Drug Metabolism and Elimination

- Elimination of drugs occurs primarily through renal mechanism
  - Secretion into bile also possible, but allows for re-absorption in the intestine
- Secretion into the urine requires ionized or hydrophilic molecules, but:
  - Most drugs are not small molecules that are highly ionized at body pH
  - Most drugs are poorly ionized and lipophilic

    => This decreases renal excretion and facilitates renal tubular reabsorption
  - Many drugs are highly protein bound, and therefore not efficiently filtered in the kidney
  - Most drugs would have a long duration of action if termination of their effects depended only on renal excretion
    - ***Inactivation versus elimination of the active drug***

Solution: Drug Metabolism

Drug Metabolism

- **Why is drug metabolism so important?** Elimination of drugs and chemicals by the kidney is often compromised because the drug/chemical is too nonpolar, lipophilic and readily "reabsorbed" from tubular fluid. Metabolism can convert the drug to a more hydrophilic compound reducing reabsorption.
- Most metabolic products are less pharmacologically active

  Important exceptions:

  - Where the metabolite is more active - 3 examples

    (Prodrugs, e.g. Erythromycin-succinate (less irritation of GI) --> Erythromycin, enaliprilat -> enalapril, codeine)
  - Where the metabolite is toxic (acetaminophen)
  - Where the metabolite is carcinogenic

- Close relationship between the biotransformation of drugs and normal biochemical processes occurring in the body:
  - Metabolism of drugs involves many pathways associated with the synthesis of endogenous substrates such as steroid hormones, cholesterol and bile acids
  - Many of the enzymes involved in drug metabolism are principally designed for the metabolism of endogenous compounds
  - These enzymes metabolize drugs only because the drugs resemble the natural compound

Examples of more active metabolites

Erythromycin – gram+ antibiotic; pH sensitive (enteric coating), nonpolar, esterified (succinic acid, proprionic acid); converted by cell esterases

Enaliprilat - ACE-Inhibitor; prodrug; esterase converts to Enalapril (active)

Codeine – O-demethylation to morphine – more active analgesic than codeine; CYP2D6 metabolic enzyme; deficient in 10% caucasians, 2% in asians; reduced analgesia for same dosage