

Introduction to Medicinal Chemistry

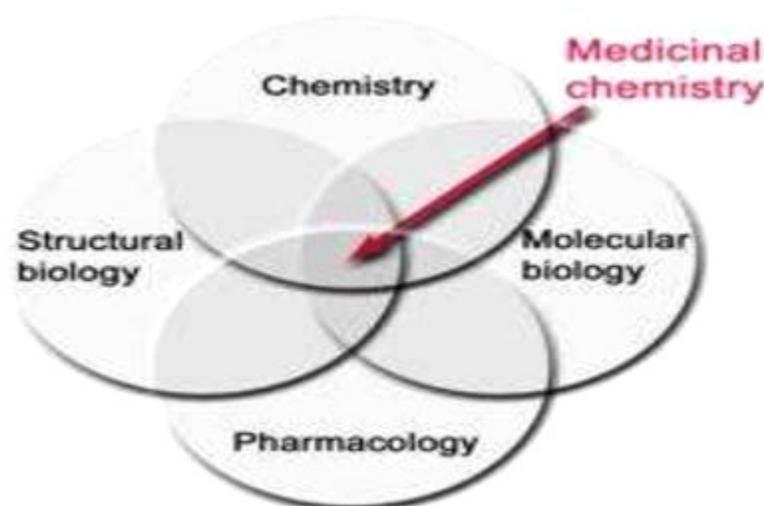
Medicinal chemistry is best to be defined as an interdisciplinary research area incorporating different branches of chemistry and biology in the research for better and new drugs (Drug Discovery).

In other words, medicinal chemistry is the science, which deals with the discovery and design of new and better therapeutic chemicals and development of these chemicals into new medicines and drugs.

Generally Medicinal Chemists can:

- Make new compounds
- Determine their effect on biological processes.
- Alter the structure of the compound for optimum effect and minimum side effects.
- Study uptake, distribution, metabolism and excretion of drugs.

Medicinal chemistry is the chemistry discipline concerned with the design, development and synthesis of pharmaceutical drugs. The discipline combines expertise from chemistry and pharmacology to identify, develop and synthesize chemical agents that have a therapeutic use and to evaluate the properties of existing drugs



Primary objective of medicinal chemistry

Generally, we can identify the following stages in drug discovery, design and development

Drug discovery-finding a lead

- Choose a disease.
- Choose a drug target.
- Identify a bioassay.
- Find a lead compound.
- Isolate and purify the lead compound if necessary.
- Determine the structure of the lead compound if necessary.

Drug design

- Identify structure-activity relationships (SARs)
- Identify the pharmacophore.
- Improve target interactions (pharmacodynamics).
- Improve pharmacokinetic properties,

Drug development

- Patent the drug.
- Carry out preclinical trials (drug metabolism, toxicology, formulation and stability test, pharmacology studies, etc).
- Design a manufacturing process (chemical and process development).
- Carry out clinical trials.
- Register and market the drug.
- Make money.

History and Development of Medicinal Chemistry

3500 BC - Sumerians report use of opium

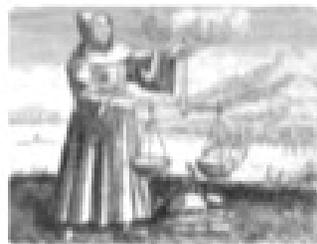
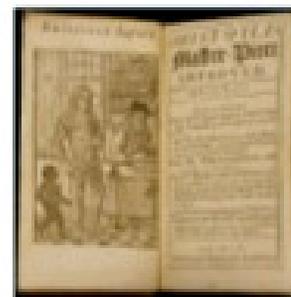
3000 BC - Chinese report use of ma huang (ephedra)



Greek culture:

Hippocrates- followed the teachings of Aristotle; focus is on the soul.

Galen- followed the teachings of Plato; focus is on experiment- believed the whole could be explained by the parts



Renaissance period:

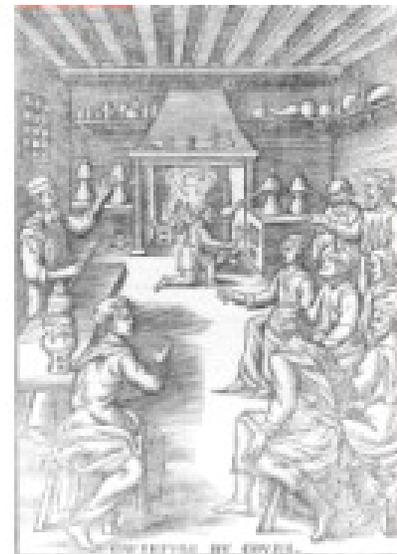
Doctors were humanists- followers of Hippocrates- treat the soul and the body will heal. Initially, there were no relationships with alchemy.

History and Development of Medicinal Chemistry

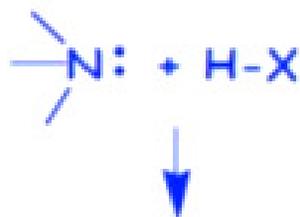
In 1793, Faureroy & Vauquehin split from the monarchy-controlled bodies and establish the Ecole Supérieure de Pharmacie- 1st to incorporate chemistry into the pharmacy curriculum. Develop research to find the active principles in plant-based drugs.



1803 - Derosome isolates a crystalline salt from opium



1817 - Sertürner publishes work demonstrating that the narcotic principle of opium is basic (alkaline) and, thus, it will form salts with acids- names the principle "morpheus"

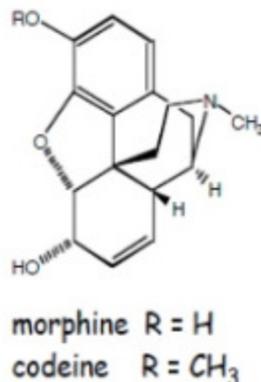
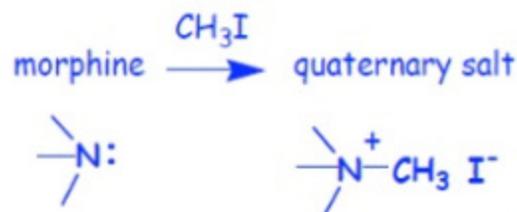


Gay-Lussac predicts that other alkaline plant extracts will have useful medical properties- changes name of morpheus to morphine

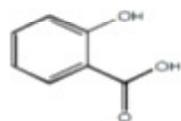
1818 - Meissner proposes the general term alkaloids

History and Development of Medicinal Chemistry

1853 - Henry How proposes that there are "functional groups" that can be chemically modified to alter reactivities....

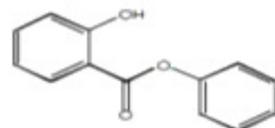


Fraser and Brown make quaternary salts of many different alkaloids (i.e., morphine, strychnine, nicotine) and find that all exhibit curare-paralyzing activities- propose that quaternary salts have curariform activity



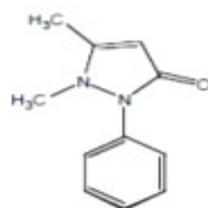
salicylic acid

1875- Carl Buss isolates salicylic acid from *Spirea ulmaria* and shows that it is an effective antipyretic- however, it is unpalatable and causes gastric distress.



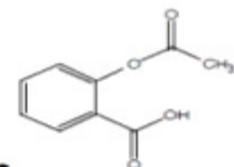
salol (phenyl salicylate)

1883- von Nencki makes a salicylate ester with phenol, salol- it has very poor solubility but it is better tolerated. It is hydrolyzed slowly in the small intestine to give salicylic acid- the first sustained release drug



phenazone

1890s - Hoffman at Bayer tests acetyl salicylic acid and finds it to be better tolerated- names it aspirin as in "a" for acetyl and "spirin" for *Spirea*. It is rapidly hydrolyzed in the gut to give active salicylic acid- it is a "pro-drug"



acetyl salicylic acid

Phenazone was synthesized in 1884 and was the most popular drug world-wide until it was taken over by aspirin in the early 1900s- in addition to being an antipyretic, it also cured headaches- a new market was born...

Drug Classification

Pure organic compounds are the chief source of agents for the cure, mitigation or the prevention of disease. These remedial agents could be classified according to their origin:

- **Natural compounds:** materials obtained from both plant and animal, e.g. vitamins, hormones, amino acids, antibiotics, alkaloids, glycosides.... etc.).
- **Synthesis compounds:** either pure synthesis or synthesis naturally occurring compounds (e.g. morphine, atropine, steroids and cocaine) to reduce their cost.
- **Semi-synthesis compounds:** Some compounds either can not be purely synthesized or can not be isolated from natural sources in low cost. Therefore, the natural intermediate of such drugs could be used for the synthesis of a desired product (e.g. semi synthetic penicillins).

Since there is no certain relation between chemical structure and pharmacological activity therefore, it would be unwise to arrange all drugs on the basis of their structures or origin.

Thus, it is better to arrange the drugs according to their medicinal use. Drugs can be classified according to their medicinal uses into two main classes:

I-Pharmacodynamic agents: Drugs that act on the various physiological functions of the body (e.g. general anaesthetic, hypnotic and sedatives, analgesic etc.).

II-Chemotherapeutic agents: Those drugs which are used to fight pathogenic (e.g. sulphonamides, antibiotics, antimalarial agents, antiviral, anticancer etc.).

Drug Classification

Drugs can be classified depending on their use to treat different types of diseases:

1-Infectious diseases: Born (transmitted) from person to person by outside agents, bacteria (pneumonia, salmonella), viruses (common cold, AIDS), fungi (thrush, athlete's foot), parasites (malaria)

2-Non-infectious diseases: disorders of the human body caused by genetic malfunction, environmental factors, stress, old age etc. (e.g. diabetes, heart disease, cancer, Haemophilia, asthma, mental illness, stomach ulcers, arthritis).

3-Non-diseases: mitigation of pain (analgesic), prevention of pregnancy (contraception), anesthesia.

Physico-chemical properties in relation to biological action

Drug action results from the interaction of drug molecules with either normal or abnormal physiological processes. Drugs normally interact with targets (which they are proteins, enzymes, cell lipids, or pieces of DNA or RNA). The ability of a chemical compound to elicit a pharmacologic /therapeutic effect is related to the influence of its various physical and chemical (physicochemical) properties.

The most pharmacologically influential physicochemical properties of organic medicinal agents (OMAs) are:

1.Solubility

2.Acidity and basicity

3.Reactivity

1- SOLUBILITY OF ORGANIC MEDICINAL AGENTS

Importance of solubility:

- (1) Formulation of the drug in an appropriate dosage form and
- (2) Bio-disposition: Disposition of OMAs in the living system after administration (absorption, distribution, metabolism, and excretion).

The solubility expression: in terms of its affinity/philicity or repulsion/phobicity for either an aqueous (hydro) or lipid (lipo) solvent.

♣ hydrophilic.....water loving

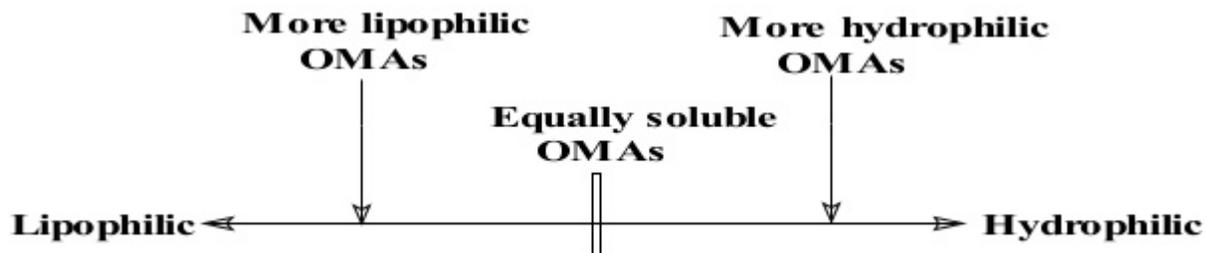
♣ lipophobic.....lipid hating

♣ lipophilic.....lipid loving

♣ hydrophobic.....water hating

Majority of OMAs possess balanced solubility (have some degree of solubility in both aqueous and lipid media). Because there is a need for OMAs to move through both aqueous (plasma, extracellular fluid, cytoplasm, etc.) and lipid media (biologic membranes) in the biological system.

Solubility of OMAs should be viewed as being on a range between high lipophilicity on one end of the spectrum and high hydrophilicity on the other.



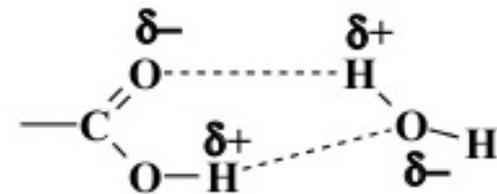
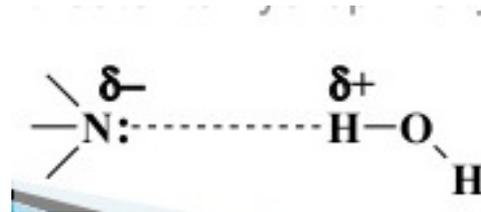
The most important intermolecular attractive forces (bonds) that are involved in the solubilization process are:

1. Van der Waals Attraction

- weakest intermolecular force (0.5-1.0 kcal/mole)
- electrostatic
- occurs between nonpolar groups (e.g. hydrocarbons)
- highly distance and temperature dependent

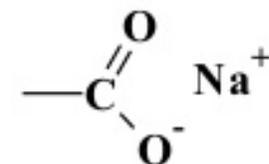
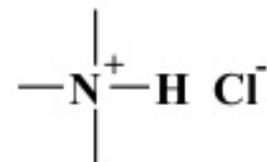
2. Dipole-Dipole Bonding

- stronger (1.0 to 10 kcal/mole)
- occurs electrostatically between electron deficient and electron excessive /rich atoms (dipoles)
- hydrogen bonding is a specific example of this bonding and serves as a prime contributor to hydrophilicity :



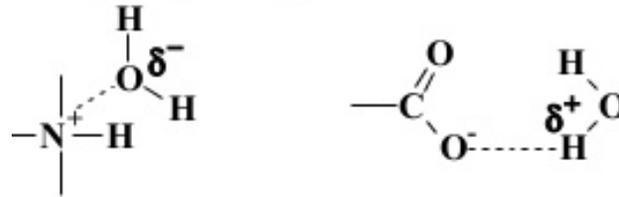
3. Ionic Bonding

- electrostatic attraction between cations and anions
- common in inorganic compounds and salts of organic molecules
- relatively strong (5 kcal/mole)



4. Ion-Dipole Bonding

- electrostatic between a cation/anion and a dipole
- relatively strong (1-5 kcal/mole)
- low temperature and distance dependence
- important attraction between OMAs and H₂O



Solubility Prediction

The relative solubility of an OMA is a function of the presence of both lipophilic and hydrophilic features within its structure, which serve to determine the extent of interaction of the OMA with lipid and/or aqueous phases.

The relative solubility of an OMA can be determined in the laboratory, i.e. **the partition coefficient [P]** the ratio of the solubility of the compound in an organic solvent to the solubility of the same compound in an aqueous environment , also sometimes expressed as **Distribution coefficient [D]**.

$P = \frac{[\text{Drug}]_{\text{lipid}}}{[\text{Drug}]_{\text{aqueous}}}$. P is often expressed as a log value.

2- Acidity and Basicity

Acidic and/or basic properties of OMAs are important in both:

- 1- Pharmaceutical phase (dosage formulation, etc.) and
- 2- Pharmacological phases (disposition, structure at target site, etc.).

Definitions: Acid: An organic compound containing a functional group that can donate a proton (H^+) Base: An organic compound that contains a functional group that can accept a H^+

Estimation of the Relative Acid/Base Strength

The ionization constant (k_a) indicates the relative strength of the acid or base.

An acid with a k_a of 1×10^{-3} is stronger acid (more ionized) than one with a k_a of 1×10^{-5}

A base with a k_a of 1×10^{-7} is weaker (less ionized) than one with a k_a of 1×10^{-9}

The negative log of the ionization constant (**pka**) also indicates the relative strength of the acid or base.

An acid with a pka of 5 ($k_a = 1 \times 10^{-5}$) is weaker (less ionized) than one with pka of 3

Whereas a base with a pka of 9 is stronger (more ionized) than one with a pka of 7 E.g.

Ionization of weak acid (e.g. acetic acid, pka = 4.76) is as follows:

3. Drug-receptor Interaction (Reactivity)

The ability of a drug to get bound to a receptor is termed as the affinity of the drug for the receptor. The receptors are also dynamic in nature and have a special chemical affinity and structural requirements for the drug. Thus, affinity represents kinetic constants that relate to the drug and the receptor.

The drug elicits a pharmacological response after its interaction with the receptor. A given drug may act on more than one receptor differing both in function and in binding characteristics (non-selective drugs). There are also many factors effect changes in receptor concentration and/or affinity.

A drug, which initiates a pharmacological action after combining with the receptor, is termed agonist.

Drugs which binds to the receptors but are not capable of eliciting a pharmacological response produce receptor blockage, these compounds are termed antagonists.

Drug Metabolism

Introduction

- **Biotransformation:** Chemical alteration of the drug in body that converts nonpolar or lipid soluble compounds to polar or lipid insoluble compounds
- **Consequences of biotransformation**
 - Active drug → Inactive metabolite : Pentobarbitone, Morphine, Chloramphenicol
 - Active drug → Active metabolite: Phenacetin
 - Inactive drug → active metabolite: Levodopa

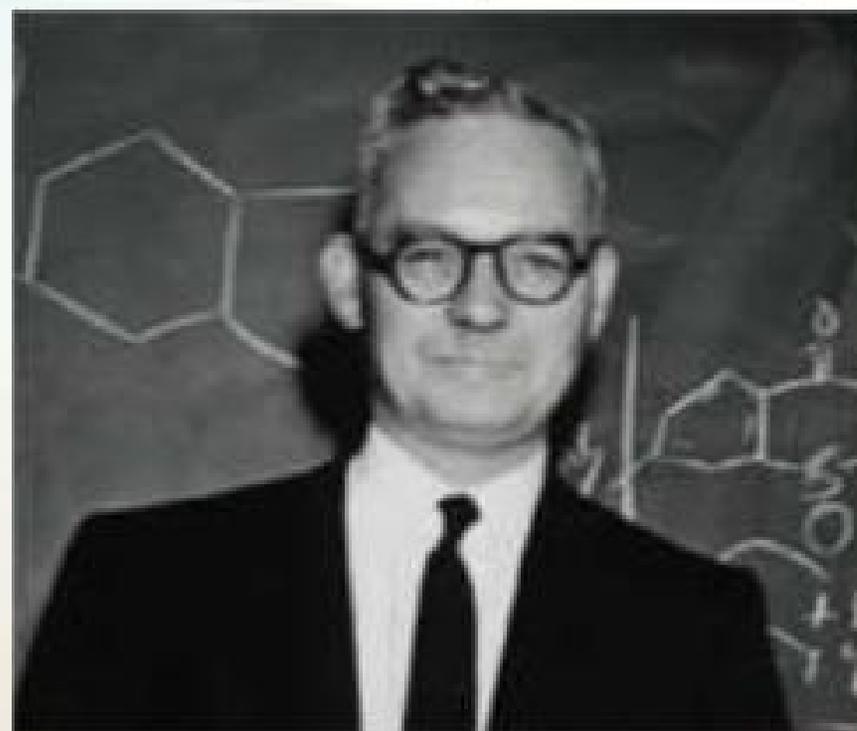
Prodrugs

- Inactive drug is converted to active metabolite
- Coined by Albert in 1958
- **Advantages:**
 - Increased absorption
 - Elimination of an unpleasant taste
 - Decreased toxicity
 - Decreased metabolic inactivation
 - Increased chemical stability
 - Prolonged or shortened action

History

- Welsh biochemist
- Metabolism of sulfonamides, benzene, aniline, acetanilide, phenacetin, thalidomide and stilbesterol
- Metabolism of TNT (Trinitrotoluene) with regard to toxicity in munitions (1942)

Richard Tecwyn Williams



1909 - 1979

Phases of Metabolism

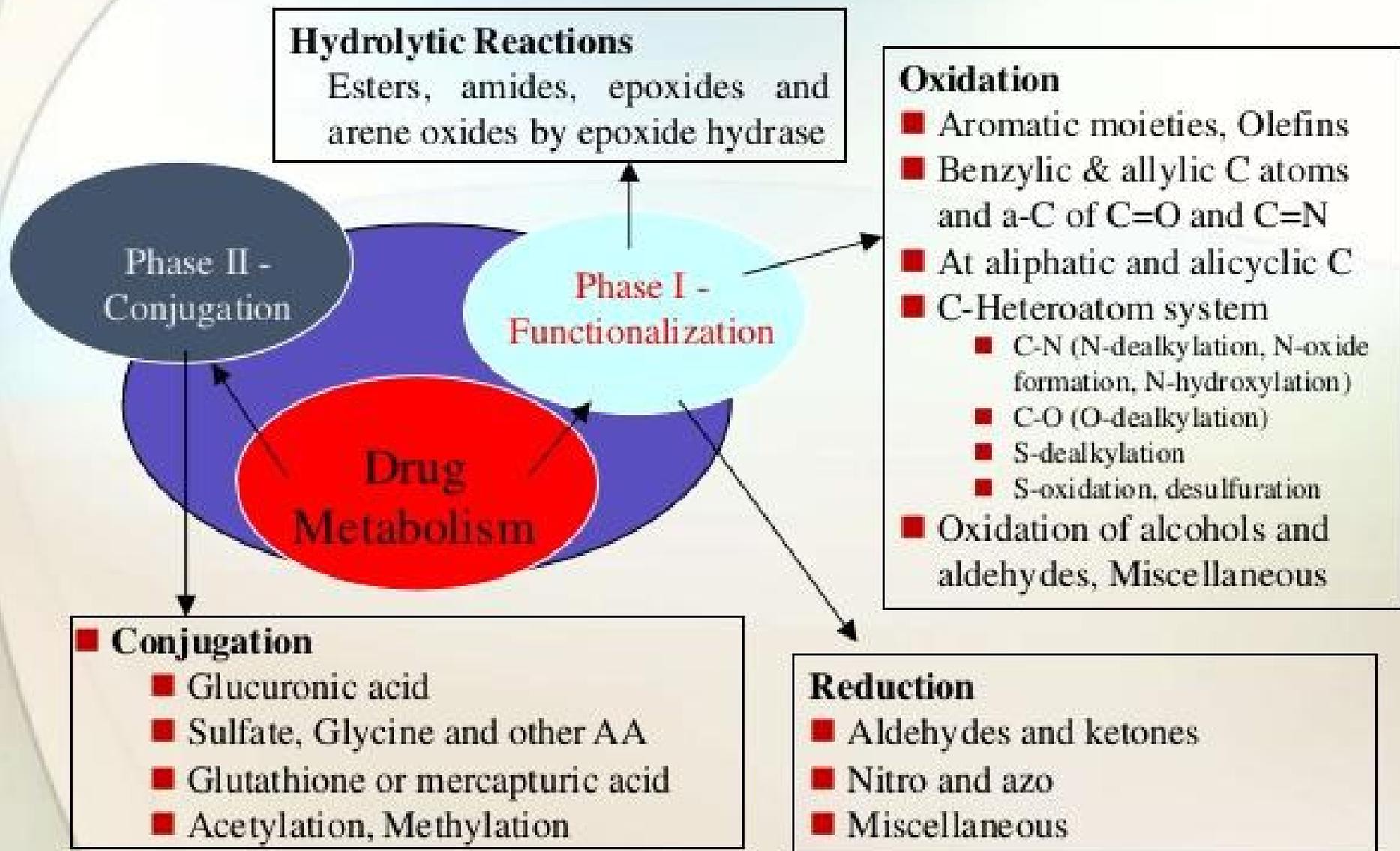
- **Phase I**

- Functionalization reactions
- Converts the parent drug to a more polar metabolite by introducing or unmasking a functional group (-OH, -NH₂, -SH).

- **Phase II**

- Conjugation reactions
- Subsequent reaction in which a covalent linkage is formed between a functional group on the parent compound or Phase I metabolite and an endogenous substrate such as glucuronic acid, sulfate, acetate, or an amino acid

Phases of Metabolism

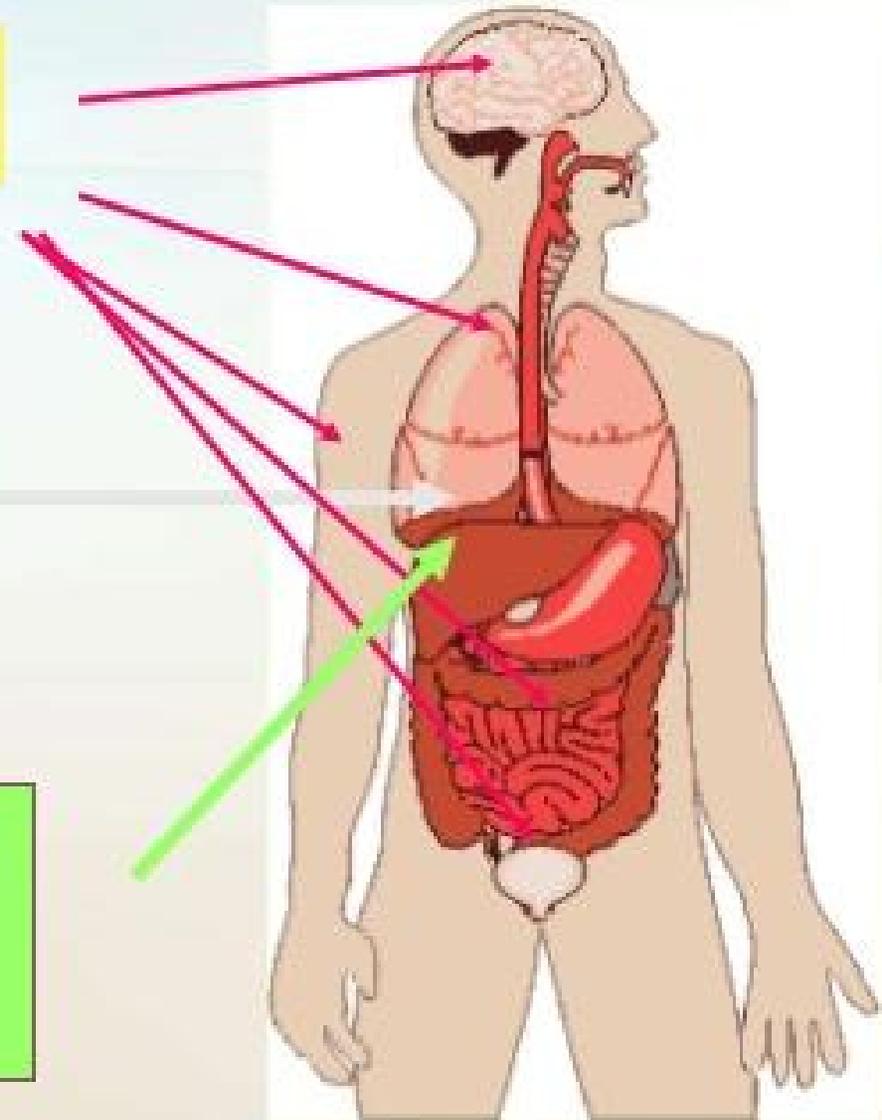


Sites of Drug Metabolism

**Extrahepatic microsomal enzymes
(oxidation, conjugation)**

**Hepatic microsomal enzymes
(oxidation, conjugation)**

**Hepatic non-microsomal enzymes
(acetylation, sulfation, GSH,
alcohol/aldehyde dehydrogenase,
hydrolysis, ox/red)**



Phase I / Non Synthetic Reactions

Oxidation

- Addition of oxygen/ negatively charged radical or removal of hydrogen/ positively charged radical.
- Reactions are carried out by group of mono-oxygenases in the liver.
- Final step: Involves cytochrome P-450 haemoprotein, NADPH, cytochrome P-450 reductase and O₂

Cytochrome P450 enzymes

- Monooxygenase enzyme family
- **Major catalyst:** Drug and endogenous compound oxidations in liver, kidney, G.I. tract, skin and lungs
- **Oxidative reactions require:** CYP heme protein, the reductase, NADPH, phosphatidylcholine and molecular oxygen
- **Location:** smooth endoplasmic reticulum in close association with NADPH-CYP reductase in 10/1 ratio
- The reductase serves as the electron source for the oxidative reaction cycle

Non-CYP Drug Oxidations

- **Monoamine Oxidase (MAO), Diamine Oxidase (DAO)**
 - MAO (mitochondrial) oxidatively deaminates endogenous substrates including neurotransmitters
 - Dopamine, serotonin, norepinephrine, epinephrine
- **Alcohol & Aldehyde Dehydrogenase**
 - Non-specific enzymes found in soluble fraction of liver
 - Ethanol metabolism
- **Flavin Monooxygenases**
 - Require molecular oxygen, NADPH, flavin adenosine dinucleotide (FAD)

Reduction

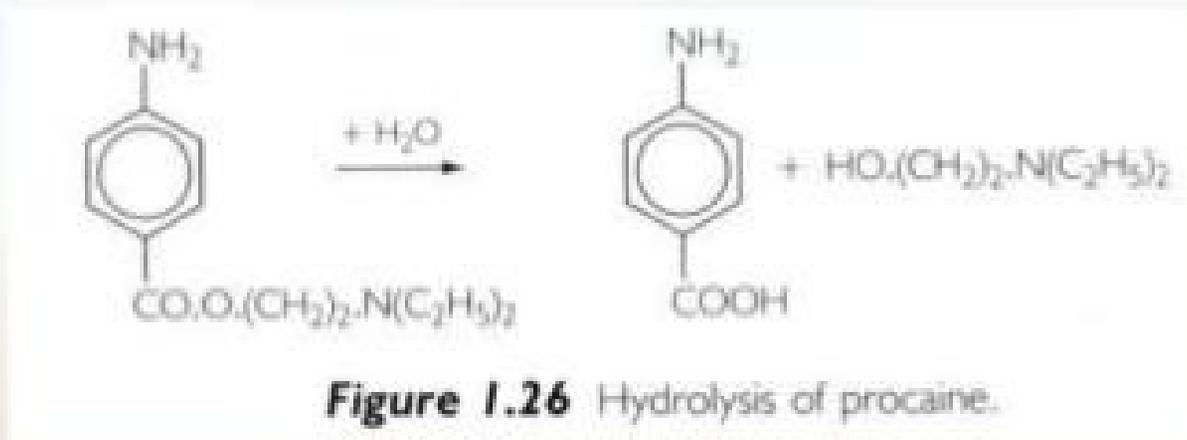
- Converse of oxidation
- Drugs primarily reduced are chloralhydrate, chloramphenicol, halothane.



Figure 1.25 Reductive defluorination of halothane.

Hydrolysis

- Cleavage of drug molecule by taking up a molecule of water.



- **Sites:** Liver, intestines, plasma and other tissues
- **Examples:** Choline esters, Procaine, Isoniazid, pethidine, oxytocin.

Cyclization and Decyclization

- **Cyclization**

- Formation of ring structure from a straight chain compound
- E.g. Proguanil

- **Decyclization**

- Opening up of ring structure of the cyclic drug molecule
- E.g. Barbiturates, Phenytoin.

Phase II/ Synthetic reactions

- Conjugation of the drug or its phase I metabolite with an endogenous substrate to form a polar highly ionized organic acid
- Types of phase II reactions
 - Glucuronide conjugation
 - Acetylation, Methylation
 - Sulfate conjugation, Glycine conjugation
 - Glutathione conjugation
 - Ribonucleoside/ nucleotide synthesis

Glucuronide Conjugation

- Conjugation to α -d-glucuronic acid
- Quantitatively the most important phase II pathway for drugs and endogenous compounds
- Products are often excreted in the bile
- Requires enzyme UDP-glucuronosyltransferase (UGT)
- Compounds with a hydroxyl or carboxylic acid group are easily conjugated with glucuronic acid which is derived from glucose

Glucuronide Conjugation Continued..

- Enterohepatic recycling may occur due to gut glucuronidases
- Drug glucuronides excreted in bile can be hydrolysed by bacteria in gut and reabsorbed and undergoes same fate.
- This recycling of the drug prolongs its action e.g. Phenolphthalein, Oral contraceptives
 - Examples: Chloramphenicol, aspirin, phenacetin, morphine, metronidazole

Acetylation

- Common reaction for aromatic amines and sulfonamides
- Requires co-factor acetyl-CoA
- Responsible enzyme is N-acetyltransferase
- Important in sulfonamide metabolism because acetyl-sulfonamides are less soluble than the parent compound and may cause renal toxicity due to precipitation in the kidney
- E.g. Sulfonamides, isoniazid, Hydralazine.

Sulfate Conjugation

- Major pathway for phenols but also occurs for alcohols, amines and thiols
- Sulfate conjugates can be hydrolyzed back to the parent compound by various sulfatases
- Sulfoconjugation plays an important role in the hepatotoxicity and carcinogenicity of N-hydroxyarylamides
- Infants and young children have predominating O-sulfate conjugation
- Examples include: α -methyldopa, albuterol, terbutaline, acetaminophen, phenacetin

Amino Acid Conjugation:

- ATP-dependent acid: CoA ligase forms active CoA-amino acid conjugates which then react with drugs by N-Acetylation:
 - Usual amino acids involved are:
 - Glycine, Glutamine, Ornithine, Arginine

Glutathione Conjugation:

- Glutathione is a protective factor for removal of potentially toxic compounds
- Conjugated compounds can subsequently be attacked by γ -glutamyltranspeptidase and a peptidase to yield the cysteine conjugate => product can be further acetylated to N-acetylcysteine conjugate
E.g. Paracetamol

Hofmann elimination

Inactivation of the drug in the body fluids by spontaneous molecular re arrangement without the agency of any enzyme

e.g. Atracurium.

Inhibition of Metabolism

- Competitively inhibit the metabolism of another drug if it utilizes the same enzyme or co factors.
- A drug may inhibit one isoenzyme while being itself a substrate of another isoenzyme
e.g. quinidine is metabolized by CYP3A4 but inhibits CYP2D6
- Inhibition of drug metabolism occurs in a dose related manner and can precipitate toxicity of the object drug.
- Blood flow limited metabolism
e.g. Propranolol reduces rate of lignocaine metabolism by decreasing hepatic blood flow.

Microsomal Enzyme Induction

- Certain drugs, insecticides and carcinogens increase the synthesis of microsomal enzyme protein.
- Different inducers are relatively selective for certain cytochrome P-450 enzyme families e.g.
 - Phenobarbitone , rifampin, glucocorticoids induce CYP3A isoenzymes
 - Isoniazid and chronic alcohol consumption induce CYP2E1
- Induction takes 4-14 days to reach its peak and is maintained till the inducing agent is present.

Consequences of Induction

- Decreased intensity or Increased Intensity of action of drug
- Tolerance- autoinduction
- Precipitation of acute intermittent porphyria
- Interfere with adjustment of dose of another drug
- Interference with chronic toxicity

Possible Uses of Induction:

Congenital non hemolytic anaemia

Cushing's Syndrome

Role of Metabolism in pediatric and elderly

- New born has low g.f.r and tubular transport is immature, so the t_{1/2} of the drug like streptomycin and penicillin is prolonged
- Hepatic drug metabolising system is inadequate in new borns e.g. chloramphenicol can produce gray baby syndrome
- In elderly the renal function progressively declines
- Reduction of hepatic microsomal activity and liver blood flow
- Incidence of adverse drug reactions is much higher in elderly

Role of Metabolism in Drug discovery

- In drug development it is important to have an information on the enzymes responsible for the metabolism of the candidate drug
- Invitro Studies can give information about
 - Metabolite stability
 - Metabolite profile
 - Metabolite Identification
 - CYP induction/Inhibition
 - Drug/Drug interaction studies
 - CYP isoform identification