Drug Biotransformation.

* Humans are exposed always to foreign compounds called Xenobiotics throw → GIT, skin, lung .....
* Xenobiotics execreted by kidney are
  - Smaller polar molecule
  - ionized at physiological pH

Xenobiotics: industrial Toxins, Drugs, enviromental Toxins

* many drugs are lipophilic at physiological pH, and readily absorbed from glomerular filtrate in the nephron, but lipophilic drug which bind to plasma protein are not.
* Such drugs are metabolized in liver to more polar molecules that can be excreted in → Urine, Bile
* Metabolic product are often less active than the parent drug and may be inactive. but there are an exeption.
  - Some Drug Metabolism have inhanced activity or even toxicity
  - Some Drugs are inactive and need activation By metabolism as prodrug
  - Some Drug are metabolised into toxins

Examples: ① Paracetomal may convert to the hepatotoxin N-acetyl-p-benzoquinone
② Halothane is metabolised and release free radical that call hepatotoxic

* Biotransformation Rxn can be classified as : (the doctor said it is philosphar technegie)

phase 1

* Converting the drug to more polar metabolites by introducing (Adding or Unmasking) polar group
  - -OH
  - -SH
  - $-NH_2$

Which makes the drug more polar = more excreation by the kidney

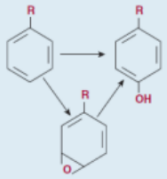
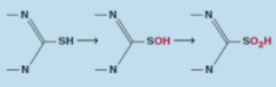
* the metabolites can Be: less active, inactive, more active
* many phase 1 product need phase 2
  - Oxidation
  - Reduction
  - Hydrolysis

Phase 2

* phase 2 is Conjugation reaction (conjugation rxn with an endogenous substrate such as
  - Glucuronatic acid
  - Sulfuric acid
  - acety CoA
  - Glutathione

* Conjugated drug usually excreted by Urine and bile
* Conjugation is synthatic rxns, involve high-energy intermediates and specific transfer enzymes called transferases
* phase 2 rxns are relatively fasten than phase 1.

* phase 1
* most Oxidation-Reduction rxns in drug metabolism carried by macrosomal mixed function oxidase or Cytochrome P450 enzyme (I really don't know what's that mean)
* Cytochrom P450 is located in Endoplasmic reticulum.
* they have low specifity and slow rxn rate.
* High lipid solubility is Common to the wide variety of structwally unrelated drugs metabolized by this system

Reaction Class	Structural Change ①	Drug Substrates
Oxidations		
Cytochrome P450-dependent oxidations:		
Aromatic hydroxylations		Acetanilide, propranolol, phenobarbital, phenytoin, phenylbutazone, amphetamine, warfarin, 17α-ethinyl estradiol, naphthalene, benzpyrene
Aliphatic hydroxylations	$RCH_2CH_3 \longrightarrow RCH_2CH_2OH$ $RCH_2CH_3 \longrightarrow RCHCH_3$ (OH)	Amobarbital, pentobarbital, secobarbital, chlorpropamide, ibuprofen, meprobamate, glutethimide, phenylbutazone, digitoxin
Epoxidation	$RCH{=}CHR \longrightarrow R{-}C(H,O,H){-}C{-}R$	Aldrin
Oxidative dealkylation		
N-Dealkylation	$RNHCH_3 \longrightarrow RNH_2 + CH_2O$	Morphine, ethylmorphine, benzphetamine, aminopyrine, caffeine, theophylline
O-Dealkylation	$ROCH_3 \longrightarrow ROH + CH_2O$	Codeine, *p*-nitroanisole
S-Dealkylation	$RSCH_3 \longrightarrow RSH + CH_2O$	6-Methylthiopurine, methitural
Cytochrome P450-independent oxidations: ③		
Flavin monooxygenase (Ziegler's enzyme)	$R_3N \longrightarrow R_3N^+ \rightarrow O^- \xrightarrow{H^+} R_3N^+OH$	Chlorpromazine, amitriptyline, benzphetamine
	$RCH_2N(H){-}CH_2R \longrightarrow RCH_2{-}N(OH){-}CH_2R \longrightarrow RCH{=}N(O^-){-}CH_2R$	Desipramine, nortriptyline
		Methimazole, propylthiouracil
Amine oxidases	$RCH_2NH_2 \longrightarrow RCHO + NH_3$	Phenylethylamine, epinephrine
Dehydrogenations	$RCH_2OH \longrightarrow RCHO$	Ethanol
Reductions		
Azo reductions	$RN{=}NR_1 \longrightarrow RNH{-}NHR_1 \longrightarrow RNH_2 + R_1NH_2$	Prontosil, tartrazine
Nitro reductions	$RNO_2 \longrightarrow RNO \longrightarrow RNHOH \longrightarrow RNH_2$	Nitrobenzene, chloramphenicol, clonazepam, dantrolene
Carbonyl reductions	$RCR' \longrightarrow RCHR'$ (O, OH)	Metyrapone, methadone, naloxone
Hydrolyses		
Esters	$R_1COOR_2 \longrightarrow R_1COOH + R_2OH$	Procaine, succinylcholine, aspirin, clofibrate, methylphenidate
Amides	$RCONHR_1 \longrightarrow RCOOH + R_1NH_2$	Procainamide, lidocaine, indomethacin

	②	
***N*-Oxidation**		
Primary amines	$RNH_2 \longrightarrow RNHOH$	Aniline, chlorphentermine
Secondary amines	$R_1R_2NH \longrightarrow R_1R_2N{-}OH$	2-Acetylaminofluorene, acetaminophen
Tertiary amines	$R_1R_2R_3N \longrightarrow R_1R_2R_3N{\rightarrow}O$	Nicotine, methaqualone
***S*-Oxidation**	$R_1R_2S \longrightarrow R_1R_2S{=}O$	Thioridazine, cimetidine, chlorpromazine
Deamination	$RCHCH_3(NH_2) \longrightarrow R{-}C(OH){-}CH_3 \longrightarrow R{-}C(=O){-}CH_3 + NH_3$	Amphetamine, diazepam
Desulfuration	$R_1R_2C{=}S \longrightarrow R_1R_2C{=}O$	Thiopental
	$R_1R_2P{=}S \longrightarrow R_1R_2P{=}O$	Parathion
Dechlorination	$CCl_4 \longrightarrow [CCl_3^{\cdot}] \longrightarrow CHCl_3$	Carbon tetrachloride

* جدول معلومات حفظ؟ نعم صحيح يا وحش الجدول الثالث مش متأكد اذا اخذف أو لا.

* Human liver Cytochrome P450 Enzyme.
* there are numerous P450 isoenzymes as CYP1A2 , CYP2C9 , CYP2D6 , CYP2E1 , CYP3A4 CYP2A6 , CYP2B6 , CYP2C19 , CYP2C8
* CYP3A4 is acount for 30 % of Human liver P450 content and metabolise more 50 % of Theraputic drugs
* CYP2C9 is acount for 20 % of Human liver P450 content and CYP 2D6 acount for 2% 5
* CYP1A2 is acount for 15 % of liver P450, but it activate Carcinogens.

* Phase 2 → the drug is conjugated with endogenous substrate yield drug conjugates

* Conjugates are polar molecule readily excreted and inactivted.

④ Glutathione (GSH) transferase

* the donor is Glutathione which is Gly - Cys - Glu
* GSH is nucleophile that reacts with electrophiles. and it replace Halogens and Conjugate epoxides.
* Glutathione conjugates don't appear in urine but in bile
* they are metabolised further to Cys - conjugates then to meraceptouric acid (N-acelytated Cys conjugates) that appear in Urine by active transport process.

⑤ S-Adenosyl-L-methionine (SAM)

* mediate O-, N-, S- methylation of drug and xenobiotics. By methyl transferases (MTS)

Biotransformation Rxns in phase II

① Uridine 5-diphosphate (UDP) - glucuronosyl transferase (UGTs)

↓

most dominant Conjugation enzyme.

Can work on

-OH -NH -SH -COOH -NHOH

② Sulfo transferases (SULTs)

* phosph adenosine 5- phospho sulfate (PAPS)
* inorganic Sulfate is limitting factor and it is source from food or S-containg amino acids.
* almost All chemical that glucuronated are sulfated
* infant more capable of Sulfation than adults.

③ N-acetyl transferase (NAT)

* Utilize Acetyl-CoA as the endogenous cofactor for conjugation

These rows are not included and also last two columns

Type of Conjugation	Endogenous Reactant	Transferase (Location)	Types of Substrates	Examples
Glucuronidation	UDP glucuronic acid	UDP glucuronosyltransferase (microsomes)	Phenols, alcohols, carboxylic acids, hydroxylamines, sulfonamides	Nitrophenol, morphine, acetaminophen, diazepam, *N*-hydroxydapsone, sulfathiazole, meprobamate, digitoxin, digoxin
Acetylation	Acetyl-CoA	*N*-Acetyltransferase (cytosol)	Amines	Sulfonamides, isoniazid, clonazepam, dapsone, mescaline
Glutathione conjugation	Glutathione (GSH)	GSH-*S*-transferase (cytosol, microsomes)	Epoxides, arene oxides, nitro groups, hydroxylamines	Acetaminophen, ethacrynic acid, bromobenzene
Glycine conjugation	Glycine	Acyl-CoA glycinetransferase (mitochondria)	Acyl-CoA derivatives of carboxylic acids	Salicylic acid, benzoic acid, nicotinic acid, cinnamic acid, cholic acid, deoxycholic acid
Sulfation	Phosphoadenosyl phosphosulfate	Sulfotransferase (cytosol)	Phenols, alcohols, aromatic amines	Estrone, aniline, phenol, 3-hydroxycoumarin, acetaminophen, methyldopa
Methylation	*S*-Adenosylmethionine	Transmethylases (cytosol)	Catecholamines, phenols, amines	Dopamine, epinephrine, pyridine, histamine, thiouracil
Water conjugation	Water	Epoxide hydrolase (microsomes)	Arene oxides, *cis*-disubstituted and monosubstituted oxiranes	Benzopyrene 7,8-epoxide, styrene 1,2-oxide, carbamazepine epoxide
		(cytosol)	Alkene oxides, fatty acid epoxides	Leukotriene A_4

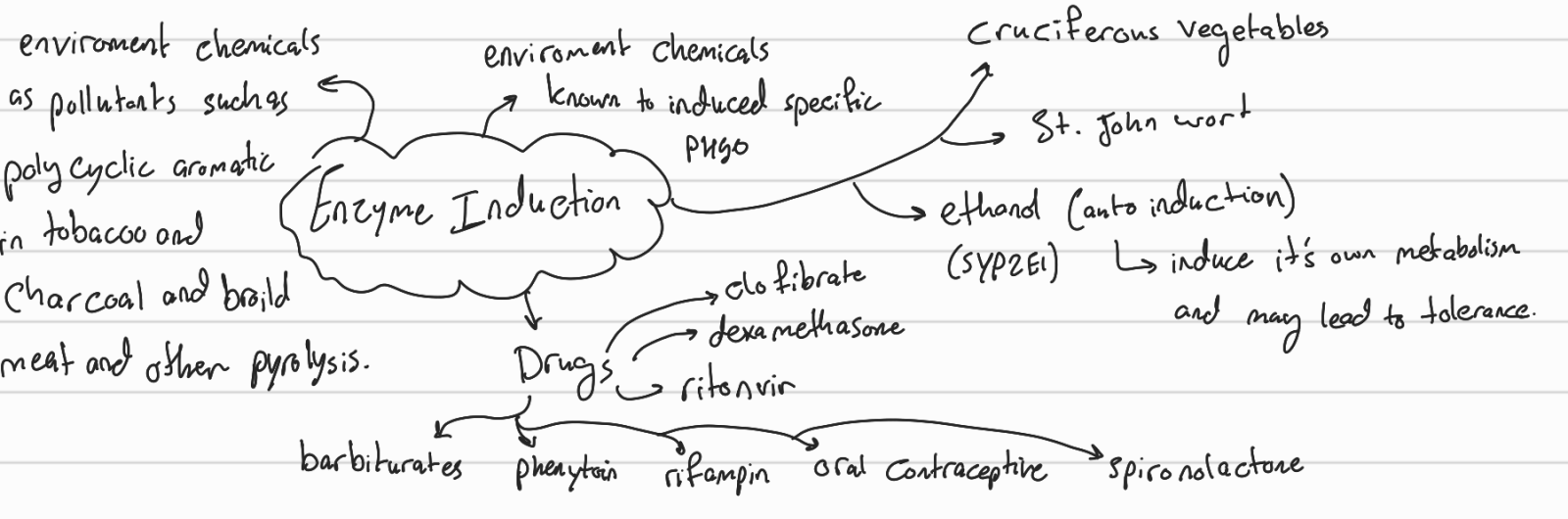
* Certain Conjugation leads to formation of Reactive Oxygen species and drug toxicities.

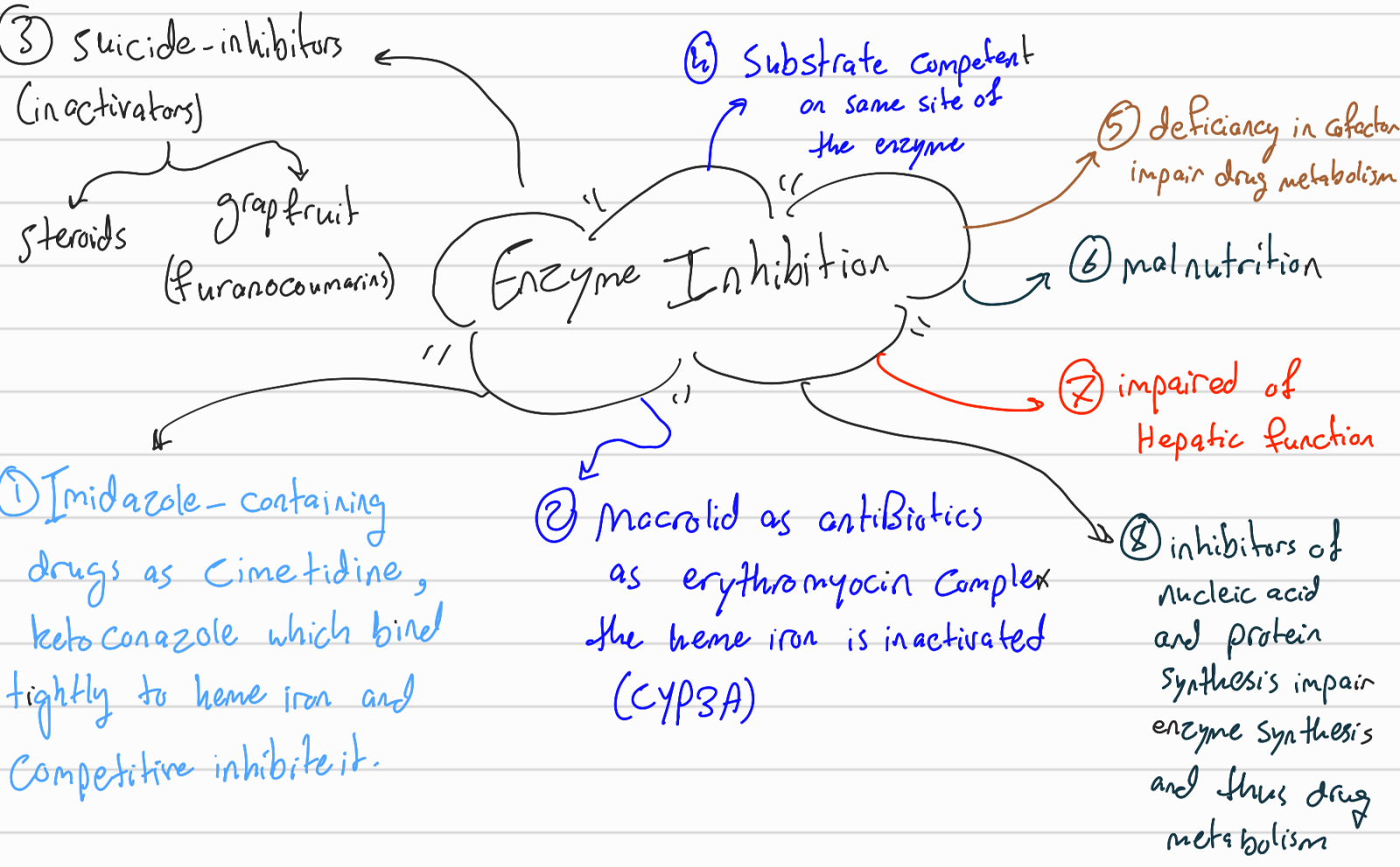
Example: ① Acel glucuronide of NSAID (Non-steroidal Anti inflamatory drugs)
② O- sulfation of N-hydroxy acetyl amino fluorine
③ N- Sulfation of isoniazid
④ Sulfation of pro drugs as minoxidil.
⑤ Morphine 6- glucuronide is more patent than morphine.

* Several drugs may be metabolised transformed to ROS (Reactive Oxygen speci
* Some Toxic rxns may become apparent at high drug dose, especially if alternative detoxification mechanism is overwhelmed or detoxifing cosubstants are depleted

GSH ← Glucuronate → Sulfate

* an example is acetaminophen (paracetamol) - induced hepatotoxicity, it is normally undergoes glucuronation and Sulfations which make 95% of excreted metabolites. and the alternative PH50 dependent pathway counts for 5%
* as long GSH is available for conjugation → No hepato toxicity.
* At high paracetamol dose with absence of GSH the toxic metabolites accomulate and cause hepatotoxicity.
* Adminstration of N-acetyl cysteine (Antidote) with 8-16 hours after acetaminophen overdose protect from hepato toxicity. and no effect of adminstration of GSH because it can not cross cell membrane.
* Enzyme Induction: it means inhanced rate of enzyme synthesis or reduce rate of degeneration
* ↳ which result in accelerated drug metabolism and usually decrease of pharmacological effect
* ↳ toxicity may increase if the drug is metabolise to active metabolites.
* ↳ induction usually starts at the gene level.





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