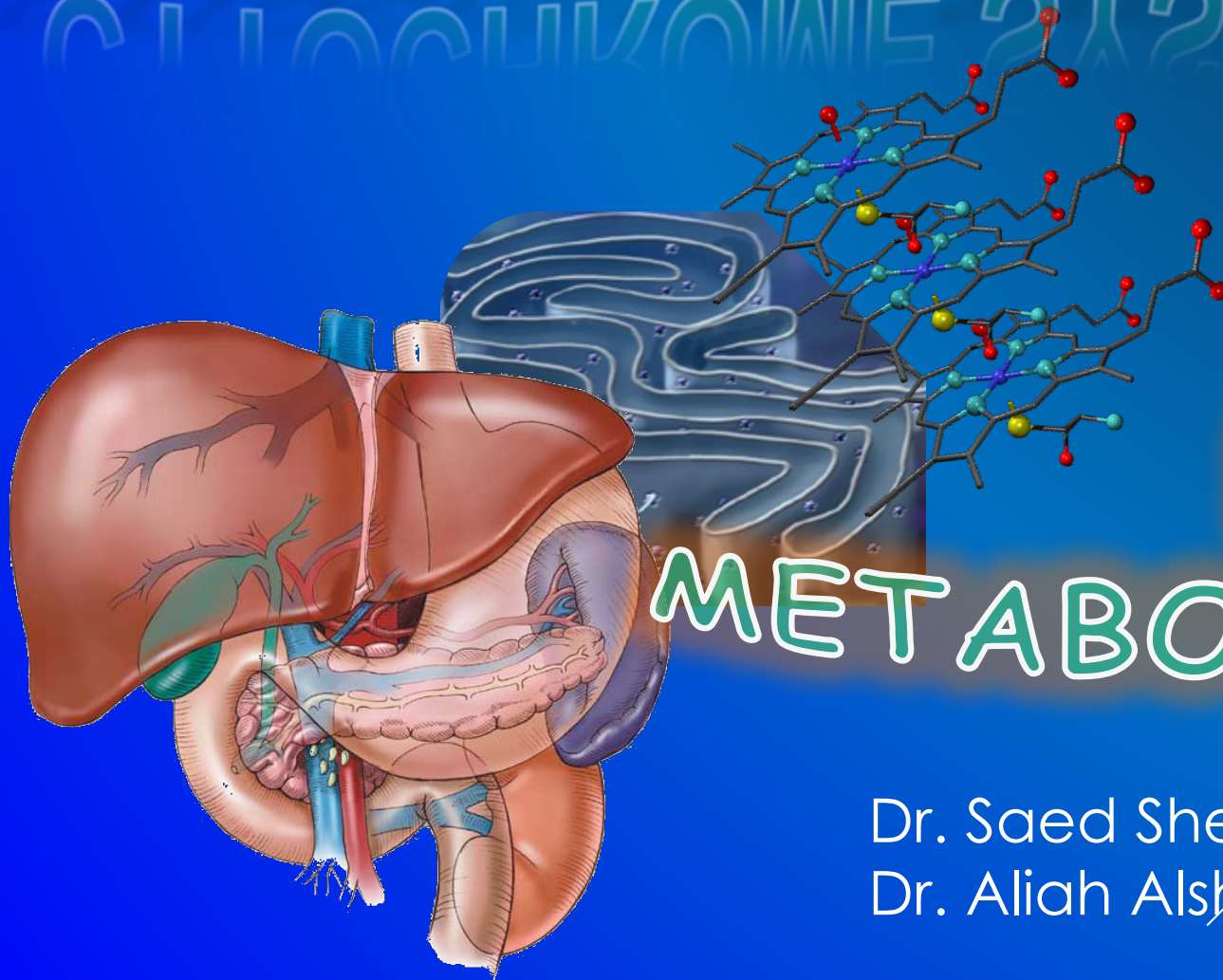


# CYTOCHROME SYSTEM



&

# DRUG METABOLISM

Dr. Saed Sheikh  
Dr. Aliah Alsharwani

# CYTOCHROME SYSTEM



# DRUG METABOLISM

- Revise the aim & phases of drug metabolism
- Define the role of **cytochrome system** in relation to drug metabolism
- Expand on the nature, location, nomenclature, structure, distribution & function of CYT P450
- Focus on its regulation; directly & indirectly, its induction & inhibition in relevance to drug interactions
- Interpret molecular mechanism of interactions by CYTP450
- Classify its different isoforms, their substrates, inducers & inhibitors
- Delineate some of its genetic variations.

# Where do drug biotransformations occur ?

RENAL Elimination



Polar product



Non-Polar product

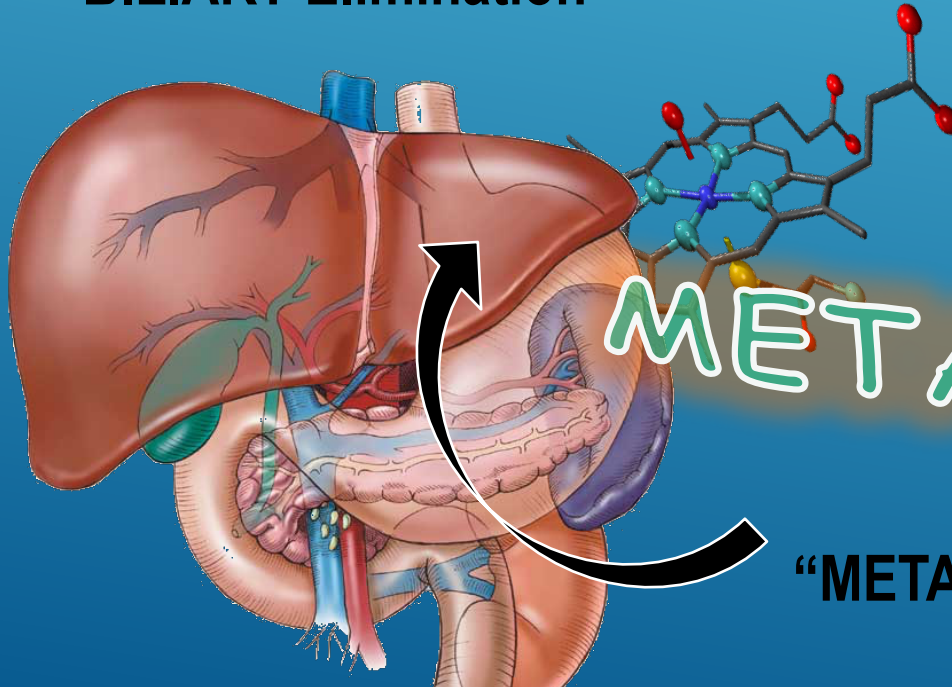


BILIARY Elimination

Being mostly lipophylic → The liver subjects them to chemical transformation (**METABOLISM**) → to become inactive & easily EXCRETED.



Identified as foreign substances that body must get rid of



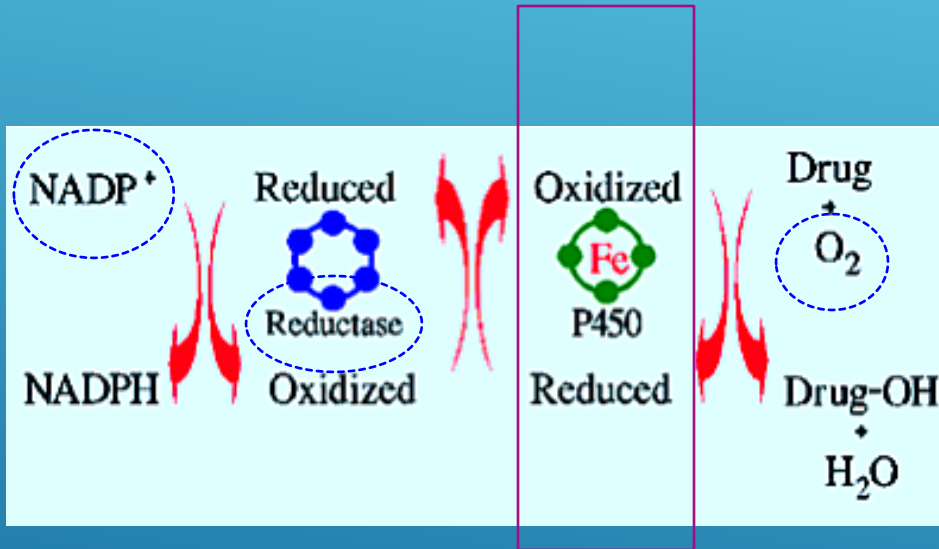
**DRUG**  
**METABOLISM** ?

Occurs mainly in the  
"METABOLIC CLEARING HOUSE"

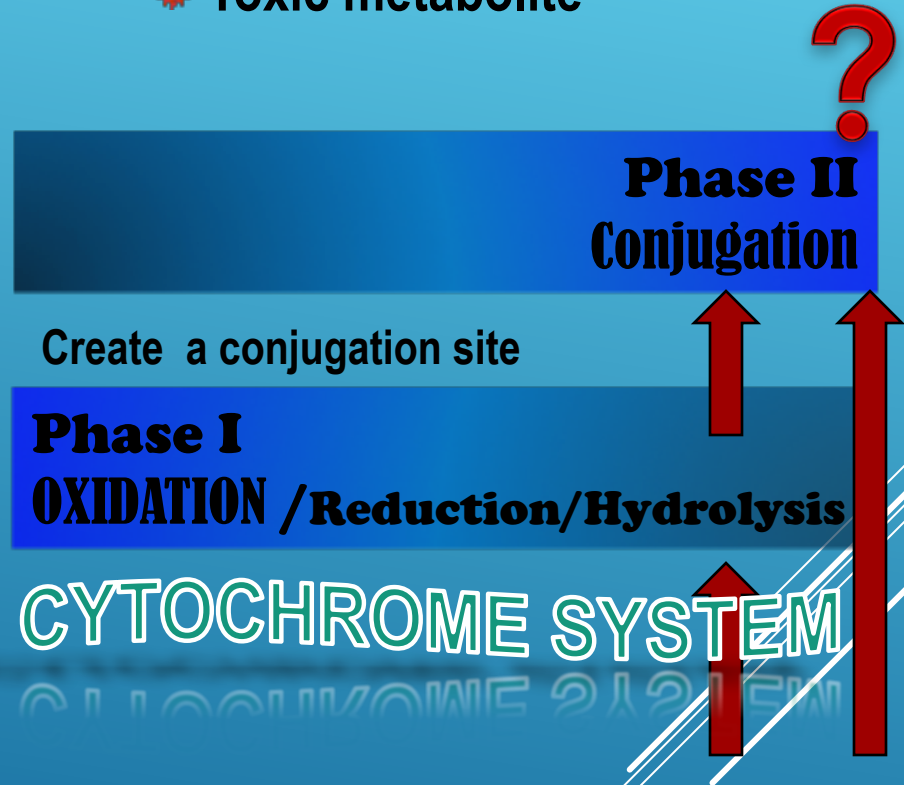
# “ Cytochrome P450 “ “ CYT 450 ”

Superfamily is the terminal rate limiting oxidase of this system

- ✿ Inactive product
- ✿ Active metabolite;
- ✿ Similar to parent
- ✿ More active than parent
- ✿ A product with different effect
- ✿ Toxic metabolite



Its enzymes are part of a cascade  
→ transfers electrons from molecular oxygen to oxidize the drugs



# DRUG METABOLISM



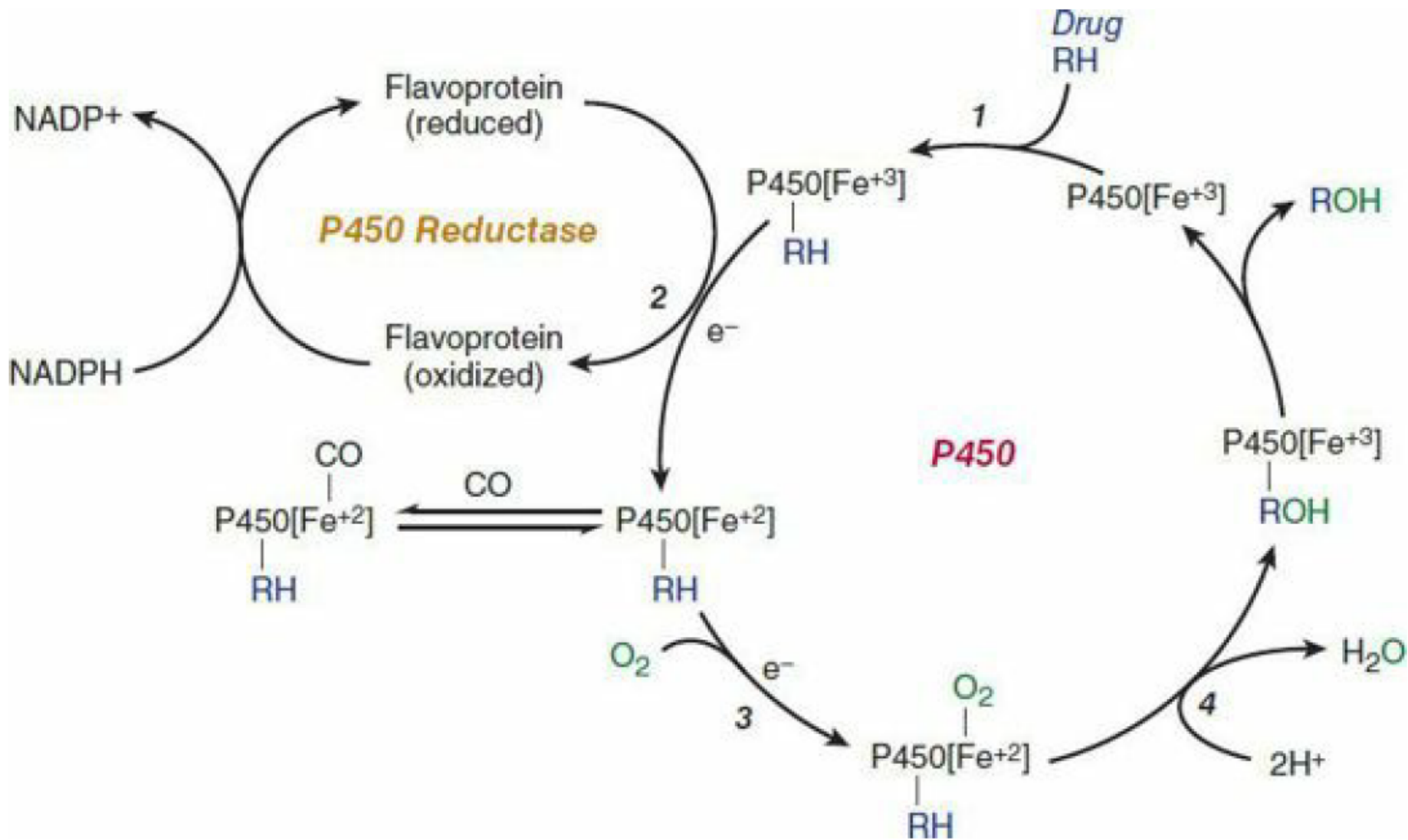
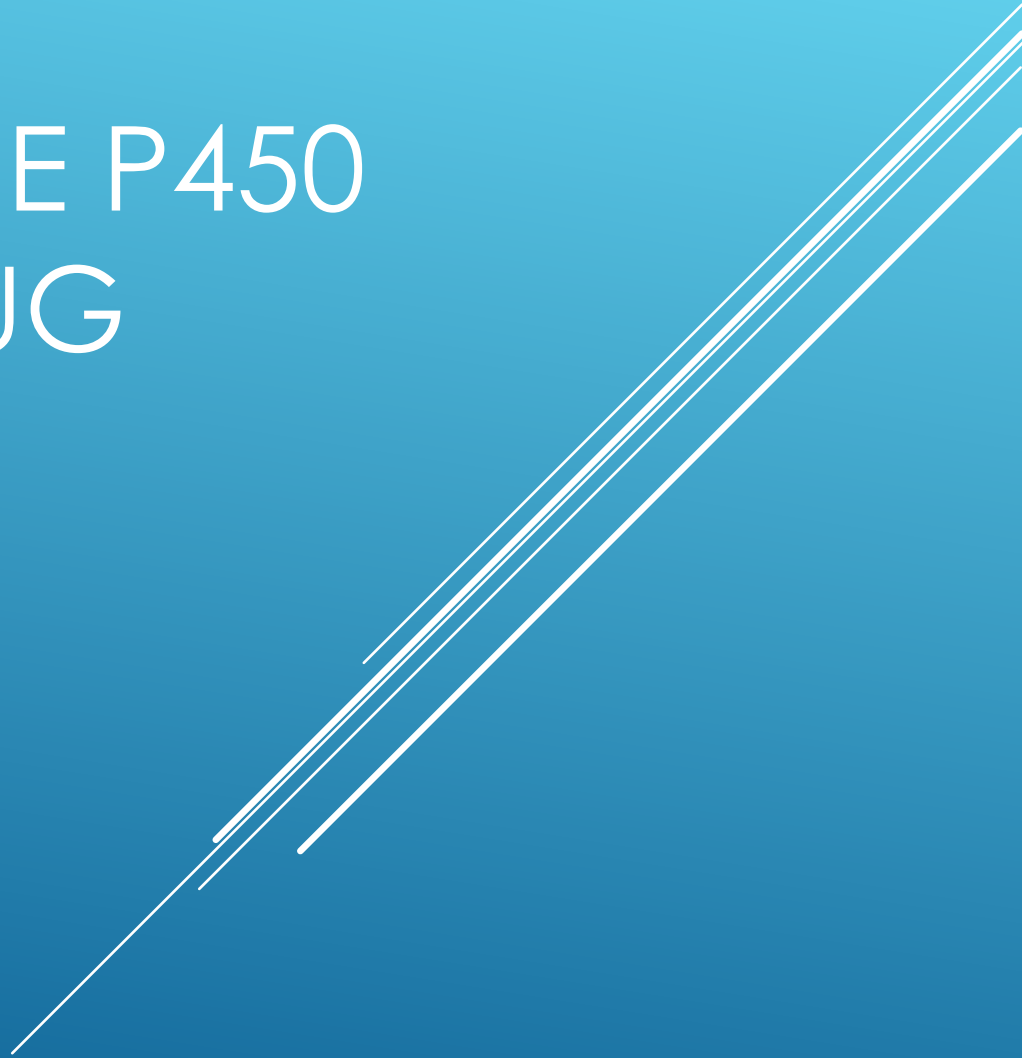

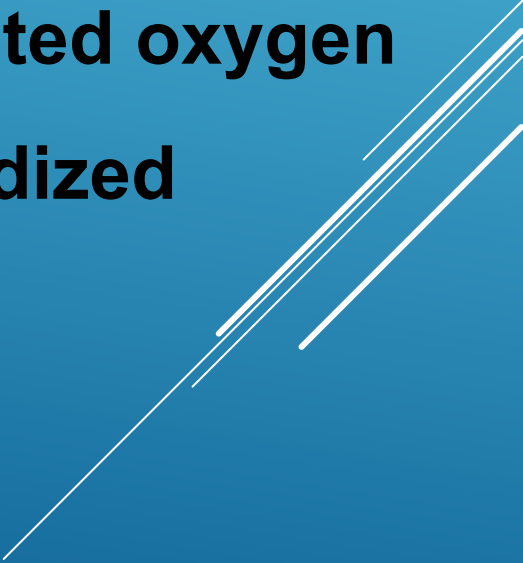


FIGURE 4-3 Cytochrome P450 cycle in drug oxidations. RH, parent drug; ROH, oxidized metabolite; e<sup>-</sup>, electron.

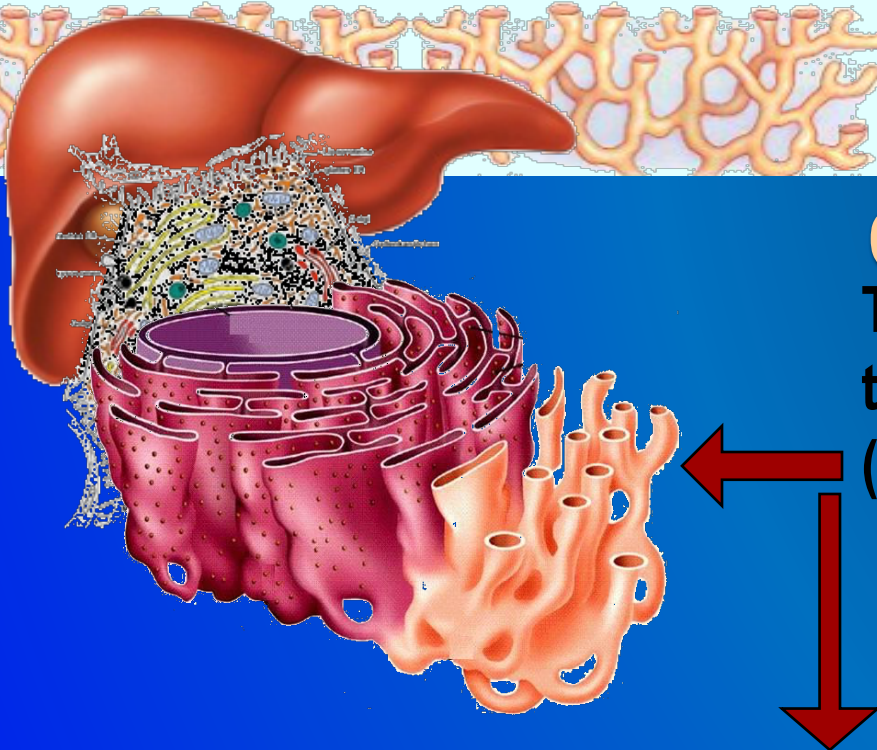
# CYTOCHROME P450 CYCLE IN DRUG OXIDATIONS



- ▶ **Microsomal drug oxidations require P450, P450 reductase, NADPH, & molecular oxygen**
  - ▶ **Briefly, oxidized ( $\text{Fe}^{3+}$ ) P450 combines with a drug substrate to form a binary complex (step 1). NADPH donates an electron to the flavoprotein P450 reductase, which in turn reduces the oxidized P450 drug complex (step 2).**
- 
- A decorative graphic consisting of several parallel white lines of varying lengths, slanted diagonally from the bottom right towards the top right, set against the blue background.

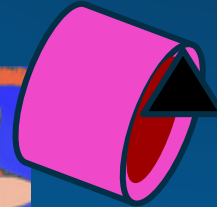
- ▶ **A second electron is introduced from NADPH via the same P450 reductase, which serves to reduce molecular oxygen & to form an activated oxygen – P450-substrate complex (step 3).**
  - ▶ **This complex in turn transfers activated oxygen to the drug substrate to form the oxidized product (step 4).**
- 
- A decorative graphic consisting of several parallel white lines of varying lengths, slanted upwards from left to right, located in the bottom right corner of the slide.



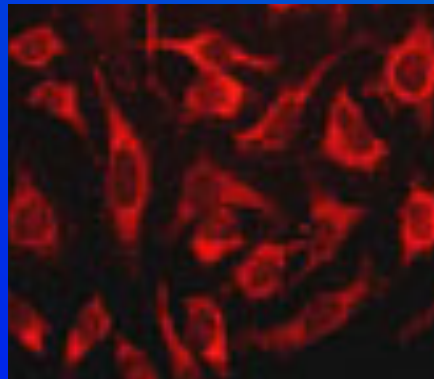


## CYTOCHROME P450 FAMILY OF ENZYMES

They are located mainly attached to the smooth endoplasmic reticulum (SER) of hepatocytes.



They are isolated in the subcellular fraction termed the **MICROSOMES**  
→ **Liver microsomal enzymes**



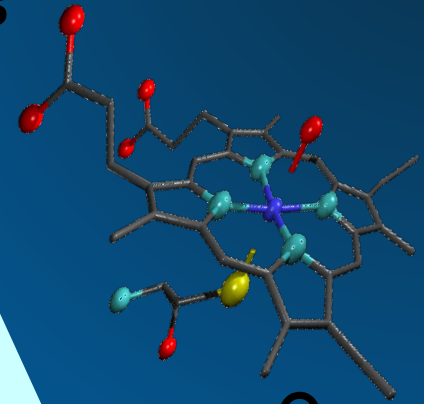
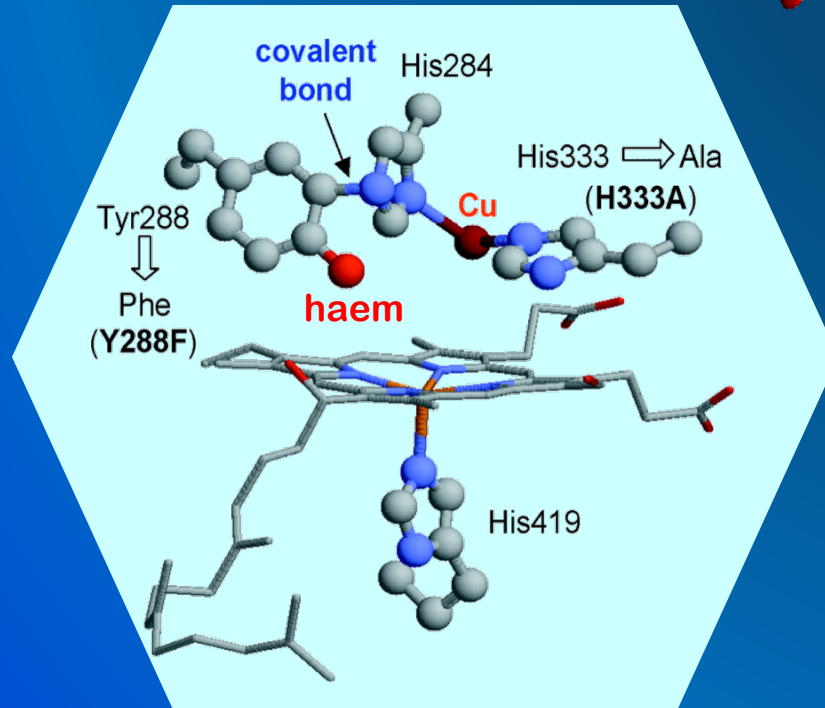
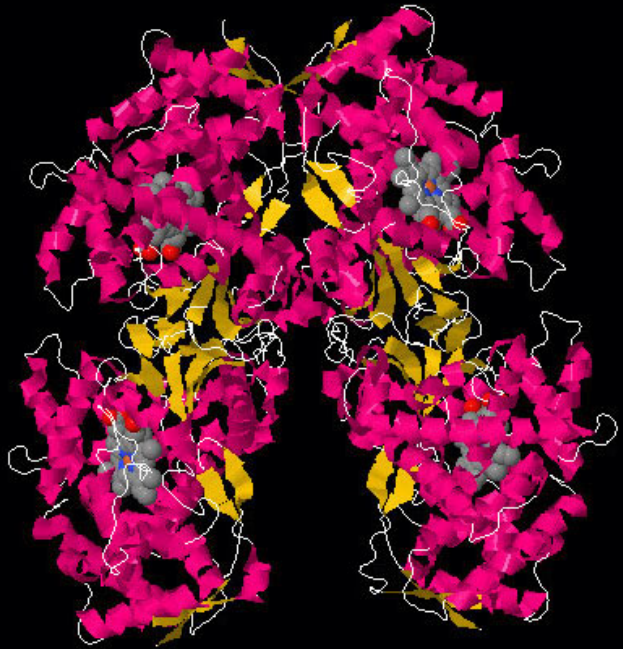
"Cytochrome" = colored cells  
They color the liver cells dark red as they contain iron

"P450" absorbs a very characteristic wavelength (450 nm) of UV light when it is exposed to carbon monoxide.

# STRUCTURE

They are heme-containing isoenzymes

Human Cytochrome P450  
from the  
Endoplasmic Reticulum



O<sub>2</sub>  
N<sub>3</sub>  
Cu  
Fe

# DISTRIBUTION

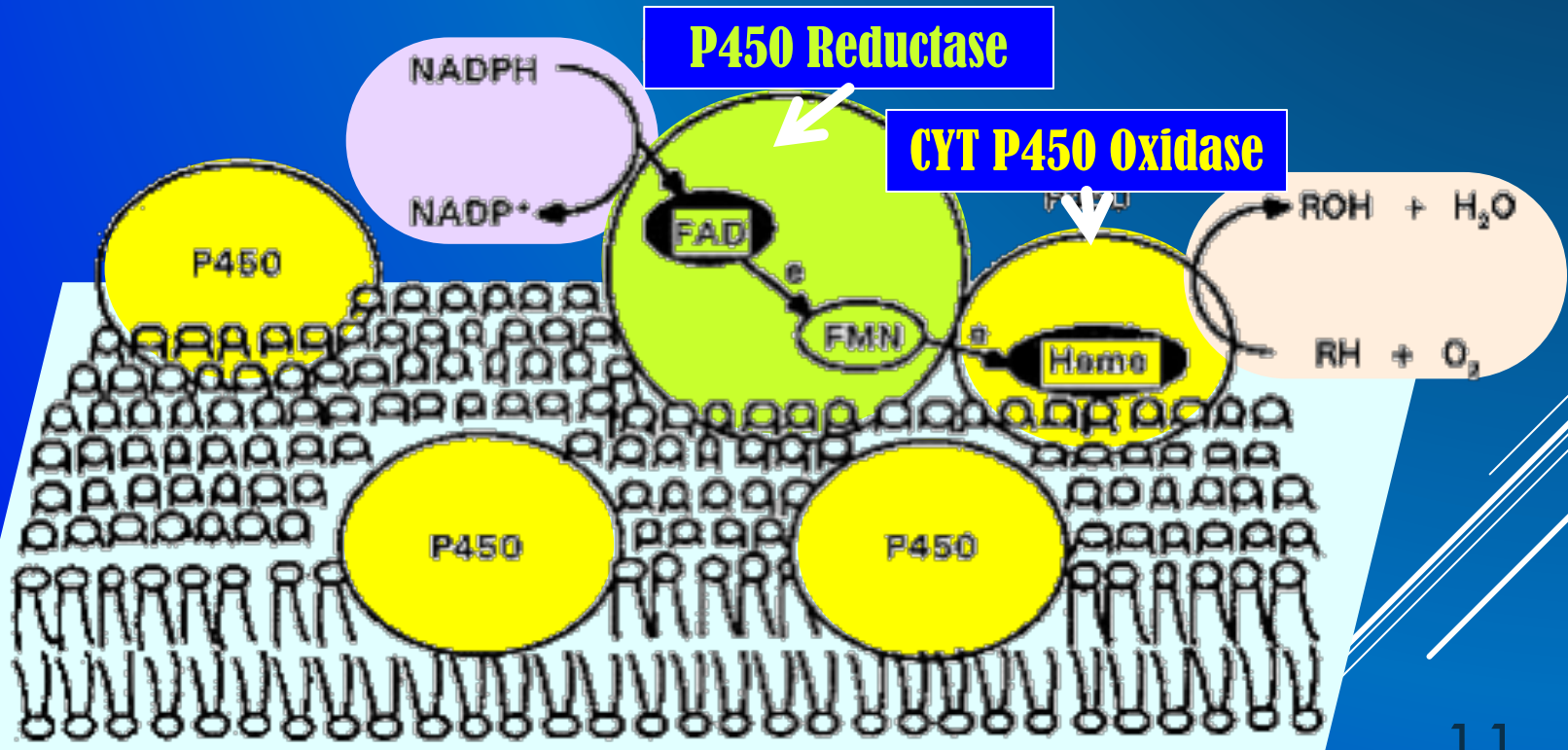
- Highly concentrated in hepatocytes
- Enterocytes of the small intestine present their principal extra-hepatic source
- Very small quantities in kidneys, lungs, & brain.

## Function

Responsible for most of the **OXIDATIVE METABOLISM** of:

- Endogenous substances: steroid hormones, prostaglandins, lipids, & fatty acids
- Exogenous compounds: diet (food & beverages) / Drugs/ environmental xenobiotics.

Substrates



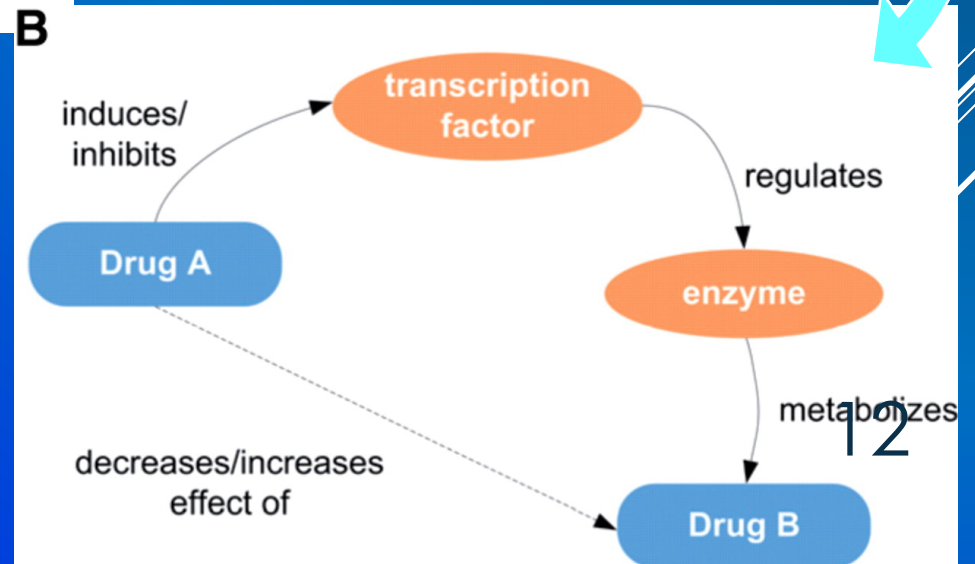
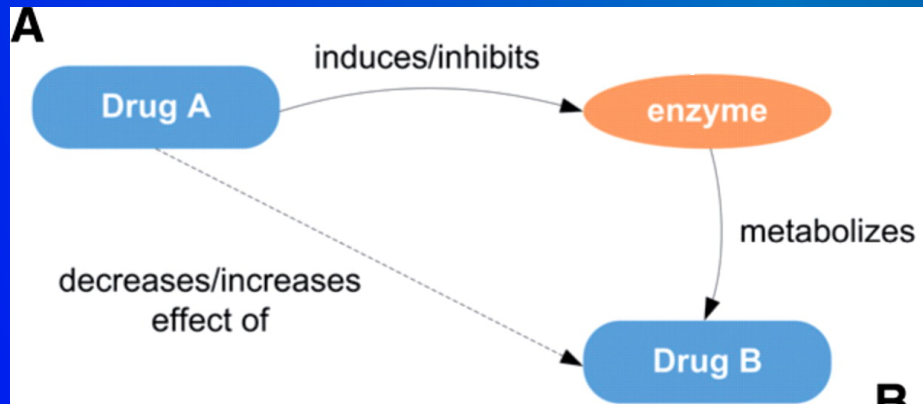


# Regulation

Activation or Inactivation of the CYT P450 can be achieved either

➤ **A: Directly**

➤ **B: Indirectly** by expression or repression of its relevant genes by  
➤ activation or inhibition of the responsible transcription factors



Activation or Inactivation can be processed by any food, intrinsic products or extrinsic xenobiotics as drugs (usually the lipophylic) that have to be metabolized.



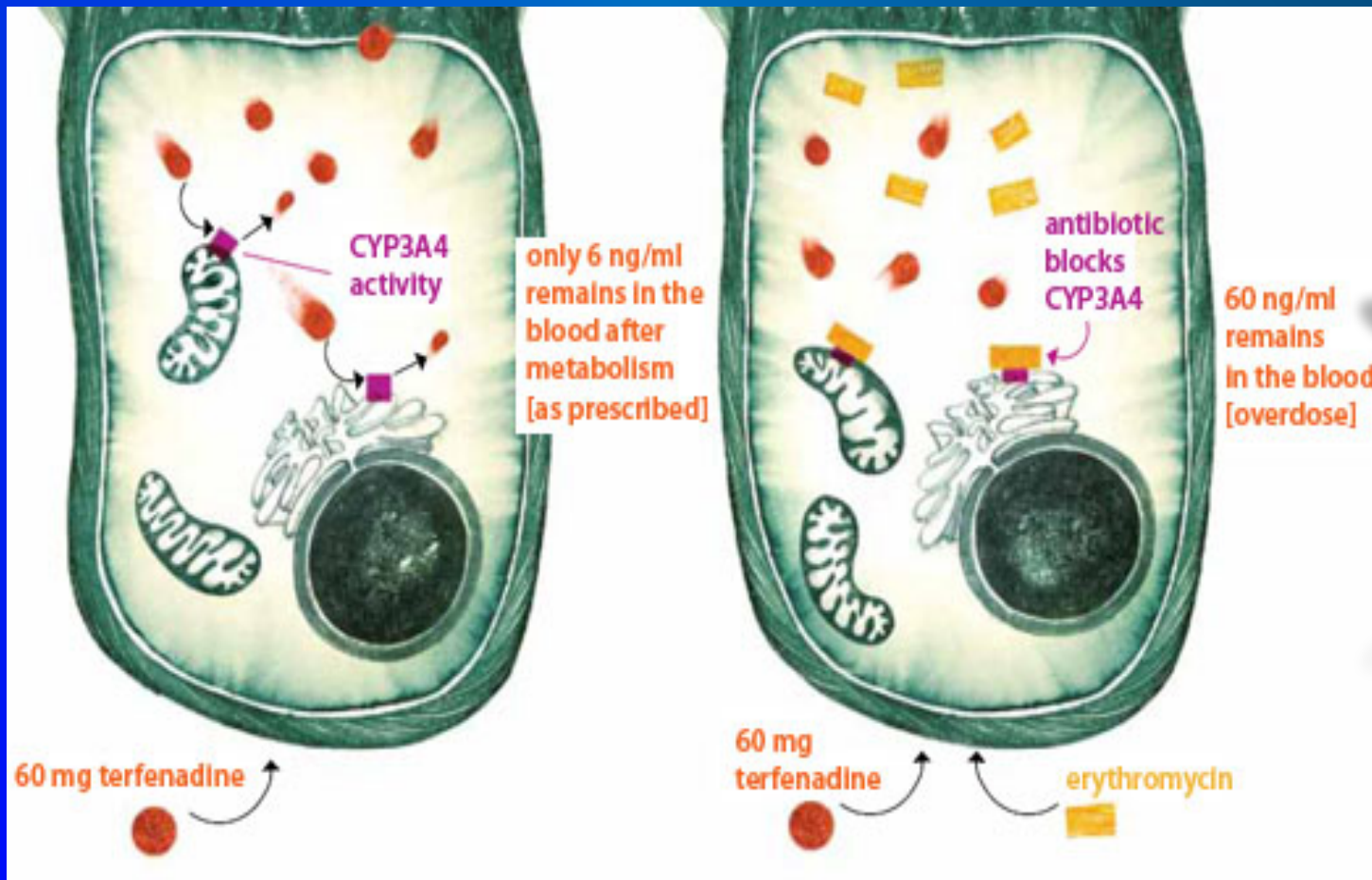
# Regulation

When drugs play a role in regulation of the CYT P450 → they are termed

● Enzyme Inducers if **Activate** the enzyme

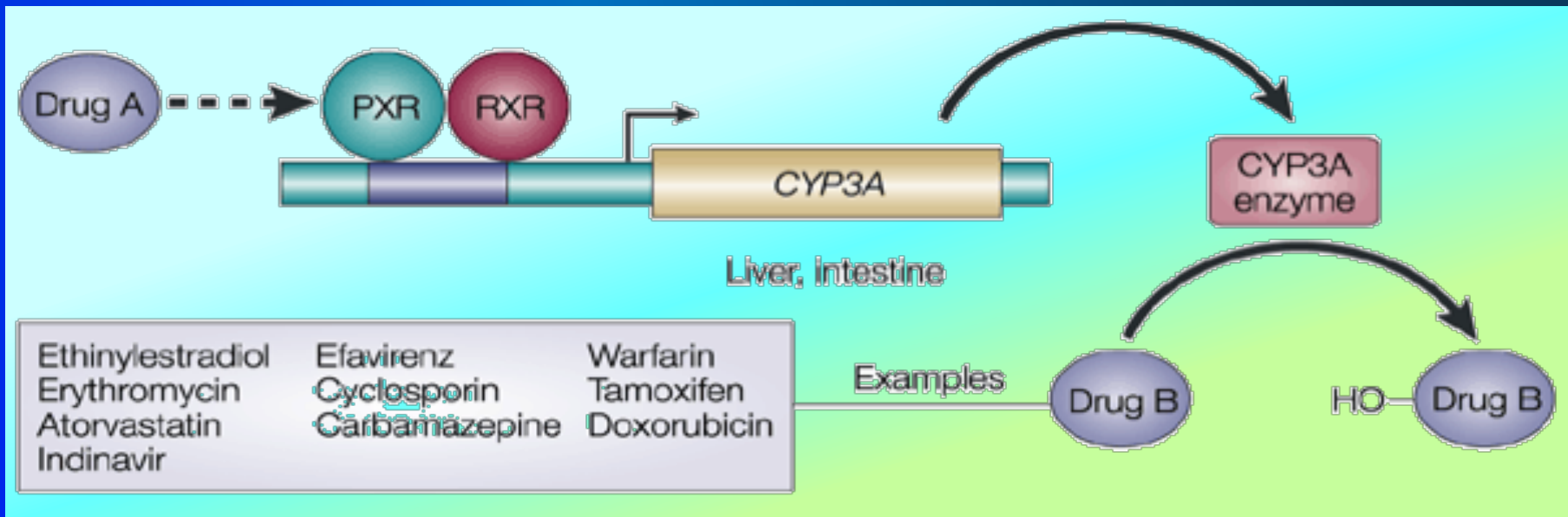
● Enzyme Inhibitors if **Inactivate** the enzyme

PHARMACOKINETIC  
DRUG-DRUG  
INTERACTION



# Molecular Basis Of Drug–drug Interaction

# Regulation



The orphan nuclear receptor **PXR** is a **TRANSCRIPTION FACTOR** that regulates the expression of the *CYP P450* genes.

If **Drug A** is **INDUCER** → it binds & activates **PXR** → which translocates in nucleus → dimerize with **RXR** → the heterodimer **PXR / RXR** will induce **EXPRESSION** of *CYT P450* isoenzymes to → ↑ metabolism of **Drug B**

If **Drug A** is an **INHIBITOR**, its binding will prevent activation →

**REPRESSION** of *CYT P450* isoenzymes → ↓ metabolism of **Drug B** 14

*PXR, pregnane X receptor*  
*RXR, retinoid X receptor.*

## IN RELATION TO ENZ **INDUCERS**

↑ metabolism of the inducer + ↓ its pharmacological action.

*Tolerance or complete nullification*

↑ metabolism of co-administered drugs

↓ **EFFICACY**

## IN RELATION TO ENZ **INHIBITORS**

↓ / Retard metabolism & excretion of inhibitor & co-administered drugs

↑ / prolong action of the inhibitor & co-administered drugs.

↑ **TOXICITY**

# Classification

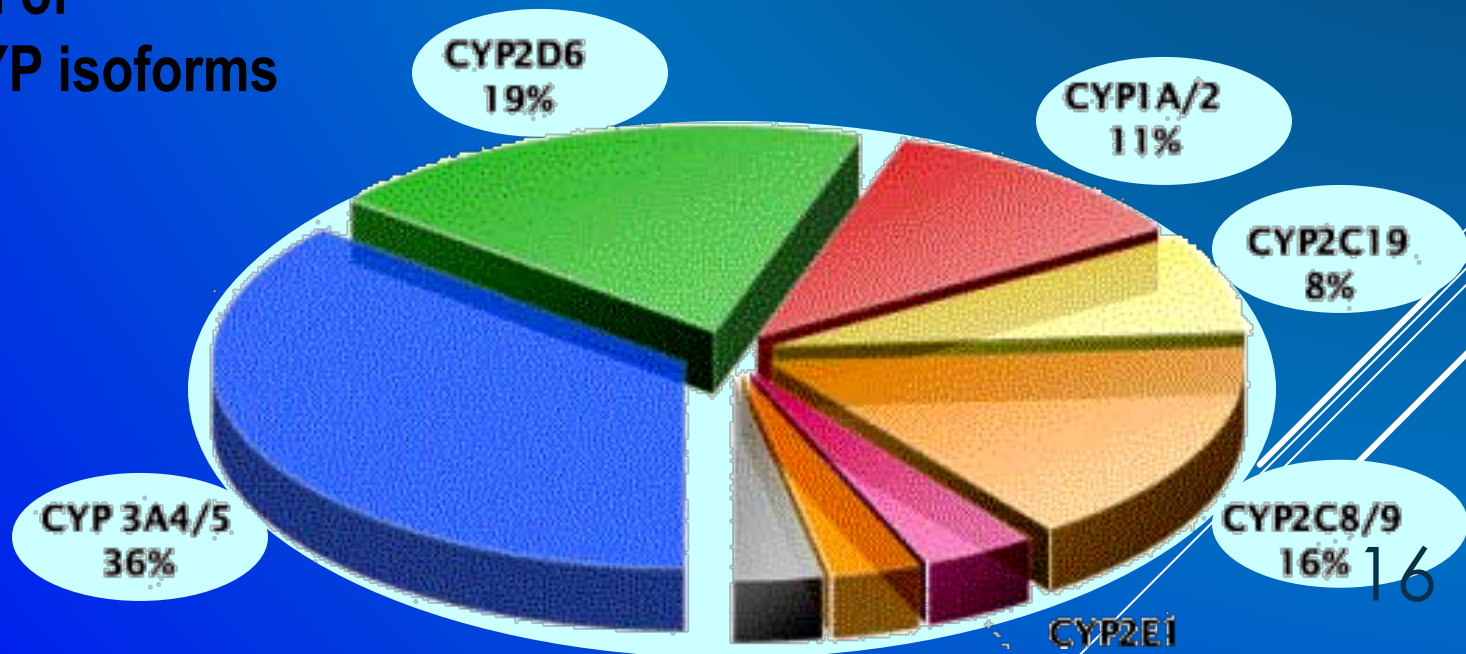


- CYT P450 has been classified into
- Families designated by Numbers
  - Sub families designated by Letters

## Cytochrome P450 Isoforms

- CYP1A2
- CYP3A
- CYP2C9
- CYP2C19
- CYP2D6

Distribution of different CYP isoforms in the liver.



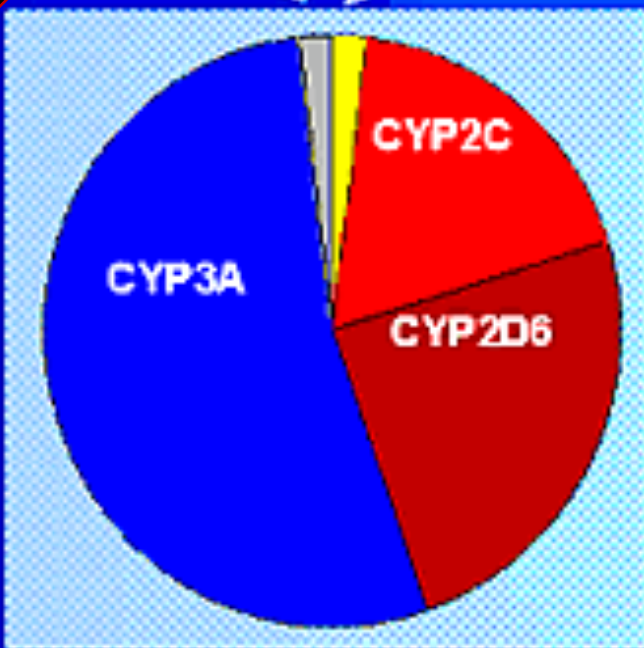


# CYP450 → Major Contributor to Phase I Metabolism

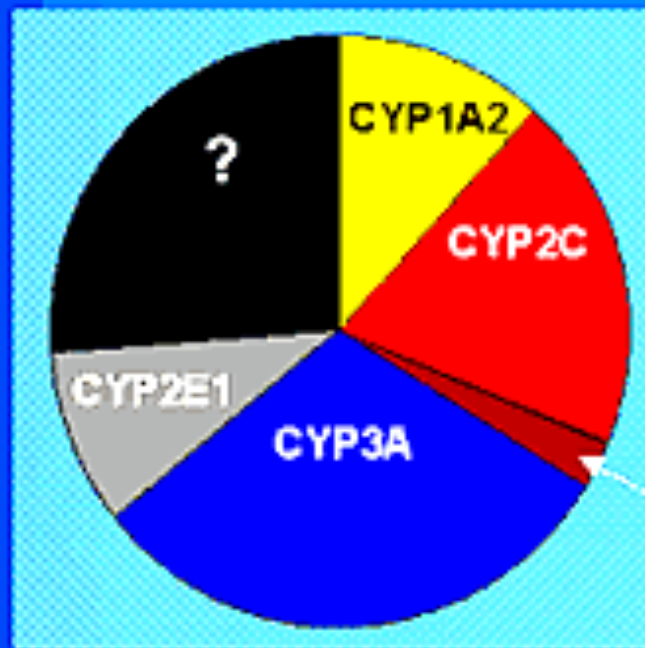
Relative Importance of P450s in Drug Metabolism

CYP2E1

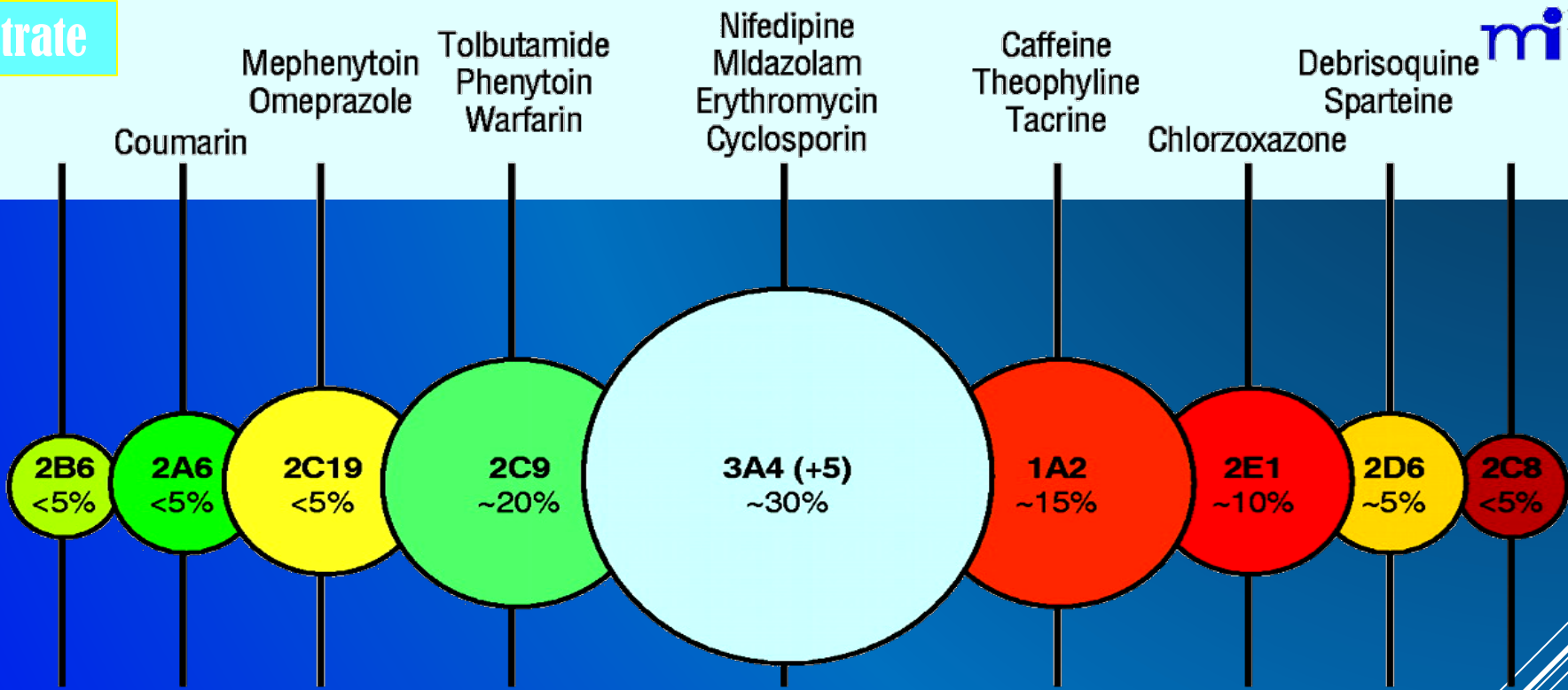
CYP1A2



Relative Quantities of P450s in Liver



# Substrate



# Inhibitors

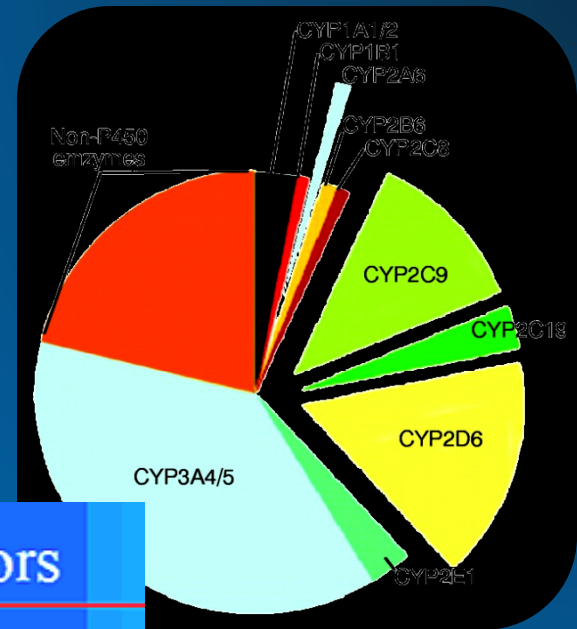
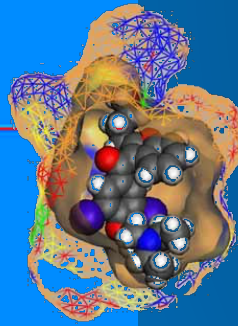
- Fluconazole
- Methoxsalen
- Sulfaphenazole
- Ketoconazole
- Gestodene
- Furafylline
- Fluvoxamine
- Disulfiram
- Quinidine

# Inducers

- Barbiturates
- Rifampicin
- Barbiturates
- Rifampicin
- Dexamethasone
- Carbamazepine
- Omeprazole
- Tobacco smoke
- Ethanol
- Isoniazid

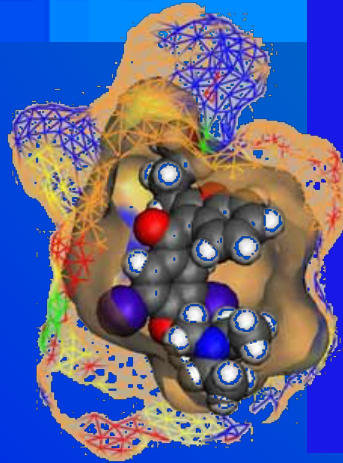
# Cytochrome P450 3A

- Responsible for metabolism of:
  - Most calcium channel blockers
  - Most benzodiazepines
  - Most HIV protease inhibitors
  - Most HMG-CoA-reductase inhibitors
  - Cyclosporine
  - Most non-sedating antihistamines
  - Cisapride
- Present in GI tract and liver



## CYP3A Inhibitors

- Ketoconazole
- Itraconazole
- Fluconazole
- Cimetidine
- Clarithromycin
- Erythromycin
- Troleandomycin
- Grapefruit juice
- Ritonavir



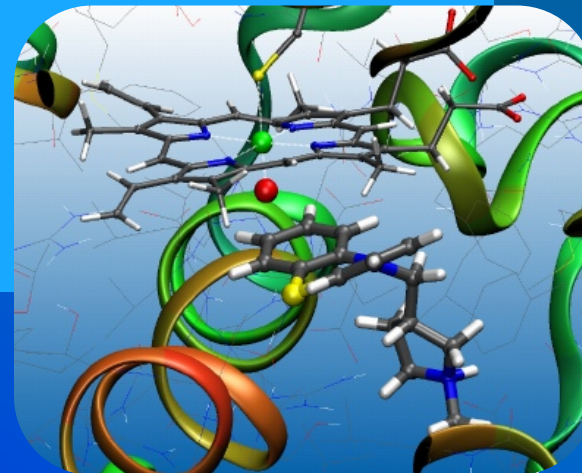
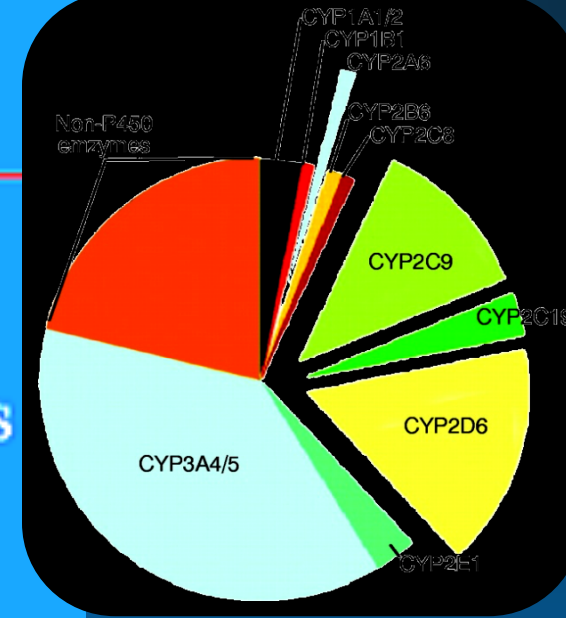
## CYP3A Inducers

- Carbamazepine
- Rifampin
- Rifabutin

19

# Cytochrome P450 2D6

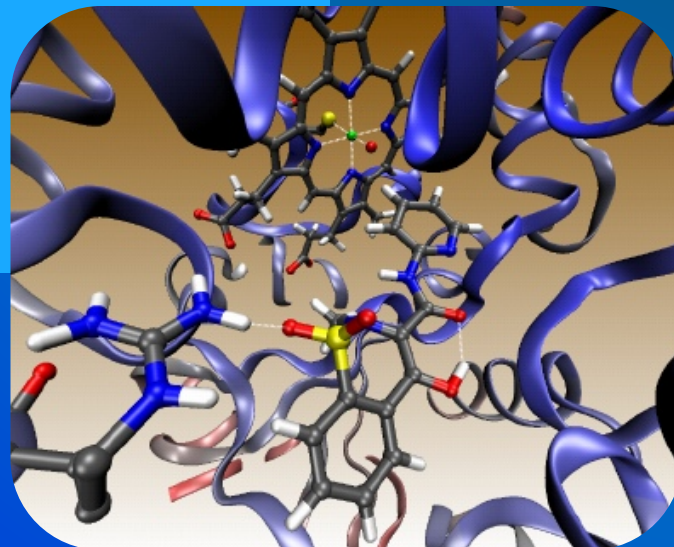
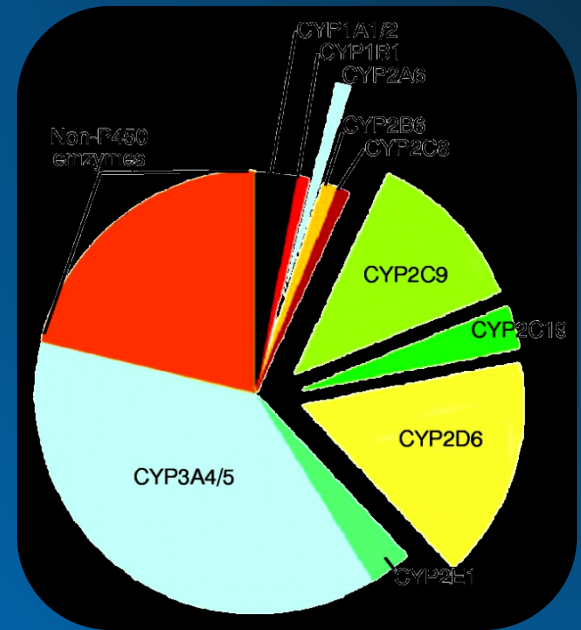
- Absent in 7% of Caucasians, 1–2% non-Caucasians
- Hyperactive in up to 30% of East Africans
- Catalyzes primary metabolism of:
  - Codeine
  - Many  $\beta$ -blockers
  - Many tricyclic antidepressants
- Inhibited by:
  - Fluoxetine
  - Haloperidol
  - Paroxetine
  - Quinidine





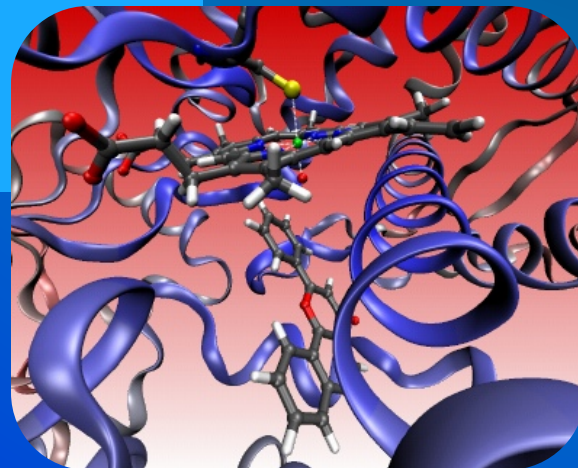
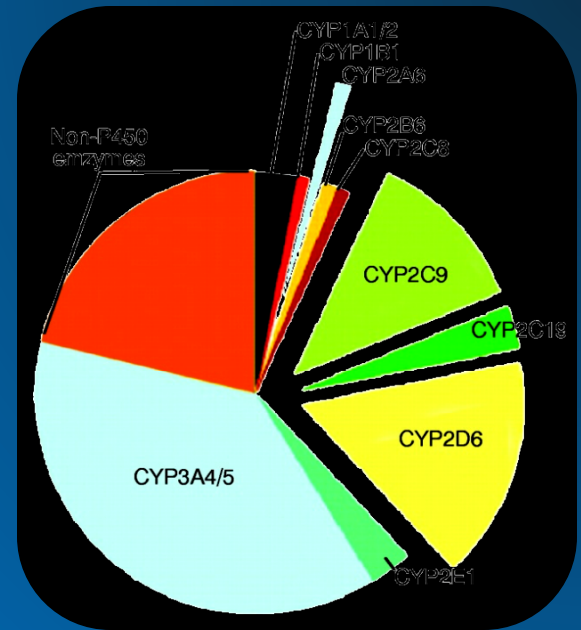
# Cytochrome P450 2C9

- Absent in 1% Caucasians and African-Americans
- Primary metabolism of:
  - Most NSAIDs (including COX-2)
  - S-warfarin (the active form)
  - Phenytoin
- Inhibited by:
  - Fluconazole



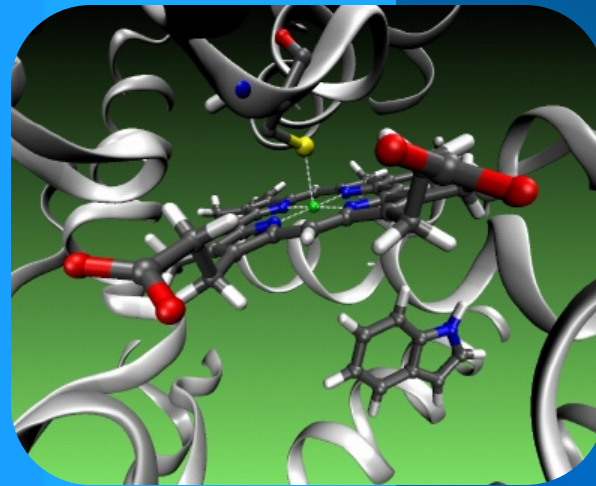
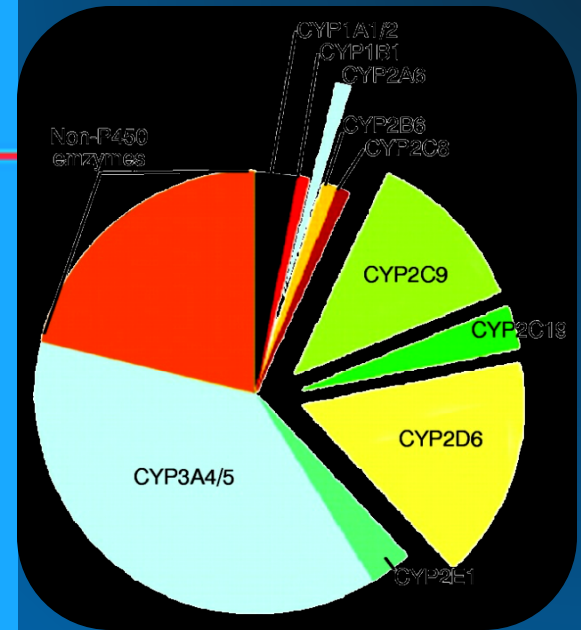
# Cytochrome P450 1A2

- Induced by smoking tobacco
- Catalyzes primary metabolism of:
  - Theophylline
  - Imipramine
  - Propranolol
  - Clozapine
- Inhibited by:
  - Many fluoroquinolone antibiotics
  - Fluvoxamine
  - Cimetidine



# Cytochrome P450 2C19

- Absent in 20–30% of Asians, 3–5% Caucasians
- Primary metabolism of:
  - Diazepam
  - Phenytoin
  - Omeprazole
- Inhibited by:
  - Omeprazole
  - Isoniazid
  - Ketoconazole



# CYT P450 3A4

## Substrates

- Immunosuppressants (Cyclosporine)
- Azole Antifungals (Fluconazole)
- Antibiotics (Erythromycin, Clarithromycin)
- Ca channel blockers (Amlodipine, Verapamil)
- Statins (Atorvastatin)
- Cancer Chemotherapy (Cyclophosphamide, Tamoxifen)
- Non-Sedating Antihistamines (Astemizole)
- Benzodiazepines (Midazolam, Clonazepam).

## Inhibitors

Ritonavir  
Cimetidine  
Chloramphenicol  
Nefazodone  
Grape Fruits

## Inducers

Phenytoin  
Carbamazepine  
Barbiturates  
Rifampicin  
Dexamethazone  
Progestins



“A 50 years old, patient was treated for the last 3 years by the hypocholestrolemic agent; **atorvastatin**. Yesterday he began to complain of severe muscle pains, weakness & reddish discoloration of urine

He receives daily multivitamins & his lab results last week, proved that he has become diabetic, for which he was prescribed metformin. He was also started on a course of **fluconazole** for a concomitant fungal infection.

From drug history, the diagnosis of his current state was likely rhabdo-myositis (severe musculoskeletal toxicity) & was verified by the lab finding of severe elevation in creatinine phosphokinase. “

Which one of the following drug-drug interaction on CYT 3A4 is the likely cause of his current state?

Metformin + Atrovastatin

Atrovastatin + Fluconazole

Metformin + Fluconazole

Fluconazole+ Multivitamins

# Genetic Variation

Genetic polymorphisms in CYT P450 isoenzymes have been observed & are reasons behind the **ALTERED RESPONSE** to drug therapy

## CYP2D6

This isoenzyme has the most frequent polymorphisms in all CYT P450

When polymorphism occurs → ↓ metabolizing capacity of CYP2D6

i.e those **who exhibit the polymorphism become poor metabolizers:**

1. Metabolism of some neuroleptics, tricyclic antidepressants, antianginal agents (perihexiline), antiarrhythmics (propafenone & metoprolol) is suppressed → so side effects & toxicity develop. i.e.

- Neuropathy after therapeutic doses of perihexiline

- Bradycardia & arrhythmias on therapeutic dose of propafenone or metoprolol

2. The pro-drugs cannot be converted to their therapeutically active metabolite; e.g poor analgesia with codeine & tramadol because they are not transformed into active forms.

# Genetic Variation

## CYP2C9.

Warfarin, phenytoin, & tolbutamide are examples of drugs with narrow therapeutic index that are metabolized by CYP2C9.

Clearance of these drugs is impaired in genetic variation of the enzyme

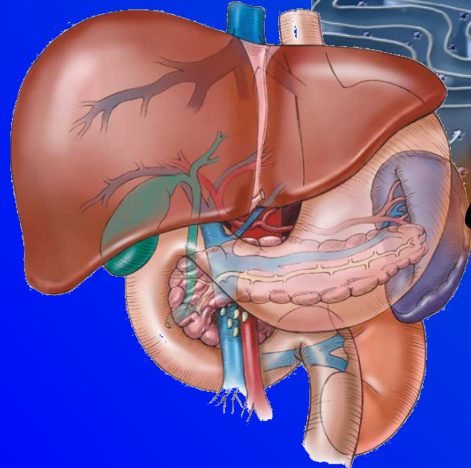
## CYP2C19

Polymorphism in CYP2C19 shows increased & prolonged action of its substrates as omeprazole

This has been an advantage as in those variants → ↑ cure rates in peptic ulcer patient with *Helicobacter pylori*.

Benefit

# CYTOCHROME SYSTEM



# & DRUG METABOLISM

G  
O  
O  
D  
L  
U  
C  
K