Metabolic functions of liver

Seminar No. 7

Compartment	Metabolic pathways
Mitochondrion	
Lysosome	
Nucleus	
Cytoplasm	
Smooth ER	
Rough ER	
Golgi app.	

Mitochondria	β-oxidation FA, oxid. decarb. of pyruvate, CAC, resp. chain, AST reaction, synthesis of urea / KB / heme / glutamine
Lysosome	nonspecific hydrolytic degradation of various substrates
Nucleus	DNA replication, RNA synthesis = transcription
Cytoplasm	glucose metabolism, ALT reaction, ethanol oxidation, Synthesis of FA / urea / uric acid / heme
Smooth ER	Synthesis of cholesterol / PL /TAG FA desaturation, biotransformation of xenobiotics (hydroxylation)
Rough ER	proteosynthesis
Golgi app.	protein glycosylation, sorting + export of proteins

Periportal hepatocytes

Process	Enzyme(s)
	ALT, AST
	succinate DH, malate DH
	LD
	carbamoyl-P-synthetase, arginase
	glutaminase
	GSH peroxidase ...
	HMG-CoA reductase
	Glc 6-phosphatase, PEPCK
	Glycogen synthase

Periportal hepatocytes

Process	Enzyme(s)
transamination	ALT, AST
CAC	succinate DH, malate DH
Gluconeogenesis (Cori cycle)	LD
Urea synthesis	carbamoyl-P-synthetase, arginase
Release of ammonia	glutaminase
ROS elimination (reduction)	GSH peroxidase ...
Cholesterol synthesis	HMG-CoA reductase
gluconeogenesis	Glc 6-phosphatase, PEPCK
Glycogen synthesis	Glycogen synthase

Perivenous hepatocytes

Process	Enzyme(s)
	GMD
	Acetyl-CoA carboxylase
	AD
	Cytochromes P-450
	Glutamine synthetase
	UDP-glucuronyl transferase
	glukokinase

Perivenous hepatocytes

Process	Enzyme(s)
Dehydrogenation deamination of Glu	GMD
FA synthesis	Acetyl-CoA carboxylase
Ethanol catabolism	AD
hydroxylations	Cytochromes P-450
Ammonia detoxication	Glutamine synthetase
Conjugation reactions	UDP-glucuronyl transferase
glycolysis	glukokinase

Q. 2

A. 2

A) **after meal:** insulin decreases blood glucose by stimulating liver glycolysis and synthesis of glycogen

B) **in fasting:** glucagon stimulates glycogenolysis and gluconeogenesis

C) **in starvation:** glucagon stimulates gluconeogenesis (liver glycogen is depleted)

Q. 3

A. 3

fructose and galactose are converted to glucose

What are dietary sources of fructose and galactose?

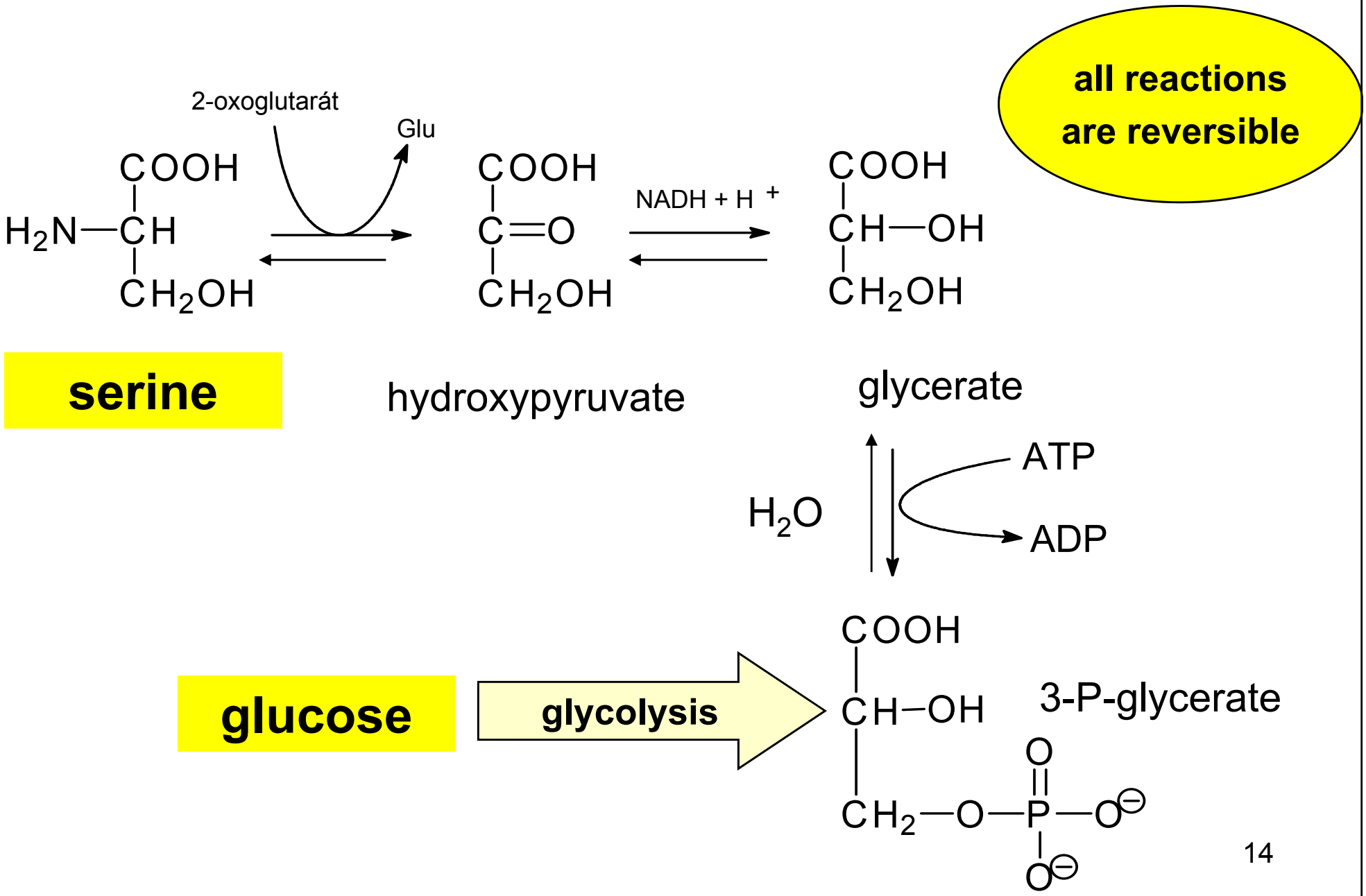
Q. 5

Glycolysis intermediate	Non-hexose product
Glc-6-P	
Fructose-6-P	
DHAP	
3-phosphoglycerate	

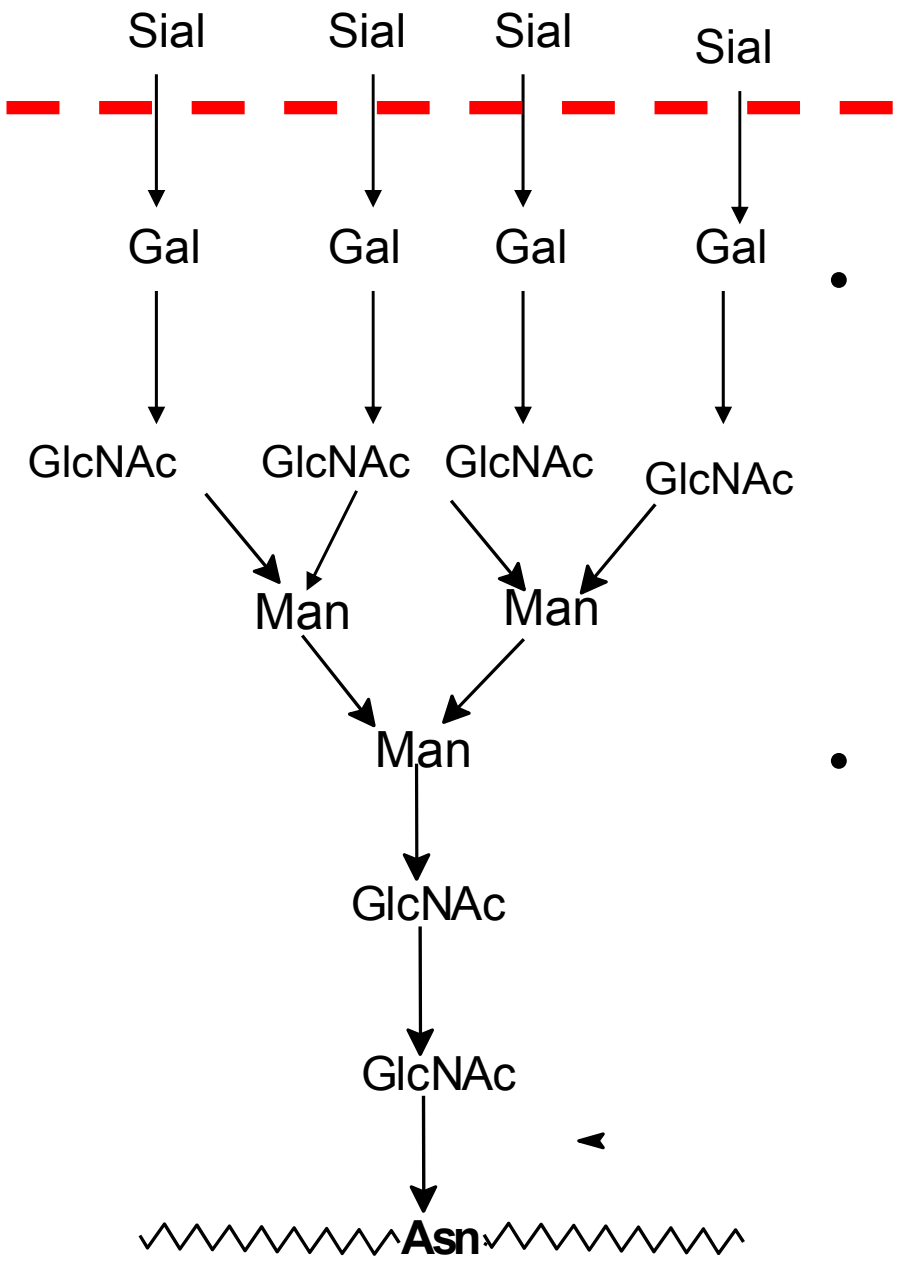
A. 5

Glycolysis intermediate	Non-hexose product
Glc-6-P	Ribose (from pentose cycle)
Fructose-6-P	Glucosamine → glycosaminoglycans
DHAP	Glycerol-3-P → TAG
3-phosphoglycerate	serine

Synthesis of serine from glucose



Q. 6



A. 6 (Harper, p. 526)

- Plasma (glyco)proteins and peptide hormons (e.g. insulin) are taken up and degraded in liver lyzosomes
- Glycoproteins lost sialic residues by the action of neuramidase = terminal galactose is the signal for **asialoglycoprotein receptor** in liver

Q. 7

A. 7

- Liver produces most plasma proteins including coagulation factors
- Severe liver damage = limited / no synthesis
- Deficit of coag. factors = increased bleeding
- Deficit of albumin (main plasma prot.) = oedemas

Q. 10

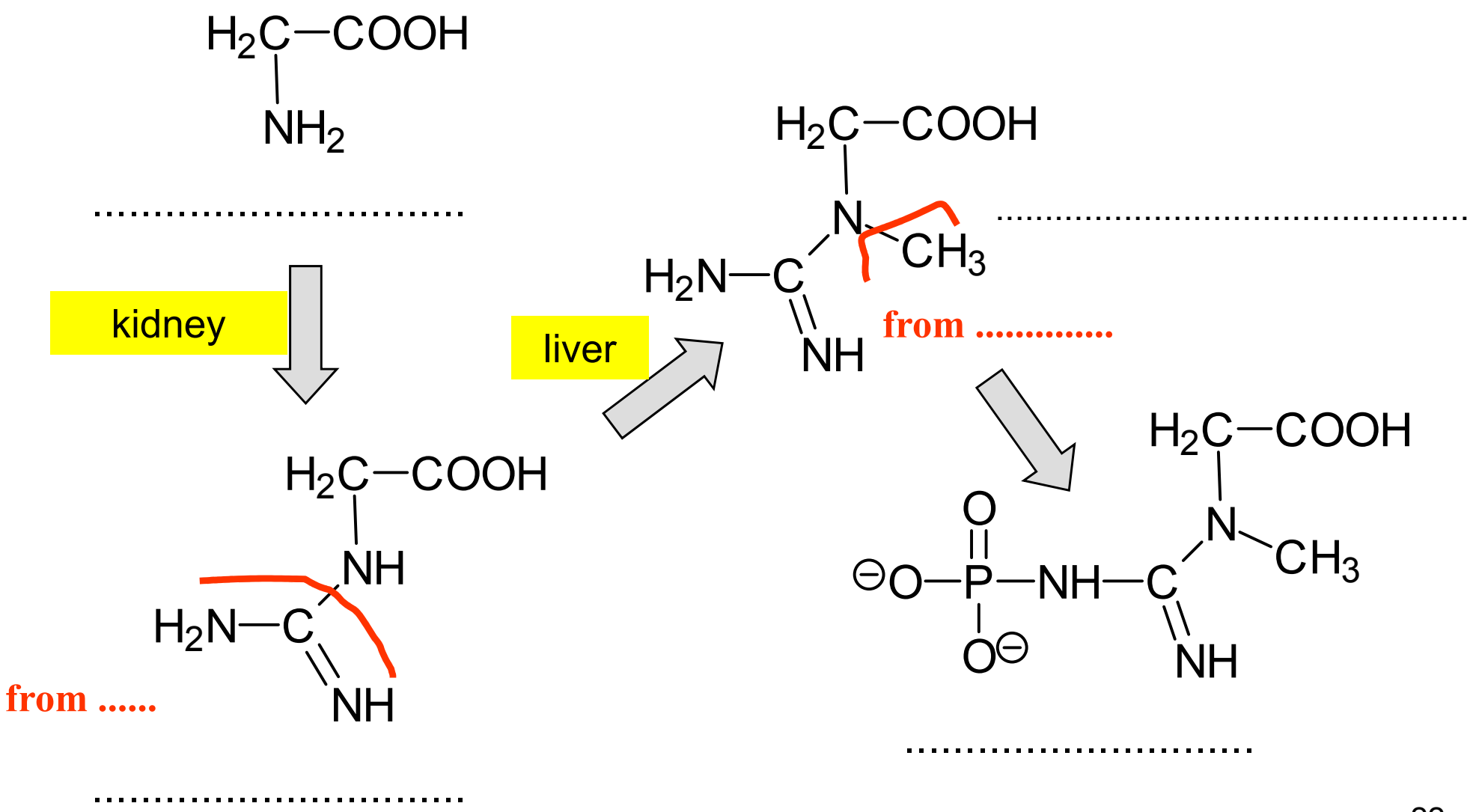
A. 10

- α_1-antitrypsin is antiprotease
- Inhibits proteases produced by tissue and plasma cells (trypsin, elastase, and other)

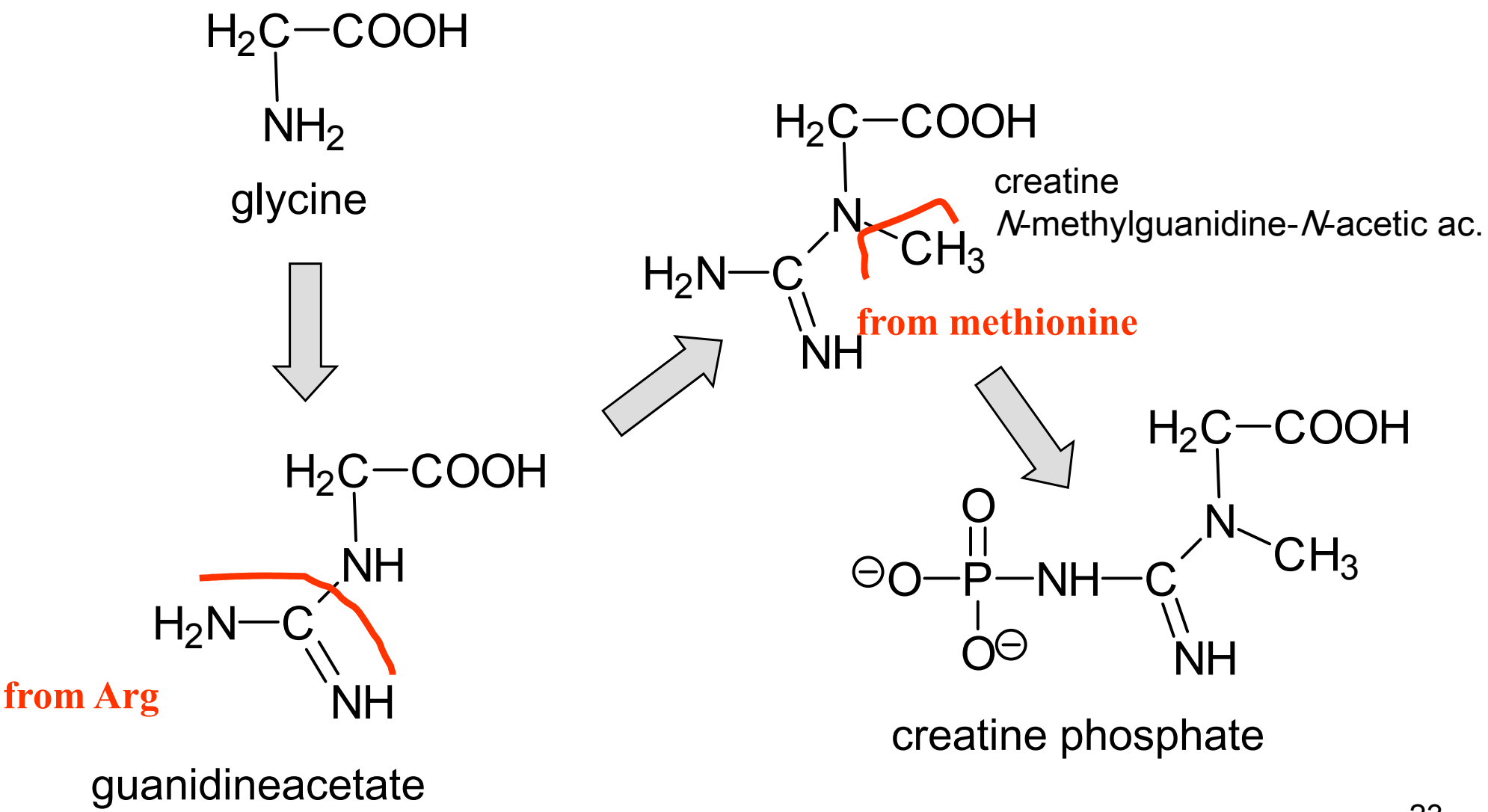
- Decreased production of α_1-antitrypsin $\Rightarrow$ active proteases in ECF $\Rightarrow$ tissue proteolysis $\Rightarrow$ tissue damages (emphysema, liver diseases)

Q. 12

A. 12 Complete the names of compounds



A. 12


H2C—COOH
NH2
glycine
H2C—COOH
NH
H2N—C
NH
from Arg
guanidineacetate
H2C—COOH
creatine
N-methylguanidine-N-acetic ac.
N
CH3
H2N—C
NH
from methionine
H2C—COOH
O
⊖O—P—NH—C
N
CH3
O⊖
NH
creatine phosphate

Q. 13

A.13 **To decrease NH_3 formation in colon and its concentration in portal blood – to protect liver**

1. **Low-protein diet**
2. **Alteration of colon microflora**

- **Probiotics** – live bacteria supporting fermentation processes in large intestine (lactobacillus, bifidobacteria)
- **Prebiotics** – nondigestible oligosaccharides – substrates for the growth of probiotics (lactulose, oligofructose, inulin)
- **Local intestinal antibiotics** (neomycin, metronidazol) – kill all intestinal microflora

Q. 14

A. 14

Dietary FA to liver:

- **Short chain FA (< 12C)** directly from portal blood (protein transporter, cotransport with Na^+)

- **Other FA** in CM remnants (apo E receptors)

- FA are oxidized to acetyl-CoA and CAC - energy

Q. 15

A. 15

A) Synthesis of VLDL, HDL

B) Degradation - CM remnants, IDL, LDL, HDL_2

(hepatic lipase, lysosome)

A. 16

A. 16

- Saccharides are necessary for CAC
- The lack of saccharides = the excess of acetyl-CoA from FA β-oxidation = synthesis of KB
- **for export only**

  succinyl-CoA:acetoacetate-CoA transferase (for activation of acetoacetate) is not expressed in liver

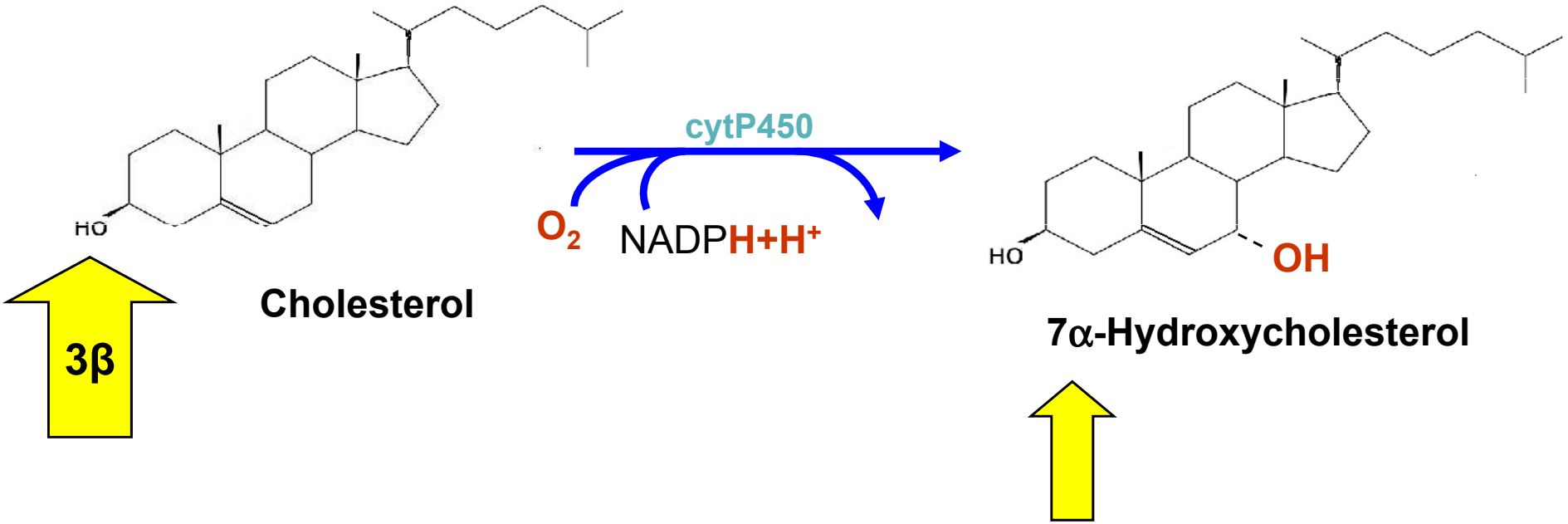
Q. 17

A. 17

- excretion of cholesterol into bile
- synthesis + conjugation of bile acids
- excretion of bile acids into bile

A. 18

The first step is 7α-hydroxylation of cholesterol



7α-Hydroxycholesterol

O_2 + NADPH+H^+
Cyt P 450

5β-Cholestane-3α,7α,12α-triol

Coenzyme A, ATP

Propionyl-CoA, ADP

Cholate

Coenzyme A, ATP

ADP

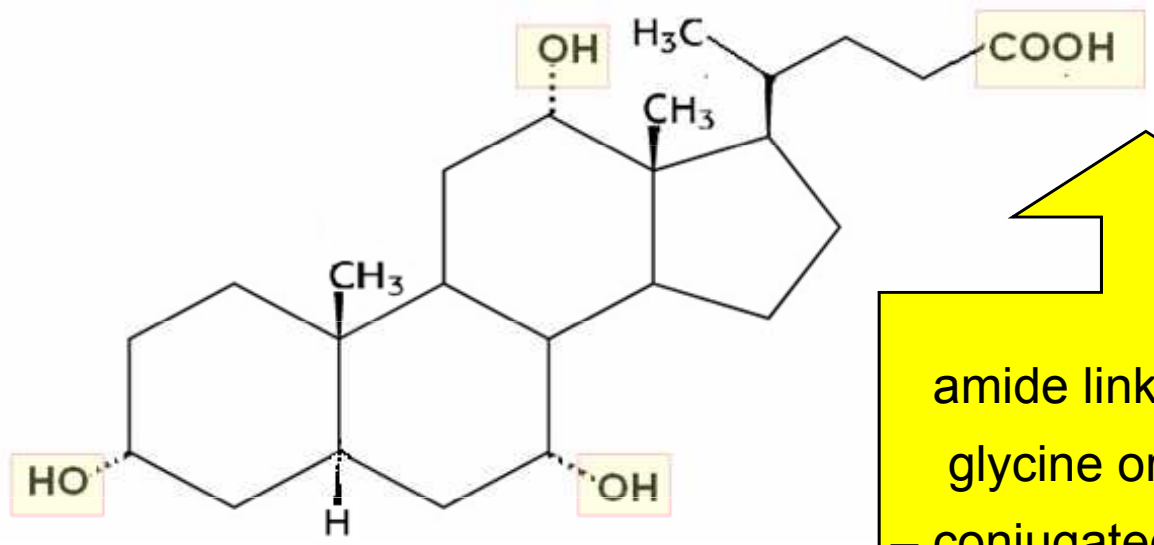
Choloyl-CoA

ER

Dehydrogenation to 3-oxo-
Isomerization of the double bond
Hydrogenation of 3-oxo and double bond at C-4

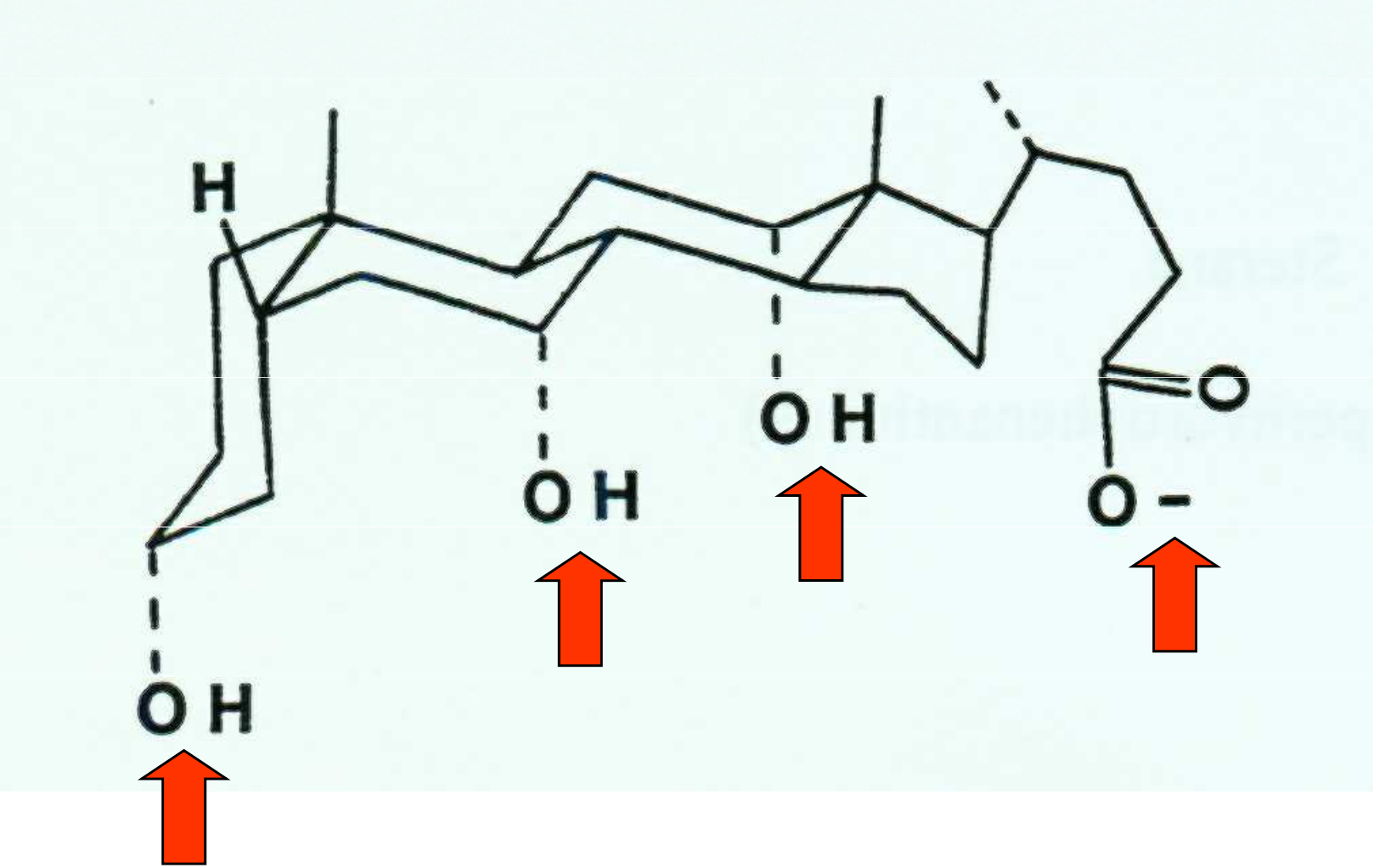
MITOCHONDRION

26-Hydroxylation
Oxidation to C-26 carboxyl
Activation to acyl-CoA
Propionyl-CoA released



amide linkage with
glycine or taurine
– conjugated bile acids

Bile acids are anionic surfactants



all polar groups are oriented on one side of molecule

Q. 22

A. 22

- Phospholipids
- Bile acids (salts)
- Cholesterol

make a special ternary micellar system

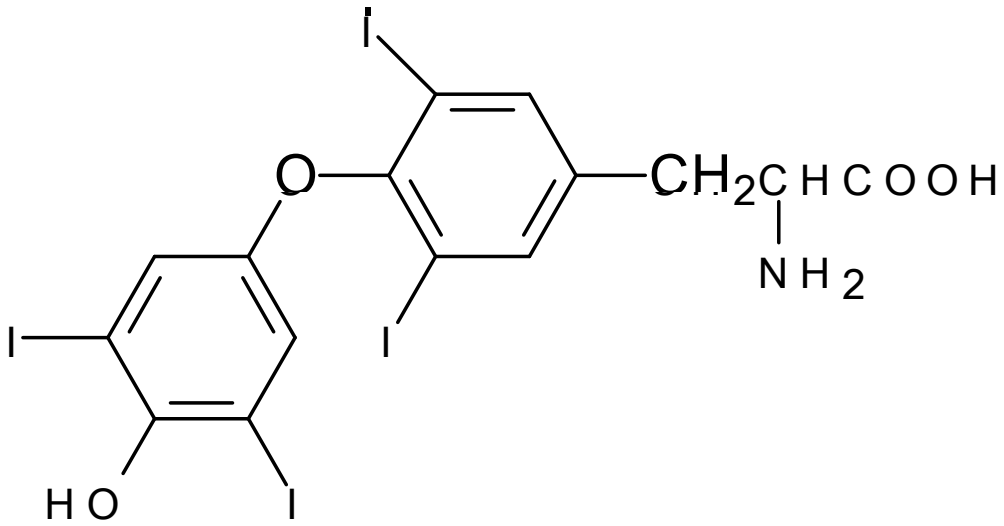
- Bilirubin – responsible for colour

Q. 23

A. 23

Feature	**Insulin**	**Glucagon**
Formation in	beta-cells, pancreas	alfa-cells, pancreas
No. of AA / chains	51 / 2	29 / 1
Precursor	(pre)proinsulin	proglucagon
Plasma half-life	3 min	5 min
Inactivation in	**liver, (kidneys)**	**liver**

Q. 24



thyroxine

A. 24

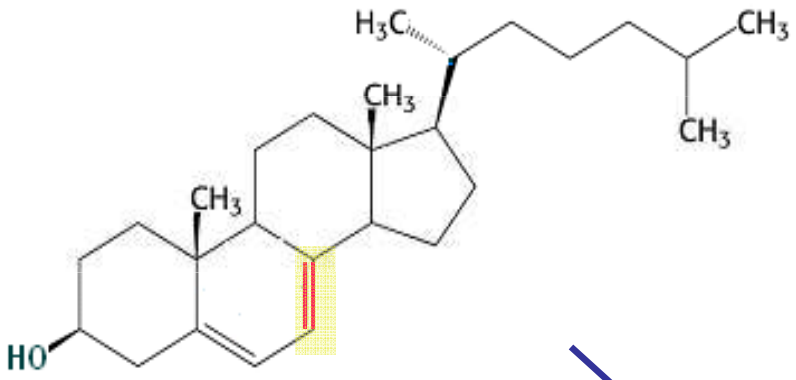
- Inactivated
- Deiodination, deamination, decarboxylation
- conjugation with glucuronic acid
- conjugation with PAPS (sulfatation)

- More polar derivatives are excreted by urine

Q. 26

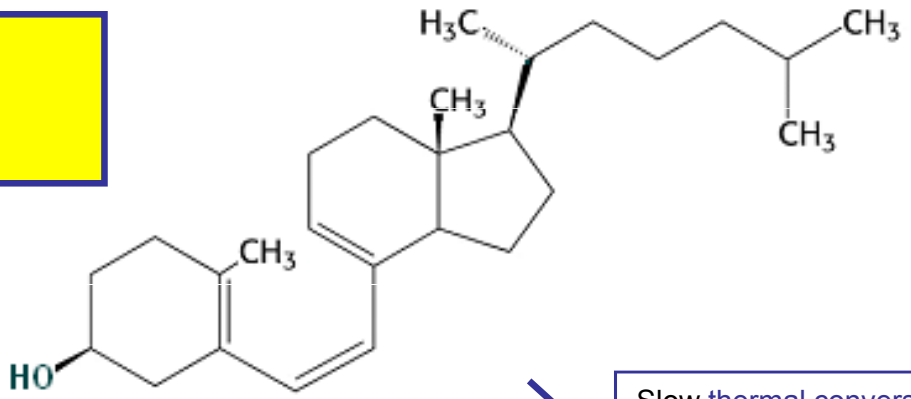
Cholesterol

LIVER
7,8-Dehydrogenation



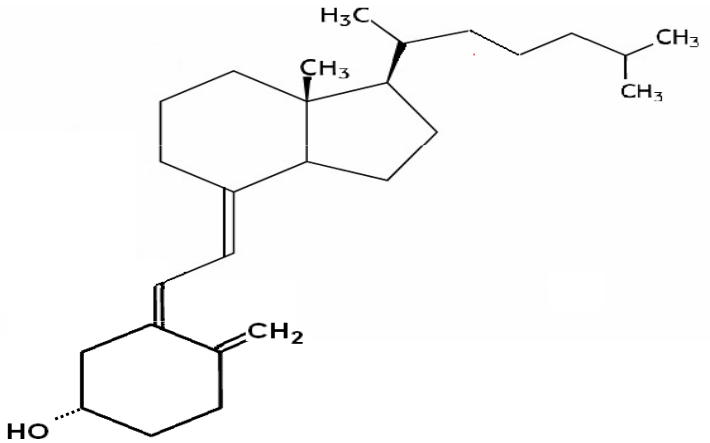
7-Dehydrocholesterol

SKIN
photolysis

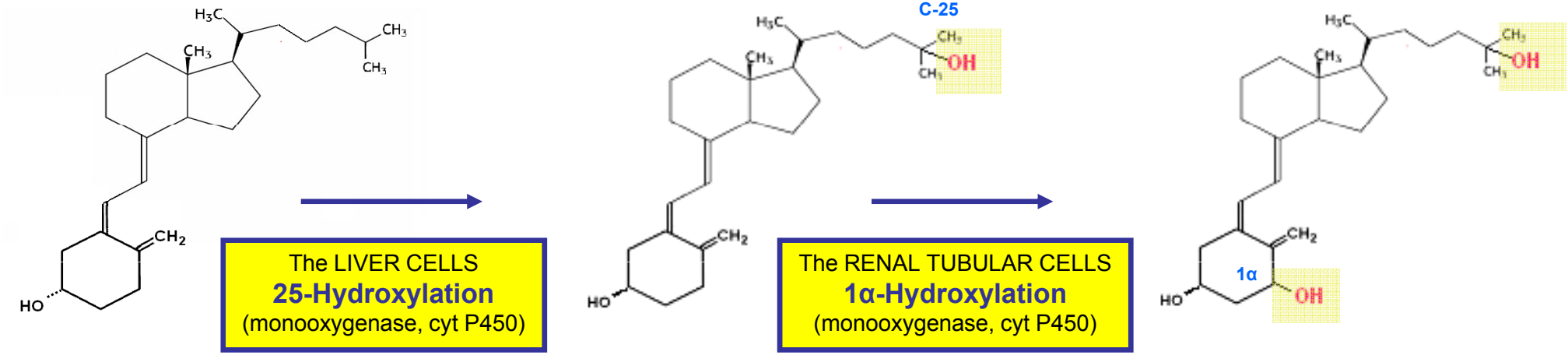


An intermediate
(praevitamin)

Slow thermal conversion



Calciol (vit. D_3)



Calciol
(Cholecalciferol)

Calcidiol
(25-Hydroxycholecalciferol)

Calcitriol
(1α,25-Dihydroxycholecalciferol)
A CALCIOTROPIC STEROID HORMONE

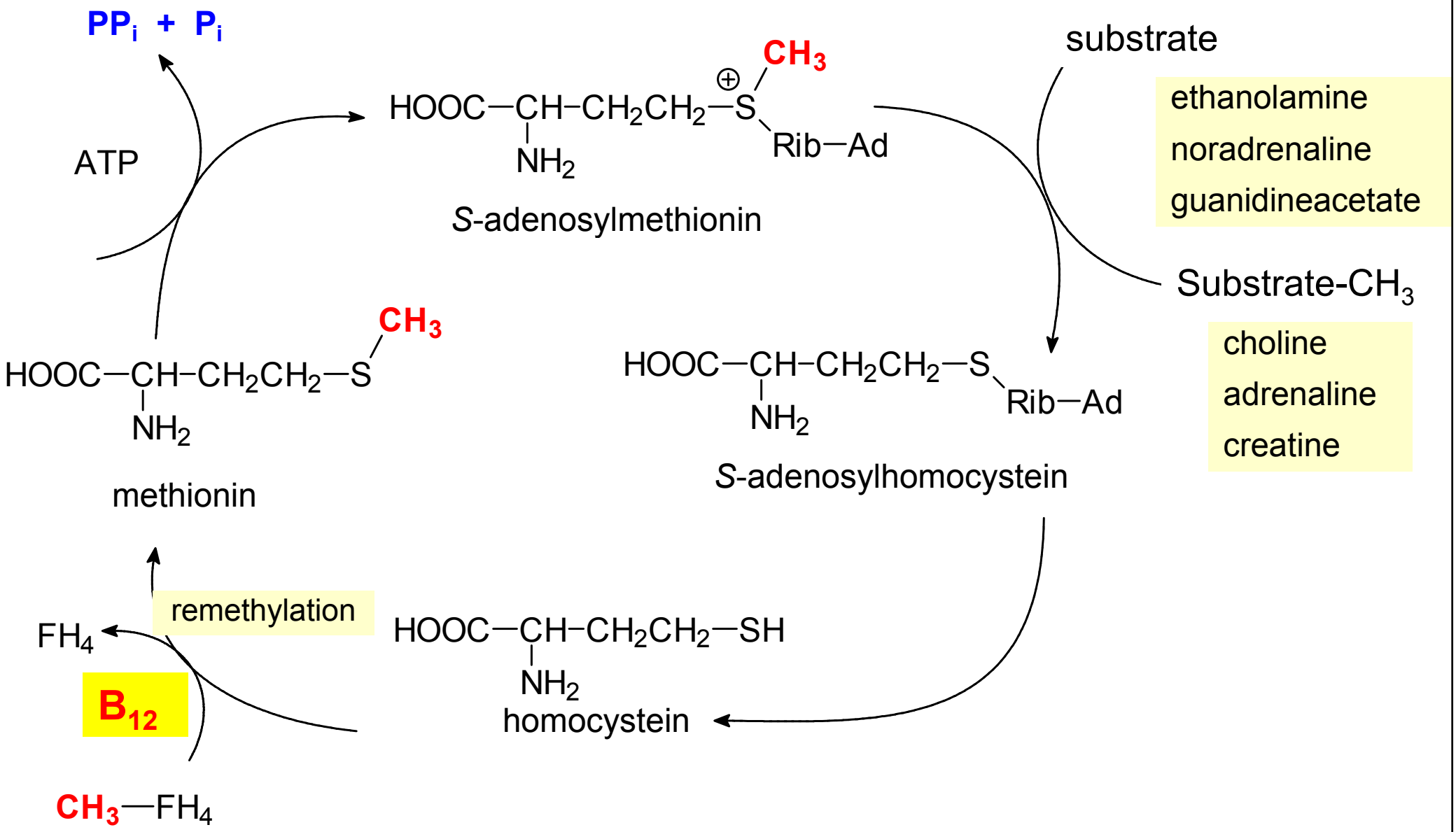
Q. 27

A. 27

- Vitamin A (retinol)
- Vitamin B_{12} (cyanocobalamin)

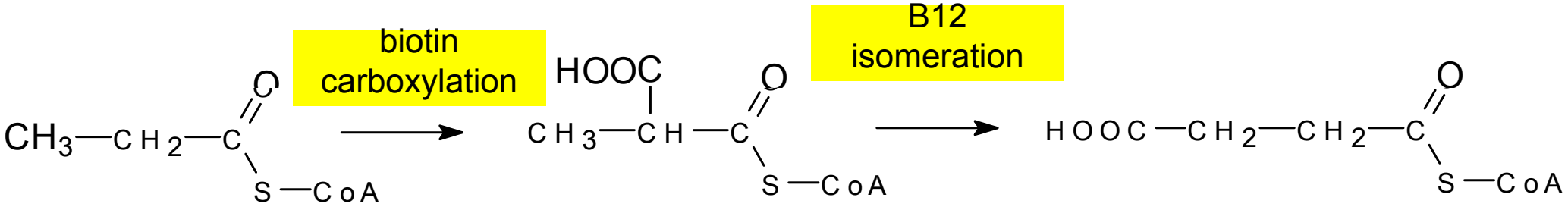
Which reactions in the body require vitamin B_{12}?

Remethylation of homocystein to methionine



Production of succinyl-CoA from some AA

(complete the names)



....

catabolism of
isoleucine
valine
methionine

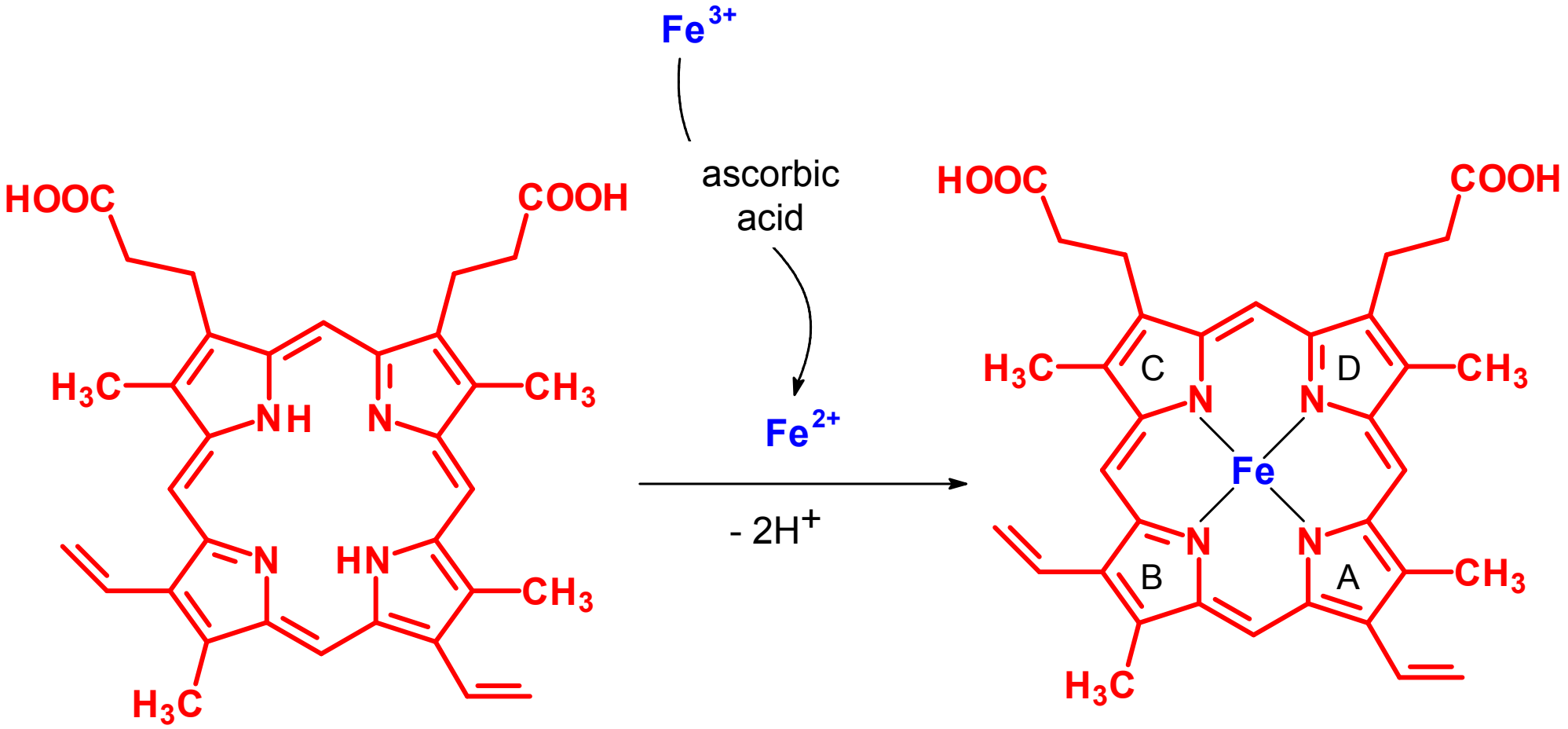
?

Catabolism of hem

Metabolism of bilirubin

What is hem?

Hem is a chelate of protoporphyrin IX with Fe^{2+}



protoporfyrin IX

hem

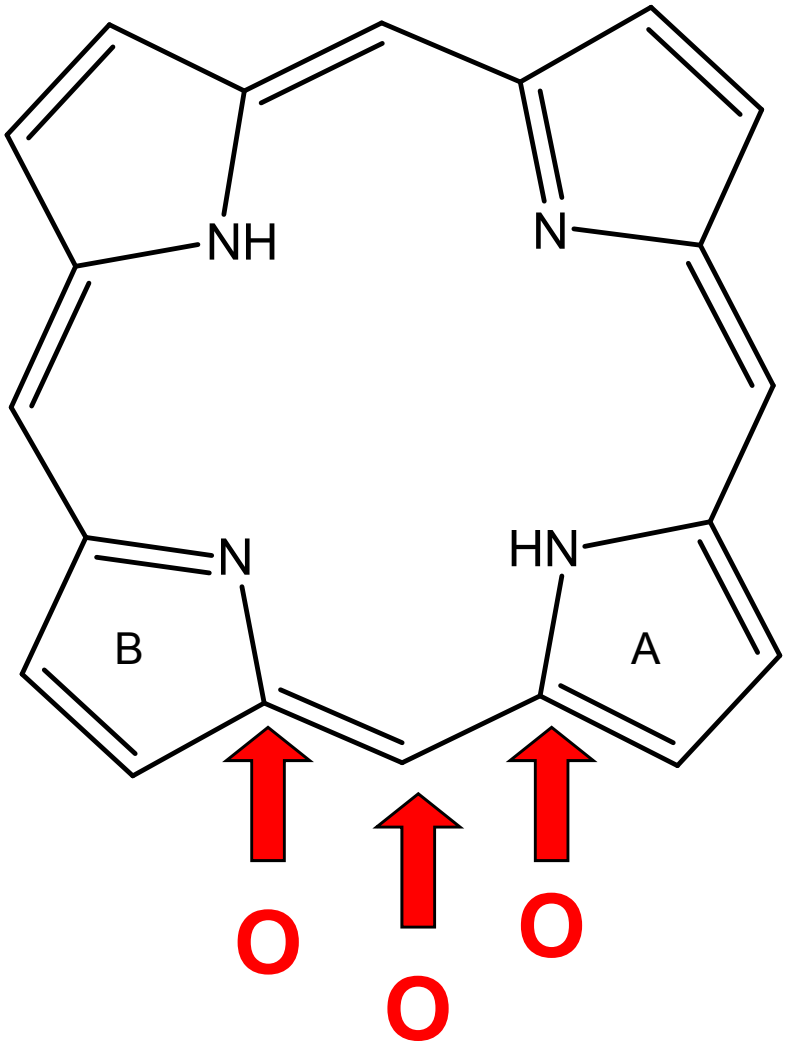
Q. 31

A. 31 - Catabolism of hem

- occurs mainly in spleen, liver, bone marrow
- hemoxygenase (O_2, NADPH, cytochrome P-450)
- Fe^{2+} is released and oxidized to **Fe^{3+}**, bound to ferritin (store)
- -CH= between A/B rings is split off as **carbon monoxide (CO)**
- two O atoms are attached to the A+B pyrrole rings → **biliverdin**
- the central **-C=** bridge between C/D rings in biliverdin is then reduced to **-CH_2-** bridge → **bilirubin**

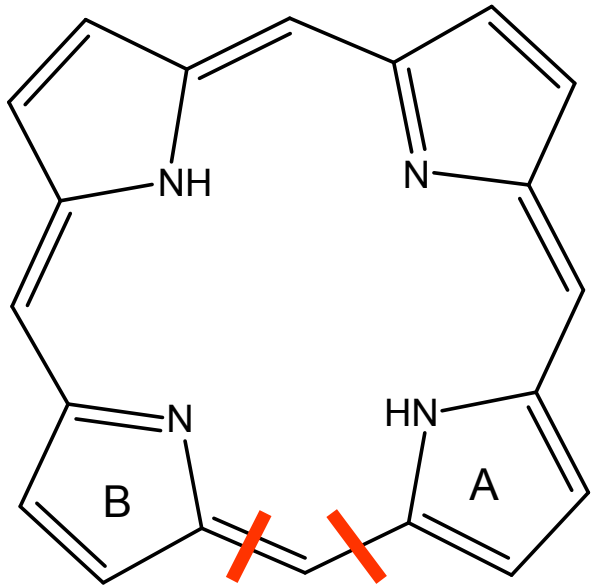
A. 31 - Three oxygen atoms attack protoporphyrin

hemoxygenase



one O is incorporated into CO, two O atoms are inserted into biliverdin

A. 31 Hem degradation provides CO and bilirubin



$3\ O_2 + 3\ NADPH+H^+$ | oxidative splitting

what happens with CO?

$CO + biliverdin + 3\ H_2O$

bilirubin

Carbonylhemoglobin (CO-Hb) in blood

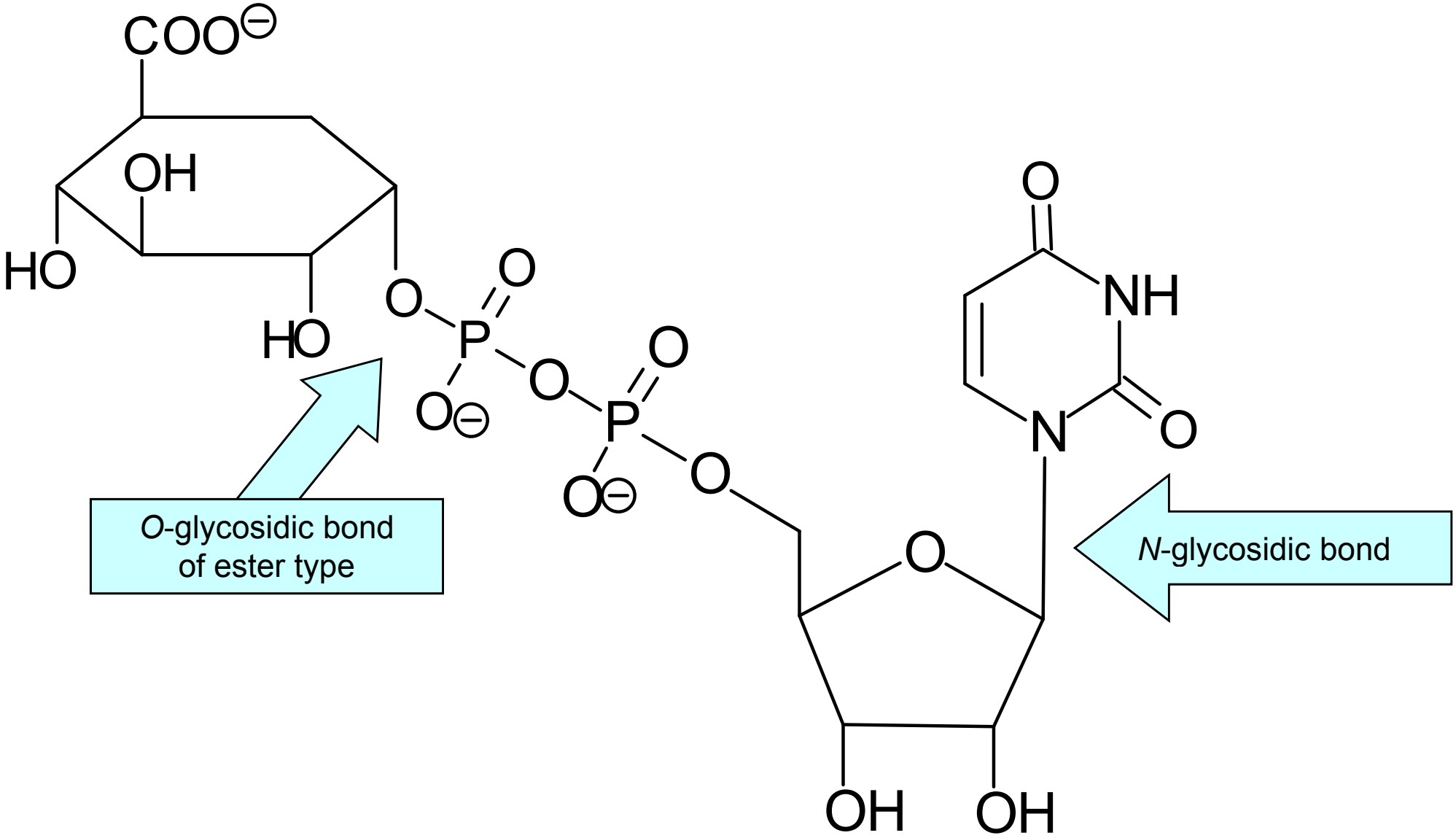
Subject / Situation	CO-Hb (%)*	
Newborns	0.4	Endogenous CO
Adults (rural areas)	1-2	
Adults (big cities)	4-5	Exogenous CO
Smokers	10-12	
Traffic policemen	12-15	
Poisoning	20-50	
Death	55-60	

* Percentage of total hemoglobin

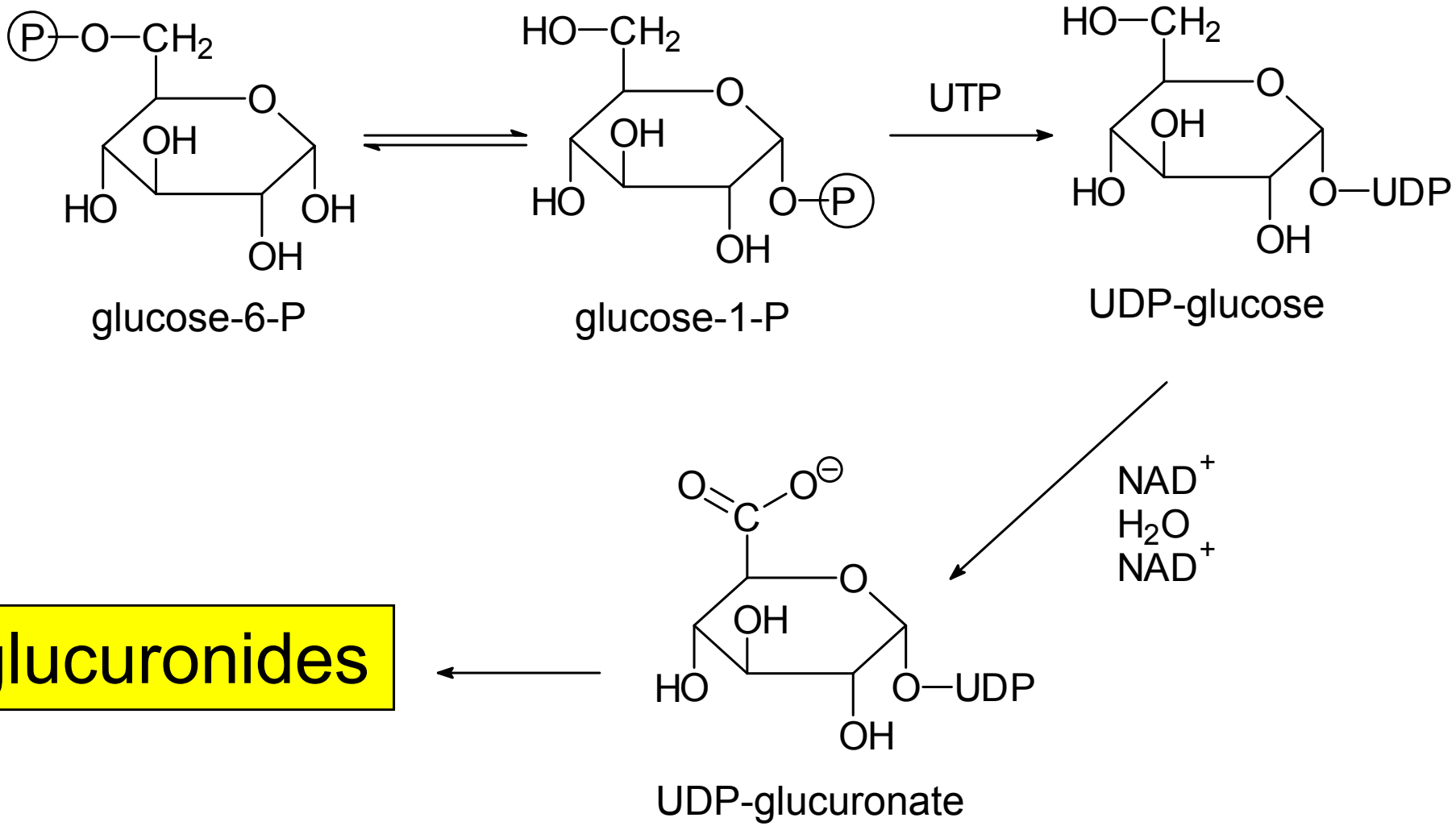
Conjugation of bilirubin in liver

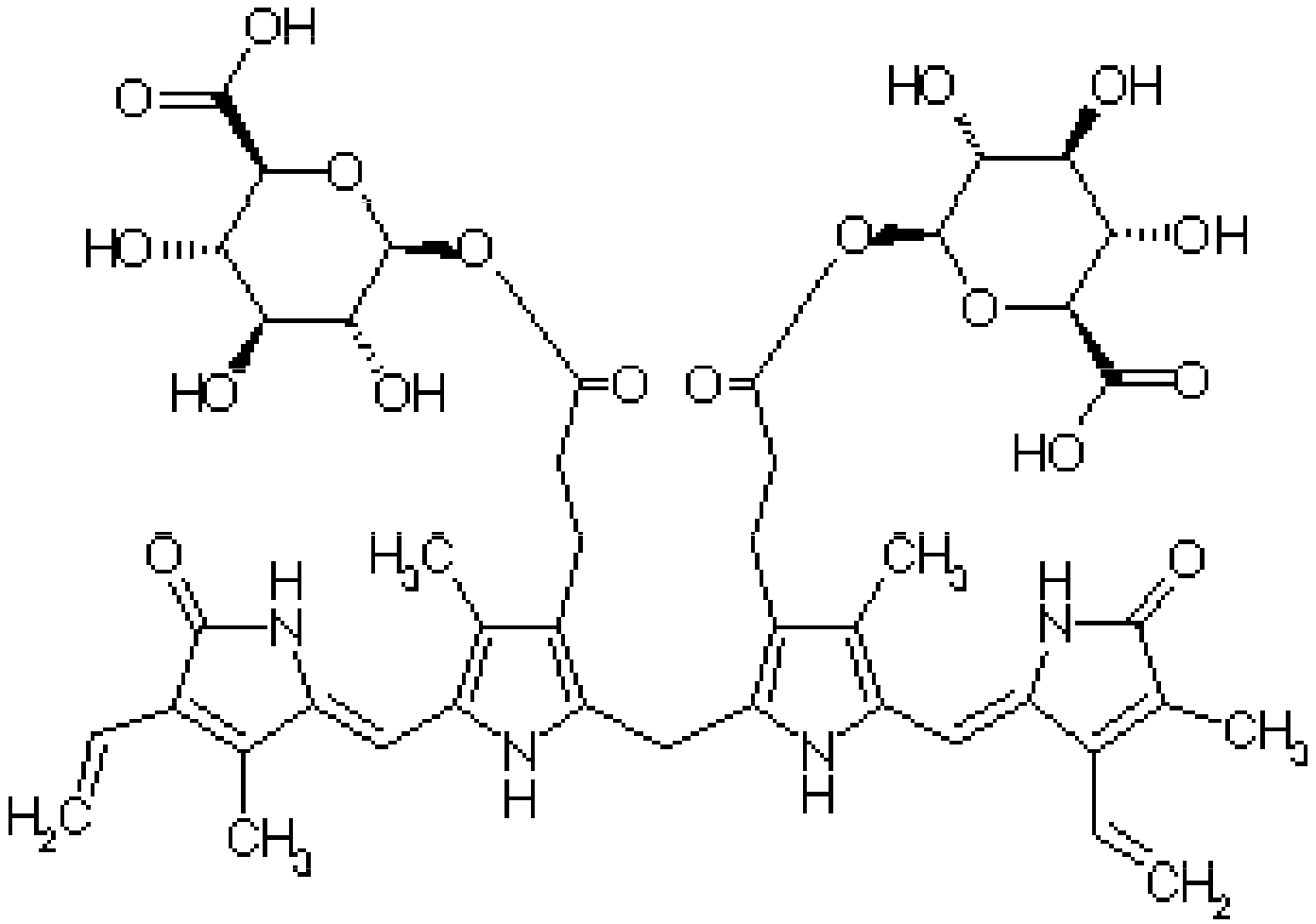
- bilirubin reacts with two molecules of **UDP-glucuronate**
- two highly polar molecules of glucuronate are attached to bilirubin with glycosidic ester bond → **bilirubin bisglucuronide**
- conjugated bilirubin is soluble in water (bile, plasma, urine)
- conj. bilirubin is excreted with bile into intestine, where it is deconjugated and hydrogenated by microflora → **urobilinogens**, they are partially absorbed by v. portae and taken up by liver

The structure of UDP-glucuronate



Biosynthesis of UDP-glucuronate





bilirubin bisglucuronide

Q. 34

A. 34 Hemoproteins

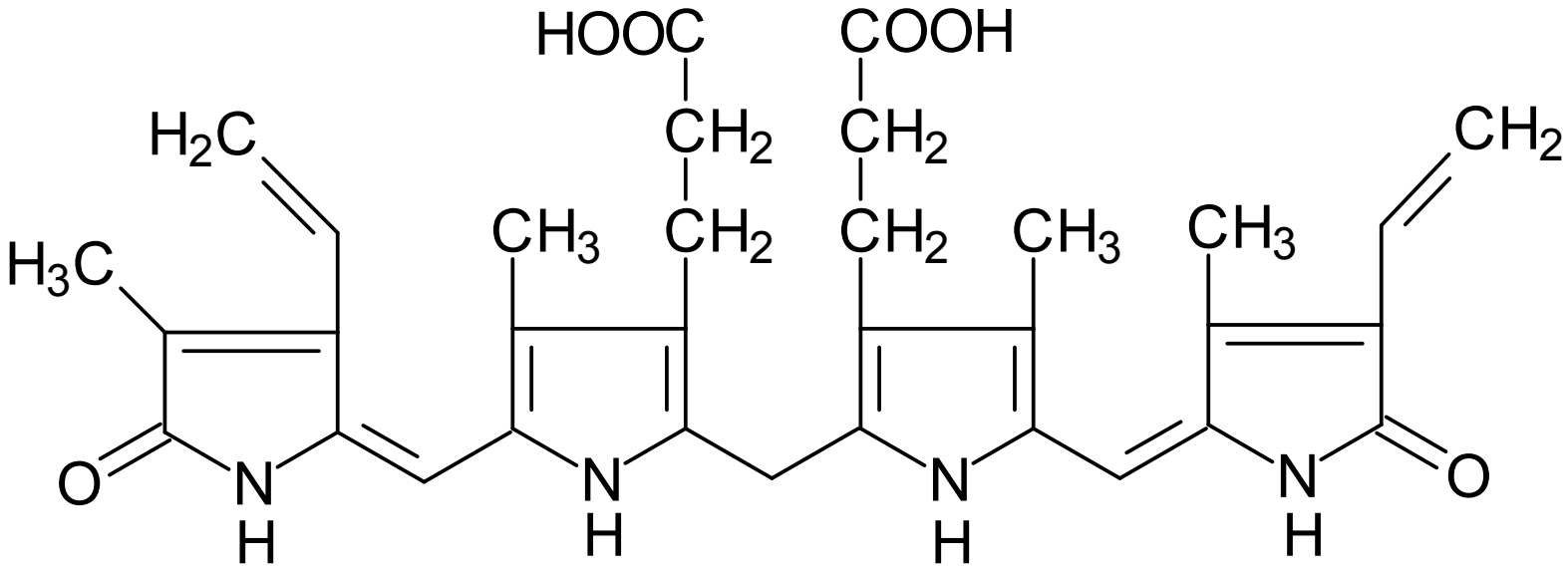
Protein	Redox state	Function
Hemoglobin	Fe^{2+}	
Myoglobin	Fe^{2+}	
Catalase	Fe^{3+}	
Peroxidase	Fe^{3+}	
Cytochromes	$Fe^{2+} \leftrightarrows Fe^{3+}$	
Cytochrome P-450	$Fe^{2+} \leftrightarrows Fe^{3+}$	

A. 34 Hemoproteins

Protein	Redox state	Function
Hemoglobin	Fe^{2+}	transport of O_2 in blood
Myoglobin	Fe^{2+}	deposit of O_2 in muscle
Catalase	Fe^{3+}	elimination of H_2O_2
Peroxidase	Fe^{3+}	elimination of peroxides
Cytochromes	$Fe^{2+} \leftrightarrows Fe^{3+}$	resp. chain components
Cytochrome P-450	$Fe^{2+} \leftrightarrows Fe^{3+}$	hydroxylation reactions

Q. 35

A. 35 Textbook structure of bilirubin



bilirubin has eight polar groups:

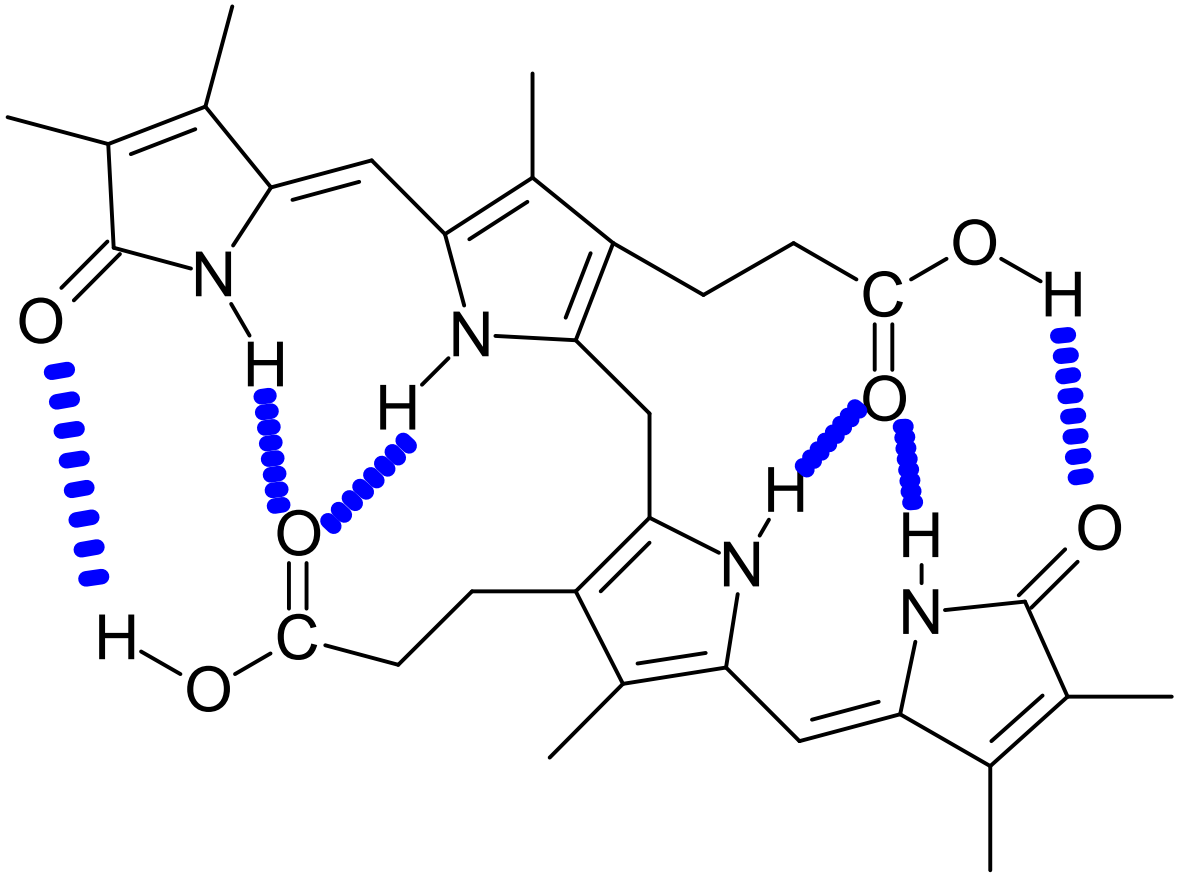
2 -COOH **2 C=O** **4 -NH-**

despite it bilirubine is **non-polar compound**

A. 35 Properties of bilirubin

- linear tetrapyrrol system
- free rotation around central -CH_2- is possible
- non-linear conformation arises, stabilized by six intramolecular H-bonds
- **all polar groups are involved in H-bonds**
- consequence: free bilirubin is non-polar, insoluble in water, in plasma – **bound to albumin**

A. 35 Real structure of bilirubin with six intramolecular H-bonds



Q. 36, 37

A. 36, 37

See Lab manual p. 60

Icterus	**S-Bilirubin** unconjug.	**S-Bilirubin** conjug.	**U-Bilirubin** conjug.	**U-Ubg**
Hemolytic	↑↑	-	-	↑
Hepatic	↑↑	↑	↑	↑↑
Obstructive	normal	↑↑	↑	-

Normal concentration of S-bilirubin

total bilirubine: 5-20 μmol/l

unconjugated up to: 12 μmol/l

conjugated up to: 5 μmol/l

S - serum, U - urine

Q. 38

A. 38

- Urobilinogens are resorbed from intestine to portal blood
- At hepatocellular disorders, the liver is incapable to take urobilinogens, they become elevated in blood and thus excreted to urine

Next seminar: 2nd Revision test

(15 Q / 20 min)

- **Seminar chapters 4 – 7**
- **Practical chapters 3 – 5**