Drug Metabolism

- Most metabolic products are less pharmacologically active

  Important exceptions:

  - Where the metabolite is more active

    (Prodrugs, e.g. Erythromycin-succinate (less irritation of GI) --> Erythromycin)
  - 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

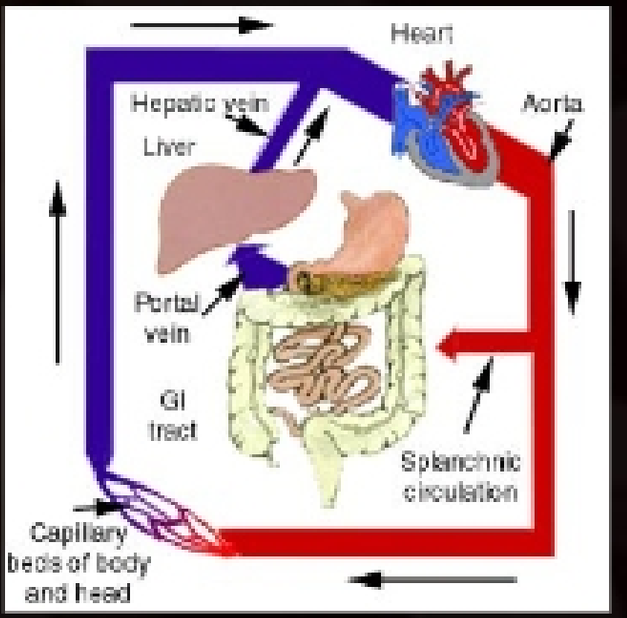
Phases of Drug Metabolism

- **Phase I Reactions**
  - Convert parent compound into a more polar (=hydrophilic) metabolite by adding or unmasking functional groups (-OH, -SH, -NH_2, -COOH, etc.)
  - Often these metabolites are inactive
  - May be sufficiently polar to be excreted readily

- **Phase II Reactions**
  - Conjugation with endogenous substrate to further increase aqueous solubility
  - Conjugation with glucoronide, sulfate, acetate, amino acid
  - Phase I usually precede phase II reactions

Liver is principal site of drug metabolism:

- Other sites include the gut, lungs, skin and kidneys
- For orally administered compounds, there is the "First Pass Effect"
  - Intestinal metabolism
  - Liver metabolism
  - Enterohepatic recycling
  - Gut microorganisms - glucuronidases



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