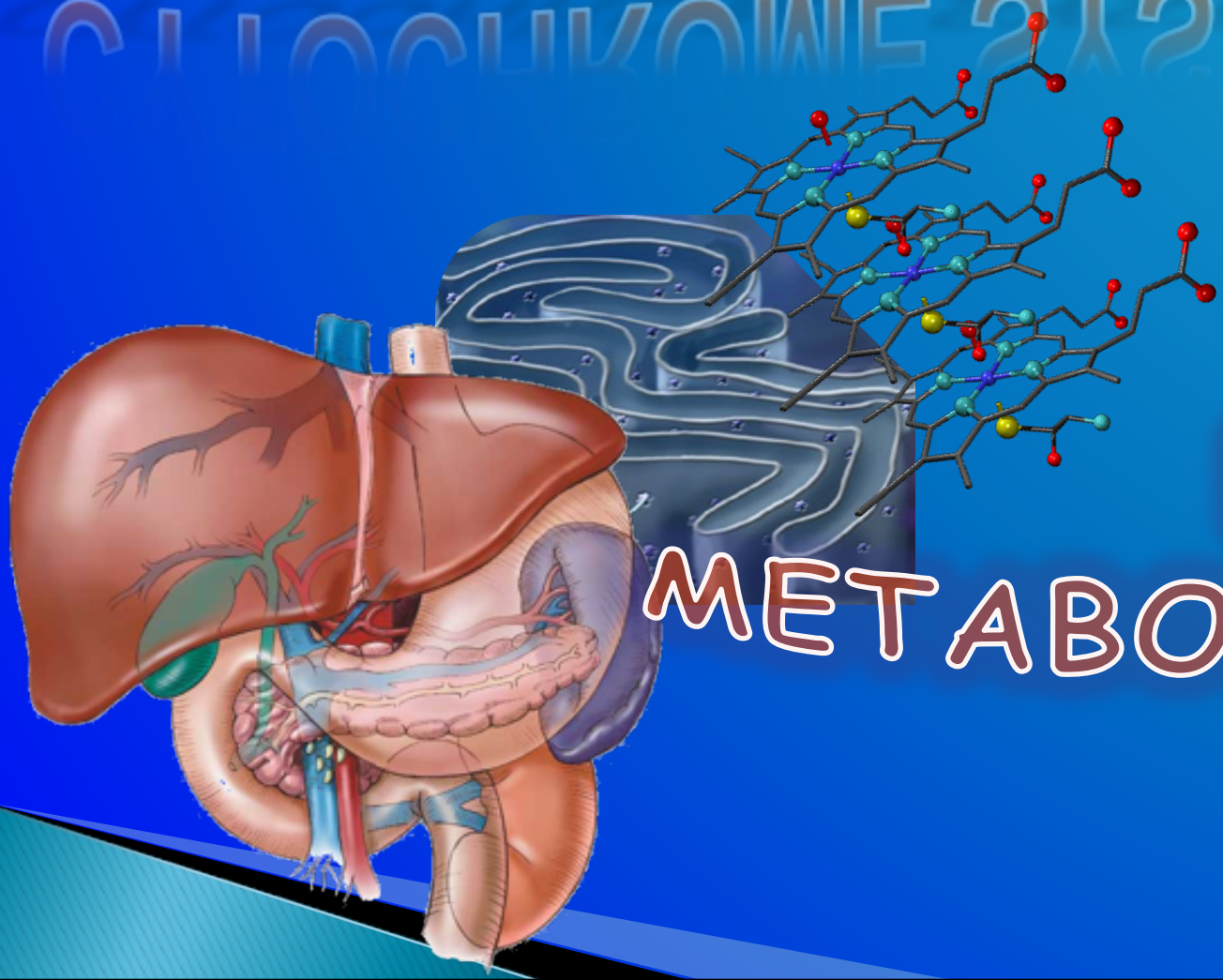
CYTOCHROME SYSTEM

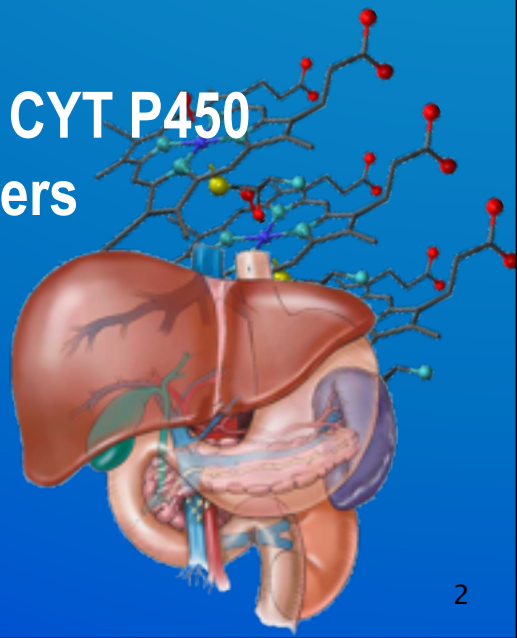
&

DRUG METABOLISM



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 its relevance to drug interactions
- Interpret the molecular mechanism of interactions by CYT P450
- Classify its different isoforms, their substrates, inducers & inhibitors
- Delineate some of its genetic variations.



RENAL
Elimination

Polar product

Non-Polar product

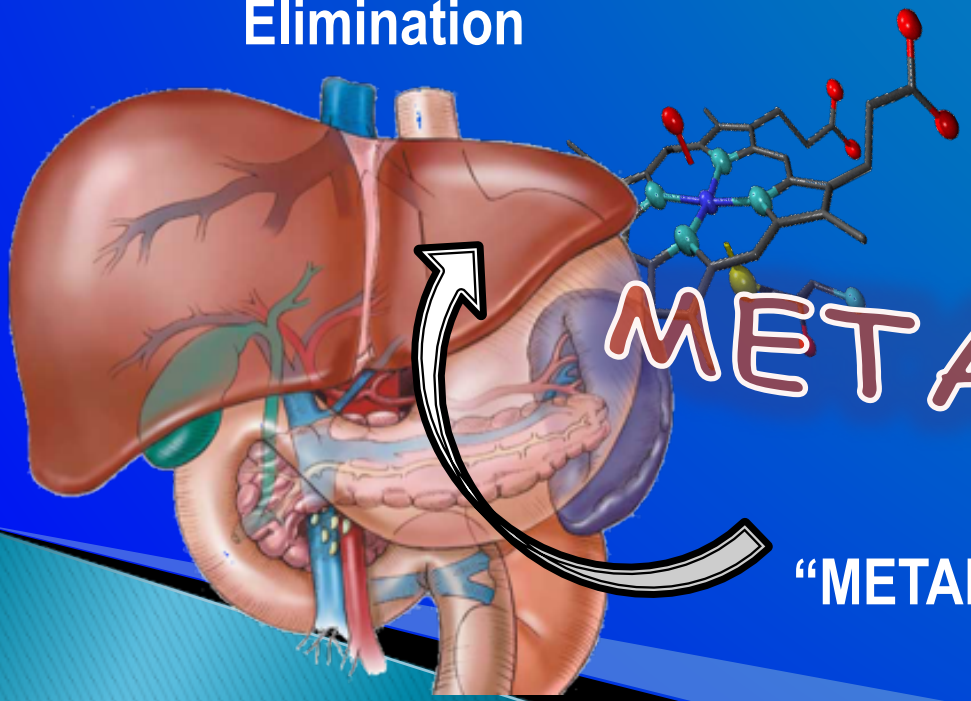
BILIARY
Elimination

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"

DRUG METABOLISM

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

?

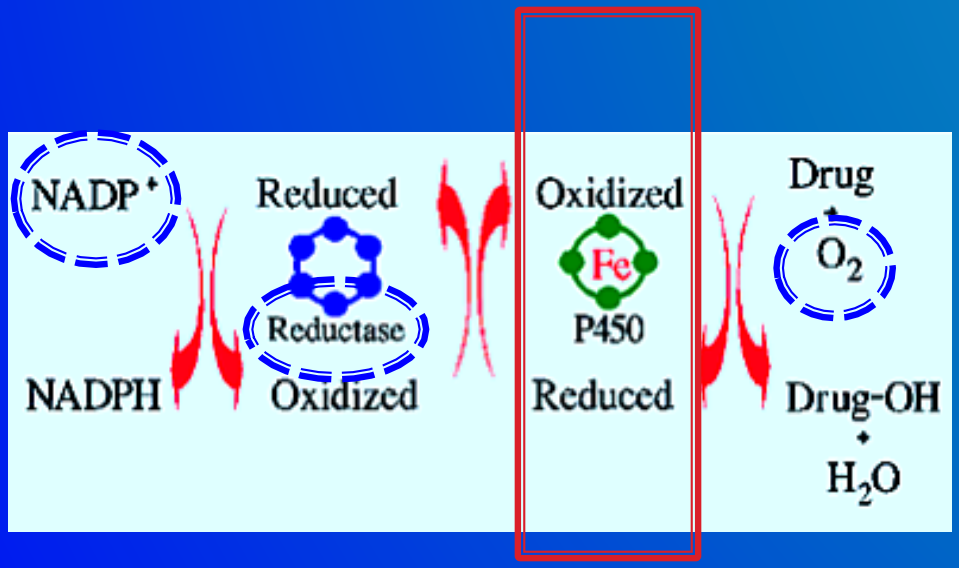
Phase II
CONJUGATION

Create a conjugation site

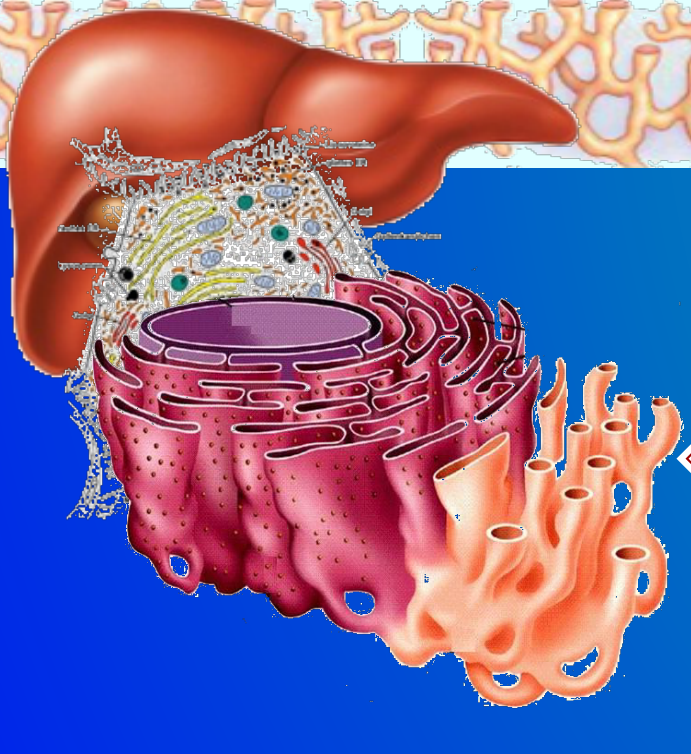
Phase I
OXIDATION /Reduction/Hydrolysis

CYTOCHROME SYSTEM

" Cytochrome P450" " CYT 450" superfamily is the terminal rate limiting oxidase of this system



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

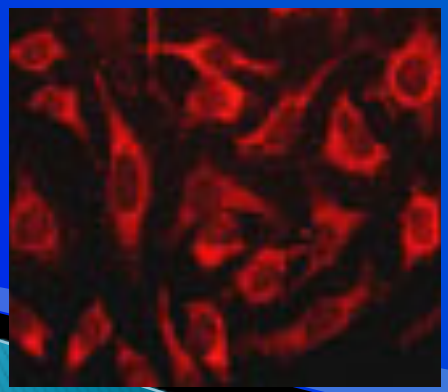


CYTOCHROME P450 FAMILY OF ENZYMES.

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



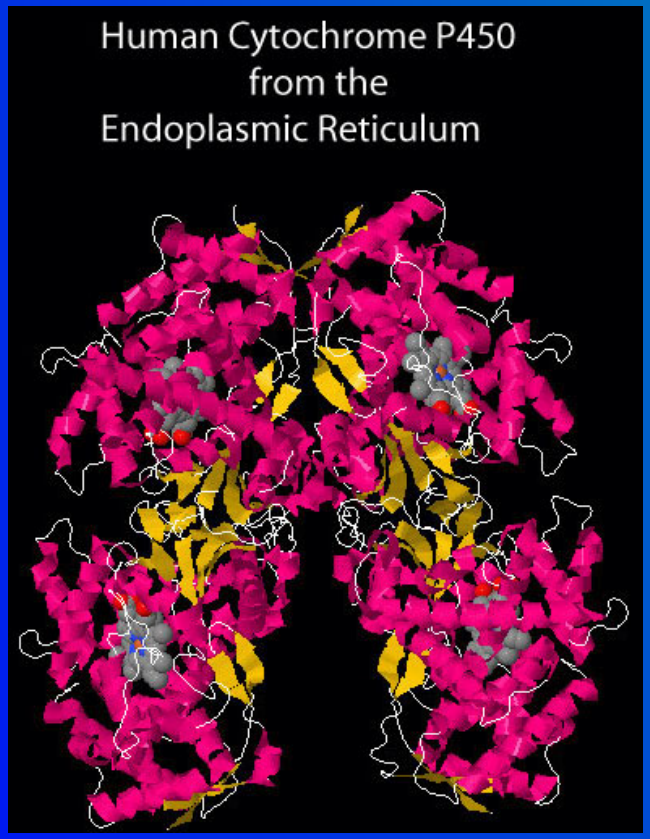
"Cytochrome" = colored cells

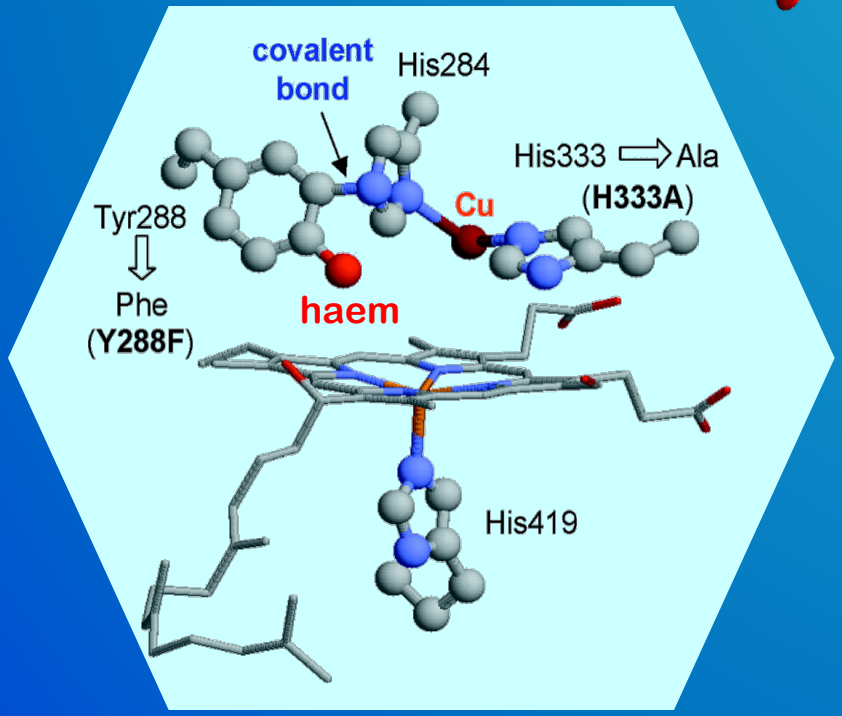
They color the liver cells dark red as they contain iron

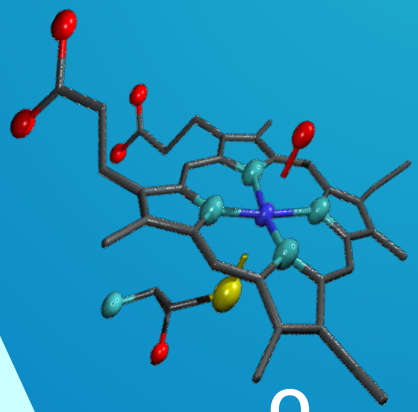
"P450" absorbs a very characteristic wavelength (450 nm) of UV light when it is exposed to carbon monoxide.

STRUCTURE

They are heme-containing isoenzymes







O_2
N_3
Su
Fe

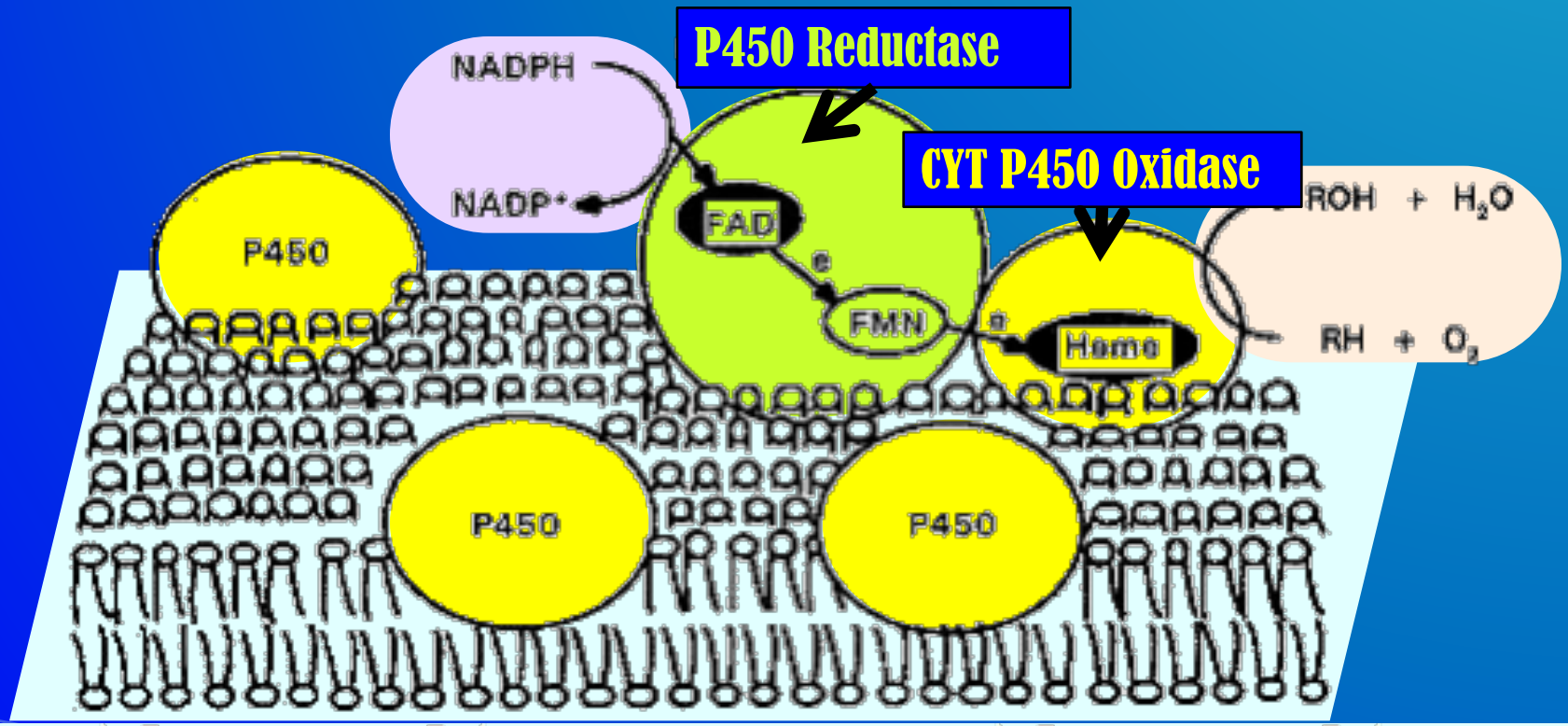
DISTRIBUTION

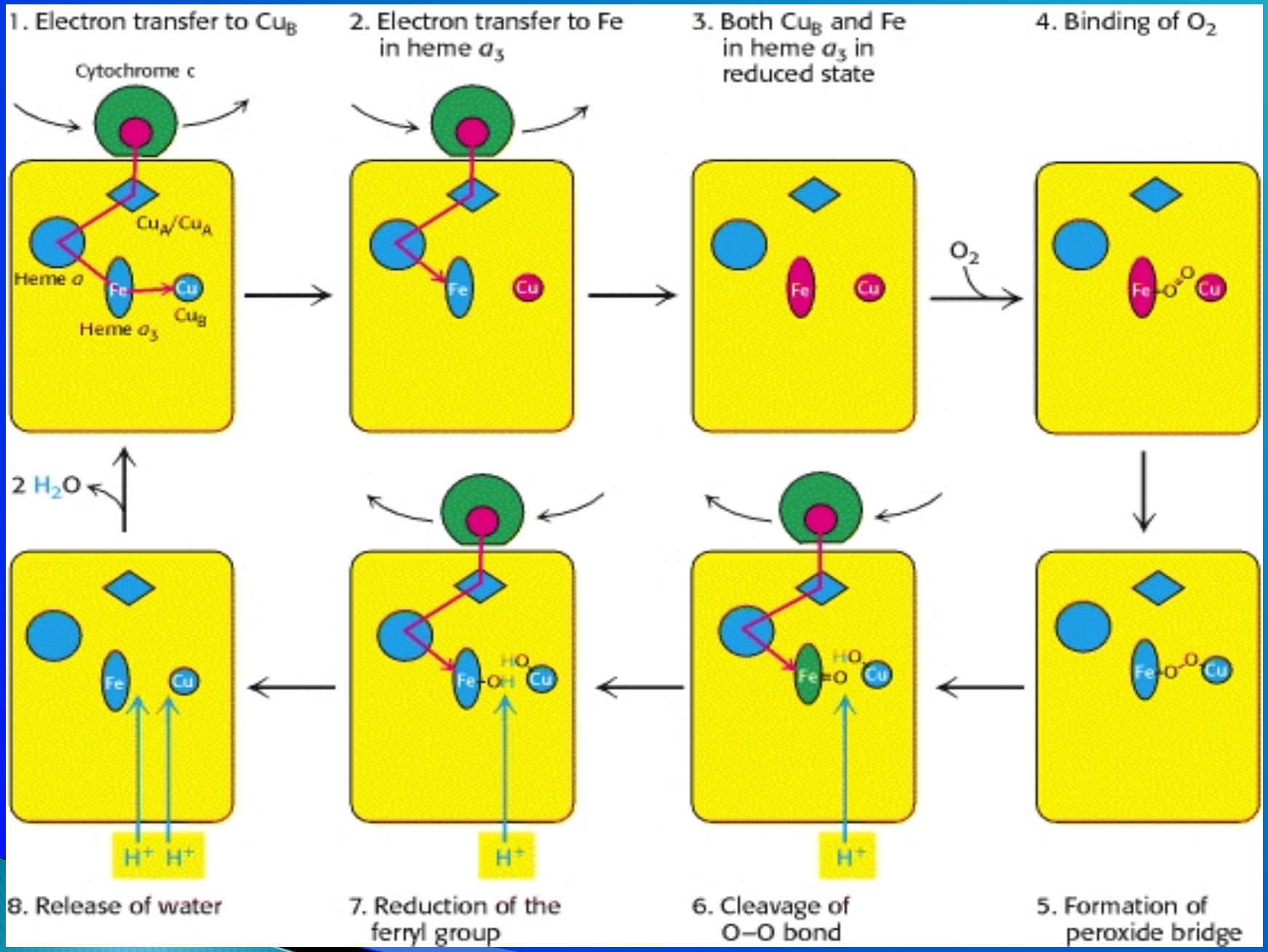
- Highly concentrated in hepatocytes
- Enterocytes of the small intestine present their principal extra-hepatic source
- Very small quantities in kidneys, lungs & brain.

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

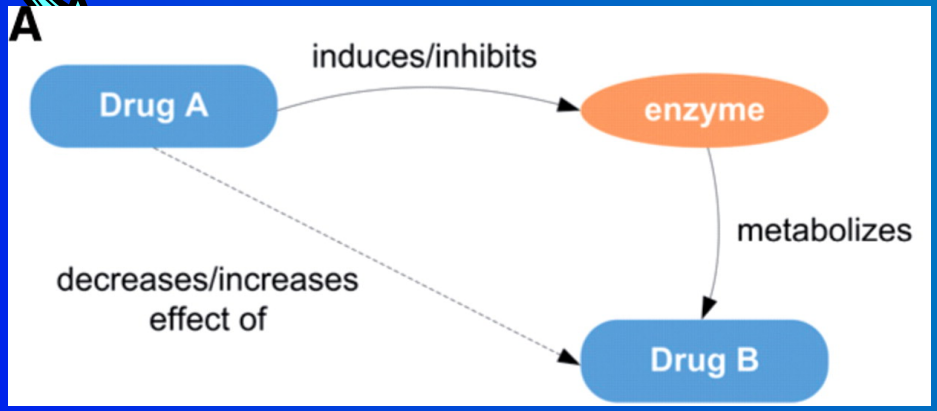



1. Electron transfer to Cu_B
Cytochrome c
Cu_A/Cu_A
Heme *a*
Fe
Cu
Cu_B
Heme a_3
2. Electron transfer to Fe in heme a_3
3. Both Cu_B and Fe in heme a_3 in reduced state
4. Binding of O_2
O_2
5. Formation of peroxide bridge
6. Cleavage of O–O bond
7. Reduction of the ferryl group
8. Release of water
2 H_2O
H^+ H^+
H^+
H^+

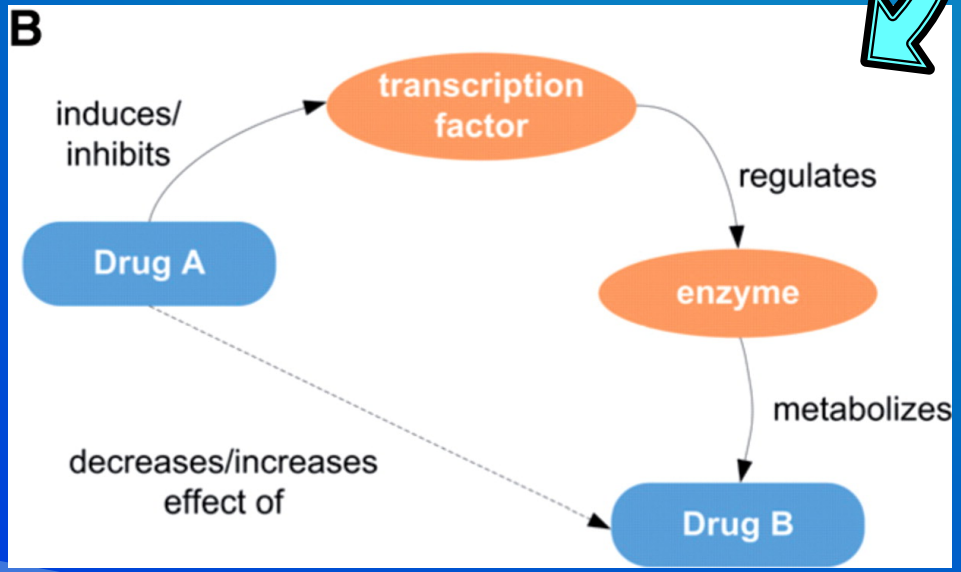
Regulation

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

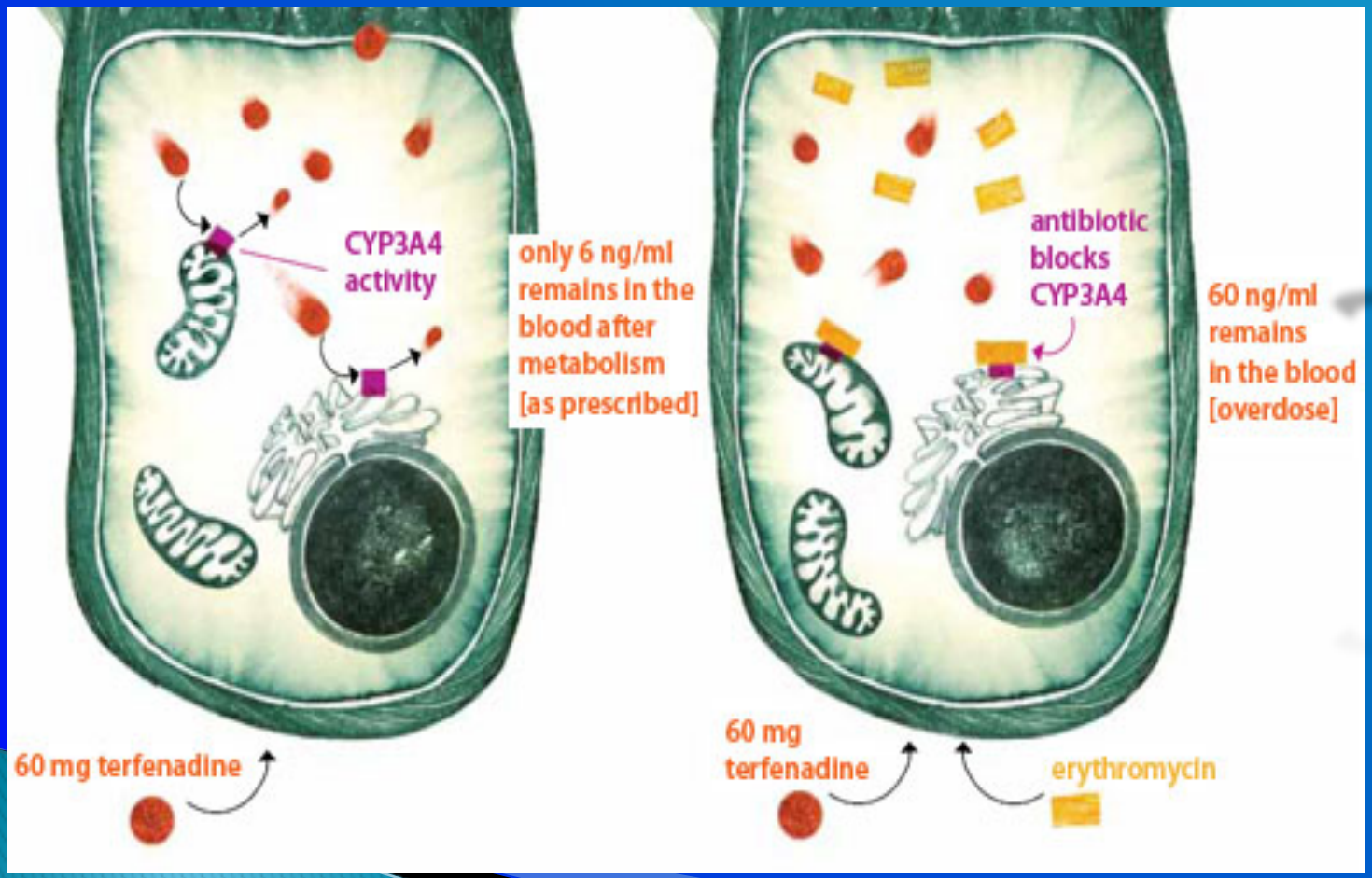


Regulation

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

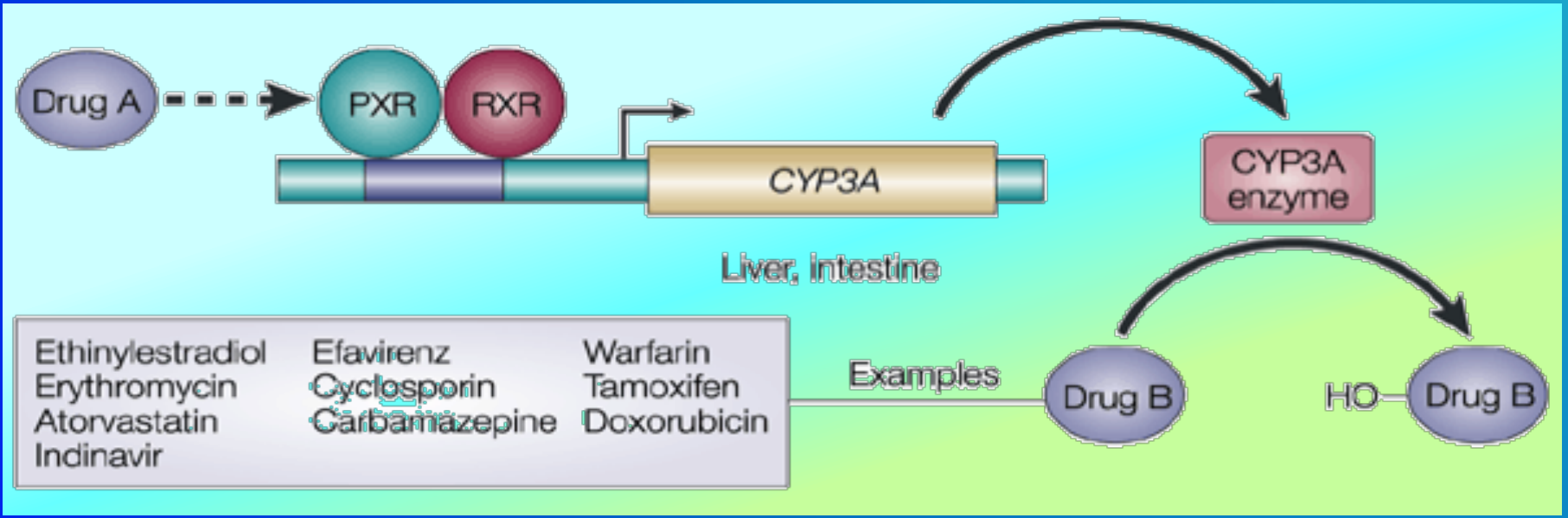
- Enzyme Inducers if Activate the enzyme
- Enzyme Inhibitors if Inactivate the enzyme

→ 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 heterodiamer **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 to → ↓metabolism of Drug B

PXR, pregnane X receptor

RXR, retinoid X receptor

Outcome Of Drug-drug Interactions Mediated By CYT P450

Regulation

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.

↑TOXCICITY

Classification

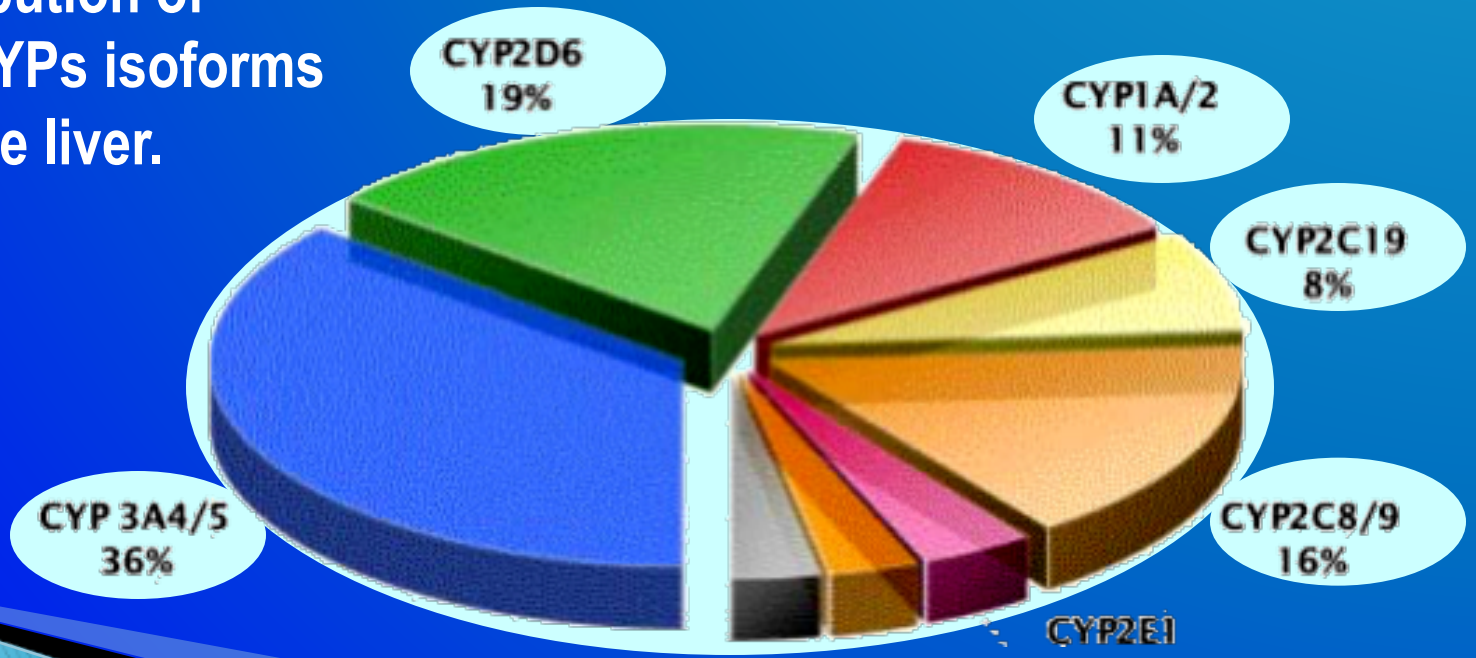
CYT P450 has been classified into

- Families designated by Numbers
- Sub families designated by Letters

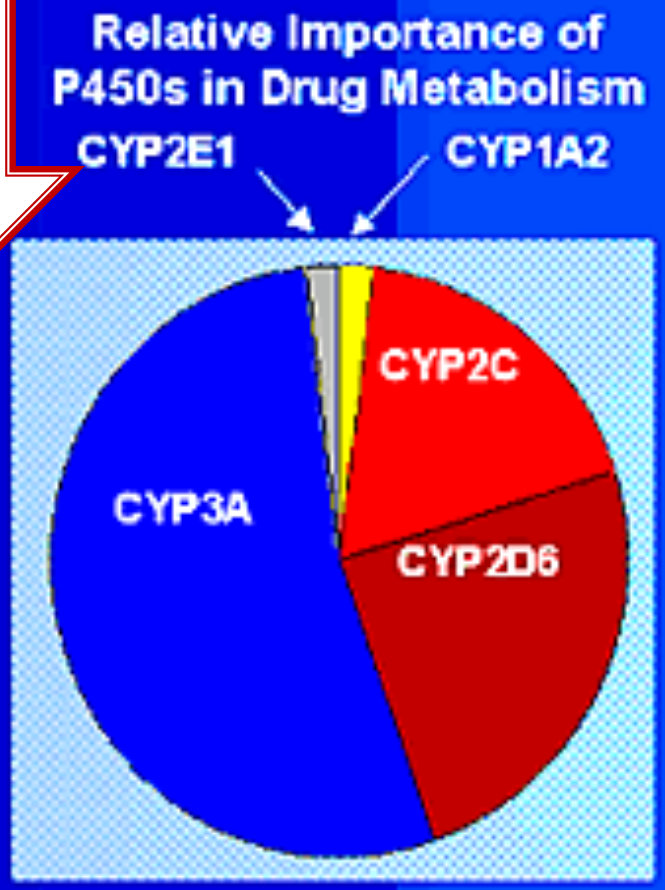
Cytochrome P450 Isoforms

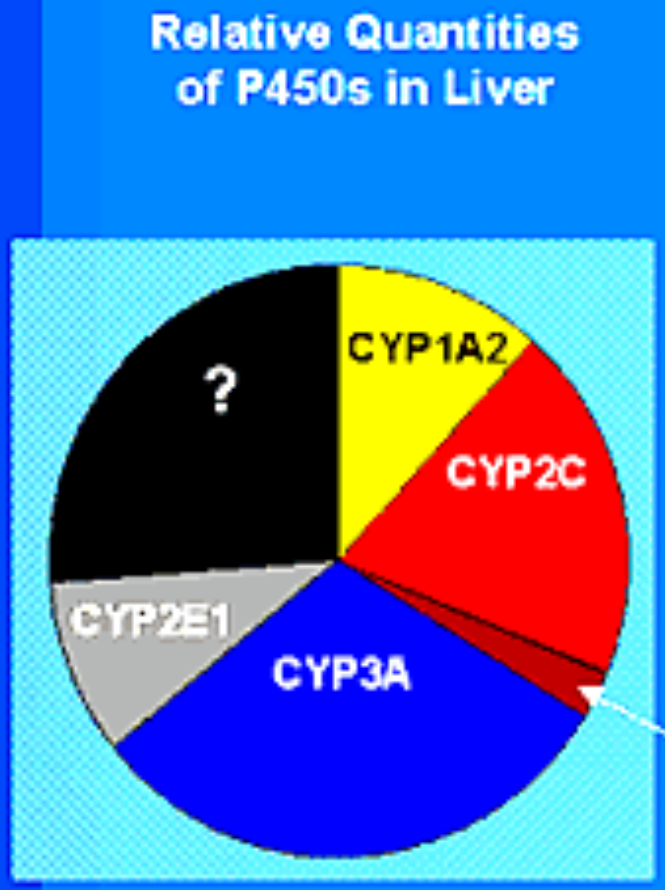
- CYP1A2
- CYP3A
- CYP2C9
- CYP2C19
- CYP2D6

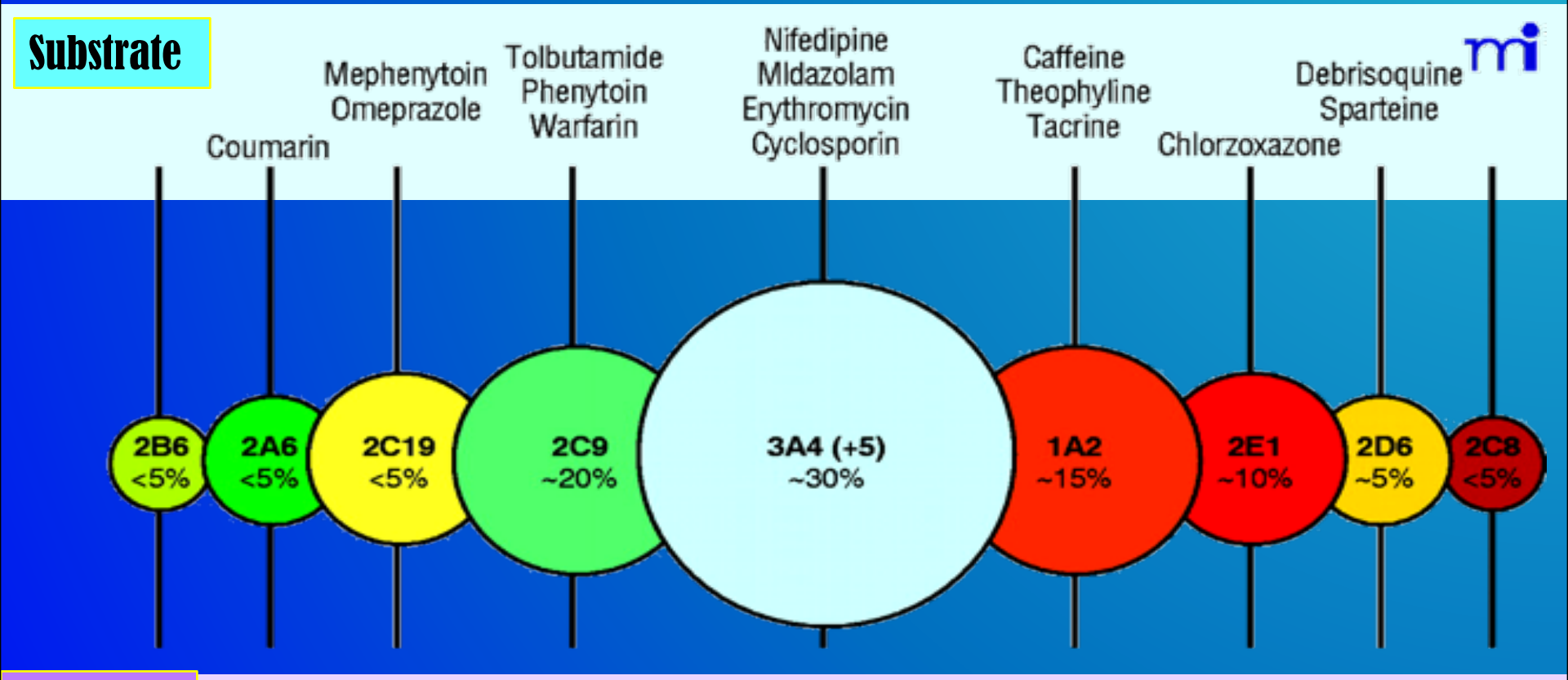
Distribution of different CYPs isoforms in the liver.



CYP450 → Major Contributor to Phase I Metabolism







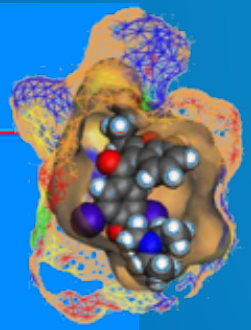
Inhibitors

Methoxsalen	Fluconazole	Sulfaphenazole	Ketoconzaole Gestodene	Furafylline Fluvoxamine	Disulfirma	Quinidine

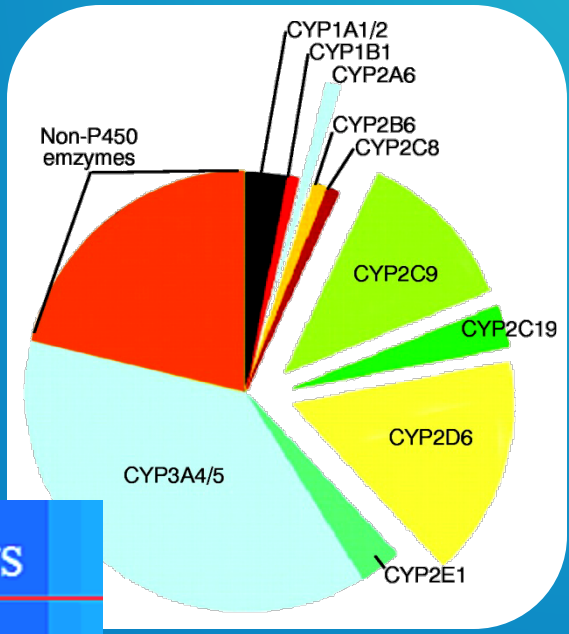
Inducers

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

Cytochrome P450 3A

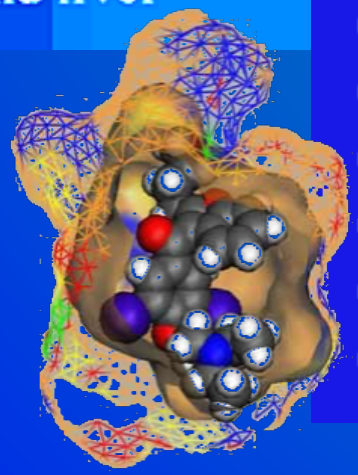


- Responsible for metabolism of:
  - Most calcium channel blockers
  - Most benzodiazepines
  - Most HIV protease inhibitors
  - Most HMG-CoA-reductase inhibitors
  - Cyclosporine
  - Most non-sedating antihistamines
  - Cisapride
- Present in GI tract and liver



CYP3A Inhibitors

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

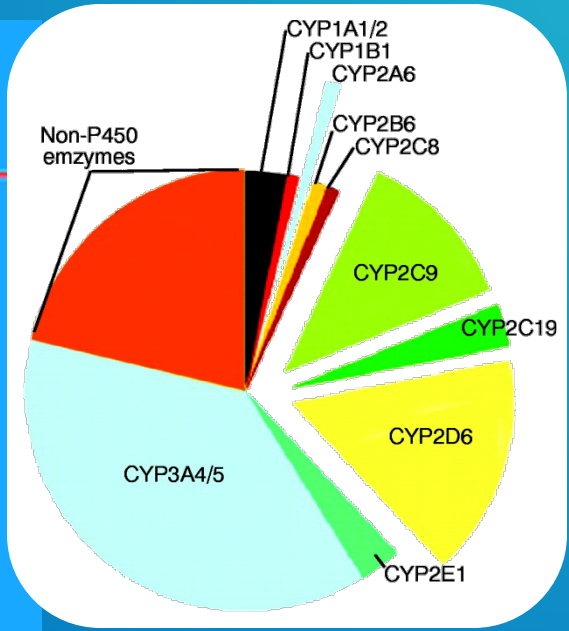


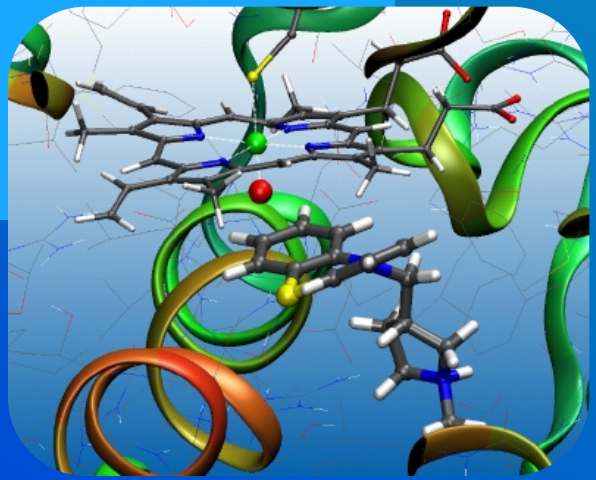
CYP3A Inducers

- Carbamazepine
- Rifampin
- Rifabutin
- Ritonavir

Cytochrome P450 2D6

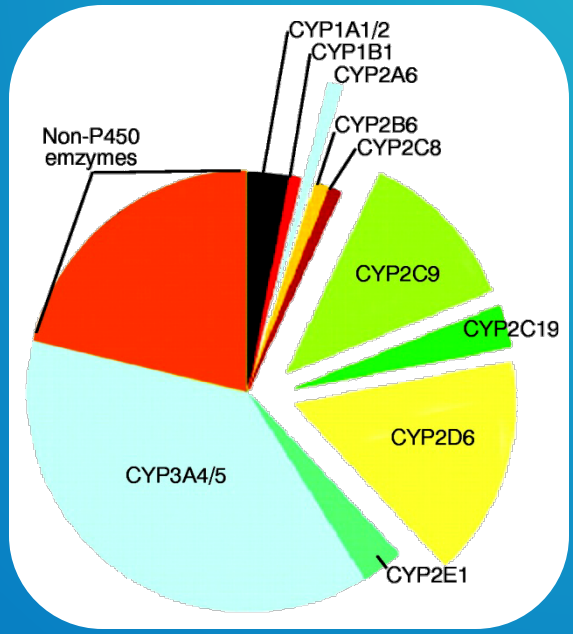
- Absent in 7% of Caucasians, 1–2% non-Caucasians
- Hyperactive in up to 30% of East Africans
- Catalyzes primary metabolism of:
  - Codeine
  - Many β-blockers
  - Many tricyclic antidepressants
- Inhibited by:
  - Fluoxetine
  - Haloperidol
  - Paroxetine
  - Quinidine

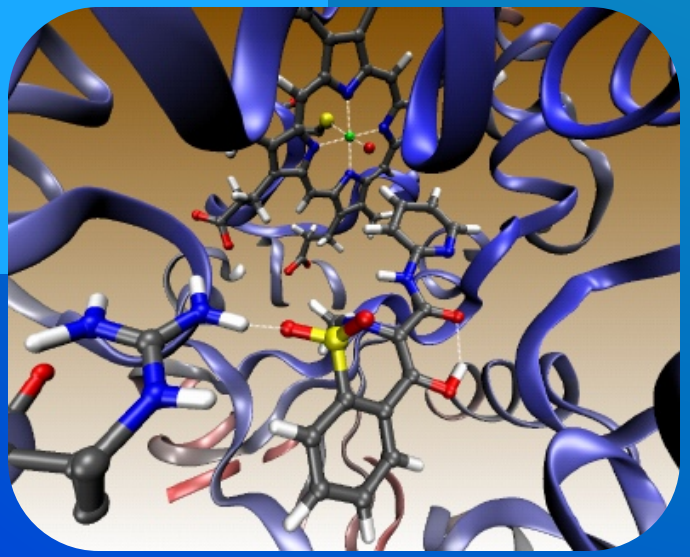




Cytochrome P450 2C9

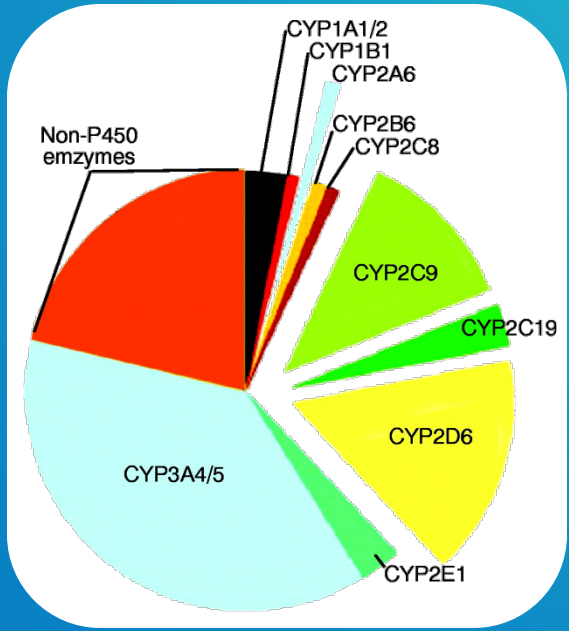
- Absent in 1% Caucasians and African-Americans
- Primary metabolism of:
  - Most NSAIDs (including COX-2)
  - S-warfarin (the active form)
  - Phenytoin
- Inhibited by:
  - Fluconazole

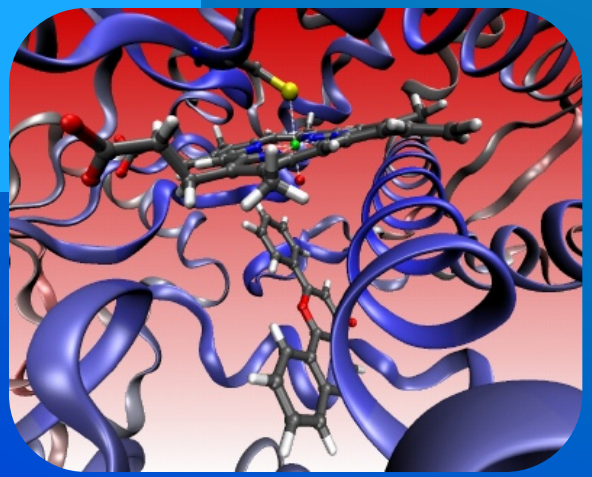




Cytochrome P450 1A2

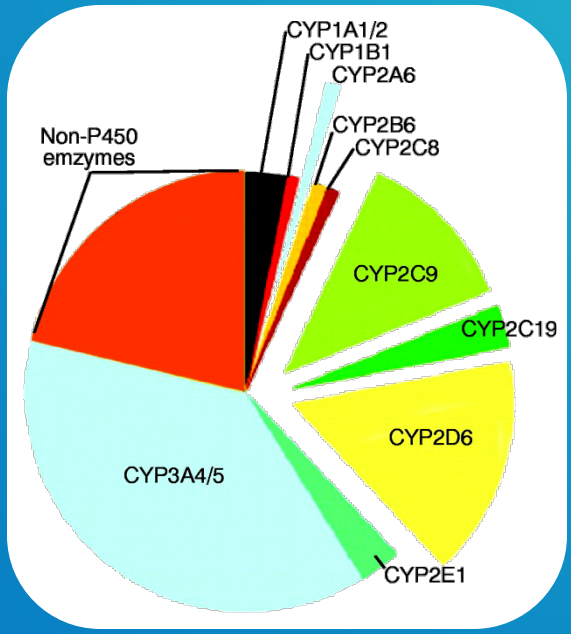
- Induced by smoking tobacco
- Catalyzes primary metabolism of:
  - Theophylline
  - Imipramine
  - Propranolol
  - Clozapine
- Inhibited by:
  - Many fluoroquinolone antibiotics
  - Fluvoxamine
  - Cimetidine

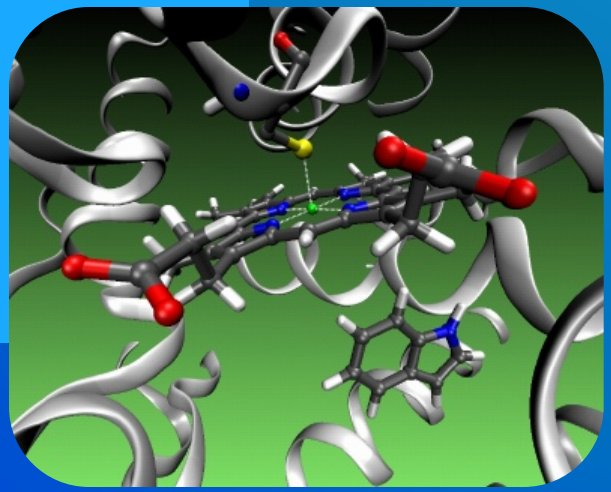




Cytochrome P450 2C19

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





CYT P450 3A4

Substrates	Inducers	Inhibitors
Immunosuppressants Cyclosporine Azole Antifungals Fluconazole Antibiotics Erythromycin, Clarithromycin Ca channel blockers Amlodepine, Verapamil Statins; Atorvastatin Amidarone Cancer Chemotherapy: Cyclophosphamide, Tamoxifen Non-Sedating Antihistaminics Astamizole Benzodiazipines Midazolam, Clonazepam	Protease Inhibitors Ritonavir Cimetidine Chloramphenicol Nefazadone Grape Fruits	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 muscloskeletal 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, antianginals agent (perihexiline), antiarrhythmics (propafenone & metoprolol) is suppressed ➔ so side effects & toxicity develop. i.e.
   - Neuropathy after therapeutic doses of perihexiline
   - Bradycardias & arrhythmias on therapeutic dose of propafenone or metaprolol
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

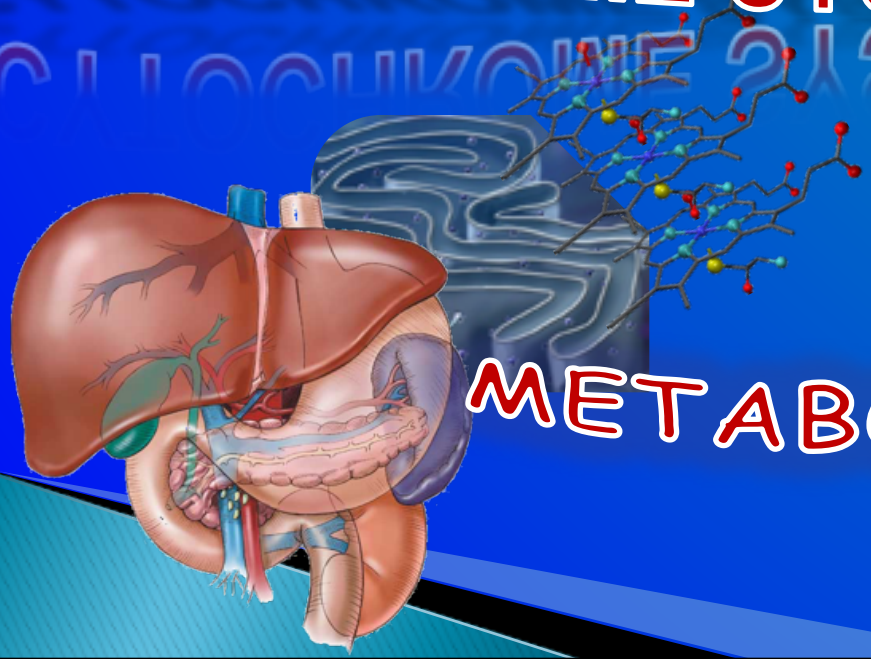
This has been an advantage as in those variants → ↑ cure rates in peptic ulcer patient with He*licobacter pylori*.

Benefit

CYTOCHROME SYSTEM

&

DRUG METABOLISM



GOOD LUCK