Topic 6 Pharmacokinetics and Drug Metabolism

Chapter 8 Patrick

Drug candidate pharmaceutics are critical: ADME

- Absorption
- Distribution
- Metabolism
- Excretion

Drug candidate pharmaceutics are critical: Drug Administration route-

1. Oral

2. Mucous membranes
    1. Rectal
    2. Oral (buccal)
3. Topical-transdermal
4. Inhaled
5. Injected
    1. Intravenous
    2. Intramuscular
    3. Subcutaneous
    4. Intrathecal-spinal
    5. Intraperotoneal

Drug candidate pharmaceutics are critical: Formulations

1. Pills, capsules
2. Liquid
3. Patch
4. Liposome/micelle

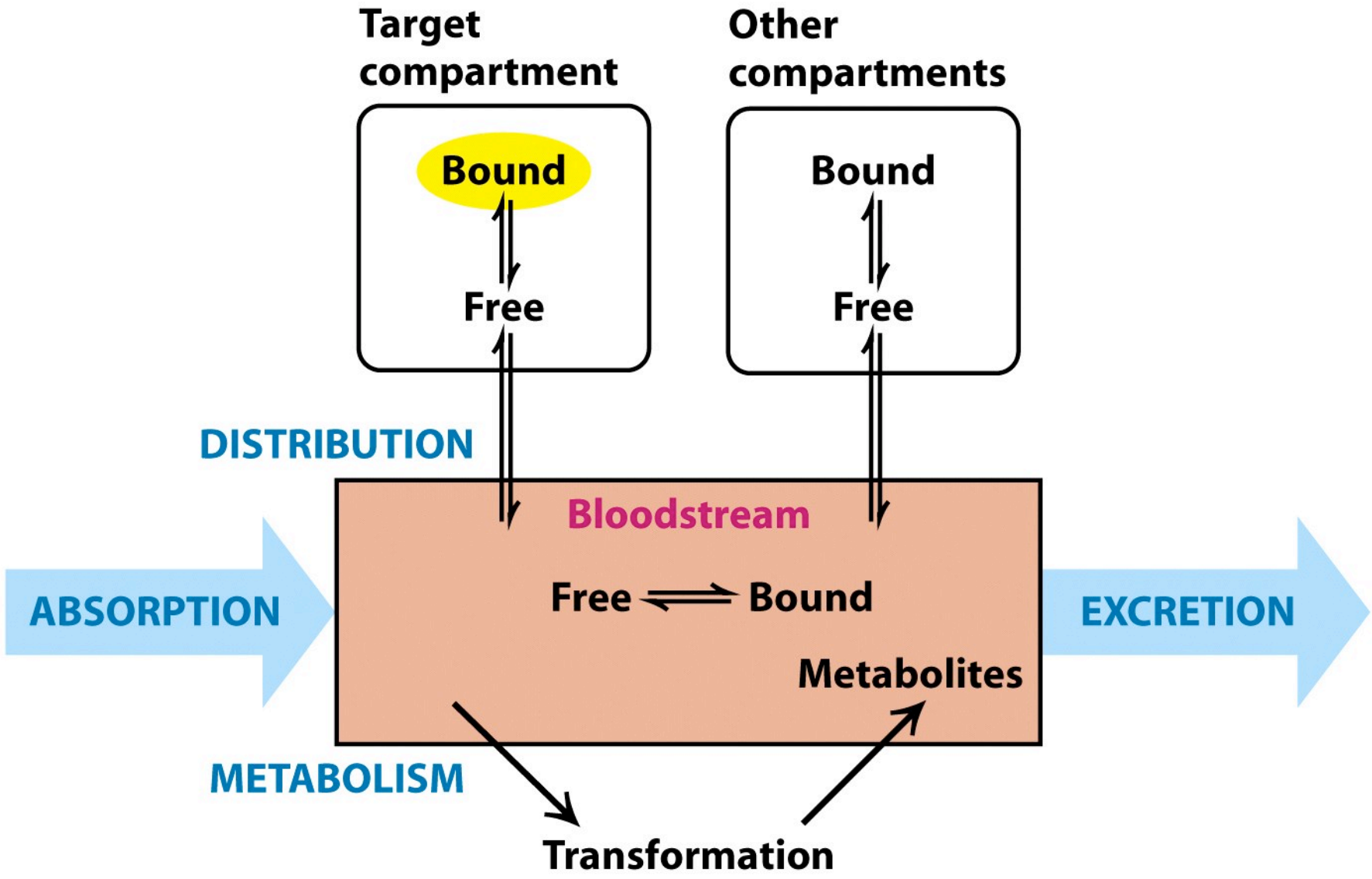

Figure 35-5
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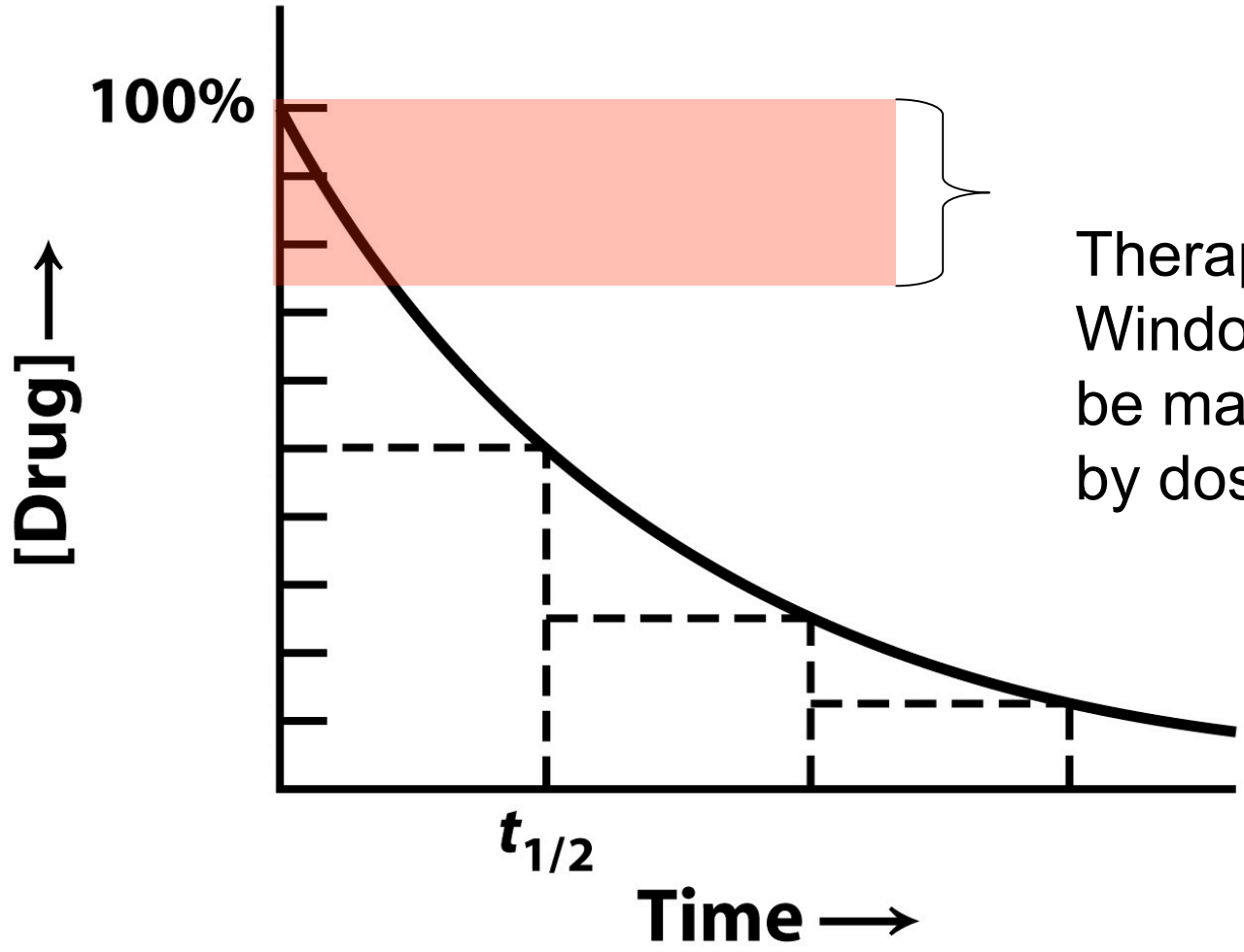
Pharmaceutics



Therapeutic Window must be maintained by dosing

Figure 35-12
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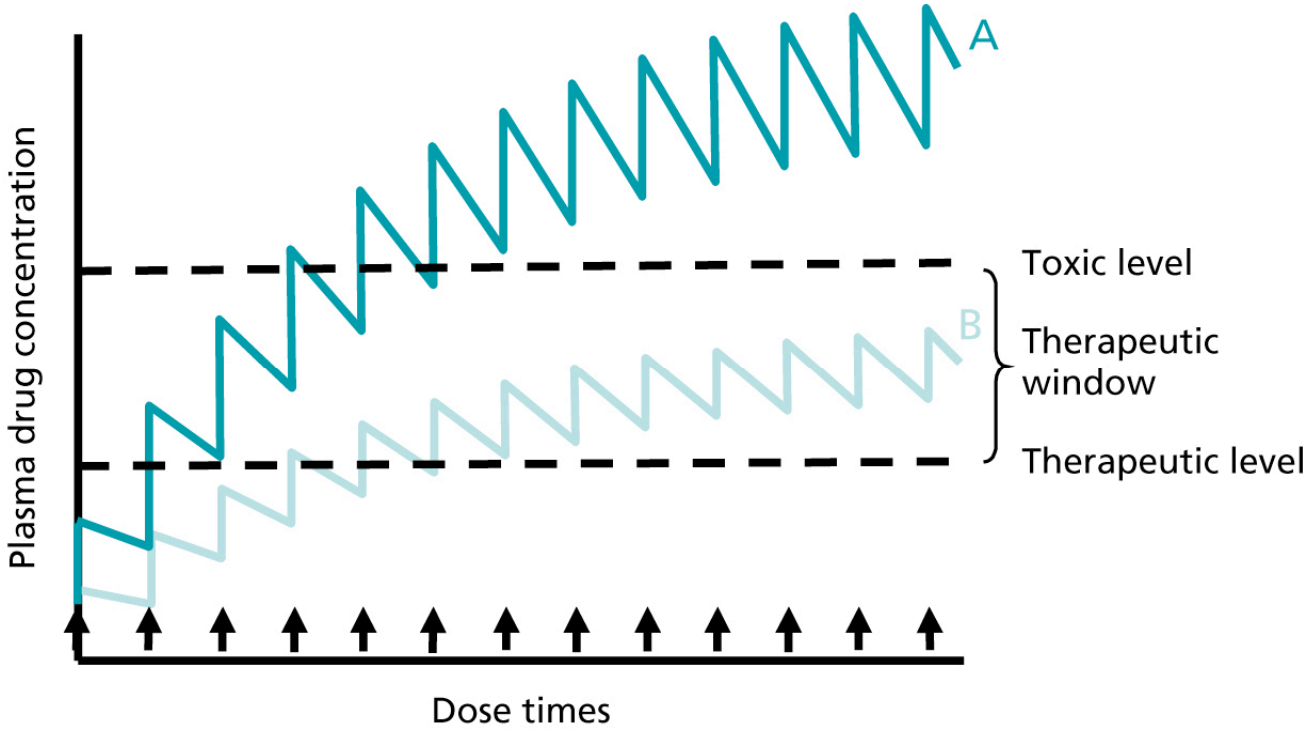
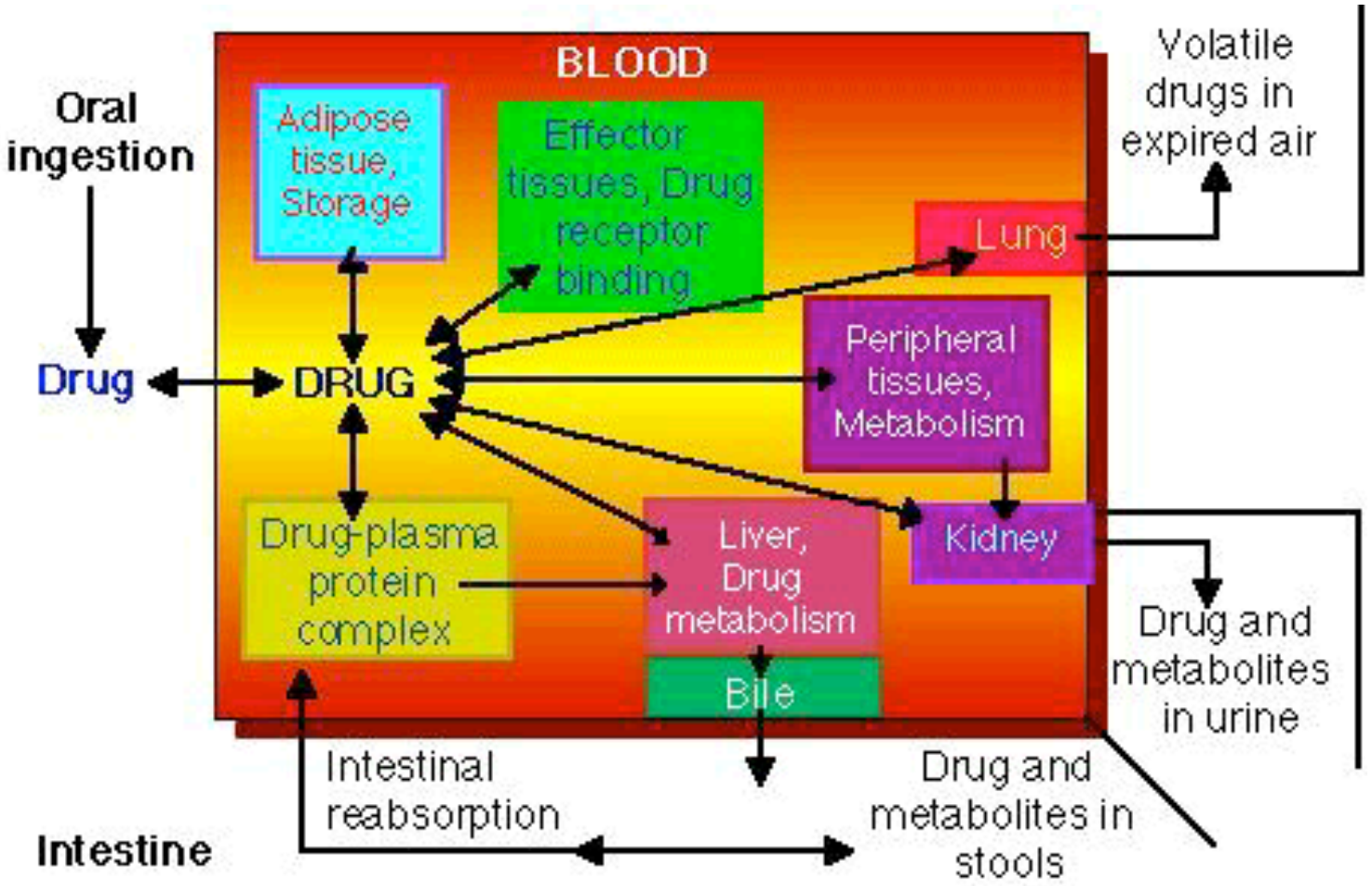
Pharmaceutics



Therapeutic Window must be maintained by dosing

Absorption

Drug Absorption, Metabolism and Excretion
http://www.cc.nih.gov/training/training/principles/schedule.html



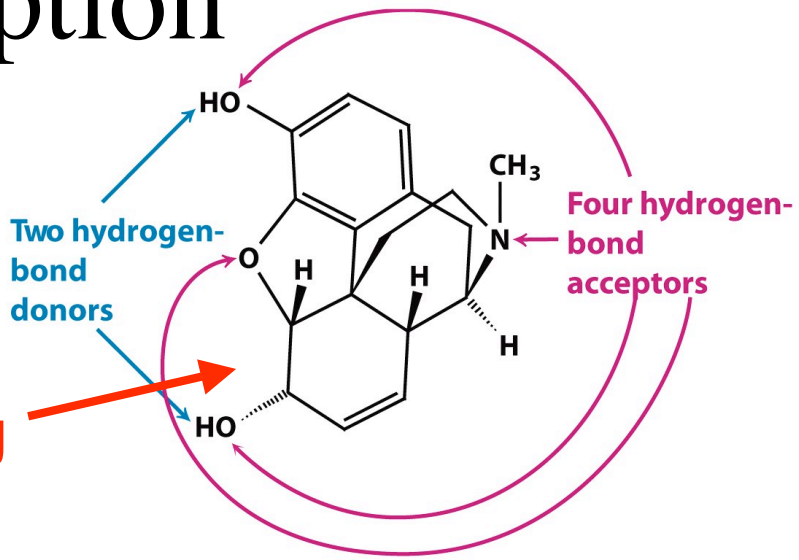
Drug molecule factors affecting absorption and distribution

1. Acid-base properties

2. Hydrophobicity/Functional groups

3. Size

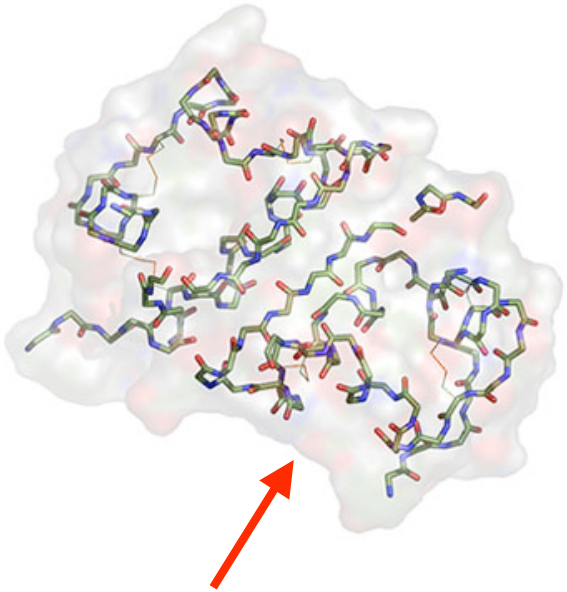
Absorption



Morphine ($C_{17}H_{19}O_3N$)

Molecular weight = 285
log(*P*) = 1.27

A "good" drug



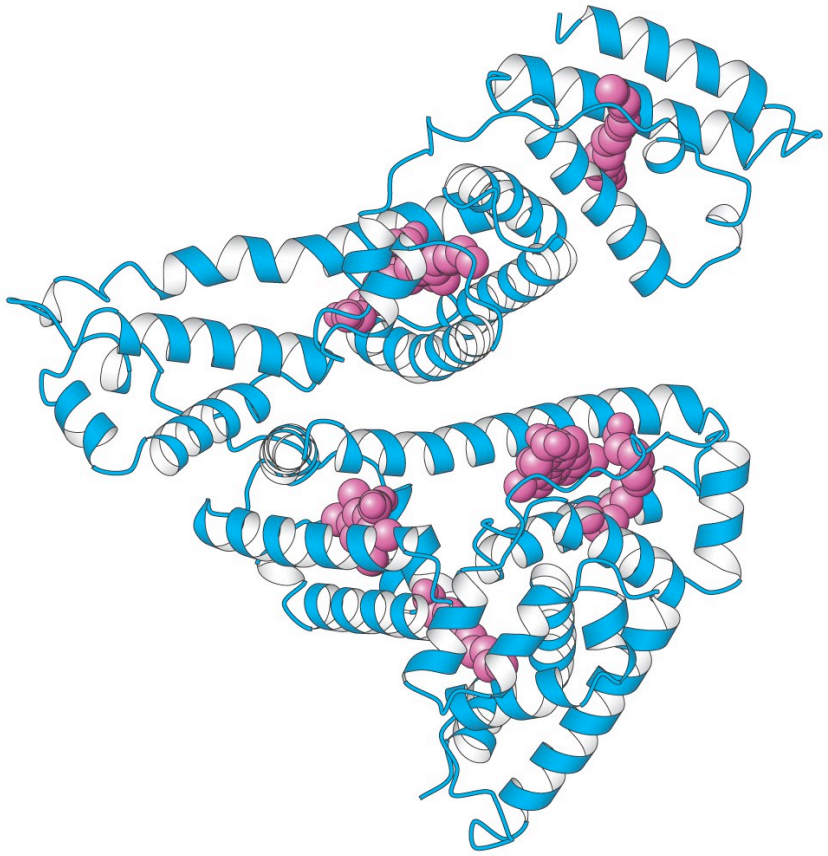
A "lousy" drug: insulin

Lipinski's rules for **lousy** drug absorption:

1. MW>500
2. H-bond donors>5
3. H-bond acceptors>10
4. log Partition coefficient > 5

   i.e. octanol /water > 100,000:1

Distribution:Serum Albumin, The distributor of non polar drugs



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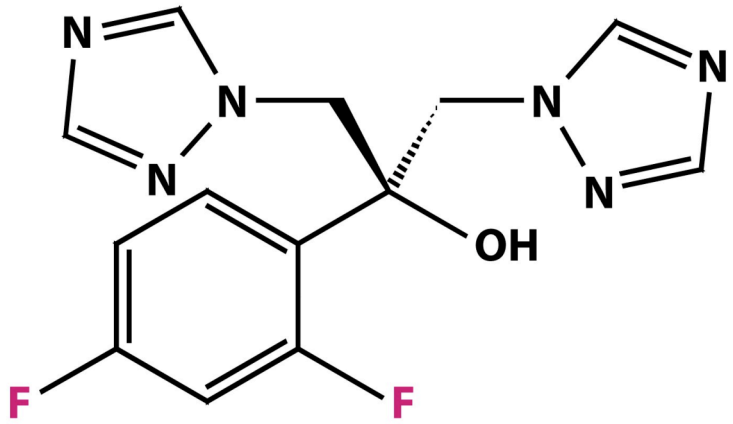
Seeing distribution: e.g. fluconazole



Fluconazole

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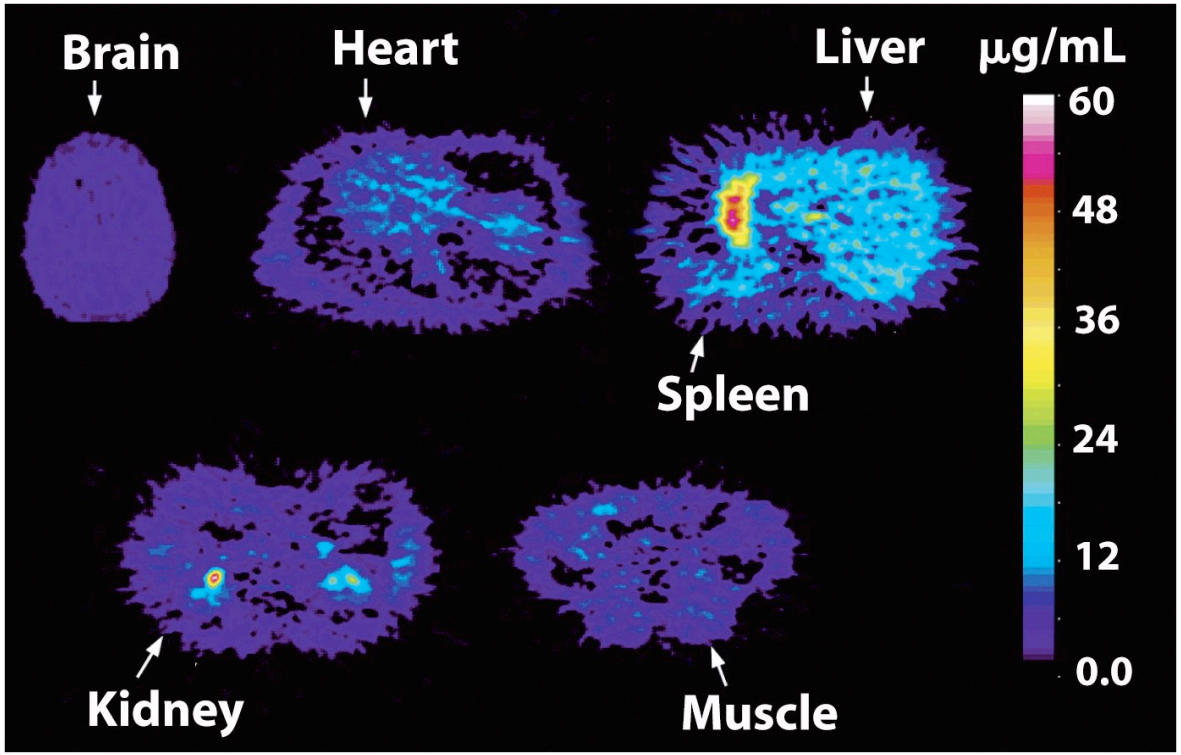

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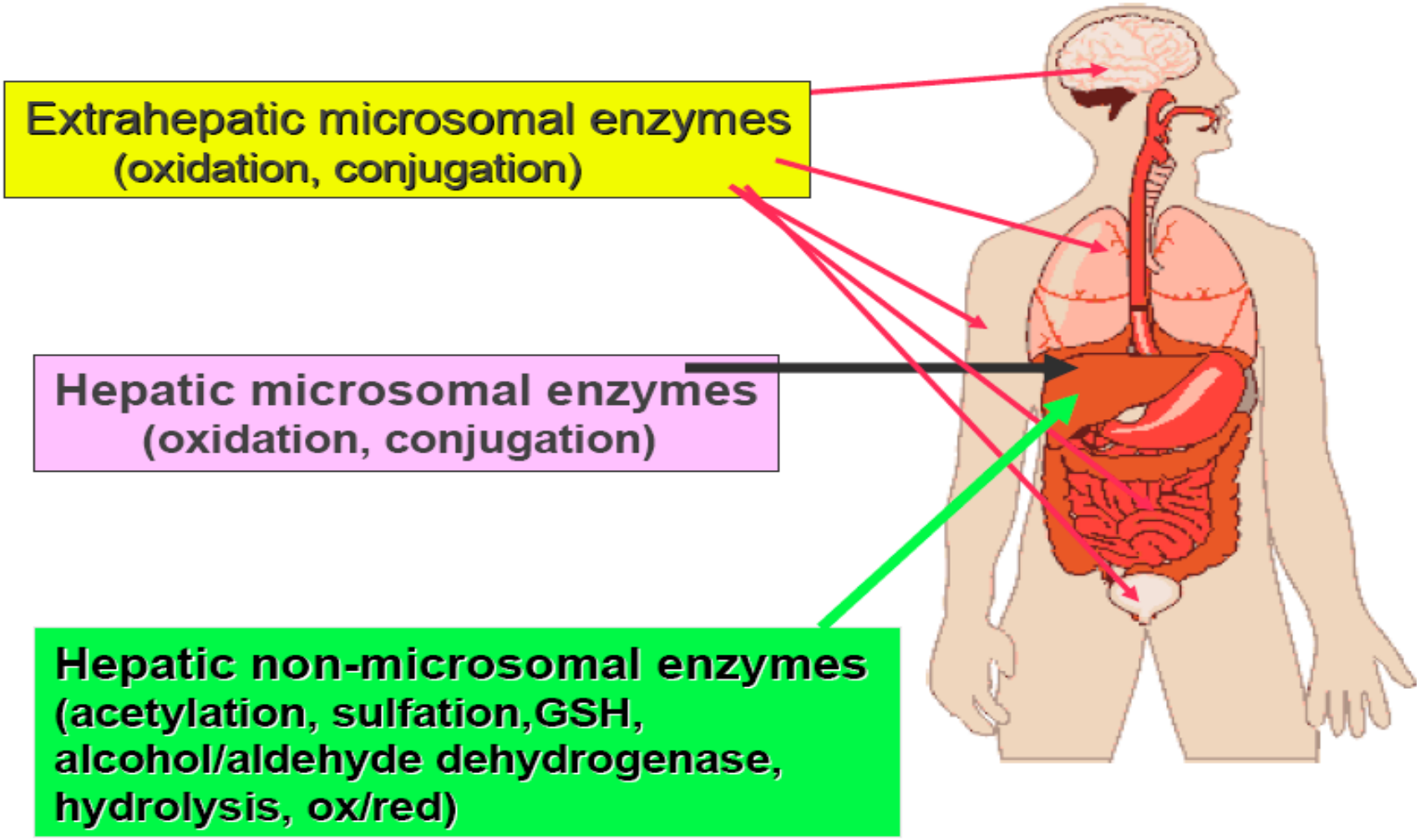
PET scan of ^{18}F fluconazole

Metabolism/excretion

Phase I Metabolism

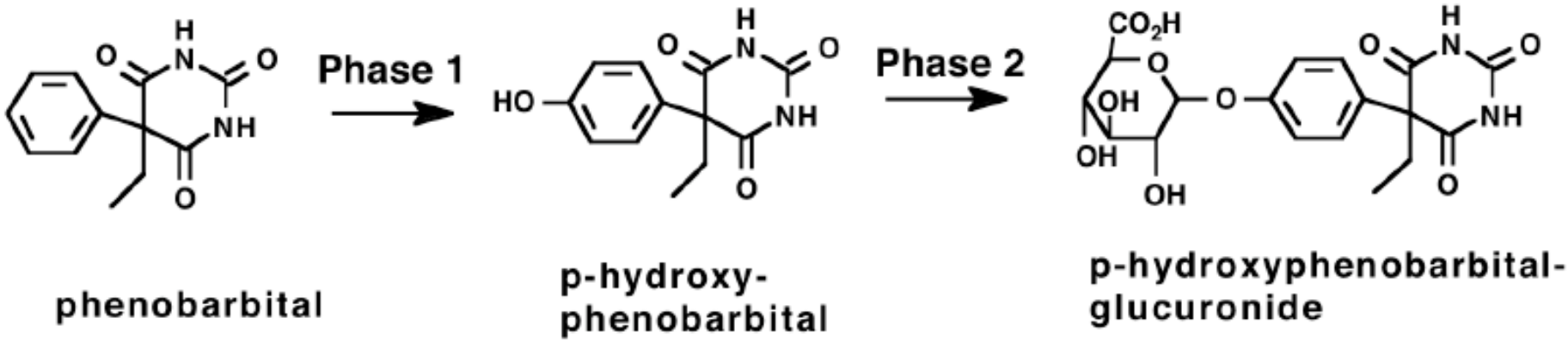
Oxidation



Metabolism/excretion

1. Phase 1 metabolism- Liver microsomal system

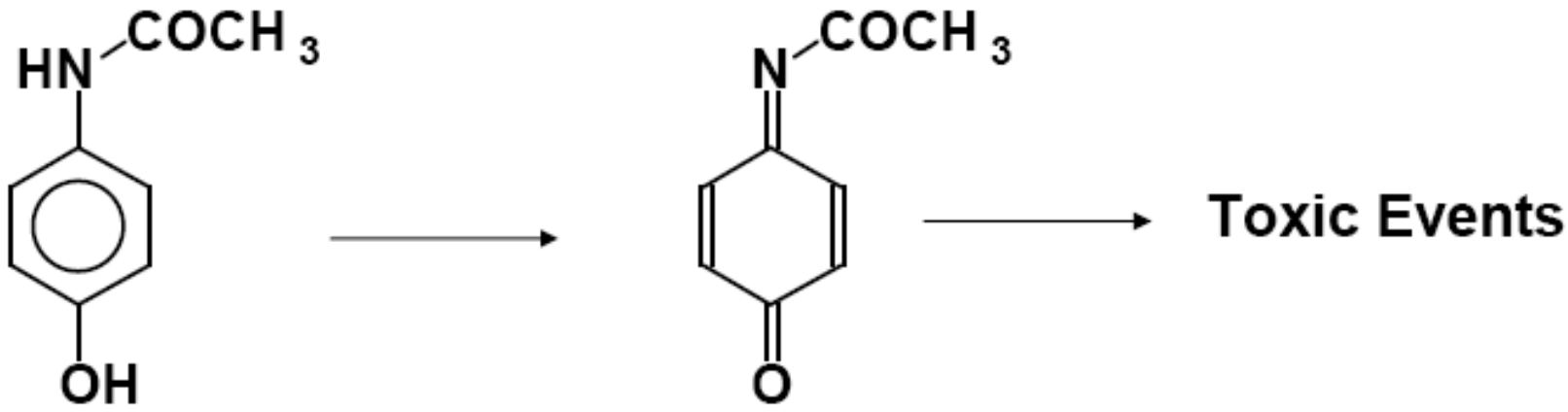
- Oxidative Reactions: Cytochrome P450 mediated
  - **Formation of an inactive polar metabolite**
    - **Phenobarbital**



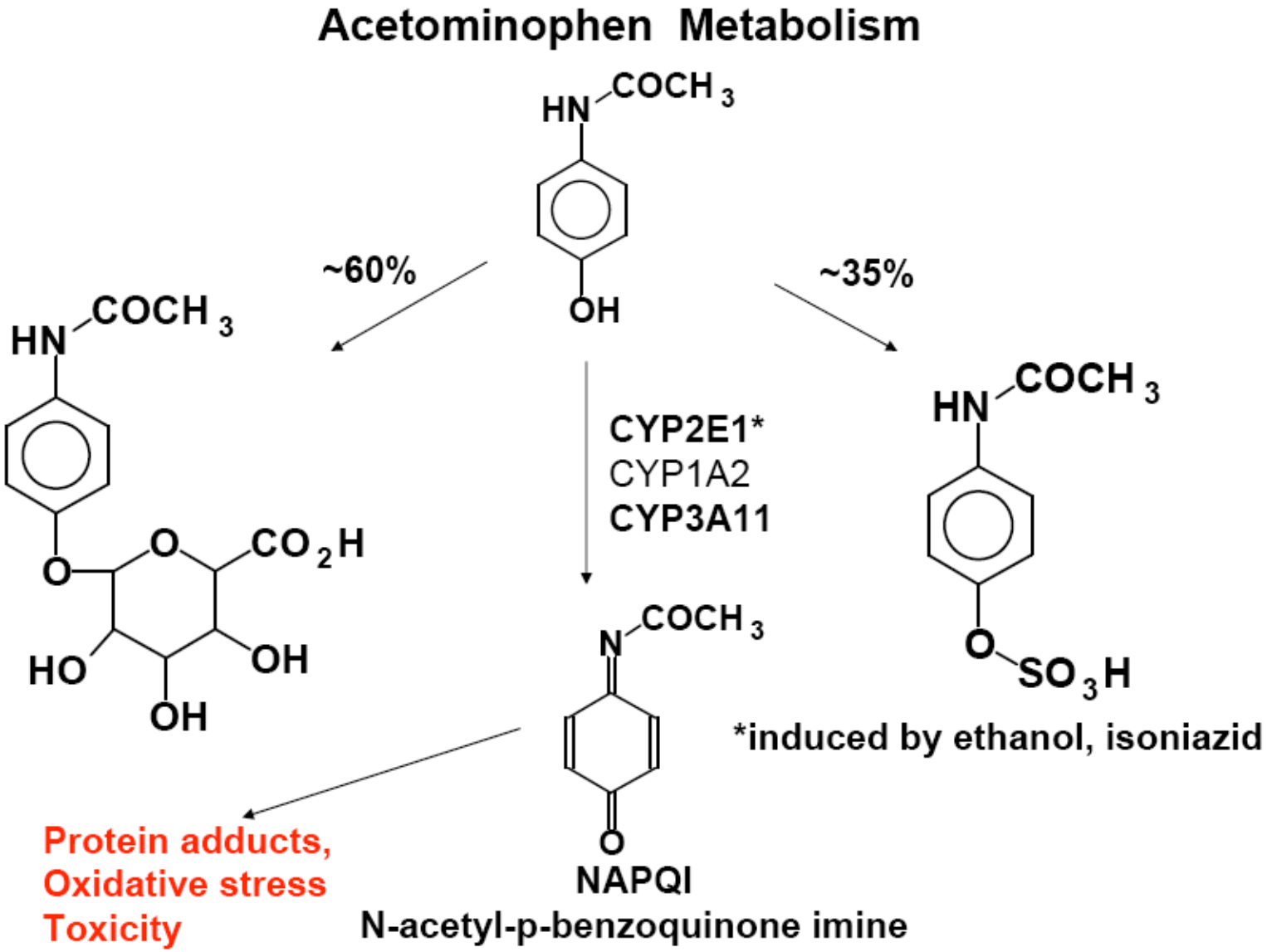
Metabolism/excretion

1. Phase 1 metabolism- Liver microsomal system

- **Formation of a toxic metabolite**
  - **Acetaminophen – NAPQI**



Metabolism/excretion



Metabolism/excretion

Poisoning Fatalities U.S. 2006

Categories associated with largest numbers of fatalities

Substance	Number
Sedative/hypnotics/antipsychotics	382
Opioids	307
Cardiovascular Drugs	252
Acetaminophen in combination	214
Antidepressants	210
Stimulants and street drugs	203
Alcohols	139
Acetaminophen only	138

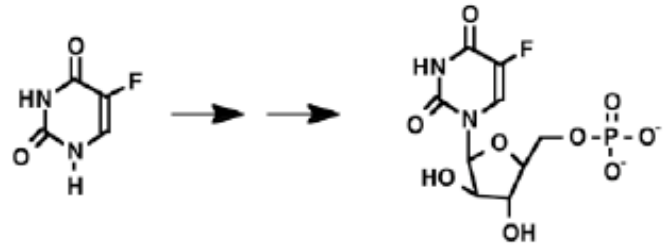
Excerpt from Table 18
"2006 Annual Report of the American Association of Poison Control Centers' National Poison Data System"
http://dx.doi.org/10.1080/15563650701754763

Metabolism/excretion

1. Phase 1 metabolism- Liver microsomal system

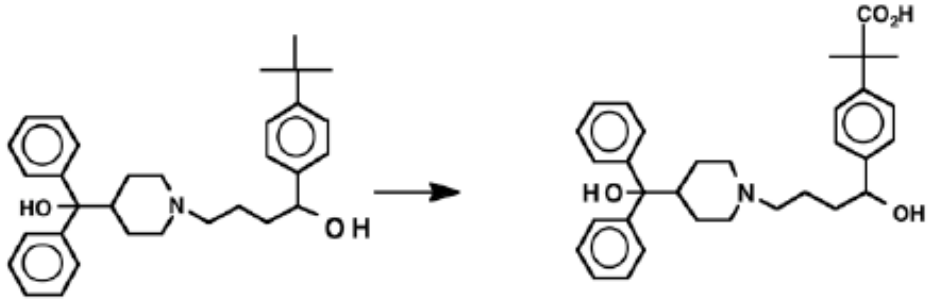
   – **Formation of an active metabolite**

   • **By Design: Purine & pyrimidine chemotherapy prodrugs**



5-FU **5-FUMP**

   • **Inadvertent: terfenadine – fexofenadine**



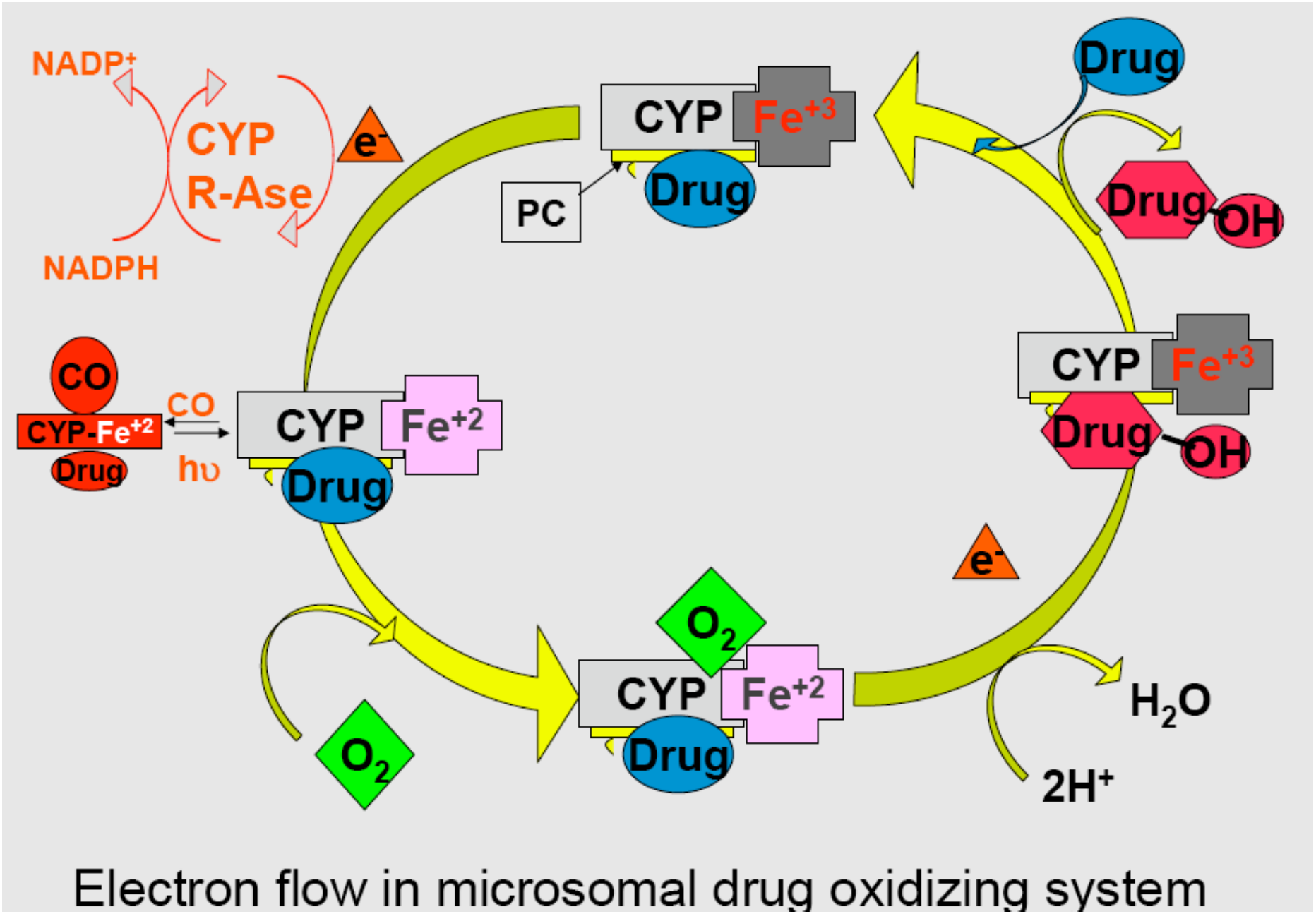
Terfenadine (Seldane) **Fexofenadine (Allegra)**

Metabolism/excretion

Cytochrome P450 Isoforms (CYPs) - An Overview

- **$NADPH + H^+ + O_2 + Drug \rightarrow NADP^+ + H_2O + Oxidized\ Drug$**
- **Carbon monoxide binds to the reduced Fe(II) heme and absorbs at 450 nm (origin of enzyme family name)**
- **CYP monooxygenase enzyme family is major catalyst of drug and endogenous compound oxidations in liver, kidney, G.I. tract, skin, lungs**
- **Oxidative reactions require the CYP heme protein, the reductase, NADPH, phosphatidylcholine and molecular oxygen**
- **CYPs are in smooth endoplasmic reticulum in close association with NADPH-CYP reductase in 10/1 ratio**
- **The reductase serves as the electron source for the oxidative reaction cycle**

Metabolism/excretion



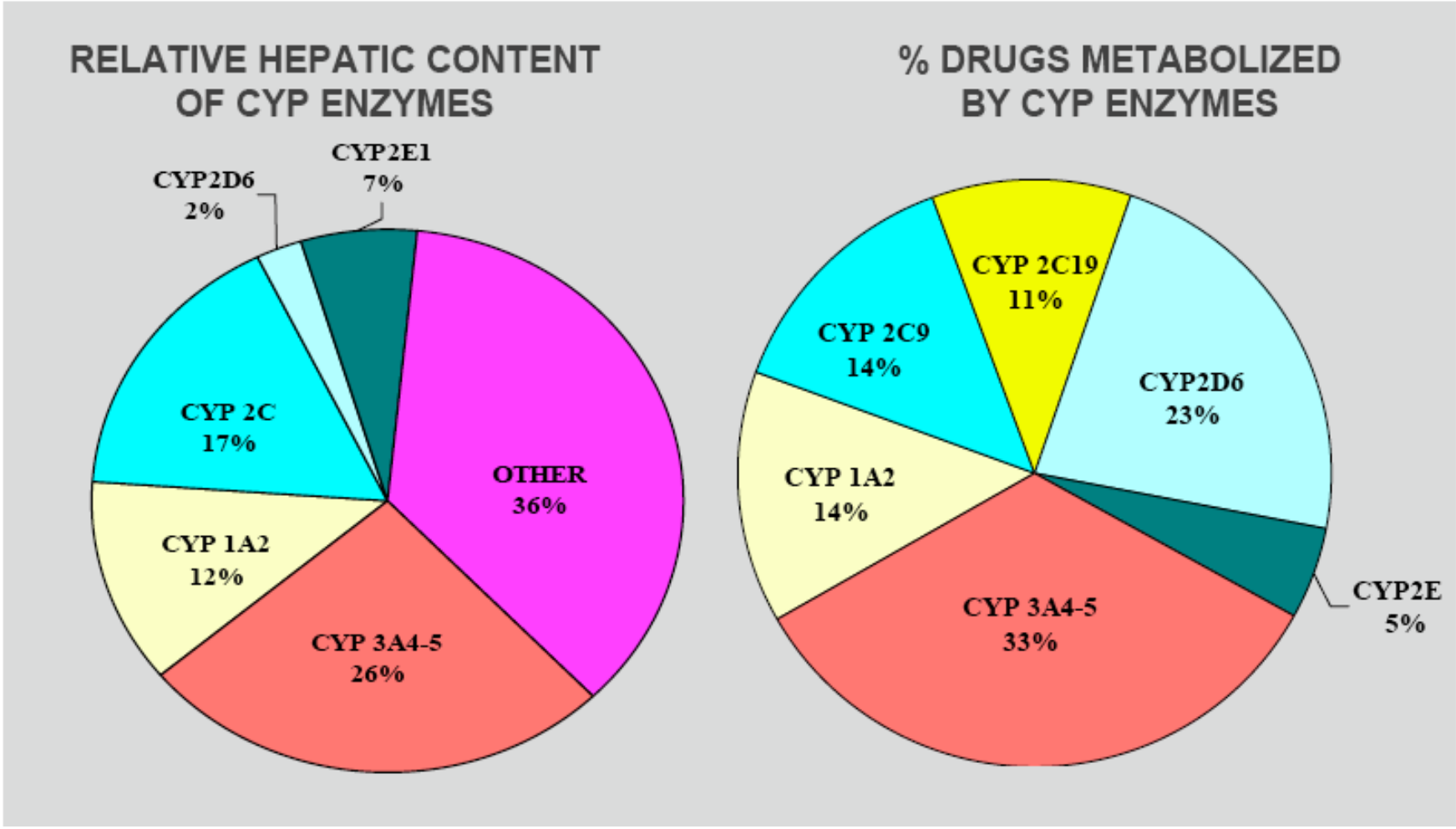
Electron flow in microsomal drug oxidizing system

Metabolism/excretion

CYP Families

- **Multiple CYP gene families have been identified in humans, and the categories are based upon protein sequence homology**
- **Most of the drug metabolizing enzymes are in CYP 1, 2, & 3 families .**
- **CYPs have molecular weights of 45-60 kDa.**
- **Frequently, two or more enzymes can catalyze the same type of oxidation, indicating redundant and broad substrate specificity.**
- **CYP3A4 is very common to the metabolism of many drugs; its presence in the GI tract is responsible for poor oral availabilty of many drugs**

ROLE OF CYP ENZYMES IN HEPATIC DRUG METABOLISM



Human Liver Drug CYPs

CYP enzyme	Level (%total)	Extent of variability
1A2	~ 13	~40-fold
1B1	<1	
2A6	~4	~30 - 100-fold
2B6	<1	~50-fold
2C	~18	25-100-fold
2D6	Up to 2.5	>1000-fold
2E1	Up to 7	~20-fold
2F1		
2J2		
3A4	Up to 28 30-60*	~20-fold 90-fold*
4A, 4B		

S. Rendic & F.J. DiCarlo, Drug Metab Rev 29:413-80, 1997
L. Wojnowski, Ther Drug Monit 26: 192-199, 2004

Participation of the CYP Enzymes in Metabolism of Some Clinically Important Drugs

CYP Enzyme	Examples of substrates
1A1	Caffeine, Testosterone, **R-Warfarin**
1A2	Acetaminophen, Caffeine, Phenacetin, **R-Warfarin**
2A6	17β-Estradiol, Testosterone
2B6	Cyclophosphamide, Erythromycin, Testosterone
2C-family	Acetaminophen, Tolbutamide (2C9); Hexobarbital, S-Warfarin (2C9,19); Phenytoin, Testosterone, **R- Warfarin**, Zidovudine (2C8,9,19);
2E1	Acetaminophen, Caffeine, Chlorzoxazone, Halothane
2D6	Acetaminophen, Codeine, Debrisoquine
3A4	Acetaminophen, Caffeine, Carbamazepine, Codeine, Cortisol, Erythromycin, Cyclophosphamide, S- and **R-Warfarin**, Phenytoin, Testosterone, Halothane, Zidovudine

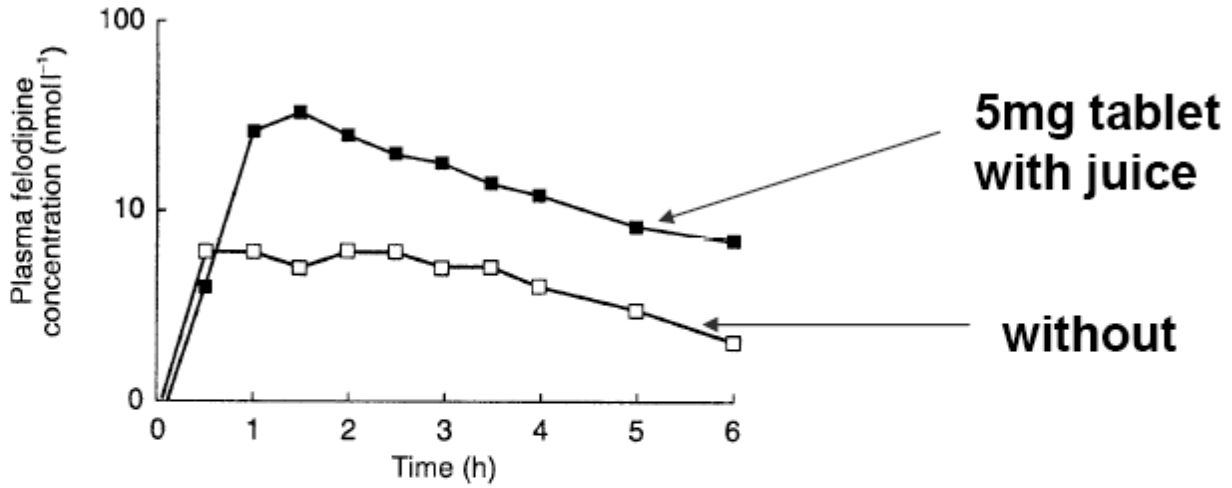
Adapted from: *S. Rendic Drug Metab Rev 34: 83-448, 2002*
Also D.F.V. Lewis, Current Medicinal Chemistry, 2003, 10, 1955-1972

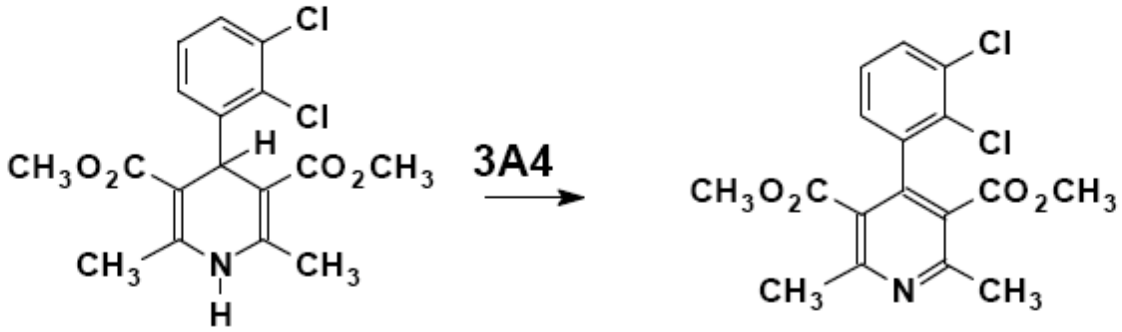
Non-nitrogenous Substances that Affect Drug Metabolism

- Grapefruit juice - CYP 3A4 inhibitor; highly variable effects; fucocoumarins
  - Bailey, D.G. et al.; Br J Clin Pharmacol 1998, 46:101-110
  - Bailey, D.G et al.; Am J Cardiovasc Drugs 2004, 4:281-97.
- St John's wort, other herbal products
  - Tirona, R.G and Bailey, D.G. ; Br J Clin Pharmacol. 2006,61: 677-81
- Isosafrole, safrole
  - CYP1A1, CYP1A2 inhibitor; found in root beer, perfume

EXAMPLE: a Ca^{2+} channel blocker for hypertension

Effect of Grapefruit Juice on Felodipine Plasma Concentration

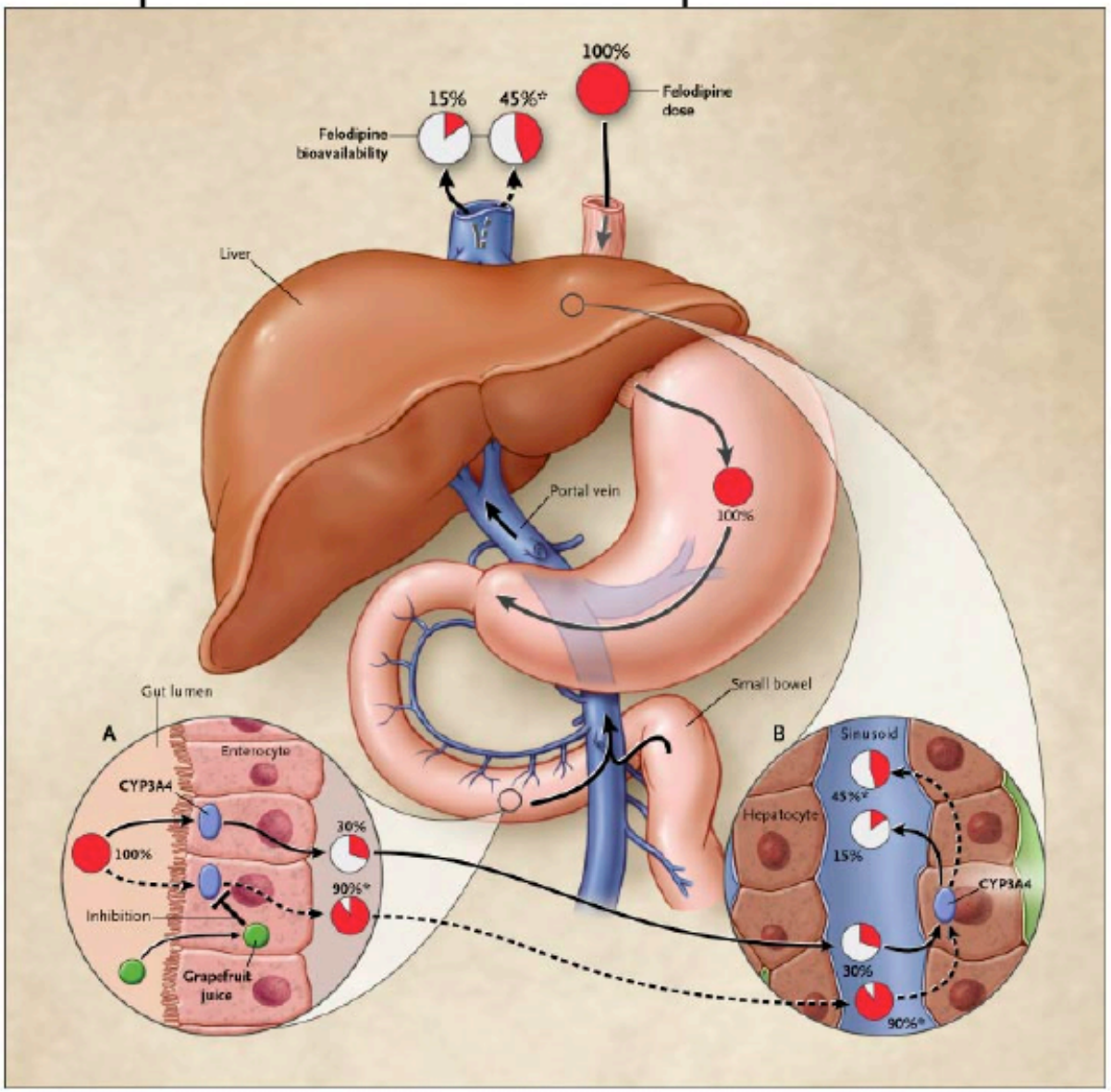




Review- D.G. Bailey, et al.; Br J Clin Pharmacol 1998, 46:101-110

EXAMPLE: a Ca $^{2+}$ channel blocker for hypertension

First-Pass Metabolism after Oral Administration of a Drug, as Exemplified by Felodipine and Its Interaction with Grapefruit Juice



Wilkinson G. N Engl J Med 2005;352:2211-2221

Human Drug Metabolizing CYPs Located in Extrahepatic Tissues

CYP Enzyme	Tissue
1A1	Lung, kidney, GI tract, skin, placenta, others
1B1	Skin, kidney, prostate, mammary,others
2A6	Lung, nasal membrane, others
2B6	GI tract, lung
2C	GI tract (small intestine mucosa) larynx, lung
2E1	Lung, placenta, others
2F1	Lung, placenta
2J2	Heart
3A	GI tract, lung, placenta, fetus, uterus, kidney
4B1	Lung, placenta
4A11	Kidney

CYP Biotransformations

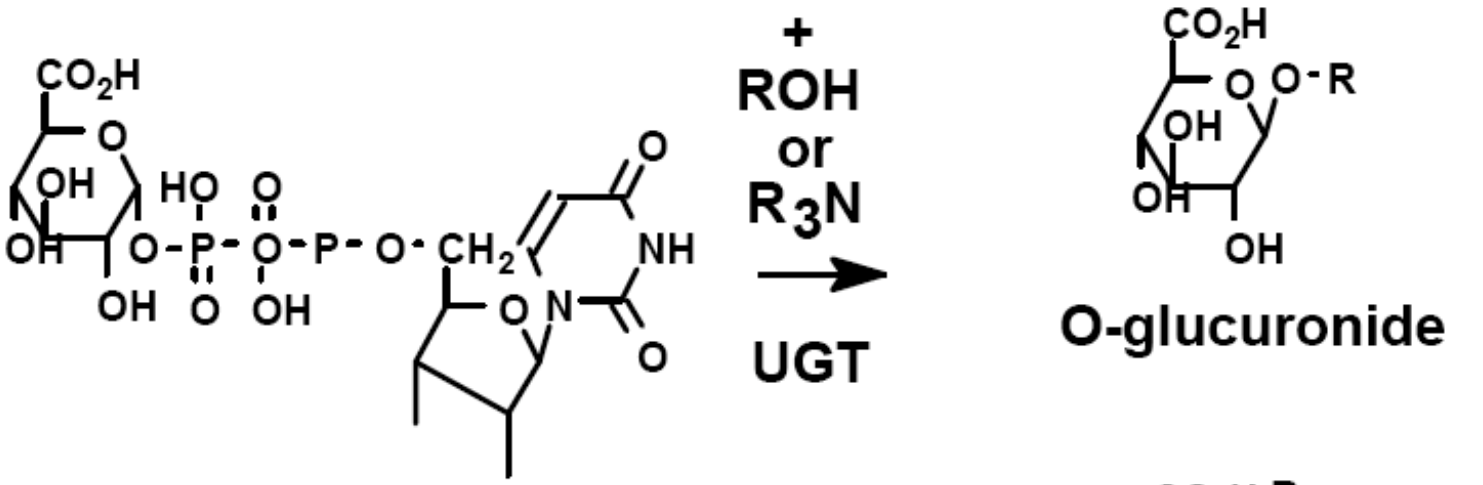
- Chemically diverse small molecules are converted, generally to more polar compounds
- Reactions include:
  - **Aliphatic hydroxylation, aromatic hydroxylation**
  - **Dealkylation (N-,O-, S-)**
  - **N-oxidation, S-oxidation**
  - **Deamination**
  - **Dehalogenation**

Non-CYP Drug Biotransformations

- Oxidations
- Hydrolyses
- **Conjugation (Phase 2 Rxs)**
  - Major Conjugation Reactions
    - **Glucuronidation** (high capacity)
    - **Sulfation** (low capacity)
    - **Acetylation** (variable capacity)
    - Examples:Procainamide, Isoniazid
  - Other Conjugation Reactions: O-Methylation, S-Methylation, Amino Acid Conjugation (glycine, taurine, glutathione)
  - Many conjugation enzymes exhibit polymorphism

Phase II Metabolism

Conjugation Reactions
Glucuronidation

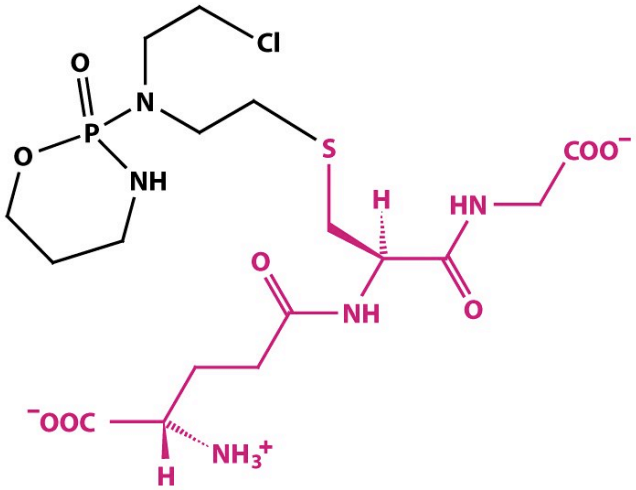


UDP-α-D-glucuronic acid

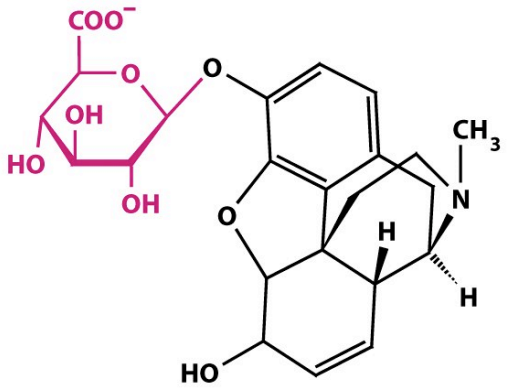
Liver has several soluble UDP-Gluc-transferases

Metabolism/excretion

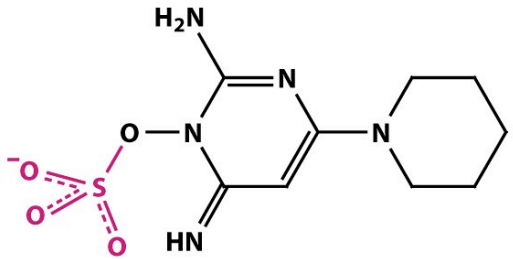
Conjugation examples



Cyclophosphamide-glutathione conjugate



Morphine glucuronidate



Minoxidil sulfate

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