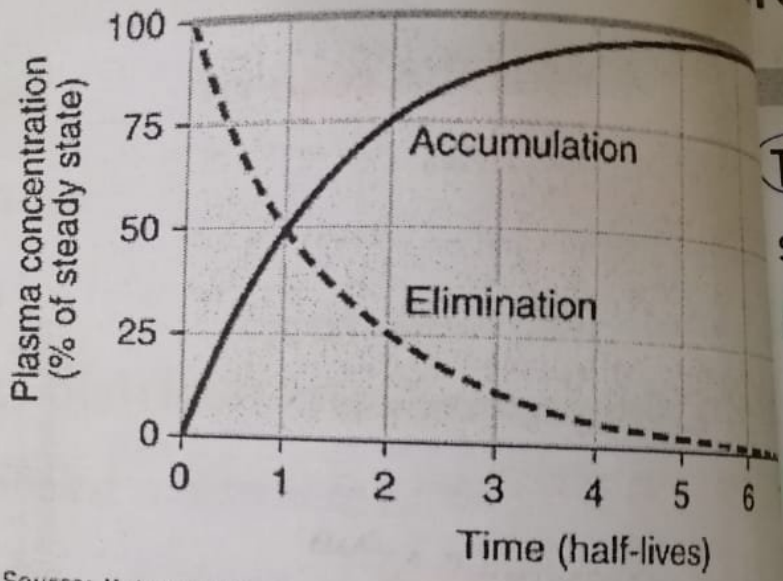
concentration of medication

Half-life

الوقت اللازم للتخلص من نصف الدواء

- Half-life ($t_{1/2}$) is the time required to change the amount of drug in the body by one-half during 50% elimination (or during a constant infusion).
- Like clearance, half-life is a constant for drugs that follow first-order kinetics.
- Disease, age, and other variables usually alter the clearance of a drug and thus will change the $t_{1/2}$.



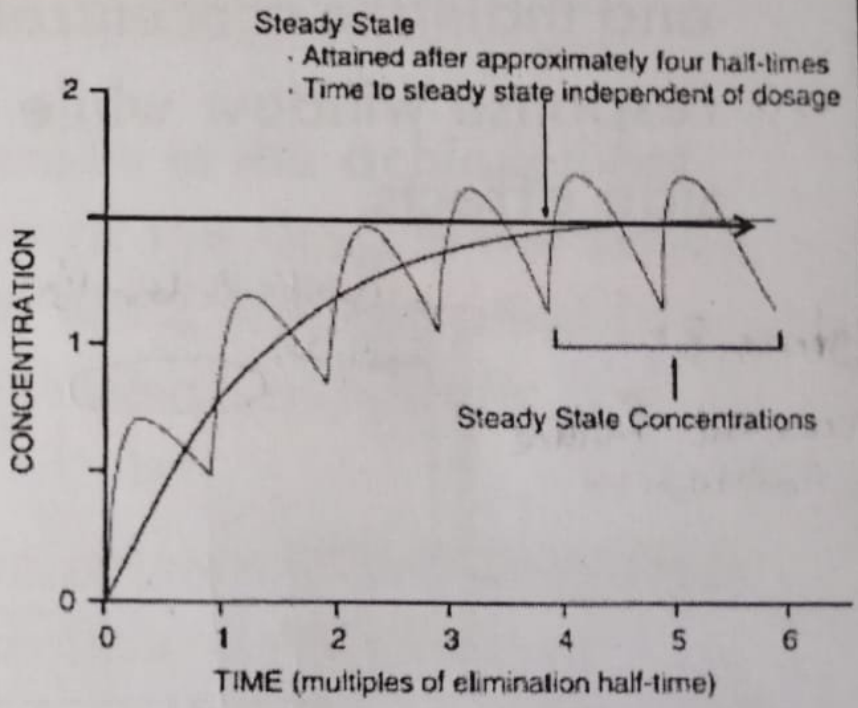
Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharm*
www.accessmedicine.com

determin half-life of drug

Steady state حالة الثبات

تركيز الدواء اصبح ثابت

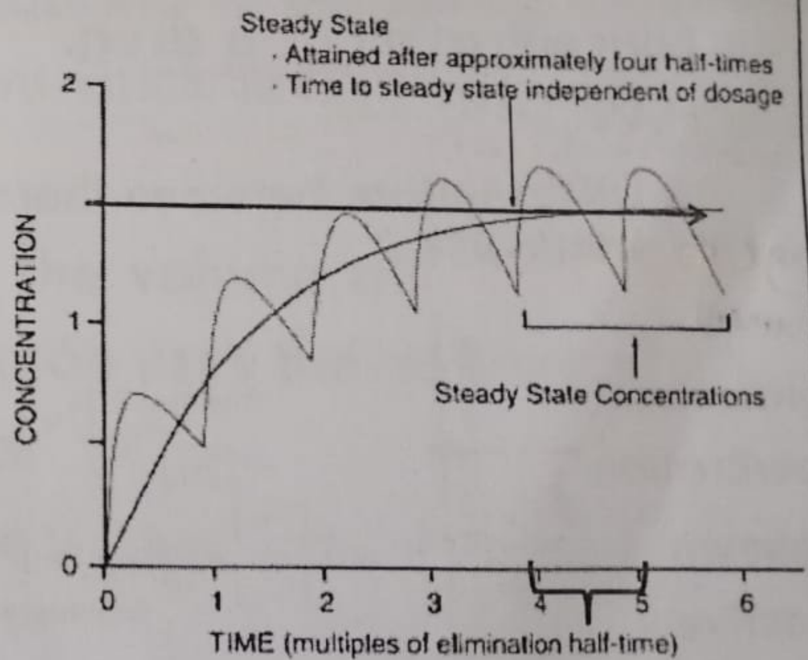
- Steady state is the condition in which the average total amount of drug in the body does not change over multiple dosing cycles; the condition in which the rate of drug elimination equals the rate of administration.



multiple doses ← أغلب الأدوية تعطى

Steady state

- The time to reach steady state concentration is dependent on the half-life of the drug (its independent on the dosage regimen).
- Steady state is reached after 4-5 half lives.



dose + frequency + duration + root of administration

dosage regimen ال ع حاجة في ال

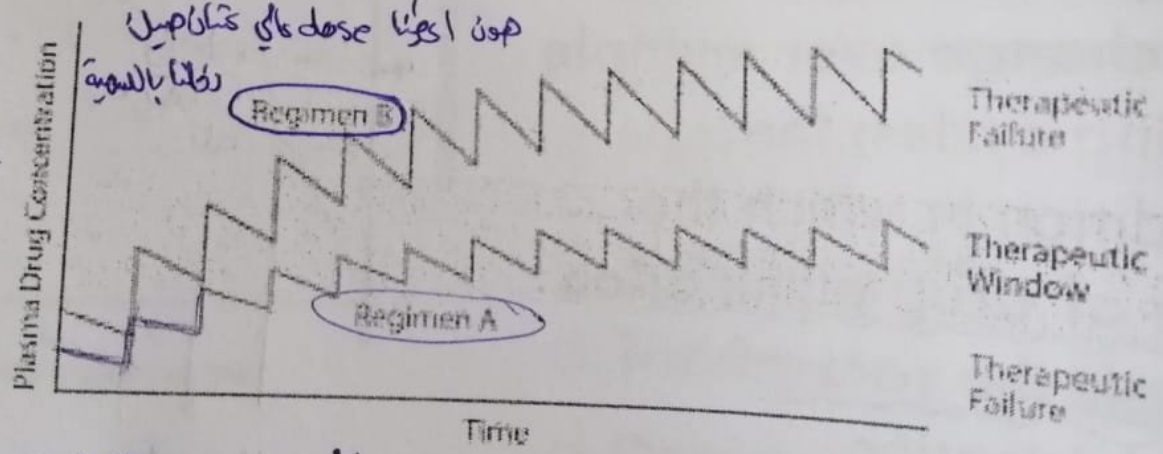
effective & toxic الفرق بين

Therapeutic window

the range between maximum minimum toxic dose & effective dose

- The goal of therapy with a given drug is to achieve and maintain concentrations within a therapeutic response window while minimizing toxicity and/or side effects.

Regimen B: treatment failure بسبب وصولنا السمية



A+B الـ frequency قليلة للاثنين

Therapeutic window

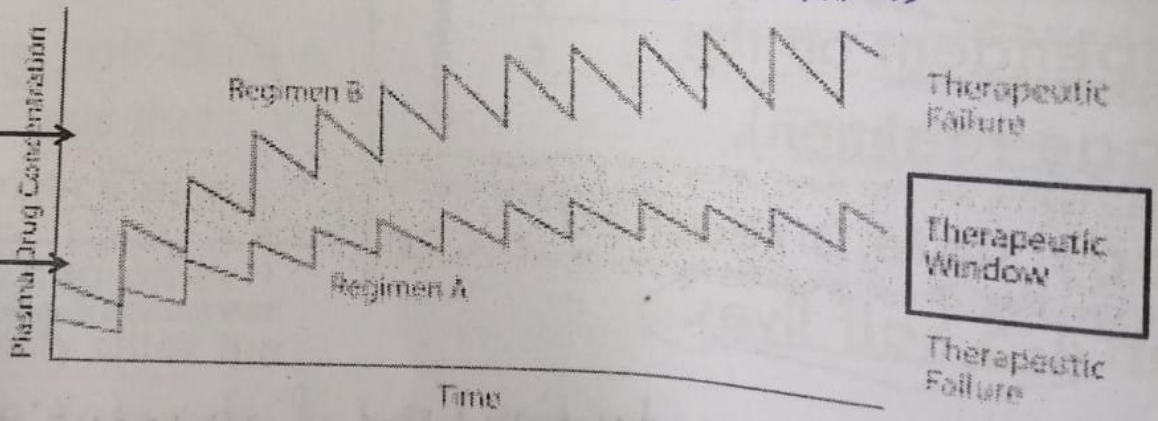
- The therapeutic window is the safe range between the minimum effective concentration and the minimum toxic concentration of a drug.
- H.W
  - Differentiate between therapeutic index and therapeutic window??

range ← in humans

ratio in animals

Minimum toxic concentration

Minimum effective concentration



Dosage regimens

- A dosage regimen is a plan for drug administration over a period of time.
- An optimal dosage regimen results in the achievement of therapeutic (effective) levels of the drug in the blood without exceeding the minimum toxic concentration (a steady state concentration within the therapeutic window).
- To maintain the plasma concentration within a specified range over long periods of therapy, a schedule of *maintenance doses* is used. If it is necessary to achieve the target plasma level rapidly, a *loading dose* is used.

Loading dose

- **Loading dose:** The dose required to achieve a specific plasma drug concentration level (Cp) with a single administration.
- Because this requires filling the volume of distribution (V_d), the calculation uses the volume of distribution (V_d) equation as:
  - Loading dose = C_p(target) x V_d; has units of mg

C_p = plasma concentration

V_d = Volume of distribution

Maintainance dose

- **Maintenance dose:** The dose required for regular administration to maintain a target plasma level.
- Because this requires restoring the amount of drug lost to elimination (clearance, CL), the calculation uses the clearance equation as:
  - Maintenance dose = C_p(target) x CL; has units of mg per time

hour

أي شيء مربط بالوقت يكون عبارة rate عن

Drug Biotransformation

metabolism

- **Biotransformation** is the process whereby a substance is changed from one chemical to another *(transformed)* by a chemical reaction within the body.

- When biotransformation results in metabolites of lower toxicity, the process is known as **detoxification**.

ازالة السمية

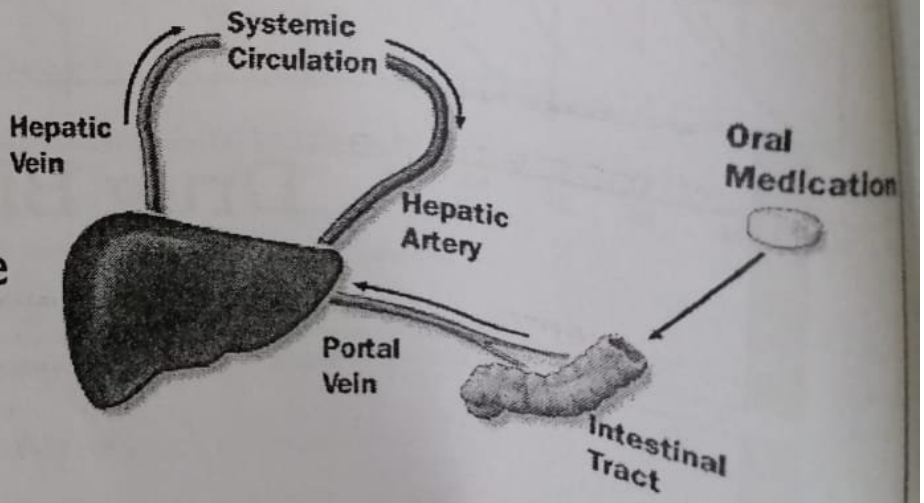
toxic → non toxic

ای مکان موجود فیه انزیمات یعنی

اي مكان موجود فيه انزيمات بيقدر يعمل metabolism

Where Do Drug Biotransformations Occur?

- Although every tissue has some ability to metabolize drugs, the liver is the principal organ of drug metabolism.
- Some drugs may undergo biotransformation in other tissues, such as the kidney and the intestines.
- After oral administration, many drugs are absorbed intact from the small intestine and transported first via the portal system to the liver, where they undergo extensive metabolism. This process is called the **first-pass effect.**



Why Is Drug Biotransformation Necessary?

the main site of excretion is the kidney

- Renal excretion plays a pivotal role in terminating the biologic activity of drugs, particularly those that possess polar characteristics.
- The kidney can't efficiently eliminate lipophylic drugs that readily cross plasma membranes and they are reabsorbed from the urine in the renal tubules.
- However, most drugs are relatively lipid soluble as given, a characteristic needed for absorption across membranes.
- Biotransformation is needed to turn nonpolar compounds into polar ones so that they are easily excreted by the kidney.

كيفان يغير الو excretion خارج الجسم [تحويل الدواء من lipophilic → hydrophi
non-Polar → polar

Drug Biotransformation

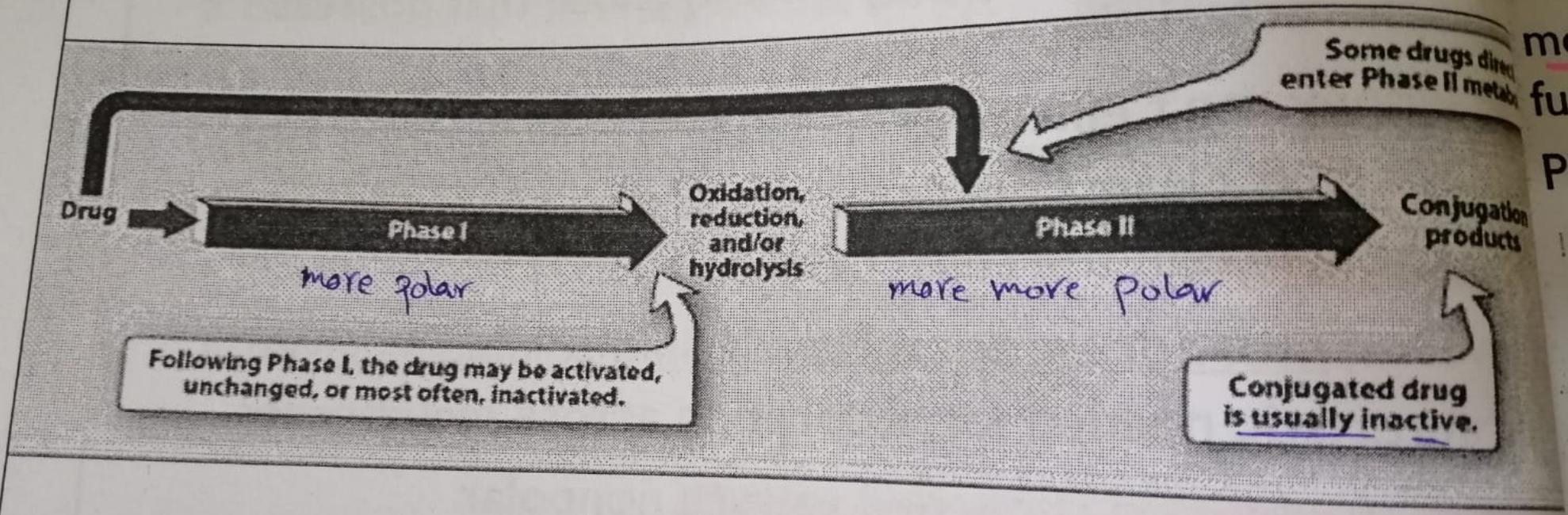
- Biotransformation is the process whereby a substance is changed from one chemical to another (transformed) by a chemical reaction within the body.

- It is an important mechanism by which the body *terminates* the action of many drugs.
- In some cases, it serves to *activate* prodrugs (Drugs that are initially administered as inactive compounds and must be metabolized to their active forms)

Likes proton pump inhibitor

Reactions Of Biotransformation

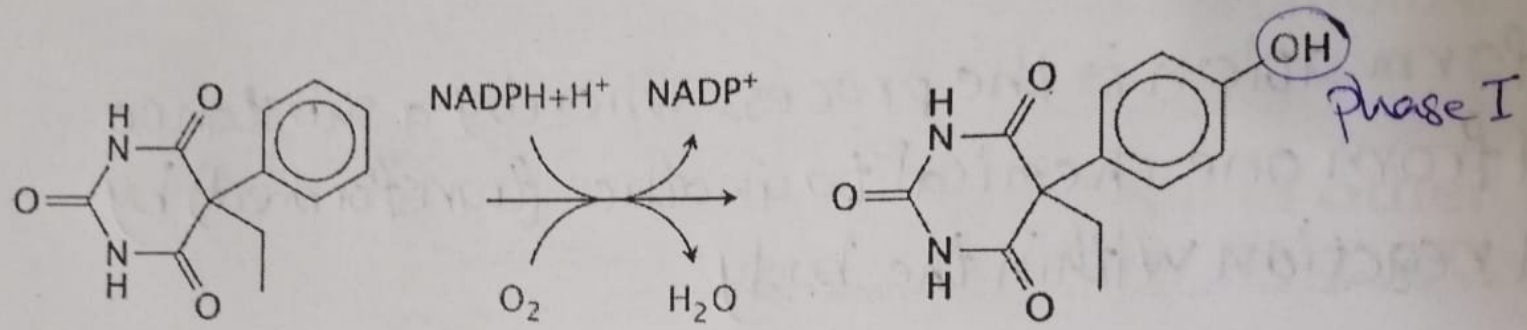
- Phase I reactions
- Phase II reactions



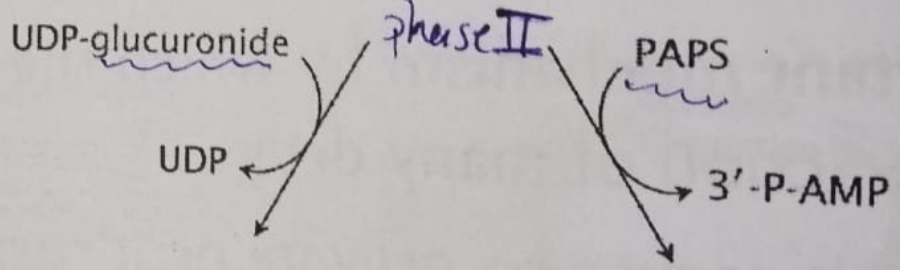
phase II & conjugation.

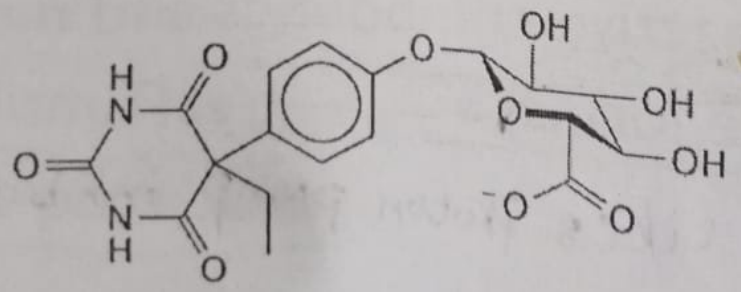
Example...
Metabolism of phenobarbital

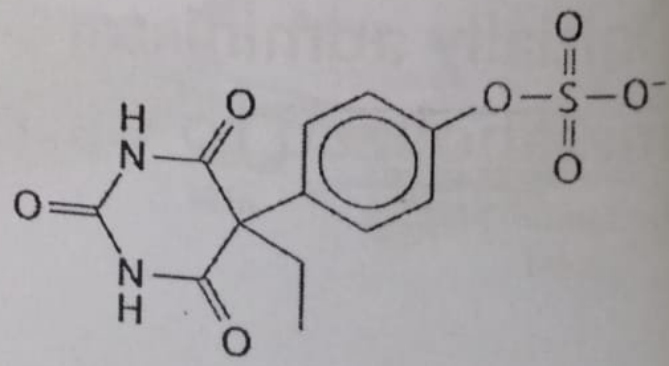
يعالج التخلص الزائد.



- non-polar drug







Phase I reactions

- Phase I reactions usually convert the parent drug to a more polar metabolite by introducing or unmasking a functional group (–OH, –NH_2, –SH).
- Phase I reactions include:

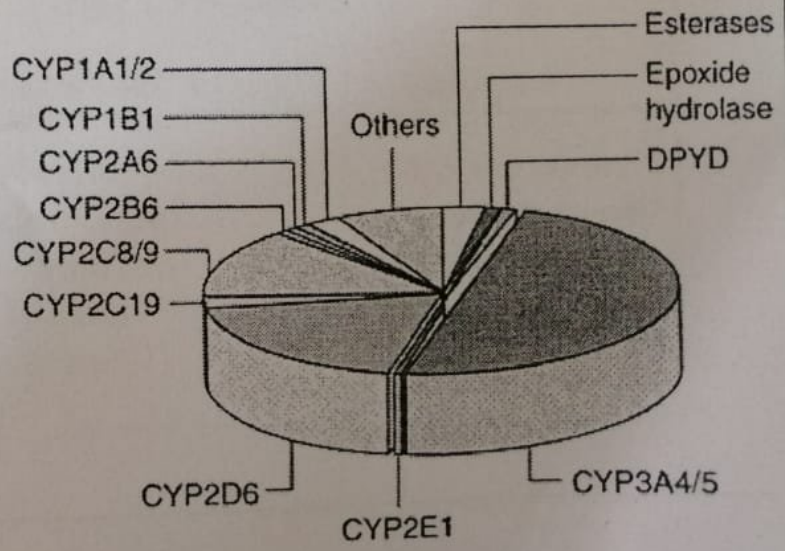
تقريباً مسؤولة عن ٧٥٪ من Biotransformation

1. Oxidation especially by the **cytochrome P450** group of enzymes (also called **mixed-function oxidases**)
2. Reduction
3. Deamination
4. Hydrolysis.

- Often these metabolites are inactive, although in some instances activity is only modified or even enhanced.
  - Example: Losartan is converted to its active form by CYP2C9.

Summary of P450 enzymes

- The P450 system is important for the metabolism of many endogenous compounds (steroids, lipids, etc.) and for the biotransformation of exogenous substances (xenobiotics).
- Cytochrome P450 enzymes (abbreviated as CYP450) are found in high concentrations in the smooth endoplasmic reticulum of the liver.
- They are not highly selective in their substrates, so a relatively small number of CYP450 isoforms are able to metabolize thousands of drugs.
- Of the drugs metabolized by phase I cytochrome P450s, approximately 75% are metabolized by just two: CYP3A4 or CYP2D6.



CYP450 induction

- Some chemicals *induce* (increase) P450 expression by enhancing the rate of its synthesis or reducing its rate of degradation.
- Consequences of CYP450 induction:
  - Decreased drug activity if the metabolite is inactive.
  - Increased drug activity if the metabolite is active.
  - Increased drug toxicity if the metabolite is toxic.

CYP450 induction

- Several drugs can induce CYP450.
- Moreover, exposure to benzo[*a*]pyrene and other polycyclic aromatic hydrocarbons, which are present in tobacco smoke and charcoal-broiled meat is known to induce CYP1A enzymes and to alter the rates of drug metabolism.

Isozyme: CYP3A4/5

COMMON SUBSTRATES	INDUCERS
Carbamazepine	*Carbamazepine*
Cyclosporine	*Dexamethasone*
Erythromycin	*Phenobarbital*
Nifedipine	*Phenytoin*
Verapamil	*Rifampin*

CYP450 inhibition

- The most common form of inhibition is through competition for the same isozyme.
- The more important CYP inhibitors are erythromycin, ketoconazole, and ritonavir, because they each inhibit several CYP isozymes.
- Natural substances such as grapefruit juice may inhibit drug metabolism.
- Inhibition of drug metabolism may lead to increased plasma levels over time with long-term medications, prolonged pharmacological drug effect, and increased drug-induced toxicities.

Phase II reactions

- Phase II reactions involve addition (conjugation) of subgroups to —OH, —NH_2, and —SH functions on the drug molecule.
- The subgroups that are added include glucuronate, acetate, glutathione, glycine, sulfate, and methyl groups.
- Most of these groups are relatively polar and make the product less lipid-soluble than the original drug molecule.
- Like phase I enzymes, phase II enzymes are not very selective.

Phase II reactions

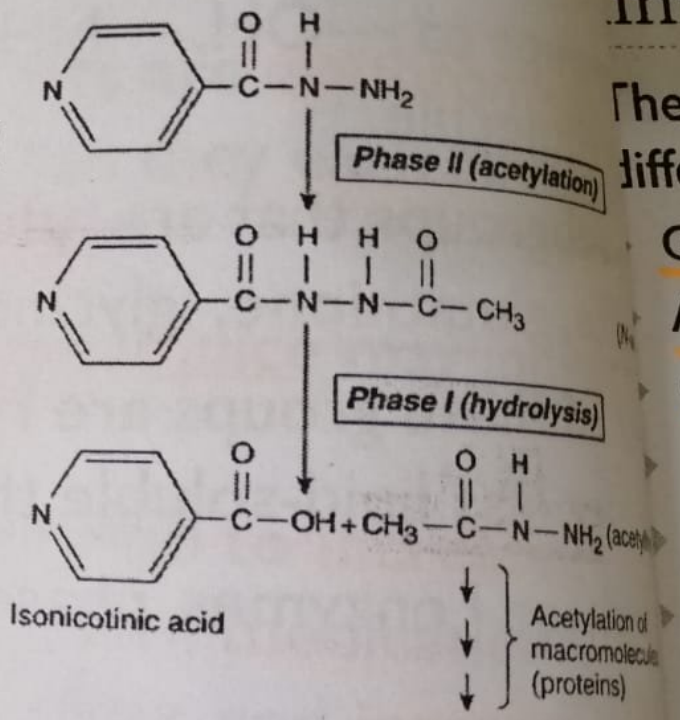
- Neonates are deficient in this conjugating system, making them particularly vulnerable to drugs such as chloramphenicol, which is inactivated by the addition of glucuronic acid.

Gray baby syndrome

Neonatal jaundice

Phase II reactions

- Drugs already possessing a suitable functional group (i.e. —OH, —NH_2) may enter Phase II directly and become conjugated without prior Phase I metabolism.
- Not all drugs undergo Phase I and II reactions in that order. For example, isoniazid is first acetylated (a Phase II reaction) by N-acetyltransferase and then hydrolyzed to isonicotinic acid (a Phase I reaction).



Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharmacology*
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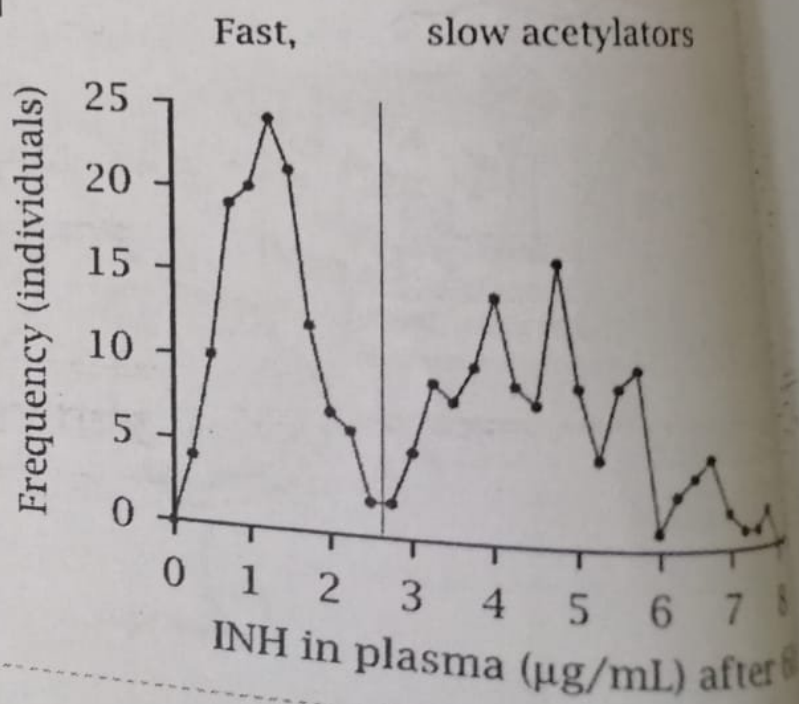
Fast vs. Slow Acetylators

- About 50% of blacks and whites in the USA are slow acetylators.
- The defect in slow acetylators of isoniazid and similar amines appears to be caused by the synthesis of less enzyme rather than an abnormal form of it.
- Slow acetylation may lead to higher blood levels of the drug and thus, to an increase in toxic reactions.



Clinical Relevance Of Drug Metabolism

- The rate of biotransformation can vary markedly between different individuals due to:
  - Genetic differences
  - Age
  - Gender
  - Diet and environmental factors
  - Disease state
  - Other medications

- Variations in drug metabolism must be considered when designing or modifying a dosage regimen.

Artery Academy

Done by Lama Nofal