

# Drug Metabolism

- ❖ **What is mean by :** drug metabolism or drug biotransformation.
- ❖ **metabolism plays an essential role in the elimination of drugs and other foreign ingested chemicals (xenobiotics) from the body**
- ❖ **In some cases, especially during oxidative metabolism, numerous chemical procarcinogens form reactive metabolites capable of covalent binding to biopolymers such as proteins and nucleic acids leading to mutagenic, teratogenic, cytotoxic and carcinogenic effects.**

## ☐ Phases of Metabolism

Drug biotransformation could be classified into two phases

### 1. Phase I (functionalization):

❖ Non polar drugs are either inactivated; or activated in some cases, by metabolic introduction of polar functional group into the substrate molecule through:

**(a) Oxidation:** hydroxylation, oxide formation, alcohol oxidation, aldehyde oxidation, deamination, dealkylation, desulfuration and dehalogenation.

**(b) Reduction:** azo reduction, nitro reduction and aldehyde or ketone reduction.

**(c) Hydrolysis** of amides and esters.

**(d) Removal** of non-polar alkyl group to expose potential polar group.

## **2. Phase II (conjugation and enzymatic synthesis):**

□ In this phase an existing functional group (already presents in the drug molecule or created by phase I metabolism) such as alcohol, phenol, amine is masked or inactivated by a process of:

**(a) Synthesis**, such as methylation, acylation, thiocyanate formation and mercaptouric acid formation.

**(b) Conjugation** with glucuronic acid, amino acids or sulfate which further increase the polarity of the drugs or (xenobiotics).

❑ Thus the administered drug can be excreted in one foreign ingested chemical of the following forms:

1- Unaltered.

2- Oxidized, reduced or hydrolyzed.

3- Conjugated.

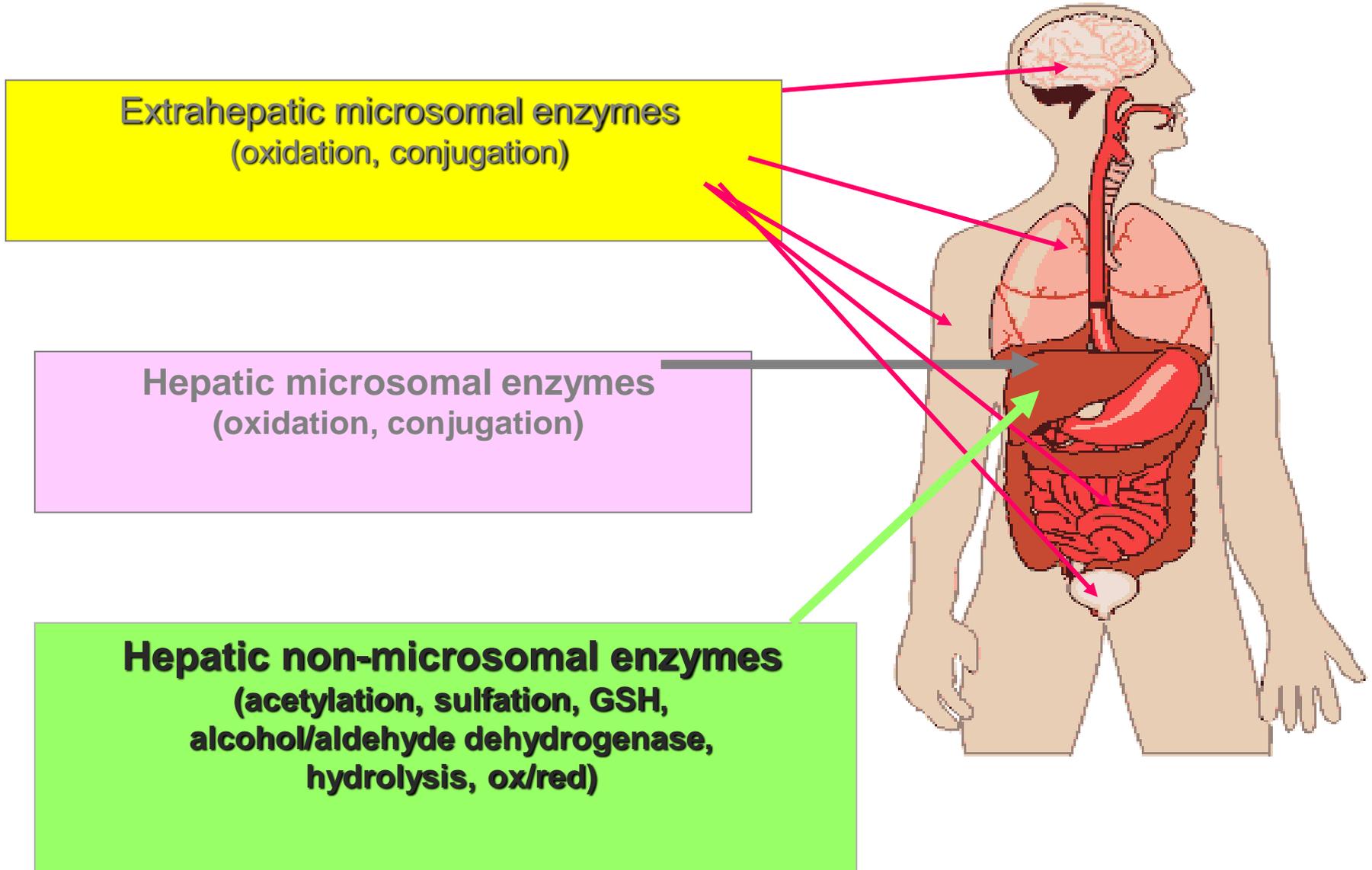
❑ Examples of some intrinsically active drugs that converted to active metabolites:

❖ The oxidation of **phenylbutazone** to **oxyphenbutazone**.

❖ The demethylation of **imipramine** to **desimpramine**.

❖ The cleavage of the ethyl ether group of **phenacetin** to **acetaminophen**.

# Sites of Drug Biotransformation:



# 1. Liver

- ❑ Hepatic metabolism continues to be the most important route of metabolism for foreign ingested chemicals (xenobiotics) and drugs.

## 2. Extra hepatic tissues:

- ❑ Intestinal mucosa, kidney, lungs, skin and adrenals  
Intestinal mucosa
- ❑ Intestinal wall is rich in esterases and lipases enzymes.
- ❑ Bacterial flora present in the intestine and colon appear to play an important role in the reduction of many aromatic azo and nitro drug.
- ❑ Sulfation and glucuronidation are presystemic intestinal first pass metabolism.

## **❑ First pass Metabolism**

**❑ It is the ability of the liver and extrahepatic tissues to metabolize substance to either pharmacologically inactive or bioactive metabolite before reaching systemic blood.**

**❖ Several orally administered drugs are known to undergo liver first pass metabolism during their transport to the systemic circulation from the gastrointestinal tract. Thus, the liver can remove substance from the gastrointestinal tract, thereby preventing distribution to other parts of the body.**

**❑ Low oral bioavailability of a given drug may be the results of either presystemic intestinal metabolism (e.g. estrogens and progestins) or hepatic first pass metabolism with cytochrome P-450 monooxygenase or conjugation reaction.**

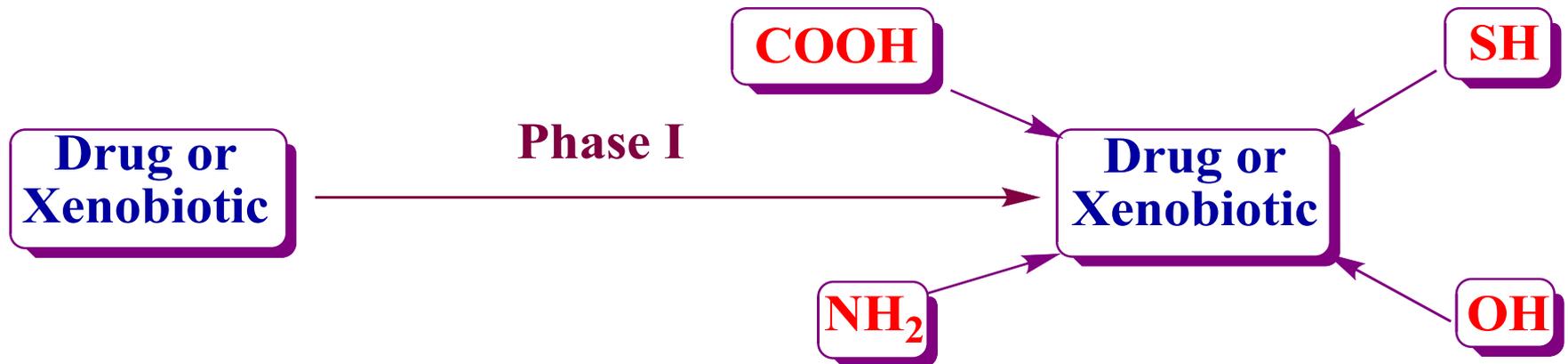
- ❑ **Other routes of administration for susceptible drugs have been investigated in an attempt to overcome the pronounced presystemic metabolism.**
- ❑ **For a non-therapeutic toxic substance, the existence of a first pass effect is desirable because the liver can bioinactivate it, preventing its distribution to other parts of the body.**
- ❑ **The extent of first pass metabolism depends on the drug delivery system, the rate of dissolution, the residence time of a drug in the gastrointestinal tract, and the dose.**

### **Examples of Drugs exhibiting first pass Metabolism:**

**Aspirin, Imipramine, Desmethylimipramine, Hydrocortisone, Lidocaine, Pentazocine, Propranolol, Terbutaline.**

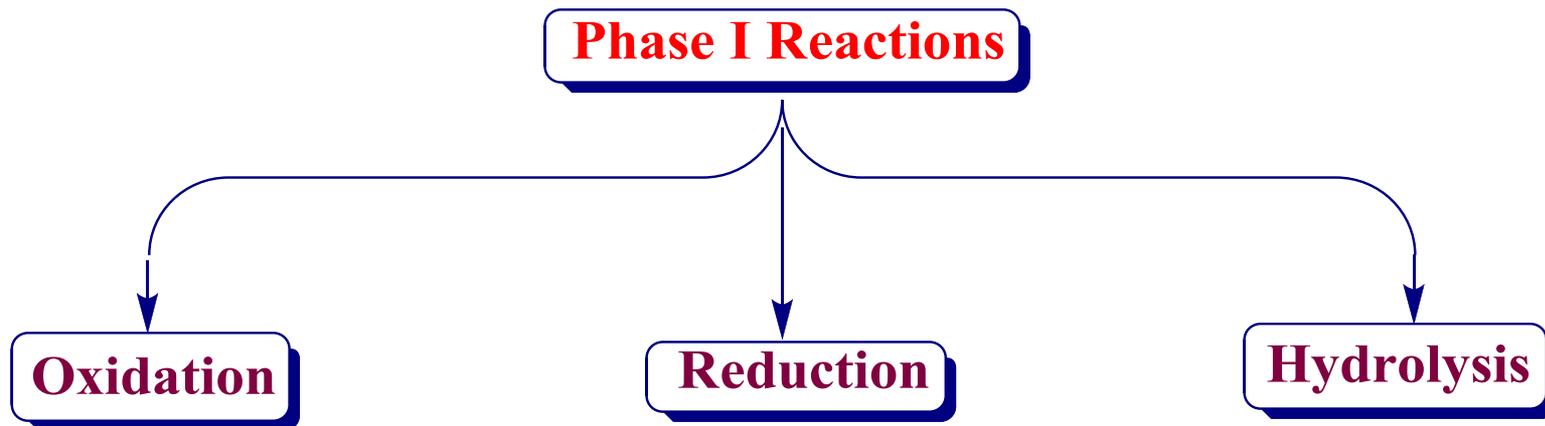
## Phase I Reactions

- The purpose of this phase is to introduce a polar functional group into the xenobiotic or drug molecule to increase its water solubility so that it can be easily excreted and /or conjugated and excreted.



This can be achieved by:

- 1- Direct introduction of the functional group (e.g., aromatic and aliphatic hydroxylation).
- 2- Modifying or "unmasking" existing functionality (e.g., hydrolysis of ester to yield a free COOH group).



## I. Oxidative Reactions

❑ Role of Cytochrome P-450 monooxygenases in oxidative biotransformation



- ❑ The enzyme systems carrying out this biotransformation are referred to as **mixed function oxidases (MFO)** or **monooxygenases** or **microsomal hydroxylase (non specific enzymes in liver)**.
- ❑ The reaction requires both molecular oxygen and the reducing agent **NADPH (Nicotinamide Adenosine Dinucleotide Phosphate)**.
- ❑ **MFO is made up of several components:**
  - 1. Cytochrome P-450** which is the most important component and is responsible for transferring an oxygen atom to the substrate **R-H**.
  - 2. Cofactors** supply the reducing equivalents (electrons) needed in the overall metabolic oxidation: **NADPH and NADH**.

- ❑ Twelve CYP gene families have been identified in humans,**
- ❑ Most of the drugs metabolizing enzymes are in CYP 1, 2, & 3 families.**
- ❑ CYPs have molecular weights of 45-60 kDa.**
- ❑ Frequently, two or more enzymes can catalyze the same type of oxidation.**
- ❑ CYP3A4 is very common to the metabolism of many drugs.**
- ❑ its presence in the GI tract is responsible for poor oral availability of many drugs**

- ❑ Cytochrome P-450 is found in high concentration in the liver, also present in other tissues like lung, kidney, intestine, skin, placenta and adrenal cortex.**
- ❑ Cytochrome P -450 is classified to several families given the Arabic numbers 1,2,3,.....up to 17.**
- ❑ Each family could exist in more than subfamily and given the letters A,B,C,D, .... e.g. CYP1A, CYP2A,...etc.**
- ❑ In case of the existence of more than one subfamilies, it is given the Arabic numbers 1,2,3,....., e.g. CYP3A4.**