METABOLISM / BIOTRANSFORMATION of TOXICANTS

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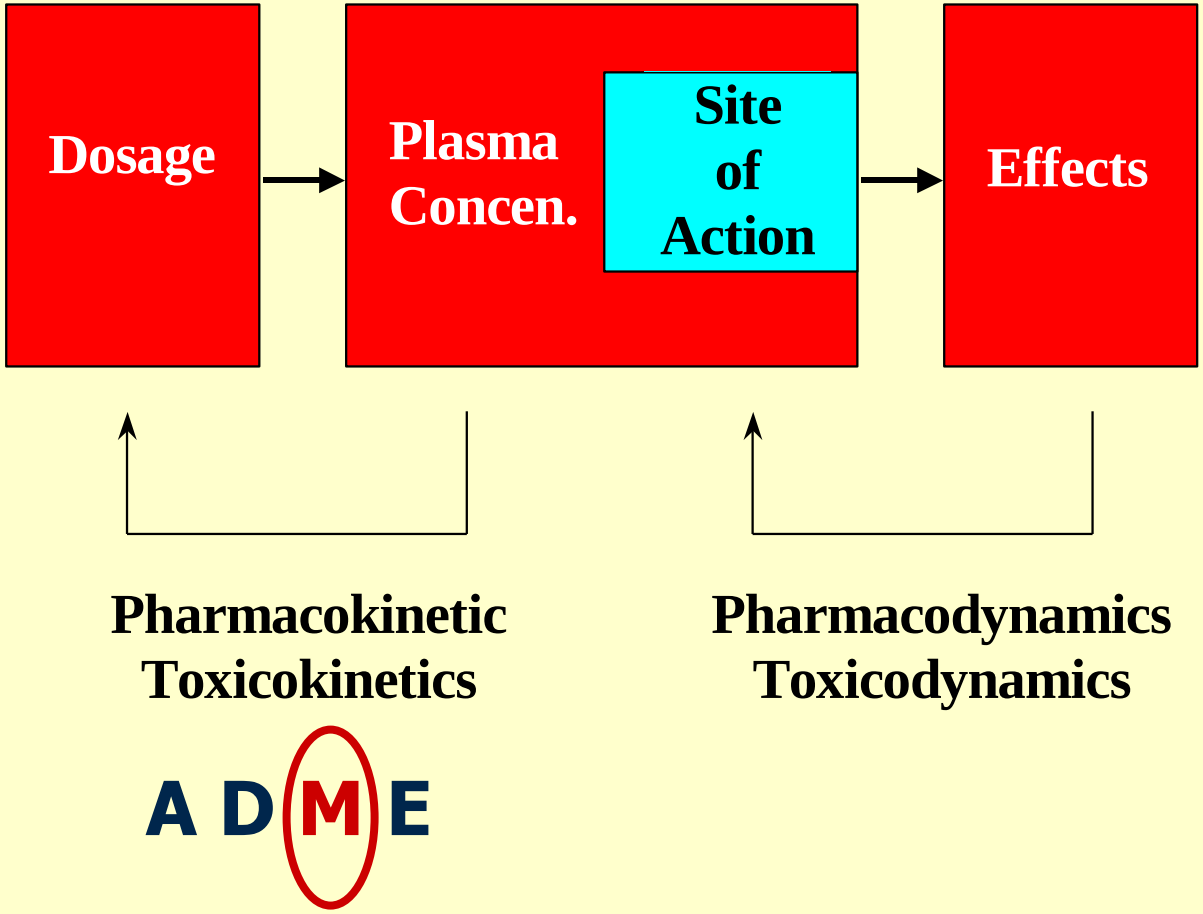
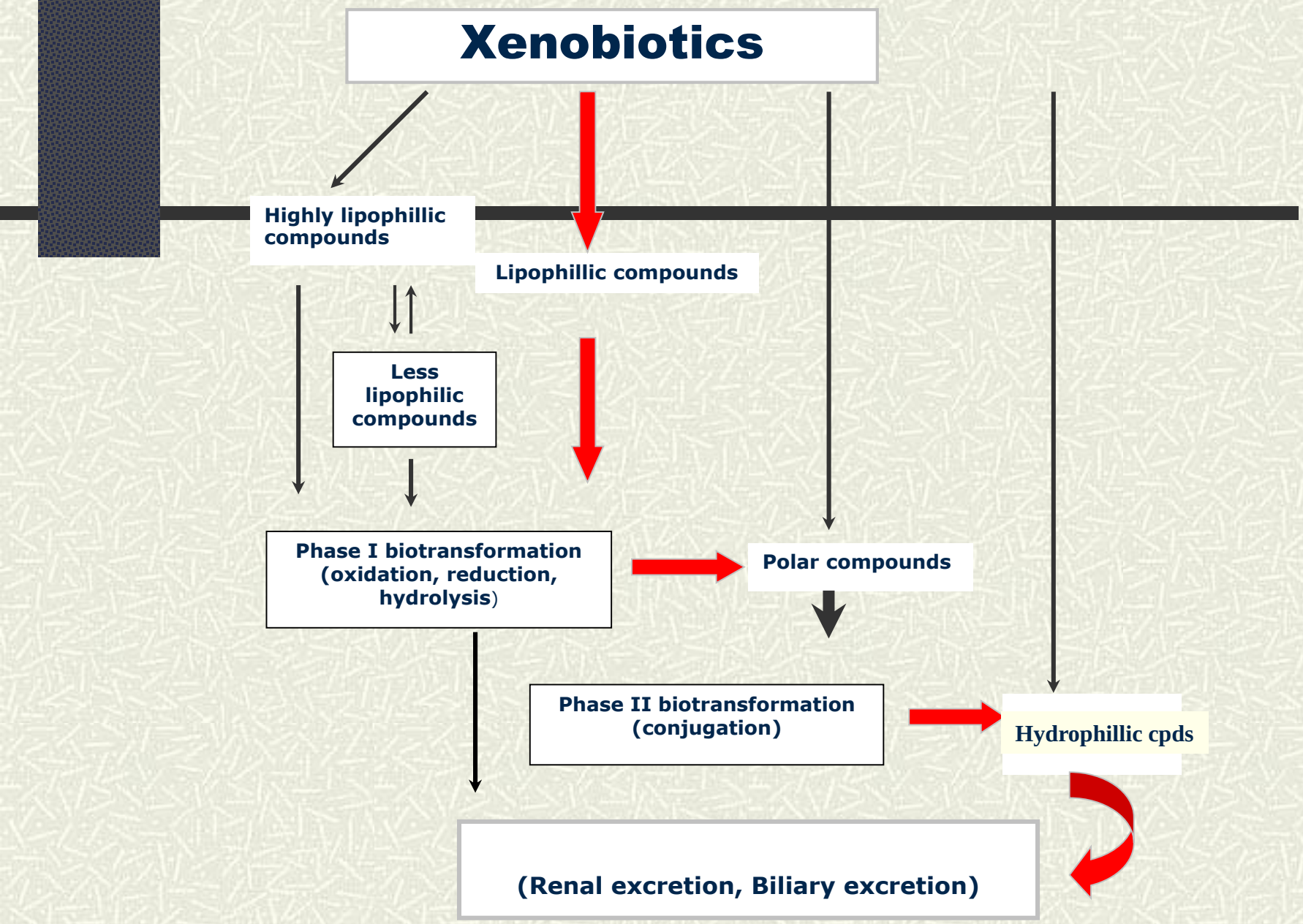
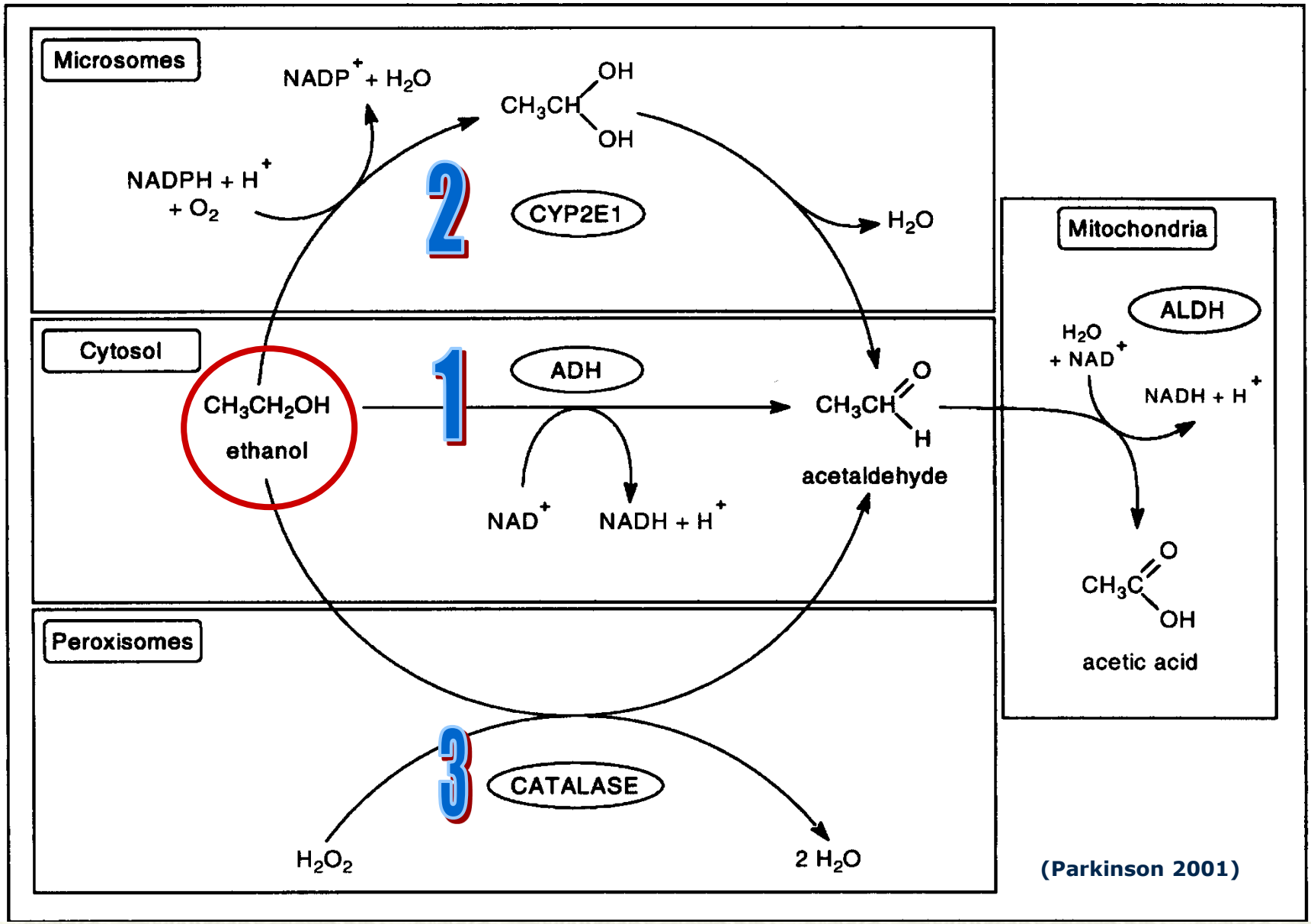

Dosage
Plasma Concen.
Site of Action
Effects
Pharmacokinetic
Toxicokinetics
Pharmacodynamics
Toxicodynamics
A D M E


Xenobiotics
Highly lipophillic compounds
Lipophillic compounds
Less lipophilic compounds
Phase I biotransformation (oxidation, reduction, hydrolysis)
Polar compounds
Phase II biotransformation (conjugation)
Hydrophillic cpds
(Renal excretion, Biliary excretion)

XENOBIOTIC METABOLISM

- Toxicants (xenobiotics) catalyzed by enzymes to form metabolite (s) with modified structure
- Several routes of metabolism found in vivo
- May inactivate or bioactivate action
- Liver is the major site of metabolism
- Genetically variation with some enzymes
- Not constant - can be changed by other chemicals; basic of many interactions



(Parkinson 2001)

XENOBIOTIC METABOLISM

… metabolism is what the body does to the toxicants …..

Toxicants may be converted to

1. Less **toxic** chemicals (metabolite) , **or**
2. **More toxic** chemicals (metabolite) , **or**
3. Chemicals with ***different*** type of effect or toxicity

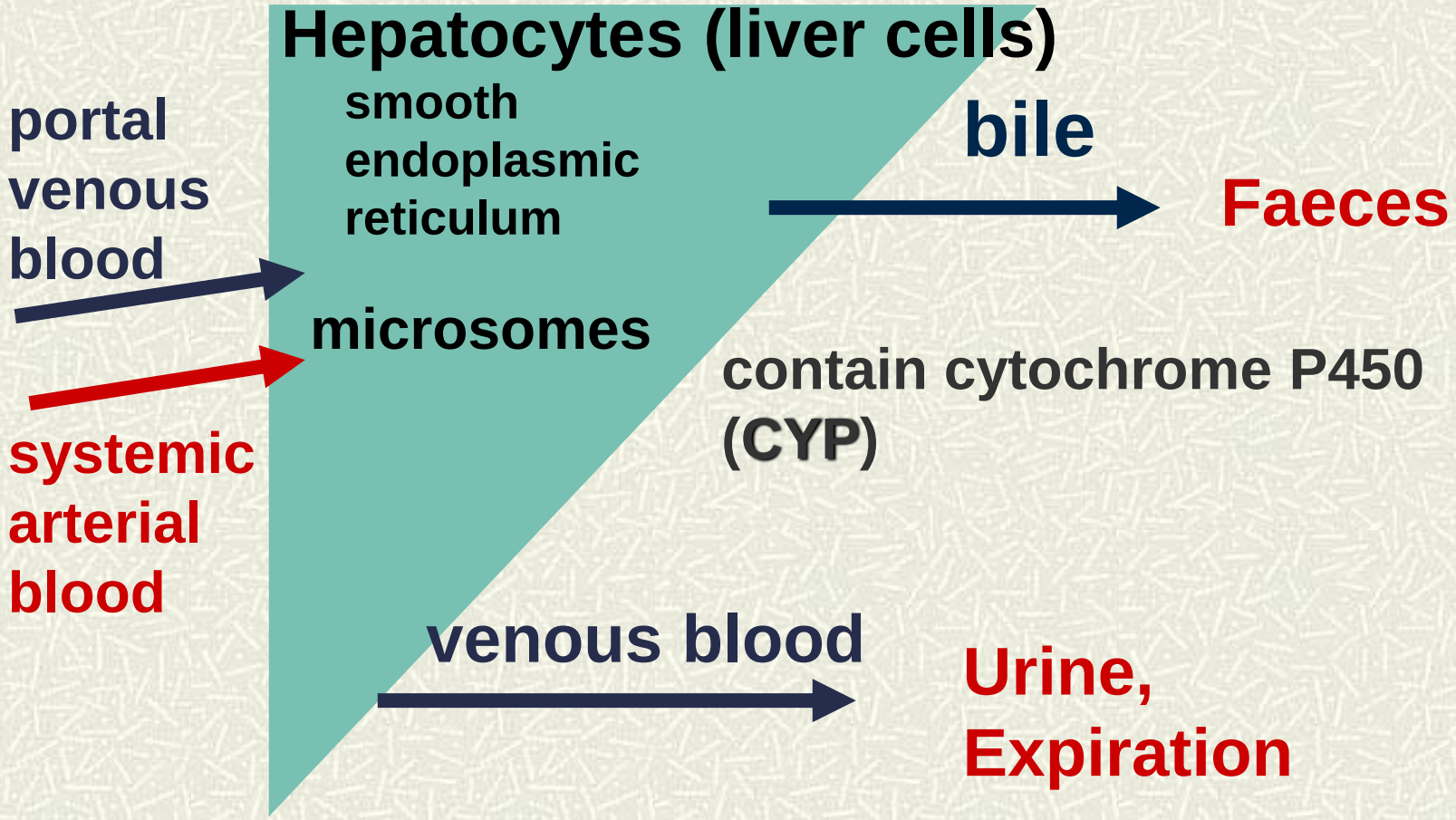
SITES OF METABOLISM

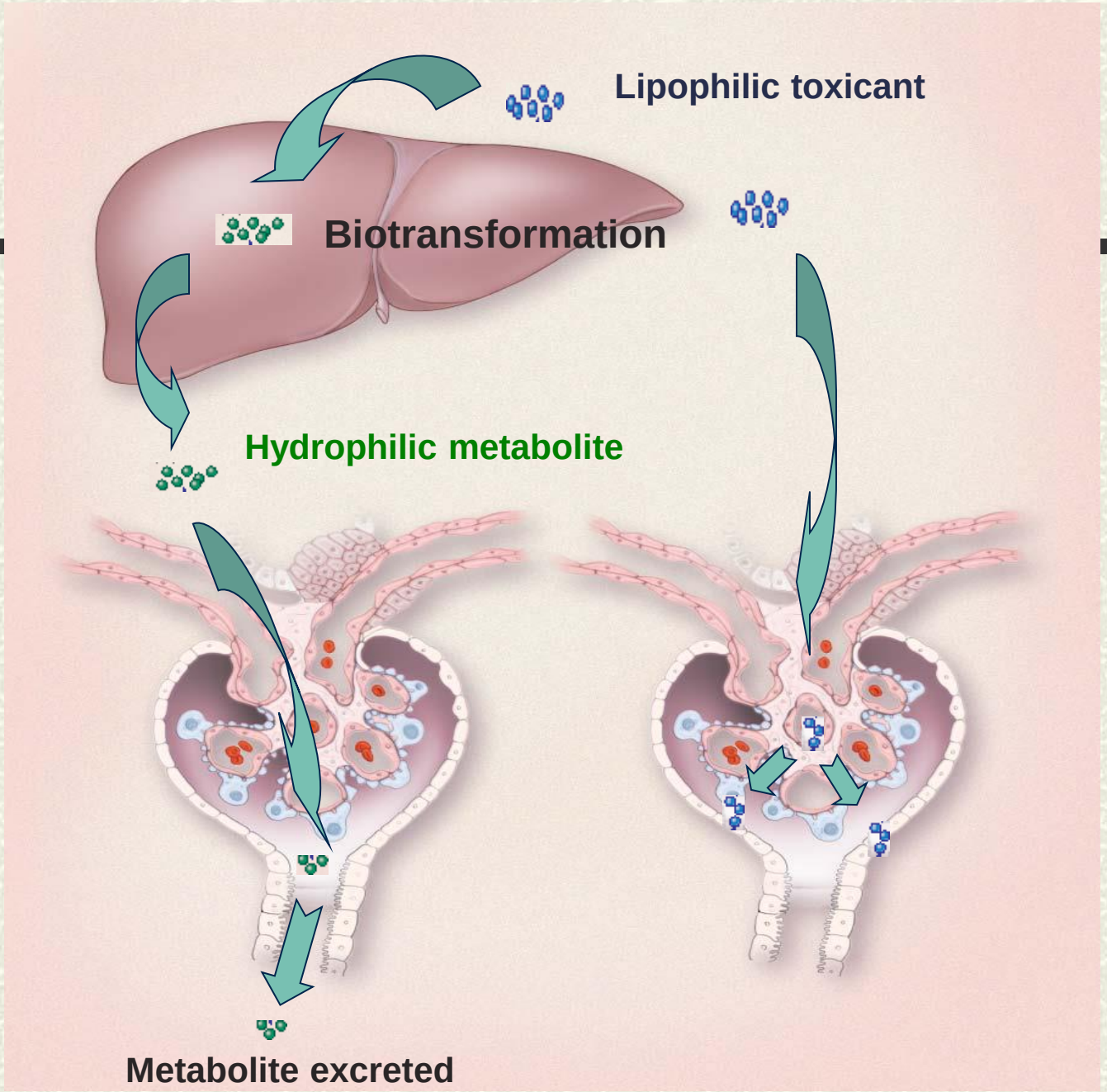
Where ever appropriate enzymes occur;

- **plasma,**
- **kidney,**
- **lung,**
- **gut wall and LIVER**

Liver is ideally placed to intercept natural ingested toxins (bypassed by injections etc) and has a major role in biotransformation

THE LIVER


Hepatocytes (liver cells)
smooth endoplasmic reticulum
portal venous blood
bile
Faeces
microsomes
contain cytochrome P450 (CYP)
systemic arterial blood
venous blood
Urine, Expiration


Lipophilic toxicant
Biotransformation
Hydrophilic metabolite
Metabolite excreted

BIOTRANSFORMATION REACTION

Any **structural** change in a molecule

Phase I - creates site for phase II reaction

Oxidation (adds O) e.g. microsomes;

Reduction ;

Hydrolysis (e.g. by plasma esterases)

others

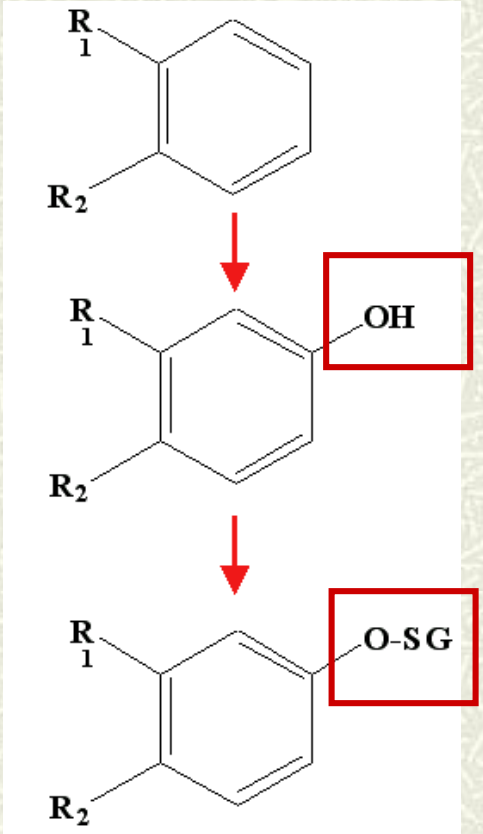
Phase II - couples group to existing (or phase I formed) conjugation site

Glucuronide (with glucuronic acid)

Sulphate

others

XENOBIOTIC-METABOLIZING ENZYMES (XME)



Phase 1

- Cytochrome P450s
- Flavin-containing monoxygenases (FMO)
- Epoxide hydrolases
- Alcohol /Aldehyde Dehydrogenases
- Monoamine Oxidases
- Xanthine oxidase

Phase 2 "Transferases"

- Sulfotransferases (ST)
- UDP-glucuronosyltransferases (UGT)
- Gluthione S-transferases (GST)

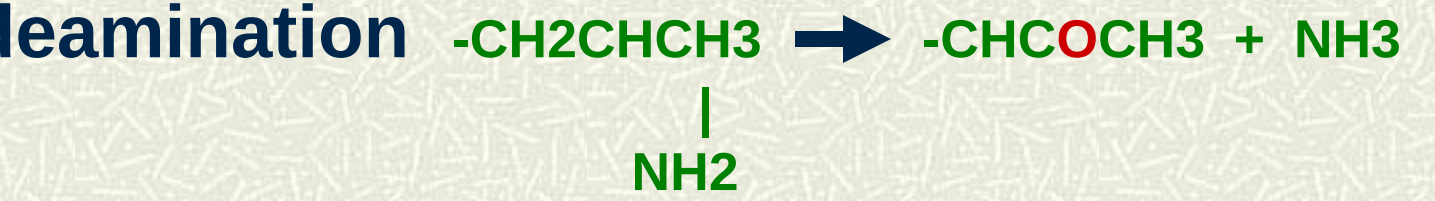
PHASE 1 REACTIONS

Hydroxylation $-CH_2CH_3 \rightarrow -CH_2CH_2OH$

Oxidation $-CH_2OH \rightarrow -CHO \rightarrow -COOH$

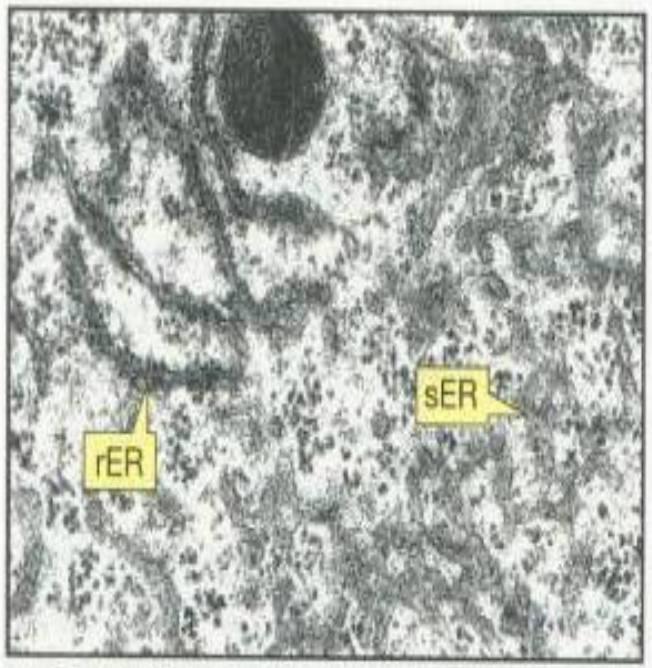
N-dealkylation $-N(CH_3)_2 \rightarrow -NHCH_3 + CH_3OH$

Oxidative deamination

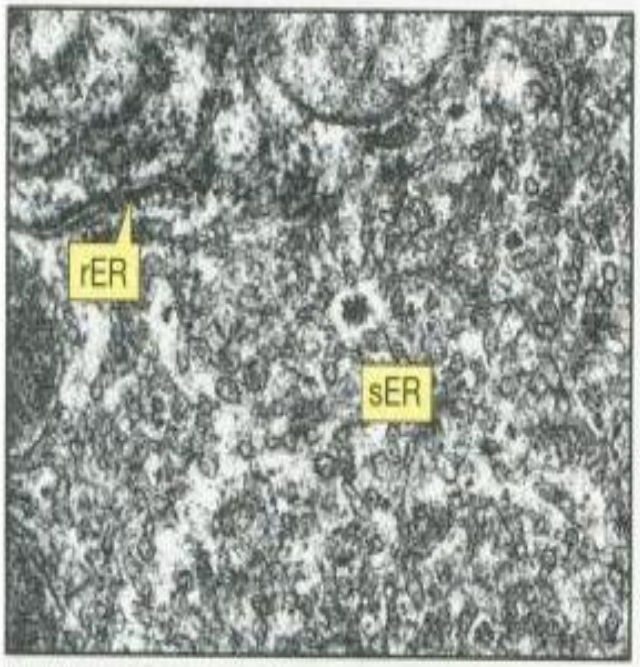


CYTOCHROME P450 (CYP)

- Most important enzyme in xenobiotic metabolism
- Membrane bound enzyme : locate in smooth endoplasmic reticulum membrane
- All require NADPH and O2
- Divided to Family : Subfamily : Isoform
- CYP1, CYP2, CYP3 : involved in the metabolism of xenobiotic



C. Normal hepatocyte



D. Hepatocyte after phenobarbital administration

CYTOCHROME P450 DEPENDENT MIXED FUNCTION OXIDASES

OTHER (NON-MICROSOMAL) PHASE I REACTIONS

- Hydrolysis in plasma by *esterases* (suxamethonium by cholinesterase)
- Alcohol and aldehyde *dehydrogenase* in liver cytosolic (ethanol)
- Monoamine *oxidase* in mitochondria (tyramine, noradrenaline, dopamine, amines)
- Xanthine *oxidase* (6-mercaptopurine, uric acid production)
- Enzymes for particular substrates (tyrosine *hydroxylase*, dopa-*decarboxylase etc*.)

PHASE 2 REACTIONS

CONJUGATIONS

- -OH, -SH, -COOH, -CONH with glucuronic acid to give glucuronides
- -OH with sulphate to give sulphates
- -NH2, -CONH2, amino acids, sulpha drugs with acetyl- to give acetylated derivatives
- -halo, -nitrate, epoxide, sulphate with glutathione to give glutathione conjugates

All tend to be less lipid soluble and therefore better excreted (less well reabsorbed)

FACTORS AFFECTING METABOLISM

- **Age** (reduced in aged & children)
- **Sex** (women more sensitive to ethanol)
- **Species** (phenylbutazone 3h rabbit, 6h horse, 8h monkey, 18h mouse, 36h man)
- **Race** (fast and slow isoniazid acetylators, fast = 95% Eskimo, 50% Brits, 13% Finns 13% Egyptians)
- **Clinical** or **physiological** conditions