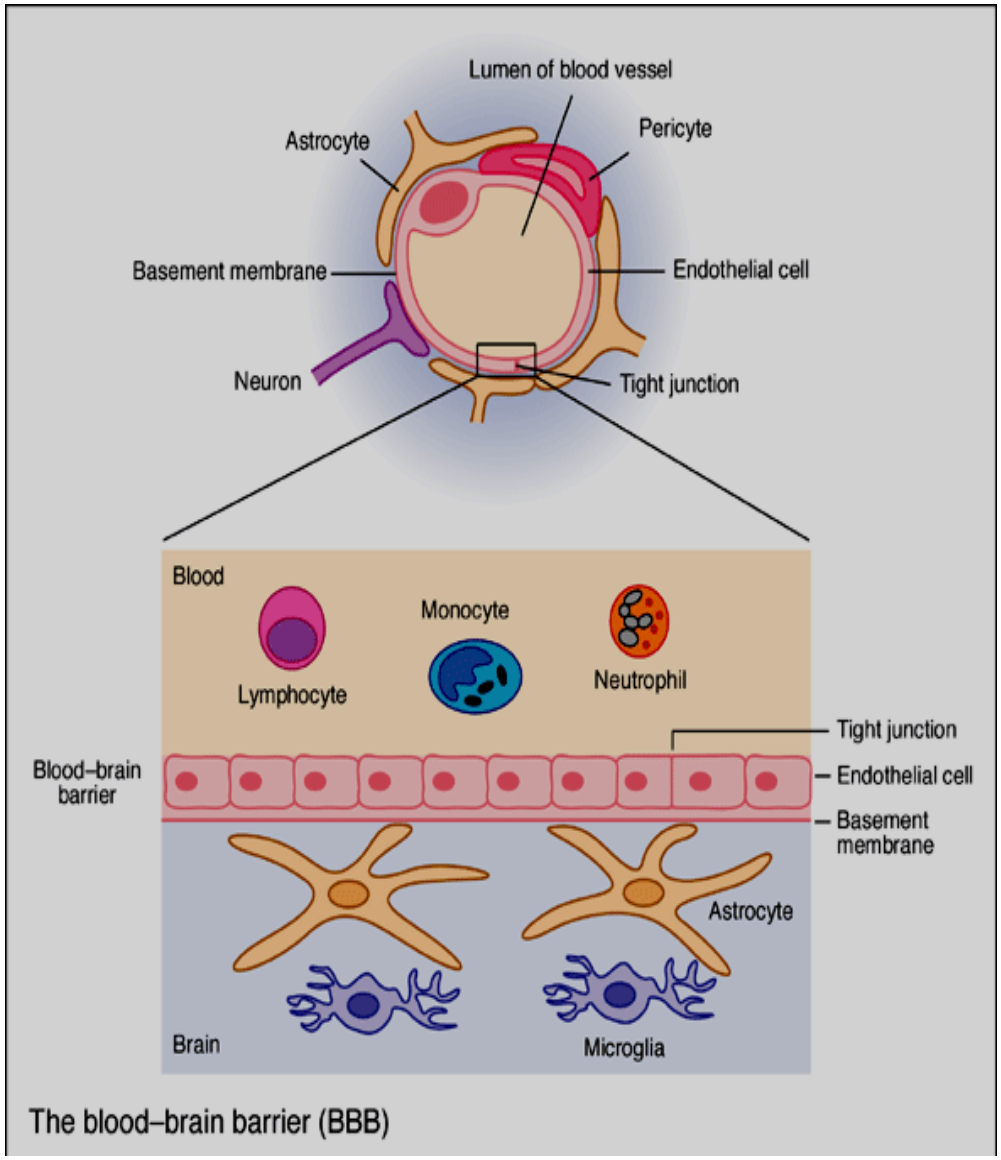
II) On the other hand, brain capillaries seem to have impermeable walls restricting the transfer of molecules from blood to brain tissue.

- Lipid soluble compounds can be readily transferred but the transfer of polar substances is severely restricted.

- This is the basis of the "blood-brain" barrier.

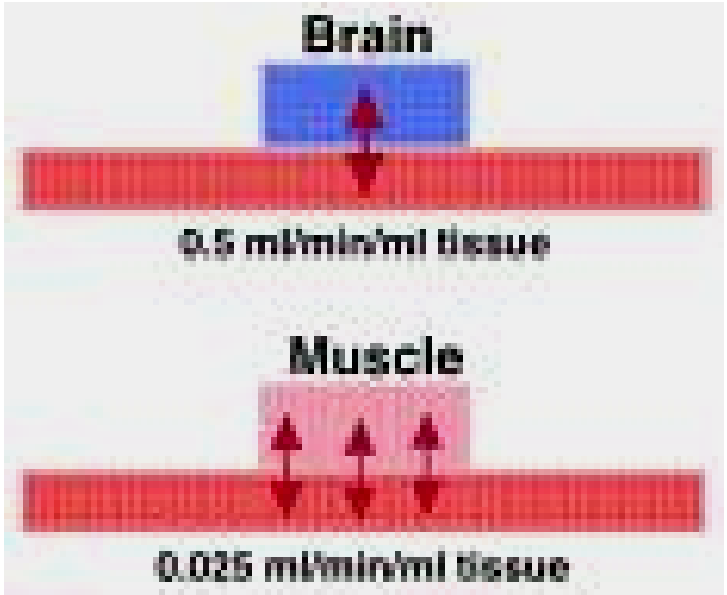


The blood–brain barrier (BBB)

Factors affecting drug distribution (Cont.):

2. Blood perfusion rate:

- The rate at which blood perfuses to different organs varies widely:



Blood Perfusion Rate		
Organ	**Perfusion Rate (mL/min/mL of tissue)**	**Percent of cardiac output (CO)**
Bone	0.02	5
Brain	0.5 - 0.55	14 - 15
Fat	0.01 - 0.03	2 - 4
Heart	0.6 - 0.7	4
Kidneys	4.0 - 4.5	22 - 24
Liver	0.8 - 0.95	25 - 27
Muscle	0.025 - 0.030	15
Skin	0.04 - 0.05	5 - 6

Factors affecting drug distribution (Cont.):

- The rate at which a drug reaches different organs and tissues will depend on the blood flow to those regions.
- Equilibration is rapidly achieved with heart, lungs, liver, kidneys and brain where blood flow is high.
- Skin, bone, and depot fat equilibrate much more slowly.

Factors affecting drug distribution (Cont.):

B. Extent of Distribution

1.Lipid Solubility:

- Lipid solubility will affect the ability of the drug to bind to plasma proteins and to cross lipid membrane barriers.

- Very high lipid solubility can result in a drug partitioning into highly vascular lipid-rich areas. Subsequently these drugs slowly redistribute into body fat where they may remain for long periods of time.

Factors affecting drug distribution (Cont.):

2. Effects of pH:

- The rate of movement of a drug out of circulation will depend on its degree of ionization and therefore its pKa.
- Changes in pH occuring in disease may also affect drug distribution. For example, blood becomes more acidic if respiration is inadequate.

3.Plasma protein binding:

- Extensive plasma protein binding will cause more drug to stay in the central blood compartment. Therefore drugs which bind strongly to plasma protein tend to have lower volumes of distribution. (↑ protein binding = ↓ V)

Factors affecting drug distribution (Cont.):

- Albumin comprises 50 % of the total proteins binds the widest range of drugs. Acidic drugs commonly bind to albumin, while basic drugs often bind to α1-acid glycoproteins and lipoproteins.
- ***Forces involved:***

- Groups on the protein molecules that are responsible for **electrostatic interactions** with drugs include:
  - NH3+ of lysine
  - N- terminal amino acids
  - NH2+ of histidine
  - S- of cysteine
  - COO- of aspartic and glutamic acid residues.

Factors affecting drug distribution (Cont.):

- In order to achieve stable complexes, the initial electrostatic attraction is reinforced by **van der Waal's forces** and **hydrogen bonding**.

What is the effect of protein binding on drug action?

1. Extensive plasma protein binding will decrease the amount of absorbed drug (decrease peak plasma level).

2. Elimination of a highly bound drug may be delayed. Since the concentration of free drug is low, drug elimination by metabolism and excretion may be delayed. This effect is responsible for prolonging the effect of the drug digoxin.

Factors affecting drug distribution (Cont.):

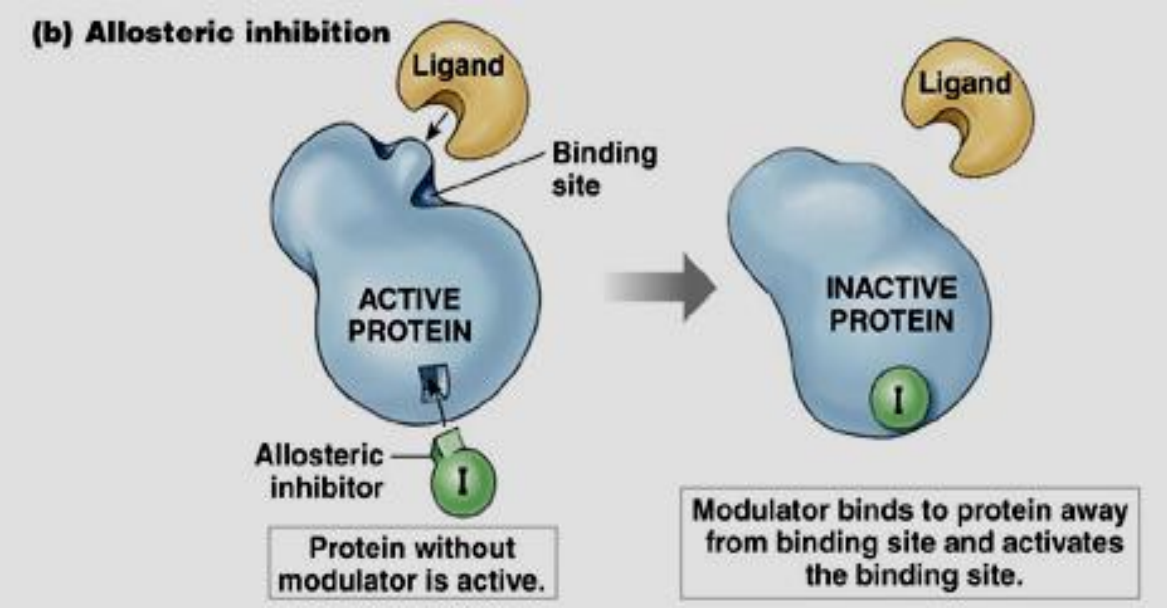
3. Changes in the concentration of plasma proteins will influence the effect of a highly bound drug.

A low plasma protein level may occur in:

- old age
- malnutrition
- illness such as liver disease (remember that most plasma proteins are made in the liver), or chronic renal failure where there is excessive excretion of albumin.

In each case the result is a smaller proportion of drug in bound form and more free drug in the plasma. The greater amount of free drug is able to produce a greater therapeutic effect and reduced drug dosages may be indicated in these cases.

Factors affecting drug distribution (Cont.):



4. There may be competition between drugs, in which agents that are bound very tightly, such as coumarin anticoagulants, are able to displace less tightly bound compounds from their binding sites.

Factors affecting drug distribution (Cont.):

- In general, plasma protein binding is reversible and obeys the law of mass action:

(free drug) + (albumin) $\underset{k_2}{\overset{k_1}{\rightleftharpoons}}$ **(drug-albumin complex)**

where k1 and k2 are the association and dissociation rate constants, respectively.

At equilibrium: $$K_D = \frac{k_2}{k_1} = \frac{[\text{free drug}] \times [\text{albumin}]}{[\text{drug-albumin complex}]}$$

- where KD is the equilibrium dissociation constant. It is a measure of the affinity of the drug for albumin:

Factors affecting drug distribution (Cont.):

- The lower the KD ⟶ the higher the affinity.
- The higher the KD ⟶ the lower the affinity.
- As the concentration of drug increases in plasma, the percent that is bound will decrease.

Factors affecting drug distribution (Cont.):

4. Tissue drug binding (tissue localization of drugs):

- In addition to plasma protein binding, drugs may bind to intracellular molecules.
- The affinity of a tissue for a drug may be due to: binding to tissue proteins or to nucleic acids, or in the case of adipose tissue, dissolution in the lipid material.

e.g. The concentration of chloroquine in the liver is due to the binding of the drug to DNA.

e.g. Barbiturates distribute extensively into adipose tissue, primarily because of their high lipid solubility.

e.g. Tetracyclines bind to bone thus should be avoided in young children or discoloration of permanent teeth may occur.

Factors affecting drug distribution (Cont.):

Other distribution considerations

1.Weight considerations:

A- Body composition of the very young and the very old may be quite different from 'normal', that is the average subject in whom the parameter values may have been originally determined.

B- Another group of patients in which body composition may be greatly altered from `normal' is the obese. These patients have a higher proportion of adipose tissue and lower percentage of water.

Thus for drugs which are relatively polar, volume of distribution values may be lower than normal.

For example the apparent volume of distribution of antipyrine is 0.62 l/kg in normal weight subjects but 0.46 l/kg in obese patients.

Other drugs such as digoxin and gentamicin are also quite polar and tend to distribute into water rather than adipose tissue.

Drug metabolism:

- **Metabolism is defined as:** The irreversible biotransformation of drug in the body → typically involves making it more polar to enhance renal excretion

- Drug metabolism often converts lipophilic chemical compounds into:

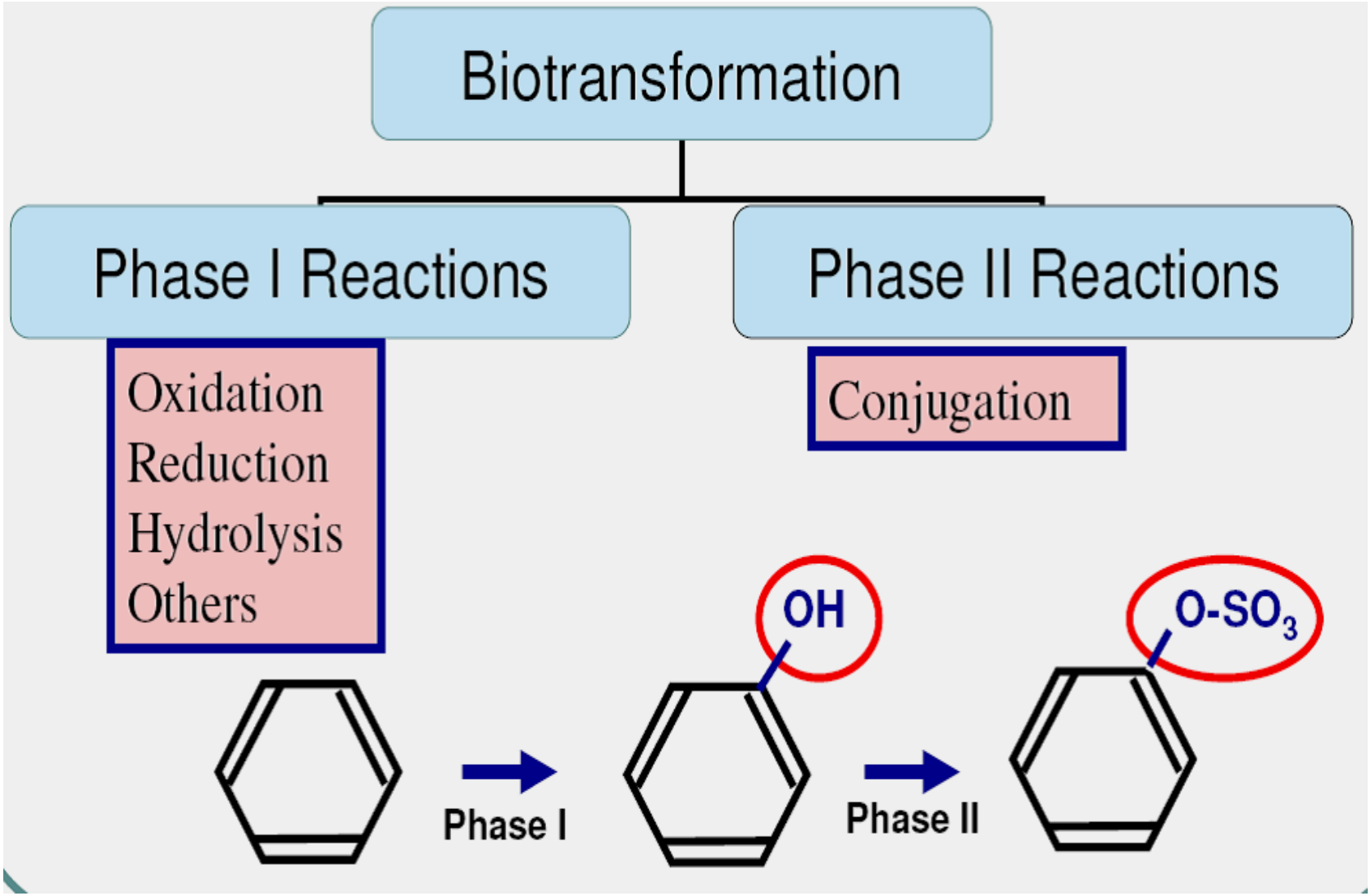
- more hydrophilic, more water soluble
- have their actions decreased (become less effective) or increased (become more effective)
- May be converted to less toxic or more toxic metabolites or to metabolites with different type of effect or toxicity

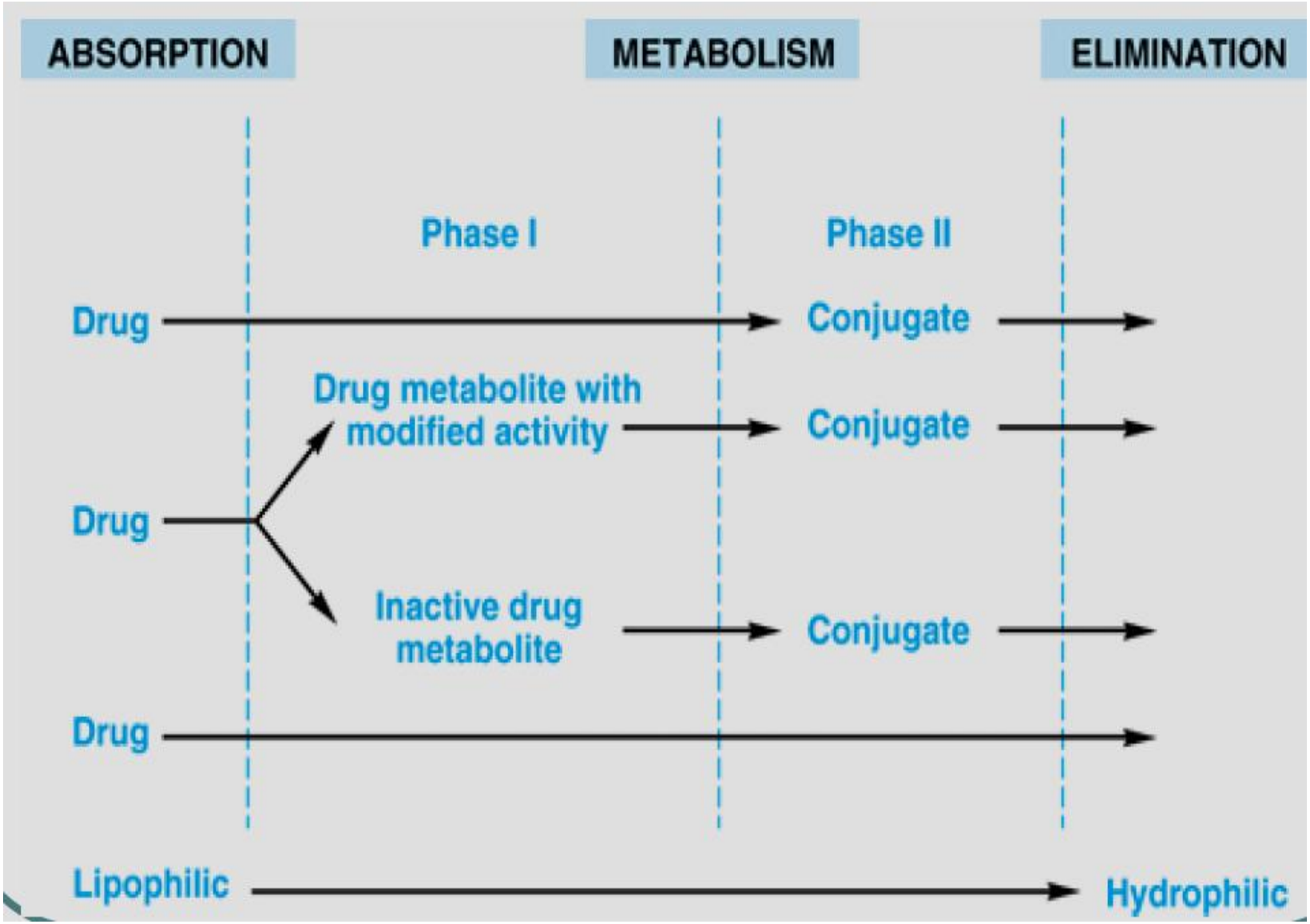
- The metabolism of drugs takes place mainly in the liver (the smooth endoplasmic reticulum of the liver cell) . However, other organs such as the kidney, lung, intestine and placenta can also be involved in this process.

Drug metabolism (Cont.):

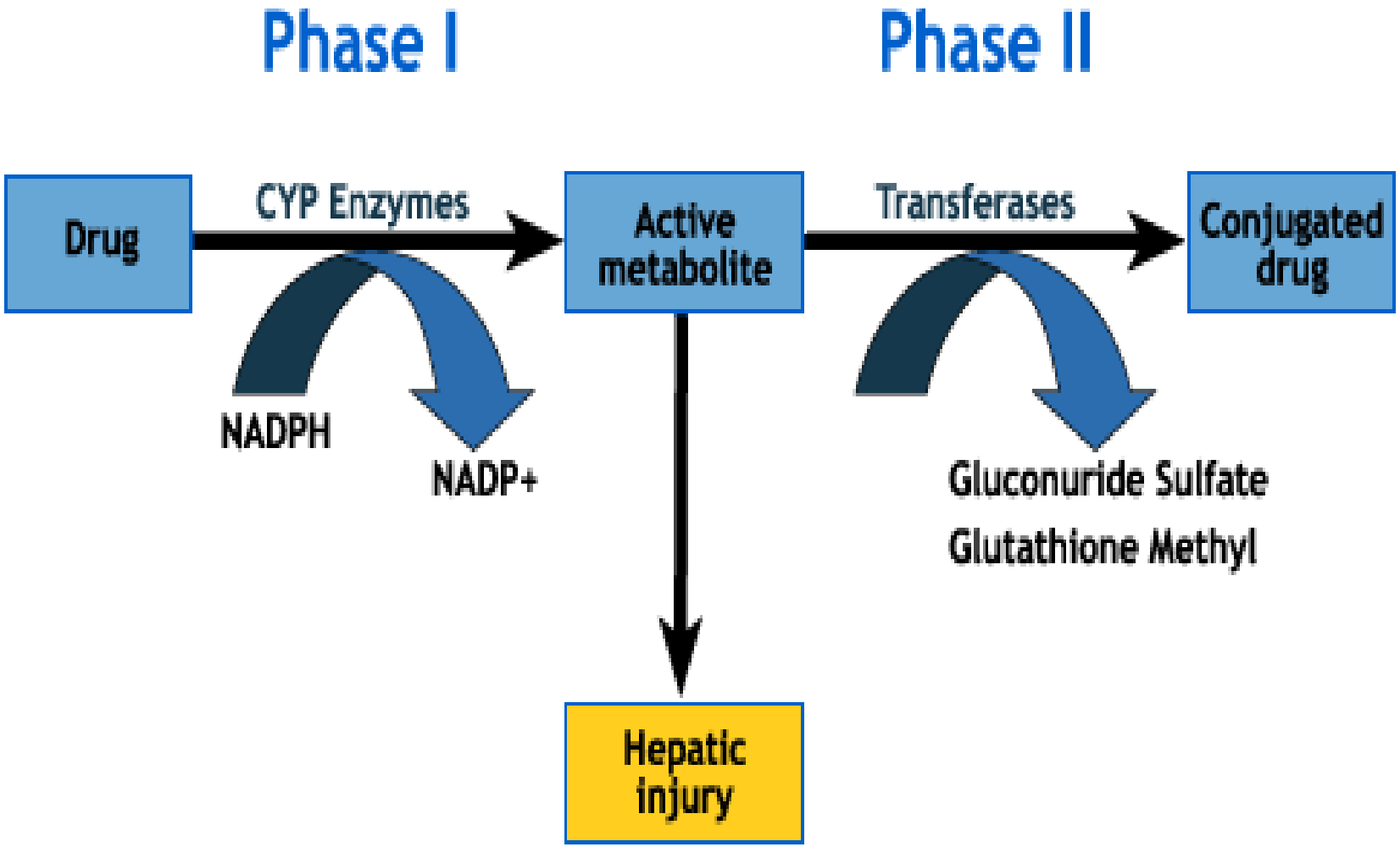
- Occasionally the metabolite is less water soluble.
- A significant example is the acetyl metabolite of some of the sulfonamides.
- Some of the earlier sulfonamides are acetylated to relatively insoluble metabolites which precipitated in urine, crystalluria.
- Now the more commonly used sulfonamides have different elimination and solubility properties and exhibit less problems.

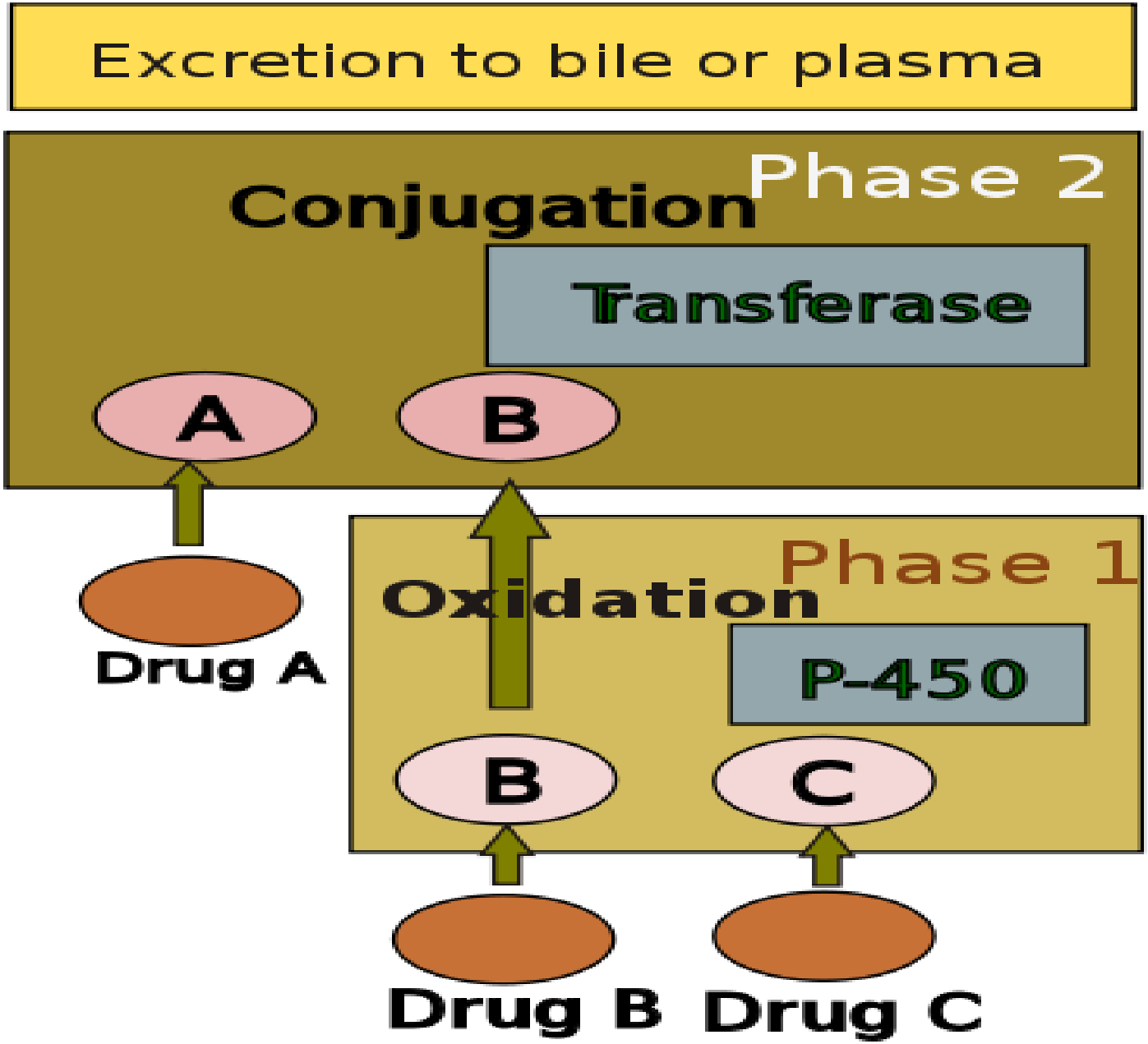
Two types of Metabolic Reactions




ABSORPTION
METABOLISM
ELIMINATION
Phase I
Phase II
Drug
Conjugate
Drug metabolite with modified activity
Conjugate
Drug
Inactive drug metabolite
Conjugate
Drug
Lipophilic
Hydrophilic

Phases of metabolism:




Excretion to bile or plasma
Phase 2
Conjugation
Transferase
A
B
Drug A
Phase 1
Oxidation
P-450
B
C
Drug B
Drug C

Phases of metabolism:

Phase I reactions:

- Change drugs to more hydrophilic metabolites which are more readily excreted
- Introduce into the drug molecule sites for phase II reactions
- May be less toxic (but not always)
- Mostly occur in the endoplasmic reticulum (microsomes) of liver cells.
- Usually involve oxidation, reduction, hydrolysis or other reactions

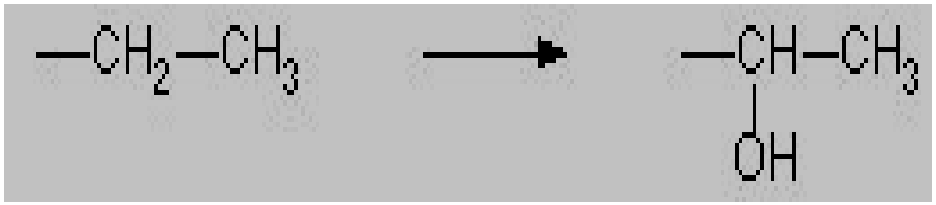
Phase I reactions:

1- Oxidation

Oxidation is the addition of oxygen and/or the removal of hydrogen, carried out by oxidases . Most oxidation steps occur in the endoplasmic reticulum. These oxidative reactions typically involve a cytochrome P450, NADPH and oxygen.

Common reactions include :-

- **Alkyl group ----> alcohol**



- **Aromatic ring ----> phenol**