General Pharmacological principles (Pharmacodynamics (PD) and pharmacokinetics (PK))

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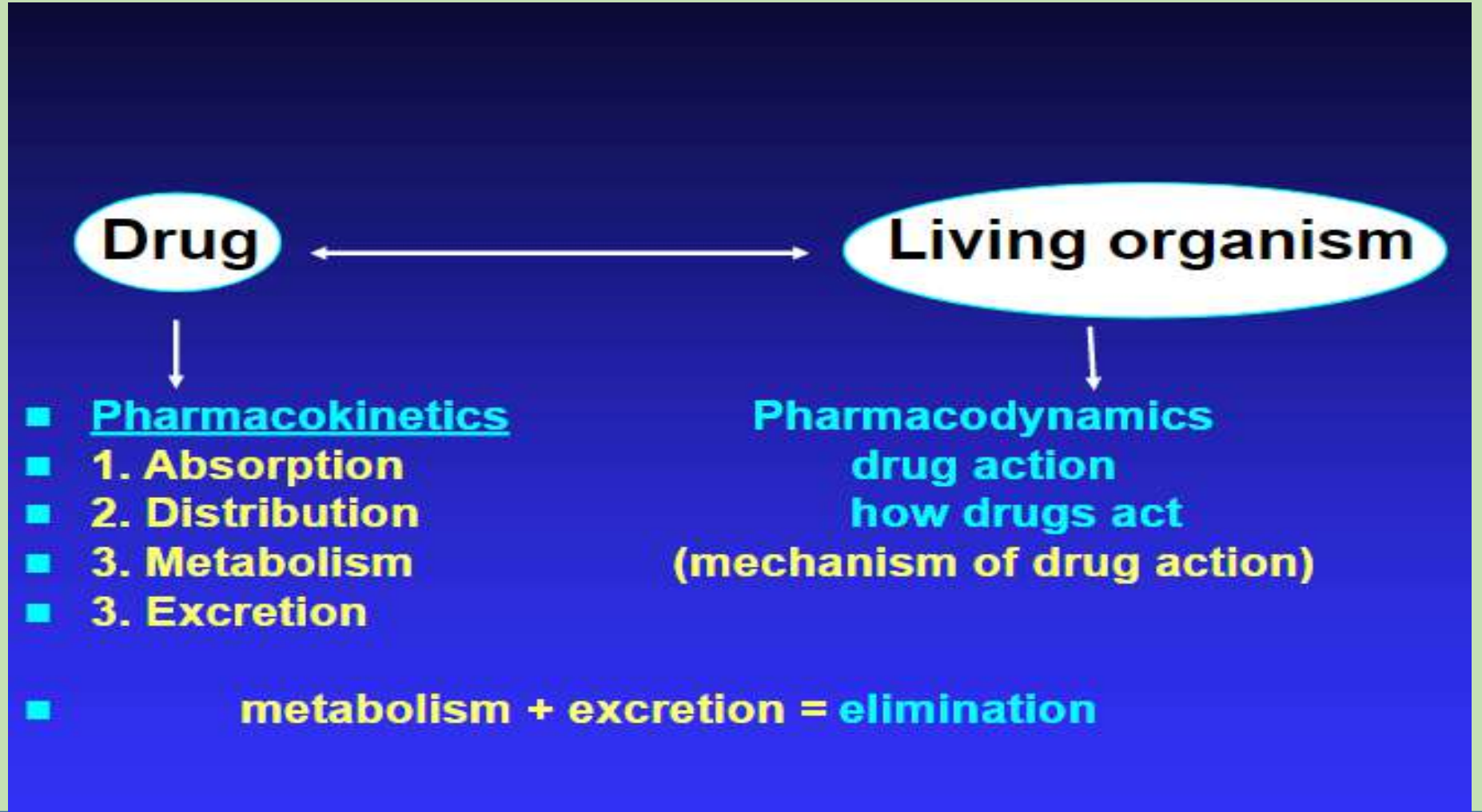
Pharmacokinetics (PK) and Pharmacodynamics (PD)

Pharmacodynamics (PD) is the study of how the drug affects the organism, while pharmacokinetics (PK) is the study of how an organism affects a drug; they are the two main branches of pharmacology.



Importance of PK (Pharmacokinetics) studies

❑Importance of PK studies

➢Patients may suffer:

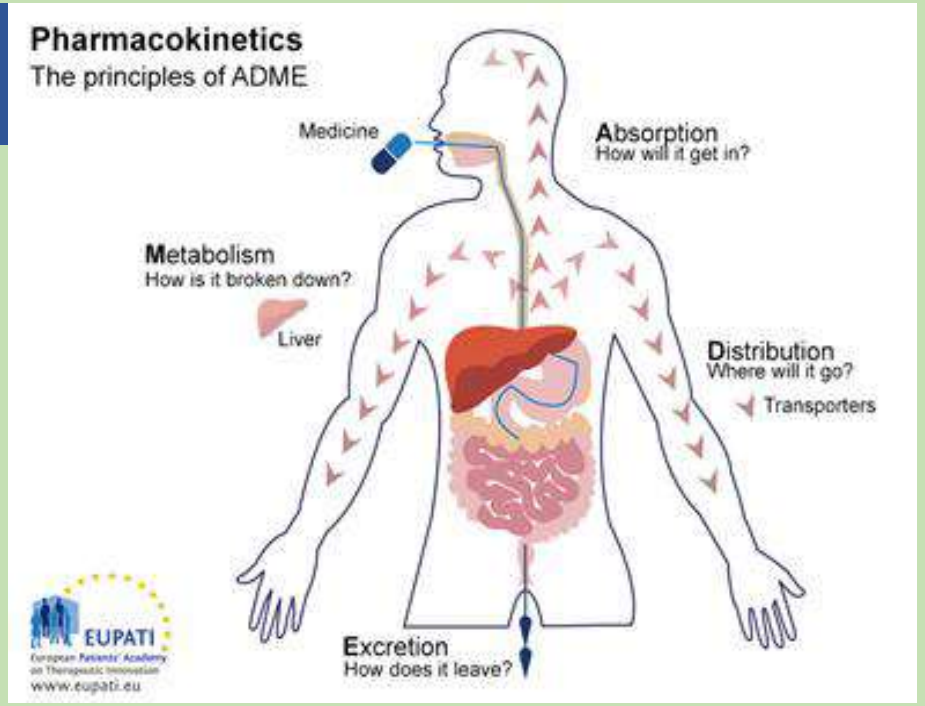
- Toxic drugs may accumulate.
- Useful drugs may have no benefit because doses are too small to establish therapy.
- A drug can be rapidly metabolized.

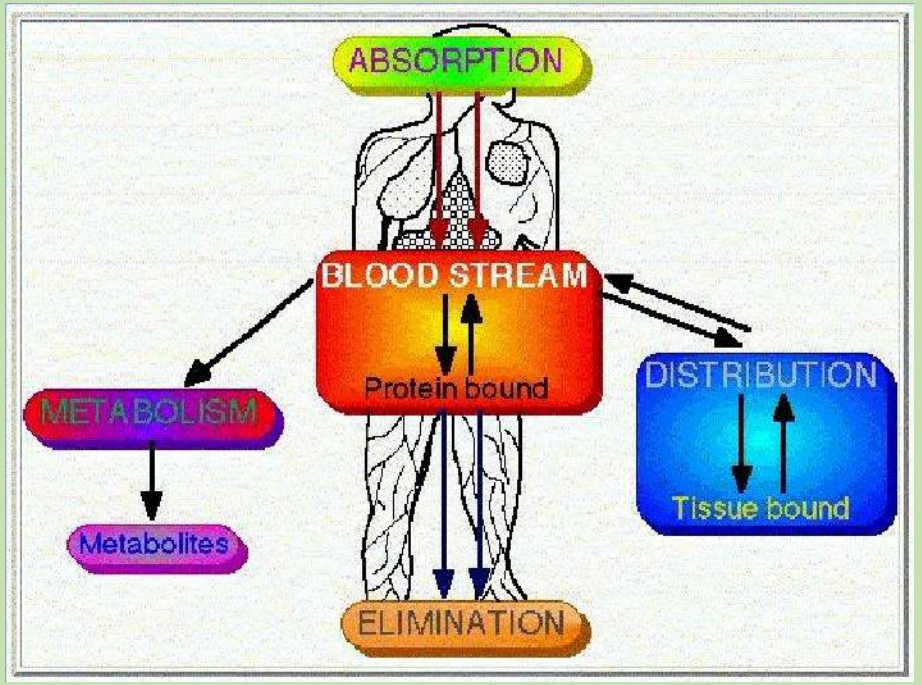
❑Why Study Pharmacokinetics (PK) and Pharmacodynamics (PD)?

- Individualize patient drug therapy
- Monitor medications with a narrow therapeutic index
- Decrease the risk of adverse effects while maximizing pharmacologic response of medications
- Evaluate PK/PD as a diagnostic tool for underlying disease states

Clinical Pharmacokinetics (PK)

- Introduction to Pharmacokinetics: Four Steps in a Drug's Journey Through the Body. Pharmacokinetics : what the body does to the drug.
  - Absorption
  - Distribution
  - Metabolism
  - Elimination
- The magnitud of the pharmacological effect of a drug depends on its concentration at the site of action.
- Drug concentration at sites of action influenced by several factors, such as:
  - Route of administration
  - Dose
  - Characteristics of drug molecules (e. g. , lipid solubility)





Routes of Drug Administration

❑Oral Drug Administration

➢Advantages:

- Relatively safe
- Economical
- Convenient
- Practical

➢Disadvantages:

- Blood levels are difficult to predict due to multiple factors that limit absorption.
- Some drugs are destroyed by stomach acids.
- Some drugs irritate the GI system.

Routes of Drug Administration / Advantages

❑Advantages of Injection Routes

- Absorption is more rapid than with oral administration.
- Rate of absorption depends on blood flow to particular tissue site (I. P. > I. M. > S. C.).

❑Advantages specific to I. V. injection

- No absorption involved (inject directly into blood).
- Rate of infusion can be controlled.
- A more accurate prediction of dose is obtained.

Routes of Drug Administration / Disadvantages

- Disadvantages/Risks of Injection
- A rapid onset of action can be dangerous in overdosing occurs.
- If administered too fast, heart and respiratory function could collapse.
- Drugs insoluble in water or dissolved in oily liquids can not be given I. V.
- Sterile techniques are necessary to avoid the risk of infection.

Absorption

- Absorption is the movement of a drug from its site of administration to the bloodstream.

❑The rate and extent of drug absorption depend on multiple factors, such as:

➢Route of administration.

➢The formulation and chemical properties of a drug.

➢Drug-food interactions.

➢The administration (e.g., oral, intravenous, inhalation) of a drug influences bioavailability, the fraction of the active form of a drug that enters the bloodstream and successfully reaches its target site.

- When a drug is given intravenously, absorption is not required, and bioavailability is 100% because the active form of the medicine is delivered immediately to the systemic circulation. However, orally administered medications have incomplete absorption and result in less drug delivery to the site of action. For example, many orally administered drugs are metabolized within the gut wall or the liver before reaching the systemic circulation. This is referred to as first-pass metabolism, which reduces drug absorption.

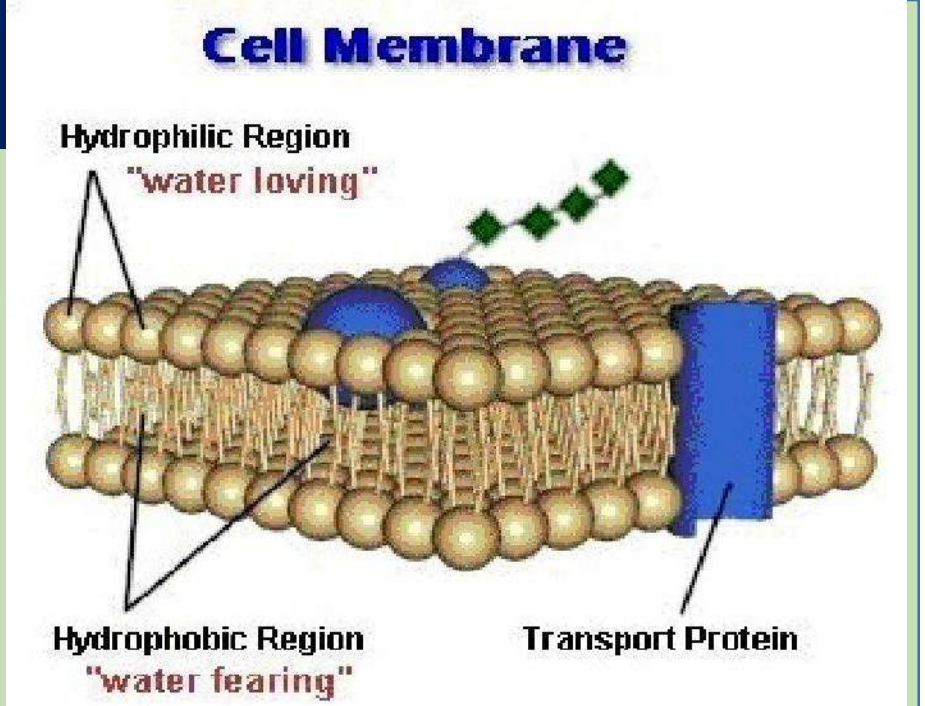
Drug Absorption

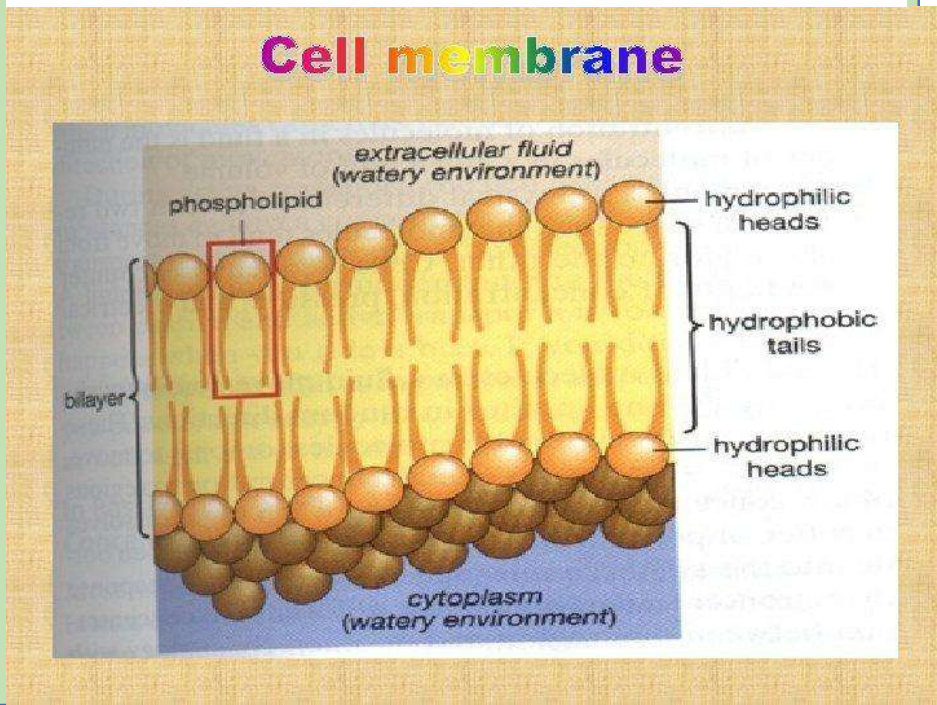
- Lipid solubility
- pKa = pH at which 50% of drug molecules are ionized (charged)
- Only uncharged molecules are lipid soluble.
- The pKa of a molecule influences its rate of absorption through tissues into the bloodstream.
- pH varies among tissue sites e. g. , stomach: 3 -4, intestines: 8 -9

DRUG ABSORPTION

- Is the passage of drug through cell membranes to reach its site of action.
- Mechanisms of drug absorption

1. Simple diffusion = passive diffusion.
2. Active transport.
3. Facilitated diffusion.
4. Pinocytosis (Endocytosis).

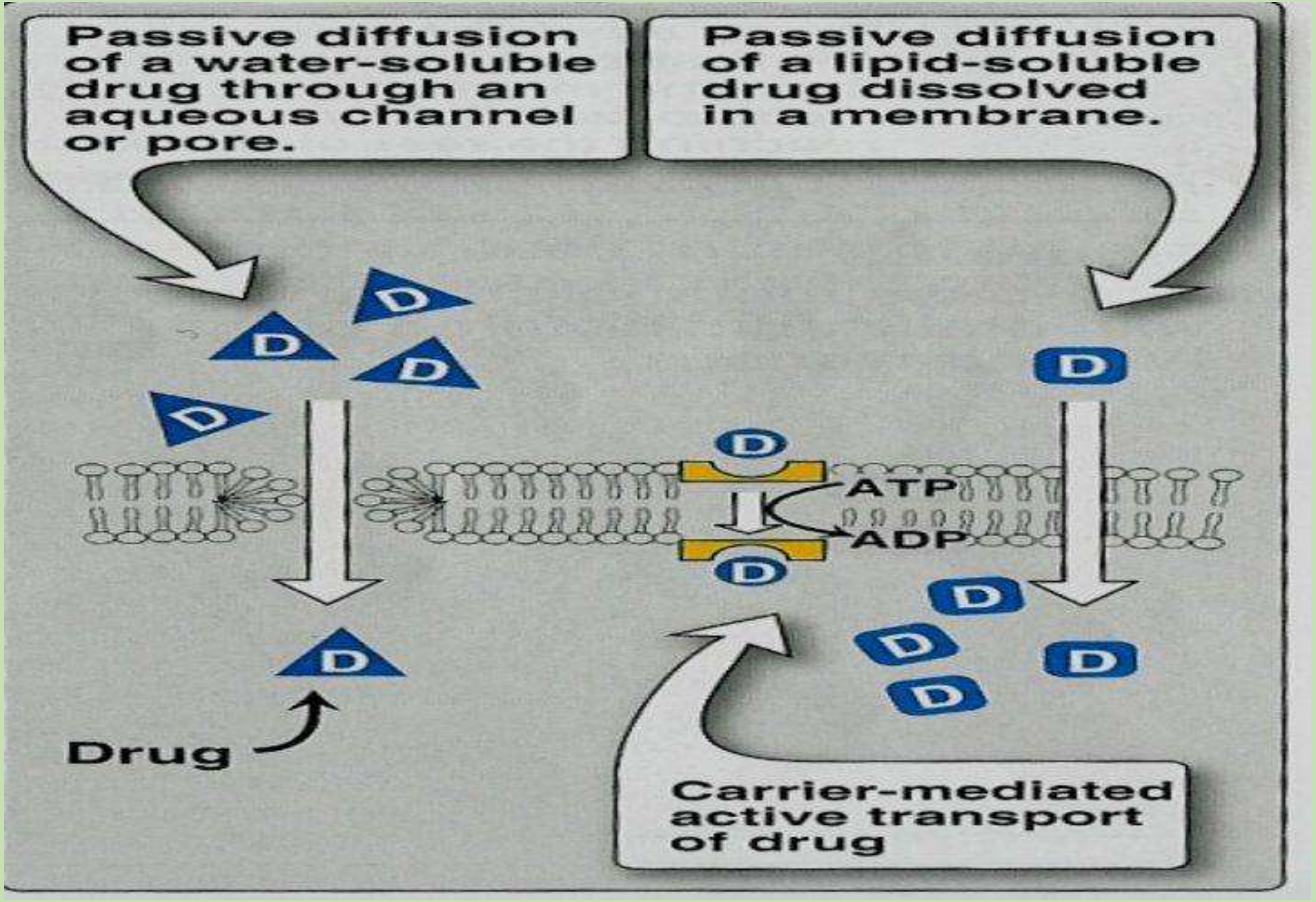




Simple or passive diffusion

- water soluble drug (ionized or polar) is readily absorbed via aqueous channels or pores in cell membrane.
- Lipid soluble drug (nonionized or non polar) is readily absorbed via cell membrane itself.

- Simple diffusion Characters
- Ø common.
- Ø Occurs along concentration gradient
- Ø Non selective
- Ø Not saturable
- Ø Requires no energy
- Ø No carrier is needed
- Ø Depends on lipid solubility
- Ø Depends on pka of drug - pH of medium


Passive diffusion of a water-soluble drug through an aqueous channel or pore.
Passive diffusion of a lipid-soluble drug dissolved in a membrane.
D
ATP
ADP
Drug
Carrier-mediated active transport of drug

- **PKa of the drug** (Dissociation or ionization constant):
- pH at which half of the substance is ionized & half is unionized.

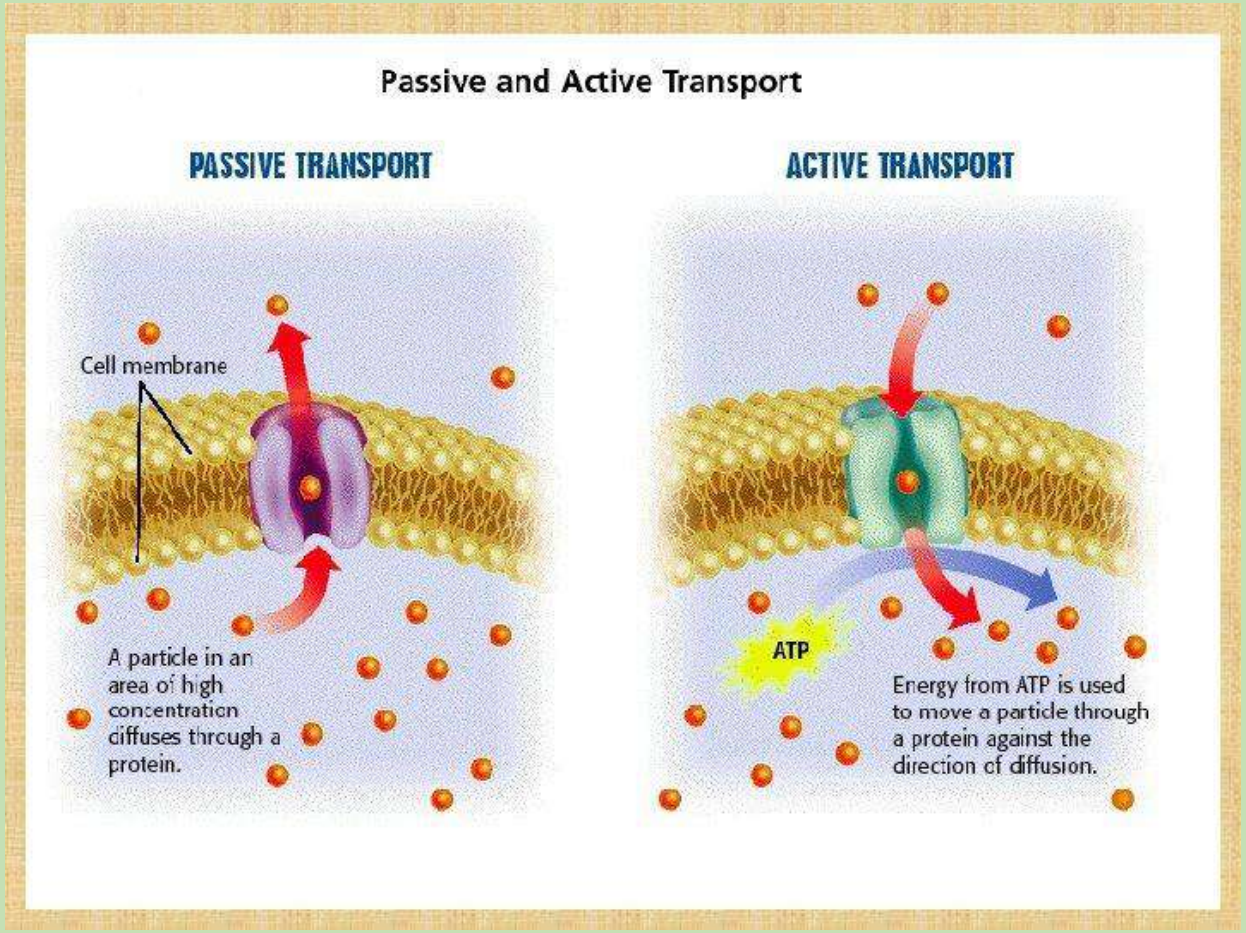
- **pH of the medium**

Affects ionization of drugs.

- – Weak acids best absorbed in stomach.
- – Weak bases best absorbed in intestine.

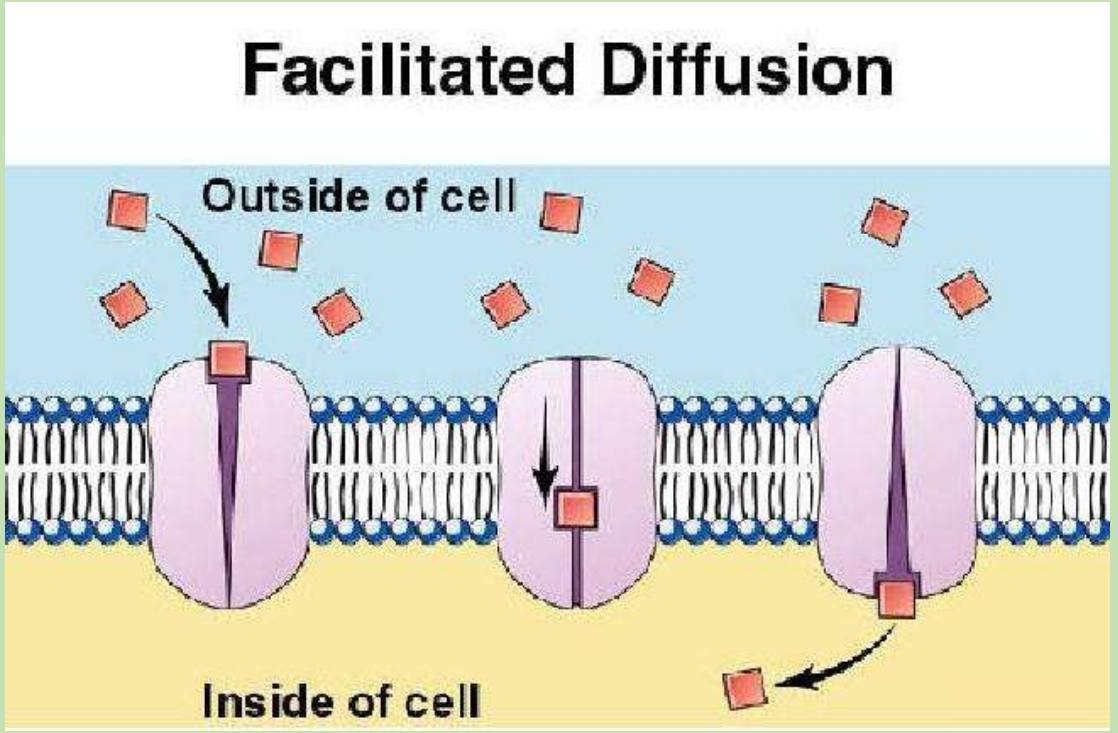
Active Transport

- Ø.Occurs against concentration gradient.
- Ø.Requires carrier and energy.
- Ø.Specific
- Ø.Saturable.
- Ø.Iron absorption.
- Ø.Uptake of levodopa by brain.



Carrier-mediated Facilitated Diffusion

- Carrier-mediated Facilitated Diffusion
- Occurs along concentration gradient.
- Requires carriers Selective.
- Saturable.
- No energy is required.



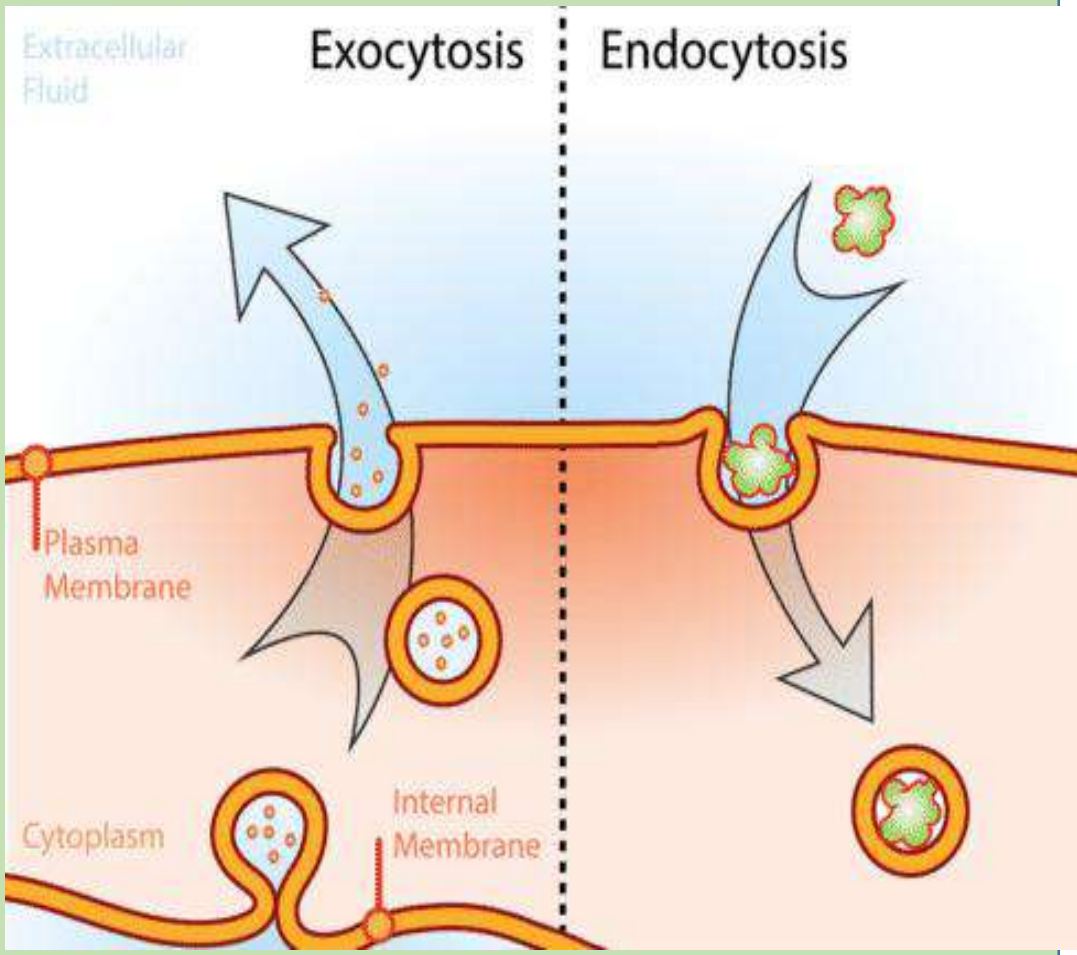
Passive transport	Active transport
Along concentration gradient (From high to low)	against concentration gradient (From low to high)
No carriers	Needs carriers
Not selective Not saturable	Selective, saturable
No energy	energy is required

Active transport	Carrier-mediated facilitated diffusion
Against concentration gradient (From low to high)	along concentration gradient (From high to low)
Needs carriers	Needs carriers
Selective, saturable	Selective, saturable
Energy is required	No energy is required

Phagocytosis process

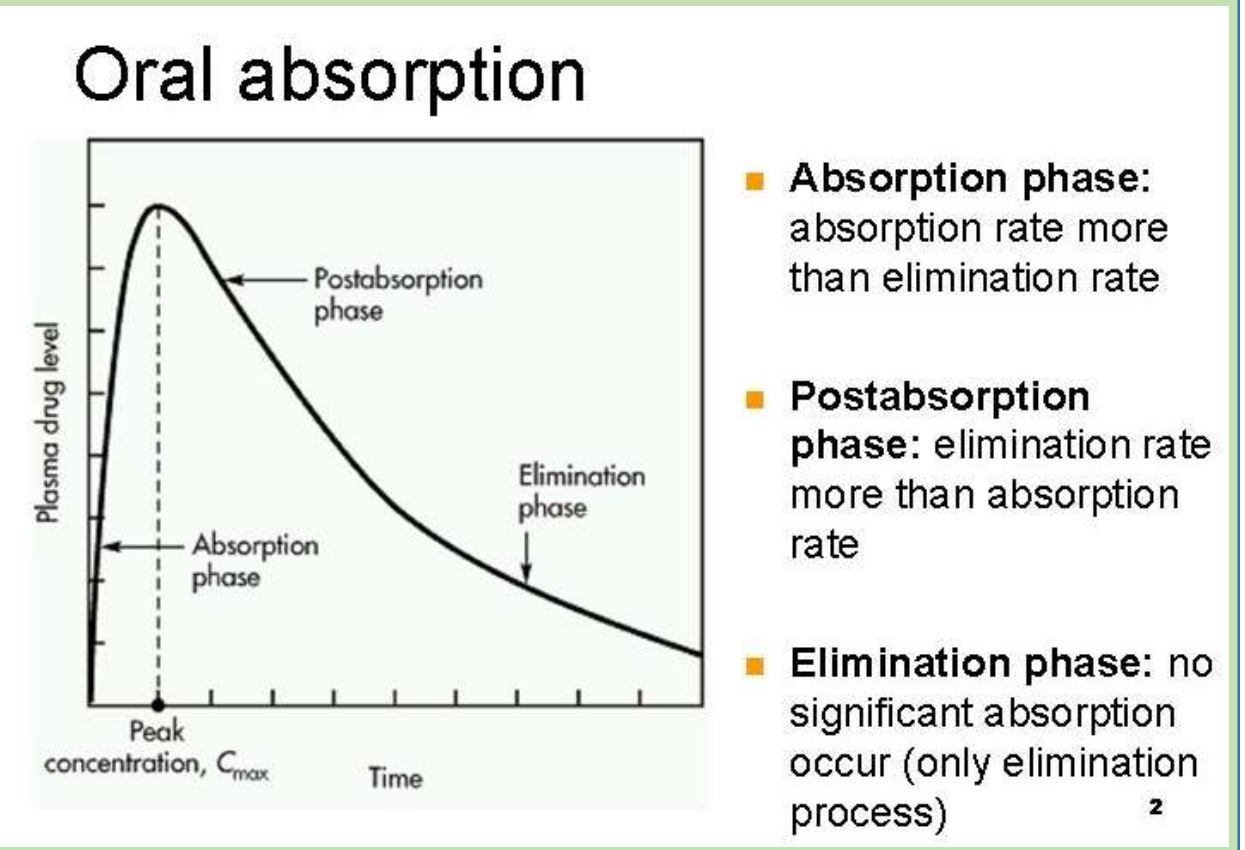
- Endocytosis: uptake of membrane-bound particles.

- Exocytosis: expulsion of membrane-bound particles. High molecular weight drugs or Highly lipid insoluble drugs



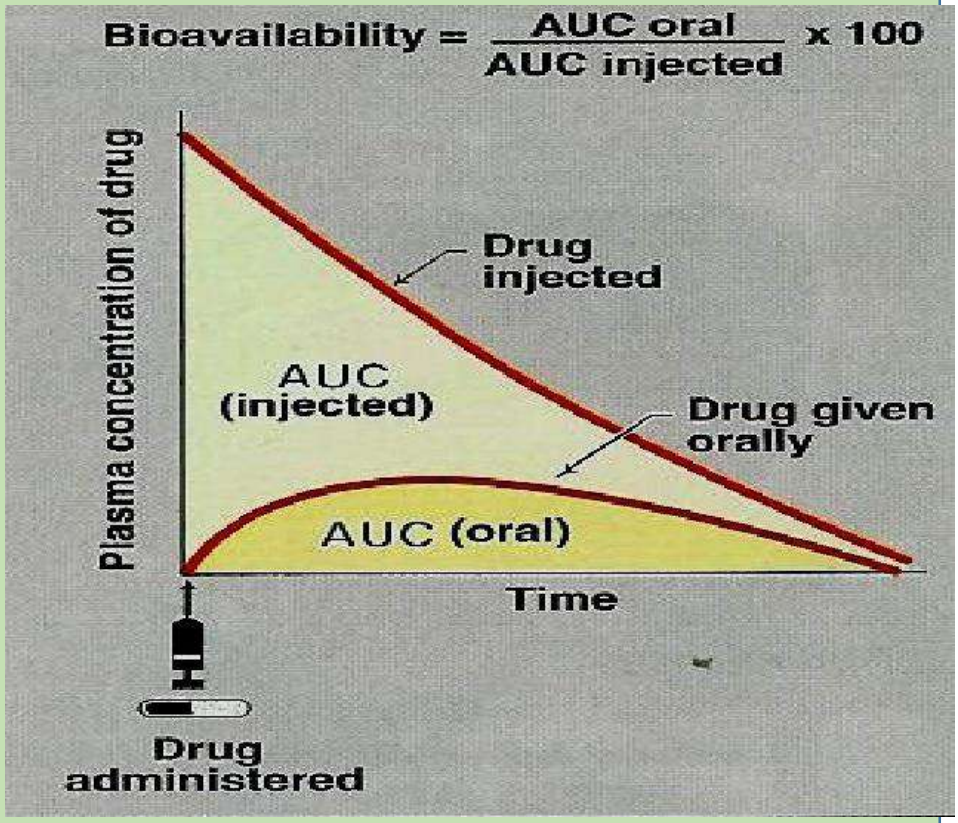
Oral absorption

- Absorption phase: absorption rate more than elimination rate
- Postabsorption phase: elimination rate more than absorption rate
- Elimination phase: no significant absorption occur (only elimination)



Bioavailability

- **Bioavailability** (F): Biologic availability or bioavailability is the fraction of an administered dose that reaches the systemic circulation **unchanged.**
- **Bioavailability** is defined as the fraction of the active form of a drug that reaches systemic circulation **unaltered**. This definition assumes 100% of the active drug that enters systemic circulation will successfully reach the target site.



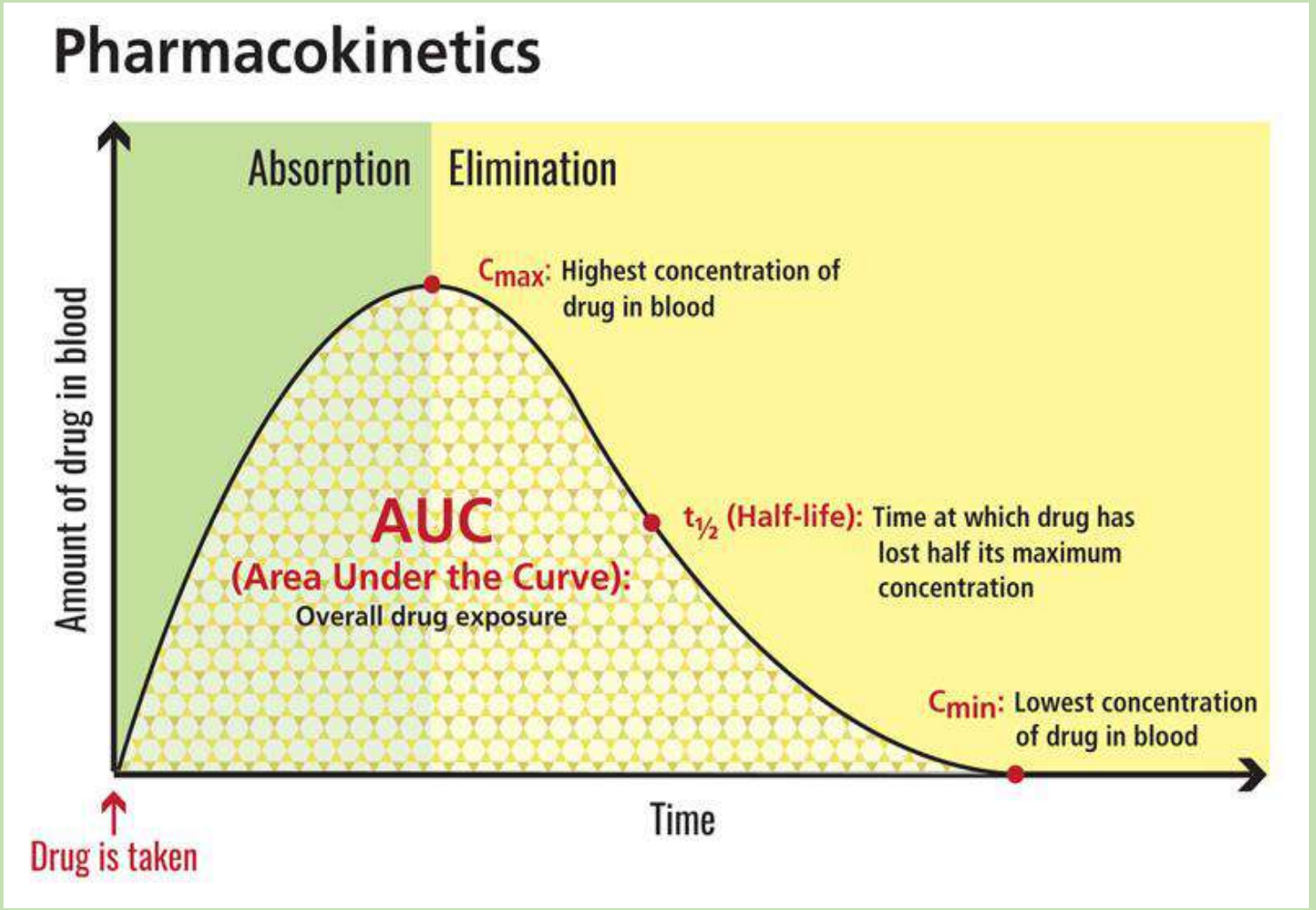
Bioavailability

- When a medication is administered intravenously, its bioavailability is 100%.
- However, when a medication is administered via routes other than intravenous, its bioavailability is generally lower than that of intravenous due to intestinal endothelium absorption and first-pass metabolism.
- Thereby, mathematically, bioavailability equals the ratio of comparing the area under the plasma drug concentration curve versus time (AUC) for the extravascular formulation to the AUC for the intravascular formulation.
- AUC is used because AUC is proportional to the dose that has entered the systemic circulation.
- The route of administration (ROA) and the dose of a drug have a significant impact on both the rate and extent of bioavailability

From Absorption to Elimination

- **Cmax Peak Concentration** A pharmacokinetic measure used to determine drug dosing. Cmax is the highest concentration of a drug in the blood, cerebrospinal fluid, or target organ after a dose is given.

- **Cmin Trough Concentration**, Trough Level A pharmacokinetic measure used to determine drug dosing. Cmin is the lowest concentration of a drug in the blood, cerebrospinal fluid, or target organ after a dose is given.

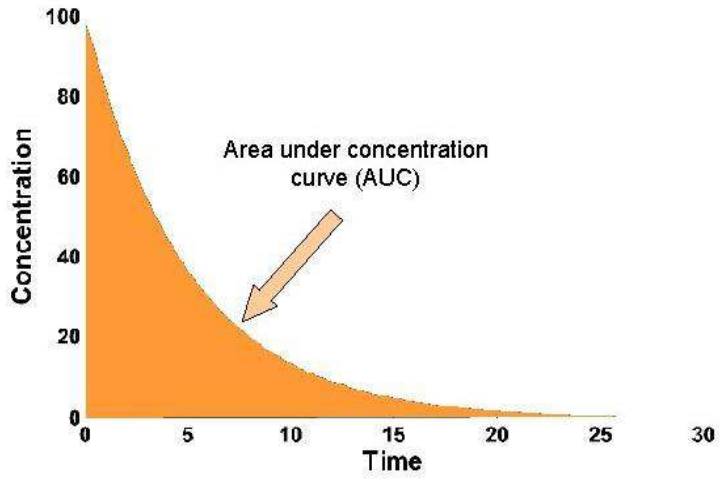


Absolute bioavailability

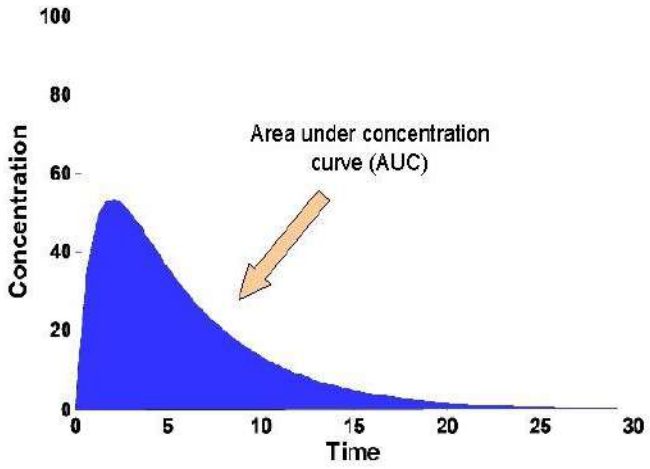
- Absolute bioavailability of a drug is the systemic availability of the drug after extravascular administration of the drug and is measured by comparing the area under the drug concentration -time curve after extravascular administration to that after IV administration.
- Extravascular administration of the drug comprises routes such as oral, rectal, subcutaneous, transdermal, nasal.

$$F(\%) = \frac{\text{(AUC after p.o. administration of dose X)}}{\text{(AUC after IV administration of dose X)}}$$

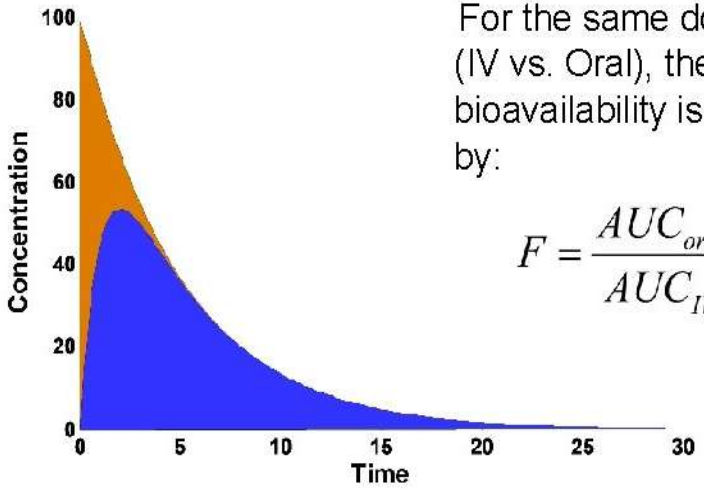
IV bolus



Oral dosage form (product A)



Absolute bioavailability



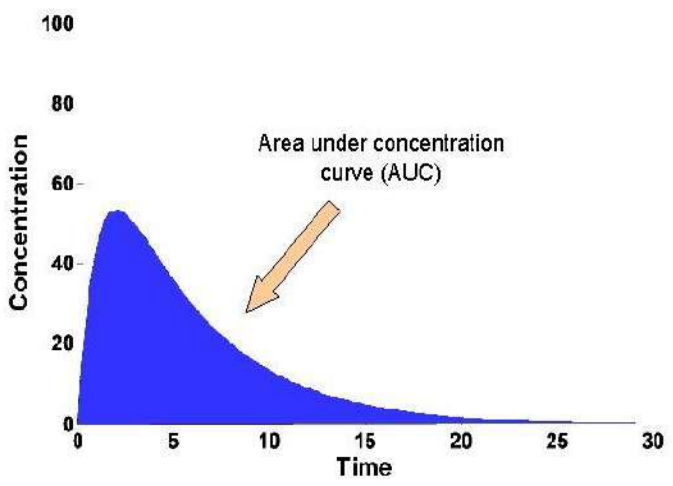
For the same dose (IV vs. Oral), the bioavailability is given by:

$$F = \frac{AUC_{oral}}{AUC_{IV}}$$

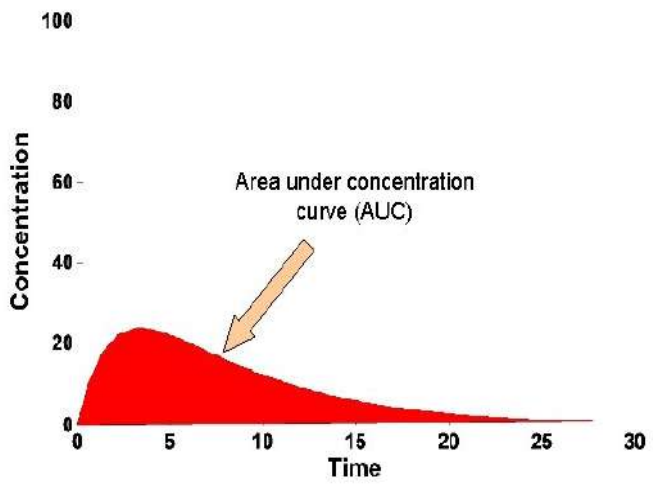
Relative bioavailability

- **Relative bioavailability**: The relative bioavailability is the systemic availability of a drug from one drug product (A) compared to another drug product (B).

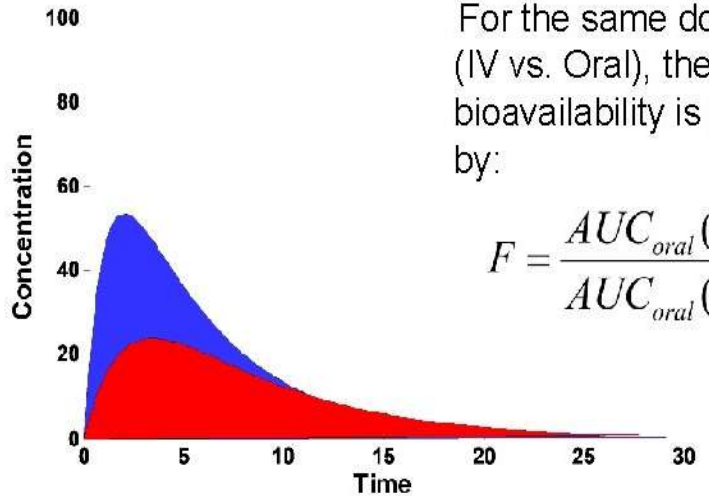
Oral dosage form (product A)



Oral dosage form (product B)



Relative bioavailability



For the same dose (IV vs. Oral), the bioavailability is given by:

$$F = \frac{AUC_{oral}(A)}{AUC_{oral}(B)}$$

Causes of low bioavailability

- Orally administered drugs must pass through the intestinal wall and then the portal circulation to the liver
- Both are common sites of first-pass metabolism (metabolism that occurs before a drug reaches systemic circulation).
- Thus, many drugs may be metabolized before adequate plasma concentrations are reached. Low bioavailability is most common with oral dosage forms of poorly water-soluble, slowly absorbed drugs.
- Insufficient time for absorption in the gastrointestinal (GI) tract is a common cause of low bioavailability.
- If the drug does not dissolve readily or cannot penetrate the epithelial membrane (eg, if it is highly ionized and polar), time at the absorption site may be insufficient. In such cases, bioavailability tends to be highly variable as well as low.
- Age, sex, physical activity, genetic phenotype, stress, disorders (eg, achlorhydria, malabsorption syndromes), or previous GI surgery (eg, bariatric surgery) can also affect drug bioavailability.
- Chemical reactions that reduce absorption can decrease bioavailability.
- They include formation of a complex (eg, between tetracycline and polyvalent metal ions), hydrolysis by gastric acid or digestive enzymes (eg, penicillin and chloramphenicol palmitate hydrolysis), conjugation in the intestinal wall (eg, sulfoconjugation of isoproterenol), adsorption to other drugs (eg, digoxin to cholestyramine), and metabolism by luminal microflora.

Distribution

- The process of drug distribution is important because it can affect how much drug ends up in the active sites, and thus drug efficacy and toxicity. A drug will move from the absorption site to tissues around the body, such as brain tissue, fat, and muscle.

❖Many factors could influence this, such as

- blood flow.
- Lipophilicity.
- molecular size.
- and how the drug interacts with the components of blood, like plasma proteins. For example, a drug like warfarin is highly protein-bound, which means only a small percentage of the drug is free in the bloodstream to exert its therapeutic effects. If a highly protein-bound drug is given in combination with warfarin, it could displace warfarin from the protein-binding site and increase the amount that enters the bloodstream.
- Additionally, there are anatomical barriers found in certain organs like the blood-brain barrier, preventing certain drugs from going into brain tissue. Drugs with certain characteristics, like high lipophilicity, small size, and molecular weight will be better able to cross the blood brain barrier.

VOLUME OF DISTRIBUTION

- Apparent volume of distribution (V d) Presuming that the body behaves as a single homogeneous compartment with volume V into which drug gets immediately and uniformly distributed.
- The volume of distribution (Vd) is a pharmacokinetic parameter representing an individual drug's propensity to either remain in the plasma or redistribute to other tissue compartments. By definition, Vd is a *proportionality constant* that relates the total amount of drug in the body to the plasma concentration of the drug at a given time. The following equation can represent Vd:
- Volume of Distribution (L) = Amount of drug in the body (mg) / Plasma concentration of drug (mg/L)
- Based on the above equation:
- A drug with a **high Vd** has a propensity to leave the plasma and enter the extravascular compartments of the body, meaning that a **higher dose** of a drug is required to achieve a given plasma concentration. (High Vd > More distribution to other tissue)
- Conversely, a drug with a **low Vd** has a propensity to remain in the plasma meaning a **lower dose** of a drug is required to achieve a given plasma concentration. (Low Vd > Less distribution to other tissue)

VOLUME OF DISTRIBUTION

- Pharmacokinetics focuses on drug movement throughout the human body via the processes of *absorption*, *distribution*, and *elimination*.
- Upon administration, a drug moves from the site of administration and gets absorbed into the systemic circulation where it will then gets distributed throughout the body.
- The process of distribution refers to the movement of a drug between the intravascular (blood/plasma) and extravascular (intracellular & extracellular) compartments of the body.
- Within each compartment of the body, a drug exists in equilibrium between a protein-bound or free form.
- Over time, drugs within the circulation will then be metabolized and excreted from the body by the liver & kidneys

Single vs. Multi-compartment models of Distribution

- Immediately after administration of an IV bolus, a drug enters the **"central" compartment,** which is composed of the plasma, highly perfused organs (liver, kidneys, etc.) and other tissues where drug distribution is instantaneous. Eventually, some drugs may begin to move from the central compartment to the **"peripheral" compartment**, which is composed of tissues to which drug distributes slower

1. Single compartment model: Some drugs display pharmacokinetics in which they distribute "instantaneously." These drugs appear to remain in the central compartment and not distribute to peripheral compartments. Therefore, any measured decline in drug plasma concentration is a result of drug elimination from the body only. These drugs are said to display **single-compartment models of distribution** as they do not move to peripheral compartments. The Vd of these drugs can be represented by a single value, which is the Vd of the central compartment **(Vc).**

- **Vc** (L) = **Dose administered** (mg) / **Co** (mg/L)

Single vs. Multi-compartment models of Distribution

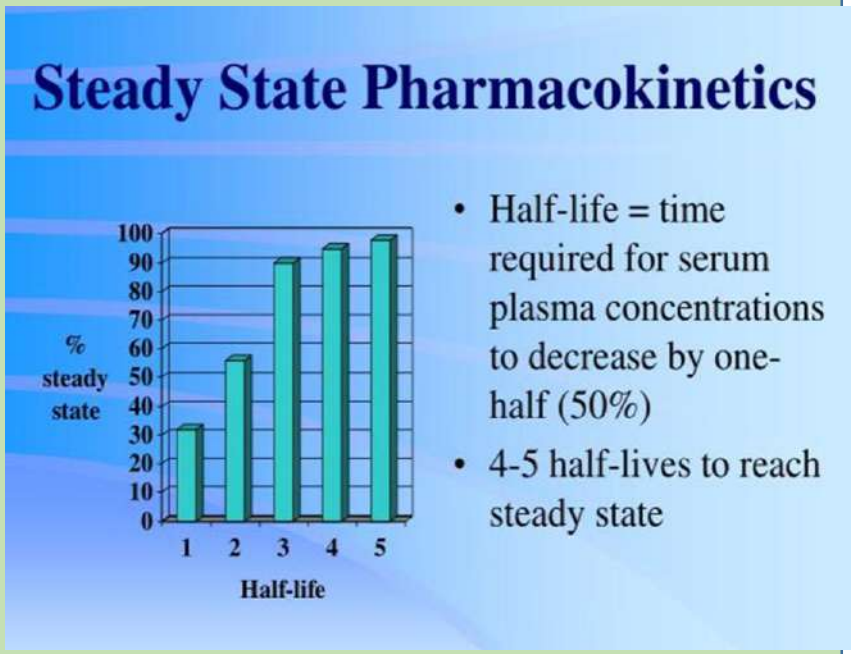
2. Multi-compartment model: Most drugs will exhibit slower distribution kinetics, which involves an early distribution phase followed by a later elimination phase. Drugs that display **multi-compartment models of distribution** will move from the central compartment into peripheral compartments before elimination. Phases associated with multi-compartment models of distribution include.

- ***Distribution phase:*** following administration plasma drug concentration will initially decline while the total amount of drug in the body remains the same. This phenomenon will cause a single drug to have *multiple* Vd values, which are each time-dependent.
- ***Terminal elimination phase***: Following the distribution phase, the drug will be eliminated from the central compartment (by the kidneys/liver) causing changes in both amounts of the drug in the body and plasma drug concentration.
- ***Steady-state:*** Between the distribution & elimination phase, there is a transition point known as "steady state." Steady-state represents a period of "dynamic equilibrium" of a drug throughout the body in which the drug has completed distribution between the central & peripheral compartments. At steady state, the net flux of drug between the central & peripheral compartments is 0. Another value for Vd can be calculated during steady-state (**Vss**). This value is generally the most clinically relevant as it is used to determine the loading dose of a drug.

- **Vd** (L) = **A(t)** (mg) / **C(t)** (mg/L)
- A(t) represents the amount of drug in the body at time = t
- C(t) represents plasma concentration of the drug at time = t

Steady State:

- The amount of drug administered is equal to the amount of drug eliminated within one dosing interval resulting in a plateau or constant serum drug level.
- As repeated doses of a drug are administered its plasma concentration builds up and reaches what is known as a steady state.
- This is when the amount of drug in the plasma has built up to a concentration level that is therapeutically effective and as long as regular doses are administered to balance the amount of drug being cleared the drug will continue to be active.
- The time taken to reach the steady state is about five times the half life of a drug.
- Drugs like digoxin and warfarin with a long half life will take longer to reach a steady state than drugs with a shorter half life.
- Drugs with short half-life reach steady state rapidly; drugs with long half-life take days to weeks to reach steady state.



Features of Drugs affecting the Volume of Distribution

1. Acid-Base Characteristics As previously discussed, drugs may have a propensity to bind proteins throughout the body where they reach a point of equilibrium between a bound & unbound phase. Depending on the charge of a drug at physiologic pH, have a drug may tend to bind macromolecules inside or outside the plasma.

- **Basic** (alkaline) molecules have strong interactions with negatively charged phospholipid head groups located on phospholipid membranes. The extent of this binding is also dependent on the overall lipophilicity of the drug. In general, basic molecules will leave the systemic circulation leading to ***higher*** **Vd** as compared to acidic molecules.
- **Acidic** molecules have a higher affinity for albumin molecules at lower lipophilicity than neutral or basic molecules. Therefore, acidic drugs are more likely to bind albumin and remain in the plasma leading to ***lower*** **Vd** as compared to more basic molecules.

Features of Drugs affecting the Volume of Distribution

2. Lipophilicity In addition to ionic/charge-related interactions between a drug and macromolecules, hydrophobic interactions also play a similar role. Drugs with higher lipophilicity have a higher lipid membrane permeability and therefore, a higher chance of leaving the plasma and interacting with other hydrophilic residues in the peripheral tissue (e.g., adipose tissue). However, plasma proteins such as albumin have a high affinity for lipophilic drugs in which case, the determinant of the extent of plasma protein binding of two equally lipophilic drugs is the acid/base characteristics as described above. But in general, the following principles apply:

- **Lipophilic** molecules are more likely to pass through lipid bilayers and therefore more likely to leave the bloodstream and distribute to areas with high lipid density (adipose) and therefore have a ***higher*** **Vd.**
- **Hydrophilic** molecules are less likely to pass through lipid bilayers and therefore more likely to remain in the bloodstream and therefore have a ***lower*** **Vd.**

half-life

- What is a drug's half-life?
- The half-life of a drug is the time it takes for the amount of a drug's active substance in your body to reduce by half. This depends on how the body processes and gets rid of the drug. It can vary from a few hours to a few days, or sometimes weeks.
- In general, a drug is no longer considered **pharmacologically active** after one half life. This means that a drug looses much of its activity or effectiveness after one half life.

- Elimination Half-life (t½) l Half-life is associated with both accumulation and elimination of drugs
- It is the time taken for the concentration of the drug in the plasma to increase (accumulation) or decrease (elimination) by half (50%)
- It is dependent on volume of distribution (Vd) and clearance (Cl)
- Half-life (t½) contd. Half life determines the time to reach constant effective concentrations in the plasma and the appropriate dosing interval to maintain that concentration
- For drugs with a short half-life e. g. ferrous sulfate dosing will need to be three or four times a day (unless in a sustained release formulation); for drugs with a long half-life e. g. thyroxine, dosing is once daily


The Half-life of
Drugs

Metabolism

- **Drug Biotransformation** Metabolism or biotransformation - complex of processes which provide decreasing of toxicity and accelerate excreting of the molecule of a drug or other foreign substance after its incoming into the organism (Chemical alteration of the drug in the body).
- Metabolism (drug metabolism) is the anabolic and catabolic breakdown of drugs by living organisms.
- Drugs and toxins are seen as foreign to patients bodies
- Drugs can undergo metabolism in the lungs, blood, and liver

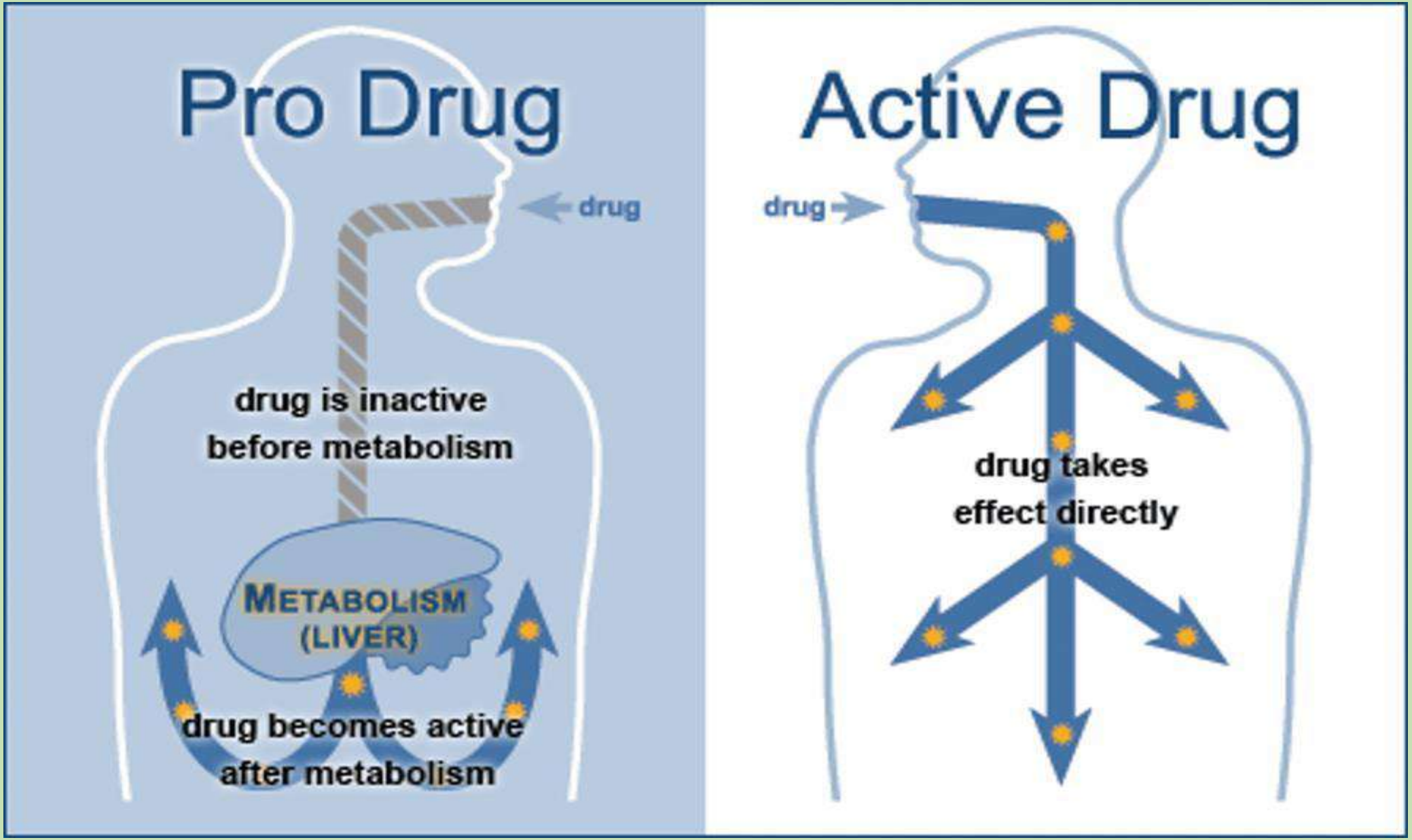
Metabolism of Drugs

- **Aim:** to convert non-polar lipid soluble compounds to polar lipid insoluble compounds to avoid reabsorption in renal tubules.

- Most hydrophilic drugs are less biotransformed and excreted unchanged – streptomycin, neostigmine and pancuronium etc.

- Biotransformation is required for protection of body from toxic metabolites
- Body works to convert drugs to less active forms and increase water solubility to enhance elimination.

- Liver may be used to convert pro-drugs (inactive) to an active state.
- Types of reactions:
- **Phase I**
- **Phase II**
- **The key difference between phase I and phase II metabolism is that the phase I reactions convert a parent drug to polar active metabolites through unmasking or insertion of polar functional groups whilst phase II reactions convert a parent drug to polar inactive metabolites through conjugation of subgroups to -SH, -OH and -NH_2 functional groups on the drug.**


Pro Drug
drug
drug is inactive
before metabolism
METABOLISM
(LIVER)
drug becomes active
after metabolism
Active Drug
drug
drug takes
effect directly

Biotransformation of drugs into active (or more active) metabolites

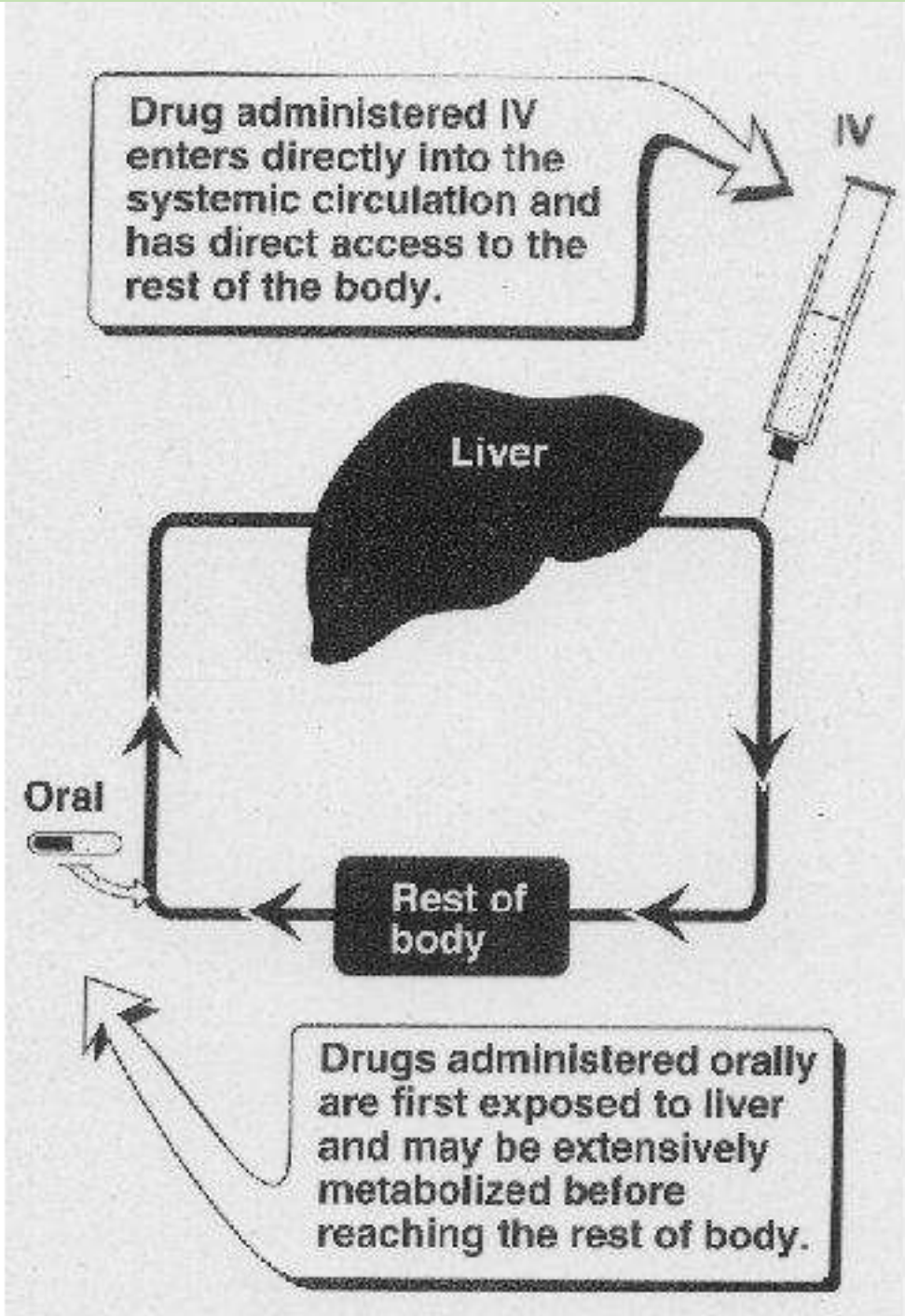
Initial drug	***Active metabolite***
Allopurinol	Aloxantin
Amitriptilin	Nortriptilin
Acetylsalicylic acid	Salicylic acid
Butadion	Oxyfenbutazon
Diazepam	Dismethyldiazepam
Digitoxin	Digoxin
Codein	Morphine
Cortizol	Hydrocortizon
Methyldopa	Methylnoradrenalin
Prednison	Prednisolon
Novocainamid	N-acetylnovocainamid
Propranolol	N-oxypropranolol

ORGANS OF DRUGS METABOLISM

- liver
- kidneys
- muscle tissue
- intestinal wall
- lungs
- skin
- blood

Results of Biotransformation

- Active drug and its metabolite to inactive metabolites - most drugs (ibuprofen, paracetamol, chlormphenicol etc.)
- Active drug to active product (phenacetin - acetminophen or paracetamol, morphine to morphine-6-glucoronide, digitoxin to digoxin etc.)
- Inactive drug to active /enhanced activity (prodrug) - levodopa - carbidopa, prednisone - prednisolone and enalapril - enalaprilat)
- No toxic or less toxic drug to toxic metabolites (Isonizide to Acetyl isoniazide)



First-Pass Metabolism can occur with orally administered drugs

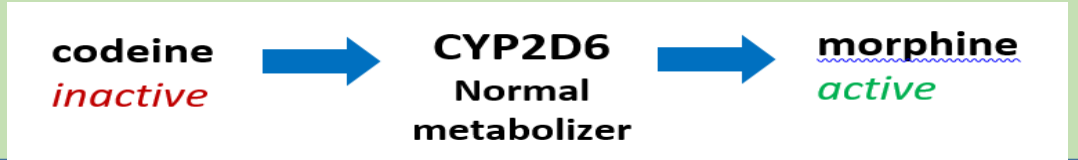
Metabolism

Cytochrome P450 (CYP450) enzymes are responsible for the biotransformation or metabolism of about 70-80% of all drugs in clinical use.

- What are some factors that affect drug metabolism?

- Genetics can impact whether someone metabolizes drugs more quickly or slowly.
- Age can impact liver function; the elderly have reduced liver function and may metabolize drugs more slowly, increasing risk of intolerability, and newborns or infants have immature liver function and may require special dosing considerations.
- Drug interactions can lead to decreased drug metabolism by enzyme inhibition or increased drug metabolism by enzyme induction.

- Generally, when a drug is metabolized through CYP450 enzymes, it results in inactive metabolites, which have none of the original drug's pharmacologic activity. However, certain medications, like codeine, are inactive and become converted in the body into a pharmacologically active drug. These are commonly referred to as prodrugs.
- As you can imagine, having genetic variations in CYP2D6, the metabolic pathway for codeine, can have significant clinical consequences. Usually, CYP2D6 poor metabolizers (PMs) have higher serum levels of active drugs. In codeine, PMs have higher serum levels of the inactive drug, which could result in inefficacy. Conversely, ultra-rapid metabolizers (UMs) will transform codeine to morphine extremely quickly, resulting in toxic morphine levels.
- The FDA added a black box warning to the codeine drug label, stating that respiratory depression and death have occurred in children who received codeine following a tonsillectomy and/or adenoidectomy and who have evidence of being a CYP2D6 UM.



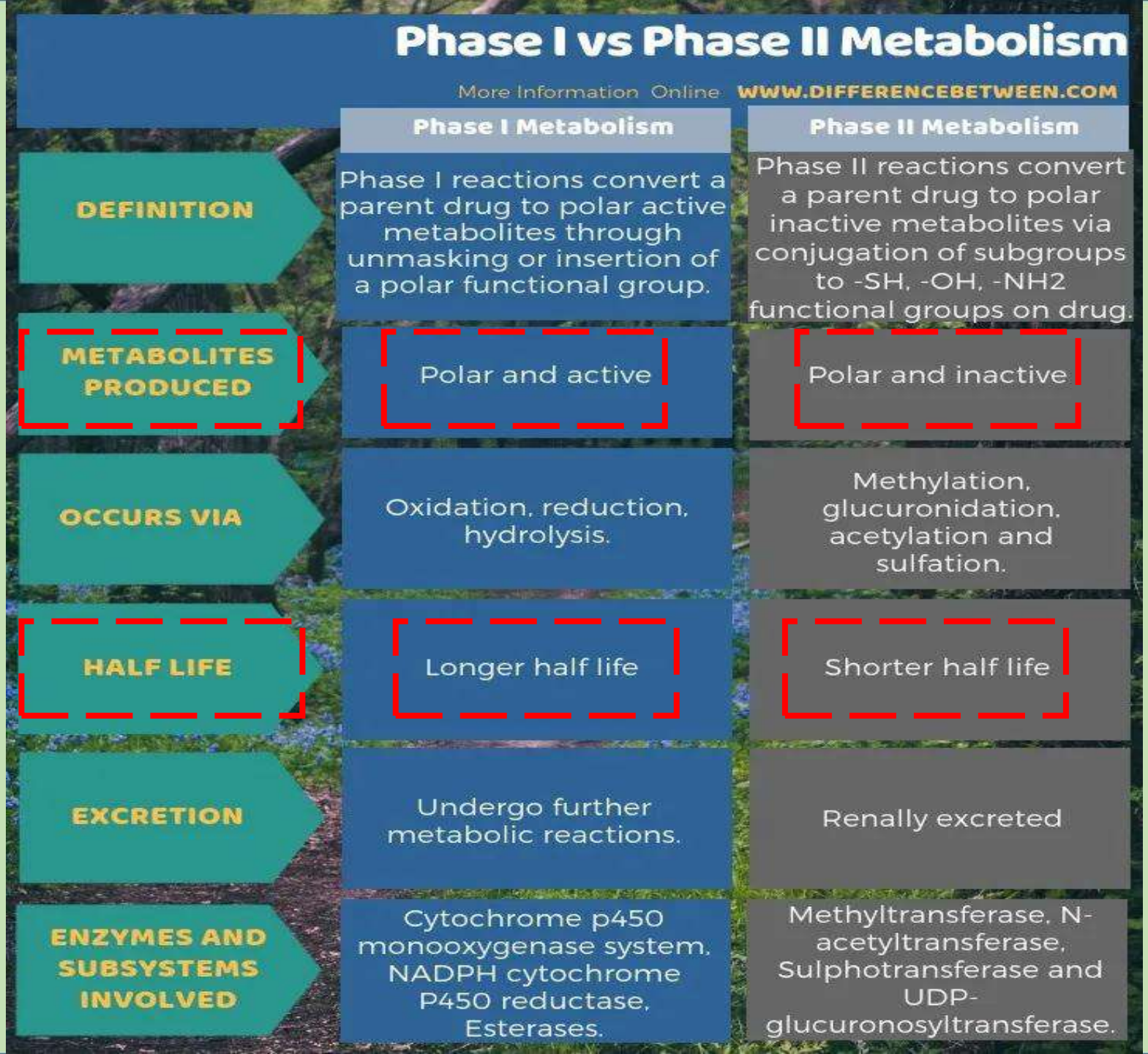
Main ways of biotransformation of drugs

1. Phase I

- Oxydation:diazepam, pentazocin, sydnocarb, phenotiazin, phenobarbital, aspirin, butadion, lidokain, morphin, codein, ethanol, rifampicin
- Reduction:hestagens, metronidazol, nitrazepam, levomycetin, chlozepid
- Hydrolysis: levomycetin, novocain, cocain, glycosides, ditilin, novocainamid, xycain, fentanyl

2. phase II

- Conjugation with sulfate:morphin, paracetamol, isadrin
- Conjugation with glucuronic acid: teturam, sulfonamides, levomycetin, morphin
- Conjugation with remains of aminoacids:nicotinic acid, paracetamol
- Acetylation:sulfonamides, isoniasid, novocainamid
- Methylation:morphin, unitiol, ethionamid, noradrenalin


Phase I vs Phase II Metabolism
More Information Online WWW.DIFFERENCEBETWEEN.COM
Phase I Metabolism
Phase II Metabolism
DEFINITION
Phase I reactions convert a parent drug to polar active metabolites through unmasking or insertion of a polar functional group.
Phase II reactions convert a parent drug to polar inactive metabolites via conjugation of subgroups to -SH, -OH, -NH2 functional groups on drug.
METABOLITES PRODUCED
Polar and active
Polar and inactive
OCCURS VIA
Oxidation, reduction, hydrolysis.
Methylation, glucuronidation, acetylation and sulfation.
HALF LIFE
Longer half life
Shorter half life
EXCRETION
Undergo further metabolic reactions.
Renally excreted
ENZYMES AND SUBSYSTEMS INVOLVED
Cytochrome p450 monooxygenase system, NADPH cytochrome P450 reductase, Esterases.
Methyltransferase, N-acetyltransferase, Sulphotransferase and UDP-glucuronosyltransferase.

Excretion

- Elimination involves both the metabolism and the excretion of the drug through the kidneys, and to a much smaller degree, into the bile.
- Excretion into the urine through the kidneys is one of the most important mechanisms of drug removal.

❖**Many factors affect excretion, such as:**

✓Direct renal dysfunction, which could prolong the half-life of certain drugs and necessitate dose adjustments.

✓Age, which can contribute to different rates of excretion and impact dosing of medications.

✓Pathologies that impact renal blood flow, such as congestive heart failure and liver disease can make drug excretion less efficient

- Whether it's a patient who just had gastric bypass surgery, a CYP2D6 poor metabolizer, or a patient with renal dysfunction, an individual's characteristics affect these four processes, which can ultimately influence medication selection.