

GENERAL PHARMACOLOGY

Introduction

- Pharmacology: study of substances that interact with living systems through chemical process, especially by binding to regulatory molecules & activating or inhibiting body process
- Basics of pharmacology:
 - Pharmacokinetics
 - Pharmacodynamics
- **Pharmacokinetics**: deals with absorption, distribution, biotransformation & excretion of drugs

Introduction cont'd

- **Pharmacodynamics:** study of biochemical & physiological effects of drugs & their mechanisms of action.
- **Pharmacotherapeutics:** Use of drugs in prevention & Rx of disease.
- **Toxicology:** Deals with undesirable effects of chemicals/drugs on living systems.
- **Drug:** any substance that brings about a change in biologic function.
- **Chemotherapy:** effect of drugs on microorganisms, parasites and neoplastic cells living & multiplying in living organism

Drugs:

- Drugs mostly interact with a specific molecule in a biologic system that plays a regulatory role [receptor].
- To interact chemically with its receptor, a drug molecule must have the appropriate :
 - **Size, electrical charge, shape & atomic composition**

Source of drugs

- Mineral: liquid paraffin, mg trisilicate
- Animals: Insulin, heparin, thyroid,
- Plants: Morphine, quinine, digoxin
- Synthetic: Aspirin, atropine, castor oil,
- Microorganism: Penicillin, streptomycin
- Genetic engineering: Human insulin

Drug nomenclature

- Existence of many names for each drug causes lamentable & confusing situation
 - Chemical names
 - Code names
 - Nonproprietary/generic name
 - Brand name/Proprietary/trademark/trade name

Generic, or non-proprietary, name;

- Used by all who wish to refer to this substance.
- Serves as an important and unique designation for the active ingredient.
- It appears with the company's trade name on drug labels, advertisements.
- Authors use generic name in clinical trial reports, hence used in publishing scientific data about investigational and established therapies.
- Much shorter, easier to remember and pronounceable

Brand Names and Generic Names for Active Ingredients

Brand: Cialis

Generic: tadalafil

Brand: Colemin, Lipex, Zocor, Vytorin

Generic: simvastatin

Brand names;

- Vary from company to company
- In rare instances, a brand name may be used for two different active ingredients in different countries.
- More commonly, a company uses different brand names in different countries for the same drug, or two countries may market the same substance under different brand names.
- Finally, as part of "brand extension" business strategies, companies use the same brand name to refer to two different active ingredients.

pharmacokinetics

- Pharmacokinetics:
 - Pharmaco: drug
 - Kinetics: motion
- Action of body on drug/ how body handles drugs
- Pharmacokinetics: ADME

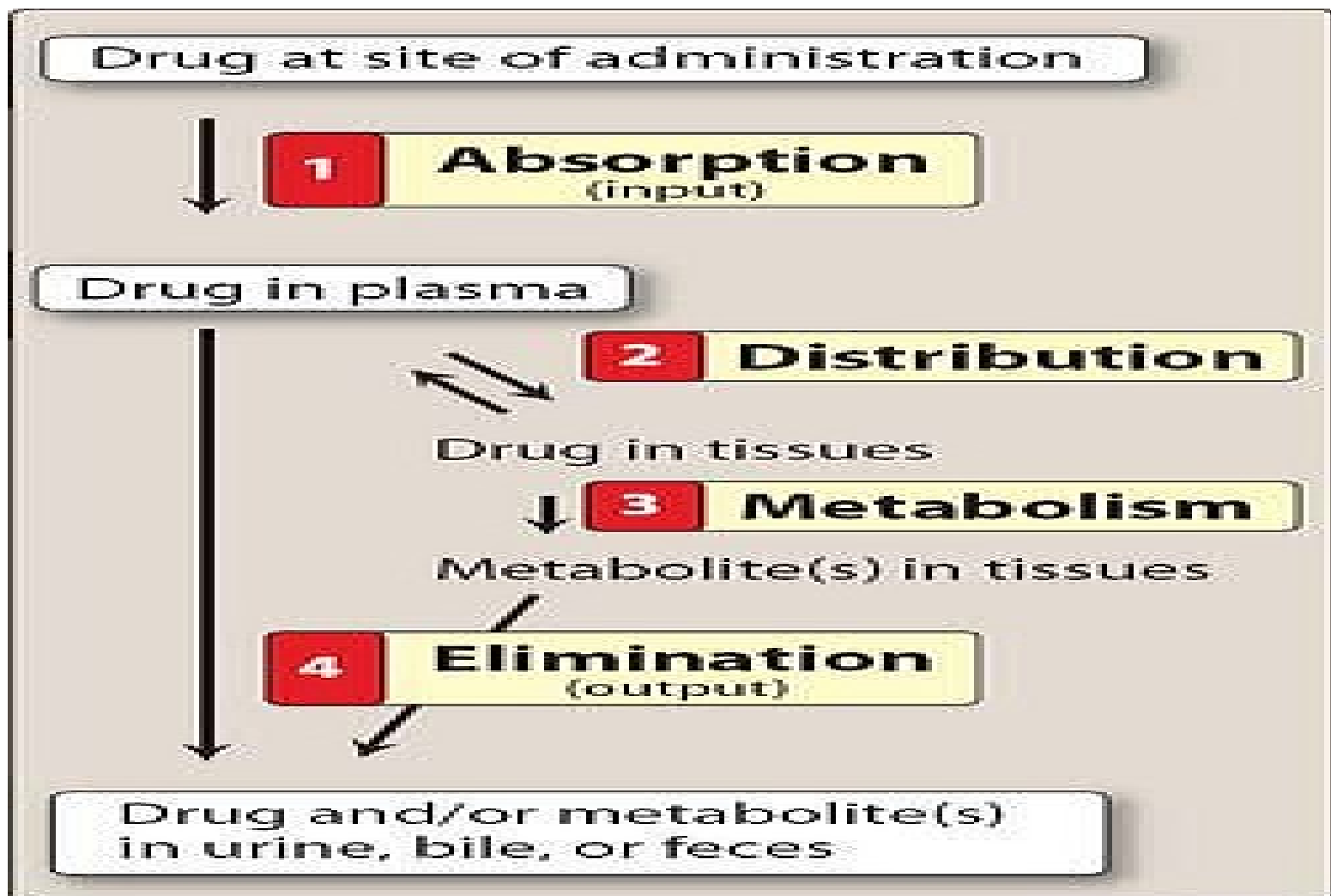


Figure 1.1 Schematic representation of drug absorption, distribution, metabolism, and elimination.

Absorption

- It is a process by which the drug leaves the site of administration to circulatory system

How???

1. Filtration [aqueous diffusion]-

- Passage of drugs through aqueous pores.
- Size should be less than size of pore
- Has to be water soluble
- Na⁺, glucose, caffeine

2. Lipid diffusion

- Drugs supposed to pass through the membrane
- Drugs must be lipid soluble
- High partition coefficient $\Rightarrow$ high absorption

Absorption cont'd

3. Carrier mediated absorption

a. Facilitated diffusion

- passive diffusion but facilitated

e.g. levodopa & aminoacid into brain

b. Active transport

- use ATP & carrier proteins
- against the concentration gradient

e.g. levodopa and methyldopa from the gut.

Absorption cont'd

4. Phagocytosis & pinocytosis

- Process by which large molecules are engulfed by the cell membrane forming a vesicle & releases them intracellularly.
 - E.g. protein, toxin

Routes of administration

- Enteral
 - Oral, rectal, sublingual, buccal
- Parenteral
 - Intramuscular, subcutaneous, intravenous, intra arterial
- Inhalation
- Topical

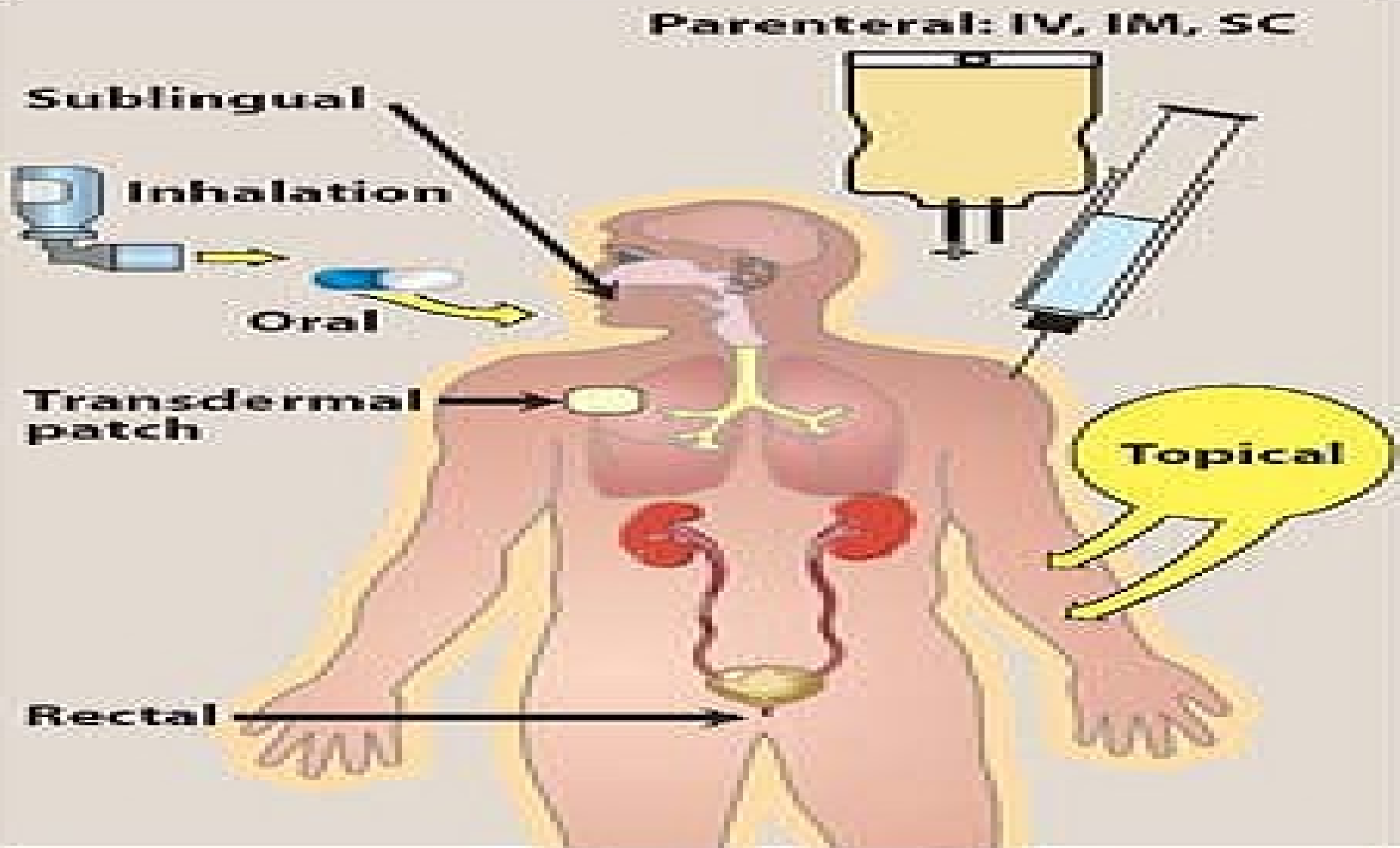
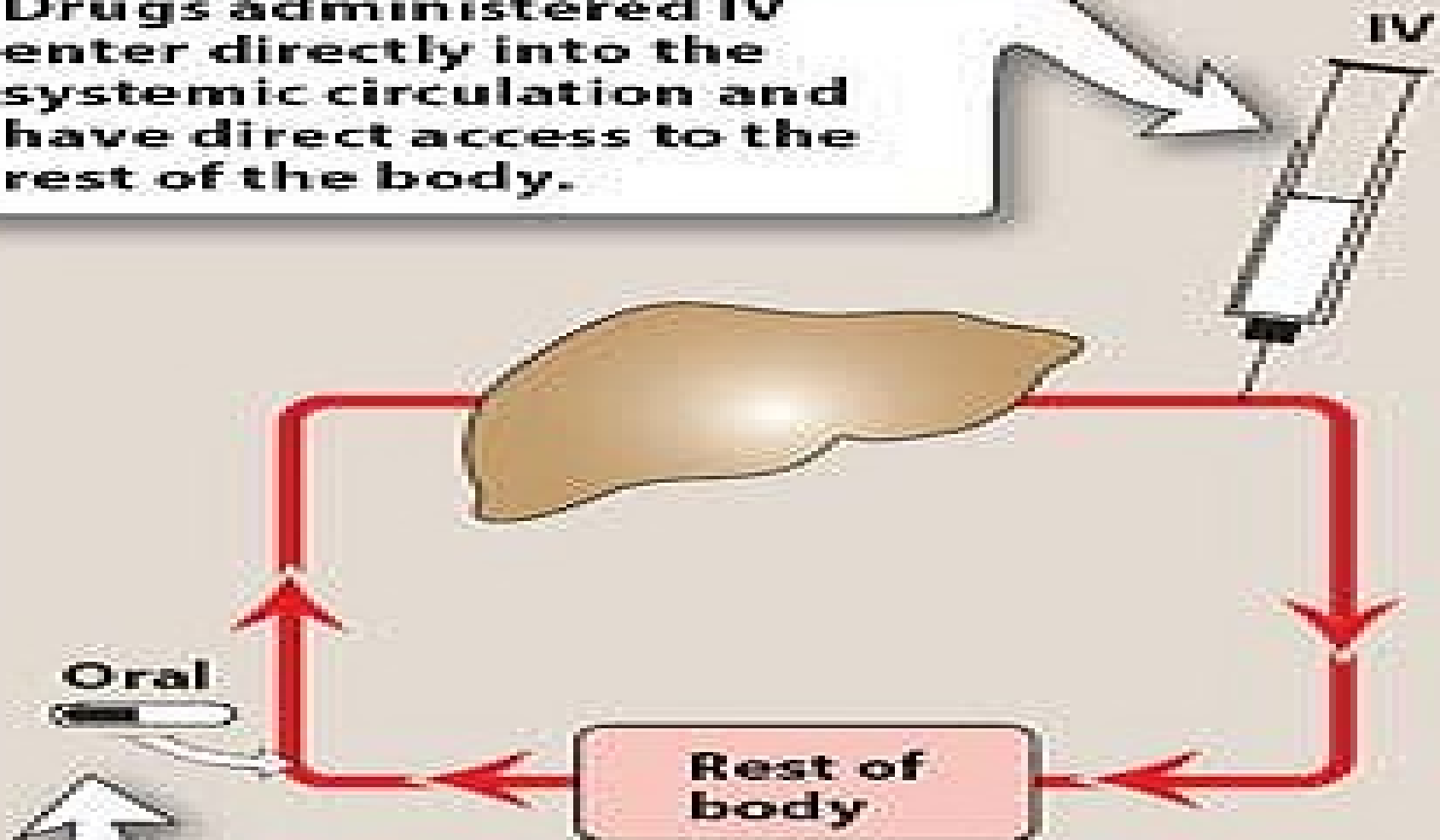


Figure 1.2 Commonly used routes of drug administration. IV = intravenous; IM = intramuscular; SC = subcutaneous.

Drugs administered IV enter directly into the systemic circulation and have direct access to the rest of the body.



Drugs administered orally are first exposed to the liver and may be extensively metabolized before reaching the rest of body.

Factors That Modify Absorption

- Drug solubility at the site of absorption
- Dosage form
- Local condition at the site of action
- Drug concentration at the site of absorption
- Circulation to the site of absorption
- Area of the absorbing surface
- The route of administration

Bioavailability

- Bioavailability: fraction of administered drug that reaches the systemic circulation
 - Amount of drug available in the circulation/site of action
 - Bioavailability is expressed in percentage
 - Bioavailability is 100% for drugs given IV.

Factors affecting bioavailability

- Extent of absorption
- First pass effect

Drug distribution

- Process by which a drug reversibly leaves the blood stream & enters the interstitium and/or cells of the tissues

Factors affecting drug distribution

1. Plasma protein binding
 - Albumin[acidic drugs]
 - γ -globulin [basic drugs]

Drug distribution cont'd

2. Tissue uptake of drugs

- adipose tissue [DDT]
- bone [TTC]
- liver [chloroquine]
- thyroid gland [iodine]

3. Barriers

Blood brain barrier & Placental barrier

4. Rate of blood flow

brain, kidney, liver & lung- highly perfused

Biotransformation/metabolism

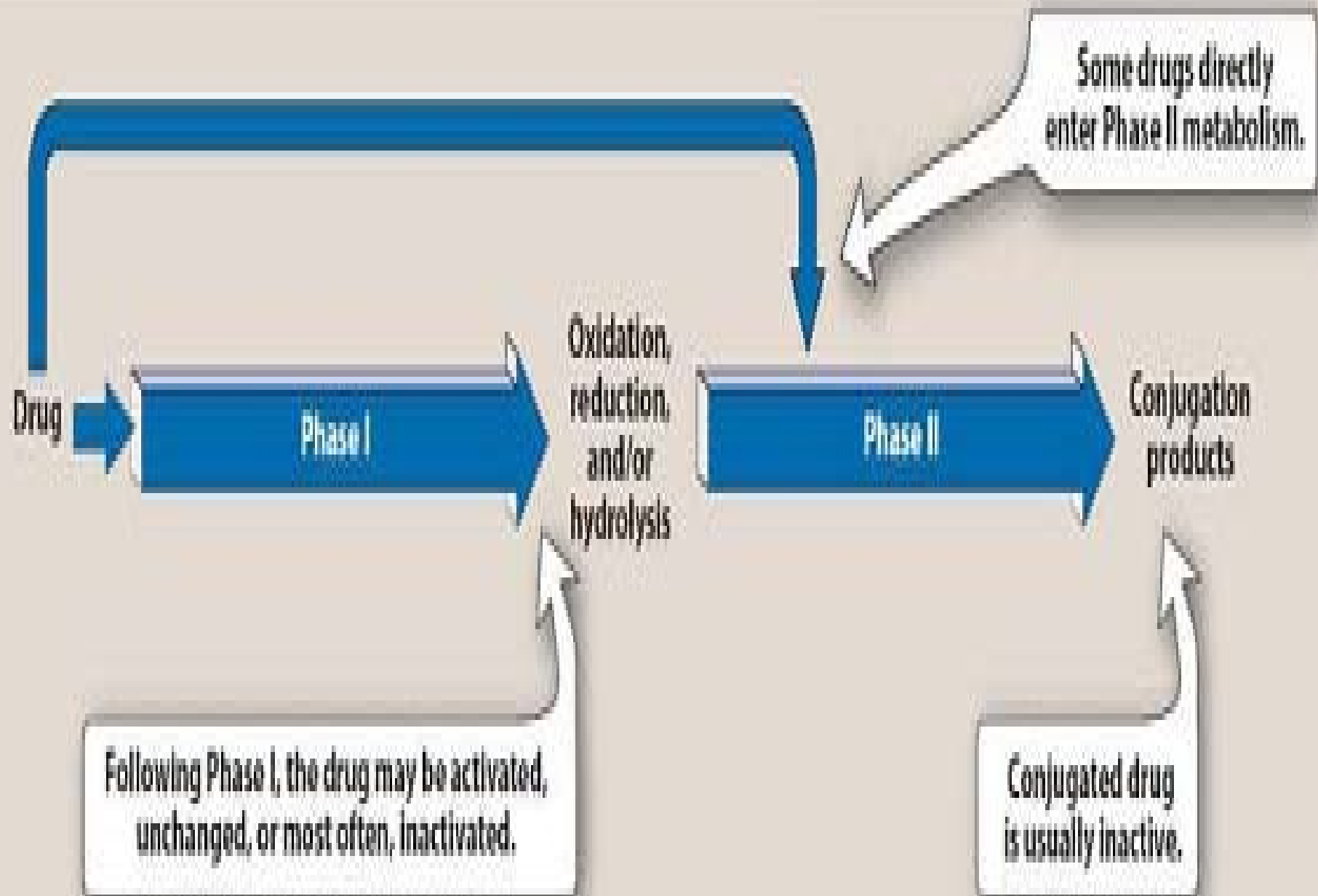
- Alteration of drug structure- w/c may result in ;
 - ✓ Inactivation
 - ✓ Activation (prodrug) of the drug.
 - ✓ Activation from another active drug
- Main site of biotransformation
 - Liver, intestine, plasma
- TWO PHASES OF BIOTRANSFORMATION
 - Phase I biotransformation
- Consists of reactions:
 - Oxidation [ethanol]
 - Reduction [estrone]
 - Hydrolysis [procaine]

Biotransformation cont'd

- The products are more reactive than parent drug
- Purpose of phase I reaction is to introduce functional groups;[NH₂, thiol, hydroxyl]

Phase II reaction [conjugation]

- Conjugating compounds include:
 - Glucoronide[CAF, Morphine, sulphonamide, ASA]
 - Acetyl [INH, hydralazine]
 - Sulphate [steroids]
 - Methyl [catecholamine]



Biotransformation cont'd

Enzymes Responsible for Metabolism of Drugs;

–**Microsomal Enzymes**-present in the smooth endoplasmic reticulum of the liver, kidney, and GIT. E.g. glucuronyl transferase, dehydrogenase, hydroxylase, CYP450 etc...

–**Non-microsomal Enzymes**-present in the cytoplasm, mitochondria of different organs. E.g. Esterase, amidase, hydroxylase etc...

- Enzyme induction

- Phenobarbitone: nonselective

- DDT: induces cyp1A1

- Enzyme inhibition

- Cimetidine –Ketoconazole

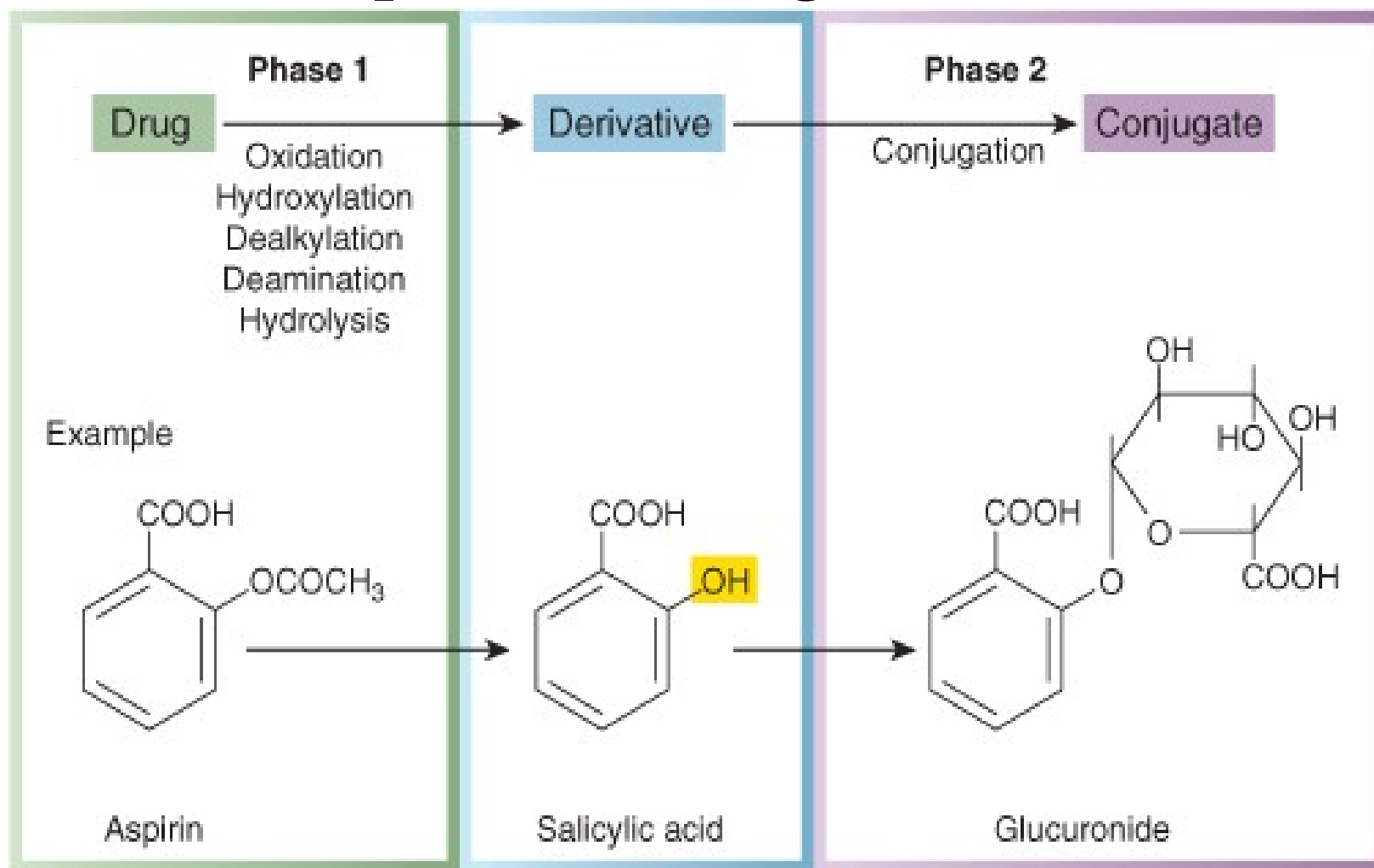
- Erythromycin –Chloramphenicol

Biotransformation cont'd

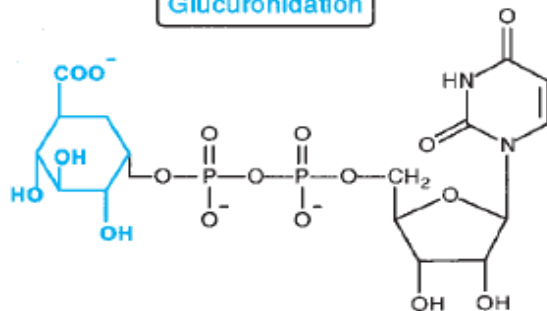
Consequences of drug biotransformation

- Activation [L-dopa $\rightarrow$ dopamine]
- Maintenance of activity [diazepam $\rightarrow$ oxazepam]
- Inactivation [Phenobarbital $\rightarrow$ hydroxypentobarbital]

The two phases of drug metabolism

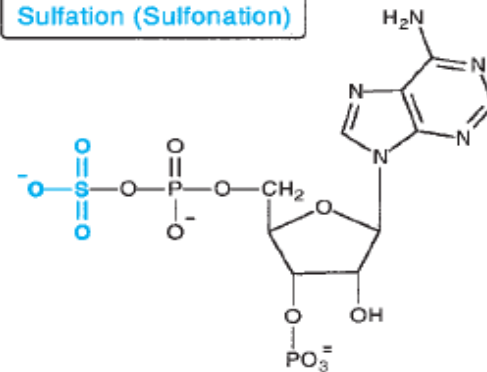


Glucuronidation



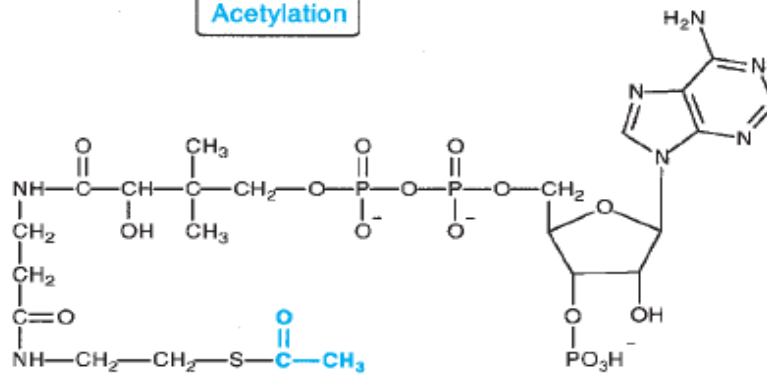
Uridine-5'-diphospho-α-D-glucuronic acid (UDP-GA)

Sulfation (Sulfonation)



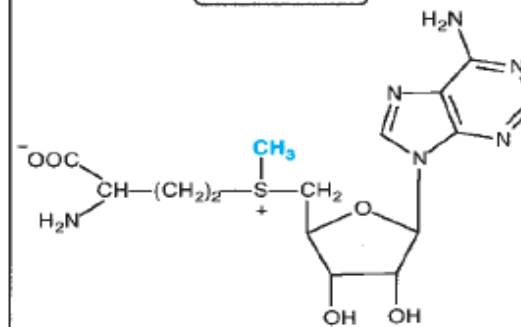
3'-Phosphoadenosine-5'-phosphosulfate (PAPS)

Acetylation



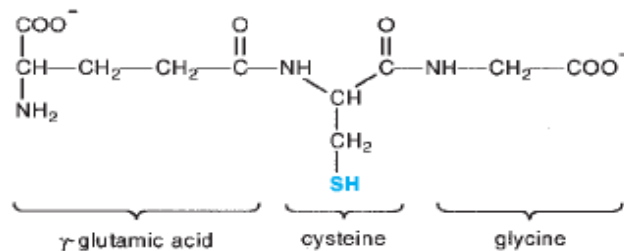
Acetyl coenzyme A

Methylation



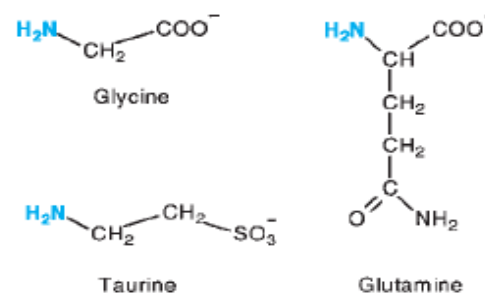
S-Adenosylmethionine (SAM)

Glutathione Conjugation



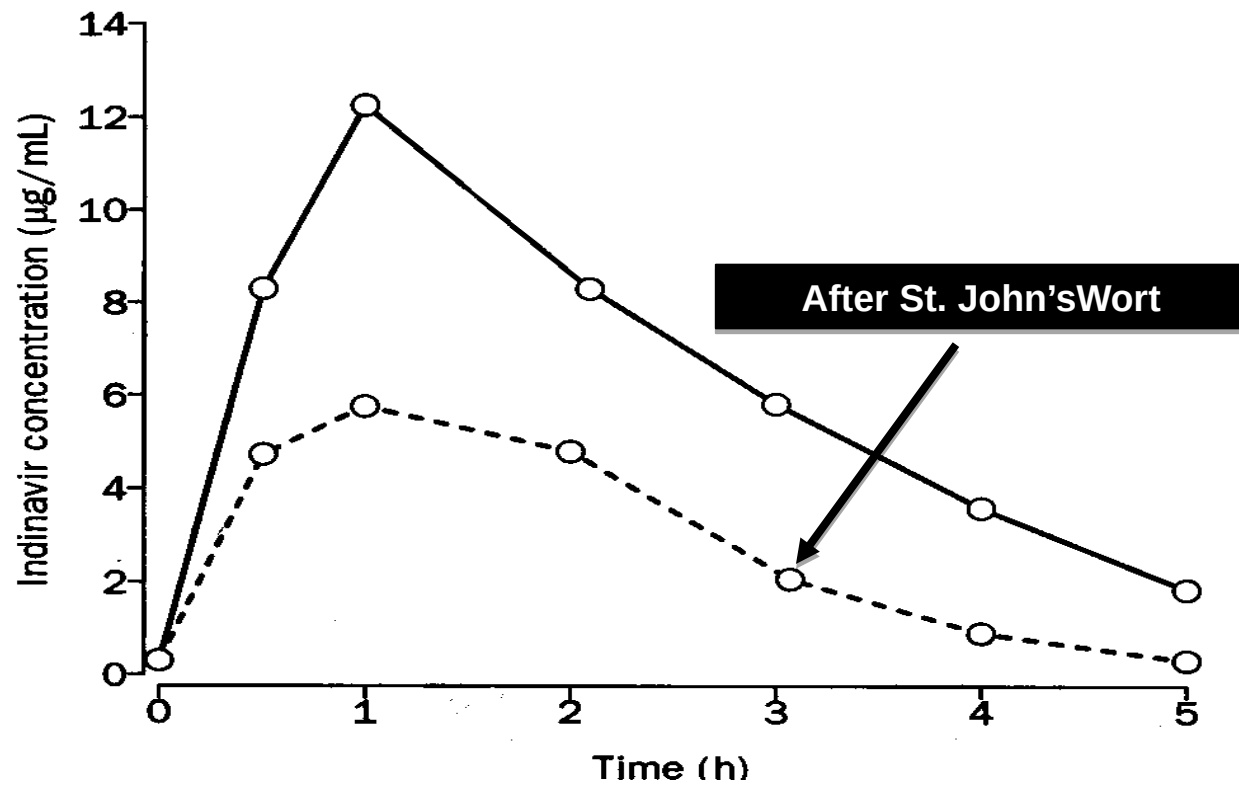
Glutathione

Amino Acid Conjugation



Enzyme Induction

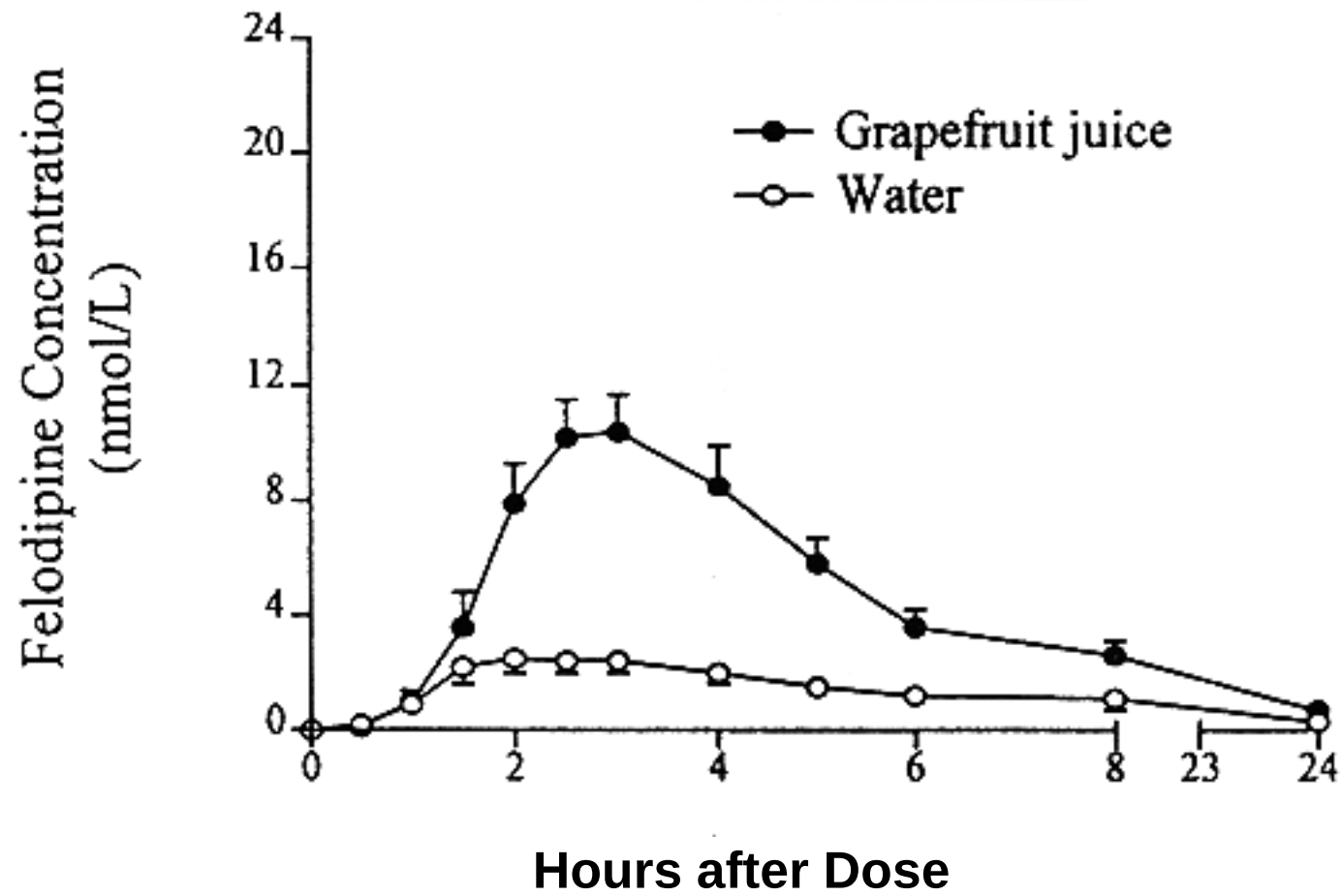
- An increased synthesis of CYP450 and hence increased rate of biotransformation.
- Induction brings about decreased bioavailability of parent drug and increased concentration of metabolite
 - E.g. Induction of metabolism of ethinylestradiol by rifampicin and phenobarbitone



Enzyme Inhibition

- Competition between two or more drugs for metabolizing enzyme may lead to a decrease in the metabolism of one of these agents
- Some drugs bind tightly to the Cytochrome P450 heme iron and reduce the metabolizing activity of the enzymes.
- It results in elevated levels of the parent drug and hence prolonged pharmacological effect and an increased incidence of drug-induced toxicity.

Single Dose Study



Factors Affecting Drug Biotransformation

- Genetic polymorphism
- Disease conditions especially of the major drug metabolizing sites.
- Age
- Predisposing factors to enzyme induction or inhibition.

Excretion of drugs

Transportation of unaltered or altered form of a drug out of the body

Minor route of excretion

- Eye, breast, skin

Intermediate route

- Lung [volatile]
- Bile [digoxin, rifampin]

Renal excretion- major route for most drugs & involves

- Glomerular filtration
- Active tubular secretion
- Passive tubular reabsorption

PHARMACODYNAMICS

- ❑ Is the study of drug effects on the body.
- ❑ A fundamental principle of pharmacodynamics is that drugs only modify underlying biochemical and physiological processes;
 - ❑ They do not create effects de novo.

Site of drug action

A drug may act:-

- a) Extracellularly e.g. Osmotic diuretics.
- b) On the cell surface eg. Digitalis, Penicillins, Catecholamines.
- c) Inside the cell eg. Anticancer drugs, steroid hormones.

- **Pharmacodynamics** studies the physiological and biochemical effects of drugs and their mechanism of action
- Drugs interact with receptors to produce their characteristic effects.
- Receptors are functional macromolecular components of the organism
 - Drugs potentially are capable of altering both the extent and rate at which any bodily function proceeds
 - Drugs do not create effects but instead modulate intrinsic physiological functions.

Mechanism of Drug Action

- Physical action
 - Mass of the drug (in bulk laxatives), adsorptive property (activated charcoal), osmotic activity (mannitol)
- Chemical action
 - Antacids, chelating agents (calcium disodium edetate)
- Through protein targets:
 - (Ion channels, carrier molecules, enzymes, receptors)
- ❖ Through enzymes
 - Drugs alter rate of enzyme catalyzed reactions
 - Actions could be
 - **Stimulation**: increased substrate affinity to enzyme
 - **Inhibition**: is a common mode of drug action and could be
 - ✓ **Competitive**: drug binds to catalytic site (mostly non-covalently); reversed. **How?**
 - ✓ **Noncompetitive**: drug binds to a site adjacent to catalytic site and as a result the catalytic property of the enzyme is lost.

4. Through receptors:

- Most drugs act by interacting with cellular components called receptors.
- Receptors are protein molecules present either on the cell surface or within the cell. eg. Adrenergic receptors, cholinergic receptors, insulin receptors.
- A drug which is able to fit on to a receptor is said to have **affinity** for that receptor.
- When a drug is able to **stimulate** a receptor, it is known as an **agonist**.
- An agonist has both an **affinity** and **efficacy** whereas an antagonist has affinity but not efficacy or intrinsic activity.
- **Efficacy** is the maximum response produced by a drug.
- When a drug blocks a receptor, it is known as **antagonist** and therefore blocks the action of the endogenous transmitter.

1 Unoccupied receptor does not influence intracellular processes.



2 Occupied receptor changes physical and chemical properties, which leads to interaction with cellular molecules to cause a biologic response.



Factors that modify drug effect & drug dosage

- Sex: m/f
- Body weight: lean/obese
- Age: child($\propto$ plasma protein binding, incomplete dev't of BBB, Underdeveloped renal & enzyme system)
- Food
- Route of administration
- Physiological variables: fluid & electrolyte
- Pathological factor (kidney & liver diseases)
- Genetic makeup: fast & slow acetylation of INH
- Tolerance to drug
- Drug interaction

Drug interaction: classification

- Pharmaceutical
 - Diazepam in infusion fluid: precipitation
- Pharmacokinetic
 - Absorption (TTC & milk, TTC & oral iron preparations)
 - Biotransformation
 - Induction (phenobarbitone & warfarin)
 - Inhibition (cimetidine and warfarin)
 - Excretion (probenecid & penicillin)
- Pharmacodynamic drug-drug interaction of drugs that occur on the receptors or on the effects of a drug.

Types of pharmacodynamic drug interaction

- Additive [$1+1=2$]- E.g. Ephedrin + Aminophyllin
- Synergism [$1+1>2$] - E.g trimethoprim + sulphamethoxazole
- Potentiation [$0+1>1$]
- Antagonism [$0+1<1$]
 - Physiological antagonism
 - Pharmacological antagonism
 - Competitive
 - Noncompetitive

Adverse drug reaction

- ADR: defined as any response to a drug that is noxious and unintended and that occurs at doses used for prophylaxis, diagnosis or therapy.
- Types of ADR:
 - **Predictable:** arise from known pharmacological property of the drug.
E.g.- **side effect & toxic effect**
 - **Non predictable:** allergy & idiosyncrasy (adverse drug reaction that occurs in a small number of persons and no correlation to dosage)
- 1. **Side effects:** are pharmacological effects produced with therapeutic dose of the drug
E.g. dryness of mouth with **atropine** and useful when used as pre-anesthetic medication
- 2. **Toxic effect:** excessive pharmacological action of the drug due to over dosage or prolonged use.

Adverse drug reaction cont'd

3. **Untoward/ Secondary effects:** indirect consequences of primary action of drug, e.g. suppression of bacterial flora by **tetracycline paves the way for superinfection**; corticosteroids weaken host defense mechanisms and latent tuberculosis gets activated.

4. **Idiosyncratic reaction:** genetically determined ADR, which could be dose related [neuropathy by INH] or dose unrelated [**hemolytic anemia by primaquine, sulphonamide, dapsone**]

5. **Hypersensitivity reaction/ allergy:**
 - Type I (Anaphylactic reaction): antigen + IgE on basophile/mast cell
 - **Anaphylaxis, asthma, hay fever or urticaria**
 - Type II (cytotoxic reaction): antigen + IgM/IgG
 - Penicillin binds RBC evokes production of antibody and lysis
 - Type III (immune complex mediated reaction): skin rashes due to NVP.

Adverse drug reaction cont'd

6. **Teratogenic effect:** the effect of drug to cause fetal abnormalities when administered to the pregnant mother.
- E.g. thalidomide cause phocomelia [absent or grossly abnormal limbs]



7. **Carcinogenicity and mutagenicity:** a drugs ability to cause cancer and genetic defects respectively.

FDA Use-in-Pregnancy Ratings of drugs

CATEGORY

INTERPRETATION

A	Adequate, well-controlled studies in pregnant women have not shown an increased risk of fetal abnormalities to the fetus in any trimester of pregnancy.
B	Animal studies have revealed no evidence of harm to the fetus, however, there are no adequate and well-controlled studies in pregnant women. OR Animal studies have shown an adverse effect, but adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus in any trimester.
C	Animal studies have shown an adverse effect and there are no adequate and well-controlled studies in pregnant women. OR No animal studies have been conducted and there are no adequate and well-controlled studies in pregnant women.
D	Adequate well-controlled or observational studies in pregnant women have demonstrated a risk to the fetus. However, the benefits of therapy may outweigh the potential risk. For example, the drug may be acceptable if needed in a life-threatening situation or serious disease for which safer drugs cannot be used or are ineffective.
X	Adequate well-controlled or observational studies in animals or pregnant women have demonstrated positive evidence of fetal abnormalities or risks. The use of the product is contraindicated in women who are or may become pregnant.

Examples of drugs in each category:

Category A;

MgSO₄, thyroxine

Category B;

Penicillin V, Amoxicillin, Paracetamol, Lignocaine

Category C;

Morphine, codeine, atropine, Corticosteroids, adrenalline

Category D;

Aspirin, Phenytoin, carbamazepine, lorazepam

Category X;

Estrogens, ergometrine