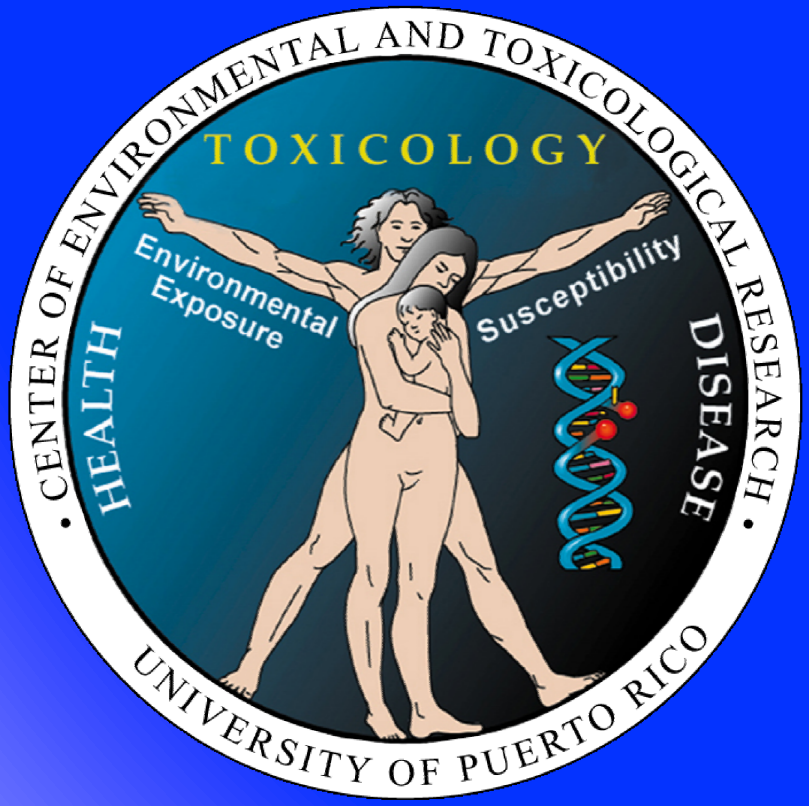
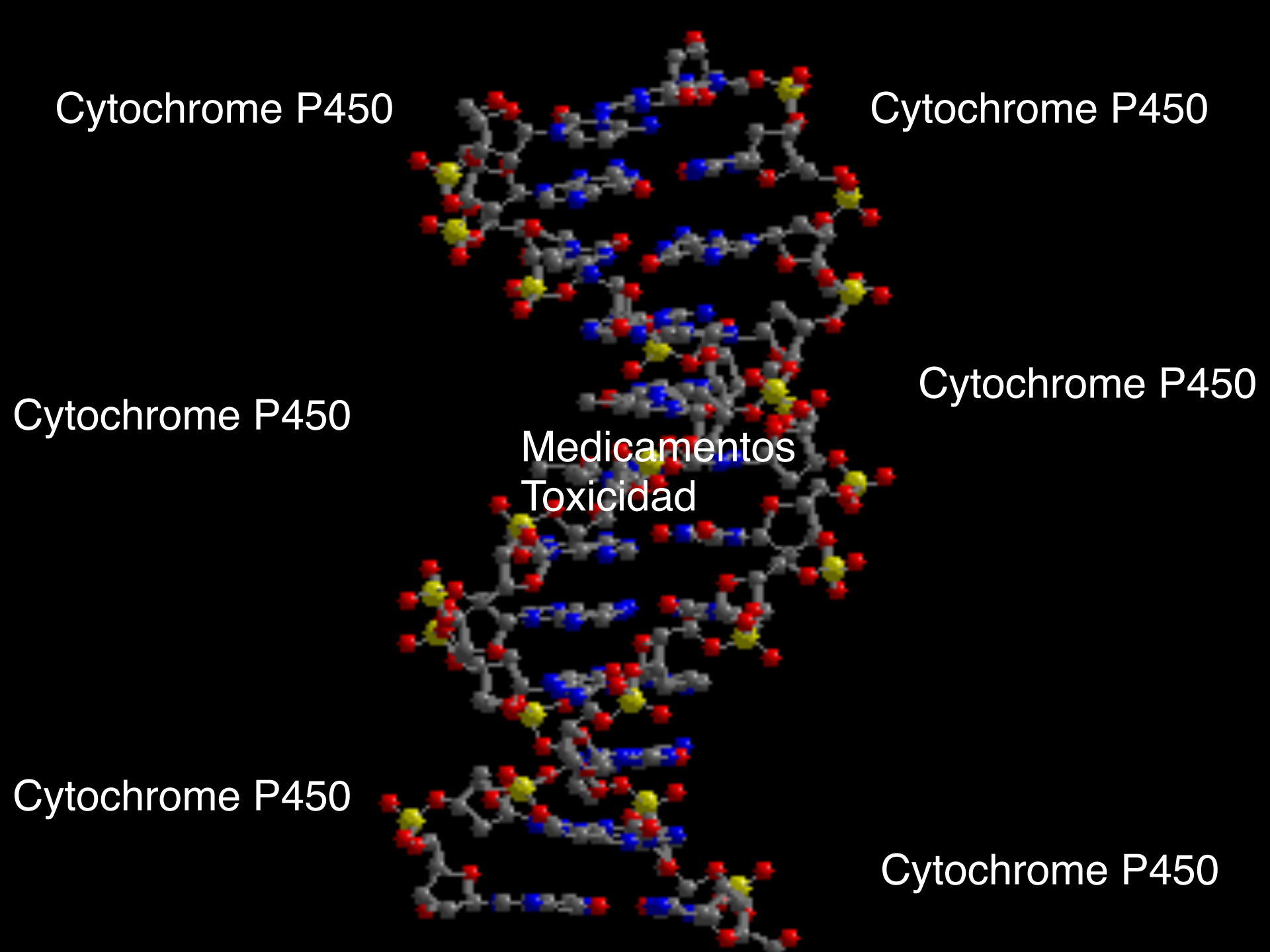
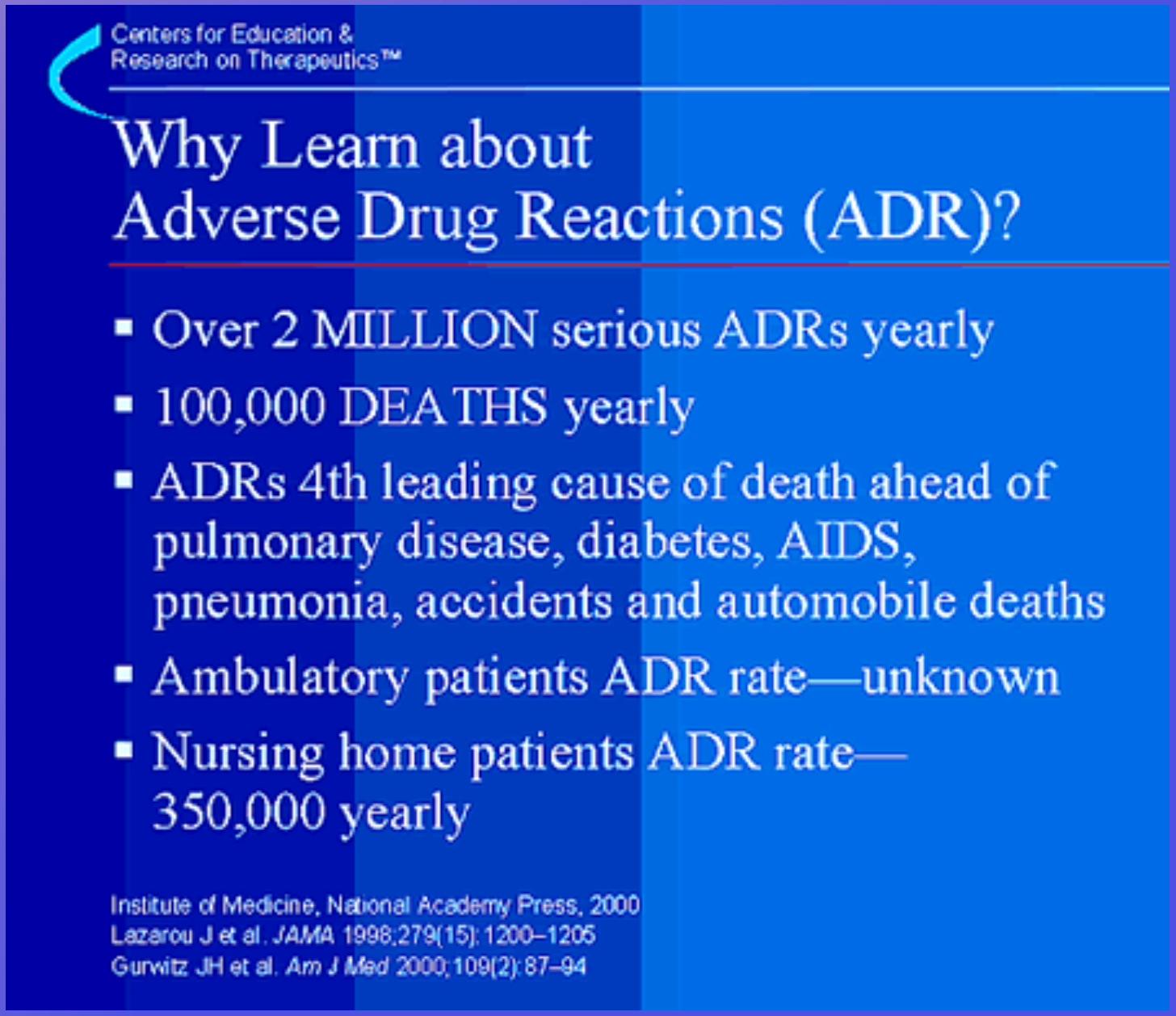
Cytochrome P450's
Toxicity and Detoxification
Bioquímica
Dr. Braulio Jiménez-Vélez

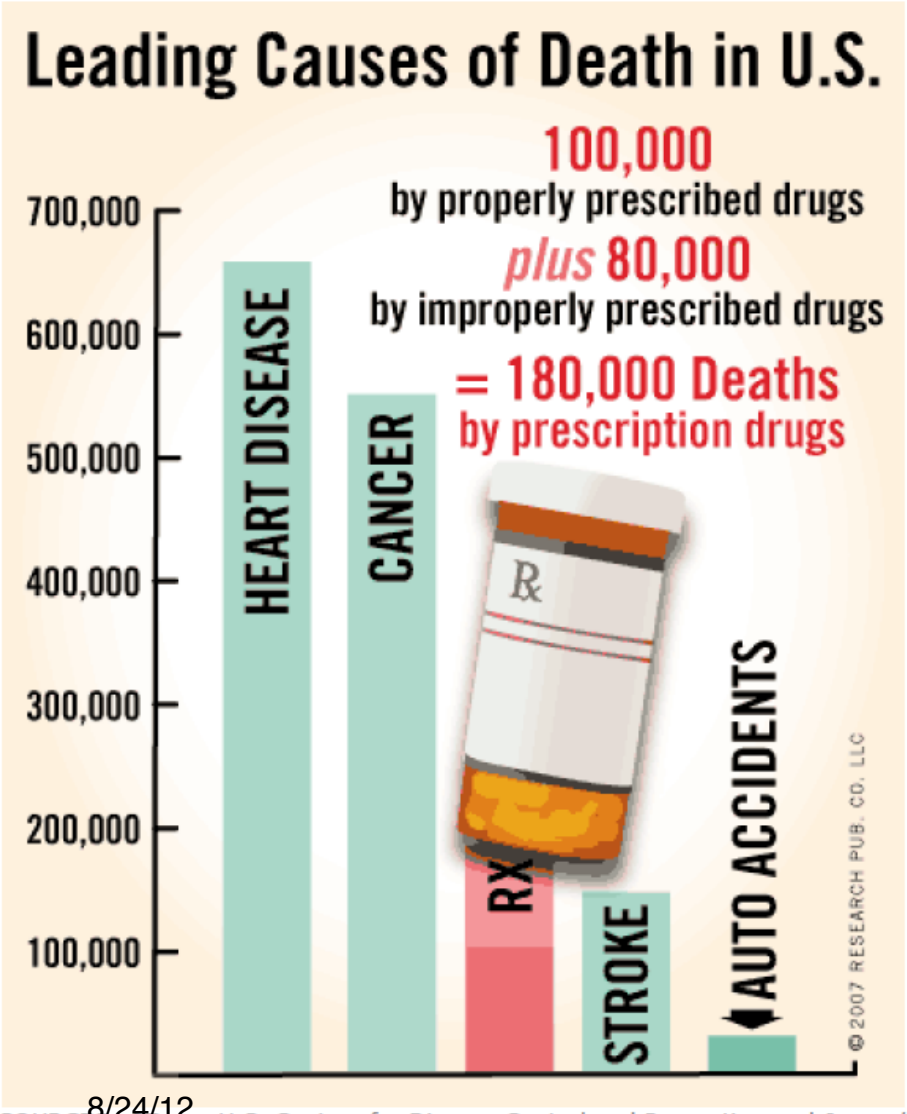



Cytochrome P450
Cytochrome P450
Cytochrome P450
Cytochrome P450
Medicamentos
Toxicidad
Cytochrome P450
Cytochrome P450



Puerto Rico unknown ?

Major Solvable Medical Problem ADR
US as an example since hardly any information LA



- 2.2 million severe reactions/year (783,936 death/y 2003 report Death by Medicine)
- $177 billion in increased direct health care costs per year
- Cost leader for malpractice payouts

SOURCES of Data: U.S. Centers for Disease Control and Prevention and *Journal of the American Medical Association (JAMA)*; links below.

Drugs

- Estimates of 700,000 people die worldwide annually from **counterfeit** drugs
- Police arrested 600 people and seized $50 million in fake goods in 13 Latin American countries(October 2010, CNN)
- *Forbes* reports as much as 30 percent of drugs sold in Latin America are fake.

Xenobiotics

- Thousands of xenobiotics are ingested daily by man
- Between 1 and 3 million unique chemical are found on this planet. Several thousands of new chemical are synthesized per year.
- These substances either occur naturally (coffee > 500 compounds, red wine > 400, cooked beef> 300, cigarette smoke > 1000 or are synthetic (drugs, food, additives,agricultural chemicals, industrial products, etc.
- **How does our body deal with these foreign Chemicals?**

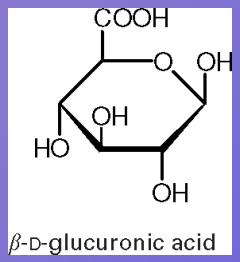
Toxicity and Detoxification
Drug metabolism

- Refers to the process by drugs are converted in the
- body into one or more structural derivatives (drug
- metabolites).

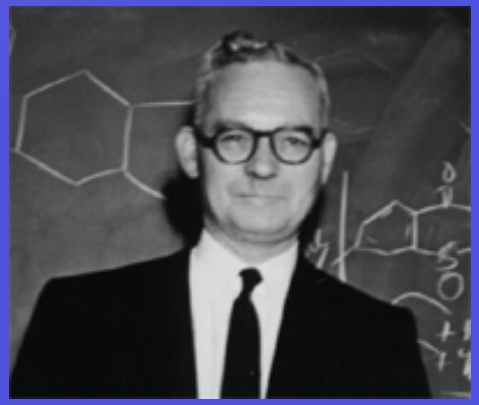
- This process is sometimes referred to as biotransformation

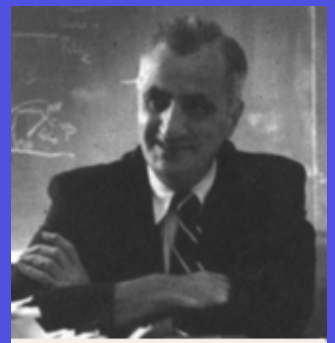
- Usually the metabolites have increased water solubility which promotes their excretion

- Metabolism may change the pharmacological activity/toxicity of the molecule



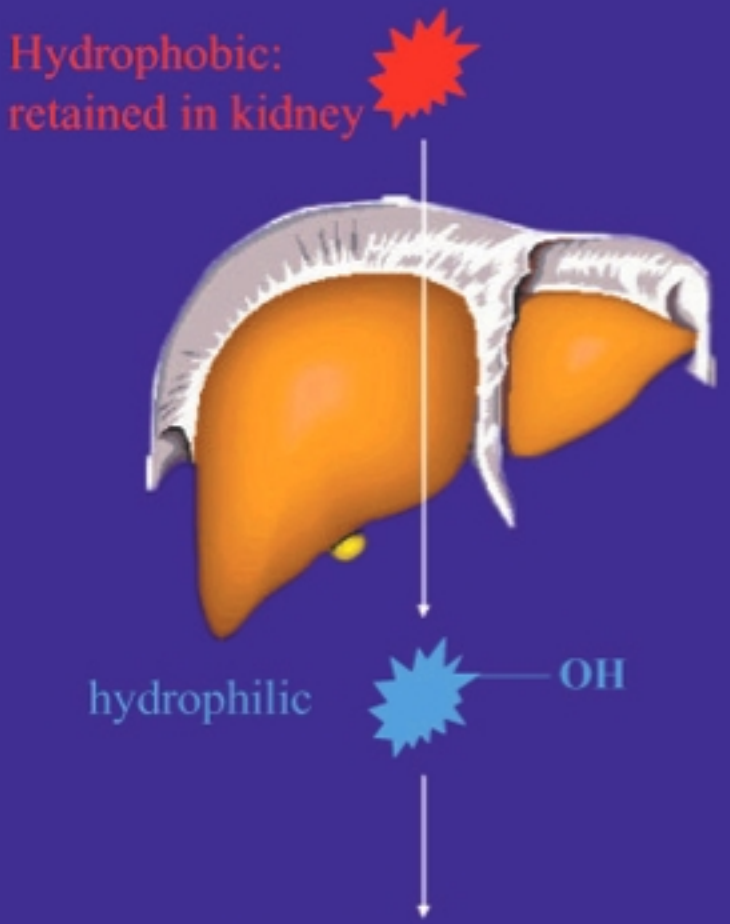
β-D-glucuronic acid




Bernard B. Brodie

- R.T. Williams - in vivo, 1947.
- Detoxification Mechanisms
- Brodie – in vitro, from late 40s till the 60s.
- Cytochrome P450 enzymes (hemeproteins) play an important role in the intracellular metabolism.
- Exist in prokaryotic and eukaryotic (plants insects fish and mammal, as well as microorganisms)
- Different P450 enzymes can be found in almost any tissue: liver, kidney, lungs and even brain.
- Plays important role in drugs metabolism and xenobiotics.

Cytochromes P-450



11500

More than 1200 CYPs known

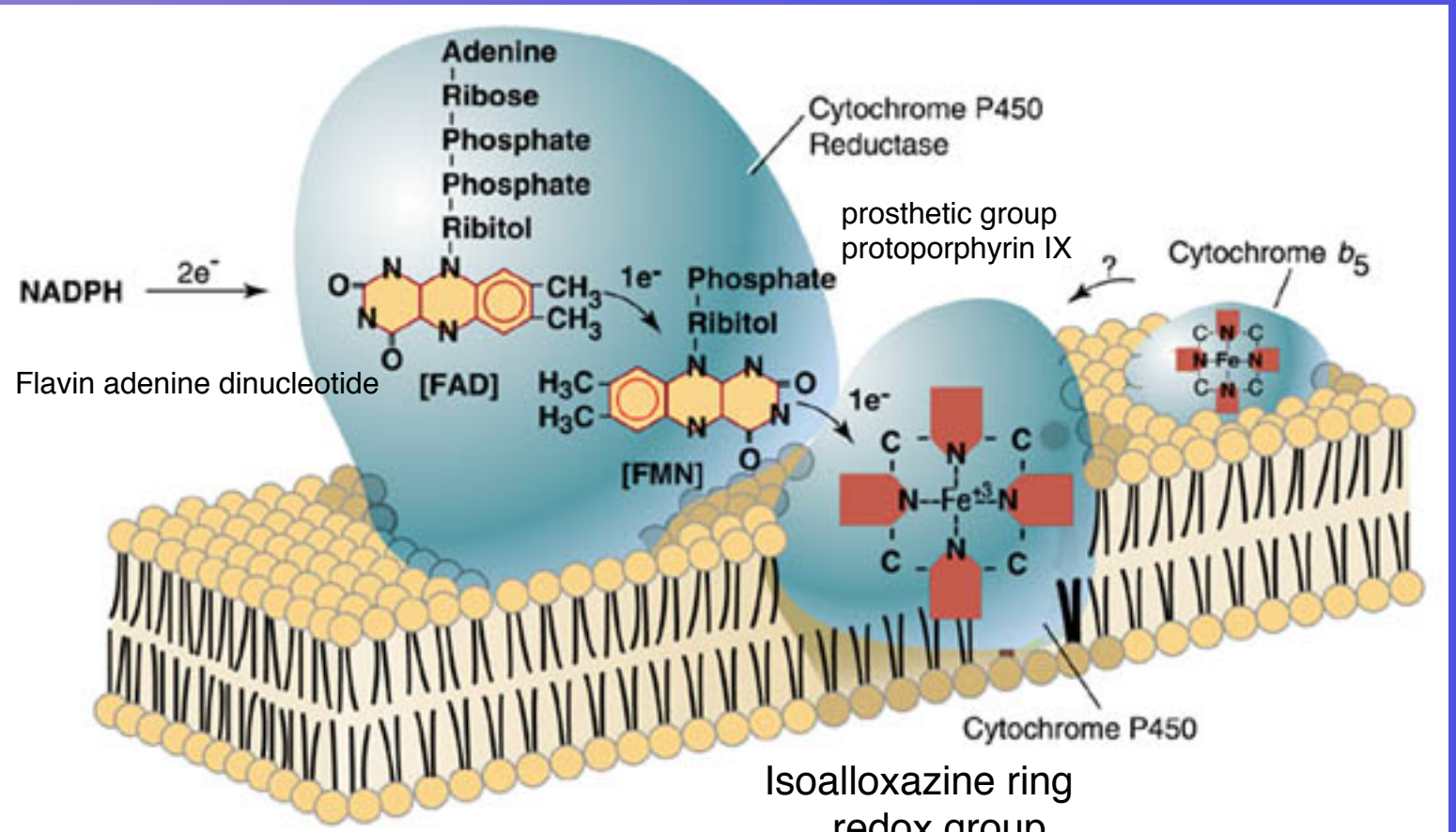
In humans: 55 CYP genes and
29 pseudogenes

Substrates:

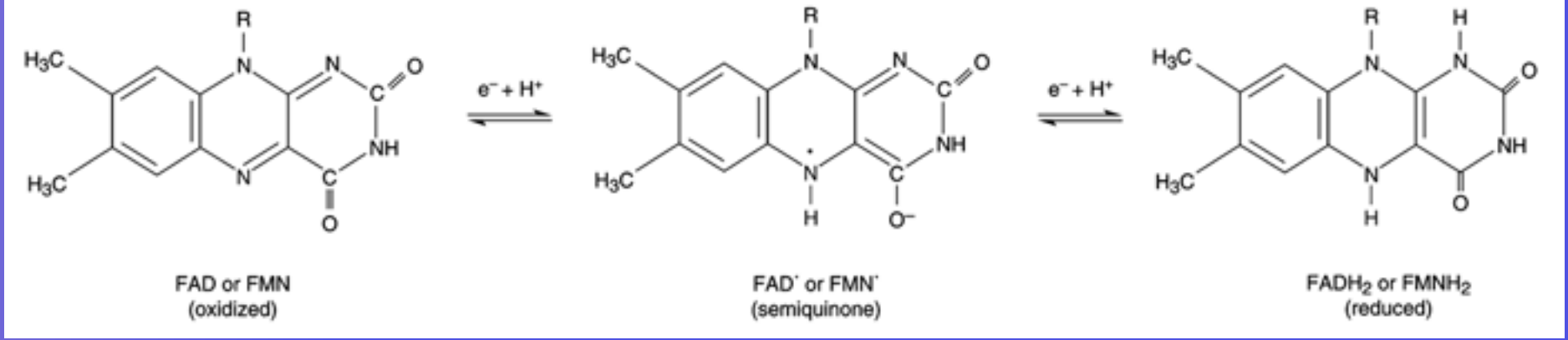
- Cholesterol
- Steroids
- Bile Acids
- Lipids
- Drugs and other xenobiotics
- ...

see: Nelson *et al.* (1996) Pharmacogenetics
Nelson (1999) Arch Biochem Biophys
http://drnelson.utmem.edu/cytochromep450.html

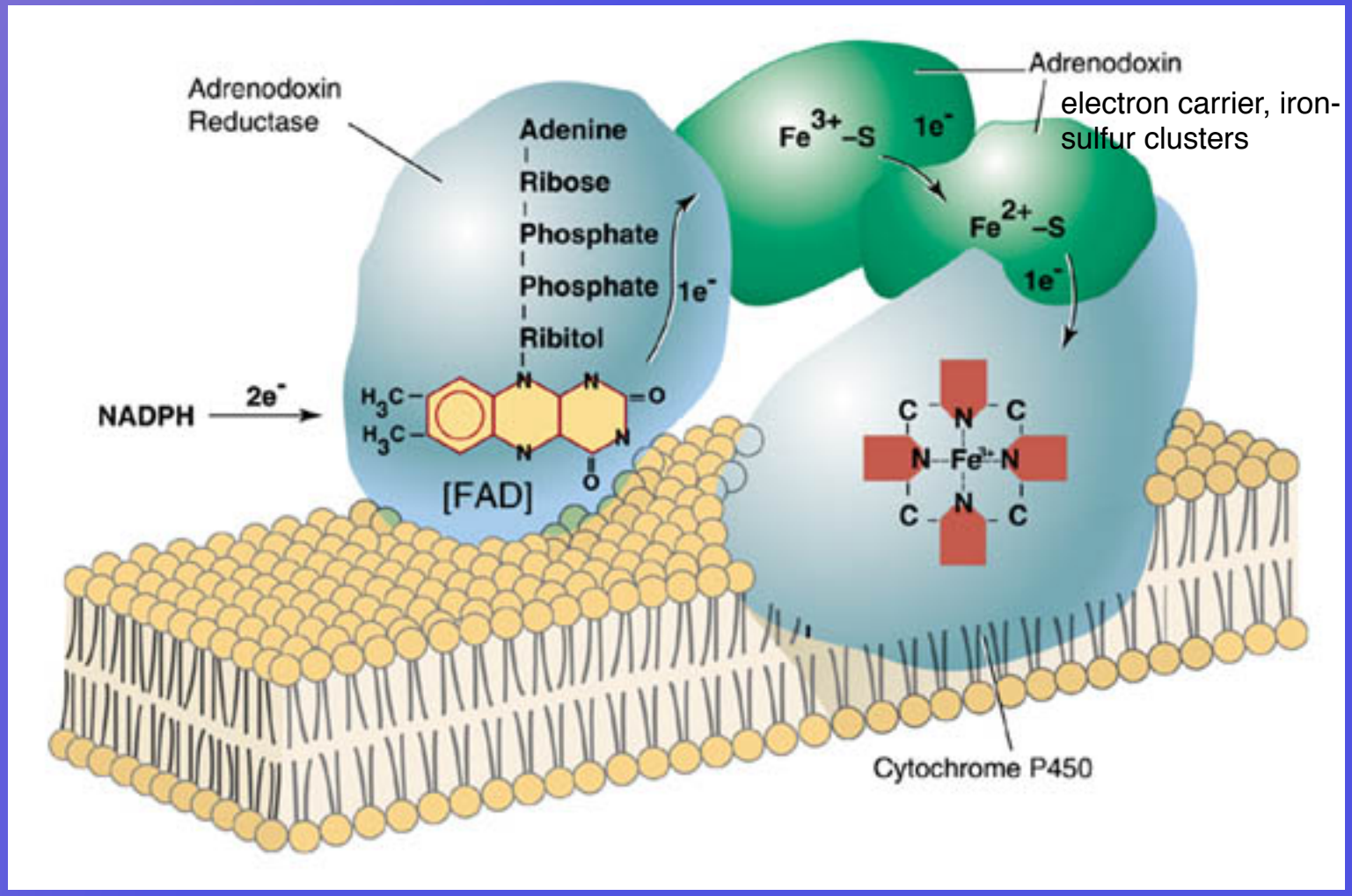
What and where, endoplasmic reticulum

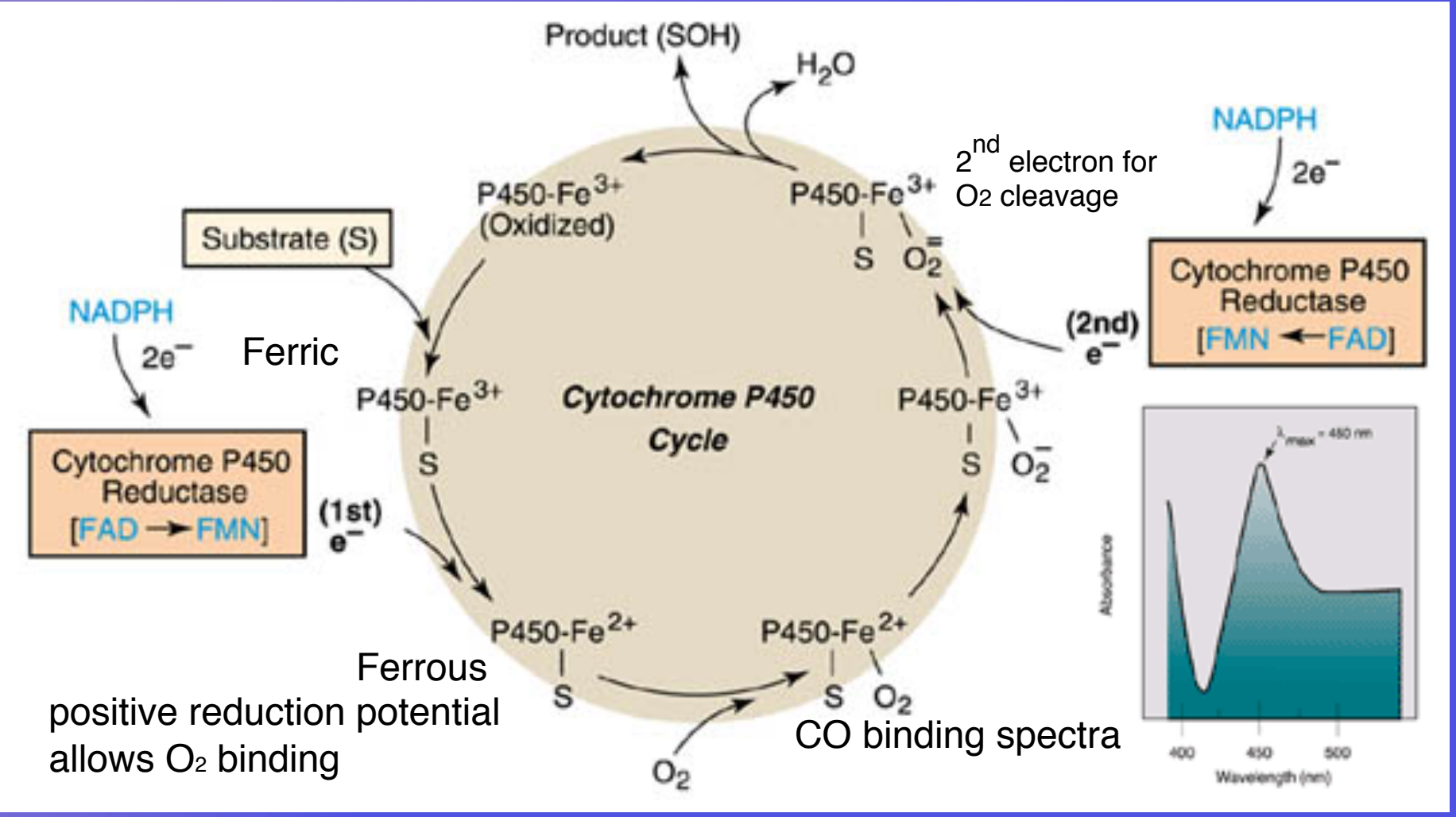


Isoalloxazine ring
redox group



In the mitochondria, NADPH-adrenodoxin reductase




Product (SOH)
H_2O
NADPH
$2e^-$
2^{nd} electron for O_2 cleavage
$P450\text{-}Fe^{3+}$ (Oxidized)
$P450\text{-}Fe^{3+}$
S
$O_2^=$
Substrate (S)
Cytochrome P450 Reductase [FMN ← FAD]
(2nd) e^-
NADPH
$2e^-$
Ferric
$P450\text{-}Fe^{3+}$
S
Cytochrome P450 Cycle
$P450\text{-}Fe^{3+}$
S
O_2^-
Cytochrome P450 Reductase [FAD → FMN]
(1st) e^-
$P450\text{-}Fe^{2+}$
S
$P450\text{-}Fe^{2+}$
S
O_2
Ferrous
positive reduction potential
allows O_2 binding
O_2
CO binding spectra
Absorbance
400
450
500
Wavelength (nm)

CLINICAL IMPORTANCE OF CYPs

What do P450s (CYPs) do?

Which ones do I have to know?

How are they regulated?

How do diseases affect CYPs?

Which diseases are caused by CYPs?

Gene therapy with CYPs? *(Mikael Oscarson)*

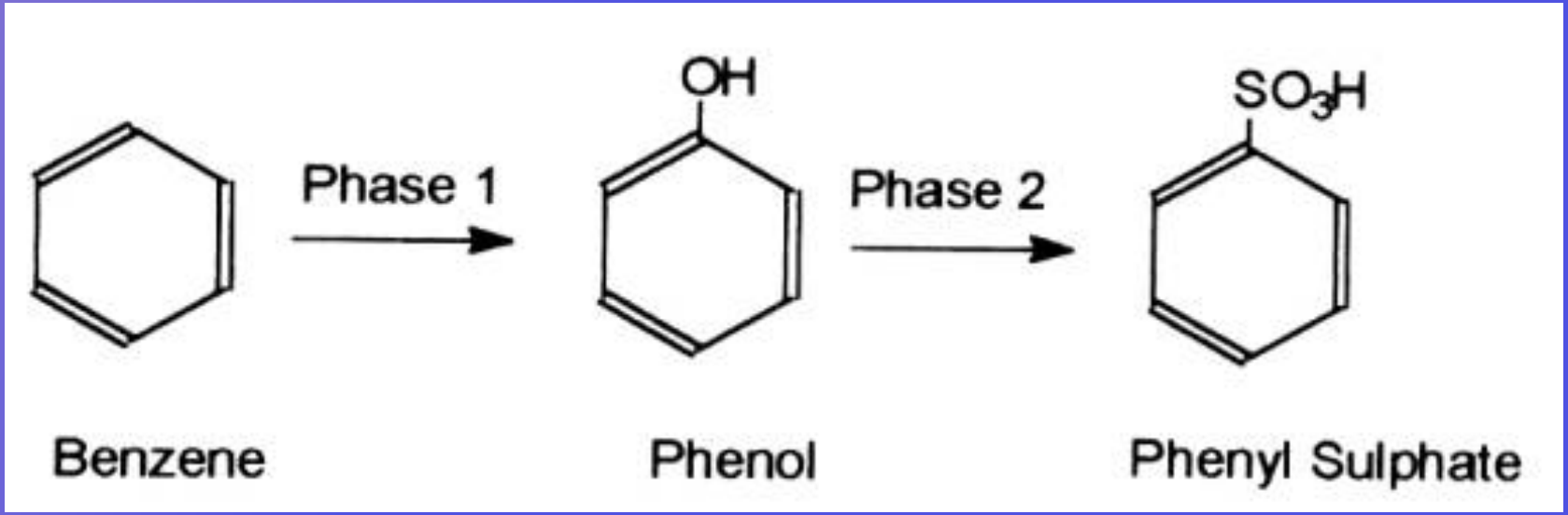
Effects of drug metabolism on pharmacological activity or toxicity

- **Most often converts an active drug to an inactive metabolite**
- **Phenobarbital (CYP2B6) induces (CYP3A4)**
- **Sometimes converts an active drug into an active drug metabolite**

- **Sometimes converts an active drug into a toxic metabolite (acetaminophen)**

- **Sometimes converts an inactive drug into an active drug (pro-drug) Zidovudine, 5-Flurouracil (intracellular); Sulfasalazine (extracellular) anticancer cyclophosphamide**
- **Codeine to morphine (CYP2D6)**

We divide metabolism into three phases



Adds functional group

NH2, -OH, -SH, -COOH)

Adds water soluble substance
to form conjugate
example sulfate, glucuronic acid
Glutathione

UDP-glucuronosyltransferase

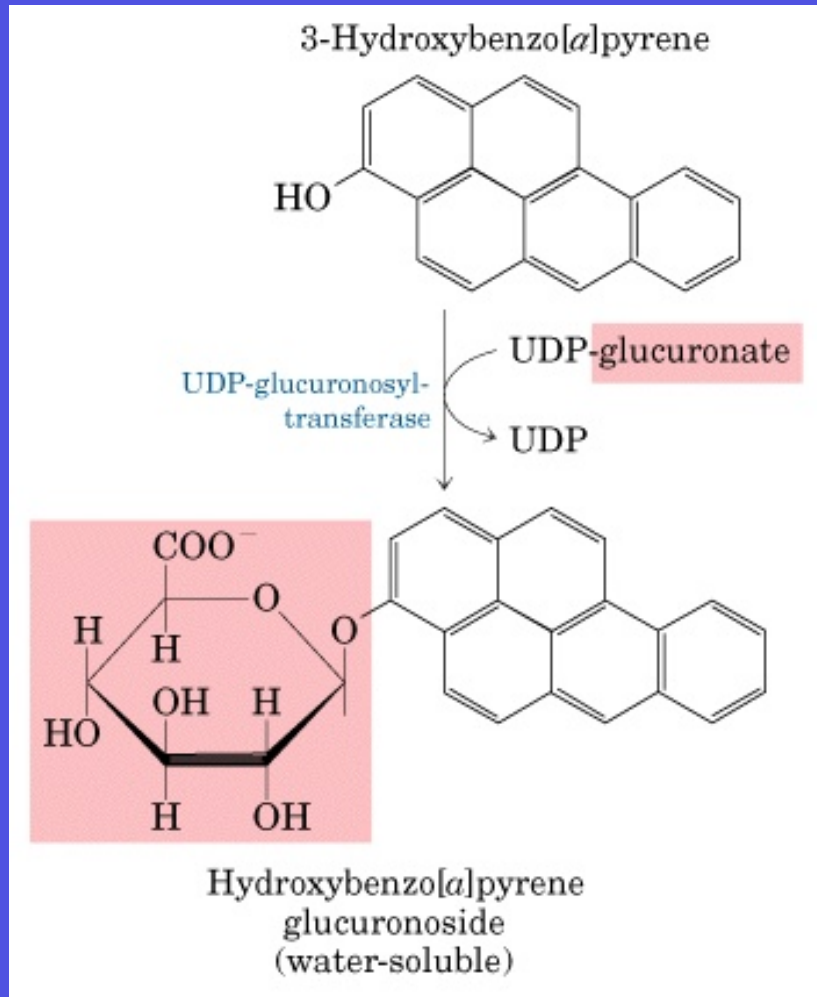
Main type of phase 2 enzyme

Represents many isozymes in two evolutionarily-related families (UGT1 and UGT2) , usually overlapping substrate specificities

Catalyze “glucuronidation” reactions

ROH + UDPGA ® R-O-Glucuronic acid + UDP + H20

Located in smooth endoplasmic reticulum (microsomal fraction) of the cell, especially abundant in liver



Different types of phase 1 and phase 2 reactions

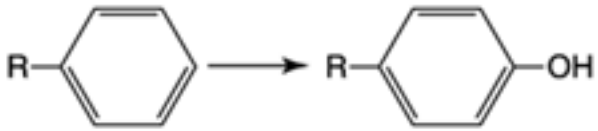
- Different types of phase 1 and phase 2 reactions are catalyzed by different enzymes
- Oxidation – Enzymes in Cytochrome P450 family most common, many other enzymes can carry out oxidations but are less common
- Hydrolysis – Esterases, Pseudocholinesterase, acetylcholesterase, others
- Glucuronidation- UDP-glucuronosyltransferase family
- Sulfation – Sulfotransferase family
- GSH- Glutathione S-transferase

Aliphatic Hydroxylation

$R{-}CH_2{-}CH_3 \rightarrow R{-}CH_2{-}CH_2{-}OH$

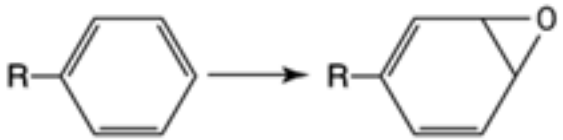
$R{-}CH_2{-}CH_3 \rightarrow R{-}CH_2OH{-}CH_3$

Aromatic Hydroxylation



Epoxidation

$R{-}CH_2{=}CH_2{-}CH_3 \rightarrow R{-}CH(O){-}CH{-}CH_3$



Dealkylation Reactions

N-dealkylation

$R{-}CH_2{-}CH_2{-}NH{-}CH_3 \rightarrow R{-}CH_2{-}CH_2{-}NH{-}CH_2OH \rightarrow R{-}CH_2{-}CH_2{-}NH_2 + HCHO$

O-dealkylation

$R{-}CH_2{-}CH_2{-}O{-}CH_3 \rightarrow R{-}CH_2{-}CH_2{-}O{-}CH_2OH \rightarrow R{-}CH_2{-}CH_2{-}OH + HCHO$

S-dealkylation

$R{-}CH_2{-}CH_2{-}S{-}CH_3 \rightarrow R{-}CH_2{-}CH_2{-}S{-}CH_2OH \rightarrow R{-}CH_2{-}CH_2{-}S + HCHO$

N-Oxidation Reactions

Primary Amines

$R{-}CH_2{-}CH_2{-}NH_2 \rightarrow R{-}CH_2{-}CH_2{-}NH{-}OH$

Secondary Amines

$R{-}CH_2{-}CH_2{-}NH{-}CH_3 \rightarrow R{-}CH_2{-}CH_2{-}NOH{-}CH_3$

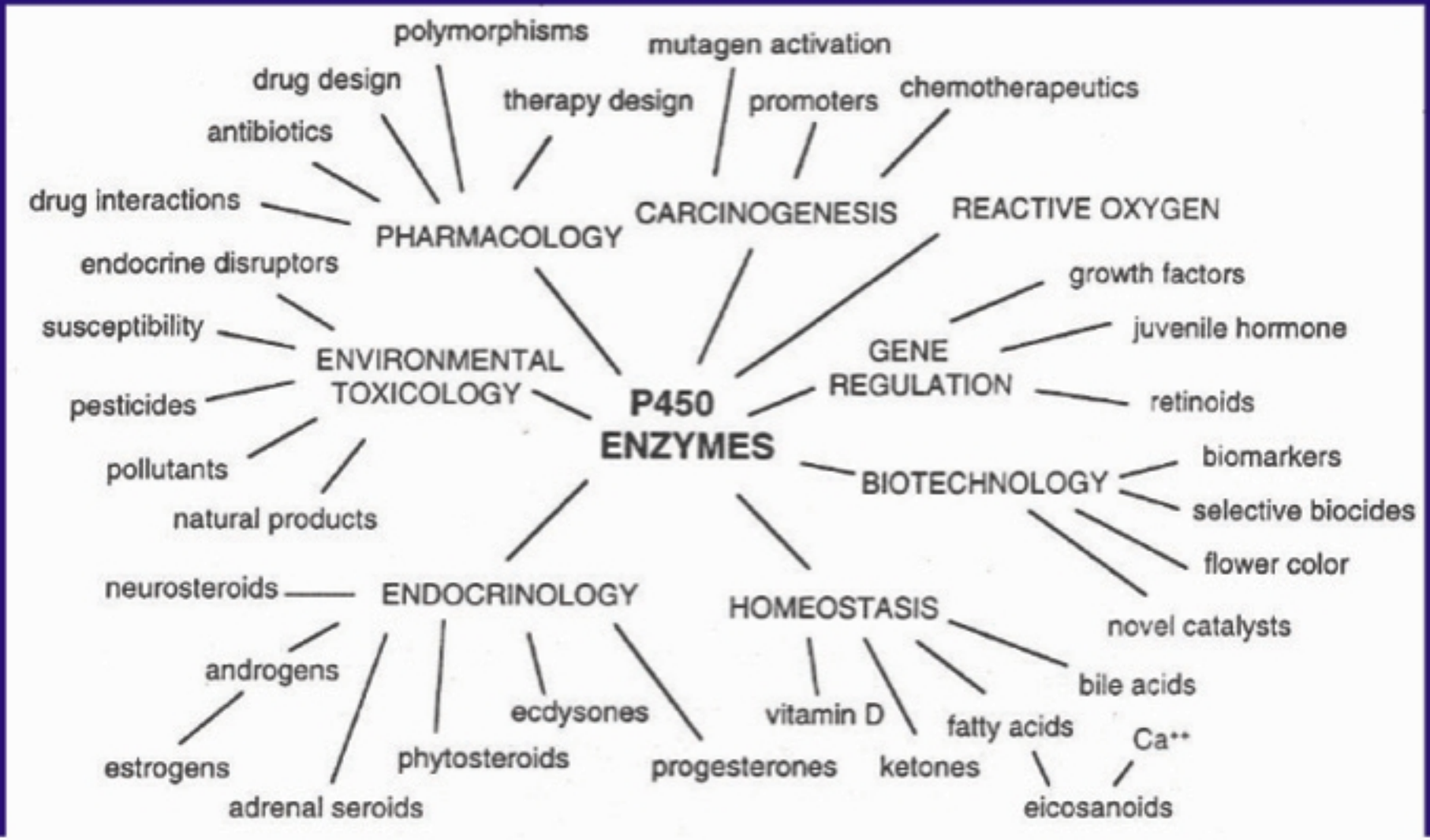
Sulfoxidation

$R{-}CH_2{-}S{-}CH_2R' \rightarrow R{-}CH_2{-}S(=O){-}CH_2R'$

Dehalogenation

$F_3C{-}CHBrCl \rightarrow F_3C{-}COOH + HCl + HBr$

CYTOCHROME P450 ENZYMES IN BIOLOGY AND MEDICINE

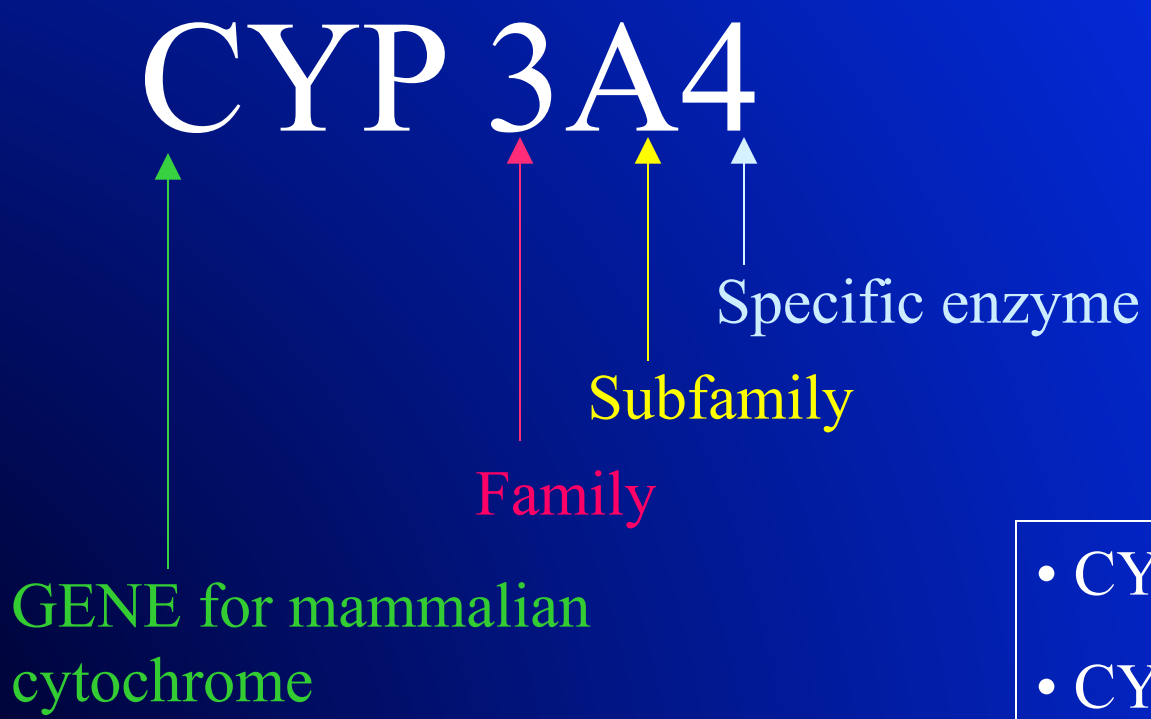


The CYP-gene superfamily

- **More than 11,000 sequences known**
- **Humans have 57 sequenced CYP genes and**
- **59 pseudo-genes about 18 families**

- *Nomenclature*
- **These are grouped in 18 families (>40 % amino acid identity) and 42 (>55 %) subfamilies**

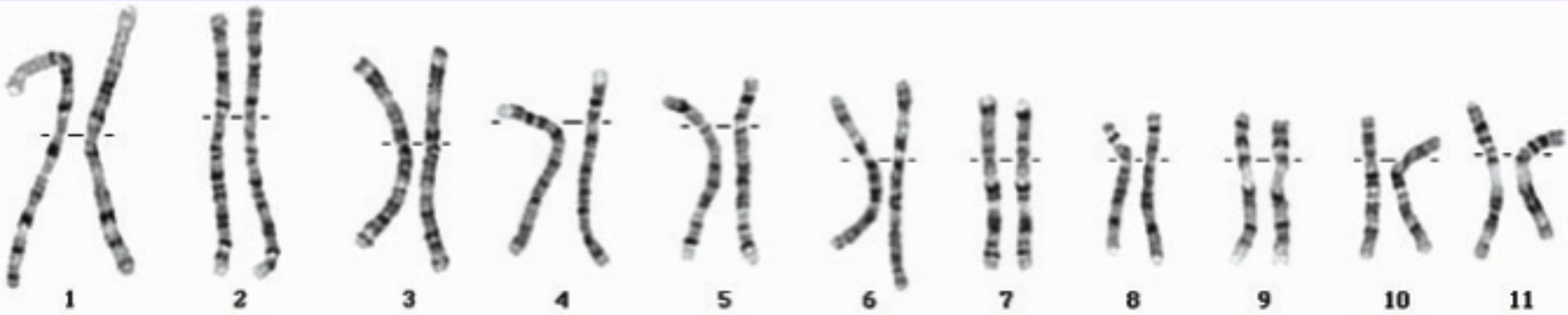
Cytochrome P450 Nomenclature



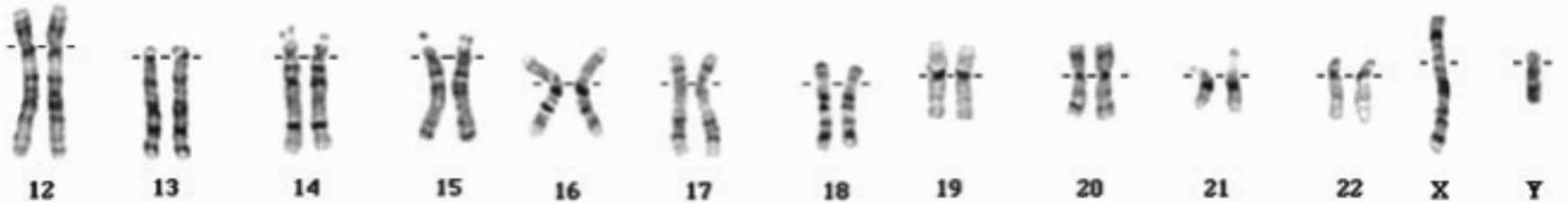
- CYP Substrates
- CYP Inducers
- CYP Inhibitors

Family	Function	Members	Names
CYP1	drug and steroid (especially estrogen) metabolism	3 subfamilies, 3 genes, 1 pseudogene	CYP1A1, CYP1A2, CYP1B1
CYP2	drug and steroid metabolism	13 subfamilies, 16 genes, 16 pseudogenes	CYP2A6, CYP2A7, CYP2A13, CYP2B6, CYP2C8, CYP2C9, CYP2C18, CYP2C19, CYP2D6, CYP2E1, CYP2F1, CYP2J2, CYP2R1, CYP2S1, CYP2U1, CYP2W1
CYP3	drug and steroid (including testosterone) metabolism	1 subfamily, 4 genes, 2 pseudogenes	CYP3A4, CYP3A5, CYP3A7, CYP3A43
CYP4	arachidonic acid or fatty acid metabolism	6 subfamilies, 12 genes, 10 pseudogenes	CYP4A11, CYP4A22, CYP4B1, CYP4F2, CYP4F3, CYP4F8, CYP4F11, CYP4F12, CYP4F22, CYP4V2, CYP4X1, CYP4Z1
CYP5	thromboxane A_2 synthase	1 subfamily, 1 gene	CYP5A1
CYP7	bile acid biosynthesis 7-alpha hydroxylase of steroid nucleus	2 subfamilies, 2 genes	CYP7A1, CYP7B1
CYP8	*varied*	2 subfamilies, 2 genes	CYP8A1 (prostacyclin synthase), CYP8B1 (bile acid biosynthesis)
CYP11	steroid biosynthesis	2 subfamilies, 3 genes	CYP11A1, CYP11B1, CYP11B2
CYP17	steroid biosynthesis, 17-alpha hydroxylase	1 subfamily, 1 gene	CYP17A1
CYP19	steroid biosynthesis: aromatase synthesizes estrogen	1 subfamily, 1 gene	CYP19A1
CYP20	unknown function	1 subfamily, 1 gene	CYP20A1
CYP21	steroid biosynthesis	2 subfamilies, 1 gene, 1 pseudogene	CYP21A2
CYP24	vitamin D degradation	1 subfamily, 1 gene	CYP24A1
CYP26	retinoic acid hydroxylase	3 subfamilies, 3 genes	CYP26A1, CYP26B1, CYP26C1
CYP27	*varied*	3 subfamilies, 3 genes	CYP27A1 (bile acid biosynthesis), CYP27B1 (vitamin D_3 1-alpha hydroxylase, activates vitamin D_3), CYP27C1 (unknown function)
CYP39	7-alpha hydroxylation of 24-hydroxycholesterol	1 subfamily, 1 gene	CYP39A1
CYP46	cholesterol 24-hydroxylase	1 subfamily, 1 gene	CYP46A1
CYP51	cholesterol biosynthesis	1 subfamily, 1 gene, 3 pseudogenes	CYP51A1 (lanosterol 14-alpha demethylase)

THE HUMAN P450 KARYOGRAM



1	2	3	4	5	6	7	8	9	10	11
4As 4B1 4X1	1B1 26B1 27A1 27B1 27C1	8B1	2U1 4V2		21A2 39A1	2W1 3As 5A1 51	2J2 7A1 7B1 11Bs		2Cs 2E1 17 26A1	2R1

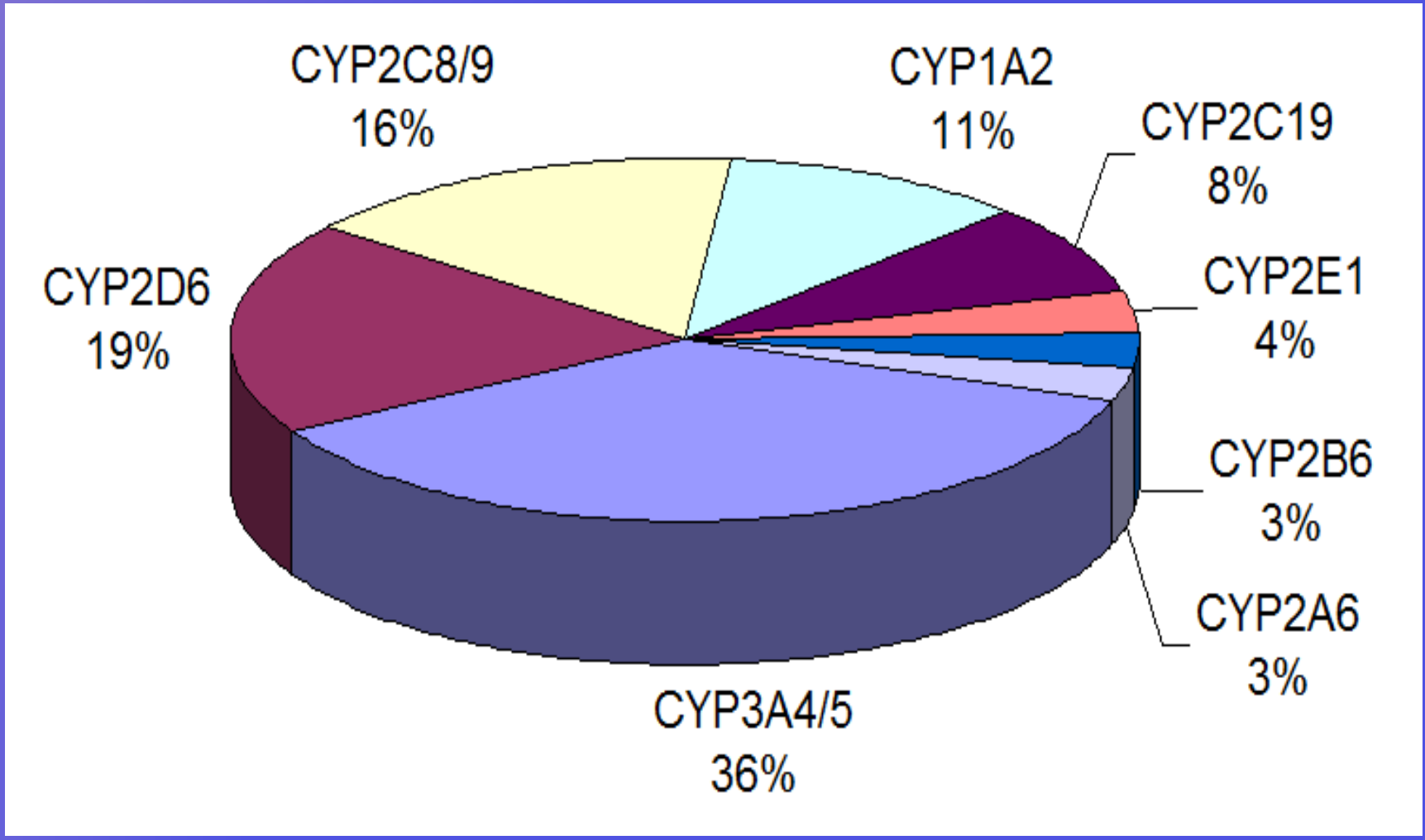


12	13	14	15	16	17	18	19	20	21	22	X	Y
		46	1As 11A1 19				2As 2B6 2F1 2S1 4Fs	8A1 24	4F28	2D6		

Different members of cytochrome P450 family and "substrate specificities"

Isozyme	Substrate examples	Reactions
CYP1A1	benzo[*a*]pyrene	hydroxylation
	7-ethoxyresorufin	*O*-de-ethylation
1A2	acetylaminofluorene	*N*-hydroxylation
	phenacetin	*O*-de-ethylation
CYP2A1	testosterone	7α-hydroxylation
2A2	testosterone	15α-hydroxylation
2A3		
CYP2B1	hexobarbital	hydroxylation
	7-pentoxyresorufin	*O*-de-ethylation
2B2	7-pentoxyresorufin	*O*-de-ethylation
	7,12-dimethylbenzanthracene	12-methyl-hydroxylation
CYP2C	S-mephenytoin	hydroxylation
CYP2D	debrisoquine	alicyclic hydroxylation
CYP2E1	*p*-nitrophenol	hydroxylation
	aniline	hydroxylation
CYP3A	ethylmorphine	*N*-demethylation
	aminopyrine	*N*-demethylation
CYP4A1	lauric acid	ω-hydroxylation
	lauric acid	ω-1-hydroxylation

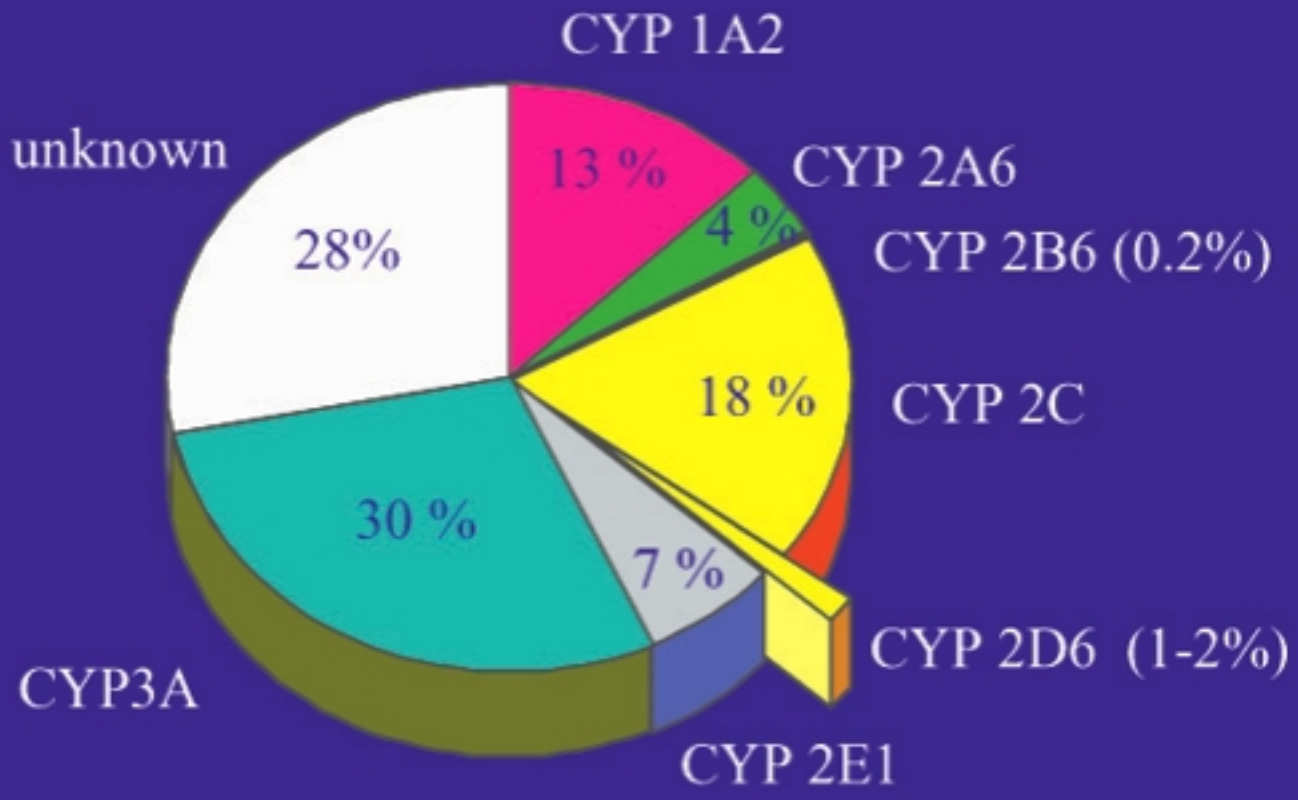
Metabolism of therapeutic drugs by CYPs



Most important cytochrome P450 in Humans

- CYP3A4 metabolizes 36% of therapeutic drugs
- CYP2D6 19%
- CYP2C9, 16% CYP2C19 6% = 25%
- CYP1A2, 11% CYP2A6, 3% CYP2B6 3 %
- The activities of certain CYP enzymes have been associated with increased risk for cancer

The Cytochromes P450 of Human Liver



Shimada et al., J. Pharm. Exp. Ther. 270:414(1994)

P450 3 Family (1)

CYP3A4 – metabolizes 1/3 of all clinically important drugs, is the most abundant of the liver isozymes (also present in the intestine, lung, uterus, placenta, kidney, and brain). It is glucocorticoid and ` phenobarbital inducible. 3A5 is also present in adults.

- Activates procarcinogens: Aflatoxin B1 & (possibly) Benzo[a]pyrenes.
- Its presence in the intestine, in combination with P-gylcoprotein on enterocytes, is likely to govern oral bioavailability(*) of drugs
- 3A4 induction by Phenobarbital may explain the DDI between barbiturates & other drugs

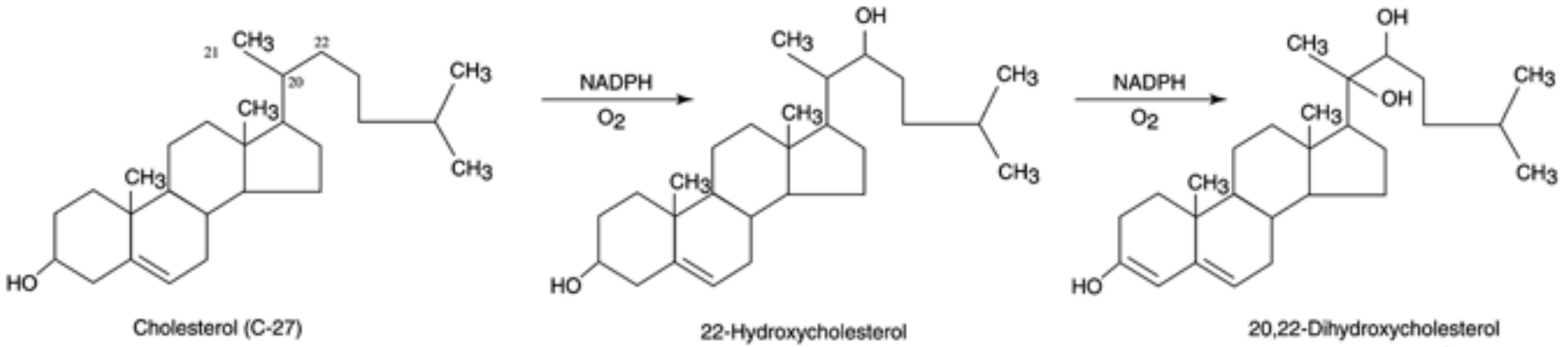
CYP3A7 is present in fetal livers (ca. 50% of the total fetal P450 enzymes). It metabolizes Dehydroepiandrosterone-3-sulfate (16α-hydroxylation), as well as allylic & benzylic carbons.

(*) Oral bioavailability is the combined result of (passive) intestinal absorption and first-pass metabolism (in the liver).

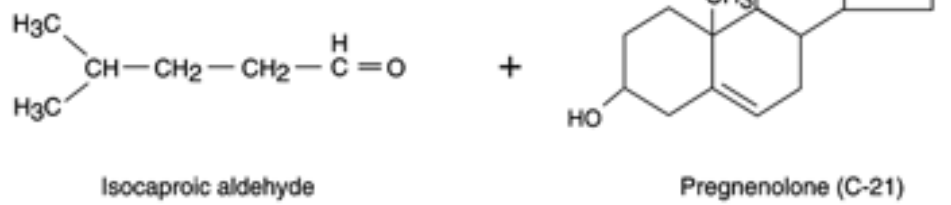
P450 2 Family (4)

CYP2E1 – known as microsomal ethanol oxidizing system (MEOS) or benzene hydroxylase, metabolizes few drugs (mostly halogenated hydrocarbons) and a range of low-MW organic compounds, e.g., dimethylformamide, acetonitrile, acetone, ethanol, benzene. **Most of its metabolites are toxic or carcinogenic**. It is expressed in liver, kidney, intesine and lung.

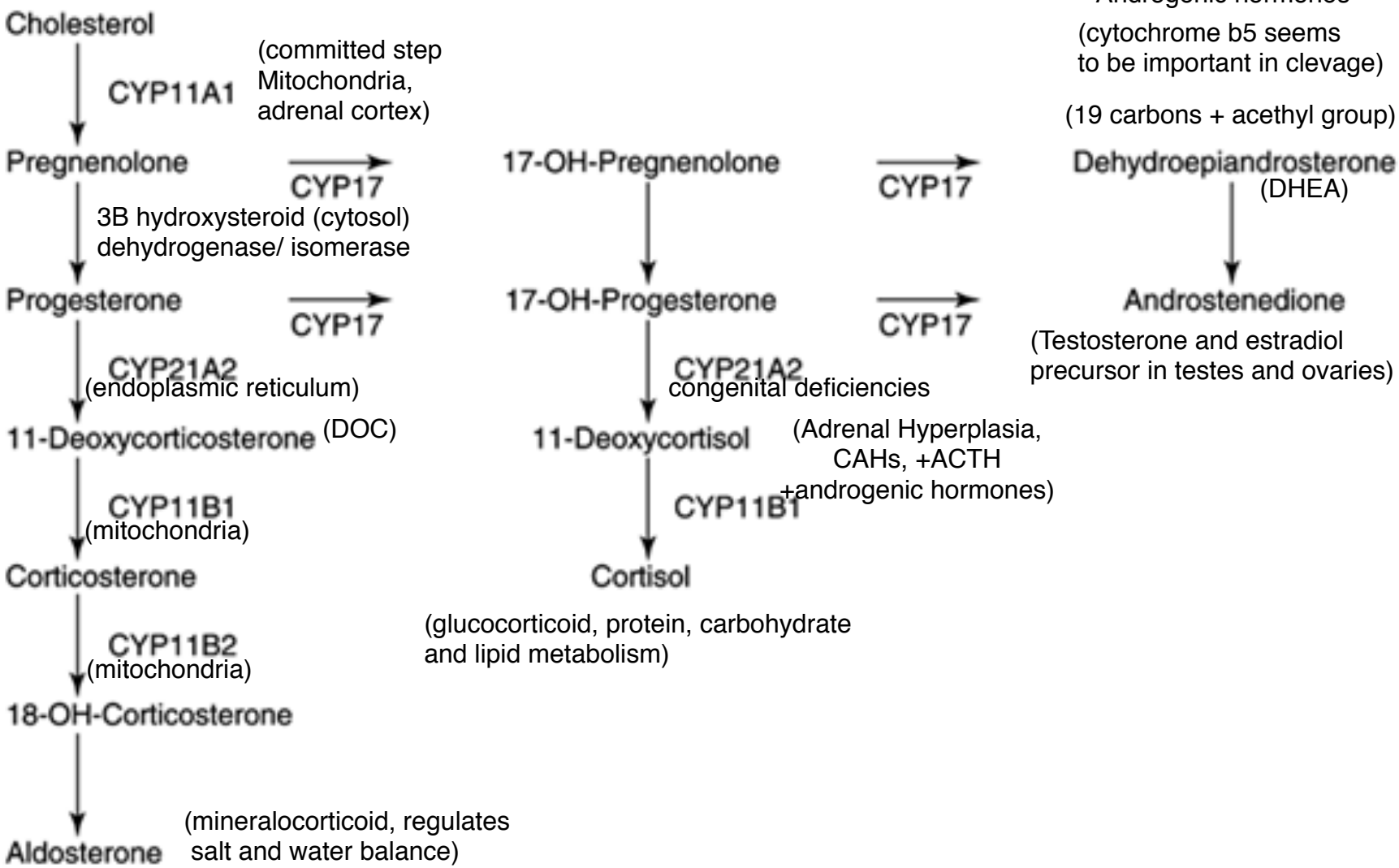
- Metabolizes:
  - Acetaminophen, activated to N-acetyl-para-benzoquinoneimine; Zoxazolamine.
  - General anesthetics: Enflurane, Halothane, Methoxyflurane, etc.
  - Styrene (epoxidation), Chloroform, Methylenechloride
  - Miscellaneous solvents: ethanol, glycerine, acetone, diethylether, aniline, benzene, acetonitrile, pyridine.
- Inducible by Ethanol, Isoniazid, 4-Methylpyrazole, also by diabetes and fasting.
- Ketogenic diets (high serum levels – low carb/high fat) enhance halogenated hydrocarbons metabolism in rats. **Chronic alcoholism increases the hepatotoxicity of halogenated hydrocarbons**.
- Polymorphism is mostly studied in Chinese-Asians.

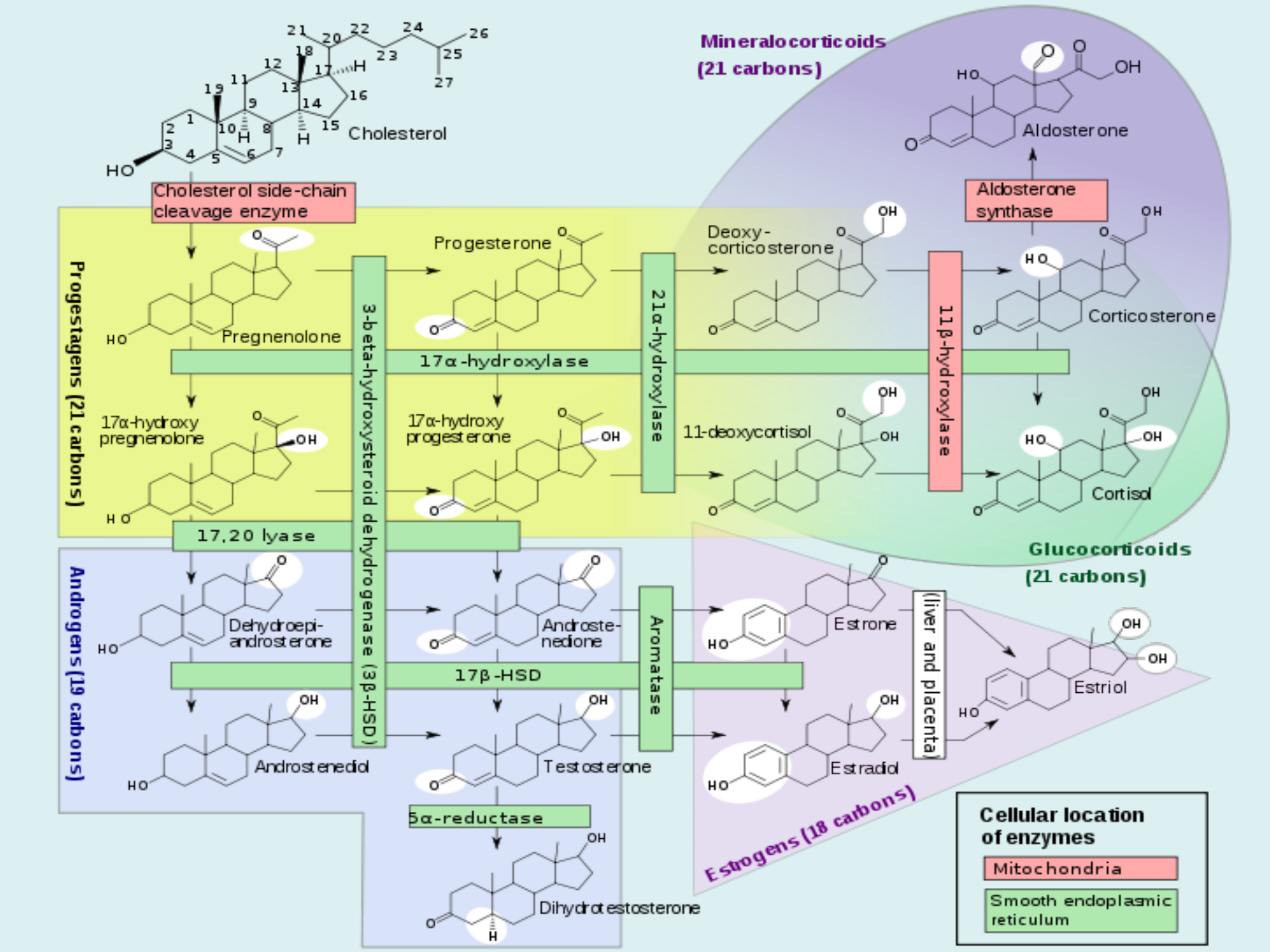


Cytochrome P450scc
side chain cleavage (20-22)
CYP11A1

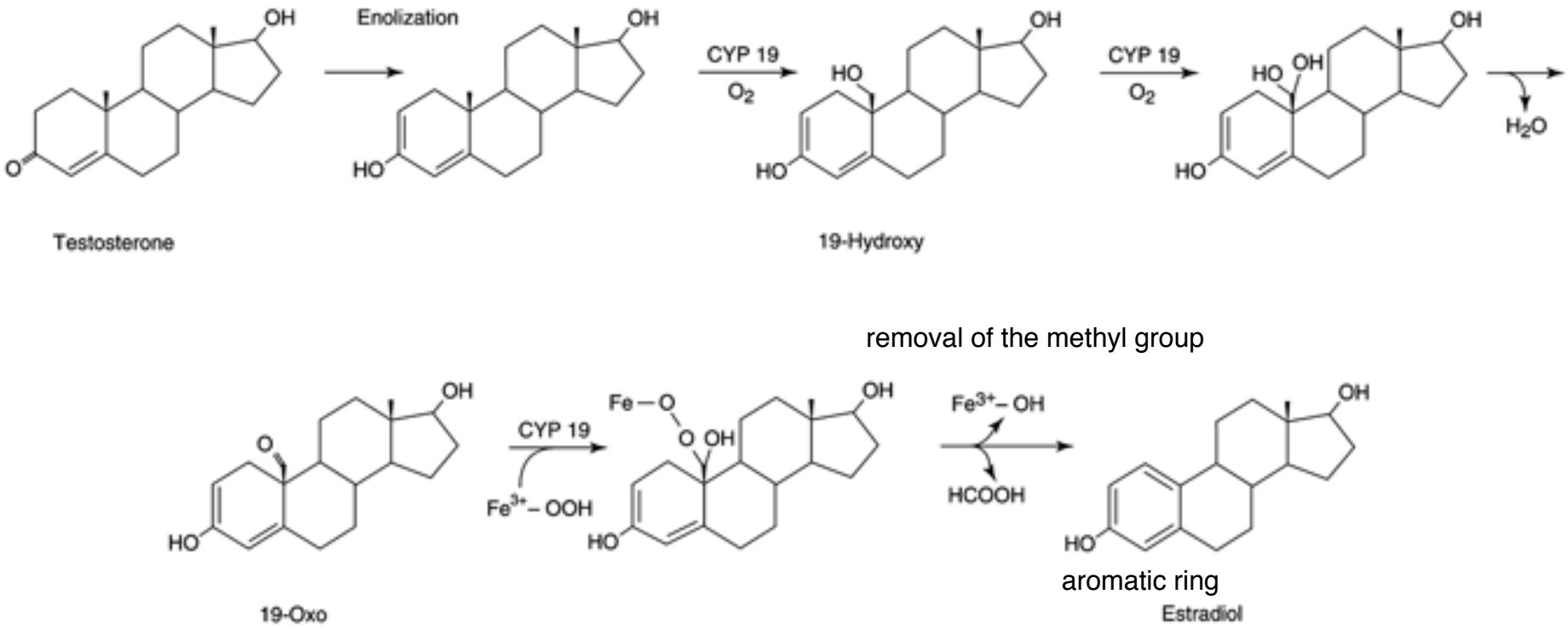


The role of cytochrome p450 in steroid synthesis




Mineralocorticoids
(21 carbons)
Aldosterone
Aldosterone synthase
Deoxy-corticosterone
Corticosterone
11β-hydroxylase
Progestagens (21 carbons)
Cholesterol side-chain cleavage enzyme
Cholesterol
Pregnenolone
Progesterone
3-beta-hydroxysteroid dehydrogenase
17α-hydroxylase
21α-hydroxylase
17α-hydroxy pregnenolone
17α-hydroxy progesterone
11-deoxycortisol
Cortisol
17,20 lyase
Glucocorticoids
(21 carbons)
Androgens (19 carbons)
Dehydroepi-androsterone
Androste-nedione
17β-HSD
Aromatase
Androstenediol
Testosterone
5α-reductase
Dihydrotestosterone
Estrone
Estradiol
(liver and placental)
Estriol
Estrogens (18 carbons)
Cellular location of enzymes
Mitochondria
Smooth endoplasmic reticulum

Synthesis of estrogens
CYP aromatase ($P450_{arom}$)

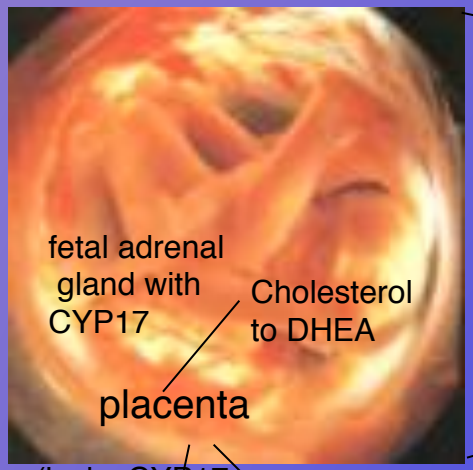


Similar to CYP11A1
one enzyme involved in two hydroxylation before cleavage

Other endogenous substrates

CYP27B1	25-Hydroxy-vitamin D_3 to 1,25 hydroxy
CYP4F3	Leukotriene B4 less active 20 hydroxy
CYP2J2, CYP2B6, CYP4A11	Arachidonic acid
CYP26A1	Retinoic acid

Cooperativity of Cytochrome P450s in fetal and maternal organs



fetal adrenal gland with CYP17

Cholesterol to DHEA

placenta

The placenta can not synthesize estrogen from Cholesterol lack of CYP 17

1000 times more estrogen in pregnancy
15-20 mg estradiol
50-100 mg estriol
250 mg progesterone

(lacks CYP17
17 a-hydroxylation &
cleavage (C1 7-20)

after 4 weeks
3B hydroxysteroid (cytosol)
dehydrogenase/ isomerase

maternal circulation

CYParom (CYP19)

progesterone and estrogens

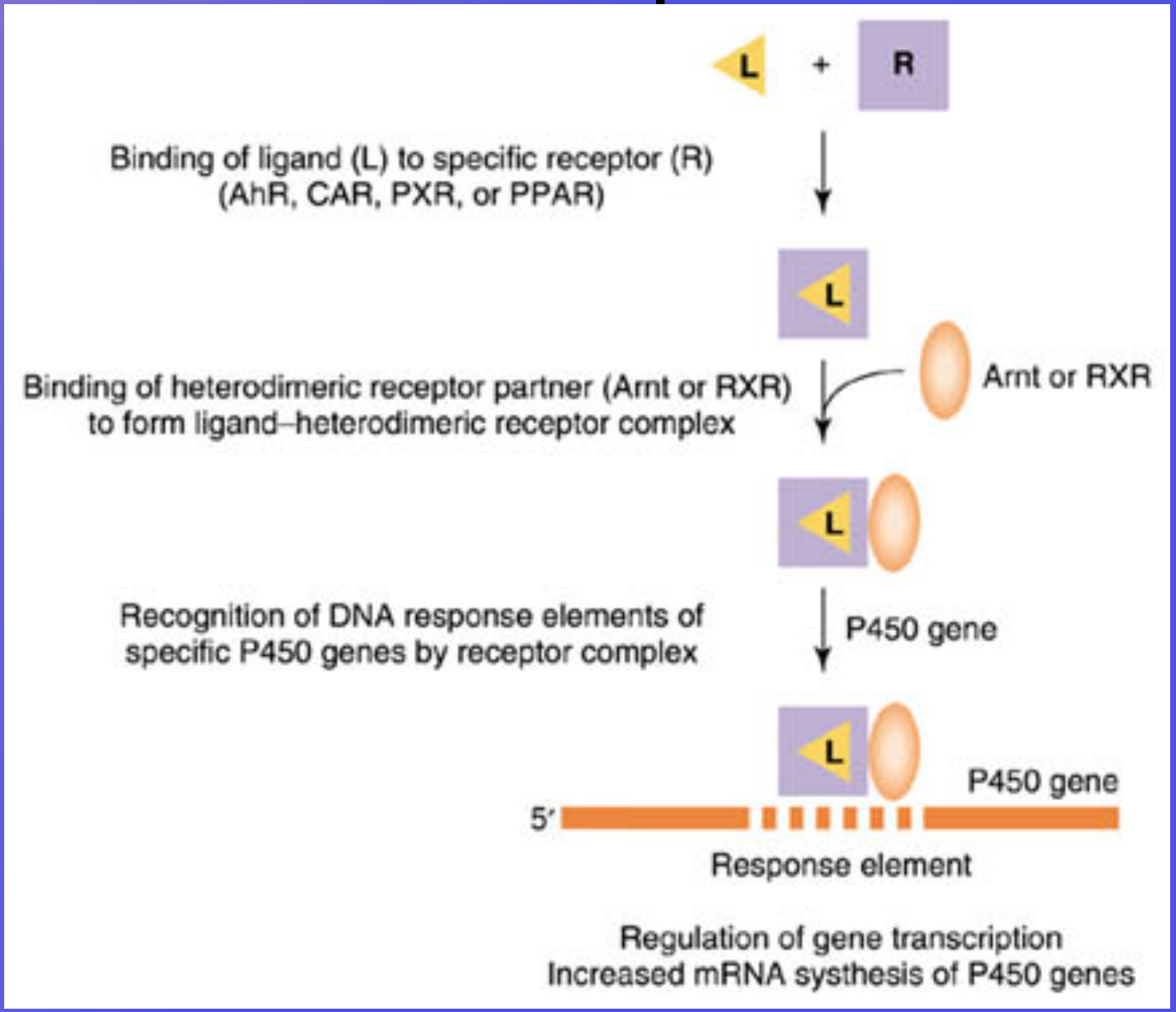
ovaries
estrogen first few weeks

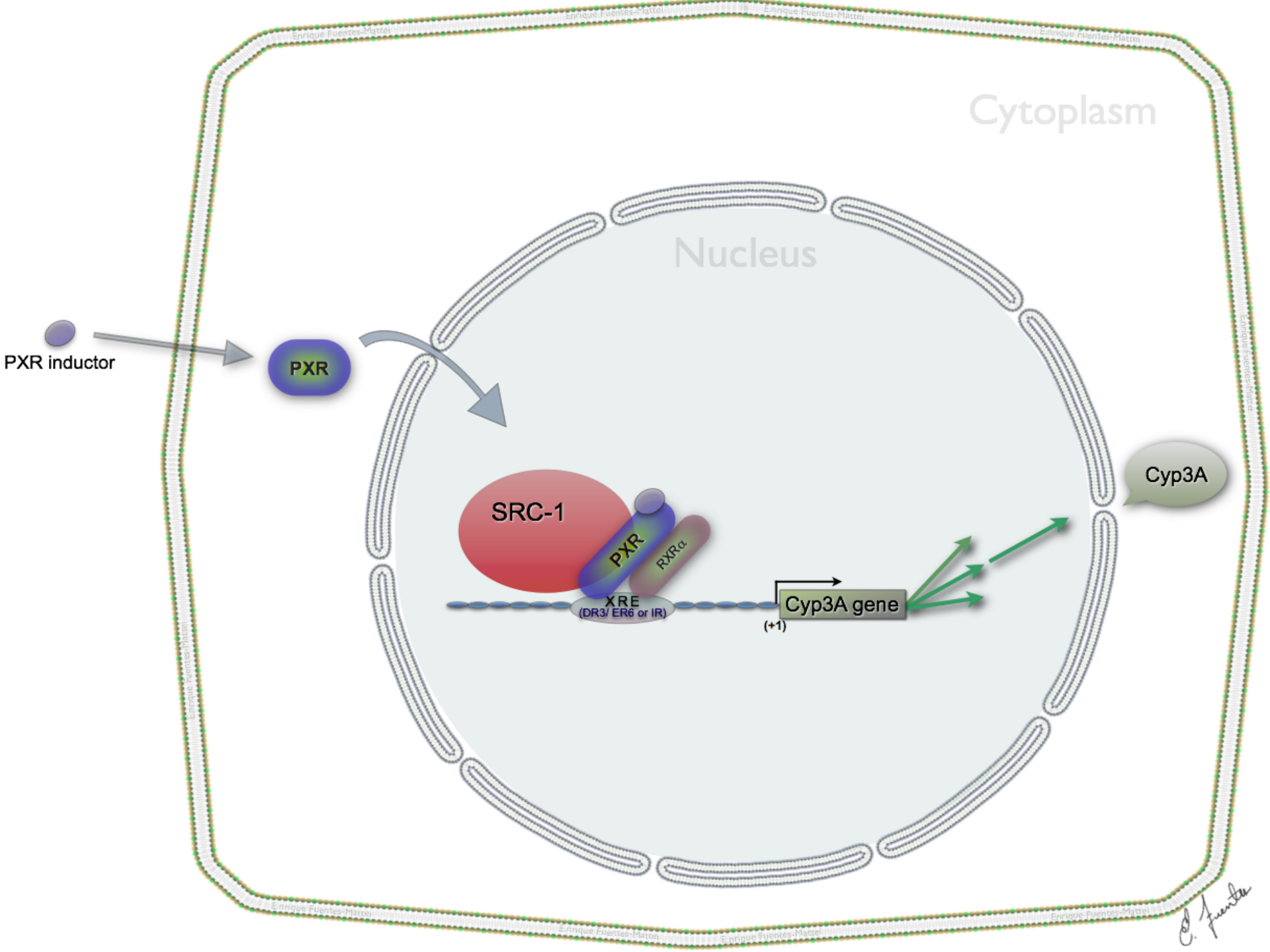
estriol

8 weeks

progesterone by the CYPscc

Receptors


L
+
R
Binding of ligand (L) to specific receptor (R)
(AhR, CAR, PXR, or PPAR)
L
Binding of heterodimeric receptor partner (Arnt or RXR)
to form ligand–heterodimeric receptor complex
Arnt or RXR
L
Recognition of DNA response elements of
specific P450 genes by receptor complex
P450 gene
L
P450 gene
5′
Response element
Regulation of gene transcription
Increased mRNA systhesis of P450 genes


Cytoplasm
Nucleus
PXR inductor
PXR
SRC-1
PXR
RXRα
XRE
(DR3/ ER6 or IR)
Cyp3A gene
(+1)
Cyp3A

Medications that interact with the CYP450 system do so in 1 of 3 ways:

- Inhibition – Generally leads to decreased rates of metabolism of other drugs metabolized by the same enzyme, resulting in higher drug levels and increased potential for toxicity.
- Inhibition is usually reversible, irreversible inhibition can occur, requiring new CYP450 enzyme to be synthesized.
- Inhibition tends to occur quickly with maximal effect occurring when highest concentrations of the inhibitor are reached.
- Example: Ritonavir (PI) and Midazolam = ↑ sedation

Medications that interact with the CYP450 system do so in 1 of 3 ways:

- Induction –results in the increased clearance of concomitant medications metabolized by the same enzyme.
- The body responds by increasing the production of specific enzymes of the CYP450 system.
- ↑ enzyme production can lead to ↑ metabolism and ↓ drug concentrations
- Example: Efavirenz and methadone = withdrawal symptoms

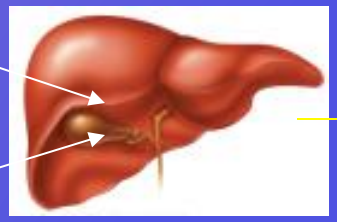
Medications that interact with the CYP450 system do so in 1 of 3 ways:

- Substrates – occupy the active site of a specific CYP450 enzyme.
- The medication's metabolism is then affected by other medications that either induce or inhibit the CYP450 enzyme system.
- Example: NNRTIs and PIs are substrates at CYP3A4 and are therefore prone to drug interactions. (Non-Nucleoside Reverse Transcriptase Inhibitors) (protease Inhibitors)
- http://www.youtube.com/watch?v=RUUyd5bE9vQ

Drug Interactions (Liver)

CYP Substrate

CYP Inhibitor

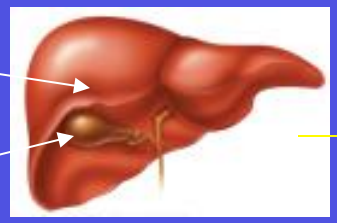


↑ Substrate concentration

↑ Toxicity

CYP Substrate

CYP Inducer



↓ Substrate concentration

↓ Efficacy

Drugs with established clinical Drug-gene Interactions and Therapeutic Recommendations

78% of drugs with guidance are processed by the main 3 CYPs

CYP2D6

Amitriptyline, Aripiprazole, Atomexetine, Carvedilol, Clomipramine, Codeine, Doxepin, Duloxetine, Flecainide, Haloperidol, Imipramine, Metoprolol, Mirtazapine, Nortriptyline, Oxycodone, Paroxetine, Propafenone, Risperidone, Tamoxifen, Tramadol, Venlafaxine, Zuclopenthixol

CYP2C9

Acenocoumarol, Glibenclamide, Gliclazide, Glimepiride, Phenprocoumon, Phenytoin, Tolbutamide

CYP2C19

Citalopram/Escitalopram, Clopidogrel, Esomeprazole, Imipramine, Lansoprazole, Moclobemide, Omeprazole, Pantoprazole, Rabeprazol, Sertraline, Voriconazole

Note: Many other drugs have drug-gene interactions but clinically confirmed therapeutic recommendations are still being determined.
http://www.nature.com/clpt/journal/v89/n5/full/clpt201134a.html

Frequency of Genetic Variation in the Cytochromes P450s

Gene	Normal	Intermediate	Poor	Ultra
CYP2D6	48%	35%	10%	7%
CYP2C9	~60%	>35%	2-4%	N/A
CYP2C19*	14-44%	24-36%	2-20%	30%

*There is wide variability among populations. People of Asian and African ancestry have a greatly increased prevalence of poor metabolizer These frequencies are not well studied in the Hispanic populations

DISEASES CAUSED BY DEFECTS IN CYPs

CYP	*DISEASE*
• CYP1B1	Congenital glaucoma
• CYP11A1, CYP11B1, CYP11B2, CYP17, CYP21	Various endocrine syndromes
• Various CYPs	Risk factor for cancer

Drug Drug Interactions (3)

- **Can DDIs be lethal?** When 3A4 substrates/inhibitors are co-administered with astemizole, cisapride, pimozide or terfenadine, this can lead to QT prolongation (on the ECG signal), which in turn can lead to **fatal ventricular arrhythmia** (known as '*Torsade des pointes*').
- As a result, Terfernadine and Cisapride are no longer in clinical use
- The Terfenadine metabolite, Fexofenadine, is marketed as Allegra
- **Can DDIs be beneficial?** When co-administered with Cyclosporine (a *very* expensive drug), 3A4 inhibitors can reduce the cost of immunosuppresive therapy. This is also valid for most HIV-1 protease inhibitors (Ritonavir, Saquinavir).
- E.g., the (poor) oral bioavailability of Saquinavir can be increased by combination with Ritonavir (3A4 inhibitor). This lead to Kaletra, a new drug combination of Ritonavir (3A4 inhibitor) and Lopinavir (3A4 substrate).

- Poor metabolizers of CYP2D6 substrates are at risk for postural hypotension and antipsychotic side effects such as over sedation, because several antipsychotic agents are metabolized by CYP2D6. In a study of 45 elderly patients (five of whom were poor metabolizers) receiving perphenazine, side effects increased five fold in the poor metabolizers compared with the extensive metabolizers. Conversely, when formation of an active metabolite is essential for drug action, poor metabolizers of CYP2D6 can exhibit less response to drug therapy compared with extensive metabolizers.

Case Studies

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HOW THE MIGHTY HAVE FALLEN

A 56-year-old teacher with a seizure disorder had been virtually seizure free for the past 10 years while taking phenytoin (Dilantin), 300 mg/day (blood level, 14.5 µg/mL). One summer, he received the news that he would not be rehired by the school for the coming academic year. This event, along with the recent death of his spouse from pancreatic cancer, led him into his first severe depressive episode. His friends advised him to visit a psychiatrist, and he accepted their advise. During the intake, he ruminated about how he had attended the same school as a teenager, and in his day he had been the class president and the starting quarterback. Now he was being rejected by a place he had considered a kind of home. His obsessional ruminations about his "lost glories," as well as a full array of neurovegetative depressive symptoms, led the psychiatrist to start the patient on fluvoxamine (Luvox), with the plan to titrate to a dosage of 150 mg/day and then wait a few weeks for a possible response.

During this fluvoxamine dosage titration, the patient progressively more sedated and slightly unsteady, but he did not want to be a “complainer,” and he decided to just “stick it out,” assuming that these were transient side effect of his new medicine that would soon abate.

However, 1 week after reaching 150 mg/day, the patient lost his balance and fell down a flight of stairs in his home. He was too delirious and debilitated to summon help himself, and he basically lay there until a friend happened to drop by 6 hours later. He was immediately taken to the local emergency room, where his phenytoin blood lever was found to be 46.7 ug/mL (Mamiya et al. 2001). (check drug interactions what can you say)

PANICKED AND CONFUSED

A 35-year-old man with long-standing schizoaffective disorder, bipolar type, and alcohol dependence in full remission was being stably maintained on haloperidol (Haldol), 10mg qhs, and divalproex sodium (Depakote), 1,000 mg bid. Benztropine (Cogentin), 2 mg bid, alleviated his haloperidol-induced tremor and stiffness without causing any further side effects.

Over the previous 2 years, both of his parents died from medical causes, this led to the emergence of frequent and debilitating panic attacks.

His psychiatric hoped to alleviate these panic attacks by adding paroxetine (Paxil), 20 mg qhs, to the patient regimen; the psychiatrist declined to use benzodiazepines to avoid rekindling the patient alcohol use.

Within 5 days, the patient experienced new-onset **blurring of his vision**, **urinary retention, and mild memory impairment.**

After taking a nap and waking in the early evening, **he could not remember what day it was or whether it was morning or evening, thus inducing another severe panic attack.**

The psychiatrist told the patient to stop taking the paroxetine and sent him to have blood levels drawn for his medications. His haloperidol and divalproex levels were essentially unchanged and in the normal range, but his benztropine level (no baseline) was 42 ng/ml. (Levels of 25 ng/ml, are considered toxic) (Specialty Laboratories 2001). On receiving this result, the psychiatrist held the patient benztropine, and his anticholinergic symptoms abated over the next 3 days (Armstrong and Schweitzer 1997).

DISCUSSION

This is an example of an inhibitor added to a substrate.

Benztropine is believed to be a 2D6 substrate, and there have been several documented instances that suggest that 2D6-inhibiting selective serotonin reuptake inhibitors such as paroxetine (von Moltke et al. 1995) inhibit benztropine's metabolism. The addition of paroxetine to the regimen impaired the ability of 2D6 to efficiently metabolize the benztropine, which led to an increase in the blood level of benztropine, even though the benztropine dosage had not been changed. The increased benztropine level led to the emergence of several anticholinergic symptoms (blurry vision due to mydriasis, urinary retention, and mild confusion).

Practice exercise

Clinical Case Study

A 74-year-old woman with insulin-dependent (type 2) diabetes had been taking metoprolol (Lopressor) and warfarin for atrial fibrillation and amitriptyline, 50 mg at bedtime, for diabetic neuropathy, for several years. On the death of her husband, she presented with symptoms of depression, and paroxetine was added to her medication regimen with the rationale that paroxetine would cause fewer side effects than an increase in the amitriptyline dosage. Three days after the initiation of paroxetine (Paxil) therapy, the woman was brought to the emergency department by her daughter, who had found her asleep at 11 a.m. On awakening, the patient complained of dry mouth and dizziness. Her International Normalized Ratio (INR) was 4.0.

ADD THESES 3 DRUGS TO THE LIST ON THE RIGHT

(Atrial fibrillation)

1. Metoprolol, beta blocker (Lopressor)
2. Warfarin

(diabetic neuropathy (antidepressant))

3. Amitriptyline

Lets look for possible drug interactions

Now lets add paroxetine (antidepressant) also known as Paxil to the list and look for drug interactions