BPS3102: Principles of Toxicology and Pharmacology

Pharmacokinetics III:

Metabolism – Biotransformation Part 1

- ***Metabolism of xenobiotics***
  - ***Purpose, scope***
  - ***Kinetics***
  - ***Phase I metabolism***
  - ***Phase II metabolism***
  - ***Phase 0/III – transport in and out of cells***

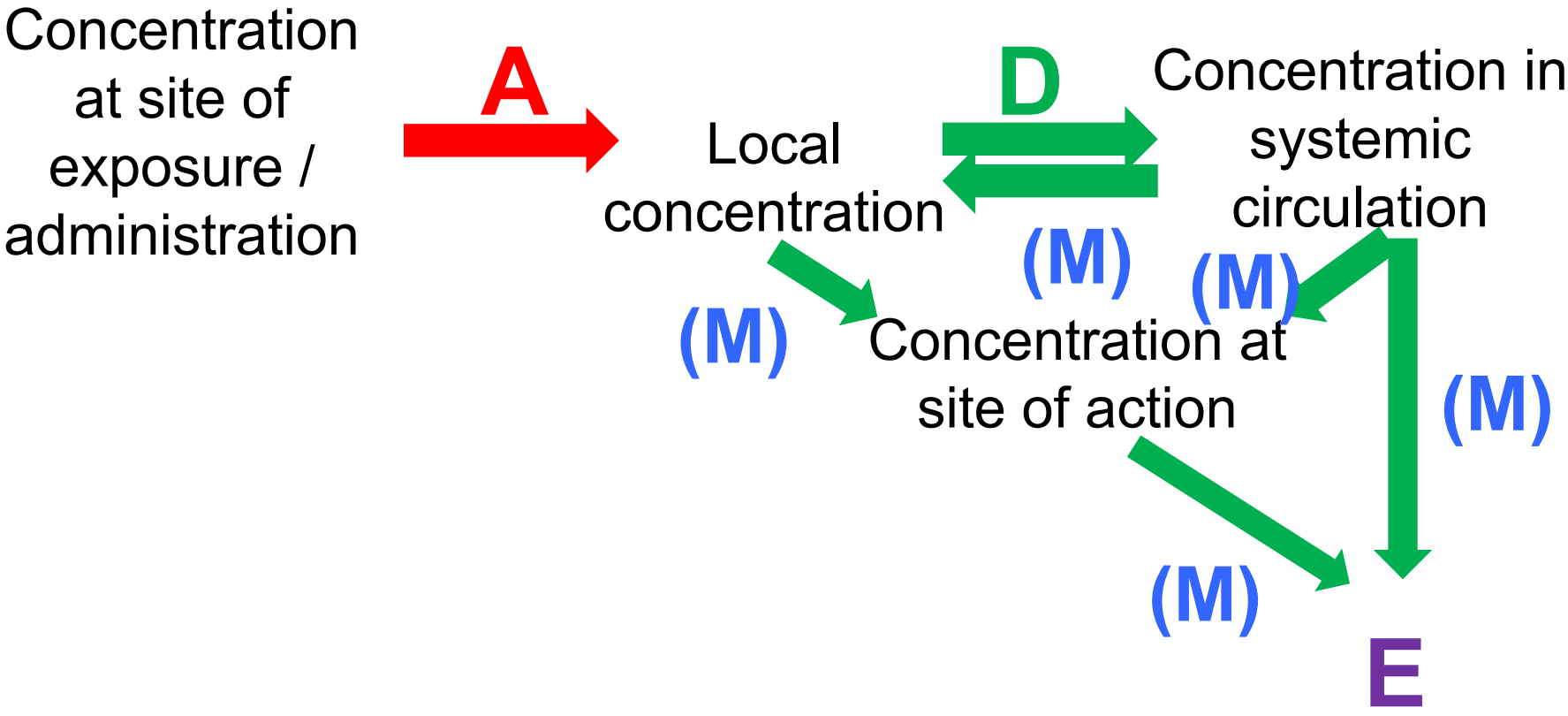
BPS3102: Principles of Toxicology and Pharmacology

Metabolism: ***Learning objectives***

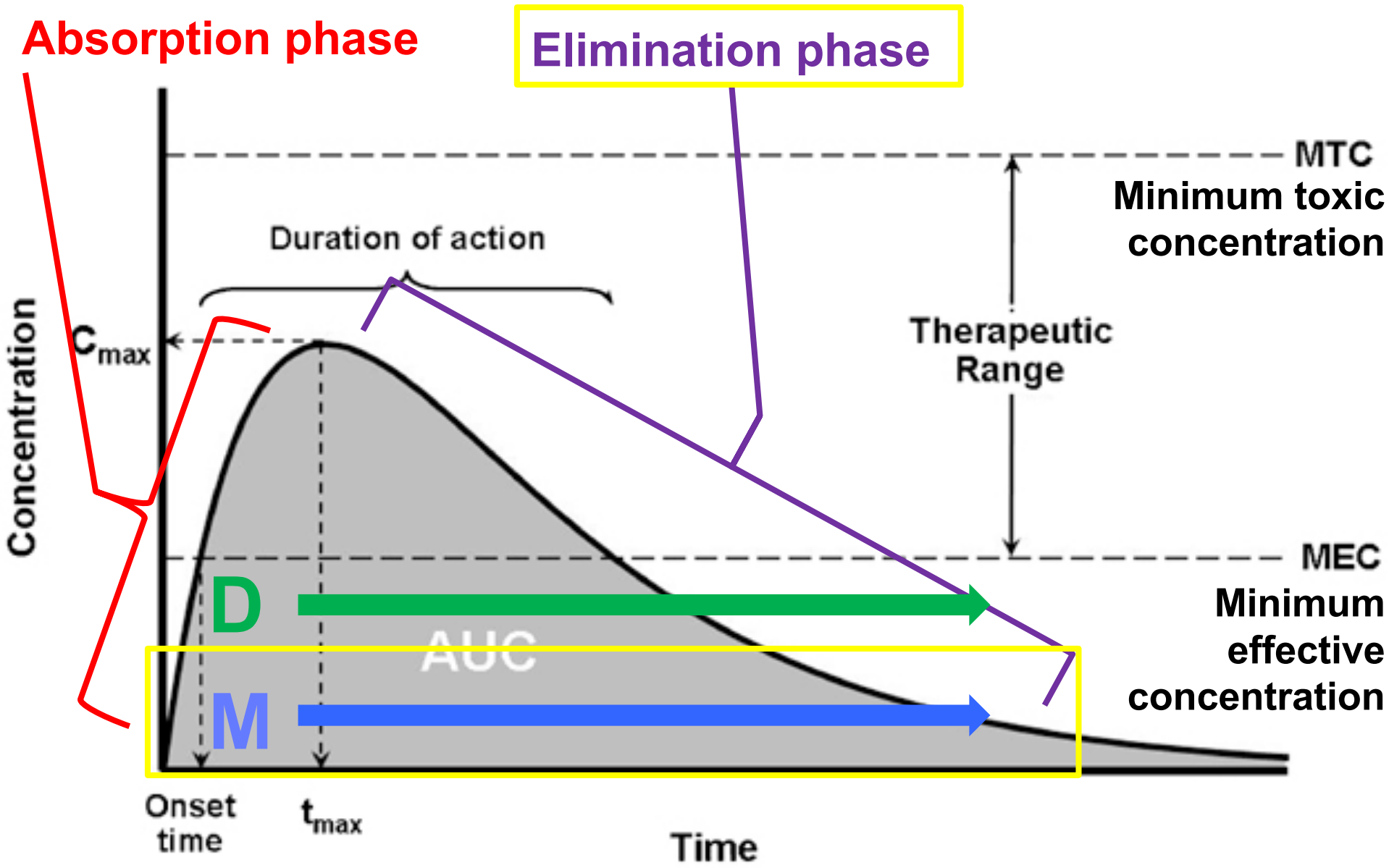
- *To understand and interpret/apply the kinetics of metabolism and the effects of induction and inhibition*
- *To differentiate between the reactions and enzymes of Phase I and Phase II metabolism*
  - *To predict how the properties of a substance and organism relate to metabolism*
  - *To predict how route of administration/exposure, absorption and distribution relate to metabolism*

  – *impacts on bioavailability and pharmacodynamics*

Pharmacokinetics

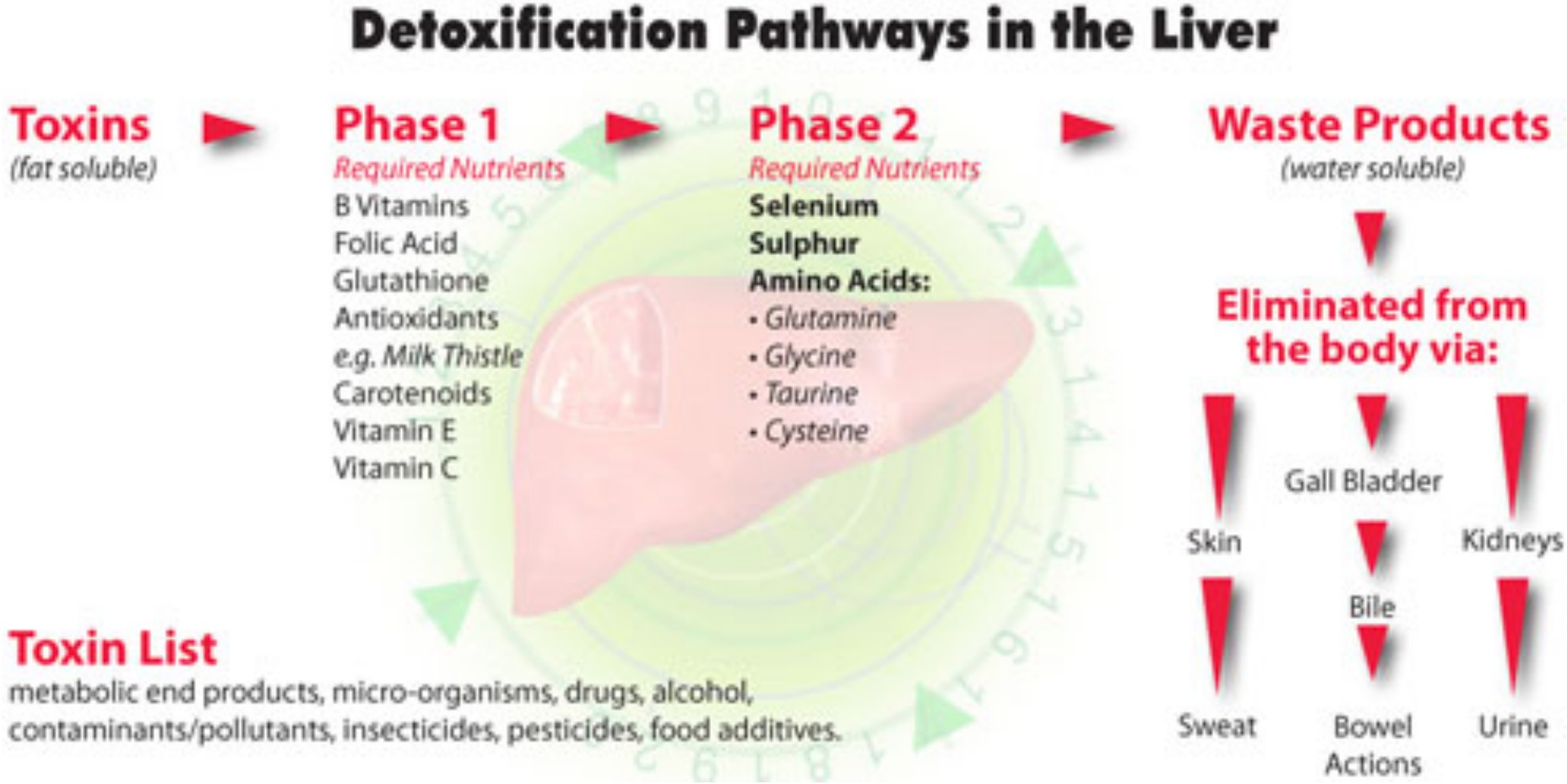


PK curve revisited

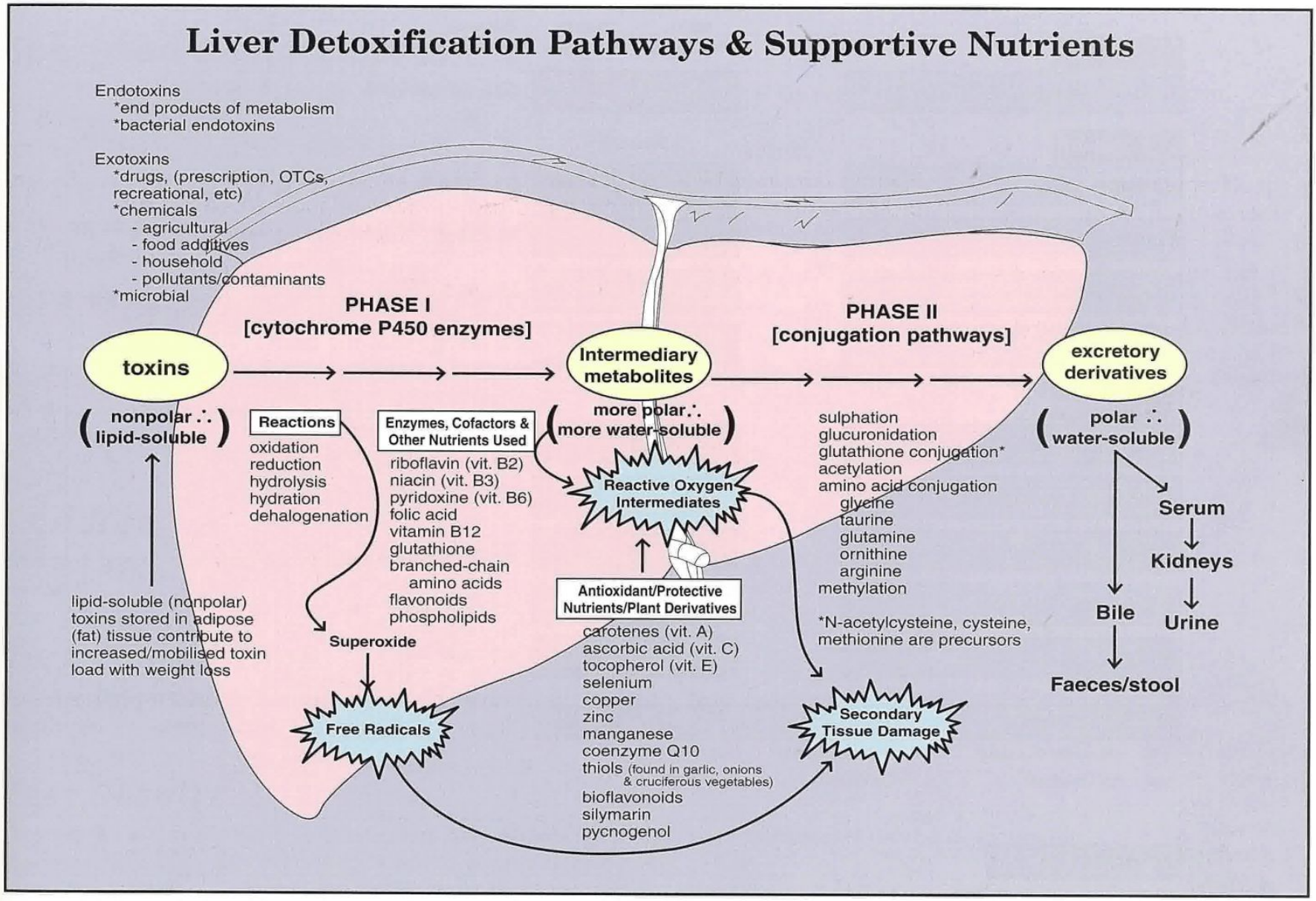


Today's lecture is dedicated to:

Liver



Today's lecture is dedicated to:



Xenobiotic metabolism

Primary objective:

- To deactivate and facilitate the elimination of xenobiotics from the body

Primary obstacle:

- Lipophilic nature of xenobiotics
  - how they got in the 1st place!

- Lipophilicity hinders elimination
  - in kidney, lipophilic compounds are largely reabsorbed into systemic circulation
  - hydrophilic compounds excreted in urine

Xenobiotic metabolism

Primary products:

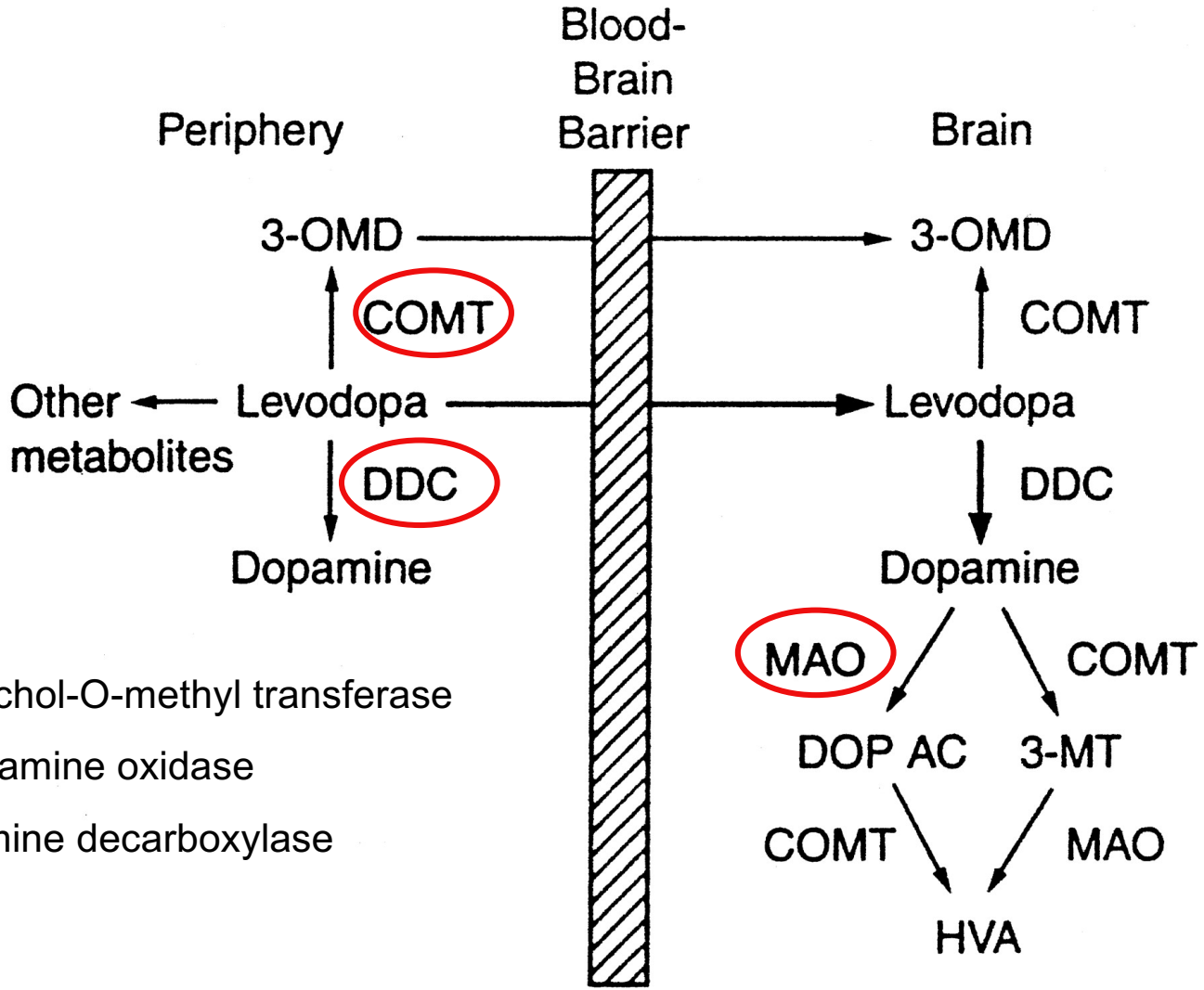
- More polar and/or charged metabolites (water soluble)
- Inactive metabolites of active substance (most drugs)
- Active metabolites of active substances (e.g. digoxin from digitoxin)
- Active metabolites from inactive or less active substances (prodrugs/toxins; e.g. levodopa)
- Also applies to endogenous compounds (e.g. steroids, vitamins, fatty acids, levodopa)

Primary sites (organs):

- ***Liver***
- Small intestine
- Kidney, lungs, skin, brain…

Xenobiotic metabolism

Prodrug – example : Levodopa



COMT: catechol-O-methyl transferase

MAO: monoamine oxidase

DDC: dopamine decarboxylase

Xenobiotic metabolism – Scope of reactions

Scope of metabolism:

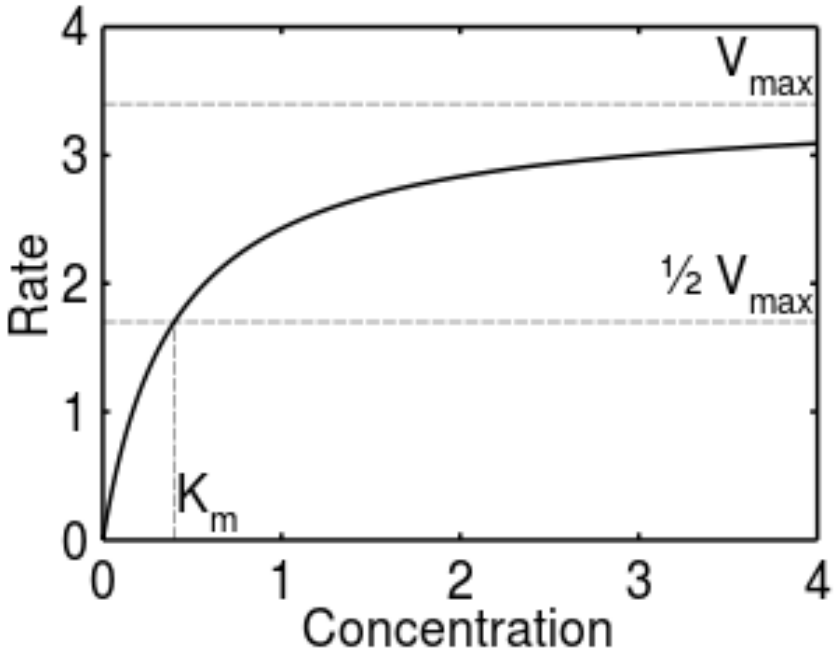
- Oxidation of C, N, S
  - Side-chain, aromatic, deamination
- Reduction – aldehyde (to alcohol), nitro, nitroso, azo (to amino)
- Hydrolysis – amides, esters, epoxides; desulphuration, dehalogenation
- Hydration
- Conjugation – amidation, esterification, etherization, hemiacetal & mixed anhydride formation
- Condensation

Xenobiotic metabolism

Kinetics:

The transformation of most xenobiotics is catalyzed by enzymatic reactions that obey Michaelis-Menten kinetics:

$$\upsilon = \frac{V_{\max}[S]}{K_m + [S]}$$



υ = reaction rate, [*S*] = substrate concentration

V_{max} = maximum rate achieved at saturating substrate concentrations.

K_m = substrate concentration at which the reaction rate is half of V_{max}

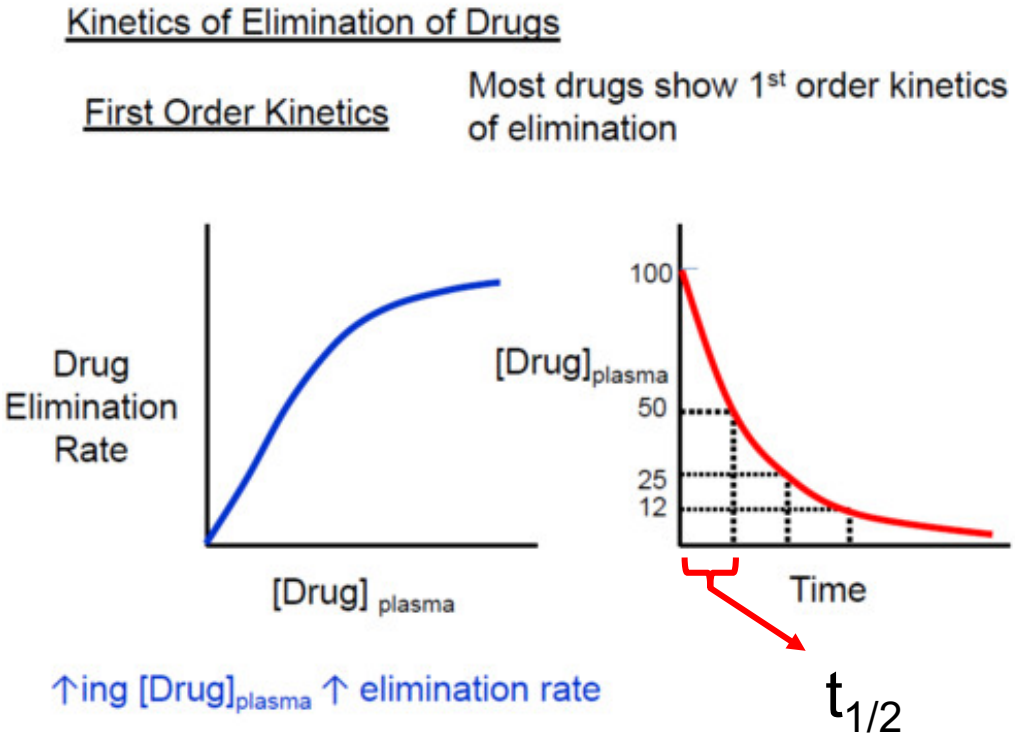
Xenobiotic metabolism

1st order kinetics: reaction rate is proportional to [S] (free/unbound state)

- In most clinical situations, [S] << *K*

$$\upsilon = \frac{V_{\max}[S]}{K_m}$$

- A constant ***fraction*** of substrate is metabolized per unit time
- Assume that clearance (hepatic or renal) mechanisms are **not** saturated
- $T_{1/2}$ = half-life
  - time required to reduced plasma concentration to ½ its initial value

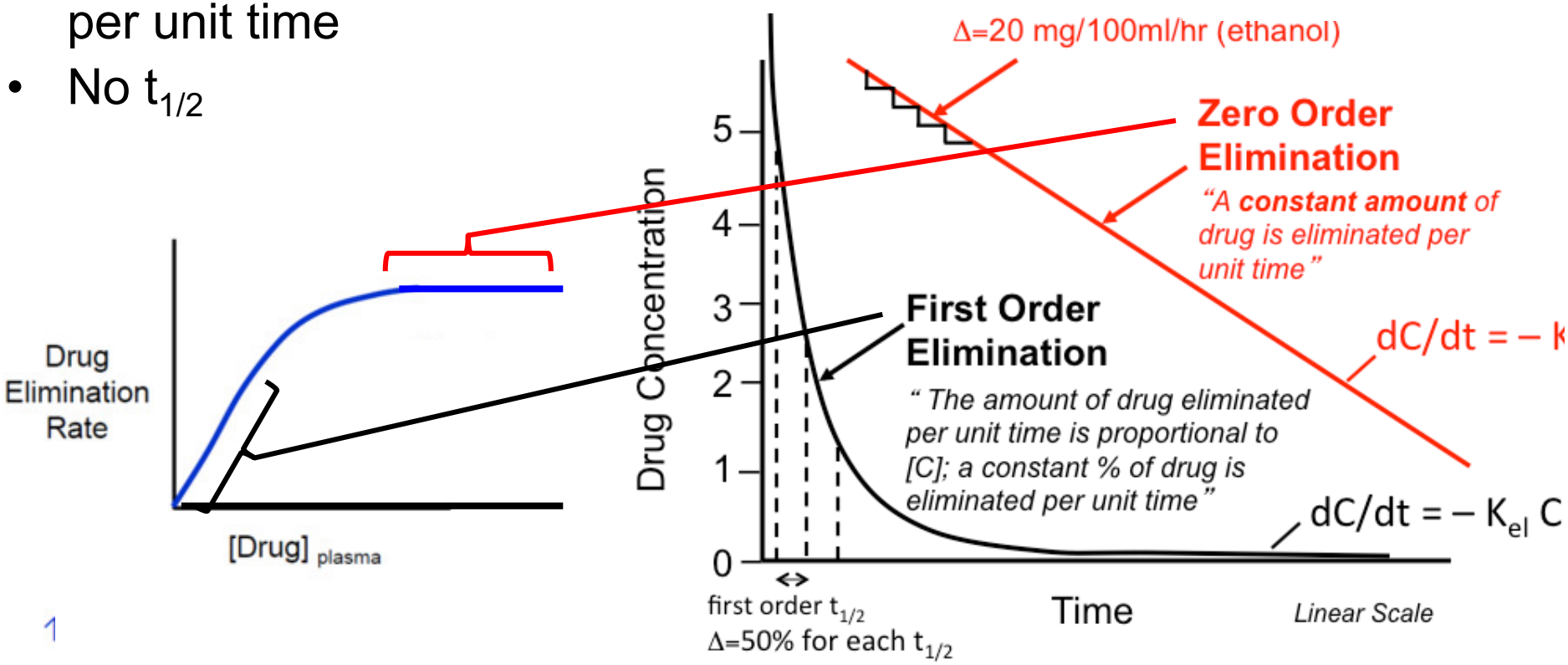


Xenobiotic metabolism

Zero-order kinetics: reaction rate is constant and independent of [S]

- With very large doses, [S] >> *K*
- A constant ***amount*** of substrate is metabolized per unit time
- No $t_{1/2}$

$$\upsilon = \frac{V_{max}[S]}{[S]}$$



Rate of absorption

(from site of exposure or administration)

Amount remaining at site

$$-\frac{dx_a}{dt} = k_a(x_a)_t$$

$$(x_a)_t = (x_a)_{t=0}e^{-k_a t} = F x_o e^{-k_a t}$$

Bioavailability

Dose

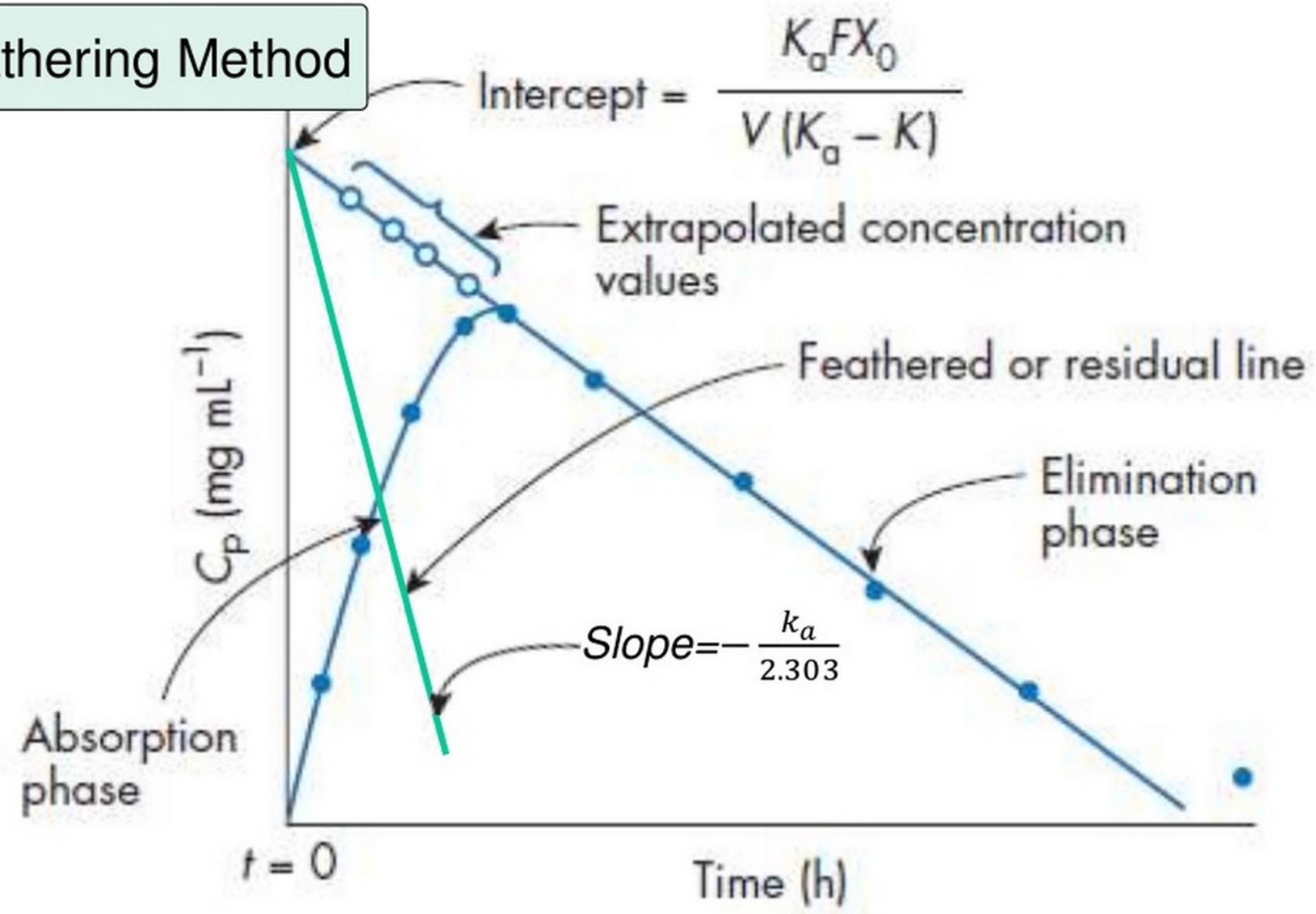
1st order kinetics: reaction rate is proportional to substance concentration

Applies to: passive diffusion, unsaturated facilitated and active processes

Calculation of absorption rate constant

Method of Residuals

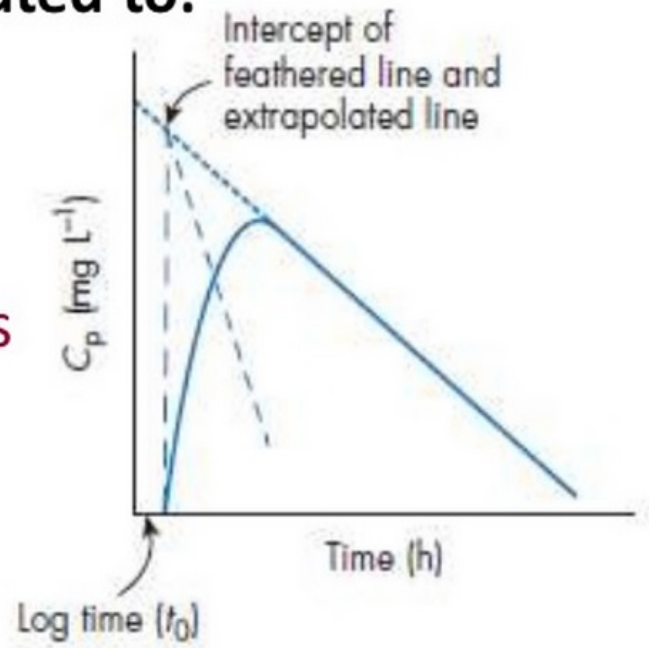
Feathering Method



Delayed absorption

Theoretically, intercepts of the terminal linear portion and the feathered line should be the same; however, sometimes, these two lines do not have the same intercepts, Sometimes absorption starts after administration, this delay may be contributed to:

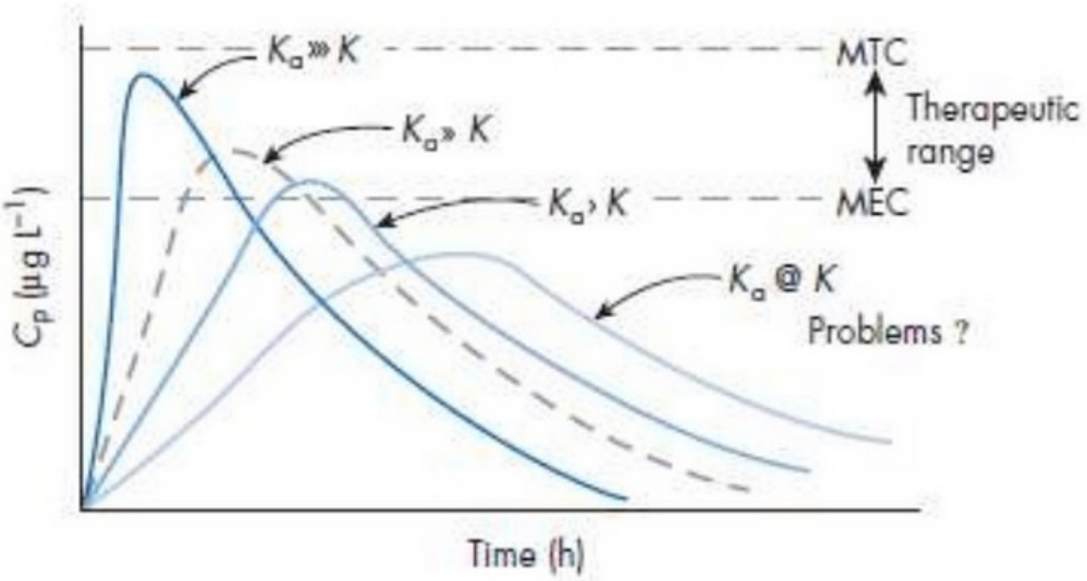
- Slow tablet disintegration
- Slow and/or poor dissolution
- Incomplete wetting of drug particles
- Poor formula
- Delayed Release formula



Influence of K_a (and K_e)

$$k_a \gg k_e$$

- Quicker Absorption
- Faster Onset of Action



Rate Constant

- K_a = absorption rate constant
- K_e = elimination rate constant

k_a for a given drug can change as a result of:

- Changing the formulation
- Changing the dosage form or the extravascular route of administration.
- Administration of a drug with or without food.
- Health of the organism

Phases of metabolism

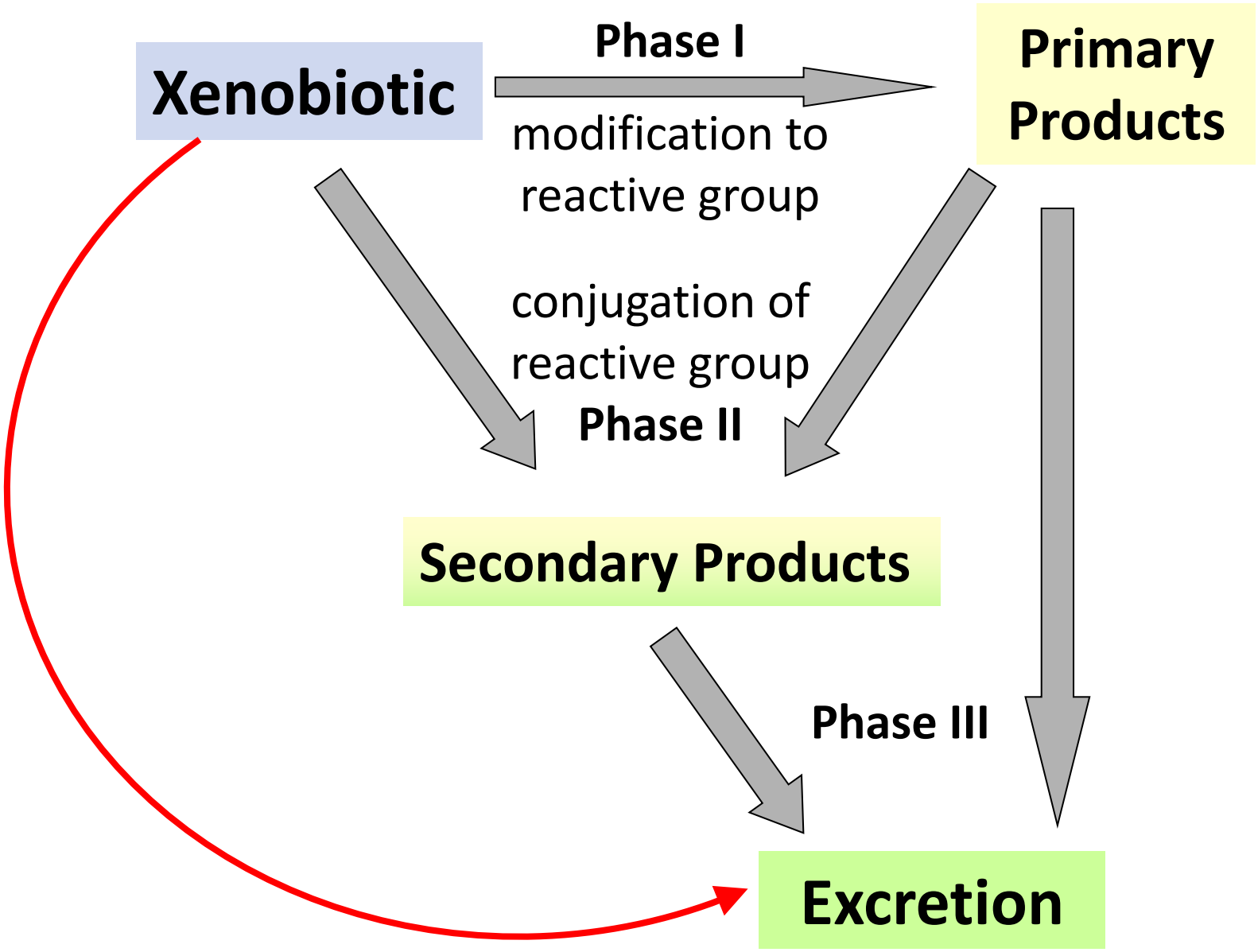
Phase 0 – transport of xenobiotics into the cell (uptake pumps)

Phase I - metabolic modification (oxidative, reductive, hydration, hydrolysis, isomerization)

Phase II - conjugation

Phase III – transport of metabolized xenobiotics (metabolites) out of cells (efflux pumps) and/or further metabolism

Phases of metabolism



Phase I & II metabolites

- **Phase I (& II)** metabolites are generally more polar and less-lipid soluble than parent
  - lower penetration into tissues
  - less tubular resorption

- **Phase II (& I) metabolites** are generally less active than parent
  - may retain some activity and toxicity
  - “inactive” at target site does not always mean inactive
  - Phase I metabolites are generally more active / toxic than Phase II metabolites

Phase I Enzymes

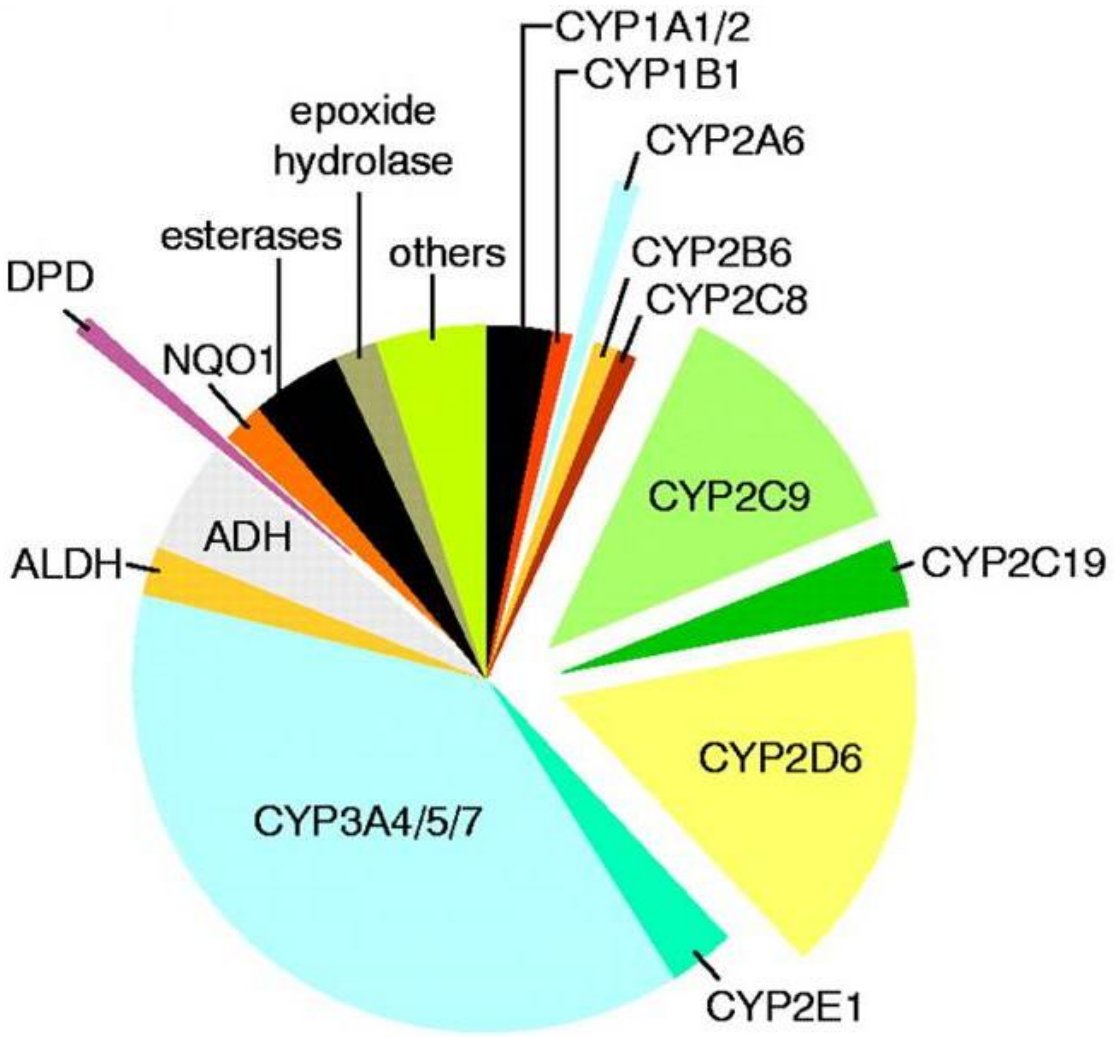
Are located predominantly in liver cells

- **ER:** rough endoplasmic reticulum – protein synthesis (ribosomes)
  smooth endoplasmic reticulum – site of xenobiotic metabolism
- Hepatic microsomes (microsomal fraction of homogenized hepatocytes)
- Abundance and diversity of enzymes with broad specificity
  - **Lipophilic xenobiotics and metabolites (Phase I)**
  - Conjugation (glucoronidation only – Phase II)
- Can be induced and inhibited

Phase I Enzymes

Add reactive groups
(e.g. -OH, -SH, $-NH_2$)

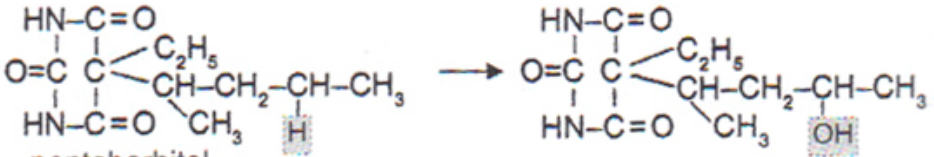
Remove/replace groups to increase polarity
(e.g. $-CH_3$, $-NH_2$)
(Oxidation)



Other enzymes:
- Dehydrogenases
  - alcohol, aldehyde, NHDPH
- Epoxide hydrolases
- Esterases
- Flavin containing monooxygenases
- Monoamine oxidase
- S-oxidases
- aldehyde and xanthine oxidases

Phase I Enzymes

1 Side-chain hydroxylation

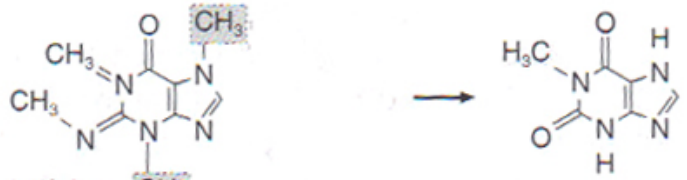


pentobarbital

2 Ring hydroxylation

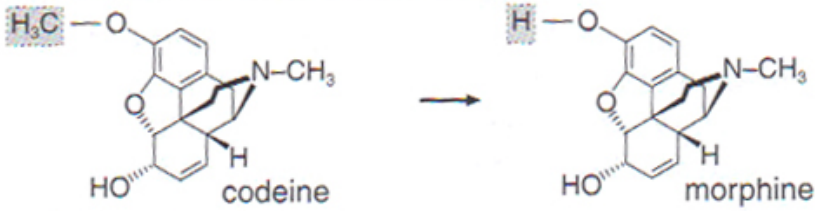
phenobarbital

3 Removal of methyl group from ring nitrogen



caffeine

4 Removal of methyl group from oxygen



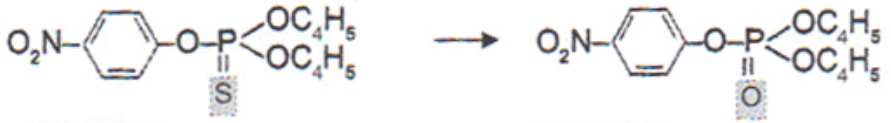
5 Oxidation of an amine

aniline

6 Removal of $-NH_2$ group

amphetamine

7 Replacement of sulfur by oxygen



parathion paraoxon

. Oxidative reactions catalyzed by microsomal enzyme systems.

Inducers and Inhibitors

- **Many Phase I enzymes can be *induced* or *inhibited***
  - CYP P450 enzymes are important targets (mechanisms) of pharmaco/toxicokinetic interactions

Inducers – substances that elicit increased activity of one or more metabolic enzymes

- ↑ biosynthesis not ↓ degradation
- ↑ biotransformation & ↓ plasma concentration of parent
- ↓ effects if metabolite is inactive or ↑ effects if metabolite is active
- Drugs, natural products, and pollutants

Inducers and Inhibitors

Inhibitors – substances that reduce or inhibit the activity of one or more metabolic enzymes

- *Competitive inhibition*: multiple substances metabolized by the same isozyme (inhibitor is also a substrate)
  - compete for the same active site
  - depends on substance concentration, affinity for the enzyme, and reaction rate
- *Non-competitive* & *uncompetitive inhibition*: substances do not compete for the same active (inhibitor is not a substrate)
  - binding of inhibitor prevents or slows enzymatic activity

- ↓ biotransformation & ↑ plasma concentration of parent
- ↑ effects (inactive metabolite) or ↓ effects (active metabolite)
- Drugs, natural products, and pollutants

Inducers and Inhibitors

Inhibitors

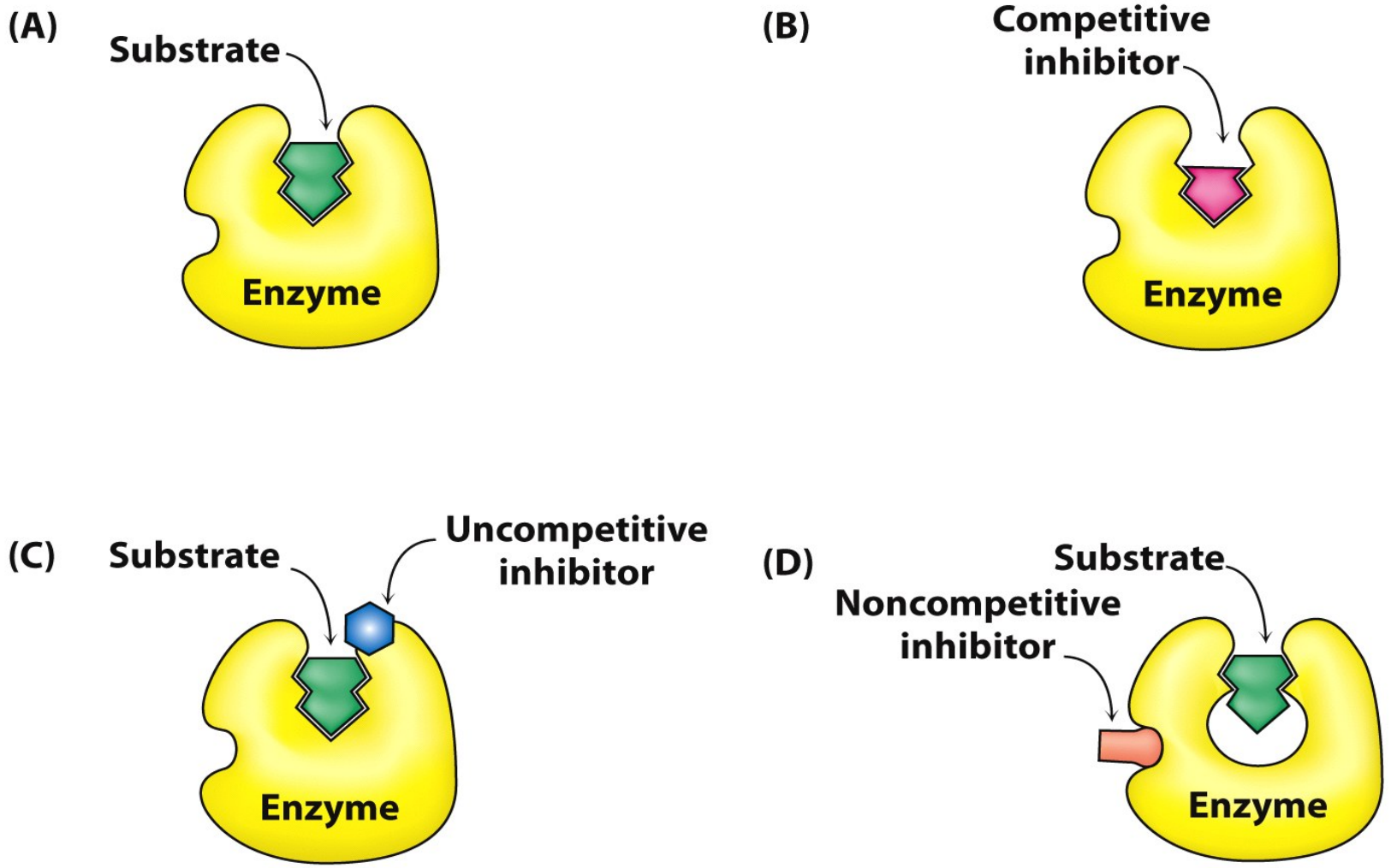
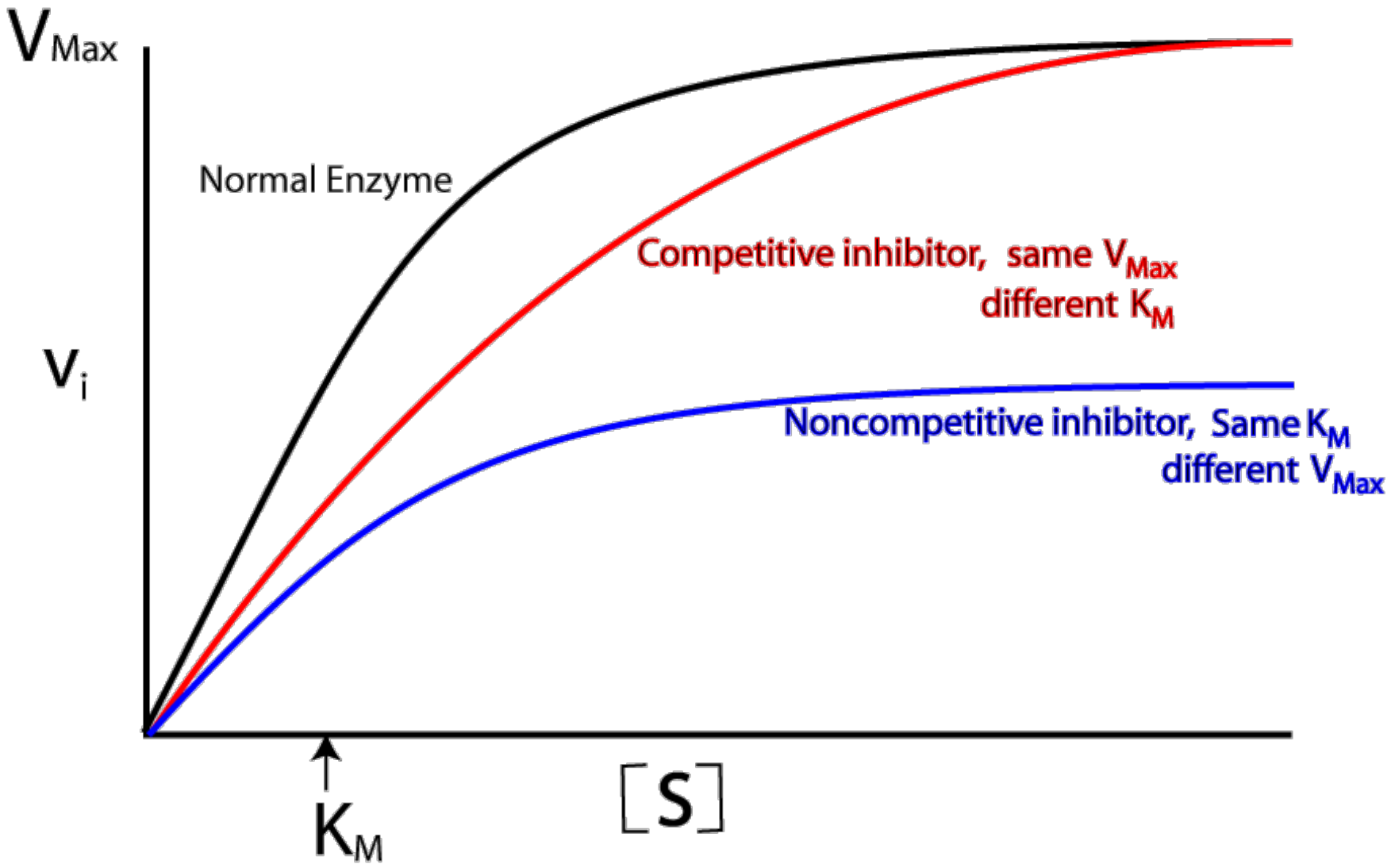


Figure 8.14
***Biochemistry*, Seventh Edition**

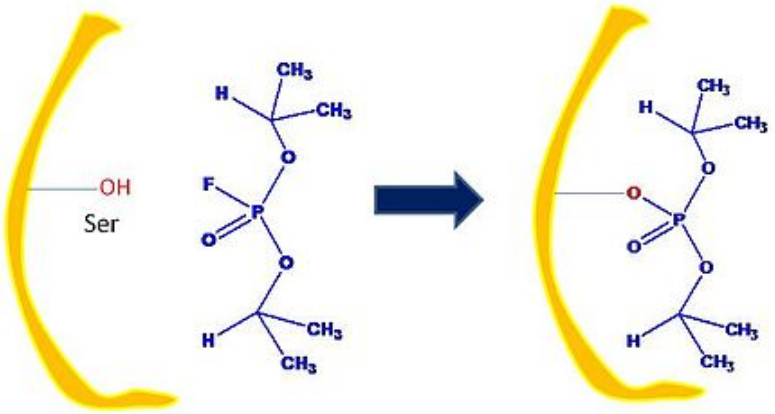
Inducers and Inhibitors

Inhibitors

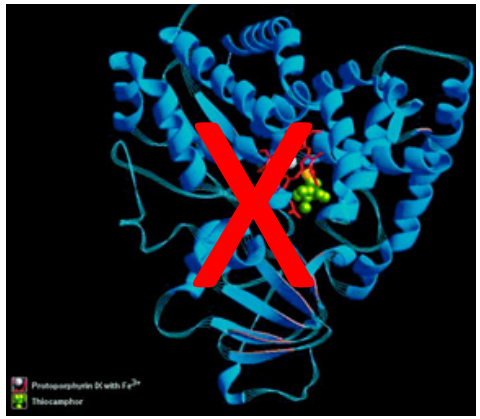


Inducers and Inhibitors

- Suicide inhibition



AChE DIFP irreversible inactivation



AChE = Acetylcholinesterase
DIFP = Diisopropyl fluorophosphate

Grapefruit furanocoumarins:

CYP: 1A1, 1A2, 2A6, 2A13, 2B1, 2B4, 2B6, 2C9, 2C19**, 2D6, 2E1, 3A4/5…**

- Affects metabolism of many substances
- Furanocoumarins and other substances capable of suicide inhibition are present in other fruits and vegetables.

Cytochrome P450 Superfamily

Superfamily of heme-thiolate proteins

(monooxygenase system)

- originally viewed as a singe non-selective enzyme

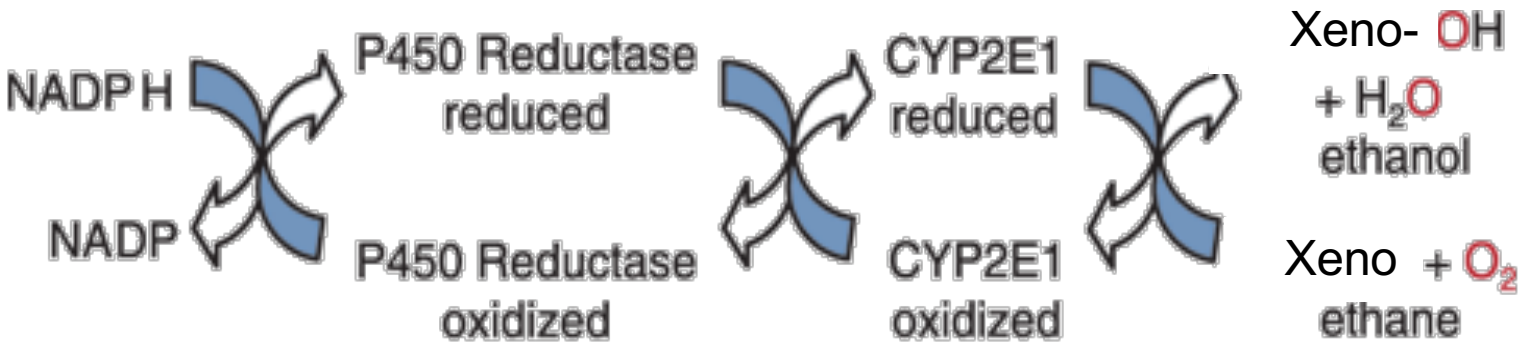
- Associated with the (smooth) endoplasmic reticulum of hepatocytes

Cytochrome P450 Superfamily

Superfamily of heme-thiolate proteins

- widely distributed in animals, bacteria, fungi, plants, protists, viruses
- more than >2700 P450 sequences identified
- microsomal, mitochondrial, bacterial

Cytochrome P450 Superfamily



CYPs are expressed in many tissues:

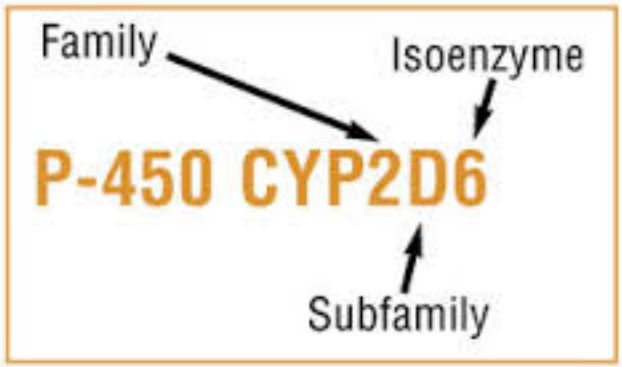
- liver, intestine, brain, kidney, placenta, lung, adrenal gland, pancreas, skin, mammary gland, uterus, ovary, testes and prostate
- Low expression in extrahepatic tissues
- Expression can be induced and up-regulated
- Basal expression and up-regulation in extrahepatic tissues can affect local disposition and toxicity

Pavek & Dvorak Curr Drug Metab, 9:129-143, 2008

Cytochrome P450 Superfamily

Rx: $XH + NADPH + 0_2 \rightarrow XOH + NADP^+ + H_2O$

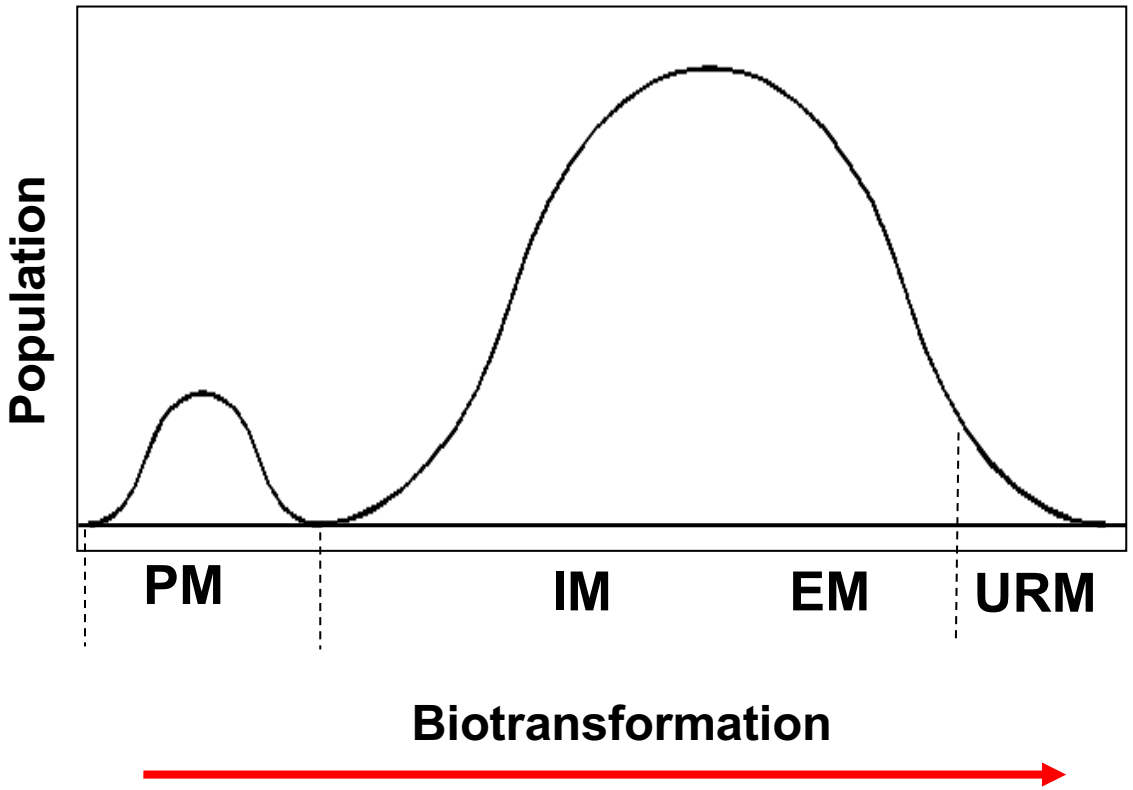
- **Human:**
  - 18 families, 43 subfamilies, polymorphic
  - 57 putatively functional genes
    - ~ half involved in drug and other xenobiotic metabolism
  - 58 pseudogenes
- **Mouse:**
  - 102 putatively functional genes
  - 88 pseudogenes



Nelson et al. Pharmacogenetics 14:1-18, 2004. Lewis DF, Pharmacogenomics 5:305-18, 2004.

Cytochrome P450 Superfamily

- **Individual variability – *polymorphic distribution***
  - A trait that demonstrates a different distribution in >1% of the population



PM = poor metabolizer

EM = intermediate

EM = extensive

URM= ultra rapid

Cytochrome P450 Superfamily

Nomenclature

- Human Cytochrome P450 (CYP) Allele Nomenclature Committee (Pharmacogenetics 10:91-93, 2000)
  - Family > 40% identical (CYP1, the number),
  - Subfamily > 55% identical (CYP1A, the letter)
  - http://www.cypalleles.ki.se/
- The gene and allele is separated by an asterisk followed by Arabic numerals and upper-case Roman letters (*CYP2D6*1*)
- Wild type allele, sequence of the first alleles sequenced (*1A)
- Protein name has a period between gene product and number (CYP2D6.1A).

Antonarakis. Hum Mutat 11(1):1-3, 1998. http://www.imm.ki.se/CYPalleles/cyp3a4.htm

Cytochrome P450 Superfamily

Specificity

Family	Substrates	Sub-families	Genes	Pseudo genees
1	Xenobiotics	3	3	1
2	Xenobiotics & steroids	13	16	16
3	Xenobiotics	1	4	3
4	Fatty acids, eicosanoids & xenobiotics	6	12?	10
5	Prostaglandin H2 (isomerization to thromboxane)	1	1 (5A1)	
7	Bile acids	2	2	

Lewis DF, Pharmacogenomics, 2004, 5(3):305-18.

Cytochrome P450 Superfamily

Specificity (for reference)

8 – prostaglandin H2 isomerization to prostacyclin synthase (A1); bile acid biosynthesis (B1)

11, 17, 19, 21 – steroid biosynthesis

- 17A1 – hydroxylase for pregnenolone & progesterone (A1)
- 19A1 – aromatase forms estrogen from androstenedione
- 21A1 – hydroxylation of C21-methyl of progesterone

24 – vitamin D3 degradation; 24-OH (A1)

26 – retinoic acid hydroxylases

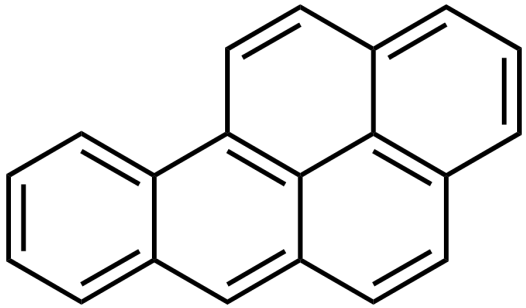
27 – cholesterol hydroxylation (A1); vitamin D3 activation (B1)

39, 46, 51 – cholesterol metabolism, steroid biosynthesis

Lewis DF, Pharmacogenomics, 2004, 5(3):305-18.

CYP1 Family

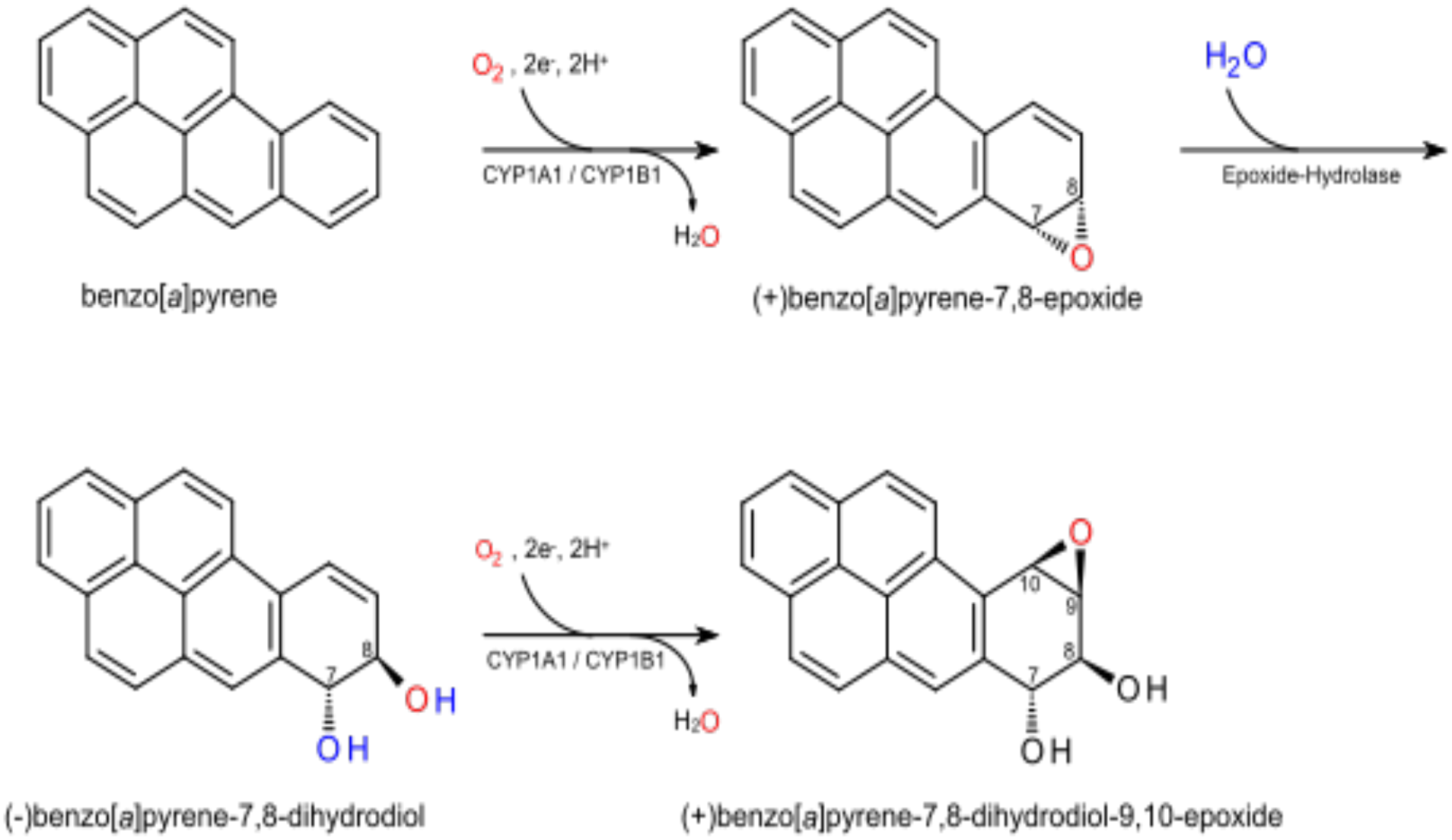
- No known endogenous substrates
  - inducible by some polycyclic aromatic hydrocarbons (PAH)
    - found in cigarette smoke and charred food
  - can activate compounds to carcinogens.



CYP1A1

- **Reaction:** major role in bioactivation of xenobiotics, activation of pro-carcinogens
- **Substrates:** polycyclic aromatic hydrocarbons (PAH), caffeine
- **Inducers:** PAH (e.g. benzo(a)pyrene), dioxins
- **Genotype – Phenotype:** trimodal distribution with 20% subjects being “high-induce” phenotype

CYP1 Family


O2 , 2e-, 2H+
CYP1A1 / CYP1B1
H2O
H2O
Epoxide-Hydrolase
O2 , 2e-, 2H+
CYP1A1 / CYP1B1
H2O
OH
OH
OH
OH
O
benzo[a]pyrene
(+)benzo[a]pyrene-7,8-epoxide
(-)benzo[a]pyrene-7,8-dihydrodiol
(+)benzo[a]pyrene-7,8-dihydrodiol-9,10-epoxide

CYP1 Family

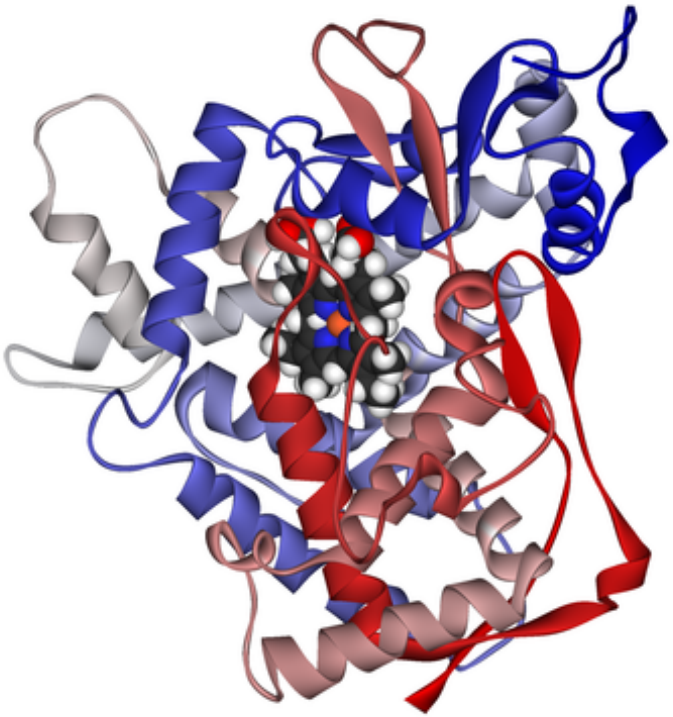
CYP1A2

- **Reaction:** oxidation of rigid and/or planar molecules of moderate volume and basicity
- **Substrates:** acetaminophen, caffeine
  - activation of pro-carcinogens: aflatoxin B1, aromatic and heterocyclic amines, nitroaromatics, naproxen, theophylline, verapamil, R-warfarin, clozapine
- **Genotype – Phenotype:** polymorphisms are rare
- **General:** expressed constitutively in liver, induced by brassica metabolites & charcoal grilled meat, inhibited by apiaceous metabolites

- High levels of CYP1A2 have been linked to an increased risk of colon cancer.

CYP2 Family

- Largest family in humans ~1/3 human P450s.
- Many can hydroxylate steroids, some expressed in a sex specific manner (as expected).
- CYP2C9, 2C19 and 2D6 mediate ~40% of the P450-mediated drug metabolism
  - Polymorphic: makes dosing problematic



Cytochrome P450, family 2, subfamily C, polypeptide 9

http://www.rcsb.org/pdb/explore/explore.do?structureId=1G2

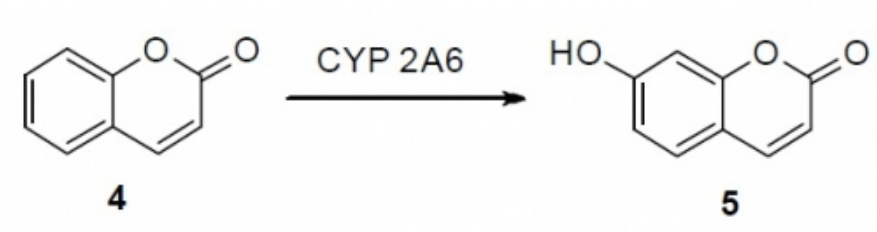
CYP2 Family

CYP2A6

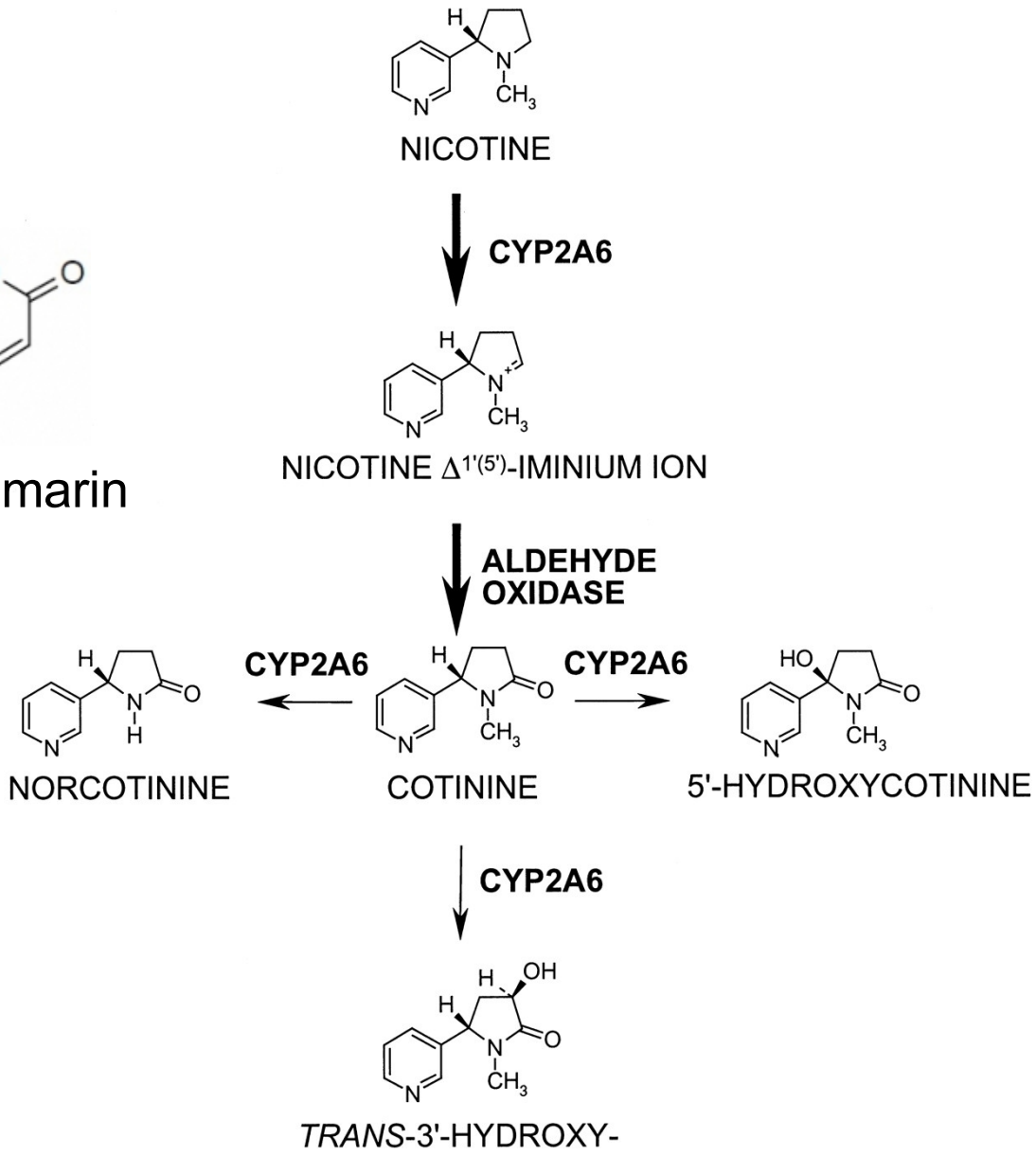
- **Frequency – Population:** differs in Caucasian, Asian and black populations; most variants have absent or reduced activity
- **Substrates:** coumarin (also inhibitor), steroids, nicotine
- **Genotype – Phenotype:** liver, inducible; may modulate smoking

CYP2 Family

CYP2A6



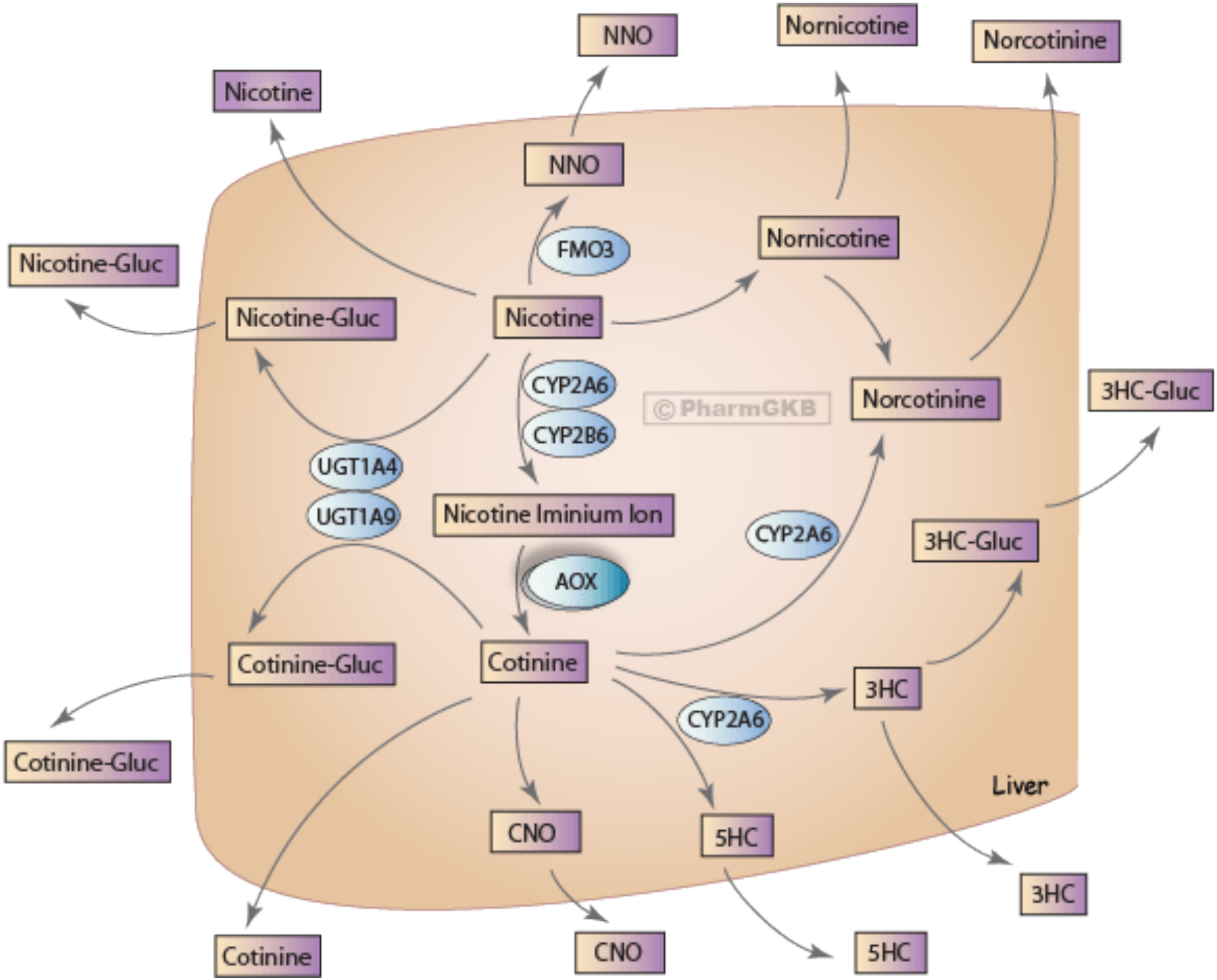
coumarin 7-hydroxycoumarin



CYP2 Family

CYP2B6

- **Reaction:** oxidation of angular, neutral or basic, medium-sized xenobiotics
- **Substrates:** cyclophosphamide, nicotine, nitrosamines, sertraline (Zoloft, inhibitor), induced by phenobarbital-type compounds
- **Genotype – Phenotype:** liver, heart; decreased activity in *5 & *7 (~14% of European pop.)


NNO
Nornicotine
Norcotinine
Nicotine
NNO
FMO3
Nornicotine
Nicotine-Gluc
Nicotine-Gluc
Nicotine
CYP2A6
CYP2B6
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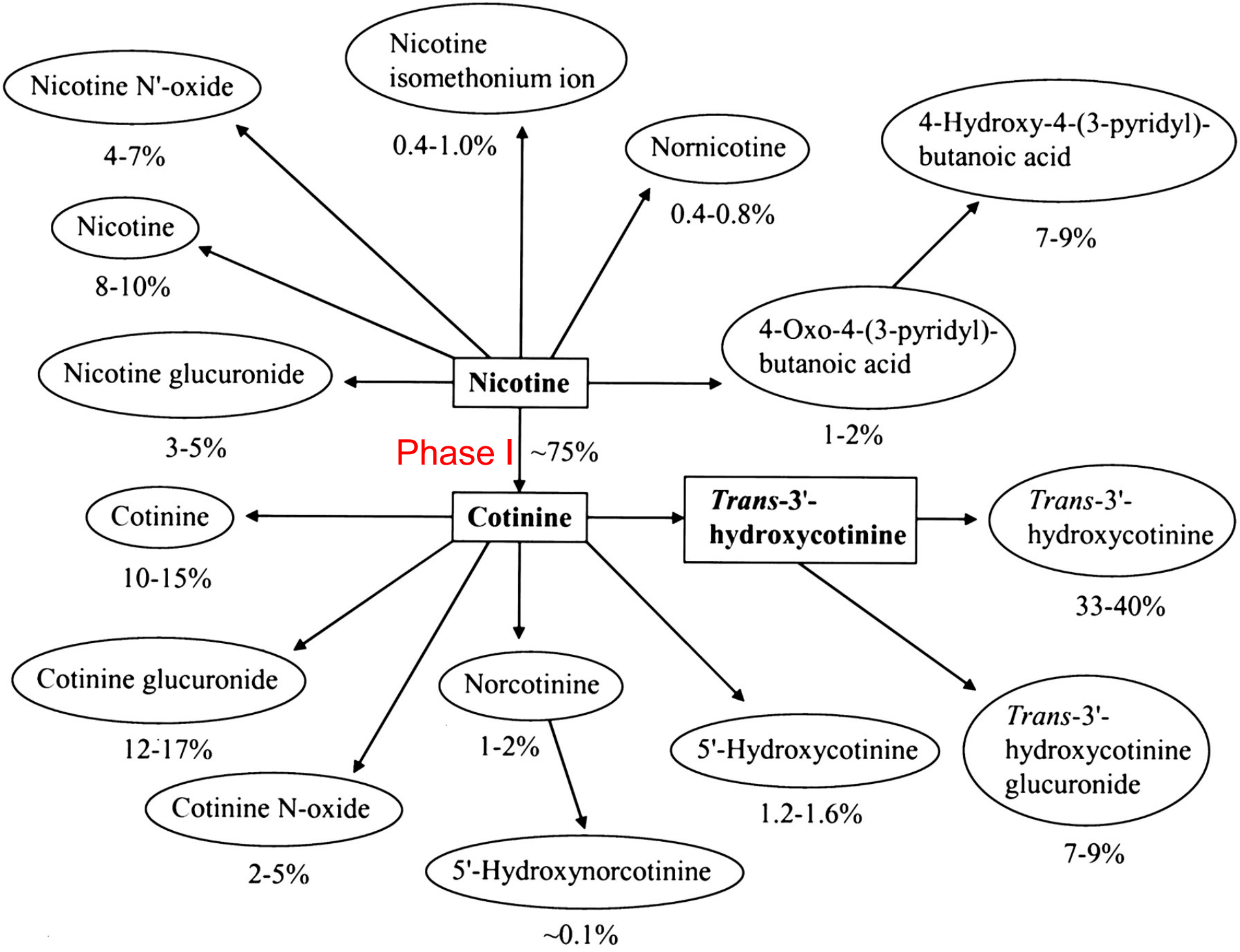
Norcotinine
3HC-Gluc
UGT1A4
UGT1A9
Nicotine Iminium Ion
CYP2A6
3HC-Gluc
AOX
Cotinine-Gluc
Cotinine
3HC
CYP2A6
Cotinine-Gluc
Liver
CNO
5HC
3HC
Cotinine
CNO
5HC


Nicotine N'-oxide
4-7%
Nicotine isomethonium ion
0.4-1.0%
Nornicotine
0.4-0.8%
4-Hydroxy-4-(3-pyridyl)-butanoic acid
7-9%
Nicotine
8-10%
4-Oxo-4-(3-pyridyl)-butanoic acid
1-2%
Nicotine glucuronide
3-5%
Nicotine
Phase I
~75%
Cotinine
10-15%
Trans-3'-hydroxycotinine
Trans-3'-hydroxycotinine
33-40%
Cotinine glucuronide
12-17%
Norcotinine
1-2%
5'-Hydroxycotinine
1.2-1.6%
Trans-3'-hydroxycotinine glucuronide
7-9%
Cotinine N-oxide
2-5%
5'-Hydroxynorcotinine
~0.1%

CYP2 Family

CYP2C subfamily

4 closely related human liver isozymes:

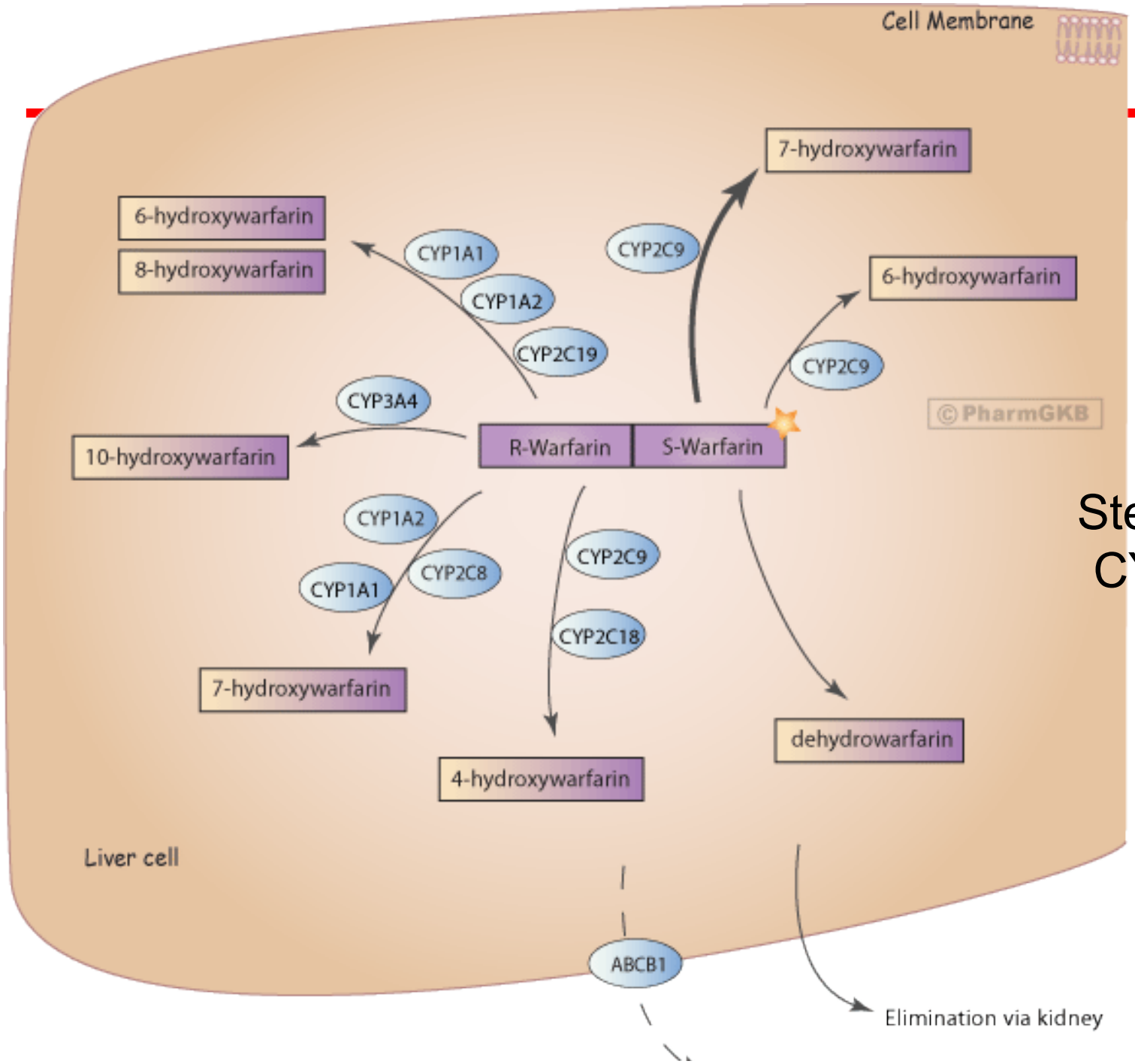
- 2C8 - all-*trans*-retinoic acid, paclitaxel, cerivastatin, rosiglitazone
- 2C9, 2C18, and 2C19 share some but not all substrates
  - do not always lead to the same preferred hydroxylation products
- Interact with areas rich in potential H-bonds;
  - N-, O-, S-dealkylation,
  - aliphatic & aromatic hydroxylation

CYP2 Family

CYP2C9

- **Reaction:** weakly anionic and lipophilic, stereoselective metabolism of (S)-warfarin
- **Frequency – Population:** differs in Caucasian, Asian and black populations, *2 >30% of N. Europeans
- **Substrates:** antipyrine, diclofenac, dronabinol (THC), glipizide, tolbutamide, ibuprofen, imipramine, losartan, phenytoin, stereoselective metabolism of (S)-warfarin, sulfaphenazole (selective inhibitor)
- **Genotype – Phenotype:** liver, differs little with 2C10 in structure and substrates, inducible

Warfarin

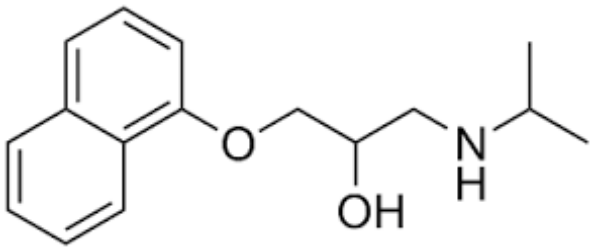


Stereoselective CYP-mediated oxidation

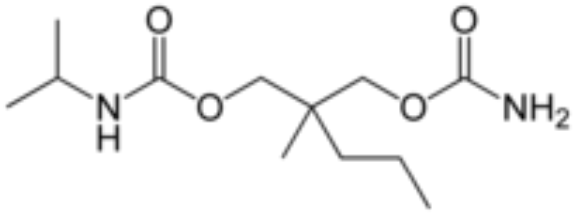
CYP2 Family

CYP2C19

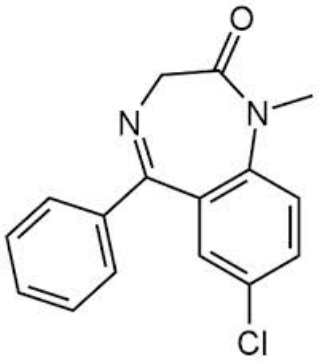
- **Reaction:** neutral or weakly basic, moderately lipophilic
- **Frequency:** frequency of poor metabolizers varies with genetic background
- **Substrates:** carisoprodol, diazepam, hexobarbital, omeprazole, clomipramine, propranolol, R-warfarin, ticlopidine (inhibitor)
- **Genotype – Phenotype:** liver, heart; inducible



propranolol



carisoprodol

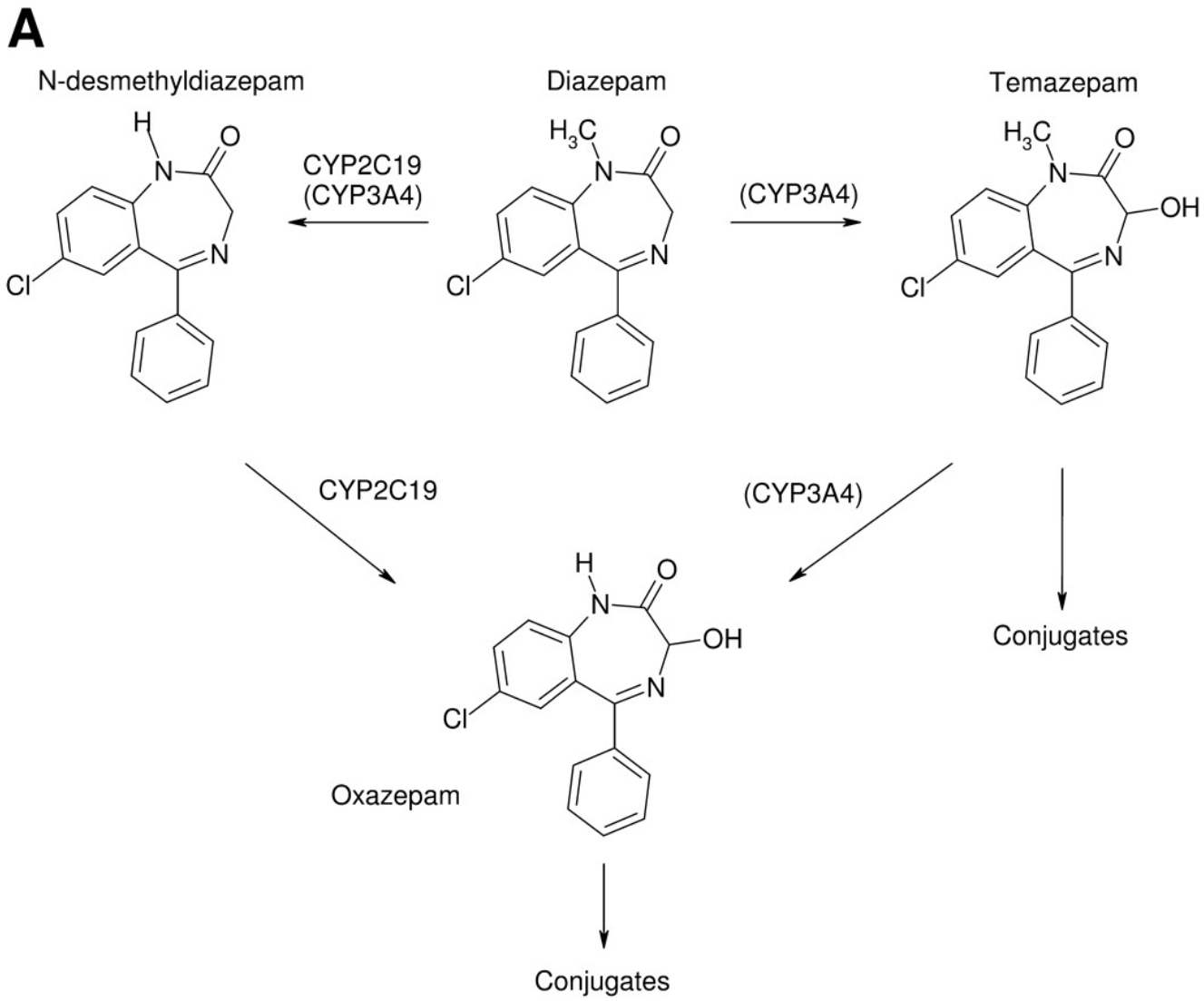


diazepam

Wedlund, Pharmacology, 61:174-183, 2000.

CYP2 Family

CYP2C19



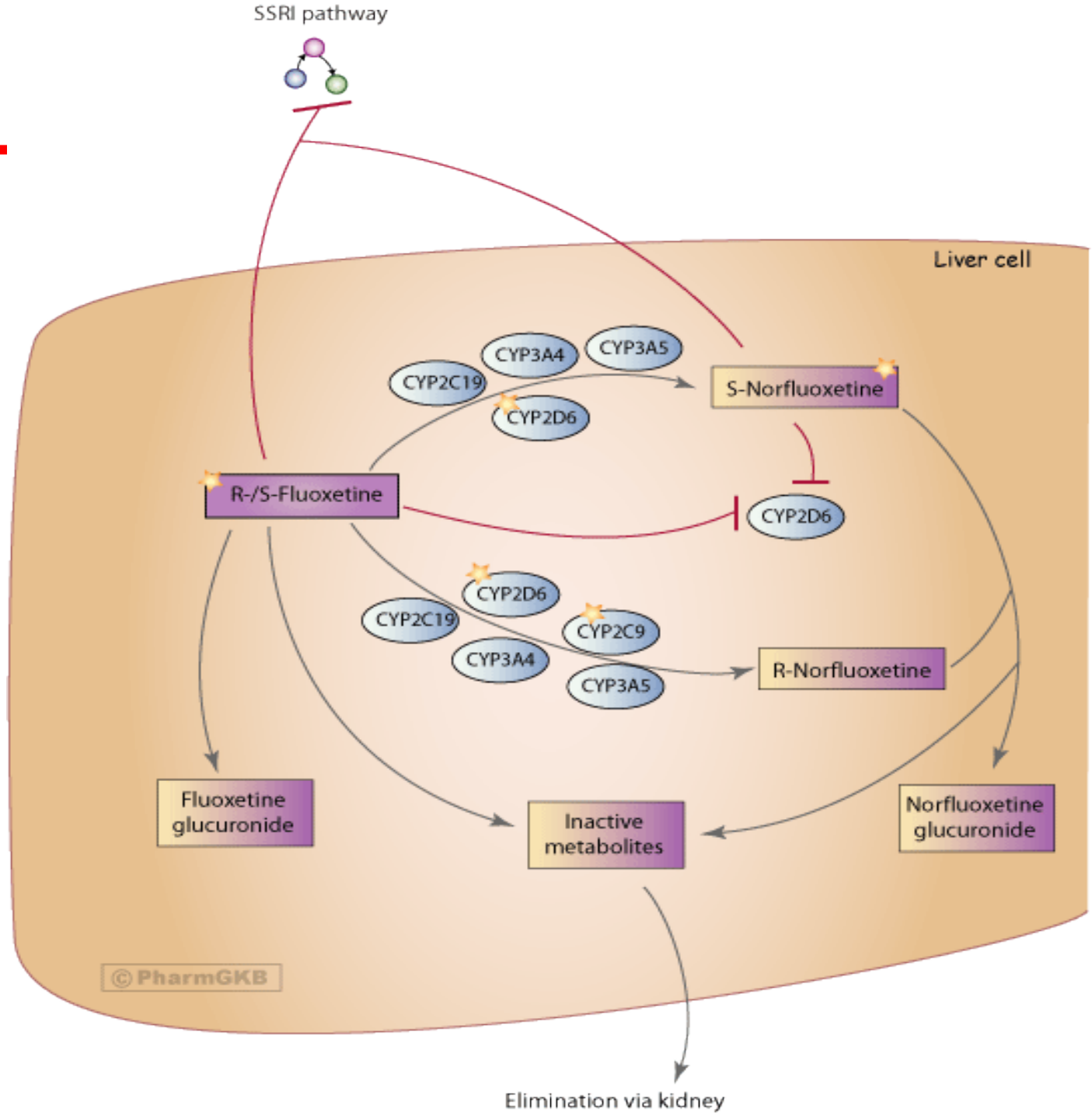
CYP2 Family

CYP2D6

- **Reaction:** oxidation of basic N-compounds, mostly hydrophilic
- **Frequency :** low frequency of PM and URM
- **Substrates:** antiarrhythmics (e.g. beta-blockers), most antidepressants (tricyclics & SSRIs) and antipsychotics (haloperidol), opioids (codeine *activation*), quinidine (inhibitor)
- **Genotype – Phenotype:** liver, brain, heart, ***NOT inducible***

Ingleman-Sundberg Pharmacogenetics 5(1):6-13, 2005

CYP2D6


SSRI pathway
Liver cell
CYP3A4
CYP3A5
CYP2C19
CYP2D6
S-Norfluoxetine
R-/S-Fluoxetine
CYP2D6
CYP2D6
CYP2C19
CYP2C9
CYP3A4
CYP3A5
R-Norfluoxetine
Fluoxetine glucuronide
Inactive metabolites
Norfluoxetine glucuronide
©PharmGKB
Elimination via kidney

CYP2D6

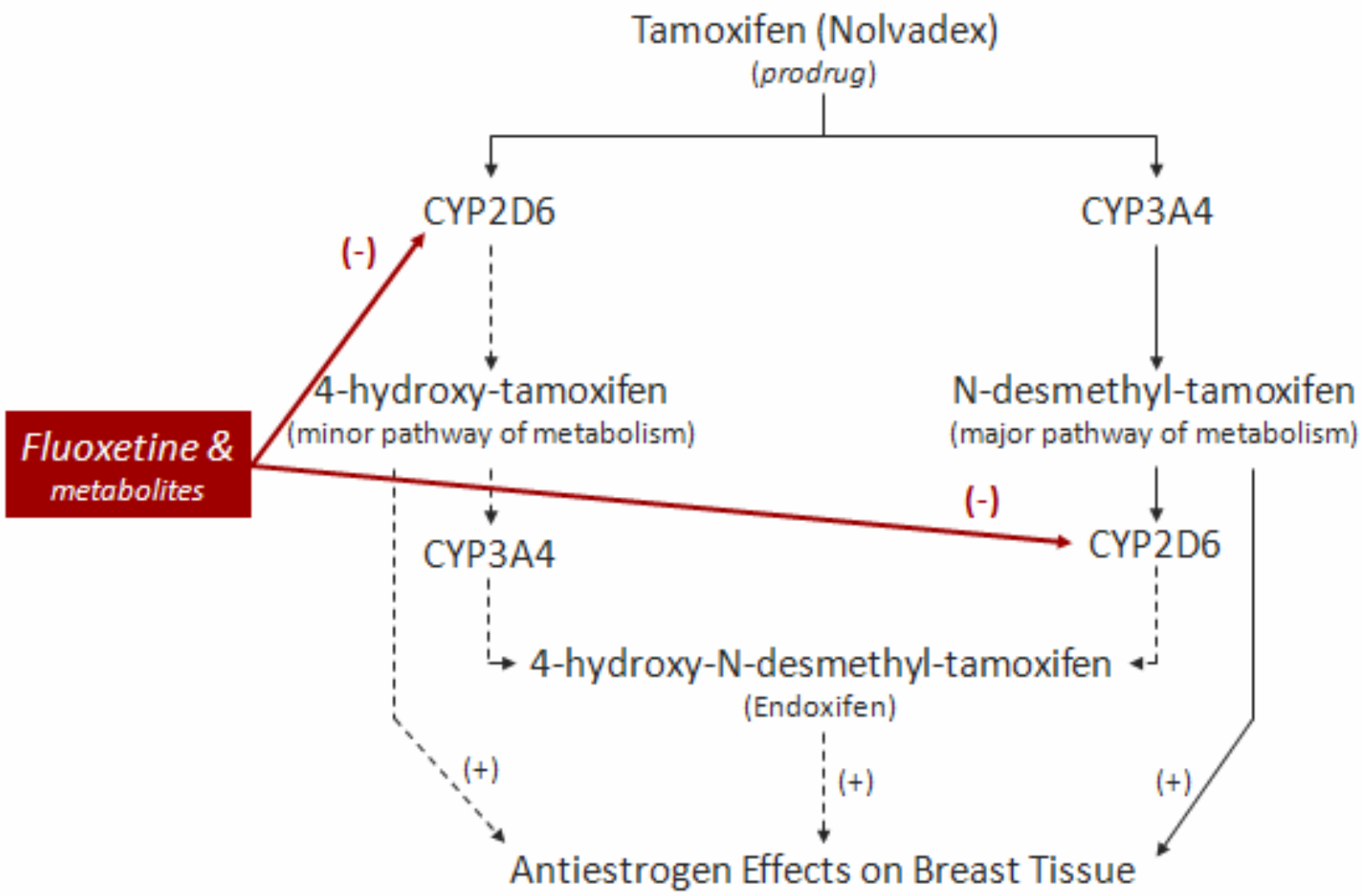


Figure 1. Drug interaction between fluoxetine and tamoxifen.
Dotted line indicates pathway that is decreased or inhibited.

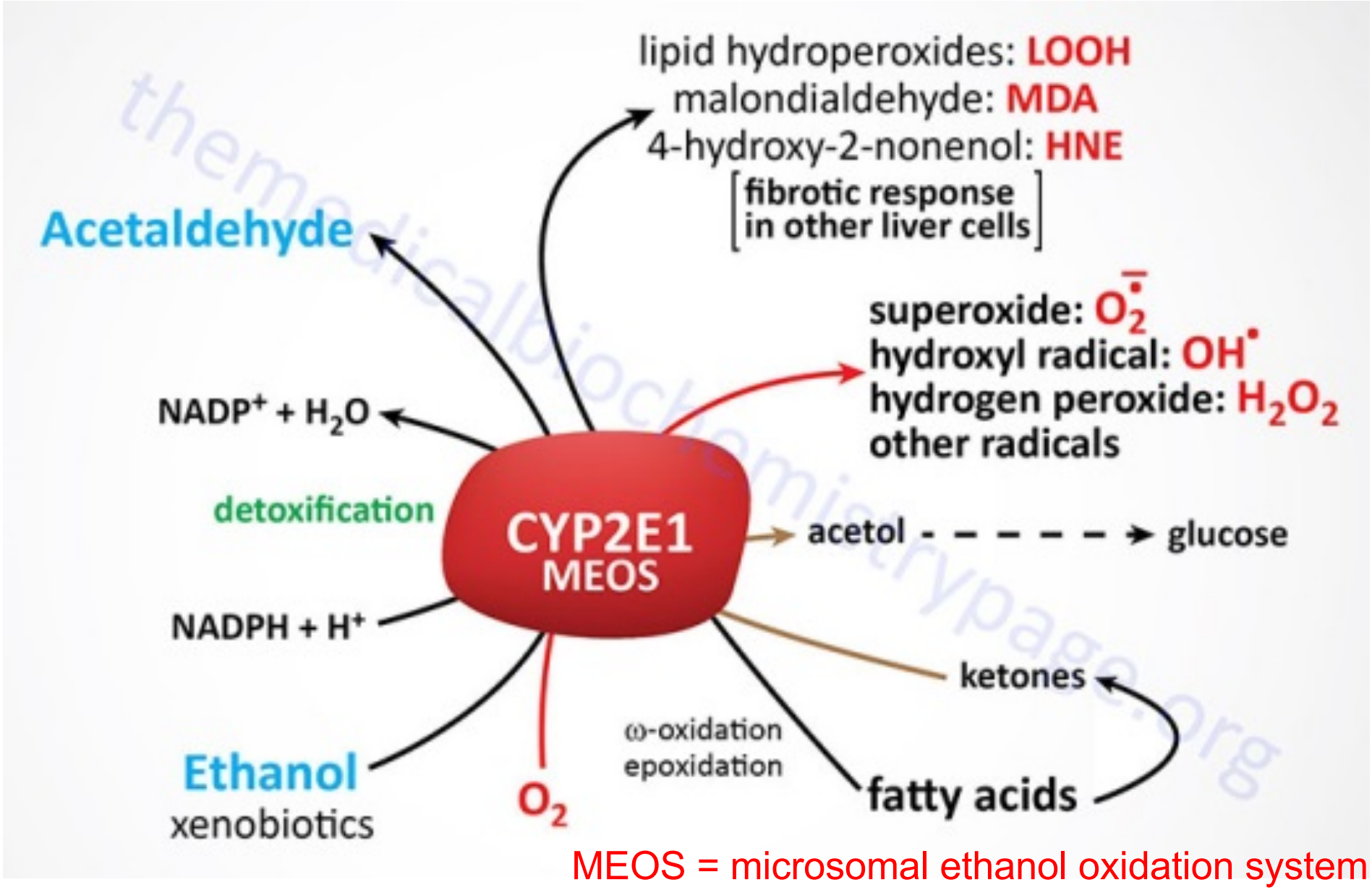
CYP2 Family

CYP2E1

- **Reaction:** relatively small, neutral, hydrophilic
- **Frequency:** low frequency of PM and URM genotypes
- **Substrates:** environmental toxicants and pro-carcinogens, acetaminophen, acetone, aniline, benzene, ethanol, halogenated HCOs, halothane, isoflurane (low molecular weight solvents). endogenous fatty acids and ketone bodies
- **Genotype – Phenotype:** tight homeostatic regulation, inducible, liver, bone marrow, brain, endothelium, heart, lung
  - inducible by acetone, EtOH, oxygen, and starvation
  - regulated by insulin, glucagon, growth hormone, leptin, and growth factors
  - possibly inhibited by garlic

Novak (2000) Arch Pharm Res. 23(4):267-82.

CYP2 Family



MEOS = microsomal ethanol oxidation system

CYP3 Family

- 1 subfamily, 4 genes – A4, A5 , A7, A43
- Most abundant P450 liver form, levels vary considerably amongst individuals
- Broad substrate specificity
- Unique:

  An observed decrease in metabolism of one position can lead to an increase in another

  – **switching** due to rotation within an active site.

  – easier for small molecules but even large molecules (e.g. testosterone) can rotate in CYP 3A4 to allow for metabolism at different positions

Wrighton et al. Drug Metab. Rev., 32:339-361, 2000. Williams et al. Drug Metab. Disp. 30:883-891, 2002.

CYP3 Family

CYP3A4

- **Reaction:** ~40-70% of all drugs
- **Substrates:** taxol, testosterone and many, many others. No ideal probes, dillapiol and grapefruit furanocouramins (inhibitors)
- **Genotype – Phenotype:** **highly conserved but high inter-individual variability;** brain, endothelium, GIT, liver, lung, lymphocytes, kidney, placenta, inducible; 60% variability may be under genetic control

CYP3 Family

CYP3A4

Table 1: CYP3A4 Inhibitors

Allopurinol	Clarithromycin	Fluconazole	Itraconazole	Ritonavir
Amiodarone	Cyclosporine	Fluoxetine	Ketoconazole	Saquinavir
Amprenavir	Darunavir	Fosamprenavir	Lapatinib	Tamoxifen
Aprepitant	Dasatinib	Grapefruit juice	Nefazodone	Verapamil
Atazanavir	Delavirdine	Imatinib	Nelfinavir	Voriconazole
Chloramphenicol	Diltiazem	Indinavir	Nifedipine	
Cimetidine	Erythromycin	Isoniazid	Posaconazole	

Source: References 1, 13, 18, 19.

CYP3A4 Substrate Specificity

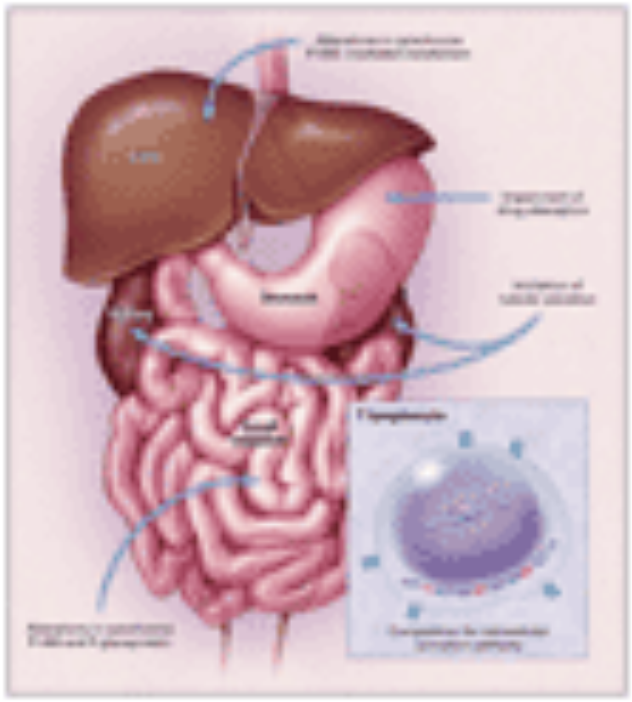
Kenworthy et al. Br. J. Clin Pharmacol. 448:716-727 (1999)

Comparison of 10 common ***probes*** used for *in vitro* investigations of 34A drug metabolism and potential drug-drug interactions:

- Evaluated the effects of 34 compounds on the metabolism of each of the 10 probes (substrates)
  - Determined Michaelis constant (K_m) and effects at inhibitor concentration of 30 uM
  - cluster analysis (strongest to weakest):
  1. Erythromycin, cyclosporine, testosterone (terfenadine)
  2. Dextromethorphan, diazepam, midazolam, triazolam (terfenadine)
  3. Nifedipine
  4. Benzyloxyresorufin

- Probes from each group should be used for in vitro evaluation of 3A4-mediated drug interactions

CYP3A4 Catalytic Activity



- based on demethylation of erythromycin

	nmol/min/mg
Liver	2.8
Duodenum	1.6
Jejunum	1.1
Ileum	0.15

Total intestinal microsomal mass is ~3 gm relative to 79 gm in liver

CYP3 Family

CYP3A5

- Reaction: less significant than 3A4
- Frequency: highly polymorphic; *3 (PM 32-90% Blacks) *1 (URP 9.2% Caucasians and 28%)
- Substrates: similar but not identical to 3A4
- Genotype – Phenotype: 88% homologous to 3A4, well expressed in intestine and foetal liver, ~20-25% adult livers depending on ancestry
- Expressed in adrenal glands, breast, kidney, lung, prostate, poorly in the remainder

Xie et al. Pharmacogenomics 5:243-272, 2004.

CYP3 Family

CYP3A7

- **Reaction:** as before with some differences
- **Substrates:** similar to 3A4 and 3A5; 16a-hydroxylation of dehydroepiandrosterone,
- **Genotype – Phenotype:** 88% homology with 3A4, foetal > adult liver reaction
  - mRNA in 50% of adult liver but expression of functional protein unconfirmed;
  - accounts for 50% of the expressed foetal liver P450

Intestinal P450 Distribution

Obach et al. Drug Metab Dispos. 2001; Paine et al. Drug Metab Dispos 34(5):880-6, 2006; Bergheim et al. Clin Pharmacol 5:4, 2005.

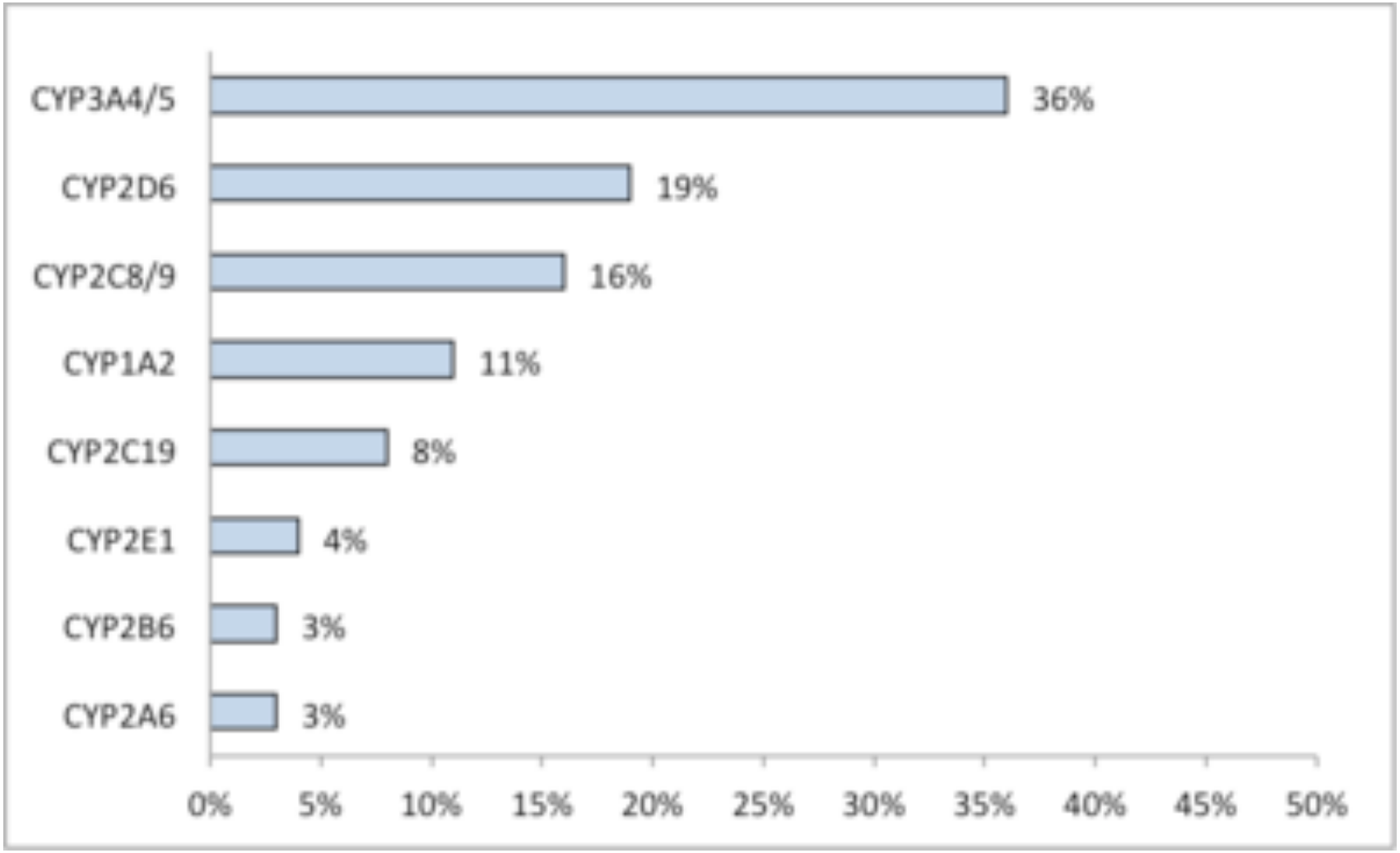
	pmol/mg	
3A4	8.8 – 150	(up to 80% of total)
3A5	4.9 – 25	(up to 50% of total 3A)
1A1	3.6 to 7.7	
2C9	2.9 – 27	[up to 15% of total]
2C19	<0.6 – 3.9	
2D6	<0.2 – 1.4	

CYP content variability

- Inter-individual differences range from:
  - 5-fold for CYP2C and 3A4 (up to 37x)
  - 12-fold for CYP2E1
  - 20-fold for CYP1A2
  - >50 fold for CYP 2A6, 2B6 and 2D6

CYP family selectivity

Proportion of antifungal drugs metabolized by different families of CYPs.[15]



Distribution and Elimination