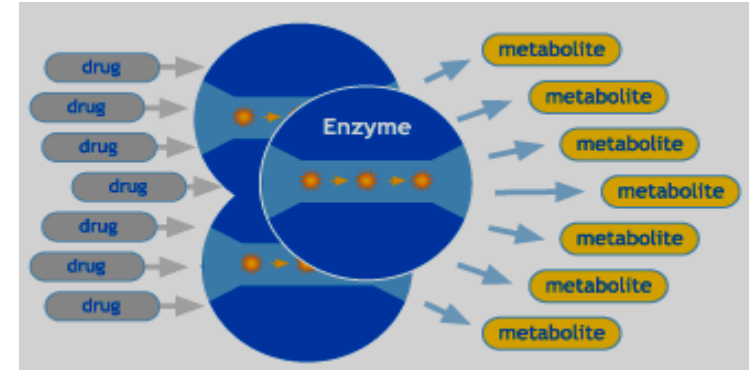
I. Induction

Induction ~ ↑ metabolic activity of enzyme = ↓ [drug]

E.g. Phenobarbitone will induce the metabolism of itself, phenytoin, warfarin, etc.

E.g. Cigarette smoking can cause increased elimination of theophylline.

E.g. alcohol

Dosing rates may need to be increased to maintain effective plasma concentrations.

Drug metabolism (Cont.):

II. Inhibition
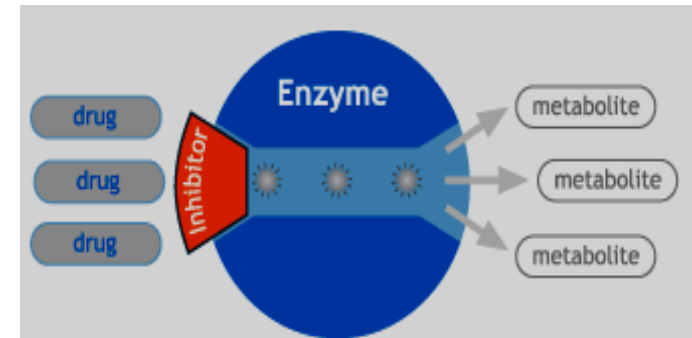
Inhibition ~ ↓ metabolic activity of enzyme = ↑ [drug]

e.g. grapefruit juice

- For example, warfarin inhibits tolbutamide elimination which can lead to the accumulation of drug and may require a downward adjustment of dose.

- Cimetidine is a therapeutic agent (prevent ulcer) that has been found to impair the in vivo metabolism of other drugs.

Drug metabolism (Cont.):

Factors that can influence drug metabolism:

1. **Age:** Drugs metabolism is slower in fetal, neonatal and elderly humans than in adults.

2. **Sex:** women metabolize alcohol more slowly than men

3. **Other drugs:** Certain drugs (enzyme inducers) can increase the rate of metabolism of active drugs (enzyme induction) and thus decrease the duration and intensity of the their action. The opposite is also true (enzyme inhibition).

Drug metabolism (Cont.):

4. Food: Grapefruit juice contains furanocoumarins which inhibit drug metabolism by interfering with hepatic cytochrome P450.

5. Genetic variation (polymorphism):

With Nacetyltransferases (involved in Phase II reactions), individual variation creates a group of people who acetylate drugs (isoniazid) slowly (slow acetylators) and those who acetylate quickly.

- This variation may have dramatic consequences, as the slow acetylators are more prone to dose dependent toxicity.

- 13% of Egyptians are slow acetylators. Warfarin (bleeding) and phenytoin (ataxia) are examples

Drug metabolism (Cont.):

6. **Physiological factors** that can influence drug metabolism include age, individual variation (e.g., pharmacogenetics), enterohepatic circulation,

nutrition, intestinal flora, or sex differences.

7. **Pathological factors** can also influence drug metabolism, including liver, kidney, or heart diseases.

Drug metabolism (Cont.):

Enterohepatic circulation:

40 mg Orally Administered Drug

Portal Circulation

Target Organ

Liver

2 mg Intravenous Administration
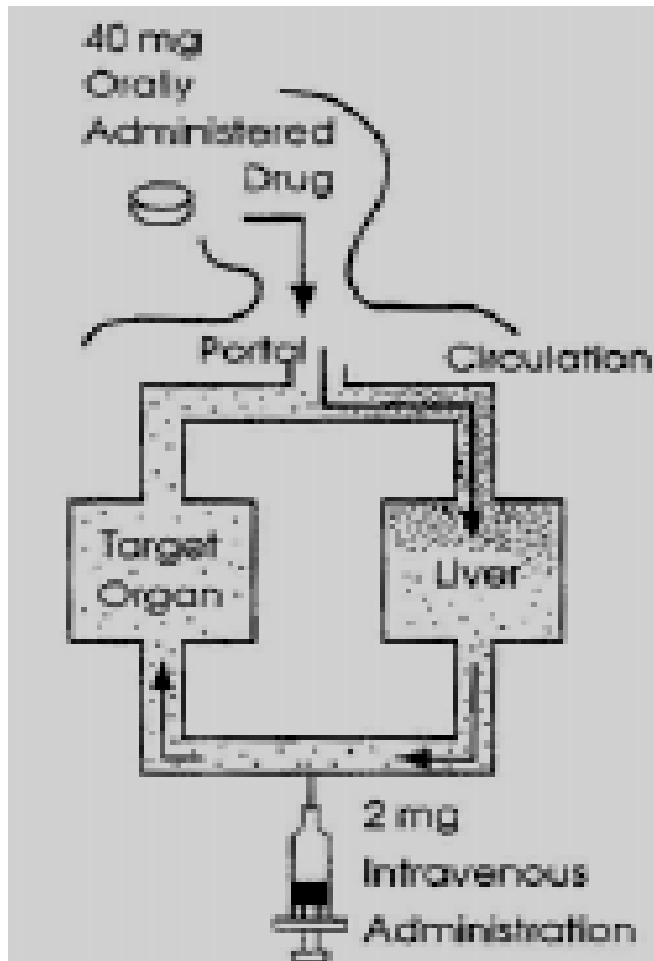
Because of hepatic metabolism, a portion of an orally administered drug dose is inactivated by the liver before reaching the systemic circulation (and ∴ the target organ) → need to adjust dosage

Diseases and Drug Metabolism:

Liver Disease:

- Acute or chronic diseases that affect liver function markedly affect hepatic metabolism of some drugs. Such conditions include fat accumulation, alcoholic cirrhosis, biliary cirrhosis, and acute viral or drug hepatitis. These conditions may impair hepatic drug-metabolizing enzymes, particularly microsomal oxidases, and thereby markedly affect drug elimination.

- For example, the half-life of diazepam in patients with liver cirrhosis or acute viral hepatitis is greatly increased, with a corresponding prolongation of its effect.

Cardiac Disease:

- Cardiac disease, by limiting blood flow to the liver, may impair disposition of those drugs whose metabolism is flow-limited.

Excretion

The irreversible loss of drug from the body

- primarily <u>via kidney and bile</u> (feces, sweat, saliva, tears, expired air & breast milk to lesser degrees)

NOTE: Excretion ≠ Elimination

Excretion: irreversible loss of drug from body

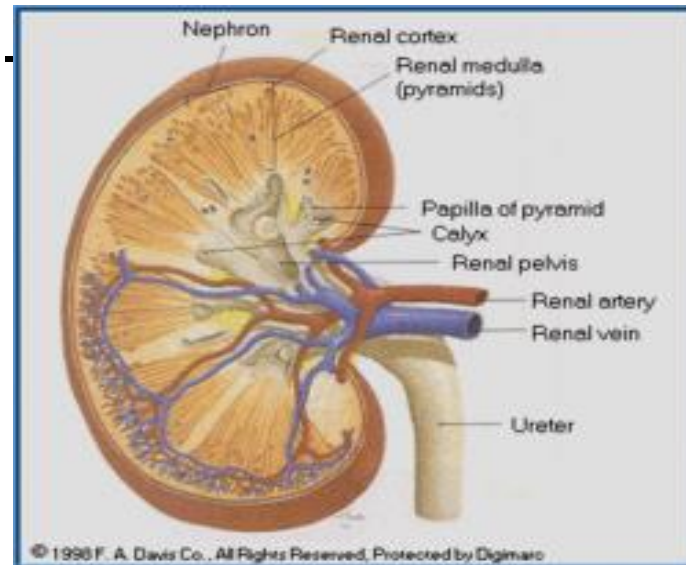Elimination: irreversible loss of parent drug by metabolism and/or excretion

∴ Elimination = Metabolism &/or Excretion

Drug excretion:

1. Renal excretion:

-The major organ for the excretion of drugs is the KIDNEY. The functional unit of the kidney is the nephron in which there are three major processes to consider:-

Renal Drug Clearance

Kidneys

Renal Filtration

Ureters

Bladder

Urinary Elimination

Nephron | Renal cortex
Renal medulla (pyramids)
Papilla of pyramid
Calyx
Renal pelvis
Renal artery
Renal vein
Ureter

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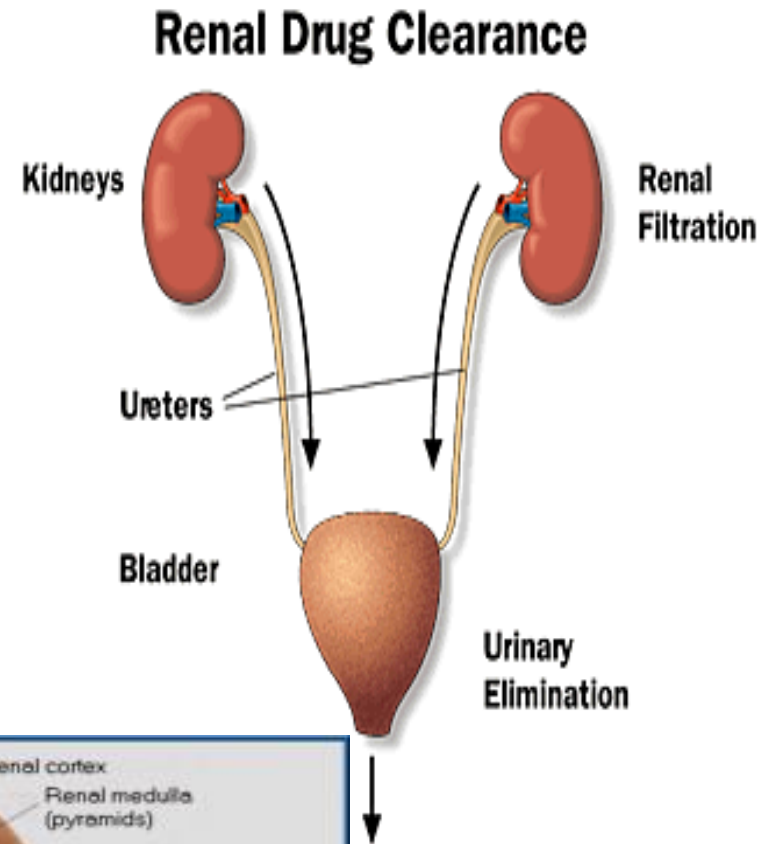
Drug excretion (Cont.):

1) Passive glomerular filtration

2) Active tubular secretion

3) Passive tubular re-absorption

Bowman's Capsule (Glomerular)
Filtration of smaller molecules

Proximal Tubule
Active secretion of weak electrolytes
(especially acids) and reabsorption of water

Distal Tubule
Passive transfer of lipid soluble
drugs and reabsorption of water

Loop of Henle
Reabsorption of water

One Nephron of the Kidney

Urine

Renal excretion:

1. **Passive Glomerular Filtration:** <u>free</u> drug <20kDa

2. **Active Tubular Secretion:** separate transport systems for weak acids and bases

3. **Passive Tubular Reabsorption:** conc. gradient drives diffusion of uncharged drug back into systemic circulation – urine pH is key

Drug excretion (Cont.):

1) Glomerular filtration

- In the glomerulus all molecules (including drugs) of low molecular weight (less than 2000) are readily filtered out of the blood unless they are tightly bound to plasma protein (albumin).
- This filtration rate is often measured by determining the renal clearance of inulin. Inulin is readily filtered in the glomerular, and is not subject to tubular secretion or re-absorption. Thus inulin clearance is equal to the glomerular filtration rate.

Drug excretion (Cont.):

2)Tubular secretion
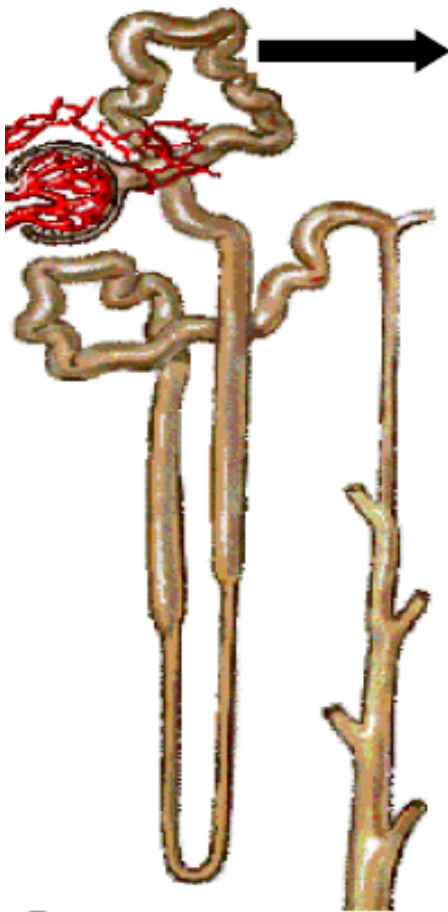
- Only less than 20% of renal plasma flow is filtered through the glomerulus, leaving at least 80% to pass on to the peritubular capillaries of the proximal tubule.
- There, drug molecules are transferred to the tubular lumen by two non-selective carriers (one transports acidic drugs, while the other handles organic bases.
- This is active transport and therefore:
- It can secrete all of the drug (even if it is bound to plasma protein) making it the most effective mechanism of renal elimination .
- **Penicillin**, for example being 80% protein-bound is cleared only slowly by filtration, but almost completely removed by proximal tubular secretion
- Competitive inhibition of the secretion of one compound by another may occur (inhibition of penicillin excretion by probenecid).

Drug excretion (Cont.):
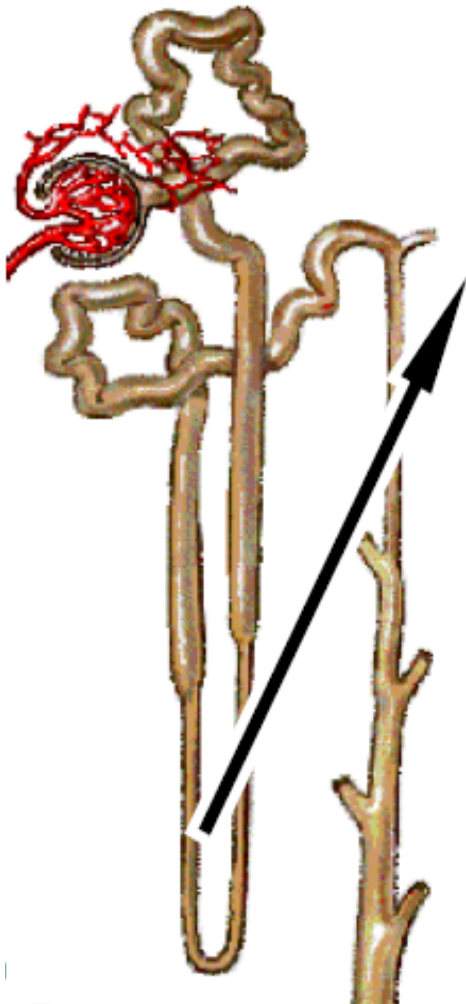
- In the loop of Henle, 99% of the filtered water is re-absorbed.
- All solutes (including drugs) in the lumen are therefore significantly concentrated.
- When the drugs reach the distal tubule, their high luminal concentration favours their re-absorption

Drug excretion (Cont.):

3)Tubular re-absorption

- In the distal tubule there is passive excretion and re-absorption of lipid soluble drugs. Filtered lipophilic drugs are extensively reabsorbed. Thus if a drug is non-ionized or in the unionized form it maybe readily reabsorbed.
- Many drugs are either weak bases or acids and therefore the pH of the filtrate can greatly influence the extent of tubular re-absorption for many drugs.
  - When urine is acidic weak acid drugs tend to be reabsorbed.
  - Alternatively when urine is more alkaline, weak bases are more extensively reabsorbed. (continued)

3)Tubular re-absorption

Urine pH varies from 4.5 to 8.0 depending on the diet (e.g. meat can cause a more acidic urine) or drugs (which can increase or decrease urine pH).

In drug overdose it is possible to increase the excretion of some drugs by suitable adjustment of urine pH.

In overdoses with weak acids (pentobarbital, aspirin) injecting sodium bicarbonate increases drug excretion.

In overdoses with weak bases (codeine, amphetamine) ammonium chloride lowers pH and increases ionization of bases

Skip

Drug excretion (Cont.):

Renal clearance:

■ One method of quantitatively describing the renal excretion of drugs is by means of the renal clearance value for the drug.

■ Renal clearance can be used to investigate the mechanism of drug excretion:

A- If the drug is filtered but not secreted or reabsorbed the renal clearance will be about 120 ml/min in normal subjects.

B- If the renal clearance is less than 120 ml/min then we can assume that at least two processes are in operation, glomerular filtration and tubular re-absorption.

C- If the renal clearance is greater than 120 ml/min then tubular secretion must be contributing to the elimination process.

Drug excretion (Cont.):

Renal clearance is then:-

$$CL_{renal} = \frac{\text{filtration rate} + \text{secretion rate} - \text{reabsorption rate}}{Cp}$$

$$\text{Renal Clearance} = \frac{\text{Rate of Excretion}}{\text{Plasma Concentration}}$$

Factors Altering Renal Drug Clearance:

Renal drug clearance is lower [therefore you must reduce dose] in:

- Elderly and Newborn
- Women (20%) than men
- Kidney and Heart Disease
- Patients taking drugs which block secretion (aspirin,probenecid)

Drug excretion (Cont.):

Hemodialysis:

- Hemodialysis or `artificial kidney' therapy is used in renal failure to remove toxic waste material normally removed by the kidneys.

- In the procedure blood is diverted externally and allowed to flow across a semi-permeable membrane that is bathed with an aqueous isotonic solution. Nitrogenous waste products and some drugs will diffuse from the blood, thus these compounds will be eliminated.

- This technique is particularly important with drugs which:-
1) have good water solubility;
2) are not tightly bound to plasma protein;
3) are smaller molecular weight; and
4) have a small apparent volume of distribution.

- Drugs which are tightly bound or extensively stored or distributed into tissues are poorly removed by this process.

Haemodialysis
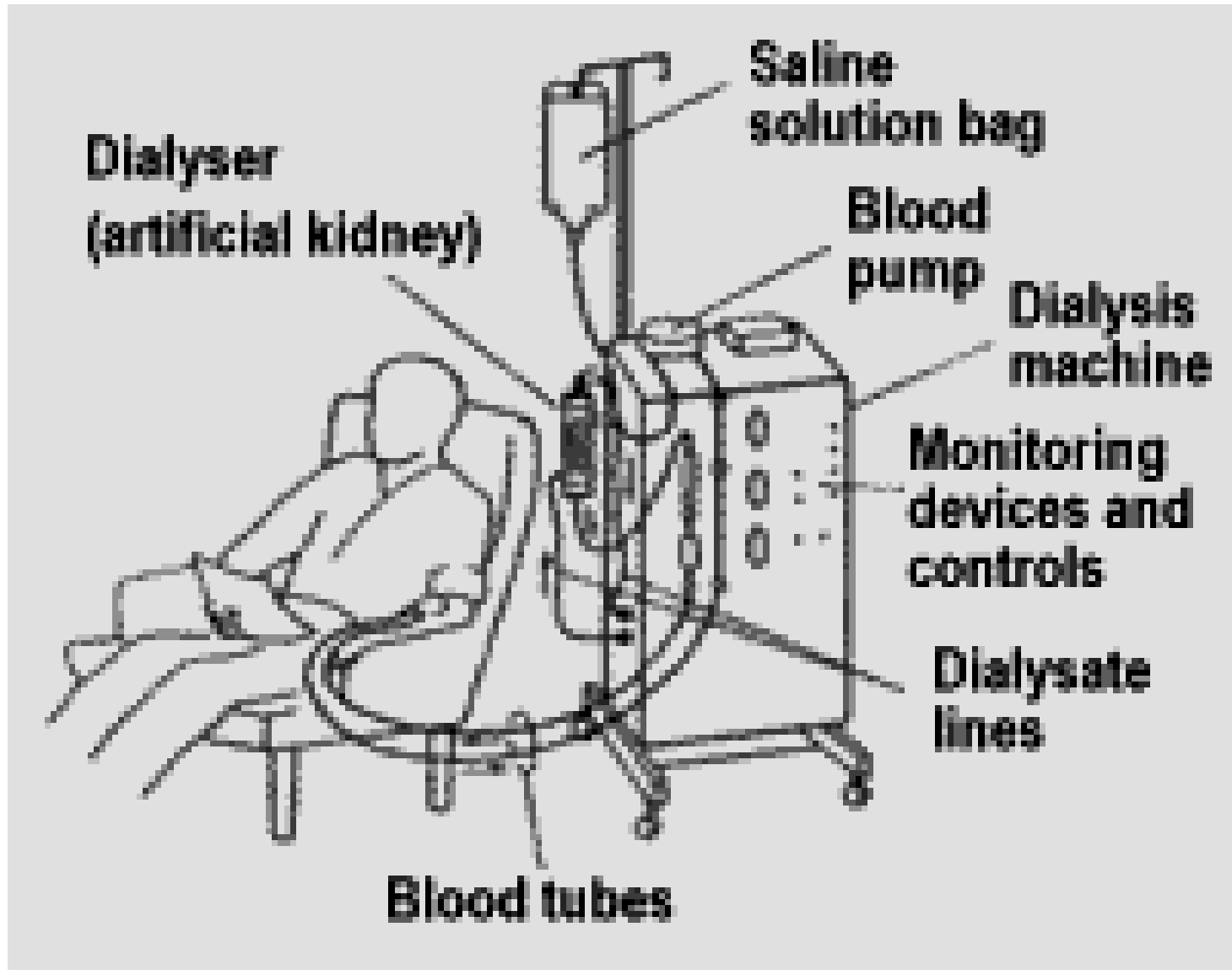
Drug excretion (Cont.):

2.Fecal excretion:

Elimination of toxicants in the feces

occurs from two processes:

A- excretion in bile:

- Some heavy metals are excreted in the bile, e.g., arsenic, lead, and mercury. However, the most likely substances to be excreted via the bile are comparatively large, ionized molecules, such as large molecular weight (greater than 300) conjugates e.g. morphine and chloramphenicol (as glucuronide).

- The biliary secretion is active since bile/plasma concentrations maybe as high as 50/1. There can also be competition between compounds.
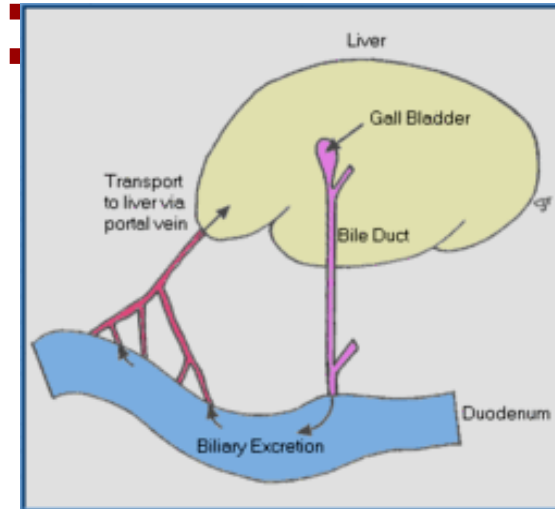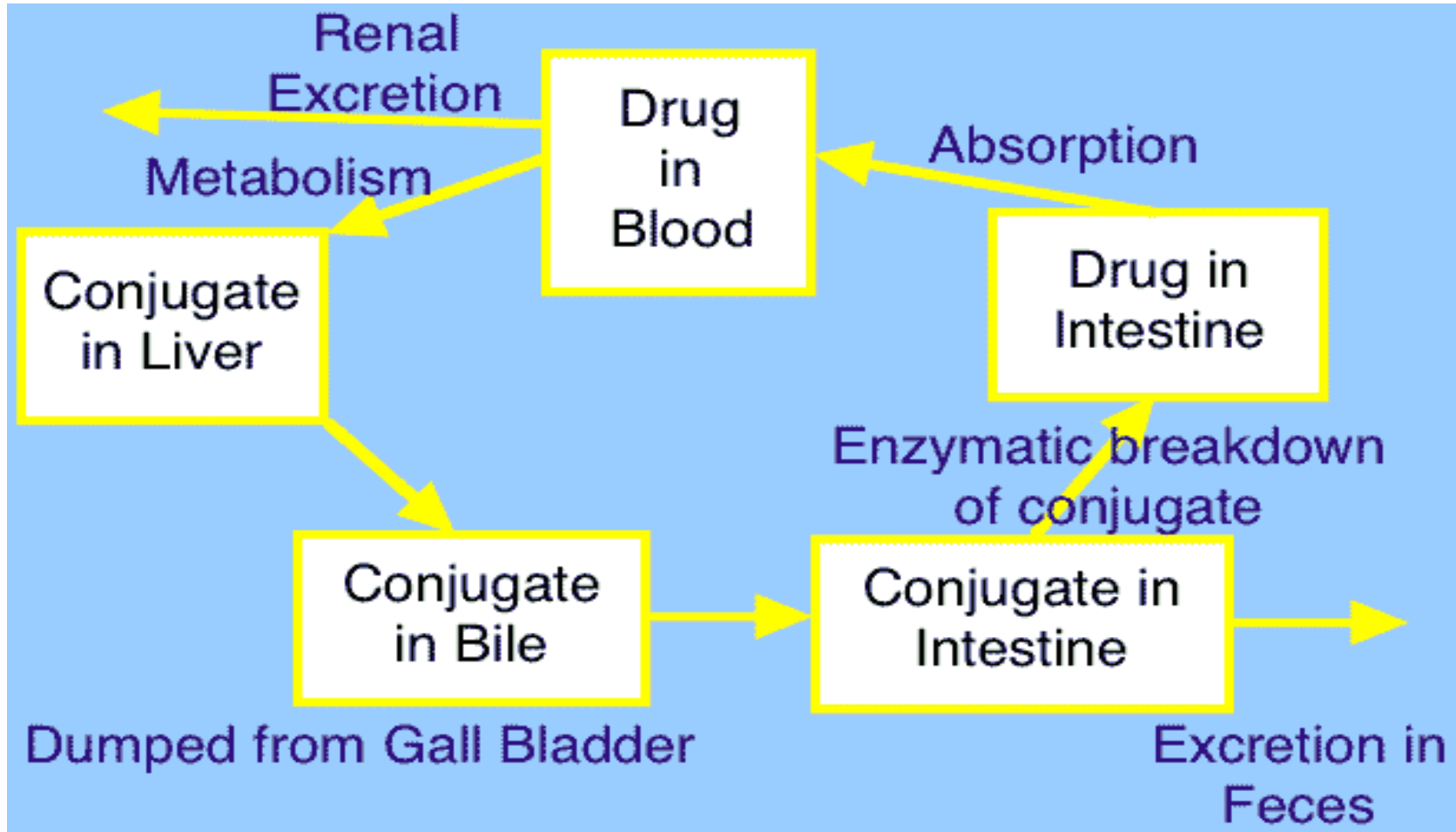
Drug excretion (Cont.):

- Once a substance has been excreted by the liver into the bile, and subsequently into the intestinal tract, it can then be eliminated from the body in the feces, or it may be reabsorbed.

- Since most of the substances excreted in the bile are water-soluble, they are not likely to be reabsorbed as such. However, enzymes in the intestinal flora are capable of hydrolyzing some glucuronide and sulfate conjugates, which can release the less-polar compounds that may then be reabsorbed. This process is known as the **enterohepatic circulation.**

- The effect of this enterohepatic circulation is to prolong the life of the drug in the body.
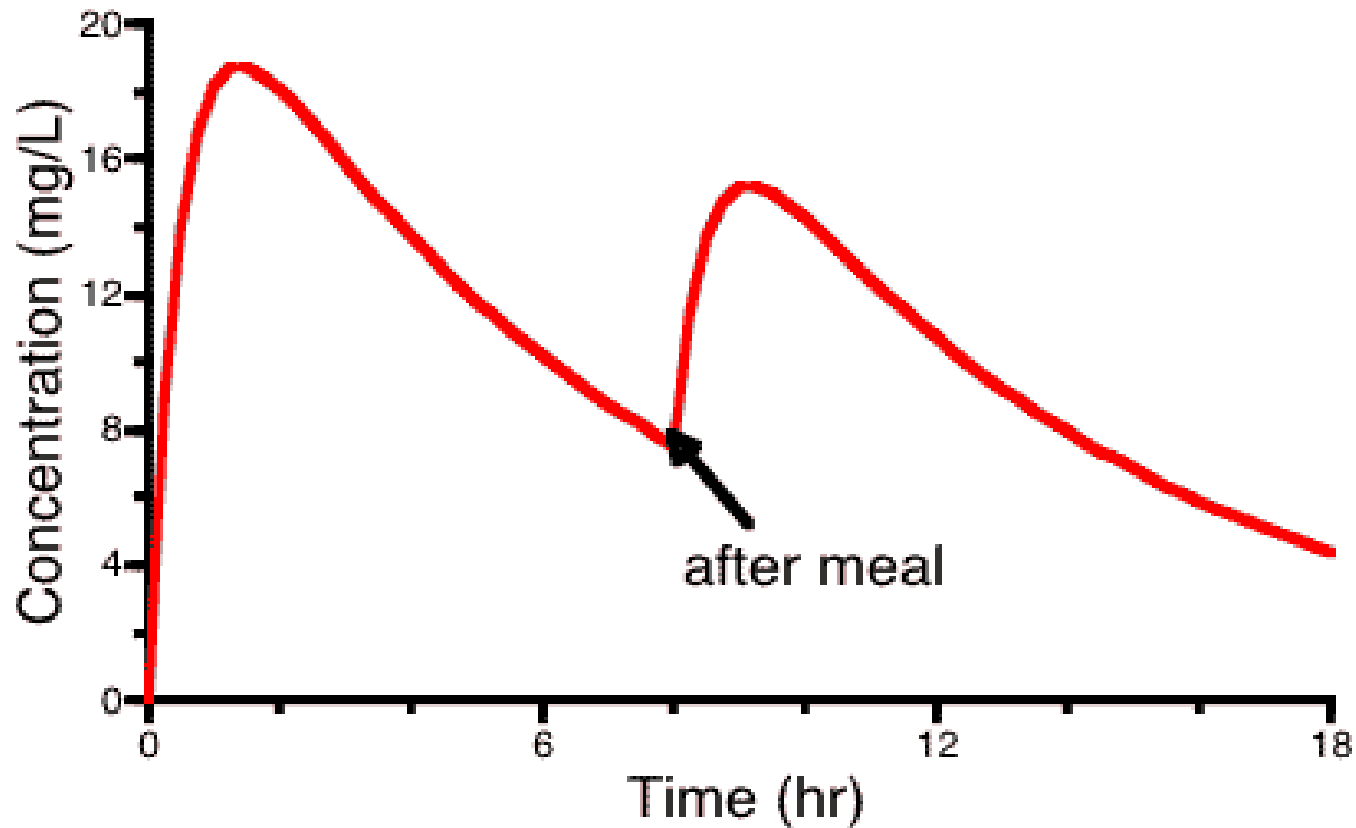
Drug excretion (Cont.):

Enteroheptic Recycling

Drug excretion (Cont.):

Cp versus Time showing a Second Peak

Drug excretion (Cont.):

■ Another way that drugs can be eliminated via the feces is by:

B- direct intestinal excretion:

- Orally administered drugs may be excreted in the feces if they are incompletely absorbed or not absorbed at all (e.g. Cholestyramine)

- Increasing the lipid content of the intestinal tract can enhance intestinal excretion of some lipophilic substances. For this reason, mineral oil is sometimes added to the diet to help eliminate toxic substances, which are known to be excreted directly into the intestinal tract.

Drug excretion (Cont.):

Drugs may be excreted by passive diffusion from:

3. Pulmonary excretion:

- The lung is the major organ of excretion for gaseous and volatile substances. Most of the gaseous anesthetics are extensively eliminated in expired air.

4. Salivary excretion:

- Drug excretion into saliva appears to be dependent on pH partition and protein binding.

- In some instances, salivary secretion is responsible for localized side effects. For example, excretion of antibiotics may cause black hairy tongue, and gingival hyperplasia can be a side effect of phenytoin.

Drug excretion (Cont.):

Examples of compounds that excreted in saliva:

- Neonatal jundice result from sulfonamide interaction with bilirubin.
- Superinfection from antibiotics.
- Dental mottling upon tetracycline ingestion.

- Mothers smoking more than 20 to 30 cigarettes a day may induce nausea, vomiting, abdominal cramps and diarrhea in the infant.

5. Skin excretion:

- Iodine, bromine, benzoic acid, salicylic acid, lead, arsenic mercury , iron and alcohol are examples of compounds that excreted in sweat.

Black hairy tongue

gingival hyperplasia

Drug excretion (Cont.):

6. Mammary excretion:

Both a-basic substances and b-lipid-soluble compounds can be excreted into milk.

Basic substances can be concentrated in milk since milk is more acidic (pH ~ 6.5) than blood plasma.

Since milk contains 3-4% lipids, lipid-soluble drugs can diffuse along with fats from plasma into the mammary gland and thus can be present in mother's milk.

C-Substances that are chemically similar to calcium can also be excreted into milk along with calcium.

D-Ethanol and tetracycline enter the milk by diffusion through membrane pores (of mammary alveolar cells).

Bioavailability and Bioequivalence:

Bioavailability:

It is a measurement of the extent of a therapeutically active drug that reaches the systemic circulation and is available at the site of action.
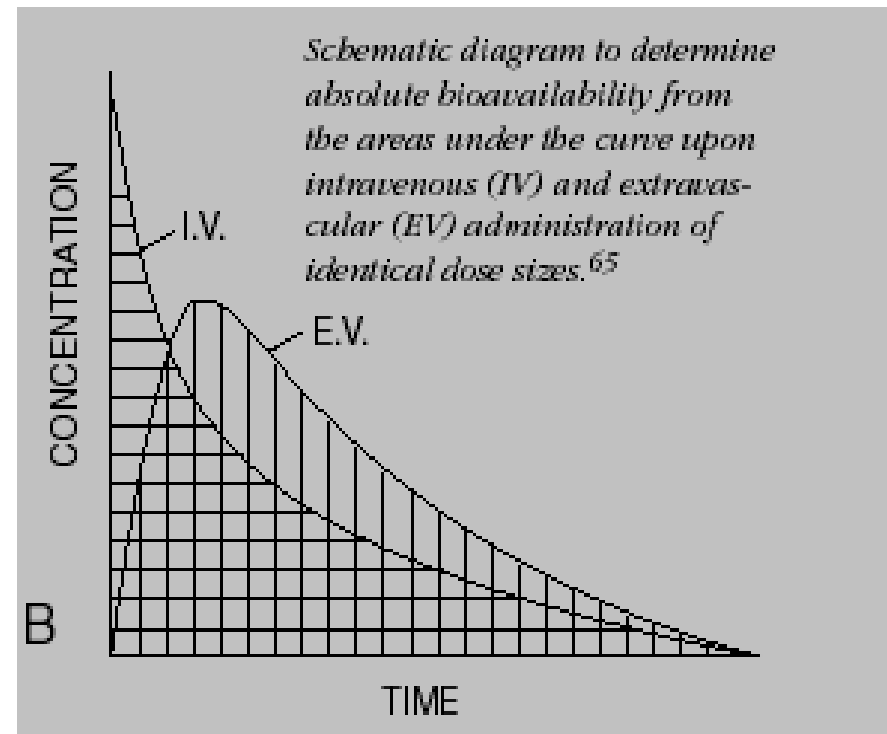
Absolute bioavailability:

Absolute bioavailability compares the bioavailability (estimated as area under the curve, or AUC) of the active drug in systemic circulation following non-intravenous administration (i.e., after oral, rectal, transdermal, subcutaneous administration), with the bioavailability of the same drug following intravenous administration.

Bioavailability and Bioequivalence:

It is the fraction of the drug absorbed through non-intravenous administration compared with the corresponding intravenous administration of the same drug.

$$F = \frac{[AUC]_{po} * dose_{IV}}{[AUC]_{IV} * dose_{po}}$$

Schematic diagram to determine absolute bioavailability from the areas under the curve upon intravenous (IV) and extravascular (EV) administration of identical dose sizes.[65]
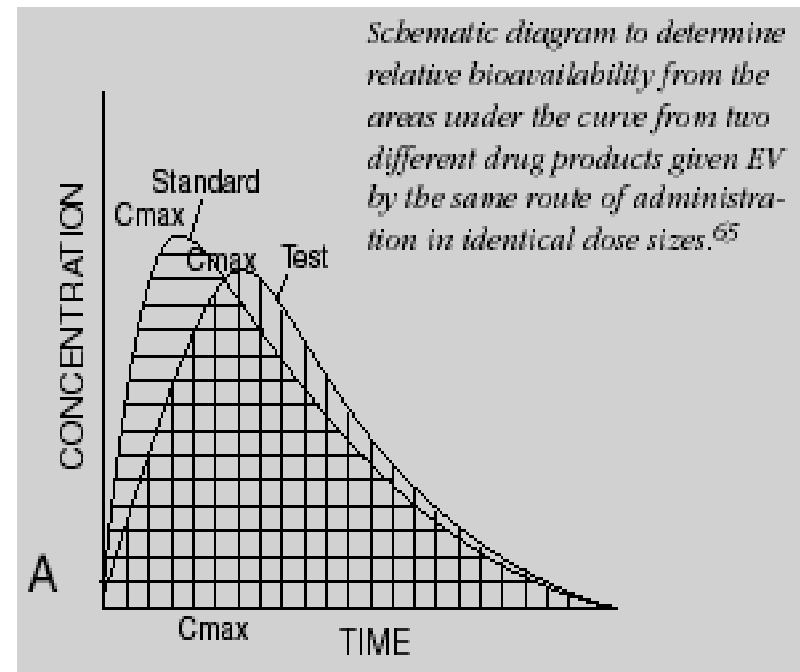
Bioavailability and Bioequivalence:

Relative bioavailability:

This measures the bioavailability (estimated as area under the curve, or AUC) of a certain drug when compared with another formulation of the same drug, usually an established standard, or through administration via a different route.

$$relative\ bioavailability = \frac{[AUC]_A * dose_B}{[AUC]_B * dose_A}$$

Schematic diagram to determine relative bioavailability from the areas under the curve from two different drug products given EV by the same route of administration in identical dose sizes.[65]
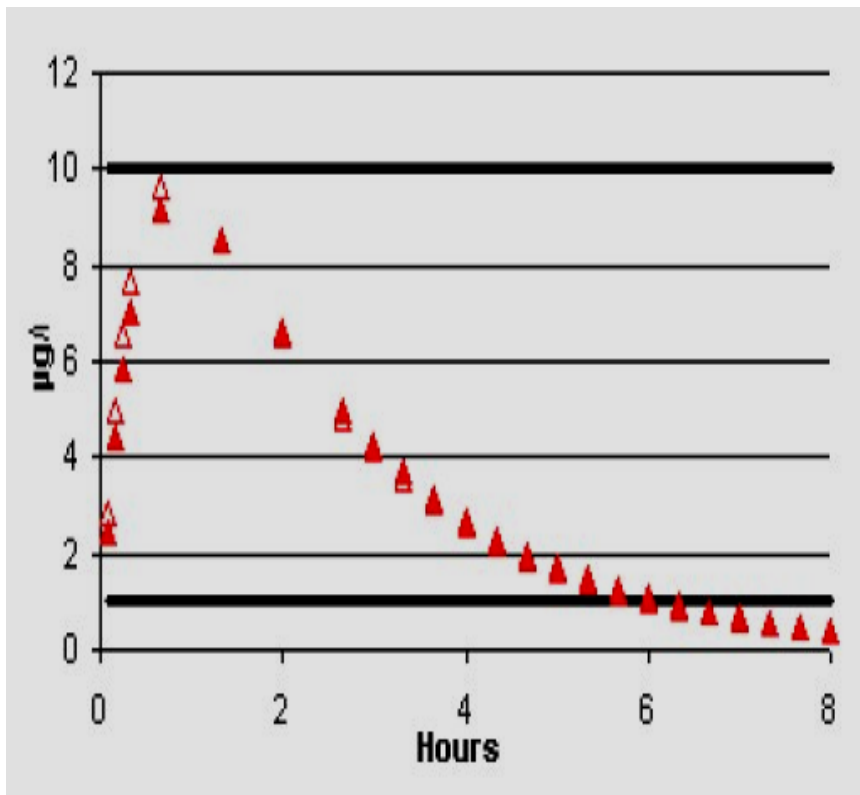
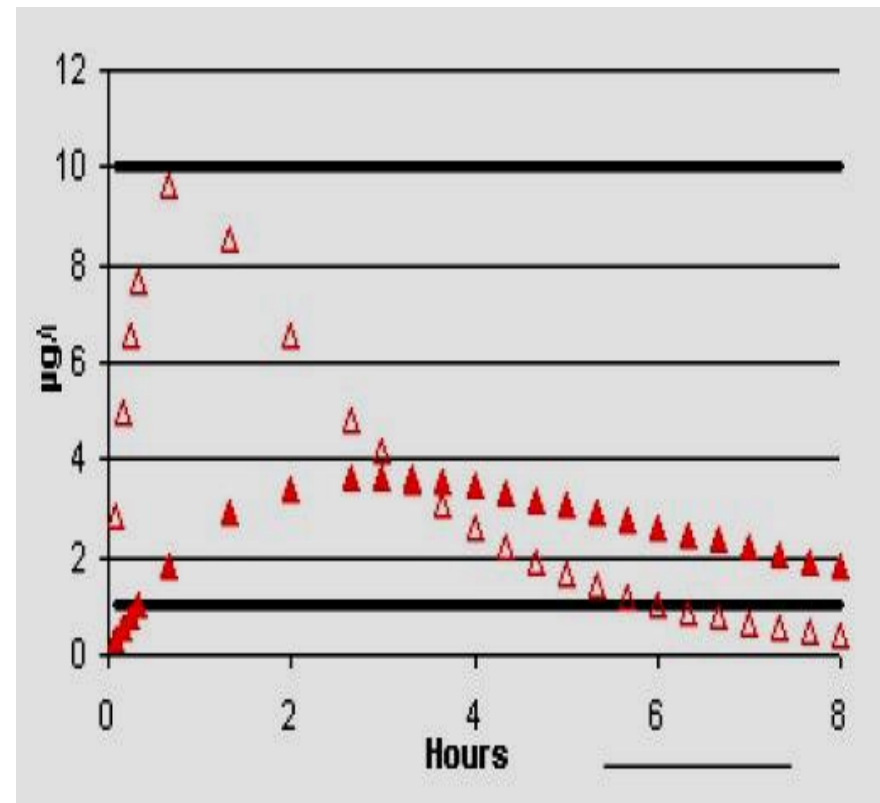# Bioavailability and Bioequivalence:

Bioequivalence:

- means pharmaceutical equivalents or pharmaceutical alternatives whose rate and extent of absorption do not show a significant difference when administered at the same molar dose of the therapeutic moiety under similar experimental conditions.

- Bioequivalence studies are usually performed to compare the rate and/or extent of absorption of a new drug product or a generic equivalent with that of a recognized standard.

-

Bioavailability and Bioequivalence:

Two dosage forms are bioequivalent:

Two dosage forms are not bioequivalent:

Bioavailability and Bioequivalence:

- **Pharmaceutical Alternatives:**

  means drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester.

- **Pharmaceutical Equivalent:**

  means drug products that contain identical amounts of the identical active drug ingredient, i.e., the salt or ester of the same therapeutic moiety, in identical dosage forms, but not necessarily containing the same inactive ingredients, and that meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and where applicable, content uniformity, disintegration times and/or dissolution rate.

- **Brand Name:** is the trade name of the drug.

- **Chemical Name:** is the name used by the organic chemist to indicate the chemical structure of the drug.

- **Generic Name:** is the established, non proprietary or common name of the active drug in a drug product.

Bioavailability and Bioequivalence:

Methods to Assess Bioavailability:

I. Dissolution at administration or absorption site:

Method of evaluation: Dissolution rate

Example: I*n vitro:* water, buffer, artificial gastric fluid, artificial intestinal fluid, artificial saliva, artificial rectal fluid.

II.Free drug in systemic circulation:
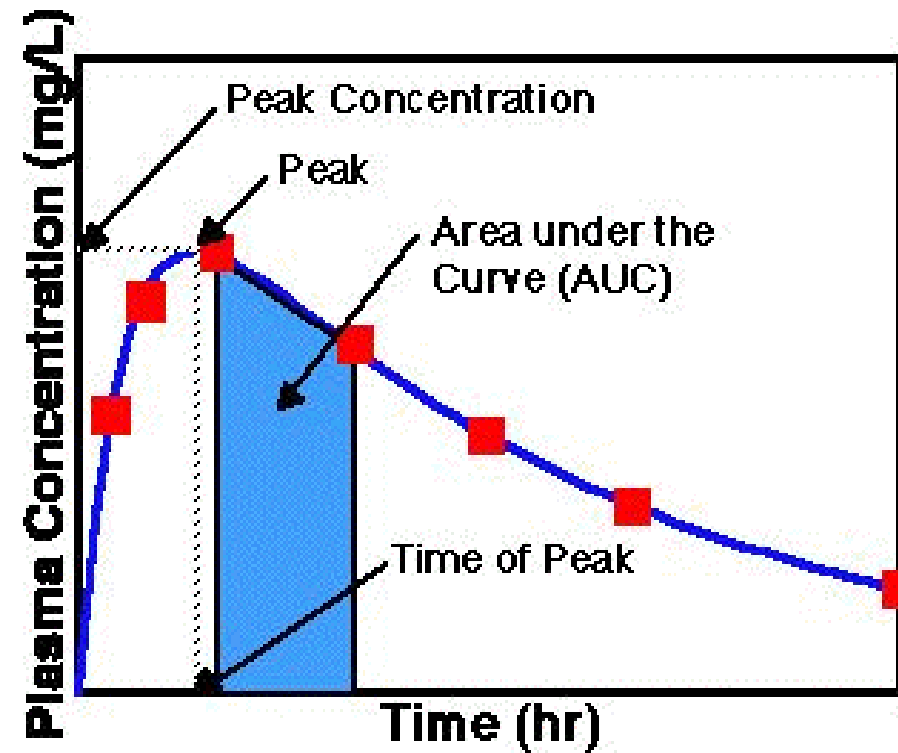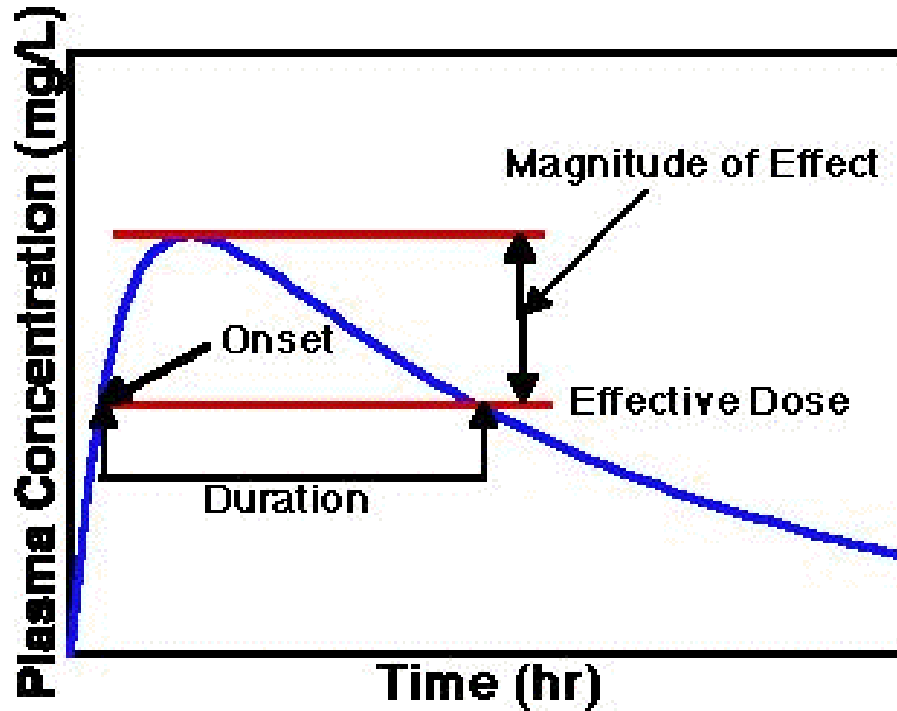
Method of evaluation: 1.Blood level time profile

2.Peak blood level

3.Time to reach peak

4.Area under blood level time curve

Example: *In vivo:* whole blood, plasma, serum

Introduction to bipharmaceutics (Cont.):

Bioavailability and Bioequivalence:

III. Pharmacologic effect:

Method of evaluation: 1.Onset of effect

2.Duration of effect

3.Intensity of effect

Example: *In vivo:* discriminate measurement of pharmacologic effect (blood pressure, blood sugar, blood coagulation time)

IV. Clinical response:

Method of evaluation: 1.Controlled clinical blind or double-blind study

2.Observed clinical success or failure

Example: *In vivo:* evaluation of clinical responses

Bioavailability and Bioequivalence:

V. Elimination:

Method of evaluation: 1.Cumulative amount of drug excreted

2.Maximum excretion rate

3.Peak time of excretion

Example: *In vivo:* urine