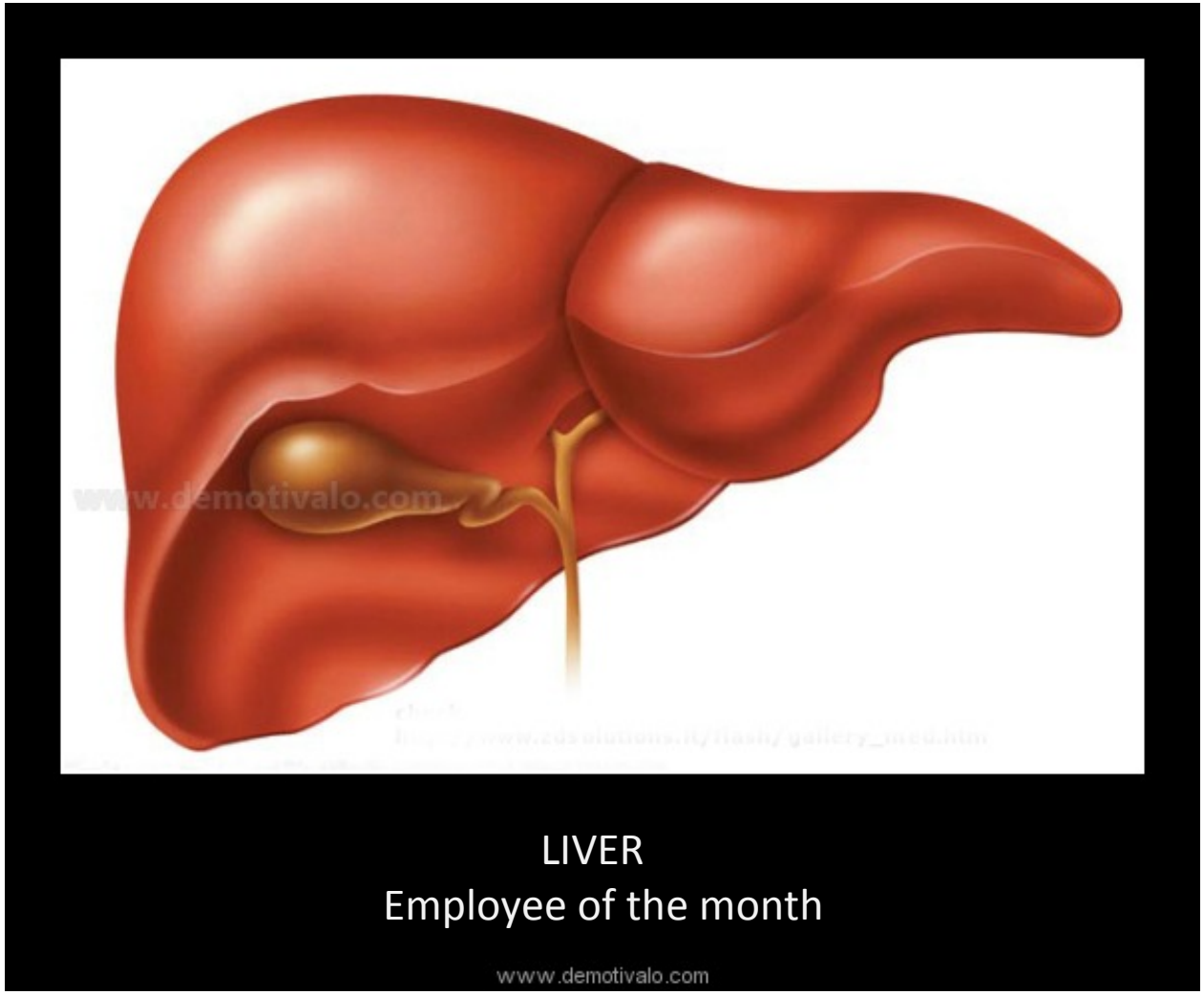
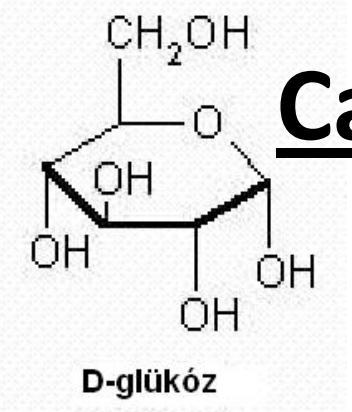
Role of liver in metabolism



Functions

- Central role in metabolic regulation and the energy transfer
- Biosynthesis: glucose, plasma proteins
- Storage: glycogen, metal ions, vitamins
- Detoxification: biotransformation, urea-cycle, bile product



Carbohydrate metabolism and the liver

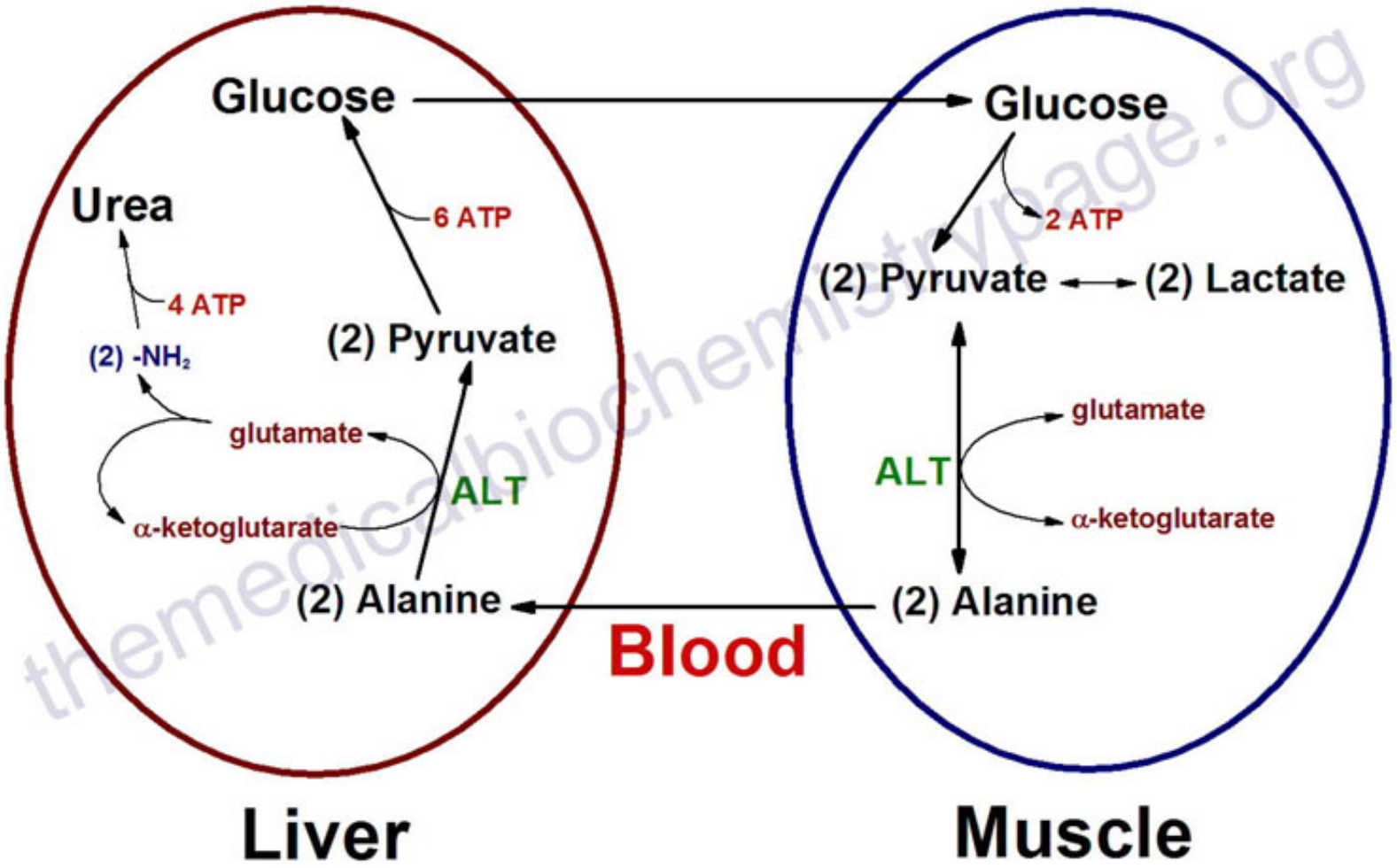
- Low blood glucose level→activation of glycogenolysis and gluconeogenesis
- High blood glucose level→activation of glycogenesis and glycolysis

- Excess glucose: acetyl-CoA->FFA->TG

- HMP-shunt
- Cori-cycle and glucose-alanine cycle

FFA: free fatty acid
TG: triglyceride

Glucose-Alanine Cycle



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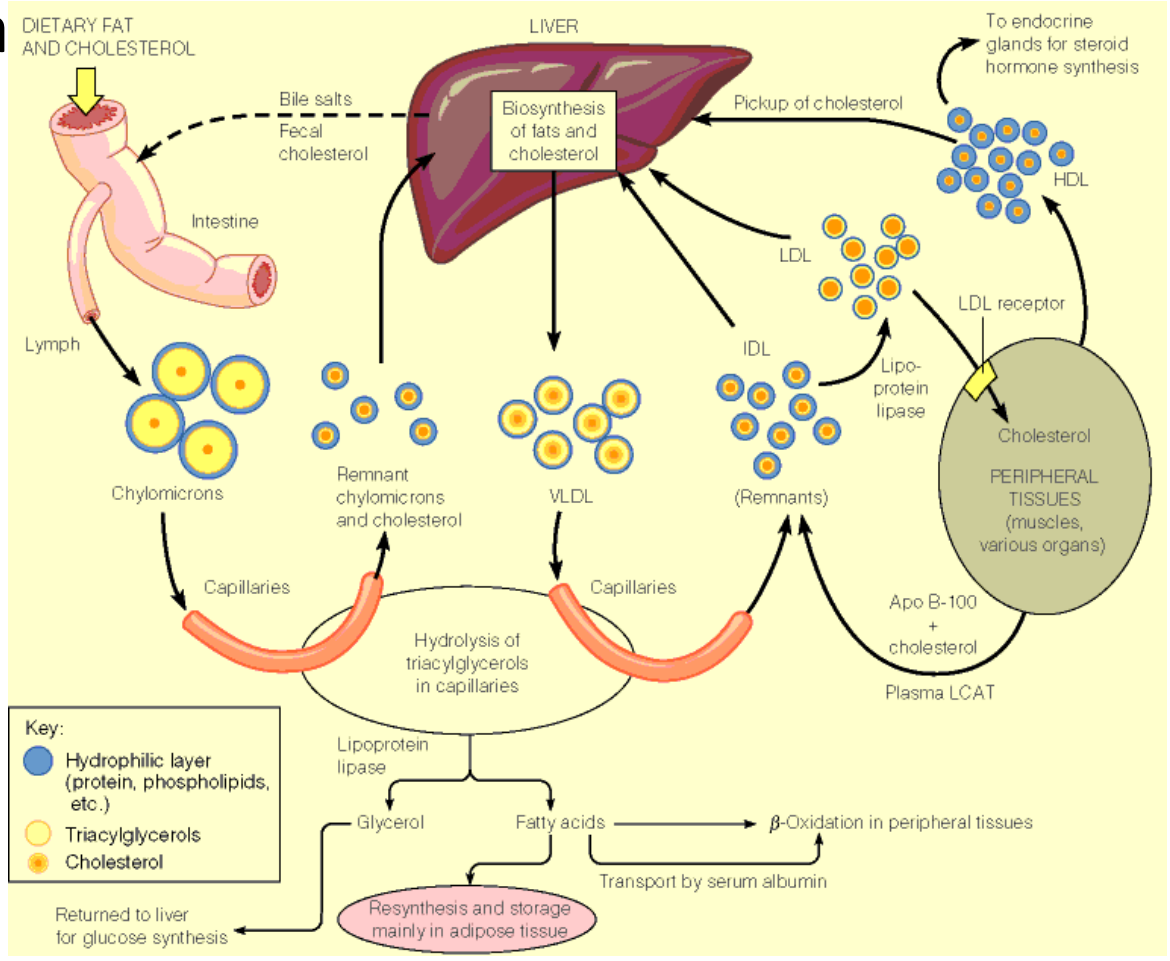
Liver specific processes in carbohydrate metabolism

- Glycolysis: glucokinase isoenzyme
- Gluconeogenesis: glucose-6-phosphatase
- Fructose metabolism
- Galactose metabolism
- Synthesis of uron acids (glucuronic acid)

- Conjugation processes

Lipid metabolism and liver

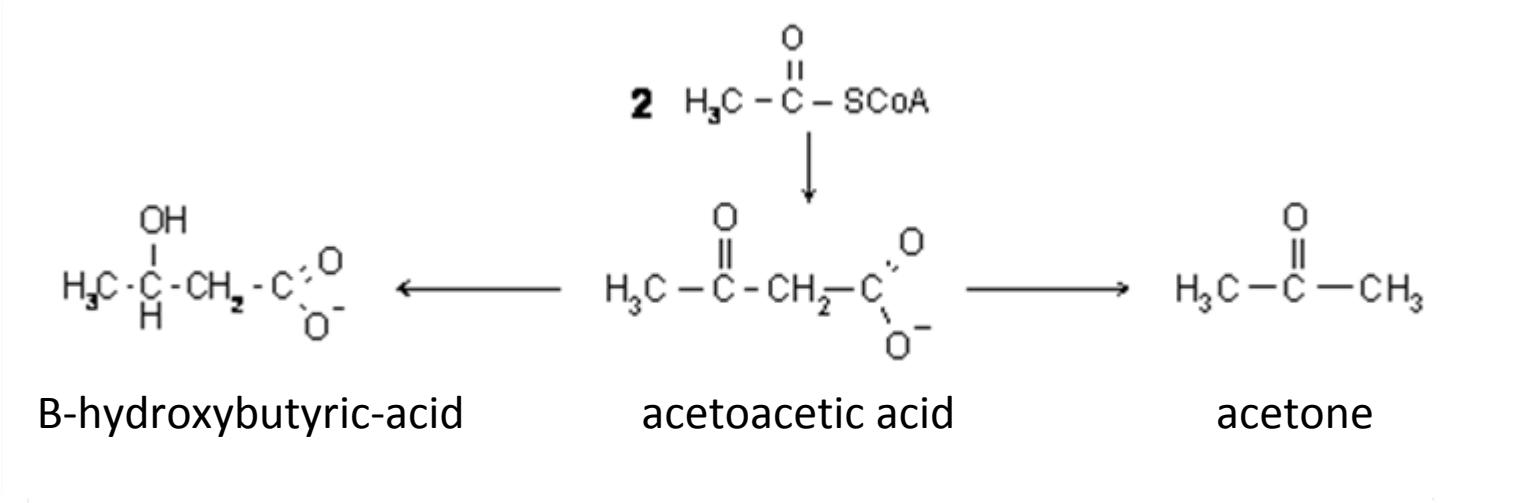
- Regulation of blood free fatty acid concentration: synthesis of TG
- Synthesis of cholesterol and lipoporotein meta



Liver specific processes in lipid metabolism

- Synthesis of ketone bodies (acetone, acetoacetic acid, beta-hydroxybutyric-acid)

- Alternative energy source
- Ketone bodies are produced from acetyl-CoA
- Use: brain, heart, sceletal muscle
- Metabolic acidosis, osmotic diuresis



Liver specific processes in lipid metabolism

- Synthesis of bile acids:

- primary ~: cholic acid, chenodeoxycholic acid

↓ conjugation with taurine or glycine ↓

secondary ~: deoxycholic acid, lithocholic acid

- Enterohepatic circulation (later)

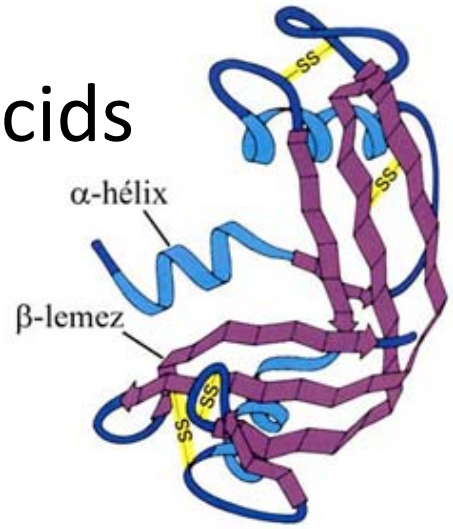
- Functions:

1. Fat digestion (emulsification)
2. Cholesterol elimination

Bile: Aqueous solution containing bile acids (80%), cholesterol (5%), phospholipids (15%), bile pigments, inorganic and other materials.

Protein metabolism and liver

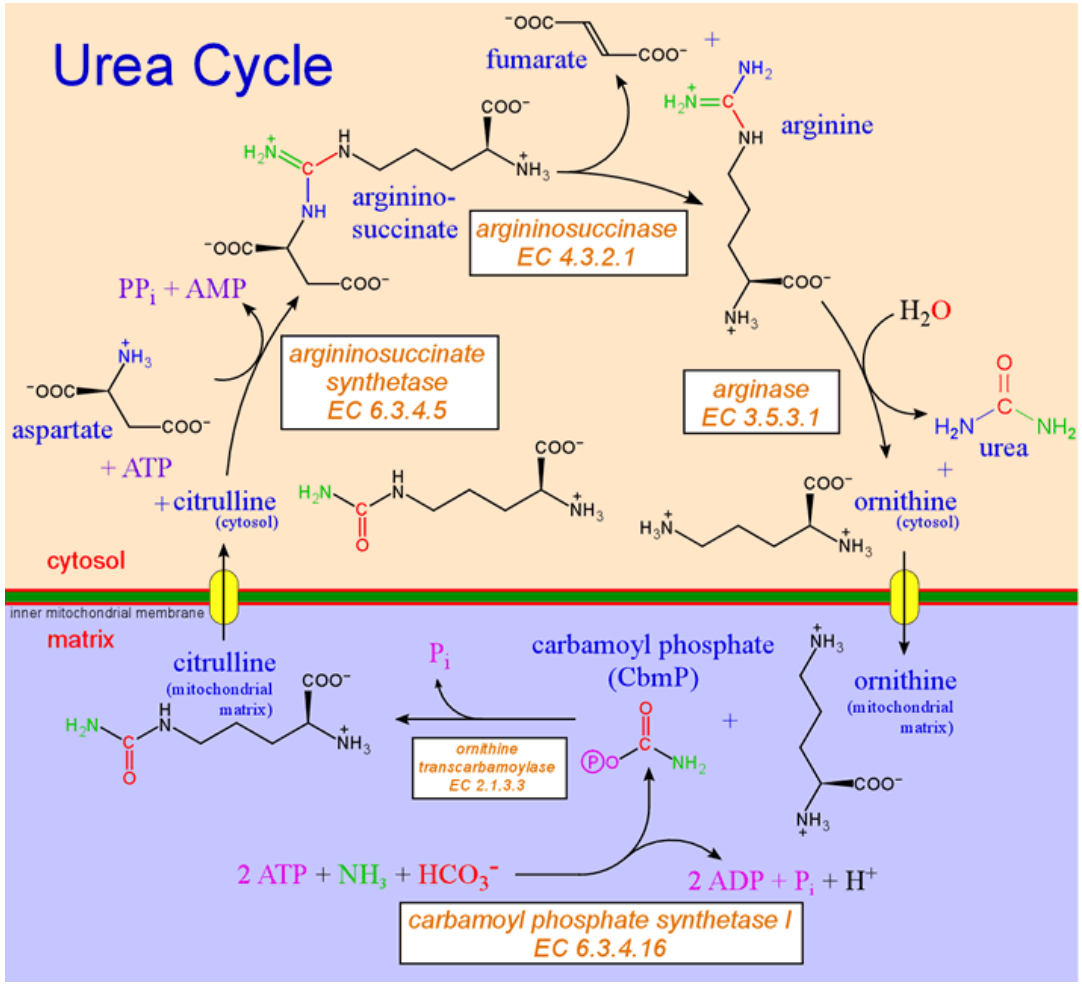
- After the absorption, amino acids are transported to the liver
- Synthesis of plasma proteins (exception: Ig)
- Synthesis of coagulation factors
- Synthesis of acute phase proteins
- Synthesis of non essential amino acids



Liver specific processes in protein metabolism

- Protein metabolism end product: ammonia

- Elimination: Urea cycle*



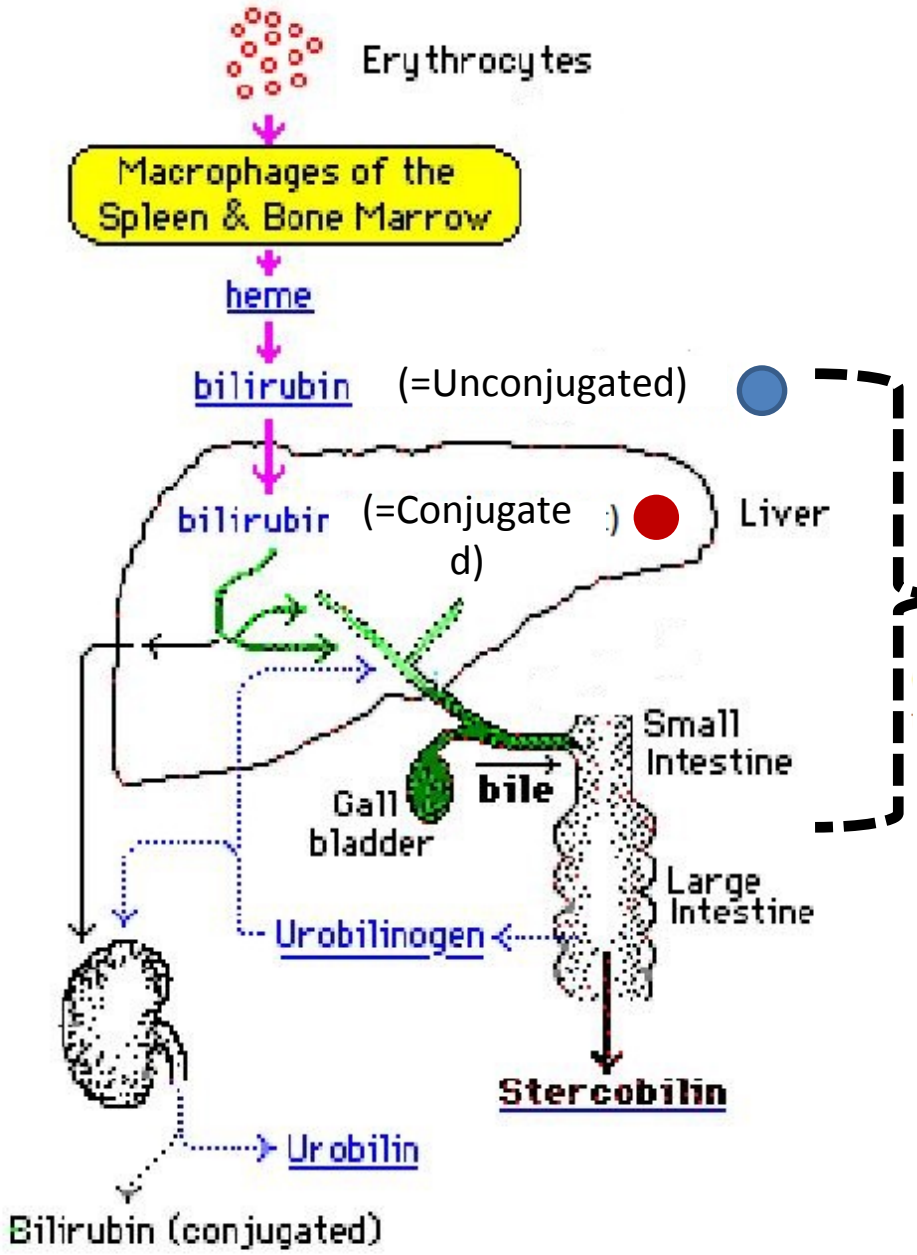
*def.: hyperammonemia

Bilirubin metabolism

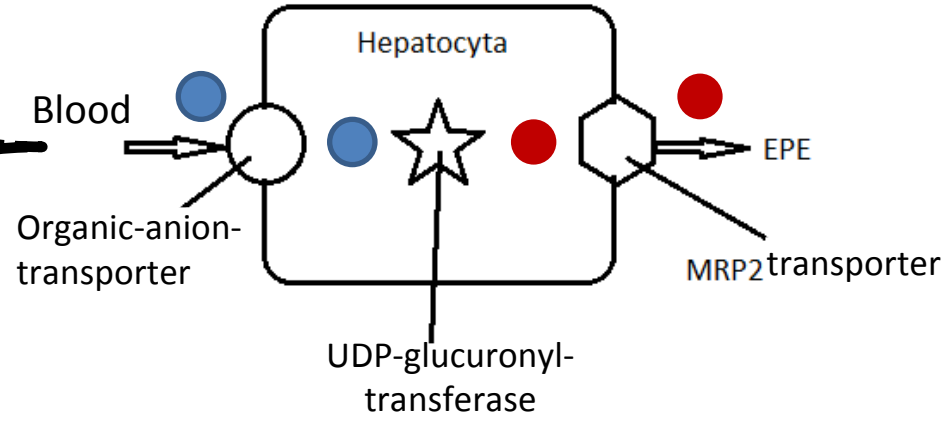
- Hemoglobin->biliverdin->bilirubin-> transfer to liver by albumin: **unconjugated=indirect bilirubin**
- Conjugation with glucuronic acid in liver (UDP-glucuronyl-transferase): **conjugated=direct bilirubin**
- It goes into the bile and thus out into the small intestine and passes into the colon
- Colonic bacteria deconjugate and metabolize the bilirubin: formed **urobilinogen** and **stercobilinogen**
- Szterkobilinogen->**stercobilin**: brown color of stool
- Urobilinogen is resorbed (enterohepatic circulation)

->**urobilin**: yellow color of urine

Bilirubin metabolism



Conjugation of bilirubin



Disease:

Icterus=Jaundice

- Icterus=hyperbilirubinemia: serum bilirubin >35mol/l (ref. <17 µmol/l)
- Yellow pigmentation of the skin, sclera and other mucous membranes
- Types:

	Serum indirect bilirubin	Serum direct bilirubin	Urine direct bilirubin	Urine UBG
Prehepatic	++	**0**	**0**	**+(n)**
Hepatic	+	+	+	++
Posthepatic	**0**	+	++	**0**

- Prehepatic icterus:

- unconjugated bilirubin ⬆
- main cause: hemolysis

- Hepatic icterus:

- conjugated and unconjugated bilirubin ⬆
(conjugated bilirubin >50%)
- main cause: liver failure

- Posthepatic icterus:

- conjugated bilirubin ⬆
- main cause: obstruction of bile duct

Genetic hyperbilirubinemia

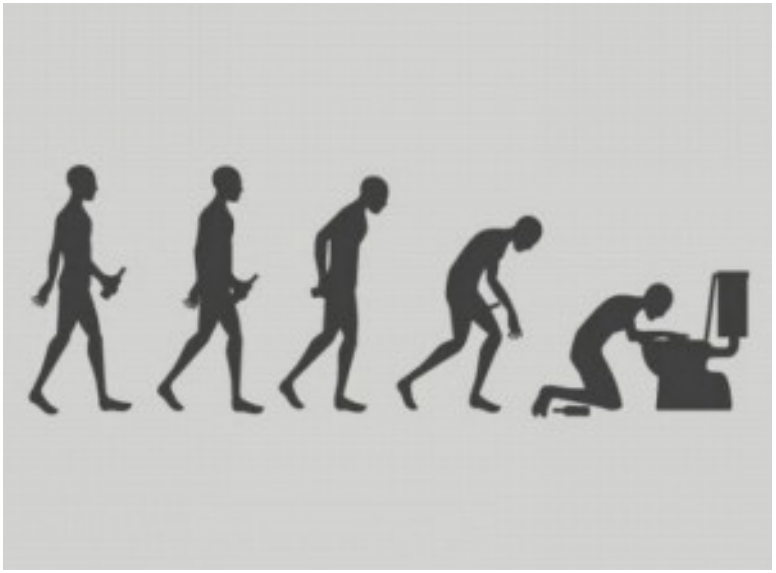
- **Unconjugated hyperbilirubinemia**:

- Gilbert-disease: defect of UDP-glucuronyl-transferase (gtriggers: alcohol, stress)
- Crigler-Najjar sy: defect of UDP-glucuronyl-transferase

- **Conjugated hyperbilirubinemia:**

- Dubin-Johnson sy: mutation of MRP2 protein
- Rotor sy:

Biotransformation and alcohol breakdown



Biotransformation

- Functions:

1. Detoxification: nonpolar compounds → polar compounds

- Exogenic and endogenic materials

2. Synthesis and inactivation of signaling molecules

- Localisation: liver
- 3 phases

Phase I: Preparation

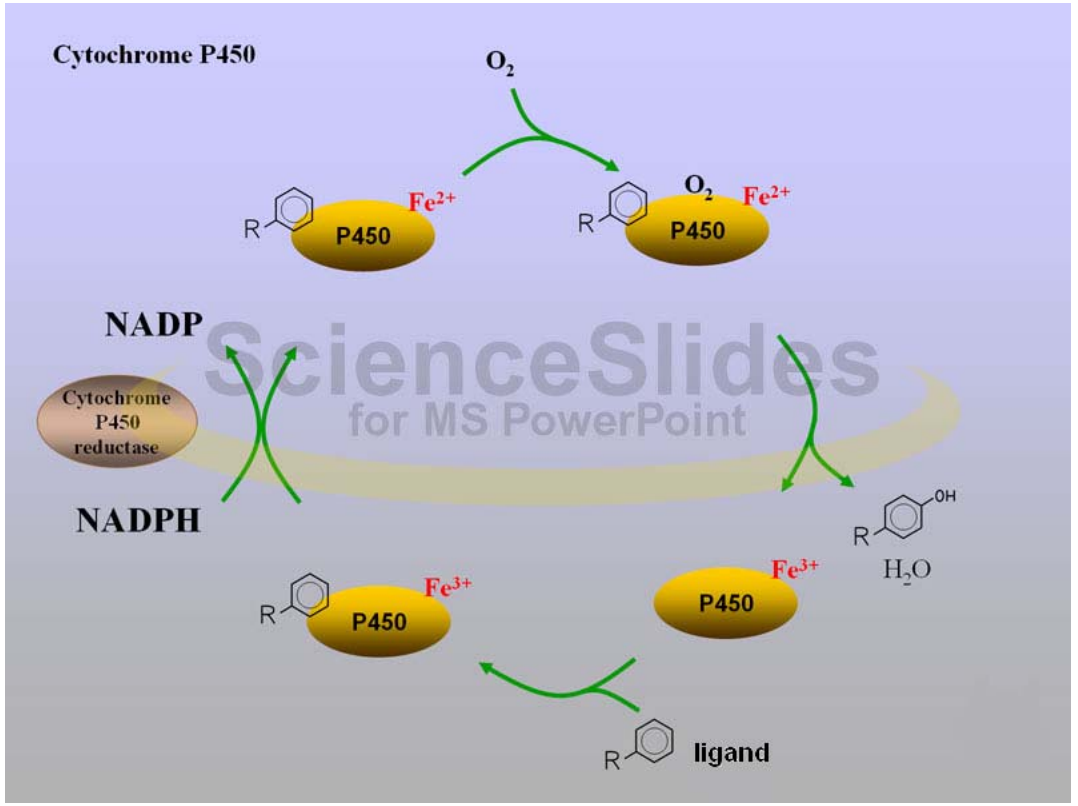
- Add functional groups(-COOH, -SH, -OH, -NH_2)

- hydrolysis
- reduction
- oxidation: Microsomial respiratory chain:

->NADPH-cytochrome P450-reductase

->Cytochrome b_5

->Cytochrome P450 isoenzymes



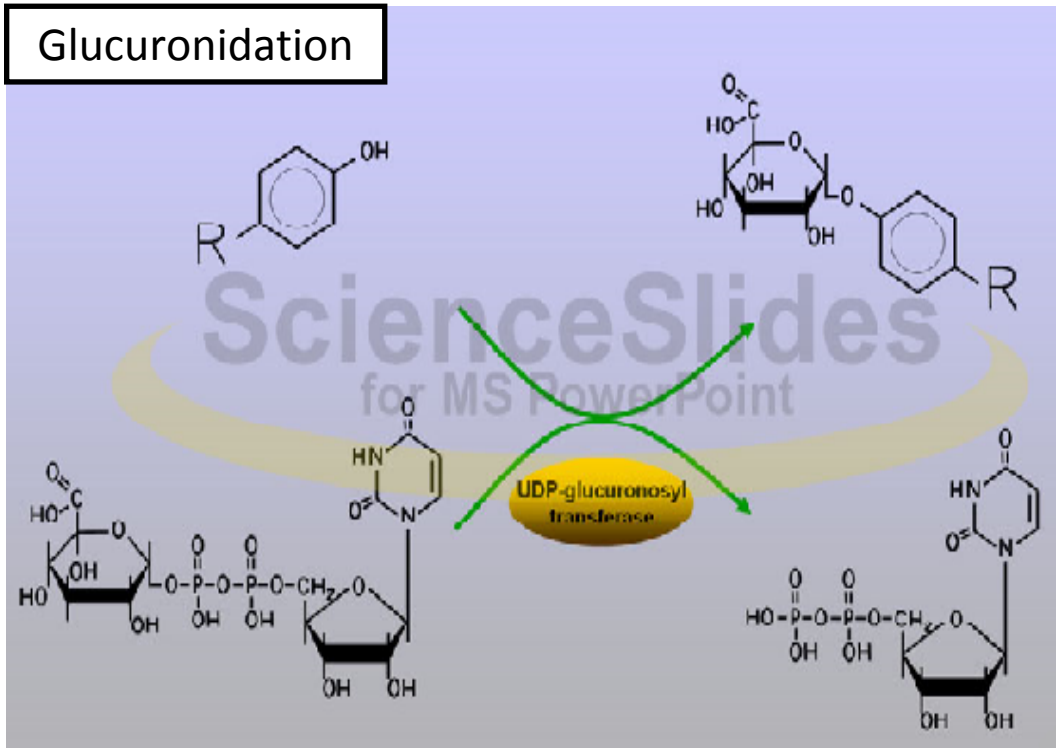
Phase II: Conjugation

- Conjugation with endogenous molecules (glucuronic acid, glutathione, amino acid)-> large increase in hydrophilicity

- glucuronidation (UDP –glucuronil-transferase)

- sulphatation (PAPS)

- methylation (SAM)

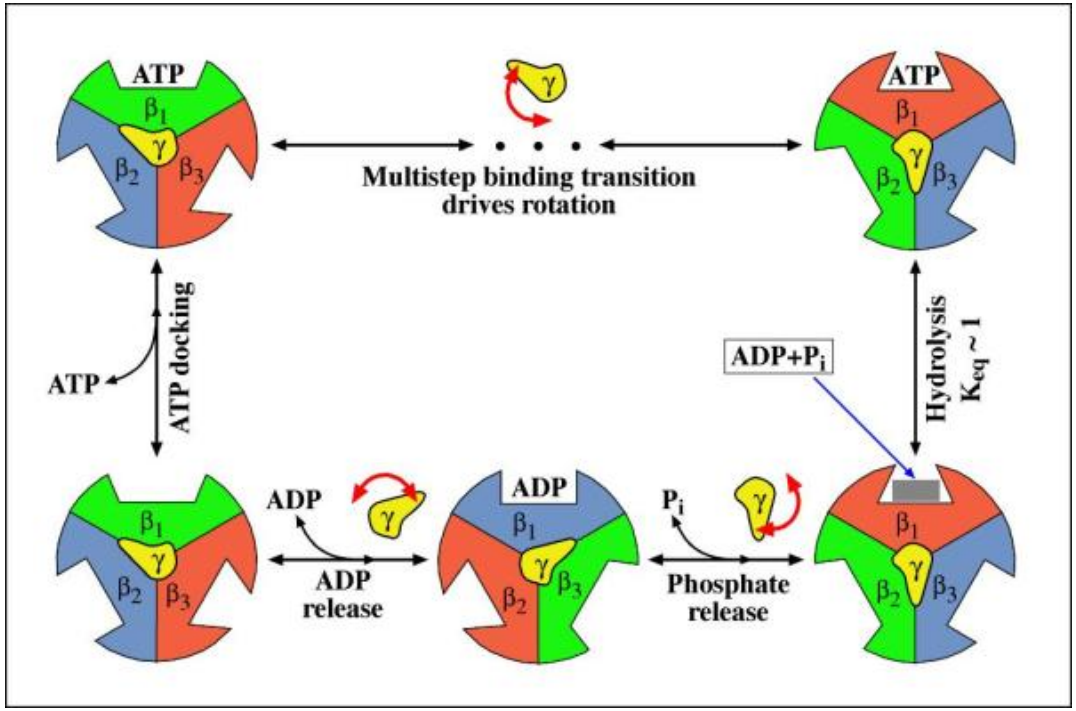


Phase III: Transport

- The resulting compounds transported to blood or bile by different transporters (active transport)

- ABC transporter

- P-type ATPase



Regulation of biotransformation

- Enzyme induction: only microsomal enzyme system

- endogenous inductor: hormones (after birth)
- exogenous inductor: drugs (antibiotics, dioxin)
- the inductors induced cofactor supply

- Cofactors: nessecery in phase I and II

- Phase I.: NADPH (oxygenase system)
- Phase II: UDP-glucuronic acid (glucuronidation)

Pathological conditions

- Non toxic materials→toxic materials

- Nitrose amine $\xrightarrow{\text{CYP2E}}$ diaso-hidroxide –> mutagenic

- Enzyme defects

- pl.: Gilbert-disease, Dubin-Johnson syndrome

Alcohol metabolism

- Drug without receptor
- Sympathetic tone ↑ (adrenalin ↑)
- Rapid absorption from the gastrointestinal system
- Metabolism:

- 1-5 mmol/l blood concentration: alcohol-dehydrogenase
- >5 mmol/l: microsomical ethanol oxidizing system

First metabolism (FPM)

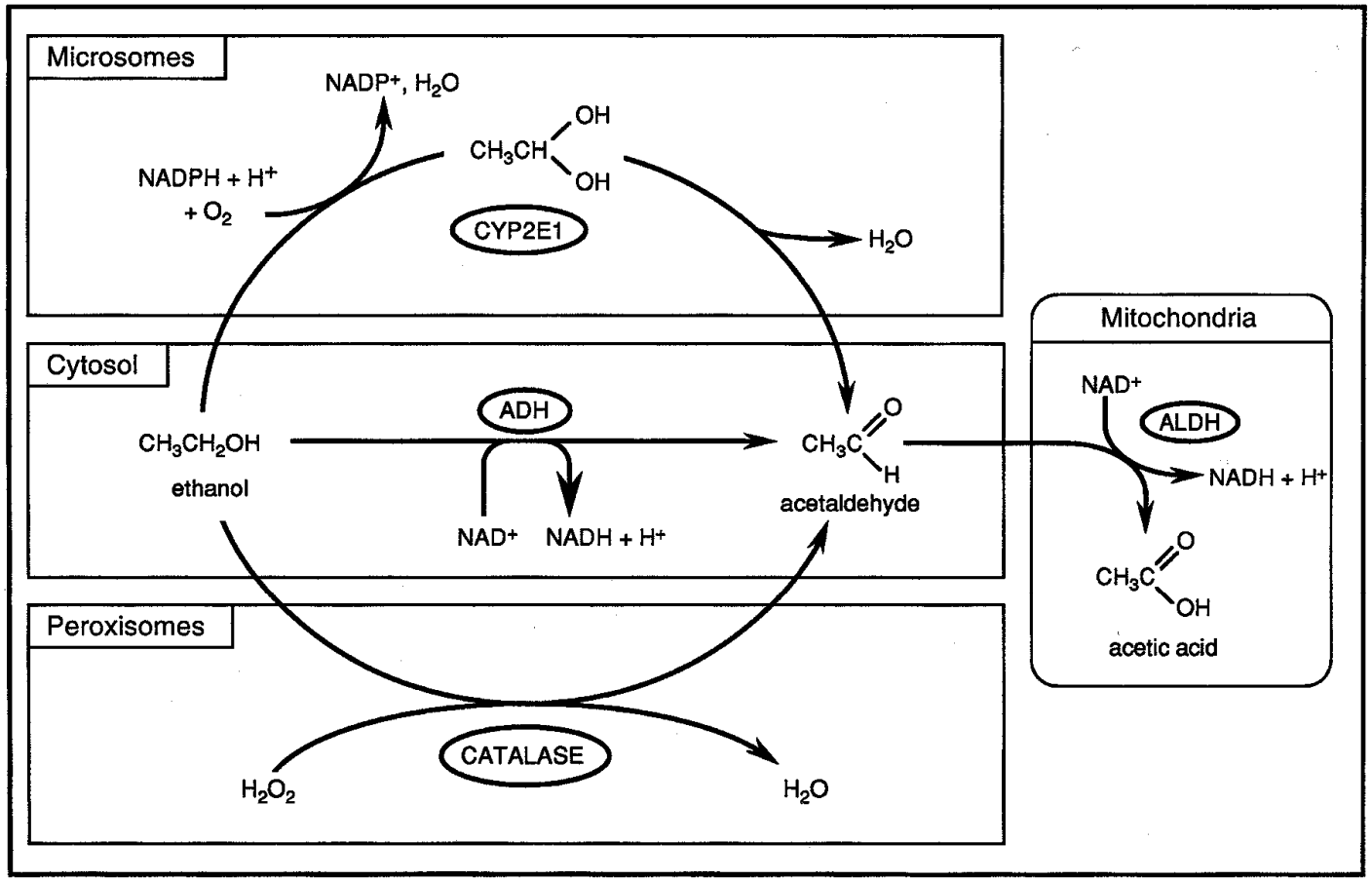
- In stomach
- 10-20%
- High alcohol concentration
- Alcohol-DH: Km>500 mM

- FPM(first pass metabolism) ↓:

- starvation
- inhibiting alcohol-DH
- low FPM: female

Secondary metabolism

- In LIVER!!!



ADH: alcohol-DH
ALDH: aldehyde-DH

CYP2E1: microsomical ethanol oxidizing system

Effect of alcohol

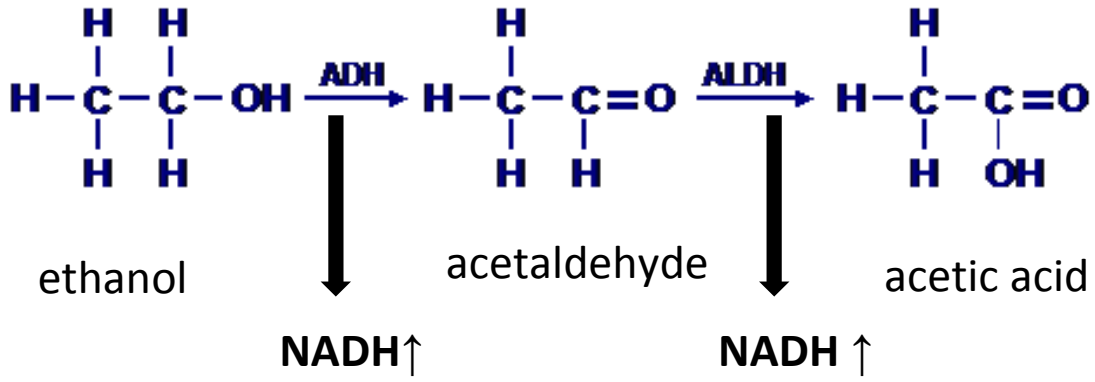
- **NADH/NAD ration ↑ (NADH↑):**

- Inhibition of fatty acid oxidation->TG↑-> fatty liver

- Inhibition of gluconeogenesis -> starvation hypoglycemia

- Inhibition of TCA cycle

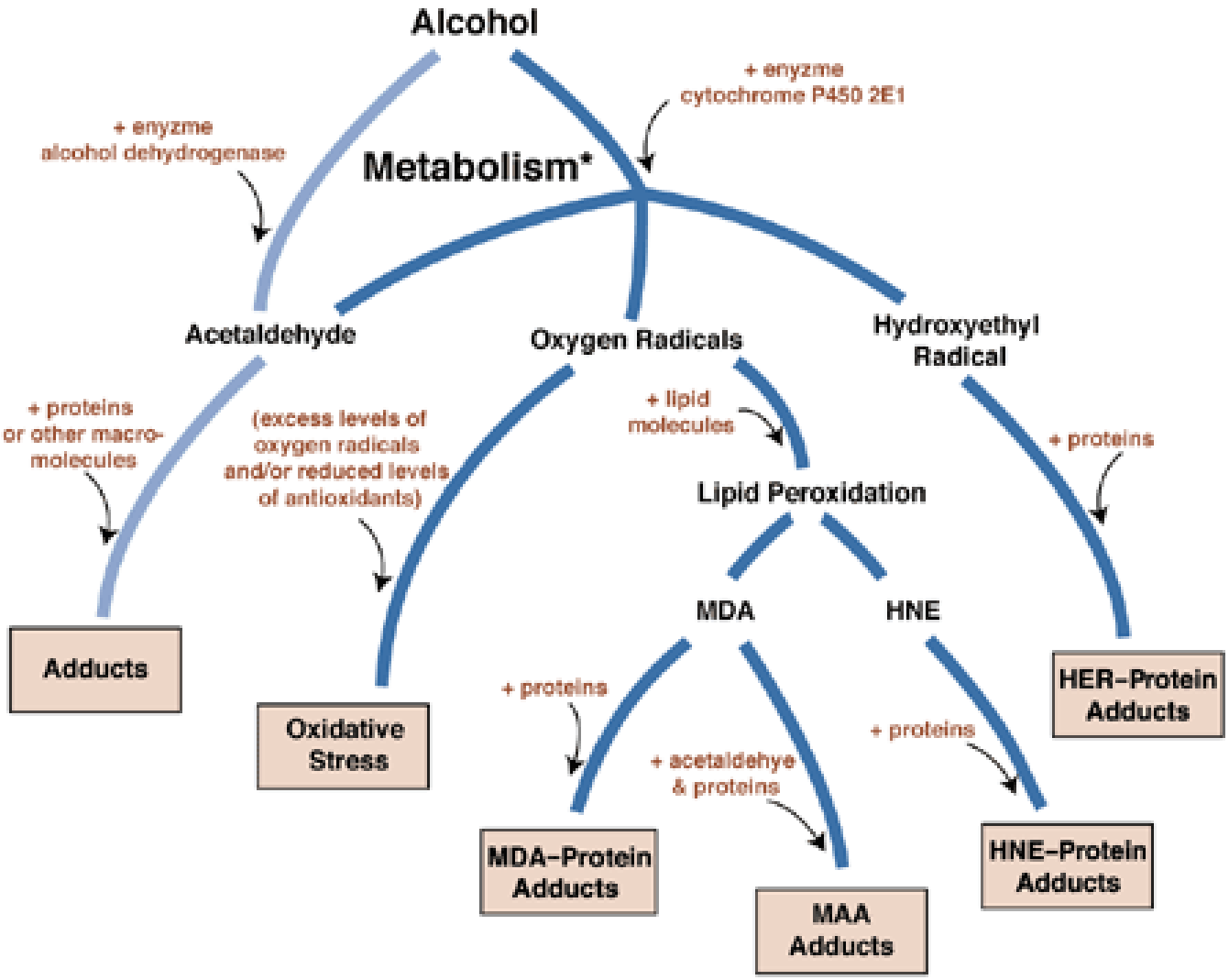
- acetyl-CoA↑



Alcohol's damaging effects

- **Production of Reactive Oxygen Species ↑ :**

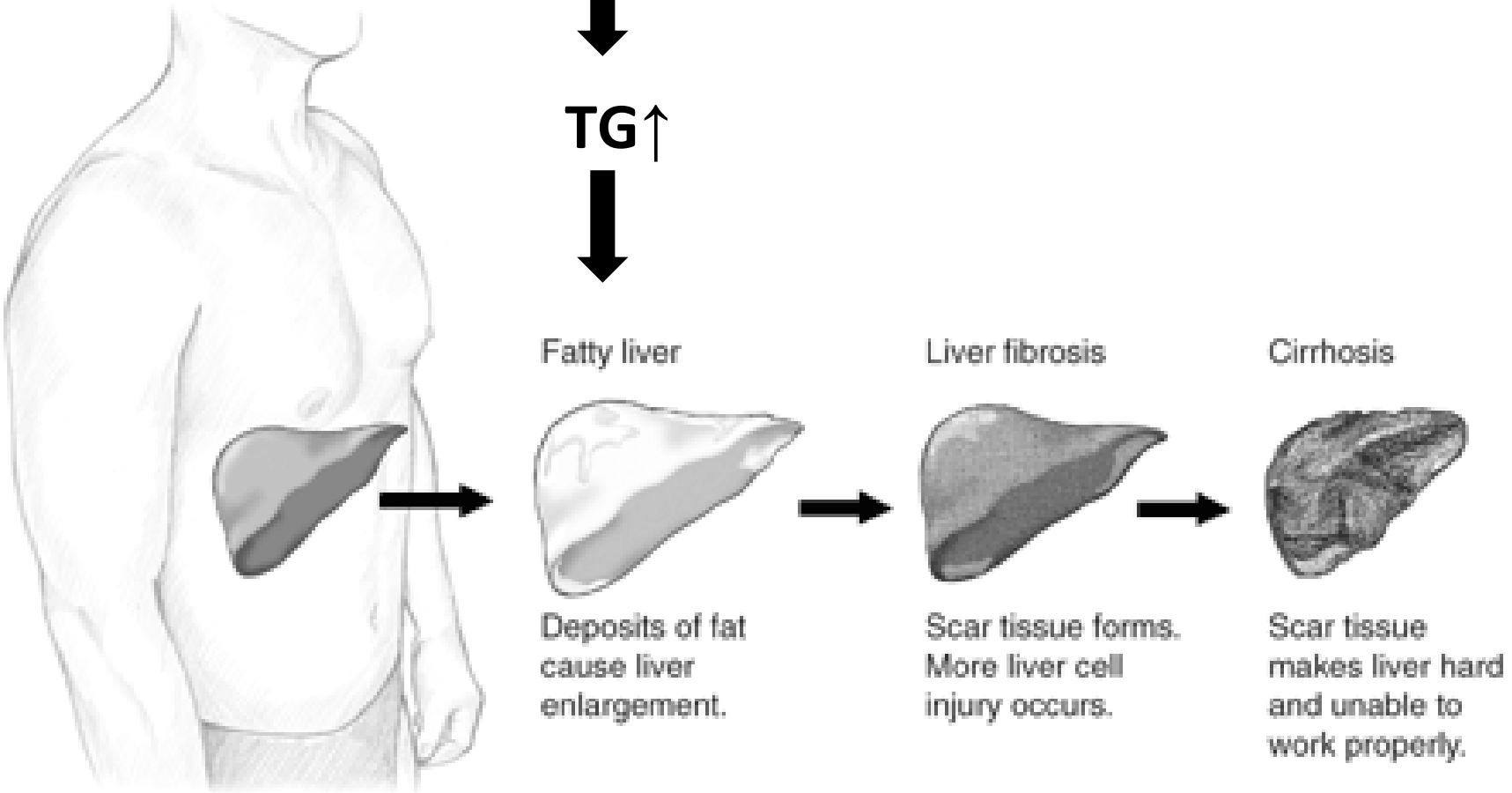
- Mithocondrial respiratory chain ->oxygen free radicals↑
- Lipid peroxidation and protein oxidation
- Elevation of intracellular free iron levels-> oxygen free radicals ↑
- Mitochondrial damage ->ATP production↓
- Activation of CYP2E1 enzyme system-> oxygen free radicals ↑
- Xantin dehydrogenase ⟶ xantin oxidase ↑ (superoxide radicals ↑)
- Antioxidant enzymes and glutathione ↓


Alcohol
+ enyzme
cytochrome P450 2E1
+ enyzme
alcohol dehydrogenase
Metabolism*
Acetaldehyde
Oxygen Radicals
Hydroxyethyl
Radical
+ proteins
or other macro-
molecules
(excess levels of
oxygen radicals
and/or reduced levels
of antioxidants)
+ lipid
molecules
+ proteins
Lipid Peroxidation
MDA
HNE
Adducts
Oxidative
Stress
+ proteins
+ acetaldehye
& proteins
+ proteins
HER-Protein
Adducts
MDA-Protein
Adducts
MAA
Adducts
HNE-Protein
Adducts

Effect of chronic alcohol consumption

NADH↑

TG↑



Alcohol's effects on the different organs

Organ	Condition	Effect
Central nerve system	Acute	confusion → coma
	Chronic	Memory disfuntcion, psychosis
	Distraction	Attack, delirium tremens
Cardiovascular system	Chronic	Cardiomyopathy
Sceletal muscle	Chronic	Myopathy
Gastric mucosa	Acute	Irritation
	Chronic	Ulcer
Liver	Chronic	Fatty liver → cirrhosis
Kidney	Acute	diuresis
Blood	Chronic	Anemia, decrease of platelets
Testes	Chronic	Impotence
Fetus	Pregnancy	Foetal alcohol syndrome