The drug elimination paradox

- Most drugs are highly lipophilic to allow them to be more readily absorbed in the GI tract and enter cells by diffusing across the PM
- Lipophilic compounds are not efficiently eliminated from the body - they can accumulate in adipose tissue & membranes
  - poorly excreted in urine because readily reabsorbed in kidney tubules by passive diffusion across PM membranes
- Active drugs that remain in the body can lead to sustained drug effects and toxicity

Most drugs are lipophilic and readily reabsorbed in the kidney

- Unbound drug molecules >20,000 Da are filtered through the glomerulus
- Some drugs are actively transported into the renal tubules by drug transporters

Water soluble drugs are excreted in the urine

Lipid soluble drugs are readily reabsorbed in the kidney tubules (influenced by pH, urine flow)

Drug Accumulation/
Toxicity

Systemic Circulation

Glomerular Filtration

Water soluble Lipid soluble

Drug Transport

KIDNEY NEPHRON
Solution to this conundrum: Drug Metabolism = Drug Biotransformation

- Drug metabolism is the enzymatic catalyzed conversion of a drug or xenobiotic compound to their metabolites.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Metabolic enzymes</th>
<th>Drug Metabolite</th>
<th>Altered chemical properties</th>
</tr>
</thead>
</table>

- The primary role of drug metabolism is to:
  - Inactivate and detoxify pharmacologically active drugs and xenobiotics
    - Although sometimes it can activate certain "inactive drug" compounds (e.g. Prodrugs)
  - Enhance drug excretion and elimination
    - Primarily converts lipophilic drugs into more hydrophilic polar metabolites
    - Polar compounds are less readily reabsorbed in the kidney tubules

- The efficiency of drug metabolism can significantly affect the intensity & duration of a drug's pharmacological action and can contribute towards drug toxicity.

Consequences of Drug Metabolism

- Lipophilic Drug → Polar Drug (all drugs)
  - Increasing Water solubility
  - Increased potential for excretion in urine or bile

- Active Drug → Inactive Drug metabolite (most drugs)
  - Toxic Xenobiotic → Non-toxic metabolite

  Prodrug (Inactive Drug) → Active Drug metabolite
  (e.g. irinotecan)  
  Active Drug (e.g. diazepam) → Active Drug metabolite(s)
  (desmethyldiazepam)  
  (SN-38)

Sites of Metabolism

- Major organ sites of drug metabolism:
  - Liver, although intestine also plays a significant role
  - Other cell types involved include skin, lung, kidney & brain
  - However, drug metabolism enzymes are expressed in essentially all cells

- Subcellular sites of drug metabolism:
  - CYP450 and some other enzymes (e.g. glucuronosyltransferases) are associated with the endoplasmic reticulum
  - Most other metabolic enzymes are present in the cytoplasm
Role of the Liver and GI tract in the First Pass Effect

- Drugs administered orally are typically absorbed in the GI tract.
- A number of drug metabolizing enzymes (e.g., CYP3A4) are expressed in the GI tract and can metabolize absorbed drugs.
- Absorbed drugs and their metabolites are then transported via the portal veins to the LIVER where they can undergo further metabolism.
- In some cases because of the efficiency of these metabolic enzymes only a small fraction of administered drug reaches the systemic circulation → LOW BIOAVAILABILITY.

First Pass Effect

- GI + Hepatic metabolism = FIRST PASS EFFECT

Drug Metabolism is comprised of two enzymatic phases

**Phase I Reactions**
- Oxidation, Reduction, Hydrolysis reactions
- Introduce (or unmask) a small functional group on the drug e.g., –OH
- Convert drug to a more polar metabolite
- Can alter the function of a drug (decreased, increased, unchanged)

**Phase II Reactions**
- Conjugation reactions introduce a large highly polar endogenous functional group onto the drug metabolite e.g., glucuronic acid, sulfuric acid, acetic acid, amino acid
- Conjugation often occurs via the functional group created by Phase I reactions
- Create a highly polar drug-conjugate (more H2O soluble)
- Drug-conjugates are typically inactive (not all, –morphine)
- Conjugation enhances drug excretion (urine/bile)

Multiple pathways of drug metabolism can lead to excretion

LIVER & GI Tract (also skin, kidney, lungs and brain)

- Phase I
- Phase II
- Excretion (Urine/Bile)

LIPOPHILIC

HYDROPHILIC

Parental Drug

Kidney/Urine

Bile/Feces
**Phase I reactions**

<table>
<thead>
<tr>
<th>A. Oxidative reactions</th>
<th>Enzyme(s) Involved</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Oxidative reactions</td>
<td>Cytochrome P450 (CYP450)*</td>
</tr>
<tr>
<td>Aromatic hydroxylations*</td>
<td>~75% of all Phase I reactions</td>
</tr>
<tr>
<td>Aliphatic hydroxylations*</td>
<td>Other enzymes (minor contributions)</td>
</tr>
<tr>
<td>Oxidative dealkylation*</td>
<td>- Flavin-containing monooxygenases</td>
</tr>
<tr>
<td>- S-Oxidation*</td>
<td>- Monooxygenases</td>
</tr>
<tr>
<td>- Deamination</td>
<td>- Alcohol dehydrogenases</td>
</tr>
<tr>
<td>- Dechlorination</td>
<td>- Aminodehydrogenase</td>
</tr>
<tr>
<td>- Amine oxidations</td>
<td>- Aldehyde dehydrogenase</td>
</tr>
<tr>
<td>- Desulfuration</td>
<td>- Alcohol dehydrogenase</td>
</tr>
<tr>
<td>- Alcohol/aldehyde dehydrogenation</td>
<td>- Alcohol dehydrogenase</td>
</tr>
</tbody>
</table>

**B. Reduction reactions**

- Azo reductions
- Nitro reductions
- Carbonyl reductions

**C. Hydrolysis reactions**

- Ester
- Amides
- Epoxides

**Cytochrome P450 Enzymes (microsomal-mixed functional oxidases)**

- A superfamily of enzymes involved in biosynthesis and metabolism
- Cytochrome P450: contains an oxygen-binding heme group to bind & facilitate transfer of molecular oxygen to the drug substrate
- Pigment purified from liver with characteristic 450 nm absorption peak in the presence of carbon monoxide
- Membrane bound enzyme located on Endoplasmic Reticulum
- Catalyzes an oxidation-reduction reaction involving molecular O2
- Mixed Function: enzyme catalyzes a reaction in which two substrates are oxidized simultaneously – Drug and NADPH cofactor
- Catalyze the oxidation of lipophilic substrates
- Oxidize both xenobiotics, drugs and endogenous substances
- Some CYP enzymes involved in steroid, bile acid & prostaglandin biosynthesis
- CYP450 enzymes account for the metabolism of ~75% of all drugs

**CYP450 enzyme reactions**

- CYP450 reactions require:
  - Drug substrate
  - Molecular oxygen – binds to the heme group in CYP450 before transfer to drug
  - NADPH + H+ – cofactor responsible for donating electrons to reduce molecular oxygen
  - NADPH-CYP450-oxido-reductase enzyme that catalyzes electron transfer from NADPH
- CYP450 enzymes catalyze a wide variety of oxidative reactions including:
  - Hydroxylations; Epoxidations; N-, S-Oxidations; O-, S-, N-dealkylations;
  - Deaminations; Desulfurations & Dechlorinations
The CYP450 superfamily

- 57 functional genes - organized into 18 families and 44 sub families

NOMENCLATURE: CYP3A4 - family 3, subfamily A, gene #4

- Expressed at highest levels in the liver and also in the GI tract
  - lower level expression in lung, kidney, CNS & other tissues

- In humans, 12 CYPs are responsible for metabolism of essentially all xenobiotics and drugs
  - CYP1A1, 1A2, 1B1, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, 3A4 and 3A5

- Most active enzymes for drug metabolism are the CYP2C, CYP2D and CYP3A sub families
  - CYP3A4 represents 30% of all CYP450 enzymes in the liver and accounts for the metabolism of >50% of clinically used drugs

CYP450 enzyme reactions

- CYP450 system has the capacity to metabolize a diverse array of drugs and xenobiotics
  - Multiple forms of CYP450s with distinct substrate specificities
    - 2C9 - weakly acidic molecules with an H-bond acceptor
    - 2C19 - neutral or weakly basic molecules or amides with 2 or 3 H-bond acceptors
    - 2D6 - basic molecules with protonatable nitrogen atom 4-7 Å from metabolic site
    - 3A4/5 - large and lipophilic molecules of diverse structures

- Enzymes are promiscuous and can metabolize multiple structurally distinct chemicals
  - A single compound can be metabolized by multiple CYP450 enzymes (different rates)
    - e.g. Citalopram is metabolized by 3A4, 2C19 and 2D6
  - Typically, most drugs are metabolized by several enzymes (redundancy)

- CYP450s can metabolize a single drug at multiple different positions on the molecule
  - e.g. 3A4 catalyzes both hydroxylation and N-demethylation of Clarithromycin

- A single CYP450 can catalyze multiple different chemical reactions
  - e.g. CYP3A4 - hydroxylation, N-demethylation, epoxidation, N,O-dealkylation and N,S-oxidation

Phase 1 metabolism of the proton pump inhibitor omeprazole by 2C19 & 3A4

- 90% Major Pathway
  - CYP2C19
  - Omeprazole (Active)
  - 5-hydroxy-omeprazole (inactive)

- 10% Minor Pathway
  - CYP3A4
  - Omeprazole sulphone (inactive)

EXCRETION
Phase II Drug Metabolism

- Lipophilic drugs that have undergone a Phase I reaction contain a polar functional group
  - e.g. –OH, –COOH, –NH₂
  - drug metabolite may still be pharmaceutically active or highly chemically reactive
  - may not be sufficiently water soluble to allow for efficient excretion

- Phase II reactions catalyze the conjugation of large endogenous polar compounds to the functional group of the drug metabolite
  - e.g. glucuronic acid, sulfuric acid, acetic acid, amino acid, glutathione
  - reactions take place in the cytoplasm (exception glucuronidation on ER membrane)
  - in most cases inactivate drug activity (not always e.g. morphine 6G is more active)
  - important for inactivating highly reactive species sometimes formed by Phase I
  - creates a highly polar drug-conjugate
  - drug-conjugate is more water soluble and unable to freely diffuse across membranes
  - enhances drug elimination in either the URINE or BILE

- Some parental drugs that contain –OH, –COOH or –NH₂ functional groups can directly undergo Phase II metabolism without prior phase I metabolism - e.g. morphine, isoniazid

Phase II reactions

- Commonly involve the transfer of a large polar molecule to the drug metabolite
  - require: - the drug substrate with suitable functional group
  - a specific enzyme
  - an “activated high energy” cofactor/co-substrate e.g. UDP-glucuronic acid

- Glucuronidation is most frequent and important of the phase II reactions
  - promotes excretion in both urine and bile

<table>
<thead>
<tr>
<th>REACTION</th>
<th>ENZYME</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucuronide conjugation</td>
<td>UDP-glucuronosyltransferase (UGT)</td>
</tr>
<tr>
<td>Glutathione conjugation</td>
<td>Glutathione S-transferase (GST)</td>
</tr>
<tr>
<td>Sulfate conjugation</td>
<td>Sulfotransferase (ST)</td>
</tr>
<tr>
<td>Acetylation</td>
<td>N-Acetyltransferase (NAT)</td>
</tr>
<tr>
<td>Methylation</td>
<td>Methyltransferase (MT)</td>
</tr>
</tbody>
</table>

Overview of the Phase I/II metabolism of the antiepileptic drug phenobarbital

Phase 1

- Phenobarbital (active)
  - CYP2C9
  - p-hydroxy phenobarbital (reactive)

Phase 2

- UDP-glucuronosyl transferase (UGT2B7)
- Drug Conjugates
Prodrugs require drug metabolism for their activation

- Prodrugs are inactive compounds that are metabolized in the body to their active forms e.g., Clopidogrel, Irinotecan, Codeine, Prednisone, Levodopa, Captopril
- Metabolism of the prodrug results in the formation of the pharmaceutically active metabolite
- The active metabolite is ultimately inactivated by further metabolism
- Useful when the prodrug has a better pharmacokinetic profile than its active metabolite e.g., solubility, absorption, distribution, stability, toxicity etc.

<table>
<thead>
<tr>
<th>Clopidogrel (INACTIVE)</th>
<th>Intermediate metabolite</th>
<th>Active metabolite</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP2C19&lt;br&gt;CYP3A4&lt;br&gt;CYP3A5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CYP2C19&lt;br&gt;CYP2D6&lt;br&gt;CYP3A4</td>
<td></td>
<td></td>
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<tr>
<td>CYP2C19&lt;br&gt;CYP2D6&lt;br&gt;CYP3A4</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Metabolism of the chemotherapeutic prodrug Irinotecan

- Water soluble moiety
- SN38 (Active metabolite)
- SN38-Glucuronide (Inactive metabolite)
- Much greater water solubility compared to active metabolite
- Cancer cell killing
- Excretion

Drug Excretion

- The KIDNEY accounts for the excretion of most drugs. Unbound water soluble polar drug metabolites are either filtered or actively secreted into the proximal tubules and excreted in the URINE.
- Some drugs and their metabolites are excreted in the BILE (Mr >500 Da with both polar and lipophilic groups)
- Drugs are actively transported into the bile and stored in the gallbladder before release into the GI tract
- Only a fraction of drug is eliminated in the feces
- Bacterial enzymes in the GI tract can hydrolyze drug conjugates
- Drugs can be reabsorbed and enter the circulation again where they undergo further hepatic metabolism.
- Enterohepatic recirculation
- This can recur until the drug is either completely metabolized or excreted by the kidney or bile
- Can significantly prolong pharmacological effect of drugs
- Reducing clearance & extending half-life
- Increases plasma exposure (AUC)
Metabolic Drug Interactions

- Interactions between drugs can occur when an individual is co-administered two or more drugs.
- The presence of one drug may affect the metabolism of another drug leading to changes in drug concentrations that can lead to:
  - Adverse effects & Toxicity
  - Changes in therapeutic efficacy
- Drugs may affect the metabolism of other drugs through two principal mechanisms:
  I. Induction of drug metabolic enzymes
  II. Inhibition of drug metabolic enzymes

Drug Interaction Mechanism I: CYP450 Enzyme Induction

- Some drugs and xenobiotics are known to induce the expression of specific CYP450 enzymes e.g. rifampin, phenytoin, phenobarbital, carbamazepine & St. John's wort all induce the CYP3A4
- Inducing drugs serve as ligands for specific transcription factors that promote the increased transcription of specific CYP450 genes

CYP450 induction:
- Increases metabolism of the CYP450 enzyme substrates
- Decreases drug activity (increases in the case of a prodrug)
- Increases drug clearance
- Can reduce drug concentration below a critical therapeutic dose and result in treatment failure

Drug Interaction Mechanism II: CYP450 Enzyme Inhibition

- Some drugs can inhibit the activity of CYP450 enzymes (+ other drug metabolizing enzymes)
  - Drugs can be both substrates and inhibitors of the same CYP450 enzyme
  - Drugs can be a substrate of one enzyme and an inhibitor of another enzyme
- Inhibition can be either – REVERSIBLE: Competitive or allosteric
  - IRREVERSIBLE: Suicide inhibitor (covalent binding)
- Inhibitors decrease drug metabolism resulting in an increase in the concentration of drug
  - Potential for toxicity - especially with drugs that have a narrow therapeutic window!
### List of some known inducers and inhibitors of CYP450 isozymes

<table>
<thead>
<tr>
<th>CYP450</th>
<th>Inhibitors</th>
<th>Inducers</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP3A4</td>
<td>Amiodarone (M)</td>
<td>Rifampin</td>
</tr>
<tr>
<td></td>
<td>Ciclosporin (W)</td>
<td>Carbamazepine</td>
</tr>
<tr>
<td></td>
<td>Diltiazem (M)</td>
<td>Phenytoin</td>
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<tr>
<td></td>
<td>Flavoxate (S)</td>
<td>Glucocorticoids</td>
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<tr>
<td></td>
<td>Verapamil (M)</td>
<td>Phenytoin</td>
</tr>
<tr>
<td></td>
<td>Ketoconazole</td>
<td>Glucocorticoids</td>
</tr>
<tr>
<td>CYP2C9</td>
<td>Amiodarone</td>
<td>Phenytoin</td>
</tr>
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<td>CYP2C19</td>
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<td>Ketoconazole</td>
<td>Carbamazepine</td>
</tr>
</tbody>
</table>

### Grapefruit juice increases the oral bioavailability of CYP3A4-metabolized drugs

- CYP3A4 is expressed in the GI tract and metabolizes drugs during the absorption process - decreasing their bioavailability (part of the first pass effect)
- Grapefruit juice contains compounds (e.g. naringin & furanocoumarins) that inhibit CYP3A4 activity
- These compounds inhibit 3A4 in enterocytes, thereby decreasing 3A4 metabolism of drug in the GI tract (No effect on hepatic CYP3A4)
- As a result, more drug reaches the liver and ultimately the systemic circulation - Increasing drug bioavailability - increased potential for ADVERSE EFFECT

### Examples of CYP450-mediated drug interactions

#### Interactions with CYP450 Inducers

<table>
<thead>
<tr>
<th>Drug</th>
<th>CYP450</th>
<th>Interaction</th>
<th>Consequence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclosporin</td>
<td>3A4 substrate</td>
<td>Rifampin - 3A4 inducer</td>
<td>- Ritampin induces 3A4 expression</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Increased expression of 3A4 increases the metabolism of cyclosporin</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Reduced levels of cyclosporin increases the risk of organ rejection</td>
</tr>
<tr>
<td>Clopidrogel</td>
<td>2C19 substrate</td>
<td>Rifampin - 2C19 inducer</td>
<td>- Ritampin increases 2C19 expression</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Increased 2C19 increases the metabolism of the clopidrogel prodrug</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Increased production of active metabolite increases risk of bleeding</td>
</tr>
</tbody>
</table>

Grapefruit juice increases the oral bioavailability of CYP3A4-metabolized drugs.
Interactions with CYP450 inhibitors

Cyclosporin – 3A4 substrate
- immunosuppressant drug
- concentration-dependent nephrotoxicity

Itranaconazole – Potent 3A4 inhibitor
- antifungal agent

Consequence
- Itranaconazole inhibits activity of 3A4
- reduced 3A4-mediated metabolism of cyclosporin
- cyclosporin levels increase
- increased potential for cyclosporin-mediated nephrotoxicity

Lopinavir – 3A4 substrate
- Anti-HIV protease inhibitor
- extensive first pass effect limits use
- difficult to achieve effective therapeutic levels

Ritonavir – potent 3A4 inhibitor
- Anti-HIV protease inhibitor
- significant GI adverse effects

Consequence
- Low does of ritonavir has no GI effects but potently inhibits 3A4
- decreases first pass metabolism of Lopinavir "Boosting" its levels
- enhanced anti-HIV effect of Lopinavir

Drug Interaction Mechanisms III- effects on UDP glucoronyltransferase enzymes

Phase II glucoronyltransferase enzymes can also be either induced or inhibited by specific compounds including other drugs
- less well understood than CYP450-mediated PK drug-drug interactions
- many drugs are metabolized by multiple UGT enzymes (redundancy may limit effect)
- clinically relevant interactions may be potentially limited to drugs that are selectively metabolized by specific UGT enzymes

<table>
<thead>
<tr>
<th>Inducers</th>
<th>Inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>e.g. Phenobarbital, Phenytoin, Rifampin Ethyl Estradiol &amp; Carbamazepine</td>
<td>e.g. Atazanavir, Erlotinib, Nilotinib &amp; Valproate</td>
</tr>
<tr>
<td>➢ Increase enzyme expression</td>
<td>➢ Decrease enzyme activity</td>
</tr>
<tr>
<td>➢ Promote Phase 2 metabolism</td>
<td>➢ Decrease Phase 2 metabolism</td>
</tr>
<tr>
<td>➢ Promote drug elimination</td>
<td>➢ Increase concentration of active drug</td>
</tr>
<tr>
<td>➢ Decrease clinical efficacy of certain drugs e.g. Lamotrigine, irinotecan (SN-38)</td>
<td>➢ Increase toxicity of certain drugs e.g. Irinotecan (SN-38), Statins</td>
</tr>
</tbody>
</table>

Factors affecting Drug Metabolism

- Age
  - Neonates vs Geriatrics: differences in enzyme expression levels
  - decreased activity of Phase I metabolism in the elderly (~30-40%) dose reduction
  - conjugating enzyme deficiency in infants
    o Cause of gray baby syndrome in infants given chloramphenicol
    o Due to a build up of a Phase I chloramphenicol oxidation metabolite resulting in circulatory collapse and cyanosis

- Pregnancy
  - the activity of some enzymes increase (2C9, 2D6 & 3A4), while others decrease (1A2 & 2C19)
• Diet and Environment
  - *grapefruit juice and other dietary components can inhibit CYP450 enzymes***
    - grapefruit juice inhibits intestinal 3A4 not hepatic 3A4
    - affects bioavailability NOT half life
    - A single 8oz glass can inhibit 3A4 for 24-48 hrs
  - ***St. John's wort a herbal medication induces CYP3A4 expression***
  - chemicals in cigarette smoke, charbroiled food and cruciferous vegetables all induce CYP1A2 (~3 fold)
    - smokers sometimes need higher doses of certain drugs metabolized by CYP1A2 e.g. theophylline (Asthma/COPD), some antidepressants
  - chronic alcohol induces expression of CYP2E1 (affects acetaminophen metabolism)
  - a number of pollutants and xenobiotics are also known to induce specific CYP450 enzymes

• Disease
  - diseases that effect the liver or blood flow to the liver (e.g. cardiac disease)
  - inflammatory cytokines decrease expression of many CYP450 isoforms

• Metabolic drug interactions
  - CYP450 induction and inhibition can affect drug toxicity/efficacy
  - some drugs induce the enzyme responsible for their own metabolism, reducing levels of active drug over time (Pharmacokinetic tolerance) e.g. Carbamazepine

• Interactions between drugs and endogenous compounds
  - Atazanavir causes indirect bilirubinemia by inhibiting UGT1A1 and preventing the glucuronidation of bilirubin leading to a build up of unconjugated bilirubin in the blood

• Genetics
  - many of the enzymes involved in drug metabolism are polymorphic
  - individuals express different enzyme alleles with different activities & expression
  - results in individual-to-individual differences in the efficiency of drug metabolism and drug responses

Summary of Drug Metabolism

| Lipophilic Drug |  >Polar Drug |
| Active Drug |  >Inactive Drug |
| Active Drug |  >Active metabolite |
| Prodrug |  >Active Drug |
| Unexcretable Drug |  >Excretable Drug |

**Phase I**
- Oxidation/Reduction
- Hydrolysis
- (CYP450 + others)
- Excreted unchanged

**Phase II**
- Conjugating Enzymes
- Glucuronidation
- (Transferases)
- Excreted unchanged

**EXCRETION**
- Urine/Bile