للوصول الى guidance الفارما و تفاريغ المادة كاملة :

كل اعمال الفريق العلمي تنشر على قناة التيليغرام

تجدون في guidance مادة الفارما على موقع النادي :

BIOTRANSFORMATION

(Metabolism)

❖ **These are**: the chemical changes that occur to drugs after absorption until excretion.

- Drug metabolism occurs **mainly in the liver**, also in other organs, e.g. intestinal lumen or wall, lung, plasma, skin and kidney.
- The aim of drug metabolism is **the conversion of the lipophilic drug to a more polar (hydrophilic, ionized)** metabolite which is easily excreted in urine.
- The hydrophilic drugs usually do not undergo metabolism and secreted unchanged in urine

❖ Types of Biotransformation Reactions

Phase I (Non-Synthetic)

- Phase I reactions include: **oxidation** (1) - **reduction** (2) - **hydrolysis** (3). بصير تفاعل واحد منهم
- **The most important reaction is oxidation** * **by cytochrome P450 enzyme system.**
- Phase I reactions result in **unmasking of a polar group** (-OH, -SH, or -NH_2) **+O → an ionized metabolite** that can be easily excreted.

functional groups

Phase II (Synthetic)

- An **endogenous substrate**, (e.g. glucuronic acid *, glycine, glutathione, sulfate or acetic acid) is **conjugated with the functional group** of the drug or its metabolite → **nontoxic highly polar**, rapidly eliminated **conjugates.**
- **The most important is conjugated with glucuronic acid.**

The kidney cannot efficiently excrete lipophilic drugs that readily cross cell membranes and are reabsorbed in the distal convoluted tubules. Therefore, lipid-soluble agents are first metabolized into more polar (hydrophilic) substances in the liver via two general sets of reactions, called phase I and phase II

Phase I reactions → Oxidation, Reduction, Hydrolysis

A. Oxidation:

- **The most important is cytochrome P450 oxidases "CYP" (mixed function oxidases) which are hepatic microsomal enzymes** (1)

CYP is further classified by family, subfamily & gene into many isozymes. The name of each one is designated by the term CYP followed by 3 characters e.g. CYP 2C9:

Nomeclature:

1. *The first Arabic numeral represents the family.*
2. *The alphabetic letter represents the subfamily.*
3. *The second Arabic numeral represents the individual gene within the subfamily.*

- Xanthine oxidase (2): converts xanthine → uric acid
- Monoamine oxidase (MAO) (3): oxidizes catecholamines & serotonin

adrenaline and noradrenaline

Notes for your knowledge :

** Allopurinol (Zyloprim) and febuxostat (Uloric) are the only FDA-approved xanthine oxidase inhibitors for the treatment of gout, we decreases uric acid synthesis = we treats Gout

**Serotonin is a chemical that carries messages between nerve cells in the brain and throughout your body. Serotonin plays a key role in such body functions as mood, sleep, digestion, nausea, wound healing, bone health, blood clotting and sexual desire.

**Catecholamines are hormones made by your adrenal glands, two small glands located above your kidneys. These hormones are released into the body in response to physical or emotional stress. The main types of catecholamines are dopamine, norepinephrine, and epinephrine(adrenaline).

B. Reduction:

- Nitroreductase → chloramphenicol احفظوا هاد بس
- Carbonyl reductase → naloxone

C. Hydrolysis:

- It occurs mainly non-microsomal (in plasma ① and body fluids ②)
  - Cholinestrase → Ach. Acetylcholine
  - Peptidase → insulin

Nots for your knowledge

**Chloramphenicol is a medication used in the management and treatment of superficial eye infections such as bacterial conjunctivitis

**Naloxone is a medication approved by the Food and Drug Administration (FDA) designed to rapidly reverse opioid overdose. It is an opioid antagonist—meaning that it binds to opioid receptors and can reverse and block the effects of other opioids, such as heroin, morphine (بيوقف شغل المورفين)

**Cholinesterase inhibitors (also called acetylcholinesterase inhibitors) are a group of medicines that block the normal breakdown of acetylcholine.

Consequences of phase I reactions:

- The activity of the drug is modified in one of the following ways:

1- Active drugs → inactive drugs (occurs with most drugs).

2- Inactive drugs (prodrugs) → active drugs, e.g. cortisone to cortisol (hydrocortisone).

Inactive Active

3- Active drug → another active one, e.g. codeine to morphine.

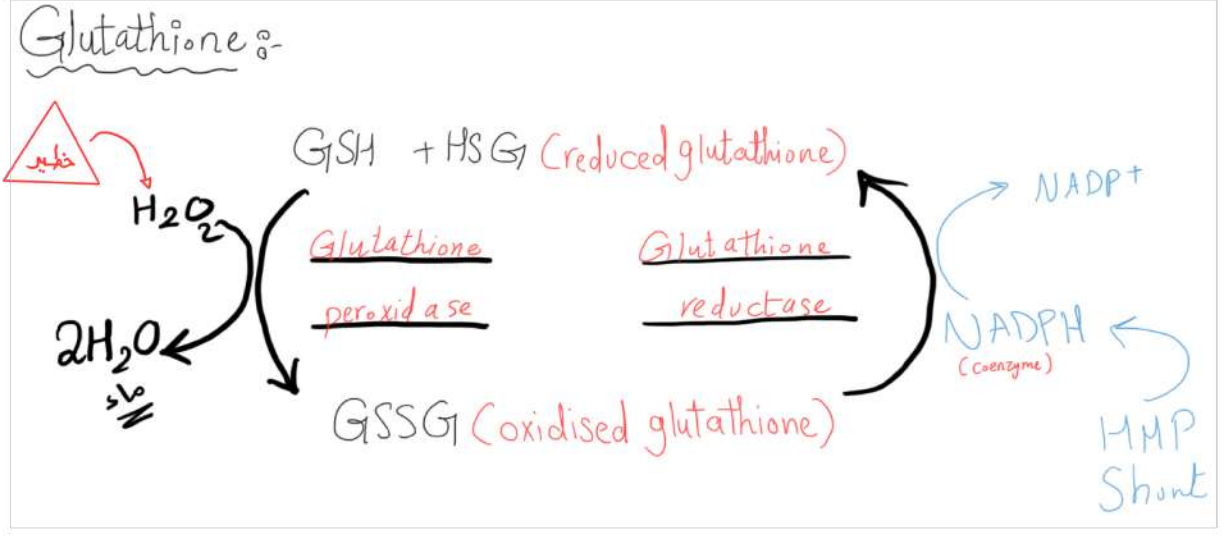
4- Active drug → a toxic metabolite e.g. methanol → formaldehyde → retinotoxic

الميثانول هو الكحول الميثيلي (الخمر) بس يشربه الشخص كتير رح يتراكم ال formaldehyde وتسببله عمى بسبب سميته على شبكية العين

paracetamol → toxic metabolite (NAPQI) → hepatotoxic in case of toxicity

ملاحظة : هاي السمية بتمثل حوالي 5% من ال matabolism و الجسم بقدر يتعامل معها عن طريق انه بدخل لل2 phase و يرتبط مع molecule مثل ال glutathione و بهاي الحالة ببطل harmfull و بصير اله secretion

و لكن الخطر لما المريض يوخد جرعة كبيرة مرة وحدة أو عدة جرعات بفترة قصيرة حيكون الtoxic كميته تفوق الglutathione الي صنعه الكبد مما يؤدي الى hepatotoxicity و liver necrosis



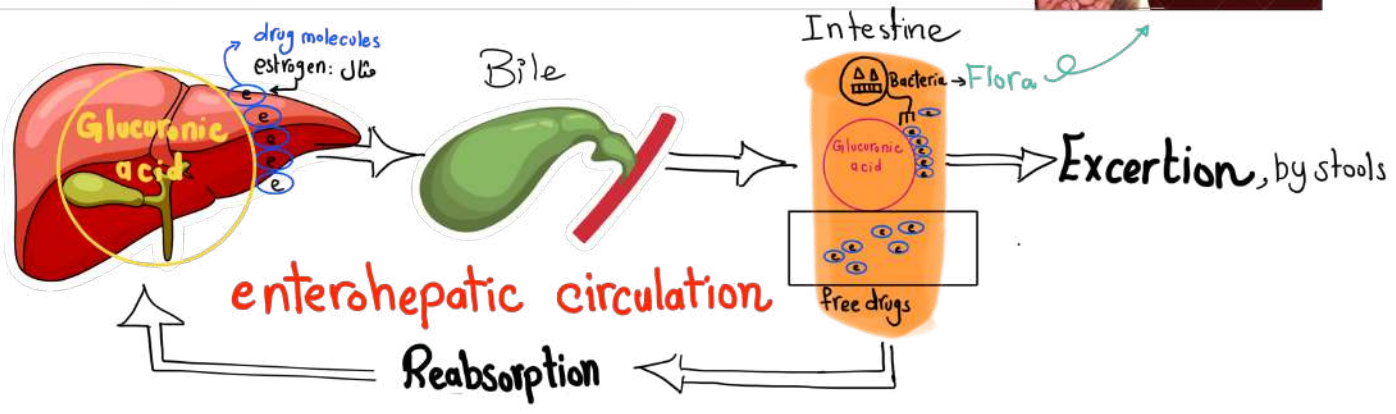
تذكير سريع لعمل الGlutathione 👀 أخذناه بالبيوكيم 😁

Phase II reactions

A. Glucuronide conjugation:

- **It is the most common conjugation reaction**
- Glucuronide conjugates secreted in bile may be hydrolyzed by intestinal bacteria and free drug can be reabsorbed again i.e. enterohepatic circulation → prolong duration of drug action e.g. estrogen (so contraceptive pills are given once daily)

حبوب منع الحمل



حتستمر هاي العملية لمدة 24h لغاية ما يصير في excertion للestrogen بنسبة 100% ، لهيك المرأة بتوخد حبوب منع الحمل كل 24h

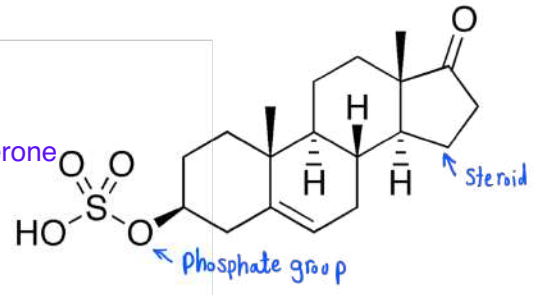
و بنلاحظ انه هاي العملية زادت من فعالية الدوا (long duration of drug action)

نطلق على هذه الدورة <- interohepatic circulation

معلومة اضافية : لو المريضة اخدت antibiotic ادى لقتل بكتيريا flora ممكن يصير حمل لأنه الدواء ما حيصير اله reabsorption

B. Non-Glucuronide conjugation:

- Sulphate formation e.g. steroids Vitamine D, estrogen, testosterone
- Glycine conjugation e.g. salicylic acid **Aspirin**
- Glutathione conjugation e.g. ethacrynic acid **diuretic**
- Acetyl conjugation (slow & rapid acetylation) e.g. isoniazid **is an antibiotic used for the treatment of tuberculosis.**
  - Because of genetic viration



Consequences of phase II reactions:

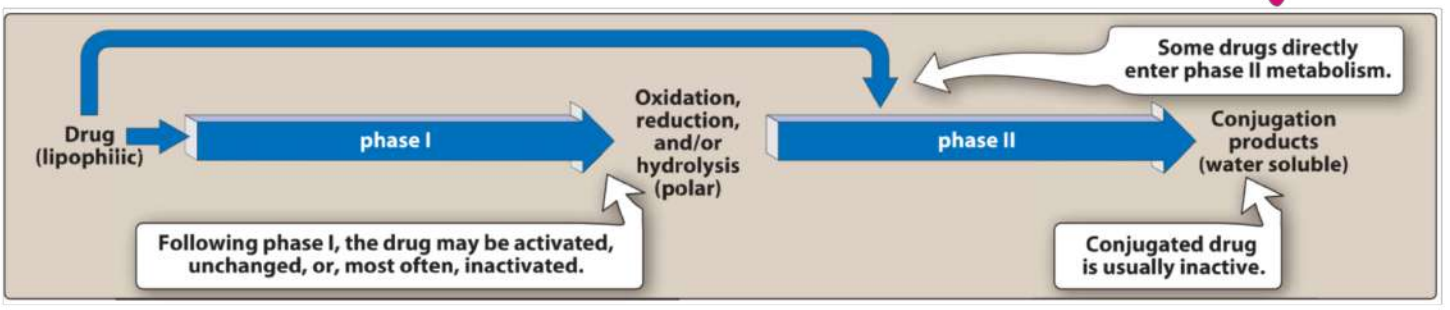
- Mostly result in drug inactivation **Active --> Inactive**
- Some exceptions can occur e.g. morphine is partially converted into morphine-6-glucuronide (active metabolite) **Active --> Active**

- **Most of drugs is metabolizes by phase-I followed by phase-II reactions**
  - Some drugs is metabolizes firstly by phase-II then by phase-I reactions e.g. isoniazid.
  - Some drugs undergo phase-I or phase-II only

حسب تركيب الدواء

من الكتاب

**It depends on their chemical structure



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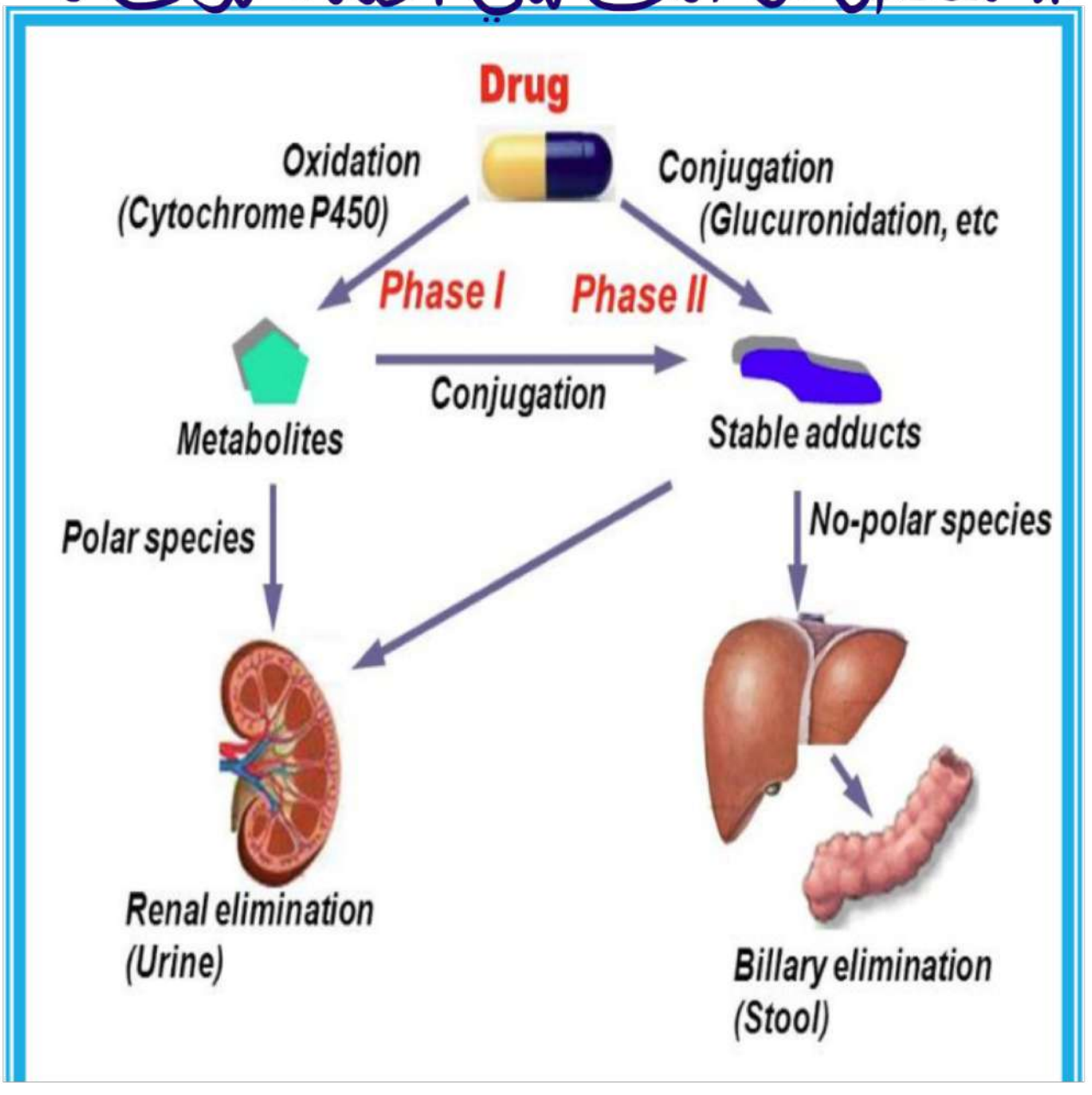
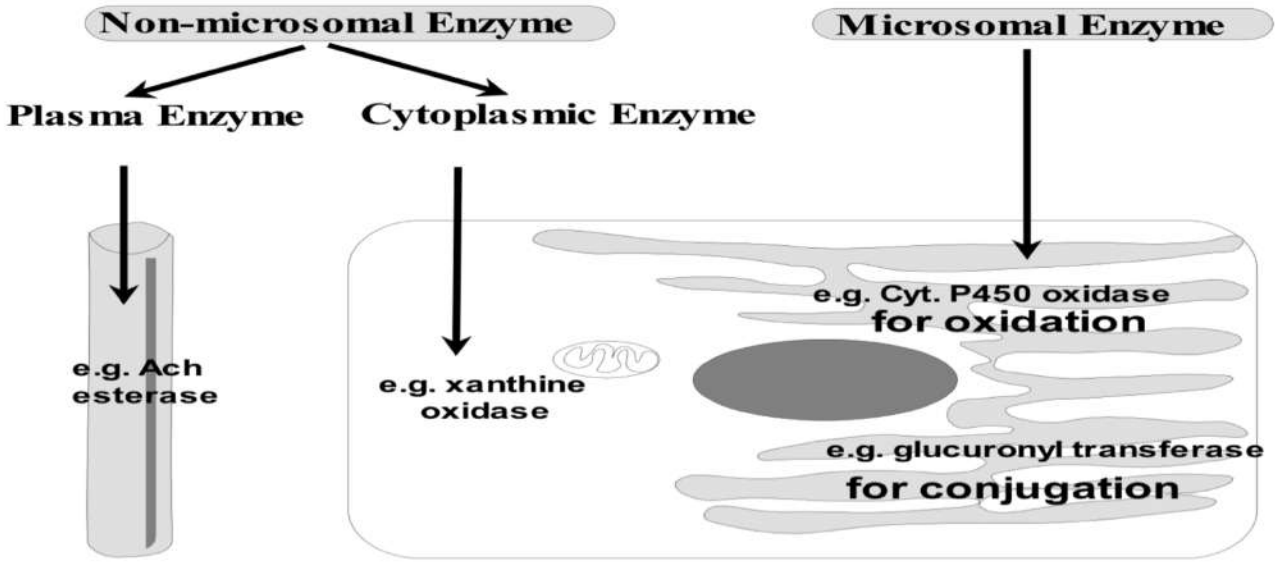
* ملخص من النت للي أخذناه للآن :



Types of enzymes responsible for biotransformation reactions



مهم

Microsomal enzymes	Non-microsomal enzymes
Site: in the liver, in microsomes of ER. So, they are called hepatic microsomal enzymes	Present in **liver**, **GIT**, **lung**, **kidney**, **plasma**, **skin**: in **cytoplasm** and **mitochondria**
Reactions: التفاعلات المسؤولة عنها :	**Reactions:**
Phase-I: Oxidation "CYP"	Phase-I: Oxidation But not "CYP"
Reduction	Reduction
Hydrolysis (few reactions) قليل جدًا	Hydrolysis (mostly) كثير
Phase-II: Glucuronic a. conjugation Only	Phase-II: All Conjugations Except Glucuronic
Substrate: **lipophilic drugs** & bilirubin	**Lipophilic , hydrophilic drugs** (to terminate action as succinylcholine) & natural body constituents
Affection by drugs: **Inducible**	**Non-inducible**

الأدوية الي بتشتغل عليها

معناته في أدوية ممكن تتحكم بعملها و تعمل الها inhibition or induction

**Succinylcholine is a depolarizing skeletal muscle relaxant used adjunctly to anesthesia and for skeletal muscle relaxation during intubation, mechanical ventilation, and surgical

ال lipophilic الي بتقدر تعمل penetration وهاد من عوامل ال distribution فهي ال lipophilic هي الي بتقدر تدخل جوا ال liver فهي الي بصيرلها metabolism

❖ Factors Affecting Biotransformation:

1. Drugs: (Enzyme induction & enzyme inhibition).

- Some drugs and environmental substances can **induce** or **inhibit** the microsomal enzyme activity and lead to undesirable drug interactions

Tolerance is a person's diminished response to a drug, which occurs when the drug is used repeatedly and the body adapts to the continued presence of the drug.

Clinical significance of Enzyme Induction:

❖ Drugs stimulating the microsomal enzyme systems → ↑ activity →

1. • ↑ their own metabolism → **tolerance** e.g. **phenobaritone.** (منوم) يقلل تأثير الدواء
2. • ↑ metabolism of other drugs metabolized by these enzymes and are given at same time → drug interactions e.g.:
   - **Rifampicin** →↑ **oral contraceptive** metabolism → pregnancy (منع حمل)

Rifampicin is used to treat TB, it increases the the metabolism, so it decreases the effect of oral contraceptive

- **Phenytoin** →↑ **cyclosporine** metabolism → transplant rejection (مثبط مناعي) رفض العضو الذي زرع

*Phenytoin is used to control certain type of seizures, and to treat and prevent seizures that may begin during or after surgery

*Ciclosporin, used as an immunosuppressant medication (مثبط للمناعة), is used mostly in organs transplantation

- **Rifampicin** →↑ **warfarin** metabolism → therapeutic failure. (مانع للتجلط) فشل بالعلاج

*warfarin treats blood clots and reduces risk of heart attacks and stroke.

3. • ↑ metabolism of endogenous substrates e.g. **phenobarbitone** → ↑ elimination of **bilirubin** → used in treatment of neonatal jaundice)

مفيدة للناس الي عندهم يرقان زي الأطفال حديثي الولادة، لحتى نزيد الmtabolism تبع bilirubin

4. • ↑ metabolism of vitamins e.g. phenytoin → ↑ of vit.D, vit.K, folic acid → osteomalacia, bleeding and megaloplastic anemia (لين العظام "الكساح")

*Vitamin D helps regulate the amount of calcium and phosphate in the body.

*Vitamin K helps to make various proteins that are needed for blood clotting and the building of bones.

*Folic acid is a B vitamin that helps your body make red blood cells.

- Enzyme induction is reversible. It occurs over a few days-months and passes off over 2-3 weeks after withdrawal of the inducer.

حفظ

Examples of Enzyme Inducers

Phenytoin & carbamazepine- **ph**enobarbitone – ri**f**ampicin - griseo**f**ulvin - ♂ androgen- nicotine- chronic alcohol ingestion.

Quiz Time ⏰

1) Which of the following reactions represents Phase II of drug metabolism?

A. Amidation

B. Hydrolysis

C. Oxidation

D. Reduction

E. Sulfation

2)Which of the following is a phaseII drug metabolism reaction associated with a genetic polymorphism?

A. Acetylation

B. Glucuronidation

C. Oxidation

D. Reduction

E. Glutathione conjugation

3)A woman is taking oral contraceptives (OCs). Which of the following drugs is unlikely to reduce the effectiveness of the OCs?

A. Carbamazepine

B. Phenytoin

C. Ketoconazole

D. Phenobarbital

E. Rifampin

4)Aprodrug is:

A. The prototype member of a class of drugs

B. The oldest member of a class of drugs

C. An inactive drug that is transformed in the body to an active metabolite

D. A drug that is stored in body tissues and is then gradually released in the circulation

5) Microsomal enzyme induction can be a cause of:

A. Tolerance

B. Physicaldependence

C. Psychological dependence

D. Idiosyncrasy

6)Which of the following types of drug metabolizing enzymes are inducible:

A. Microsomal enzymes

B. Nonmicrosomal enzymes

C. Both microsomal and non microsomal enzymes

D. Mitochondrial enzymes