PHARMACOKINETICS – METABOLISM

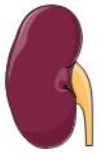
4.1 DRUG METABOLISM

- Metabolism is the enzyme mediated alteration of a drug's structure.
- Metabolism is also referred to as biotransformation.
- Sites of drug metabolism include:

Liver – primary site of drug metabolism.

Intestine – Enterocytes that line the gut are able to metabolize drugs.

Stomach – A site for the metabolism of alcohol.

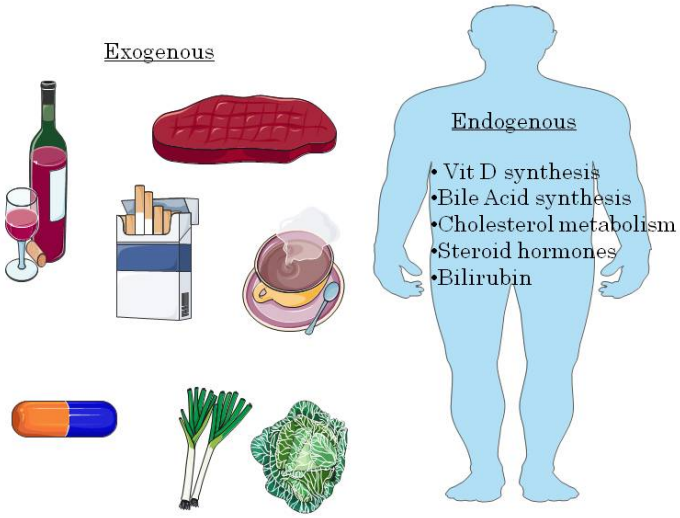


Kidney – Underappreciated as a metabolic organ.

Intestinal Bacteria – Normal bacterial flora play an important role in drug metabolism.

Why do we need drug metabolism?

- Drug metabolism is important in humans to protect us from a number of environmental toxins as well as synthesize essential endogenous molecules.
- A summary of common exogenous toxins that drug metabolism protects us from are summarized below. Similarly, essential endogenous molecules synthesized by drug metabolizing enzymes are shown.
- Note that even things like vegetables considered to be healthy would by toxic if we didn't have enzymes to process them!



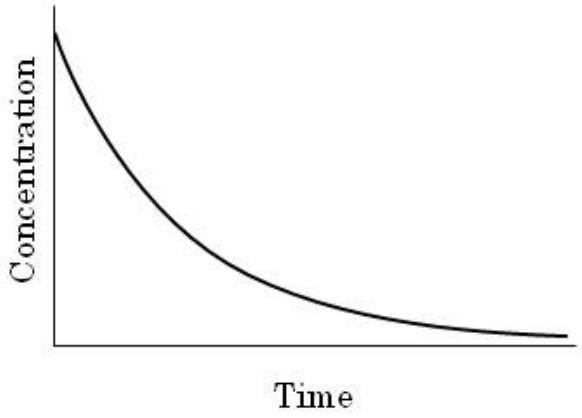
Therapeutic Consequences of Drug Metabolism

- Drug metabolism can have several different consequences.
- Therapeutic consequences of drug metabolism are summarized below:
    1) **Increase water solubility of drugs to promote their excretion**
       Lipophilic → Hydrophilic
    2) **Inactivate drugs**.
       Active → Inactive
    3) **Increase drug effectiveness**
       Active → More active
    4) **Activate prodrugs (prodrugs are inactive until metabolized)**
       Prodrug (inactive) → Active drug
    5) **Increase drug toxicity**
       Non-toxic → Toxic

4.2 KINETICS OF DRUG METABOLISM

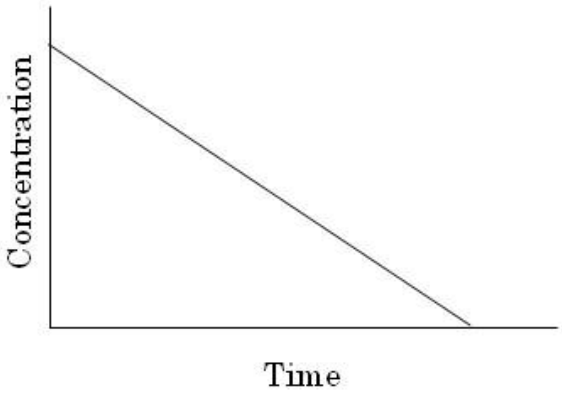
First Order

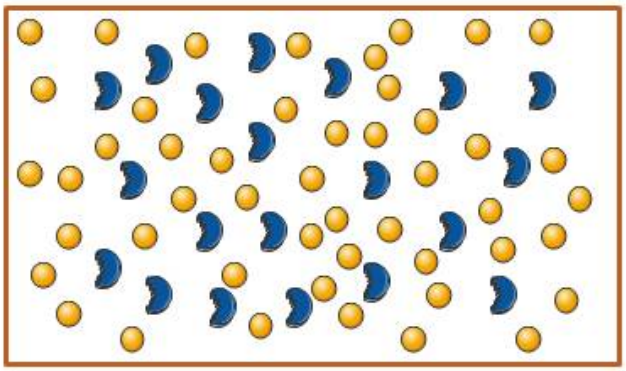
- In most clinical situations the concentration of drug is much lower than the metabolic capacity of the body. In these situations drug metabolism displays 1st order kinetics.
- In 1st order kinetics drug metabolism is directly proportional to the concentration of free drug.
- This means a constant **fraction** of drug is metabolized per unit time.
- The figure on the right shows an example of 1st order metabolism. The top panel shows how the plasma concentration changes over time. Notice how the concentration decreases faster when there are higher drug concentrations than at the end when the drug concentrations are low. The bottom panel shows the amount of drug and the amount of enzyme. Notice how there is much more enzyme than there is drug. This is typical in drugs that display first order metabolism.



Zero Order

- In zero order kinetics, the plasma drug concentration is much higher than the metabolic capacity of the body.
- In zero order kinetics drug metabolism is constant over time.
- This means a constant **amount** of drug is metabolized per unit time.
- One of the best examples of zero order kinetics is ethanol.
- The figure in the right shows an example of zero order metabolism. The top panel shows how the plasma concentration changes over time. Notice how a constant amount of drug is eliminated over time. This means that the metabolism is independent of drug concentration. The bottom panel shows the amount of drug and the amount of enzyme. Notice this time how there is much more drug than there is enzyme. This is typical in drugs that display zero order metabolism.





= Drug

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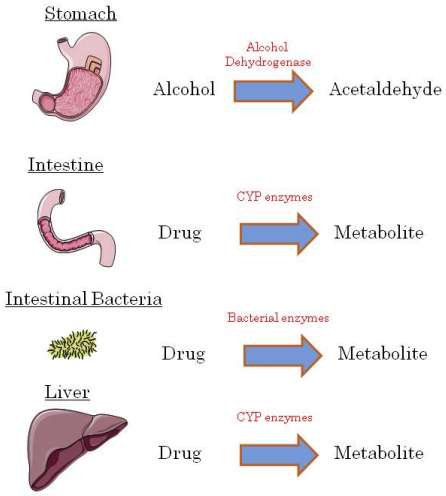
4.3 FIRST PASS METABOLISM

- PO drugs may undergo significant metabolism prior to entering the systemic circulation. This is called 1st pass metabolism.
- First pass metabolism can occur via:

1. Hepatocytes in the liver
2. Intestinal enterocytes
3. Stomach
4. Intestinal bacteria

- The result of 1st pass metabolism is a decreased amount of parent drug that enters systemic circulation.



Extraction Ratio

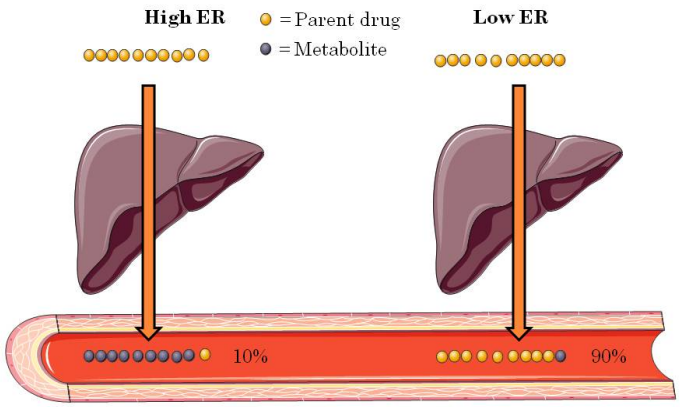
- The amount of metabolism on the first pass through the liver can greatly determine a drug's bioavailability.
- Drugs are characterized as having high or low extraction ratio (ER) depending on how much metabolism occurs on the first pass through the liver.

High ER Drugs

- Have low oral bioavailability (1- 20%)
- PO doses are usually much higher than IV doses (to compensate for high first pass metabolism).
- Small changes in hepatic enzyme activity produce large changes in bioavailability.
- Very susceptible to drug-drug interactions

Low ER Drugs

- Have high oral bioavailability (> 80%) PO doses are usually similar to IV doses.
- Small changes in hepatic enzyme activity have little effect on bioavailability.
- Not very susceptible to drug-drug interactions.
- Take many passes through the liver via the systemic circulation before they are completely metabolized.



4.4 TYPES OF DRUG METABOLISM

- Drug metabolism is broadly divided into 2 phases, phase I metabolism and phase II metabolism.

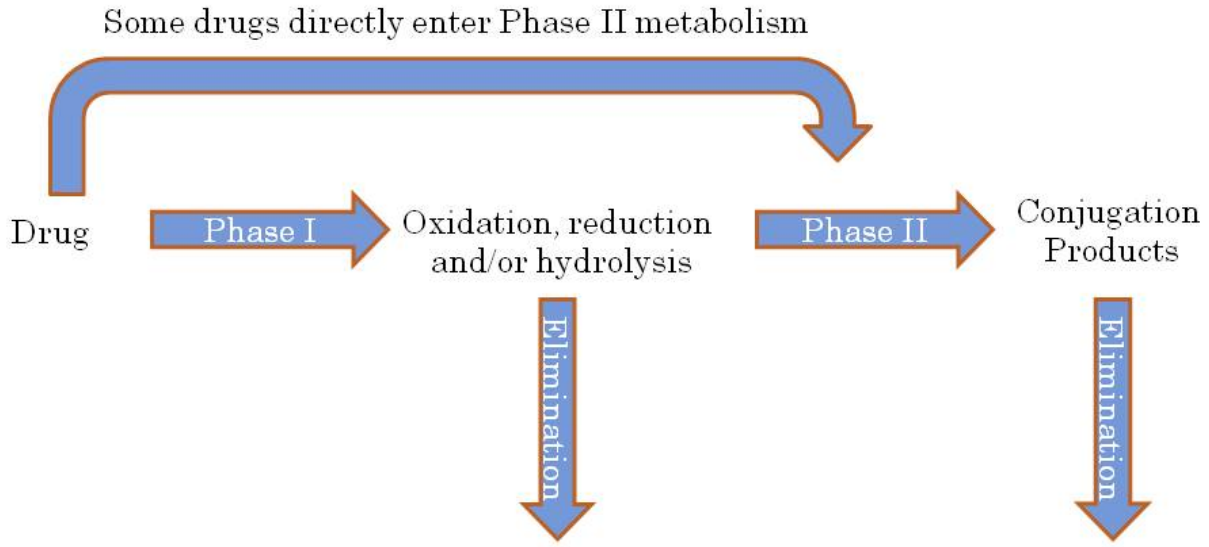
Phase I metabolism

- Convert lipophilic drugs to more polar molecules by introducing or unmasking polar functional groups such as hydroxyl (-OH) or amine ($-NH_2$).
- Involves oxidation, reduction and hydrolysis reactions.
- Mediated by cytochrome P450 enzymes, esterases and dehydrogenases.
- Metabolites formed can be more active, less active or equally active as the parent drug.

Phase II Metabolism

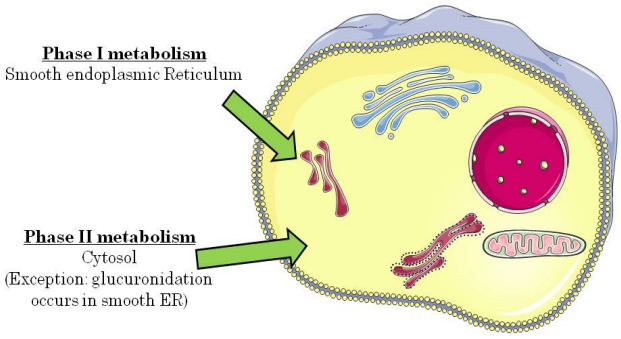
- Increase the polarity of lipophilic drugs by conjugation reactions (addition of large water soluble molecule to drug).
- Conjugates include glucuronic acid (a sugar), sulfate ($-SO_4$), acetate or amino acids (i.e. glycine).
- Metabolites are less active than the parent drug.

Exception: Morphine 6-glucuronide is a more potent analgesic (pain reliever) than morphine.



Intracellular Site of Drug Metabolizing Enzymes

Phase I – Phase I drug metabolizing enzymes are localized to the smooth endoplasmic reticulum (ER).
Phase II – Phase II drug metabolizing enzymes are localized predominantly in the cytosol of the cell with the exception of glucuronidation which is localized to the smooth ER.

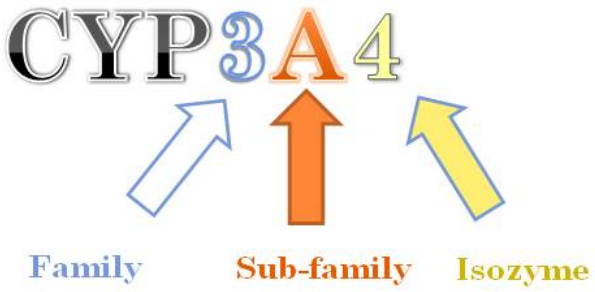


4.5 CYTOCHROME P-450 DRUG METABOLIZING ENZYMES

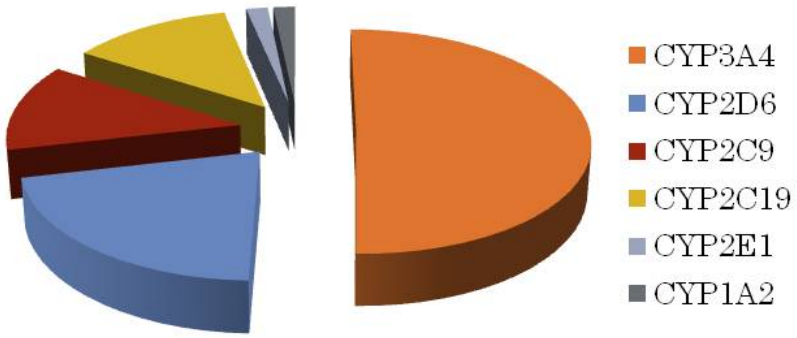
- CYPs are a large family of drug metabolizing enzymes.
- CYPs are the predominant phase I drug metabolizing enzyme system.
- The majority of drug metabolism in the body is performed by hepatic CYP enzymes.
- CYPs oxidize drugs by inserting one atom of oxygen into the drug molecule producing water as a by product.

$$Drug + O_2 + NADPH + H^+ \rightarrow Drug_{oxidized} + H_20 + NADP^+$$

- There are 12 families of CYPs with 3 accounting for the majority of drug metabolism.
- Malnutrition can decrease CYP activity as these enzymes require dietary protein, iron, folic acid and zinc for full activity.
- Nomenclature:



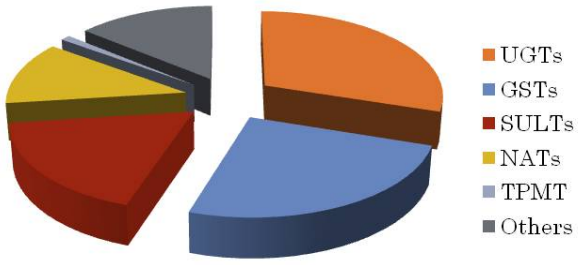
- CYP3A4 metabolizes the largest fraction of currently marketed drugs.



4.6 PHASE II DRUG METABOLIZING ENZYMES

- Phase II drug metabolizing enzymes include:

1. UDP-glucuronosyltransferases (UGTs)
2. Sulfotransferases (SULTs)
3. Glutathione S Transferases (GSTs)
4. N-acetyltransferases (NATs)
5. Thiopurine Methyltransferase (TPMT)



- Unlike CYPs, the fraction of drugs metabolized by phase II enzymes is relatively equally split between UGTs, SULTs, GSTs and NATs.

1. UDP-glucuronosyltransferases (UGTs)
   - Are localized in the smooth endoplasmic reticulum and are part of phase II drug metabolism.
   - Catalyze the transfer of a glucuronic acid (sugar) to a drug.
   - Glucuronidated drugs are more polar and therefore more easily excreted.
   - There are 19 human UGT enzymes.

UGT

Drug + UDP-glucuronic acid → drug-glucuronide + UDP

2. Sulfotransferases (SULTs)
   - Are cytosolic phase II drug metabolizing enzymes.
   - Catalyze the transfer of a sulfate group to a hydroxyl group of drugs.
   - Sulfated drugs are more polar and therefore more easily excreted.
   - There are 11 human SULT enzymes.

SULT

Drug + sulfate → drug-sulfate

3. Glutathione S Transferases (GSTs)
   - Are phase II drug metabolizing enzymes that may be cytosolic or microsomal.
   - Catalyze the transfer of a glutathione molecule to a drug.
   - Glutathione (GSH) is an intracellular anti-oxidant.
   - Transfer of a glutathione onto a reactive (i.e. toxic) drug renders the metabolite less toxic.
   - There are over 20 human GST enzymes.

GST

Reactive Drug + GSH → drug-GSH

4. N-acetyltransferases (NATs)
   - Are cytosolic phase II drug metabolizing enzymes.
   - Catalyze the transfer of an acetyl group from acetyl CoA to a drug.
   - Subject to genetic polymorphisms which is a major cause in variability to drug response.
   - There are 2 human NAT enzymes, NAT 1 and NAT2.

NAT

Drug + Acetyl CoA → Acetylated Drug + CoA

5. Thiopurine Methyltransferase (TPMT)
   - Are cytosolic phase II drug metabolizing enzymes.
   - Catalyze the transfer of a methyl group from S-adenosylmethionine to a drug.
   - Subject to genetic polymorphisms. Although rare, these polymorphisms have dramatic effect on drug safety (more later).

TPMT

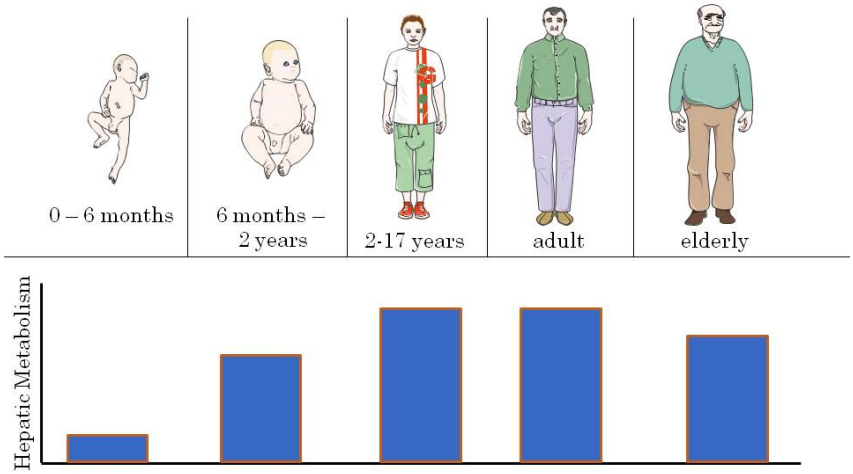
Drug + S-adenosylmethionine → Drug-CH_3 + Methionine

4.7 FACTORS AFFECTING DRUG METABOLISM

- There are a number of factors that affect drug metabolism. These include:
    1. Age
    2. Drug interactions (enzyme inducers and enzyme inhibitors).
    3. Disease state
    4. Genetic Polymorphisms

1. Age

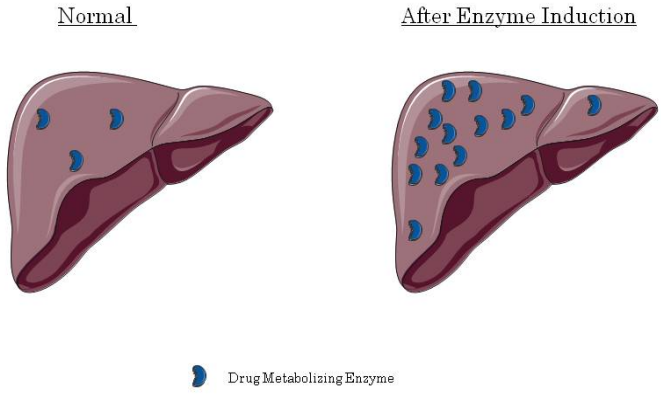
- The expression and activity of drug metabolizing enzymes changes as we age.
- For example, infants have almost no CYP activity. It takes babies approximately 1 year after birth until they have a reasonable level of drug metabolizing enzymes.
- By age 2, babies have the same amount of drug metabolizing enzymes as adults do.



2. Drug interactions (enzyme inducers and enzyme inhibitors)

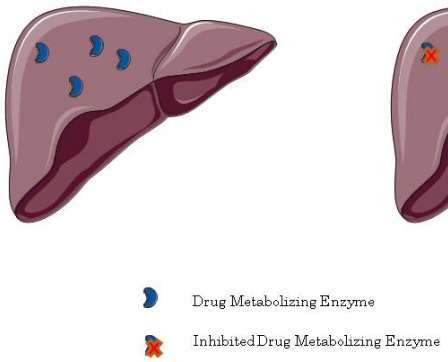
Enzyme Induction

- Induction is a process where a cell synthesizes an enzyme in response to a drug or other chemical.
- Certain CYP isozymes are susceptible to induction by drugs.
- The consequence of CYP induction is increased drug metabolism.
- Enzyme induction plays an important role in drug interactions (more later).



- Consequences of increased drug metabolism may include:
    1. Decreased plasma drug concentration.
    2. Decreased drug activity (if metabolite is inactive).
    3. Increased drug activity (if metabolite is active).

Enzyme Inhibition



- Some drugs and natural compounds can inhibit CYPs.
- The consequence of CYP inhibition is decreased drug metabolism.
- Decreased drug metabolism may result in:
    1) Higher plasma drug concentration.
    2) Increased therapeutic effect of drugs.
    3) Increased drug toxicity.

3. Disease state

- Disease can play a critical role in determining CYP activity.
- Diseases that decrease CYP activity include:
    1) Liver disease
    2) Kidney Disease
    3) Inflammatory diseases
    4) Infection

4. Genetic Polymorphisms

- Genes for some drug metabolizing enzymes have genetic polymorphisms also known as single nucleotide polymorphisms (SNPs).
- A SNP is a change of a single nucleotide (A, T, G or C) in our DNA.
- SNPs often affect the protein (i.e. drug metabolizing enzyme) that is produced.
- There are a number of SNPs in drug metabolizing enzymes that cause pronounced differences to the response of drugs.

Phase I SNPs

CYP2C9

- Metabolizes the anticoagulant drug warfarin.
- Polymorphism of CYP2C9 results in an enzyme with decreased activity.
- Patients with a polymorphism in CYP2C9 require a lower dose of warfarin.
- If the dose is not lowered, patients may experience extensive bleeding, a side effect of warfarin.

CYP2D6

- Metabolizes codeine to morphine, morphine is a more potent analgesic than codeine.
- CYP2D6 has many genetic polymorphisms that can result in 4 distinct phenotypes: Ultra-rapid metabolizer (UM), Extensive metabolizer (EM), Intermediate metabolizer (IM) and poor metabolizer (PM).
- Extensive metabolizers are considered have normal enzymatic activity.
- Intermediate metabolizers have reduced metabolic activity whereas poor metabolizers have almost no metabolic activity.
- Ultra-rapid metabolizers have significantly increased CYP2D6 activity.
- Ultra-rapid metabolizers possess multiple copies of the CYP2D6 gene.

Phase II SNPs

UGT1A1

- Is part of the UGT family of enzymes.
- Glucuronidates the anti-cancer compound SN-38 (the active metabolite of irinotecan).
- Polymorphisms in UGT1A1 decrease its activity.
- Patients with UGT1A1 polymorphisms are at increased risk of diarrhea and dose limiting bone marrow suppression (potentially fatal).

NAT2

- Acetylates the drug isoniazid (used to treat tuberculosis), caffeine and various cancer causing chemicals.
- There are over 23 different SNPs in the NAT2 gene.
- Patients are classified as either rapid or slow acetylators based on their genotype.
- Slow acetylators are more susceptible to isoniazid toxicity (neuropathy, hepatotoxicity) than rapid acetylators.
- Slow acetylators have a higher risk for developing certain types of cancer.