

DRUG TRANSFORMATION

3 Phases:

1. Pharmaceutical phase = Dissolution / Disintegration

2. Pharmacokinetic phase = What the body does to the drug.

- Absorption

- Distribution

- Metabolism (Biotransformation)

- Excretion

Kidneys = major

Lungs

Biliary (bile + feces)

Intestines

Breast milk
Saliva
Sweat

3. Pharmacodynamic phase = what a drug does to the body.

↑ Increase (Induce)

↓ Decrease (Inhibit)

Replace

} Enzymes

} Hormones

} Metabolic functions

* Duration of action = Time during which the drug is present in a concentration large enough to produce a response.

PHASE I = ER + Cytosol = Xenobiotic
modifying
enzymes.

1. Hydroxylation by CYPs
⇒ Mainly (hetero) aromatic compounds
 $Ar-H \rightarrow Ar-OH$
2. Sulfoxidation
⇒ Diarylsulfide (R-S-R) → Sulfoxide (R-SO-R)
3. Dehydrogenation
- alcohol → aldehyde
4. Reduction
⇒ nitro compounds (R-NO₂) → amines (R-NH₂)
5. Hydrolysis
⇒ Ester → acid + alcohol
⇒ Amide → acid + amine

CYPs

- Hemoproteins (Heme / Fe²⁺)
- > 57 human genes
- 2 enzymes 1. NADPH: CYP reductase)
($2H \rightarrow 2H^+ + 2e^-$)
- 2. Cytochrome P450 hydroxylase
- 3 main cofactors
 - NADPH
 - FAD
 - Heme (Iron)

PHASE 1

PHASE 2

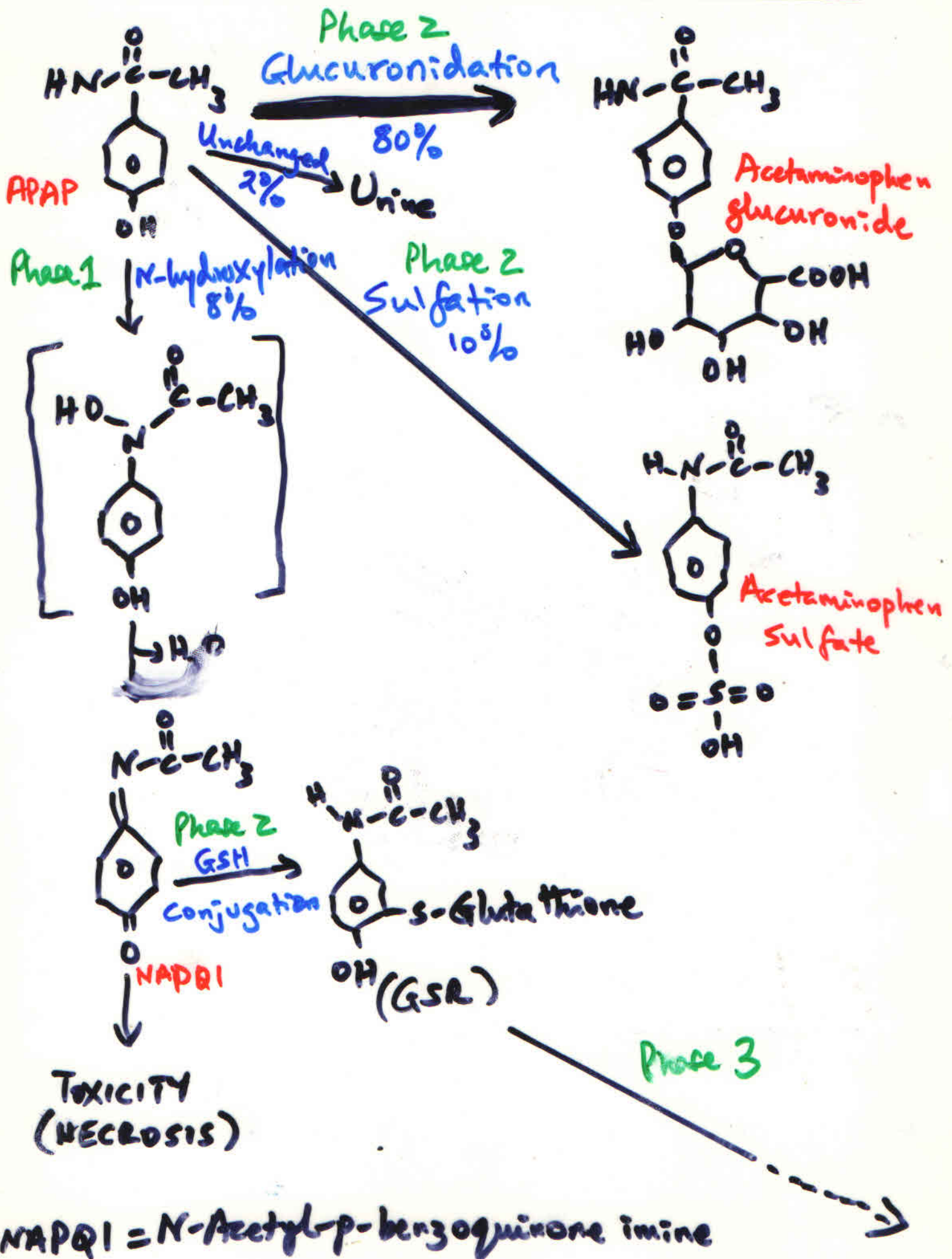
R-OH → Glucuronidation R-Gl
→ Sulfation R-SO₃H
→ O-Methylation R-O-CH₃

R-NH₂ → Glucuronidation
→ Acetylation R-Ac
→ N-Methylation R-N-CH₃

R-COOH → Glucuronidation
→ Amino acid conjugation
e.g. Benzoate + Glycine
→ Hippurate

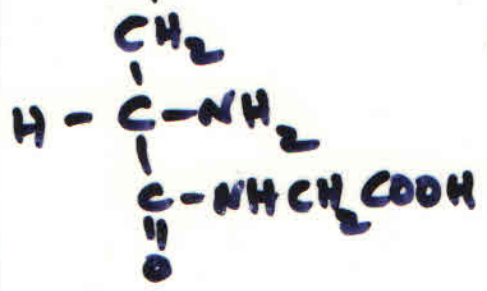
BIOTRANSFORMATION OF ACETAMINOPHEN

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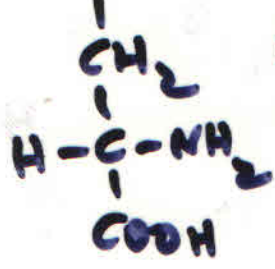
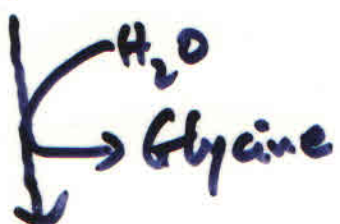


NAPQI = N-Acetyl-p-benzoquinone imine

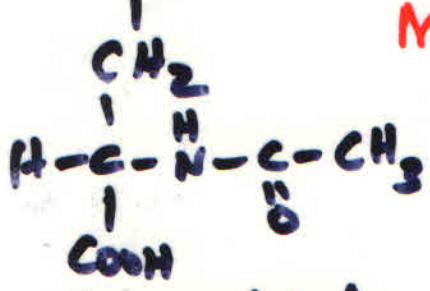
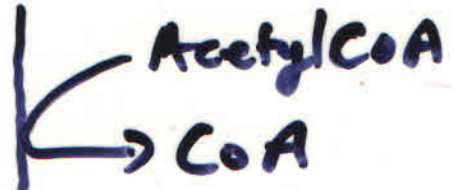
GSR = Glutathione conjugate



Cysteinylglycine conjugate



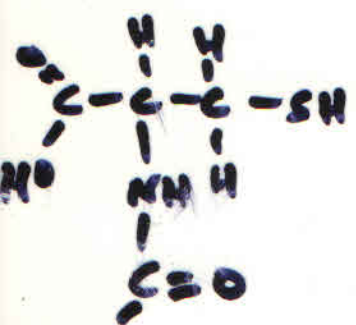
Cysteine conjugate → Urine



Mercapturic acid derivative → Urine

(Acetylated Cysteine conjugate)

NAC
N-Acetylcysteine



GSH = δ-glutamylcysteinylglycine = Tripeptide