Pharmacokinetics
Metabolism

Learning object

- **Know the processes involved in ADME of drugs**
- **Know how these processes may affect the action of xenobiotics**
- **Appreciate how these processes can affect the outcome of the treatment of patients with drugs**
- **Appreciate how differences in these processes between patients can affect therapy**
- **Know how these processes have been exploited to improve therapy**
- **Be able to exemplify the above**

BIOTRANSFORMATION (Metabolism)

- Chemical alteration of the drug in the body is called as **biotransformation**.

- It is needed to render

  Nonpolar (lipid-soluble) compounds

  ↓

  polar (Water soluble)

  ↓

  excreted in urine.

- Most Polar (hydrophilic drugs) e.g. Streptomycin

  ↓

  little biotransformed

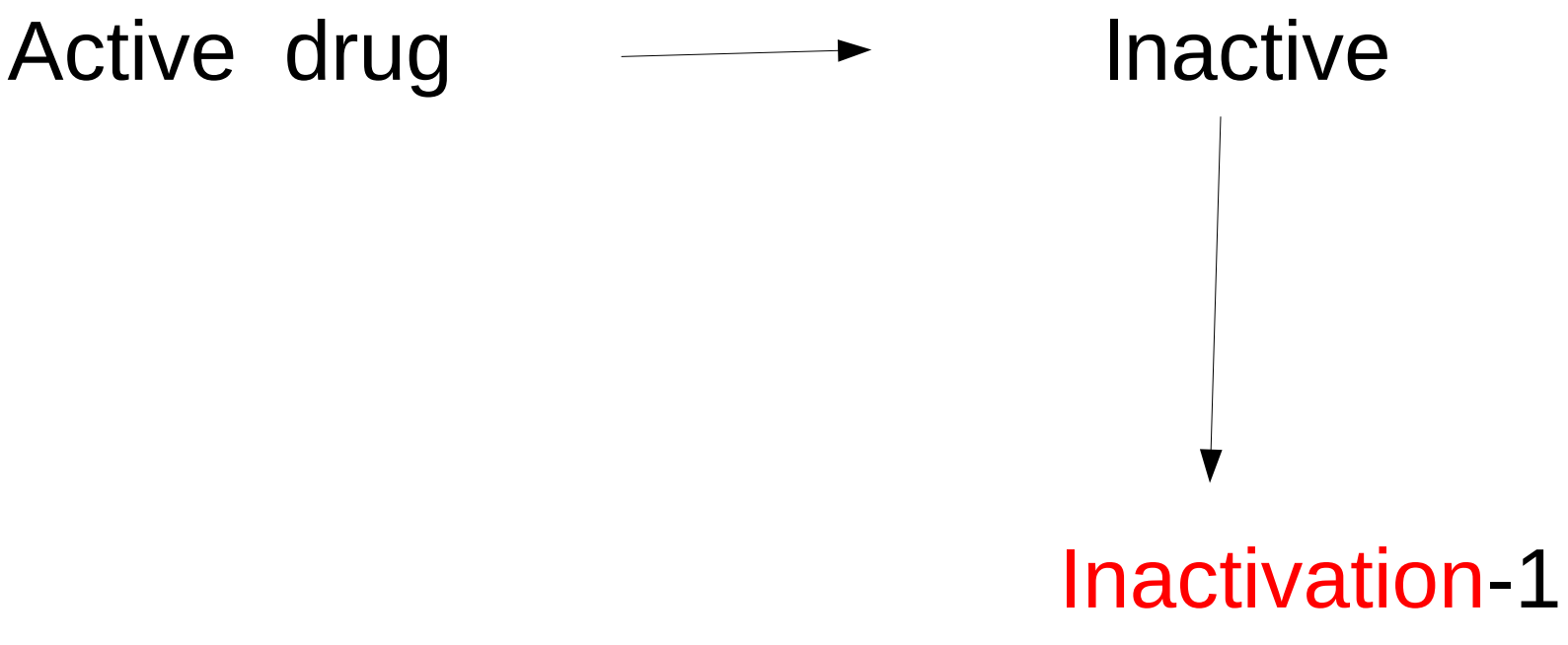
  ↓

  excreted unchanged.

- The primary site for drug metabolism is liver

- Others sites are:-
  - kidney
  - intestine
  - lungs
  - Plasma

- Biotransformation of drugs may lead to



- eg. ibuprofen, paracetamol

2. Active drug → Active metabolite

Eg.

- Morphine → Morphine-G glucuronide

  (Active) (active)

3. Inactive drug ⟶ Active drug

- eg. Prodrug such as:

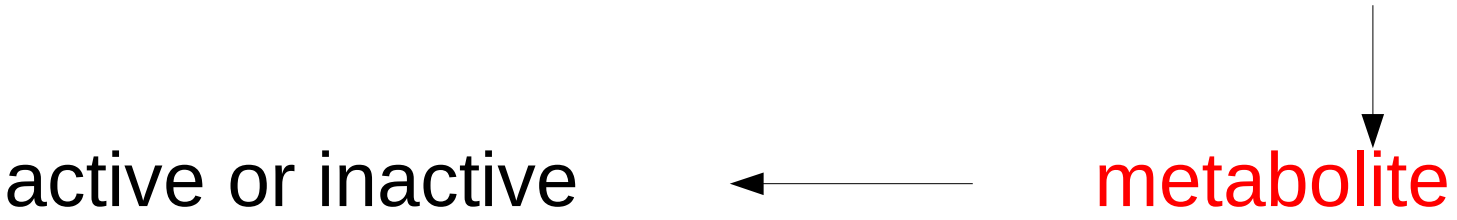
Levodopa ⟶ Dopamine

(Inactive) (Active)

- Advantages of prodrug over the active form
  - more stability,
  - better bioavailability
  - activated selectively at the site of action
  - less side effects and toxicity

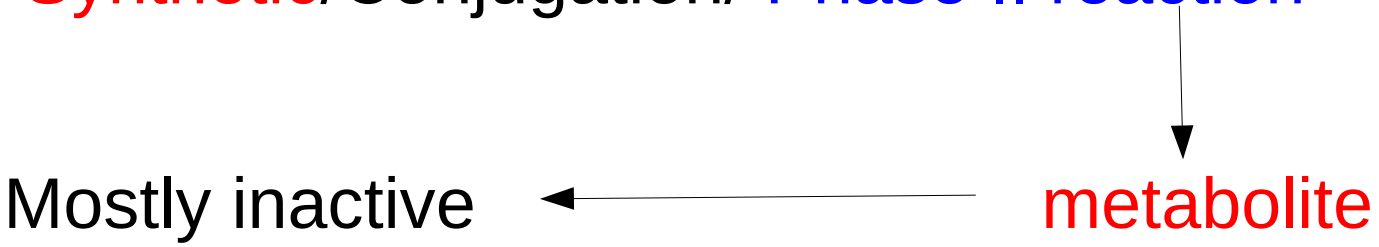
Classification of biotransformation reaction

I. Nonsynthetic/Phase I/Functionalization reactions



- 5 types
  - Oxidation
  - Reduction
  - Hydrolysis
  - Cyclization
  - Decyclization

II. Synthetic/Conjugation/ Phase II reaction



- **VII Types:**

  (i) Glucuronide conjugation

  (ii) Acetylation

  (iii) Methylation

  (iv) Sulfate conjugation

  (v) Glycine conjugation

  (vi) Glutathione conjugation

  (vii) Ribonucleoside/nucleotide synthesis

Nonsynthetic reactions

(i) Oxidation: This reaction involves addition of oxygen/negatively charged radical or removal of hydrogen/positively charged radical.

- Eg. Barbiturates, phenothiazines, imipramine, ibuprofen, paracetamol

(ii) Reduction: This reaction is the converse of oxidation

- Involves cytochrome P-450 enzymes working in the **opposite direction**.

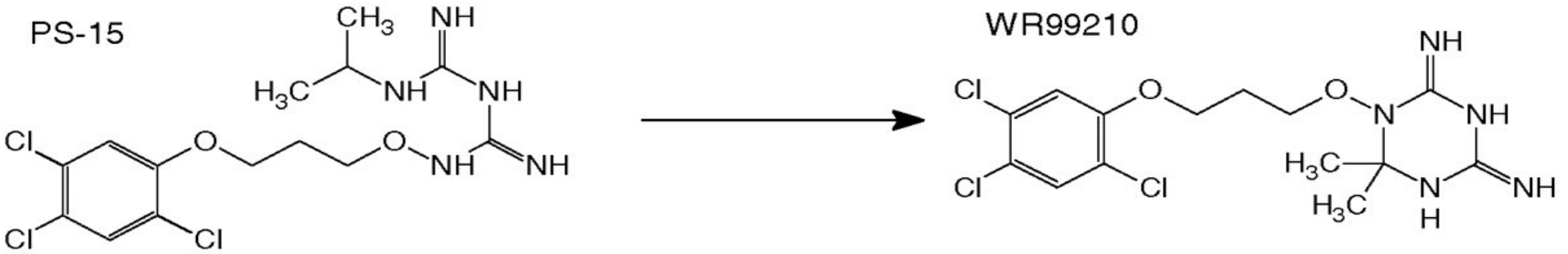
- Eg. Chloralhydrate, chloramphenicol, halothane, warfarin.

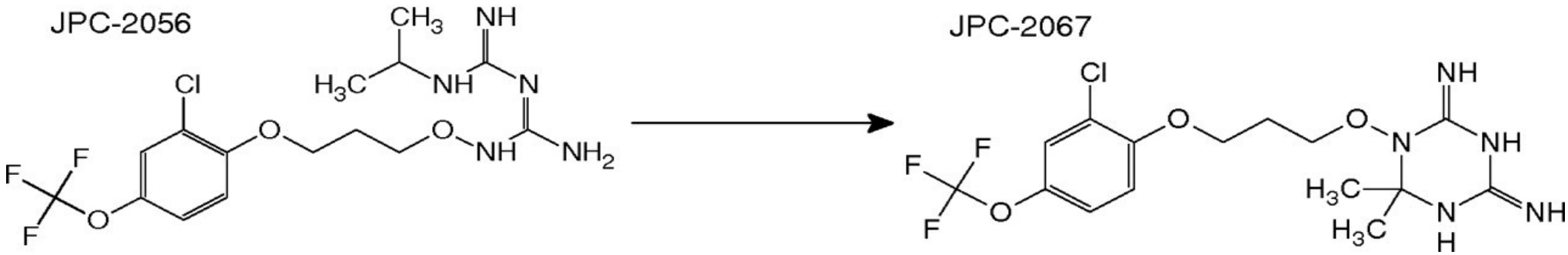
(iii) **Hydrolysis** This is cleavage of drug molecule by taking up a molecule of water.

Hydrolysis occurs in liver, intestines, plasma and other tissues.

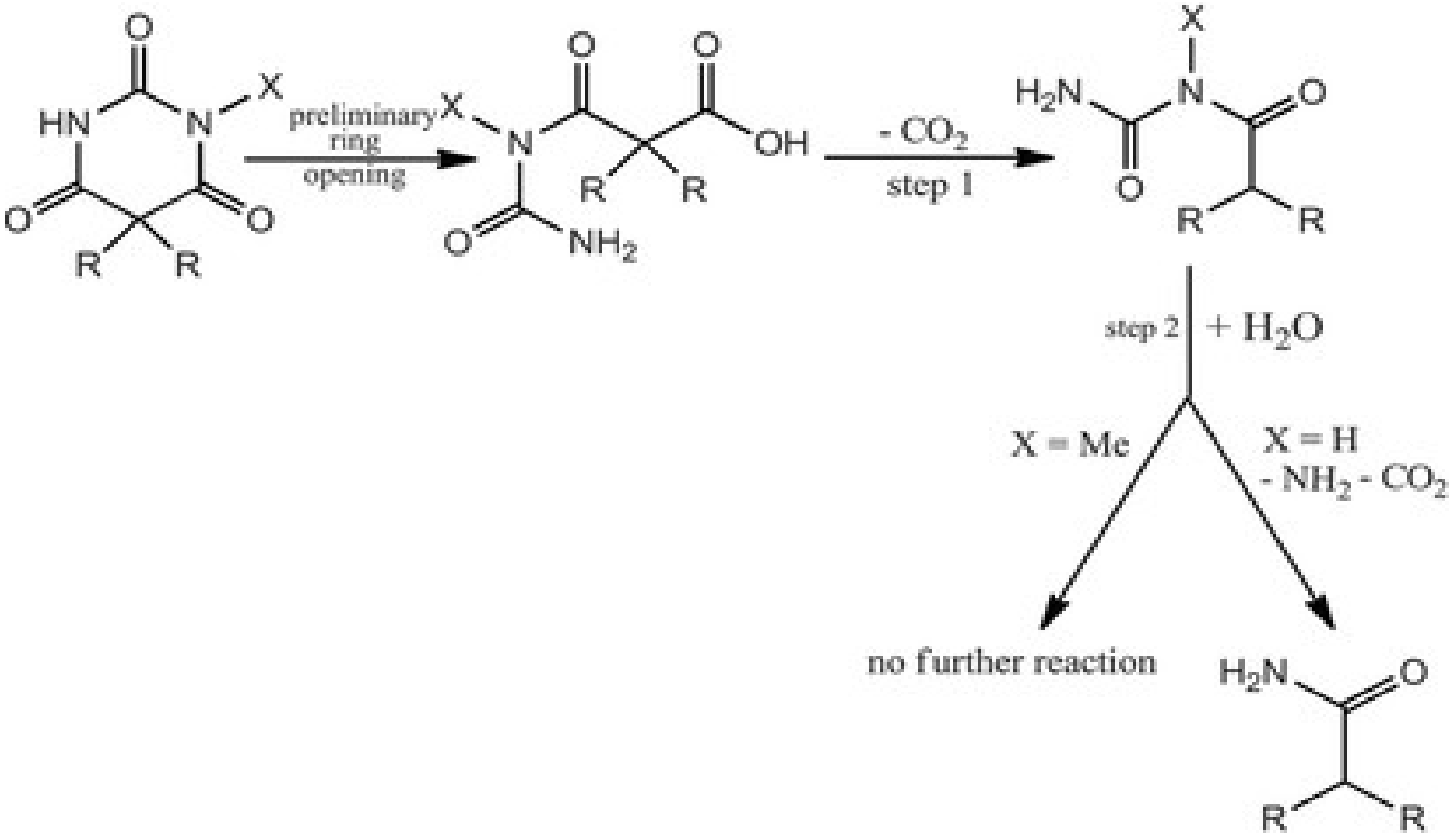
- Eg: Procaine, lidocaine, procainamide, aspirin.

(iv) **Cyclization**: This is formation of ring structure from a straight chain compound e.g. Proguanil.





(v) **Decyclization**: This is opening up of ring structure of the cyclic drug molecule e.g. Barbiturates, phenytoin.



Phase II: Synthetic reactions

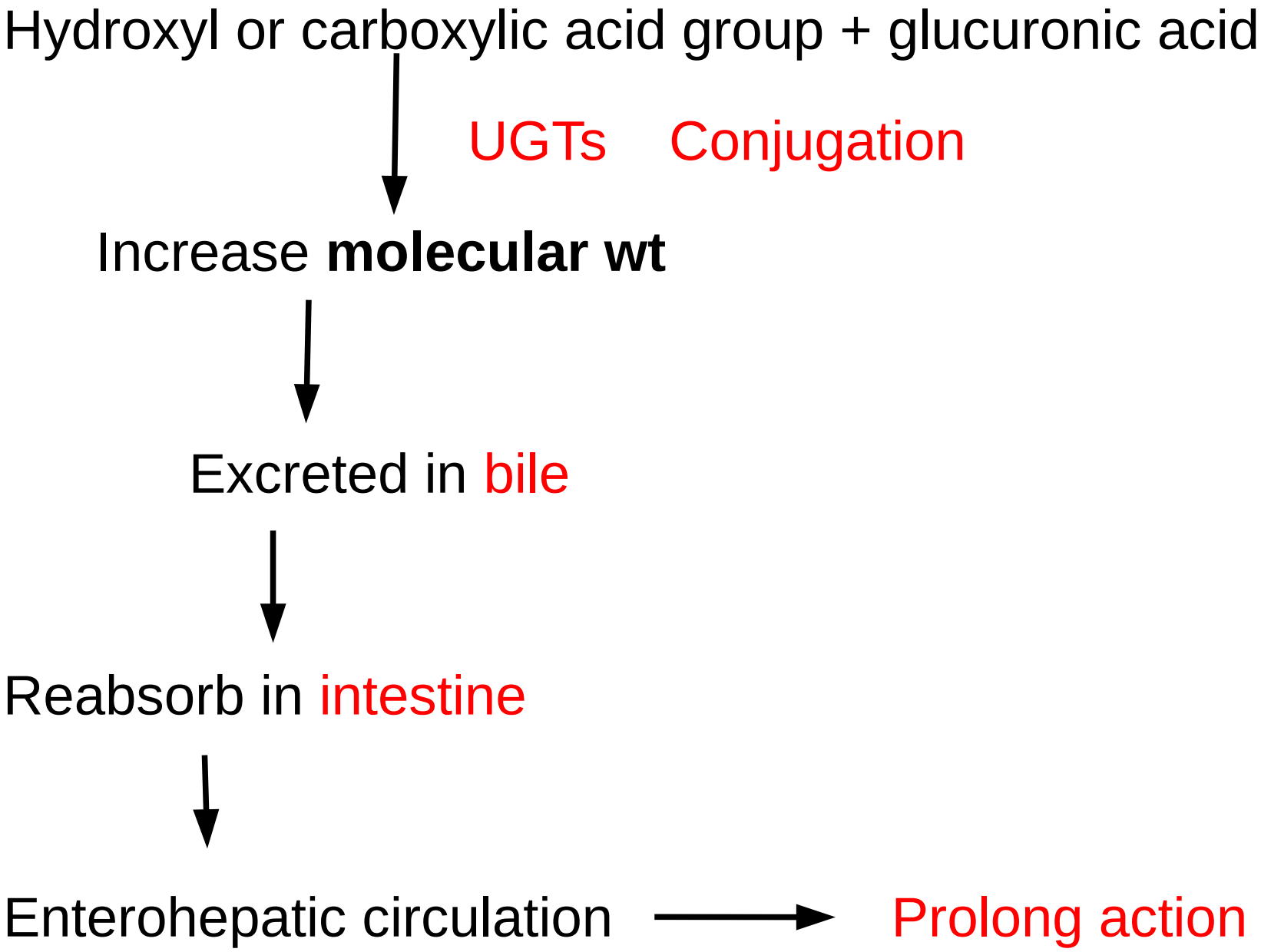
- These involve conjugation of the drug or its phase I metabolite **with an endogenous substrate** to form a polar highly ionized organic acid which is easily excreted in urine or bile.

1. Glucuronide conjugation

- This is the most important synthetic reaction carried out by a group of UDP-glucuronosyl transferases (UGTs).

- Compounds with a hydroxyl or carboxylic acid group are easily conjugated with glucuronic acid which is derived from glucose.

- Eg. chloramphenicol, aspirin, paracetamol, morphine, metronidazole.


Hydroxyl or carboxylic acid group + glucuronic acid
UGTs Conjugation
Increase molecular wt
Excreted in bile
Reabsorb in intestine
Enterohepatic circulation
Prolong action

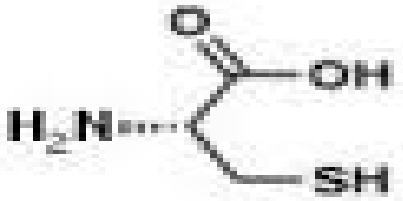
(ii) Acetylation

- Compounds having amino or hydrazine residues are conjugated with the help of acetyl coenzyme-A e.g. sulfonamides, isoniazid.

- It shows genetic polymorphism (slow and fast acetylators).

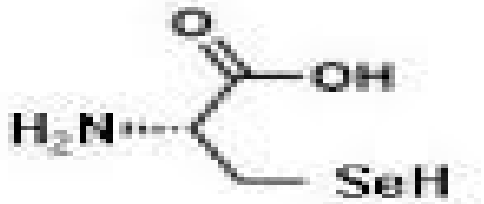
(iii) Methylation

- The amines and phenols group of drugs can be methylated
- Methionine and cysteine acting as methyl donors e.g. histamine.

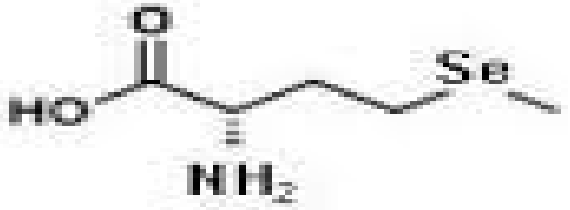


Cysteine

Methionine



Se-cysteine



Se-methionine

(iv) Sulfate conjugation

- The phenolic compounds and steroids are sulfated by sulfotransferases (SULTs)

- e.g. chloramphenicol, sex steroids

(v) Glycine conjugation

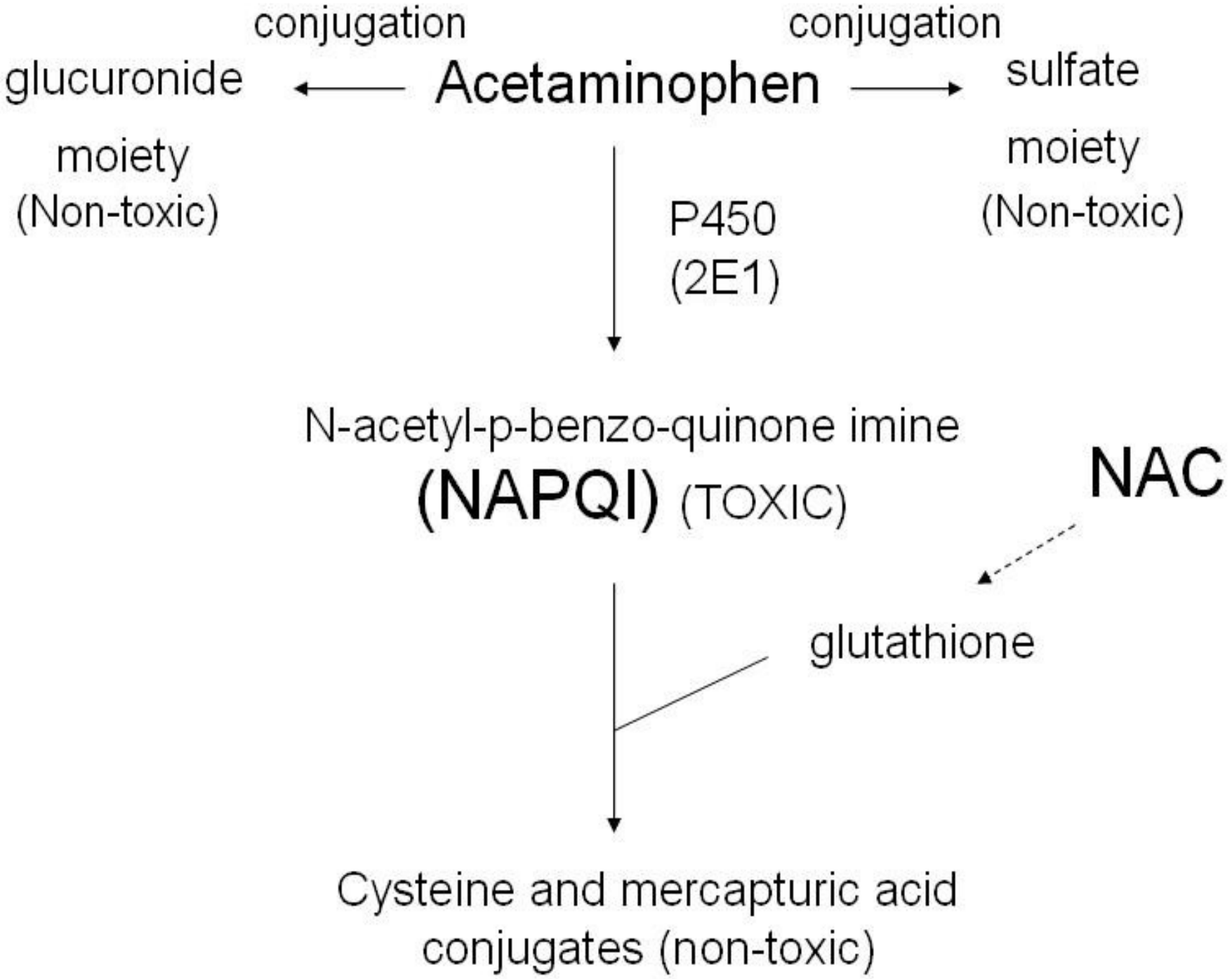
- Salicylates and other drugs having carboxylic acid group are conjugated with glycine,

- It is not a major pathway of metabolism.

(vi) Glutathione conjugation

- Highly reactive quinone or epoxide intermediates conjugate with glutathione ↓ **mercapturate**.

- It serves to inactivate highly reactive quinone or epoxide intermediates formed during metabolism of certain drugs e.g. paracetamol


conjugation
conjugation
glucuronide
Acetaminophen
sulfate
moiety
(Non-toxic)
moiety
(Non-toxic)
P450
(2E1)
N-acetyl-p-benzo-quinone imine
(NAPQI) (TOXIC)
NAC
glutathione
Cysteine and mercapturic acid
conjugates (non-toxic)

large amount of quinine or epoxide intermediate

↓

Glutathione supply falls short

↓

Formation of toxic adducts with tissue constituents

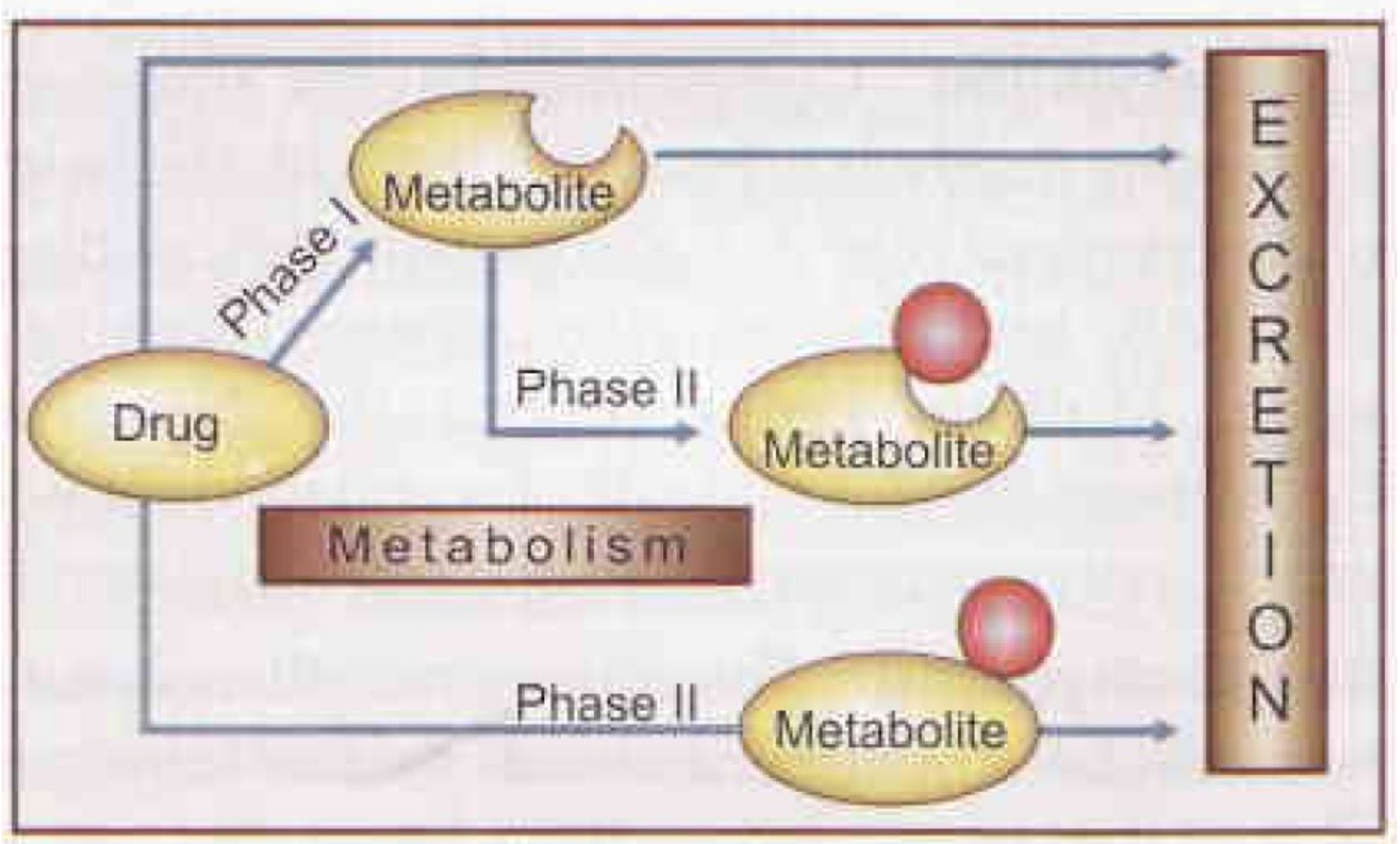
↓

Tissue damage.

(vii) Ribonucleoside/nucleotide synthesis

- This pathway is important for the activation of many purine and pyrimidine antimetabolites used in cancer chemotherapy.

Simultaneous or sequiential metabolism of drugs



Drug Metabolizing Enzymes

- Microsomal enzymes
- Non-microsomal enzymes

Microsomal enzymes

- **Location**: smooth endoplasmic reticulum, primarily in liver, also in kidney, intestinal mucosa and lungs.

- Eg. of ME
  - Monooxygenases,
  - cytochrome P 450,
  - glucuronyl transferase etc.

- ME catalyse
  - oxidations,
  - reductions,
  - hydrolysis
  - and glucuronide conjugation

- Microsomal enzymes are inducible by
  - drugs
  - diet.

Non microsomal enzymes

- **Location**: Cytoplasm, mitochondria of Liver & Plasma.

Eg of NME

- Flavoprotein oxidases,
- esterases,
- amidase
- And conjugases.

- Reaction catalysed are:
  - Some oxidations and reductions,
  - many hydrolytic reactions
  - and all conjugations excep: glucuronidation.

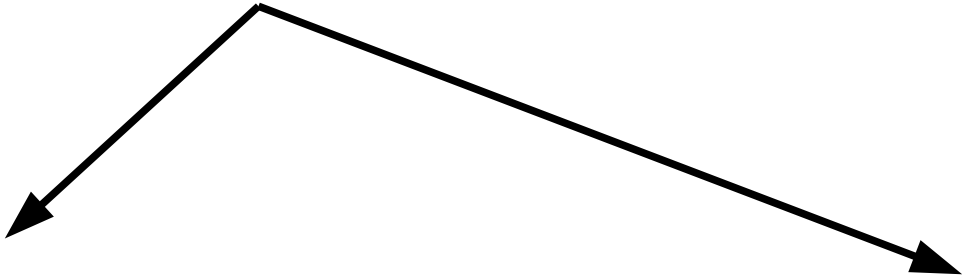
- The **nonmicrosomal enzymes** are

  - not inducible

  - but many show genetic polymorphism.

- Both microsomal and nonmicrosomal enzymes are deficient in the newborn

more susceptible to many drugs e.g. chloramphenicol, opioids.



Low dose of drug used usual dose prod toxicity

INHIBITION OF DRUG METABOLISM

- 2 types

  1. Competetive enzyme inhibition
  2. Non competative enzyme inhibition

- One drug can competitively inhibit metabolism of another if it utilizes the same enzyme or cofactors.

- Occurs in a dose related manner and can precipitate toxicity of the object drug.

- Metabolism of **drugs with high hepatic extractionis**

↓

dependent on liver blood flow.

- eg. Propranolol decreases hepatic blood flow.

↓

Reducese rate of lidocaine metabolism

MICROSOMAL ENZYME INDUCTION

Many drugs, insecticides and carcinogens interact with DNA

↓

Increase the synthesis of microsomal enzyme protein (cytochrome P-450 and glucuronyl transferase).

↓

Increases rate of metabolism.

- Eg. Phenobarbiton - inducers of Cyp3A and Cyp2D6

↓

Increase the rate of metabolism by 2-4 fold.

- Polycyclic hydrocarbons like 3-methyl cholanthrene and benzopyrene found in

  - cigarette smoke
  - charcoal boiled meat
  - and industrial pollutants

↓

Induce CYP1A isoenzymes.

- Other **important enzyme inducers are**:
  - Chloral hydrate,
  - phenylbutazone,
  - griseofulvin.

Consequences of microsomal enzyme induction

1. Decrease intensity or duration of action of drugs that are inativated by metabolism.

Eg. Oral contraceptives

2. Increase intensity of action of drugs that are activeted by metabolism.

Eg. Acute paracetamole toxicity

3. Tolerance: In case of autoinduction.

Eg. Carbamazapine.

4. Precipitation of acute intermittent porphyria- disease in which an important part of hemoglobin, called heme, is not made properly.

5. Interfere with adjustment of dose of another drug.

6. Interfere with chronic toxicity testing in animal.

7. It affect metabolism of other drugs eg.

1. Phenytoin
2. Warfarine
3. oral contraceptive
4. chloramphenicol etc.

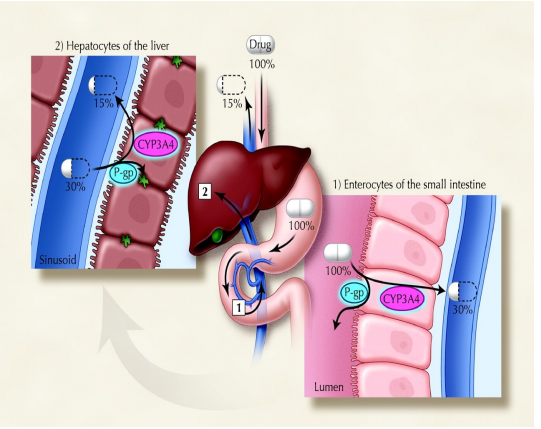
Summary

- Decrease the intensity
- Increases intensity of drug
- Tolerance
- Prophyria
- Interfere with adjustment of dose
- Interfere with chronic toxicity testing

FIRST PASS (PRESYSTEMIC) METABOLISM

- **Definition:**

  Metabolism of drug during its passage from site of absorption into systemic circulation.



1. Orally administered drug

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Come in contact with intestinal & liver enzyme

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Undergoes first pass metabolism

2. It is also occure in skin & lungs

lower magnitude

Table 3.1: Extent of first pass metabolism of some important drugs

Low	*Intermediate*	*High*	
		not given orally	*high oral dose*
Phenobarbitone	Aspirin	Isoprenaline	Propranolol
Phenylbutazone	Quinidine	Lidocaine	Alprenolol
Tolbutamide	Desipramine	Hydrocortisone	Verapamil
Theophylline	Nortriptyline	Testosterone	Salbutamol
Pindolol	Chlorpromazine		Glyceryl trinitrate
Isosorbide mononitrate	Pentazocine		Morphine
	Metoprolol		Pethidine

Attributes of drugs with high first pass metabolism:

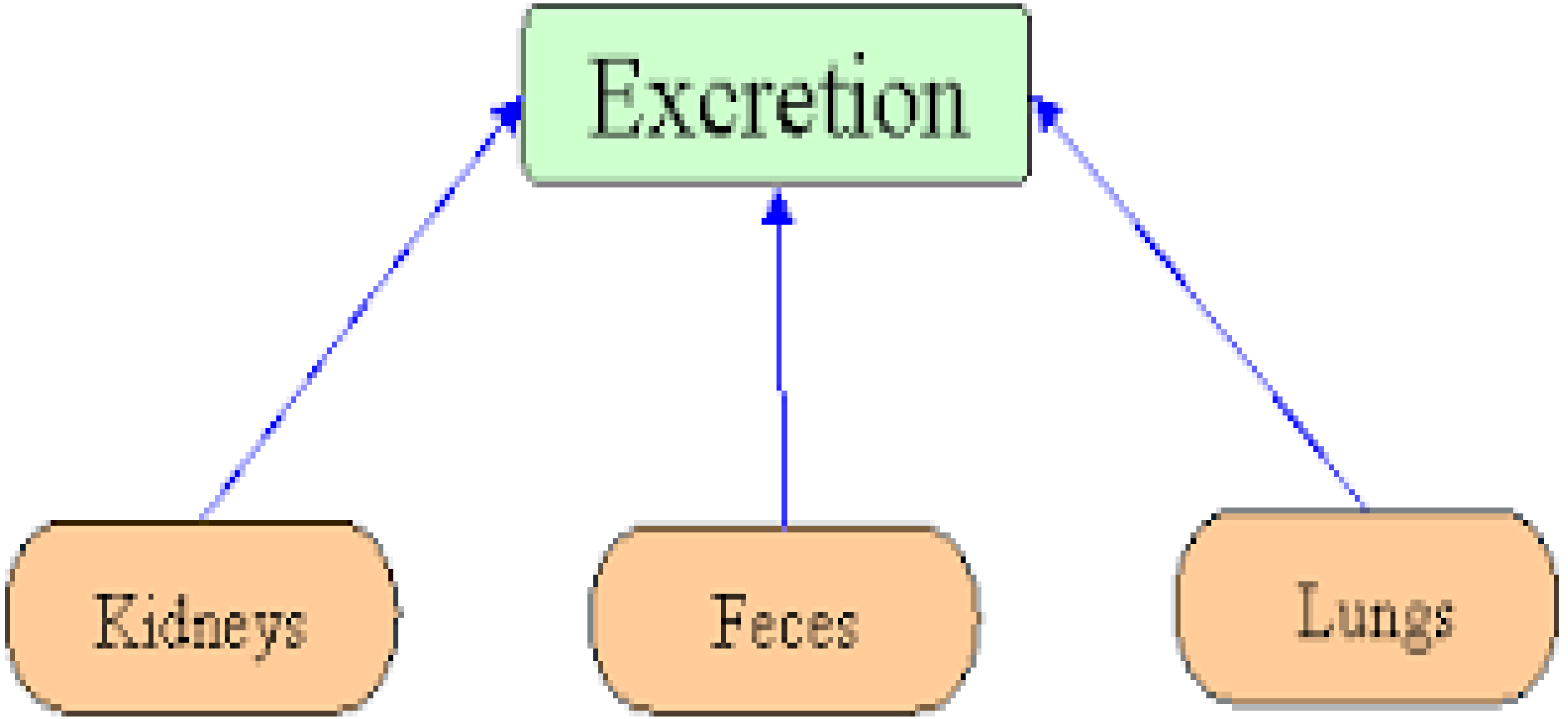
(a) **Higher oral dose** than sublingual or parenteral dose.

(b) **Marked individual variation** in the oral dose due to differences in the extent of first pass metabolism.

(c) **Oral bioavailability is apparently increased** in patients with severe liver disease.

(d) Oral bioavailability of a drug is increased

if another drug competing with it for first pass metabolism (e.g. Chlorpromazine and propranolol).


Excretion
Kidneys
Feces
Lungs

Excretion of drug

- Drug can be excreted in their unchanged form or as metabolites by
  - Kidney
  - lungs
  - intestine

- And to lesser extend by the
  - sweat
  - salivary
  - and mammary glands.

- **More water soluble** a drug or meatabolite

  ↓

  More efficiently it is elimineted from the body.

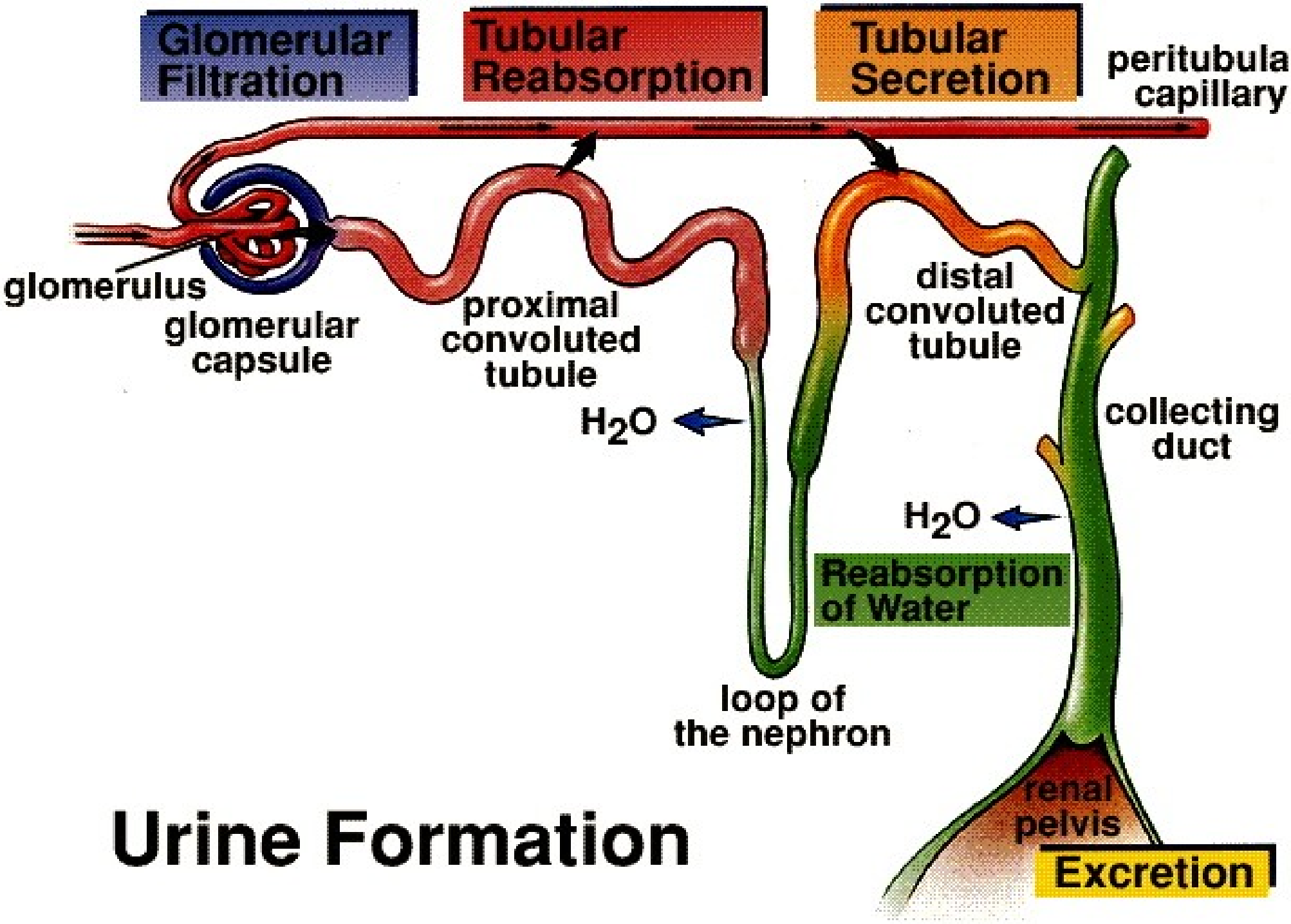
- **<u>Renal excretion:</u>**

  3 major process involve in the excretion of drugs by the kidney

  1. Glomerular filtration

  2. Tubular secreation

  3. Tubular reabsorption



Urine Formation

- Glomerular filtration & Tubular secreation

↓

Remove the drug from plasma

- Tubular reabsorption

↓

Retain drug in plasma

- The net excretion of drug depends therfore on sum total of three processes.

Glomerular filtration

- By this process drug molecules diffuse out of the blood --- **filtrating** the glomeruli of the nephron -- passes into the tubuls of the kidney.

- Drug with **molecular wt** of 500 or less

Unimpeded diffusion of the drug

Drug with mol wt 5000-69000

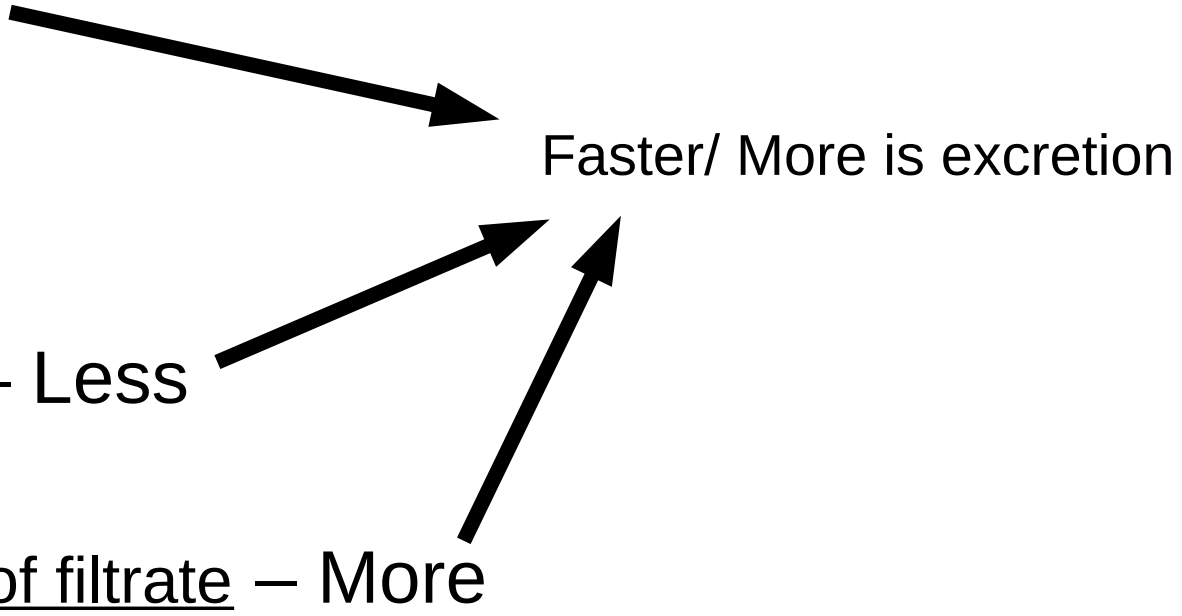
partially impeded diffusion.

Result:

- All the drug which are **not protein bound** appear in the glomerular filtrate.

- Glomerular filtrate - 120 L / day
- But daily urine volume - 1-2 % of this volume.
- **Factors influence renal excretion by glomerular filatration**:

1. Molecular size – small
2. Plasma protein binding– Less
3. Renal flow and volume of filtrate – More



Tubular secretion

- **Proximal renal tubul** - actively secreate certain drug and transporting them from the blood stream ⟶ the tubular fluid.

- **Acidic drugs** eg. salicylates & penicilline.
- **Basic drugs** eg. Adrenaline & noradrenaline.

- Many drugs which are secreted by tubuls are also filtered by the glomeruli

Having very short duration of action

- Eg Penicilline

How to overcome short duration of action of penicillin due to tubular secreation:

- Since tubular secretion required energy, it can be inhibited by certain drug.

- Eg. **Probenicide** is often combined with **penicillin**

↓

inhibit active secretion process of penicilline.

↓

Prolonging the **duration of action** of penicilline

Tubular reabsorption

- **Location**: Almost throughout renal tubul.
- Reabsorption retained drug back into the blood.
- Similar to absorption from the gut wall.
- Drug molecule passively transported through tubular reabsorption.

Enhancing the excretion of drug in case of overdosing and poisoning

Drug existing in the non ionized **lipid soluble state**

↓

completely reabsorbed

- **Weakly acidic drug** e.g salicylate excreted better if PH become alkaline and vice versa.

- **Acidification or alkalization** of urine with drug like ascorbic acid or sodium bicarbonate

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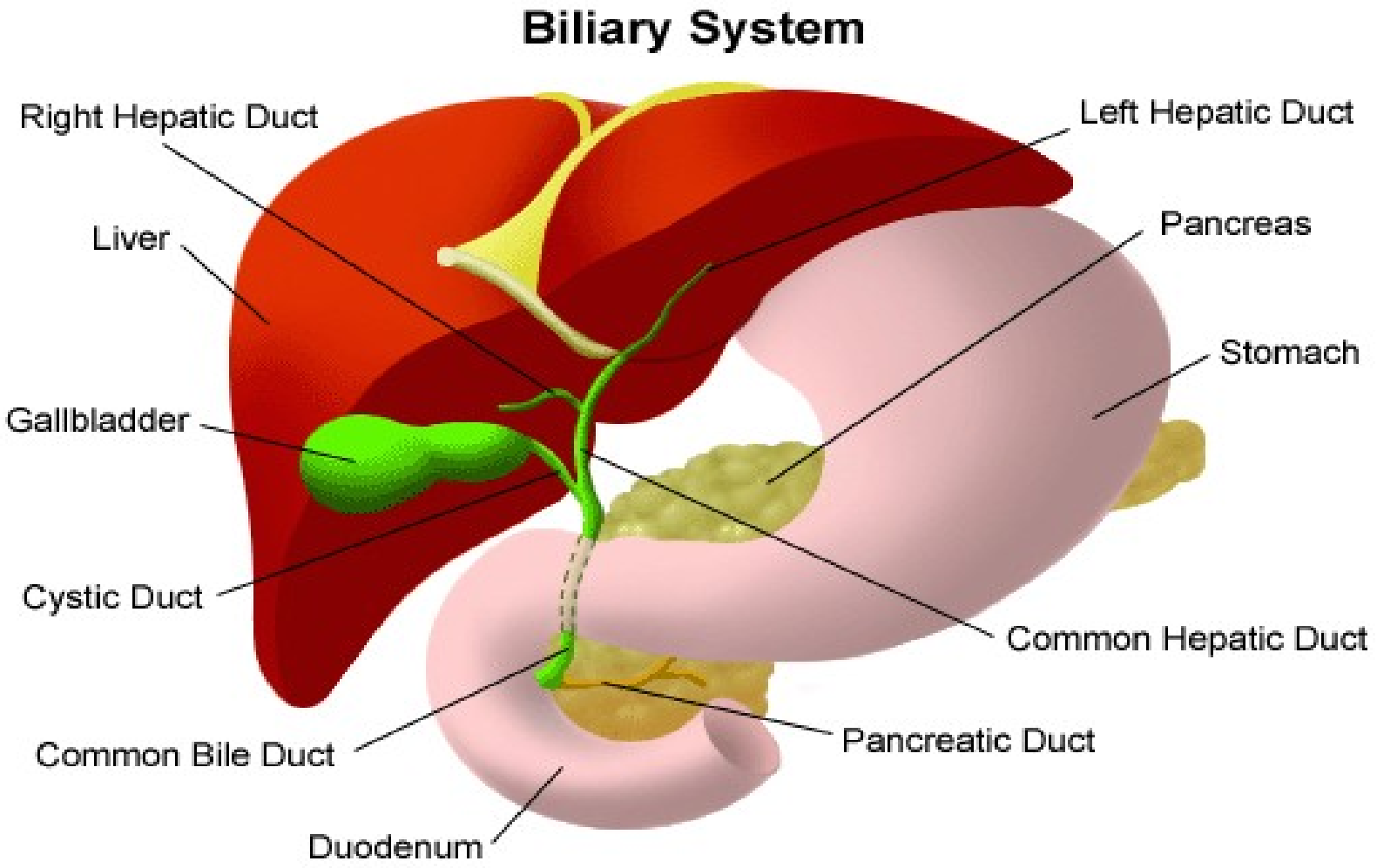
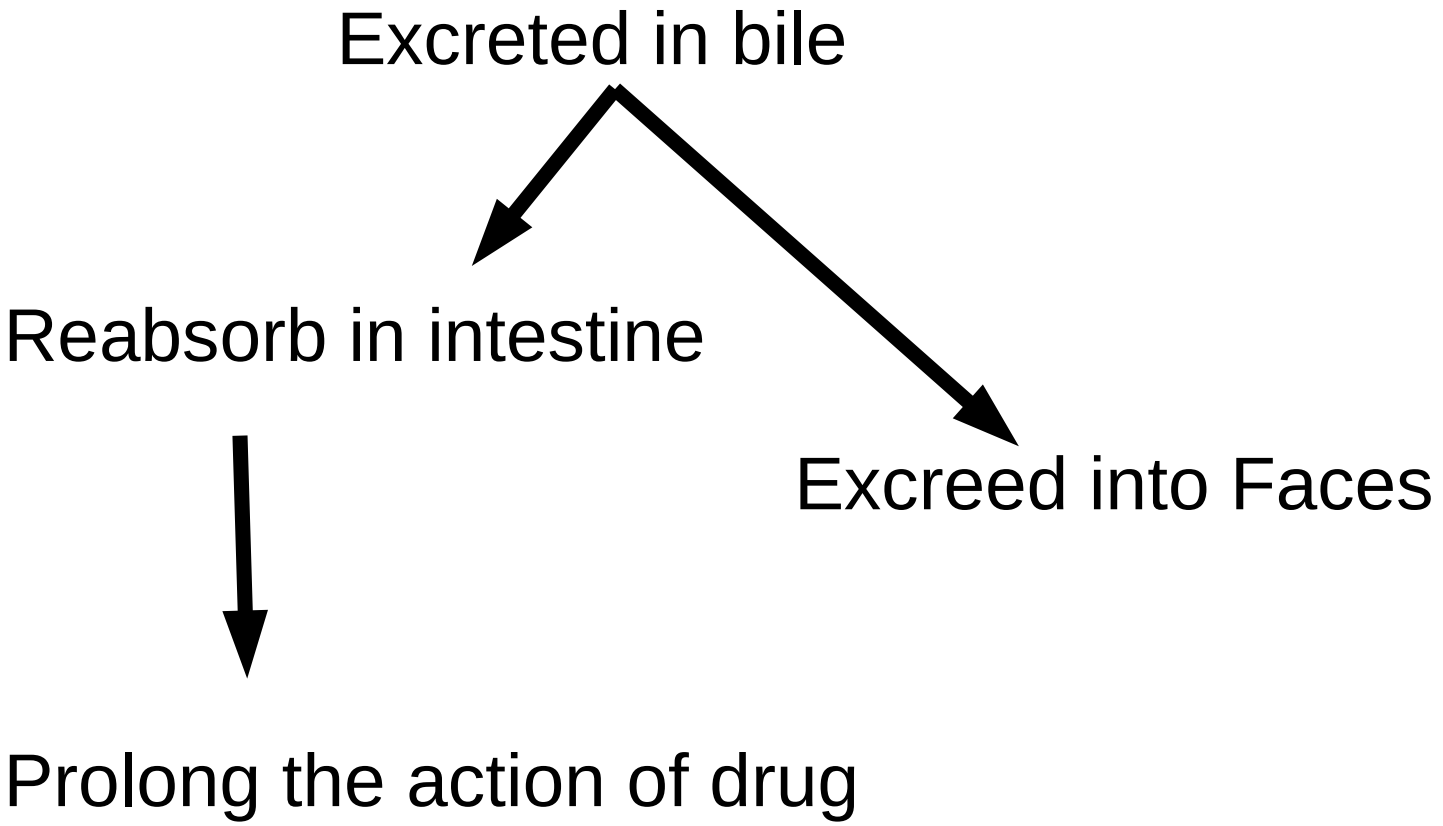
used to hasten the excretion of drug in case of **overdosing or poisoning**.

Biliary excretion

- **Minor rout of elimination** for unmetabolized drug.



- **Major rout of elimination** for metabolites eg. Water soluble conjugates like glucoronides.


Excreted in bile
Reabsorb in intestine
Excreed into Faces
Prolong the action of drug

Pulmonary excretion

- Important for gaseous and volatile liquid like general anasthetics.

- Blood stream → Alveolar membrane

Expired air

- **Breathometer** is often used to estimate the blood level of alcohol which correlate with degree of intoxication.

Excretion in sewat, saliva, milk and gastric juice

- Occur by passive diffusion of **non-ionized** form of drug.

- Some are transported to suckling infant in **breast milk**

Drug used by **breast feeding** mother should be restricted to minimum.