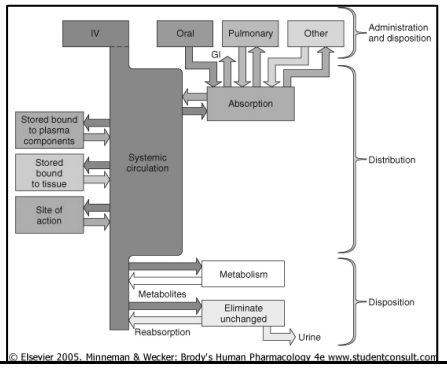
Drug Metabolism



Biotransformation Drug Molecules

- Drug changed chemically → metabolite
  - Prodrugs must be metabolized for action
- Chemical alteration by enzymatic reactions
- Generally nonpolar, lipid-sol compounds → more polar, water-soluble
  - Now easier urinary excretion
- Some metabolites active (or more active) than parent drugs
  - Ex: demethlyation diazepam → (less) active agent but with longer ½ life than parent

Biotransformation Drug Molecules

- Drug metabolizing enzymes mostly in liver
- BUT most other tissues also can metabolize
  - Lung
  - Kidney
  - Gi
  - Placenta
  - Gi bacteria

Biotransformation Drug Molecules

- Four important types chemical reactions for drug metabolism
  - Oxidation
  - Reduction
  - Conjugation
  - Hydrolysis
- Oxidation, conjugation most important
- Enzymes carry out these reactions

Drug metabolism reactions :

Phase 1 (addition or uncovering of a reactive group)

- Oxidation
- Reduction
- Hydrolysis

→ Makes the molecule more susceptible to Phase 2 reactions

Phase 2 (conjugation of endogenous molecule with drug)

- Glucuronide
- Sulphate
- Amino acids, GSH
- Acetylation/methylation

→ Makes the molecule more polar, ideal substrates for active transport, and excretion

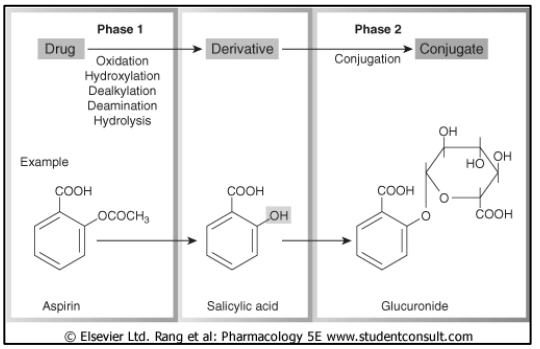
Drug Metabolism

- Phase I Reactions
  - Catabolic
    - Mostly oxidations
  - Functionalization:
    - Intro reactive group (ex: hydroxyl)
    - Products more chemically reactive, hydrophilic than parent
    - Serves as point of chemical attack

Drug Metabolism

- Phase II Reactions
  - Anabolic (synthetic)
  - Involve conjugations reactions
    - Attachment substituent
    - Large, hydrophilic
- Liver major site Phase I, II reactions
  - Metabolic enzymes
    - Microsomal
    - Stereoselective
- Both types reactions → more polar, hydrophilic metabolites

Drug Metabolism



Phase I Reactions

- General reaction:

DH + NAD(P)H + H+ + O_2 → DOH + NAD(P)+ + H_2O

where DH = drug
NAD(P)H = red'd coenzyme
DOH = ox'd drug
NAD(P)+ = ox'd coenzyme
O_2 = final electron acceptor

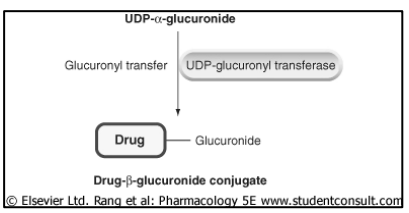
- Complicated cycle results in 1 O atom added to drug, other O → water
  - Free radical or iron-radical grps formed at parts of cycle
    - Highly reactive, dangerous

Phase II Reactions

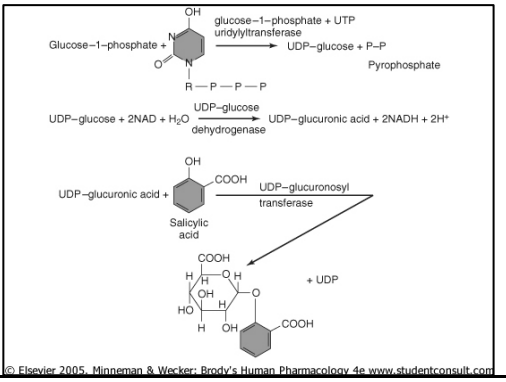
- Attachment substituent group on parent/ metabolite
  - Typically added at hydroxyl, thiol, amino
  - Substituent first "activated"
    - Phosphorylation
    - Attached to CoA
    - S-Adenosyl methionine
- Reaction enzyme-catalyzed
- Product almost always inactive, less lipid soluble
  - Excreted in urine, bile

Phase II Reactions

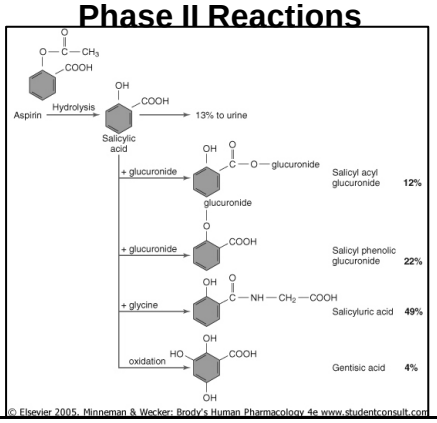
- Common conjugated substituents
  - Glucuronyl
  - Sulfate
  - Methyl
  - Acetyl
  - Glycyl
  - Glutathione



Phase II Reactions



Phase II Reactions

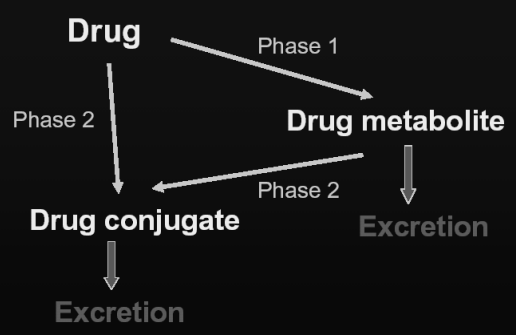


Drug Metabolism results in:

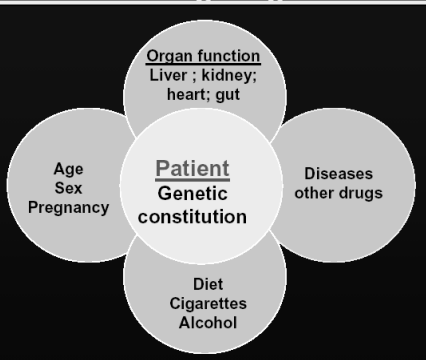
Drug $\xrightarrow[\text{enzyme}]{\text{metabolising}}$ More H_2O soluble metabolite

- Less likely to diffuse into cells to reach receptors
- Favours increased excretion in urine or bile
- Usually abolishes activity and terminates drug action, but :
- Can promote activity - prodrug – eg, acetylsalicylate
- No change in activity – eg, diazepam ---> nordiazepam
- Produce toxic metabolites – eg, paracetamol

Drug Metabolism



Factors influencing drug metabolism :



Inhibition of drug metabolism :

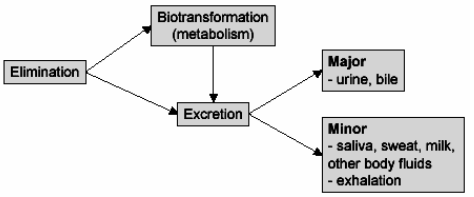
- **Rapid onset within 1 day**
- **Exaggerated response with increased risk of toxicity**
- **Competitive reversible inhibitors:**
  - Cimetidine, ketoconazole, quinolone antibiotics, oestrogens, grapefruit juice
- **Heavy metals:** (complex with CYP450)
  - Lead, cadium, mercury
- **Suicide substrates:** (destroys CYP450 in liver)
  - Allobarbitone (cpds containing double & triple bonds)

Elimination of Drugs

Excretion is the process whereby compounds are removed from the body to the external environment

Elimination of Drugs

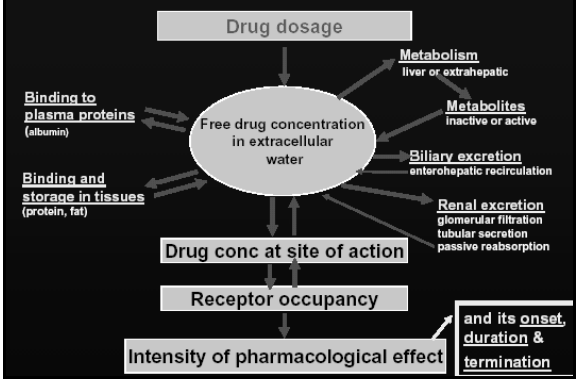
- Drugs have a finite duration of action in the body
- Elimination processes (biotransformation and excretion) are the major determinants of this duration



Sites of drug excretion :

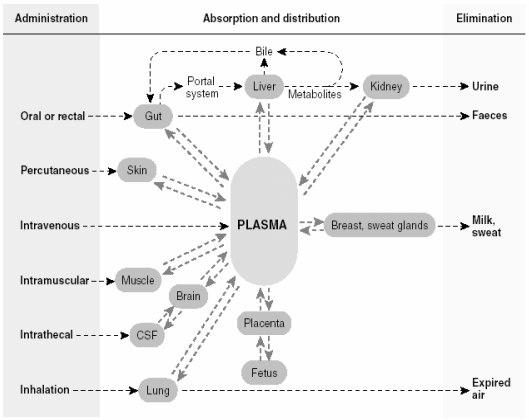
- **Kidney** – most important
- **Biliary excretion** - important for some drugs, usually MW >400 and ionized; eg Glucuronides (MW + 177)
- **Lungs** – (eg, anaesthetic gases)

Summary of drug disposition in the body



Summary

- Pharmacokinetics provides a quantitative description of the time course of drug concentrations in the body
- Drug absorption, distribution and elimination are the major determinants of the concentration and time-course of drug action
- Perturbation of drug metabolism is a major source of undesirable drug interactions
- Pharmacokinetics are very often predictive of pharmacodynamic effects, however
- Ultimately, patient response (benefit or toxicity) should be the primary factor guiding the course of therapeutics



Are We Having Fun Yet?