CYTOCHROME_P450 METABOLISM

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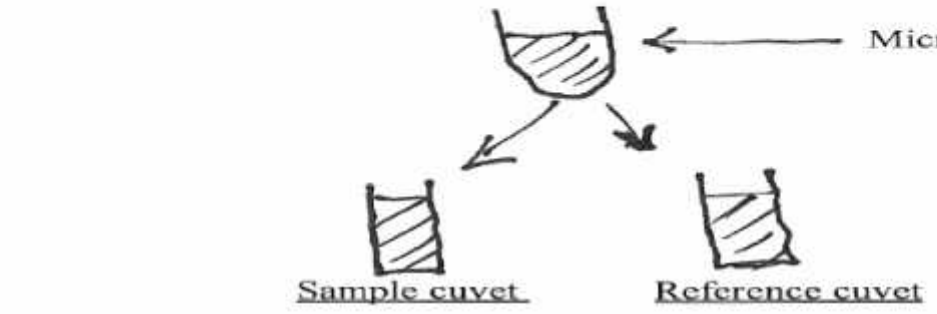
CONTENTS

INTRODUCTION

- The cytochrome p450 enzymes (cyps) are a diverse super family of enzymes which taken together,are capable of metabolising wide variety of endogenous and xenobiotic substances including drug molecules.
- Cytochrome P450 enzymes (hemoproteins) play an important role in the intra-cellular metabolism.
- Cyps have been extensively studied in animals (rats,mice dogs and to less extent in zebra fish), in bacteria ,in fungi,in insects, in plants and in humans, (prokaryotic and Eucaryotic).

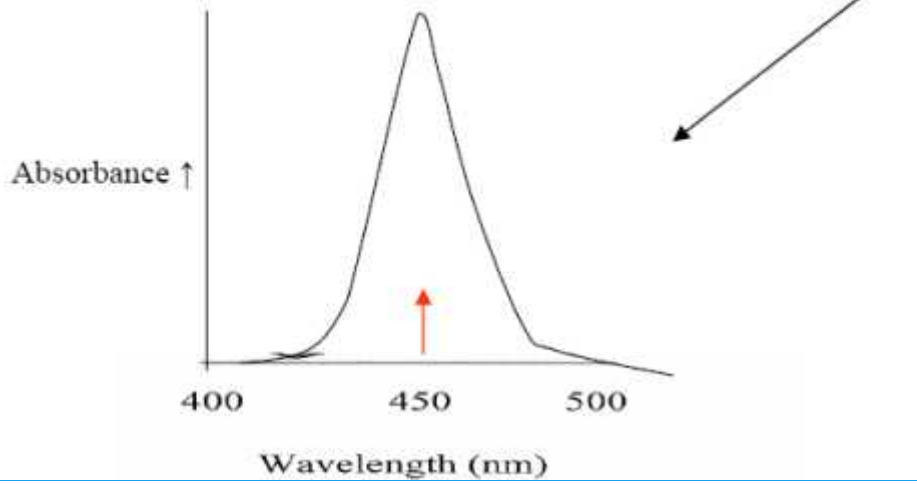
2. Structural: CYP is a heme-containing protein (hemoprotein) with a characteristic light absorption spectrum. Its absorption spectrum (Maximum = 450 nm) is the basis of its name

P450 got its name from its "absorption spectrum"



	Sample cuvet	Reference cuvet
Reducing agent (NADPH; to reduce $Fe^{3+} \rightarrow Fe^{2+}$)	+	+
Carbon monoxide (binds Fe^{2+}, not Fe^{3+}	+	-

Scan in a spectrophotometer



P450 absorption spectrum:

-maximum (peak) at 450 nm

-not observed in the absence of heme

-not observed in the absence of carbon monoxide

- carbon monoxide necessary for obtaining the spectrum but inhibits drug metabolism by P450
  - because it competes with oxygen for binding to heme

-used for determining tissue levels of total CYP

• peak height (absorbance) is proportional to the amount of CYP

Introduction contd...

- “LIVER” is the major site of drug metabolism .
- The other xenobiotic –metabolising enzymes are present in nervous tissue, kidney, lung, plasma and the GIT (digestive secretions , bacterial f lora and the intestinal wall).
- Drugs that undrego first pass metabolism show reduced bioavailability.
- Genetic polymorphisms could effect metabolism , clearence and tolerance.

  At least 30% of the cyp 450 –dependent metabolism is performed by polymorphic enzymes.

Introduction contd….

- Synonymns ------- mixed function oxidase (MFO)
  or
  M icrosomal hydroxylase

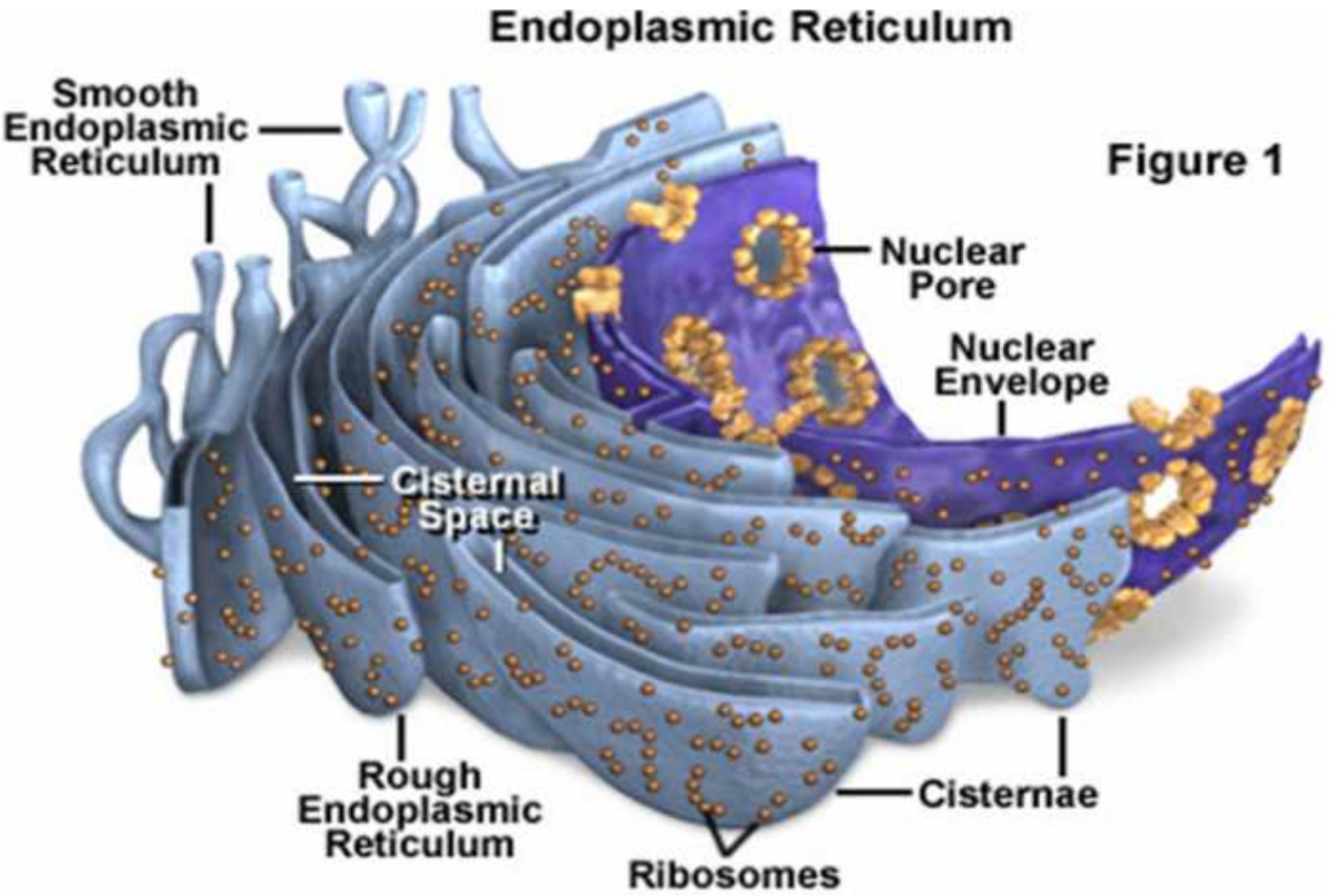
- **It is know that the gene for cytochrome P-450 has existed for more then 3.5 billion years. This indicates drug metabolism by the P-450 system is a new and secondary role for these enzyme systems.**

- These enzymes are of particular importance in drug metabolism and drug biotransformation.

Introduction contd…...

- . Although almost all tissue in the body have some ability to metabolize chemicals, smooth endoplasmic reticulum in liver is the principal "metabolic clearing house" for both endogenous chemicals (e.g., cholesterol, steroid hormones, fatty acids, and proteins), and exogenous substances (e.g. drugs)

Cytochrome P-450 is the terminal oxidase component of an electron transport chain.


Endoplasmic Reticulum
Smooth Endoplasmic Reticulum
Figure 1
Nuclear Pore
Nuclear Envelope
Cisternal Space
Rough Endoplasmic Reticulum
Cisternae
Ribosomes

CYTOCHROME P450 NOMENCLATURE

- For eg.,
- CYP2E1
- CYP ------ cytochrome p450 (p is for pigment)
- 2 ------ genetic family
- E ------ genetic sub family
- 1 ------ specific gene
- genes encoding for the p450 enzymes and the enzymes themselves, are designated with the abbreviations CYP.
- CYP2E1 is the gene encoding for CYP2E1– One of the enzymes involved in paracetamol (acetaminophen) metabolism.

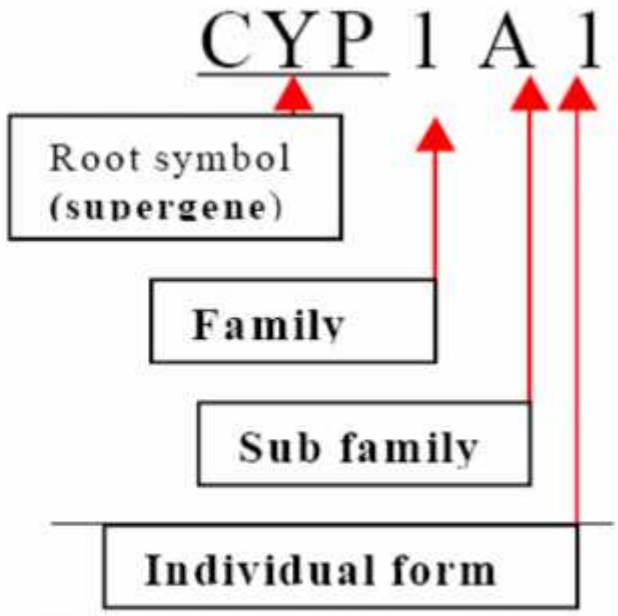
3. Multiplicity: CYP exists in multiple forms

a. Classification and nomenclature

	Supergene	Family	Subfamily	Form
Protein designation:	CYP	1,2,3 etc.	A,B,C, etc.	1,2,3, etc:
Protein sequence homology:		>40%	>55%	

Gene designation: *italicized* (e.g., *CYP1A1*)

Protein designation: straight type (e.g., CYP1A1)

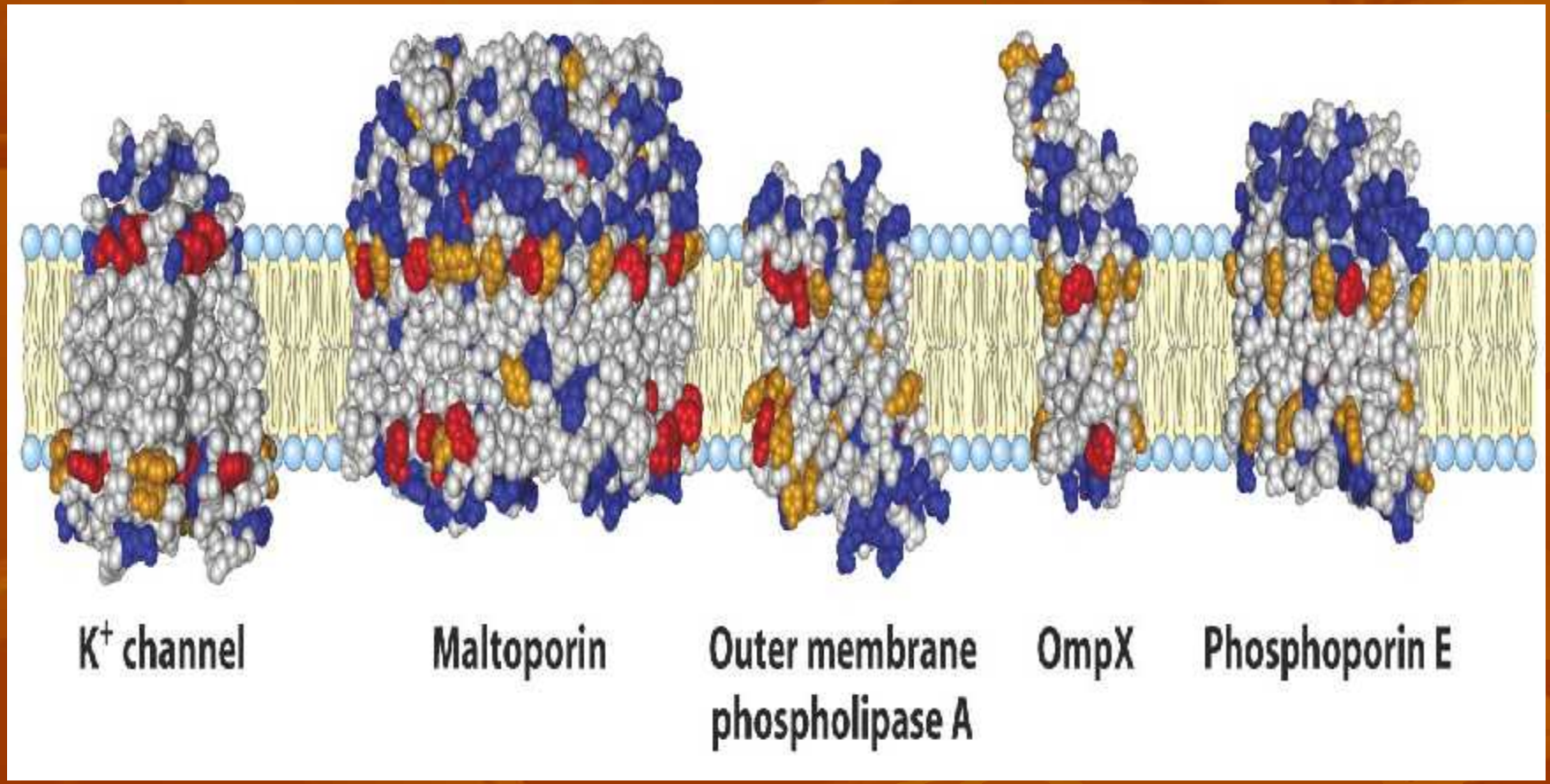


The quantity of each form of P450 protein in a tissue can be determined using specific antibodies

COMPONENTS OF CYP450

- Cyp450 consists of two protein components
- a heme protein ----- cytochrome p450
- a flavo protein ----- NADPH-CYP450 reductase containing both flavin mono nucleotide (FMN) and flavin dinucleotide (FDN).
- The third component essential for electron transport from NADPH to CYP450 is a phospholipid , phosphotidylcholine that facilitates the transfer of electron from NADPH-CYP450 reductase to cyp450.
- The cyp450 is an integral membrane protein deeply imbedded in the membrane matrix.

Cytochrome P450's are integral membrane proteins found in the endoplasmic reticulum-membrane network in cells



MECHANISM

THE P450 CATALYTIC CYCLE

- The most important reaction catalysed by cyp450 are monooxygenase (oxidative) reactions.

$$RH + O2 + 2H+ + 2e– \rightarrow ROH + H2O$$

- GENERAL FEATURES OF CYTOCHROME P450 CATALYSIS ::

- The active site of cytochrome P450 contains a heme iron center.
- The substrate binds to the active site of the enzyme, in close proximity to the heme group, on the side opposite to the peptide chain.
- . The bound substrate induces a change in the conformation of the active site, often displacing a water molecule from the distal axial coordination position of the heme iron, and sometimes changing the state of the heme iron from low-spin to high-spin.

Contd….

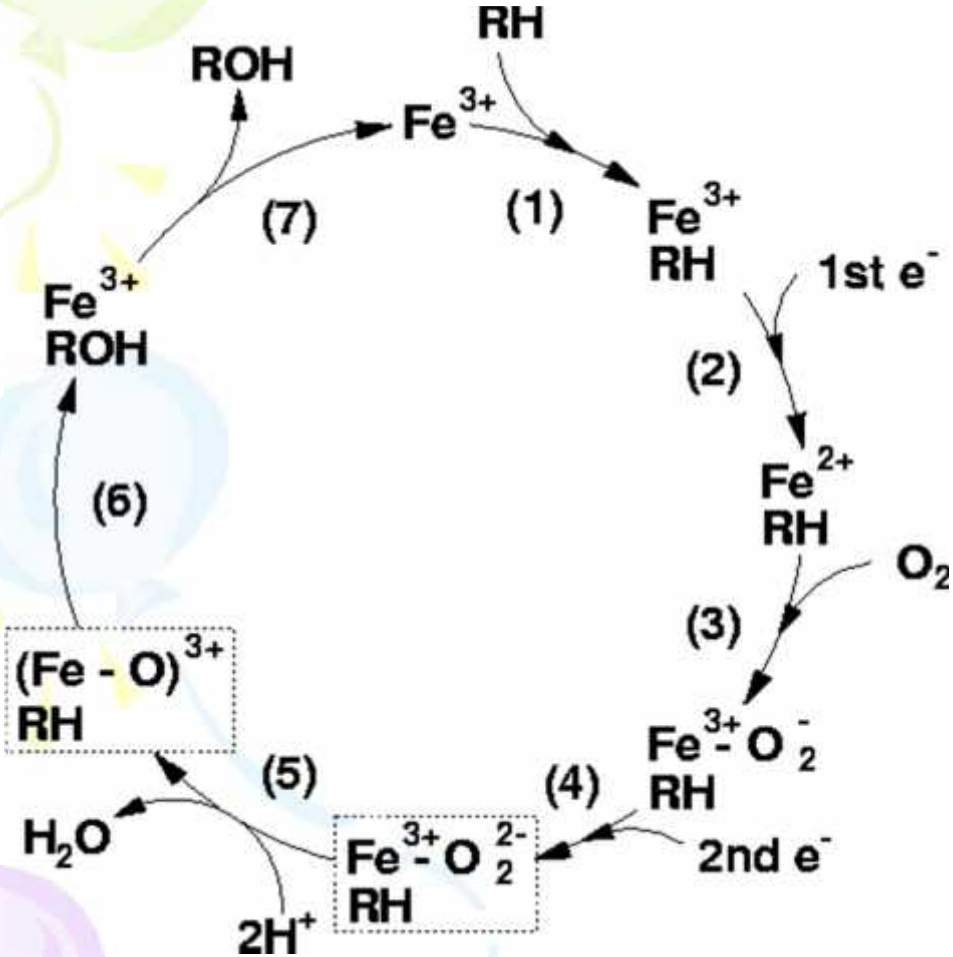
- The change in the electronic state of the active site favors the transfer of an electron from NAD(P)H via cytochrome P450 reductase or another associated reductase. This takes place by way of the electron transfer chain, reducing the ferric heme iron to the ferrous state.
- Molecular oxygen binds covalently to the distal axial coordination position of the heme iron. The cysteine ligand is a better electron donor than histidine, with the oxygen consequently being activated to a greater extent than in other heme proteins. However, this sometimes allows the bond to dissociate, the so-called "decoupling reaction", releasing a reactive superoxide radical, interrupting the catalytic cycle.
- A second electron is transferred via the electron-transport system, either from cytochrome P450 reductase, ferredoxins, or cytochrome b5, reducing the dioxygen adduct to a negatively charged peroxo group. This is a short-lived intermediate state.

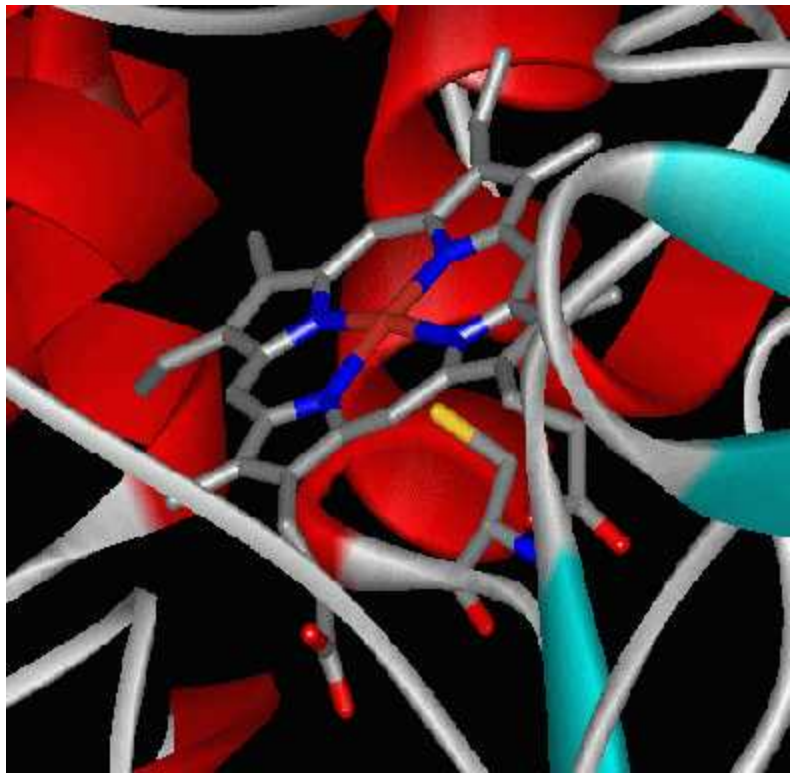
Contd…

- The peroxo group formed in step 4 is rapidly protonated twice by local transfer from water or from surrounding amino-acid side chains, releasing one water molecule, and forming a highly reactive iron-oxo species.
- 6: Depending on the substrate and enzyme involved, P450 enzymes can catalyse any of a wide variety of reactions. A hypothetical hydroxylation is shown in this illustration. After the product has been released from the active site, the enzyme returns to its original state, with a water molecule returning to occupy the distal coordination position of the iron nucleus.
- If carbon monoxide (CO) binds to reduced P450, the catalytic cycle is interrupted. This reaction yields the classic CO difference spectrum with a maximum at 450 nm.

The substrates are monooxygenated in a catalytic cycle

the iron is a part of haem moiety





Cytochrome P450 gene families

Human 14+

Molluscs 1

CYP450

Plants 22

Bacteria 18

Insects 3

Fungi 11

Yeasts 2

Nematodes 3

HUMAN CYTOCHROME P450 FAMILY

- Humans have 57 genes and more than 59 pseudogenes divided among 18 families of cytochrome P450 genes and 43 subfamilies.

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Cytochrome P450 Isoforms

- CYP1A2
- CYP3A
- CYP2C9
- CYP2C19
- CYP2D6

Contd…

Family	Function	members	Names
CYP1	Drug and steroid (especially estrogen) metabolsm	3 sub families , 3 genes, 1 pseudogene	CYP1A1,CYP1A2,CYP 1B1,CYO1A8P(pseudo gene)
CYP2	Drug and steroid metabolsm	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 (especially testosterone) metabolsm	1 subfamily, 4 genes, 2 pseudogenes	CYP3A4, CYP3A5, CYP3A7, CYP3A43
CYP4	arachidonic acid or fatty acid metabolism	6 subfamilies, 11 genes, 10 pseudogenes	CYP4A11, CYP4A22, CYP4B1, CYP4F2, CYP4F3, CYP4F8, CYP4F11, CYP4F12, CYP4F22, CYP4V2, CYP4X1, CYP4Z1

Contd….

Family	Function	Members	Names
CYP5	thromboxane A2 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

Contd….

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, 2 genes, 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 D3 1-alpha hydroxylase, activates vitamin D3), CYP27C1 (unknown function)
CYP39	7-alpha hydroxylation of 24-hydroxycholesterol	l1 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)

Cyp450 in animals

- Many animals have as many or more CYP genes than humans do.

- mice have genes for 101 CYPs, and sea urchins have even more (perhaps as many as 120 genes). enzymes are presumed to have monooxygenase activity, as is the case for most mammalian CYPs that have been investigated (except for e.g. CYP19 and CYP5).

Cyp450 in bacteria

- Bacterial cytochromes P450 are often soluble enzymes and are involved in critical metabolic processes.
- Cytochrome P450cam (CYP101) originally from *Pseudomonas putida* This enzyme is part of a camphor-hydroxylating catalytic cycle consisting of two electron transfer steps from putidaredoxin, a 2Fe-2S cluster-containing protein cofactor.
- Cytochrome P450 eryF (CYP107A1) originally from the actinomycete bacterium *Saccharopolyspora erythraea* is responsible for the biosynthesis of the antibiotic erythromycin by C6-hydroxylation of the macrolide 6-deoxyerythronolide B.
- Cytochrome P450 BM3 (CYP102A1) from the soil bacterium *Bacillus megaterium* catalyzes the NADPH-dependent hydroxylation of several long-chain fatty acids at the ω–1 through ω–3 positions
- Thus, BM3 is potentially very useful in biotechnological applications.

P450s in fungi

- The commonly used azole antifungal agents work by inhibition of the fungal cytochrome P450 14α-demethylase. This interrupts the conversion of lanosterol to ergosterol, a component of the fungal cell membrane.

P450s in plants

- Plant cytochrome P450s are involved in a wide range of biosynthetic reactions, leading to various fatty acid conjugates, plant hormones, defensive compounds, or medically important drugs. Terpenoids, which represent the largest class of characterized natural plant compounds, are often substrates for plant CYPs

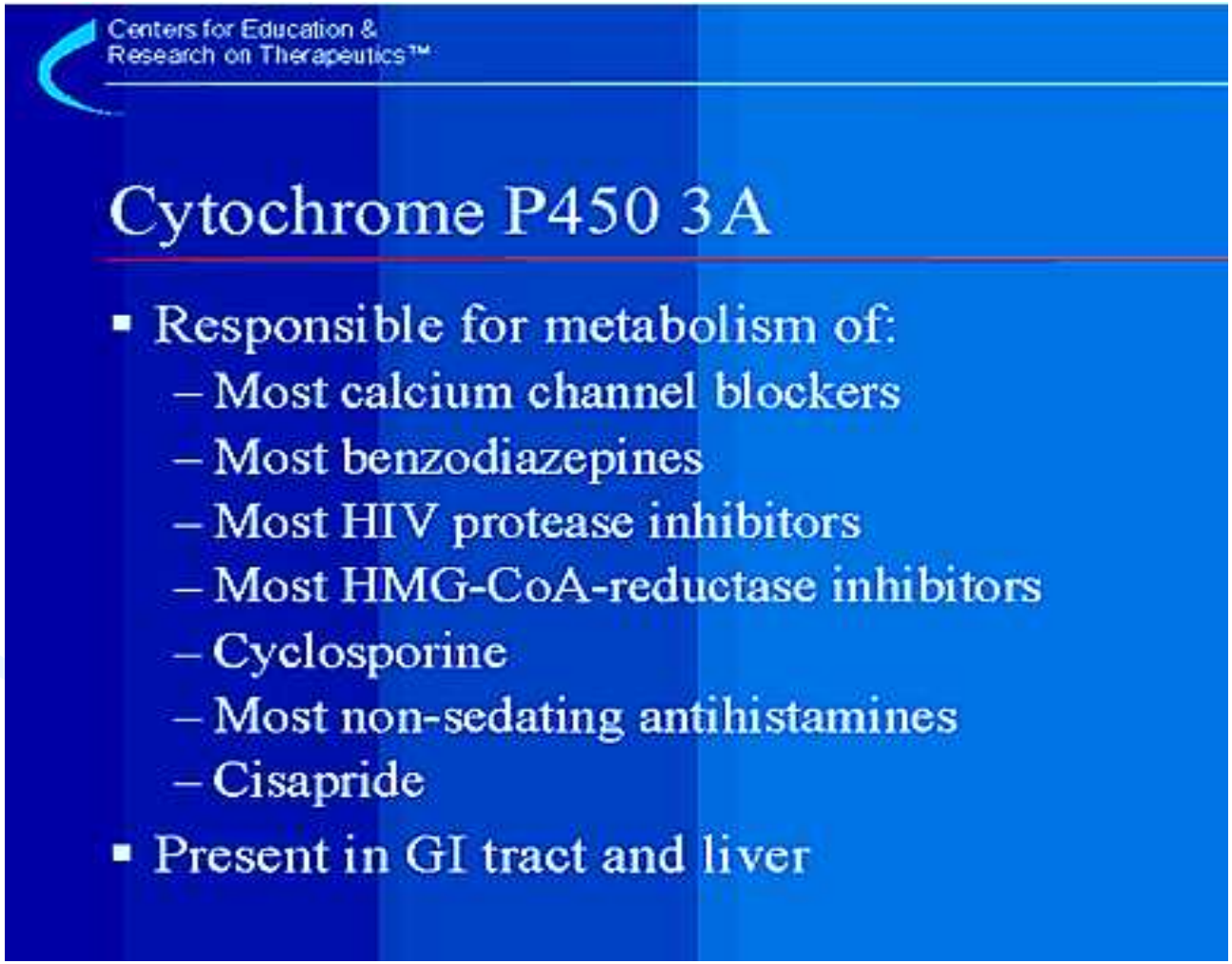
InterPro subfamilies

- InterPro subfamilies:
- Cytochrome P450, B-class *IPR002397*
- Cytochrome P450, mitochondrial *IPR002399*
- Cytochrome P450, E-class, group I *IPR002401*
- Cytochrome P450, E-class, group II *IPR002402*
- Cytochrome P450, E-class, group IV *IPR002403*

Different members of the cytochrome P450 superfamily with their "favorite" substrates

Gonzalez et al, TIPS (1992)

ROLE, INDUCERS AND INHIBITORS OF P450s



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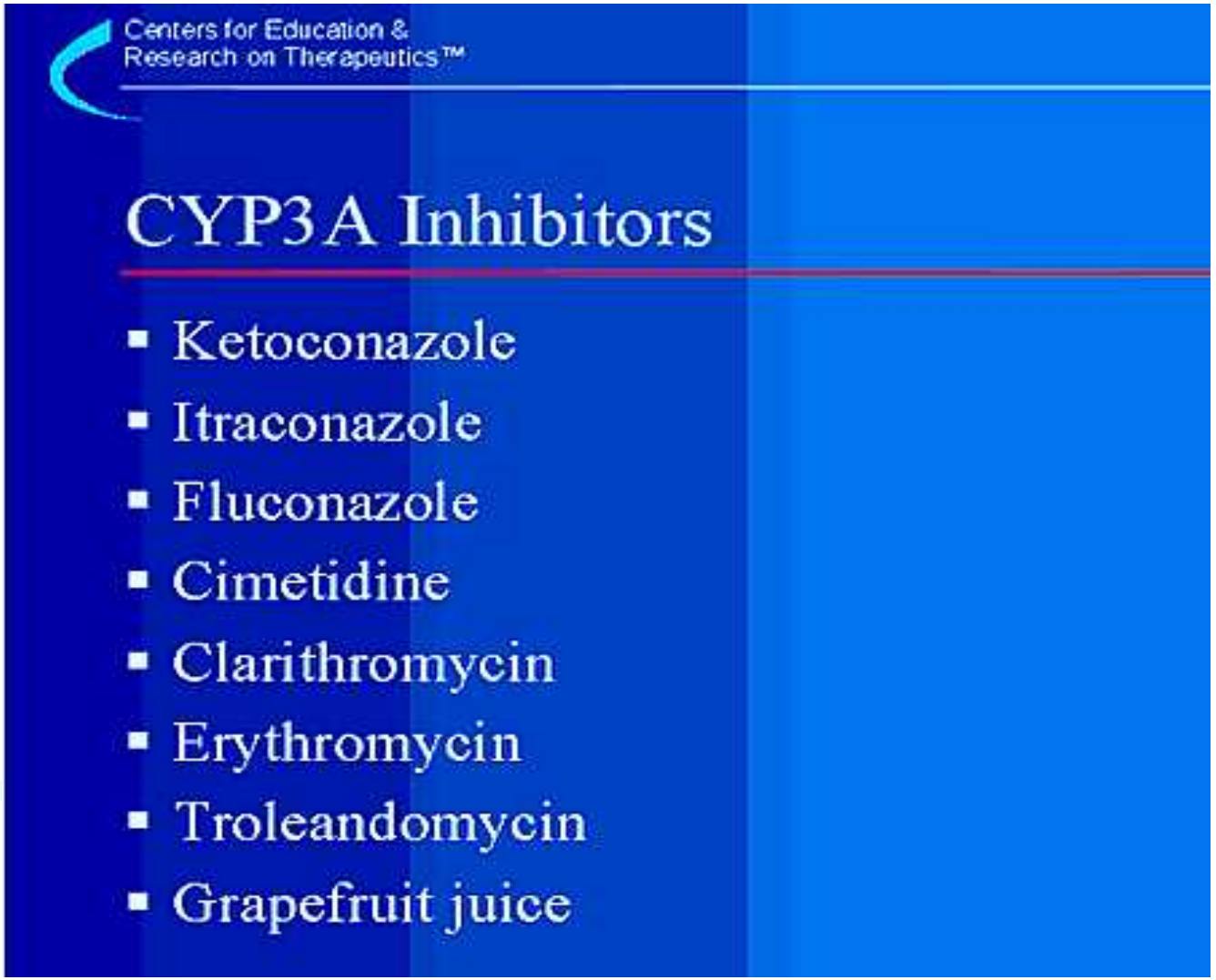
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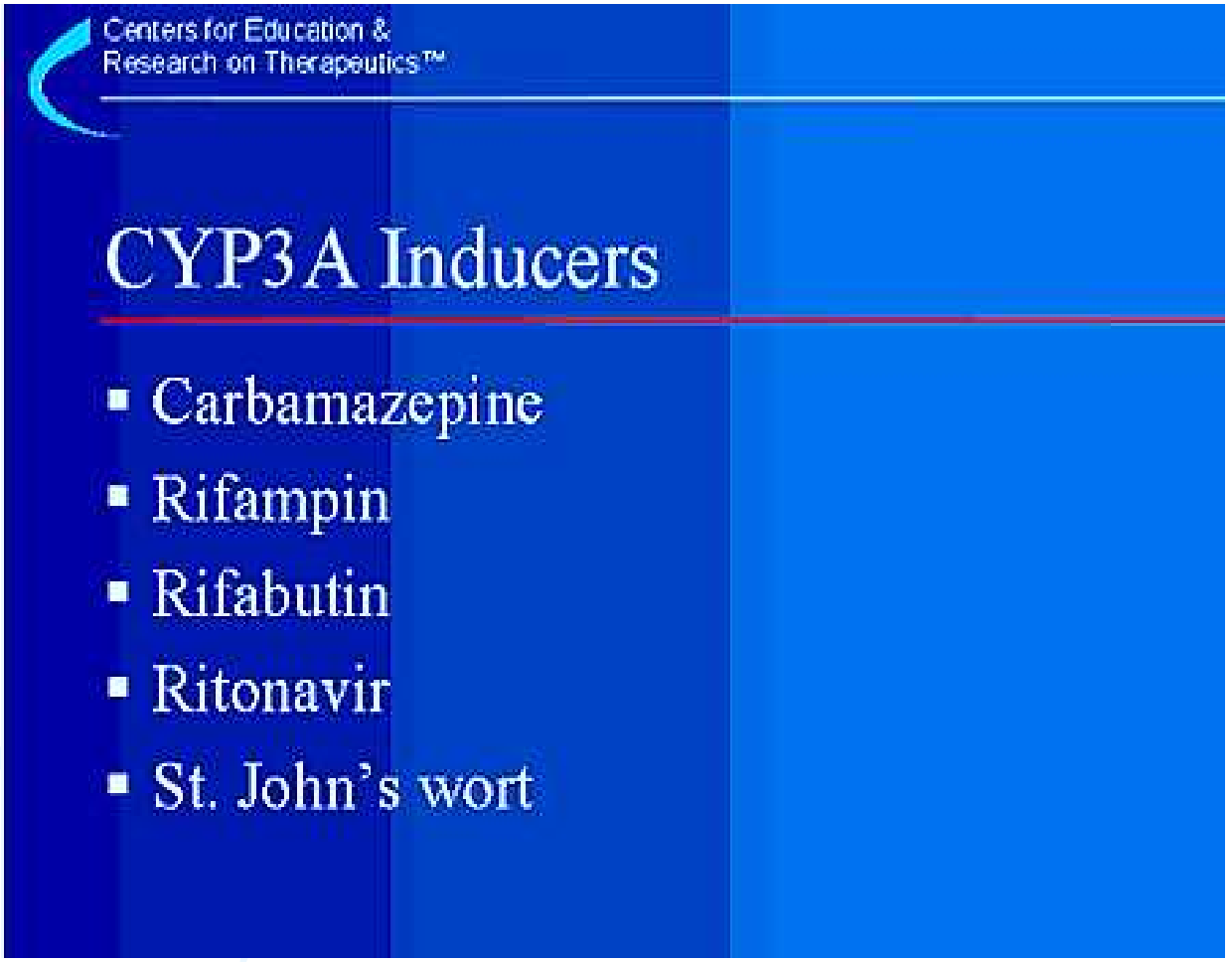
CYP3A Inhibitors
Ketoconazole
Itraconazole
Fluconazole
Cimetidine
Clarithromycin
Erythromycin
Troleandomycin
Grapefruit juice

Contd....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CYP3A Inducers
Carbamazepine
Rifampin
Rifabutin
Ritonavir
St. John's wort

CYP2D6

- Absent in 7% of caucasians
  1-2% of non-caucasians
  Hyperactive in upto 30% of east africans.
  Catalyses primary metabolism of
  - codeine
  - many β blockers
  - many tricyclic antidepressants
  Inhibited by
  - fluoxetine
  - haloperidol
  - paroxetine
  - quinidine
  Inducers
  - dexamethasone
  - rifampin
  Genetics
  -chromosome 22
  And is polymorphic in distribution.

CYP2C9

- Absent in 1% Caucasisans , African-Americans

Primary metabolism of

- NSAIDS(including COX -2)
- S-warfarin (the active form)
- phenytoin

Inhibitors

- fluconazole

Inducers

- secobarbitol

Genetics

- chromosome 10

Polymorphic in distribution.

CYP2C19

- Absent in 20-30 % of africans,
  3-5 % of caucasians

primary metabolism of
- diazepam
- phenytoin
- omeprazole

Inhibitors
- omeprazole
- isoniazid
- ketaconazole

Inducers
- carbamazepine
- norethindrone
- prednisone

Genetics
- chromosome 10

Polymorphic in distribution.

CYP1A2

- Induced by smoking tobacco.
- Catalyses primary metabolism of
  - theophylline
  - imipramine
  - clozapine
  - propranolol

Inhibited by

- many fluoroquinolone antibiotics
- fluoxamine
- cimetidine

Genetics

- chromosome 15

CYP2B6

- Substrates
  - cyclophosphamide
  - methadone

Inhibitors
  - thiotepa
  - ticlopidine

Inducers
  - phenobarbitol

Genetics
  - chromosome 19

Polymorphic in distribution.

CYP2C9

- Substrates
  - paclitaxol
  - torsemide

Inhibitors
  - trimethoprim
  - quercetin

Inducers
  - rifampin

Genetics
  - chromosome 10

CYP2D6

- Substrates
  - β-blockers
  - anti depressants
  - many anti psychotics

Inhibitors
- amiodarone
- celecoxib
- bupropion

Inducers
- rifampin
- dexamethasone

Genetics
- chromosome 22

Polymorphic in distribution.

CYP2E1

- Substrates
  - anesthetics

Inhibitors
  - diethyl thiocarbamate
  - disulfuram

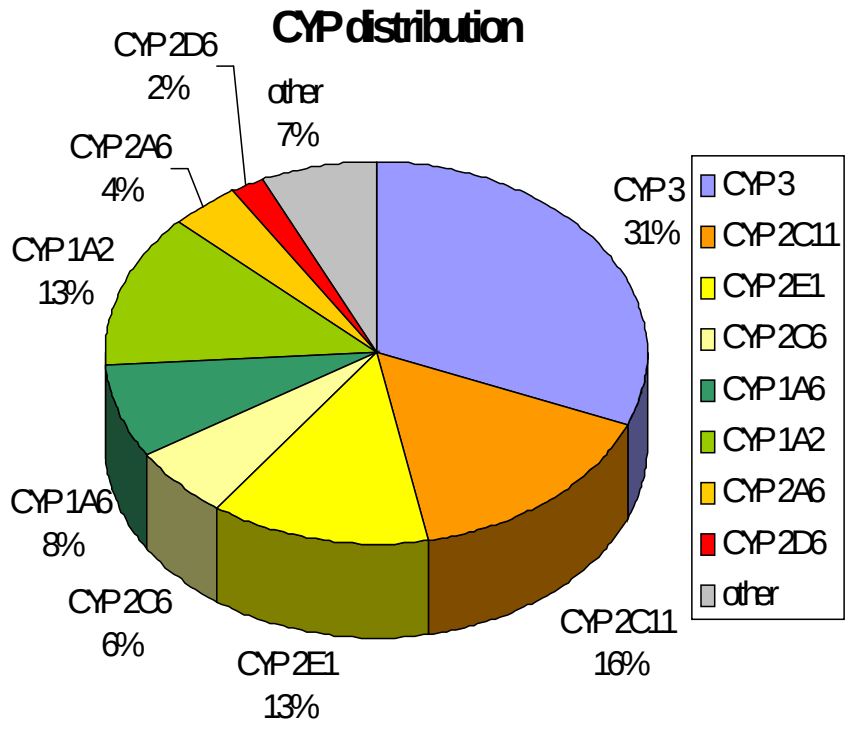
Inducers
  - ethanol
  - isoniazid

Genetics
  - chromosome 10

Cytochrome P450 enzymes

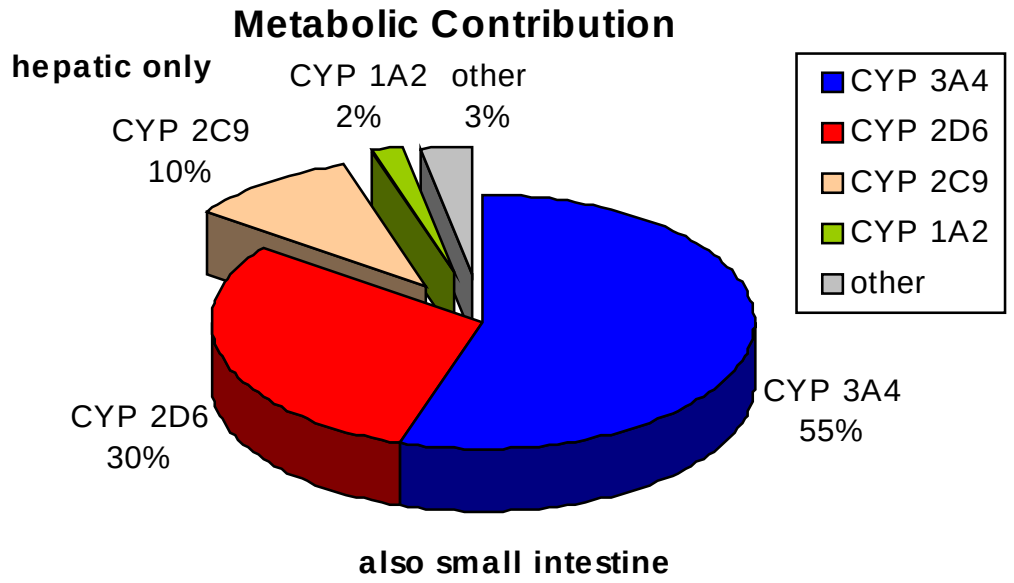
- The majority of CYPs is found in the liver, but certain CYPs are also present in the wall cells of the inestine.

- The *mammalian* CYPs are bound to the endoplasmic reticulum, and are therefore membrane bound.



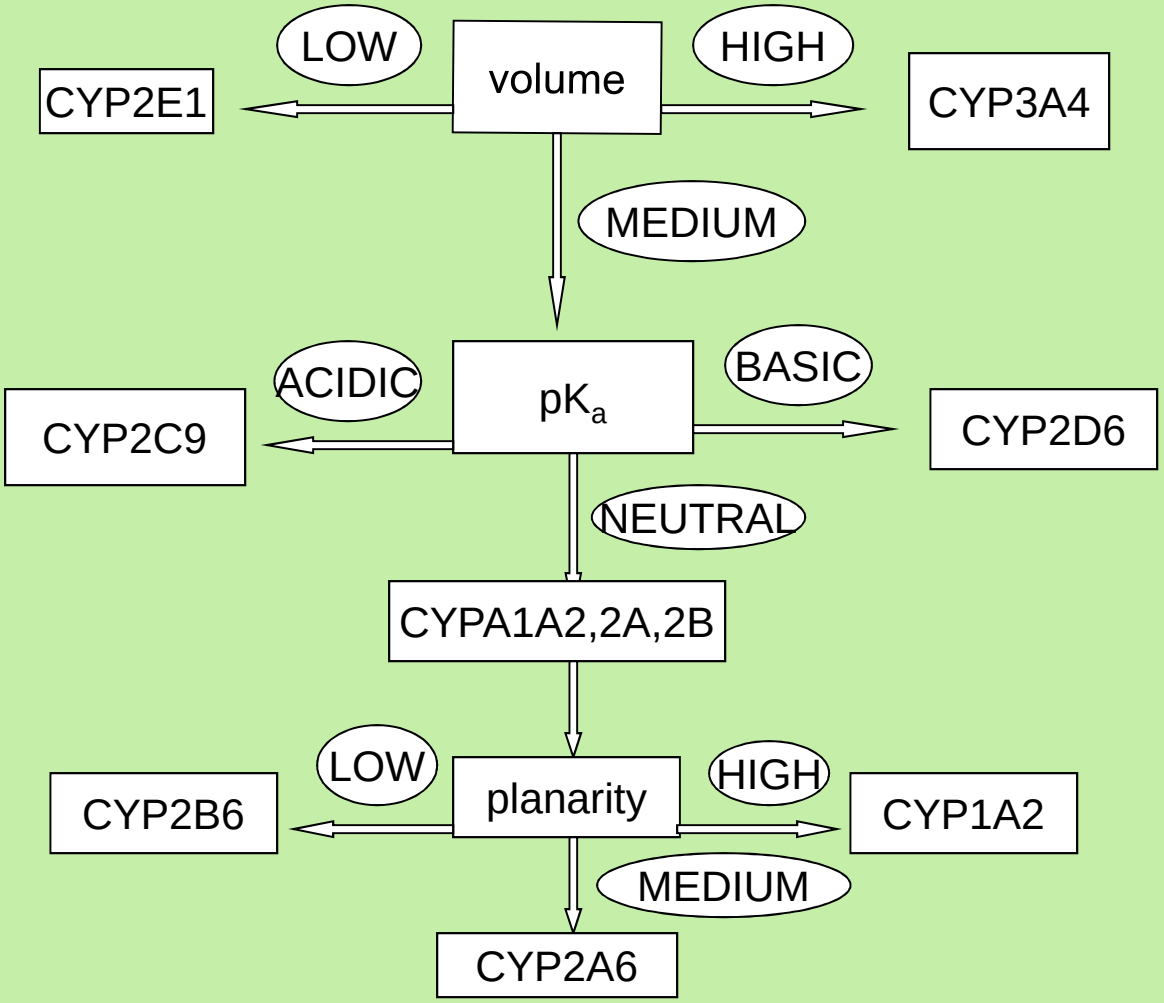
Cytochrome P450 enzymes

- Especially CYP 3A4, CYP 2D6, and CYP 2C9 are involved in the metabolism of xenobiotics and drugs

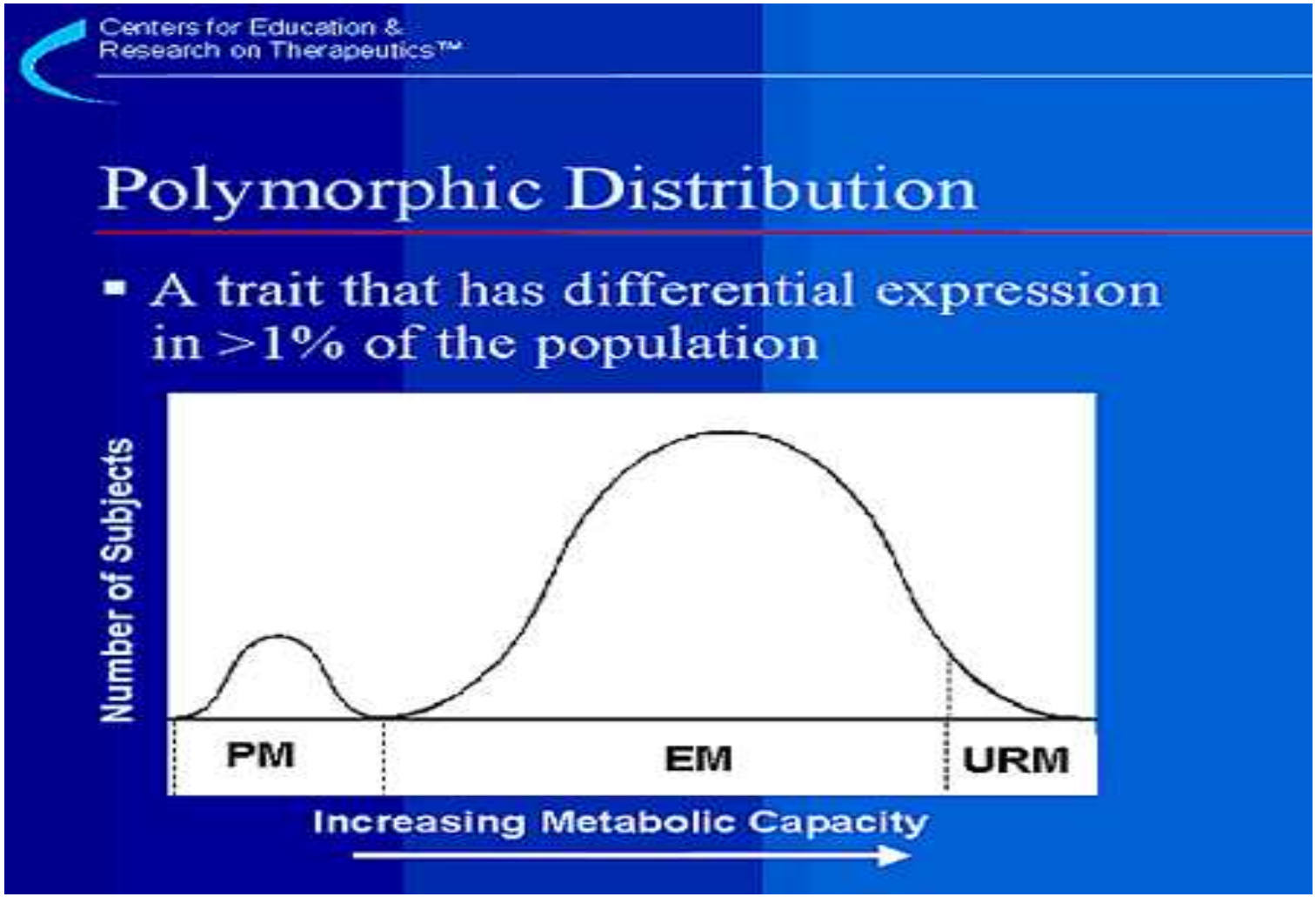


Substrate specificity of CYPs

- Decision tree for human P450 substrates
- CYP 1A2, CYP 2A-E, CYP 3A4



GENETIC POLYMORPHISM



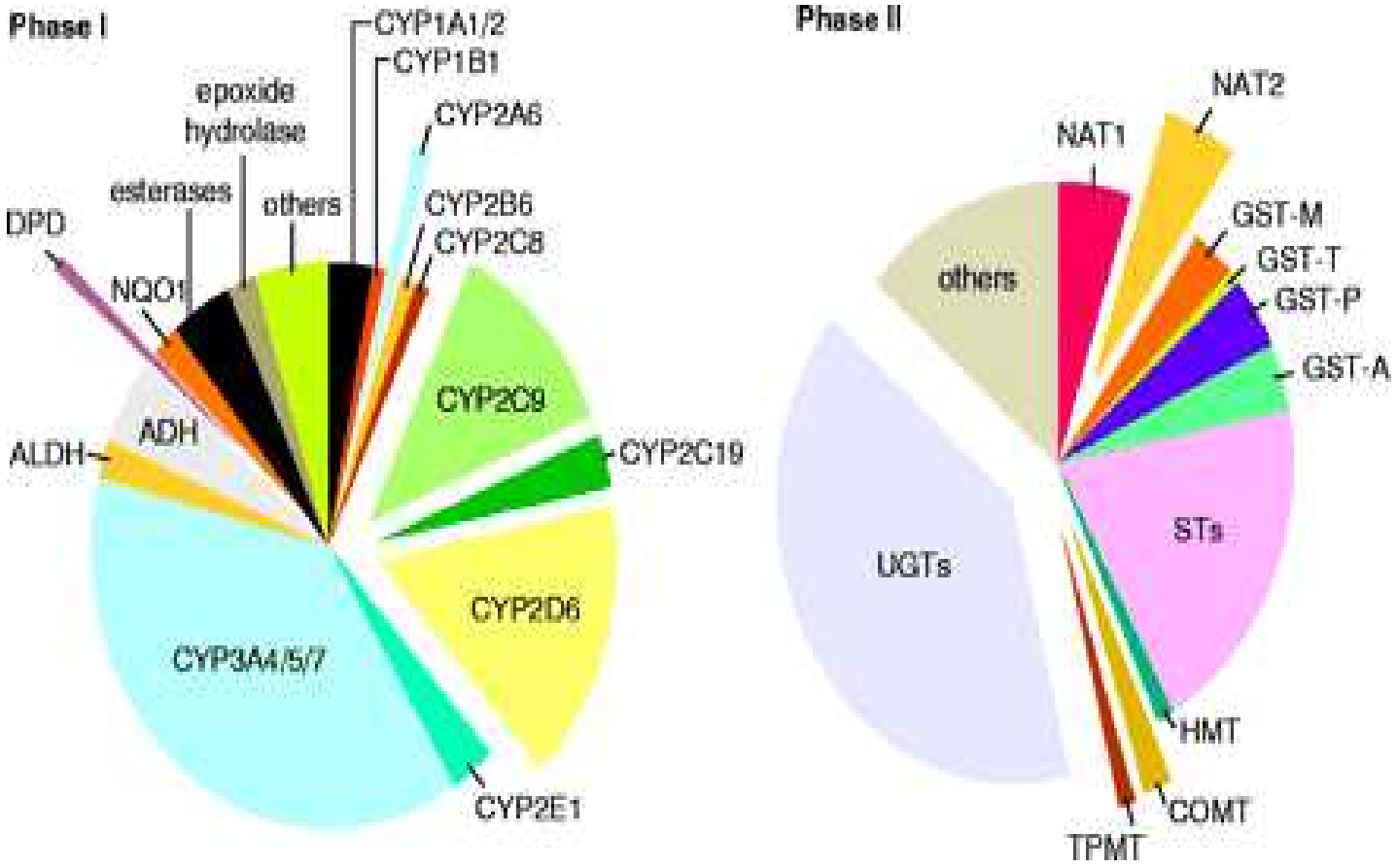
Contd….

- Genetic factors have an important impact on the oxidative metabolism and pharmacokinetics of drugs.
- mutations in one or more of the nucleic acids in the DNA sequence expressing a given cytochrome P450 isozyme.
- If the mutation is relatively common (more than 1%) it creates a polymorphism—–this is a trait that has genetic variation.
- Mutant DNA sequences can lead to inter individual differences in drug metabolism.
- The polymorphic isoforms most important for drug metabolismm include CYP2A6,CYP2C9,CYP2C19,2D6.
- This graph demonstrates a population drug metabolism distribution for CYP2D6.
- Mutations in the CYP2D6 gene result in poor (PM) , immediate (or extensive EM) and ultra rapid (UM) metabolizers of CYP2D6 substrates.
- Each of these phenotypic subgroups experience different responses to drugs extensively metabolised by the CYP2D6 pathway, ranging from severe toxicity to complete lack of efficacy.
- Thus, genetic studies confirm that “one does does not fit all”.
- Importantly, pharmacogenomic testing (the study of inheritable traits affecting patient response to drug treatment) can significantly increase the likelihood of developing drug regimens that benefit most patients with out severe adverse events.

Polymorphisms of further CYPs

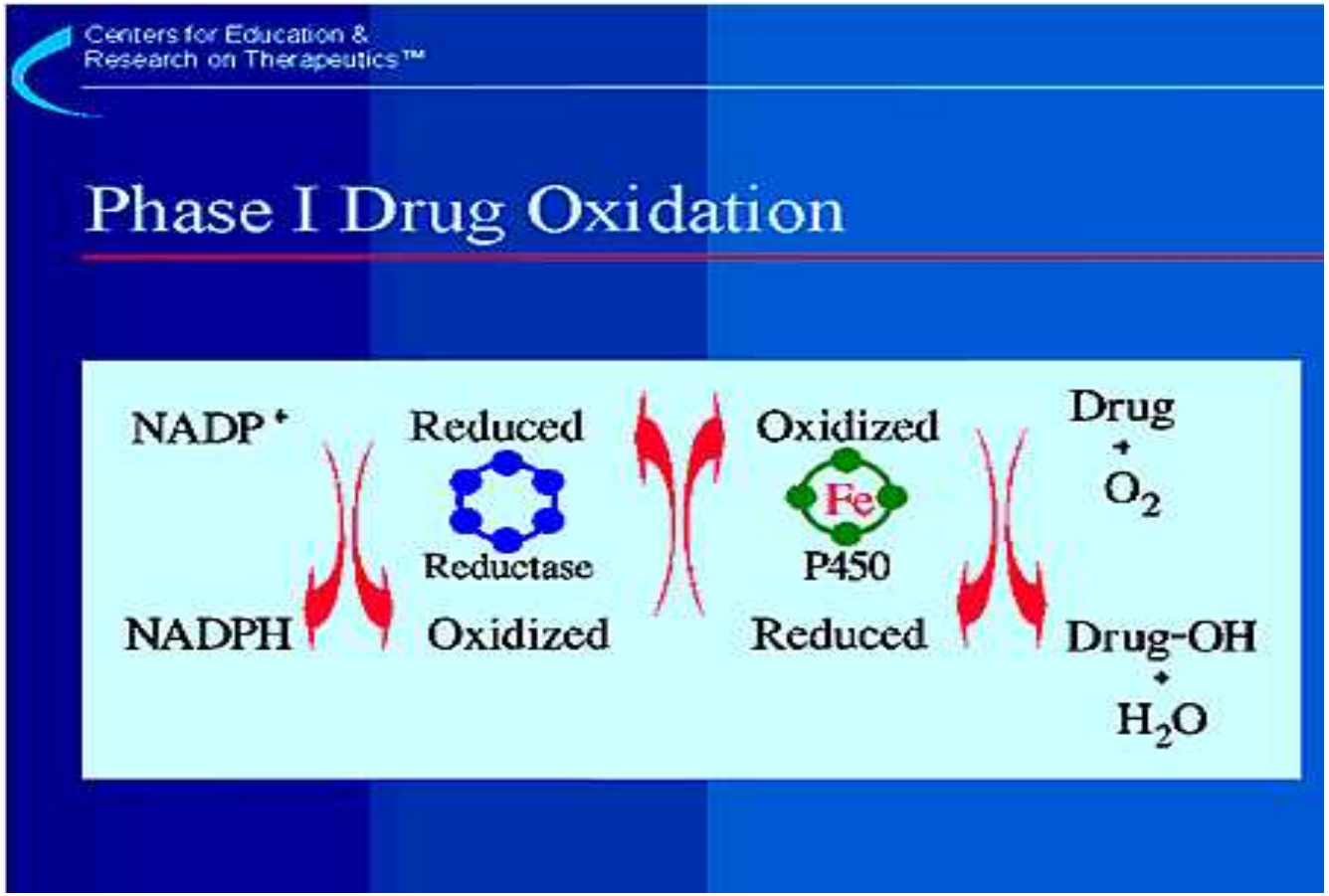
- CYP 1A2 individual: fast, medium, and slow turnover of caffeine
- CYP 2B6 missing in 3-4 % of the caucasian population
- CYP 2C9 deficit in 1-3 % of the caucasian population
- CYP 2C19 individuals with inactive enzyme (3-6 % of the caucasian and 15-20 % of the asian population)
- CYP 2D6 poor metabolizers in 5-8 % of the european,
  10 % of the caucasian, and <1% of the japanese population. Over expression (gene duplication) among parts of the african and oriental population.
- CYP 3A4 only few mutations

Genetic polymorphisms in drug metabolizing enzymes



Phases of Drug metabolism

OXIDATION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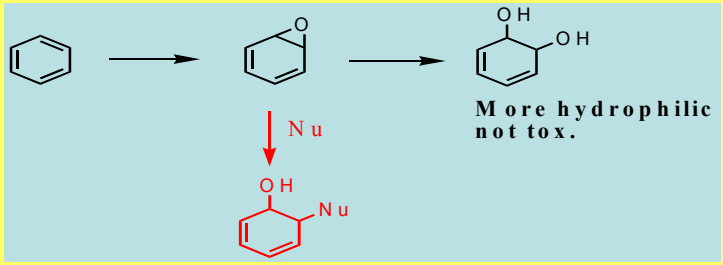
Phase I Drug Oxidation
NADP+
Reduced
Reductase
Oxidized
NADPH
Oxidized
Fe
P450
Reduced
Drug
+
O2
Drug-OH
+
H2O

ROLE OF CYP450 IN DRUG METABOLISM

- **Family 1:**
- **CYP1A1**
- **Aromatic hydrocarbon hydroxylase, metabol. PAH etc.**



- **CYP1A2**
- **Ox of arylamines, nitrosamines, aromatic hydrocarbons**

- **Family 2:**
- **CYP2A6**
- **CYP2B6**
- **CYP2C**
- **CYP2D6: Often enantioselective, lipophil. amines**
- **CYP2E1: Halogenated hydrocarbons, other org solvents**

- **Family 3:**
- **CYP3A4**

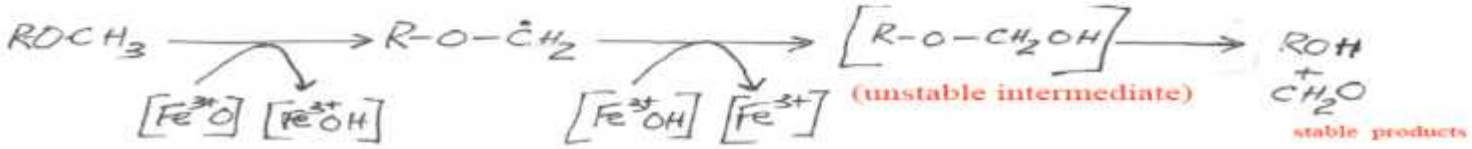
PHASE 1 REACTIONS

- **A) Oxidative Reactions**
- **1) Oxidation of aromatic carbon atoms(M) ex: propranolol,warfarin…**
- **2) Oxidation of olefins (C=C bonds)(M) ex : carbamazepine…**
- **(3) Oxidation of benzylic (tolbutamide) , allylic (hexobarbitol) carbon atoms and carbon atoms alpha to carbonyl and imines (diazepam) (M)**
- **(4) Oxidation of aliphatic carbon atoms ex : valproic acid (M)**
- **(5) Oxidation of alicyclic carbon atoms(M) ex : minoxidil**
- **(6) Oxidation of carbon-heteroatom systems :**
- **(a) Carbon-Nitrogen systems (aliphatic and aromatic amines)**
- **(i) N-Dealkylation(M) ex : imipramine , isoniazid…**
- **(ii) Oxidative deamination (M), (N) ex : amphetamine**
- **(iii) N-Oxide formation(M) ex : nicotine , imipramine**
- **(iv) N-Hydroxylation(M) ex : lidocaine**
- **(b) Carbon-Sulfur systems :**
- **(i) S-Dealkylation(M) ex : 6-methyl mercaptopurine**
- **(ii) Desulfuration(M) ex : thiopental, parathion**
- **(iii) S-oxidation(M) ex : phenothiazine**
- **(c) Carbon-Oxygen systems (O-dealkylation)(M) ex : phenacetin , codeine …**

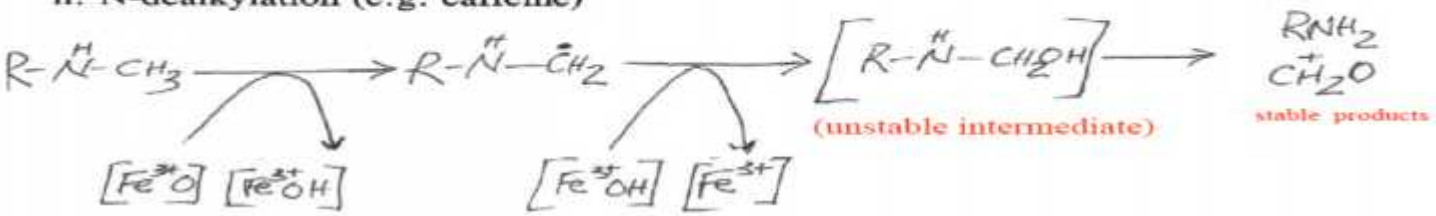
- **(7) Oxidation of alchol, carbonyl and acid functions(M),(N)**
- **(8) Miscellaneous oxidative reactions**

Mechanisms: α -carbon hydroxylation → unstable α-hydroxy intermediate → stable products

i. O-dealkylation (e.g., codeine)



ii. N-dealkylation (e.g. caffeine)



c. Oxidative desulfuration (e.g., thiopental)

2. Epoxidation

a. Aromatic (e.g., phenytoin, benzene, benzo(a)pyrene)

b. Aliphatic (e.g. carbamazepine)

Carbamazepine → Carbamazepine-10,11-epoxide

Phase 1 reactions

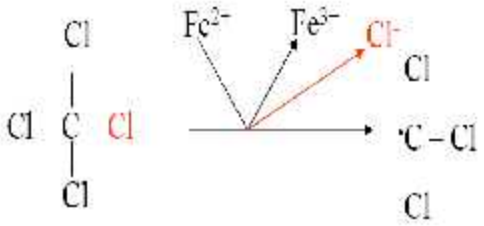
- (B) Reductive Reactions :
- (1)Reduction of carbonyl functions (aldehydes/ketones)(M),(N) ex : choral hydrate, methanol…
- (2)Reduction of alcohols and C=C bonds(M) ex: bencyclane,norethindrone
- (3) Reduction of N-compounds (nitro, azo and N-oxide)(M),(N) ex: nitrazepam, prontosil
- (4)Miscellaneous reductive reactions
- (C) Hydrolytic Reactions :
- (1)Hydrolysis of esters and ethers(M),(N) ex: clofibrate,aspirin…
- (2)Hydrolysis of amides(M),(N) ex: procainamide,lidocaine…
- (3)Hydrolytic cleavage of nonaromatic heterocycles(M),(N) ex: pencillin, thalidomide…
- (4)Hydrolytic dehalogenation ex: DDT
- (5) Miscellaneous hydrolytic reactions

Phase 1 reactions

B. Reductive reactions

- are usually catalyzed by Fe^{+2} rather than $F^{+3}O$ as the CYP species
- are usually inhibited by oxygen

1. Dehalogenation (e.g. carbon tetrachloride)



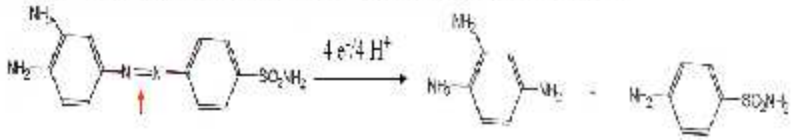
Carbon tetrachloride Trichloromethyl radical

Oxygen inhibits reductive metabolism by CYP:

by forming an $Fe^{2}IO_2$ complex, which renders Fe^{2-} unavailable to reduce CCl_4

B. Reductive reactions

Azo-reduction (e.g. Prontosil): *Bioactivation*

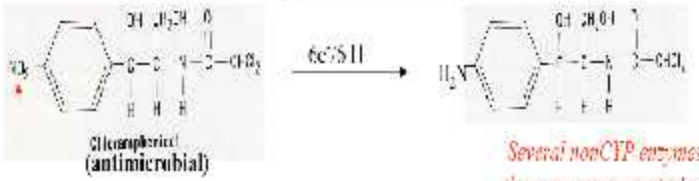


Prontosil
(prodrug)

(antimicrobial)

Several nonCYP enzymes (including those in gastrointestinal bacteria) can also catalyze nitro reduction

Nitro-reduction (e.g. Chloramphenicol): *Inactivation*



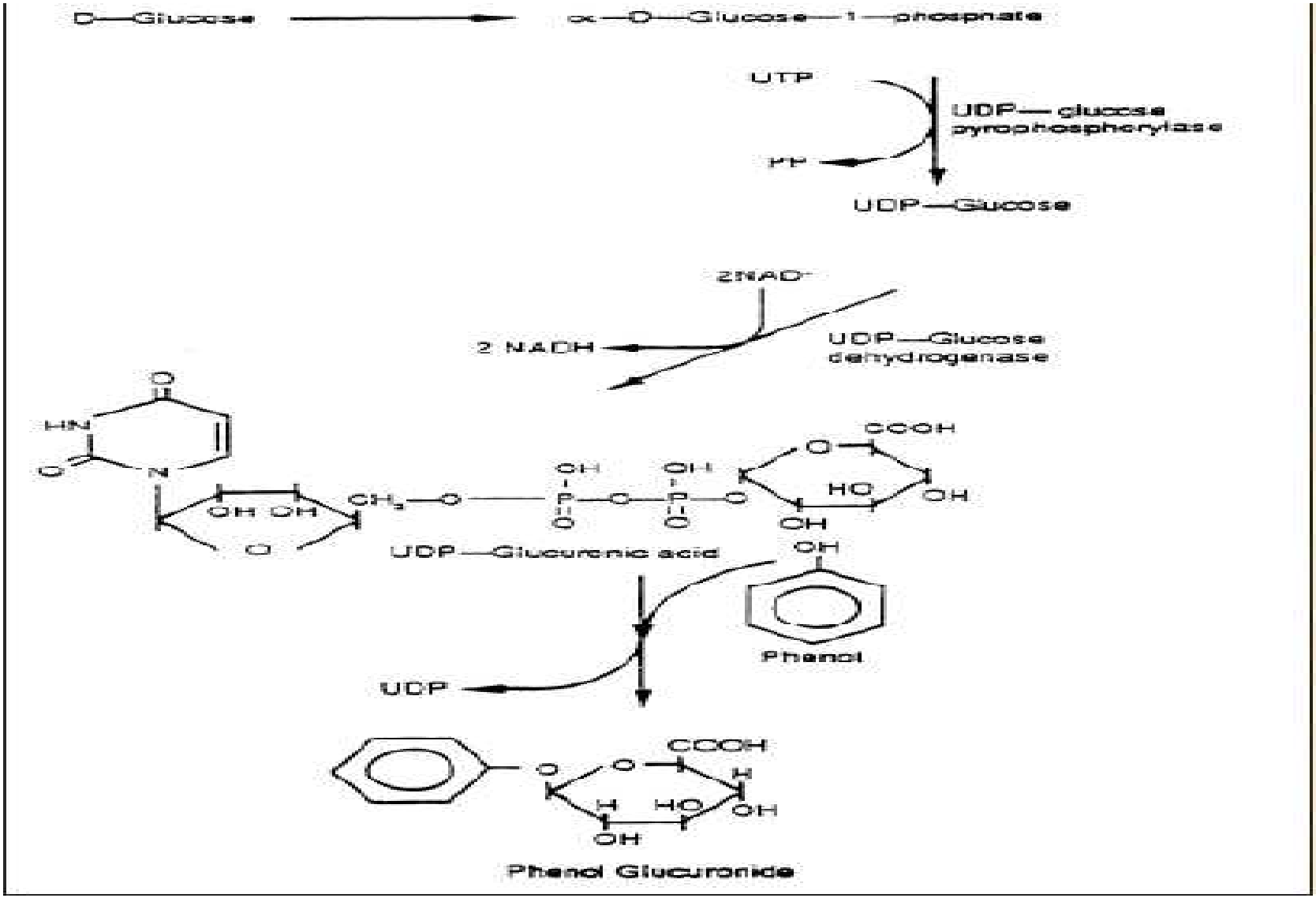
(antimicrobial)

Several nonCYP enzymes (including those present in gastrointestinal bacteria) can also catalyze nitro reduction.

Phase – 2 reactions

- (1)Conjugation with glucuronic acid(M) ex: chloramphenicol,paracetamol…
- (2)Conjugation with sulfate moieties(N) ex: paracetamol, aniline…
- (3)Conjugation with alpha amino acids(N) ex: salicylic acid, nicotinic acid…
- (4)Conjugation with glutathione and mercapturic acid formation(N)
- (5)Acetylation reactions(N) ex: histamine,PAS…
- (6)Methylation reactions(N) ex: morphine,propylthiouracil…
- (7)Miscellaneous conjugation reactions(N)

Glucuronidation of phenol



Sulfation of phenol and toulene

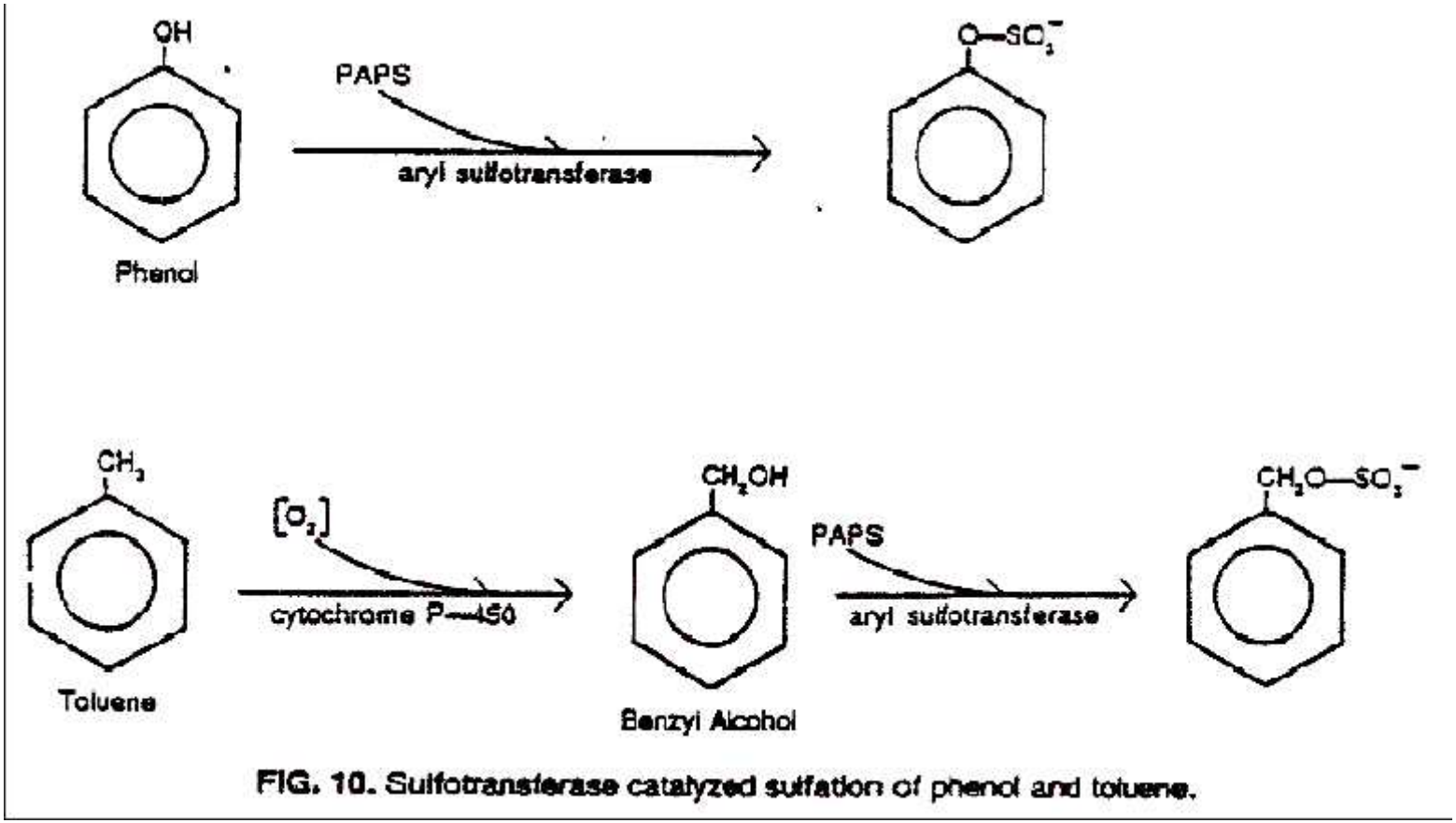


FIG. 10. Sulfotransferase catalyzed sulfation of phenol and toluene.

GSH conjugation of acetaminophen

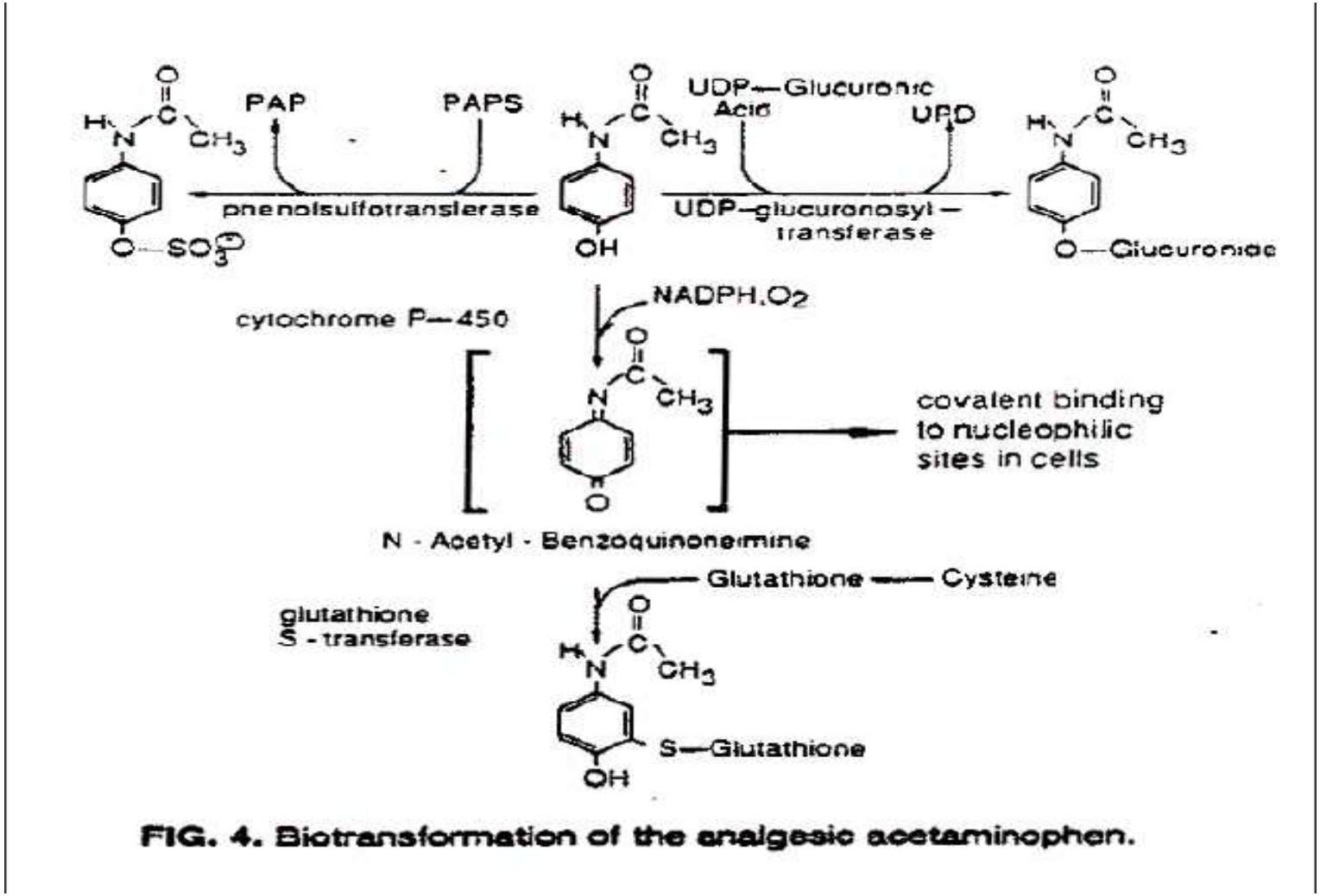
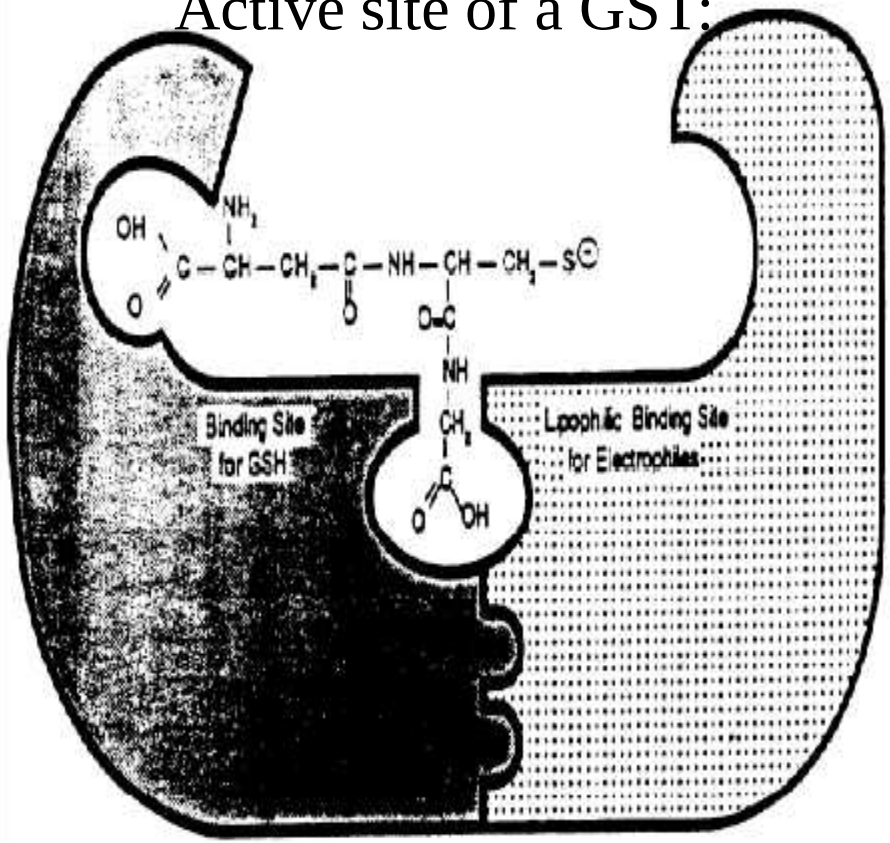


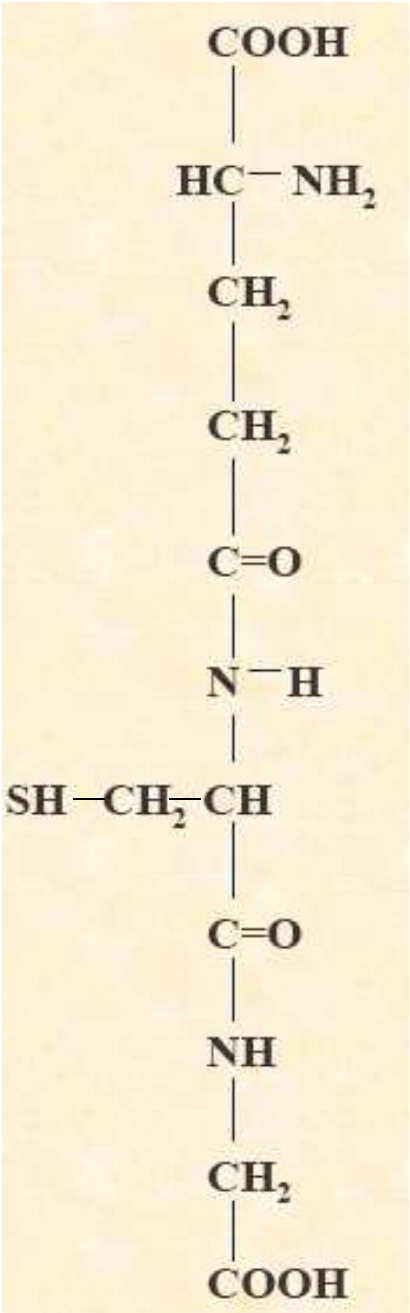
FIG. 4. Biotransformation of the analgesic acetaminophen.

Glutathione

γ-glutamyl-cysteinyl-glycine

Active site of a GST:





Major enzymes and pathways

Phase I Oxidation

Cytochrome P450 monooxygenase system
Flavin-containing monooxygenase system
Alcohol dehydrogenase and *aldehyde dehydrogenase*
Monoamine oxidase
Co-oxidation by peroxidases

Reduction

NADPH-cytochrome P450 reductase
Reduced (ferrous) cytochrome P450

Hydrolysis

Esterases and amidases
Epoxide hydrolase

Phase II

Methylation

Methyl Transferase

Sulphation

Glutathione S-transferases
Sulfotransferases

Acetylation

N-acetyltransferases
Amino acid N-acyl transferases

Conjugation

UDP-glucuronosyltransferases
Mercapturic acid biosynthesis

Contd…

- Flavin mono-oxygenases
- (FMO) catalyzed reactions

- Nitrogen compounds

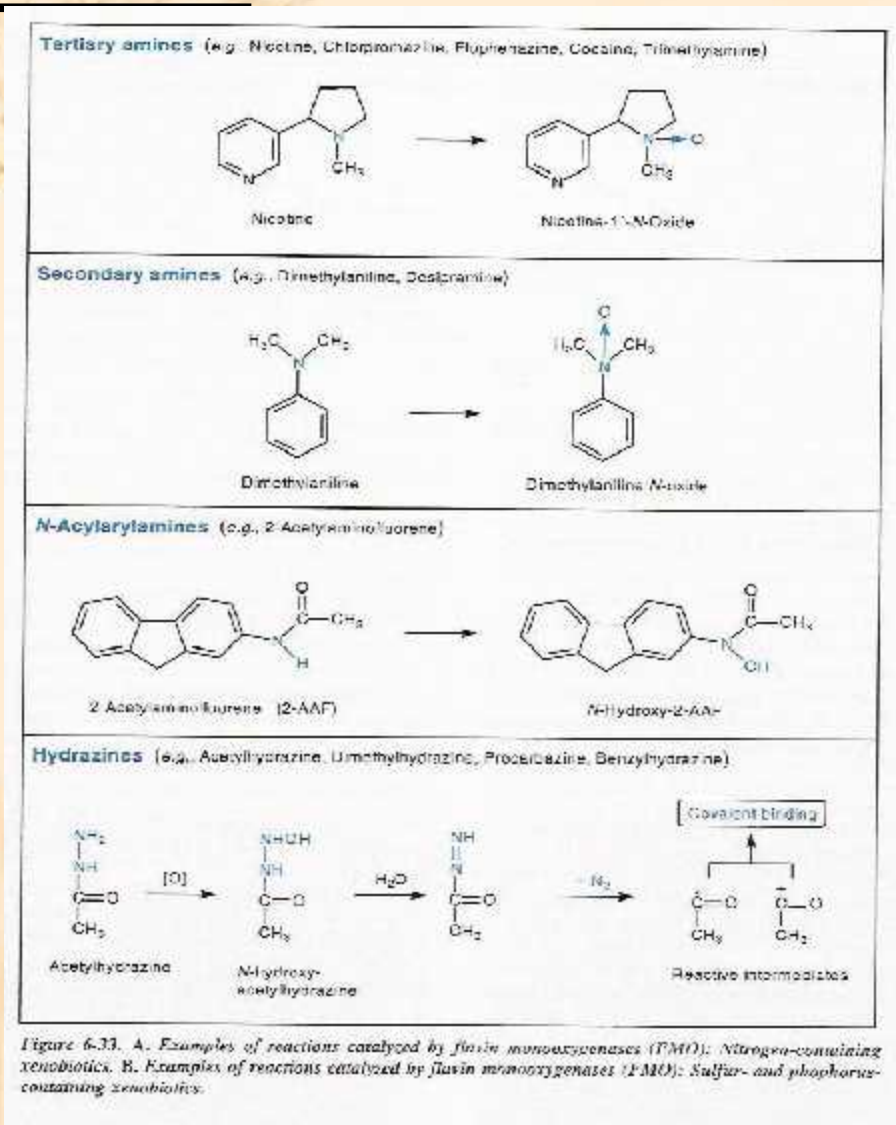
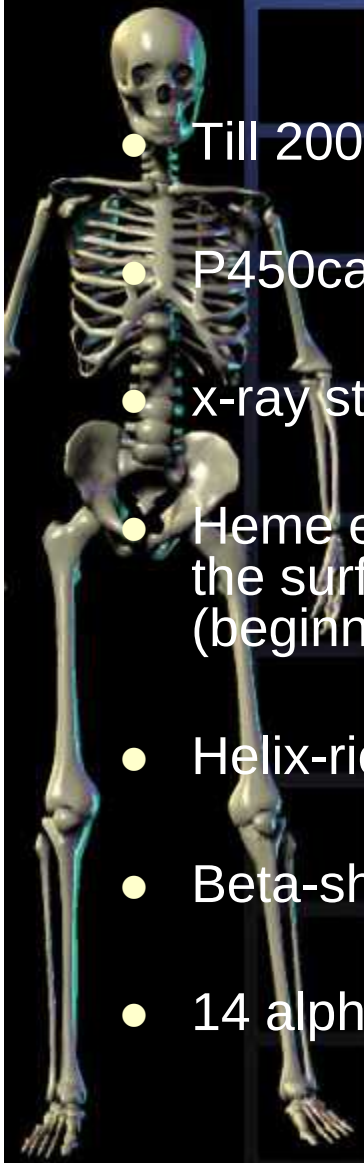


Figure 6-33. A. Examples of reactions catalyzed by flavin monooxygenases (FMO): Nitrogen-containing xenobiotics. B. Examples of reactions catalyzed by flavin monooxygenases (FMO): Sulfur- and phosphorus-containing xenobiotics.

Spectrum of consequences of drug metabolism

- Ina
- Act
- Sin
- Act
- Ne
- To

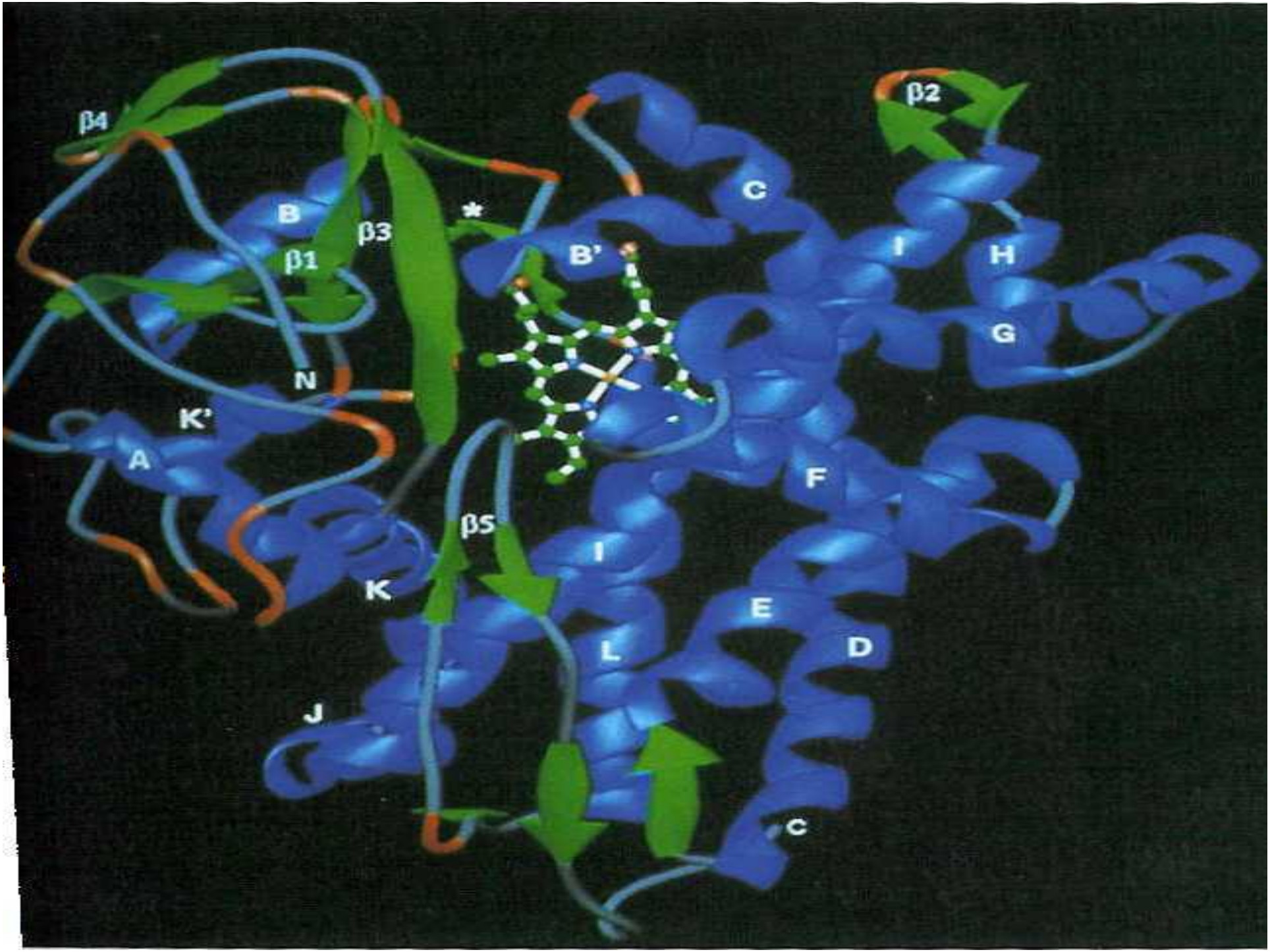
Structure of cyp450



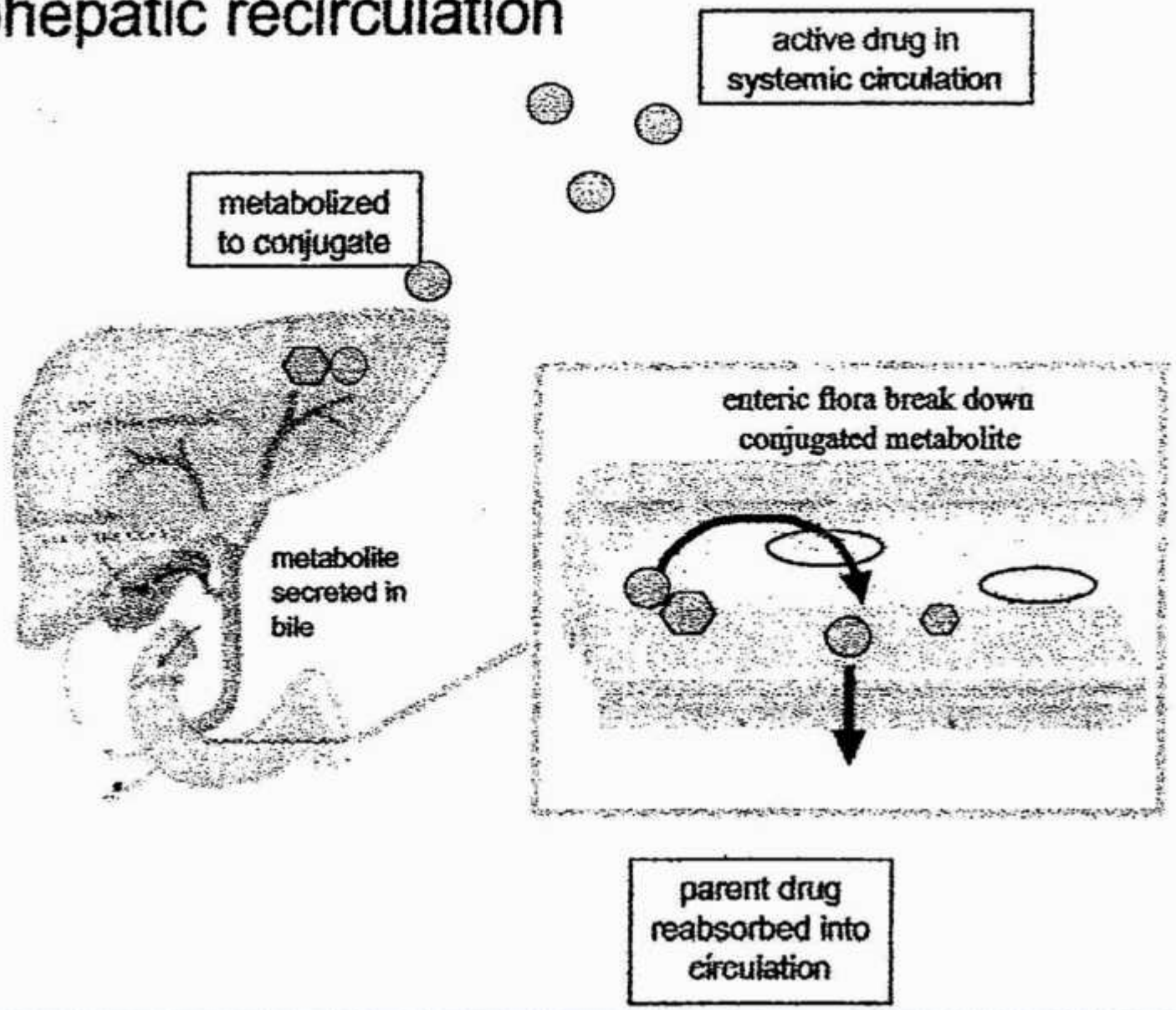
- Till 2001 there was no mammal CYP.
- P450cam structure was solved in 1987
- x-ray structure of P450cam with different substrate and inhibitors.
- Heme exists in hydrophobic environment, oriented nearly parallel to the surfaces between the L and I helices. Heme-ligating Cys-357 (beginning of L)
- Helix-rich on the right side
- Beta-sheet-rich on the left side
- 14 alpha helices, 5 anti parallel beta-sheets

Contd….

- Compact structure, especially the helical region.
- Closed structure, conformational dynamic is essential.
- No obvious substrate channel.
- The area bounded by B' F/G and beta 5 identified as the channel.
- 6 water molecule fill the substrate active site
- Substrate binding loop residues 80-103
- Binding free energy is most likely due to hydrophobic interactions of the substrate and the heme, Leu-244 and Val-295


β4
β2
B
β3
*
C
β1
B'
I
H
G
N
K'
A
F
βs
I
K
E
L
D
J
C

enterohepatic recirculation



APPLICATIONS

DRUG DESIGNING

PRODUCTION OF LONGER HALF LIFE DRUGS

USE OF A P450 FOR GENE THERAPY IN CANCER

USE OF DIOGNOSIS(AMPLICHIP CYP 450 TEST)

IN PRESENCE OF P-GP (P GLYCOPROTEIN) IT ACT AS SINERGIDTIC EFFECT THROUGH EFFLUX MECHANISM

conclusion

- Cytochrome p450 enzymes play an important role in humans as these are major metabolisng enzymes in the animals, these serve as defense, detoxification of xenobiotics achieved by cypp450.these prevents toxic materials enter into our body. these provide applications in drug designing , diagnosis, drug therapy. these also produce toxic effects with their variations in drug metabolism.
- Now a days more research is going on world wide and we may hope that cyp450 may become available in pharmaceutical industry there by helps to get good therapy with the help of finding in genetic variations.

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THANK YOU